TECHNISCHE UNIVERSITÄT WIEN

Dissertation

QUATERNARY AMMONIUM SALTS AS ALTERNATIVE REAGENTS IN HYDROCARBONYLATION REACTIONS

ausgeführt zum Zwecke der Erlangung des akademischen Grades eines Doktors der technischen Wissenschaften unter der Leitung von

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eingereicht an der Technischen Universität Wien
Fakultät für Technische Chemie

von

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Wien, Februar 2024

Life is [...]

riding a

bicycle.

- *loosely based on Albert Einstein*

Acknowledgements

Doing a PhD is kind of a journey, one that stretches your limits, tests your resilience, and pushes you to the edge of what you thought possible. And throughout this demanding expedition, with all its highs and lows, having companions by your side makes all the difference. They are the ones who cheer with you when you managed to climb a tough mountain, but even more important, they are the ones who walk with you through long hauls and deeper valleys, offering support, encouragement, or just the right portion of distracting your mind during the toughest stretches of the journey. To all those who have been my companions on this journey and beyond I am eternally grateful.

First and foremost, I am immensely thankful to you, Michl, as my supervisor for not only unexpectedly offering me this position at the coffee machine and awarding me with the supporting wheel in gold just some weeks later for my efforts in performing dramatic bike crashes, but also for the perfect mix of valuable guidance, patience, and dedication, together with encouraging and fully supporting me in pursuing my own ideas and (future) ways. I'm genuinely proud of everything we have achieved during these four years and all the works we have published, which would not have been possible without your full support.

Thanks to all the PIs in our group, Flo, Christian, and Marko, for your input and ideas during the seminars and all your help. And to a man that makes Mr. Gadget look pale next to him, UFlo, for always helping me whenever I needed something urgently or not sooo urgently.

A huge thanks to the best lab mates and former lab mates in the world, to being more than just colleagues.
To our youngsters, Verena, Christoph, Nika, and Max aka. premium graphic designer, thanks for bringing a breath of fresh air into our group – make the best out of your upcoming years! Dominik, Viktor, Simon, Kathi, Christoph, Pierre, Stefan, Lydia, Julia, Tom, Richard, Raheleh, Freddy, Chrise, Hubert, Nanditha, Michi, Nik and Eleni for all your support and for entertaining evenings that sometimes perfectly distracted the mind. Special appreciation goes to Eleni and Nina for sharing memorable days at conferences. I extend my gratitude to my diligent bachelor students, Edma Gjata, Filippa Getzner, and Nina Wildhack, for their assistance with synthetic work. Thanks to Max, the burgeoning expert in mechanochemistry, for his invaluable contributions to our discussions and his infectious enthusiasm for exploring new reactions.

To the G10 lab family, thank you for enduring my music all day, engaging in conversations during columns, and making every lab day enjoyable. A heartfelt thanks to you, Astrid, for your dedicated efforts in the lab and your warm-hearted nature; the lab wouldn't be the same without you.

And of course, thanks to my lab mate in crime, Nina. Because everybody needs somebody to cheer you up, share laughs, binge-watch series, go for a run, just talk, and simply be a friend when everything seems a bit upside down.
My two exceptional post-docs, Björn and Jorge, thank you for inspiring conversations and spending so many fun evenings together with always someone saying: “We could go home, ooor …?!”.
To my former colleagues, pro-baristas David and Drasi, Clemens the machine, and Heci aka. boom-boom Basti, for making the start into my PhD so much easier, for having you as friends, and for an amazing slipstream at road-bike trips (or for having fun losing someone from that slipstream).

Talking about biking, I want to extend a big thank you to the incredible members of Team Templ-Tier, including our Chief Snack Officer, Tobi, and Soapbox Car Officer, Wilko. No one could have pushed me beyond what I thought was possible, all while having so much fun throughout 22:47 hours – Admittedly, perhaps more so in the car than on the bike! You are truly incredible!

And I am entirely grateful that I can call the most special people in the world my childhood friends. Sesi, David, Simone, Iris, Mitsch, Anna, Verena, and Kathi, there are only a few people in the world with whom I've shared as much joy and laughter. Thank you for pulling me out of my university bubble and for accepting me for who I am, without placing importance on academic titles. Even during times when I haven't returned home for a while (perhaps because there's no street named after me yet), you always welcome me with open arms and without reproach. Being with you feels like I've never been away.

Sebastian, you are truly the best brother I could have ever wished for, even though I couldn’t show it to you every single moment when we were kids – I always felt it in my tiny heart. Thank you for always being there for me and for grounding me whenever I feel like I'm losing my footing.

Der größte Dank gilt ohne Zweifel meinen unglaublichen Eltern. Ohne eure bedingungslose Unterstützung, euer grenzenloses Vertrauen, euren ehrlichen Zuspruch und eure unvergleichbare Herzlichkeit wäre ich heute nicht hier, wo ich bin. Und damit meine ich nicht (nur), dass ich dieses Kapitel erfolgreich abgeschlossen habe, sondern, dass ich genau dort im Leben stehe, wo ich glücklicher nicht sein könnte. Es fällt mir schwer, all das in Worte zu fassen, wofür ich euch so unendlich dankbar bin. Ich hoffe jedoch, dass dafür keine geschriebenen Worte notwendig sind, sondern einfach eine herzliche Umarmung.

To you, Tobi, my steadfast companion on every step of my life’s journey, my greatest teammate, and my place to calm down. The past few years have been filled with richness, joy, and unforgettable memories. Your gift to bring laughter into my life every single day is truly remarkable. With your endless support everything was so much easier. You are truly incredible, and I couldn't be happier to have you on my side. Thank you, Tobi!

Abstract

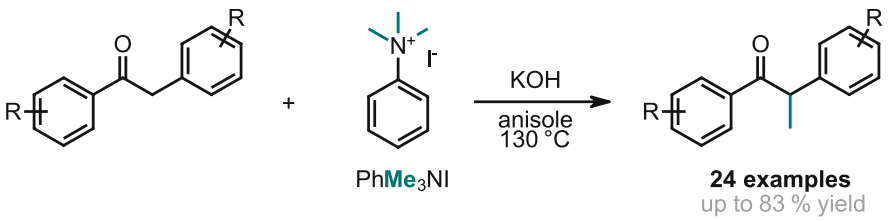
Hydrocarbonylation reactions are pivotal in organic chemistry, with wide-ranging implications in fields like agriculture, polymer chemistry, petrochemistry, biochemistry, and medicinal chemistry. Particularly in drug discovery, alkylation reactions, especially involving methyl groups, play a key role in enhancing potency, modulating half-life, improving solubility, and altering binding affinity.

However, conventional alkylating and alkenylating agents often pose substantial health and exposure risks due to their toxicity, mutagenicity, carcinogenicity, flammability, and explosiveness.

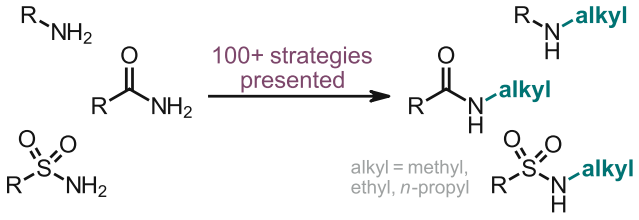
Quaternary ammonium salts (QAS) present a promising alternative for these transformations while posing significantly lower hazards. QAS used for hydrocarbonylation reactions have short organic residues and inorganic anions, making them crystalline solids, easy-to-handle, air and moisture-stable, with reduced inhalation risk. They offer lower health risks, being non-cancerogenic, non-mutagenic, non-flammable, and non-corrosive. Despite their potential, their use in direct organic transformations remains underexplored.

This thesis explores several strategies for harnessing QAS as alternative alkylating and allylating reagents. The development of these methodologies not only expands the toolbox of synthetic chemists but also contributes to safer and more sustainable practices in chemical synthesis.

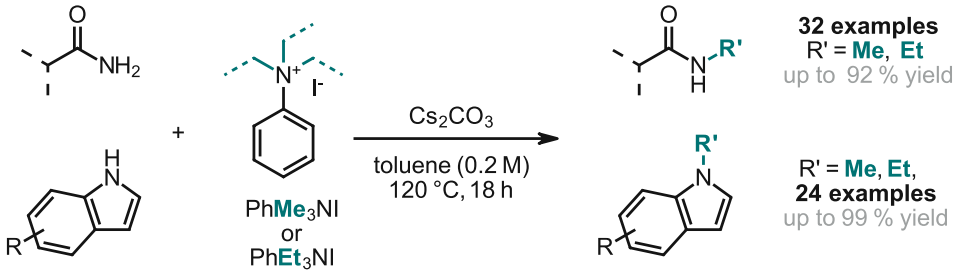
Phenyl trimethylammonium iodide was established as methylating agent for the mono-selective methylation at the α-carbon of aryl ketones, offering a safer alternative to toxic reagents like methyl iodide or dimethylsulfate. This methodology has demonstrated broad applicability across various substrates with different functional groups, giving the α-methylated products in up to 85 % yield. Moreover, the protocol has been extended to facilitate α-C-ethylation and -benzylation using phenyl triethylammonium iodide or benzyl trimethylammonium chloride, respectively.



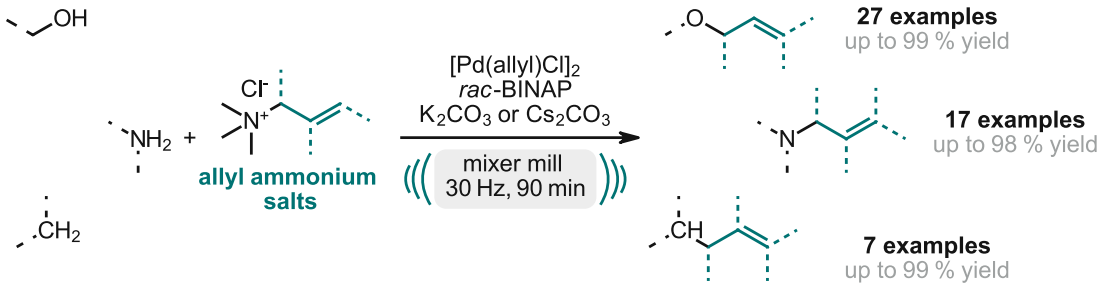
We further extended this protocol to facilitate the N-methylation and N-ethylation of primary amides. In general, nitrogen-containing motifs are prone to over-alkylation due to the increasing nucleophilicity of the nitrogen with higher degrees of substitution. To control the degree of substitution in primary amines, amides, and sulfonamides, several strategies have been developed and are comprehensively presented in the review on "Mono-Selective N-Methylation, N-Ethylation, and N-*n*-Propylation of Primary Amines, Amides, and Sulfonamides and Their Applicability in Late-Stage Modification".



Within the scope of this pre-doctoral study, we established a strategy for mono-selective alkylation of primary amides using phenyl trialkylammonium iodides. Presumably the steric bulk of this alternative alkylating agent hampers a second alkylation event, offering superior control over the degree of substitution compared to conventionally used alkylating agents like methyl iodide. This novel protocol could be further expanded to include indoles and related structures and proved suitable for late-stage methylation of bioactive compounds.



In our most recent development, we leveraged the leaving group ability of quaternary ammonium moieties in allylic position for the allylation of O-, N-, and C-nucleophiles in a palladium-catalyzed Tsuji-Trost reaction. The reactions were conducted mechanochemically in a mixer mill, eliminating the use of solvent and significantly reducing the environmental impact. This approach offers short reaction times, low catalyst and ligand loading, mild conditions, high selectivity, and excellent functional group tolerance. Several structurally complex molecules, including bioactive compounds, could be allylated in excellent yields and high purity. Furthermore, the feasibility of an enantioselective reaction using chiral ligands has been demonstrated, setting a starting point for further research in this area.



Kurzfassung

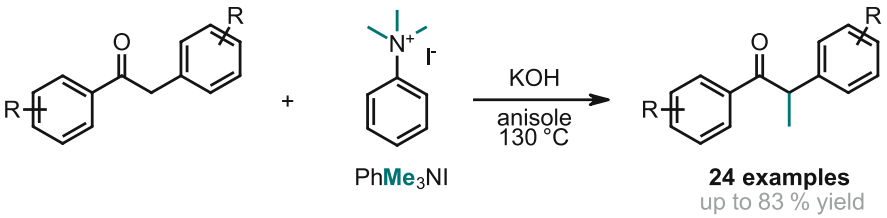
Hydrocarbonylierungsreaktionen sind in der organischen Chemie von zentraler Bedeutung und gehören zu den grundlegenden Reaktionen in Bereichen der Agro-, Polymer-, Petro-, und Biochemie, sowie in der medizinischen Chemie. Vor allem bei der Entwicklung neuer Arzneimittel spielen Alkylierungsreaktionen, insbesondere Methylierungen, oftmals eine entscheidende Rolle bei der Erhöhung der Wirksamkeit, der Modulation der Halbwertszeit, der Verbesserung der Löslichkeit und der Veränderung der Affinität eines Wirkstoffes.

Allerdings bergen konventionelle Alkylierungs- und Alkenylierungsreagenzien oft erhebliche Gesundheits- und Expositionsrisiken aufgrund ihrer Toxizität, Mutagenität, Karzinogenität, Entflammbarkeit und Explosivität.

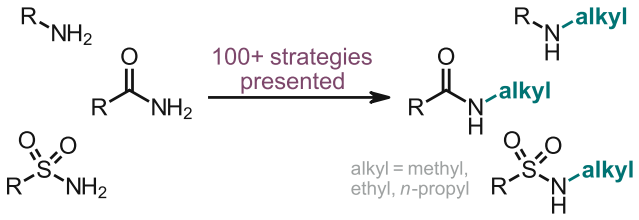
Im Gegensatz dazu bieten Quartäre Ammoniumsalze (QAS) eine vielversprechende Alternative zu jenen Reagenzien, da sie deutlich geringere Risiken bergen. QAS, die für Hydrocarbonylierungsreaktionen verwendet werden, haben kurze organische Reste und anorganische Anionen: Diese strukturelle Eigenschaft begünstigt die Ausbildung von Kristallstrukturen und macht jene Reagenzien zu Feststoffen, die leicht zu handhaben und darüber hinaus luft- und feuchtigkeitsbeständig sind. Außerdem verringert sich die Gefahr einer Aufnahme jener Reagenzien über den Atemtrakt deutlich. QAS weisen weiters signifikant niedrigere Gesundheitsrisiken auf, da sie nicht krebserregend, nicht mutagen, nicht entflammbar und nicht ätzend sind. Trotz ihres Potentials als Reagenzien in organischen Transformationen ist ihr Einsatz noch sehr wenig erforscht und entwickelt.

Diese Arbeit untersucht verschiedene Strategien zur Nutzung von QAS als alternative Alkylierungs- und Allylierungsmittel. Die Entwicklung dieser Methoden soll nicht nur das Repertoire synthetischer Chemiker erweitern, sondern auch zu nachhaltigeren Reaktionen und größerer Sicherheit innerhalb der Synthesechemie beitragen.

Phenyltrimethylammoniumiodid wurde als Methylierungsmittel für eine monoselektive Methylierung am α-Kohlenstoff von Arylketonen verwendet und bietet eine sicherere Alternative zu giftigen Reagenzien wie Methyliodid oder Dimethylsulfat. Diese Methode kann für ein breites Spektrum an Substanzen, die unterschiedliche funktionelle Gruppen tragen, angewendet werden und liefert die α-C-methylierten Produkte in Ausbeuten von bis zu 85 %. Darüber hinaus wurde das Protokoll um α-C-Ethylierungen und -Benzylierungen unter der Verwendung von Phenyltriethylammoniumiodid bzw. Benzyltrimethylammoniumiodid erweitert.

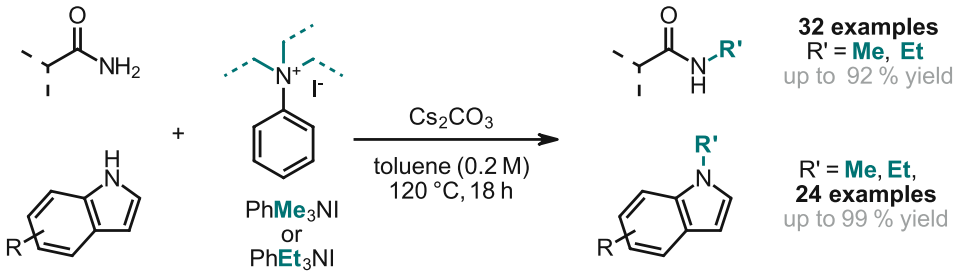


Anschließend wurde jene Methode weiterentwickelt, um N-Methylierungen und N-Ethylierungen von primären Amiden zu ermöglichen. Im Allgemeinen neigen stickstoffhaltige funktionellen Gruppen aufgrund der zunehmenden Nukleophilie des Stickstoffs bei höherem Substitutionsgrad zur Überalkylierung. Um Kontrolle über den Substitutionsgrad in primären Aminen, Amiden und Sulfonamiden zu erlangen, wurden verschiedene Strategien entwickelt und sind in einer umfassenden Übersicht über „Monoselektive N-Methylierung, N-Ethylierung und N-*n*-Propylierung von primären Aminen, Amiden und Sulfonamiden“ zusammengefasst.



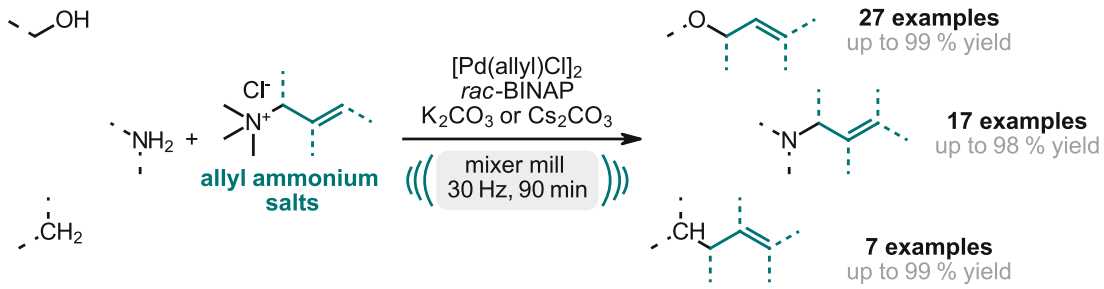
Im Rahmen der Doktorarbeit ist es uns gelungen durch die Verwendung von Phenyltrimethylammoniumiodid als Alkylierungsmittel eine Methode für die monoselektive Alkylierung von primären Amiden zu etablieren. Wahrscheinlich verhindert der sterische

Effekt dieses Alkylierungsmittels eine zweite Alkylierung und bietet damit eine gute Kontrolle über den Substitutionsgrad im Vergleich zu konventionellen Alkylierungsmitteln wie z.B. Methyliodid. Jenes Protokoll wurde um Indole und verwandte Strukturen erweitert und hat sich für eine Methylierung von bioaktiven Verbindungen in einem späten Stadium als geeignet erwiesen.



In unserer jüngsten Forschung haben wir die Abgangsgruppenfähigkeit quartärer Ammoniumgruppen in allylischer Position für die Allylierung von *O*-, *N*- und *C*-Nukleophilen in einer palladiumkatalysierten Tsuji-Trost-Reaktion genutzt. Die Reaktionen wurden mechanochemisch in einer horizontal mischenden Kugelmühle durchgeführt, wodurch der Einsatz von Lösungsmitteln eliminiert und somit die negative Auswirkung auf die Umwelt drastisch reduziert werden konnte.

Dieser Ansatz bietet kurze Reaktionszeiten, milde Bedingungen, hohe Selektivität und eine ausgezeichnete Toleranz gegenüber funktionellen Gruppen. Mehrere strukturell komplexe Moleküle, einschließlich bioaktiver Verbindungen, konnten in hervorragenden Ausbeuten und hoher Reinheit allyliert werden. Darüber hinaus konnte gezeigt werden, dass enantioselektive Reaktionen unter der Verwendung chiraler Liganden möglich sind, wodurch sich weitere Forschungsansätze in diesem Bereich eröffnen.



Structure of the Thesis

The thesis, authored by Johanna Templ, is composed as cumulative dissertation. All papers within this thesis were generated during the Ph.D. program and are included as published or accepted manuscripts.

The thesis is structured as follows:
It begins with an introduction providing an overview of the topic, its relevance in the context of organic synthesis, and current research. The subsequent section comprises all published manuscripts as original work, prefaced with a list of contributions, followed by a brief summary of each the paper and a statement detailing contributions. If available, the corresponding supporting information is appended immediately after the manuscript itself. Lastly, a conclusion and perspective are given, followed by a list of publications from this thesis and a curriculum vitae.
Compounds are numbered numerically per chapter.

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A I Introduction

Hydrocarbonylation reactions represent fundamental transformations in organic chemistry, holding significant importance across various fields including agricultural,[1] and polymer chemistry,[2] petrochemistry,[3] biochemistry[4] and medicinal chemistry.[5] Particularly in the area of drug discovery through late-stage modification strategies, alkylation reactions play a pivotal role.[5a, 5b, 6] The introduction of the smallest alkyl moiety, namely the methyl group, often exerts a crucial impact by enhancing a drug's potency, modulating its half-life, improving solubility and selectivity, or altering its binding affinity.[7] However, not only the CH_3 group itself is a prominent motif, but also a variety of longer aliphatic, cyclic, saturated, and unsaturated hydrocarbon moieties are frequently encountered in the skeletal structure of bioactive compounds (Figure 1, left).

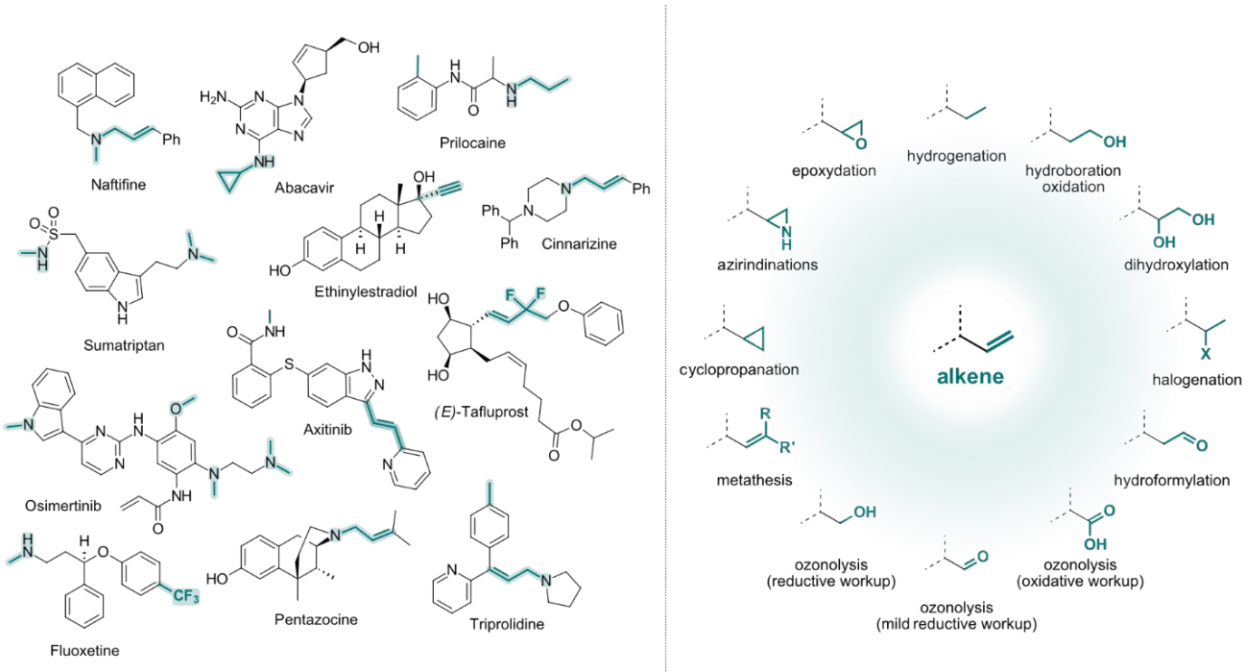


Figure 1. Selected examples of pharmaceuticals with important structural hydrocarbon motifs (left) and strategies for double bond modification (right).

Introducing unsaturated groups into compounds, for instance, *via* vinylation or allylation, can provide handles for further chemical modifications such as epoxidations, dihydroxylations, cyclopropanations, aziridination, ozonolysis, halogenations, metathesis, and radical reactions[8] (Figure 1, right). The latter reactions are particularly important in polymer chemistry, where radical polymerization and cross-linking of specifically designed building blocks can give access to novel materials with finely-tuned and application-oriented properties.

Traditional alkylating and alkenylating agents, however, often pose significant health and exposure risks, rendering their application undesirable. These hazards include high toxicity, mutagenicity, and carcinogenicity (e.g., MeI, allyl halides, dimethyl sulfate, methyl fluorosulfonate, trimethylsilyl diazomethane), high flammability (e.g., organometallic reagents, vinyl halides, allyl halides, dimethyl carbonate), and explosiveness (e.g., diazomethane).[9] Additionally, these reagents may exhibit properties such as rapid hydrolysis (e.g., trimethylsilyl diazomethane, trialkyloxonium tetrafluoroborates, organometallic reagents) and high volatility (e.g., diazomethane, MeI, vinyl chloride, allyl chloride, ethene), which can significantly complicate their handling, especially on a lab-scale basis (Figure 2, right).[10]

Considering these toxicological and hazard concerns, the need for new, inherently safer alkylating and alkenylating agents becomes apparent. Quaternary ammonium salts (QAS) present themselves as promising alternatives and were investigated as such within this thesis. While quaternary ammonium salts are well established as ionic liquids,[11] surfactants,[11b, 12] and phase transfer catalysts,[11a, 13] their application as reagents for hydrocarbonylation reactions is relatively unexplored. Unlike the long hydrophobic residues attached to QAS for use in ionic liquids and surfactants, the ammonium salts used as reagents typically bear relatively short-chain organic residues and inorganic anions. This structural feature enables the formation of highly crystalline solids, making these reagents easy-to-handle, air and moisture-stable. Consequently, their application is remarkably convenient, with reduced risk of inhalation compared to highly volatile reagents such as methyl iodide. Overall, QAS exhibit significantly lower health risks, being non-cancerogenic, non-mutagenic, non-flammable, and non-corrosive (Figure 2, left). Despite their potential, the utilization of QAS as alternative reagents for direct organic transformations remains limited.

The following sections will outline selected examples of current strategies, with a focus on aliphatic hydrocarbonylation methodologies. Arylation and benzylation cross-coupling methodologies involving C-N bond cleavage of benzyl- and phenyl-containing ammonium salts will not be discussed extensively, as numerous reports comprehensively cover these transformations.[11a, 14] Furthermore, rearrangement reactions of QAS, such as the Stevens- and the Sommelet-Hauser rearrangement, fall beyond the scope of this work and will not be covered herein.[15]

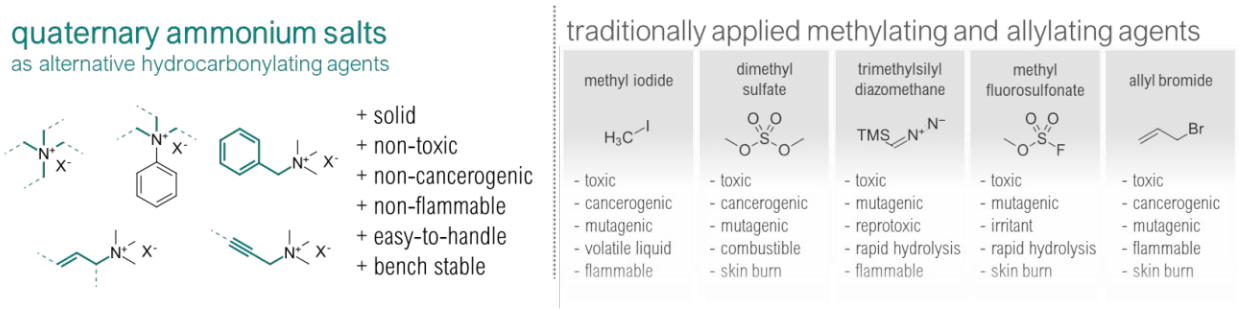


Figure 2. Chemical structures of quaternary ammonium salts used as hydrocarbonylating agents (left) and toxicological concerns and hazards of traditionally applied methylating and allylating agents (right).

Current methods for alkylating and alkenylating with QAS as the hydrocarbonylating agent typically fall into two categories: metal-free nucleophilic substitution or transition-metal catalyzed mechanisms. The latter may involve radical intermediates, although this is not always the case.

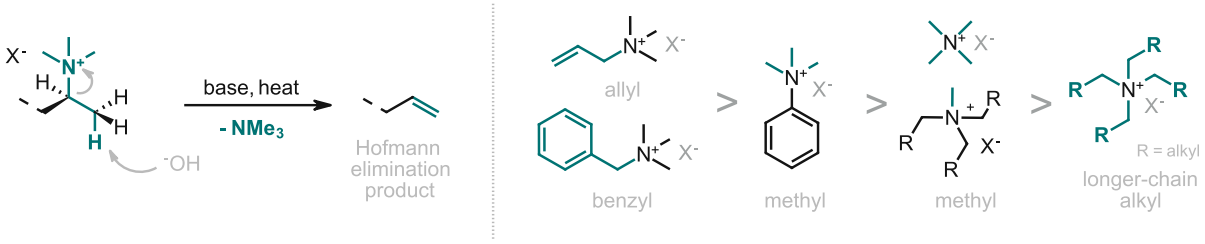
Metal-free aliphatic hydrocarbonylations using QAS

QAS can be employed as substrates in nucleophilic substitution reactions, giving access to a variety of alkylated, allylated, and benzylated *O*-, *N*-, *S*-, or *C*-nucleophiles. Typically conducted under basic conditions and often requiring elevated temperatures, these reactions release a tertiary amine as leaving group, with its structure dictated solely by the chemical composition of the ammonium salt. Strategic modification of the QAS substrate can exploit the properties of the leaving group, with options including the utilization of the liberated tertiary amine group as an *in situ* generated base (e.g., triethylamine) or the release of gaseous trimethylamine to shift the equilibrium towards the product side and facilitate subsequent purification, as the leaving group is traceless.

However, for the reaction design, it should be considered that under basic conditions, Hofmann elimination can occur as a concurrent reaction.[16] Hereby the quaternary ammonium compound undergoes an E2-like elimination reaction mediated by the base, resulting in the loss of the least sterically hindered beta-hydrogen and the quaternary ammonium moiety and formation of a double bond (Scheme 1, left). While this reaction can be intentionally utilized for *in situ* alkene formation,[17] as discussed in greater detail later, it can lead to undesired degradation of the QAS in reactions where direct nucleophilic substitution is desired, potentially diminishing yields. Optimization of reaction conditions and careful fine-tuning of substituents on the QAS may be necessary.

For hydrocarbonylation reactions involving QAS bearing different substituents on the ionium nitrogen, the selectivity for which C-N bond is preferentially cleaved and subsequently transferred to the nucleophile is described in literature.[18] Allyl and benzyl substituents exhibit the highest transfer rates, followed by methyl groups and longer primary alkyl chains (Scheme 1, right). Additionally, electron-withdrawing substituents on the nitrogen atom, such as phenyl, can accelerate the rate of C-N cleavage for adjacent alkyl groups. We also observed this trend in our studies on C- and N-methylation using QAS as methylating agent (see Manuscript 1 and 3). Tetramethyl ammonium salts showed lower yields for desired *C*- and *N*-methylated products compared to phenyl trimethylammonium salts under optimized conditions. Regarding the influence of the anion in the QAS on the rate of alkylation, no definitive trends were observed in literature or throughout our studies.

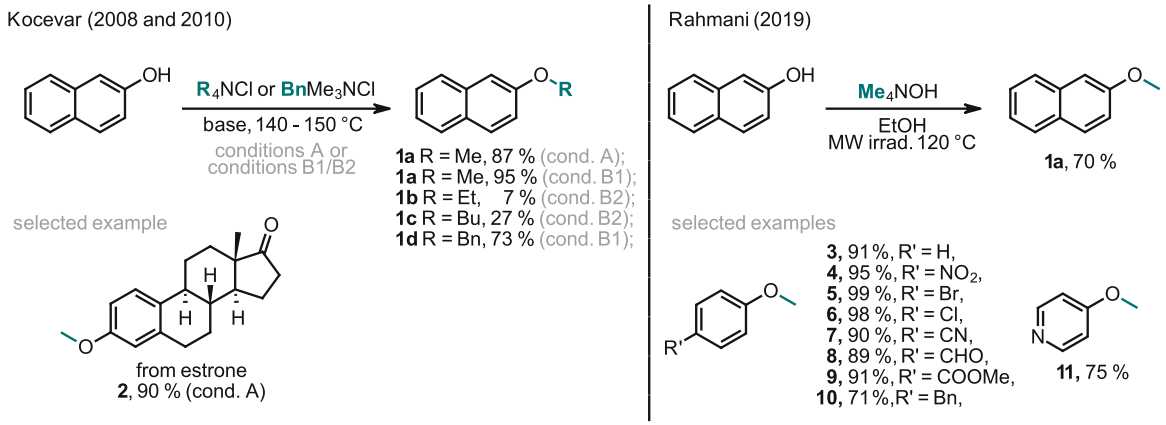
Despite the demonstration of QAS as alkylating agents over 70 years ago on a limited set of nucleophiles,[19] the development of general alkylation protocols suitable for broad and convenient application in synthesis took more than 50 years to emerge.



Scheme 1. Base mediated Hofmann elimination (left) and selectivity for C-N cleavage and transfer rates of hydrocarbon substituents in quaternary ammonium salts (right; transferred group in blue, from left to right: high to low rates)

In 2008, the group of Kocevar was the first to extensively utilize tetramethylammonium chloride for the methylation of phenolic substrates under mild basic conditions using microwave irradiation.[20] While NaOH gave higher yields for the O-methylation of 2-naphthol, they opted for K_2CO_3 or Cs_2CO_3 as bases due to their safer application in a microwave setup. 1,2-Dimethoxyethane was used as solvent of choice, however, the authors demonstrated comparable yields using toluene in four examples. Various phenol derivatives, including the bioactive compound estrone, were methylated in up to 96% isolated yield. Just two years later, the same group expanded their protocol from tetramethyl to benzyl trimethyl ammonium chlorides.[21] As discussed previously, *O*-benzyl phenyl ethers were predominantly formed when using benzyl trimethylammonium chloride and negligible amounts of the methylated products were detected. Ethylation and butylation using tetraalkylammonium chlorides yielded only 7% and 27% yield, respectively (Scheme 2, left).

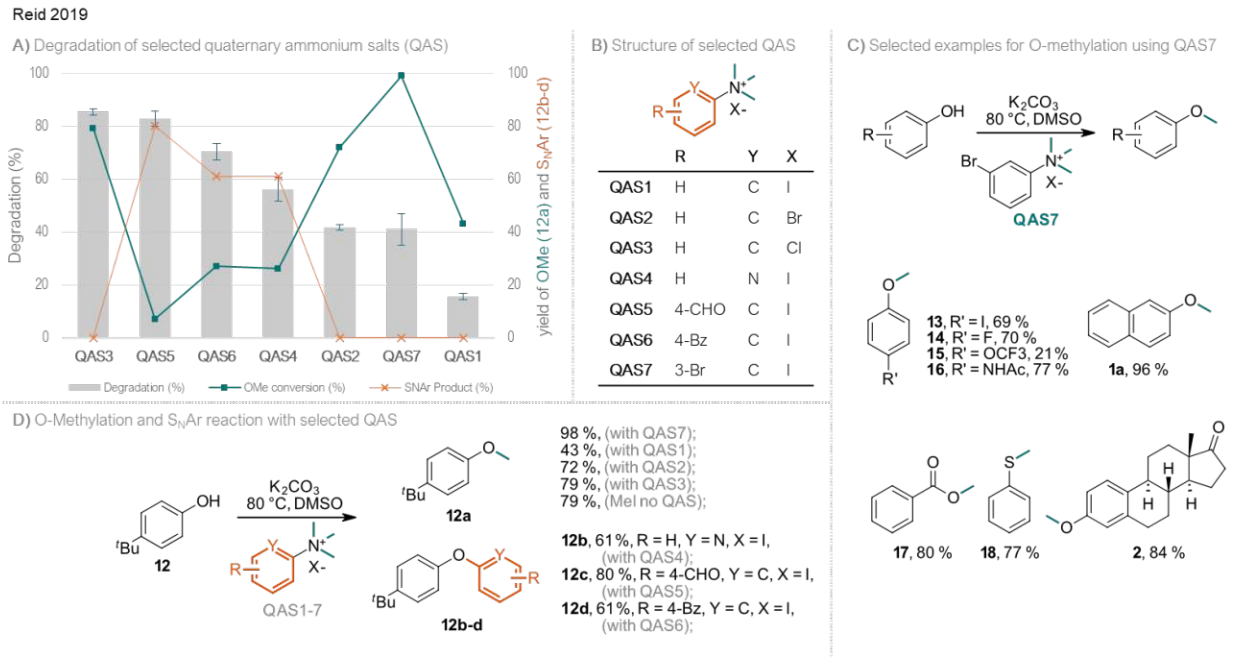
A similar protocol for *O*-methylation of various phenols was disclosed in 2019 by Rahmani and co-workers. They employed a 25% aqueous solution of tetramethylammonium hydroxide under microwave irradiation at 120 °C in ethanol as a solvent to successfully methylate a range of substituted phenol derivatives in up to 85 % isolated yield (Scheme 2, right).[22]



Scheme 2. O-Alkylation using tetraalkylammonium chlorides by Kocevar (left)[20-21] and O-methylation using tetramethylammonium hydroxide by Rahmani (right).[22]; Conditions A: K_2CO_3, 1,2-dimethoxyethane, microwave irradiation 145 °C, 20-60 min; Conditions B1: K_2CO_3, diglyme, reflux; Conditions B2: K_2CO_3, polyethylene glycol, 150-160 °C.

An impressive study on the stability of various quaternary ammonium salts and their application for O-methylation of phenols was conducted by Reid's group in 2021.[23] Instead of tetramethylammonium salts, they utilized *N*,*N*,*N*-trimethylanilinium salts (Scheme 3, B). These aryl-containing ammonium salts exhibit dual reaction sites: the electrophilic *N*-methyl group and the aryl group itself. While the reactivity of the latter has been previously exploited in cross-coupling reactions,[14a, 14b, 14d, 14e] Reid's group was the first to employ aryl trimethylammonium halides as methylating agents for phenolic compounds. Their protocol harnessed the inherently higher reaction rates of these aryl-containing ammonium salts in alkyl transfer reactions, compared to their tetramethylammonium analogs. Interestingly, they tested a range of aryl trimethyl ammonium halides with modified aryl systems both for their thermal stability and their performance in O-methylation reactions (Scheme 3, A). The authors hypothesized that aryl ammonium salts with lower thermal stability would, in turn, perform best in O-methylation reactions as higher availability of *in situ* generated MeI, acting as methylating agent itself, is given. To their surprise, these thermally instable salts bearing strong electron withdrawing substituents on the aryl gave only poor yields of the *O*-methylated product (**12a**). In turn, these reagents yielded significant amounts of the S_NAr product (**12b-d**, Scheme 3, D).

They identified the best performing reagent in terms of O-methylation being 3-bromo-*N*,*N*,*N*-trimethylanilinium iodide (QAS7) in DMSO at 80 °C, providing the desired methyl phenol ethers in up to 98 % yield. They further expanded their scope to thiophenol and benzoic acid, both methylated in high yields of 77 % for product **18** and 80 % for **17**.



Scheme 3. A. Thermal degradation of a set of quaternary ammonium salts in DMSO at 80 °C after 20 minutes; **B**. Structures of aryl ammonium salts used within this protocol; **C**. Selected examples for O-methylation using 3-bromo-*N*,*N*,*N*-trimethylanilinium iodide (QAS 7); **D**. O-Methylation and S_NAr reaction of *p*-*tert*-butyl-phenol **(12)** with various aryl ammonium salts by Reid.[23]

Research into the mechanisms of these reactions suggests that methyl iodide formed *in situ* from thermal decomposition of 3-bromo-*N*,*N*,*N*-trimethylanilinium iodide is likely the primary methylating agent involved. However, it is probable that two reaction pathways proceed concurrently: one *via* in situ formed MeI as the alkylating agent, and the other *via* S_N2 reaction with the ammonium species, leading to the O-methylated product. This theory is supported by experiments showing lower yields (79 %) when using pure MeI compared to 3-bromo-*N*,*N*,*N*-trimethylaniline (98 %) under otherwise identical conditions.

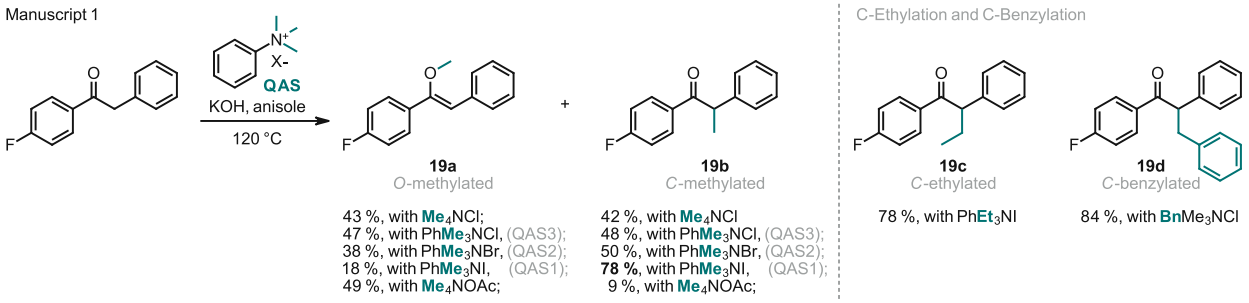
In our studies on the methylation of *C*- and *N*-nucleophiles using $PhMe_3NI$ as the alkylating agent,[24] which will be discussed in the following, we observed a pathway likely proceeding exclusively *via* S_N2 reaction between the nucleophile and the methyl ammonium salt, with thermal decomposition of the latter species to MeI being highly improbable. Our protocols, outlined in Manuscript 1 and 3, involved reactions in apolar solvents (anisole or toluene) at 120 °C, using phenyl trimethylammonium iodide (QAS1) as the methylating agent. This contrasts with the approach of Reid's group, who utilized DMSO as a highly polar solvent at 80°C, employing an aryl trimethylammonium salt with a strong electron-withdrawing aryl substituent (cf. Scheme 3, B, QAS7). This difference in reaction parameters might explain the contrasting observations on thermal decomposition of the ammonium salt to MeI.

In 2022, we established the use of phenyl trimethylammonium iodide as an alternative methylating agent for an α-C-methylation of aryl ketones. A detailed description can be found in the Manuscript 1.[24a]

While aryl ketones were prone to methylation not only at the α-carbon but also on the oxygen upon enol formation, using tetramethyl ammonium halides mainly resulted in 1:1 mixtures of *C*- **(19b)** and *O*-methylated **(19a)** species. The same ratio could be observed when using $PhMe_3NCl$. However, changing the methylating agent to $PhMe_3NBr$ and finally to $PhMe_3NI$ significantly favored the desired α-*C*-methylated product (4.3:1, **19b**:**19a** ratio). During our optimization studies, we observed a substantial amount of the *O*-methylated product alongside α-*C*-methylation, which suggests a mechanism different from the one proposed by Reid involving thermal decomposition to MeI. Interestingly, when replacing $PhMe_3NX$ with MeI as the methylating agent for the C-methylation of aryl ketones under comparable conditions, only α-*C*-methylated product **(19b)** and no *O*-methylated product **(19a)** can be observed. Additionally, Reid and colleagues observed thermal degradation of $PhMe_3NCl$ up to 85% in 20 minutes in DMSO at 80 °C, while $PhMe_3NI$ showed much greater thermal stability, with only 20 % degradation. Assuming a similar trend in thermal stability for these salts in toluene at reflux temperature, we would expect the chloride salt ($PhMe_3NCl$) to produce a higher concentration of *in situ* formed MeX compared to the iodide salt ($PhMe_3NI$). This would lead us to expect that the *O*-Me to α-*C*-Me ratio should

be significantly shifted towards the α-*C*-Me product for the chloride salt, as MeX is apparently less prone to O-methylation in this system. However, we observed the opposite outcome, with $PhMe_3NCl$ giving a 1:1 ratio and $PhMe_3NI$ a 4.3:1 ratio of the α-*C*- **(19b)** versus the *O*-methylated product **(19a)**.

