PHOSPHONIUM-SALT MEDIATED ACTIVATION OF C-O BONDS: APPLICATIONS AND MECHANISTIC STUDIES

by

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ABSTRACT

The C-O single bond is found in numerous functional motifs including carboxylic acids, alcohols, and ethers. These compounds represent ideal precursors towards C-X (X = C, H, or heteroatom) bond formation due to their inherent stability and abundance in nature. As such, synthetic chemists continue to develop new technologies for the transformation of these precursors into biologically useful targets such as amides and amines. However, due to the stability of the C-O single bond, accessing such targets remains a consistent challenge. The activation of the carboxylic acids towards peptide synthesis has been facilitated through various coupling agents, including organoboron and transition metal catalysts. However, coupling agents can generate stochiometric, difficult-to-remove, toxic waste by-products. Organoboron/transition metal catalyzed condensations offer a more atom economical approach but suffer from varying degrees of optical erosion and poor sustainability. Phosphonium-based deoxyaminative technologies provide access to amines from alcohols via a phosphorus oxygen double bond formation driving force, but possesses a narrow nucleophilic nitrogen source scope, and poor atom economy. Transition metal/enzyme catalyzed “hydrogen borrowings” represent atom economical deoxyaminative alternatives. Still, their respective use of costly metals, and multiple enzymatic cascade steps severely limit the sustainability and scope of such protocols.

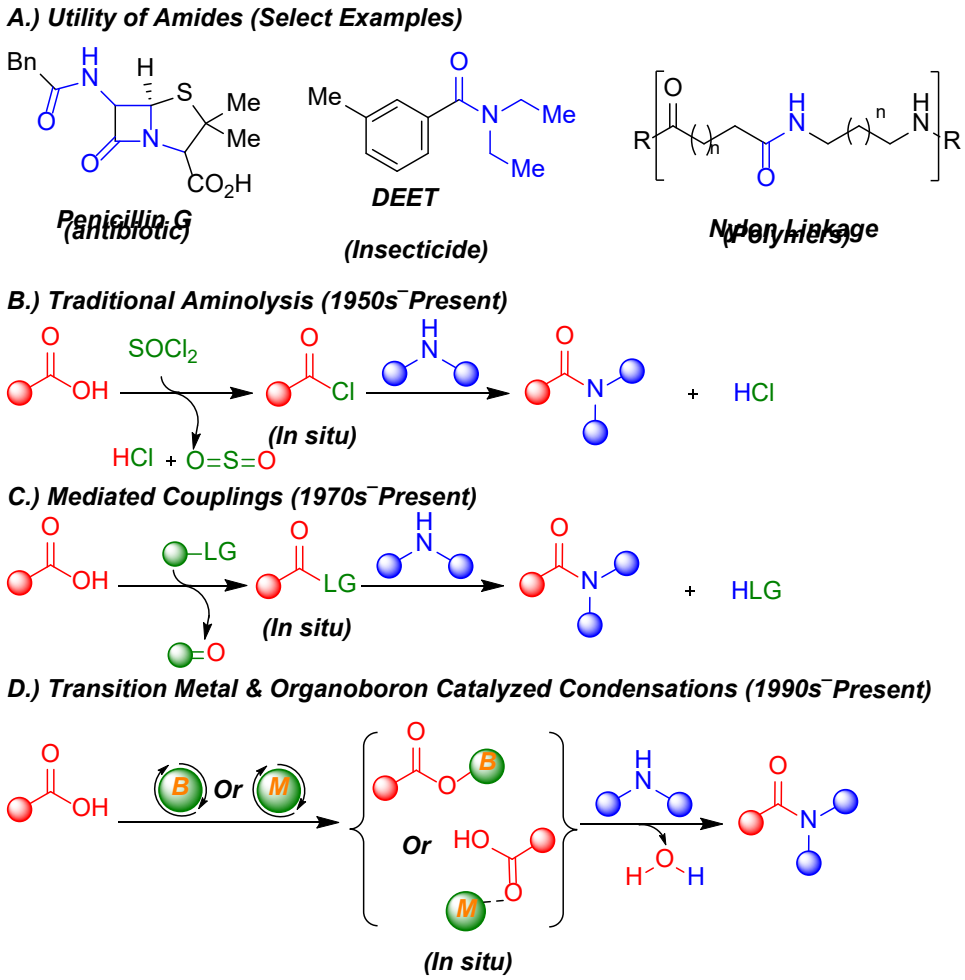
An ambient deoxyamidation of carboxylic acids and deoxyamination of alcohols was developed through the use of *N*-haloimides activated by triphenylphosphine. Such technologies were found to possess broad functional tolerance and formed C-N bonds via a coupling to free amines, and the direct installment of the imide motif. Mechanistic experiments suggest that such transformations take place via the *in situ* generation of two separate phosphonium reactive species.

CHAPTER 1. ACTIVATION OF THE C-O BOND TOWARDS NEW BOND FORMATIONS: PAST, PRESENT, AND FUTURE OUTLOOK

1.1 Deoxyamidations Of Carboxylic Acids Towards Amide Formation

1.1.1 Introduction

In the pharmaceutical industry, amide formations are one of the most frequent reactions employed due to the ubiquitous nature of the amide motif in biologically active compounds.[1] It is for this reason that the amide motif holds significant value in the field of agriculture[2] as well as in the formation of synthetic polymers/adhesives[3] (Scheme 1.1 A). Carboxylic acids represent ideal amide precursors due to their natural and commercial abundance, however direct thermal aminolysis requires forcing conditions to overcome the initial formation of the kinetically favored ammonium salt, and the corresponding scope is limited to simple aliphatic substrates.[4] As such, the bulk of amide formations in literature aim at first converting the carboxylic acid into a more reactive intermediate, *in situ,* prior to the introduction of the amine. A traditional example of this strategy would be the conversion of carboxylic acids into acyl chlorides for subsequent aminolysis (Scheme 1.1 B).[5a-b] While efficient, such methods are highly moisture sensitive and the generated acyl chloride intermediates can behave as lachrymators, which presents a potential safety risk with respect to large-scale/industrial synthesis. The past two decades has observed a shift towards the development of amide formations that employ the ideal carboxylic acid precursor but facilitate the initial activation through the formation of less reactive reagents or intermediates. Such technologies can be broadly divided into stochiometric mediated couplings[6-8] (Scheme 1.1 C) and more atom economical amide formations catalyzed by either an organoboron[9] reagent or a transition metal[10] catalyst (Scheme 1.1 D).

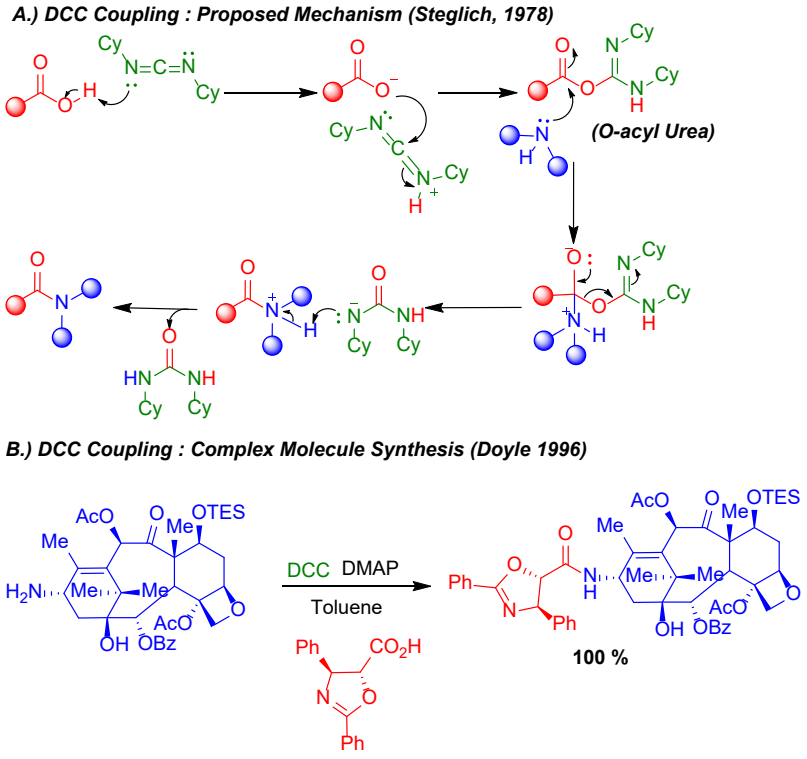


Scheme 1.1 : Deoxyamidations of Carboxylic Acids Traditional *vs* Recent Examples

1.1.2 Mediated Couplings

One of the most well-known synthetic methods employed in peptide synthesis is the *N*,*N*'-dicyclohexylcarbodiimide (DCC) mediated coupling reaction established over forty years ago by Steglich.[6a] This seminal work demonstrated that in the presence of carbodiimides, carboxylic acids can be quantitatively converted into the corresponding *O*-acyl ureas. *O*-acyl ureas can then react rapidly in the presence of amine nucleophiles to generate amides as well as the subsequent urea by-product (Scheme 1.2 A). While racemization in the case of chiral amino acid substrates can be observed, such issues can be mediated via additional cooling and reduced reactions times. Additionally, the use of common racemization suppressants has also largely alleviated the original protocol's stereoretention issues.[11] This technology has become a common staple in the formation of amides facilitating deoxyamidations of even the most complex carboxylic acid starting materials

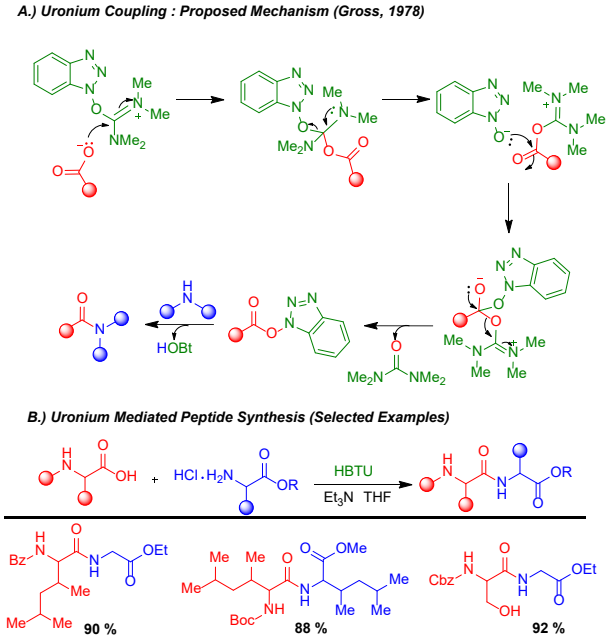
(Scheme 1.2 B). However, as carbodiimide reagents are known allergens, especially upon repeated exposure, further research has been conducted towards the development of efficient and safe-to-handle coupling agent alternatives. One such alternative involves the use of uronium salt agents, which provide access to amides from carboxylic acids via a similar mechanism (Scheme 1.3 A) to DCC-based couplings. However, the key difference is the formation of the activated benzotriazole ester intermediate instead of the *O*-acyl urea observed in DCC couplings. Seminal work by Gross facilitated the initial development of the uronium salt coupling agents via the initial reaction between phosgene and tetramethyl urea, followed by the addition of hydroxybenzotriazole (HOBt) under anhydrous conditions.[7]



Scheme 1.2 : DCC Coupling Mechanism & Synthetic Utility in Complex Molecule Synthesis

Gross' initial report illustrated the utility of uronium salts such as *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) towards peptide synthesis through the coupling of *O*-protected glycine derivatives to various *N*-protected amino acids[7a] (Scheme 1.3 B). Notably, the technology facilitated peptide bond formation in the presence of motifs commonly used in complex peptide synthesis (e.g. benzoyl, & Boc), generating the

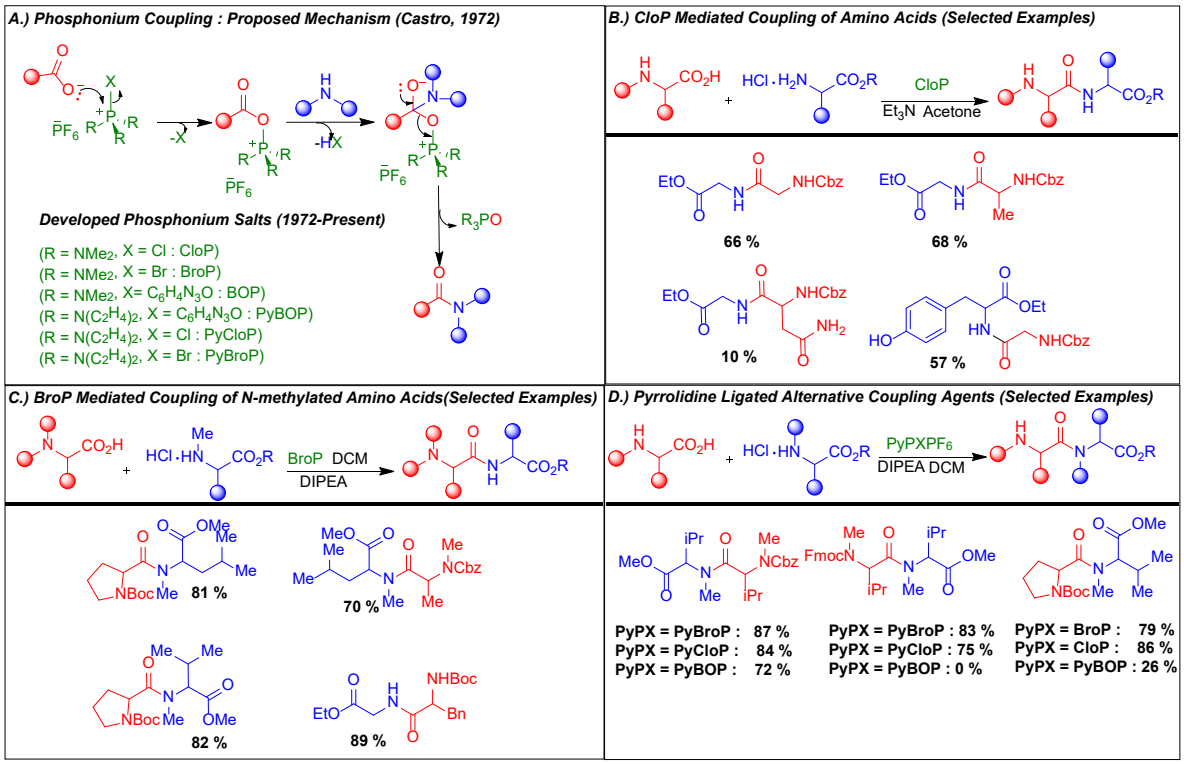
corresponding dipeptides in excellent yields. Importantly, the free primary alcohol of the serine residue was fully tolerated illustrating the selectivity of uronium activating agents for carboxylic acids in the presence of alcohols. It is known that due to the liberation of the hydroxybenzotriazole (HOBt) motif in uronium salt coupling agent, such technologies can offer improved stereoretention when compared to other coupling protocols.[7b] However, in this particular report the degree of racemization post-amide formation was observed to be substrate specific and ranged from negligible to moderate. Specifically, while Boc and Cbz protected amine residues yielded trace racemization, benzoyl protected amine residues were observed to produce the corresponding amide with significant racemization. Following Gross' seminal works, further uronium salt development would first be conducted by Knor who synthesized a series of uronium salt derivatives for peptide coupling and compared degrees of amide racemization to other common peptide coupling agents.[7b] During the course of this study Knor was able to develop a protocol using 2-oxo-1(2H)pyridyl))-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TPTU) and HOBt that generated ≤ 0.1 % racemization post-peptide formation. Further work by Caprino led to the discovery of the true crystalline structure of the uronium salt previously used by others and how to selectively generate the uronium isomer for a more efficient peptide synthesis.[7c-e]



Scheme 1.3 : Uronium Salt Coupling Agents By Gross, Mechanism & Dipeptide Synthesis

Around the same time that Steglich and Gross began developing their respective carbodiimide and uronium salt coupling technologies, Castro began conducting research on the use of phosphonium-based salt reagents towards peptide synthesis.[8a] Castro's seminal work (Scheme 1.4) presented the synthesis of a bench-stable chlorophosphonium salt (CloP) that facilitated the coupling of *N*-protected amino acids with amine-hydrochloride salts through a phosphorus-oxygen double bond (P=O) formation driving force (Scheme 1.4 A). Castro probed the coupling of various *N*-Cbz-protected amino acids with ethyl glycinate generating the corresponding dipeptides in moderate yields (Scheme 1.4 B). Notably, in all cases only negligible racemization was observed, highlighting the improved degree of stereocontrol when compared to DCC peptide couplings. A noted weakness of this initial phosphonium salt was its reactivity with the probed Cbz protected asparagine residue. Specifically in the case of this coupling the bulk of the mass was lost due to unwanted dehydration, suggesting a competition between the hydroxy motif of the carboxylic acid and the carbonyl moiety of the primary amide.[12] Interestingly, CloP was observed to selectively activate carboxylic acids even in the presence of other oxygen-containing motifs such as phenols. Later, Castro further demonstrated the advantages of such phosphonium mediated couplings through the use of a brominated analogue of CloP denoted as BroP as an activator to facilitate the peptide coupling in the presence of *N*-methylated amino acid residues (Scheme 1.4 C).[8b] Due to increasing sterics as well as basicity, the activation of *N*-methylated amino acid residues can be challenging using traditional peptide bond forming reactions, suffering from low to erratic yields with high degrees of racemization.[13] BroP was able to facilitate the generation of a wide series of *N*-methylated containing dipeptides from the corresponding residues in excellent yields. Common protecting groups employed in peptide synthesis such as Boc and Cbz motifs were tolerated. Additionally, dipeptides containing multiple *N*-methylated moieties were synthesized as well with only a small decrease in yield, and no significant racemization was detected in any of the performed couplings. While Castro's seminal works illustrated the advantages of employing his phosphonium coupling agents over more traditional DCC/uronium technologies, in the case of both CloP and BroP a known carcinogen, hexamethylphosphoramide (HMPA), is generated stoichiometrically as by-product, thus limiting the industrial applicability of these initial works.[14a] To mediate these issues Castro later developed several new phosphonium coupling reagents through an auxiliary ligand exchange to pyrrolidine as well as a change in leaving group motif and subsequently confirmed the viability of these new

peptide coupling reagents.[8c-d] Castro then conducted an extensive study into the mechanism of peptide formation with respect to these new pyrrolidine (Py)-type salts and probed an extensive series of peptide residues to illustrate the generality of these new coupling agents (Scheme 1.4 D).[8e] *N*-methylated amines were well tolerated, with two separate valine residues being coupled together in good yields when employing each Py-type coupling agent. While PyCloP and PyBroP both tolerated Fmoc, protected residues, PyBOP was observed to be an ineffective coupling agent when employing the ester protecting group. The coupling of amino acids, *N*-Boc-protected amine motifs was observed to be more varied amongst the different coupling agents due to unwanted cyclizations post-activation of the carboxylic acid motif. Additionally, as with his precursor technologies, these new Py-type phosphonium salts generated dipeptide products with little to no racemization.



Scheme 1.4 : Phosphonium Salt Coupling Agents by Castro

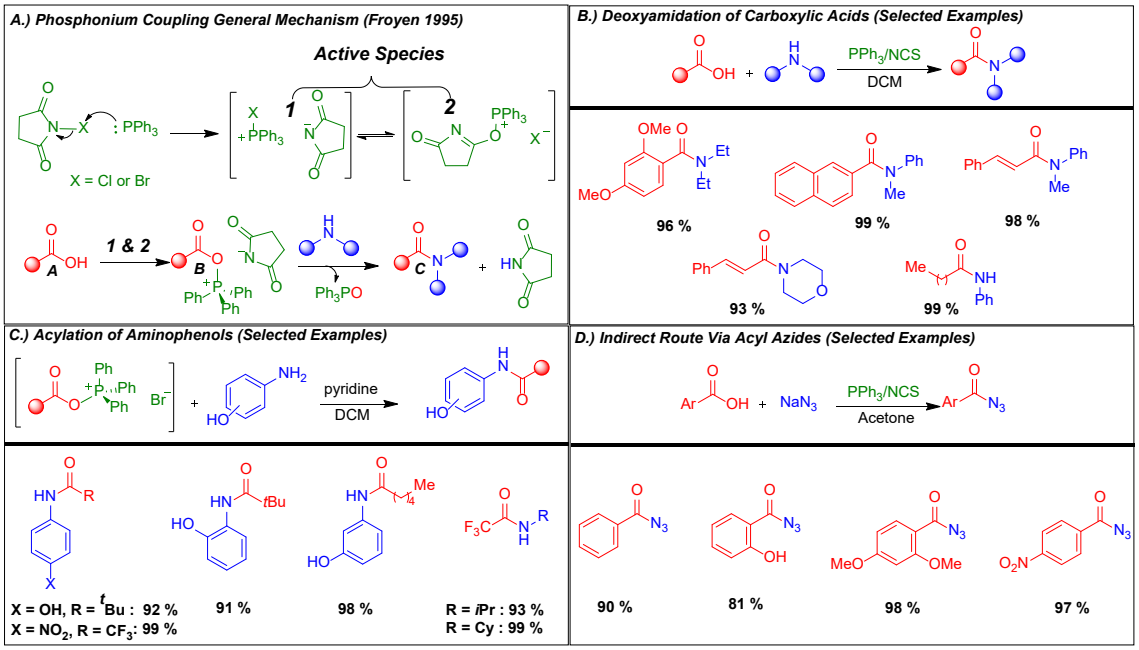
While Castro's seminal works led to the development of a series of useful phosphonium-based peptide coupling agents, these technologies were still observed to possess several inherent

drawbacks. For example, while the use of dimethylamine auxiliary ligands was exchanged for pyrrolidine, thus removing the generation of toxic HMPA from the synthetic platform, current Castro's salts still present a potential explosive hazard.

Around the same time that Castro developed his Py-type phosphonium salt reagents, Frøyen reported an efficient amide formation through a proposed phosphonium active species made *in situ* via the interaction between bench-stable triphenylphosphine (PPh_3) and *N*-chlorosuccinimide (NCS)[8f] (Scheme 1.5). The proposed mechanism (Scheme 1.5 A) took inspiration from previous reports noting the unique reactivity observed upon the introduction of PPh_3 to *N*-bromosuccinimide (NBS).[8j-k] The reaction was proposed to begin via a Lewis-based interaction between the lone pair of PPh_3 and the electrophilic bromine of NBS. Two unique reactive phosphonium species are then generated *in situ*, a halophosphonium species ***1*** akin to the Appel reaction,[15a] and an imidophosphonium species ***2***, with the literature showing conflicting hypotheses[15b] as to the nature of the phosphorus-heteroatom bond. Both ***1*** and ***2*** are proposed to interact with the carboxylic acid starting material ***A*** to generate the key acyloxyphosphonium intermediate ***B***. ***B*** is then proposed to collapse upon the introduction of the nucleophilic nitrogen source, ejecting triphenylphosphine oxide (Ph_3PO) and generating the desired amide ***C***. Frøyen's direct free amine coupling probed a wide series of substrates with respect to both carboxylic acids and amines (Scheme 1.5 B). Specifically, benzoic acid derivatives were coupled to both aliphatic secondary amines and methylated aniline nucleophiles generating the amides at excellent yields. Similar reactivity was observed with respect to cinnamic acid derivatives, and aliphatic carboxylic acids were coupled to free anilines as well. Surprisingly, in contrast to Castro,[8a-e] Frøyen did not report the coupling of any amino acid residues, presumably due the use of excess amine not allowing his platform to tolerate common peptide protecting groups (e.g Fmoc).

Inspired by the high reactivity of the proposed acyloxyphosphonium intermediate towards amines, Frøyen subsequently developed a chemoselective aminophenol *N*-acylation via the pre-synthesis of the acyloxyphosphonium species as a reagent (Scheme 1.5 C).[8m] Notably, the chemoselective *N*-acylation tolerated para-, ortho-, and meta- substituted anilines generating the desired amides at excellent yields. Deactivated substrates such as 4-nitroaniline were viable as well, yielding the corresponding amide in nearly a quantitative yield. However, the use of a trifluoroacetic acid substrate would suggest that a highly reactive acyloxyphosphonium intermediate was required to facilitate the deoxyamidation. Aliphatic amines were found to

generate the corresponding amides as well thereby demonstrating a similar scope of reactivity when compared to the original PPh_3/NCS technology.[8f]



Scheme 1.5 : Frøyen *In situ* Generated Phosphonium Active Species

While one of the proposed mechanisms mirrors Frøyen's general phosphonium coupling mechanism, an alternative penta-coordinate intermediate is proposed as well.[15b,16] Lastly, using his PPh_3/NCS coupling system, Frøyen developed a straightforward conversion of carboxylic acids into acyl azides,[8l] allowing an indirect access towards amides.[17] The scope of the reaction (Scheme 1.5 D) was found to include both activated and deactivated benzoic acid derivatives, generating the corresponding azides in excellent yields. As no base additive was included into the reaction, presumably this selectivity is largely dependent on the differences in pK_a between the two competing motifs. In contrast to his subsequent amine couplings, Frøyen did not report the azidation of aliphatic carboxylic acids. While Frøyen did not provide an explanation for this drastic difference in carboxylic acid scope, upon further investigation into the reaction conditions presented in his subsequent amide formations,[8f,8m] there was an observed solvent exchange from acetone to dichloromethane. As it is known that an exchange of solvent can have a drastic effect on the pK_a of carboxylic acids,[4] this solvent exchange to dichloromethane from acetone could provide an explanation to the differences in reaction scope amongst Frøyen's technologies. While

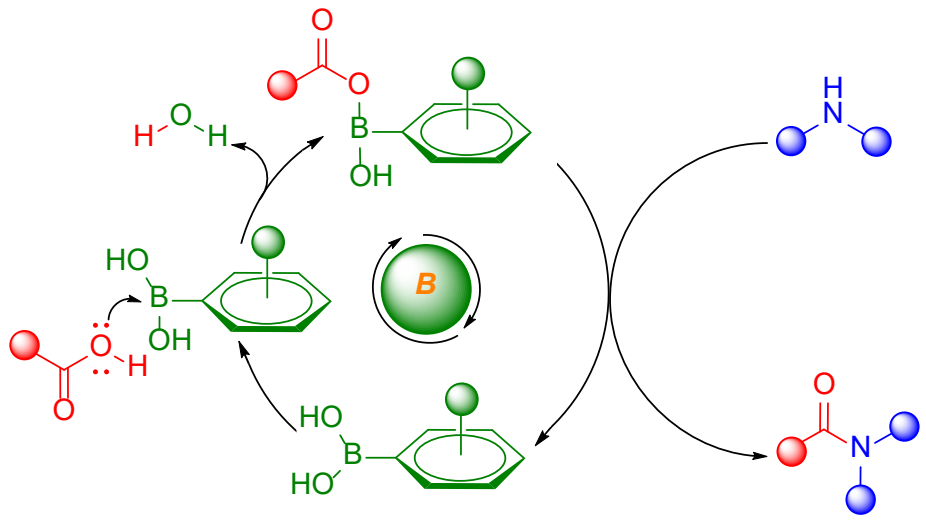
his work provided foundational knowledge on the use of *in situ* generated phosphonium salts for the formation of amides, to the same degree as observed when employing uronium or BOP-type reagents, unlike Gross and Castro, Frøyen neglected to report on the use of additional phosphonium active species containing imido-motifs besides the classic succinimide moiety. This was a surprise as employing different imido motifs could in theory open the door to enhance and access different types of reactivity.

While coupling reagent technologies represent the bulk of methods employed in peptide synthesis due to their straightforward set up and efficiency, such synthetic platforms do possess two significant drawbacks. First, in the case of optically active substrates racemization post amide formation remains consistent issue in such coupling technologies with the degree of optical erosion varying from factors including but not limited to employed protecting groups and or coupling agent. Such issues must be overcome through a suppressant additive, although the use of such reagents can represent a safety hazard. Secondly, as these technologies require the stochiometric use of activating reagents or additional additives, they possess inherently poor atom economy and, in some cases, generate difficult to remove (e.g. urea) or toxic (e.g. HMPA) by-products. In response to these significant issues, the past twenty years has seen a rise in the development of catalytic condensation reactions that employ either organoboron or transition metal catalysts to facilitate the atom economical coupling between carboxylic acids and amines, with higher and more reproducible degrees of stereocontrol, while generating water as the sole by-product. It should also be noted that select organoboron-catalyzed amide formations following a hydrogen evolution mechanism have been reported as well.

1.1.3 Organoboron Catalyzed Condensations & Hydrogen Evolutions

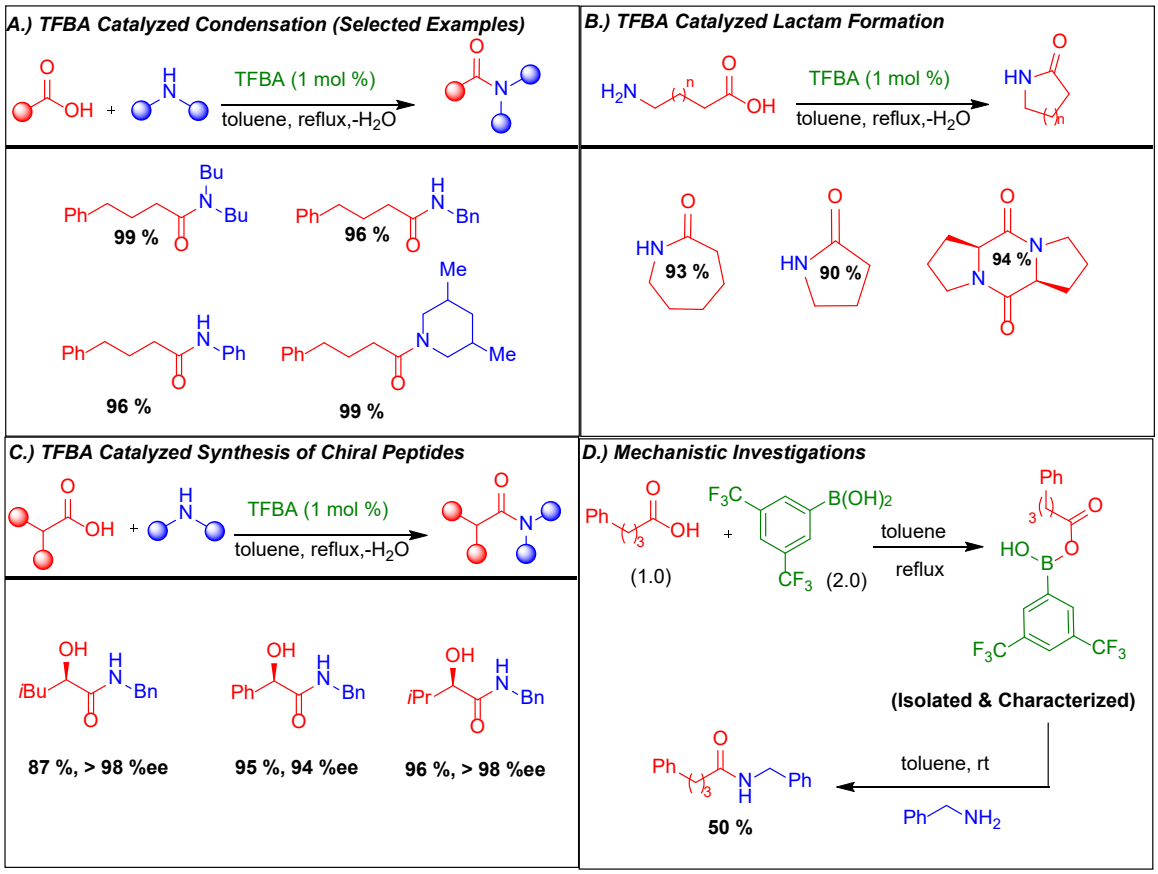
The general mechanism (Scheme 1.6) of all organoboron-catalyzed amide condensations follows an initial hydrogen bond induced activation of the carboxylic acid as well as a Lewis interaction between the empty p-orbital of the catalyst and the lone pair of the hydroxy moiety. A subsequent loss of water then generates an activated acylboronate ester species, that when introduced to nucleophilic amines, is displaced, yielding the desired amide product while simultaneously regenerating the organoboron catalyst. Additional noteworthy characteristics of such technologies include racemization suppression, generation of water as sole product, and the

requirement of anhydrous conditions either through a Dean-Stark apparatus or through the use of a dehydration agent.



Scheme 1.6 : Organoboron-Catalyzed Condensations, General Mechanism

Yamato reported the first example of an organoboron-catalyzed condensation of carboxylic acids and free amines towards amide formation via the use of 3,4,5-trifluorophenyl boronic acid (Scheme 1.7).[9a-b] While previous organoboron-mediated precursor protocols generated amides efficiently, upon amide formation the organoboron reagent in such technologies would then be converted into an inactive species thereby preventing the formation of a catalytic cycle.[18] However, Yamato postulated that deactivated boronic acids might possess a strong enough Lewis acidity to increase the rate of formation of the acyl(oxy)boron intermediate and enhance its reactivity with amines. Indeed, during the optimization of the reaction the degree of amide formation was observed to be highly dependent on electronics within the aryl ring of the probed boronic acid catalysts.

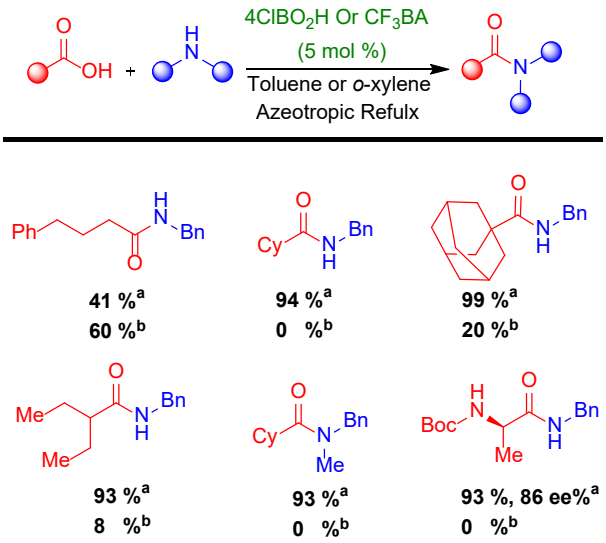


Scheme 1.7 : Yamato's Seminal Amide Condensation Catalyzed by TFBA

Yamato initially demonstrated the utility of this seminal work[9a] through the coupling of 4-phenylbutanoic acid to both primary (benzylic, aryl) and secondary amines (cyclic, acyclic) generating the corresponding amides at excellent yields (Scheme 1.7 A). Additionally, 3,4,5-trifluorophenyl boronic acid (TFBA) was able to catalyze the cyclization of several amino acids including 4-aminobutanoic acid and 6-aminohexanoic acid, generating the corresponding 6- and 7-membered rings, respectively (Scheme 1.7 B). Importantly, several (*R*)-2-hydroxy-2-phenylacetic acid derivatives were coupled to benzylamine generating the corresponding amide in up to 96 % yield with < 98 % enantiomeric excess (% ee) (Scheme 1.7 C). Indeed, this illustrated the capability of organoboron catalysis to not only generate amides from carboxylic acids in an efficient and chemoselective manner, but to do so in an enantioselective manner as well. During the investigation of the mechanism, Yamato was able to isolate and characterize the proposed acyl(oxy)boron intermediate, subsequent introduction to the amine nucleophile decomposed the

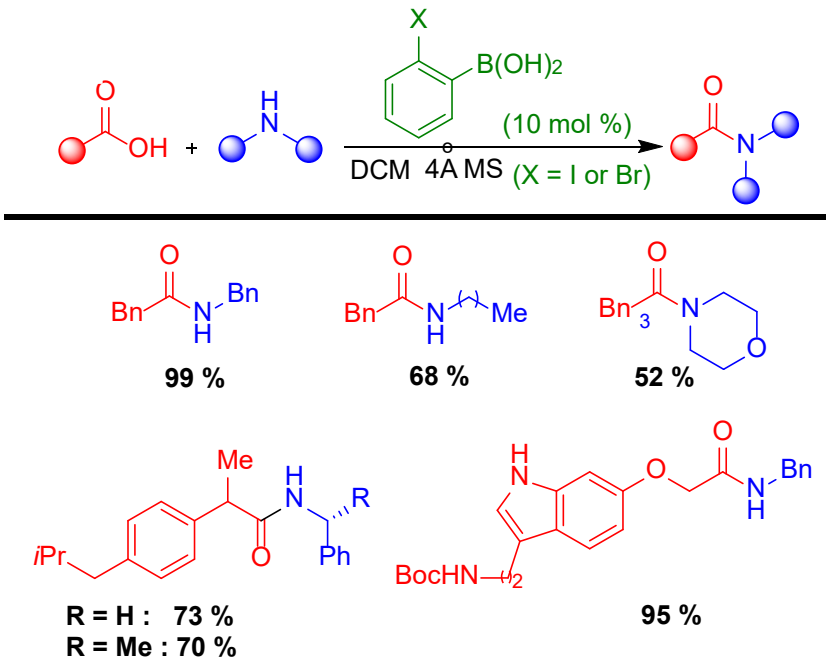
intermediate and generated the corresponding amide at 50 % owing to the lack of proper Dean-Stark conditions. As this reaction was carried out under room temperature conditions, the formation of the acyl(oxy)boron intermediate was proposed to be the rate-determining step.

Following this seminal work, Yamato later presented an organoboron-catalyzed amide formation focusing on the formation of sterically hindered peptides using 4,5,6,7-tetrachlorobenzo[d][1,3,2]dioxaborole ($4ClBO_2H$).[9c] To demonstrate the synthetic value of this new catalyst, a competitive study was done using 3,5-trifluoromethylphenylboronic acid (CF_3BA) (Scheme 1.8) which was observed to facilitate amide formation at yields comparable to TFBA.[9a] Indeed, while both catalysts coupled benzoic acid with benzylamine at comparable yields, as steric bulk was observed to increase in the carboxylic acid starting material the differences in catalytic reactivity became more apparent. While CF_3BA coupled 1-adamantanecarboxylic acid to benzylamine at only 20 %, by exchanging CF_3BA for $4ClBO_2H$, the corresponding amide was isolated at nearly a quantitative yield. A similar reactivity trend was also observed for branched aliphatic carboxylic acids as well. Additionally, while CF_3BA was found to be unable to facilitate the coupling of secondary amines to carboxylic acids, $4ClBO_2H$ was able to couple 1-cyclohexylcarboxylic acid to *N*-methylbenzylamine at 93% yield. Notably an *N*-Boc-protected glycine derivative was coupled to benzylamine generating the corresponding peptide at an excellent 91% yield. However, moderate erosion of optical purity was noted upon amide formation, demonstrating the advantages of Yamato's previous boronic acid catalyst in terms of enantioselectivity.



Scheme 1.8 : Yamato's Activation of Sterically Hindered Carboxylic Acids. (Selected Examples) [a]Using $4ClBO_2H$. [b]Using CF_3BA

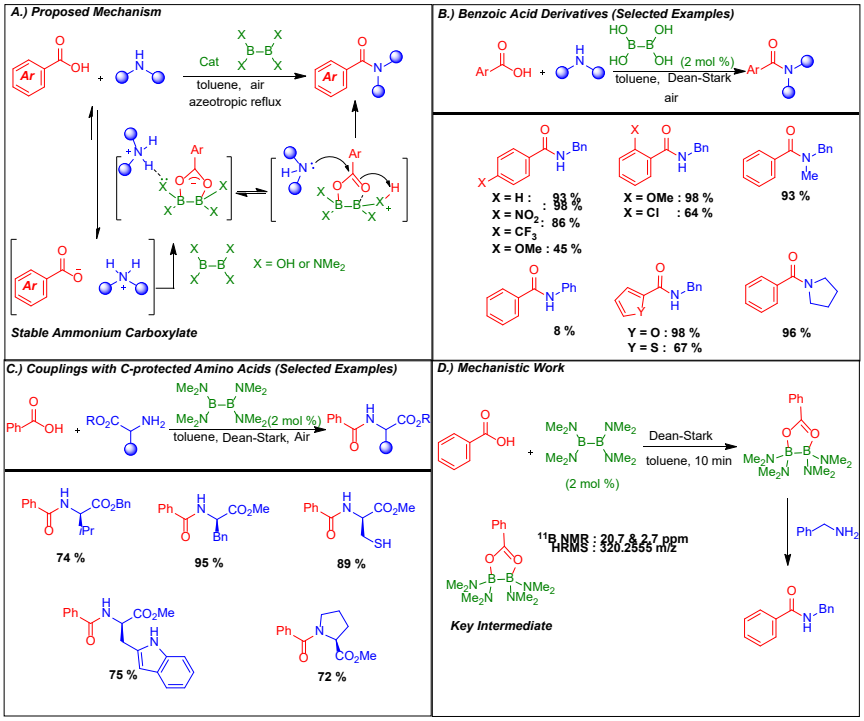
Inspired by Yamato's work[9a], Hall later developed a modified condensation using ortho-halogenated aryl boronic acid catalysts and using molecular sieves as a water scavenger, thereby making the technology more operationally simplistic (Scheme 1.9).[9d] The method was proposed to follow the general condensation mechanism (Scheme 1.6). The *ortho*-selective reactivity of the employed catalysts suggested an additional hydrogen bonding activation of the hydroxy group in the carboxylic acid starting material.[9f] Phenylacetic acid was coupled to various activated and unactivated amines. Impressively, (*S*)-ibuprofen was coupled to both benzylamine and *N*-methylbenzylamine generating the corresponding amides with less than 5% racemization[19] and at 73% and 70%, respectively. Lastly, tryptophan-like carboxylic acids were tolerated as well generating amides at excellent yields, further demonstrating the applicability of this technology towards peptide synthesis. Additionally, it was noted that the organocatalyst could be recovered in high yield via a simple base work up which in combination with their use of molecular sieves as a water scavenger makes this technology a waste-free alternative to Yamato's original protocol.[9a] The proposed mechanism mirrored Yamato's original report, although a diacylboronate intermediate could not be ruled out.



Scheme 1.9 : Waste-Free Condensation Catalyzed by *ortho*-Halogenated Aryl Boronic Acids (Select Examples)

More recently, Saito reported a diboron-catalyzed condensation focusing on the coupling between various benzoic acid derivatives and with both primary and secondary amines (Scheme 1.10).[9h] The working hypothesis for the mechanism of this condensation followed the activation of the carboxylate ammonium salt via both the simultaneous coordination of the carboxyl group into each boron center as well as activation of the ammonium ion via hydrogen bonding (Scheme 1. 10 A). Saito probed a wide scope of benzoic acid derivatives (Scheme 1. 10 B) coupling such compounds to both primary and secondary amines. While both 4-nitrobenzoic acid and the corresponding 4-trifluoromethyl derivative were coupled to benzylamine at excellent yields, the corresponding coupling with the 4-methoxy analog generated the corresponding amide at a more modest 45 %, suggesting a sensitivity toward electronic tuning effects. However, reactivity was recovered by placing the methoxy motif in the ortho position, possibly due to increased hydrogen bond activation of the ammonium ion as it approaches the coordination sphere of the key intermediate. While aniline was observed to be a poor coupling partner, subsequent *N*-methylation allowed for the recovery of amide formation back to excellent yields. Pyrrolidine was coupled to benzoic acid at 96% yield, illustrating a strong tolerance for increasing steric factors. A series of *C*-protected α-amino acids were coupled to benzoic acid generating the corresponding chiral

peptides in good to excellent yields, with slight to moderate degrees of optical erosion. Importantly, both cysteine and tryptophan residues were tolerated demonstrating the chemoselectively of the diboron catalyst both with respect to the initial boron coordination and hydrogen bond-based activation of the ammonium species. Control experiments confirmed the key intermediate as the boron-bound carboxylate via ^{11}B-NMR and high-resolution mass spectrometry. While organoboron-catalyzed condensations provide an atom economical, ambient, and environmentally friendly alternative to mediated couplings, however currently racemization of optical substrates remains a consistent challenge with degrees of optical erosion varying from slight to significant depending on the organoboron employed.

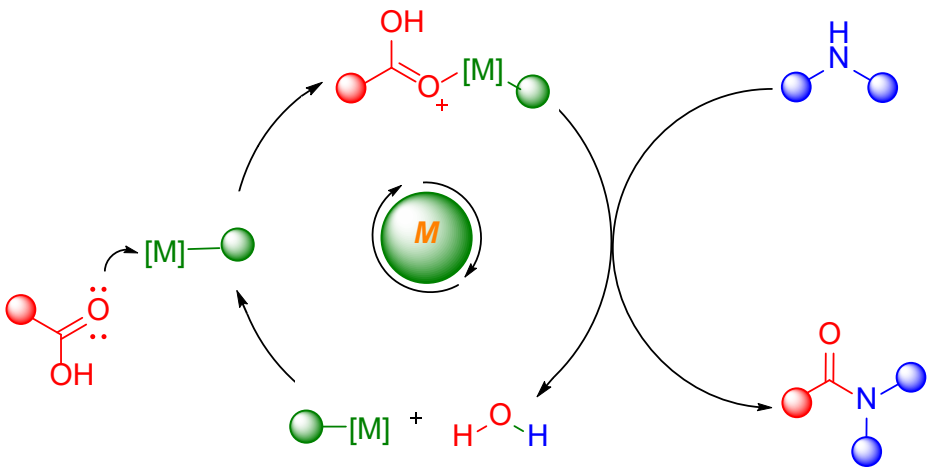


Scheme 1.10 : Saito's Diboron-Catalyzed Condensation of Benzoic Acids

1.1.4 Transition Metal Catalyzed Condensations

The use of transition metal catalysts has become a well-established staple in asymmetric synthesis.[20] Indeed, since the time of Yamato's seminal work there has been a proportional rise in the development of transition metal catalyzed carboxylic acid condensations towards amide formaitons.[10] Notably, such technologies are not only characterized by efficient peptide bond formation, but in the case of optically active precursors, such protocols facilitate the coupling of

carboxylic acids to amides with little to no erosion of the stereocenter, due to the unique chemical environment (sterics, intermolecular forces, etc.) present in the metal catalyst providing an enhanced degree of enantioselectivity. Similar to organoboron-catalyzed condensations, the general mechanism (Scheme 1.11) of transition metal catalyzed condensations initially takes place via a Lewis interaction between the carboxylic acid and the catalyst. The key difference however lies in the functional motifs that participate in the initial activation step, specifically in transition metal catalyzed protocols, it is the lone pair of the carbonyl that coordinates into the metal catalyst to increase the reactivity of the carboxylic acid towards deoxyamidation.

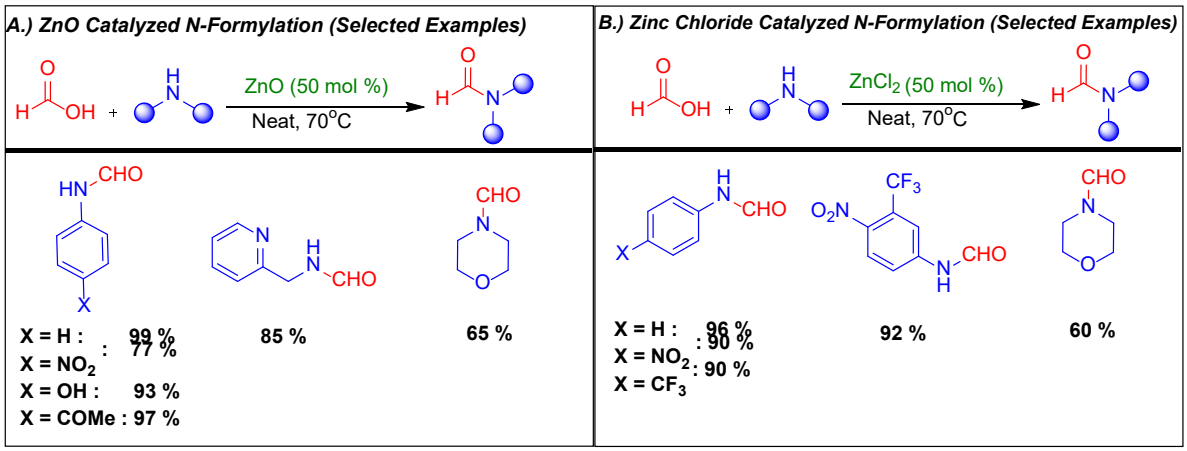


Scheme 1.11 : Transition Metal Catalyzed Condensation Couplings, General Mechanism

Seminal work by Carlson first illustrated the potential of transition metal catalysis as a synthetic tool for the synthesis of amides.[10h] However, while conducting these initial experiments, it was observed that reactivity was highly substrate specific, and often required the use of different catalysts. *N*-Formylations by Sharghi[10a] (Scheme 1.12 A) and Rao[10b] (Scheme 1.12 B) represent early examples of transition metal catalyzed carboxylic acid condensations employing a single catalyst. Both technologies were facilitated by earth-abundant Zinc-based catalysts and were run under neat conditions, thereby limiting waste. The scope of Shargi's protocol was observed to include both activated and deactivated aniline derivatives. Notably, 4-aminophenol was formylated chemoselectively at 93% presumably due to competitive aryl ring activation via the

electron donating *p*-hydroxy group. Such a hypothesis was found to also coincide with the complete lack of reactivity reported for the corresponding *O*-formylation of phenols and alcohols. While 4-nitroaniline was formylated at a lower 77%, this was presumed to be due to the strong electron withdrawing effect of the nitro group.[21] Indeed, 4-aminoacetophenone generated the corresponding formyl derivative at 97% yield, suggesting the protocol exhibits a strong tolerance towards electronic factors.

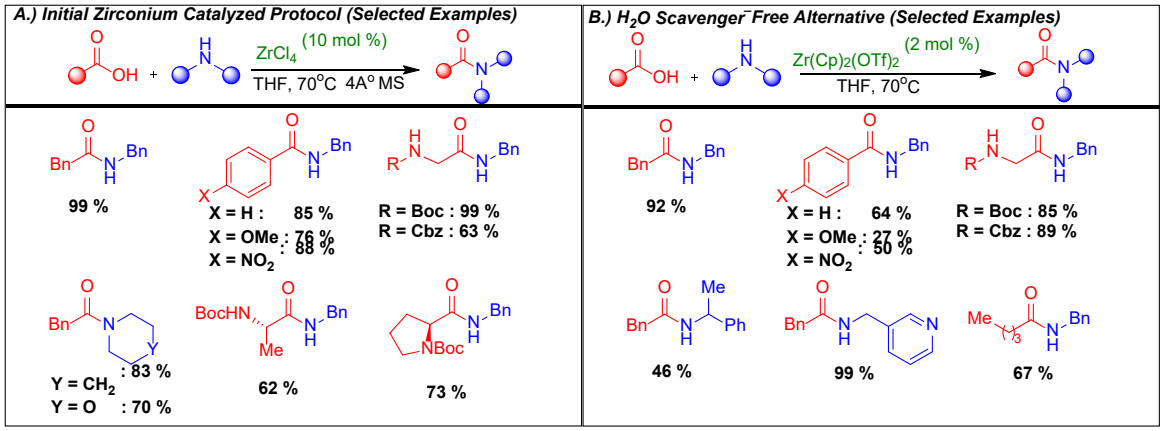
Pyridine-containing amines were also formylated in good yields as were unactivated amines. Rao's subsequent technology demonstrated a comparable scope to Sharghi's earlier protocol, but it was noted that Rao's method demonstrated an even stronger tolerance towards electronic effects. While these protocols were a noted advancement from Carlson's seminal work their limited carboxylic acid scope placed severe limitations on the application of these technologies towards peptide synthesis.



Scheme 1.12 : Zinc Catalyzed *N*-Formylations.

Subsequent transition metal catalyzed condensations have since been able to expand the scope of such couplings to include a more diverse set of carboxylic acids and or amines.[10d-g] Indeed, seminal work by the Adolfsson group has demonstrated the efficiency of zirconium[10d,10f] and hafnium[10e] catalysis towards the enantioselective condensation of carboxylic acids into amides. Adolfsson's initial protocol employed zirconium(IV) chloride ($ZrCl_4$) as the transition metal catalyst and was run under moderate heating to minimize any potential amide formation due to background reactions (Scheme 1.13 A).

This initial technology deoxyamidated both aromatic and aliphatic carboxylic acids in good to excellent yields. Notably, the probing of various benzoic acid derivatives illustrates a strong tolerance to electronic effects. Additionally, *N*-protected glycine derivatives were amidated at good to excellent yields, initially illustrating the potential of the technology towards peptide synthesis. Subsequent chiral α-amino acid containing substrates were probed as well through the coupling to benzylamine. In such cases the amide product was obtained with no racemization, thus confirming the protocol's applicability towards enantioselective peptide synthesis. While the scope of amine coupling partners was mainly comprised of benzylamine derivatives, aliphatic unactivated amines were effectively coupled to carboxylic acids as well. Later, Adolfsson developed an alternative zirconium-catalyzed deoxyamidation without the need for molecular sieves as a water scavenger (Scheme 1.13 B) using bis(cyclopentadienyl)zirconium(IV) bis(trifluoromethanesulfonate) ($Zr(Cp)_2(OTf)_2$). While this new technology demonstrates comparable reactivity to its $ZrCl_4$ catalyzed precursor, there were several observed notable differences between the two protocols.

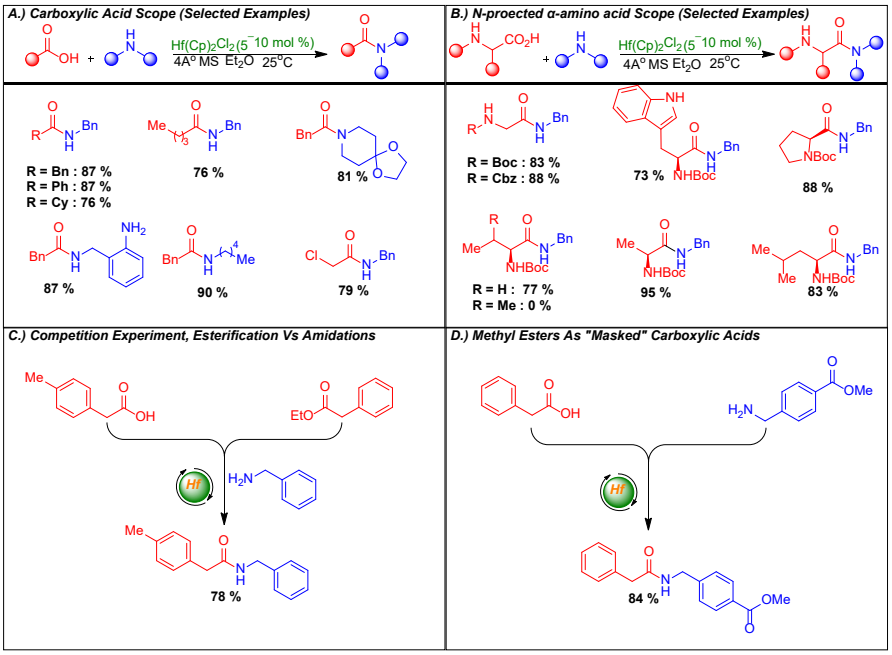


Scheme 1.13 : Zirconium Catalyzed Condensations by Adolfsson

In contrast to the initial technology, benzoic acid derivatives were amidated at significantly lower yields and the scavenger free protocol appeared to be greatly affected by electronic tuning within the aromatic ring. Another noted difference was the $Zr(Cp)_2(OTf)_2$ catalyzed technology's inherent weakness towards increasing steric considerations with respect to amine coupling partner. Indeed, while benzylamine was coupled to phenylacetic acid at 92% yield, the corresponding α-methylated benzylamine derivative generated the corresponding amide at a more modest 46%.

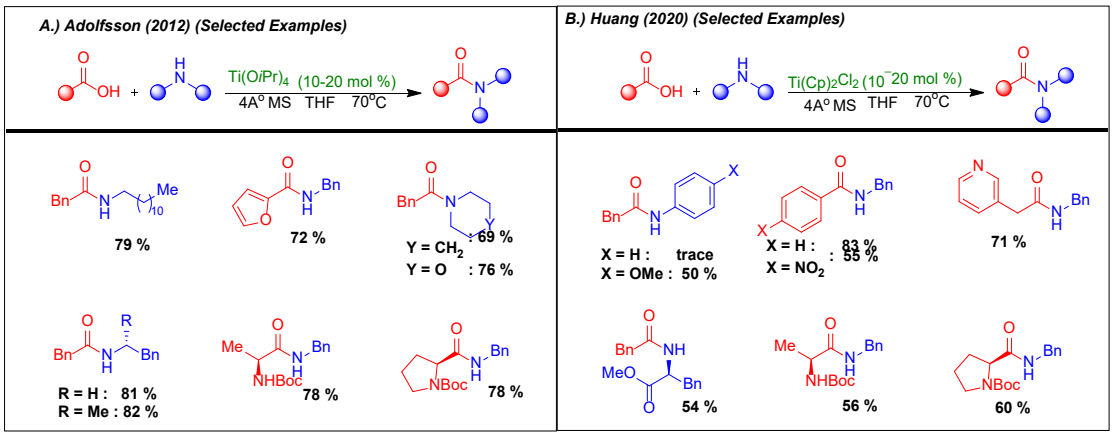
Another interesting report by Adolfsson presented a chemoselective hafnium catalyzed condensation of carboxylic acids (Scheme 1.14)[10e] at ambient conditions only found in a handful of previous organoboron catalyzed amide formations.[9d,21] Benzylic, aliphatic (acyclic and cyclic), and aromatic carboxylic acids were all coupled to benzylamine at good yields under the hafnium catalyzed technology (Scheme 1.14 A). Additionally, the protocol was found to be selective for the acylation of primary amines when in the presence of aniline motifs, generating *N*-(2-aminobenzyl)-2-phenylacetamide at 87 % yield. Surprisingly, chloroacetic acid was amidated at 79 % with a complete retention of the alkyl chloride moiety. Both unactivated primary and secondary amines were viable coupling partners as well generating the corresponding amides at excellent yields.

To further demonstrate the synthetic utility of this technology, Adolfsson probed a series of *N*-protected α-amino acid residue substrates (Scheme 1.14 B). Both Boc-protected and Cbz-protected glycine were coupled to benzylamine at 83 % and 88 % yield, respectively. Furthermore, several other Boc protected *α*-amino acid residues including tryptophan, proline, leucine, and alanine, were coupled to benzylamine at good to excellent yields. However, a noted weakness of the protocol was its inherent sensitivity to increased sterics at the *β* position of the amino acid residue. Further competition studies demonstrated that the hafnium catalyzed carboxylic acid condensation was chemoselective for amines in the presence of alcohols, preferentially generating the corresponding amides (Scheme 1. 14 C). Adolfsson creatively used the chemoselective nature of the protocol to employ methyl esters as a new carboxylic acid protecting group (Scheme 1.14 D).



Scheme 1.14 : Hafnium-Catalyzed Condensation by Adolfsson

While Adolfsson's technologies, represent foundational development in the field of asymmetric transition metal catalyzed carboxylic acid condensations, his protocols employ rare earth metals thus placing limits on the sustainability and cost-effectiveness of such methods for industrial scale up. However, more recently the literature has observed reports of more cost-effective carboxylic acid condensations employing more earth abundant transition metal catalysts. Within the past decade Adolfsson[10i] and Huang[10g] have developed titanium catalyzed condensations of carboxylic acids as cost effective alternatives to previous transition metal catalyzed precursor technologies (Scheme 1.15).



Scheme 1.15 : Titanium Catalyzed Condensation Couplings

Adolfsson initially employed a titanium(IV) isopropoxide (Ti(O-*i*-Pr)$_4$) to catalyze the direct coupling of carboxylic acids to free amines (Scheme 1.15 A). Phenylacetic acid was coupled to unactivated and activated aliphatic amines at good yields. Notably, increased sterics at the α position resulted in negligible changes in yield, suggesting an increased steric tolerance when compared to his hafnium catalyzed protocol. Furan-2-carboxylic acid was coupled to benzylamine at 72 % yield, suggesting aromatic carboxylic acids were viable amide precursors as well. Lastly, several *N*-Boc protected α amino acids were coupled to benzylamine generate the corresponding amides in good yields with full stereoretention. Huang's protocol employed air-stable bis(cyclopentadienyl)titanium dichloride (Ti(Cp)$_2$Cl$_2$) as an alternative catalyst towards the deoxyamidation of carboxylic acids (Scheme 1.15 B). While the protocol was able to couple benzoic acid derivatives to benzylamine, it was observed to be highly sensitive to electronic effects. This electronic sensitivity was also observed with respect to amine coupling partners. Indeed, while the coupling of aniline to phenylacetic acid resulted in trace amide formation, the corresponding coupling to 4-methoxyanaline resulted in an isolated amide yield of 50 %. The coupling *N*-Boc protected α amino acids to benzylamine generated the corresponding amides at more moderate yields when compared to Adolfsson's Ti(O-*i*-Pr)$_4$ catalyzed protocol. However, in the case of each peptide formation there was a complete retention of stereochemistry.

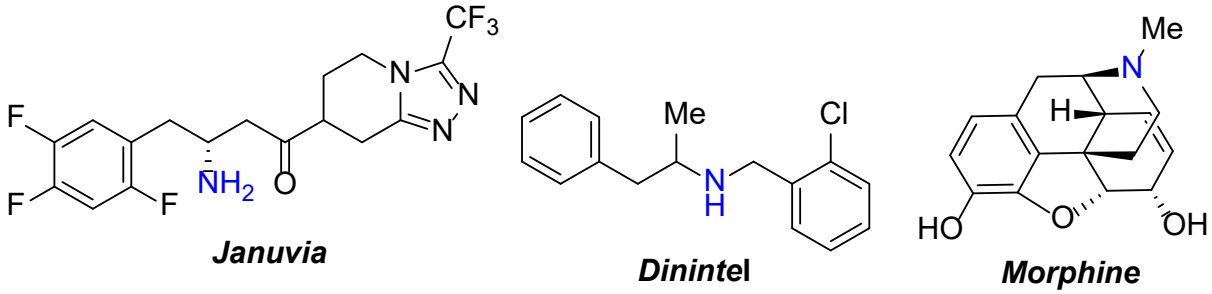
1.1.5 Summary of Current Deoxyamidations & Future Considerations

Due to their ubiquitous nature in biologically active compounds, the development of new peptide bond forming protocols remains an area of continued interest for synthetic chemists. Currently, when employing the ideal carboxylic acid precursor, peptide bonds are formed either through a mediated process through the use of carbodiimides[6], uronium[7] salt, or phosphonium[8] salt activating reagents. While efficient and straightforward, such synthetic platforms relay on the use of reagents that are known allergens, can require significantly anhydrous conditions and can present a significant explosive hazard. Peptide synthesis can sometimes be challenging as well with such technologies, as some commonly employed protecting groups are not fully tolerated and or can result in greater degrees of optical erosion. Additionally, asymmetric synthesis requires additional additives or unique reagents to suppress racemization. Lastly, as these methods require the use of stochiometric reagents, they are limited in terms of atom economy and the generated by-products can sometimes be difficult to remove. Organoboron catalyzed protocols offer an environmentally friendly and atom economical alternative, generating water as the sole by-product. Additionally, this synthetic platform offers increased stereocontrol without the need for racemization suppressants. However, the degree of stereocontrol can vary based on the organoboron employed. In this regard transition metal catalyzed protocols can provide an enhanced degree of stereocontrol; however the bulk of these technologies require costly catalysts. *A noteworthy addition to the current peptide synthetic "toolbox" would be a method capable generating amides in high yields while tolerating common motifs employed in peptide synthesis. Additionally, the method must be run under ambient conditions as to avoid peptide racemization. Furthermore, this technology should employ bench-stable and cost-effective reagents. Lastly, to improve overall atom economy the coupling system would ideally serve a dual purpose reagent capable of facilitating both direct and indirect deoxyamidation.*

1.2 Deoxyaminations of Alcohols Towards Amine Synthesis

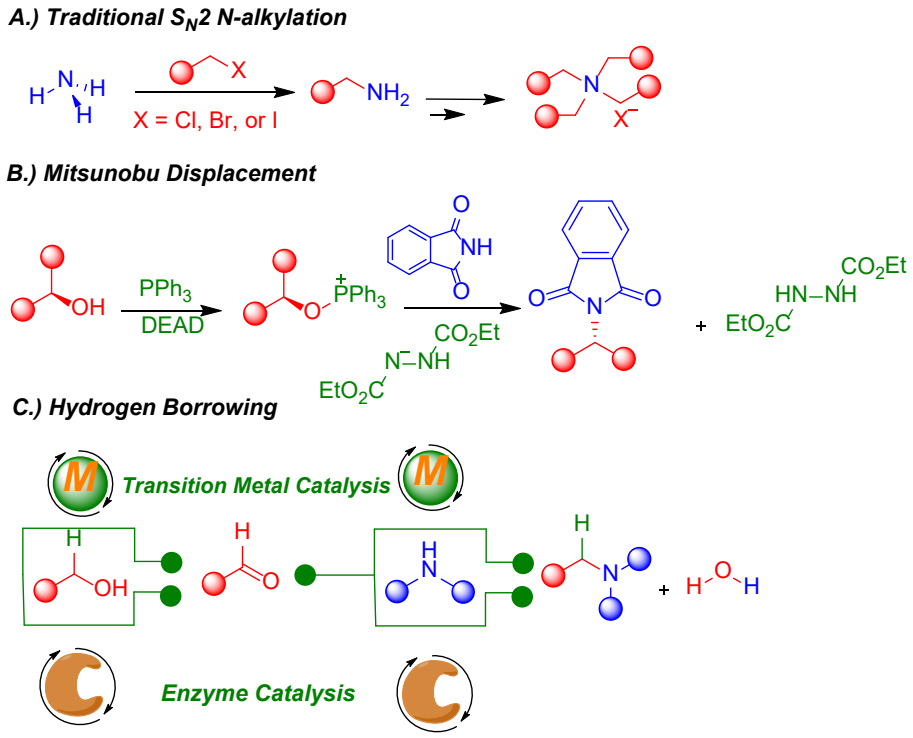
1.2.1 Introduction

Amines are ubiquitous in pharmaceutical compounds with many FDA approved drugs possessing the nitrogen-containing moiety in their chemical structure (Scheme 1.16).



Scheme 1.16 : Examples of FDA Approved Amine-Containing Drugs

Traditionally, amines are accessed via the direct substitution reaction with alkyl halide electrophiles (Scheme 1.17 A), however this synthetic method possesses poor selectivity owing to unwanted polyalkylation. Additionally, the use of alkyl halides as *N*-alkylation agents holds issue due to the reagents' inherent instability. In contrast, the use of alcohols represents an ideal alternative owing to their stability and abundance in nature. As such, much attention has been placed on the development of deoxyaminative technologies towards the generation of amines (primary, secondary, and tertiary) from alcohol precursors. Such synthetic platforms can be broadly divided into three subsets, the first of which being phosphonium-based technologies. Similar to the deoxyamidation technologies presented by Castro and Frøyen, phosphonium deoxyaminations[23] are centered on a P = O bond formation driving force, and such technologies in the literature focus on providing additional enhancements to the classic Mitsunobu reaction (Scheme 1.17 B) which allows indirect access to primary amines selectively via the Gabriel intermediate. The second and third subsets are transition metal catalyzed[24] and bio/enzyme[25] catalyzed deoxyaminations which can allow for the generation of various *N*-alkylated amines through a "hydrogen borrowing" strategy (Scheme 1.17 C).

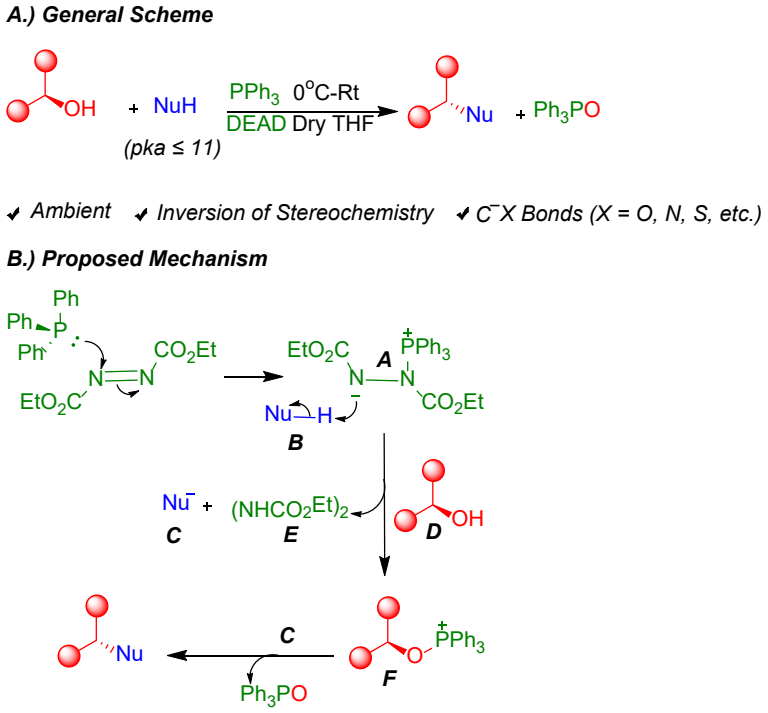


Scheme 1.17 : Deoxyaminations of Alcohols Traditional Vs Recent Examples

1.2.2 Mitsunobu Technologies

Since its original development by Oyo Mitsunobu in the 1960's, the Mitsunobu reaction persists as an essential tool employed by synthetic chemists seeking to form new carbon-heteroatom bonds from stable alcohol precursors.[23a] The original reaction was facilitated through the combination of PPh_3 and diethylazodicarboxylate (DEAD) and proposed to go through a concerted-type mechanism (Scheme 1.18). Specifically, the initial activation of DEAD by PPh_3 generates a ylide-type species ***A*** with a nitrogen anion and a positively charged phosphonium moiety. Upon introduction of the proper pronucleophile ***B*** ($pK_a \leq 11$) the negatively charged nitrogen abstracts a proton from the pronucleophile generating the conjugate base ***C***. At the same time the lone pair from the alcohol ***D*** coordinates into the electrophilic phosphonium species liberating the DEAD-byproduct ***E*** and generating the key alkoxyphosphonium intermediate ***F***. Subsequent nucleophilic attack by ***C*** converts ***F*** into the desired product forming the new carbon-heteroatom. The final step of the mechanism consists of an S_N2 nucleophilic displacement reaction,

in the case of chiral alcohol starting materials, the Mitsunobu reaction will result in an inversion of stereochemistry upon product formation.

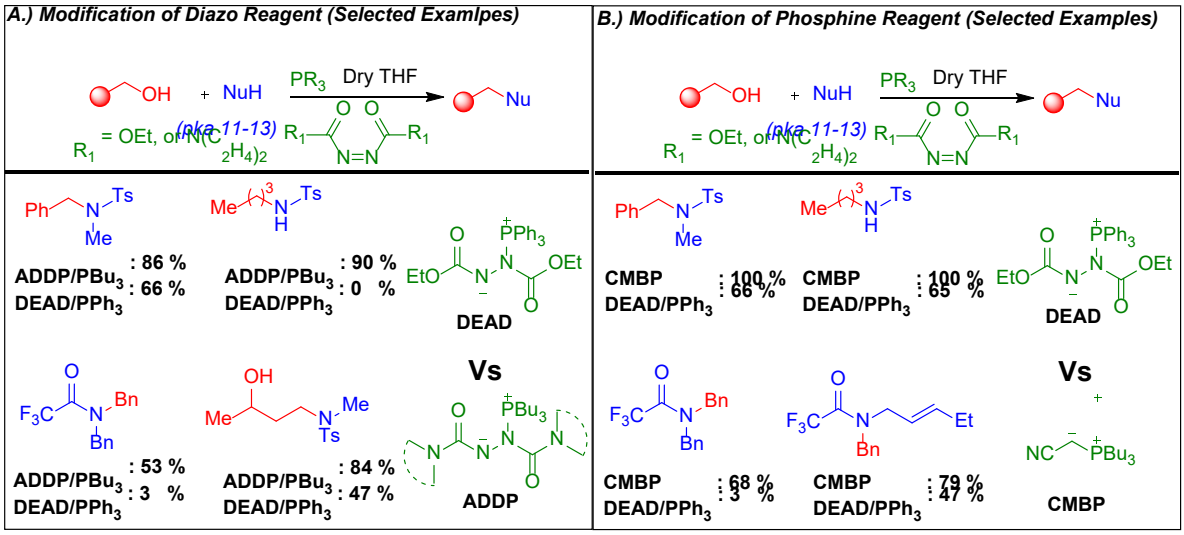


Scheme 1.18 : The Mitsunobu Reaction

While the Mitsunobu reaction is a common and efficient method for the formation of new carbon-heteroatom bonds from alcohol precursors, the original technology was observed to have two key drawbacks. First, the reaction is known to have a very specific pK_a restriction thereby limiting the pronucleophile scope significantly. Most nitrogen containing pronucleophiles typically possess a pK_a >> 11. Second, as the reaction requires the stochiometric use of PPh_3 and DEAD, this places significant strain on the technology's atom economy, and the corresponding triphenylphosphine oxide (Ph_3PO) by-product causes difficulties with respect to purification.[26] Over the past twenty years, numerous groups have worked to modify the original Mitsunobu conditions to circumvent these inherent drawbacks.[23b-l] Specifically, the pK_a restriction has been tackled either through the modification of the original PPh_3/DEAD or through the employment of

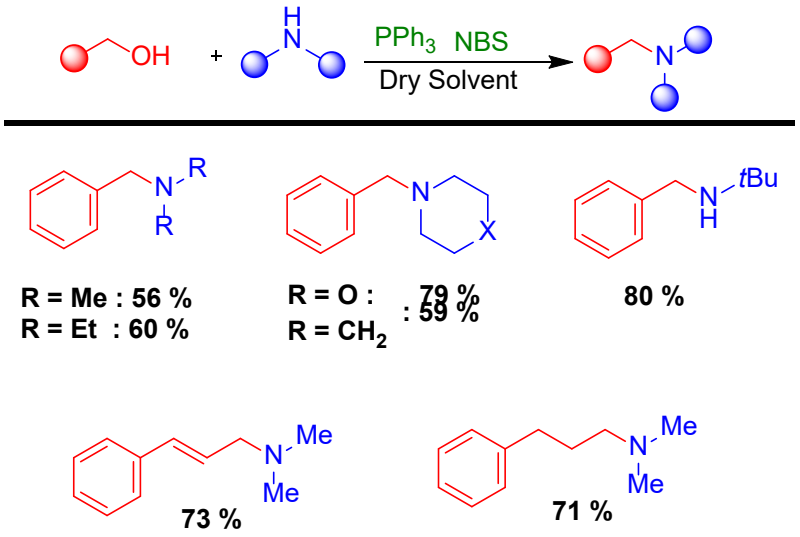
new phosphonium-based coupling systems. Additionally, several catalytic Mitsunobu designs have also been developed to improve upon the overall atom economy of the reaction.

Seminal works (Scheme 1.19) by Ito illustrated that either through structural modification of the diazocarboxylate activator[23b] or phosphine reagent,[23c] the pK_a restriction of the Mitsunobu reaction could be increased by several orders of magnitude ($pK_a \leq 13$). Initially, Ito found that by exchange the carboxylate moiety of the diazo reagent for a piperidine motif, generating the corresponding 1,1′-(azodicarbonyl)dipiperidine (ADDP), the pronucleophile scope could be expanded to include weakly acidic sulfonamides ($pK_a \approx 11.7$), Michael donors ($pK_a \approx 13.3$), and amides ($pK_a \approx 13$). Presumably, the increased localization of the negative charge on the diazo nitrogen increased the initial Mitsunobu ylides' corresponding basicity. To confirm the utility of this modification for less reactive pronucleophiles, a competition study was performed with a series of various alcohols both under traditional Mitsunobu conditions (PPh_3/DEAD) and Ito's own Mitsunobu method employing ADDP with a tributylphosphine (PBu_3) reagent (Scheme 1.19 A). From the initial deoxyamination of benzyl alcohol via a *N*-benzyl-*N*,4-dimethylbenzenesulfonamide the difference in reactivity between the two Mitsunobu systems began to be seen. Indeed, while under Ito's system sulfonamides served as viable pronucleophiles generating the deoxyaminated product at excellent yields, the traditional system generated the desired products in more moderate yields and in some cases not at all. While more basic amides were generated in moderate yields under Ito's system, following traditional Mitsunobu conditions only generated the desired product in trace amounts. Lastly, Ito further demonstrated the utility of his system through the enhanced chemoselective deoxyamination of diol substrates. Specifically, the primary hydroxy motif of 1,3-butanediol was chemoselectively deoxyaminated at twice the amount compared to traditional conditions. This was presumed to be due to enhanced steric crowding in the ADDP ylide resulting in a more chemoselective hydroxy coordination step to the electrophilic phosphine center. Building from this initial work, Ito designed an alternative phosphine ylide reagent that served the dual purpose of converting the alcohol into the key alkyloxyphosphonium species as well as priming the corresponding pronucleophiles (sulfonamides, amides, etc.) for nucleophilic displacement of the alkyloxyphosphonium. The scope of this technology (Scheme 1.19 B) was observed to be comparable to his previous ADDP/PBu_3 system and generated the deoxyaminated products at significantly higher yields when compared to the traditional conditions.



Scheme 1.19 : Ito's Pronucleophile Expansions.

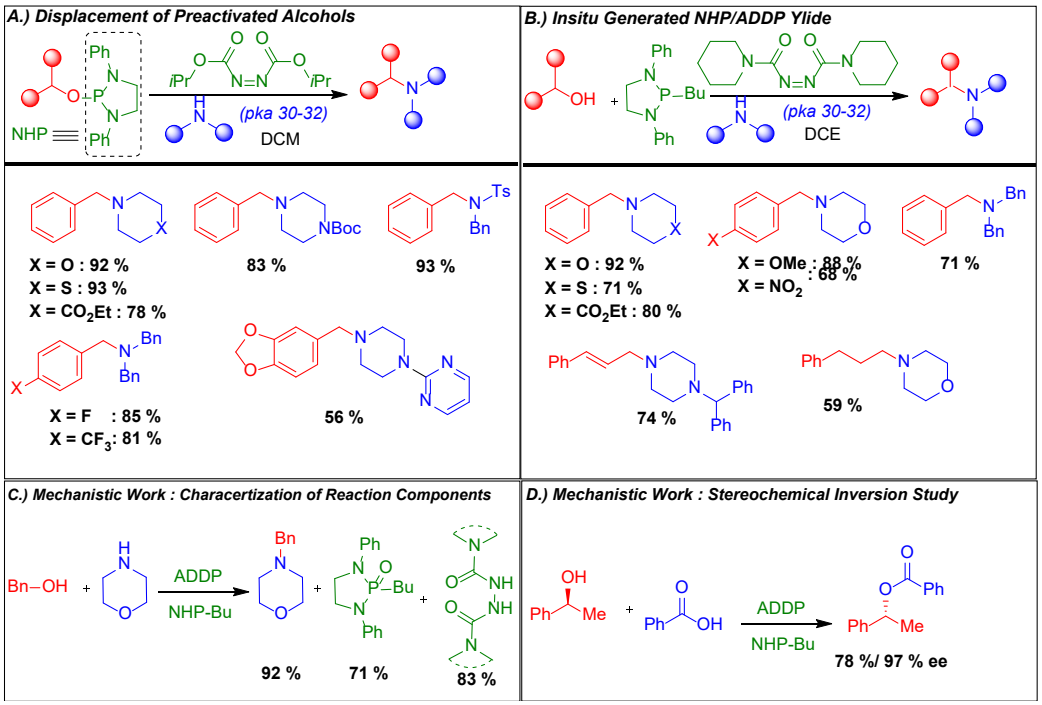
Around the same time, through the use a PPh_3/NBS coupling system, Frøyen presented a Mitsunobu reaction devoid of diazocarboxylate activating reagent (Scheme 1.20).[231] Frøyen initially probed the coupling of benzyl alcohol to secondary unactivated aliphatic (cyclic and acyclic) amines. Both dimethylamine and diethylamine pronucleophiles generated the corresponding tertiary amines in 56% and 60% yield, respectively. Cyclic amine coupling partners, such as morpholine and piperidine, generated the deoxyaminated products at 79% and 59%, respectively. It was noted that Frøyen reported only one example of primary amine coupling via the use of *tert*-butylamine. As the corresponding secondary amine was isolated in 80% yield, the lack of primary amine coupling partners could be attributed to uncontrolled polyalkylation. Lastly, the alcohol scope was observed to include allylic alcohols and unactivated alcohols as well. The proposed mechanism was found to follow the initial *in situ* formation of the phosphonium reactive species presented in Frøyen's previous works.[8f-I] While the final step in the proposed deoxyamination follows a standard S_N2 displacement of the alkyloxyphosphonium, based on Frøyen's subsequent deoxyiododination[27] and dexoynitration[28] of alcohols, intermediary halogenation or a penta-coordinated intermediate was not ruled out.



