Radical methods for the synthesis of aliphatic amines

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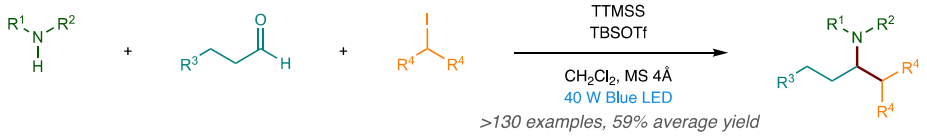
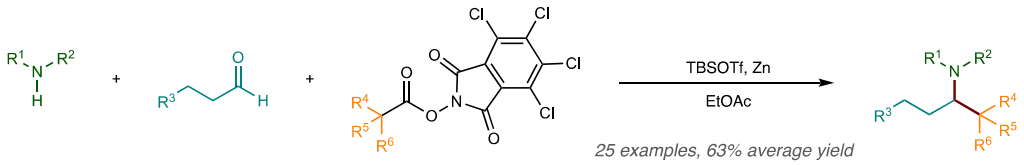
Abstract - Radical methods for the synthesis of aliphatic amines

The aliphatic amine motif is a ubiquitous and uniquely important functional group in pharmaceutical agents and the development of ever more efficient synthetic methods for their synthesis is a continuous challenge. This thesis details the development of three new radical reactions for the synthesis of aliphatic amines.

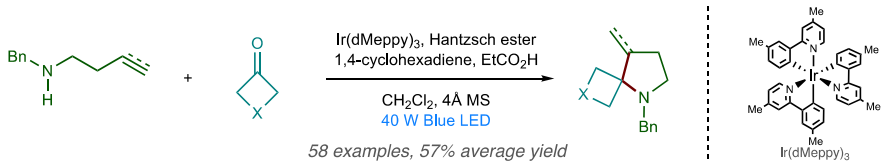
Following an introduction to radical chemistry and a summary of previous advances in amine synthesis, chapter 2 will describe a general carbonyl alkylative amination reaction, a successful version of which has been sought for over 70 years. Facilitated by visible light and a silane reducing agent, the operationally straightforward reaction forms tertiary amines *via* the coupling of aldehydes and secondary amines with alkyl halides. Combining an efficient radical-chain mechanism with the structural and functional diversity of readily available starting materials, the carbonyl alkylative amination provides a flexible strategy for the streamlined synthesis of complex tertiary amines.



In chapter 3, an improved carbonyl alkylative amination was sought by replacing the alkyl halide with a more abundant radical precursor. This led to the development of a new carbonyl alkylative amination reaction using tetrachloro *N*-hydroxyphthalimide esters, prepared from carboxylic acids, in conjunction with inexpensive and environmentally friendly zinc dust instead of the costly silane reducing agent. The use of a carboxylic acid derived nucleophile enabled a broader scope in both amine and nucleophile components and the full potential of this reaction is currently being developed.



In chapter 4, a visible light-mediated direct synthesis of *N*-heterospirocycles is reported. A photocatalyst was employed to reduce an aliphatic iminium ion to the corresponding α-amino radical, which was cyclized to afford polar, heteroatom-rich spirocycles. The reaction tolerated a range of polar functional groups and the resulting scaffolds were shown to occupy a promising yet less exploited area of chemical space, making the reaction relevant for fragment-based drug discovery.



Nils Flodén

Till mamma och pappa

Denna avhandling dedikeras med vördnad till
standardmuffinsen, den sista SI-enheten

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Till sist så är jag evigt tacksam till mamma, pappa och Alex för deras stöd som gjort att jag har kunnat gå min egen väg.

Abbreviations

1,4-CHD	1,4-cyclohexadiene
4Cz-IPN	1,2,3,5-tetrakis(carbazole-9-yl)-4,6-dicyanobenzene
Å	Ångström
Ac	Acetyl
acac	Acetylacetonate
AIBN	Azobisisobutyronitrile
aq.	Aqueous
Ar	Aryl
ARC	Aminium radical cation
BDE	Bond dissociation enthalpy
BINOL	2,2′-Dihydroxy-1,1′-dinaphthyl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bpy	2,2’-Bipyridine
br	Broad
BTPP	*tert*-Butylimino-tri(pyrrolidino)phosphorane
Bu	Butyl
Bz	Benzoyl
CAA	Carbonyl alkylative amination
cal	Calories
cat.	Catalytic
Cbz	Carboxylbenzyl
CFL	Compact fluorescence light
COD	1,4-cyclooctadiene
CNS	Central nervous system
Cy	Cyclohexyl
d	doublet
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	Dichloroethane
DIPEA	Di*iso*propyl ethylamine
dppf	1,1'-*bis*(diphenylphosphino)ferrocene
d.r.	Ciastereomeric ratio
DTBM-SEG	5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole.
dF(Me)ppy	3,5-difluoro-2-[5-(methyl)-2-phenyl]pyridine

dF(CF_3)ppy	3,5-difluoro-2-[5-(trifluoromethyl)-2-phenyl]pyridine
DFT	Density functional theory
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
dMeppy	4-Methyl-2-(*m*-tolyl)-pyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dtbbpy	4,4'-di-tert-butyl-2,2'-bipyridine
$E_{1/2}$	Half-wave potential
EDA	Electron donor-acceptor
e.e.	Enantiomeric excess
equiv.	Equivalents
ESI	Electrospray ionization
ESR	Electron-spin resonance spectroscopy
Et	Ethyl
EWG	Electron-withdrawing group
fac	Facial
FT-IR	Fourier-transform infrared spectroscopy
GC-FID	Gas chromatography–flame ionization detection
glyme	Ethylene glycol dimethyl ether
h	Hour(s)
HAT	Hydrogen atom transfer
HEH	Hantzsch ester
HFIP	Hexafluoroisopropanol
HLF-reaction	Hofmann-Löffler-Freytag reaction
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
Hz	Hertz
i	*iso*
J	Coupling constant
k	kilo
L	Ligand (2-electron)
LDA	Lithium di*iso*butylaluminium hydride
LED	Light emitting diode
LUMO	Lowest unoccupied molecular orbital
m	Multiplet

m	*meta*
Me	Methyl
MLCT	Metal-to-ligand charge transfer
MS 4Å	Molecular sieves 4Å
NMR	Nuclear magnetic resonance
NHPI	*N*-hydroxy phthalimide
NOE	Nuclear Overhauser effect
Nu	Nucleophile
o	Ortho
p	*para*
P. E.	Petroleum ether
PCET	Proton coupled electron transfer
Ph	Phenyl
Phth	Phthalimide
Pin	Pinacolato
pK_a	Logarithmic acid dissociation constant
PMI	Principal moment of inertia
ppm	Parts per million
ppy	2-Phenylpyridinato
Pr	Propyl
PTFE	Polytetrafluoroethylene
PTH	10-Phenylphenothiazine
PTOC	*N*-Hydroxypyridine-2-thione
py	Pyridine
q	quartet
quint	quintet
R	Undefined organic group
RAMP	*R*-1-Amino-2-(methoxymethyl)pyrrolidine
r.t.	Room temperature
s	singlet
SAMP	*S*-1-Amino-2-(methoxymethyl)pyrrolidine
sat	Saturated
SCE	Saturated calomel electrode
SCX	Strong cation exchange
SET	Single-electron transfer
sext	sextet

SOMO	Singly-occupied molecular orbital
spt	septet
t	triplet
TBHP	*tert*-Butyl hydrogen peroxide
TBS	*tert*-Butyldimethylsilyl
TCNHPI	Tetrachloro *N*-hydroxyphthalimide
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
TRIP	Tri*iso*propyl
Ts	Tosyl
TTMSS	Tris(trimethylsilyl)silane
UV	Ultraviolet
UV-Vis	Ultraviolet–visible spectrophotometry
vs	Versus
X	Halogen
λ	Wavelength
τ	Excited state lifetime

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1 Introduction

1.1 Properties and importance of aliphatic amines

In 1878, A. W. Hofmann was studying the structure of piperidine.[1] It was known at the time that piperidine belonged to the amino class of compounds, a derivative of ammonia whose molecular formula had been determined as NH_3.[2] Hofmann's interest in piperidine stemmed from the properties of its more complex cousin, morphine, which had been isolated in 1804 as the first pure alkaloid.[3] Following the commercialization of morphine as a potent pain-killer in the mid 19th century, interest in amines surged and today the aliphatic amine motif is present in over 40% of all small-molecule drugs (Figure 1).[4]

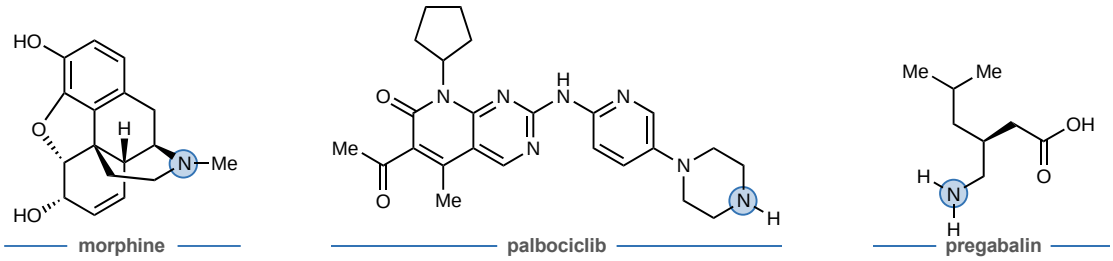


Figure 1 | Examples of important tertiary, secondary and primary amine drugs.

The abundance of amines in pharmaceutical compounds can be understood by the unique properties the nitrogen atom bestows upon its parent molecule, as can exemplified by morphine. The lipophilic nature of the tertiary amine motif enables the drug to pass through the blood-brain barrier and enter the central nervous system (CNS). However, as the pK_a of morphine (pK_a = 8.21)[5] is similar to the physiological pH inside the CNS, the tertiary amine becomes partially protonated, resulting in a strong ionic interaction with the opioid receptor.[6] In a more general sense, aliphatic amines can balance the need for lipophilicity and solubility[4] whilst allowing for specific ionic and hydrogen-bonding interactions that enhance potency. These properties are particularly important for drugs targeting the CNS, of which over 70% contain an aliphatic amine.[7]

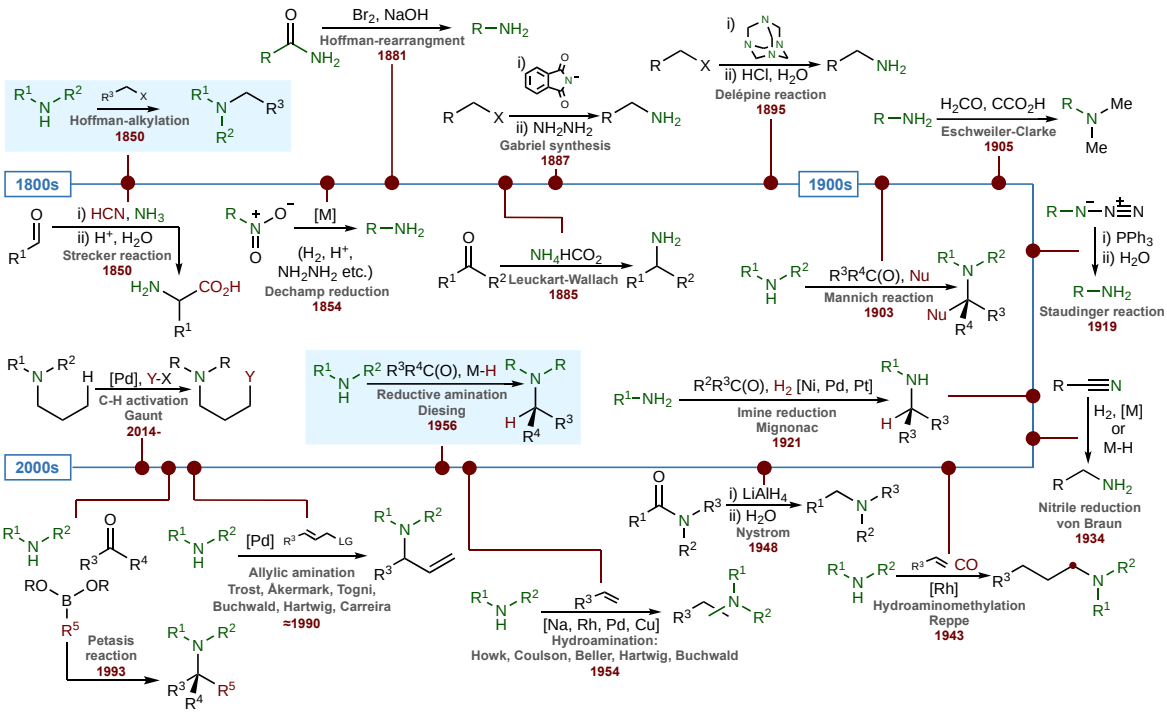
1.2 Synthesis of aliphatic amines

Organic chemists have developed a plethora of reactions with which to synthesize aliphatic amines. These reactions can be divided into methods utilizing two-electron (closed-shell) or single-electron (open-shell) pathways. In the following section, the more numerous polar methods, which have been reviewed elsewhere,[8] will be discussed briefly in order to put an in-depth discussion about radicals and radical methods for aliphatic amine synthesis into a wider context. Throughout this thesis, focus will be

placed on methods that construct *aliphatic amines* while avoiding methods that construct or use amine-derivatives e.g. *N*-aryl amines or aliphatic amine precursors such as carbamates or amides in order to highlight the unique challenges that follow with this constraint.

1.2.1 Polar methods for aliphatic amine synthesis

The archetypical polar method for aliphatic amine synthesis is the S_N2 displacement of a halide by an aliphatic amine, developed by Hofmann (Scheme 1).[9] Although it is still frequently employed within the pharmaceutical industry using a range of electrophilic coupling partners,[10] the efficiency of the Hofmann alkylation can be hampered by elimination and over-alkylation side-reactions. This is a consequence of the (usually) greater nucleophilicity of the product compared to the starting material and therefore, a large excess of amine has to be employed.[11] Common electrophiles such as alkyl halides also generate large quantities of waste, an issue that has primarily been addressed through the catalytic activation of alcohols to generate H_2O as the only by-product.[12–14] This work was pioneered by Griggs[15] and Watanabe,[16] who showed in two separate but simultaneous reports that rhodium, ruthenium and iridium catalysts could be used to activate alcohols in the reaction with aromatic and aliphatic amines.



Scheme 1 | Polar methods towards the synthesis of aliphatic amines with the two most commonly used methods highlighted in blue.

As a complement to *N*-alkylation, a wealth of reductive amination methods has been developed wherein carbon-nitrogen double or triple bonds act as electrophiles to access the corresponding aliphatic amine. In this context, early discoveries with high atom-economy such as the Leuckart-Wallach reaction (1885),[17–19] the Eschweiler-Clarke reaction (1905) for methylation,[20,21] the catalytic reduction imines

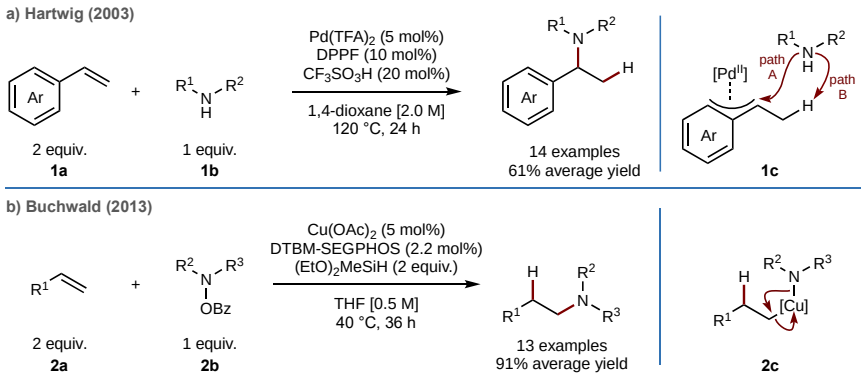
(1921)[22] to their corresponding amine have all been employed in kilogram-scale industrial processes. A significant milestone was reached in 1956 when Diesing[23] reported the reductive amination of Schiff-bases by $NaBH_4$ and this study was followed by similar reports from Schellenberg[24] and Durst.[25] The reaction can be used to access all classes (1°, 2° and 3°) of amines and both aldehydes and ketones are tolerated as substrates, although increasing steric hinderance on both the amine and ketone components can afford significantly lower yields. Nevertheless, the reductive amination reaction has evolved to become the gold standard of laboratory-scale amine synthesis, particularly following the development of acid-stable reagents such as $NaBH_3CN$[26] and $NaBH(OAc)_3$.[27] Indeed, reductive amination is the 8th most commonly employed reaction in medicinal chemistry.[10]

Imine or iminium ion intermediates have also been used as electrophiles in conjunction with non-hydride nucleophiles. Notable examples includes Strecker's amino acid synthesis (using cyanide as the nucleophile), the Mannich[28,29] reaction as well as more recent work on redox-triggered α-amino functionalization.[30–33] Another important advance is the Petasis reaction, where boronic acids and esters are activated *in situ* to generate a nucleophile which adds to an iminium ion.[34] It has a broad scope in the amine component but the boronic acid or ester is largely limited to aryl or allyl examples.[35] The reactivity of the nucleophilic enamines, as opposed to their tautomeric imines or iminium ions, has also been exhaustively explored with a large number of applications as catalysts and substrates in reactions such as, but not limited to, alkylations and cycloadditions.[36]

Transition metal catalysis is increasingly being used to access aliphatic amines.[8] In this approach, the reactivity of the nucleophilic nitrogen is tuned through coordination to a metal but, so far, these methods often require some form of protection of the amine, which limits their scope.[37–39] A reason for this deficiency is the high basicity of aliphatic amines, creating stable metal-amine complexes that inhibit catalysis.[40,41] As a comparison, the Buchwald-Hartwig amination[42] affords aryl-amines (anilines) which are substantially less nucleophilic and hence more readily tolerated in catalysis, resulting in a broad scope.[43,44]

Despite this challenge, the use of transition metal catalysis can facilitate several conceptually powerful reactions. A particularly important transformation is the hydroamination reaction of an aliphatic secondary amine and an alkene, which is highly attractive due to the commercial availability of the starting materials and high atom-economy.[45] It has been studied in an industrial context by Howk (1954; using base metal catalysts)[46] and later by Coulson (1971; using iridium or rhodium catalysis)[47] and Beller (1999, using rhodium catalysis)[48] but these early discoveries were limited to ethylene or afforded mixtures of products. Hydroamination is a near thermoneutral process which cannot be accelerated using high temperatures as it would result in a thermodynamic equilibrium of starting materials and products.[49] This is particularly problematic for intermolecular variants, which in addition have to

navigate challenges of regioselectivity. Unsurprisingly therefore, most synthetic applications of hydroamination can be found among intramolecular reactions.[50] Yet more challenging, the nucleophilic nature of the amine (with its lone pair) and alkene (with its filled π-orbital) requires a catalyst which can perform an umpolung reaction by reversing the "philicity" of either component.[51] An important advance in this regard was reported by Hartwig and co-workers who developed hydroamination of unactivated aliphatic amines with styrenes (Scheme 2a).[52] Employing palladium catalysis, they could access the key η^3-arylethyl intermediate **1c,** which turns the nucleophilic alkene **1a** into an electrophile. Subsequent electrophilic attack by an aliphatic amine (**1b**) on **1c** afforded the desired tertiary amines in good yields. However, the protocol was less suitable for basic amines as competing deprotonation at the methyl-position of **1c** occurred. In a complementary advance, Buchwald and co-workers described the copper-hydride mediated hydroamination of terminal aliphatic alkenes (Scheme 2b).[53] They proposed that benzoylhydroxylamine **2b** underwent oxidative addition with the alkyl-copper species (resulting from insertion of alkene **2a** into a Cu–H bond) to afford **2c**. C–N Reductive elimination then afforded the desired tertiary amines in high yields. This reaction was advanced further in a later publication from the same group, where they reported an enantioselective addition of activated aliphatic amines to unactivated internal olefins.[54] However, the copper-catalyzed approach to hydroamination suffers from the long synthetic sequence to access **2b**, long reaction times and must be partially carried out in a glove-box.

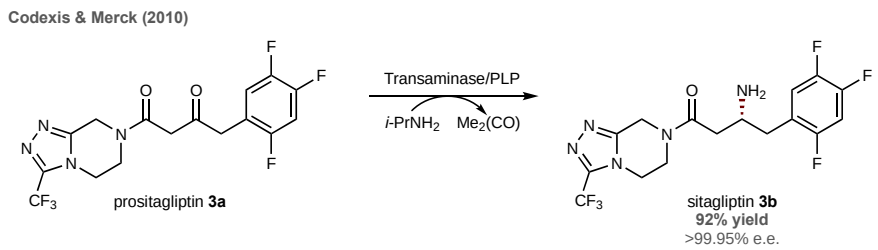


Scheme 2 | a) Hartwig's Markovnikov-selective hydroamination reaction proceeding *via* a palladium-allyl complex. b) Buchwald's copper-catalyzed, anti-Markovnikov-selective hydroamination reaction. (DPPF = 1,1'-bis(diphenylphosphino)-ferrocene; DTBM-SEG = 5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole.)

The hydroamination reaction can also be carried out in a three-component fashion, a hydroaminoalkylation reaction, as pioneered by Reppe – under an atmosphere of CO, a molecule of CO is inserted to afford a homologated hydroamination product.[55] Other powerful approaches include the use of amine-nucleophiles in the Tsuji-Trost reaction and similar allylic aminations.[56–58] Recent advances to address the issue of amine-binding to the transition metal catalyst have been made in the context of aliphatic amine C–H activation by the Gaunt group. They developed a range of transformations where the basic nitrogen atom acts to facilitate the cleavage of an unreactive C–H bond

to promote the formation of aziridines or azetidines as well as introduce important moieties such as hydroxyl or heteroaromatic groups.[40,59,60] Carbene or carbenoid insertion into N–H bonds is another area of active research. Most examples employ aromatic amines[61] but exceptions exist[62,63] and recently an asymmetric Cu-catalyzed carbenoid insertion into aliphatic amines was reported.[41]

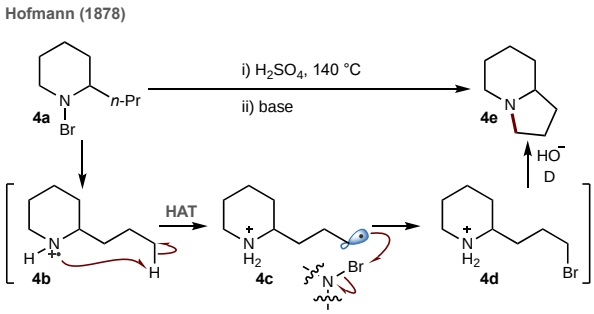
Finally, the field of biocatalysis has seen a steady rise to prominence over the past 30 years.[64,65] Whereas chemists have discovered a wealth of new modes of reactivities, enzymes offer the possibility of exquisite regio- and stereoselectivity by virtue of controlling the environment around the reacting molecule(s).[66] In a telling example, researchers at Codexis and Merck refined the synthesis of sitagliptin (**3b**) by introducing a transaminase-catalyzed reductive amination instead of a previously used Rh-catalyzed hydrogenation (Scheme 3).[67] This example highlights the potential of enzyme-catalysis in the synthesis of enantiopure amines.



Scheme 3 | Biocatalytic hydrogen-borrowing reduction in the synthesis of sitagliptin. (PLP = pyridoxal phosphate).

1.3 Radical methods for the synthesis of aliphatic amines

Returning to Hofmann's studies of piperidine in 1878, he was attempting to establish whether piperidine contained an unsaturated bond by reacting it with bromine. However, as is now known, piperidine does not contain an alkene and reaction with bromine resulted in the formation of *N*-bromo piperidine (**4a**). Upon treatment of **4a** with hot sulfuric acid and subsequent basic work-up, a cyclization occurred to form the bicyclic amine **4e** through what has become known as the Hofmann-Löffler-Freytag (HLF) reaction, following later studies by Löffler and Freytag.[68] The mechanism of the reaction remained unknown, however, until the work of Thelen and Wawzonek in 1950.[69,70] They proposed that the reaction proceeded *via* homolysis of the weak N–Br bond to form an aminium radical cation (ARC) **4b** (Scheme 4). This species then underwent a 1, 5-hydrogen-atom transfer (HAT) to afford primary alkyl radical **4c**, which could propagate the reaction *via* homolytic substitution of the N–Br bond of another molecule of **4a**.

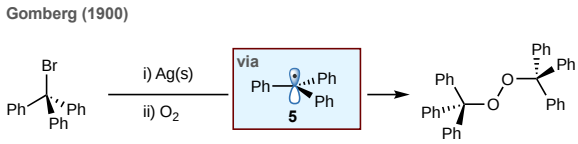


Scheme 4 | Proposed mechanism of the HLF-reaction.

Unknowingly, at the time, the HLF-reaction heralded the arrival of radical methods for amine synthesis. In following section, the discussion of synthetic methods that constructs aliphatic amines will be briefly interrupted by a thorough background on the concepts underlying radical reactivity. Then, an overview of classical radical methods to access aliphatic amines will be given together with more recent advances from the fields of photoredox and metallophotoredox catalysis.

1.3.1 Concepts of radical chemistry

The term "radical" had originally been introduced by Lavoisier in reference to a part of a molecule that did not change its connectivity throughout a chemical reaction.[71] This meaning would change in 1900 when Gomberg reported that the treatment of triphenylmethyl bromide with elemental silver under an atmosphere of carbon dioxide formed brightly colored triphenylmethyl radicals **5** in solution (Scheme 5).[72] Radicals, such as **5**, are open-shell, neutral species with an orbital containing a single unpaired electron, which is referred to as a singly-occupied molecular orbital (SOMO).



Scheme 5 | The discovery of "trivalent carbon", a radical, reported by Gomberg.

1.3.1.1 Structure, stability and electronic character of radicals

The nature of a radical is influenced by its molecular surroundings and this has a significant effect on its structure and its reactivity. For example, the methyl radical (**6a**) is planar in order to minimize Pauli-repulsions between the C–H σ-orbitals and to accommodate for differences in electronegativity (Figure 2).[73,74]

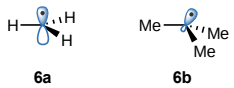


Figure 2 | Structure of the methyl and *tert*-butyl radicals.

The *tert*-butyl radical (**6b**), however, is bent; such a structure enables the SOMO-orbital to interact through hyperconjugation with the vicinal σ*(C–H)-orbitals (Figure 3a).[75] This interaction increases the energy of the SOMO, which becomes *nucleophilic*, whilst lowering the overall energy of the molecule. The importance of conjugative stabilization of radicals can be further exemplified with the cases of the α-methoxy and α-carbonyl radicals (Figure 3b & 3c). Akin to the σ(C–H)-orbitals in the *tert*-butyl radical, the lone pair of the oxygen atom interacts with the SOMO to increase its energy (to a greater extent than through hyperconjugation). In contrast, the interaction with the π*-orbital of the carbonyl-group lowers the energy of the SOMO-orbital, making it *electrophilic* in nature. These interactions resemble those observed for carbocations with one crucial difference – both the α-methoxy and the α-carbonyl groups *stabilize* the radical by lowering the overall energy of the molecule. Hence, the neighboring groups exert an electronic effect that influences the stability (a thermodynamic factor) but also the reactivity (the electrophilic or nucleophilic nature i.e. a kinetic factor) of radicals and consequently provides the basis for how they interact with other species.[75] It must be stressed, however, that the concept of "*philicity*" in the context of radicals is less accurate than for polar nucleophiles and electrophiles. For example, whilst a frontier molecular orbital treatment suggests that α-carbonyl radical is a good electrophile, other theoretical studies based on for example ionization potential have classified it as only a weak electrophile[76] and experiments suggest that it is *ambiphilic*, showing both electrophilic[77] and nucleophilic[78] character.

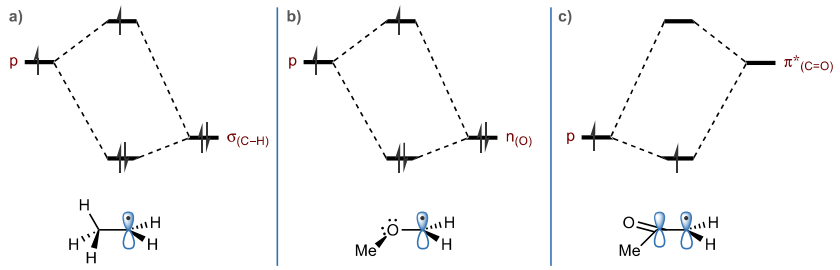


Figure 3 | The effect on the energy of a SOMO-orbital if the adjacent functional group is a) a C–H bond, b) a methoxy-group or c) a carbonyl group.

When the electronic effects of neighboring groups are combined with steric effects, a picture emerges whereby radicals can be divided into four categories – transient *versus* persistent and destabilized *versus* stabilized. The term *persistent* radical was introduced by Ingold in reference to "…a radical that has a lifetime significantly greater than methyl under the same conditions".[79] Persistency is, therefore, a kinetic measure that arises from both steric and electronic effects. For example, the triphenylmethyl radical (**7d**) is persistent, resulting in part from the bulk of the adjacent phenyl rings but also from the overlap of the aromatic π-orbitals with the SOMO (Figure 4). The phenyl radical (**7a**), on the other hand, is sterically unhindered and electronically *destabilized*, resulting in a highly reactive *transient* radical. However, a phenyl radical can become persistent if large substituents are introduced, such as

in **7b**. Meanwhile, groups such as methoxy, carbonyl or aryl (e.g. **7c**) all *stabilize* an adjacent alkyl radical, but such radicals are still classified as *transient* due to their short half-lives. Finally, some radicals are sufficiently stabilized through electronic and steric effects that they have practically infinite half-lives. These radicals are referred to as *stable* and the most common example is perhaps that of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO; **7e**).[80,81]

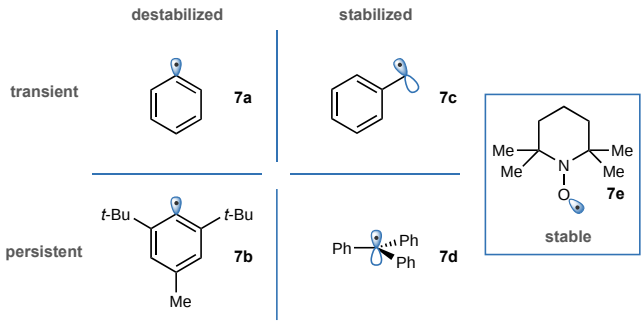


Figure 4 | Types of radicals classified by kinetic and thermodynamic stability.

1.3.1.2 Reactivity of radicals

1.3.1.2.1 Addition to π-bonds

In considering the reaction of radicals with other species, there are three main elementary steps (Figure 5).[1] The effects of the electronic character, as discussed above (see section 1.3.1.1), on the reactivity of radicals was first systematically studied in the context of radical addition to alkenes by Mayo, Walling and Lewis[82,83] and was expanded upon and summarized by Giese in 1983 (Figure 5a).[84]

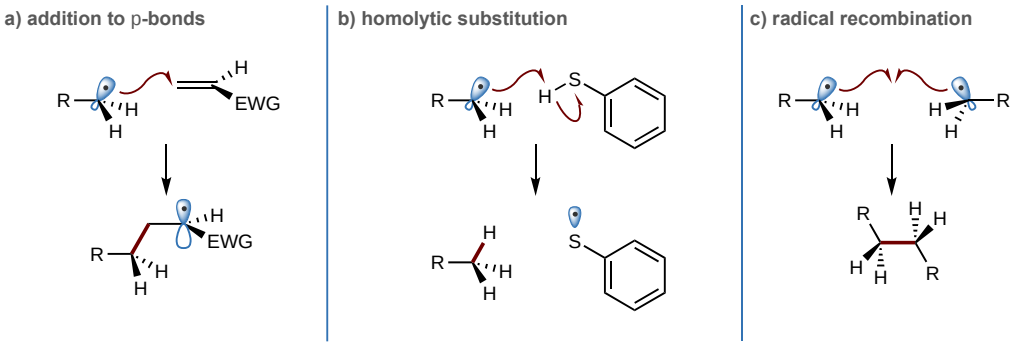


Figure 5 | a-c) Common modes of radical reactivity.

These studies found that the rate of radical addition to an alkene was determined by three factors: i) the thermodynamic stability of the reacting and resulting radicals, ii) the polarity-match of the radical and

[1] Another important radical reaction is homolytic aromatic substitution (S_HAr) and the reader is directed to a recent review.[527] Radicals can also be generated *via* oxidation or reduction (i.e. single-electron processes) and these will be discussed in section 1.3.3.

the alkene, and iii) the steric hinderance of the starting materials. Whilst the effect on the rate of reaction of ΔG can be understood in the context the rate-equilibrium relationship,[85] the polar effects remain a topic of debate (Figure 6a). The studies of Giese[84] showed that the rate of radical addition to an electron-deficient alkene increases with the nucleophilicity of the attacking radical (**8a**, figure 6a) in the order Me• < Et• < Cy•. Similarly, the rate of addition of Cy• to substituted alkenes increases with the electrophilicity of the alkene in the order styrene < methyl acrylate < acrylonitrile. The origin of these results is typically attributed to charge-transfer effects in the transition state where a partial electron-transfer occurs from the electron-rich radical to the electron-deficient alkene.[74] A more electron-rich alkyl radical (i.e. lower ionization potential) and a more electron-deficient alkene (i.e. greater electron affinity) results in a larger contribution from the charge-transfer resonance form and lowers ΔG^{TS}. The same argument can be made based on frontier molecular orbital theory. The most significant orbital-interaction is between the SOMO of the alkyl radical and the π*-orbital of the alkene (Figure 6b). As a consequence, making the alkyl radical more electron-rich will raise the energy of the SOMO and improve overlap with the LUMO, leading to a lower energetic penalty upon approaching the transition state (as described by the Klopman-Salem equation) and consequently a faster reaction rate.[75]

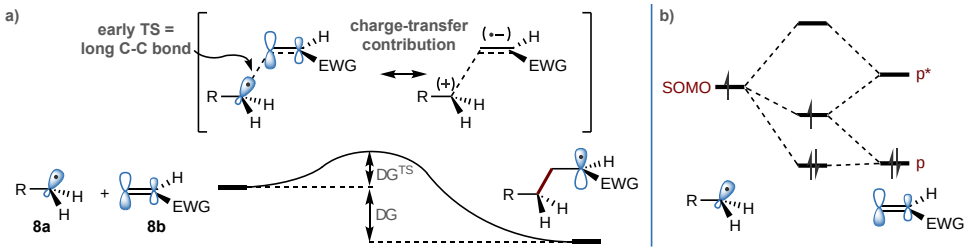
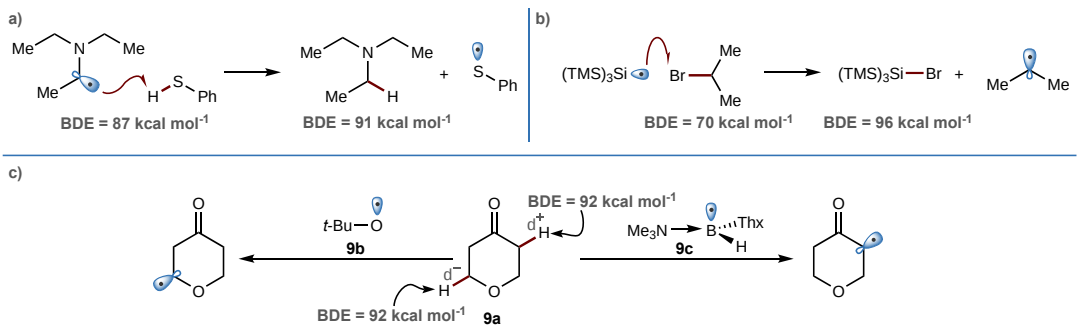


Figure 6 | a) Intermediate and reaction coordinate and b) orbital diagram for alkyl radical addition to electron-deficient olefins.

The last aspect governing the reactivity of alkyl radicals with alkenes are steric effects. It has been suggested that "Due to their early transition states and lack of stifling aggregation spheres, free radical reactions are generally insensitive to steric crowding".[86] Although this statement is not always incorrect, even *remote* steric hinderance typically has a significant impact on the rate of reactivity. For example, upon replacing a hydrogen with a *tert*-butyl group at the α-position of acceptor **8b** (Figure 6a), the rate of addition of Cy• is reduced by a factor of 4.2. However, if a *t*-Bu group is introduced at the β-carbon, the rate of addition is more than 4 orders of magnitude smaller! Meanwhile, increasing substitution of the alkyl radical also has a significant steric impact although this effect is typically overshadowed by the increase in nucleophilicity due to enhanced hyperconjugation.[84] In other words, steric effects can by no means be ignored in radical reactions.

1.3.1.2.2 Homolytic substitution (S_H2)

The homolytic substitution reaction is another common reaction pathway for both alkyl and heteroatomic radicals (Figure 6b).[87] Albeit conceptually similar to the polar S_N2 reaction, the S_H2 reaction is unique in that it rarely occurs at carbon and instead, the most common variants are the halogen- or hydrogen-atom transfer reactions (Scheme 7a & 7b). The most significant factors determining the outcome of a homolytic substitution reaction are the overall exothermicity (thermodynamics)[87] and polarity-match of the starting materials (kinetics).[88] The thermodynamic effect can be approximated by comparing the bond-dissociation enthalpies (BDE) of the forming and breaking bonds. For example, the intermolecular abstraction of a hydrogen atom from thiophenol by an α-amino radical is favoured as the C–H bond formed is 4.2 kcal mol^{-1} stronger than the weak S–H bond which is broken. Similarly, the abstraction of a bromine atom by the tris(trimethylsilyl)silyl radical proceeds with ease as the strong Si–Br bond is 26 kcal mol^{-1} stronger than the C–Br bond that is broken.[74]



Scheme 7 | Thermodynamics of the HAT from a) thiophenol to an α-amino radical and b) 2-iodopropane to a silyl radical. c) Kinetic selectivity of HAT from an α-carbonyl or α-ether position to alkoxy and boryl radicals.

The thermodynamic component is not the only driving force in the above reactions. Polar effects are, in each of the above cases, perfectly matched so that the protonic thiol hydrogen is abstracted by an electron-rich α-amino radical and the abstraction of the halogen atom has a large charge-transfer component in the transition state resulting in a fast reaction. In fact, polar effects are so significant in homolytic substitution that they can be employed to differentiate between two hydrogen atoms of similar bond strength. Using ketone **9a** as the starting material, the electrophilic alkoxy radical **9b** abstracts mainly the *electron-rich* hydrogen atom adjacent to the ester oxygen atom (Scheme 7c). On the contrary, the electron-rich amino-boryl radical **9c** abstracts the *electron-deficient* hydrogen adjacent to the carbonyl moiety.[89] Careful choice of hydrogen abstractor can even enable differentiation between C–H bonds of similar strength *and* polarity, as highlighted by the recent radical-mediated epimerization of unprotected carbohydrates.[90]

1.3.1.2.3 Radical recombination

As exemplified in figure 4, radicals are, in general, highly reactive species with short half-lives. The high reactivity renders reactions such as addition to unsaturated bonds very fast with low kinetic barriers ($k \approx 10^4$-10^8 dm^3 mol^{-1} s^{-1}). The reaction of two reactive radicals is, unsurprisingly, even faster and radical recombination reactions occur without barrier at rates limited by the diffusion of radicals in solution ($k \approx 10^9$-10^{10} dm^3 mol^{-1} s^{-1}) (Figure 5c).[91] This is often quoted as the reason why "…synthetic chemists have avoided radical reactions as messy, unpredictable, unpromising and essentially mysterious".[92] However it has long been established that deleterious side-reactions such as radical recombination can be avoided by ensuring a low concentration of radicals[93] and if a reaction is designed such that it produces one reactive and one less reactive (persistent) radical, radical recombination can even be employed synthetically by exploiting the "persistent radical effect".[81]

1.3.1.2.4 Solvation effects

The open-shell, yet neutral, nature of radicals has another important consequence with regards to solvent effects. Whilst factors such as the dielectric constant have significantly lower impact on reaction rates of neutral radical reactions (but not ionic radical reactions)[94] compared to their polar counterparts,[95] the solvent has to be carefully chosen as to avoid direct reaction with the radicals present (Figure 7). For example, ethereal solvents with hydridic C–H bonds are often incompatible with unstabilized or electron-deficient radicals; unwanted hydrogen-abstraction from THF[96] has often been exploited in stand-alone synthetic methods.[97,98] Instead alkanes or aromatic solvents can be employed.[99] Acetonitrile is also a commonly employed solvent in radical reactions but is incompatible with highly electron-rich amino-boryl radicals, typically affording a range of by-products.[89] Toluene, with three weak benzylic C–H bonds (BDE = 86 kcal mol^{-1}),[100] might, at first sight, be a poor choice of solvent, but in the absence of electron-deficient heteroatomic radicals it has been used with good results.[101] Benzene on the other hand has six strong C–H bonds (BDE = 106 kcal mol^{-1}) but can undergo homolytic aromatic substitution with particularly reactive radicals such as Me•[102] and on such occasions, even less reactive solvents such as linear or strained alkanes may be used.[103] As these examples highlight, general trends, such as the use of polar aprotic solvents for bimolecular nucleophilic substitutions (S_N2),[104] are harder to discern for radical reactions and the choice of solvent has to be considered from the perspective of it being a potential reactant.[95]

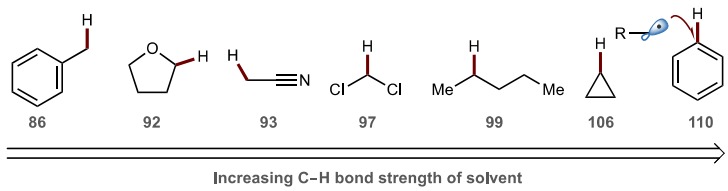
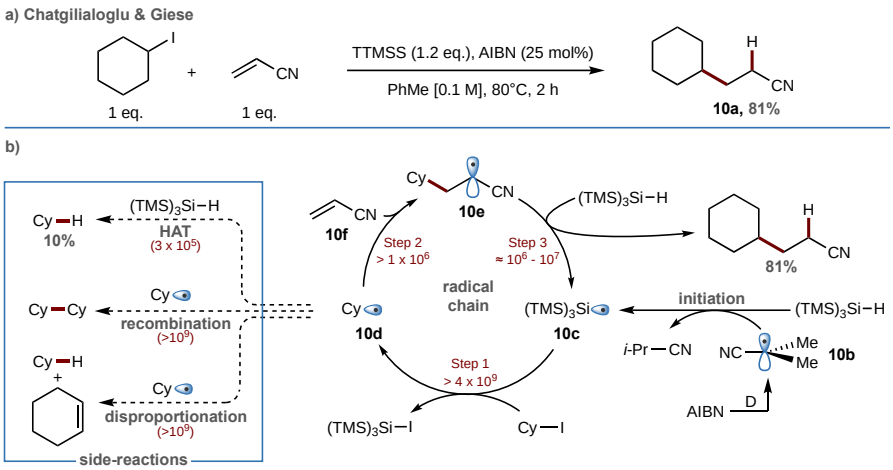


Figure 7 | Bond dissociation energies of common organic solvents.

1.3.1.3 Radical chain reactions

Most radical reactions proceed *via* a radical chain mechanism. Proposed by Kuivila in 1962,[105] it can be exemplified by the reaction of cyclohexyl iodide with acrylonitrile, often referred to as the Giese reaction (Scheme 8a).[101] The reaction is initiated by the thermal decomposition of AIBN to afford N_2 and two molecules of radical **10b** (Scheme 8b). The electron-deficient nature of **10b** enables it to abstract a hydrogen from electron-rich $(TMS)_3Si–H$ (TTMSS; BDE = 84 kcal mol^{-1}) to generate silyl radical **10c**. Silyl radicals, akin to other group 14 elements such as tin or germanium, form strong bonds with halides and the homolytic substitution with cyclohexyl iodide proceeds rapidly to afford cyclohexyl radical **10d**. As discussed previously, the alkyl radical can add to electron-deficient olefins such as acrylonitrile to generate the stabilized yet electron-deficient radical **10e**. This species can propagate the radical chain by abstracting a hydrogen atom from TTMSS to afford the product **10a**.



Scheme 8 | a) The Giese-reaction. b) Proposed mechanism with rate constants[106–108] for the Giese reaction.

Several aspects of the radical chain mechanism warrants attention. Firstly, the sub-stoichiometric amounts of AIBN decomposes slowly ($t_{1/2}$ = 2 h at 80°C) to afford radicals **10b** in low steady-state concentrations, typically on the order of 10^{-7}-10^{-8} M.[109] This extends the radical chain by reducing the rate of chain termination through radical recombination and disproportionation, both of which have a second order dependence on the concentration of alkyl radical **10d**. Secondly, the reaction partners – in this case cyclohexyl iodide and acrylonitrile – must be carefully chosen in order to compete with termination events. For example, given that the steady-state concentration of alkyl radicals is ≈ 10^{-7} M and that radicals such as **10d** react at the diffusion limit (k ≈ 10^{10} dm^3 mol^{-1} s^{-1}), the rate of radical recombination is given by:

$$rate\ (recombination) = k * [\mathbf{10d}] = 10^{10} * [10^{-7}]^2 = 10^{-4}\ mol\ dm^{-3} s^{-1}$$

In order to compete with chain termination, the rate of chain propagation in the above reaction must be at least two orders of magnitude greater than the rate of termination:

$$rate\ (propagation) = k_2 * [\mathbf{10d}] * [\mathbf{10f}] = k_2 * [10^{-7}] * [0.1] = k_2 * 10^{-8}$$

At the concentrations specified in, each propagating step (steps 1-3, scheme 8b) must have a rate constant of:[93]

$$k_2 * 10^{-8} \geq 10^{-2}$$

$$k_2 \geq 10^{6}$$

As shown in scheme 8b, this is the case and the product can be obtained in high yields. Interestingly, the rate of the non-productive (but not terminating) reaction between **10d** and TTMSS is about one order of magnitude slower than the propagating chain and is obtained in 10% yield, as would be expected from the kinetic treatment above.

1.3.2 Classical radical methods in the synthesis of aliphatic amines

The radical methods developed for aliphatic amine synthesis can be conceptually categorized according to their modes of reactivity (Figure 8). Type 1 reactivity proceeds through the intermediacy of neutral or cationic nitrogen-centered radicals, i.e. an open-shell orbital is based on nitrogen. In contrast, reactions where a C-centered radical reacts with a closed-shell nitrogen species such as an imine or an enamine can be categorized as type 2. The last category, type 3, falls in between the other two in that an open-shell orbital is located on carbon, but its character is heavily influenced by an adjacent nitrogen atom.

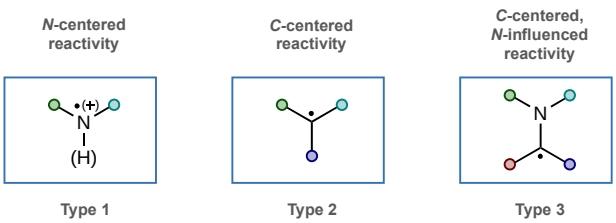
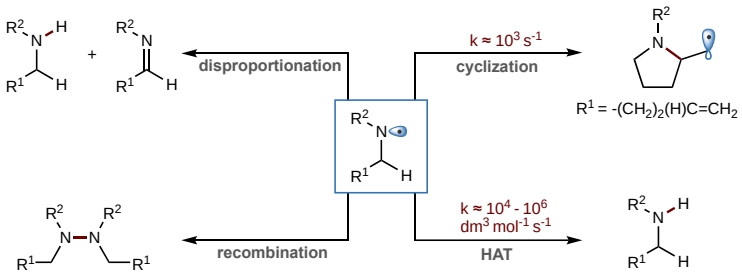


Figure 8 | Types of reactivity in the radical synthesis of aliphatic amines.

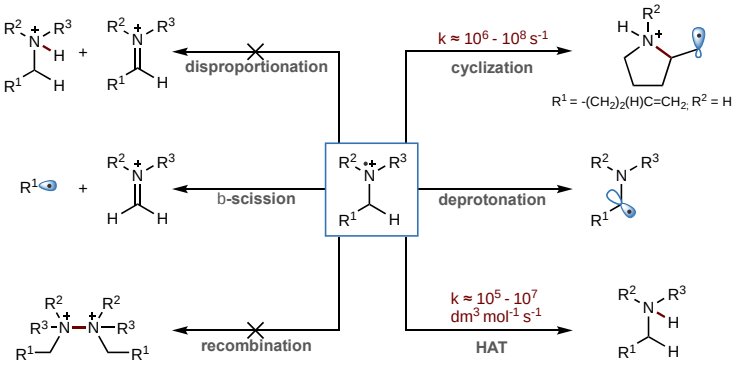
1.3.2.1 Type 1 – aminyl radicals and aminium radical cations

Neutral aminyl radicals have found limited use in organic synthesis[110] but several reports have studied their reactivity.[111–114] In contrast to their alkoxy analog, aminyl radicals are slightly nucleophilic[115] – the abstraction of a hydrogen atom from thiophenol (BDE = 87 kcal mol^{-1}) is almost two orders of magnitude faster than that from Bu_3SnH (BDE = 78 kcal mol^{-1}) despite the lower BDE of the stannane (Scheme 9).[114,116] Aminyl radicals can be made to react with alkenes if appropriately substituted[117] but the rate of addition is generally slower than that of alkyl radicals onto alkenes as the resulting C–N bond is weaker than the corresponding C–C bond.[118] Therefore, the slow alkene-addition usually cannot compete with hydrogen-atom transfer from weak X–H bonds (e.g. allylic positions) or through recombination (to form hydrazines) or disproportionation pathways,[119] resulting in mixtures of products.[120] More useful reactivity have been obtained using aminyl radical precursors such as *N*-chloroamines or *O*-substituted hydroxylamines in conjunction with copper-[121] or nickel-catalysis[115] where aminyl radical intermediates are proposed to be trapped by a transition metal catalyst. This allows access to a broad variety of metal-mediated reactivity and has been employed in the synthesis of tertiary amines *via* hydroamination as well as dialkylanilines through the coupling with boronic esters.[122,123]



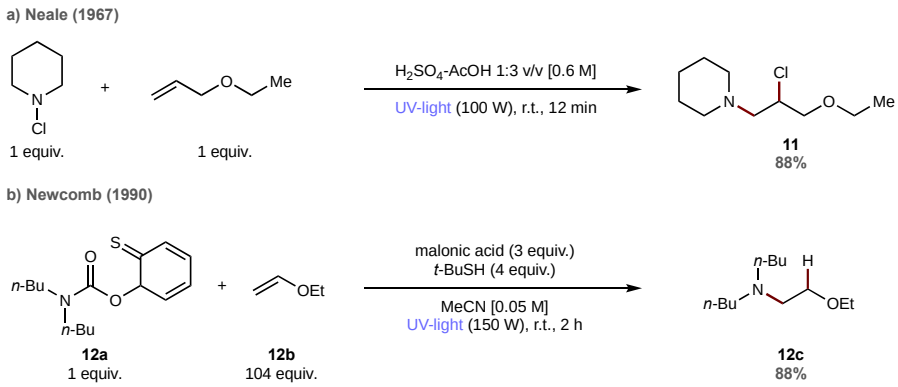
Scheme 9 | Reactivity of aminyl radicals.[111,114]

Synthetically more useful *N*-centered radicals can be obtained if electron-deficient groups are introduced, for example as amidyl or sulfonamidyl radicals, or upon protonation to form aminium radical cations (ARC). ARCs, prepared *via* thermolytic or photolytic conditions, are highly electrophilic intermediates and have found substantially more use than their neutral counterpart (Scheme 10).[124] The HLF-reaction discussed earlier represents one important application and ARCs have frequently been used as C–H activation catalysts in photoredox chemistry.[125] The greater utility of ARCs in organic synthesis *vis à vis* aminyl radicals stem from two reasons: ARCs are thermodynamically destabilized (BDE ($R_3N^{\bullet+}$) = 101 kcal mol^{-1} vs BDE($R_2N^{\bullet}$) = 92 kcal mol^{-1})[126]; and the decomposition pathways seen for aminyl radicals through radical recombination or disproportionation are slow for ARCs due to coulombic repulsion and steric interactions.



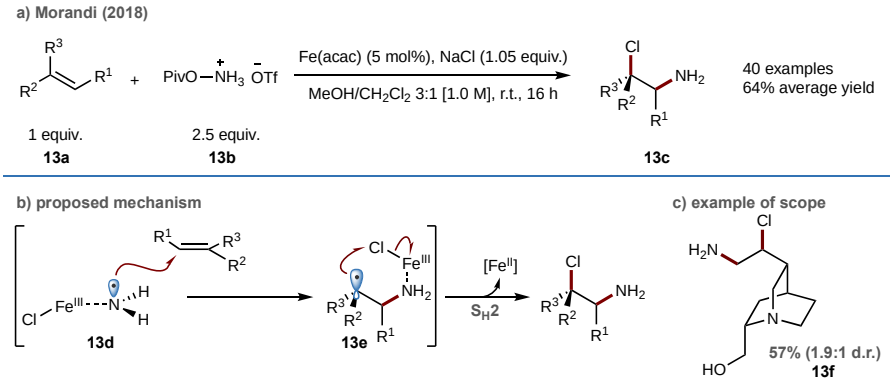
Scheme 10 | Reactivity of aminium radical cations. [119,127] It should be noted that the chemistry of α-amino radicals is discussed in section 1.3.2.3. Furthermore, as β-scission is rarely used in organic synthesis, the reader is directed to a rare study.[128]

These properties have been exploited in the context of 1,2-difunctionalization of alkenes. In a series of papers from 1963 to 1967,[129–132] Neale detailed the addition of *N*-chloroamine derived aminium radical cations to a variety of neutral or electron-deficient alkenes to obtain tertiary amines, such as **11,** in good yields (Scheme 11a).[131] Electron-rich alkenes afforded lower yields, which was attributed to competing electrophilic chlorination.[129] The reaction was proposed to proceed *via* a radical-chain mechanism, in which the alkyl radical formed upon the addition of the aminium radical cation to the alkene abstracts a chlorine atom from *N*-chloropiperidine to propagate the chain. Minisci later expanded the scope of olefins through the use of stoichiometric ferrous sulphate[133] but akin to the HLF-reaction,[134] the strongly acidic conditions limited the scope of these early transformations in complex molecule synthesis. An important advance in this regard was reported by Newcomb and Kumar (Scheme 11b).[135] They showed that UV-light could cleave the Barton-inspired *N*-hydroxypyridine-2-thione (PTOC) carbamate **12a** to form a neutral *N*-centered radical,[114] which after protonation ($pK_a \approx 7.0$)[118] with malonic acid afforded the aminium radical cation. This intermediate then underwent addition to an electron-rich olefin **12b** to give tertiary amine **12c** after hydrogen-atom transfer from *tert*-butyl thiol. Importantly, the only mildly acidic conditions were crucial in order to tolerate the acid-labile enol ether **12b**.



Scheme 11 | a) UV-light mediated hydroamination of alkenes by *N*-chloroamines. b) PTOC-carbamates as a source of *N*-centered radicals under mild conditions for the synthesis of fused tetrahydrofurans.

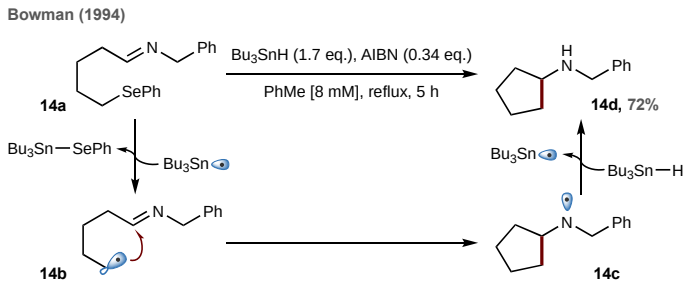
An intermediate approach, wherein a neutral aminyl radical is complexed with a metal has also been thoroughly investigated. Although the formal oxidation state of nitrogen in such complexes is hard to deduce, their reactivity approaches that of ARCs, as observed by Newcomb's studies on BF_3-mediated aminyl radical cyclizations.[136] Building on a wealth of historic precedence,[70,118,137,138] Morandi recently reported a substantial advancement of Neale's aminochlorination reaction by combining unactivated olefins **13a** and hydroxylamine hydrochloride **13b** under Fe-catalysis (Scheme 12a).[139] The proposed mechanism involved the formation of Fe^{III}-coordinated aminyl radical **13d**, formed *via* reduction of *O*-pivylated hydroxylamine hydrochloride **13b**, which underwent radical addition to form **13e** (Scheme 12b). Homolytic substitution afforded the desired product and regenerated Fe^{II}. Notably, the final step occurred with moderate *cis*-stereoselectivity, indicating that the rate of S_H2 is faster than the rate of a C–C bond rotation. The mechanism is substrate-dependent, however, as both *cis*- and *trans*-styrenes afforded the same stereochemical outcome and this was rationalized by an alternative polar-crossover mechanism. The reaction enabled access to range of simple and complex β-amino alkyl chlorides **13c** such as quincoridine-derivative **13f** (Scheme 12c).



Scheme 12 | a) Fe-catalyzed hydroamination of unactivated olefins by hydroxylamine hydrogen chlorides. b) Proposed mechanism and c) an example of Morandi's Fe-catalyzed hydroamination.

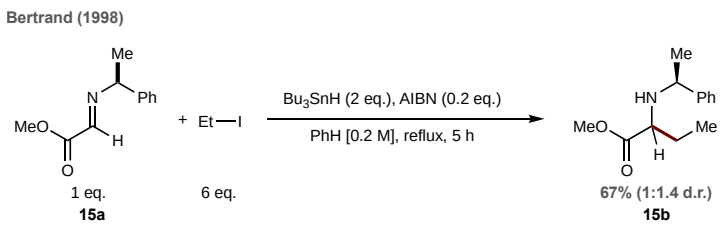
1.3.2.2 Type 2 – imines, iminium ions and enamines

While alkyl radical addition to C=C bonds have been exhaustively studied, the analogous addition onto C=N to give aliphatic amines has received less attention.[140] The first example of an alkyl radical addition to an aliphatic imine was reported by Bowman (Scheme 13).[141] Employing the Bu_3SnH/AIBN initiator system, homolytic cleavage of the weak C–Se bond in **14a** afforded alkyl radical **14b** that underwent a 5-*exo*-trig cyclization at the electrophilic site of the C=N bond. The resulting aminyl radical **14c** then abstracted a hydrogen atom from Bu_3SnH to form the product **14d** and propagate the radical chain. The slow addition of Bu_3SnH in combination with very dilute conditions was found to be crucial for reactivity, presumably in order to avoid hydrodeselenation and radical recombination/disproportionation pathways.



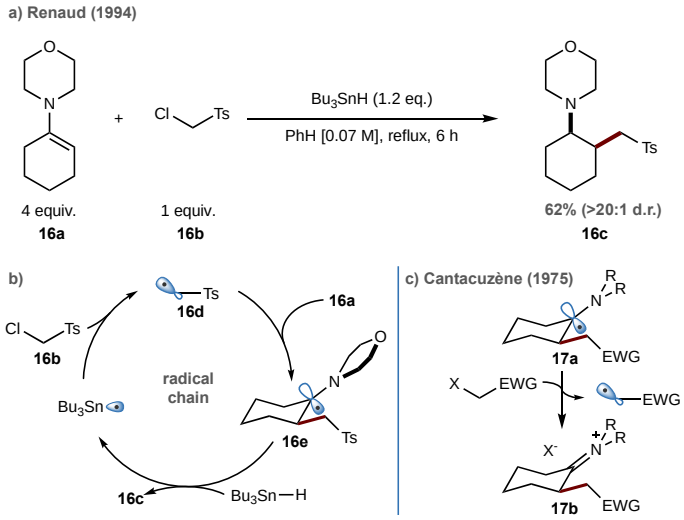
Scheme 13 | Bowman's synthesis of aminocyclopentanes *via* radical cyclization.

An intermolecular example was reported by Bertrand[142] where they employed a similar radical initiation system to that used by Bowman to affect alkyl radical addition to chiral glyoxalic ester derived imine **15a** and yielded the product **15b** in good yield but poor diastereoselectivity (Scheme 14). Presumably, in the absence of an entropic driving force evident in the intermolecular example above (c.f. Scheme 13), the glyoxalic ester enhances the electrophilicity of the imine to favour the addition of electron-rich alkyl radicals.



Scheme 14 | Bertrand's intermolecular radical addition to glyoxylate imines.

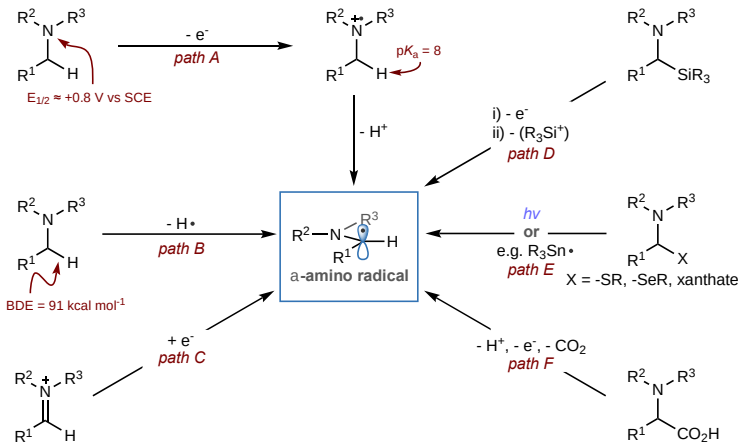
Electron-deficient C=N bonds can react with nucleophilic alkyl radicals (c.f. Schemes 14). In contrast, enamines can readily act as an acceptor for electron-deficient alkyl-radicals.[143] Renaud employed electron-deficient α-tosyl radicals in order to accomplish a diastereoselective radical addition to alicyclic ketone-derived enamines using a radical chain mechanism (Scheme 15a).[144] Addition of radical **16d** to enamine **16a** affords an α-amino radical intermediate **16e** which was trapped from the less hindered face to afford **16c** with complete diastereoselectivity (Scheme 15b). An alternative approach to chain-propagation in radical addition to enamines was reported by Cantacuzène (Scheme 15c).[145] It exploits the reductive nature of α-amino radicals, such as **17a** ($E_{1/2} \approx -1.0$ vs saturated calomel electrode (SCE) in MeCN),[146] in order to reduce an electron-deficient alkyl halide and subsequently generate a new alkyl radical after mesolysis. The product iminium ion **17b** can then be hydrolyzed to afford a ketone (or aldehyde). Interestingly, a recent report has suggested that these reactions might not proceed through electron-transfer but rather *via* a homolytic substitution where the electron-rich α-amino radical abstracts a halogen atom (much akin to the electron-rich stannanes or silanes) from an alkyl or aryl halide, enabled by polar effects.[147]



Scheme 15 | a) Renaud's addition of electron-deficient alkyl radicals to enamines, b) the proposed mechanism and c) Cantacuzène's mechanistically distinct variant.

1.3.2.3 Type 3 – α-amino radicals

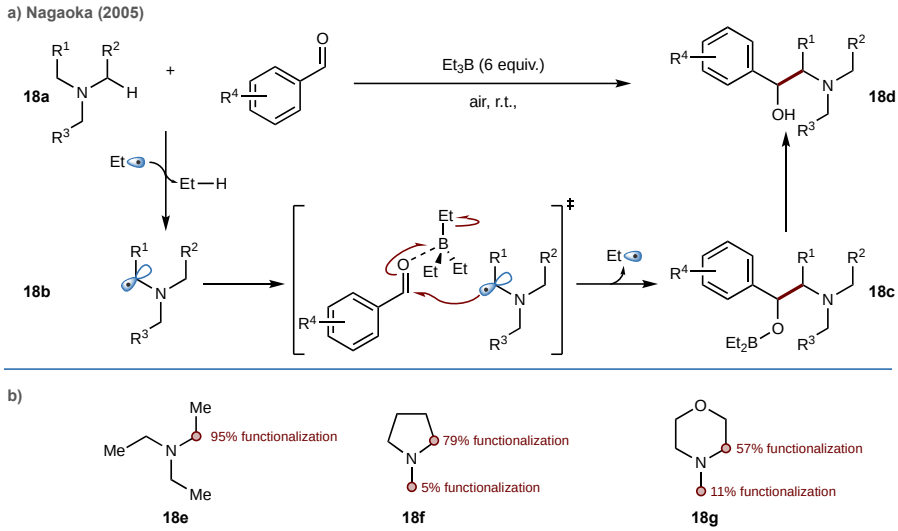
The majority of radical methods that can be used to synthesize amines proceed *via* α-amino radical intermediates. The α-amino radical is nucleophilic due to the neighboring lone-pair on the nitrogen atom, which increases the energy of the SOMO orbital, and can be formed from a number of different precursors (Scheme 16).



Scheme 16 | Overview of methods that generate α-amino radical intermediates.[148–150]

A common way to access α-amino radicals exploits the low reduction potential of aliphatic amines (path A). Oxidation of the amine affords an aminium radical cation where the adjacent α-hydrogen is greatly acidified, and deprotonation affords the α-amino radical. Alternatively, a hydrogen of a weak α-C–H bond can be abstracted by an electrophilic radical such as the *tert*-butoxy radical ($k = 1.1 * 10^8$ dm^3 mol^{-1} s^{-1}) (path B).[151] Reductive methods can also be employed. Starting from the corresponding iminium ion ($E_{1/2} \approx$ -1.1 to -1.9 V vs SCE),[152] SmI_2 can donate a single electron to form the neutral α-

amino radical (path C).[153,154] Other methods employ α-substituted amines where both redox and homolytic processes are used (paths D-F).[155–158]



Scheme 17 | a) Nagaoka's borane-mediated addition of α-amino radicals to aldehydes. b) Examples of aliphatic amines in Nagaoka's hydroxyalkylation of amines.

Most reactions exploiting α-amino radical reactivity proceed in an *intramolecular* fashion and these have been reviewed elsewhere.[159] A significant advance in this regard was the *intermolecular* hydroxyalkylation of tertiary amines to give 1,2-aminoalcohols **18d**, reported by Nagaoka and co-workers (Scheme 17a).[160] Using triethylborane and oxygen as the initiation/propagation system, an ethyl radical abstracts a hydrogen from the tertiary amine **18a** (c.f. path B in Scheme 16) to form α-amino radical **18b,** which subsequently reacts with the C=O bond to afford **18c**. The use of BEt_3 was crucial as it activates the carbonyl and forms a strong B–O bond that makes the otherwise endothermic addition irreversible. The formation of the B–O bond also serves to cleave another C–B bond to propagate the radical chain. The scope of the reported method highlights, however, the inherent challenge in forming an α-amino radical with high regioselectivity through hydrogen-atom abstraction. Only three aliphatic amines were examined, and both of the unsymmetrical examples led to a mixture of products (**18e-g**, Scheme 17b).

1.3.3 Photoredox-catalysed methods for amine synthesis

1.3.3.1 General concepts of photoredox

The term photoredox-catalysis refers to the ability of certain molecules to act as single-electron reductants or oxidants after absorption of a photon.[161] One of the most heavily investigated complexes is $Ru(bpy)_3^{2+}$ (**19**; Figure 9). Upon *absorption* of a photon of visible light, an electron is promoted to the first singlet excited state (S_1). Each electronic state has an infinite number of vibrational states and following excitation, the electron will relax through vibrational motion (*vibrational relaxation*) to the

lowest energy singlet state (S_1). Singlet-excited states are high-energy, short-lived species with a net zero spin (i.e., all electrons are paired). A singlet state species can relax rapidly to the ground-state (S_0) through *internal conversion* (a non-radiative process) or *fluorescence* (by emitting a photon, a radiative process).[162] It can also undergo *intersystem crossing* from the singlet-state to a triplet-state.[163] In this process, the molecule in question changes spin from s = 0 to s = 1, which is a quantum mechanically forbidden transition, i.e. it cannot occur. However, if the molecule contains a heavy atom, such as ruthenium, the spin-forbidden intersystem crossing *can* occur by exploiting a mechanism called spin-orbit coupling.[164] Following this mechanism, the change in spin angular momentum is *offset* by a change in orbital angular momentum. This requires the orbital that harbors the lone ground-state electron remaining after excitation to be able to interchange with other orbitals of similar energy and shape. This explains the origin of the heavy-atom effect as symmetrical transition metal complexes have several *d*-orbitals of similar shapes and energies to facilitate spin-orbit coupling and hence intersystem crossing. The practical significance of a favourable intersystem crossing is that the then-formed T_1 state is kinetically more stable than the S_1 state (the radiative relaxation to the ground-state is spin-forbidden and hence slow) resulting in a long triplet-state life-time (τ = 1 100 ns for $Ru(bpy)_3^{2+}$).[165] The long life-time allows triplet excited state complexes to engage in bimolecular reactions and be useful as photoredox catalysts.

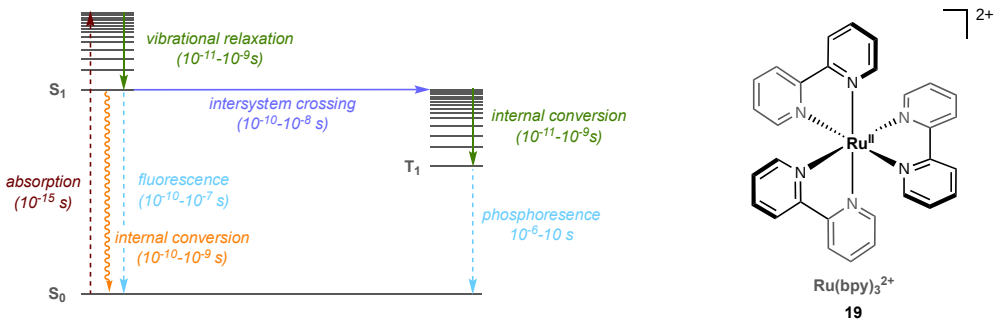


Figure 9 | Structure and Jablonski diagram for $Ru(bpy)^{2+}$.

The practical consequence of this quantum mechanical effect is that triplet-excited state complexes are sufficiently long-lived to interact with other molecules in energy- or electron-transfer processes. In particular, $[Ru(bpy)_3^{2+}]^*$ can act both as an oxidant *and* a reductant from its T_1-state. This can be understood from an orbital perspective (Figure 10).[163] Upon absorption of visible light, an electron from a metal-based t_{2g}-orbital is excited to a ligand-centered π^*-orbital in a metal-to-ligand charge transfer transition (MLCT). Acting as an oxidant, $[Ru(bpy)_3^{2+}]^*$ (**20**) accepts an electron from an electron-donor into the hole of its t_{2g}-orbital. As a reductant, the same species donates the excited electron in the π^*-orbital to an electron-acceptor.

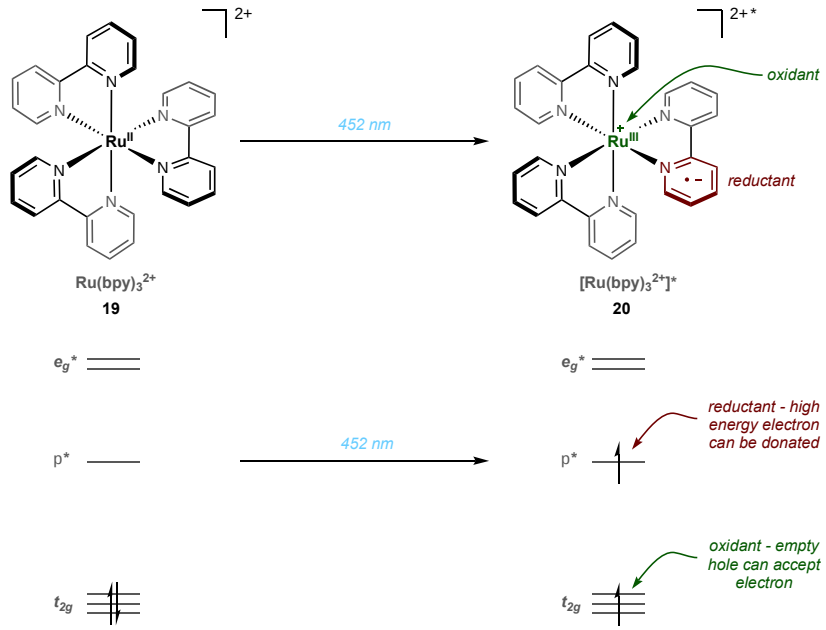
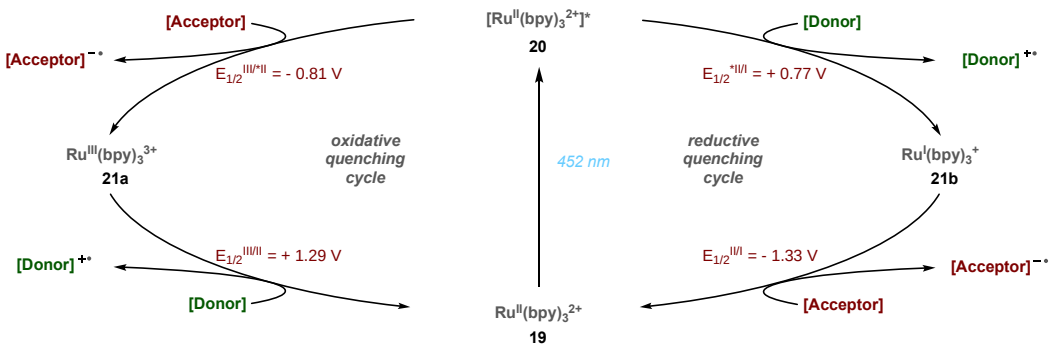


Figure 10 | Orbitals diagram of the ground and triplet excited states of $Ru(bpy)^{2+}$.

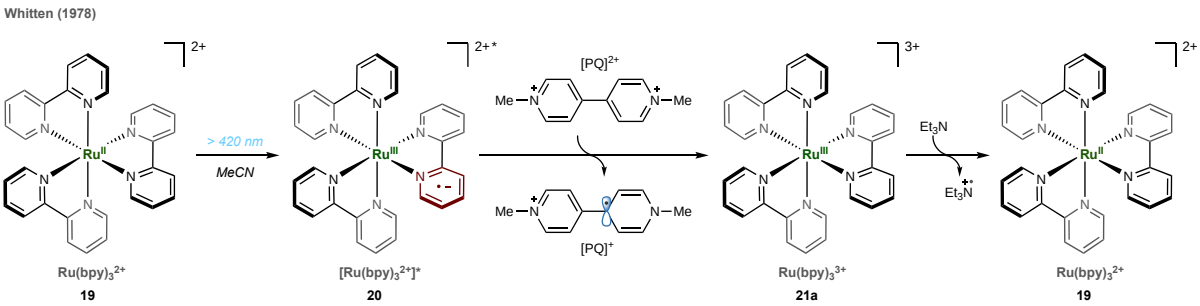
Upon single-electron reduction or oxidation of $[Ru(bpy)_3^{2+}]^*$ two new species are formed, namely $Ru(bpy)_3^{+}$(**21a**) and $Ru(bpy)_3^{3+}$(**21b**). They can reform ground-state $Ru(bpy)_3^{2+}$ by donating or accepting an electron respectively. This allows for two *quenching cycles* (Scheme 18), where $[Ru(bpy)_3^{2+}]^*$ reacts with an acceptor first and a donor second (termed oxidative quenching cycle) or vice versa (termed reductive quenching cycle).[166]



Scheme 18 | Oxidative and reductive quenching cycles for $Ru(bpy)^{2+}$.

The foundation for the use of complexes such as $Ru(bpy)_3^{2+*}$ (**20**) in organic synthesis was laid out by Whitten who recognized that, in order to be useful, the initially formed complex, e.g. $Ru(bpy)_3^{+}$ in a reductive quenching cycle, must react quickly with an external electron acceptor in order to avoid a back-electron transfer with the just-oxidized $[donor]^{+\bullet}$.[167–170] To favour the *forward* reaction, the reduction potential of $Ru(bpy)_3^{+}$ and the acceptor should be matched so that the electron-transfer step is net exothermic, although exceptions to this rule do exist.[171] In one example, Whitten found that upon subjecting a mixture of $Ru(bpy)_3$, *N,N'*-dimethyl-4,4'-bipyridinium (PQ^{2+}) and Et_3N in acetonitrile to

visible light, PQ^{2+} ($E_{1/2}^{2+/+}$ = -0.45 V vs SCE in MeCN)[172] is reduced to PQ^{+} and $Ru(bpy)_3^{3+}$ (Scheme 19).[168] Due to the low concentration of [PQ^{+}], $Ru(bpy)_3^{3+}$ ($E_{1/2}^{III/II}$ = +1.29 V vs SCE in MeCN) reacts with Et_3N ($E_{1/2}$ = +0.83 V vs SCE)[173] instead to reform $Ru(bpy)_3^{2+}$. The formation of PQ^{+} as the only long-lived radical species was supported by electron-spin resonance spectroscopy (ESR).[168] The order of the reaction, i.e. whether the initial reaction $[Ru(bpy)_3^{2+}]^*$ involves reduction of PQ^{2+} or oxidation of Et_3N was determined with Stern-Volmer quenching, where the reduction in phosphorescence of the T_1 state of $[Ru(bpy)_3^{2+}]^*$ is measured upon addition of a quencher. Those studies found that the rate of quenching was significantly greater with PQ^{2+} than Et_3N, suggesting an oxidative quenching cycle.



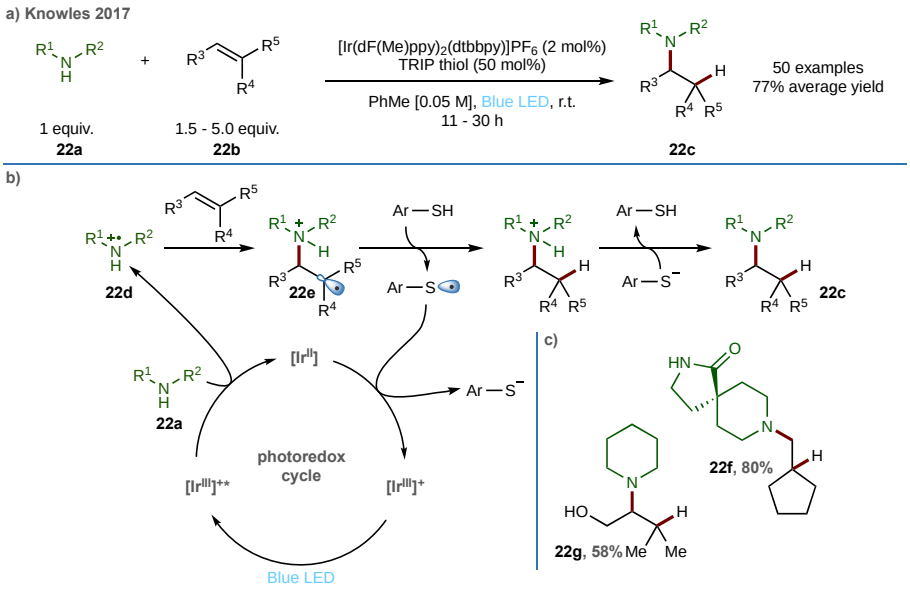
Scheme 19 | Whitten showed that an external oxidant and reductant can regenerate $Ru(bpy)^{2+}$ in an oxidative quenching cycle.

Following the studies of Whitten, Kellogg[174,175] reported the first $Ru(bpy)_3^{2+}$ mediated synthetic transformation (reduction of sulfonium salts to sulfides using Hantzsch ester (HEH) as a reductant) and Deronzier outlined the first photocatalytic cycle in a visible light-mediated Pschor reaction.[176,177] In contrast, Barton[178] found that $Ru(bpy)_3^{2+}$-mediated reactions need not proceed with a photocatalytic mechanism – the "photocatalyst" can simply act as an initiator for an efficient radical chain. However, it was only following the reports of MacMillan,[179] Yoon[180] and Stephenson[181] that the application of photoredox-methods to synthetic problems gained wider acceptance.[165]

1.3.3.2 Type 1 – Aminyl radicals and aminium radical cations

The utilization of a photoredox catalyst under visible light irradiation has had a significant impact on the synthesis of amines *via* radical methods.[165,182,183] In the particular context of aliphatic amines, it has enabled known synthetic intermediates to be accessed under milder and more practical reaction conditions, unlocking a wider scope and greater functional group tolerance. One such intermediate is the aminium radical cation (ARC), typically generated under highly acidic conditions through heating or UV-light irradiation (see section 1.3.2.1). In 2017, the Knowles group reported a visible light mediated hydroamination of unactivated alkenes **22b** with aliphatic amine **22a** which employed an iridium photocatalyst in order to generate the ARC (Scheme 20a).[184] The reaction could be carried out at room temperature and under neutral conditions using catalytic tri*iso*propylbenzenethiol as a

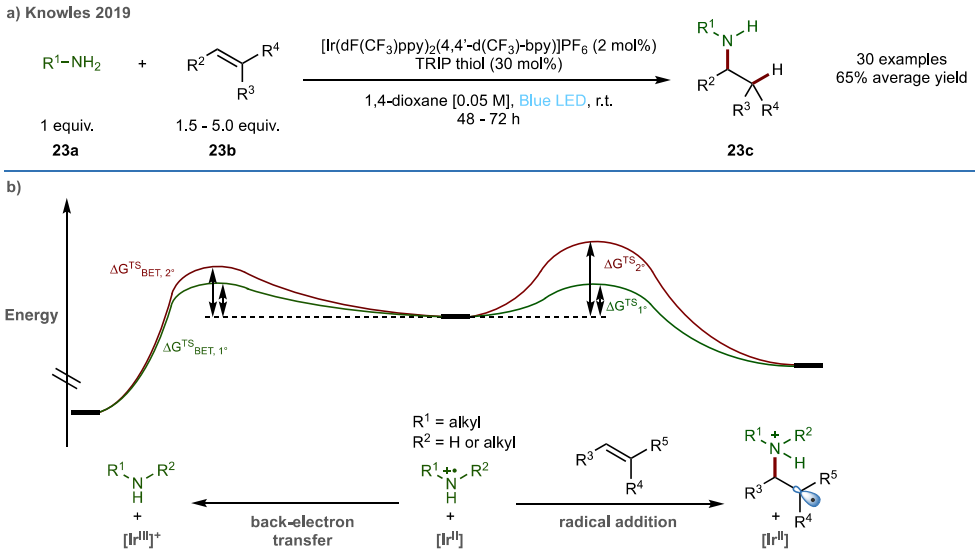
hydrogen-shuttle. The mechanism was proposed to proceed *via* the oxidation of a secondary amine (**22a**, $E_{1/2} \approx +0.9$ V vs SCE in MeCN) by the excited state of [Ir(dF(Me)ppy)$_2$(dtbbpy)] ($E_{1/2}^{*III/II} = +0.97$ V vs SCE in MeCN)[185] to generate an ARC (**22d**, Scheme 20b). The ARC then underwent rapid addition to an unactivated alkene **22b** to afford a C-centered alkyl radical **22e** that following HAT and deprotonation afforded the amine product **22c**. This represents the first example of a radical hydroamination reaction that merges unfunctionalized amines and feedstock alkenes under mild conditions. The net reaction is thermodynamically uphill for highly substituted alkenes and is enabled only by the action of an excited state photocatalyst, which provides an alternative and irreversible reaction surface. This enabled the synthesis of functionalized amines such as **22f** and **22g**.



Scheme 20 | a) Knowles' visible light mediated hydroamination of unactivated olefins with secondary amines. b) Proposed mechanism and c) selected examples of Knowles' visible light mediated hydroamination.

In the original report from Knowles, primary amines were not competent substrates. Theoretically, a reaction using a primary amine starting material could be compromised as the secondary amine product would be easier to oxidize than the primary amine starting material, yielding a tertiary amine product. Nevertheless, in 2019, the Knowles group reported the extension of their hydroamination platform to primary amines **23a** (Scheme 21a). The reaction displayed a broad scope with high yields and they found that the use of a more oxidizing photocatalyst, [Ir(dF(CF$_3$)ppy)$_2$(4,4'-d(CF$_3$)-bpy)]PF$_6$ ($E_{1/2}^{*III/II} = +1.27$ V vs Fc^+/Fc in MeCN)[186] was crucial due to the lower reduction potential of the primary amines ($E_{1/2} \approx +1.2$ V vs Fc^+/Fc in MeCN).[187] In order to rationalize why the tertiary amine resulting from over-alkylation could not be observed (in one case a 1:34 ratio of 2°:3° amine was obtained), the authors suggested that the addition of a more electron-deficient primary aminium radical cation (ARC) to an alkene **23b** is significantly *faster* than that of a secondary ARC. Meanwhile, the rate of back-electron transfer is *less* affected by the amine structure. Therefore, addition of the primary ARC to the alkene can outcompete the back-electron transfer reaction with the [Ir^{II}] photocatalyst. However, in the case of

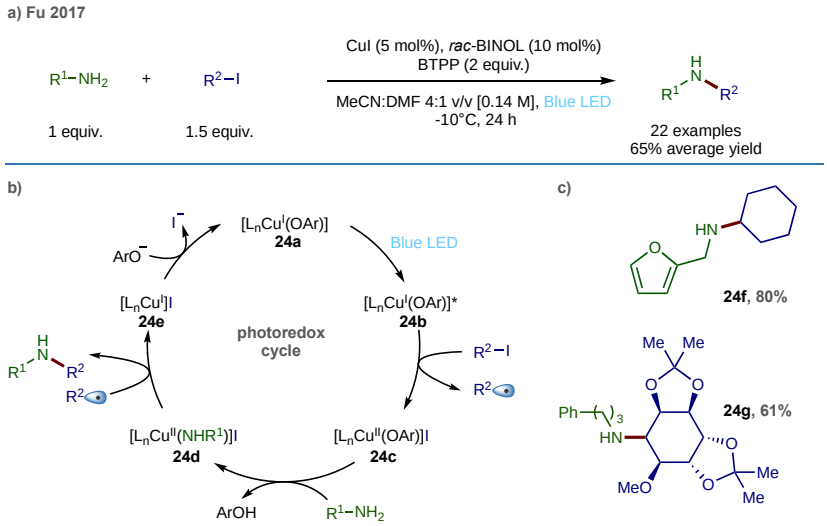
a secondary ARC, the rate of back-electron transfer is faster than addition to the alkene and consequently over-alkylation is not observed (Scheme 21b).



Scheme 21 | a) Knowles' visible light mediated hydroamination of unactivated olefins with primary amines. b) Proposed mechanistic rationale for Knowles' visible light mediated hydroamination.

1.3.3.3 Type 2 – Carbon-centered radicals

In classical radical methodology, alkyl radicals were limited to the reaction with π-systems of enamines (for electron-deficient radicals) or imines (for electron-rich radicals). However, using photoredox-chemistry in conjunction with Cu-catalysis, the Peters and Fu groups expanded on these two classical modes of reactivity to develop a radical variant of the Hofmann alkylation reaction under mild conditions (Scheme 22a).[188] The radical approach has several advantages in comparison to the polar version, namely that it does not require heating and alkyl iodides that are unreactive in S_N2-type chemistry, such as neopentyl iodide, can be reacted efficiently.

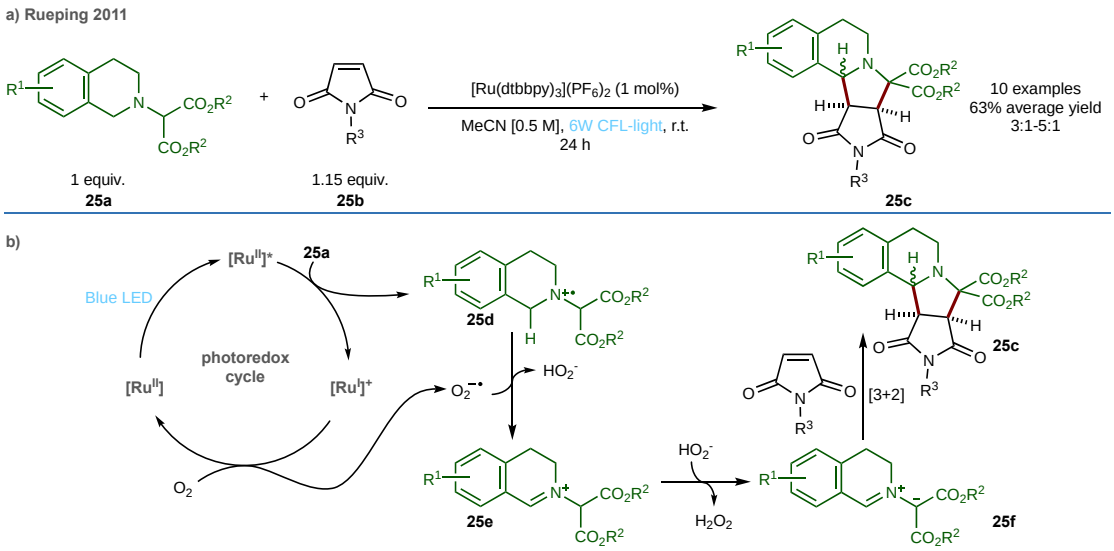


Scheme 22 | a) Fu's Cu-catalyzed variant of the Hofmann-alkylation. b) Proposed mechanism and c) selected examples from Fu's Cu-catalyzed synthesis of secondary amines.

The proposed mechanism involves a Cu(I)(BINOL)-complex **24a** absorbing a photon of visible light to afford **24b** (Scheme 22b). Electron-rich **24b** can then reduce the alkyl halide through single-electron transfer to afford complex **24c** and generate an alkyl radical. The presence of "out-of-cage" alkyl radicals was, according to the authors, supported by the use of TEMPO as a radical trap. The alkyl radical then reacts with **24d**, formed after ligand exchange of a phenol with a primary amine in **24c**, to afford the resulting product and a new copper(I)-complex 24e. The exact nature of the key C–N bond-forming step remains unknown. Although there is precedent for S_H2-type reactivity employing a transition-metal as the "leaving-group", only C–C bond-forming examples have been reported.[189]

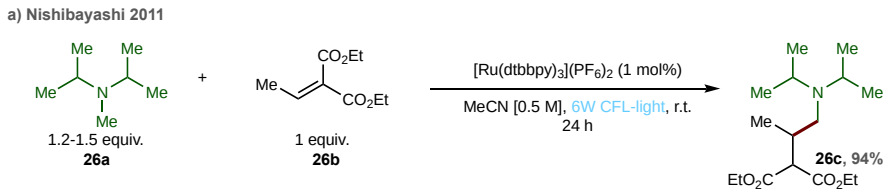
1.3.3.4 Type 3 – α-Amino radicals

As suggested by the early experiments of Whitten,[168] photoredox catalysis could potentially provide a powerful means by which to access α-amino radical reactivity without using stoichiometric metal reagents (e.g. SmI_2) or UV-light.[159] However, the strongly reducing nature of α-amino radicals (see scheme 16) often results in further single-electron oxidation to afford an iminium ion. Indeed, Stephenson and others have exploited this reactivity by trapping such iminium ions with nucleophiles.[183,190] However, these examples almost exclusively employed aryl amines. An exception is the polar-crossover synthesis of *N*-heterocycles by Rueping and co-workers (Scheme 23a).[191] According to their mechanistic proposal, when aliphatic amine **25a** and a ruthenium-photocatalyst are subjected to visible light irradiation, the amine is oxidized to the radical cation **25d** (Scheme 23b). The weak C–H bond adjacent to the nitrogen-moiety (BDE = 42 kcal mol^{-1})[182] is homolytically cleaved by the superoxide radical anion, formed by single-electron transfer from the reducing $[Ru^{I}]^{+}$-complex, to afford iminium ion **25e**. The pK_a of the C–H bond in the adjacent malonyl moiety is low and is suggested to undergo deprotonation by the hydroperoxide anion (pK_a = 11.8) to afford ylide **25f**, which undergoes a [3+2] cycloaddition in the presence of dipolarophile **25b** to form the desired heterocycle **25c**.



Scheme 23 | a) Rueping's Ru-catalyzed pyrrolidine synthesis. b) Proposed mechanism.

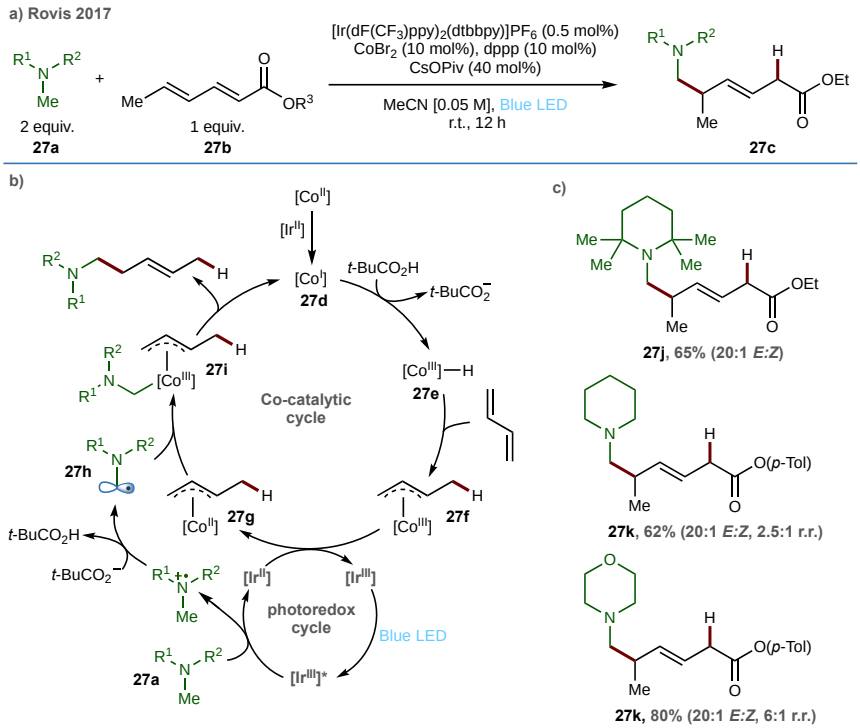
Significant efforts have been directed at harnessing α-amino radical reactivity of less contrived substrates than those employed by Rueping, but these attempts have been hampered by poor regioselectivity and over-oxidation. For this reason, the α-amino radicals of symmetrical *N*-aryl amines[192] or *N*-carbamates[193] have been more widely explored instead. Nevertheless, in 2012, Nishibayashi showed that α-amino radicals, formed from the oxidation and subsequent deprotonation of tertiary aliphatic amines such as **26a**, can be intercepted by ethylidene malonate **26b** before over-oxidation occurs (Scheme 24).[194] After the subsequent Giese-addition the resulting α-carbonyl radical is reduced by the photocatalyst and protonation affords the desired product **26c**. Although it represented an early advance in the use of α-amino radicals for aliphatic amine synthesis, the bulk of the scope employed *N*-aryl amines as the starting material.



Scheme 24 | a) Nishibayashi's Ru-catalyzed Giese-addition.

The Rovis group has also exploited the ease with which α-amino radicals can be accessed using photoredox catalysis (Scheme 25a).[195] In a dual catalytic approach, an iridium photocatalyst is reductively quenched by tertiary amine **27a** to generate α-amino radical **27h** after deprotonation (Scheme 25b). Meanwhile, a Co^{I}-species (**27d)** is protonated to form a Co^{III}-hydride **27e** which, based on the precedent of Kambe,[196] is proposed to react with dienes to form allyl-complex **27f**. This electron-deficient cobalt-complex can then be reduced by the photocatalyst Ir^{II}-complex (**$E_{1/2}^{III/II}$** = -1.37 V vs

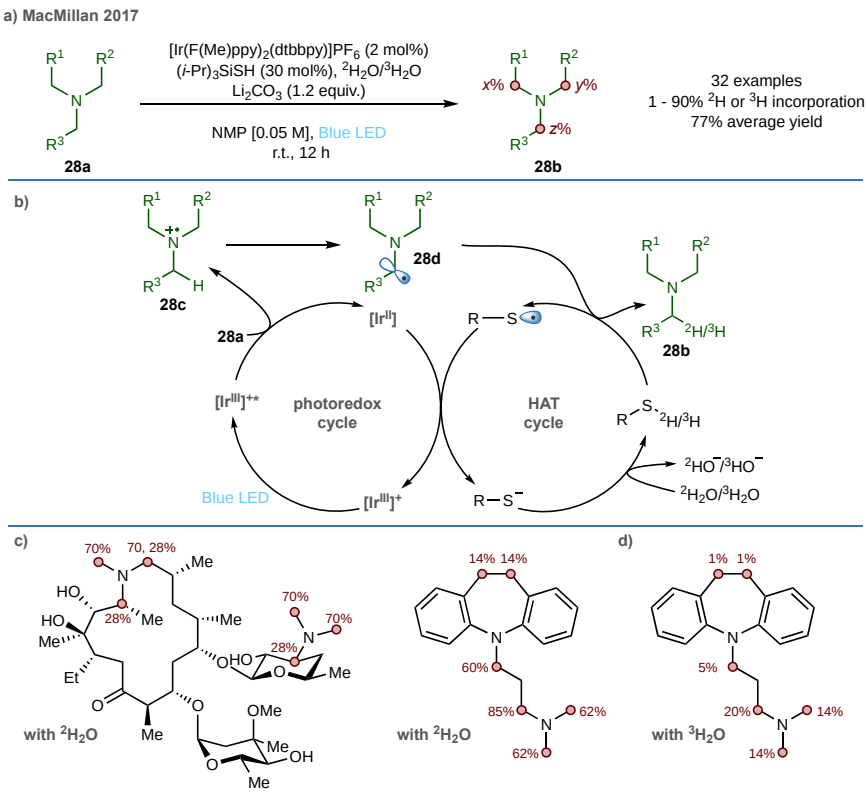
SCE in MeCN). Formal oxidative addition of **27h** to the allyl Co^{II}-complex **27g** forms **27i**, which upon reductive elimination affords the desired product. Alternatively, an S_H2 pathway *via* direct attack of radical **27h** to the allyl substituent could occur (not shown). Whilst the method provides access to a range of functionalized aromatic tertiary amines, only three examples of all-alkyl tertiary amine substrates were reported (**27j-l**, scheme 25b). In addition, these amines were formed with moderate regioselectivity.



Scheme 25 | a) Rovis' Co-catalyzed synthesis of homoallylic aliphatic amines. b) Proposed mechanism and c) selected examples of Rovi's Co-catalyzed synthesis of homoallylic amines.

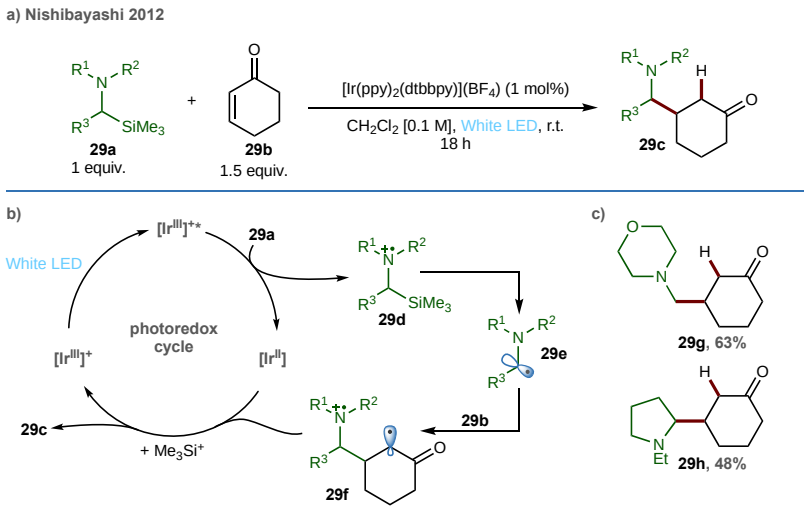
As noted in the work of Rovis, an issue that has complicated efforts to use photoredox catalysis to generate α-amino radicals is the lack of regioselectivity in the deprotonation step.[197] MacMillan and co-workers turned this into an advantage in the deuteration and tritiation of tertiary amine-containing pharmaceutical compounds (Scheme 26a).[198] The amines **28a** underwent isotopic exchange of C–H bonds adjacent to the nitrogen-atom to afford deuterated or tritiated products **28b** with varying levels of isotope-incorporation. The mechanistic proposal states that the excited state of the photocatalyst is quenched by the tertiary amine which fragments to form an α-amino radical after deprotonation of the aminium radical cation **28c** (Scheme 26b). Radical **28d** subsequently undergoes polarity-matched hydrogen-atom transfer with a deuterated or tritiated thiol to afford the isotopically modified tertiary amine **28b**. The thiyl radical is then reduced by $[Ir^{II}]$ ($E_{1/2}^{III/II}$ = -1.50 V vs SCE in MeCN) to form a thiolate anion that can undergo exchange with ^2H_2O (for deuteration) or ^3H_2O (for tritiation). It is also possible that this reaction could proceed *via* a radical chain mechanism, using the photocatalyst as an

initiator, as proposed by Bertrand for the AIBN/RSH-mediated racemization of aliphatic amines.[199] However, quantum yield measurements to elucidate this matter were not undertaken.



Scheme 26 | a) MacMillan's Ir-catalyzed deuteration and tritiation of tertiary aliphatic amines. b) Proposed mechanism and c) selected examples.

Although the lack of regioselectivity in α-amino radical formation could be exploited in the context of isotope-labelling, it is generally a disadvantage for synthetic applications. An early solution to this problem was used by Mariano and co-workers who employed α-silylamines, which underwent fragmentation to expel a silylinium cation upon single-electron oxidation and form an α-amino radical.[200,201] Following this strategy, Nishibayashi showed that α-silyl tertiary amines, such as **29a,** could be alkylated in good yields without the formation of di- or trialkylated products **29c** (Scheme 27a). However, even in this example, most of the scope focused on the use of aryl amines. The proposed mechanism outlines a reductive quenching cycle wherein amine **29a** is oxidized to form radical cation **29d** (Scheme 27b). Following mesolysis, the resulting α-amino radical **29e** reacts with the electron-deficient olefin **29b** to form α-carbonyl radical **29f**. Such radicals are readily reduced to form the corresponding enolate, which is trapped by the positively charged silylinium species. The resulting silyl enol ether is then converted into the desired product upon acidic work-up.



Scheme 27 | a) Nishibayashi's Ir-catalyzed Giese-addition. b) Proposed mechanism and c) selected examples of Nishibayashi's Ir-catalyzed Giese-addition.

1.4 Summary and outlook

Driven by the utility of aliphatic amines, a plethora of synthetic methods for their construction have been developed over the past two centuries. In the previous sections, the key advances have been presented in order to put them into context as well as to enable a comparison between radical and polar methods. From a historical perspective, it is obvious to the observer that the majority of general methods for amine synthesis have come from the polar arena. It is, however, increasingly apparent that this observation is becoming *decreasingly* accurate following the wealth of radical methods developed over the past 20-30 years that utilize alternative reaction pathways with complementary feedstock starting materials. In particular, the rise of photoredox catalysis has advanced the field of aliphatic amine synthesis *via* radical intermediates from the early, conceptual advances of the 70s and 80s into full-fletched synthetic methods using milder reaction conditions and achieving broader reaction scopes.

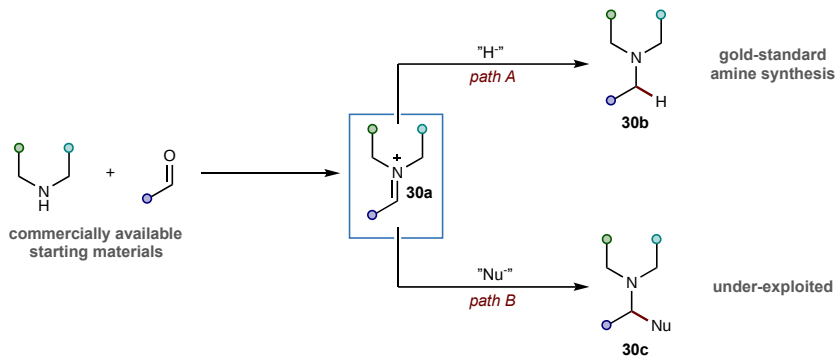
As noted earlier, any method of categorization unavoidably has its flaws and this thesis is no exception. Therefore, it is instructive to compare the synthetic methods detailed earlier not by *reactivity*, but in terms of the *connectivity* that they afford. Some methods, such as the Hofmann-alkylation, allow the construction of *new* C–N bonds and can be used to rapidly increase complexity towards any given target. Alternatively, other methods utilize the intrinsic reactivity of the nitrogen atom in order to *functionalize* or *derivatize* an aliphatic amine starting material. Whilst such methods, exemplified by amine-directed C–H activation, might be less suitable at the early stages of target-driven synthesis, they can be invaluable in the late-stage functionalization of pharmaceutical lead compounds.

From this alternative perspective, a third class of methods for the synthesis of amines emerges namely *multi-component* methods. This class of amine-constructing reactions combines the formation of a *new* C–N bond with the concurrent or subsequent functionalization elsewhere on the molecular scaffold. This approach to amine synthesis, arguably, offers the most rapid increase in complexity by introducing several new modular fragments in a single transformation. An illustrative example is the three-component hydroaminomethylation reaction that combines feedstock alkenes, amines and carbon monoxide and unsurprisingly, such methods have been intensely studied. Whilst the development of generally applicable and environmentally reasonable conditions for this and other related transformations has proved challenging, this should, in the author's opinion, not detract from the conceptual attractiveness of the approach. Consequently, it is with the development of *multi-component radical methods for amine synthesis* that this thesis is concerned

2 Visible light-mediated carbonyl alkylative amination for tertiary amine synthesis

2.1 Introduction

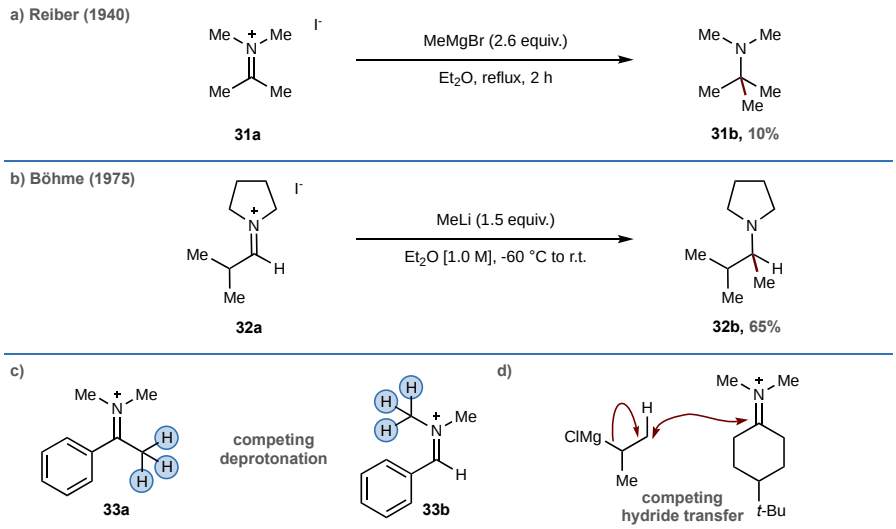
Tertiary amines represent the most abundant amine motif in pharmaceutical agents, making their straightforward synthesis an important task for synthetic organic chemists.[4] The gold-standard method for laboratory-scale amine synthesis is reductive amination, where commercially available secondary amines are condensed with aldehydes or ketones to form an iminium ion (**30a**, Scheme 28). [10,27] Because of its modular nature and the selective action of mild reducing agents that convert the iminium ion **30a** into the amine product **30b** (path A), reductive amination has become one of the most commonly used reactions of synthetic organic chemistry.[10]



Scheme 28 | Strategies towards the synthesis of tertiary amines using reductive amination (path A) and alkylative amination (path B).

2.1.1 Polar alkylation of C=N bonds

In principle, the utility of the reductive amination reaction would be significantly enhanced if the hydride nucleophile could be replaced by other nucleophilic components (path B, Scheme 28). For example, the Strecker reaction, in which cyanide is employed as a nucleophile, has been used frequently in both natural product synthesis and large-scale pharmaceutical production.[202,203] Another useful, albeit hitherto unexploited, transformation would be an alkylative variant, wherein an alkyl nucleophile is added to the C=N bond. Interestingly, such an "alkylative amination" was reported in 1940 by Reiber who showed that a methyl Grignard reagent could alkylate acetone derived iminium ion **31a** to afford **31b** in low 10% yield (Scheme 29a).[204] Following this report, the reaction was employed by Leonard as a tool for the structural determination of sparteines[205–207] and Böhme later published the first systematic studies using both Grignard and organolithium reagents (Scheme 29b).[208,209]

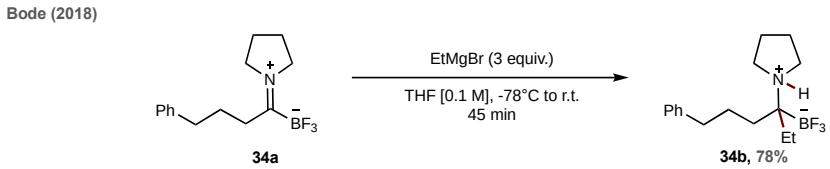


Scheme 29 | a) Reiber's synthesis of tertiary amines from alkyl Grignard reagents and iminium ions. b) Böhme's synthesis of tertiary amines from alkyl lithium reagents and iminium ions. c) Acidic protons on iminium ions that have caused side-reactions with basic organometallics. d) Hydride-transfer from hindered Grignard reagents to iminium ions.

However, despite these early results and the potential utility of the approach, the addition of alkyl nucleophiles to C=N bonds has not become widely used in organic chemistry (possibly with the exception of the Mannich reaction). There are several reasons for this. Firstly, the reaction is highly dependent on the structure of the iminium ion. The basic nature of both Grignard and organolithium reagents can cause deprotonation of the C–H bonds adjacent to the iminium carbon atom (pK_a (**33a**) = 6.8,[206] Scheme 29c) to afford enamines.[208–210] Indeed, the facile nature of this reaction was originally reported in the reactions of Grignard-reagents with Schiff-bases by Short and Watt.[211] In the absence of acidic α-C–H bonds, even the C–H bonds on the *N*-substituent can be deprotonated (e.g. **33b**; pK_a >> 22);[212] that by-product was observed by Böhme.[209] Further complicating the matter, certain hindered Grignard reagents, such as *i*-PrMgCl, *s*-BuMgCl and *t*-BuMgCl can affect a hydride transfer to the iminium ion,[213] resulting in the corresponding reductive amination product (Scheme 29d).[214] Taken together, these side-reactions have limited the utility of iminium ion alkylation to scaffolds without α-C–H bonds.[215] For example, Eschenmoser's salt, formed from the condensation of formaldehyde and dimethylamine under acidic conditions, has been successfully employed in 1,2-addition reactions.[216] Some studies have suggested that additives might improve the scope of this transformation but have provided little experimental evidence to strengthen that claim.[217] A broader scope has been found for allyl and propargyl magnesium halide reagents where the 1,2-addition is reported to be favoured over deprotonation although the reason for this divergence has not been studied. [218]

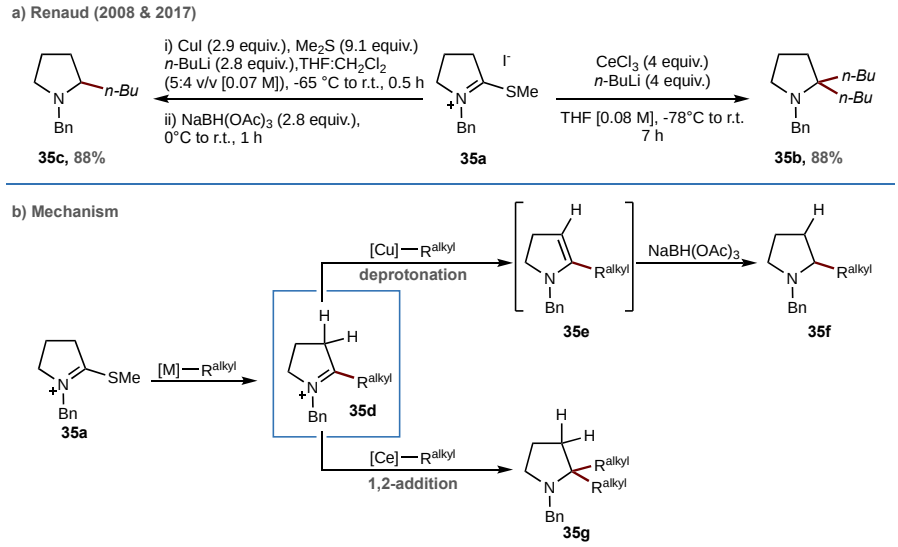
Another hurdle facing the alkylation of iminium ions is the preparation of the starting material. The obvious synthesis of an iminium ion is through the condensation of an amine with a carbonyl compound, affording water as a by-product. However, as organometallic reagents are generally moisture-sensitive, the unstable iminium ions have to be prepared beforehand using tedious synthetic procedures resulting

in low yields.[219,220] A solution to this problem was suggested by Bode, who showed that stable trifluoroborate iminium ions **34a,** prepared from the corresponding potassium acyltrifluoroborates, readily react in a 1,2-fashion to afford the corresponding tertiary amines **34b** without any deprotonation by-product (Scheme 30).[221] Although Bode's protocol avoids the issue of preparing unstable iminium ions, the method employs bespoke starting materials that require multi-step syntheses to access, making it less practical as a general strategy.



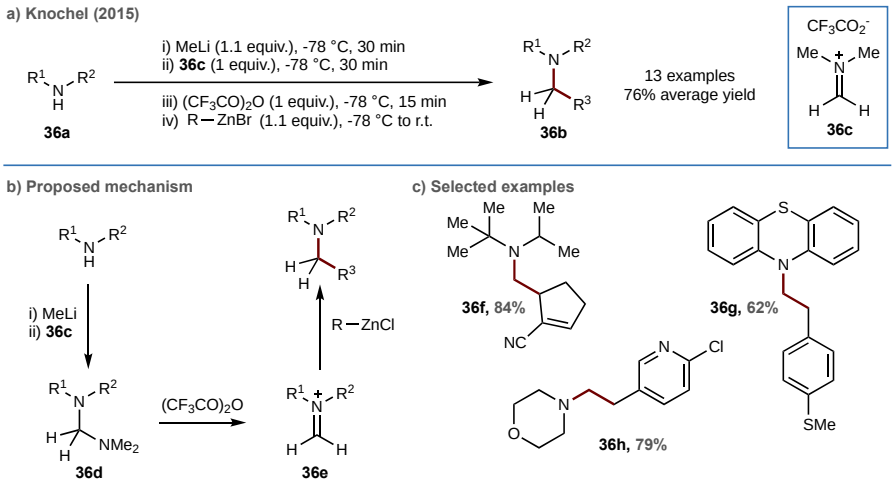
Scheme 30 | Bode's synthesis of tertiary amines *via* alkyl Grignard addition to iminium trifluoroborates.

A fundamental limitation of Grignard or organolithium reagents is the inherent functional group incompatibility. In view of this limitation, more recent studies have explored softer (and less basic) organometallic reagents.[222,223] For example, Renaud has employed both organocerium and organocuprates in order to functionalize thioiminium ions such as **35a** (Scheme 31a).[224,225] Whereas cerium-based organometallics afforded the double-addition product **35b**, only mono-addition was observed with organocuprates (**35c**). Although pyrrolidine and piperidine derived iminium ions could be functionalized in this way, the starting materials require a two-step synthesis from the corresponding amide in moderate yields and the functional group tolerance was not explored. The divergence of the copper- and cerium-reagents were rationalized on the basis of the more basic organocuprate reagents (Scheme 31b). Both reagents give rise to the same monoalkylated iminium intermediate **35d**, which is less electron-deficient than the thioiminium starting material. Consequently, the more basic organocuprate effects deprotonation to afford enamine **35e** which, via its corresponding iminium ion, is reduced by sodium triacetoxyborohydride to afford **35f**. The organocerium-reagent, which is known to only deprotonate highly acidic protons,[226,227] reacts in a 1,2-addition to afford **35g**.



Scheme 31 | a) Renaud's synthesis of tertiary amine via cerium- or copper-mediated addition of alkyl nucleophiles to iminium ions. b) Proposed mechanism to rationalize the divergent outcome with copper- or cerium-reagents.

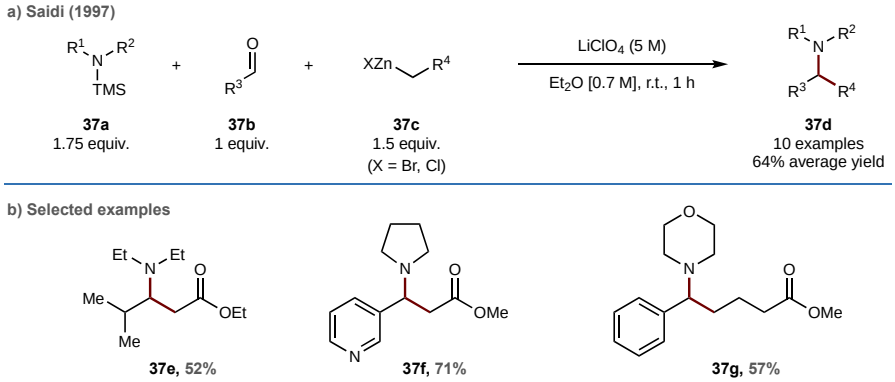
Aliphatic organozinc reagents have been frequently used in cross-coupling reactions and have proven to be compatible with a range of functional groups.[228] Knochel exploited this property in the first systematic study of alkylzinc addition to aliphatic iminium ions (**36c**, Scheme 32a).[229] Using mixed aminal **36d**, formed from amine **36a** and Eschenmoser's salt **36c**, as a precursor for iminium ion **36e**, a broad range of linear and heterocyclic amines were reacted with benzylic and allylic organozinc reagents to afford tertiary amines in good yields (Figure 32b & 32c). The reaction could be carried out as a one-pot procedure, but the scope remains limited to formaldehyde as the formal carbonyl component and only benzylic and allylic organozinc reagents were reported.



Scheme 32 | a) Knochel's alkylation of Eschenmoser-type iminium ions. b) Mechanistic proposal. c) Selected examples from the scope.

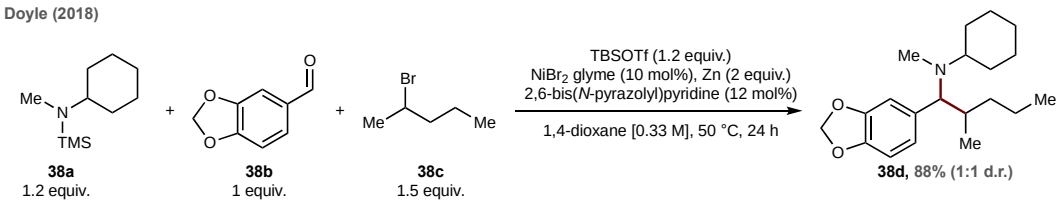
Saidi and co-workers reported a broader scope (c.f. Knochel's report) of organozinc addition to iminium ions when lithium perchlorate was used as a promoter (Scheme 33a).[230] The authors proposed that the iminium ion intermediate is in equilibrium with its trimethylsilyl hemiaminal, enabling electron-

deficient aldehydes such as pyridine-carboxaldehyde to undergo efficient reaction. However, the scope was still mainly limited to activated organozinc reagents and aromatic aldehydes (**37e-g**, Scheme 33b). Furthermore, the organozinc reagents are, to varying degrees, air- and moisture-sensitive as well as laborious to prepare which limits the practicality of the method.[231]



Scheme 33 | a) Saidi's synthesis of tertiary amines using alkylzinc reagents. b) Selected examples from Saidi's zinc-mediated synthesis of tertiary amines.

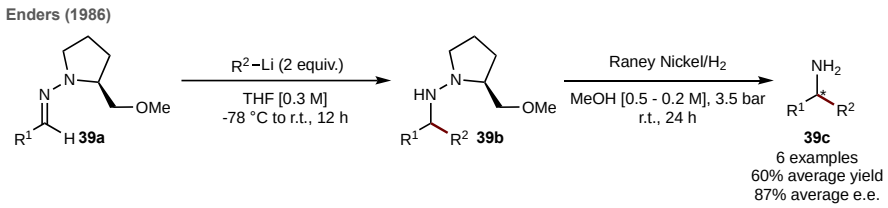
Recently, Doyle reported a similar method using silylamines, aromatic aldehydes and arylzinc reagents to access benzhydrylamines (Scheme 34).[37] Unlike Saidi's work, the scope did not include any alkyl aldehydes and only a single example (**38d**) of an *alkyl*-zinc reagent. Doyle proposed that the reaction, in the case of *aryl* halides, proceeds via a 2-electron processes whereby an *in-situ* formed iminium ion undergoes oxidative addition to a Ni^{I}-species followed by product-forming reductive elimination. However, in the case of *alkyl* halide **38c**, the reaction proceeded in low yield (11%) even in the absence of nickel, suggesting that a different mechanism might be operative.



Scheme 34 | Doyle's Ni-catalyzed reductive alkylation reaction.

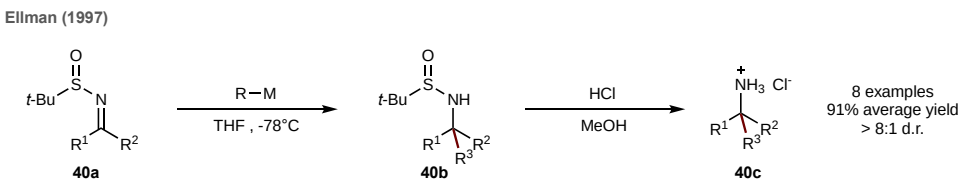
In addition to the alkylations of all-alkyl iminium ions outlined above, organometallic addition to imines and imine-derivatives has been extensively explored. Unactivated imines are poorly reactive[211] and largely suffer from the same side-reactions (e.g. deprotonation or reduction) as iminium ions.[232] In order to achieve reactivity with simple imines, the use of boron-[233] or silicon-based[234] Lewis acidic additives is necessary but the scopes are limited. A more promising strategy for the organometallic addition of an alkyl group to a C=N bond is to use activating auxiliaries. These can either be positioned adjacent to the nitrogen or the iminyl carbon atoms. The advantage of such auxiliaries is that they can induce stereoselectivity. For example, the 1-amino-2-(methoxymethyl)pyrrolidine auxiliary (**39a**, abbreviated

SAMP or RAMP depending on the stereochemistry) was developed by Enders for the asymmetric synthesis of primary amines **39c** (Scheme 35). The organolithium reagent had to be used in excess for substrates bearing α-iminyl C–H bonds. Later, organocerium nucleophiles were employed to address the low yields and competing deprotonation, generally affording higher yields.[235]



Scheme 35 | Enders' SAMP-ligand enabled asymmetric alkylation of C=N bonds

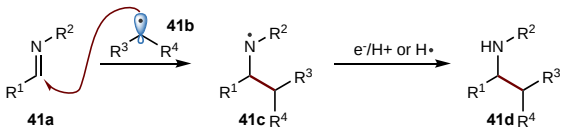
Arguably, the most commonly employed auxiliary for organometallic addition to C=N bonds is the sulfinyl-group. It was used by Ellman who showed that the addition of Grignard reagents to sulfinimine **40a** gave the corresponding sulfinamides **40b** in high yields (Scheme 36).[236,237] After treatment of **40b** with hydrochloric acid in methanol, the α-tertiary primary amines **40c** could be accessed in high yields and high enantiomeric excess as their HCl-salts. However, this strategy is of lesser utility in the context of tertiary amine synthesis as it would require multiple additional steps to access tertiary amines from **40c**. Furthermore, it could not be readily applied to the synthesis of cyclic amines, which constitute some of the most important building blocks in medicinal chemistry.[238]



Scheme 36 | Ellman's synthesis of α-tertiary primary amines via the addition of alkyl Grignard or alkyl lithium reagents to sulfinimines.

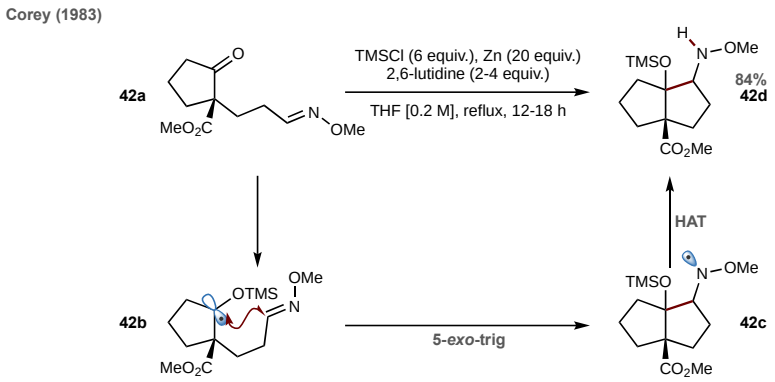
2.1.2 Radical alkylation of C=N bonds

An alternative strategy to the organometallic approach has relied on the addition of nucleophilic C-centered radicals to electrophilic C=N bonds.[239] Typically, an alkyl radical (**41b**) would undergo 1,2-addition to an imine-derivative (**41a**) to afford an *N*-centered radical intermediate (**41c**, Scheme 37). This radical can then be trapped by an electron or a hydrogen atom to afford **41d**.



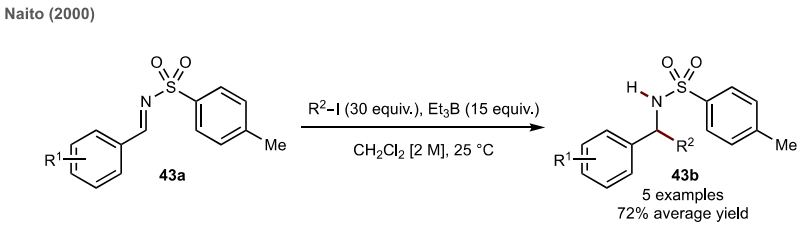
Scheme 37 | Radical addition to C=N bonds to afford amines and amine-derivatives.

Following early reports on the dimerization of Schiff bases[240] and radical addition to nitronates,[241] Corey and Pyne reported the first synthetically useful radical addition to oximes in 1983 (Scheme 38).[242] Building on previous work by Motherwell,[243] they hypothesized that ketone **42a** could be reduced by TMSCl activated zinc-powder to afford silyl ketyl radical **42b**. The ketyl radical would then cyclize through the preferred 5-*exo*-trig mode[244] to afford aminyl radical **42c** which after hydrogen-atom transfer (HAT) from THF would afford the hydroxylamine product **42d**. Testing this hypothesis, they found that when 2,6-lutidine was employed as a base to avoid acid-catalyzed decomposition of the formed tertiary silyl ether, the desired bicycle **42d** was obtained in 84% yield.



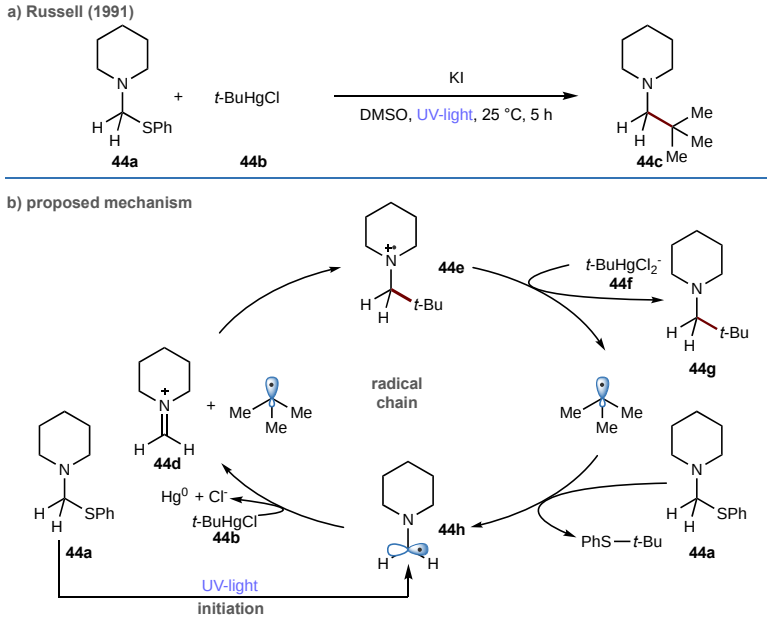
Scheme 38 | Corey's radical cyclization onto oximes.

Since the report of Corey, hundreds of examples have emerged using oximes, hydrazones and aryl imines as radical acceptors in both intramolecular and intermolecular reactions.[239,245] Other classes, such as the radical addition to sulfonyl-protected imines **43a** using the alkyl halide/borane radical generation system, have also been reported albeit less frequently (Scheme 39).[246]



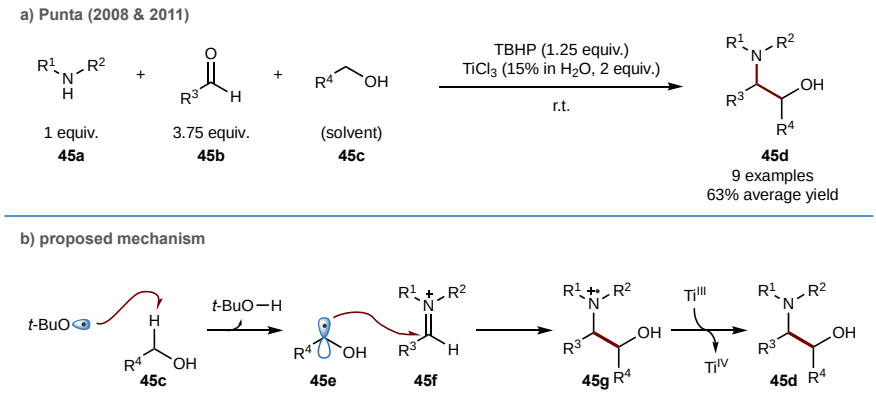
Scheme 39 | Naito's radical addition to sulfonyl-imines.

It is striking that, akin to the polar organometallic 1,2-additions, very few examples of radical addition to unactivated and unbiased C=N bonds have been reported. The first unbiased intermolecular example was reported by Russell and co-workers (Scheme 40a).[247] In a single example, a *tert*-butyl radical generated from an alkylmercury halide (**44b**) underwent 1,2-addition to iminium ion **44d**, formed from the corresponding thiohemiaminal **44a** (Figure 40b). The resulting aminium radical cation (ARC) **44e** then underwent a single-electron transfer from anionic mercury complex **44f** to afford the tertiary amine product **44g**.



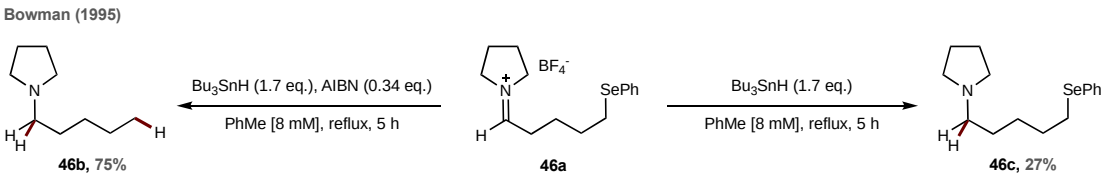
Scheme 40 | a) Russell's study of alkyl addition to iminium ions. b) Proposed mechanism of Russell's alkylmercury-mediated synthesis of tertiary amines.

Following this report, a handful of papers reported a formal alkyl radical addition to *N*-alkyl substituted iminium ions or imines with each example containing a feature which enhanced reactivity and biased the applicable scaffolds. Such bias could entail the use of strained azirine electrophiles[96,248–250] or imines carrying adjacent electron-withdrawing groups such as glyoxylate esters and α-trifluoromethyl imines.[251–254] The only 1,2-additions to unbiased iminium ions were reported by Punta in 2008 and 2011, who combined aliphatic amines **45a**, aldehydes **45b** and an alcohol solvent (**45c**) to afford the desired amino alcohols **45d** (Figure 41a).[255,256] Using a *tert*-butoxy radical (generated from *tert*-butyl hydrogen peroxide) to abstract a hydrogen from the C–H bond of the alcoholic solvent, the resulting α-alkoxy radical **45e** could be added to *in-situ* generated iminium ions **45f** of secondary and primary amines (Figure 41b). Although the reaction scope was limited by having the alcohol-component as the solvent, poor tolerance of aldehyde substituents and use of harsh stoichiometric reagents, it constitutes a rare example of a one-pot alkylative amination of aliphatic aldehydes and aliphatic amines from commercial starting materials.



Scheme 41 | a) Punta's synthesis of tertiary amines via hydrogen-atom abstraction. b) Proposed mechanism of Punta's tertiary amine synthesis.

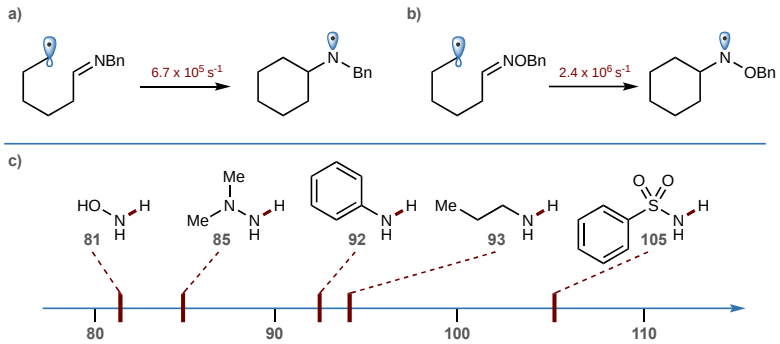
However, despite these examples from Punta and Russell, it is evident that the use of unfunctionalized iminium ions as a radical acceptor imposes significant constraints on the reaction conditions. For example, Bowman and co-workers attempted the tin-mediated cyclisation of iminium salt **46a** (Scheme 42).[257] However, upon subjecting **46a** to standard Bu_3SnH/AIBN radical cyclization conditions, only the reduced product **46b** was observed. Speculating that Bu_3SnH might be too hydridic,[258] the authors examined TTMSS as a less electron-rich hydrogen donor but with similar results. To confirm the hypothesis, **46a** was subjected to the cyclisation conditions in the absence of AIBN. This left the selenyl-ether intact but reduced the iminium ion to the tertiary amine (**46c**), suggesting that a polar hydride-mechanism was responsible for the reduction of the C=N bond. This example underscores the challenge of compatibility when using iminium ions in radical chemistry.



Scheme 42 | Iminium ions can be reduced in the absence of radical initiators by tin hydrides.

Several other factors also serve to explain why electrophiles such as oximes, hydrazones, *N*-aryl imines or *N*-tosyl imines have been frequently employed in 1,2-radical addition reactions whilst no synthetic methods using completely unbiased systems have been reported. In the cases of oximes, hydrazones and *N*-aryl imines, the 1,2-addition exhibits greater rate constants than the corresponding cyclisation onto an unactivated imine (Scheme 43a & 43b) as the resulting radicals are stabilized by the adjacent heteroatom or aryl group (Scheme 43c). In contrast, 1,2-additions to *N*-tosyl imines form a destabilized aminyl radical (BDE = 105 kcal mol^{-1}, Scheme 43c) but are feasible due to the greater polarity of the C=N bond; the sulfonyl moiety increases the positive charge on the imine carbon and therefore favours the addition of a nucleophilic alkyl radical. Furthermore, *N*-tosyl imines are often employed with radical generation systems such as zinc-powder,[259] superstoichiometric triethylborane[260] or ethereal solvent.[261]

These species can quench the electron-deficient *N*-centered radical rapidly through SET, HAT or S_H2-mechanisms, making an unfavourable, endothermic 1,2-addition feasible by coupling it to a fast and irreversible quenching step. Considering these observations in the context of radical addition to unactivated C=N bonds, such a reaction would lack the exothermicity of the oxime and hydrazine examples as well as the high reactivity of sulfonamide radicals that can promote a fast quenching step. Indeed, it was previously noted (see chapter 1.3.2.1) that aminyl radicals react only slowly with e.g. hydrogen-atom donors.



Scheme 43 | a) Rate of 6-*exo*-trig cyclisation onto *N*-benzyl imine.[239] b) Rate of 6-*exo*-trig cyclisation onto *O*-benzyl oxime.[239] c) BDE of common N–H bonds.[239,262–265]

2.2 Project aims

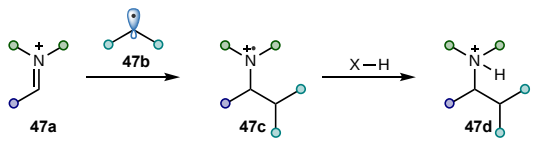
Despite a large effort stretching from the early organometallic reports of Böhme to recent radical advances by Naito, Miyabe, Punta and others, no general carbonyl alkylative amination reaction has been reported. Although the reported advances towards such a strategically important transformation now number in the hundreds, no reaction has demonstrated the capacity to couple unactivated aliphatic amines, aldehydes with an unactivated alkyl nucleophile in a general fashion.

The potential significance of a general carbonyl alkylative amination is two-fold. Firstly, the multicomponent nature would allow synthetic chemists to create complex molecules from simple starting materials. For example, the 4-component Ugi-reaction has become an indispensable tool in combinatorial chemistry and fragment library construction.[266,267] Furthermore, the ability of aliphatic amines to modulate potency, solubility and bioavailability has made them a mainstay motif in medicinal chemistry and as such require efficient methods for their construction.[4] Secondly, by sharing the same intuitive disconnection as the reductive amination reaction, an alkylative amination reaction would present an easily recognizable option in a retrosynthetic campaign which would likely increase its rate of adoption in the pharmaceutical industry.[10]

In considering the previous organometallic and radical approaches to a carbonyl alkylative amination, the latter presents several advantages. Unlike the harsh and basic organometallics, alkyl radicals can tolerate a wealth of base- and nucleophile-sensitive functional groups such as alkyl chlorides or

carbonyl moieties. This is particularly important in order to avoid the deprotonation and reductive side-reactions observed in previous organometallic studies (c.f. scheme 29c). Radicals can undergo similar side-reaction via hydrogen-atom transfer, but the rates of such side-pathways are generally slower and pose a smaller problem than for organometallic reagents. Organometallic reagents are typically formed *in-situ* through oxidative addition of e.g. magnesium or zinc into C–X bonds[268] (or sometimes through hydrometallation of olefins),[269] limiting the number of commercially available nucleophile precursors. In contrast, an ever-increasing number of functional groups have been employed to generate radicals, enabling a greater scope in the nucleophile component.[86] While organometallics are highly sensitive to moisture and sometimes pyrophoric, alkyl radicals can be generated from a range of bench-stable precursors and can be used in water.[245]

To realize a radical *carbonyl alkylative amination* (CAA), two key steps were identified (Scheme 44). Firstly, an alkyl radical **47b** must add to an *in-situ* formed iminium ion **47a**. The formation of **47a** *in-situ* is important as iminium ions are highly unstable[270] and hard to isolate in pure form. Following the 1,2-radical addition, the resulting aminium radical cation (ARC) **47c** could be trapped through hydrogen-atom transfer with an electron-rich HAT reagent to afford the product as its ammonium salt **47d** which upon work-up yields the desired tertiary amine. The hydrogen-atom transfer to an ARC is known and has been exploited to achieve C–H activation of both activated[125] and unactivated C–H bonds.[271,272] These central elementary steps could then be coupled with a radical generation system using either a radical chain or a photocatalytic mechanism.



Scheme 44 | Mechanistic outline of the key steps and strategy towards a general CAA-reaction.

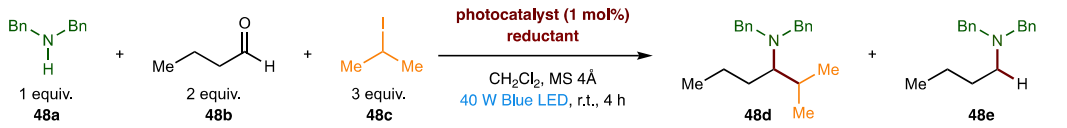
Due to the collaborative nature of this project, all work undertaken by others (Dr. R. Kumar and Dr. W. G. Whitehurst) than the author is attributed by name both within the text and schemes.

2.3 Discovery and Previous work

In the search for a suitable method of radical generation to be coupled with the key mechanistic steps outlined in scheme 44, it was noted that Stephenson had previously suggested that the excited state of $Ir(ppy)_3$ ($E_{1/2}^{IV/III*}$ = -1.73 V vs SCE in MeOH/EtOH 1:1)[165] is capable of reducing unactivated alkyl halides to afford the corresponding alkyl radical ($E_{1/2}^{red} \approx$ -1.8 V vs SCE in MeCN).[273,274] In Stephenson's work, the excited state of $Ir(ppy)_3$ is proposed to be quenched by an alkyl halide to form an $[Ir^{IV}]$-species which is reduced by Hantzsch ester (HEH) to reform $[Ir^{III}]$. In the context of the design

plan outlined in scheme 44, HEH could act as a reductant for the photocatalyst as well as donating a hydrogen atom to the ARC.

Based on this precedent, Dr. R. Kumar reacted dibenzylamine **48a**, butyraldehyde **48b** and 2-iodopropane **48e** with $Ir(ppy)_3$ and HEH under visible light irradiation to afford the desired product **48d** in 10% yield (Entry 1, Table 1) with the major product being that of reductive amination (**48e**). The formation of **48e** is not unsurprising as HEH is a potent hydride donor in the reduction of aldehydes and imines.[275] Interestingly, replacing HEH with 2,6-dimethylthiophenol afforded exclusive reductive amination (Entry 2, Table 1). It is likely that the iminium ion formed from condensation of **48a** with **48b** is reduced by $Ir(ppy)_3$, as has been reported by Gaunt and co-workers,[276] to afford α-amino radicals which undergo a polarity matched hydrogen-atom transfer with the thiophenol.[277] Such a radical reduction should be disfavoured when electron-rich hydrogen-atom donors are employed. Indeed, although $(EtO)_3SiH$ and Et_3SiH only gave poor yields of the desired product, the formation of **48e** was significantly reduced. Evaluating silanes with weaker Si–H bonds, TTMSS afforded **48d** in substantially improved yields (Entry 5, Table 1). Interestingly, upon running the control experiment without the photocatalyst, **48d** was still obtained in 63% yield and the amount of reductive amination by-product was further reduced (Entry 6, Table 1). Presumably, after a facile HAT from TTMSS to the ARC intermediate (e.g. **47c**, Scheme 44), the so-formed silyl-radical abstracts an iodine atom from **48c** to propagate a radical chain.[105] Further adjustments of the reaction concentration afforded the desired tertiary amine in an optimized 96% yield with only low amounts of **48e** (4%) (Entries 7 & 8, Table 1).

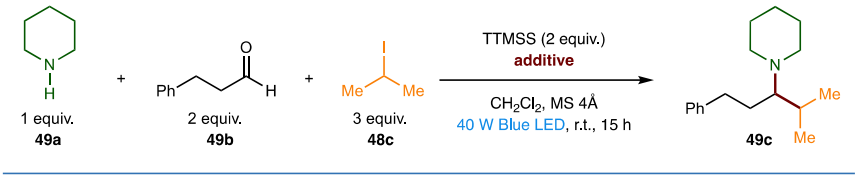


Entry	Photocatalyst	Reductant	Conc.	Yield **48d**	Yield **48e**[a]
1	$Ir(ppy)_3$	HEH (1.5 equiv.)	0.1 M	10%	60%
2	$Ir(ppy)_3$	2,6-dimethylthiophenol (1.5 equiv.)	0.1 M	0%	80%
3	$Ir(ppy)_3$	$(EtO)_3SiH$ (2 equiv.)	0.1 M	20%	20%
4	$Ir(ppy)_3$	Et_3SiH (2 equiv.)	0.1 M	15%	20%
5	$Ir(ppy)_3$	TTMSS (2 equiv.)	0.1 M	60%	20%
6	None	TTMSS (2 equiv.)	0.1 M	63%	10%
7	None	TTMSS (2 equiv.)	0.2 M	55%	30%
8	None	TTMSS (2 equiv.)	0.03 M	96% (80%)	4%

Table 1 | Exploratory studies towards a CAA-reaction. *All reactions in this table were carried out by Dr. R. Kumar.* [a]Yields determined by ^1H NMR against 1,1,2,2-tetrachloroethane internal standard.

2.4 Results and discussion

The ability to use cyclic secondary amines in the CAA reaction would be important due to their omnipresence in bioactive compounds.[278] Therefore, the set of conditions found by Dr. R. Kumar for dibenzylamine were tested with piperidine as a representative cyclic amine. However, in contrast to the results obtained with dibenzylamine, piperidine afforded tertiary amine **49c** in a complex mixture in low but uncertain yield using the same conditions (Entry 1, Table 2). Consequently, a re-optimization effort was undertaken.

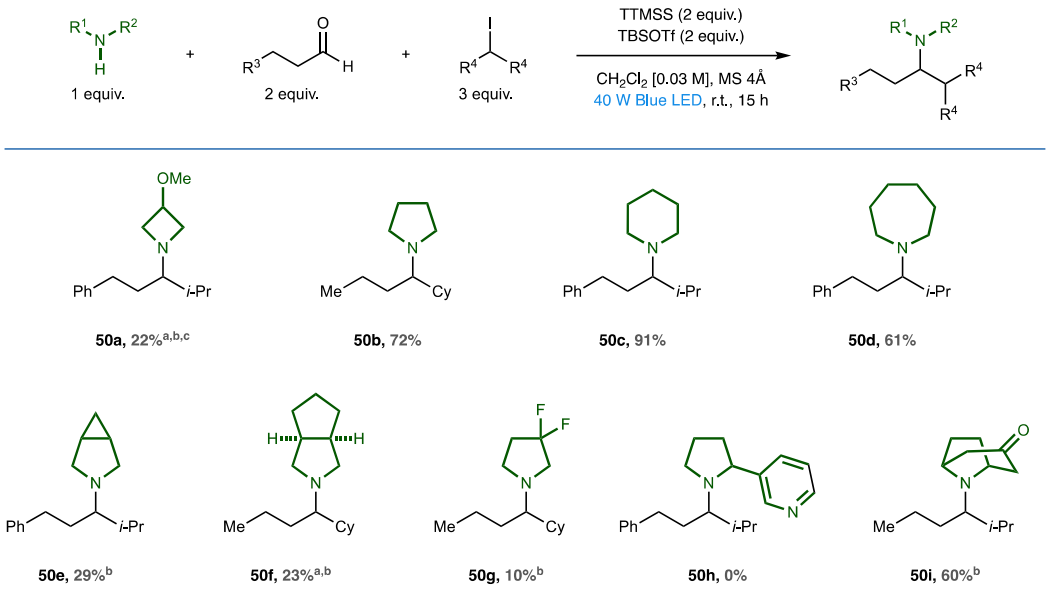


Entry	Additive	Yield **49c** (%)
1	None	complex mixture
2	$EtCO_2H$ (1 equiv.)	complex mixture
3	TFA (1 equiv.)	50%
4	TMSOTf (1 equiv)	87%
5	TBSOTf (2 equiv)	91%

Table 2 | Optimization studies towards a CAA-reaction using piperidine. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

In considering why piperidine afforded lower yields, it was noted that piperidine is substantially more basic than dibenzyl amine (pK_a (piperidine) = 11.3 versus pK_a (dibenzylamine) = 7.7)[279] and since iminium ion formation requires acidic conditions, it was speculated that the concentration of the iminium ion was too low. As a comparison, the related Giese-addition employs the unsaturated acceptor in stoichiometric quantities.[84] To ensure that the enamine (formed from **49a** and **49b**) is efficiently protonated to yield the iminium ion, a range of acid derivatives were evaluated. The addition of propionic acid did not have a significant impact on the reaction, whereas TFA gave 50% yield by ^{1}H NMR (Entries 2 & 3, Table 2). Silyl-triflate based Lewis acids were then tested and both TMSOTf and TBSOTf afforded **49c** in excellent yields (Entries 4 & 5, Table 2). The use of TBSOTf, however, afforded a cleaner reaction profile and hence became the acid of choice. The role of the silyl triflate additive might be two-fold: silylation of the amine enhances its nucleophilicity while interaction with the carbonyl group increases its electrophilicity, both favouring condensation with the aldehyde.[37,280] Secondly, triflate anion serves as a non-coordinating anion to the iminium cation, making it more reactive. In the case of the more sterically hindered TBSOTf, the second effect is likely more important.

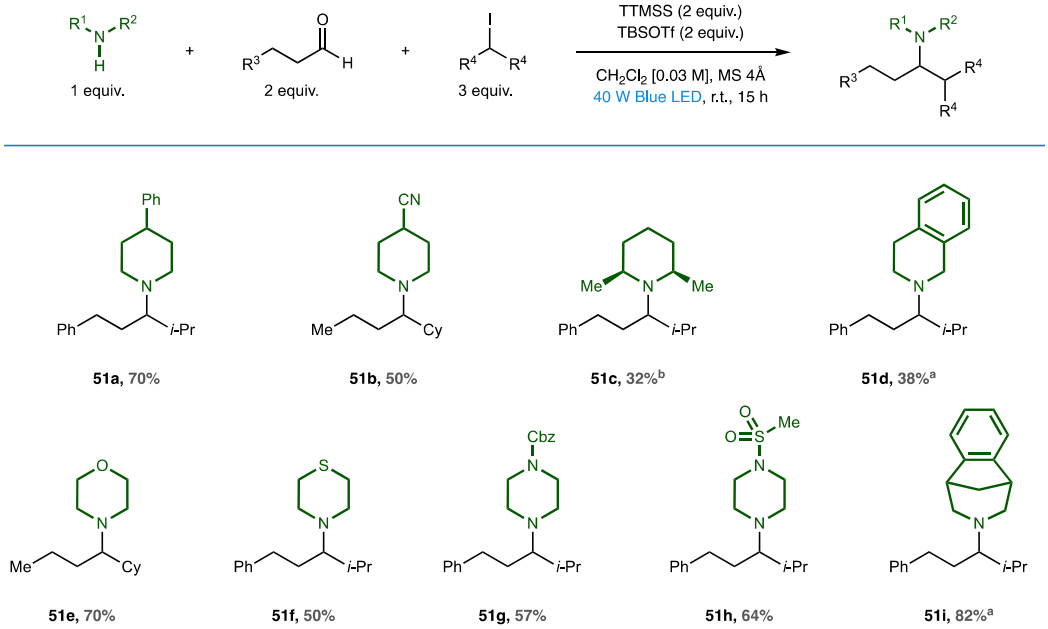
2.4.1 Scope



Scheme 45 | Heterocyclic amine scope of the CAA-reaction. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard. [b]HCl-salt of the amine was used. No TBSOTf. [c]*Reaction conducted by Dr. R. Kumar.*

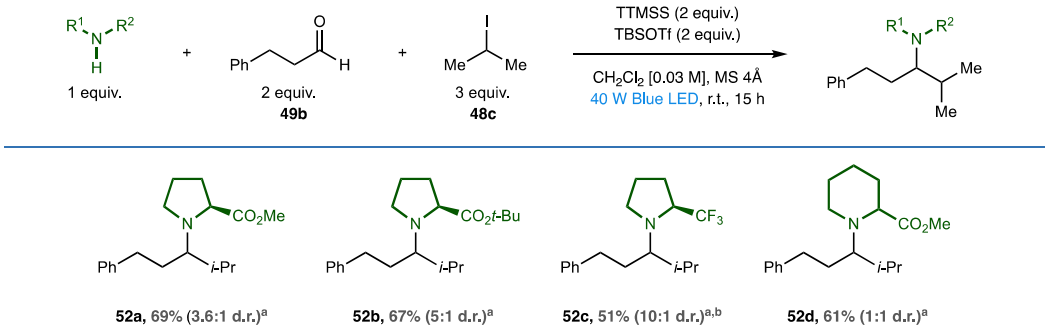
A broader set of cyclic amines were then evaluated (**50a-50i**, scheme 45). The ability to use cyclic amines in the CAA-reaction is important because they would be challenging to synthesize using any of the radical or organometallic additions to activated imines (see section 2.1.1). Since these employ activating auxiliaries to enable the alkylation step, a second deprotection step is required to afford primary amines which in turn can only be converted into a limited number of aliphatic heterocycles through dialkylation. The azetidine-based tertiary amine **50a** was obtained in a low 22% yield – presumably due to unfavourable iminium ion formation resulting from the strain induced by the exocyclic C=N bond. Nevertheless, the ability to form azetidinyl-products even in low yield is important as the azetidine core can be found in a wealth of pharmaceutical agents.[281] Furthermore, to the best of the authors knowledge, alkylation of unbiased azetidinyl iminium ions has not been reported and Strecker addition to azetidinyl iminium ions required activating groups on the C=N carbon atom in order to proceed.[282] Moving to larger aminyl rings (pyrrolidine, piperidine and azepane) afforded the desired tertiary amines in high yields (**50b-50d**). The isolation of these compounds was simplified by washing the ammonium salt of the product with hexane to remove non-ionic by-products. However, the isolated yields were generally 10%-20% lower than those measured by ^{1}H NMR. For example, fused bicyclic amines **50e** and **50f** were both obtained in > 40% yield by ^{1}H NMR but purification *via* chromatography resulted in poor isolated yields. Akin to **50a**, the lesser ability of a fused bicyclic system to accommodate an iminium ion without inducing significant angle and torsional strain is likely the reason for the low yields observed. Similarly, electron-deficient pyrrolidine **50g** is likely to

disfavour iminium ion formation resulting in low yields. The synthesis of nicotine-derivative **50h**, on the other hand, is hampered by competing Minisci-type addition to the pyridine under acidic conditions. Encouragingly, complete chemoselectivity was observed when nortropinone, presenting a cyclic ketone moiety, could be reacted to afford **50i** in 60% yield without affording any self-condensation side-reactions.



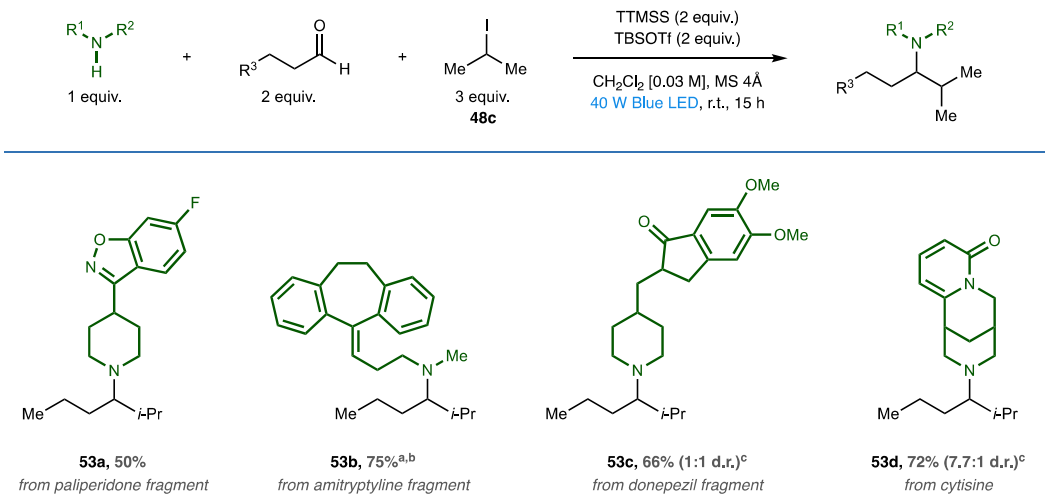
Scheme 46 | Heterocyclic amine scope of the CAA-reaction. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard. [b]Amine, aldehyde and MS 4Å in CH_2Cl_2 were pre-heated at 80 °C for 1 h.