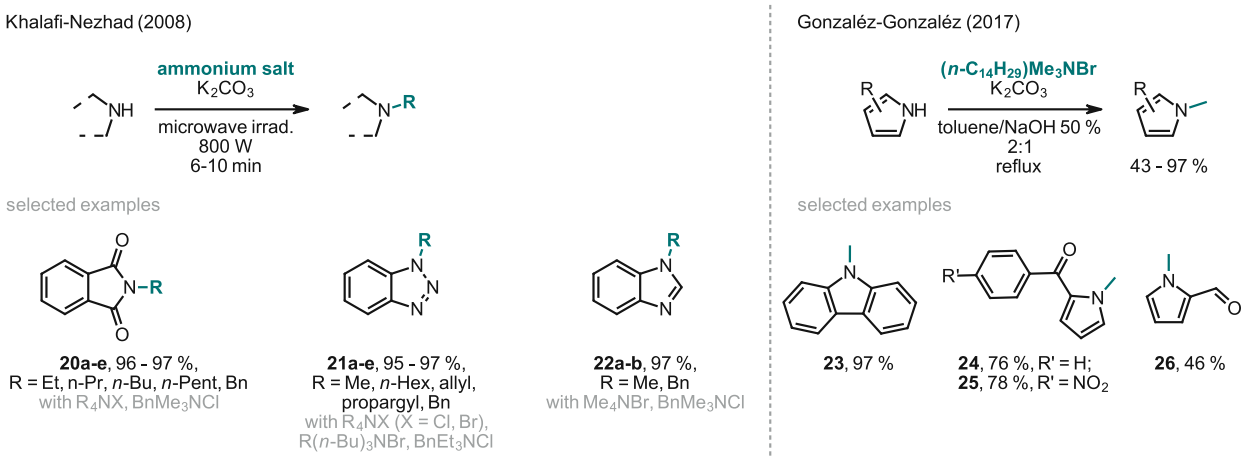
Additionally, experiments with Me_4NOAc as the methylating agent further supported our hypothesis of direct S_N2 reaction between the nucleophile and the ammonium salt rather than *via* an *in situ* formed MeX-pathway.



Scheme 4. Methylation of ketones using $PhMe_3NI$ as methylating agent and the observed product distribution of O-methylation of a previously formed enolate **(19a)** and α-C-methylation **(19b)** (left) and the applicability of this method for α-C-ethylation using $PhEt_3NI$ and α-C-benzylation using $BnMe_3NCl$ (right).[24b]

The contrasting observations between Reid's group and ours might be attributed to differences in reaction parameters. (Ried: DMSO 80 °C, 3 -bromo-*N*,*N*,*N*-trimethylanilinium iodide; Templ & Schnürch: anisole 120 °C, trimethylanilinium iodid).

In addition to oxygen and carbon, nitrogen nucleophiles can also undergo alkylation using ammonium salts. In 2008, Khalafi-Nezhad *et al.* disclosed a protocol for the efficient N-alkylation of various azaheterocycles using quaternary ammonium salts as alkylating agents under neat conditions in a microwave reactor at 800 W for 6-10 minutes, employing K_2CO_3 as a very mild base.[25] This protocol facilitated not only N-methylation but also higher carbon alkylations, allylation, propargylation, and benzylation using either tetraalkylammonium bromides (R_4NBr, with R = Me, Et, *n*-Pr, *n*-Bu, *n*-Pent, *n*-Hex) or mixed ammonium salts (allyl(*n*-Bu)$_3$NBr for allylation, propargyl(*n*-Bu)$_3$NBr for propargylation, or $BnMe_3NCl$ for benzylation). The *N*-alkylated products were obtained in excellent yields, up to 97 % (Scheme 5, left).

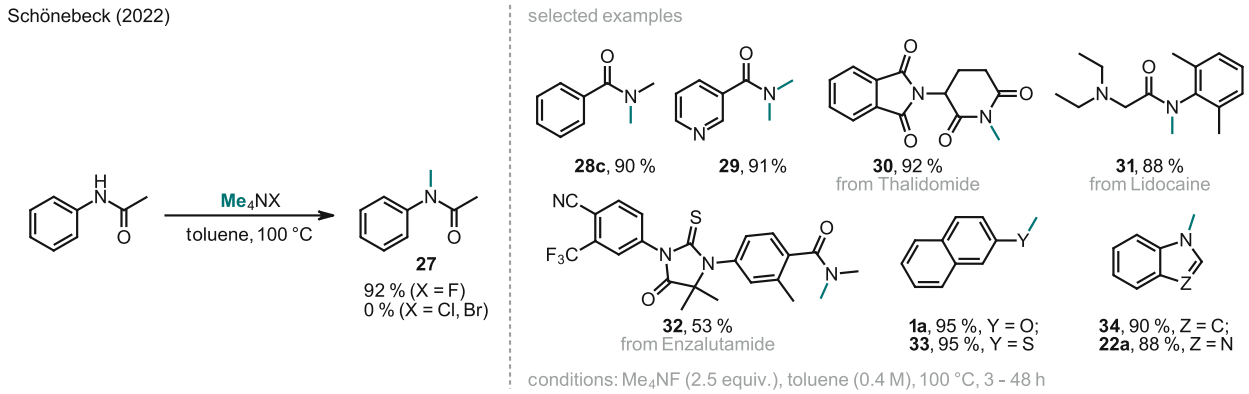


Scheme 5. N-Alkylation of various azaheterocycles using quaternary ammonium salts under microwave irradiation by Khalafi-Nezhad (left)[25] and N-methylation of azaheterocycles using tetradecyl trimethylammonium bromide by Gonzaléz-Gonzaléz (right).[26]

Nearly 10 years later, González-González *et al.* utilized tetradecyl trimethylammonium bromide to methylate various *N*-heterocycles in toluene under basic conditions at reflux temperatures, obtaining the *N*-methylated products in 43 to 97 % yield (Scheme 5, right).[26]

A pioneering work on N-methylation using ammonium salts was published in 2020 by the group of Schönebeck.[27] They employed tetramethylammonium fluoride (Me_4NF) in toluene at 100 °C to methylate various nucleophiles including amides, indoles, alcohols, thiophenols, pyrroles, and imidazoles, with a focus on the first two compound classes (Scheme 6, right). Their protocol did not require the use of an additional base; however, it is suggested that the fluorine ion of the ammonium salt is nucleophilic enough to act as a base. This crucial role of the fluorine is strongly supported by control experiments where the Me_4NF was substituted by Me_4NCl or Me_4NBr leading to a complete shutdown of the reaction (Scheme 6, left). Computational studies support the assumption of a concerted deprotonation/methylation mechanism.

Interestingly, for primary amides, the *N*,*N*-bis-methylated products (cf. product **29**) were obtained exclusively, with no control over the degree of substitution. However, since several bioactive compounds contain a secondary *N*-methylated amide moiety (Figure 1, left), the demand for highly mono-selective methylation protocols suitable for late-stage functionalization of bioactive compounds becomes evident.



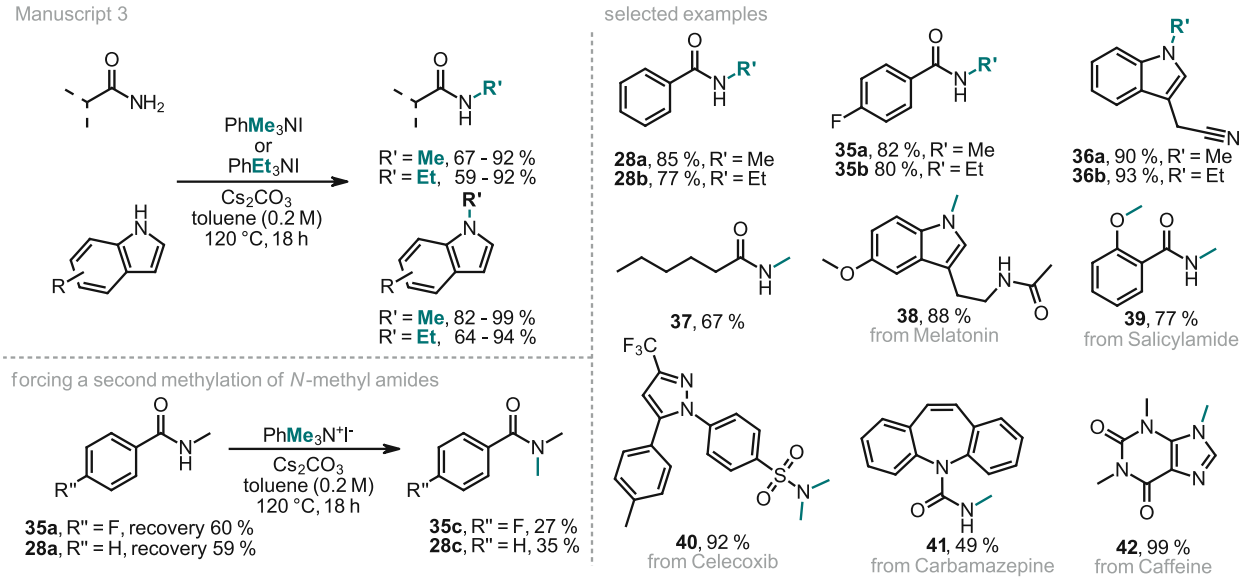
Scheme 6. N-Methylation of amides, indoles, thiophenols, pyrroles, and imidazoles using tetramethylammonium fluoride by Schönebeck.[27]

Several strategies for mono-selective N-methylation, N-ethylation, and N-*n*-propylation of amines, amides, and sulfonamides are summarized in the review written during the pre-doctoral studies by the author of this thesis (manuscript 2).[28]

To meet the demand for mono-selective N-methylation reactions and combine it with the use of alternative solid and non-toxic methylating agents, we developed a protocol using phenyl trimethylammonium iodide as the methylating agent under mildly basic conditions (Cs_2CO_3) in toluene at reflux temperatures, exhibiting outstanding mono-selectivity for the methylation of primary amides (manuscript 3).[24b] We hypothesized that the high mono-selectivity arises from the bulky nature of the methylating agent $PhMe_3NI$. Presumably, the primary amide is still susceptible to methylation, whereas the steric hindrance of the mono-methylated amide hampers a second methylation to form the tertiary amide (Scheme 7, left, bottom). This hypothesis of alkylating agent-dependent selectivity gains further support when the amide methylation is performed with MeI instead of $PhMe_3NI$ under basic conditions. Using MeI as the methylating agent, the *N*,*N*-bis-methylated product is formed exclusively, with no observed mono-selectivity.[29]

This finding once again supports our theory that methylation using $PhMe_3NI$ proceeds *via* S_N2 reaction of the nucleophile with the ammonium salt, rather than thermal decomposition of the latter species to MeI being the actual methylating agent, as hypothesized by the group of Reid and previously discussed within this chapter.

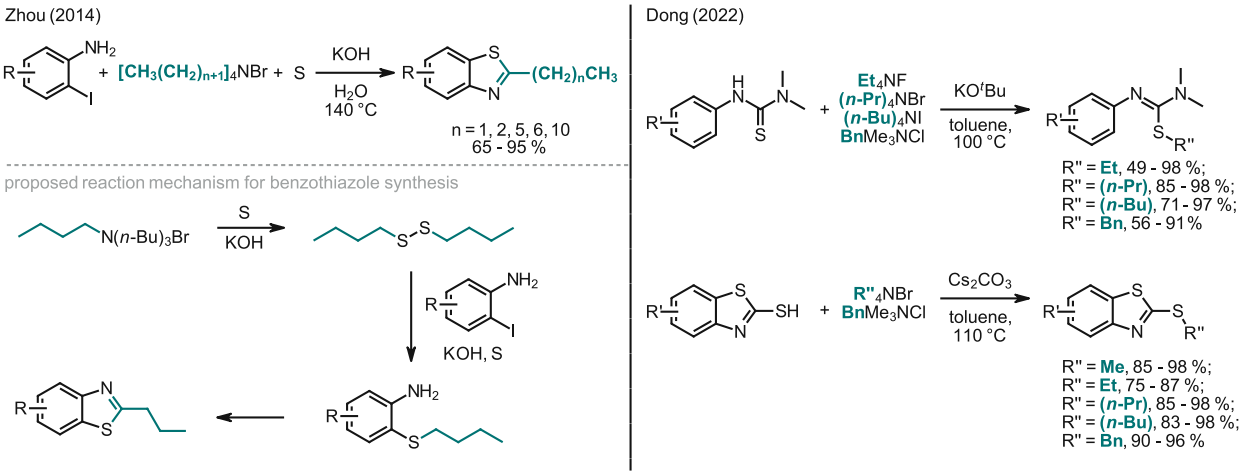
The protocol presented in manuscript 3 allowed for the mono-selective N-methylation of a range of amides, indoles, and related structures in up to quantitative yields (Scheme 7, right). We demonstrated that this method is also feasible for the mono-selective N-ethylation thereof using $PhEt_3NI$ under otherwise identical reaction conditions.



Scheme 7. Mono-selective N-methylation and N-ethylation of primary amides, indoles, and related structures using $PhMe_3NI$ or $PhEt_3NI$ as alkylating agent by Templ *et al.*[24b]

In 2014, Zhou and colleagues applied quaternary ammonium salts in a three-component reaction for the synthesis of benzothiazoles.[30] They utilized *o*-iodoaniline derivatives, quaternary ammonium salts, and elemental sulfur as powder under basic conditions in water at 140 °C. Within these reactions, the ammonium salt played a dual role as a phase transfer catalyst and an actual reagent. While ammonium salts bearing long-chain alkyl residues (R_4NBr, with $R = CH_3(CH_2)_n$ and $n \geq 6$) performed slightly better than short-chain analogs, the nature of the anion (for Bu_4NX with $X = I^-$, Br^-, Cl^-, F^-, HSO_4^-, OH^-, CH_3COO^-) did not significantly influence the reaction outcome (Scheme 8, left, top). Mechanistic investigations suggested that the initial step of the reaction is the formation of a disulfide ether by the reaction of sulfur with the ammonium species. This disulfide species subsequently reacts with the *o*-iodoaniline to form a 2-(butylthio)benzenamine intermediate, which eventually forms the benzothiazole product (Scheme 8, left, bottom).

A diverse set of benzothiazoles could be obtained in overall high yields. However, the authors did not comment on the use of Me_4NX or $PhMe_3NX$ salts, leaving the question of whether benzothiazoles with no substituent on the 2-position could be obtained by employing methyl-donating ammonium salts.

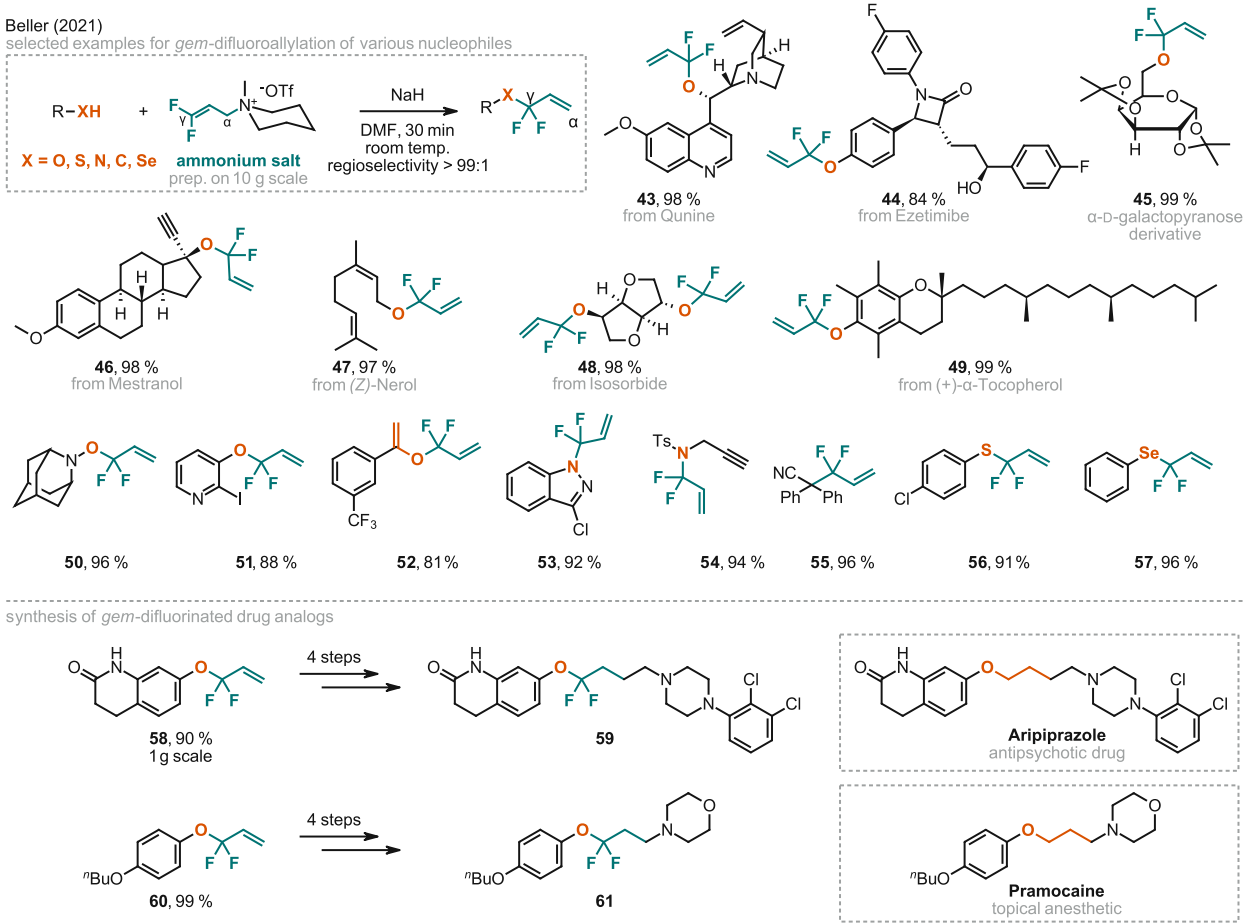


Scheme 8. Synthesis of benzothiazoles *via* a three-component reaction utilizing tetraalkylammonium salts as the alkylating agent by Zhou (left)[30] and the S-alkylation and S-benzylation of phenyl thioureas and 2-mercaptobenzothiazoles using alkyl and benzyl ammonium salts by Dong (right).[31]

Another protocol allowing for the alkylation of sulfur nucleophiles by quaternary ammonium salts was recently reported by Dong and co-workers.[31] They successfully alkylated and benzylated a set of phenyl thioureas and 2-mercaptobenzothiazoles under basic conditions in toluene at 110 °C using the respective tetraalkylammonium halides (R_4NX, with R = Me, Et, *n*-Pr, *n*-Bu) for S-alkylation or benzyl trimethylammonium bromide for S-benzylation. The desired products could be obtained in overall high yields with an average yield of >80 % (Scheme 8, right).

An utterly outstanding use of ammonium salts as alkylating agents was reported by the group of Beller in 2021.[32] They synthesized a class of novel 3,3-difluoroallyl ammonium salts which allowed for selective *gem*-difluoroallylation of diverse nucleophiles exhibiting an exceptional regioselectivity. This milestone marked the first example of introducing a

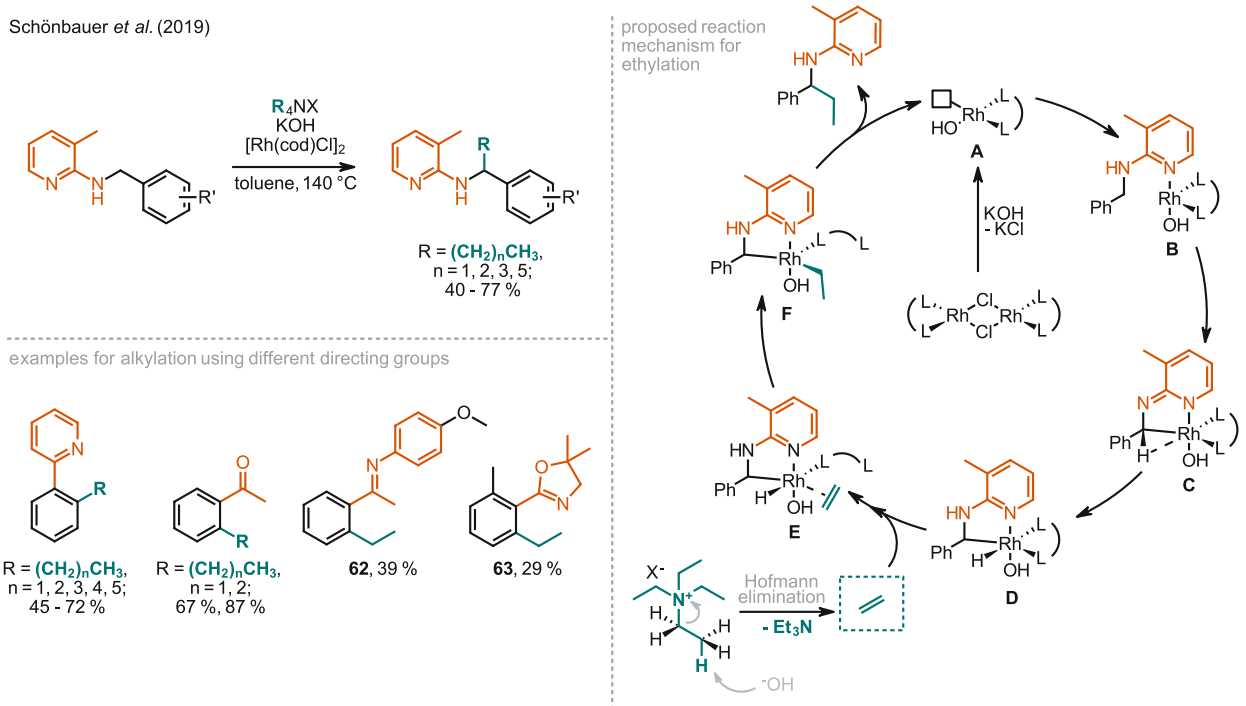
fluorinated hydrocarbon moiety with quaternary ammonium salts. NaH was used as base and the reaction proceeded in DMF at room temperature with a highly regioselective attack (>99:1) of the nucleophile at the γ-position. The ammonium salt could be easily prepared on a 10 g scale and stored under ambient conditions without detectable degradation. Various *O*-, *N*-, *S*-, *Se*-, and *C*-nucleophiles underwent *gem*-difluoroallylation in up to quantitative yields in only 30 minutes reaction time (Scheme 9, top). The authors demonstrated the applicability of this method for late-stage functionalization of bioactive compounds on an impressive number of structurally highly diverse natural products and drug molecules, including steroid derivatives **(46)**, carbohydrates **(45)**, tocopherol **(49)**, quinine **(43)**, nerol **(47)**, ezetimibe **(44)**, and isosorbide **(48)**. Furthermore, they synthesized *gem*-difluorinated analogs of approved drug candidates (Aripiprazole analog **59** and Pramocaine analog **61**) by employing their novel protocol and further modifying the introduced double bond. (Scheme 9, bottom)



Scheme 9. Selected examples for *gem*-difluoroallylation of various nucleophiles using 3,3-difluroallyl ammonium triflates as allylating agent (top) and the method's application for the synthesis of difluorinated drugs (bottom) by Beller.[32]

Metal-catalyzed aliphatic hydrocarbonylations using QAS

In recent years, QAS have gained significant attention as powerful electrophilic cross-coupling partners in metal-catalyzed transformations.[11a, 14] While various protocols have been developed to use aryl- and benzyl ammonium salts in Suzuki,[33] Negishi,[34] Buchwald-Hartwig,[35] Kumada,[36] and cross-electrophile couplings,[37] their application as alkyl, allyl, or propargyl donors in metal-catalyzed reactions, is still an under-explored field.

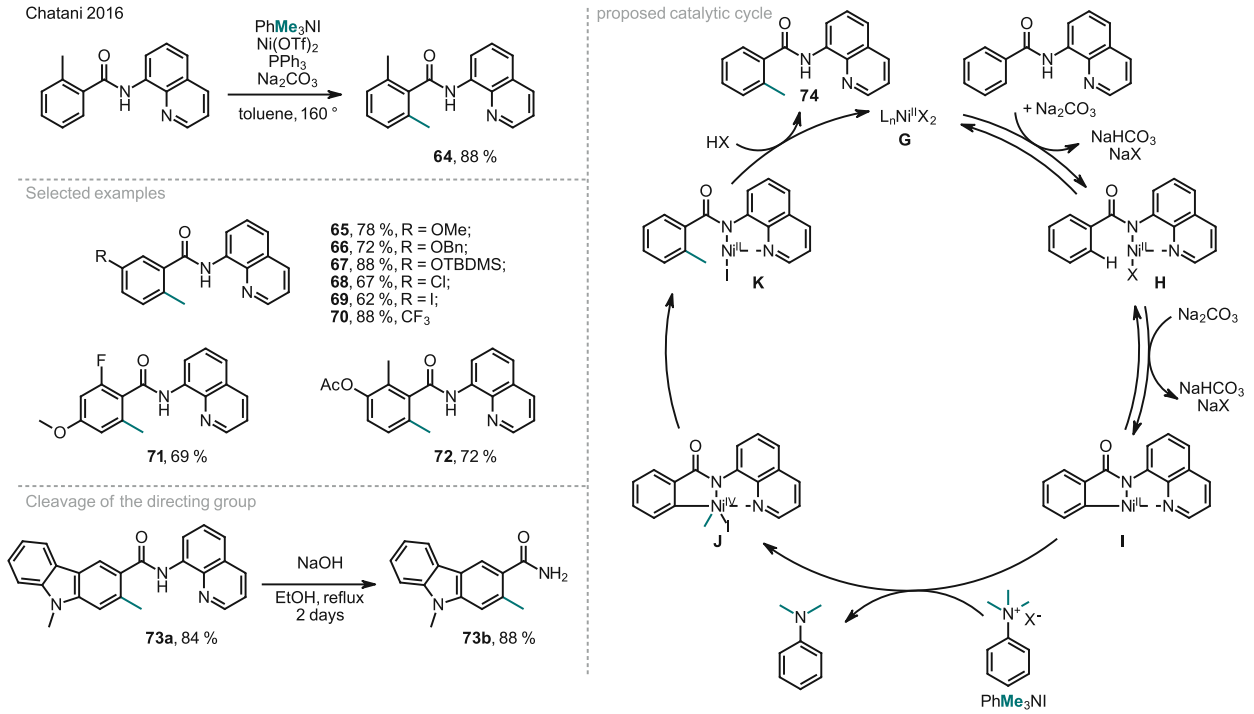


Scheme 10. C(sp^2)-Alkylation using tetraalkylammonium halides as olefin precursors *via* Rh-catalyzed directing group mediated C-H activation (left) and a proposed catalytic cycle for ethylation (right) by Schönbauer *et al.*[17b]

In 2017 and 2019, our group reported a novel approach utilizing QAS as alkylating agents in C-H activation reactions, exploiting the directing group ability of a 2-aminopyridine group for direct C-H alkylation on an adjacent benzylic position.[17] Interestingly, the QAS served as a solid olefin precursor, providing the desired gaseous reactant *in situ* and ensuring a high concentration of the unsaturated compound in the liquid phase (Scheme 10, right). This innovative method exploited an often-undesired reaction of QAS, the Hofmann elimination, under basic conditions, leading to the formation of unsaturated compounds. The elegance of this approach becomes evident, when considering that no special equipment

for external gas insertion is necessary, but the reaction vessel is simply charged by the solid and air-stable QAS and base, which delivers the gaseous reagent *in situ* upon reaction progress. Under rhodium catalysis at 140 °C in toluene using KOH as the base, they successfully performed C-alkylation on range of benzyl aminopyridines in 40 to 77 % yield, with the general trend observed that yield slightly decreased with growing alkyl chain length (68 % for ethylation using Et_4NBr vs. 61 % for *n*-hexylation using Hex_4NBr). Additionally, they tested other directing groups such as ketone, imine, oxazoline, and pyridine for direct C(sp^2)-alkylation on an adjacent aromatic system (Scheme 10, left).

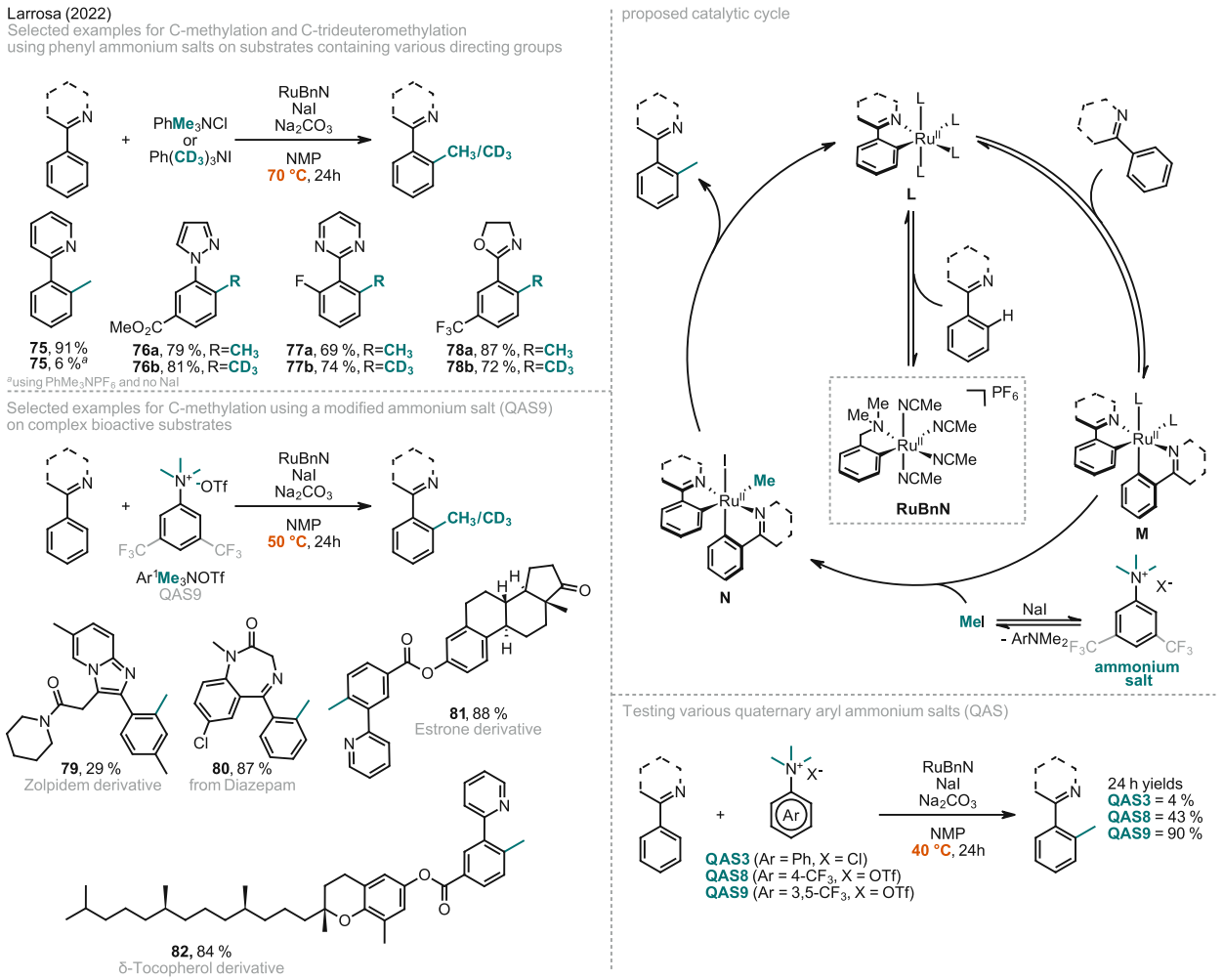
Other strategies employing QAS as alkyl donors in metal-catalyzed C-H activation reactions were presented by Chatani's group in 2016 and more recently by the Larrosa group. Both strategies utilized aryl trimethylammonium salts as methylating agent in a directing-group controlled C(sp^2)-methylation on an aromatic system.



Scheme 11. C(sp^2)-Methylation using $PhMe_3NI$ under Ni-catalysis and selected examples thereof (left, top), the cleavage of the 8-aminoquinoline directing group (left, bottom) and the proposed catalytic cycle (right) by Chatani.[38]

Chantani's protocol featured a $Ni(OTf)_2/PPh_3$ catalytic system operating under mild basic conditions (K_2CO_3) in toluene at a relatively high temperature of 160 °C.[38] Two equivalents of $PhMe_3NI$ were used to mono-selectively methylate a range of substituted aromatic amides in high yields up to 93 % with 8-aminoquinoline serving as directing group (Scheme 11, left, top). If necessary, this directing group can be cleaved under basic conditions giving the primary amides (Scheme 11, left, bottom). Mechanistic investigations unveiled a catalytic cycle operating *via* Ni^{II}/Ni^{IV} intermediates, excluding the involvement of radical intermediates (Scheme 11, right). Interestingly, no arylated products were detected. A plausible explanation might be that the authors employed a Ni^{II}-catalyst, whereas typical literature-known cross-coupling arylations using $PhMe_3NX$ are frequently catalyzed by Ni^0-species.[34-35, 39] This suggests that Ni^0 might not be a key intermediate in the catalytic-cycle of Chatani's methylation protocol. However, the authors could not rule out the possibility that MeI, originating from the thermal decomposition of the QAS, might serve as the actual methylating agent in this transformation.

Inspired Chatani's work and their previous research on RuBnN catalyzed alkylations using alkyl halides[40] the group of Larrosa introduced a ruthenium-catalyzed mono-selective C(sp^2)-methylation protocol broadly applicable for various substrates containing directing groups.[41] They employed either $PhMe_3NCl$ (Scheme 12, left, top) or an aryl-modified trimethylammonium triflate as the methyl precursor (Scheme 12, left, bottom). Detailed mechanistic studies suggested that MeI might act as the actual methylating agent, slowly released *in situ* from the QAS upon halogen exchange with NaI and subsequent thermal decomposition (Scheme 12, right, top). Under their optimized reaction conditions (5 mol% RuBnN, 2 equiv. NaI, 1 equiv. Na_2CO_3 in NMP at 70 °C), methylation of 2-phenylpyridine with $PhMe_3NCl$ gave the desired product in 91 % yield. In contrast, exchanging the ammonium salt for $PhMe_3NPF_6$ in the absence of NaI, where MeI formation is not possible, the product was obtained in a very poor yield of 6 %.
They tested several substituted phenylpyridines under the optimized reaction conditions using $PhMe_3NCl$ or $PhCD_3NI$, obtaining an impressive number of mono-methylated and mono-trideuteromethylated compounds with different functional groups well tolerated. Furthermore, pyrazoles, oxazolines, and pyrimidines were successfully utilized as directing groups in this conversion.

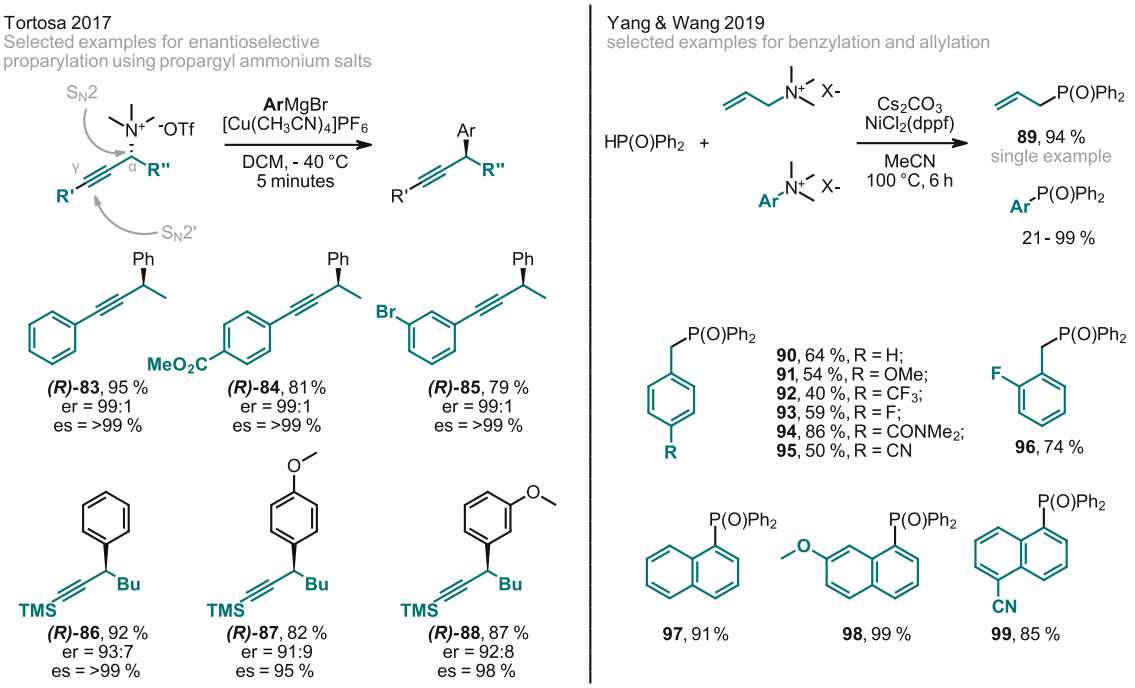


Scheme 12. C-Methylation and C-Trideuteromethylation using $PhMe_3NCl$ (left, top) and a modified aryl ammonium salt (QAS9; left bottom) by directing group mediated C-H activation with the proposed catalytic cycle (right, top) and the testing of aryl-modified ammonium salt for their influence of reaction rates by Larrosa.[41]

Despite these successes, initial attempts to apply the protocol using $PhMe_3NCl$ in late-stage methylation of complex bioactive compounds were ineffective. Inspired by the previously discussed study by Reid[23] on the rate of thermal decomposition of QAS, the Larrosa group hypothesized that modifying the aryl group in the aryl ammonium salt, particularly by attaching strongly electron withdrawing groups, might facilitate the release of MeI *in situ*, thereby increasing the overall reaction rate for methylation (Scheme 12, right, bottom). Introducing two CF_3 substituents on the aryl in *meta*-position led to a drastic increase in yield when now using this modified aryl ammonium salt (Ar^1Me_3NOTf, QAS9) for reactions that previously proceed rather sluggish with $PhMe_3NCl$. This optimized methyl donor

(Ar^1NMe_3OTf, QAS9) enabled the late-stage methylation of highly complex bioactive molecules in good to excellent yields (Scheme 12, left, bottom).

Early work by Langlois in 1979[42] and Hosomi in 1987,[43] focusing on the copper-catalyzed reaction of allyl ammonium salts with Grignard reagents, served as inspiration for the Tortosa group to explore the copper-catalyzed propargylation of aryl Grignard reagents using QAS as the propargylating agent (Scheme 13, left).[44]



Scheme 13. Enantioselective propargylation using chiral propargyl ammonium triflates and Grignard reagents by Tortosa (left)[44] and selected examples of P-arylation, -benzylation, and -allylation using aryl and allyl ammonium triflates by Yang & Wang (right).[45]

In their protocol, they utilized a commercially available $Cu(CH_3CN)_4PF_6$ catalyst, and the reaction took place in dichloromethane at -40 °C with an impressively fast reaction time of 5 minutes. The authors proposed that the reaction proceeds *via* an S_N2 pathway involving an aryl cuprate intermediate, although in-depth mechanistic investigations were not provided. Notably, this method ensured both an exclusive α-regioselective attack of the Grignard reagent and a highly stereospecific outcome with complete inversion of the stereogenic center in the substrate. The propargylation reaction demonstrated a broad substrate compatibility, allowing for the use of various aryl propargyl ammonium triflates

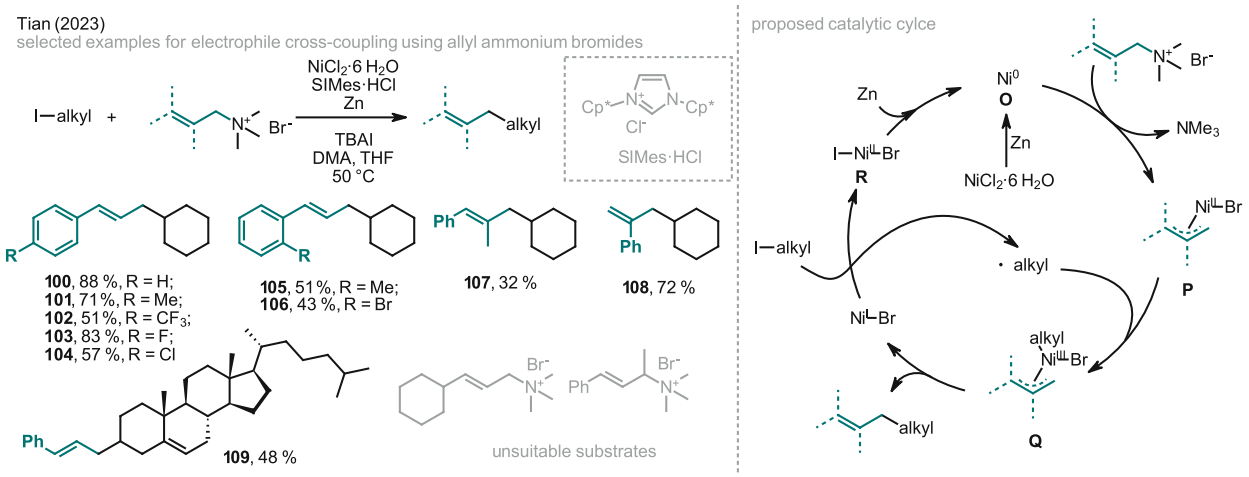
with different substituents on the aryl group. These substrates provided the corresponding alkynes in high yields, with some reaching up to 93 %. Additionally, TMS-acetylene-containing ammonium salts readily reacted with phenyl Grignard reagents, further expanding the applicability of the method.

As previously mentioned, the leaving group ability of a quaternary ammonium moiety in the allylic position makes it suitable for nucleophilic substitution, as demonstrated in the work of Beller and colleagues.[32] This characteristic can be further exploited in various metal-catalyzed reactions. Similar to the mechanism observed with allyl halides, the metal can coordinate to the unsaturated ammonium compound and upon leaving group elimination (NR_3), an η^3-complex is formed. This intermediate can then undergo addition, insertion, or elimination reactions. Despite its potential, the utilization of quaternary allyl ammonium compounds in metal-catalyzed allylation reactions remains significantly underexplored.

In 2019, Yang and Wang investigated the utilization of ammonium salts in Ni-catalyzed cross-coupling reactions for C-P bond formation.[45] Under basic conditions in acetonitrile at 100 °C using $NiCl_2$(dppf) as catalyst, a range of benzylated and arylated diphenylphosphine oxides could be obtained using the respective benzyl or aryl ammonium triflates (Scheme 13, right). However, their investigation into aliphatic hydrocarbonylations was limited, with the allylation of diphenylphosphine oxide achieved in 94 % yield using allyl trimethylammonium triflate as the single example provided.

More recently, Tian and co-workers disclosed a protocol for Ni-catalyzed reductive cross-electrophile coupling using allyl trimethylammonium bromides and alkyl iodides for C(sp^3)-C(sp^3) bond formation.[46] Their system featured $NiCl_2$ $6H_2O$ (10 mol%), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene hydrochloride (SIMes · HCl, 15 mol%), four equivalents of Zn, and tetrabutylammonium iodide (TBAI) in a dimethylamine/water mixture at 50 °C. The reaction proceeded smoothly for a range of cinnamyl-derived ammonium salts and similar structures bearing a phenyl substituent in γ-position, giving exclusively linear products in 32 to 88 % yield. However, the allyl ammonium scope seemed to be limited to α-unsubstituted cinnamyl derived structures. The reaction with α-methyl cinnamyl and γ-cyclohexyl allyl containing ammonium salts failed (Scheme 14, left).

Mechanistic investigations and radical trapping experiments suggested a pathway involving the formation of an alkyl radical from homolytic alkyl iodide cleavage, which subsequently attacked the previously formed Ni-allyl complex (Scheme 14, right).