Scheme 1.20 : Frøyen's Free Amine Deoxyamination Via PPh_3/NBS (Selected Examples)

More recently, Huang developed a novel Mitsunobu capable of employing basic free amines (Scheme 1.21)[23e-f] via the use of diazaphosphites[23e] (Scheme 1.21 A) or through the use of a highly nucleophilic *N*-heterocyclic phosphine (NHP)-butane[23f] in the presence of ADDP (Scheme 1.21 B). Huang's initial Mitsunobu protocol first required the pre-activation of alcohols by their transformation into diazaphosphites. Due to the inherent nucleophilicity of such compounds upon their introduction to diazocarboxylate reagents such as diisopropyl azodicarboxylate (DIAD), Huang presumed that the corresponding negatively charged *N*-centered anion of the ylide would be basic enough to facilitate the use of free amines as pronucleophiles (Scheme 1.21A). Indeed, Huang initially probed the deoxyamination of various benzyl alcohols with both free and *N*-protected secondary amines. Notably, several morpholine derivatives behaved as viable pronucleophiles, with the formation of ethyl 1-benzylpiperidine-4-carboxylate at 78 % illustrating an ambient deoxyamination. 4-Fluorobenzyl alcohol and 4-trifluoromethyl benzyl alcohol were coupled to dibenzylamine at 85% and 81%, respectively, thereby demonstrating the method's tolerance of mild to strong electron withdrawing groups. To further demonstrate the utility of this initial protocol Huang used this approach to facilitate the formation of piribedil, a known antiParkinsonian agent in 56% yield. In the same year Huang presented a modified technology that did not require the conversion of alcohols into diazaphosphites, but rather generated the highly basic ylide intermediate *in situ* the interaction between ADDP and a highly nucleophilic NHP-butane (Scheme 1.21 B). The new protocol demonstrated comparable reactivity

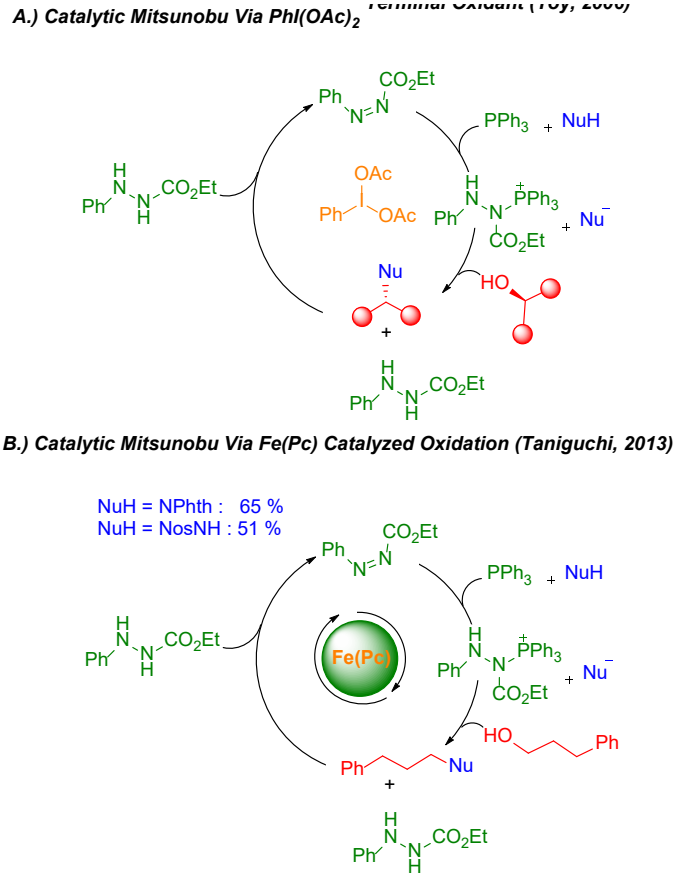
to its diazaphosphite-based precursor with respect to the deoxyamination of benzylic alcohols. However, a noted difference was that the alcohol scope for the NHP-butane/ADDP ylide system was found to include allylic alcohols and unactivated alcohols generating the deoxyaminated product at good to moderate yields, respectively. It was noted that with respect to both technologies, Huang was unable to mediate poly-*N*-alkylation, thereby limiting nitrogen source scope to secondary amines. Through both the isolation/characterization of all reaction products (Scheme 1.21 C) as well as the performed stereoinversion experiment with (*S*)-phenylethyl alcohol, Huang proposed that the mechanism of both reactions most likely mirrors the traditional Mitsunobu reaction pathway (Scheme 1.21 D).



Scheme 1.21 : Huang's Mitsunobu Pronucleophile Expansions

As mentioned previously, the original Mitsunobu technology also suffers from inherently poor atom economy due to its stochiometric use of both phosphine and diazocarboxylate reagents. However, the past twenty years has observed the development of several seminal works aimed at tackling this issue through the development of various catalytic Mitsunobu protocols.[23h-k] The first report of a catalytic Mitsunobu synthetic platform was presented by Toy (Scheme 1.22 A).[23h] The method only required a catalytic amount of diazocarboxylate through the use of (diacetoxyiodo)benzene ($PhI(OAc)_2$) as a terminal oxidant. While initial screening demonstrated

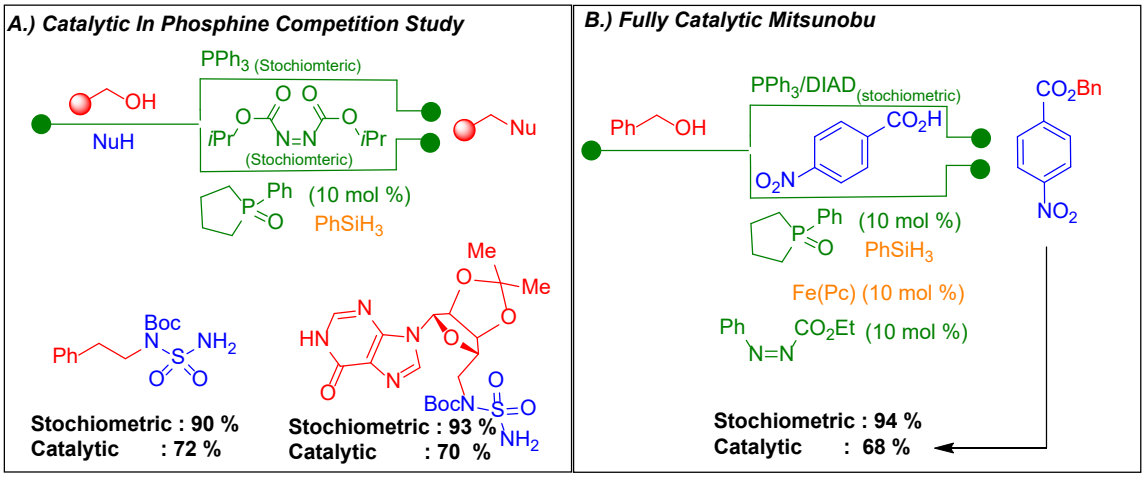
that $PhI(OAc)_2$ was incapable of recycling commonly used DIAD, by exchanging one of the carboxylate motifs for a phenyl ring, catalysis was achieved. While the scope of this technology placed special emphasis on the traditional esterification reaction, Toy's work provided the initial foundation from which several currently published catalytic Mitsunobu technologies take inspiration.



Scheme 1.22 : Mitsunobu Technologies, Catalytic in Diazocarboxylate

An example of this is the subsequent work performed by Taniguchi who developed a diazo-recycling protocol based on the use of an iron phthalocyanine (Fe(Pc)) catalyst under aerobic conditions (Scheme 1.22 B).[23i] While this method focused largely on the coupling of alcohols to carboxylic acids, both phthalimide (NPhth) and *N*-benzyl-2-nitrobenzenesulfonamide (NosNH) were reacted with 3-phenylpropanol, generating the corresponding deoxyaminated products at 65% and 51% yield, respectively.

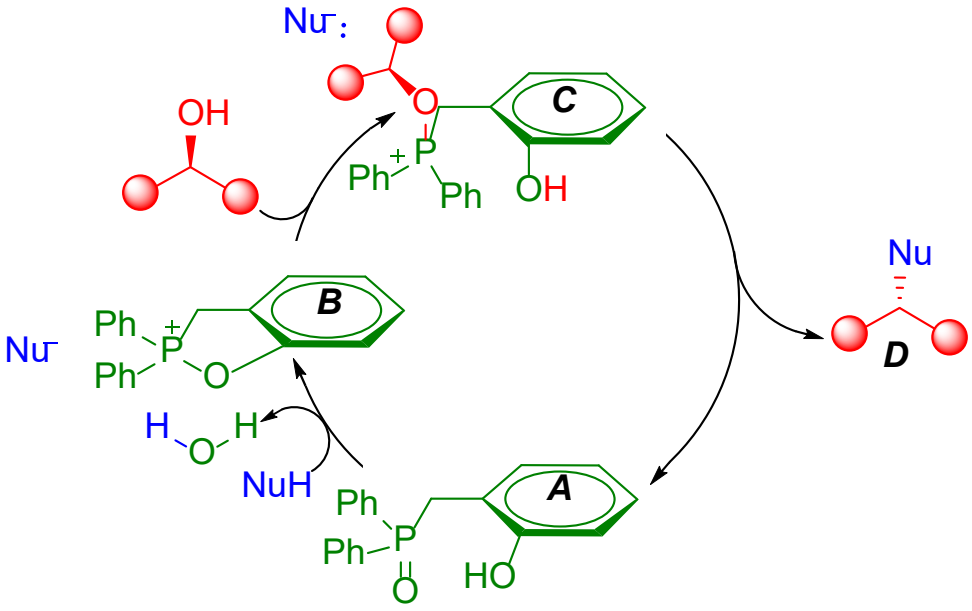
Inspired by the seminal works of Toy[23h] and Taniguchi,[23i] Aldrich[23j] developed two separate catalytic Mitsunobu technologies (Scheme 1.23). The first technology was conducted with catalytic use of a phosphine oxide pre-catalyst that was activated and recycled via a phenylsilane terminal reductant. Once optimized, Aldrich conducted a competition study to compare the new catalytic Mitsunobu to traditional stochiometric DEAD conditions (Scheme 1.23 A). While the scope of the esterification represented the bulk of the investigated scope, *N*-Boc protected sulfonamines were investigated as potential nitrogen sources. Stochiometric DEAD conditions resulted in approximately 20% increase in yield when compared to Aldrich's catalytic-in-phosphine protocol. However, it should be noted that unactivated linear and carbohydrate-based alcohols were deoxyaminated in good yields, demonstrating the potential for Aldrich's initial catalyzed protocol as an additional atom economical Mitsunobu alternative.



Scheme 1.23 : Catalytic Mitsunobu Reactions By Aldrich

Encouraged by the results of his initial catalytic protocol, Aldrich decided to probe as to whether or not Toy's[23h] and or Taniguchi's[23i] diazocarboxylate recycling conditions could align with his catalytic phosphine technology. Gratifyingly, Aldrich discovered that his technology tolerated both previous diazocarboxylate strategies providing the first example of a fully catalytic Mitsunobu reaction through the tandem use of phenylsilane reductant and either oxidation system employed by Toy or Taniguchi (Scheme 1.23 B). Following the same trend observed in competition study performed with respect to his catalytic phosphine protocol, the fully catalytic Mitsunobu technology was found to facilitate the esterification of alcohols at more

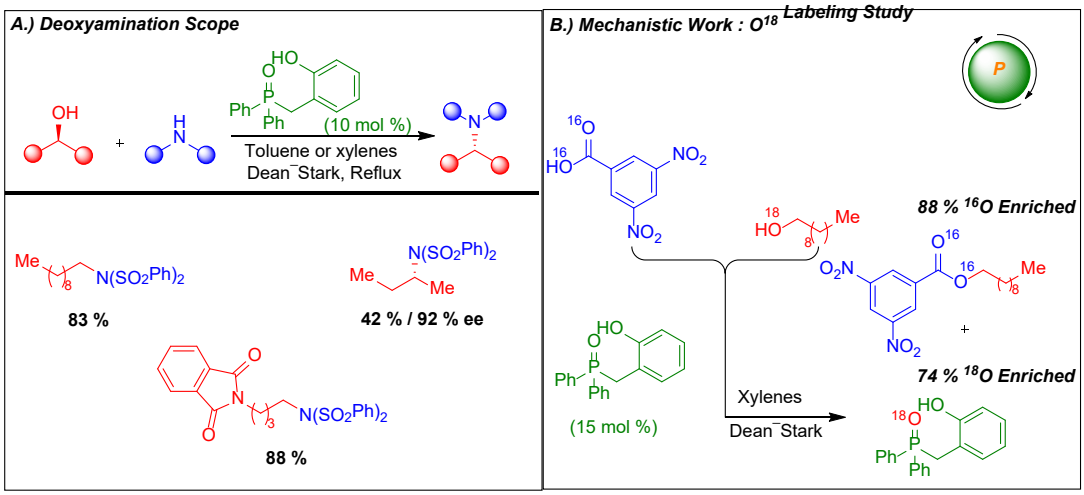
moderate yields when compared to stochiometric DEAD conditions. While the seminal works of Toy, [23h] Taniguchi, [23i] and Aldrich[23j] have laid a foundation for the development of catalytic Mitsunobu technologies, they all held a significant limitation with respect to atom economy in that a terminal oxidant and or reductant was needed to drive the catalytic cycle forward. Recently, this limitation was circumvented by Denton[23k] developed a redox neutral Mitsunobu protocol through the use of a novel phosphine organocatalyst (Scheme 1.24).



Scheme 1.24 : Organocatalytic Redox Neutral Mitsunobu Reaction

It was noted that classic Mitsunobu pronucleophiles such as benzoic acid ($pK_a \approx 5$) could not promote measurable catalysis, presumably due to insufficient protic activation of the phosphine oxide double bond (Scheme 1.24). Specifically, Denton hypothesized that in the presence of the appropriate Bronstead acid pronucleophile, the phosphine oxide organocatalyst ***A*** would cyclize to generate the phosphonium intermediate ***B***. An incoming alcohol would then coordinate into the electrophilic phosphine moiety of ***B*** generating the alkyloxyphosphonium intermediate ***C***. ***C*** would then collapse generating the final product ***D*** with an inversion of stereochemistry due to nucleophilic displacement by conjugate anion of the original Bronstead acid initiator. Indeed, upon introduction of the 3,5-dinitrobenzoic acid pronucleophile ($pK_a \approx 1.4$) significant catalysis was observed. Due to pK_a restriction, the overall deoxyamination scope was found to be limited

compared to previous catalytic and mediated Mitsunobu technologies[23b-j] with only dibenzenesulfonamides serving as viable nitrogen sources (Scheme 1.25 A). However, dibenzenesulfonamides were coupled to unactivated alcohols at excellent yields. Increasing steric crowding in alcohols was observed to be deleterious as observed by the deoxyamination of (+)-2-octanol only taking place at 42%, there was a complete observed inversion of stereochemistry suggesting a traditional Mitsunobu mechanism. This hypothesis was further supported by Denton's subsequent ^{18}O labeling study (Scheme 1.25 B).



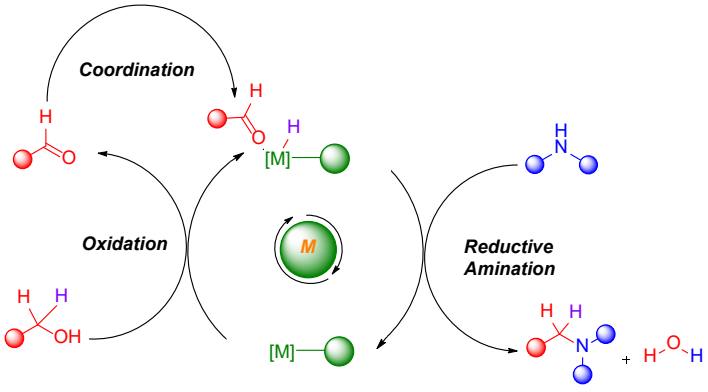
Scheme 1.25 : Redox Neutral Organocatalytic Mitsunobu, Scope and Mechanistic Work

Phosphonium-based deoxyaminations provide an efficient route for the formation of new C-N bonds via a P = O bond formation driving force. Furthermore, while the initial Mitsunobu protocol possessed significant restrictions with respect to pronucleophile scope and atom economy, the past forty years has seen the development of numerous modifications towards the original Mitsunobu conditions addressing such drawbacks. However, such technologies are only capable of addressing either the issue of atom economy or pronucleophile scope alone. Uncontrolled *N*-polyalkylation still remains a consistent issue as well with respect to more nucleophilic pronucleophiles. Lastly, while the Mitsunobu reaction itself is characterized in part by its ability to affect the stereochemistry of chiral alcohols, the final product configuration is always the inverted stereocenter, which can cause issue with respect to asymmetric synthesis if retention of configuration is desired. Alternatively, the use of transition metal catalyzed deoxyaminations[24]

provide an atom economical route towards the formation of new C-N bonds from alcohol precursors, and can provide both a less restrictive pronucleophile scope, and a greater degree of stereochemical control.[24c,24i]

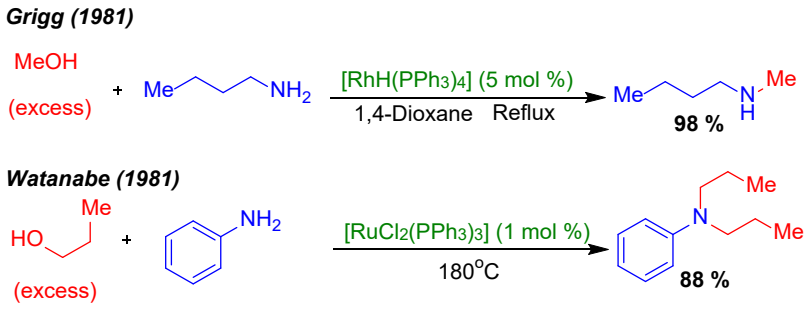
1.2.3 Transition Metal Catalyzed "Hydrogen Borrowing" Technologies

The bulk of transition metal catalyzed deoxyaminations follow a two-part mechanism known as "hydrogen borrowing" (Scheme 1.26).[24e] Generally, such reactions begin with a coordination of the alcohol starting material into a metal catalyst, with subsequent beta-hydride elimination resulting in the initial "hydrogen borrowing" and the *in situ* oxidation of the alcohol into the aldehyde intermediate. Afterwards, free amines (or alternative nitrogen sources) react with the aldehyde intermediate to form the imine which then coordinates into the hydrogen-containing metal catalyst. The "borrowed" hydrogen is then used in a reductive amination step to generate the final *N*-alkylated amine and recycle the transition metal catalyst.[24e]



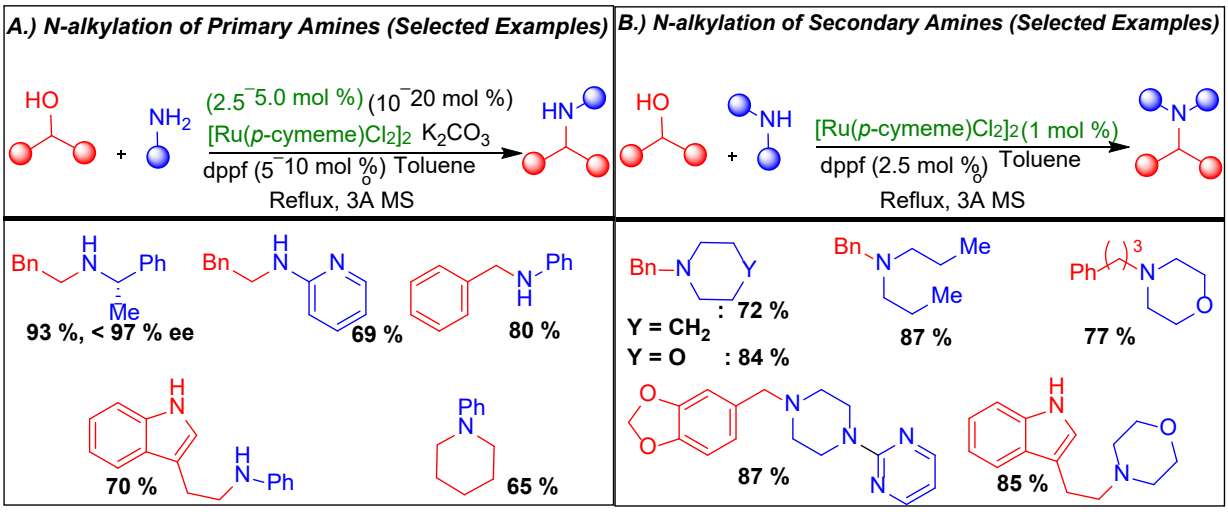
Scheme 1.26 : General Mechanism of Transition Metal Catalyzed "Hydrogen Borrowing",

Seminal works by Grigg[24a] and Watanabe[24b] first demonstrated the utility of transition metal catalysis towards deoxyaminations (Scheme 1.27). However, these initial technologies required excessive heating, were limited to structurally simple alcohols, and suffered from uncontrolled polyalkylation. Over two decades passed before Williams[24c] was able to expand upon these seminal works through the development of a ruthenium-catalyzed deoxyamination (Scheme 1.28).



Scheme 1.27 : Seminal Works By Griggs and Watanabe

Williams initial scope investigation (Scheme 1.28 A) found that alcohols, both activated and unactivated, could be coupled to aliphatic primary amines and aniline derivatives generating the corresponding secondary amines at good to excellent yields. Notably, the coupling of phenylethyl alcohol to a racemic mixture of 1-phenylethan-1-amine not only generated the corresponding secondary amine at 93% but also as the (*S*)-enantiomer with < 97% *ee*. A slight drop in yield was observed with respect to aniline coupling partners, owing to the inherent drop in nucleophilicity. Interestingly, the cyclization of 1,5-diol was catalyzed through the introduction of an aniline nucleophile at 65% yield. Importantly, it was noted that uncontrolled polyalkylation was effectively mediated via the employed catalytic design. Later, Williams developed an analogous technology to expand upon the initial amine scope (Scheme 1.28 B) to include secondary amines.[24d] Various unactivated (cyclic and acyclic) amines were coupled to benzylic and aliphatic alcohols generating the corresponding tertiary amines at good yields.

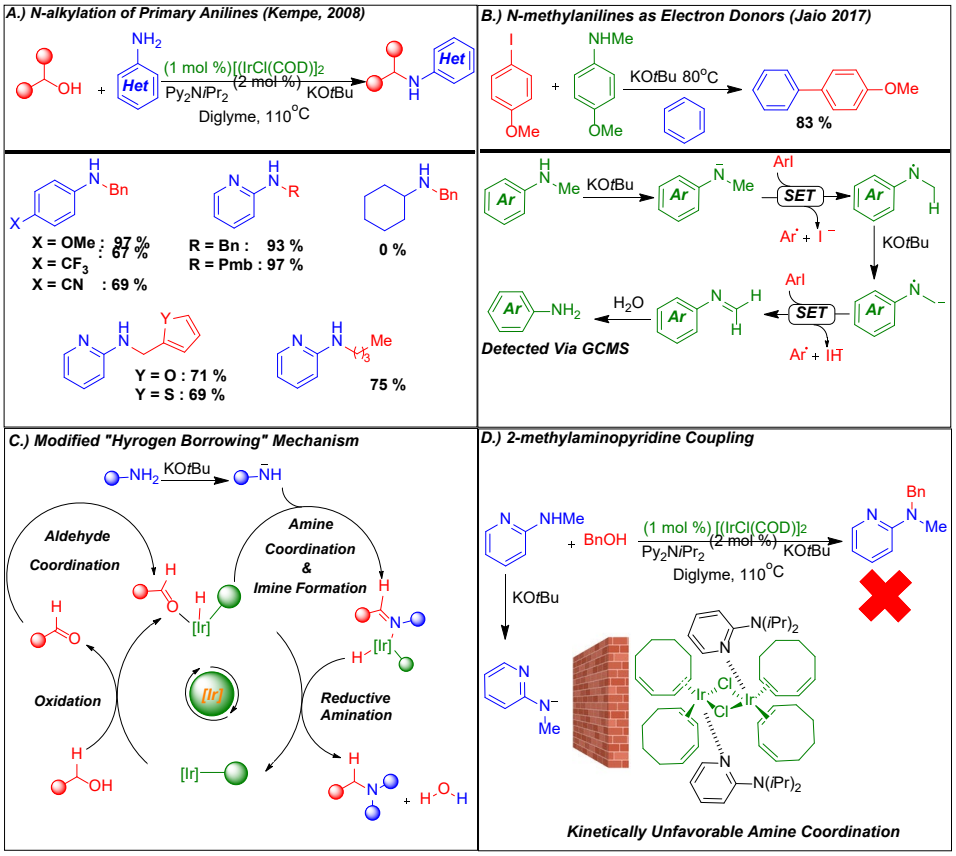


Scheme 1.28 : Ruthenium Catalyzed Deoxyamination of Alcohols By Williams

Furthermore, to demonstrate the synthetic utility of this technology the antiparkinsonian agent Piribedil was produced at 87 % yield. Surprisingly, it was noted that with respect to both technologies, 2-(1H-indol-3-yl)ethan-1-ol was deoxyaminated at good yields with full retention of the indole alkene motif, illustrating a chemoselective reductive amination in the "hydrogen borrowing" catalytic cycle.

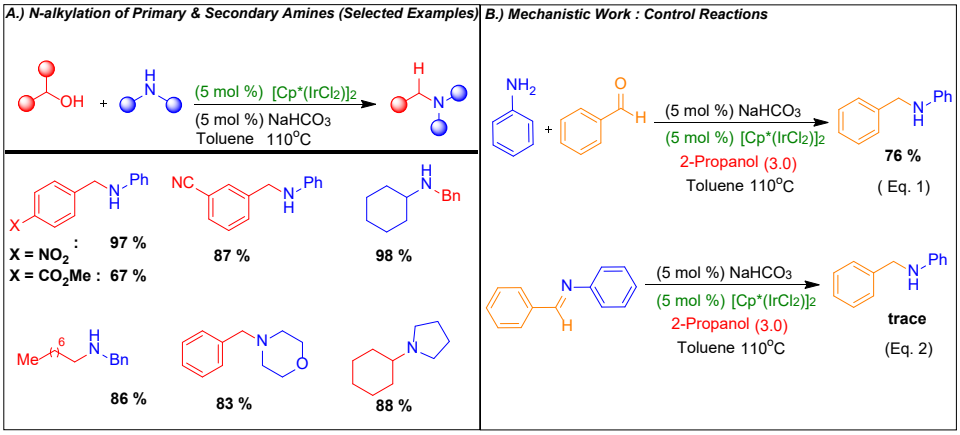
Both Kempe[24f] and Fujita[24g] subsequently reported deoxyaminative technologies catalyzed by iridium simultaneously. Kempe's iridium-catalyzed deoxyamination (Scheme 1.29) was focused on the coupling between various aniline derivatives and alcohols (Scheme 1.29 A). Initially, the technology was observed to be sensitive to electronic tuning effects with respect to aniline coupling partners. Indeed, while 4-methoxyaniline was coupled to benzyl alcohol at 97% yield, deoxyaminations with 4-cyano/4-trifluoromethylaniline generated the corresponding secondary amines at 69% and 67%, respectively. 2-Aminopyridines were tolerated as well and coupled to various activated alcohols in good to excellent yields. Interestingly, while unactivated alcohols could be coupled to 2-aminopyridines, unactivated aliphatic amines were completely unreactive in the employed catalytic platform. During the optimization of the reaction it was noted that potassium *tert*-butoxide (KO*t*Bu) showed significantly higher reactivity when compared to other base additives. Upon a review of recent literature, KO*t*Bu has been cited as a viable base towards the abstraction of protons from aniline compounds (Scheme 1.29 B).[29a] Additionally, as free imine formation occurs readily upon the introduction of anilines to the appropriate carbonyl[29b]

the lack of reactivity with respect to aliphatic amines could suggest a modified "hydrogen borrowing" mechanism. (Scheme 1.29 C). As mechanistic work by Fujita suggests,[24g] it was not the free aniline that generated the imine intermediate, but rather the conjugate anion, post-coordination, into the metal center. Furthermore, the deprotonation step requirement is specific to Kempe's sterically hindered bis(1,5-cyclooctadiene)diiridium(I) dichloride [(IrCl(COD)]$_2$ catalyst. Fujita's deoxyamination employed a different pentamethylcyclopentadienyl iridium dichloride dimer [Cp*(IrCl$_2$)]$_2$ catalyst and gave high reactivity when using aliphatic amine nitrogen sources.[24g] Indeed, the lack of reactivity with respect to coupling 2-methylaminopyridine to benzyl alcohol (Scheme 1.29 D) suggests catalytic reductive amination is largely influenced by the sterics of the incoming amine. Specifically, as KO*t*Bu is expected to deprotonate the N-H bond of 2-methylaminopyridine,[29a] the lack of deoxyamination would suggest that increasing sterics with respect to aniline nitrogen sources is deleterious to reactivity under the [IrCl(COD)]$_2$-catalyzed method.



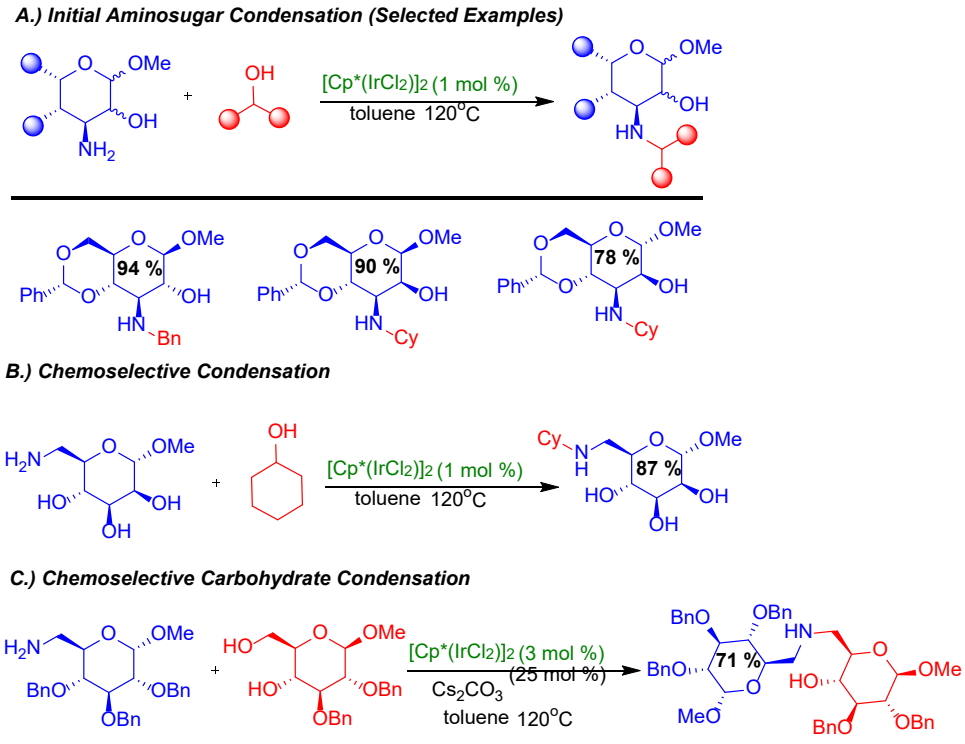
Scheme 1.29 : Mono-*N*-Alkylation of Anilines Catalyzed by [(IrCl(COD)$_2$)]

As stated previously, at the same time that Kempe published his $IrCl(COD)_2$ catalyzed technology, Fujita reported a similar deoxyamination catalyzed by $[Cp^*(IrCl_2)]_2$ with a much broader scope of amine nitrogen sources (Scheme 1.30). Initially, Kempe deoxyaminated a series of benzyl alcohols with various free primary and secondary amines (Scheme 1.30 A). Several benzyl alcohols containing various functional groups sensitive towards reduction, such as nitro, ester, and nitrile motifs, were coupled to aniline at excellent yields, demonstrating the chemoselectivity of the $[Cp^*(IrCl_2)]_2$ reductive hydride transfer step. 1-Octanol and cyclohexanol were deoxyaminated via the coupling to benzylamine, generating the corresponding secondary amines at 86%, and 98%, respectively. Furthermore, such couplings demonstrate a strong resistance to uncontrolled polyalkylation, even in the case of extremely nucleophilic nitrogen sources. Lastly, morpholine and pyrrolidine were alkylated via their coupling to benzyl alcohol and cyclohexanol generating the corresponding tertiary amines in 83% and 88% yield, respectively. To gain insight into the mechanism of the reaction, Kempe performed two separate control experiments (Scheme 1.30 B). First, he coupled aniline with benzaldehyde under his ideal conditions (Scheme 1.30 B, Eq 1), employing 2-propanol as a sacrificial "hydrogen" source and generated the desired secondary amine at 76%, thus supporting the formation of the aldehyde as a key intermediary step in the Ir-catalyzed deoxyamination. However, when the corresponding imine was pre-synthesized and placed under the same conditions, only trace amounts of deoxyamination were observed (Scheme 1.30 B, Eq 2). This suggested that imine formation and reductive amination must both take place in the coordination sphere of the Ir-catalyst to facilitate product formation.



Scheme 1.30 : *N*-Alkylation of Primary & Secondary Amines Catalyzed by $[Cp^*(IrCl_2)]_2$

While the collective works of Williams,[24c-d] Kempe,[24f] and Fujita[24g] provided a comprehensive "toolkit" for facilitating various deoxyaminations, each technology only focused on the synthesis of simple molecules. However, inspired by these seminal works, Cumpstey developed a novel, enantioselective iridium-catalyzed condensation of alcohols and amines (Scheme 1.31) towards the synthesis of aminosugars.[24i] Several hexopyranosides were probed and coupled to cyclohexanol and benzyl alcohol yielding the corresponding aminosugars in good to excellent yields (Scheme 1.31 A). Notably, the condensation was observed to be selective towards primary alcohols when in the presence of competing secondary hydroxy motifs (Scheme 1.31 B). Specifically, the coupling of (2*R*,3*S*,4*S*,5*S*,6*S*)-2-(aminomethyl)-6-methoxytetrahydro-2H-pyran-3,4,5-triol to cyclohexanol generated the corresponding *N*-cyclohexyl derivative at 87% showing a strong preference for coupling over competing cyclization into the 5-membered ring species. Lastly, through the incorporation of an additional cesium carbonate (Cs_2CO_3)[24e] additive, Cumpstey was able to couple two separate carbohydrate molecules to one another chemoselectively (Scheme 1.31 C). Importantly, no epimerization was observed with respect to any of the synthesized aminosugars.

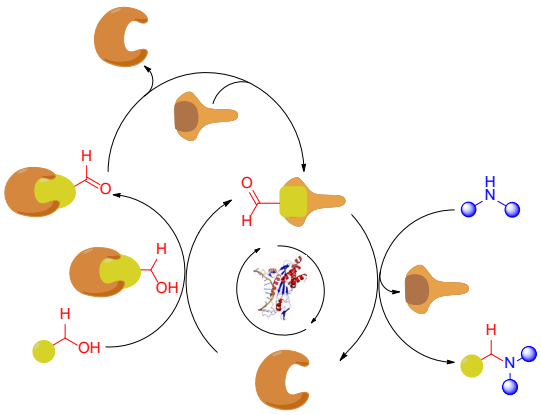


Scheme 1.31 : $[Cp^{*}(IrCl_2)]_2$-Catalyzed Aminosugar Synthesis

Within the literature, transition metal catalysis has demonstrated its value towards the formation of new C-N bonds as an atom economical synthetic platform for deoxyaminative reactions, providing a wide scope in terms of both alcohol starting materials and amine coupling partners. Additionally, several works have illustrated that, through transition metal catalyzed "hydrogen borrowing," amines can be accessed from alcohols not only in high yields but in high degrees of enantiomeric excess with respect to optically active starting materials. However, the scope of such technologies is limited to either secondary or tertiary amines, with known works demonstrating the analogous ammonia reaction, presumably due to competitive coordination into the metal center. Additionally, the bulk of transition metal deoxyaminative literature employs catalysts derived from rare earth metals, thus limiting the applicability of such protocols with respect to industrial scale-up. To circumvent this obstacle and provide a cost-effective atom economical alternative for industrial purposes, the past decade has seen a rise in reports dealing in catalytic deoxyaminations facilitated by naturally occurring and abundant biological enzyme catalysts.

1.2.4 Biocatalyzed/Enzyme Catalyzed "Hydrogen Borrowing" Technologies

Biological catalysis has recently gained attention as not only a cost-effective alternative to transition metal catalysis, due to the inherent specificity involved in enzyme activity,[30] but also as a valuable tool in asymmetric synthesis. When dealing with the enzyme-catalyzed deoxyamination of alcohols, most reports follow the same "hydrogen borrowing" mechanism reported in transition metal catalyzed analogues, exchanging the metal catalyst for two or more enzyme cascade reactions (Scheme 1.32).



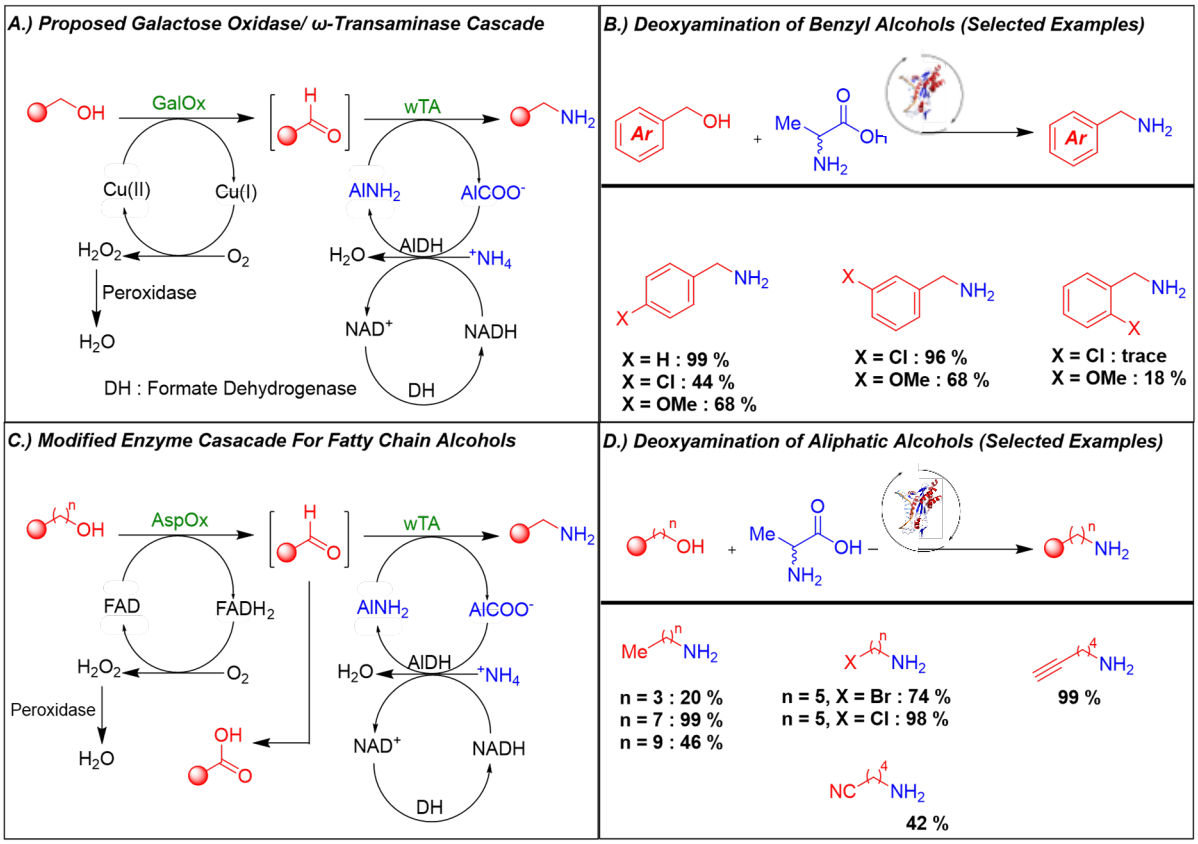
Scheme 1.32 : Enzyme Catalyzed "Hydrogen Borrowing"

In the past decade, a handful of protocols have been reported demonstrating the utility of biocatalysis as a effective route towards enantioselective deoxyaminations.[25] Early works by Faber[25a,25d] and Mutti[25b] provided initial insight into the potential held in biocatalyzed deoxyaminations. Both of their works employed novel oxidation-transamidation enzyme cascades to convert primary alcohols into the corresponding primary amines (Scheme 1.33). The mechanism was proposed to take place via two simultaneous enzyme cascade reactions (Scheme 1.33 A). The initial alcohol oxidation was facilitated through the use of a galactose oxidase (GalOx) enzyme derived from *Fusarium* NRRL 2903, held under aerobic conditions.[31] The subsequent reductive amination was conducted via a simultaneous ω-transaminase (wTA) cycle employing alanine ($AlNH_2$) as the nitrogen source recycled *in situ* from its pyruvate conjugate ($AlCOO^-$) through alanine dehydrogenase (AlDH) and NAD^+/NADH cycle. Faber investigated the scope of this enzymatic cascade by probing conducting a series of deoxyaminations of benzyl alcohol derivatives (Scheme 1.2.18 B). While benzyl alcohol was deoxyaminated in nearly quantitative

yield, the corresponding 4-chloro and 4-methoxy derivatives were aminated at 44% and 68%, respectively. Similarly 3-chlorobenzyl alcohol was aminated at 96%, while 2-chlorobenzyl alcohol was only aminated in trace amounts. Such results suggested that functional group placement on the aromatic ring had a significant influence on reactivity. It was noted that no unactivated alcohol deoxyaminations were reported suggesting a significantly more limited reaction scope when compared to analogous transition metal catalyzed protocols.[24] Surprisingly, no investigation of enantioselective amine synthesis was reported, presumably due to the technology's observed weakness towards increased steric crowding.

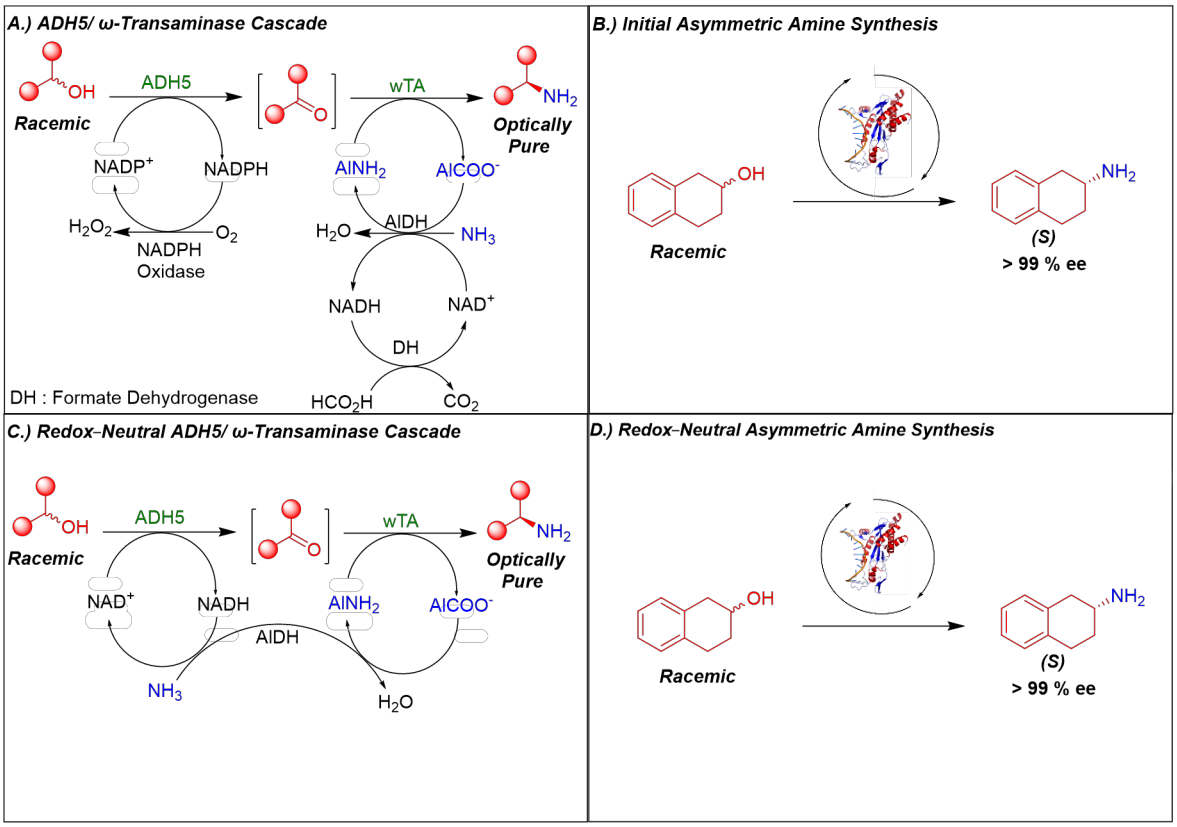
Later, Faber presented a modified enzyme cascade (Scheme 1.33 C), exchanging GalOx for an oxidase derived from *Aspergillus fumigatus* (AspOx) which allowed for the deoxyamination of fatty chain aliphatic primary alcohols (Scheme 1.33 D).[25d] 1-octanol generated the corresponding primary amine at a nearly quantitative yield, longer chain alcohols were observed to be significantly less reactive. Haloalcohols (X = Cl or Br) were tolerated, allowing for the synthesis of aliphatic amino halides in good to excellent yields, thus speaking to the mild nature of the employed nitrogen source. Hex-5-yn-1-ol was aminated in nearly quantitative yield, however the corresponding nitrile analogue compound was aminated at a more modest 42% yield.[32] While reducible, alkynes traditionally are hydrogenated under Birch conditions, making their tolerance with respect to this ambient deoxyamination reasonable.

However, a recent review of literature has shown precedent for the *N*-alkylation of nitriles via alcohols and a hydrogen borrowing strategy,[32] thus providing insight into the poor tolerance shown for cyano-containing alcohols. Several other functional moieties were found to shutdown reactivity including free amino-, hydroxy-, and thiol motifs, potential due to competitive oxidative processes. Additionally, secondary alcohols were found to be non-viable substrates for the modified enzyme cascade.



Scheme 1.33 : Deoxyamination of Alcohols Catalyzed by Oxidase/ ω-Transaminase Cascades

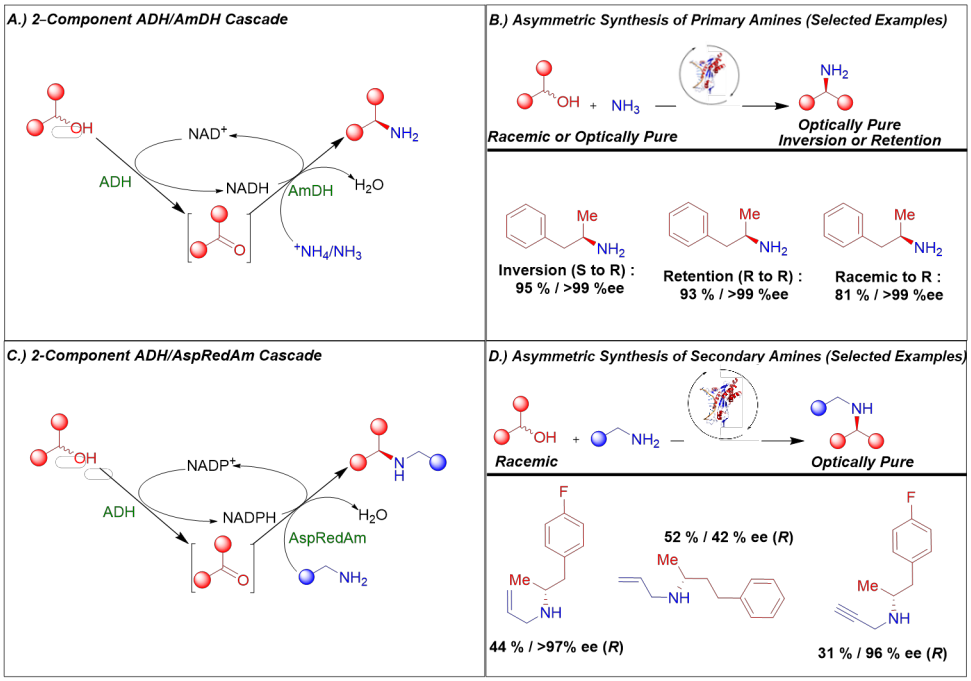
Inspired by Faber's seminal work[25a], Kroutil[25e] developed two multi-enzyme catalyzed networks for the asymmetric deoxyamination of *sec*-alcohols (Scheme 1.34). Specifically, while the transamination sequence mirrors enzyme cascades developed by Faber,[25a,25d] the initial alcohol oxidation sequence is facilitated by an alcohol dehydrogenase (ADH) encoded by the ADH5 gene and regenerated via an NADP+/NADPH cycle (Scheme 1.34 A). Impressively, Kroutil's initial enzyme network was capable of taking racemic alcohol mixtures and generating a series of enantiopure amines (Scheme 1.34 B) via the use of (*R*) or (*S*) selective enantiopure ADHs providing a reagent-saving alternative to Mitsunobu technologies[23] with a higher degree of stereocontrol. Encouraged by these initial results, Kroutil also developed a more straightforward 3-component enzyme cascade that removed the need for external redox reagents (Scheme 1.34 C). Importantly, the redox-neutral cascade was found to show comparable yields to the original network and generated chiral amines at up to 96% enantiomeric excess from racemic alcohol mixtures (Scheme 1.34 D).



Scheme 1.34 : Enantioselective Deoxyaminative ADH/ ω TA Enzyme Cascade

Later, Turner[25f,25c] developed two separate technologies for the collective asymmetric synthesis of primary[25f] and secondary[25c] amines from alcohol precursors (Scheme 1.35). Both technologies follow a 2-component enzymatic design consisting of a specific ADH enzyme to facilitate the oxidation of secondary alcohols into the ketone intermediates with the respective reductive aminations carried out by an amine dehydrogenase (AmDH) and reductive aminase. Turner's first technology employed the use of an ADH/AmDH cascade (Scheme 1.35 A) with only catalytic amounts of nicotinamide coenzyme needed to shuttle the "borrowed hydride" from the oxidative to the reductive step. Impressively, this initial technology provided access to enantiopure amines (% ee > 99%) from racemic alcohol mixtures, as well as the ability to control inversion vs retention of configuration based on the optically pure enzyme(s) employed (Scheme 1.35 B). In subsequent work, Turner developed a modified protocol exchanging AmDH for a reductive aminase derived from *Aspergillus oryzae* which allowed for the first enzyme-catalyzed "hydrogen borrowing"-based asymmetric coupling of chiral alcohols to primary amines (Scheme 1.35 C). While the corresponding secondary amines were synthesized (Scheme 1.35 D) in more modest

yields, the coupling of primary amines to alcohols was found to exhibit the same degree of enantioselectivity as the ADH/AmDH cascade.



Scheme 1.35 : Asymmetric Synthesis of Chiral Amines Via 2-Component Enzyme Cascade

1.2.5 Summary of Current Deoxyaminations & Future Considerations

Amines are ubiquitous in naturally occurring biologically active products and in pharmaceuticals. In turn, alcohols represent ideal precursors for amine synthesis due to their stability and natural abundance. Within the current literature, deoxyaminative methodologies can be divided into three categories which are i.) Mitsunobu/phosphonium[23] protocols, ii.) transition metal catalyzed[24] "hydrogen borrowing" methodologies, and iii.) bio/enzyme-catalyzed[25] "hydrogen borrowing" technologies. Since its creation, the Mitsunobu reaction remains a staple in the synthetic chemist's "toolbox". However, the reactions' traditional pronucleophile pK_a restriction ($pK_a \leq 11$) can present a significant challenge, specifically with respect to deoxyaminations as most viable nitrogen-based pronucleophiles possess a $pK_a > 11$. While several technologies have been developed that have expanded the Mitsunobu scope to include more basic pronucleophiles,[23b-c, 23e-f] such methods require the use of unique diazo activators, and/or phosphine reagents, or pre-activation of the alcohol. "Hydrogen Borrowing" catalytic strategies

offer a more atom-economical approach towards deoxyaminations with a greater degree of enantioselectivity. Still, transition metal catalyzed technologies require costly metals and excessive heating which can hold issue with sensitive functional motifs. Enzyme catalysis offers the potential for full stereocontrol, however the need for multiple enzyme cascades can lead to unwanted side-reactivity, thus limiting the functional tolerance of such protocols. Additionally, the cost and time associated with respect to the purification steps required to make the necessary enantioselective biocatalysts can present significant issues with respect to large-scale applications.[25b] Lastly, while "hydrogen borrowing" technologies have collectively provided access to routes towards the generation of primary to tertiary amines, there currently exists no single protocol, transition metal or enzyme catalyzed, whose scope includes the *N*-alkylation of all amines. *A noteworthy addition to the current deoxyaminative "toolbox" would be a technology capable of activating alcohols with the efficiency of the Mitsunobu and that does not possess the same pronucleophile restrictions. Ideally, this method would also possess some manner by which to circumvent the inherent poor atom economy associated with current Mitsunobu technologies. Lasty, the technology should provide access (directly or indirectly) to all N-alkylated amines, ideally in a cost-effective manner.*

CHAPTER 2. DEOXYAMIDATION OF CARBOXYLIC ACIDS VIA IN SITU GENERATED PHOSPHONIUM REACTIVE SPECIES : SYNTHESIS OF AMIDES & ACYL PHTHALIMIDE DERIVIATIVES

2.1.1 Introduction

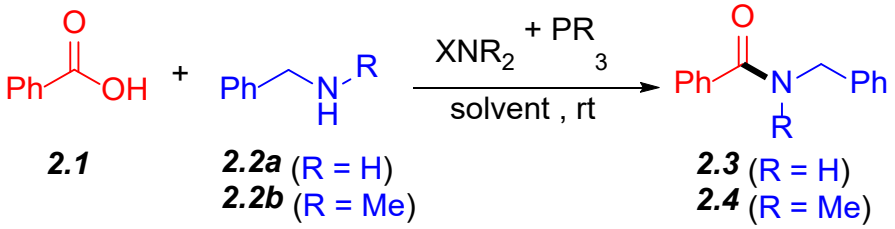
The carboxylic acid motif represents an ideal precursor for amide synthesis due to the stability of such compounds as well as their natural and commercial abundance. While effective for select substrates, the direct thermal condensation of carboxylic acids and amines suffers from a large kinetic energy barrier, which has led to the development of numerous technologies focusing on the activation of carboxylic acids to promote a more ambient and kinetically favorable deoxyamidation.[6-10] Inspired by the seminal work conducted by Frøyen,[8f] we hypothesized that a change in the molecular framework of the *in situ* generated phosphonium reactive species would not only allow for an ambient free amine coupling, but could also "open-the-door" to new types of reactivity, similar to the differences of reactivity observed in Castro's various works.[8a-e] Indeed, *N*-chlorophthalimide (NCPhth) activated by PPh_3 generated two reactive phosphonium salt species capable of facilitating a wide scope of deoxyamidations between various amines and carboxylic acids.[33] Furthermore, through the addition of a base additive, the deoxyamidation was extended to include the direct installment of the phthalimide (NPhth) motif, generating the corresponding acyl phthalimide derivatives. Lastly, to provide mechanistic insight with regards to our own deoxyamidation, as well as the work previously conducted by Frøyen,[8f] a series of NMR ($^{1}H/^{31}P$) and high-resolution-mass spectrometry (HRMS) studies were conducted to better characterize the proposed phosphonium reactive species.

2.1.2 Reaction Optimization: Amide Formation

We began our investigation using benzoic acid (***2.1***) as our carboxylic acid substrate and both benzylamine (***2.2a***) and benzylmethylamine (***2.2b***) as I° and II° amine substrates. Optimal reaction conditions (Table 2.1, entry 1) were obtained using 1.5 equiv of PPh_3 and NCPhth at room temperature for 12 h. Primary amine ***2.2a*** consistently afforded the corresponding amide in better yield than secondary amine ***2.2b***. Presumably, the increase in steric hindrance is responsible for the reduced yield. The use of other commercially available *N*-haloimides such as NCS, NBS, and

N-iodosuccinimide (NIS) also generated the desired products but in lower yields (Table 2.1,entries 2−4). It was noted that the drop in yield was most drastic in the case of NCS and 2b. A review of literature indicated that undesired deaminative oxygenation of ***2.2b*** was a potential cause for the unusual reactivity.[34] Indeed, a competitive haloamine formation would explain the slight recovery in amide formation with respect to other *N*-halosuccinimides[35] (Table 2.1, entries 3-4). This would also explain Frøyen's choice of secondary amine coupling partners,[8f] which were limited to bulky or aromatic amines whose interaction with NCS would be inhibited by a high energy barrier.[35g] Importantly, control experiments in the absence of phosphine or *N*-haloimide reagents did not provide the desired amides in significant yields (Table 2.1, entries 5 and 6). Screening of other phosphines as suitable activators of NCPhth (Table 2.1, entries 7−9) gave mixed results, while tricyclohexylphosphine (PCy_3, Table 2.1, entry 7) did afford product ***2.3*** in good yields (85%), the formation of product ***2.4*** seems to be lackluster (43%). Similarly, tributylphosphine ($P(n\text{-}Bu)_3$) and tri(*o*-tolyl) phosphine ($P(o\text{-}tol)_3$) proceeded through the reaction but with lower yields (Table 2.1, entries 8 and 9). The increase in the Tolman angle[36] from PPh_3 (145°), PCy_3 (179°), and $P(o\text{-}tol)_3$ (194°) may be preventing the efficient nucleophilic attack of the NCPhth. Finally, the reaction also proceeds efficiently in a variety of anhydrous polar aprotic solvents such as dichloromethane, ethyl acetate, and acetonitrile for the formation of product ***2.3*** (Table 2.1, entries 10−12). Product ***2.4*** is also formed under those conditions but anhydrous acetonitrile provides the best yields at 72% (Table 2.1, entry 12).

Table 2.1: Reaction Optimization. Amide Formation.



2.1 **2.2a** (R = H) **2.2b** (R = Me) **2.3** (R = H) **2.4** (R = Me)

Entry	*R_3P*	*XNR_2*	*Solvent*	*yield[b] (%) (2.3/2.4)*
1	PPh_3	NCPhth	Toluene	**94% (83%)[c]/ 63%**
2	PPh_3	NCS	Toluene	74 %/ 26 %
3	PPh_3	NBS	Toluene	66%/ 54%
4	PPh_3	NIS	Toluene	59%/ 59%
5	None	NCPhth	Toluene	6%/ 0%
6	PPh_3		Toluene	2%/ 2%
7	PCy_3	NCPhth	Toluene	85 %/ 43 %
8	P(*n*-Bu)$_3$	NCPhth	Toluene	57 %/ 42 %
9	P(*o*-tol)$_3$	NCPhth	Toluene	34 %/ 27 %
10	PPh_3	NCPhth	DCM	91 %/ 60 %
11	PPh_3	NCPhth	EtOAc	81 %/ 59 %
12	PPh_3	NCPhth	MeCN	**90%/ 72 % (65%)[c]**

[a]All reactions were performed using 1 mL of anhydrous, solvent, 0.164 mmol (1 equiv) of benzoic acid, 0.246 mmol (1.5 equiv) of *N*-haloimide and phosphine reagents, and 0.492 mmol (3 equiv) of amine substituent. The reactions were performed at room temperature (24 °C) with constant stirring for 12 h. [b]NMR yield obtained using dibromomethane as the internal standard. [c]Isolated yield.

2.1.3 Amide Scope: Deoxyamidations of Benzoic Acid

With the established optimal conditions in hand, we proceeded to first examine the scope of amine substrates ***2*** compatible with our reaction conditions. Gratifyingly, the protocol was efficient for the amidation of a diverse set of I° and II° amines (Figure 2.1). Our protocol was effective for a variety of aliphatic amines (***2.3***−***2.8***) with yields ranging from moderate to excellent. However, the increase of steric hindrance in the α-position of I° alkyl amines has a deleterious effect on yield. Indeed, coupling products ***2.6*** through ***2.7*** were obtained in lower yields as more substituents were added in the α-position. The alkene functionality in oleylamine is tolerated (***2.8***), but isolation of the corresponding amide was challenging using column chromatography. Bulky esters that do not readily transamidate are also tolerated and provided product ***2.9*** in 54% yield (Figure 2.1). Interestingly, both I° and II° aniline derivatives also afforded the corresponding amides (***2.10***−***2.12***) in moderate to good, isolated yields. While aniline reacted in 69% yield, increasing sterics around the nitrogen led to erosion in yield with ***2.11*** and ***2.12*** providing the amides in 56 and 49% yields, respectively. Yet, our protocol seems more efficient at coupling sterically bulky aniline derivatives compared to analogous protocols.[37,38a] Additionally, this methodology possesses a wider scope with respect to secondary amine substrates than similar procedures.[37] Reactions using diphenylamine and *N*-methylaniline worked in moderate yields at 55 and 65%, respectively. Cyclic II° amines also amidated in moderate to good yields with pyrrolidine affording product ***2.15*** in 71% yield, piperidine affording product ***2.16*** in 45% yield, and morpholine generating product ***2.17*** in 41% yield (Figure 2.1).

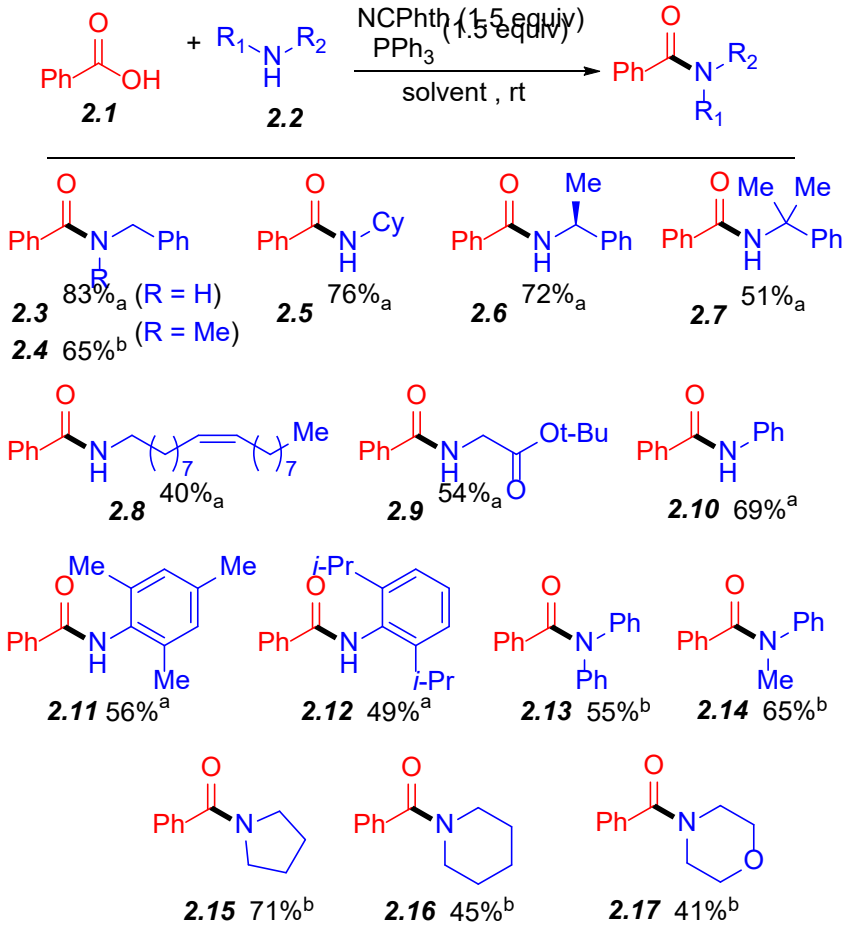


Figure 2.1: Deoxyamidation, Amine Scope.

All reactions were performed in 3 mL of solvent, 2.1 (0.82 mmol) 2.2 (2.4 mmol), NCPhth (1.2 mmol), and PPh3 (1.2 mmol). [a]Reactions performed using toluene as the solvent. [b]Reactions performed using acetonitrile as the solvent. Yields reported are isolated yields.

2.1.4 Amide Scope : Acylation of Primary & Secondary Amines

Next, we examined the compatibility of our optimal reaction conditions with different carboxylic acids and using benzyl amine ***2.2a*** and benzylmethylamine ***2.2b*** as the amine substrates (Figure 2.2). As shown in Figure 2.2, the method enabled the amidation of electron rich (***2.18a/b*** (87%/86%)) and electron poor (***2.21a*** 42% and ***2.24/b*** (40%/73%)) aryl carboxylic acids in good to excellent yields. However, reactivity varied significantly among substrates, and secondary amines seem to sometimes fail to perform the transformation (***2.21b***). Aryl halides provided the desired products in good to excellent yields for both I° and II° amines (***2.21a***, ***2.21b***). Alkyl carboxylic acids were also well tolerated and afforded products in moderate to excellent yields

(***2.22a/b***, ***2.25a/b***, and ***2.26/b***). Protected tryptophan amino acid was also converted into the corresponding amide in moderate yields when coupling with primary amines (***2.23a*** 54% yield) but failed to provide the desired product with secondary amines (***2.24b***) most likely due to amine-induced Fmoc deprotection. Finally, our method enabled the synthesis of antifungal agrochemical Mepronil ***2.27*** from the ortho-substituted carboxylic acid in 55% yield in milder conditions than current approaches.[37d,39]

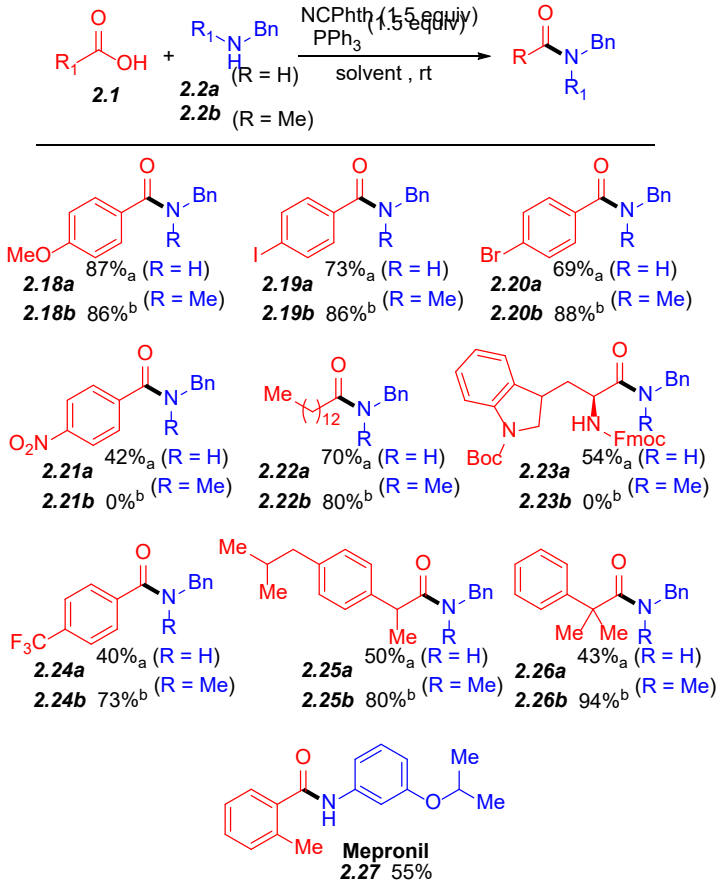


Figure 2.2 : Deoxyamidation. Carboxylic Acid Scope.

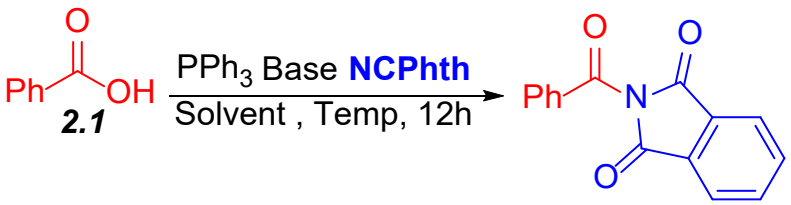
All reactions were performed in 3 mL of solvent, 2.1 (100 mg), 2.2a (3 equiv), 2.2b (3 equiv), NCPhth (1.5 equiv), PPh_3 (1.5 equiv). aReactions performed using toluene as the solvent. bReactions performed using acetonitrile as the solvent. Yields reported are isolated yields.

2.1.5 Reaction Optimization & Scope : Acyl Phthalimide Formation

Another possible transformation we envisioned with our methodology was the direct formation of acyl phthalimides from carboxylic acids in the cases where amine coupling partners are not added to the reaction mixture (Figure 2.3). Acyl phthalimides are important precursors for the formation of the biologically active *N*-,*O*-acetal motifs found in several natural products.[40] Acyl phthalimides also hold merit as potential anxiolytic, antibacterial, and antifungal compounds.[41] Synthetic applications have also been explored using acyl imides as efficient acylating and coupling agents in metal-catalyzed reactions.[42] Lastly, acyl imides have been used as transamidation agents in metal-free methodologies.[43] Initially, strong *tert*-butoxide bases were found to only yield acyl phthalimides in trace amounts in DMF due to competitive reactivity with NCPhth (Table 2.2, Entry 1).[44] Gratifyingly, switching to more delocalized phosphate bases and bulky pyridines improved reactivity significantly (Table 2.2, Entries 2-3).

Further optimization found that the use of 4-dimethylaminopyridine (DMAP) at 80 °C in toluene afforded the best yields (Table 2.2 Entry 5). The use of heat is required here to promote the nucleophilic attack of the phthalimide unto the activated carboxylic acid. Initially, it was believed that the non-nucleophilic base was required to ensure full deprotonation of the benzoic acid, however when employing a 2,6 lutadiene base additive under the same reaction conditions acyl phthalimide formation was significantly lower. Additionally, the base control (Table 2.2, Entry 7) would suggest that the reactivity observed with 2,6-lutadiene (Table 2.2, Entry 6) could be due to background reaction. These observations could suggest that a potential pyridium intermediate species similar to the Steglich esterification[6a] could be the cause for the observed acyl phthalimide formation. Indeed, the phosphine mediated deoxyamidation is sensitive to changes in the steric crowding (Table 2.1, Entries 7-9) of the proposed acyl(oxy)phosphonium intermediate[8f] and *in situ* formation of a pyridinium intermediate would represent a significant decrease in steric crowding, thereby lowering the overall energy barrier towards the installment of the sterically bulky phthalimide motif. Importantly, both PPh_3 and NCPhth were needed in tandem to facilitate the acyl phthalimide formation (Table 2.2, Entries 8-9)

Table 2.2 : Reaction Optimization. Acyl Phthalimide Formation.



Entry	*Base*	*Solvent*	*Temp (°C)*	*Yield[b] (%)*
1	KO*t*Bu	DMF	25	Trace
2	KH_2PO_4	DMF	25	44
3	2,6 lutadiene	DMF	25	40
4	DMAP	Toluene	50	53
5	**DMAP**	**Toluene**	**80**	**81[a]/60[b]**
6	2,6 lutadiene	Toluene	80	20
7	None	Toluene	80	20
8[c]	DMAP	Toluene	80	0
9[d]	DMAP	Toluene	80	0

[a]Reactions carried out with 2.1 (0.164 mmol/1eqv), NCPhth (1.5 equiv), PPh_3 (1.5 equiv), Base (1.5 equiv), and solvents (1 mL each) overnight at the indicated temperature. a. NMR yields obtained using 1,3,5-trimethoxybenzene. [b]Isolated Yield. [c]Reaction run without NCPhth. [d]Reaction run without PPh_3.

Once the reaction had been optimized the scope of acyl phthalimide technology was investigated (Figure 2.3) Overall, our conditions were found to generate the desired products albeit in moderate yields. Electron-neutral and electron-rich carboxylic acids (***2.28***–***2.30***) reacted to afford the acyl phthalimide adducts in 60, 44, and 70% yield, respectively. It should be noted that this method did not work with a substrate bearing an electron-withdrawing group. Aliphatic carboxylic acids were also transformed in moderate yields (***2.31***).

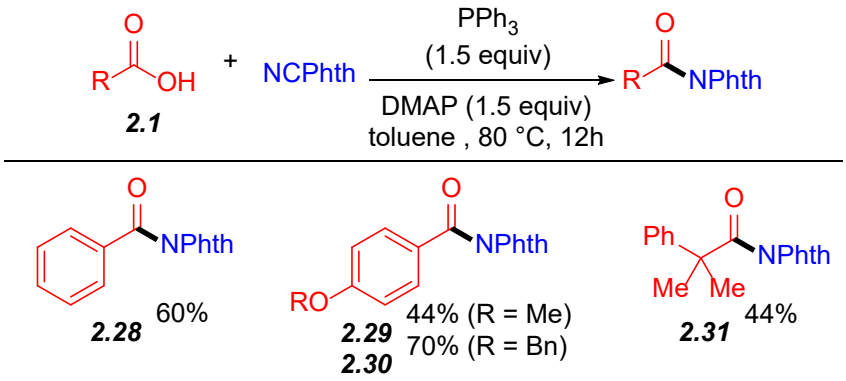


Figure 2.3 : Deoxyamidation, Synthesis of Acyl Phthalimides.

All reactions were run in 3 mL of solvent, carboxylic acid (100 mg), NCPhth (1.5 equiv), PPh3 (1.5 equiv), and DMAP (1.5 equiv).

2.1.6 Mechanistic Work

To gain insights into the mechanism of the amidation reaction, we carried out a series of ^{31}P NMR experiments with the hope of identifying and characterizing the reactive intermediates in this methodology. As proposed by Frøyen[8f-I,8l-m] and others[8j-k], ^{31}P NMR experiments showed that NCPhth and PPh_3 react together to form two phosphonium salt species: (i) a chloro-phosphonium salt at 64 ppm and (ii) an imido-phosphonium salt at 32 ppm (Figure 2.4). Ph_3PO and unreacted PPh_3 were also present.

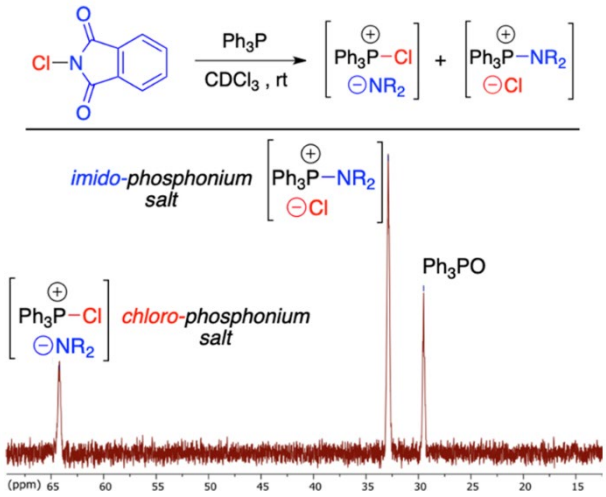


Figure 2.4 : In situ Generated Phosphonium Reactive Species, Initial Detection Via ^{31}P NMR.

In situ generated phosphonium salts observed via ^{31}P NMR. Reaction mixture consisted of triphenylphosphine (0.08 mmol, 1 equiv) and NCPhth (0.08 mmol, 1 equiv) dissolved in $CDCl_3$.

We confirmed the identity of the chloro-phosphonium salt at 64 ppm through its synthesis using oxalyl chloride[45] and comparing it with different *N*-chlorimides (Figure 2.5). These experiments further emphasized our hypothesis that the peak at 32 ppm corresponds to the imido-phosphonium salt. We confirmed this observation using HRMS detection. To the best of our knowledge, these imido-phosphonium salts had not been characterized before.

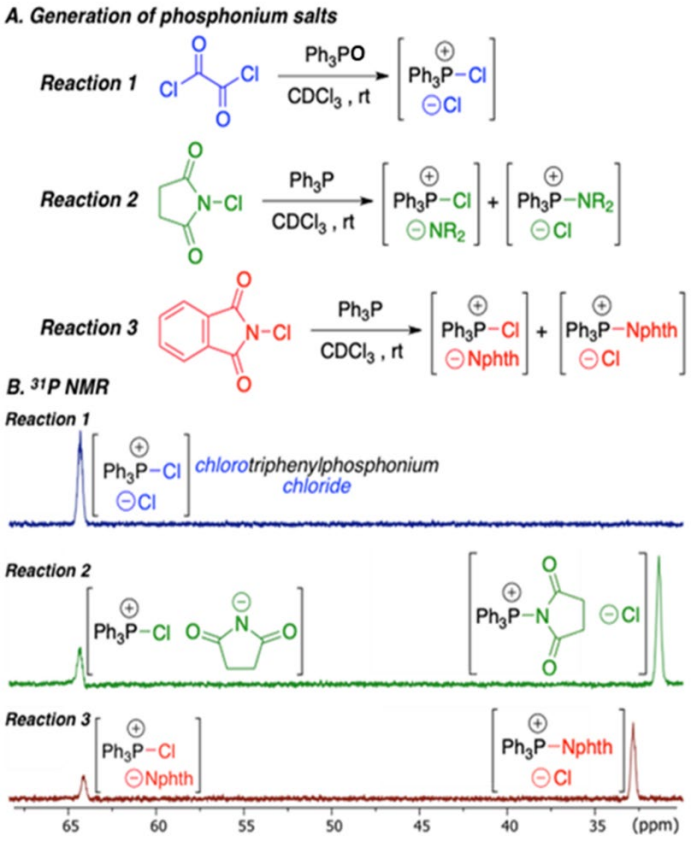


Figure 2.5 : In situ Generated Phosphonium Salts Observed via ^{31}P NMR.

Reaction 1 mixture consisted of Ph_3PO (0.07 mmol, 1 equiv) and oxalyl chloride $(COCl)_2$ (0.09 mmol, 1.3 equiv). Reaction 2 mixture consisted of PPh_3 (0.08 mmol, 1 equiv) and *N*-chlorosuccinimide (0.08 mmol, 1 equiv). Reaction 3 consisted of PPh_3 (0.08 mmol, 1 equiv) and NCPhth (0.08 mmol, 1 equiv). All reaction mixtures were dissolved in $CDCl_3$.

Following the identification and characterization of the phosphonium salts generated in situ, we attempted to observe other intermediates formed throughout the reaction. To do so, we added sodium benzoate (PhCOONa) to the previous NCPhth/PPh_3 mixture, and we observed a new peak at 23 ppm by ^{31}P NMR (Figure 2.6). We identified this new signal as being the (acyloxy)-phosphonium salt species for which a HR-MS was also obtained. Upon the formation of the (acyloxy)-phosphonium intermediate, we observed the complete consumption of the chloro-phosphonium salt at 64 ppm, while some imidophosphonium salts at 32 ppm were still present. This observation highlights the difference in reactivity between these two species. More specifically, this suggests that the chloro-phosphonium species favorably reacts, kinetically, with the carboxylic acid. The imido-phosphonium intermediate may then serve as a precursor to the more reactive chlorophosphonium species; however, we cannot exclude the possibility that the imido-phosphonium intermediate also reacts with the carboxylic acid at a slower rate.

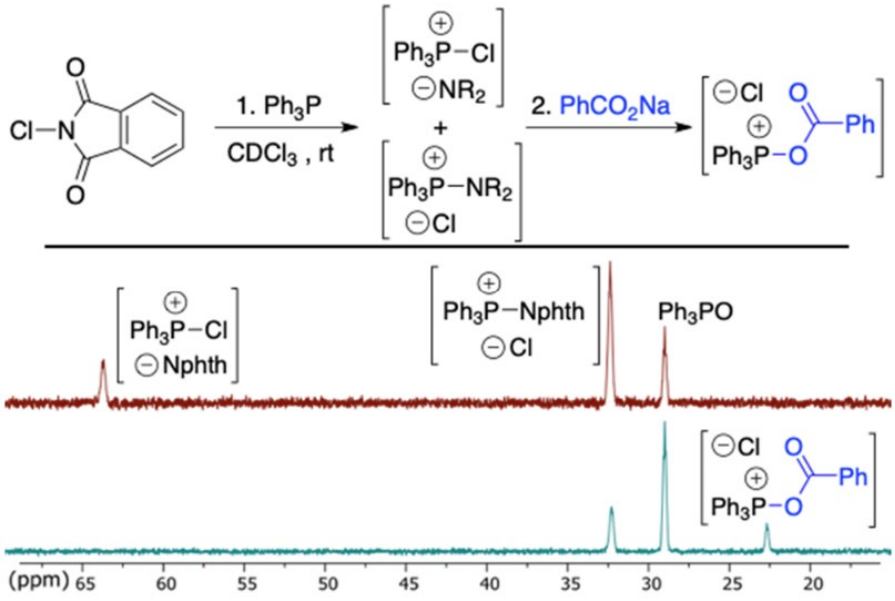


Figure 2.6 : Detection of Key Acyl(oxy)phosphonium Intermediate Via ^{31}P NMR.