Piperidine is the most common aliphatic heterocycle in pharmaceutical agents and substantial efforts have been directed towards the synthesis of this motif.[283] In the CAA-reaction, 4-substituted piperidines were well-tolerated (**51a** & **51b**) but the standard conditions did not afford any product with the sterically hindered 2,6-dimethylpiperidine (to afford **51c**, Scheme 46). However, heating the amine and aldehyde at 80 °C for one hour before adding the remaining reagents afforded **51c** in 32% yield. Tetrahydroisoquinoline **51d** was obtained in a poor 38% yield by ^{1}H NMR. This could be rationalized, in part, by its fused bicyclic nature hampering condensation, but also the potential intramolecular decomposition of the aminium radical cation intermediate, to afford a stabilized benzylic radical, could also outcompete the desired hydrogen-atom transfer.[284] Other aliphatic heterocycles could also be employed; morpholine and thiomorpholine gave tertiary amines **51e** & **51f** in high yields. Similarly, piperazine-based heterocycles were also well tolerated, giving **51g** & **51h** in 57% and 64% yield respectively and seven-membered heterocycle **51i** was also obtained in high yield.



Scheme 47 | α-Substituted heterocyclic amine scope of the CAA-reaction. [a]Amine, aldehyde and MS 4Å in CH_2Cl_2 were pre-heated at 80 °C for 1 h. [b]*Reaction conducted by Dr. R. Kumar.*

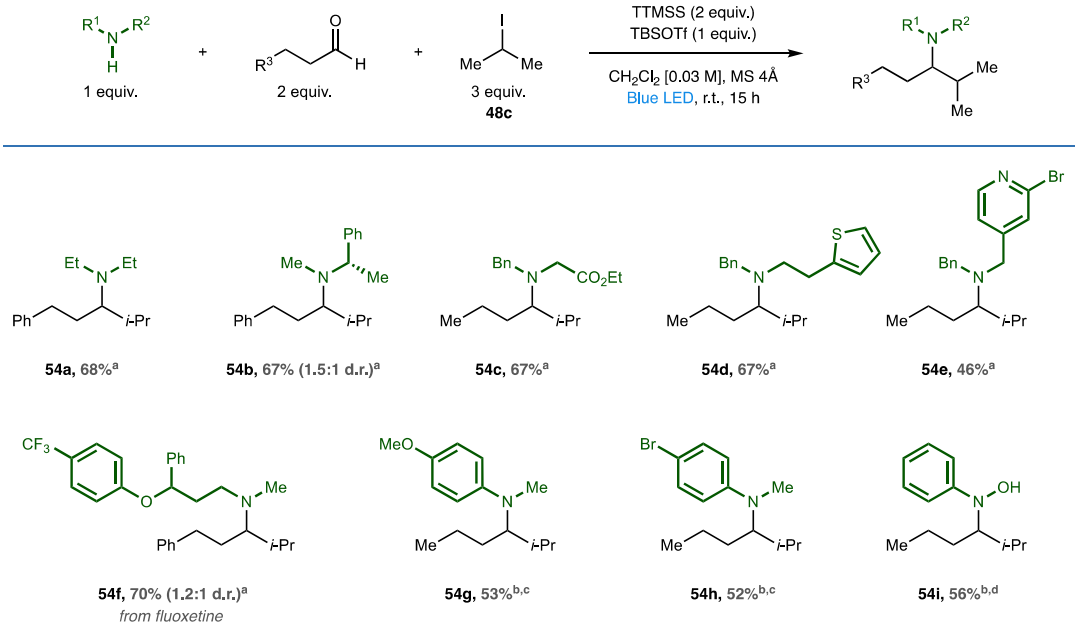
In previous reports of radical addition to C=N bonds, enantioenriched amines with an α-stereogenic center could impart stereoselectivity in the 1,2-addition.[142] A similar result was obtained in the CAA-reaction; the methyl ester of (*S*)-proline afforded the alkylated product **52a** in 3.6:1 d.r. and 69% yield (Scheme 47). Upon making the α-substituent more hindered, the selectivity increased to 5:1 d.r. (for the *tert*-butyl ester, **52b**) and 10:1 d.r. (using 2-trifluoromethylpyrrolidine). These results are in accordance with the A-value of the corresponding substituents. For example, a primary alkyl ester has an A-value of 1.2 (giving 3.6:1 d.r.) but when the bulkier trifluoromethyl group was employed (A = 2.1), the diastereoselectivity increased to 10:1 (**52c**).[285] In contrast to the pyrrolidine scaffolds, α-substituted piperidine did not impart any stereoselectivity and **52d** was obtained in 1:1 d.r. and 61% yield.



Scheme 48 | Scope of pharmaceutical agents or fragments in the CAA-reaction. [a]*Reaction conducted by Dr. R. Kumar.* [b]1 equiv. TBSOTf. [c]Amine, aldehyde and MS 4Å in CH_2Cl_2 were pre-heated at 80 °C for 1 h.

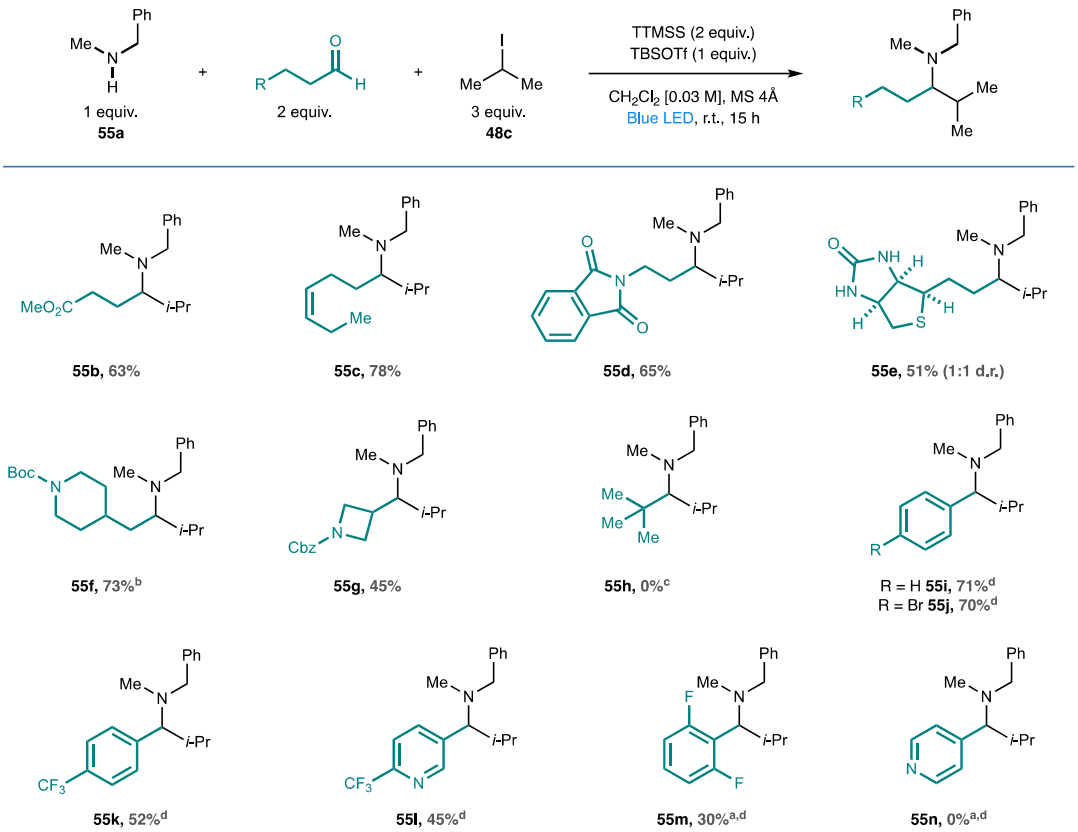
We next evaluated the compatibility of the CAA-reaction with amine scaffolds commonly encountered in pharmaceutical agents (Scheme 48). A reaction using the isoxazole fragment from paliperidone afforded **53a** in 50% yield and amitriptyline-derived tertiary amine **53b** was obtained in 75% yield. In neither case was promiscuous reactivity with other functional moieties such as the benzisooxazole (in

53a) or the styrene moieties (in **53b**). The electron-rich aromatic fragment of donepezil was well tolerated (**53c**) and cytisine could be used to afford **53d** in 72% yield.



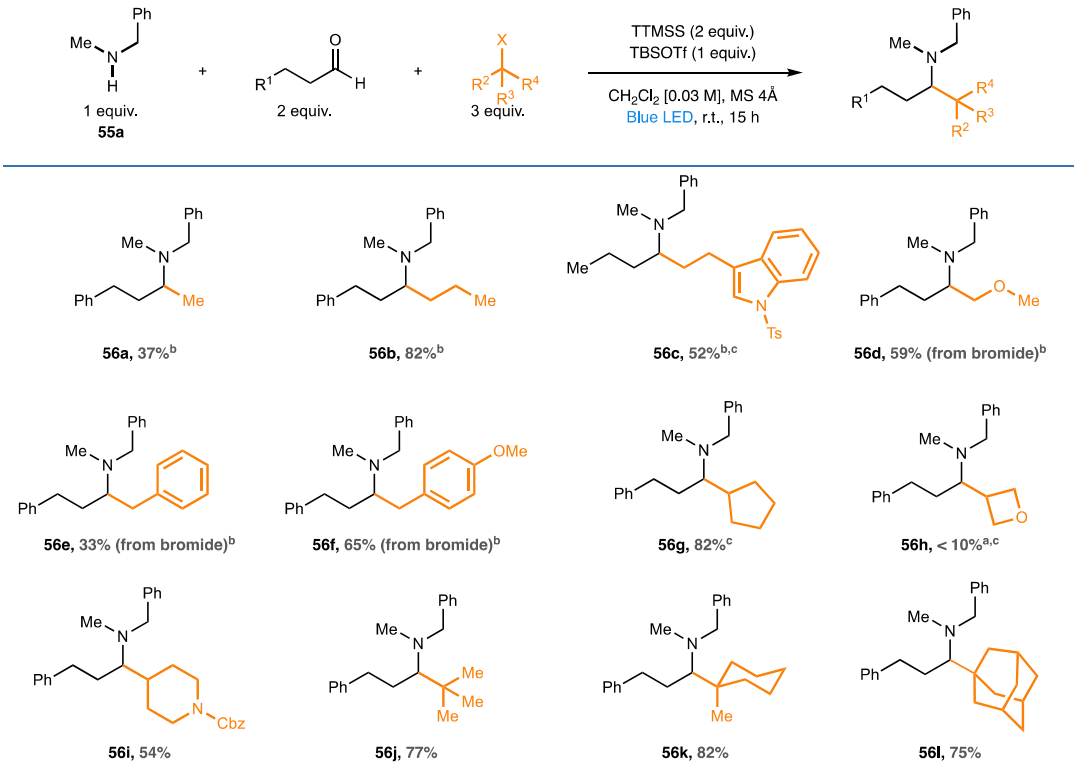
Scheme 49 | Scope of pharmaceutical agents or fragments in the CAA-reaction. [a]*Reaction conducted by W. G. Whitehurst.* [b]*Reaction conducted by Dr. R. Kumar.* [c]2 equiv. TBSOTf. [d]3 equiv. TBSOTf.

Dr.W. G. Whitehurst showed that acyclic amines were excellent substrates in the CAA-reaction, affording diethyl-substituted tertiary amine **54a** in 68% yield (Scheme 49). Unlike the proline-based cyclic amines, however, poor stereoselectivity was observed when a stereocenter was included on an acyclic scaffold (**54b**). A range of functional groups could be included in the amine component such as esters (**54c**), thiophene (**54d**), pyridine (**54e**) and electron-rich aromatics (**54f**). Interestingly, little or no competing reductive amination product was observed apart from when the amine carried an adjacent electron-withdrawing group such as **54c**, where 23% of the corresponding reductive amination product was formed. Dr.R. Kumar showed that anilines were compatible in the CAA-reaction, affording **54g** and **54h** in 53% and 52% yield respectively. The reaction could even be extended to use *N*-phenyl hydroxylamine hydrogen chloride as the starting material to afford hydroxylamine **54i** in 56%, which could be used as a precursor for the corresponding secondary aniline following reduction.[286]



Scheme 50 | Aldehyde scope of the CAA-reaction. *All reactions were conducted by Dr. R. Kumar*. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard. [b]No acid. [c]Amine, aldehyde and MS 4Å in CH_2Cl_2 were pre-heated at 80 °C for 1 h. [d]2.5 equiv. TMSOTf instead of TBSOTf.

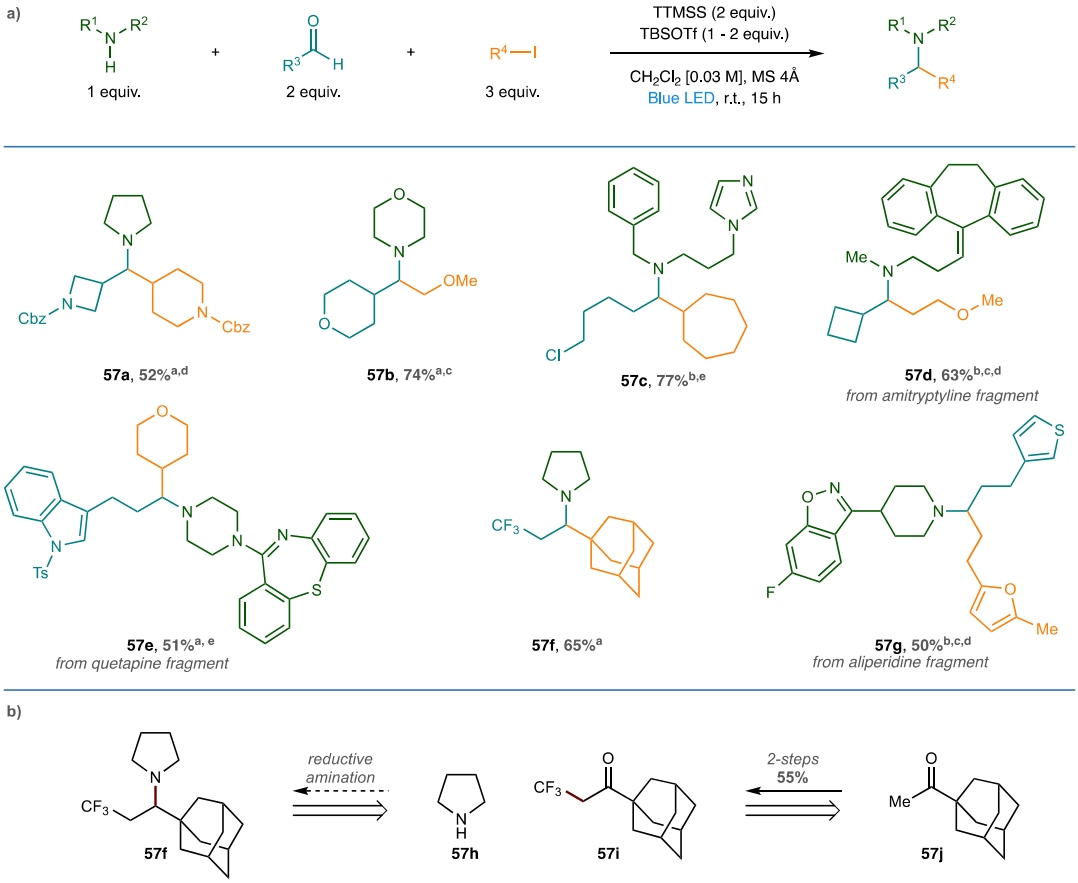
In evaluating the aldehyde component, Dr. R. Kumar found that a range of aliphatic aldehydes were competent under the reaction conditions (**55b**–**55g**, Scheme 50). Biologically relevant motifs such as biotin could be incorporated and piperidine and azetidine features were tolerated in 73% and 45% yield respectively. Aromatic aldehydes were also competent in the reaction (**55i** – **55m**). Electron-rich aldehydes generally afforded higher yields (e.g. **55i** & **55j**) whilst electron-deficient examples gave lower yields of the product. Sterically hindered aldehydes such as pivaldehyde (**55h**) or electron-deficient pyridinecarboxaldehyde (e.g. **55n**) afforded no or low yields.



Scheme 51 | Alkyl halide scope of the CAA-reaction. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard. [b]5-10 mol% ethyl 2-iodo-2-methylpropionate was added. [c]*Reaction conducted by W. G. Whitehurst.*

In evaluating the alkyl halide scope, both methyl and *n*-propyl radicals, affording **56a** & **56b**, were competent reaction partners although the yield of the former was decreased due to its lower nucleophilicity and high reactivity (Scheme 51). However, the ability to use methyl radicals is important as methylation is often used to probe and modulate binding properties of pharmaceutical lead compounds.[287] It is important to note that when primary alkyl halides were used, ethyl 2-iodo-2-methylpropanoate was added as an initiator.[288] For example, in the absence of initiator, tertiary amine **56b** was obtained in 53% yield as compared to 92% yield (by ^{1}H NMR) with initiator. The indole moiety was readily tolerated (**56c**) and α-heteroatom and benzylic radicals (**56d**-**56f**) all afforded the desired product in moderate to good yields. The lower yield of **56e** is likely due to a fast β-scission of the aminium radical cation, which has been observed previously.[289] Introducing a *para*-methoxy group on the benzylic radical (to afford **56f)** increased the yield to 65% – presumably the more electron-rich radical undergoes 1,2-addition with a greater rate constant. In the case of stabilized radicals (e.g. **56d**-**56f**), alkyl bromides were employed as the corresponding iodides were prone to decomposition. Importantly, the alkyl bromides were only competent in the presence of a sub-stoichiometric amount of ethyl 2-iodo-2-methylpropanoate, affording no product in its absence. Secondary alkyl radicals could also be used, affording **56g** in 82% yield. Heterocyclic alkyl radicals were then tested; the 4-piperidinyl radical afforded **56i** in 54% yield whilst the 3-iodooxetane only afforded **56h** in low yield. Oxetanyl-radicals have been employed in radical addition to pyridinium ions but in consistently moderate to poor

yields.[290] More electron-rich tertiary alkyl radicals were potent reaction partners, affording consistently high yields of the resulting tertiary amines (**56j-56l**).



Scheme 52 | a) Mixed scope of the CAA-reaction. b) Alternative route to synthesize **57f** without CAA. [a]2 equiv. TBSOTf. [b]1 equiv. TBSOTf. [c]5-10 mol% ethyl 2-iodo-2-methylpropionate was added. [d]*Reaction conducted by Dr. R. Kumar.* [e]*Reaction conducted by W. G. Whitehurst.*

The strength of the three-component CAA-reaction lies in its ability to rapidly access complex, pharmaceutically relevant structures in a single synthetic step. For example, **57a** containing three heterocyclic amines could be obtained in 52% yield as could a number of drug fragment containing tertiary amines (**57b-57g**, Scheme 52a). These examples not only highlight the ease with which highly polar motifs can be readily assembled but also showcase how the CAA-reaction can reduce the number of synthetic steps required to access such scaffolds. As a comparison, **57f** could alternatively be disconnected through a reductive amination reaction to afford pyrrolidine **57h** and known ketone **57i**, previously prepared in two steps from **57j** in moderate 55% yield (Scheme 52b).[291] Reductive amination between a sterically hindered ketone and a secondary amine is known to be highly challenging and constitutes a significant limitation of the reductive amination reaction.[27] In contrast to this lengthy and likely low-yielding sequence, the CAA-reaction can afford **57f** in 65% yield in a single synthetic step from commercial starting material.

2.4.2 Mechanistic investigations of the CAA-reaction

In order to deepen the understanding for the light-mediated CAA-reaction, a few mechanistic scenarios were considered. The key bond-forming step of the mechanistic hypothesis outlined in scheme 44 is the addition of an alkyl radical to an all-alkyl iminium ion (Figure 12). However, it is also conceivable that the reaction might proceed through an α-amino radical which could undergo radical recombination to form the same product.

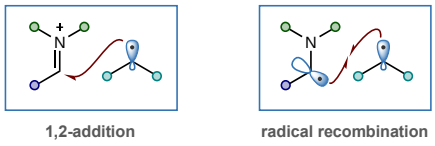
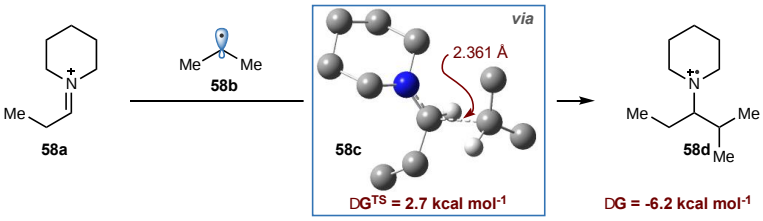


Figure 12 | Two possible mechanistic scenarios for the CAA-reaction.

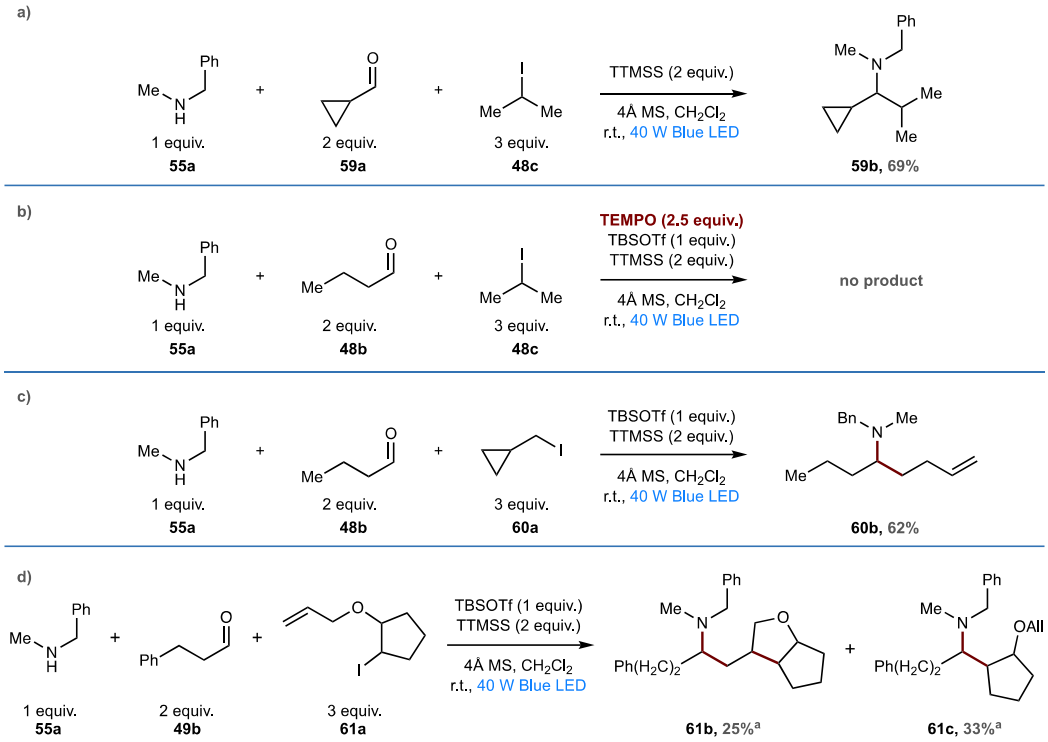
The feasibility of a radical addition to an all-alkyl iminium ion was first probed by density functional theory (DFT) calculations. Using a functional (UTPSS) and a basis set (def2-QZVP) previously benchmarked for radical addition to unsaturated bond,[292] the addition of *iso*-propyl radical **58b** to piperidine-derived iminium ion **58a** was found to exhibit an early transition state (**58c**) with an activation energy of +2.7 kcal mol^{-1} and was overall exothermic (ΔG = -6.2 kcal mol^{-1})(Scheme 53), suggesting a feasible, albeit potentially reversible, radical addition step. It is instructive to compare these values with those typically observed for radical addition to alkenes, where $\Delta G^{TS} \approx 0$ to +10 kcal mol^{-1} and ΔG ≈ -5 to -43 kcal mol^{-1}.[293] The exothermicity of the radical addition is in the lower range of what has typically been observed for alkyl radical addition to alkenes, reflecting the lack of stabilization of the aminium radical cation **58d**. At the same time, the low barrier of activation indicates substantial polar effects in the transition state. As to the geometric features of the transition state, it proceeds via an early transition state with a long bond distance of the forming C–C bond (2.361 Å) whilst at the same time exhibiting an angle-of-attack of the *iso*-propyl radical of 109°, close to that observed in the product.



Scheme 53 | DFT-modelling (UTPSSTPSS/def2QZVP) of the radical addition of isopropyl radical **58b** to model iminium ion **58a**.

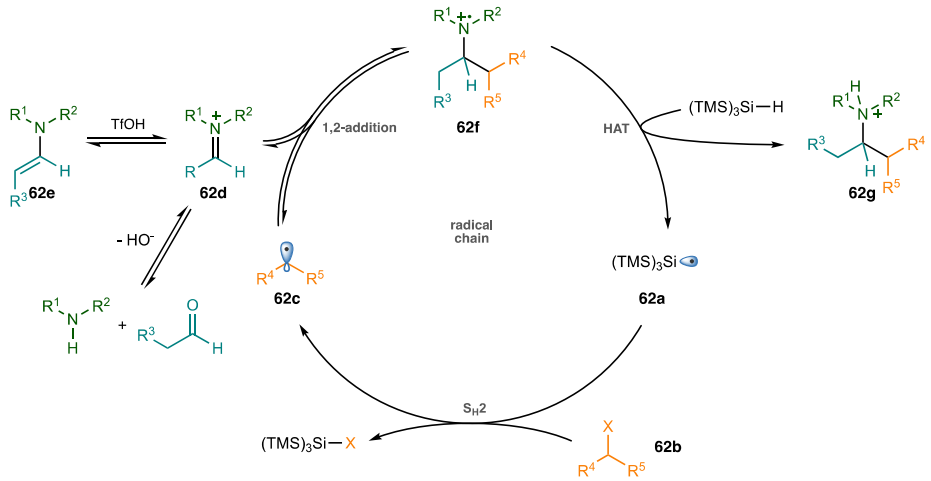
A set of control reactions were then carried out to probe the radical nature of the reaction and the possibility of an α-amino radical mechanism (Scheme 54). Dr. R. Kumar subjected cyclopropyl carboxaldehyde **59a** to the reaction conditions, affording **59b** in 69% yield. The absence of ring-opened

product was interpreted as evidence against an α-amino radical mechanism. Importantly, to avoid any Lewis acid-mediated ring-opening of the cyclopropyl moiety, TBSOTf was omitted in this experiment. Evidence of radical intermediates was obtained from experiments with TEMPO as a radical trap, affording no product (Scheme 54b), and through the use of iodomethylcycloprane **60a** which underwent ring-opening to form alkene **60b** in 62% yield (Scheme 54c). W. G. Whitehurst undertook further radical clock experiments, subjecting alkyl iodide **61a** to the reaction conditions (Scheme 54d). This afforded a mixture of cyclized **61b** and uncyclized products **61c** in a 1.3:1 ratio. Given that the rate of radical cyclization of the 1-hexenyl radical is known (k = 1.0 x 10^5 s^{-1}),[74] this provides an estimate of the rate of secondary radical addition to iminium ions at ≈ 10^5 M^{-1} s^{-1}.



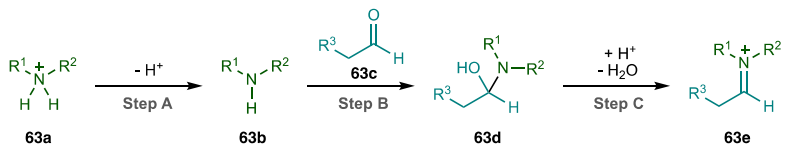
Scheme 54 | a) Experiment to probe the existence α-amino radical intermediates. *Experiment conducted by Dr. R. Kumar.* b) Experiment with TEMPO as a radical inhibitor or trap. *Experiment conducted by Dr. R. Kumar.* c) Experiment to probe the existence of radical intermediates from the alkyl halide component. *Experiment conducted by Dr. R. Kumar.* d) Experiment to probe the existence of radical intermediates from the alkyl halide component and the rate of radical addition to the iminium ion. *Experiment conducted by Dr. W. G. Whitehurst.* [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

Based on these data, together with the known ability of silyl radicals to abstract halogen atoms from alkyl halides and the previously reported abstraction of weakly bound hydrogen atoms by ARCs, a radical chain mechanism can be proposed (Scheme 55). Following an initiation step, a silyl radical **62a** abstracts a halogen atom from an alkyl halide **62b** to afford alkyl radical **62c**. Meanwhile, iminium ion **62d** is formed from enamine **62e** following protonation by *in-situ* generated triflic acid. Alkyl radical **62c** then undergoes 1,2-addition to iminium ion **62d** to form ARC **62f** which, after HAT affords the protonated product **62g**.



Scheme 55 | Proposed radical chain mechanism of the CAA-reaction.

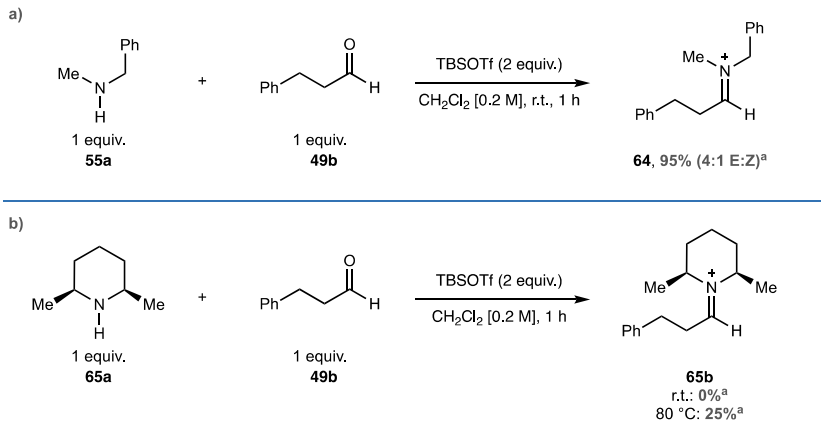
It is noteworthy, that the radical chain is essentially identical to that suggested by Giese and Chatgilialoglu for the TTMSS mediated Giese addition of alkyl halides to electron-deficient alkenes.[294] The polarization of the C=N bond provided by the positive charge mimics the effects of the cyano or ester substituents of acrylonitrile or acrylates and provides favourable polar effects in the transition state.[84] However, despite these conceptual similarities, several mechanistic aspects of the CAA-reaction distinguishes it from the Giese-addition. An important consideration is the ability to form iminium ion **62d** in high concentration in order to favour the rate of formation of **62f** (Scheme 55). Otherwise, alkyl radical **62c** can undergo undesired side-reactions (see section 1.3.1.3). The ability to form iminium ion **62d** is dependent on both kinetics and thermodynamics. Kinetically, the rate-determining step of iminium formation under acidic conditions has been found to be the deprotonation of protonated amine **63a** (Step A, scheme 56)[295] or the nucleophilic attack by the amine **63b** to the carbonyl moiety of **63c** (Step B, Scheme 56).[296] That makes it difficult to predict the electronic effects on the rate of iminium formation, as an electron-rich amine lowers the rate of step A whilst it increases the rate of step B.



Scheme 56 | Mechanism of iminium ion formation from a protonated amine.

Increased steric hindrance in the amine or aldehyde components, however, is generally detrimental to the rate of iminium formation. For example, iminium ion **64** can be formed in essentially quantitative yield within one hour but no 2,6-dimethylpiperidine-derived iminium ion **65b** is observed under identical reaction conditions (Scheme 57a & 57b). However, upon preheating 2,6-dimethylpiperidine **65a** and hydrocinnamaldehyde **49b** for 1 hour and then adding TBSOTf, **65b** is obtained in 30% yield.

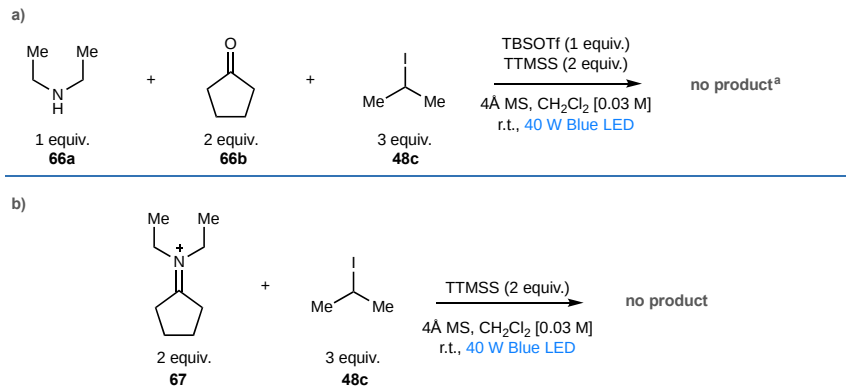
Indeed, the yield of iminium ion formation was strongly correlated with the outcome of the CAA-reaction – methylbenzylamine-derived tertiary amine was obtained in 96% yield (by ^{1}H NMR, see **68** in table 3) while that of 2,6-dimethylpiperidine (via iminium ion **65b**) was isolated in 32% yield (see **51c**, scheme 46).[297]



Scheme 57 | a) Synthesis of iminium ion **64**. b) Synthesis of iminium ion **65b**. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

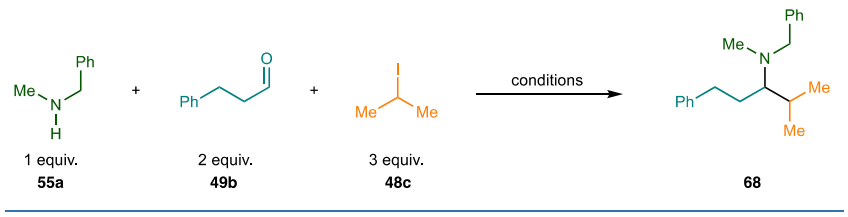
The thermodynamic stability of the iminium ion is also an important factor. For example, Richard and co-workers found that the iminium ion derived from glycine and 4-pyridinecarboxaldehyde was less stable than that derived from glycine and benzaldehyde.[298] This can be understood through an inductive electron-withdrawing effect of the pyridine moiety, destabilizing the positively charged iminium ion. This effect was observed in the CAA-reaction, where benzaldehyde afforded tertiary amine **55i** in 71% yield whereas 4-pyridinecarboxaldehyde gave no product (Scheme 50).

Steric and electronic factors also influence the reactivity of iminium ion **62d** (Scheme 55) towards radical addition. For example, the reaction of diethylamine, cyclopentanone and 2-iodopropane under standard CAA conditions with or without heating afforded no desired product (Scheme 58a). This could be the consequence of either a) low yield of iminium ion formation or b) poor reactivity of the iminium ion with the *iso*-propyl radical. To rule out the former, the tetrafluoroborate salt of iminium ion **67** was prepared, isolated and subjected to the reaction conditions but again, no desired product was observed (Scheme 58b). This observation, that substitution at the reacting carbon atom of the unsaturated bond hampers reactivity, is well-known from Giese addition to 2,2-disubstituted acrylates.[84,293] In this case, it is likely that the additional substituent c.f. aldehyde-derived iminium ions not only increases the steric hindrance but also decreases the electrophilicity of the C=N bond due to hyperconjugation. Together, all these factors can decrease the rate of radical addition to the C=N bond to such an extent that deleterious side-reactions become competitive (c.f. section 1.3.1.3).



Scheme 58 | a) Attempts towards using ketones in the CAA-reaction. b) Experiment using a pre-formed, ketone-derived iminium ion in the CAA-reaction. [a]Reaction was tested with and without pre-heating.

Another crucial difference between the mechanism outlined in scheme 55 and the classical radical chain mechanism for the Giese addition lies in the mode of initiation. Classically, stannane- or silane-mediated radical reactions are initiated through UV-light (to homolyze alkyl halides) or through the thermal decomposition of radical initiators such as AIBN. However, in the CAA-reaction these conditions are not productive, affording little or no yield (Entries 1 & 2, Table 3). Using acid-free, standard CAA conditions on the other hand afforded **68** in 82% yield with 15% reductive amination product. Interestingly, AIBN could be used as an initiator under acidic conditions (Entry 4) but the reaction is less efficient than under light irradiation (Entry 5). Upon conducting the reaction in darkness, only trace amounts of product were obtained.



Entry	Conditions	Yield **68** (%)
1	Bu_3SnH, AIBN, 70°C	0%
2	TTMSS, AIBN, 70°C	< 10%
3	TTMSS, r.t., 40 W Blue LED	82% (15%)
4	TTMSS, AIBN, TBSOTf, 70°C	75% (25%)
5	TTMSS, TBSOTf, r.t., 40 W Blue LED	96%
6	TTMSS, TBSOTf, (no 40 W Blue LED)	trace

Table 3 | Control reactions for the CAA-reaction to evaluate different radical initiation systems.

Two conclusions can be drawn from the results presented in table 3. The high yield observed (albeit with significant amounts of by-product) with TTMSS/AIBN/TBSOTf (entry 4) suggests that light is not necessary in order to sustain the radical chain. Together with the lack of reactivity when light is removed (entry 6), this suggests that the blue LED provides a mild initiation pathway at room temperature in the presence of TTMSS and TBSOTf. Initially, it was hypothesized that 2-iodopropane **48c** was homolyzed by a small number of higher energy, near-UV photons emitted by the blue LED as suggested previously by Studer and co-workers.[299] This would also rationalize why alkyl bromides,

whose C–Br bond is ≈ 16 kcal mol^{-1} stronger than a C–I bond and hence require shorter wavelength light to homolyze, were only competent in the presence of ethyl 2-iodo-2-methylpropanoate. To test this hypothesis, the emission spectrum of the blue LED was compared with the absorption spectrum of **48c**. However, essentially no overlap was observed, suggesting that the reaction is not initiated by direct homolysis of the alkyl halide.

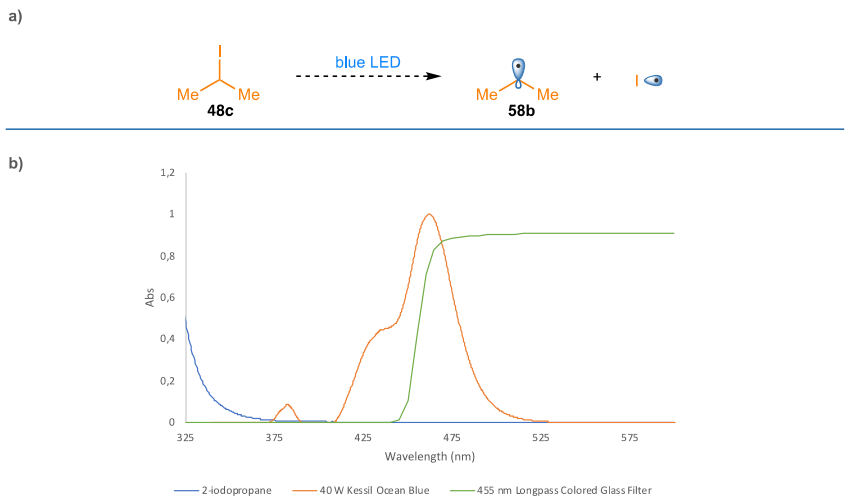
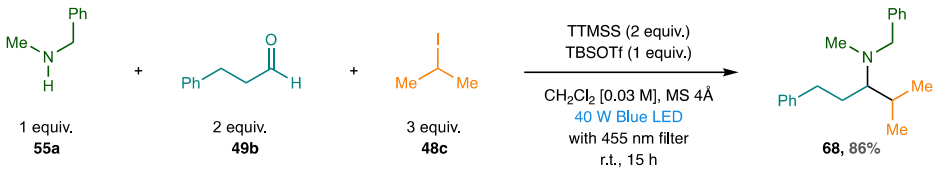


Figure 13 | a) Possible radical initiation pathway. b) UV-vis studies to elucidate the role of the alkyl halide during initiation. *Experiment conducted by Dr. R. Kumar.*

To strengthen this finding, the reaction was performed using a long-pass filter, which removes all photons below 455 nm, and hence would provide no overlap with the absorption spectrum of 2-iodopropane. Under these conditions, the product **68** was obtained in a still excellent 86% yield (c.f. 96% without filter), clearly demonstrating that another light-mediated initiation pathway must be operative (Scheme 59).



Scheme 59 | Control reaction using 455 nm long-pass filter. *Experiment conducted by Dr. R. Kumar.*

The fact that the reaction could be initiated through the use of ethyl 2-iodo-2-methylpropanoate is significant as it implies the involvement of the alkyl iodide in the initiation step. In other words, any mechanistic rationale must involve both an alkyl iodide and visible light. This rule out hypotheses such as light-mediated excitation of iminium ions that could afford open-shell species which could abstract a hydrogen atom from TTMSS. An alternative hypothesis would rely on the known ability of enamines (e.g. **69a**) to be absorb visible light to form a potent reductant (**69b**, Figure 14a).[300,301] This species could then affect a single-electron reduction of the alkyl halide (e.g. **48c**). However, akin to a direct

excitation of alkyl iodides by visible light, this requires overlap between the photons of the blue LED and the absorption spectrum of the enamine. Although a minor overlap at 375 nm could be observed, when the long-pass filter is applied no overlap occurs, suggesting that this is not a viable hypothesis (Figure 14b).

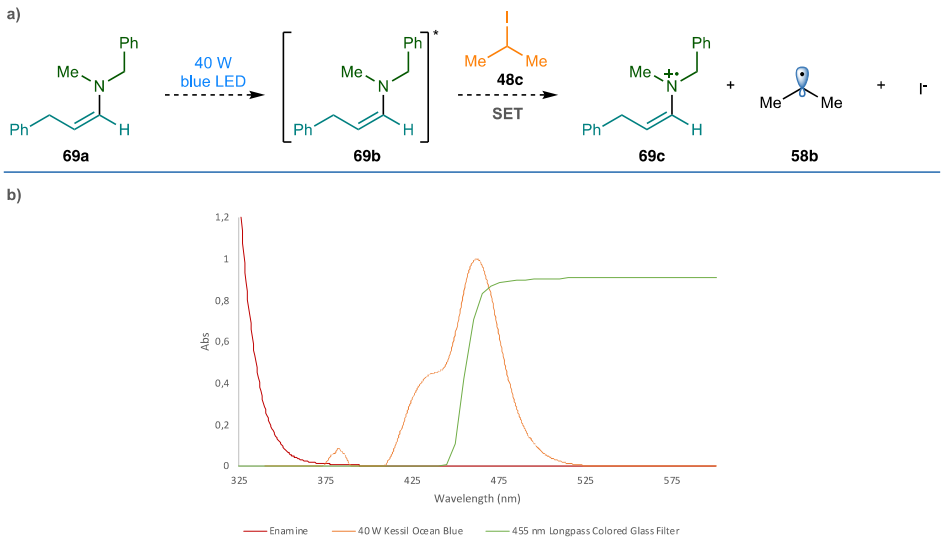


Figure 14 | a) Possible mechanism of radical initiation via excitation of an enamine intermediate. b) UV-vis studies to elucidate the role of an enamine intermediate in radical initiation. *Experiment conducted by Dr. R. Kumar.*

The presence of transient electron donor-acceptor (EDA) complexes was then considered. An EDA complex can absorb a photon of lower energy light than either of the donor or acceptor components on their own, a feature which, if the light absorbed is in the visible region, can render a solution of an EDA complex colored despite each individual component being colourless.[302] Absorption of a photon leads to the transfer an electron within the complex, from the donor to the acceptor, to a radical pair. Alkyl halides have previously been used as "acceptors" in EDA complexes and enamines[303] and TTMSS[304] have both been used as "donors". Therefore, mixture of 2-iodopropane (**48c**) and either enamine (**69a**) or TTMSS were studied by UV-vis spectroscopy (Figure 15a & 15b). However, no red-shift in the > 450 nm region was observed when the UV-vis spectra were recorded (Figure 15c & 15d).

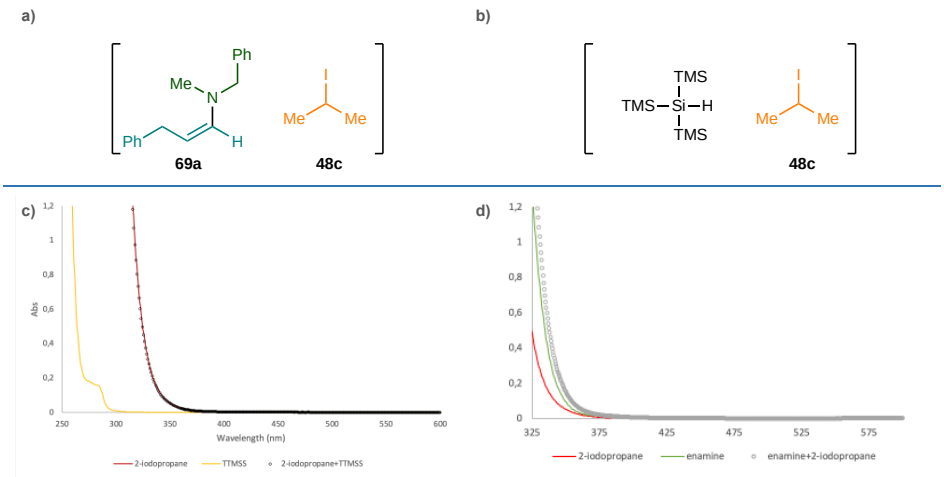


Figure 15 | a) Possible EDA-complex between an enamine intermediate and the alkyl iodide. b) Possible EDA-complex between TTMSS and the alkyl iodide. c & d) UV-vis studies to elucidate the existence of EDA-complexes between the alkyl iodide and either an enamine or the silane. *Experiment conducted by Dr. R. Kumar.*

Lacking a convincing mechanistic rationale for the initiation step, more complex reaction mixtures were studied. Specifically, upon combining TTMSS, enamine **69a** and 2-iodopropane, a new red-shifted band was observed in the UV-spectrum (Figure 16a). Significantly, this band extended beyond the shorter wavelengths blocked by the 455 nm long-pass filter and could hence be involved in radical chain initiation. Furthermore, no such red-shifted band was observed for 2-bromopropane, in accordance with the lack of reactivity of this alkyl bromides in the absence of initiator (Figure 16b).

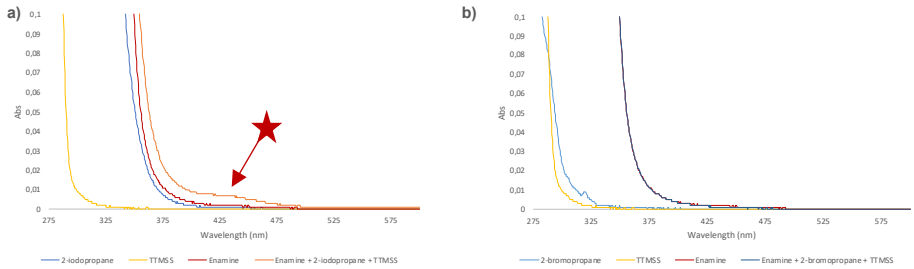
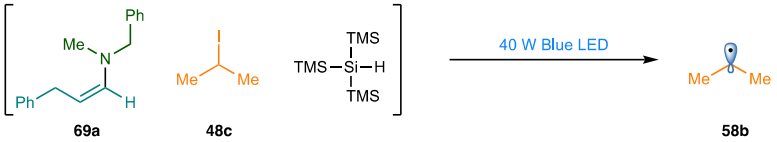


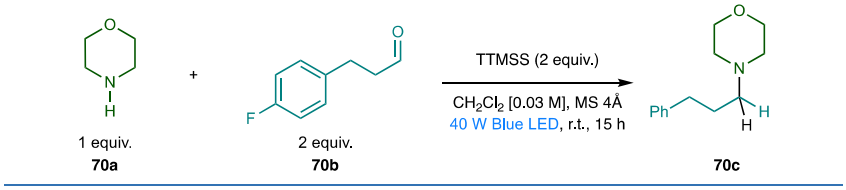
Figure 16 | UV-vis studies to probe the existence of ternary interactions that might affect radical initiation with a) alkyl iodides or b) alkyl bromides. The star highlights the new band observed. *Experiment conducted by Dr. R. Kumar.*

These results could suggest that a ternary interaction between enamine **69a**, iodopropane **48c** and TTMSS occurs to produce an alkyl radical (Scheme 60). In the case of secondary and tertiary iodides, the formed radical will add to the iminium ion to initiate the radical chain. In the case of primary alkyl radicals and alkyl bromides, the initiator (ethyl 2-iodo-2-methylpropionate) replaces the starting material alkyl halide in this ternary mixture and forms an electron-deficient radical which initiates the radical chain by abstracting a hydrogen atom from TTMSS. It is important to note, however, that the existance of a light-absorbing ternary complex is highly speculative. It is possible that the C–I bond is weakened through halogen-bonding to the silane following by electron or energy transfer from enamine **69b** but no direct evidence in this regard has been obtained.



Scheme 60 | Possible origin of radical initiation in the CAA-reaction.

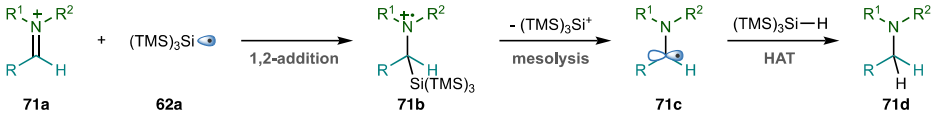
Another important mechanistic aspect to address is the formation of reductive amination by-product (see entry 1, Table 4). Due to the hydridic nature of TTMSS, both polar and radical pathways could be suggested. If reductive amination occurred through a polar pathway, it should proceed in the absence of visible light. However, when morpholine **70a** and aldehyde **70b** were allowed to react in darkness in the presence of TTMSS with or without TBSOTf, no reductive amination was observed (Entries 1 & 2, Table 4). However, when ethyl 2-iodo-2-methylpropanoate and blue LED irradiation were introduced, reductive amination product **70c** was observed in 44% yield, suggesting that a radical pathway was operative.



Entry	Deviation	Yield **70c** (%)
1	None	trace
2	TBSOTf (1 equiv.)	trace
3	TBSOTf (1 equiv.), ethyl 2-iodo-2-methylpropanoate	44%
4	TBSOTf (1 equiv.), no light ethyl 2-iodo-2-methylpropanoate	trace

Table 4 | Control reactions to elucidate the mechanism of the reductive amination by-product.

Considering the mechanistic proposal outlined in scheme 55, upon formation of silyl radical **62a**, this radical can either abstract a halogen atom from an alkyl halide or add across the C=N bond of the iminium ion to form aminium radical cation **71b** (Scheme 61). This is akin to the initial step of the hydrosilylation reaction observed as a by-product in the Giese addition using TTMSS and has been observed in the context of pyridinium ions. However, instead of abstracting a hydrogen atom, **71b** can undergo a rapid mesolysis to afford α-amino radical **71c** and TMS-silylenium cation.[305] The subsequent abstraction of a hydrogen atom from TTMSS by **71c** is slow due to unfavourable polar effects and disfavours the reductive amination pathway during the CAA-reaction. Consequently, reductive amination is only observed when the desired 1,2-addition is slow. However, this mechanism is not consistent with the absence of dimerization by-products that would have been expected following radical recombination of α-amino radical **71c**. Therefore, an alternative hypothesis is a radical-polar crossover mechanism wherein silahemiaminal **71b** undergoes HAT to the aminium radical cation moiety followed by protodesilylation to form **71d**.



Scheme 61 | Possible mechanism of reductive amination side-pathway.

2.5 Summary

This chapter has detailed the development of a multicomponent carbonyl alkylative amination for the synthesis of tertiary amines. Built on the same retrosynthetic logic as the gold-standard reductive amination reaction, it fuses amines, aldehyde and alkyl halides via the action of a simple silane and visible light to afford complex amine scaffolds in a single synthetic step. Proceeding under acidic conditions, the amine and aldehyde reacts to form an electrophilic iminium to which an alkyl radical, generated from the alkyl halide through halogen-atom abstraction, adds to form an aminium radical cation. This intermediate is trapped by a silane reducing agent to afford the product and propagate a radical chain mechanism. The visible light serves to initiate the reaction through a ternary complex, the exact nature of which remains to be elucidated. The scope of the transformation was broad, encompassing alkyl iodides (1°, 2° and 3°), alkyl bromides (2° and 3°), amines (cyclic, acyclic, aliphatic, aromatic) and aldehydes (aliphatic, aromatic). The reaction was tolerant to a range of functional groups, including polar heterocycles which are prevalent in drug discovery. Consequently, it presents a general and modular strategy for tertiary amine synthesis which might be of immediate use in academia and industry alike.

3 Carbonyl alkylative amination employing alcohol- and carboxylic acid-based nucleophiles

3.1 Background

An important area of research in the field of organic radical chemistry has been the development of new alkyl radical precursors.[86] As alkyl radicals are intermediates in a range of C–C, C–N, C–O and C–X bond-forming reactions, the ability to use different precursors unlocks a larger pool of starting materials and enables new retrosynthetic disconnections.[306] Furthermore, it is also important from a functional group tolerance perspective. For example, Nicewicz showed that α-carbamyl radicals could be generated via single-electron oxidation of Boc-protected secondary amines using strongly oxidizing acridinium photocatalysts ($E_{1/2}^{*n/n+1}$ = +2.15 V vs SCE in MeCN).[307] However, these conditions are not compatible with common functional groups such as substituted alkenes ($E_{1/2}^{red} \approx$ +2.0 V vs SCE) or aliphatic amines ($E_{1/2}^{red} \approx$ +0.5 to +1.0 V vs SCE).[173] As a complementary approach, carboxylic acids could be used as precursors instead to generate the same radical intermediate but under milder (less oxidizing) reaction conditions.[308]

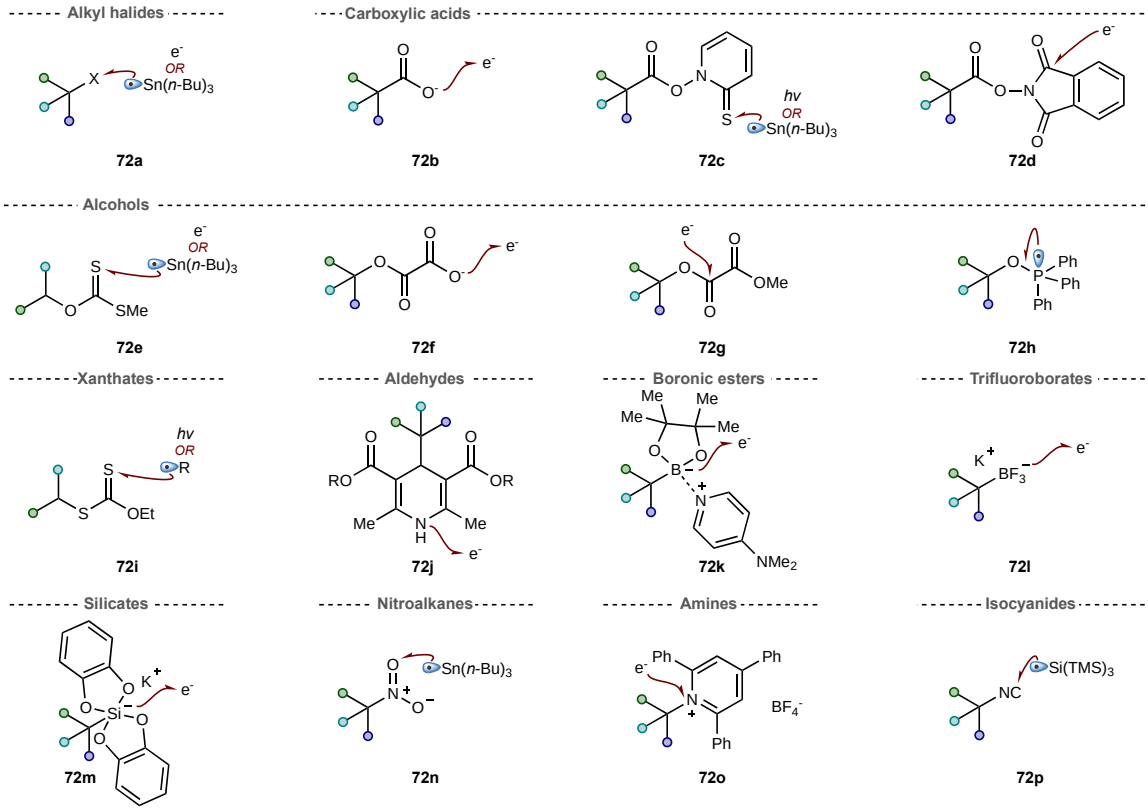
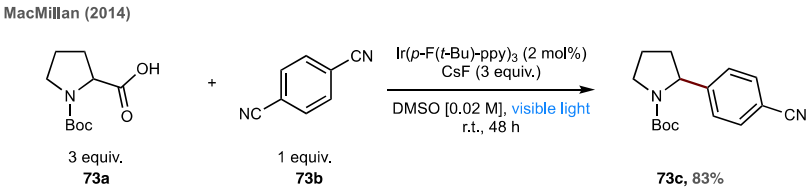


Figure 17 | Alkyl radical precursors from different functional groups showing the initiating step preceding fragmentation and the resulting formation of alkyl radicals.

Historically, alkyl halides (**72a**, figure 17) have been the most commonly employed sources of alkyl radicals, dating back to the experiments of Gomberg (see section 1.3).[72] Following the discovery that

stannyl radicals can cleave C–X bonds (X = I, Br, Cl),[105,309] the *n*-Bu_3SnH/AIBN/R–X radical generation system became a cornerstone of the early applications of radical solutions to synthetic problems.[93,310] Since then, a range of alternative precursors have been developed in order to broaden the scope of fundamental radical modes of reactivity, such as addition to unsaturated bonds, radical recombination or hydrogen-atom transfer.[86]

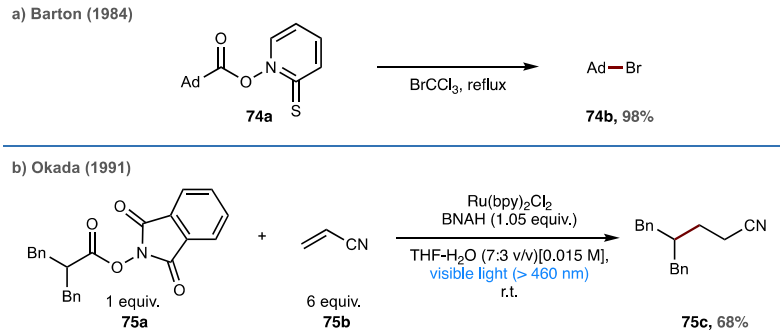
One of the earliest examples of radical precursors are carboxylic acids and their derivatives (**72b**-**72d**, Figure 17). Kolbe used electrochemical oxidation to effect the decarboxylation of carboxylate anions (**72b**)[311] whereas Hunsdiecker and Hunsdiecker used silver salts to affect the halogenation of carboxylic acids and esters.[312] In 2014, MacMillan and Zuo reported a more practical decarboxylation reaction in their photocatalytic generation of α-carbamyl radicals from amino acids (**73a**) mediated by visible light (Scheme 62).[313] Crucially, the presence of a weak base (CsF) ensured deprotonation of the carboxylic acid to form a carboxylate intermediate ($E_{1/2}^{red}$ = +0.95 V vs SCE in MeCN) which can be readily oxidized by Ir(*p*-F(*t*-Bu)ppy)$_3$ ($E_{1/2}^{IV/III}$ ≈ +1.0 V vs SCE). The resulting alkyl radical then underwent radical recombination with the radical anion of **73b** to afford the α-arylated product **73c**.



Scheme 62 | α-Arylation of carbamates via photocatalyst-induced decarboxylation.

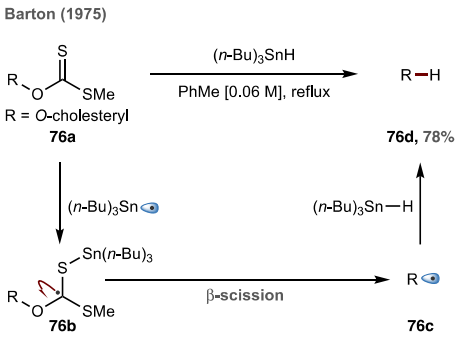
Alkyl radicals can also be generated from carboxylic acid derivatives such as the *N*-hydroxypyridine-2-thione esters (**72c**, figure 17, often referred to as PTOC or Barton esters) which was first introduced by Barton, Crich and Motherwell in 1983 to affect reductive decarboxylation using *n*-Bu_3SnH as a stoichiometric reductant. This method for radical generation has since been employed in numerous settings[314] – for example, Barton reported that PTOC ester **74a** underwent decarboxylation upon addition of a •CCl_3 radical to the thiocarbonyl moiety (Scheme 63a)[315] and the resulting alkyl radical could then be trapped by $BrCCl_3$ to afford an alkyl bromide **74b**. This was an important advance as tertiary alkyl halides are generally challenging to prepare and at the time relied on stoichiometric amounts of heavy metals (c.f. the Hunsdiecker reaction). In 1991, Okada[316] reported that *N*-hydroxyphthalimides (**75a**) were reduced by $[Ru(bpy)_3]^{2+*}$ ($E_{1/2}^{III/II*}$ ≈ -0.81 V vs SCE) to affect a photocatalytic Giese-addition (Scheme 63b). Based on the discovery of the photocatalytic cycle by Deronzier,[176,177] Okada used 1-benzyl-1,4-dihydronicotinamide (BNAH) as a biomimetic, stoichiometric reductant. Importantly, the development of a reductive method to generate alkyl radicals from carboxylic acid derivatives was an important complement to precursors that required oxidizing

conditions and *N*-hydroxyphthalimides have since been extensively applied in the fields of photoredox- and transition metal-catalysis.[317]



Scheme 63 | a) Alkyl halide synthesis from thiohydroxamate esters. b) Giese addition using *N*-hydroxyphthalimide esters as radical precursors.

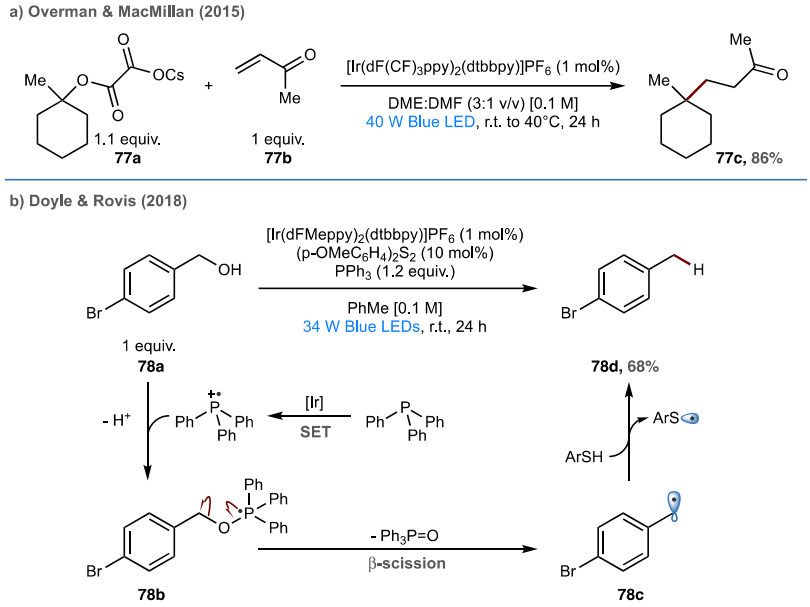
Alcohols have also been frequently used as precursors for alkyl radicals (**72e**-**72h**, Figure 17). Barton and McCombie showed that alcohol-derived dithiocarbonate **76a** underwent efficient deoxygenation to afford alkyl radicals (Scheme 64).[318] The reaction is driven by the formation of a strong C=O bond (upon collapse of intermediate **76b**) instead of the much weaker C=S bond. However, the method is limited to 1° and 2° alcohols as tertiary xanthate esters are challenging to prepare and handle without decomposition *via* the Chugaev reaction[319] (although a few successful examples exist).[320–322]



Scheme 64 | Barton's deoxygenation of dithiocarbonates.

In a complementary approach, Overman and MacMillan[323] expanded on the precedent of Yokoyama[324] to show that oxalate caesium-salts could be oxidized ($E_{1/2}^{red}$ = +1.28 V vs SCE in MeCN) by an iridium-based photocatalyst to induce a double decarboxylation to generate 3° but also 2° alkyl radicals (Scheme 65a). Crucially, the devised method is redox-neutral in nature and hence does not rely on the use of stoichiometric, toxic stannane reducing agents that can be hard to remove from a crude reaction mixture. Studer later showed that oxalate *esters* (**72g**, Figure 17) could be reduced to affect radical decarboxylation and afford tertiary alkyl radicals.[325] Recently, Rovis and Doyle[326] leveraged on the original studies of Buckler[327] and Rogers[328] to use phosphines to deoxygenate unfunctionalized alcohols **78a** *via* a phosphoranyl radical complex (**78b**, Scheme 65b). Specifically, triphenylphosphine ($E_{1/2}^{red}$ = +0.98 vs SCE in DMF) is proposed to be oxidized by the excited state of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$

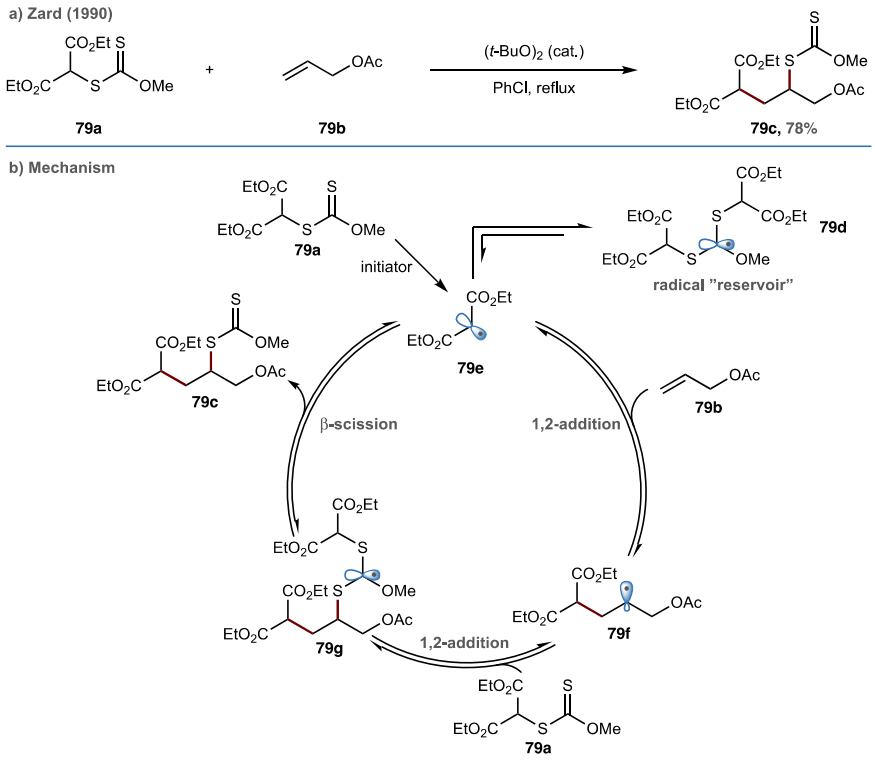
($E_{1/2}^{III*/II}$ = +0.97 vs SCE in MeCN) to afford a phosphine radical cation which is attacked by the nucleophilic hydroxyl group. The resulting phosphoranyl radical **78b** undergoes β-scission, driven by the formation of a strong P=O bond, to afford benzylic radical **78c** which was trapped by a thiol to afford the desired product (**78d**). The thiyl radical then donates an electron to the photocatalyst to turn over the catalytic cycle.



Scheme 65 | a) Overman and MacMillan introduced oxalates as sources of alkyl radicals for redox-neutral Giese addition. b) Doyle & Rovis' deoxygenation of unfunctionalized alcohols.

The xanthate radical precursor (**72e**, figure 17) fragments to form an alkyl radical and a new C=O bond. Zard showed that when the sulfur-atom carries an alkyl group which better stabilizes the forming radical than the group on the oxygen atom, that fragmentation occurs instead. This seemingly subtle change has significant mechanistic implications and enables the addition of alkyl radicals to *unactivated* alkenes (Scheme 66a). In this approach, which has been coined degenerative xanthate transfer, the radical **79d** fragments to form the alkyl radical **79e** through β-scission of the C–S bond in a reversible process (Scheme 66b).[329,330] This equilibrium is biased towards the stabilized radical **79d**, which cannot undergo deleterious radical recombination or disproportionation side-reactions, and hence forms a "reservoir" of radicals that enables a longer effective radical half-life in solution.[331] **79e**, which is present in extremely low concentration, can therefore engage with unactivated acceptor **79b** to form adduct radical **79f**. Importantly, this radical must be *less stable* than **79e**. If this is not the case, then intermediate **79g**, resulting from the trapping of **79f** by **79a**, will reverse to reform **79f** instead of forming the product **79c** and propagating the chain. In other words, the more *endothermic* the radical addition step is, the more efficient the xanthate-transfer reaction will be.[332] This stands in stark contrast to e.g. the Giese addition which typically requires activated alkenes for a productive reaction.[84] In addition, the reversible conditions can be used to reverse the selectivity in radical cyclization reactions

by favouring the thermodynamic 6-*endo*-trig cyclization over the commonly observed 5-*exo*-trig.[333] The resulting xanthate can serve as a functional handle to introduce a range of other functionality.[334]



Scheme 66 | a) Degenerative xanthate-transfer enables radical addition to unactivated alkenes. b) Mechanism of Zard's degenerative xanthate transfer reaction.

Together, alkyl halides, carboxylic acids and alcohols constitute the foundation of alkyl radical precursors. However, a range of other functional groups can also be used to generate radicals (**72j-72p**, Figure 17). Primary amines can be reacted with pyrylium salts to form "Katritzky reagents" such as **72o**. Their low reduction potential ($E_{1/2}^{red} \approx$ -0.9 V vs SCE in DMF) and relative ease of preparation has enabled their use in both C–C and C–B bond-forming reactions but are less efficient in the generation of primary alkyl radicals.[306,335] Nishibayashi[336] and Molander[337] introduced aldehyde-derived dihydropyridines **72j** as alkyl radical sources in photoredox catalysis but the slow rate of alkyl radical fragmentation has largely limited their use to the generation of benzylic radicals. Furthermore, the preparation of tertiary variants of **72j** is hampered by steric hindrance. Ley and co-workers introduced Lewis base-activated boronic esters[338] (and acids)[339] as radical precursors via single-electron oxidation (**72l**), while Molander[340] and Fensterbank[341] have developed a range of C–C bond forming reactions based on the single-electron oxidation trifluoroborates.[342] Whilst the latter radical precursor has been more frequently employed, the method of Ley avoids the synthesis of poorly soluble, charged trifluoroborate salts and the boron Lewis base complexes are more easily oxidized ($E_{1/2}^{red} \approx$ +0.7 V vs SCE in MeCN for **72k** versus $E_{1/2}^{red}$ > +1.0 V vs SCE in MeCN for **72l**). Another disadvantage with trifluoroborates has been inability to use unactivated primary trifluoroborates. To solve this problem,

and to avoid boron fluoride by-products which are challenging to remove after the reaction, Fensterbank introduced catechol silicates **72m** as alkyl radical precursors.[343] Based on earlier studies by Kumada,[344] they found that catechol silicates have lower reduction potentials than trifluoroborates ($E_{1/2}^{red} \approx +1.0$ V vs SCE for **72m**)[274] and readily fragments upon oxidation to afford primary, secondary and tertiary alkyl radicals. Nitroalkanes (**72n**, Figure 17) have also been used to generate alkyl radicals but are less commercially available than other functional groups.[345] Similarly, isocyanides[346] **72p** can afford alkyl radicals in the presence of silyl or stannyl radicals but are synthetically more cumbersome to access.

3.2 Project aims

During the development of the multicomponent carbonyl alkylative amination (CAA) reaction (see Chapter 2), several aspects that impeded its generality and utility were identified. While the reaction exhibited a broad scope in the amine and aldehyde components, the alkyl halide coupling partner presented several deficiencies. For example, although a range of alkyl iodides and bromides have been made commercially available, their availability diminishes in comparison to more common functional molecules such as alcohols or carboxylic acids. The stability of tertiary halides is often poor and the methods by which they can be prepared are limited.[347,348] This also holds true for benzylic or α-heteroatom substituted alkyl halides. Indeed, such halides were so unstable that the bromide derivatives (as the iodide variants were too unstable) had to be purified and used immediately in the CAA-reaction to avoid decomposition. As a consequence, the scope of tertiary nucleophiles, for example, was limited in the CAA-reaction despite the fact that nucleophilic tertiary radicals such as *t*-Bu• afforded products in consistently high yields.

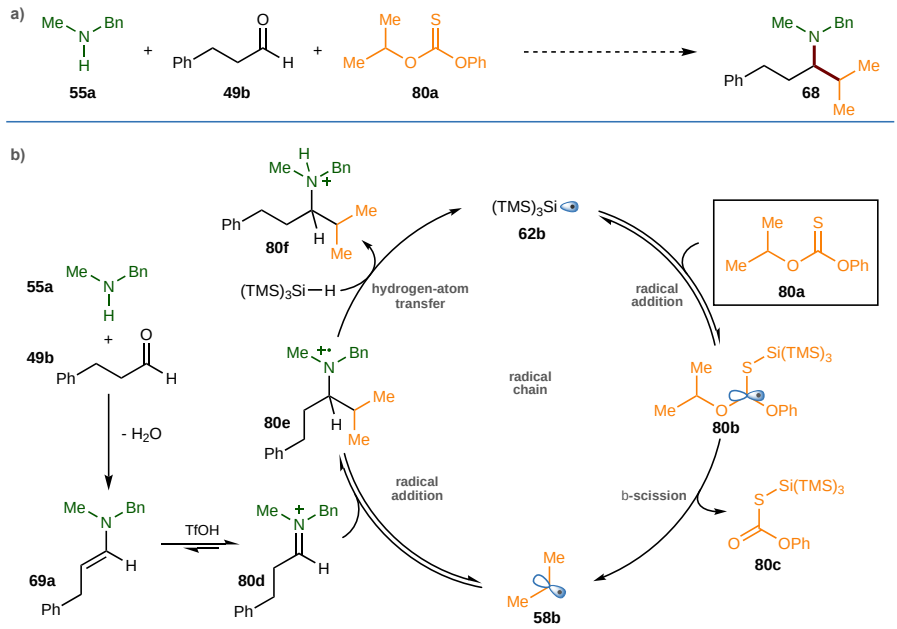
With these deficiencies in mind, the aim of this project was to expand the classes of alkyl radical precursors that could be used in the CAA-reaction described previously (see Chapter 2). The project sought to use precursors that would complement and expand the scope established with alkyl halides with a particular focus on the generation of tertiary and α-heteroatom substituted alkyl radicals.

Due to the collaborative nature of this project, all work undertaken by others (Dr. R. Kumar) than the author is attributed by name both within the text and schemes.

3.3 Results and discussion

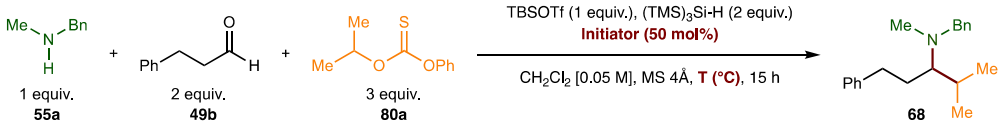
The aliphatic alcohol motif is the most common functional group in natural products and primary, secondary and tertiary alcohols are all widely commercially available.[349] Consequently, alcohol-based alkyl radical precursors were evaluated first. Among the many alcohol-based precursors for alkyl radicals, xanthates presented a particularly compelling alternative in the context of the CAA-reaction.[350]

Mindful that the decomposition of xanthates proceed through the addition of a stannyl radical at the thiocarbonyl moiety,[157] it was hypothesized that the alkyl halide could be directly replaced by a xanthate **80a** (Scheme 67a). In the mechanistic hypothesis, silyl radical **62b** would react with **80a** to afford stabilized radical **80b** instead of abstracting a halogen atom from an alkyl halide (Scheme 67b). Radical **80b** can then undergo β-scission, driven by the formation of a strong C=O bond, and afford alkyl radical **58b**. The alkyl radical **58b** would then react following the reaction mechanism postulated for the original CAA-reaction via addition to an iminium and HAT from the silane to the so-formed aminium radical cation.



Scheme 67 | a) Proposed CAA-reaction using alcohol-derived xanthates as alkyl radical source. b) Proposed mechanism of the CAA-reaction with alcohol-derived xanthates as alkyl radical source.

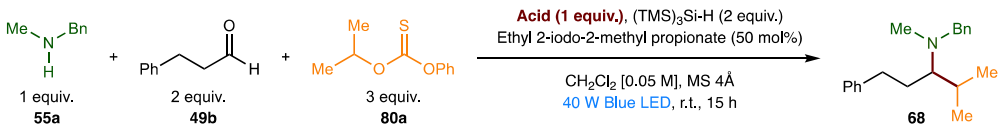
Based on this reasoning, isopropanol-derived xanthate **80a** was subjected to the standard CAA-conditions employing methyl benzylamine **55a** and hydrocinnamaldehyde **49b** as coupling partners, yielding the desired product **68** in 45% yield by ^{1}H NMR (Entry 1, Table 5). The rate of decomposition of the stabilized radical **80b** (Scheme 67) is temperature dependent[157] and therefore several thermal initiators were evaluated. However, classical thermal conditions employing AIBN at 70 °C afforded no product (Entry 2, Table 5) and omission of TBSOTf, which could bind to the thiocarbonyl moiety and hence hinder radical addition, did not afford any product (Entry 3, Table 5). Other initiators with xanthate-based radical precursors, such as benzoyl peroxide[99] or Mn_2CO_{10},[351] were also unsuccessful (Entries 4 & 5, Table 5).



Entry	Initiator	Yield **68** (%)[a]
1	Ethyl 2-iodo-2-methyl propionate, 40 W Blue LED, r.t.	45%
2	AIBN, 70 °C	0%
3	AIBN, no TBSOTf, 70 °C	0%
4	Benzoyl perodixe, 70 °C	0%
5	Mn_2CO_{10}, 70 °C	0%

Table 5 | Evaluation of the effect of initiator on the xanthate CAA-reaction. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

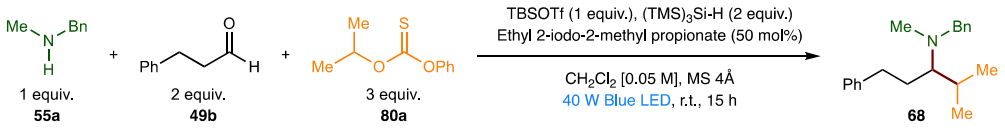
Returning to the light-mediated conditions, the effect of acid additives was evaluated. Increasing the equivalents of TBSOTf resulted in decreased reaction efficiency (Entry 2, Table 6). Replacing TBSOTf with TMSOTf did not significantly impact the reaction outcome but yielded larger amounts of by-products (Entry 3, Table 6). The use of acids with more strongly coordinating counteranions substantially lowered the yield (Entries 4 & 5, Table 6). The effect of counteranions on the reactivity of iminium ions has been systematically studied and trifluoromethanesulfonates have often been used due to their non-coordinating properties.[352] However, no improvement of the reaction yield was observed employing trifluoromethanesulfonate-based Lewis acids, which can generate triflic acid *in-situ*,[353] such as $Sc(OTf)_3$ or $Zn(OTf)_3$ (Entries 6 & 7, Table 6).



Entry	Acid	Yield **68** (%)[a]
1	TBSOTf	45%
2	TBSOTf (2 equiv.)	34%
3	TMSOTf instead of TBSOTf	46%
4	TFA instead of TBSOTf	22%
5	$EtCO_2H$ instead of TBSOTf	14%
6	$Sc(OTf)_3$ instead of TBSOTf	37%
7	$Zn(OTf)_2$ instead of TBSOTf	trace

Table 6 | Evaluation of the effect of acid on the xanthate CAA-reaction. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

Further adjustments of reaction stoichiometry or change of solvents did not afford any improvement (Entries 1-6, Table 7). However, increasing the reaction concentration afforded a slightly increased 61% yield by ^{1}H NMR (Entry 7, Table 7). Under these reaction conditions, a significant amount of amine starting material remained unreacted. Hypothesizing that the amine might be reacting with by-product **80c** (scheme 67), the reaction was doped with 50 mol% of **80c**, affording a lower 41% yield by ^{1}H NMR (Entry 8, Table 7).



Entry	Deviation	Yield **68** (%)[a]
1	None	45%
2	**80a** (2 equiv.)	31%
3	**80a** (5 equiv.)	49%
4	TTMSS (1.5 equiv.)	29%
5	TTMSS (3 equiv.)	44%
6	CH_2Cl_2 [0.01]	27%
7	CH_2Cl_2 [0.2]	61%
8	CH_2Cl_2 [0.2], **80c** (50 mol%)	41%

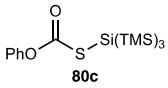
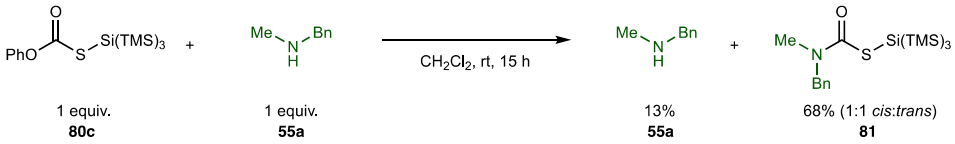


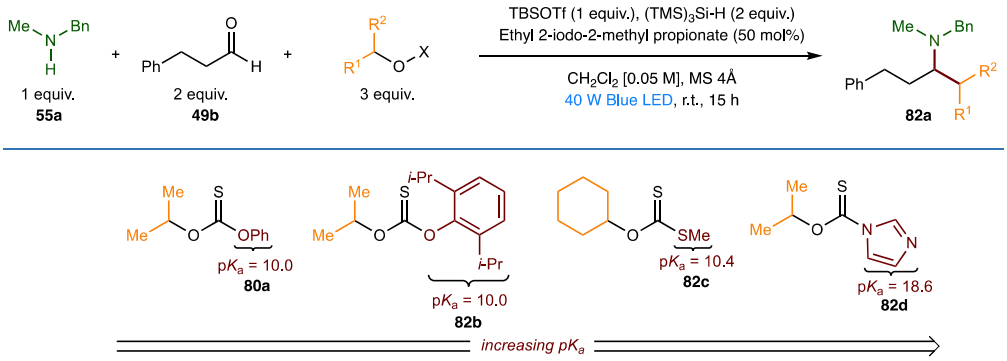
Table 7 | Evaluation of the effect of reaction stoichiometry and concentration on the xanthate CAA-reaction. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

In order to validate this hypothesis, by-product **80c** was independently prepared and characterized and then reacted with amine **55a** in dichloromethane (Scheme 68).[354] After 15 hours, analysis of the crude ^{1}H NMR spectrum indicated that thiocarbamate **81** had formed in 68% yield with 25% remaining amine starting material. In this reaction, the phenol acts as a leaving group due to its lower acidity (pK_a 10.0 vs 10.7). This by-product subsequently hydrolyzes upon work-up to form a carbamic acid which can release CO_2 to return the starting material amine.



Scheme 68 | Reaction of methyl benzylamine with the by-product of the xanthate CAA-reaction.

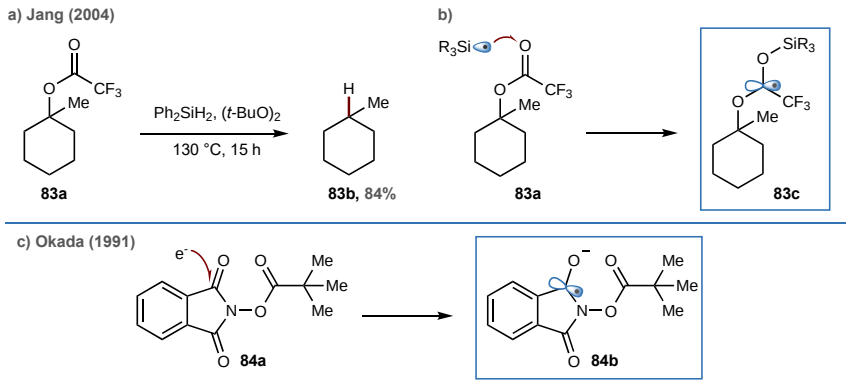
Given the acidity of phenol, it was questioned whether the formation of **81** could be suppressed by employing a more sterically hindered or less acidic leaving group. Unfortunately, all attempts at preparing the sterically encumbered xanthate ester **82b** (Table 8) afforded mixtures of S=C and O=C containing products. Instead, several known alternative radical precursors with varying pK_a of the "leaving group" were synthesized and tested (Entries 1-3, Table 8). Unfortunately, no improvement in yield was observed.



Entry	Radical precursor	Yield (%)[a]
1	**82b**	61%
2	**82c**	0%
3	**82d**	20%

Table 8 | Evaluation of the effect of xanthate structure on the xanthate CAA-reaction. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

Although silyl or stannyl radical addition to the sulfur atom of S=C bonds is the most common mode of radical deoxygenation, examples of deoxygenation *via* radical addition to the oxygen atom of C=O bonds have also been reported. For example, the addition of a silyl radical to (mainly) alkyl benzoates was first reported by Khoo and Lee[355] and later expanded on by Jang in the context of trifluoroacetates (**83a**) as a means to deoxygenate alcohols (Scheme 69a).[356] Unfortunately, various attempts at employing trifluoroacetates in the context of CAA chemistry failed with full recovery of the starting material. Presumably, the greater propensity of silyl radicals to engage with the thiocarbonyl moiety than with an ester can rationalize this disparity as the subsequent fragmentation steps should exhibit similar rates.[357]

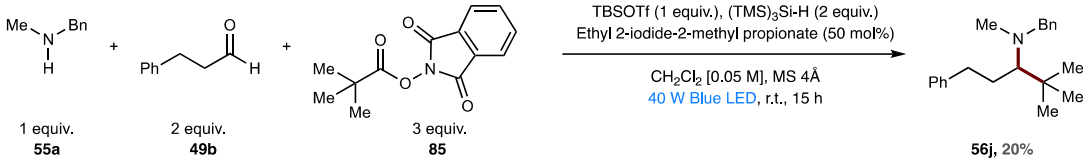


Scheme 69 | a) Jang's deoxygenation of trifluoroacetates. b) Proposed mechanism of Jang's deoxygenation of trifluoroacetates. c) Key-step of alkyl radical formation from *N*-hydroxyphthalimides via single-electron reduction.

Mechanistically, the silyl radical addition to the oxygen atom of a C=O bond affords an α-bisalkoxy radical **83c** which subsequently undergoes β-scission (Scheme 69b). Considering the structure of intermediate **83c** more broadly, it resembles the suggested intermediate **84b** in the decomposition of *N*-hydroxyphthalimide esters (**84a**, Scheme 69b). However, based on the early discovery by Okada,[316] the

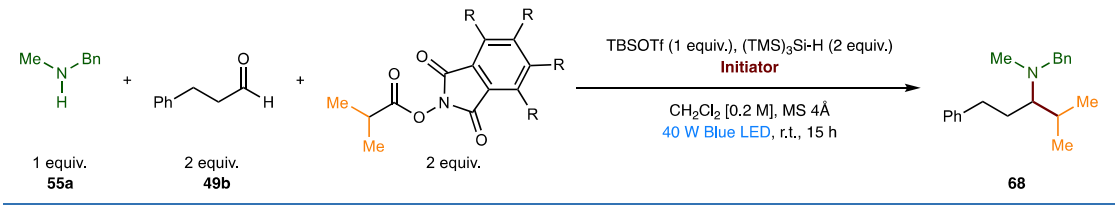
method of choice to generate intermediate **84b** has been through single-electron reduction of ester **84a** rather than the addition of a silyl radical to the C=O oxygen atom.

Speculating that a silyl-radical might be able to decompose **84a** is the same way that it affects the fragmentation of the trifluoroacetate **83a**, Dr. R. Kumar subjected *N*-hydroxyphthalimide ester **85** to the standard CAA conditions (Scheme 70). This afforded the desired product **56j** in a low but still synthetically useful yield of 20%.



Scheme 70 | Dr. R. Kumar's finding that alkyl radical can be generated from *N*-hydroxyphthalimides with TTMSS and participate in the CAA-reaction.

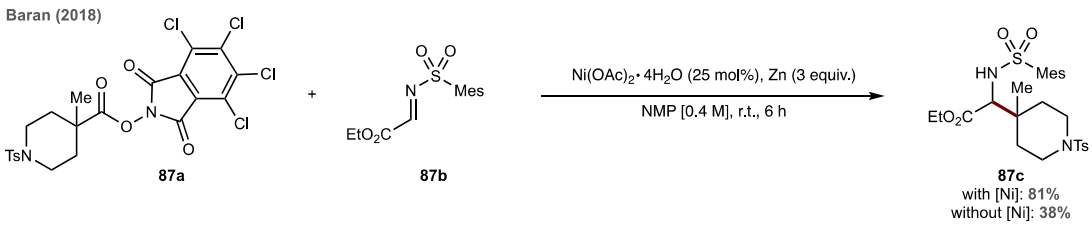
Hypothesizing that the electron-withdrawing trifluoromethyl moiety was crucial in order to affect silyl radical addition to the C=O oxygen in the work of Jang, the more electron-deficient ester **86**, originally developed by Baran as an electrocatalyst,[358] was synthesized and tested as a radical-precursor. This afforded the product in 63% yield, as compared to only trace amounts with non-chlorinated derivative **85** (Entries 1 & 2, Table 9). The low reduction potential of **86** ($E_{1/2} \approx$ -0.8 vs SCE in MeCN)[359] has made them suitable partners in Cu-catalyzed cross-couplings, where for example weakly reducing Cu^{I}-species has been implicated in transferring an electron to the phthalimide moiety resulting in decarboxylation.[360,361] Speculating that a photoredox-catalyst could perform a single-electron reduction to **86** to initiate a radical chain,[362] several photocatalysts were evaluated. $Ir(ppy)_3$ ($E_{1/2}^{IV/III*}$ = -1.73 V vs SCE in MeOH/EtOH 1:1) and $Ru(bpy)_3Cl_2$ ($E_{1/2}^{III/II*}$ = -0.81 V vs SCE in MeCN) afforded the product in low 9% and 15% respectively (Entries 3 & 4).[165] In contrast, $Ir(dMeppy)_2(dtbbpy)PF_6$ ($E_{1/2}^{IV/III*}$ = -0.87 V vs SCE)[363] afforded **68** in 42% yield (Entry 5). Organic photocatalyst 4Cz-IPN ($E_{1/2}^{+/0*}$ = -1.18 V vs SCE)[364] increased the yield further to 51% but no photocatalyst afforded similarly high yields as the tertiary iodide initiator (Entry 6).



Entry	R =	Initiator	Yield (%)[a]
1	Cl (**86**)	Ethyl 2-iodo-2-methyl propionate (50 mol%)	63%
2	H (**85**)	Ethyl 2-iodo-2-methyl propionate (50 mol%)	trace[b]
3	Cl	$Ir(ppy)_3$ (1 mol%)	9%
4	Cl	$Ru(bpy)_3Cl_2$ (1 mol%)	15%
5	Cl	$Ir(dMeppy)_2(dtbbpy)PF_6$ (1 mol%)	42%
6	Cl	4Cz-IPN (10 mol%)	51%

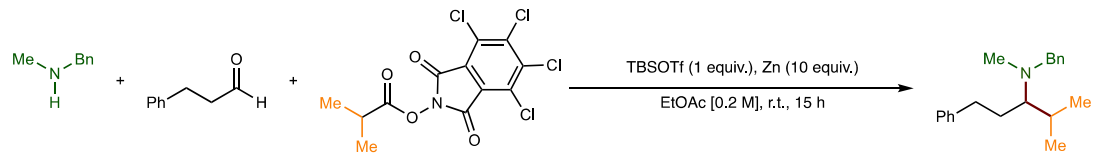
Table 9 | Evaluation of the effect of initiator on the *N*-hydroxyphthalimide CAA-reaction. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard. [b]*Reaction conducted by Dr. R. Kumar.*

In Baran's Ni-mediated synthesis of α-amino acids (**87c**) through radical addition to Ellman-type imines (**87b**), the authors reported that upon omission of the Ni-catalyst, the reaction still afforded the desired product in 38% yield (Scheme 71).[365] Although they did not comment further on this observation, it is plausible that zinc, present as a stoichiometric reductant proposed to turn over the Ni-catalyst, can directly reduce **87a** to generate alkyl radicals. From a thermodynamic perspective, this reduction would be favourable as the reduction potential of zinc is well-matched with that of the tetrachlorophthalimide ($E_{1/2}$ = -1.0 V vs SCE in MeCN).[37]



Scheme 71 | Baran's asymmetric synthesis of amino acids *via* Ni-catalyzed radical addition to imines.

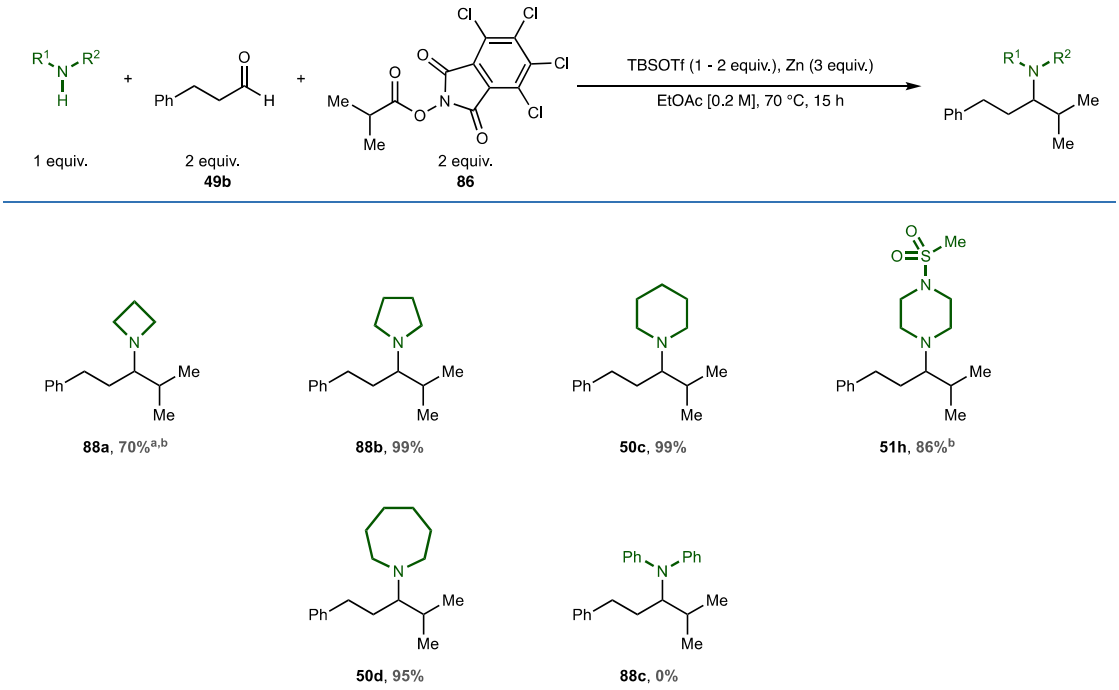
In testing this hypothesis, the silane/tertiary iodide/blue LED initiation system was replaced by Zn-powder. Using a large excess of zinc, these simplified reaction conditions afforded the desired product in 59% yield by ^{1}H NMR (Entry 1, Table 10). However, upon evaluating different solvents, it was found that conducting the reaction in EtOAc afforded a substantial improvement to give **68** in 94% yield after isolation (Entry 2, Table 10). Reducing the loading of zinc significantly impacted the reaction (Entries 3 & 4, Table 10) but if the temperature was increased to 70 °C, the loading could be reduced to 3 equivalents with similar efficiency (Entry 5, Table 10). Unlike the previous CAA-reaction (see chapter 2), molecular sieves were detrimental to the reaction under zinc-conditions (Entry 6, Table X10).



Entry	Deviation	Yield (%)[a]
1	CH_2Cl_2 instead of EtOAc	59%
2	None	95% (94%)
3	Zn (5 equiv)	77%
4	Zn (1 equiv)	trace
5	Zn (3 equiv), 70 °C	90%
6	MS 4Å	complex mixture

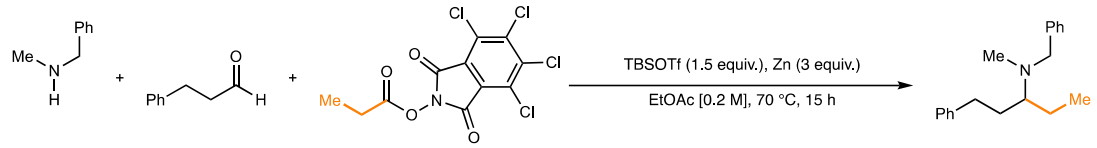
Table 10 | Evaluation of the Zn-mediated *N*-hydroxyphthalimide CAA-reaction. Isolated yields in brackets. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

In order to establish the robustness of the optimized conditions above, a range of cyclic aliphatic amines were evaluated.[278] Using azetidine•HCl as a starting material afforded the desired tertiary amine **88a** in 70% yield by ^{1}H NMR (Scheme 72) whereas the original CAA-conditions only afforded low yields in the case of azetidine substrates (c.f. section 2.4.1). It is known that the formation of small-ring, strained iminium ions is associated with a high kinetic barrier but it was hypothesized that this barrier was overcome by the higher reaction temperature compared to the previous work.[366] Larger ring-sized tertiary amines **88b, 50c, 50d** & **51h** could also be accessed in excellent yields, affording 5, 6 and 7-membered cyclic tertiary amines. In comparison to the heating conditions, reactions at ambient temperature with higher zinc-loading afforded the tertiary amine in slightly diminished yields with the exception of azetidine **88a,** which was accessed in only trace amounts. Unfortunately, neither set of reaction conditions was capable of reacting diphenylamine to afford tertiary amine **88c**.



Scheme 72 | Scope of cyclic amines of the Zn-mediated *N*-hydroxyphthalimide CAA-reaction. [a]HCl-salt of the amine was used. No TBSOTf. [b]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

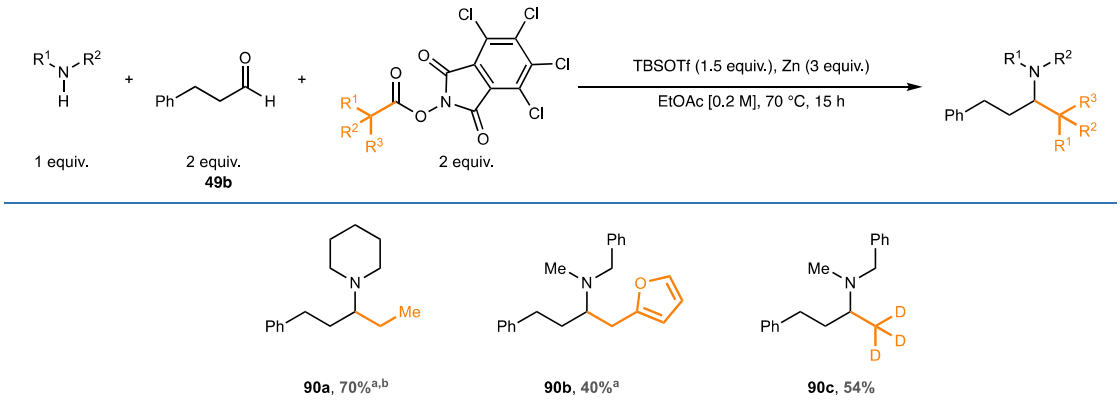
Having established that the conditions were applicable to a range of secondary amines and that they afforded generally improved yields compared to the light-mediated conditions developed earlier, attention was shifted to the *N*-hydroxyphthalimide ester. Using the ethyl radical precursor **89a**, slightly modified thermal conditions using 1.5 equivalents of TBSOTf afforded tertiary amine **89b** in 86% yield (Entry 1, Table 1). Varying the amount of Lewis acid had a slight detrimental effect on the yield (Entry 2 – 3, Table 1). Interestingly, the room temperature conditions developed above afforded only trace amounts of the desired amine (Entry 4, Table 1). Considering that the unimolecular fragmentation involves a substantial increase in entropy (forming three new molecular entities including gaseous CO_2), it would be anticipated that thermal conditions should favour the more challenging decarboxylation of primary acids. Transition metal salts of copper and nickel have frequently been used in order to generate primary alkyl radicals from *N*-hydroxyphthalimide ester at room temperature.[360,367] Indeed, additives such as CuI or $Ni(OAc)_2$ increased the yield substantially at ambient temperature but were still inferior to the thermal conditions (Entries 5 & 6, Table 11).



Entry	Deviation	Yield (%)[a]
1	None	86%
2	TBSOTf (1 equiv.)	60%
3	TBSOTf (2 equiv.)	78%
4	Zn (10 equiv.), r.t.	trace
5	Zn (10 equiv.), CuI (1 equiv.), r.t.	66%
6	Zn (10 equiv.), $Ni(OAc)_2$ (1 equiv.), r.t.	52%

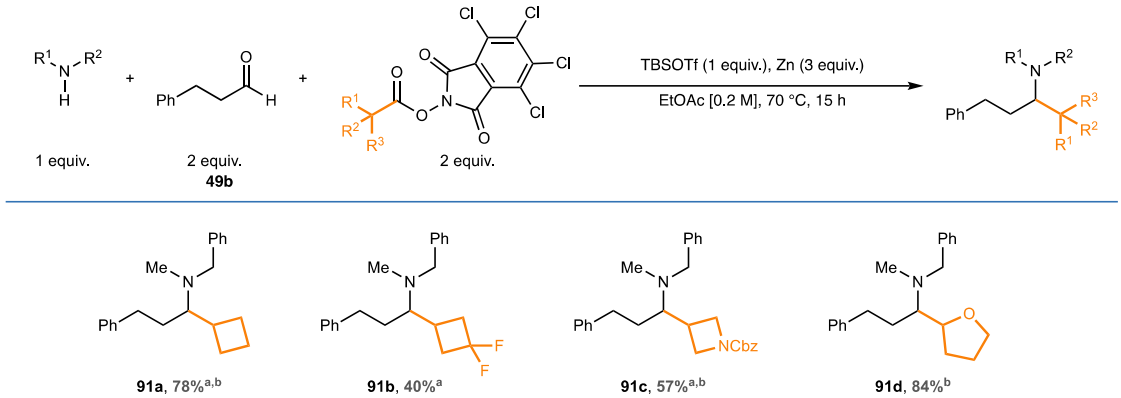
Table 11 | Evaluation of a Zn-mediated *N*-hydroxyphthalimide CAA-reaction. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

With a set of thermal conditions in hand, a variety of primary alkyl nucleophile precursors were tested (Scheme 73). Addition of an ethyl fragment to the iminium ion formed from piperidine and hydrocinnamaldehyde afforded **90a** in 70% yield. Furanylic derivative **90b** could also be accessed in a slightly lower yet synthetically useful yield. It is noteworthy that the corresponding halide is highly unstable and was not compatible with previous CAA conditions. Finally, the fully deuterated CD_3 moiety could be introduced (**90c**), enabling facile access to metabolically stable, deuterated tertiary amines.[368]



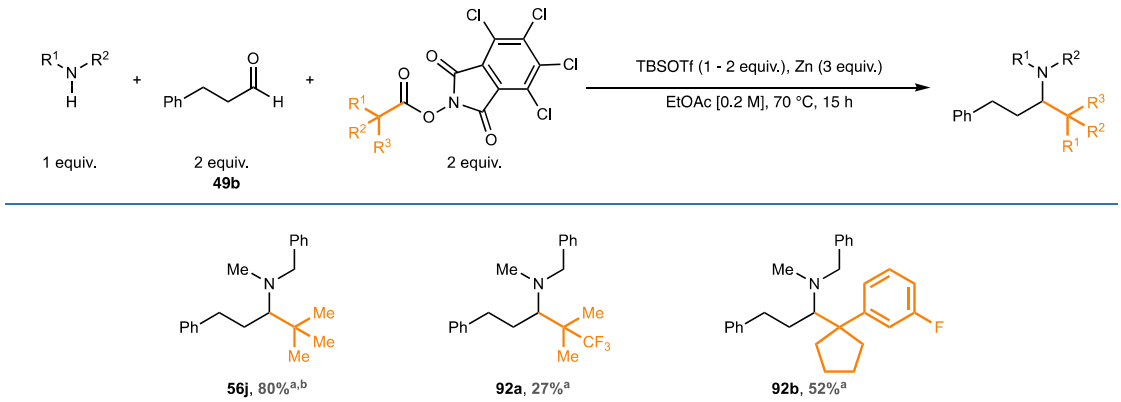
Scheme 73 | Scope of 1° *N*-hydroxyphthalimide esters. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard. [b]2 equiv. TBSOTf.

Secondary nucleophile precursors could also be employed, affording cyclobutyl substituted amine **91a** in high yield (Scheme 74). The difluorocyclobutyl or the Cbz-azetidinyl precursors, which are less nucleophilic due to inductive effects, afforded the desired tertiary amines (**91b** & **91c**) in synthetically useful yields. Notably, these could not be accessed using the previous CAA-conditions (see section 2.4.1). The utility of the bench-stable *N*-hydroxyphthalimides as a nucleophile precursor was further demonstrated through the addition of the tetrahydrofuran nucleophile to afford **91d**. The reaction proceeded in high yield and highlights the utility of *N*-hydroxyphthalimides in cases where the corresponding alkyl halide is unstable.

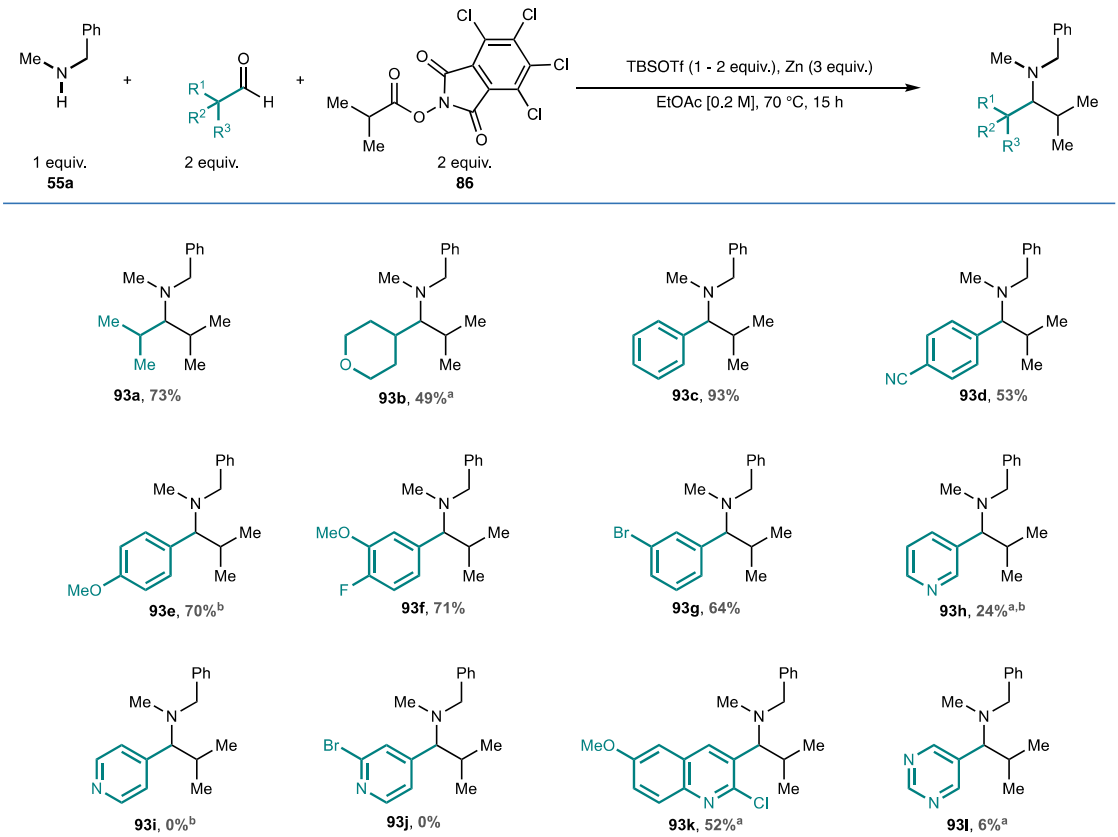


Scheme 74 | Scope of 2° *N*-hydroxyphthalimide esters. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard. [b]Reaction conducted at r.t. with 10 equiv. Zn.

The greater abundance of tertiary carboxylic acids compared to tertiary alkyl halides confers another advantage to using tetrachloro *N*-hydroxyphthalimide esters as nucleophile precursors. While the *tert*-butyl nucleophile afforded **56j** in similar yield compared to the alkyl halide-based CAA-reaction, tertiary amines **92a** and **92b** could not have been accessed using the previous method as the corresponding halides have not been reported (Scheme 75). Indeed, it is likely that their synthesis would present a significant challenge as the acidic conditions often employed to access tertiary alkyl halides can cause internal rearrangements.[348,369]



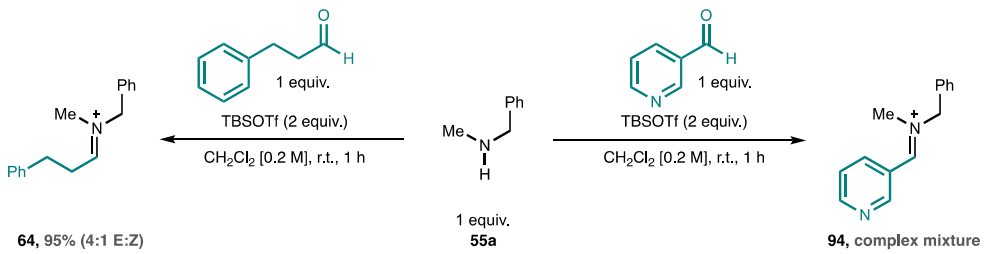
Scheme 75 | Scope of 3° *N*-hydroxyphthalimide esters. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard. [b]Reaction conducted at r.t. with 10 equiv. Zn.



Scheme 76 | Scope of aldehydes. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard. [b]3 equiv. TBSOTf.

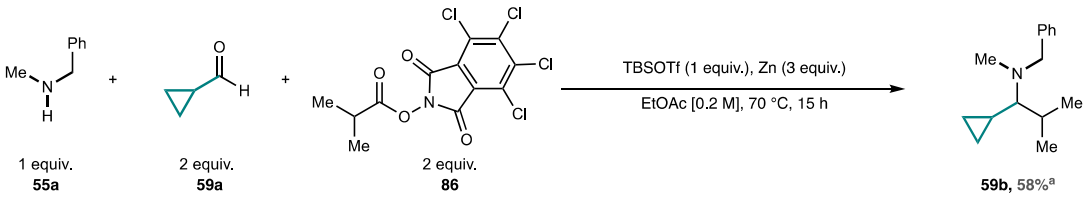
Next, the scope of the aldehyde was evaluated (Scheme 76). Sterically hindered, branched aliphatic aldehydes could be tolerated in good yields (**93a** & **93b**). Benzaldehyde afforded the desired tertiary amine **93c** in 93% yield. Both electron-rich and electron-deficient aromatic aldehydes as well as bromo-substituted variants were successfully utilized, generating the desired tertiary amines in good to excellent yields (**93d-93g**). The lower yield of **93d** than **93e** is informative from a mechanistic point of view. It could be argued that the addition of a nucleophile would be favoured if the aromatic ring carried electron-withdrawing substituents. Instead, the higher yield of *para*-methoxy substituted aromatic **93e**

indicates that the greater stability and consequently higher concentration of the less electron-deficient iminium ion is more important. Unfortunately, heteroaromatic aldehydes afforded consistently low yields with the exception of **93k** where the electronic effect of the quinoline nitrogen is modulated by the α-chloro substituent. As a comparison with the cyano- and methoxy-substituted examples discussed above, the 4-substituted pyridine carboxaldehyde (**93i**) afforded no product whilst the 3-substituted variant afforded **93h** in 24% yield. This is consistent with the hypothesis that the stability of the iminium ion is more important than its ability to react with an alkyl nucleophile. For example, whilst iminium ion **64** can be formed in 95% yield and affords high yields in the CAA-reaction, only trace amounts of iminium ion **94** in a complex mixture can be observed under the same reaction conditions, resulting in a low yield under thermal or light-mediated CAA conditions (Scheme 77).



Scheme 77 | Effect of the aldehyde component on the ability to form iminium ions.

Cyclopropylcarboxaldehyde **59a** was subjected to the reaction conditions to probe the presence of α-amino radical (Scheme 78). Notably, only the intact methine cyclopropyl substituted tertiary amine **59b** was observed. This indicates that a mechanism where an α-amino radical and an alkyl radical forms tertiary amine **59b** *via* radical-radical recombination is unlikely under the reaction conditions.



Scheme 78 | Control experiment to rule out the presence of α-amino radical intermediates in the *N*-hydroxyphthalimide CAA-reaction. [a]Yield determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

3.4 Summary

This chapter has reported the development of methods that use alcohol- and carboxylic acid-derived alkyl nucleophile precursors in the CAA-reaction (see also chapter 2). Alcohol-derived xanthates were found to afford tertiary amines in moderate yields using silanes as the reducing agents. Although these studies have not yet afforded an optimized set of conditions due to deleterious side-reactions of the starting material and reaction by-product, it is expected that a more thorough evaluation of different xanthate-structures might provide a solution in this regard. Encouragingly, it was found that *N*-hydroxyphthalimide esters, derived from carboxylic acids, can serve as potent nucleophile precursors. Only moderate yields were obtained when using silane-based reducing agents, but a set of Zn-mediated conditions were developed that afforded the desired tertiary amines in high yields. It is hypothesized that zinc serves as a single-electron reductant which reduces the electron-deficient *N*-hydroxyphthalimide esters. Under these conditions, the combination of zinc-powder and acid in ethyl acetate as a green solvent, fused amines, aldehydes and *N*-hydroxyphthalimide esters even in the absence of visible light. Importantly, the reaction concentration is 10- to 100-fold greater than in the work detailed in chapter 2, which facilitates scalability. Consequently, these conditions are simpler, cheaper and greener compared to the reaction developed in chapter 2 whilst at the same time expanding the scope by virtue of the more numerous carboxylic acids from which *N*-hydroxyphthalimide esters are derived. For example, it was found that α-heteroatom nucleophiles, whose alkyl halides are difficult or impossible to access and handle, were potent substrates in the CAA-reaction using the corresponding *N*-hydroxyphthalimide esters. Other structures such as azetidines, which were incompatible with the previous conditions, can now be used. Although the early results are promising, the full scope as well as studies into the mechanism of this new transformation are yet to be undertaken.

4 Visible light-mediated synthesis of *N*-heterospirocycles

4.1 Introduction

Spirocycles are molecular fragments where two ring-systems are joined together through a single atom. They are present in natural products[370–375] as well as in medicinal chemistry where they have been employed for over 50 years.[376] In this period, 17 pharmaceuticals containing a spirocyclic motif have been brought to the market, such as spironolactone (for the treatment of heart failure) and ledipasvir (to cure hepatitis C) (Figure 18).[377]

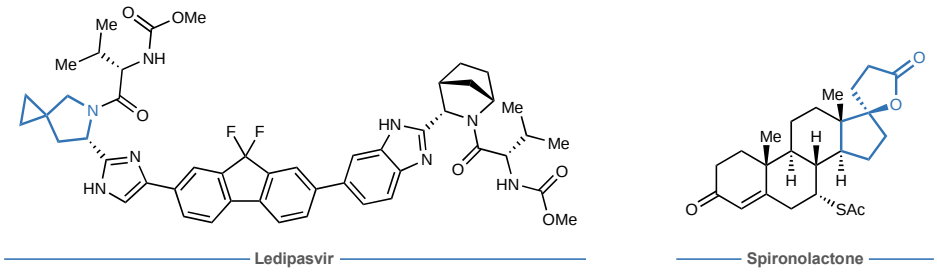


Figure 18 | FDA-approved pharmaceutical agents containing a spirocycle.

Among spirocycles, *hetero*spirocycles are experiencing increased attention from medicinal chemists[378] due to their polar, C(sp^3)-rich structures.[379] Additionally, they remain relatively unexploited compared to other scaffolds such as planar aromatic rings.[380,381] Heterospirocycles have typically been employed in two ways: as structural substitutes (bioisosteres) for carbonyl-moieties and saturated heterocycles such as piperidine in lead optimization[382] or as fragments in high-throughput screening campaigns.[383] The high heteroatom count and C(sp^3)/C(sp^2) fraction of heterospirocycles have benefitted both of these drug discovery endeavors. Specifically, these unique properties create fragments of greater polarity where specific polar interaction can drive binding affinity and increase specificity.[6] Unlike planar aromatics, the C(sp^3)-carbons of spirocycles endow these ring-systems with a structural diversity that can be used to explore binding-interactions within, for example, an enzymatic pocket whilst at the same time maintaining a low molecular weight.[384] The utility of this property is enhanced by the rigidity of the spirocycle, which reduces the entropic penalty upon binding to a biological target.[385] The concept of conformational restriction, wherein a flexible chain can be replaced by a rigid spirocycle, has been used to increase potency and reduce lipophilicity in lead optimization.[386–388] Furthermore, the rigidity of the scaffold also improves the reliability of computational structure-activity relationship predictions.[389] These desirable properties have contributed towards the privileged status of certain spirocyclic scaffolds, such as C3-spirocyclic indolines, indolinones or spiropiperidines.[390–394]

In an early example of spirocyclic "bioisosterism", Carreira and co-workers showed that spirocyclic fragments can be used as substitutes for cyclic amines in order to modulate acidity, which often proves crucial in balancing solubility and membrane permeability (Figure 19a).[395] Meanwhile, spirocyclic oxetanes have been used as carbonyl substitutes leading to increased metabolic stability relative to the parent carbonyl compound (Figure 19b)[396–399] Spirocyclic cyclopropanes have been used as a replacement for alkenes which have shown configurational instability.[400]

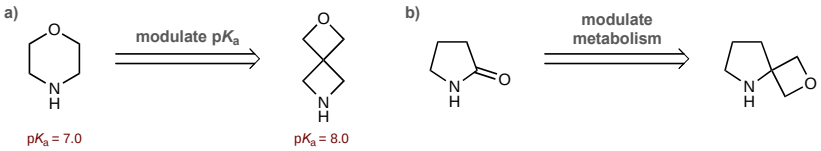


Figure 19 | a) The pK_a of morpholine is decreased in the spirocyclic bioisostere as the number of bonds between the heteroatoms increase. b) Enzymatic degradation due to enolization can be avoided by using oxetane as a bioisostere.

In addition to their use as bioisosteres, spirocyclic fragments have also been exploited in high-throughput screening.[401] As fragments, they combine inherent three-dimensionality[402,403] with higher polarity and well-defined exit-vectors, which together can be used to modify the scaffold if a hit is found (Figure 20).[378,384] Finally, another driving-force to include spirocycles in hit-identification libraries has been their improved patentability.[377]

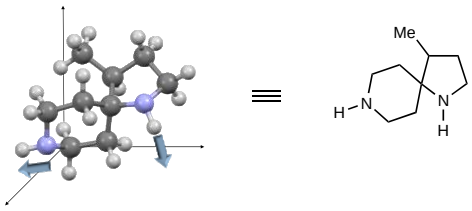
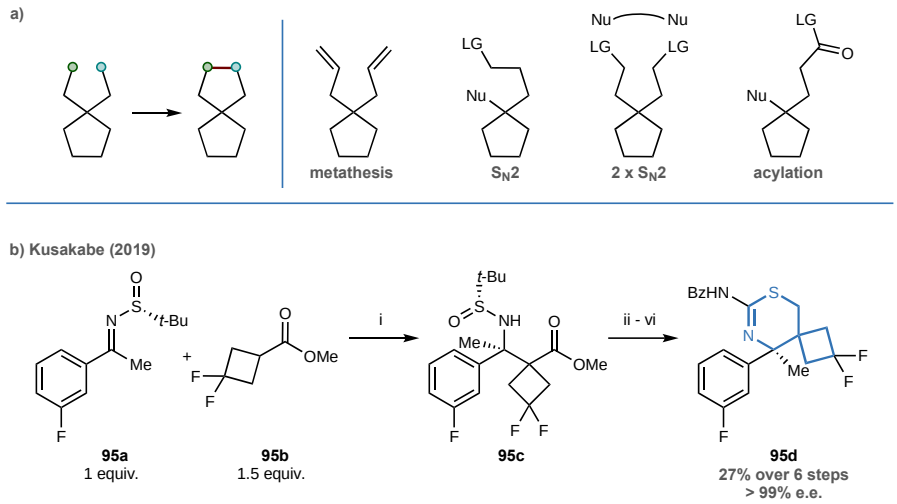


Figure 20 | Rigid *N*-heterospirocyclic fragments can be substituted in well-defined orientations *via* the heteroatoms (e.g. nitrogen) using reliable chemical methods.

4.1.1 Synthetic approaches to spirocycles

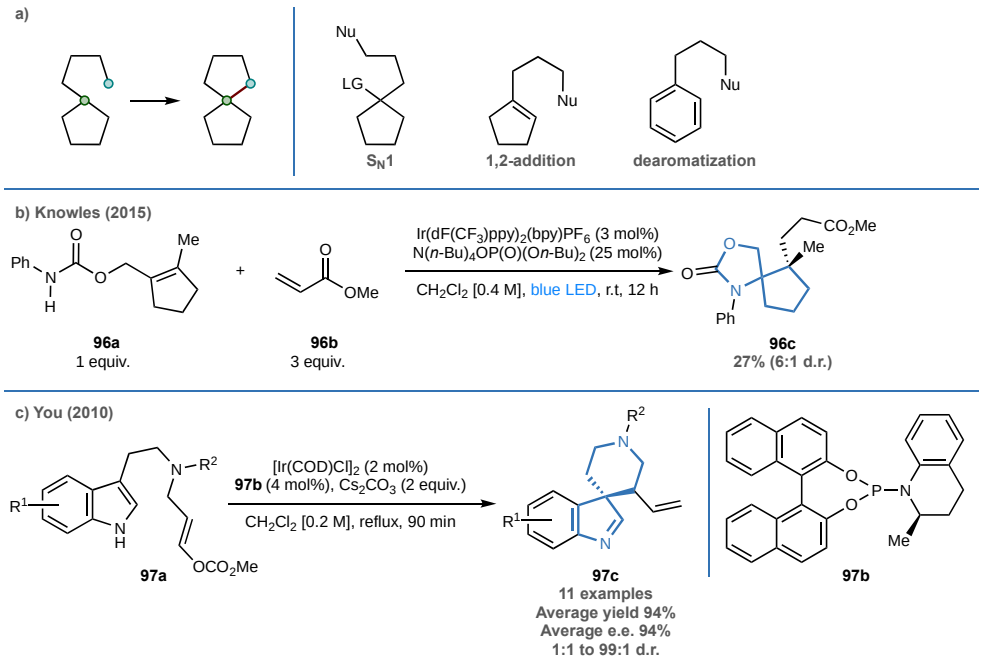
A significant hurdle in using heterospirocyclic fragments in drug discovery lies in the lack of direct methods through which they can be synthesized. Traditionally, heterospirocycles have been accessed using orthodox synthetic methods via long, linear sequences that are highly dependent on the target spirocycle.[378,404–407] The most commonly employed approaches can be categorized into three classes, depending on the nature of the spirocycle-forming step.[408] In the first strategy, the spirocycle is formed without breaking or forming new bonds at the spirocyclic junction (Scheme 80a). A plethora of reactions have been used to affect cyclization but olefin metathesis[409,410] or *N*-, *O*- or *S*-alkylation are the most commonly used methods.[378] Another frequently used method is the intramolecular acylation of *N*-, *O*- or *S*-nucleophiles,[411] as exemplified by the asymmetric synthesis of BACE1-inhibitor

precursor **95d** by Kusakabe and co-workers (Scheme 80b).[412] Starting from imine **95a**, LDA-mediated alkylation afforded cyclization-precursor **95c**. Deprotection of the sulfinimide **95c**, reaction with benzoyl-protected isothiocyanate and, finally, cyclization afforded the desired spirocycle **95d** in 27% yield over 6 steps.



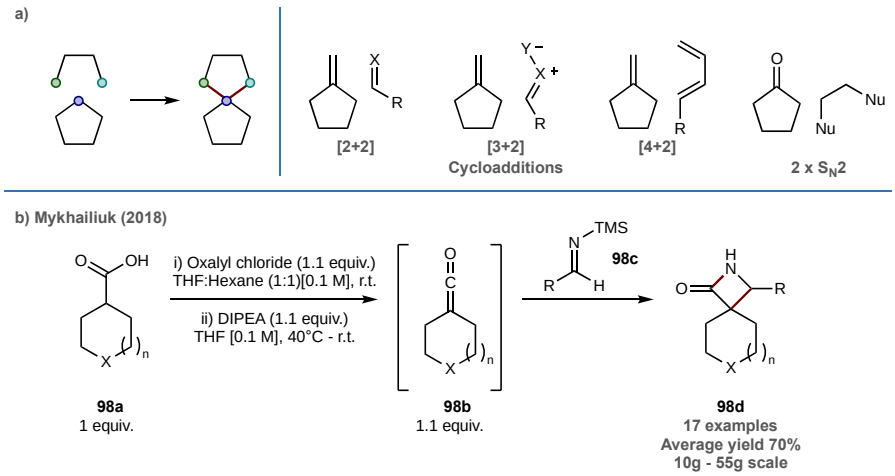
Scheme 80 | a) Approaches to spiro compounds *via* intramolecular ring-closing. b) Synthesis of spirocycles *via* imine alkylation followed by acylative cyclization: i) LDA, ClTi(O*i*-Pr)$_3$, THF, -78 °C. ii) LiBH$_4$, MeOH, THF, 0 °C. iii) 4 M HCl in 1,4-dioxane, MeOH, r.t. iv) BzNCS, CH$_2$Cl$_2$, r.t. v) Ghosez's reagent, CH$_2$Cl$_2$, r.t. vi) H$_2$NNH$_2$•H$_2$O, MeOH, THF, r.t.

The second approach relies on an intramolecular spirocyclization to form a new bond at the spirocyclic centre (Scheme 81a). Historically, this involved the S_N1-reaction of tertiary alkyl halides with an appended heteroatom nucleophile under harsh conditions.[413] Recently, a number of methods have utilized transition metal catalysts,[404] such as platinum,[414] palladium,[415,416] iron[392,417] and copper,[418] to mediate spirocyclization *via* nucleophilic addition to alkenes or the addition of alkenes to carbonyl groups. In this context, Knowles reported the radical cyclization of amido-radicals to afford spirocarbamate **96c** (Scheme 81b).[419] The *N*-centered radicals, derived from otherwise strong N–H bonds (BDE ≈ 99 kcal mol^{-1}),[420] could be generated through proton-coupled electron transfer (PCET) by using a phosphate base in conjunction with an iridium-photocatalyst under blue LED irradiation.[421] Dearomatization of aromatic or heteroarenes have also been employed to construct spirocycles[422,423] and a number of catalysts based on iron,[424] palladium[425] and iridium[426] have been developed. An early application towards the synthesis of heterospirocycles was made by You and co-workers.[427] Building on Tamaru's discovery that indoles can reliably act as C3-nucleophiles in Tsuji-Trost allylations,[428] they reported a method for the synthesis of indoline-based spirocycles **97c**, an important class of biologically active natural products (Scheme 81c).[391] The use of enantiopure phosphoramidite ligand **97b** allowed for facial selectivity in the enantiodetermining nucleophilic addition of the indole to an Ir-allyl intermediate and afforded products in consistently excellent enantio- and diastereoselectivity.



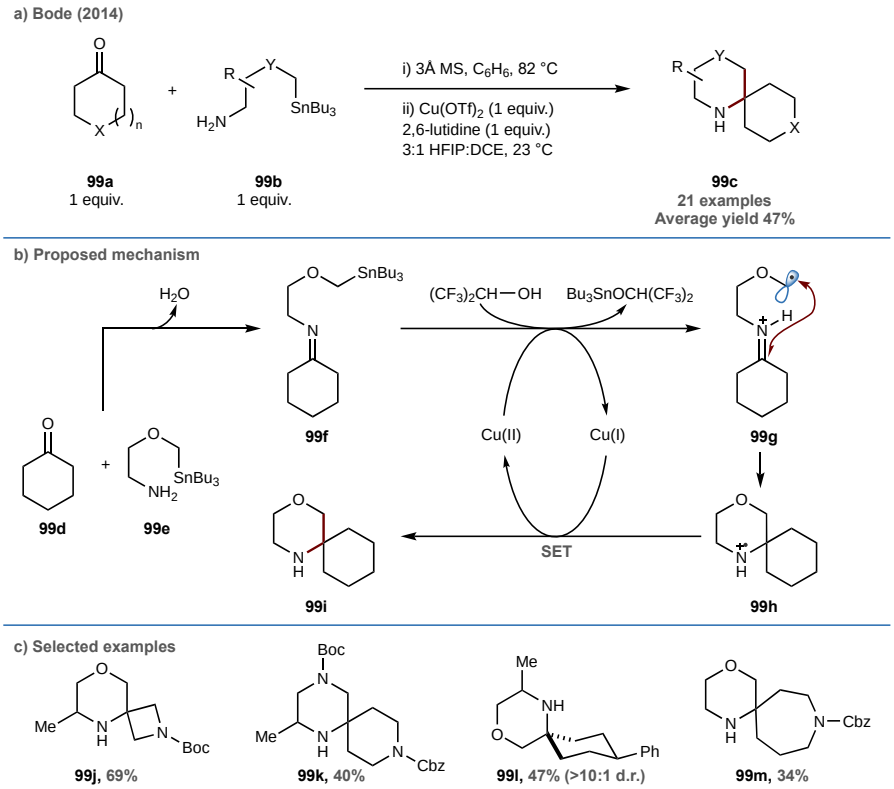
Scheme 81 | a) Approaches to spiro compounds *via* intramolecular ring-closing at the spirocyclic carbon. b) Proton-coupled electron transfer mediated spirocyclization of alkenyl amides. c) Iridium-catalyzed synthesis of spiroindolenines.

The disadvantage of these intramolecular cyclization strategies, outlined above, are the long linear synthetic routes required to access the often complex spirocyclization precursors and the difficulty with which each structure can be readily diversified. An alternative strategy that addresses these shortcomings is the use of multicomponent methods (Scheme 82a), often using cycloaddition-based tactics. In this regard, the utility of [3+2] as well as [4+2]-cycloadditions in spirocycle construction has been demonstrated by Carreira[429] and others.[430] Mykhailiuk and co-workers showed that azetidinone-based spirocycles **98d** could be accessed through a Staudinger reaction on decagram-scale (Scheme 82b).[431] Proceeding *via* a [2+2] cycloaddition of *in-situ* formed ketene **98b** and silyl-imine **96c**, a library of heterospirocycles could be readily accessed. Notably, the use of commercially available carboxylic acid and aldehyde starting materials obviates the need for multi-step starting material syntheses and simplifies the preparation of larger compound collections as the substitution on either ring can be easily modified.



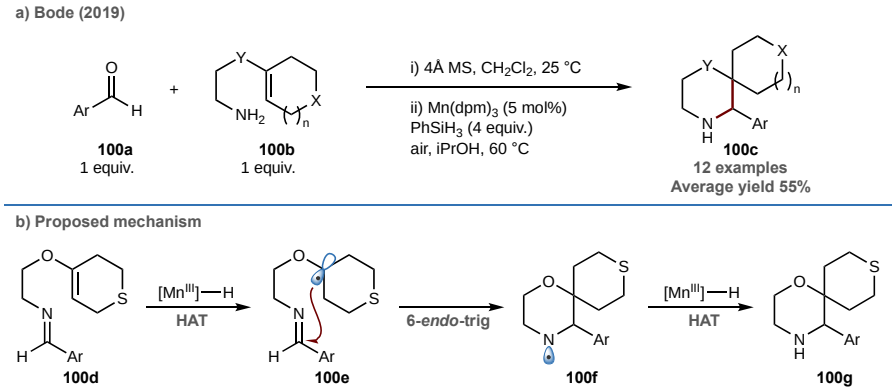
Scheme 82 | a) Multicomponent approaches to spiro compounds b) Synthesis of spirolactams *via* a Staudinger reaction.

The vast majority of spirocycle syntheses employ well-established chemical reactivity to construct the spirocyclic framework. However, as the demand for rapid access to new spirocyclic scaffolds increases, efforts have been directed towards the development of direct, modular methods for their synthesis. In this regard, Bode reported the synthesis of spirocycles **99c** from ketones and amino-stannane reagents (Scheme 83a).[432] The recently commercialized aminostannane-reagents **99e** were pre-mixed with the ketone **99d** to afford imine **99f** (Scheme 83b). The organostannane-moiety is then oxidized by a copper(II)-species to initiate a bimolecular fragmentation of the resulting stannane cation radical to afford **99g**.[433] The electron-rich radical **99g** then undergoes a cyclization to afford the aminium radical cation **99h,** which gives the spirocyclic product after reduction. As evidence to support this mechanistic proposal, the trapping product of **99g** with TEMPO was isolated. Cyclopropane radical-trap experiments further supported the existence of **99h**.[434] The method was applied to a range of heterocyclic ketones to afford azetidine (**99j**), piperidine (**99k**) and azepane-based (**99m**) spirocycles in moderate to good yields (Scheme 83c). Notably, the potential of this method lies in its modularity using commercially available reagents in a one-pot procedure, which has enabled access to novel spirocyclic fragments for high-throughput screening.[435] In addition, a recent application employed the ketone-aminostannane reaction to access bio-inspired, spirocyclic polymers[436] and the method has been extensively studied in the context of non-spirocyclic heterocycle synthesis.[437,438]



Scheme 83 | a) Copper-mediated synthesis of spirocyclic amines using amino-stannane reagents. b) Proposed mechanism of Bode's copper-mediated synthesis of *N*-heterospirocycles. c) Selected examples of the scope of Bode's copper-mediated synthesis of *N*-heterospirocycles.

In a similar, yet distinct, approach, Bode and co-workers also reported the development of a HAT-mediated spirocyclization (Scheme 84a).[439] The use of amino-olefin reagents circumvented the toxicity of amino-stannanes and allowed for a complementary scope compared to their previous work. Although little mechanistic work was undertaken, it was proposed that HAT from (an *in-situ* formed) manganese hydride to the olefin would afford α-alkoxy radical **100e** (Scheme 84b). Then, radical addition to the aryl imine would afford *N*-centered radical **100f**. Although hydrogen-atom transfer to nucleophilic dialkylamine *N*-centered radicals (for example, from stannanes which display similar reactivity compared to silanes) is relatively slow,[119,440] the weak metal-hydrogen bond (BDE (Mn–H) ≈ 68 kcal mol^{-1})[441] presumably increases the rate of this step sufficiently to afford product **100g**. The study was based on the extensive studies into hydrogen-atom transfer to alkenes by Halpern[442] and later synthetic examples by Mukaiyama, Carreira and others.[443,444]



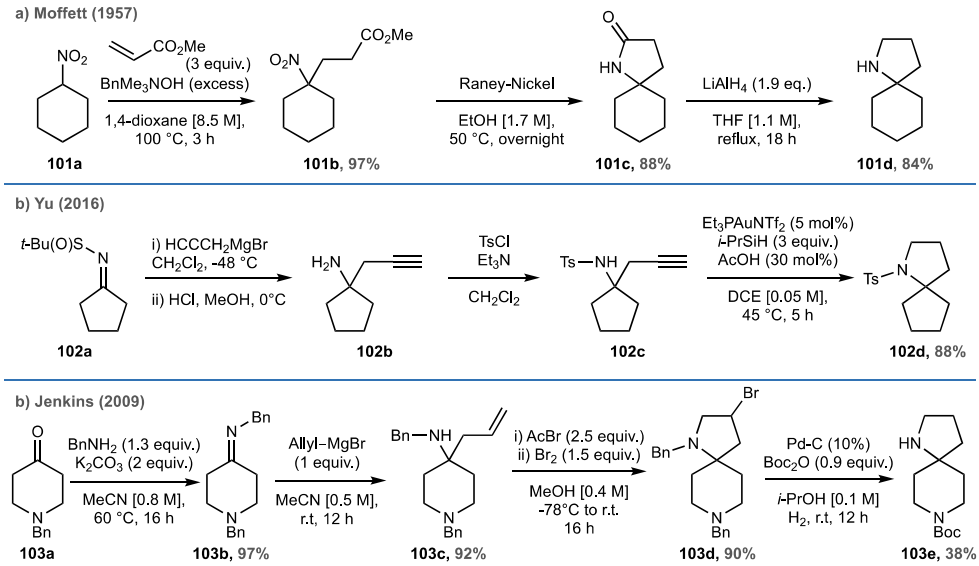
Scheme 84 | a) Manganese-catalyzed synthesis of piperidine-based spirocycles. b) Proposed mechanism of Bode's manganese catalyzed synthesis of *N*-heterospirocycles.

4.2 Project aims & background

Among spirocyclic scaffolds, *N*-heterospirocycles constitute a particularly privileged class of compounds. The presence of one or more trivalent nitrogen atoms enables the spirocyclic fragments to be linked to other fragments through, for example, Buchwald-Hartwig or amide couplings as well as forming important non-covalent interactions with biological targets. These properties, together with the low molecular weight and polar, non-planar architecture of *N*-heterospirocycles, allow such fragments to drive binding affinity through specific polar interactions without significantly increasing lipophilicity.[377]

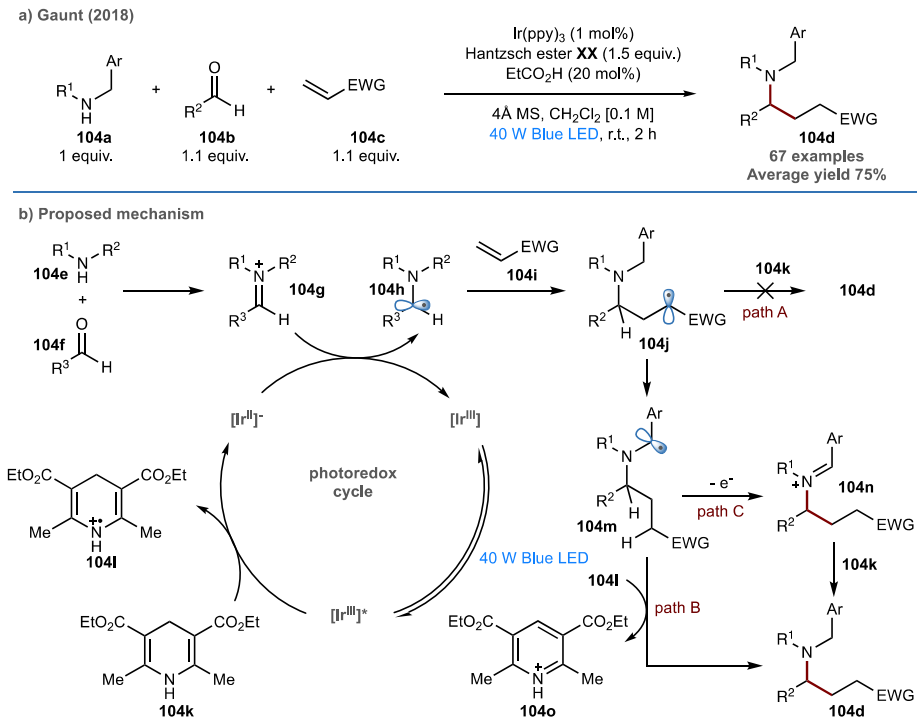
Because of their utility as bioisosteres as well as their relatively low abundance amongst pharmaceutical compounds, small-ring *N*-heterospirocycles are of particular interest to medicinal chemists.[378] However, efforts to develop new direct methods to access *N*-heterospirocycles have mainly been focused on the synthesis of piperidine and larger ring spirocycles. This is at odds with the observed trends in modern medicinal chemistry, where pyrrolidine-based spirocycles are well-represented among pharmaceutical lead candidates but their syntheses are primarily based on indirect, classical methods.[238] For example, Moffett and co-workers detailed an early synthesis of the structurally unbiased spirocyclic fragment **101d** in three synthetic steps (Scheme 85a).[445] Although this method could in principle access a large variety of α,α-disubstituted [4,*n*] (n = 2, 3, 4 etc) pyrrolidine spirocycles, the lack of commercially available (hetero)cyclic nitro compounds, as well as safety concerns regarding scalability has limited this approach. For this reason, methods using ketones as a starting point have been heavily investigated due to the commercial availability of both alicyclic and heterocyclic variants. Yu reported that propargylic tosyl-amine **102c**, which is prepared from ketone-derived sulfinimine **102a** in three steps, could be cyclized using an electrophilic gold-catalyst to afford **102d** (Scheme 85b).[446,447] In addition to the longer step-count, the method is further restricted by the high loading of the expensive gold-catalyst as well as the difficulty of removing the tosyl protecting group. In contrast, the synthetic

sequence developed by Jenkins[448] and scaled to 100-gram scale by Ryabukhin[449] uses comparatively cheap yet robust methods but each spirocycle (e.g. **103e**) still requires four synthetic steps to obtain (Scheme 85c).



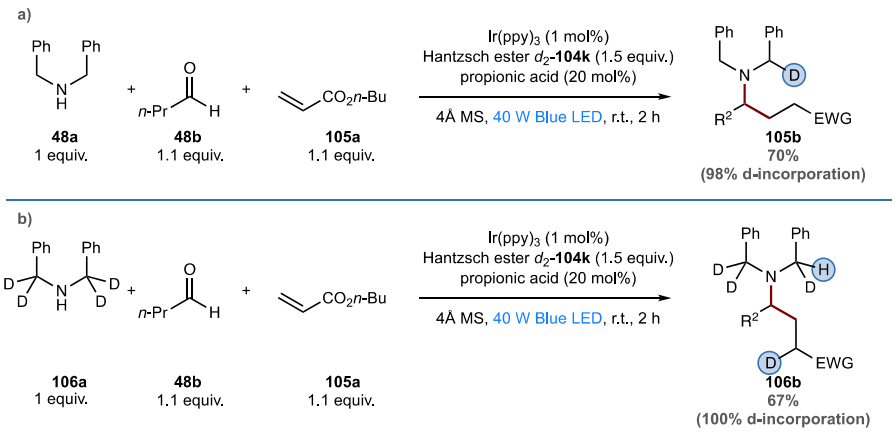
Scheme 85 | a) Moffett's synthesis of *N*-heterospirocycles from nitroalkanes. b) Yu's synthesis of *N*-heterospirocycles from sulfinimines. c) Jenkins' route to *N*-heterospirocycles from heterocyclic ketones.

In this context, it was hypothesized that a new direct method with which to access pyrrolidine-based *N*-heterospirocycles could be developed based on the recent discovery of a light-mediated α-amino radical Giese-addition by Dr. A. Trowbridge and Dr. D. Reich (Scheme 86a).[276] They had found that an iridium-photocatalyst could reduce all-alkyl iminium ions, something which had previously only been explored with aromatic imines.[450–453] Specifically, following condensation of amine **104e** with aldehyde **104f**, the resulting iminium ion **104g** underwent single-electron reduction to afford α-amino radical **104h** (Scheme 86b). Crucially, the excited $Ir(ppy)_3$ catalyst could not directly affect this reduction, as shown by Stern-Volmer quenching studies, but is first reduced by Hantzsch ester (as a stoichiometric reductant) to form a highly reducing $[Ir^{II}]$-species ($E_{1/2}^{III/II}$ = -2.19 V vs SCE in MeCN)[454] which can affect the desired reduction. Then, the α-amino radical **104h** undergoes 1,4-addition to electron-deficient olefin **104i** to give α-carbonyl radical **104j**.



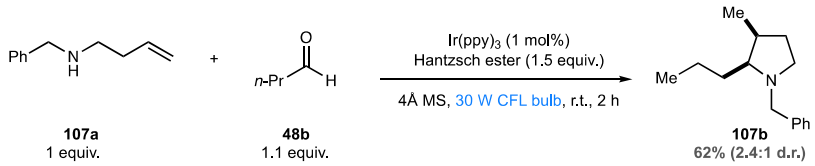
Scheme 86 | a) Gaunt's visible light-mediated synthesis of tertiary alkyl amines. b) Proposed mechanism of Gaunt's synthesis of tertiary alkyl amines.

Interestingly, despite the electron-deficient nature of **104j**, deuterium labelling showed that the direct abstraction of a hydrogen atom from the electron-rich Hantzsch ester **104k** (path A, scheme 86b) does not occur (Scheme 87a). Instead, a 1,5-HAT process proceeds to give stabilized radical **104m**. The use of deuterated dibenzylamine **106a** lent further support to this mechanism by showing that one deuterium atom was transferred from the benzylic position to the α-carbonyl position, strongly suggesting the depicted 1,5-HAT mechanism (Scheme 87b). It was hypothesized that either of two pathways (paths B or C, Scheme 86), radical or polar, may be operative to give the desired product **104d**.



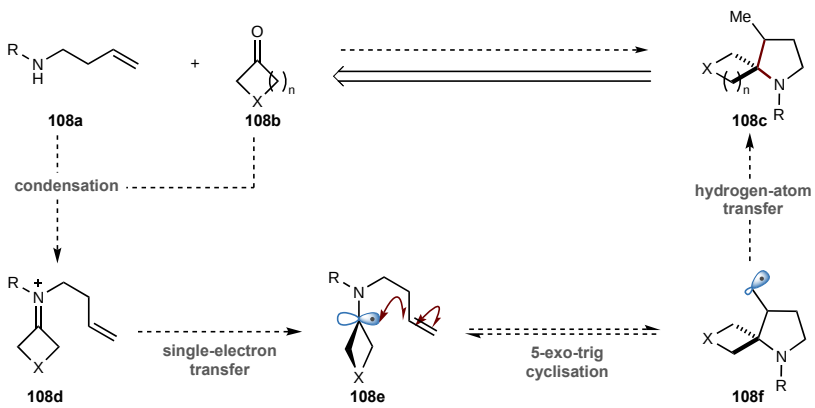
Scheme 87 | a) Employing deuterated Hantzsch ester leads to deuterium incorporation at the benzylic position. *Conducted by Dr. D. Reich.*[455] b) Deuterium transfer from the benzylic substituent to the α-carbonyl position. *Conducted by Dr. D. Reich.*[455]

In the course of the development of the intermolecular protocol, Dr. A. Trowbridge found that the process could be carried out in an intramolecular fashion if an alkene was appended to the amine starting material (Scheme 88).[456] This afforded pyrrolidine **107b** in good yield but poor diastereoselectivity. Notably, in the intramolecular reaction the olefin did not require activation by an electron-withdrawing or radical-stabilizing group, either of which were without exception required in the intermolecular reaction.



Scheme 88 | a) Early result towards α-amino radical mediated synthesis of pyrrolidines. *Conducted by Dr. A. Trowbridge.*[456]

Although this reaction is interesting in its own right as a catalytic variant of the SmI_2-mediated pyrrolidine synthesis first reported by Katritzky and co-workers in 1999,[457,458] if it could be developed to tolerate ketones it would constitute a rare example of a direct spirocyclic pyrrolidine synthesis from commercial and readily accessible starting materials. Whilst α-amido radicals have been used to affect spirocyclization,[432,459,460] no such examples have been reported with aliphatic α-amino radicals. Specifically, we envisioned that spirocyclic pyrrolidine **108c** could be disconnected adjacent to the pyrrolidine nitrogen atom to afford a ketone **108b** and alkenyl amine **108a**, proceeding *via* a 5-*exo*-trig radical cyclization (**108e**, Scheme 89). The amine **108a** could be readily accessed in a single step *via* alkylation, reductive amination or Petasis reactions.



Scheme 89 | a) Mechanistic hypothesis and design plan towards an α-amino radical mediated synthesis of *N*-heterospirocycles.

In several regards, the reaction depicted in scheme 89 is substantially different in comparison to both the aldehydic cyclization (Scheme 88) and the intermolecular variant (Scheme 86), creating a unique set of challenges. Firstly, condensation of a secondary amine with a ketone is significantly slower than with an aldehyde.[461] Once formed, the ketone-derived iminium ion exhibits a more negative reduction potential than its aldehydic counterpart due to hyperconjugation of two new adjacent C–H bonds. This

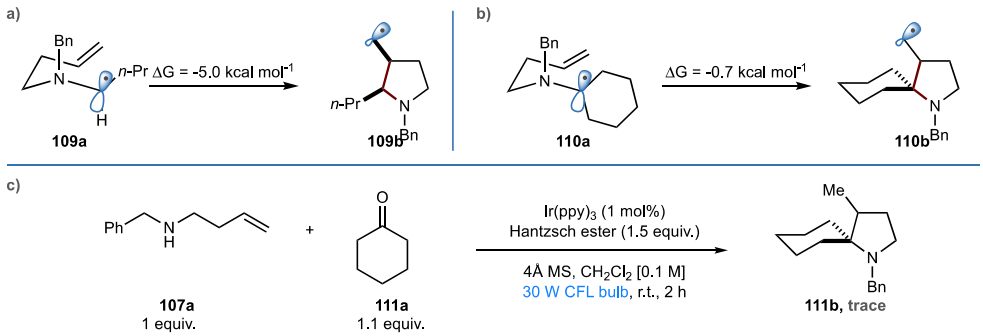
thermodynamic barrier might not be possible to overcome with known photocatalysts although a few selected examples had been demonstrated in the previous intermolecular protocol.[152,276] If the α-amino radical **108e** could be accessed, it would be more stable than that derived from an aldehyde (tertiary versus secondary) and hence the radical cyclization to afford **108f** would be less exothermic. Furthermore, the use of polarizing or stabilizing substituents on the alkene would have to be avoided as the amino-alkene component might become too synthetically cumbersome to access. This disfavours the radical cyclization step through a lack of polarity-matched effects and due to the formation of an unstable primary alkyl radical (**108f**).

Due to the collaborative nature of this project, all work undertaken by others (Dr. A. Trowbridge, Dr. D. Willcox, Dr. S. Walton and Y. Kim) than the author is attributed by name both within the text and schemes.

4.3 Results and discussion

4.3.1 Reaction discovery and optimization

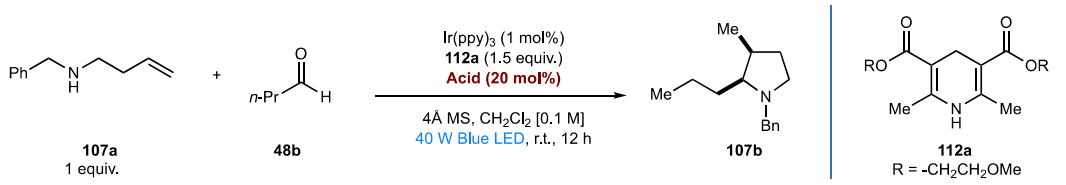
The proposed spirocyclization reaction was first examined *in-silico* to probe the thermodynamics of the proposed radical cyclization step. The cyclization of benzyl homoallylamine derived α-amino radical **109a**, which Dr. A. Trowbridge had shown proceeded to afford the cyclized product in good yield, was exothermic by 5.0 kcal mol^{-1} (Scheme 90a). In contrast, cyclization of cyclohexanone derived **110a** was essentially thermoneutral (Scheme 90b). Indeed, upon subjecting cyclohexanone (**111a**) and benzyl homoallylamine (**107a**) to the cyclization conditions (c.f. scheme 88), only trace amounts of the desired spirocycle **111b** was observed (Scheme 90c).



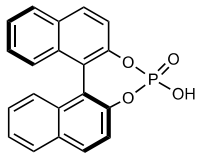
Scheme 90 | a) DFT-modelling (UTPSSTPSS/defTZVP) of radical cyclization of aldehyde-derived α-amino radicals. b) DFT-modelling (UTPSSTPSS/defTZVP) of radical cyclization of ketone-derived α-amino radicals. c) Studies towards α-amino radical-mediated synthesis of *N*-heterospirocycles.

At this stage, it was decided to first optimize the conditions using an aldehyde carbonyl component, with the hope to transfer any successful results onto the evidently more challenging ketones. Attempts

to reproduce the reaction discovered by Dr. A. Trowbridge afforded the desired product in 51% yield by ^{1}H NMR (Entry 1, Table 12). Increasing the amount of aldehyde afforded slightly improved yield but the results suffered from reproducibility issues. Hypothesizing that this might be because of the poor solubility of Hantzsch ester in CH_2Cl_2, it was replaced by the more soluble derivative **112a**, which afforded similar but more consistent yields (Entry 3). The choice of acid was then evaluated (Entries 3 – 12). No clear correlation between acidity and reaction outcome was observed with propionic acid (pK_a = 4.8) and benzenesulfonic acid (pK_a = -6.5) affording similar yields (c.f. entries 3 & 8). Interestingly, the use of a chiral binol phosphoric acid **112b** (Entry 9) did not affect the diastereoselectivity of the reaction (c.f. entries 3 & 9), suggesting that the cyclization occurs *via* an unprotonated α-amino radical intermediate as opposed to an α-ammonium radical intermediate which has been proposed previously.[154] Ammonium-based Brönsted acids or Lewis acid $Yb(OTf)_3$ did not improve the reaction outcome (Entries 10-12).