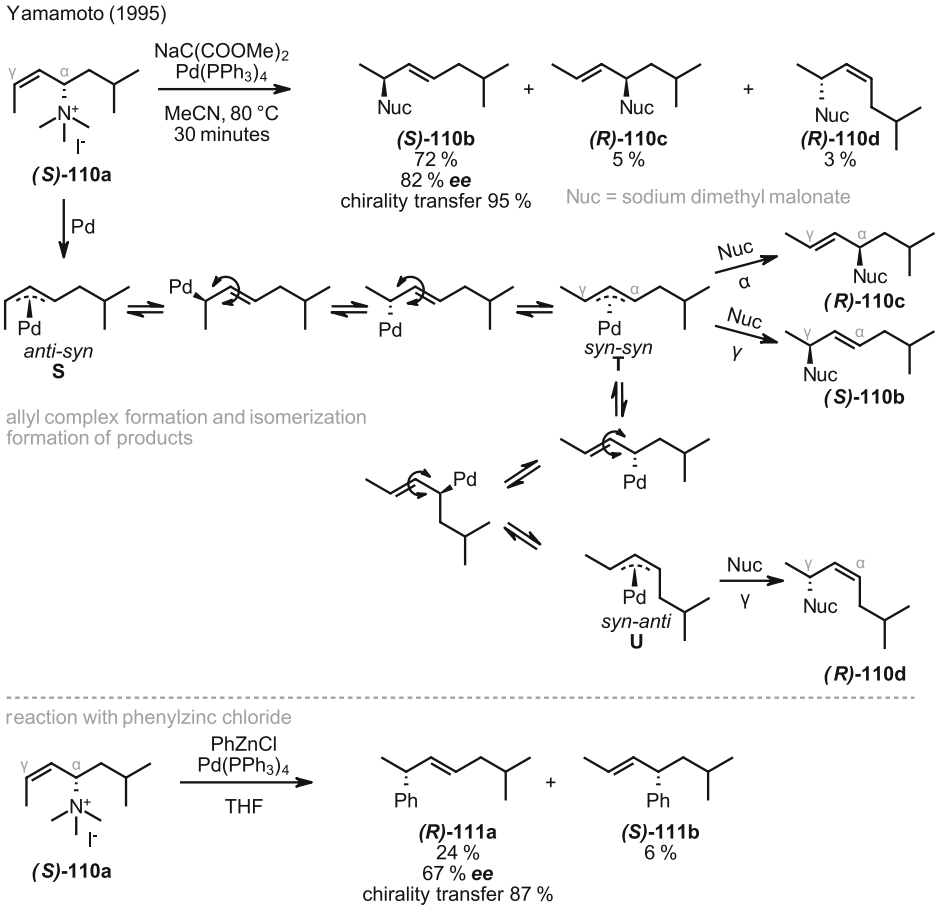
Scheme 14. Nickel-catalyzed reductive cross-electrophile coupling using allyl trimethylammonium bromides (left) and the proposed catalytic cycle (right) by Tian.[46]

Palladium is well known to undergo η^3-complex formation and readily facilitates allylic substitution reactions of nucleophiles. This type of reaction, named after two pioneers in the field, Jiro Tsuji and Barry Trost, is a very prominent and fundamental reaction in organic chemistry.[47] Nowadays, several protocols for Tsuji-Trost type reactions involving different catalytic systems and a wide array of allylic compounds are well established.[47-48] Leaving groups in allylic position are crucial for facilitating Pd-η^3-complex formation, which can then be attacked by a nucleophile. Commonly used leaving groups include halides, carbonates, acetates, amides, and hydroxy groups.[47a, 48a] However, quaternary ammonium salts are still seldomly employed as leaving groups.[42-43, 49]

In an early work, Yamamoto and co-workers investigated the use of chiral allyl ammonium salts and their potential for chirality transfer in a Pd-catalyzed allylation of carbon nucleophiles, particularly sodium dimethyl malonate. For chiral ammonium compound *(S)*-**110a**, the reaction yielded a product *(S)*-**110b** with the newly formed C-C bond predominantly in γ-position of the leaving group in a maximum yield of 73 % and a remarkable chirality transfer of 95 % (Scheme 15, top). The authors hypothesized that the initially formed, stereoinverted *anti-syn*-ally Pd-complex (S) rapidly epimerizes towards a

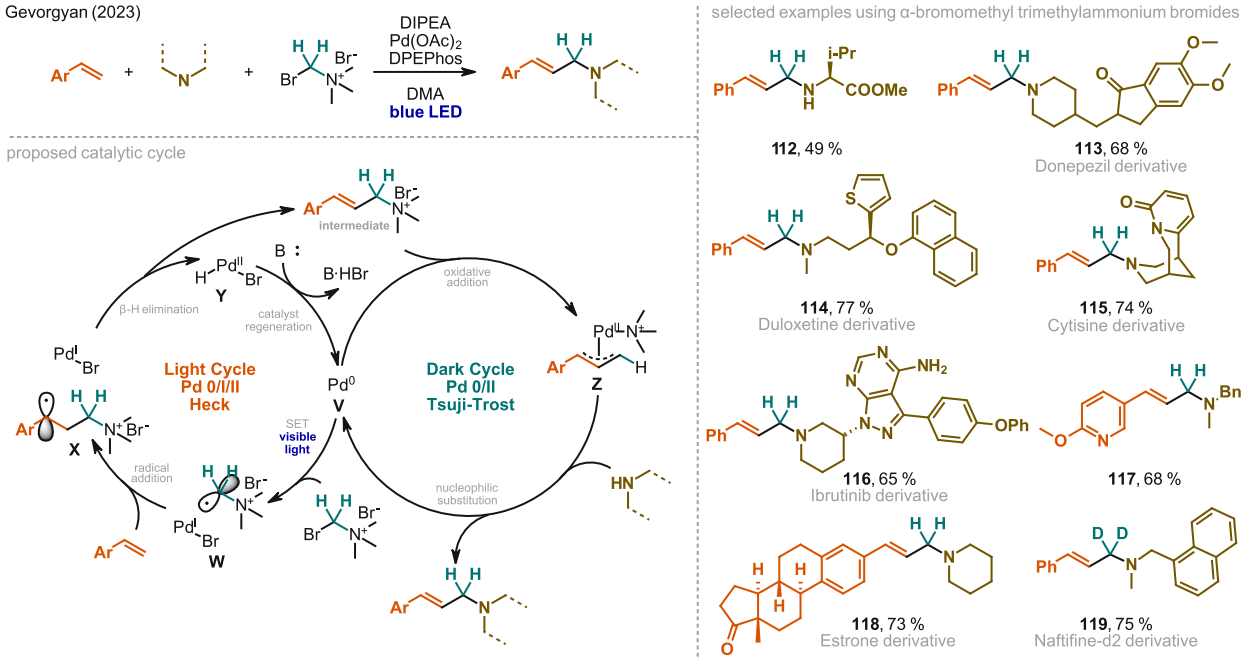
more stable *syn-syn*-complex (**T**). The soft nucleophile subsequently attacks the η^3-complex from the less sterically hindered side, being the opposite face with respect to the palladium, resulting in the product with net retention of the starting materials' stereochemistry (Scheme 15, middle).

They also tested phenylzinc chloride considered as hard nucleophile, which should theoretically add directly to the metal of the intermediate allyl-palladium complex and then undergo reductive elimination, resulting in a net stereoinverted product. However, the reaction with phenylzinc chloride in THF yielded two products, ***(R)*-111a** and ***(S)*-111b**, in a 4:1 ratio and a relatively poor yield of 30 %, with a significantly reduced chirality transfer of 87 % for compound ***(R)*-111a** (Scheme 15, bottom). Further investigations to expand the scope or improve the stereocontrol of these reactions have not been conducted to date.



Scheme 15. Pd-catalyzed allylation of chiral ammonium salts with dimethyl malonate (top) and phenylzinc chloride (bottom) by Yamamoto.[50]

However, considering the vast natural feedstock for chiral amines that can be easily converted into their quaternary ammonium analogs by exhaustive alkylation, this strategy holds great potential to access novel enantiomerically enriched compounds.



Scheme 16. Three-component homologative Heck/Tsuji-Trost reaction involving α-halomethyl ammonium salts proceeding in a light and dark cycle (left, bottom) and selected examples (right) by Gevorgyan.[49d]

Another groundbreaking work in the field of Pd-catalyzed allylations using allyl ammonium salts was recently reported by the Gevorgyan group.[49d] Their outstandingly elegant approach combined a photocatalyzed Heck reaction (light cycle) with a Tsuji-Trost reaction (dark cycle) using a single catalyst in a homologative three-component reaction (Scheme 16. left). A 1,1-dielectrophile, particularly an α-halomethyl ammonium salt, was coupled with a styrene derivative in the first step. The resulting allyl ammonium product then immediately underwent a Tsuji-Trost reaction with a variety of primary and secondary nitrogen nucleophiles. Interestingly, the stereocontrol of the Tsuji-Trost reaction was solely governed by steric effects of the former 1,1-dielectrophile. Tested for a range of substituted 1,1-dibromides, the authors found that sterically demanding groups on the 1,1-dielectrophile, such as silyl ethers, governed the nucleophilic attack towards the γ-position of the allyl intermediate. In contrast, non-substituted α-bromomethyl trimethylammonium bromides ($(BrCH_2)Me_3NBr$) and α-bromodeuteromethyl trimethylammonium bromides ($(BrCD_2)Me_3NBr$) are substituted exclusively on the α-position. Using a

$Pd(OAc)_2$/DPEPhos catalytic system with *N*,*N*-diisopropylethylamine (DIPA) as the base and dimethylamine (DMA) as solvent under blue light irradiation, an impressive number of complex bioactive *N*-nucleophiles and styrene derivatives were successfully coupled *via* α-halomethyl ammonium dielectrophiles giving the desired homoelongated products in high average yields up to 80 % (Scheme 16, right).

Encouraged by our experience in using QAS as solid alkylating agents, we were prompted to further advance the rater unexplored field of utilizing these compounds in Tsuji-Trost type reactions (Manuscript 4).[51]

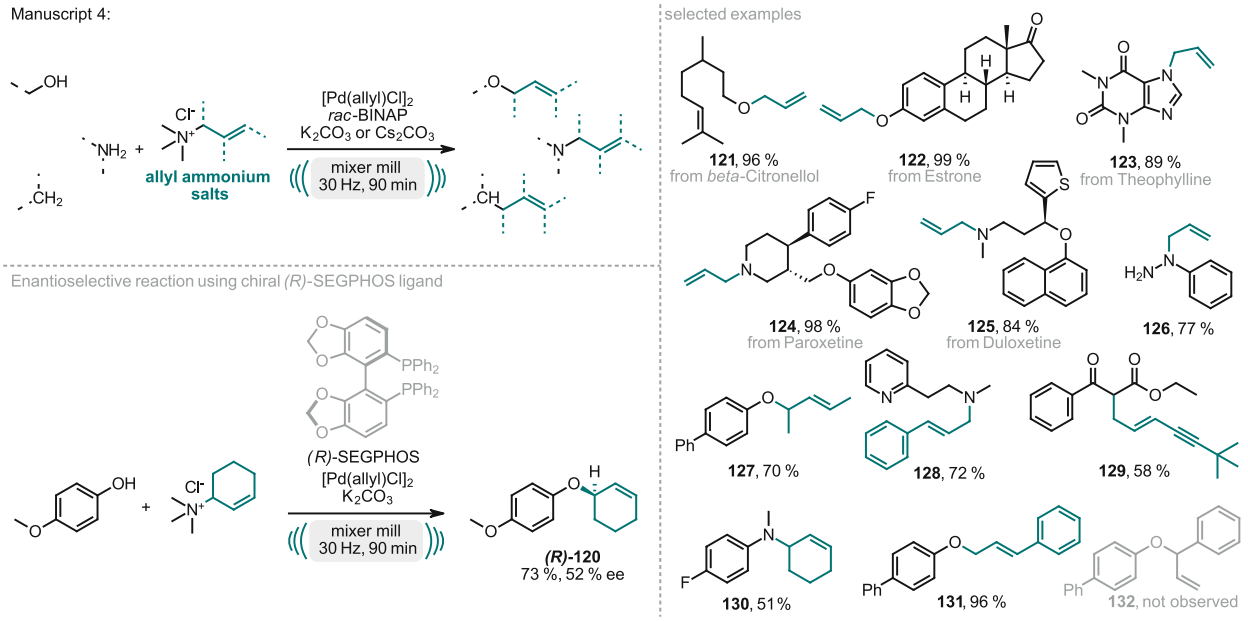
Furthermore, we aimed to make this transformation as environmentally benign as possible and thus highly attractive for fine-chemical and pharmaceutical industries. One significant cost and environmental factor for these industries is the vast amount of solvent waste generated during product synthesis, work-up procedures, and purification.[52] One strategy to clearly reduce solvent waste production in synthesis is conducting reactions in a solvent-free fashion.[53]

Generally speaking, the energy required for chemical conversion can be provided by conventional means of external heating or by less conventional methods such as light irradiation or mechanical force. However, conducting bulk reactions under neat conditions often comes with significant challenges regarding this energy provision: an insufficient mixing of the reactants can drastically affect heat transfer and/or light absorption and distribution. One strategy to overcome this limitation is switching from bulk to a flow reaction setup and by this means increase the overall surface area of the reaction, which allows for more efficient energy transfer. However, conducting a reaction in flow becomes complicated when all reactants are solid.[54] Mechanochemistry, a concept known for decades,[55] provides a solution by applying mechanical force to efficiently mix solid reaction components and provide the energy needed for chemical conversion through impact and shear force.[53, 56] This approach, previously realized by manually mixing the reaction components with a mortar and pistil, can now be fully automated in milling devices such as planetary or mixer mills and extruders.[55, 57]

Mechanochemistry offers several distinct advantages: As already mentioned, reactions can be conducted either completely solvent-free or with a minimal amount of solvents, a concept termed as liquid assisted grinding.[58] Furthermore, mechanochemical reactions often exhibit

significantly faster reaction rates compared to reactions in solution. Additionally, solvent-free mechanochemical reactions often result in increased stability of transition-metal catalysts towards air and moisture. This means that reactions that typically require an inert atmosphere when conducted in solution can be frequently performed at ambient atmosphere in a solvent-free setup.[53, 55-57, 59]

We recently established a mechanochemically driven Tsuji-Trost reaction using allyl ammonium salts as solid and non-toxic alternative allylating agents (manuscript 4).[51] Applying a $Pd(allyl)_2Cl_2$/*rac*-BINAP catalytic system with remarkably low catalyst and ligand loadings of 0.5 mol% and 1 mol%, respectively, in combination with a mild carbonate base, we successfully performed the allylation of various *O*-, *N*-, and *C*-nucleophiles in up to quantitative yield within short reaction times of 90 minutes (Scheme 17, left, top). Remarkably, we could prove the methods' potential for an application in late-stage allylation of various complex bioactive molecules.



Scheme 17. Pd-Catalyzed mechanochemically driven Tsuji-Trost allylation (left, top), selected examples (right), and an example for an enantioselective reaction using chiral *(R)*-SEGPHOS ligand, cf. Manuscript 4.[51]

A range of electrophilic allyl ammonium salts could be easily synthesized from the respective chlorides with a solution of trimethylamine in EtOH and subsequently applied in this protocol. We found that as little as 5 equivalents of water drastically increased the reaction

rates. However, further research on the role that water in this reaction needs to be conducted.[60]

For unsymmetrically substituted allyl ammonium salts, such as the ammonium salt derived from cinnamyl chloride, linear products were obtained (cf. **131** and **132**) exclusively by full conversion, with silica filtration sufficient to obtain pure products. In contrast, performing the reaction with cinnamyl chloride directly under the optimized conditions resulted in a crude mixture of linear and branched products alongside leftover starting material (Scheme 17, right).

Finally, we tested a small set of chiral ligands on a suitable prochiral substrate for enantioselective reaction, with *(R)*-SEGPHOS giving an enantioenriched cyclohexenyl ether ***(R)*-120** in 52 % enantiomeric excess (***ee***) (Scheme 17 left, bottom). With this successful demonstration of the first ligand-induced enantioselective mechanochemical reaction, we established a starting point for further efforts to increase the ***ee*** of this transformation.[61]

I sincerely hope this work contributes to a better understanding and increased application of quaternary ammonium salts as alternative solid reagents in aliphatic hydrocarbonylation reactions and further promotes mechanochemistry as powerful reaction setup for more sustainable and environmentally benign syntheses.

A II Additional Note

The introduction of this thesis was adapted and submitted as an invited review with the title *"Strategies for using Quaternary Ammonium Salts as Alternative Reagents in Aliphatic Hydrocarbonylations"* to Chemistry – a European Journal on 19th of february 2024.

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B Contributions

B I List of Contributions

Manuscript 1

Johanna Templ and Michael Schnürch

Selective α-Methylation of Aryl Ketones Using Quaternary Ammonium Salts as Solid Methylating Agents

J. Org. Chem. 2022, 87, 6, 4305 – 4315. doi: 10.1021/acs.joc.1c03158

Manuscript 2

Johanna Templ and Michael Schnürch

A Guide for Mono-Selective N-Methylation, N-Ethylation, and N-*n*-Propylation of Primary Amines, Amides, and Sulfonamides and Their Applicability in Late-Stage Modification

Chem. Eur. J. 2024, e202304205. doi: 10.1002/chem.202304205

Manuscript 3

Johanna Templ, Edma Gjata, Filippa Getzner, and Michael Schnürch

Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents

Org. Lett. 2022, 24, 40, 7315–7319. doi: 10.1021/acs.orglett.2c02766

Manuscript 4

Johanna Templ and Michael Schnürch

Allylation of *C*-, *N*-, and *O*-Nucleophiles *via* a Mechanochemically-Driven Tsuji–Trost Reaction Suitable for Late-Stage Modification of Bioactive Molecules

Angew. Chem. Int. Ed. 2024, 63, e202314637. doi: 10.1002/anie.202314637

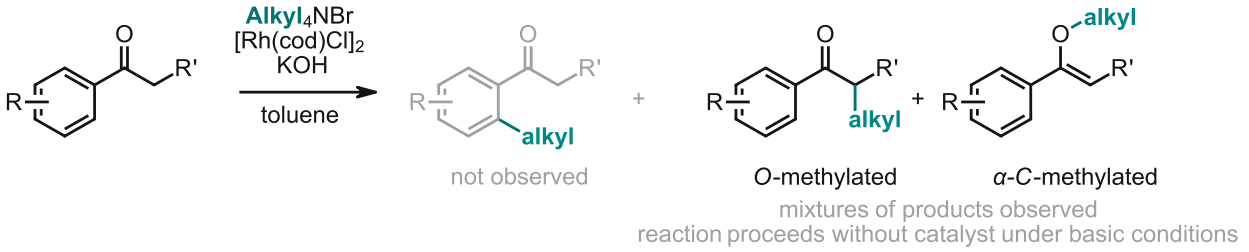
B II Context of Contributions

The following section contains a concise summary of each manuscript, outlining the initial idea and the subsequent outcome.

B II.1 Manuscript 1

Selective α-Methylation of Aryl Ketones Using Quaternary Ammonium Salts as Solid Methylating Agents

This publication represents the first investigations into the utilization of quaternary ammonium salts (QAS) as solid alternatives for methylating agents in our research group. Originally, our aim was to employ QAS as alkylating agents in directing group-mediated metal-catalyzed alkylation reactions, building upon previous work within our group.[1] However, during the screening for suitable directing groups, we discovered that a ketone moiety, intended to serve as a directing group for transition-metal catalyzed C(sp^2)-alkylation, was alkylated to a significant extent at the α-carbon and enol oxygen under basic conditions, even in the absence of a metal catalyst (Scheme B II.1).



Scheme B II.1. Preliminary observations during the investigation of metal-catalyzed C-H alkylation using tetraalkylammonium bromides.

Consequently, our focus shifted to methylation reactions using quaternary ammonium halides as alternative methylating agents, since traditionally applied methylating agents pose far more exposure risks than longer chain alkylating agents. Subsequent optimization efforts aimed to favor the formation of the α-*C*-methylated product over the *O*-methylated product. While tetramethylammonium halides initially yielded a 1:1 mixture of *O*-Me and α-*C*-Me species, we found that phenyl trimethylammonium iodide provided the desired α-C-methylated product in a synthetically useful yield. Further investigations were conducted to elucidate the mechanism of this methylation reaction, specifically whether it

proceeds *via* direct nucleophilic attack on the ammonium salt in an S_N2-fashion or if the ammonium salt thermally decomposes to generate MeI, serving as the actual methylating agent. One experiment involved methylation using Me_4NOAc, which upon thermal decomposition could yield MeOAc, a species unsuitable as a methylating agent in this reaction. However, under our reaction conditions, the use of Me_4NOAc resulted in the formation of methylated products in a 5.3:1 ratio of *O*-Me to α-*C*-Me giving hints on a S_N2 mechanism. Additional details can be found in the manuscript and supporting information.

B II.2 Manuscript 2

A Guide for Mono-Selective N-Methylation, N-Ethylation, and N-*n*-Propylation of Primary Amines, Amides, and Sulfonamides and Their Applicability in Late-Stage Modification

This comprehensive review provides an overview of current methodologies for the mono-selective N-methylation, N-ethylation, and N-*n*-propylation of primary amines, amides, and sulfonamides. It also highlights the potential of selected strategies for the late-stage modification of bioactive compounds. Various alkylating agents are discussed within this context, including unconventional and environmentally friendly alternatives aimed at promoting more sustainable syntheses.

B II.3 Manuscript 3

Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents

This research builds upon the project outlined in manuscript 1. Motivated by earlier investigations into N-methylation using QAS,[2] we expanded our established protocol to facilitate N-methylation employing $PhMe_3NI$ for primary amides. Encouragingly, this protocol demonstrated remarkable mono-selectivity in this N-methylation reaction. We replaced KOH with an even milder base (Cs_2CO_3) and subsequently broadened our protocol to encompass indoles and related structures.

B II.4 Manuscript 4

Allylation of *C*-, *N*-, and *O*-Nucleophiles *via* a Mechanochemically-Driven Tsuji–Trost Reaction Suitable for Late-Stage Modification of Bioactive Molecules

Prompted by the scarce use of quaternary ammonium groups in allylic position within palladium-catalyzed allylation reactions,[3] our aim was to broaden this limited scope and establish allyl ammonium salts as viable allylating agents in such transformations. The reaction proceeds *via* a Tsuji-Trost type allylation, with the ammonium moiety serving as a leaving group in the allylic position, facilitating the formation of the active allyl-palladium complex, which can then be attacked by a nucleophile. Preliminary experiments were conducted in toluene at 60 °C with 4-phenylphenol serving as the nucleophile, allyl trimethylammonium chloride and substoichiometric amounts of Cs_2CO_3 using $Pd(allyl)_2Cl_2$/*rac*-BINAP as catalytic system[4] and we could observe a significant amount of the O-allylated product formed. Given that all reactants were solids, we investigated whether the reaction could be performed in a mechanochemical setup. Encouragingly, the reaction proceeded smoothly, affording the desired allylated products in high yields and purity. Lastly, we screened a small set of chiral ligands for an enantioselective reaction with a prochiral allyl ammonium salt, identifying *(R)*-SEGPHOS as the best-performing ligand, albeit with a moderate enantiomeric excess of 52%. Further efforts to enhance the enantioselectivity of this reaction are currently underway in our laboratories.

B III Literature – Contributions

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C Statement of Contributions

Manuscript 1

The applicant, **Johanna Templ**, conducted the synthetic work, which involved reaction optimization, design, synthesis of compounds within the substrate scope, and experiments required during the manuscript revision. The manuscript was composed by the applicant. Michael Schnürch and Johanna Templ contributed to the experimental design, manuscript discussion, and corrections.

Manuscript 2

The applicant composed and researched the review. Michael Schnürch and Johanna Templ contributed to the manuscript discussion and correction.

Manuscript 3

The applicant initiated the research and planned the reaction design. The main synthetic work was performed by the applicant. Edma Gjata contributed to the reaction optimization and the substrate scope of the methylation reaction. Filippa Getzner added to the substrate scope for the ethylation reaction. The applicant composed the manuscript and conducted additional synthetic work necessary for the review process. Michael Schnürch and Johanna Templ contributed to the manuscript discussion and correction.

Manuscript 4

The applicant initiated the research and devised the reaction design. All synthetic work, including reaction optimization and synthesis of the substrate scope, was carried out by the applicant. The applicant composed the manuscript. Michael Schnürch and Johanna Templ contributed to the manuscript discussion and correction.

D Original Work

D I.1 Manuscript 1

Johanna Templ and Michael Schnürch

Selective α-Methylation of Aryl Ketones Using Quaternary Ammonium Salts as Solid Methylating Agents

J. Org. Chem. 2022, 87, 6, 4305 – 4315. doi: 10.1021/acs.joc.1c03158

JOC The Journal of Organic Chemistry

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Selective α-Methylation of Aryl Ketones Using Quaternary Ammonium Salts as Solid Methylating Agents

Johanna Templ and Michael Schnürch*

Cite This: J. Org. Chem. 2022, 87, 4305−4315 Read Online

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ABSTRACT: We describe the use of phenyl trimethylammonium iodide ($PhMe_3NI$) as an alternative methylating agent for introducing a CH_3 group in α-position to a carbonyl group. Compared to conventional methylating agents, quaternary ammonium salts have the advantages of being nonvolatile, noncancerogenic, and easy-to-handle solids. This regioselective method is characterized by ease of operational setup, use of anisole as green solvent, and yields up to 85%.

INTRODUCTION

Incorporating a methyl group into small organic or bioactive molecules can positively affect their physical properties and biological effectiveness.[1,2] The latter feature is commonly referred to as the "magic methyl effect".[3] This renders the methyl group a prevalent structural motif in small-molecule drugs.[4,5] Owing to its considerable impact, a late-stage introduction of a CH_3 group has become a particularly promising strategy in drug discovery.[6−8] Hence, the development of efficient and new strategies for selective methylation attracts broad interest in medicinal chemistry and basic research, respectively.[9−13]

Traditionally applied methylating agents often suffer from inconvenient physical properties (*e.g.*, MeBr, b.p. 4 °C, MeI, b.p. 42 °C) or high toxicity (*e.g.*, MeI, Me_2SO_4). Several organometallic reagents used for methylation (*e.g.*, $MeB(OH)_2$, Me_4Sn, Me_3Al, MeMgCl, or Me_2Zn) are quite challenging to handle, as some are air-sensitive, show low functional group tolerance, or have to be freshly prepared.[14,15] These toxicological and safety concerns encouraged us to search for a novel, safe, and easy-to-handle reagent for direct methylation. From previous findings in our group, we established different quaternary ammonium salts as alkylating agents in metal-catalyzed C−H activation reactions.[16,17]

The predominant role of quaternary ammonium salts in organic reactions is their application as phase transfer catalysts[18] and ionic liquids.[19] However, their use as alkylating agents in general and methylating agents in particular is quite an unexplored field. There are a few reports on *O*-methylation of phenolic compounds with tetramethylammonium chloride (Me_4NCl, Figure 1, I)[20,21] or hydroxide (Me_4NOH)[22] and phenyl trimethylammonium ($PhMe_3NCl$) chloride.[21] *N*-Methylation *via* ammonium salts was achieved in azahetero-

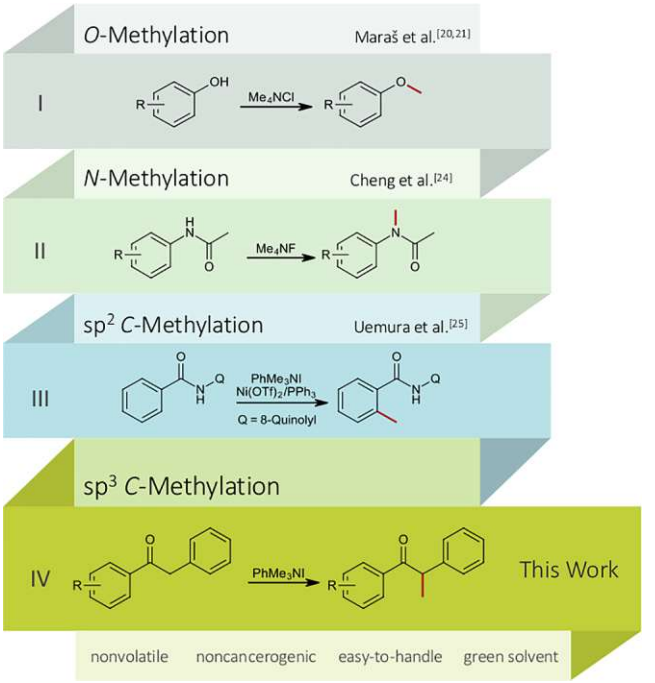
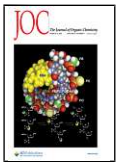


Figure 1. Methylation strategies using quaternary ammonium salts.

Received: December 30, 2021
Published: March 7, 2022



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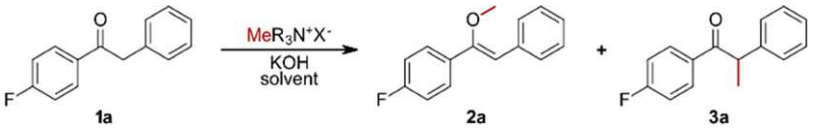
J. Org. Chem. 2022, 87, 4305−4315

Table 1. Optimization of the Reaction Conditions[a]



			yield (%)[b]		
entry	solvent	ammonium salt	1a	2a	3a
1	toluene	Me_4NBr	0	41	34
2	MeTHF[c]	Me_4NBr	25	14	11
3	anisole	Me_4NBr	0	40	43
4	CPME	Me_4NBr	4	36	24
5	anisole	Me_4NCl	0	43	42
6	anisole	Me_4NI	30	23	29
7[d]	anisole	Me_4NOAc	0	49	9
8	anisole	$PhMe_3NCl$	0	47	48
9	anisole	$PhMe_3NBr$	0	38	50
10	anisole	$PhMe_3NI$	0	18	78
11	anisole	Bu_3MeNCl	6	25[e]	39
12	anisole	$BnMe_3NCl$	0	0	0[f]
13	anisole	$(C_{16}H_{33})Me_3NBr$	0	47	25
14	anisole	betaine	30	2	5

[a]Reactions were performed on a 0.23 mmol scale, with KOH (2 equiv) as base, and 1.5 equiv of the ammonium salt under Ar atmosphere; reaction times: 22 h (entries 1−4) and 18 h (entries 5−15), 130 °C. [b]Yield was determined by ^{19}F NMR using trifluoro toluene as internal standard. [c]100 °C. [d]Reaction time 3 h. [e]13% *O*^{n}Bu-ether formation. [f]64% α-benzylation.

cycles using tetramethylammonium bromide (Me_4NBr)[23] and more recently in amides, N-heterocycles, alcohols, and thiols using tetramethylammonium fluoride (Me_4NF, Figure 1, II).[24] Direct methylation of C(sp^2)−H bonds using phenyl trimethylammonium iodide and bromide as methyl source was realized by Uemura et al.[25] under Ni^{II}-catalysis (Figure 1, III).

With the below-described novel, safe, and metal-free method for α-methylation, we want to set a starting point in the relatively uncharted field of using quaternary ammonium salts as alkylating agents for C(sp^3)−H bonds (Figure 1, IV).

RESULTS AND DISCUSSION

We started by investigating the methylation of benzyl 4-fluorophenyl ketone **1a** since quantification in all optimization steps can be accomplished *via* ^{19}F NMR using trifluoro toluene as an internal standard without preceding workup or solvent removal. Initially, Me_4NBr was used as the methylating agent and KOH as the base in toluene at 130 °C. Here, we observed the methyl enol ether **2a** and the α-methylated product **3a** forming in a 1.2:1 ratio (Table 1, Entry 1). In a next step, it was investigated whether switching the solvent could shift the product distribution toward the desired product **3a**. Since the process should be as benign as possible, we aimed to find a suitable green solvent in combination with an inexpensive base. 2-Methyl-THF, anisole,[26] and cyclopentylmethylether[27] are considered green solvents and were tested (among others; see the SI for full list) in this transformation. Anisole (entry 3) showed the highest overall conversion and additionally slightly favored the desired product **3a** (entry 3, 1:1.08 ratio of **2a** and **3a**). 2-Methyl-THF and cyclopentylmethylether gave lower conversion and additionally favored the undesired product **2a** (entries 2 and 4). Other benign solvents proved to be inefficient (see complete solvent screening list in the SI). We further investigated the influence and efficiency of different bases. Hydroxy bases gave the best yields, with the initially used KOH surpassing NaOH. KO^{t}Bu and Cs_2CO_3 showed significantly lower conversion. The other bases tested turned out to be inefficient (see the SI for details).

Before continuing with optimization of the methylating reagent, it was tested whether the *O*- and the α-methylated products **2a** and **3a** are formed independently or whether **2a** might be the actual methylating agent. The kinetic profile showed that both the *O*- and the α-methylated product are formed simultaneously under the given reaction conditions within 30 minutes, and no shift in product ratio could be observed at prolonged reaction times (see Figure 2). Furthermore, enol ether **2a** was subjected to the reaction conditions without any formation of **3a**.

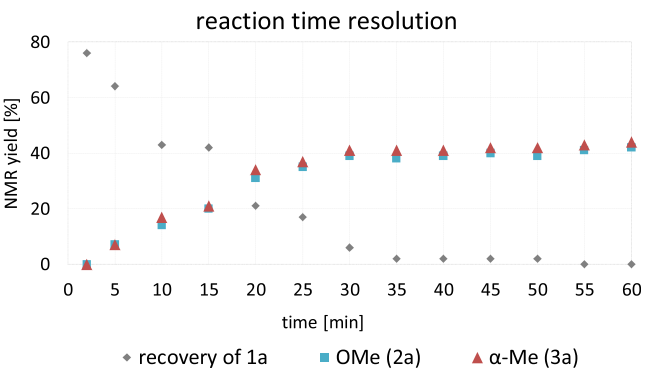


Figure 2. Reaction time screening; conditions: Me_4NBr (1.5 equiv), KOH (2 equiv), anisole (0.2 M), 130 °C.

And finally, a 1:1 mixture of **1a** and **2a** was subjected to the reaction conditions in the absence of Me_4NBr without any formation of **3a**. This excludes that the two products are interconvertible under the applied conditions and are indeed formed independently (*cf.* Table 2).

https://doi.org/10.1021/acs.joc.1c03158
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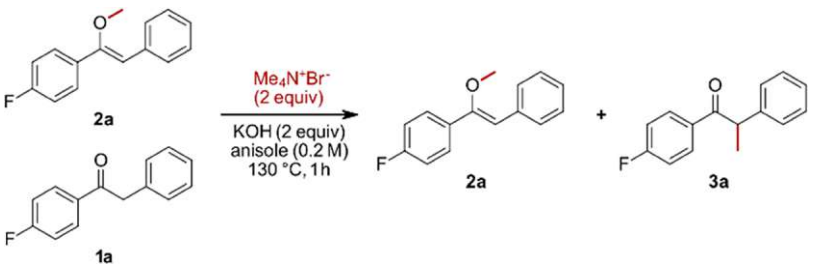
Table 2. Studies for Interconversion of Products 2a and 3a



	substrate		yield (%)[b]		
entry	**1a** [mmol]	**2a** [mmol]	**1a**	**2a**	**3a**
1	0.093		0	42	43
2	0.047	0.044	0	73	9
3		0.088	0	86	0
4[a]	0.047	0.044	30	44	0

[a]The reaction was performed in the absence of the methylating agent (Me_4NBr). [b]Yield was determined by ^{19}F NMR using trifluoro toluene as internal standard.

Next, we screened for different ammonium salts as methyl sources. We found that Me_4NCl and Me_4NBr gave equal yields and product ratios, whereas Me_4NI gave incomplete conversion (entries 5 and 6). Tetramethylammonium acetate favored the *O*-methyl enol ether (entry 7). When using ammonium salts with different substituents on the quaternary nitrogen, we observed additional *O*-butylation (13%) with Bu_3MeNCl (entry 11) and mainly α-benzylation (64%) with $BnMe_3NCl$ (entry 12). When using $(C_{16}H_{33})Me_3NBr$ as an alkylating agent, only **2a** and **3a** were formed, but no hexadecylated compound of any kind (entry 13). The naturally occurring ammonium salt betaine was practically ineffective (entry 14). Gratifyingly, we identified phenyl trimethylammonium salts giving significantly higher overall yields. Going from the chloride and bromide to the iodide salt, we observed a shift towards the desired α-methylated product **3a** (entries 8−10). Compared with tetramethylammonium salts, a phenyl substituent on the ammonium most probably withdraws electron density from the adjacent methyl substituents, which then, in turn, are more prone to react with the "soft" α-carbon of the enolate rather than being attacked by the carbonyl oxygen. Finally, we found the optimal reaction conditions being $PhMe_3NI$ (1.5 equiv) and KOH (2 equiv) in anisole (0.23 M) at 130 °C, wherein the desired 1-(4-fluorophenyl)-2-phenyl-1-propanone (**3a**) was obtained in 78% yield after 18 h (entry 10) determined by ^{19}F NMR.

The outcome of the optimization efforts corresponds to previous studies on quaternary ammonium compounds as alkylating agents present in the literature.[28,29] Accordingly, for ammonium salts with different organic substituents on the nitrogen, a benzyl group is transferred preferentially from the ammonium salt to a nucleophile, followed by methyl substituents, and finally, other primary alkyl chains. The substituents on the ammonium ion further impact the cleavage rate of neighboring alkyl groups. If an aryl substituent is present within the ammonium salt, an adjacent alkyl group is transferred more readily compared to an aliphatic chain from tetraalkylammonium salts.

To exclude a reaction pathway *via* thermal decomposition of the ammonium salt to the respective methyl halide, which could act as the actual methylating reagent, we choose a reaction setup that would allow transfer of gaseous reactants between two spatially divided reaction vessels. For this purpose, a COware vial (Skrydstrup vial[30]) was used, with two separate reaction chambers connected at their upper part for gas exchange. Chamber 1 was charged with the ammonium salt, base, and anisole as solvent, and chamber 2 was charged with substrate **1a**, base, and solvent. The whole vessel was heated to 130 °C, where possibly formed methyl halide from chamber 1 should reach chamber 2 *via* the gas phase. However, no methylated product could be observed, and solely starting material was recovered. Furthermore, methylation occurred when Me_4NOAc was used as CH_3 source, which again corroborates the hypothesis of direct nucleophilic substitution rather than thermal decomposition to a methylating agent. Additionally, when methylating phenyl benzyl ketone by MeI, solely the α-mono- and α-bis-methylated products form, but no O-methylation is observed.[31] Furthermore, we successfully performed α-methylation using $PhMe_3NI$ at lower temperatures by exploiting microwave irradiation. A decrease of reaction temperature as low as 90 °C still afforded the desired product **3** in comparable yields (see the SI for details).

With the optimized reaction conditions in hand, we performed α-methylation reactions on various substrates to demonstrate the scope of this direct transformation (Scheme 1).

In this reaction *N,N*-dimethylaniline is formed stoichiometrically from the methylating agent $PhMe_3NI$. This byproduct, however, can be easily quenched *in situ* and fully separated from the desired product in form of its water-soluble HCl salt by a mild acidic workup procedure. The desired methylated compounds were obtained in isolated yields up to 85%. Interestingly, the formation of any α,α-dimethylated products was never observed. We performed the methylation of benzyl 4-fluorophenyl ketone **1a** on a 1.4 mmol scale to prove the scalability of this method. The desired product **3a** was isolated in a yield of 85%. Significantly lower yields were observed for the sterically more hindered substrate 1-(pentamethylphenyl)-2-phenylethanone (product **3d**). Substrates that are less susceptible to enolization, *e.g.*, 4-phenylcyclohexanone **3t**, also resulted in diminished yields, and mainly starting material was recovered. A variety of functional groups, including halides (products **3a**, **3e**, **3f**, and **3q**), CF_3 (product **3i**), ether (products **3g** & **3h**, **3m**−**3p**), and

https://doi.org/10.1021/acs.joc.1c03158
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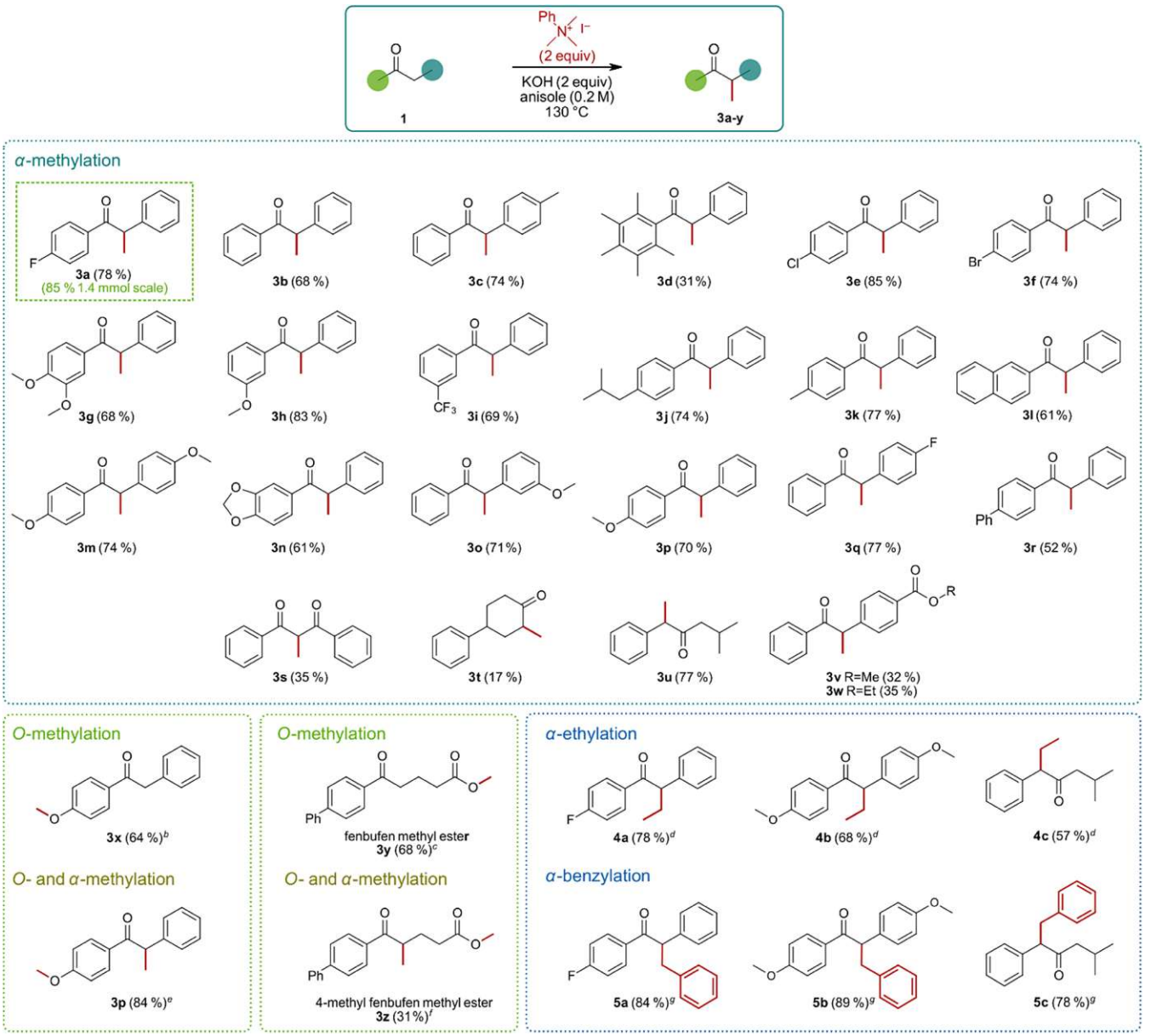
Scheme 1. Scope of α-Methylation[a]



[b]1 equiv $PhMe_3NI$. [d]$PhEt_3NI$ (2 equiv) as ammonium salt. [e]Reaction time 6 h, addition of KOH (2 equiv) and $PhMe_3NI$ (2 equiv) after 3 h. [f]Addition of KOH (2 equiv) and $PhMe_3NI$ (2 equiv) after 3 h and 48 h; reaction time, 4 days. [g]$BnMe_3NCl$ (1 equiv) as ammonium salt [c]3 equiv KOH, reaction time 24 h. [a]Isolated yields are shown. Standard conditions: Substrate (100 mg, 1 equiv), $PhMe_3NI$ (2 equiv), KOH (2 equiv), in anisole (2 mL, 0.2 M) at 130 °C, 2−5 h, closed vessel, inert atmosphere.

phenyl groups (product **3r**) were well tolerated in different positions of the aryl ring. Substrates bearing even more reactive functional groups on the aryl ring, *e.g.*, ester moieties, can also be methylated in moderate yields (product **3v** and **3w**). As assumed, when 1-(4-hydroxyphenyl)-2-phenylethanone was subjected to the respective conditions, methylation initially occurred at the phenolic oxygen, and subsequently at the α-position of the carbonyl (product **3x** and **3p**). Our method, however, is not only limited to bisaromatic compounds but can also be applied for monoaromatic substrates. 4-Methyl-1-phenyl-2-pentanone was methylated regioselectively at the benzylic position giving product **3u** in 77% yield. Aliphatic ketones without any benzylic α-carbons, *e.g.*, 8-pentadecanone, formed only the aldol product and hence are not mentioned in this paper. As a proof of concept, we performed late-stage methylation of the biologically active compound fenbufen. Herein, the carboxylic acid moiety is preferentially methylated (product **3y**). Upon addition of fresh reagent after prolonged reaction times, however, the fenbufen methyl ester could be further methylated at the α-position (product **3z**; see the SI for details).