Reaction mixture consisted of PPh_3 (1 equiv), NCPhth (1 equiv), and PhCOONa (0.5 equiv), all solids dissolved in $CDCl_3$.

Another observation worth noting in Figure 2.5 is the relative ratio of chloro-phosphonium to imido-phosphonium salts across both *N*-haloimides in reactions 2 and 3. When using NCS as the *N*-haloimide source, the ratio of chlorophosphonium to imido-phosphonium salts is 1:3 (Reaction 2, Figure 6), while it is 1:2 for NCPhth (Reaction 3, Figure 6). This difference in the formation of both species could be due to the difference in pK_a between succinimide (9.5) and phthalimide (8.3). Although, competing electronic and dispersion factors could provide an alternative explanation as well.[35g] Given that the chlorophosphonium intermediate seems to react faster, we believe this could explain some of the different reactivity between our method and previously published ones,[8f] while providing future research on this topic is an avenue for further exploration and optimization.

Based on previous halophosphonium-mediated amidations[8f,37-38] and our experimental observations, we propose that the reaction begins with the *in situ* generation the chloro- and imido-phosphonium salts, ***5*** and ***6***, respectively (Figure 2.7). These species then react with the carboxylic acids to generate the activated carboxylate ***7*** in the form of an (acyloxy)phosphonium salt. From intermediate ***7***, three possible pathways (***A***, ***B***, and ***C***) can lead to the final amide products. Transformation of (acyloxy)-phosphonium ***7*** into an acyl chloride via pathway ***A*** is analogous to previously proposed transformations that use halophosphonium-mediated amidations.[37a,38b,8h] Similarly, pathway ***C*** involves the reaction of intermediate ***7*** with phthalimide to generate acyl phthalimide species, which we have shown can be generated efficiently if the amine coupling partner is replaced by a bulky base (compounds 4a−4d, Figure 2.3). Finally, pathway ***B*** is the direct transformation of the (acyloxy)-phosphonium ***7*** into the desired amide.

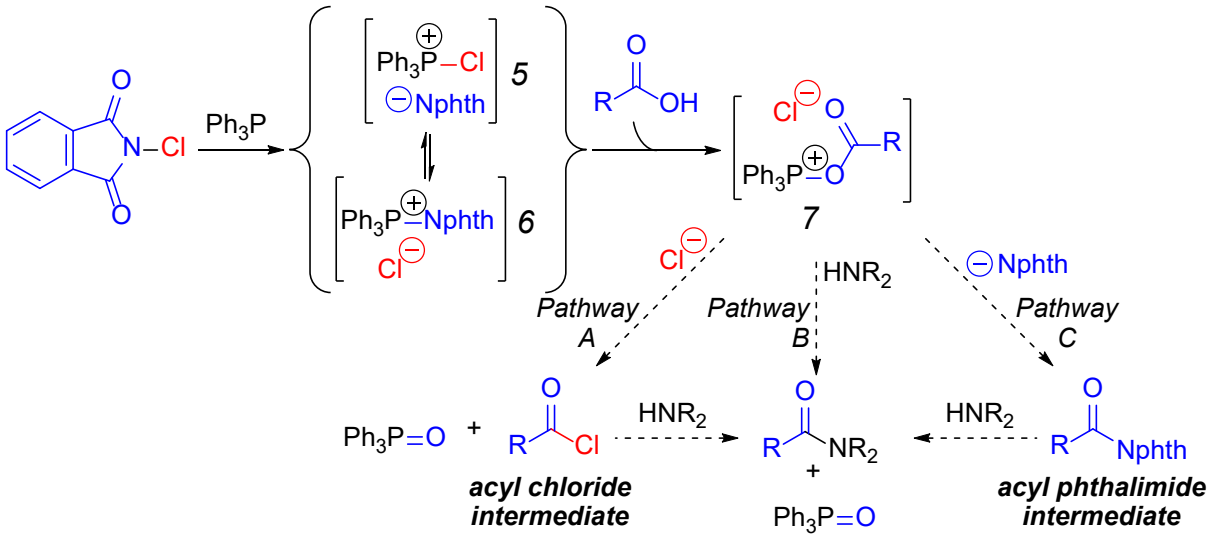


Figure 2.7 : Potential Mechanistic Pathways For Deoxyamidation

To determine which of these three possible pathways is most likely at play under our reaction conditions, we conducted a ^{31}P NMR study to quantify the rate of decomposition of the (acyloxy)-phosphonium intermediate ***7*** over time (Figure 2.8 A). We hypothesize that, if pathways ***A*** and ***C*** are main contributors for the formation of the final product, then intermediate ***7*** should decompose relatively quickly into the acyl chloride and the acyl phthalimide in a nonreversible reaction that produces triphenylphosphine oxide, even when amine is not present. Indeed, intermediate ***7*** can react with the chloride or phthalimide anion present in the reaction as counter ions. As shown in Figure 2.8 A, (acyloxy)-phosphonium species ***7*** does not seem to decompose significantly over the course of 90 min, indicating that pathways ***A*** and ***C*** are unlikely to be major contributors under our reaction conditions. Indeed, a previous report by Frøyen observed that the deoxyhalogenation of carboxylic acids via phosphine activated *N*-haloimides did not take place even under excessive heating of ***7***.[8h] On the other hand, as shown in Figure 2.8 B, the addition of benzylamine to the reaction leads to almost the instantaneous consumption of intermediate ***7*** and the consumption of the imido-phosphonium salt ***5***.

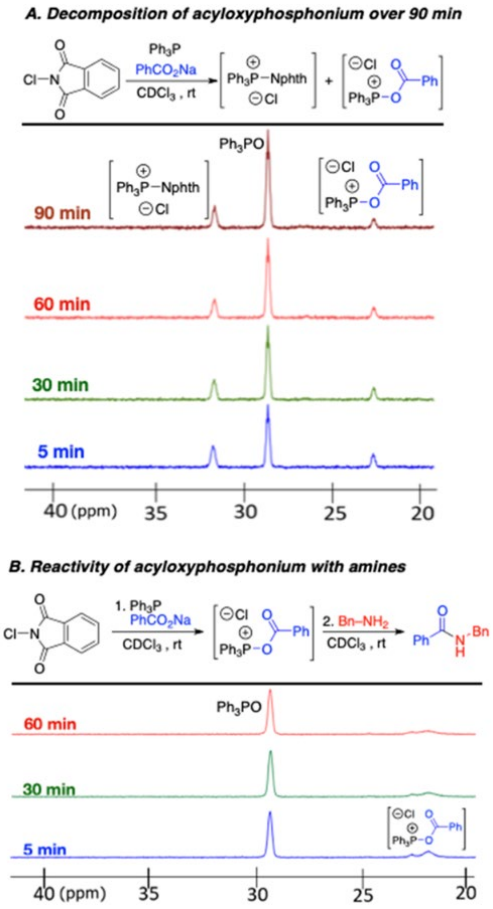


Figure 2.8 : ^{31}P NMR Stability of Acyl(oxy)phosphonium Intermediate.

(A) ^{31}P NMR at different time frames of a reaction mixture containing PPh_3 (1 equiv), NCPhth (1 equiv), and PhCOONa (0.5 equiv) in $CDCl_3$. (B) ^{31}P NMR at different time frames of a reaction mixture containing PPh_3 (1 equiv), NCPhth (1 equiv), benzylamine (1 equiv), and PhCOONa (0.5 equiv), in $CDCl_3$.

To further discard pathway ***C*** that involves the formation of the acyl phthalimide intermediate, which we were able to synthesize in Figure 2.3, we ran the control reaction presented in Figure 2.9 A. When the acyl phthalimide is reacted with benzylamine, it does not produce the corresponding *N*-benzylbenzamide. Instead, it generates the primary benzamide ***8*** and phthalimide-protected benzylamine ***9*** via a phthalimide transfer pathway. This observation is also supported by literature precedent showing that when introduced to amine nucleophiles acyl phthalimides cleave to provide the phthalimide-protected amine and primary benzamide derivative.[46] Therefore, this observation further supports that an acyl phthalimide intermediate following pathway ***C*** is unlikely. Lastly, we conducted a TEMPO radical trapping experiment to

discard any possible radical pathways (Figure 2.9 B). Indeed, when TEMPO was added to our reaction mixture, the desired amide product was still generated albeit in slightly eroded yields.

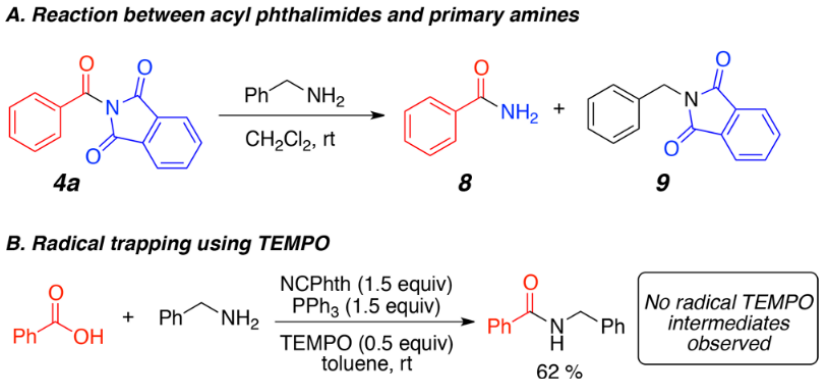


Figure 2.9 : Acyl Phthalimide & Radical Pathway Controls.

Based on the results above, we propose that the reaction begins with the *in situ* generation of the chloro- and imidophosphonium salts, ***5*** and ***6***, respectively (Figure 2.10). These species then react with the carboxylic acids to generate the activated carboxylate *7* in the form of an acyloxy-phosphonium salt. Importantly, our NMR experiments indicate that salt ***5*** is more reactive than ***6*** in the presence of a carboxylate (Figure 2.6). Then, the (acyloxy)-phosphonium species *7* undergoes direct amidation generating the desired product and forming triphenylphosphine oxide as a by-product.

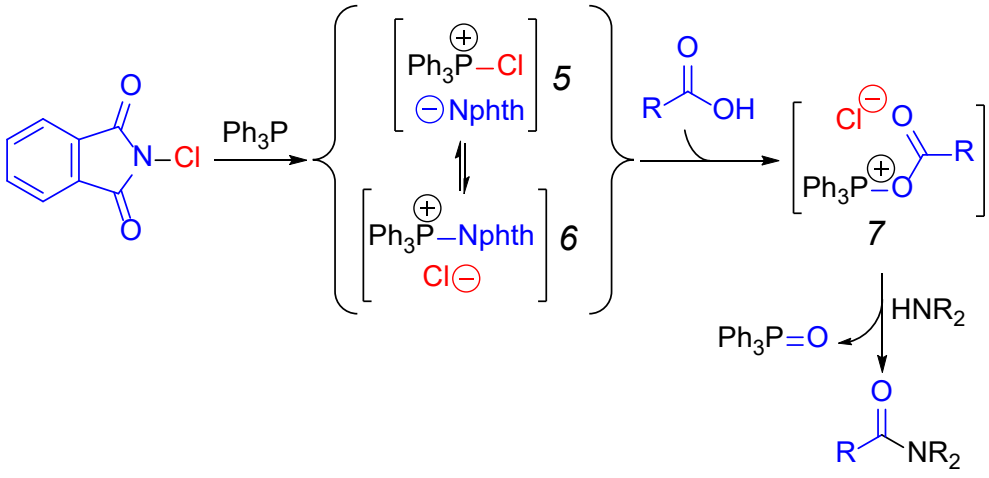


Figure 2.10 : Deoxyamidation Proposed Mechanism

2.1.7 Conclusions

In summary, we have developed a mild methodology for the amidation of carboxylic acids with both I° and II° amines. This work uses triphenylphosphine and *N*-chlorophthalimide as bench-stable reagents to generate in situ reactive phosphonium species that efficiently activate carboxylic acids. Our mechanistic work employed ^{31}P NMR and HR-MS techniques to observe and characterize the different intermediates generated throughout the reaction. Our work is the first to characterize imido-phosphonium intermediates and observe its reactivity differences with chloro-phosphonium species. These observations can help the continual improvement of Phosphonium-based transformations and characterize the species involved. Future work in our lab aims at employing similar strategies to enable other deoxyamination transformations.

CHAPTER 3. DEOXYAMINATIONS OF ALCOHOLS VIA DUAL PURPOSE IN SITU GENERATED PHOSPHONIUM REACTIVE SPECIES : SYNTHESIS OF N-ALKYLPHTHALIMIDES, N-ALKYLIMIDES, & AMINES

3.1.1 Introduction

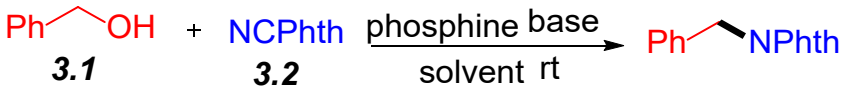
Building from the previously developed deoxyamidative technology[33] we sought to ascertain whether or not the *in situ* generated phosphonium species derived from the combination of PPh_3 and NCPhth could be used to facilitate additional deoxyaminative transformations. Specifically, our interest lied in optimizing the PPh_3/NCPhth system towards serving as a dual-purpose activation and amination technology as observed in Figure 2.3 and our synthesis of acyl phthalimides from carboxylic acid precursors. To that end we envisioned the deoxyamination of alcohols to be the ideal transformation to investigate so that we might provide a more atom economical and potentially less restrictive Mitsunobu technology. Indeed, through the use of our PPh_3/NCPhth system in conjunction with a base additive we were able to deoxyaminative a wide series of both activated and unactivated alcohols with various *N*-haloimide nitrogen sources. Additionally, we were able to perform the corresponding free amine coupling reaction through a PPh_3/NCS system. Lastly, through $^1H/^{31}P$ NMR analysis we were able to characterize the various intermediates present in the deoxyamination.

3.1.2 Reaction Optimization, Synthesis of *N*-alkylphthalimides

Initial investigations were performed with benzyl alcohol (***3.1***) as our model substrate, PPh_3, and NCPhth (***3.2***) as both the activating agent and the pronucleophile (Table 3.1). Cs_2CO_3 was used as base and freshly distilled DMF was used as the solvent (Table 3.1, Entry 1). Gratifyingly, the *N*-benzylphthalimide was obtained in 86% NMR yield, with an isolated yield of 78%. Increasing reaction temperature (Table 3.1, Entries 2–3) resulted in negligible change in yield. However, the reaction was observed to be sensitive to changes in solvent (Table 3.1, Entries 4 & 5). Ethereal solvents completely inhibit the desired reactivity and generate some of the aminated THF[44a], but anhydrous toluene afforded the desired product albeit in lower yields. Using phosphines other than PPh_3 did not provide better yields, and the use of $P(Cy)_3$ lead to a complete shutdown in reactivity (Table 3.1, Entries 6-7). Similarly, using bases other than Cs_2CO_3 had a

deleterious effect on yield, potentially due to solubility considerations or an inherent "cesium effect(s)"[47] in conjunction with a carbonate-induced hydrogen bond activation of the alcohol[24e] (Table 3.1, Entries 8–10). Indeed, such a hypothesis would also provide an explanation for the moderate reactivity observed with phosphate bases[48] (Table 3.1, Entry 10). Bases that can react with NCPhth, such as LiO*t*Bu, were observed to compete with PPh_3 leading to decomposition of the *N*-haloimide.[44a] Lastly, a series of control screens show that the base and the phosphine reagents are required to effectuate the desired reactivity (Table 3.1, Entries 11 & 12).

Table 3.1 : Reaction Optimization. *N*-alkylphthalimide Formation.



Entry	*Base*	*Phosphine*	*Solvent*	*Temp (°C)*	*[b]Yield (%)*
1	**Cs_2CO_3**	**PPh_3**	**DMF**	**25**	**90 (86)[c]**
2	Cs_2CO_3	PPh_3	DMF	60	88
3	Cs_2CO_3	PPh_3	DMF	80	79
4	Cs_2CO_3	PPh_3	THF	rt	0
5	Cs_2CO_3	PPh_3	Toluene	25	65
6	Cs_2CO_3	P(*o*-tol)$_3$	DMF	25	62
7	Cs_2CO_3	P(Cy)$_3$	DMF	25	0
8	K_2CO_3	PPh_3	DMF	25	19
9	LiO*t*Bu	PPh_3	DMF	25	39
10	K_3PO_4	PPh_3	DMF	25	63
11	None	PPh_3	DMF	25	0
12	Cs_2CO_3	None	DMF	25	0

[a]Reaction conditions: 3.1 (0.185 mmol, 1 equiv), 3.2 (0.27 mmol, 1.5 equiv), base (0.27 mmol, 1.5 equiv), phosphine (0.27 mmol, 1.5 equiv), freshly distilled anhydrous solvent (1 mL), room temperature was 25°C. [b]^{1}H-NMR yields using dibromomethane as internal standard. [c]Isolated yield

3.1.3 Deoxyamination Alcohol Scope

With the optimized conditions in hand, we initiated an alcohol scope study using NCPhth as our aminating source (Figure 3.1). Both electron donating and electron withdrawing groups in the para position were well tolerated for benzyl alcohols. Methyl, methoxy, and phenyl groups provided the desired products ***3.4***, ***3.5***, and ***3.6*** in good yields (70–76%) with several substrates showing comparable yields to traditional Mitsunobu approaches.[49a-b] All aromatic halogens provided the desired products in good yields (61–75%), showing tolerance to mild electronic changes within the aromatic ring and thereby mirroring previous Mitsunobu reactivity (Figure 3.1, products ***3.7-3.10***).[49c,23d] Piperonyl alcohol provided the desired product ***3.11*** in 72% yield, illustrating the protocol's compatibility with acetals. 2-Naphthalenemethanol provided product ***3.12*** in 78% yield while and 1-naphthalenemethanol gave product ***3.13*** in 67% yield, both well within range of analogous Mitsunobu protocols.[49d] Using a tertiary alcohol failed to provide the desired product ***3.14*** strongly suggesting that the reaction proceeds via an S_N2 mechanism and not a carbocation intermediate 1-Phenyl-1-pentanol, provided product ***3.15*** in 50% with the remaining mass generating the styrene by-product via a competitive elimination process which is less frequent in similar Mitsunobu reactions.[49e] Low yields were obtained when 2-pyridinemethanol was used to generate products ***3.16*** (32%). The para acetoxy product ***3.17*** was obtained at 33%, presumably as a result of base induced hydrolysis of the ester motif. Other activated alcohol substrates such as allylic trans cinnamyl alcohol gave product ***3.18*** (20%) and propargylic alcohols provided products ***3.19***–***3.21*** in 21%, 29%, and 50%, respectively. Initial attempts to make unactivated alcohols undergo the transformation failed to provide the desired product. But further optimization showed that switching base from Cs_2CO_3 to K_3PO_4 and increasing the temperature to 70°C enabled the formation of products ***3.22***–***3.25***. As such, 2-phenylethanol generated the desired amination product ***3.22*** in 78% yield over its thermodynamically favored styrene elimination product. 4-Phenylbutanol also provided the desired product ***3.23*** (83%). These yields are comparable to the yields obtained using traditional Mitsunobu reaction conditions,[49f] but with greater atom economy due to the dual role of the NCPhth as activating agent and pronucleophile. Finally, product ***3.24*** was also obtained in excellent yield (85%), while secondary unactivated alcohols afforded product ***3.25*** in poor yield (11%) due to increased steric hindrance.

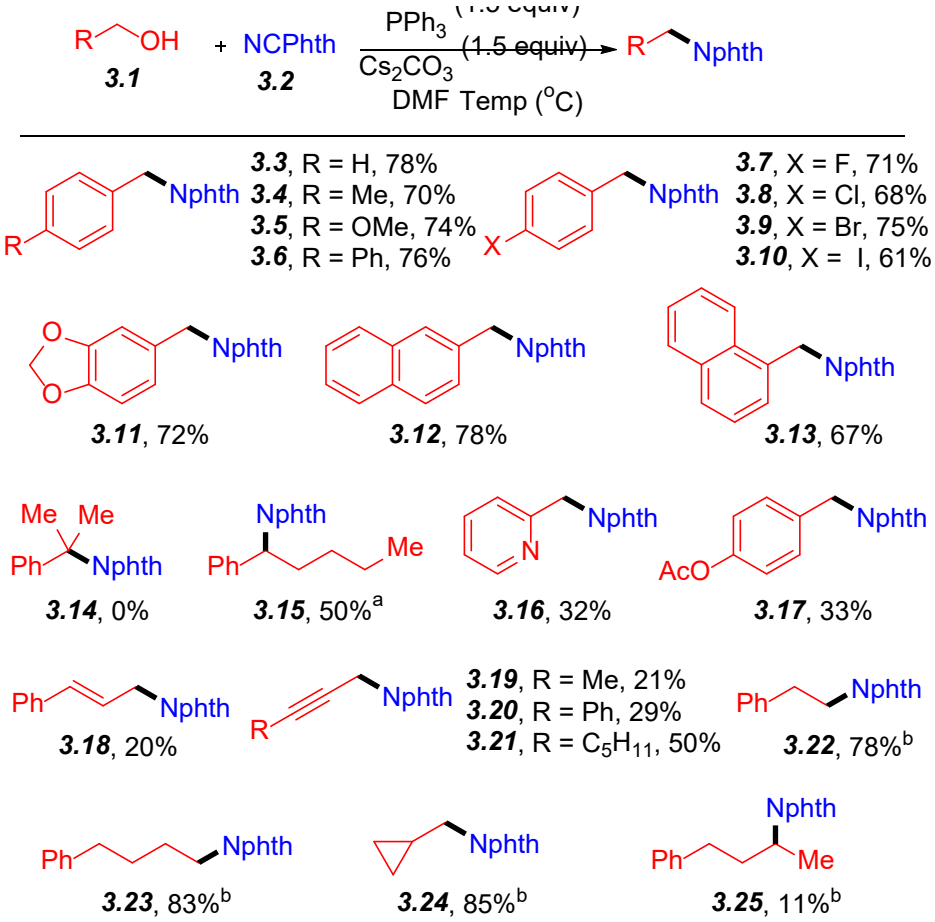


Figure 3.1 : Deoxyamination Alcohol Scope.

[a]Reaction conditions: unless stated otherwise, reactions were performed with (100 mg) of 3.1, 3.2 (1.5 equiv), PPh_3 (1.5 equiv), Cs_2CO_3 (1.5 equiv), in freshly distilled anhydrous DMF (3 mL), stirred at room temperature for 12–16 h. All yields are isolated. [a]Reaction was stirred at 60°C for 48 h. [b]Unactivated alcohols were reacted using K_3PO_4 (2 equiv) as a base, stirred overnight at 70°C in freshly distilled anhydrous DMF, (0.4 M) concentration.

3.1.4 Deoxyamination *N*-haloimide Scope

Various *N*-haloimides were then investigated as additional nitrogen sources (Figure 3.2). *N*-halosuccinimides were observed to react in modest to good yields (44–73%) for compounds ***3.26***, ***3.27***, and ***3.28***. *N*-bromoimides were less efficient nitrogen sources, presumably due to unwanted interactions with the solvent.[50] Gratifyingly, *N*-chlorosuccinimide (NCS) gave the desired aminated product from primary aliphatic alcohols at a nearly quantitative yield (Figure 3.2, ***3.29***, 99%). Increased yields were obtained reacting benzyl alcohols with *N*-chloro-3,3-dimethyl-glutarimide, affording products ***3.30***, ***3.31***, and ***3.32*** (56%, 43%, and 80% respectively), providing potential access to molecular analogues of some stimulants of the central nervous system.[51] Reaction of *N*-chloroglutarimide with 4-phenylbutanol afforded product ***3.33*** in lower yields (46%). Our protocol was capable of producing isatin derivative, which are known to be cytotoxic[52], in moderate to good yields starting from commercially available 1-chloro-2,3-indoledione (products ***3.34*** and ***3.35***).

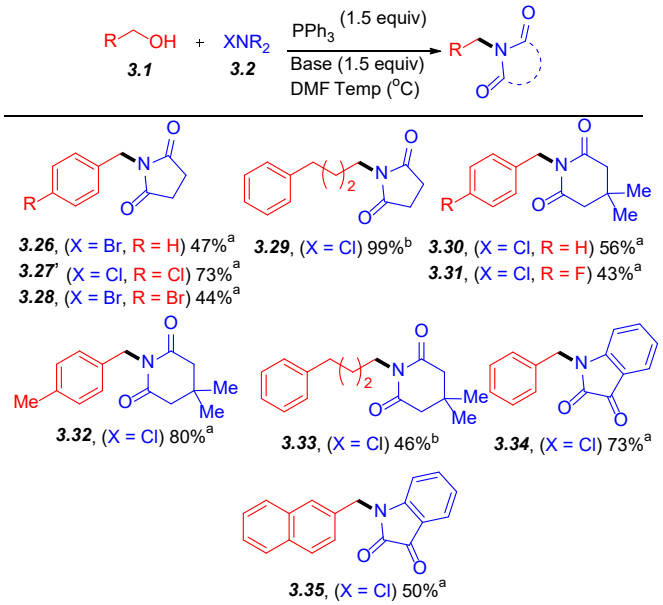


Figure 3.2 : Deoxyamination *N*-haloimide Scope.

[a]Reactions were performed with 100 mg, (1 equiv) of 3.1, 3.2 (1.5 equiv), PPh_3 (1.5 equiv), Cs_2CO_3 (1.5 equiv),freshly distilled anhydrous DMF (3 mL), stirred at room temperature for 12– 16 h. [b]Unactivated alcohols were reacted using K_3PO_4 (2 equiv) as a base, stirred overnight at 70°C in freshly distilled anhydrous DMF, (0.4 M) concentration.

3.1.5 Deoxyamination Free Amine Coupling

Inspired by Frøyen's work[23l] and based on our observation that *N*-chloroimides provided better yields than their bromo counterparts, we hypothesized that employing NCS as an activator in place of NBS might improve the efficiency of Frøyen's original methodology for the coupling of primary and secondary amines. After a brief optimization (see supporting information), we discovered that stirring NCS and PPh_3 in the presence of benzyl alcohol and 3 equivalents of amine in DMF at room temperature afforded product yields comparable to Frøyen's procedure but with a wider substrate scope of primary amines.

Using our NCS/PPh_3 procedure benzylamine was successfully coupled to benzyl alcohol (Figure 3.3) to afford product ***3.36*** in 76% yield. Electron-rich and electron-poor benzyl alcohols afforded products ***3.37*** and ***3.38*** in 60% and 69% yield, respectively. Cyclohexylamine was also coupled to 4-methylbenzyl alcohol in good yield (***3.39***, 80%). Other primary amines coupled to alcohols in moderate to good yields affording products ***3.40*** and ***3.41*** in 61% and 82% yields, respectively. Secondary cyclic amines were also well tolerated under the reaction conditions; both pyrrolidine and morpholine, common motifs in biologically active compounds[53], reacted efficiently and afforded products ***3.42*** and ***3.43*** in 78% yield, which were comparable to Frøyen's original NBS protocol. Secondary alcohols however showed similar limitations to the methodology presented above; coupling 1-phenylethan-1-ol to 4methylpiperidine afforded the product ***3.44*** in a modest 23% yield. Overall, our results illustrated that an NCS-based coupling system maintained the efficiency of the analogous NBS technology and also help expand the reaction scope. To illustrate the utility of this amine coupling protocol, we synthesized the anti-Parkinson's agent Piribedil from piperonyl alcohol and 2-(piperazin-1-yl)pyrimidine (Figure 3.3, ***3.45***) at a modest 48% yield, providing a complementary synthetic method to previous approaches.[54]

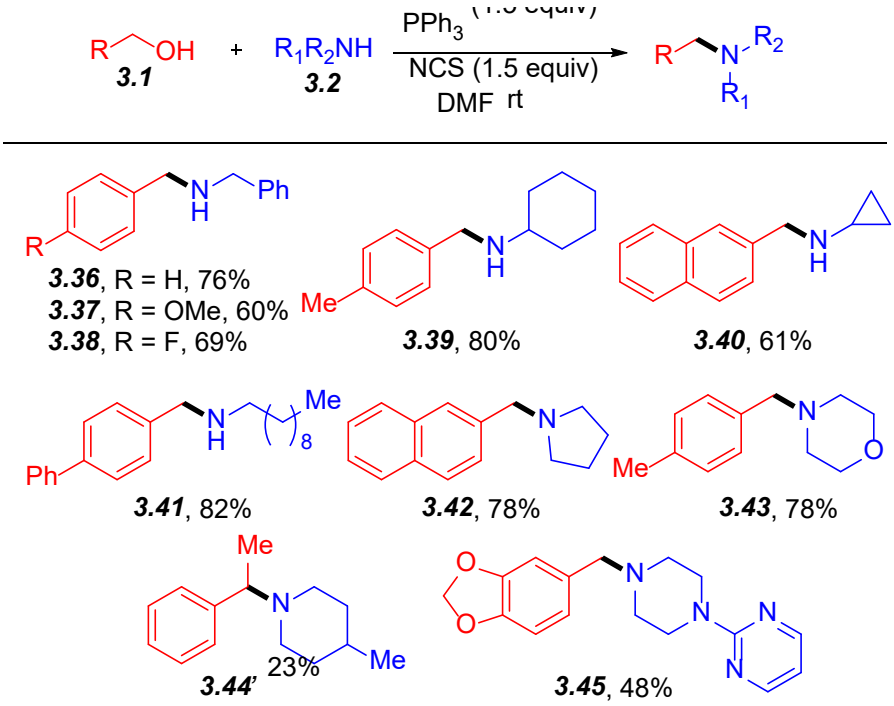


Figure 3.3 : Deoxyamination, Free Amine Coupling.

Reaction conditions: All were performed with (0.83 mmol, 1 equiv) of 3.1, NCS (1.5 equiv), PPh_3(1.5 equiv), and 3.2 (3 equiv), all dissolved in DMF (3 mL), stirred overnight at room temperature.

3.1.6 Mechanistic Work

We conducted several mechanistic investigations to better understand the reactive species and intermediated generated throughout the reaction. In our previous work,[33] we showed that mixing *N*-haloimides in presence of PPh_3 generates a mixture of chloro-phosphonium (***A***) and imido-phosphonium (***B***) salts (Figure 3.4). We hypothesized that performing the reaction in DMF would lead to the formation of DMF adduct ***C*** as proposed in the literature.[34a-b] Using ^{31}PNMR studies we started introducing DMF directly to our standard PPh_3/NCPhth mixture (Figure 3.4). After adding 1 equivalent of DMF a new peak at 16.9 ppm was observed, which was presumed to be a Vilsmier-Heck phosphonium ***C***. As we increased the concentration of DMF (Figure 3.4 ; 3 equiv. to 5 equiv.) we observed increased formation of ***C*** with a proportional decrease in the imido-phosphonium ***B*** and complete removal of the chlorophosphonium ***A***. This suggests that in DMF both phosphonium species ***A*** and ***B*** are completely consumed to form species ***C***. Therefore, species ***C*** is the reactive species that reacts with alcohols to generate the alkoxy-phosphonium intermediate

D that undergoes displacement to afford the desired product and generate triphenylphosphine oxide. In toluene, however, which was also shown to be a suitable solvent, species ***A*** and ***B*** would be the reactive species.

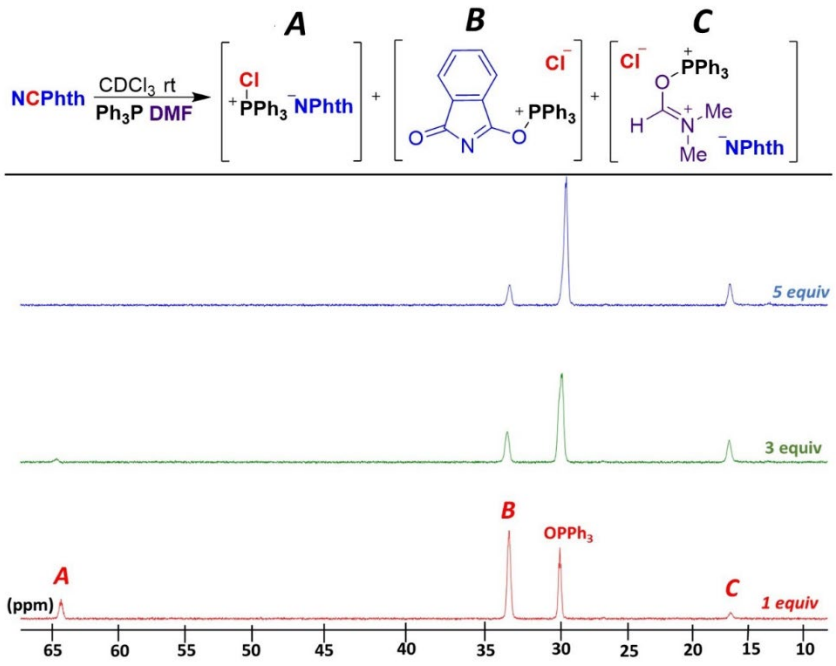


Figure 3.4 : ^{31}P NMR Detection of Vilsmier-Heck Phosphonium Species.

DMF (1-5 equiv), PPh_3 (0.405 mmol, 1.5 equiv), NCPhth (0.405 mmol, 1.5 equiv). All materials dissolved in $CDCl_3$

Additional mechanistic investigations were guided by previous reports that NCS in presence of PPh_3 reacts with alcohols to provide the chlorinated products,[35] reactivity similar to the Appel Reaction. Given the similarity of reagents, as well as a previous precedent set forth by Frøyen[27] we hypothesized that our own deoxyamination might proceed, at least partially, through a chlorinated intermediate that is then displaced by the imide anion. To investigate these assumptions, ^{1}H NMR time studies of the model substrate were performed to see what products are generated throughout the course of the reaction (Figure 3.5). At the 30 minutes time frame three distinct products were observed: benzyl alcohol (4.61 ppm, ***BnOH***) starting material, benzyl chloride (4.68 ppm, ***BnCl***) intermediate, and benzyl phthalimide (4.85 ppm, ***BnNPhth***). This clearly indicates that deoxychlorination partially occurs under the reaction conditions. At 90 minutes, a decrease in the peak intensity of BnOH as well as a proportional increase in signal

intensity of BnCl and BnNPhth is observed. Once the reaction had reached completion, a complete consumption of BnOH is observed as well as a change in signal ratio between BnCl and BnNPhth from 1 : 1 to 1 : 5. These results suggest that both chlorination and amination compete as nucleophilic displacements steps of the oxyphosphonium intermediate, but the presence of base in our reaction conditions facilitates reaction of the phthalimide with the benzyl chloride and or alkyloxyphosphonium intermediates to generate the final desired product.

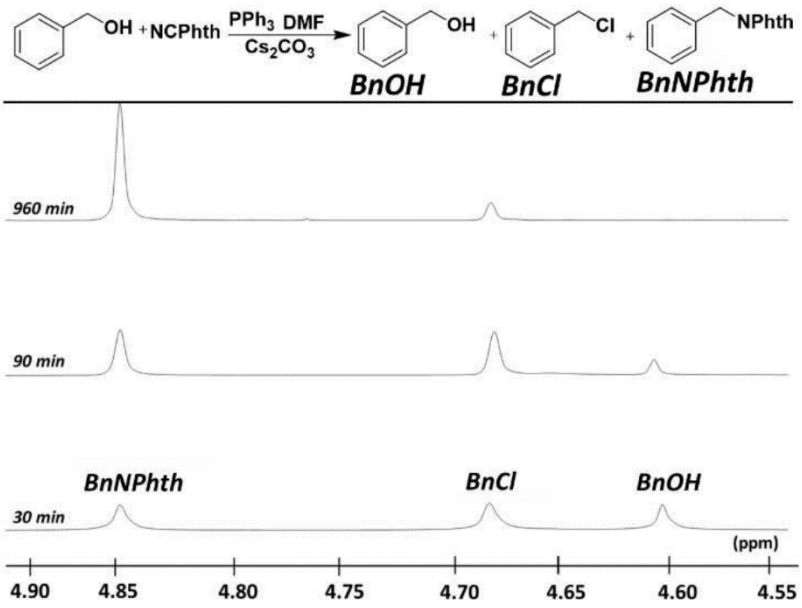


Figure 3.5 : ^{1}HNMR Detection of *In situ* Chlorination.

Each reaction was run using BnOH (0.185 mmol, 1 equiv), NCPhth (0.278 mmol, 1.5 equiv), PPh_3 (0.278 mmol, 1.5 equiv), Cs_2CO_3 (0.278 mmol, 1.5 equiv), dissolved in anhydrous DMF (1 mL) and stopped and worked-up at the shown time intervals. $CDCl_3$ was used for ^{1}H NMR analysis.

Based on the experimental results above, we propose a mechanism (Figure 3.6) beginning with the activation of the *N*-haloimides via PPh_3 to generate the chlorophosphonium ***A*** as well as imidophosphonium ***B***. In DMF, ***A*** and ***B*** are consumed to generate intermediate ***C***. Reaction of species ***C*** with alcohols in the presence of a base leads to the formation of alkoxyphosphonium ***D***. Thereafter, intermediate ***D*** can react through three pathways; 1) ***D*** directly reacts with phthalimide anion to generate desired final imide product ***F*** and generate Ph_3PO; 2) ***D*** reacts with the amine substrate to generate the final amine product ***G*** as well as Ph_3PO; and 3) ***D*** first reacts with chloride

to generate the chlorinated by-product ***E***, which can further react with phthalimide anion or amine substrate to give the final products ***F*** and ***G***, respectively.

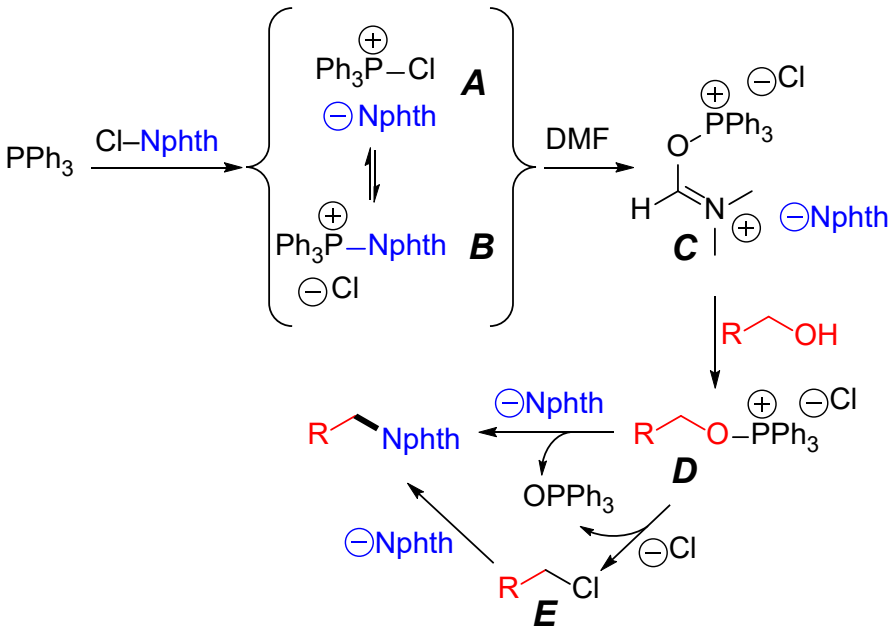


Figure 3.6 : Deoxyamination, Proposed Mechanism

3.1.7 Conclusions

In summary we have developed a diazo-free deoxyamination of alcohols using PPh_3 and *N*-haloimides in which the imide section of the activating agent is incorporated into the final product as the nitrogen source. Our method allows for the construction of new C-N bonds via the direct amination of unactivated and activated alcohols with imide coupling partners as well as free amines when NCS is used as the activating agent. Products containing the phthalimide moiety can be deprotected to the primary amine using hydrazine or methyl-hydrazine.[57] We conducted $^{1}H/^{31}P$ NMR studies of our reaction in order to identify noteworthy reactive species and intermediates to provide a detailed picture of the transformation and its mechanism.

APPENDIX A. COMPOUND SYNTHESIS & CHARACTERIZATION

Chapter 2. Deoxyamidation of Carboxylic Acids Via In situ Generated Phosphonium Reactive Species : Synthesis of Amides & Acyl Phthalimide Derivatives

General Method A: Amide Synthesis. A flame-dried 10 mL microwave vial was charged with N-chlorophthalimide (1.5 equiv), triphenylphosphine (1.5 equiv), and the desired carboxylic acid (100 mg, 1 equiv) under an argon atmosphere. A solvent (3 mL of toluene or acetonitrile) was then added, and the resulting solution was stirred for 1 min before adding the desired amine reagent (3 equiv). The resulting mixture was stirred at room temperature for 12 h in an inert atmosphere. The crude reaction was then dissolved in 10 mL of ethyl acetate, and the solution was washed using a saturated solution of sodium bicarbonate (8 mL) and a brine solution (8 mL). The organic layer was dried with sodium sulfate and then concentrated via rotatory evaporation. The corresponding amide was isolated via column chromatography.

General Method B: Acyl Phthalimide Synthesis. A flame-dried 10 mL microwave vial was charged with N-chlorophthalimide (1.5 equiv), triphenylphosphine (1.5 equiv), DMAP (1.5 equiv), and the desired carboxylic acid (100 mg, 1 equiv) under an argon atmosphere. Toluene (3 mL) was then added, and the resulting solution was stirred for 12 h at 80 °C in an inert atmosphere. The crude reaction was then dissolved in 10 mL of ethyl acetate, and the solution was washed using a saturated solution of sodium bicarbonate (8 mL) and a brine solution (8 mL). The organic layer was dried with sodium sulfate and then concentrated via rotatory evaporation. The corresponding acyl phthalimide was isolated via column chromatography.

Preparation of N-Benzylbenzamide (***2.3***). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 263 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.53, DCM/hexane/EtOAc = 5:3:1) and isolated in 83% yield, 140 mg. Spectra data matched reported data.[58]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.60 (m, 2H), 7.44−7.35 (m, 1H), 7.36−7.25 (m, 2H), 7.25 (m, 4H), 6.51 (s, 1H), 4.53 (d, J = 5.7 Hz, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167.4, 138.3, 134.5, 131.5, 128.8, 128.6, 127.9, 127.6, 127, 44.1.

Preparation of N-Benzyl-N-methylbenzamide (***2.4***). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 199 mg of *N*-

benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.62, DCM/hexane/EtOAc = 5:3:1) and isolated in 65% yield, 120 mg. Spectra data matched reported data.[59]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.08 (m, 10H), 4.49 (d, 2H), 2.79 (d, J = 72.1 Hz, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 169, 136.3, 129.6, 128.8, 128.5, 127.6, 127, 126.9, 55.2, 50.9, 37, 33.2.

Preparation of N-Cyclohexylbenzamide (***2.5***). Using general method A, (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 244 mg of cyclohexylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.59, DCM/hexane/ EtOAc = 5:3:1) and isolated in 76% yield, 130 mg. Spectra data matched reported data.[60]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.74 (m, 2H), 7.53−7.45 (m, 1H), 7.44−7.38 (m, 2H), 6.14 (s, 1H), 3.99 (m, 1H), 2.03 (m, 2H), 1.81−1.70 (m, 2H), 1.70−1.61 (m, 1H), 1.48−1.35 (m, 2H), 1.32−1.13 (m, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 166.5, 135.2, 131.2, 128.5, 126.9, 48.7, 33.2, 25.6, 25.

Preparation of (S)-N-(1-Phenylethyl)benzamide (***2.6***). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 298 mg of (*S*)-(−)-1-phenylethylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.63, DCM/hexane/EtOAc = 5:3:1) and isolated in 72% yield, 150 mg. Spectra data matched reported data.[61]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.66 (m, 2H), 7.43−7.37 (m, 1H), 7.35−7.25 (m, 6H), 7.21−7.17 (m, 1H), 6.36 (s, 1H), 5.25 (p, J = 7.1 Hz, 1H), 1.52 (d, J = 7.0 Hz, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 166.9, 143.2, 134.7, 131.4, 128.8, 128.6, 127.5, 127, 126.3, 49.2, 21.8.

Preparation of N-(2-Phenylpropan-2-yl)benzamide (***2.7***). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 332 mg of cumylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.67, DCM/hexane/EtOAc = 5:3:1) and isolated in 51% yield, 100 mg. Spectra data matched reported data.[62]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.76 (m, 2H), 7.56− 7.46 (m, 3H), 7.50−7.40 (m, 2H), 7.38 (t, J = 8.6, 7.6, 7.0 Hz, 2H), 7.30−7.25 (m, 1H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 166, 146.9, 135.5, 131.3, 128.6, 128.5, 126.9, 126.8, 124.8, 56.3, 29.2.

Preparation of(Z)-N-(Octadec-9-en-1-yl)benzamide (***2.8***). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 657 mg of oleylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.76, DCM/hexane/EtOAc = 5:3:1) and isolated in 40% yield, 122 mg. Spectra data matched reported data.[63]

^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.0, 1.8 Hz, 2H), 7.51−7.39 (m, 3H), 6.36 (s, 1H), 5.44−5.32 (m, 2H), 3.44 (m, 3H), 2.17−1.90 (m, 4H), 1.62 (p, J = 7.1 Hz, 2H), 1.43−1.21 (m, 22H), 0.87 (s, 3H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.5, 135, 134.5,131.2, 130.6, 129.8, 128.9, 128.5, 126.9, 40.1, 31.9, 29.8, 29.7, 29.5, 27.2, 22.7, 14.1.

Preparation of tert-Butyl Benzoylglycinate (***2.9***). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 323 mg of *tert*-butyl, 2-aminoacetate, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.49, DCM/hexane/EtOAc = 5:3:1) and isolated in 54% yield, 100 mg. Spectra data matched reported data.[64]

^1H NMR (400 MHz, $CDCl_3$) δ 7.87−7.79 (m, 2H), 7.56− 7.48 (m, 1H), 7.48−7.40 (m, 2H), 6.71 (s, 1H), 4.15 (d, J = 4.9 Hz, 2H), 1.52 (s, 9H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 167.2, 134, 131.7, 128.6, 127, 82.5, 42.5, 28.1.

Preparation of N-Phenylbenzamide (***2.10***). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 229 mg of aniline, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.84, DCM/hexane/EtOAc = 5:3:1) and isolated in 69% yield, 111 mg. Spectra data matched reported data.[65]

^1H NMR (400 MHz, $CDCl_3$) δ 7.92−7.83 (m, 3H), 7.70− 7.61 (m, 2H), 7.59−7.51 (m, 1H), 7.51−7.43 (m, 2H), 7.41−7.32 (m, 2H), 7.20−7.11 (m, 1H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.8, 138, 135.1, 131.9, 129.1, 128.8, 127, 124.6, 120.3.

Preparation of N-Mesitylbenzamide (***2.11***). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 332 mg of 2,4,6-trimethylaniline, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.28, 100% DCM) and isolated in 56% yield, 110 mg. Spectra data matched reported data.[66]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.76 (m, 2H), 7.55− 7.45 (m, 1H), 7.40 (dd, J = 7.5, 1.3 Hz, 2H), 7.33 (d, 1H), 6.84 (s, 2H), 2.22 (s, 3H), 2.15 (s, 6H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 166.3, 137.1, 135.3, 134.7, 131.7, 131.3, 129, 128.7, 127.2, 21, 18.4.

Preparation of N-(2,6-Diisopropylphenyl)benzamide (***2.12***). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 435 mg of 2,6-diisopropylaniline, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.39, 100% DCM) and isolated in 49% yield, 113 mg. Spectra data matched reported data.[67]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.79 (m, 2H), 7.52−7.46 (m, 1H), 7.44−7.38 (m, 2H), 7.33−7.24 (m, 2H), 7.16 (t, J = 8.3 Hz, 2H), 3.07 (hept, J = 6.8 Hz, 2H), 1.14 (d, J = 6.9 Hz, 12H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 166.9, 146.5, 134.7, 131.8, 131.2, 128.9, 128.5, 127.2, 28.9, 23.7.

Preparation of N,N-Diphenylbenzamide (***2.13***). Using general method B (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 277 mg of diphenylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.55, hexane/EtOAc = 2:1) and isolated in 55% yield, 123 mg. Spectra data matched reported data.[68]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 2H), 7.24−7.17 (m, 5H), 7.15−7.04 (m, 8H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 170.2, 144, 136.2, 130.2, 129.2, 129.1, 127.9, 127.5, 126.4.

Preparation of N-Methyl-N-phenylbenzamide (***2.14***). Using general method B (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 176 mg of N-methylaniline, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.47, DCM/hexane/ EtOAc = 5:3:1) and isolated in 65% yield, 112 mg. Spectra data matched reported data.[69]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 2H), 7.26− 7.18 (m, 3H), 7.14 (m, 3H), 7.09−6.97 (m, 2H), 3.54−3.47 (m, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 170.2, 144.9, 136, 129.6, 129.2, 128.7, 127.3, 126.9, 126.5, 38.4.

Preparation of Phenyl(pyrrolidin-1-yl)methanone (***2.15***). Using general method B (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 117 mg of pyrrolidine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.29,

DCM/hexane/EtOAc = 5:2:3) and isolated in 71% yield, 102 mg. Spectra data matched reported data.[70]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.30 (m, 3H), 3.62−3.20 (m, 3H), 1.94−1.72 (m, 4H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 169.7, 137.3, 133, 129.7, 128.2, 127.1, 49.5, 46.1, 26.4, 24.4.

Preparation of Phenyl(piperidin-1-yl)methanone (***2.16***). Using general method B (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 139 mg of piperidine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.60, 100% EtOAc) and isolated in 45% yield, 70 mg. Spectra data matched reported data.[71]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 5H), 3.42 (d, J = 148.3 Hz, 4H), 1.79−1.09 (m, 5H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 170, 136.5, 129.2, 128.3, 126.7, 48.7, 43.1, 26.4, 25.7, 24.5.

Preparation of Morpholino(phenyl)methanone (***2.17***). Using general method B (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 143 mg of morpholine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.33, petroleum ether/ EtOAc = 1:1) at 41% yield, 64 mg. Spectra data matched reported data.[72]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 3.47 (m, 8H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 170.3, 135.3, 132, 131.9, 129.8, 128.5, 128.4, 127.4, 66.7, 48.1, 42.6.

Preparation of *N-Benzyl-4-methoxybenzamide* (***2.18a***). Using general method A (100 mg of 4-methoxy-benzoic acid, 259 mg of triphenylphosphine, 179 mg of *N*-chlorophthalimide, 211 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.14, hexane/EtOAc = 3:1) and isolated in 84% yield, 166 mg. Spectra data matched reported data.[73]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.8 Hz, 2H), 7.29−7.11 (m, 4H), 6.82 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 6.40 (s, 1H), 3.75 (s, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 166.8, 162.3, 138.6, 128.8, 128.7, 127.9, 127.5, 126.7, 113.8, 55.4, 44.1.

Preparation of N-Benzyl-4-methoxy-N-methylbenzamide (***2.18b***). Using general method A, (100 mg of 4-methoxybenzoic acid, 259 mg of triphenylphosphine, 179 mg of *N*-chlorophthalimide, 160 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.40, hexane/EtOAc = 1:1) and isolated in 87% yield, 182 mg. Spectra data matched reported data.[74]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.39 (m, 2H), 7.39− 7.33 (m, 2H), 7.32−7.23 (m, 2H), 6.89 (d, J = 8.2 Hz, 2H), 4.65 (s, 2H), 3.81 (s, 3H), 2.95 (s, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 160.8, 137.1, 129, 128, 127, 113.7, 55.3.

Preparation of N-Benzyl-4-iodobenzamide (***2.19a***). Using general method A (100 mg of 4-iodo-benzoic acid, 159 mg of triphenylphosphine, 110 mg of *N*-chlorophthalimide, 121 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.52, EtOAc/hexane/DCM = 1:2.5:1) and isolated in 73% yield, 100 mg. Spectra data matched reported data.[75]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.76 (m, 2H), 7.56− 7.50 (m, 2H), 7.41−7.33 (m, 5H), 6.40 (s, 1H), 4.65 (d, J = 5.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 138, 137.9, 137.8, 133.8, 128.9, 128.6, 128, 127.8, 98.5, 44.3.

Preparation of N-Benzyl-4-iodo-N-methylbenzamide (***2.19b***). Using general method A (100 mg of 4-iodo-benzoic acid, 159 mg of triphenylphosphine, 110 mg of *N*-chlorophthalimide, 98 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.48, DCM/hexane/EtOAc = 1:2.5:1) and isolated in 87% yield, 123 mg. Spectra data matched reported data.[73]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 2H), 7.45−7.07 (m, 7H), 4.61 (d, J = 96.0 Hz, 2H), 2.93 (d, J = 67.1 Hz, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 137.6, 128.8, 127.7, 95.8, 55.2, 51, 37, 33.4.

Preparation of N-Benzyl-4-bromobenzamide (***2.20a***). Using general method A (100 mg of 4-bromo-benzoic acid, 196 mg of triphenylphosphine, 135 mg of *N*-chlorophthalimide, 160 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.60, DCM/hexane/ EtOAc = 1:2.5:1) and isolated in 69% yield, 100 mg. Spectra data matched reported data.[76]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.60 (m, 2H), 7.61−7.53 (m, 2H), 7.41−7.30 (m, 5H), 4.64 (d, J = 5.6 Hz, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 166.3, 137.9, 133.3, 131.9, 128.9, 128.6, 128, 127.8, 126.3, 44.3.

Preparation of N-Benzyl-4-bromo-N-methylbenzamide (***2.20b***). Using general method A (100 mg of 4-bromo-benzoic acid, 196 mg of triphenylphosphine, 135 mg of *N*-chlorophthalimide, 120 mg

of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.48, DCM/hexane/EtOAc = 1:2.5:1) and isolated in 88% yield, 133 mg. Spectra data matched reported data.[77]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m,2H), 7.39−7.22 (m, 6H), 7.22−7.04 (m, 1H), 4.61 (d, J = 97.5 Hz, 2H), 2.94 (d, J = 68.3 Hz, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 206.6, 135.1, 131.7, 128.9, 128.2, 127.7, 126.6, 124, 55.2, 51, 30.9.

Preparation of N-Benzyl-4-nitrobenzamide (***2.21a***). Using general method A (100 mg of 4-nitro-benzoic acid, 236 mg of triphenylphosphine, 163 mg of *N*-chlorophthalimide, 192 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.57, DCM/hexane/EtOAc = 5:3:1) and isolated in 42% yield, 66 mg. Spectra data matched reported data.[78]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.16 (m, 2H), 8.00− 7.89 (m, 2H), 7.40−7.29 (m, 5H), 6.60 (s, 1H), 4.65 (d, J = 5.6 Hz, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 165.3, 149.7, 140, 137.5, 129, 128.2, 128, 127.9, 123.8, 44.5.

Preparation of N-Benzyltetradecanamide (***2.22a***). Using general method B (100 mg of myristic acid, 173 mg of triphenylphosphine, 119 mg of *N*-chlorophthalimide, 141 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.57, DCM/hexane/EtOAc = 5:3:1) and isolated in 70% yield, 97 mg. Spectra data matched reported data.[79]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.11 (m, 5H), 5.75 (s, J = 5.7 Hz, 1H), 4.36 (d, J = 5.7 Hz, 2H), 2.19−1.97 (m, 2H), 1.56 (q, J = 7.2 Hz, 2H), 1.39−0.97 (m, 19H), 0.90−0.55 (m, 3H).

^{13}C{1H}NMR (100 MHz, $CDCl_3$) δ 173.1, 138.5, 128.7, 127.8, 127.5, 123.5, 43.6, 36.8, 31.9, 29.7, 29.6, 29.5, 29.4, 25.8, 23.7, 14.1.

Preparation of N-Benzyl-N-methyltetradecanamide (***2.22b***). Using general method A (100 mg of myristic acid, 173 mg of triphenylphosphine, 119 mg of *N*-chlorophthalimide, 106 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.63, DCM/ hexane/EtOAc = 5:3:1) and isolated in 80% yield, 116 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.03 (m, 5H), 4.56 (d, J = 24.3 Hz, 2H), 2.92 (d, J = 10.7 Hz, 3H), 2.42−2.27 (m, 2H), 1.67 (m, 2H), 1.41−1.11 (m, 22H), 0.94−0.72 (m, 3H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.7, 173.3, 137.7, 128.9, 128.6, 128, 127.6, 127.3, 126.3, 53.4, 50.8, 34.8, 33.9, 33.6, 33.2, 31.9, 29.7, 29.6, 29.5, 29.4, 25.5, 25.2, 22.7, 14.1.

HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{38}NO^+$, 332.2948 m/z; found, 332.2886 m/z.

IR (cm^{-1}): 2930, 2856, 1653, 1457, 1265, 1094.

Preparation of tert-Butyl 3-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(benzylamino)-4-oxobutyl)1H-indole-1-carboxylate (***2.23a***). Using general method A (100 mg of Fmoc-Trp(Boc)-OH, 76 mg of triphenylphosphine, 53 mg of *N*-chlorophthalimide, 61 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.83, DCM/hexane/EtOAc = 2:1:1) and isolated in 54% yield, 63 mg.

^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 7.6 Hz, 2H) 7.6−7.09 (m, 14H), 6.87 (m, 2H), 5.66 (d, J = 146.0 Hz, 2H), 4.51−3.85 (m, 5H), 3.43−2.82 (m,2H), 1.57 (s, 9H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.6, 143.7, 141.3, 137.3, 128.6, 127.8, 127.6, 127.5, 127.1, 125, 124.8, 124.4, 123, 120, 119, 115.4, 83.9, 67.2, 47.1, 43.7, 28.6, 28.2.

HRMS (ESI): $[M+ H]^+$ calcd for $C_{38}H_{38}N_3O_5^+$, 616.2806 m/z; found, 616.2550 m/z.

IR (cm^{-1}): 3304, 3064, 1734, 1684, 1649, 1549, 1453, 1374, 1080.

Preparation of N-Benzyl-4-(trifluoromethyl)benzamide (***2.24a***). Using general method A (100 mg of 4-triflourobenzoic acid, 210 mg of triphenylphosphine, 145 mg of *N*-chlorophthalimide, 170 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.47, DCM/hexane/EtOAc = 7:3:1) and isolated in 40% yield, 59 mg. Spectra data matched reported data.[80]

^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.50−7.16 (m, 5H), 6.55 (s, 1H), 4.67 (d, J = 5.6 Hz, 2H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 137.8, 137.7, 128.9, 128, 127.9, 127.5, 125.7, 125.6, 44.3.

Preparation of N-Benzyl-N-methyl-4-(trifluoromethyl)benzamide (***2.24b***). Using general method A (100 mg of 4triflourobenzoic acid, 210 mg of triphenylphosphine, 145 mg of *N*-chlorophthalimide, 129 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.45, DCM/hexane/EtOAc = 10:3:1) and isolated in 73% yield, 113 mg. Spectra data matched reported data.[59]

^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.49 (d, m, 2H), 7.26 (m, 4H), 7.07 (m, 1H), 4.54 (d, J = 117.4 Hz, 2H), 2.87 (d, J = 87.4 Hz, 3H),

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 139.9, 136.7, 136.1, 131.8, 131.4, 129, 128.9, 127.9, 127.7, 55, 50.9, 36.9, 33.3.

Preparation of N-Benzyl-2-(4-isobutylphenyl)propanamide (***2.25a***). Using general method A (100 mg of 2(4-isobutylphenyl)propanoic acid, 194 mg of triphenylphosphine, 134 mg of *N*-chlorophthalimide, 157 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.59, DCM/hexane/EtOAc = 7:3:1) and isolated in 50% yield, 71 mg. Spectra data matched reported data.[81]

^1H NMR (400 MHz, $CDCl_3$) δ 7.20−7.09 (m, 5H), 7.06−6.98 (m, 4H), 5.66 (s, 1H), 4.29 (d, J = 5.8 Hz, 2H), 3.50 (q, J = 7.2 Hz, 1H), 2.37 (d, J = 7.2 Hz, 2H), 1.76 (m, 1H), 1.46 (d, J = 7.2 Hz, 3H), 0.81 (d, J = 6.6 Hz, 6H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.4, 140.8, 138.5, 129.7, 128.6, 127.4, 127.3, 46.8, 45, 43.5, 30.2, 22.4, 18.5.

Preparation of N-Benzyl-2-(4-isobutylphenyl)propanamide (***2.25b***). Using general method A (100 mg of 2(4-isobutylphenyl)propanoic acid, 194 mg of triphenylphosphine, 134 mg of *N*-chlorophthalimide, 116 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f= 0.68, DCM/hexane/ EtOAc = 7:3:1) and isolated in 80% yield, 120 mg.

^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.16 (m, 6H), 7.12 (m, 2H), 7.05−7.01 (m, 1H), 4.85−4.28 (m, 2H), 3.91 (m, 1H), 2.89 (d, J = 47.2 Hz, 3H), 2.48 (d, J = 7.1 Hz, 2H), 1.88 (m, 1H), 1.50 (m, 3H), 0.93 (dd, J = 6.6, 2.6 Hz, 6H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 174, 140.3, 140, 139.2, 138.9, 137.6, 136.9, 129.6, 129.5, 128.8, 128.5, 127.9, 127.5, 127.2, 127, 126.5, 52.9, 51.2, 45, 43.1, 42.8, 34.8, 34.1, 30.2, 22.4, 21.1, 20.8.

HRMS (ESI): [M+ H]+ calcd for $C_{21}H_{28}NO^+$, 310.2165 m/z; found, 310.2115 m/z.

IR (cm^{-1}): 3048, 2948, 2865, 1740, 1648, 1449, 1267, 1059.

Preparation of N-Benzyl-2-methyl-2-phenylpropanamide (***2.26a***). Using general method A (100 mg of 2-phenylisobutyric acid, 241 mg of triphenylphosphine, 167 mg of *N*-chlorophthalimide, 196 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.49, DCM/hexane/EtOAc = 7:3:1) and isolated in 43% yield, 66 mg. Spectra data matched reported data.[82]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.23 (m, 4H), 7.22− 7.12 (m, 3H), 7.07−7.00 (m, 2H), 5.39 (s, 1H), 4.29 (d, J = 5.8 Hz, 2H), 1.53 (s, 6H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 177.3, 145.1, 138.6, 128.8, 128.6, 127.3, 127.1, 126.5, 47.1, 43.7, 27.1.

Preparation of N-Benzyl-N,2-dimethyl-2-phenylpropanamide (***2.26b***). Using general method A (100 mg of 2phenylisobutyric acid, 241 mg of triphenylphosphine, 167 mg of *N*-chlorophthalimide, 148 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.65, DCM/hexane/EtOAc = 7:3:1) and isolated in 94% yield, 153 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−6.61 (m, 10H), 5.10−3.69 (m, 2H), 2.82−2.26 (m, 3H), 1.50 (s, 6H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 176.3, 146.4, 128.9, 128.5, 127.2, 126.4, 124.9, 47.2, 28.4.

HRMS (ESI): $[M+ H]^+$ calcd for $C_{18}H_{22}NO^+$, 268.1696 m/z; found, 268.1660 m/z.

IR (cm^{-1}): 3100, 2990, 2925, 2249, 1714, 1648, 1400, 1088.

Preparation of N-(3-Isopropoxyphenyl)-2-methylbenzamide (***2.27***). Using general method A (100 mg of *o*-toluic acid, 322 mg of triphenylphosphine, 291 mg of *N*-chlorophthalimide, 335 mg of 3-isopropoxyaniline, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.54, DCM/hexane/EtOAc = 10:3:1) and isolated in 55% yield, 109 mg. Spectra data matched reported data.[38c]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.33−7.24 (m, 2H), 7.24−7.16 (m, 1H), 7.14−7.07 (m, 3H), 7.01−6.94 (m, 1H), 6.60 (dd, J = 8.3, 2.4 Hz, 1H), 4.49 (sept, J = 6.2 Hz, 1H), 2.35 (s, 3H), 1.23 (d, J = 6.1 Hz, 6H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168.1, 158.6, 139.3, 136.4, 131.2, 130.2, 129.8, 126.7, 125.9, 112.2, 111.9, 107.6, 70, 60.4, 22.1, 19.8, 14.2.

Preparation of 2-Benzoylisoindoline-1,3-dione (***2.28***). Using general method B (100 mg of benzoic acid, 323 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 150 mg of DMAP, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.4, DCM/hexane = 2:1) and isolated in 60% yield, 123 mg. Spectra data matched reported data.[83]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.90−7.82 (m, 4H), 7.72−7.61 (m, 1H), 7.56−7.43 (m, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167.9165.9, 135.3, 134.5, 131.5, 130.5, 128.7, 124.5.

Preparation of 2-(4-Methoxybenzoyl)isoindoline-1,3dione (***2.29***). Using general method B (100 mg of 4-methoxybenzoic acid, 259 mg of triphenylphosphine, 179 mg of *N*-chlorophthalimide, 120 mg of DMAP, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.7, DCM/hexane/EtOAc = 5:3:1) and isolated in 44% yield, 81 mg. Spectra data matched reported data.[84]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.90−7.81 (m, 4H), 6.96 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 166.1, 164.7, 135.1,133.2, 131.7, 125, 124.4, 114.1, 55.6.

Preparation of 2-(4-(Benzyloxy)benzoyl)isoindoline-1,3dione (***2.30***). Using general method B 100 mg of 4-(benzyloxy)benzoic acid, 173 mg of triphenylphosphine, 120 mg of *N*-chlorophthalimide, 80 mg of DMAP, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.7, DCM/hexane/EtOAc = 5:3:1) and isolated in 70% yield, 110 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.91−7.81 (m, 4H), 7.13−6.97 (m, 2H), 5.15 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 165.6, 163.5, 135.9, 135.1, 133.2, 131.7, 128.8, 128.4, 127.5, 125.2, 124.4, 115, 70.4.

HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{16}NO_4^+$, 358.1074 m/z; found, 358.1101 m/z.

IR (cm^{-1}): 3078, 3032, 2946, 1784, 1683, 1510, 1105.

Preparation of 2-(2-Methyl-2-phenylpropanoyl)isoindoline-1,3-dione (***2.31***). Using general method B (100 mg of 2-phenyl isobutyric acid, 240 mg of triphenylphosphine, 166 mg of *N*-chlorophthalimide, 112 mg of DMAP, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.6, EtOAc/hexane = 3:5) and isolated in 48% yield, 86 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.78 (m, 2H), 7.76−7.71 (m, 2H), 7.40−7.18 (m, 5H), 1.81 (s, 6H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 178.9, 165.1, 142.5, 134.9, 131.3, 128.3, 127, 126.5, 124.1, 51.5, 26.9.

HRMS (ESI): $[M+H]^+$ calcd for $C_{18}H_{16}NO_3$; 358.1074 m/z, found 358.1101 m/z.

IR (cm^{-1}): 3100, 3060, 2960, 2940, 2000, 1790, 1760, 1500, 1060.

Chapter 3. Deoxyaminations of Alcohols Via Dual Purpose In situ Generated Phosphonium Reactive Species : Synthesis of N-alkylphthalimides, N-alkylimdes, & Amines

General Method A: On a bench top, a 10 mL microwave vial was charged with the appropriate *N*-chlorimide, triphenylphosphine (and alcohol substrate if solid) covered with a Kim wipe and tightened with a rubber band. The vial was then brought into an argon filled glovebox before adding the base and capped with a 20 mm microwave crimp caps with septa in the glovebox. The vail was then removed from the glovebox and 3 mL DMF was added. The reaction was then stirred at room temperature to 70 °C overnight. After this time, the reaction mixture was dissolved in 10 mL of ethyl acetate and washed once with a saturated sodium bicarbonate solution and once with brine (8 mL each). The organic extract was dried with sodium sulfate and the resulting solution was concentrated in vacuo prior to isolation via column chromatography.

General Method B: On a bench top, a 10 mL microwave vial was charged with the appropriate *N*-chlorimide, triphenylphosphine (and alcohol substrate if solid) covered with a Kim wipe and tightened with a rubber band. The vial was then brought into an argon filled glovebox before adding the base and capped with a 20 mm microwave crimp caps with septa in the glovebox. The vail was then removed from the glovebox and 3 mL DMF was added. The reaction was then stirred at 60 °C for 48 hours. After this time, the reaction mixture was dissolved in 10 mL of ethyl acetate and washed once with a saturated sodium bicarbonate solution and once with brine (8 mL each). The organic extract was dried with sodium sulfate and the resulting solution was concentrated in vacuo prior to isolation via column chromatography.

General Method C: On a bench top, a 10 mL microwave vial was charged with *N*-chlorosuccinimide and triphenylphosphine (and alcohol substrate if solid). Afterwards the vial was capped and degassed five times for five minutes each. The solids are dissolved in DMF (3 mL) and stirred for five minutes at room temperature. Afterwards, the appropriate amine is added (alcohol is added prior to amine if alcohol is a liquid) and the reaction mixture is allowed to stir overnight at room temperature. After this time, the reaction mixture was dissolved in 10 mL of ethyl acetate and washed twice with a saturated sodium bicarbonate solution and once with brine (8 mL each). The organic extract was dried with sodium sulfate and the resulting solution was concentrated in vacuo prior to isolation via column chromatography.

Preparation of 2-benzylisoindoline-1,3-dione (***3.3***): Using general method A, (100 mg benzyl alcohol, 253 mg *N*-chlorophthalimide, 367 mg triphenylphosphine, 457 mg cesium carbonate, and

3 mL DMF, room temperature, 16h), the product was then purified via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.55) at 78 % yield, 171 mg. Spectra data matched reported data.[85]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.71 (m, 2H), 7.56 – 7.39 (m, 2H), 7.38 – 7.18 (m, 3H), 4.87 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168, 136.4, 134, 132.2, 128.7, 128.6, 127.8, 123.3, 41.6

Preparation of 2-(4-methylbenzyl)isoindoline-1,3-dione (***3.4***): Following procedure A, (100 mg 4-methylbenzyl alcohol 223 mg *N*-chlorophthalimide, 323 mg triphenylphosphine, 401 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.49) at 70% yield, 144 mg. Spectra data matched reported data.[86]

^{1}H NMR (400 MHz $CDCl_3$) δ 7.85 (m, 2H), 7.71 (m, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 4.82 (s, 2H), 2.33 (s, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168, 137.5, 133.9, 133.5, 132.2, 129.3, 128.6, 123.3, 41.4

Preparation of 2-(4-methoxybenzyl)isoindoline-1,3-dione (***3.5***): Following procedure A, (100 mg 4-methoxybenzyl alcohol, 200 mg *N*-chlorophthalimide, 289 mg triphenylphosphine, 359 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.35) at 74 % yield, 143 mg. Spectra data matched reported data.[85]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.71 (m, 2H), 7.49 – 7.32 (m, 2H), 6.94 – 6.75 (m, 2H), 4.82 (s, 2H), 3.80 (s, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168, 159.3, 133.9, 132.2, 130.1, 128.7, 123.3, 114, 55.3, 41.1

Preparation of 2-([1,1'-biphenyl]-4-ylmethyl)isoindoline-1,3-dione (***3.6***): Following procedure A, (100 mg [1,1'-biphenyl]- 4-ylmethanol, 172 mg *N*-chlorophthalimide, 249 mg triphenylphosphine, 310 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.53) at 76% yield, 129 mg. Spectra data matched reported data.[87]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 2H), 7.55 (m, 2H), 7.47 – 7.38 (m, 6H), 7.28 (t, J = 7.6 Hz, 2H), 7.23 – 7.15 (m, 1H), 4.77 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168.1, 140.8, 140.7, 135.5, 134, 132.2, 129.1, 128.8, 127.5, 127.4, 127.1, 123.4, 41.4

Preparation of 2-(4-fluorobenzyl)isoindoline-1,3-dione (***3.7***): Following procedure A, (100 mg 4-fluoro benzyl alcohol 216 mg *N*-chlorophthalimide, 312 mg triphenylphosphine, 388 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was then purified via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.39) at 71 % yield, 144 mg. Spectra data matched reported data.[85]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 2H), 7.60 (m, 2H), 7.40 – 7.25 (m, 2H), 6.94 – 6.81 (m, 2H), 4.71 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168, 163.6, 161.2, 134, 134, 132.1, 130.6, 130.5, 123.3, 115.6, 115.4, 41.6.

Preparation of 2-(4-chlorobenzyl)isoindoline-1,3-dione (***3.8***): Following procedure A, (100 mg 4-chloro benzyl alcohol, 190 mg *N*-chlorophthalimide, 275 mg triphenylphosphine, 343 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.43) at 68 % yield, 129 mg. Spectra data matched reported data.[85]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.72 (m, 2H), 7.46 – 7.37 (m, 2H), 7.33– 7.23 (m, 2H), 4.82 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167.9, 134.9, 134, 132.1, 130.1, 128.9, 123.4, 41.

Preparation of 2-(4-bromobenzyl)isoindoline-1,3-dione (***3.9***): Following procedure A, (100 mg 4-bromo benzyl alcohol, 147 mg *N*-chlorophthalimide, 212 mg triphenylphosphine, 264 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.49) at 75 % yield, 118 mg. Spectra data matched reported data.[87]

^{1}HNMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.72 (m, 2H), 7.50 – 7.39 (m, 2H), 7.37 – 7.28 (m, 2H), 4.81 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167.9, 135.4, 134.1, 132, 131.8, 130.4, 123.4, 121.9, 41.

Preparation of 2-(4-iodobenzyl)isoindoline-1,3-dione (***3.10***): Following procedure A, (100 mg 4-iodo benzyl alcohol, 118 mg *N*-chlorophthalimide, 171 mg triphenylphosphine, 212 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.45) at 61 % yield, 156 mg. Spectra data matched reported data.[88]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.72 (m, 2H), 7.68 – 7.58 (m, 2H), 7.19 (d, J = 8.2 Hz, 2H), 4.79 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167.9, 137.8, 136, 134.1, 132.1, 130.6, 123.4, 93.6, 41.1.

Preparation of 2-(benzo[d][1,3]dioxol-5-ylmethyl)isoindoline-1,3-dione (***3.11***): Following procedure A, (100 mg piperonyl alcohol, 180 mg *N*-chlorophthalimide, 260 mg triphenylphosphine, 323 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.41) at 72% yield, 133 mg. Spectra matches reported data.[85]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.71 (m, 2H), 7.03 – 6.93 (m, 2H), 6.84 – 6.67 (m, 1H), 5.93 (s, 2H), 4.76 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168, 147.8, 147.2, 134, 132.2, 130.2, 123.3, 122.3, 109.3, 108.3, 101.1, 41.

Preparation of 2-(naphthalen-2-ylmethyl)isoindoline-1,3-dione (***3.12***): Following procedure A, (100 mg 2-napthlenemethanol, 172 mg *N*-chlorophthalimide, 249 mg triphenylphosphine, 310 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.49) at 67% yield, 122 mg. Spectra data matched reported data.[87]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.74 – 7.63 (m, 5H), 7.54 (m, 2H), 7.44 (m, 1H), 7.36 – 7.26 (m, 2H), 4.89 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168.1, 134, 133.9, 133.3, 132.9, 132.2, 128.5, 128, 127.7, 127.6, 126.4, 126.2, 126.1, 123.4, 41.8.

Preparation of 2-(naphthalen-1-ylmethyl)isoindoline-1,3-dione (***3.13***): Following procedure A, (100 mg naphthalen-1- ylmethanol, 172 mg *N*-chlorophthalimide, 249 mg triphenylphosphine, 310 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.45) at 78% yield, 142 mg. Spectra data matched reported data.[89]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (m, 1H), 7.90 – 7.77 (m, 4H), 7.68 (m, 2H), 7.64 – 7.55 (m, 2H), 7.50 (m, 1H), 7.43 (m, 1H), 5.34 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168.2, 134, 133.8, 132.1, 131.4, 128.7, 128.6, 127.3, 126.5, 125.8, 125.3, 123.5, 123.4, 39.5

Preparation of 2-(1-phenylpentyl)isoindoline-1,3-dione (***3.15***): Following procedure B, (100 mg 1-phenyl-1-pentanol, 167 mg *N*-chlorophthalimide, 241 mg triphenylphosphine, 300 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.69) at 50% yield, 89 mg. Spectra data matched reported data.[90]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.60 (m, 2H), 7.50 – 7.45 (m, 2H), 7.27 – 7.21 (m, 2H), 7.20 – 7.15 (m, 1H), 5.25 (dd, J = 9.7, 6.6 Hz, 1H), 2.61 – 2.37 (m, 1H), 2.20 (m, 1H), 1.37 – 1.11 (m, 4H), 0.81 (t, J = 7.1 Hz, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168.2, 139.9, 133.9, 131.9, 128.5, 128.2, 127.4, 123.2, 55.1, 30.7, 29.2, 22.3, 14.

Preparation of Preparation of 2-(pyridin-2-ylmethyl)isoindoline-1,3-dione (***3.16***): Following procedure A, (100 mg 2- pyridinemethanol, 250 mg *N*-chlorophthalimide, 362 mg triphenylphosphine, 450 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (1:1 Hexanes: Ethyl Acetate, R_f = 0.38) at 32% yield, 70 mg. Spectra data matched reported data.[91]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.37 (m, 1H), 7.80 (m, 2H), 7.73-7.58 (m, 2H), 7.56 (m, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.08 (dd, J = 7.6, 4.9 Hz, 1H), 4.94 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168.1, 155.4, 149.7, 136.7, 134, 132.3, 123.5, 122.5, 121.5, 43

Preparation of 4-((1,3-dioxoisoindolin-2-yl)methyl)phenyl acetate (***3.17***): Following procedure A, (100 mg 4-acetoxy benzyl alcohol, 163 mg *N*-chlorophthalimide, 236 mg triphenylphosphine, 293 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (5:3:1 DCM: Hexanes: Ethyl Acetate, R_f = 0.61) at 33% yield, 58 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.70 (m, 2H), 7.50 – 7.38 (m, 2H), 7.07 – 6.91 (m, 2H), 4.82 (s, 2H), 2.27 (s, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 169.3, 167.7, 150.7, 134, 133.9, 132.1, 130, 123.4, 121.8, 41, 21.1.

HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{14}NO_4^+$, 296.0917 m/z; found, 296.0882 m/z.

Preparation of 2-cinnamylisoindoline-1,3-dione (***3.18***): Following procedure A, (100 mg trans cinnamyl alcohol, 205 mg *N*-chlorophthalimide, 296 mg triphenylphosphine, 386 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column

chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.50) at 20% yield, 39 mg. Spectra data matched reported data.[92]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.63 (m, 2H), 7.29 – 7.10 (m, 5H), 6.58 (d, J = 15.8 Hz, 1H), 6.18 (dt, J = 15.8, 6.5 Hz, 1H), 4.36 (dd, J = 6.4, 1.4 Hz, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167.9, 136.3, 134, 133.9, 132.2, 128.5, 127.9, 126.6, 123.3, 122.8, 39.7

Preparation of 2-(but-2-yn-1-yl)isoindoline-1,3-dione (***3.19***): Following procedure A, (100 mg 2-butyn-1-ol, 390 mg *N*-chlorophthalimide, 564 mg triphenylphosphine, 701 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (2:1 DCM: Hexanes, R_f = 0.49) at 21% yield, 60 mg. Spectra data matched reported data.[93]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 –7.81(m, 2H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 4.39 (q, J = 2.4 Hz, 2H), 1.76 (t, J = 2.4 Hz, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167, 134.1, 132.2, 132.1, 132, 128.6, 128.4, 123.6, 123.5, 79.3, 72.6, 27.4, 3.49

Preparation of 2-(3-phenylprop-2-yn-1-yl)isoindoline-1,3-dione (***3.20***): Following procedure A, (100 mg 3-phenyl-2-propyn-1-ol, 207 mg *N*-chlorophthalimide, 299 mg triphenylphosphine, 369 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (1:3:1 DCM: Hexanes: Ethyl Acetate, R_f = 0.59) at 29% yield, 57 mg. Spectra matches reported data.[94]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.67 (m,2H), 7.44 – 7.29 (m, 2H), 7.24 – 7.10 (m, 3H), 4.61 (s, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167.2, 134.1, 132.2, 132, 128.5, 128.2, 123.5, 122.4, 27.9.

Preparation of 2-(oct-2-yn-1-yl)isoindoline-1,3-dione (***3.21***): Following procedure A, (100 mg 2-octyn-1-ol, 218 mg *N*-chlorophthalimide, 315 mg triphenylphosphine, 392 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.39) at 50% yield, 101 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.71 (m, 2H), 4.40 (t, J = 2.2 Hz, 2H), 2.11 (m, 2H), 1.45 (m, 2H), 1.45 (m, 2H), 0.89 – 0.75 (m, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167, 134, 132.2, 123.4, 83.8, 73.4, 31, 28.1, 27.5, 22.1, 18.6, 13.9.

HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{18}NO_2^+$, 256.1332 m/z; found, 256.1270 m/z.