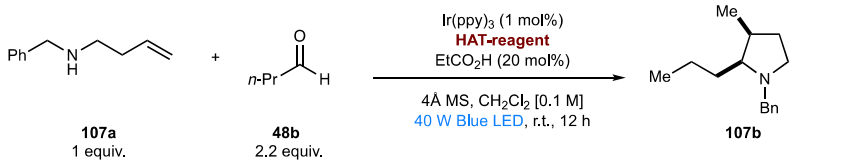
Entry	Equiv. (XX)	Acid	pK_a	Yield **107b**[a]	d.r.
1	1.1	$EtCO_2H$	4.8	51%[b]	2.5:1
2	2.2	$EtCO_2H$	4.8	59%[b]	2.5:1
3	2.2	$EtCO_2H$	4.8	60%	2.5:1
4	2.2	$AdCO_2H$	4.8	58%	2.6:1
5	2.2	$PhCO_2H$	4.2	60%	2.6:1
6	2.2	$(p\text{-OMe})C_6H_4CO_2H$	4.5	56%	2.6:1
7	2.2	$(p\text{-}NO_2)C_6H_4CO_2H$	3.4	32%	2.6:1
8	2.2	$PhSO_2H$	-6.5	55%	2.3:1
9	2.2	**112b**	3.4	45%	2.6:1
10	2.2	$Et_3N\cdot HCl$	≈ 9.2	50%	2.9:1
11	2.2	DIPEA·HCl	≈ 9.2	47%	3.0:1
12	2.2	$Yb(OTf)_3$	N/A	54%	2.8:1



112b

Table 12 | Evaluation of Brönsted and Lewis acids in the light-mediated synthesis of pyrrolidines. [a]Yields determined by GC-FID against dodecane internal standard. [b]Hantzsch ester (1.5 equiv.) was used instead of **112a**.

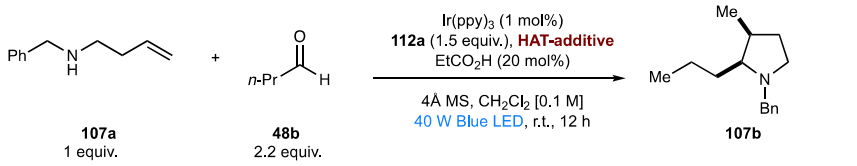
Different HAT-reagents were then evaluated (Table 13). Increasing the amount of Hantzsch ester (BDE = 69 kcal mol^{-1}) afforded little improvement (Entries 1 & 2). Methanol (BDE = 96 kcal mol^{-1})[116] was a competent HAT-source but afforded significantly lower yield of **107b** whereas 2,6-dimethylthiophenol (87 kcal mol^{-1})[116] only afforded reductive amination product (not shown), likely *via* a polarity-matched hydrogen-atom transfer to the α-amino radical (Entries 3 & 4).[277] Cyclohexadiene (76 kcal mol^{-1})[116] and its 1-methoxy substituted derivative afforded slightly reduced yields (Entries 5-7), as did TTMSS (BDE = 84 kcal mol^{-1}).[106]



Entry	HAT-reagent	Yield **107b**[a]	d.r.
1	**112a** (1.5 equiv.)	56%	2.5:1
2	**112a** (2 equiv.)	57%	2.5:1
3	MeOH (25 equiv.)	24%	2.9:1
4	2,6-dimethylthiophenol (2 equiv.)	0%[b]	N/A
5	1,4-cyclohexadiene (2 equiv.)	30%	2.9:1
6	1,4-cyclohexadiene (3 equiv.)	40%	2.2:1
7	1-Methoxy-1,4-cyclohexadiene (3 equiv.)	39%	2.4:1
8	TTMSS (2 equiv.)	37%	2.5:1

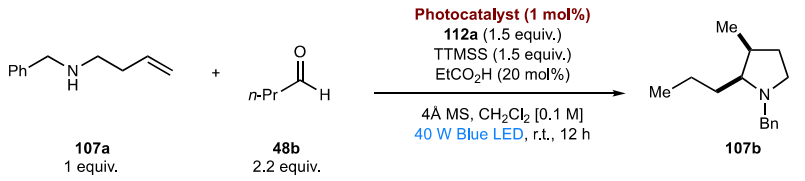
Table 13 | Evaluation of HAT-reagents in the light-mediated synthesis of pyrrolidines. [a]Yields determined by GC-FID against dodecane internal standard. [b]31% reductive amination product (*N*-benzyl-*N*-butylbut-3-en-1-amine) was observed.

In considering the role of the HAT-reagent, it was noted that it must achieve two tasks: donate a hydrogen atom to the cyclized primary alkyl radical **104m** and an electron to turn-over the photocatalytic cycle (Scheme 86b). In considering the latter, it was noted that only Hantzsch ester-derivative **112a** ($E_{1/2}$ = +0.51 V vs Fc^+/Fc in MeCN)[462] had a sufficiently low reduction potential to be oxidized by $Ir(ppy)_3$ whereas in the case of e.g. TTMSS (E_p = +1.44 V vs Ag^+/Ag in MeCN), some other transient intermediate radical must be responsible for turning-over the reaction.[463] Consequently, a combination of an external species as a HAT-reagent and Hantzsch ester as a single-electron donor might improve the reaction efficiency. Testing this hypothesis, the combination of 1 or 1.5 equivalent of TTMSS and 1.5 equivalents of Hantzsch ester afforded the desired product in improved 69%-70% yield (Entries 1 & 2, Table 14). Other silanes containing stronger Si–H bonds were less efficient (Entries 3-5) while 1,4-cyclohexadiene afforded a similar yield compared 1,4-cyclohexadiene (Entry 6).



Entry	HAT-additive	Yield **107b**[a]	d.r.
1	TTMSS (1 equiv.)	69%	2.6:1
2	TTMSS (1.5 equiv.)	70%	2.5:1
3	$PhSiH_3$ (1 equiv.)	55%	2.4:1
4	Me_2PhSiH (1 equiv.)	24%	2.9:1
5	$Me(OEt)_2SiH$ (1 equiv.)	55%	2.6:1
6	1,4-cyclohexadiene (1.5 equiv.)	70%	2.4:1

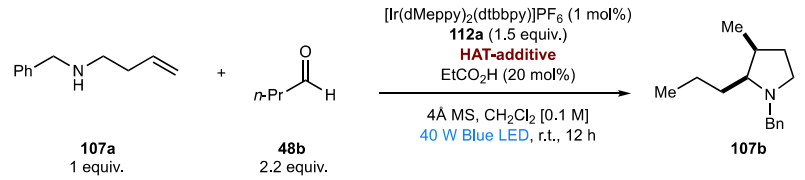
Table 14 | Evaluation of HAT-reagents in combination with **112a** in the light-mediated synthesis of pyrrolidines. [a]Yields determined by GC-FID against dodecane internal standard.



Entry	Photocatalyst	$E_{1/2}^{(n+1/n^*)}$ (vs SCE)	$E_{1/2}^{(n/n-1)}$ (vs SCE)	Yield **107b**[a]	d.r.
1	$Ir(ppy)_3$	- 1.73 V	- 2.19 V	71%	2.6:1
2	$Ir(dMeppy)_3$	- 1.86 V	- 1.96 V	74%	2.4:1
3	PTH (5 mol%)	- 2.1 V	N/A	26%	2.9:1
4	$[Ir(dFCF_3ppy)_2(dtbbpy)]PF_6$	- 0.89 V	- 1.37 V	73%	2.5:1
5	$[Ir(dMeppy)_2(dtbbpy)]PF_6$	- 0.87 V	- 1.48 V	77%	2.4:1

Table 15 | Evaluation of photocatalyst with different reduction potentials[363,454,464,465] in the light-mediated synthesis of pyrrolidines. [a]Yields determined by GC-FID against dodecane internal standard.

With a new dual-HAT reagent system in hand, the effect of the photocatalyst was evaluated. Interestingly, little correlation was observed between the reduction potential of the photocatalyst and the yield of the reaction (Entries 1 - 5, Table 15). Only PTH, whose shorter excited state life-time might hamper the efficient reduction of the short-lived nature of the iminium ion, gave significantly lower yields.[161] Encouragingly, the use of $[Ir(dMeppy)_2(dtbbpy)]PF_6$ improved the yield of **107b** to 77% (Entry 5).

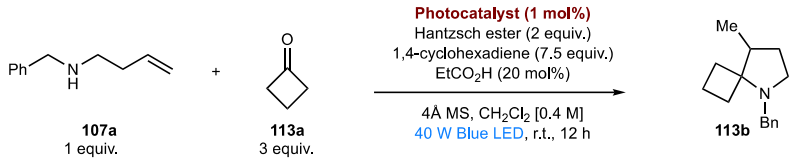


Entry	HAT-additive	Yield **107b**[a]	d.r.
1	TTMSS (1.5 equiv.)	77%	2.4:1
2	1,4-cyclohexadiene (1 equiv.)	60%	2.4:1
3	1,4-cyclohexadiene (3 equiv.)	85%	2.9:1
4	1,4-cyclohexadiene (7.5 equiv.)	98%	2.3:1
5	1,4-cyclohexadiene (7.5 equiv.)	95%[b]	2.4:1

Table 16 | Re-evaluation of HAT-reagents in combination with **112a** in the light-mediated synthesis of pyrrolidines. [a]Yields determined by GC-FID against dodecane internal standard. [b]Hantzsch ester (1 equiv.) used instead of **112a**.

Having found a set of near-optimal reaction conditions, the choice of HAT-additive was re-evaluated (Table 16). Interestingly, with the less reducing $[Ir(dMeppy)_2(dtbbpy)]PF_6$, superstoichiometric amounts of 1,4-cyclohexadiene proved a more effective HAT-reagent (Entries 2-4). Under these conditions, Hantzsch ester glycolate **112a** could be replaced by Hantzsch ester, which is commercially available, without significant loss of yield or reproducibility to provide the optimized reaction conditions (Entry 5).

Having found a set of optimal conditions with butyraldehyde, attention returned to the reaction with ketones. After minor changes to the equivalency of Hantzsch ester (2 equivalents) and concentration (0.4 M), the conditions afforded the desired product in 75% yield (Entry 1, Table 17). Interestingly, the reaction efficiency was more sensitive to the choice of photocatalyst than in the case of butyraldehyde (c.f. Table 15) with $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ affording spirocycle **113b** in only 28% yield (Entry 2). Mindful that ketone-derived iminium ions exhibit more negative reduction potentials, more reducing $Ir(dMeppy)_3$ afforded the product in 91% yield (Entry 3).

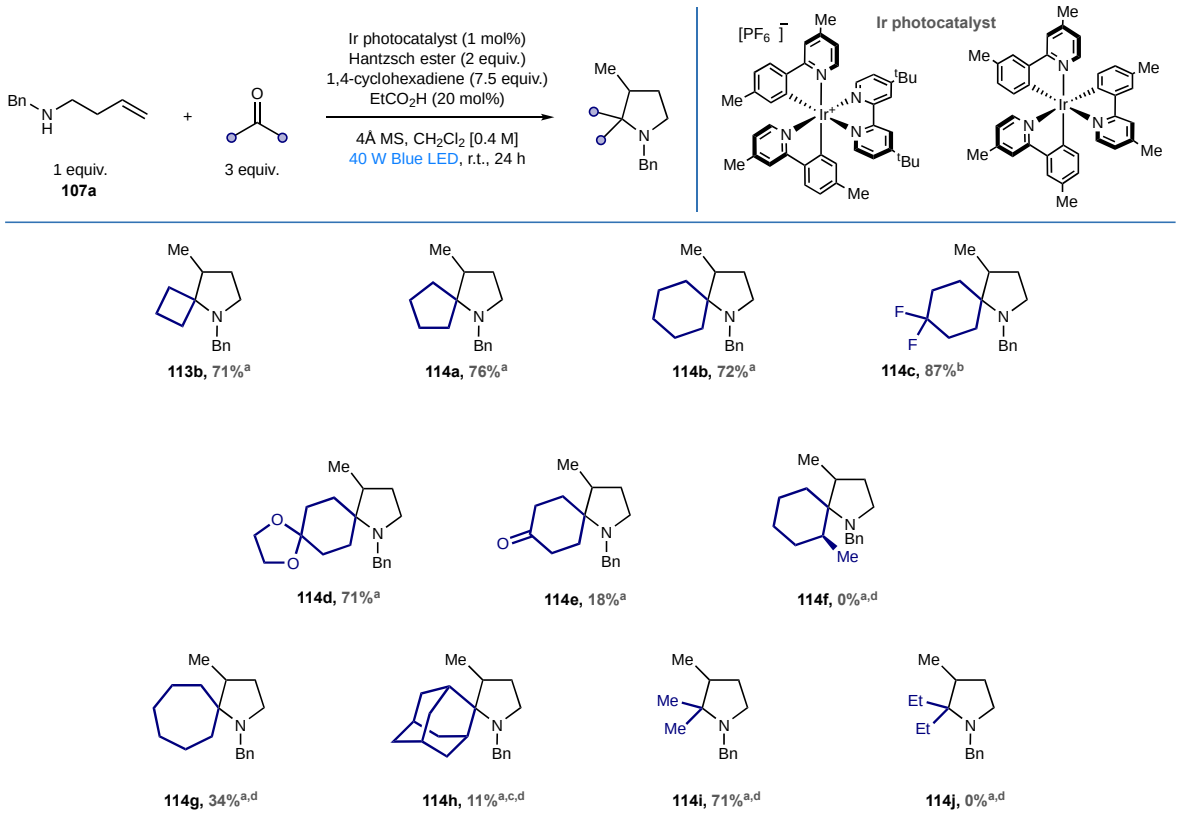


Entry	Photocatalyst	$E_{1/2}^{(n+1/n^*)}$ (vs SCE)	Yield **113b**[a]
1	$[Ir(dMeppy)_2(dtbbpy)]PF_6$	- 0.87 V	75%
2	$[Ir(dFCF_3ppy)_2(dtbbpy)]PF_6$	- 0.89 V	28%
3	$Ir(dMeppy)_3$	- 1.86 V	91%

Table 17 | Evaluation of photocatalysts in the light-mediated synthesis of *N*-heterospirocycles. [a]Yields determined by GC-FID against dodecane internal standard.

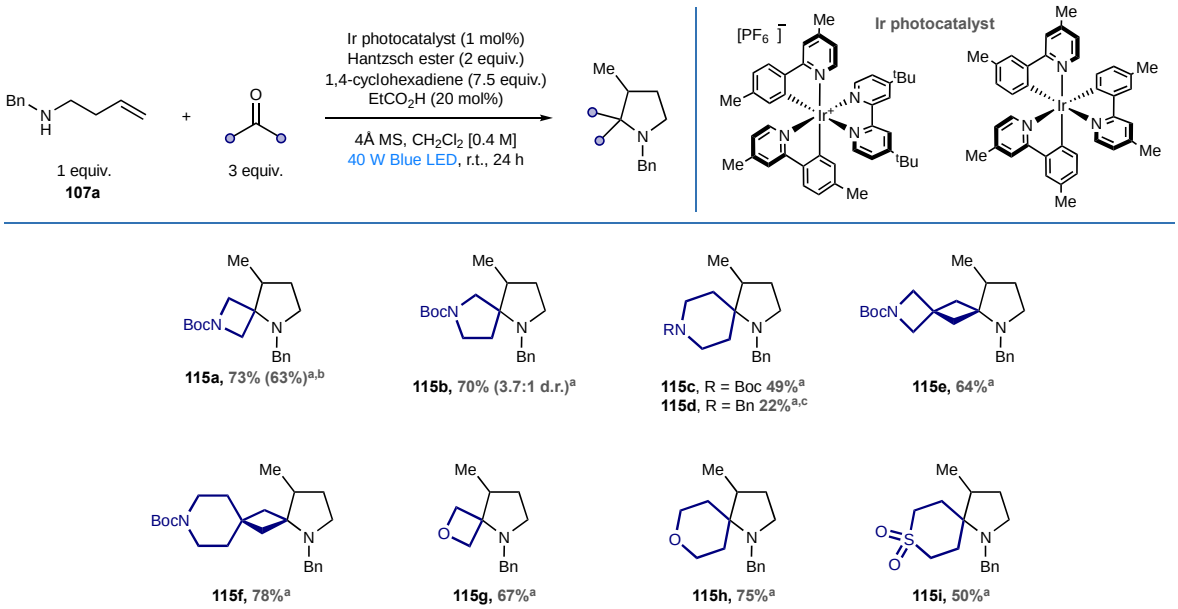
4.4 Scope

The scope of the transformation was then evaluated with respect to aliphatic ketones (Scheme 91). Four-, five- and six-membered ketones afforded all afforded high assay yields (**113b**, **114a** & **114b**) although the isolated yields were reduced by 10%-20% due to poor recovery from column chromatography. Substituted cyclohexanone-derived spirocycles (**114c** & **114d**) were also obtained in high yield. 4-Oxocyclohexanone, presenting two carbonyl functional groups, afforded **114e** in low yield and sterically hindered α-methylcyclohexanone did not give any product **114f**. Cycloheptanone also proved a challenging substrate, affording only traces of product **114g**. This could be improved by pre-heating the ketone and amine with molecular sieves for one hour, resulting in 34% yield. The same conditions were applied to 2-adamantanone with little success (**114h**). Acyclic ketones were limited to acetone, affording spirocycle **114i** in 71% yield, whereas 3-pentanone afforded no product (**114j**), presumably due to the challenging iminium ion formation.



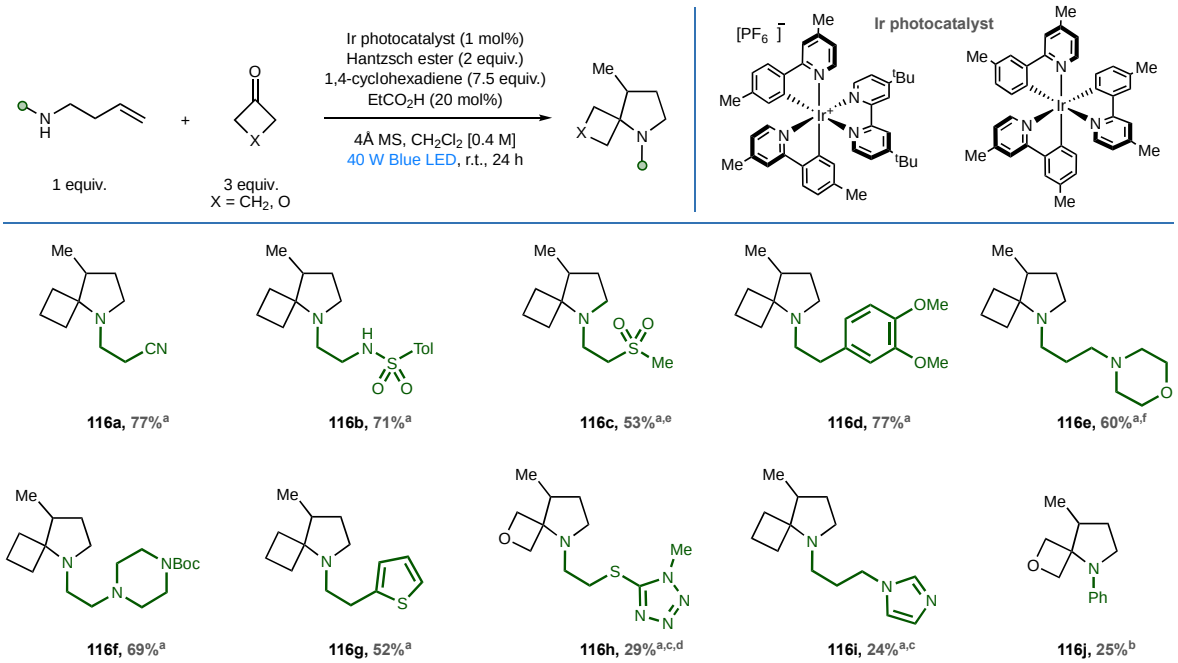
Scheme 91 | Aliphatic ketone scope in the light-mediated synthesis of *N*-heterospirocycles. [a]Reaction using $Ir(dMeppy)_3$. [b]Reaction using $[Ir(dMeppy)_2(dtbbpy)]PF_6$. [c]Yields determined by ^1H NMR against 1,1,2,2-tetrachloroethane internal standard. [d]Amine, ketone and 4Å MS were pre-heated at 80°C for 1-14 h.

Recently, a number of methods have been reported for the synthesis of bis-amino spirocycles following the reports of Carreira and co-workers who highlighted that the rigid scaffold presents two orthogonal vectors for substitution of the nitrogen atoms.[378,466] The two amino-handles are useful in attaching the spirocyclic fragments to a larger molecular construct in a drug-discovery setting. They have also seen extensive use as β-turn mimetics in the study of protein-protein interactions.[410,467–469] Interestingly, the less reducing photocatalyst $[Ir(dMeppy)_2(dtbbpy)]PF_6$ afforded higher yields when *N*-heterocyclic ketones were subjected to the reaction conditions, affording a large set of polar bis-amino spirocycles (**115a-115i**, scheme 92). The origin of this effect is likely the inductive electron-withdrawing effect that the carbamate nitrogen has on the iminium ion. Bis-spirocycles **115e** and **115f** were obtained in 64% and 78% yield respectively, and oxygen and sulfone-containing spirocycles could also be obtained in good to excellent yields (**115g-115i**).



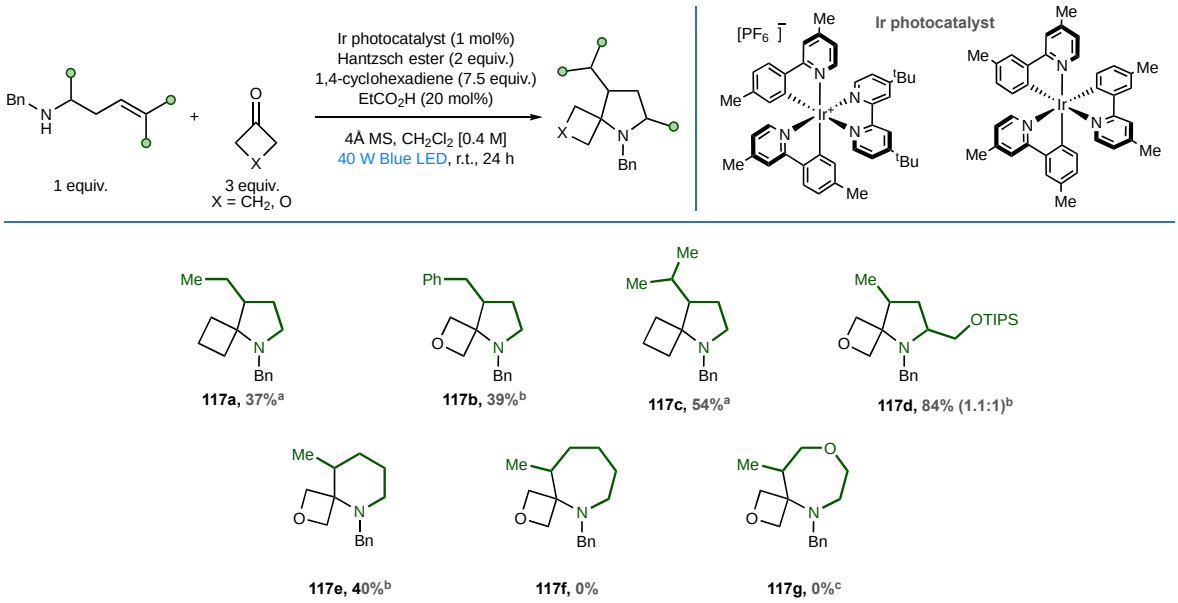
Scheme 92 | Heterocyclic ketone scope in the light-mediated synthesis of *N*-heterospirocycles. [a]Reaction using $[Ir(dMeppy)_2(dtbbpy)]PF_6$. [b]10 mmol scale. [c]Yields determined by ^1H NMR against 1,1,2,2-tetrachloroethane internal standard.

The reaction was also tolerant to substitution on the nitrogen-atom (Scheme 93). In this way, a range of functional groups such as cyano-moieties, sulfonamides and sulfones could be tolerated (**116a-116c**) as well as dopamine derivative **116d**. Pharmaceutically relevant saturated heterocycles such as **116e** or **116f** could be accessed in 60% and 69% yield respectively. Unsaturated, highly polar spirocycles **116g-116i** were also obtained in low but synthetically useful yields. Significantly less nucleophilic *N*-homoallylaniline could also be used as substrate, affording **116j** in 25% yield.



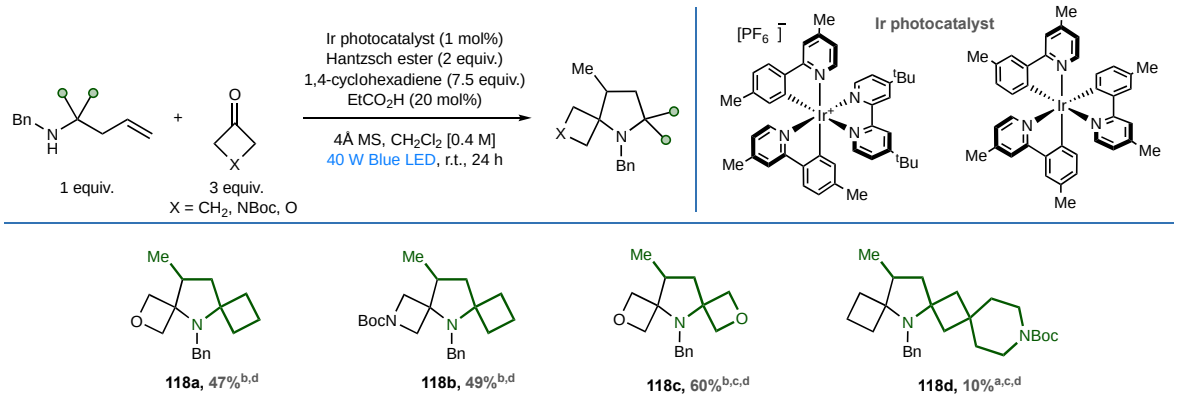
Scheme 93 | Nitrogen-substituent scope in the light-mediated synthesis of *N*-heterospirocycles. [a]Reaction using $Ir(dMeppy)_3$. [b]Reaction using $[Ir(dMeppy)_2(dtbbpy)]PF_6$. [c]*Purified by HPLC by Dr. S. Walton.* [d]Isolated as its HCl-salt. [e]*Reaction conducted by Y. Kim.* [f]*Starting material prepared by Y. Kim.*

At this point, the effects of substitution on the alkene and the carbon-backbone of the amine were explored (Scheme **94**). Surprisingly, the introduction of substituents on the alkene reduced the efficiency of the reaction, affording products in moderate to good yields (**117a-117c**). Substitution on the carbon-backbone was tolerated, however, affording aminoalcohol-derivative **117d** in 84% yield but no diastereoselectivity. Importantly, piperidine spirocycle **117e** was obtained in moderate yield, which could serve as a useful starting point in targeting medium to large ring-sized *N*-heterospirocycles. However, seven-membered variants **117f** and **117g** could not be obtained at this stage. It is likely that the comparatively poor reactivity of these larger rings arises from a slower cyclization step ($k_{5\text{-}exo} = 10^5$ s^{-1} versus $k_{6\text{-}exo} \approx 10^3$ s^{-1}).[74]



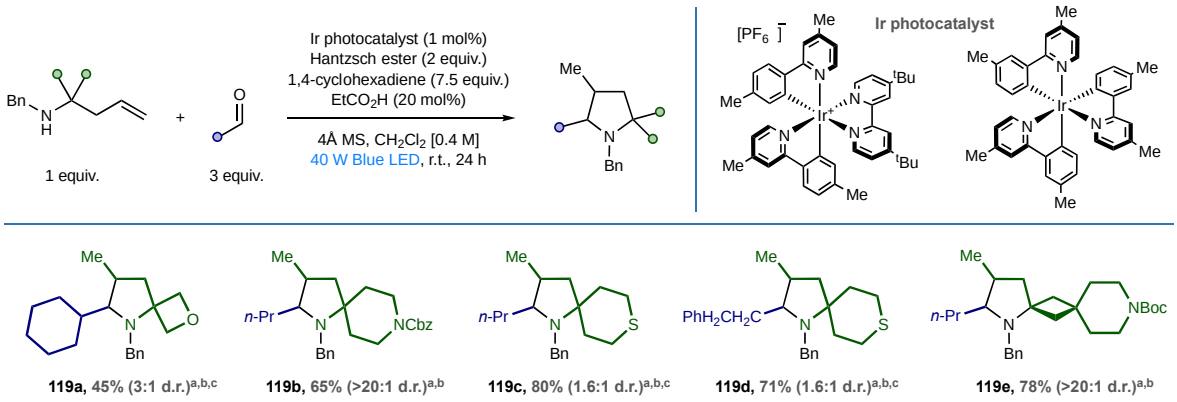
Scheme 94 | Alkene scope in the light-mediated synthesis of *N*-heterospirocycles. [a]Reaction using $Ir(dMeppy)_3$. [b]Reaction using $[Ir(dMeppy)_2(dtbbpy)]PF_6$. [c]*Starting material prepared by Dr. A. Trowbridge.*

α-Tertiary amines can be readily prepared from the corresponding amine and ketones through the Petasis reaction.[35] When subjected to the reaction conditions, they afforded a set of bis-spirocyclic amines in good to poor yields (**118a-118d**, Scheme 95). Very few methods for the synthesis of such scaffolds have been reported; those that have required harsh reaction conditions and elevated temperatures in order to form the extremely hindered bis α-quarternary amines.[411,470,471] Although the reactions had to be carried out with greater amounts of Hantzsch ester and prolonged reaction times, it highlights the ability of the current method to access essentially unexplored parts of chemical space that, due to the $C(sp^3)$-rich nature of such fragments, are likely to be relevant in drug discovery projects.



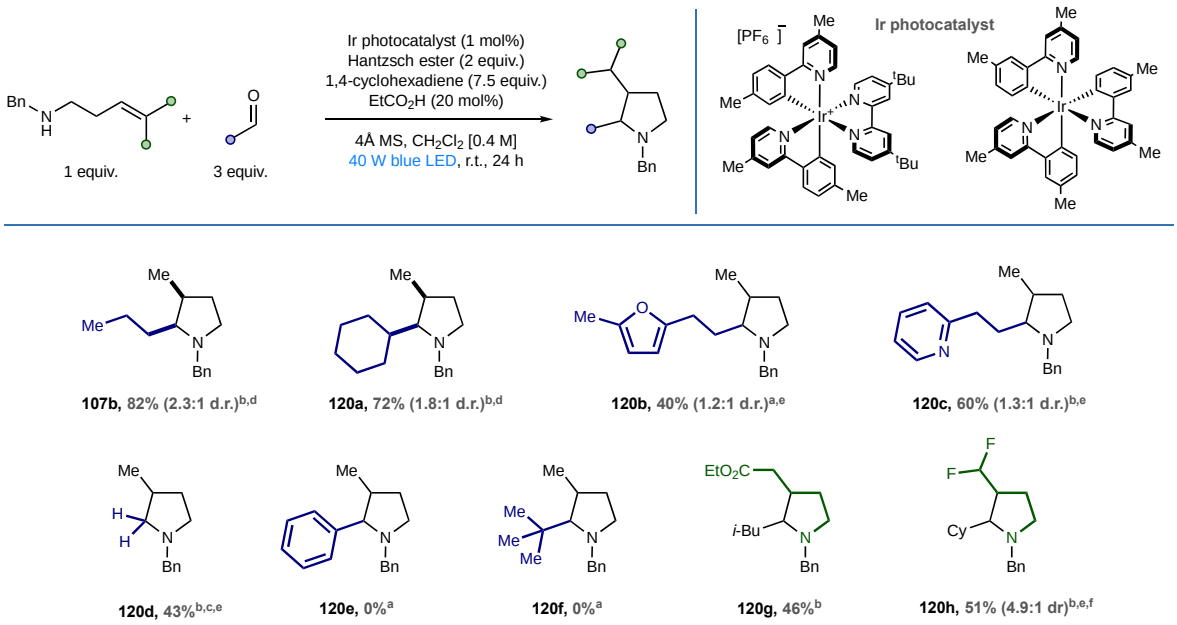
Scheme 95 | Bis-spirocyclic scope in the light-mediated synthesis of *N*-heterospirocycles. [a]Reaction using $Ir(dMeppy)_3$. [b]Reaction using $[Ir(dMeppy)_2(dtbbpy)]PF_6$. [c]Yields determined by ^1H NMR against 1,1,2,2-tetrachloroethane internal standard. [d]*Starting material prepared by Dr. D. Willcox.*

Dr. D. Willcox then showed that using the α-tertiary amines with aldehyde starting materials also afforded *N*-heterospirocycles in good to excellent yields (**119a-119e**, Scheme 96). Oxygen, nitrogen and sulfur containing ring could be tolerated. Interestingly, while oxetane or thiopyran-spirocycles (**119a**, **119c** & **119d**) were obtained as diastereomeric mixtures, complete diastereoselectivity was observed for bis-amino spirocycles (**119b** & **119e**), despite the fact that the structural differences are remote from the reactive center.



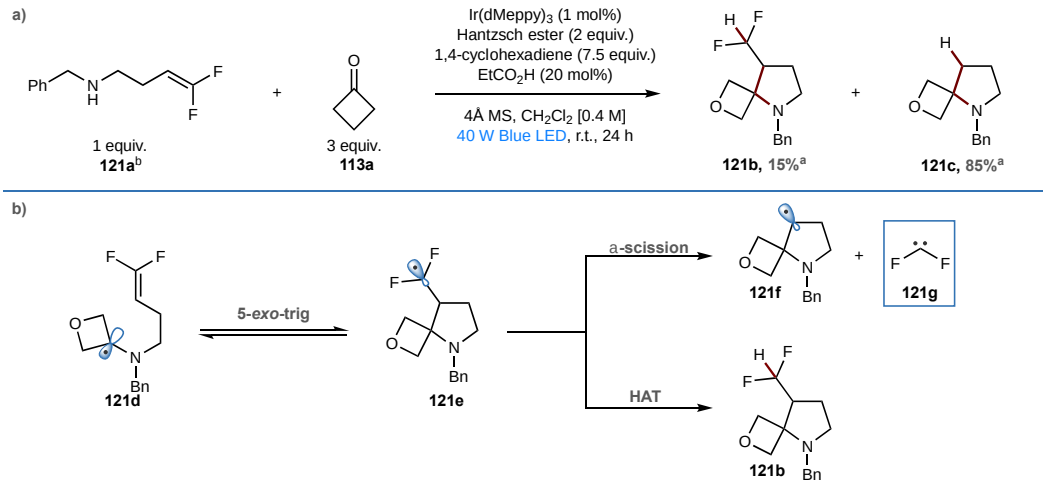
Scheme 96 | Aldehyde scope in the light-mediated synthesis of *N*-heterospirocycles. [a]Reaction using $[Ir(dMeppy)_2(dtbbpy)]PF_6$. [b]*Reaction conducted by Dr. D. Willcox.* [c]*Diastereomers were purified by HPLC by Dr. S. Walton.*

The scope of non-spirocyclic pyrrolidines was then evaluated (Scheme 97). Aliphatic aldehydes could be employed to afford **107b** and **120a** in high yields and Mr Y. Kim showed that furan as well as a pyridine group could be tolerated (**120b** & **120c**). It is worth noting that when basic substituents were tested, a stoichiometric amount of propionic acid was used. Formaldehyde afforded pyrrolidine **120d** in 43% yield, but aromatic or sterically hindered aldehydes did not give any product (**120e** & **120f**). As noted earlier, substituents on the alkene could be tolerated but afforded lower yields (**120g** & **120h**).



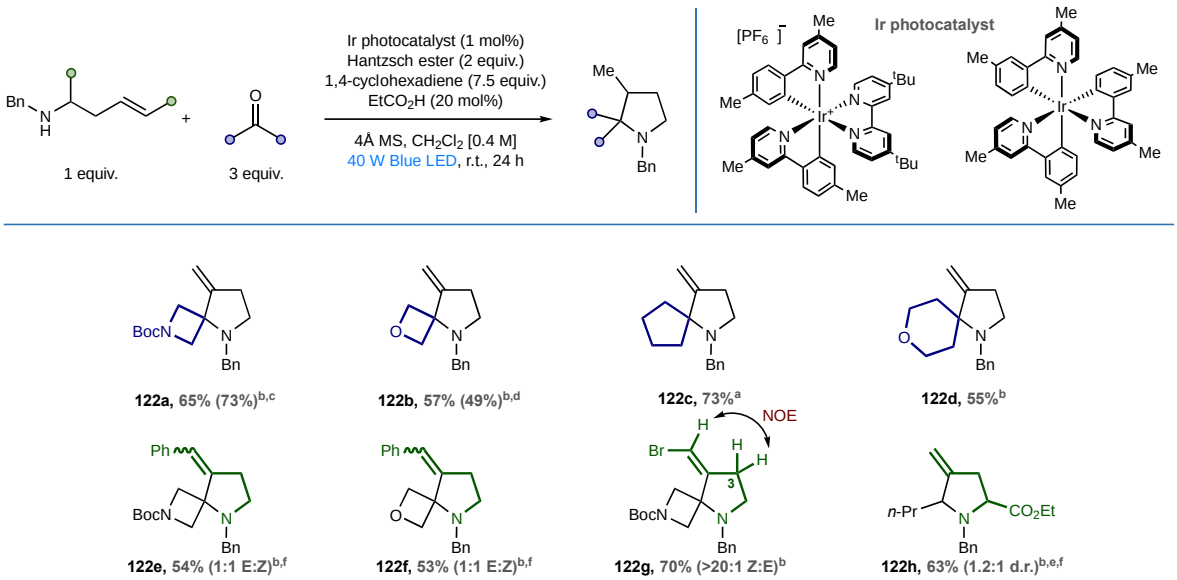
Scheme 97 | Aldehyde and alkene scopes in the light-mediated synthesis of pyrrolidines. [a]Reaction using $Ir(dMeppy)_3$. [b]Reaction using $[Ir(dMeppy)_2(dtbbpy)]PF_6$. [c]Yields determined by ^1H NMR against 1,1,2,2-tetrachloroethane internal standard. [d]*Reaction conducted by Dr. D. Willcox.* [e]*Reaction conducted by Y. Kim.* [f]*Starting material prepared by Dr. A. Trowbridge.*

Interestingly, when difluoroalkene **121a** was reacted with cyclobutanone **113a**, as opposed to cyclohexane carboxaldehyde which had afforded **120h** (Scheme 97), only 15% yield by ^1H NMR of the desired product **121b** was observed together with 85% yield of spirocycle **121c** (Scheme 98a). Tentatively, the loss of CF_2 was rationalized *via* α-scission of intermediate **121e** to give difluorocarbene **121g** instead of the desired hydrogen-atom transfer (Scheme 98b). It is possible that the more hindered nature of ketone derived **121e** (as opposed to an aldehyde derivative) slows down the rate of HAT. At the same time, steric interactions between the difluoromethylradical group and the more hindered ketone moiety accelerates the α-scission. Attempts to trap the putative difluoromethyl carbene so-formed, a common intermediate in cyclopropanation reactions, with *para*-methoxy styrene did not afford any cyclopropanated product.[472]



Scheme 98 | a) Reactivity of difluoroalkenylamines in the light-mediated synthesis of *N*-heterospirocycles. b) Mechanistic hypothesis to rationalize the loss of difluoromethyl fragment **121g**. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard. [b]*Starting material prepared by Dr. A. Trowbridge*.

Whilst early studies of radical cyclization of α-amino radicals onto alkenes had provided important insight to the current work,[457] α-amino radical cyclization onto alkynes had not been reported. However, Stalinski and Curran had shown that alkyl radical cyclization onto alkynes proceeds with high reaction rate constants ($k \approx 10^6$-10^7 s^{-1}) and consequently, alkynyl amines were explored with the current method.[473] This afforded a range of heterospirocyclic amines with an exocyclic alkene in good to high yields (Scheme 99). Importantly, reactions run on 2 and 10 mmol scales afforded similar yield to small-scale reactions (**122a** & **122b**). Substituents on the alkene could be tolerated (**122e**-**122g**) as well as on the backbone using an aldehydic substrate. Interestingly, the synthesis of **122e** and **122f** proceeded with no diastereoselectivity whilst **122g** was obtained as a single diastereomer.



Scheme 99 | Aldehyde and alkene scopes in the light-mediated synthesis of pyrrolidines. [a]Reaction using Ir(dMeppy)$_3$. [b]Reaction using [Ir(dMeppy)$_2$(dtbbpy)]PF$_6$. [c]2 mmol scale. [d]10 mmol scale. [e]*Reaction conducted by Y. Kim.* [f]*Diastereomers were purified by HPLC by Dr. S. Walton.*

The diastereoselectivity observed in the synthesis of **122g** can be rationalized by considering the structures of the phenyl versus the bromo-substituted alkenyl radicals (**123a** versus **123b** and **123c**, Figure 21).[474] The α-phenyl ethylene radical **123a** has been proposed to be linear (or bent but rapidly interconverting at ambient temperature) on the basis of ESR-studies[475] whereas a stable bent structure has been proposed for bromo-substituted alkenyl radicals.[476] The radical in **123a** is located in a p-orbital, which is parallel with neighboring 4-membered ring, and provides no facial selectivity. For the bromine-substituted radicals **123b** and **123c**, however, a strong bias is observed in favour of the less hindered radical **123b** as it reacts faster with the hydrogen-atom donor. The stereochemistry of **122g** was confirmed by an NOE-correlation between the alkenyl hydrogen and the C3 hydrogens on the pyrrolidine ring (Scheme 99).

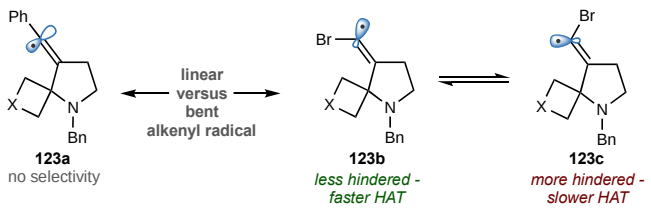
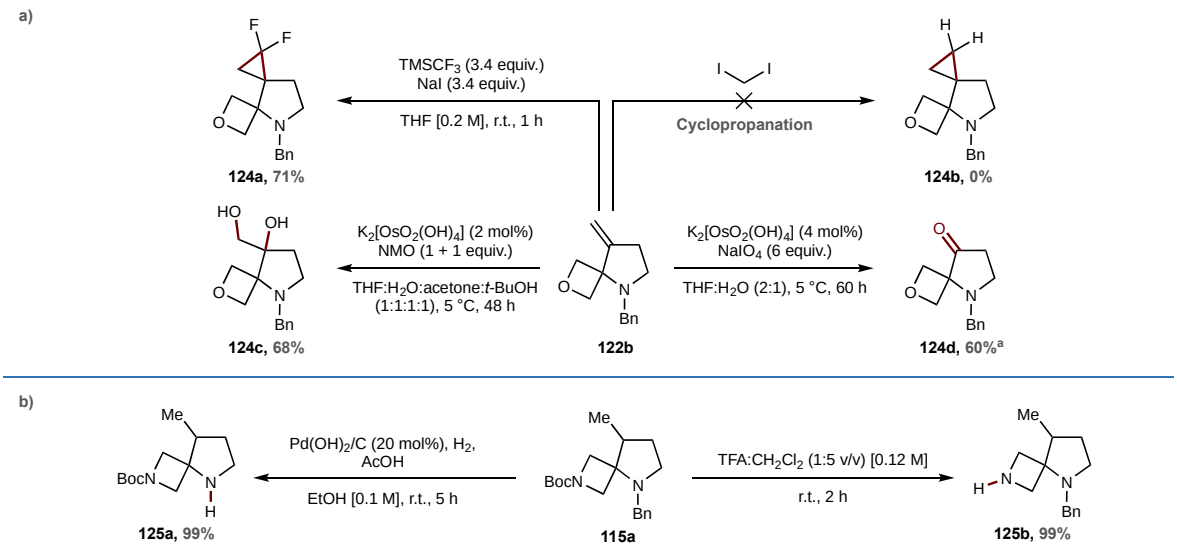


Figure 21 | Structure of alkenyl radicals to rationalize the diastereomeric outcome of the light-mediated synthesis of *N*-heterospirocycles.

Cyclization onto alkynes afforded a handle in the product structure that could be used for further derivatization (Scheme 100a). Osmium-catalyzed oxidation afforded diol **124c** and ketone **124d** in good yields. It was also shown that another spirocycle could be introduced using modified[477] conditions of Grygorenko's difluorocyclopropnation reaction,[478] affording dispirocycle **124a** in 71% whose structure was confirmed by x-ray diffraction of a single crystal. Simmons-Smith cyclopropanation using Et_2Zn/CH_2I_2 led to the decomposition of **122b**. In order to utilize the spirocyclic fragments reported in this chapter, the ability to selectively deprotect the amines is paramount. Under standard hydrogenation or Boc-deprotection conditions, **125a** and **125b** were obtained in quantitative yields (Scheme 100b).



Scheme 100 | a) Derivatization of *N*-heterospirocycle **122b**. b) Selective deprotection of *N*-heterospirocycle **115a**. [a]*Reaction conducted by Dr. A. Trowbridge.*

4.4.1 Topological analysis

Throughout this chapter, reference has been made to the 3-dimensionality of *N*-heterospirocycles and to the concept that they occupy underutilized areas of chemical space. One way of evaluating the "3-dimensionality" of the structures synthesized in this work is by using a Principal Moment of Inertia (PMI) analysis which classifies molecules according to their rod, sphere and disk-like properties.[479,480] As the deprotection studies above (Scheme 100b) proved that the fragments could readily be deprotected, "*in silico*" deprotection of the entire spirocyclic substrate scope afforded a library of 52 compounds. PMI analysis showed that the library covered a wide area of chemical topology, with 83% of the compounds exhibiting shapes outside of "flatland" (Figure 22).[379,481] The fragment collection was also compared with the library of drugs and natural products compiled by Tan *et al*.[482] Whereas our spirocyclic fragment library occupied similar topological regions as the natural product collection, it exhibited shapes significantly further away from flatland in comparison to the collection of 40 small molecule drugs of which 47% resided in flatland. This indicates that the spirocyclic fragments synthesized herein can access pharmaceutically lesser-explored topological domains and hence could prove valuable in future screening efforts.

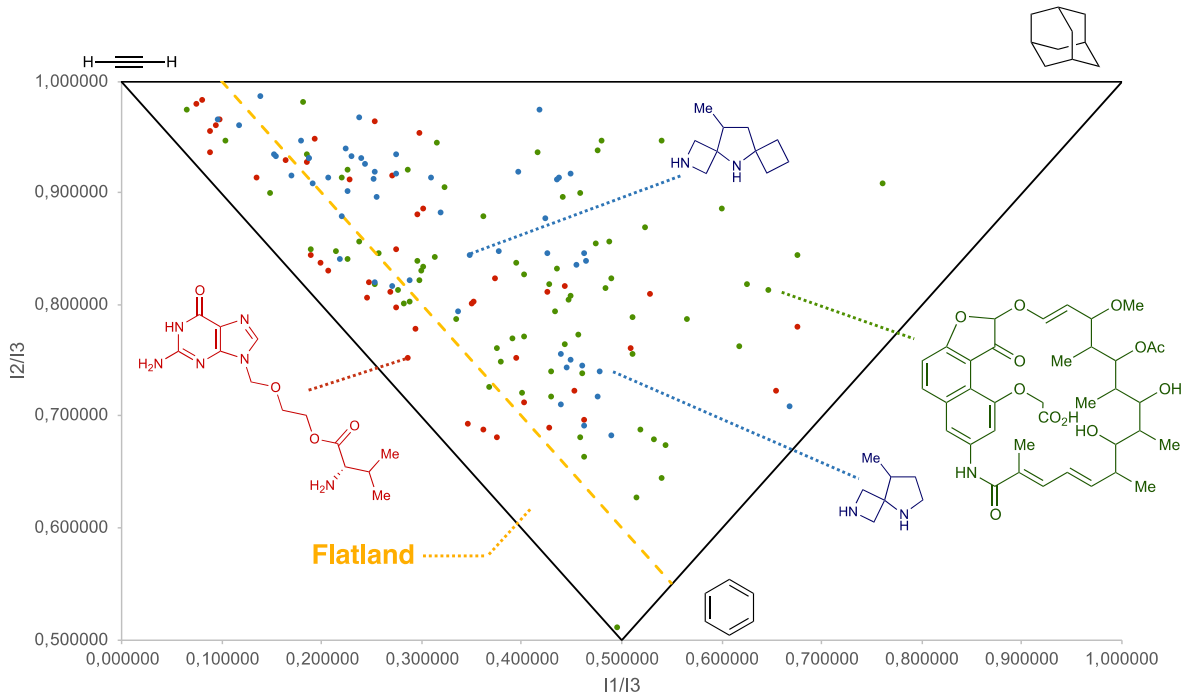
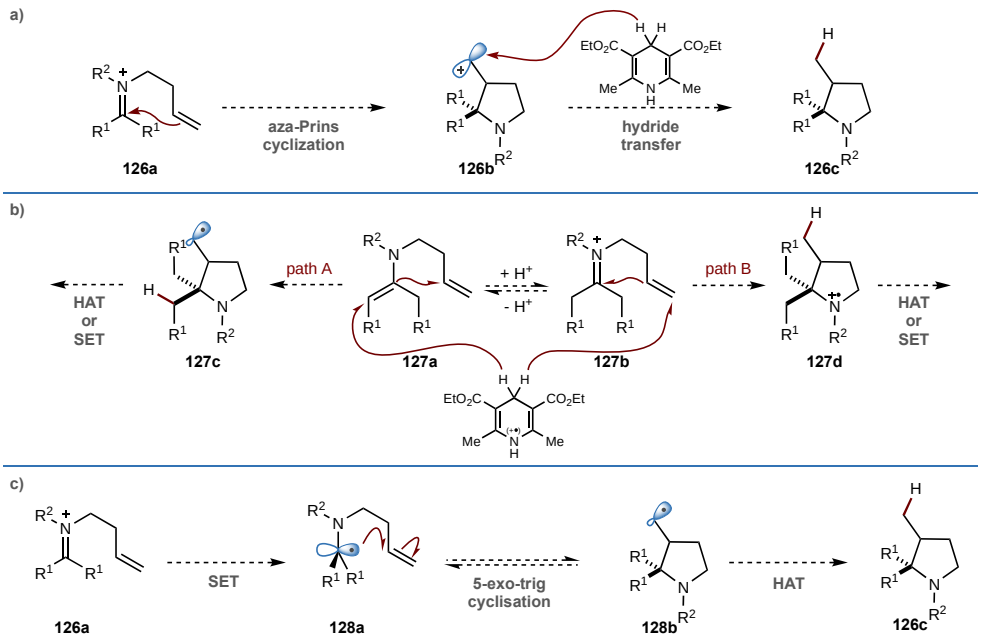


Figure 22 | PMI plot of the compounds (blue) synthesized in this work compared to two reference collection of natural products (green) and drugs (red). Each edge corresponds to the shapes of the three compounds depicted (propyne/linear, adamantane/spherical, benzene/flat). The space to the left of the yellow line is commonly referred to as "flatland".[483]

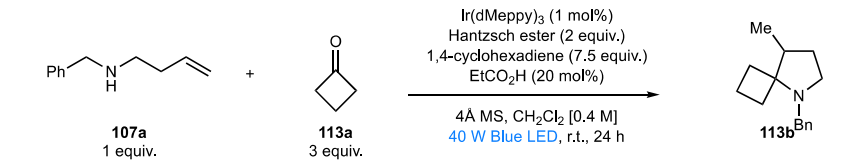
4.4.2 Mechanistic investigation

Despite the ease with which *N*-heterospirocycles could be synthesized with the method outlined in this chapter, the mechanistic picture of the reaction remained opaque. The reaction relied on the crucial combination of two hydrogen-atom donors, Hantzsch ester and 1,4-cyclohexadiene, whereas in theory, only one should suffice. Two different photocatalysts were also employed on a case-by-case basis depending on the electronic nature of the iminium ion involved. Both of these photocatalysts have two quenching cycles, either of which could be operative. As well as this, both photocatalysts are competent energy-transfer agents, complicating matters further. Although a radical-cyclization mechanism was hypothesized during the development of the above reaction, three conceptually different mechanisms were considered in the mechanistic investigations (Scheme 101). Firstly, a polar aza-Prins mechanism could be operative, where the alkene in **126a** acted as a nucleophile to afford a carbocation **126b** that could be trapped, possibly in a concerted fashion, through hydride-transfer from Hantzsch ester to form **126c** (Scheme 101a).[484] Alternatively, a HAT-mediated process whereby a hydrogen atom is transferred to the enamine (**127a**, path A) or the alkene (**127b**, path B) from Hantzsch ester to affect a cyclization step (Scheme 101b). This is analogous to the well-precedented metal-hydride mediated methods reported by Bode and co-workers.[439] Finally, a radical cyclization initiated *via* α-amino radical **128a** to form **128b1** was considered (Scheme 101c).



Scheme 101 | Possible mechanistic pathways for the light-mediated synthesis of *N*-heterospirocycles. a) Polar, aza-Prins type mechanism. b) Hydrogen-atom transfer mechanism. c) α-Amino radical mechanism.

To evaluate the first, polar hypothesis, a set of control reactions were run (Table 18). In the absence of light or photocatalyst, the reaction is almost completely inhibited (Entry 1 vs 2 & 3). The acid could be removed, but the yield was reduced to 46% (Entry 4). Reaction efficiency was slightly reduced upon exposure to air (Entries 5 & 6) and significantly inhibited when TEMPO was used. Taken together, these results indicate that a radical, not a polar, mechanism is operative.

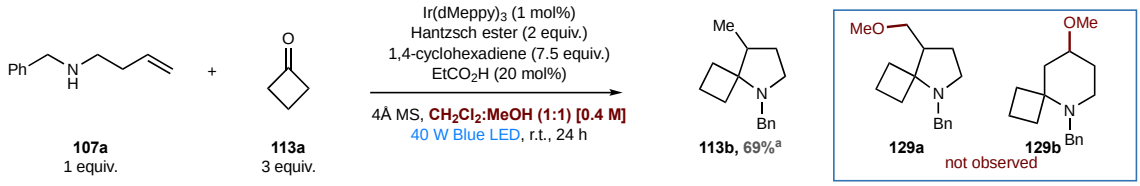


Entry	Deviation	Yield **113b**
1	None	91%
2	No light	0%
3	No Ir(dMeppy)$_3$	6%
4	No *n*-PrCO$_2$H	46%
5	Under air	78%
6	Under air, no degassed CH_2Cl_2	73%
7	TEMPO (1 equiv)	11%

Table 18 | Control reactions for the light-mediated synthesis of *N*-heterospirocycles.

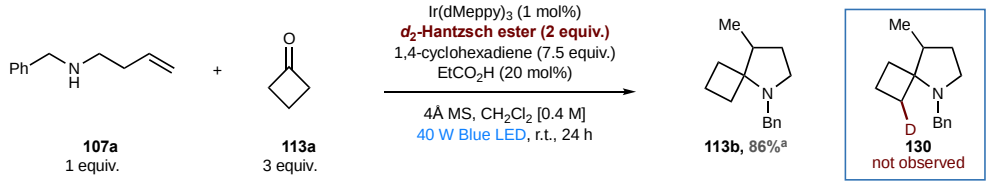
To further rule out a polar mechanism, the reaction was run using a 1:1 mixture of dichloromethane and methanol (Scheme 102). Methanol has been employed in related mechanistic investigations to support the existence of cationic intermediates in alkenyl cyclizations by trapping the transient cation. [485,486] However, no such trapping-product (**129a**) was observed and the desired product was obtained in 69% yield. This strongly disfavours a polar mechanism. Furthermore, if a polar mechanism was operative, it

would be expected, based on previous reports,[484] that a 6-*endo* type cyclization, to form **129b**, would prevail due to the greater stability of secondary versus primary alkyl cations but no such product was observed.[164,487]



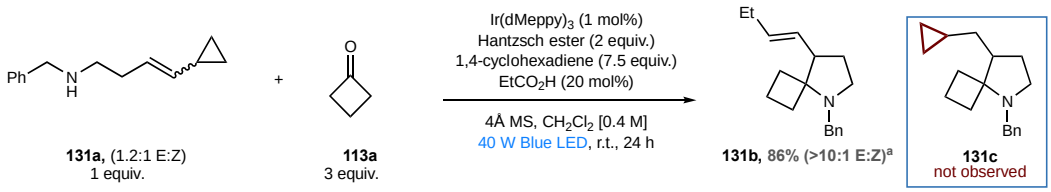
Scheme 102 | Control reaction to evaluate whether carbocationic intermediates are present in the light-mediated synthesis of *N*-heterospirocycles.

The second mechanistic proposal (Scheme 101b) was then considered. Within this general mechanism, two pathways could be operative: hydrogen-atom addition to the enamine (Path A, Scheme 101b) or addition to the alkene (Path B, Scheme 101b). To study this, d_2-Hantzsch ester was employed but deuterated product **130** was not observed, suggesting that the reaction is not mediated by HAT to an unsaturated bond (Scheme 103). This observation was strengthened in the case of "Path A" by the fact that enamines of 4-membered ketones are highly strained and are usually formed under harsh basic conditions,[488] reducing the concentration of the required enamine intermediate required for this pathway.



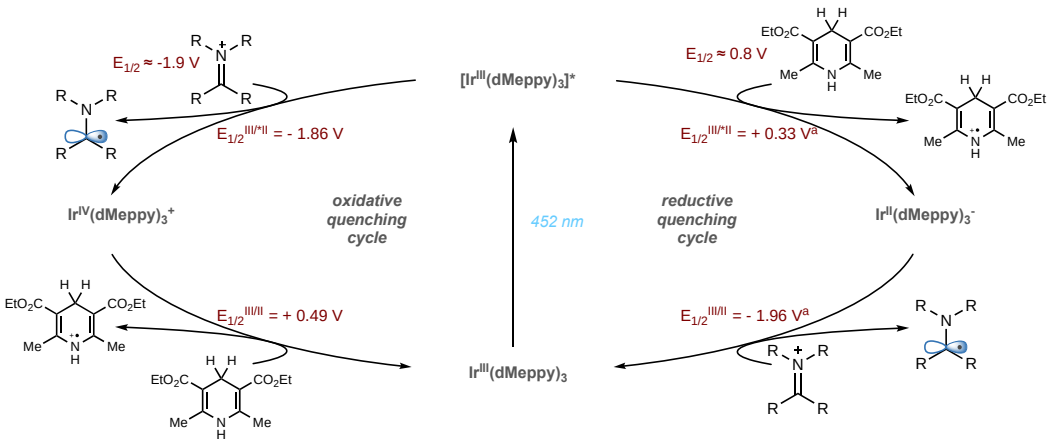
Scheme 103 | Control reaction to evaluate whether hydrogen-atom transfer to an enamine intermediate is operative in the light-mediated synthesis of *N*-heterospirocycles.

Further evidence was gathered with respect to "Path B" by introducing a cyclopropyl moiety in the alkenyl-amine starting material (**131a**, Scheme 104). When this was subjected to the reaction conditions, only ring-opened product **131b** was observed and as opposed to **131c**, which would be expected to form if "Path B" (Scheme 101b) was operative. This pathway is also disfavoured by the observed regioselectivity in spirocycle **113b** (e.g. scheme 103), where a HAT to the alkene would afford a more stable tertiary radical, resulting in a 6-*endo* radical cyclization as opposed to a 5-*exo* cyclization.



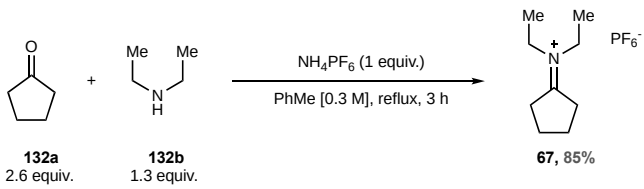
Scheme 104 | Control reaction using a cyclopropyl radical trap to evaluate if hydrogen-atom transfer to the alkene operative in the light-mediated synthesis of *N*-heterospirocycles.

Whilst the ring-opening of the radical trap in **131a** (Scheme 104) disfavoured the HAT-mechanism outlined in scheme 101b, it strongly supports a radical mechanism proceeding *via* an α-amino radical intermediate (Scheme 101c). In this mechanism, the α-amino radical **128a** formed from iminium ion intermediate **126a** cyclizes onto the alkene to afford alkyl radical **128b**. The presence of this radical is supported by the cyclopropyl-trapping experiment above and hence, indirectly, support the α-amino radical cyclization as the key mechanistic step (Scheme 101c). However, within this rather general mechanistic outline, there were several open questions. The first uncertainty concerns the formation of the putative α-amino radical **128a**. Using $Ir^{III}(dMeppy)_3$ as a photocatalyst, it could form *via* direct reduction by $Ir^{III}(dMeppy)_3$* (oxidative quenching cycle) or *via* reduction by $Ir^{II}(dMeppy)_3^-$ (reductive quenching cycle)(Scheme 105). In the latter case, Hantzsch ester ($E_{1/2}$ = +0.51 V vs Fc^+/Fc in MeCN)[462] could act as a stoichiometric single-electron reductant.



Scheme 105 | Two possible photocatalytic quenching cycles in the light-mediated synthesis of *N*-heterospirocycles. All reduction potentials are given versus SCE. [a]Computed values.[489]

To elucidate which cycle might be operative, Stern-Volmer quenching studies were undertaken to evaluate which reaction component quenched the excited state of the photocatalyst with the largest rate constant. To this end, the hexafluorophosphate salt of iminium ion **67** was prepared as a model substrate and isolated as a white crystalline solid (Scheme 106). Unfortunately, attempts at preparing an iminium salt carrying the pendant alkene failed as the desired product always contained small (≈ 10%) amounts of impurities.



Scheme 106 | Synthesis of a model iminium ion for Stern-Volmer studies.

With **67** in hand, **67** and Hantzsch ester were tested as quenchers. Interestingly, in contrast to previous reports using $Ir(ppy)_3$, Hantzsch ester proved a poor quencher of $Ir(dMeppy)_3$* (Figure 23).[456] In contrast, with iminium ion **67**, significant quenching was observed. This suggested that the excited state

of Ir(dMeppy)$_3$ directly engages with the iminium ion to produce an α-amino radical. This can be understood be observing the reduction potentials of the involved species (see scheme 105). While reduction potential of Ir(dMeppy)$_3$* essentially matches that of the iminium ion (oxidative quenching cycle, scheme 105), the ability of Ir(dMeppy)$_3$* to oxidize Hantzsch ester is thermodynamically uphill by 0.5 eV, indicating that this process will be slower.

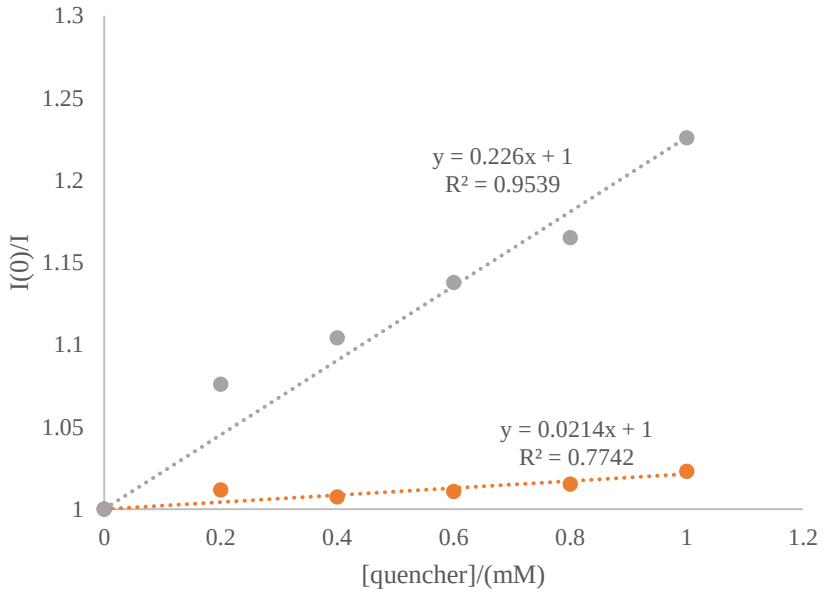


Figure 23 | Stern-Volmer quenching studies of Ir(dMeppy)$_3$ with Hantzsch ester (orange curve) and iminium ion **67** (grey curve).

Mindful that the Stern-Volmer studies do not indicate the *type* of quenching, i.e. *via* single-electron transfer or *via* energy-transfer, the latter case was considered. If the excitation of Ir(dMeppy)$_3$ induced energy-transfer to the iminium ion intermediate, the resulting species could oxidize the alkene and cyclize *via* a radical-radical recombination mechanism. Such mechanisms have been postulated and thoroughly studied by Mariano who used UV-light to affect a π-π* transition.[490,491] However, in the current context, two pieces of evidence strongly disfavours such a mechanism. Firstly, akin to the putative aza-Prins cyclization discussed above (Scheme 101a), this mechanism would afford a carbocation that should be methoxylated when methanol is used as a solvent, but this product is not observed (see scheme 102). In addition, when aldehydes were employed as substrate in the current reaction (see scheme 97), the corresponding pyrrolidine products were obtained with poor to excellent d.r. (see schemes 96 & 97). If the reaction was proceeding *via* a radical-radical recombination mechanism, it is highly unlikely that any diastereoselectivity would be observed.

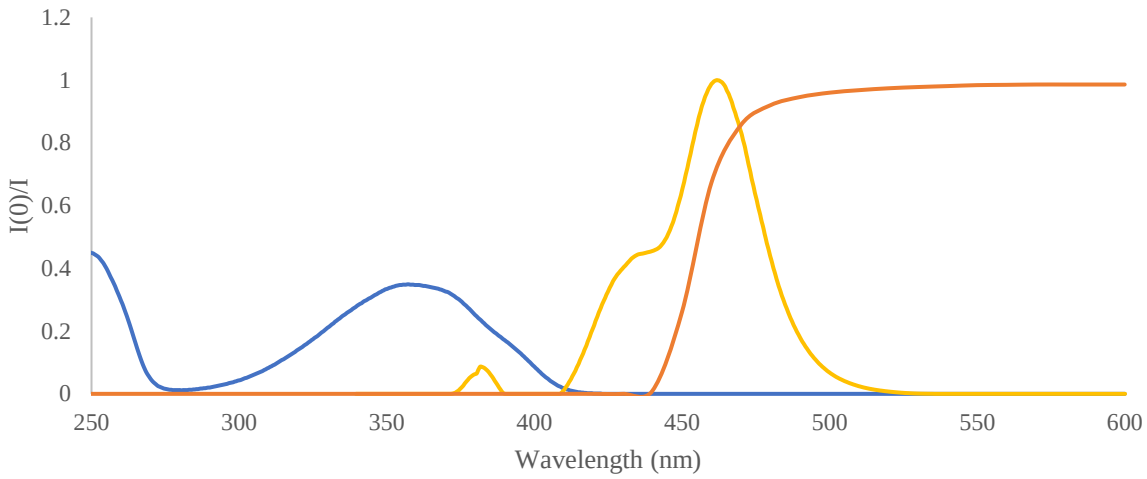
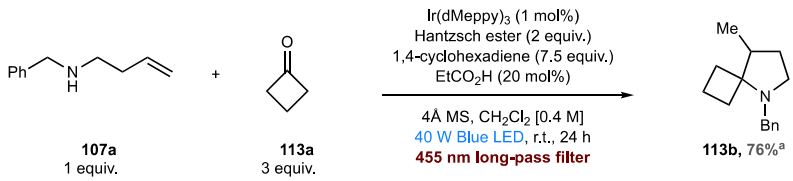


Figure 24 | UV-vis studies to elucidate whether an excited state Hantzsch ester species is operative in the light-mediated synthesis of *N*-heterospirocycles. Blue curve = Hantzsch ester absorption. Yellow curve = Emission of the 40 W Blue LED. Orange curve = Cut-off wavelength of a 455 nm long-pass filter.

These studies suggested that a single-electron reduction of iminium ion **126a** (Scheme 101c) by the excited state of $Ir(dMeppy)_3$ was a feasible pathway. However, Hantzsch ester could also be excited to form a highly reducing species ($E_{1/2}$ = -2.23 vs Fc^+/Fc in CH_2Cl_2)[492] and consequently might be responsible for reducing **126a** under the reaction conditions. In particular, the comparatively higher loading of Hantzsch ester versus $Ir(dMeppy)_3$ (200-fold) would mean that the concentration of excited state Hantzsch ester might be significantly higher. To probe the involvement of excited state Hantzsch ester, the UV-vis spectrum was recorded (blue curve, Figure 24) and compared to the emission from the 40 W blue LED light used (yellow curve). This comparison showed that there is a small overlap at 380 nm, suggesting that single-electron reduction of iminium ion **126a** by excited state Hantzsch ester could be operative. To rule this out, a 455 nm long-pass filter was employed, which removes all photons below the cut-off wavelength (orange curve). This filter was then used under the reaction conditions and the product was obtained in slightly reduced 76% yield (c.f. 91% yield without filter).



Scheme 107 | Effect of applying a 455 nm long-pass filter to remove near UV-light on the light-mediated synthesis of *N*-heterospirocycles. [a]Yields determined by ^1H NMR against 1,1,2,2-tetrachloroethane internal standard.

While the long-pass filter removes all the photons capable of exciting Hantzsch ester, it also removes a substantial amount of the irradiation that is responsible for exciting the iridium-photocatalyst (Figure 25).

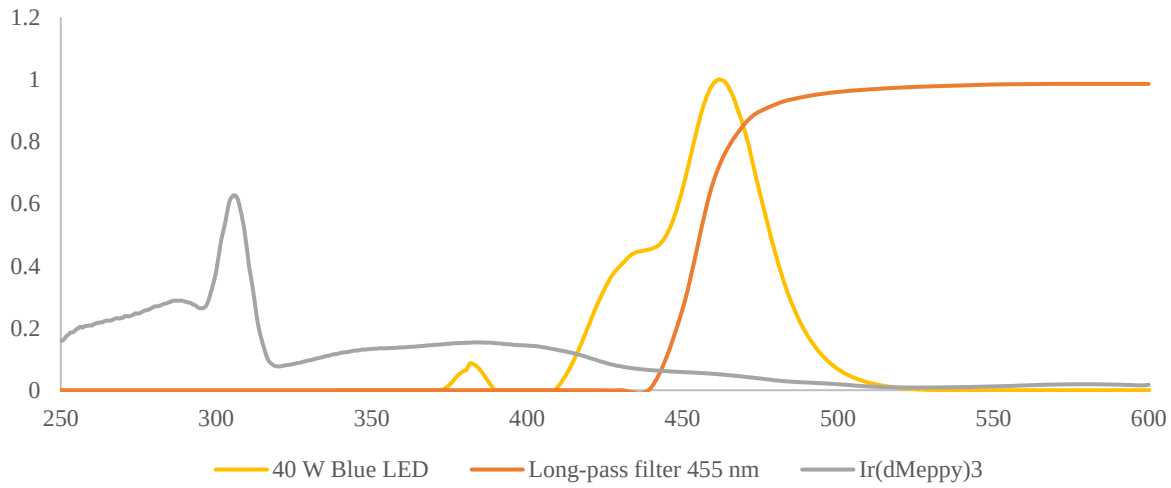


Figure 25 | Effect of applying a 455 nm long-pass filter to the ability to excite Ir(dMeppy)$_3$. Grey curve = Absorption of Ir(dMeppy)$_3$. Yellow curve = Emission of the 40 W Blue LED. Orange curve = Cut-off wavelength of a 455 nm long-pass filter.

Speculating that this might be the reason for the small drop in yield when the filter was employed, the reaction yield was investigated at different light intensities (Figure 26). It shows a strong correlation between the photon flux (intensity) and the yield of spirocycle **113b**. This is consistent with the intermolecular α-amino radical Giese reaction which also exhibited flux-limited behavior.[456] Taken together, this suggests that the small drop in yield when a filter is employed is due to a lower photon flux and that the formation of α-amino radicals *via* iminum ion reduction by excited state Hantzsch ester is not operative under the reaction conditions in this work.

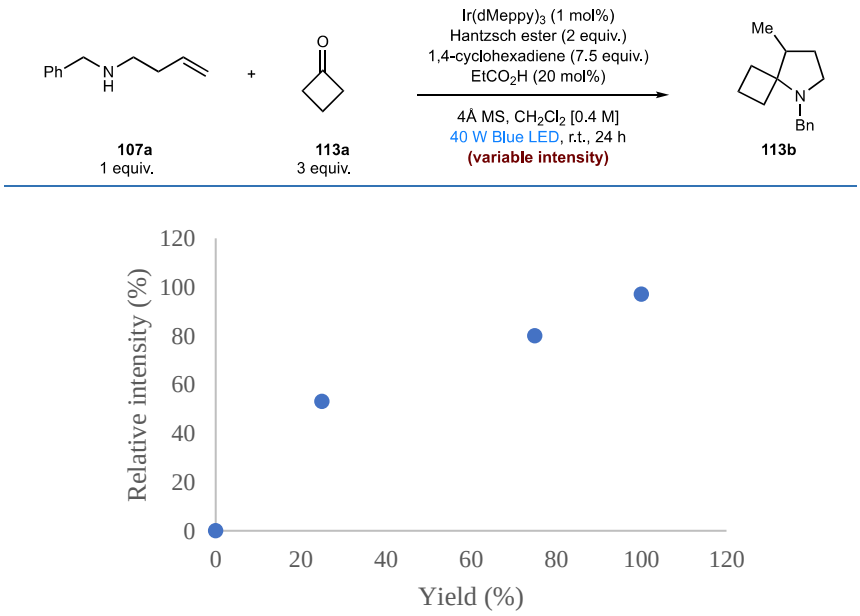
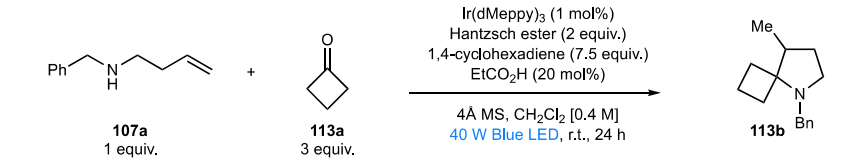


Figure 26 | Effect of light intensity on the light-mediated synthesis of *N*-heterospirocycles. Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

Having established that single-electron transfer from $Ir^{III}(dMeppy)_3$* is the most likely pathway *via* which iminium ion **126a** is converted into α-amino radical **128a**, attention was shifted to the nature of the subsequent hydrogen-atom transfer. Control experiments showed that both Hantzsch ester and 1,4-cyclohexadiene were required to obtain **113b** in high yield (Entries 1-3, Table 19). Importantly, the effect of using both HAT-reagents was greater than the effect of either employed individually. Interestingly, in contrast to the results obtained during the aldehyde optimization studies (c.f. Tables 14 & 16), TTMSS afforded significantly lower yields both on its own and in conjunction with Hantzsch ester (Entries 4 & 5, Table 19). These control experiments points to the importance of a fast hydrogen-atom transfer step to terminate the reaction, presumably as a result of the lack of thermodynamic driving-force from the thermoneutral cyclization step (see Scheme 90). The poor results obtained with TTMSS can rationalized by the higher BDE compared to 1,4-cyclohexadiene and Hantzsch ester. In addition, the greater number of available hydrogen atoms will result in a more favourable frequency factor (A-factor) in the latter cases.



Entry	Deviation	Yield **113b**[a]
1	None	91%
2	No 1,4-cyclohexadiene	24%
3	No Hantzsch ester	43%
4	TTMSS (2 equiv.), no Hantzsch ester or 1,4-cyclohexadiene	4%
5	TTMSS (2 equiv.), no 1,4-cyclohexadiene	31%

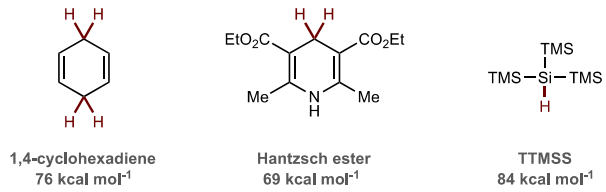


Table 19 | Control experiments to elucidate the origin of the dual-HAT-reagent effect observed in the light-mediated synthesis of *N*-heterospirocycles. [a]Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

The requirement to use both 1,4-cyclohexadiene and Hantzsch ester inevitably begs the question of "who is doing what". To this end, both C4 d_2-Hantzsch ester and deuterated 1,4-cyclohexadiene surrogate **133a**, which was prepared by Dr. A. Trowbridge, were tested in the reaction in the reaction. Unfortunately, the reaction with **133a** afforded only 5% deuterium incorporation (Figure 27a) whilst d_2-Hantzsch ester **133b** afforded 0% deuterium incorporation (Figure 27b). Running the reaction in deuterated dichloromethane did not affect the reaction outcome. Currently, no explanation for this unexpected result has been found.

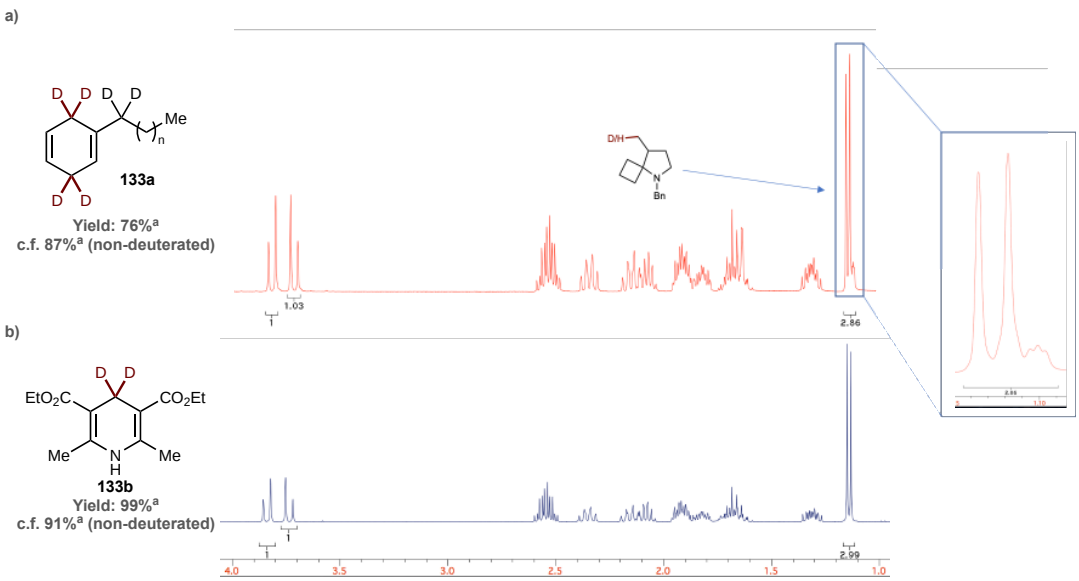


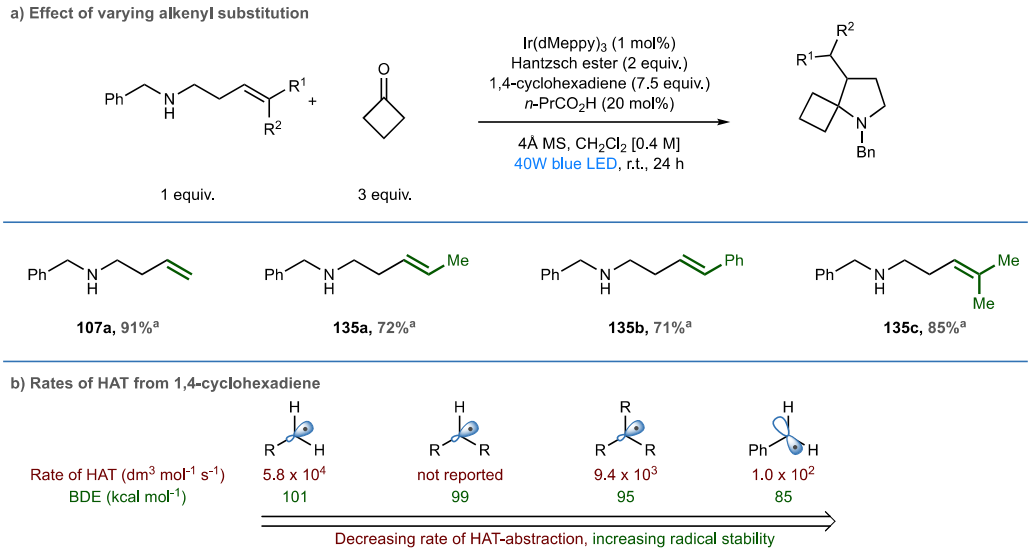
Figure 27 | a) Deuterium-labelling experiment using deuterated cyclohexadiene-derivative **133a**, *the synthesis of which was conducted by Dr. A. Trowbridge.* b) Deuterium-labelling experiment using d_2-Hantzsch ester.[493] Yields determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

As the deuterium-labelling studies did not provide any conclusive results, attempts were made to support the existence of putative radical **128b** by other means. Strong evidence in this regard had already been found by the cyclopropyl radical trap (see Scheme 104). Bromotrichlorometane is also a known intermolecular radical trap due to the weak C–Br bond (BDE = 55 kcal mol^{-1}).[116,494] Replacing 1,4-cyclohexadiene with $BrCCl_3$ proceeded readily to afford bromide **134** in 79% yield by ^{1}H NMR (Scheme 108). Unfortunately, this species proved difficult to purify, as every round of silica or alumina chromatography induced decomposition. Nevertheless, this result provided additional support in favour of a radical cyclization mechanism.

Scheme 108 | Bromine-trapping experiment to support a radical cyclization mechanism for the light-mediated synthesis of *N*-heterospirocycles. [a]Yield determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

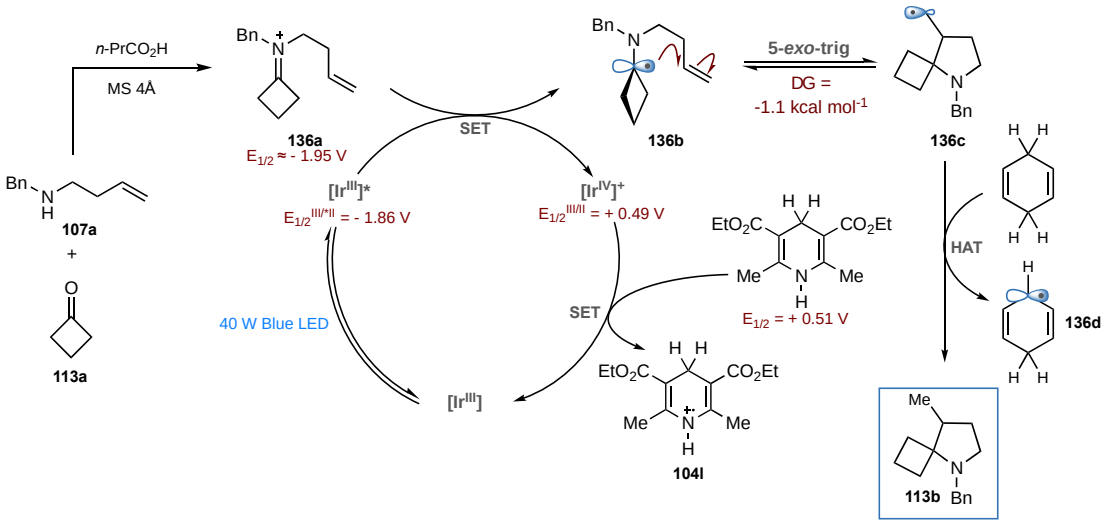
An interesting observation was made when the substitution pattern of the alkene was varied. The unsubstituted alkene substrate **107a** afforded the corresponding product in higher yield than the substituted alkenes (**135a-135c**). Typically, substituted alkenes afford higher yield in radical addition reactions and only in particular examples, such as in degenerative xanthate transfer, do unactivated alkenes afford higher yields.[99] The reason for this is that increasing substitution of the alkene, in particular using aromatic groups, increases the stability of the resulting radical, making the cyclization step more exothermic. However, as the stability of the resulting radical increases, the rate with which it can abstract a hydrogen atom from 1,4-cyclohexadiene or Hantzsch ester to terminate the reaction

decreases. Consequently, a high rate constant of HAT is more important than an increased concentration of the cyclized radical **128b** (scheme 109) in improving the overall rate of the HAT-step.



Scheme 109 | a) Effect of varying the substitution pattern on the alkene in the light-mediated synthesis of *N*-heterospirocycles. b) Rates of hydrogen-atom transfer from 1,4-cyclohexadiene to various alkyl radicals.[74] [a]Yield determined by ^{1}H NMR against 1,1,2,2-tetrachloroethane internal standard.

Based on the mechanistic insights outlined above, a comprehensive mechanistic proposal can be put forward (Scheme 110). Following the condensation of amine **107a** with ketone **113a**, the iminium ion **136a** ($E_{1/2} \approx +1.95$ V vs SCE in MeCN) can be reduced by the excited state $[Ir^{III}]^*$ ($E_{1/2}^{IV/III*} = -1.86$ V vs SCE in CH_2Cl_2). Although the reported reduction potential for the all-alkyl iminium ions is slightly more negative than that of the photocatalyst, electron-transfer as exothermic as 0.6 V has been reported as feasible and the step is further supported by the Stern-Volmer quenching studies.[171,495] The resulting α-amino radical **136b** will be in an equilibrium with its cyclized isomer **136c**, with the exact position being dependent on the ketone or aldehyde employed. For example, the strained nature of cyclobutanone-derived radical 136b provides a small additional driving-force compared to less strained ketones (c.f. **110a**, Scheme 90).[496] The alkyl radical **136c** can then abstract a hydrogen atom from 1,4-cyclohexadiene (or from **136d** or **104l**) to afford the desired product. Meanwhile, the photocatalytic cycle is turned over by the oxidation of Hantzsch ester (or **136d**) to form **104l**.



Scheme 110 | Proposed mechanism of the light-mediated synthesis of *N*-heterospirocycles.

This proposal also provides a putative explanation as to the need for two different stoichiometric reductants. In the absence of Hantzsch ester, it is feasible to suggest that radical **136d** could turn-over the photocatalytic cycle. However, this is not efficient, as **136d** will only be present in at most 0.004 M concentration which would lower the rate of the HAT-step. This will allow α-amino radical **136b** to react with $[Ir^{IV}]^+$ in back-electron transfer to reform the starting materials or to engage in other deleterious side-pathways. Similarly, in the absence of 1,4-cyclohexadiene, the abstraction of a hydridic hydrogen atom from Hantzsch ester by **136c** is likely to be slow. This is further complicated by the poor solubility of Hantzsch ester, limiting its concentration to ≈ 0.8 M in dichloromethane. In contrast, low-molecular weight 1,4-cyclohexadiene is a liquid and can easily be employed in superstoichiometric quantities. Consequently, it is proposed that 1,4-cyclohexadiene and Hantzsch ester fulfill complementary roles as hydrogen atom versus single-electron reductants. By-products resulting from **136d** or **104l** have not been isolated, although the mass corresponding to dimerized Hantzsch ester molecules has been observed by LC-MS.

4.5 Summary

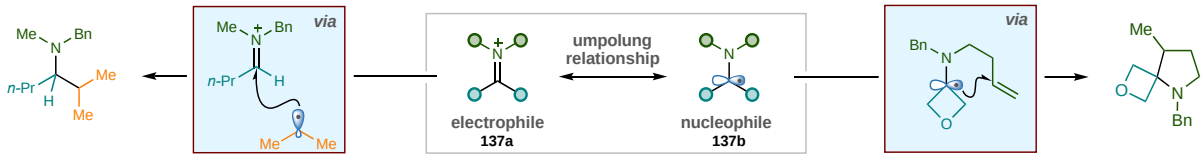
In this chapter, the development of a visible light-mediated synthesis of *N*-heterospirocycles has been described. The reaction uses commercially available alicyclic or heterocyclic ketones together with readily available homoallyl-amine reagents that combine to form iminium ions which after single-electron reduction by a photocatalysts provides access to α-amino radicals. This versatile synthetic intermediate facilitates a radical cyclization event to afford a range of *N*-heterospirocyclic scaffolds. Crucial to the success of the reaction is the synergistic combination of Hantzsch ester and 1,4-cyclohexadiene as complementary reducing agents, providing an electron, to the iminium ion, and a hydrogen atom, to the cyclization product, respectively. This unlocked a broad scope with respect to both reaction components; A variety of 4- to 6-membered heterocyclic ketones could be tolerated, as could alicyclic and some acyclic ketones. The reaction showed an excellent functional group tolerance as a range of *N*-substituted homoallyl and homopropargyl amines could be reacted to afford spirocycles in high yields. Mechanistic investigations established that the α-amino radical is obtained *via* single-electron reduction from an excited Ir^{III} species while polar and energy-transfer pathways could be ruled out. Finally, bioinformatics studies indicated that the method accessed scaffolds which are not well explored in medicinal chemistry and hence might be of use in future drug discovery efforts. Taken together, the method constitutes a rare example of a direct method with which to access pharmaceutically relevant *N*-heterospirocycles and as such might be of interest in the pharmaceutical industry.

5 Conclusions and outlook

Aliphatic amines represent one of the most important functional groups in pharmaceutical agents, driven by their ability to balance solubility, membrane permeability and potency. It is therefore not surprising that the development of new reactions to synthesize aliphatic amines using different retrosynthetic disconnections or more abundant and readily accessed starting materials is a highly active field of research. The vast majority of methods that construct aliphatic amines use polar, 2-electron chemistry whereas, in comparison, radical methods have been less heavily exploited.

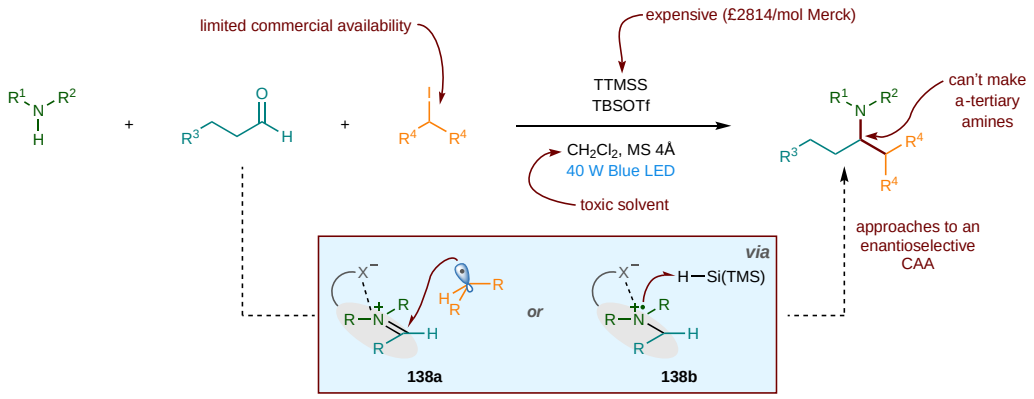
Most areas in organic chemistry advance in waves, each time spurred by a new set of discoveries. Arguably, synthetic radical chemistry can be considered to have undergone at least two waves. The first wave in the 1970s and onwards followed the determination of rate constants, reactivity patterns and the resulting understanding that radical reactions can indeed be controlled. The second wave followed with the revival of photoredox catalysis in 2008, which brought new means by which radicals could be generated and provided a solution to the conundrum of how to have an oxidant and a reductant present in the same reaction vessel. Even before the first wave, studies by Löffler & Freytag,[134] Bamford[497] and Norrish[498] had established the reactivity of *N*-centered radicals whereas Cookson[499–501] and Bryce-Smith[502,503] later established the reactivity of α-amino radicals in their addition to alkenes and recombination with other *C*-centered radicals. This knowledge was then used by Neale,[131] Minisci,[271] Newcomb[135] and Mariano[155] in the development of new synthetic reactions. However, possibly with the exception of the HLF reaction, it was only recently that synthetically useful (with regards to scope and functional group tolerance) radical reactions for aliphatic amine synthesis were developed by, for example, Knowles,[504] Fu[188] and Morandi.[139]

In this thesis, the development of three new radical methods for the synthesis of aliphatic amines have been presented. The three reactions are unified through the umpolung relationship of the iminium ion (**137a**) and the corresponding α-amino radical (**137b**, Scheme 111). Specifically, the iminium ion can be used either as an electrophile for the addition of alkyl radicals (Chapters 2 and 3) or as a nucleophile following single-electron reduction to provide access to an α-amino radical (Chapter 4).



Scheme 111 | Overview of the conceptual similarity and umpolung relationship between the CAA-reaction (left; Chapters 2 & 3) versus the *N*-heterospirocycle synthesis (right; Chapter 4) detailed in this thesis.

The carbonyl alkylative amination reaction developed in chapter 2 provides a solution to the long-standing challenge of adding alkyl nucleophiles to iminium ions (Scheme 112). While polar organometallic addition to iminium ions has been explored for over 70 years, the basic organometallic reagents have proved incompatible with the sensitive iminium ion intermediate. The radical approach detailed herein overcame this problem – the alkyl radicals often nucleophilicity of the organometallic reagents whilst hydrogen-atom transfer from the α-position of the iminium ion is slow. Building on the extensive studies by Miyabe & Naito,[245] Friestad[239] and others, the use of a silane reducing agent allowed both radical generation (from an alkyl halide) and trapping of the aminium radical cation – a process inspired by the Giese-addition.[84] In what way then, does this reaction complement the current literature? To answer that question, one has to consider the competition. Whilst it is true that the addition of organometallic reagents to iminium ions is nowhere near general and is rarely used except for the synthesis of primary amines (with Ellman's or Enders' auxiliaries), tertiary amines can be synthesized on a routine basis via reductive amination or *N*-alkylation. However, the CAA-reaction is three-component, rather than two – this means that one can create libraries of compounds using commercial aldehydes, halides and amines without the need to synthesize the less abundant ketone (which would be needed for the corresponding reductive amination). One might argue that ketones are easy to synthesize using Weinreb's amide[505] or, more recently, photoredox catalysis,[506,507] but in a time-pressured environment such as drug discovery, the CAA-reaction has an advantage. Furthermore, reductive amination of ketones with secondary amines are challenging, typically proceeding in low yields even at high reaction temperatures and using strong Lewis acids (e.g. Ti(*i*-PrO)$_4$).[508] In contrast, the CAA-reaction is far less sensitive to sterics and is run at room temperature – the addition of tertiary alkyl fragments yielded excellent yields without exception due to their electron-rich nature. If the CAA-reaction is compared to *N*-alkylation, it is noteworthy that nucleophilic substitution by secondary amines to secondary alkyl halides is slow and requires forcing conditions. The lack of a large variety of commercially available secondary alkyl halides is another problem for *N*-alkylation. Consequently, it can be concluded that the CAA-reaction indeed offers immediate advantages and complementarity when compared to current state-of-the-art methods.

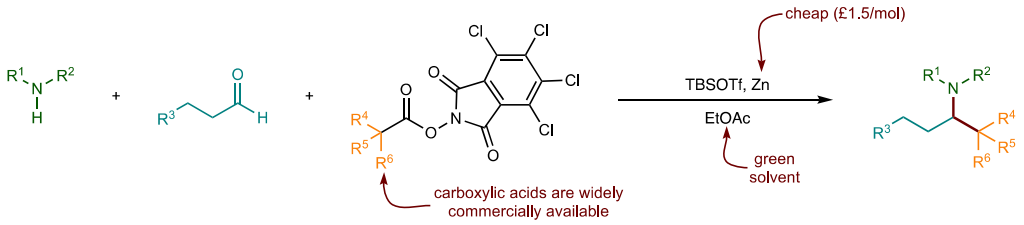


Scheme 112 | Overview of the CAA-reaction, its shortcomings and approaches to the development of an enantioselective variant.

This positive view of the CAA-reaction would be further brightened if some of its shortcomings could be addressed. Expanding the scope to encompass ketones (to access α-tertiary amines) would provide an additional edge over both reductive amination and *N*-alkylation. Although early attempts (see Chapter 2, Scheme 58) failed, J. H. Blackwell has shown (in unpublished work) that activated ketones can facilitate this process and hence constitute an important step on the way. The CAA-reaction would also benefit immensely if nucleophile precursors other than alkyl halides could be used to further widen the scope and this was addressed in chapter 3. In its current form, the CAA-reaction is racemic, but it is conceivable that the use of chiral counteranions to differentiate either the 1,2-addition (**138a**) or the hydrogen-atom transfer to the aminium radical cation (**138b**) might provide an enantioselective variant.[509] Towards this end, important mechanistic work has to be undertaken to establish the degree of reversibility in the 1,2-addition through β-scission. In light of the rise of biocatalysis in combination with visible light, an enzyme-encapsulated hydrogen-atom transfer might present a promising direction.[510] Finally, the low reaction concentration and expensive silane reagent leaves additional room for improvement from an environmental and cost perspective.

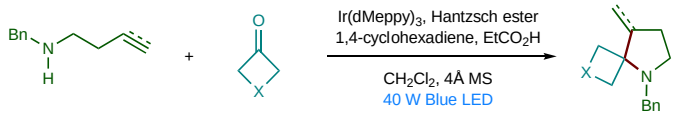
Attempts at addressing some of these shortcomings have already been outlined in chapter 3, focusing on the use of alternative nucleophiles. The commercially available alkyl halides often carry little or no functionality and would hence likely need to be prepared beforehand, undermining the practicality of the CAA-reaction. Furthermore, tertiary alkyl halides remain a synthetic challenge and when an α-heteratom or α-aromatic group is introduced, their stability becomes a serious concern. This problem was addressed through the introduction of tetrachloro *N*-hydroxyphthalimide esters, derived from carboxylic acids, as nucleophile precursors (Scheme 113). These are bench-stable, crystalline solids and both tertiary and α-heteroatom variants are readily prepared. To obtain high yields, the previously used silane was replaced by stoichiometric amounts of zinc-powder and the reaction can now be run in the absence of light. In addition, the use of thermal conditions enabled previously incompatible amines such as azetidines to react under these new CAA conditions. The full scope and limitations, however, need to be established before any final conclusions can be made. Although the use of tetrachloro *N*-hydroxyphthalimide esters suffers from poor atom-economy, the ability to leverage on the enormous variety of carboxylic acids marks a substantial advance of the original CAA-reaction. The new reaction conditions also require in-depth mechanistic investigations. It is not clear whether the Zn-conditions proceed via radical addition to the iminium ion or if in fact the “historical challenge” of finding mild organometallic conditions for carbonyl alkylative amination have, by accident, been “solved”. One could also envisage a radical-polar cross-over mechanism, which would complicate the interpretation of radical clock experiments. However, if the reaction proceeded via an organozinc reagent, the use of ligands that bind this reactive intermediate might provide another route for enantioselective carbonyl alkylative amination. In conclusion, the ability of both CAA-conditions (i.e. the conditions from

chapters 2 and 3) to tolerate a range of pharmaceutically relevant scaffolds and polar biomolecules such as biotin in conjunction with the simple reaction conditions and commercial starting materials suggest that they will find application in medicinal chemistry. The simple yet powerful retrosynthetic logic that underpins the reaction might further increase the rate of adoption.



Scheme 113 | Overview of the zinc-mediated CAA-reaction of tetrachloro *N*-hydroxyphthalimide esters (Chapter 3) and its advances compared to the original CAA-reaction (Chapter 2).

N-Heterospirocycles constitute an under-explored scaffold in medicinal chemistry. However, as the advantageous properties of these rigid, polar and C(sp^3)-rich motifs have become apparent, there has been a rapidly increasing interest in their synthesis and application. *N*-heterospirocycles are typically synthesized with traditional chemical methods in long, linear sequences. This has made it more difficult to readily include these promising motifs in screening-libraries and as alternatives in lead optimization. Meanwhile, direct methods using commercially available starting materials remain rare. In chapter 4, we have addressed this methodological deficiency through the development of a visible light mediated synthesis of *N*-heterospirocycles, proceeding *via* an α-amino radical intermediate (Scheme 114). The reaction uses commercially available ketones together with easily synthesized alkenyl or alkynyl amine reagents as starting materials, hence avoiding long linear synthetic routes. Mechanistic studies established a reaction mechanism wherein an excited state Ir^{III}-photocatalyst enabled the formation of an α-amino radical intermediate which after cyclization and trapping afforded the desired spirocyclic products. These were found to occupy lesser explored areas of chemical space in a partial moment of inertia analysis and could be derivatized to obtain densely functionalized scaffolds. Future work would include targeting small-ring spirocycles based on the azetidine motif. This transformation will require a thermodynamically unfavourable 4-*exo*-trig cyclization to be coupled with a fast terminating step in order to proceed. Another interesting avenue would entail the synthesis and deprotection of a variety of *N*-heterospirocycles to be evaluated in fragment-based drug discovery.



Scheme 114 | Visible light mediated synthesis of *N*-heterospirocycles (Chapter 4)

6 Experimental section

6.1 General experimental

All reactions were performed under nitrogen using oven-dried glassware unless stated otherwise. Yields refer to isolated, chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise indicated. Diastereomeric ratios were determined using crude ^{1}H NMR unless stated otherwise. All synthesized compounds that had been previously reported in literature gave rise to spectra in agreement with the literature reference cited.

Diethyl ether and tetrahydrofuran were distilled over lithium aluminium hydride; acetonitrile, dichloromethane and toluene over calcium hydride. Dichloromethane for use in the visible light mediated reactions was degassed (freeze-pump-thaw x 3) and stored over 4Å MS (beads). Powdered 4Å MS were activated by heating (250°C) under vacuum (≈1 mbar) and stored under vacuum (≈1 mbar). Ketones were used as supplied whereas aldehydes were distilled and used immediately. Aqueous ammonia solution contained 28-30% NH_3. All other materials and solvents were obtained from commercial suppliers and used without further purification unless stated otherwise. Flash chromatography was performed on silica gel (Merck Kieselgel 60 F254 230-400 mesh; CAS: 7631-86-9) or alumina (Merck Aluminium Oxide 90; CAS: 1344-28-1) unless otherwise stated. Thin Layer Chromatography was performed on Merck glass-backed plates pre-coated with silica (0.2 mm, 60 F254) which were visualized either by quenching of ultraviolet fluorescence (λ_{max}= 254 and 366 nm) or by staining with 10% $KMnO_4$ in 1 M H_2SO_4.

Irradiation of the reaction mixtures was achieved using a 40 W Kessil A160WE LED – Tuna blue aquarium light (setup: max blue, max intensity). Clear glass vials with PTFE/silicon septum lined screw caps (VWR, 548-0521) or microwave vials with PTFE/silicon septum were used as the standard reaction vessels.

Infra-red (IR) spectra were recorded as thin films on a Perkin-Elmer Spectrum One FT-IR instrument or an a Thermo Fisher Scientific Nicolet Summit PRO FTIR spectrometer. Only selected absorbances are reported. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz, 500 MHz or 600 MHz on Bruker AM-400/500/600 instruments. Chemical shifts (δH) are quoted in parts per million (ppm), referenced to the $CHCl_3$ residual solvent peak as an internal standard at 7.26 ppm. Coupling constants (*J*) are reported to the nearest 0.1 Hz. Peak assignment: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, app = apparent or combinations of any two. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 101 MHz on Bruker AM-400 instrument. Chemical shifts (δC) are quoted in ppm, referenced to the $CHCl_3$ residual solvent peak as an internal standard at 77.16 ppm. 2D NMR data (COSY, HSQC, HMBC) were used to support the assignment of peaks where necessary. If an environment was split into two rotameric peaks, or if the sample contained a mixture of diastereomers, the integration given is that of the environment as a whole.

High-resolution mass spectra (*m/z*) were recorded at the EPSRC Mass Spectrometry Service at the University of Swansea on an LTQ Orbitrap XL spectrometer with positive ion nano-electrospray. High Resolution Mass Spectrometry (HRMS) measurements are valid to ± 5 ppm. GC analyses were carried out using a Shimadzu QP2010-SE fitted with a BPX5 column (10 m, 0.1 mm, 0.1 mm film). Stern-Volmer quenching was performed using a Shimadzu RF-6000 spectrofluorometer. Experiments were

recorded using a quartz cell (Hellma Analytics, Sigma Aldrich code: 117-100F-10-40). Melting points (m.p.) were recorded using a Gallenkamp melting point apparatus and are reported uncorrected.

All purifications with High-Performance Liquid Chromatography (for Chapter 4) were conducted by Dr. S. Walton using the following conditions: Preparative reverse phase HPLC (RP HPLC) was performed on C18 reversed-phase silica typically using a Waters XSelect CSH C18 OBD column (5 μm silica, 30 mm diameter, 100 mm length) using decreasingly polar mixtures as eluent, for example utilising water as solvent A and acetonitrile as solvent B [with additional modifier stream to provide a mobile phase containing 0.1% formic acid or 0.3-5% aqueous ammonium hydroxide (d=0.91)]; a typical procedure would be as follows: a solvent gradient over 10-20 minutes, at 40-50mL per minute, from a 95:5 mixture of solvents A and B respectively to a 5:95 mixture of solvents A and B (or alternative ratio as described). Preparative chiral SFC was performed on various chiral columns (described in the method) using either a Sepiatec preparative SFC 100, or Waters preparative SFC 100. Typically, gradient of 30% MeOH + 0.1% NH_3 / 70% $scCO_2$ at a flow rate of 90 mL/min (Sepiatec) or 100 mL/min (Waters). The BPR did not exceed 120 bar and column temperature was set to 40 ˚C.

6.2 Experimental procedures

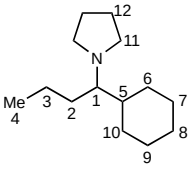
6.2.1 Visible light-mediated carbonyl alkylative amination for tertiary amine synthesis

General procedure A – Carbonyl Alkylative Amination:

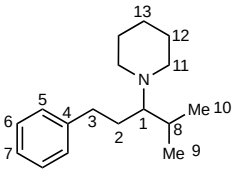
An oven dried microwave vial was charged with a stir bar and pre-dried 4Å MS (300 mg). The vial was sealed with a septum, evacuated and backfilled three times with 1 atm of N_2. To this was added dry and degassed CH_2Cl_2 (0.016–0.1 M) followed by addition of amine (0.20 mmol, 1.0 equiv.), aldehyde (2.0equiv.), alkyl halide (3.0 equiv.), tris(trimethylsilyl)silane (2.0equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0–2 equiv) *via* microsyringe. The reaction mixture was irradiated using a 40 W blue LED lamp (Kessil A160WE Tuna Blue) stirred for 14 h at room temperature. The reaction mixture was filtered through Celite® and hexane (10 mL) was added. The mixture was concentrated *in vacuo* until approximately 3 mL remained and the liquids were decanted. The resulting residue was washed with hexane (5 mL x 3). CH_2Cl_2 (15 mL) was added and the solution neutralized by stirring with NaOH (10 mL, 10% aq.) for 15 minutes. The resulting biphasic mixture was transferred to a separating funnel and the organic layer was extracted with CH_2Cl_2 (10 mL x 2). The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography.

Deviation A: The amine, aldehyde and MS 4Å were added to a microwave vial which was sealed with a septum, evacuated and backfilled with N_2 three times. CH_2Cl_2 was added and the mixture was heated at 80 °C for 1 hour. The vial was cooled to room temperature and the remaining reagents (tris(trimethylsilyl)silane, *tert*-butyldimethylsilyl trifluoromethanesulfonate and alkyl halide) were added *via* microsyringe and the reaction irradiated as described above.

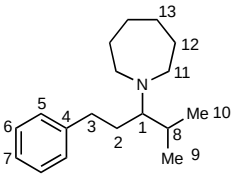
Deviation B: Performed as described in the general procedure but without TBSOTf. This deviation was used when acid-sensitive moieties were present, when the corresponding HCl-salts of the secondary amines were employed and in several instances for benzylamine substrates.



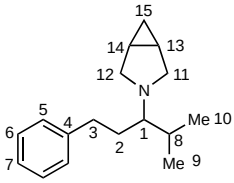
1-(1-Cyclohexylbutyl)pyrrolidine (**50b**). The title compound was prepared according to general procedure A using pyrrolidine (17 µL, 0.20 mmol), butyraldehyde (36 µL, 0.40 mmol), iodocyclohexane (77 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and trimethylsilyl trifluoromethanesulfonate (72.0 µL, 0.40 mmol) in CH_2Cl_2 (6 mL). The crude reaction mixture was purified by filtration through an SCX-column (eluting with 7N NH_3 in MeOH) to afford the title compound as a colourless oil (30 mg, 0.14 mmol, 72% yield).**^{1}H NMR** (400 MHz; $CDCl_3$): δ 2.63 (d, J = 2.4 Hz, 4H, H_{11}), 2.06 (app d, J = 3.7 Hz, 1H, H_1), 1.77–1.03 (m, 19H, H_{2-3} & H_{5-10} & H_{12}), 0.90 (q, J = 7.3 Hz, 3H, H_4); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 68.2 (C_1), 51.2 (C_{11}), 41.9 (C_5), 31.8, 31.0, 28.3, 27.1, 26.8, 23.6, 22.9, 14.7 (C_4); **IR** (film, cm^{-1}): 2924, 2853, 2785, 1664, 1450, 1379, 1153, 1032, 842; **HRMS** (NSI+): *m/z* calcd for $C_{14}H_{28}N$, $[M+H]^+$, 210.2216; found, 210.2216 (Δ = -0.1 ppm). Note: Two ^{13}C peaks overlap.



1-(4-Methyl-1-phenylpentan-3-yl)piperidine (**50c**). The title compound was prepared according to general procedure A using piperidine (20 µL, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude mixture afforded a spectroscopically pure sample of the title compound without further purification as a yellow oil (32 mg, 91% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.31–7.26 (m, 2H, H_6), 7.23–7.16 (m, 3H, H_5 & H_7), 2.77 (ddd, J = 13.6, 10.4, 5.3 Hz, 1H, H_3), 2.66–2.54 (m, 5H, H_3 & H_{11}), 2.14 (ddd, J = 7.6, 6.3, 4.6 Hz, 1H, H_1), 1.89–1.76 (m, 2H, H_8 &), 1.65–1.54 (m, 5H), 1.48–1.43 (m, 2H), 0.92 (dd, J = 6.8, 3.6 Hz, 6H, H_{9-10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.4 (C_4), 128.5 (C_5 or C_6), 128.4 (C_5 or C_6), 125.7 (C_7), 70.1 (C_1), 50.7 (C_{11}), 35.1 (C_3), 29.8, 29.7 (C_8), 27.0, 25.3, 21.9 (C_9), 20.3 (C_{10}); **IR** (film, cm^{-1}): 2932, 2789, 1494, 1452, 1377, 1163, 1096, 1030, 745, 695; **HRMS** (NSI+): *m/z* calcd for $C_{17}H_{28}N_1$, $[M+H]^+$, 246.2216; found, 246.2218 (Δ = 0.7 ppm).

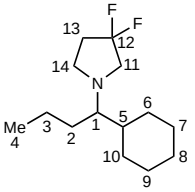


1-(4-Methyl-1-phenylpentan-3-yl)azepane (**50d**). The title compound was prepared according to general procedure A using azepane (23 µL, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude mixture was purified by flash column chromatography (0–1.5% (10% aq. NH_3 in MeOH) in CH_2Cl_2) to afford the title compound as a colourless oil (43 mg, 0.12 mmol, 61% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.28 (m, 2H, H_6), 7.20 (m, 3H, H_5 & H_7), 2.86–2.72 (m, 5H, H_3 & H_{11}), 2.63–2.57 (m, 1H, H_3), 2.20–2.13 (m, 1H, H_1), 1.75–1.61 (m, 11H, H_2 & H_8 & H_{12-13}), 0.94 (d, J = 6.7 Hz, 3H, H_9), 0.89 (d, J = 6.6 Hz, 3H, H_{10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.7 (C_4), 128.5 (C_5 or C_6), 128.4 (C_5 or C_6), 125.6 (C_7), 71.9 (C_1), 52.3 (C_{11}), 34.7 (C_3), 32.5 (C_2), 31.8 (C_8), 30.9 (C_{12} or C_{13}), 27.4 (C_{12} or C_{13}), 21.8 (C_9), 21.0 (C_{10}); **IR** (film, cm^{-1}): 2920, 2865, 1603, 1452, 1355, 1133, 1074, 907, 733, 695; **HRMS** (NSI+): *m/z* calcd for $C_{18}H_{30}N_1$, $[M+H]^+$, 260.2373; found, 260.2375 (Δ = 0.9 ppm).

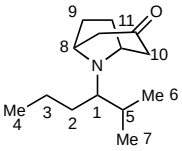


3-(4-Methyl-1-phenylpentan-3-yl)-3-azabicyclo[3.1.0]hexane (**50e**). The title compound was prepared according to general procedure A (deviation B) using 3-azabicyclo[3.1.0]hexane hydrochloride (24 mg, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol) and 4Å MS (300 mg) in CH_2Cl_2 (12 mL). The crude reaction mixture was purified by flash column chromatography (0–1% (10% aq. NH_3 in MeOH) in CH_2Cl_2) to afford the title compound as a colourless oil (14 mg, 0.058 mmol, 29% yield). Note: C_2 and C_8 peaks are overlapping. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.30–7.26 (m, 2H, H_6), 7.21–7.16 (m, 3H, H_5 & H_7), 2.87 (d, J = 7.8 Hz, 2H, H_{12}), 2.72–2.63 (m, 3H, H_3 & H_{11}), 2.59–2.51 (m, 1H, H_3), 2.19 (t, J = 5.1 Hz, 1H, H_1), 1.81–1.74 (m, 1H, H_8), 1.69–1.62 (m, 2H), 1.29 (dd, J = 8.6, 5.2 Hz, 2H, H_{13-14}), 0.88–0.85 (m, 6H, H_{9-10}), 0.69–0.68 (m, 1H, H_{13}), 0.36–0.31 (m, 1H, H_{13}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.4 (C_4), 128.5 (C_5 or C_6), 128.4 (C_5 or C_6),

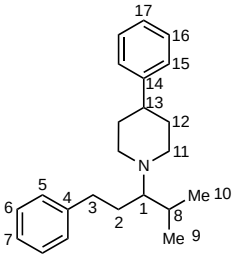
125.7 (C_7), 64.2 (C_1), 51.0 (C_{11}), 50.4 (C_{12}), 35.1 (C_3), 31.2 (C_2 & C_8), 20.8 (C_9 or C_{10}), 19.3 (C_9 or C_{10}), 15.4 (C_{13}), 15.2 (C_{14}), 7.1 (C_{15}); **IR** (film, cm^{-1}): 2956, 2873, 2793, 1684, 1601, 1496, 1452, 1365, 1163, 1030, 749, 657; **HRMS** (NSI+): *m/z* calcd for $C_{17}H_{26}N_1$, $[M+H]^+$, 244.2060; found, 244.2062 (Δ = 0.9 ppm).



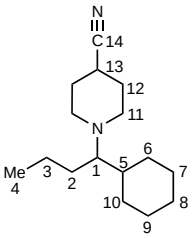
1-(1-Cyclohexylbutyl)-3,3-difluoropyrrolidine (**50g**). The title compound was prepared according to general procedure A (deviation B) using 3,3-difluoropyrrolidine hydrochloride (29 mg, 0.20 mmol, 1.0 equiv.), butyraldehyde (36 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol) and 4Å MS (300 mg) in CH_2Cl_2 (12 mL). The crude reaction mixture was purified by flash column chromatography (0–10% CH_2Cl_2 in 40°–60° Petroleum Ether) in CH_2Cl_2) to afford the title compound as a colourless oil (5.0 mg, 0.020 mmol, 10% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 2.95 (td, *J* = 13.7, 1.9 Hz, 2H, H_{11}), 2.85–2.74 (m, 2H), 2.25–2.14 (m, 2H, H_{13}), 2.12–2.09 (m, 1H, H_1), 1.75–1.64 (m, 5H), 1.44–0.99 (m, 10H), 0.91–0.87 (m, 3H, H_4); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 129.0 (dd, *J* = 504.1, 257.0 Hz, C_{12}), 66.0 (C_1), 58.5 (t, *J* = 28.8 Hz, C_{11}), 49.0 (t, *J* = 3.9 Hz, C_{14}), 45.1, 41.3 (C_5), 35.5 (t, *J* = 23.9 Hz, C_{13}), 30.8, 30.6, 29.2, 26.94, 26.89, 26.7, 22.3, 14.6 (C_4); **^{19}F NMR** (376 MHz; $CDCl_3$): *δ* -93.3; **IR** (film, cm^{-1}): 2927, 2854, 1450, 1333, 1108, 928, 745; **HRMS** (NSI+): *m/z* calcd for $C_{14}H_{26}N_1F_2$, $[M+H]^+$, 246.2033; found, 246.2037 (Δ = 1.6 ppm).



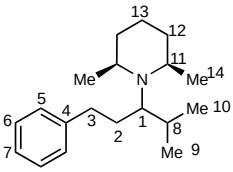
8-(2-Methylhexan-3-yl)-8-azabicyclo[3.2.1]octan-3-one (**50i**). The title compound was prepared according to general procedure A (deviation B) using nortropinone hydrochloride (32 mg, 0.20 mmol), butyraldehyde (36 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol) and 4Å MS (300 mg) in CH_2Cl_2 (12 mL). The crude reaction mixture was purified by flash column chromatography (0–1% (10% aq. NH_3 in MeOH) in CH_2Cl_2) to afford the title compound as a colourless oil (27 mg, 0.12 mmol, 60% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 3.69–3.66 (m, 2H, H_8), 2.66 (dd, *J* = 15.8, 4.3 Hz, 1H, H_{10a}), 2.56 (dd, *J* = 15.5, 4.0 Hz, 1H, H_{10a}), 2.47–2.44 (m, 1H, H_1), 2.15 (t, *J* = 2.1 Hz, 1H, H_{10b}), 2.11 (t, *J* = 2.2 Hz, 1H, H_{10b}), 1.99–1.90 (m, 3H, H_5 & H_9), 1.61–1.29 (m, 6H, H_{2-3} & H_9), 0.94–0.89 (m, 9H, H_4 & H_{6-7}); **^{13}C NMR** (101 MHz; $CDCl_3$): *δ* 211.1 (C_{11}), 60.9 (C_1), 57.1 (C_8), 55.5 (C_8), 46.8 (C_{10}), 46.6 (C_{10}), 31.9 (C_2), 30.1 (C_5), 29.0 (C_9), 28.9 (C_9), 22.7 (C_3), 19.7 (C_6), 16.5 (C_7), 14.9 (C_4); **IR** (film, cm^{-1}): 2960, 2869, 1714, 1468, 1347, 1195, 1141, 1000, 907, 729; **HRMS** (NSI+): *m/z* calcd for $C_{14}H_{26}N_1O_1$, $[M+H]^+$, 224.2009; found, 224.2009 (Δ = 0.0 ppm).



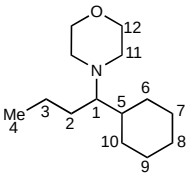
1-(4-Methyl-1-phenylpentan-3-yl)-4-phenylpiperidine (**51a**). The title compound was prepared according to general procedure A using 4-phenylpiperidine (23 µL, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude mixture was purified by flash column chromatography (0–1% (10% aq. NH_3 in MeOH) in CH_2Cl_2) to afford the title compound as a colourless oil (45 mg, 0.14 mmol, 70% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 7.36–7.21 (m, 10H, H_{5-7} & H_{15-17}), 2.95–2.93 (m, 1H, H_{11}), 2.88–2.79 (m, 2H, H_3 & H_{11}), 2.72–2.66 (m, 1H, H_3), 2.64–2.58 (m, 2H, H_{11}), 2.52–2.48 (m, 1H, H_{13}), 2.24–2.20 (m, 1H, H_1), 1.93–1.62 (m, 7H, H_2 & H_8 & H_{12}), 0.99–0.96 (m, 6H, H_{9-10}); **^{13}C NMR** (101 MHz; $CDCl_3$): *δ* 147.2 (C_{14}), 143.4 (C_4), 128.6 (C_5 or C_6 or C_{15} or C_{16}), 128.5 (C_5 or C_6 or C_{15} or C_{16}), 128.4 (C_5 or C_6 or C_{15} or C_{16}), 127.0 (C_5 or C_6 or C_{15} or C_{16}), 126.1 (C_7 or C_{17}), 125.7 (C_7 or C_{17}), 69.8 (C_1), 50.4 (C_{11}), 50.3 (C_{11}), 43.6 (C_{13}), 35.1 (C_3 or C_{12}), 34.7 (C_3 or C_{12}), 34.6, 29.93 (C_2), 29.89 (C_8), 21.8 (C_9), 20.4 (C_{10}); **IR** (film, cm^{-1}): 2928, 2797, 1601, 1496, 1450, 1379, 1244, 1094, 1004, 747, 697; **HRMS** (NSI+): *m/z* calcd for $C_{23}H_{32}N_1$, $[M+H]^+$, 322.2529; found, 322.2532 (Δ = 0.8 ppm).



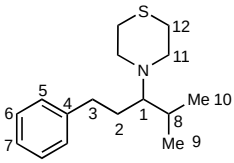
1-(1-Cyclohexylbutyl)piperidine-4-carbonitrile (**51b**). The title compound was prepared according to general procedure A (deviation A) using 4-cyanopiperidine (22 µL, 0.20 mmol), butyraldehyde (36 µL, 0.40 mmol), iodocyclohexane (77 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (6 mL). The crude reaction mixture was purified by filtration through an SCX-column (eluting with 7N NH_3 in MeOH) followed by flash column chromatography (0–0.5% MeOH in CH_2Cl_2) to afford the title compound as a colourless oil (25 mg, 0.10 mmol, 50% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 2.73 (dddd, J = 15.5, 11.5, 6.8, 4.0 Hz, 2H, H_{11}), 2.56 (dtd, J = 12.3, 8.1, 4.1 Hz, 1H, H_{13}), 2.50 (ddt, J = 11.7, 7.9, 3.8 Hz, 1H, H_{11}), 2.43 (ddd, J = 11.7, 8.3, 3.3 Hz, 1H, H_{11}), 2.07 (td, J = 7.0, 4.5 Hz, 1H, H_1), 1.88–1.62 (m, 9H, H_{12}), 1.46–1.06 (m, 8H, $H_{2\text{-}3}$), 1.01–0.86 (m, 5H, H_4); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 122.3 (C_{14}), 69.7 (C_1), 48.2 (C_{11}), 47.7 (C_{11}), 40.4 (C_5), 31.5, 31.0, 30.1, 29.8, 29.7, 27.0 (C_{13}), 26.8, 26.8, 26.7, 22.2, 14.6 (C_4); **IR** (film, cm^{-1}): 2920, 2853, 2238, 1446, 1379, 1149, 983, 729; **HRMS** (NSI+): *m/z* calcd for $C_{16}H_{29}N_2$, $[M+H]^+$, 249.2331; found, 249.2330 (Δ = -0.4 ppm). Note: $H_{5\text{-}10}$ could not be unambigously assigned.



(2*S*,6*R*)-2,6-Dimethyl-1-(4-methyl-1-phenylpentan-3-yl)piperidine (**51c**). The title compound was prepared according to general procedure A (deviation A) using 2,6-*cis*-dimethylpiperidine (27 µL, 0.20 mmol), butyraldehyde (36 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (6 mL). The crude reaction mixture was purified by filtration through an SCX-column (eluting with 7N NH_3 in MeOH) followed by flash column chromatography (0–0.5% MeOH in CH_2Cl_2) to afford the title compound as a colourless oil (17 mg, 0.064 mmol, 32% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.31–7.25 (m, 2H, H_6), 7.19 (dd, J = 17.2, 7.4 Hz, 3H, H_5 & H_7), 2.85 (m, 3H, H_1 & H_3 & H_{11}), 2.63–2.49 (m, 2H, H_3 & H_{11}), 1.90–1.56 (m, 6H), 1.42–1.28 (m, 3H), 1.10–1.03 (m, 6H, H_{14}), 1.03–0.89 (m, 6H, $H_{9\text{-}10}$); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.6 (C_4), 128.5 (C_5 & C_6), 125.7 (C_7), 65.8 (C_1), 52.7 (C_{11}), 52.5 (C_{11}), 36.3 (C_3), 34.6 (C_{12}), 34.4 (C_{12}), 33.1 (C_8), 32.1 (C_2), 23.9 (C_{12}), 23.7 (C_{12}), 22.2 (C_9 or C_{10}), 21.3 (C_9 or C_{10}), 21.1 (C_{13}); **IR** (film, cm^{-1}): 2928, 2865, 1454, 1371, 1163, 1044, 907; **HRMS** (NSI+): *m/z* calcd for $C_{19}H_{32}N_1$, $[M+H]^+$, 274.2529; found, 274.2531 (Δ = 0.6 ppm).

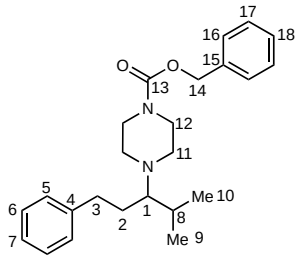


4-(1-Cyclohexylbutyl)morpholine (**51e**). The title compound was prepared according to general procedure A (deviation A) using morpholine (17.5 µL, 0.20 mmol), butyraldehyde (36 µL, 0.40 mmol), iodocyclohexane (77 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude reaction mixture was purified by flash column chromatography (0–0.5% MeOH in CH_2Cl_2) to afford the title compound as a colourless oil (27 mg, 0.12 mmol, 61% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 3.63 (t, J = 4.6 Hz, 4H, H_{12}), 2.60–2.49 (m, 4H, H_{11}), 2.03 (q, J = 5.6 Hz, 1H, H_1), 1.83–1.80 (m, 1H, H_5), 1.74–1.63 (m, 4H), 1.49–0.93 (m, 10H, $H_{2\text{-}3}$), 0.89 (t, J = 7.1 Hz, 3H, H_4); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 69.4 (C_1), 67.9 (C_{12}), 50.0 (C_{11}), 40.1 (C_5), 31.4 (C_6), 30.7 (C_{10}), 29.8 (C_3), 26.9 (C_7 or C_8 or C_9), 26.9 (C_7 or C_8 or C_9), 26.7 (C_7 or C_8 or C_9), 22.3 (C_2), 14.6 (C_4); **IR** (film, cm^{-1}): 2920, 2849, 1448, 1258, 1117, 1000, 854, 733; **HRMS** (NSI+): *m/z* calcd for $C_{14}H_{28}N_1O_1$, $[M+H]^+$, 226.2165; found, 226.2167 (Δ = 0.7 ppm).

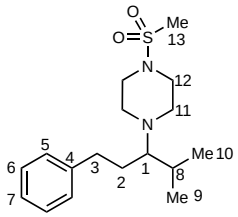


4-(4-Methyl-1-phenylpentan-3-yl)thiomorpholine (**51f**). The title compound was prepared according to general procedure A (deviation A) using thiomorpholine (20 µL, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude mixture was purified by flash column chromatography (0–30% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (30 mg, 0.11 mmol, 57% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.30–7.26 (m, 2H, H_6), 7.20–7.18 (m, 3H, H_5 & H_7), 2.97–2.86

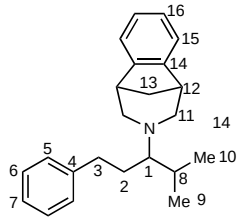
(m, 4H, H_{11}), 2.77 (ddd, J = 13.8, 9.9, 5.2 Hz, 1H, H_3), 2.65–2.56 (m, 5H, H_3 & H_{12}), 2.07 (ddd, J = 8.7, 7.0, 4.2 Hz, 1H, H_1), 1.81–1.70 (m, 2H, H_2 & H_8), 1.63 (dddd, J = 14.1, 10.3, 6.5, 3.9 Hz, 1H, H_2), 0.90 (app t, J = 7.1 Hz, 6H, H_{9-10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.1 (C_4), 128.5 (C_5 or C_6), 128.4 (C_5 or C_6), 125.8 (C_7), 71.6 (C_1), 52.3 (C_{11}), 34.7, 30.3 (C_8), 30.2 (C_2), 29.0 (C_{12}), 21.8 (C_9), 20.6 (C_{10}); **IR** (film, cm^{-1}): 2952, 2904, 2801, 1603, 1496, 1452, 1375, 1276, 1105, 973, 745, 695; **HRMS** (NSI+): *m/z* calcd for $C_{16}H_{26}N_1S_1$, $[M+H]^+$, 264.1786; found, 264.1780 (Δ = -2.3 ppm).



Benzyl 4-(4-methyl-1-phenylpentan-3-yl)piperazine-1-carboxylate (**51g**). The title compound was prepared according to general procedure A using 1-carbobenzoxyiperazine (39 µL, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude reaction mixture was purified by filtration through an SCX-column (eluting with 7N NH_3 in MeOH) followed by flash column chromatography (0–1% (10% aq. NH_3 in MeOH) in CH_2Cl_2) to afford the title compound as a colourless oil (43 mg, 0.11 mmol, 57% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.38–7.27 (m, 7H, H_{5-7} and/or H_{16-18}), 7.21–7.17 (m, 3H, H_{5-7} and/or H_{16-18}), 5.15 (s, 2H, H_{14}), 3.48 (t, J = 4.9 Hz, 4H, H_{12}), 2.74 (ddd, J = 13.7, 10.0, 5.4 Hz, 1H, H_3), 2.62 (m, 5H, H_3 & H_{11}), 2.17 (ddd, J = 8.0, 6.4, 4.4 Hz, 1H, H_1), 1.86–1.71 (m, 2H, H_2 & H_8), 1.68–1.59 (m, 1H, H_2), 0.92 (app dd, J = 6.7, 1.3 Hz, 6H, H_{9-10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 155.4 (C_{13}), 142.9 (C_4), 137.0 (C_{15}), 128.6 (C_{5-7} or C_{16-18}), 128.5 (C_{5-7} or C_{16-18}), 128.4 (C_{5-7} or C_{16-18}), 128.1 (C_{5-7} or C_{16-18}), 128.0 (C_{5-7} or C_{16-18}), 125.8 (C_{5-7} or C_{16-18}), 69.6 (C_1), 67.1 (C_{14}), 49.2 (C_{11}), 44.9 (C_{12}), 34.8 (C_3), 29.7 (C_8), 29.6 (C_2), 21.6 (C_9 or C_{10}), 20.2 (C_9 or C_{10}); **IR** (film, cm^{-1}): 2948, 2865, 1692, 1427, 1240, 1119, 907, 729, 697; **HRMS** (NSI+): *m/z* calcd for $C_{24}H_{33}N_2O_2$, $[M+H]^+$, 381.2537; found, 381.2537 (Δ = 0.1 ppm).

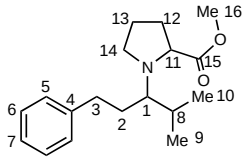


1-(4-Methyl-1-phenylpentan-3-yl)-4-(methylsulfonyl)piperazine (**51h**). The title compound was prepared according to general procedure A using 1-methanesulfonylpiperazine (33 mg, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude mixture afforded a spectroscopically pure sample of the title compound without further purification as a yellow oil (42 mg, 0.13 mmol, 64% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.30–7.26 (m, 2H, H_6), 7.20–7.17 (m, 3H, H_5 & H_7), 3.18–3.15 (m, 4H, H_{12}), 2.77–2.75 (m, 3H, H_{13}), 2.75–2.62 (m, 6H, H_3 & H_{11}), 2.19 (ddd, J = 8.1, 6.5, 4.4 Hz, 1H, H_1), 1.86–1.61 (m, 3H, H_2 & H_8), 0.91 (app dd, J = 6.7, 0.9 Hz, 6H, H_{9-10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 142.7 (C_4), 128.5 (C_{5-6}), 125.9 (C_7), 69.5 (C_1), 48.7 (C_{11}), 46.8 (C_{12}), 34.7 (C_3), 34.1 (C_{13}), 29.8 (C_8), 29.6 (C_2), 21.5 (C_9 or C_{10}), 20.2 (C_9 or C_{10}); IR (film, cm^{-1}): 2948, 2849, 2813, 1724, 1454, 1454, 1343, 1324, 1157, 959, 776, 695; **HRMS** (NSI+): *m/z* calcd for $C_{17}H_{29}N_2O_2S$, $[M+H]^+$, 325.1950; found, 325.1947 (Δ = -0.9 ppm).

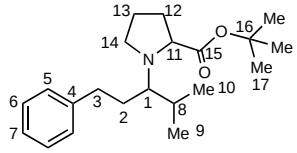


3-(4-Methyl-1-phenylpentan-3-yl)-2,3,4,5-tetrahydro-1*H*-1,5-methanobenzo[*d*]azepine (**51i**). The title compound was prepared according to general procedure A using 2,3,4,5-tetrahydro-1*H*-1,5-methanobenzo[d]azepine hydro-chloride (39 mg, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol) and 4Å MS (300 mg) in CH_2Cl_2 (9 mL). The crude mixture was purified by flash column chromatography (0–0.25% (10% aq. NH_3 in MeOH) in CH_2Cl_2) to afford the title compound as a colourless oil (24 mg, 0.076 mmol, 38% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.24–7.11 (m, 7H), 6.96 (d, J = 7.2 Hz, 2H), 3.11 (m, 3H, H_{11-12}), 2.96 (d, J = 10.1 Hz, 1H, H_{11}), 2.76 (dd, J = 9.9, 1.7 Hz, 1H, H_{11}), 2.66 (dd, J = 9.8, 1.5 Hz, 1H, H_{11}), 2.36–2.31 (m, 1H, H_{13}), 2.07–1.90 (m, 2H, H_3), 1.83 (q, J = 6.8 Hz, 1H, H_1), 1.75–1.62 (m, 2H, H_8 & H_{13}), 1.51–1.45 (m, 2H, H_2), 0.75 (d, J = 6.7 Hz, 3H, H_{10}), 0.64 (d, J = 6.7 Hz, 3H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 147.0 (C_{14}), 146.9 (C_{14}), 143.6 (C_4), 128.6 (C_{5-7} or C_{15-16}), 128.1 (C_{5-7} or C_{15-16}), 126.4 (C_{5-7} or C_{15-16}), 126.3 (C_{5-7} or C_{15-16}), 125.4

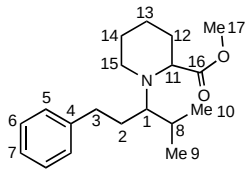
(C_{5-7} or C_{15-16}), 121.7 (C_{5-7} or C_{15-16}), 121.6 (C_{5-7} or C_{15-16}), 68.3 (C_1), 55.1 (C_{11}), 51.6 (C_{11}), 43.9 (C_{13}), 41.8 (C_{12}), 41.6 (C_{12}), 33.1 (C_3), 30.82 (C_8), 30.77 (C_2), 21.5 (C_9), 20.7 (C_{10}); **IR** (film, cm^{-1}): 3023, 2964, 1712, 1601, 1456, 1284, 1032, 757; **HRMS** (NSI+): *m/z* calcd for $C_{23}H_{30}N_1$, $[M+H]^+$, 320.2378; found, 320.2383 (Δ = 1.6 ppm).



Methyl 1-(4-methyl-1-phenylpentan-3-yl)pyrrolidine-2-carboxylate (**52a**). The title compound was prepared according to general procedure A (deviation A) using L-proline methyl ester (26 mg, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude mixture was purified by flash column chromatography (50–100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (40 mg, 0.14 mmol, 69% yield, 3.6:1 d.r.). Major diastereomer: **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.29–7.25 (m, 2H, H_6), 7.21–7.14 (m, 3H, H_5 & H_7), 3.72 (dd, J = 8.4, 3.0 Hz, 1H, H_{11}), 3.67 (s, 3H, H_{16}), 3.07 (td, J = 7.4, 3.4 Hz, 1H, H_{14}), 2.87–2.77 (m, 2H, H_3 & H_{14}), 2.55–2.47 (m, 2H, H_1 & H_3), 2.05–1.92 (m, 3H, H_{12-13}), 1.88–1.73 (m, 3H, H_2 & H_8 & H_{13}), 1.69–1.59 (m, 1H, H_2), 0.90 (app dd, J = 6.8, 1.9 Hz, 6H, H_{9-10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 176.3 (C_{15}), 143.6 (C_4), 128.5 (C_5 or C_6), 128.4 (C_5 or C_6), 125.6 (C_7), 64.2 (C_1), 62.8 (C_{11}), 51.5 (C_{16}), 47.4 (C_{14}), 34.3 (C_3), 32.2 (C_2), 30.8 (C_8), 30.1 (C_{12}), 24.5 (C_{13}), 21.2 (C_9), 19.9 (C_{10}); **IR** (film, cm^{-1}): 2948, 2869, 1732, 1454, 1167, 907, 731, 699; **HRMS** (NSI+): *m/z* calcd for $C_{18}H_{28}N_1O_2$, $[M+H]^+$, 290.2115; found, 290.2117 (Δ = 0.8 ppm).

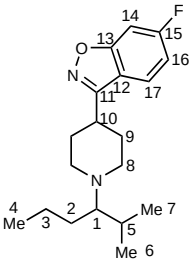


tert-Butyl 1-(4-methyl-1-phenylpentan-3-yl)pyrrolidine-2-carboxylate (**52b**). The title compound was prepared according to general procedure A (deviation A) using L-proline *tert*-butyl ester (34 mg, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude mixture was purified by flash column chromatography (50–100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (44 mg, 0.13 mmol, 67% yield, >20:1 d.r.). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.29–7.25 (m, 2H, H_6), 7.21–7.15 (m, 3H, H_5 & H_7), 3.58 (dd, J = 8.3, 2.9 Hz, 1H, H_{11}), 3.07 (td, J = 7.5, 3.3 Hz, 1H, H_{14}), 2.88–2.81 (m, 2H, H_3 & H_{14}), 2.58–2.50 (m, 2H, H_1 & H_3), 2.03–1.85 (m, 4H, H_8 & H_{12-13}), 1.83–1.72 (m, 2H, H_2 & H_{13}), 1.70–1.61 (m, 1H, H_2), 1.45 (s, 9H, H_{17}), 0.90 (app t, J = 6.6 Hz, 6H, H_{9-10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 175.3 (C_{15}), 143.6 (C_4), 128.5 (C_5 or C_6), 128.4 (C_5 or C_6), 125.6 (C_7), 80.1 (C_{16}), 64.4 (C_1), 63.5 (C_{11}), 48.1 (C_{14}), 34.7 (C_3), 32.0 (C_2), 30.6 (C_8), 30.2 (C_{12}), 28.3 (C_{17}), 24.4 (C_{13}), 21.2 (C_9), 19.6 (C_{10}); **IR** (film, cm^{-1}): 2956, 2869, 1718, 1454, 1367, 1143, 842, 697; **HRMS** (NSI+): *m/z* calcd for $C_{21}H_{34}N_1O_2$, $[M+H]^+$, 332.2584; found, 332.2587 (Δ = 0.9 ppm).

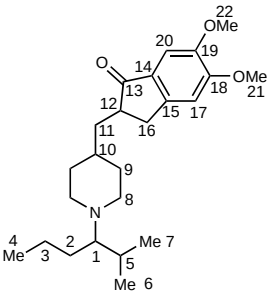


Methyl 1-(4-methyl-1-phenylpentan-3-yl)piperidine-2-carboxylate (**52d**). The title compound was prepared according to general procedure A using methyl piperidine-2-carboxylate (28 µL, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude mixture was purified by flash column chromatography (50–100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (28 mg, 0.094 mmol, 47% yield, 1:1 d.r.). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.30–7.26 (m, 2H, H_6), 7.18 (m, 3H, H_5 & H_7), 3.68 (s, 3H, H_{17}), 3.67 (s, 3H, H_{17}), 3.48 (t, J = 5.5 Hz, 1H, H_{11}), 3.39 (dd, J = 8.0, 3.9 Hz, 1H, H_{11}), 3.06 (ddd, J = 11.3, 6.8, 4.2 Hz, 1H, H_{15}), 3.00–2.95 (m, 1H, H_{15}), 2.82–2.76 (m, 1H, H_3), 2.69–2.50 (m, 1H, H_3), 2.46–2.40 (m, 1H, H_{15}), 2.36–2.29 (m, 2H, H_1 & H_{15}), 2.14–2.09 (m, 1H, H_1), 1.92–1.31 (m, 9H, H_2 & H_8 & H_{12}-H_{14}), 0.95 (t, J = 6.6 Hz, 6H, H_{9-10}), 0.87 (d, J = 6.8 Hz, 6H, H_{9-10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 175.4 (C_{16}), 175.3 (C_{16}), 143.6 (C_4), 143.1 (C_4), 128.5 (C_5 or C_6), 128.5 (C_5 or C_6), 128.4 (C_5 or C_6), 128.4 (C_5 or C_6), 125.8 (C_7), 125.6 (C_7), 67.8 (C_1), 67.4 (C_1), 63.9 (C_{11}), 63.7 (C_{11}), 51.5 (C_{17}), 51.3 (C_{17}), 44.4 (C_{15}), 44.3 (C_{15}),

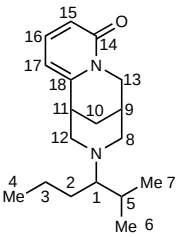
35.7 (C_3), 34.3 (C_3), 31.3 (C_8), 30.4 (C_2), 30.2 (C_2), 30.0 (C_{12}), 29.8 (C_{12}), 29.1 (C_8), 26.4 (C_{13} or C_{14}), 26.0 (C_{13} or C_{14}), 23.2 (C_{13} or C_{14}), 22.7 (C_{13} or C_{14}), 21.2 (C_9 or C_{10}), 20.9 (C_9 or C_{10}), 20.6 (C_9 or C_{10}), 20.1 (C_9 or C_{10}); **IR** (film, cm^{-1}): 3023, 2936, 1736, 1454, 1159, 1052, 697; **HRMS** (NSI+): *m/z* calcd for $C_{19}H_{30}N_1O_2$, $[M+H]^+$, 304.2277; found, 304.2278 (Δ = 0.3 ppm). Note: The spectra contain a mixture of two diastereomers and consequently, most peaks are reported twice



6-Fluoro-3-(1-(2-methylhexan-3-yl)piperidin-4-yl)benzo[*d*]isoxazole (**53a**). The title compound was prepared according to general procedure A using 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole (44 mg, 0.20 mmol), butyraldehyde (36 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (6 mL). The crude mixture was purified by flash column chromatography (0–3% (10% aq. NH_3 in MeOH) in CH_2Cl_2) to afford the title compound as a yellow oil (32 mg, 0.10 mmol, 50% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.67 (dd, J = 8.7, 5.1 Hz, 1H, H_{17}), 7.22 (dd, J = 8.5, 2.1 Hz, 1H, H_{14}), 7.04 (td, J = 8.8, 2.1 Hz, 1H, H_{16}), 3.05–2.97 (m, 1H, H_{10}), 2.89 (dt, J = 10.1, 4.6 Hz, 2H, H_8), 2.66–2.60 (m, 1H, H_8), 2.56–2.49 (m, 1H, H_8), 2.14–2.10 (m, 1H, H_1), 1.99–1.91 (m, 4H, H_9), 1.81–1.73 (m, 1H, H_5), 1.53–1.24 (m, 4H, H_{2-3}), 0.95–0.89 (m, 9H, H_4 & H_{6-7}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 164.2 (d, J = 250.5 Hz, C_{15}), 163.9 (d, J = 13.6 Hz, C_{13}), 161.7 (C_{11}), 122.8 (d, J = 10.8 Hz, C_{17}), 117.6 (C_{12}), 112.3 (d, J = 25.1 Hz, C_{16}), 97.5 (d, J = 26.8 Hz, C_{14}), 70.4 (C_1), 51.0 (C_8), 48.7 (C_8), 35.5 (C_{10}), 31.8 (C_9), 31.5 (C_9), 30.4 (C_5), 30.2 (C_2 or C_3), 22.2 (C_2 or C_3), 21.5 (C_9), 20.5 (C_{10}), 14.6 (C_4); **^{19}F NMR** (376 MHz; $CDCl_3$): δ -109.9; **IR** (film, cm^{-1}): 2952, 1615, 1415, 1274, 1119, 955, 838, 812; **HRMS** (NSI+): *m/z* calcd for $C_{19}H_{28}N_2O_1F_1$, $[M+H]^+$, 319.2180; found, 319.2182 (Δ = 0.6 ppm).

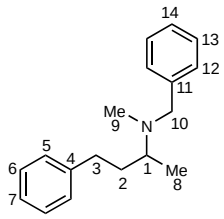


5,6-dimethoxy-2-((1-(2-methylhexan-3-yl)piperidin-4-yl)methyl)-2,3-dihydro-1*H*-inden-1-one (**53c**). The title compound was prepared according to general procedure A (deviation A) using 5,6-dimethoxy-2-(piperidin-4-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (65 mg, 0.20 mmol), butyraldehyde (36 µL, 0.40 mmol), 2-iodopropane (60 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (6 mL). The crude mixture was purified by flash column chromatography (0–4% (10% aq. NH_3 in MeOH) in CH_2Cl_2) to afford the title compound as a yellow oil (51 mg, 0.13 mmol, 66% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.15 (s, 1H, H_{20}), 6.85 (s, 1H, H_{17}), 3.95 (s, 3H, H_{21}), 3.89 (s, 3H, H_{22}), 3.23 (dd, J = 17.6, 8.1 Hz, 1H, H_{16}), 2.84–2.80 (m, 2H, H_8), 2.69 (m, 2H, H_{12} & H_{16}), 2.50–2.36 (m, 2H, H_8), 2.18–2.15 (m, 1H, H_1), 1.91–1.80 (m, 2H, H_{11} & H_5), 1.72–1.66 (m, 2H, H_{9-10}), 1.53–1.24 (m, 8H, H_{2-3} & H_{11} & H_9), 0.93–0.84 (m, 9H, H_4 & H_{6-7}). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 208.0 (C_{13}), 155.6 (C_{18}), 149.5 (C_{19}), 149.0 (C_{14}), 129.4 (C_{15}), 107.5 (C_{17}), 104.5 (C_{20}), 70.4 (C_1), 56.3 (C_{21} or C_{22}), 56.2 (C_{21} or C_{22}), 51.0 (C_8), 51.0 (C_8), 49.0 (C_8), 49.0 (C_8), 45.5 (C_{12}), 38.9 (C_{11}), 34.9 (broad, C_9), 33.6 (C_{16}), 33.5 (C_{16}), 32.2 (broad, C_{10}), 29.9 (C_2 or C_3), 29.8 (C_5), 22.4 (C_2 or C_3), 21.6 (C_6 or C_7), 19.9 (C_6 or C_7), 14.6 (C_4); **IR** (film, cm^{-1}): 2960, 2924, 2865, 1694, 1498, 1310, 1262, 1119, 1032, 915, 727; **HRMS** (NSI+): *m/z* calcd for $C_{24}H_{38}N_1O_3$, $[M+H]^+$, 388.2846; found, 388.2843 (Δ = -0.8 ppm). Note: The sample contains a mixture of diastereomers and some peaks are broadened/split due to rotamers (eg. C_{8-10}).

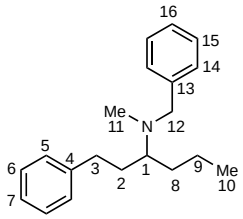


3-(2-Methylhexan-3-yl)-3,4,5,6-tetrahydro-1*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocine-8(2*H*)-one (**53d**). The title compound was prepared according to general procedure A (deviation A) using 3,4,5,6-tetrahydro-1*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8(2*H*)-one (19 mg, 0.10 mmol), butyraldehyde (18 µL, 0.20 mmol), 2-iodopropane (30 µL, 0.30 mmol), tris(trimethylsilyl)silane (62 µL, 0.20 mmol), 4Å MS (150 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (46 µL, 0.20 mmol) in CH_2Cl_2 (3 mL). The crude mixture was purified by flash column chromatography (0–5% (10% aq. NH_3 in MeOH) in CH_2Cl_2) to afford the title compound as a yellow oil (21 mg, 0.072 mmol, 72% yield, 7.7:1 d.r.). **^{1}H NMR** (500 MHz; $CDCl_3$): δ

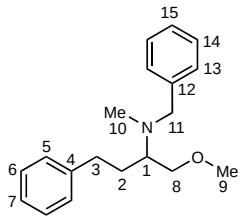
7.23 (ddd, J = 9.0, 6.8, 2.2 Hz, 1H, H_{16}), 6.41 (dt, J = 9.0, 1.3 Hz, 1H, H_{15}), 5.95 (dd, J = 6.9, 1.4 Hz, 1H, H_{17}), 4.02 (d, J = 15.3 Hz, 1H, H_{13}), 3.87–3.82 (m, 1H, H_{13}), 2.89–2.72 (m, 5H, H_8 & H_{11-12}), 2.35 (dd, J = 5.4, 2.4 Hz, 1H, H_9), 1.93–1.86 (m, 2H, H_1 & H_{10}), 1.78–1.74 (m, 1H, H_{10}), 1.65 (dq, J = 13.4, 6.7 Hz, 1H, H_5), 1.48 (dq, J = 13.9, 6.9 Hz, 1H, H_5), 1.40–1.32 (m, 1H, H_2), 1.25–0.94 (m, 3H, H_{2-3}), 0.79 (t, J = 7.1 Hz, 3H, H_6 or H_7), 0.72 (m, 9H, H_4 & H_{6-7}), 0.49 (d, J = 6.7 Hz, 3H, H_6 or H_7); **^{13}C NMR** (126 MHz; $CDCl_3$): δ 163.7 (C_{14}), 163.7 (C_{14}), 152.2 (C_{18}), 152.1 (C_{18}), 138.5 (C_{16}), 138.5 (C_{16}), 116.5 (C_{15}), 116.4 (C_{15}), 104.6 (C_{17}), 104.5 (C_{17}), 69.9 (C_1), 69.8 (C_1), 58.7 (C_8 or C_{12}), 57.8 (C_8 or C_{12}), 56.8 (C_8 or C_{12}), 56.1 (C_8 or C_{12}), 50.3 (C_{13}), 50.3 (C_{13}), 36.2 (C_{11}), 35.9 (C_{11}), 30.5 (C_5), 30.1 (C_{2-3} or C_9), 29.8 (C_{2-3} or C_9), 29.8 (C_5), 28.7 (C_9), 28.5 (C_9), 26.5 (C_{2-3} or C_9), 26.5 (C_{2-3} or C_9), 21.7 (C_{2-3} or C_9), 21.3 (C_6 or C_7), 20.9 (C_{2-3} or C_9), 20.6 (C_6 or C_7), 20.2 (C_6 or C_7), 20.2 (C_6 or C_7), 14.4 (C_4), 14.4 (C_4); **IR** (film, cm^{-1}): 2956, 2797, 1647, 1544, 1466, 1351, 1141, 794; **HRMS** (NSI+): *m/z* calcd for $C_{18}H_{29}N_2O_1$, $[M+H]^+$, 289.2280; found, 289.2281 (Δ = 0.3 ppm). Note: The sample contains a mixture of diastereomers.



N-Benzyl-*N*-methyl-4-phenylbutan-2-amine (**56a**). The title compound was prepared according to general procedure A using *N*-benzylmethylamine (13 µL, 0.10 mmol), hydrocinnamaldehyde (26 µL, 0.20 mmol), iodomethane (19 µL, 0.30 mmol), tris(trimethylsilyl)silane (61 µL, 0.20 mmol), 4Å MS (150 mg), ethyl 2-iodo-2-methylpropionate (2.0µL, 0.013 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (46 µL, 0.10 mmol) in CH_2Cl_2 (4.5 mL). The crude mixture was purified by flash column chromatography (0–30% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (12 mg, 0.037 mmol, 37% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.37–7.16 (m, 10H, H_{5-7} & H_{12-14}), 3.61 (d, J = 13.4 Hz, 1H, H_{10}), 3.46 (d, J = 13.4 Hz, 1H, H_{10}), 2.80–2.64 (m, 3H, H_1 & H_3), 2.15 (s, 3H, H_9), 1.95–1.85 (m, 1H, H_2), 1.64–1.57 (m, 1H, H_2), 1.03 (d, J = 6.6 Hz, 3H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.1 (C_4 or C_{11}), 140.6 (C_4 or C_{11}), 128.9 (C_5 or C_6 or C_{12} or C_{13}), 128.6 (C_5 or C_6 or C_{12} or C_{13}), 128.4 (C_5 or C_6 or C_{12} or C_{13}), 128.3 (C_5 or C_6 or C_{12} or C_{13}), 126.8 (C_7 or C_{14}), 125.7 (C_7 or C_{14}), 57.7 (C_{10}), 57.3 (C_1), 36.6 (C_9), 36.2 (C_3), 33.3 (C_2), 13.4 (C_8); **IR** (film, cm^{-1}): 2928, 2789, 1603, 1494, 1452, 1367, 1028, 731, 701; **HRMS** (NSI+): *m/z* calcd for $C_{18}H_{24}N_1$, $[M+H]^+$, 254.1909; found, 254.1904 (Δ = -2.0 ppm).

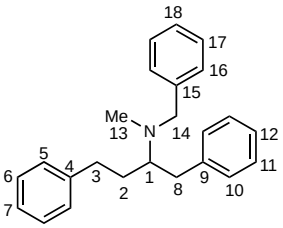


N-Benzyl-*N*-methyl-1-phenylhexan-3-amine (**56b**). The title compound was prepared according to general procedure A using *N*-benzylmethylamine (13 µL, 0.10 mmol), hydrocinnamaldehyde (26 µL, 0.20 mmol), 1-iodopropane (29 µL, 0.30 mmol), tris(trimethylsilyl)silane (61 µL, 0.20 mmol), 4Å MS (150 mg), ethyl 2-iodo-2-methylpropionate (2.0 µL, 0.013 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (23 µL, 0.10 mmol) in CH_2Cl_2 (4.5 mL). The crude mixture was purified by flash column chromatography (0–5% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (23 mg, 0.082 mmol, 82% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.41–7.21 (m, 10H, H_{5-7} & H_{14-16}), 3.63 (d, J = 13.5 Hz, 1H, H_{12}), 3.58 (d, J = 13.5 Hz, 1H, H_{12}), 2.82–2.78 (m, 1H, H_3), 2.72 (dd, J = 10.1, 6.2 Hz, 1H, H_3), 2.58 (t, J = 6.8 Hz, 1H, H_1), 2.21 (s, 3H, H_{11}), 1.90–1.81 (d, J = 10.1 Hz, 1H, H_2), 1.69–1.60 (m, 2H, H_2 & H_8), 1.69–1.60 (m, 3H, H_{8-9}), 0.95 (t, J = 7.2 Hz, 3H, H_{10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.3 (C_4 or C_{11}), 140.9 (C_4 or C_{11}), 128.8 (C_5 or C_6 or C_{14} or C_{15}), 128.6 (C_5 or C_6 or C_{14} or C_{15}), 128.4 (C_5 or C_6 or C_{14} or C_{15}), 128.3 (C_5 or C_6 or C_{14} or C_{15}), 126.7 (C_4 or C_{11}), 125.7 (C_4 or C_{11}), 62.1 (C_1), 58.0 (C_{12}), 36.5 (C_{11}), 33.7 (C_3), 32.5 (C_3 or C_8), 31.8 (C_3 or C_8), 20.5 (C_9), 14.5 (C_{10}); **IR** (film, cm^{-1}): 2956, 2861, 2785, 1494, 1452, 1359, 1028, 729, 695; **HRMS** (NSI+): *m/z* calcd for $C_{20}H_{28}N_1$, $[M+H]^+$, 282.2222; found, 282.2222 (Δ = 0.0 ppm).