Finally, we wanted to briefly outline the applicability of this new protocol for introducing larger substituents than methyl. Selective α-ethylation can be accomplished accordingly, using phenyltriethylammonium iodide ($PhEt_3NI$) as the alkyl source. Benzyl 4-fluorophenyl ketone **1a** was successfully ethylated at the α-position in 78% yield using $PhEt_3NI$ (product **4a**). Substrates containing electron-donating substituents on the aryl ring (product **4b**), as well as monoaromatic compounds (product **4c**) can also be ethylated in yields of 68 and 57%,

https://doi.org/10.1021/acs.joc.1c03158
J. Org. Chem. 2022, 87, 4305−4315

respectively. Benzylation is of interest since the phenyl benzyl ketone motif can be found in several drugs or promising drug candidates, as, for example, desoxybenzoin derivatives[32] or ring-truncated deguelin analogues.[33] SAR studies identified the latter as promising candidates for HIF-1α inhibitors.[34] One of those analogues, SH-1242, further inhibits Hsp90 activity and shows potent anticancer efficacy.[35] We could demonstrate the applicability of this method for benzylation of selected substrates using $BnMe_3NCl$ as a benzylating agent. Products **5a**–**5c** were obtained in high yields of 84, 89, and 78%, respectively. Since methylating agents, however, are by far more hazardous than traditionally applied ethylating and benzylating reagents, we did not further investigate the latter strategies.

CONCLUSIONS

In conclusion, we described the use of quaternary ammonium salts as alternative alkylating and benzylating agents. Phenyl trimethylammonium iodide and related salts were successfully established as selective, highly efficient, safe, and easy-to-handle methylating reagents for direct $C(sp^3)$–$C(sp^3)$ bond formation.

EXPERIMENTAL SECTION

General. All chemicals were purchased from commercial suppliers and, unless noted otherwise, used without further purification. NaO^{t}Bu, $Pd_2(dba)_3$, and DPE-Phos were strictly stored and handled in a glovebox under argon atmosphere. Degassed and dry THF was stored over molecular sieves under argon using AcroSeal septum. Glass vials (8 mL) were sealed with Wheaton screw caps containing a PTFE faced 14B styrene-butadiene rubber liner for small-scale reaction above room temperature and heated in a metallic reaction block. All reaction temperatures refer to external temperatures.

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance UltraShield 400 at ambient temperature. Chemical shifts (δ) are reported in ppm, using Me_4Si as internal standard. Coupling constants (J) are given in hertz (Hz), and multiplicities are assigned as s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

Thin-layer chromatography (TLC) analysis was performed on aluminum-backed unmodified Merck silica gel 60 F_{245} plates. Visualization was realized under UV irradiation or *via* heat staining using a ceric ammonium molybdate aqueous solution. For flash column chromatography, Merck silica gel 60 (40–63 μm) was used and purification was either done by hand column or on a Büchi Pure C-850 FlashPrep System.

HRMS analysis was performed on an Agilent 6230 LC TOFMS mass spectrometer equipped with an Agilent Dual AJS ESI-Source. The mass spectrometer was connected to a liquid chromatography system of the 1100/1200 series from Agilent Technologies, Palo Alto, CA. The system consisted of a 1200SL binary gradient pump, a degasser, a column thermostat, and an HTC PAL autosampler (CTC Analytics AG, Zwingen, Switzerland). A silica-based Phenomenex C-18 Security Guard Cartridge was used as a stationary phase. Data evaluation was performed using Agilent MassHunter Qualitative Analysis B.07.00. Identification was based on peaks obtained from extracted-ion chromatograms (extraction width, ±20 ppm).

Optimization Screening. The optimization of reaction conditions was conducted following the general procedure A (see the SI for details). Yields were determined by ^{19}F NMR using trifluoro toluene as internal standard.

1-Fluoro-4-(1-methoxy-2-phenylethenyl)benzene[36] ***(2a)***. An 8 mL glass vial equipped with a magnetic stirring bar was charged with benzyl 4-fluorophenyl ketone (**1**) (100 mg, 0.467 mmol, 1 equiv), Me_4NBr (119 mg, 770 mmol, 1.65 equiv), and KOH (79 mg, 1.4 mmol, 3 equiv). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. The toluene (2 mL, 0.23 M) was added *via* a syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block. After 18 h at respective temperatures, the reaction was cooled to room temperature and solids were centrifuged off. The supernatant solution was transferred to a round-bottom flask, and the solid residue was washed three times with small amounts DCM. The combined organic phases were concentrated. The crude oil was further purified *via* hand column chromatography (8 g silica LP/Et_3N 100:1) to yield 46 mg (43%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.67 (m, 2H), 7.60–7.50 (m, 2H), 7.42–7.32 (m, 2H), 7.28–7.19 (m, 1H), 7.16–7.03 (m, 2H), 6.06 (s, 1H), 3.63 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 163.0 (d, J = 247.9 Hz), 155.4, 135.9, 132.6 (d, J = 3.3 Hz), 128.7, 128.6, 128.5 (d, J = 8.1 Hz), 126.8, 115.6 (d, J = 21.7 Hz), 112.8 (d, J = 1.4 Hz), 58.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −113.2 HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{14}FO$: 229.1023; found: 229.1000

General Procedure B for Precursor Synthesis. In the glovebox, a flame-dried 8 mL glass vial equipped with a magnetic stirring bar was charged with NaO^{t}Bu (2.6 mmol, 1.3 equiv), $Pd_2(dba)_3$ (5 mol %), and DPE-Phos (10 mol %). THF (2 mL, 1 M) was added, and the dark brownish-green mixture was stirred for 5 min at ambient temperatures. The aryl bromide (2 mmol, 1 equiv) was added *via* Eppendorf pipette, followed by rapid addition of the acetophenone (2.4 mmol, 1.2 equiv) in one portion as solid or *via* Eppendorf pipette if liquid. Immediate solid formation could be observed. The vial was closed with a Wheaton screw cap and transferred out of the glovebox. The mixture was heated to 70 °C in a metallic reaction block and stirred for 2–18 h at respective temperatures. After complete consumption of the starting material (GC-MS monitoring), water (10 mL) was added and the mixture was extracted three times with diethyl ether (30 mL each). The combined organic phases were washed once with sat. NH_4Cl solution and once with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified *via* gradient flash column chromatography on silica gel using a mixture of light petroleum (LP) and EtOAc.

1-(3,4-Dimethoxyphenyl)-2-phenylethanone[37] ***(1g)***. Prepared following the general procedure B from 3,4-dimethoxyacetophenone and bromobenzene heated for 2 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0–40%) to yield 443 mg (86%) of the title compound as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, J = 8.4, 2.1 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.39–7.22 (m, 5H), 6.89 (d, J = 8.4 Hz, 1H), 4.26 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 196.3, 153.3, 149.1, 135.1, 129.7, 129.3, 128.6, 126.8, 123.5, 110.7, 110.0, 56.0, 55.9, 45.2.

1-(3-Methoxyphenyl)-2-phenylethanone[38] ***(1h)***. Prepared following the general procedure B from 3-methoxyacetophenone and bromobenzene heated for 3 h. The crude product was purified *via* flash hand column chromatography (60 g silica, LP/EtOAc 70:1, 60:1, 40:1) to yield 305 mg (67%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.58 (m, 1H), 7.55 (dd, J = 2.7, 1.6 Hz, 1H), 7.43–7.31 (m, 3H), 7.31–7.26 (m, 3H), 7.11 (ddd, J = 8.2, 2.7, 0.9 Hz, 1H), 4.28 (s, 2H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 197.5, 159.9, 138.0, 134.6, 129.6, 129.5, 128.7, 126.9, 121.3, 119.7, 112.9, 55.4, 45.7.

2-Phenyl-1-[3-(trifluormethyl)phenyl]ethenone[39] ***(1i)***. Prepared following the general procedure B from 3-trifluoromethylacetophenone and bromobenzene heated for 4 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0–15%) to yield 391 mg (74%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (tt, J = 1.8, 0.8 Hz, 1H), 8.16 (dt, J = 7.3, 1.1 Hz, 1H), 7.81–7.70 (m, 1H), 7.56 (tt, J = 7.9, 0.8 Hz, 1H), 7.38–7.29 (m, 2H), 7.29–7.18 (m, 3H), 4.29 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 196.3, 137.1, 133.9, 131.9 (d, J = 1.4 Hz), 131.2 (q, J = 34.0 Hz), 129.6 (q, J = 3.6 Hz), 129.5,

https://doi.org/10.1021/acs.joc.1c03158
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129.4, 128.9, 127.3, 125.5 (q, J = 3.8 Hz), 123.7 (d, J = 274.8 Hz), 45.70.

1-[4-(2-Methylpropyl)phenyl]-2-phenylethanone (**1j**). Prepared following the general procedure B from 4′-isobutylacetophenone and bromobenzene heated for 4 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0−20%) to yield 415 mg (82%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03−7.96 (m, 2H), 7.42−7.23 (m, 7H), 4.30 (s, 2H), 2.57 (d, J = 7.2 Hz, 2H), 2.04−1.86 (m, J = 6.9 Hz, 1H), 0.96 (d, J = 6.7 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 197.2, 147.6, 134.8, 134.4, 129.5, 129.3, 128.6, 126.8, 45.3, 30.1, 22.3.

1-(4-Methylphenyl)-2-phenylethanone[40] (**1k**). Prepared following the general procedure B from 4-methylacetophenone and bromobenzene heated for 3 h. The crude product was purified *via* flash hand column chromatography (55 g silica, LP/EtOAc 80:1, 70:1, 60:1, 40:1) to yield 302 mg (72%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.9 Hz, 2H), 7.36−7.24 (m, 7H), 4.28 (s, 2H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 197.4, 144.1, 134.9, 134.2, 129.5, 129.4, 128.8, 128.7, 126.9, 45.5, 21.7.

1-(2-Naphthalenyl)-2-phenylethanone[40] (**1l**). Prepared following the general procedure B from 2-acetylnaphthalene and bromobenzene heated for 18 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0−40%) to yield 396 mg (80%) of the title compound as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 8.6, 1.8 Hz, 1H), 7.88 (dd, J = 8.1, 1.4 Hz, 1H), 7.85−7.73 (m, 2H), 7.57−7.41 (m, 2H), 7.32−7.15 (m, 5H), 4.34 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 197.6, 135.6, 134.7, 134.0, 132.5, 130.4, 129.7, 129.5, 128.7, 128.6, 128.6, 127.8, 126.9, 126.8, 124.3, 45.6.

1-(1,3-Benzodioxol-5-yl)-2-phenylethanone[40] (**1n**). Prepared following the general procedure B from 5-acetyl-1,3-benzodiocole and bromobenzene heated for 10 h. The crude product was purified *via* flash column chromatography (90 g silica, LP and EtOAc 0−40%) to yield 471 mg (98%) of the title compound as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, J = 8.2, 1.8 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.39−7.29 (m, 2H), 7.29−7.21 (m, 3H), 6.85 (d, J = 8.2 Hz, 1H), 6.03 (s, 2H), 4.21 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 195.8, 151.9, 148.3, 134.9, 131.5, 129.4, 128.7, 128.7, 126.9, 125.1, 108.8, 108.4, 107.9, 101.9, 45.4.

2-(3-Methoxyphenyl)-1-phenylethanone[40] (**1o**). Prepared following the general procedure B from acetophenone and 4-bromoanisole heated for 18 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0−40%) to yield 267 mg (59%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06−7.97 (m, 2H), 7.60−7.51 (m, 1H), 7.51−7.41 (m, 2H), 7.25 (t, J = 7.8 Hz, 1H), 6.91−6.77 (m, 3H), 4.26 (s, 2H), 3.79 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 197.5, 159.8, 136.6, 136.1, 133.2, 129.7, 128.7, 121.9, 115.2, 112.4, 55.2, 45.6.

2-(4-Fluorphenyl)-1-phenylethanone[38] (**1q**). Prepared following the general procedure B from acetophenone and 1-bromo-4-fluorobenzene heated for 18 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0−40%) to yield 255 mg (60%) of the title compound as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06−7.94 (m, 2H), 7.62−7.52 (m, 1H), 7.52−7.39 (m, 2H), 7.28−7.19 (m, 2H), 7.08−6.97 (m, 2H), 4.27 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 197.5, 162.0 (d, J = 245.2 Hz), 136.6, 133.4, 131.2 (d, J = 8.0 Hz), 130.3 (d, J = 3.3 Hz), 128.8, 128.6, 115.6 (d, J = 21.4 Hz), 44.6.

1-[1,1′-Biphenyl]-4-yl-2-phenylethanone[40] (**1r**). Prepared following the general procedure B from 4′-phenylacetophenone and bromobenzene heated for 18 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0−40%) to yield 207 mg (38%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12−8.04 (m, 2H), 7.70−7.64 (m, 2H), 7.64−7.59 (m, 2H), 7.50−7.43 (m, 2H), 7.43−7.22 (m, 6H), 4.31 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 197.2, 145.8, 139.8, 135.3, 134.7, 129.5, 129.3, 129.0, 128.7, 128.3, 127.3, 127.3, 126.9, 45.6

Methyl 4-(2-Oxo-2-phenylethyl)benzoate[41] (**1v**). Prepared following the general procedure B from acetophenone methyl 4-iodobenzoate heated for 4 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0−20%) to yield 285 mg (37%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04−7.98 (m, 4H), 7.62−7.54 (m, 1H), 7.51−7.44 (m, 2H), 7.37−7.32 (m, 2H), 4.35 (s, 2H), 3.90 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 196.9, 167.0, 139.9, 136.5, 133.5, 130.0, 129.7, 129.0, 128.8, 128.6, 77.4, 52.2, 45.5.

Ethyl 4-(2-Oxo-2-phenylethyl)benzoate[42] (**1w**). Prepared following the general procedure B from acetophenone ethyl 4-iodobenzoate heated for 4 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0−20%) to yield 360 mg (45%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04−7.97 (m, 4H), 7.62−7.53 (m, 1H), 7.51−7.42 (m, 2H), 7.37−7.31 (m, 2H), 4.41−4.31 (m, 4H), 1.38 (t, J = 7.1 Hz, 3H) ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 196.9, 166.5, 139.8, 136.5, 133.5, 130.0, 129.6, 128.8, 128.6, 61.0, 45.5, 14.4.

General Procedure C for Methylation, Ethylation, and Benzylation Reactions. An 8 mL glass vial equipped with a magnetic stirring bar was charged with the respective diaryl ethanone (100 mg, 1 equiv), the ammonium salt (1.1 for $BnMe_3NCl$ or 2 equiv for $PhMe_3NI$ and $PhEt_3NI$), and KOH (2 equiv). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. Anisole (2 mL, 0.2 M) was added *via* a syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton cap and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block for 2−4 h. After complete consumption of the starting material (TLC analysis), the reaction was cooled to room temperature. HCl (2 N, 2 mL) was added, and the mixture was extracted three times with EtOAc (5 mL each). The combined organic phases were washed twice with 2 N HCl (1 mL each) and once with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. For benzylation reactions, the mixture was not subjected to aqueous workup but filtered over a short plug of silica, washed with EtOAc, and concentrated. The obtained crude product was purified *via* hand column with unmodified silica.

1-(4-Fluorophenyl)-2-phenyl-1-propanone[43] (**3a**). Prepared following the general procedure C from commercially available starting material with a reaction time of 3 h. The crude product was purified *via* column chromatography (8 g silica LP/EtOAc 50:1, 45:1, 40:1) to yield 83 mg (78%) of the title compound.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97−7.87 (m, 2H), 7.28−7.18 (m, 4H), 7.18−7.11 (m, 1H), 7.03−6.93 (m, 2H), 4.57 (q, J = 6.8 Hz, 1H), 1.48 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 198.8, 165.6 (d, J = 254.6 Hz), 141.5, 133.0 (d, J = 3.0 Hz), 131.5 (d, J = 9.3 Hz), 129.20, 127.8, 127.1, 115.7 (d, J = 21.7 Hz), 48.1, 19.6.^{19}F NMR (376 MHz, $CDCl_3$): δ = −105.6. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{14}FO$: 229.1023; found: 229.1000

Compound **3a** was also prepared on a 1.4 mmol scale as follows: A 25 mL round-bottom flask was charged with benzyl 4-fluorophenyl ketone (**1a**) (300 mg, 1.4 mmol, 1 equiv), $PhMe_3NI$ (751 mg, 2.8 mmol, 2 equiv), and KOH (157 mg, 2.8 mmol, 2 equiv). The flask was closed with a septum. Using a cannula, the flask was evacuated and backfilled with argon three times. Anisole (6 mL, 0.23 M) was added *via* a syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. The resulting inhomogeneous mixture was heated to 130 °C in an oil bath. After 5 h at respective temperatures, the reaction was cooled to room temperature. HCl (2 N, 10 mL) were added, and the mixture was extracted three times with EtOAc (25 mL each). The combined organic phases were washed twice with 2 N HCl (3−5 mL each) and once with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The obtained crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0−40%) to yield 273 mg (85%) of the title compound as a colorless oil. Analytical data were in accordance with the previous finding.

https://doi.org/10.1021/acs.joc.1c03158
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1,2-Diphenyl-1-propanone[38] ***(3b)***. Prepared following the general procedure C from commercially available starting material with a reaction time of 3 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 50:1, 40:1) to yield 73 mg (68%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01−7.93 (m, 2H), 7.53−7.43 (m, 1H), 7.43−7.34 (m, 2H), 7.30 (d, J = 4.3 Hz, 4H), 7.21 (ddd, J = 8.8, 4.8, 3.9 Hz, 1H), 4.70 (q, J = 6.9 Hz, 1H), 1.55 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 200.4, 141.6, 136.6, 132.9, 129.1, 128.9, 128.6, 127.9, 127.0, 48.0, 19.6.

2-(4-Methylphenyl)-1-phenyl-1-propanone[44] ***(3c)***. Prepared following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 50:1) to yield 76 mg (74%) of the title compound as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01−7.94 (m, 2H), 7.52−7.43 (m, 1H), 7.43−7.34 (m, 2H), 7.23−7.16 (m, 2H), 7.15−7.08 (m, 2H), 4.67 (q, J = 6.8 Hz, 1H), 2.30 (s, 3H), 1.54 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 200.5, 138.6, 136.6, 136.6, 132.8, 129.8, 128.9, 128.6, 127.7, 47.6, 21.1, 19.6. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{17}O$: 225.1274; found: 225.1265

2-(2,3,4,5,6-Pentamethylphenyl)-1-phenyl-1-propanone ***(3d)***. Prepared following the general procedure C from commercially available starting material with a reaction time of 3.5 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 50:1) to yield 31 mg (31%) of the title compound as off-white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32−7.16 (m, 5H), 4.13 (q, J = 7.0 Hz, 1H), 2.23 (s, 15H), 1.64 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 211.1, 140.1, 138.7, 135.5, 132.8, 128.8, 128.5, 127.1, 54.9, 16.9, 16.8, 16.0. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{25}O$: 281.1900; found: 281.1895

1-(4-Chlorophenyl)-2-phenyl-1-propanone[45] ***(3e)***. Prepared following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 50:1) to yield 87 mg (85%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92−7.84 (m, 2H), 7.38−7.16 (m, 7H), 4.62 (q, J = 6.8 Hz, 1H), 1.53 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 199.1, 141.3, 139.3, 134.9, 130.3, 129.2, 128.9, 127.8, 127.2, 48.2, 19.5. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{14}ClO$: 245.0728; found: 245.0712

1-(4-Bromophenyl)-2-phenyl-1-propanone[45] ***(3f)***. Prepared following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 50:1) to yield 75 mg (74%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84−7.76 (m, 2H), 7.56−7.46 (m, 2H), 7.36−7.25 (m, 3H), 7.25−7.16 (m, 2H), 4.61 (q, J = 6.8 Hz, 1H), 1.53 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 199.3, 141.3, 135.2, 131.9, 130.4, 129.2, 128.0, 127.8, 127.2, 48.2, 19.5. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{14}BrO$: 289.0223; found: 289.0218

1-(3,4-Dimethoxyphenyl)-2-phenyl-1-propanone[46] ***(3g)***. Prepared following the general procedure C from compound **1g** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 40:1, 20:1, 10:1) to yield 72 mg (68%) of the title compound. R_f = 0.54 (LP/EtOAc 2:1) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (dd, J = 8.4, 2.0 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.29 (d, J = 4.4 Hz, 4H), 7.19 (ddd, J = 8.6, 4.9, 3.9 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 4.65 (q, J = 6.9 Hz, 1H), 3.88 (d, J = 4.1 Hz, 6H), 1.52 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 199.0, 153.1, 149.0, 142.2, 129.7, 129.1, 127.7, 126.9, 123.5, 111.1, 110.0, 56.1, 56.0, 47.6, 19.7. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{19}O_3$: 271.1329; found: 271.1323

1-(3-Methoxyphenyl)-2-phenyl-1-propanone[47] ***(3h)***. Prepared following the general procedure C from compound **1h** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 70:1) to yield 88 mg (83%) of the title compound as a slightly orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (ddd, J = 7.7, 1.6, 1.0 Hz, 1H), 7.47 (dd, J = 2.7, 1.6 Hz, 1H), 7.34−7.21 (m, 5H), 7.21−7.12 (m, 1H), 6.99 (ddd, J = 8.3, 2.7, 1.0 Hz, 1H), 4.64 (q, J = 6.9 Hz, 1H), 3.76 (s, 3H), 1.51 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 200.2, 159.8, 141.6, 138.0, 129.5, 129.1, 127.8, 127.0, 121.5, 119.4, 113.2, 55.4, 48.1, 19.6. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{17}O_2$: 241.1223; found: 241.1205

2-Phenyl-1-[3-(trifluoromethyl)phenyl]-1-propanone[44] ***(3i)***. Prepared following the general procedure C from compound **1i** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 80:1) to yield 73 mg (69%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (tt, J = 1.8, 0.8 Hz, 1H), 8.11−8.04 (m, 1H), 7.73−7.66 (m, 1H), 7.52−7.43 (m, 1H), 7.33−7.28 (m, 1H), 7.28−7.25 (m, 2H), 7.25−7.15 (m, 2H), 4.65 (q, J = 6.8 Hz, 1H), 1.54 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 199.0, 140.9, 137.1, 132.0 (d, J = 1.5 Hz), 131.2 (q, J = 32.8 Hz), 129.3, 129.3 (q, J = 3.8 Hz), 129.2, 127.8, 127.3, 125.7 (q, J = 3.9 Hz), 123.0 (d, J = 275.8 Hz), 48.43, 19.47. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{14}F_3O$: 279.0991; found: 279.0986

1-[4-(2-Methylpropyl)phenyl]-2-phenyl-1-propanone ***(3j)***. Prepared following the general procedure C from compound **1j** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 100:1) to yield 78 mg (74%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93−7.85 (m, 2H), 7.35−7.25 (m, 4H), 7.25−7.18 (m, 1H), 7.18−7.12 (m, 2H), 4.69 (q, J = 6.9 Hz, 1H), 2.48 (d, J = 7.2 Hz, 2H), 1.85 (dh, J = 13.4, 6.7 Hz, 1H), 1.54 (d, J = 6.9 Hz, 3H), 0.88 (dd, J = 6.6, 0.6 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 200.0, 147.3, 141.7, 134.3, 129.3, 128.9, 128.8, 127.8, 126.8, 47.7, 45.4, 30.1, 22.4, 22.3, 19.6. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{23}O$: 267.1743; found: 267.1739

1-(4-Methylphenyl)-2-phenyl-1-propanone[48] ***(3k)***. Prepared following the general procedure C from compound **1k** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 70:1) to yield 82 mg (77%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91−7.84 (m, 2H), 7.34−7.25 (m, 4H), 7.25−7.14 (m, 3H), 4.68 (q, J = 6.9 Hz, 1H), 2.35 (s, 3H), 1.54 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 200.0, 143.6, 141.8, 134.1, 129.3, 129.0, 129.0, 127.8, 126.9, 47.8, 21.7, 19.6. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{17}O$: 225.1274; found: 225.1252

1-(2-Naphthyl)-2-phenyl-1-propanone[49] ***(3l)***. Prepared following the general procedure C from compound **1l** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 80:1) to yield 64 mg (61%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52−8.47 (m, 1H), 8.03 (dd, J = 8.7, 1.8 Hz, 1H), 7.90 (dd, J = 8.1, 1.4 Hz, 1H), 7.82 (dd, J = 8.6, 1.8 Hz, 2H), 7.58-7.49 (m, 2H), 7.40−7.24 (m, 4H), 7.24−7.15 (m, 1H), 4.86 (q, J = 6.9 Hz, 1H), 1.61 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 200.4, 141.7, 135.5, 134.0, 132.6, 130.6, 129.7, 129.1, 128.5, 128.4, 127.9, 127.8, 127.0, 126.8, 124.7, 48.1, 19.7. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{17}O$: 261.1274; found: 261.1267

1,2-Bis(4-methoxyphenyl)-1-propanone[50] ***(3m)***. Prepared following the general procedure C from commercially available starting material with a reaction time of 4 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 10:1) to yield 76 mg (74%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98−7.90 (m, 2H), 7.24−7.16 (m, 2H), 6.90−6.78 (m, 4H), 4.60 (q, J = 6.8 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 1.49 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 199.2, 163.3, 158.5, 134.1, 131.2, 129.6, 128.8, 114.5, 113.8, 55.5, 55.3, 46.7, 19.7. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{19}O_3$: 271.1329; found: 271.1326

1-(2H-1,3-Benzodioxol-5-yl)-2-phenyl-1-propanone[51] ***(3n)***. Prepared following the general procedure C from compound **1n** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 80:1) to yield 65 mg (61%) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, J = 8.2, 1.8 Hz, 1H), 7.44 (d, J = 1.7 Hz, 1H), 7.34−7.22 (m, 4H), 7.22−7.15 (m, 1H), 6.76 (d, J = 8.2 Hz, 1H), 5.98 (s, 2H), 4.59 (q, J = 6.8 Hz, 1H), 1.51 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR

https://doi.org/10.1021/acs.joc.1c03158
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(101 MHz, $CDCl_3$): δ = 198.5, 151.6, 148.2, 141.9, 131.4, 129.1, 127.8, 127.0, 125.1, 108.7, 107.9, 101.9, 47.8, 19.7. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{15}O_3$: 255.1016; found: 255.1006

2-(3-Methoxyphenyl)-1-phenyl-1-propanone[44] ***(3o)***. Prepared following the general procedure C from compound **1o** with a reaction time of 3 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 80:1) to yield 75 mg (71%) of the title compound as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01−7.93 (m, 2H), 7.53−7.42 (m, 1H), 7.42−7.33 (m, 2H), 7.26−7.16 (m, 1H), 6.89 (ddd, J = 7.7, 1.7, 1.0 Hz, 1H), 6.84 (dd, J = 2.6, 1.7 Hz, 1H), 6.75 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 4.66 (q, J = 6.8 Hz, 1H), 3.76 (s, 3H), 1.54 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 200.2, 160.1, 143.1, 136.6, 132.9, 130.1, 128.8, 128.6, 120.3, 113.6, 112.2, 55.3, 48.0, 19.5. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{17}O_2$: 241.1223; found: 241.1217

1-(4-Methoxyphenyl)-2-phenyl-1-propanone[44] ***(3p)***. Prepared following the general procedure C from commercially available starting material with a reaction time of 3 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 60:1, 50:1) to yield 73 mg (70%) of the title compound as a slightly yellow oil.

Procedure for One-Pot O- and α-Methylation. Prepared following the general procedure C from commercially available 1-(4-hydroxyphenyl)-2-phenylethanone with a reaction time of 6 h. After 3 h reaction time and before the workup, another 2 equiv of $PhMe_3NI$ and KOH each were added at room temperature, and the reaction was subsequently heated up again to 130 °C for another 3 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 70:1-50:1) to yield 95 mg (84%) of the title compound as a slightly yellow oil. Spectra were according to compound **3p**. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00−7.91 (m, 2H), 7.33−7.24 (m, 4H), 7.24−7.15 (m, 1H), 6.90−6.81 (m, 2H), 4.65 (q, J = 6.9 Hz, 1H), 3.81 (s, 3H), 1.52 (d, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 199.0, 163.3, 142.0, 131.2, 129.6, 129.0, 127.8, 126.9, 113.8, 55.5, 47.6, 19.7. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{17}O_2$: 241.1223; found: 241.1236

2-(4-Fluorophenyl)-1-phenyl-1-propanone[44] ***(3q)***. Prepared following the general procedure C from compound **1q** with a reaction time of 2.5 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 80:1) to yield 82 mg (77%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98−7.91 (m, 2H), 7.54−7.45 (m, 1H), 7.44−7.34 (m, 2H), 7.31−7.21 (m, 2H), 7.04−6.93 (m, 2H), 4.70 (q, J = 6.9 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 200.3, 161.9 (d, J = 245.4 Hz), 137.2 (d, J = 3.3 Hz), 136.4, 133.0, 129.4 (d, J = 8.0 Hz), 128.8, 128.7, 115.9 (d, J = 21.3 Hz), 47.0, 19.7. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{14}FO$: 229.1023; found: 229.1003

1-[1,1′-Biphenyl]-4-yl-2-phenyl-1-propanone[44] ***(3r)***. Prepared following the general procedure C from compound **1r** with a reaction time of 2.5 h. The crude product was purified *via* column chromatography (8 g silica, LP/EtOAc 75:1) to yield 55 mg (52%) of the title compound as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09−8.02 (m, 2H), 7.65−7.55 (m, 4H), 7.48−7.36 (m, 4H), 7.36−7.28 (m, 4H), 7.28−7.19 (m, 1H), 4.74 (q, J = 6.8 Hz, 1H), 1.59 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 199.9, 145.5, 141.6, 139.9, 135.2, 129.4, 129.1, 129.0, 128.2, 127.8, 127.3, 127.2, 127.0, 48.0, 19.6. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{19}O$: 287.1430; found: 287.1439

2-Methyl-1,3-diphenyl-1,3-propanedione[52] ***(3s)***. Prepared following the general procedure C from commercially available starting material with a reaction time of 2.5 h. The crude product was purified *via* column chromatography (LP/EtOAc 80:1, 50:1, 20:1) to yield 36 mg (35%) of the title compound as white crystals. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00−7.92 (m, 4H), 7.60−7.50 (m, 2H), 7.49−7.39 (m, 4H), 5.28 (q, J = 7.0 Hz, 1H), 1.60 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 197.3, 135.7, 133.5, 128.9, 128.6, 51.0, 14.4. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{15}O_2$: 239.1067; found: 239.1052

2-Methyl-4-phenylcyclohexanone[53] ***(3t)***. Prepared following the general procedure C from commercially available starting material with a reaction time of 18 h. The crude product was purified *via* column chromatography (8 g silica LP/EtOAc 80:1-10:1) to yield 18 mg (17%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33−7.23 (m, 2H), 7.23−7.14 (m, 3H), 3.10 (tt, J = 12.4, 3.5 Hz, 1H), 2.64−2.53 (m, 1H), 2.53−2.42 (m, 2H), 2.26−2.14 (m, 2H), 1.98−1.81 (m, 1H), 1.69−1.57 (m, 1H), 1.03 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 212.7, 144.9, 128.7, 126.8, 126.7, 44.9, 43.6, 43.5, 41.7, 35.1, 14.6. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{17}O$: 189.1274; found: 189.1277

5-Methyl-2-phenyl-3-hexanone[54] ***(3u)***. Prepared following the general procedure C from commercially available starting material with a reaction time of 16 h. The crude product was purified *via* flash column chromatography (15 g silica, LP/EtOAc 80:1) to yield 80 mg (77%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.27 (m, 2H), 7.29−7.19 (m, 1H), 7.21−7.16 (m, 2H), 3.71 (q, J = 7.0 Hz, 1H), 2.30−2.15 (m, 2H), 2.09 (dp, J = 13.4, 6.6 Hz, 1H), 1.38 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 210.5, 140.6, 128.9, 128.0, 127.2, 53.4, 50.1, 24.5, 22.7, 22.4, 17.5.

Methyl 4-(1-Methyl-2-oxo-2-phenylethyl)benzoate[55] ***(3v)***. Prepared following the general procedure C from compound **1v** with a reaction time of 2 h. The crude product was purified *via* flash column chromatography (15 g silica, LP/EtOAc 20:1, 10:1) to yield 34 mg (32%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00−7.89 (m, 4H), 7.53−7.44 (m, 1H), 7.43−7.32 (m, 4H), 4.74 (q, J = 6.8 Hz, 1H), 3.87 (s, 3H), 1.55 (d, J = 6.9 Hz, 3H) $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 199.79, 166.89, 146.74, 136.33, 133.17, 130.41, 128.99, 128.84, 128.71, 127.97, 52.19, 47.97, 19.42. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{17}O_3$: 269.1172; found: 269.1196

Ethyl 4-(1-Methyl-2-oxo-2-phenylethyl)benzoate[51] ***(3w)***. Prepared following the general procedure C from compound **1w** with a reaction time of 2 h. The crude product was purified *via* flash column chromatography (15 g silica, LP/EtOAc 20:1, 10:1) to yield 37 mg (37%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01−7.95 (m, 2H), 7.95−7.89 (m, 2H), 7.52−7.44 (m, 1H), 7.43−7.32 (m, 4H), 4.74 (q, J = 6.9 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.55 (d, J = 6.9 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 199.79, 166.41, 146.63, 136.34, 133.14, 130.38, 129.35, 128.84, 128.70, 127.91, 61.03, 48.00, 27.90, 19.42, 14.44. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{19}O_3$: 283.1329; found: 283.1338

1-(4-Methoxyphenyl)-2-phenylethanone[56] ***(3x)***. Prepared following the general procedure C, with the deviation of using only 1 equiv of $PhMe_3NI$, from commercially available starting material with a reaction time of 2 h. The crude product was purified *via* column chromatography (LP/EtOAc 70:1−50:1) to yield 68 mg (64%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02−7.94 (m, 2H), 7.34−7.17 (m, 5H), 6.95−6.86 (m, 2H), 4.21 (s, 2H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 196.3, 163.6, 135.1, 131.0, 129.7, 129.5, 128.7, 126.9, 113.9, 55.5, 45.3.

Methyl 4-(Biphenyl-4-yl)-4-oxobutanoate[57] ***(3y)***. Prepared following the general procedure C, with the deviation of using 3 equiv of KOH, from commercially available fenbufen with a reaction time of 24 h. The crude product was purified *via* column chromatography (LP/EtOAc 30:1−1:1) to yield 72 mg (68%) of the title compound as yellow crystals. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10−8.02 (m, 2H), 7.73−7.66 (m, 2H), 7.66−7.59 (m, 2H), 7.52−7.43 (m, 2H), 7.43−7.36 (m, 1H), 3.72 (s, 3H), 3.35 (t, J = 6.7 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 197.7, 173.5, 146.0, 139.9, 135.3, 129.1, 128.7, 128.4, 127.4, 51.9, 33.5, 28.2. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{19}O_3$: 283.1329; found: 283.1333

Methyl 3-Methyl-4-oxo-4-(4-phenylphenyl)butanoate ***(3z)***. An 8 mL glass vial equipped with a magnetic stirring bar was charged with fenbufen (100 mg, 1 equiv), $PhMe_3NI$ (2 equiv), and KOH (3 equiv). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. Anisole (2 mL,

https://doi.org/10.1021/acs.joc.1c03158
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0.2 M) was added *via* a syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block for 3 h. The reaction mixture was cooled to room temperature, and additional $PhMe_3NI$ (2 equiv) and KOH (2 equiv) were added. Subsequently, the reaction was heated up to 130 °C and stirred for 4 days (with further addition of 2 equiv $PhMe_3NI$ and 2 equiv KOH after 48 h). The reaction was cooled to room temperature. HCl (2 N, 2 mL) were added, and the mixture was extracted three times with EtOAc (20 mL each). The combined organic phases were washed twice with 2 N HCl (3 mL each) and once with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The obtained crude product was purified *via* hand column with unmodified silica gel (15 g silica, LP/EtOAc 30:1−1:1), yielding 34 mg (31%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11−8.04 (m, 2H), 7.74−7.67 (m, 2H), 7.67−7.59 (m, 2H), 7.52−7.43 (m, 2H), 7.43−7.36 (m, 1H), 3.99 (dqd, J = 8.5, 7.2, 5.7 Hz, 1H), 3.66 (s, 3H), 3.00 (dd, J = 16.8, 8.4 Hz, 1H), 2.49 (dd, J = 16.8, 5.7 Hz, 1H), 1.27 (d, J = 7.2 Hz, 3H) $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 202.3, 172.9, 145.8, 140.0, 134.6, 129.1, 129.0, 128.3, 127.4, 127.3, 51.8, 37.3, 37.3, 18.0. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{21}O_3$: 297.1485; found: 297.1490

1-(4-Fluorophenyl)-2-phenyl-1-butanone[53] ***(4a)***. Prepared following the general procedure C, except for the use of $PhEt_3NI$ (2 equiv) instead of $PhMe_3NI$, from commercially available starting material with a reaction time of 5 h. The crude product was purified *via* column chromatography (8 g silica LP/EtOAc 50:1−40:1) to yield 83 mg (78%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, J = 8.9, 5.4 Hz, 2H), 7.52−7.11 (m, 5H), 7.03 (dd, J = 9.0, 8.3 Hz, 1H), 4.36 (t, J = 7.2 Hz, 2H), 2.17 (dp, J = 12.8, 7.3 Hz, 1H), 1.83 (dp, J = 13.6, 7.4 Hz, 1H), 0.88 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 198.6, 165.6 (d, J = 254.6 Hz), 139.6, 133.5, 131.4 (d, J = 9.2 Hz), 129.0, 128.3, 127.2, 115.7 (d, J = 21.8 Hz), 55.6, 27.2, 12.4 ^{19}F NMR (376 MHz, $CDCl_3$): δ = −105.7 HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{16}FO$: 243.1180; found: 243.1186

1,2-Bis(4-methoxyphenyl)-1-butanone[58] ***(4b)***. Prepared following the general procedure C, except for the use of $PhEt_3NI$ (2 equiv) instead of $PhMe_3NI$, from commercially available starting material with a reaction time of 4 h. The crude product was purified *via* column chromatography (15 g silica LP/EtOAc 30:1−20:1) to yield 74 mg (68%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00−7.91 (m, 2H), 7.25−7.17 (m, 2H), 6.90−6.78 (m, 4H), 4.35 (t, J = 7.3 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 2.23−2.08 (m, 1H), 1.82 (dq, J = 13.6, 7.4 Hz, 1H), 0.89 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 198.9, 163.2, 158.6, 132.2, 131.0, 130.1, 129.3, 114.3, 113.7, 55.5, 55.3, 54.2, 27.2, 12.4. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{21}O_3$: 285.1485; found: 285.1492

2-Methyl-5-phenyl-4-heptanone ***(4c)***. Prepared following the general procedure C, except for the use of $PhEt_3NI$ (2 equiv) instead of $PhMe_3NI$, from commercially available starting material with a reaction time of 18 h. The crude product was purified *via* column chromatography (15 g silica LP/Et_2O 100:1−100:3) to yield 65 mg (57%) of the title compound as a slightly yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.30 (m, 2H), 7.29−7.24 (m, 1H), 7.24−7.18 (m, 2H), 3.51 (t, J = 7.4 Hz, 1H), 2.33−2.17 (m, 2H), 2.17−2.00 (m, 2H), 1.72 (dp, J = 13.7, 7.5 Hz, 1H), 0.89−0.80 (m, 6H), 0.76 (d, J = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 210.2, 139.0, 128.8, 128.4, 127.1, 61.3, 51.0, 25.3, 24.3, 22.7, 22.3, 12.2. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{21}O$: 205.1587; found: 205.1593

1-(4-Fluorophenyl)-2,3-diphenylpropan-1-one[59] ***(5a)***. Prepared following the general procedure C, except for the use of $BnMe_3NCl$ (1.1 equiv) instead of $PhMe_3NI$, from commercially available starting material with a reaction time of 1 h. The crude product was purified *via* column chromatography (15 g silica, LP/EtOAc 150:1−100:1) to yield 119 mg (84%) of the title compound as white crystals. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99−7.89 (m, 2H), 7.32−7.13 (m, 8H), 7.13−7.06 (m, 2H), 7.05−6.96 (m, 2H), 4.78 (t, J = 7.2 Hz, 1H), 3.58 (dd, J = 13.7, 7.5 Hz, 1H), 3.08 (dd, J = 13.7, 7.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 197.7, 165.6 (d, J = 254.9 Hz), 139.7, 139.0, 133.2 (d, J = 3.0 Hz), 131.4, 131.3, 129.2, 129.1, 128.3 (d, J = 4.6 Hz), 127.3, 126.3, 115.6 (d, J = 21.9 Hz), 56.0, 40.2. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{18}FO$: 305.1336; found: 305.1354

1,2-Bis-(4-methoxy-phenyl)-3-phenyl-propan-1-one[60] ***(5b)***. Prepared following the general procedure C, except for the use of $BnMe_3NCl$ (1.1 equiv) instead of $PhMe_3NI$, from commercially available starting material with a reaction time of 2 h. The crude product was purified *via* column chromatography (15 g silica, LP/EtOAc 100:1, 40:1, 20:1, 10:1) to yield 121 mg (89%) of the title compound as white crystals. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96−7.87 (m, 2H), 7.24−7.11 (m, 5H), 7.11−7.04 (m, 2H), 6.87−6.75 (m, 4H), 4.72 (t, J = 7.2 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.53 (dd, J = 13.7, 7.3 Hz, 1H), 3.04 (dd, J = 13.7, 7.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 198.0, 163.3, 158.6, 140.1, 131.6, 131.0, 129.8, 129.3, 129.2, 128.2, 126.1, 114.3, 113.7, 55.5, 55.2, 54.7, 40.2. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{23}O_3$: 347.1642; found: 347.1650

5-Methyl-1,2-diphenyl-3-hexanone ***(5c)***. Prepared following the general procedure C, except for the use of $BnMe_3NCl$ (1.1 equiv) instead of $PhMe_3NI$, from commercially available starting material with a reaction time of 2 h. The crude product was purified *via* column chromatography (15 g silica, LP/Et_2O 100:1−100:3) to yield 115 mg (78%) of the title compound as white crystals. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47−7.29 (m, 7H), 7.29−7.23 (m, 1H), 7.22−7.16 (m, 2H), 4.07−3.98 (m, 1H), 3.56 (ddd, J = 13.7, 7.9, 1.6 Hz, 1H), 3.03 (ddd, J = 13.7, 6.8, 1.4 Hz, 1H), 2.29 (dt, J = 6.3, 1.3 Hz, 2H), 2.25−2.09 (m, 1H), 0.89 (dd, J = 6.6, 1.2 Hz, 3H), 0.79 (dd, J = 6.5, 1.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 209.3, 139.9, 138.5, 129.1, 128.9, 128.5, 128.3, 128.0, 127.3, 127.1, 126.1, 61.3, 51.4, 38.7, 24.2, 22.6, 22.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{23}O$: 267.1743; found: 267.1755

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c03158.

Detailed procedure for quantitative ^{19}F NMR measurements, complete optimization screening data, experimental procedures, and characterization data for all compounds isolated (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

Open Access is funded by the Austrian Science Fund (FWF).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the Austrian Science Fund (FWF, project number P33064-N).

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https://doi.org/10.1021/acs.joc.1c03158
J. Org. Chem. 2022, 87, 4305−4315

D I.2 Manuscript 1 – Supporting Information

Detailed procedure for quantitative ^{19}F-NMR measurements, complete optimization screening data, experimental procedures, and characterization data for all compounds isolated.