Preparation of 2-phenethylisoindoline-1,3-dione (***3.22***): Following procedure A, (49 mg 2-Phenylethanol, 109 mg *N*-chlorophthalimide, 158 mg triphenylphosphine, 212 mg potassium phosphate tribasic, and 3 mL DMF, stirred at 70 °C, 16h), the product was then purified via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.53) at 78 % yield, 78 mg. Spectra matches reported data.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 –7.80 (m, 2H), 7.77 – 7.64 (m, 2H), 7.34 – 7.21 (m, 5H), 4.04 – 3.87 (m, 2H), 3.19 – 2.82 (m, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168.1, 138, 133.9, 132.1, 128.9, 128.6, 126.7, 123.2, 39.3, 34.6.

Preparation of 2-(4-phenylbutyl)isoindoline-1,3-dione (***3.23***): Following procedure A, (60 mg 4-Phenyl-1-butanol, 109 mg *N*-chlorophthalimide, 158 mg triphenylphosphine, 212 mg potassium phosphate tribasic, and 3 mL DMF, stirred at 70 °C, 16h), the product was then purified via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.59) at 83 % yield, 92 mg. Spectra matches reported data.[96]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.76 (m, 2H), 7.72 – 7.59 (m, 2H), 7.26 (m, 2H), 7.17 (m, 3H), 3.71 (t, J = 6.8 Hz, 2H), 2.65 (t, J = 7.3 Hz, 2H), 1.85 – 1.60 (m, 4H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168.4, 142, 133.9, 132.2, 128.5, 128.4, 125.8, 123.2, 37.8, 35.4, 28.7, 28.2.

Preparation of 2-(cyclopropylmethyl)isoindoline-1,3-dione (***3.24***): Following procedure A, (29 mg cyclopropanemethanol, 109 mg *N*-chlorophthalimide, 158 mg triphenylphosphine, 212 mg potassium phosphate tribasic, and 3 mL DMF, stirred at 70 °C, 16h), the product was then purified via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.59) at 85 % yield, 68 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.72 (m, 2H), 3.56 (d, J = 7.2 Hz, 2H), 1.22 (m, 1H), 0.56 –0.48 (m, 2H), 0.43 – 0.37 (m, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168.5, 133.8, 132.3, 123.2, 42.6, 10.5, 3.9

HRMS (ESI): $[M + H]^+$ calcd for $C_{12}H_{12}NO_2^+$ 202.2325 m/z, found 202.2818 m/z.

Preparation of 2-(4-phenylbutan-2-yl)isoindoline-1,3-dione (***3.25***): Following procedure A, (60 mg 4-phenyl-2-butanol, 109 mg *N*-chlorophthalimide, 158 mg triphenylphosphine, 212 mg potassium phosphate tribasic, and 3 mL DMF, stirred at 70 °C, 16h), the product was then purified via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.64) at 11 % yield, 10 mg. Spectra matches reported data.[97]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.76 (m, 2H), 7.70 (m, 2H), 7.21 (t, J = 7.5 Hz, 2H), 7.16 – 7.12 (m, 2H), 7.12 – 7.06 (m, 1H), 4.42 (m, 1H), 2.79 – 2.46 (m, 3H), 2.22 –1.91 (m, 1H), 1.50 (d, J = 6.9 Hz, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 168.5, 141.2, 133.8, 132, 128.3, 125.8, 123, 47.4, 35, 33.3, 18.9

Preparation of 1-benzylpyrrolidine-2,5-dione (***3.26***): Following procedure A, (100 mg benzyl alcohol, 250 mg *N*-bromosuccinimide, 367 mg triphenylphosphine, 457 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (2:1 Ethyl Acetate: Hexanes, R_f = 0.66) at 47% yield, 82 mg. Spectra matches reported data.[98]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.26 – 7.14 (m, 3H), 4.56 (s, 2H), 2.59 (s, 4H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 178, 135.9, 128.9, 128.6, 128, 42.4, 28.2.

Preparation of 1-(4-chlorobenzyl)pyrrolidine-2,5-dione (***3.27***): Following procedure A, (100 mg 4-chloro benzyl alcohol, 142 mg *N*-chlorosuccinimide, 278 mg triphenylphosphine, 346 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (2:1 Ethyl Acetate: Hexanes, R_f = 0.58) at 73% yield, 115 mg. Spectra matches reported data.[99]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 1H), 7.23 – 7.15 (m, 2H), 4.54 (s, 2H), 2.63 (s, 4H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 176.8, 134.3, 130.4, 128.8, 41.7, 28.2.

Preparation of 1-(4-bromobenzyl)pyrrolidine-2,5-dione (***3.28***): Following procedure A, (100 mg 4-bromo benzyl alcohol, 145 mg *N*-bromosuccinimide, 213 mg triphenylphosphine, 264 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (2:1 Ethyl Acetate: Hexanes, R_f = 0.57) at 44% yield, 63 mg. Spectra matches reported data.[99]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.3 Hz, 2H), 7.23 – 7.11 (m, 2H), 4.52 (s, 2H), 2.63 (s, 4H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 176.3, 134.7, 131.8, 130.8, 122.1, 41.8, 28.2.

Preparation of 1-(4-phenylbutyl)pyrrolidine-2,5-dione (***3.29***): Following procedure A, (60 mg 4-phenylbutanol, 81 mg *N*-chlorosuccinimide, 158 mg triphenylphosphine, 212 mg potassium phosphate tribasic, and 3 mL DMF, stirred at 70 °C, 16h), the product was then purified via column

chromatography (1:1 Hexanes: Ethyl Acetate, R_f = 0.44) at 99 % yield, 91.4 mg. Spectra matches reported data.[100]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 –7.15 (m, 2H), 7.10 (m, 3H), 3.54 – 3.33 (m, 2H), 2.60 (s, 4H) 2.55 (m, 2H), 1.69 – 1.33 (m, 4H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 177.24, 141.9, 128.4, 128.3, 125.9, 38.6, 35.4, 28.6, 28.2, 27.3

Preparation of 1-benzyl-4,4-dimethylpiperidine-2,6-dione (***3.30***): Following procedure A, (100 mg benzyl alcohol, 245 mg 1-chloro-4,4-dimethylpiperidine-2,6-dione, 367 mg triphenylphosphine, 457 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (1:1 Ethyl Acetate: Hexanes, R_f = 0.71) at 56% yield, 120 mg. Spectra matches reported data.[101]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 2H), 7.22 – 7.08 (m, 3H), 4.86 (s, 2H), 2.41 (s, 4H), 0.94 (s, 6H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 171.7, 137.4, 128.7, 128.3, 127.4, 46.4, 42.7, 29.2, 27.7.

Preparation of 1-(4-fluorobenzyl)-4,4-dimethylpiperidine-2,6-dione (***3.31***): Following procedure A, (100 mg 4-fluorobenzyl alcohol, 208 mg 1-chloro-4,4-dimethylpiperidine-2,6-dione, 312 mg triphenylphosphine, 388 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (1:1Hexanes: Ethyl Acetate, R_f = 0.69) at 43% yield, 85 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 –7.28 (m, 2H), 6.97 (m, 2H), 4.93 (s, 2H), 2.53 (s, 4H), 1.05 (s, 6H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 171.9, 163.4, 160.9, 133.1, 130.9, 115.3, 46.4, 41.9, 29.2, 27.6.

HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{17}FNO_2^+$, 250.1238 m/z; found, 250.1178 m/z.

Preparation of 4,4-dimethyl-1-(4-methylbenzyl)piperidine-2,6-dione (***3.32***): Following procedure A, (100 mg 4-methyl benzyl alcohol, 216 mg 1-chloro-4,4-dimethylglutameride, 323 mg triphenylphosphine, 401 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (1:1 Hexanes: Ethyl Acetate, R_f = 0.73) at 81% yield, 163 mg.

^{1}H NMR (400 MHz, CDCl3) δ 7.18 (d, J = 7.7 Hz, 2H), 7.00 (d, J = 7.8 Hz, 2H), 4.83 (s, 2H), 2.42 (s, 4H), 2.21 (s, 3H), 0.95 (s, 6H).

$^{13}C\{1H\}$ NMR (100 MHz, CDCl3) δ 171.9, 137, 134.4, 131.6, 129.1, 128.9, 46.44, 42.4, 29.2, 27.7, 21.1.

HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_{20}NO_2^+$, 246.1489 m/z; found, 246.1199 m/z.

Preparation of 1-(4-phenylbutyl)pyrrolidine-2,5-dione (***3.33***): Following procedure A, (60 mg 4-phenylbutanol, 105 mg 1-chloro-4,4-dimethylpiperidine-2,6-dione, 158 mg triphenylphosphine, 212 mg potassium phosphate tribasic, and 3 mL DMF, stirred at 70 °C, 16h), the product was then purified via column chromatography (1:1 Hexanes: Ethyl Acetate, R_f = 0.77) at 46 % yield, 50.1 mg.

^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 2H) 7.16 (m, 3H), 3.80 (t, J = 7.1 Hz, 2H), 2.62 (t, J = 7.4 Hz, 2H), 2.48 (s, 3H), 1.71 – 1.50 (m, 4H), 1.06 (s, 6H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 174, 71.9, 142.3, 128.4, 128.3, 125.8, 125.7, 46.5, 39.3, 35.6, 29.1, 29, 28.9, 27.7

HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{24}NO_2^+$ 274.1802 m/z, found 274.1384 m/z.

Preparation of 1-benzylindoline-2,3-dione (***3.34***): Following procedure A, (100 mg benzyl alcohol, 254 mg 1-chloroindoline- 2,3-dione, 367 mg triphenylphosphine, 457 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Hexanes: Ethyl Acetate, R_f = 0.35) at 73% yield, 160 mg. Spectra matches reported data.[99]

^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 1H), 7.47 (m, 1H), 7.37 – 7.24 (m, 5H), 7.08 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 4.92 (s, 2H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 183, 158.6, 150.2, 138.4, 134.5, 129.1, 128.1, 127.4, 125.4, 123.9, 117.8, 111, 44.1

Preparation of 1-(naphthalen-2-ylmethyl)indoline-2,3-dione (***3.35***): Following procedure A, (100 mg 2- naphthalenemethanol, 172 mg 1-chloroindoline-2,3-dione, 249 mg triphenylphosphine, 310 mg cesium carbonate, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography(5:3:1 DCM: Hexanes: Ethyl Acetate, R_f = 0.5) at 50% yield, 91 mg. Spectra matches reported data.[102]

^1H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.75 (m, 4H), 7.67 – 7.53 (m, 1H), 7.54 – 7.37 (m, 4H), 7.07 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 5.09 (s, 2H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 183, 158.4, 138.2, 133.3, 133.1, 132, 129.2, 127.8, 126.6, 126.4, 125.4, 125.1, 123.9, 117.8, 111.1.

Characterization of Products : Free Amine Coupling

Preparation of Dibenzylamine (***3.36***): Following procedure B, (90 mg benzyl alcohol, 267 mg benzylamine, 167 mg *N*-chlorosuccinimide, 326 mg triphenylphosphine, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (1:1 Hexanes: Ethyl Acetate w/ 0.5 % Et_3N, R_f = 0.41) at 76% yield, 125 mg. Spectra matches reported data.[103]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 8H), 7.21 – 7.15 (m, 2H), 3.74 (s, 4H), 2.09 –1.87 (m, 1H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 140, 128.4, 128.2, 127, 53.1

Preparation of N-benzyl-1-(4-methoxyphenyl)methanamine (***3.37***): Following procedure B, (114 mg 4-Methoxy benzyl alcohol, 267 mg benzylamine, 167 mg *N*-chlorosuccinimide, 326 mg triphenylphosphine, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (Ethyl Acetate w/ 0.5 % Et_3N, R_f = 0.48) at 60% yield, 113 mg. Spectra matches reported data.[103]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 4H), 7.21 – 7.13 (m, 3H), 6.79 (d, J = 8.6 Hz, 2H), 3.72 (s, 5H), 3.67 (s, 2H), 1.53 (s, 1H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 158.7, 140.5, 132.5, 129.3, 128.4, 128.2, 126.9, 113.8, 55.3, 53.1, 52.6

Preparation of N-benzyl-1-(4-fluorophenyl)methanamine (***3.38***): Following procedure B, (105 mg 4-Fluoro benzyl alcohol, 267 mg benzylamine, 167 mg *N*-chlorosuccinimide, 326 mg triphenylphosphine, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (2:1 Ethyl Acetate: Hexanes w/ 0.5 % Et_3N, R_f = 0.4) at 69% yield, 123 mg. Spectra matches reported data.[105]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.17 (m, 7H), 7.01 (m, 2H), 3.79 (d, J = 9.7 Hz, 4H), 1.58 (s, 1H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 163.2, 160.7, 140.3, 136.1, 129.7, 129.6, 128.4, 128.1, 127, 115.3, 115, 53.2, 52.4

Preparation of N-(4-methylbenzyl)cyclohexanamine (**3.39**): Following procedure B, (102 mg 4-Methyl benzyl alcohol, 247 mg cyclohexylamine, 167 mg *N*-chlorosuccinimide, 326 mg triphenylphosphine, and 3 mL DMF), the product was isolated via column chromatography (1:1 Ethyl Acetate: Hexanes w/ 0.5 % Et_3N, R_f = 0.25) at 80% yield, 135 mg. Spectra matches reported data.[106]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.8 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 3.80 (s, 2H), 2.50 (m, 1H), 2.36 (s, 3H) 2.01 – 1.90 (m, 2H), 1.86 –1.72 (m, 2H), 1.64 (m, 1H), 1.42 – 1.08 (m, 5H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 138, 136.3, 129.1, 128, 56.1, 50.8, 33.6, 26.3, 25, 21.1

Preparation of N-(naphthalen-2-ylmethyl)cyclopropanamine (**3.40**): Following procedure B, (131 mg 2-napthlenemethanol, 142 mg cyclopropylamine, 167 mg *N*-chlorosuccinimide, 326 mg triphenylphosphine, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (1:1 Ethyl Acetate: Hexanes w/ 0.5 % Et_3N, R_f = 0.35) at 61% yield, 100 mg.

^1H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.52 (m, 4H), 7.31 (m, 3H), 3.85 (s, 2H), 2.04 (m, 1H), 1.92 (s, 1H), 0.31 (d, 4H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.2, 133.6, 132.7, 128.1, 127.8, 127.7, 126.8, 126.5, 126.0, 125.6, 53.9, 30.2, 6.6.

HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{16}N^+$ 198.1282 m/z, found 198.0970 m/z.

Preparation of N-([1,1'-biphenyl]-4-ylmethyl)decan-1-amine (**3.41**): Following procedure B, (153 mg 4-Phenyl benzyl alcohol, 391 mg decylamine, 167 mg *N*-chlorosuccinimide, 326 mg triphenylphosphine, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (Ethyl Acetate w/ 0.5 % Et_3N, R_f = 0.29) at 82% yield, 220 mg.

^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 4H), 7.37 – 7.25 (m, 4H), 7.22 (m, 1H), 3.72 (s, 2H), 2.75 – 2.40 (m, 4H), 1.43 (p, J = 7.0 Hz, 2H), 1.18 13 (m, 14H), 0.79 (t, J = 6.7 Hz, 3H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.8, 141.0, 139.9, 139.6, 128.8, 128.6, 127.2, 127.1, 53.7, 49.5, 32.0, 30.1, 29.7, 29.4, 27.4, 22.8, 14.2.

HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{34}N^+$ 324.2691 m/z, found 324.2408 m/z.

Preparation of 1-(naphthalen-2-ylmethyl)pyrrolidine (**3.42**): Following procedure B, (131 mg 2-napthlenemethanol, 175 mg pyrrolidone, 167 mg *N*-chlorosuccinimide, 326 mg triphenylphosphine, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (1:1 Ethyl Acetate: Hexanes w/ 0.5 % Et_3N, R_f = 0.30) at 78% yield, 137 mg. Spectra matches reported data.[107]

^1H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.73 (m, 4H), 7.61 – 7.43 (m, 3H), 3.78 (s, 2H), 2.56 (m, 3H), 2.09 – 1.63 (m, 5H).

$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.1, 133.4, 132.7, 127.8, 127.7, 127.6, 127.4, 127.2, 125.9, 125.5, 60.9, 54.3, 23.5

Preparation of 4-(4-methylbenzyl)morpholine (***3.43***): Following procedure B, (102 mg 4-Methyl benzyl alcohol, 217 mg morpholine, 167 mg *N*-chlorosuccinimide, 326 mg triphenylphosphine, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography

(1:1 Ethyl Acetate: Hexanes w/ 0.5 % Et_3N, R_f = 0.34) at 78% yield, 124 mg. Spectra matches reported data.[108]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 3.80– 3.61 (m, 4H), 3.46 (s, 2H), 2.44 (m, 4H), 2.34 (s, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 136.8, 134.7, 129.2, 129, 67.1, 63.2, 53.6, 21.1

Preparation of 4-methyl-1-(1-phenylethyl)piperidine (***3.44***): Following procedure B, (100 mg 1-phenylethan-1-ol, 142 mg 4-methylpiperidine, 165 mg *N*-chlorosuccinimide, 323 mg triphenylphosphine, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (3:1 Ethyl Acetate: Hexanes w/ 0.5 % Et_3N, R_f = 0.54) at 23% yield, 38 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 4H), 7.18 – 7.11 (m, 1H), 3.31 (q, J = 6.7 Hz, 1H), 3.02 – 2.86 (m, 1H), 2.68 (m, 1H), 1.85 (m, 1H), 1.74 (m, 1H), 1.54 (m, 1H), 1.44 (m, 1H), 1.29 (d, J = 6.7 Hz, 3H), 1.19 (m, 2H), 1.08 (m, 1H), 0.81 (d, J = 5.8 Hz, 3H).

^{13}C{1H} NMR (100 MHz, CDCl3) δ 144.1, 128.1, 127.8, 126.7, 65.0, 51.0, 34.7, 30.9, 21.9, 19.7.

HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{22}N^+$ 204.1747 m/z, found 204.1323 m/z.

IR (cm^{-1}): 3100, 2920, 2850, 1740, 1450, 1130.

Preparation of 2-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)pyrimidine (**3.45**): Following procedure B, (156 mg piperonyl alcohol, 142 mg cyclopropylamine, 209 mg *N*-chlorosuccinimide, 401 mg triphenylphosphine, and 3 mL DMF, room temperature, 16h), the product was isolated via column chromatography (1:1 Ethyl Acetate : Hexanes w/ 0.5 % Et_3N, R_f = 0.30) at 48 % yield, 146 mg. Spectra matched reported data.[23e]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, 2H), 6.81 (s, 1H), 6.68 (s, 2H), 6.39-3.37 (t, 1H), 5.86 (s, 2H), 3.75-3.73 (t, 4H), 3.37 (s, 2H), 2.42-2.39 (t, 4H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 161.7, 157.7, 147.7, 146.7, 131.9, 122.2, 109.7, 109.5, 107.9, 100.9, 62.9, 52.8, 43.7.

Starting Material(s) Characterization : Alcohols, N-chloroimides, & Amines

Preparation of 4-(hydroxymethyl)phenyl acetate: The alcohol starting material was synthesized following literature procedure.[109a] (300 mg 4-hydroxy benzyl alcohol, 189 mg chloroformate, 245 mg triethylamine, all dissolved in 30 mL ethyl acetate) Product was isolated via column chromatography (3:2 Hexanes: Ethyl Acetate, R_f = 0.26) at 49 % yield, 197 mg Spectra data matched reported data.[109b]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.5 Hz, 2H), 7.12 – 6.90 (m, 2H), 4.55 (s, 2H), 3.08 (s, 1H), 2.28 (s, 3H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 169.3, 150, 138.6, 128, 121.5, 64.2, 21.1.

Preparation of (E)-3-phenylprop-2-en-1-ol: The alcohol starting material was synthesized via reduction of *trans*-cinnamaldehyde (200 mg) with sodium borohydride (116 mg) in dissolved in 3 mL methanol and ran in an ice bath for 15 minutes and then at room temperature for two hours. Afterwards the solution was dissolved in 10 mL of DCM and washed with a saturated ammonium chloride solution (8 mL). The subsequent organic extract was then dried with sodium sulfate and concentrated via rotovap. The product was isolated via column chromatography (1:1 Hexanes: Ethyl Acetate, R_f= 0.61) at 54 % yield, 110 mg. Spectra data matched reported data.[110]

$_{1}$H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.26 (m, 5H), 6.64 (dd, J = 16.0, 1.6 Hz, 1H), 6.39 (dt, J = 15.9, 5.7 Hz, 1H), 4.33 (dd, J = 5.7, 1.6 Hz, 2H).

$_{13}$C{1H} NMR (100 MHz, $CDCl_3$) δ 136.8, 130.9, 128.7, 127.7, 126.5, 63.5.

Preparation of 1-chloro-4,4-dimethylpiperidine-2,6-dione: The *N*-chloroimide starting material was synthesized following literature procedure.[111a] 4,4-dimethylpiperidine-2,6-dione (500 mg), trichloroisocyanuric acid (270 mg), glacial acetic acid (1.2 mL) were all dissolved in 20 mL DI water. Product was isolated via column chromatography (1:1 Hexanes: Ethyl Acetate, R_f =0.63) at 68 %, 422 mg. Spectra data matched reported data.[111b]

^{1}HNMR (400 MHz, $CDCl_3$) δ 2.73 (s, 4H), 1.14 (s, 6H)

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167.3, 47.4, 29.5, 27.4.

Preparation of 1-chloroindoline-2,3-dione: To a flame dried and N_2 evacuated round bottom flask, indoline-2,3-dione (736 mg) was added and dissolved in DCM (30 mL) and allowed to cool to 0 °C. Afterwards trichloroisocyanuric acid (1.22 g) was added and the resulting mixture was removed from the ice bath and allowed to run overnight at room temperature. The mixture was then filtered through celite and the resulting pure product was dried via vacuum. 67 % yield, 607 mg. Spectra data matched reported data.[112]

^{1}HNMR (400 MHz, $CDCl_3$) δ 7.85 – 7.39 (m, 2H), 7.25 – 6.91 (m, 2H).

^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 178.2, 155.3, 149.5, 139.1, 125.3, 119.7, 111.4.

Preparation of 2-(piperazin-1-yl)pyrimidine: The amine compounds was synthesized following the literature procedure[113a] (1.0 g 4-chloropyrimidine, 1.88 g piperazine, 1.11 g potassium carbonate, all dissolved in 10 mL DI water). Product was isolated via column chromatography (9:1 DCM: MeOH, R_f= 0.17) at 83% yield, 1.20 g. Spectra data matched reported data[113b]

^{1}HNMR(400 MHz, $CDCl_3$) δ 8.23 (d, 2H), 6.41 (t, 1H), 3.73 (t, 4H), 2.86 (t, 4H), 1.95 (s, 1H).

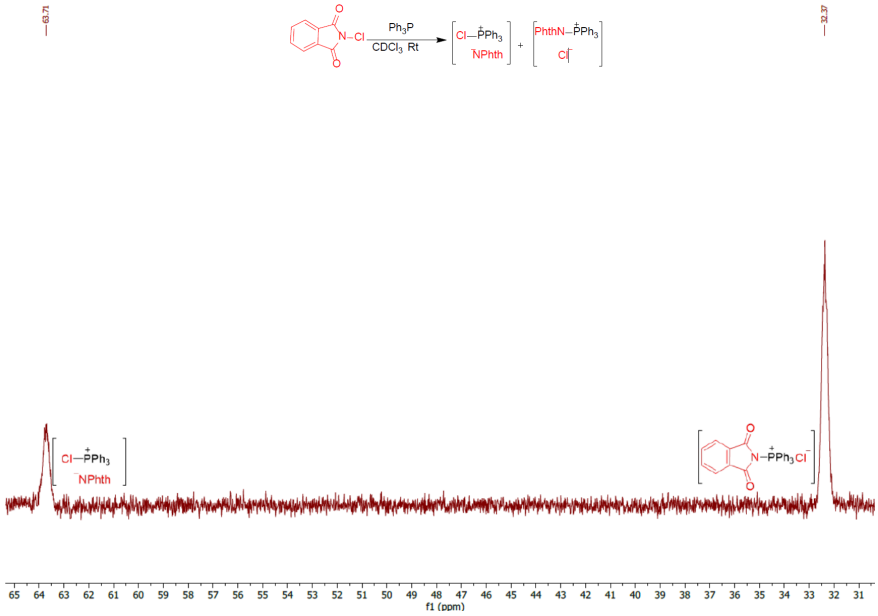
$^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.8, 157.7, 109.7, 46.0, 44.8.

APPENDIX B. EXPERIMENTAL SPECTRA

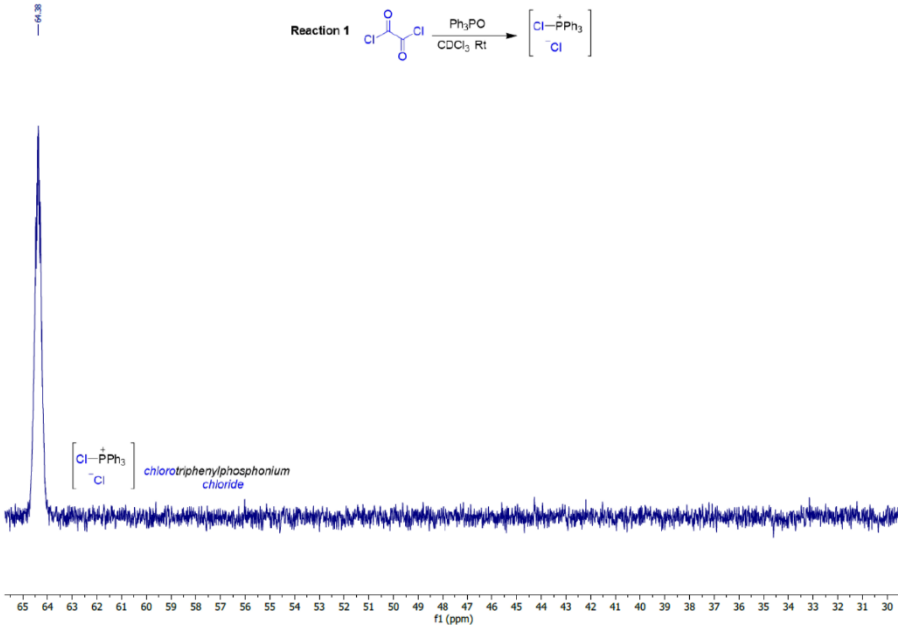
CHAPTER 2. Deoxyamidation of Carboxylic Acids Via In situ Generated Phosphonium Reactive Species : Synthesis of Amides & Acyl Phthalimide Derivatives

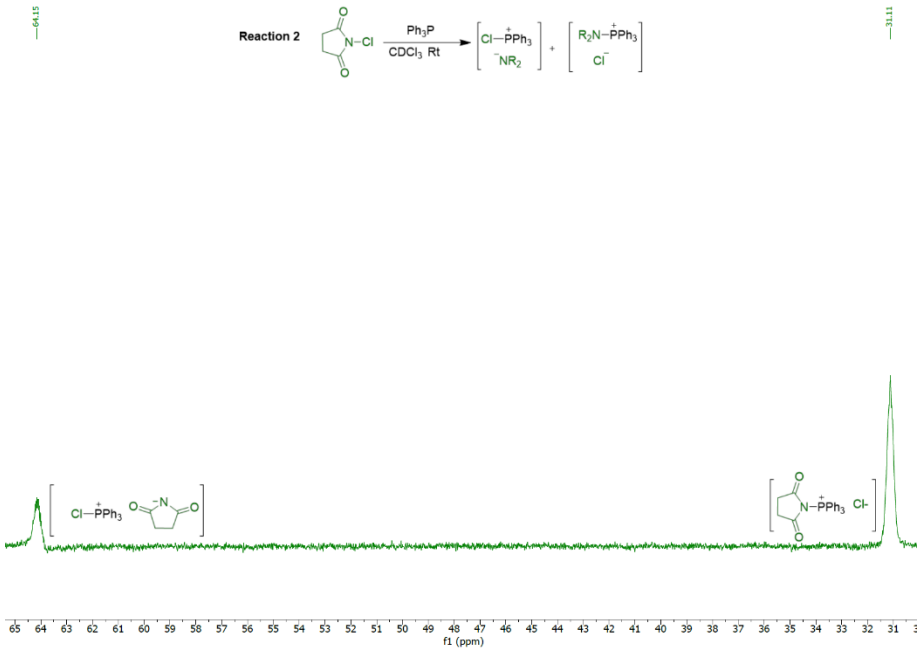
I.) ^{31}P NMR Spectra

A.) ^{31}P NMR Studies: PPh3/NCPhth Mixture & Observation of Reactive Species

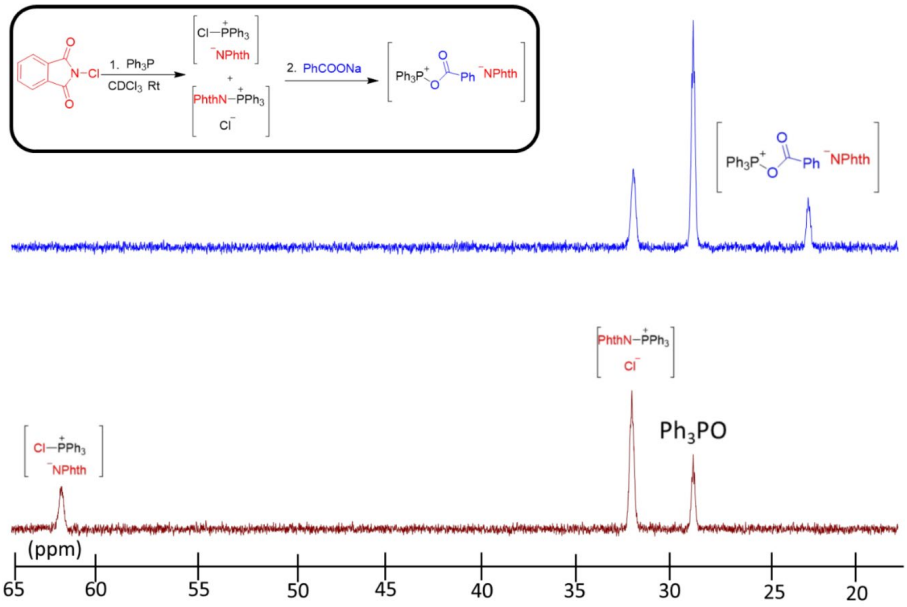


B.) ^{31}P NMR Studies: Confirmation of Reactive Species, Chlorophosphonium Vs Imidophosphonium

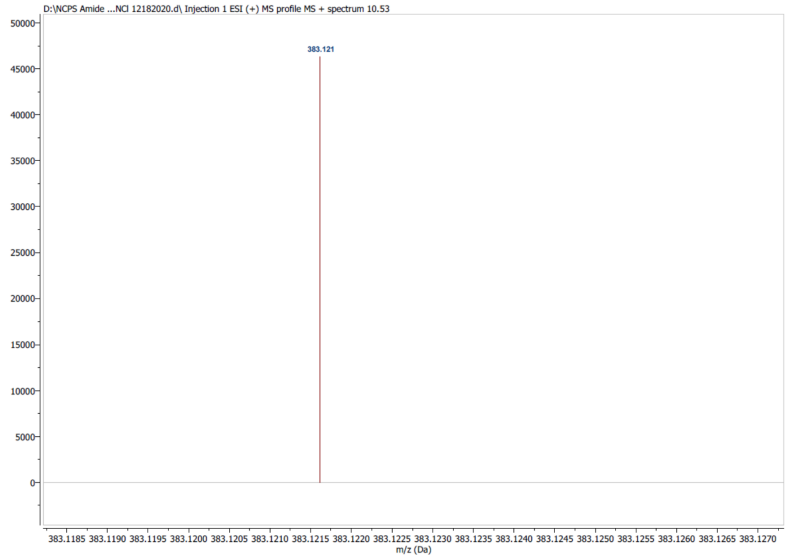




C.) ^{31}P NMR Studies: Acyloxyphosphonium Intermediate Detection



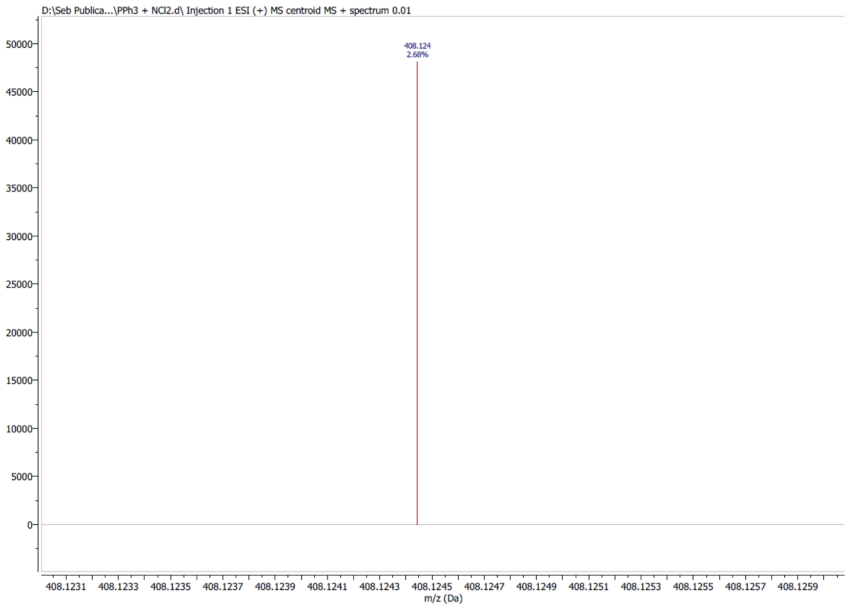
B.) High Resolution Detection of Acyloxyphosphonium Key Intermediate



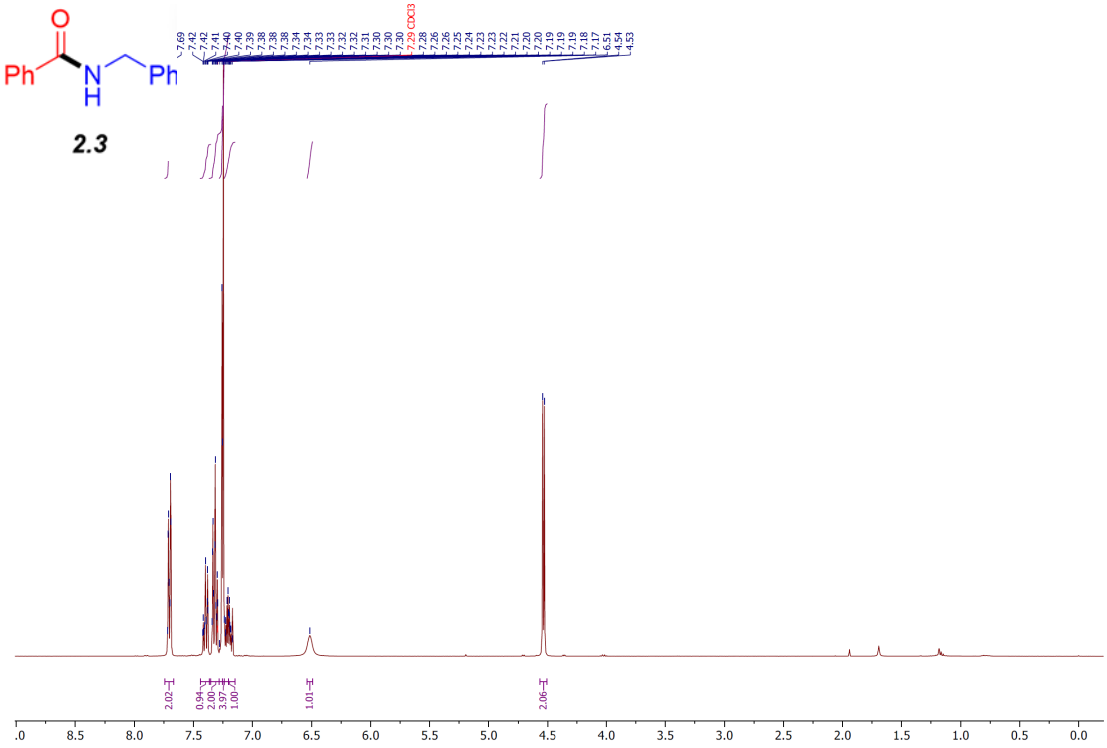
Detection of Acyloxyphosphonium Intermediate. Reaction was carried out under direct injection procedure, run under positive mode with two separate solutions (PPh_3/NCPhth & PhCOONa) both at a concentration of 50 µM. All solids were dissolved in freshly distilled anhydrous acetonitrile. Calculated Mass (383.1195 m/z) for $C_{25}H_{20}O_2P^+$, Observed Mass (M^+, 383.1215).

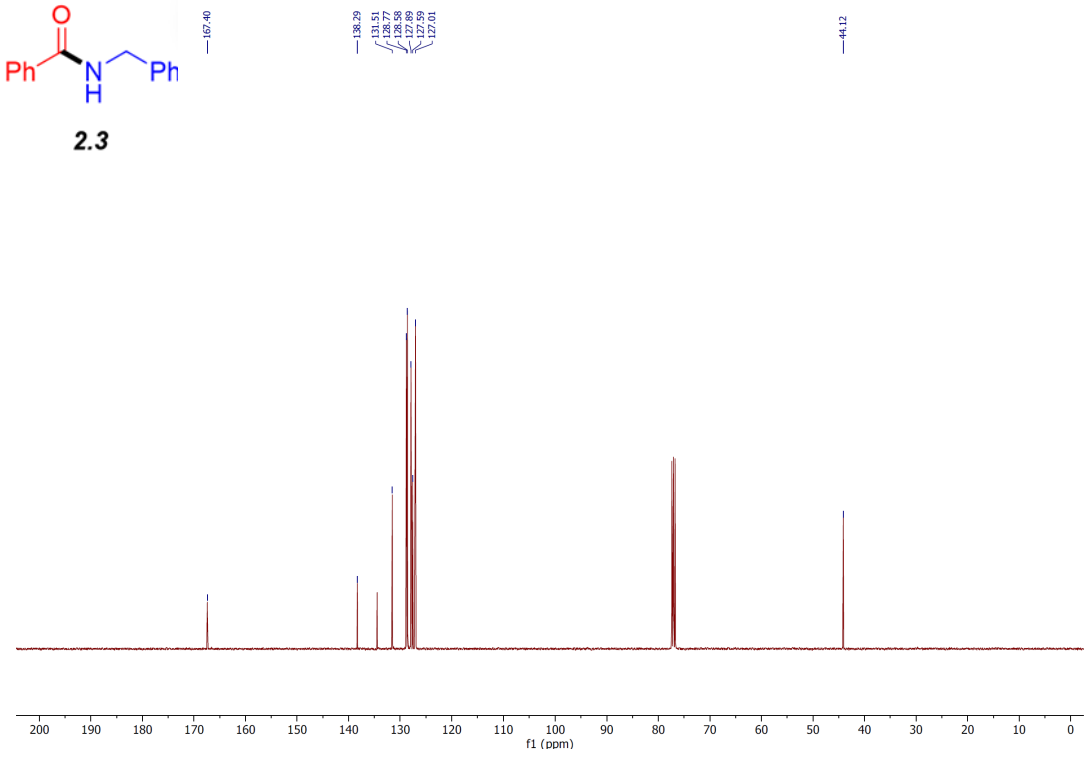
II.) HRMS Spectra of Phosphonium Species

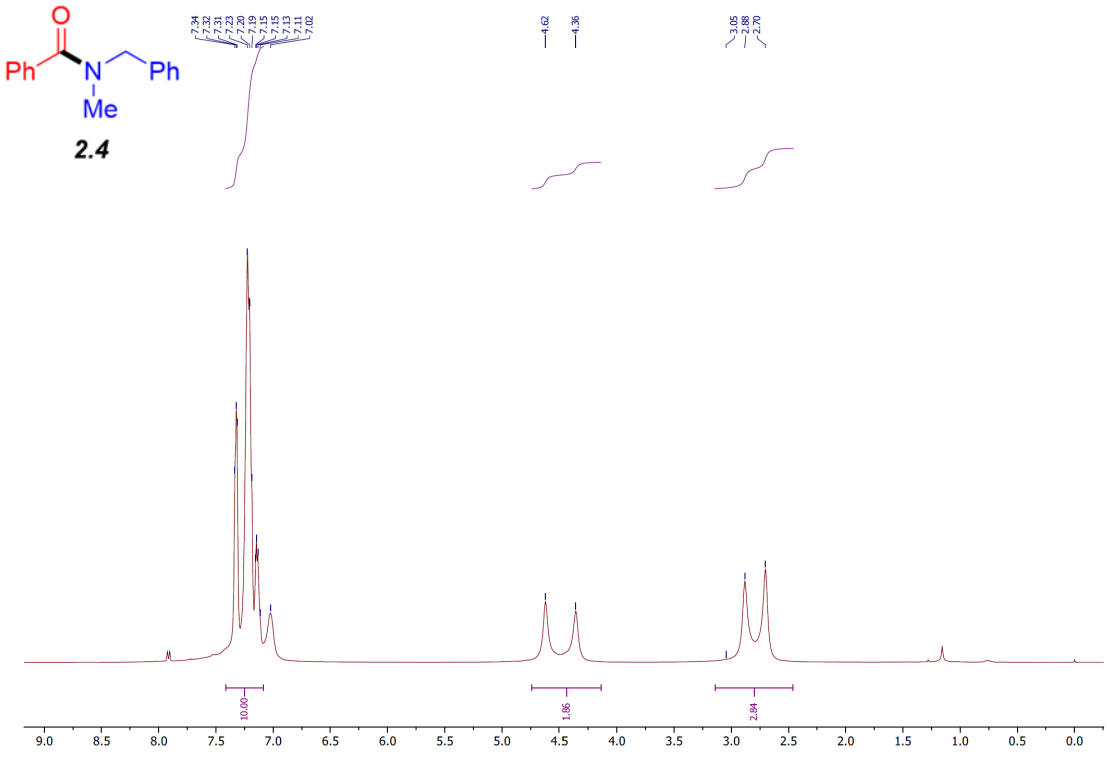
A.) High Resolution LCMS Detection of Reactive Species

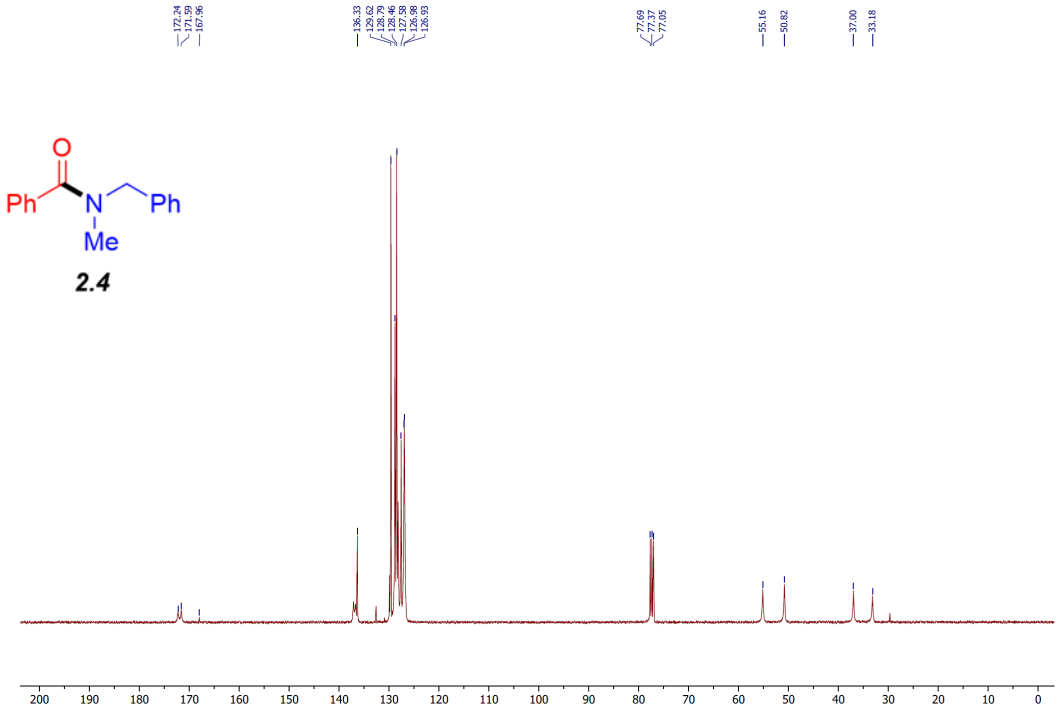


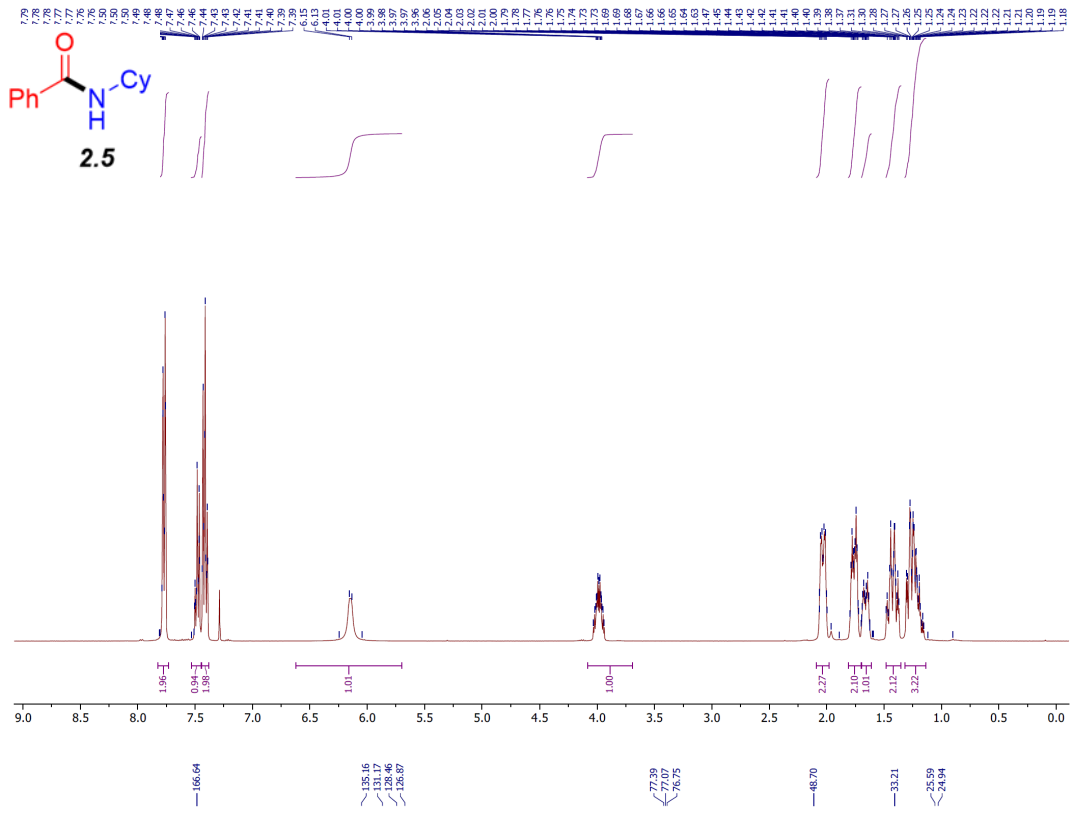
Detection of Imidophosphonium Intermediate. Reaction was carried out under direct injection procedure, run under positive mode with two separate solutions (PPh_3 & NCPhth) both at a concentration of 50 µM. All solids were dissolved in freshly distilled anhydrous acetonitrile. Calculated Mass (408.1148 m/z) for $C_{26}H_{19}NO_2P^+$, Observed Mass (M^+, 408.1248).

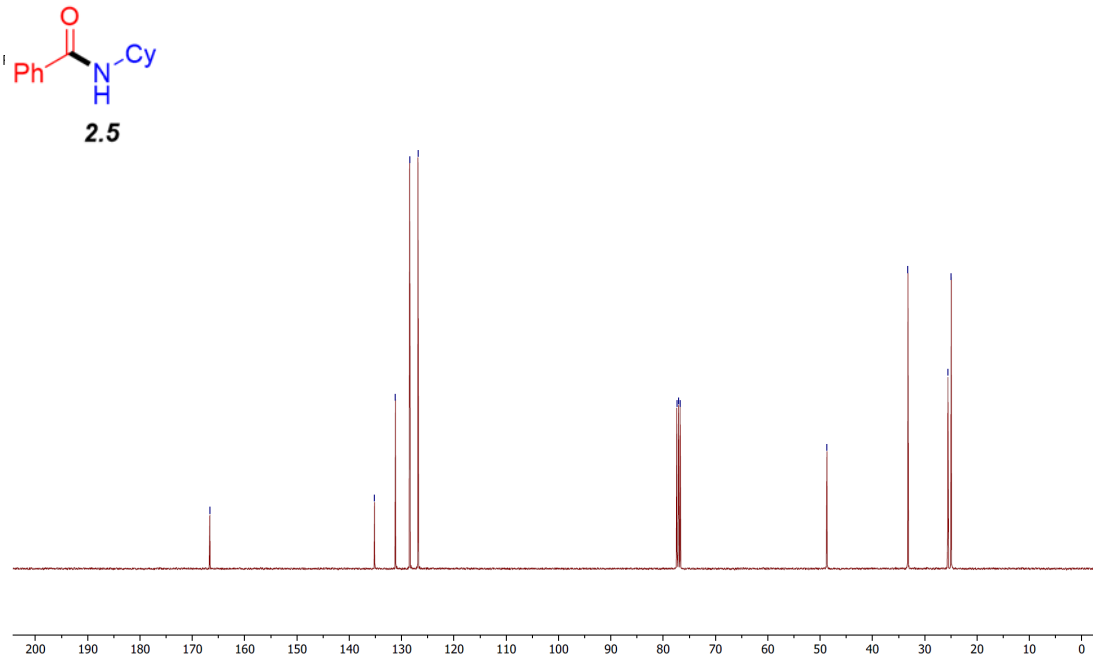

Ph
N
H
Ph
2.3
7.69
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.38
7.38
7.38
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.30
CDCl3
7.28
7.26
7.26
7.25
7.24
7.23
7.23
7.22
7.21
7.20
7.20
7.19
7.19
7.19
7.18
7.17
6.51
4.54
4.53
2.02
0.94
2.00
3.97
1.00
1.01
2.06
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

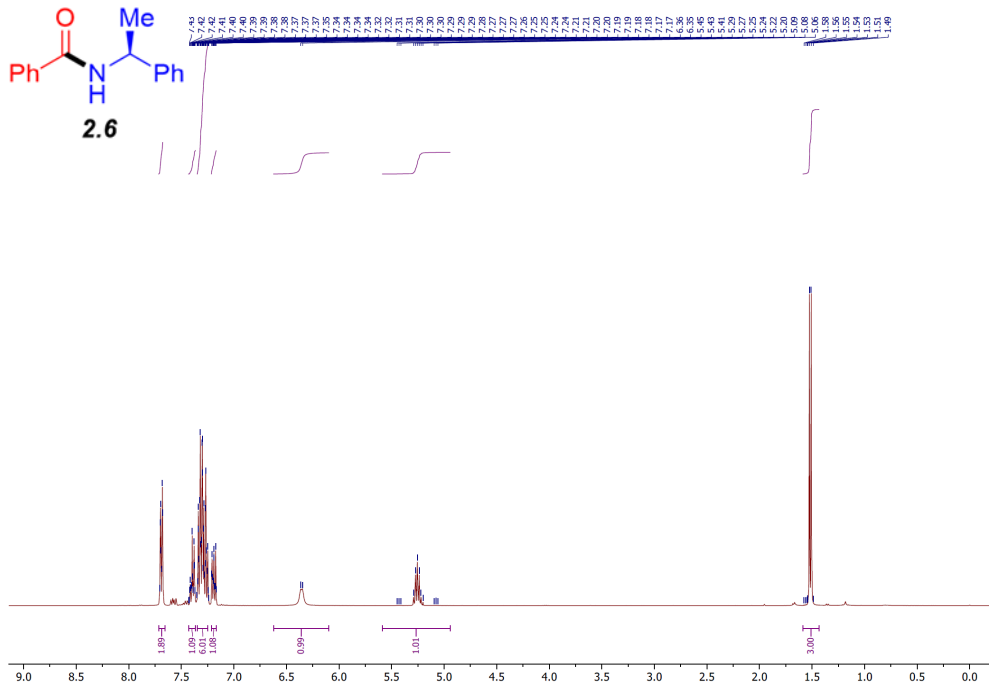

Ph
N
H
Ph
2.3
167.40
138.29
131.51
128.77
128.58
127.89
127.59
127.01
44.12
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

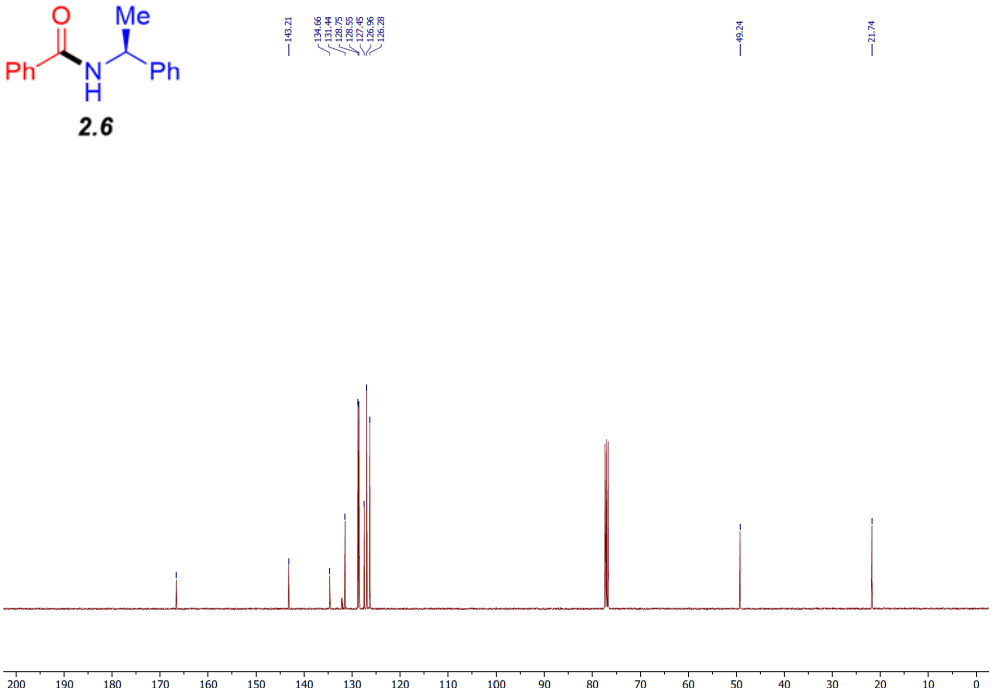

Ph
N
Ph
Me
2.4
7.34
7.32
7.31
7.23
7.20
7.19
7.15
7.13
7.11
7.02
4.62
4.36
3.05
2.88
2.70
10.00
1.86
2.84
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

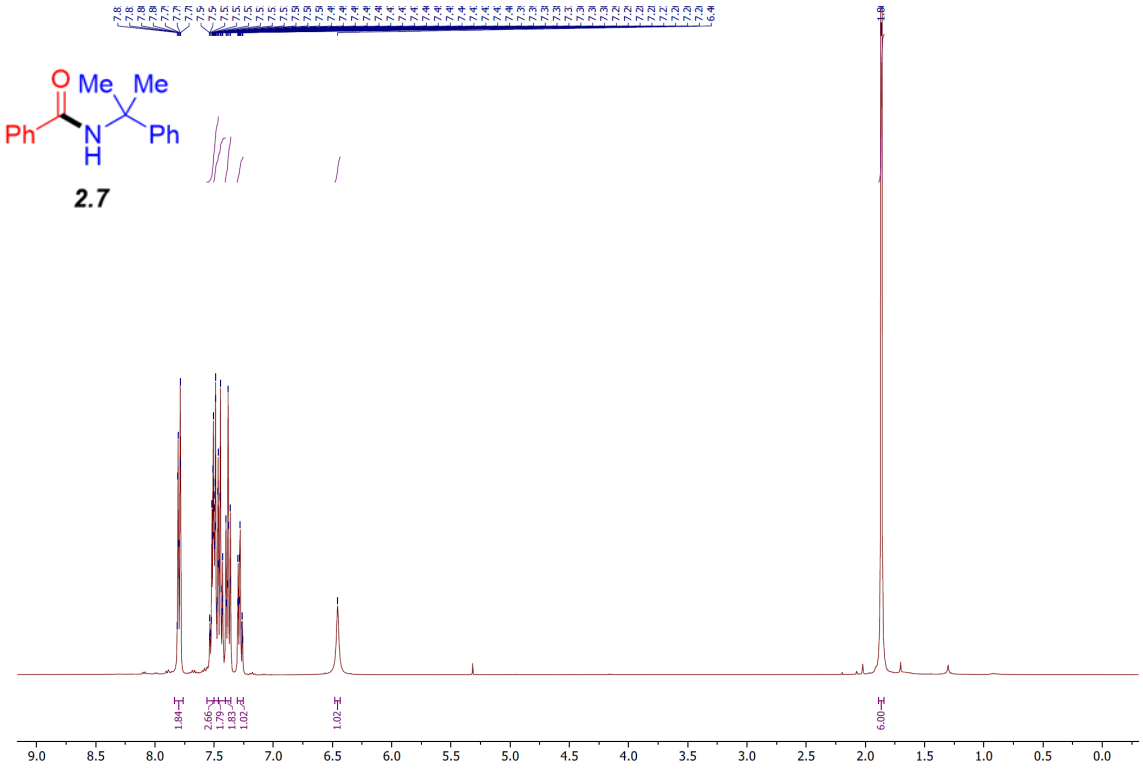

172.24
171.59
167.96
136.33
129.62
128.79
128.46
127.58
127.38
126.98
126.93
77.69
77.37
77.05
55.16
50.82
37.00
33.18
Ph
N
Ph
Me
2.4
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

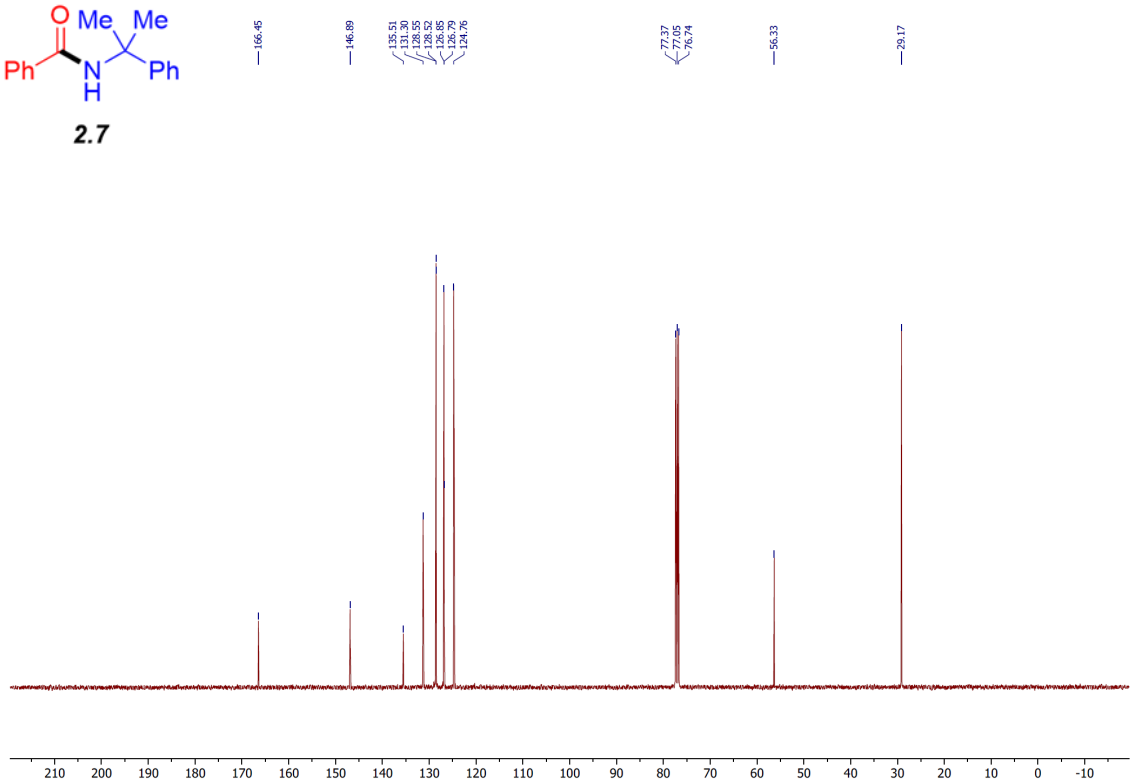

Ph
N
H
Cy
2.5

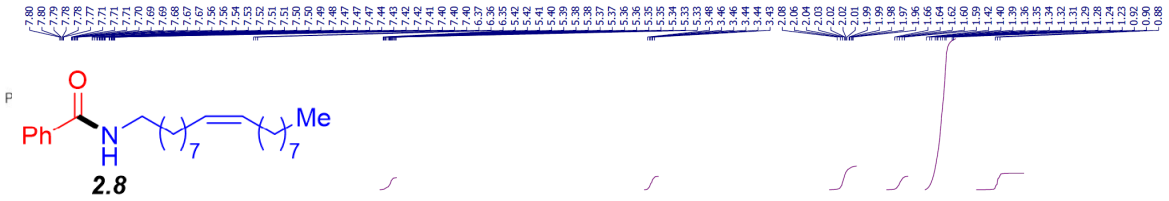

Ph
N
H
Cy
2.5


Ph
N
H
Me
Ph
2.6
1.89
1.09
6.01
1.08
0.99
1.01
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Ph
N
H
Me
Ph
2.6
143.21
134.66
131.44
128.75
128.55
127.45
127.45
126.96
126.28
69.24
21.74
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

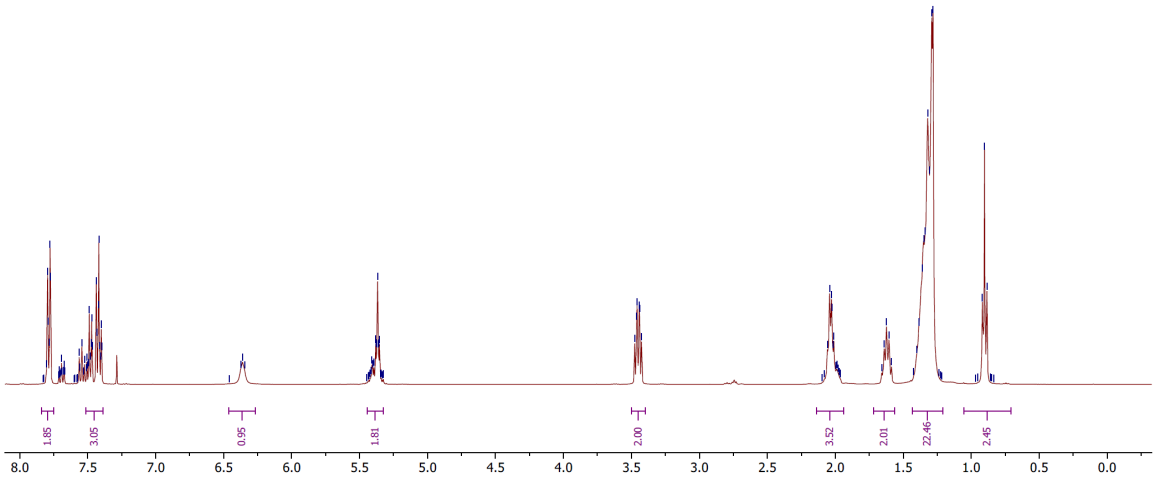

Me
Me
O
Ph
N
H
Ph
2.7
1.84
2.66
1.79
1.83
1.02
1.02
6.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

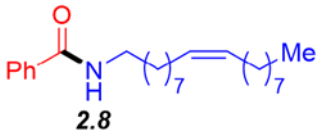

Me
Me
O
Ph
N
H
Ph
2.7
166.45
146.89
135.51
131.30
128.55
128.52
126.85
126.79
124.76
77.37
77.05
76.74
56.33
29.17
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



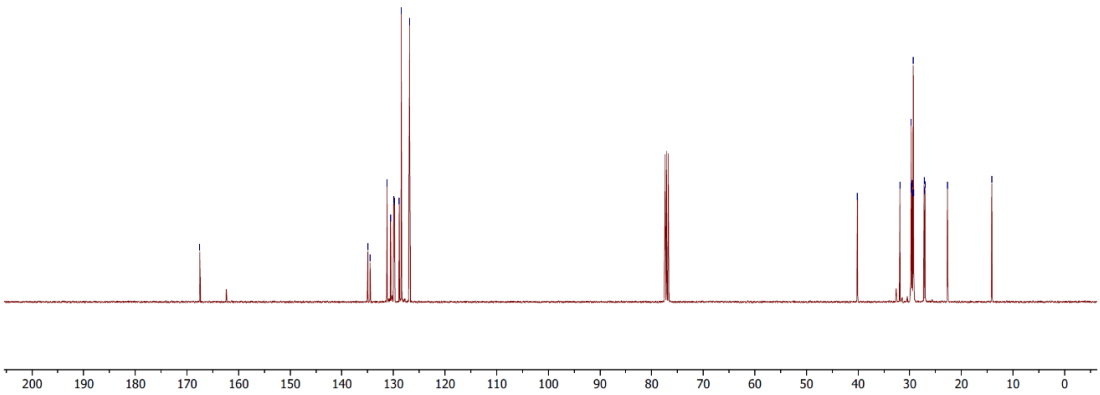
O
Ph
N
H
7
7
Me

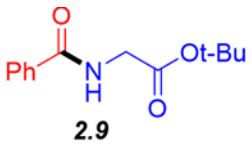
2.8


1.85
3.05
0.95
1.81
2.00
3.52
2.01
22.46
2.45
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

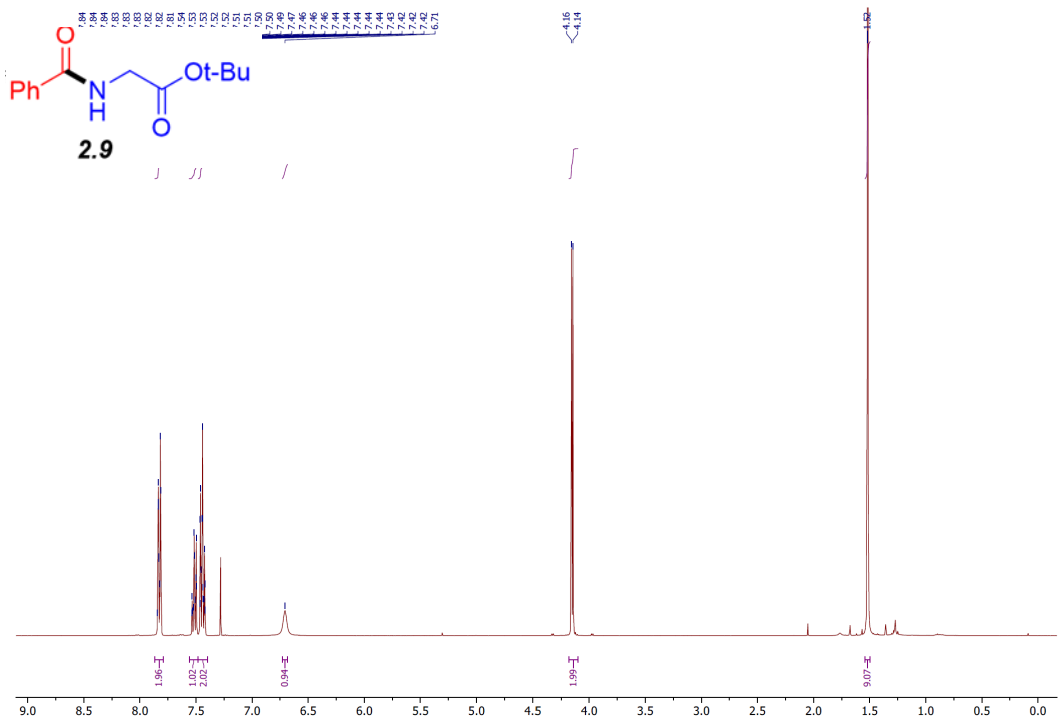

O
Ph
N
H
7
7
Me

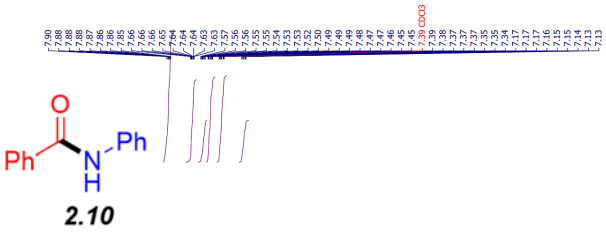
2.8


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

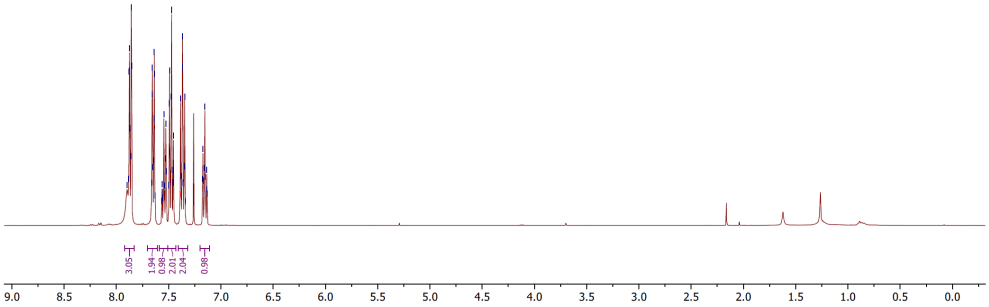

O
Ph
N
H
Ot-Bu
O
2.9

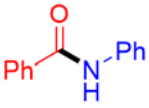
133.98
131.65
128.57
127.03
82.51
42.54
28.08
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


O
Ph
N
H
Ot-Bu
O
2.9
4.16
4.14
1.82
1.96
1.02
2.02
0.94
1.99
9.07
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

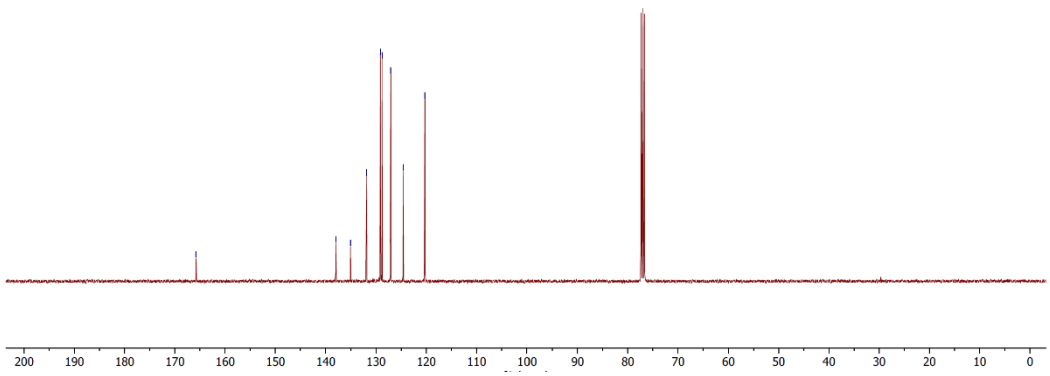

Ph
N
H
Ph
O

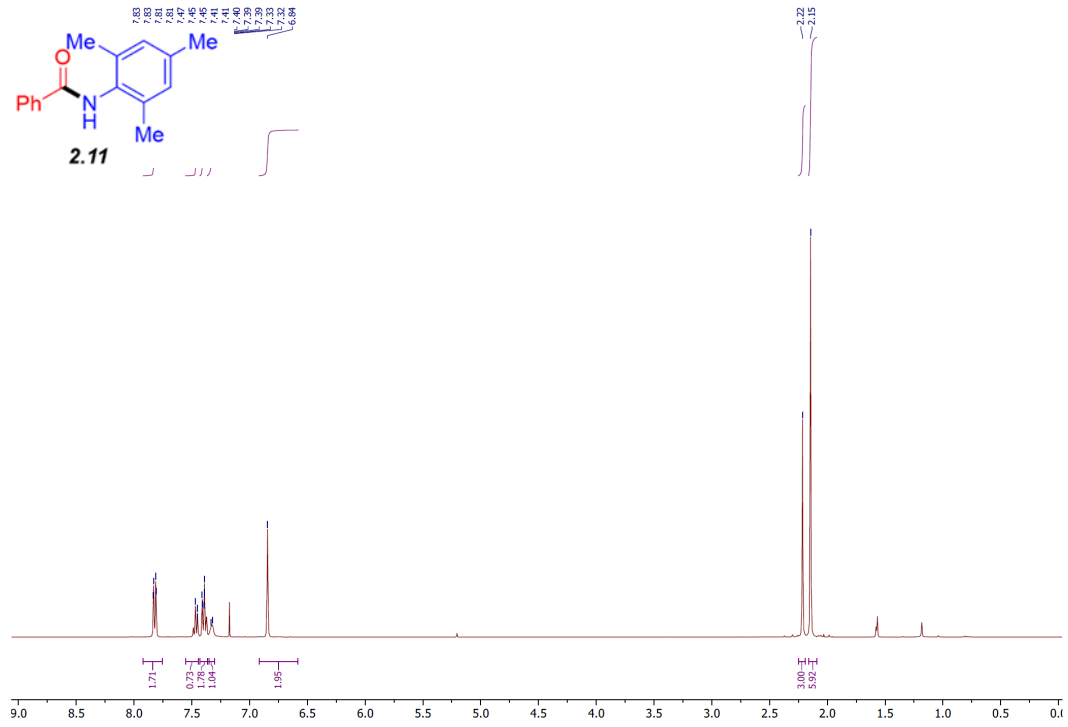
2.10

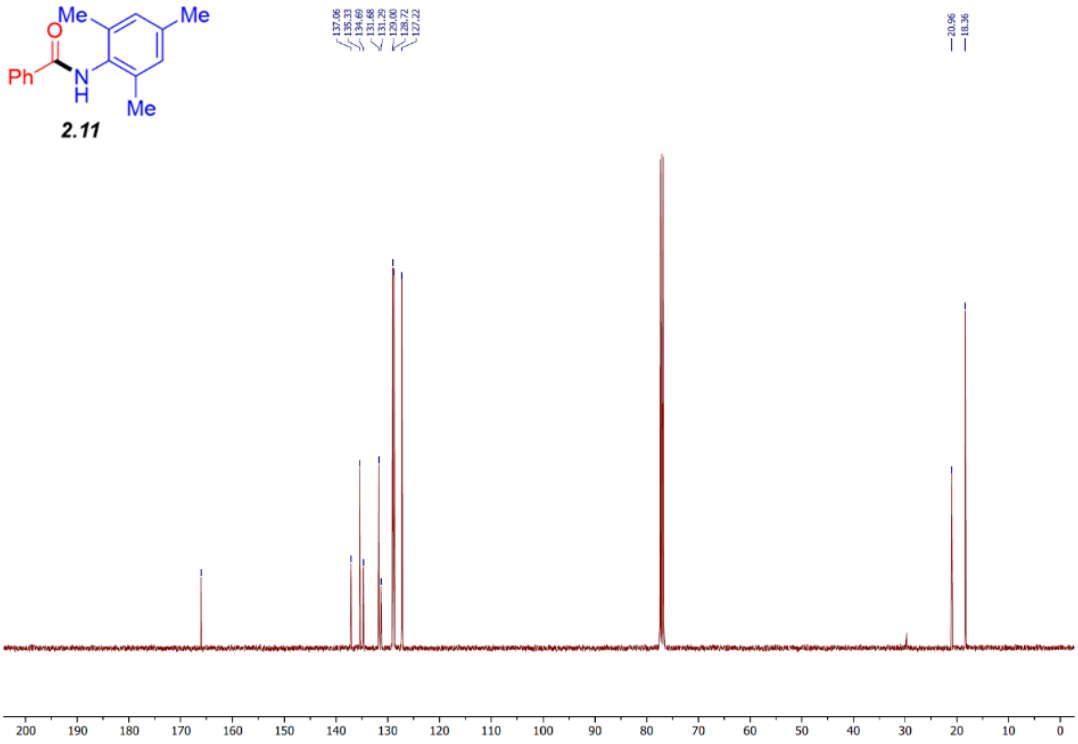

3.05
1.94
0.98
2.01
2.04
0.98
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

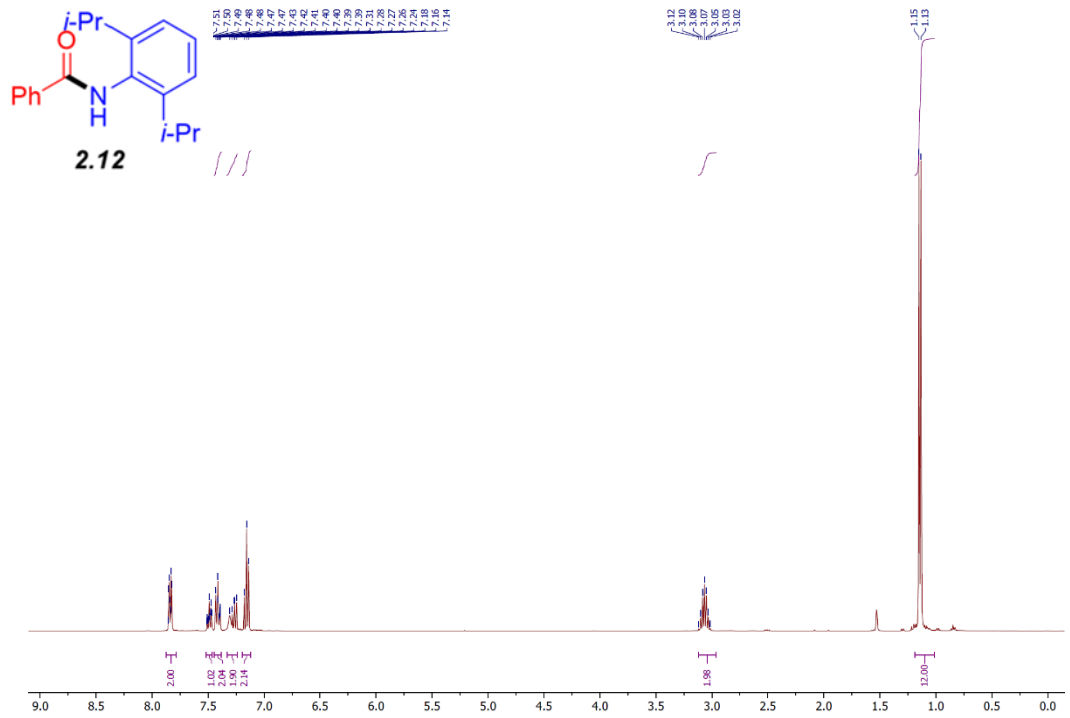

Ph
N
H
Ph
O

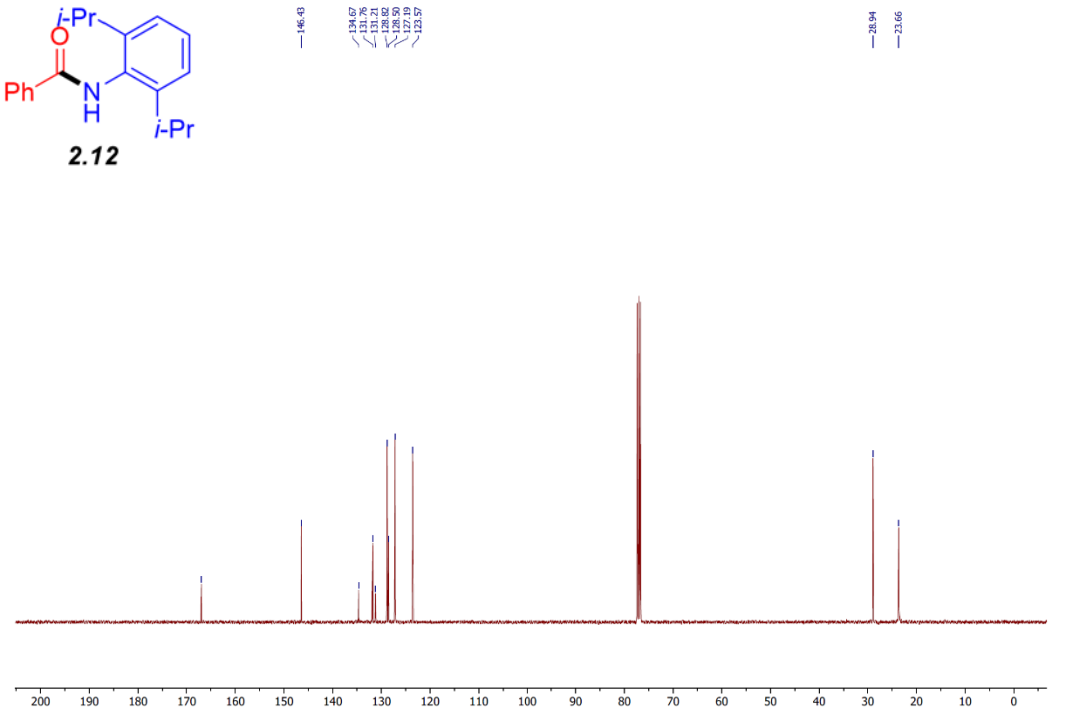
2.10

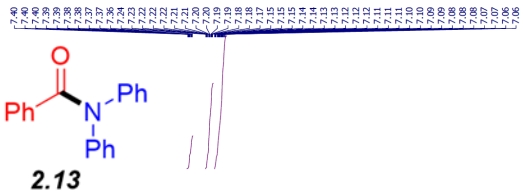

165.77
137.97
135.06
131.65
129.10
128.79
127.04
124.39
120.26
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Me
Me
O
Ph
N
H
Me
2.11
7.83
7.83
7.81
7.81
7.81
7.47
7.45
7.45
7.41
7.41
7.40
7.39
7.39
7.33
7.32
6.84
2.22
2.15
1.71
0.73
1.78
1.04
1.95
3.00
5.92
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