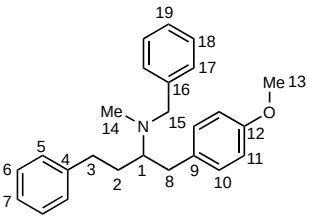


N-Benzyl-1-methoxy-*N*-methyl-4-phenylbutan-2-amine (**56d**). The title compound was prepared according to general procedure A using *N*-benzylmethylamine (13 µL, 0.10 mmol), hydrocinnamaldehyde (26 µL, 0.20 mmol), bromomethyl methyl ether (9.8 µL, 0.12 mmol), tris(trimethylsilyl)silane (61 µL, 0.20 mmol), 4Å MS (150 mg), ethyl 2-iodo-2-methylpropionate (2.0 µL, 0.013 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (23 µL, 0.10

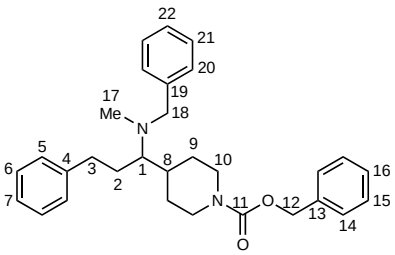
mmol) in CH_2Cl_2 (6 mL). The crude mixture was purified by flash column chromatography (0–20% Et_2O in 40°–60° Petroleum Ether) followed by filtration through an SCX-column (eluting with 7N NH_3 in MeOH) to afford the title compound as a colourless oil (17 mg, 0.059 mmol, 59% yield). Note: For reproducible results the bromide must be freshly distilled under high-vacuum without heating and used immediately. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.38–7.16 (m, 10H, H_{5-7} & H_{13-15}), 3.75 (d, J = 13.6 Hz, 1H, H_{11}), 3.67–3.60 (m, 2H, H_8 & H_{11}), 3.39–3.35 (m, 4H, H_{8-9}), 2.86–2.81 (m, 2H, H_1 & H_3), 2.69 (ddd, J = 13.7, 9.8, 6.6 Hz, 1H, H_3), 2.26 (s, 3H, H_{10}), 1.84 (qd, J = 9.1, 4.5 Hz, 1H, H_2), 1.73 (dtd, J = 14.6, 10.9, 6.5 Hz, 1H, H_2); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 142.9 (C_4 or C_{12}), 140.6 (C_4 or C_{12}), 128.8 (C_5 or C_6 or C_{13} or C_{14}), 128.6 (C_5 or C_6 or C_{13} or C_{14}), 128.5 (C_5 or C_6 or C_{13} or C_{14}), 128.4 (C_5 or C_6 or C_{13} or C_{14}), 128.3 (C_5 or C_6 or C_{13} or C_{14}), 126.8 (C_4 or C_{12}), 125.8 (C_4 or C_{12}), 73.1 (C_8), 61.5 (C_9), 59.0 (C_1), 58.7 (C_{11}), 37.2 (C_{10}), 33.3 (C_3), 31.0 (C_2); **IR** (film, cm^{-1}): 2920, 2857, 2801, 1601, 1494, 1452, 1193, 1117, 1028, 909, 733, 697; **HRMS** (NSI+): *m/z* calcd for $C_{19}H_{26}N_1O_1$, $[M+H]^+$, 284.2014; found, 284.2013 (Δ = -0.4 ppm).



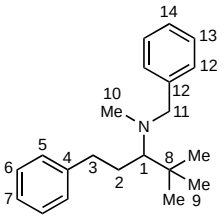
N-Benzyl-*N*-methyl-1,4-diphenylbutan-2-amine (**56e**). The title compound was prepared according to general procedure A using *N*-benzylmethylamine (13 µL, 0.10 mmol), hydrocinnamaldehyde (26 µL, 0.20 mmol), benzyl bromide (21.3 µL, 0.18 mmol), tris(trimethylsilyl)silane (61 µL, 0.20 mmol), 4Å MS (150 mg), ethyl 2-iodo-2-methylpropionate (2.0 µL, 0.013 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (46 µL, 0.10 mmol) in CH_2Cl_2 (4.5 mL). The crude mixture was purified by flash column chromatography (0–30% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (11 mg, 0.033 mmol, 33% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.32–7.09 (m, 15H, H_{5-7} & H_{10-12} & H_{16-18}), 3.75 (d, J = 13.5 Hz, 1H, H_{14}), 3.61 (d, J = 13.5 Hz, 1H, H_{14}), 3.03 (dd, J = 13.2, 4.8 Hz, 1H, H_3), 2.90–2.82 (m, 2H, H_1 & H_3), 2.49 (m, 2H, H_8), 2.29 (s, 3H, H_{13}), 1.84–1.77 (m, 1H, H_2), 1.70–1.63 (m, 1H, H_2); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.0 (C_4 or C_9 or C_{15}), 141.0 (C_4 or C_9 or C_{15}), 140.4 (C_4 or C_9 or C_{15}), 129.4 (C_{5-6} or C_{10-11} or C_{16-17}), 128.8 (C_{5-6} or C_{10-11} or C_{16-17}), 128.5 (C_{5-6} or C_{10-11} or C_{16-17}), 128.4 (C_{5-6} or C_{10-11} or C_{16-17}), 128.4 (C_{5-6} or C_{10-11} or C_{16-17}), 128.3 (C_{5-6} or C_{10-11} or C_{16-17}), 126.9 (C_7 or C_{12} or C_{18}), 125.8 (C_7 or C_{12} or C_{18}), 125.7 (C_7 or C_{12} or C_{18}), 64.4 (C_1), 58.2 (C_{14}), 36.5 (C_{13}), 35.2 (C_3), 33.4 (C_8), 32.7 (C_2); **IR** (film, cm^{-1}): 3027, 2932, 2789, 1601, 1494, 1452, 1026, 905, 731, 697; **HRMS** (NSI+): *m/z* calcd for $C_{24}H_{28}N$, $[M-H]^+$, 330.2216; found, 330.2217 (Δ = 0.2 ppm).



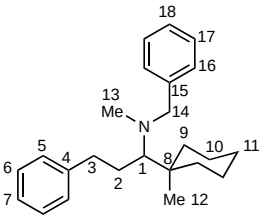
N-Benzyl-*N*-methyl-1-(1-methylcyclohexyl)-3-phenylpropan-1-amine (**56f**). The title compound was prepared according to general procedure A (deviation A) using *N*-benzylmethylamine (13 µL, 0.10 mmol), hydrocinnamaldehyde (26 µL, 0.20 mmol), 1-(bromomethyl)-4-methoxybenzene (36.2 mg, 0.18 mmol), tris(trimethylsilyl)silane (62 µL, 0.20 mmol), 4Å MS (150 mg), ethyl 2-iodo-2-methylpropionate (2.0 µL, 0.013 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (23 µL, 0.10 mmol) in CH_2Cl_2 (4.5 mL). The crude mixture was purified by flash column chromatography (0–8% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (23 mg, 0.065 mmol, 65% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.36–7.12 (m, 10H, H_{5-7} & H_{17-19}), 7.05 (d, J = 8.5 Hz, 2H, H_{10}), 6.85–6.82 (m, 2H, H_{11}), 3.82 (s, 3H, H_{13}), 3.76 (d, J = 13.5 Hz, 1H, H_{15}), 3.62 (d, J = 13.5 Hz, 1H, H_{15}), 2.99 (dd, J = 13.3, 4.7 Hz, 1H, H_8), 2.89–2.84 (m, 1H, H_3), 2.81 (dt, J = 9.1, 4.5 Hz, 1H, H_1), 2.52 (dt, J = 6.5, 3.4 Hz, 1H, H_3), 2.42 (dd, J = 13.3, 9.0 Hz, 1H, H_8), 2.29 (s, 3H, H_{14}), 1.86–1.76 (m, 1H, H_2), 1.71–1.62 (m, 1H, H_2); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 157.8 (C_{12}), 143.1 (C_4 or C_9 or C_{16}), 140.5 (C_4 or C_9 or C_{16}), 133.0 (C_4 or C_9 or C_{16}), 130.2 (C_{5-6} or C_{11} or C_{17-18}), 128.8 (C_{5-6} or C_{11} or C_{17-18}), 128.5 (C_{5-6} or C_{11} or C_{17-18}), 128.4 (C_{5-6} or C_{11} or C_{17-18}), 128.3 (C_{5-6} or C_{11} or C_{17-18}), 126.8 (C_7 or C_{19}), 125.7 (C_7 or C_{19}), 113.8 (C_9 & C_{11}), 64.5 (C_1), 58.2 (C_{15}), 55.4 (C_{13}), 36.5 (C_{14}), 34.2 (C_3), 33.4 (C_8), 32.7 (C_2); **IR** (film, cm^{-1}): 2952, 2841, 1450, 1262, 1133, 1111, 1094, 963, 862; **HRMS** (NSI+): *m/z* calcd for $C_{25}H_{30}N_1O_1$, $[M+H]^+$, 360.2327; found, 360.2331 (Δ = 1.1 ppm).



Benzyl 4-(1-(benzyl(methyl)amino)-3-phenylpropyl)piperidine-1-carboxylate (**56i**). The title compound was prepared according to general procedure A using *N*-benzylmethylamine (13 µL, 0.10 mmol), hydrocinnamaldehyde (26 µL, 0.20 mmol), benzyl 4-iodopiperidine-1-carboxylate (69 mg, 0.30 mmol), tris(trimethylsilyl)silane (61 µL, 0.20 mmol), 4Å MS (150 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol) in CH_2Cl_2 (4.5 mL). The crude mixture was purified by flash column chromatography (0–20% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as an amorphous solid (24 mg, 0.054 mmol, 54% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.38–7.18 (m, 15H, H_{5-7} & H_{14-16} & H_{20-22}), 5.14 (s, 2H, H_{12}), 4.23–4.17 (m, 2H, H_{10}), 3.72–3.64 (m, 2H, H_{18}), 2.82–2.71 (m, 3H, H_{10} & H_3), 2.70–2.61 (m, 1H, H_3), 2.37 (td, J = 7.3, 4.8 Hz, 1H, H_1), 2.22 (s, 3H, H_{12}), 1.98–1.85 (m, 2H, H_2 & H_9), 1.72–1.62 (m, 3H, H_2 & H_8 & H_9), 1.30–1.18 (m, 2H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 155.4 (C_{11}), 142.8 (C_4), 140.5 (C_{19}), 137.1 (C_{13}), 128.6 (C_{5-7} or C_{14-16} or C_{20-22}), 128.6 (C_{5-7} or C_{14-16} or C_{20-22}), 128.5 (C_{5-7} or C_{14-16} or C_{20-22}), 128.4 (C_{5-7} or C_{14-16} or C_{20-22}), 128.3 (C_{5-7} or C_{14-16} or C_{20-22}), 128.0 (C_{5-7} or C_{14-16} or C_{20-22}), 128.0 (C_{5-7} or C_{14-16} or C_{20-22}), 126.9 (C_{5-7} or C_{14-16} or C_{20-22}), 126.0 (C_{5-7} or C_{14-16} or C_{20-22}), 67.1 (C_{12}), 66.9 (C_1), 59.6 (C_{18}), 44.6 (C_{10}), 44.4 (C_{10}), 39.2 (C_8), 36.8 (C_{17}), 35.2 (C_3), 30.7 (C_2 or C_9), 30.0 (C_2 or C_9); **IR** (film, cm^{-1}): 2936, 2857, 1698, 1429, 1222, 1026, 735, 697; **HRMS** (NSI+): *m/z* calcd for $C_{30}H_{37}N_2O_2$, $[M+H]^+$, 457.2850; found, 457.2841 (Δ = -1.9 ppm).

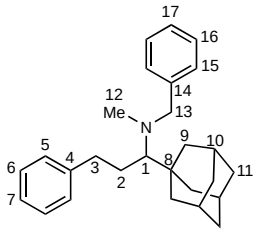


N-benzyl-*N*,4,4-trimethyl-1-phenylpentan-3-amine (**56j**). The title compound was prepared according to general procedure A using *N*-benzylmethylamine (26 µL, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 2-iodo-2-methylpropane (72 µL, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (46 µL, 0.20 mmol) in CH_2Cl_2 (6 mL). The crude mixture was purified by flash column chromatography (0–1% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (46 mg, 0.15 mmol, 77% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.40–7.38 (m, 2H), 7.34–7.29 (m, 4H), 7.26–7.19 (m, 4H), 3.97 (d, J = 14.0 Hz, 1H, H_{11}), 3.88 (d, J = 14.0 Hz, 1H, H_{11}), 2.91 (ddd, J = 13.6, 11.0, 4.9 Hz, 1H, H_3), 2.64 (ddd, J = 13.6, 10.5, 6.2 Hz, 1H, H_3), 2.42 (dd, J = 10.1, 2.9 Hz, 1H, H_1), 2.38 (s, 3H, H_{10}), 1.95 (dtd, J = 14.9, 9.8, 4.9 Hz, 1H, H_2), 1.82 (dddd, J = 14.2, 11.0, 6.2, 3.0 Hz, 1H, H_2), 0.97 (s, 9H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.2 (C_4), 141.5 (C_{12}), 128.5 (C_{5-6} or C_{12-13}), 128.4 (C_{5-6} or C_{12-13}), 128.3 (C_{5-6} or C_{12-13}), 126.7 (C_7 or C_{14}), 125.9 (C_7 or C_{14}), 72.9 (C_1), 61.4 (C_{11}), 39.3 (C_{10}), 37.9 (C_8), 36.1 (C_3), 29.7 (C_2), 28.5 (C_9); **IR** (film, cm^{-1}): 2948, 2865, 2785, 1603, 1496, 1452, 1359, 1074, 1028, 733, 695; **HRMS** (NSI+): *m/z* calcd for $C_{21}H_{30}N_1$, $[M+H]^+$, 296.2378; found, 296.2380 (Δ = 0.7 ppm).

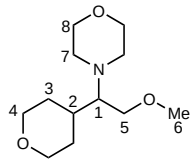


N-Benzyl-*N*-methyl-1-(1-methylcyclohexyl)-3-phenylpropan-1-amine (**56k**). The title compound was prepared according to general procedure A (deviation A) using *N*-benzylmethylamine (26 µL, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 1-iodo-1-methylcyclohexane (134.4 mg, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol) in CH_2Cl_2 (6 mL). The crude mixture was purified by flash column chromatography (0-2% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (55 mg, 0.16 mmol, 82% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.43 (d, J = 7.1 Hz, 2H, H_{5-7} or H_{16-18}), 7.37–7.32 (m, 4H, H_{5-7} or H_{16-18}), 7.29–7.21 (m, 4H, H_{5-7} or H_{16-18}), 4.04 (d, J = 14.0 Hz, 1H, H_{14}), 3.91 (d, J = 14.1 Hz, 1H, H_{14}), 2.92 (ddd, J = 13.6, 11.0, 4.9 Hz, 1H, H_3), 2.65 (ddd, J = 13.6, 10.5, 6.2 Hz, 1H, H_3), 2.51 (dd, J = 10.1, 2.7 Hz, 1H, H_1), 2.41 (s, 3H, H_{13}), 1.99 (dtd, J = 14.8, 10.0, 4.8 Hz, 1H, H_2), 1.88 (tdd, J = 11.3, 6.0, 2.9 Hz, 1H, H_2), 1.60–1.35 (m, 9H, H_{9-11}), 1.27–1.21 (m, 1H, H_{11}), 0.96 (s, 3H, H_{12}). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.2 (C_4), 141.6 (C_{15}), 128.5 (C_{5-6} or C_{16-17}), 128.5 (C_{5-6} or C_{16-17}), 128.4 (C_{5-6} or C_{16-17}), 128.3 (C_{5-6} or C_{16-17}), 126.6 (C_7 or C_{18}), 125.9 (C_7 or C_{18}), 72.9 (C_1), 61.8 (C_{14}), 40.3 (C_8), 40.0 (C_{13}), 36.3 (C_3), 36.2 (C_{10} or C_9), 28.8 (C_2), 26.7 (C_{11}), 22.4 (C_{10} or C_9), 22.1 (C_{10} or C_9), 20.7

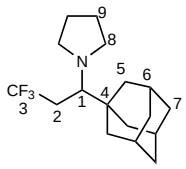
(C_{12}); **IR** (film, cm^{-1}): 2920, 2781, 1450, 1046, 1026, 731, 697; **HRMS** (NSI+): *m/z* calcd for $C_{24}H_{34}N_1$, $[M+H]^+$, 336.2686; found, 336.2689 (Δ = 1.0 ppm).



1-(Adamantan-1-yl)-*N*-benzyl-*N*-methyl-3-phenylpropan-1-amine (**56l**). The title compound was prepared according to general procedure A using *N*-benzylmethylamine (26 µL, 0.20 mmol), hydrocinnamaldehyde (53 µL, 0.40 mmol), 1-iodoadamantane (157 mg, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol) in CH_2Cl_2 (6 mL). The crude mixture was purified by flash column chromatography (0–2% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (56 mg, 0.15 mmol, 75%). The title compound (30.5 mg, 0.082 mmol, 41% yield) could also be accessed using 1-bromoadamantane (129 mg, 0.40 mmol) with ethyl 2-iodo-2-methylpropionate (4.0 µL, 0.025 mmol) initiator. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.45–7.43 (m, 2H, H_{5-7} or H_{15-17}), 7.37–7.32 (m, 4H, H_{5-7} or H_{15-17}), 7.29–7.21 (m, 4H, H_{5-7} or H_{15-17}), 4.00 (d, *J* = 14.0 Hz, 1H, H_{13}), 3.89 (d, *J* = 14.1 Hz, 1H, H_{13}), 2.91 (ddd, *J* = 13.6, 10.6, 5.4 Hz, 1H, H_3), 2.64 (ddd, *J* = 13.6, 10.1, 6.4 Hz, 1H, H_3), 2.40 (s, 3H, H_{12}), 2.24 (dd, *J* = 9.5, 3.6 Hz, 1H, H_1), 1.99 (d, *J* = 10.1 Hz, 3H, H_{10}), 1.96–1.86 (m, 2H, H_2), 1.77–1.64 (m, 12H, H_9 & H_{11}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.3 (C_4), 141.6 (C_{14}), 128.5 (C_{5-6} or C_{15-16}), 128.4 (C_{5-6} or C_{15-16}), 128.3 (C_{5-6} or C_{15-16}), 126.6 (C_7 or C_{17}), 125.8 (C_7 or C_{17}), 73.8 (C_1), 61.5 (C_{13}), 40.4 (C_9 or C_{11}), 39.9 (broad, C_{12}), 39.9 (C_8), 37.5 (C_9 or C_{11}), 36.2 (C_3), 28.9 (C_9 or C_{11}), 28.2 (C_2); **IR** (film, cm^{-1}): 2900, 2841, 1601, 1490, 1450, 1264, 1028, 731, 695; **HRMS** (NSI+): *m/z* calcd for $C_{27}H_{36}N_1$, $[M+H]^+$, 374.2842; found, 374.2841 (Δ = -0.3 ppm). Note: Two aromatic carbon peaks overlap.



4-(2-methoxy-1-(tetrahydro-2*H*-pyran-4-yl)ethyl)morpholine (**57b**). The title compound was prepared according to general procedure A using morpholine (8.7 µL, 0.10 mmol), 4-formyltetrahydropyran (23 µL, 0.20 mmol), bromomethyl methyl ether (9.8 µL, 0.12 mmol), tris(trimethylsilyl)silane (62 µL, 0.20 mmol), 4Å MS (150 mg), ethyl 2-iodo-2-methylpropionate (2.0 µL, 0.013 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (23 µL, 0.10 mmol) in CH_2Cl_2 (6 mL). The crude mixture was purified by flash column chromatography (0–50% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (17 mg, 0.074 mmol, 74% yield). Note: For reproducible results the bromide must be freshly distilled under high-vacuum <u>without</u> heating and used immediately.**^{1}H NMR** (400 MHz; $CDCl_3$): δ 4.00–3.94 (m, 2H, H_5), 3.64 (qdd, *J* = 11.1, 6.4, 3.2 Hz, 4H, H_8), 3.49 (qd, *J* = 10.7, 4.2 Hz, 2H, H_4), 3.39–3.33 (m, 2H, H_4), 3.29 (s, 3H, H_6), 2.74 (ddd, *J* = 10.8, 6.7, 3.5 Hz, 2H, H_7), 2.47 (ddd, *J* = 11.2, 6.3, 3.1 Hz, 2H, H_7), 2.20 (ddd, *J* = 9.1, 5.5, 3.4 Hz, 1H, H_1), 1.92 (ddd, *J* = 13.6, 3.6, 2.0 Hz, 1H, H_3), 1.82–1.73 (m, 1H, H_2), 1.58 (ddd, *J* = 13.0, 3.5, 2.0 Hz, 1H, H_3), 1.39–1.23 (m, 2H, H_3); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 69.6 (C_4 or C_5), 68.7 (C_1), 68.6 (C_4 or C_5), 68.0 (C_4 or C_5), 67.9 (C_8), 58.8 (C_6), 50.4 (C_7), 34.3 (C_2), 31.2 (C_3), 30.7 (C_3); **IR** (film, cm^{-1}): 2947, 2911, 2844, 1450, 1291, 1262, 1235, 1133, 1113, 1093, 1021, 963, 864; **HRMS** (NSI+): *m/z* calcd for $C_{12}H_{24}N_1O_3$, $[M+H]^+$, 230.1756; found, 230.1754 (Δ = -0.9 ppm).



1-(1-(Adamantan-1-yl)-3,3,3-trifluoropropyl)pyrrolidine (**57f**). The title compound was prepared according to general procedure A using pyrrolidine (17 µL, 0.20 mmol), 3,3,3-trifluoropropanal (45 mg, 0.40 mmol), 1-iodoadamantane (157 mg, 0.60 mmol), tris(trimethylsilyl)silane (123 µL, 0.40 mmol), 4Å MS (300 mg) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (90 µL, 0.40 mmol) in CH_2Cl_2 (15 mL). The crude mixture was purified by flash column chromatography (0–4% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (39 mg, 0.13 mmol, 65% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 2.86–2.70 (m, 4H, H_8), 2.59–2.57 (m, 1H, H_1), 2.35–2.26 (m, 1H, H_2), 2.19–2.12 (m, 1H, H_2), 1.97 (s, 3H, H_6), 1.70–1.50 (m, 16H, H_5 & H_7 & H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 128.0 (q, *J* = 276.5 Hz, C_3), 62.6 (C_1), 50.3 (C_8), 39.6 (C_5 or C_7), 39.2 (C_4), 37.3 (C_5 or C_7), 28.7 (C_6), 28.1 (q, *J* = 27.5 Hz, C_2), 24.8 (C_9); **^{19}F NMR** (376 MHz; $CDCl_3$): δ -63.4; **IR** (film, cm^{-1}): 2968, 2904, 1672, 1448, 1254, 1101, 907, 727; **HRMS** (NSI+): *m/z* calcd for $C_{17}H_{27}F_3N_1$, $[M+H]^+$, 302.2096; found, 302.2098 (Δ = 0.7 ppm).

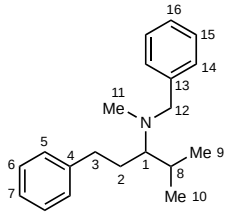
6.2.2 Carbonyl alkylative amination employing alcohol- and carboxylic acid-based nucleophiles

General procedure B – Room temperature, zinc-mediated carbonyl alkylative amination:

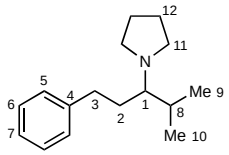
A microwave vial was charged with a stir bar, zinc-powder (1 mmol, 10 equiv.) and *N*-hydroxyphthalimide ester (0.20 mmol, 2.0 equiv.) before being sealed with a septum, evacuated and backfilled three times with 1 atm of N_2. In the instance that any of the other starting materials were solid, they were added at this stage too. To this was added dry and degassed EtOAc (0.20 M) followed by addition of amine (0.10 mmol, 1.0 equiv.), aldehyde (0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.1-0.20 mmol, 1-2.0 equiv.) *via* microsyringe. The reaction mixture was stirred for 14 h at r.t. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (10 mL) and hexane (10 mL) was added. The mixture was concentrated *in vacuo* until approximately 3 mL remained, which were decanted. The resulting residue was washed with hexane (5 mL x 3). CH_2Cl_2 (15 mL) was added and the solution was neutralized upon stirring with NaOH (10 mL, 10% aq.) for 15 minutes. The product was extracted into CH_2Cl_2 (10 mL x 2). The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography.

General procedure C – Heated, zinc-mediated carbonyl alkylative amination:

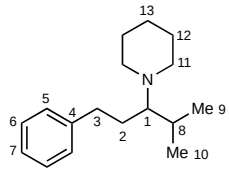
A microwave vial was charged with a stir bar, zinc-powder (0.30 mmol, 3.0 equiv.) and *N*-hydroxyphthalimide ester (0.20 mmol, 2.0 equiv.) before being sealed with a septum, evacuated and backfilled three times with 1 atm of N_2. In the instance any of the other starting materials were solid, they were added at this stage too. To this was added dry and degassed EtOAc (0.20 M) followed by addition of amine (0.10 mmol, 1.0 equiv.), aldehyde (0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.1-0.20 mmol, 1-2.0 equiv.) *via* microsyringe. The reaction mixture was stirred for 14 h at 70 °C. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (10 mL) and hexane (10 mL) was added. The mixture was concentrated *in vacuo* until approximately 3 mL remained, and then decanted. The resulting residue was washed with hexane (5 mL x 3). CH_2Cl_2 (15 mL) was added and the solution was neutralized upon stirring with NaOH (10 mL, 10% aq.) for 15 minutes. The product was extracted into CH_2Cl_2 (10 mL x 2). The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography.



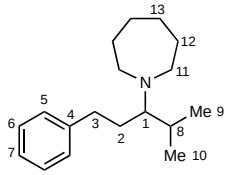
N-Benzyl-*N*,4-dimethyl-1-phenylpentan-3-amine (**68**). The title compound was prepared according to general procedure B using *N*-methyl benzylamine (13 µL, 0.10 mmol, 1.0 equiv.), hydrocinnamaldehyde (26 µL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (73 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.50 mL, 0.20 M). The crude reaction mixture was purified by filtration through an SCX-column (eluting with 7N NH_3 in MeOH) to afford the title compound as a colourless oil (27 mg, 0.094 mmol, 94% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.42–7.32 (m, 6H, $H_{5\text{-}7}$ & $H_{14\text{-}16}$), 7.30–7.22 (m, 4H, $H_{5\text{-}7}$ & $H_{14\text{-}16}$), 3.74 (app s, 2H, H_{12}), 2.88 (ddd, J = 13.6, 10.8, 5.4 Hz, 1H, H_3), 2.70 (ddd, J = 13.6, 10.8, 6.0 Hz, 1H, H_3), 2.36 (td, J = 7.3, 4.3 Hz, 1H, H_1), 2.27 (s, 3H, H_{11}), 2.00–1.85 (m, 2H, H_2 & H_8), 1.72 (dddd, J = 14.1, 10.7, 6.1, 4.5 Hz, 1H, H_2), 1.04 (d, J = 6.8 Hz, 3H, H_9), 1.00 (d, J = 6.7 Hz, 3H, H_{10}). Spectral data was in agreement with literature.[297]



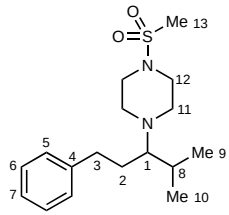
1-(4-Methyl-1-phenylpentan-3-yl)pyrrolidine (**88b**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), pyrrolidine (8.3 µL, 0.10 mmol, 1.0 equiv.), hydrocinnamaldehyde (26 µL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (73 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by filtration through an SCX-column (eluting with 7N NH_3 in MeOH) to afford the title compound as a colourless oil (23.0 mg, 0.10 mmol, quant.). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.33–7.28 (m, 2H, H_6), 7.23–7.19 (m, 3H, H_5 & H_7), 2.76 (ddd, J = 13.7, 10.1, 6.7 Hz, 1H, H_3), 2.67–2.60 (m, 5H, H_3 & H_{11}), 2.13 (q, J = 4.6 Hz, 1H, H_1), 2.04–1.94 (m, 1H, H_8), 1.83–1.73 (m, 6H, H_2 & H_{12}), 0.94 (app, dd, J = 6.8, 4.1 Hz, 6H, $H_{9\text{-}10}$); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.1 (C_4), 128.5 (C_5 or C_6), 128.4 (C_5 or C_6), 125.8 (C_7), 68.2 (C_1), 51.2 (C_{11}), 35.8 (C_3), 31.0 (C_2), 30.8 (C_8), 23.6 (C_{12}), 20.5 (C_{10}), 17.6 (C_9); **IR** (film, cm^{-1}): 2963, 1717, 1664, 1496, 1454, 1374, 752, 701;



1-(4-Methyl-1-phenylpentan-3-yl)piperidine (**50c**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), piperidine (9.9 µL, 0.10 mmol, 1.0 equiv.), hydrocinnamaldehyde (26 µL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (73 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by filtration through an SCX-column (eluting with 7N NH_3 in MeOH) to afford the title compound as a colourless oil (24.3 mg, 0.10 mmol, quant.).

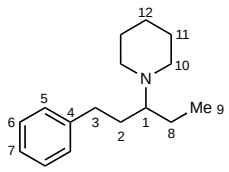


1-(4-Methyl-1-phenylpentan-3-yl)azepane (**50d**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), azepane (11 µL, 0.10 mmol, 1.0 equiv.), hydrocinnamaldehyde (26 µL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (73 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by filtration through an SCX-column (eluting with 7N NH_3 in MeOH) to afford the title compound as a colourless oil (24.7 mg, 0.095 mmol, 95% yield).

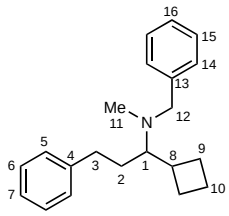


1-(4-Methyl-1-phenylpentan-3-yl)-4-(methylsulfonyl)piperazine (**51h**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), 1-(methylsulfonyl)-piperazine (16 mg, 0.10 mmol, 1.0 equiv.), hydrocinnamaldehyde (26 µL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (73 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by

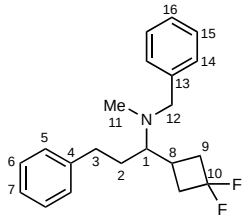
filtration through an SCX-column (eluting with 7N NH_3 in MeOH) to afford the title compound as a colourless oil (24 mg, 0.10 mmol, quant.).



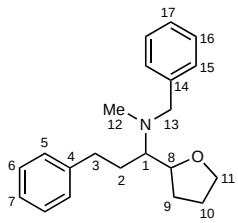
1-(1-phenylpentan-3-yl)piperidine (**89b**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), piperidine (16 mg, 0.10 mmol, 1.0 equiv.), hydrocinnamaldehyde (26 µL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl propanoate **S1** (71 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0–40% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (16 mg, 0.070 mmol, 70% yield). **^{1}H NMR** (600 MHz; $CDCl_3$): δ 7.28–7.25 (m, 2H, H_6), 7.21–7.15 (m, 3H, H_5 & H_7), 2.71–2.62 (m, 2H, H_3), 2.54–2.43 (m, 4H, H_{10}), 2.28–2.25 (m, 1H, H_1), 1.79–1.75 (m, 1H, H_2), 1.62–1.50 (m, 6H, H_2 & H_8 & H_{11}), 1.43 (m, 2H, H_{12}), 1.36–1.26 (m, 1H, H_8), 0.89 (t, J = 7.4 Hz, 3H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.5 (C_4), 128.6 (C_5 or C_6), 128.3 (C_5 or C_6), 125.6 (C_7), 65.7 (C_1), 49.6 (C_{10}), 33.6 (C_3), 32.1 (C_2), 27.0 (C_{11}), 25.4 (C_{12}), 22.4 (C_8), 12.2 (C_9); **IR** (film, cm^{-1}): 2928, 2872, 2786, 1494, 1453, 1026, 730, 695.



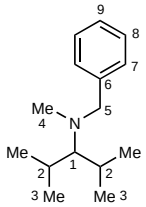
N-benzyl-1-cyclobutyl-*N*-methyl-3-phenylpropan-1-amine (**91a**). The title compound was prepared according to general procedure B, using zinc (65 mg, 1.0 mmol, 10 equiv.), *N*-methyl benzylamine (13 µL, 0.10 mmol, 1.0 equiv.), hydrocinnamaldehyde (26 µL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl cyclobutanecarboxylate **S3** (77 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0-10% EtOAc in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (18 mg, 0.062 mmol, 62% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.38–7.17 (m, 10H, $H_{5\text{-}7}$ & $H_{14\text{-}16}$), 3.70–3.62 (m, 2H, H_{12}), 2.90–2.83 (m, 1H, H_3), 2.68–2.50 (m, 3H, H_1 & H_3 & H_8), 2.20 (s, 3H, H_{11}), 2.11–2.03 (m, 1H, H_{10}), 1.97–1.86 (m, 3H, H_3 & H_{10}), 1.75–1.59 (m, 4H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.5 (C_4 or C_{13}), 141.1 (C_4 or C_{13}), 128.62 ($C_{5\text{-}6}$ or $C_{14\text{-}15}$), 128.57 ($C_{5\text{-}6}$ or $C_{14\text{-}15}$), 128.4 ($C_{5\text{-}6}$ or $C_{14\text{-}15}$), 128.3 ($C_{5\text{-}6}$ or $C_{14\text{-}15}$), 126.7 (C_7 or C_{16}), 125.7 (C_7 or C_{16}), 68.2 (C_1), 59.0 (C_{12}), 38.4 (C_8), 37.2 (C_{11}), 33.7 (C_3), 31.1 (C_2), 29.2 (C_9), 28.1 ($C_{9'}$), 19.2 (C_{10}); **IR** (film, cm^{-1}): 3025, 2933, 2856, 2787, 1494, 1453, 1020, 733, 698.



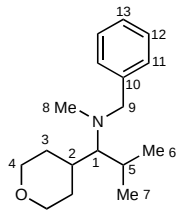
N-benzyl-1-(3,3-difluorocyclobutyl)-*N*-methyl-3-phenylpropan-1-amine (**91b**). The title compound was prepared according to general procedure B, using zinc (65 mg, 1.0 mmol, 10 equiv.), *N*-methyl benzylamine (13 µL, 0.10 mmol, 1.0 equiv.), hydrocinnamaldehyde (26 µL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 3,3-difluorocyclobutanecarboxylate **S4** (84 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 µL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0–5% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (15 mg, 0.045 mmol, 45% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.33–7.19 (m, 10H, $H_{5\text{-}7}$ & $H_{14\text{-}16}$), 3.66 (s, 2H, H_{12}), 2.83 (ddd, J = 14.0, 9.8, 4.7 Hz, 1H, H_3), 2.71–2.55 (m, 4H, H_1 & H_3 & H_9), 2.51–2.30 (m, 2H, $H_{8\text{-}9}$), 2.25–2.13 (m, 4H, H_{11} & H_9), 1.84 (dtd, J = 14.0, 9.3, 4.9 Hz, 1H, H_2), 1.63–1.54 (m, 1H, H_2); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 142.6 (C_4), 140.3 (C_{13}), 128.6 ($C_{5\text{-}6}$ or $C_{14\text{-}15}$), 128.53 ($C_{5\text{-}6}$ or $C_{14\text{-}15}$), 128.47 ($C_{5\text{-}6}$ or $C_{14\text{-}15}$), 128.4 ($C_{5\text{-}6}$ or $C_{14\text{-}15}$), 127.0 (C_7 or C_{16}), 126.0 (C_7 or C_{16}), 120.1 (dd, J = 287.2, 269.8 Hz,), 67.2 (app t, J = 2.3 Hz, C_1), 59.0 (C_{12}), 40.5 (dd, J = 21.6, 19.3 Hz, C_9), 40.1 (dd, J = 21.6, 19.3 Hz, C_9), 36.9 (C_{11}), 33.7 (C_3), 31.0 (C_2), 25.9 (dd, J = 13.8, 3.2 Hz, C_8); **IR** (film, cm^{-1}): 3026, 2945, 2857, 2790, 1293, 1167, 898, 733, 697.



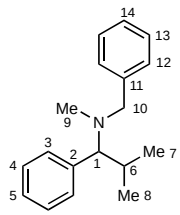
N-Benzyl-*N*-methyl-3-phenyl-1-(tetrahydrofuran-2-yl)propan-1-amine (**91d**). The title compound was prepared according to general procedure B, using zinc (65 mg, 1.0 mmol, 10 equiv.), *N*-methyl benzylamine (13 μL, 0.10 mmol, 1.0 equiv.), hydrocinnamaldehyde (26 μL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl tetrahydrofuran-2-carboxylate (80 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 μL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0–15% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (26 mg, 2:1 d.r., 0.084 mmol, 84% yield). Data for the major diastereomer: **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.39 (d, J = 7.4 Hz, 2H, H_{15}), 7.33–7.16 (m, 8H, H_{5-7} & H_{16-17}), 4.01 (q, J = 7.1 Hz, 1H, H_8), 3.88–3.72 (m, 4H, H_{11} & H_{13}), 2.97–2.90 (m, 1H, H_3), 2.69 (ddd, J = 13.7, 9.6, 6.8 Hz, 1H, H_3), 2.62–2.57 (m, 1H, H_1), 2.32 (s, 3H, H_{12}), 1.93–1.71 (m, 4H, H_2 & H_{9-10}), 1.64–1.53 (m, 2H, H_2 & H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.2 (C_4), 141.4 (C_{14}), 128.8 (C_{5-6} or C_{15-16}), 128.6 (C_{5-6} or C_{15-16}), 128.5 (C_{5-6} or C_{15-16}), 128.2 (C_{5-6} or C_{15-16}), 126.7 (C_7 or C_{17}), 125.8 (C_7 or C_{17}), 80.6 (C_8), 67.8 (C_{11}), 66.0 (C_1), 59.9 (C_{13}), 37.1 (C_{12}), 33.6 (C_3), 30.8 (C_2), 30.1 (C_9), 26.1 (C_{10}); **IR** (film, cm^{-1}): 3025, 2947, 2860, 1495, 1453, 1065, 1040, 1028, 734, 698.



N-Benzyl-*N*,2,4-trimethylpentan-3-amine (**93a**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), *N*-methyl benzylamine (13 μL, 0.10 mmol, 1.0 equiv.), isobutyraldehyde (18 μL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (74 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 μL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0–3% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (16 mg, 0.072 mmol, 72% yield). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.36 (dd, J = 7.9, 1.0 Hz, 2H, H_7 or H_8), 7.32–7.28 (m, 2H, H_7 or H_8), 7.23–7.19 (m, 1H, H_9), 3.77 (s, 2H, H_5), 2.24 (s, 3H, H_4), 2.10–1.96 (m, 3H, H_{1-2}), 0.99 (dd, J = 6.7, 3.7 Hz, 12H, H_3). Spectral data was in agreement with literature.[297]

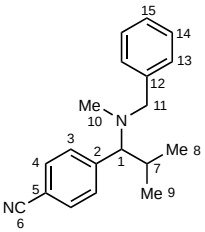


N-Benzyl-*N*,2-dimethyl-1-(tetrahydro-2*H*-pyran-4-yl)propan-1-amine (**93b**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), *N*-methyl benzylamine (13 μL, 0.10 mmol, 1.0 equiv.), tetrahydropyran-4-carbaldehyde (23 mg, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (74 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 μL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.50 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0–30% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (11 mg, 0.040 mmol, 40% yield). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.38–7.30 (m, 4H, H_{11-12}), 7.26–7.22 (m, 1H, H_{13}), 4.05–3.99 (m, 2H, H_4), 3.80 (app s, 2H, H_9), 3.47–3.39 (m, 2H, H_4), 2.28 (s, 3H, H_8), 2.24–2.20 (m, 1H, H_1), 2.10–2.02 (m, 1H, H_5), 1.97–1.90 (m, 1H, H_2), 1.80–1.76 (m, 1H, H_3), 1.65–1.46 (m, 3H, H_3), 1.06 (d, J = 6.8 Hz, 3H, H_6), 1.01 (d, J = 7.0 Hz, 3H, H_7). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 141.1 (C_{10}), 128.5 (C_{11} or C_{12}), 128.3 (C_{11} or C_{12}), 126.7 (C_{13}), 73.1 (C_1), 68.8 (C_4), 68.3 (C_4), 60.9 (C_9), 38.6 (C_8), 36.6 (C_2), 32.1 (C_3), 31.8 (C_3), 28.0 (C_5), 21.30 (C_6 or C_7), 21.27 (C_6 or C_7); **IR** (film, cm^{-1}): 2952, 2840, 1466, 1388, 1238, 1095, 1021, 699.

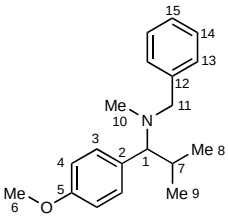


N-Benzyl-*N*,2-dimethyl-1-phenylpropan-1-amine (**93c**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), *N*-methyl benzylamine (13 μL, 0.10 mmol, 1.0 equiv.), benzaldehyde (20 μL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (74 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 μL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture upon work-up afforded the product as a yellow oil (24 mg, 0.093 mmol, 93% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.37–7.17 (m, 10H, H_{3-5} & H_{12-14}), 3.51 (d, J = 13.5 Hz, 1H, H_{10}), 3.24 (d, J = 13.5 Hz, 1H, H_{10}), 3.15 (d, J = 9.7 Hz, 1H, H_1), 2.36–2.31 (m, 1H, H_6), 2.06 (s, 3H, H_9), 1.14 (d, J

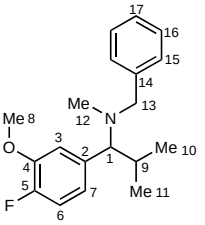
= 6.5 Hz, 3H, H_8), 0.72 (d, J = 6.5 Hz, 3H, H_7); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 140.5 (C_{11}), 137.6 (C_2), 129.5 (C_{3-4} or C_{12-13}), 128.8 (C_{3-4} or C_{12-13}), 128.3 (C_{3-4} or C_{12-13}), 127.7 (C_{3-4} or C_{12-13}), 126.8 (C_5 or C_{14}), 126.7 (C_5 or C_{14}), 74.8 (C_1), 58.7 (C_{10}), 37.5 (C_9), 28.7 (C_6), 20.9 (C_7), 20.1 (C_8); **IR** (film, cm^{-1}): 3027, 2956, 2934, 2872, 2844, 2790, 1493, 1467, 1452, 1384, 1366, 1101, 1021.



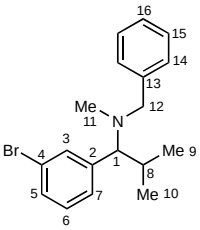
4-(1-(Benzyl(methyl)amino)-2-methylpropyl)benzonitrile (**93d**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), *N*-methyl benzylamine (13 μL, 0.10 mmol, 1.0 equiv.), 4-cyanobenzaldehyde (26 mg, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (74 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 μL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0–100% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (15 mg, 0.053 mmol, 53% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.65 (d, J = 7.8 Hz, 2H, H_4), 7.34–7.22 (m, 7H, H_3 & H_{13-15}), 3.46 (d, J = 13.5 Hz, 1H, H_{11}), 3.22–3.19 (m, 2H, H_1 & H_{11}), 2.37–2.28 (m, 1H, H_7), 2.05 (s, 3H, H_{10}), 1.10 (d, J = 6.5 Hz, 3H, H_9), 0.70 (d, J = 6.6 Hz, 3H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.5 (C_2), 139.6 (C_{12}), 131.7 (C_{3-4} or C_{13-14}), 130.0 (C_{3-4} or C_{13-14}), 128.7 (C_{3-4} or C_{13-14}), 128.4 (C_{3-4} or C_{13-14}), 127.0 (C_{15}), 119.2 (C_2), 110.8 (C_5), 74.4 (C_1), 58.9 (C_{11}), 37.5 (C_{10}), 28.6 (C_7), 20.7 (C_8), 20 (C_9); **IR** (film, cm^{-1}): 2959, 2934, 2790, 2227, 1453, 1019, 909, 731, 698, 568.



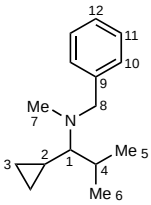
N-Benzyl-1-(4-methoxyphenyl)-*N*,2-dimethylpropan-1-amine (**93e**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), *N*-methyl benzylamine (13 μL, 0.10 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (24 μL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (74 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 μL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0–100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a yellow oil (20 mg, 0.069 mmol, 69% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.32 (dt, J = 13.4, 6.9 Hz, 4H, H_{13-14}), 7.22 (t, J = 7.0 Hz, 1H, H_{15}), 7.10 (d, J = 8.4 Hz, 2H, H_3), 6.89 (d, J = 8.4 Hz, 2H, H_4), 3.83 (s, 3H, H_6), 3.50 (d, J = 13.5 Hz, 1H, H_{11}), 3.21 (d, J = 13.5 Hz, 1H, H_{11}), 3.10 (d, J = 9.6 Hz, 1H, H_1), 2.33–2.24 (m, 1H, H_7), 2.04 (s, 3H, H_{10}), 1.12 (d, J = 6.5 Hz, 3H, H_8), 0.71 (d, J = 6.6 Hz, 3H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 158.5 (C_5), 140.6 (C_{12}), 130.4 (C_3 or C_{13-14}), 129.8 (C_2), 128.8 (C_3 or C_{13-14}), 128.2 (C_3 or C_{13-14}), 126.7 (C_{15}), 113.1 (C_4), 74.1 (C_1), 58.7 (C_{11}), 55.3 (C_6), 37.5 (C_{10}), 29.0 (C_7), 21.0 (C_9), 20.1 (C_8); **IR** (film, cm^{-1}): 2954, 1509, 1247, 1237, 1179, 1035, 1022, 908, 834, 730, 698.



N-Benzyl-1-(4-fluoro-3-methoxyphenyl)-*N*,2-dimethylpropan-1-amine (**93f**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), *N*-methyl benzylamine (13 μL, 0.10 mmol, 1.0 equiv.), 4-fluoro-3-methoxybenzaldehyde (31 mg, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (74 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 μL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0–80% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a yellow oil (22 mg, 0.071 mmol, 71% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.32 (q, J = 7.3 Hz, 4H, H_{15-16}), 7.26–7.22 (m, 1H, H_{17}), 7.05 (dd, J = 11.2, 8.3 Hz, 1H, H_6), 6.78 (d, J = 8.4 Hz, 1H, H_3), 6.72–6.68 (m, 1H, H_7), 3.90 (s, 3H, H_8), 3.51 (d, J = 13.5 Hz, 1H, H_{13}), 3.21 (d, J = 13.5 Hz, 1H, H_{13}), 3.11 (d, J = 9.3 Hz, 1H, H_1), 2.32–2.23 (m, 1H, H_9), 2.08 (s, 3H, H_{12}), 1.10 (d, J = 6.5 Hz, 3H, H_{11}), 0.73 (d, J = 6.5 Hz, 3H, H_{10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 151.5 (d, J = 244.1 Hz, C_5), 147.0 (d, J = 10.6 Hz, C_4), 140.2 (C_{14}), 134.1 (d, J = 3.9 Hz, C_2), 128.7 (C_{15} or C_{16}), 128.3 (C_{15} or C_{16}), 126.9 (C_{17}), 121.7 (d, J = 6.6 Hz, C_7), 115.2 (d, J = 18.0 Hz, C_6), 114.7 (d, J = 1.7 Hz, C_3), 74.2 (C_1), 58.9 (C_{13}), 56.5 (C_8), 37.6 (C_{12}), 29.0 (C_9), 20.8 (C_{10}), 19.7 (C_{11}); **IR** (film, cm^{-1}): 2956, 1512, 1464, 1452, 1272, 1216, 1143, 1123, 1023, 816, 769, 735, 698.

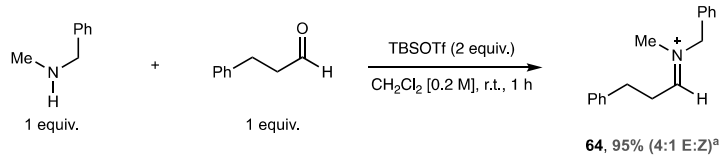


N-Benzyl-1-(3-bromophenyl)-*N*,2-dimethylpropan-1-amine (**93g**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), *N*-methyl benzylamine (13 μL, 0.10 mmol, 1.0 equiv.), 3-bromobenzaldehyde (24 μL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (74 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 μL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.5 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0–40% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a yellow oil (21 mg, 0.063 mmol, 63% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.42 (d, J = 7.9 Hz, 1H, H_5), 7.32 (q, J = 6.6 Hz, 5H, H_3 or H_6 & H_{14-15}), 7.26–7.21 (m, 2H, H_3 or H_6 & H_{16}), 7.11 (d, J = 7.6 Hz, 1H, H_7), 3.49 (d, J = 13.5 Hz, 1H, H_{12}), 3.23 (d, J = 13.5 Hz, 1H, H_{12}), 3.12 (d, J = 9.6 Hz, 1H, H_1), 2.32–2.27 (m, 1H, H_8), 2.06 (s, 3H, H_{11}), 1.12 (d, J = 6.5 Hz, 3H, H_{10}), 0.72 (d, J = 6.5 Hz, 3H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 140.2 (C_2 or C_{13}), 140.0 (C_2 or C_{13}), 132.2 (C_3), 130.0, 129.4, 128.8, 128.3, 128.0, 126.9 (C_{16}), 122.3 (C_4), 74.3 (C_1), 58.7 (C_{12}), 37.4 (C_{11}), 28.7 (C_8), 20.8 (C_9), 19.9 (C_{10}); **IR** (film, cm^{-1}): 2956, 1453, 1022, 1073, 781, 734, 708, 697.

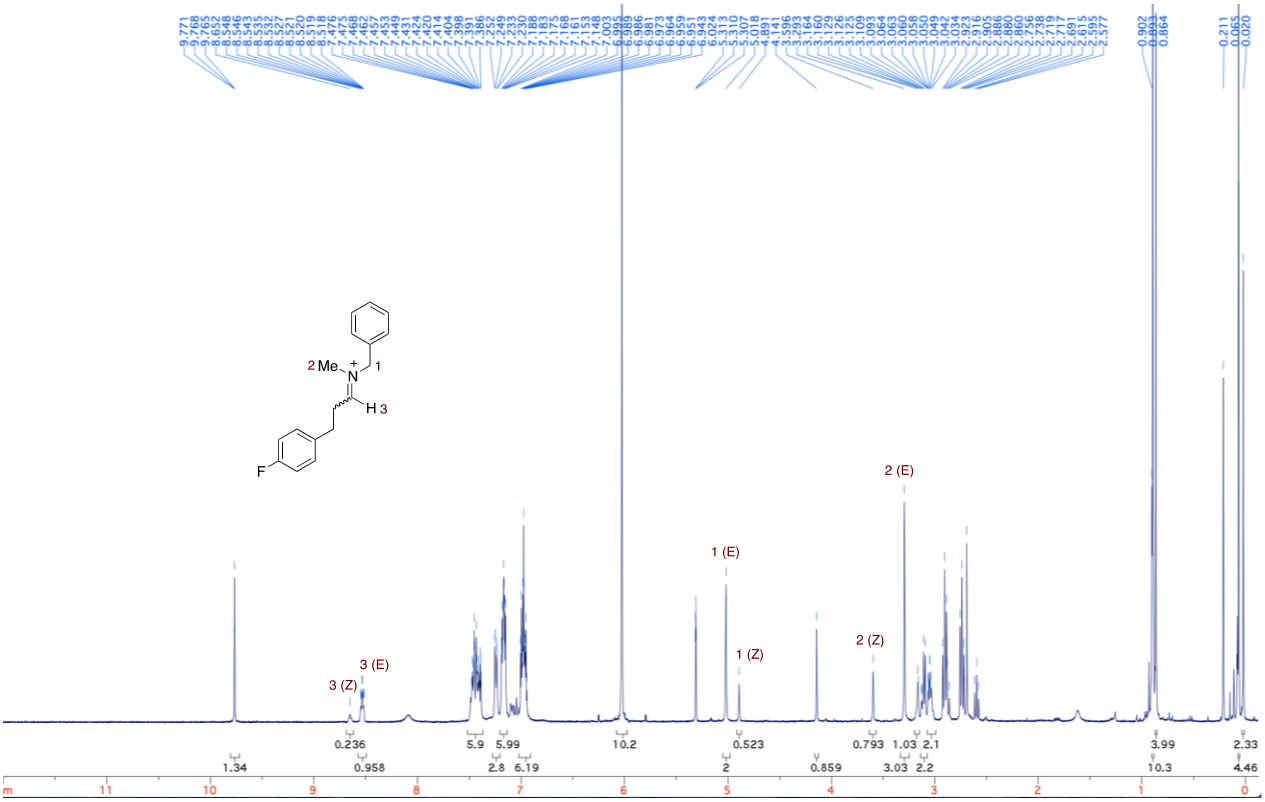


N-Benzyl-1-cyclopropyl-*N*,2-dimethylpropan-1-amine (**59b**). The title compound was prepared according to general procedure C, using zinc (20 mg, 0.30 mmol, 3.0 equiv.), *N*-methyl benzylamine (13 μL, 0.10 mmol, 1.0 equiv.), cyclopropylcarboxaldehyde (15 μL, 0.20 mmol, 2.0 equiv.), 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate[367] (74 mg, 0.20 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (45 μL, 0.20 mmol, 2.0 equiv.) in EtOAc (0.50 mL, 0.20 M). The crude reaction mixture was purified by flash column chromatography (0-10% EtOAc in 40°–60° Petroleum Ether) to afford the title compound as a yellow oil (9.5 mg, 0.044 mmol, 44% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.37–7.26 (m, 4H, H_{10-11}), 7.23–7.19 (m, 1H, H_{12}), 3.85–3.81 (m, 1H, H_8), 3.69–3.66 (m, 1H, H_8), 2.25 (s, 3H, H_7), 1.97–1.88 (m, 1H, H_1), 1.49–1.45 (m, 1H, H_4), 1.07–1.03 (m, 6H, H_{5-6}), 0.79–0.72 (m, 1H, H_2), 0.58–0.48 (m, 2H, H_3), 0.41–0.35 (m, 1H, H_3), 0.12–0.08 (m, 1H, H_3); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 141.5 (C_9), 128.7 (C_{10} or C_{11}), 128.2 (C_{10} or C_{11}), 126.6 (C_{12}), 74.9 (C_1), 60.2 (C_8), 38.1 (C_7), 32.8 (C_4), 21.8 (C_5), 21.1 (C_6), 9.9 (C_2), 3.7 (C_3), 3.2 (C_3); **IR** (film, cm^{-1}): 3078, 2953, 2872, 2788, 1469, 1453, 1026, 737, 698.

Mechanistic investigations



3-(4-Fluorophenyl)propanal (15 mg, 0.10 mmol, 2.0 equiv.), *N*-methyl benzylamine (6.5 µL, 0.050 mmol, 1.0 equiv.) and MS 4Å (75 mg) were stirred in CD_2Cl_2 (1.5 mL) for 30 minutes. Then, TBSOTf (12 µL, 0.050 mmol, 1.0 equiv.) was added and the resulting mixture was stirred for an additional 30 min to afford the corresponding iminium ion (**64**) as a 4:1 E:Z mixture in 95% yield by ^{1}H-NMR, determined by integration of the benzylic methylene signals (H1) with 1,1,2,2-tetrachloroethane as an internal standard.



6.2.3 Visible light-mediated synthesis of *N*-heterospirocycles

General procedure D for the visible light-mediated synthesis of *N*-heterospirocycles:

A 4-mL screw-cap vial was charged with a magnetic stirrer bar, diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzsch ester) (101 mg, 0.40 mmol, 2.0 equiv.), $Ir(dMeppy)_3$ (1.5 mg, 2.0 μmol, 1.0 mol%) and MS 4Å (50 mg). If the ketone or amine were solids, they were added at this stage. The vial was sealed with a cap containing a PTFE-septum and evacuated and backfilled with N_2 three times. Then CH_2Cl_2 (0.50 mL, 0.40 M), amine (0.20 mmol, 1.0 equiv.), 1,4-cyclohexadiene (141 mL, 1.5 mmol, 7.5 equiv.), propionic acid (3.0 μL, 0.040 mmol, 20 mol%) and ketone (0.60 mmol, 3 equiv.) were added in order via microsyringe. The resulting mixture was irradiated with a 40W Kessil A160WE lamp.

Depending on the structure of the pyrrolidine-product, two purification techniques were used:

For substrates without base-labile functionalities:

The resulting mixture was filtered through Celite® and conc. *in vacuo*. To the crude was added $LiOH•H_2O$ (84 mg, 2.0 mmol, 10 equiv.), THF (5.0 mL) and H_2O (1.0 mL) and the resulting mixture was heated to 80°C in a sealed tube for 3 h. The resulting solution was poured into sat. aq. $NaHCO_3$ (10 mL), extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude material was purified by flash column chromatography to yield the title compounds.

For substrates with base-labile functionalities:

The resulting mixture was conc. *in vacuo* and purified directly by flash column chromatography to yield the title compounds.

Deviation for heterocyclic or electron-deficient ketones:

For heterocyclic ketones, $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 mmol, 1.0 mol%) was used as a catalyst instead of $Ir(dMeppy)_3$.

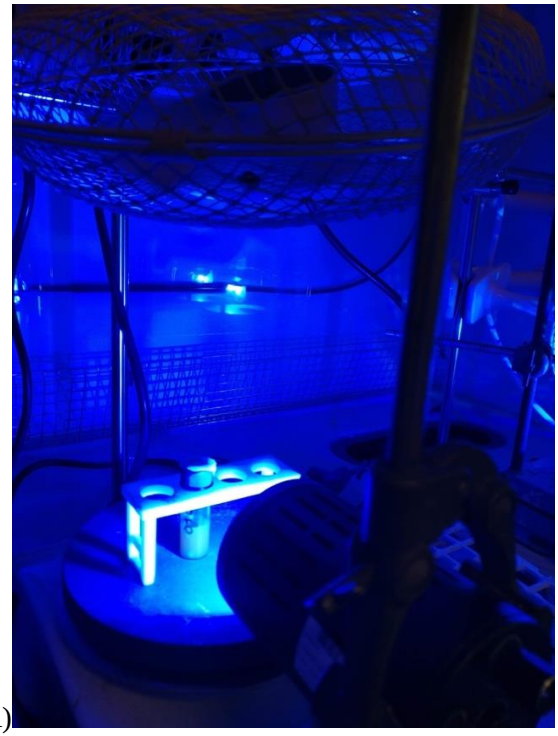
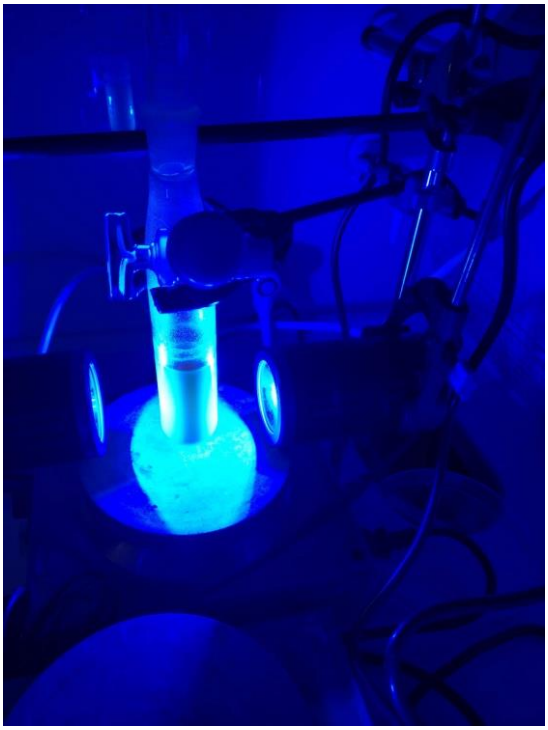
Deviation for hindered ketones:

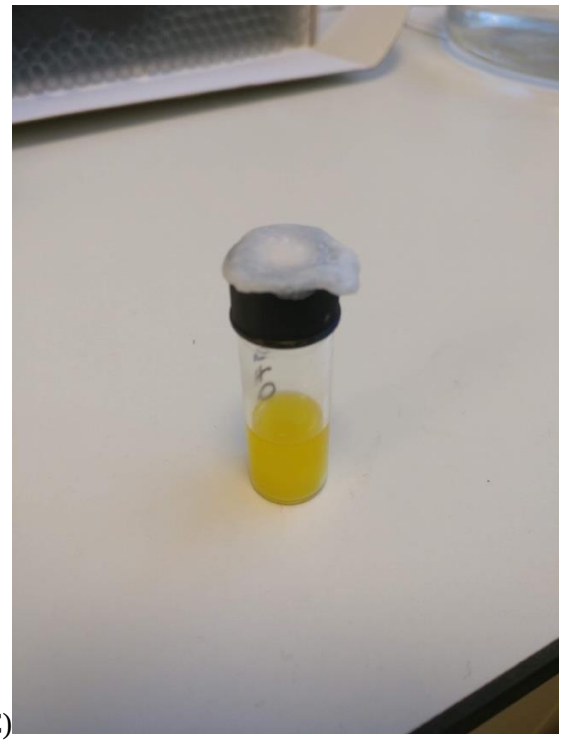
For a few hindered ketones, the ketone, amine and 4Å molecular sieves were heated in CH_2Cl_2 at 80 °C overnight before adding the remaining reagents and irradiating the reaction mixture as described above.

Deviation to avoid purification issues:

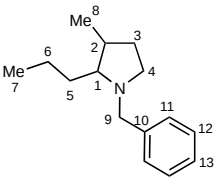
For reactions where small quantities of Hantzsch ester derivatives remained after hydrolysis and co-eluted with the product subsequent flash column chromatography, Hantzsch ester could be replaced by its more polar analogue bis(methoxyethyl) 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**112a**) without any erosion of the yield.

Reaction setup

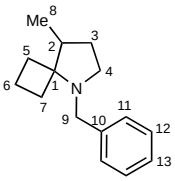
A)  B) 

C) 

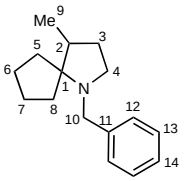
A) Reaction on 0.2 mmol scale. B) Reaction on 10 mmol scale. Note that a fan was removed temporarily in order to capture the photo. C) Example of reaction vial after the reaction on 0.2 mmol scale.



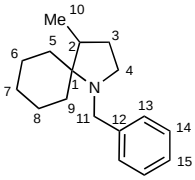
1-Benzyl-3-methyl-2-propylpyrrolidine (**107b**). Prepared according to general procedure D using *N*-benzylbut-3-en-1-amine **(1)** (32 mg, 0.20 mmol, 1.0 equiv.), butyraldehyde (40 μL, 0.44 mmol, 2.2 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 30% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (36 mg, 0.16 mmol, 81% yield, 2.4:1 d.r.). Spectral data was in agreement with literature.[511] **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.34–7.27 (m, 4H, H_{11-12}), 7.25–7.20 (m, 1H, H_{13}), 4.02 (dd, J = 13.1, 5.0 Hz, 1H, H_9), 3.22 (d, J = 13.3 Hz, 1H, $H_{9(cis)}$), 3.13 (d, J = 12.9 Hz, 1H, $H_{9(trans)}$), 2.95–2.89 (m, 1H), 2.83–2.81 (m, 1H), 2.40–2.36 (m, 1H), 2.23–2.08 (m, 2H), 1.96–1.82 (m, 2H), 1.53–1.22 (m, 6H), 1.01–0.93 (m, 3H, H_8). Note: Isolated as a mixture of *cis* and *trans* diastereomers.



5-Benzyl-8-methyl-5-azaspiro[3.4]octane (**113b**). Prepared according to general procedure D using *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 μL, 0.60 mmol, 3.0 equiv.) and $Ir(dMeppy)_3$ (1.5 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 20% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (30 mg, 0.14 mmol, 71% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.40–7.31 (m, 4H, H_{11-12}), 7.27–7.23 (m, 1H, H_{13}), 3.84 (d, J = 13.4 Hz, 1H, H_9), 3.74 (d, J = 13.4 Hz, 1H, H_9), 2.60–2.49 (m, 2H, H_4), 2.36 (q, J = 10.5 Hz, 1H, H_5), 2.20–2.05 (m, 2H, H_2 & H_7), 1.96–1.88 (m, 2H, H_3 & H_7), 1.86–1.79 (m, 1H, H_5), 1.74–1.61 (m, 2H, H_6), 1.36–1.27 (m, 1H, H_3), 1.14 (d, J = 6.9 Hz, 3H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 140.8 (C_{10}), 128.3 (C_{11}), 128.1 (C_{12}), 126.5 (C_{13}), 69.0 (C_1), 53.7 (C_9), 49.7 (C_4), 41.6 (C_2), 29.03 (C_3), 28.92 (C_5), 23.5 (C_7), 16.1 (C_8), 13.6 (C_6); **IR** (film, cm^{-1}): 2955, 2872, 2788, 1604, 1494, 1453, 1424, 1361, 1310, 1251, 1208, 1154, 1073, 1028, 980, 925, 806, 732, 696; **HRMS** (NSI+): *m/z* calcd for $C_{15}H_{22}N_1$, $[M+H]^+$, 216.1747; found, 216.1747 (Δ = 0.1 ppm).

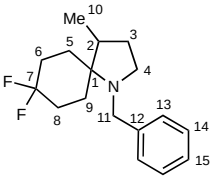


1-Benzyl-4-methyl-1-azaspiro[4.4]nonane (**114a**). Prepared according to general procedure D using *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), cyclopentanone (53 μL, 0.60 mmol, 3.0 equiv.) and $Ir(dMeppy)_3$ (1.5 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 20% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (34.8 mg, 0.15 mmol, 76% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.34 (d, J = 7.1 Hz, 2H, H_{12}), 7.34–7.28 (m, 2H, H_{13}), 7.23–7.19 (m, 1H, H_{14}), 3.73 (d, J = 13.1 Hz, 1H, H_{10}), 3.41 (d, J = 13.1 Hz, 1H, H_{10}), 2.63 (td, J = 9.3, 5.4 Hz, 1H, H_4), 2.36 (td, J = 9.8, 4.7 Hz, 1H, H_4), 2.02–1.95 (m, 1H, H_2), 1.89 (m, 1H, H_3), 1.85–1.77 (m, 1H, H_5), 1.73–1.45 (m, 7H, H_5 & H_6 & H_7 & H_8), 1.30 (m, 1H, H_3), 0.95 (s, 3H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 141.0 (C_{11}), 128.4 (C_{12}), 128.1 (C_{13}), 126.4 (C_{14}), 74.0 (C_1), 53.7 (C_{10}), 49.8 (C_4), 43.0 (C_2), 33.8 (C_5), 30.0 (C_3), 26.4 (C_6), 25.9 (C_7), 25.0 (C_8), 15.6 (C_9); **IR** (film, cm^{-1}): 3028, 2949, 2870, 2788, 1494, 1452, 1362, 1324, 1216, 1189, 1166, 1113, 1070, 1028, 960, 942, 906, 825, 733, 695; **HRMS** (NSI+): *m/z* calcd for $C_{16}H_{24}N_1$, $[M+H]^+$, 230.1903; found, 230.1906 (Δ = 1.2 ppm).

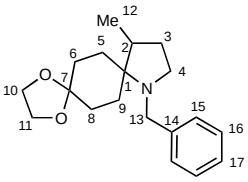


1-Benzyl-4-methyl-1-azaspiro[4.5]decane (**114b**). Prepared according to general procedure D using diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (152 mg, 0.60 mmol, 3.0 equiv.), *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), cyclohexanone (62 μL, 0.60 mmol, 3.0 equiv.) and $Ir(dMeppy)_3$ (1.5 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 48 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 20% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (35 mg, 0.14 mmol, 72% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.35 (d, J = 7.4 Hz, 2H, H_{13}), 7.31–7.27 (m, 2H, H_{14}), 7.20 (t, J = 7.2 Hz, 1H, H_{15}), 3.97 (d, J = 13.7 Hz, 1H, H_{11}), 3.25 (d, J = 13.8 Hz, 1H, H_{11}), 2.94–2.91 (m, 1H, H_4), 2.37 (dd, J = 9.8, 4.8 Hz, 1H, H_4), 2.23 (m, 1H, H_2), 2.05 (m, 1H, H_3), 1.74–1.50 (m, 5H, H_{5-9}), 1.44–1.27 (m, 5H, H_3 & H_5 & H_{7-9}), 1.17–1.14 (m, 1H, H_7), 1.01 (d, J = 6.9 Hz, 3H, H_{10}). **^{13}C**

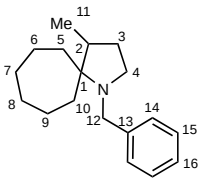
NMR (101 MHz; $CDCl_3$): δ 142.2 (C_{12}), 128.1 (C_{13-14}), 126.4 (C_{15}), 64.7 (C_1), 52.2 (C_{11}), 49.6 (C_4), 36.4 (C_2), 31.5 (C_5), 29.9 (C_3), 28.6 (C_9), 26.5 (C_7), 24.22 (C_6), 24.06 (C_8), 17.7 (C_{10}); **IR** (film, cm^{-1}): 3026, 2928, 2857, 2794, 1704, 1602, 1493, 1451, 1362, 1309, 1180, 1135, 1072, 1027, 906, 844, 728, 696, 648; **HRMS** (NSI+): *m/z* calcd for $C_{17}H_{26}N_1$, $[M+H]^+$, 244.2060; found, 244.2061 (Δ = 0.5 ppm).



1-Benzyl-8,8-difluoro-4-methyl-1-azaspiro[4.5]decane (**114c**). Prepared according to general procedure D using diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (152 mg, 0.60 mmol, 3.0 equiv.), *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), 4,4-difluorocyclohexanone (81 mg, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 48 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 20% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (48 mg, 0.17 mmol, 87% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.34–7.28 (m, 4H, H_{13-14}), 7.24–7.22 (m, 1H, H_{15}), 3.94 (d, *J* = 13.7 Hz, 1H, H_{11}), 3.28 (d, *J* = 13.7 Hz, 1H, H_{11}), 2.96 (td, *J* = 9.5, 5.4 Hz, 1H, H_4), 2.39 (td, *J* = 10.1, 5.1 Hz, 1H, H_4), 2.26–2.22 (m, 1H, H_2), 2.17–2.04 (m, 3H, H_3 & H_6 & H_8), 1.97–1.76 (m, 3H, H_5 & H_6 & H_8), 1.72–1.54 (m, 3H, H_5 & H_9), 1.37 (dddd, *J* = 12.5, 9.7, 5.2, 2.6 Hz, 1H, H_3), 1.05 (d, *J* = 6.9 Hz, 3H, H_{10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 141.3 (C_{12}), 128.2 (C_{13} or C_{14}), 128.0 (C_{13} or C_{14}), 126.6 (C_{15}), 123.7 (t, *J* = 240.8 Hz, C_7), 63.8 (C_1), 52.2 (C_{11}), 49.6 (C_4), 36.3 (C_2), 31.9 (d, *J* = 23.9 Hz, C_6), 31.5 (d, *J* = 24.3, C_8), 29.8 (C_3), 26.9 (d, *J* = 8.4 Hz, C_5), 24.4 (d, *J* = 9.4 Hz, C_9), 17.7 (C_{10}); **^{19}F NMR** (376 MHz; $CDCl_3$): δ –92.9 (d, *J* = 234.1 Hz), –101.8 (d, *J* = 234.1 Hz); **IR** (film, cm^{-1}): 2957, 2799, 1492, 1447, 1374, 1269, 1144, 1101, 972, 909, 733, 695; **HRMS** (NSI+): *m/z* calcd for $C_{17}H_{24}N_1F_2$, $[M+H]^+$, 280.1871; found, 280.1875 (Δ = 1.3 ppm).

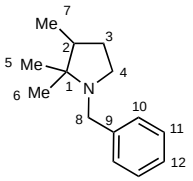


9-Benzyl-12-methyl-1,4-dioxa-9-azadispiro[4.2.4^8.2^5]tetradecane (**114d**). Prepared according to general procedure D using diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (152 mg, 0.60 mmol, 3.0 equiv.), *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), 1,4-cyclohexanedione monoethylene acetal (94 mg, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 72 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 40% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (43 mg, 0.14 mmol, 71% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.33–7.26 (m, 4H, H_{15-16}), 7.19 (t, *J* = 7.1 Hz, 1H, H_{17}), 4.00–3.94 (m, 5H, H_{10-11} & H_{13}), 3.25 (d, *J* = 13.8 Hz, 1H, H_{13}), 2.92 (td, *J* = 9.4, 5.2 Hz, 1H, H_4), 2.38–2.32 (m, 1H, H_4), 2.28–2.23 (m, 1H, H_2), 2.10–2.03 (m, 1H, H_3), 1.82–1.60 (m, 6H, H_{5-6} & H_{8-9}), 1.57–1.48 (m, 2H, H_5 & H_9), 1.35–1.28 (m, 1H, H_3), 1.02 (d, *J* = 6.9 Hz, 3H, H_{12}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 141.9 (C_{14}), 128.14 (C_{15} or C_{16}), 128.07 (C_{15} or C_{16}), 126.4 (C_{17}), 109.0 (C_7), 64.41 (C_{10} or C_{11}), 64.38 (C_{10} or C_{11}), 64.1 (C_1), 52.2 (C_{13}), 49.6 (C_4), 36.1 (C_2), 32.7 (C_6 or C_8), 32.5 (C_6 or C_8), 29.8 (C_3), 28.0 (C_5 or C_9), 25.4 (C_5 or C_9), 18.0 (C_{12}); **IR** (film, cm^{-1}): 2951, 2876, 2795, 1493, 1452, 1369, 1268, 1152, 1100, 1035, 945, 896, 850, 730, 697, 660; **HRMS** (NSI+): *m/z* calcd for $C_{19}H_{28}O_2N_1$, $[M+H]^+$, 302.2115; found, 302.2117 (Δ = 0.8 ppm).

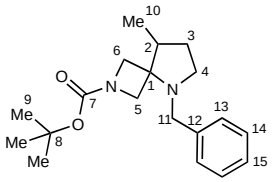


1-Benzyl-4-methyl-1-azaspiro[4.6]undecane (**114g**). Prepared according to general procedure D using diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (152 mg, 0.60 mmol, 3.0 equiv.), *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), cycloheptanone (71 μL, 0.60 mmol, 3.0 equiv.) and $Ir(dMeppy)_3$ (1.5 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 72 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 20% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (17 mg, 0.068 mmol, 34% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.35–7.26 (m, 4H, H_{14-15}), 7.20 (t, *J* = 7.1 Hz, 1H, H_{16}), 3.79 (d, *J* = 13.2 Hz, 1H, H_{12}), 3.54 (d, *J* = 13.2 Hz, 1H, H_{12}), 2.63 (td, *J* = 9.5, 4.8 Hz, 1H, H_4), 2.38 (td, *J* = 9.5, 5.3 Hz, 1H, H_4), 2.00–1.88 (m, 2H, H_2 & H_3), 1.84–1.77 (m, 1H, H_5), 1.69–1.46 (m, 11H, H_{5-10}), 1.28 (dt, *J* = 11.8, 4.7 Hz, 1H, H_3), 1.03 (d, *J* = 6.8 Hz, 3H, H_{11}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 142.2 (C_{13}), 128.7 (C_{14} or C_{15}), 128.5 (C_{14} or C_{15}), 126.8 (C_{16}), 67.5 (C_1), 53.7 (C_{12}),

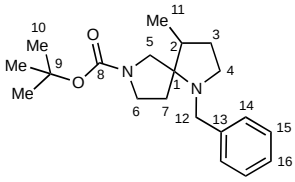
49.7 (C_4), 43.5 (C_2), 35.5 (C_5), 32.0 (C_6 or C_{9-10}), 31.7 (C_6 or C_{9-10}), 31.4 (C_6 or C_{9-10}), 30.4 (C_3), 24.9 (C_7 or C_8), 24.7 (C_7 or C_8), 17.8 (C_{16}); **IR** (film, cm^{-1}): 3027, 2919, 2854, 2792, 1603, 1493, 1453, 1363, 1202, 1157, 1124, 1069, 1028, 951, 906, 867, 838, 736, 696, 616; **HRMS** (NSI+): *m/z* calcd for $C_{18}H_{28}N_1$, $[M+H]^+$, 258.2216; found, 258.2220 (Δ = -0.5 ppm).



1-Benzyl-2,2,3-trimethylpyrrolidine (**114i**). Prepared according to general procedure D using diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (152 mg, 0.60 mmol, 3.0 equiv.), *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), cyclohexanone (62 μL, 0.60 mmol, 3.0 equiv.) and $Ir(dMeppy)_3$ (1.5 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 48 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 20% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (35 mg, 0.14 mmol, 71% yield).**^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.34–7.27 (m, 4H, H_{10-11}), 7.23–7.21 (m, 1H, H_{12}), 3.84 (d, J = 13.1 Hz, 1H, H_8), 3.25 (d, J = 13.0 Hz, 1H, H_8), 2.79–2.77 (m, 1H, H_4), 2.33 (td, J = 9.8, 4.3 Hz, 1H, H_4), 1.92–1.85 (m, 2H, H_2 & H_3), 1.31 (ddd, J = 10.6, 5.4, 2.9 Hz, 1H, H_3), 1.11 (s, 3H, H_6) 0.92 (d, J = 6.6 Hz, 3H, H_7), 0.78 (s, 3H, H_5); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 141.0 (C_9), 128.5 (C_{10}), 128.1 (C_{11}), 126.5 (C_{12}), 62.0 (C_1), 53.5 (C_7), 49.5 (C_4), 43.4 (C_2), 29.6 (C_3), 25.1 (C_5), 15.3 (C_7), 13.8 (C_6); **IR** (film, cm^{-1}): 3027, 2958, 2875, 2791, 1494, 1453, 1382, 1361, 1347, 1310, 1254, 1192, 1165, 1062, 1028, 932, 905, 881, 807, 735, 695; **HRMS** (NSI+): *m/z* calcd for $C_{14}H_{22}N_1$, $[M+H]^+$, 204.1747; found, 204.1747 (Δ = 0.1 ppm).

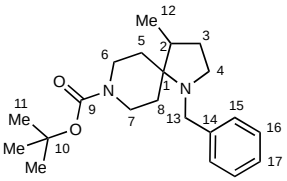


tert-butyl 5-benzyl-8-methyl-2,5-diazaspiro[3.4]octane-2-carboxylate (**115a**). Prepared according to general procedure D using bis(methoxyethyl) 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (114 mg, 0.40 mmol, 2.0 equiv.), *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), *N*-Boc 3-azetidinone (103 mg, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 50% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (46 mg, 0.15 mmol, 73% yield). *10 mmol scale reaction:* Prepared according to general procedure A using diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (5.1 g, 20 mmol, 2.0 equiv.), *N*-benzylbut-3-en-1-amine (1.6 g, 10 mmol, 1.0 equiv.), *N*-Boc 3-azetidinone (5.1 mg, 30 mmol, 3.0 equiv.), $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (49 mg, 0.050 mmol, 0.5 mol%), MS 4Å (2.5 g) and propionic acid (0.15 mL, 2.0 mmol, 20 mol%) in CH_2Cl_2 (25 mL, 0.40 M). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 60% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a colourless oil (2.0 g, 6.3 mmol, 63% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.35–7.29 (m, 4H, H_{13-14}), 7.25–7.22 (m, 1H, H_{15}), 4.06 (d, J = 9.3 Hz, 1H, H_5), 3.91–3.84 (m, 3H, H_6 & H_{11}), 3.79 (d, J = 13.6 Hz, 1H, H_{11}), 3.70 (d, J = 9.3 Hz, 1H, H_5), 2.63–2.55 (m, 2H, H_4), 2.15 (q, J = 7.3 Hz, 1H, H_2), 1.95–1.89 (m, 1H, H_3), 1.45 (s, 9H, H_9), 1.35–1.27 (m, 1H, H_3), 1.12 (d, J = 6.9 Hz, 3H, H_{10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 156.5 (C_7), 139.9 (C_{12}), 128.4 (C_{13} or C_{14}), 128.2 (C_{13} or C_{14}), 126.9 (C_{15}), 79.5 (C_8), 64.8 (C_1), 55.8 (broad, C_5), 53.4 (C_{11}), 52.2 (broad, C_6), 49.8 (C_4), 40.8 (C_2), 29.3 (C_3), 28.5 (C_9), 16.0 (C_{10}); **IR** (film, cm^{-1}): 2964, 2879, 1697, 1476, 1453, 1390, 1365, 1247, 1158, 1104, 1028, 919, 860, 771, 730, 698, 646; **HRMS** (NSI+): *m/z* calcd for $C_{19}H_{29}O_2N_2$, $[M+H]^+$, 317.2224; found, 317.2225 (Δ = 0.5 ppm).

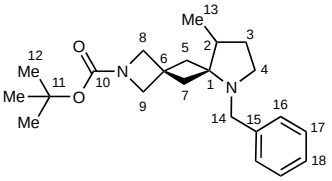


tert-Butyl 1-benzyl-4-methyl-1,7-diazaspiro[4.4]nonane-7-carboxylate (**115b**). Prepared according to general procedure D using *N*-benzylbut-3-en-1-amine (**107a**) (32 mg, 0.20 mmol, 1.0 equiv.), *N*-Boc 3- pyrrolidinone (111 mg, 0.60 mmol, 3.0 equiv.) and [Ir(dMeppy)2(dtbbpy)]PF6 (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 60% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound, a pale yellow oil, as a mixture of diastereomers (47 mg, 0.14 mmol, 70% yield, 1:3.7 d.r.). Note: This mixture of

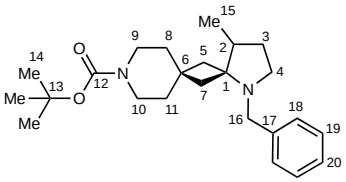
diastereomers also exist as rotamers that converge at 102°C. Note: There are two sets of carbon signals, corresponding to the two diastereomers, for all carbon environments apart from a) C_9 b) C_{10} c) C_{16}. These signals show significant broadening but, as they are the furthest away from the stereocentres, are not resolved into two separate signals for the two diastereomers. **^{1}H NMR** (500 MHz; DMSO-d_6, 102 °C): δ 7.29–7.27 (m, 4H, H_{14-15}), 7.22–7.19 (m, 1H, H_{16}), 3.67 (dd, J = 13.6, 5.8 Hz, 1H), 3.63 (d, J = 13.5 Hz, 1H), 3.46–3.25 (m, 3H), 3.17 (dd, J = 28.5, 11.6 Hz, 1H), 2.58–2.54 (m, 2H), 2.11–1.87 (m, 3H), 1.84–1.71 (m, 1H), 1.42 (d, J = 1.3 Hz, 9H), 1.37–1.28 (m, 1H), 0.99 (m, 3H, H_{11}); **^{13}C NMR** (126 MHz; DMSO-d_6, 102 °C): δ 153.1 (C_8), 153.1 (C_8), 139.9 (C_{13}), 139.9 (C_{13}), 127.5 (C_{14} or C_{15}), 127.4 (C_{14} or C_{15}), 127.3 (C_{14} or C_{15}), 127.3 (C_{14} or C_{15}), 125.9 (C_{16}), 77.7 (C_9), 71.4 (C_1), 71.0 (C_1), 52.1 (C_{12}), 52.0 (C_{12}), 51.3 (C_4), 49.2 (C_4), 49.0 (C_5), 46.0 (C_5), 44.6 (C_6), 43.9 (C_2), 41.3 (C_2), 40.1 (C_6), 31.1 (C_3), 29.6 (C_3), 29.1 (C_7), 27.7 (C_{10}), 25.2 (C_7), 15.5 (C_{11}), 15.1 (C_{11}); **IR** (film, cm^{-1}): 2972, 2876, 2801, 1688, 1395, 1169, 1101, 909, 729; **HRMS** (NSI+): *m/z* calcd for $C_{20}H_{31}O_2N_1$, [M+H] , 331.2380; found, 331.2382 (Δ = 0.6 ppm).



tert-Butyl 1-benzyl-4-methyl-1,8-diazaspiro[4.5]decane-8-carboxylate (**115c**). Prepared according to general procedure D using *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), 1-Boc-4-piperidone (120 mg, 0.60 mmol, 3.0 equiv.) and [Ir(dMeppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 48 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 30% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as an off-white solid (34 mg, 0.10 mmol, 49% yield). **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.36–7.26 (m, 4H, H_{15-16}), 7.21 (t, J = 7.1 Hz, 1H, H_{17}), 4.04–4.03 (m, 2H, H_{6-7}), 3.91 (d, J = 13.6 Hz, 1H, H_{13}), 3.27 (d, J = 12.8 Hz, 1H, H_{13}), 2.93–2.83 (m, 3H, H_4 & H_{6-7}), 2.40 (t, J = 3.8 Hz, 1H, H_4), 2.29–2.27 (m, 1H, H_2), 2.10–2.03 (m, 1H, H_3), 1.65–1.51 (m, 3H, H_5 & H_8), 1.52–1.40 (m, 10H, H_8 & H_{11}), 1.40–1.34 (m, 1H, H_3), 1.03 (t, J = 6.5 Hz, 3H, H_{12}); **^{13}C NMR** (126 MHz; $CDCl_3$): δ 155.1 (C_9), 141.4 (C_{14}), 128.2 (C_{15} or C_{16}), 128.1 (C_{15} or C_{16}), 126.6 (C_{17}), 79.5 (C_{10}), 63.3 (C_1), 52.1 (C_{13}), 49.5 (C_4), 41.9 (broad, C_6 & C_7), 36.1 (C_2), 30.4 (C_5), 29.8 (C_3), 28.6 (C_{11}), 28.3 (C_8), 17.7 (C_{12}); **IR** (film, cm^{-1}): 2957, 1689, 1421, 1364, 1243, 1165, 1145, 1019, 867, 759, 697; **HRMS** (NSI+): *m/z* calcd for $C_{21}H_{33}N_2O_2$, $[M+H]^+$, 345.2542; found 345.2549 (Δ = 2.0 ppm).

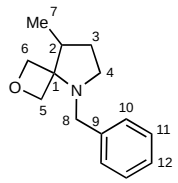


tert-Butyl 7-benzyl-10-methyl-2,7-diazadispiro[3.1.4^6.1^4]undecane-2-carboxylate (**115e**). Prepared according to general procedure D using *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (63 mg, 0.60 mmol, 3.0 equiv.) and [Ir(dMeppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 30% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (45 mg, 0.13 mmol, 64% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.36–7.30 (m, 4H, H_{16-17}), 7.26–7.24 (m, 1H, H_{18}), 3.97–3.92 (m, 2H, H_8), 3.90 (s, 2H, H_9), 3.64 (q, J = 12.2 Hz, 2H, H_{14}), 2.57–2.45 (m, 3H, H_4 & H_5), 2.31–2.19 (m, 2H, H_7), 2.05–1.89 (m, 3H, H_2 & H_3 & H_5), 1.45 (s, 9H, H_{12}), 1.35–1.27 (m, 1H, H_3), 1.03 (d, J = 6.7 Hz, 3H, H_{13}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 156.1 (C_{10}), 140.4 (C_{15}), 128.2 (C_{16-17}), 126.7 (C_{18}), 79.2 (C_{11}), 64.5 (C_1), 61.4 (broad, C_8 & C_9), 53.4 (C_{14}), 49.5 (C_4), 41.5 (C_2), 40.0 (C_5), 35.0 (C_6), 29.9 (C_7), 28.9 (C_3), 28.4 (C_{12}), 16.4 (C_{13}); **IR** (film, cm^{-1}): 2956, 2871, 1689, 1477, 1454, 1403, 1365, 1311, 1251, 1157, 1089, 1028, 907, 861, 771, 727, 698, 646; **HRMS** (NSI+): *m/z* calcd for $C_{22}H_{33}O_2N_2$, $[M+H]^+$, 357.2537; found, 357.2541 (Δ = -0.2 ppm).

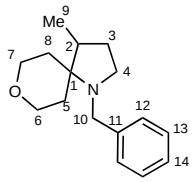


tert-Butyl 1-benzyl-4-methyl-1,10-diazadispiro[4.1.5^7.1^5]tridecane-10-carboxylate (**115f**). Prepared according to general procedure D using *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), *tert*-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (144 mg, 0.60 mmol, 3.0 equiv.) and [Ir(dMeppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 30% CH_2Cl_2 in 40°–60°

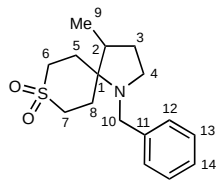
Petroleum ether) to afford the title compound as a pale yellow oil (60 mg, 0.16 mmol, 78% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.35–7.28 (m, 4H, H_{18-19}), 7.22 (m, 1H, H_{20}), 3.89 (d, J = 13.4 Hz, 1H, H_{16}), 3.50 (d, J = 13.4 Hz, 1H, H_{16}), 3.33 (m, 4H, H_9 & H_{10}), 2.67 (d, J = 5.3 Hz, 1H, H_4), 2.28 (d, J = 5.3 Hz, 1H, H_4), 2.10–2.01 (m, 2H, H_2 & H_5), 1.97–1.87 (m, 3H, H_3 & H_7), 1.54 (m, 5H, H_5, H_8 & H_{11}), 1.45 (s, 9H, H_{14}), 1.34–1.29 (m, 1H, H_3), 1.03 (d, J = 6.8 Hz, 3H, H_{15}). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 155.1 (C_{12}), 141.1 (C_{17}), 128.3 (C_{18} or C_{19}), 128.2 (C_{18} or C_{19}), 126.7 (C_{20}), 79.3 (C_{13}), 63.9 (C_1), 53.8 (C_{16}), 49.1 (C_4), 43.2 (C_2), 41.0 (C_9 & C_{10}), 38.4 (C_8), 37.8 (C_5), 37.3 (C_{11}), 35.1 (C_6), 29.3 (C_7), 28.9 (C_3), 28.6 (C_{14}), 17.3 (C_{15}); **IR** (film, cm^{-1}): 3029, 2960, 2799, 1603, 1494, 1448, 1374, 1354, 1271, 1144, 1128, 1102, 972, 907, 732, 696, 539; **HRMS** (NSI+): *m/z* calcd for $C_{24}H_{37}O_2N_2$, $[M+H]^+$, 385.2850; found, 385.2847 (Δ = -0.7 ppm).



5-Benzyl-8-methyl-2-oxa-5-azaspiro[3.4]octane (**115g**). Prepared according to general procedure D using *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), 3-oxetanone (38.5 µL, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (SiO_2; 0% to 10% EtOAc in 40°–60° Petroleum ether with 1% Et_3N) to afford the title compound as a pale yellow oil (29 mg, 0.13 mmol, 67% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.40–7.33 (m, 4H, H_{10-11}), 7.29–7.27 (m, 1H, H_{12}), 4.91 (d, J = 6.8 Hz, 1H, H_5), 4.76 (d, J = 7.1 Hz, 1H, H_6), 4.71 (d, J = 7.1 Hz, 1H, H_6), 4.52 (d, J = 6.7 Hz, 1H, H_5), 4.13 (d, J = 13.8 Hz, 1H, H_8), 4.07 (d, J = 13.8 Hz, 1H, H_8), 2.65–2.60 (m, 2H, H_4), 2.24 (q, J = 7.4 Hz, 1H, H_2), 1.92 (dtd, J = 12.9, 7.7, 5.4 Hz, 1H, H_3), 1.37–1.30 (m, 1H, H_3), 1.24 (d, J = 6.9 Hz, 3H, H_7); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 140.2 (C_9), 128.4 (C_{10} or C_{11}), 128.2 (C_{10} or C_{11}), 126.9 (C_{12}), 79.1 (C_5), 75.2 (C_6), 69.6 (C_1), 53.6 (C_8), 49.9 (C_4), 40.4 (C_2), 29.7 (C_3), 16.2 (C_7); **IR** (film, cm^{-1}): 3027, 2931, 2869, 2795, 1703, 1604, 1494, 1452, 1368, 1247, 1201, 1159, 1028, 977, 827, 735, 697; **HRMS** (NSI+): m/z calcd for $C_{14}H_{20}O_1N_1$, $[M+H]^+$, 218.1539; found, 218.1540 (Δ = 0.3 ppm).

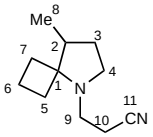


1-Benzyl-4-methyl-8-oxa-1-azaspiro[4.5]decane (**115h**). Prepared according to general procedure D using *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), tetrahydro-4*H*-pyran-4-one (55 µL, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 20% EtOAc in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (37 mg, 0.15 mmol, 75% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.36 (d, J = 7.1 Hz, 2H, H_{12} or H_{13}), 7.33–7.29 (m, 2H, H_{12} or H_{13}), 7.23 (t, J = 7.0 Hz, 1H, H_{14}), 4.02–3.95 (m, 3H, H_6 & H_7 & H_{10}), 3.60 (td, J = 11.9, 2.4 Hz, 1H, H_7), 3.52 (td, J = 11.8, 1.8 Hz, 1H, H_6), 3.30 (d, J = 13.7 Hz, 1H, H_{10}), 2.96 (td, J = 9.4, 5.0 Hz, 1H, H_4), 2.44–2.37 (m, 2H, H_4 & H_2), 2.09 (dddd, J = 13.2, 10.3, 8.2, 5.0 Hz, 1H, H_3), 1.80 (dtd, J = 29.4, 12.7, 4.7 Hz, 2H, H_5 & H_8), 1.55 (dq, J = 13.8, 2.2 Hz, 1H, H_5), 1.42–1.35 (m, 2H, H_3 & H_8), 1.04 (d, J = 6.9 Hz, 3H, H_9). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 141.5 (C_{11}), 128.1 (C_{12} or C_{13}), 128.0 (C_{12} or C_{13}), 126.5 (C_{14}), 66.3 (C_6), 65.9 (C_7), 62.4 (C_1), 51.9 (C_{10}), 49.3 (C_4), 36.2 (C_2), 31.3 (C_5), 29.8 (C_3), 29.4 (C_8), 17.8 (C_9); **IR** (film, cm^{-1}): 3027, 2952, 2848, 2795, 1603, 1493, 1453, 1387, 1364, 1297, 1233, 1216, 1183, 1164, 1106, 1011, 939, 835, 729, 696, 629; **HRMS** (NSI+): *m/z* calcd for $C_{16}H_{24}O_1N_1$, $[M+H]^+$, 246.1852; found, 246.1855 (Δ = 1.1 ppm).

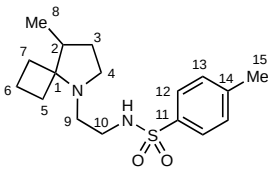


1-Benzyl-4-methyl-8-thia-1-azaspiro[4.5]decane 8,8-dioxide (**115i**). Prepared according to general procedure D using diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (152 mg, 0.60 mmol, 3.0 equiv.), *N*-benzylbut-3-en-1-amine **107a** (32 mg, 0.20 mmol, 1.0 equiv.), tetrahydrothiopyran-4-one 1,1 dioxide (89 mg, 0.60 mmol, 3.0 equiv.), $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 µmol, 1.0 mol%) in CH_2Cl_2 (1 mL, 0.2 M). The reaction mixture was irradiated for 72 h. The crude mixture after hydrolysis was purified by column chromatography (SiO_2; 0% to 20% EtOAc in 40°–60° Petroleum ether) and preparative TLC (SiO_2; 60% Et_2O in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (30 mg, 0.10 mmol, 50% yield, including an unidentified

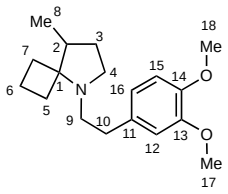
impurity that could not be removed using a variety of separation techniques). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.30 (q, J = 5.3 Hz, 4H, H_{12-13}), 7.23 (dt, J = 7.0, 3.3 Hz, 1H, H_{14}), 3.96 (d, J = 13.6 Hz, 1H, H_{10}), 3.32 (d, J = 13.6 Hz, 1H, H_{10}), 3.19–3.01 (m, 4H, H_{6-7}), 2.97 (td, J = 9.9, 5.8 Hz, 1H, H_4), 2.41 (td, J = 10.4, 4.8 Hz, 1H, H_4), 2.35–2.16 (m, 3H, H_2 & H_5 & H_8), 2.10 (tdd, J = 10.3, 7.7, 5.2 Hz, 1H, H_3), 2.01–1.93 (m, 2H, H_5 & H_8), 1.46–1.38 (m, 1H, H_3), 1.08 (d, J = 6.9 Hz, 3H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 140.4 (C_{11}), 128.4 (C_{12} or C_{13}), 128.0 (C_{12} or C_{13}), 126.9 (C_{14}), 63.2 (C_1), 52.2 (C_{10}), 49.3 (C_4 or C_{6-7}), 49.0 (C_4 or C_{6-7}), 36.6 (C_2), 29.6 (C_3), 28.8 (C_8), 26.4 (C_5), 17.4 (C_9); **IR** (film, cm^{-1}): 2957, 2804, 1723, 1601, 1494, 1452, 1403, 1373, 1293, 1202, 1124, 1075, 1028, 965, 909, 843, 728, 697, 666, 647; **HRMS** (NSI+): *m/z* calcd for $C_{16}H_{24}N_1O_2S$, $[M+H]^+$, 294.1528; found 294.1534 (Δ = 2.0 ppm).



3-(8-Methyl-5-azaspiro[3.4]octan-5-yl)propanenitrile (**116a**). Prepared according to general procedure D using 3-(but-3-en-1-ylamino)-propanenitrile **S8** (25 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 µL, 0.60 mmol, 3.0 equiv.) and Ir(dMeppy)$_3$ (1.5 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture purified by column chromatography (Alumina; 0% to 40% CH_2Cl_2 in 40°–60° Petroleum ether) without hydrolysis to afford the title compound as a pale yellow oil (27 mg, 0.15 mmol, 77% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 2.97–2.92 (m, 1H, H_9), 2.87–2.83 (m, 1H, H_9), 2.72 (td, J = 8.9, 5.8 Hz, 1H, H_4), 2.60 (td, J = 9.2, 4.7 Hz, 1H, H_4), 2.47 (t, J = 7.1 Hz, 2H, H_{10}), 2.14 (d, J = 12.0 Hz, 1H, H_5), 1.98–1.83 (m, 4H, H_2 & H_3), 1.78–1.70 (m, 1H, H_5), 1.62–1.55 (m, 2H, H_6), 1.32 (dd, J = 5.5, 4.1 Hz, 1H, H_3), 1.05 (d, J = 6.8 Hz, 3H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 119.2 (C_{11}), 69.0 (C_1), 49.7 (C_4), 45.9 (C_9), 41.6 (C_2), 29.3 (C_5), 29.1 (C_3), 23.9 (C_7), 18.6 (C_{10}), 15.8 (C_8), 13.5 (C_6); **IR** (film, cm^{-1}): 2954, 2874, 2812, 2248, 1460, 1425, 1373, 1250, 1156, 1117, 966, 932, 807, 625; **HRMS** (ESI+): *m/z* calcd for $C_{11}H_{19}N_2$, $[M+H]^+$, 179.1543; found 179.1537 (Δ = -3.5 ppm).

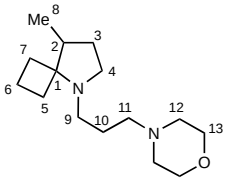


4-Methyl-*N*-(2-(8-methyl-5-azaspiro[3.4]octan-5-yl)ethyl)benzene sulfonamide (**116b**). Prepared according to general procedure D using *N*-(2-(but-3-en-1-ylamino)ethyl)-4-methylbenzenesulfonamide **S9** (54 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 µL, 0.60 mmol, 3.0 equiv.) and Ir(dMeppy)$_3$ (1.5 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (SiO_2; 0% to 1% MeOH:aq. NH_3 (9:1) in CH_2Cl_2) to afford the title compound as a pale yellow oil (45.8 mg, 0.11 mmol, 53% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.75–7.72 (m, 2H, H_{12}), 7.32–7.29 (m, 2H, H_{13}), 5.10 (br s, 1H, N<u>H</u>), 2.98–2.94 (m, 2H, H_{10}), 2.67 (ddd, J = 12.1, 6.8, 5.2 Hz, 1H, H_9), 2.60–2.56 (m, 1H, H_8), 2.42 (s, 3H, H_{15}), 2.31 (dt, J = 9.2, 4.6 Hz, 1H, H_4), 2.23 (td, J = 9.4, 4.9 Hz, 1H, H_4), 2.02–1.97 (m, 1H, H_7), 1.91 (dd, J = 14.6, 7.1 Hz, 1H, H_2), 1.84–1.74 (m, 3H, H_3 & H_5), 1.65 (dt, J = 8.8, 4.6 Hz, 1H, H_7), 1.56–1.50 (m, 2H, H_6), 1.24–1.17 (m, 1H, H_3), 1.02 (d, J = 6.9 Hz, 3H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.4 (C_{11}), 136.8 (C_{14}), 129.7 (C_{13}), 127.3 (C_{12}), 68.6 (C_1), 48.7 (C_4), 47.5 (C_9), 41.6 (C_2), 41.0 (C_{10}), 28.9 (C_3 & C_7), 23.7 (C_5), 21.6 (C_{15}), 15.9 (C_8), 13.4 (C_6); **IR** (film, cm^{-1}): 3281, 2956, 2876, 2813, 1599, 1458, 1395, 1325, 1155, 1090, 907, 814, 727; **HRMS** (NSI+): *m/z* calcd for $C_{17}H_{27}N_2O_2S$, [M+H] , 323.1788; found, 323.1789 (Δ = 0.4 ppm).

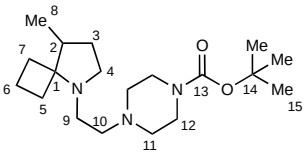


5-(3,4-Dimethoxyphenethyl)-8-methyl-5-azaspiro[3.4]octane (**116d**). Prepared according to general procedure D using *N*-(3,4-dimethoxyphenethyl)but-3-en-1-amine (47 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 µL, 0.60 mmol, 3.0 equiv.) and Ir(dMeppy)$_3$ (1.5 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Preparative TLC (SiO_2); 70% EtOAc in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (30 mg, 0.11 mmol, 53% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 6.82–6.77 (m, 3H, H_{12} & H_{15-16}), 3.88 (s, 3H, H_{17} or H_{18}), 3.86 (s, 3H, H_{17} or H_{18}), 2.90–2.84 (m, 2H, H_4 & H_9), 2.76–2.66 (m, 3H, H_{9-10}), 2.58 (td, J = 9.6, 4.6 Hz, 1H, H_4), 2.28–2.21 (m, 1H, H_5), 2.04–1.95 (m, 2H, H_2 & H_7), 1.92 (dd, J = 10.6, 5.8 Hz, 1H, H_3), 1.78–1.72 (m, 2H, H_5 & H_7), 1.59–1.53 (m, 2H, H_6), 1.35–1.25 (m, 1H, H_3), 1.09 (d, J = 6.7 Hz, 3H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 148.9 (C_{13} or C_{14}), 147.4 (C_{13} or C_{14}), 133.8 (C_{11}), 120.7 (C_{16}), 112.3 (C_{12}), 111.3 (C_{15}), 69.0

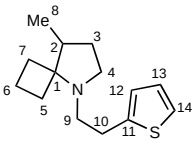
(C_1), 56.0 (C_{17} or C_{18}), 55.9 (C_{17} or C_{18}), 52.3 (C_9), 50.0 (C_4), 41.9 (C_2), 35.8 (C_{10}), 29.2 (C_3), 28.8 (C_5), 22.6 (C_7), 15.8 (C_8), 13.5 (C_6); **IR** (film, cm^{-1}): 2951, 2833, 1590, 1513, 1462, 1417, 1368, 1259, 1234, 1184, 1154, 1139, 1029, 912, 850, 802, 763, 729, 643, 614; **HRMS** (ESI+): *m/z* calcd for $C_{18}H_{28}N_1O_2$, $[M+H]^+$, 290.2120; found 290.2114 (Δ = -2.1 ppm).



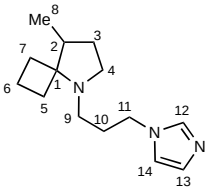
4-(3-(8-Methyl-5-azaspiro[3.4]octan-5-yl)propyl)morpholine (**116e**). Prepared according to general procedure D using *N*-(3-morpholinopropyl)but-3-en-1-amine[512] (40 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 μL, 0.60 mmol, 3.0 equiv.) and $Ir(dMeppy)_3$ (1.5 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (SiO_2; 0% to 4% MeOH:aq. NH_3 (9:1) in CH_2Cl_2) to afford the title compound as a pale yellow oil (31 mg, 0.12 mmol, 60% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 3.73 (t, *J* = 4.7 Hz, 4H, H_{13}), 2.73 (m, 2H, H_4 & H_9), 2.53–2.38 (m, 8H, H_4 & H_9 & H_{11-12}), 2.24 (dt, *J* = 12.3, 9.6 Hz, 1H, H_5), 2.08–1.95 (m, 2H, H_2 & H_7), 1.93–1.85 (m, 1H, H_3), 1.78–1.65 (m, 4H, H_5 & H_7 & H_{10}), 1.65–1.53 (m, 2H, H_6), 1.28 (dddd, *J* = 12.2, 10.0, 7.8, 5.8 Hz, 1H, H_3), 1.08 (d, *J* = 6.8 Hz, 3H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): *δ* 69.0 (C_1), 67.2 (C_{13}), 57.3 (C_{11}), 53.9 (C_{12}), 49.9 (C_4), 47.7 (C_9), 41.8 (C_2), 29.1 (C_3), 28.8 (C_5), 26.4 (C_{10}), 22.6 (C_7), 15.8 (C_8), 13.6 (C_6); **IR** (film, cm^{-1}): 2952, 2869, 2800, 1455, 1354, 1269, 1117, 1070, 1007, 916, 862, 731; **HRMS** (NSI+): *m/z* calcd for $C_{15}H_{29}N_2O$, $[M+H]^+$, 253.2283; found 253.2280 (Δ = 1.2 ppm).



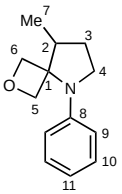
tert-Butyl 4-(2-(8-methyl-5-azaspiro[3.4]octan-5-yl)ethyl)piperazine-1-carboxylate (**116f**). Prepared according to general procedure D using *tert*-butyl 4-(2-(but-3-en-1-ylamino)ethyl)piperazine-1-carboxylate **S10** (57 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 μL, 0.60 mmol, 3.0 equiv.) and $Ir(dMeppy)_3$ (1.5 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (SiO_2; 0% to 5% MeOH:aq. NH_3 (9:1) in CH_2Cl_2) to afford the title compound as a pale yellow oil (47 mg, 0.14 mmol, 69% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 3.41 (t, *J* = 5.0 Hz, 4H, H_{12}), 2.88–2.75 (m, 2H, H_4 & H_9), 2.64–2.58 (m, 1H, H_9), 2.51–2.39 (m, 7H, H_4 & H_{10-11}), 2.22–2.17 (m, 1H, H_7), 2.02–1.84 (m, 3H, H_{2-3} & H_5), 1.74 (ddd, *J* = 13.2, 9.1, 4.1 Hz, 2H, H_5 & H_7), 1.59–1.52 (m, 2H, H_6), 1.43 (s, 9H, H_{15}), 1.25 (tdd, *J* = 8.9, 4.2, 2.3 Hz, 1H, H_3), 1.05 (d, *J* = 6.7 Hz, 3H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): *δ* 154.8 (C_{13}), 79.7 (C_{14}), 69.2 (C_1), 58.1 (C_{10}), 53.6 (C_{11}), 50.4 (C_4), 47.6 (C_9), 43.5 (broad, C_{12}), 41.6 (C_2), 29.2 (C_7), 28.8 (C_3), 28.5 (C_{15}), 22.6 (C_5), 15.6 (C_8), 13.5 (C_6); **IR** (film, cm^{-1}): 2948, 2809, 1696, 1454, 1417, 1363, 1242, 1167, 1123, 1002, 868, 766; **HRMS** (ESI+): *m/z* calcd for $C_{19}H_{36}N_3O_2$, [M+H] , 338.2802; found 338.2803 (Δ = 0.3 ppm).



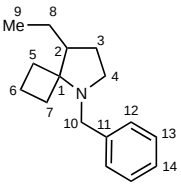
8-Methyl-5-(2-(thiophen-2-yl)ethyl)-5-azaspiro[3.4]octane (**116g**). Prepared according to general procedure D using *N*-(2-(thiophen-2-yl)ethyl)but-3-en-1-amine **S11** (36 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 μL, 0.60 mmol, 3.0 equiv.) and $Ir(dMeppy)_3$ (1.5 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 20% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (25 mg, 0.10 mmol, 52% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 7.03 (dd, *J* = 5.1, 1.2 Hz, 1H, H_{14}), 6.83 (dd, *J* = 5.1, 3.4 Hz, 1H, H_{13}), 6.76–6.75 (m, 1H, H_{12}), 2.95–2.82 (m, 3H, H_{9-10}), 2.77–2.66 (m, 2H, H_4 & H_9), 2.53 (td, *J* = 9.5, 4.8 Hz, 1H, H_4), 2.19–2.11 (m, 1H, H_5), 1.97–1.88 (m, 2H, H_2 & H_7), 1.87–1.79 (m, 1H, H_3), 1.72–1.62 (m, 2H, H_5 & H_7), 1.47 (tt, *J* = 11.1, 6.7 Hz, 2H, H_6), 1.23 (dddd, *J* = 12.2, 9.9, 7.7, 5.8 Hz, 1H, H_3), 1.00 (d, *J* = 6.8 Hz, 3H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): *δ* 143.4 (C_{11}), 126.6 (H_{13}), 124.7 (H_{12}), 123.6 (H_{14}), 69.2 (C_1), 51.7 (C_9), 49.8 (C_4), 41.8 (C_2), 30.1 (C_{10}), 29.1 (C_3), 28.8 (C_5), 23.1 (C_7), 15.8 (C_8), 13.6 (C_6); **IR** (film, cm^{-1}): 2950, 2800, 1458, 1438, 1368, 1249, 1159, 1110, 1029, 908, 850, 818, 730, 689; **HRMS** (ESI+): *m/z* calcd for $C_{14}H_{22}N_1S_1$, $[M+H]^+$, 236.1473; found 236.1474 (Δ = 0.4 ppm).



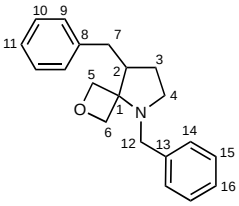
5-(3-(1*H*-Imidazol-1-yl)propyl)-8-methyl-5-azaspiro[3.4]octane (**116i**). Prepared according to general procedure D using *N*-(3-(1*H*-imidazol-1-yl)propyl)but-3-en-1-amine **S13** (33 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 μL, 0.60 mmol, 3.0 equiv.) and Ir(dMeppy)$_3$ (1.5 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. *The crude mixture after hydrolysis was purified by Dr. S. Walton by preparative HPLC* (gradient of 30-60% H_2O:MeCN + 0.3% NH_4OH) to afford the title compound as a yellow oil (11 mg, 0.060 mmol, 29% yield). *NMR-spectra were collected by Dr. S. Walton.* **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.45 (s, 1H, H_{12}), 7.03 (s, 1H, H_{13}), 6.90 (s, 1H, H_{14}), 4.00 (t, J = 6.8 Hz, 2H, H_{11}), 2.60 (tt, J = 8.6, 4.3 Hz, 1H, H_9), 2.57–2.50 (m, 2H, H_4 & H_9), 2.48–2.41 (m, 1H, H_4), 2.13–2.04 (m, 1H, H_{10}), 1.98 (dt, J = 13.7, 7.0 Hz, 1H, H_2), 1.94–1.87 (m, 4H, H_5 & H_7), 1.80–1.71 (m, 1H, H_3), 1.70–1.59 (m, 1H, H_{10}), 1.55–1.47 (m, 2H, H_6), 1.34–1.26 (m, 1H, H_3), 1.06 (d, J = 6.9 Hz, 3H, H_8); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 137.3 (C_{12}), 129.1 (C_{13}), 118.9 (C_{14}), 69.0 (C_1), 49.1 (C_4), 45.4 (C_9), 44.5 (C_{11}), 41.5 (C_2), 29.8 (C_3), 28.8 (C_5 or C_7), 28.4 (C_5 or C_7), 23.2 (C_{10}), 15.9 (C_8), 13.4 (C_6); **IR** (film, cm^{-1}): 2953, 2807, 1716, 1507, 1446, 1369, 1267, 1228, 1077, 663; **HRMS** (NSI+): *m/z* calcd for $C_{14}H_{24}N_3$, $[M+H]^+$, 234.1970; found, 234.1970 (Δ = 0.0 ppm).



8-Methyl-5-phenyl-2-oxa-5-azaspiro[3.4]octane (**116j**). Prepared according to general procedure D using *N*-(but-3-en-1-yl)aniline[513] (29 mg, 0.20 mmol, 1.0 equiv.), 3-oxetanone (39 μL, 0.60 mmol, 3.0 equiv.) and [Ir(dMeppy)$_2$(dtbbpy)]PF_6 (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 50% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (11 mg, 0.050 mmol, 25% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.33–7.29 (m, 2H, H_{10}), 7.16–7.14 (m, 2H, H_9), 6.77 (t, J = 7.2 Hz, 1H, H_{11}), 5.45 (d, J = 7.1 Hz, 1H, H_5), 5.19 (d, J = 7.3 Hz, 1H, H_6), 4.76 (d, J = 7.3 Hz, 1H, H_6), 4.52 (d, J = 7.1 Hz, 1H, H_5), 3.40–3.30 (m, 2H, H_4), 2.26–2.20 (m, 1H, H_2), 1.98 (dtd, J = 12.1, 6.1, 3.5 Hz, 1H, H_3), 1.52–1.48 (m, 1H, H_3), 1.32 (d, J = 6.9 Hz, 3H, H_7); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 145.9 (C_8), 129.5 (C_{10}), 116.7 (C_{11}), 113.0 (C_9), 78.2 (C_5), 75.6 (C_6), 67.1 (C_1), 48.7 (C_4), 43.3 (C_2), 30.3 (C_3), 14.5 (C_7); **IR** (film, cm^{-1}): 2958, 2876, 1599, 1504, 1484, 1382, 1356, 1337, 1209, 1137, 977, 746, 698; **HRMS** (NSI+): *m/z* calcd for $C_{13}H_{18}O_1N_1$, $[M+H]^+$, 204.1383; found, 204.1383 (Δ = 0.0 ppm).

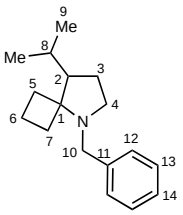


5-Benzyl-8-ethyl-5-azaspiro[3.4]octane (**117a**). Prepared according to general procedure D using (*E*)-*N*-benzylpent-3-en-1-amine[514] (35 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 μL, 0.60 mmol, 3.0 equiv.) and Ir(dMeppy)$_3$ (1.5 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 1% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (17 mg, 0.74 mmol, 37% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.36–7.28 (m, 4H, H_{12-13}), 7.24–7.20 (m, 1H, H_{14}), 3.86 (d, J = 13.3 Hz, 1H, H_{10}), 3.65 (d, J = 13.3 Hz, 1H, H_{10}), 2.59 (td, J = 9.1, 5.7 Hz, 1H, H_4), 2.43 (td, J = 9.6, 4.8 Hz, 1H, H_4), 2.38–2.30 (m, 1H, H_5), 2.16–2.09 (m, 1H, H_7), 1.93–1.82 (m, 3H, H_3 & H_5 & H_7), 1.81–1.74 (m, 2H, H_2 & H_8), 1.71–1.59 (m, 2H, H_6), 1.35–1.25 (m, 2H, H_3 & H_8), 0.97 (t, J = 7.3 Hz, 3H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 141.1 (C_{11}), 128.5 (C_{12} or C_{13}), 128.3 (C_{12} or C_{13}), 126.6 (C_{14}), 69.0 (C_1), 53.8 (C_{10}), 49.82 (C_4), 49.67 (C_2), 29.3 (C_5), 26.5 (C_3), 23.8 (C_8), 23.4 (C_7), 13.8 (C_6), 12.9 (C_9); **IR** (film, cm^{-1}): 3027, 2957, 2872, 2789, 1494, 1453, 1425, 1360, 1315, 1250, 1167, 1070, 1028, 965, 909, 809; **HRMS** (NSI+): *m/z* calcd for $C_{16}H_{24}N_1$, $[M+H]^+$, 230.1903; found 230.1905 (Δ = 0.8 ppm).

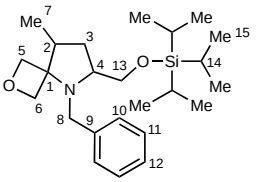


5,8-Dibenzyl-2-oxa-5-azaspiro[3.4]octane (**117b**). Prepared according to general procedure D using (*E*)-*N*-benzylphenylbut-3-en-1-amine[514] (47 mg, 0.20 mmol, 1.0 equiv.), 3-oxetanone (39 μL, 0.60 mmol, 3.0 equiv.) and [Ir(dMeppy)$_2$(dtbbpy)]PF_6 (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 40% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (23 mg, 0.080 mmol, 39%

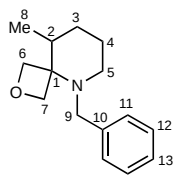
yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.38–7.20 (m, 10H, H_{9-11} & H_{14-16}), 4.94 (d, J = 6.9 Hz, 1H, H_5), 4.81 (s, 2H, H_6), 4.57 (d, J = 6.9 Hz, 1H, H_5), 4.11 (s, 2H, H_{12}), 3.25 (dd, J = 13.3, 3.8 Hz, 1H, H_7), 2.68–2.54 (m, 3H, H_4 & H_7), 2.42 (ddd, J = 11.3, 7.5, 3.7 Hz, 1H, H_2), 1.73–1.67 (m, 1H, H_3), 1.46–1.38 (m, 1H, H_3); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 140.8 (C_8), 140.1 (C_{13}), 129.0 (C_9), 128.6 (C_{10}), 128.4 (C_{14}), 128.2 (C_{15}), 127.0 (C_{16}), 126.2 (C_{11}), 79.1 (C_5), 75.6 (C_6), 69.5 (C_1), 53.5 (C_{12}), 49.8 (C_4), 47.7 (C_2), 37.3 (C_7), 27.1 (C_3); **IR** (film, cm^{-1}): 3028, 2937, 2869, 1603, 1494, 1453, 1453, 1368, 1245, 1156, 1074, 1028, 977, 906, 826, 726, 697, 646; **HRMS** (NSI+): *m/z* calcd for $C_{20}H_{24}O_1N_1$, $[M+H]^+$, 294.1852; found 294.1855 (Δ = 0.9 ppm).



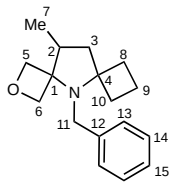
5-Benzyl-8-isopropyl-5-azaspiro[3.4]octane (**117c**). Prepared according to general procedure D using *N*-benzyl-4-methylpent-3-en-1-amine[515] (38 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 µL, 0.60 mmol, 3.0 equiv.) and $Ir(dMeppy)_3$ (1.5 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 2% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (26 mg, 0.11 mmol, 54% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.36–7.28 (m, 4H, H_{12-13}), 7.24–7.20 (m, 1H, H_{14}), 3.97 (d, J = 13.4 Hz, 1H, H_{10}), 3.56 (d, J = 13.4 Hz, 1H, H_{10}), 2.55 (td, J = 9.2, 4.1 Hz, 1H, H_4), 2.35–2.26 (m, 2H, H_4 & H_2), 2.21–2.09 (m, 2H, H_5), 2.02–1.94 (m, 1H, H_6 or H_7), 1.90 (dt, J = 9.2, 5.4 Hz, 1H, H_2), 1.81–1.66 (m, 4H, H_3 & H_6 & H_7), 1.48–1.39 (m, 1H, H_3), 0.99 (d, J = 6.7 Hz, 3H, H_9), 0.87 (d, J = 6.7 Hz, 3H, H_9); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 141.2 (C_{11}), 128.4 (C_{12}), 128.2 (C_{13}), 126.6 (C_{14}), 69.4 (C_1), 53.4 (C_{10}), 52.5 (C_2), 49.8 (C_4), 29.5 (C_7), 29.3 (C_8), 25.5 (C_5), 22.7 (C_3), 22.4 (C_9), 18.9 (C_9), 14.2 (C_6); **IR** (film, cm^{-1}): 2952, 1873, 2793, 1603, 1452, 1363, 1262, 1155, 1028, 733, 697; **HRMS** (NSI+): *m/z* calcd for $C_{17}H_{26}N_1$, $[M+H]^+$, 244.2060; found 244.2061 (Δ = 0.5 ppm).



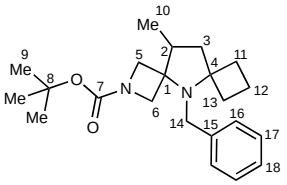
5-Benzyl-8-methyl-6-(((tri*iso*propylsilyl)oxy)methyl)-2-oxa-5-azaspiro[3.4] octane (**117d**). Prepared according to general procedure D using bis(methoxyethyl) 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (171 mg, 0.60 mmol, 3.0 equiv.), *N*-benzyl-1-((triisopropylsilyl)oxy)pent-4-en-2-amine **S14** (70 mg, 0.20 mmol, 1.0 equiv.), 3-oxetanone (39 µL, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 96 h. The crude mixture was purified by column chromatography (Alumina; 0% to 30% CH_2Cl_2 in 40°–60° Petroleum ether) without hydrolysis to afford the title compound as a pale yellow oil (67.7 mg, 84% yield, 1:1.1 d.r.). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.35–7.26 (m, 4H, H_{10-11}), 7.24–7.19 (m, 1H, H_{12}), 4.89 (d, J = 6.6 Hz, 1H), 4.84 (d, J = 7.0 Hz, 1H, H_5 or H_6, a or b), 4.72 (d, J = 6.8 Hz, 1H, H_5 or H_6, a or b), 4.61 (d, J = 7.1 Hz, 1H, H_5 or H_6, a or b), 4.57 (d, J = 7.1 Hz, 1H, H_5 or H_6, a or b), 4.53 (m, 3H, H_{8a} & H_5 and/or H_6, a or b), 4.40 (d, J = 6.6 Hz, 1H, H_5 or H_6, a or b), 4.36 (d, J = 15.5 Hz, 1H, H_{8b}), 4.08 (d, J = 15.5 Hz, 1H, H_{8b}), 3.83 (d, J = 14.3 Hz, 1H, H_{8a}), 3.34 (qd, J = 11.2, 5.0 Hz, 1H, H_{13}, a or b), 3.12–3.03 (m, 1H, H_{13}, a or b), 3.00 (ddd, J = 8.2, 4.0, 2.1 Hz, 1H, H_4, a or b), 2.90–2.86 (m, 1H, H_4, a or b), 2.23 (q, J = 7.1 Hz, 1H, H_2, a or b), 2.17–2.10 (m, 1H, H_2, a or b), 2.03 (dt, J = 12.9, 8.0 Hz, 1H, H_3, a or b), 1.94 (ddd, J = 12.7, 6.7, 2.3 Hz, 1H, H_3, a or b), 1.49–1.36 (m, 1H, H_3, a or b), 1.27 (d, J = 6.8 Hz, 2H, H_7, a or b), 1.21 (d, J = 6.9 Hz, 2H, H_7, a or b), 0.97–0.90 (m, 21H, H_{14-15}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 141.6 (C_9, d.r. 1 or d.r. 2), 141.4 (C_9, d.r. 1 or d.r. 2), 128.24 (C_{10} or C_{11}), 128.22 (C_{10} or C_{11}), 128.20 (C_{10} or C_{11}), 127.5 (C_{10} or C_{11}), 126.8 (C_{12}, a or b), 126.6 (C_{12}, a or b), 79.8, 79.4, 77.5, 73.8, 70.5 (C_1, a or b), 70.4 (C_1, a or b), 66.0, 65.7, 63.8 (C_4, a or b), 62.5 (C_4, a or b), 53.1 (C_{8a}), 50.8 (C_{8b}), 39.6 (C_2, a or b), 37.8 (C_2, a or b), 33.7, 33.2, 18.0 (C_{15}, a or b), 17.92 (C_{15}, a or b), 16.2 (C_7, a or b), 14.4 (C_7, a or b), 11.9 (C_{14}, a or b), 11.8 (C_{14}, a or b); **IR** (film, cm^{-1}): 2941, 2865, 1454, 1367, 1245, 1209, 1097, 1065, 980, 881, 784, 731, 698, 680, 657; **HRMS** (NSI+): *m/z* calcd for $C_{24}H_{42}O_2N_1Si_1$, $[M+H]^+$, 216.1383; found, 216.1381 (Δ = -0.8 ppm). Note: The samples used for characterization is a mixture of diastereomers, these are referred to as “a” and “b” in the assignment.



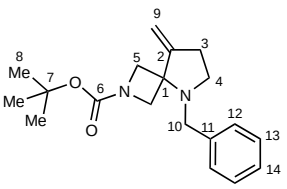
5-Benzyl-9-methyl-2-oxa-5-azaspiro[3.5]nonane (**117e**). Prepared according to general procedure D using bis(methoxyethyl) 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (114.1 mg, 0.40 mmol, 2.0 equiv.), *N*-benzylpent-4-en-1-amine[516] (35.1 mg, 0.20 mmol, 1.0 equiv.), 3-oxetanone (38.5 μL, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 48 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 100% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (18.0 mg, 39% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.40 (dd, J = 7.9, 1.0 Hz, 2H, H_{12}), 7.34–7.30 (m, 2H, H_{11}), 7.26–7.22 (m, 1H, H_{13}), 4.74 (d, J = 6.5 Hz, 1H, H_6), 4.65 (d, J = 6.8 Hz, 1H, H_7), 4.50 (m, 2H, H_6 & H_7), 3.91 (d, J = 14.5 Hz, 1H, H_9), 3.80 (d, J = 14.7 Hz, 1H, H_9), 2.46–2.37 (m, 2H, H_5), 2.03 (td, J = 7.2, 3.9 Hz, 1H, H_2), 1.63–1.56 (m, 1H, H_3), 1.52–1.46 (m, 2H, H_4), 1.32–1.27 (m, 1H, H_3), 1.16 (d, J = 6.9 Hz, 3H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 140.8 (C_{10}), 128.4 (C_{11} or C_{12}), 128.2 (C_{11} or C_{12}), 126.8 (C_{13}), 77.2 (C_7), 76.74 (C_6), 65.4 (C_1), 53.0 (C_9), 47.8 (C_5), 34.4 (C_2), 28.9 (C_3), 21.1 (C_4), 15.3 (C_8); **IR** (film, cm^{-1}): 3028, 2929, 2871, 1603, 1493, 1451, 1368, 1186, 1072, 981, 836, 732, 697; **HRMS** (NSI+): *m/z* calcd for $C_{15}H_{22}N_1O_1$, $[M+H]^+$, 232.1701; found 232.1710 (Δ = 3.9 ppm).



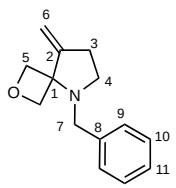
5-Benzyl-11-methyl-2-oxa-5-azadispiro[3.1.3^6.2^4]undecane (**118a**). A 4-mL screw-cap vial was charged with a magnetic stirrer bar, diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (50.7 mg, 0.40 mmol, 1 equiv.), $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 μmol, 1.0 mol%) and 4Å molecular sieves (50 mg). The vial was sealed with a cap containing a PTFE-septum and evacuated and backfilled with N_2 three times. Then CH_2Cl_2 (0.5 mL, 0.40 M), 1-allyl-*N*-benzylcyclobutanamine[512] (40.3 mg, 0.20 mmol, 1 equiv.), 1,4-cyclohexadiene (141 μL, 1.5 mmol, 7.5 equiv.), propionic acid (3 μL, 0.04 mmol, 20 mol%) and 3-oxetanone (38.5 μL, 0.60 mmol, 3 equiv.) were added in this order *via* microsyringe. The resulting mixture was irradiated with a 40W Kessil A160WE lamp for 120 h. During this period, 4 additional batches of diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (50.7 mg, 0.40 mmol, 1 equiv.) were added every 24 h. The resulting mixture was filtered through Celite® and conc. *in vacuo*. To the crude was added LiOH•H_2O (84 mg, 2.0.0 mmol, 10 equiv.), THF (5 mL) and H_2O (1 mL) and the resulting mixture were heated to 80°C in a sealed tube for 3 h. The resulting solution was poured into sat. aq. $NaHCO_3$ (10 mL), extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude material was purified by flash column chromatography (Alumina; 0% to 30% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (24.2 mg, 47% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.37–7.35 (m, 2H, H_{13}), 7.32–7.28 (m, 2H, H_{14}), 7.23–7.19 (m, 1H, H_{15}), 4.75 (d, J = 6.7 Hz, 1H, H_5), 4.55 (d, J = 7.0 Hz, 1H, H_6), 4.46 (d, J = 7.0 Hz, 1H, H_6), 4.36 (d, J = 6.7 Hz, 1H, H_5), 4.33 (m, 2H, H_{11}), 2.27–2.06 (m, 4H, $H_{2\text{-}3}$ & $H_{8\text{-}9}$), 1.65–1.41 (m, 5H, H_3 & $H_{8\text{-}10}$), 1.25 (d, J = 6.8 Hz, 3H, H_7); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.5 (C_{12}), 128.3 (C_{14}), 127.2 (C_{13}), 126.5 (C_{15}), 81.0 (C_5), 77.4 (C_6), 69.8 (C_1), 65.3 (C_4), 46.0 (C_{11}), 45.8 (C_3), 38.6 (C_2), 34.4 (C_8), 33.7 (C_{10}), 16.2 (C_7), 14.1 (C_9); **IR** (film, cm^{-1}): 2956, 2928, 2869, 1692, 1530, 1492, 1452, 1393, 1371, 1256, 1199, 1153, 951, 735, 699; **HRMS** (NSI+): *m/z* calcd for $C_{17}H_{24}N_1O_1$, $[M+H]^+$, 258.1852; found 258.1842 (Δ = -4.0 ppm).



tert-Butyl 5-benzyl-11-methyl-2,5-diazadispiro[3.1.3^6.2^4]undecane-2-carboxylate (**118b**). A 4-mL screw-cap vial was charged with a magnetic stirrer bar, diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (50.7 mg, 0.40 mmol, 1 equiv.), [Ir(dMeppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2.0 μmol, 1.0 mol%), *N*-Boc 3-azetidinone (102.7 mg, 0.60 mmol, 3 equiv.) and 4Å molecular sieves (50 mg). The vial was sealed with a cap containing a PTFE-septum and evacuated and backfilled with N_2 three times. Then CH_2Cl_2 (0.5 mL, 0.40 M), 1-allyl-*N*-benzylcyclobutanamine[512] (40.3 mg, 0.20 mmol, 1 equiv.), 1,4-cyclohexadiene (141 μL, 1.5 mmol, 7.5 equiv.) and propionic acid (3 μL, 0.04 mmol, 20 mol%) were added in order *via* microsyringe. The resulting mixture was irradiated with a 40W Kessil A160WE lamp for 120 h. During this period, 4 additional batches of diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarboxylate (50.7 mg, 0.40 mmol, 1 equiv.) were added every 24 h. The resulting mixture was filtered through Celite® and conc. *in vacuo*. To the crude was added LiOH•H_2O (84 mg, 2.0.0 mmol, 10 equiv.), THF (5 mL) and H_2O (1 mL) and the resulting mixture were heated to 80°C in a sealed tube for 3 h. The resulting solution was poured into sat. aq. $NaHCO_3$ (10 mL), extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude material was purified by flash column chromatography (Alumina; 0% to 60% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (35.1 mg, 49% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.36–7.34 (m, 2H, H_{16}), 7.31–7.27 (m, 2H, H_{17}), 7.23–7.19 (m, 1H, H_{18}), 4.15 (d, J = 16.4 Hz, 1H, H_{14}), 4.10 (d, J = 16.4 Hz, 1H, H_{14}), 3.94–3.91 (m, 1H, H_5), 3.80 (d, J = 9.6 Hz, 1H, H_6), 3.64–3.59 (m, 2H, H_5 & H_6), 2.27–2.17 (m, 2H, H_3 & H_{13}), 2.14–2.07 (m, 2H, H_2 & H_{11}), 1.64–1.45 (m, 5H, H_3 & $H_{11\text{-}13}$), 1.40 (s, 9H, H_9), 1.13 (d, J = 6.9 Hz, 3H, H_{10}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 156.3 (C_7), 143.0 (C_{15}), 128.3 (C_{17}), 127.4 (C_{16}), 126.6 (C_{18}), 79.3 (C_8), 65.4 (C_4), 65.1 (C_1), 57.8 (broad, C_5), 54.9 (broad, C_6), 46.2 (C_{14}), 45.9 (C_3), 39.1 (C_2), 34.4 (C_{13}), 34.0 (broad, C_{11}), 28.5 (C_9), 16.0 (C_{10}), 14.3 (C_{12}); **IR** (film, cm^{-1}): 2959, 2879, 1701, 1453, 1391, 1365, 1292, 1255, 1156, 1111, 1028, 933, 862, 772, 747, 699; **HRMS** (NSI+): *m/z* calcd for $C_{22}H_{33}N_2O_2$, $[M+H]^+$, 357.2537; found 357.2540 (Δ = 1.0 ppm).

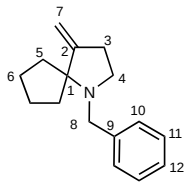


tert-Butyl 5-benzyl-8-methylene-2,5-diazaspiro[3.4]octane-2-carboxylate (**122a**). Prepared according to general D using *N*-benzylbut-3-yne-1-amine **S15** (32 mg, 0.20 mmol, 1.0 equiv.), *N*-Boc 3-azetidinone (102.7 mg, 0.60 mmol, 3.0 equiv.) and [Ir(dMeppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 50% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (41.1 mg, 65% yield). 2.0 mmol scale reaction: Prepared according to general procedure A using diethyl 1,4-dihydro-2,6-dimethyl-2,5-pyridinedicarbozylate (1.01 g, 4.0 mmol, 2 equiv.), *N*-benzylbut-3-yne-1-amine (318 mg, 2.0.0 mmol, 1.0 equiv.), *N*-Boc 3-azetidinone (1.03 g, 6.0 mmol, 3.0 equiv.), [Ir(dMeppy)$_2$(dtbbpy)]PF$_6$ (19 mg, 0.02 mmol, 1.0 mol%), MS 4Å (2.5 g) and propionic acid (0.15 mL, 0.40 mmol, 20 mol%) in CH_2Cl_2 (5 mL, 0.40 M). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 60% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a colourless oil (461 mg, 73% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.39–7.32 (m, 4H, $H_{12\text{-}13}$), 7.30–7.26 (m, 1H, H_{14}), 5.30 (t, J = 2.5 Hz, 1H, H_9), 5.10 (t, J = 2.2 Hz, 1H, H_9), 4.24 (d, J = 9.2 Hz, 2H, H_5), 3.90–3.87 (m, 4H, H_5 & H_{10}), 2.61 (t, J = 6.7 Hz, 2H, H_4), 2.47 (ddd, J = 5.0, 4.1, 3.8 Hz, 2H, H_3), 1.49 (s, 9H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 156.4 (C_6), 155.1 (C_2), 139.2 (C_{11}), 128.50 (C_{12} or C_{13}), 128.46 (C_{12} or C_{13}), 127.2 (C_{14}), 106.0 (C_9), 79.7 (C_7), 63.6 (C_1), 59.0 (broad, C_5), 53.3 (C_{10}), 49.7 (C_4), 30.0 (C_3), 28.5 (C_8); **IR** (film, cm^{-1}): 2977, 2881, 2801, 1691, 1393, 1366, 1285, 1256, 1155, 1124, 908, 727, 698; **HRMS** (NSI+): *m/z* calcd for $C_{19}H_{27}O_2N_2$, $[M+H]^+$, 315.2067; found, 315.2070 (Δ = 0.9 ppm).

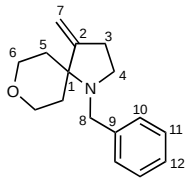


5-Benzyl-8-methylene-2-oxa-5-azaspiro[3.4]octane (**122b**). Prepared according to general D using *N*-benzylbut-3-yne-1-amine **S15** (32 mg, 0.20 mmol, 1.0 equiv.), 3-oxetanone (39 μL, 0.60 mmol, 3.0 equiv.) and [Ir(dMeppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2.0 μmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 50%

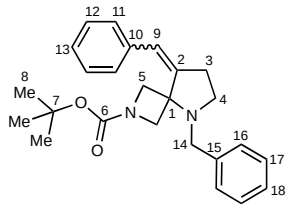
CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (25 mg, 0.11 mmol, 57% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.40–7.32 (m, 4H, H_{9-10}), 7.29–7.25 (m, 1H, H_{11}), 5.55 (t, J = 2.5 Hz, 1H, H_6), 5.17 (t, J = 2.2 Hz, 1H, H_6), 5.02–5.00 (dd, J = 6.6, 0.5 Hz, 2H, H_5), 4.65 (dd, J = 6.6, 0.5 Hz, 2H, H_5), 4.08 (s, 2H, H_7), 2.61–2.58 (m, 2H, H_4), 2.45–2.41 (m, 2H, H_3); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 154.3 (C_2), 139.4 (C_8), 128.51 (C_9 or C_{10}), 128.48 (C_9 or C_{10}), 127.1 (C_{11}), 106.4 (C_6), 81.7 (C_5), 68.9 (C_1), 53.6 (C_7), 49.8 (C_4), 30.2 (C_3); **IR** (film, cm^{-1}): 3027, 2937, 2868, 2795, 1703, 1660, 1603, 1495, 1453, 1368, 1294, 1232, 1195, 1158, 1114, 980, 888, 735, 697; **HRMS** (NSI+): *m/z* calcd for $C_{14}H_{18}O_1N_1$, $[M+H]^+$, 216.1383; found, 216.1381 (Δ = -0.9 ppm).



1-Benzyl-4-methylene-1-azaspiro[4.4]nonane (**122c**). Prepared according to general D using *N*-benzylbut-3-yne-1-amine **S15** (32 mg, 0.20 mmol, 1.0 equiv.), cyclopentanone (53 µL, 0.60 mmol, 3.0 equiv.) and $Ir(dMeppy)_3$ (1.5 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 5% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (33 mg, 0.14 mmol, 72% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.37–7.29 (m, 4H, H_{10-11}), 7.26–7.22 (m, 1H, H_{12}), 4.86 (t, J = 2.4 Hz, 1H, H_7), 4.79 (t, J = 2.1 Hz, 1H, H_7), 3.61 (s, 2H, H_8), 2.59 (t, J = 6.7 Hz, 2H, H_4), 2.51–2.47 (m, 2H, H_3), 1.98–1.93 (m, 2H, H_5), 1.74–1.63 (m, 6H, H_5 & H_6); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 160.4 (C_2), 140.4 (C_9), 128.8 (C_{10} or C_{11}), 128.3 (C_{10} or C_{11}), 126.8 (C_{12}), 102.9 (C_7), 74.6 (C_1), 53.1 (C_8), 49.5 (C_4), 34.0 (C_5), 30.0 (C_3), 25.9 (C_6); **IR** (film, cm^{-1}): 3027, 2949, 2868, 2789, 1655, 1603, 1494, 1451, 1362, 1308, 1229, 1186, 1148, 1114, 1071, 1028, 971, 951, 875, 735, 696; **HRMS** (NSI+): *m/z* calcd for $C_{16}H_{22}N_1$, $[M+H]^+$, 228.1747; found, 228.1749 (Δ = 1.0 ppm).

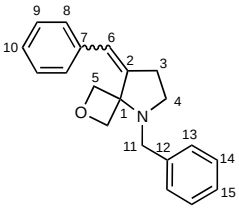


1-Benzyl-4-methylene-8-oxa-1-azaspiro[4.5]decane (**122d**). Prepared according to general D using *N*-benzylbut-3-yne-1-amine **S15** (32 mg, 0.20 mmol, 1.0 equiv.), tetrahydro-4*H*-pyran-4-one (55 µL, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 0% to 40% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (27 mg, 0.11 mmol, 55% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.32 (dt, J = 14.0, 7.8 Hz, 4H, H_{10-11}), 7.26–7.23 (m, 1H, H_{12}), 5.21 (t, J = 2.3 Hz, 1H, H_7), 4.98 (t, J = 2.1 Hz, 1H, H_7), 3.96 (dt, J = 11.5, 4.4 Hz, 2H, H_6), 3.83 (td, J = 11.1, 2.6 Hz, 2H, H_6), 3.64 (s, 2H, H_8), 2.72 (t, J = 7.1 Hz, 2H, H_4), 2.52 (ddt, J = 7.1, 4.8, 2.3 Hz, 2H, H_3), 1.96 (ddd, J = 14.2, 10.1, 4.5 Hz, 2H, H_5), 1.59 (d, J = 13.7 Hz, 2H, H_5); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 156.3 (C_2), 140.6 (C_9), 128.5 (C_{10} or C_{11}), 128.3 (C_{10} or C_{11}), 126.9 (C_{11}), 106.1 (C_{12}), 64.9 (C_6), 62.0 (C_1), 52.5 (C_8), 47.8 (C_4), 31.3 (C_5), 30.3 (C_3); **IR** (film, cm^{-1}): 3027, 2918, 2850, 2796, 1652, 1603, 1494, 1353, 1225, 1153, 1099, 1026, 944, 884, 837, 739, 698, 640; **HRMS** (NSI+): *m/z* calcd for $C_{16}H_{22}O_1N_1$, $[M+H]^+$, 244.1696; found, 244.1699 (Δ = 1.3 ppm).

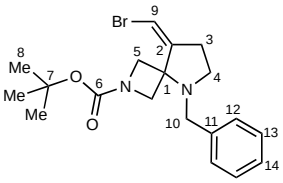


tert-Butyl 5-benzyl-8-benzylidene-2,5-diazaspiro[3.4]octane-2-carboxylate (**122e**). Prepared according to general procedure D using *N*-benzyl-4-phenylbut-3-yne-1-amine[517] (47 mg, 0.20 mmol, 1.0 equiv.), *N*-Boc 3-azetidinone (103 mg, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (SiO_2; 0% to 50% EtOAc in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (42 mg, 0.14 mmol, 70% yield, 1:1 E:Z). The diastereoisomers were separated by Dr. S. Walton by preparative HPLC (gradient 40-80% H_2O: MeCN + 0.1% HCOOH) to afford diastereomerically pure compound for spectroscopic analysis. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.43–7.18 (m, 10H, H_{11-13} & H_{16-18}), 6.70 (t, J = 2.4 Hz, 1H, H_9), 4.31 (d, J = 9.3 Hz, 2H, H_5), 3.99 (d, J = 9.4 Hz, 2H, H_5), 3.89 (s, 2H, H_{14}), 2.79–2.63 (m, 4H, H_{3-4}), 1.49 (s, 9H, H_8); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.5 (C_6), 147.9 (C_{10}), 139.1 (C_{15}), 137.7 (C_9), 128.6 (C_{11} or C_{12} or C_{16} or C_{17}), 128.5 (C_{11} or C_{12} or C_{16} or C_{17}), 128.5 (C_{11} or C_{12} or C_{16} or C_{17}), 128.4 (C_{11} or C_{12} or C_{16} or C_{17}), 127.3 (C_{13} or C_{18}), 126.8 (C_{13} or C_{18}), 121.8 (C_2), 79.9 (C_7), 65.1 (C_5), 53.2 (C_{14}), 50.3 (C_4), 29.7 (C_3), 28.6 (C_8); **IR (film,**

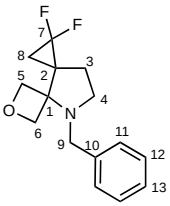
cm^{-1}): 3059, 2976, 2888, 1696, 1393, 1365, 1151, 858, 735, 699; **HRMS** (NSI+): *m/z* calcd for $C_{25}H_{31}N_2O_2$, $[M-H]^+$, 391.2380; found, 391.2381 (Δ = 0.2 ppm).



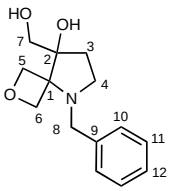
5-Benzyl-8-benzylidene-2-oxa-5-azaspiro[3.4]octane (**122f**). Prepared according to general procedure D using *N*-benzyl-4-phenylbut-3-yne-1-amine[517] (47 mg, 0.20 mmol, 1.0 equiv.), 3-oxetanone (39 µL, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (SiO_2; 0% to 40% EtOAc in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (31 mg, 0.11 mmol, 53% yield, 1:1.4 *E*:*Z*). The diastereomers could be separated by preparative HPLC (gradient of 25-50% H_2O: MeCN + 0.1% HCOOH) to afford diastereomerically pure compound for spectroscopic analysis. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.56–7.47 (m, 2H, H_{8-10} or H_{13-15}), 7.43–7.19 (m, 8H, H_{8-10} or H_{13-15}), 6.65 (s, 1H, H_6), 4.90 (d, *J* = 7.2 Hz, 2H, H_5), 4.81 (d, *J* = 7.2 Hz, 2H, H_5), 4.10 (s, 2H, H_{11}), 2.66–2.60 (m, 2H, H_4), 2.60–2.54 (m, 2H, H_3); **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* 143.5 (C_7), 139.4 (C_{12}), 136.6 (C_6), 129.0 (C_{8-10} or C_{13-15}), 128.4 (C_{8-10} or C_{13-15}), 128.4 (C_{8-10} or C_{13-15}), 128.3 (C_{8-10} or C_{13-15}), 127.0 (C_{8-10} or C_{13-15}), 126.9 (C_{8-10} or C_{13-15}), 125.1 (C_2), 78.2 (C_5), 68.1 (C_1), 52.9 (C_{11}), 48.6 (C_4), 32.8 (C_3); **IR** (film, cm^{-1}): 3026, 2946, 2879, 2798, 1702, 1598, 1494, 1452, 1369, 1255, 1183, 979, 931, 825, 738, 695, 618; **HRMS** (NSI+): *m/z* calcd for $C_{20}H_{22}O_1N_1$, $[M+H]^+$, 292.1696; found, 292.1698 (Δ = 0.7 ppm).



tert-Butyl (*Z*)-5-benzyl-8-(bromomethylene)-2,5-diazaspiro[3.4]octane-2-carboxylate (**122g**). Prepared according to general D using *N*-benzyl-4-bromobut-3-yne-1-amine[512] (48 mg, 0.20 mmol, 1.0 equiv.), *N*-Boc 3-azetidinone (103 mg, 0.60 mmol, 3.0 equiv.) and $[Ir(dMeppy)_2(dtbbpy)]PF_6$ (1.9 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (Alumina; 20% to 100% CH_2Cl_2 in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (55 mg, 0.14 mmol, 70% yield, 17:1 E:Z). Note: Two ^{13}C peaks are observed for C_5 due to rotamers. **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 7.36–7.30 (m, 4H, H_{12-13}), 7.28–7.24 (m, 1H, H_{14}), 6.16 (t, *J* = 1.9 Hz, 1H, H_9), 4.52 (m, 2H, H_5), 4.12 (m, 2H, H_5), 3.97–3.89 (m, 2H, H_{10}), 2.57 (td, *J* = 6.2, 2.4 Hz, 2H, H_4), 2.42–2.39 (m, 2H, H_3), 1.46 (s, 9H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): *δ* 156.8 (C_6), 147.6 (C_9), 139.0 (C_{11}), 128.5 (C_{12} or C_{13}), 128.4 (C_{12} or C_{13}), 127.2 (C_{14}), 98.7 (C_2), 79.6 (C_7), 64.0 (C_1), 56.7 (C_5), 55.3 (C_5), 52.1 (C_{10}), 49.5 (C_4), 33.1 (C_3), 28.5 (C_8); **IR** (film, cm^{-1}): 2972, 2884, 2785, 1694, 1391, 1367, 1161, 1127, 1105, 1068, 983, 919, 860, 778, 729, 697; **HRMS** (NSI+): *m/z* calcd for $C_{19}H_{26}N_2O_2Br$, $[M+H]^+$, 393.1178; found 393.1171 (Δ = -1.8 ppm).



8-Benzyl-1,1-difluoro-6-oxa-azadispiro[2.0.3.3]decane (**124a**). $TMSCF_3$ (51 mL, 0.34 mmol, 3.4 equiv.) was added dropwise to a stirred suspension of alkene **122b** (22 mg, 0.10 mmol, 1.0 equiv.) and NaI (53 mg, 0.34 mmol, 3.4 equiv.) in THF (0.5 mL, 0.2M) at rt. After 1 h, the mixture was filtered through Celite®, conc. *in vacuo* and purified by column chromatography (SiO_2; 0% to 10% EtOAc in 40°–60° Petroleum ether) to afford the resulting product as a yellow oil (19 mg, 0.072 mmol, 72% yield). ^{1}H NMR (400 MHz; $CDCl_3$): *δ* 7.41–7.39 (m, 2H, H_{11}), 7.36–7.33 (m, 2H, H_{12}), 7.29–7.25 (m, 1H, H_{13}), 4.78 (m, 2H, H_{5-6}), 4.73 (d, *J* = 7.6 Hz, 1H, H_5), 4.59 (d, *J* = 7.3 Hz, 1H, H_6), 4.06 (s, 2H, H_9), 2.71 (ddd, *J* = 8.3, 6.3, 1.9 Hz, 2H, H_4), 2.15–2.09 (m, 1H, H_3), 1.76 (ddt, *J* = 13.7, 8.9, 4.7 Hz, 1H, H_8), 1.70–1.62 (m, 1H, H_3), 1.31 (ddd, *J* = 12.5, 8.5, 3.9 Hz, 1H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): *δ* 139.2 (C_{10}), 128.5 (C_{11} or C_{12}), 128.5 (C_{11} or C_{12}), 127.2 (C_{13}), 113.9 (dd, *J* = 290.3, 287.0 Hz, C_7), 76.2 (app t, *J* = 2.6 Hz, C_6), 75.5 (app d, *J* = 5.9 Hz, C_5), 68.8 (app d, *J* = 1.4 Hz, C_1), 53.1 (C_9), 48.8 (C_4), 35.3 (app d, *J* = 9.0 Hz, C_2), 26.9 (app d, *J* = 4.5 Hz, C_3), 19.0 (app t, *J* = 10 Hz, C_8); **^{19}F {^{1}H} NMR** (376 MHz; $CDCl_3$): δ -129.8 (d, *J* = 160.0 Hz), -139.4 (d, *J* = 160.0 Hz); **IR (film, cm^{-1}):** 2948, 2880, 2805, 1466, 1371, 1222, 1137, 983, 699; **HRMS** (NSI+): *m/z* calcd for $C_{15}H_{18}N_1O_1F_2$, $[M+H]^+$, 266.1351; found, 266.1354 (Δ = 1.1 ppm).



5-Benzyl-8-(hydroxymethyl)-2-oxa-5-azaspiro[3.4]octan-8-ol (**124c**). To a solution of alkene **122b** (22 mg, 0.10 mmol, 1.0 equiv.) in THF (0.15 mL), acetone (0.15 mL), H_2O (0.15 mL) and ^{t}BuOH (0.15 mL) was added $K_2[OsO_2(OH)_4]$ (0.7 mg, 2 μmol, 2 mol%) and NMO x H_2O (12 mg, 0.10 mmol, 1.0 equiv.) and the mixture was stirred at rt for 24 h when another batch of NMO x H_2O (12 mg, 0.10 mmol, 1.0 equiv.) was added. The mixture stirred for an additional 24 h, quenched with $Na_2S_2O_3$ (5.0 mL), extracted with EtOAc (3 x 5.0 mL), dried over Na_2SO_4 and conc. *in vacuo*. The crude mixture was purified by column chromatography (SiO_2; 0% to 5% MeOH:aq. NH_3 (9:1) in CH_2Cl_2) to afford the resulting product as an amorphous solid (17.0 mg, 0.068 mmol, 68% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.36–7.30 (m, 4H, H_{10-11}), 7.29–7.25 (m, 1H, H_{12}), 4.93 (d, J = 7.2 Hz, 1H, H_5 or H_6), 4.75 (app d, J = 7.6 Hz, 2H, H_5 or H_6), 4.70 (d, J = 7.6 Hz, 1H, H_5 or H_6), 4.09 (d, J = 13.5 Hz, 1H, H_8), 4.05 (d, J = 13.6 Hz, 1H, H_8),, 3.88 (d, J = 11.1 Hz, 1H, H_7), 3.78 (d, J = 11.1 Hz, 1H, H_7), 3.12 (s, 1H, O<u>H</u>), 2.87 (s, 1H, O<u>H</u>), 2.70 (td, J = 9.6, 5.5 Hz, 1H, H_4), 2.54 (td, J = 9.6, 5.3 Hz, 1H, H_4), 1.91 (ddd, J = 13.6, 9.5, 5.5 Hz, 1H, H_3), 1.77 (ddd, J = 13.9, 9.3, 5.0 Hz, 1H, H_3); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 138.8 (C_9), 128.6 (C_{10} or C_{11}), 128.4 (C_{10} or C_{11}), 127.3 (C_{12}), 79.2 (C_2), 74.2 (C_6 or C_5), 73.5 (C_6 or C_5), 71.8 (C_1), 66.8 (C_7), 53.0 (C_8), 47.7 (C_4), 32.5 (C_3); **IR (film, cm^{-1}):** 3384, 2960, 2880, 1454, 1371, 1209, 1155, 1048, 973, 737, 697; **HRMS** (NSI+): *m/z* calcd for $C_{14}H_{20}N_1O_3$, $[M-H]^+$, 250.1438; found, 250.1435 (Δ = -1.0 ppm).

Mechanistic studies – Stern Volmer studies

Stern-Volmer studies were conducted with iminium salt (**67**) and Hantzsch ester. Standard solutions of iminium salt (**67**), Hantzsch ester and $Ir(dMeppy)_3$ were prepared in CH_2Cl_2. The solutions (0.01 mM Ir photocatalyst) and varying concentrations quenchers were irradiated:

Iminium salt (**67**): Irradiated at 385 nm and luminescence was measured at 528 nm.