Johanna Templ and Michael Schnürch

Supporting Information for

Selective α-Methylation of Aryl Ketones Using Quaternary Ammonium Salts as Solid Methylating Agents

J. Org. Chem. 2022, 87, 6, 4305 – 4315. doi: 10.1021/acs.joc.1c03158

Supporting Information

Selective α-Methylation of Aryl Ketones using Quaternary Ammonium salts as solid Methylating Agents

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General Experimental Details

All Chemicals were purchased from commercial suppliers and, unless noted otherwise, used without further purification. NaO^{t}Bu, $Pd_2(dba)_3$, and DPE-Phos were strictly stored and handled in the glove box under argon atmosphere. Degassed and dry THF was stored over molecular sieves under argon using AcroSeal™ septum. The 8 mL glass vials were sealed with Wheaton® screw caps containing a PTFE faced 14B styrene-butadiene rubber liner for small-scale reaction above room temperature and heated in a metallic reaction block. All reaction temperatures refer to external temperatures.

^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR spectra were recorded on a Bruker Avance UltraShield 400 at ambient temperature. Chemical Shifts (δ) are reported in ppm, using Me_4Si as internal standard. Coupling constants (*J*) are given in Hertz (Hz) and multiplicities are assigned as s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.
Quantitative ^{19}F-NMR spectra were recorded in a non-decoupled mode with a prolonged relaxation delay (d1 = 20 s), a narrowed spectral width (SW = 70 ppm), and a modified transmitter excitation frequency (O1T) to place the center of the spectrum between the peaks of interest (for details see Optimization Screening).

Thin Layer Chromatography (TLC) analysis was performed on aluminum-backed unmodified Merck silica gel 60 F_{245} plates. Visualization was realized under UV irradiation or *via* heat staining using a ceric ammonium molybdate aqueous solution. For flash column chromatography, Merck silica gel 60 (40 µm – 63 µm) was used, and purification was either done by hand-column or on a Büchi® Pure C-850 FlashPrep System.

GC-MS analysis was carried out on a Thermo Finnigan Focus GC/DSQ II with a standard capillary column RXi-5Sil MS column (30 m, 0.25 mm ID, 0.25 µm df) using the following standardized temperature program: 2 min at 100 °C, 35 °C/min until 300 °C, 4 min at 300 °C.

HR-MS analysis was performed on an Agilent 6230 LC TOFMS mass spectrometer equipped with an Agilent Dual AJS ESI-Source. The mass spectrometer was connected to a liquid chromatography system of the 1100/1200 series from Agilent Technologies, Palo Alto, CA, USA. The system consisted of a 1200SL binary gradient pump, a degasser, a column thermostat, and an HTC PAL autosampler (CTC Analytics AG, Zwingen, Switzerland). A silica-based Phenomenex C-18 Security Guard Cartridge was used as a stationary phase. Data evaluation was performed using Agilent MassHunter Qualitative Analysis B.07.00. Identification was based on peaks obtained from extracted ion chromatograms (extraction width ± 20 ppm).

General Procedures

Optimization Screening

General Procedure A:

An 8 mL glass vial equipped with a magnetic stirring bar was charged with benzyl 4-fluorophenyl ketone **(1a)** (50 mg, 0.233 mmol, 1 equiv.), the desired ammonium salt (350 mmol, 1.5 equiv. *or 0.467 mmol, 2 equiv.*) and the base (0.467 mmol, 2 equiv.). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. The solvent (1

mL, 0.23 M) was added *via* a syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton® cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 100 °C (for low boiling solvents) or 130 °C in a metallic heating block. After 18 – 22 h at respective temperatures, the reaction was cooled to room temperature.

Sample preparation for quant. ^{19}F-NMR:
100 µL of a solution of trifluorotoluene in $CHCl_3$ (0.49 mol/mL) was added to the reaction mixture *via* Eppendorf® pipette. The inhomogeneous mixture was centrifuged, and 0.5 mL of the supernatant solution were transferred to an NMR tube. 0.3 mL $CDCl_3$ were added to the NMR tube, and the liquid content was homogenized thoroughly.

Quant. ^{19}F-NMR instrument parameters and processing:
NMR spectra were shimmed for $CDCl_3$ and recorded with the following changes in acquisition parameters:

- transmitter excitation frequency (O1T) = -87 ppm
- spectral width = 70 ppm
- relaxation delay = 20 s

After standard Fourier transformation, the recorded spectra were processed by MestReNova v12 software as following[1]:

- Apodization along t1: exponential 0.50 Hz
- Zero filling along t1: 512K
- Auto Phase Correction (Algorithms: Global, Selective, Metabonomics, Whitening, Min. Entropy, Baseline Optimization, Regions Analysis; Initial Phase: Zero)
- Auto Baseline Correction along t1: Ablative (5 Points, 10 Passes)

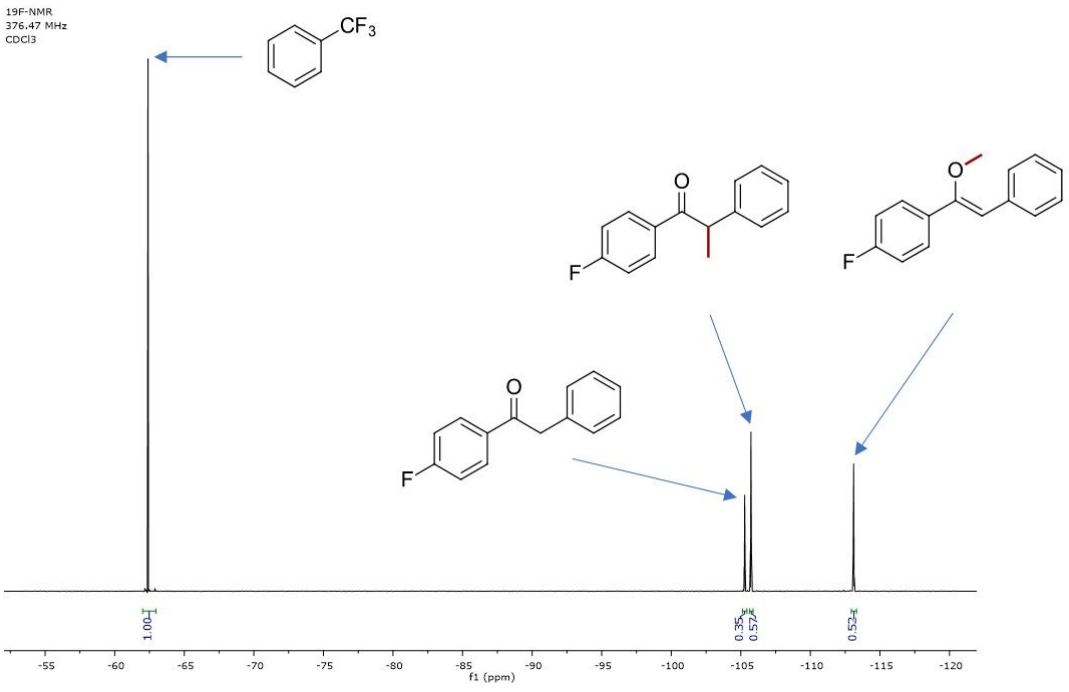
The following ^{19}F-NMR should serve as an example spectrum used for evaluation.

2a

3a

1a

Figure S1. example spectrum for quantitative ^{19}F-NMR used for evaluation



Precursor Synthesis

The α-monoarylated acetophenones **1g-l, 1n, 1o, 1q, 1r, 1v, 1w** were synthesized *via* Heck-type coupling of the acetophenone enolates and the respective aryl bromides, according to literature.[2]

General Procedure B:

In the glove box, a flame dried 8 mL glass vial equipped with a magnetic stirring bar was charged with NaO^{t}Bu (2.6 mmol, 1.3 equiv.), $Pd_2(dba)_3$ (5 mol-%) and DPE-Phos (10 mol-%). THF (2 mL, 1 M) was added, and the dark brownish-green mixture was stirred for 5 minutes at ambient temperatures. The aryl bromide (2 mmol, 1 equiv.) was added *via* Eppendorf® pipette, followed by rapid addition of the acetophenone (2.4 mmol, 1.2 equiv.) in one portion as solid or *via* Eppendorf® pipette if liquid. Immediate solid formation could be observed. The vial was closed with a Wheaton® screw cap and transferred out of the glove box. The mixture was heated to 70 °C in a metallic reaction block and stirred for 2-18 h at respective temperatures. After complete consumption of the starting material (GC-MS monitoring), water (10 mL) was added, and the mixture was extracted three times with diethyl ether (30 mL each). The combined organic phases were washed once with sat. NH_4Cl solution and once with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified *via* gradient flash column chromatography on silica gel using a mixture of LP and EtOAc.

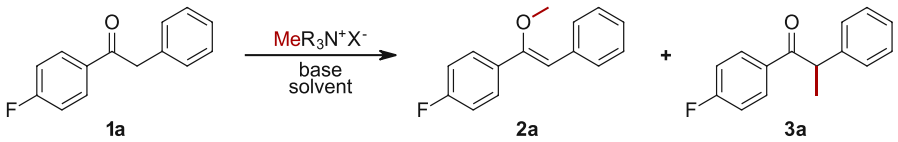
Substrate Scope Methylation

General Procedure C:

An 8 mL glass vial equipped with a magnetic stirring bar was charged with the respective diaryl ethanone (100 mg, 1 equiv.), trimethylphenyl ammonium iodide (2 equiv.), and KOH (2 equiv.). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. Anisole (2 mL, 0.2 M) was added *via* syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton® cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block for 2-4 h. After complete consumption of the starting material (TLC analysis), the reaction was cooled to room temperature. 2 mL of 2 N HCl were added, and the mixture was extracted 3 times with EtOAc (5 mL each). The combined organic phases were washed twice with 2 N HCl (1 mL each) and once with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The obtained crude product was purified *via* hand column with unmodified silica gel using a mixture of LP and EtOAc as eluent.

Optimization Screening for Methylation Reaction

Yields, determined by quant. ^{19}F-NMR, for the depicted reaction, are shown in the tables below. The following parameters were screened:



1a **2a** **3a**

Solvent

Reactions were performed following general procedure A using $Me_4N^+Br^-$ (0.350 mmol, 1.5 equiv.) as methylating agent and KOH (0.467 mmol, 2 equiv.) as base with 1 mL solvent (0.23 M) at respective temperatures for 22 h.

- toluene [CAS: 108-88-3] at 130 °C
- MeTHF [CAS: 96-47-9] at 100 °C
- anisole [CAS: 100-66-3] at 130 °C
- CPME [CAS: 5614-37-9] at 130 °C
- EtOAc [CAS: 141-78-6] at 100 °C
- *γ*-valerolactone [CAS: 108-29-2] at 130 °C
- sulfolane [CAS: 126-33-0] at 130 °C
- NPr_3 [CAS: 102-69-2] at 130 °C
- *t*-BuOH [CAS: 75-65-0] at 100 °C
- pyridine [CAS: 110-86-1] at 130 °C

Table S1. Solvent Screening

entry	variation	yield (%)		
	solvent	**1a**	**2a**	**3a**
1	toluene	0	41	34
2	MeTHF	25	14	11
3	anisole	0	40	43
4	CPME	4	36	24
5	EtOAc	95	0	0
6	γ-valerolactone	94	0	0
7	sulfolane	8	4	4
8	NPr_3	10	4	4
9	*t*-BuOH	38	6	6
10	pyridine	0	33	22

Base

Reactions were performed following the general procedure A using $Me_4N^+Br^-$ (0.350 mmol, 1.5 equiv.) as methylating agent, 0.467 mmol (2 equiv.) of the respective base and anisole (1 mL, 0.23 M) as solvent at 130 °C for 18 h.

- $LiOH \cdot H_2O$ [CAS: 1310-66-3]

- NaOH [CAS: 1310-73-2]
- KOH [CAS: 1310-58-3]
- LiO^{t}Bu [CAS: 1907-33-1]
- KO^{t}Bu [CAS: 865-47-4]
- Cs_2CO_3 [CAS: 534-17-8]
- K_2CO_3 [CAS: 584-08-7]
- imidazole [CAS: 288-32-4]

Table S2. Base Screening

entry	variation	yield (%)		
	base	**1a**	**2a**	**3a**
1	no base	82	0	0
2	$LiOH \cdot H_2O$	99	0	0
3	NaOH	22	32	36
4	KOH	2	42	44
5	LiO^{t}Bu	-	-	-
6	KO^{t}Bu	8	32	22
7	Cs_2CO_3	41	26	27
8	K_2CO_3	94	0	0
9	imidazole	92	0	0

Reaction Time

Reactions were performed following general procedure A using $Me_4N^+Br^-$ (0.350 mmol, 1.5 equiv.) as methylating agent, KOH (0.467 mmol, 2 equiv.) as base, and anisole (1 mL, 0.23 M) as solvent at 130 °C.

Table S3. Reaction Time Screening

entry	variation	yield (%)		
	time [min]	**1a**	**2a**	**3a**
1	2	76	0	0
2	5	64	7	7
3	10	43	14	17
4	15	42	20	21
5	20	21	31	34
6	25	17	35	37
7	30	6	39	41
8	35	2	38	41
9	40	2	39	41
10	45	2	40	42
11	50	2	39	42
12	55	0	41	43
13	60	0	40	43

Studies for interconversion between *O*- and α-methylated product

Reactions were performed following general procedure A using $Me_4N^+Br^-$ (0.187 mmol, 2 equiv.) as methylating agent, KOH (0.187 mmol, 2 equiv.) as base, and anisole (0.4 mL, 0.23 M) as solvent at 130 °C for 1 h. The vials were charged with the following substrates:

- entry 1:
  benzyl 4-fluorophenyl ketone **(1a)** (0.093 mmol)
- entry 2:
  benzyl 4-fluorophenyl ketone **(1a)** (0.047 mmol), 1-Fluoro-4-(1-methoxy-2-phenylethenyl)benzene **(2a)** (0.044 mmol)
- entry 3:
  1-Fluoro-4-(1-methoxy-2-phenylethenyl)benzene **(2a)** (0.088 mmol)
- entry 4:
  benzyl 4-fluorophenyl ketone **(1a)** (0.047 mmol), 1-Fluoro-4-(1-methoxy-2-phenylethenyl)benzene **(2a)** (0.044 mmol)

Table S4. Screening for Independency of Product Formations

entry	substrate		yield (%)		
	1a [mmol]	**2a** [mmol]	**1a**	**2a**	**3a**
1	0.093	-	0	42	43
2	0.047	0.044	0	73	9
3	-	0.088	0	86	0
4	0.047	0.044	30	44	0

Ammonium Salt

Reactions were performed following the general procedure A using KOH (0.467 mmol, 2 equiv.) as base, 0.350 mmol (1.5 equiv.) of the respective ammonium salt and anisole (1 mL, 0.23 M) as solvent at 130 °C for 18 h.

- Me_4NCl [CAS: 75-57-0]
- Me_4NBr [CAS: 64-20-0]
- Me_4NI [CAS: 75-58-1]
- Me_3PhNCl [CAS: 138-24-9]
- Me_3PhNBr [CAS: 16056-11-4]
- Me_3PhNI [CAS: 98-04-4]
- Bu_3MeNCl [CAS: 56375-79-2]
- $BnMe_3NCl$ [CAS: 56-93-9]
- $(C_{16}H_{33})Me_3NBr$ [CAS: 57-09-0]
- betaine [CAS: 107-43-7]

Table S5. Ammonium Salt Screening

entry	variation	yield (%)		
	ammonium salt	**1a**	**2a**	**3a**
1	Me_4NCl	0	43	42
2	Me_4NBr	0	44	44

3	Me_4NI	30	23	29
4	Me_4NOAc	0	49	9
5	$PhMe_3NCl$	0	47	48
6	$PhMe_3NBr$	0	38	50
7	$PhMe_3NI$	0	18	78
8	Bu_3MeNCl	6	25	39
9	$BnMe_3NCl$	0	6	4
10	$(C_{16}H_{33})Me_3NBr$	0	47	25
11	betaine	30	2	5

Heating *via* microwave irradiation

An 8 mL round bottom microwave vial equipped with a magnetic stirring bar was charged with benzyl 4-fluorophenyl ketone **(1a)** (50 mg, 0.233 mmol, 1 equiv.), $PhMe_3NI$ (125 mg, 467 mmol, 2 equiv.) and KOH (26 mg, 0.467 mmol, 2 equiv.). The vial was sealed with a septum. Using a cannula, the vial was evacuated and backfilled with argon three times. The solvent (1 mL, 0.23 M) was added *via* a syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a microwave vial septum cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 110, 100, 90, and 80 °C, respectively, in a microwave oven. After 1 h the reaction was cooled to room temperature, and each sample was prepared for quant. ^{19}F-NMR following the general procedure A.

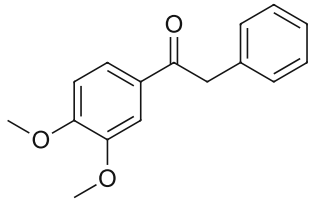
Table S6. Temperature Screening via Microwave Irradiation

entry	variation	yield (%)		
	temperature [°C]	**1a**	**2a**	**3a**
1	110	0	11	76
2	100	6	12	64
3	90	7	22	62
4	80	48	13	21

Characterization data for all synthetic compounds

All compounds synthesized are described in the literature, except **3d** and **3z**. For known compounds, spectral data is in agreement with the literature.

Precursor Synthesis



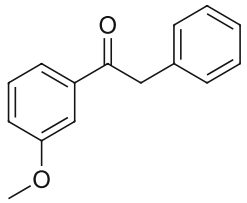
1-(3,4-Dimethoxyphenyl)-2-phenylethanone[3] (1g) [CAS: 3141-93-3]

Prepared, following the general procedure B from 3,4-dimethoxyacetophenone and bromobenzene heated for 2 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0-40 %) to yield 443 mg (86 %) of the title compound as a slightly yellow oil.

R_f = 0.47 (LP:EtOAc 2:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.58 (d, *J* = 2.1 Hz, 1H), 7.39 – 7.22 (m, 5H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.26 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 196.3, 153.3, 149.1, 135.1, 129.7, 129.3, 128.6, 126.8, 123.5, 110.7, 110.0, 56.0, 55.9, 45.2.



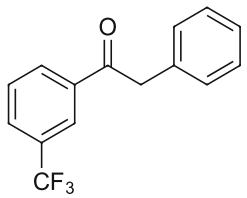
1-(3-Methoxyphenyl)-2-phenylethanone[2] (1h) [CAS: 62381-24-2]

Prepared, following the general procedure B from 3-methoxyacetophenone and bromobenzene heated for 3 h. The crude product was purified *via* flash hand-column chromatography (60 g silica, LP:EtOAc 70:1, 60:1, 40:1) to yield 305 mg (67%) of the title compound as a colorless oil.

R_f = 0.30 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 – 7.58 (m, 1H), 7.55 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.43 – 7.31 (m, 3H), 7.31 – 7.26 (m, 3H), 7.11 (ddd, *J* = 8.2, 2.7, 0.9 Hz, 1H), 4.28 (s, 2H), 3.84 (s, 3H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 197.5, 159.9, 138.0, 134.6, 129.6, 129.5, 128.7, 126.9, 121.3, 119.7, 112.9, 55.4, 45.7.



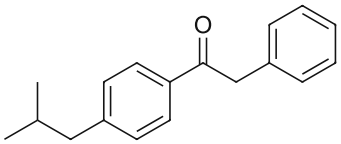
2-Phenyl-1-[3-(trifluormethyl)phenyl]ethanone[4] (1i) [CAS: 1533-04-6]

Prepared, following the general procedure B from 3-trifluoromethylacetophenone and bromobenzene heated for 4 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0-15 %) to yield 391 mg (74 %) of the title compound as orange oil.

R_f = 0.36 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.26 (tt, *J* = 1.8, 0.8 Hz, 1H), 8.16 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.81 – 7.70 (m, 1H), 7.56 (tt, *J* = 7.9, 0.8 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.29 – 7.18 (m, 3H), 4.29 (s, 2H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 196.3, 137.1, 133.9, 131.9 (d, *J* = 1.4 Hz), 131.2 (q, *J* = 34.0 Hz), 129.6 (q, *J* = 3.6 Hz), 129.5, 129.4, 128.9, 127.3, 125.5 (q, *J* = 3.8 Hz), 123.7 (d, *J* = 274.8 Hz), 45.70.



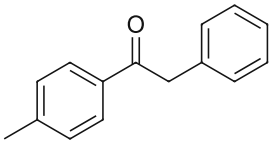
1-[4-(2-Methylpropyl)phenyl]-2-phenylethanone (1j) [CAS: 60312-92-7]

Prepared, following the general procedure B from 4'-Isobutylacetophenone and bromobenzene heated for 4 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0-20 %) to yield 415 mg (82 %) of the title compound as a yellow oil.

R_f = 0.45 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.03 – 7.96 (m, 2H), 7.42 – 7.23 (m, 7H), 4.30 (s, 2H), 2.57 (d, *J* = 7.2 Hz, 2H), 2.04 – 1.86 (m, *J* = 6.9 Hz, 1H), 0.96 (d, *J* = 6.7 Hz, 6H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 197.2, 147.6, 134.8, 134.4, 129.5, 129.3, 128.6, 126.8, 45.3, 30.1, 22.3.



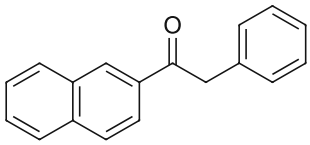
1-(4-Methylphenyl)-2-phenylethanone[5] (1k) [CAS: 2001-28-7]

Prepared, following the general procedure B from 4-Methylacetophenone and bromobenzene heated for 3 h. The crude product was purified *via* flash hand-column chromatography (55 g silica, LP:EtOAc 80:1, 70:1, 60:1, 40:1) to yield 302 mg (72 %) of the title compound as a colorless oil.

R_f = 0.40 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.9 Hz, 2H), 7.36 – 7.24 (m, 7H), 4.28 (s, 2H), 2.42 (s, 3H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 197.4, 144.1, 134.9, 134.2, 129.5, 129.4, 128.8, 128.7, 126.9, 45.5, 21.7.



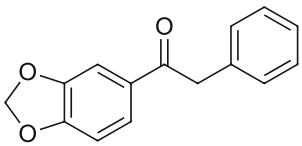
1-(2-Naphthalenyl)-2-phenylethanone[5] (1l) [CAS: 1762-15-8]

Prepared, following the general procedure B from 2-acetylnaphthalene and bromobenzene heated for 18 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0-40 %) to yield 396 mg (80 %) of the title compound as an off-white solid.

R_f = 0.34 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 1.8 Hz, 1H), 8.00 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.88 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.85 – 7.73 (m, 2H), 7.57 – 7.41 (m, 2H), 7.32 – 7.15 (m, 5H), 4.34 (s, 2H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 197.6, 135.6, 134.7, 134.0, 132.5, 130.4, 129.7, 129.5, 128.7, 128.6, 128.6, 127.8, 126.9, 126.8, 124.3, 45.6.



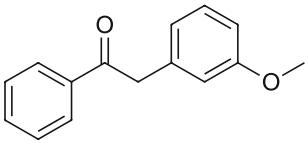
1-(1,3-Benzodioxol-5-yl)-2-phenylethanone[5] (1n) [CAS: 126266-77-1]

Prepared, following the general procedure B from 5-acetyl-1,3-benzodiocole and bromobenzene heated for 10 h. The crude product was purified *via* flash column chromatography (90 g silica, LP and EtOAc 0-40 %) to yield 471 mg (98%) of the title compound as a slightly yellow oil.

R_f = 0.27 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.49 (d, *J* = 1.7 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.29 – 7.21 (m, 3H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.03 (s, 2H), 4.21 (s, 2H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 195.8, 151.9, 148.3, 134.9, 131.5, 129.4, 128.7, 128.7, 126.9, 125.1, 108.8, 108.4, 107.9, 101.9, 45.4.



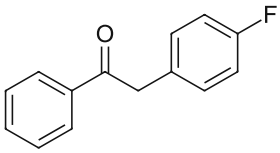
2-(3-Methoxyphenyl)-1-phenylethanone[5] (1o) [CAS: 29955-26-8]

Prepared, following the general procedure B from acetophenone and 4-bromoanisole heated for 18 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0-40 %) to yield 267 mg (59 %) of the title compound as a yellow oil.

R_f = 0.32 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06 - 7.97 (m, 2H), 7.60 – 7.51 (m, 1H), 7.51 – 7.41 (m, 2H), 7.25 (t, *J* = 7.8 Hz, 1H), 6.91 – 6.77 (m, 3H), 4.26 (s, 2H), 3.79 (s, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 197.5, 159.8, 136.6, 136.1, 133.2, 129.7, 128.7, 121.9, 115.2, 112.4, 55.2, 45.6.



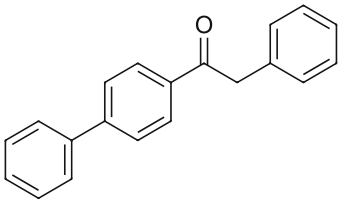
2-(4-Fluorphenyl)-1-phenylethanone[2] (1q) [CAS: 347-91-1]

Prepared, following the general procedure B from acetophenone and 1-bromo-4-fluorobenzene heated for 18 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0-40 %) to yield 255 mg (60 %) of the title compound as a slightly yellow oil.

R_f = 0.31 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06 – 7.94 (m, 2H), 7.62 – 7.52 (m, 1H), 7.52 – 7.39 (m, 2H), 7.28 – 7.19 (m, 2H), 7.08 – 6.97 (m, 2H), 4.27 (s, 2H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 197.5, 162.0 (d, *J* = 245.2 Hz), 136.6, 133.4, 131.2 (d, *J* = 8.0 Hz), 130.3 (d, *J* = 3.3 Hz), 128.8, 128.6, 115.6 (d, *J* = 21.4 Hz), 44.6.



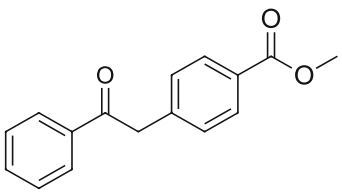
1-[1,1'-Biphenyl]-4-yl-2-phenylethanone[5] (1r) [CAS: 2001-23-2]

Prepared, following the general procedure B from 4'-phenylacetophenone and bromobenzene heated for 18 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0-40 %) to yield 207 mg (38 %) of the title compound as a colorless oil.

R_f = 0.31 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.12 – 8.04 (m, 2H), 7.70 – 7.64 (m, 2H), 7.64 – 7.59 (m, 2H), 7.50 – 7.43 (m, 2H), 7.43 – 7.22 (m, 6H), 4.31 (s, 2H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 197.2, 145.8, 139.8, 135.3, 134.7, 129.5, 129.3, 129.0, 128.7, 128.3, 127.3, 127.3, 126.9, 45.6.



Methyl 4-(2-oxo-2-phenylethyl)benzoate[6] (1v) [CAS: 94161-45-2]

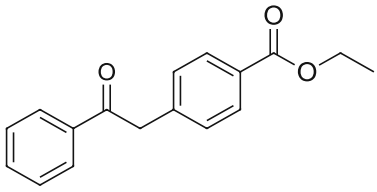
Prepared, following the general procedure B from acetophenone methyl 4-iodobenzoate heated for 4 h. The crude product was

purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0-20 %) to yield 285 mg (37 %) of the title compound as a white solid.

R_f = 0.58 (LP:EtOAc 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04 – 7.98 (m, 4H), 7.62 – 7.54 (m, 1H), 7.51 – 7.44 (m, 2H), 7.37 – 7.32 (m, 2H), 4.35 (s, 2H), 3.90 (s, 3H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 196.9, 167.0, 139.9, 136.5, 133.5, 130.0, 129.7, 129.0, 128.8, 128.6, 77.4, 52.2, 45.5.



Ethyl 4-(2-oxo-2-phenylethyl)benzoate[7] (1w) [CAS: 898776-62-0]

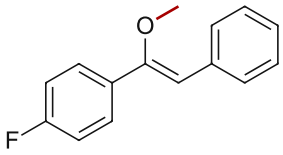
Prepared, following the general procedure B from acetophenone ethyl 4-iodobenzoate heated for 4 h. The crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0-20 %) to yield 360 mg (45 %) of the title compound as a white solid.

R_f = 0.55 (LP:EtOAc 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04 – 7.97 (m, 4H), 7.62 – 7.53 (m, 1H), 7.51 – 7.42 (m, 2H), 7.37 – 7.31 (m, 2H), 4.41 – 4.31 (m, 4H), 1.38 (t, J = 7.1 Hz, 3H)

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 196.9, 166.5, 139.8, 136.5, 133.5, 130.0, 129.6, 128.8, 128.6, 61.0, 45.5, 14.4.

Substrate Scope Methylation



1-Fluoro-4-(1-methoxy-2-phenylethenyl)benzene (2a)[8] [CAS 874394-40-8]

An 8 mL glass vial equipped with a magnetic stirring bar was charged with benzyl 4-fluorophenyl ketone **(1a)** (100 mg, 0.467 mmol, 1 equiv.), Me_4NBr (119 mg, 770 mmol, 1.65 equiv.) and KOH (79 mg, 1.4 mmol, 3 equiv.). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. The toluene (2 mL, 0.23 M) was added *via* syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton® cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block. After 18 h at respective temperatures, the reaction was cooled to room temperature, and solids were centrifuged off. The supernatant solution was transferred to a round bottom flask, and the solid residue was washed three times with small amounts DCM. The combined organic phases were concentrated. The crude oil was further purified *via* hand-column chromatography (8 g silica LP:Et_3N 100:1) to yield 46 mg (43 %) of the title compound as white crystals. NMR shifts indicate mainly Z-isomer formation.

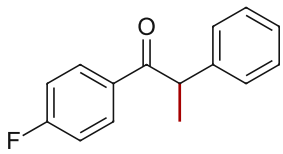
R_f = 0.57 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74 – 7.67 (m, 2H), 7.60 – 7.50 (m, 2H), 7.42 – 7.32 (m, 2H), 7.28 – 7.19 (m, 1H), 7.16 – 7.03 (m, 2H), 6.06 (s, 1H), 3.63 (s, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 163.0 (d, *J* = 247.9 Hz), 155.4, 135.9, 132.6 (d, *J* = 3.3 Hz), 128.7, 128.6, 128.5 (d, *J* = 8.1 Hz), 126.8, 115.6 (d, *J* = 21.7 Hz), 112.8 (d, *J* = 1.4 Hz), 58.0.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -113.2

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{14}FO$: 229.1023; found: 229.1000



1-(4-Fluorophenyl)-2-phenyl-1-propanone (3a)[9] [CAS: 49660-97-1]

Prepared, following the general procedure C from commercially available starting material with a reaction time of 3 h. The crude product was purified *via* column chromatography (8 g silica LP:EtOAc 50:1, 45:1, 40:1) to yield 83 mg (78 %) of the title compound.

R_f = 0.46 (LP:EtOAc 5:1)

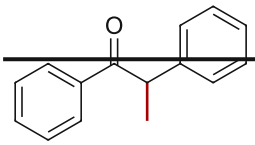
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 – 7.87 (m, 2H), 7.28 – 7.18 (m, 4H), 7.18 – 7.11 (m, 1H), 7.03 – 6.93 (m, 2H), 4.57 (q, *J* = 6.8 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 198.8, 165.6 (d, *J* = 254.6 Hz), 141.5, 133.0 (d, *J* = 3.0 Hz), 131.5 (d, *J* = 9.3 Hz), 129.20, 127.8, 127.1, 115.7 (d, *J* = 21.7 Hz), 48.1, 19.6.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -105.60.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{14}FO$: 229.1023; found: 229.1000

Compound **3a** was also prepared on a 1.4 mmol scale as follows:
A 25 mL round bottom flask was charged with benzyl 4-fluorophenyl ketone **(1a)** (300 mg, 1.4 mmol, 1 equiv.), $PhMe_3NI$ (751 mg, 2.8 mmol, 2 equiv.) and KOH (157 mg, 2.8 mmol, 2 equiv). The flask was closed with a septum. Using a cannula, the flask was evacuated and backfilled with argon three times. Anisole (6 mL, 0.23 M) was added *via* syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. The resulting inhomogeneous mixture was heated to 130 °C in an oil bath. After 5 h at respective temperatures, the reaction was cooled to room temperature. 10 mL of 2 N HCl were added, and the mixture was extracted 3 times with EtOAc (25 mL each). The combined organic phases were washed twice with 2 N HCl (3-5 mL each) and once with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The obtained crude product was purified *via* flash column chromatography (90 g silica, LP, and EtOAc 0-40 %) to yield 273 mg (85 %) of the title compound as a colorless oil. Analytical data were in accordance with the previous finding.



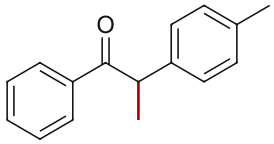
1,2-Diphenyl-1-propanone[2] (3b) [CAS: 2024-85-5]

Prepared, following the general procedure C from commercially available starting material with a reaction time of 3 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 50:1, 40:1) to yield: 73 mg (68 %) of the title compound as a colorless oil.

R_f = 0.35 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 – 7.93 (m, 2H), 7.53 – 7.43 (m, 1H), 7.43 – 7.34 (m, 2H), 7.30 (d, *J* = 4.3 Hz, 4H), 7.21 (ddd, *J* = 8.8, 4.8, 3.9 Hz, 1H), 4.70 (q, *J* = 6.9 Hz, 1H), 1.55 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 200.4, 141.6, 136.6, 132.9, 129.1, 128.9, 128.6, 127.9, 127.0, 48.0, 19.6.



2-(4-Methylphenyl)-1-phenyl-1-propanone[10] (3c) [CAS: 107271-15-8]

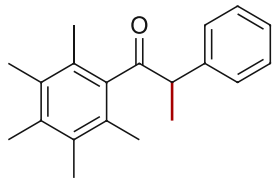
Prepared, following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 50:1) to yield 76 mg (74 %) of the title compound as a slightly yellow oil.

R_f = 0.39 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 – 7.94 (m, 2H), 7.52 – 7.43 (m, 1H), 7.43 – 7.34 (m, 2H), 7.23 – 7.16 (m, 2H), 7.15 – 7.08 (m, 2H), 4.67 (q, *J* = 6.8 Hz, 1H), 2.30 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 200.5, 138.6, 136.64, 136.6, 132.8, 129.8, 128.9, 128.6, 127.7, 47.6, 21.1, 19.6.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{17}O$: 225.1274; found: 225.1265



2-(2,3,4,5,6-Pentamethylphenyl)-1-phenyl-1-propanone (3d)

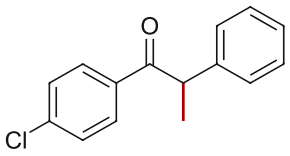
Prepared, following the general procedure C from commercially available starting material with a reaction time of 3.5 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 50:1) to yield 31 mg (31 %) of the title compound as off-white crystals.

R_f = 0.47 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 – 7.16 (m, 5H), 4.13 (q, *J* = 7.0 Hz, 1H), 2.23 (s, 15H), 1.64 (d, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 211.1, 140.1, 138.7, 135.5, 132.8, 128.8, 128.5, 127.1, 54.9, 16.9, 16.8, 16.0. [10]

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}O$: 281.1900; found: 281.1895



1-(4-Chlorophenyl)-2-phenyl-1-propanone[11] (3e) [CAS: 126866-24-8]

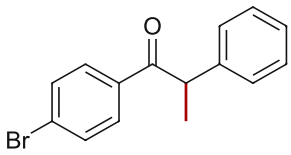
Prepared, following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 50:1) to yield 87 mg (85%) of the title compound.

R_f = 0.51 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.92 – 7.84 (m, 2H), 7.38 – 7.16 (m, 7H), 4.62 (q, *J* = 6.8 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 199.1, 141.3, 139.3, 134.9, 130.3, 129.2, 128.9, 127.8, 127.2, 48.2, 19.5.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{14}ClO$: 245.0728; found: 245.0712



1-(4-Bromophenyl)-2-phenyl-1-propanone[11] (3f) [CAS: 1133798-25-0]

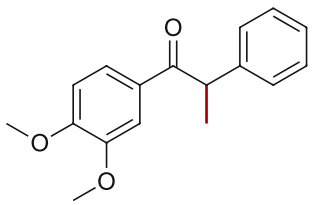
Prepared, following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 50:1) to yield 75 mg (74 %) of the title compound.

R_f = 0.48 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84 – 7.76 (m, 2H), 7.56 – 7.46 (m, 2H), 7.36 – 7.25 (m, 3H), 7.25 – 7.16 (m, 2H), 4.61 (q, *J* = 6.8 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 199.3, 141.3, 135.2, 131.9, 130.4, 129.2, 128.0, 127.8, 127.2, 48.2, 19.5.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{14}BrO$: 289.0223; found: 289.0218



1-(3,4-Dimethoxyphenyl)-2-phenyl-1-propanone[12] (3g) [CAS: 144053-89-4]

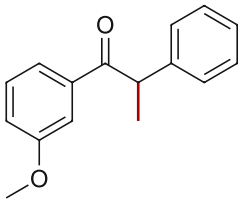
Prepared, following the general procedure C from compound **1g** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 40:1, 20:1, 10:1) to yield 72 mg (68 %) of the title compound.

R_f = 0.54 (LP:EtOAc 2:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.29 (d, *J* = 4.4 Hz, 4H), 7.19 (ddd, *J* = 8.6, 4.9, 3.9 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 4.65 (q, *J* = 6.9 Hz, 1H), 3.88 (d, *J* = 4.1 Hz, 6H), 1.52 (d, *J* = 6.8 Hz, 3H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ = 199.0, 153.1, 149.0, 142.2, 129.7, 129.1, 127.7, 126.9, 123.5, 111.1, 110.0, 56.1, 56.0, 47.6, 19.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}O_3$: 271.1329; found: 271.1323



1-(3-Methoxyphenyl)-2-phenyl-1-propanone[13] (3h) [CAS: 77669-94-4]

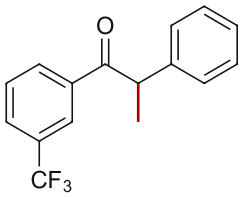
Prepared, following the general procedure C from compound **1h** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 70:1) to yield 88 mg (83 %) of the title compound as a slightly orange oil.

R_f = 0.32 (LP:EtOAc 5:1)

^1H-NMR (400 MHz, $CDCl_3$): δ = 7.51 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H), 7.47 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.34 – 7.21 (m, 5H), 7.21 – 7.12 (m, 1H), 6.99 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 4.64 (q, *J* = 6.9 Hz, 1H), 3.76 (s, 3H), 1.51 (d, *J* = 6.9 Hz, 3H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ = 200.2, 159.8, 141.6, 138.0, 129.5, 129.1, 127.8, 127.0, 121.5, 119.4, 113.2, 55.4, 48.1, 19.6.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{17}O_2$: 241.1223; found: 241.1205



2-Phenyl-1-[3-(trifluoromethyl)phenyl]-1-propanone[10] (3i) [CAS: 1776098-79-3]

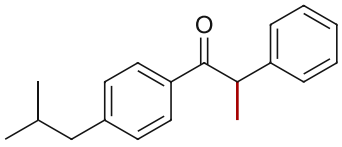
Prepared, following the general procedure C from compound **1i** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 80:1) to yield 73 mg (69 %) of the title compound.

R_f = 0.40 (LP:EtOAc 5:1)

^1H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (tt, *J* = 1.8, 0.8 Hz, 1H), 8.11 – 8.04 (m, 1H), 7.73 – 7.66 (m, 1H), 7.52 – 7.43 (m, 1H), 7.33 – 7.28 (m, 1H), 7.28 – 7.25 (m, 2H), 7.25 – 7.15 (m, 2H), 4.65 (q, *J* = 6.8 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ = 199.0, 140.9, 137.1, 132.0 (d, *J* = 1.5 Hz), 131.2 (q, *J* = 32.8 Hz), 129.3, 129.3 (q, *J* = 3.8 Hz), 129.2, 127.8, 127.3, 125.7 (q, *J* = 3.9 Hz), 123.0 (d, *J* = 275.8 Hz), 48.43, 19.47.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{14}F_3O$: 279.0991; found: 279.0986



1-[4-(2-Methylpropyl)phenyl]-2-phenyl-1-propanone (3j) [CAS: 1933951-19-9]

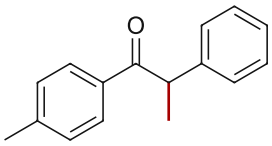
Prepared, following the general procedure C from compound **1j** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 100:1) to yield: 78 mg (74 %) of the title compound.

R_f = 0.48 (LP:EtOAc 5:1)

^1H-NMR (400 MHz, $CDCl_3$): δ = 7.93 – 7.85 (m, 2H), 7.35 – 7.25 (m, 4H), 7.25 – 7.18 (m, 1H), 7.18 – 7.12 (m, 2H), 4.69 (q, *J* = 6.9 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.85 (dh, *J* = 13.4, 6.7 Hz, 1H), 1.54 (d, *J* = 6.9 Hz, 3H), 0.88 (dd, *J* = 6.6, 0.6 Hz, 6H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ = 200.0, 147.3, 141.7, 134.3, 129.3, 128.9, 128.8, 127.8, 126.8, 47.7, 45.4, 30.1, 22.4, 22.3, 19.6.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{23}O$: 267.1743; found: 267.1739



1-(4-Methylphenyl)-2-phenyl-1-propanone[14] (3k) [CAS: 14161-82-1]

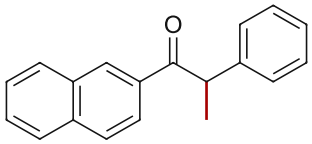
Prepared, following the general procedure C from compound **1k** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 70:1) to yield: 82 mg (77 %) of the title compound as a yellow oil.

R_f = 0.47 (LP:EtOAc 5:1)

^1H-NMR (400 MHz, $CDCl_3$): δ = 7.91 – 7.84 (m, 2H), 7.34 – 7.25 (m, 4H), 7.25 – 7.14 (m, 3H), 4.68 (q, *J* = 6.9 Hz, 1H), 2.35 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 3H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ = 200.0, 143.6, 141.8, 134.1, 129.3, 129.0, 129.0, 127.8, 126.9, 47.8, 21.7, 19.6.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{17}O$: 225.1274; found: 225.1252



1-(2-Naphthyl)-2-phenyl-1-propanone[15] (3l) [CAS: 113487-89-1]

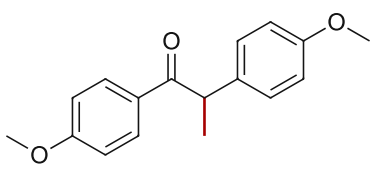
Prepared, following the general procedure C from compound **1l** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 80:1) to yield: 64 mg (61 %) of the title compound.

R_f = 0.39 (LP:EtOAc 5:1)

^1H-NMR (400 MHz, $CDCl_3$): δ = 8.52 – 8.47 (m, 1H), 8.03 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.90 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.82 (dd, *J* = 8.6, 1.8 Hz, 2H), 7.58-7.49 (m, 2H), 7.40 – 7.24 (m, 4H), 7.24 – 7.15 (m, 1H), 4.86 (q, *J* = 6.9 Hz, 1H), 1.61 (d, *J* = 6.9 Hz, 3H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ = 200.4, 141.7, 135.5, 134.0, 132.6, 130.6, 129.7, 129.1, 128.5, 128.4, 127.9, 127.8, 127.0, 126.8, 124.7, 48.1, 19.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{17}O$: 261.1274; found: 261.1267



1,2-Bis(4-methoxyphenyl)-1-propanone[16] (3m) [CAS: 35258-41-4]

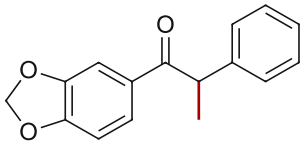
Prepared, following the general procedure C from commercially available starting material with a reaction time of 4 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 10:1) to yield 76 mg (74 %) of the title compound.

R_f = 0.20 (LP:EtOAc 5:1)

^1H-NMR (400 MHz, $CDCl_3$): δ = 7.98 – 7.90 (m, 2H), 7.24 – 7.16 (m, 2H), 6.90 – 6.78 (m, 4H), 4.60 (q, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 1.49 (d, *J* = 6.9 Hz, 3H).