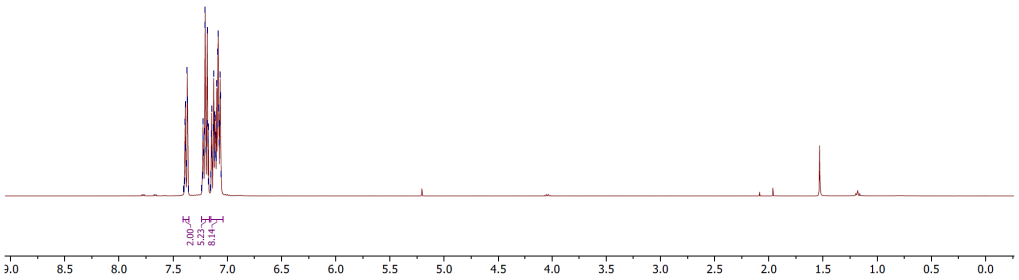

Me
Me
O
Ph
N
H
Me
2.11
137.06
135.33
134.69
131.68
131.20
129.00
128.72
127.22
20.96
18.36
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

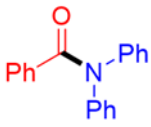

i-Pr
O
Ph
N
H
i-Pr
2.12


i-Pr
O
Ph
N
H
i-Pr
2.12


O
Ph
N
Ph
Ph

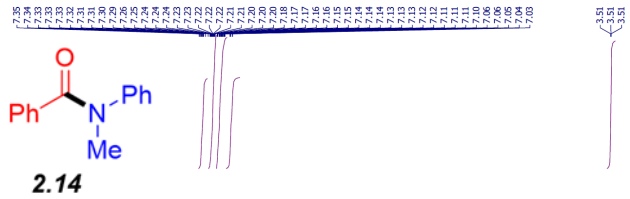
2.13

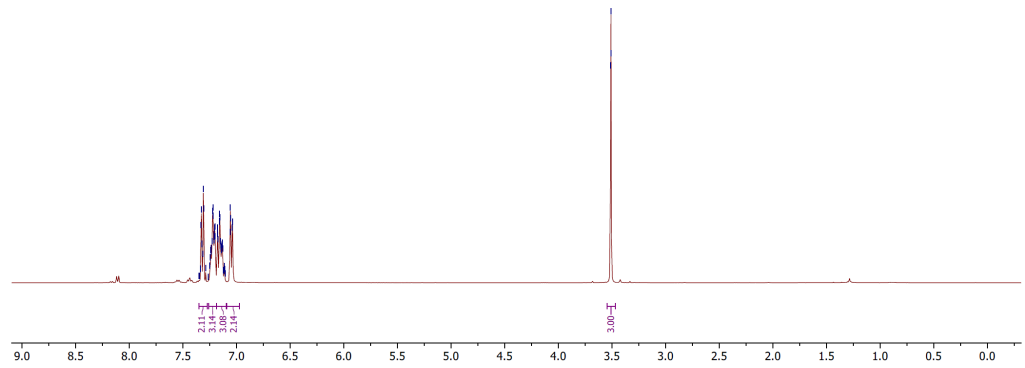

2.00
5.23
8.14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

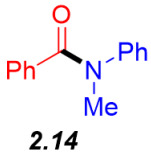

O
Ph
N
Ph
Ph

2.13

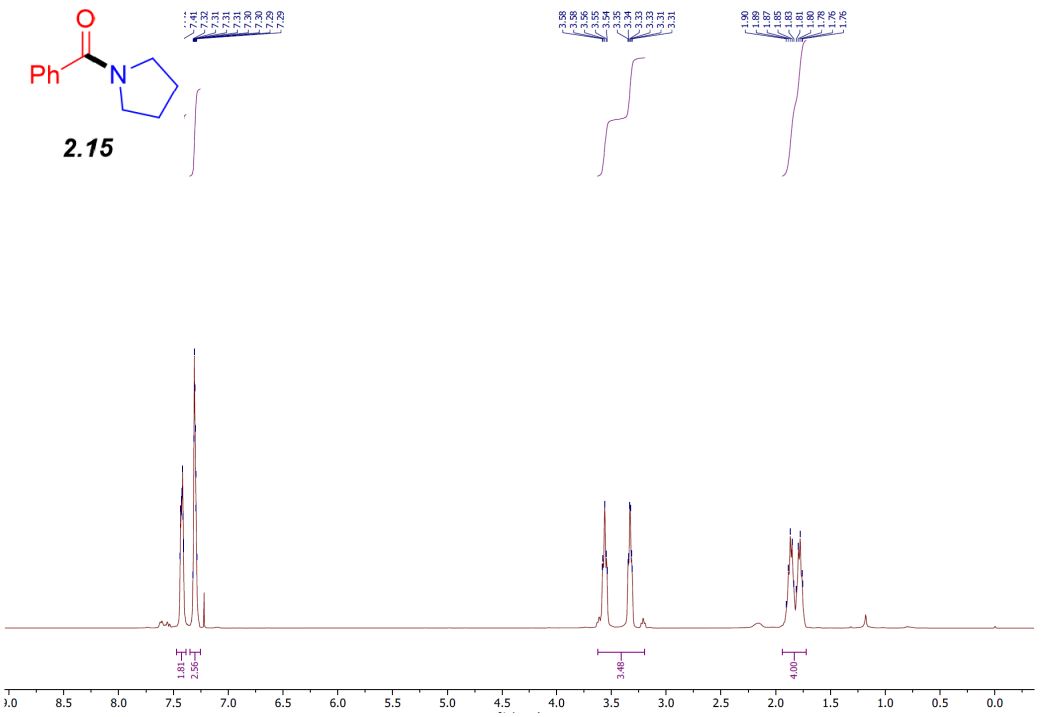
170.64
143.96
136.17
130.16
129.18
129.11
127.87
127.52
126.35
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

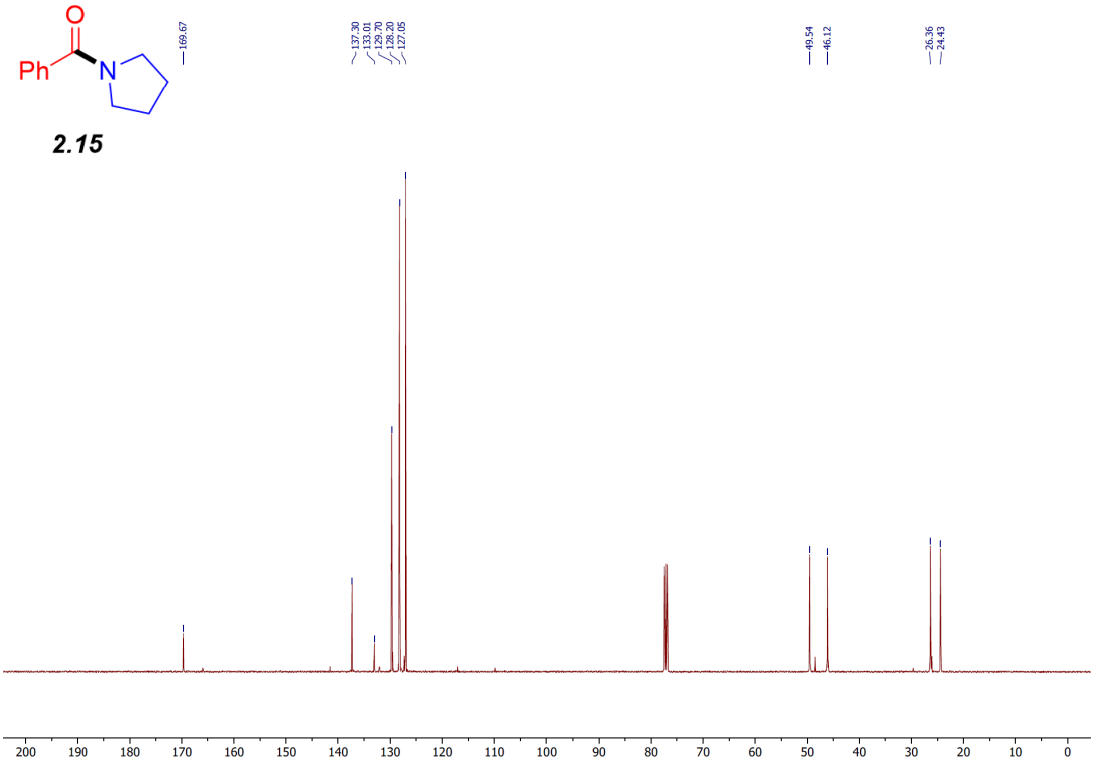






2.14


Ph
N
O
2.15
1.81
2.56
3.48
4.00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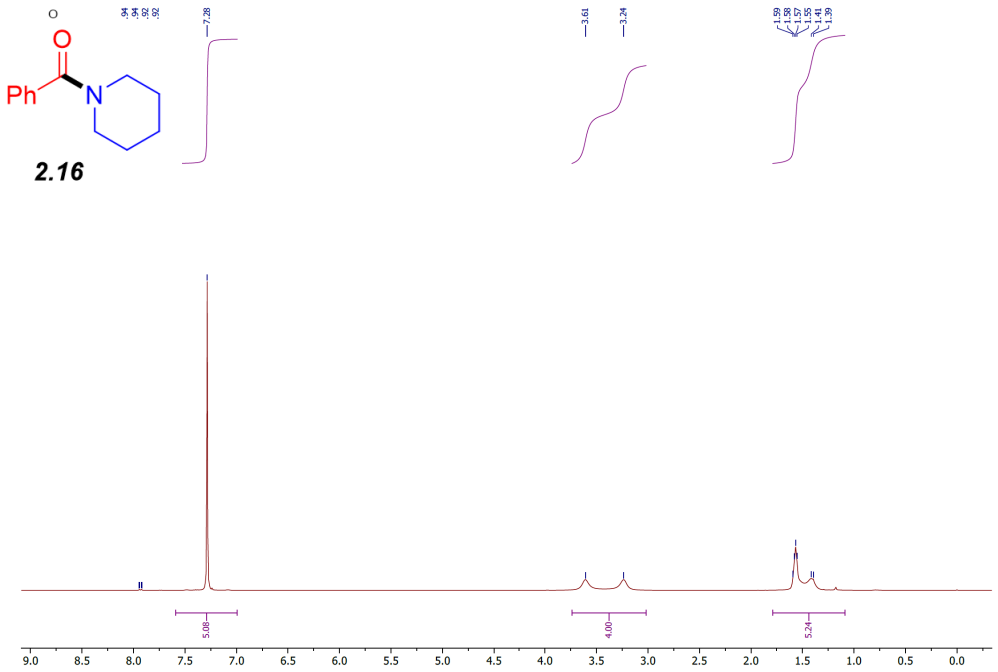
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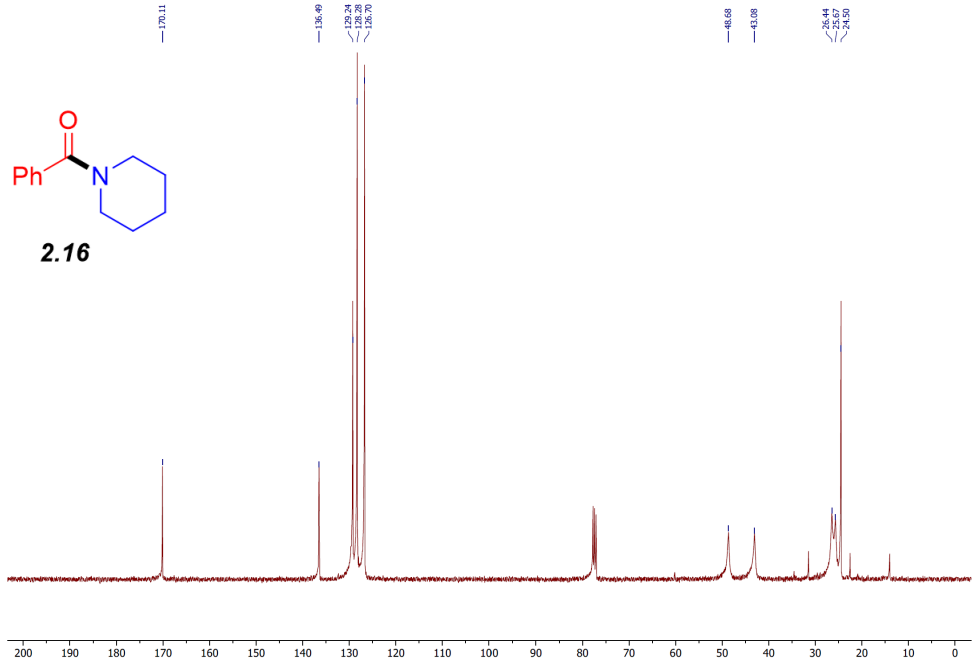
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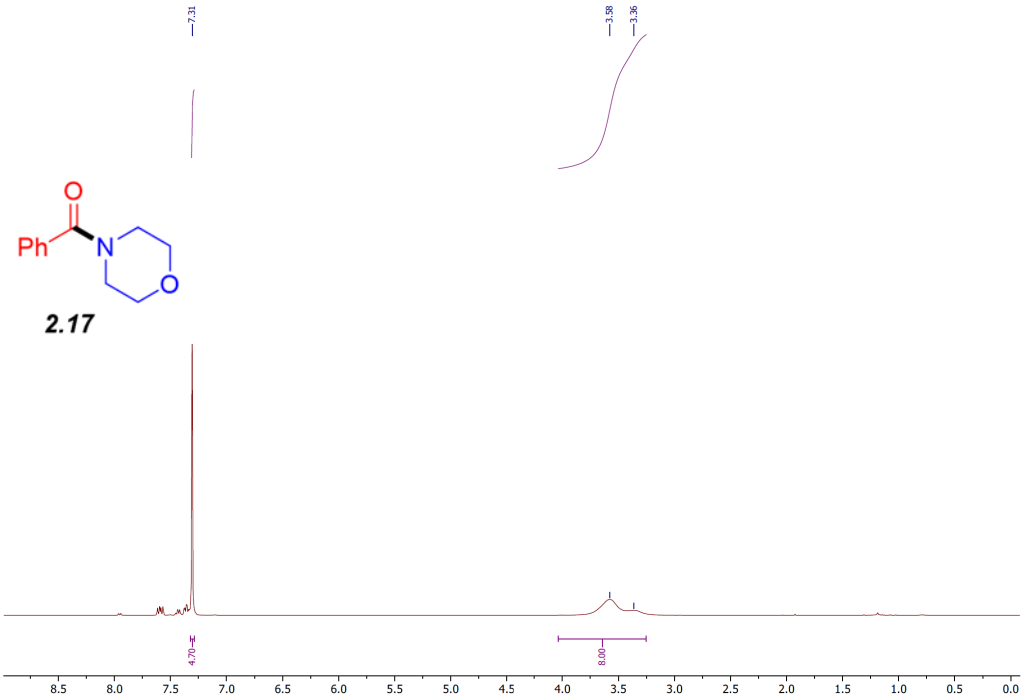
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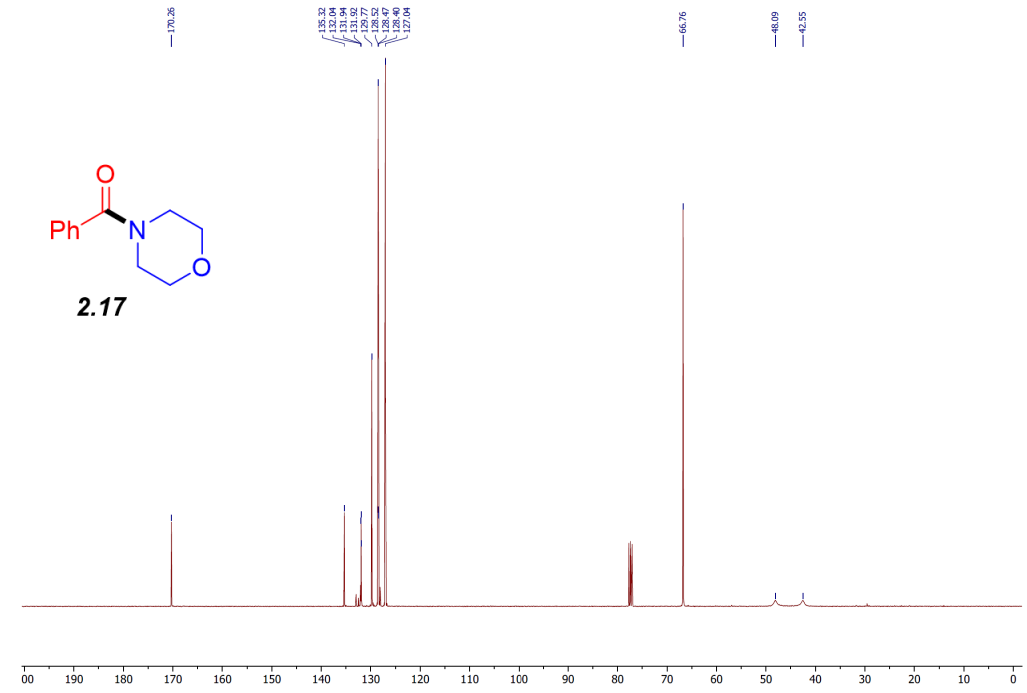
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42.55
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Ph
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O
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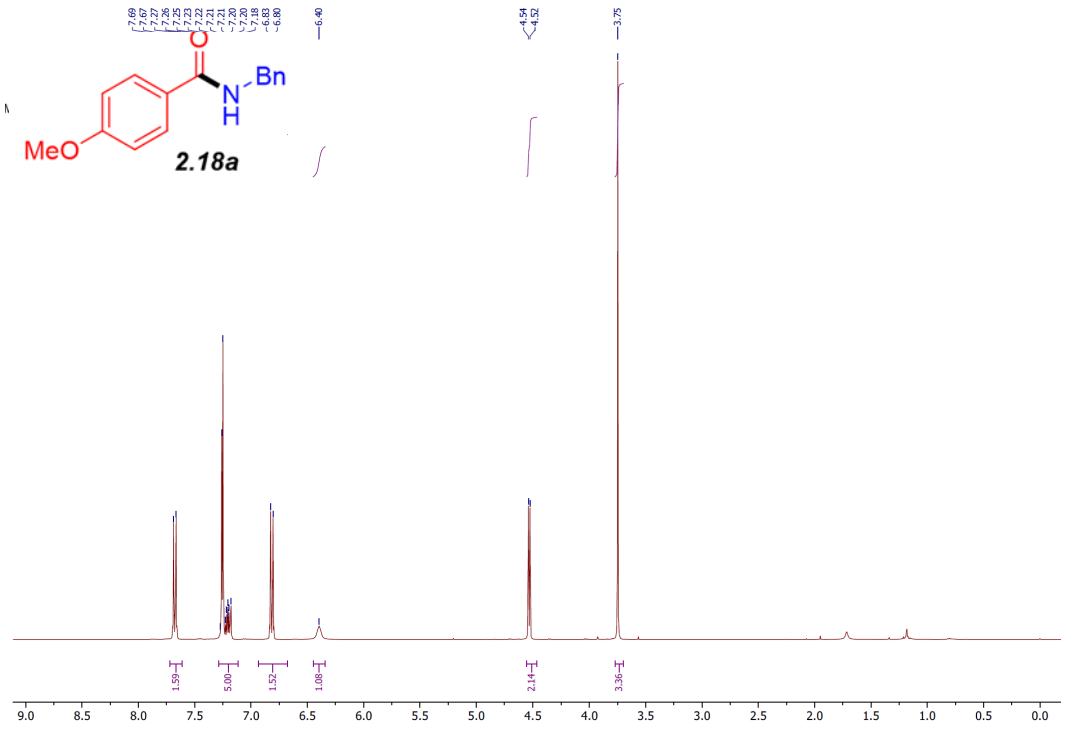
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7.18
6.83
6.80
6.40
4.54
4.52
3.75
1.59
5.00
1.52
1.08
2.14
3.36
9.0
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8.0
7.5
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6.0
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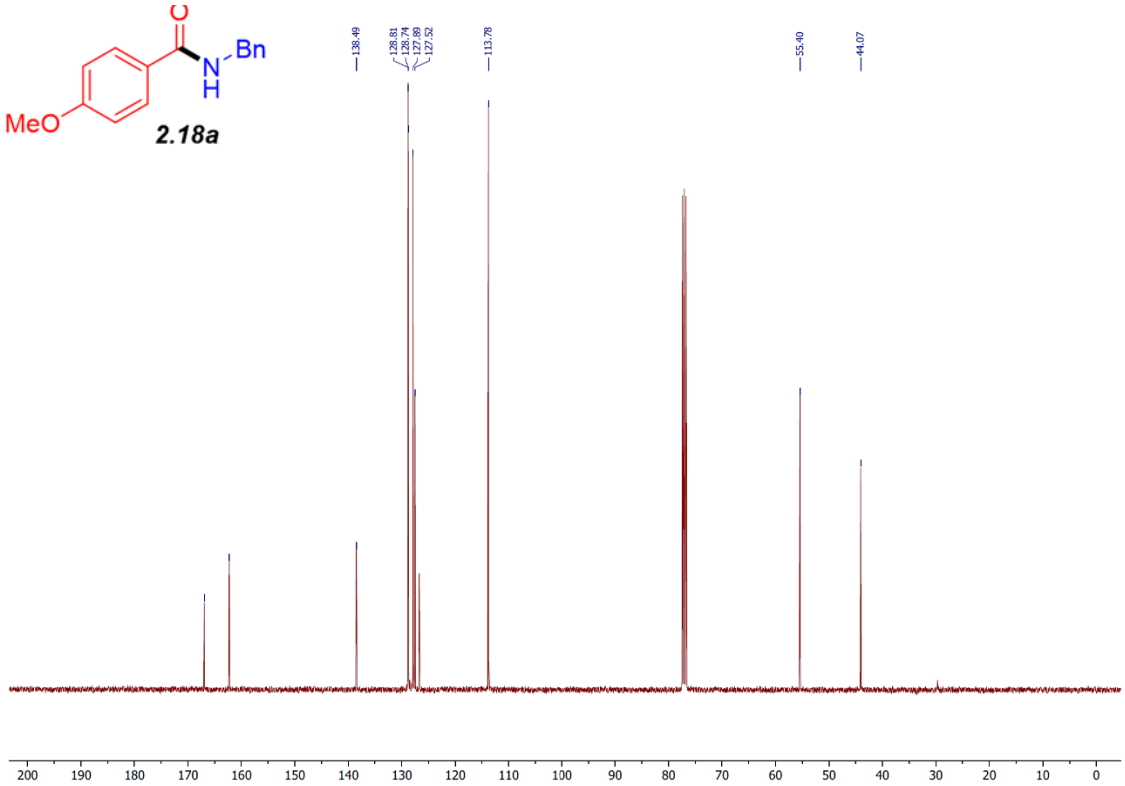
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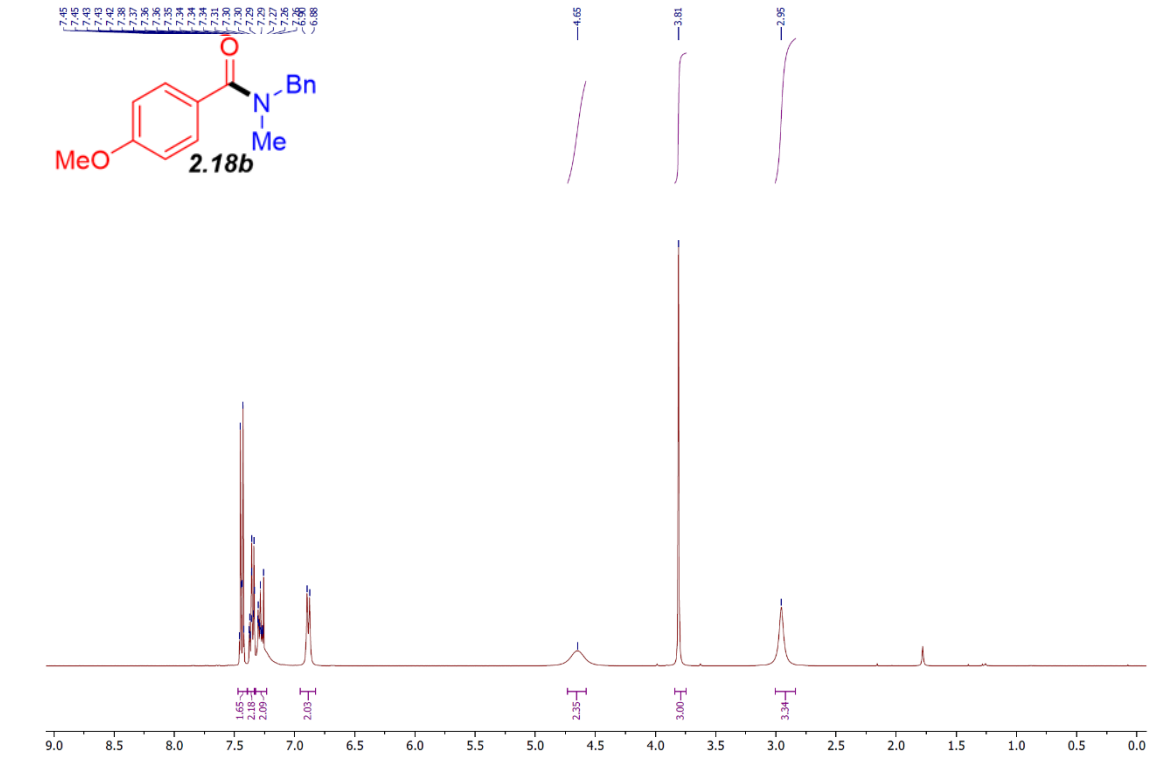
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2.09
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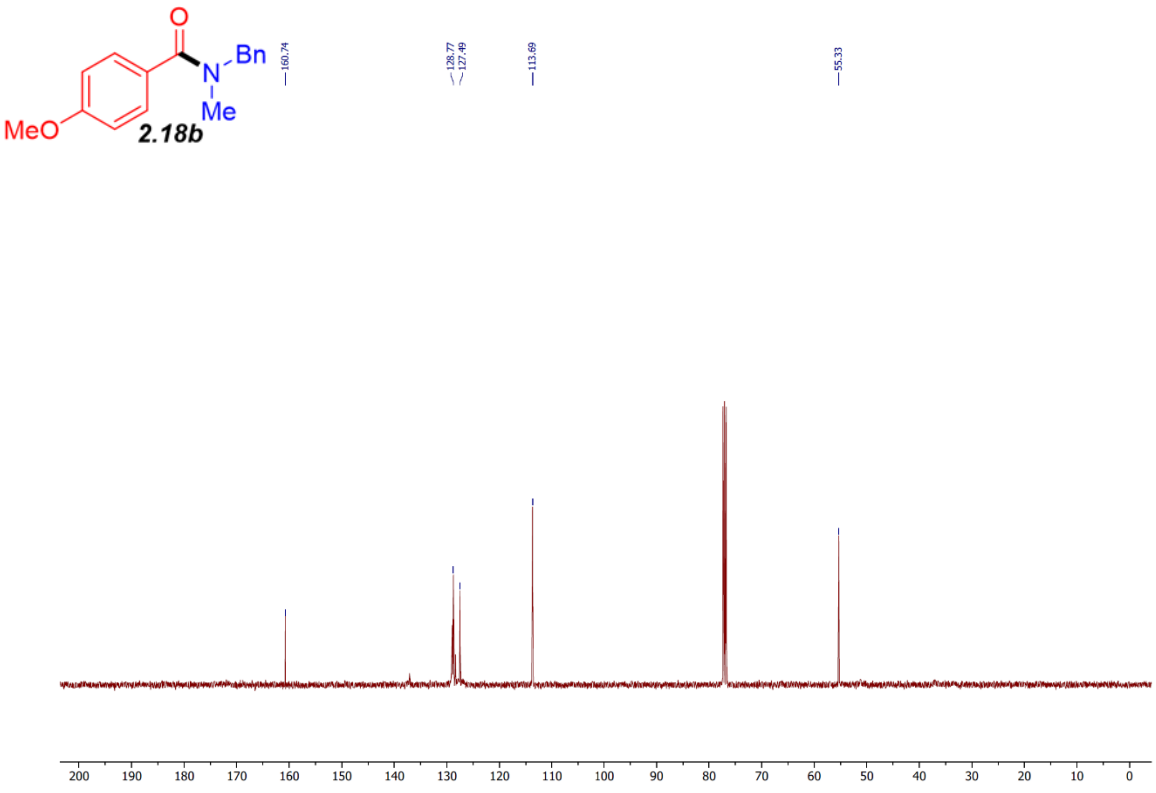
2.35
3.00
3.34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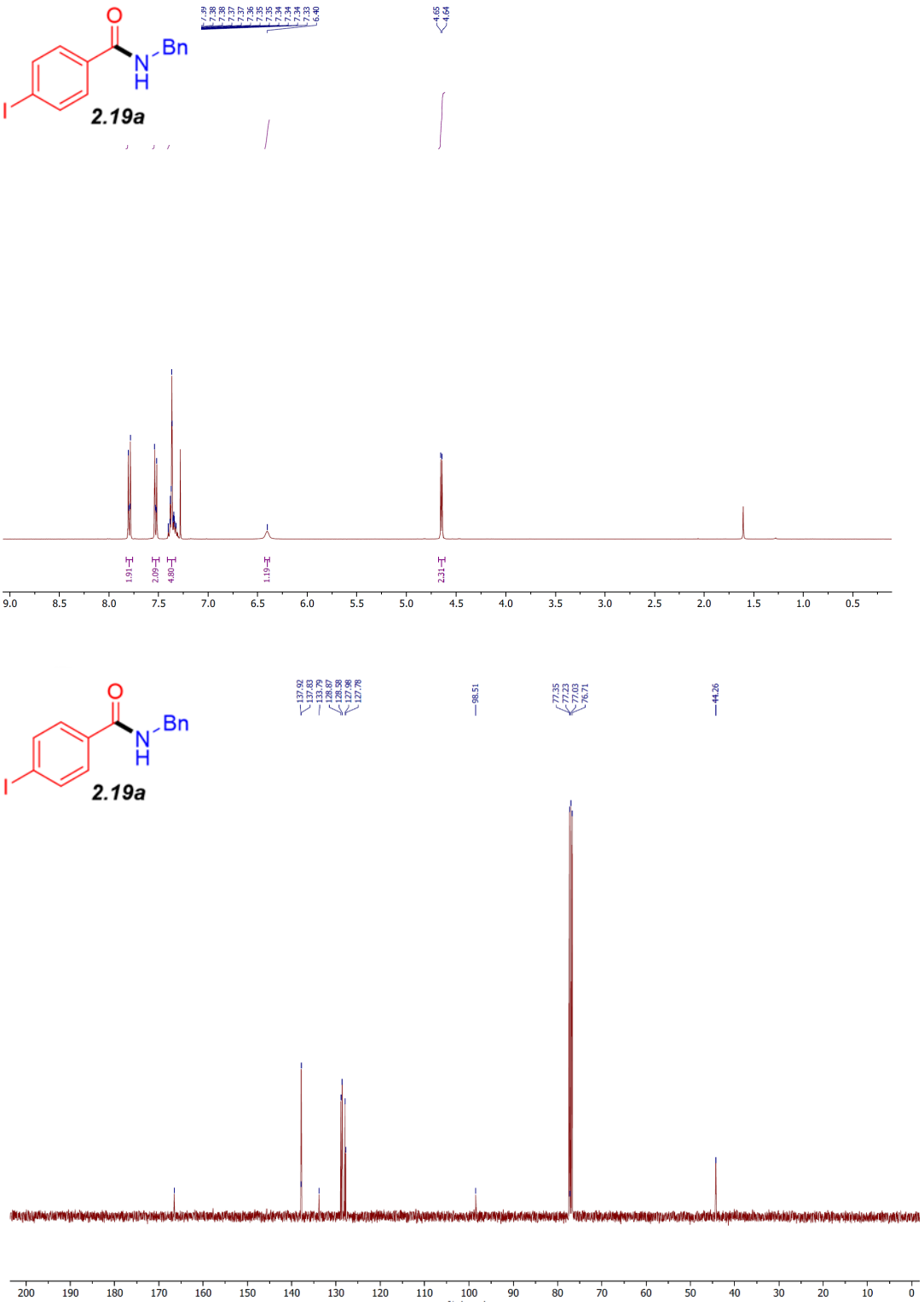
55.33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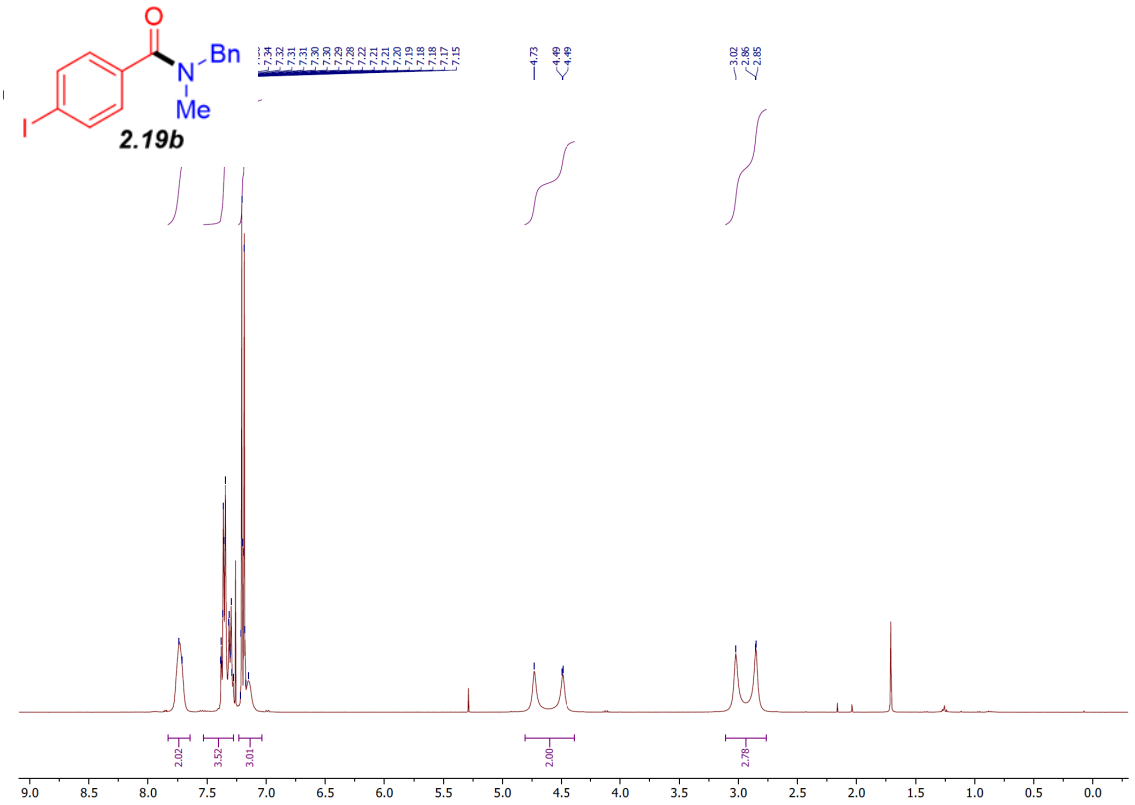
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Me
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O
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7.28
7.22
7.21
7.21
7.20
7.19
7.18
7.18
7.17
7.15
4.73
4.49
4.49
3.02
2.96
2.85
2.02
3.52
3.01
2.00
2.78
9.0
8.5
8.0
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7.0
6.5
6.0
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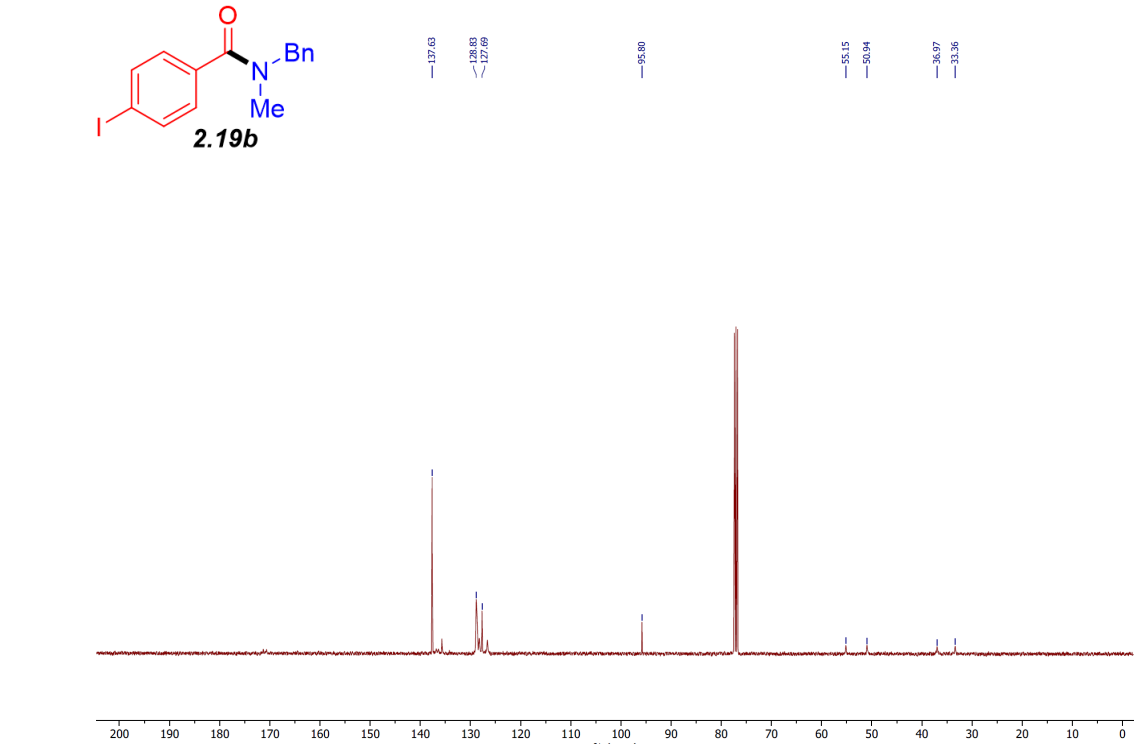
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O
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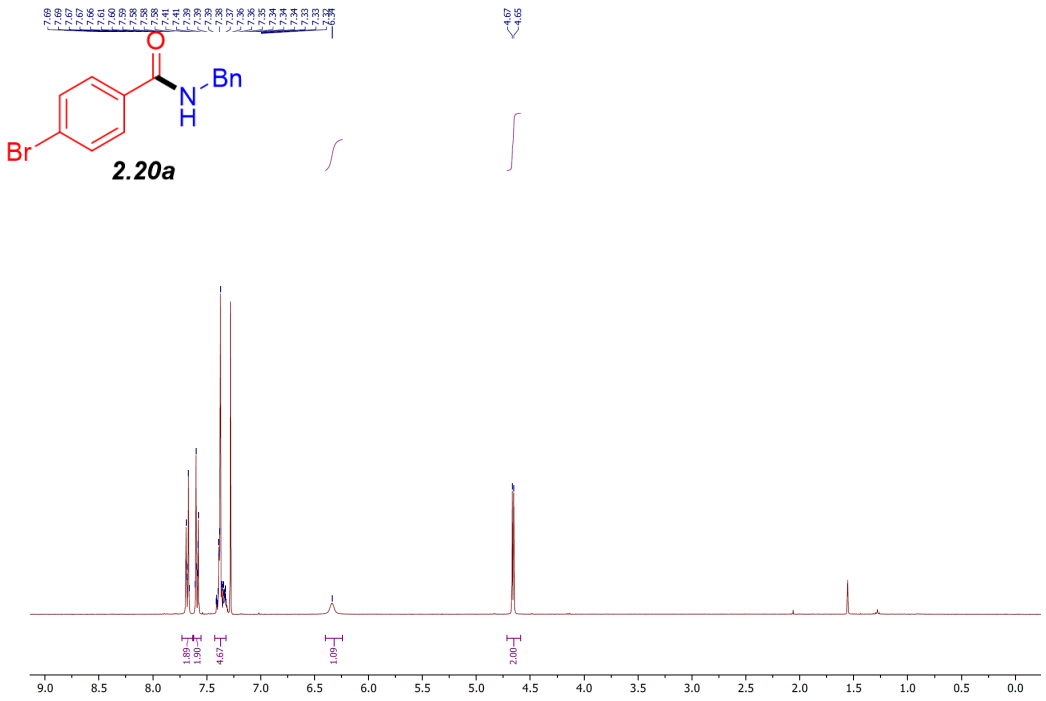
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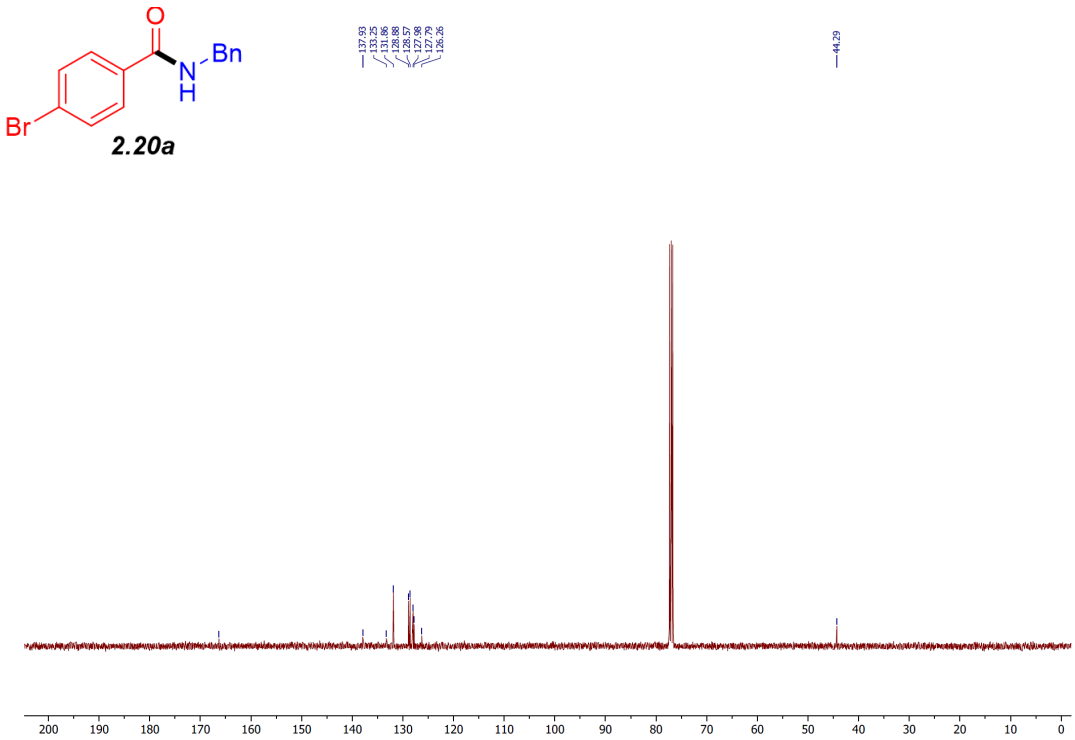
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H
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Bn
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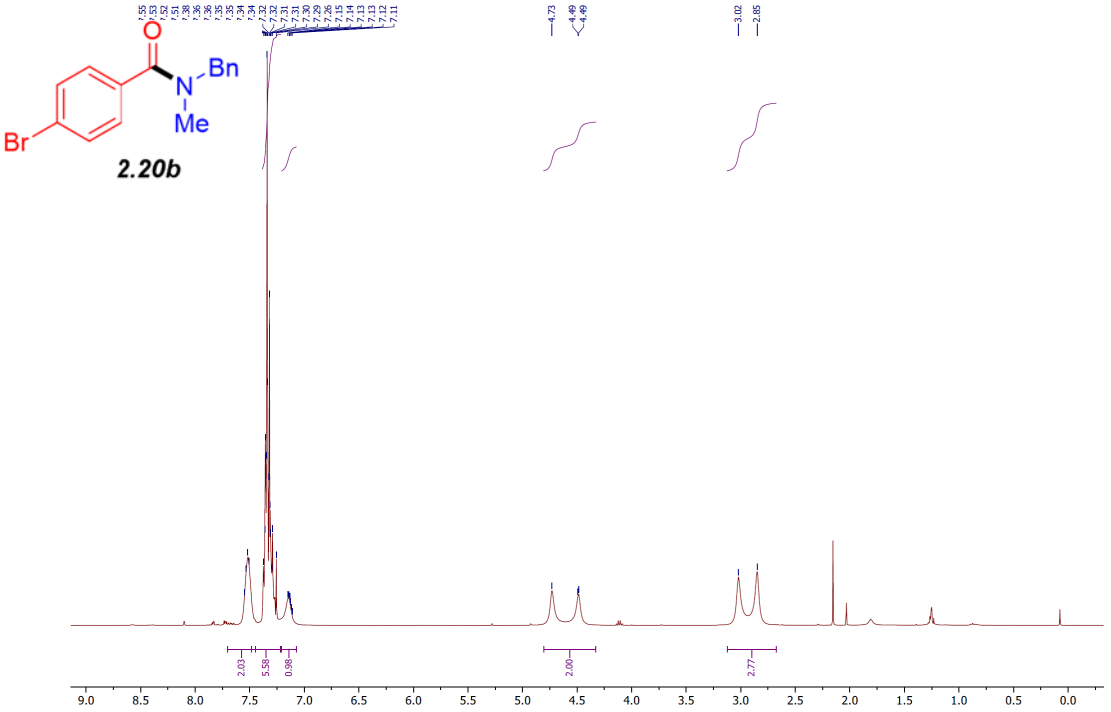
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Me
O
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7.36
7.36
7.35
7.34
7.34
7.32
7.32
7.31
7.31
7.30
7.29
7.26
7.15
7.14
7.13
7.13
7.12
7.11
4.73
4.49
4.49
3.02
2.85
2.03
5.58
0.98
2.00
2.77
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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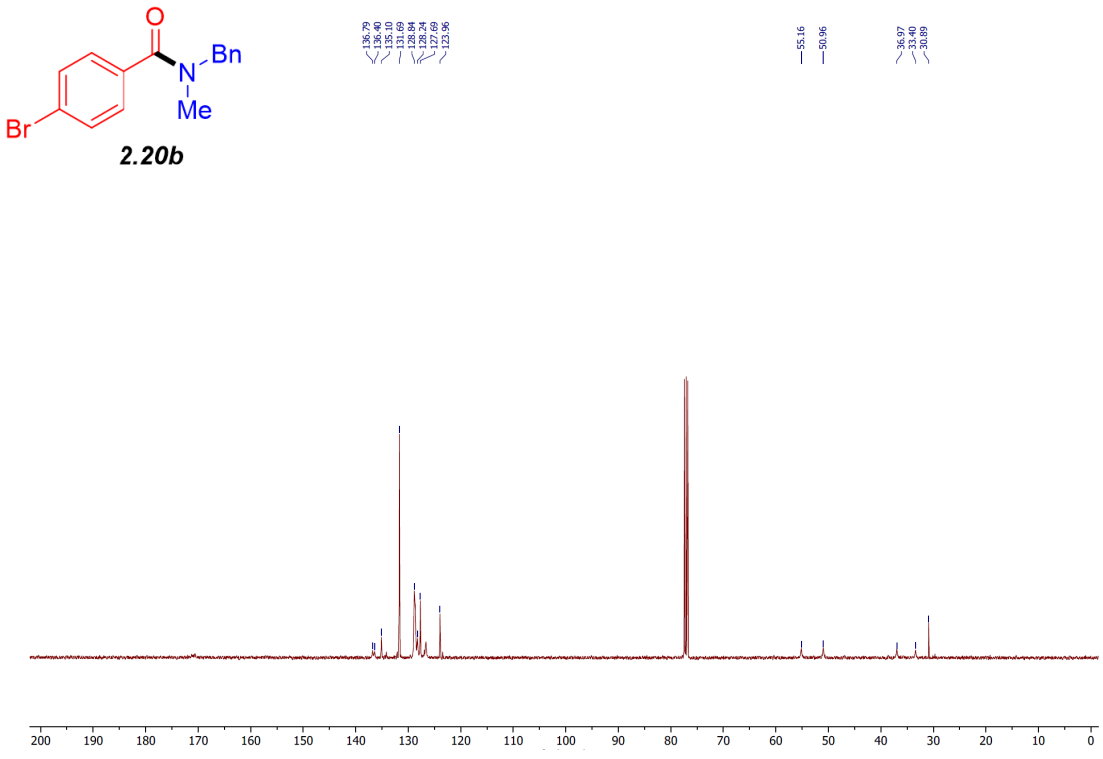
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O
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30.89
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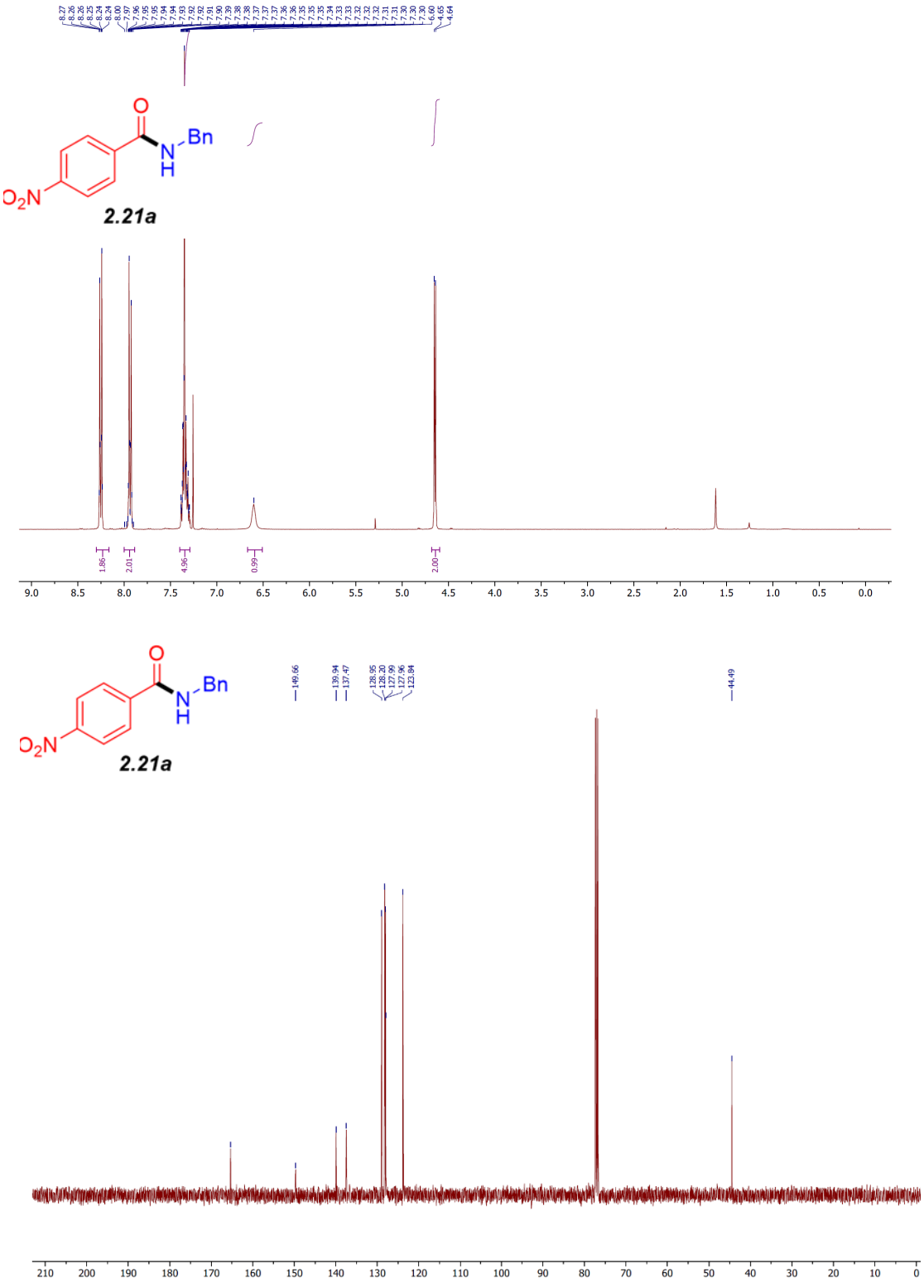
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H
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2.00
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8.0
7.5
7.0
6.5
6.0
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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137.47
128.95
128.20
127.99
127.96
123.84
44.49
210
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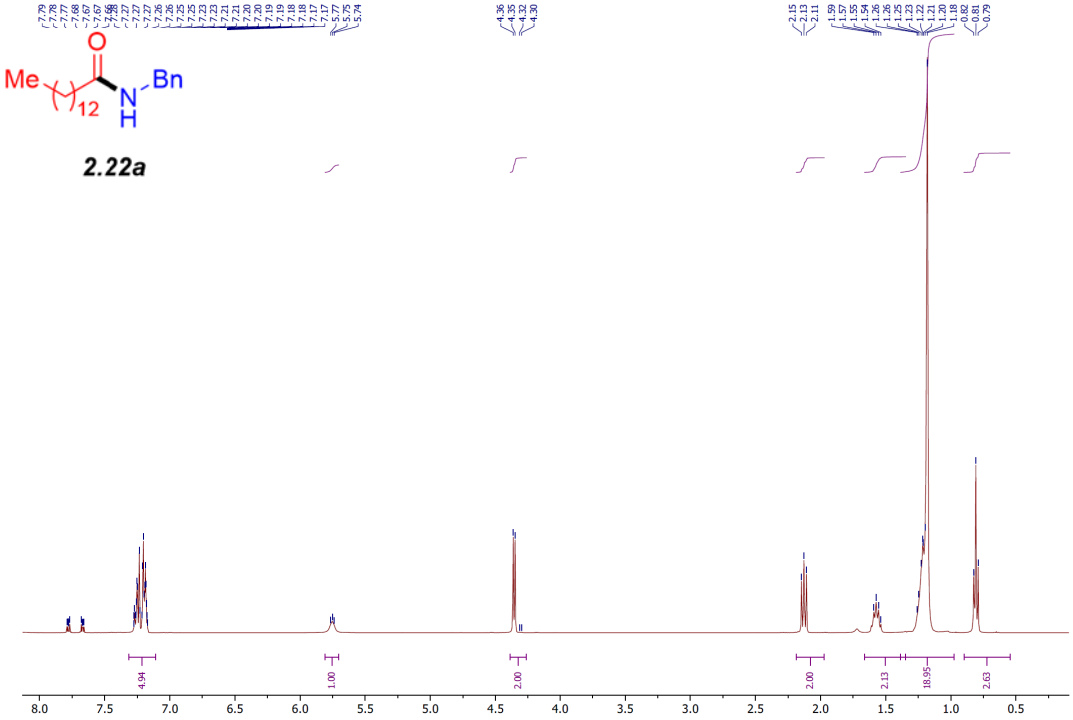

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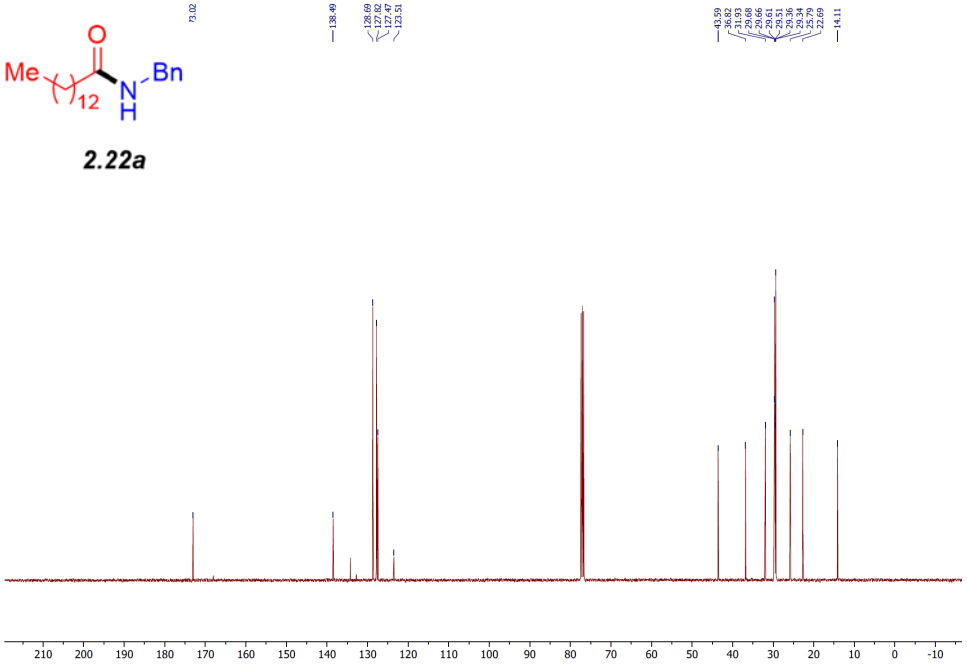

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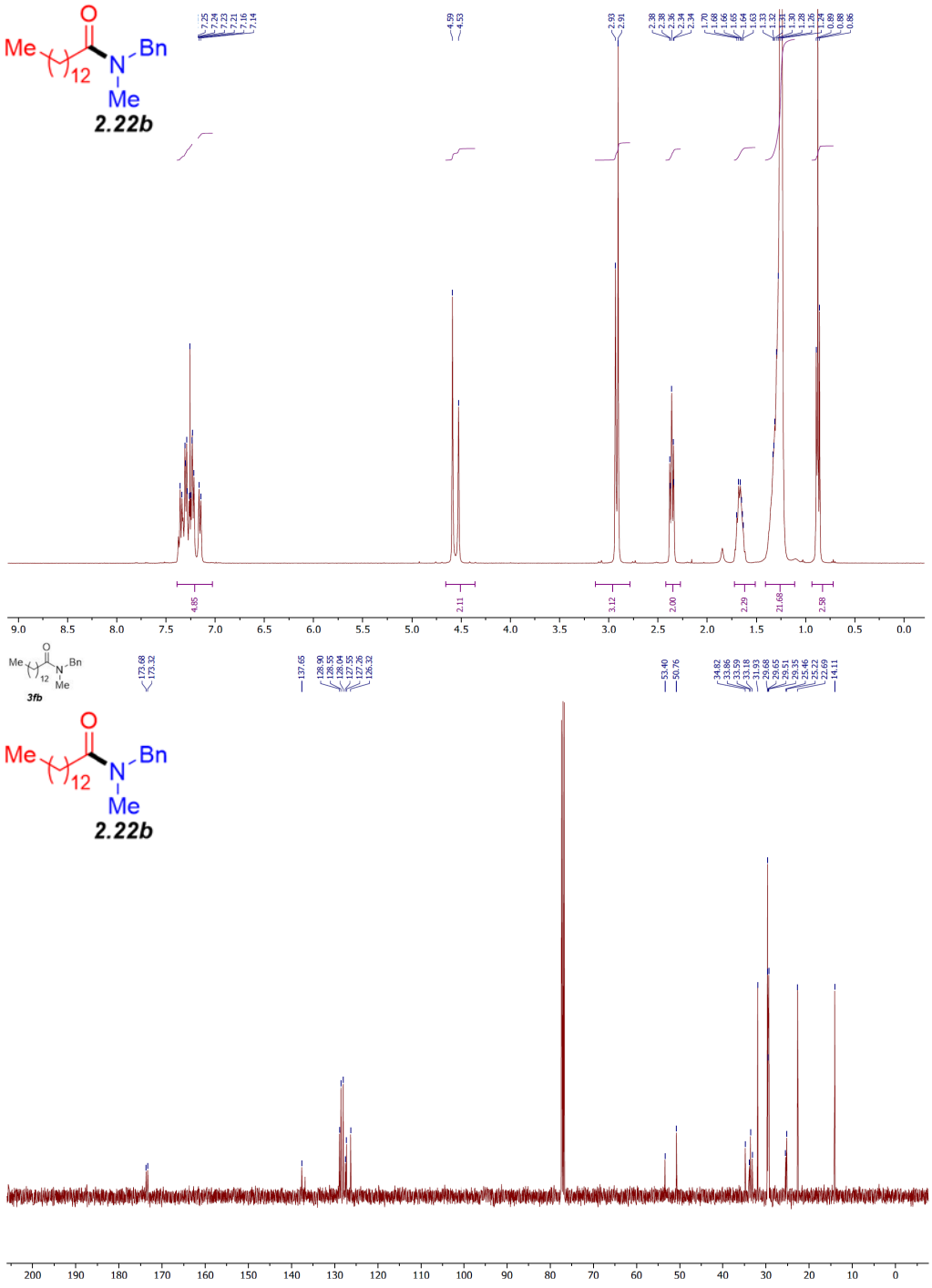
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Bn
Me
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4.53
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2.91
2.38
2.36
2.34
1.70
1.68
1.66
1.65
1.64
1.63
1.33
1.32
1.31
1.30
1.28
1.26
1.24
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0.88
0.86
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2.11
3.12
2.00
2.29
21.68
2.58
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3fb
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173.32
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128.55
128.04
127.55
127.26
126.52
53.40
50.76
34.82
33.86
33.59
33.18
31.93
29.68
29.65
29.51
29.35
25.46
25.22
22.69
14.11
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150
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110
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20
10
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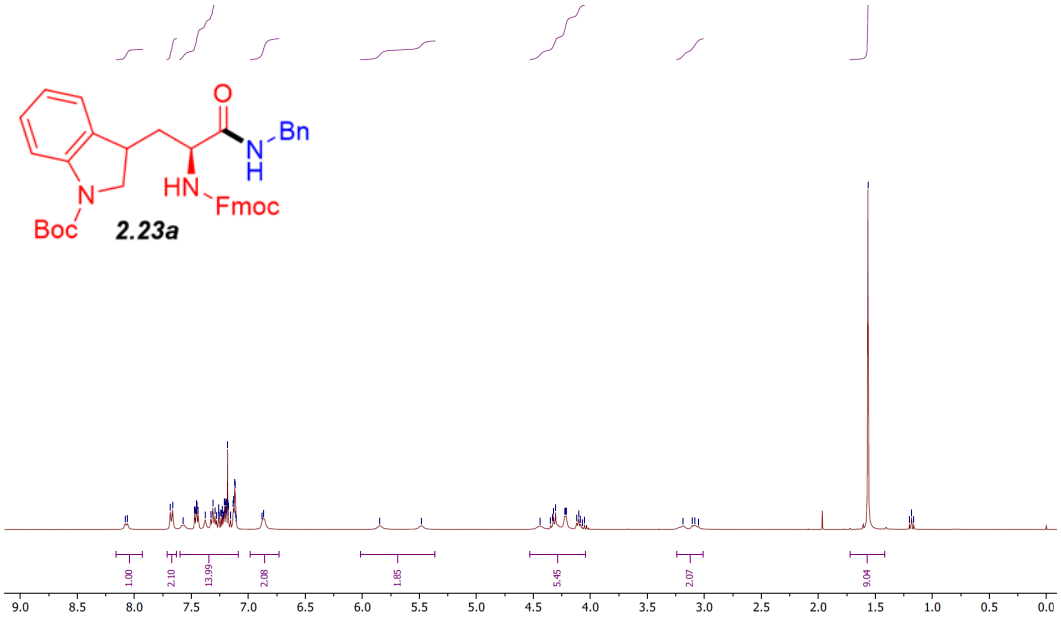
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Bn
H
HN
Fmoc
N
Boc
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1.00
2.10
13.99
2.08
1.85
5.45
2.07
9.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.5
4.0
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3.0
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2.0
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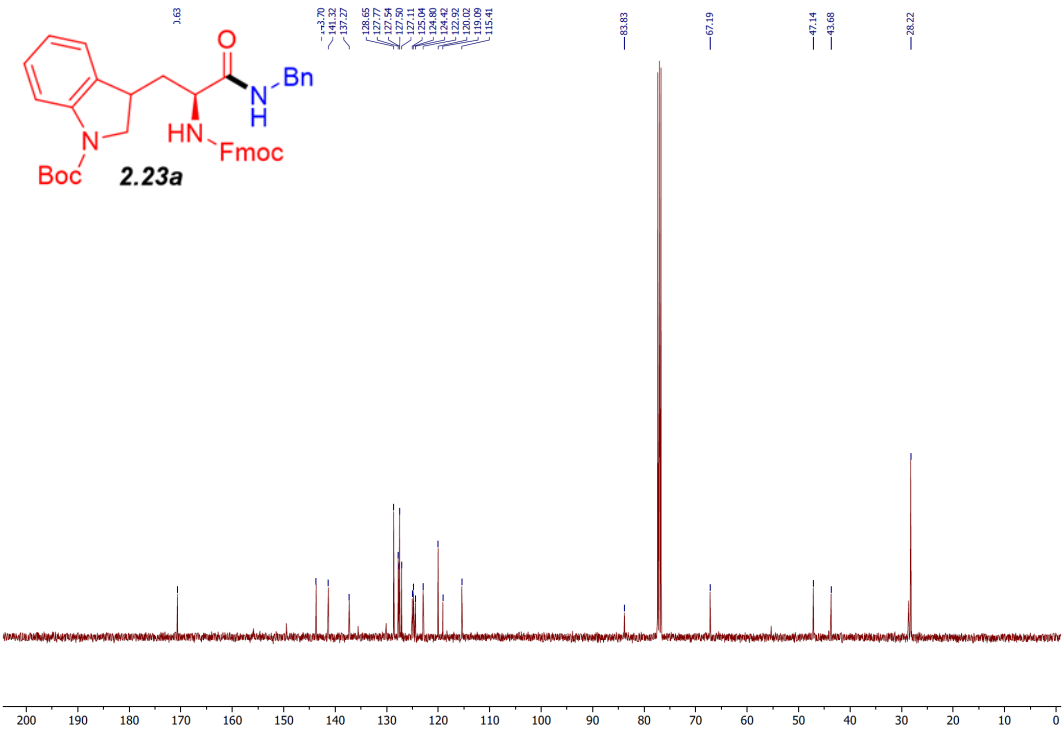
O
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Bn
H
HN
Fmoc
N
Boc
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67.19
47.14
43.68
28.22
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150
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110
100
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70
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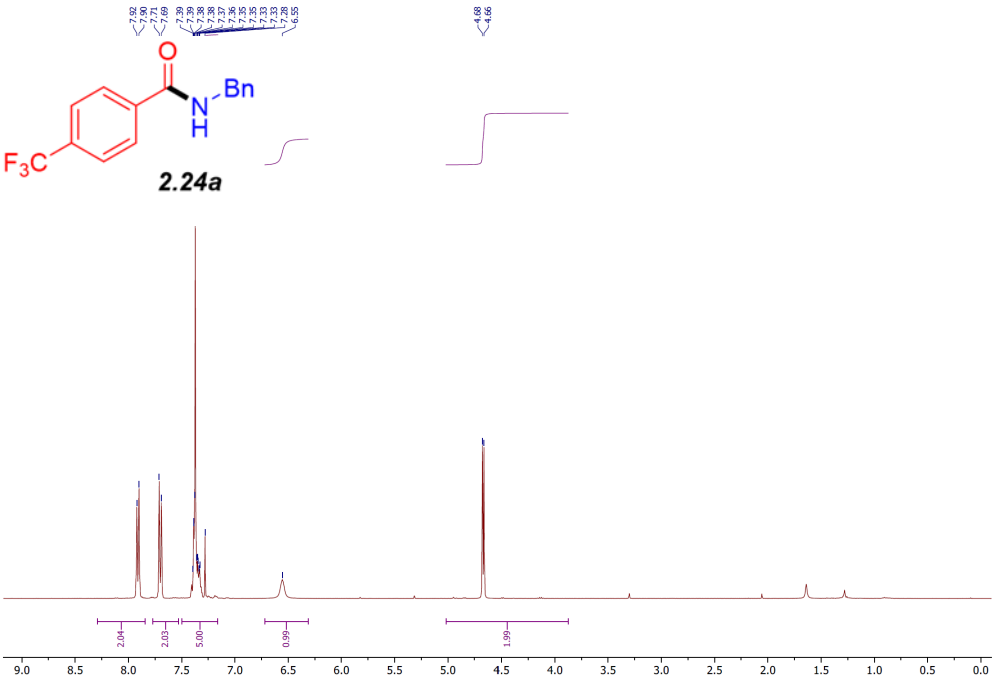
30
20
10
0