Hantzsch ester: Irradiated at 430 nm and luminescence was measured at 528 nm. The longer excitation wavelength was used in order to avoid direct excitation of Hantzsch ester, which is possible at λ_{max} of the Ir-photocatalyst at 385 nm.

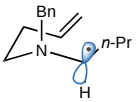
[(67 mM)]	**0.0**	**0.2**	**0.4**	**0.6**	**0.8**	**1.0**
Run 1	1	1.096	1.140	1.160	1.184	1.220
Run 2	1	1.056	1.068	1.116	1.146	1.231
Average	**1**	**1.076**	**1.104**	**1.138**	**1.165**	**1.226**

[Hantzsch Ester]	**0.0**	**0.2**	**0.4**	**0.6**	**0.8**	**1.0**
Run 1	1	1.052	1.077	1.010	1.074	1.034
Run 2	1	1.007	0.980	1.021	0.994	1.010
Run 3	1	0.975	0.965	1.001	0.978	1.025
Average	**1**	**1.011**	**1.007**	**1.011**	**1.015**	**1.023**

Computational Methods and Data

All calculations were performed using the Gaussian 16 (Revision A.03) program.[518] All geometries were optimised at the UTPSS/def2-TZVP level of theory. Single-point energies of the optimised structures were calculated at the UPW6B95-D3/def2-QZVP level of theory. Electronic, thermal corrections and Gibbs Free Energies are reported for each compound in hartrees. These functionals and/or basis sets have been employed for calculations of radical additions to alkenes previously.[292] Dispersion was accounted for using Grimme's DFT-D3 scheme[519] with Becke-Johnson damping.[520]

109a

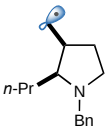


Geometry optimisation:
UTPSS-D3BJ/def2-TZVP Energy = -639.906528416
Thermal correction to Gibbs Free Energy = 0.280690
Imaginary frequency = n/a

Single-point energy calculation:
UPW6B95-D3BJ/def2-QZVP Energy = -640.631679172
[UPW6B95-D3BJ/def2-QZVP + UTPSS-D3BJ/def2-TZVP] Gibbs Free Energy = -640.350989172

C	-1.71325500	3.07924500	-1.04205800
C	-1.39208500	2.77171500	0.21791500
C	-0.00327300	2.45141800	0.68424600
C	0.12017200	1.09776800	1.42425900
N	-0.39561600	-0.05243700	0.68133500
C	-1.78132500	-0.22607400	0.74967800
H	-2.19460500	-0.01416100	1.73440000
C	0.28133400	-0.32609100	-0.58968900
C	1.76957400	-0.51648400	-0.40105400
C	2.24990700	-1.46532400	0.50989000
C	3.61966300	-1.65048000	0.68268600
C	4.52957100	-0.88911400	-0.05577800
C	4.06019900	0.05715800	-0.96526300
C	2.68602500	0.24167900	-1.13305400
H	-0.96308000	3.09409700	-1.83059400
H	-2.73247000	3.31754000	-1.33161200
H	-2.17135900	2.76660200	0.97997600
H	0.34063600	3.22445700	1.38723600
H	0.68761800	2.47377300	-0.16704400
H	-0.43497400	1.13926300	2.36770500
H	1.17406000	0.91842100	1.66095500
H	0.10157800	0.47320000	-1.32732000
H	-0.15504200	-1.24227400	-0.99835900
H	1.53757700	-2.04535600	1.09128500
H	3.98068200	-2.39047600	1.39195500
H	5.59786700	-1.03306800	0.07997200
H	4.76131700	0.65624300	-1.53992900
H	2.31930400	0.98328300	-1.83970300
C	-2.50027700	-1.19459000	-0.12905400
H	-2.35744000	-0.93720800	-1.19011900
C	-4.00630200	-1.21239600	0.17052000
H	-2.10838600	-2.22637100	-0.01789800
H	-4.40218300	-0.19648500	0.04696600
H	-4.15818000	-1.48116500	1.22444400
C	-4.77602400	-2.18552100	-0.72585100
H	-4.66169400	-1.91876400	-1.78322700
H	-5.84626800	-2.18091200	-0.49283100
H	-4.40906900	-3.21104200	-0.59995200

109b

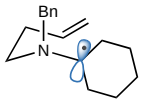


Geometry optimisation:
UTPSS-D3BJ/def2-TZVP Energy = -639.918053253
Thermal correction to Gibbs Free Energy = 0.284257
Imaginary frequency = n/a

Single-point energy calculation:
UPW6B95-D3BJ/def2-QZVP Energy = -640.643882706
[UPW6B95-D3BJ/def2-QZVP + UTPSS-D3BJ/def2-TZVP] Gibbs Free Energy = -640.359625706

C	-2.65555600	0.31396500	1.71495800
C	-2.81168800	-0.07558300	0.28719100
H	-3.59186700	0.53418400	-0.17827800
C	-3.16632000	-1.60328500	0.13694800
C	-1.90158300	-2.24366100	-0.46114000
C	-1.49178000	0.03537100	-0.52396400
H	-1.76483300	0.06106100	-1.60241100
C	-0.63606700	1.26348900	-0.22669300
C	-1.37434100	2.57675700	-0.50877700
C	-0.48238900	3.80051800	-0.28031600
N	-0.84515300	-1.25315600	-0.21997400
C	0.38235500	-1.54370200	-0.95945900
C	1.62401100	-0.92382100	-0.35142900
C	2.64254100	-0.42420700	-1.16768900
C	3.80107800	0.11906300	-0.61095800
C	3.95223900	0.16904300	0.77473700
C	2.93985600	-0.33063000	1.59671500
C	1.78535000	-0.87467600	1.03707600
H	-3.46945100	0.78360000	2.25907900
H	-1.78944700	-0.02337400	2.27695500
H	-4.03352800	-1.74288600	-0.51465800
H	-3.40890800	-2.03216100	1.11246800
H	-2.04088600	-2.41900300	-1.54599900
H	-1.63470100	-3.19919300	0.00193000
H	0.27386700	1.22821700	-0.83725100
H	-0.30983900	1.23697200	0.81913700
H	-2.25861800	2.64240900	0.13783900
H	-1.74049500	2.57479500	-1.54498700
H	-0.12841800	3.83571800	0.75651900
H	-1.02063100	4.73246400	-0.48465900
H	0.39972600	3.76960300	-0.93060400
H	0.29813700	-1.24283600	-2.02176700
H	0.50322000	-2.63517900	-0.95538500
H	2.52123200	-0.44999300	-2.24893400
H	4.58092700	0.51022800	-1.25894400
H	4.85014700	0.59737300	1.21150500
H	3.05040800	-0.29333400	2.67738500
H	0.98379600	-1.24841800	1.66768900

110a



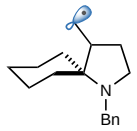
Geometry optimisation:
UTPSS-D3BJ/def2-TZVP Energy = -717.379843772
Thermal correction to Gibbs Free Energy = 0.318599
Imaginary frequency = n/a

Single-point energy calculation:
UPW6B95-D3BJ/def2-QZVP Energy = -718.195365807
[UPW6B95-D3BJ/def2-QZVP + UTPSS-D3BJ/def2-TZVP] Gibbs Free Energy = -717.876766807

C	-2.92513700	-1.64252400	1.79559300
C	-2.96542100	-1.56847800	0.46110300
C	-2.21709200	-2.48432700	-0.46074400
C	-1.31246700	-1.73848600	-1.47094700
N	-0.34076000	-0.83904200	-0.84384500
C	-0.84794000	0.39568500	-0.38641500
C	-1.37829500	1.34736200	-1.42133600
C	-2.39524000	2.33585300	-0.82897500
C	-1.82548200	3.02361200	0.41653000
C	-1.40507700	1.98615100	1.46248100
C	-0.36469900	1.00064800	0.89570300
C	0.67314300	-1.52712700	-0.04915700
C	1.98902400	-0.77673100	0.00370100
C	2.79434300	-0.84982100	1.14337800
C	4.02326700	-0.19174900	1.19109500
C	4.45676000	0.55684500	0.09651800
C	3.65495100	0.63867000	-1.04341000
C	2.43044600	-0.02597300	-1.09000100
H	-2.92970200	-3.08236400	-1.04831500
H	-1.61895400	-3.19081900	0.12776700
H	-1.93825200	-1.14544500	-2.14369800
H	-0.76868000	-2.46772600	-2.08366000
H	-1.82292100	0.81121100	-2.26730100
H	-0.53423000	1.92876600	-1.84626100
H	-3.30785900	1.79029200	-0.55248400
H	-2.67666700	3.07943400	-1.58464300
H	-2.56421800	3.71416700	0.84165200
H	-0.95166500	3.62701100	0.12933900
H	-2.28800700	1.41978800	1.78495800
H	-0.99171100	2.48299100	2.34900300
H	-0.16259100	0.22300900	1.63966700
H	0.58770500	1.54513200	0.75068500
H	0.83495200	-2.50064500	-0.53120200
H	0.33649900	-1.74316000	0.97802000
H	2.44998500	-1.41894000	2.00475100
H	4.63691400	-0.25504300	2.08573200
H	5.40950600	1.07775400	0.13363300
H	3.98426000	1.22378300	-1.89811600
H	1.79481100	0.04343500	-1.96824100
H	-3.49892500	-0.96846900	2.42469700
H	-2.30551400	-2.37910100	2.30336900
H	-3.59991900	-0.81943200	-0.01314100

110b

Geometry optimisation:
UTPSS-D3BJ/def2-TZVP Energy = -717.385593546
Thermal correction to Gibbs Free Energy = 0.323087
Imaginary frequency = n/a

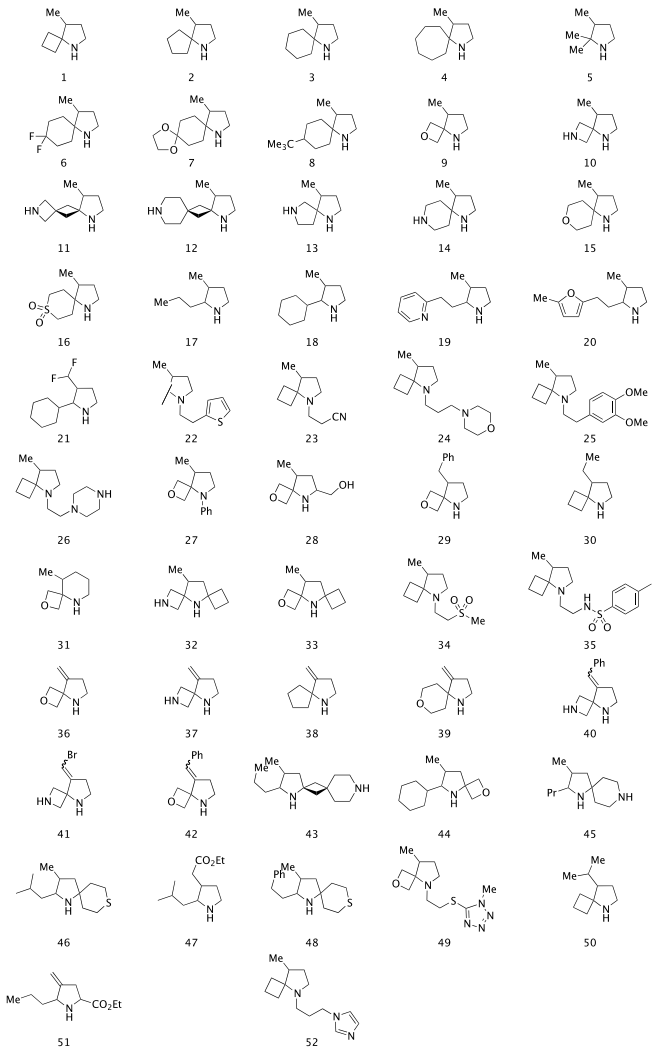


Single-point energy calculation:
UPW6B95-D3BJ/def2-QZVP Energy = -718.201551261
[UPW6B95-D3BJ/def2-QZVP + UTPSS-D3BJ/def2-TZVP] Gibbs Free Energy = -717.878464261

C	-2.35184200	-1.71558100	1.76642400
C	-2.66108100	-0.84543800	0.60764600
H	-3.54351700	-0.23639700	0.85207800
C	-2.88319000	-1.64285900	-0.70466900
C	-1.81091700	-1.11351600	-1.69215900
C	-1.51277700	0.20595700	0.20464300
C	-0.65656700	0.65839000	1.39430200
C	0.31073900	1.80827500	1.07419500
C	-0.39894700	2.99898800	0.42060500
C	-1.20442700	2.53674300	-0.79839600
C	-2.20614700	1.45685600	-0.38318800
N	-0.75559200	-0.48844400	-0.87204500
C	0.20990500	-1.49396900	-0.38420400
C	1.61925400	-0.95996400	-0.24673000
C	2.38703100	-1.24696300	0.88362800
C	3.69378200	-0.76916500	0.99852700
C	4.24687800	0.00058700	-0.02403300
C	3.48741600	0.28671300	-1.16153800
C	2.18331000	-0.19026200	-1.27056900
H	-2.07265400	-2.75682400	1.63094600
H	-2.36521400	-1.32551400	2.77995500
H	-3.89720500	-1.51943100	-1.09622900
H	-2.73696800	-2.71159200	-0.51676000
H	-2.23414800	-0.36030600	-2.36301400
H	-1.37712300	-1.89778400	-2.31712800
H	-0.10999800	-0.18948600	1.81912000
H	-1.35804900	0.98746100	2.17381600
H	1.09293300	1.44770000	0.40044000
H	0.80967000	2.12070000	1.99986300
H	0.33504900	3.76164500	0.13363900
H	-1.08199600	3.46859000	1.14411000
H	-0.52628700	2.12251100	-1.55496100
H	-1.73327600	3.38215300	-1.25551100
H	-2.85532200	1.18150000	-1.22085000
H	-2.86574400	1.85764600	0.39906900
H	0.22485500	-2.30424800	-1.12305800
H	-0.10744200	-1.94652500	0.56978100
H	1.95218900	-1.83831300	1.68715100
H	4.27558900	-0.99162900	1.88902600
H	5.26149200	0.37890300	0.06474700
H	3.91281300	0.88741700	-1.96122200
H	1.57498400	0.05218000	-2.13760500

Principal Moment of Intertia (PMI)

The PMI-plot (see section 4.4.1, figure 22) was created in the following way. The protecting groups were removed from the spirocyclic structures synthesized in chapter 4 to create the "spirocyclic data set". The geometry of each structure was optimized with Merck Molecular Force Field 94 (MMFF94S) using the Avagadro software.[521,522] The resulting .mol files were then processed by the KNIME data-mining platform using the Vernalis cheminformatics node.[523]



Spirocyclic	I1 / I3	I2 / I3
1	0.464640789	0.845644571
2	0.456957787	0.835297919
3	0.449999118	0.917973033
4	0.41949717	0.974285052
5	0.670468477	0.708200617
6	0.310032148	0.913334284
7	0.241524955	0.931190485
8	0.23856893	0.966728684
9	0.462049662	0.744886449
10	0.478869445	0.74016012
11	0.254039275	0.918311164
12	0.255553652	0.896386676
13	0.465981975	0.839028016
14	0.439243837	0.914130591
15	0.43733417	0.911057573
16	0.275163391	0.934531589
17	0.272860245	0.816440853
18	0.274900743	0.916672014
19	0.140004747	0.986603389
20	0.15431996	0.934709868
21	0.289015982	0.821058464
22	0.225238372	0.939891307
23	0.42555198	0.877289312
24	0.117986083	0.959802295
25	0.188695722	0.931770682
26	0.188066927	0.931367088
27	0.33779564	0.794334192
28	0.446616313	0.743497478
29	0.320954193	0.88262296
30	0.491132858	0.681929498
31	0.47709194	0.718047907
32	0.37946863	0.84819827
33	0.349461685	0.843885012
34	0.254425709	0.910324405
35	0.245237451	0.9263809
36	0.4410173	0.756084233
37	0.451347635	0.750732556
38	0.427637592	0.846240473
39	0.398359019	0.918774137
40	0.226768835	0.900738988
41	0.254785752	0.8193171
42	0.208802129	0.914207863
43	0.171747438	0.915357562
44	0.221109944	0.878780417
45	0.180076583	0.946076422
46	0.230421003	0.93210717
47	0.439945888	0.710648754
48	0.09659829	0.966093371
49	0.192191816	0.90833196
50	0.464445349	0.691674244
51	0.21863923	0.840372499
52	0.154735723	0.932170844

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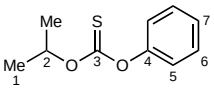
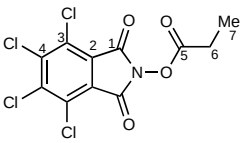
8 Appendix I – Experimental procedures for the synthesis of starting materials

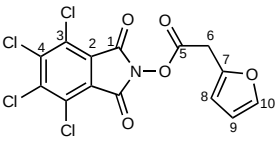
8.1 Carbonyl alkylative amination employing alcohol- and carboxylic acid-based nucleophiles



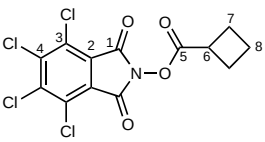
*O-Iso*propyl *O*-phenyl carbonothioate (**80a**). Pyridine (0.82 mL, 10 mmol, 2.0 equiv.) was added dropwise to a solution of 2-propanol (0.38 mL, 5.0 mmol, 1.0 equiv.) and *O*-phenyl chlorothionoformate (0.83 mL, 5.6 mmol, 1.2 equiv.) in CH_2Cl_2 (30 mL, 0.17 M) at r.t. and stirred for 2 hours. The mixture was neutralized with HCl (30 mL, 1 M), washed with H_2O (30 mL), $NaHCO_3$ (sat., 30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (0.25% Et_2O in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (711 mg, 3.6 mmol, 72% yield). ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.43–7.40 (m, 2H, H_6), 7.30–7.27 (m, 1H, H_7), 7.12–7.10 (m, 2H, H_5), 5.48 (sept, J = 6.2 Hz, 1H, H_2), 1.45 (d, J = 6.3 Hz, 6H, H_1). Spectral data was in agreement with literature.[524]



4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl propionate (**S1**). Propanoic acid (0.30 mL, 4.0 mmol, 1.0 equiv.), *N*-hydroxyphthalimide (1.0 g, 6.0 mmol, 1.5 equiv.), *N*,*N*'-dicyclohexylcarbodiimide (0.82 g, 3.99 mmol, 1.0 equiv.) and 4,*N*,*N*-dimethylaminopyridine (20 mg, 0.16 mmol, 4.0 mol%) were dissolved in CH_2Cl_2 (10 mL, 0.40 M) at 0°C. The mixture was allowed to warm to r.t. and stirred for 14 hours. The resulting mixture was filtered through a frit, concentrated *in vacuo* and purified by flash column chromatography (0–100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (0.63 g, 1.8 mmol, 45% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 2.71 (q, J = 7.5 Hz, 2H, H_6), 1.32 (t, J = 7.5 Hz, 3H, H_7); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 170.0 (C_5), 157.7 (C_1), 141.1 (C_2 or C_3 or C_4), 130.6 (C_2 or C_3 or C_4), 124.9 (C_2 or C_3 or C_4), 24.6 (C_6), 8.9 (C_7); **IR** (film, cm^{-1}): 2974, 2943, 1743, 1374, 1357; 1142, 1093, 1050, 1032, 988, 825, 795, 727, 708.

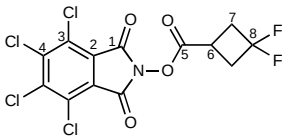


4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl 2-(furan-2-yl)acetate (**S2**). 2-(Furan-2-yl)-acetic acid (504 mg, 3.4 mmol, 1.0 equiv.), *N*-hydroxyphthalimide (0.85 g, 5.1 mmol, 1.5 equiv.), *N*,*N*'-dicyclohexylcarbodiimide (0.70 g, 3.4 mmol, 1.0 equiv.) and 4,*N*,*N*-dimethylaminopyridine (17 mg, 0.14 mmol, 4.0 mol%) were dissolved in CH_2Cl_2 (8.5 mL, 0.40 M) at 0°C. The mixture was allowed to warm to r.t. and stirred for 14 hours. The resulting mixture was filtered through a frit, concentrated *in vacuo* and purified by flash column chromatography (0–100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (358 mg, 0.88 mmol, 26% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.42 (dd, J = 1.8, 0.8 Hz, 1H, H_{10}), 6.41–6.37 (m, 2H, $H_{8\text{-}9}$), 4.07 (s, 2H, H_6); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 165.2 (C_5), 157.4 (C_1), 144.5 (C_7), 143.0 (C_{10}), 141.3 (C_2 or C_3 or C_4), 130.7 (C_2 or C_3 or C_4), 124.7 (C_2 or C_3 or C_4), 110.9 (C_8 or C_9), 109.4 (C_8 or C_9), 31.0 (C_6); **IR** (film, cm^{-1}): 2962, 2926, 1739, 1378, 1352, 1149, 1066, 1031, 1012, 745, 725.

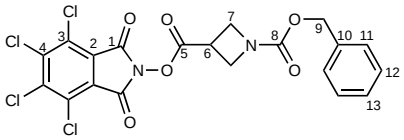


4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl cyclobutanecarboxylate (**S3**). Cyclobutane carboxylic acid (0.38 mL, 4.0 mmol, 1.0 equiv.), *N*-hydroxyphthalimide (1.0 g, 6.0 mmol, 1.5 equiv.), *N*,*N*'-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol, 1.0 equiv.) and 4,*N*,*N*-dimethylaminopyridine (20 mg, 0.16 mmol, 4 mol%) were dissolved in CH_2Cl_2 (10 mL, 0.40 M) at 0°C. The mixture was allowed to warm to r.t. and stirred for 14 hours. The resulting mixture was filtered through a frit, concentrated *in vacuo* and purified by flash column

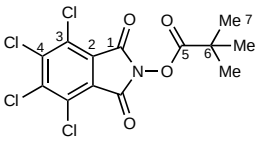
chromatography (0–100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (0.98 g, 2.6 mmol, 64% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 3.50 (quintet, J = 8.4 Hz, 1H, H_6), 2.54–2.37 (m, 4H, H_7), 2.17–2.02 (m, 2H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.1 (C_5), 157.8 (C_1), 141.1 (C_2 or C_3 or C_4), 130.6 (C_2 or C_3 or C_4), 124.9 (C_2 or C_3 or C_4), 35.0 (C_6), 25.5 (C_7), 18.9 (C_8); **IR** (film, cm^{-1}): 2994, 2950, 1741, 1380, 1365, 1157, 1041, 994, 792, 723.



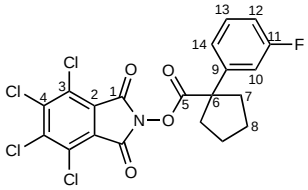
4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl 3,3-difluorocyclobutane-1-carboxylate (**S4**). 3,3-Difluorocyclobutane carboxylic acid (544 mg, 4.0 mmol, 1.0 equiv.), *N*-hydroxyphthalimide (1.0 g, 6.0 mmol, 1.5 equiv.), *N*,*N*'-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol, 1.0 equiv.) and 4,*N*,*N*-dimethylaminopyridine (20 mg, 0.16 mmol, 4.0 mol%) were dissolved in CH_2Cl_2 (10 mL, 0.40 M) at 0°C. The mixture was allowed to warm to r.t. and stirred for 14 hours. The resulting mixture was filtered through a frit, concentrated *in vacuo* and purified by flash column chromatography (0–100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (0.72 g, 1.7 mmol, 43% yield). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 3.38–3.31 (m, 1H, H_6), 3.13–2.99 (m, 4H, H_7); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 169.6 (C_5), 157.5 (C_1), 141.4 (C_2 or C_3 or C_4), 130.8 (C_2 or C_3 or C_4), 124.7 (C_2 or C_3 or C_4), 118.1 (dd, J = 283.7, 271.2 Hz, C_8), 39.3 (t, J = 25.5 Hz, C_7), 24.2 (dd, J = 14.8, 6.0 Hz, C_6); **^{19}F NMR** (376 MHz; $CDCl_3$): δ -83.3 (d, J = 195.6 Hz), -96.0 (d, J = 195.4 Hz); **IR** (film, cm^{-1}): 2984, 1739, 1378, 1300, 1234, 1154, 1105, 1042, 958, 916, 886, 876, 788, 723, 705, 611.



1-Benzyl 3-(4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl) azetidine-1,3-dicarboxylate (**S5**). 1-((Benzyloxy)carbonyl)azetidine-3-carboxylic acid (941 mg, 4.0 mmol, 1.0 equiv.), *N*-hydroxyphthalimide (1.0 g, 6.0 mmol, 1.5 equiv.), *N*,*N*'-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol, 1.0 equiv.) and 4,*N*,*N*-dimethylaminopyridine (20 mg, 0.16 mmol, 4.0 mol%) were dissolved in CH_2Cl_2 (10 mL, 0.40 M) at 0°C. The mixture was allowed to warm to r.t. and stirred for 14 hours. The resulting mixture was filtered through a frit, concentrated *in vacuo* and purified by flash column chromatography (50-100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (0.69 g, 1.3 mmol, 33% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.39–7.30 (m, 5H, H_{11-13}), 5.11 (s, 2H, H_9), 4.36 (d, J = 7.4 Hz, 4H, H_7), 3.77 (quintet, J = 7.4 Hz, 1H, H_6); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 168.6 (C_5), 157.4 (C_1), 156.1 (C_8), 141.4 (C_2 or C_3 or C_4), 136.3 (C_{10}), 130.8 (C_2 or C_3 or C_4), 128.7 (C_{11} or C_{12} or C_{13}), 128.4 (C_{11} or C_{12} or C_{13}), 128.2 (C_{11} or C_{12} or C_{13}), 124.7 (C_2 or C_3 or C_4), 67.2 (C_9), 51.8 (broad, C_7), 30.1 (C_6); **IR** (film, cm^{-1}): 1745, 1701, 1414, 1376, 1361, 1348, 1300, 1151, 1102, 1075, 1045, 754, 725, 702.



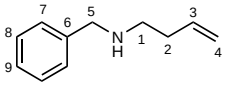
4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl pivalate (**S6**). Pivalic acid (460 µL, 4.0 mmol, 1.0 equiv.), *N*-hydroxyphthalimide (1.0 g, 6.0 mmol, 1.5 equiv.), *N*,*N*'-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol, 1.0 equiv.) and 4,*N*,*N*-dimethylaminopyridine (20 mg, 0.16 mmol, 4.0 mol%) were dissolved in CH_2Cl_2 (10 mL, 0.40 M) at 0°C. The mixture was allowed to warm to r.t. and stirred for 14 hours. The resulting mixture was filtered through a frit, concentrated *in vacuo* and purified by flash column chromatography (50–100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (0.64 g, 1.7 mmol, 42% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 1.43 (s, 9H, H_7); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 174.0 (C_5), 157.9 (C_1), 141.1 (C_2 or C_3 or C_4), 130.5 (C_2 or C_3 or C_4), 125.0 (C_2 or C_3 or C_4), 38.6 (C_6), 27.1 (C_7); **IR** (film, cm^{-1}): 2987, 2976, 1736, 1379, 1364, 1353, 1155, 1053, 1007, 851, 791, 723, 698.



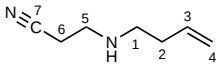
4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl 1-(3-fluorophenyl) cyclopentane-1-carboxylate (**S7**). 1-(3-Fluorophenyl)cyclopentane-1-carboxylic acid (833 mg, 4.0 mmol, 1.0 equiv.), *N*-hydroxyphthalimide (1.0 g, 6.0 mmol, 1.5 equiv.), *N*,*N*'-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol, 1.0 equiv.) and 4,*N*,*N*-dimethylaminopyridine (20 mg, 0.16 mmol, 4.0 mol%) were dissolved in CH_2Cl_2 (10 mL, 0.40 M) at 0°C. The mixture

was allowed to warm to r.t. and stirred for 14 hours. The resulting mixture was filtered through a frit, concentrated *in vacuo* and purified by flash column chromatography (50–100% CH_2Cl_2 in 40°–60° Petroleum Ether) to afford the title compound as a colourless oil (0.68 g, 1.4 mmol, 35% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.40–7.34 (m, 1H, H_{13} or H_{14}), 7.26–7.23 (m, 1H, H_{13} or H_{14}), 7.17 (dd, J = 10.3, 1.3 Hz, 1H, H_{10}), 7.04–7.00 (m, 1H, H_{12}), 2.79–2.74 (m, 2H, H_7), 2.14–2.07 (m, 2H, H_7), 1.96–1.83 (m, 4H, H_8); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.8 (C_5), 162.9 (d, J = 246.3 Hz, C_{11}), 157.7 (C_1), 143.3 (d, J = 7.2 Hz, C_9), 141.2 (C_2 or C_3 or C_4), 130.6 (C_2 or C_3 or C_4), 130.3 (d, J = 8.2 Hz, C_{13}), 124.9 (C_2 or C_3 or C_4), 122.8 (d, J = 2.9 Hz, C_{14}), 114.8 (d, J = 21.0 Hz, C_{10} or C_{12}), 114.1 (d, J = 22.6 Hz, C_{10} or C_{12}), 57.9 (C_6), 37.2 (C_7), 23.9 (C_8); **IR** (film, cm^{-1}): 2955, 1741, 1379, 1354, 1154, 1067, 1038, 966, 789, 723, 684.

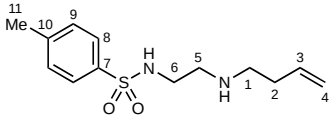
8.2 Visible light-mediated synthesis of *N*-heterospirocycles



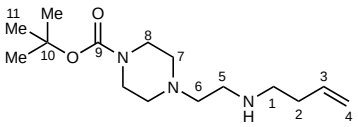
N-Benzylbut-3-en-1-amine (**107a**). Benzylamine (4.6 mL, 42 mmol, 4.9 equiv.), 4-bromobut-1-ene (0.86 mL, 8.5 mmol, 1.0 equiv.), NaI (40 mg, 0.27 mmol, 3.0 mol%) and EtOH (20 mL, 0.40 M) were heated at 80 °C in a sealed tube for 10 h. The resulting solution was conc. *in vacuo*, redissolved in CH_2Cl_2 (50 mL), washed with aq. NaOH (50 mL, 10% w/v), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude mixture was purified by column chromatography (SiO_2; 20% to 50% EtOAc in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (1.1 g, 6.8 mmol, 80% yield). Spectral data was in agreement with literature.[487] ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.35–7.30 (m, 4H, $H_{7\text{-}8}$), 7.26–7.23 (m, 1H, H_9), 5.79 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H, H_3), 5.12–5.02 (m, 2H, H_4), 3.80 (s, 2H, H_5), 2.71 (d, J = 13.7 Hz, 2H, H_1), 2.29 (q, J = 6.8 Hz, 2H, H_2), 1.38 (s, 1H, N<u>H</u>).



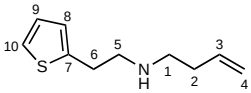
3-(But-3-en-1-ylamino)propanenitrile (**S8**). 3-Aminopropionitrile (257 µL, 3.5 mmol, 4.0 equiv.), 4-bromobut-1-ene (91 µL, 0.9 mmol, 1.0 equiv.), NaI (5.0 mg, 33 µmol, 4.0 mol%) and EtOH (2.5 mL, 0.40 M) were heated at 80 °C in a sealed tube for 10 h. The resulting solution was conc. *in vacuo*, redissolved in CH_2Cl_2 (10 mL), washed with aq. NaOH (10 mL, 10% w/v), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude mixture was purified by column chromatography (SiO_2; 20% to 50% EtOAc in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (83 mg, 0.66 mmol, 74% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 5.77 (ddtd, J = 17.1, 10.2, 6.9, 0.7 Hz, 1H, H_3), 5.12–5.04 (m, 2H, H_4), 2.92 (td, J = 6.7, 0.9 Hz, 2H, H_5), 2.70 (td, J = 6.8, 0.8 Hz, 2H, H_1), 2.52–2.49 (m, 2H, H_6), 2.28–2.22 (m, 2H, H_2), 1.30 (s, 1H, N<u>H</u>); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 136.0 (C_3), 118.8 (C_7), 116.9 (C_4), 48.2 (C_1), 45.1 (C_5), 34.3 (C_2), 18.8 (C_6); **IR** (film, cm^{-1}): 3073, 2914, 2836, 2247, 1640, 1472, 1419, 1359, 1125, 995, 914, 735, 735, 643; **HRMS** (ESI+): *m/z* calcd for $C_7H_{13}N_2$, $[M+H]^+$, 125.1073; found 125.1073 (Δ = -0.1 ppm).



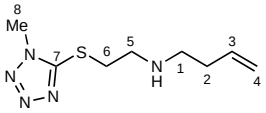
N-(2-(But-3-en-1-ylamino)ethyl)-4-methylbenzenesulfonamide (**S9**). *N*-(*p*-Toluenesulfonyl)-ethylene diamine (750 mg, 3.5 mmol, 3.9 equiv.), 4-bromobut-1-ene (91 µL, 0.9 mmol, 1.0 equiv.), NaI (5.0 mg, 33 µmol, 4.0 mol%), and EtOH (2.5 mL, 0.40 M) were heated in a sealed vial at 80 °C for 10 h. The resulting solution was conc. *in vacuo*, redissolved in CH_2Cl_2 (10 mL), washed with aq. NaOH (10 mL, 10% w/v), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude mixture was purified by column chromatography (SiO_2; 0% to 3% MeOH:aq. NH_3 (9:1) in CH_2Cl_2) to afford the title compound as a pale yellow oil (150 mg, 0.50 mmol, 56% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.76–7.73 (m, 2H, H_8), 7.32–7.28 (m, 2H. H_9), 5.71 (ddt, J = 17.0, 10.3, 6.8 Hz, 1H, H_3), 5.06–5.01 (m, 2H, H_4), 2.98–2.95 (m, 2H, H_6), 2.69–2.66 (m, 2H, H_5), 2.51 (t, J = 6.8 Hz, 2H, H_1), 2.42 (s, 3H, H_{11}), 2.15 (qt, J = 6.8, 1.3 Hz, 2H, H_2); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 143.5 (C_7), 136.9 (C_{10}), 136.2 (C_3), 129.8 (C_9), 127.3 (C_8), 116.7 (C_4), 48.1 (C_1), 47.7 (C_5), 42.4 (C_6), 34.3 (C_2), 21.7 (C_{11}); **IR** (film, cm^{-1}): 3277, 3067, 2928, 2833, 1641, 1599, 1446, 1322, 1153, 1092, 913, 812; **HRMS** (ESI+): *m/z* calcd for $C_{13}H_{21}N_2O_2S_1$, $[M+H]^+$, 269.1318; found 269.1320 (Δ = 0.6 ppm).



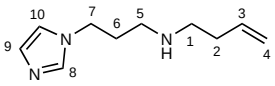
tert-Butyl 4-(2-(but-3-en-1-ylamino)ethyl)piperazine-1-carboxylate (**S10**). 4-*N*-(2-Aminoethyl)-1-*N*-Boc-piperazine (688 mg, 3.0 mmol, 4.0 equiv.), 4-bromobut-1-ene (76 µL, 0.75 mmol, 1.0 equiv.), NaI (5.0 mg, 33 µmol, 4.0 mol%) and EtOH (2.5 mL, 0.40 M) were heated at 80 °C in a sealed tube for 10 h. The resulting solution was conc. *in vacuo*, redissolved in CH_2Cl_2 (10 mL), washed with aq. NaOH (10 mL, 10% w/v), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude mixture was purified by column chromatography (SiO_2; 0% to 6% MeOH:aq. NH_3 (9:1) in CH_2Cl_2) to afford the title compound as a pale yellow oil (166 mg, 0.59 mmol, 78% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 5.73 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H, H_3), 5.07–4.99 (m, 2H, H_4), 3.36 (t, J = 5.0 Hz, 4H, H_8), 2.81 (s, 1H, N<u>H</u>), 2.70 (td, J = 6.5, 4.5 Hz, 4H, H_7), 2.48 (t, J = 6.1 Hz, 2H, H_1), 2.34 (t, J = 4.9 Hz, 4H, $H_{5\text{-}6}$), 2.26 (q, J = 6.9 Hz, 2H, H_2), 1.40 (s, 9H, H_{11}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 154.8 (C_9), 136.0 (C_3), 116.7 (C_4), 79.6 (C_{10}), 57.4 (C_7), 53.0 (C_5), 48.7 (C_1), 46.0 (C_6), 43.6 (broad, C_8), 33.8 (C_2), 28.5 (C_{11}); **IR** (film, cm^{-1}): 3384, 2940, 2797, 1690, 1415, 1246, 1169, 1121, 1000, 866, 770; **HRMS** (ESI+): *m/z* calcd for $C_{15}H_{30}N_3O_2$, $[M+H]^+$, 284.2338; found 284.2351 (Δ = 4.6 ppm).



N-(2-(Thiophen-2-yl)ethyl)but-3-en-1-amine (**S11**). 2-Thiophenethylamine (450 mg, 3.5 mmol, 3.9 equiv.), 4-bromobut-1-ene (91 µL, 0.9 mmol, 1.0 equiv.), NaI (5.0 mg, 33 µmol, 4.0 mol%) and EtOH (2.5 mL, 0.40 M) were heated at 80 °C in a sealed tube for 10 h. The resulting solution was conc. *in vacuo*, redissolved in CH_2Cl_2 (10 mL), washed with aq. NaOH (10 mL, 10% w/v), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude mixture was purified by column chromatography (SiO_2; 20% to 50% EtOAc in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (151 mg, 0.84 mmol, 93% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.13 (dd, J = 5.1, 1.2 Hz, 1H, H_{10}), 6.93 (dd, J = 5.1, 3.4 Hz, 1H, H_9), 6.83–6.82 (m, 1H, H_8), 5.76 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H, H_3), 5.09–4.99 (m, 2H, H_4), 3.02 (t, J = 6.9 Hz, 2H, H_5), 2.93–2.89 (m, 2H, H_6), 2.70 (t, J = 6.9 Hz, 2H, H_1), 2.27–2.22 (m, 2H, H_2), 1.50 (s, 1H, N<u>H</u>); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 142.7 (C_7), 136.4 (C_3), 126.9 (C_8 or C_9 or C_{10}), 125.09 (C_8 or C_9 or C_{10}), 125.05 (C_8 or C_9 or C_{10}), 123.6 (C_8 or C_9 or C_{10}), 116.5 (C_4), 51.2 (C_5), 48.7 (C_1), 34.4 (C_2), 30.6 (C_6); **IR** (film, cm^{-1}): 3075, 2919, 2814, 1639, 1438, 1363, 1240, 1122, 1041, 994, 912, 849, 821, 690; **HRMS** (NSI+): *m/z* calcd for $C_{10}H_{16}N_1S_1$, $[M+H]^+$, 182.0998; found 182.0994 (Δ = -2.3 ppm).

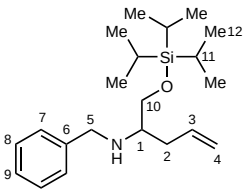


N-(2-((1-Methyl-1*H*-tetrazol-5-yl)thio)ethyl)but-3-en-1-amine **(S12).** {2-[(1-Methyl-1H-tetrazol-5-yl)thio]ethyl}amine hydrochloride (587 mg, 3.0 mmol, 3.8 equiv.), 4-bromobut-1-ene (78 µL, 0.8 mmol, 1.0 equiv.), NaI (5.0 mg, 33 µmol, 4.0 mol%), K_2CO_3 (414 mg, 3.0 mmol, 3.8 equiv.) and EtOH (2.5 mL, 0.40 M) were heated at reflux for 10 h. The resulting solution was conc. *in vacuo*, redissolved in CH_2Cl_2 (10 mL), washed with aq. NaOH (10 mL, 10% w/v), dried over $MgSO_4$ and conc. *in vacuo.* The resulting crude mixture was purified by column chromatography (SiO_2; 0% to 4% MeOH:aq. NH_3 (9:1) in CH_2Cl_2) to afford the title compound as a pale yellow oil (83 mg, 0.38 mmol, 48% yield). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 5.76 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H, H_3), 5.10–5.02 (m, 2H, H_4), 3.91 (s, 3H, H_8), 3.48 (t, J = 6.4 Hz, 2H, H_6), 3.05 (t, J = 6.4 Hz, 2H, H_5), 2.71 (t, J = 6.8 Hz, 2H, H_1), 2.24 (dt, J = 6.8, 1.3 Hz, 2H, H_2), 1.36 (s, 1H, N<u>H</u>); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 154.5 (C_7), 136.2 (C_3), 116.8 (C_4), 48.3 (C_1), 48.2 (C_5), 34.3 (C_2), 33.9 (C_6), 33.5 (C_8); **IR** (film, cm^{-1}): 3317, 3075, 2980, 2928, 2817, 1639, 1460, 1409, 1387, 1278, 1228, 1169, 1119, 998, 913, 703; **HRMS** (NSI+): *m/z* calcd for $C_8H_{16}N_5S_1$, $[M+H]^+$, 214.1121; found 214.1121 (Δ = 0.0 ppm).



N-(3-(1*H*-Imidazol-1-yl)propyl)but-3-en-1-amine (**S13**). 1-(3-Aminopropyl)imidazole (1.43 mL, 12 mmol, 4.0 equiv.), 4-bromobut-1-ene (0.30 mL, 3.0 mmol, 1.0 equiv.), NaI (30 mg, 0.20 mmol, 15 mol%) and EtOH (8 mL, 0.40 M) were heated at 80 °C in a sealed tube for 10 h. The resulting solution was conc. *in vacuo* and purified by column chromatography (SiO_2; 0% to 10% MeOH:aq. NH_3 (9:1) in CH_2Cl_2) to afford the title compound as a pale yellow oil (206 mg, 1.1 mmol, 38% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.46 (s, 1H, H_8), 7.04 (s, 1H, H_{10}), 6.90 (s, 1H, H_9), 5.76 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H, H_3), 5.09–5.02 (m, 2H, H_4), 4.02 (t, J = 6.9 Hz, 2H, H_7), 2.64 (t, J = 6.8 Hz, 2H, H_5), 2.57 (t, J = 6.8 Hz, 2H, H_1), 2.22 (q, J = 6.8 Hz, 2H, H_2), 1.91 (quintet, J = 6.9 Hz, 2H, H_2), 1.56 (s, 1H, N<u>H</u>); **^{13}C NMR** (101 MHz;

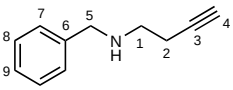
$CDCl_3$): δ 137.3 (C_8), 136.4 (C_3), 129.5 (C_{10}), 118.9 (C_9), 116.6 (C_4), 48.9 (C_1), 46.3 (C_5), 44.9 (C_7), 34.3 (C_2), 31.5 (C_6); **IR** (film, cm^{-1}): 3291, 2930, 1640, 1509, 1456, 1282, 1229, 1109, 1079, 915, 741; **HRMS** (NSI+): *m/z* calcd for $C_{10}H_{18}N_3$, $[M+H]^+$, 180.1501; found 180.1505 (Δ = 2.2 ppm).



N-Benzyl-1-((triisopropylsilyl)oxy)pent-4-en-2-amine (**S14**). **Step 1** To a stirred solution of 2-aminopent-4-enoic acid (1.0 g, 8.7 mmol) in anhydrous ethanol (10 mL) under N_2 was added thionyl chloride (1.9 mL, 26 mmol) dropwise at 0 °C. The resulting solution was warmed to room temperature over 16 h and the solvent removed *in vacuo*. The resulting residue was triturated with diethyl ether to yield ethyl 2-aminopent-4-enoate hydrochloride **S14a** as a white solid (1.0 g, 5.8 mmol, 67% yield), which was used without further purification. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 5.78 (app. sxt, J = 7.5 Hz, 1H), 5.33 (d, J = 6.8 Hz, 1H), 5.30 (s, 1H), 4.33 (qt, J = 7.1 Hz, 2H), 4.24 (t, J = 5.8 Hz, 1H), 2.82–2.68 (m, 2H), 1.31 (t, J = 7.0 Hz, 3H).

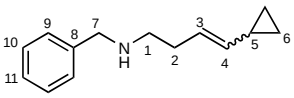
Step 2. To a stirred solution of ethyl 2-aminopent-4-enoate hydrochloride **S14a** (0.90 g, 5.0 mmol) from step 1, sodium bicarbonate (0.42 g, 5.5 mmol) and 4Å molecular sieves (1.0 g) in anhydrous MeOH was added benzaldehyde (0.51 mL, 5.0 mmol) at room temperature under N_2. The resulting solution was stirred for 16 h, filtered over Celite® and the solvent removed *in vacuo*. The resulting residue was rigorously dried under hi-vac and dissolved in anhydrous THF (25 mL) under N_2. The resulting solution was cooled to 0 °C, treated portion-wise with lithium aluminium hydride (0.57 g, 15 mmol), and warmed to room temperature over 2 h. The mixture was subsequently cooled to 0 °C and quenched with water (0.75 mL), 10% aqueous NaOH (1.0 mL) and water (2.0 mL). Additional diethyl ether and magnesium sulfate were added, and the mixture was filtered over Celite® and washed with copious amounts of diethyl ether and hot CH_2Cl_2. The solvent was removed *in vacuo* to afford 2-(benzylamino)pent-4-en-1-ol **S14b** (0.91 g, 4.8 mmol, 95% yield) as a pale yellow oil, which was used without further purification. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.83–5.73 (m, 1H), 5.15 (app. d, J = 6.4 Hz, 1H), 5.11 (app. s, 1H), 3.85 (d, J = 13.0 Hz, 1H), 3.80 (d, J = 13.0 Hz, 1H), 3.70 (dd, J = 4.1, 10.7 Hz, 1H), 3.38 (dd, J = 5.6, 10.7, 1H), 2.80 (qd, J = 4.1, 6.3 Hz, 1H), 2.29 (app. qt, J = 6.9 Hz, 2H), 2.10 (br. s, 1H);

Step 3. *N*-Benzyl-1-((triisopropylsilyl)oxy)pent-4-en-2-amine (**S14**). Triisopropylsilyl chloride (0.96 mL, 4.5 mmol) was added dropwise to a solution of 2-(benzylamino)pent-4-en-1-ol **S14b** (0.91 mL, 4.8 mmol) form step 2 and triethylamine (1.0 mL, 7.2 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C. The resulting solution was allowed to warm to room temperature over 16 h and was quenched with H_2O (20 mL). The organics were separated and washed with additional H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4 and removed *in vacuo*. The crude oil was purified by flash column chromatography (gradient elution: 0 to 10% EtOAc in 40°–60° Petroleum ether) to provide the desired amine as a colourless oil (0.38 g, 1.0 mmol, 23% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.33–7.29 (m, 4H, $H_{7\text{-}8}$), 7.25–7.21 (m, 1H, H_9), 5.81 (ddt, J = 17.2, 10.1, 7.1 Hz, 1H, H_3), 5.11–5.04 (m, 2H, H_4), 3.85 (d, J = 13.2 Hz, 1H, H_5), 3.81 (d, J = 13.2 Hz, 1H, H_5), 3.69 (dd, J = 9.8, 5.1 Hz, 1H, H_{10}), 3.62 (dd, J = 9.8, 6.4 Hz, 1H, H_{10}), 2.78–2.72 (m, 1H, H_1), 2.28–2.23 (m, 2H, H_2), 1.05 (q, J = 4.4 Hz, 21H, $H_{11\text{-}12}$); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 140.9 (C_6), 135.9 (C_3), 128.5 (C_7 or C_8), 128.2 (C_7 or C_8), 126.9 (C_9), 117.1 (C_4), 65.3 (C_{10}), 58.4 (C_1), 51.7 (C_5), 36.1 (C_2), 18.2 (C_{12}), 12.1 (C_{11}); **IR** (film, cm^{-1}): 3026, 2942, 2865, 1640, 1462, 1106, 1067, 995, 913, 881, 789, 730; **HRMS** (NSI+): *m/z* calcd for $C_{21}H_{38}NOSi$, $[M-H]^+$, 348.2723; found, 348.2723 (Δ = 0.0 ppm).

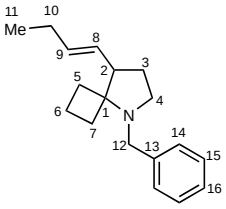


N-Benzylbut-3-en-1-amine (**S15**). Benzylamine (4.6 mL, 42 mmol, 4.9 equiv.), 4-bromobut-1-yne (0.79 mL, 8.5 mmol, 1.0 equiv.), NaI (40 mg, 0.27 mmol, 3.0 mol%) and EtOH (20 mL, 0.40 M) were heated at 80 °C in a sealed tube for 10 h. The resulting solution was conc. *in vacuo*, redissolved in CH_2Cl_2 (50 mL), washed with aq. NaOH (50 mL, 10% w/v), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude mixture was purified by column chromatography (SiO_2; 20% to 50% EtOAc in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (0.95 g, 6.0 mmol, 70% yield). Spectral data was in agreement with literature.[525] **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.34–7.30 (m, 4H, $H_{7\text{-}8}$), 7.28–7.23 (m, 1H, H_9), 3.82 (s,

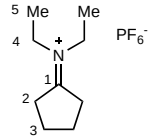
2H, H_5), 2.81 (t, J = 6.6 Hz, 2H, H_1), 2.42 (td, J = 6.6, 2.6 Hz, 2H, H_2), 1.99 (t, J = 2.6 Hz, 1H, H_4), 1.62 (s, 1H, N<u>H</u>).



N-Benzyl-4-cyclopropylbut-3-en-1-amine **(131a).** To a solution of (cyclopropylmethyl)triphenyl phosphonium bromide (2.9 g, 7.3 mmol, 1.3 equiv.) in THF (8 mL) was added a solution of KO^{t}Bu (1.6 g, 14 mmol, 2.5 equiv.) in THF (15 mL) at 0 °C over 20 min. The mixture was then allowed to stir for 30 min at rt before a solution of *tert*-butyl benzyl(3-oxopropyl) carbamate[526] (1.5 g, 5.8 mmol, 1.0 equiv.) in THF (3.0 mL) was added dropwise. The resulting solution was stirred at rt for 1 h and then quenched with aq. HCl (25 mL, 1 M). The phases were separated and the aqueous phase was extracted by EtOAc (3 x 50 mL), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude mixture was used immediately without further purification. To a solution of crude alkene (1.0 g, 3.3 mmol, 1.0 equiv.) in CH_2Cl_2 (27 mL, 0.12 M) was added trifluoroacetic acid (0.40 mL) dropwise and the resulting solution was stirred for 2 h at rt. The reaction was quenched by the addition of aq. NaOH (10 mL, 10% w/v), the phases were separated and the aqueous phase was extracted by CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$ and conc. *in vacuo*. The resulting crude mixture was purified by column chromatography (SiO_2; 0% to 50% EtOAc in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (120 mg, 0.60 mmol, 10% yield, 1.2:1 Z:E). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.35–7.30 (m, 4H, $H_{9\text{-}10}$), 7.27–7.22 (m, 1H, H_{11}), 5.50–5.43 (dt, J = 14.9, 7.3 Hz, 1H, H_3 *E*), 5.29 (dt, J = 10.7, 7.4 Hz, 1H, H_3 *Z*), 5.04 (ddt, J = 15.2, 8.6, 1.2 Hz, 1H, H_4 *E*), 4.86–4.81 (m, 1H, H_4 cis), 3.82 (s, 2H, H_7 cis), 3.79 (s, 2H, H_7 *E*), 2.72 (t, J = 6.9 Hz, 2H, H_1 *Z*), 2.66 (t, J = 6.9 Hz, 2H, H_1 *E*), 2.41 (qd, J = 7.1, 1.4 Hz, 2H, H_2 *Z*), 2.21 (qd, J = 6.9, 1.3 Hz, 2H, H_2 *E*), 1.63–1.30 (m, 2H, N<u>H</u> & H_5), 0.75–0.70 (m, 1H, H_6 *Z*), 0.68–0.63 (m, 1H, H_6 *E*), 0.32 (qt, J = 4.4, 2.2 Hz, 2H, H_6 *E* & *Z*); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 140.6 (C_8), 136.1 (C_4, *E* or *Z*), 136.1 (C_4, *E* or *Z*), 128.5 (C_{10}), 128.3 (C_9, *Z* or *E*), 128.2 (C_9, *Z* or *E*), 127.0 (C_{11}), 125.4 (C_3, *Z* or *E*), 125.4 (C_3, *Z* or *E*), 54.1 (C_7), 49.3 (C_1, *Z* or *E*), 49.1 (C_1, *Z* or *E*), 33.1 (C_2 *E*), 28.4 (C_2 *Z*), 13.7 (C_5 *E*), 9.9 (C_5 *Z*), 7.1 (C_6), 6.6 (C_6); **IR (film, cm^{-1}):** 3000, 2908, 2809, 1454, 1115, 961, 731, 693; **HRMS** (NSI+): *m/z* calcd for $C_{14}H_{20}N_1$, $[M+H]^+$, 202.1590; found 202.1590 (Δ = -0.1 ppm).



(*E*)-5-Benzyl-8-(but-1-en-1-yl)-5-azaspiro[3.4]octane (**131b**). Prepared according to general procedure A using *N*-benzyl-4-cyclopropylbut-3-en-1-amine **131a** (40 mg, 0.20 mmol, 1.0 equiv.), cyclobutanone (45 µL, 0.60 mmol, 3.0 equiv.) and Ir(dMeppy)$_3$ (1.5 mg, 2.0 µmol, 1.0 mol%). The reaction mixture was irradiated for 24 h. The crude mixture after hydrolysis was purified by column chromatography (SiO_2; 0% to 3% EA in 40°–60° Petroleum ether) to afford the title compound as a pale yellow oil (25 mg, 0.10 mmol, 50% yield). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.36–7.28 (m, 4H, $H_{14\text{-}15}$), 7.25–7.20 (m, 1H, H_{16}), 5.65–5.49 (m, 2H, $H_{8\text{-}9}$), 3.86 (d, J = 13.4 Hz, 1H, H_{12}), 3.64 (d, J = 13.3 Hz, 1H, H_{12}), 2.65–2.57 (m, 1H, H_4), 2.55–2.45 (m, 2H, H_2 & H_4), 2.37–2.29 (m, 1H, H_5), 2.18–2.06 (m, 3H, H_7 & H_{10}), 1.92–1.79 (m, 3H, H_3 & H_5 & H_7), 1.65–1.46 (m, 3H, H_3 & H_6), 1.03 (t, J = 7.5 Hz, 3H, H_{11}); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 140.9 (C_{13}), 133.2 (C_9), 130.5 (C_8), 128.5 (C_{15}), 128.3 (C_{14}), 126.7 (C_{16}), 69.1 (C_1), 53.9 (C_{12}), 51.4 (C_2), 50.1 (C_4), 29.2 (C_7), 27.7 (C_3), 25.9 (C_{10}), 24.1 (C_5), 14.3 (C_{11}), 13.3 (C_6); **IR** (film, cm^{-1}): 3027, 2960, 2797, 1704, 1605, 1494, 1452, 1357, 1250, 1173, 969, 731, 695; **HRMS** (NSI+): *m/z* calcd for $C_{18}H_{26}N_1$, $[M+H]^+$, 256.2060; found 256.2061 (Δ = 0.5 ppm).



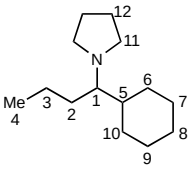
N-Cyclopentylidene-*N*-ethylethanaminium hexafluorophosphate (**67**). To a pre-dried flask under nitrogen, connected to a Dean-Stark trap and a reflux condenser, was added cyclopentanone (1.1, 12 mmol, 2.6 equiv.), diethylamine (0.62 mL, 6 mmol, 1.3.0 equiv.) and toluene (20 mL). To this stirred mixture was added NH_4PF_6 (1.5 g, 4.6 mmol, 1.0 equiv.) in one portion and the flask was immediately lowered into a pre-heated oil-bath. The vigorously stirred reaction was refluxed for 3 h, cooled to rt and filtered. The solids where washed with Et_2O (3 x 10 mL) and dried under high-vacuum to afford the title compound as a white crystalline solid (1.1g, 3.9 mmol, 85% yield). **^{1}H NMR** (400 MHz; CD_2Cl_2): δ 3.78 (q, J = 7.3 Hz, 4H, H_4), 2.88 (q, J = 4.6 Hz, 4H, H_2), 1.92–1.88 (m, 4H, H_3), 1.28 (t, J = 7.3 Hz, 6H, H_5); **^{13}C NMR** (101 MHz; CD_2Cl_2): δ 205.4 (C_1), 55.4 (C_4), 39.9 (C_2), 29.4 (C_3), 16.7 (C_5); **^{19}F NMR** (376 MHz; CD_2Cl_2): δ -73.2 (d, J = 712.5 Hz); **IR (film, cm^{-1}):** 2996, 2960, 2888, 1690, 1478, 1454, 1389, 1337,

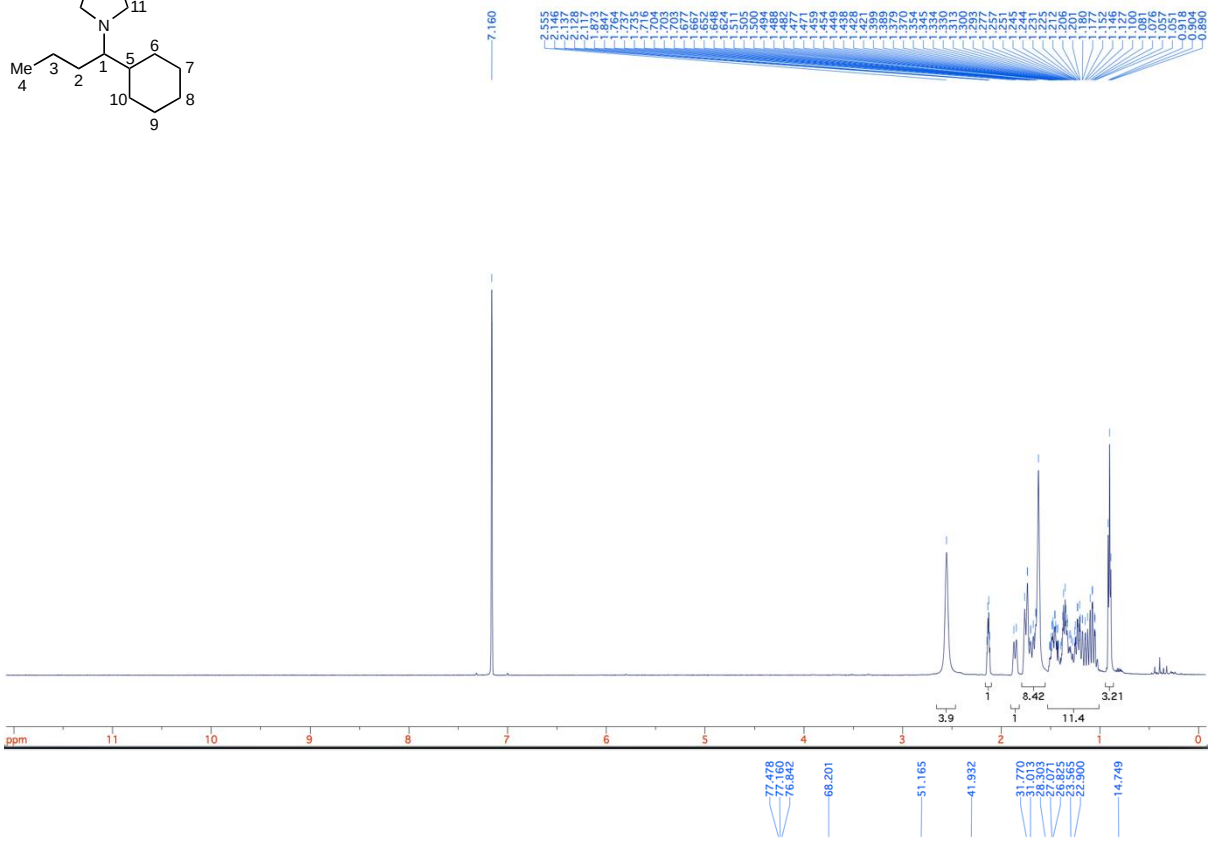
1236, 1111, 1056, 877, 822; **HRMS** (NSI+): *m/z* calcd for $C_9H_{18}N_1$, $[M+H]^+$, 140.1434; found 140.1432 (Δ = -1.0 ppm).

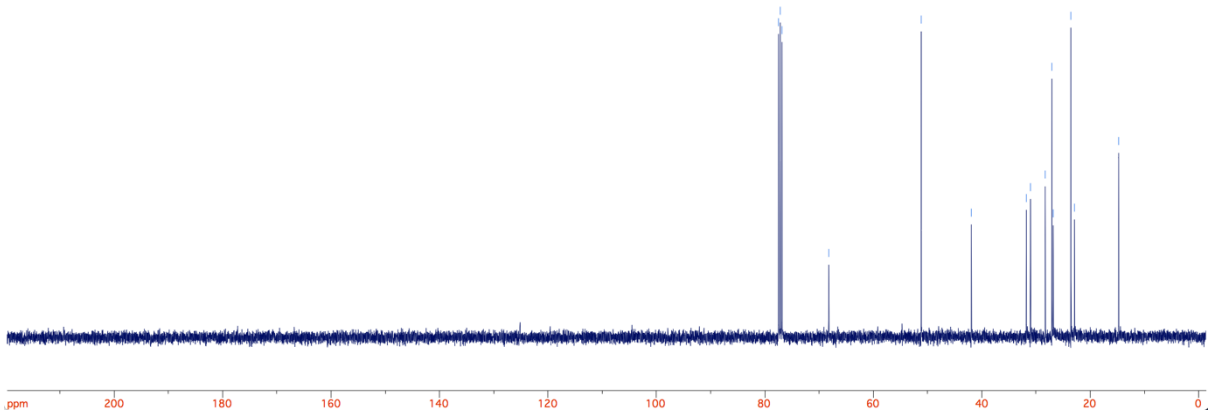
9 Appendix II – Spectra of synthesized compounds

9.1 Spectra for chapter 2

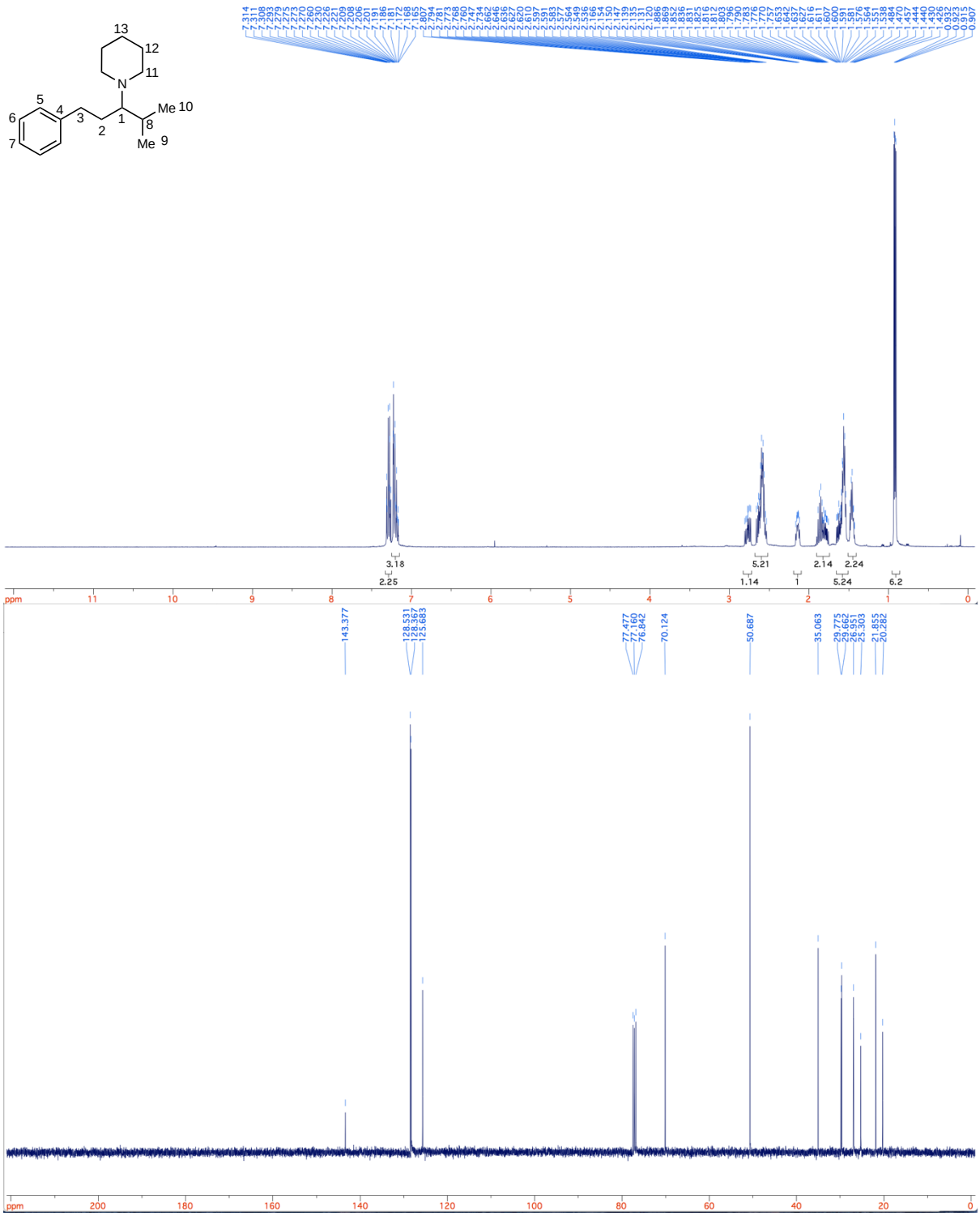
50b



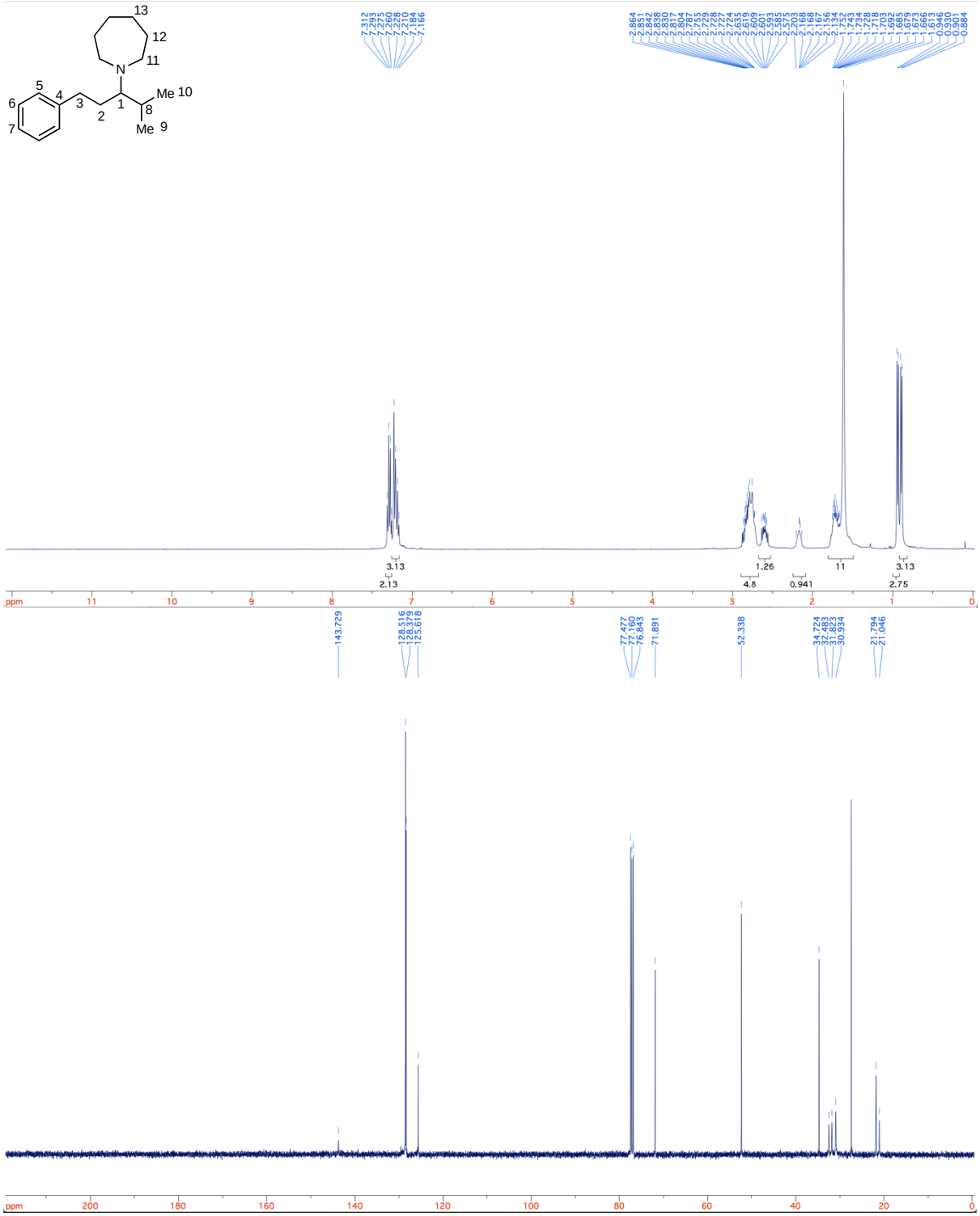




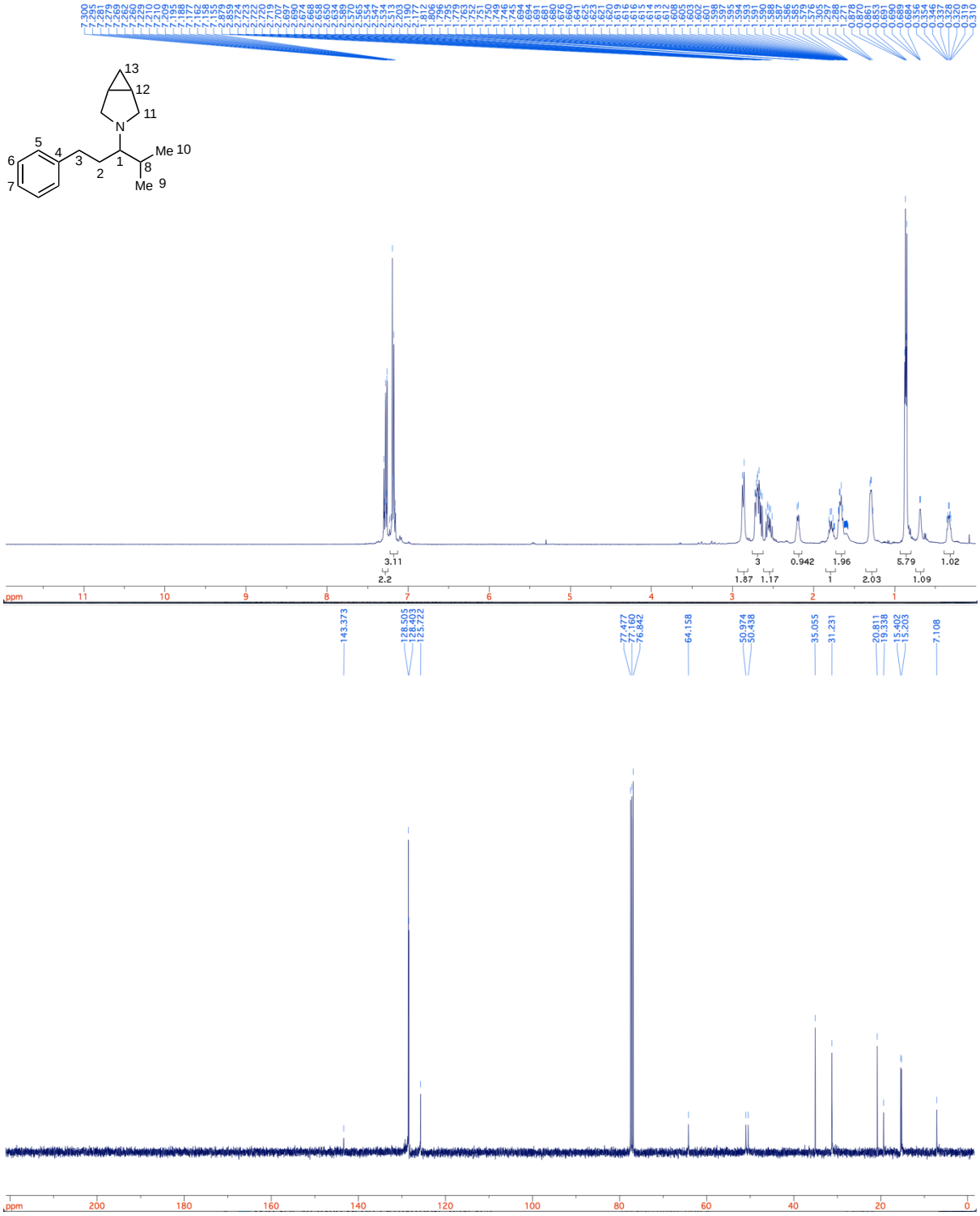
50c


13
12
11
N
5
4
3
1
Me 10
6
2
8
7
Me 9
3.18
2.25
5.21
1.14
2.14
1
2.24
5.24
6.2
ppm
143.377
128.531
128.317
125.683
77.477
77.160
76.842
70.124
50.687
35.063
29.775
29.667
26.951
25.303
21.855
20.282
ppm

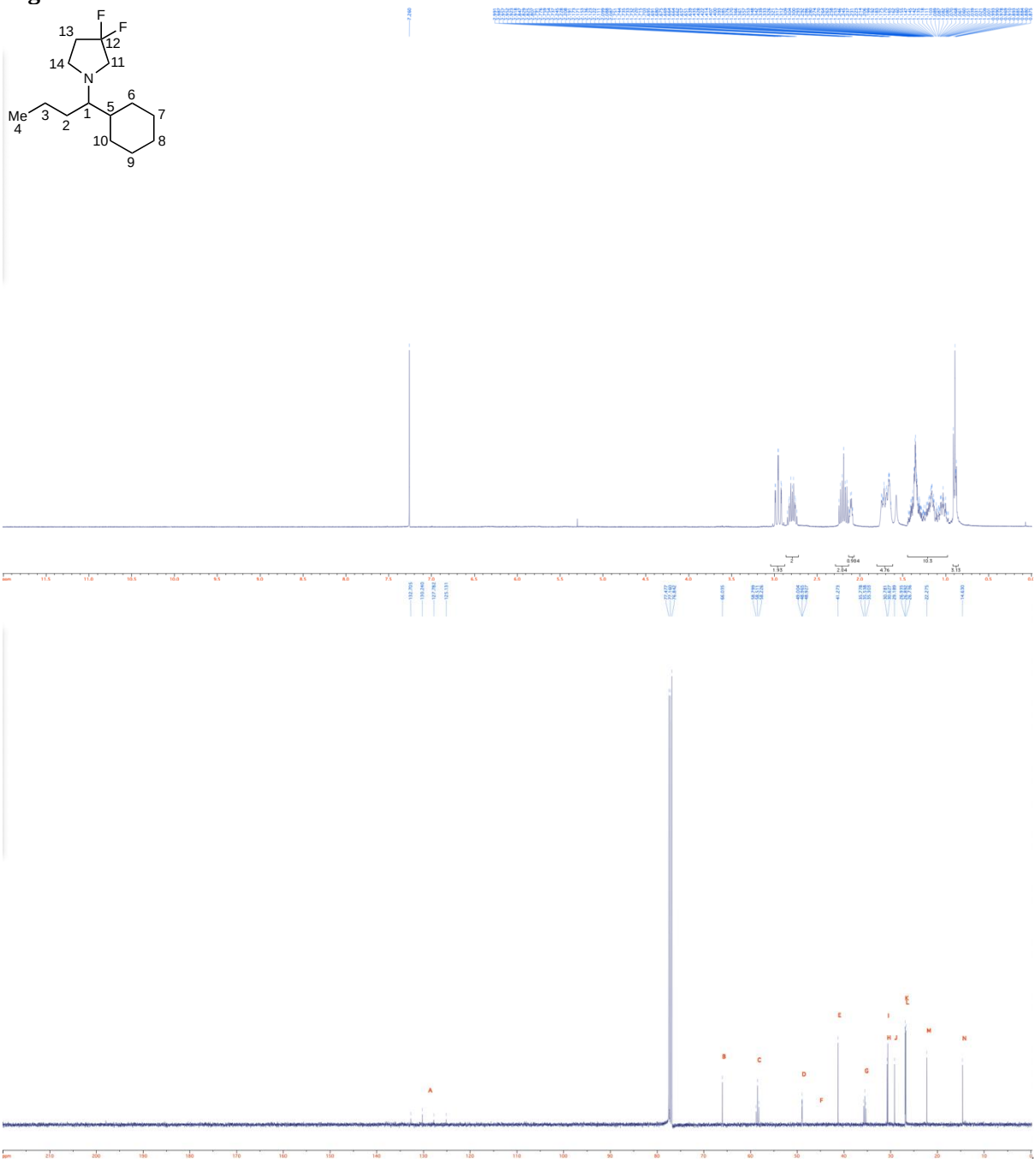
50d

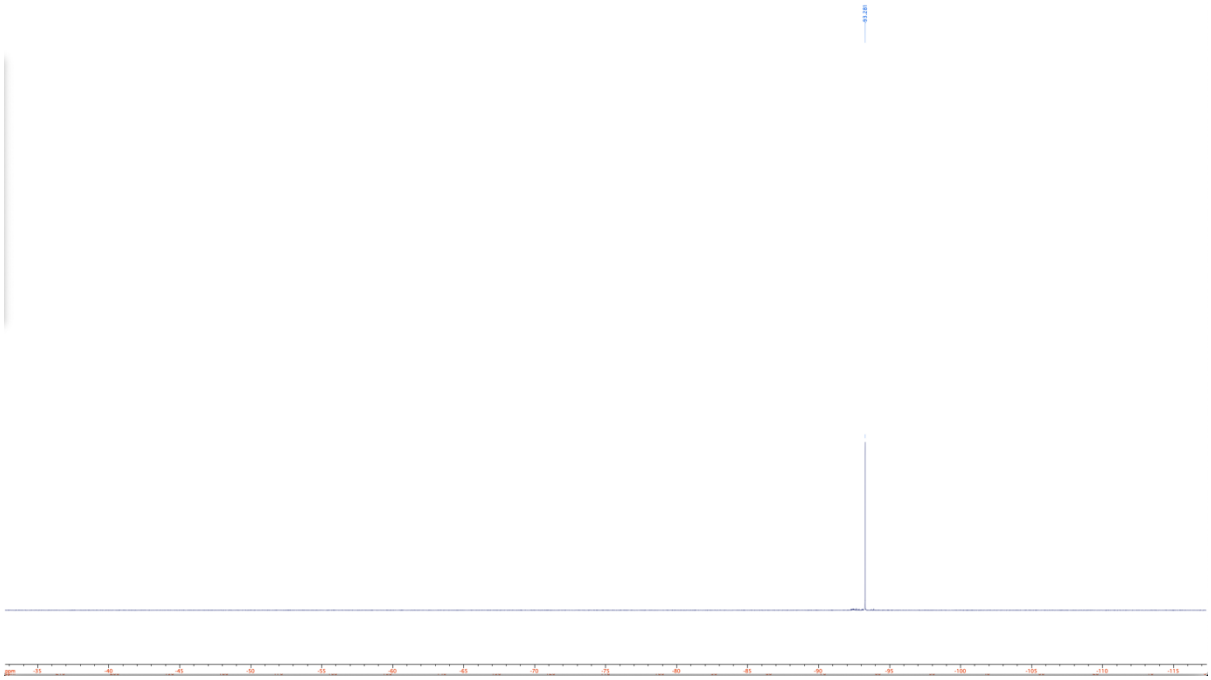

13
12
11
N
5
4
3
1
Me 10
6
2
8
7
Me 9
3.13
2.13
1.26
4.8
0.941
11
3.13
2.75
ppm
143.729
128.516
128.379
125.618
77.477
77.160
76.843
71.891
52.338
34.724
32.483
31.823
30.934
21.794
21.046
ppm

50e

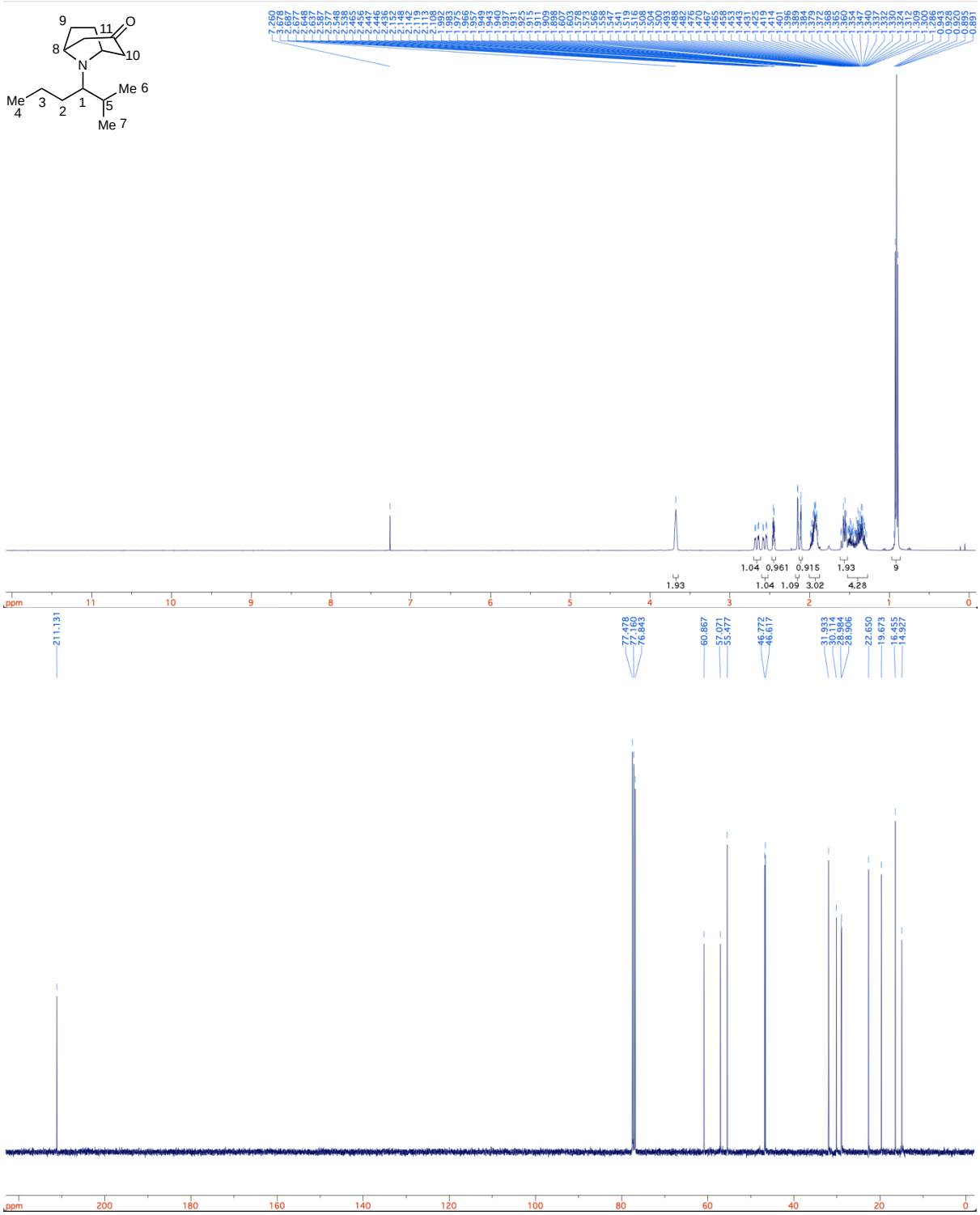

13
12
11
N
5
4
6
3
1
Me 10
2
8
7
Me 9
3.11
2.2
3
0.942
1.96
5.79
1.02
1.87
1.17
1
2.03
1.09
ppm
143.373
128.505
128.403
125.722
77.477
77.160
76.842
64.158
50.974
50.438
35.055
31.231
20.811
19.338
15.402
15.203
7.108

50g

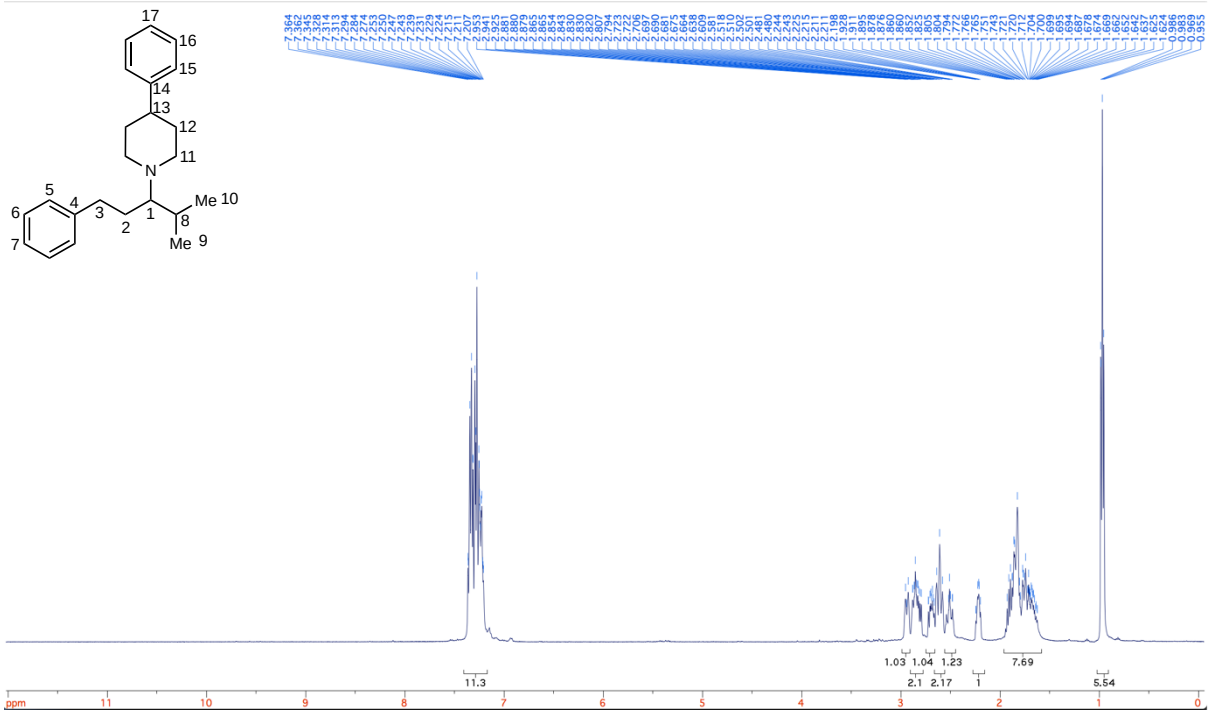


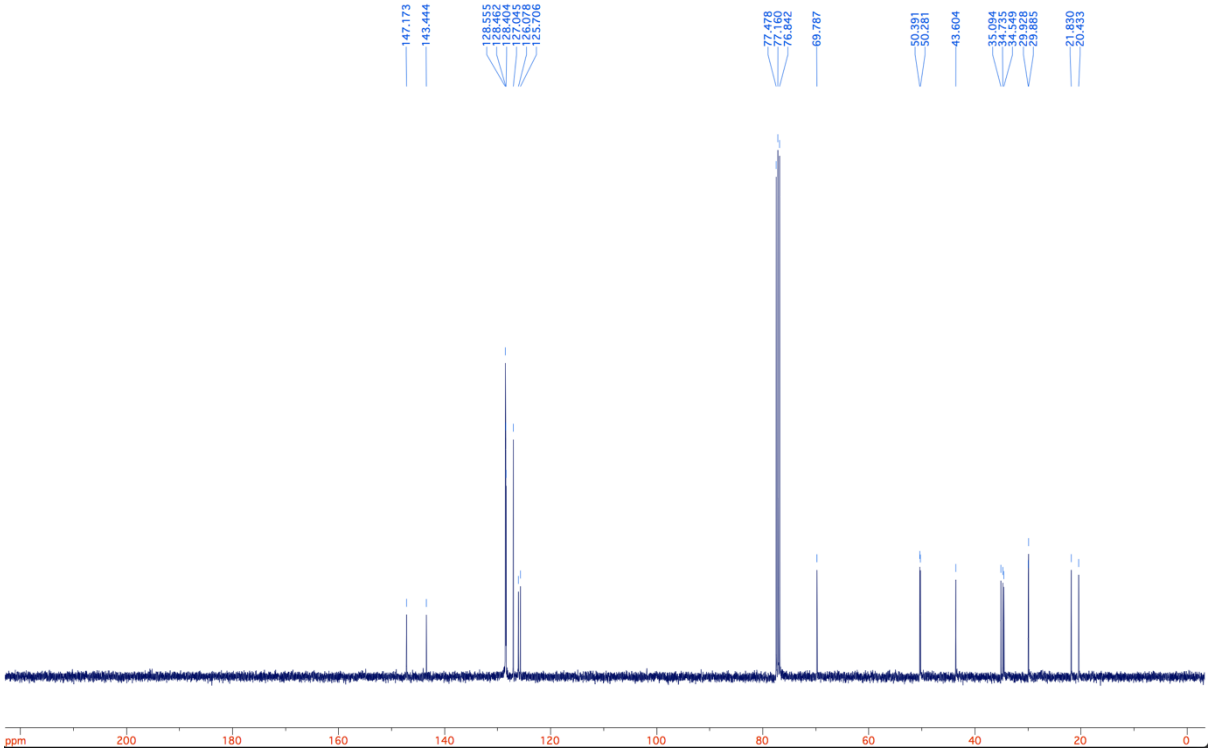


50i

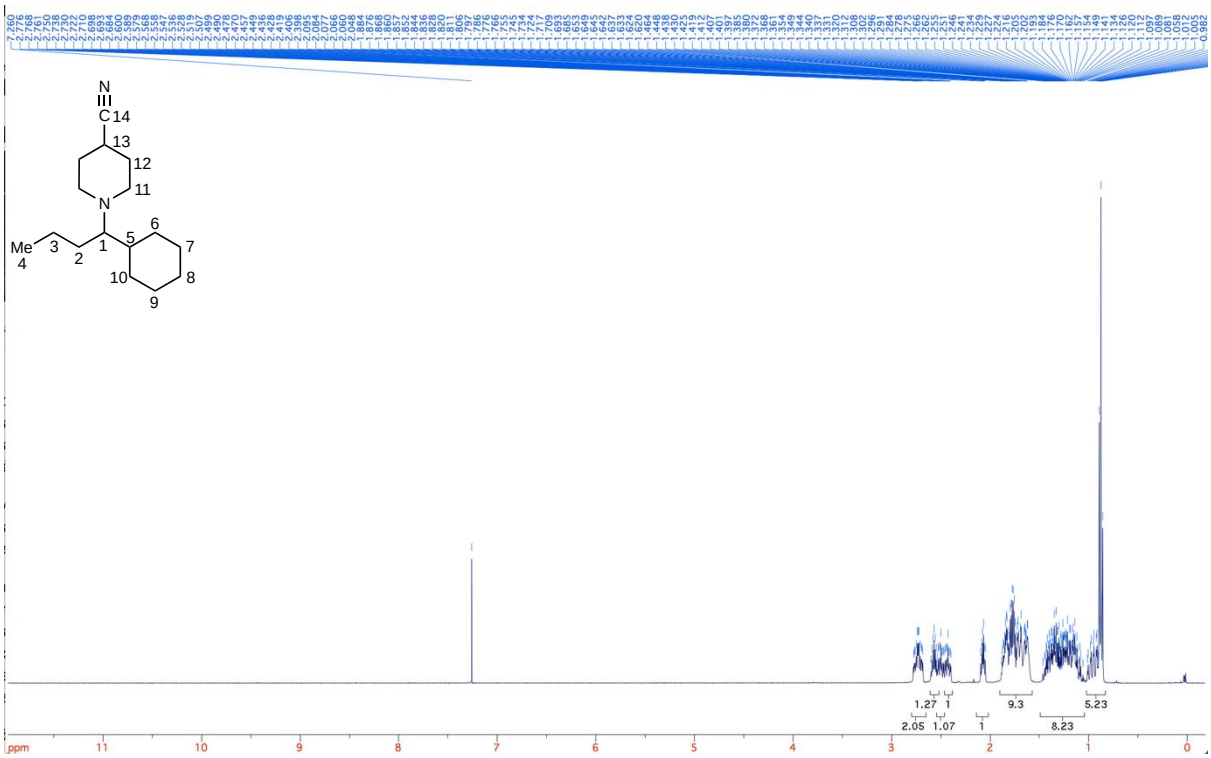

9
11
O
8
10
N
Me 6
Me
4
3
2
1
5
Me 7
1.04 0.961 0.915 1.93 9
1.93 1.04 1.09 3.02 4.28
ppm
211.131
77.478
77.160
76.843
60.867
57.071
55.477
46.772
46.617
31.933
30.114
29.984
28.906
22.650
19.673
16.455
14.327

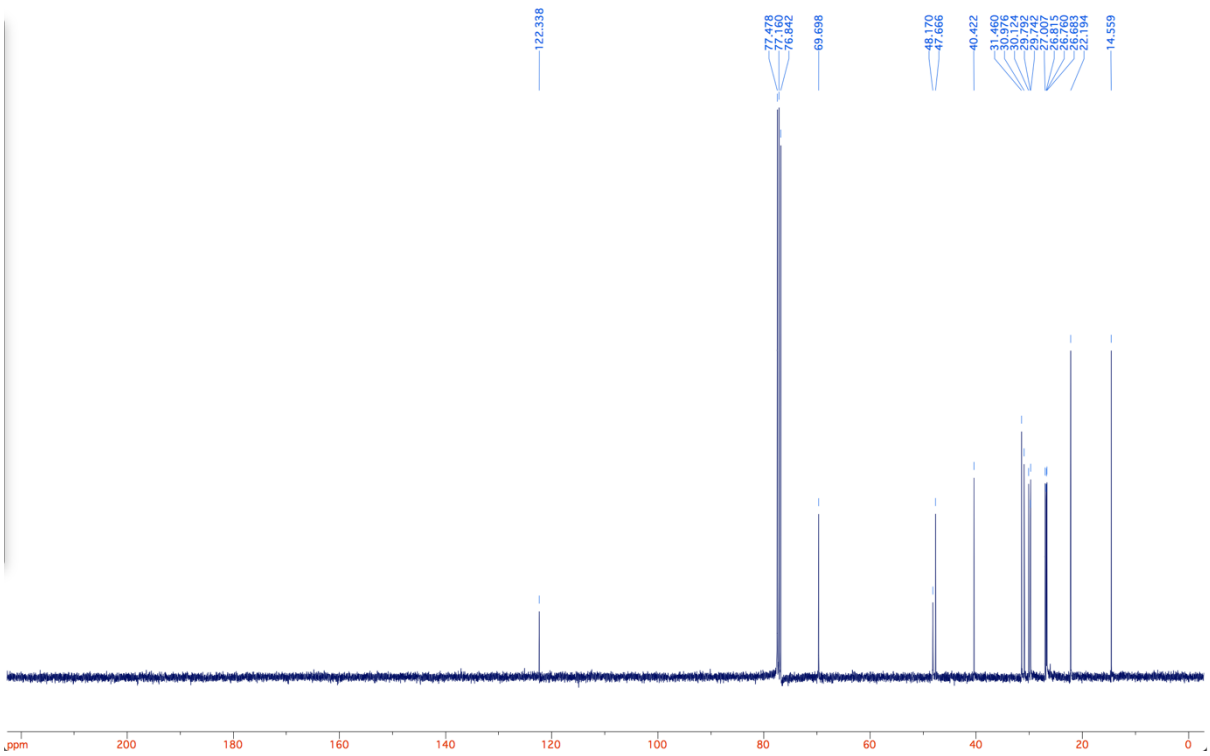
51a


17
16
15
14
13
12
11
N
5
4
3
1
Me 10
6
2
8
7
Me 9
11.3
1.03 1.04 1.23
2.1 2.17 1
7.69
5.54
ppm

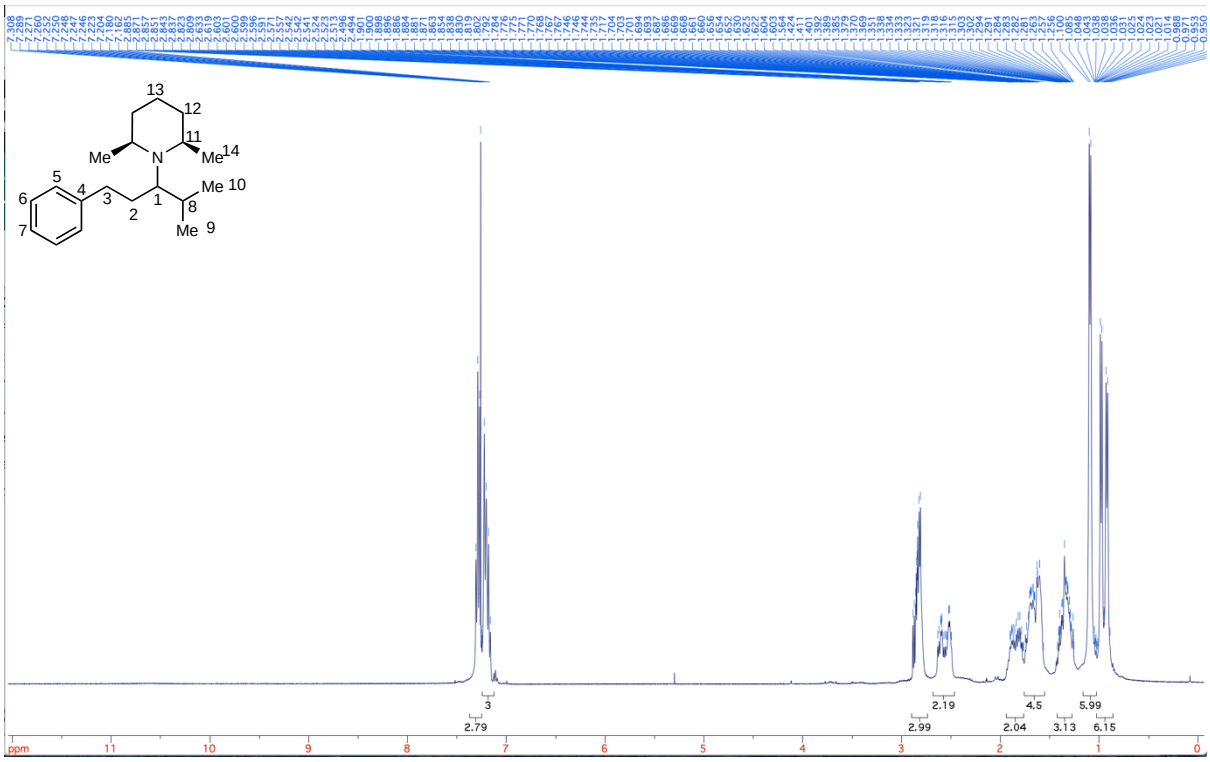

147.173
143.444
128.555
128.446
128.404
127.045
126.078
125.706
77.478
77.160
76.842
69.787
50.391
50.281
43.604
35.094
34.735
34.549
29.928
29.885
21.830
20.433
ppm

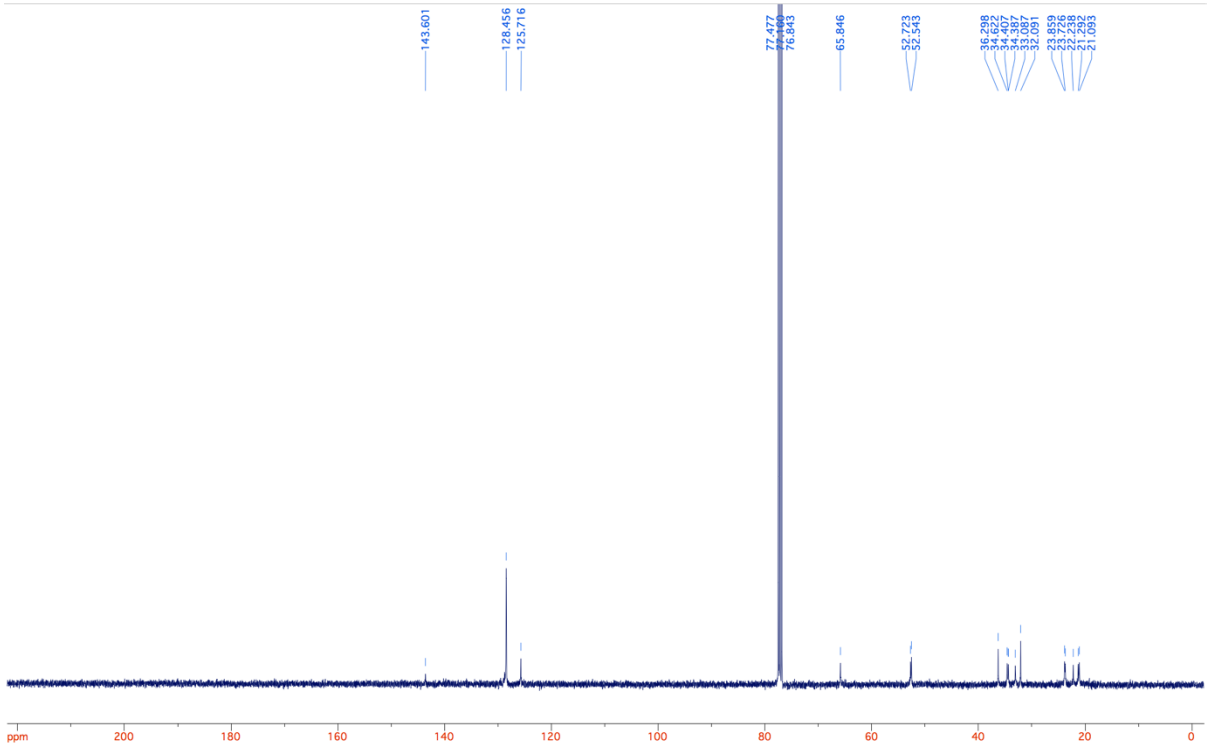
51b


N
C 14
13
12
11
N
Me
4
3
2
1
5
6
7
8
9
10
1.27
1
9.3
5.23
2.05
1.07
1
8.23
ppm

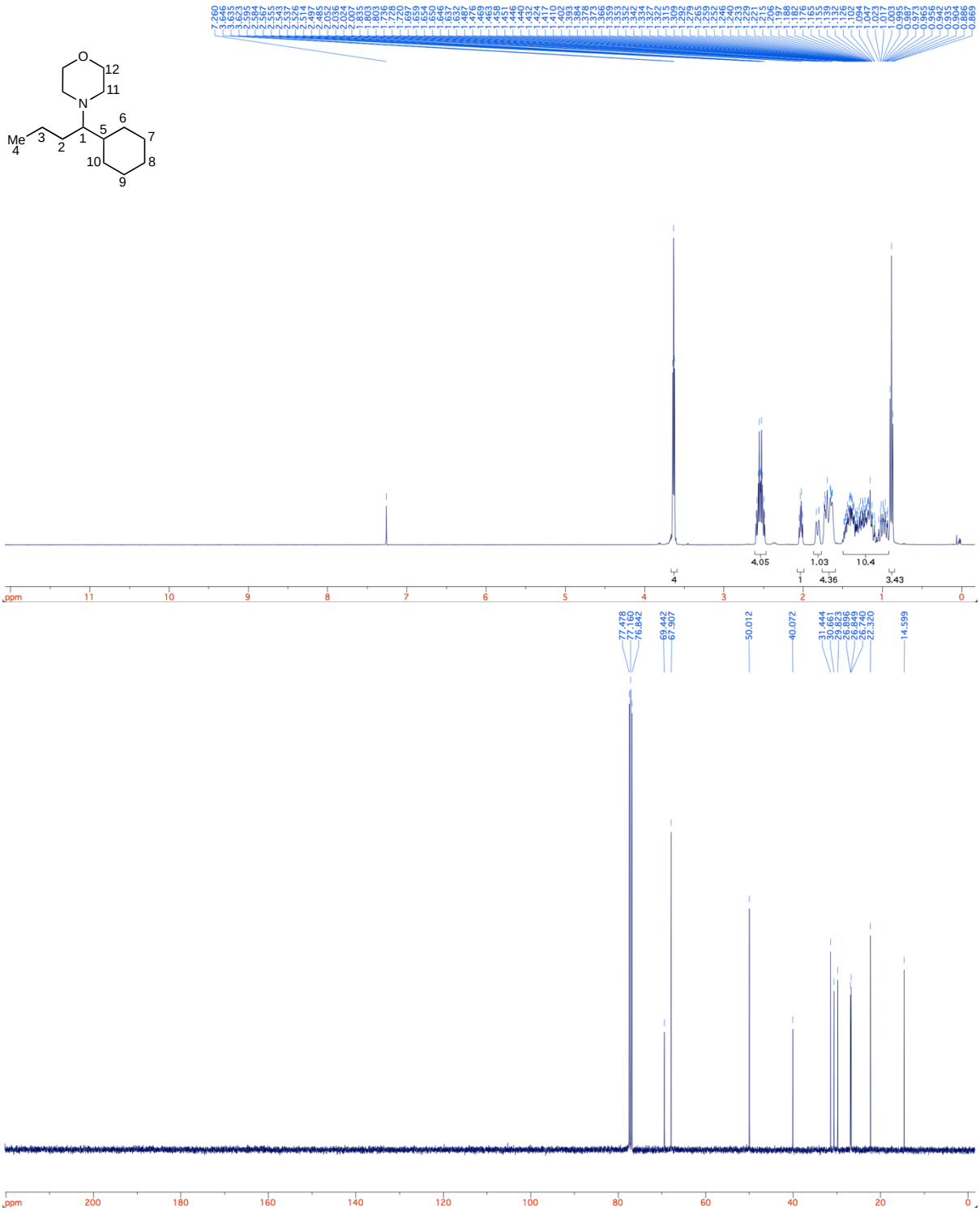

122.338
77.478
77.060
76.642
69.698
48.170
47.666
40.422
31.460
30.976
30.724
29.792
29.742
29.007
26.811
26.760
26.683
22.194
14.559
ppm

51c

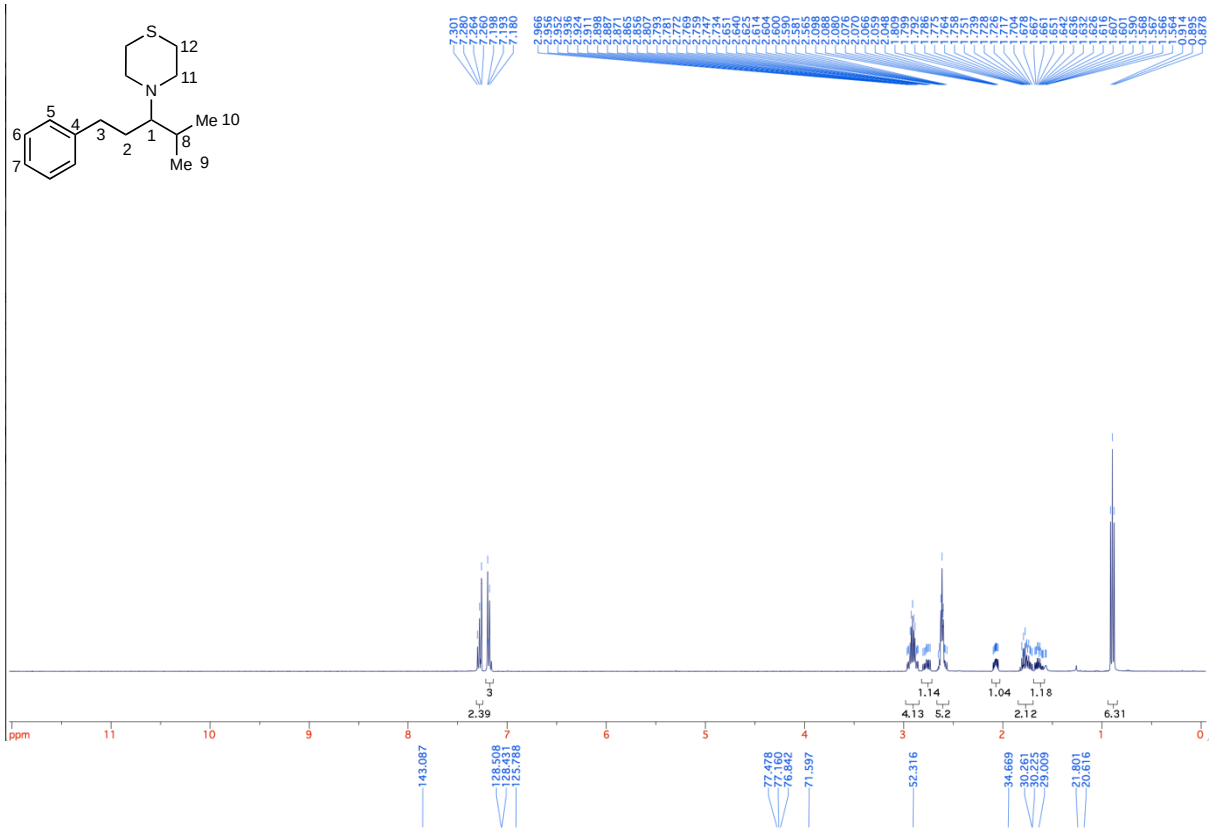

13
12
11
Me
N
Me 14
5
4
3
2
1
6
7
Me 10
8
Me 9
3
2.79
2.19
2.99
4.5
2.04
3.13
5.99
6.15
ppm

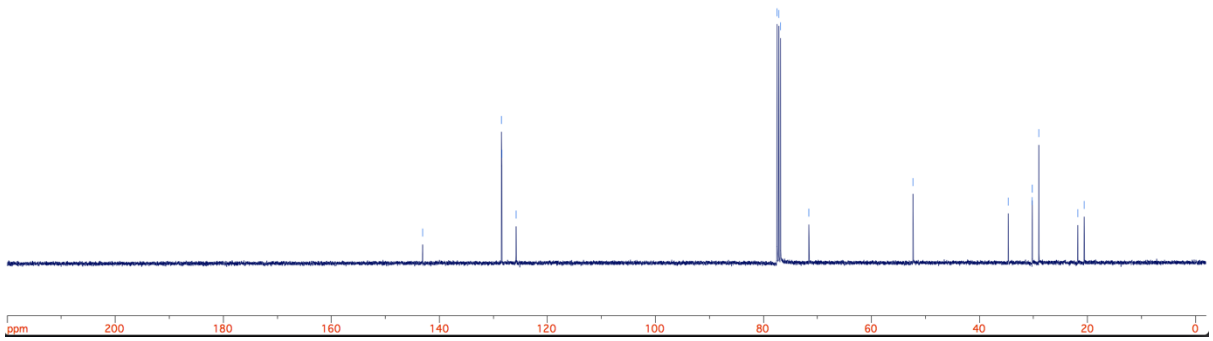

143.601
128.456
125.716
77.477
77.163
76.843
65.846
52.723
52.543
36.298
34.622
34.407
34.187
33.087
32.091
23.859
23.726
23.228
21.292
21.093
ppm

51e

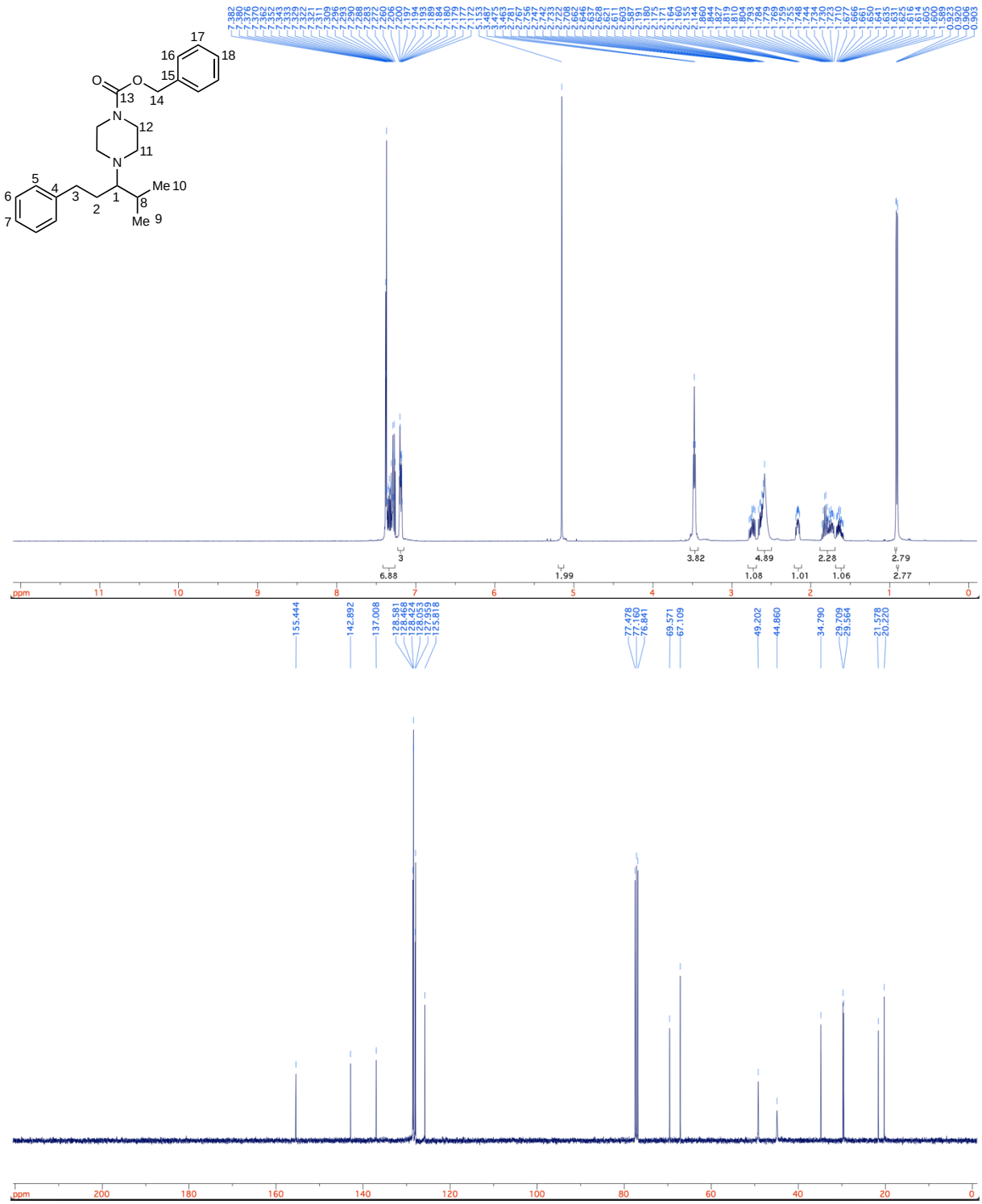

O
N
Me
4
3
2
1
5
6
7
8
9
10
11
12
4.05
1.03
10.4
4
1
4.36
3.43
ppm
77.478
77.160
76.842
69.442
67.907
50.012
40.072
31.444
30.661
29.823
26.846
26.649
26.740
22.320
14.599

51f

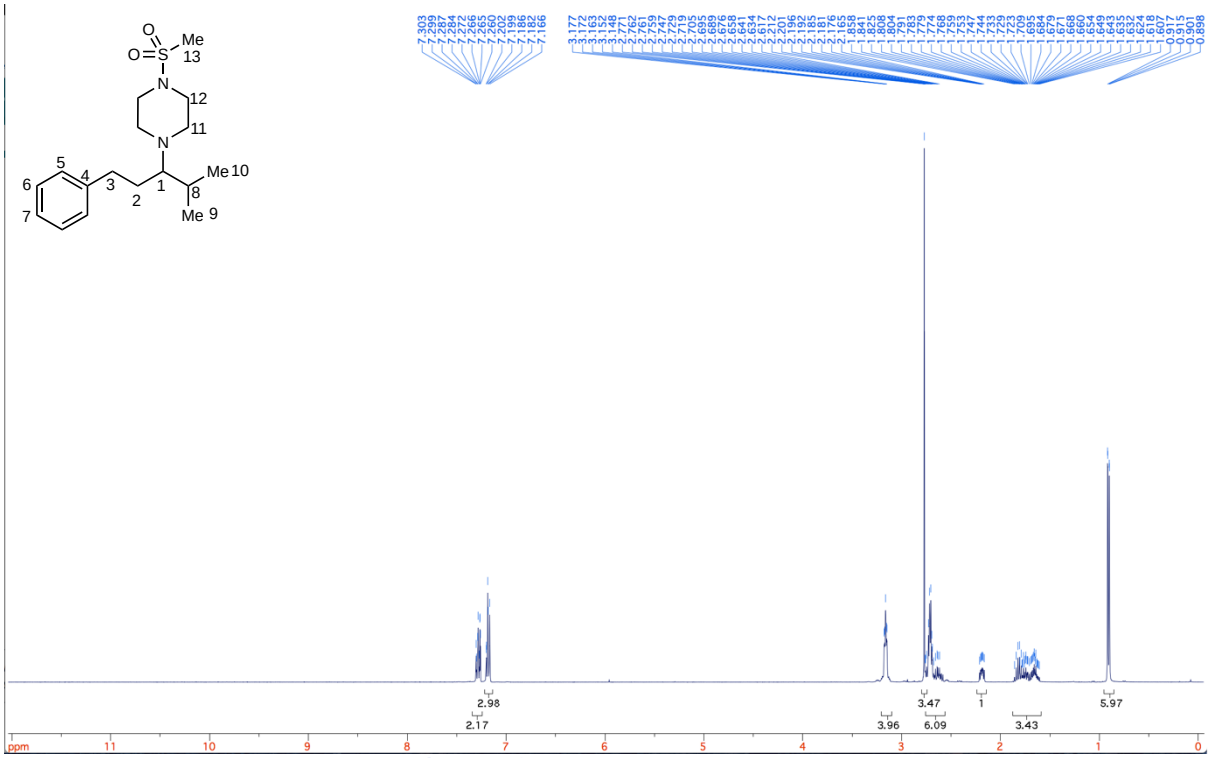

S
12
11
N
5
4
3
1
Me 10
6
2
8
7
Me 9
7.301
7.280
7.264
7.260
7.198
7.193
7.180
2.966
2.956
2.952
2.936
2.924
2.911
2.899
2.887
2.871
2.865
2.856
2.807
2.793
2.781
2.772
2.769
2.759
2.747
2.737
2.734
2.651
2.640
2.625
2.614
2.604
2.600
2.590
2.581
2.565
2.098
2.088
2.080
2.076
2.070
2.066
2.059
2.048
1.809
1.799
1.792
1.786
1.775
1.765
1.764
1.758
1.751
1.739
1.728
1.726
1.717
1.704
1.678
1.667
1.661
1.651
1.642
1.632
1.626
1.616
1.607
1.601
1.590
1.588
1.567
1.566
1.554
0.914
0.895
0.878
3
2.39
1.14
4.13
5.2
1.04
1.18
2.12
6.31
ppm
11
10
9
8
7
6
5
4
3
2
1
0
143.087
128.508
128.431
125.788
77.478
77.160
76.842
71.597
52.316
34.669
30.261
30.225
29.009
21.801
20.616

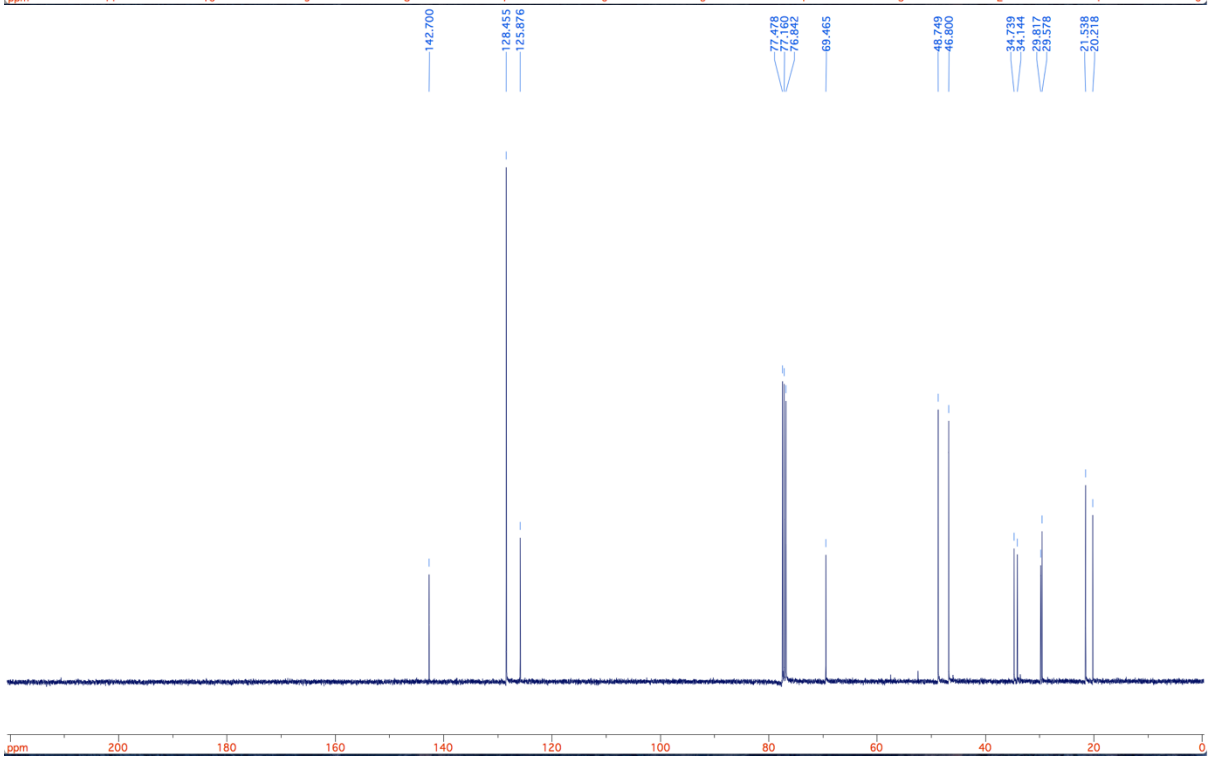

ppm
200
180
160
140
120
100
80
60
40
20
0

51g

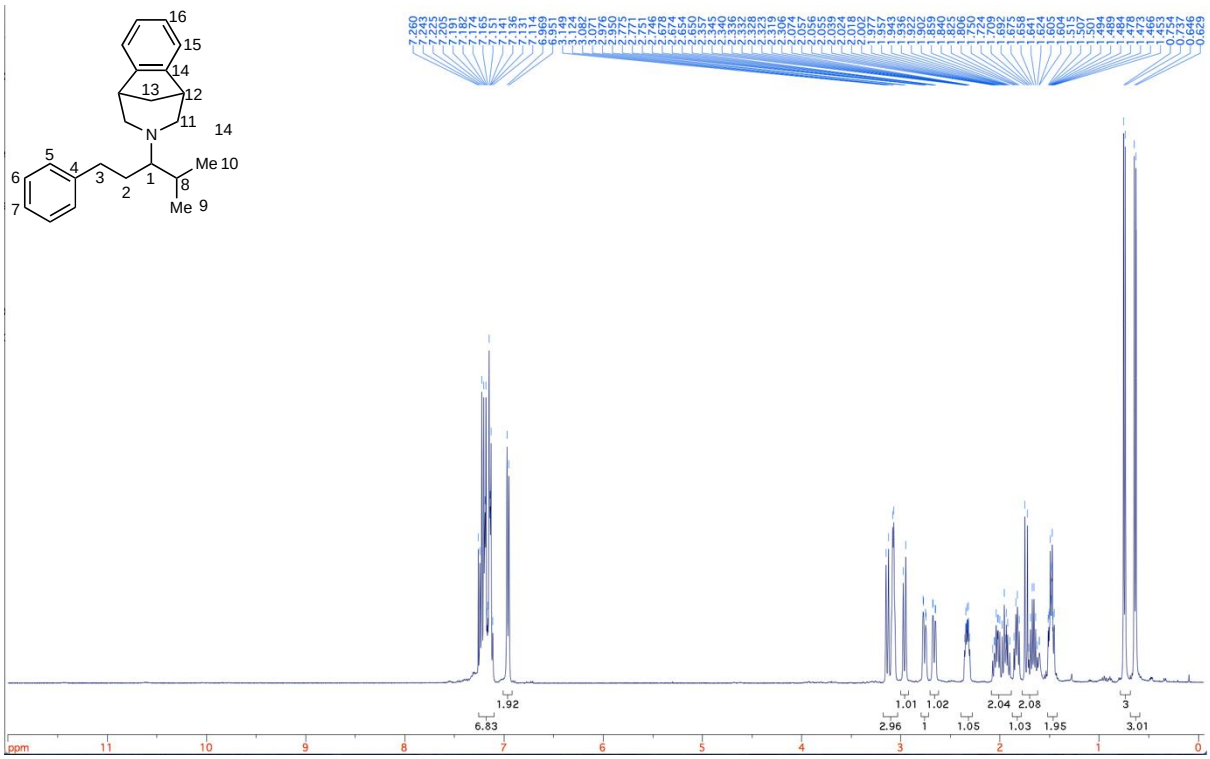

3
6.88
1.99
3.82
4.89
1.08
1.01
2.28
1.06
2.79
2.77
ppm
155.444
142.892
137.008
128.581
128.468
128.424
128.357
127.955
125.818
77.478
77.160
76.841
69.571
67.109
49.202
44.860
34.790
29.709
29.564
21.578
20.220

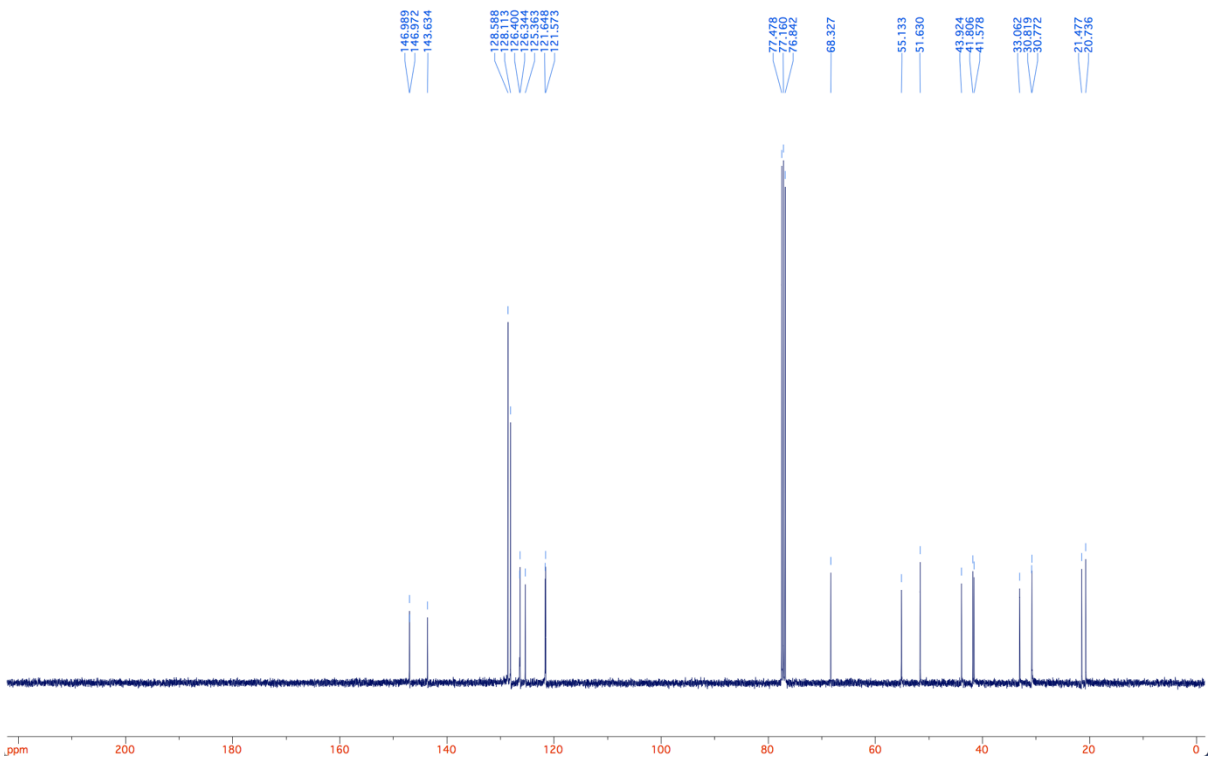
51h


Me
13
12
11
Me 10
Me 9
2.98
2.17
3.96
3.47
6.09
1
3.43
5.97
ppm

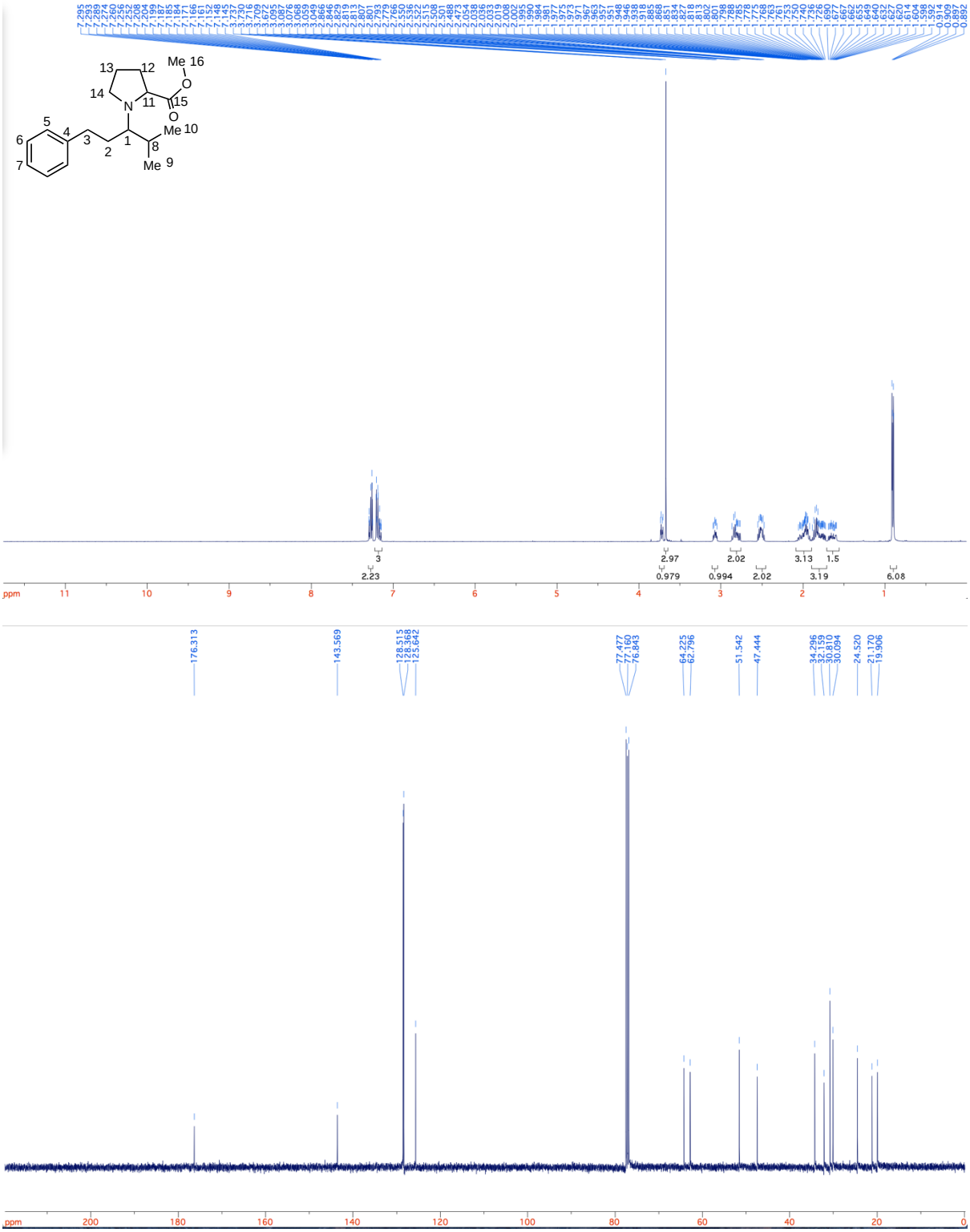

142.700
128.455
125.876
77.478
77.160
76.842
69.465
48.749
46.800
34.739
34.144
29.817
29.578
21.538
20.218
ppm

51i

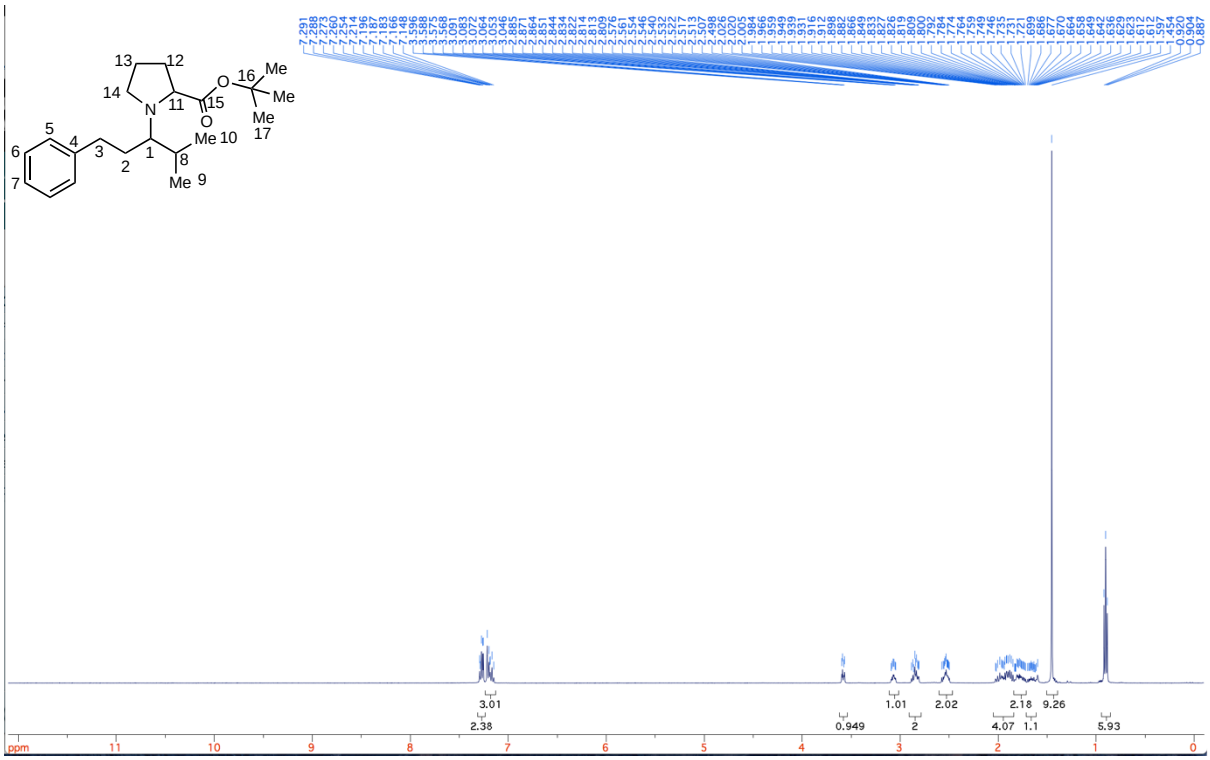

16
15
14
13
12
11
14
N
5
4
6
3
1
Me 10
2
8
7
Me 9
1.92
6.83
1.01
1.02
2.04
2.08
3
2.96
1
1.05
1.03
1.95
3.01
ppm

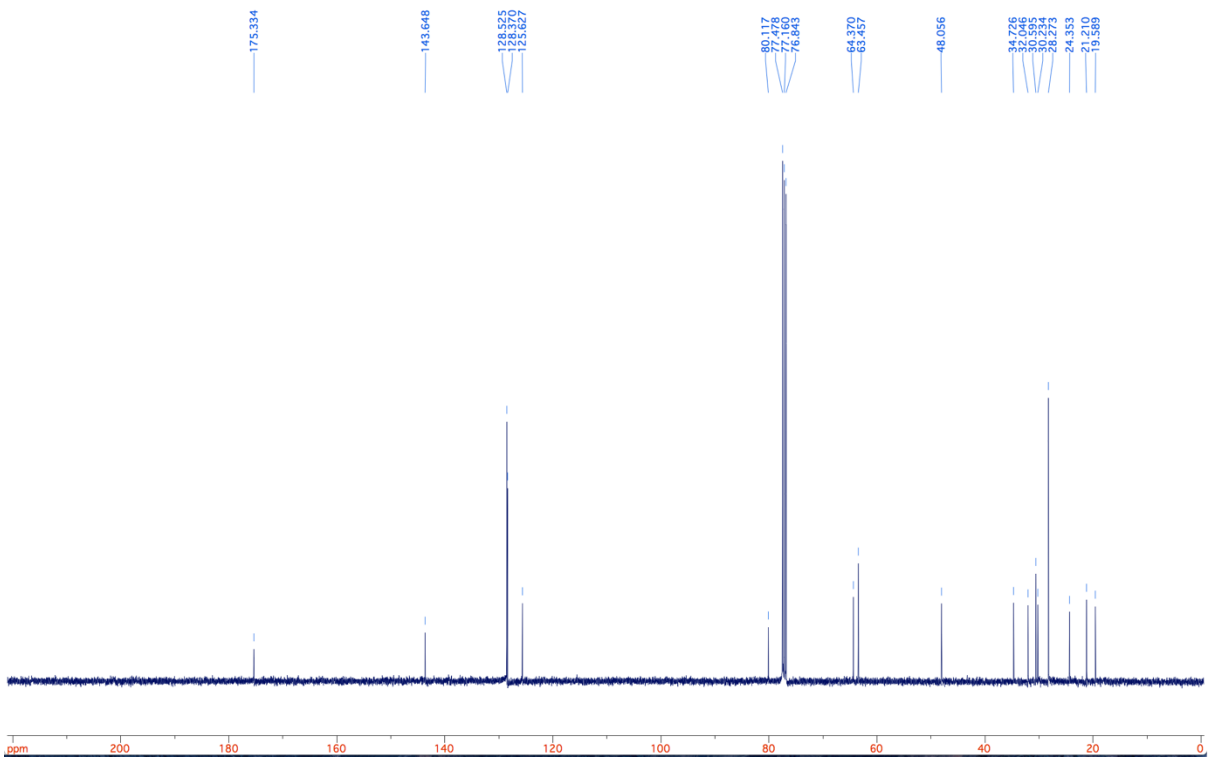

146.989
146.972
143.634
128.588
128.113
126.400
125.344
125.363
121.648
121.573
77.478
77.160
76.842
68.327
55.133
51.630
43.924
41.806
41.578
33.062
30.819
30.772
21.477
20.736
ppm

52a

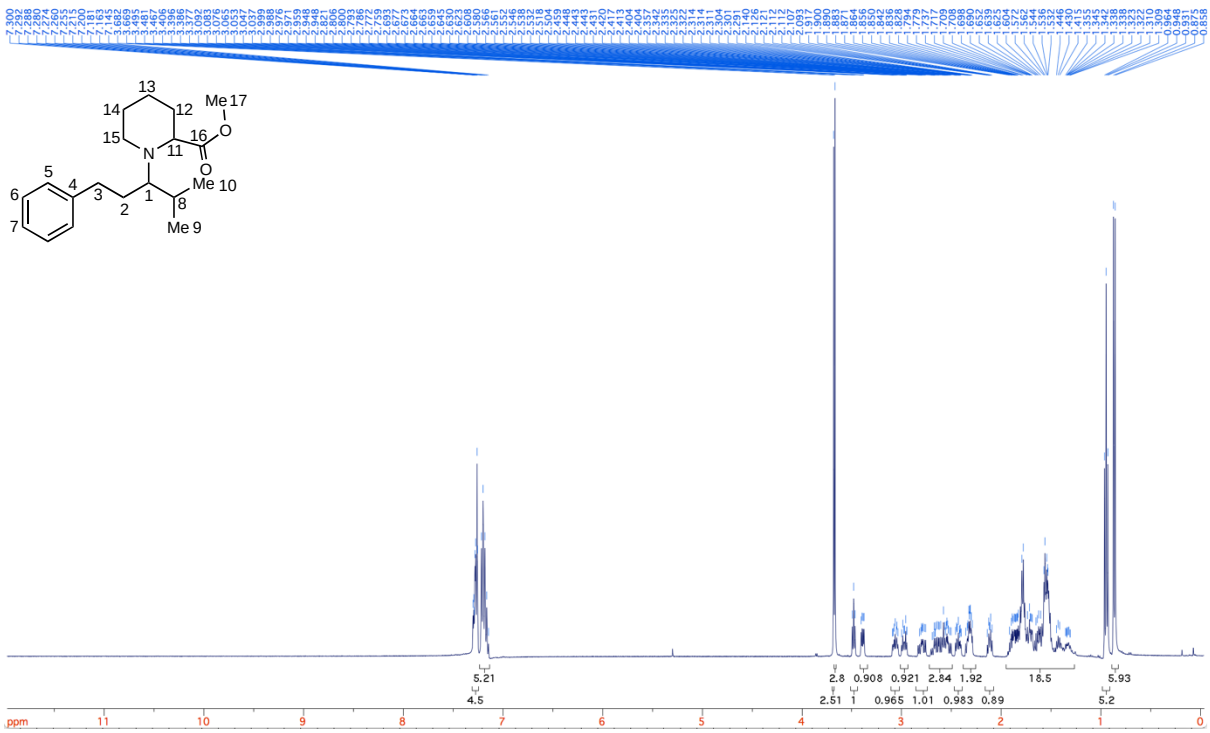

Me 16
O
13
12
14
N
11
15
O
5
4
6
3
1
Me 10
2
8
7
Me 9
3
2.23
2.97
0.979
2.02
0.994
2.02
3.13
3.19
1.5
6.08
ppm
176.313
143.569
128.515
128.365
126.360
125.642
77.477
77.160
76.843
64.225
62.796
51.542
47.444
34.296
32.159
30.810
30.094
24.520
21.170
19.906
ppm

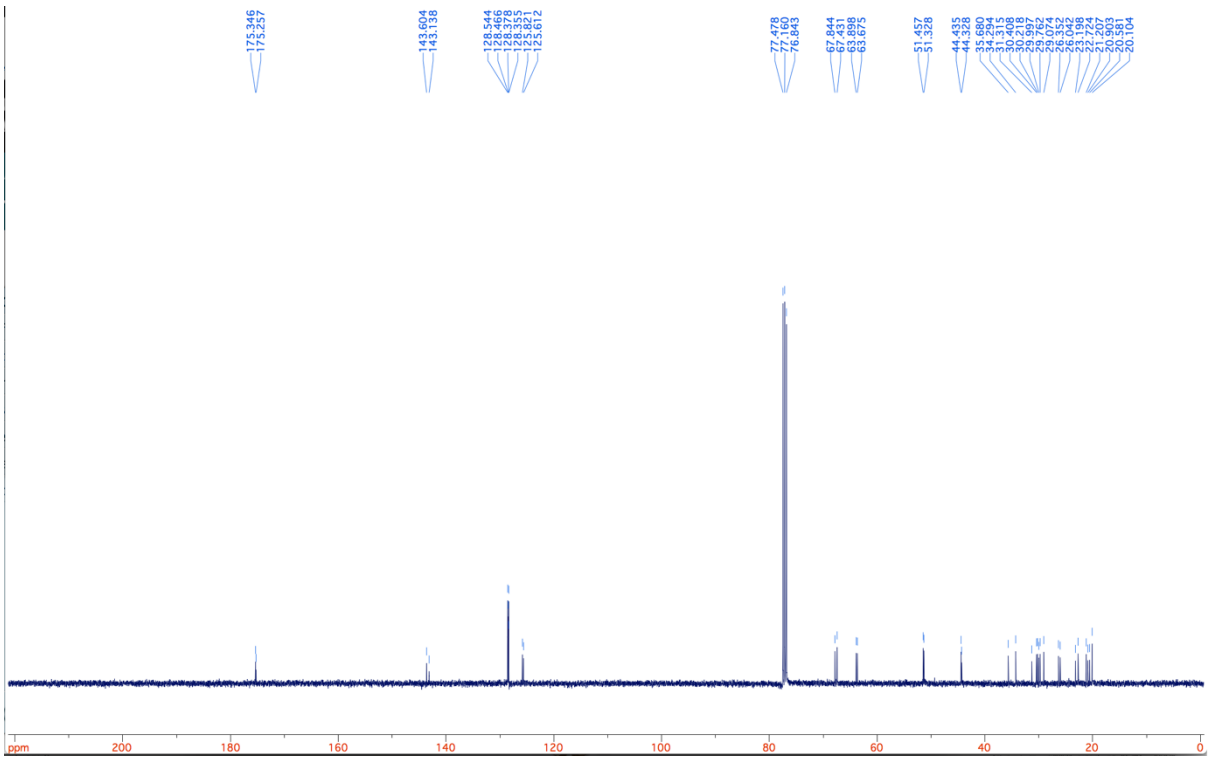
52b


3.01
2.38
0.949
1.01
2
2.02
2.18
4.07
1.1
9.26
5.93
ppm

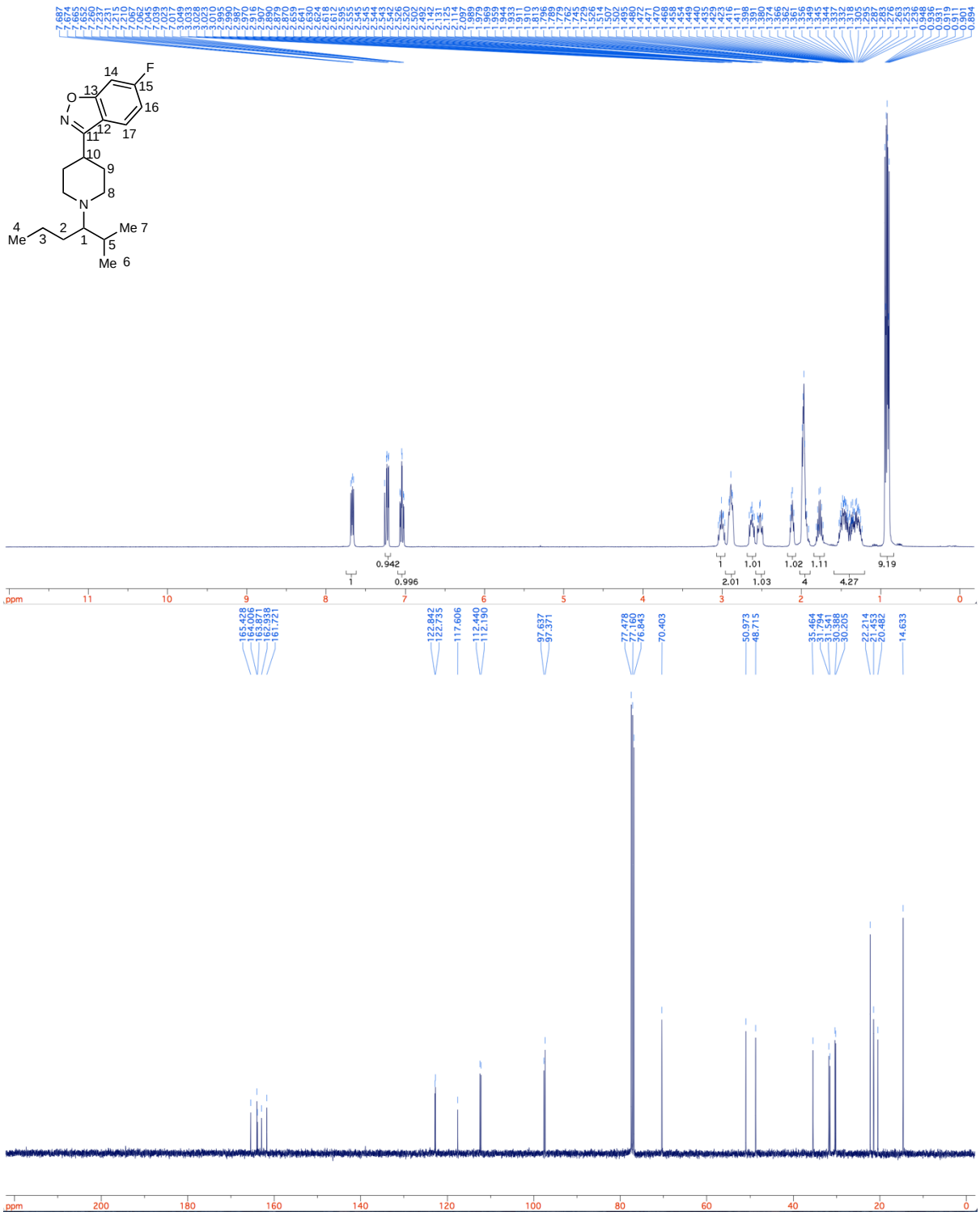

175.334
143.648
128.525
128.370
125.627
80.117
77.476
77.160
76.843
64.370
63.457
48.056
34.726
32.046
30.595
30.274
28.273
24.353
21.210
19.589
ppm

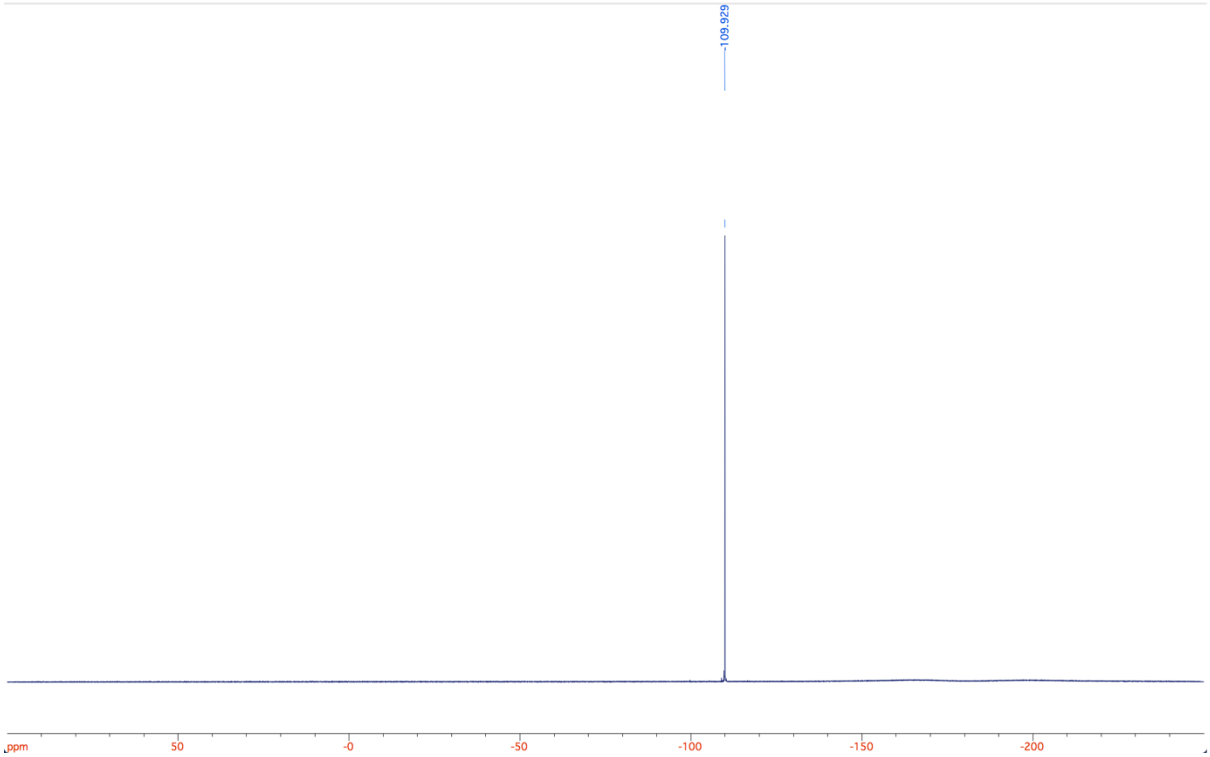
52d


13
14
12
Me 17
15
16
O
N
11
O
Me 10
5
4
6
3
1
8
2
7
Me 9
5.21
4.5
2.8
2.51
0.908
1
0.921
0.965
2.84
1.01
1.92
0.983
0.89
18.5
5.93
5.2
ppm
11
10
9
8
7
6
5
4
3
2
1
0