$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ = 199.2, 163.3, 158.5, 134.1, 131.2, 129.6, 128.8, 114.5, 113.8, 55.5, 55.3, 46.7, 19.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}O_3$: 271.1329; found: 271.1326



1-(2H-1,3-Benzodioxol-5-yl)-2-phenyl-1-propanone[17] (3n)

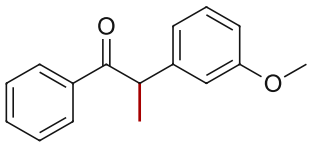
Prepared, following the general procedure C from compound **1n** with a reaction time of 2 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 80:1) to yield 65 mg (61 %) of the title compound as white crystals.

R_f = 0.32 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.44 (d, *J* = 1.7 Hz, 1H), 7.34 – 7.22 (m, 4H), 7.22 – 7.15 (m, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 5.98 (s, 2H), 4.59 (q, *J* = 6.8 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 198.5, 151.6, 148.2, 141.9, 131.4, 129.1, 127.8, 127.0, 125.1, 108.7, 107.9, 101.9, 47.8, 19.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}O_3$: 255.1016; found: 255.1006



2-(3-Methoxyphenyl)-1-phenyl-1-propanone[10] (3o) [CAS: 197640-99-6]

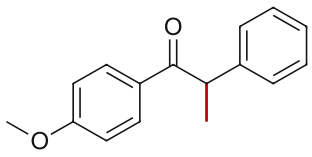
Prepared, following the general procedure C from compound **1o** with a reaction time of 3 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 80:1) to yield 75 mg (71 %) of the title compound as a yellow oil.

R_f = 0.35 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 – 7.93 (m, 2H), 7.53 – 7.42 (m, 1H), 7.42 – 7.33 (m, 2H), 7.26 – 7.16 (m, 1H), 6.89 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 6.84 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.75 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 4.66 (q, *J* = 6.8 Hz, 1H), 3.76 (s, 3H), 1.54 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 200.2, 160.1, 143.1, 136.6, 132.9, 130.1, 128.8, 128.6, 120.3, 113.6, 112.2, 55.3, 48.0, 19.5.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{17}O_2$: 241.1223; found: 241.1217



1-(4-Methoxyphenyl)-2-phenyl-1-propanone[10] (3p) [CAS: 35258-38-9]

Prepared, following the general procedure C from commercially available starting material with a reaction time of 3 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 60:1, 50:1) to yield 73 mg (70 %) of the title compound as a slightly yellow oil.

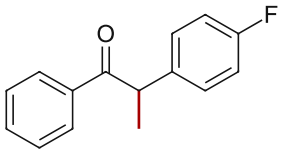
Procedure for one-pot *O*- and *α*-methylation: Prepared, following the general procedure C from commercially available 1-(4-hydroxyphenyl)-2-phenylethanone with a reaction time of 6 h. After 3 h reaction time and before the workup, another 2 equiv of $PhMe_3NI$ and KOH each were added at room temperature, and the reaction was subsequently heated up again to 130 °C for another 3 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 70:1-50:1) to yield 95 mg (84 %) of the title compound as a slightly yellow oil. Spectra were according to compound **3p**.

R_f = 0.30 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 – 7.91 (m, 2H), 7.33 – 7.24 (m, 4H), 7.24 – 7.15 (m, 1H), 6.90 – 6.81 (m, 2H), 4.65 (q, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 1.52 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 199.0, 163.3, 142.0, 131.2, 129.6, 129.0, 127.8, 126.9, 113.8, 55.5, 47.6, 19.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{17}O_2$: 241.1223; found: 241.1236



2-(4-Fluorophenyl)-1-phenyl-1-propanone[10] (3q) [CAS: 413615-59-5]

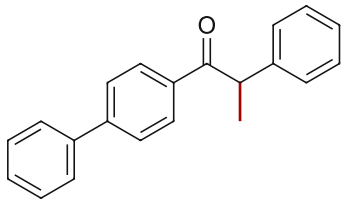
Prepared, following the general procedure C from compound **1q** with a reaction time of 2.5 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 80:1) to yield: 82 mg (77 %) of the title compound as a colorless oil.

R_f = 0.39 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 – 7.91 (m, 2H), 7.54 – 7.45 (m, 1H), 7.44 – 7.34 (m, 2H), 7.31 – 7.21 (m, 2H), 7.04 – 6.93 (m, 2H), 4.70 (q, *J* = 6.9 Hz, 1H), 1.53 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 200.3, 161.9 (d, *J* = 245.4 Hz), 137.2 (d, *J* = 3.3 Hz), 136.4, 133.0, 129.4 (d, *J* = 8.0 Hz), 128.8, 128.7, 115.9 (d, *J* = 21.3 Hz), 47.0, 19.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{14}FO$: 229.1023; found: 229.1003



1-[1,1'-Biphenyl]-4-yl-2-phenyl-1-propanone[10] (3r) [CAS: 187676-86-4]

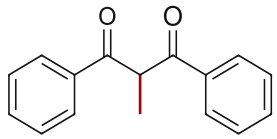
Prepared, following the general procedure C from compound **1r** with a reaction time of 2.5 h. The crude product was purified *via* column chromatography (8 g silica, LP:EtOAc 75:1) to yield: 55 mg (52 %) of the title compound as an off-white solid.

R_f = 0.40 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.09 – 8.02 (m, 2H), 7.65 – 7.55 (m, 4H), 7.48 – 7.36 (m, 4H), 7.36 – 7.28 (m, 4H), 7.28-7.19 (m, 1H), 4.74 (q, *J* = 6.8 Hz, 1H), 1.59 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 199.9, 145.5, 141.6, 139.9, 135.2, 129.4, 129.1, 129.0, 128.2, 127.8, 127.3, 127.2, 127.0, 48.0, 19.6.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{19}O$: 287.1430; found: 287.1439



2-Methyl-1,3-diphenyl-1,3-propanedione[18] (3s) [CAS: 1846-29-3]

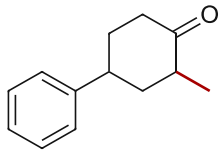
Prepared, following the general procedure C from commercially available starting material with a reaction time of 2.5 h. The crude product was purified *via* column chromatography (LP:EtOAc 80:1, 50:1, 20:1) to yield 36 mg (35 %) of the title compound as white crystals.

R_f = 0.15 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 – 7.92 (m, 4H), 7.60 – 7.50 (m, 2H), 7.49 – 7.39 (m, 4H), 5.28 (q, *J* = 7.0 Hz, 1H), 1.60 (d, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 197.3, 135.7, 133.5, 128.9, 128.6, 51.0, 14.4.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{15}O_2$: 239.1067; found: 239.1052



2-Methyl-4-phenylcyclohexanone[19] (3t) [CAS: 88958-99-0]

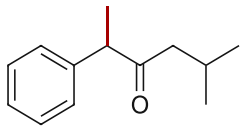
Prepared, following the general procedure C from commercially available starting material with a reaction time of 18 h. The crude product was purified *via* column chromatography (8 g silica LP:EtOAc 80:1-10:1) to yield 18 mg (17 %) of the title compound as a colorless oil.

R_f = 0.42 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.23 (m, 2H), 7.23 – 7.14 (m, 3H), 3.10 (tt, *J* = 12.4, 3.5 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.53 – 2.42 (m, 2H), 2.26 – 2.14 (m, 2H), 1.98 – 1.81 (m, 1H), 1.69 – 1.57 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 212.7, 144.9, 128.7, 126.8, 126.7, 44.9, 43.6, 43.5, 41.7, 35.1, 14.6.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{17}O$: 189.1274; found: 189.1277



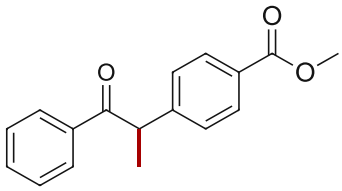
5-Methyl-2-phenyl-3-hexanone[20] (3u) [CAS: 103392-14-9]

Prepared, following the general procedure C from commercially available starting material with a reaction time of 16 h. The crude product was purified *via* flash column chromatography (15 g silica, LP:EtOAc 80:1) to yield 80 mg (77 %) of the title compound as a colorless oil.

R_f = 0.44 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.27 (m, 2H), 7.29 – 7.19 (m, 1H), 7.21 – 7.16 (m, 2H), 3.71 (q, *J* = 7.0 Hz, 1H), 2.30 – 2.15 (m, 2H), 2.09 (dp, *J* = 13.4, 6.6 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 210.5, 140.6, 128.9, 128.0, 127.2, 53.4, 50.1, 24.5, 22.7, 22.4, 17.5.



Methyl 4-(1-methyl-2-oxo-2-phenylethyl)benzoate[21] (3v) [CAS: 255836-39-6]

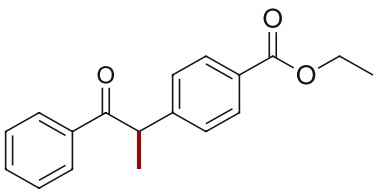
Prepared, following the general procedure C from compound **1v** with a reaction time of 2 h. The crude product was purified *via* flash column chromatography (15 g silica, LP:EtOAc 20:1, 10:1) to yield 34 mg (32 %) of the title compound as a colorless oil.

R_f = 0.36 (LP:EtOAc 1:3)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 – 7.89 (m, 4H), 7.53 – 7.44 (m, 1H), 7.43 – 7.32 (m, 4H), 4.74 (q, J = 6.8 Hz, 1H), 3.87 (s, 3H), 1.55 (d, J = 6.9 Hz, 3H)

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 199.7, 166.8, 146.7, 136.3, 133.1, 130.4, 128.9, 128.8, 128.7, 127.9, 52.1, 47.9, 19.4.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{17}O_3$: 269.1172; found: 269.1196



Ethyl 4-(1-methyl-2-oxo-2-phenylethyl)benzoate[17] (3w) [CAS: 255836-41-0]

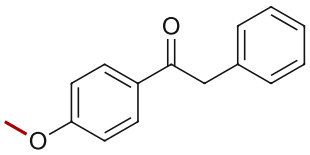
Prepared, following the general procedure C from compound **1w** with a reaction time of 2 h. The crude product was purified *via* flash column chromatography (15 g silica, LP:EtOAc 20:1, 10:1 to yield 37 mg (37 %) of the title compound as a colorless oil.

R_f = 0.32 (LP:EtOAc 1:3)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 – 7.95 (m, 2H), 7.95 – 7.89 (m, 2H), 7.52 – 7.44 (m, 1H), 7.43 – 7.32 (m, 4H), 4.74 (q, J = 6.9 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.55 (d, J = 6.9 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 199.7, 166.4, 146.6, 136.3, 133.1, 130.3, 129.3, 128.8, 128.7, 127.9, 61.0, 48.0, 27.9, 19.4, 14.4.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{19}O_3$: 283.1329; found: 283.1338



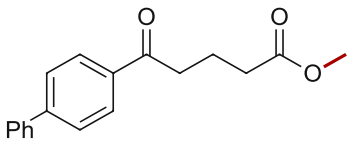
1-(4-Methoxyphenyl)-2-phenylethanone[22] (3x) [CAS: 1023-17-2]

Prepared, following the general procedure C, with the deviation of using only 1 equiv of $PhMe_3NI$, from commercially available starting material with a reaction time of 2 h. The crude product was purified *via* column chromatography (LP:EtOAc 70:1-50:1) to yield 68 mg (64 %) of the title compound as a colorless oil.

R_f = 0.18 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.02 – 7.94 (m, 2H), 7.34 – 7.17 (m, 5H), 6.95 – 6.86 (m, 2H), 4.21 (s, 2H), 3.82 (s, 3H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 196.3, 163.6, 135.1, 131.0, 129.7, 129.5, 128.7, 126.9, 113.9, 55.5, 45.3.



Methyl 4-(biphenyl-4-yl)-4-oxobutanoate[23] (3y) [CAS: 54011-27-7]

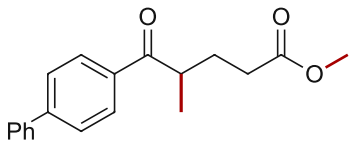
Prepared, following the general procedure C, with the deviation of using 3 equiv of KOH, from commercially available fenbufen with a reaction time of 24 h. The crude product was purified *via* column chromatography (LP:EtOAc 30:1-1:1) to yield 72 mg (68 %) of the title compound as yellow crystals.

R_f = 0.49 (LP:EtOAc 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.10 – 8.02 (m, 2H), 7.73 – 7.66 (m, 2H), 7.66 – 7.59 (m, 2H), 7.52 – 7.43 (m, 2H), 7.43 – 7.36 (m, 1H), 3.72 (s, 3H), 3.35 (t, *J* = 6.7 Hz, 2H), 2.80 (t, *J* = 6.6 Hz, 2H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 197.7, 173.5, 146.0, 139.9, 135.3, 129.1, 128.7, 128.4, 127.4, 51.9, 33.5, 28.2.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{19}O_3$: 283.1329; found: 283.1333



Methyl 3-methyl-4-oxo-4-(4-phenylphenyl)butanoate (3z) [CAS: 1305108-60-4]

An 8 mL glass vial equipped with a magnetic stirring bar was charged with fenbufen (100 mg, 1 equiv.), $PhMe_3NI$ (2 equiv.) and KOH (3 equiv.). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. Anisole (2 mL, 0.2 M) was added *via* syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton® cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block for 3 h. The reaction mixture was cooled to room temperature, and additional $PhMe_3NI$ (2 equiv) and KOH (2 equiv) were added. Subsequently, the reaction was heated up to 130 °C and

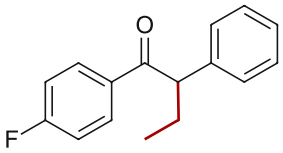
stirred for 4 days (with further addition of 2 equiv $PhMe_3NI$ and 2 equiv KOH after 48 h). The reaction was cooled to room temperature. 2 mL of 2 N HCl were added, and the mixture was extracted 3 times with EtOAc (20 mL each). The combined organic phases were washed twice with 2 N HCl (3 mL each) and once with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The obtained crude product was purified *via* hand column with unmodified silica gel (15 g silica, LP:EtOAc 30:1-1:1), yielding 34 mg (31 %) of the title compound as a colorless oil.

R_f = 0.55 (LP:EtOAc 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.11 – 8.04 (m, 2H), 7.74 – 7.67 (m, 2H), 7.67 – 7.59 (m, 2H), 7.52 – 7.43 (m, 2H), 7.43 – 7.36 (m, 1H), 3.99 (dqd, *J* = 8.5, 7.2, 5.7 Hz, 1H), 3.66 (s, 3H), 3.00 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.49 (dd, *J* = 16.8, 5.7 Hz, 1H), 1.27 (d, *J* = 7.2 Hz, 3H)

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 202.3, 172.9, 145.8, 140.0, 134.6, 129.1, 129.0, 128.3, 127.4, 127.3, 51.8, 37.3, 37.3, 18.0.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{21}O_3$: 297.1485; found: 297.1490



1-(4-Fluorophenyl)-2-phenyl-1-butanone[19] (4a) [CAS: 1097034-09-7]

Prepared, following the general procedure C, except for the use of $PhEt_3NI$ (2 equiv.) instead of $PhMe_3NI$, from commercially available starting material with a reaction time of 5 h. The crude product was purified *via* column chromatography (8 g silica LP:EtOAc 50:1-40:1) to yield 83 mg (78 %) of the title compound.

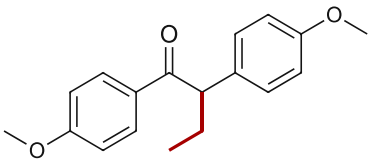
R_f = 0.36 (LP:EtOAc 7:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.52 – 7.11 (m, 5H), 7.03 (dd, *J* = 9.0, 8.3 Hz, 1H), 4.36 (t, *J* = 7.2 Hz, 2H), 2.17 (dp, *J* = 12.8, 7.3 Hz, 1H), 1.83 (dp, *J* = 13.6, 7.4 Hz, 1H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 198.6, 165.6 (d, *J* = 254.6 Hz), 139.6, 133.5, 131.4 (d, *J* = 9.2 Hz), 129.0, 128.3, 127.2, 115.7 (d, *J* = 21.8 Hz), 55.6, 27.2, 12.4

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -105.7

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{16}FO$: 243.1180; found: 243.1186



1,2-Bis(4-methoxyphenyl)-1-butanone[24] (4b) [CAS:4390-94-7]

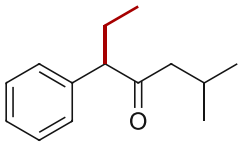
Prepared, following the general procedure C, except for the use of $PhEt_3NI$ (2 equiv.) instead of $PhMe_3NI$, from commercially available starting material with a reaction time of 4 h. The crude product was purified *via* column chromatography (15 g silica LP:EtOAc 30:1-20:1) to yield 74 mg (68 %) of the title compound.

R_f = 0.57 (LP:EtOAc 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 – 7.91 (m, 2H), 7.25 – 7.17 (m, 2H), 6.90 – 6.78 (m, 4H), 4.35 (t, J = 7.3 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 2.23 – 2.08 (m, 1H), 1.82 (dq, J = 13.6, 7.4 Hz, 1H), 0.89 (t, J = 7.4 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 198.9, 163.2, 158.6, 132.2, 131.0, 130.1, 129.3, 114.3, 113.7, 55.5, 55.31, 54.2, 27.2, 12.4.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{21}O_3$: 285.1485; found: 285.1492



2-Methyl-5-phenyl-4-heptanone (4c) [CAS: 1129271-28-8]

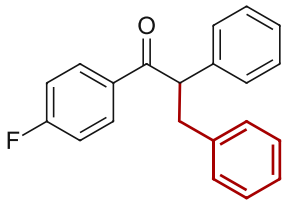
Prepared, following the general procedure C, except for the use of $PhEt_3NI$ (2 equiv.) instead of $PhMe_3NI$, from commercially available starting material with a reaction time of 18 h. The crude product was purified *via* column chromatography (15 g silica LP:Et_2O 100:1-100:3) to yield 65 mg (57 %) of the title compound as slightly yellow oil.

R_f = 0.35 (LP:EtOAc 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 7.24 – 7.18 (m, 2H), 3.51 (t, J = 7.4 Hz, 1H), 2.33 – 2.17 (m, 2H), 2.17 – 2.00 (m, 2H), 1.72 (dp, J = 13.7, 7.5 Hz, 1H), 0.89 – 0.80 (m, 6H), 0.76 (d, J = 6.6 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 210.2, 139.0, 128.8, 128.4, 127.1, 61.3, 51.0, 25.3, 24.3, 22.7, 22.3, 12.2.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{21}O$: 205.1587; found: 205.1593



1-(4-Fluorophenyl)-2,3-diphenylpropan-1-one[25] (5a) [CAS: 2149042-05-5]

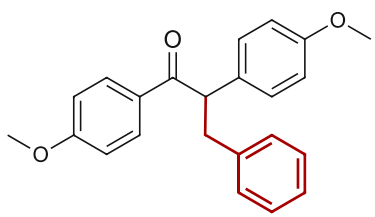
An 8 mL glass vial equipped with a magnetic stirring bar was charged with benzyl 4-fluorophenyl ketone **1a** (100 mg, 1 equiv.), benzyl trimethyl ammonium chloride (1.1 equiv.), and KOH (2 equiv.). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. Anisole (2 mL, 0.2 M) was added *via* syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton® cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block for 1 h. After complete consumption of the starting material (TLC analysis), the reaction was cooled to room temperature, filtered over a short plug of silica, and concentrated. The obtained crude product was purified *via* hand column with unmodified silica gel (15 g silica, LP:EtOAc 150:1-100:1), yielding 119 mg (84 %) of the title compound as white crystals.

R_f = 0.39 (LP:EtOAc 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 – 7.89 (m, 2H), 7.32 – 7.13 (m, 8H), 7.13 – 7.06 (m, 2H), 7.05 – 6.96 (m, 2H), 4.78 (t, *J* = 7.2 Hz, 1H), 3.58 (dd, *J* = 13.7, 7.5 Hz, 1H), 3.08 (dd, *J* = 13.7, 7.0 Hz, 1H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 197.7, 165.6 (d, *J* = 254.9 Hz), 139.7, 139.0, 133.2 (d, *J* = 3.0 Hz), 131.4, 131.3, 129.2, 129.1, 128.3 (d, *J* = 4.6 Hz), 127.3, 126.3, 115.6 (d, *J* = 21.9 Hz), 56.0, 40.2.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{18}FO$: 305.1336; found: 305.1354



1,2-Bis-(4-methoxy-phenyl)-3-phenyl-propan-1-one[26] (5b) [CAS: 854692-29-8]

An 8 mL glass vial equipped with a magnetic stirring bar was charged with desoxyanisoin (100 mg, 1 equiv.), benzyl trimethyl ammonium chloride (1.1 equiv.), and KOH (2 equiv.). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. Anisole (2 mL, 0.2 M) was added *via* syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no

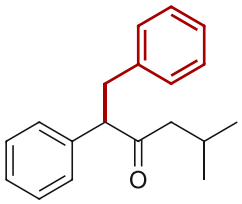
boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton® cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block for 2 h. After complete consumption of the starting material (TLC analysis), the reaction was cooled to room temperature, filtered over a short plug of silica, and concentrated. The obtained crude product was purified *via* hand column with unmodified silica gel (15 g silica, LP:EtOAc 100:1, 40:1, 20:1, 10:1), yielding 121 mg (89 %) of the title compound as colorless oil.

R_f = 0.29 (LP:EtOAc 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 – 7.87 (m, 2H), 7.24 – 7.11 (m, 5H), 7.11 – 7.04 (m, 2H), 6.87 – 6.75 (m, 4H), 4.72 (t, J = 7.2 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.53 (dd, J = 13.7, 7.3 Hz, 1H), 3.04 (dd, J = 13.7, 7.2 Hz, 1H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 198.0, 163.3, 158.6, 140.1, 131.6, 131.0, 129.8, 129.3, 129.2, 128.2, 126.1, 114.3, 113.7, 55.5, 55.2, 54.7, 40.2.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{23}O_3$: 347.1642; found: 347.1650



5-Methyl-1,2-diphenyl-3-hexanone (5c)

An 8 mL glass vial equipped with a magnetic stirring bar was charged with 1-phenyl-4-methyl-pentanone (100 mg, 1 equiv.), benzyl trimethyl ammonium chloride (1.1 equiv.), and KOH (2 equiv.). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. Anisole (2.5 mL, 0.2 M) was added *via* syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton® cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block for 18 h. After complete consumption of the starting material (TLC analysis), the reaction was cooled to room temperature, filtered over a short plug of silica, and concentrated. The obtained crude product was purified *via* hand column with unmodified silica gel (15 g silica, LP:Et_2O 100:1-100:3), yielding 115 mg (78 %) of the title compound as colorless oil.

R_f = 0.4 (LP:EtOAc 10:1)

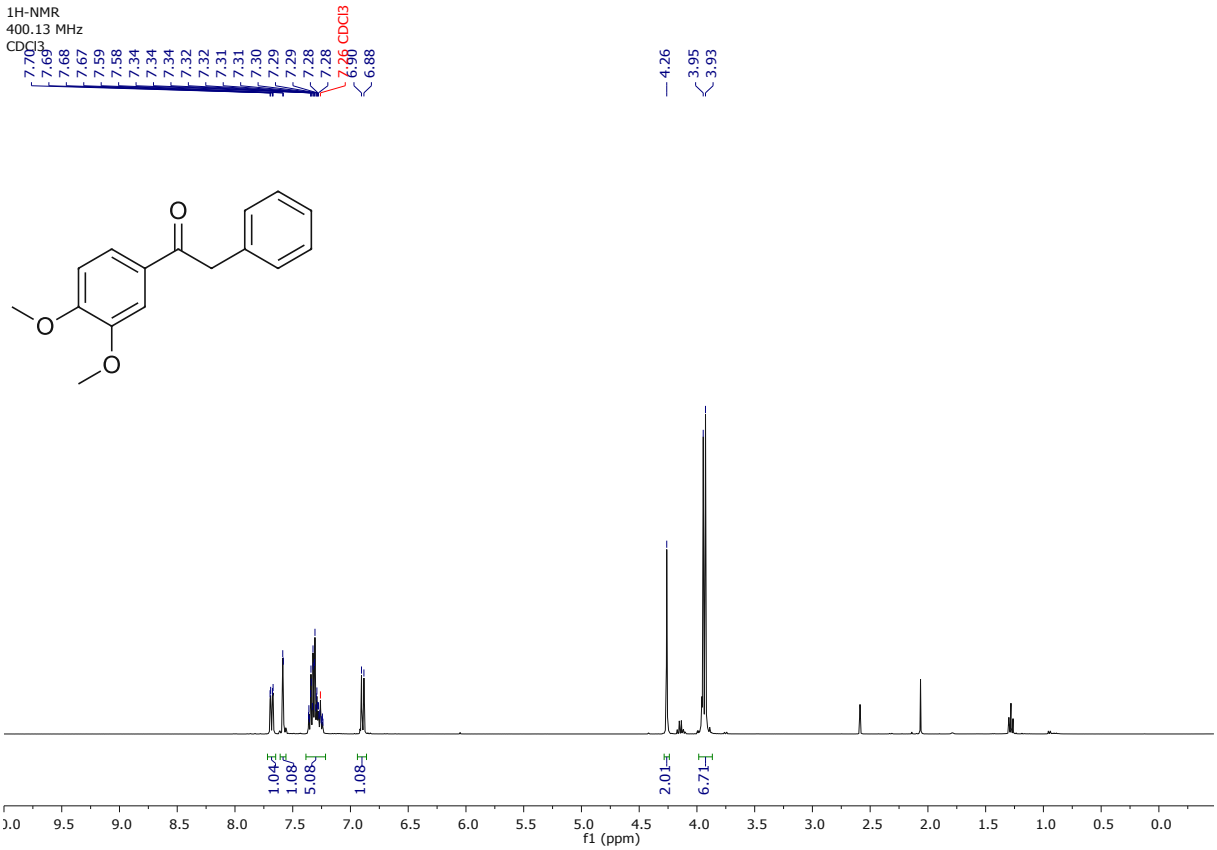
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.47 – 7.29 (m, 7H), 7.29 – 7.23 (m, 1H), 7.22 – 7.16 (m, 2H), 4.07 – 3.98 (m, 1H), 3.56 (ddd, J = 13.7, 7.9, 1.6 Hz, 1H), 3.03 (ddd, J = 13.7, 6.8, 1.4 Hz, 1H), 2.29 (dt, J = 6.3, 1.3 Hz, 2H), 2.25 – 2.09 (m, 1H), 0.89 (dd, J = 6.6, 1.2 Hz, 3H), 0.79 (dd, J = 6.5, 1.2 Hz, 3H).

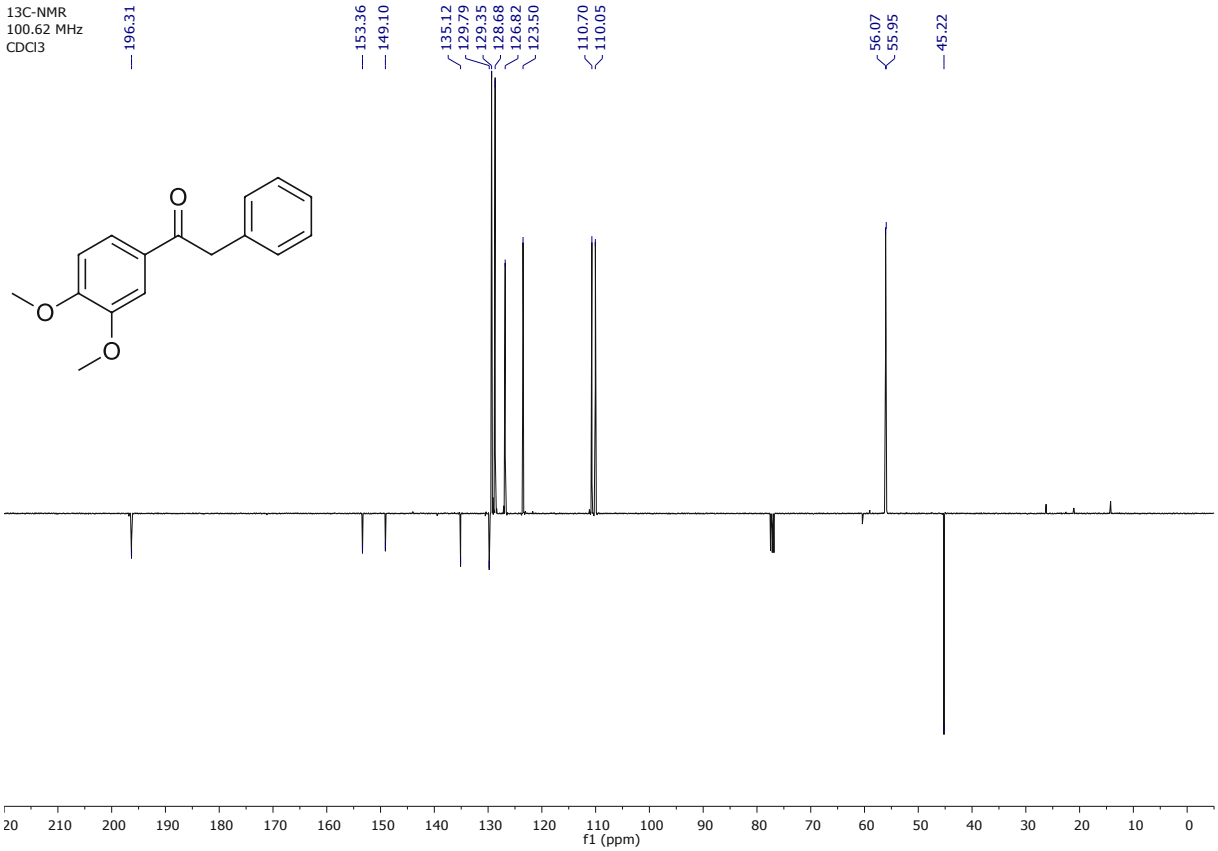
^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 209.3, 139.9, 138.5, 129.1, 128.9, 128.5, 128.3, 128.0, 127.3, 127.1, 126.1, 61.3, 51.4, 38.7, 24.2, 22.6, 22.1.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{23}O$: 267.1743; found: 267.1755

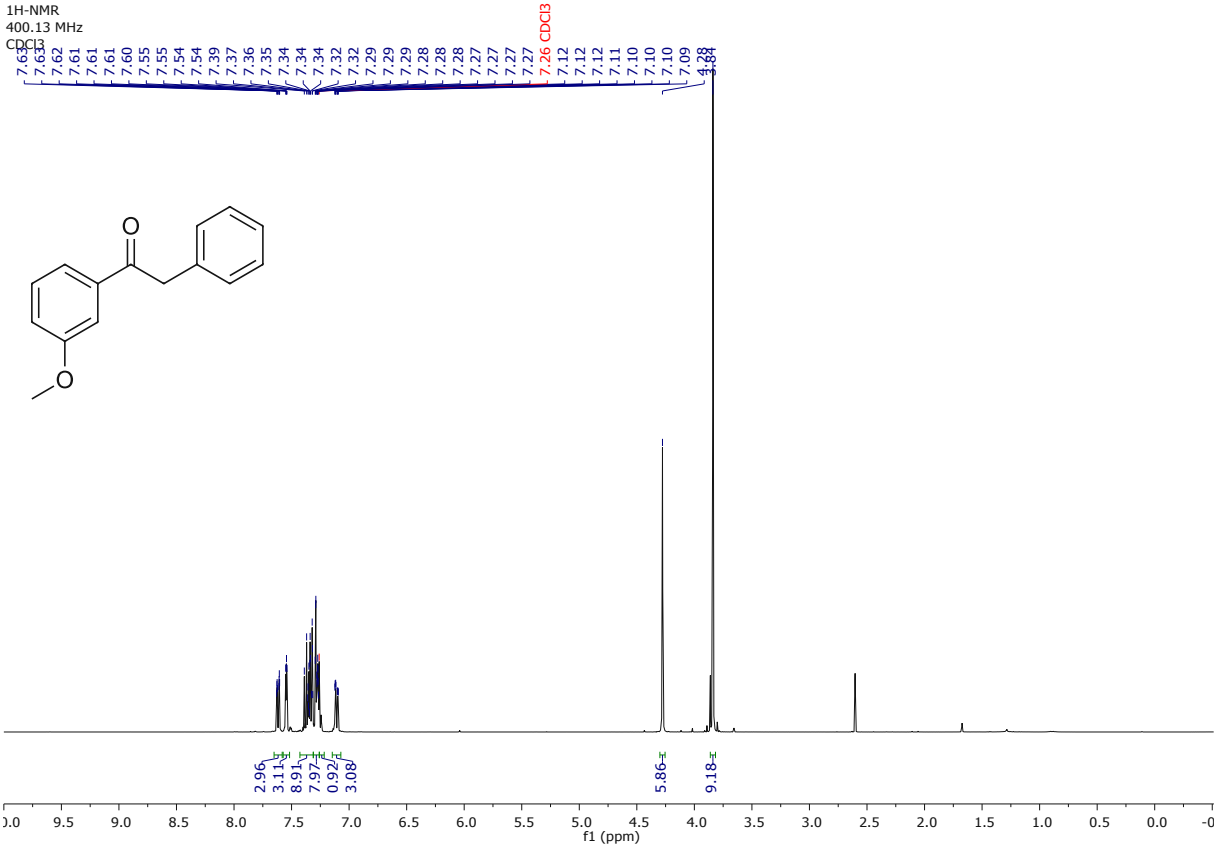
NMR-Spectra

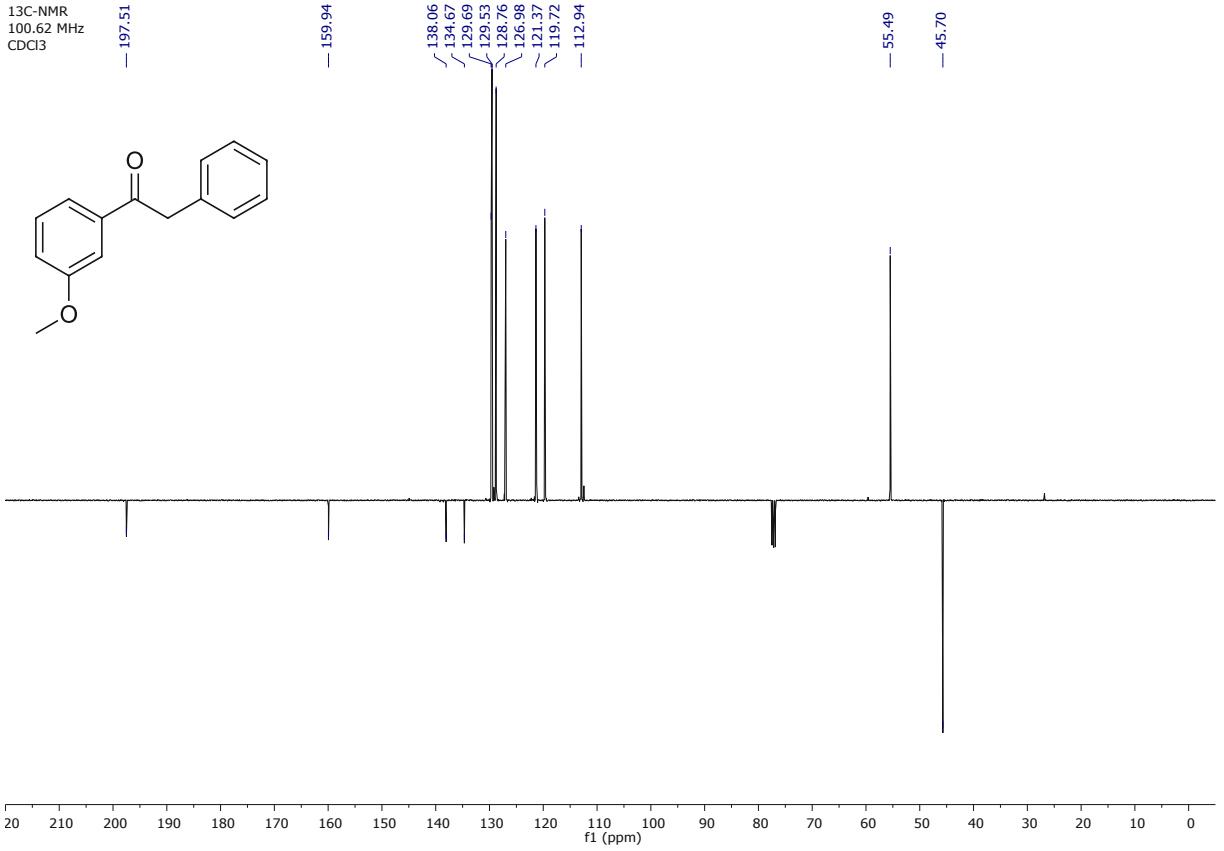
1-(3,4-Dimethoxyphenyl)-2-phenylethanone (1g)



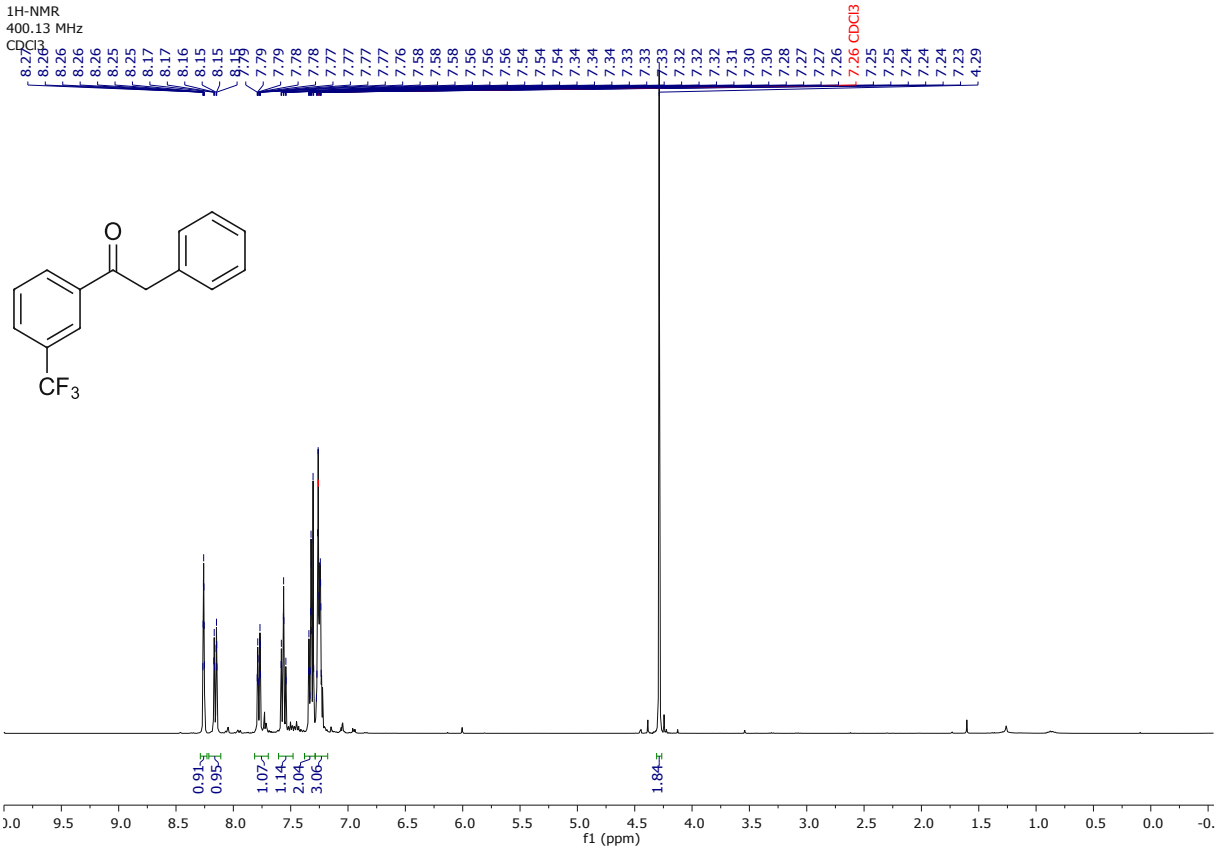


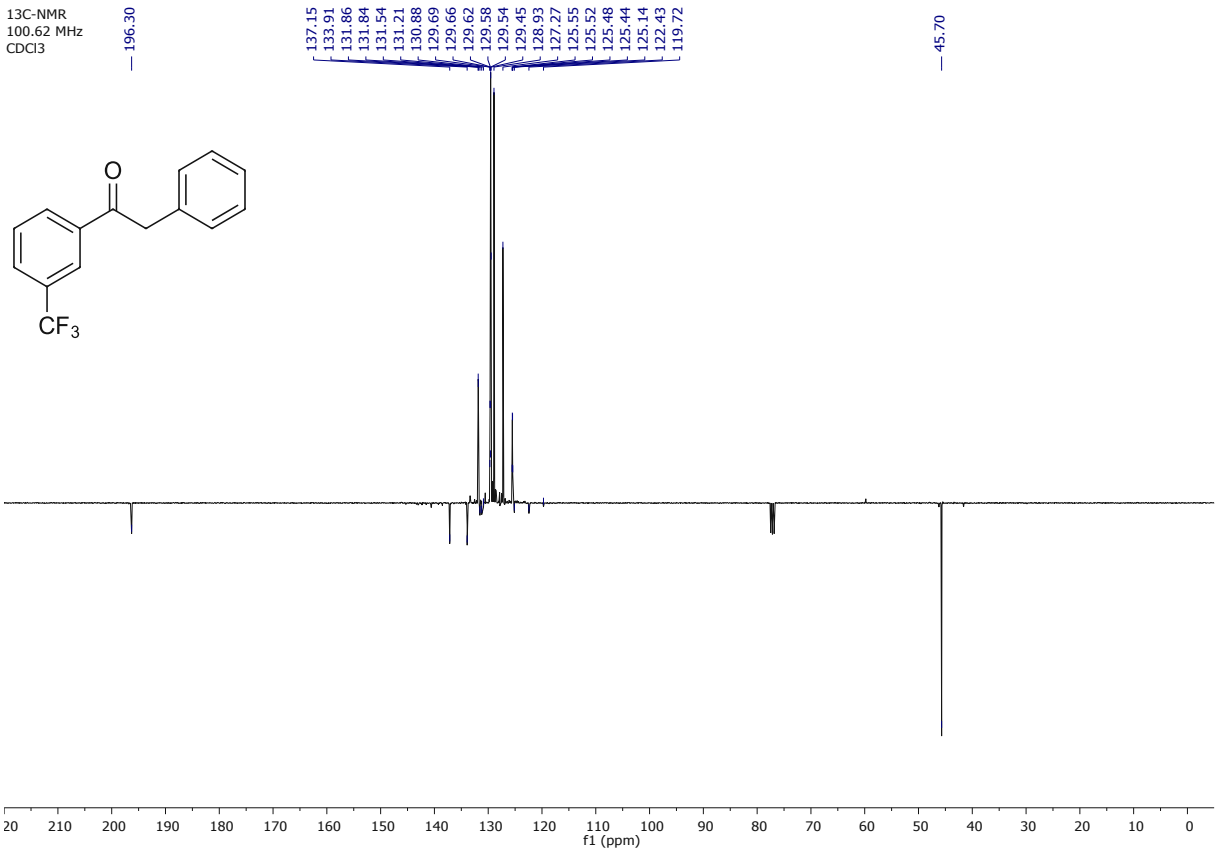
1-(3-Methoxyphenyl)-2-phenylethanone (1h)