7.92
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7.37
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7.35
7.33
7.28
6.55
4.68
4.66
O
N
H
Bn
F3C
2.24a
2.04
2.03
5.00
0.99
1.99
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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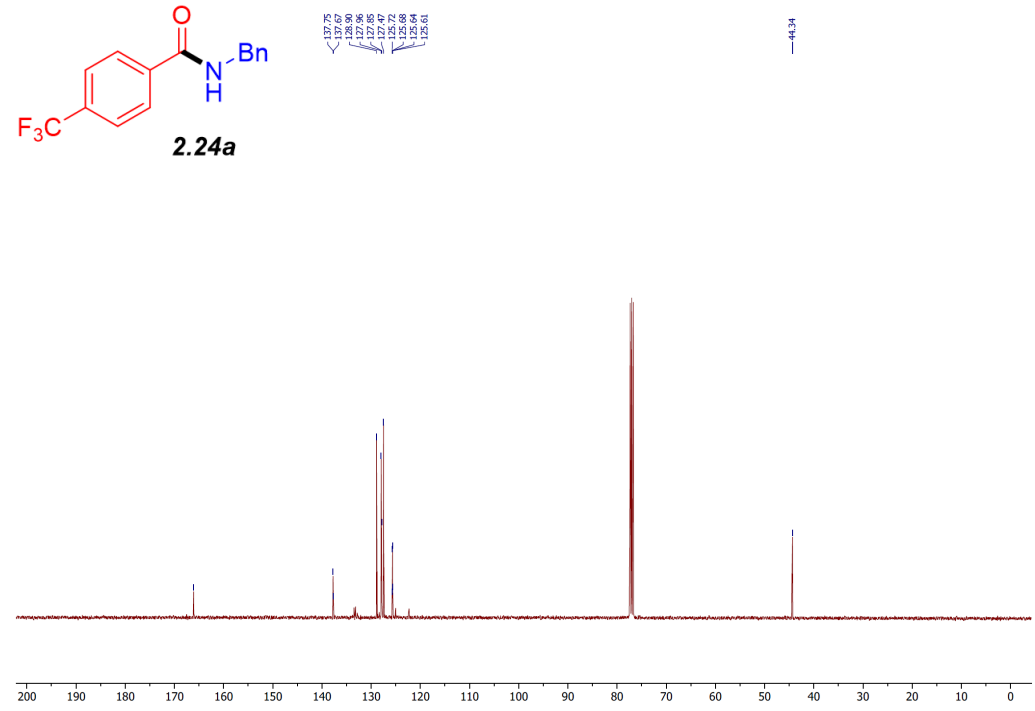
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125.64
125.61
44.34
O
N
H
Bn
F3C
2.24a
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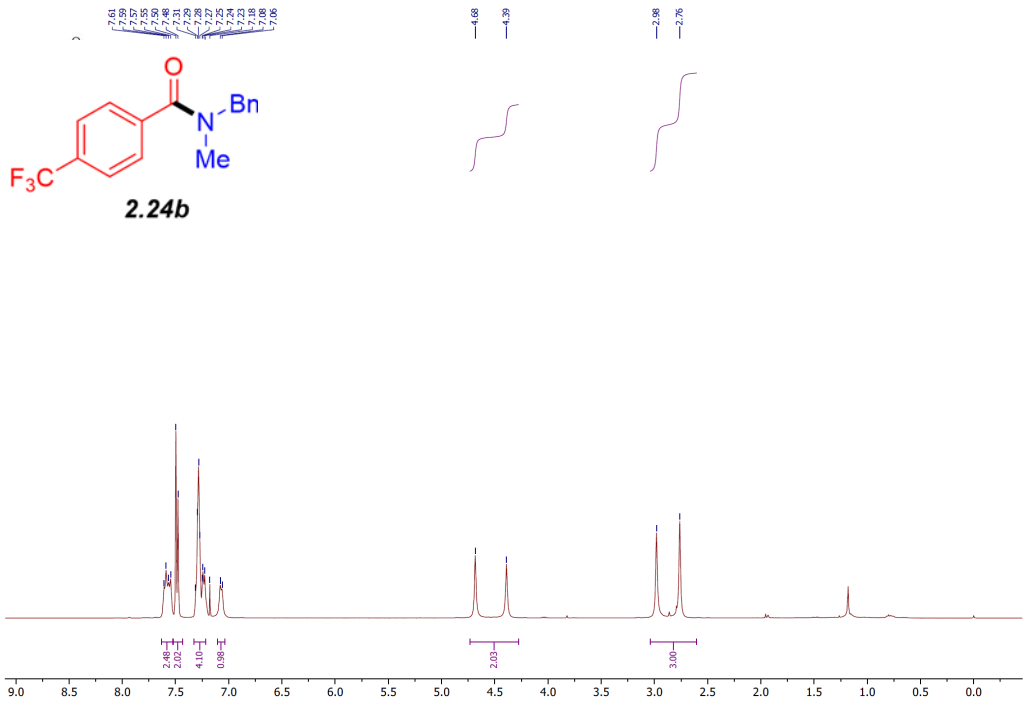
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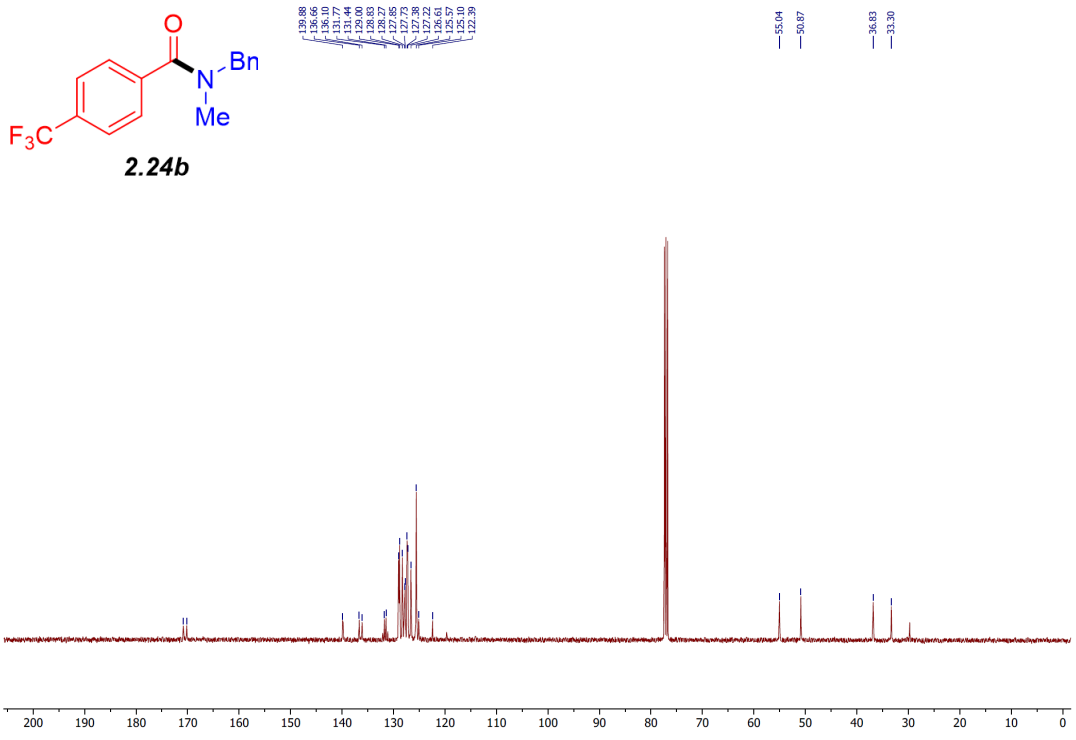
Bn
Me
F3C
2.24b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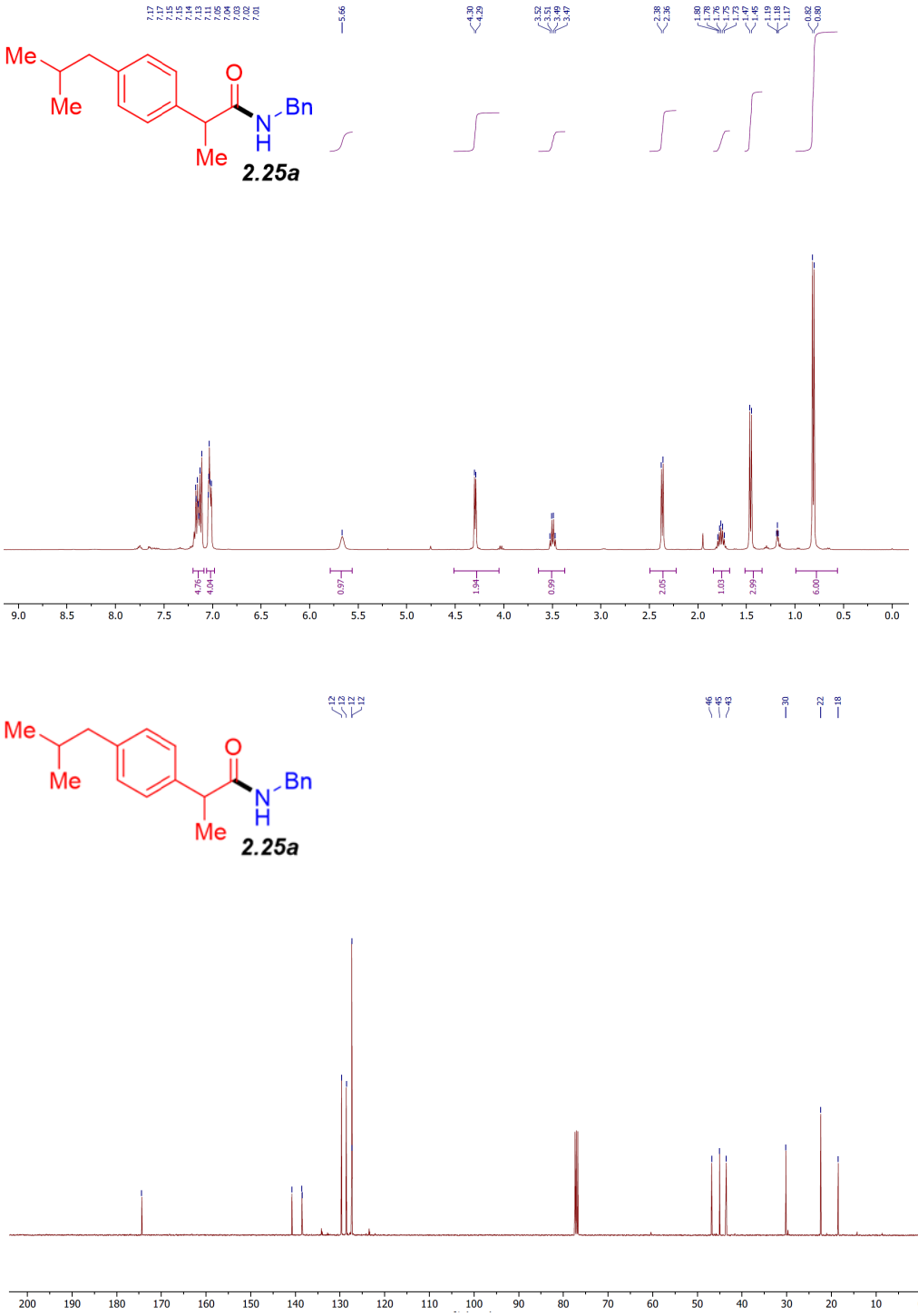
Bn
Me
F3C
2.24b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Bn
Me
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7.13
7.11
7.05
7.04
7.03
7.02
7.01
5.66
4.30
4.29
3.52
3.51
3.49
3.47
2.38
2.36
1.80
1.78
1.76
1.75
1.73
1.47
1.45
1.19
1.18
1.17
0.82
0.80
4.76
4.04
0.97
1.94
0.99
2.05
1.03
2.99
6.00
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6.5
6.0
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4.0
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2.0
1.5
1.0
0.5
0.0
Me
Me
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N
H
Bn
Me
2.25a
12
12
12
12
46
45
43
30
22
18
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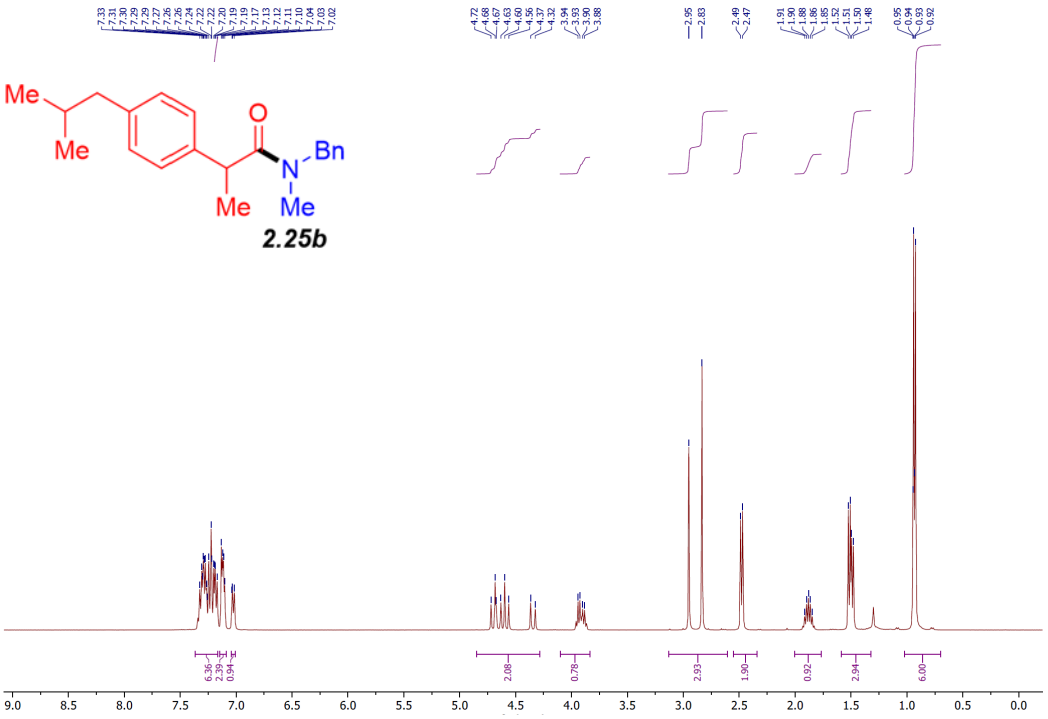
Me
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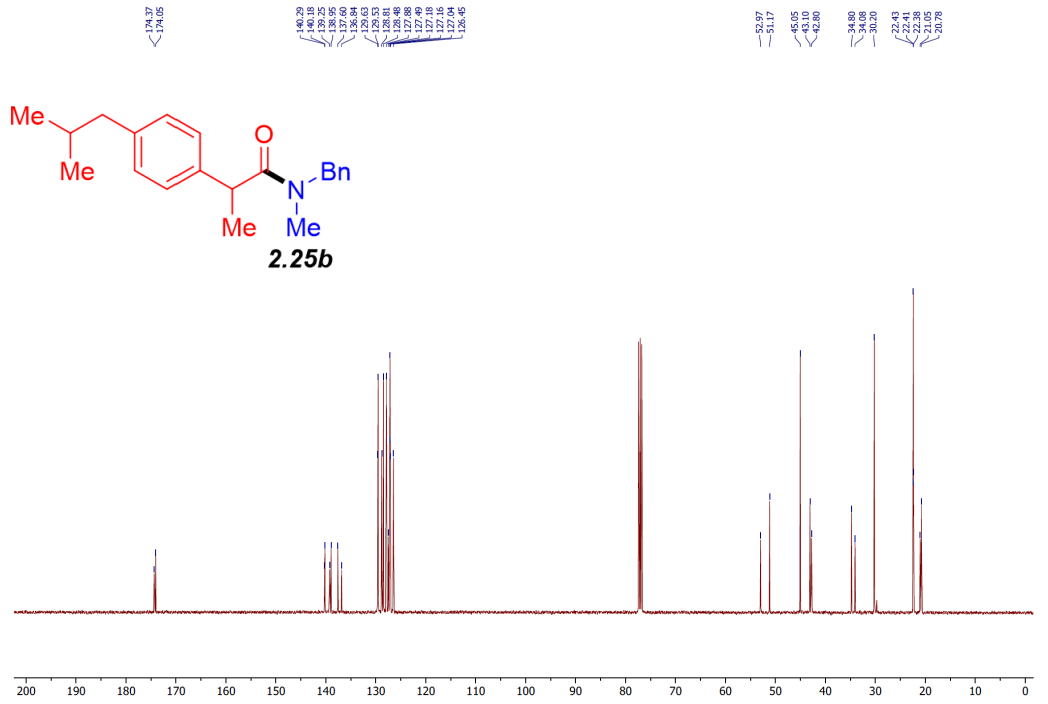
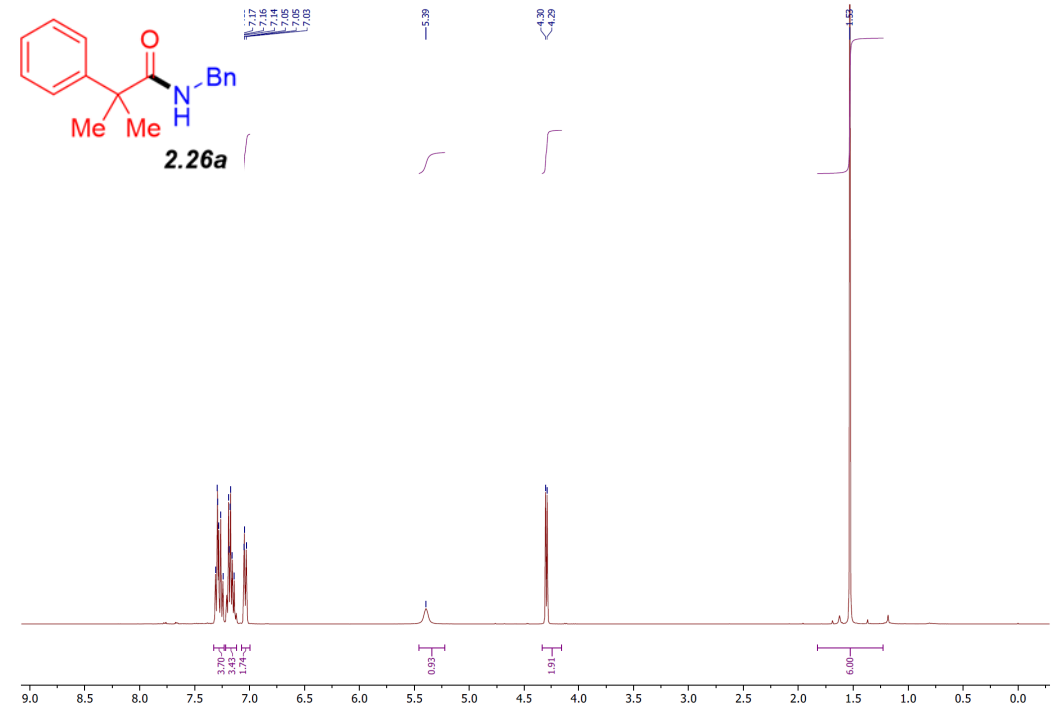
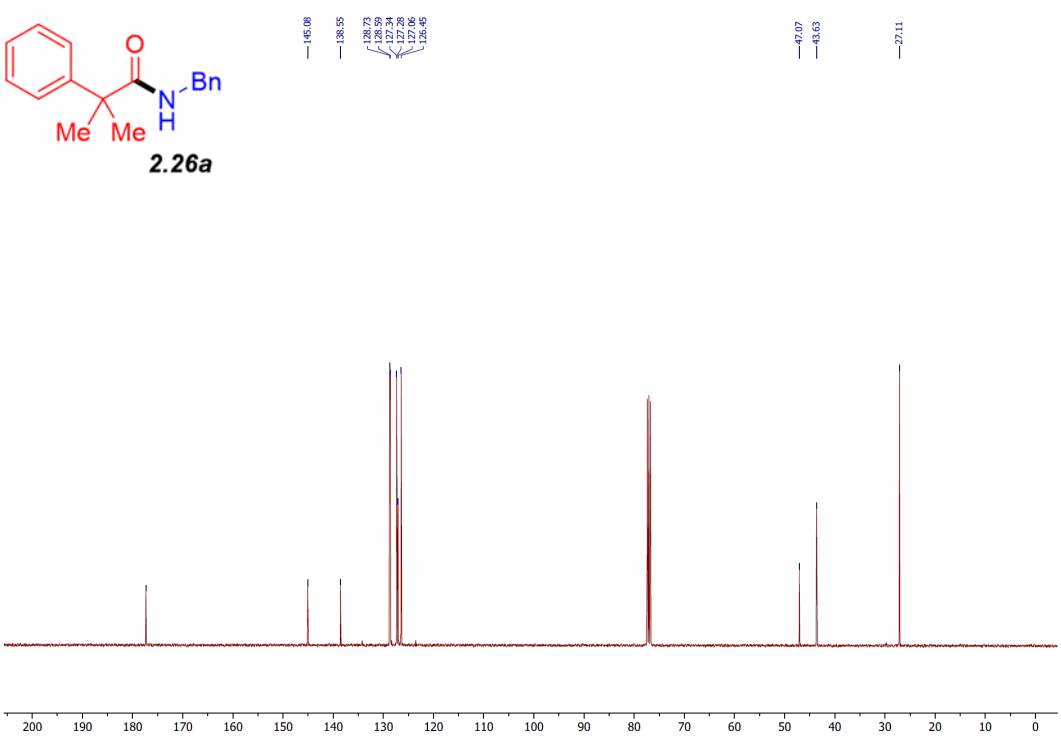
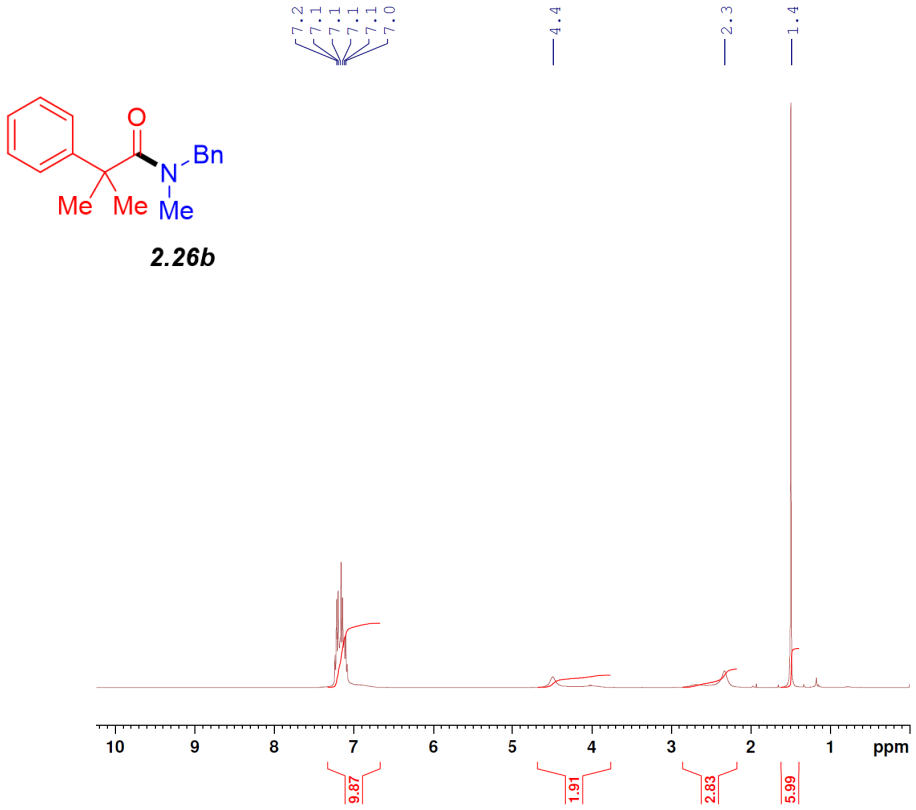
Bn
Me
Me
2.25b

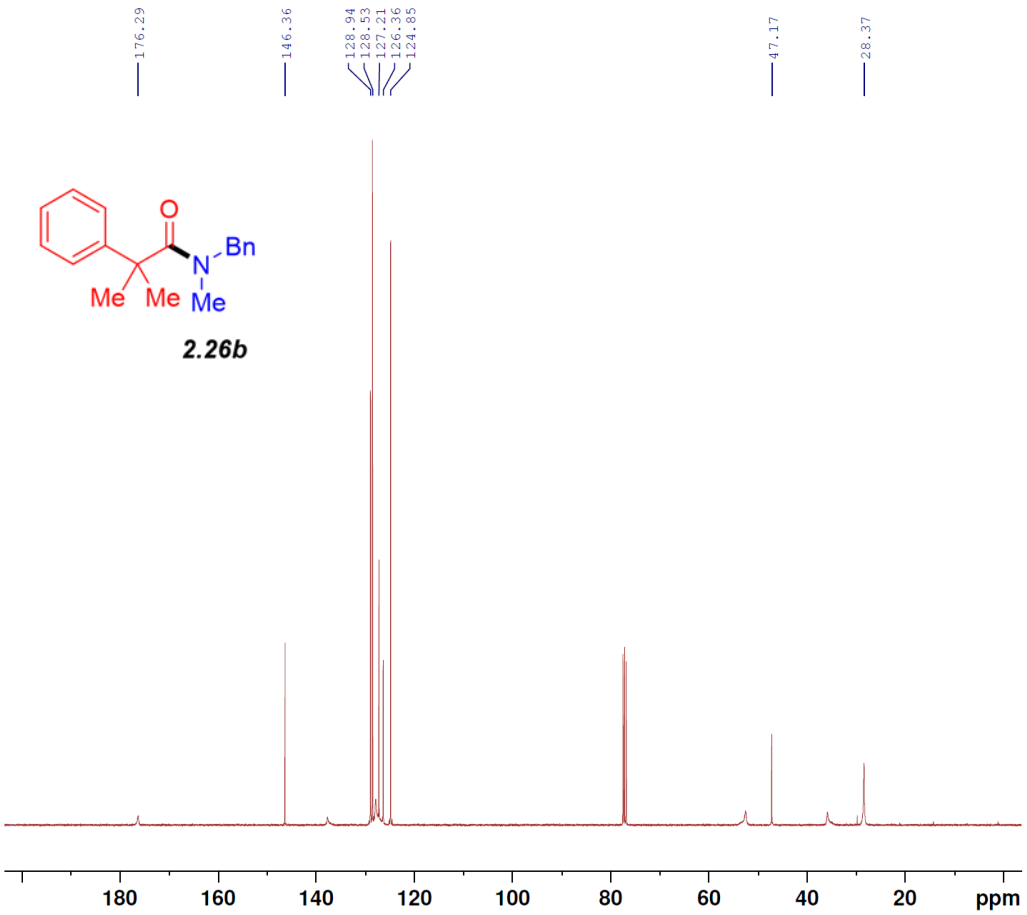

Me
Me
O
N
Bn
Me
Me
2.25b

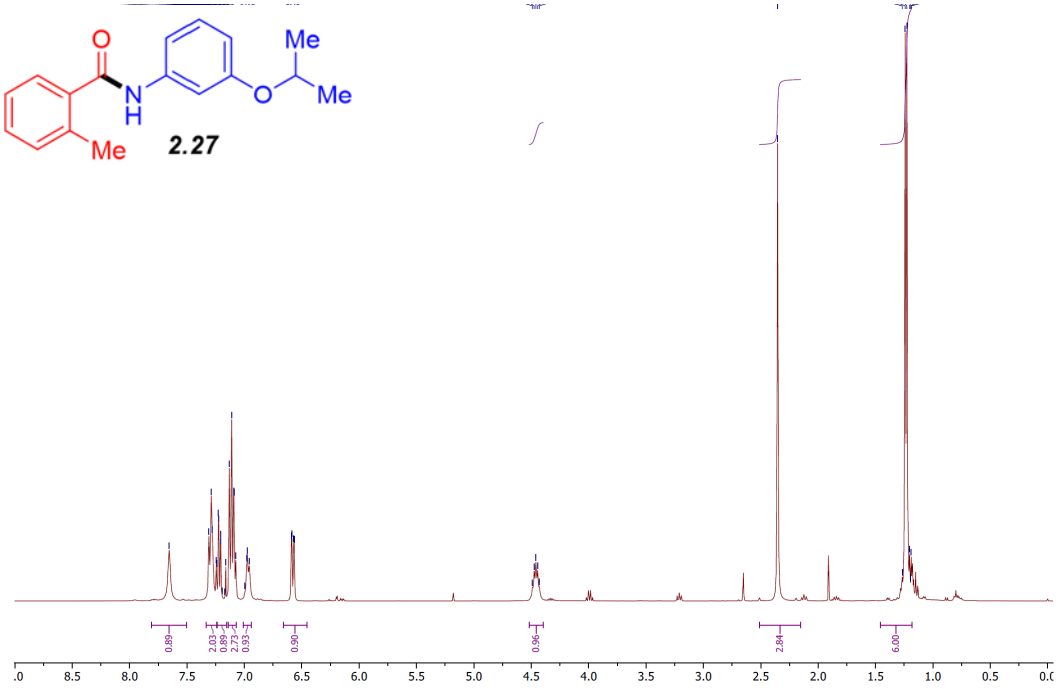

O
N
H
Bn
Me
Me
2.26a

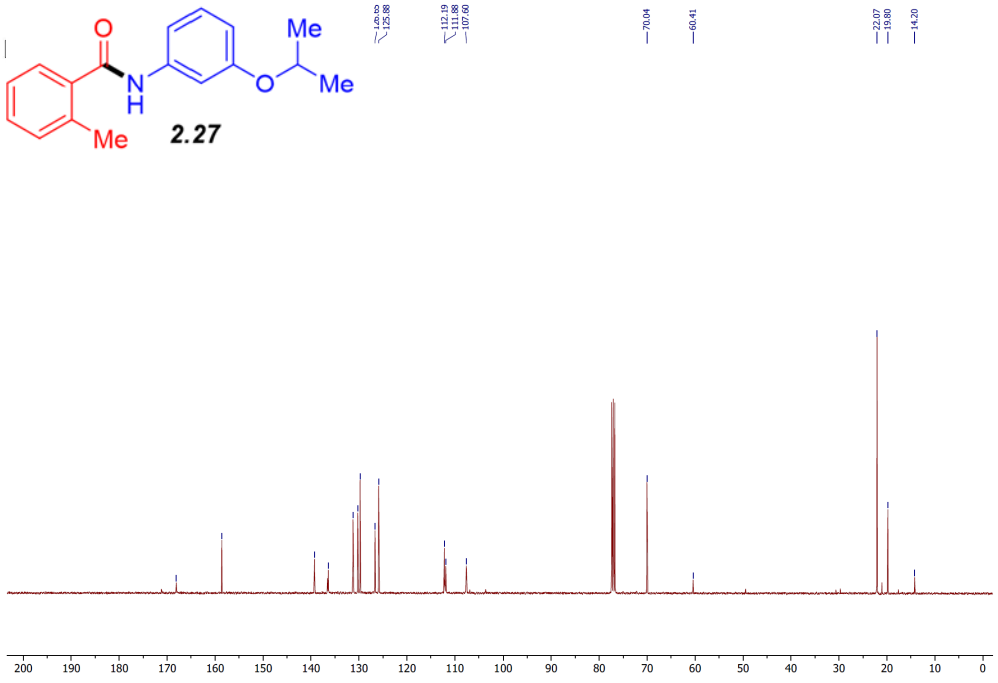

O
N
H
Bn
Me
Me
2.26a


7.2
7.1
7.1
7.1
7.1
7.0
4.4
2.3
1.4
O
N
Bn
Me
Me
Me
10
9
8
7
6
5
4
3
2
1
ppm
9.87
1.91
2.83
5.99

2.26b


176.29
146.36
128.94
128.53
127.21
126.36
124.85
47.17
28.37
O
N
Bn
Me
Me
Me
2.26b
180
160
140
120
100
80
60
40
20
ppm

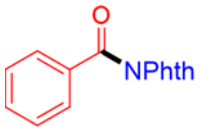

O
N
H
Me
O
Me
Me
2.27
0.89
2.03
0.89
2.27
0.93
0.90
0.96
2.84
6.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


O
N
H
Me
O
Me
Me
2.27
146.92
125.88
112.19
111.88
107.60
70.04
60.41
22.07
19.80
14.20
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
NPhth

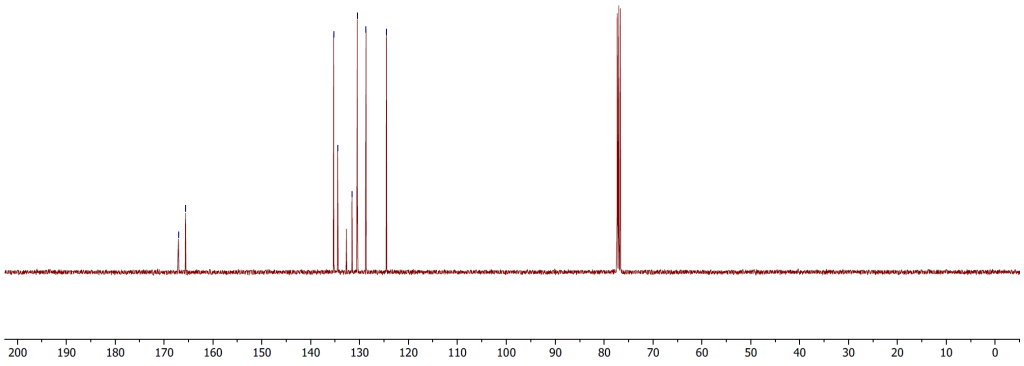
2.28

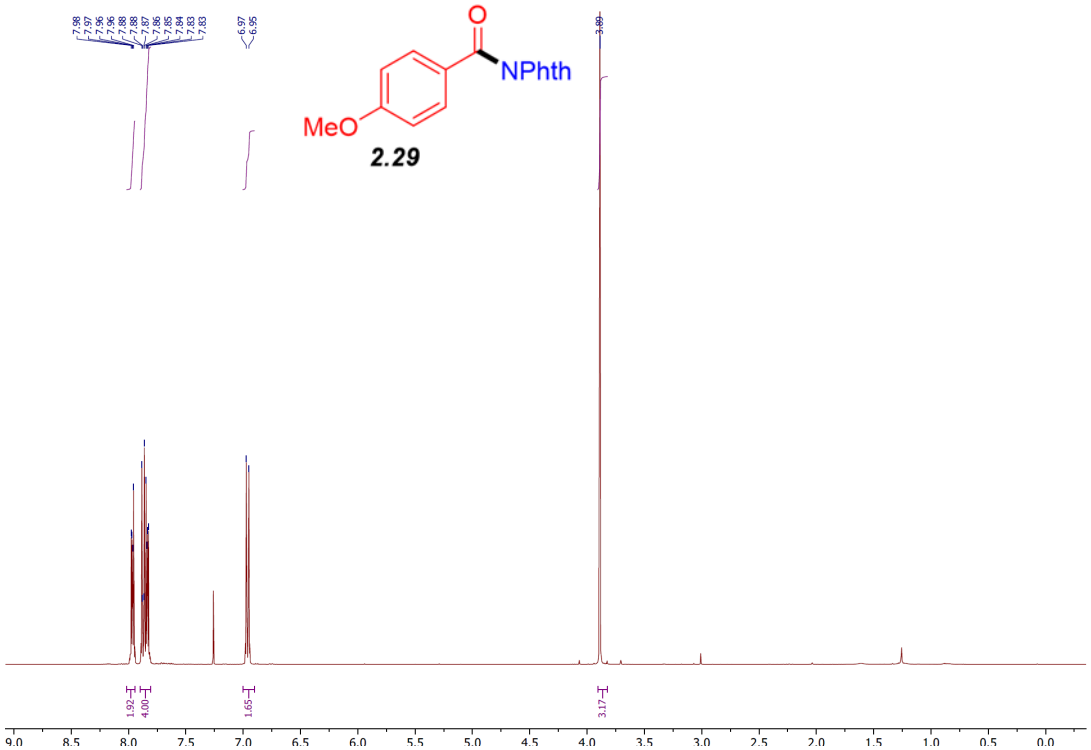
2.00
4.31
1.11
2.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

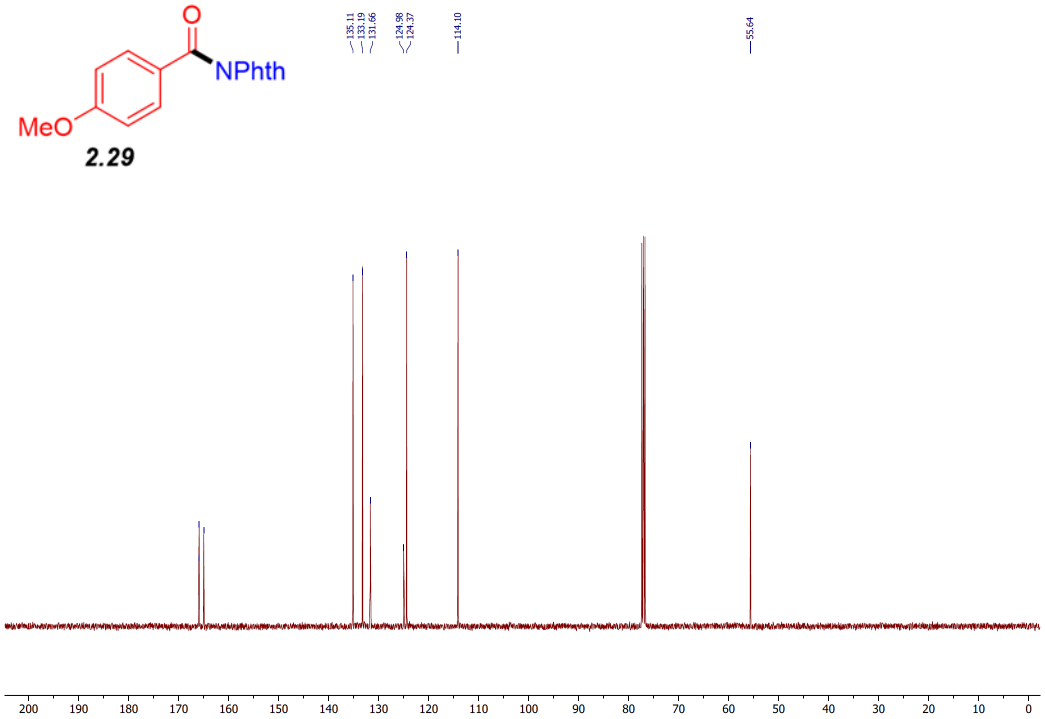

O
NPhth

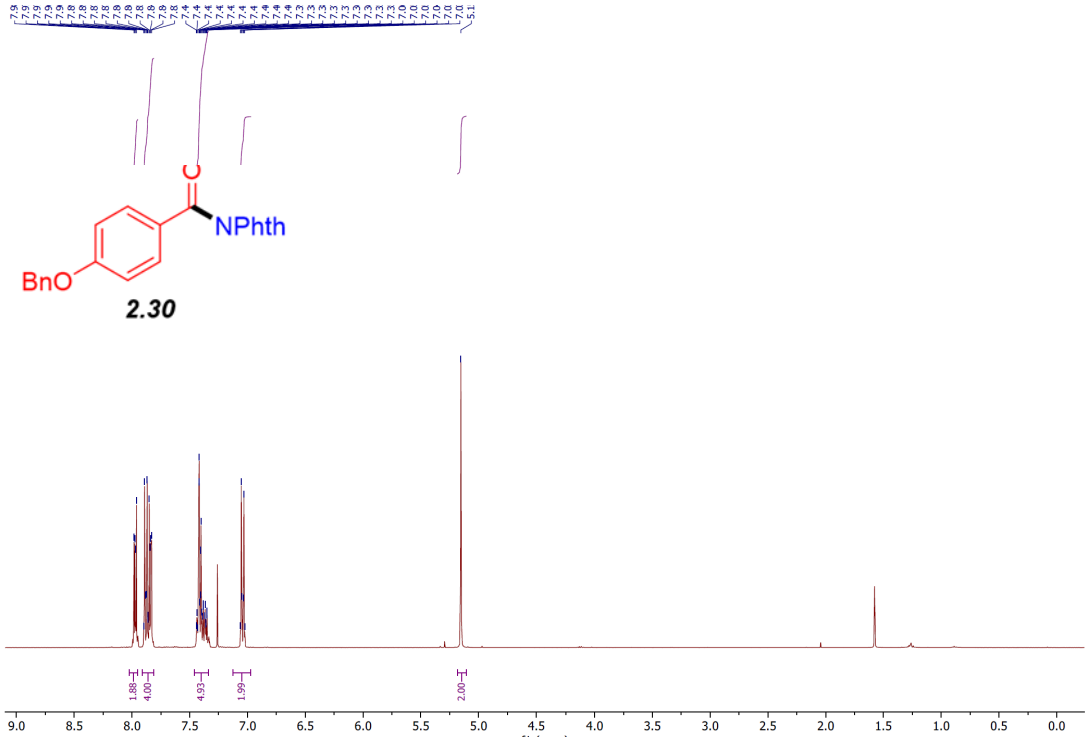
2.28

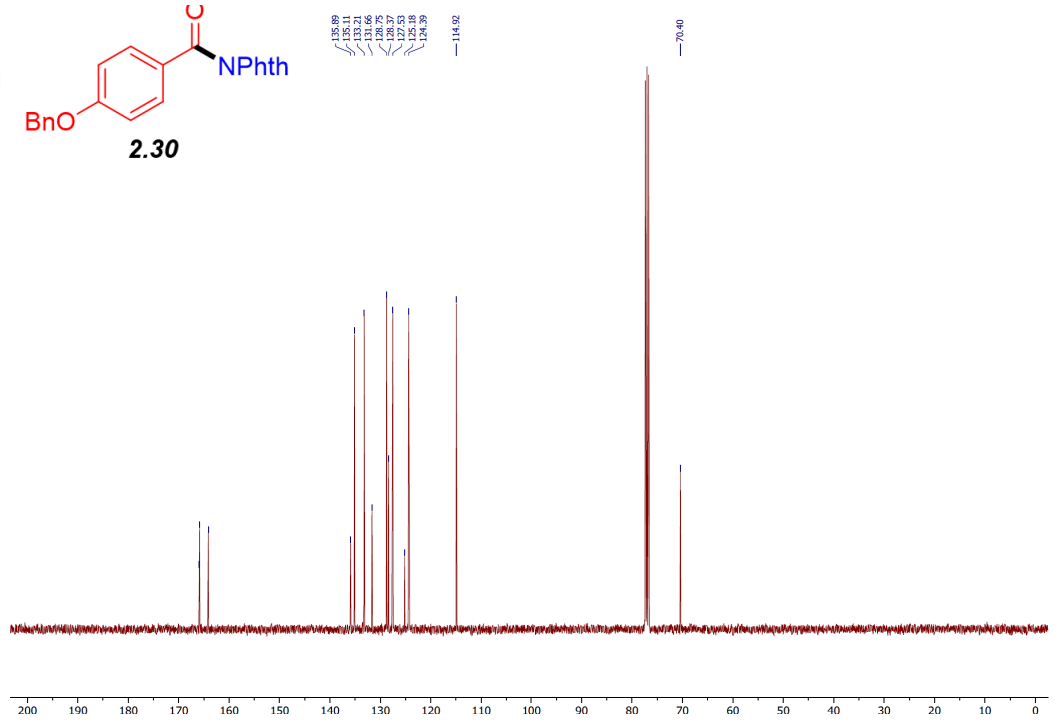

135.28
134.48
131.53
128.45
123.86
124.49

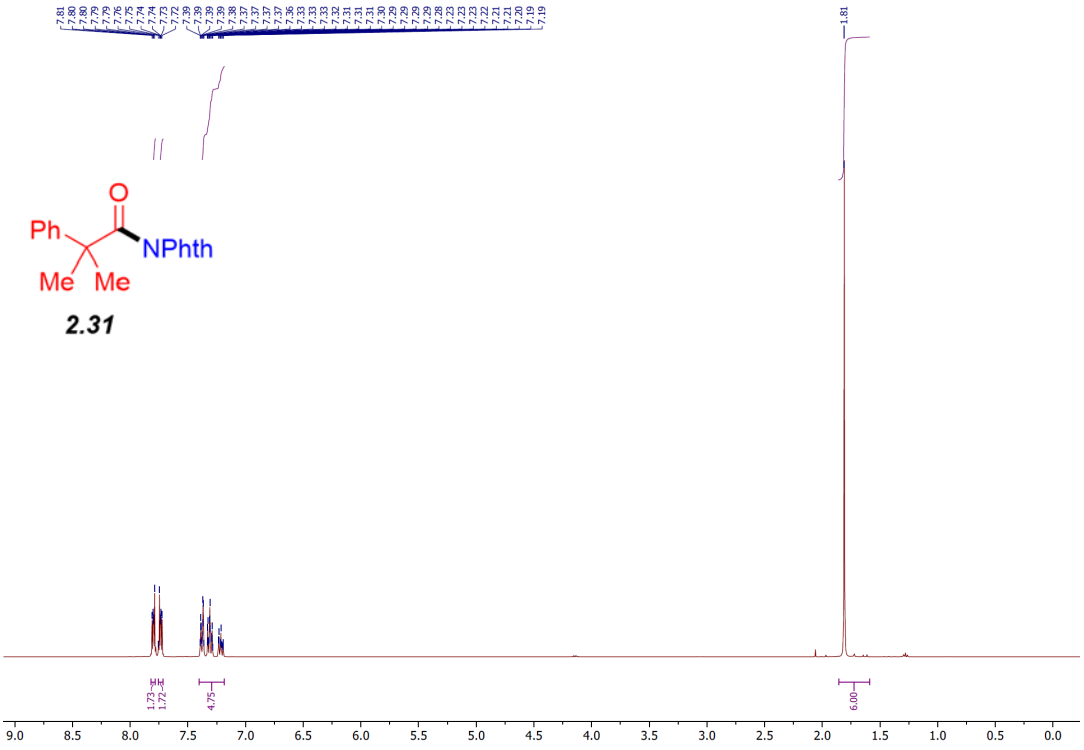

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

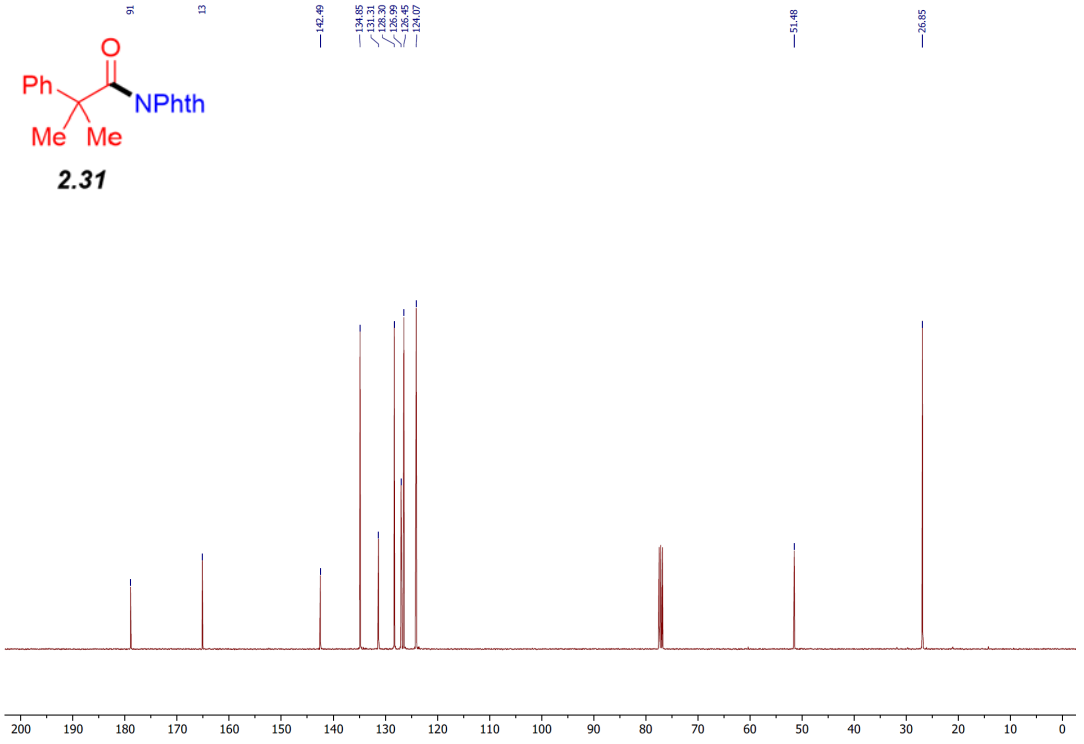

NPhth
MeO
2.29


NPhth
MeO
2.29


NPhth
BnO
2.30

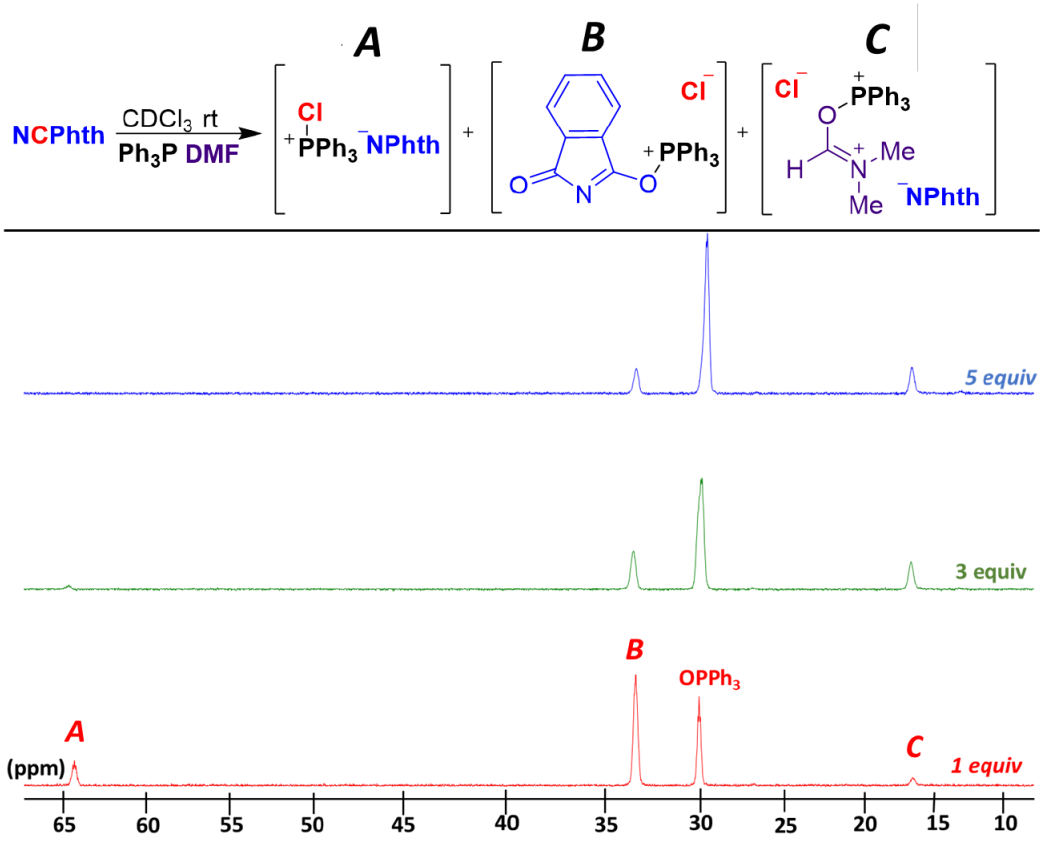

NPhth
BnO
2.30


Ph
NPhth
Me Me
2.31


Ph
NPhth
Me Me
2.31

I.) ^{31}P NMR Spectra

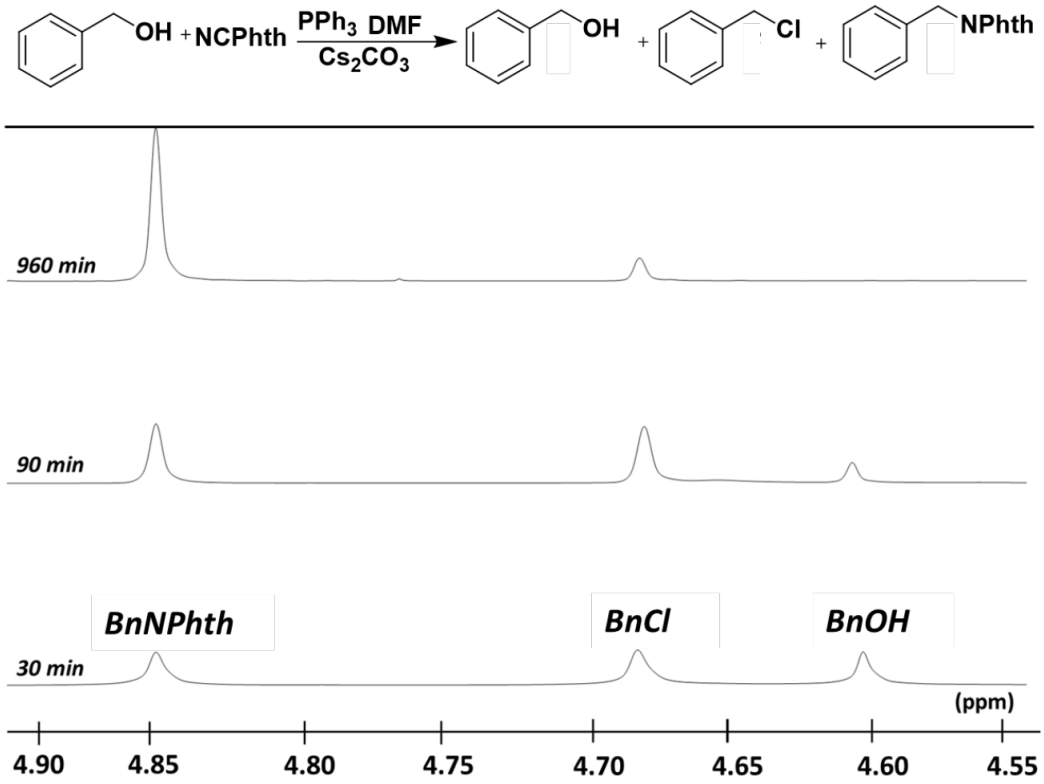
A.) Detection of Phosphonium Species



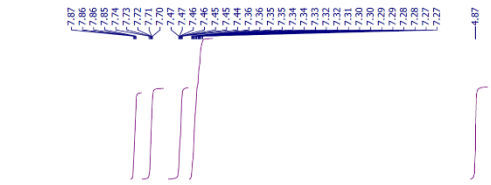
DMF (1-5 equiv), PPh_3 (0.405 mmol/1.5 equiv), NCPhth (0.405 mmol/1.5 equiv). All materials dissolved in $CDCl_3$.

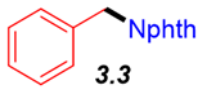
II.) ^{1}H NMR Spectra

A.) Detection of Chlorination Products

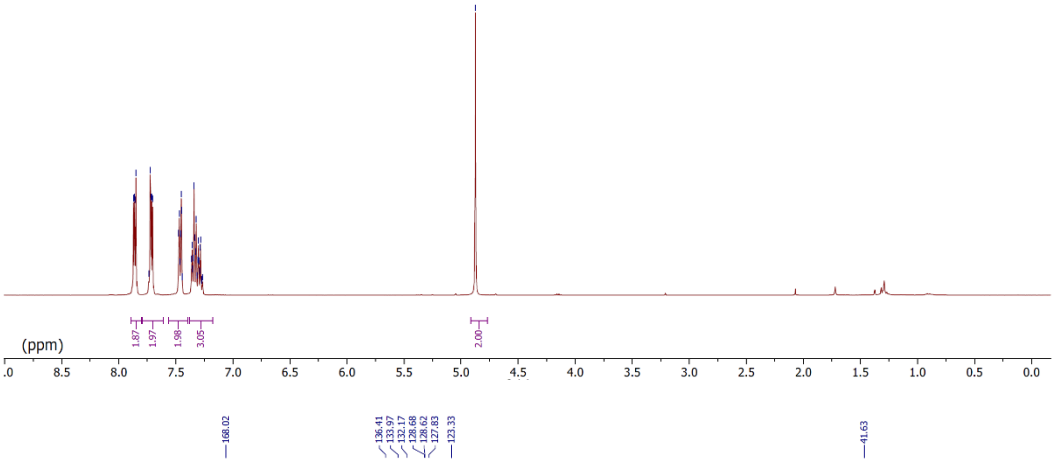


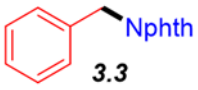
Each reaction was run using BnOH (0.185 mmol), NCPhth (0.278 mmol), PPh_3 (0.278 mmol), Cs_2CO_3 (0.278 mmol), dissolved in anhydrous DMF (1 mL) and stopped at different time intervals. All reactions were dissolved in $CDCl_3$ post-workup for ^{1}HNMR Analysis.



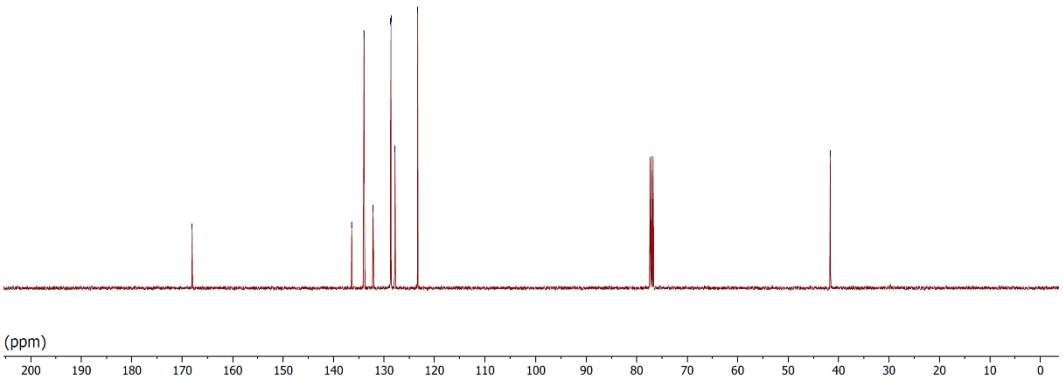


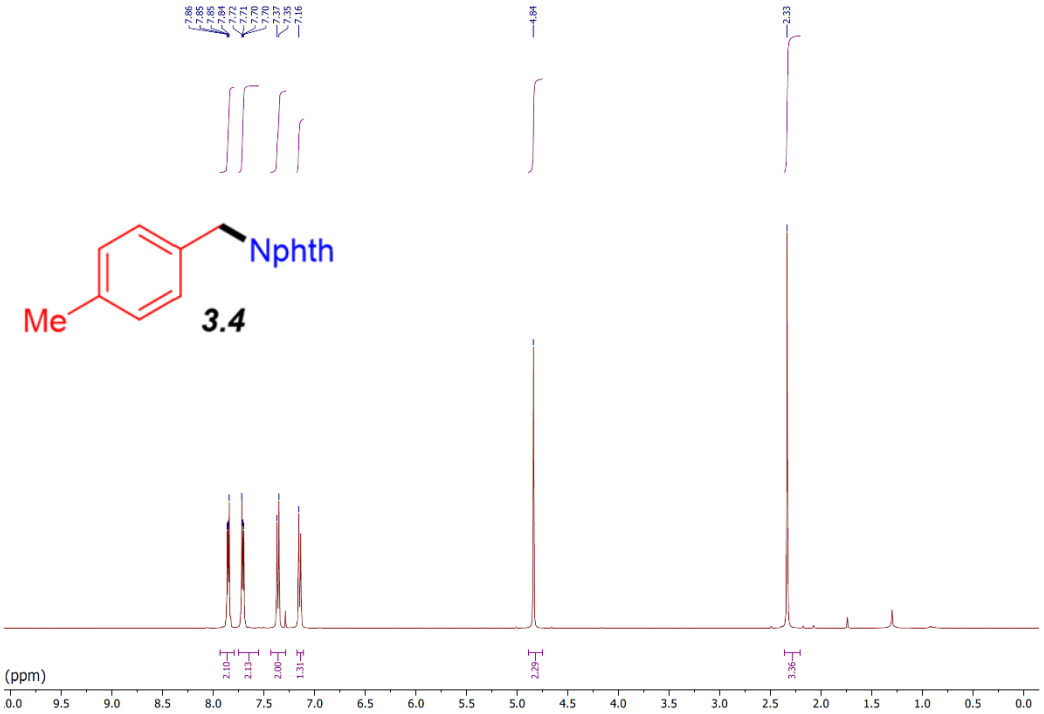
3.3

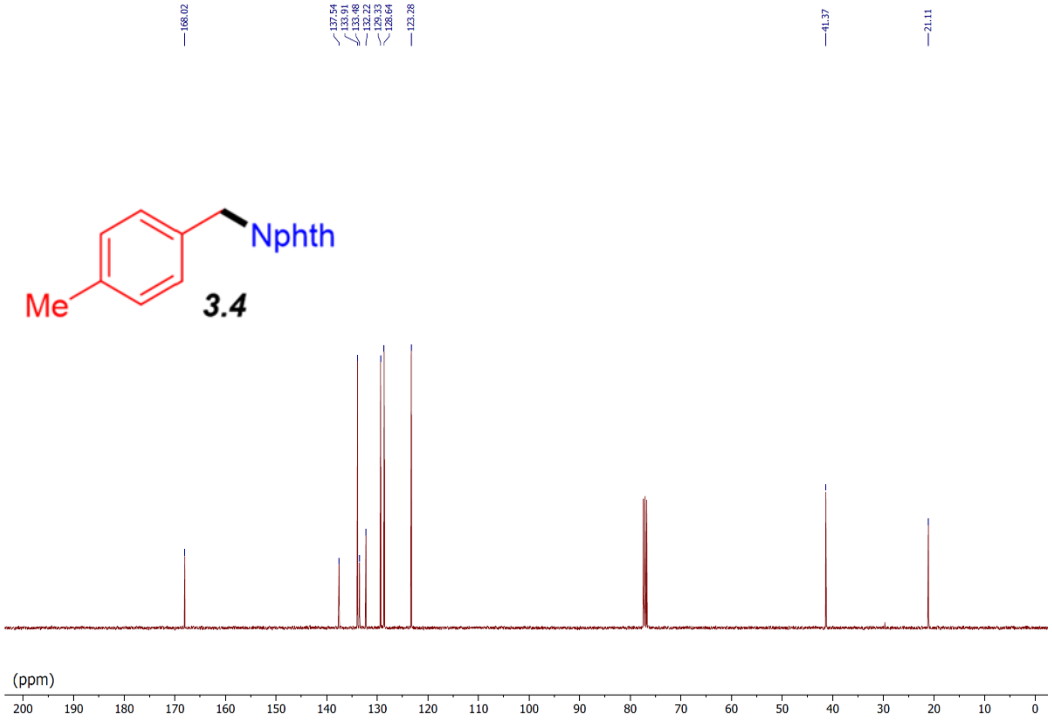


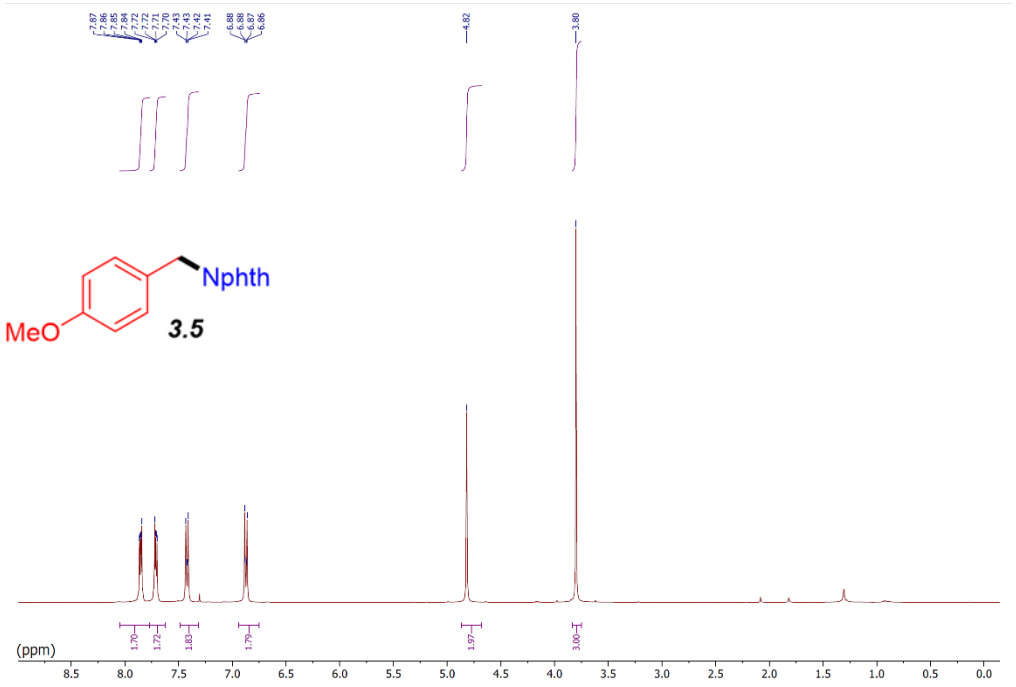


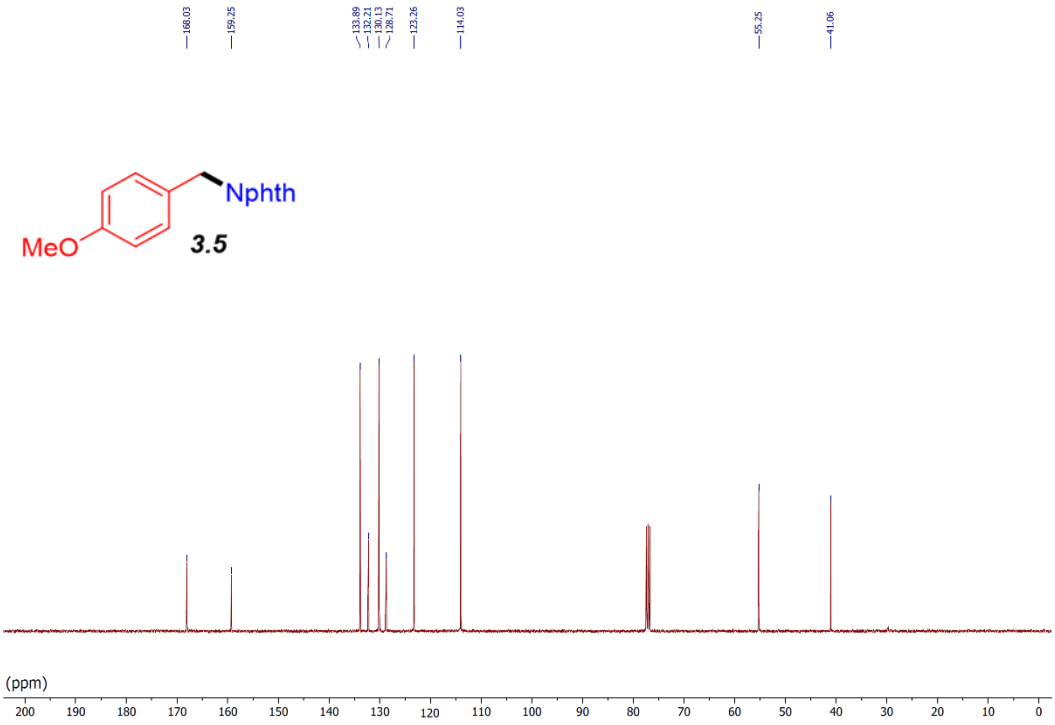
3.3

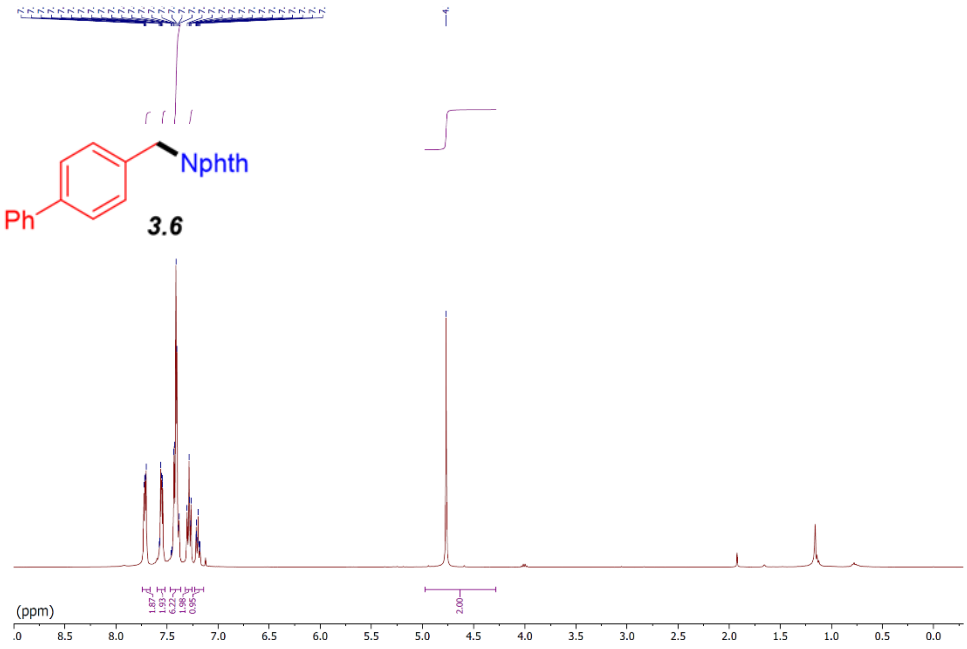


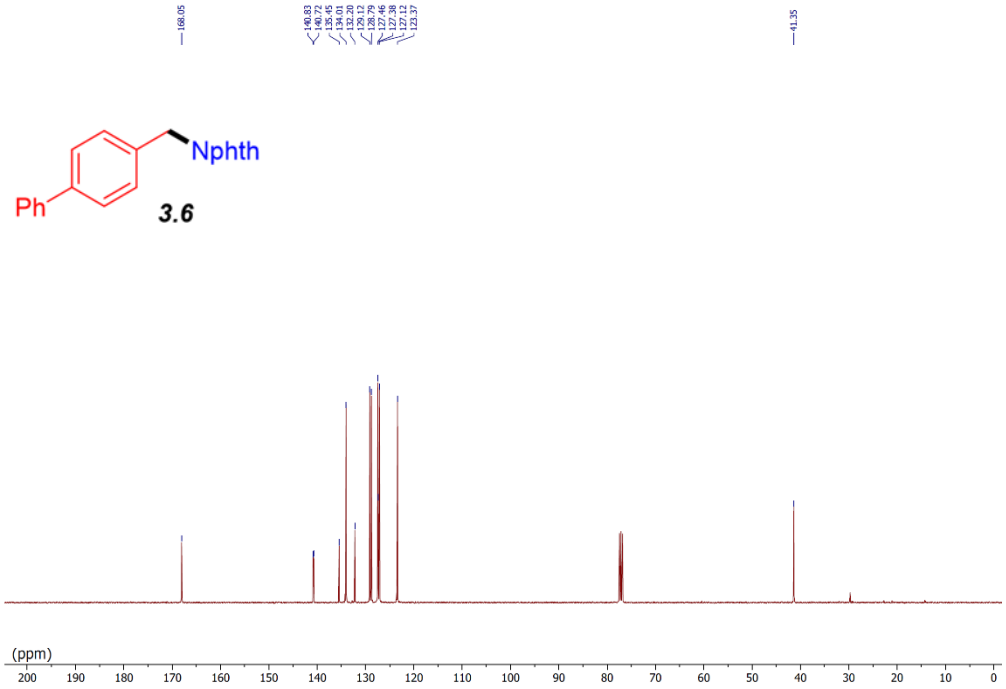

7.86
7.85
7.85
7.84
7.72
7.71
7.70
7.70
7.37
7.35
7.16
4.84
2.33
Nphth
Me
3.4
2.10
2.15
2.00
1.31
2.29
3.36
(ppm)
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


168.02
137.54
133.91
133.48
132.22
129.33
128.64
123.28
41.37
21.11
Nphth
Me
3.4
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

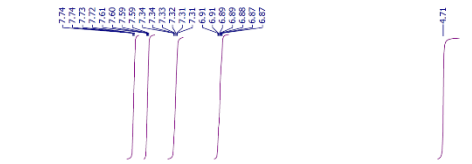

7.87
7.86
7.85
7.84
7.72
7.72
7.71
7.70
7.43
7.43
7.42
7.41
6.88
6.88
6.87
6.86
4.82
3.80
Nphth
MeO
3.5
1.70
1.72
1.83
1.79
1.97
3.00
(ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

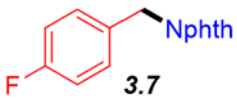

168.03
159.25
133.89
132.21
130.13
128.71
123.26
114.03
55.25
41.06
Nphth
MeO
3.5
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

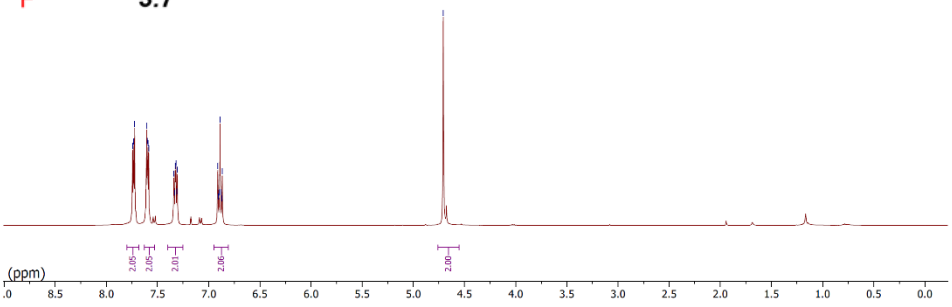

Nphth
Ph
3.6
(ppm)

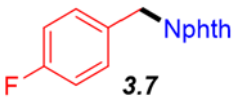

Nphth
Ph
3.6
(ppm)

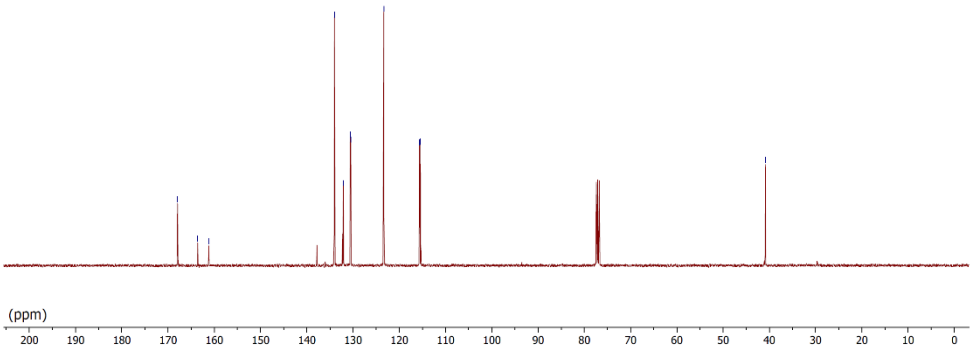
\




Nphth
F
3.7


(ppm)


Nphth
F
3.7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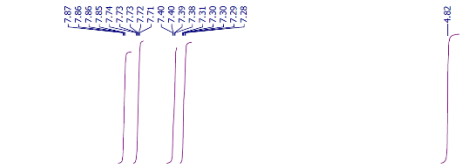
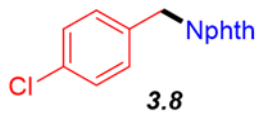
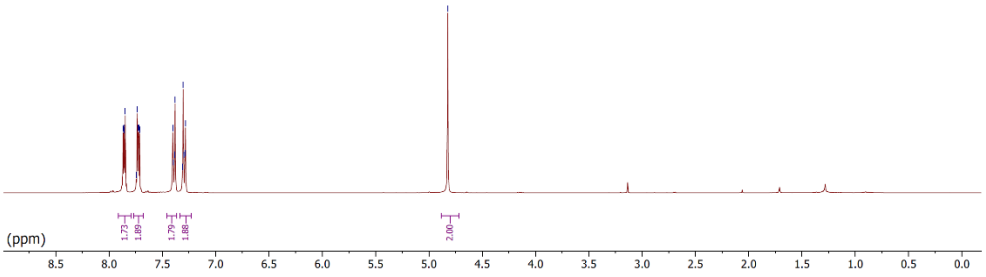
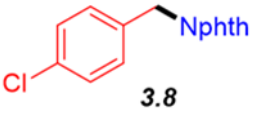


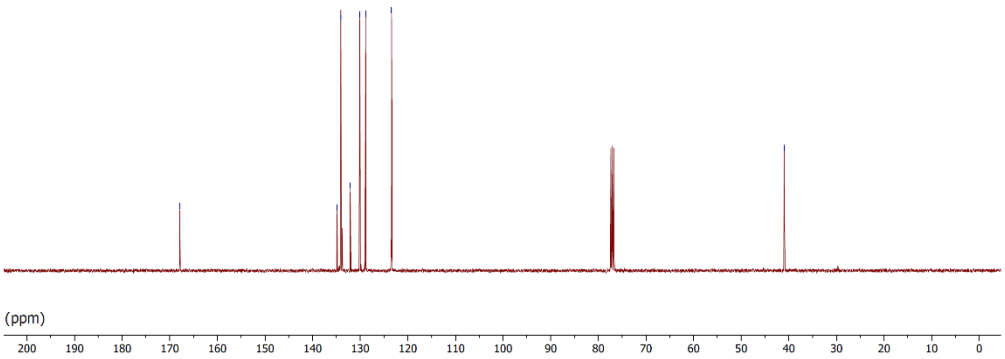


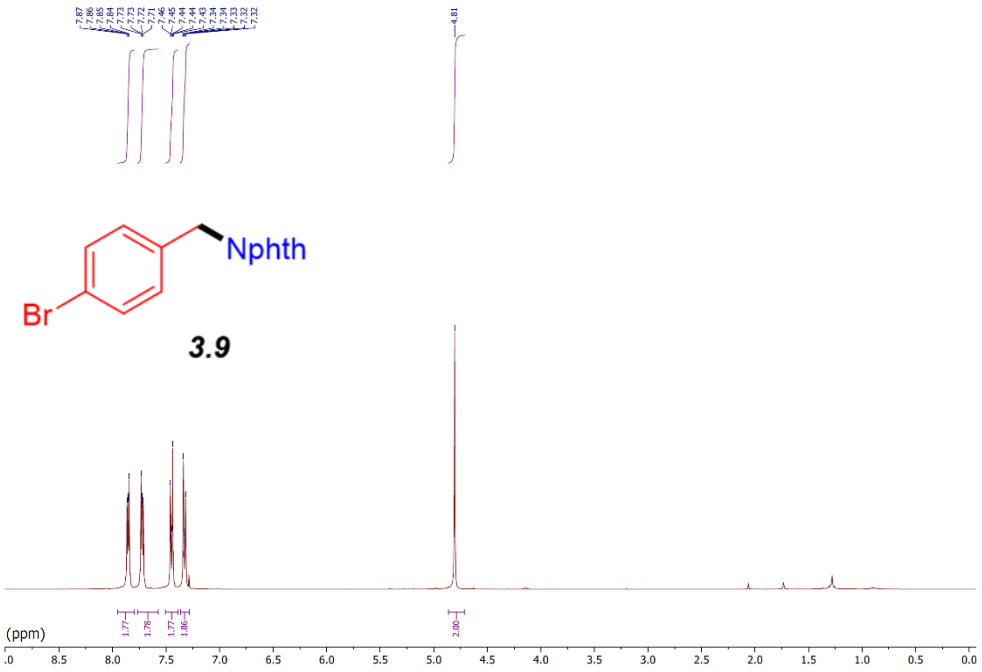
3.8

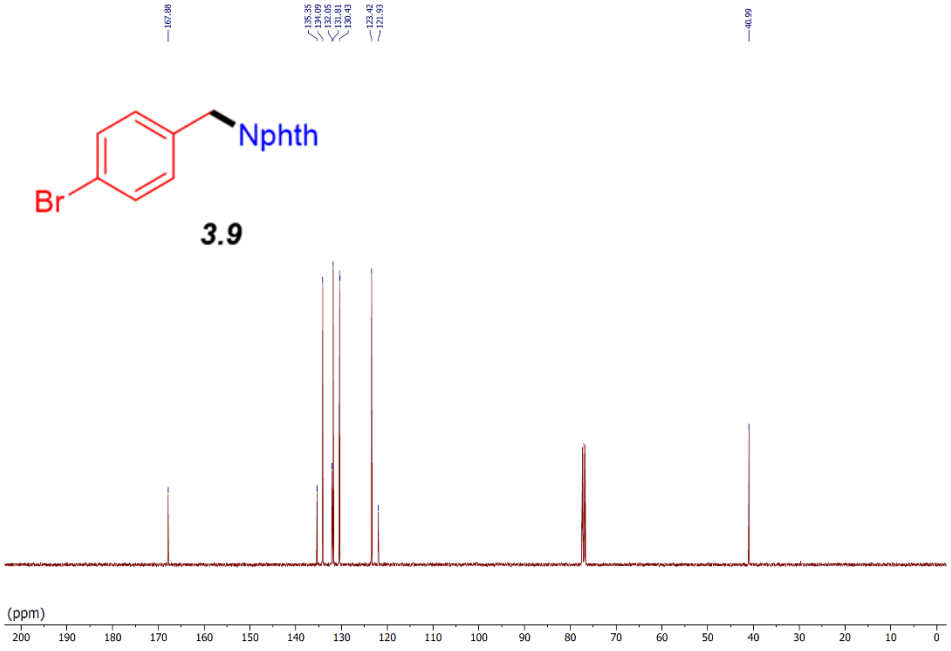




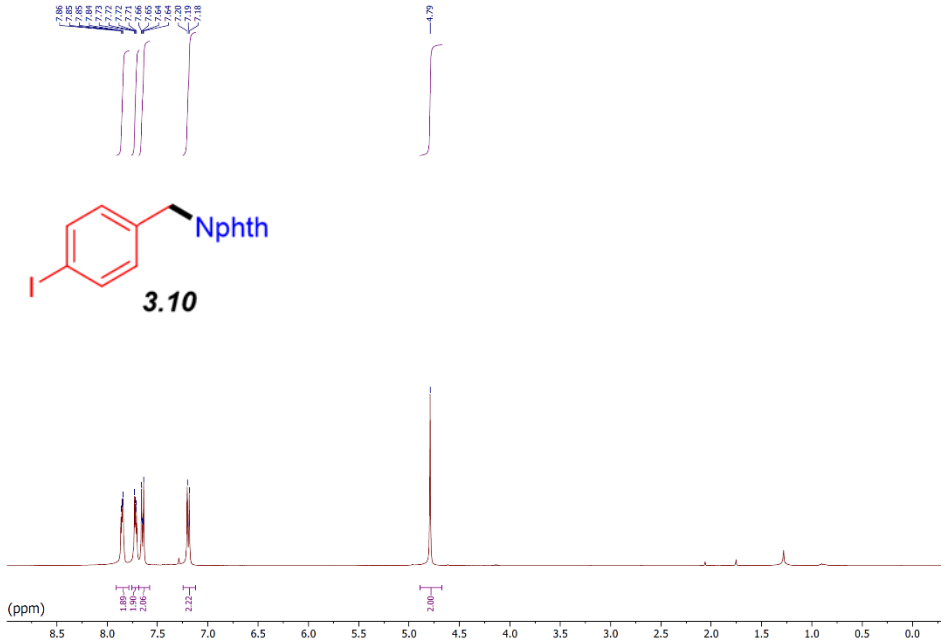
3.8

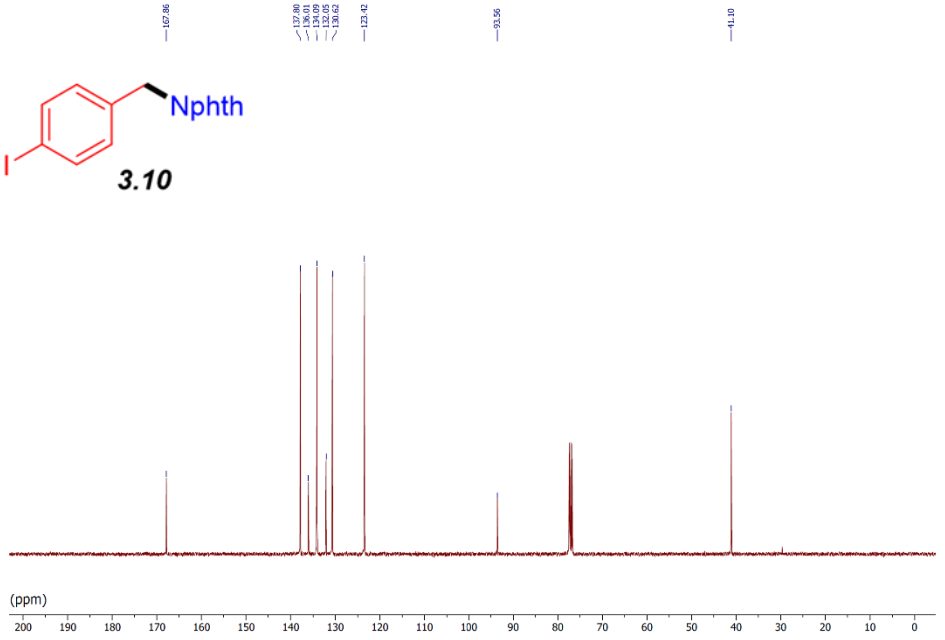


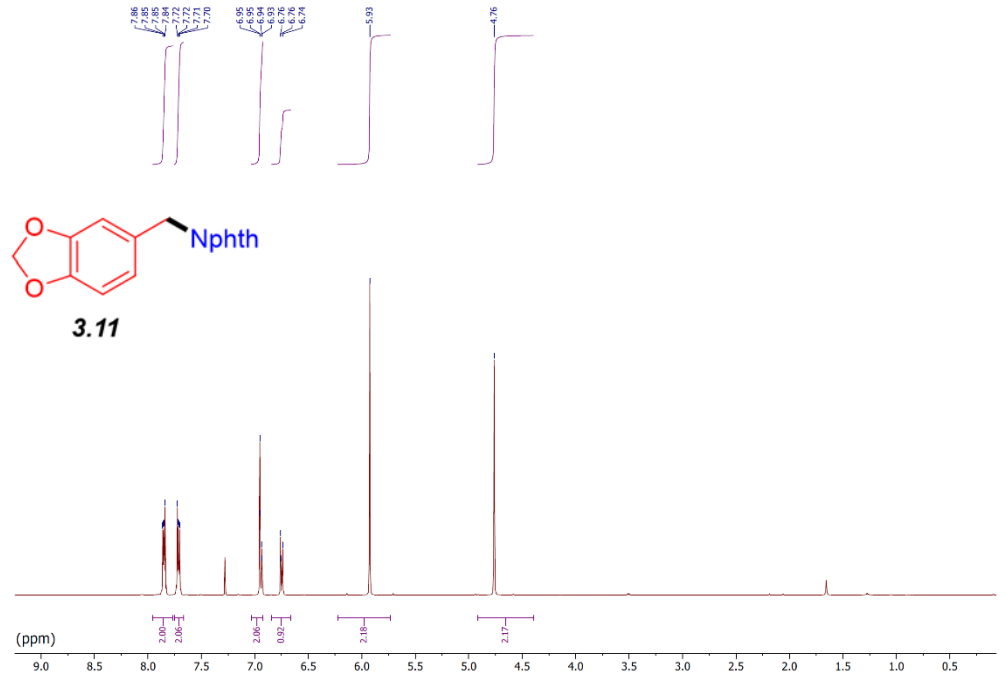

Nphth
Br
3.9
(ppm)

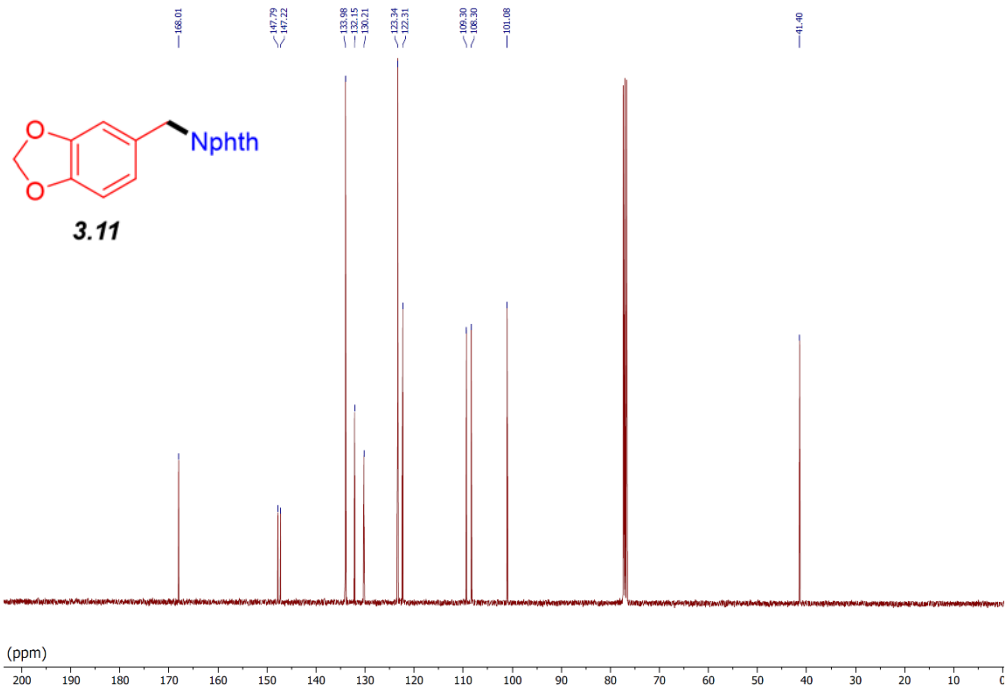

Nphth
Br
3.9
(ppm)

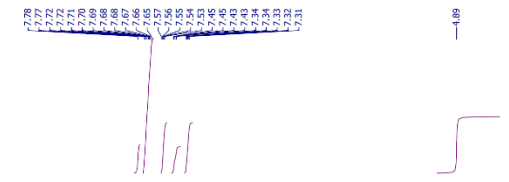
‘

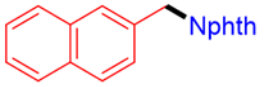

Nphth
3.10
(ppm)


Nphth
3.10
(ppm)

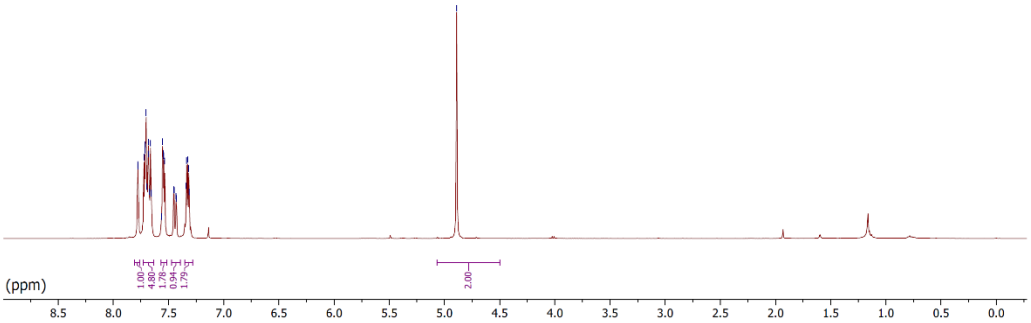

7.86
7.85
7.85
7.84
7.72
7.72
7.71
7.70
6.95
6.95
6.94
6.93
6.76
6.76
6.74
5.93
4.76
Nphth
3.11
2.00
2.06
2.06
0.92
2.18
2.17
(ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