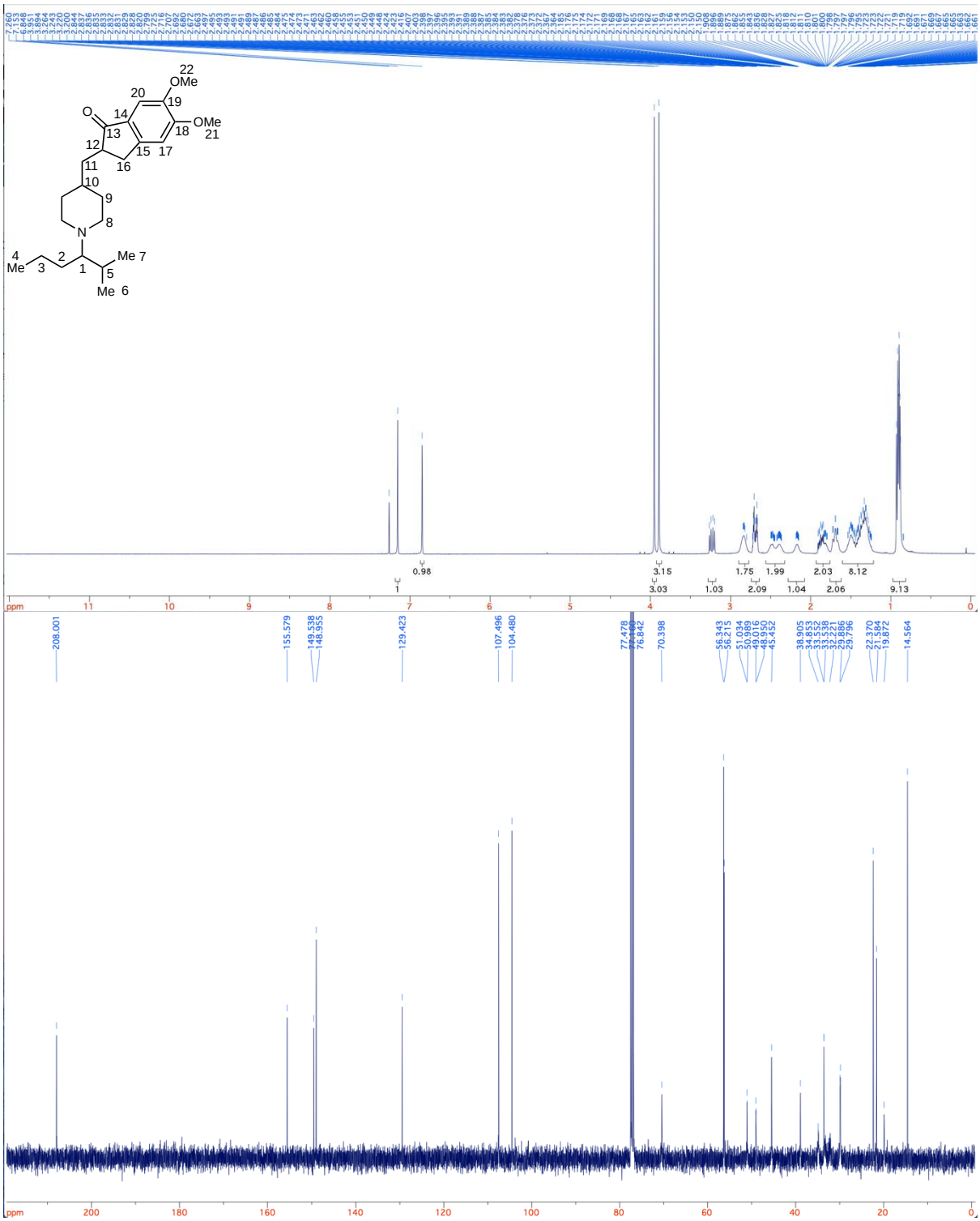

175.346
173.257
143.604
143.138
128.544
128.466
128.378
128.355
125.871
125.612
77.478
77.160
76.843
67.844
67.431
63.898
63.675
51.457
51.328
44.435
44.328
35.680
34.231
31.151
30.408
30.218
29.897
29.762
29.074
26.352
26.042
23.198
22.724
21.207
20.903
20.581
20.104
ppm
200
180
160
140
120
100
80
60
40
20
0

53a

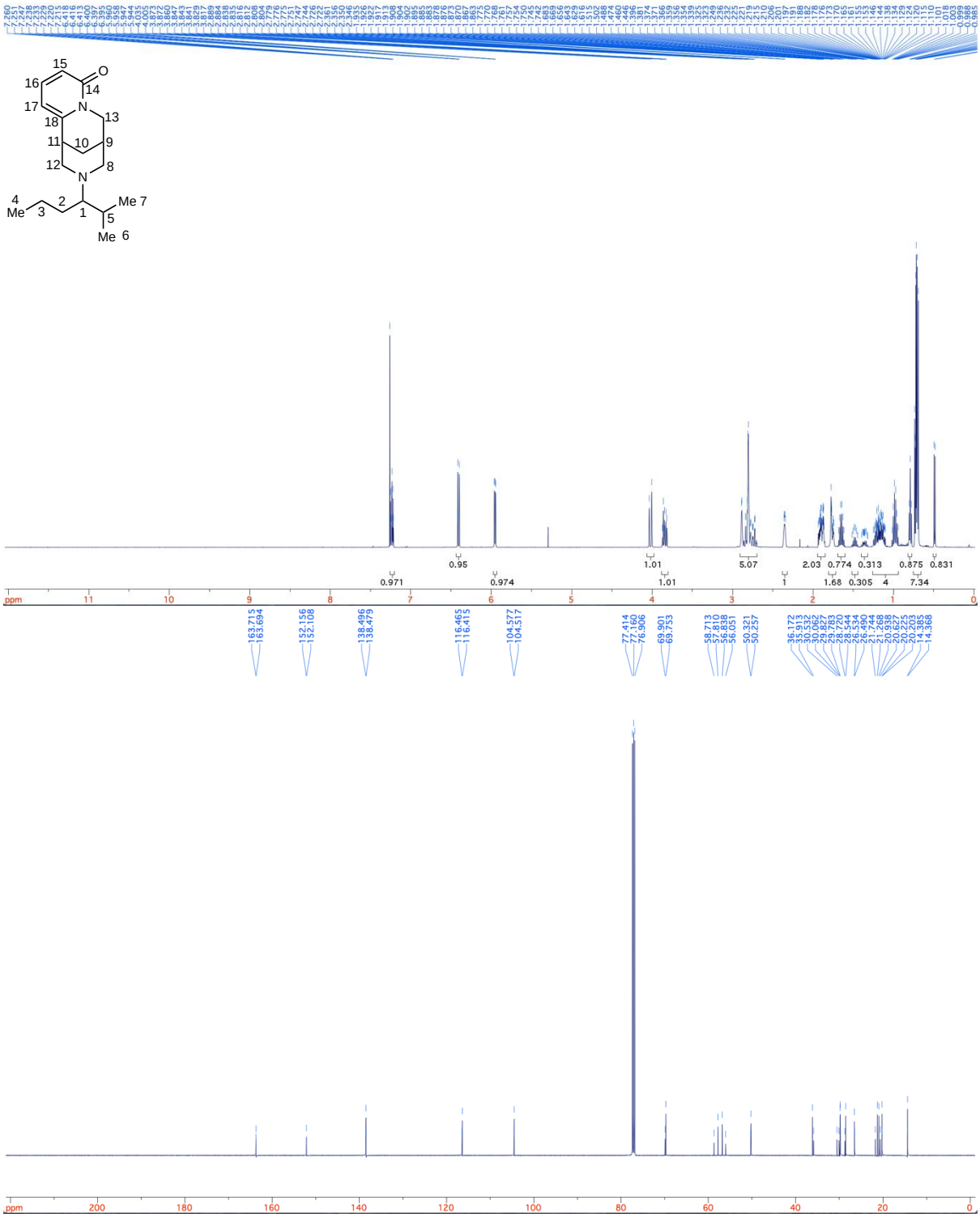

F
14
15
16
13
O
N
12
11
17
10
9
8
N
4
Me
3
2
1
5
Me 7
Me 6
0.942
1
0.996
1
1.01
1.02
1.11
9.19
2.01
1.03
4
4.27
ppm
11
10
9
8
7
6
5
4
3
2
1
0
165.428
164.006
163.871
162.978
161.721
122.842
122.735
117.606
112.440
112.190
97.637
97.371
77.478
77.160
76.843
70.403
50.973
48.715
35.464
33.794
31.541
30.388
30.205
22.214
21.453
20.482
14.633
ppm
200
180
160
140
120
100
80
60
40
20
0


-109.929
ppm
50
-0
-50
-100
-150
-200

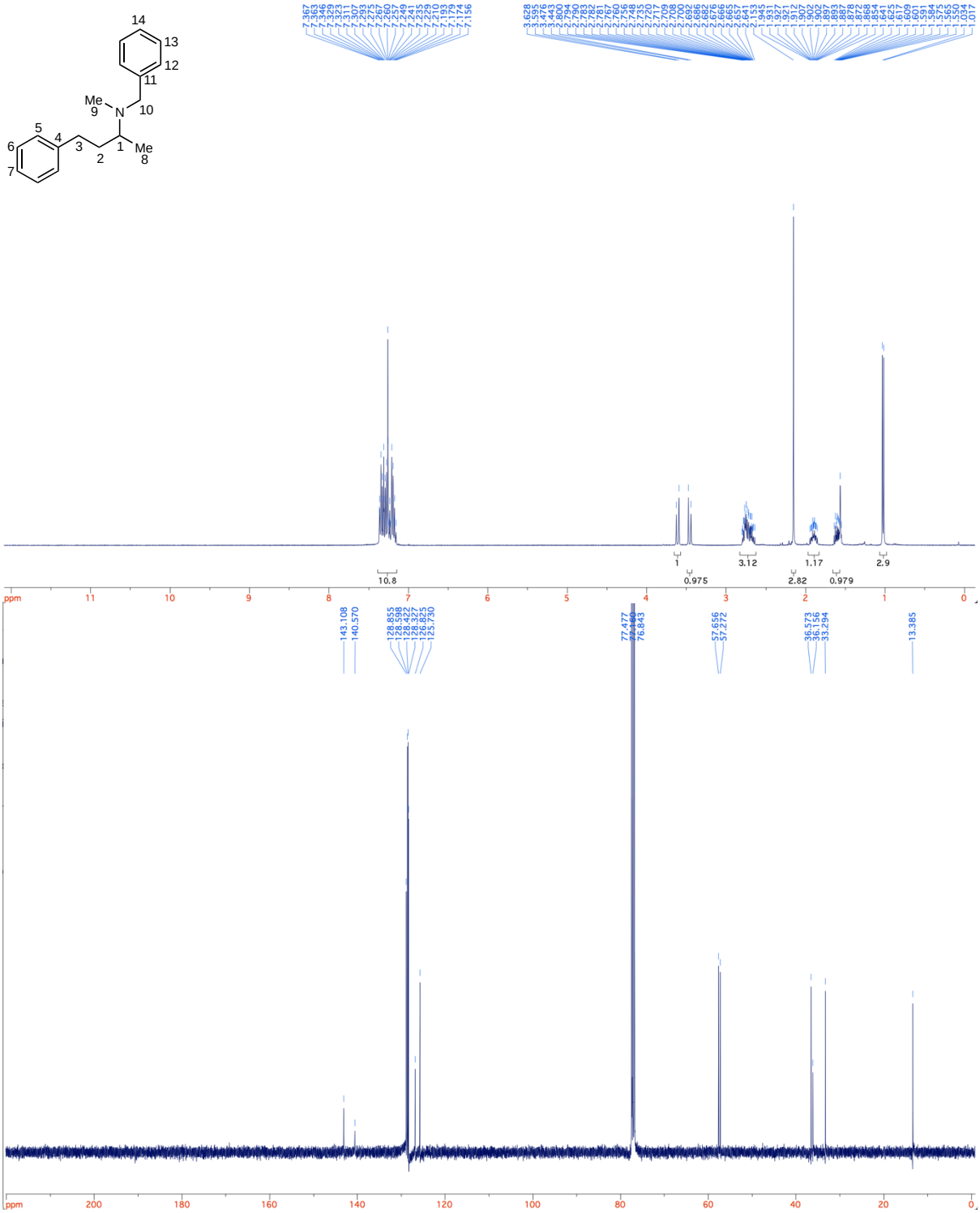
53c


22
OMe
20
19
O
14
OMe
21
13
18
12
15
17
11
16
10
9
8
N
4
Me
3
2
1
Me 7
5
Me 6
0.98
3.15
1.75
1.99
2.03
8.12
1
3.03
1.03
2.09
1.04
2.06
9.13
ppm
208.001
155.579
149.538
148.955
129.423
107.496
104.480
77.478
77.160
76.842
70.398
56.343
56.215
51.034
50.089
49.016
48.516
45.452
38.905
34.853
33.552
33.538
32.271
29.886
29.796
22.370
21.584
19.872
14.564

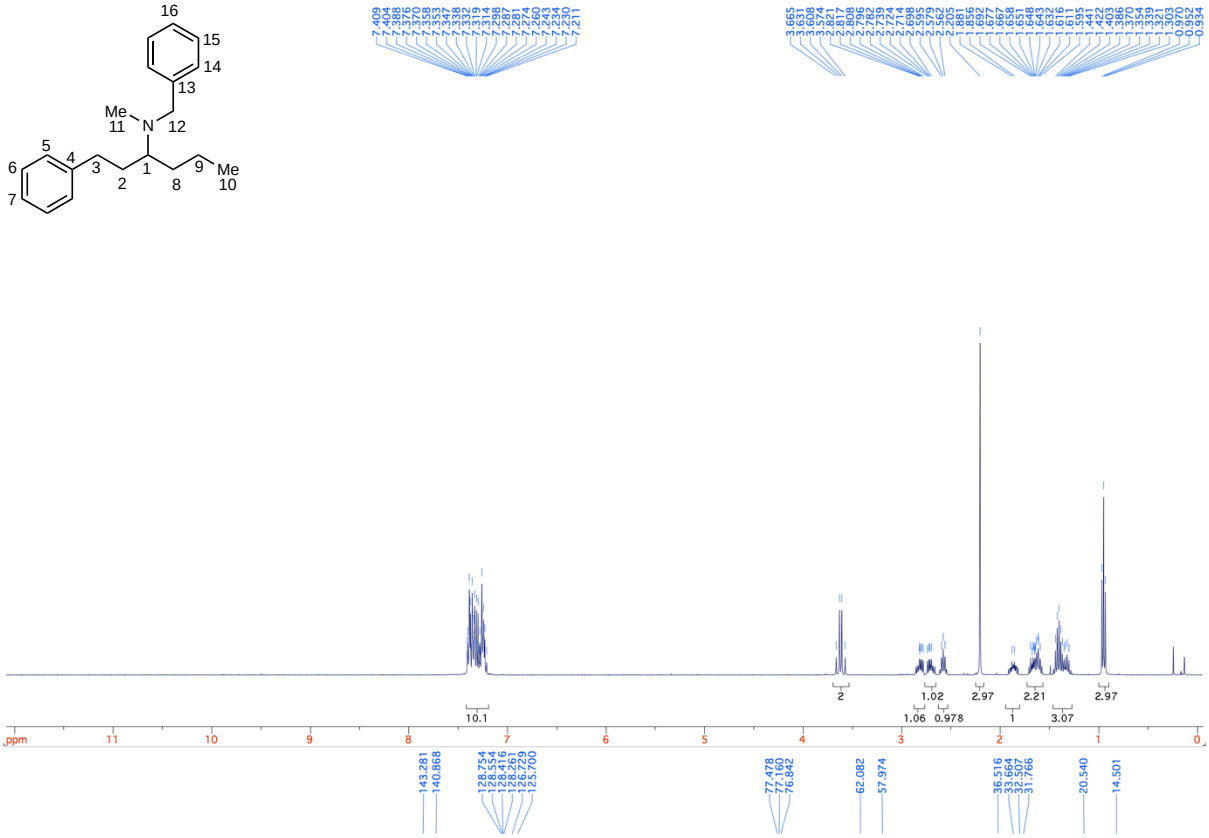
53d



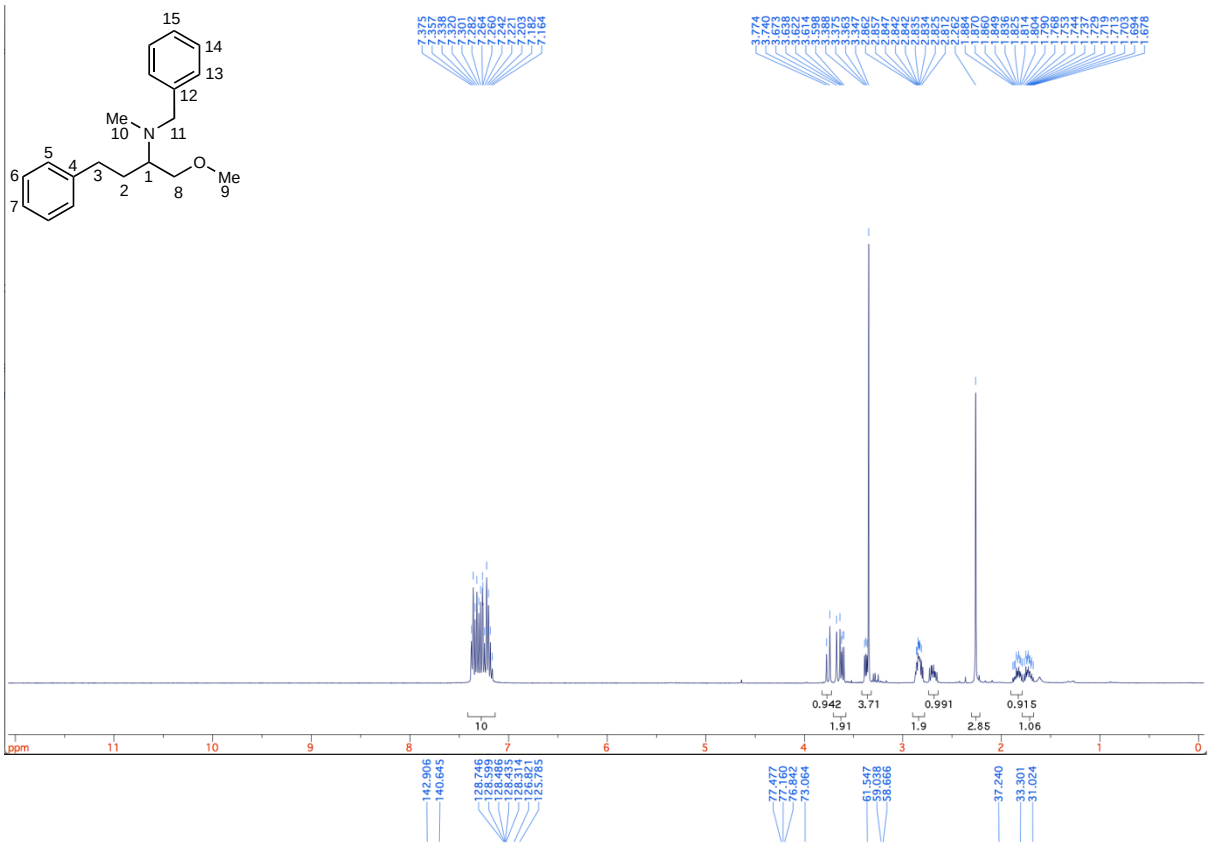
56a

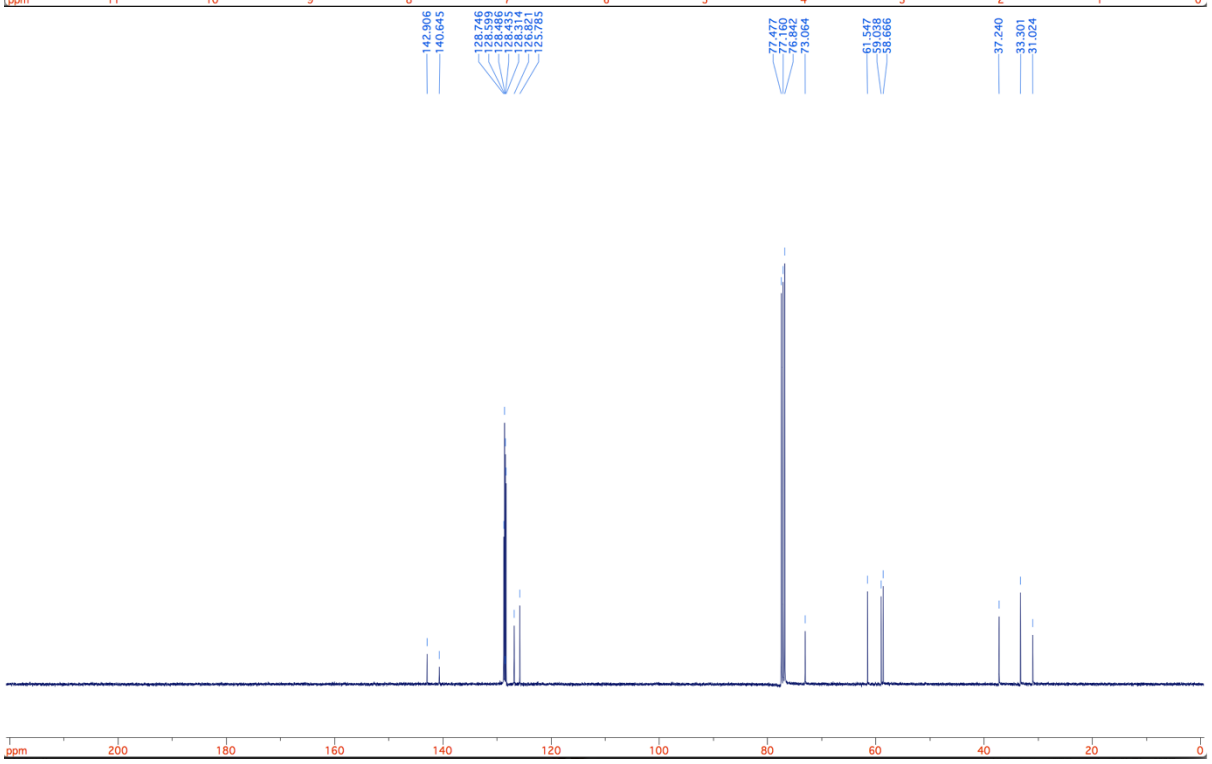

14
13
12
11
Me
9
N
10
5
4
6
3
1
Me
8
2
7
10.8
1
0.975
3.12
2.82
1.17
0.979
2.9
ppm
143.108
140.570
128.855
128.598
128.422
128.327
126.825
125.730
77.477
77.160
76.843
57.656
57.272
36.573
36.156
33.294
13.385
ppm

56b

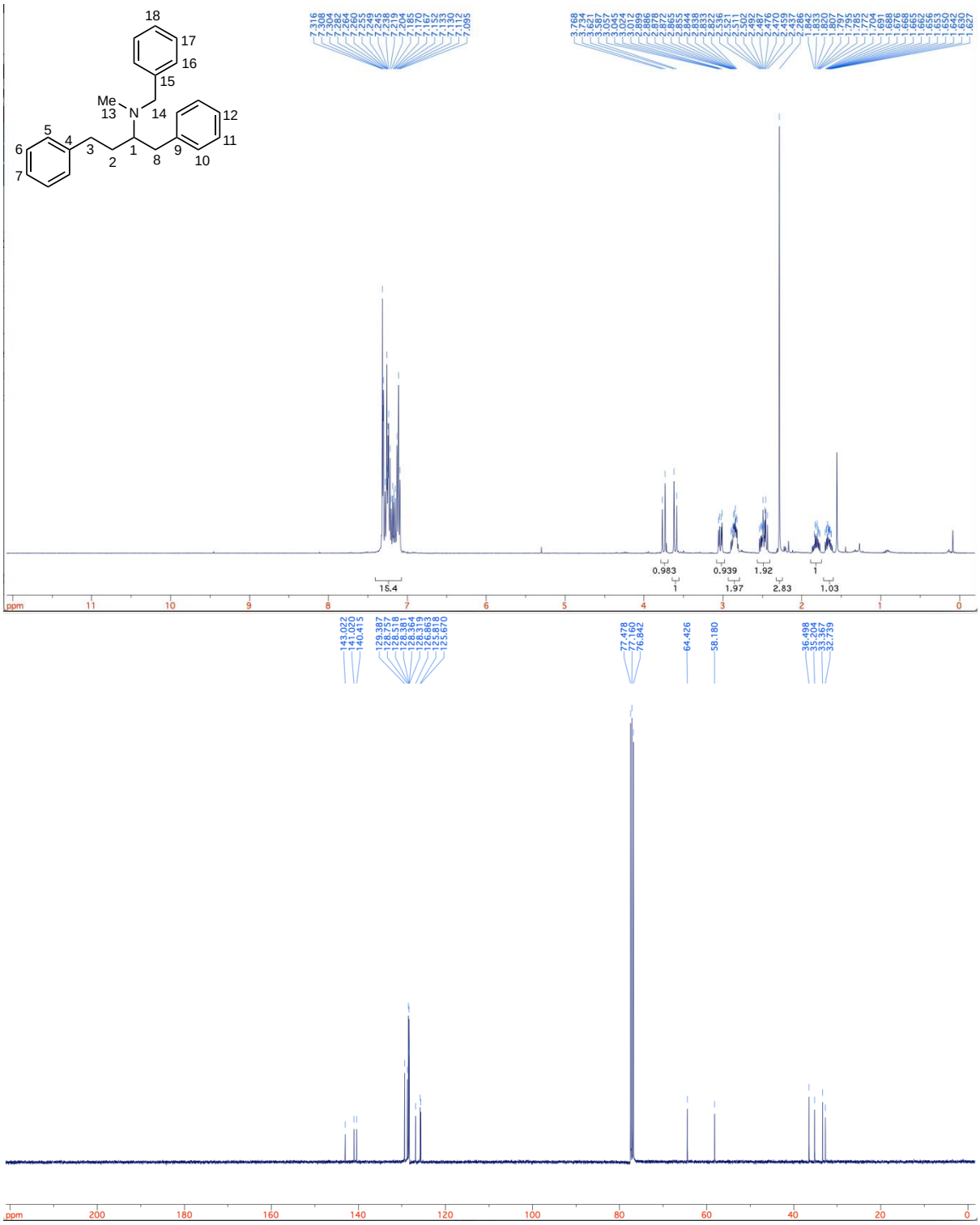

16
15
14
13
Me
11
N
12
5
4
6
3
1
9
Me
10
7
2
8
7.409
7.404
7.384
7.376
7.370
7.358
7.353
7.347
7.339
7.334
7.319
7.314
7.289
7.287
7.281
7.274
7.260
7.243
7.234
7.220
7.211
3.665
3.631
3.608
3.574
3.527
3.517
2.808
2.795
2.785
2.739
2.714
2.698
2.595
2.579
2.562
2.205
1.881
1.856
1.692
1.677
1.667
1.658
1.651
1.648
1.643
1.632
1.616
1.611
1.595
1.441
1.422
1.402
1.386
1.370
1.354
1.339
1.321
1.303
0.970
0.952
0.934
10.1
2
1.02
2.97
2.21
2.97
1.06
0.978
1
3.07
ppm
143.281
140.868
128.754
128.554
128.416
128.271
126.729
125.700
77.478
77.160
76.842
62.082
57.974
36.516
33.664
32.507
31.766
20.540
14.501

56d

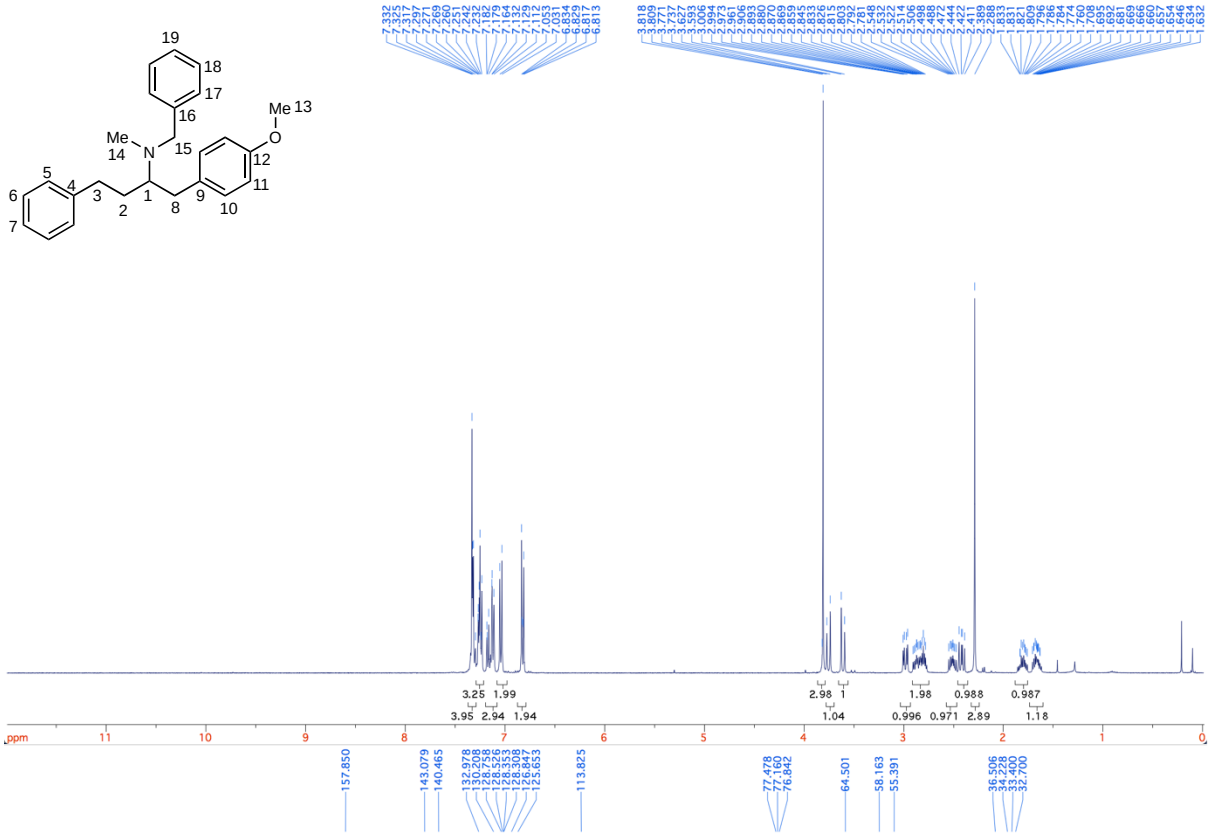

15
14
13
12
Me
10
N
11
5
6
4
3
2
1
O
Me
9
8
7
7.375
7.357
7.338
7.320
7.301
7.282
7.264
7.260
7.242
7.221
7.203
7.182
7.164
3.774
3.740
3.677
3.638
3.622
3.614
3.598
3.388
3.363
3.347
2.862
2.857
2.847
2.842
2.835
2.834
2.823
2.817
2.762
1.884
1.870
1.860
1.849
1.836
1.827
1.814
1.804
1.790
1.760
1.753
1.744
1.737
1.729
1.719
1.713
1.703
1.694
1.678
10
0.942
3.71
0.991
0.915
1.91
1.9
2.85
1.06
ppm
11
10
9
8
7
6
5
4
3
2
1
0

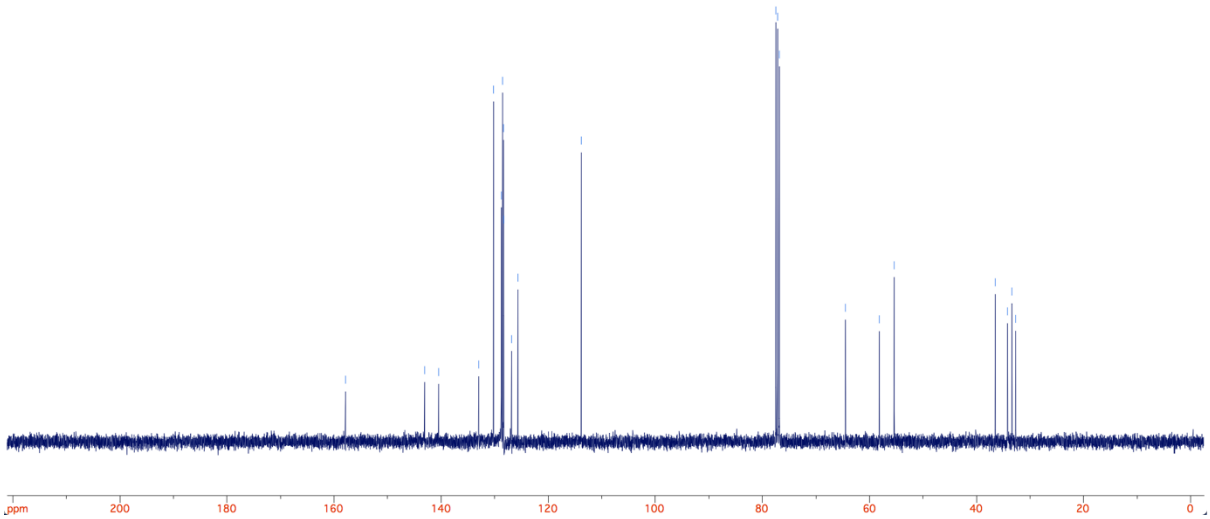

142.906
140.645
128.746
128.599
128.456
128.455
128.314
126.721
125.755
77.477
77.160
76.842
73.064
61.547
59.708
58.668
37.240
33.301
31.024
ppm
200
180
160
140
120
100
80
60
40
20
0

56e

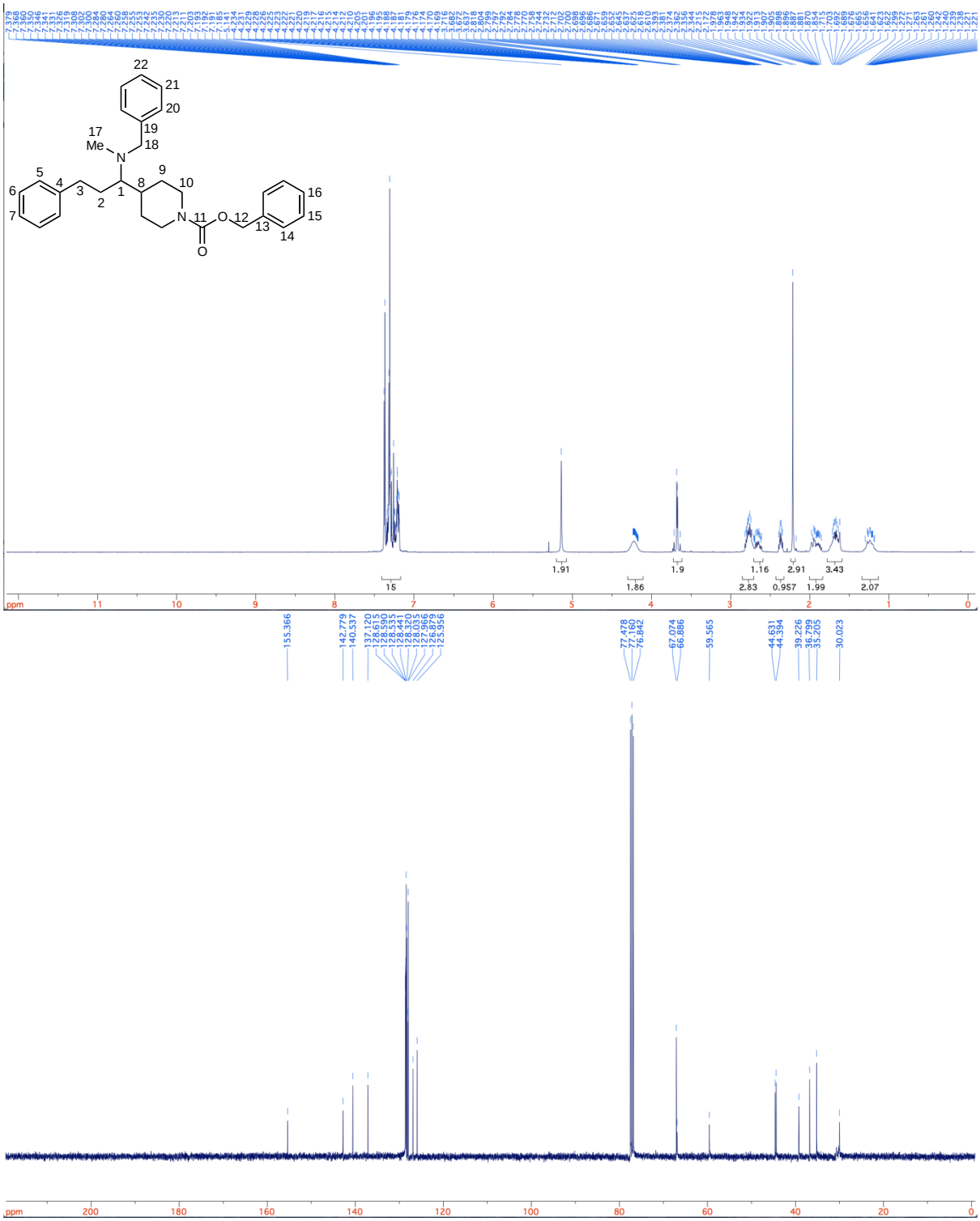

Me
N
15.4
0.983
0.939
1.92
1
1
1.97
2.83
1.03
ppm
143.022
141.020
140.415
129.387
128.757
128.531
128.381
128.364
128.319
126.883
126.648
125.670
77.478
77.160
76.842
64.426
58.180
36.498
35.204
33.567
32.739

56f

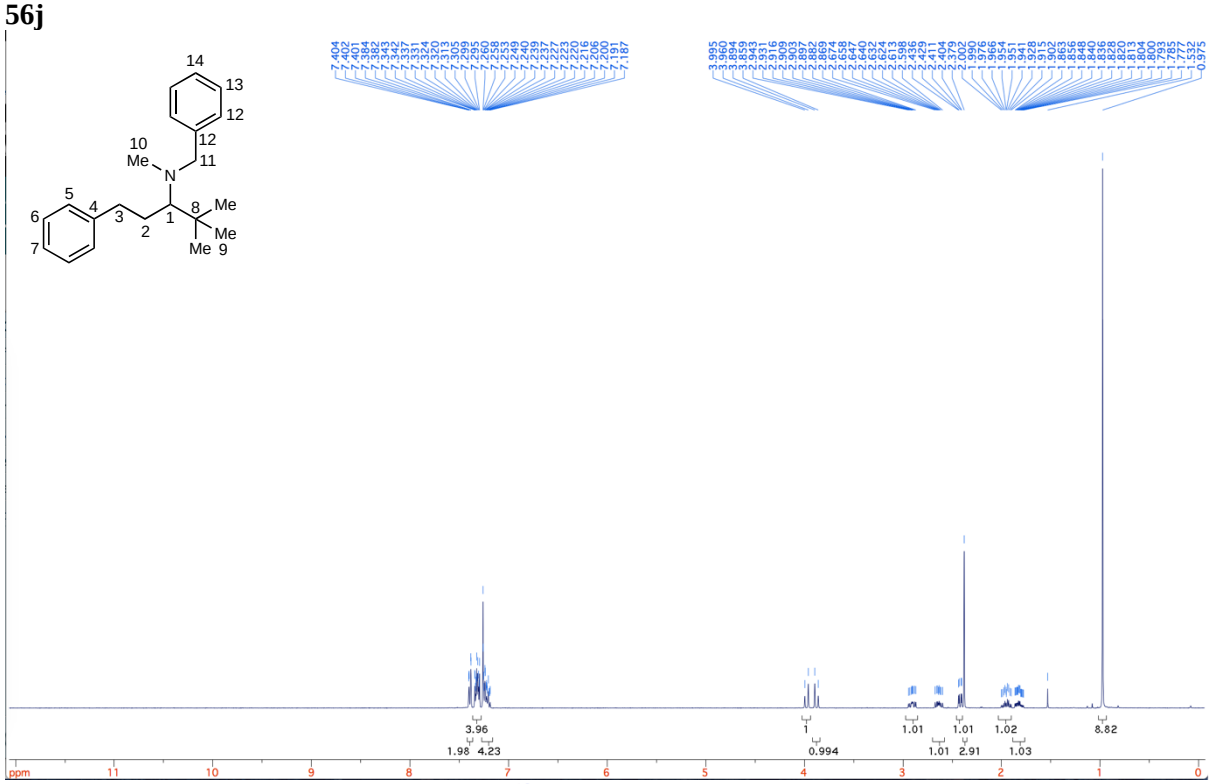

19
18
17
16
Me 13
Me
14
N
15
O
12
11
5
4
6
3
1
9
7
2
8
10
3.25 1.99
3.95 2.94 1.94
2.98 1
1.04
1.98 0.988 0.987
0.996 0.971 2.89 1.18
ppm
11 10 9 8 7 6 5 4 3 2 1 0
157.850
143.079
140.465
132.978
130.208
128.738
128.536
128.353
128.308
128.047
125.653
113.825
77.478
77.160
76.842
64.501
58.163
55.391
36.506
34.728
33.428
33.400
32.700

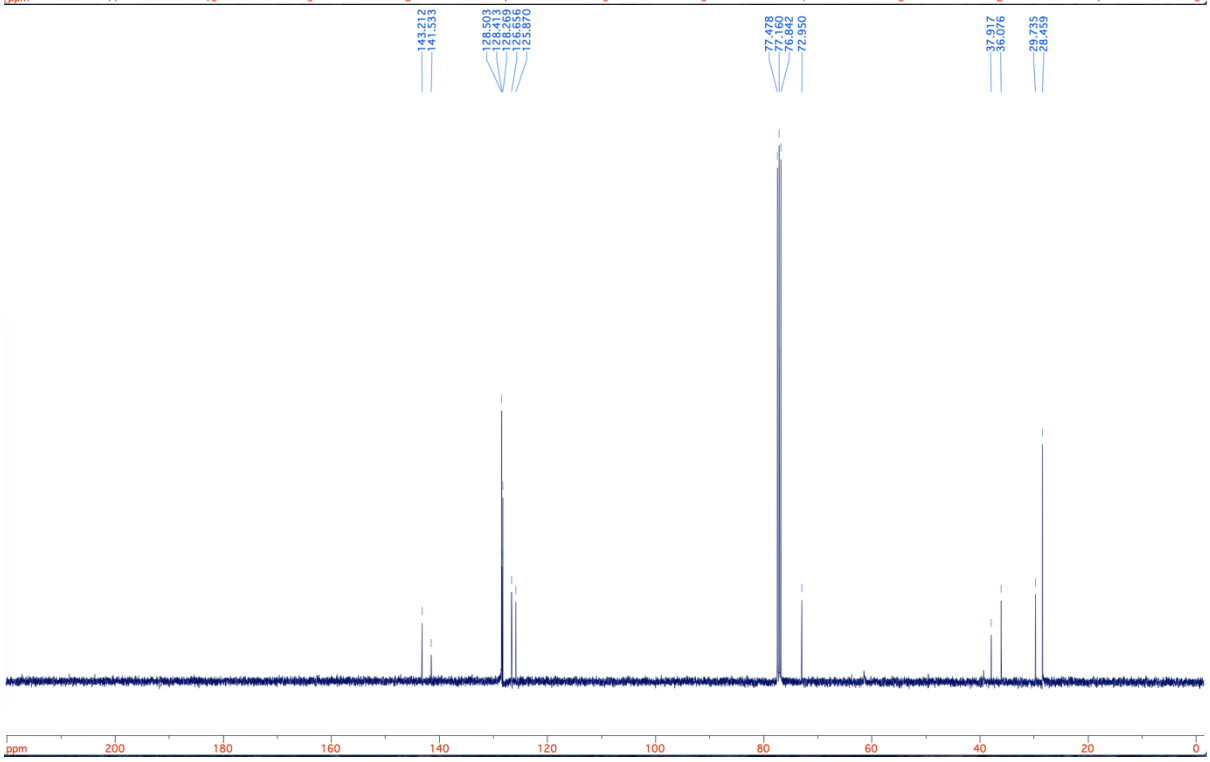

ppm
200 180 160 140 120 100 80 60 40 20 0

56i

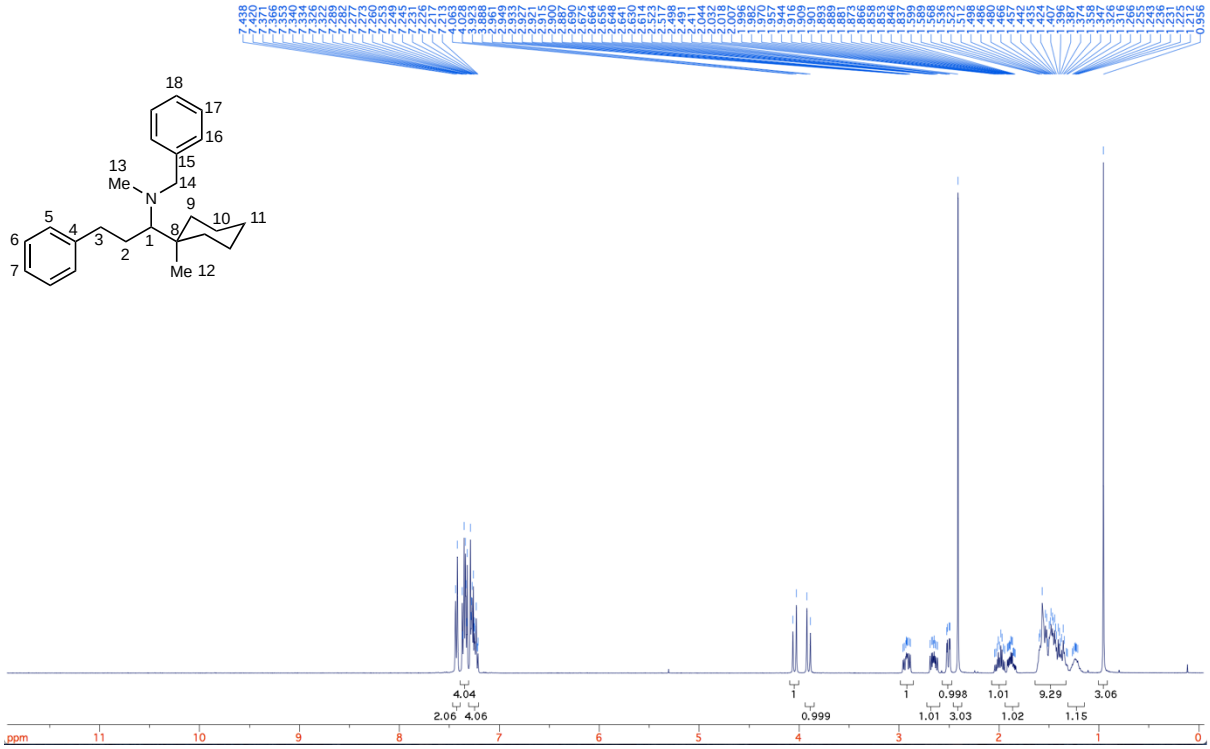

Me
N
O
O
1.91
1.9
1.86
1.16
2.91
3.43
15
2.83
0.957
1.99
2.07
ppm
155.366
142.779
140.537
137.120
128.615
128.590
128.451
128.441
128.320
128.035
127.956
126.879
125.956
77.478
77.160
76.842
67.074
66.886
59.565
44.631
44.394
39.226
36.799
35.205
30.023

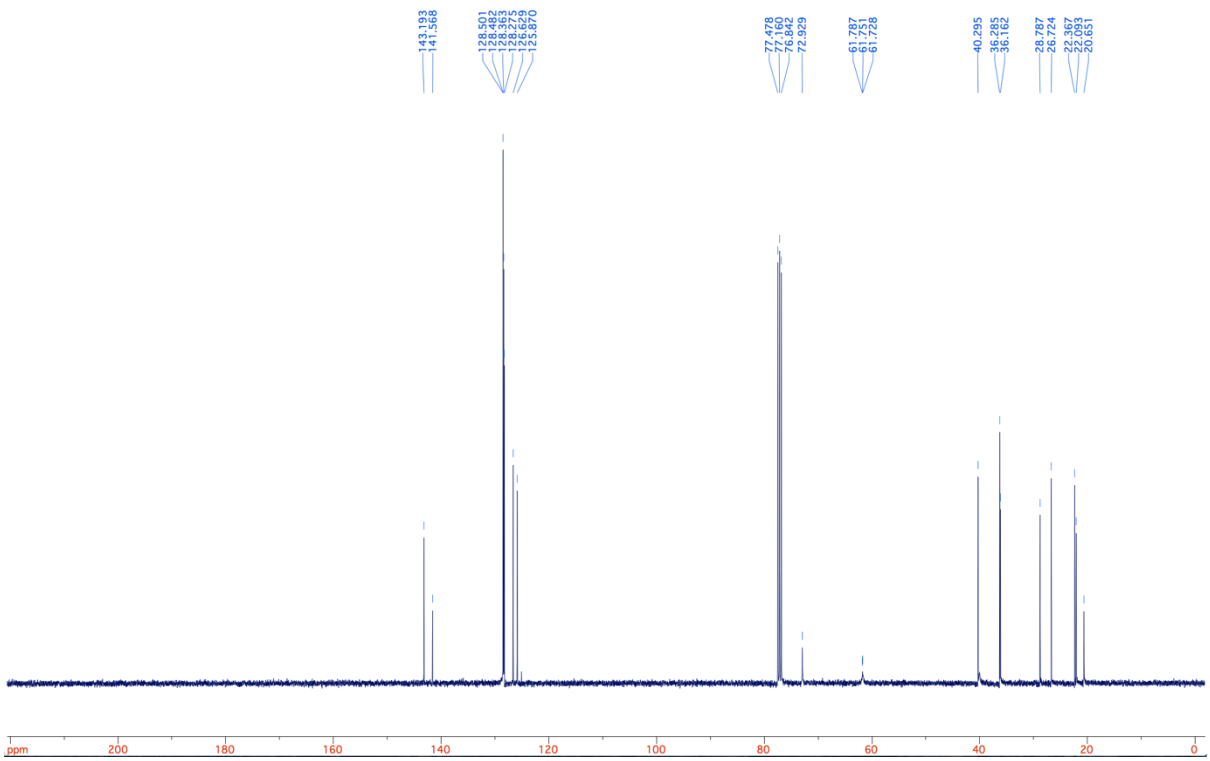
56j


14
13
12
12
10
Me
N
11
5
4
3
1
8
Me
6
2
Me
7
Me 9
3.96
1.98
4.23
1
0.994
1.01
1.01
2.91
1.02
1.03
8.82
ppm

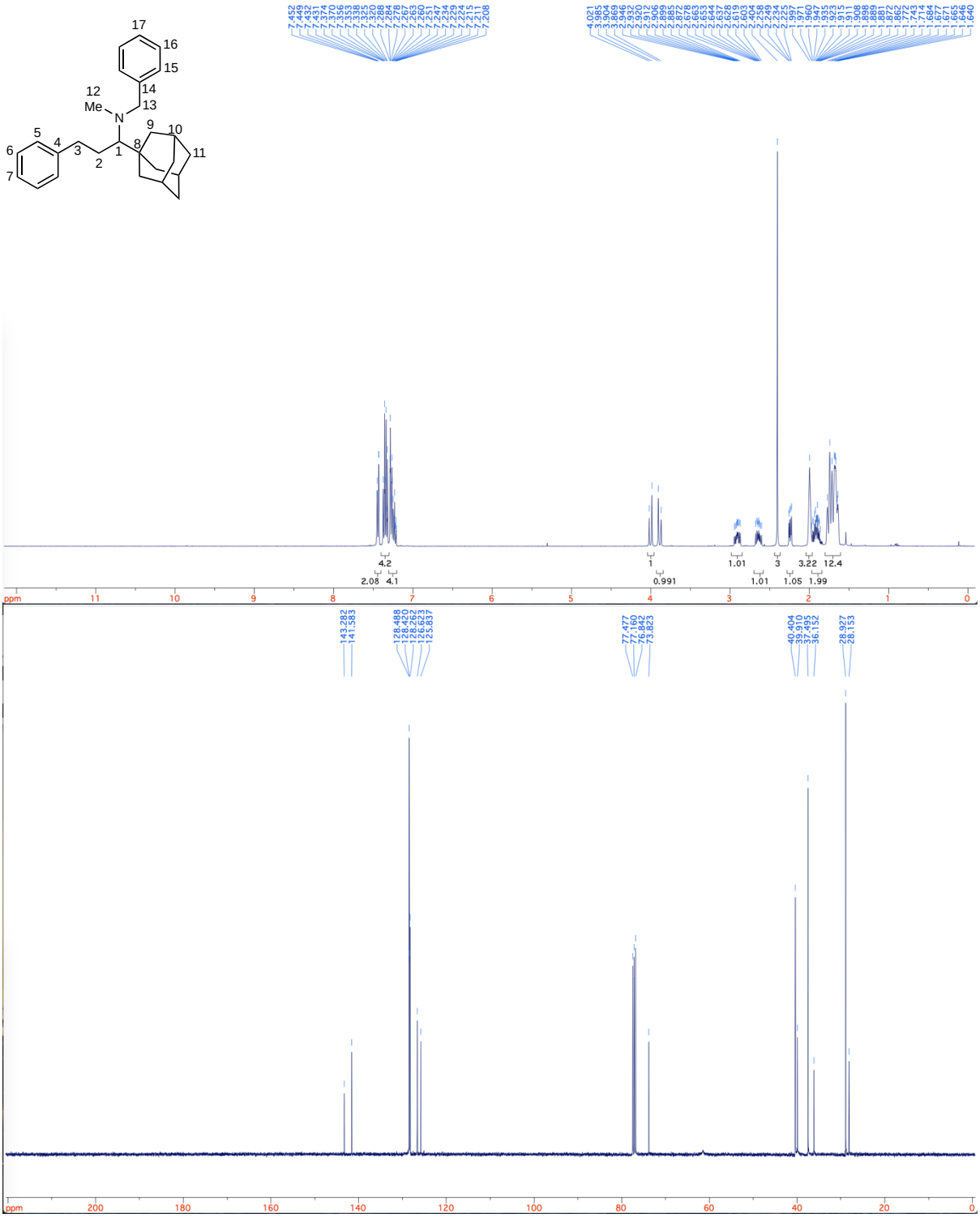

143.212
141.533
128.503
128.413
128.269
126.656
125.870
77.478
77.150
76.842
72.950
37.917
36.076
29.735
28.459
ppm

56k

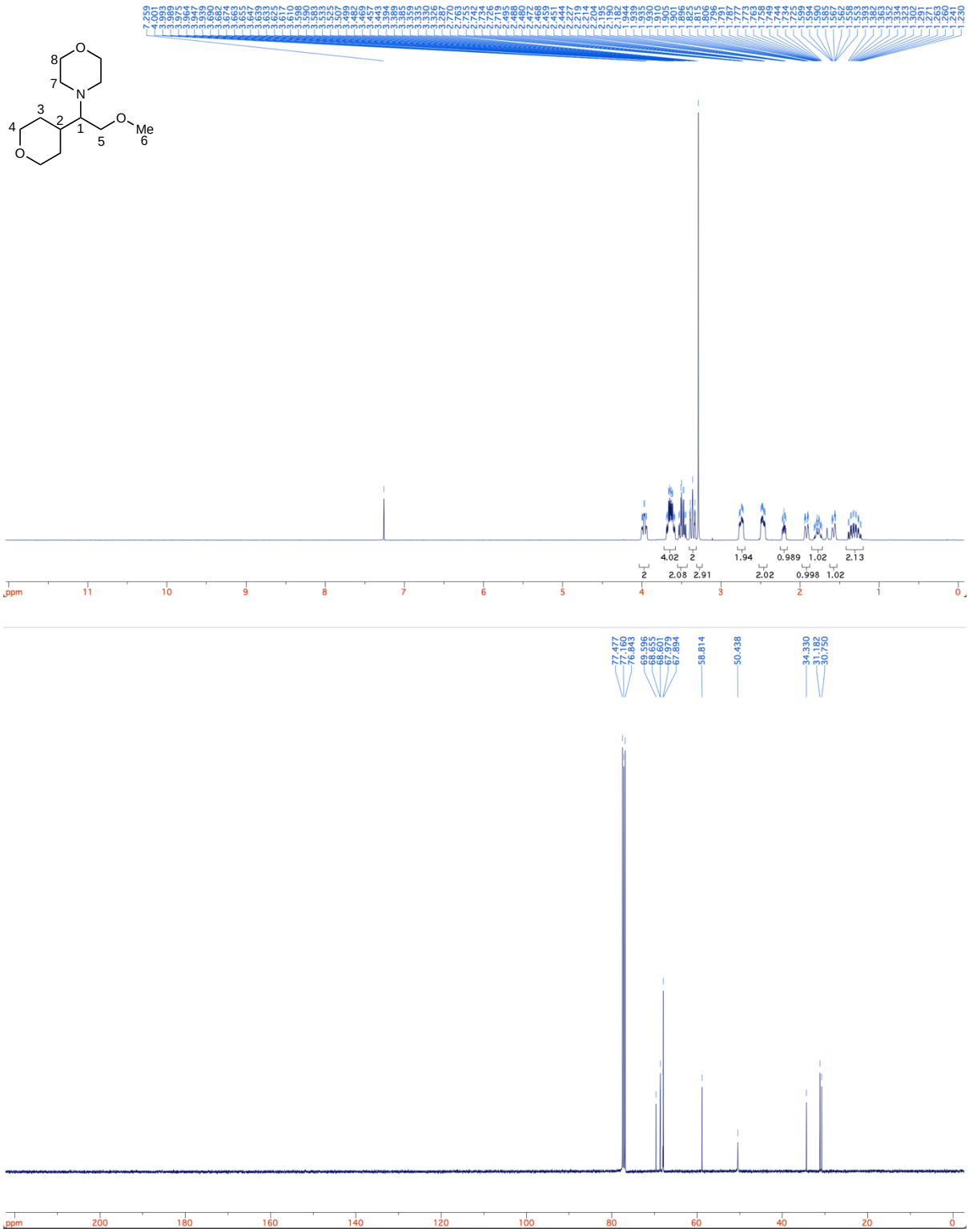

18
17
16
15
14
13
Me
N
9
10
11
5
4
3
1
8
6
2
7
Me 12
4.04
2.06 4.06
1
0.999
1
0.998
1.01
1.01 3.03
1.02
9.29
1.15
3.06
ppm


143.193
141.568
128.501
128.482
128.363
128.275
126.629
125.870
77.478
77.160
76.842
72.929
61.787
61.751
61.726
40.295
36.285
36.162
28.787
26.724
22.367
22.093
20.651
ppm

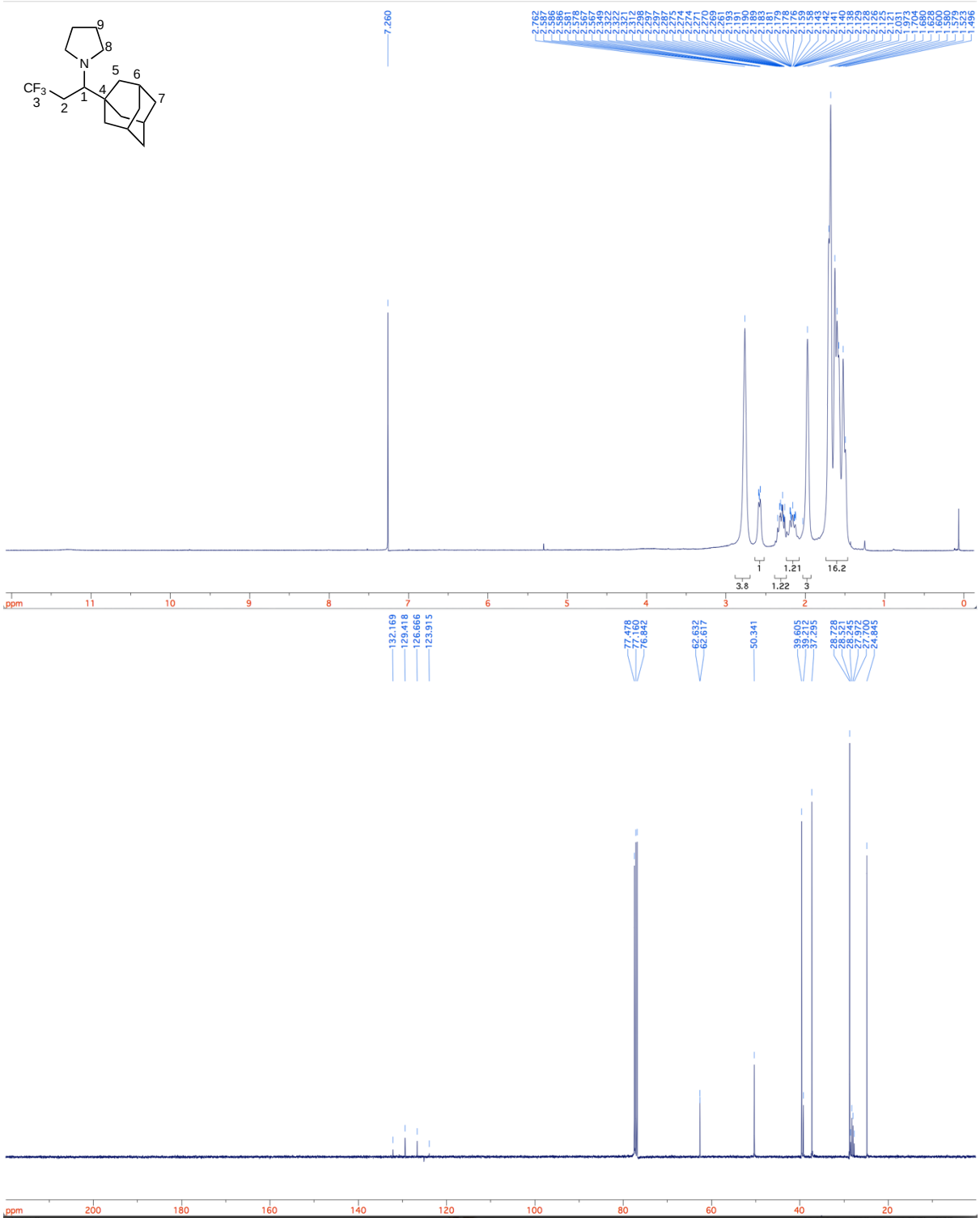
56l

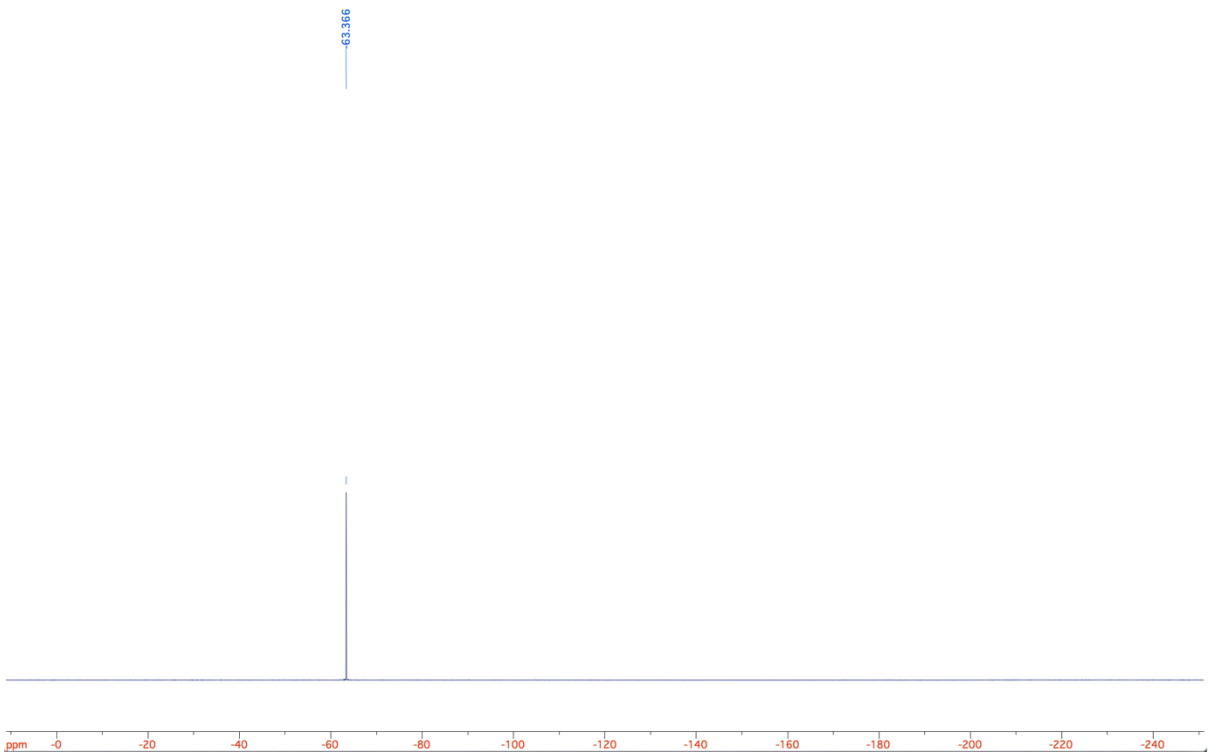

17
16
15
14
12
Me
13
N
9
10
5
4
6
3
1
8
11
2
7
4.2
2.08
4.1
1
0.991
1.01
1.01
3
1.05
3.22
1.99
12.4
ppm
143.282
141.583
128.488
128.420
128.202
126.623
125.837
77.477
77.160
76.842
73.823
40.404
39.910
37.495
36.152
28.927
28.153

57b


O
8
7
N
3
2
1
4
5
O
O
Me
6
4.02
2
1.94
0.989
1.02
2.13
2
2.08
2.91
2.02
0.998
1.02
ppm
11
10
9
8
7
6
5
4
3
2
1
0
77.477
77.140
76.843
69.596
68.655
68.601
67.879
67.894
58.814
50.438
34.330
31.182
30.750
ppm
200
180
160
140
120
100
80
60
40
20
0

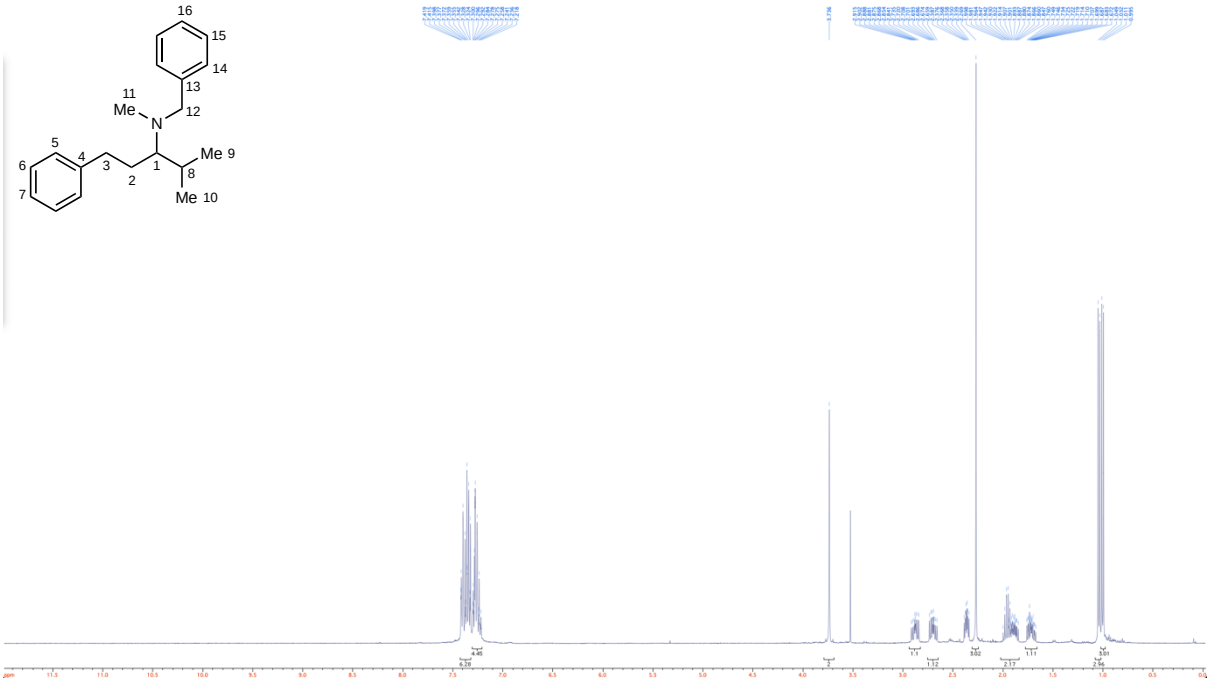
57f


CF3
3
2
1
4
5
6
7
8
9
N
7.260
1
1.21
16.2
3.8
1.22
3
ppm
132.169
129.418
126.666
123.915
77.478
77.160
76.842
62.632
62.617
50.341
39.605
39.212
37.295
28.728
28.521
28.245
27.972
27.700
24.845

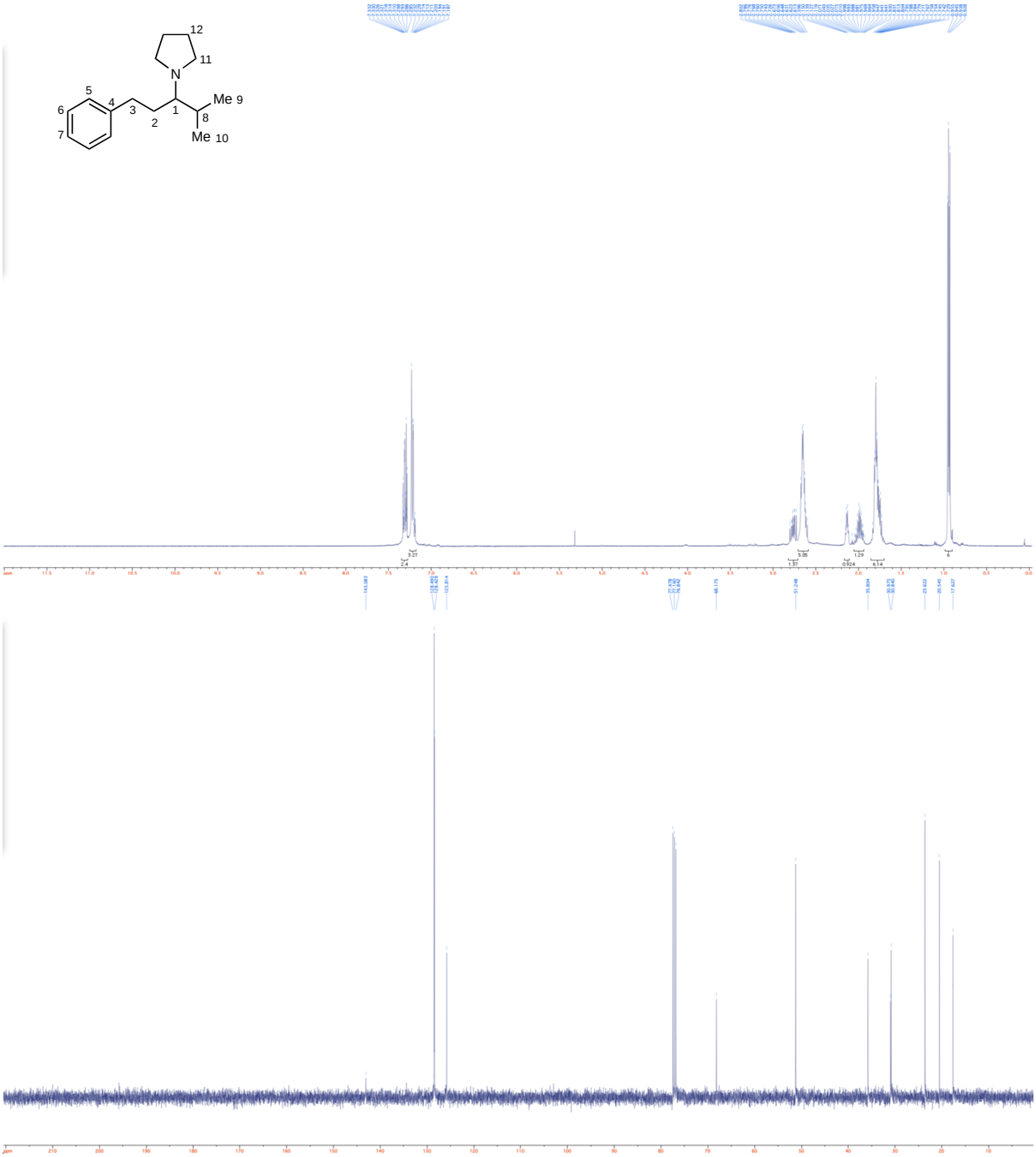

-63.366
ppm
-0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240

9.2 Spectra for chapter 3

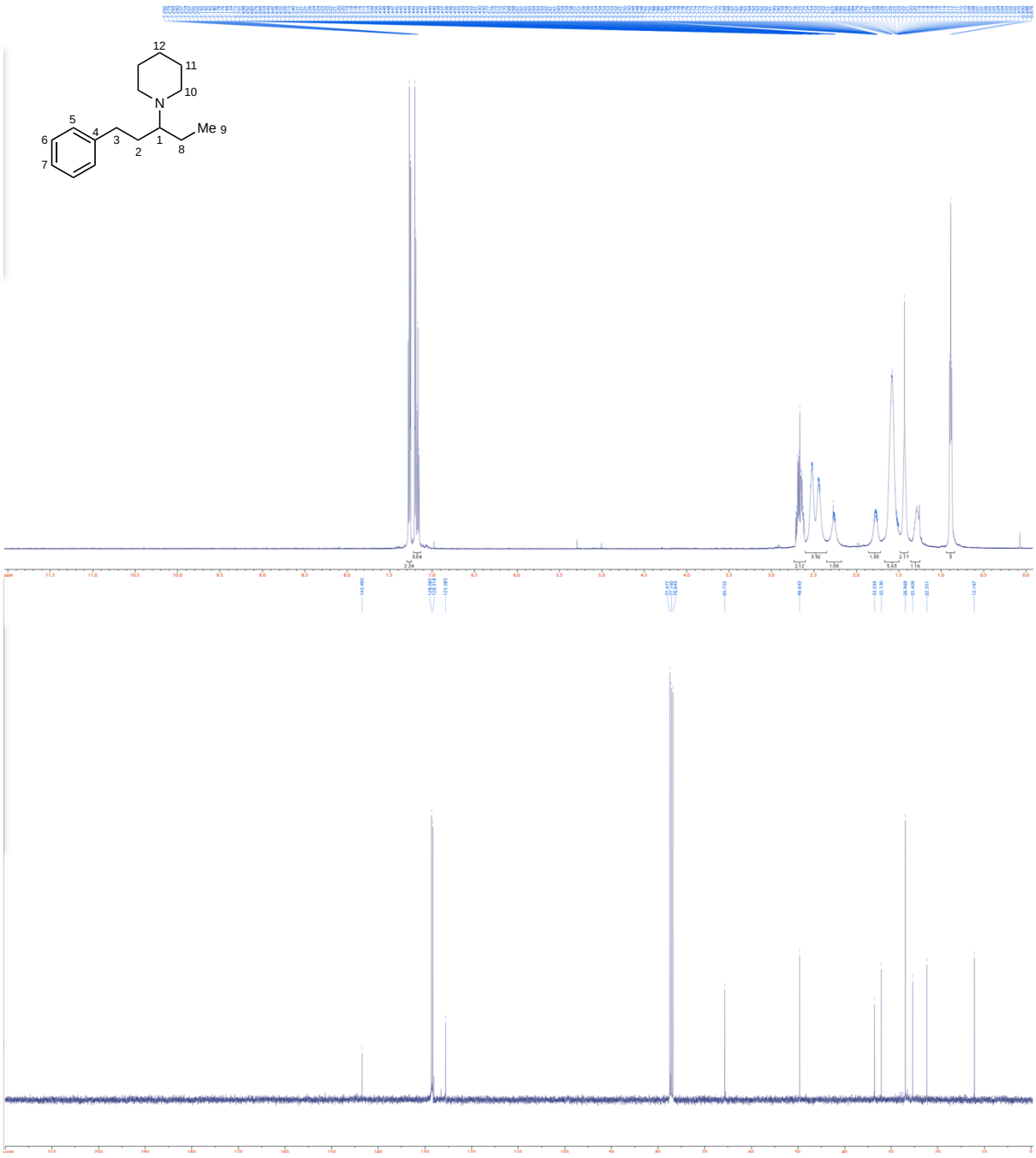
68



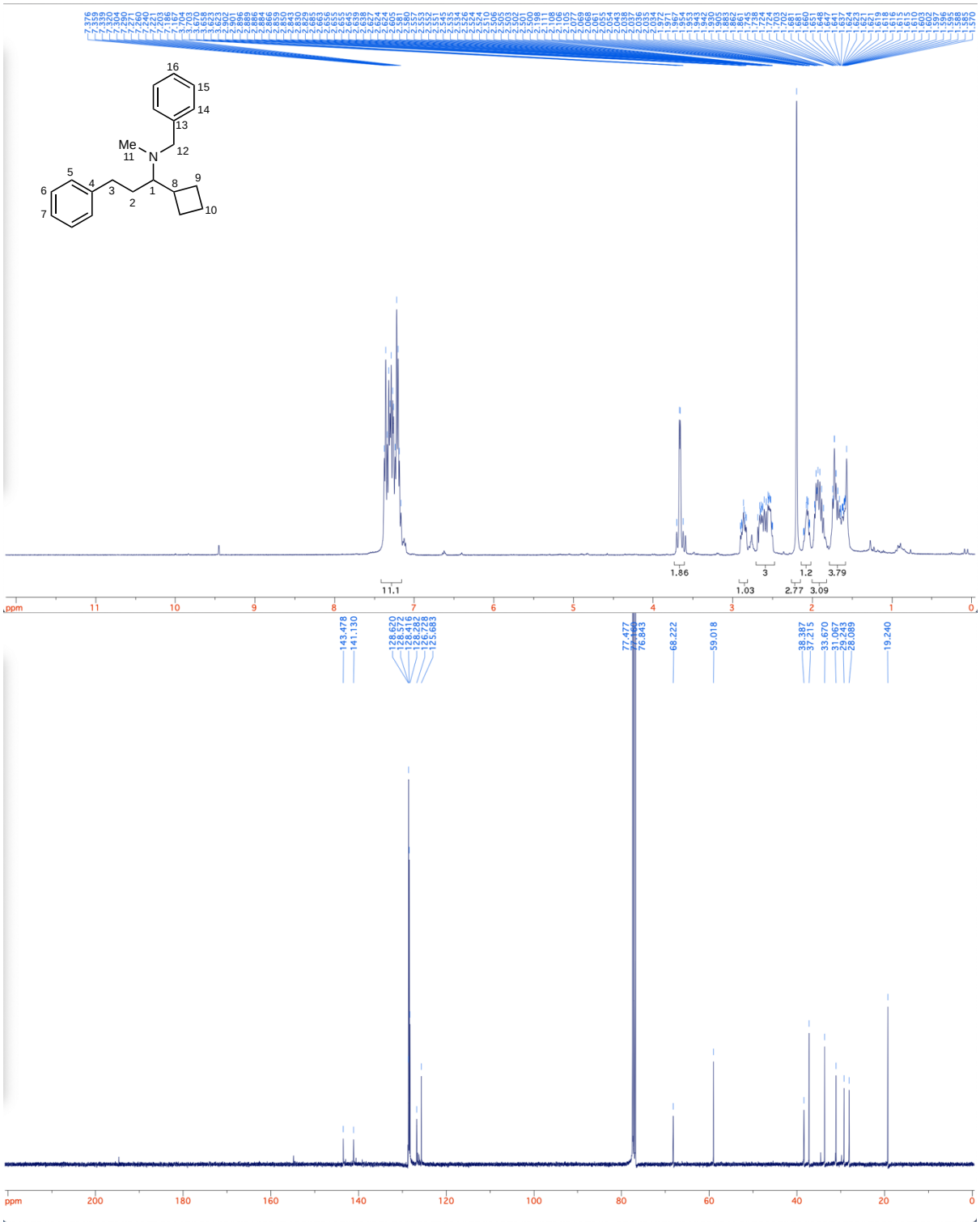
88b



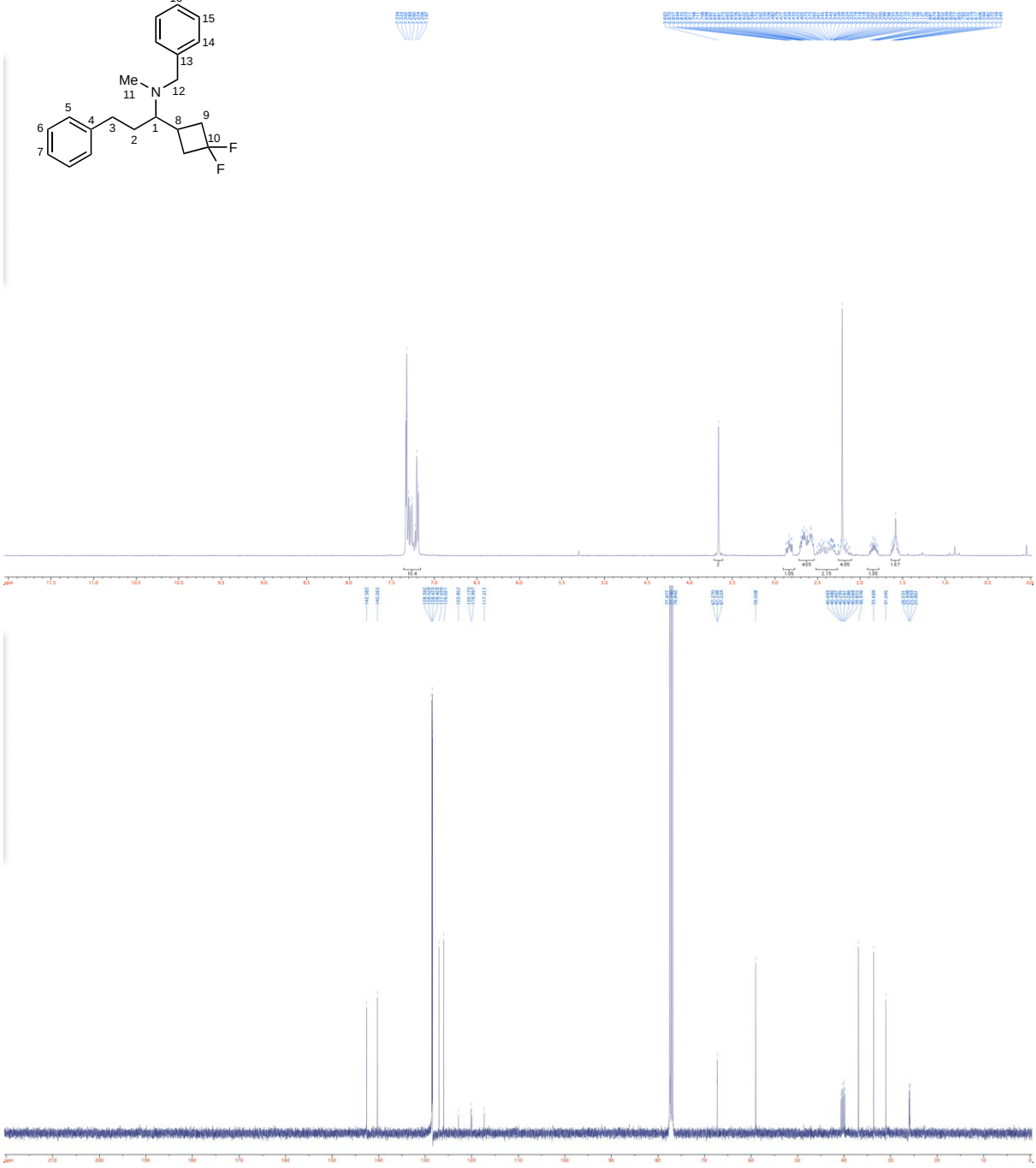
89b

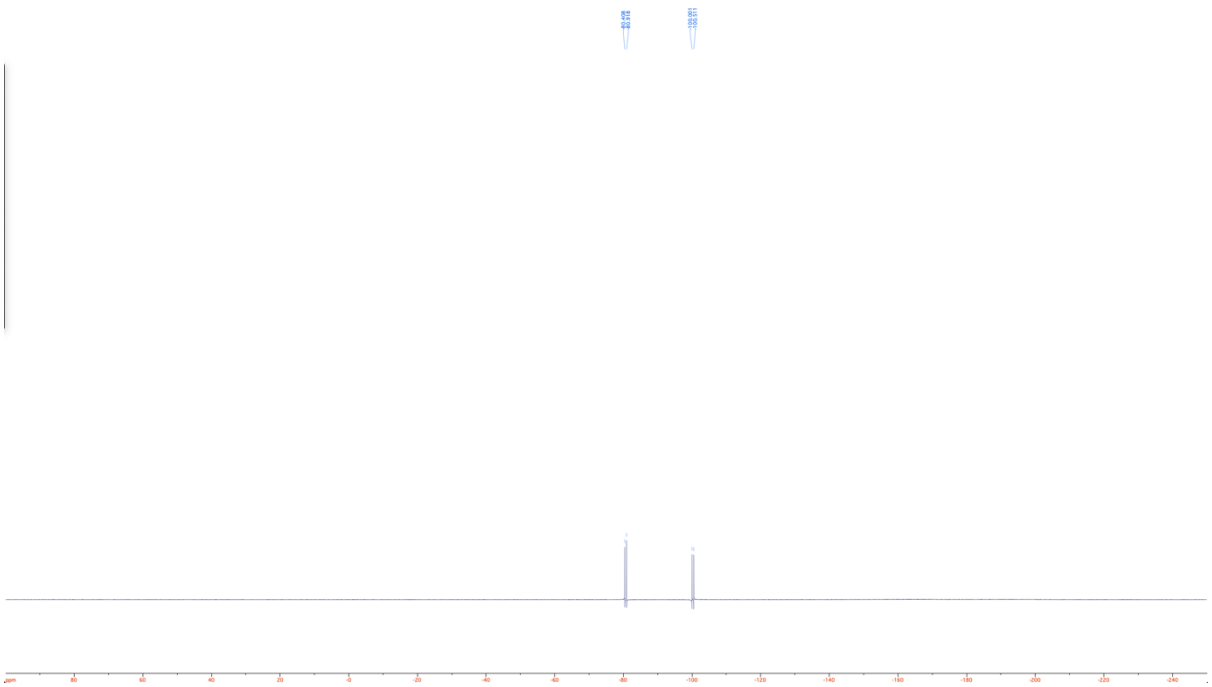


91a

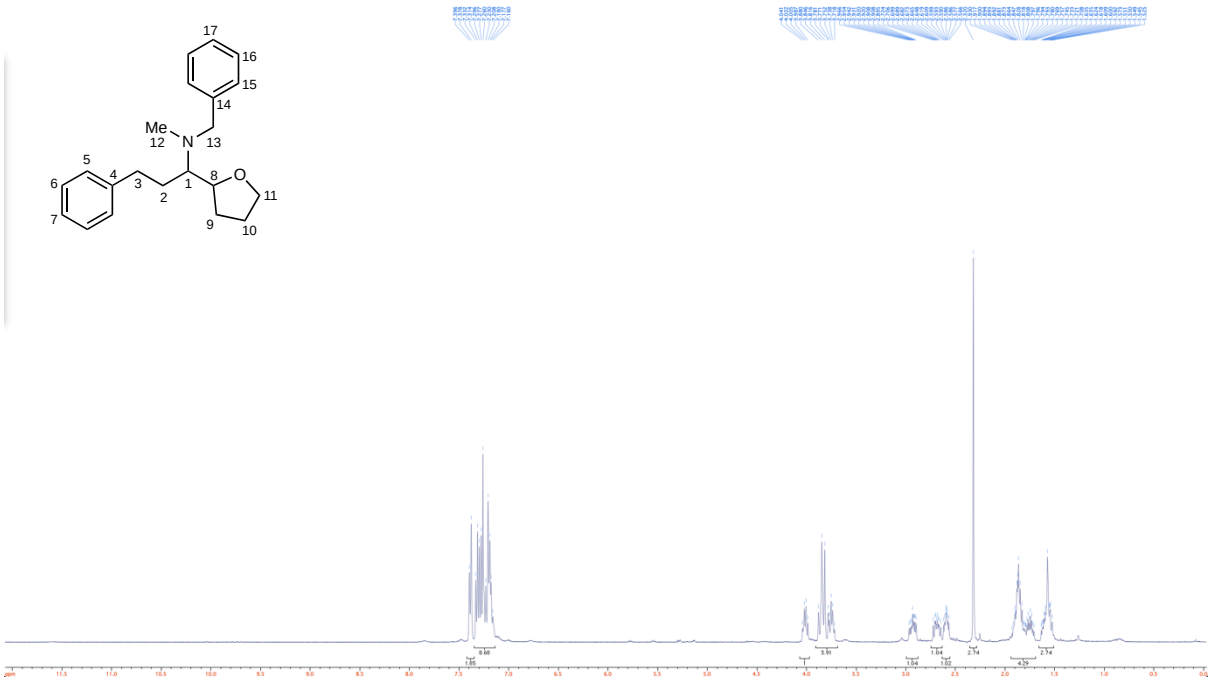

Me
N
11.1
1.86
1.03
3
2.77
1.2
3.09
3.79
143.478
141.130
128.620
128.577
128.416
128.292
127.728
125.683
77.477
76.843
68.222
59.018
38.387
37.215
33.670
31.067
30.143
28.089
19.240

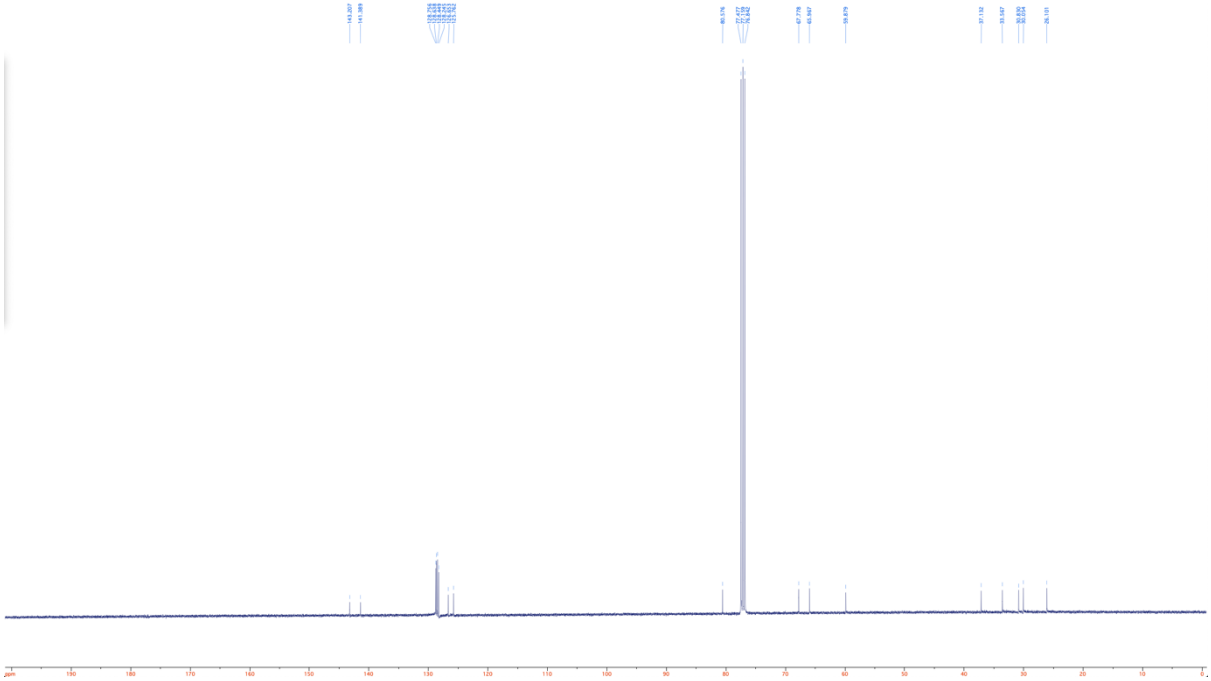
91b



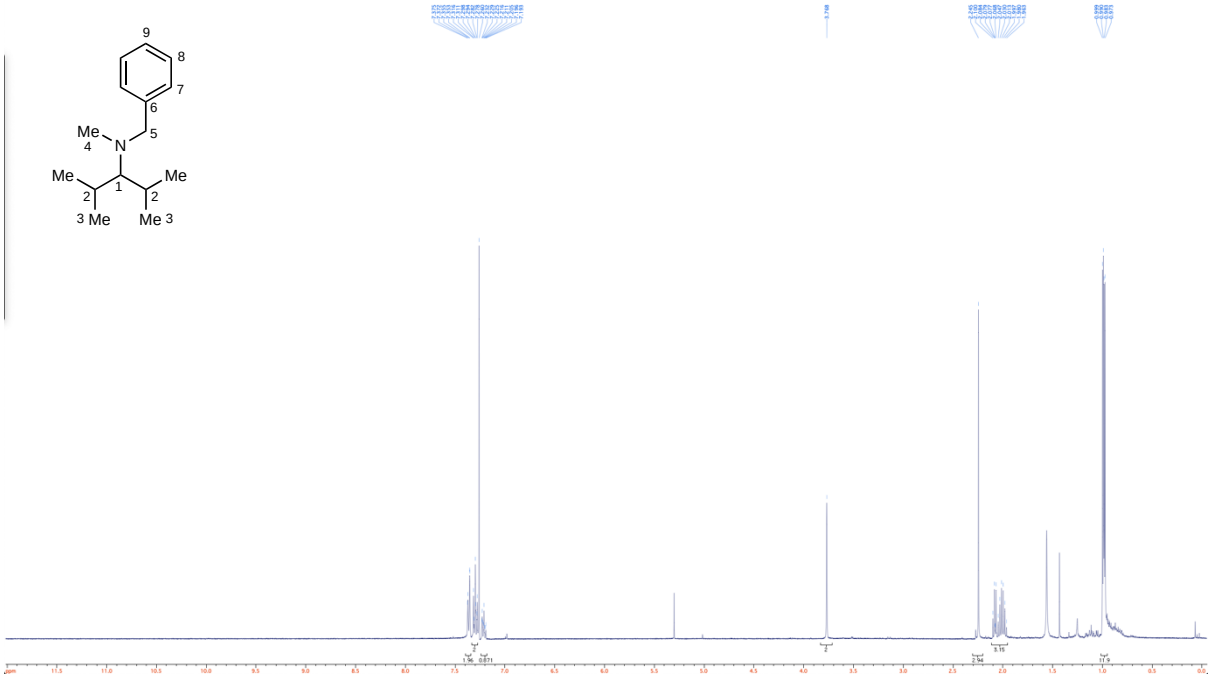


91d

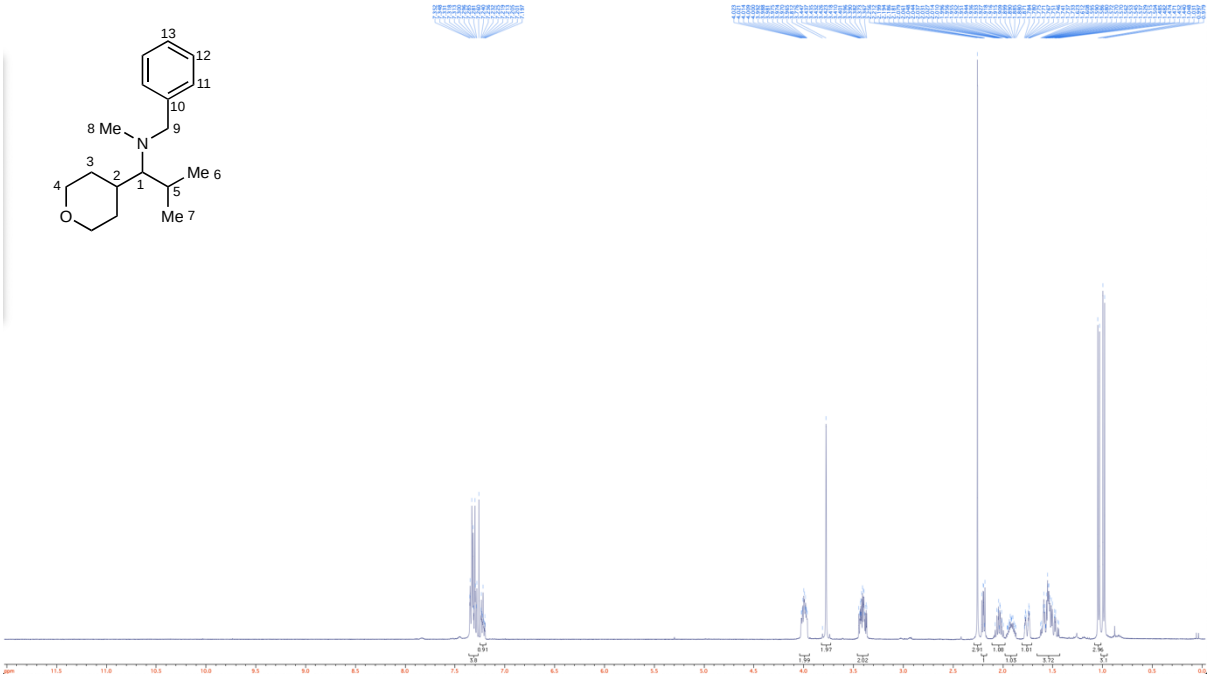


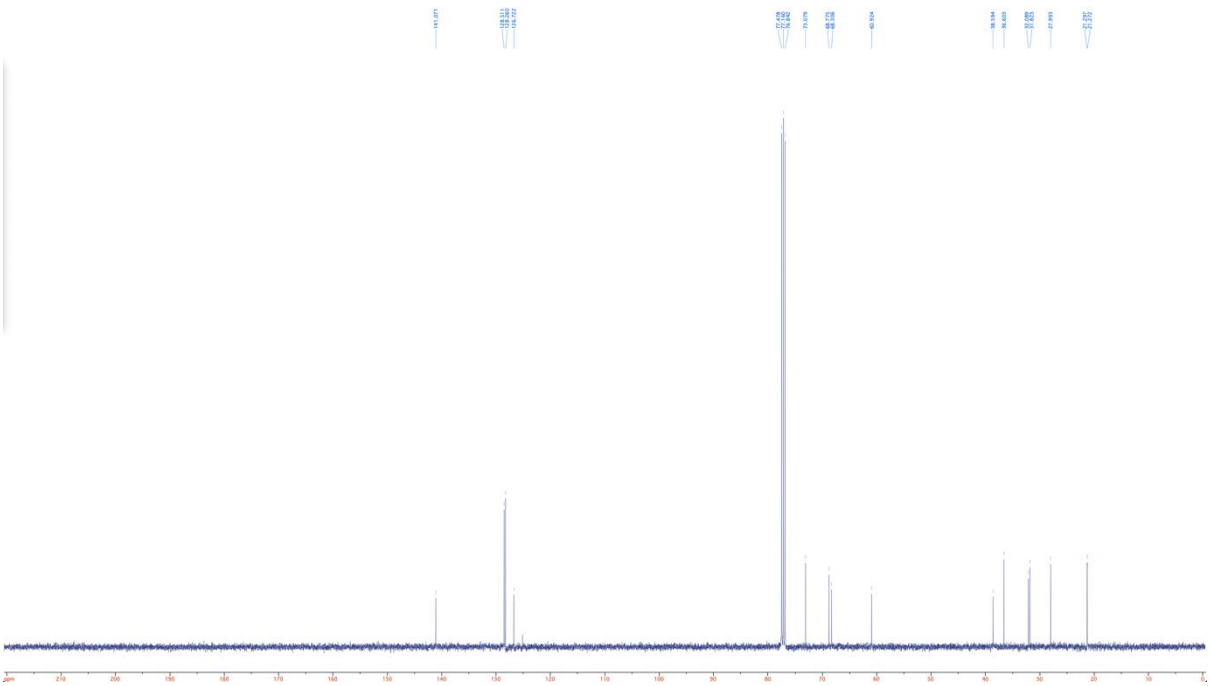


93a

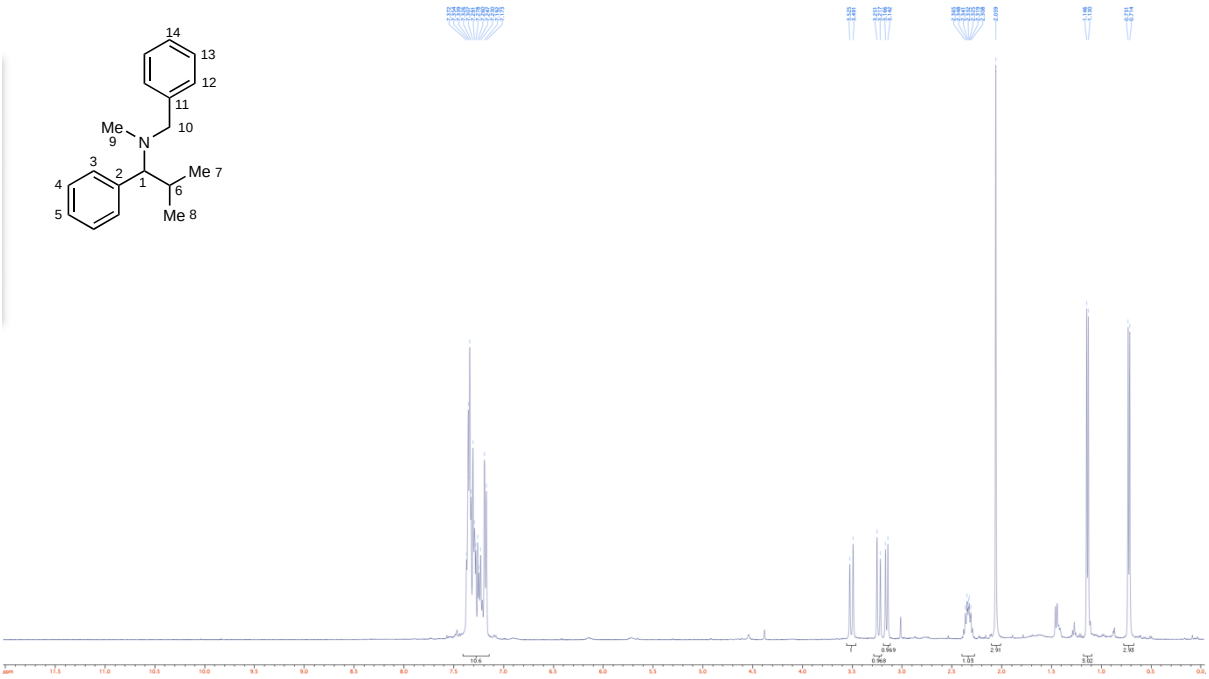


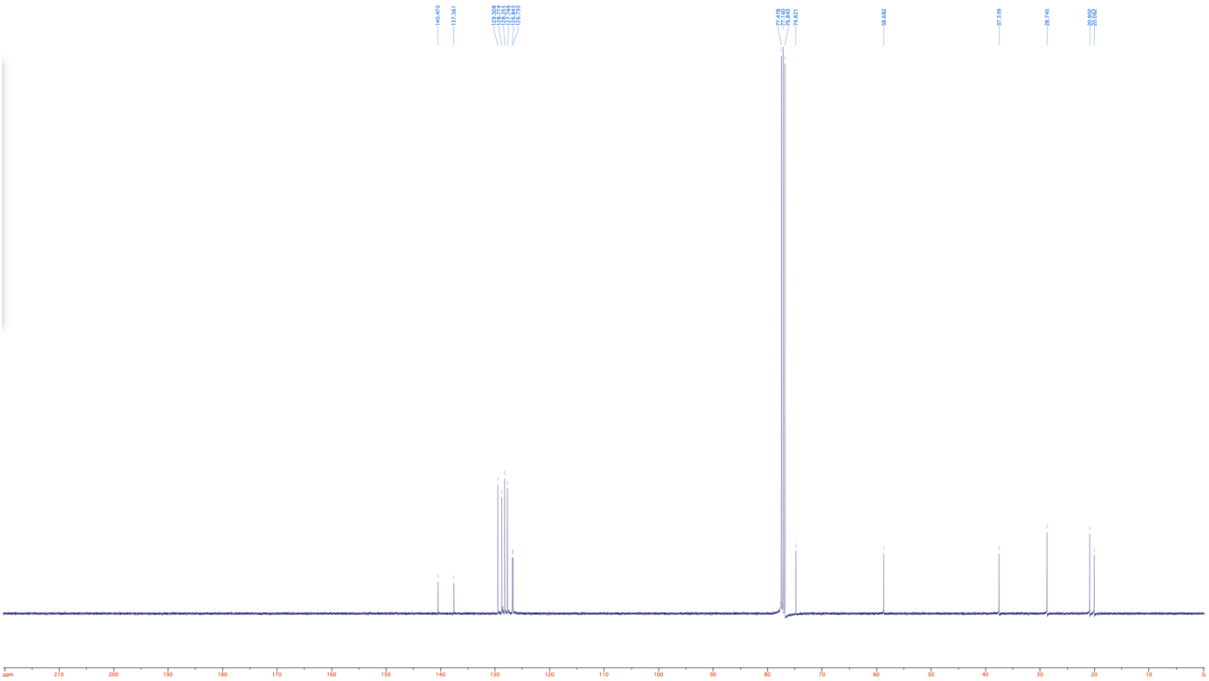
93b



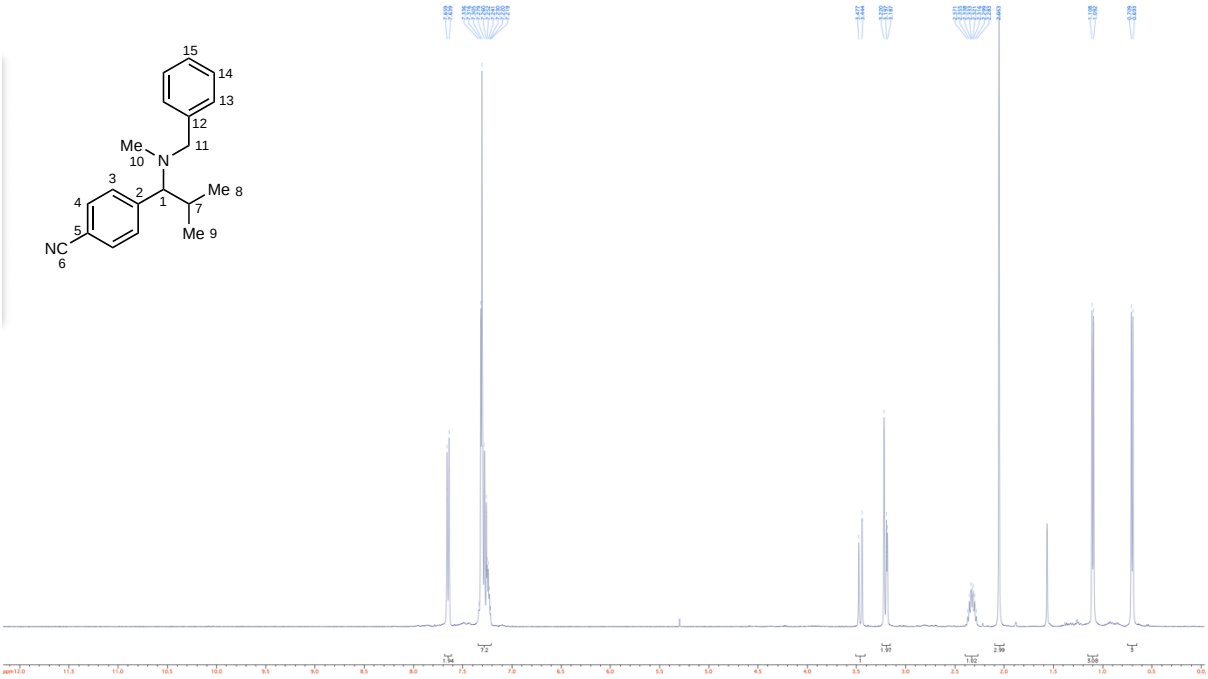


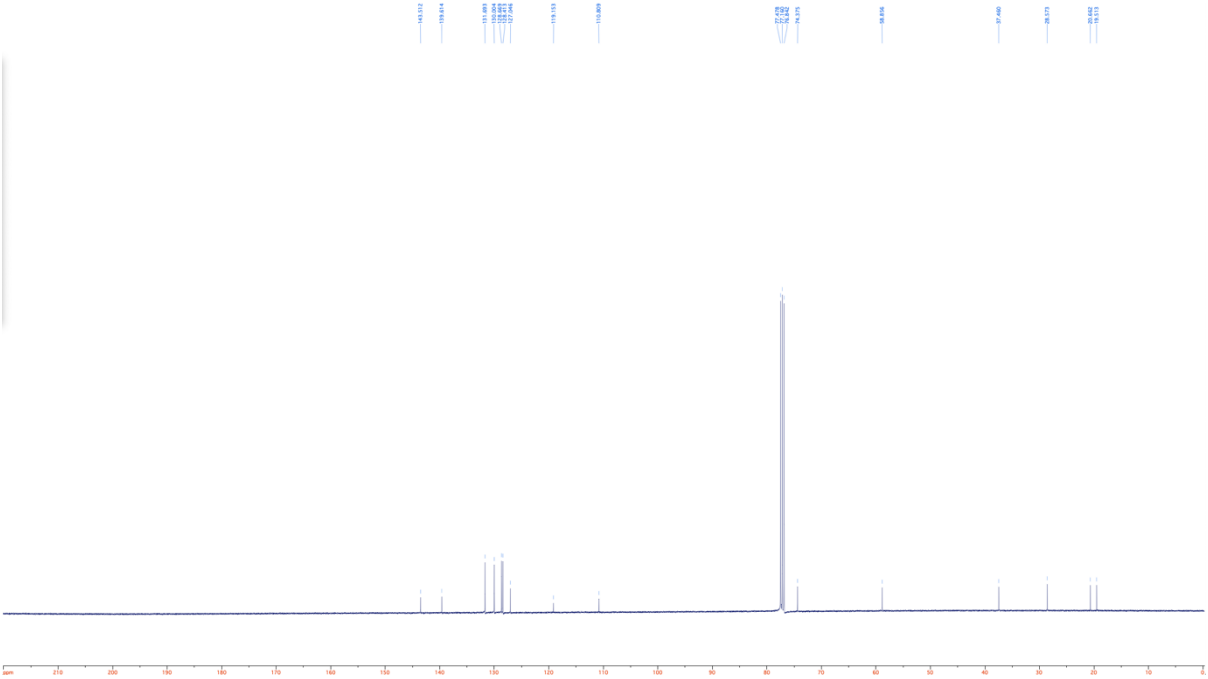
93c



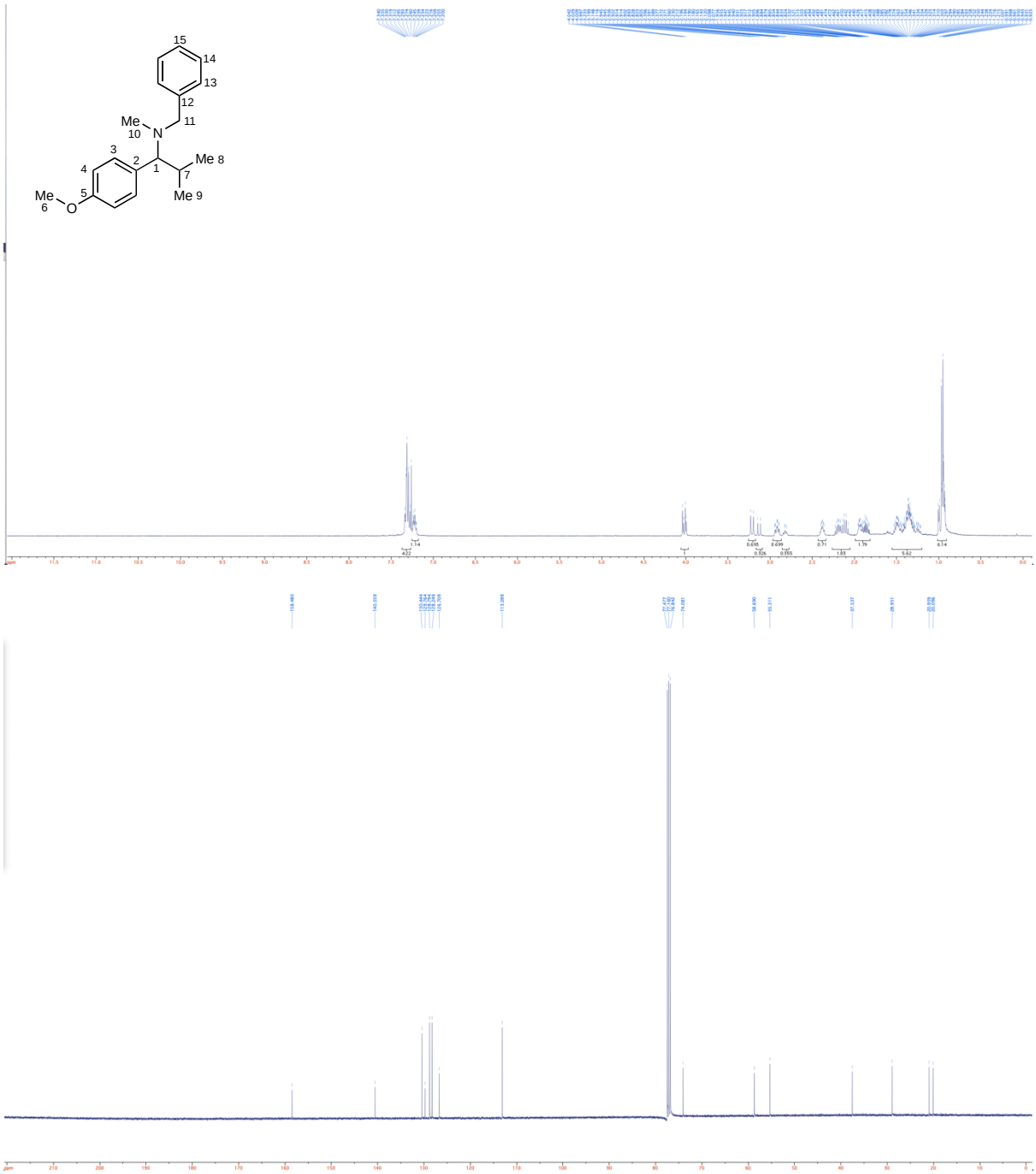


93d

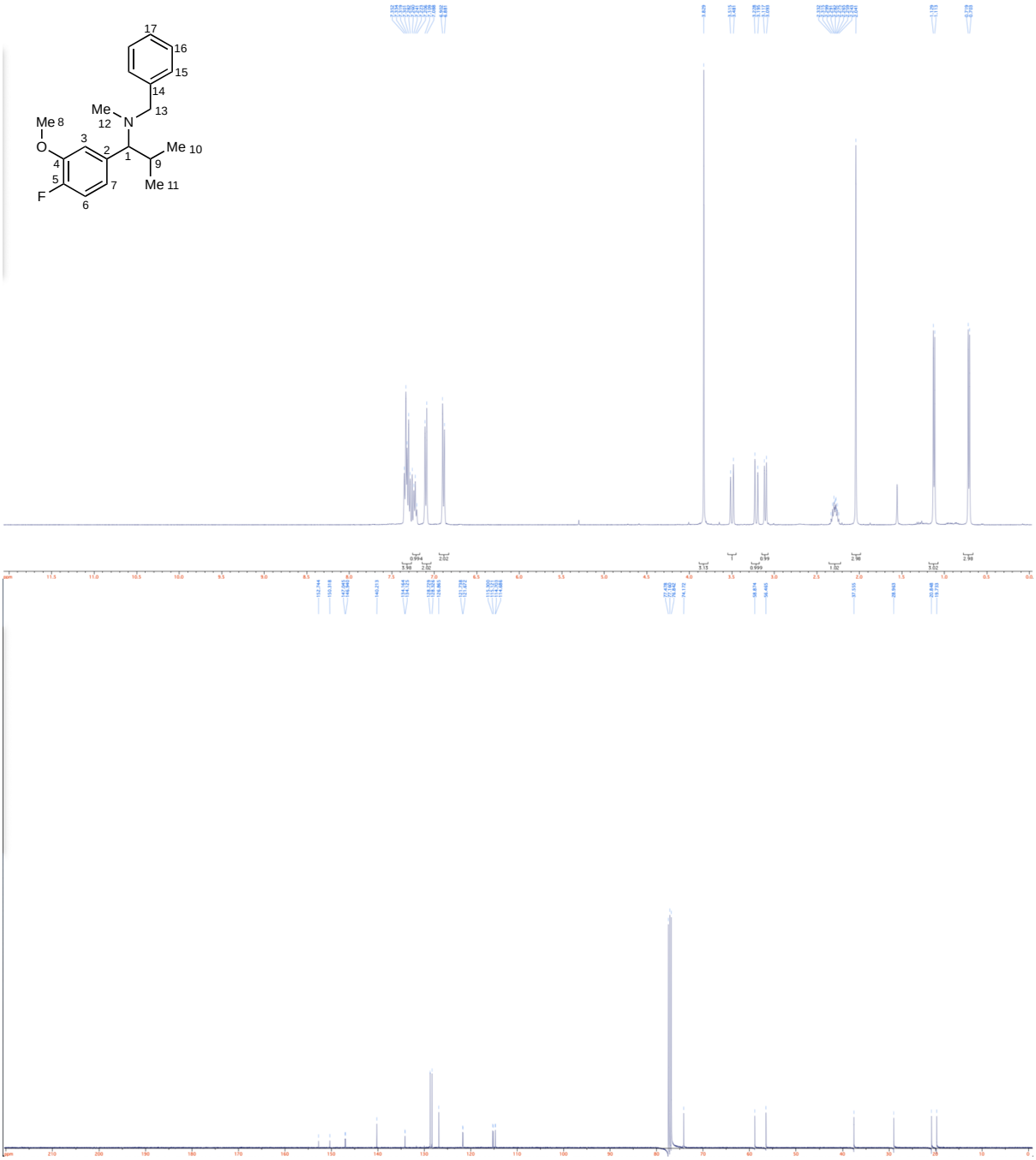




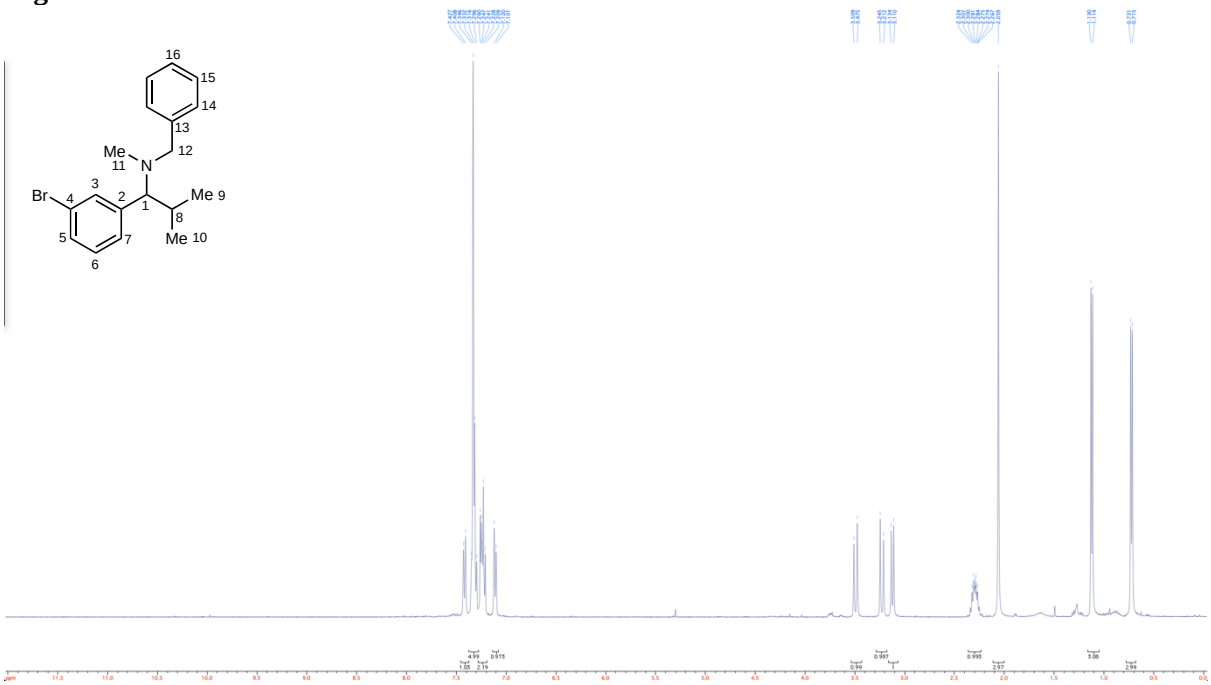
93e

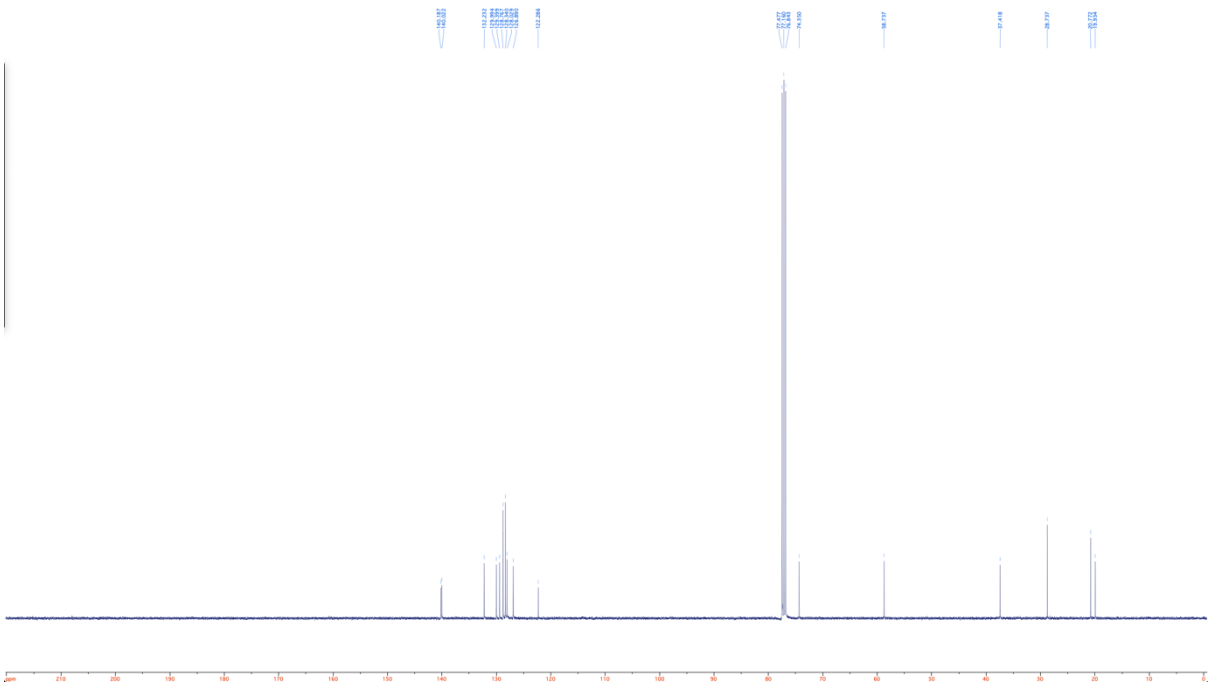


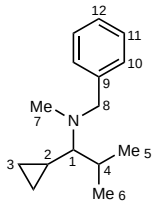
93f



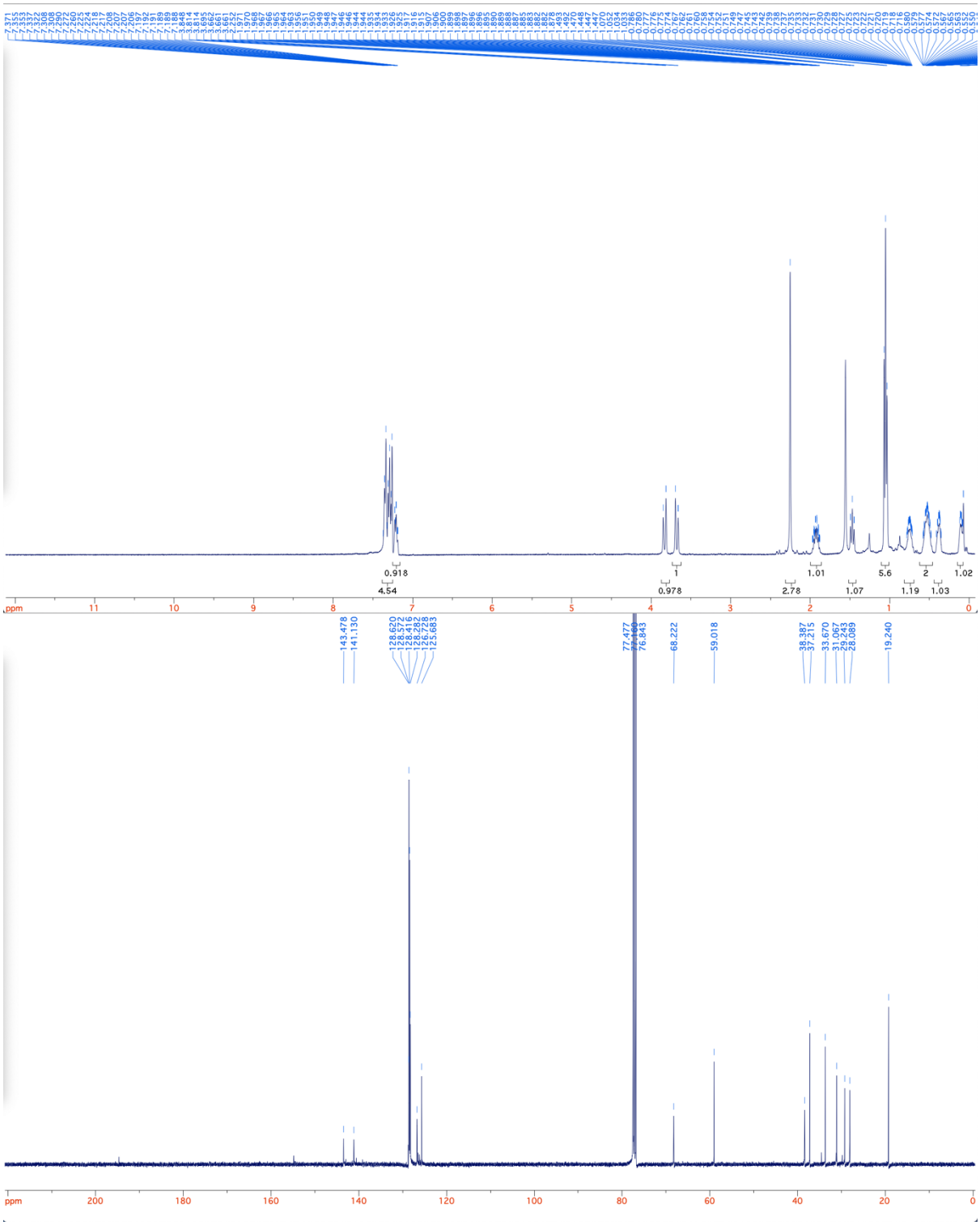
93g





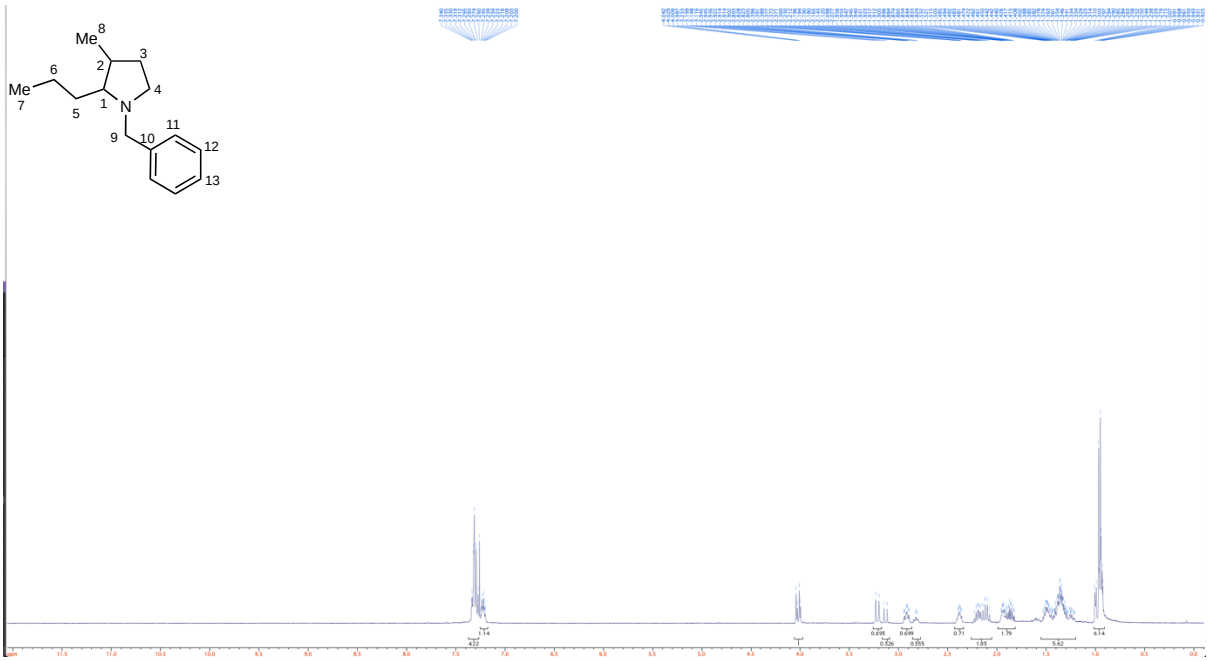

12
11
10
9
8
Me
7
N
Me 5
3
2
1
4
Me 6

59b


0.918
4.54
1
0.978
1.01
2.78
1.07
5.6
1.19
2
1.03
1.02
ppm
143.478
141.130
128.620
128.572
128.416
128.292
126.728
125.683
77.477
77.160
76.843
68.222
59.018
38.387
37.215
33.670
31.067
29.243
28.089
19.240
ppm

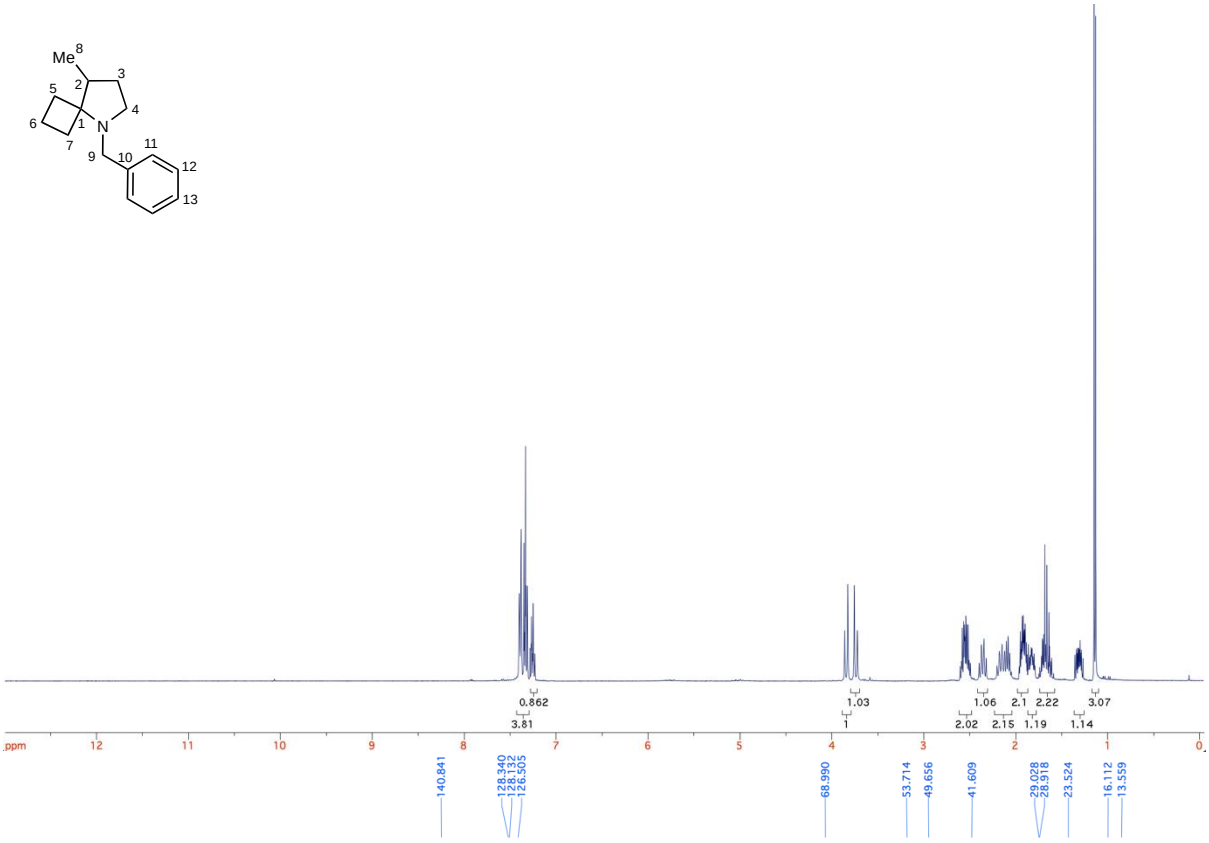
9.3 Spectra for chapter 4

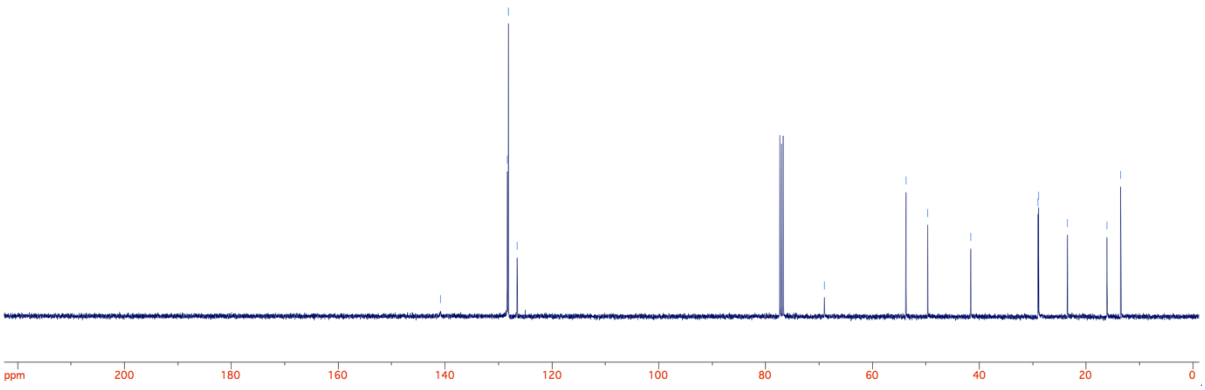
107b



113b

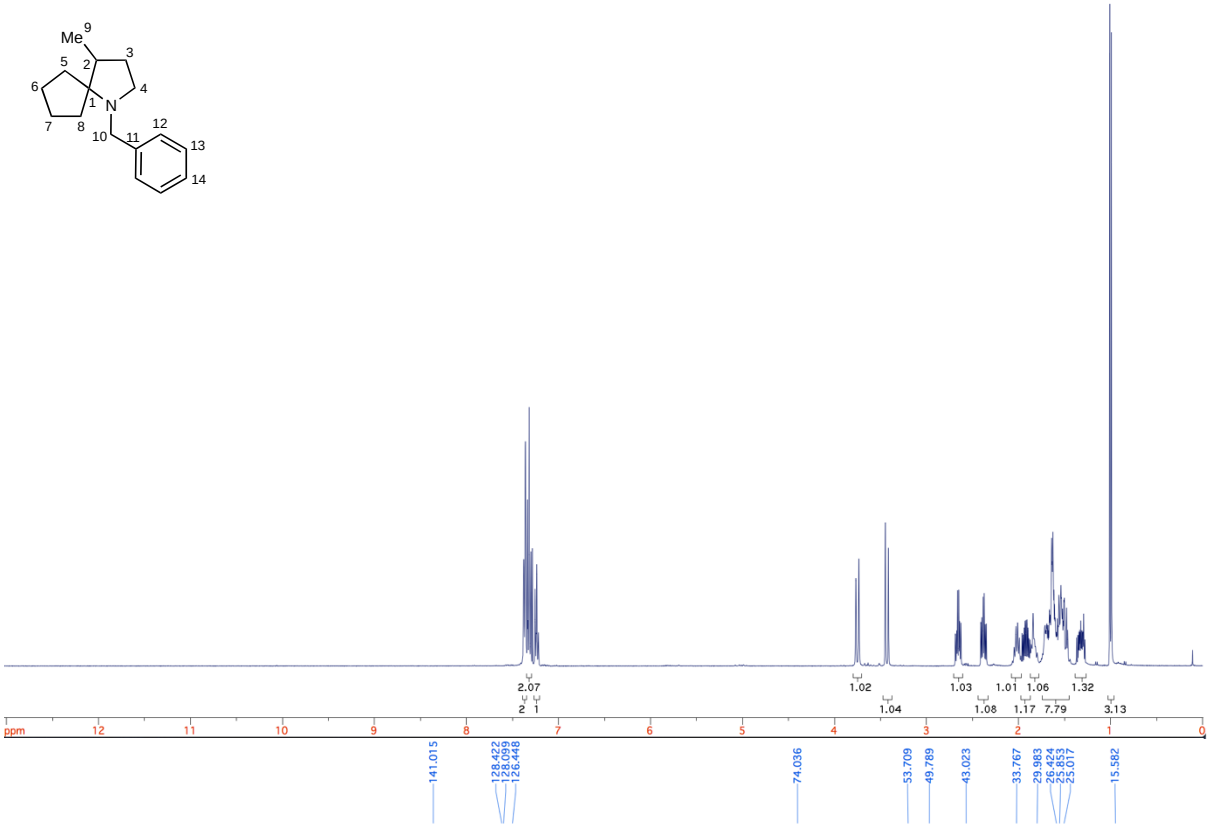
Me
8
2
3
5
4
6
1
N
7
9
10
11
12
13

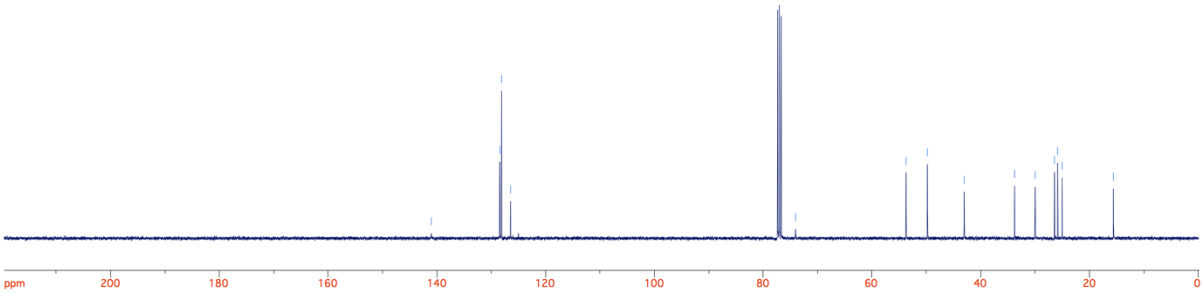

0.862
3.81
1.03
1
1.06
2.02
2.1
2.15
2.22
1.19
3.07
1.14
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0
140.841
128.340
127.132
126.505
68.990
53.714
49.656
41.609
29.028
28.918
23.524
16.112
13.559


ppm
200
180
160
140
120
100
80
60
40
20
0

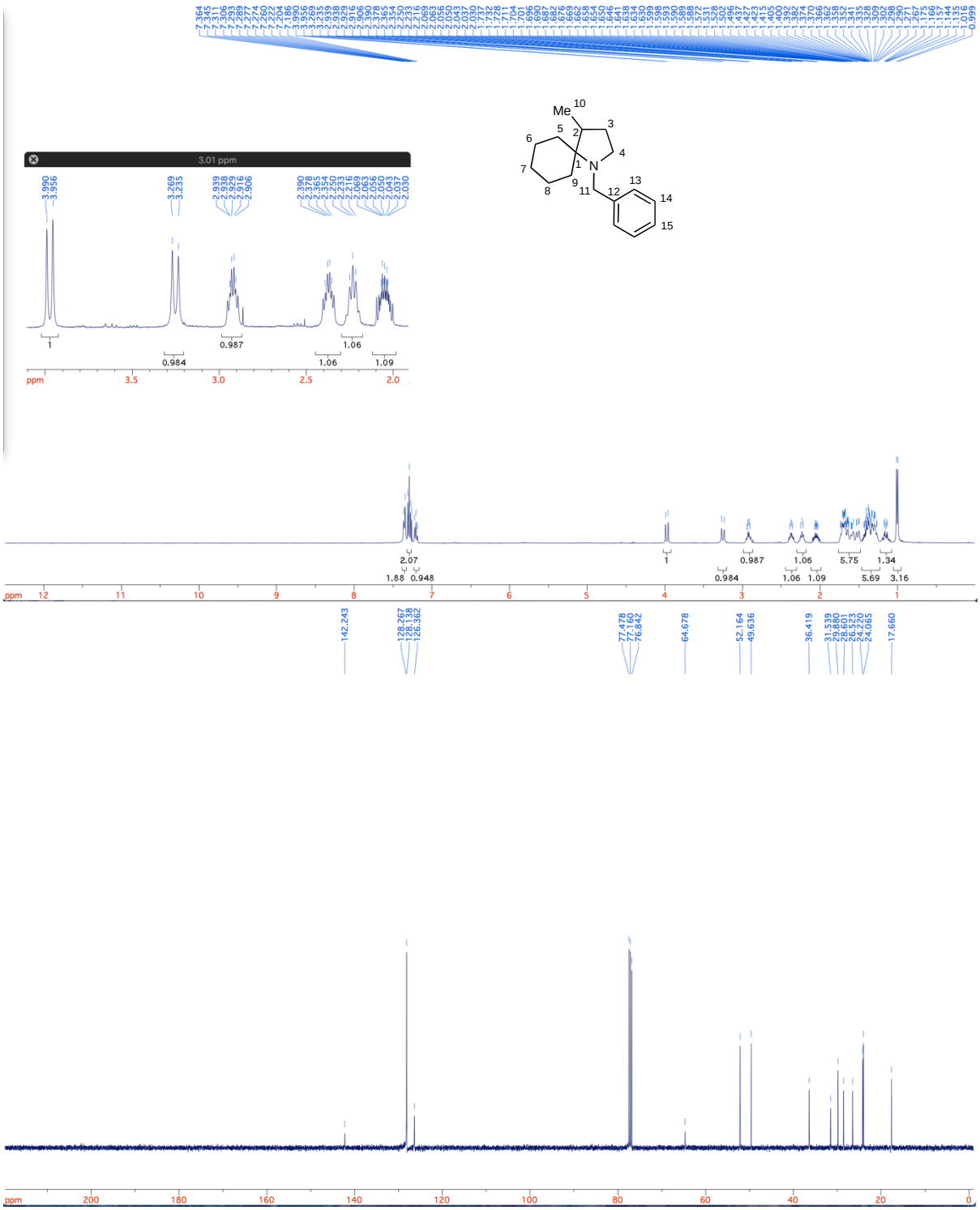
114a

Me
9
3
5
2
4
6
1
N
7
8
10
11
12
13
14


2.07
2
1
1.02
1.04
1.03
1.08
1.01
1.17
1.06
7.79
1.32
3.13
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0
141.015
128.422
128.099
126.448
74.036
53.709
49.789
43.023
33.767
29.983
26.424
25.653
25.017
15.582

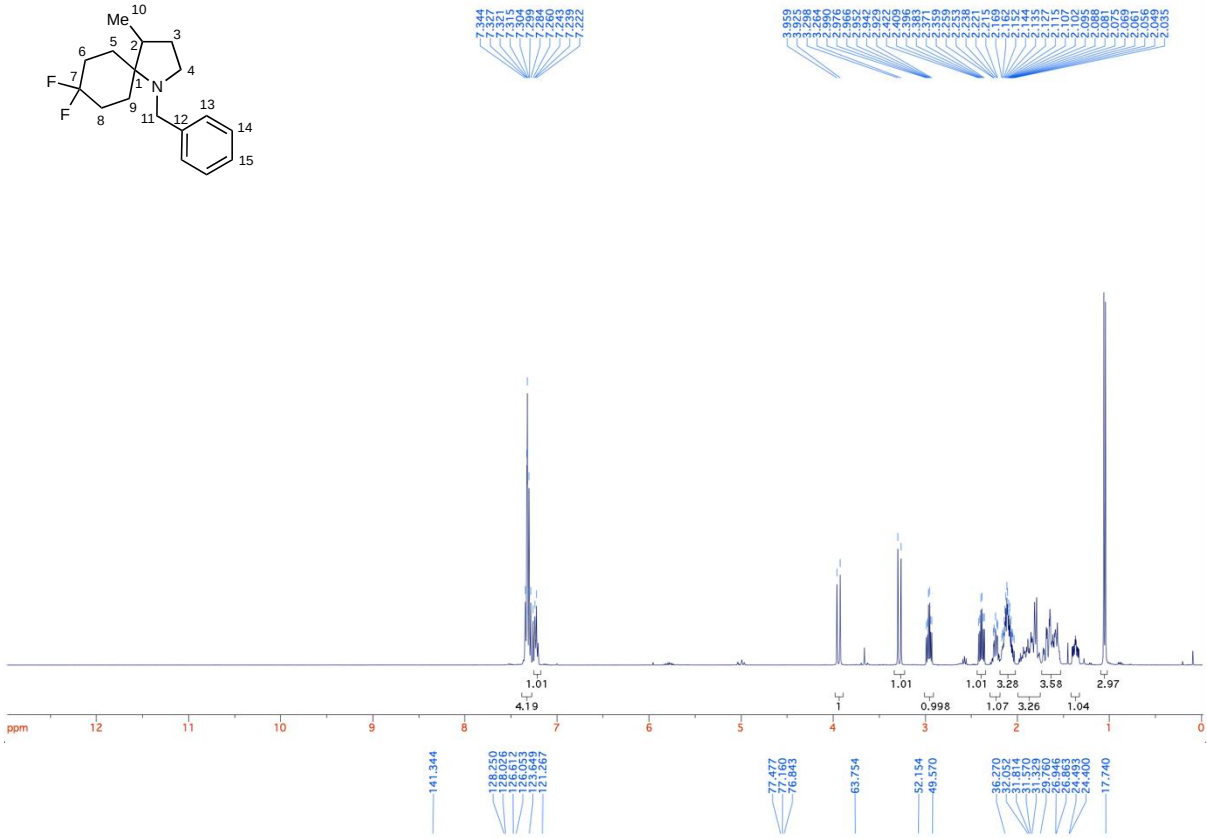

ppm
200
180
160
140
120
100
80
60
40
20
0

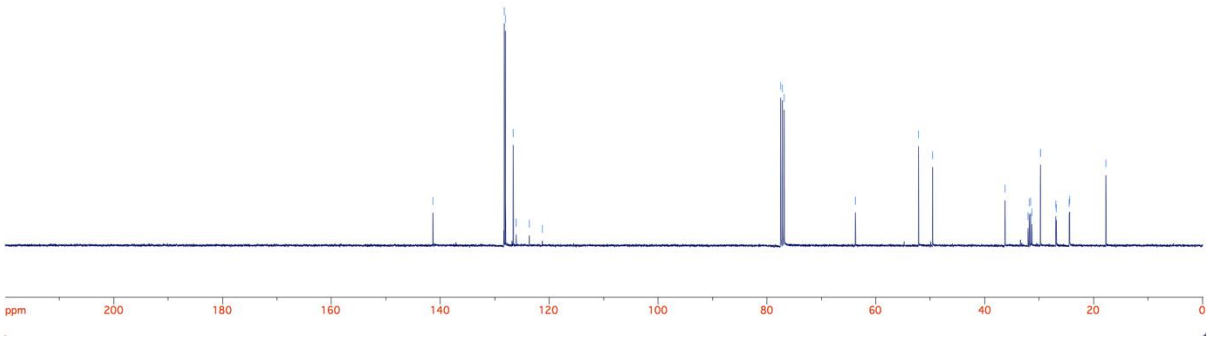
114b

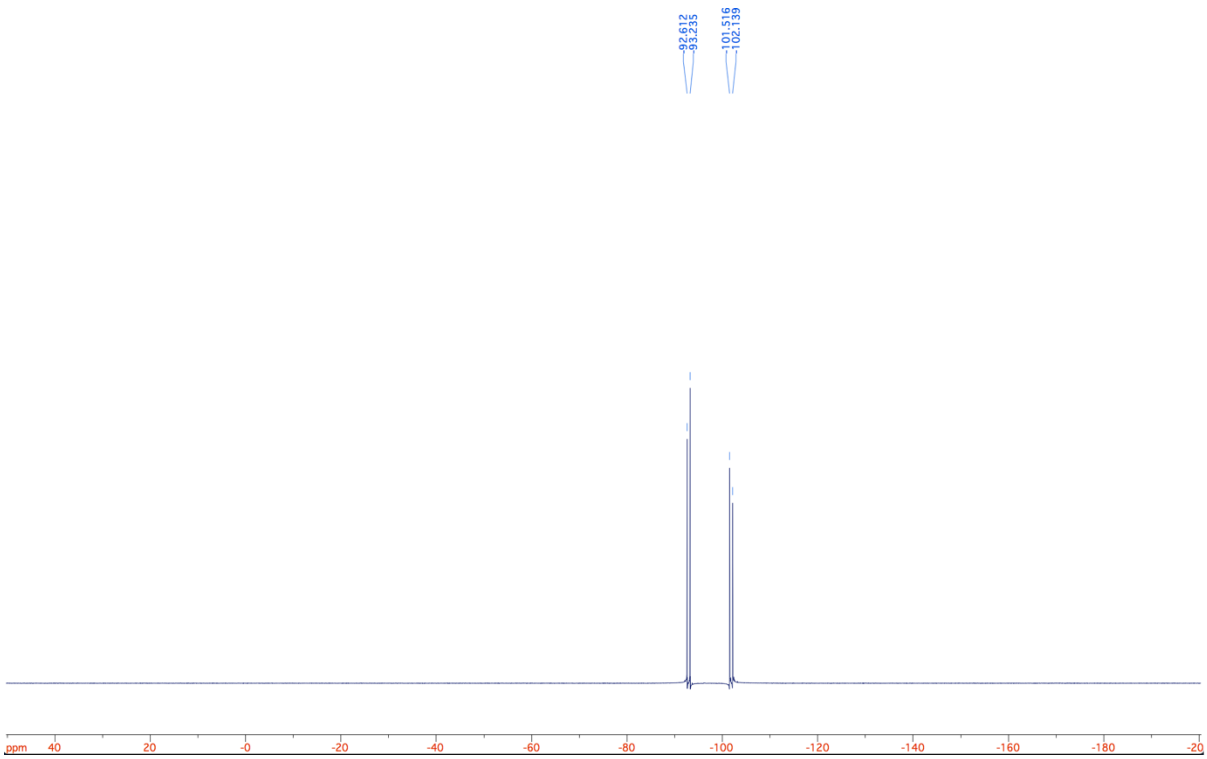

Me
N
3.01 ppm
ppm
142.243
128.267
128.138
126.362
77.478
77.160
76.842
64.678
52.164
49.636
36.419
31.539
29.800
29.601
26.523
24.220
24.065
17.660

114c

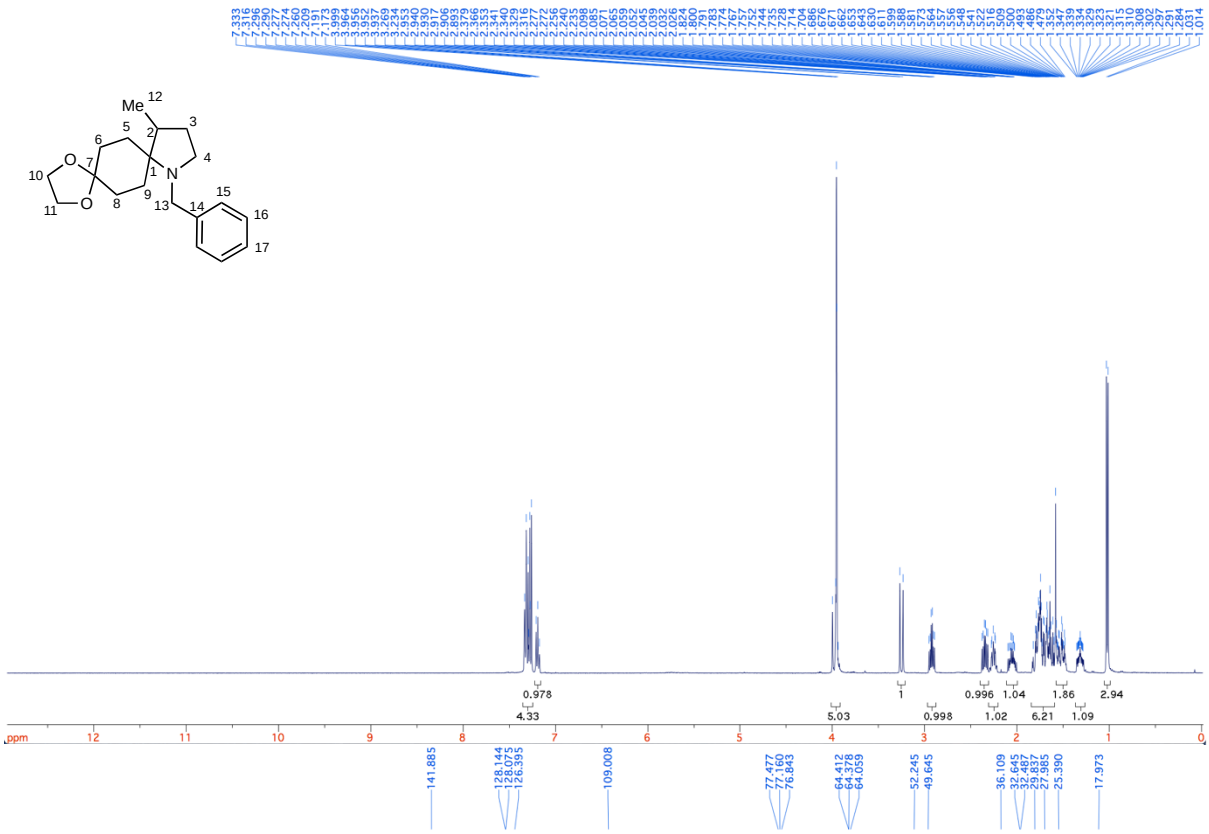
Me
10
3
2
5
6
4
F
7
1
N
F
8
9
11
12
13
14
15