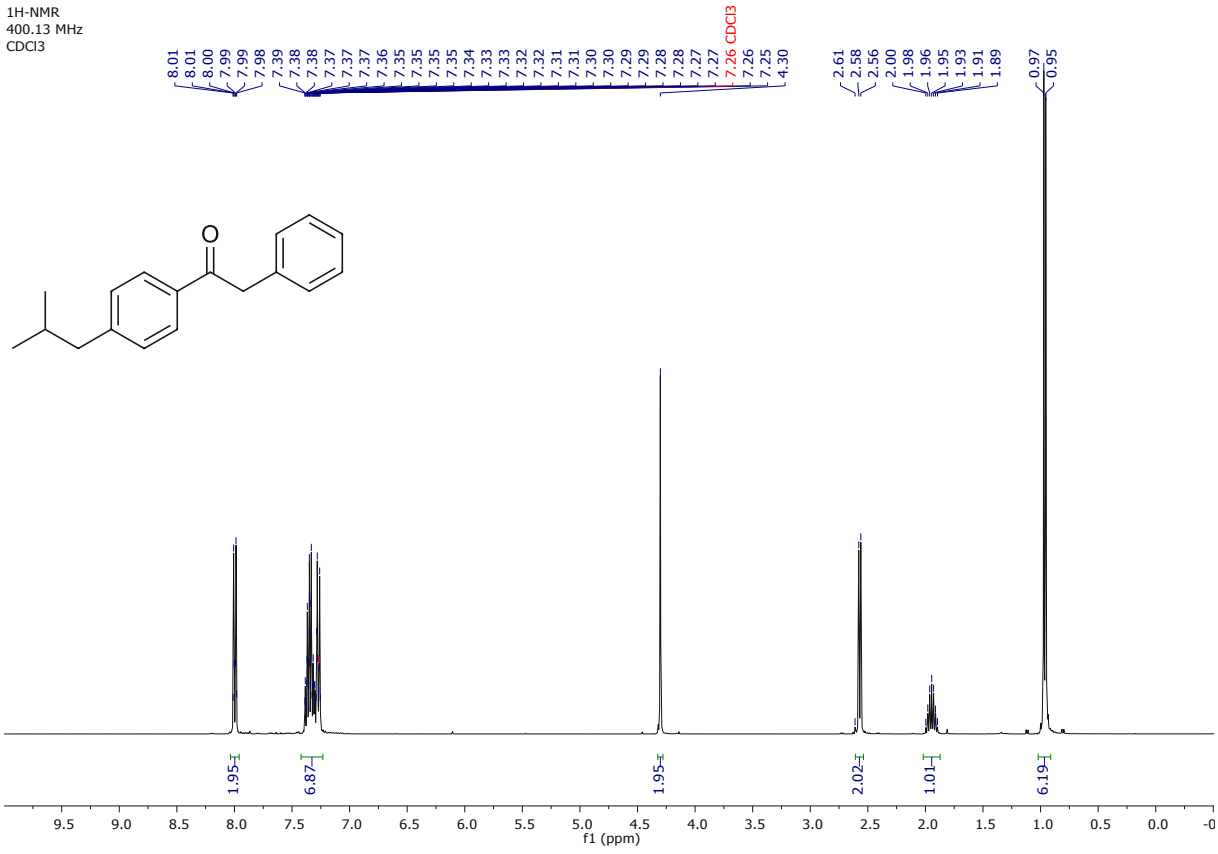


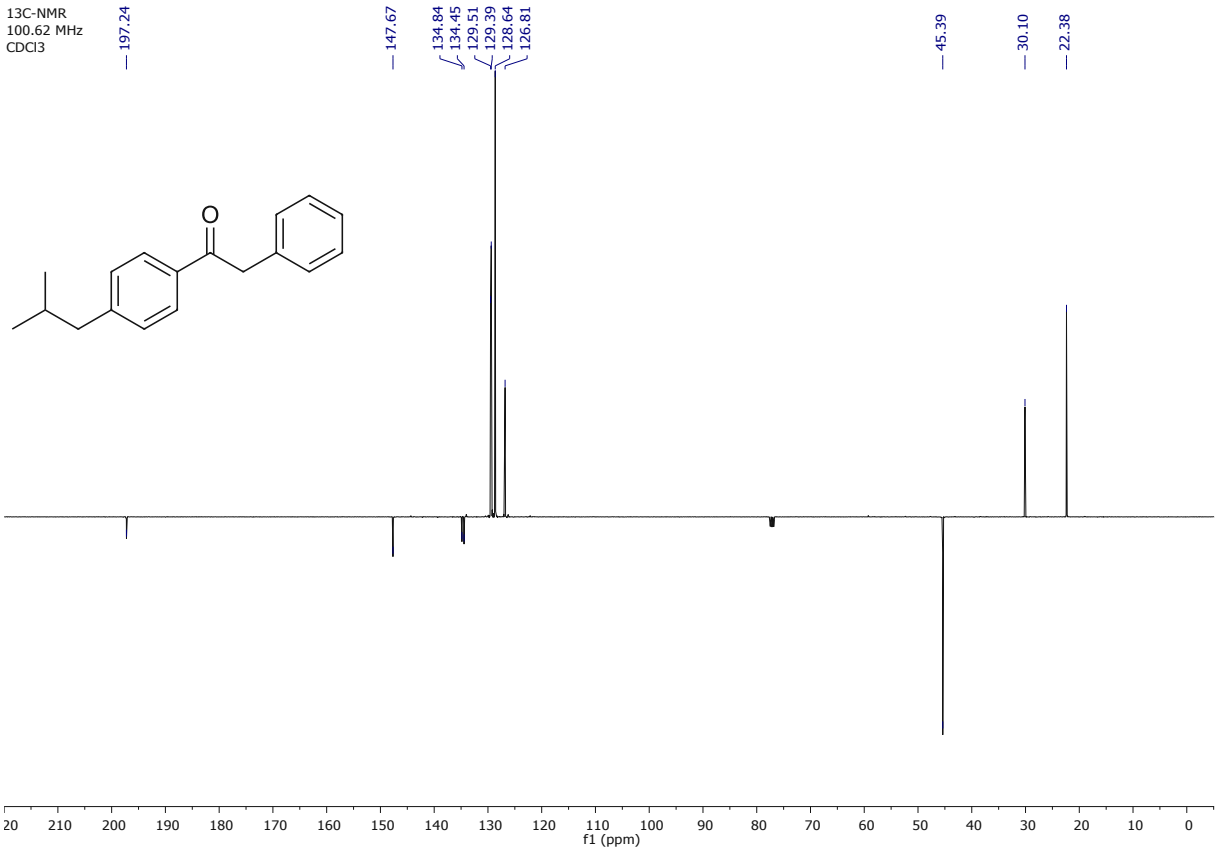
2-Phenyl-1-[3-(trifluormethyl)phenyl]ethanone (1i)



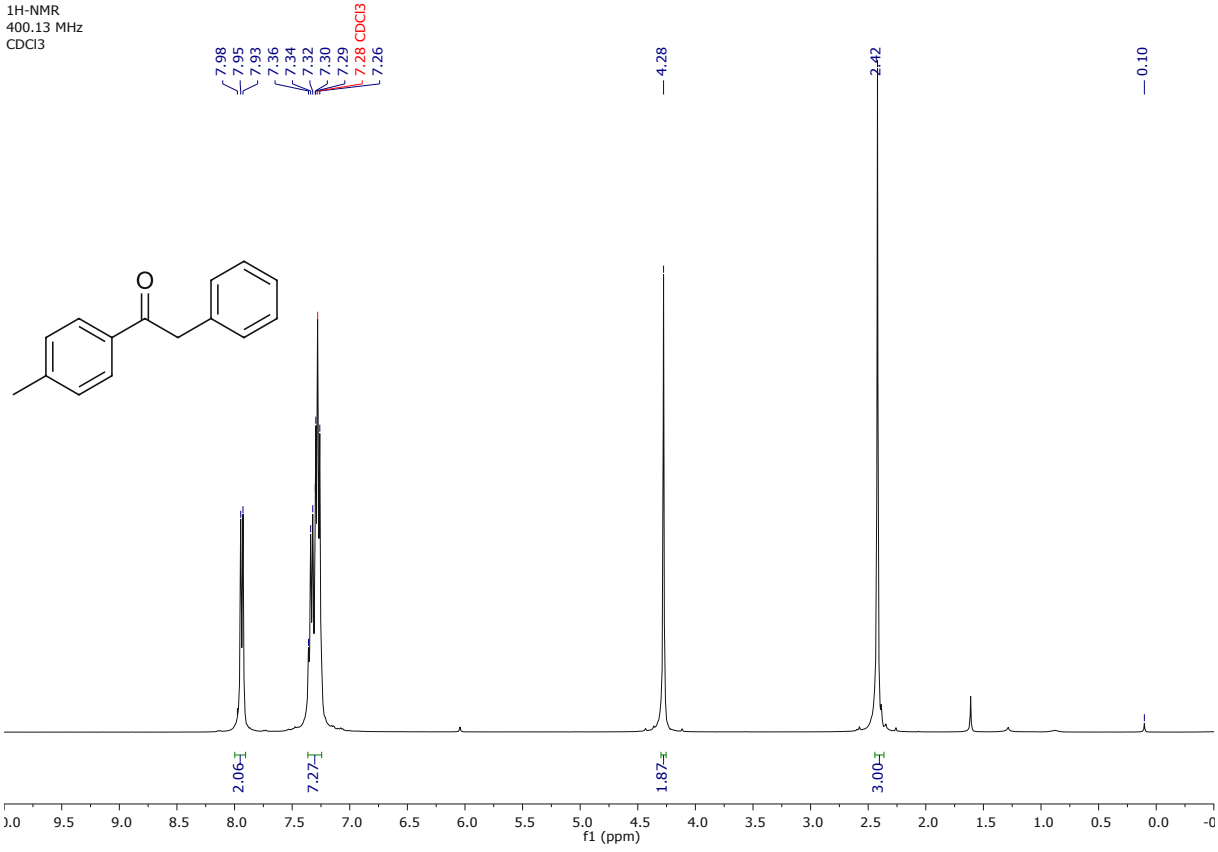


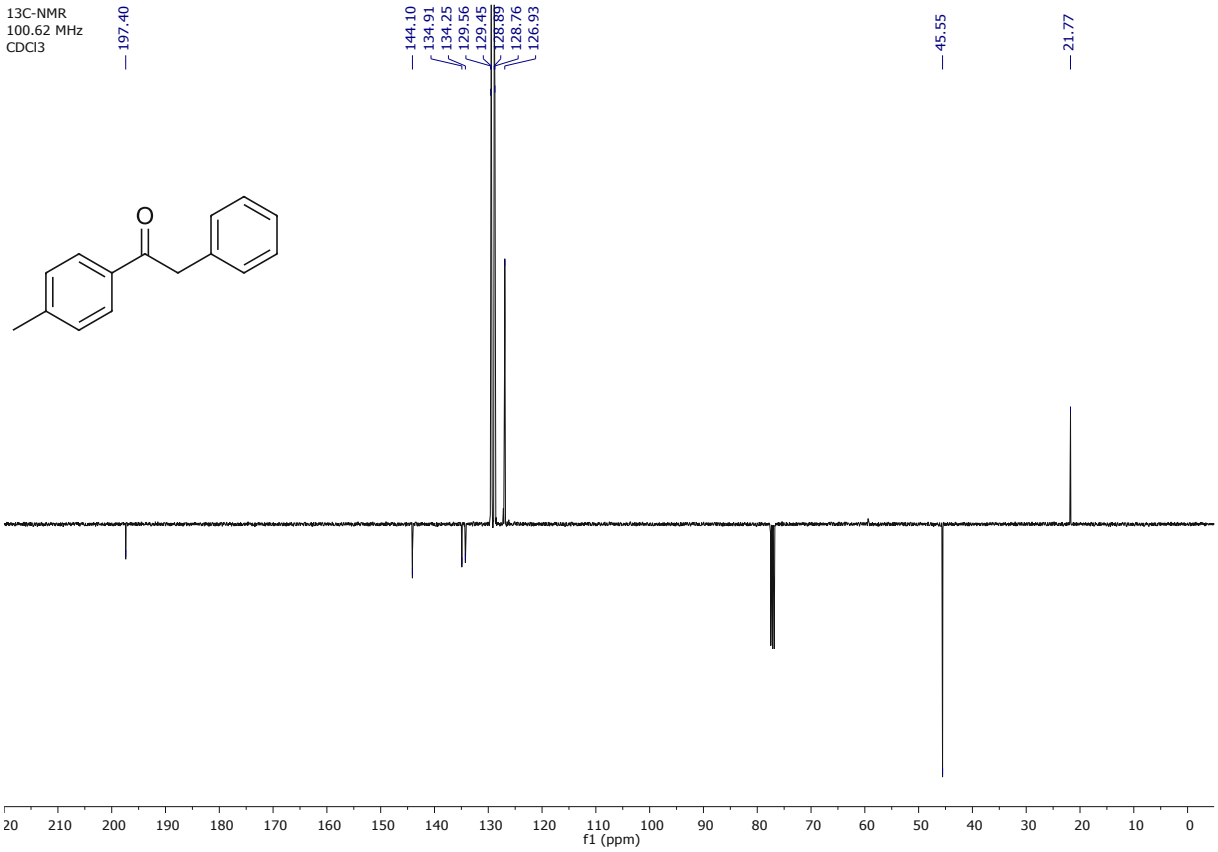
1-[4-(2-Methylpropyl)phenyl]-2-phenylethanone (1j)



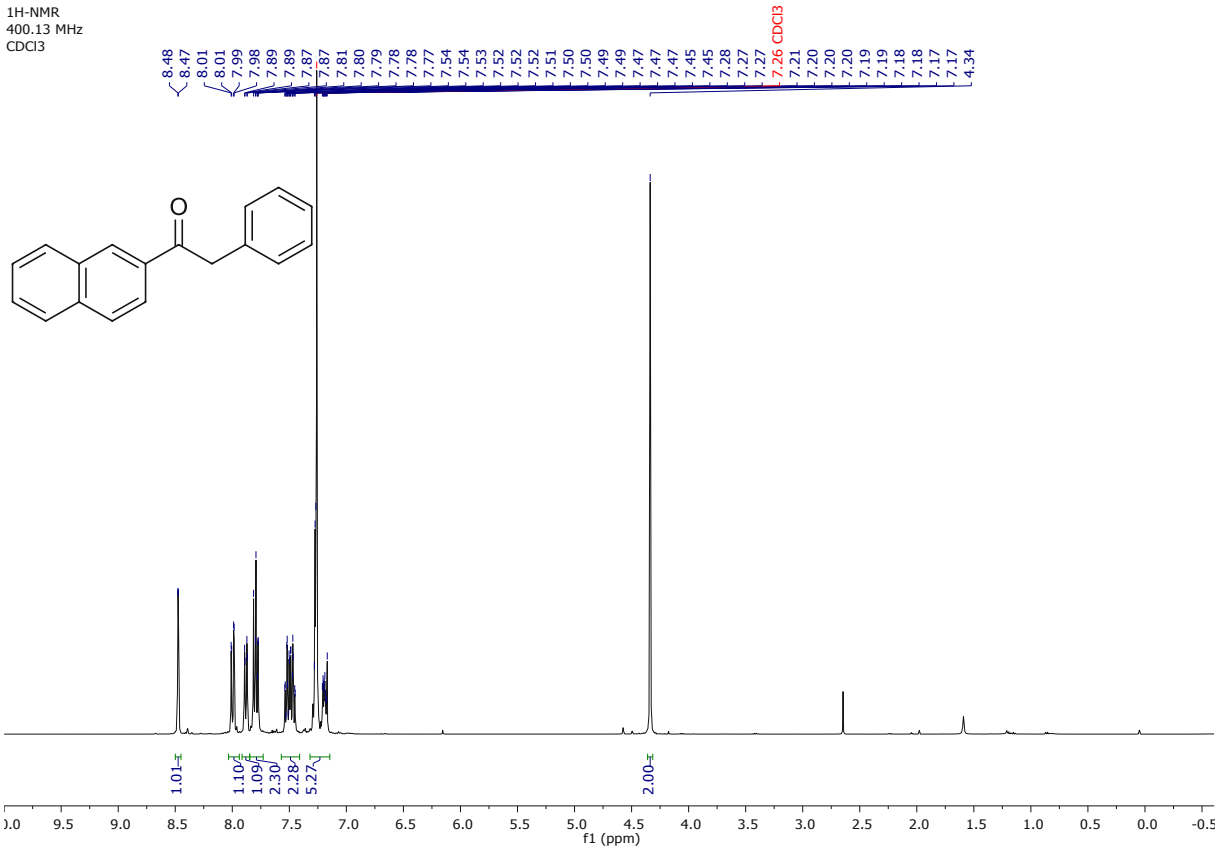


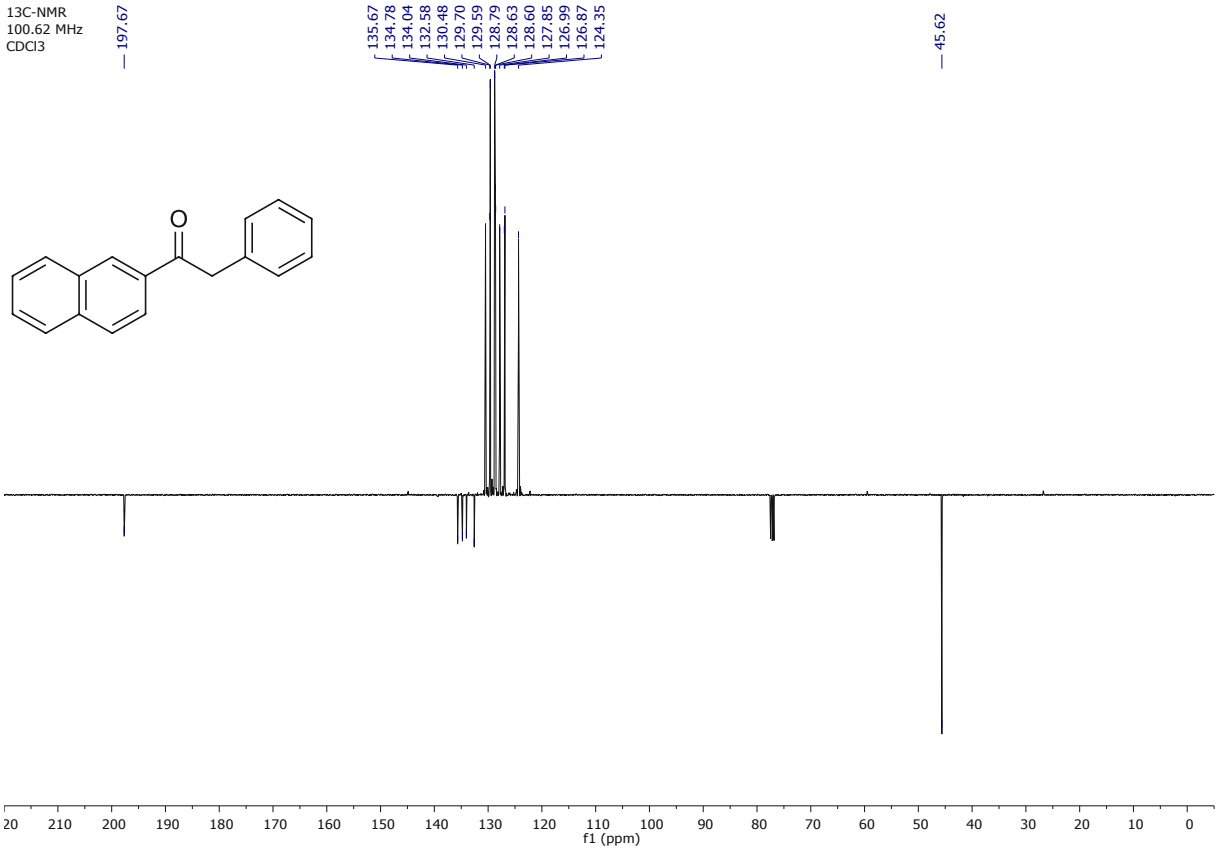
1-(4-Methylphenyl)-2-phenylethanone (1k)



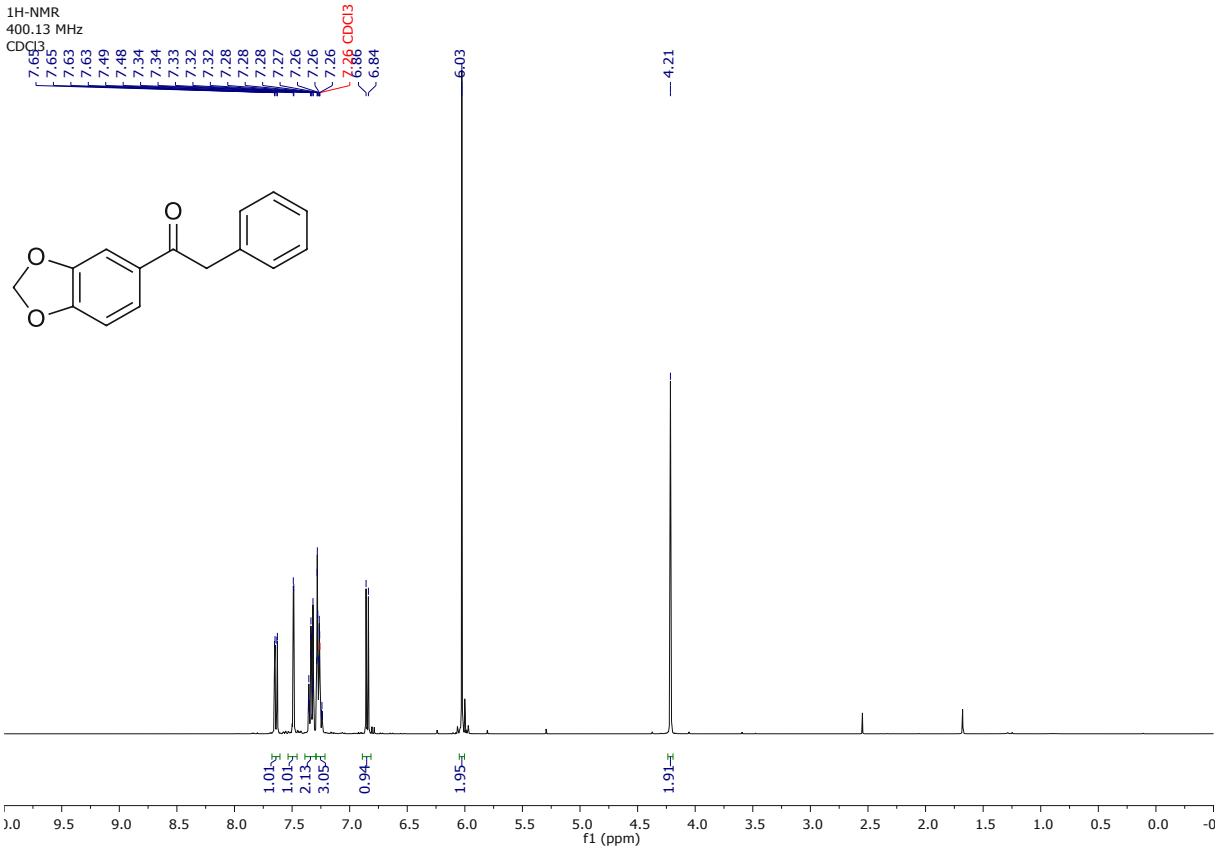


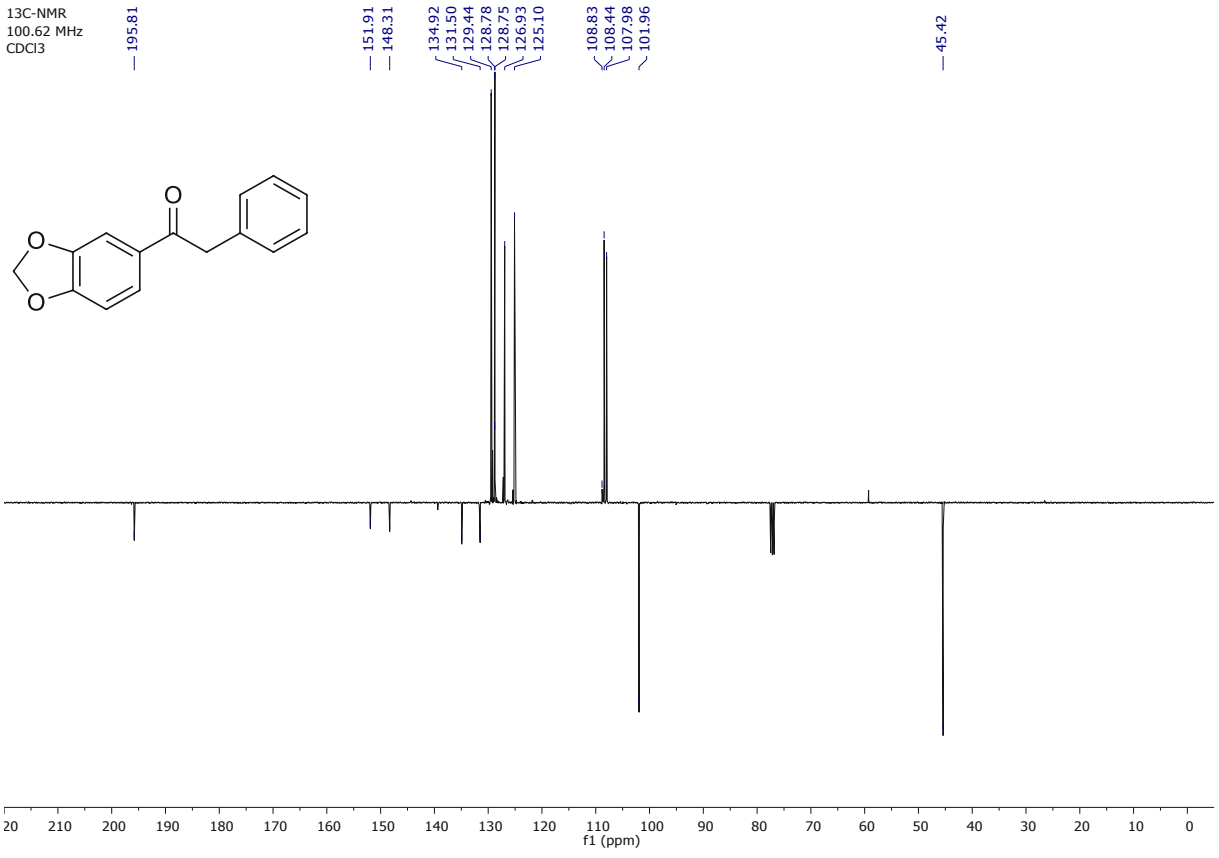
1-(2-Naphthalenyl)-2-phenylethanone (1l)



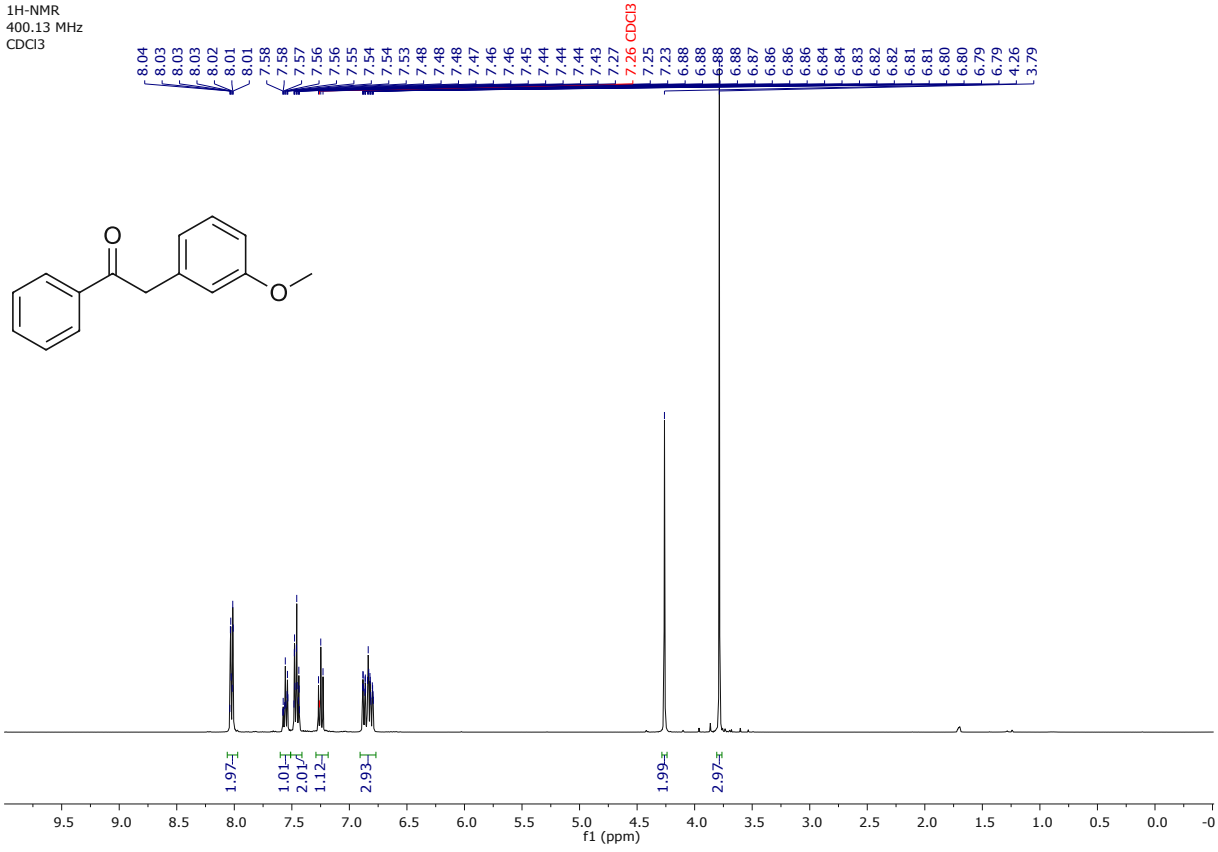


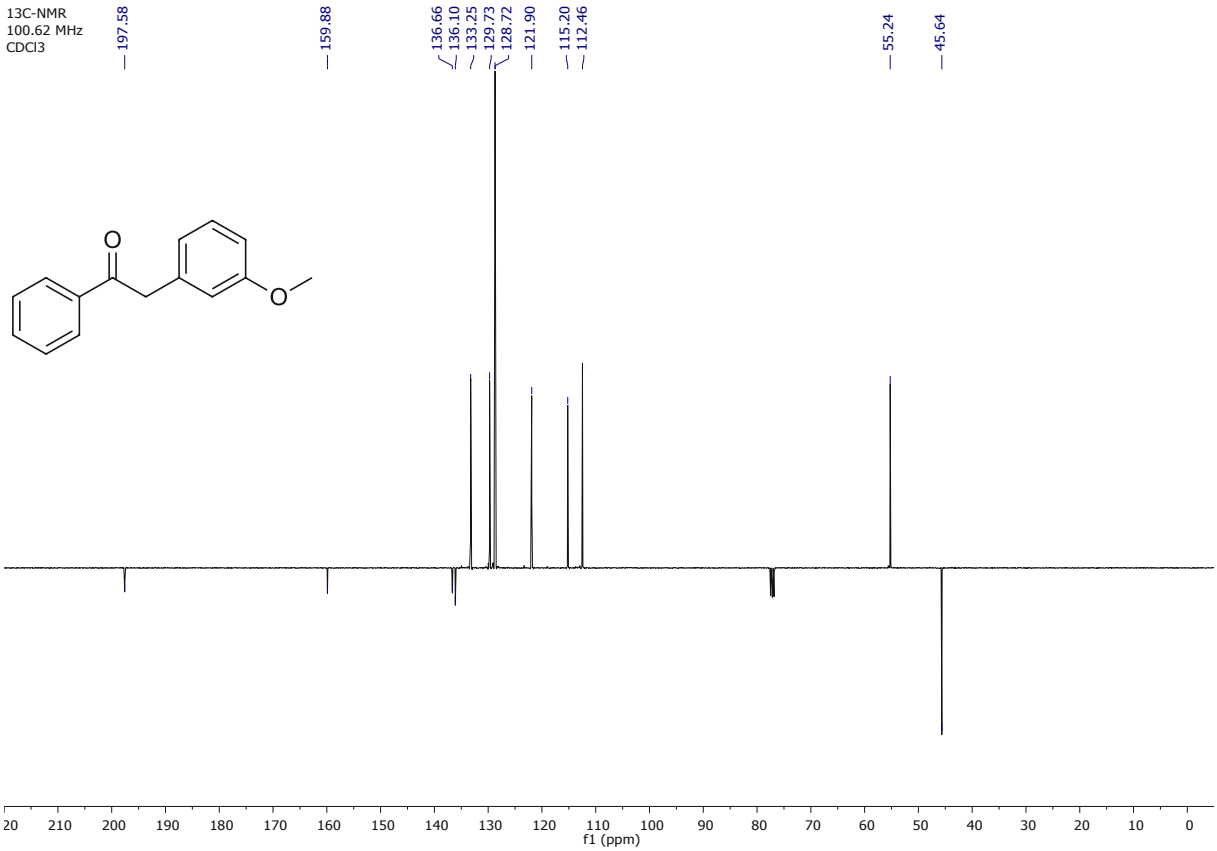
1-(1,3-Benzodioxol-5-yl)-2-phenylethanone (1n)



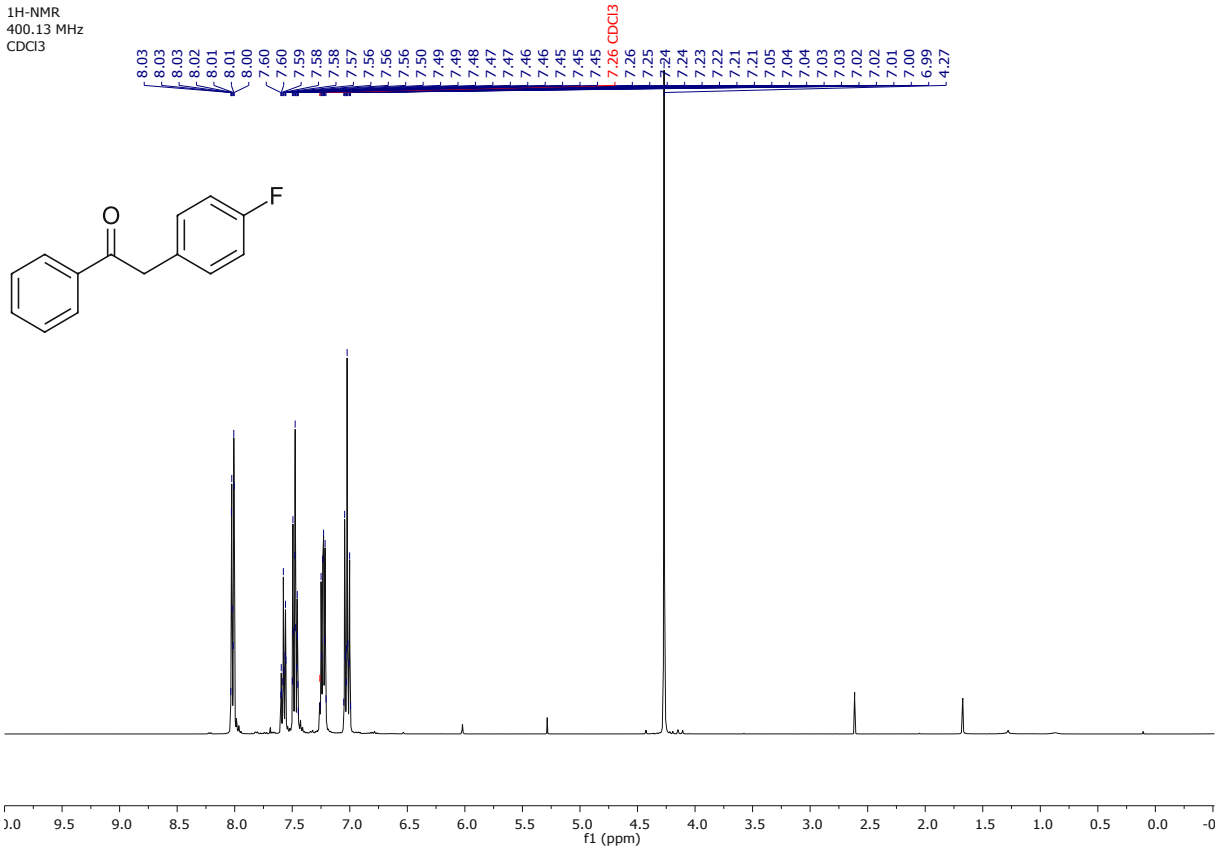


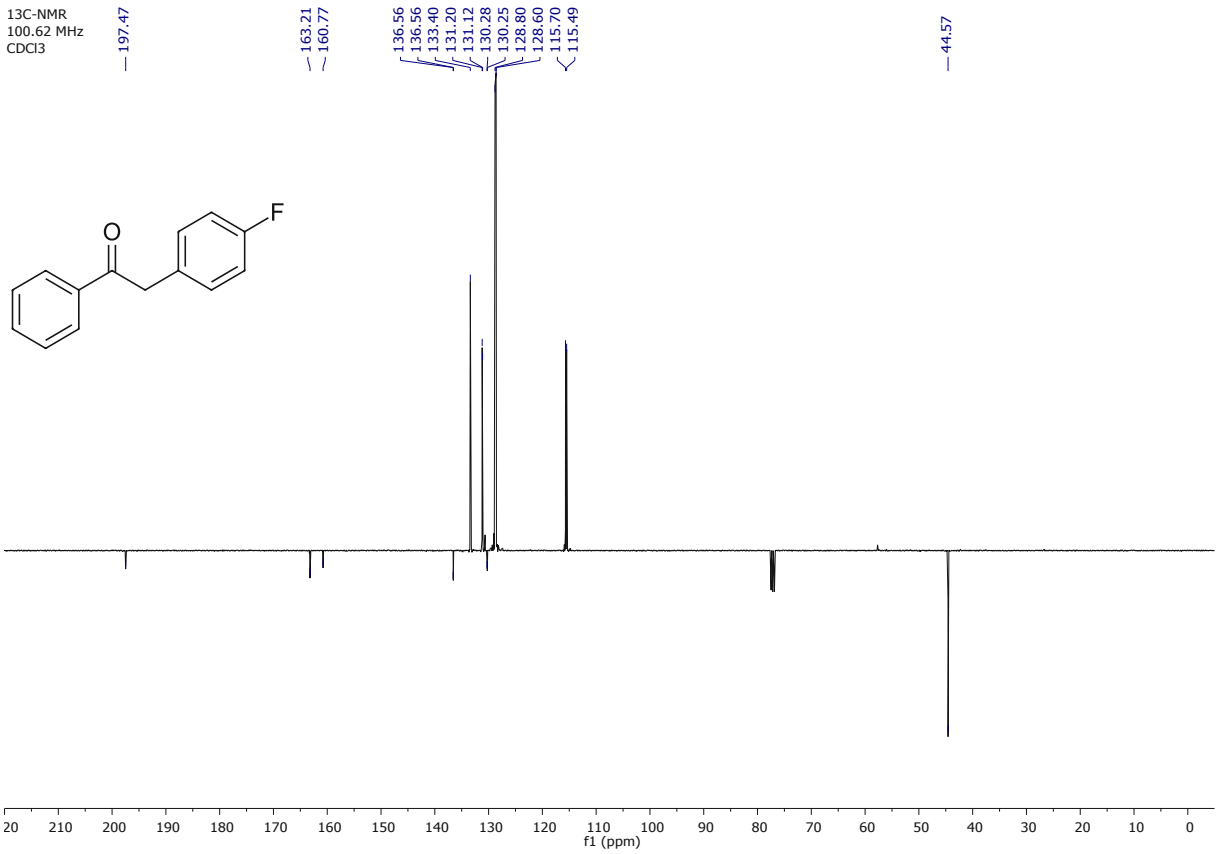
2-(3-Methoxyphenyl)-1-phenylethanone (1o)



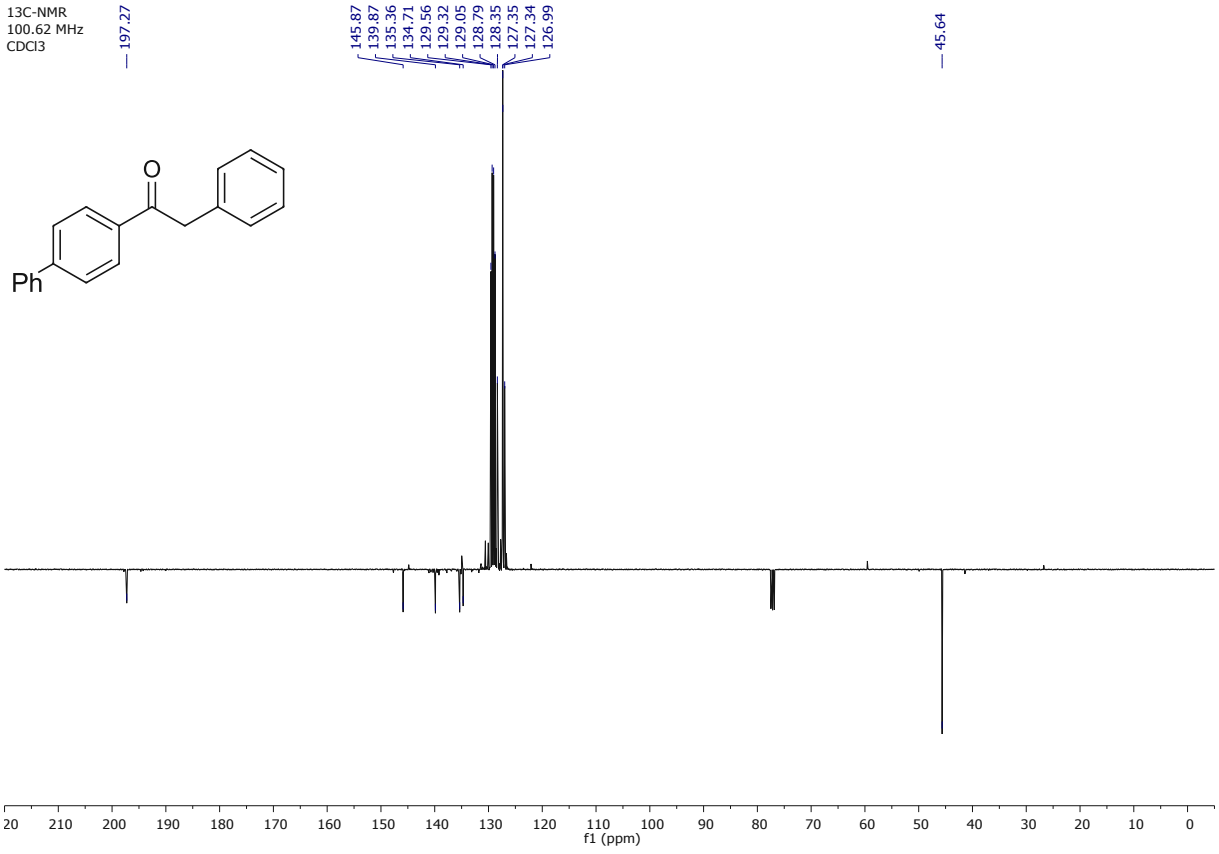


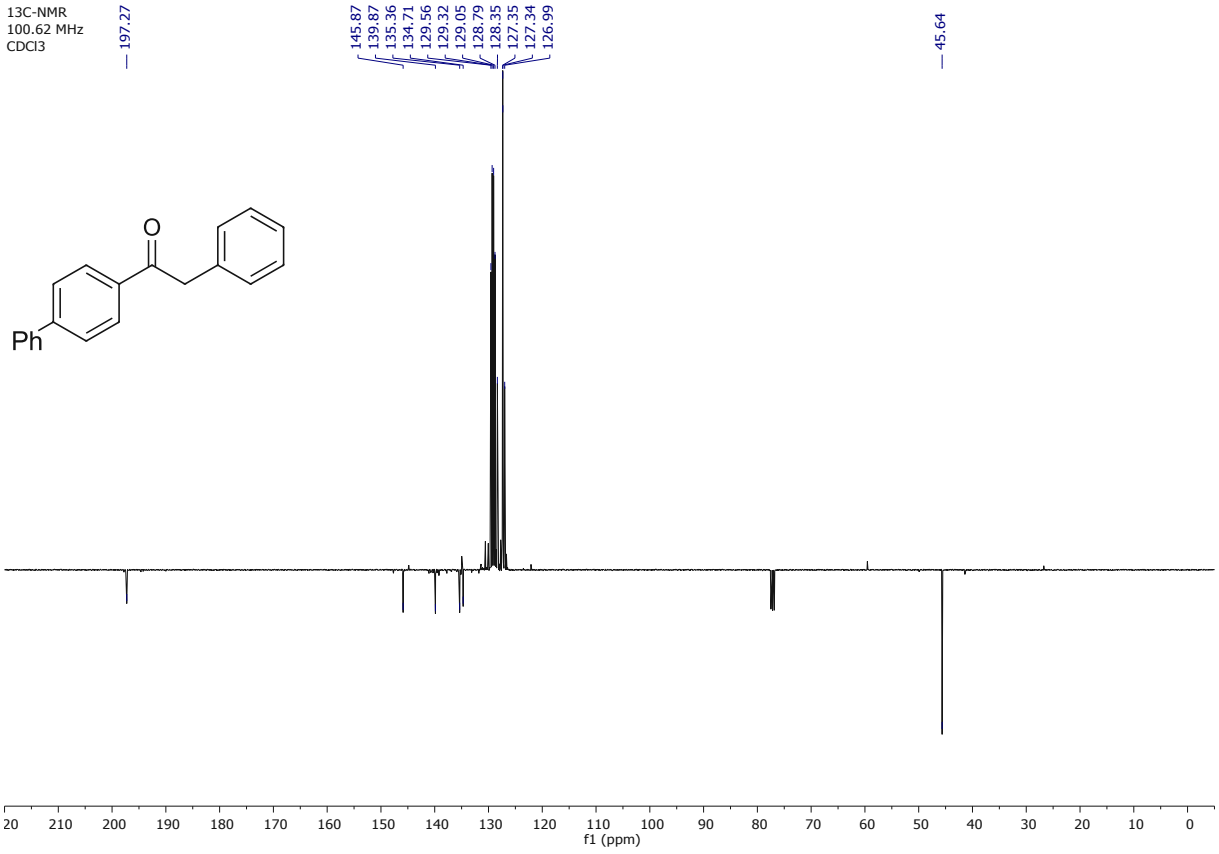
2-(4-Fluorphenyl)-1-phenylethanone (1q)