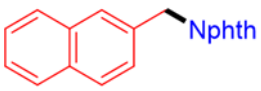

168.01
147.79
147.22
133.98
132.15
130.21
123.34
122.31
109.30
108.30
101.08
41.40
Nphth
3.11
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



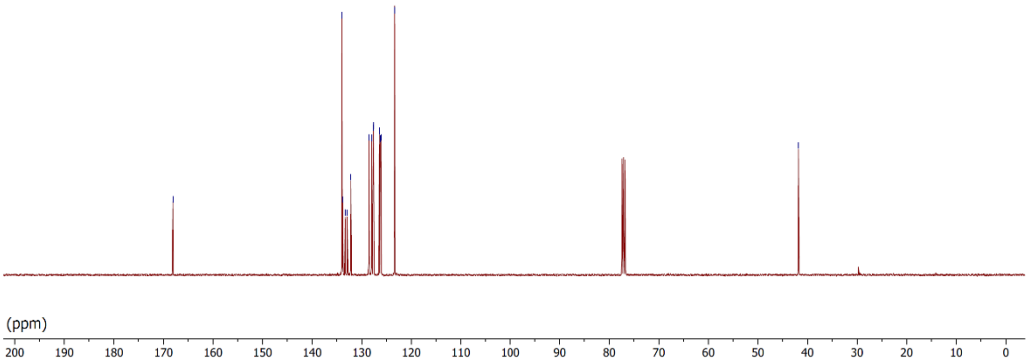


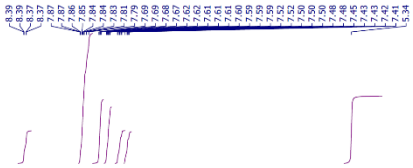
3.12

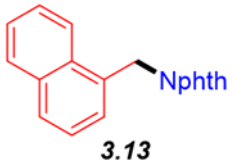




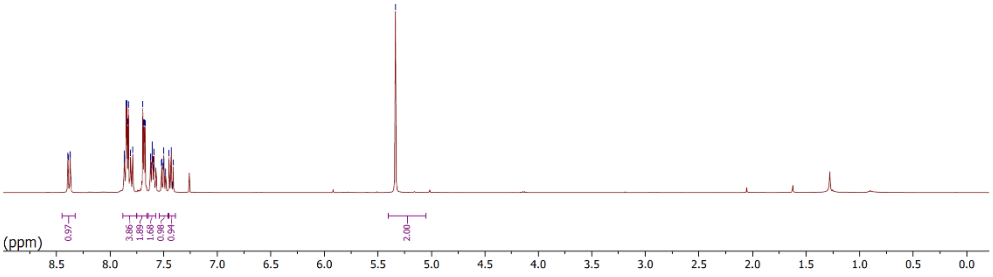
3.12

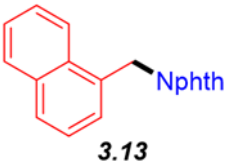




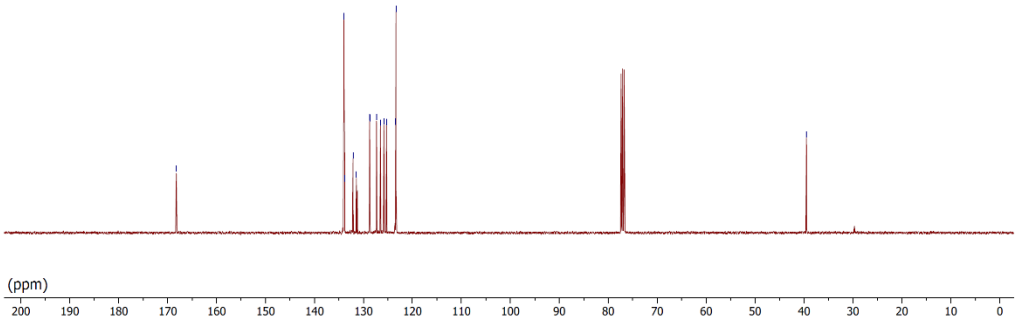

Nphth

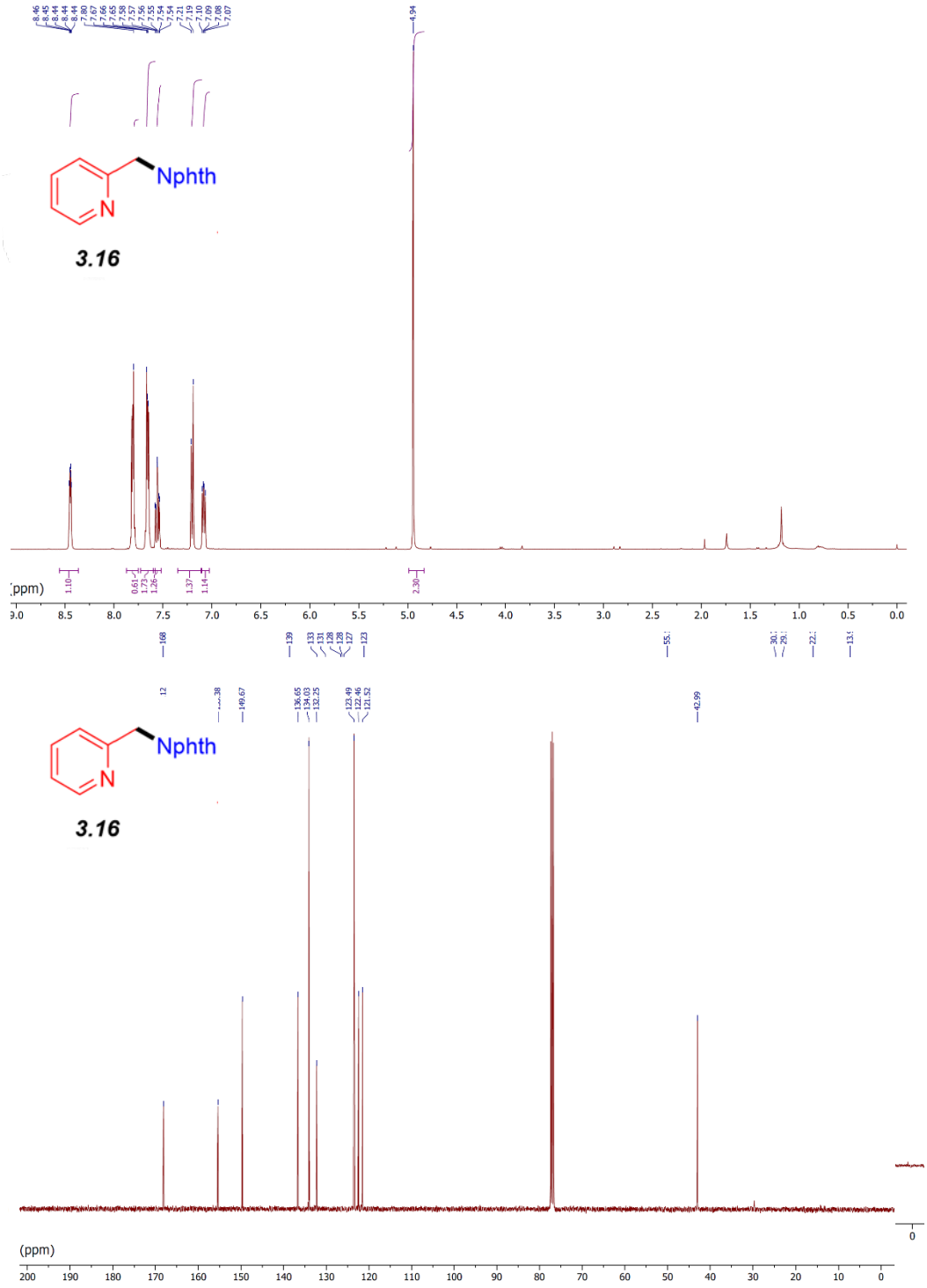
3.13

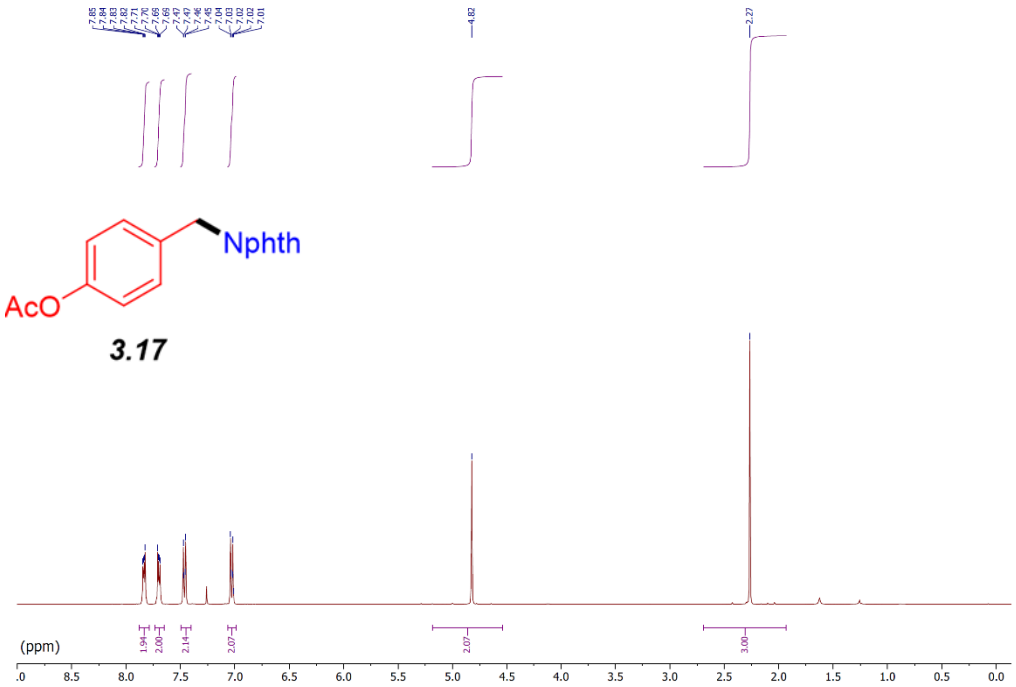

(ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

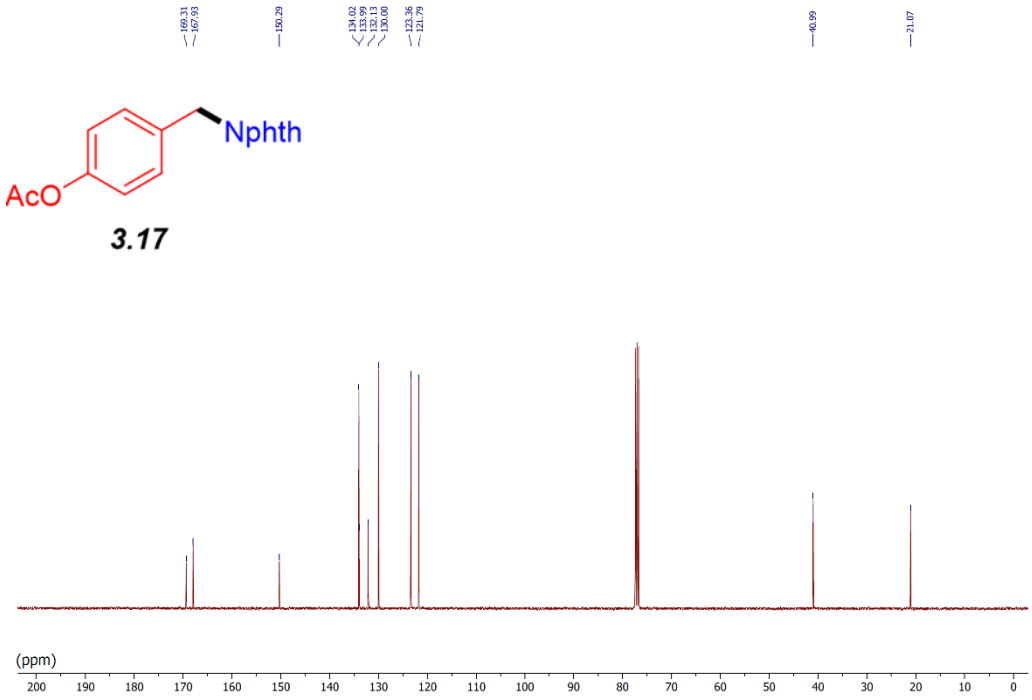

Nphth

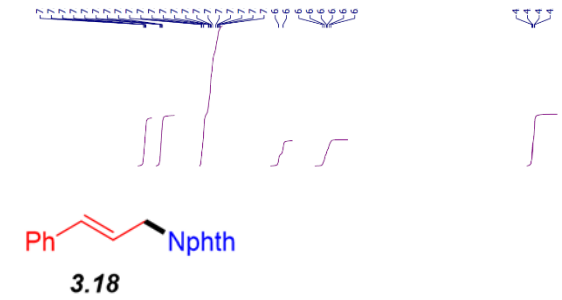
3.13


(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

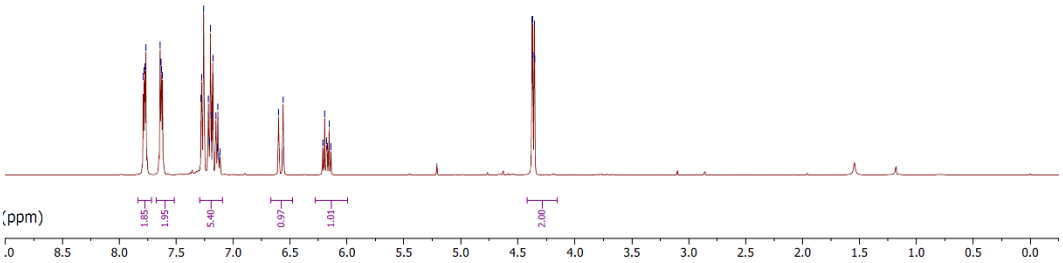

Nphth
N
3.16
(ppm)
Nphth
N
3.16
(ppm)


Nphth
AcO
3.17
(ppm)

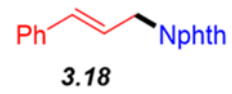

Nphth
AcO
3.17
(ppm)


Ph
Nphth

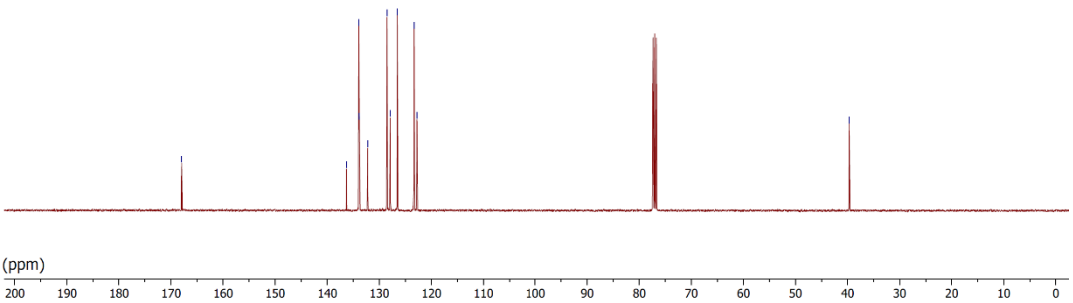
3.18

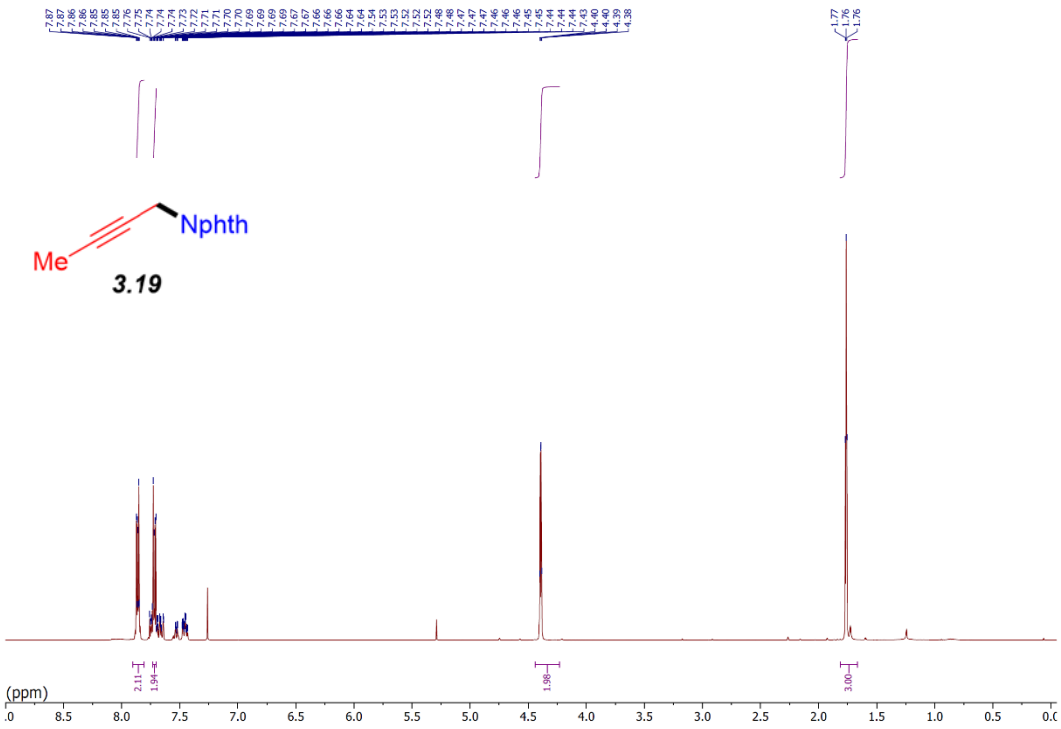

(ppm)
1.85
1.95
5.40
0.97
1.01
2.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

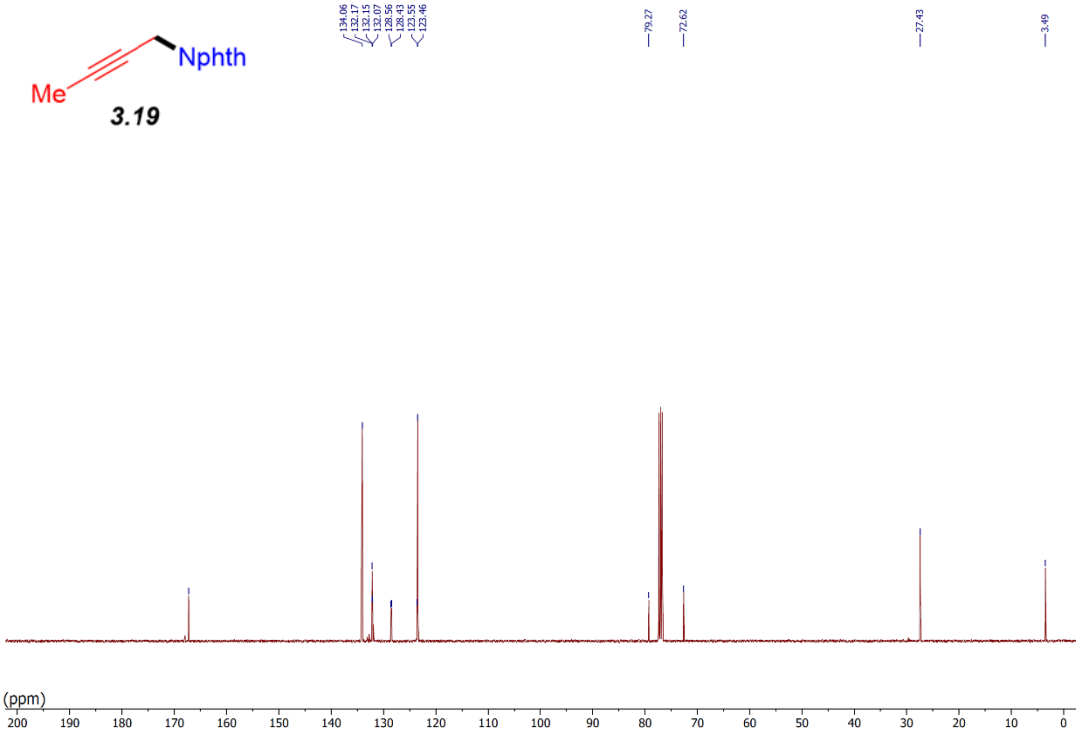

167.94
136.30
133.97
133.85
128.24
128.15
127.89
126.55
123.31
122.78
39.69

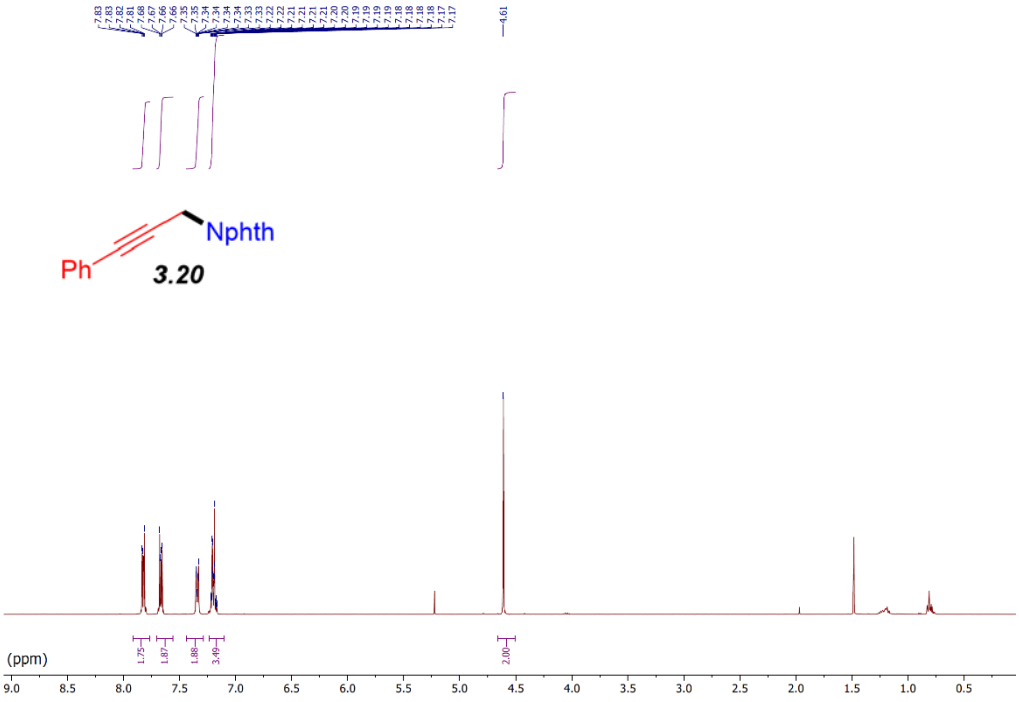

Ph
Nphth

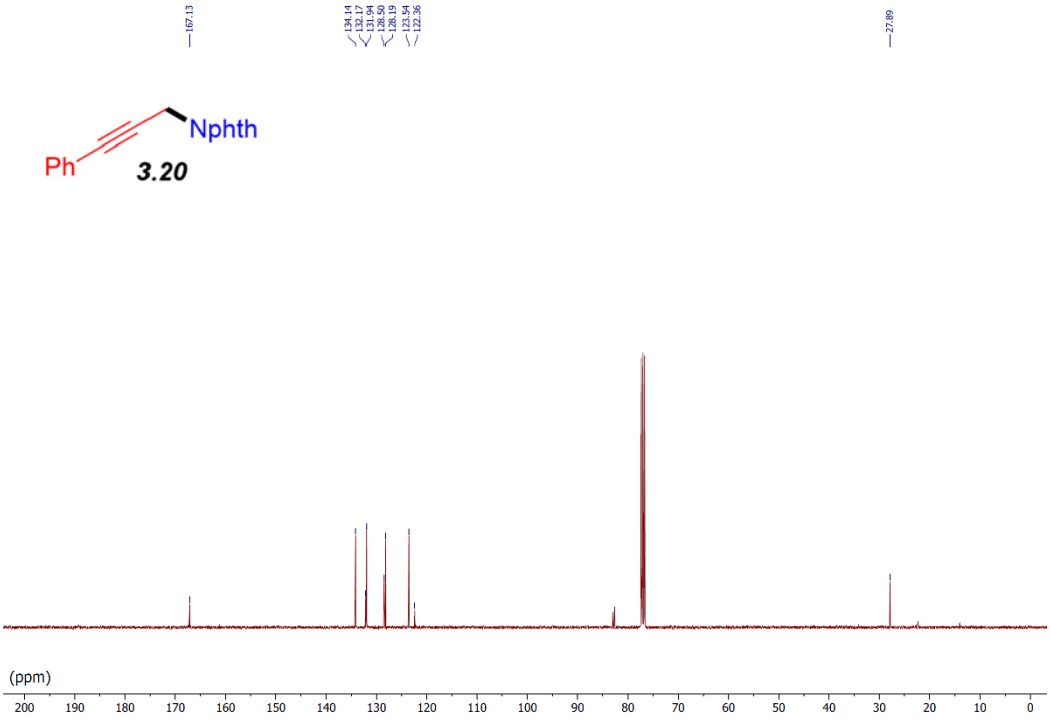
3.18

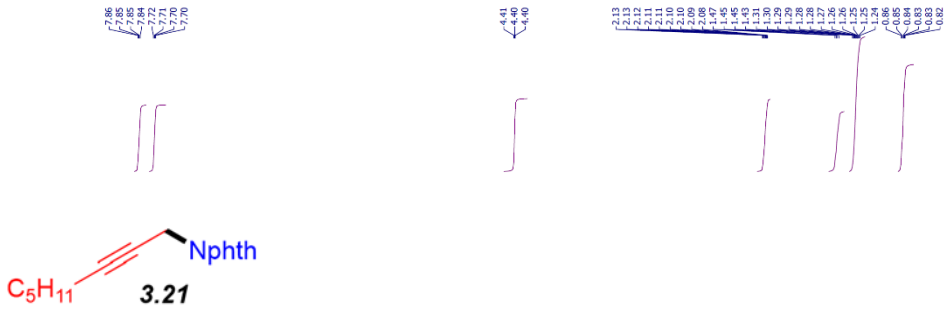

(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

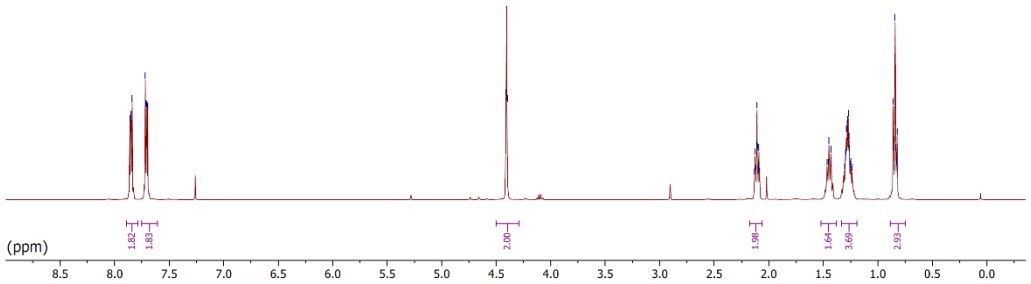

Nphth
Me
3.19
(ppm)

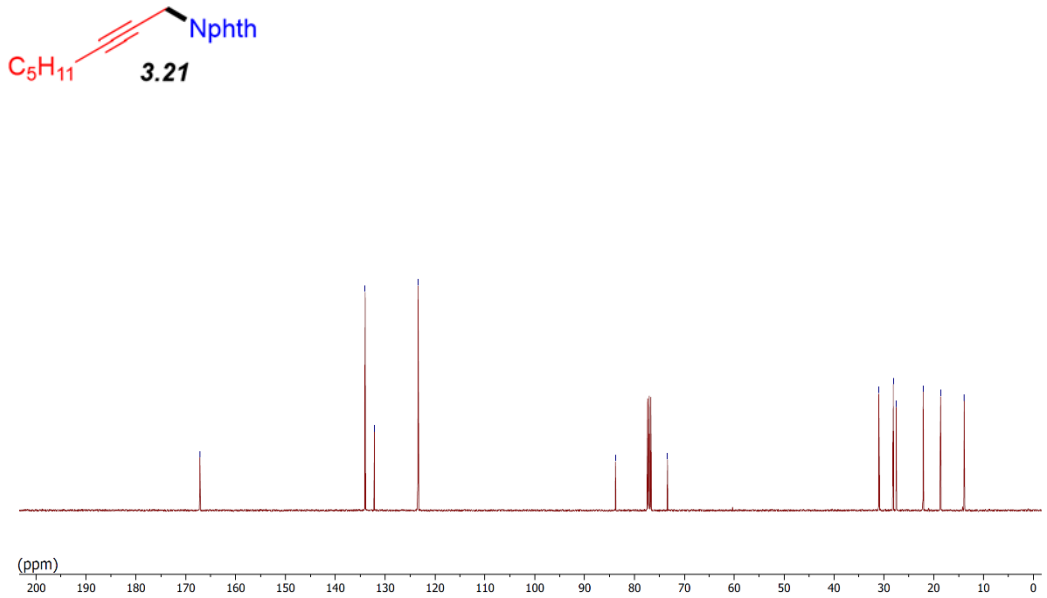

Nphth
Me
3.19
(ppm)

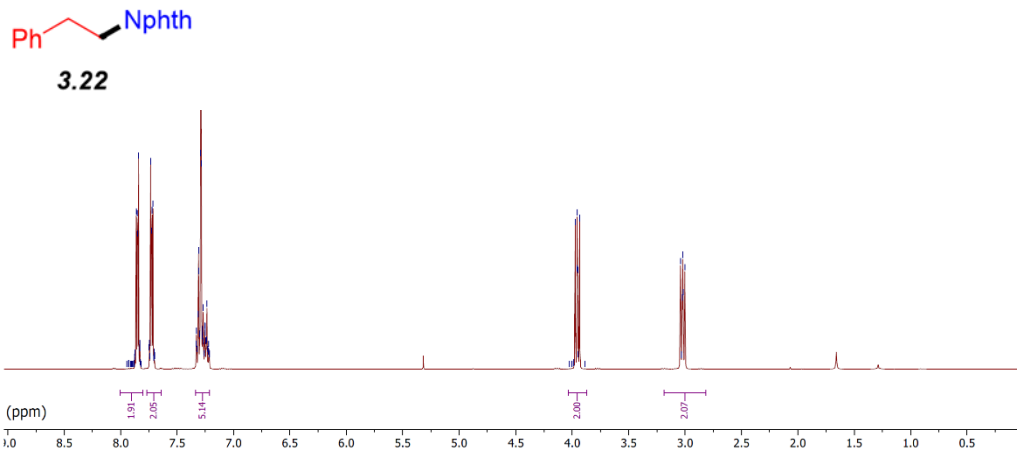

Nphth
Ph
3.20
(ppm)

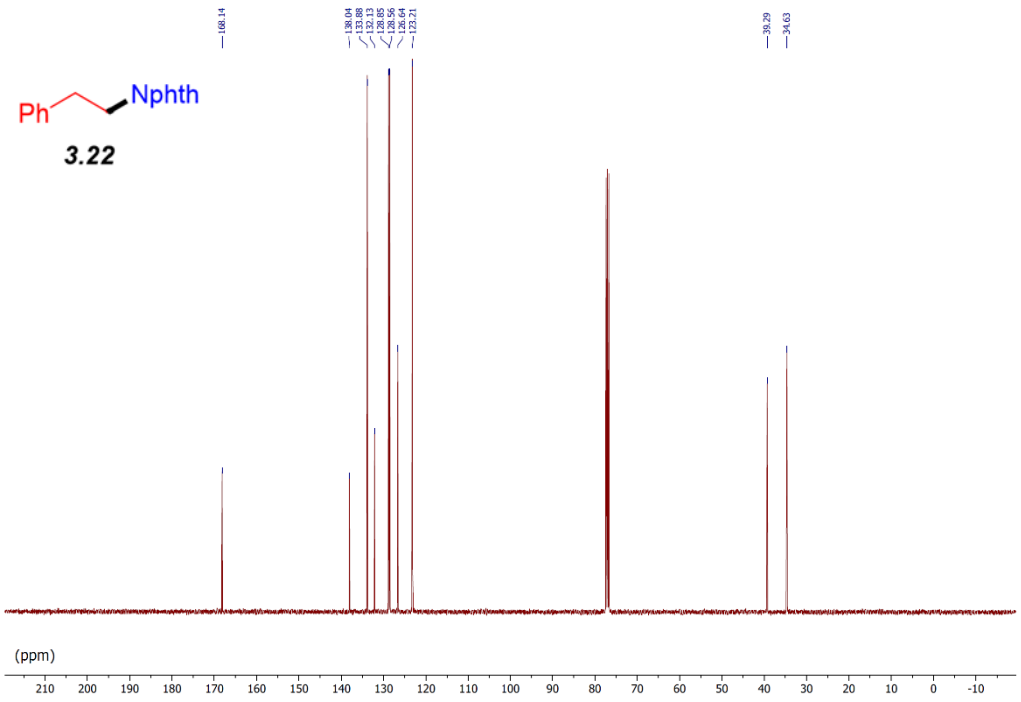

Nphth
Ph
3.20
(ppm)

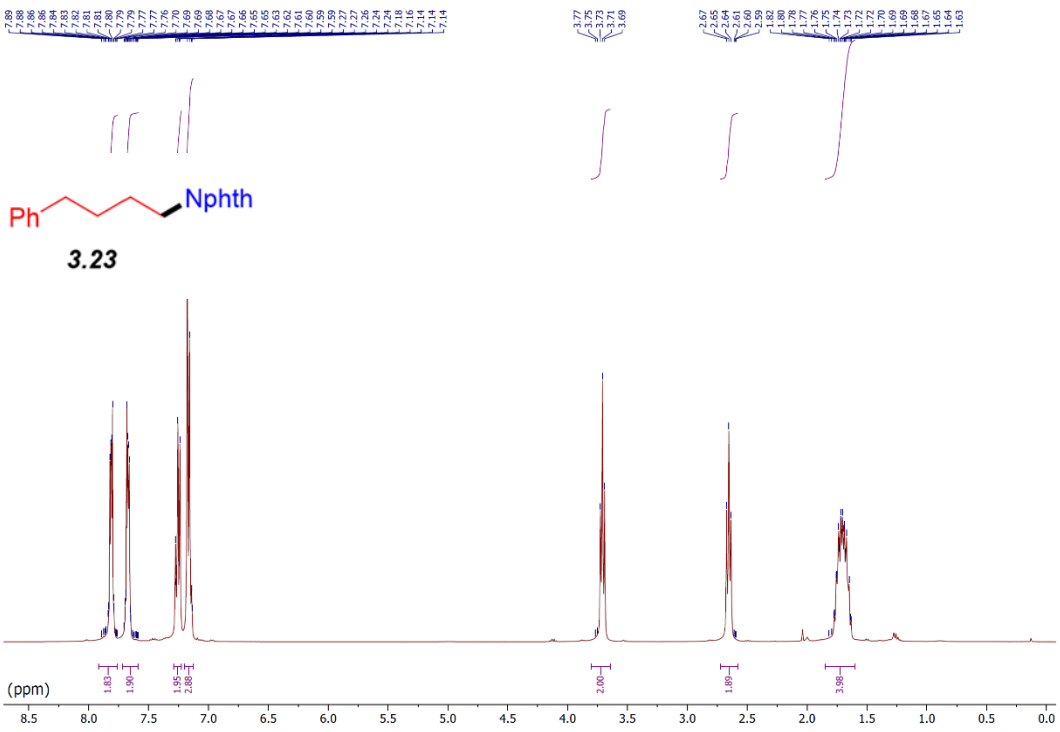

Nphth
C_5H_{11}
3.21

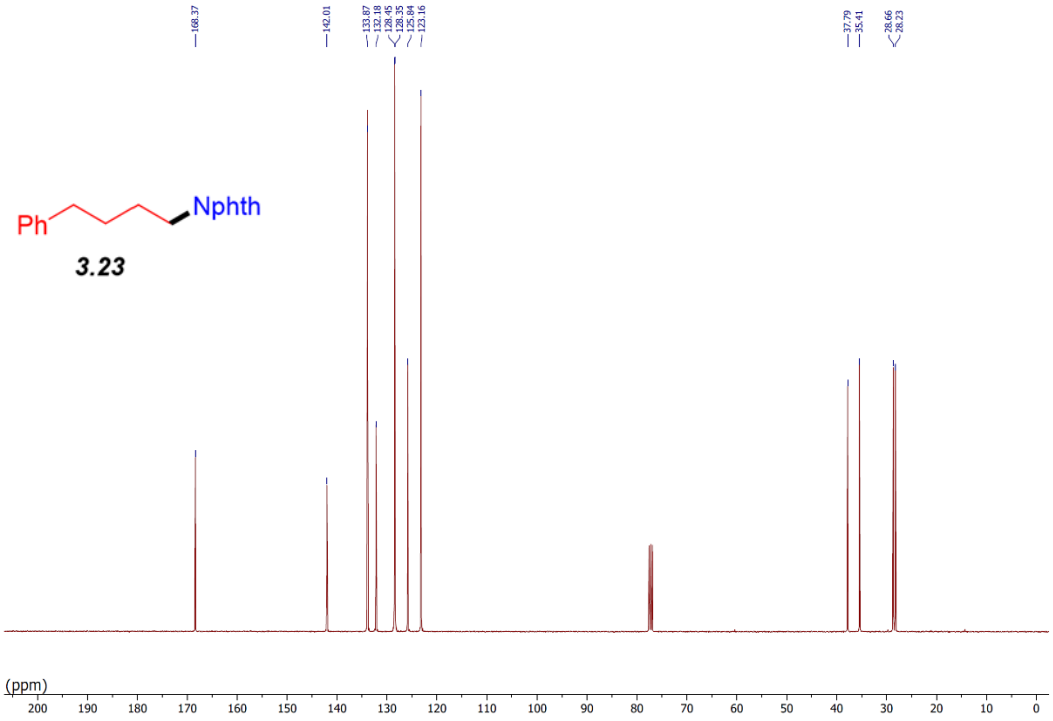

(ppm)

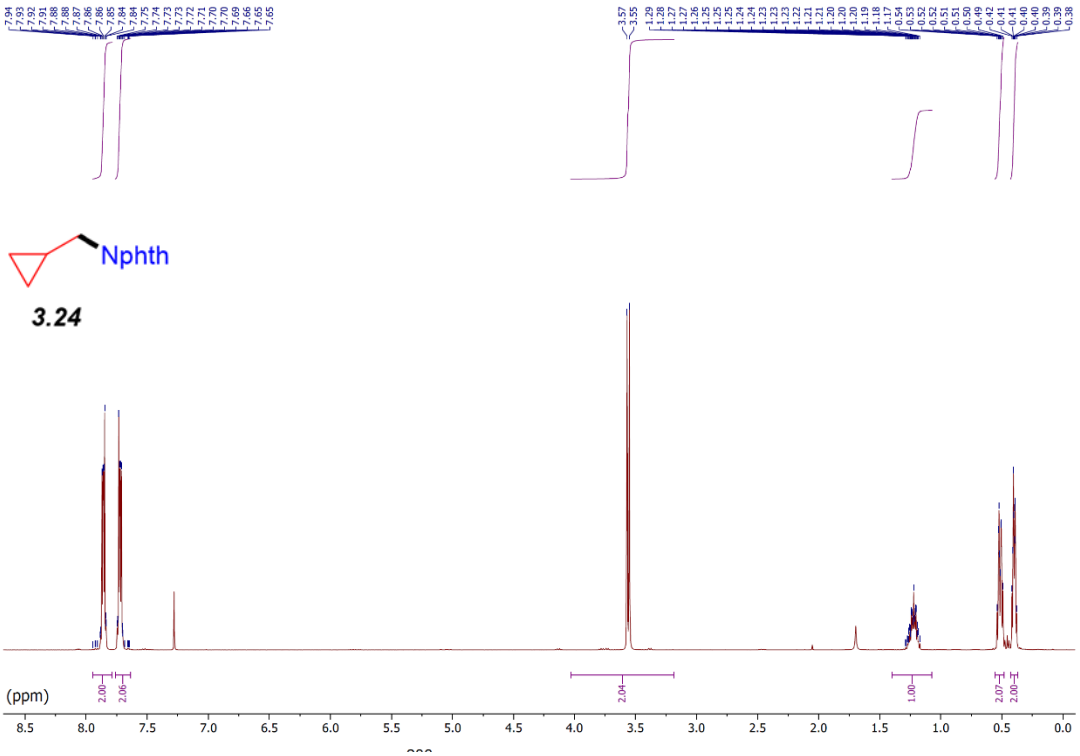

Nphth
C_5H_{11}
3.21
(ppm)

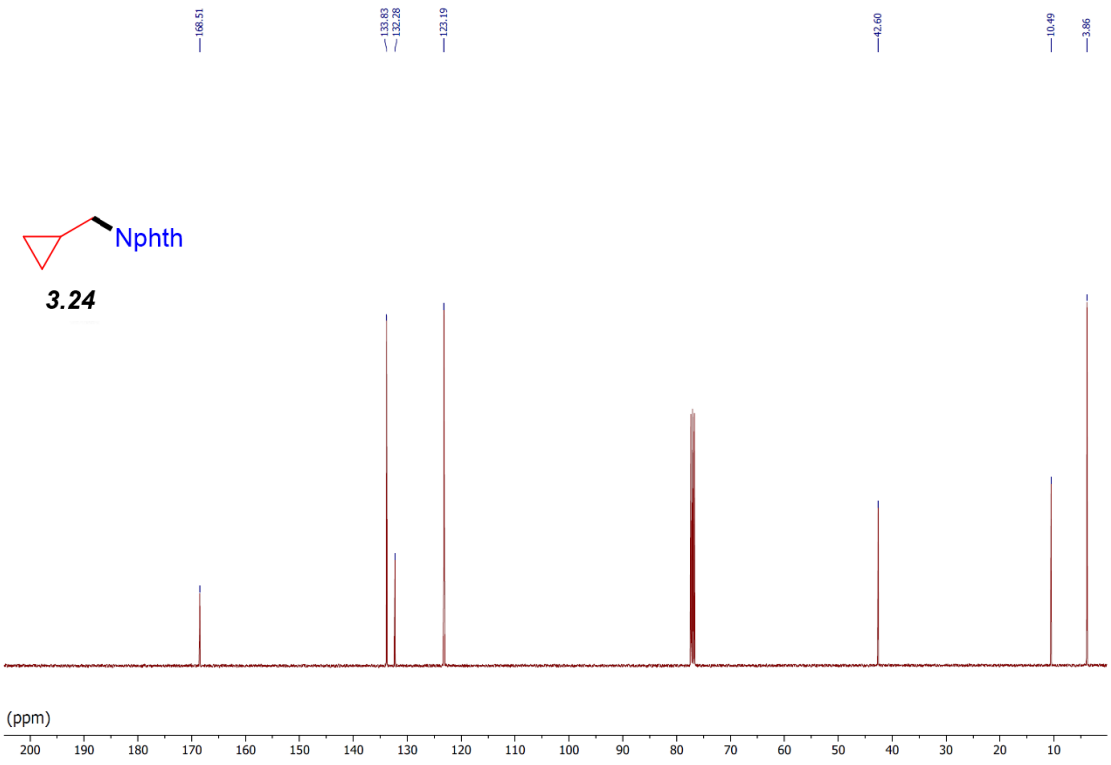

Ph
Nphth
3.22
(ppm)
1.91
2.05
5.14
2.00
2.07

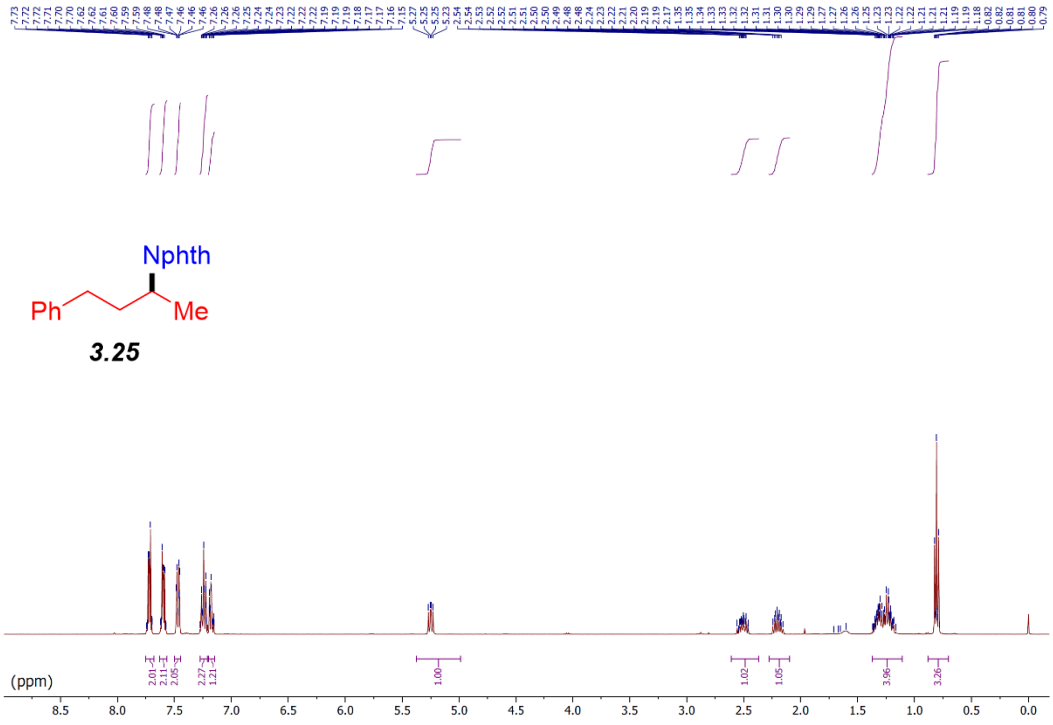

Ph
Nphth
3.22
168.14
138.04
133.88
132.13
128.85
128.56
126.44
123.21
39.29
34.63
(ppm)

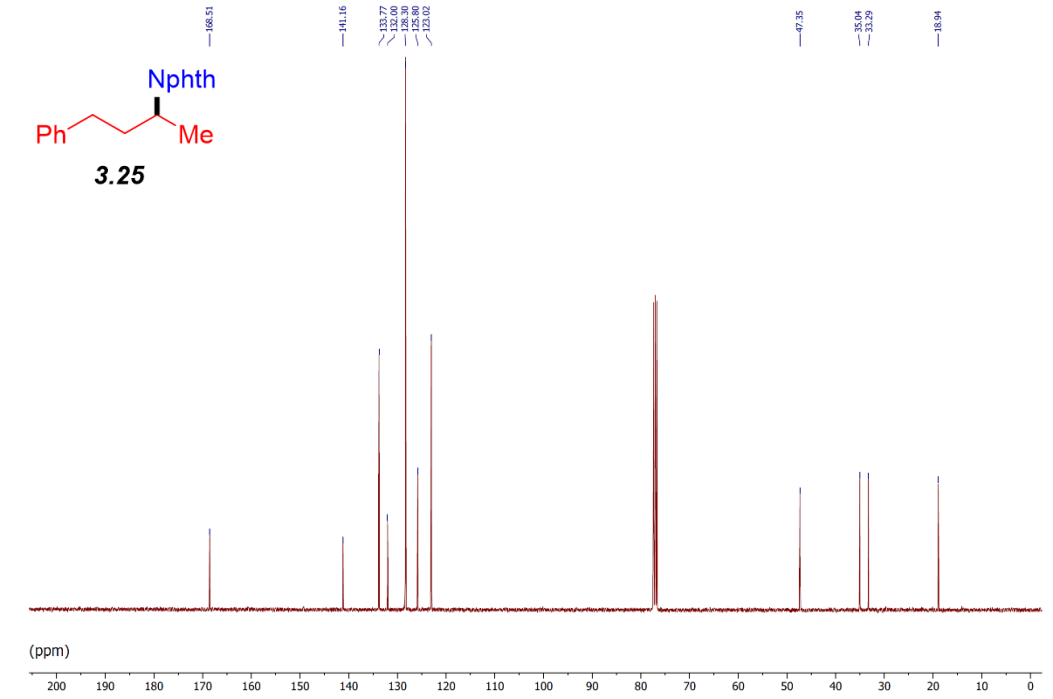

Ph
Nphth
3.23
(ppm)

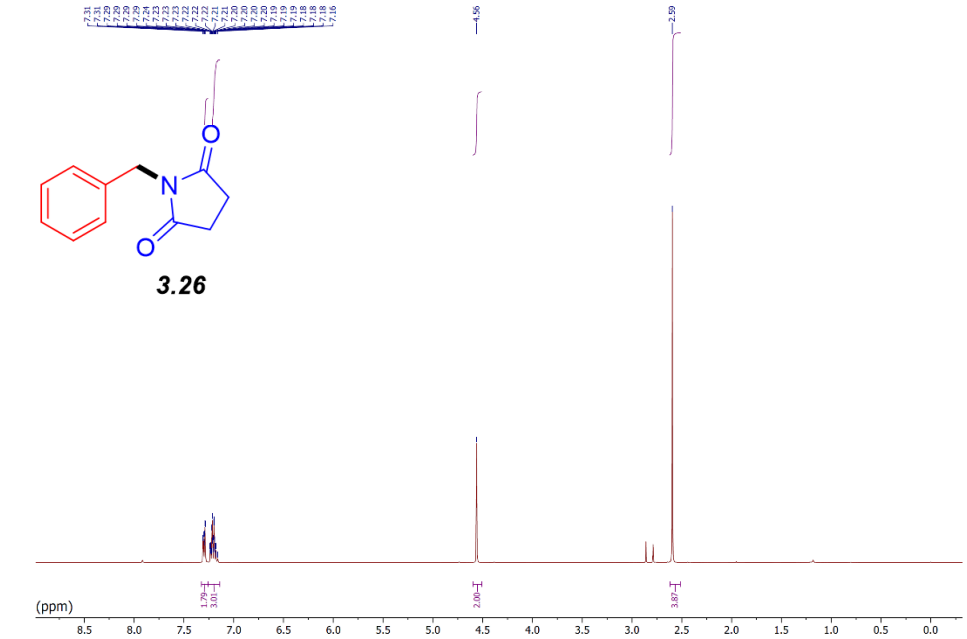

Ph
Nphth
3.23
(ppm)


Nphth
3.24
(ppm)

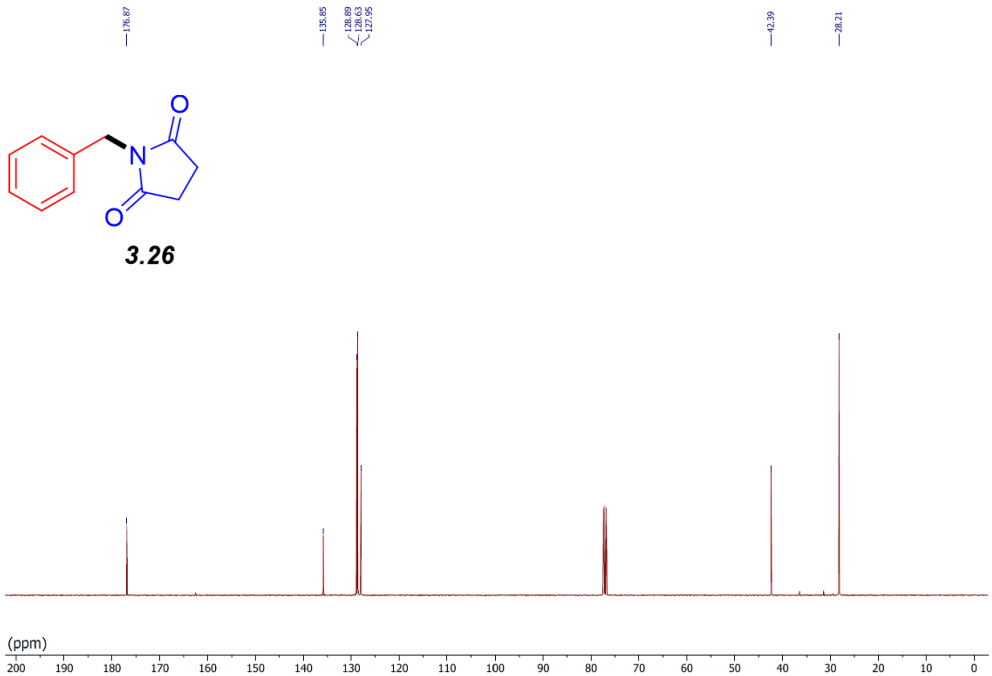

Nphth
3.24
(ppm)


Nphth
Ph
Me
3.25
(ppm)

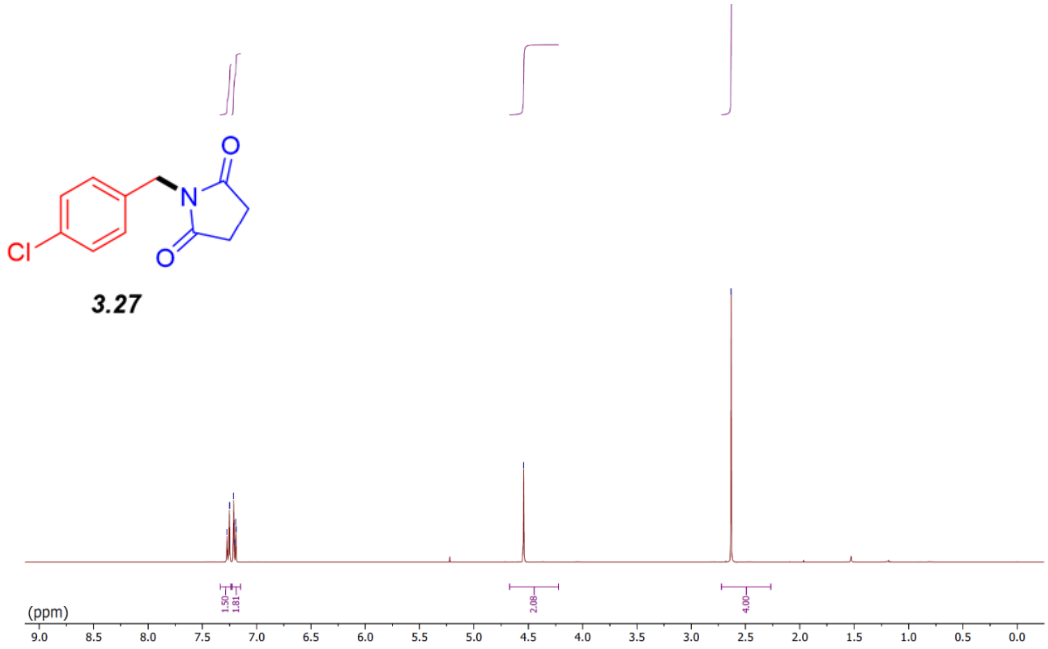

Nphth
Ph
Me
3.25
(ppm)


7.31
7.31
7.30
7.30
7.29
7.29
7.24
7.23
7.23
7.23
7.22
7.22
7.22
7.21
7.21
7.20
7.20
7.20
7.20
7.19
7.19
7.19
7.18
7.18
7.16
4.56
2.59
O
N
O
1.29
3.01
2.00
3.87
(ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

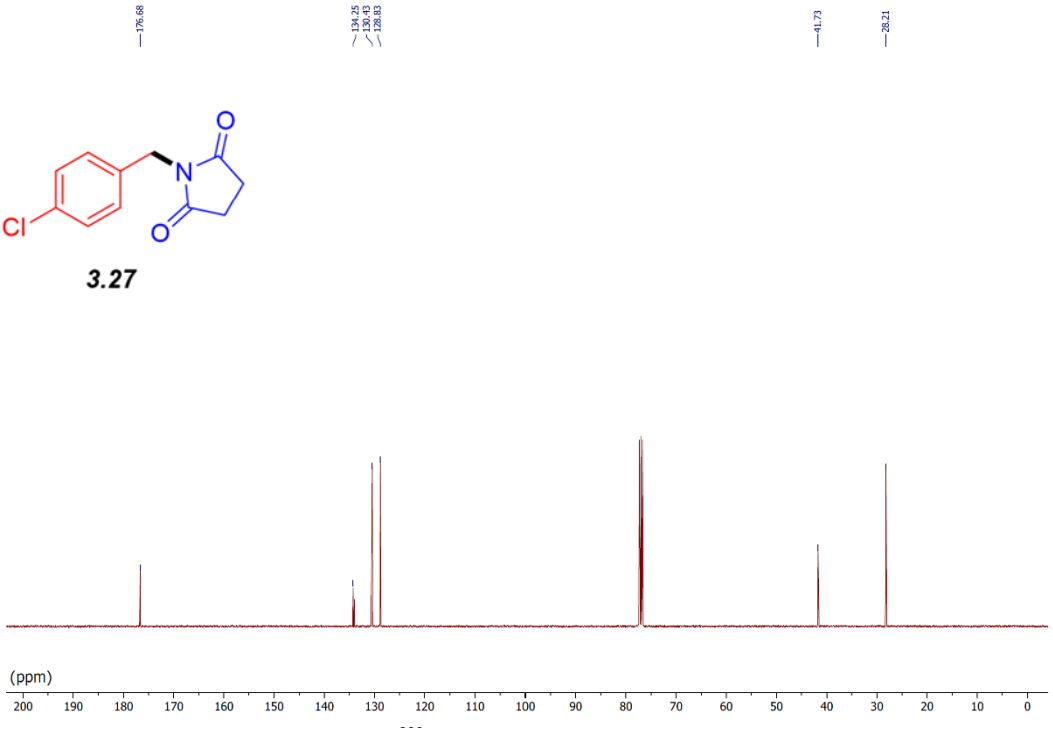
3.26


176.87
135.85
128.69
128.63
127.95
42.39
28.21
O
N
O
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

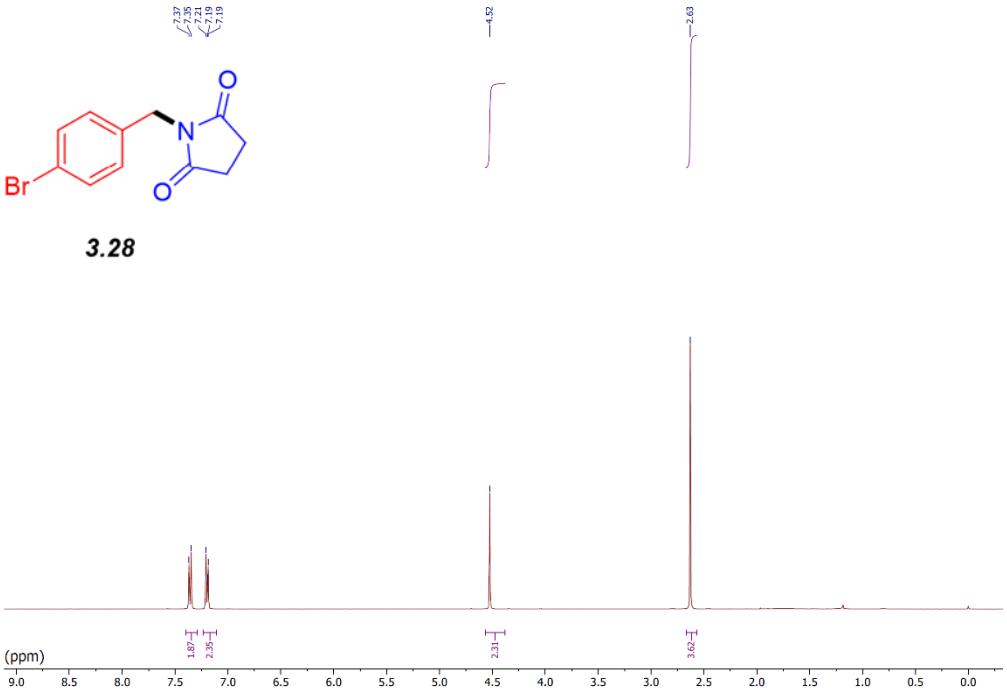
3.26


O
N
O
Cl
1.50
1.81
2.08
4.00
(ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

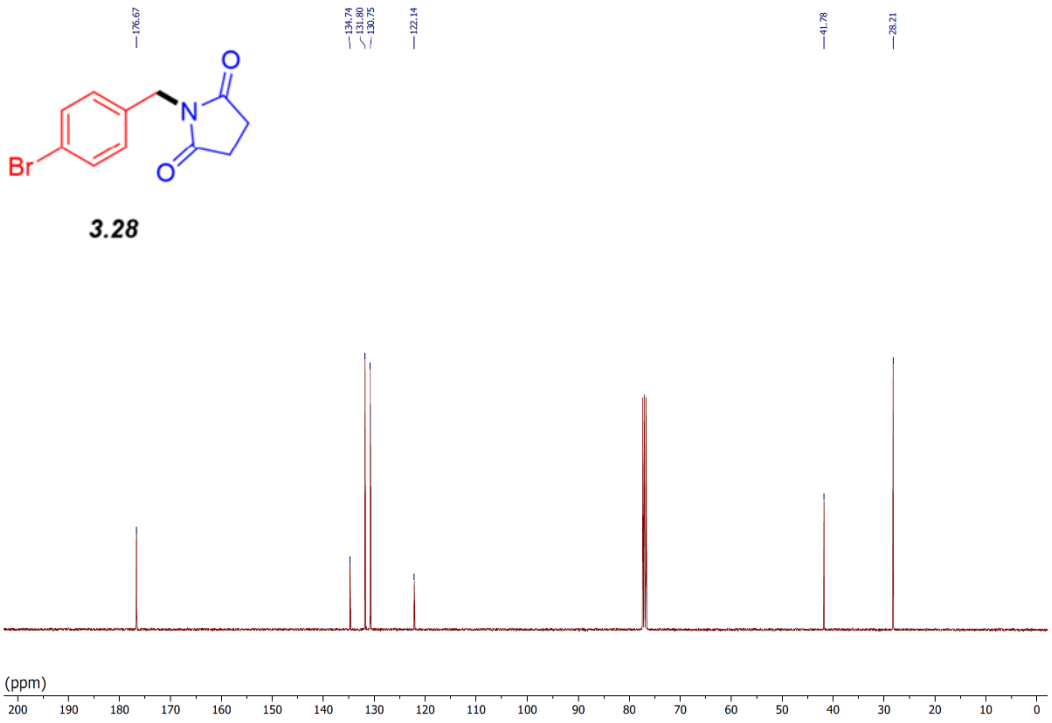
3.27


176.68
134.25
130.43
128.83
41.73
28.21
O
N
O
Cl
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

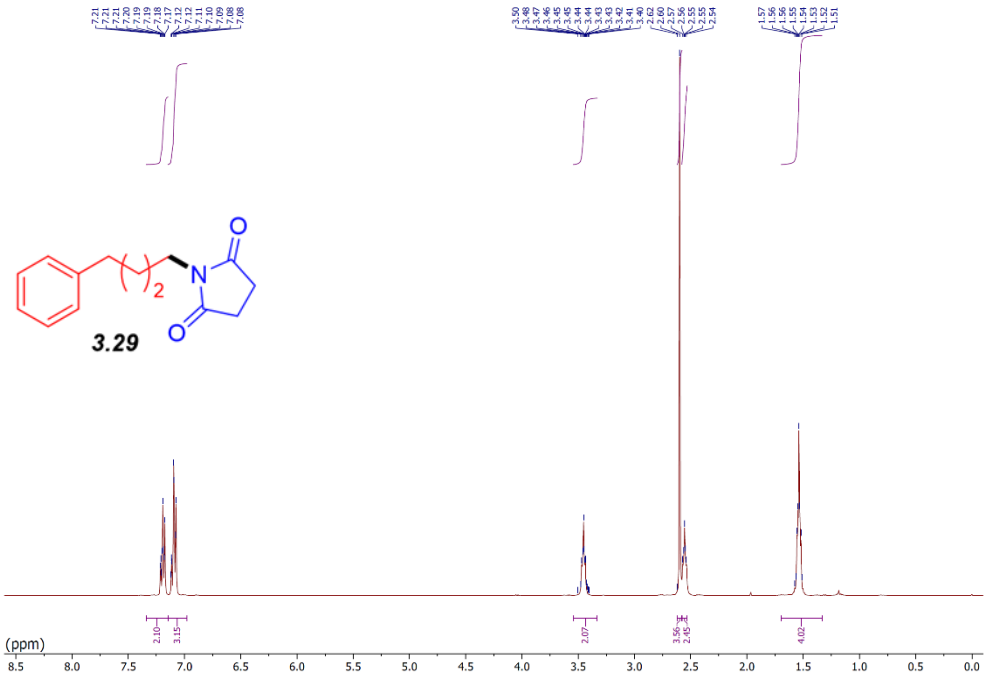
3.27

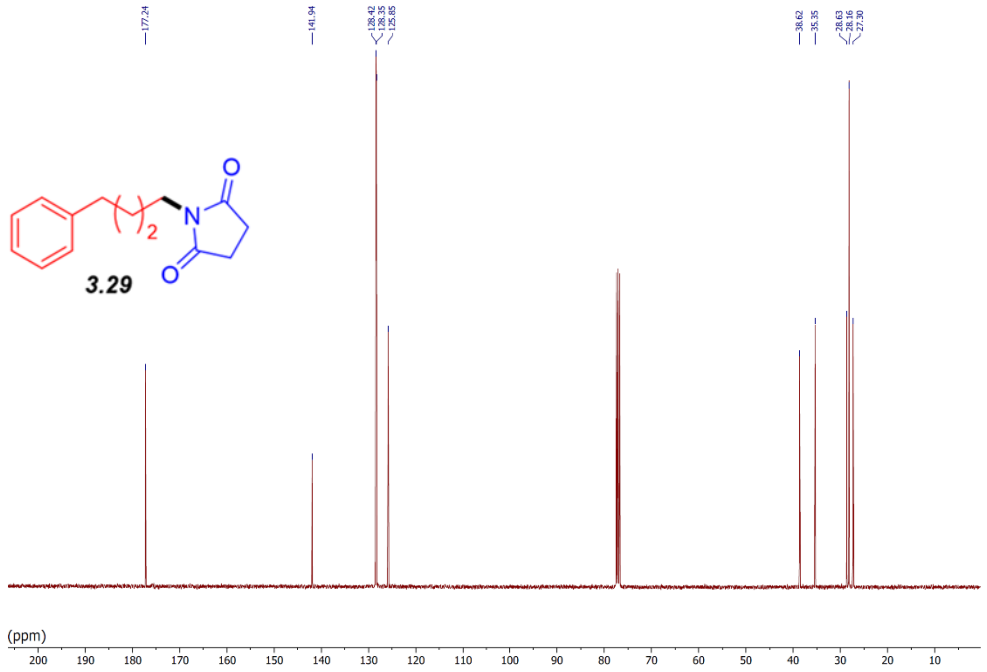

7.37
7.35
7.21
7.19
7.19
4.52
2.63
Br
O
N
O
(ppm)
1.87
2.35
2.31
3.62
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

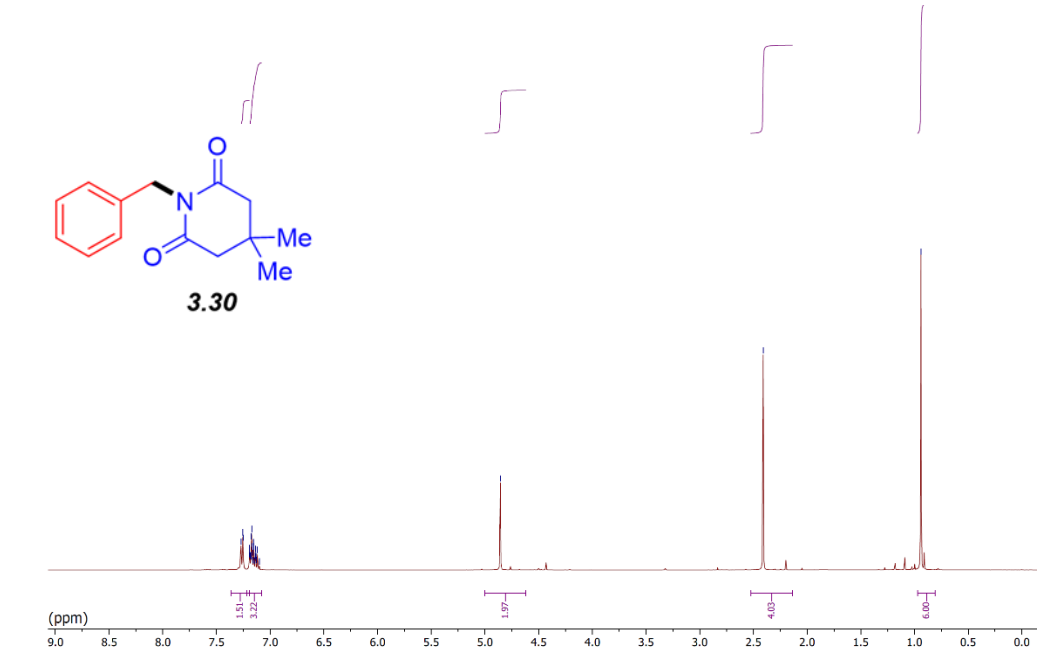
3.28

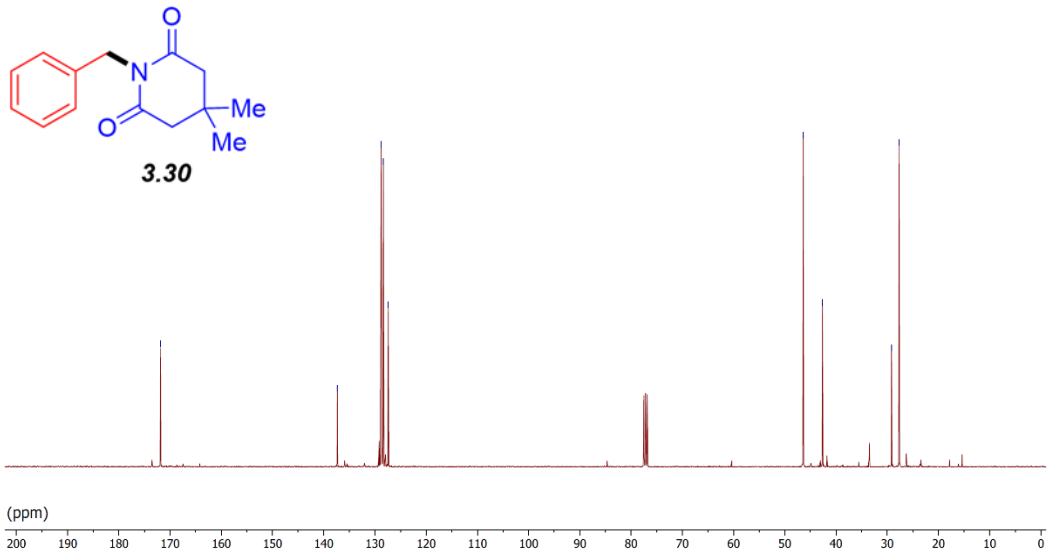

176.67
134.74
131.80
130.75
122.14
41.78
28.21
Br
O
N
O
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

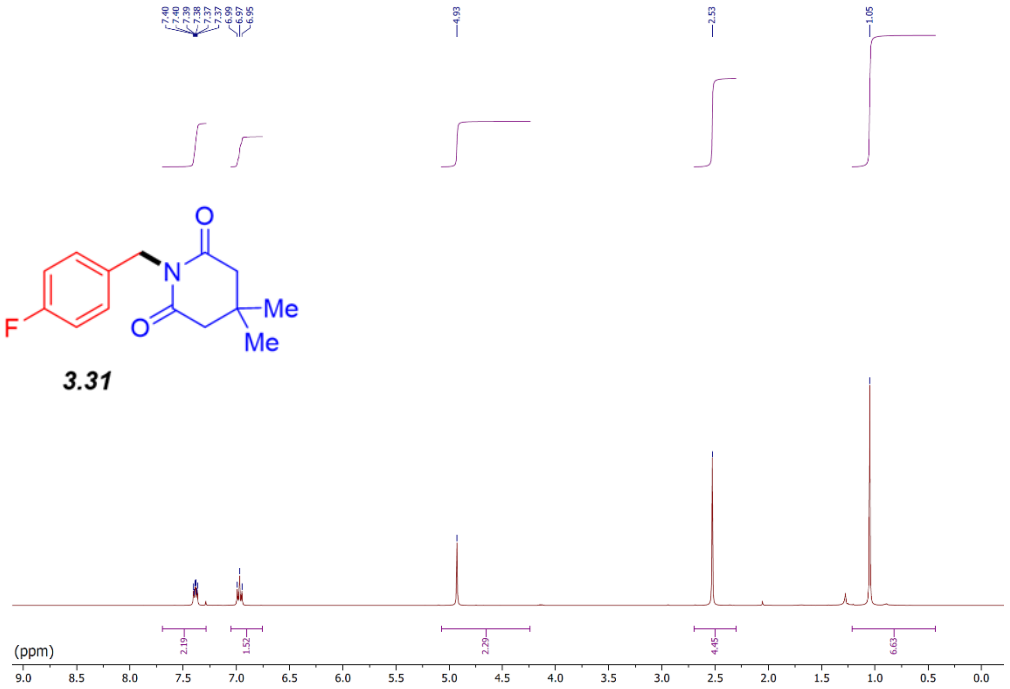
3.28

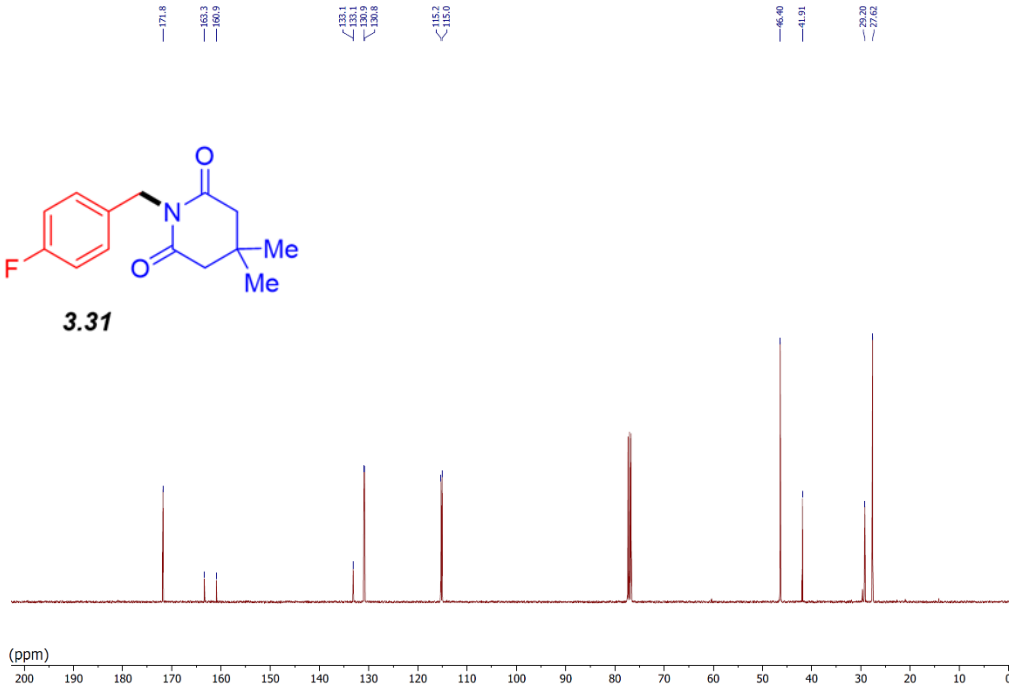

3.29
(ppm)

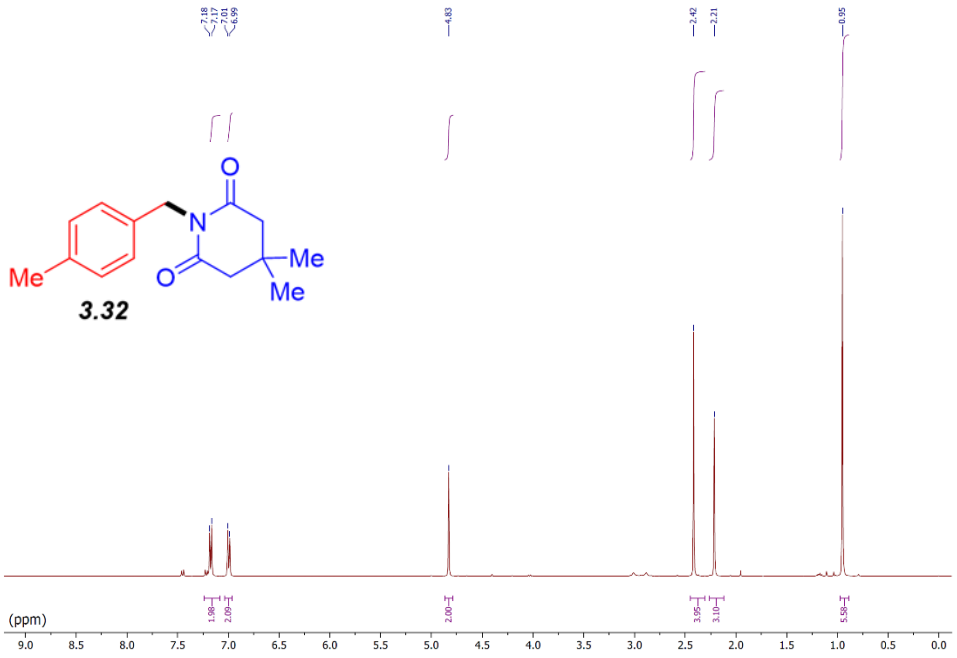

3.29
(ppm)

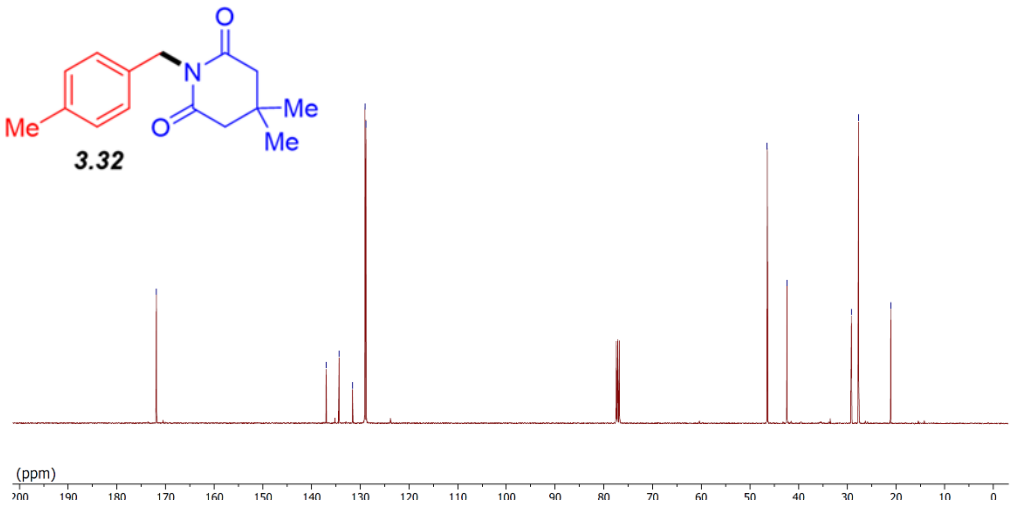

O
N
O
Me
Me
3.30
1.51
3.22
1.97
4.03
6.00
(ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