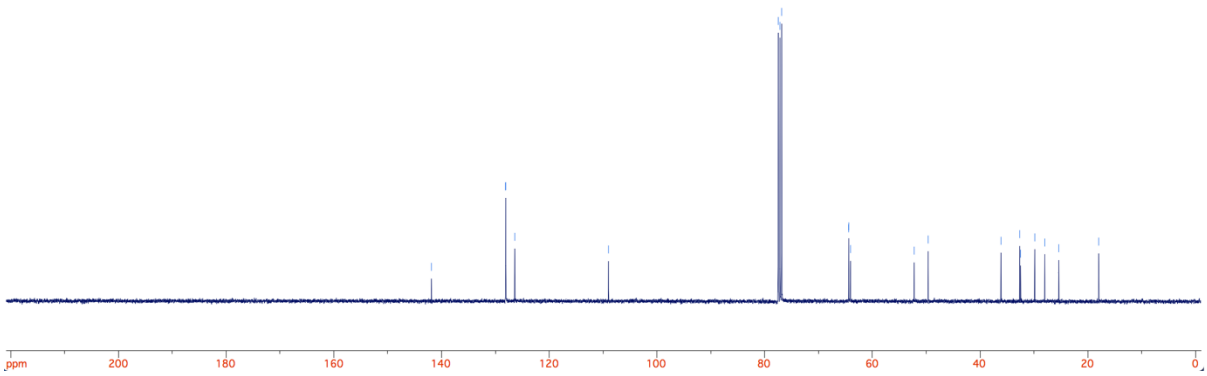

1.01
4.19
1
1.01
0.998
1.01
1.07
3.28
3.26
3.58
1.04
2.97
ppm


ppm

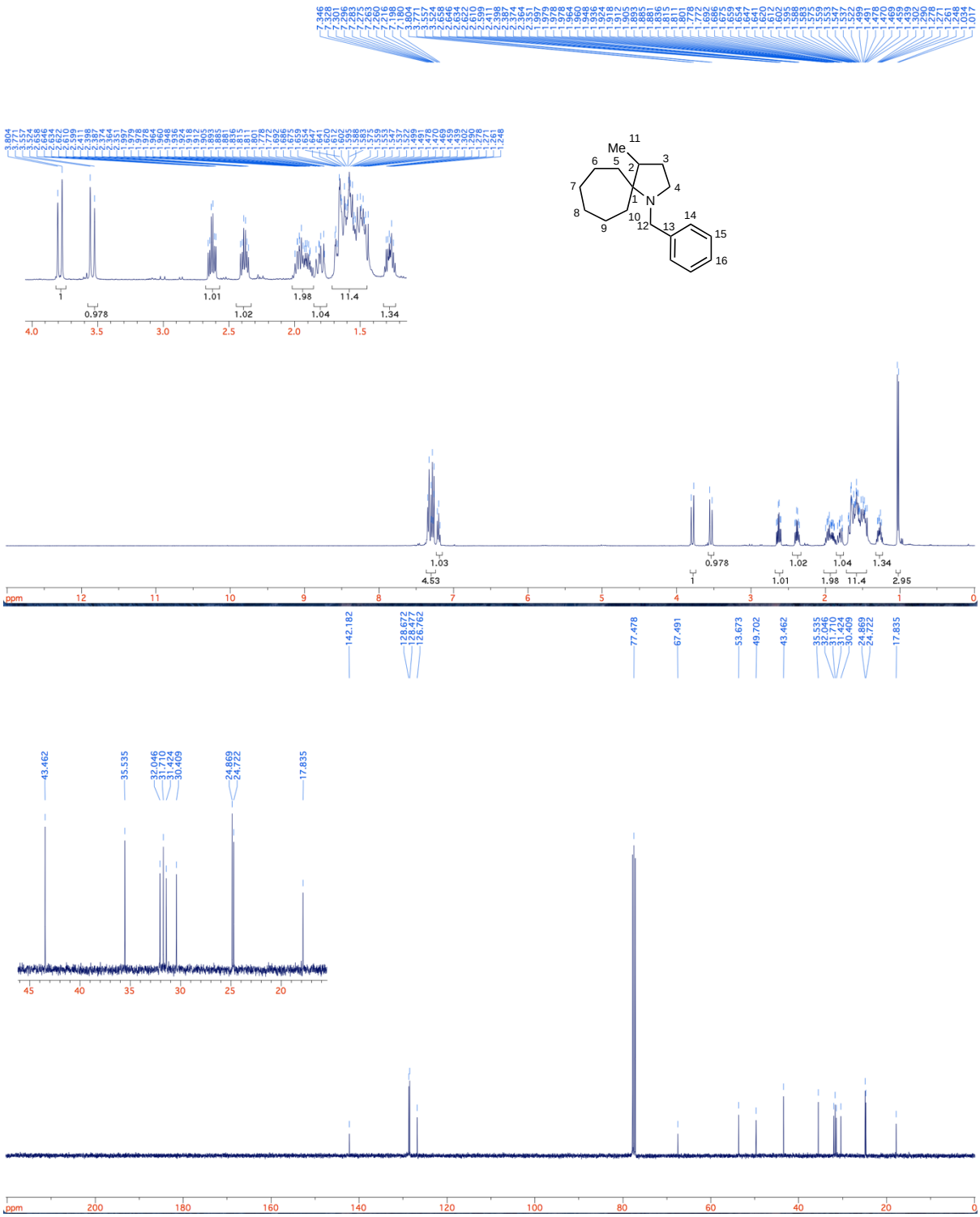

-92.612
-93.235
-101.516
-102.139
ppm
40
20
-0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-20

114d

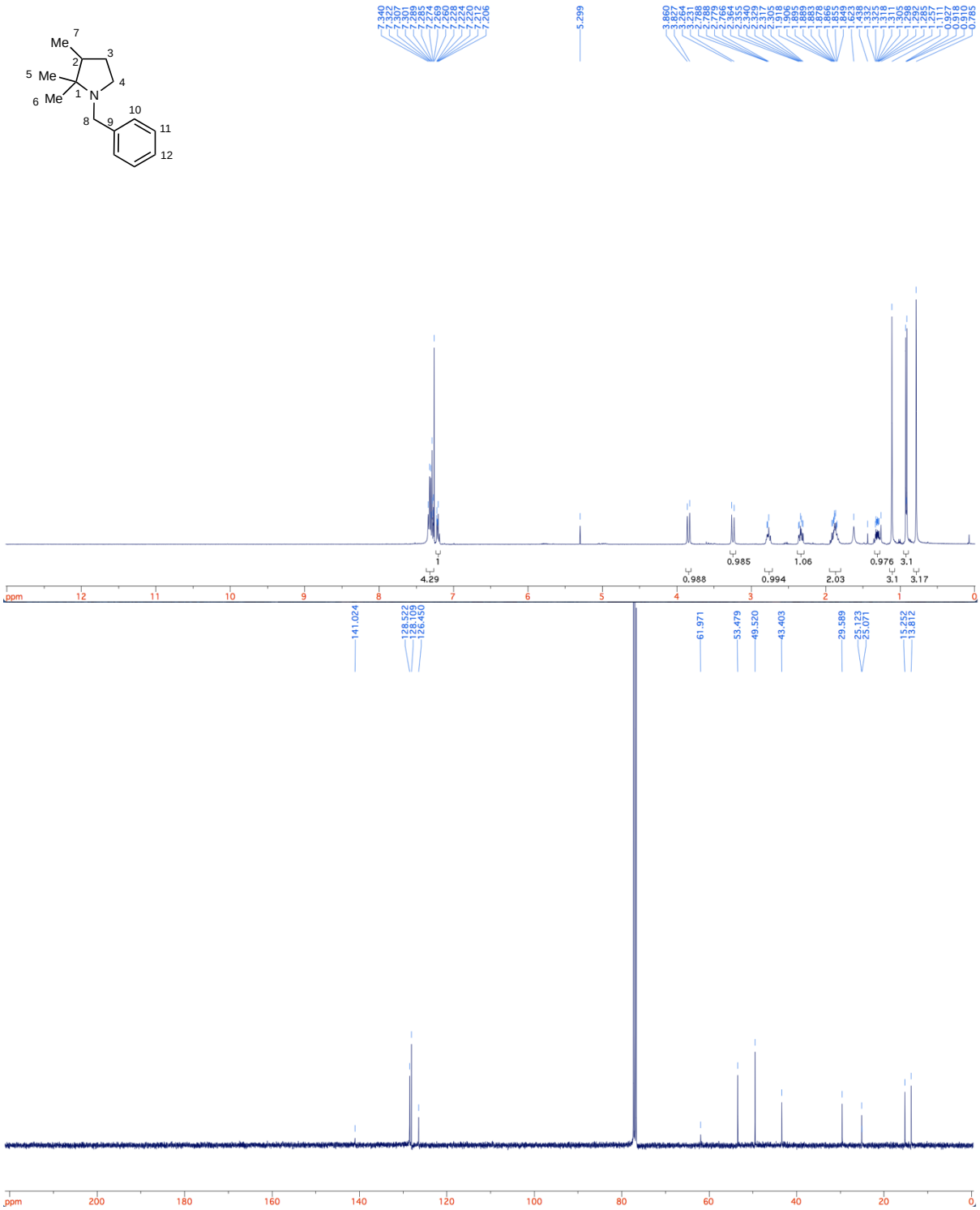

Me
12
5
2
3
6
4
O
7
1
N
10
9
15
11
O
8
13
14
16
17
0.978
4.33
5.03
1
0.998
0.996
1.04
1.02
1.86
6.21
1.09
2.94
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0


141.885
128.144
128.075
126.395
109.008
77.477
77.160
76.843
64.412
64.378
64.059
52.245
49.645
36.109
32.645
32.487
29.837
27.985
25.390
17.973
ppm
200
180
160
140
120
100
80
60
40
20
0

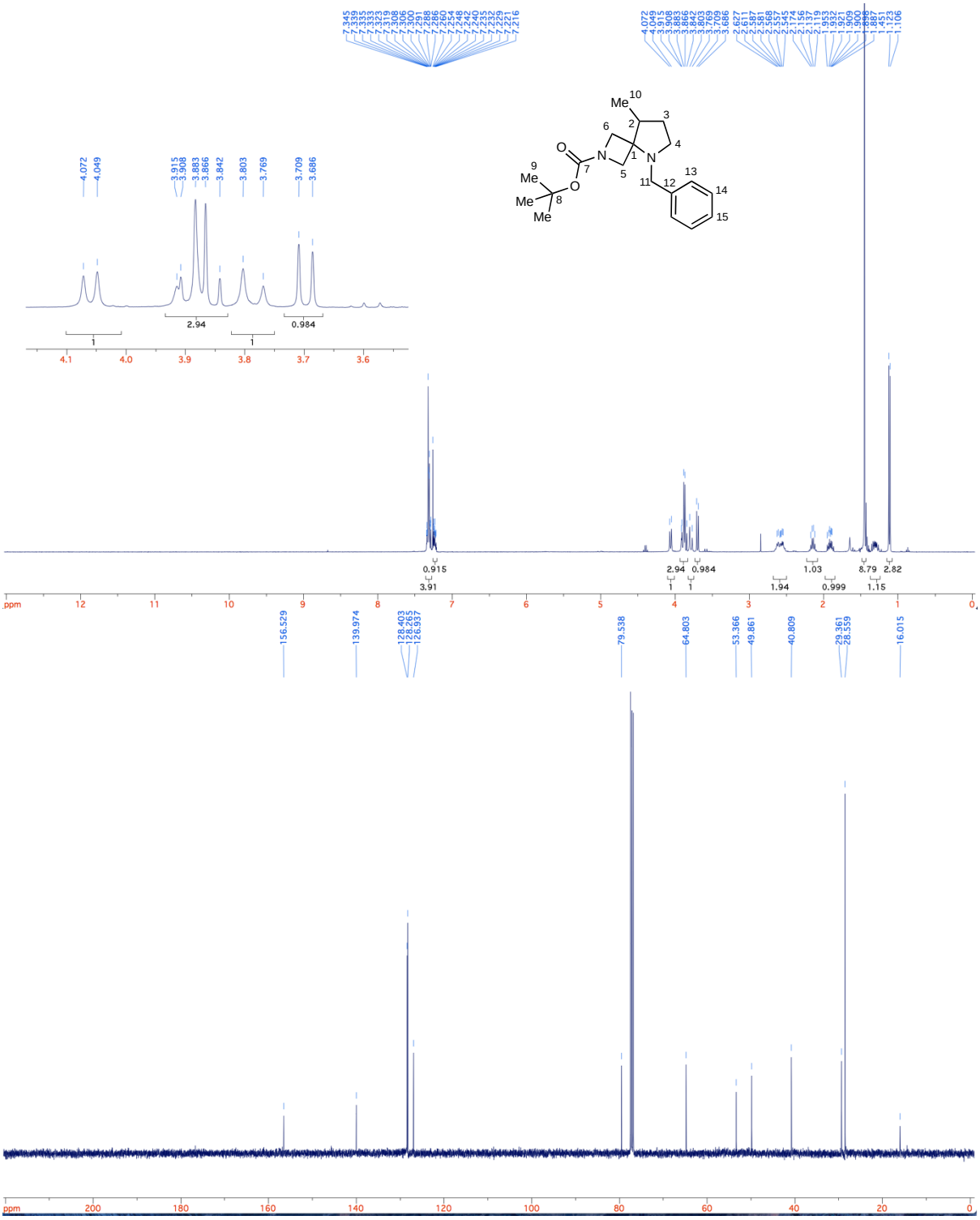
114g


Me
N
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
1
0.978
1.01
1.02
1.98
1.04
11.4
1.34
4.0
3.5
3.0
2.5
2.0
1.5
1.03
4.53
0.978
1
1.02
1.01
1.04
1.98
11.4
1.34
2.95
ppm
142.182
128.672
128.477
126.762
77.478
67.491
53.673
49.702
43.462
35.535
32.046
31.710
31.424
30.409
24.869
24.722
17.835
43.462
35.535
32.046
31.710
31.424
30.409
24.869
24.722
17.835
45
40
35
30
25
20
ppm
200
180
160
140
120
100
80
60
40
20
0

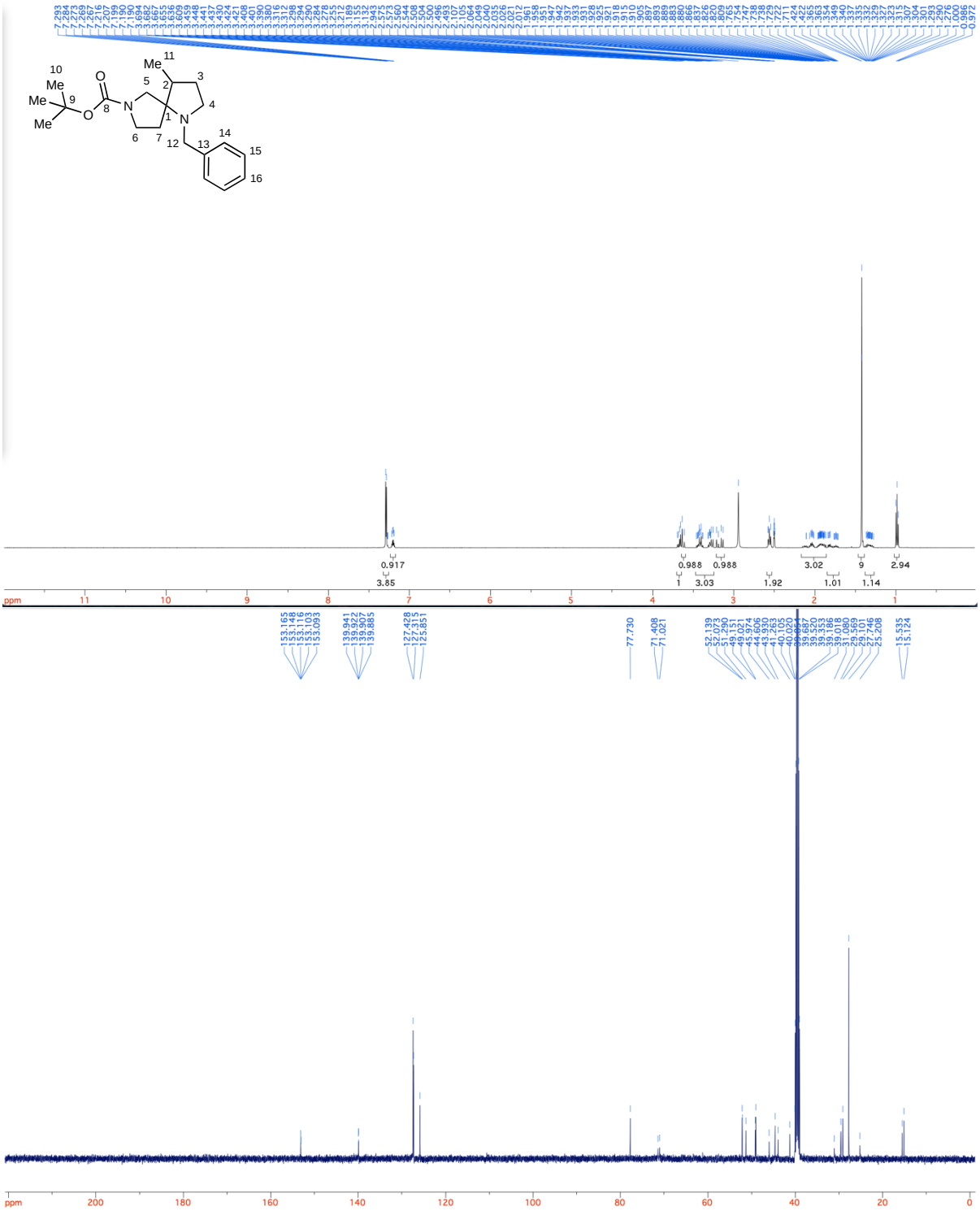
114i


Me
Me
Me
N
7.340
7.322
7.307
7.301
7.289
7.285
7.274
7.269
7.260
7.228
7.224
7.220
7.212
7.206
5.299
3.860
3.827
3.764
3.731
3.718
2.788
2.779
2.766
2.764
2.355
2.340
2.329
2.317
2.305
2.116
2.106
1.906
1.895
1.889
1.883
1.878
1.866
1.855
1.845
1.623
1.438
1.432
1.325
1.318
1.311
1.301
1.298
1.292
1.286
1.257
1.111
1.107
0.927
0.918
0.910
0.785
1
4.29
0.988
0.985
0.994
1.06
2.03
0.976
3.1
3.1
3.17
ppm
141.024
128.522
128.106
126.450
61.971
53.479
49.520
43.403
29.589
25.123
23.071
15.252
13.812

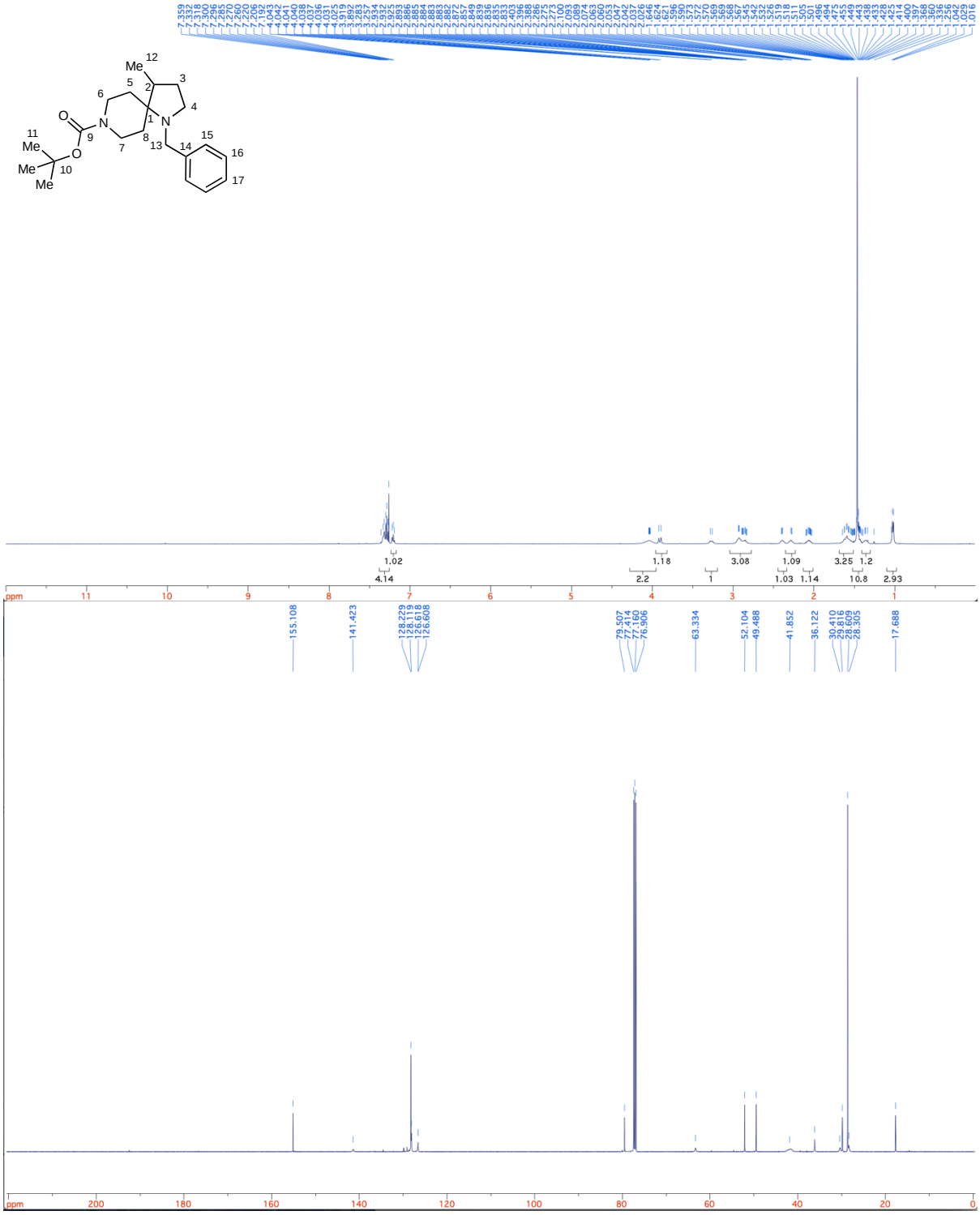
115a


Me
10
3
2
6
4
O
N
1
N
7
5
9
Me
O
11
12
13
14
Me
8
15
Me
4.072
4.049
3.915
3.908
3.883
3.866
3.842
3.803
3.769
3.709
3.686
2.94
0.984
1
1
4.1
4.0
3.9
3.8
3.7
3.6
0.915
3.91
2.94
0.984
1
1
1.03
1.94
0.999
8.79
1.15
2.82
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0
156.529
139.974
128.403
128.265
126.937
79.538
64.803
53.366
49.861
40.809
29.361
28.559
16.015
ppm
200
180
160
140
120
100
80
60
40
20
0

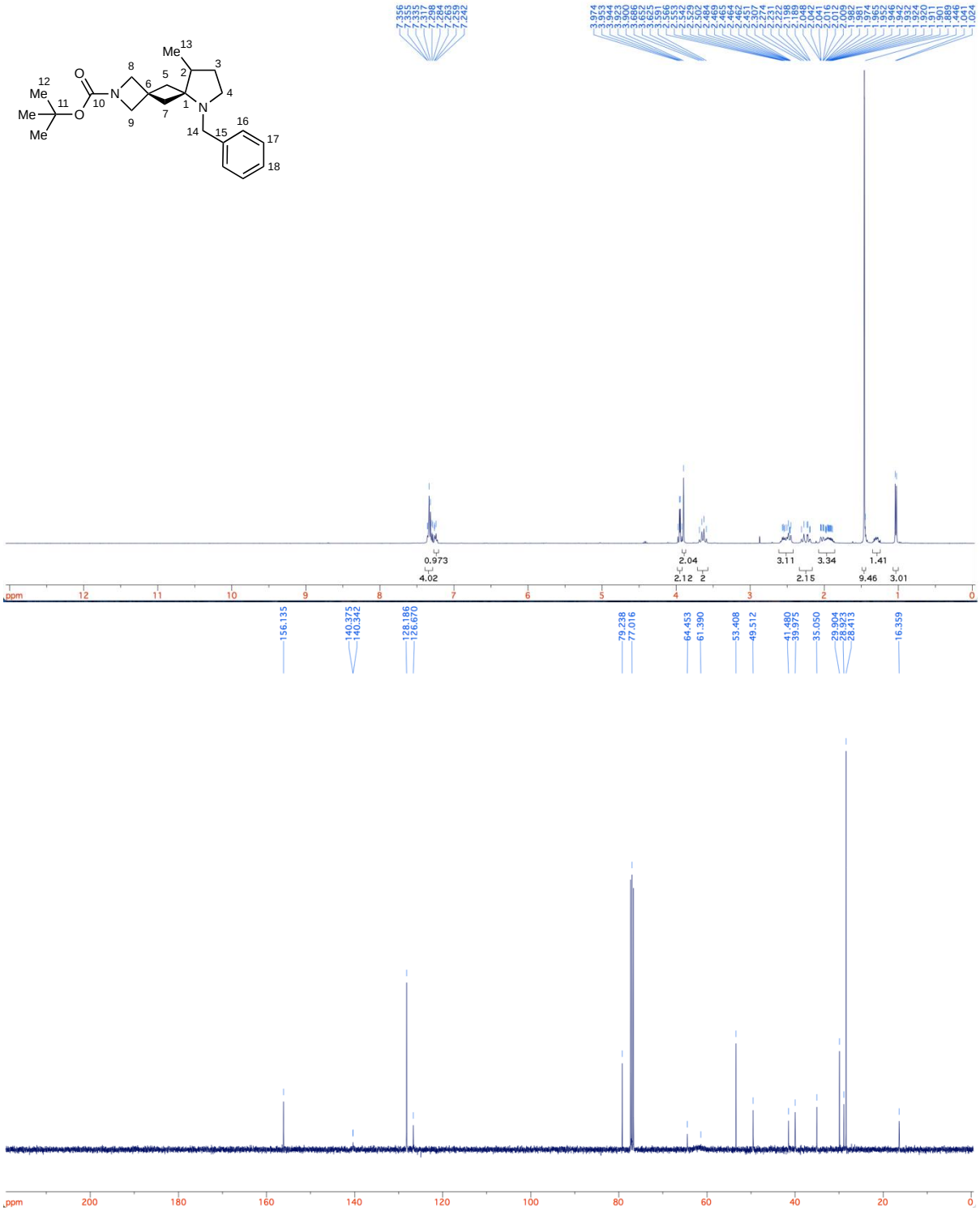
115b


Me
Me
Me
O
O
N
N
Me
0.917
3.85
0.988
0.988
1
3.03
1.92
3.02
1.01
9
1.14
2.94
ppm
153.165
153.148
153.116
153.103
153.093
139.941
139.922
139.907
139.885
127.428
127.315
125.851
77.730
71.408
71.021
52.139
52.073
52.290
51.151
40.021
45.974
45.786
45.930
43.263
41.105
40.025
38.687
38.520
35.553
33.166
31.018
30.080
29.569
29.101
27.146
25.208
15.535
15.124
ppm

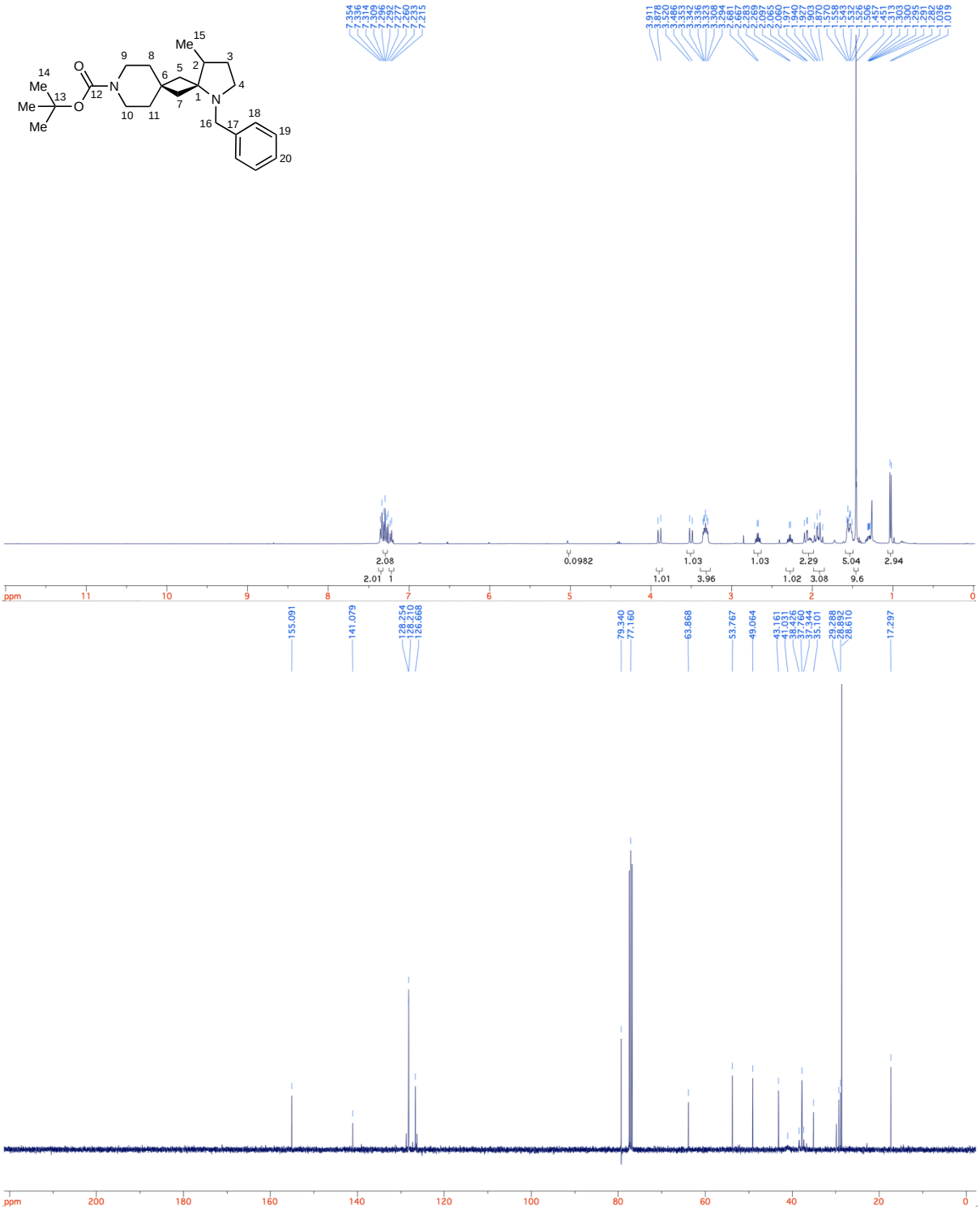
115c


Me
12
3
5
2
6
4
O
N
1
N
11
9
8
15
Me
7
13
14
16
O
Me
10
17
Me
1.02
1.18
3.08
1.09
3.25
1.2
4.14
2.2
1
1.03
1.14
10.8
2.93
ppm
155.108
141.423
128.229
128.119
126.618
126.608
79.507
77.414
77.160
76.906
63.334
52.104
49.488
41.852
36.122
30.410
29.816
28.609
28.505
17.688

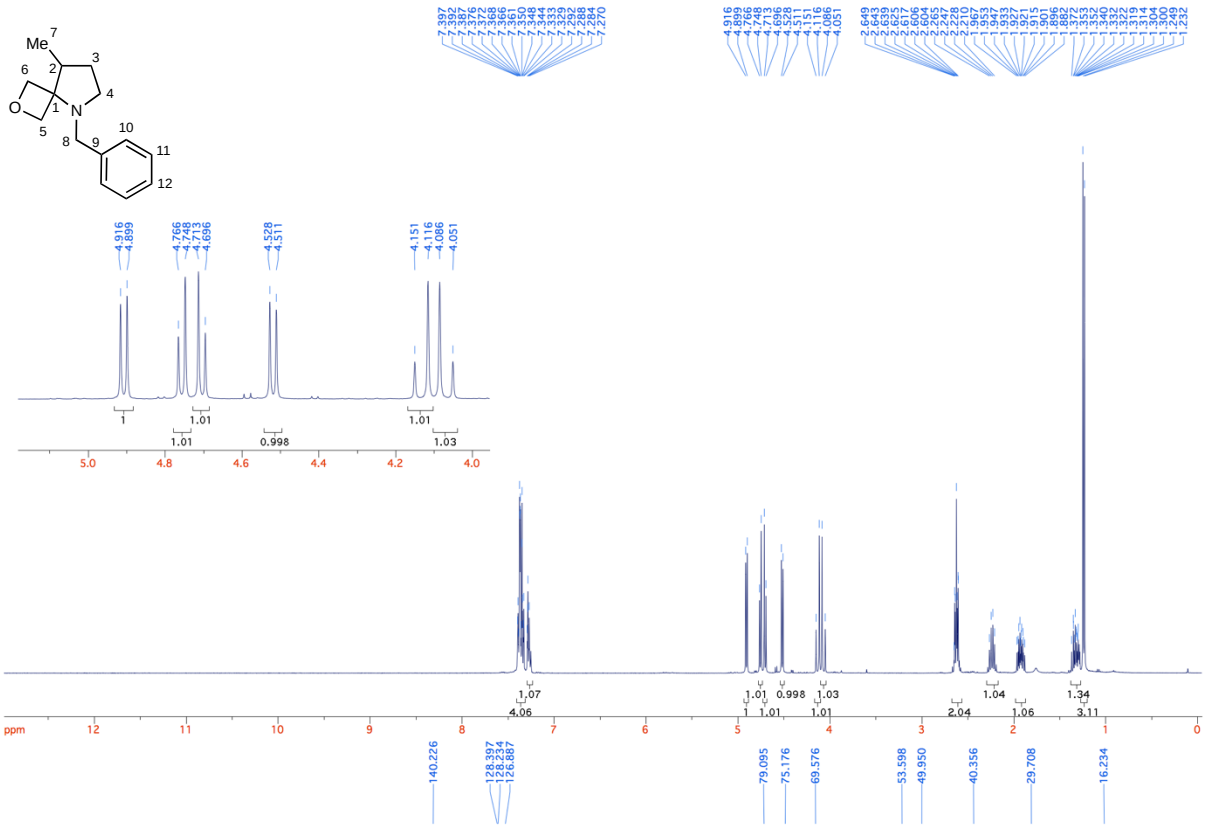
115e

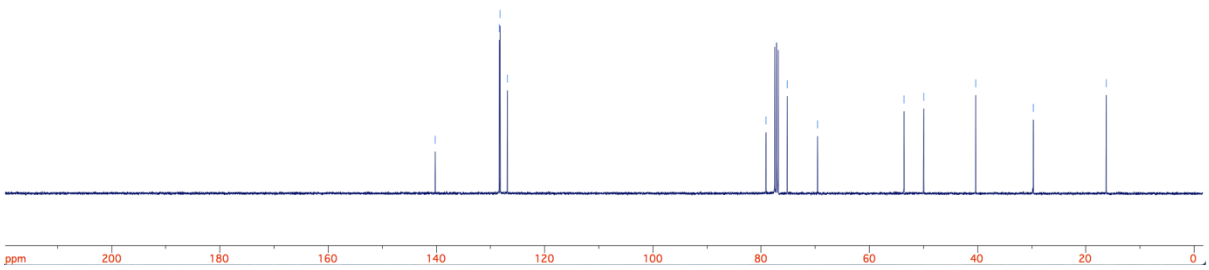

Me
13
12
Me
Me
11
O
O
10
N
8
9
6
5
7
2
1
3
4
N
14
15
16
17
18
0.973
4.02
2.04
2.12
2
3.11
2.15
3.34
9.46
1.41
3.01
ppm
156.135
140.375
140.342
128.186
126.670
79.238
77.016
64.453
61.390
53.408
49.512
41.480
39.975
35.050
29.904
28.923
28.413
16.359
ppm

115f

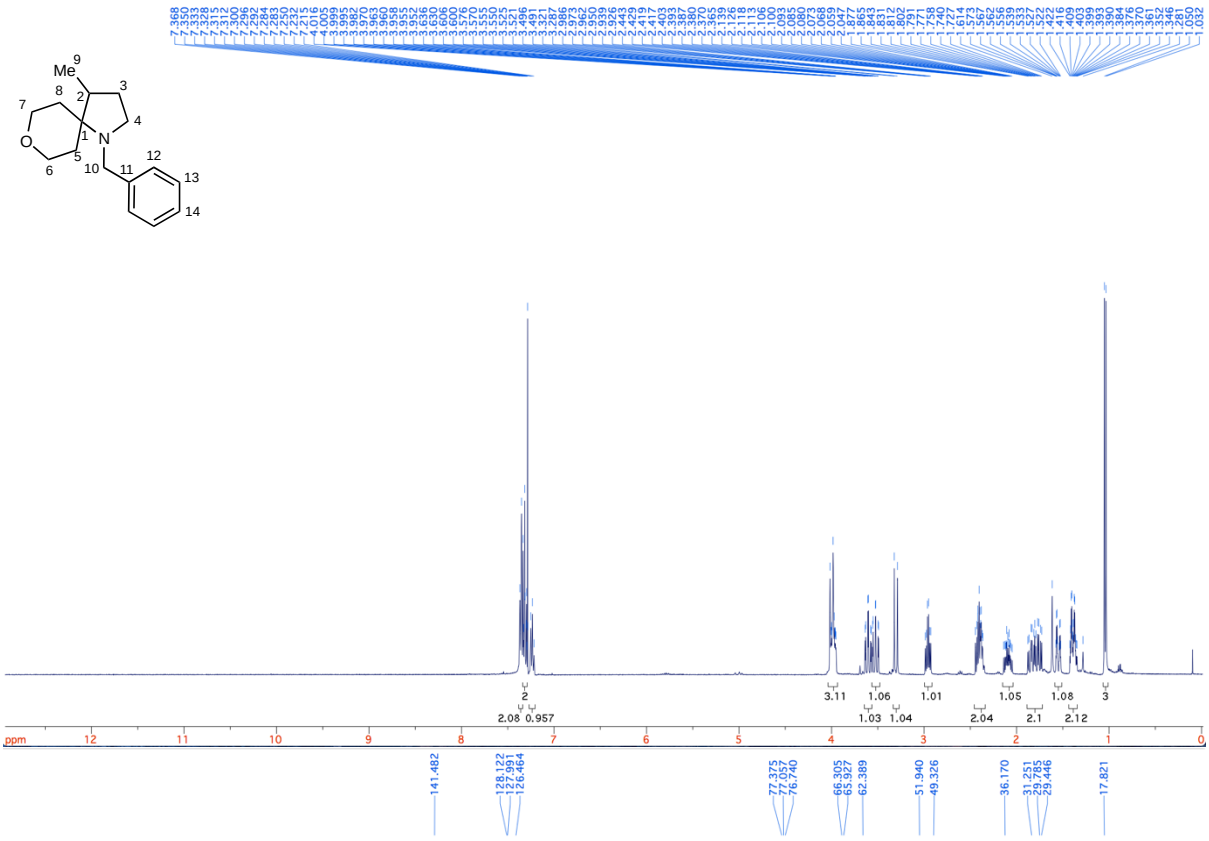

7.354 7.316 7.314 7.309 7.296 7.277 7.277 7.260 7.233 7.215
3.911 3.878 3.520 3.486 3.353 3.342 3.336 3.329 3.308 3.284 3.261 2.667 2.283 2.269 2.097 2.065 2.050 1.970 1.940 1.927 1.923 1.870 1.570 1.548 1.543 1.532 1.526 1.506 1.457 1.451 1.313 1.303 1.300 1.295 1.281 1.282 1.036 1.019
2.08 2.01 1 0.0982 1.01 1.03 3.96 1.03 1.02 2.29 3.08 5.04 9.6 2.94
ppm 11 10 9 8 7 6 5 4 3 2 1 0
155.091 141.079 128.254 128.210 126.668 79.340 77.160 63.868 53.767 49.064 43.161 41.031 38.426 37.620 37.544 35.101 29.288 28.892 28.610 17.297
ppm 200 180 160 140 120 100 80 60 40 20 0

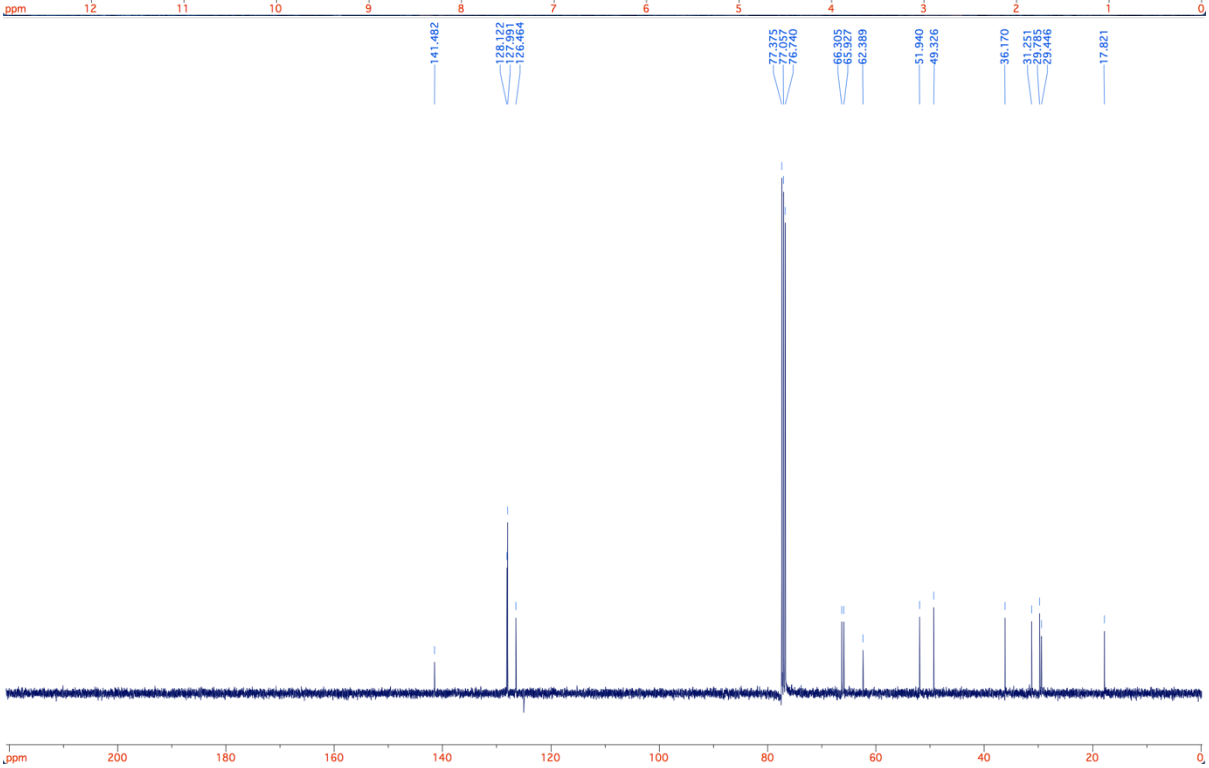
115g



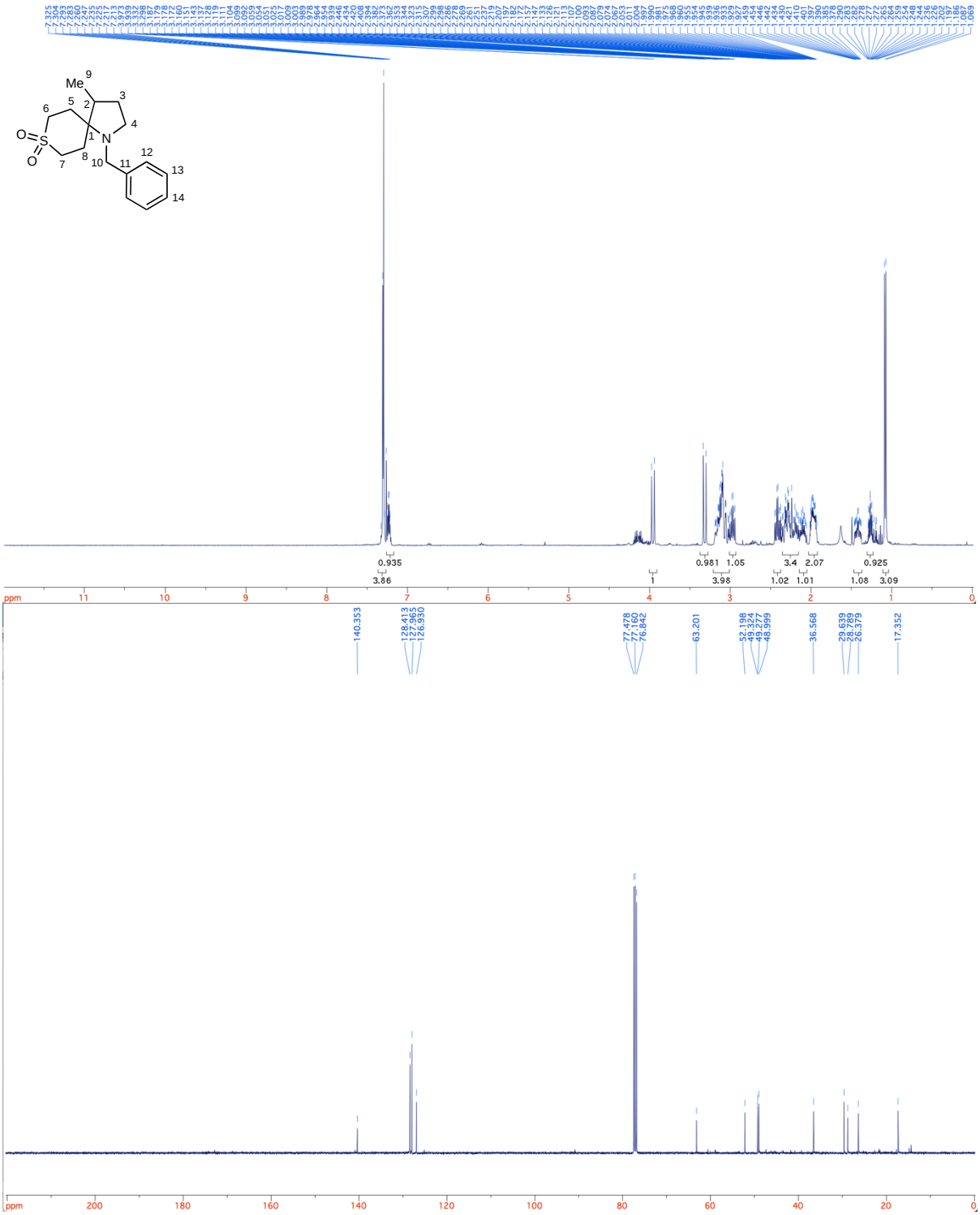


115h

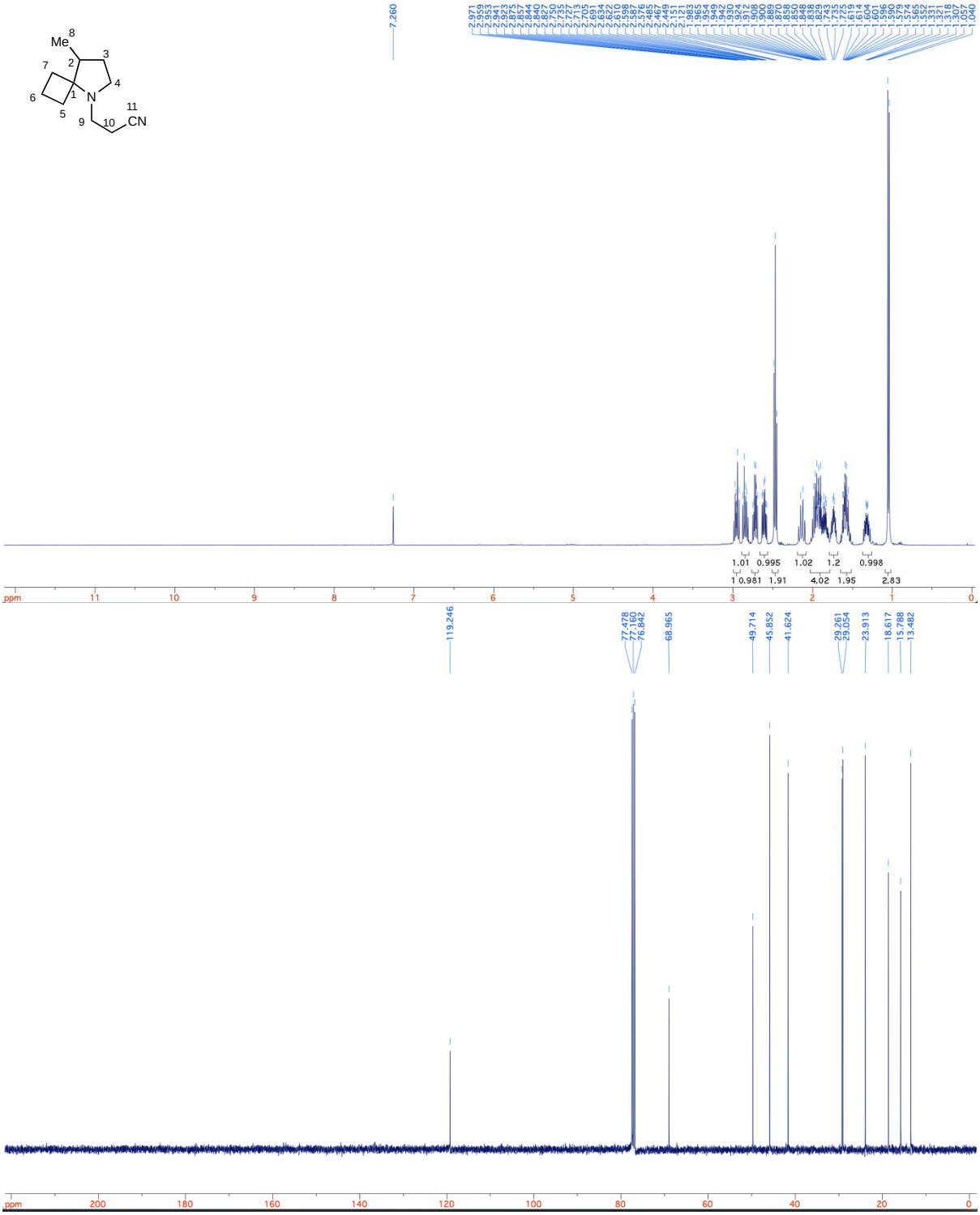

Me
9
8
2
3
7
4
O
1
N
5
6
10
11
12
13
14
2
2.08
0.957
3.11
1.06
1.01
1.05
1.08
3
1.03
1.04
2.04
2.1
2.12
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0


141.482
128.122
127.491
126.464
77.375
77.057
76.740
66.305
65.927
62.389
51.940
49.326
36.170
31.251
29.785
29.446
17.821
ppm
200
180
160
140
120
100
80
60
40
20
0

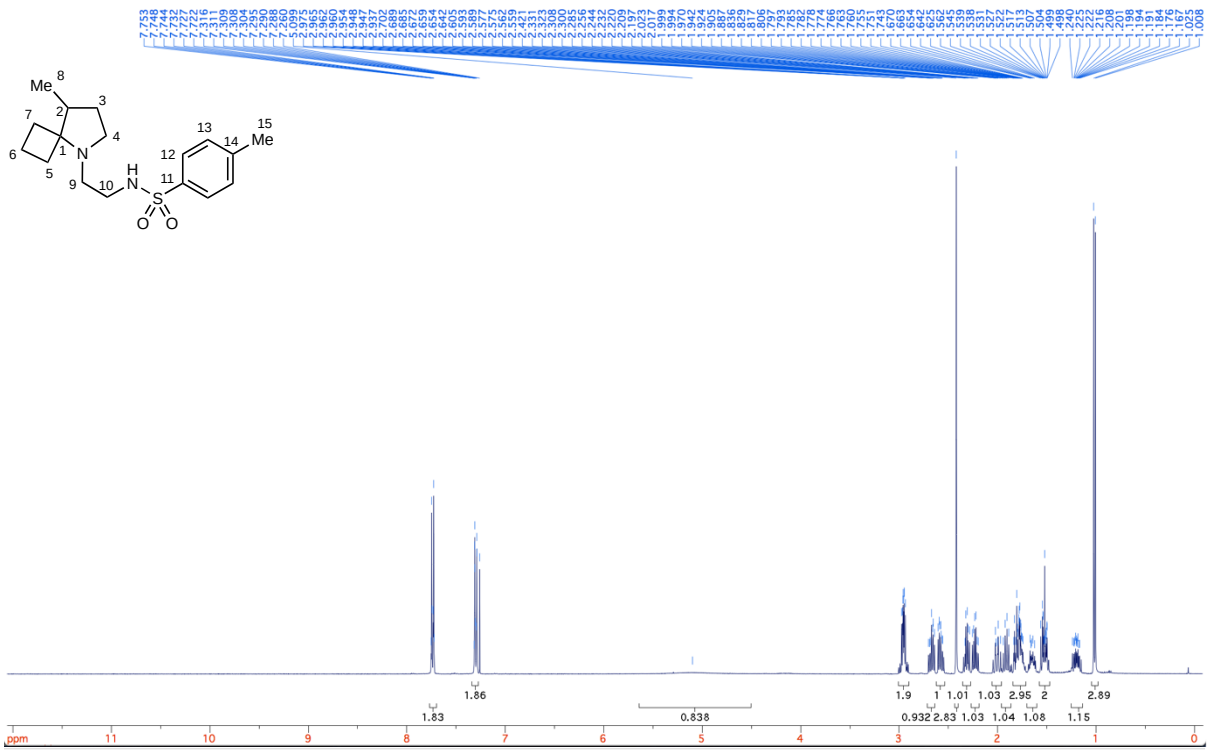
115i

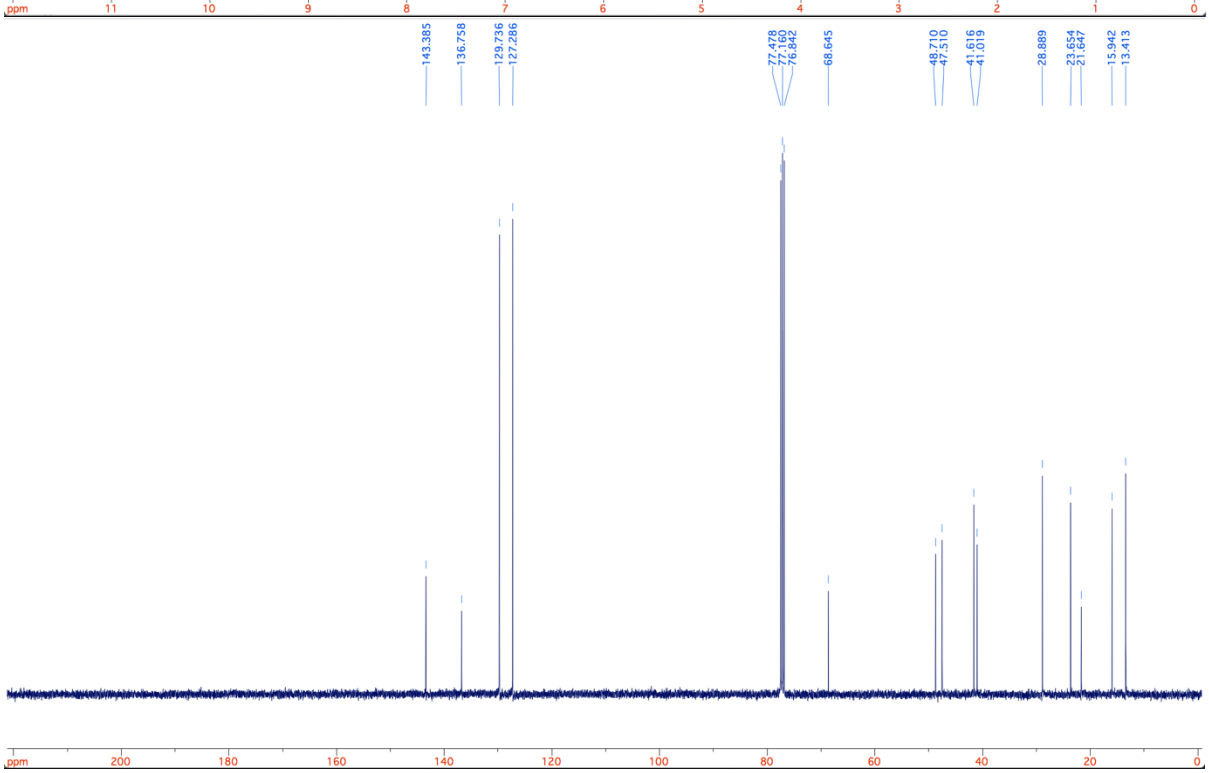

Me
O
S
O
N
0.935
3.86
1
0.981
1.05
3.98
3.4
2.07
1.02
1.01
0.925
1.08
3.09
ppm
140.353
129.413
129.185
126.930
77.478
77.160
76.842
63.201
52.198
49.324
49.277
48.999
36.568
29.639
28.789
26.379
17.352

116a

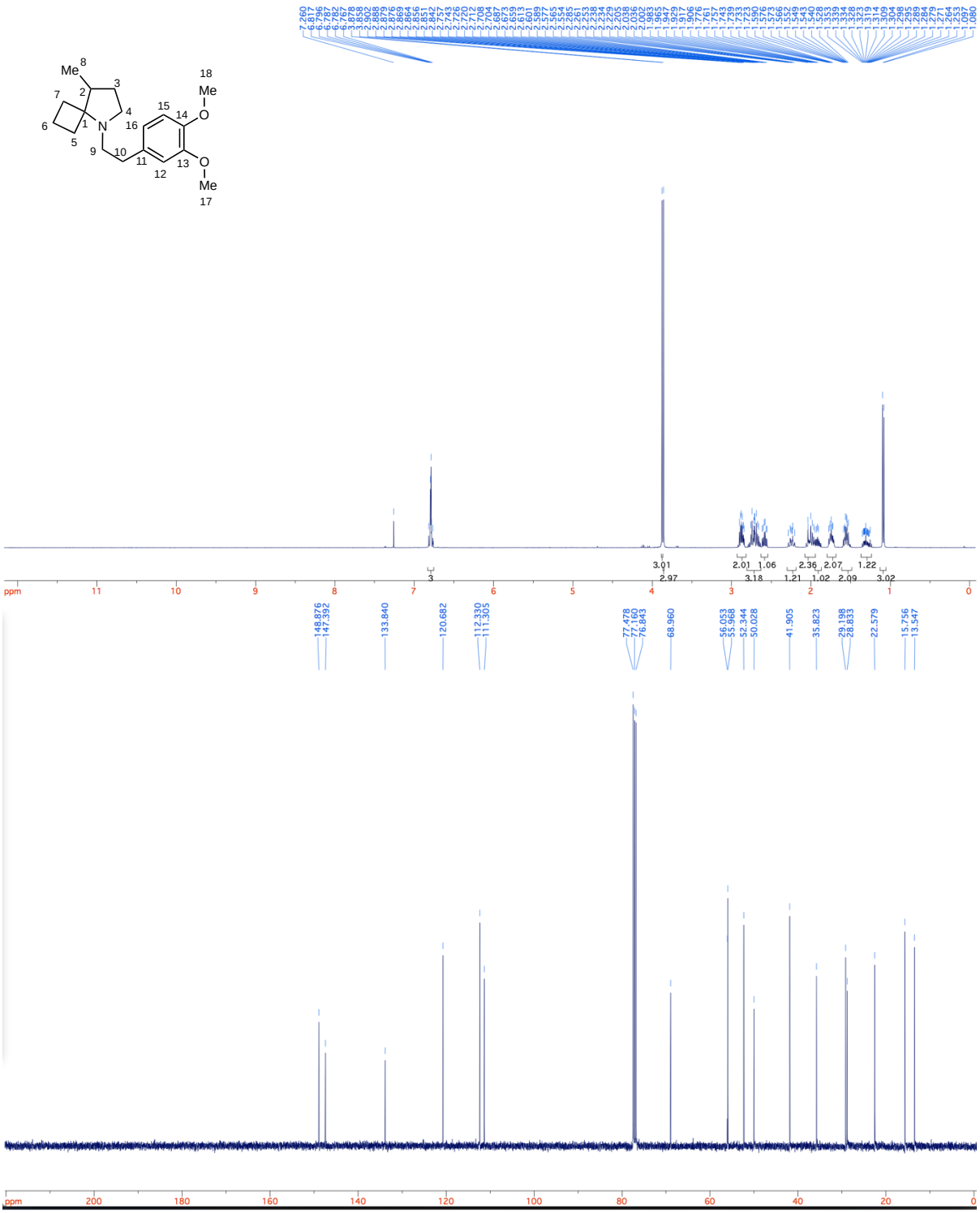

Me
8
3
2
7
4
6
1
N
5
9
10
11
CN
7.260
1.01
0.995
1.02
1.2
0.998
1.0
0.981
1.91
4.02
1.95
2.83
ppm
119.246
77.478
77.160
76.842
68.965
49.714
45.852
41.624
29.261
29.054
23.913
18.617
15.788
13.482
ppm

116b

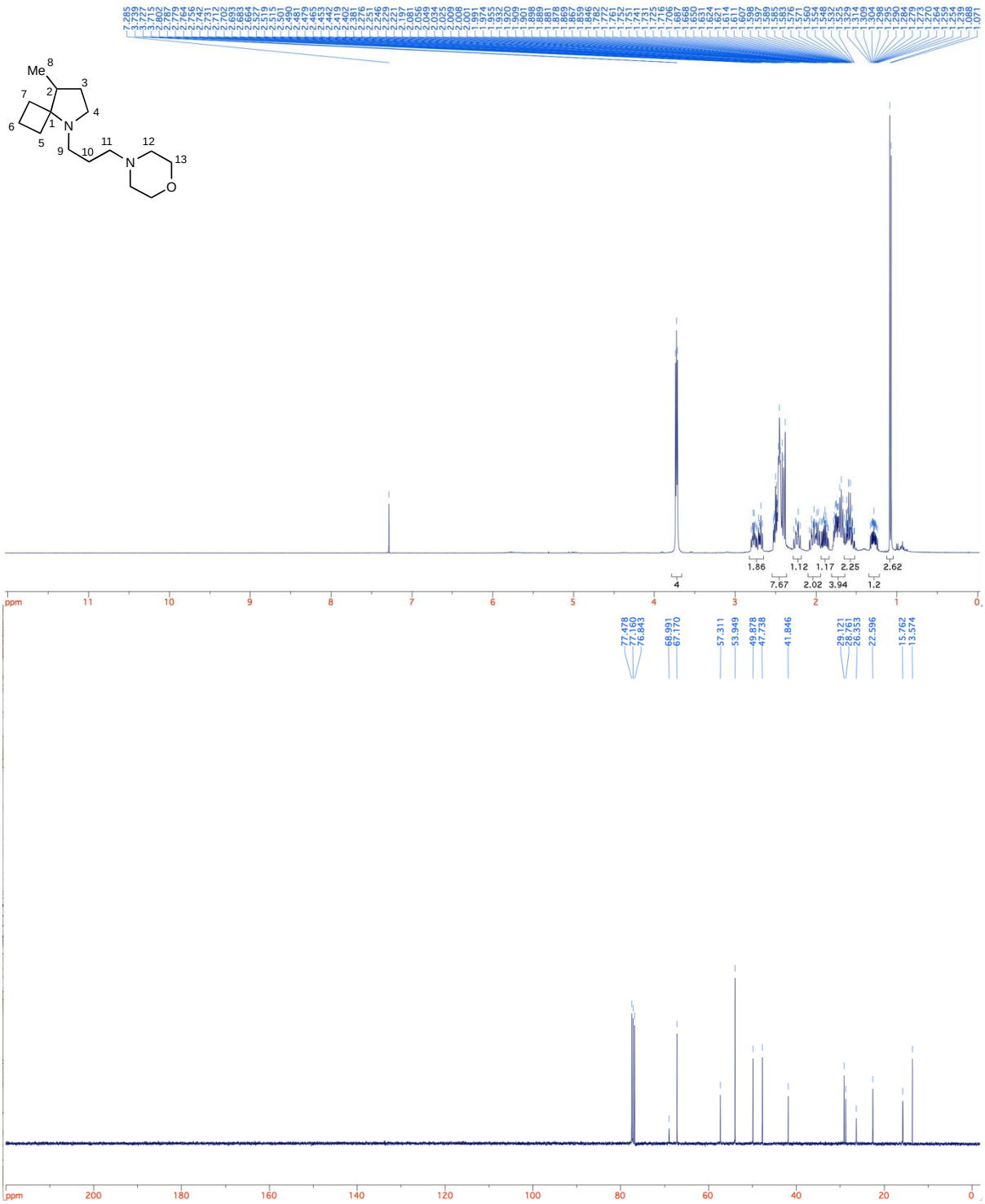

Me
8
3
2
7
4
1
N
6
5
9
10
H
N
S
O
O
13
14
15
Me
12
11
1.83
1.86
0.838
1.9
1
1.01
1.03
2.95
2
2.89
0.932
2.83
1.03
1.04
1.08
1.15
ppm


143.385
136.758
129.736
127.286
77.478
77.160
76.842
68.645
49.710
47.510
41.616
41.019
28.889
23.654
21.647
15.942
13.413
ppm

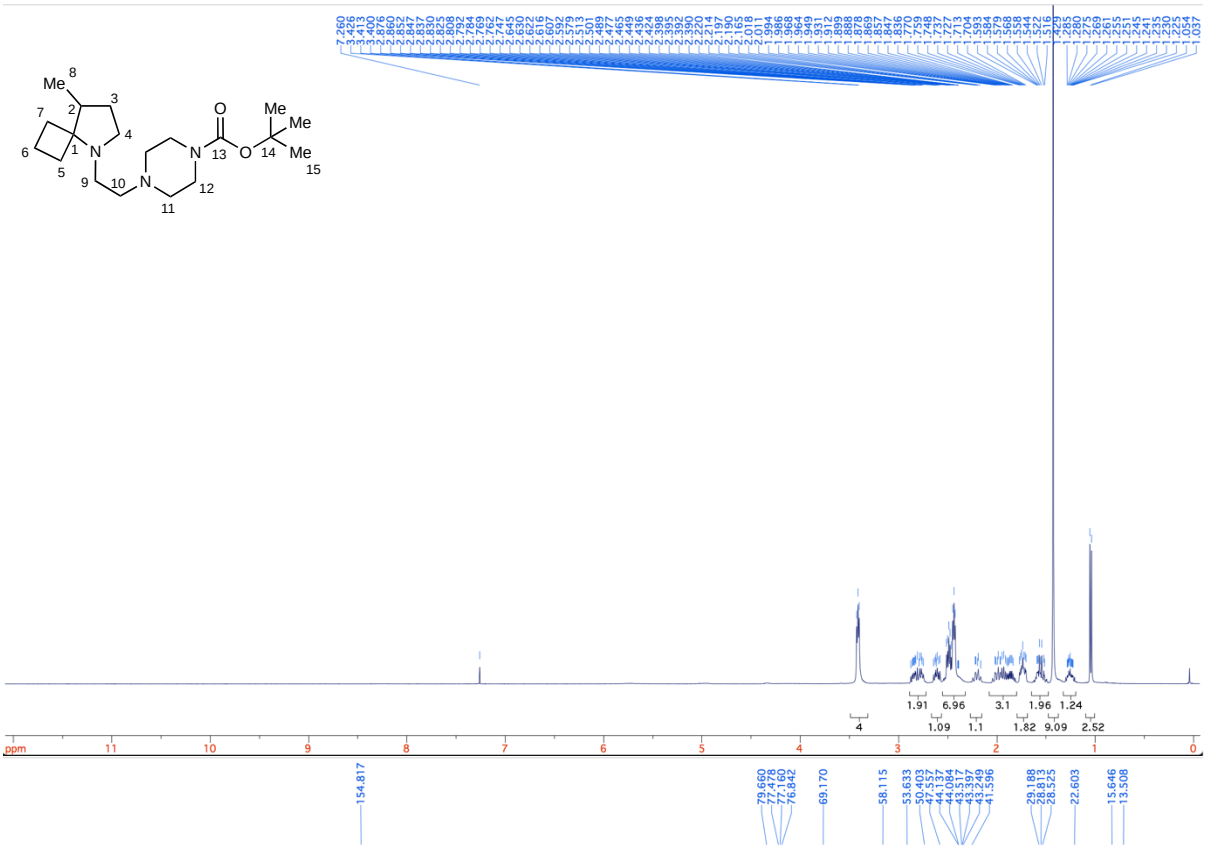
116d

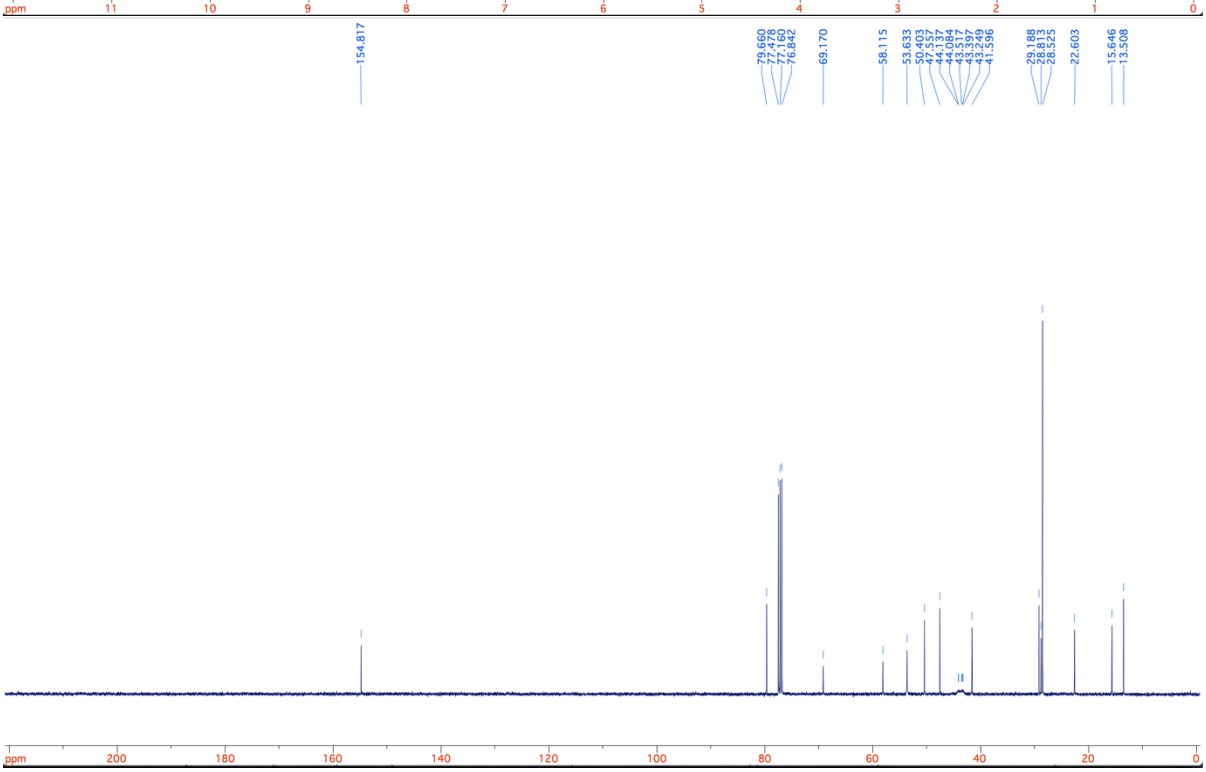

Me
8
3
2
7
4
6
1
N
5
9
10
11
12
13
14
15
16
18
Me
O
O
Me
17
3.01
2.97
2.01
1.06
3.18
2.36
1.21
2.07
1.02
2.09
1.22
3.02
148.876
147.392
133.840
120.682
112.330
111.305
77.478
77.160
76.843
68.960
56.053
55.968
52.344
50.028
41.905
35.823
29.198
28.833
22.579
15.756
13.547
ppm

116e

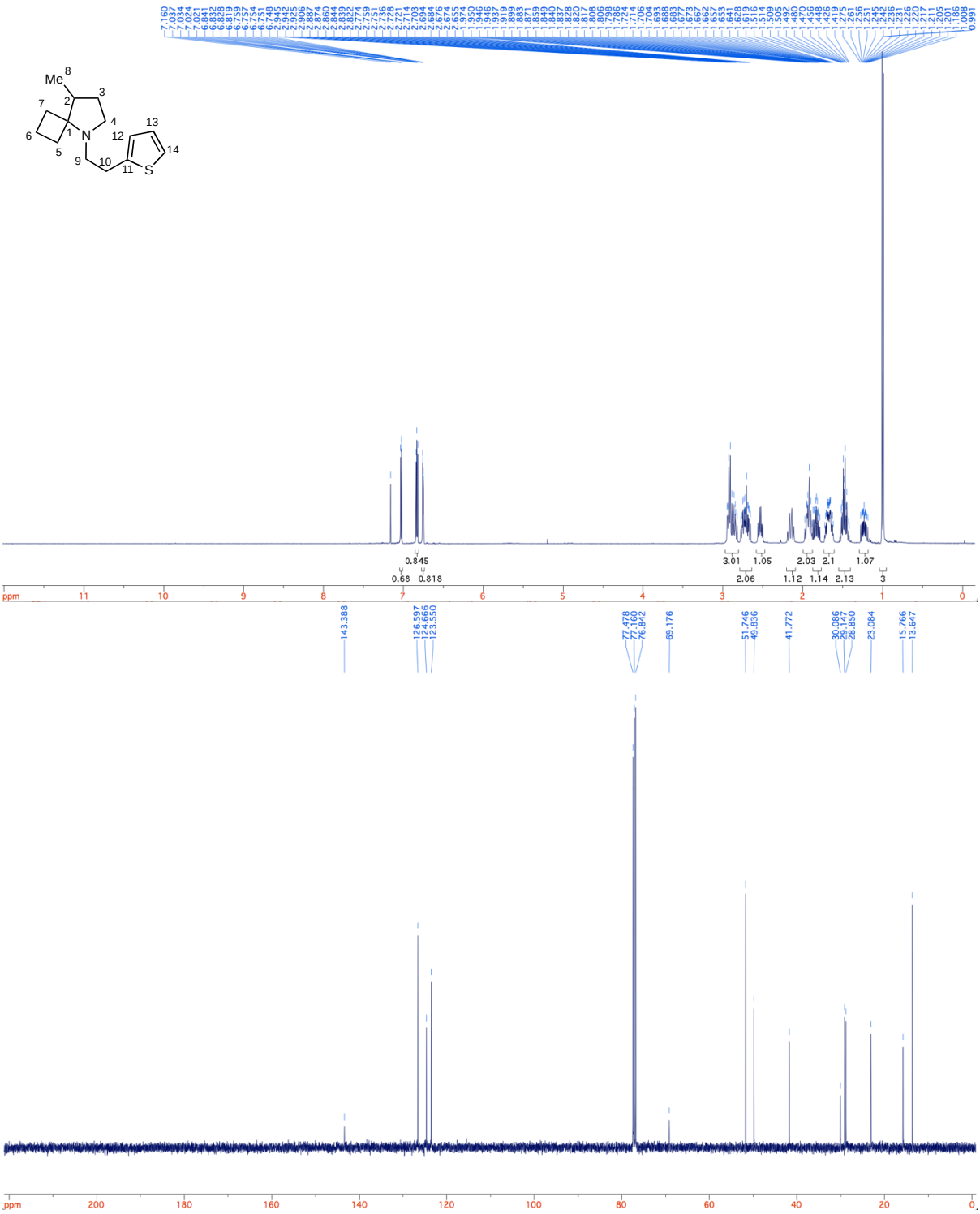

Me
8
3
7
2
4
6
1
N
5
9
10
11
12
N
13
O
1.86
1.12
1.17
2.25
2.62
4
7.67
2.02
3.94
1.2
ppm
77.478
77.160
76.843
68.991
67.170
57.311
53.949
49.878
47.738
41.846
29.121
28.761
26.353
22.596
15.762
13.574
ppm

116f

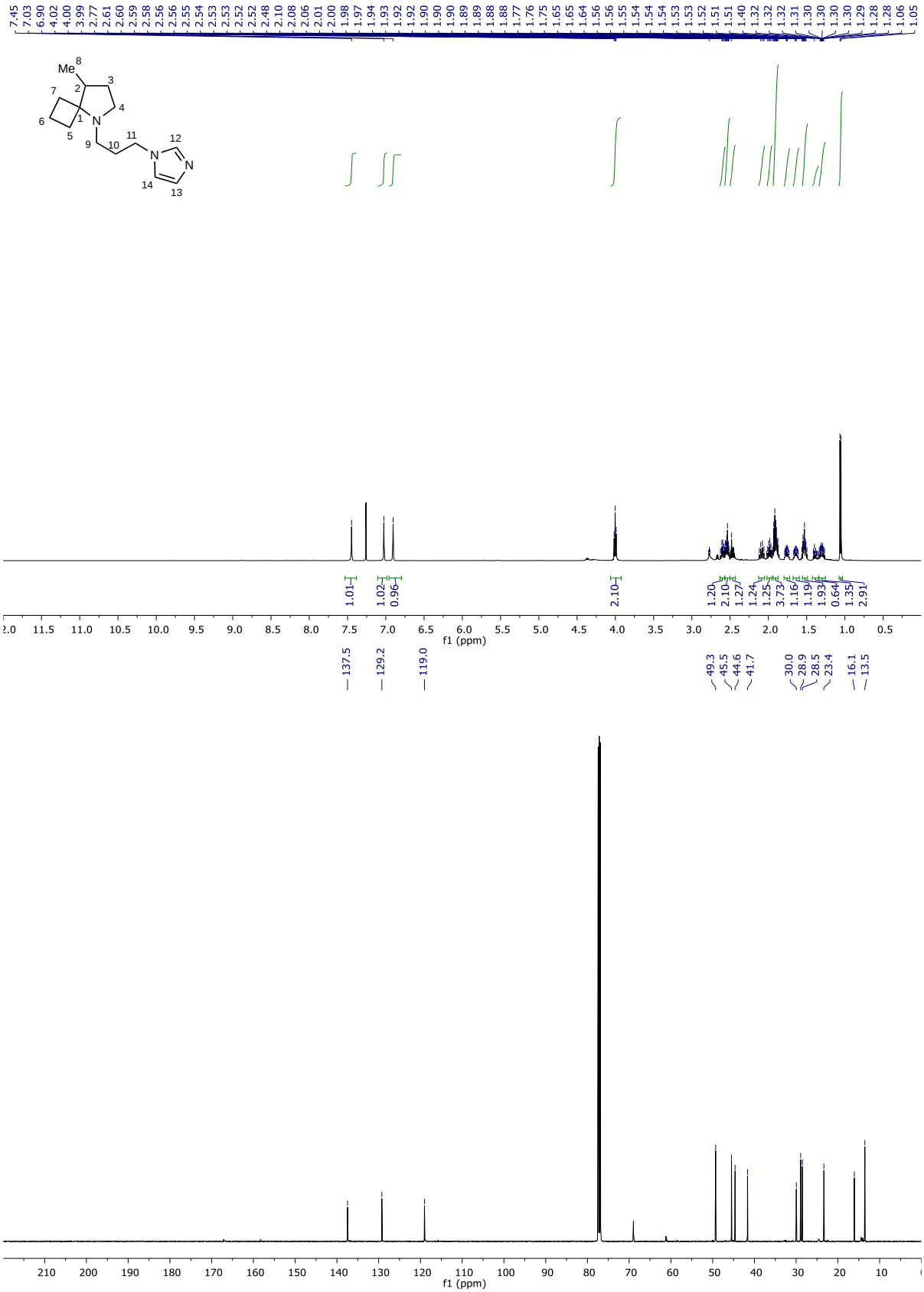

Me
8
7
2
3
4
6
1
N
5
9
10
N
11
12
N
13
O
O
14
Me
Me
Me
15
1.91
6.96
3.1
1.96
1.24
4
1.09
1.1
1.82
9.09
2.52
ppm


154.817
79.660
77.478
77.160
76.842
69.170
58.115
53.633
50.403
47.537
44.137
44.084
43.877
43.397
43.249
41.596
29.188
28.813
28.525
22.603
15.646
13.508
ppm

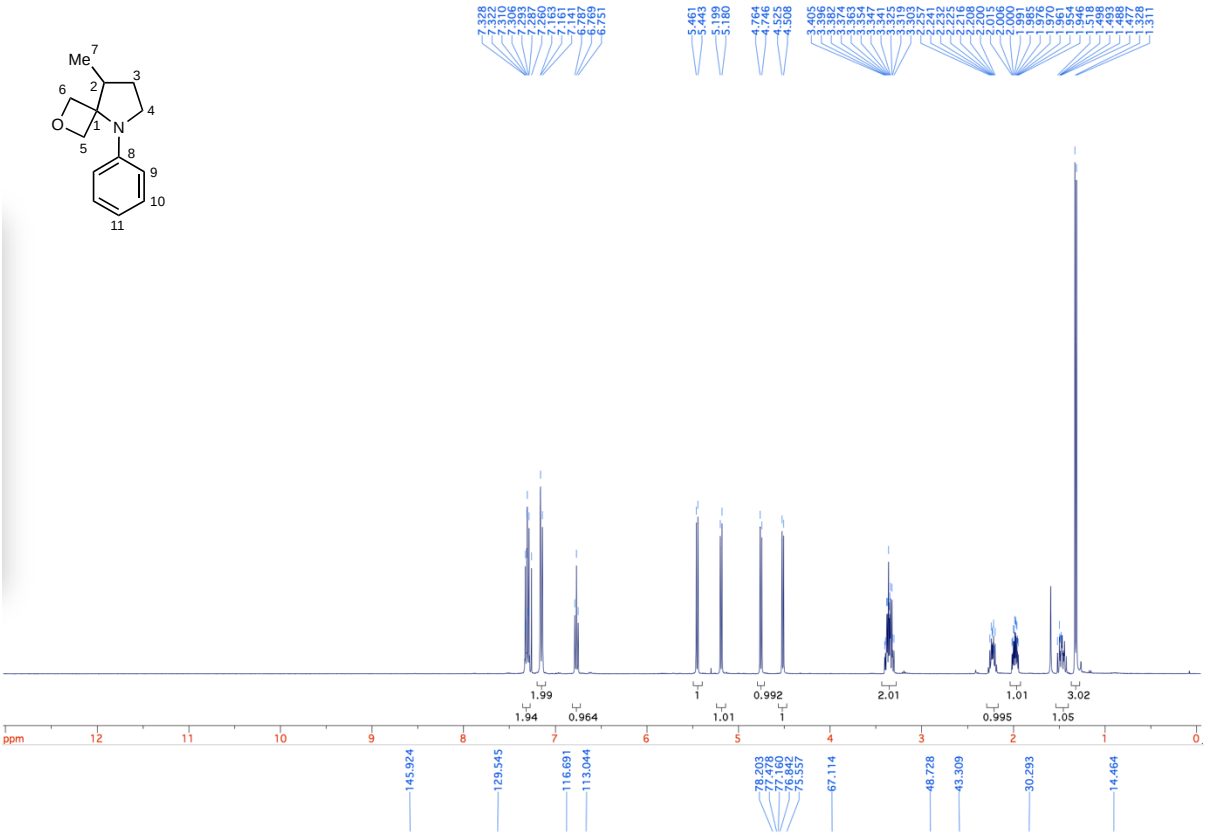
116g

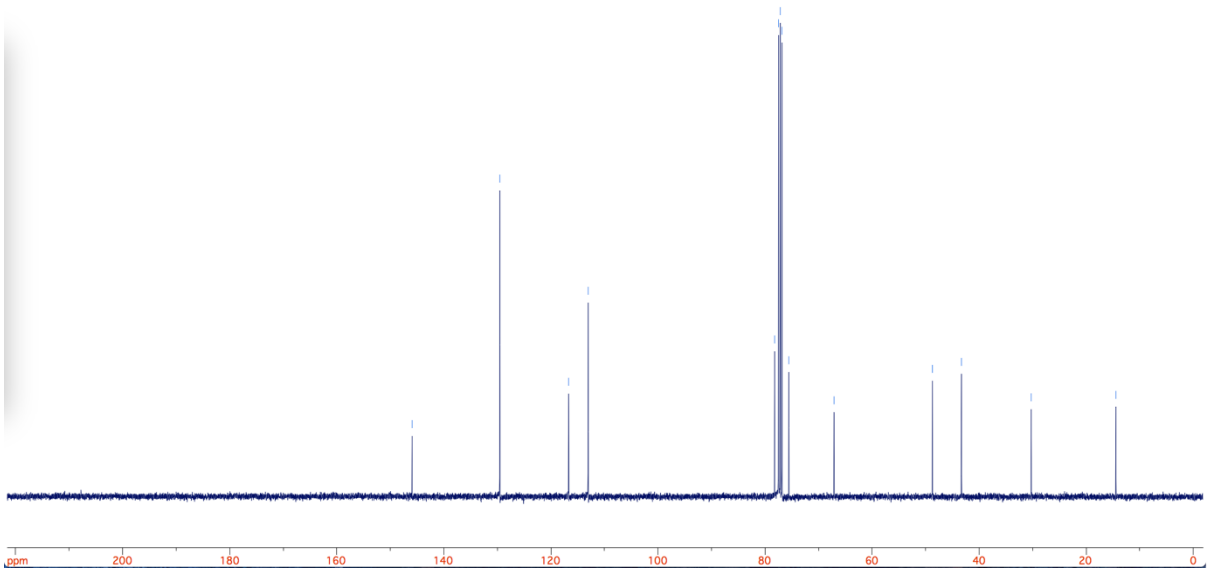

Me
8
7
2
3
4
6
1
N
5
9
10
11
S
12
13
14
0.845
0.68
0.818
3.01
1.05
2.06
2.03
2.1
1.12
1.14
2.13
1.07
3
ppm
143.388
126.597
124.656
123.550
77.478
77.160
76.842
69.176
51.746
49.836
41.772
30.096
29.147
28.850
23.084
15.766
13.647

116i

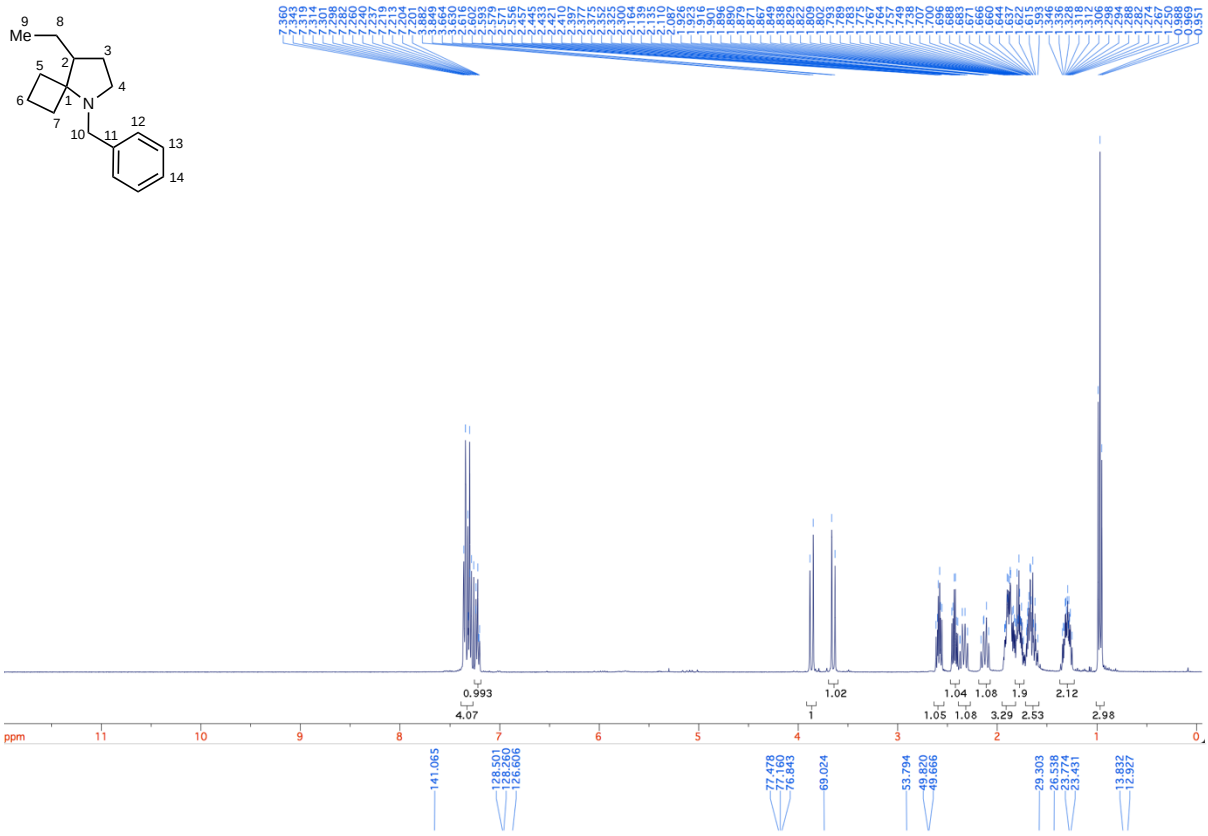


116j

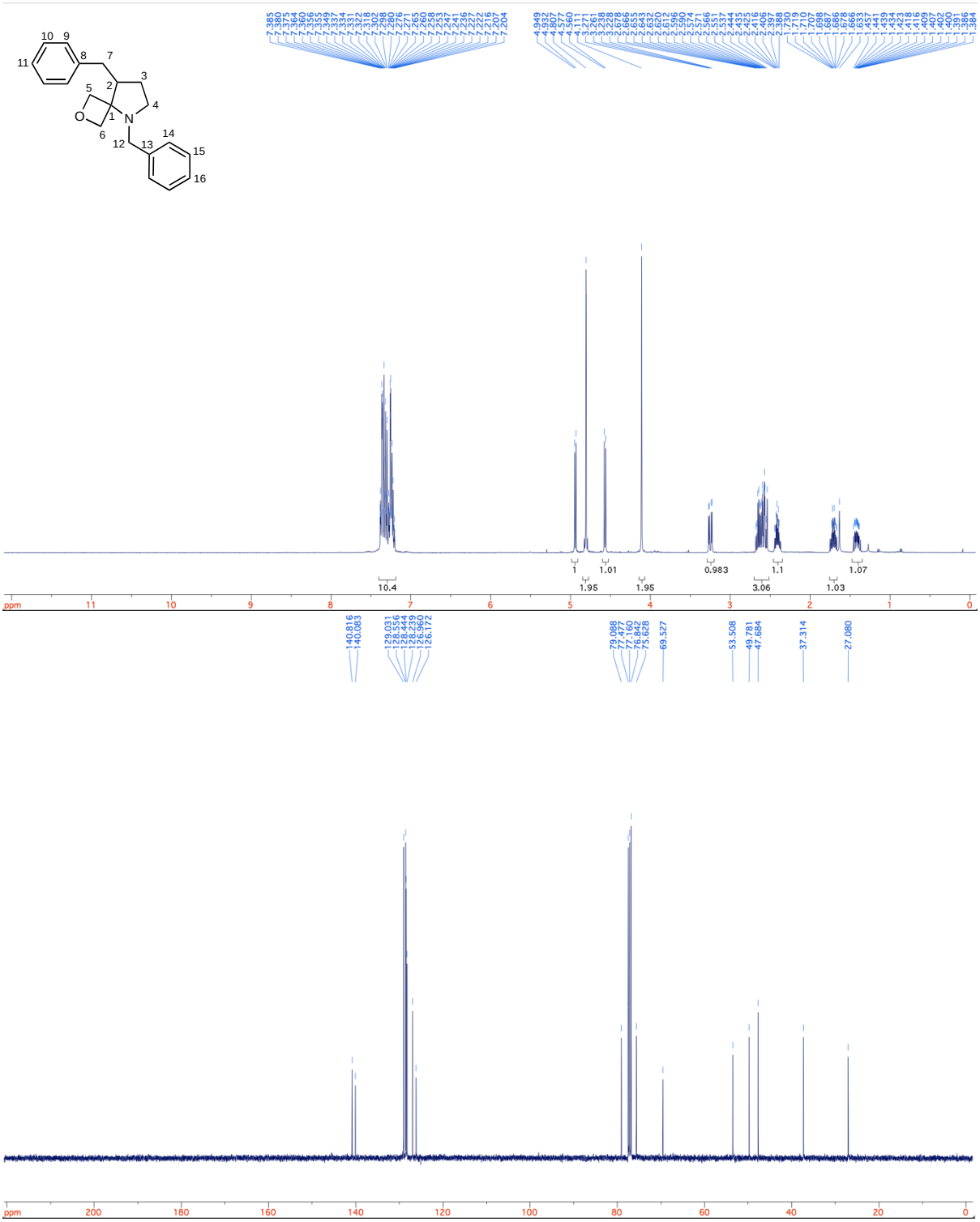

Me
7
6
2
3
4
O
1
N
5
8
9
10
11
7.328
7.322
7.310
7.306
7.293
7.287
7.260
7.153
7.161
7.141
7.137
6.787
6.789
6.751
5.461
5.443
5.199
5.180
4.764
4.746
4.575
4.558
3.405
3.396
3.382
3.374
3.363
3.347
3.341
3.325
3.319
3.303
2.257
2.241
2.232
2.225
2.216
2.208
2.200
2.015
2.006
2.000
1.991
1.985
1.976
1.970
1.961
1.954
1.946
1.518
1.498
1.493
1.488
1.477
1.473
1.311
1.99
1.94
0.964
1
1.01
0.992
1
2.01
1.01
0.995
3.02
1.05
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0


145.924
129.545
116.691
113.044
78.203
77.478
77.160
76.842
75.557
67.114
48.728
43.309
30.293
14.464
ppm
200
180
160
140
120
100
80
60
40
20
0

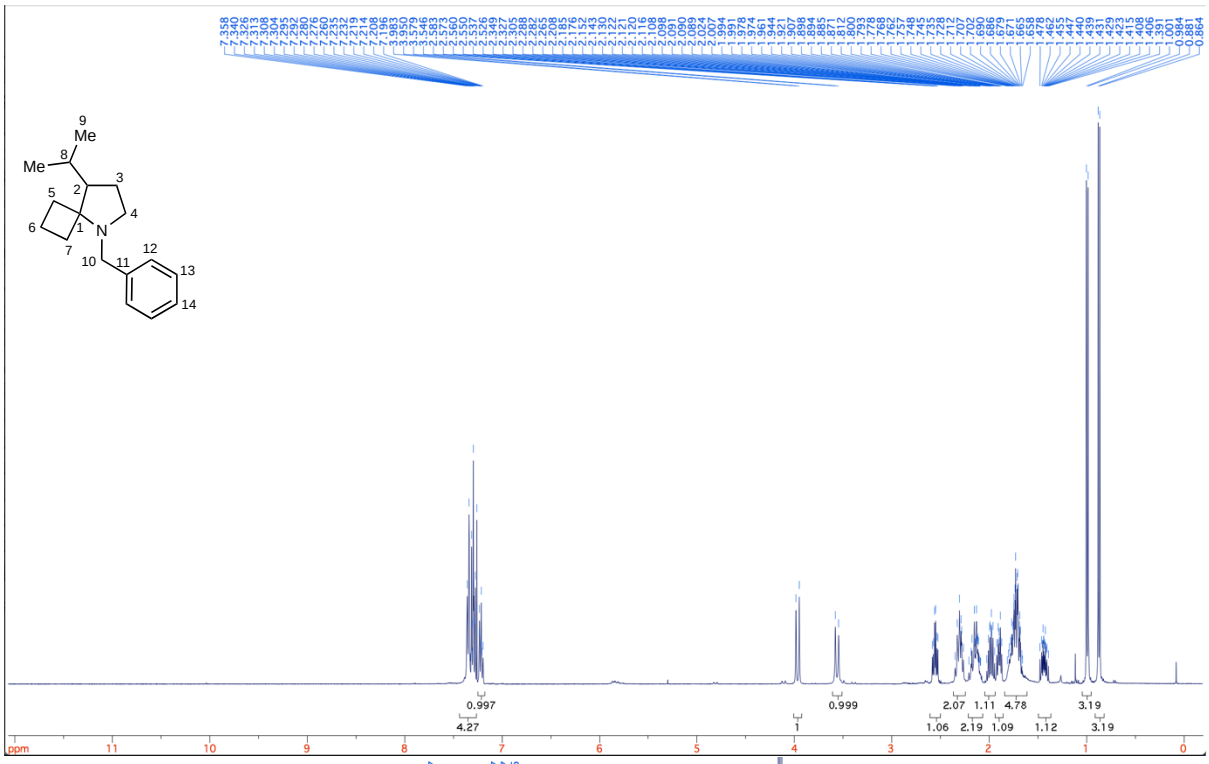
117a

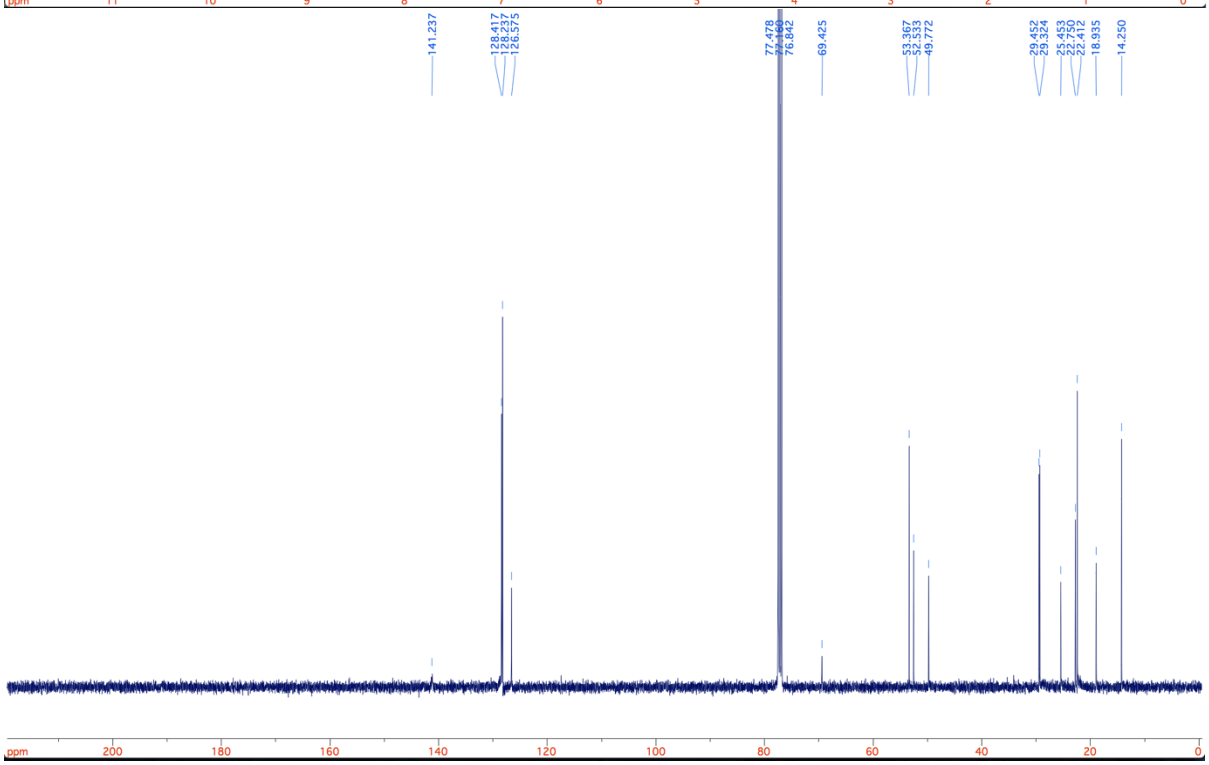

Me
N
0.993
4.07
1.02
1
1.04
1.05
1.08
1.08
1.9
3.29
2.53
2.12
2.98
ppm
141.065
128.501
128.260
126.606
77.478
77.160
76.843
69.024
53.794
49.820
49.666
29.303
26.538
23.774
23.431
13.832
12.927

117b

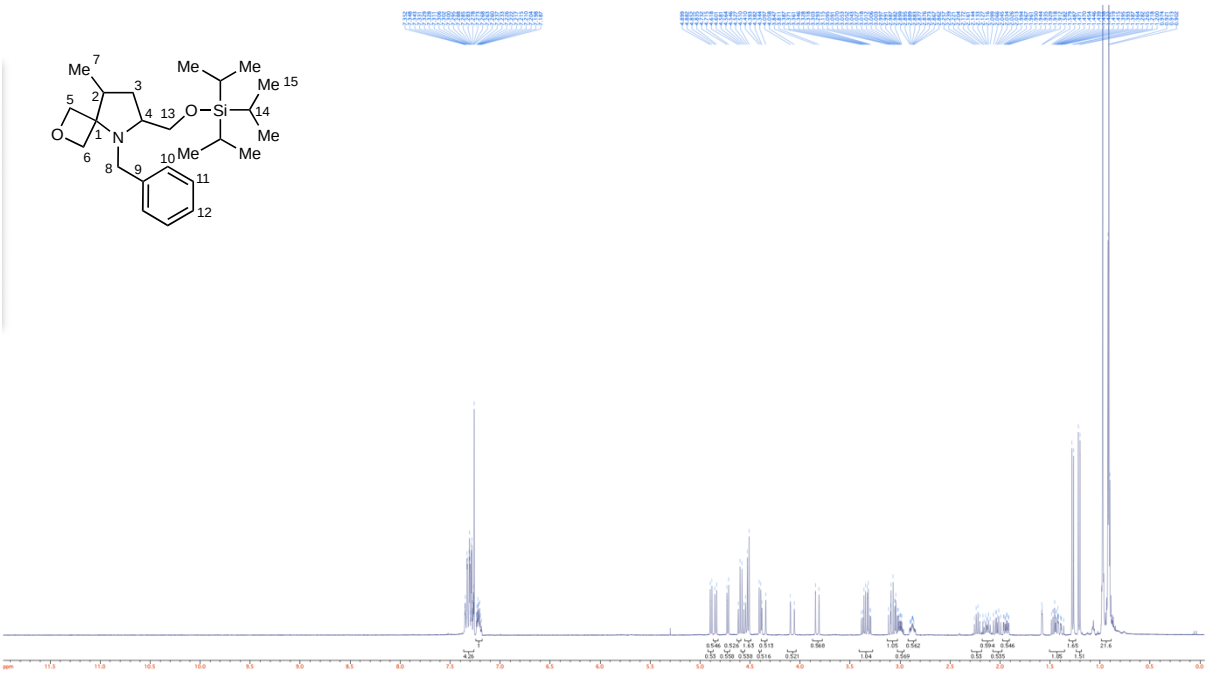

10 9
11
8
7
3
2
5
4
O
1
N
6
12
13
14
15
16
1
1.01
0.983
1.1
1.07
10.4
1.95
1.95
3.06
1.03
ppm
140.816
140.083
129.031
128.556
128.444
128.249
126.960
126.172
79.088
77.477
77.159
76.842
75.628
69.527
53.508
49.781
47.684
37.314
27.080
ppm

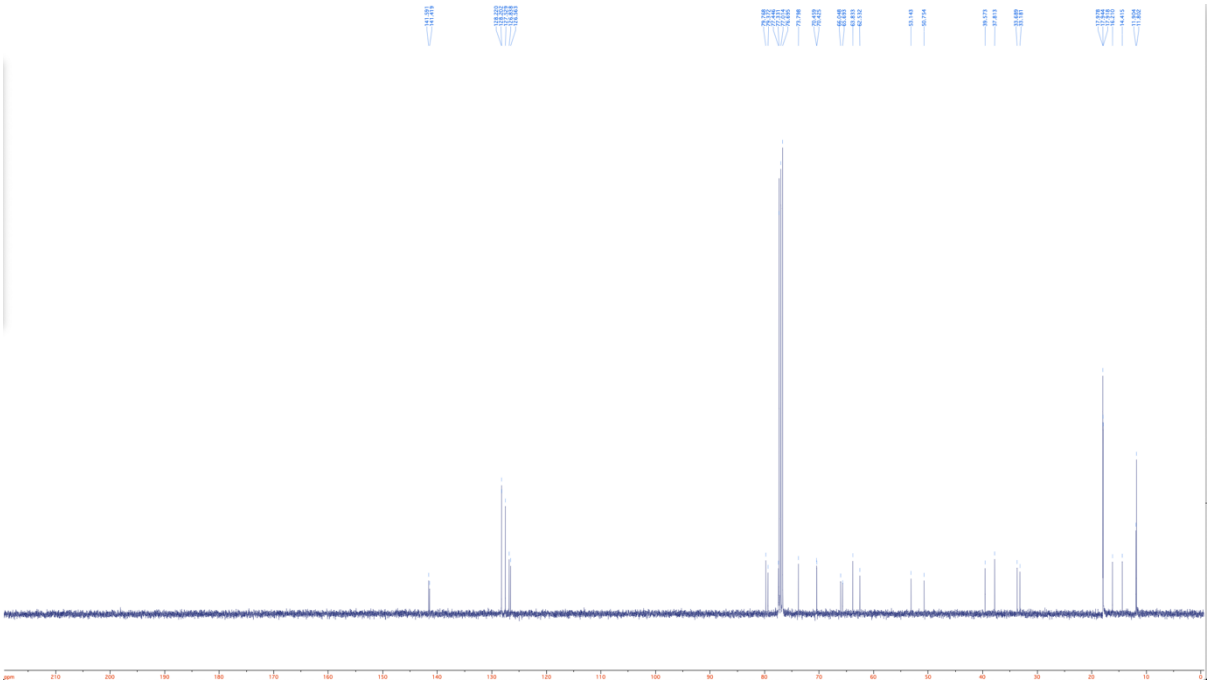
117c


Me
Me
N
0.997
4.27
1
0.999
2.07
1.11
4.78
1.06
2.19
1.09
1.12
3.19
3.19
ppm

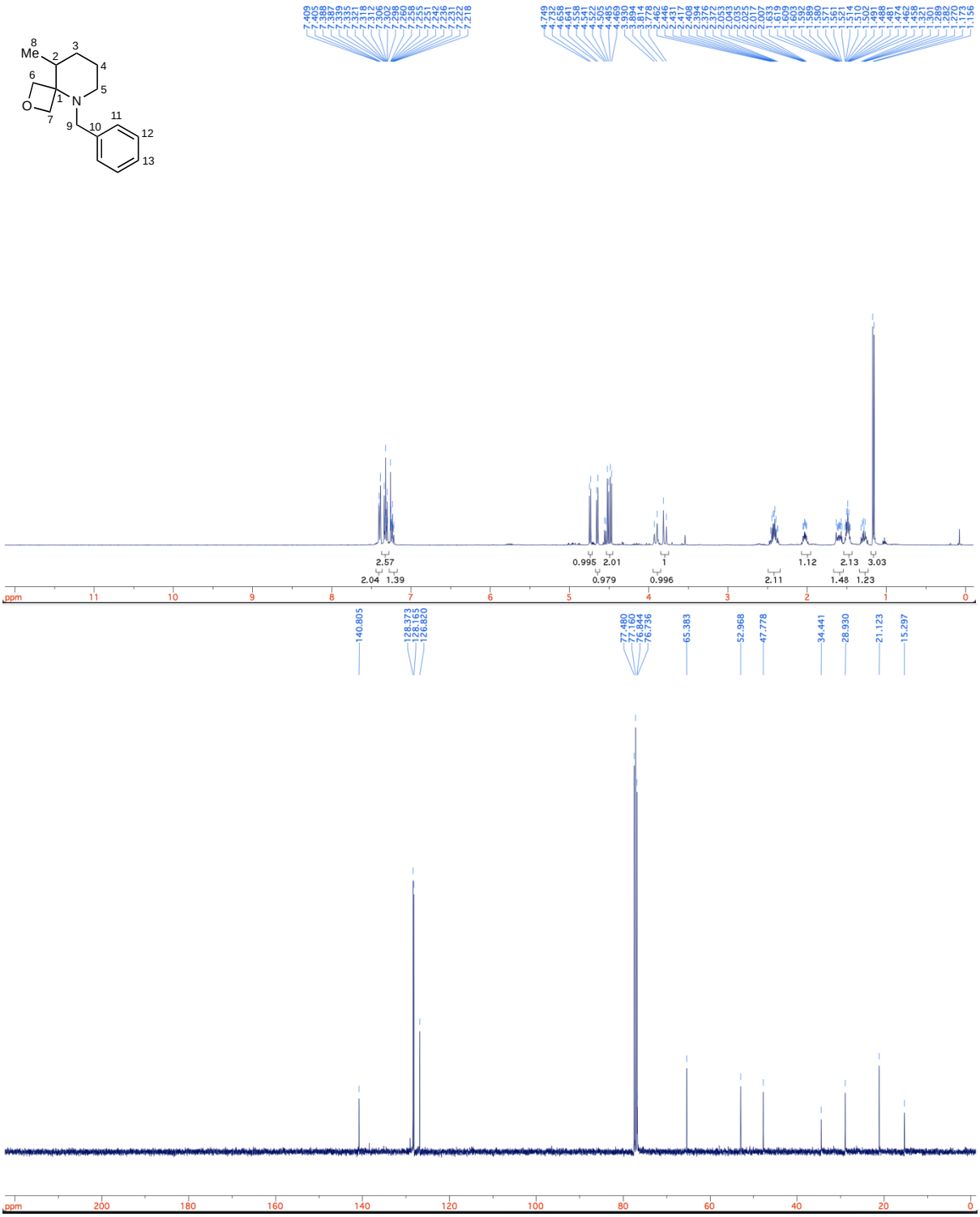

141.237
128.417
128.237
126.575
77.478
77.040
76.842
69.425
53.367
52.353
49.772
29.452
29.324
25.453
22.750
22.412
18.935
14.250
ppm

117d

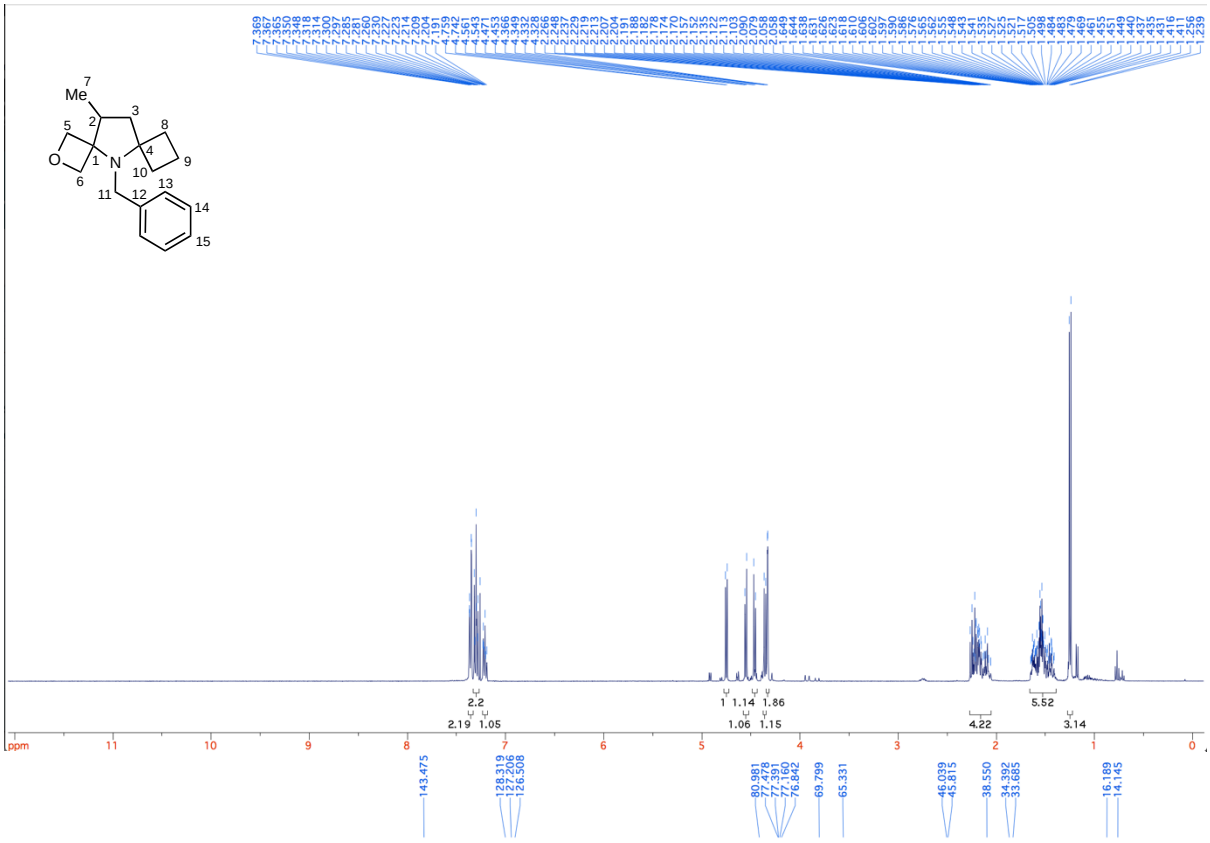


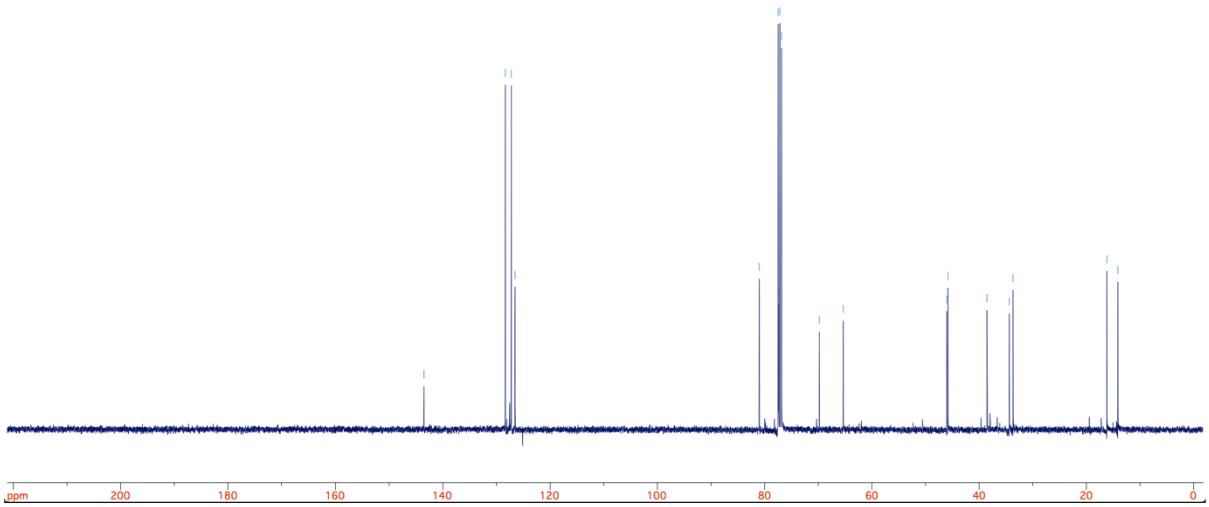


117e

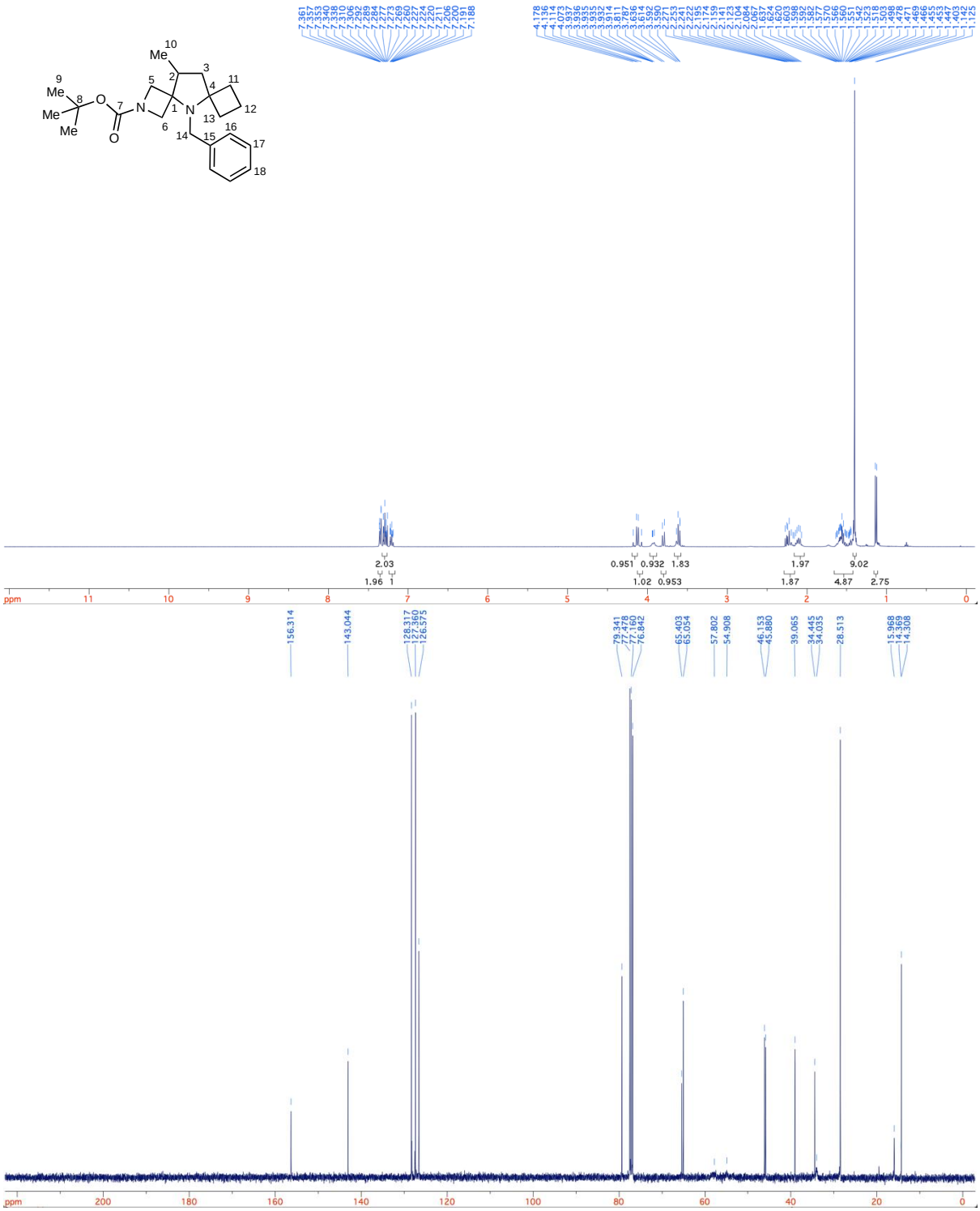

Me
O
N
2.57
2.04
1.39
0.995
2.01
0.979
1
0.996
1.12
2.11
2.13
1.48
3.03
1.23
ppm
140.805
128.373
128.155
126.820
77.480
77.160
76.844
76.736
65.383
52.968
47.778
34.441
28.930
21.123
15.297

118a

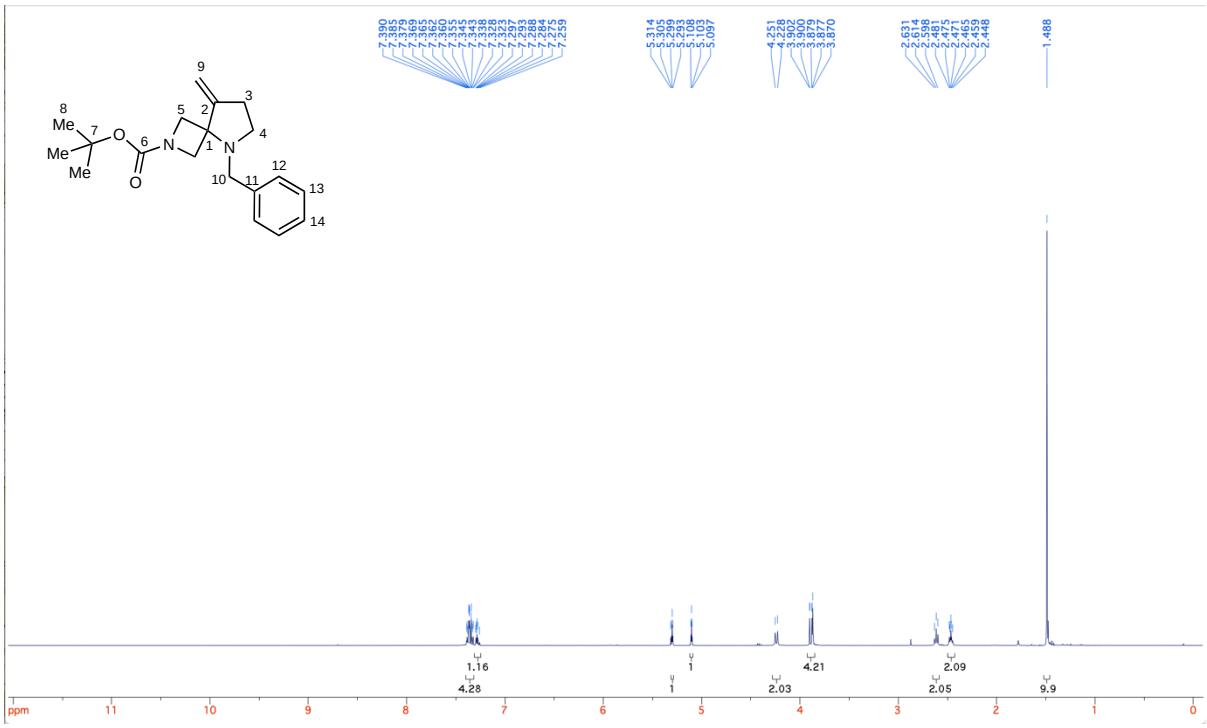

Me
7
3
2
5
8
O
1
N
4
9
6
10
11
12
13
14
15
2.2
2.19
1.05
1
1.14
1.86
1.06
1.15
4.22
5.52
3.14
ppm

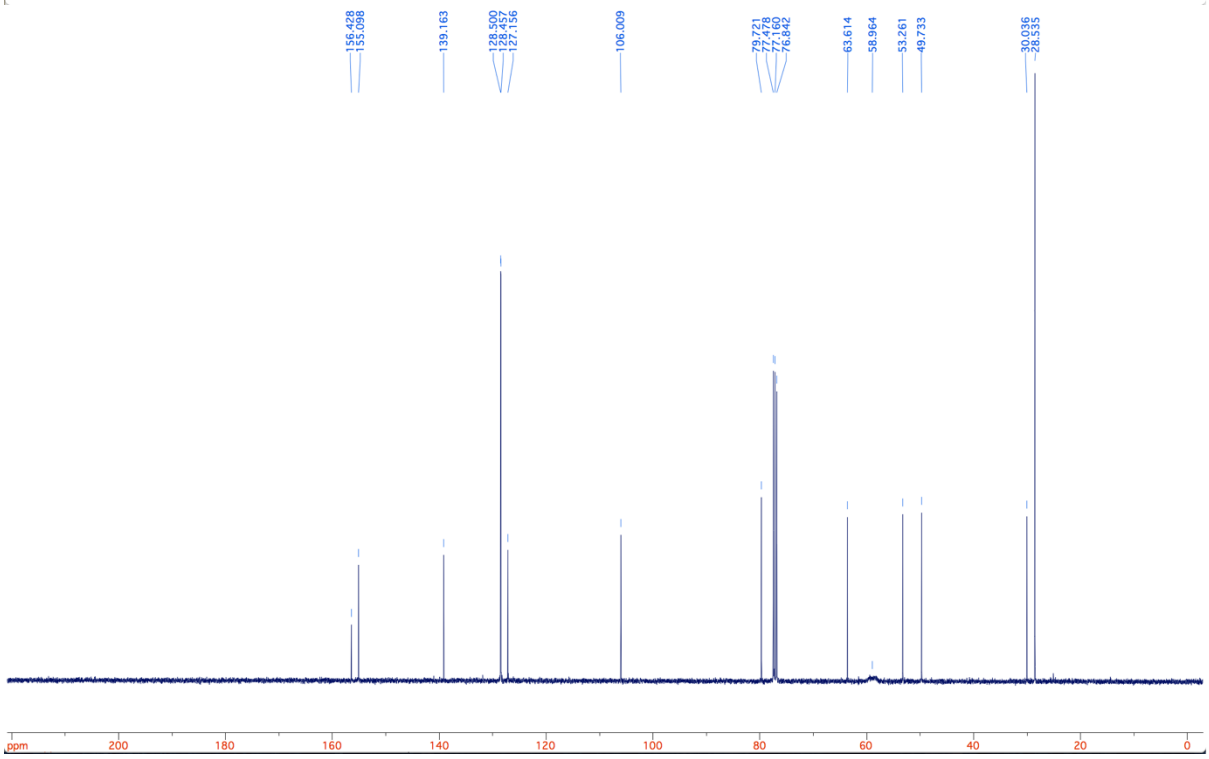

143.475
128.319
127.216
126.508
80.981
77.478
77.391
77.160
76.842
69.799
65.331
46.039
45.815
38.550
34.392
33.685
16.189
14.145
ppm

118b


Me
Me
Me
Me
O
O
N
N
O
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
2.03
1.96
1
0.951
0.932
1.83
1.02
0.953
1.97
1.87
9.02
4.87
2.75
ppm
156.314
143.044
128.317
127.390
126.575
79.341
77.478
77.160
76.842
65.403
65.054
57.802
54.908
46.153
45.880
39.065
34.445
34.035
28.513
15.968
14.369
14.308
ppm

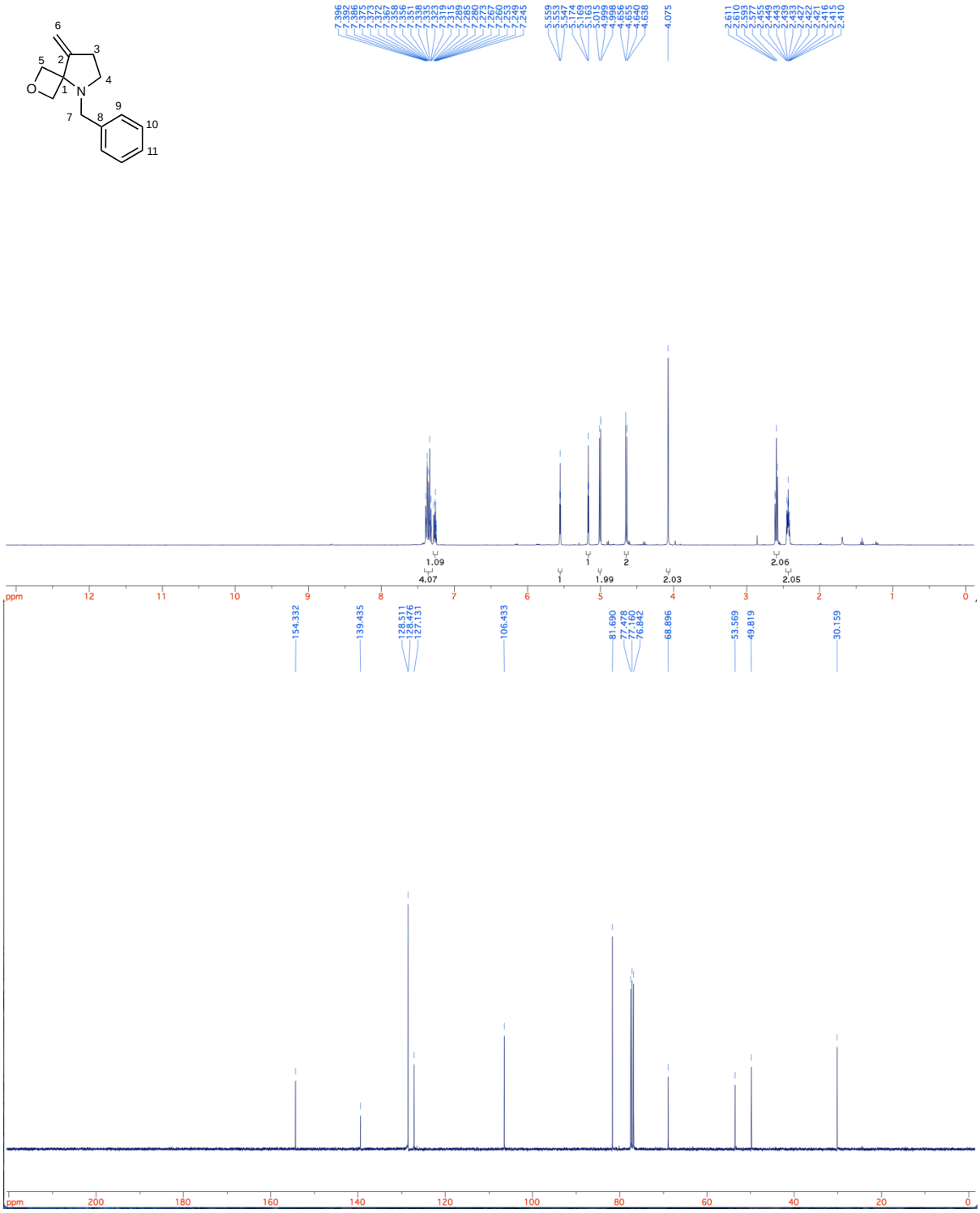
122a


7.390 7.385 7.379 7.369 7.365 7.362 7.350 7.345 7.338 7.328 7.323 7.297 7.288 7.264 7.255 7.259
5.314 5.305 5.299 5.293 5.108 5.103 5.097
4.251 4.228 4.207 4.202 3.900 3.879 3.877 3.870
2.631 2.614 2.598 2.495 2.481 2.475 2.471 2.465 2.449 2.448
1.488
1.16 4.28
1 1
4.21 2.03
2.09 2.05
9.9
ppm 11 10 9 8 7 6 5 4 3 2 1 0


156.428 155.098
139.163
128.500 128.457 127.156
106.009
79.721 77.478 77.160 76.842
63.614
58.964
53.261
49.733
30.036 28.535
ppm 200 180 160 140 120 100 80 60 40 20 0

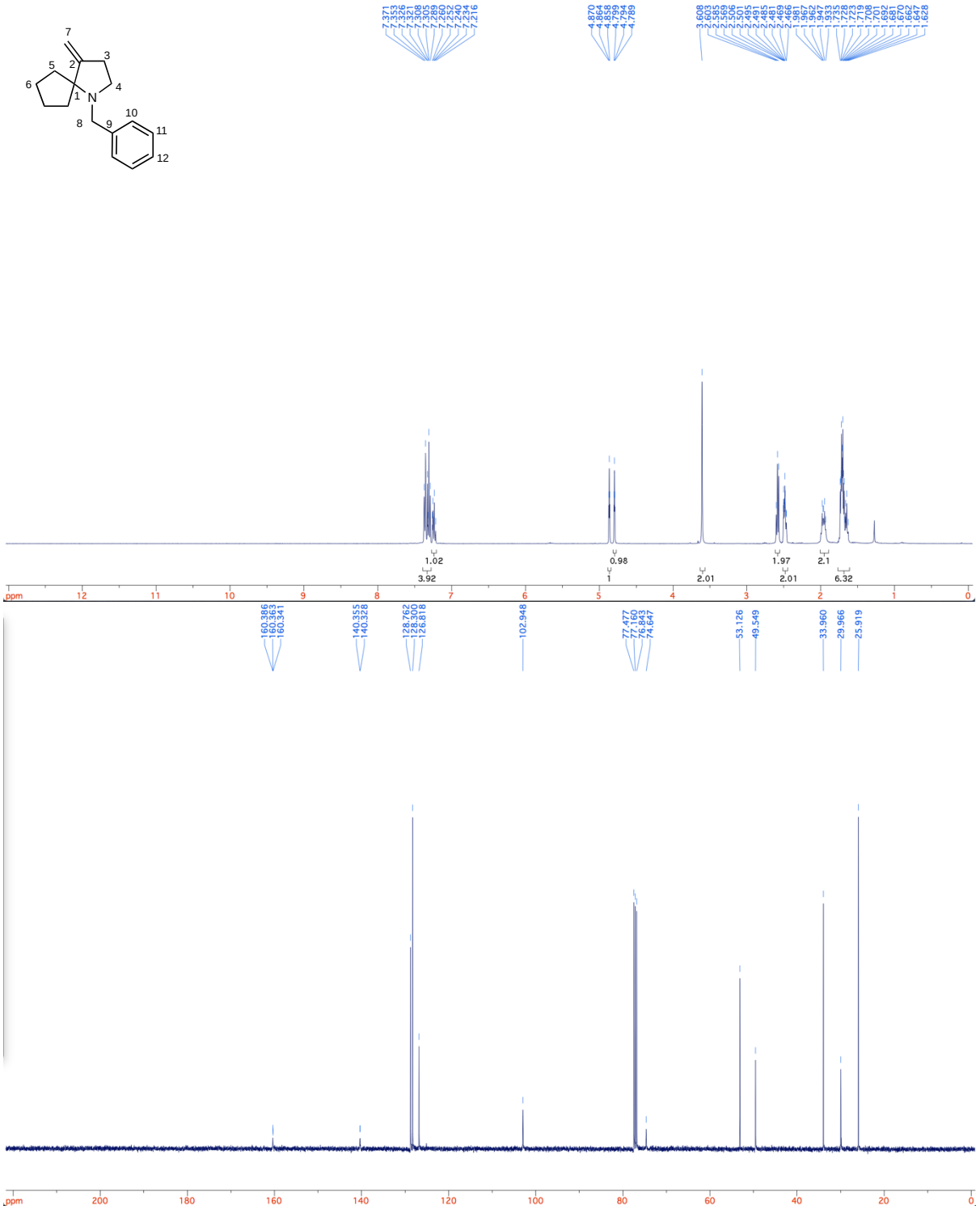
122b

6
5
2
3
4
O
1
N
7
8
9
10
11

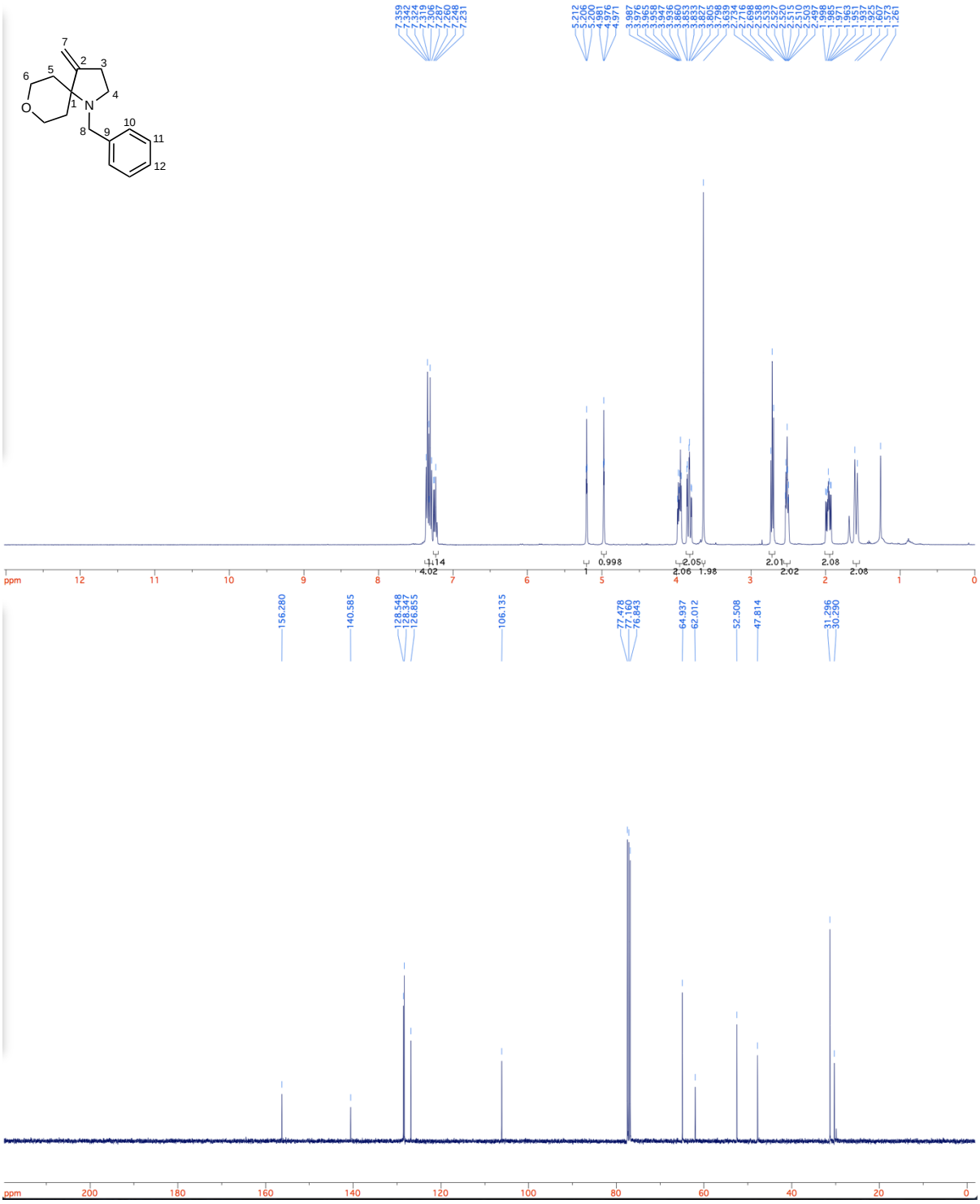

7.396 7.392 7.386 7.375 7.373 7.372 7.367 7.358 7.356 7.351 7.338 7.335 7.323 7.319 7.315 7.289 7.285 7.280 7.273 7.267 7.260 7.253 7.249 7.245
5.559 5.553 5.547 5.174 5.169 5.163 5.155 4.999 4.998 4.656 4.655 4.640 4.638
4.075
2.611 2.610 2.593 2.577 2.455 2.449 2.443 2.439 2.433 2.427 2.422 2.421 2.416 2.415 2.410
1.09 4.07 1 1 1.99 2 2.03 2.06 2.05
ppm 12 11 10 9 8 7 6 5 4 3 2 1 0
154.332 139.435 128.511 128.476 127.131 106.433 81.690 77.478 77.160 76.842 68.896 53.569 49.819 30.159
ppm 200 180 160 140 120 100 80 60 40 20 0

122c

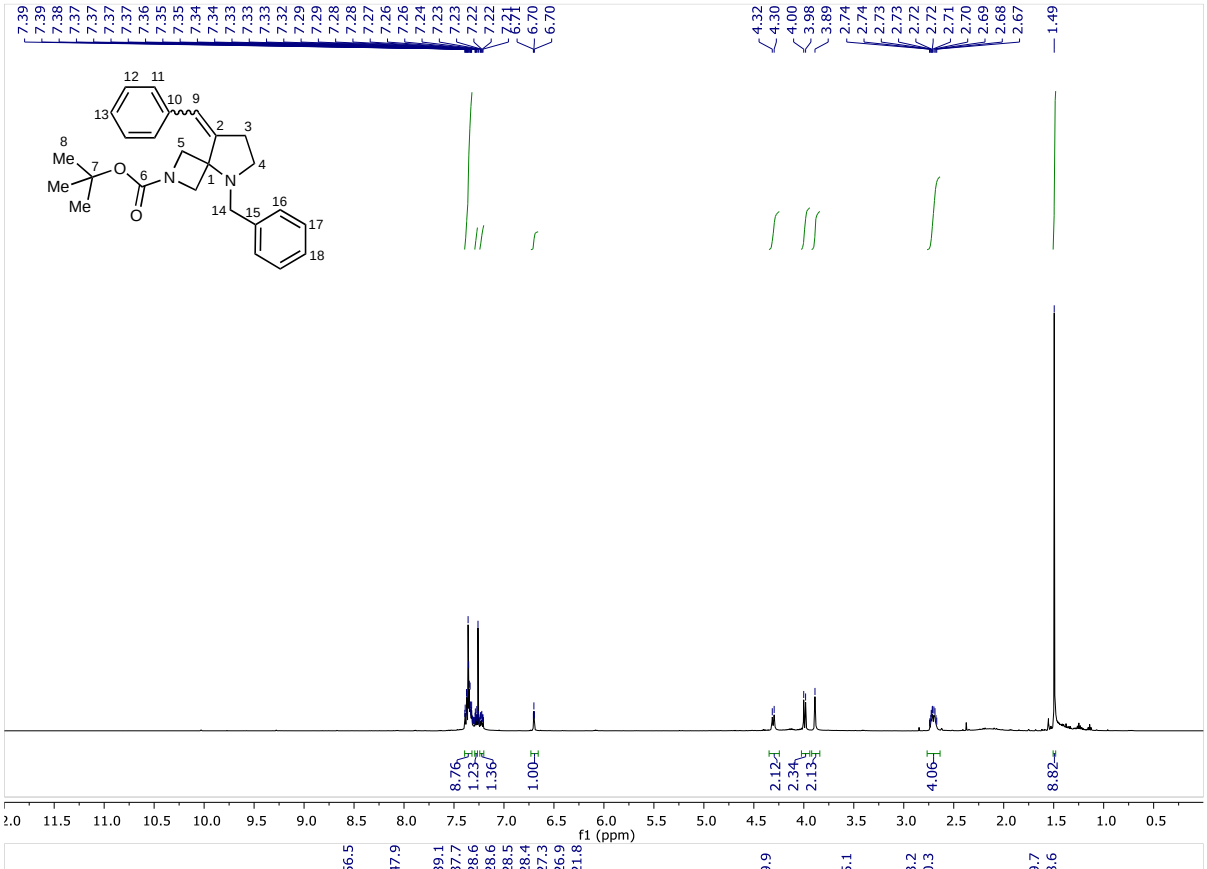
7
5
2
3
6
1
N
4
8
9
10
11
12

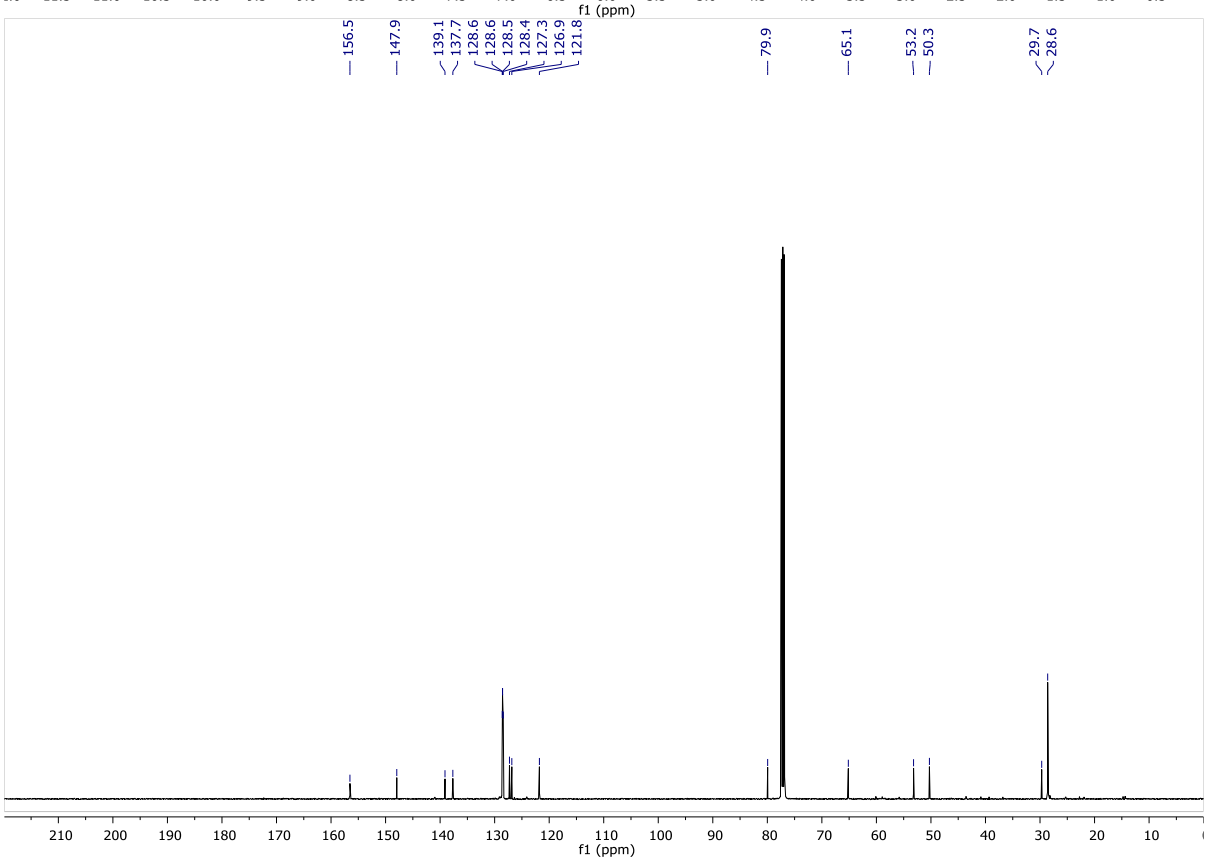

7.371
7.353
7.336
7.321
7.308
7.295
7.289
7.260
7.252
7.240
7.234
7.216
4.870
4.864
4.858
4.839
4.794
4.789
3.608
3.603
2.585
2.569
2.556
2.501
2.495
2.491
2.485
2.481
2.469
2.466
2.461
1.967
1.962
1.947
1.933
1.735
1.728
1.723
1.719
1.708
1.701
1.692
1.681
1.670
1.662
1.647
1.628
1.02
0.98
1.97
2.1
3.92
1
2.01
2.01
6.32
ppm
160.386
160.363
160.341
140.355
140.328
128.762
128.470
128.018
102.948
77.477
77.160
76.843
74.647
53.126
49.549
33.960
29.966
25.919
ppm

122d

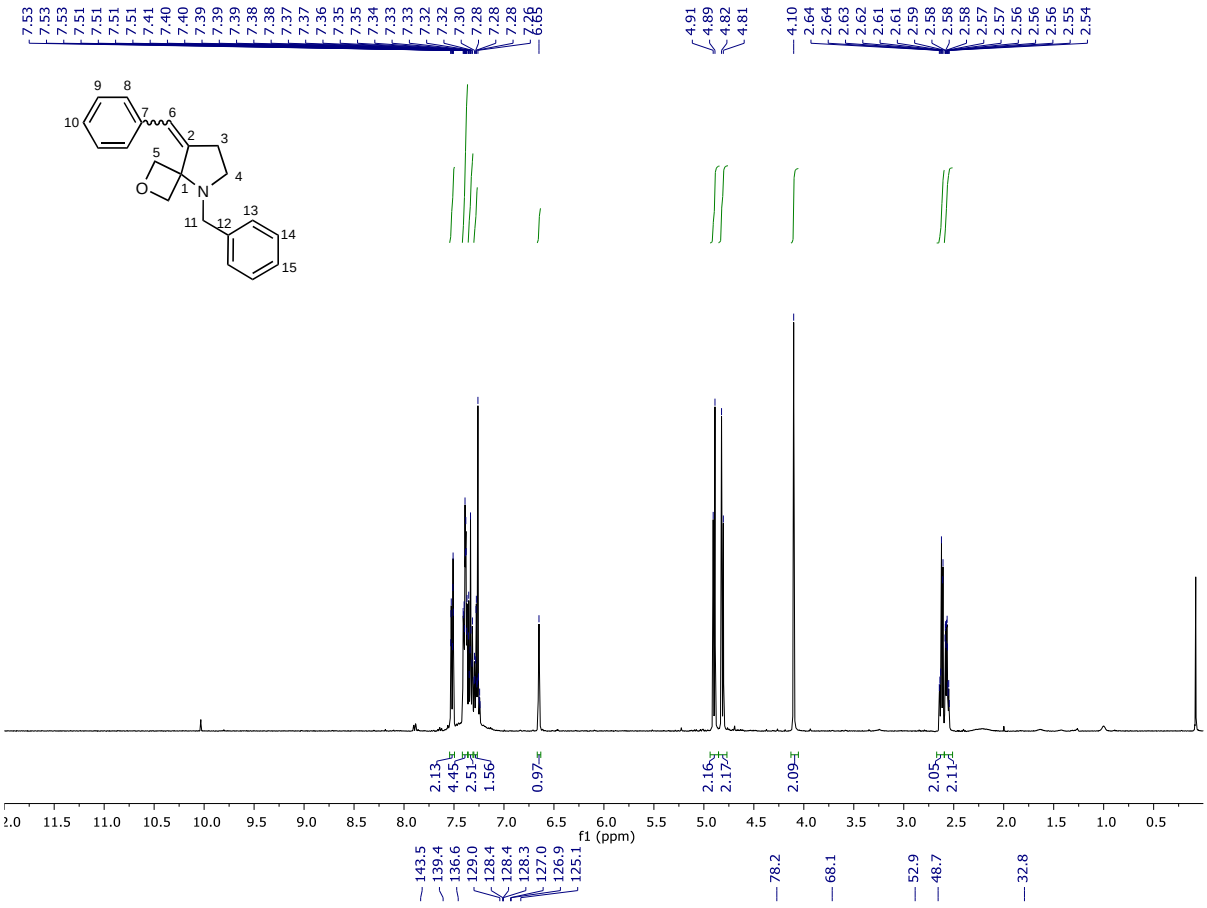

7.359
7.342
7.324
7.319
7.306
7.287
7.267
7.260
7.248
7.231
5.212
5.206
5.200
4.981
4.976
4.971
3.987
3.976
3.965
3.958
3.947
3.936
3.860
3.850
3.833
3.827
3.805
3.798
3.639
3.624
2.719
2.698
2.538
2.535
2.527
2.520
2.515
2.510
2.503
2.497
1.998
1.985
1.971
1.965
1.951
1.937
1.907
1.807
1.573
1.261
1.14
4.02
0.998
1
2.05
2.06
1.98
2.01
2.02
2.08
2.08
ppm
156.280
140.585
128.548
128.347
128.244
126.555
106.135
77.478
77.160
76.843
64.937
62.012
52.508
47.814
31.296
30.290
ppm

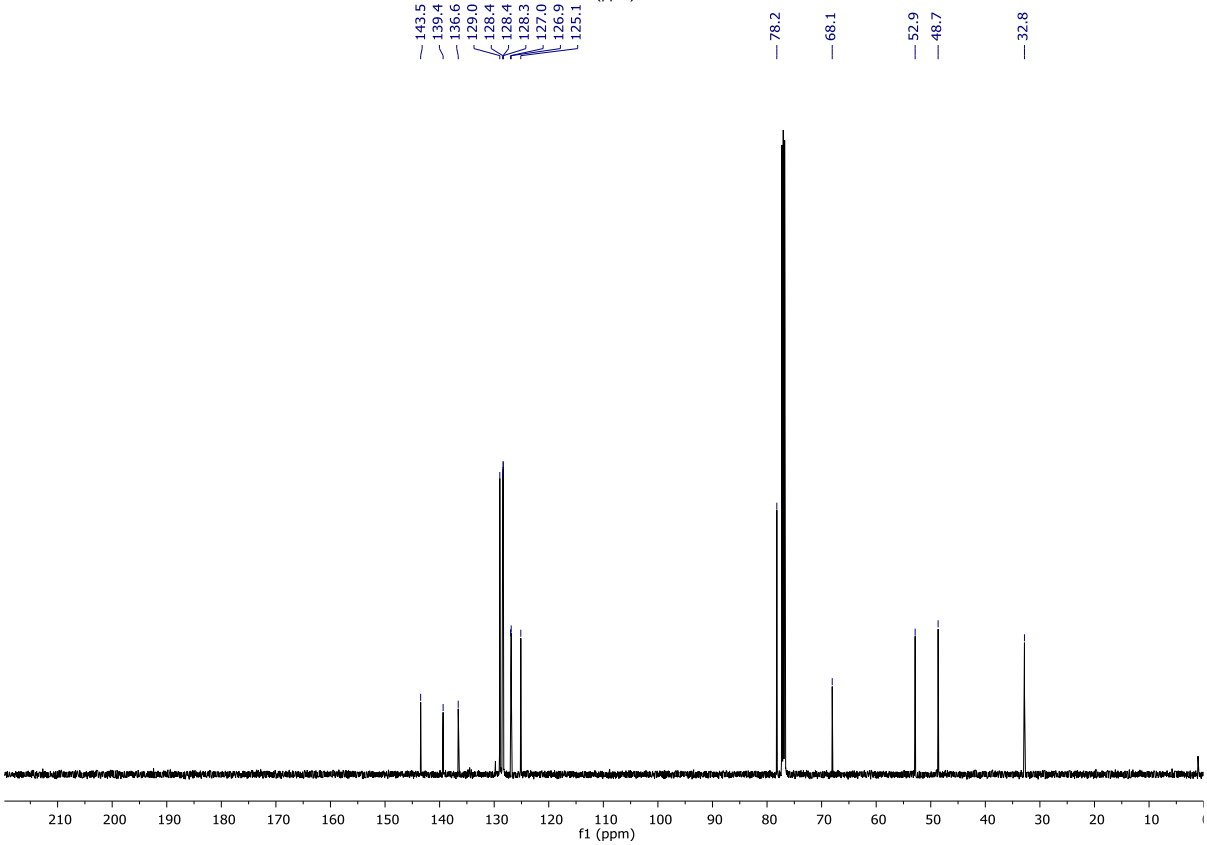
122e


7.39 7.39 7.38 7.37 7.37 7.37 7.37 7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.33 7.32 7.29 7.29 7.28 7.28 7.27 7.26 7.26 7.24 7.23 7.23 7.22 7.22 7.21 6.71 6.70 6.70
4.32 4.30 4.00 3.98 3.89 2.74 2.74 2.73 2.73 2.72 2.72 2.71 2.70 2.69 2.68 2.67 1.49
8.76 1.23 1.36 1.00 2.12 2.34 2.13 4.06 8.82
f1 (ppm)

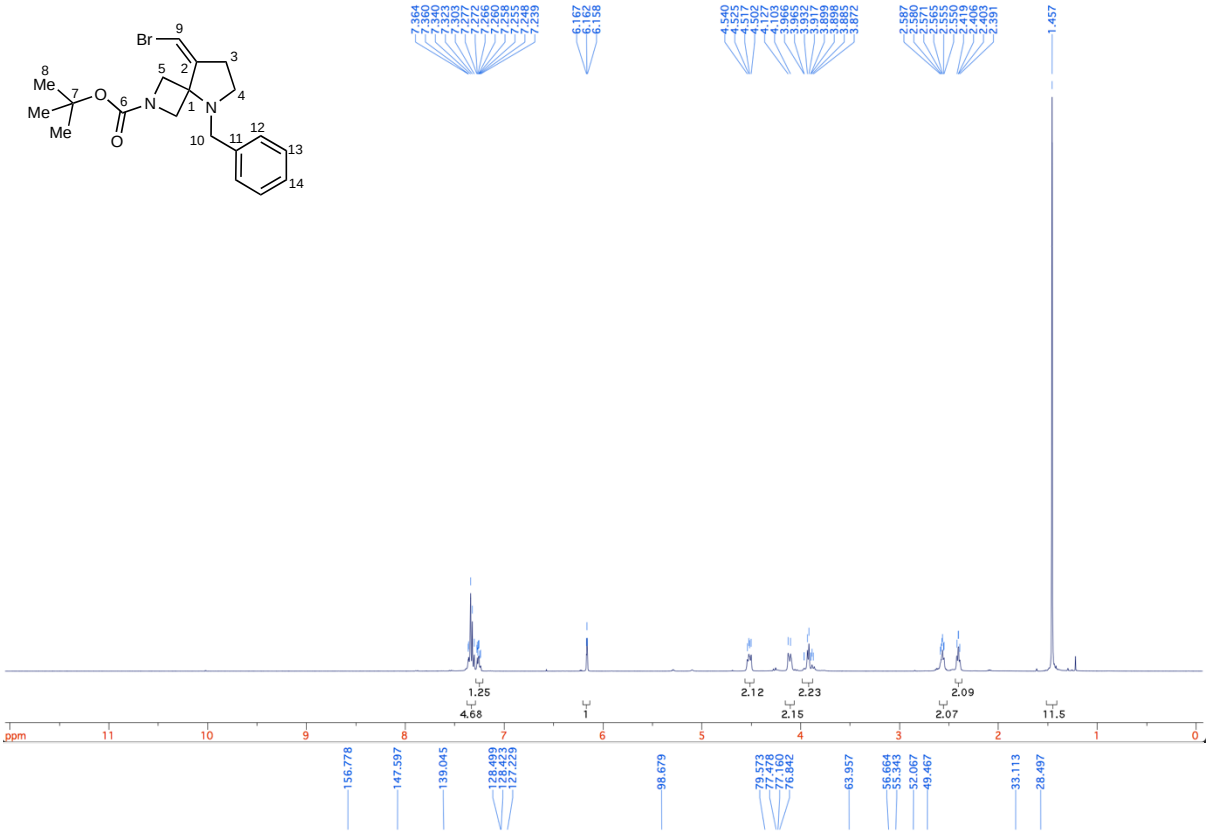

156.5 147.9 139.1 137.7 128.6 128.6 128.5 128.4 127.3 126.9 121.8 79.9 65.1 53.2 50.3 29.7 28.6
f1 (ppm)

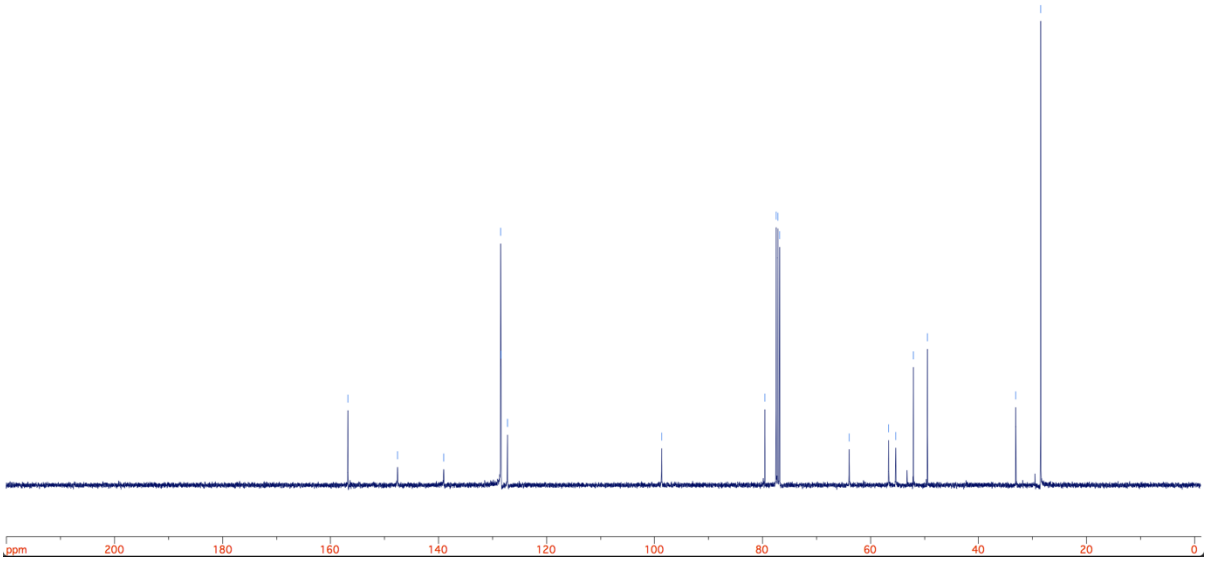
122f


7.53 7.53 7.53 7.51 7.51 7.51 7.51 7.41 7.40 7.40 7.39 7.39 7.39 7.38 7.38 7.37 7.37 7.36 7.35 7.35 7.34 7.33 7.33 7.32 7.32 7.30 7.28 7.28 7.28 6.65
4.91 4.89 4.82 4.81
4.10
2.64 2.64 2.63 2.62 2.61 2.61 2.59 2.58 2.58 2.58 2.57 2.57 2.56 2.56 2.56 2.55 2.54
2.13 4.45 2.51 1.56 0.97 2.16 2.17 2.09 2.05 2.11
f1 (ppm)

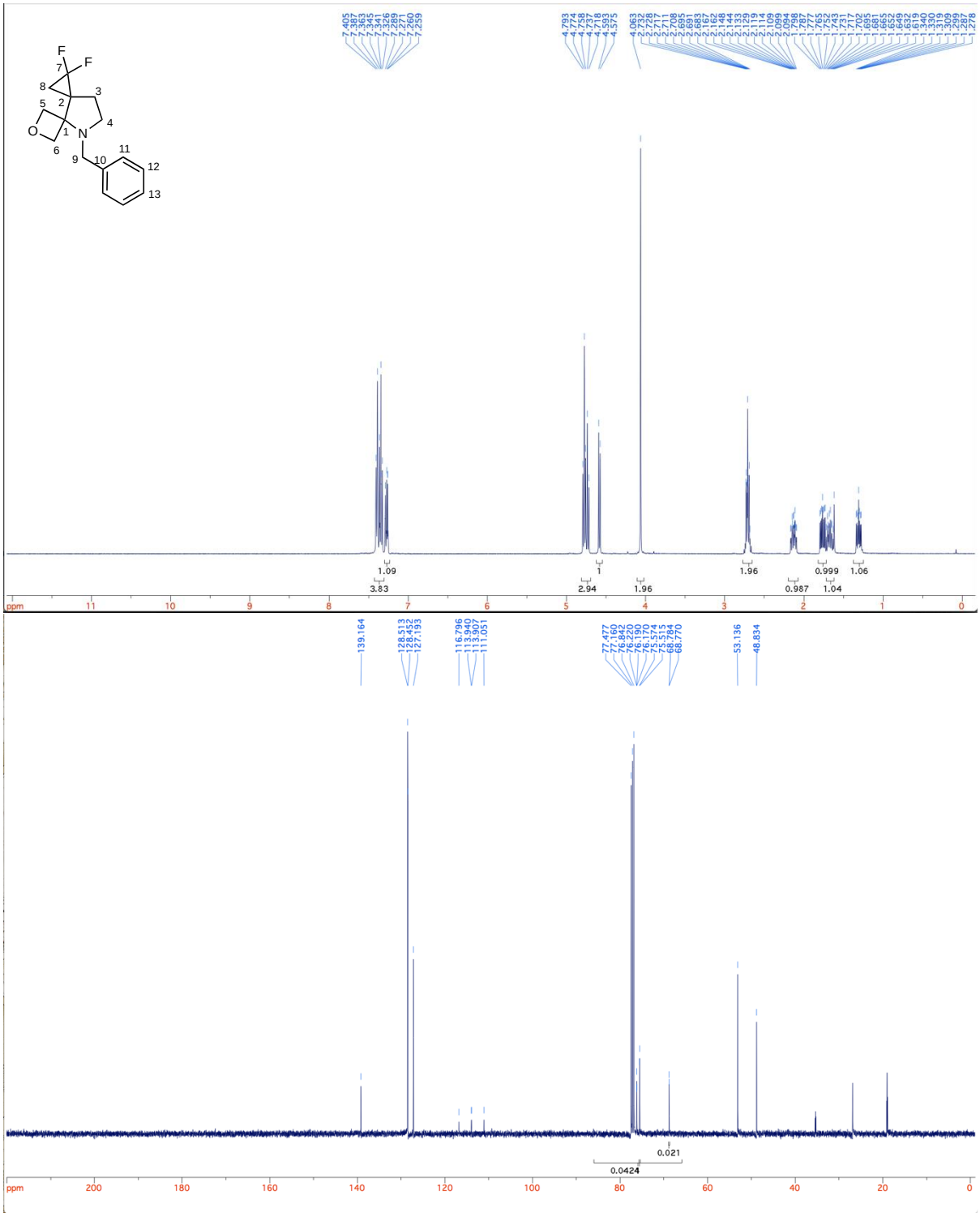

143.5 139.4 136.6 129.0 128.4 128.4 128.3 127.0 126.9 125.1
78.2
68.1
52.9 48.7
32.8
f1 (ppm)

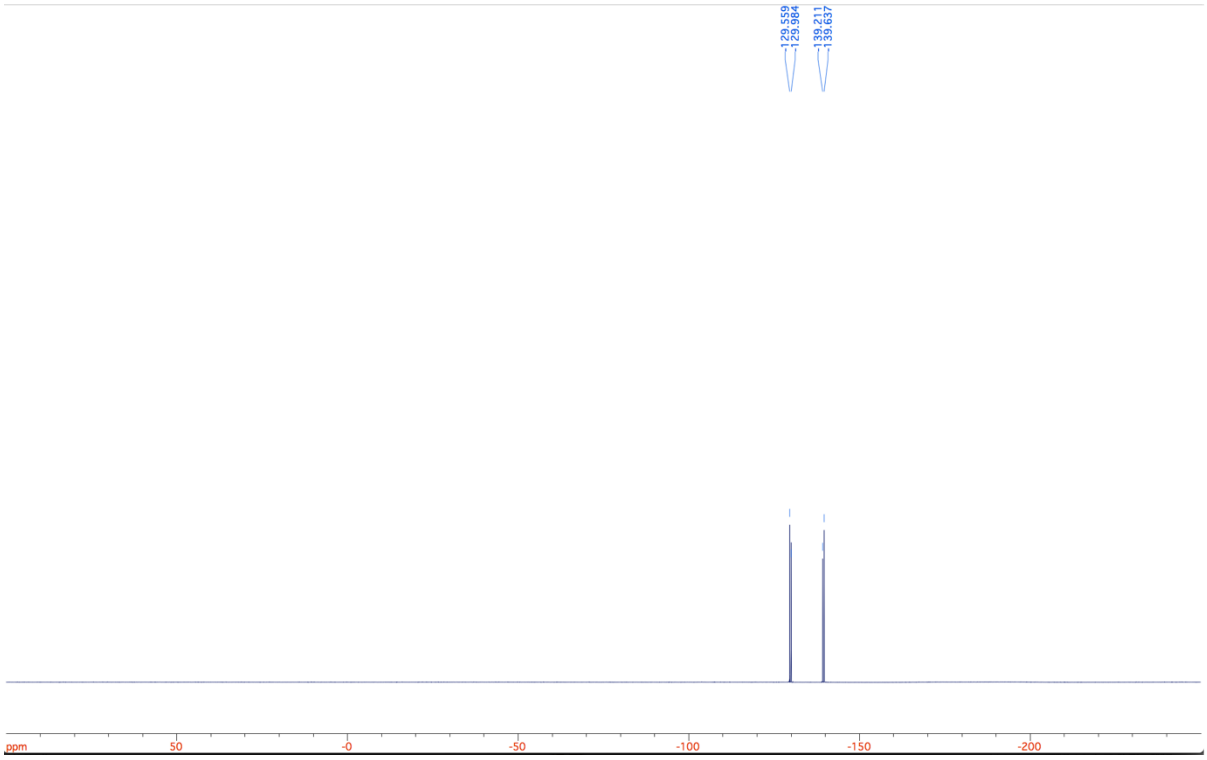
122g



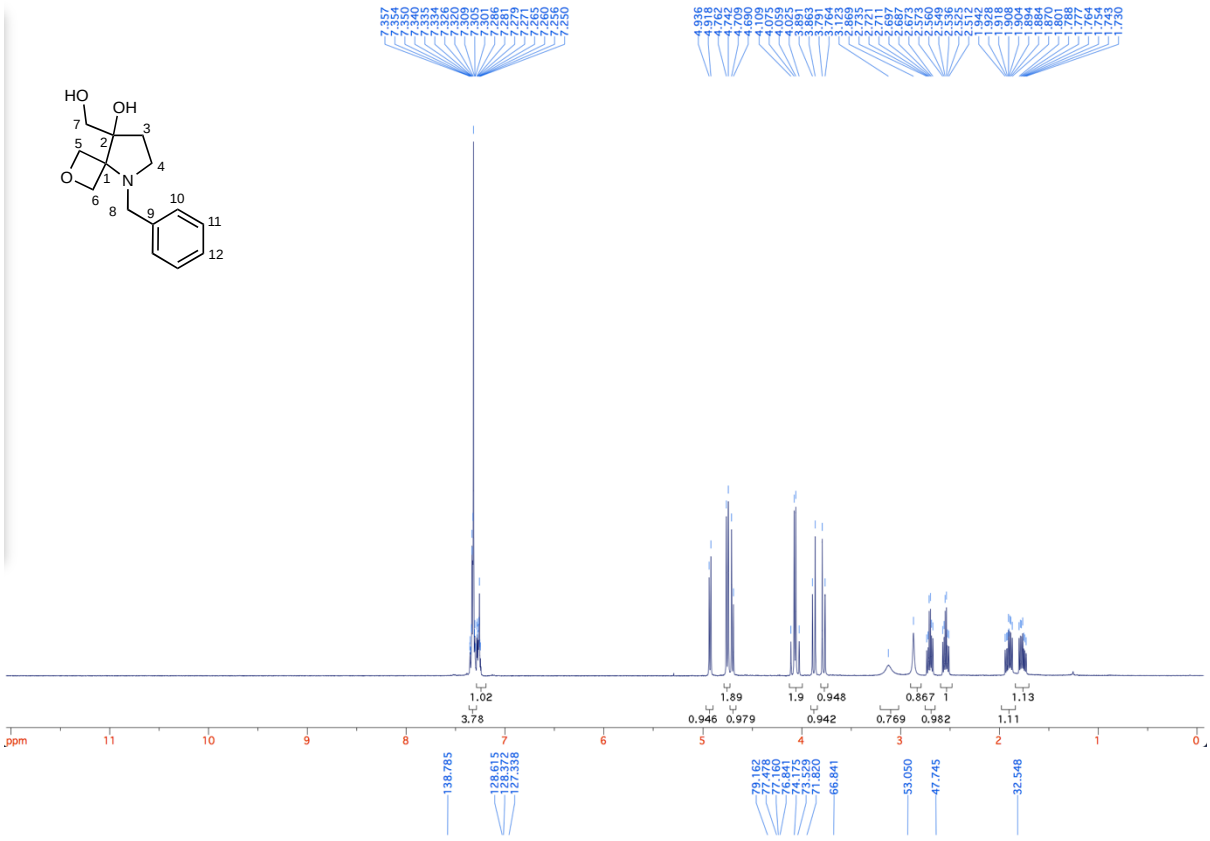


124a


F
F
O
N
1
2
3
4
5
6
7
8
9
10
11
12
13
7.405 7.387 7.363 7.345 7.326 7.289 7.277 7.260 7.259
4.793 4.774 4.758 4.737 4.718 4.593 4.575
4.083 2.772 2.728 2.717 2.711 2.708 2.695 2.683 2.667 2.162 2.148 2.144 2.133 2.129 2.119 2.114 2.109 2.089 2.084 1.798 1.797 1.777 1.765 1.752 1.743 1.731 1.717 1.702 1.695 1.681 1.665 1.652 1.649 1.632 1.619 1.594 1.590 1.319 1.309 1.299 1.287 1.278
1.09
3.83
1
2.94
1.96
1.96
0.987
0.999
1.04
1.06
ppm
11 10 9 8 7 6 5 4 3 2 1 0
139.164
128.513 128.452 127.193
116.796 113.940 113.907 111.051
77.477 77.160 76.842 76.420 76.190 76.170 75.574 75.515 68.784 68.770
53.136
48.834
0.021
0.0424
ppm
200 180 160 140 120 100 80 60 40 20 0

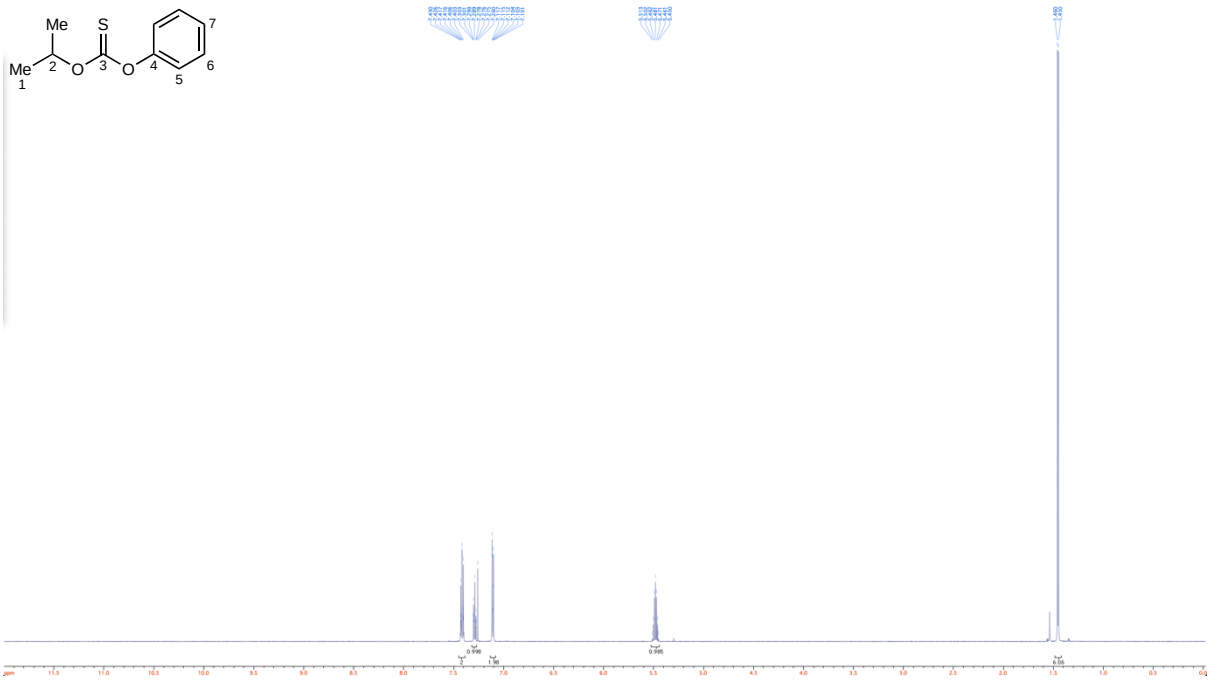

129.559
129.984
139.211
139.637
ppm
50
-0
-50
-100
-150
-200

124c

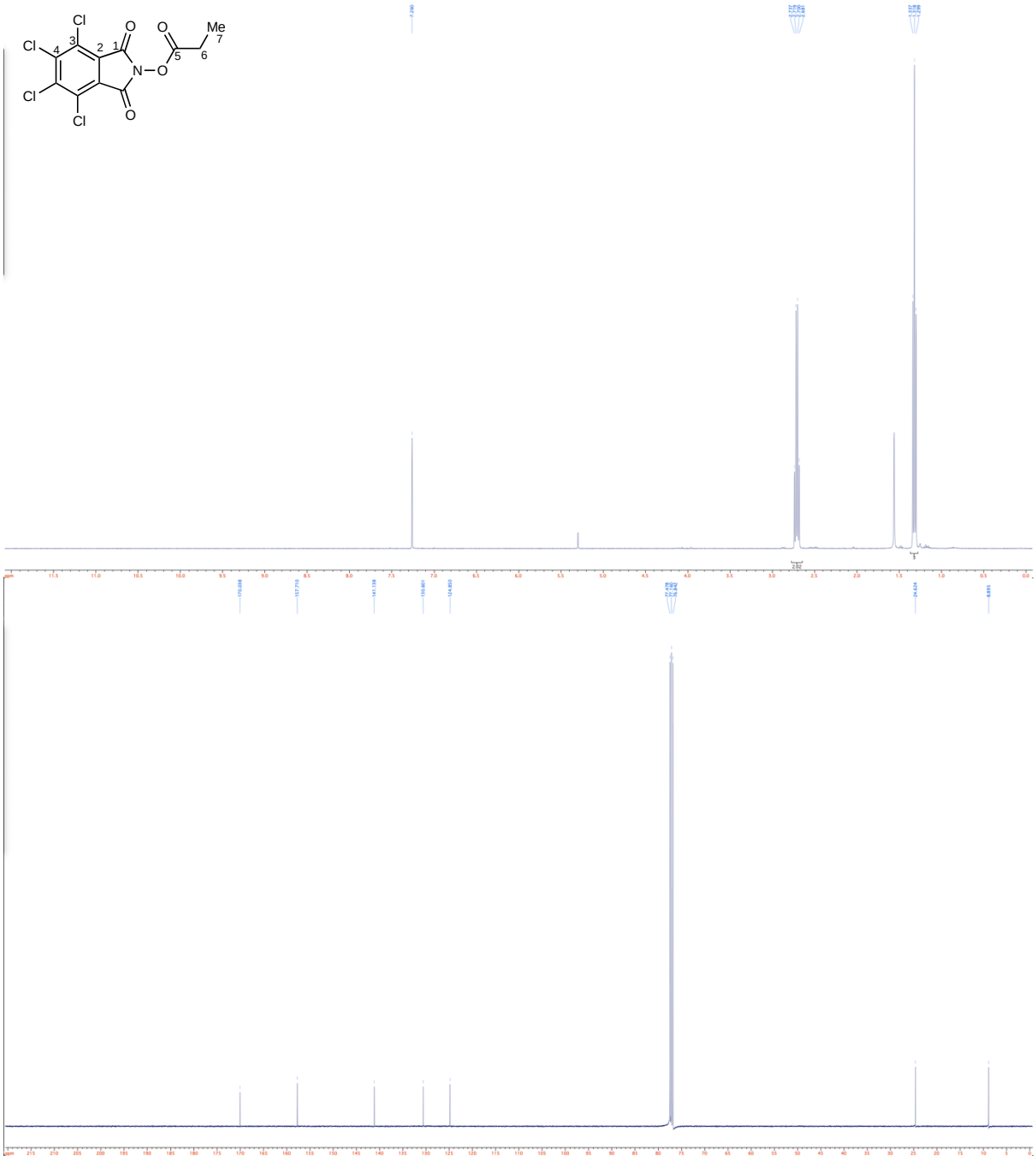

HO
OH
O
N
1
2
3
4
5
6
7
8
9
10
11
12
7.357 7.354 7.350 7.340 7.330 7.334 7.326 7.320 7.309 7.305 7.301 7.296 7.281 7.279 7.271 7.265 7.260 7.256 7.250
4.836 4.818 4.761 4.742 4.709 4.690 4.109 4.075 4.059 4.050 3.891 3.863 3.781 3.764 3.123 2.969 2.950 2.721 2.701 2.687 2.673 2.563 2.560 2.549 2.536 2.522 2.511 1.942 1.918 1.908 1.904 1.894 1.884 1.870 1.801 1.788 1.777 1.764 1.754 1.743 1.730
1.02
3.78
1.89
0.946 0.979
1.9 0.948
0.942
0.867 1
0.769 0.982
1.13
1.11
ppm
11
10
9
8
7
6
5
4
3
2
1
0
138.785
128.615
128.372
127.338
79.162
77.478
77.160
76.841
74.175
73.559
71.820
66.841
53.050
47.745
32.548
ppm
200
180
160
140
120
100
80
60
40
20
0

9.4 Spectra for appendix I

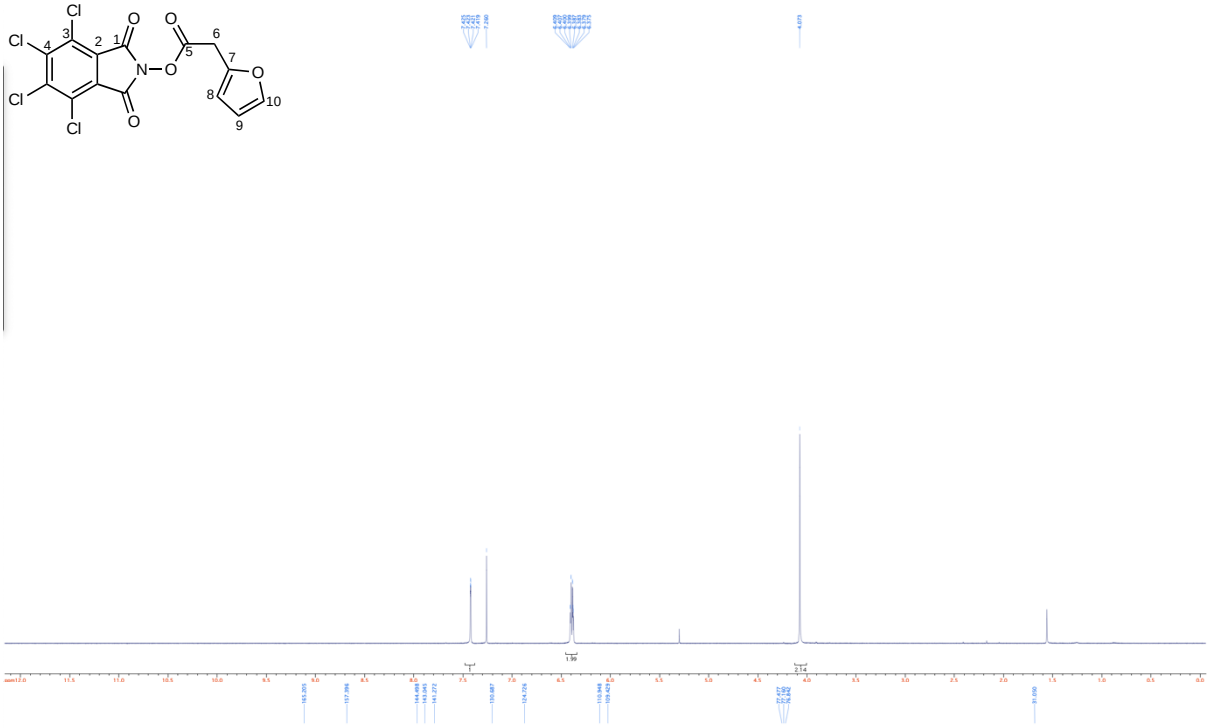
80a

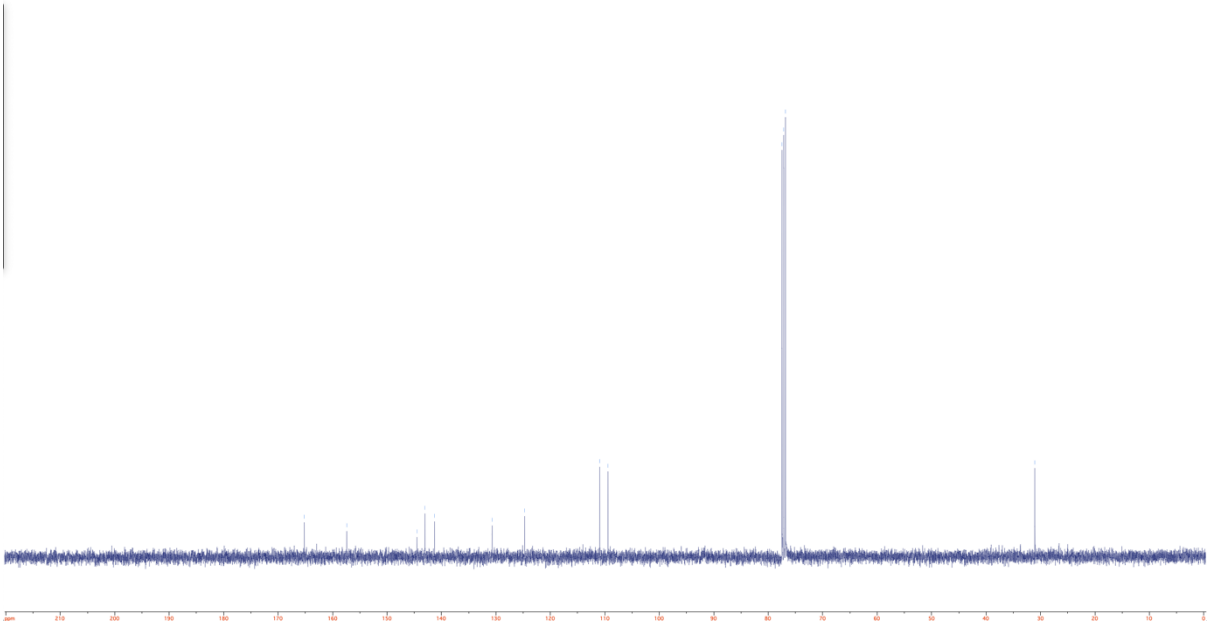


S1

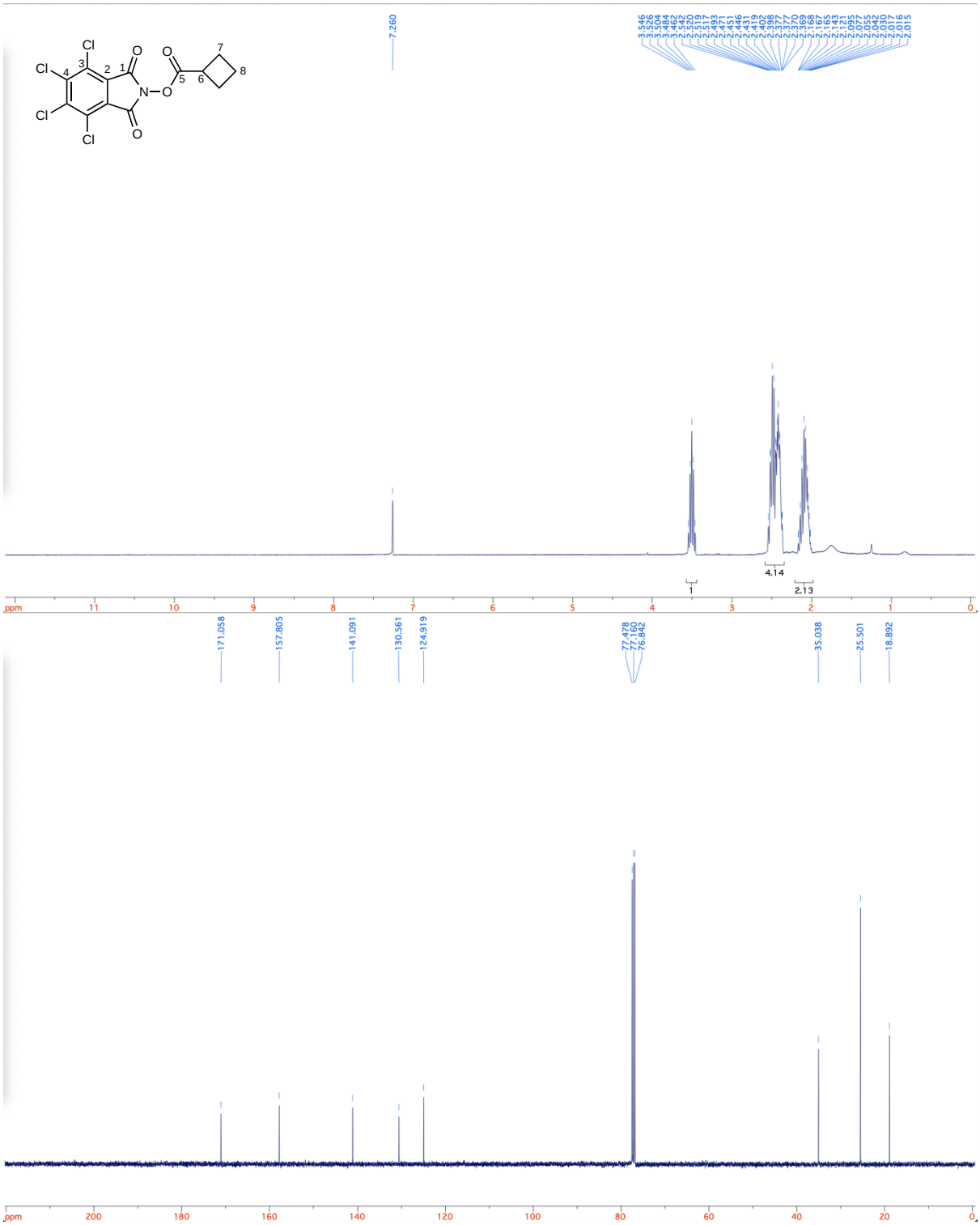


S2

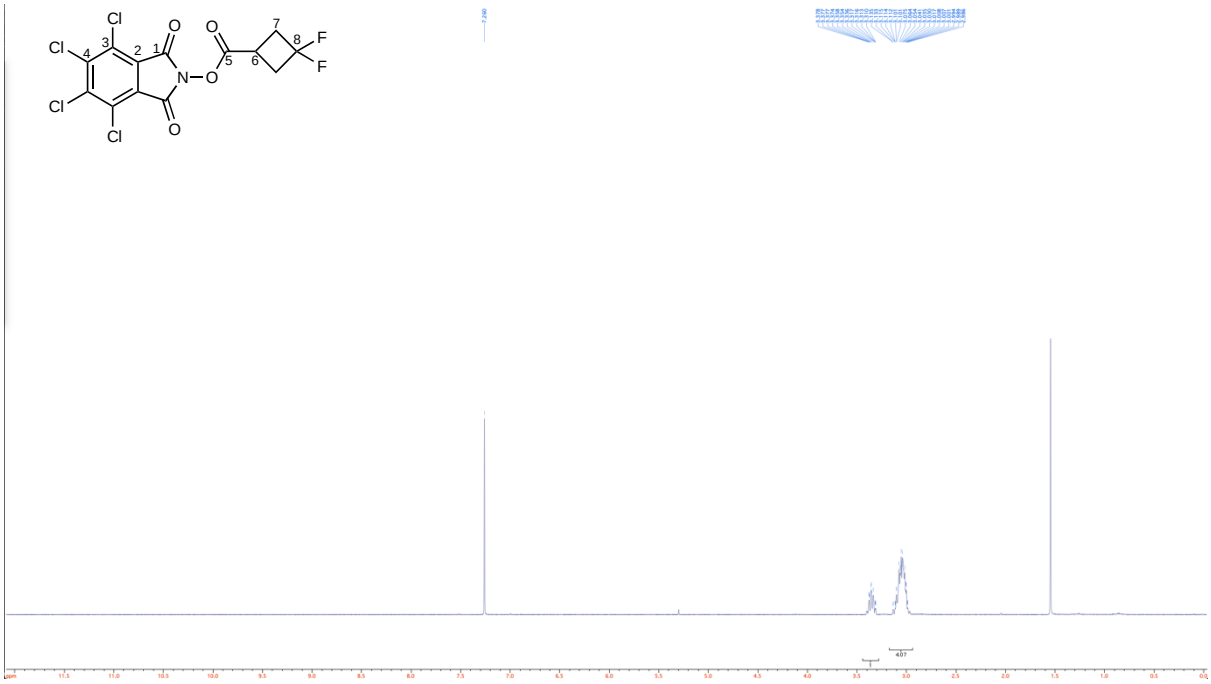


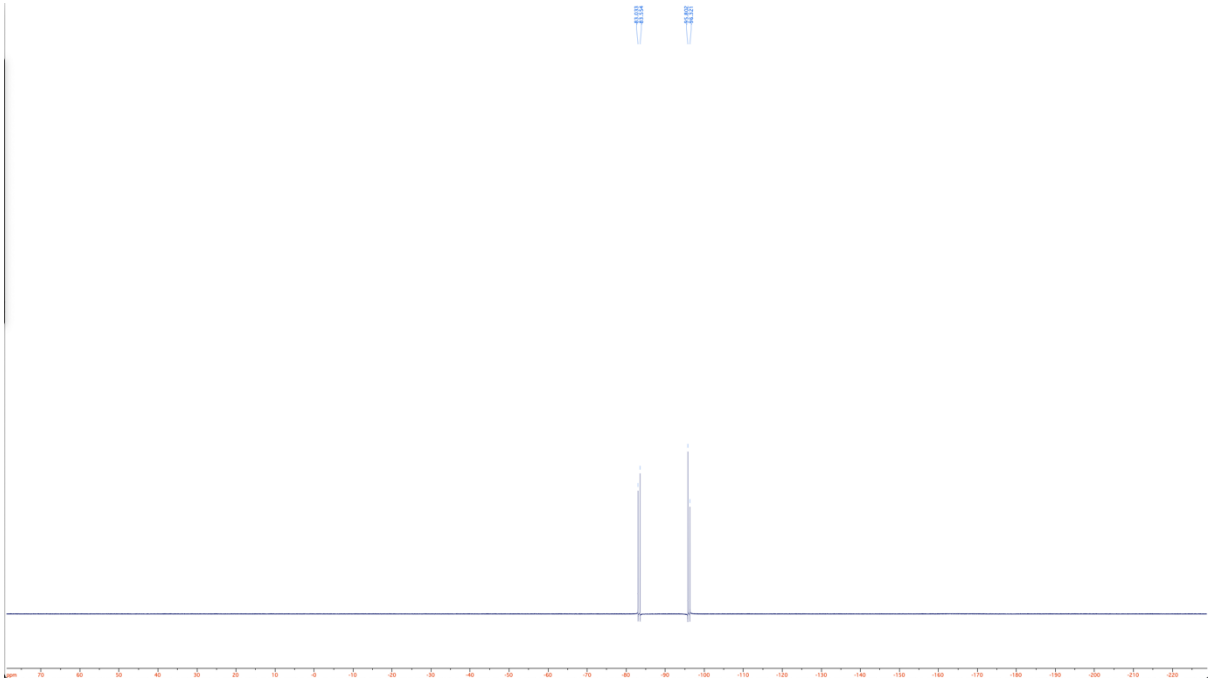


S3

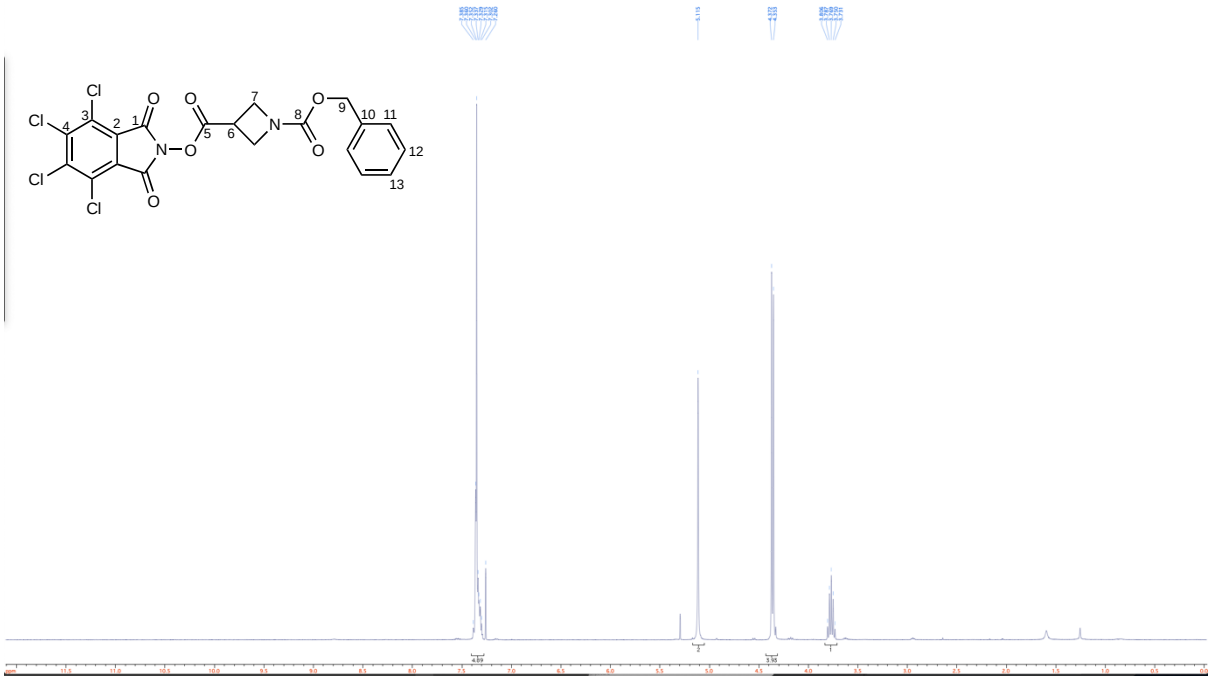

7.260
4.14
2.13
171.058
157.805
141.091
130.561
124.919
77.478
77.160
76.842
35.038
25.501
18.892

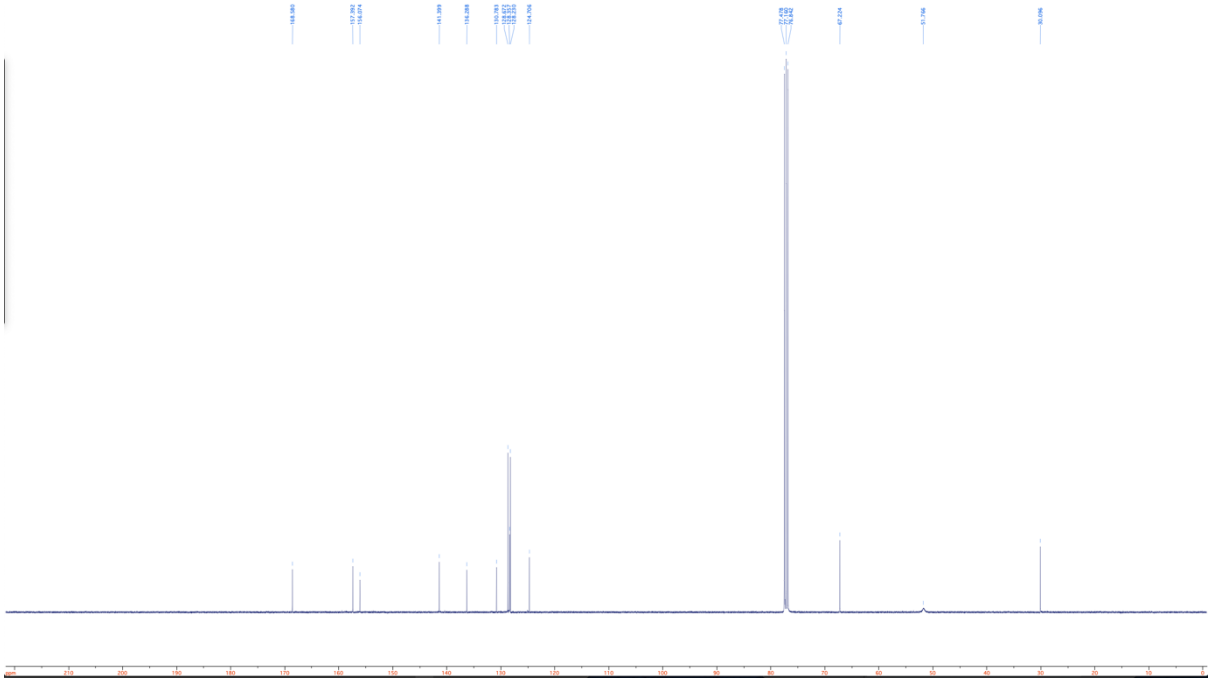
S4



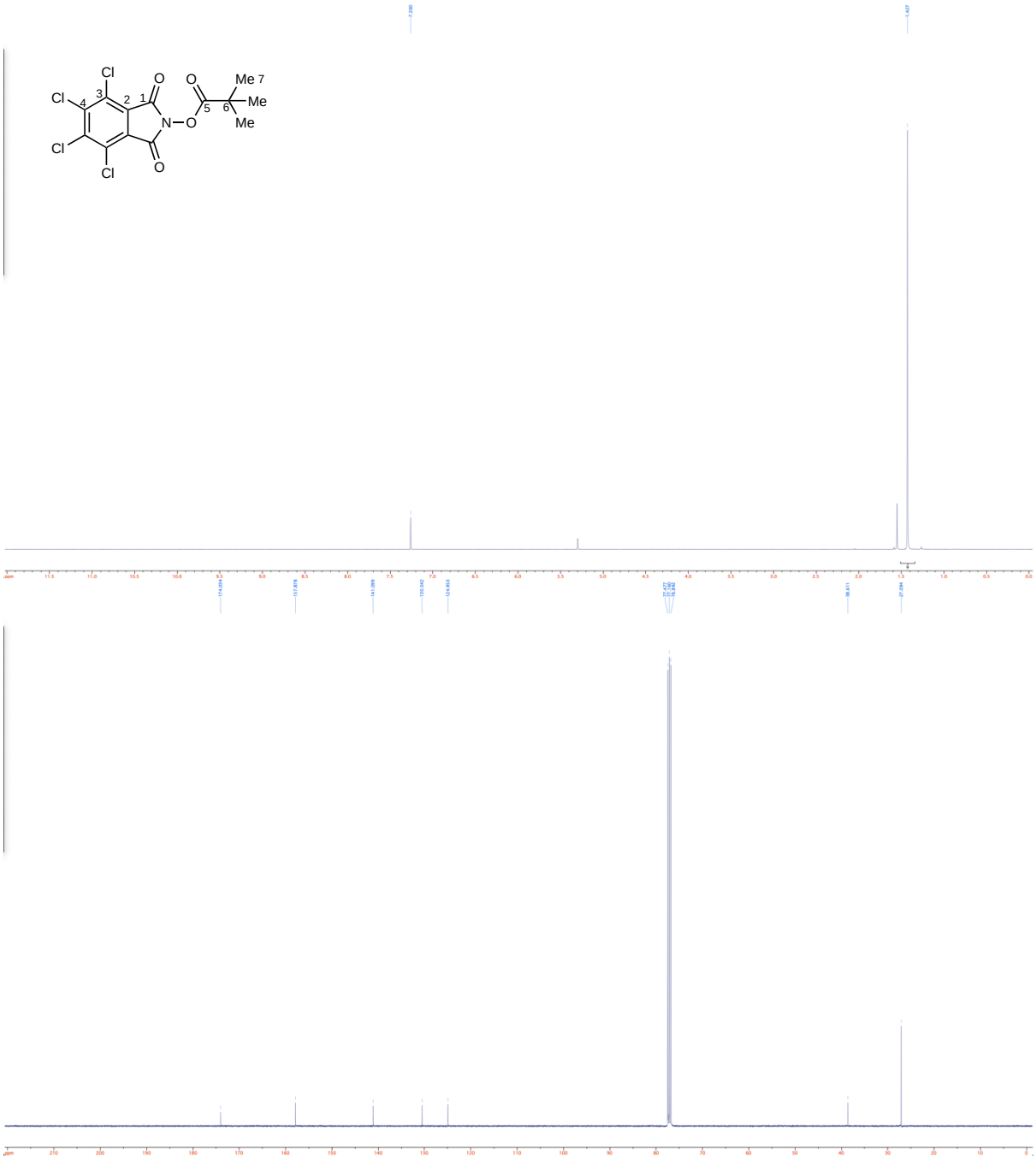


S5

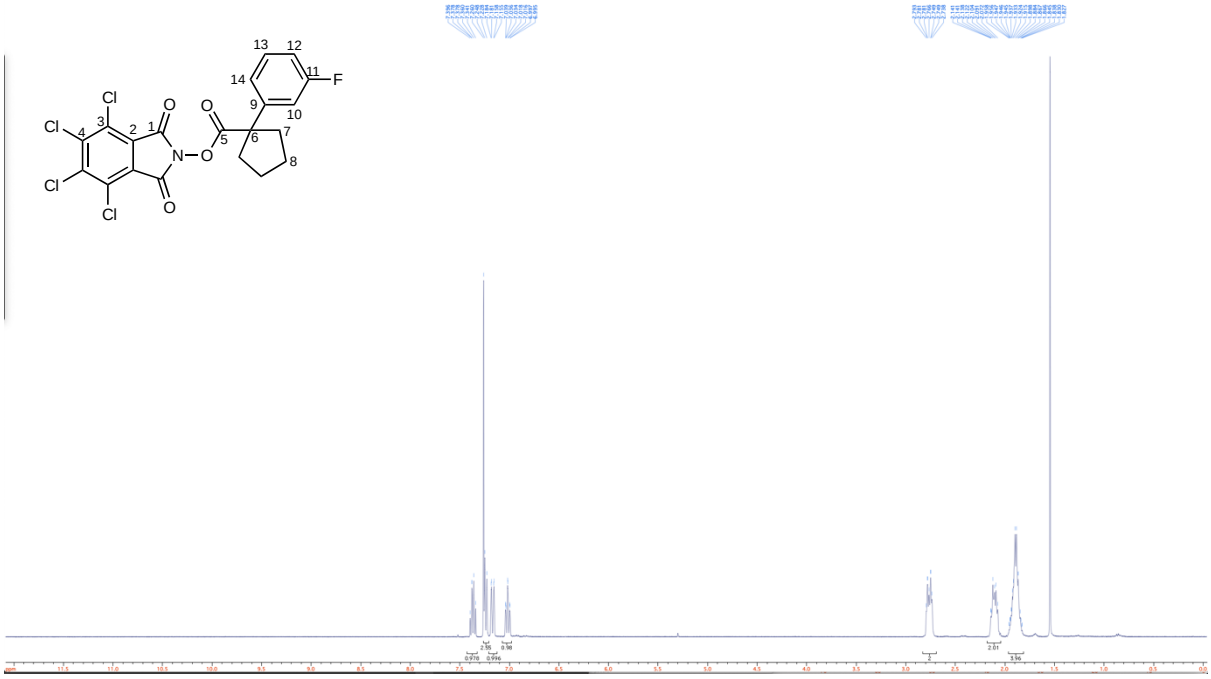


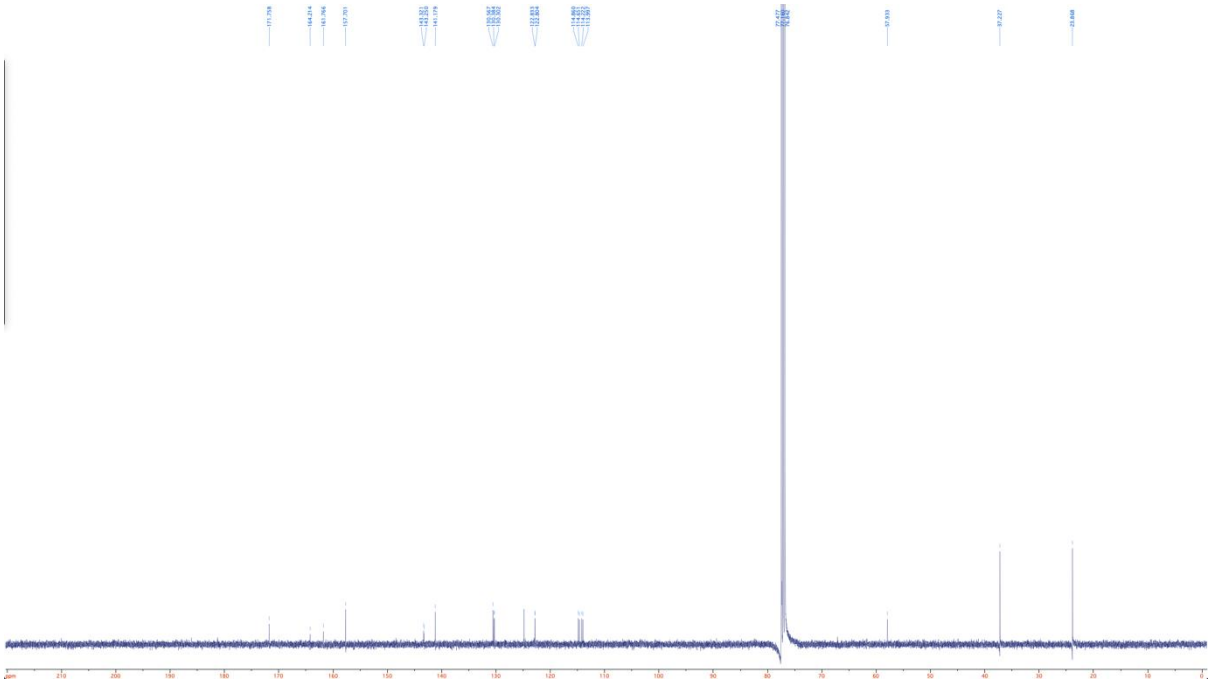


S6

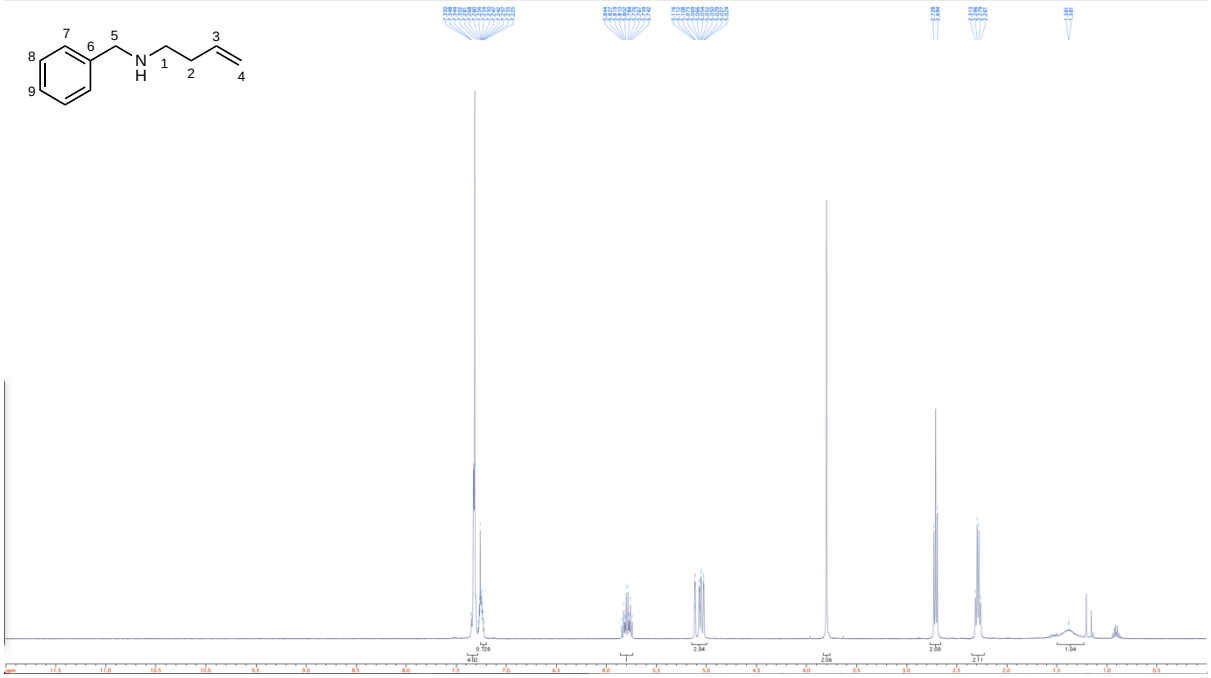


S7

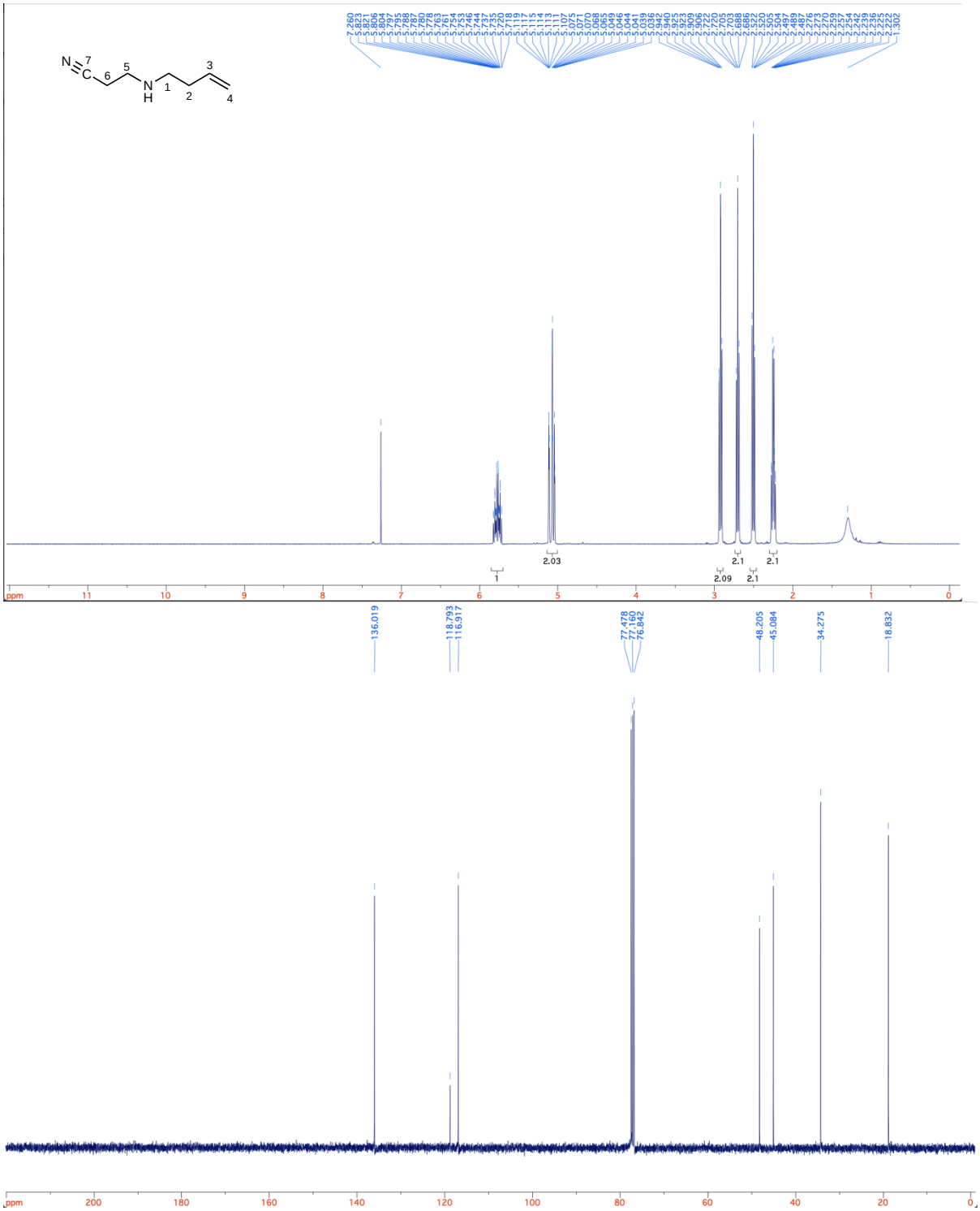




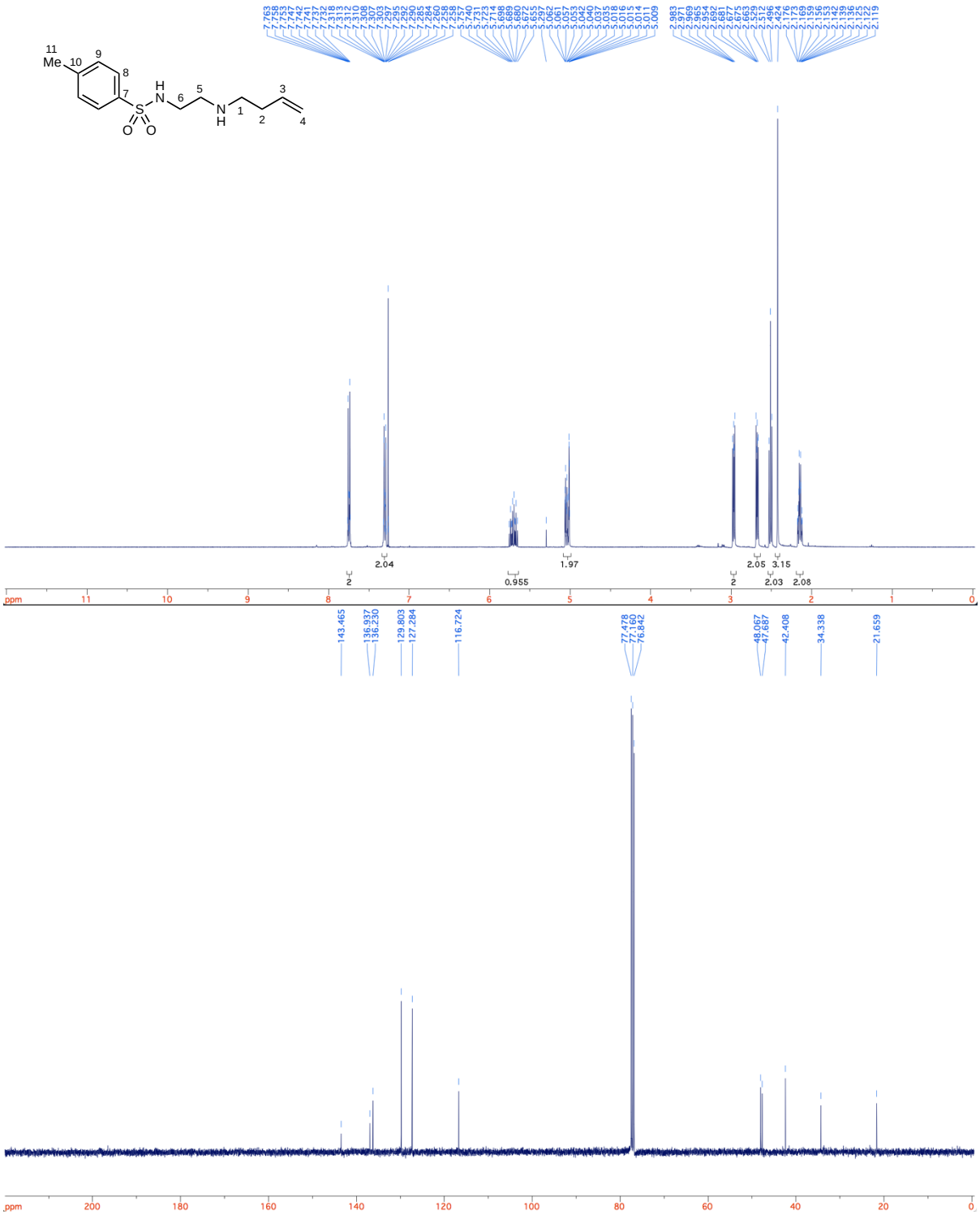
107a



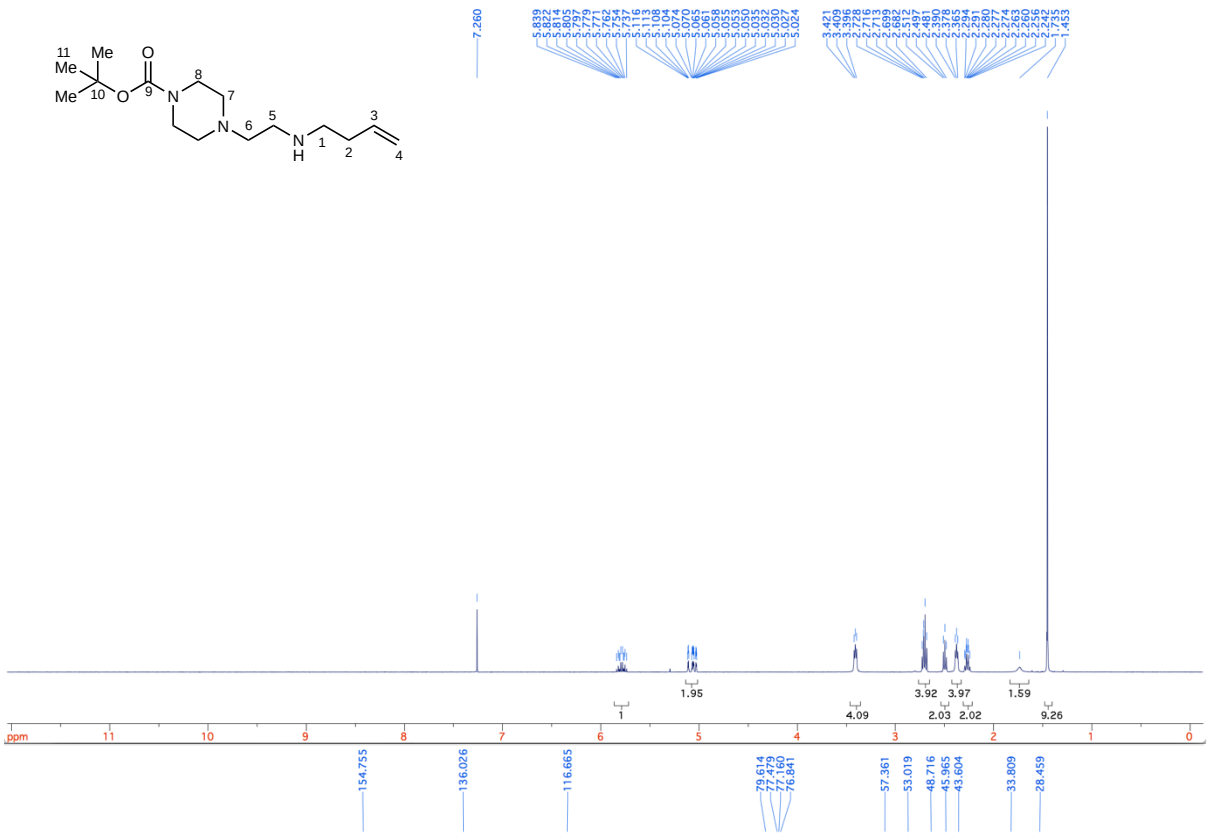
S8

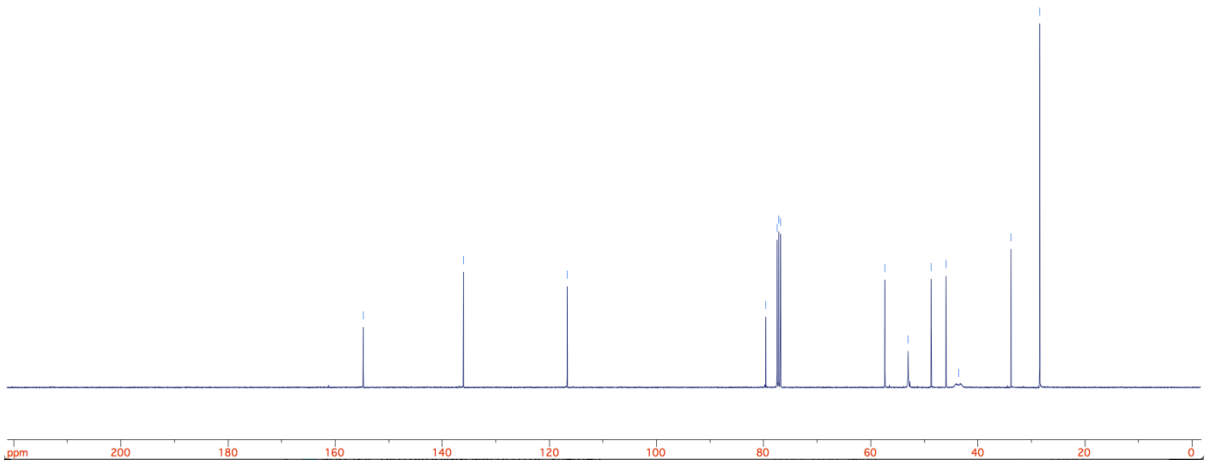

N
C
N
H
1
2
3
4
5
6
7
2.03
1
2.09
2.1
2.1
2.1
ppm
136.019
118.793
116.917
77.478
77.160
76.842
48.205
45.084
34.275
18.832
ppm

S9


Me
11
10
9
8
7
6
5
4
3
2
1
H
N
S
O
O
N
H
2.04
1.97
2.05
3.15
2
0.955
2
2.03
2.08
ppm
143.465
136.937
136.230
129.803
127.284
116.724
77.478
77.160
76.842
48.067
47.687
42.408
34.338
21.659
ppm

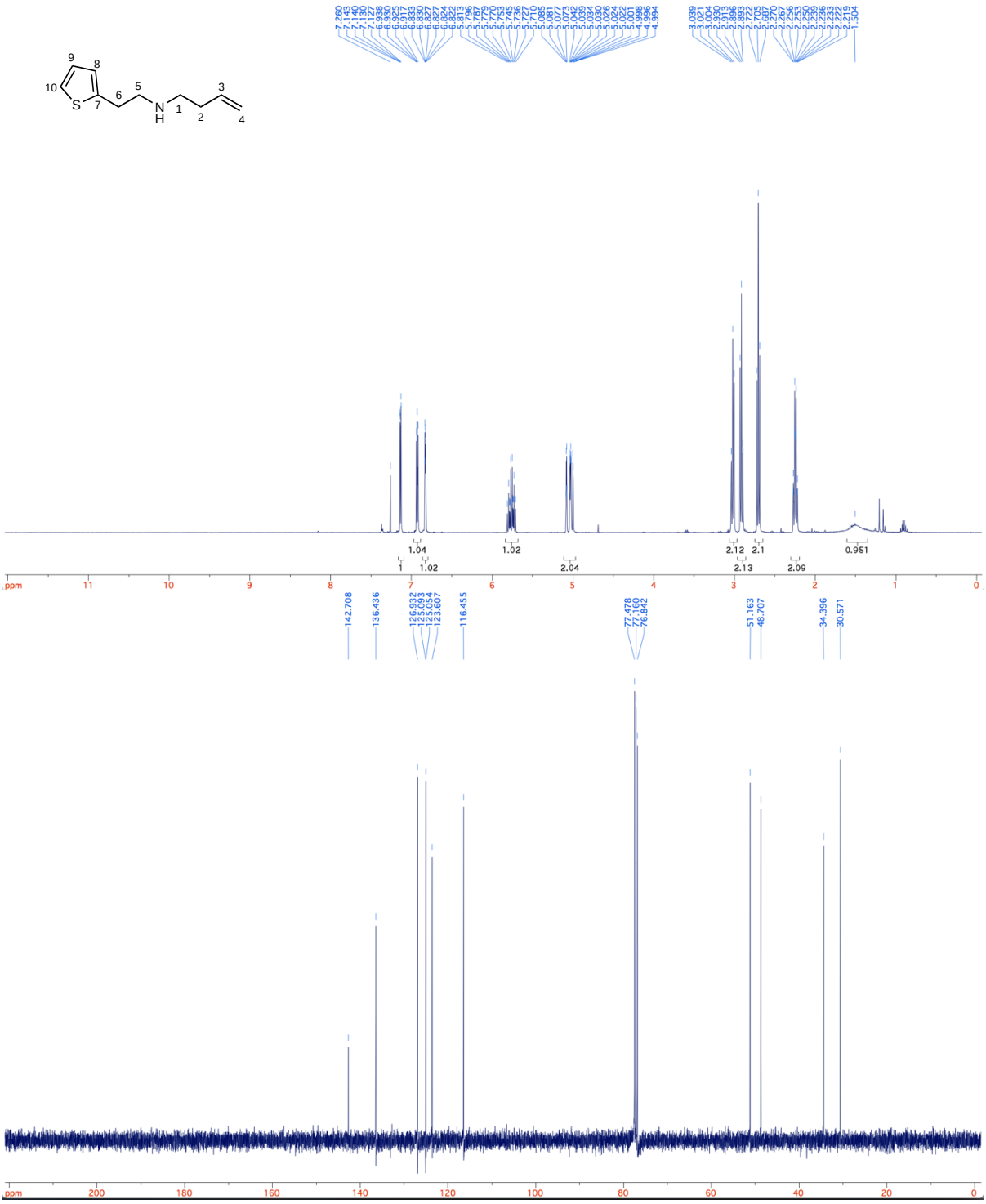
S10


7.260
1.95
1
4.09
3.92
3.97
2.03
2.02
1.59
9.26
ppm

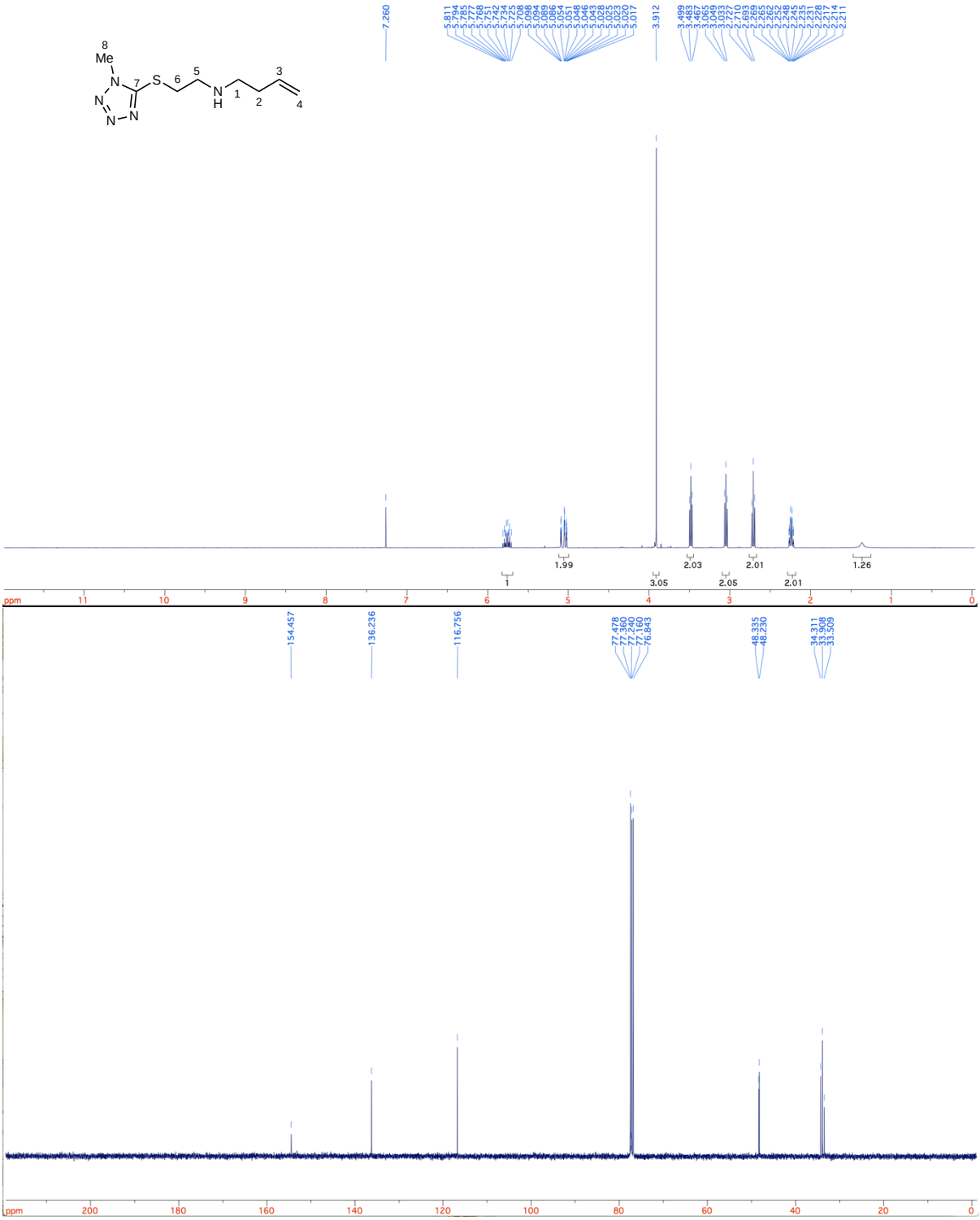

154.755
136.026
116.665
79.614
77.479
77.160
76.841
57.361
53.019
48.716
45.965
43.604
33.809
28.459
ppm

S11

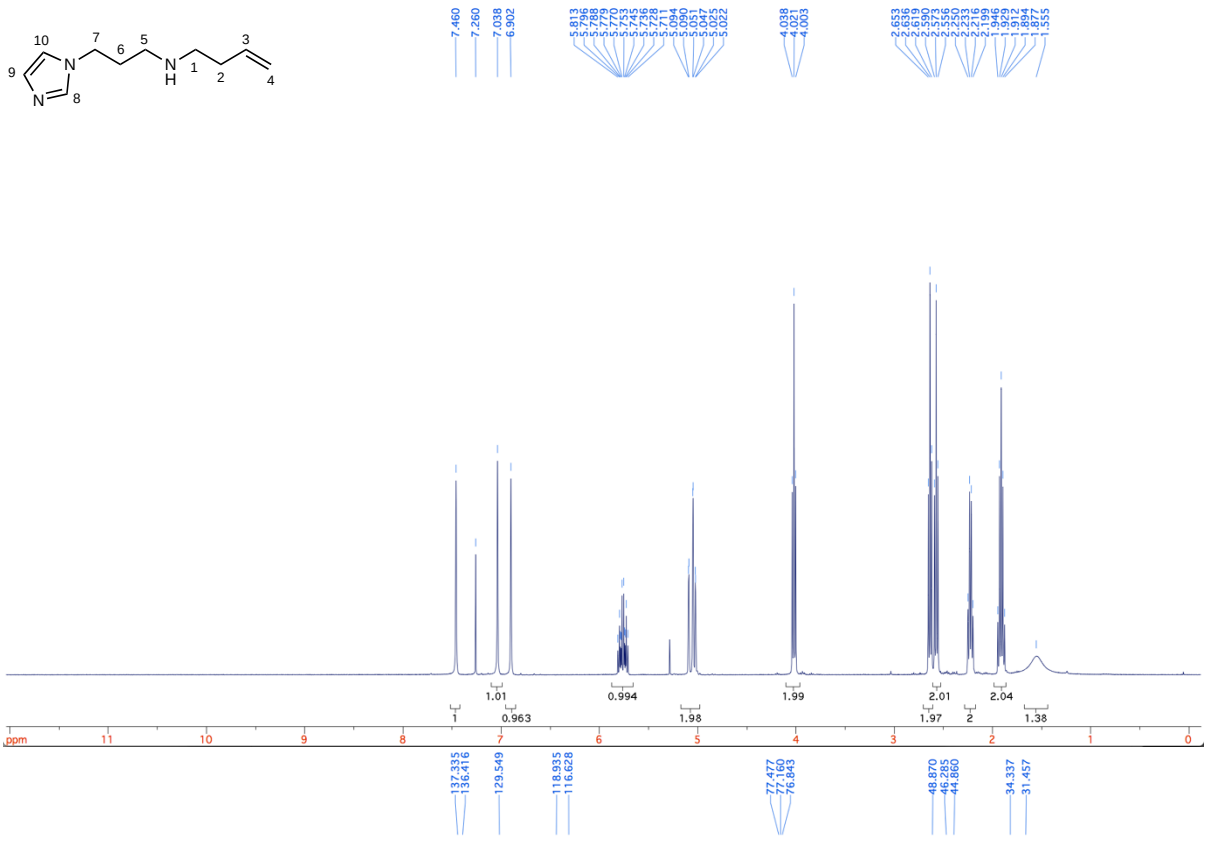
9
8
10
S
7
6
5
N
H
1
2
3
4

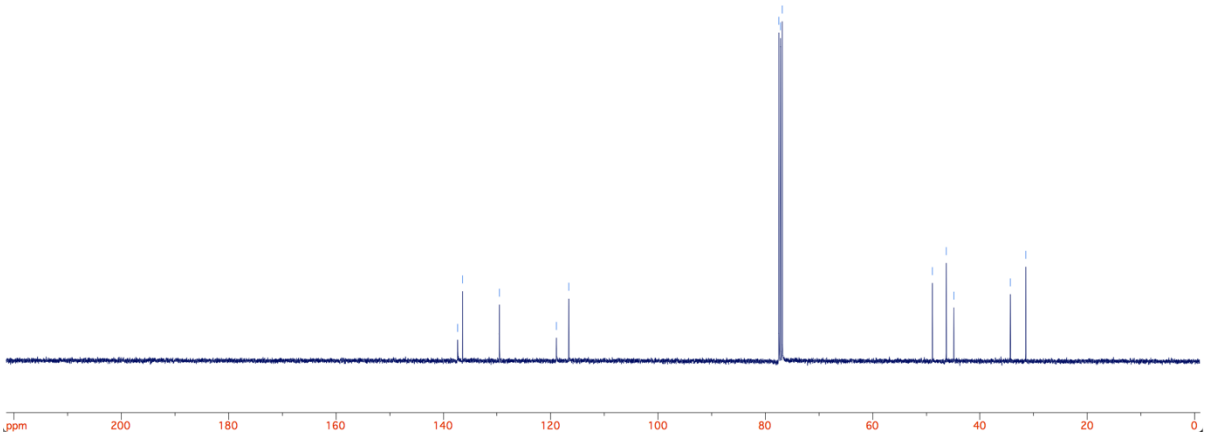

7.260
7.143
7.140
7.137
7.130
7.127
6.958
6.930
6.917
6.915
6.833
6.830
6.827
6.824
6.822
6.813
6.796
5.787
5.779
5.770
5.753
5.745
5.736
5.727
5.710
5.085
5.081
5.077
5.073
5.042
5.039
5.034
5.030
5.026
5.024
5.022
5.001
4.998
4.996
4.994
3.039
3.021
3.004
2.931
2.913
2.896
2.893
2.872
2.705
2.687
2.270
2.267
2.256
2.253
2.250
2.239
2.236
2.233
2.227
2.219
1.504
1.04
1.02
2.04
2.12
2.1
0.951
1
1.02
2.13
2.09
ppm
11
10
9
8
7
6
5
4
3
2
1
0
142.708
136.436
126.932
125.093
125.064
123.607
116.455
77.478
77.160
76.842
51.163
48.707
34.396
30.571
ppm
200
180
160
140
120
100
80
60
40
20
0

S12

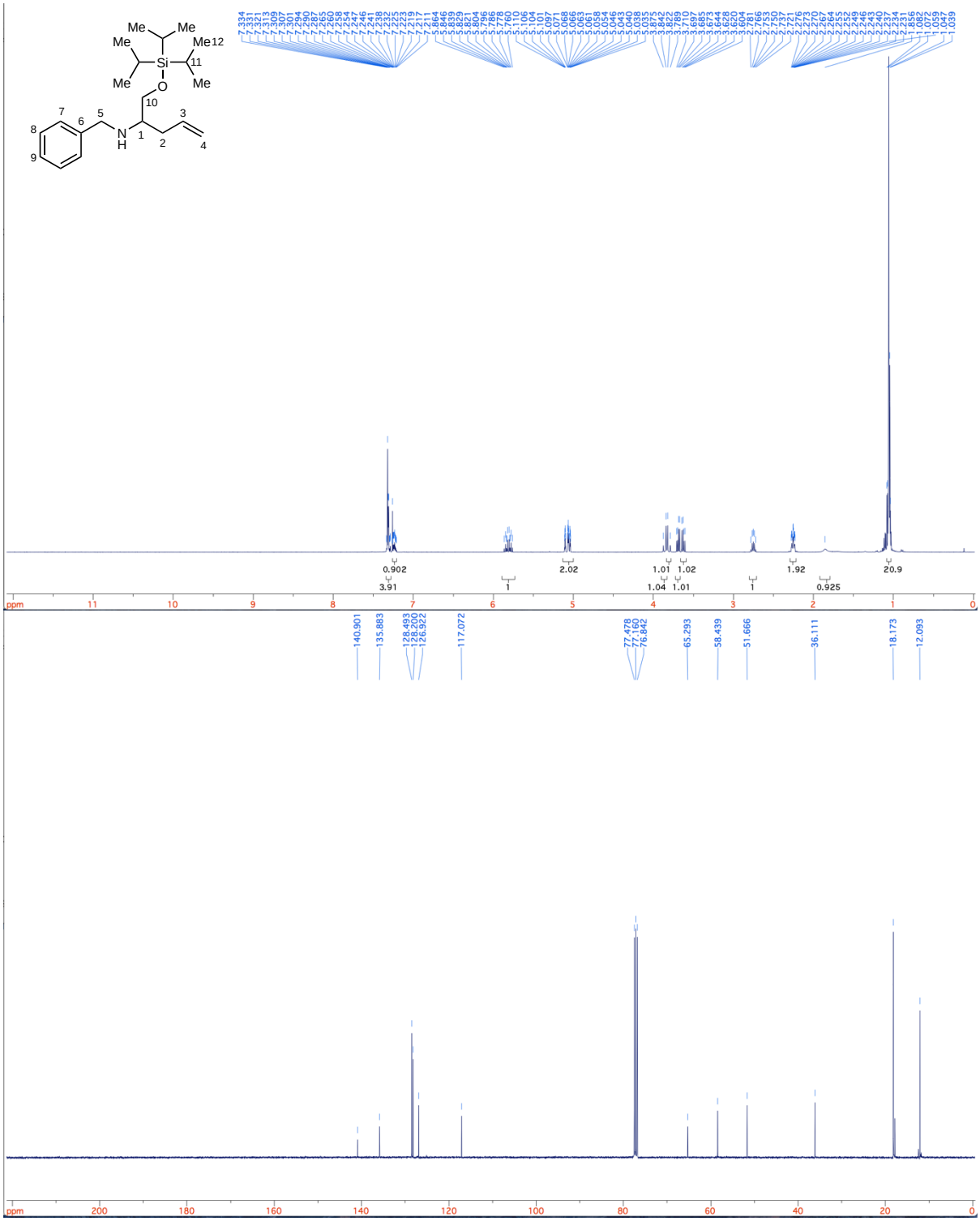

8
Me
N
7
S
6
5
N
H
1
2
3
4
N
N
N
7.260
5.811
5.794
5.785
5.777
5.768
5.751
5.742
5.724
5.725
5.708
5.698
5.089
5.066
5.064
5.051
5.048
5.046
5.043
5.028
5.025
5.023
5.020
5.017
3.912
3.499
3.493
3.467
3.065
3.049
3.043
2.727
2.710
2.693
2.689
2.265
2.262
2.252
2.248
2.245
2.235
2.231
2.228
2.217
2.214
2.211
1.99
2.03
2.01
1.26
1
3.05
2.05
2.01
ppm
11
10
9
8
7
6
5
4
3
2
1
0
154.457
136.236
116.756
77.478
77.360
77.240
77.160
76.843
48.335
48.230
34.311
33.908
33.509
ppm
200
180
160
140
120
100
80
60
40
20
0

S13

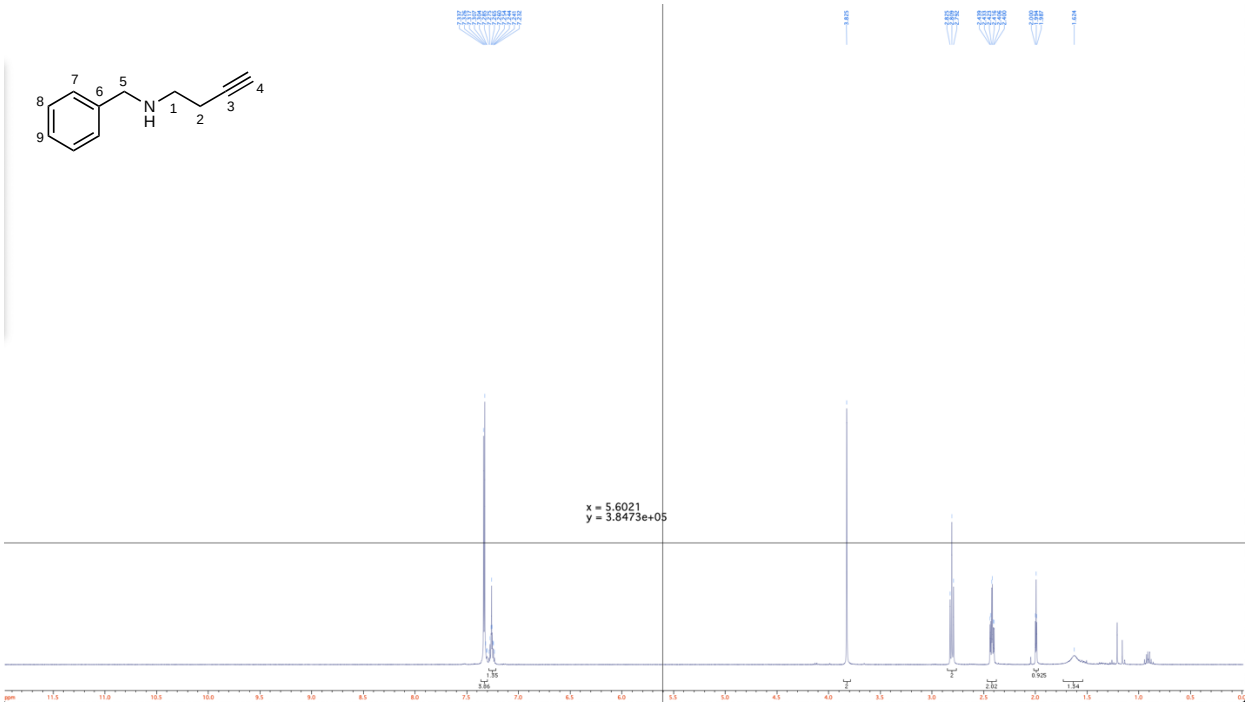

7.460
7.260
7.038
6.902
5.813
5.796
5.788
5.779
5.770
5.753
5.745
5.736
5.728
5.721
5.711
5.094
5.090
5.051
5.047
5.025
5.022
4.038
4.021
4.003
2.653
2.636
2.619
2.590
2.573
2.556
2.539
2.233
2.216
2.199
1.946
1.929
1.912
1.894
1.877
1.555
1.01
0.994
1.99
2.01
2.04
1
0.963
1.98
1.97
2
1.38
ppm
137.335
136.416
129.549
118.935
116.628
77.477
77.160
76.843
48.870
47.255
44.860
34.337
31.457


ppm

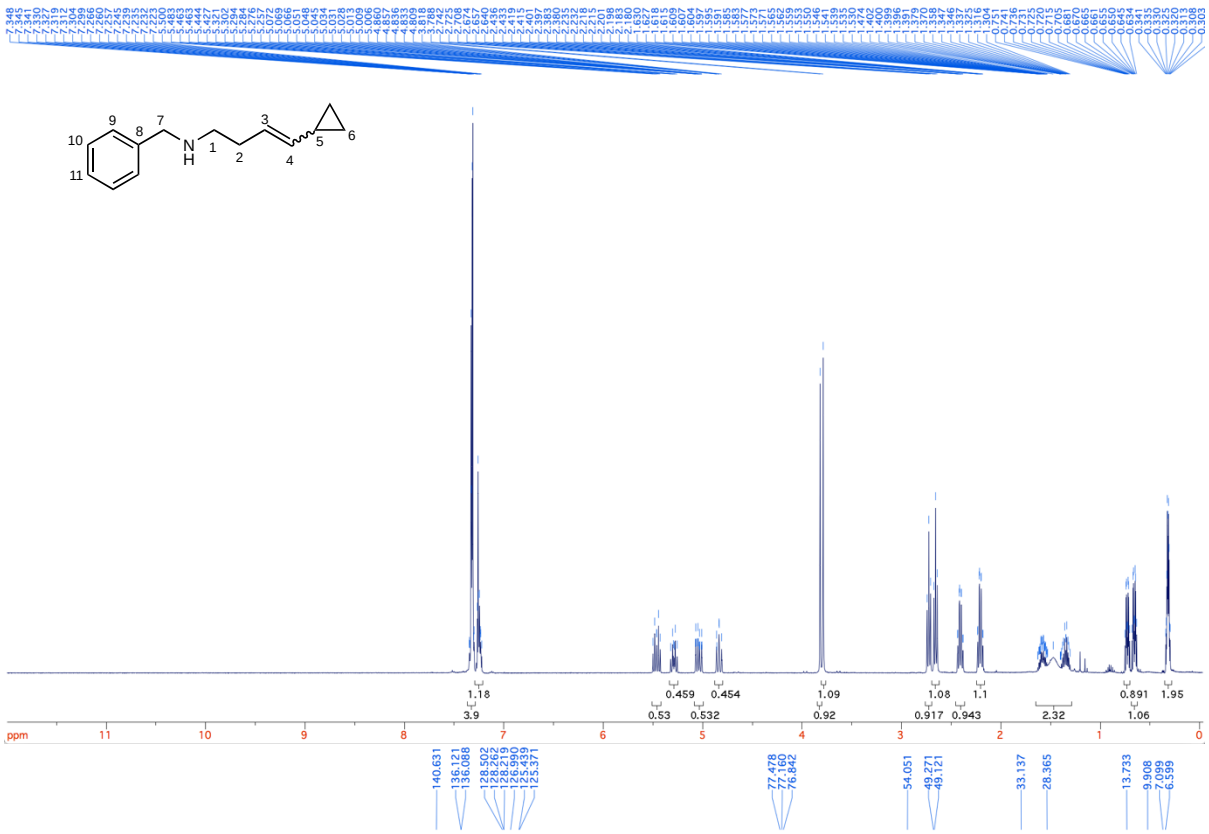
S14


Me
Me
Me
Me12
Si
11
Me
O
Me
10
7
6
5
3
8
N
H
1
2
4
9
0.902
3.91
1
2.02
1.01
1.02
1.04
1.01
1
1.92
0.925
20.9
ppm
140.901
135.883
128.493
128.200
126.922
117.072
77.478
77.160
76.842
65.293
58.439
51.666
36.111
18.173
12.093
ppm

S15



131a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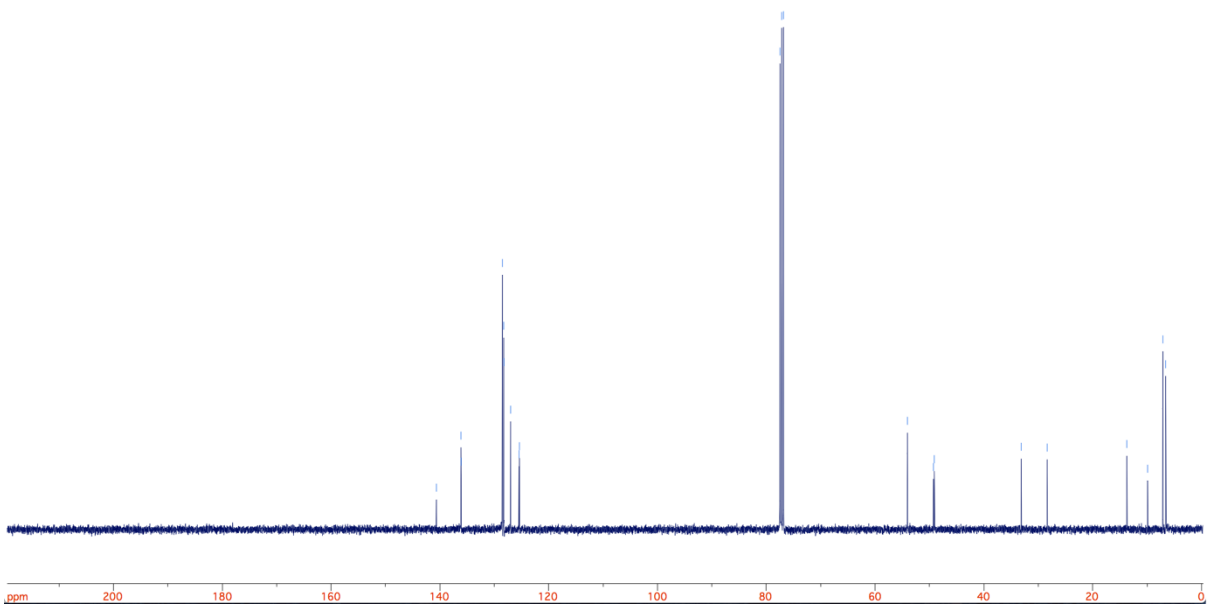
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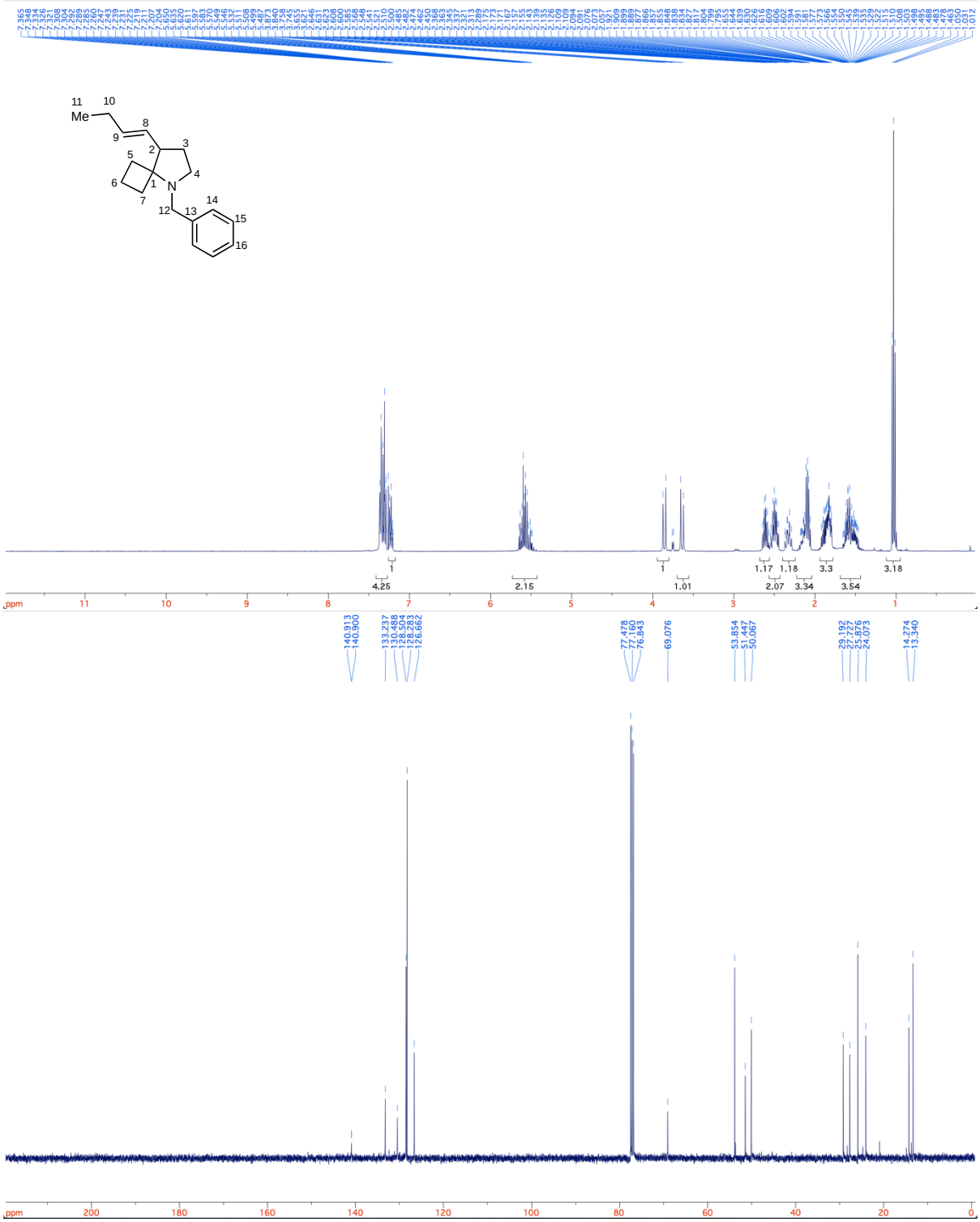
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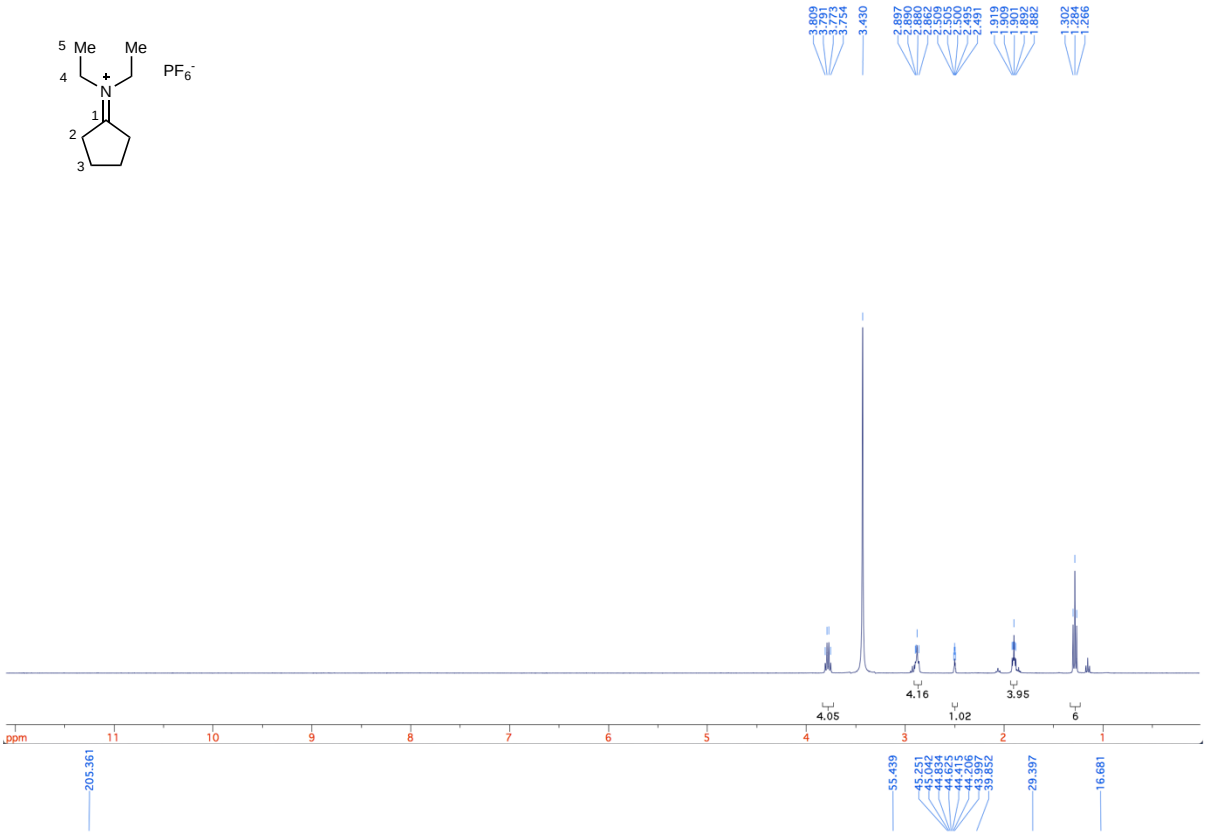
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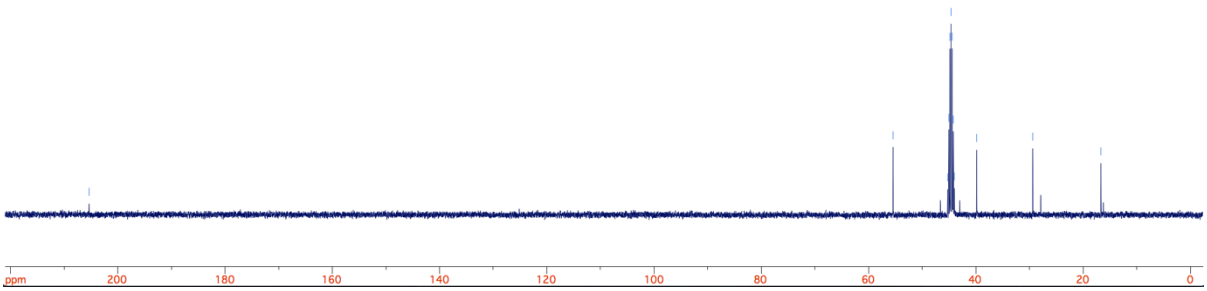
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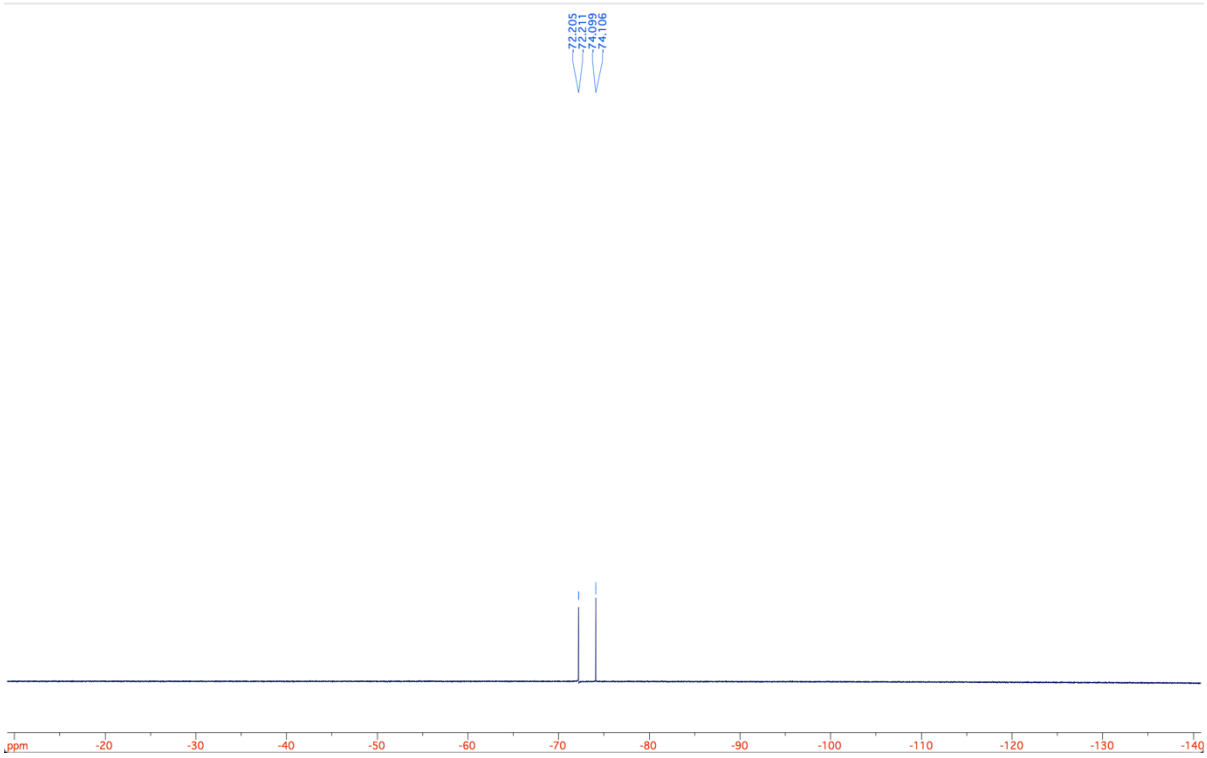
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10 Appendix III – Published work

Article

A general carbonyl alkylative amination for tertiary amine synthesis

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The ubiquity of tertiary alkylamines in pharmaceutical and agrochemical agents, natural products and small-molecule biological probes[1,2] has stimulated efforts towards their streamlined synthesis[3–9]. Arguably the most robust method for the synthesis of tertiary alkylamines is carbonyl reductive amination[3], which comprises two elementary steps: the condensation of a secondary alkylamine with an aliphatic aldehyde to form an all-alkyl-iminium ion, which is subsequently reduced by a hydride reagent. Direct strategies have been sought for a 'higher order' variant of this reaction via the coupling of an alkyl fragment with an alkyl-iminium ion that is generated in situ[10–14]. However, despite extensive efforts, the successful realization of a 'carbonyl alkylative amination' has not yet been achieved. Here we present a practical and general synthesis of tertiary alkylamines through the addition of alkyl radicals to all-alkyl-iminium ions. The process is facilitated by visible light and a silane reducing agent, which trigger a distinct radical initiation step to establish a chain process. This operationally straightforward, metal-free and modular transformation forms tertiary amines, without structural constraint, via the coupling of aldehydes and secondary amines with alkyl halides. The structural and functional diversity of these readily available precursors provides a versatile and flexible strategy for the streamlined synthesis of complex tertiary amines.

Carbonyl reductive amination is an effective method for the preparation of linear tertiary alkylamines; however, the synthesis of branched variants is more problematic[3]. The condensation of a secondary alkylamine with a di-alkylketone is often slow and may require the use of activating reagents; di-alkylketones are also not as readily available as aldehydes and may require multi-step syntheses. A method by which an alkyl group could be directly added to an aldehyde-derived alkyl-iminium ion would circumvent these problems and would increase complexity by leveraging three, rather than two, programmable feedstocks into a tertiary alkylamine synthesis. Unfortunately, the most logical approach to this multi-component strategy—the direct addition of common organometallic nucleophiles to alkyl-iminium ions—is seldom successful in delivering the tertiary alkylamine product[11–14]. Organometallic reagents—such as Grignard and alkyl-lithium reagents—are rarely compatible with in-situ iminium ion formation from alkyl aldehydes and secondary alkylamines, necessitating the pre-formation and isolation of an unstable iminium ion[12,15]. Additionally, the high basicity of these organometallic reagents results in competitive deprotonation of the C–H bond adjacent to the carbon–nitrogen double bond of the iminium ion, substantially restricting the scope of the process[16]. Less reactive zinc- or cerium-based organometallic compounds also exhibit limited scope and are restricted to activated alkyl fragments[12,13,15,17,18]. The Petasis reaction offers broader scope in the amine component, but has specific substrate requirements for the carbonyl and organoboron-derived components[19]. More efficient reactivity has been demonstrated with C(*sp*)-nucleophiles[20,21], C(sp^2)-nucleophiles[19,22] and allyl-nucleophiles[19,23], or with activating auxiliary-derived imines[4]; however, the successful deployment of a suitably reactive and generally available source of unactivated alkyl nucleophile for addition to an alkyl-iminium ion continues to prove challenging. Considering the limitations of the organometallic methods, strategies based on the addition of neutral alkyl-radical species to imine-derivatives have also been investigated[10,24–26]. However, the low electrophilicity of the carbon–nitrogen double bond means that the use of an activating group either on the nitrogen atom (R^1) or in the carbonyl component (R^2) is essential to render the imine-derivative sufficiently reactive towards alkyl-radicals, thereby limiting the scope and practical application of these reactions with respect to the downstream synthesis of tertiary amine targets[10,24–26] (Fig. 1b).

In our efforts to develop a direct carbonyl alkylative amination (CAA) method, we proposed that the addition of a neutral carbon-centred radical to an in-situ-generated, positively charged, alkyl-iminium ion would obviate the requirement for auxiliary-activated imines and provide a single-step synthesis of tertiary alkylamines. To the best of our knowledge, the elementary step comprising the direct intermolecular addition of an alkyl-radical to an alkyl-iminium ion has not been reported, with the exception of one example from 1991, in which an organo-mercury salt was irradiated with ultraviolet (UV) light to generate an alkyl-radical that was added to a formaldehyde-derived iminium ion[27]. Addition of a neutral nucleophilic alkyl-radical to an alkyl-iminium ion would afford an aminium radical cation, a species that could then be intercepted through hydrogen atom transfer to form the protonated tertiary alkylamine (Fig. 1c). A radical-based CAA requires the orchestration of a number of simultaneously occurring events to

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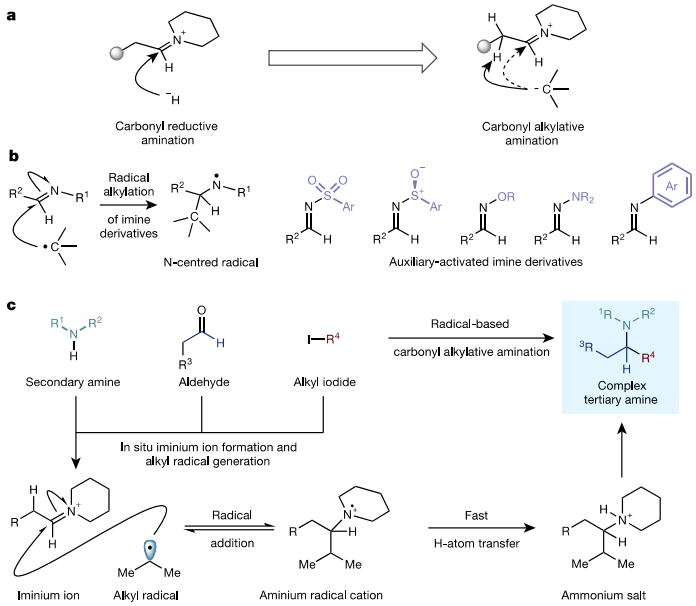

Fig. 1 | Evolution of a strategy for carbonyl alkylative amination. a, Addition of alkyl groups to alkyl-iminium ions remains a challenging transformation. **b**, Radical alkylation of auxiliary-activated imine derivatives. **c**, Carbonyl alkylative amination for the synthesis of complex tertiary alkylamines: the addition of alkyl radicals to alkyl-iminium ions.

form reactive intermediates, each of which is capable of following competitive and deleterious reaction pathways. For example, it is necessary to maintain a high concentration of the reactive alkyl-iminium ion in order to effectively engage the incipient alkyl-radical. Furthermore, the reagent effecting the hydrogen atom transfer must be capable of rapidly intercepting the transient aminium radical cation but must not reduce the iminium ion. Here we report the realization of our hypothesis through the development of modular and efficient CAA, a method that combines three abundant feedstocks—secondary amine, aldehyde and alkyl-halide—in a single step. A key part of this strategy is the use of visible light to facilitate a radical initiation step under mild conditions, leading to a practical and general synthesis of complex tertiary alkylamines.

Our initial investigations focused on a representative reaction between *N*-methylbenzylamine (**1a**), hydrocinnamaldehyde (**2a**) and 2-iodopropane (**3a**) (Fig. 2a). Attempts to achieve CAA using classical protocols for radical generation failed to produce an efficient reaction[28]. For example, the use of tributyltin hydride (Bu_3Sn–H) and azobisisobutyronitrile (AIBN) produced trace amounts of alkylamine **4a** (entry 1); this could be modestly improved by using tris(trimethylsilyl) silane ($(Me_3Si)_3Si$–H) in place of the tin reagent (entry 2)[29]. We evaluated the use of different additives in order to promote the high concentrations of alkyl-iminium required to effectively intercept the alkyl-radical. High conversion was achieved in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), as determined by ^{1}H nuclear magnetic resonance (NMR) spectroscopy (Supplementary Information 1). For example, a thermal reaction combining $(Me_3Si)_3Si$–H, AIBN and TBSOTf produced the desired alkylamine **4a**, but as a 3:1 mixture with the corresponding reductive amination product **4a′** (entry 3; **4a′** not shown). Notably, a reaction that combined TBSOTf with Bu_3Sn–H and AIBN under thermal conditions resulted exclusively in reductive amination to **4a′** (entry 4). Further exploration of the target transformation (Supplementary Information 1) led us to identify a set of unique and simpler reaction conditions that exploited the effect of visible-light activation; after parameter optimization, this approach produced high yields of the desired alkylamine **4a** (92% assay yield and 80% isolated yield) with only trace amounts of reductive amination (entry 5). When TBSOTf was omitted, **4a** was still obtained in 82% assay yield, providing a set of conditions that could be used when acid-sensitive functional groups were present. An important aspect of these mild reaction conditions is the distinct nature of the radical initiation step. Although there are a number of possible explanations for this phenomenon, homolysis of the C–I bond seems unlikely given that a control reaction using a 455-nm long-pass filter—which removes the minor UV and near-UV components of the blue LED lamp that are required for the homolysis[30,31]—still generated **4a** in 86% yield (entry 7). We then systematically studied the light-absorbing properties of each component and of likely intermediates involved in the CAA reaction—secondary amine, alkyl-aldehyde, alkyl-iodide, enamine, iminium and $(Me_3Si)_3Si$–H—as well as their combinations, in order to investigate the possibility of photosensitization or an electron donor–acceptor complex that could be involved in radical generation[32]. Although neither any component alone nor the combination of any two components showed absorption above or close to 455 nm, the UV–visible absorption spectrum of a ternary mixture comprising enamine (formed by condensation of **1a** and **2a**), 2-iodopropane (**3a**) and $(Me_3Si)_3Si$–H revealed a new, red-shifted band (400–500 nm). Although at present we do not have sufficient evidence to invoke a specific interaction, this observation potentially supports a multi-component interaction, which leads to radical initiation upon excitation with visible light (Supplementary Information 1). In any case, this radical initiation process offers distinct advantages over other light-mediated processes: whereas previous reports have been restricted to the formation of carbon–heteroatom bonds involving the initiating reagent[31,33]; in this process the $(Me_3Si)_3Si$–H is not

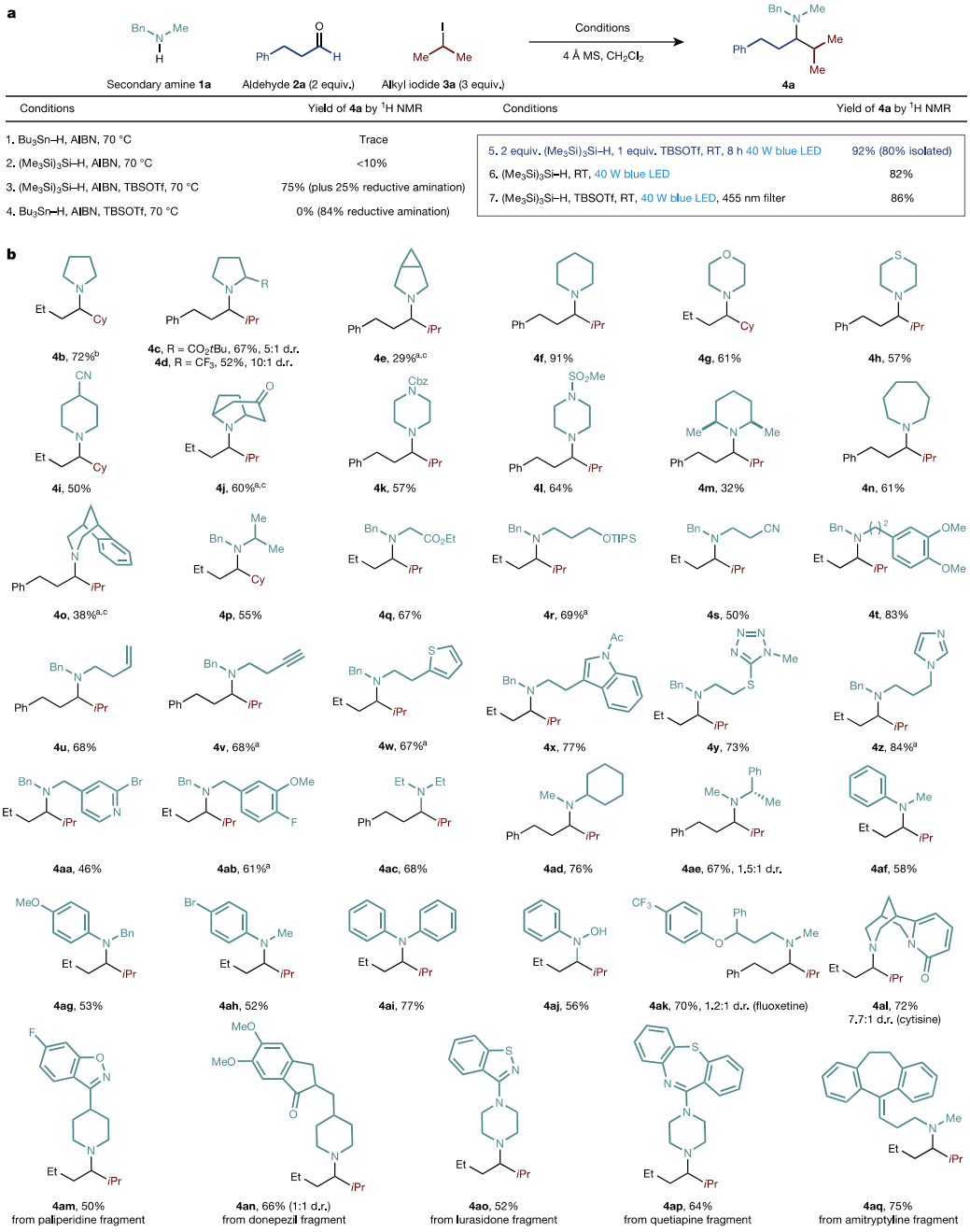

Fig. 2 | Scope of the amine component in carbonyl alkylative amination. **a**, Optimal reaction conditions. MS, molecular sieves. **b**, Scope of the amine component. [a]No TBSOTf used. [b]TMSOTf (trimethylsilyl trifluoromethanesulfonate) used instead of TBSOTf. [c]Amine·HCl salt used. Cbz, benzyloxycarbonyl; Cy, cyclohexyl; TIPS, triisopropylsilyl; d.r., diastereomeric ratio.

Article

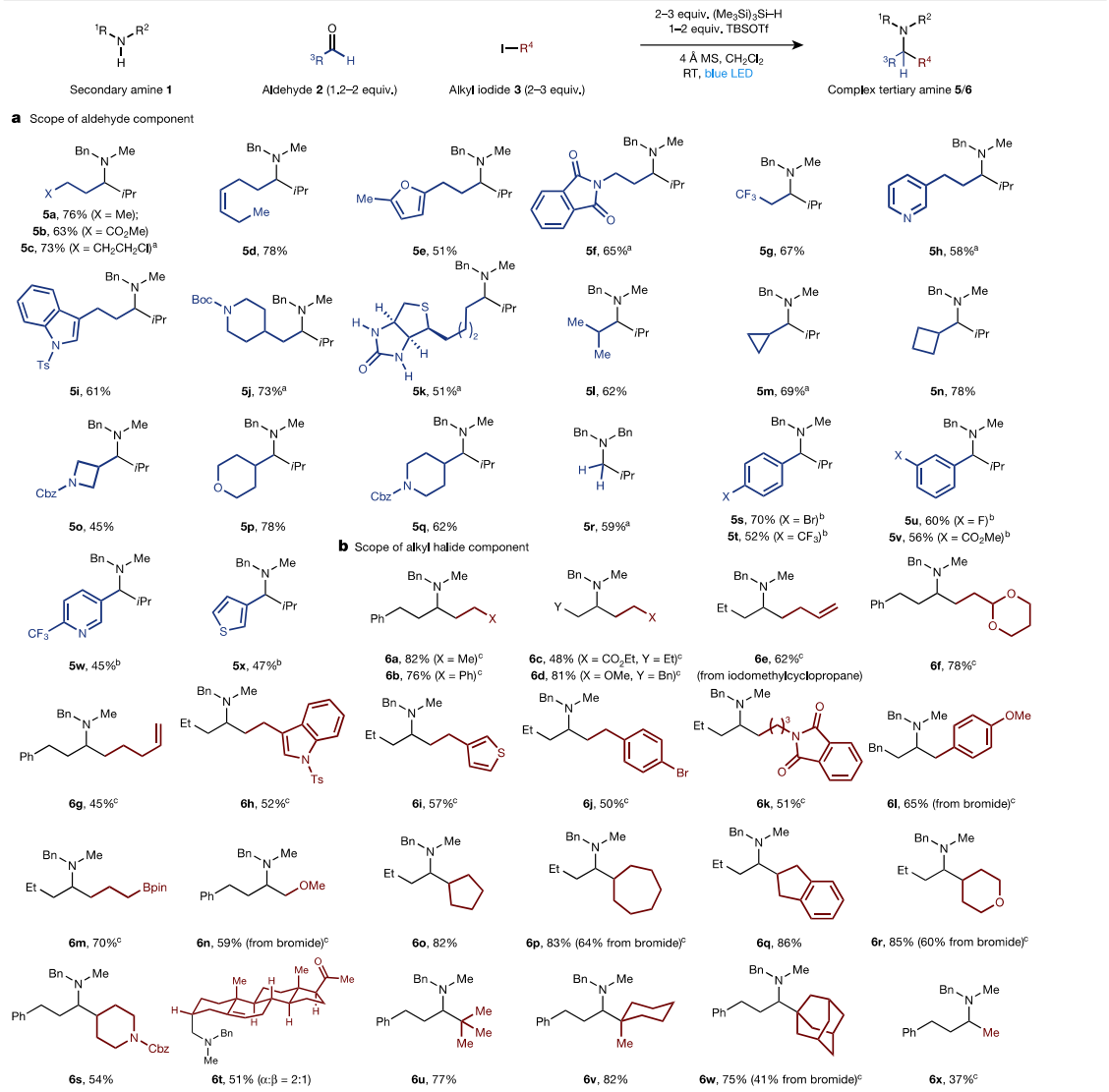

Fig. 3 | Scope of the carbonyl alkylative amination reaction. a, Scope of the aldehyde component. **b**, Scope of the alkyl halide component. [a]No TBSOTf used. [b]TMSOTf used instead of TBSOTf. [c]5–10 mol% 2-methyl-2-iodopropionate used as an initiator.

incorporated in the newly formed bond, thus enabling the generation of a C(sp^3)–C(sp^3) bond. Furthermore, the benign nature of the new radical generation step, in the absence of classical chemical initiators, could aid the development of straightforward, metal-free radical C(sp^3)–C(sp^3) bond-forming reactions from alkyl-halides.

Having established a viable protocol, we began an extensive investigation of the scope of CAA by first testing its capacity to produce α-branched cyclic tertiary alkylamines. A wide range of functionalized saturated cyclic and heterocyclic secondary alkylamines could be successfully used in this radical-based process (Fig. 2b), producing the desired alkylamines (**4b**–**4o**). Notably, auxiliary-activated radical-addition methods cannot readily access this class of tertiary alkylamines, which can be produced in a single step using the new protocol. We found that *N*,*N*-dialkylamines with a range of both linear and branched functionalized alkyl substituents—including aromatic heterocycles—gave the tertiary alkylamines **4a**, **4p**–**4ae** in good yields.

For certain amines with electron-withdrawing groups close to the nitrogen atom, reductive amination was observed as a competing side reaction (10% with **4s**). *N*-alkyl anilines and even poorly nucleophilic diarylamines could be used effectively (**4af**–**4ai**), which expands the

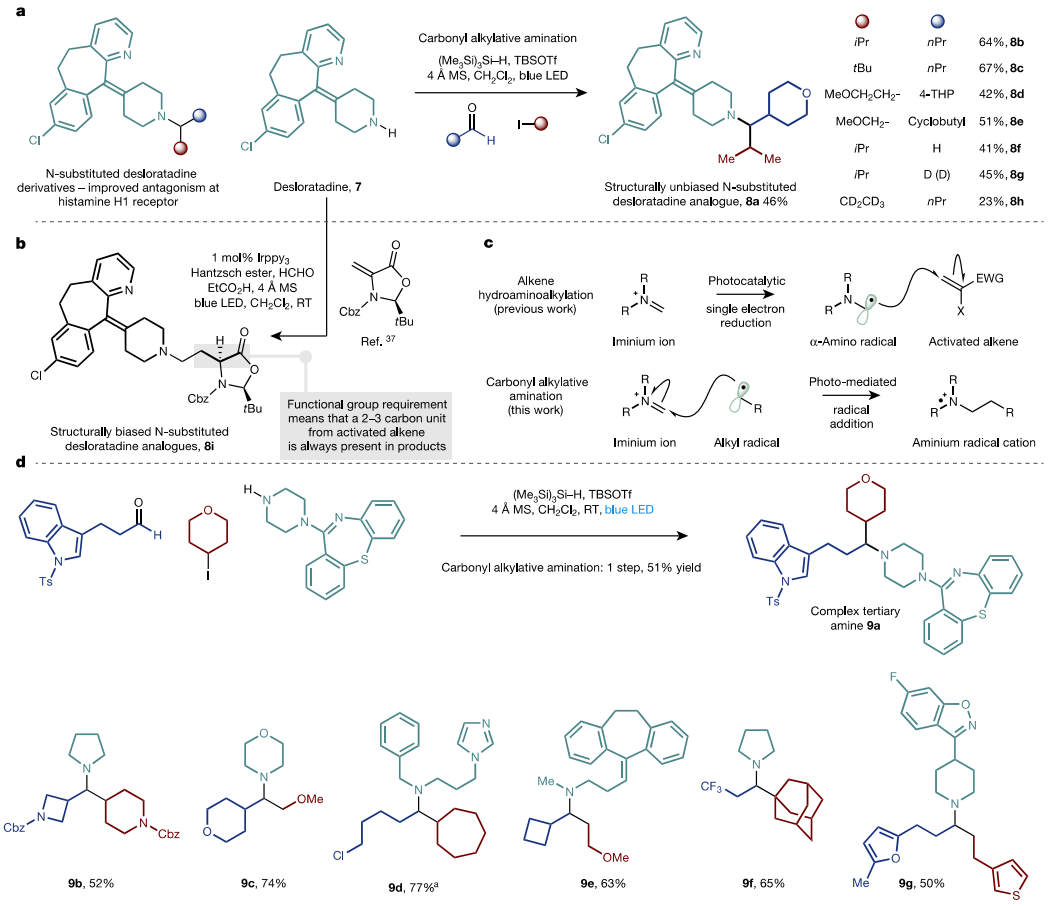

Fig. 4 | One-step synthesis of complex tertiary alkylamines via carbonyl alkylative amination and its comparison with related methods. a, Rapid and streamlined synthesis of desloratadine analogues by CAA. **b**, An example of amine synthesis using photocatalytic alkene hydroaminoalkylation, highlighting the 'biased' nature of the products resulting from the activated alkene acceptor. EWG, electron withdrawing group. **c**, The distinct mechanistic pathways of alkene hydroaminoalkylation and CAA. **d**, Structurally diverse tertiary alkylamines formed by CAA in one step from readily available building blocks. [a]No TBSOTf used.

potential scope of the CAA process as these functionalities are ubiquitous in pharmaceutically relevant molecules. A reaction using *N*-phenyl hydroxylamine produced the expected product (**4aj**) via addition to the corresponding nitrone intermediate. To demonstrate the compatibility of this process with features that are typically encountered in pharmaceutical agents, we showed that a range of drug fragments could tolerate the reaction conditions, resulting in the desired complex tertiary amine products in synthetically useful yields (**4ak**–**4aq**).

Using a selection of functionalized linear aldehydes, we were able to prepare the corresponding tertiary alkylamines (Fig. 3a, **5a**–**5k**). Branched aldehydes—including those with saturated cyclic and heterocyclic rings—also performed well, forming the hindered tertiary alkylamines **5l**–**5q**. Beyond aliphatic aldehydes, we found that formaldehyde (to **5r**), substituted benzaldehydes (to **5s**–**5v**) and heteroaryl aldehydes (**5w**–**5x**) function well in the reaction, and their successful conversion to amine products considerably expands the scope of CAA.

In the case of primary alkyl iodides, the reaction was aided by the addition of 5–10 mol% of the radical chain initiator ethyl 2-iodo-2-methylpropionate[34], which can generate alkyl radicals more easily than can primary alkyl iodides. Both simple and functionalized primary alkyl iodides proved to be good coupling partners under these conditions, with linear alkane fragments added to alkyl-iminium ions to form tertiary alkylamines **6a**–**6n**. Although the reaction could accommodate various functional groups in the alkyl-halide, slightly lower yields were observed for radicals containing proximal electron withdrawing groups (**6c**). This is likely to originate from a competitive hydrogen atom transfer between the silane and the alkyl-radical, as well as the slower rate of addition of a less nucleophilic alkyl-radical to the iminium ion. Benzyl bromides and methoxymethyl bromide, the iodides of which are unstable, were found to be suitable alkylating agents and gave the amine products in synthetically useful yields (**6l**, **6n**). As expected, secondary alkyl-halides were competent substrates

and formed amines **6o**–**6t** in good yields. Tertiary alkyl-iodides were also excellent coupling partners: the hindered alkylamine products **6u**–**6w**, which would be challenging to prepare via reductive amination, were obtained in high yield. A selection of unactivated alkyl-bromides reacted under the modified conditions—with the radical chain initiator[34]—to give reasonable yields of the tertiary alkylamines **6p**, **6r** and **6w**; this provides an alternative protocol if an alkyl-iodide is not available. We were pleased to find that iodomethane, acting as a source of methyl-radical, could be added to an iminium ion to provide access to an important class of branched tertiary alkylamines (**6x**). In addition to the 90 examples of successful CAA documented in Figs. 2 and 3, we have detailed an extended assessment of the reaction scope (Supplementary Fig. 9, Supplementary Information 1) that includes substrates that give moderate—but still synthetically useable—yields, as well as examples for which the process is low yielding or unsuccessful.

As a further demonstration of this methodology, we showed that the pharmaceutical agent desloratadine, which contains a secondary amine, can be used as the amine component of this CAA to directly append two interchangeable molecular fragments within the α-branched tertiary alkylamine product (Fig. 4a). Tertiary amine derivatives of desloratadine have recently attracted attention owing to their improved pharmacokinetic properties, and convey a longer duration of antagonism at the histamine H1 receptor[35]. Using the standard coupling conditions, we showed that a collection of desloratadine-derived α-branched tertiary amine products can be readily prepared in a modular fashion (**8a**–**g**). As a demonstration of the efficacy of these reactions, we prepared an α-d_2-*N*-alkyl derivative of desloratadine (>95% deuterium incorporation, **8g**) in a single step from commercial d_2-paraformaldehyde and 2-iodopropane. Furthermore, a similar reaction using d_5-iodoethane and a linear aldehyde provided direct access to a different class of labelled tertiary amine (**8h**)[36].

Direct CAA on desloratadine is distinct from our previous work[37] on photoredox-mediated alkylamine synthesis, which was based on alkene hydroaminoalkylation via the generation and reaction of α-amino radicals (Fig. 4b, c). Although we previously showed that this secondary amine can engage activated alkenes (to **8i**), the tertiary alkylamine products prepared by that approach always contain the structural signature derived from the intrinsic requirements of a reaction that necessitates use of an activated alkene acceptor. By contrast, the present mechanistically distinct reaction enables the use of a wide range of primary, secondary and tertiary alkyl-halides, providing direct access to tertiary alkylamines that are unbiased by any functional requirements of the transformation and contain no trace of the activating groups required in the readily available building blocks.

A major advantage of this CAA strategy is its modularity; the vast array of coupling partners within each of the three abundant feedstocks required for this reaction means that structural and functional diversity can be easily programmed into the tertiary amine products (Fig. 4d). To illustrate this, we evaluated the cross-compatibility of the process by varying each reaction component in order to produce a range of complex tertiary alkylamines with diverse structural and functional properties. The robust nature of the reaction is reflected by the ease with which densely functionalized alkylamines **9a**–**9g** can be produced in a single step from readily available building blocks, highlighting the suitability of such alkylamines for early-stage drug discovery applications (Fig. 4d). The streamlined nature by which these products are prepared demonstrates the synthetic potential of this process.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-020-2213-0.

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Data availability

Materials and methods, experimental procedures, useful information, mechanistic studies, optimization studies, ^{1}H NMR spectra, ^{13}C NMR spectra and mass spectrometry data are available in the Supplementary Information. Raw data are available from the corresponding author on reasonable request.

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Additional information

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Streamlined Synthesis of C(sp^3)-Rich *N*-Heterospirocycles Enabled by Visible-Light-Mediated Photocatalysis

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Supporting Information

ABSTRACT: We report a general visible-light-mediated strategy that enables the construction of complex C(sp^3)-rich *N*-heterospirocycles from feedstock aliphatic ketones and aldehydes with a broad selection of alkene-containing secondary amines. Key to the success of this approach was the utilization of a highly reducing Ir-photocatalyst and orchestration of the intrinsic reactivities of 1,4-cyclohexadiene and Hantzsch ester. This methodology provides streamlined access to complex C(sp^3)-rich *N*-heterospirocycles displaying structural and functional features relevant to fragment-based lead identification programs.

Growing evidence suggests that an increasing number of aromatic rings in lead compounds can result in greater attrition rates among pharmaceutical candidates due to poor solubility, bioavailability, and pharmacokinetics.[1] However, libraries of lead-like structures often comprise compounds with predominantly C(sp^2)-rich scaffolds. Consequently, the assessment of structurally distinct libraries of C(sp^3)-rich small molecules displaying diverse polar functionality could help to identify new lead candidates in fragment-based screening approaches that may exhibit enhanced physical and biological properties.[2] In considering the design of novel C(sp^3)-rich small molecules for fragment-based approaches,[3] it is noticeable that conformationally restricted scaffolds show highly reproducible results in *in silico* screening programs; the well-defined spatial orientation of molecular features in a candidate compound often leads to increased binding affinities. One approach toward limiting structural flexibility within C(sp^3)-rich small molecules is through the introduction of a spirocycle.[4] In comparison to aromatic scaffolds, fine-tuning the structural and functional features in these frameworks offers an alternative means through which to probe interactions with target binding sites by varying ring size, adjusting electronic properties, and manipulating substituent effects.[5] As a result, spirocyclic motifs displaying polar functionality are emerging in pharmaceutical agents and lead compounds (Figure 1a).[4]

Despite the attractive properties offered by rigid saturated polar spirocyclic scaffolds, access to diversely functionalized variants mainly relies on multistep alkyl- and acylative methods.[5] Notable advances on these approaches include dearomatization-based strategies, using Pd, Ir, or Fe catalysts,[6a−c] which harness the intrinsic reactivity of tethered (hetero)arene building blocks for the generation of a selection of spirocyclic *N*-heterocycles with different ring sizes. Bode and co-workers produced a range of spirocyclic *N*-heterocycles using their SnAP technology;[6d,e]

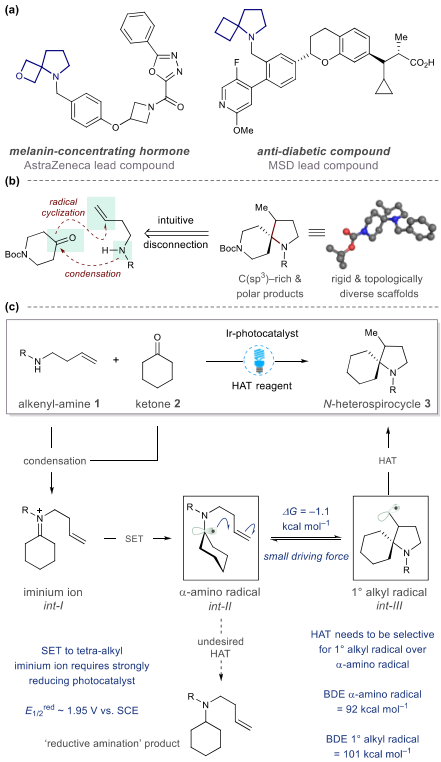

Figure 1. Evolution of the cyclization strategy. Gibbs free energy calculated by DFT methods (UPW6B95-D3BJ/def2-QZVP). Hydrogens removed for clarity.

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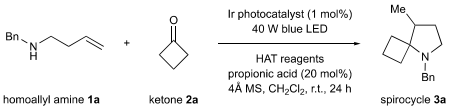
iminium ion formation between amino-stannane reagents and cyclic ketones enables a stoichiometric copper(II) cyclization to access free(NH)-secondary amino-spirocyclic products. To complement these approaches, we reasoned that a photocatalytic strategy[7] based on an intuitive retrosynthetic disconnection of tertiary amine-based *N*-heterospirocycles directly to feedstock ketones and readily available alkenyl-derived secondary amines could be realized through the intermediacy of an α-amino radical (Figure 1b).[8] The structurally distinct C(sp^3)-rich polar *N*-heterospirocycles generated by such a catalytic transformation could be of interest to synthetic and medicinal chemists.

We envisioned that visible-light-mediated photocatalytic single-electron reduction of an alkyl-iminium ion (*int-I*, Figure 1c), formed from the condensation of a saturated cyclic ketone with a secondary alkylamine, would form a cyclic-tertiary α-amino radical (*int-II*). Addition of this α-amino radical to an appended alkene on the amine component would give rise to a substituted pyrrolidine-based spirocyclic scaffold. Recent work from our group established a photocatalytic platform for the addition of nucleophilic α-amino radicals (formed from the corresponding iminium ions) to electron-deficient olefins.[9] Critically, however, a catalytic manifold for the addition of all-alkyl-substituted α-amino radicals to unactivated alkenes remains an unsolved problem, principally due to the mismatched electronics and low thermodynamic driving force for such a reaction. The lone pair on the nitrogen atom stabilizes the α-amino radical but also renders it nucleophilic. Therefore, its addition to an unactivated alkene is polarity-mismatched and produces an alkyl radical (*int-III*) with no stabilizing substituents that, in turn, can undergo the reverse reaction to re-form the α-amino radical via C−C bond β-scission. Indeed, the use of SmI_2, a strong stoichiometric reductant, was required to trap related alkyl radicals via organosamarium intermediates following addition to unactivated alkenes.[10] However, the metal waste produced in these reactions and frequent need for highly dilute conditions hinder the wider application of this type of process.[11] We, therefore, questioned whether an alkyl radical could be selectively intercepted in a milder fashion by way of a hydrogen-atom-transfer (HAT) reaction and in preference to HAT to the α-amino radical.

Herein, we detail the successful realization of these ideas through the development of a streamlined strategy for the synthesis of complex C(sp^3)-rich *N*-heterospirocycles from readily available secondary amines and ketones enabled by visible-light photocatalysis. Keys to the success of this strategy were utilizing a highly reducing Ir-photocatalyst and orchestrating the intrinsic reactivities of 1,4-cyclohexadiene (1,4-CHD) and Hantzsch ester, which facilitated controlled generation and the fate of the radical intermediates present in the reaction. Under optimized conditions, the process combines a range of feedstock aliphatic ketones and aldehydes with alkene-containing secondary amines to forge complex C(sp^3)-rich *N*-heterospirocycles displaying structural, functional, and physical features that are likely to be attractive in fragment-based lead identification programs.

We began our investigations by testing reaction conditions based on our previously established photocatalytic process.[9] Using amine **1a** and cyclobutanone (**2a**) as substrates, 1 mol% of $Ir(ppy)_3$, and 2.0 equiv of Hantzsch ester, we were encouraged by the formation of spirocycle **3a** in 30% yield and only trace amounts of the corresponding reductive amination product (Table 1, entry 1). Following extensive optimization, we found that the use of 1,4-CHD as an additive (entry 2) and a more reducing photocatalyst, $Ir(dMeppy)_3$ ($[E_{1/2}^{red}(Ir^{IV}/{}^*Ir^{III})] = -1.86$ V vs SCE in CH_2Cl_2) (entry 3), improved the yield to 97%.[12] We reasoned that the use of 1,4-CHD as a HAT-donor in high concentration would restrict the role of the Hantzsch ester to turning over the Ir(IV) species formed after single-electron reduction of the iminium ion, while the more reducing photocatalyst would provide a stronger driving force for the reduction step. A series of control experiments showed that the yield of the reaction dropped to 24% in the absence of 1,4-CHD (entry 4); to 43% without the Hantzsch ester (entry 5); and to trace amounts without photocatalyst or light or in the absence of both 1,4-CHD and Hantzsch ester (entries 6 and 7).

Table 1. Selected Optimization Data[a]



entry	catalyst	Hantzsch ester (equiv)	1,4-CHD (equiv)	yield (%)
1	$Ir(ppy)_3$	2.0	–	30
2	$Ir(ppy)_3$	2.0	7.5	45
3	$Ir(dMeppy)_3$	2.0	7.5	97
4	$Ir(dMeppy)_3$	2.0	–	24
5	$Ir(dMeppy)_3$	–	7.5	43
6	–	2.0	7.5	trace
7	$Ir(dMeppy)_3$	–	–	trace

[a]Reactions employed a 40 W Blue Kessil lamp, and yields were calculated by GC assay with dodecane as internal standard.

Having evaluated the reaction conditions, a range of commercially available ketones (Table 2) were reacted to afford *N*-heterospirocycles **3a−3i**. Aldehydes also reacted to afford the corresponding pyrrolidines **3j−3m**, with the *syn*-isomer of **3k** being the major diastereomer. The reaction was amenable to heterocyclic ketones, with a series of saturated *N*-heterocycles readily transformed into rigid, C(sp^3)-rich, and polar bis-*N*-heterospirocyclic scaffolds with orthogonal protecting groups on the two nitrogen atoms (**3n−3t**), facilitating further derivatization. The reaction to form azetidine-derived spirocycle **3p** could be performed on a gram scale, even with a reduced catalyst loading of 0.5 mol%, forming the product in a 63% yield; the *N*-groups in **3p** could also be selectively deprotected for further derivatization.[13] Such derivatives are frequently employed as β-turn mimetics for GPCR protein binding, where the orthogonality of the two nitrogen substituents is key to achieve the desired turn-characteristics.[14] While the $Ir(dMeppy)_3$ photocatalyst had proven optimal for reactions using electron-rich ketones (to form **3a−3e**, **3i**, **3l**), higher yields were observed for electron-deficient ketones (to form **3f−3h**, **3j**, **3k**, and **3m−3t**) using the less-reducing $[Ir(dMeppy)_2\{dtbbpy\}]PF_6$ photocatalyst.

We next assessed *N*-substituted alkenylamines **3u−3an**, where useful functional groups such as sulfonamide, *N*-Boc-piperidine, heteroaryl motifs (**3u−3ab**), and a less nucleophilic aniline (**3ac**) could be built into the spirocycle products. Substitution on the alkene was tolerated (**3ad−3ah**), introducing valuable functionalities such as the ester and *gem*-difluoro in useful yields. While no cyclized product was observed from attempts at reacting *N*-benzyl allylamine (to afford azetidine-based spirocycles), a piperidine scaffold **3ai** could be assembled via a 6-*exo* cyclization, further expanding scope of the process. Homoallylic amines containing α-substitutents were effective in the

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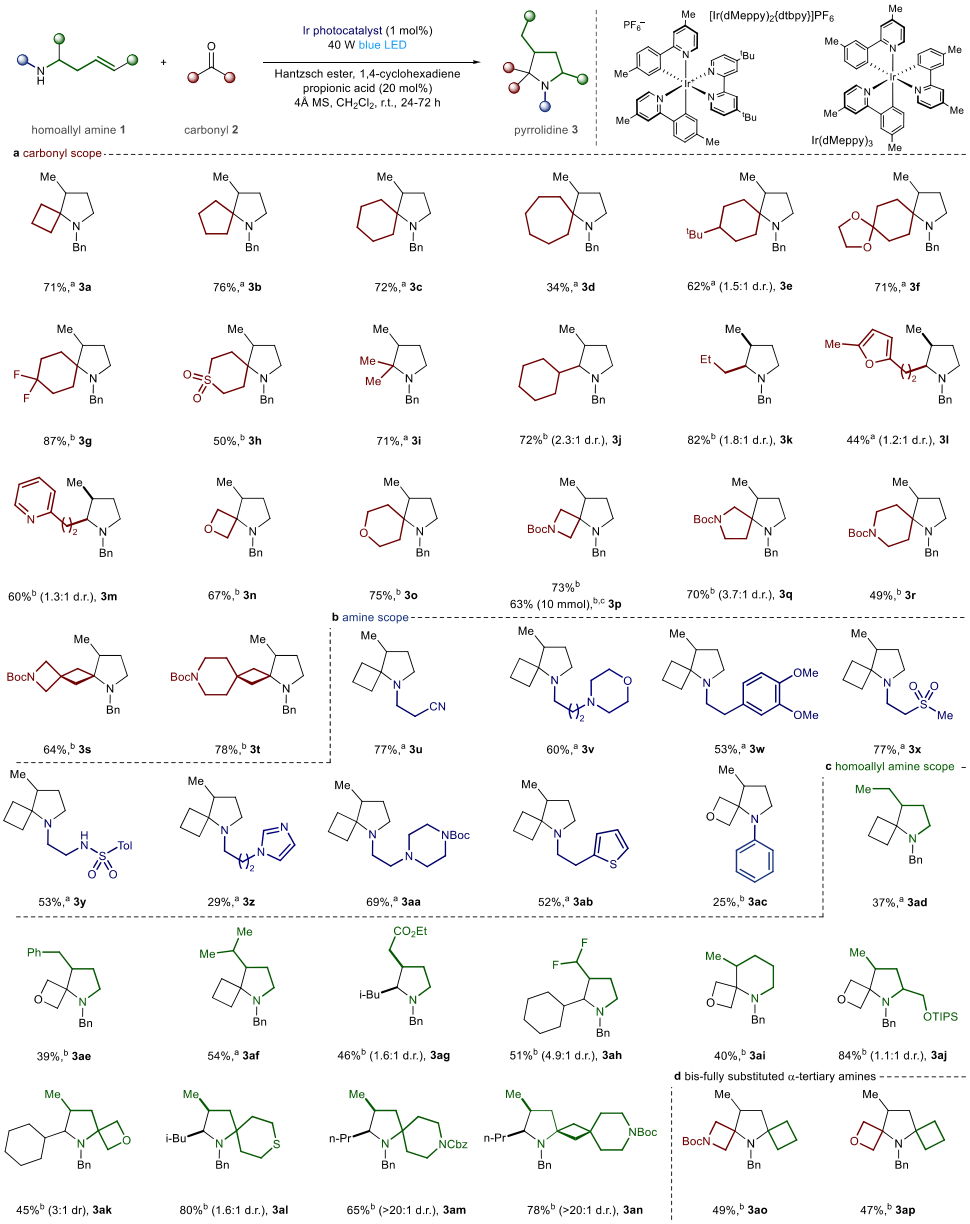
Table 2. Scope of Photocatalytic Synthesis of *N*-Heterospirocycles



[a]Reaction using Ir(dMeppy)$_3$. [b]Reaction using [Ir(dMeppy)$_2${dtbpy}]PF$_6$. [c]0.5 mol% [Ir].

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cyclization process with both aldehydes and functionalized alicyclic ketones, in some cases with surprisingly high diastereoselectivities **3aj**−**3an**. We found that the exceptionally hindered spirocycles **3ao** and **3ap** could be accessed in 49% and 47% yield respectively, affording access to a class of compounds that are challenging to synthesize using classical C−N bond-forming methods.[6e,15,16]

Next, we questioned whether we could apply the α-amino radical to a cyclization process with simple alkynes, affording *N*-heterospirocycles carrying a useful alkenyl handle for further functionalization. *N*-Benzyl-4-aminobutyne derivatives smoothly reacted with a range of cyclic ketones, furnishing the desired spirocycles **4a**−**4g** in 53−73% yield (Figure 2a). Finally,

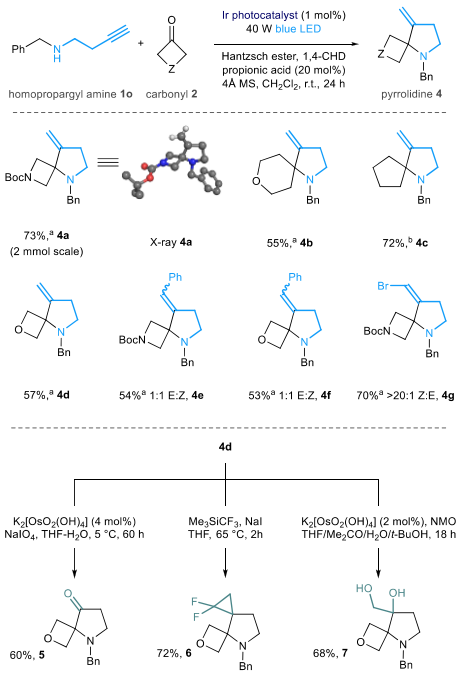

Figure 2. Cyclization on alkynes and amine derivatizations. [a]Reaction using Ir(dMeppy)$_3$. [b]Reaction using [Ir(dMeppy)$_2${dtbpy}]PF$_6$.

the alkenyl handle of **4d** could be derivatized through a difluorocyclopropanation to afford **6** in 72% yield, whose structure comprises three different-sized ring systems and two adjacent spirocyclic centers, as well as different oxidative transformations (**5** and **7**, Figure 2b).[17]

We found that the addition of TEMPO, as a radical trap, significantly inhibited the reaction (Figure 3a). A reaction with cyclopropyl-substituted alkenylamine **1r** led to the ring-opened product, supporting the existence of a cyclized radical intermediate (cf. *Int-III*). Stern−Volmer studies on a representative iminium ion (**8**) showed effective quenching of the excited state of the Ir(dMeppy)$_3$ photocatalyst in comparison to Hantzsch ester (Figure 3c). On the basis of of these studies and those outlined in our optimization (Table 1), we propose a

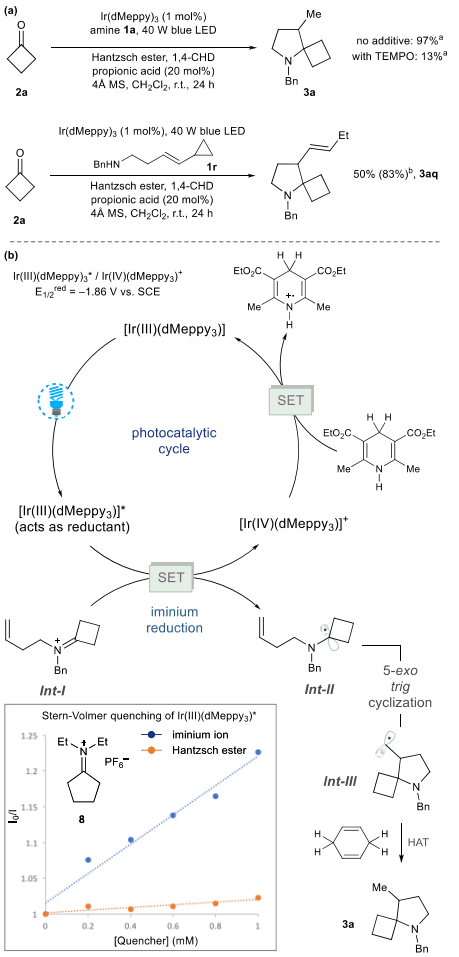

Figure 3. Mechanistic studies. [a]Yield determined by GC assay with dodecane as internal standard. [b]Yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard.

tentative mechanism for the reaction which begins with visible-light excitation of Ir(dMeppy)$_3$ to Ir(dMeppy)$_3$* (Figure 3c). Single-electron reduction of the iminium ion (*Int-I*) by Ir(dMeppy)$_3$* forms the α-amino radical (*Int-II*), which engages the pendant alkene in a 5-*exo-trig* cyclization to form an alkyl radical (*Int-III*). HAT from 1,4-CHD to the alkyl radical then forms *N*-heterospirocycle **3**. The oxidized Ir(IV)(dMeppy)$_3$ species is reduced to the active catalyst by single-electron transfer from the Hantzsch ester, closing the catalytic cycle.

In summary, we have developed a visible-light-mediated process to enable the facile synthesis of heterospirocyclic compounds from readily available starting materials. The photoredox strategy offers an intuitive retrosynthetic discon-

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nection for difficult-to-access C(sp^3)-rich *N*-heterospirocyclic scaffolds that may be of interest to practitioners of both synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b03372.

Experimental procedures and spectral data (PDF)

X-ray crystallographic data for **6** (CIF)

X-ray crystallographic data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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