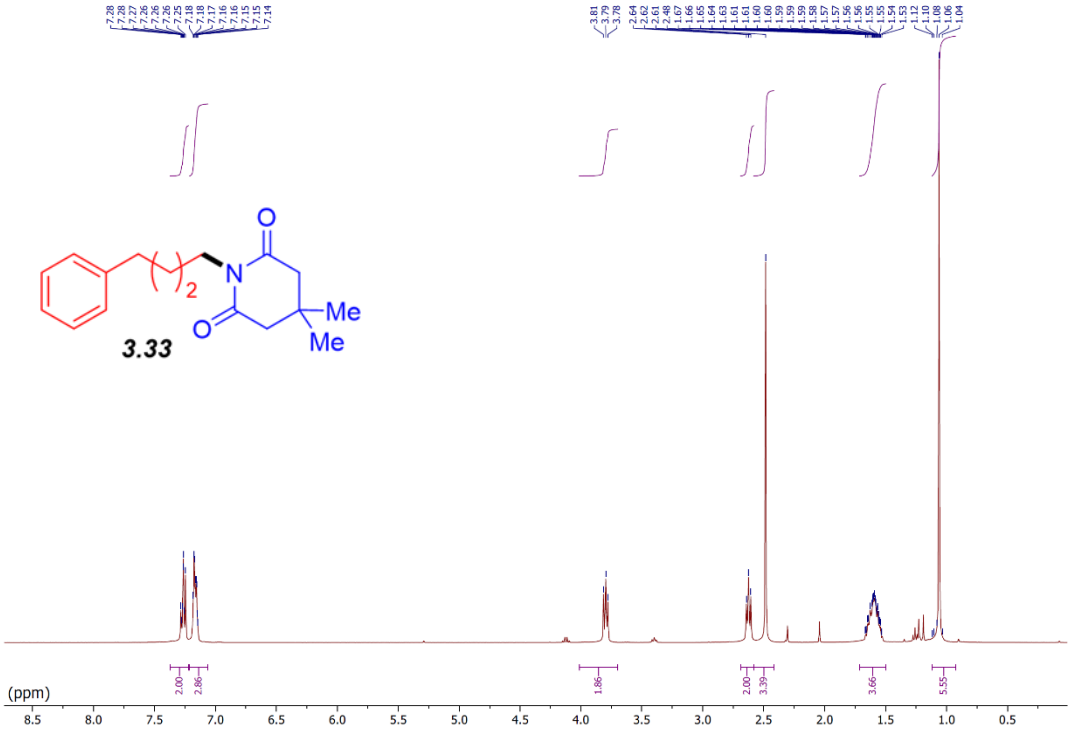

O
N
O
Me
Me
3.30
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

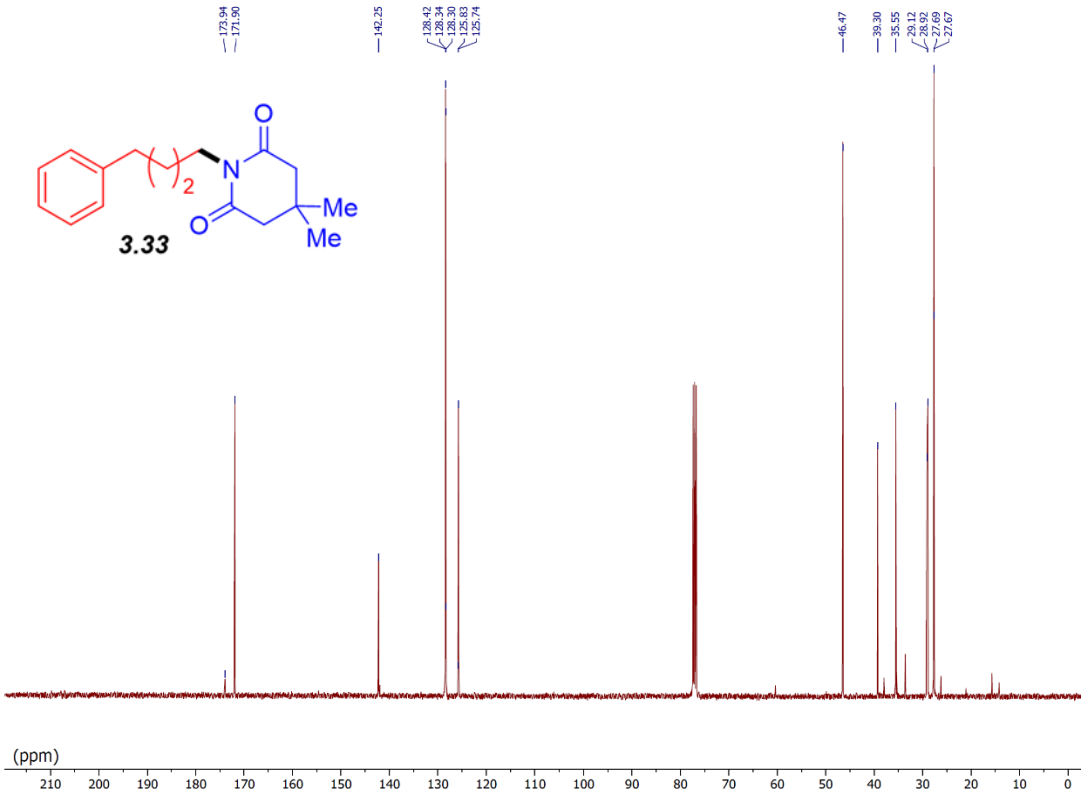

7.40
7.40
7.39
7.38
7.37
7.37
6.99
6.97
6.95
4.93
2.53
1.05
O
N
O
Me
Me
F
3.31
2.19
1.52
2.29
4.45
6.63
(ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

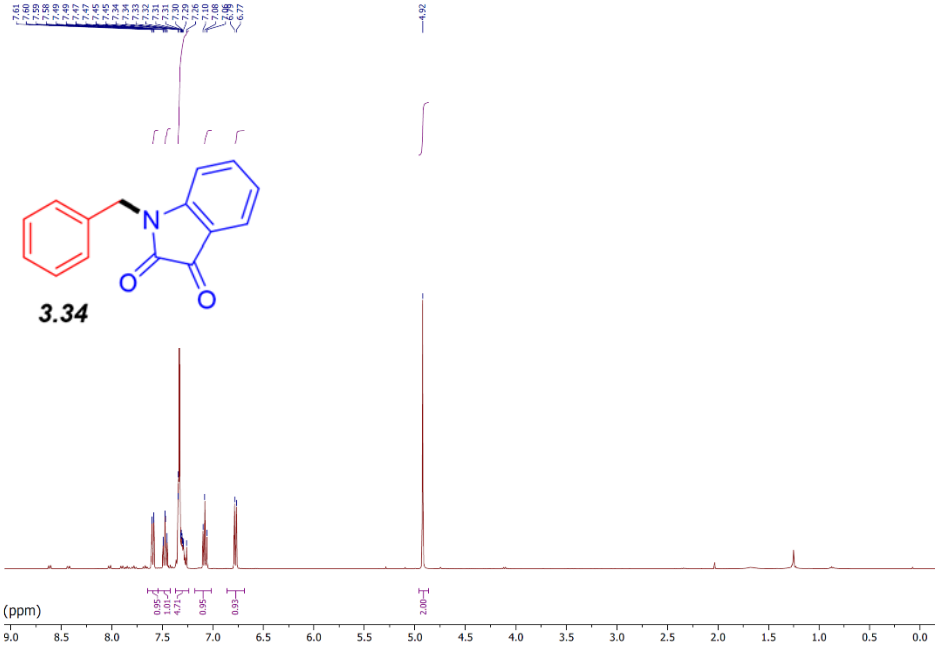

171.8
163.3
160.9
133.1
133.1
130.9
130.8
115.2
115.0
46.40
41.91
29.20
27.62
O
N
O
Me
Me
F
3.31
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

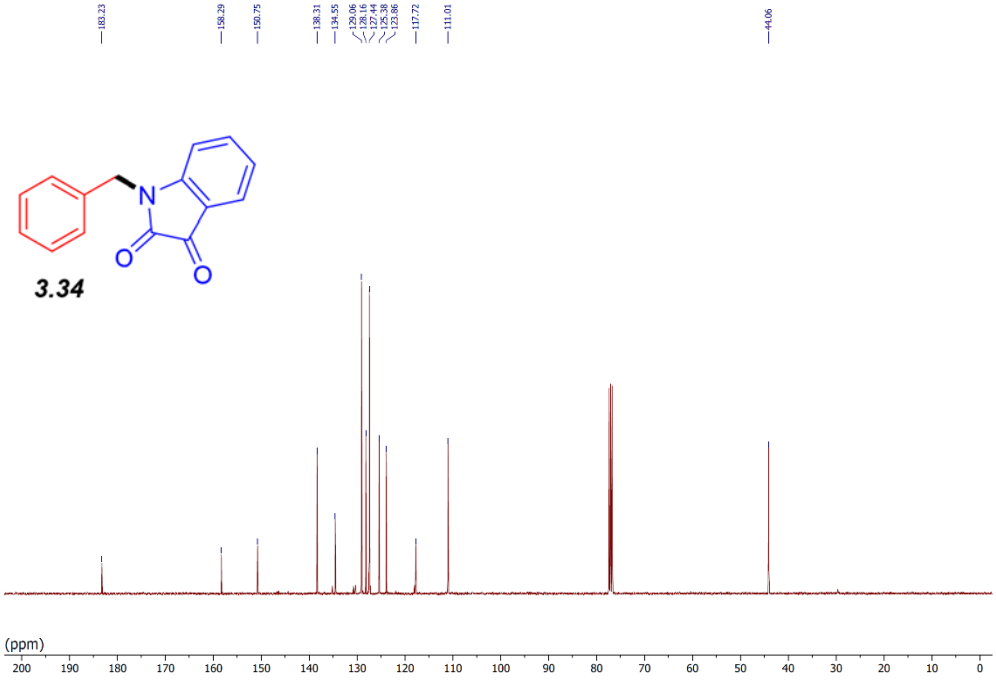

7.18
7.17
7.01
6.99
4.83
2.42
2.21
0.95
O
N
O
Me
Me
Me
3.32
1.98
2.09
2.00
3.95
3.10
5.58
(ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

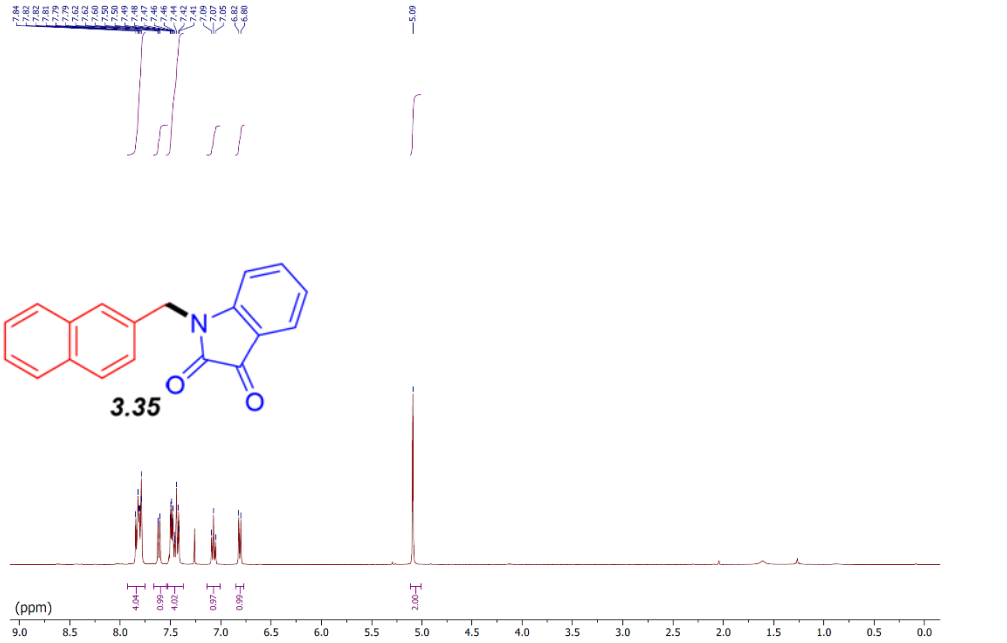

O
N
O
Me
Me
Me
3.32
(ppm)

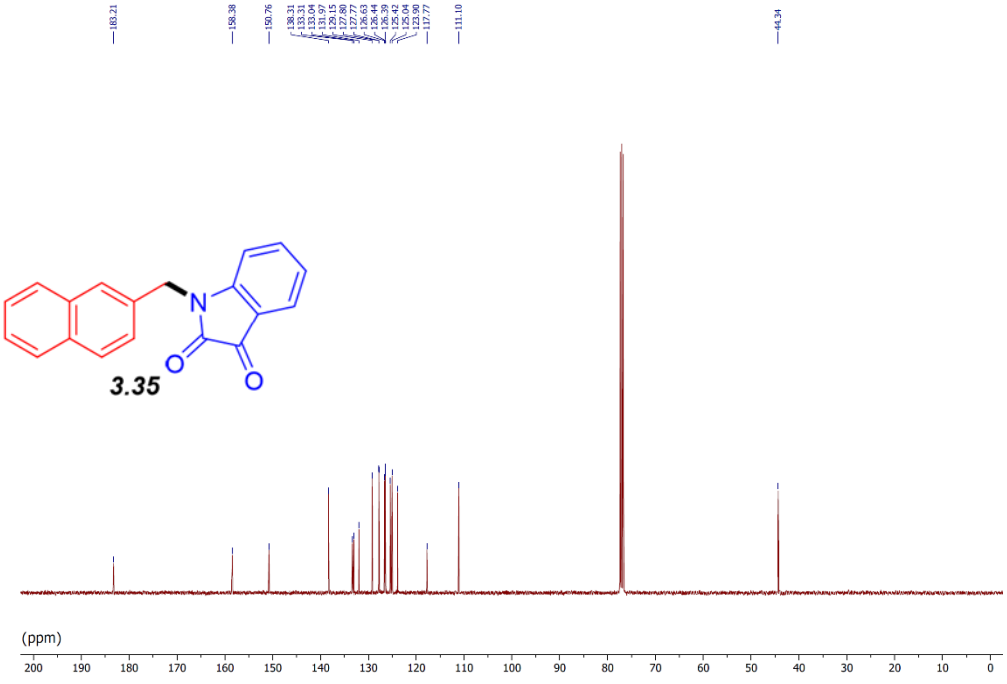

3.33
(ppm)

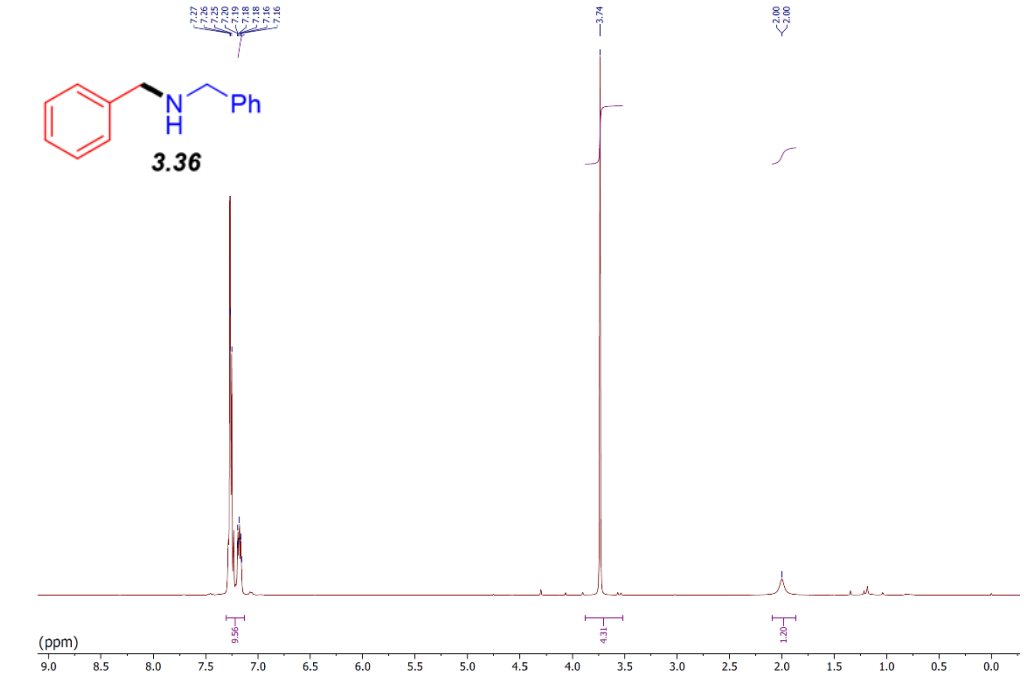

3.33
(ppm)

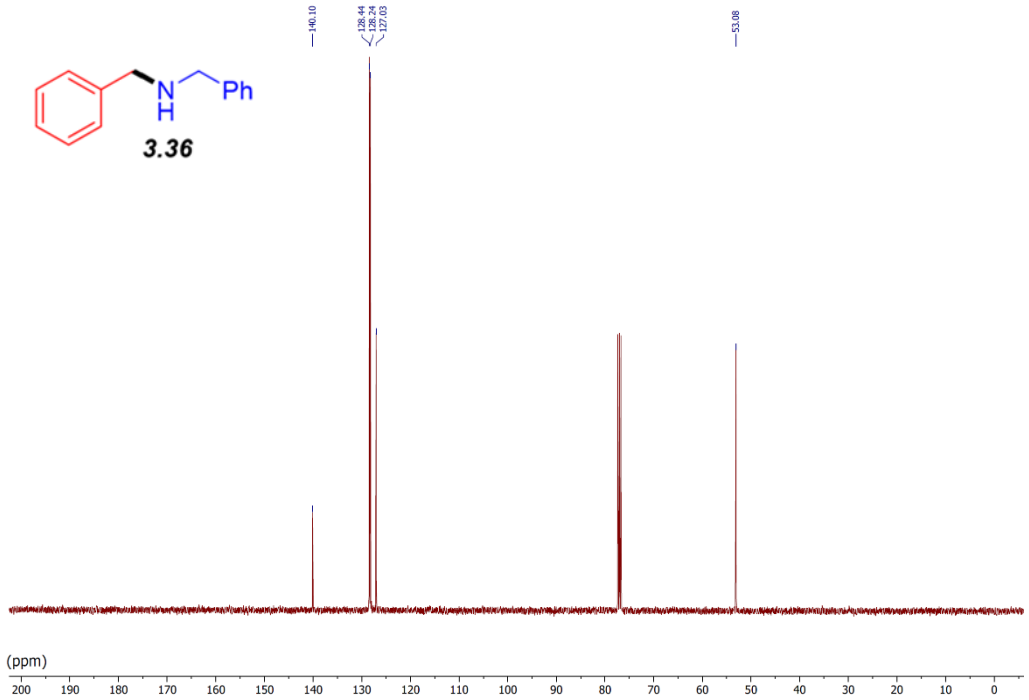

3.34
(ppm)

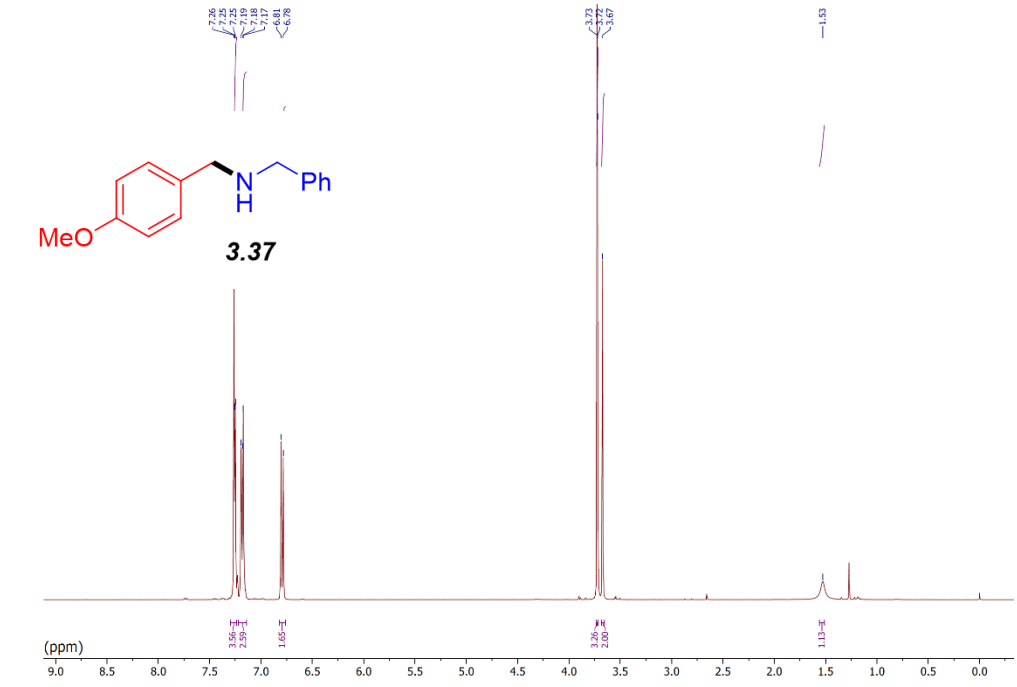

3.34
(ppm)

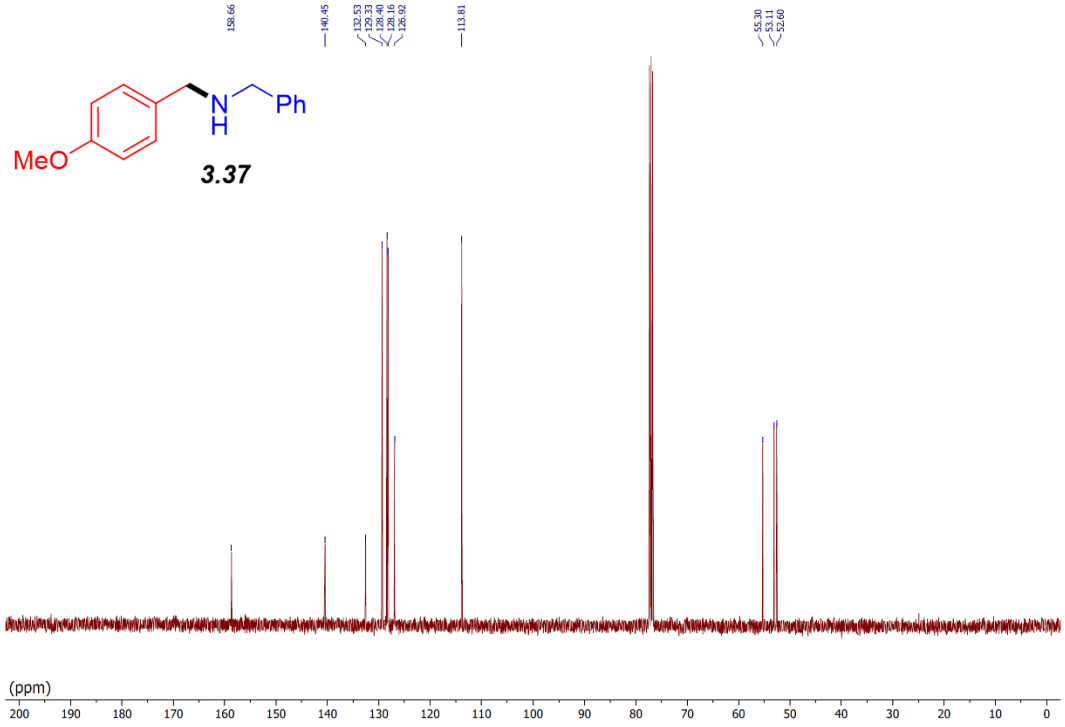

3.35
(ppm)

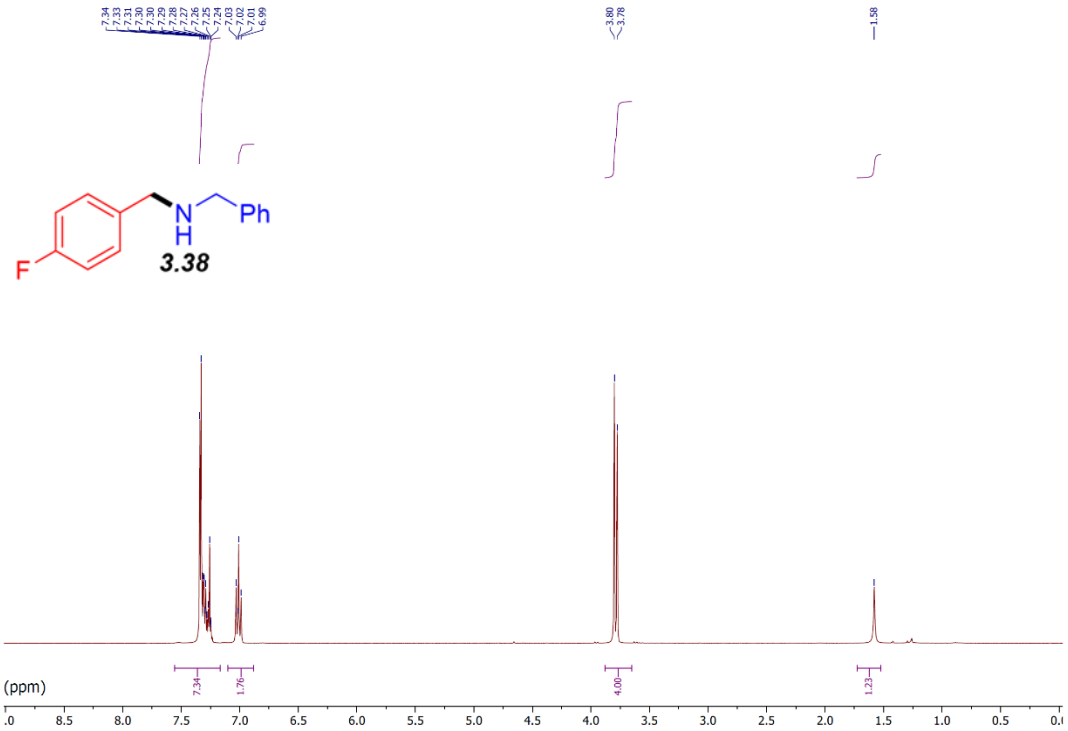

3.35
(ppm)

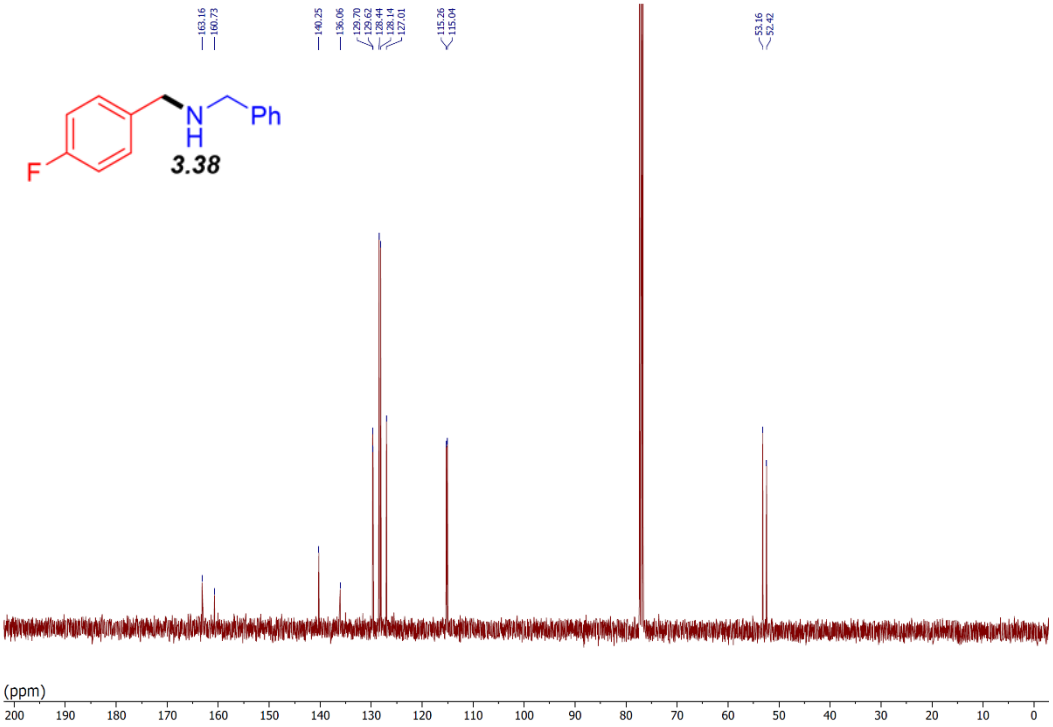

7.27
7.26
7.25
7.20
7.19
7.18
7.18
7.16
7.16
3.74
2.00
2.00
N
H
Ph
3.36
9.56
4.31
1.20
(ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

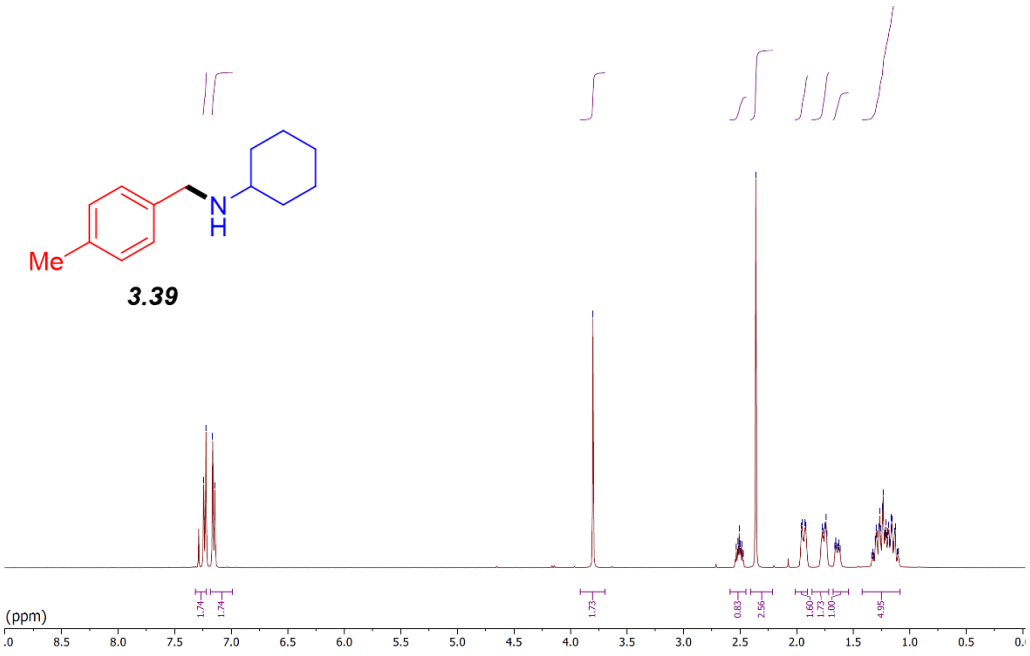

140.10
128.44
128.24
127.03
53.08
N
H
Ph
3.36
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

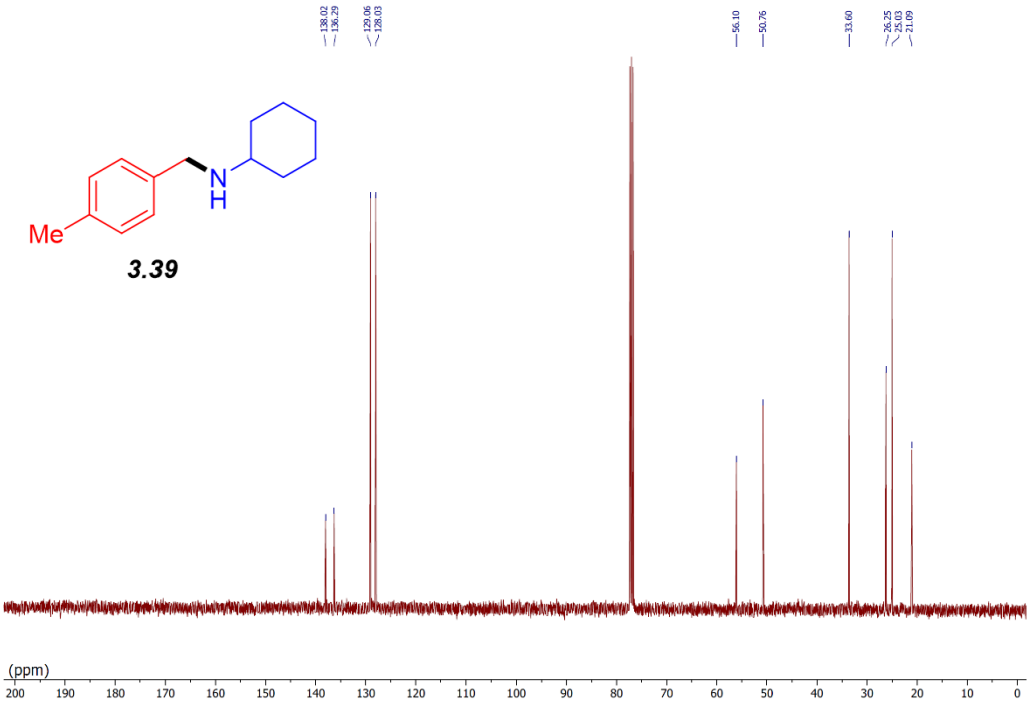

7.26
7.25
7.25
7.19
7.18
7.17
6.81
6.80
3.73
3.72
3.67
1.53
N
H
Ph
MeO
3.37
3.56
2.59
1.65
3.26
2.00
1.13
(ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

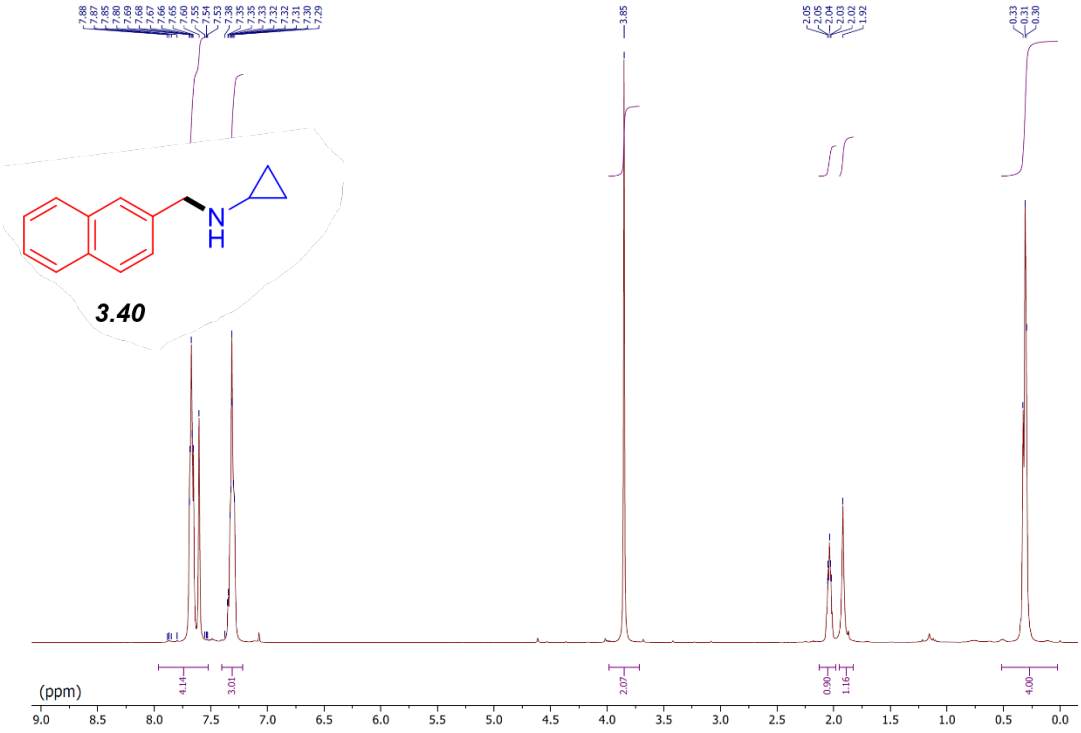

158.66
140.45
132.53
129.33
128.40
128.16
126.92
113.81
55.30
53.11
52.60
N
H
Ph
MeO
3.37
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

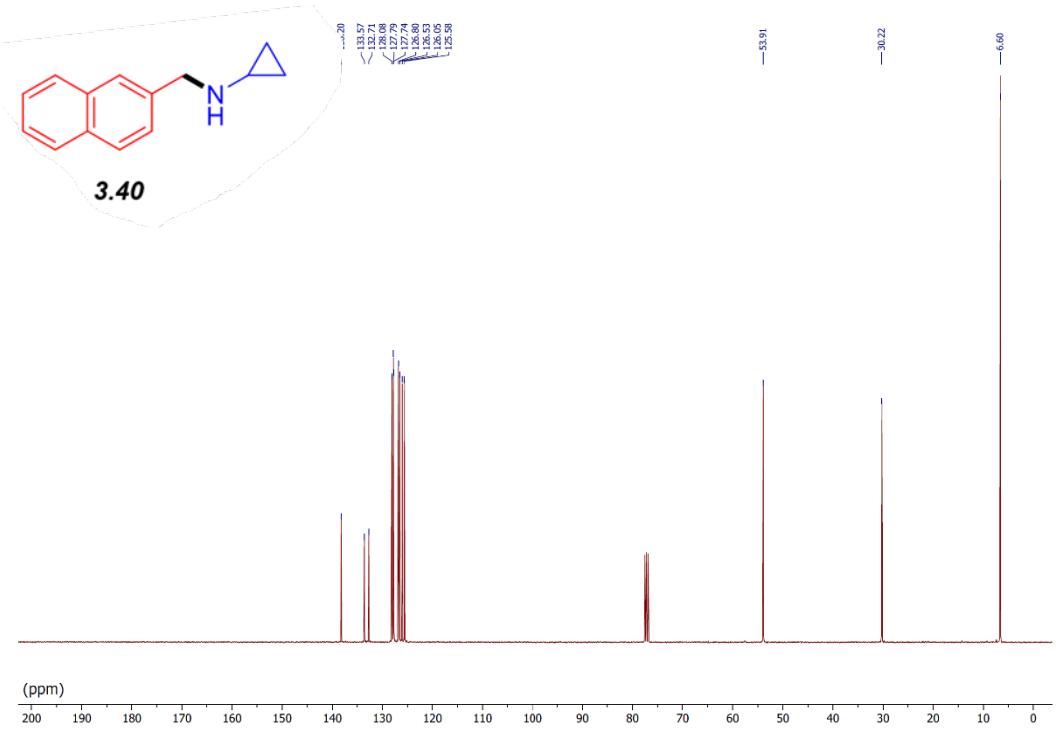

7.34
7.33
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.24
7.03
7.02
7.01
6.99
3.80
3.78
1.58
N
H
Ph
F
3.38
7.34
1.76
4.00
1.23
(ppm)
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.

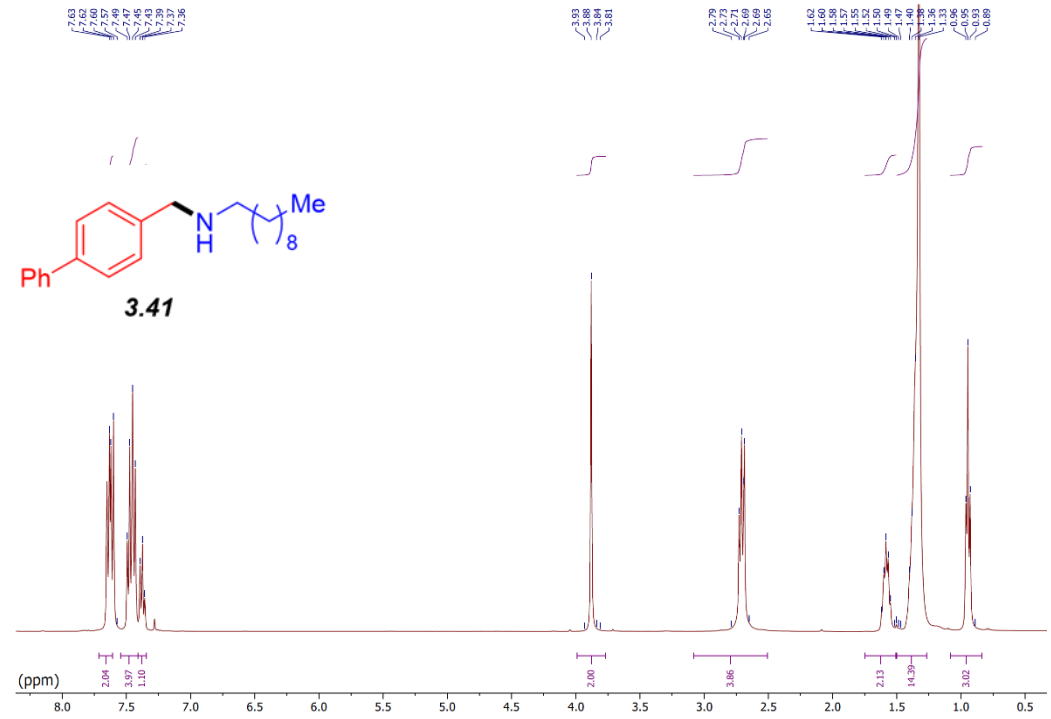

163.16
160.73
140.25
136.06
129.70
128.62
128.44
128.14
127.01
115.26
115.04
53.16
52.42
N
H
Ph
F
3.38
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

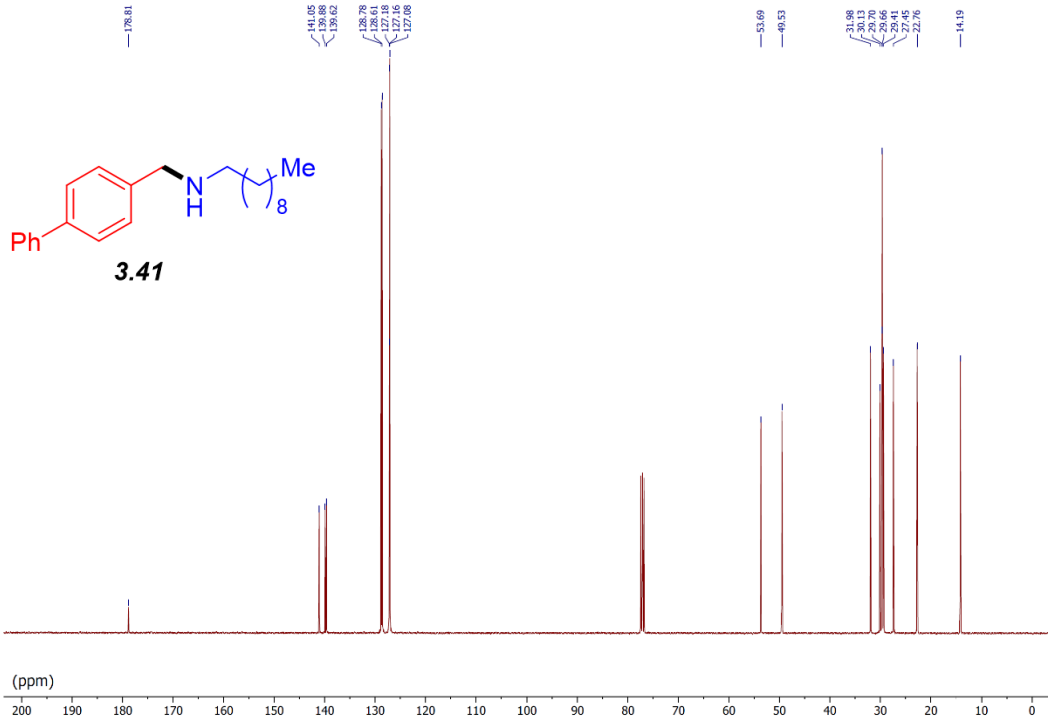

Me
N
H
3.39
1.74
1.74
1.73
0.83
2.56
1.60
1.73
1.00
4.95
(ppm)
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.

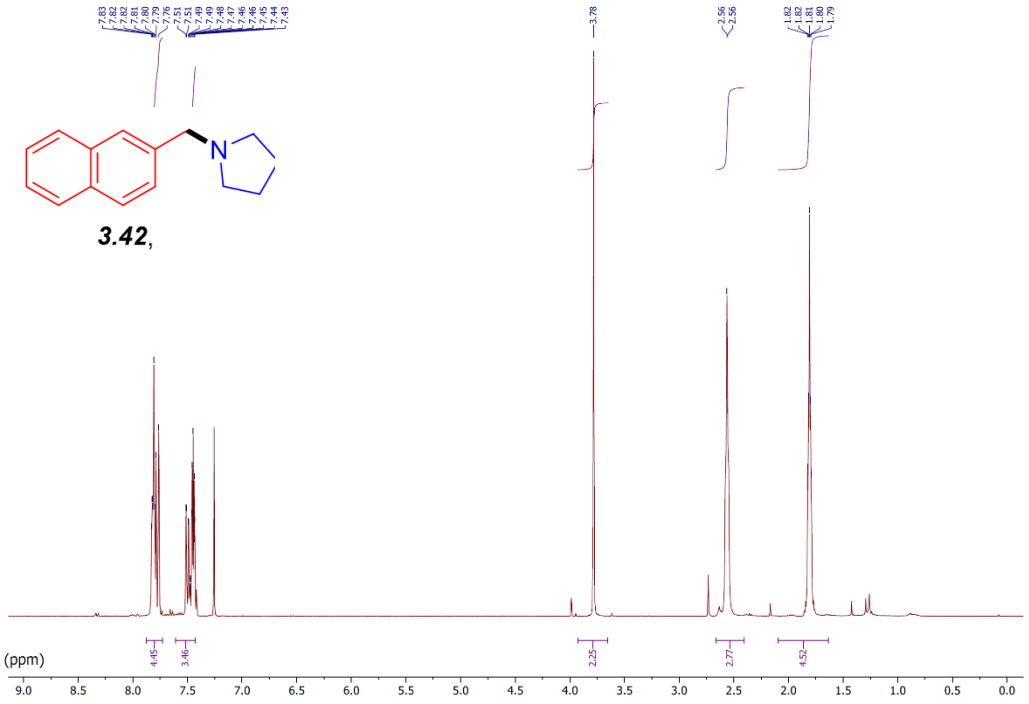

138.02
136.29
129.06
128.03
56.10
50.76
33.60
26.25
25.03
21.09
Me
N
H
3.39
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


3.40
(ppm)

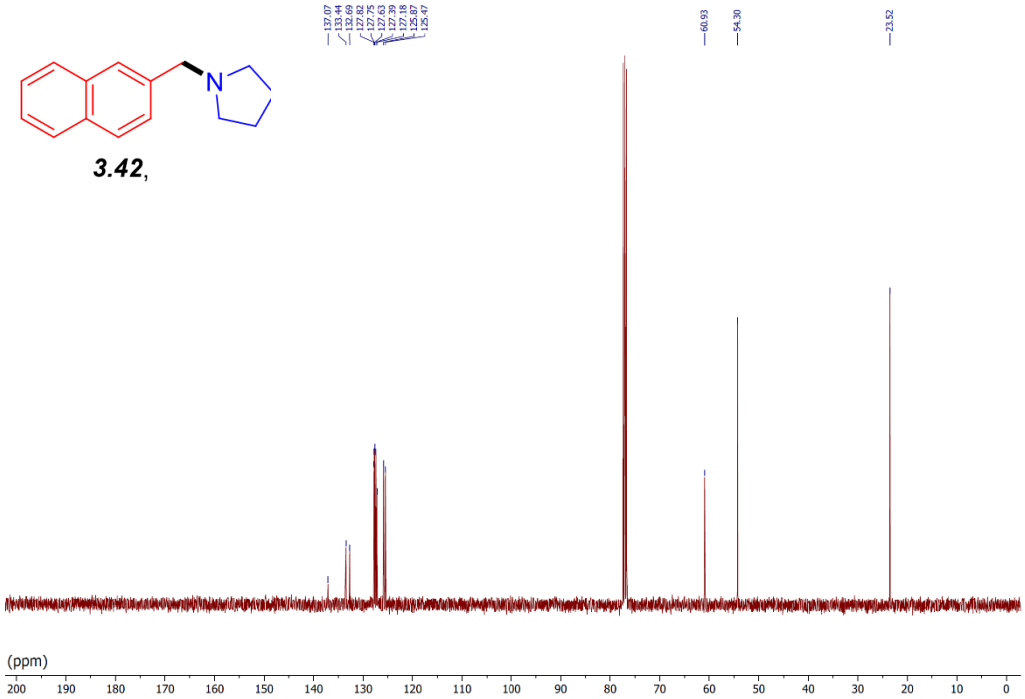

3.40
(ppm)


Ph
N
H
Me
8
3.41
(ppm)

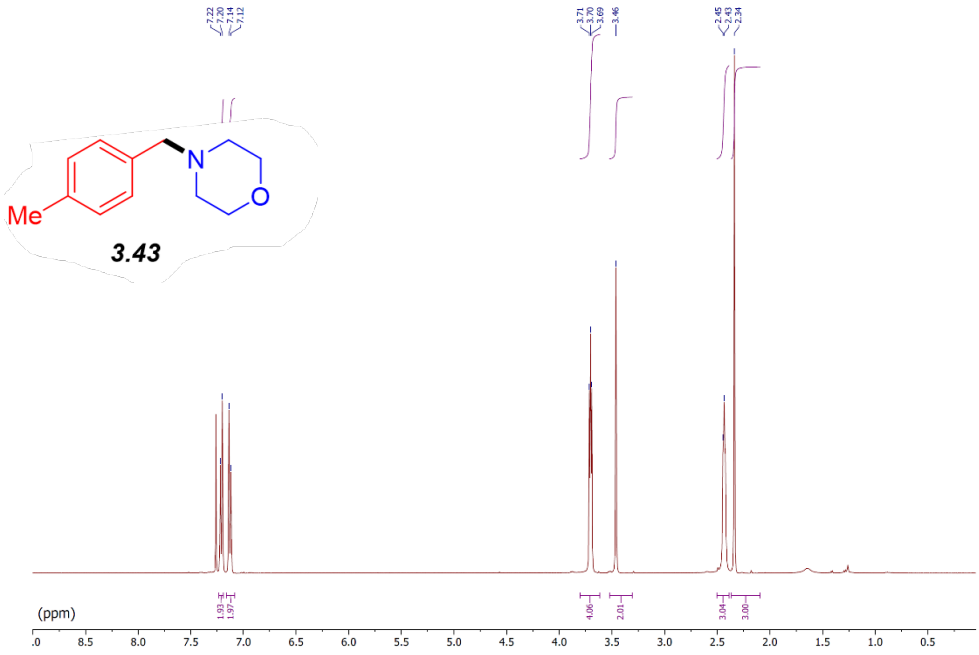

Ph
N
H
Me
8
3.41
(ppm)

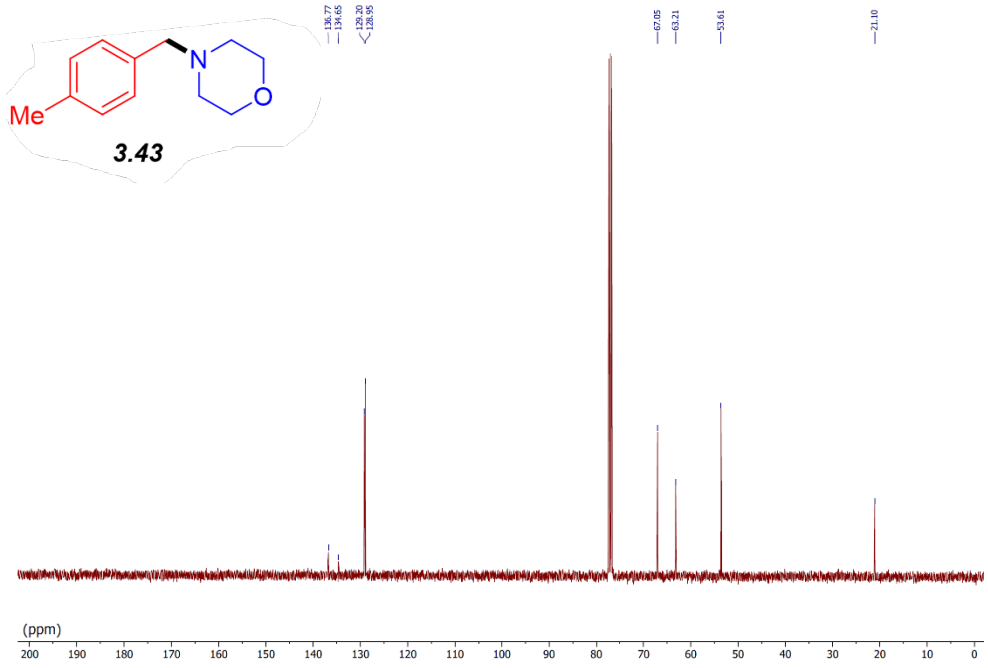

7.83
7.82
7.82
7.81
7.80
7.79
7.76
7.51
7.51
7.49
7.49
7.48
7.47
7.47
7.46
7.46
7.45
7.44
7.43
3.78
2.56
2.56
1.82
1.82
1.81
1.80
1.79
4.46
3.46
2.25
2.77
4.52
(ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

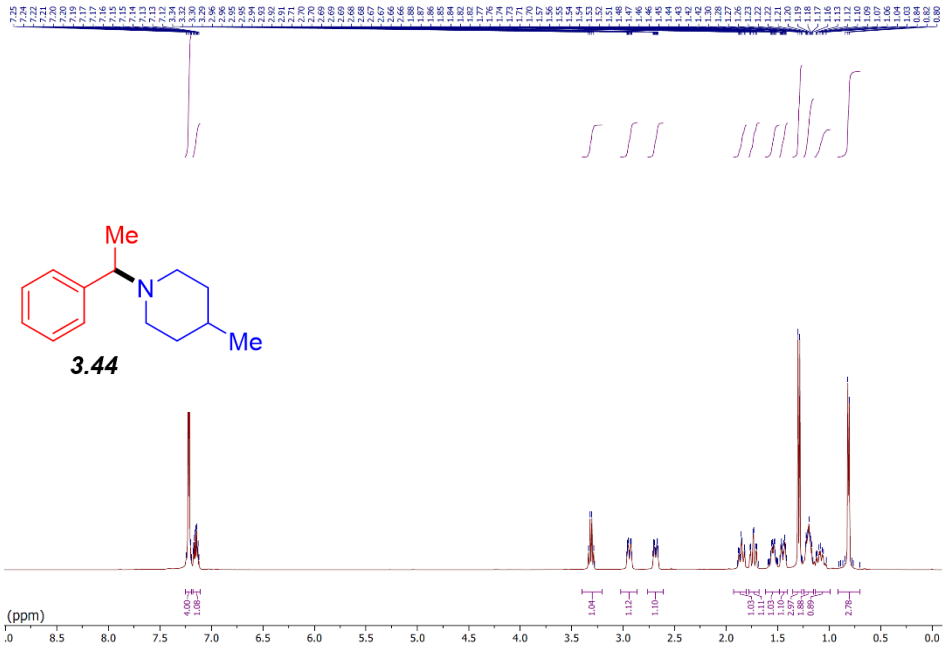
3.42,

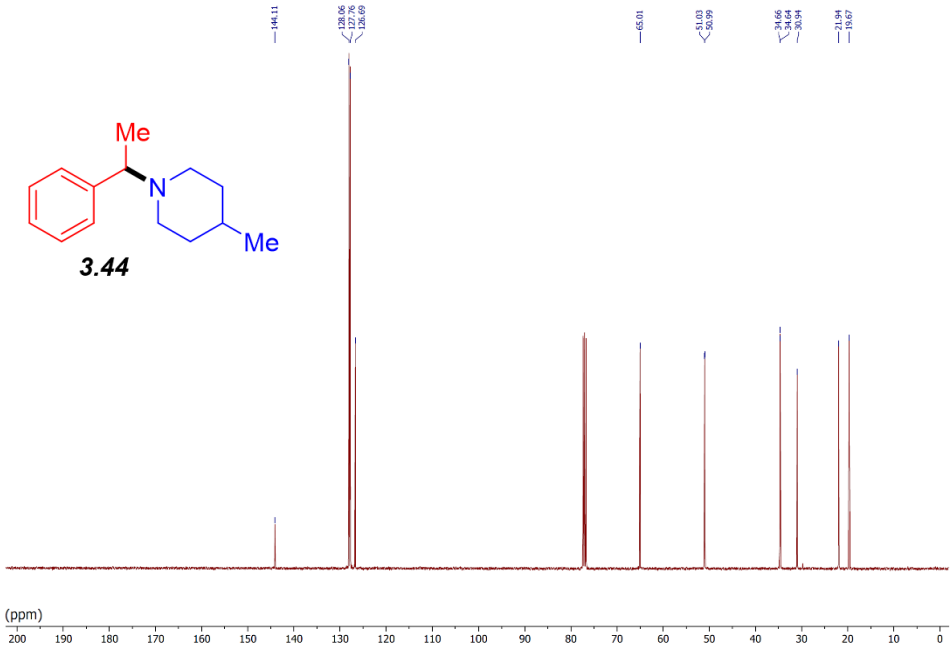

137.07
133.44
132.69
127.82
127.75
127.63
127.39
127.18
126.87
125.47
60.93
54.30
23.52
(ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

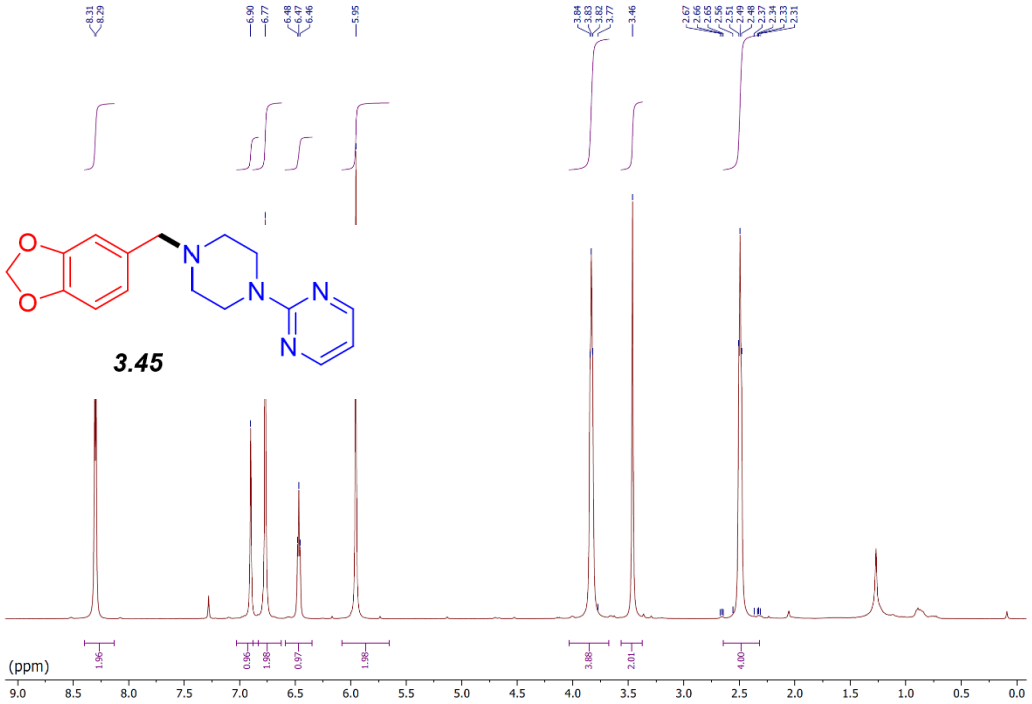
3.42,

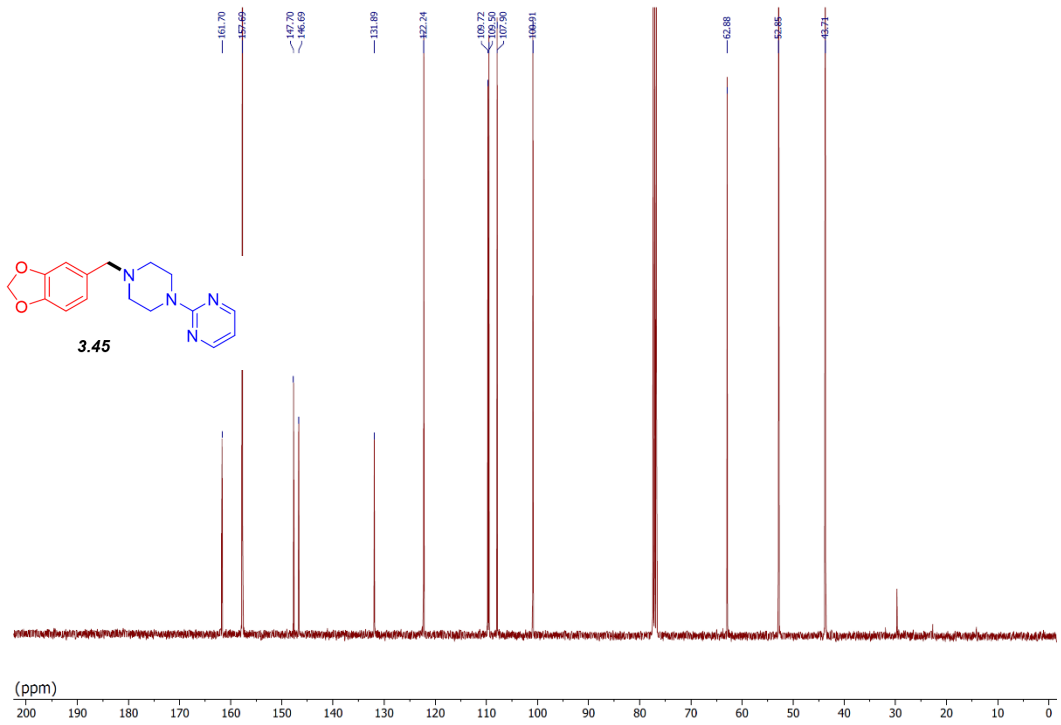

Me
N
O
3.43
(ppm)

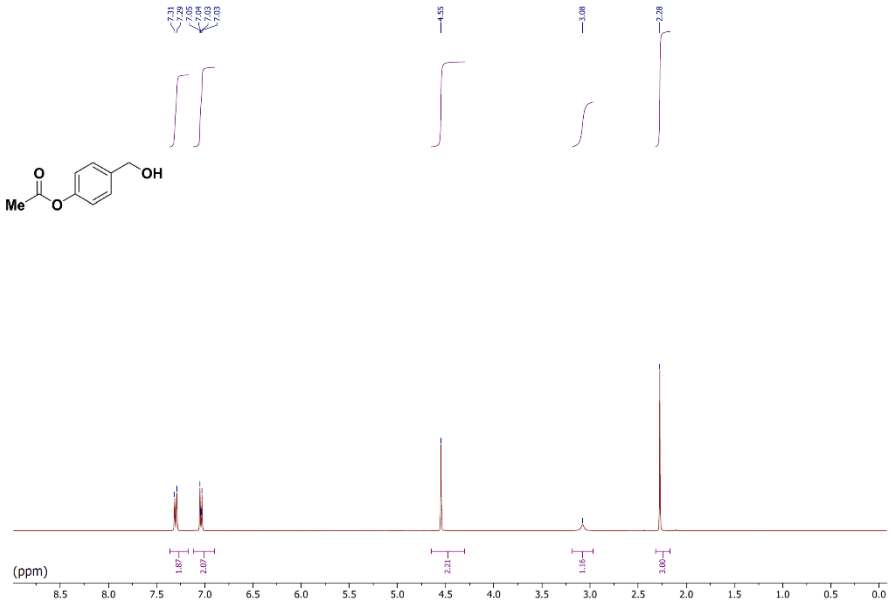

Me
N
O
3.43
(ppm)


Me
N
Me
3.44
(ppm)


144.11
128.06
127.76
126.69
65.01
51.03
50.99
34.66
34.64
30.94
21.94
19.67
Me
N
Me
3.44
(ppm)


8.31
8.29
6.90
6.77
6.48
6.47
6.46
5.95
3.84
3.83
3.82
3.77
3.46
2.67
2.66
2.65
2.56
2.51
2.49
2.48
2.37
2.34
2.33
2.31
3.45
1.96
0.96
1.98
0.97
1.98
3.88
2.01
4.00
(ppm)


161.70
157.69
147.70
146.69
131.89
122.24
109.72
109.50
107.90
100.91
62.88
52.85
43.71
3.45
(ppm)


7.31
7.29
7.05
7.04
7.03
7.03
4.55
3.08
2.28
O
Me
O
OH
1.67
2.07
2.21
1.18
3.00
(ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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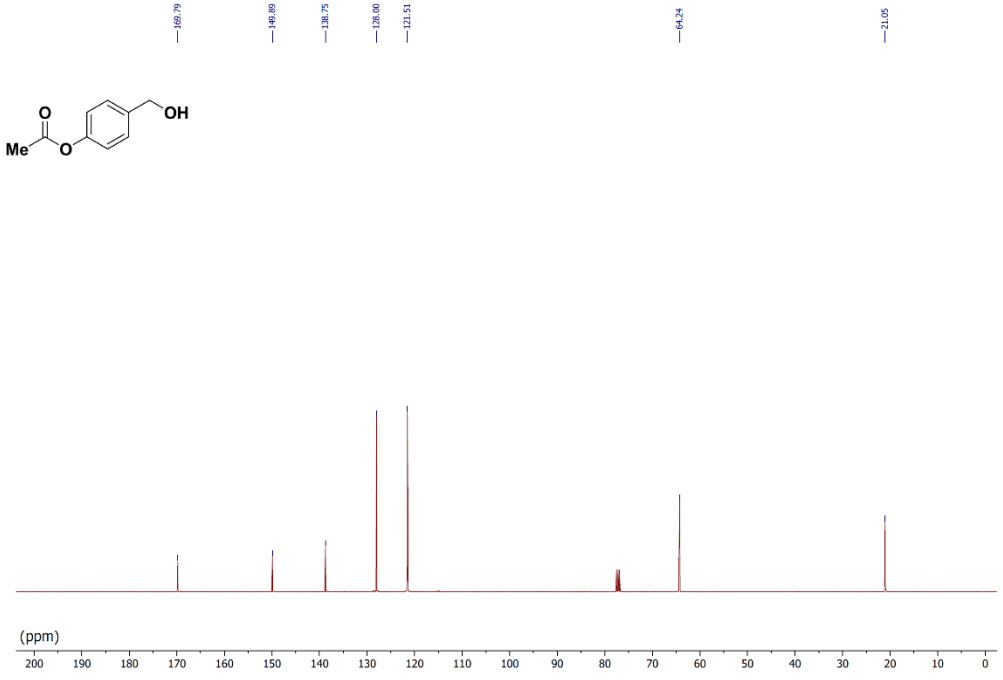
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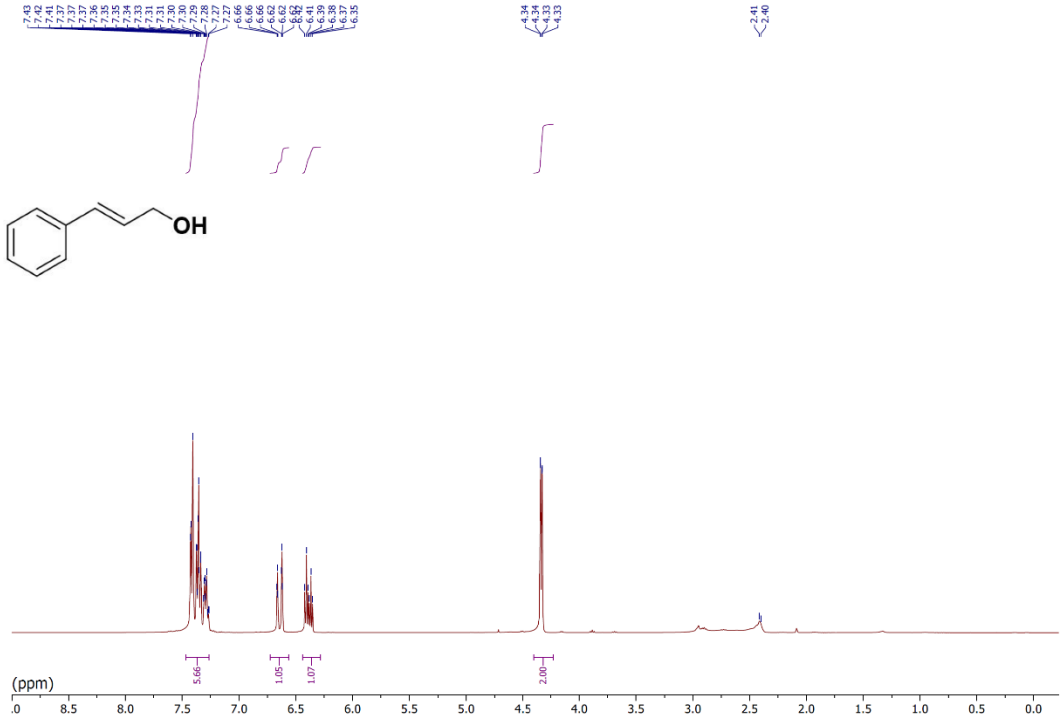
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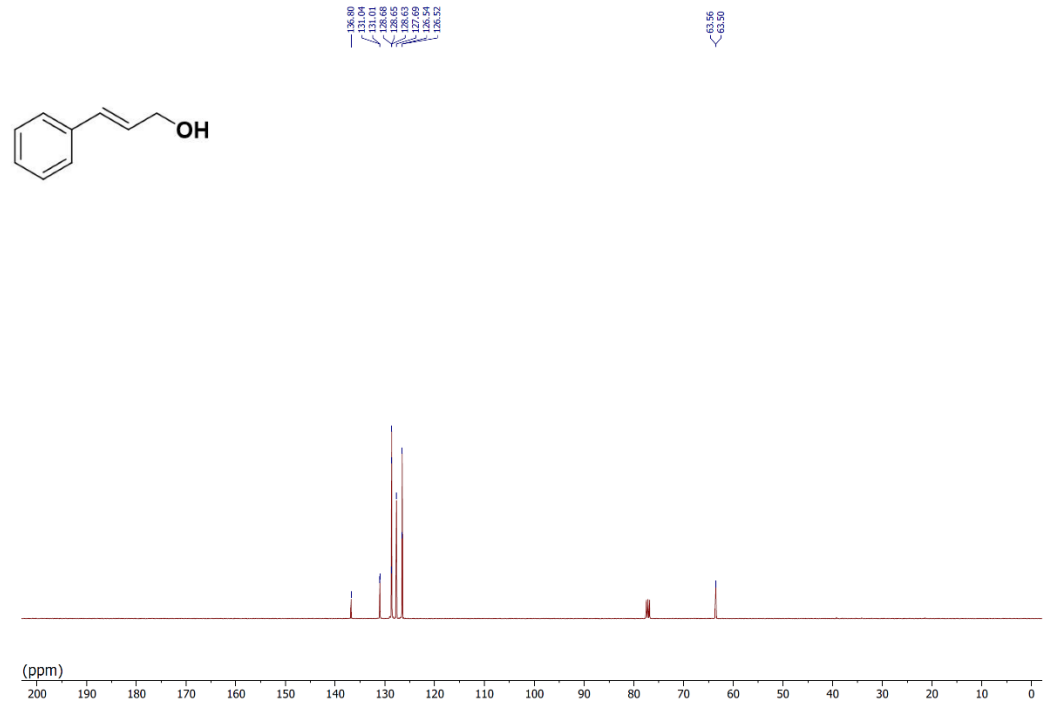
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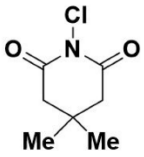
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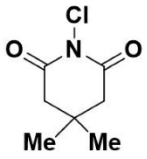
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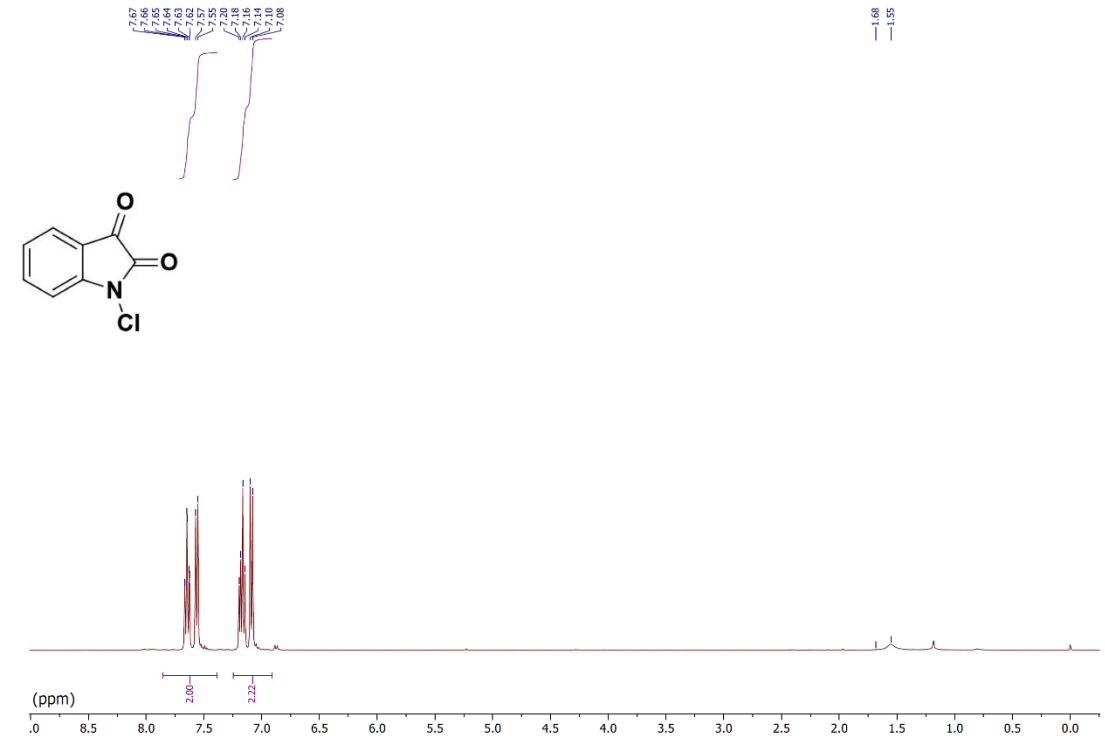
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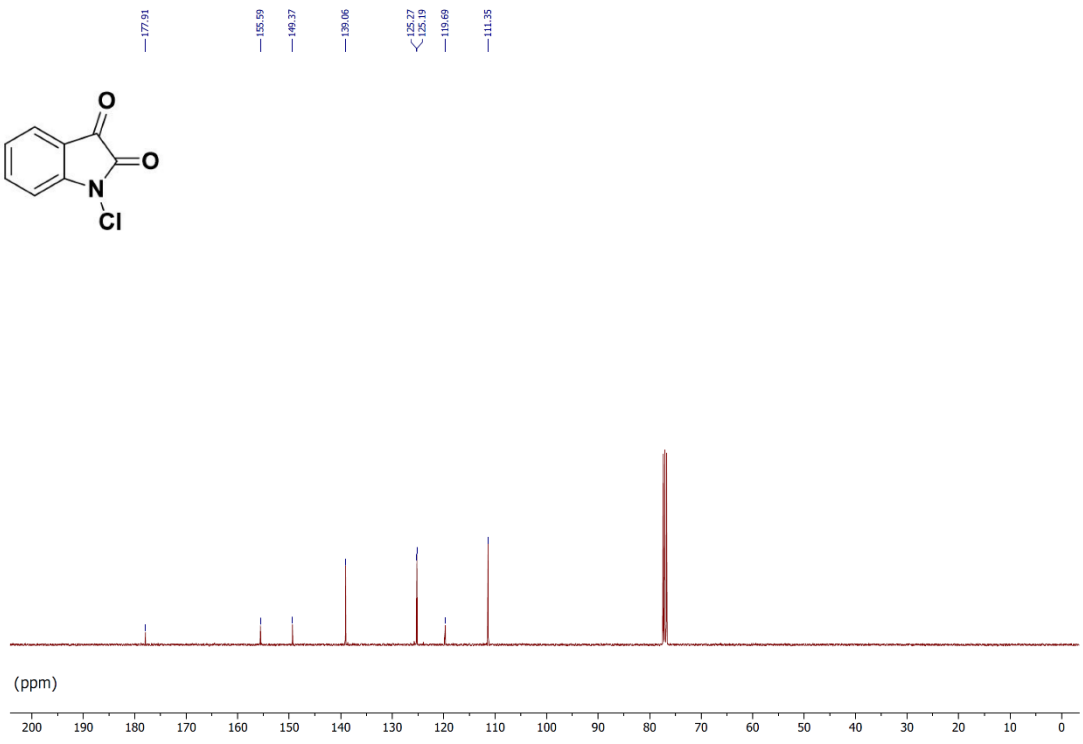
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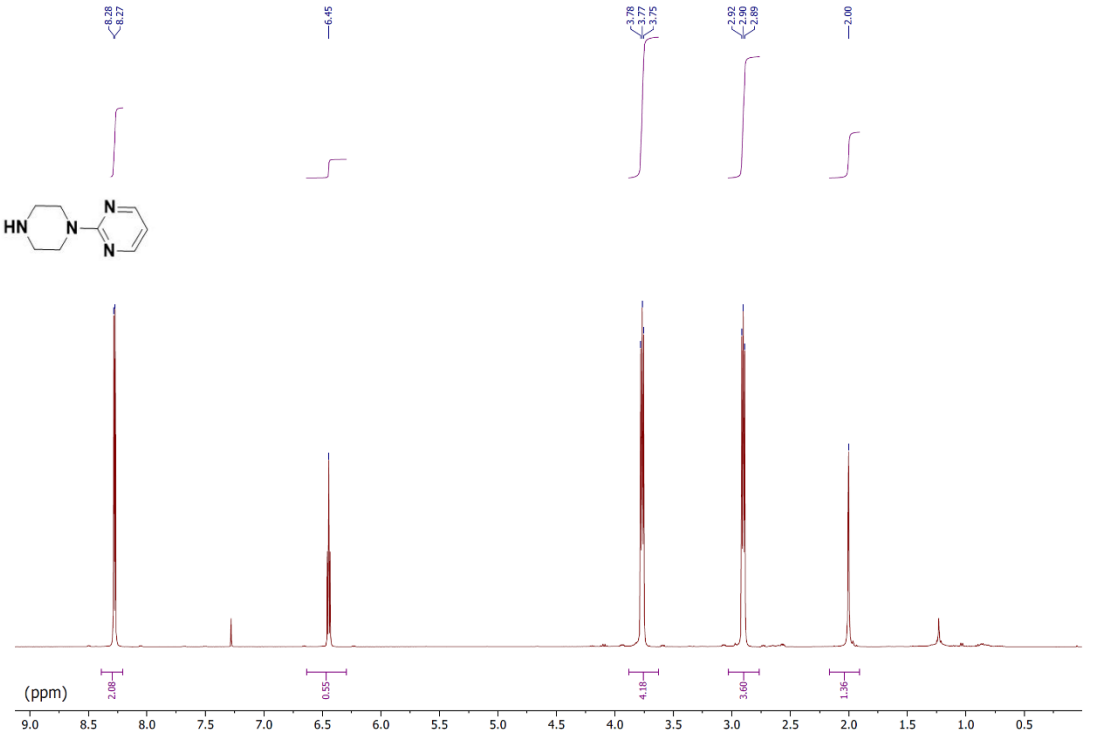
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(ppm)
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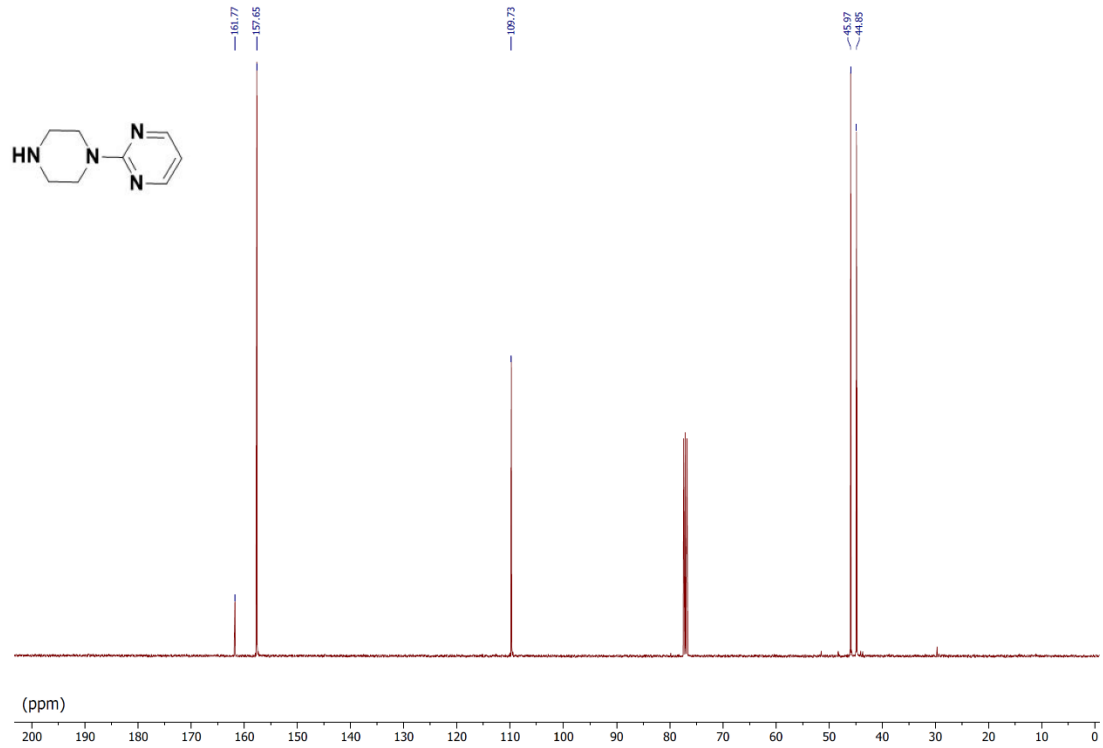
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80
70
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30
20
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0

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