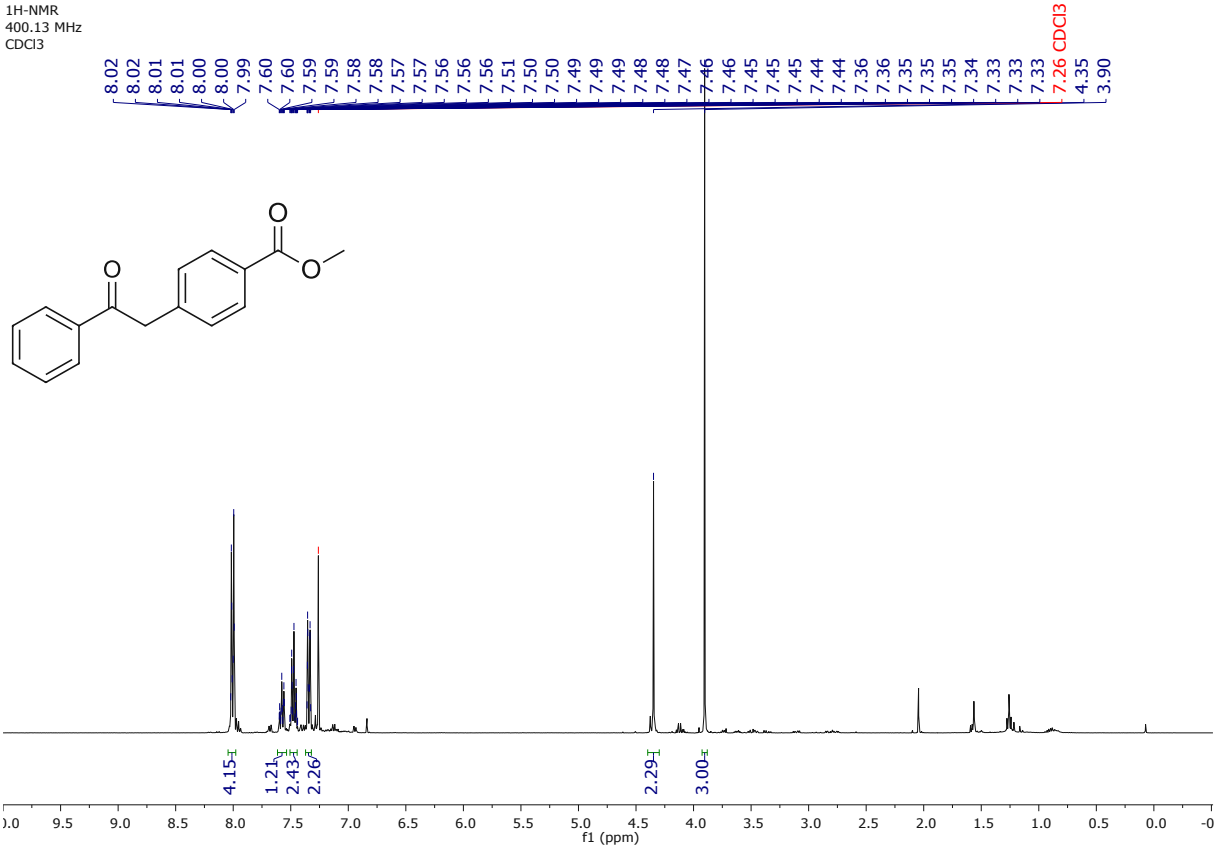


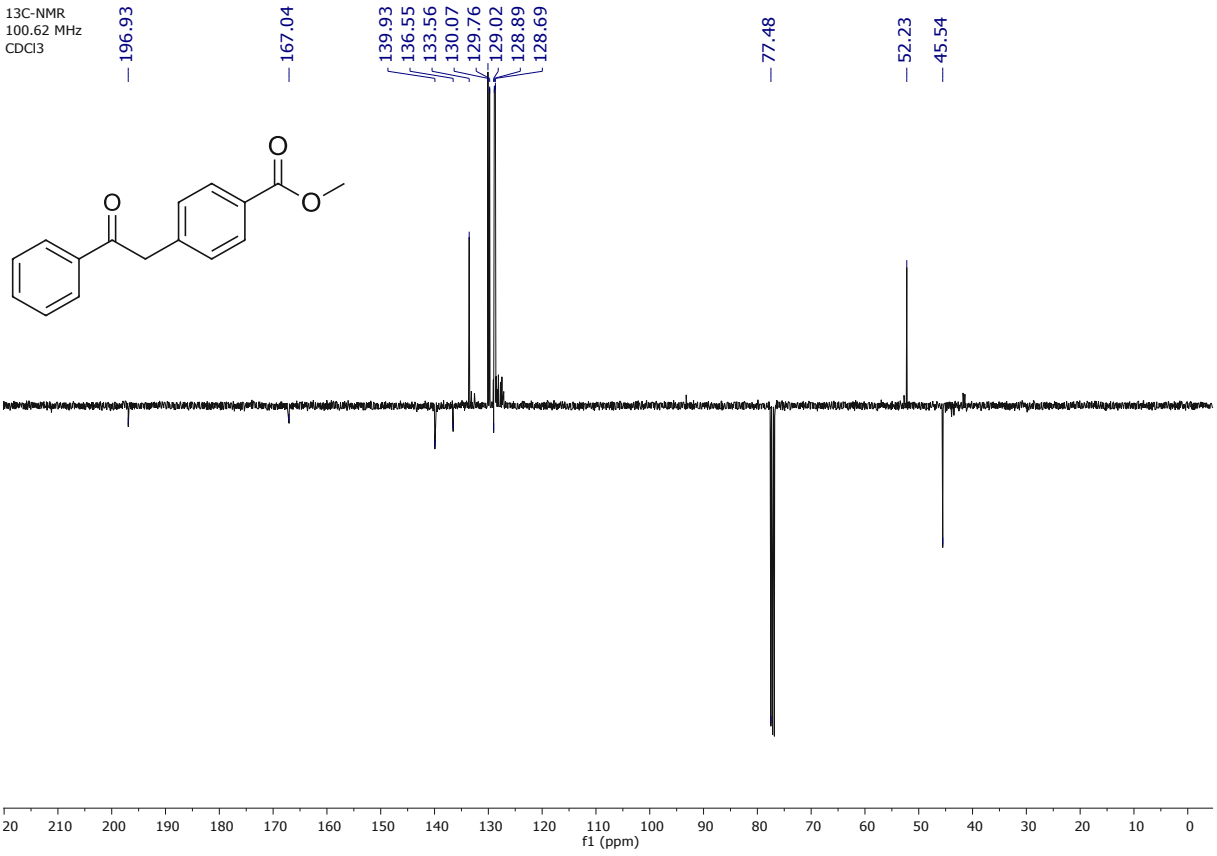
1-[1,1'-Biphenyl]-4-yl-2-phenylethanone (1r)



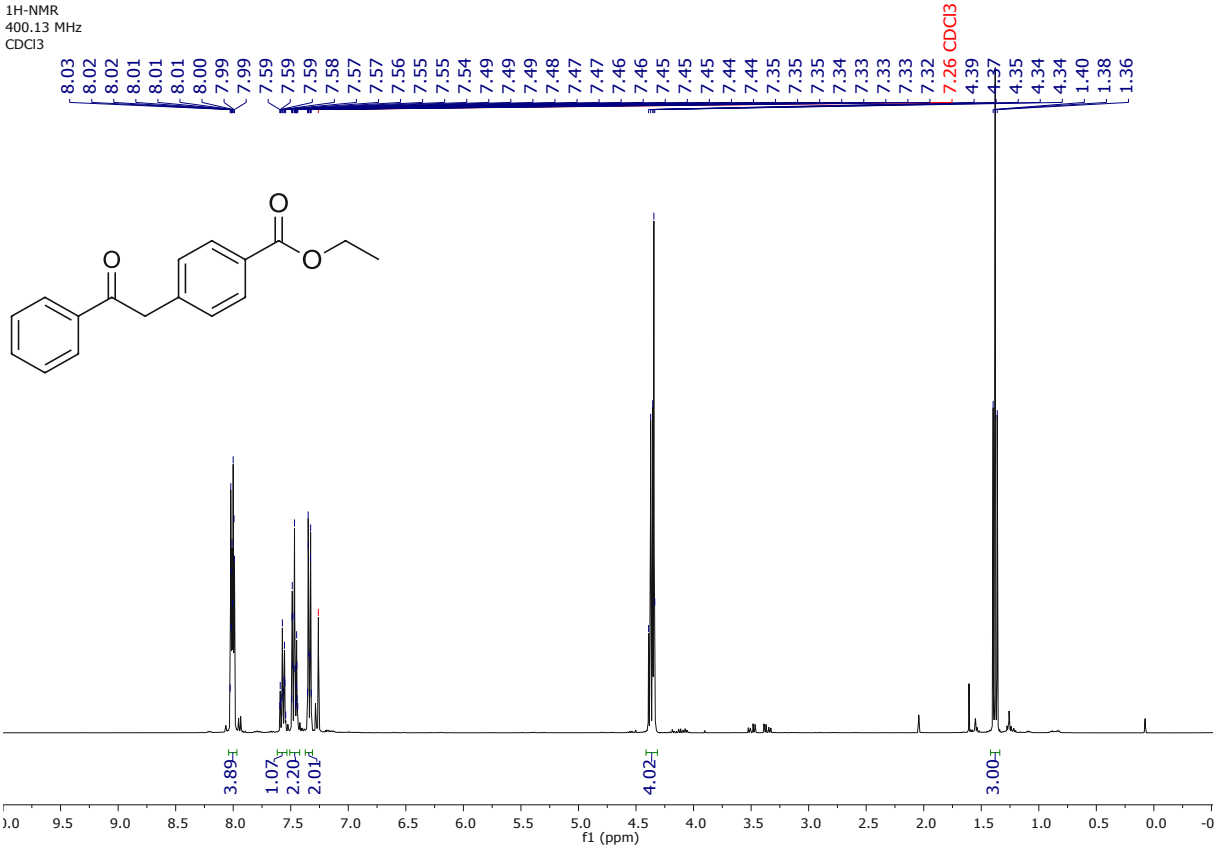


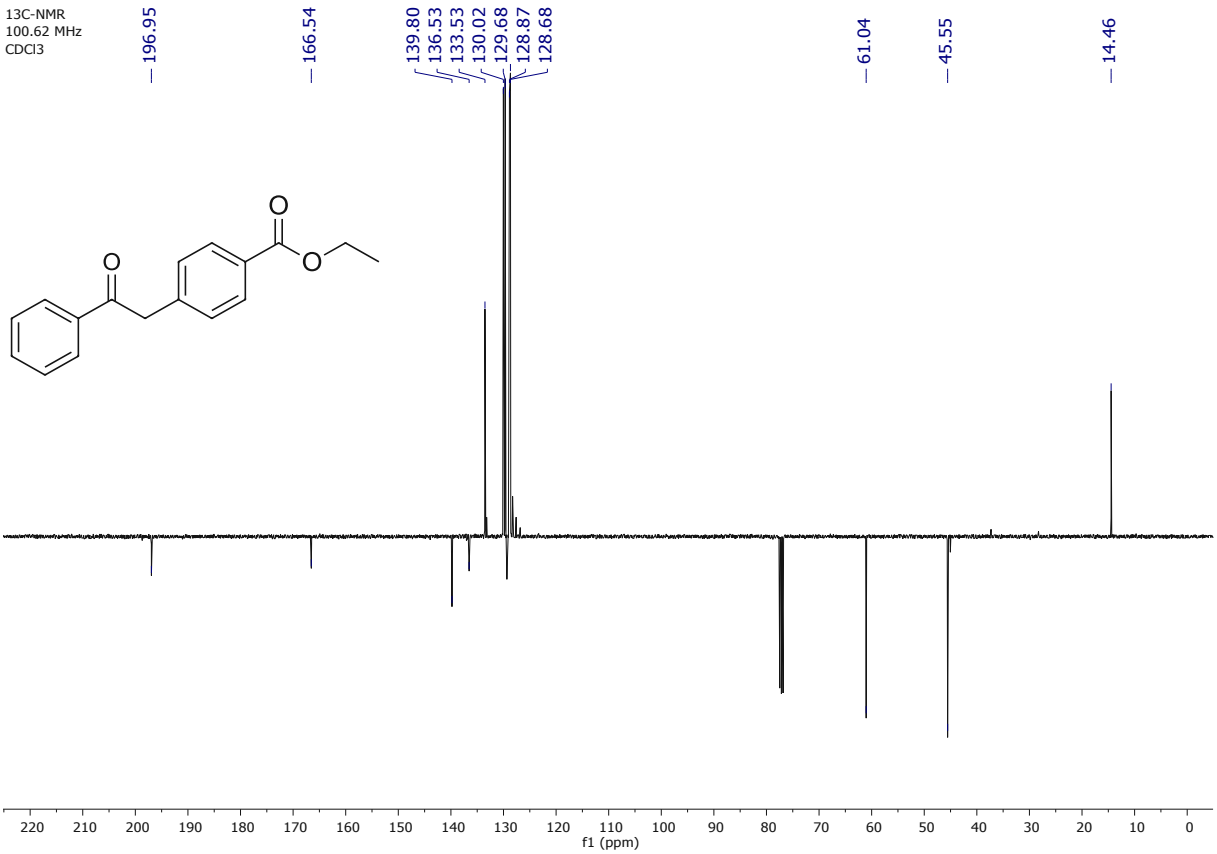
Methyl 4-(2-oxo-2-phenylethyl)benzoate (1v)



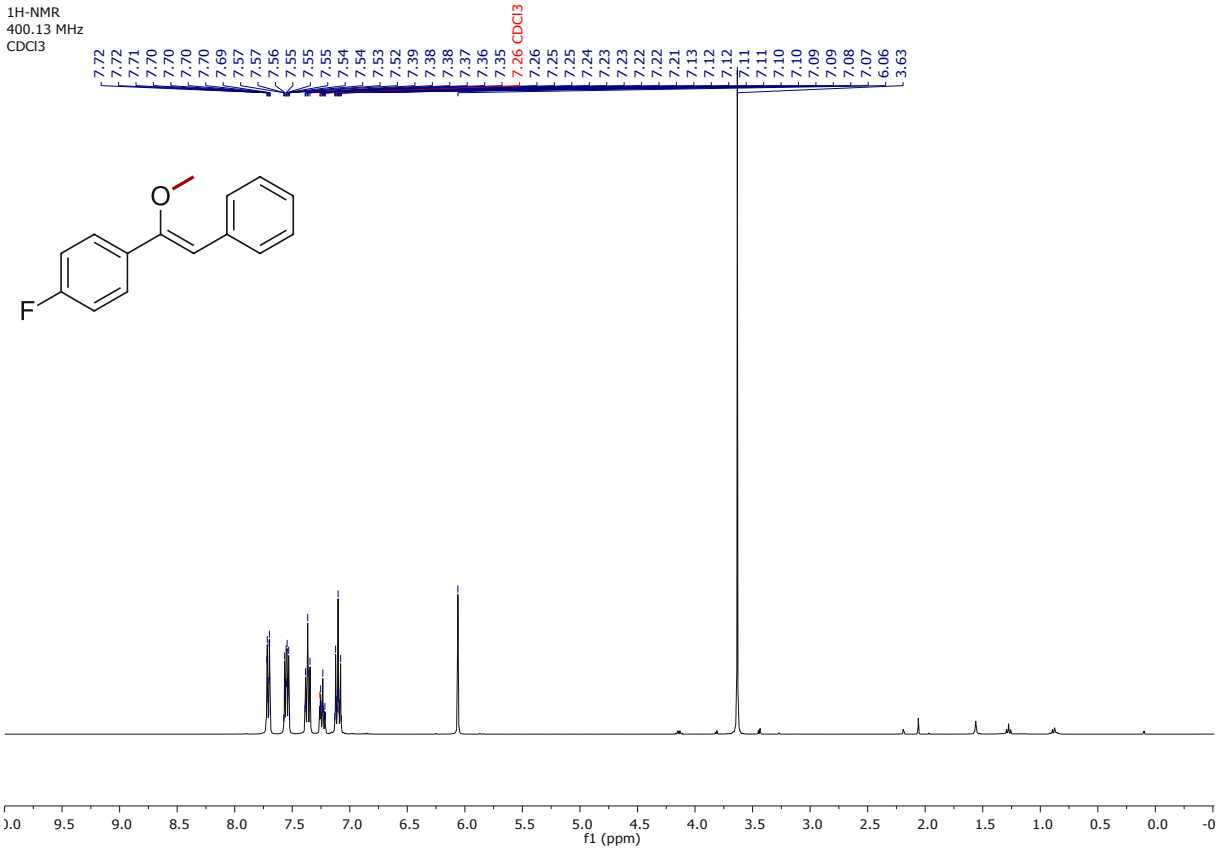


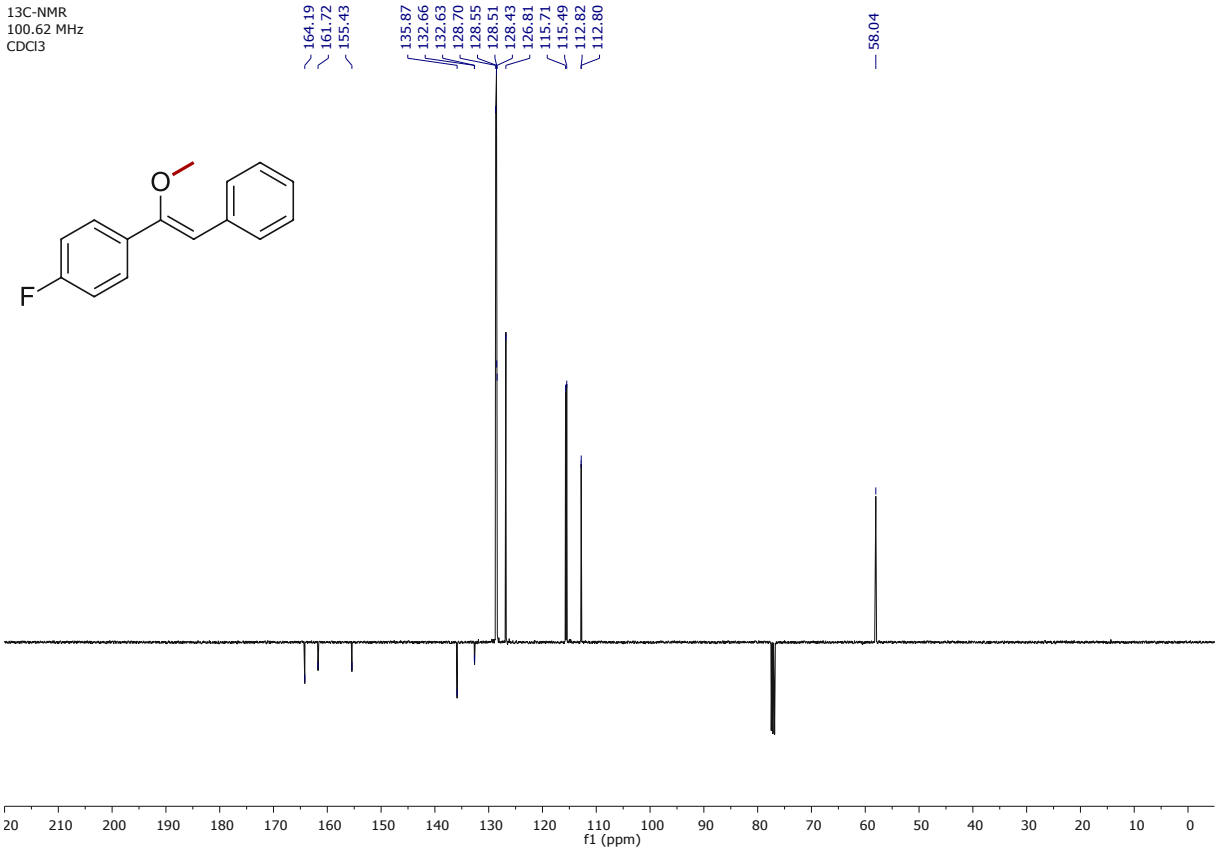
Ethyl 4-(2-oxo-2-phenylethyl)benzoate (1w)



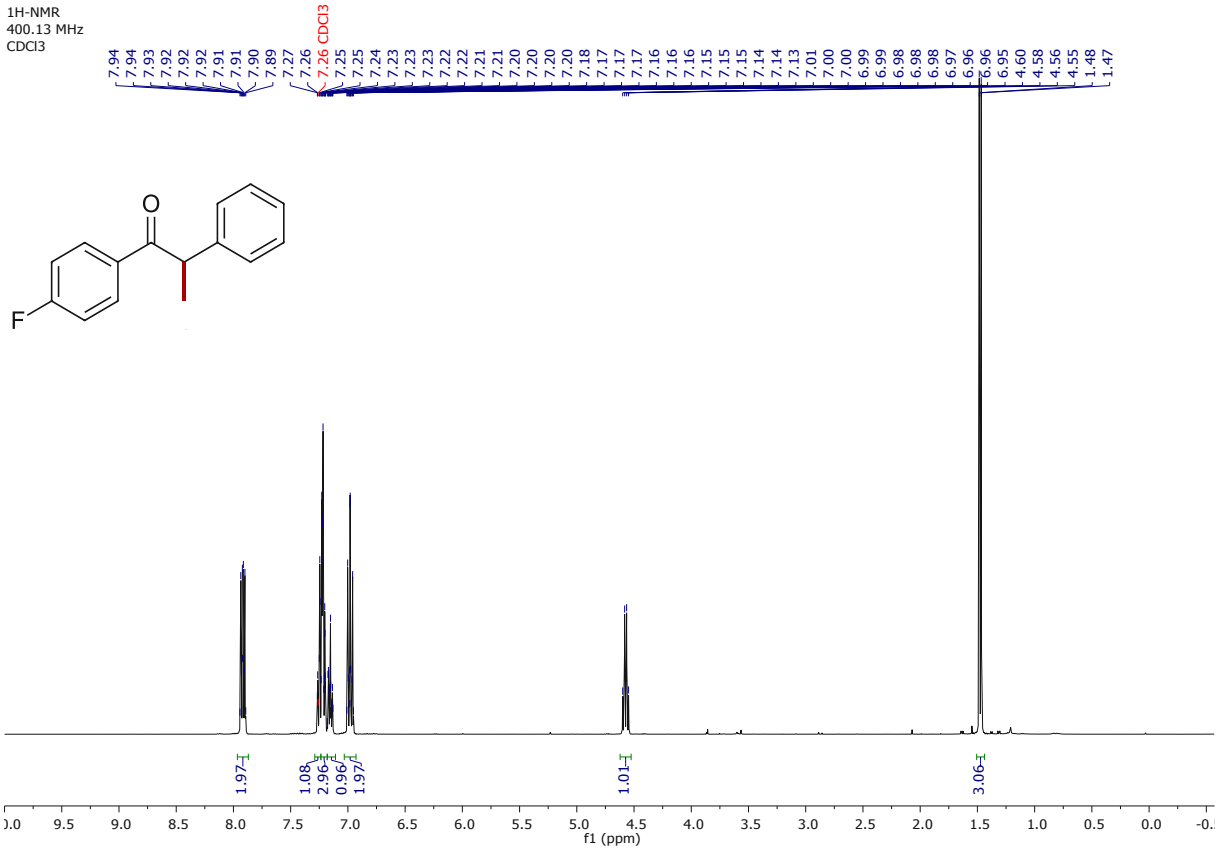


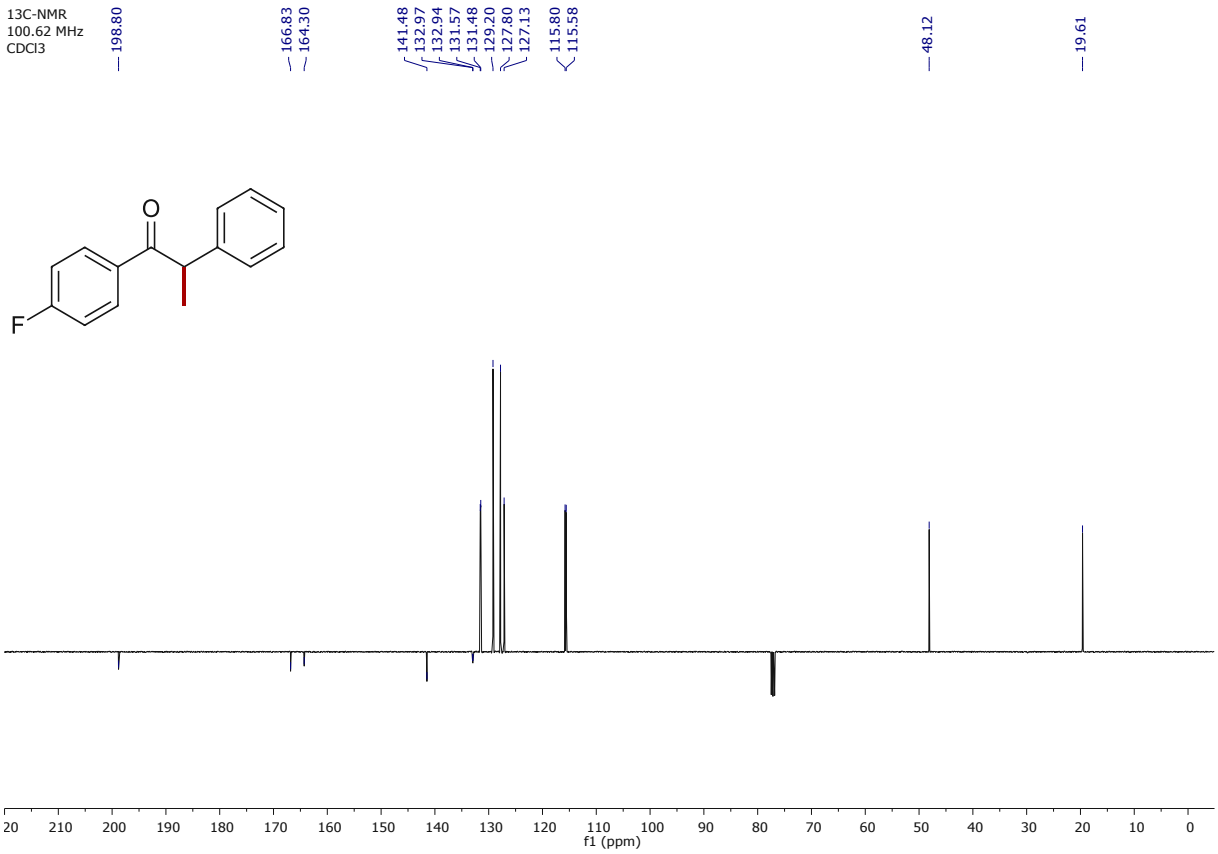
1-Fluoro-4-(1-methoxy-2-phenylethenyl)benzene (2a)

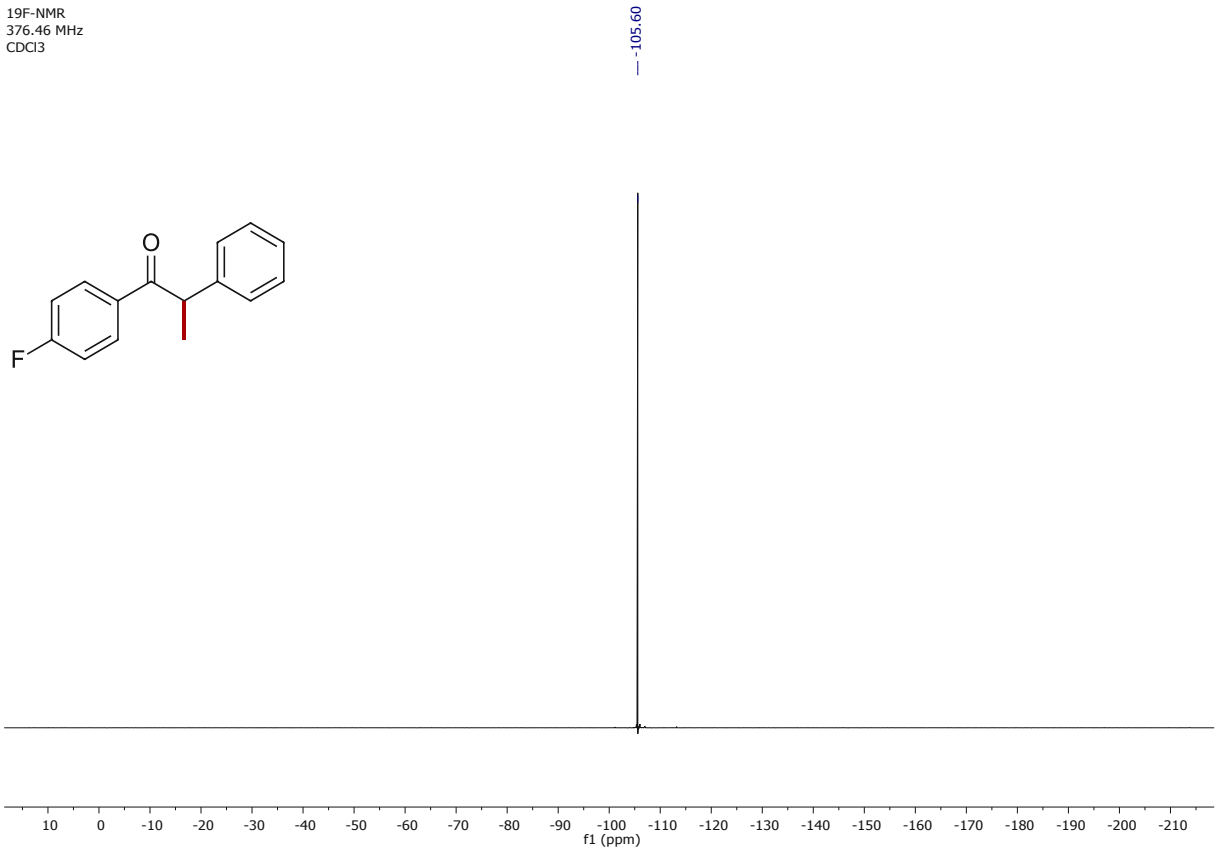




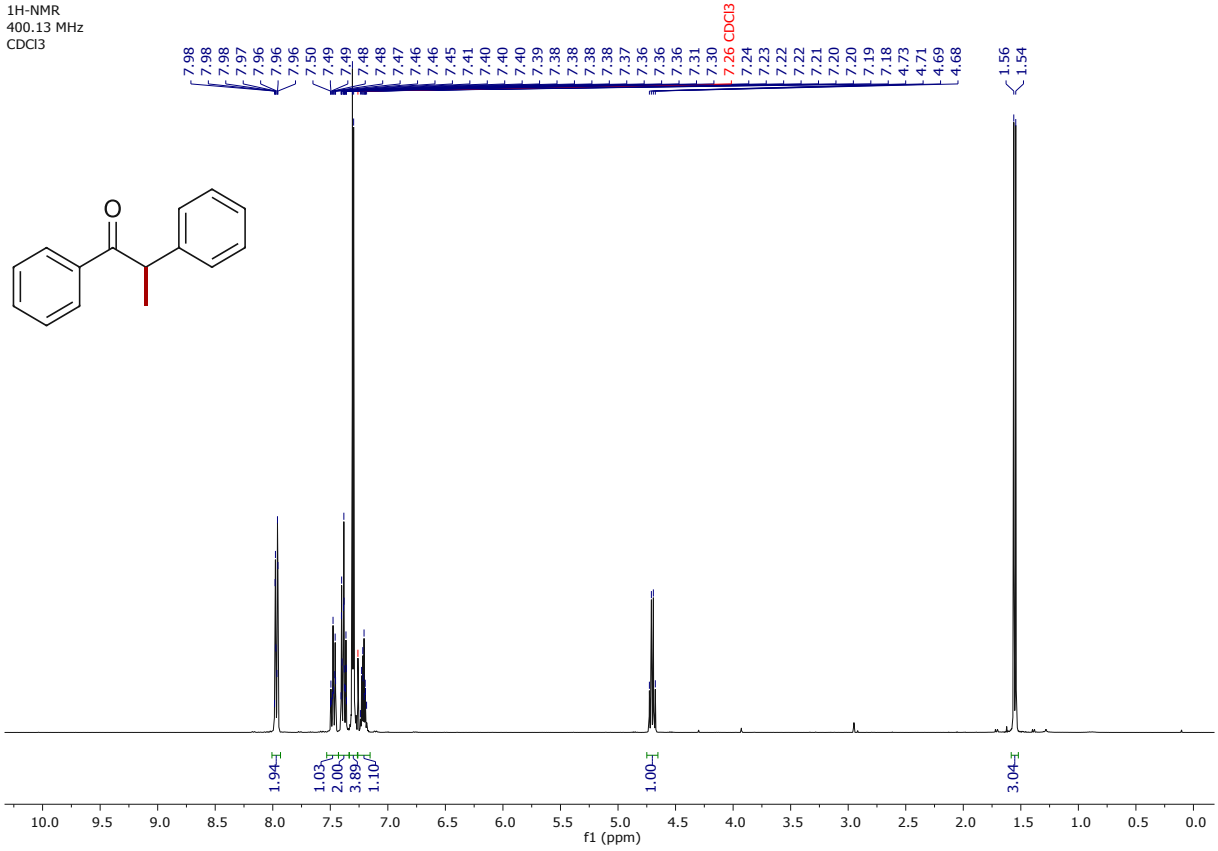
1-(4-Fluorophenyl)-2-phenyl-1-propanone (3a)

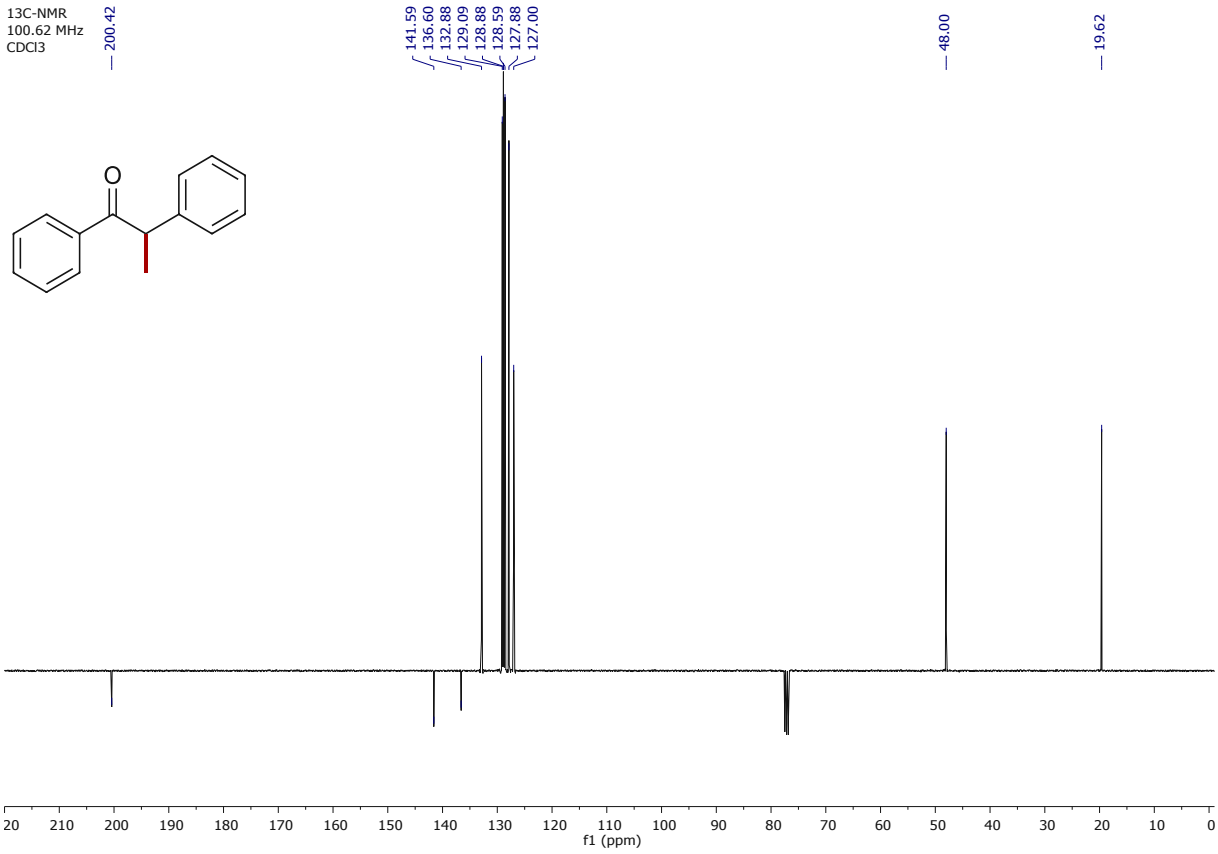




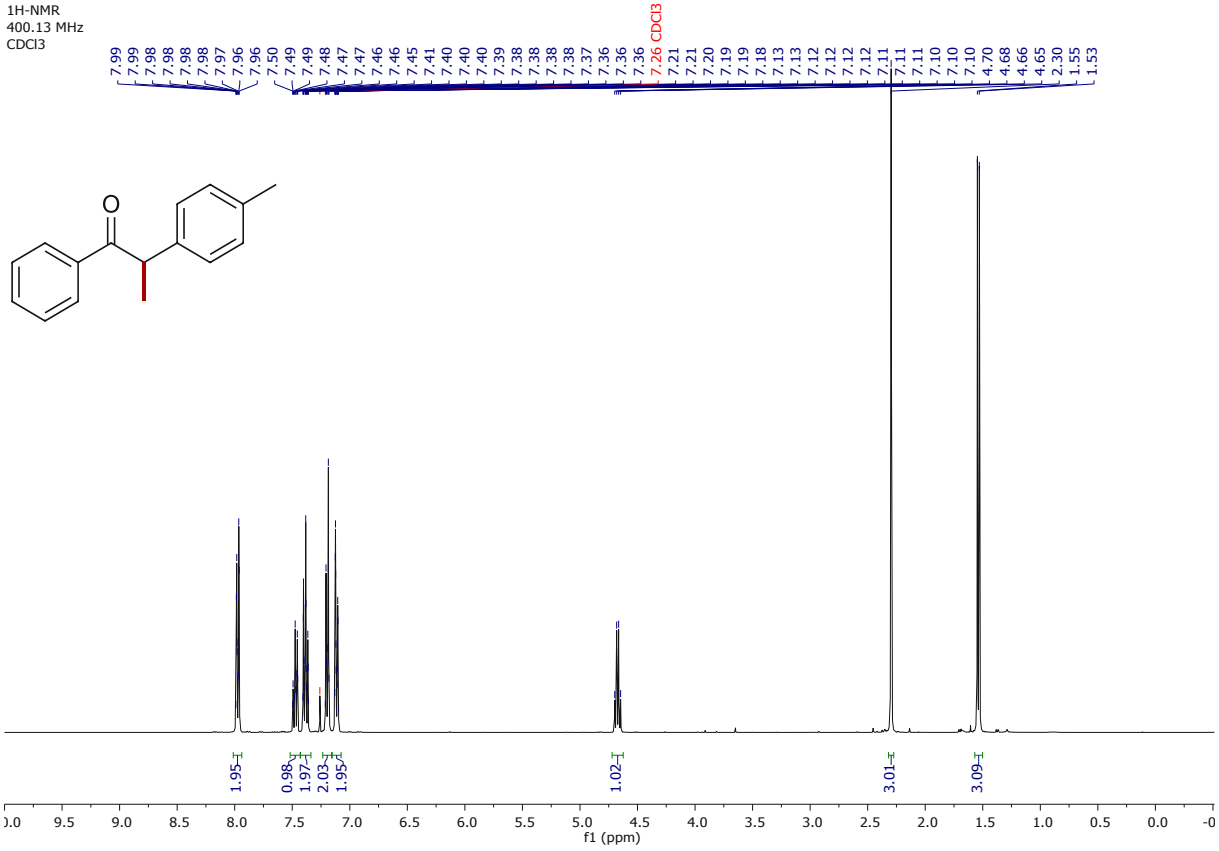


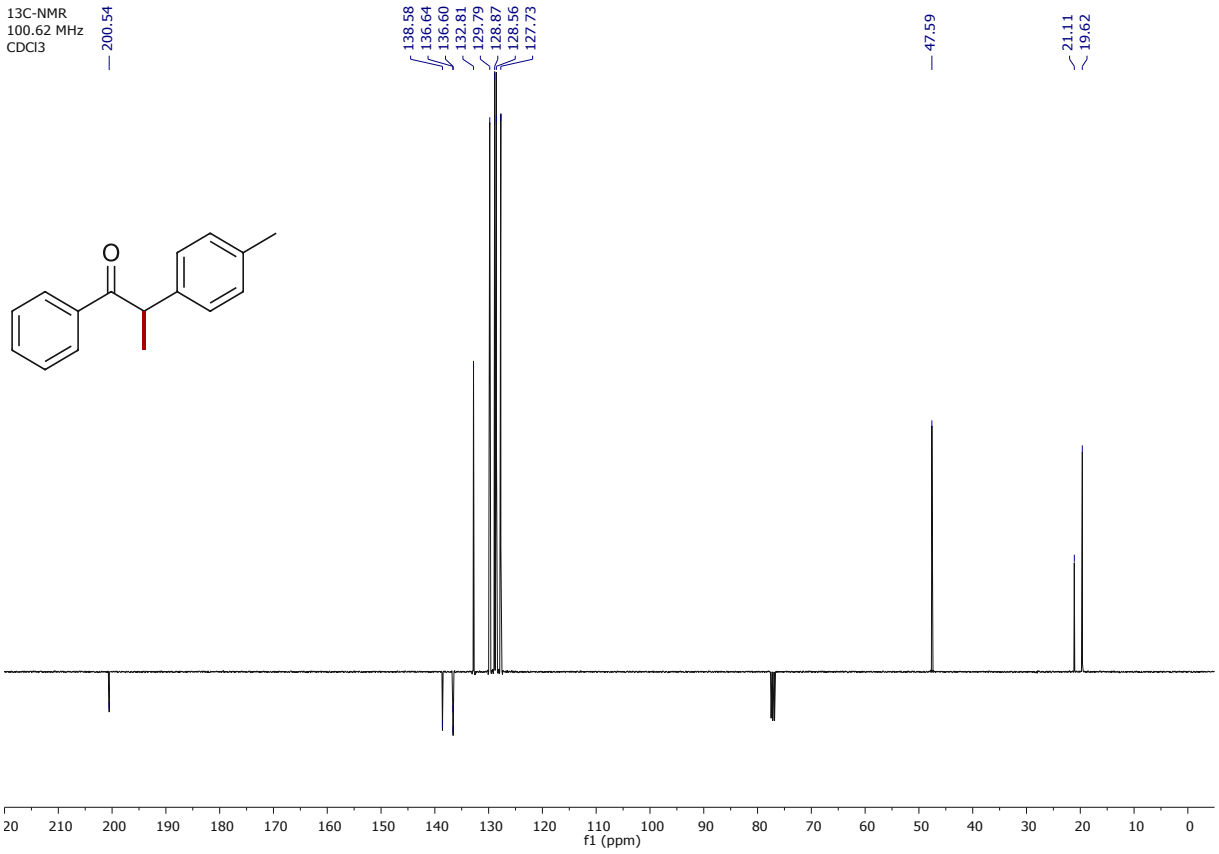
1,2-Diphenyl-1-propanone (3b)



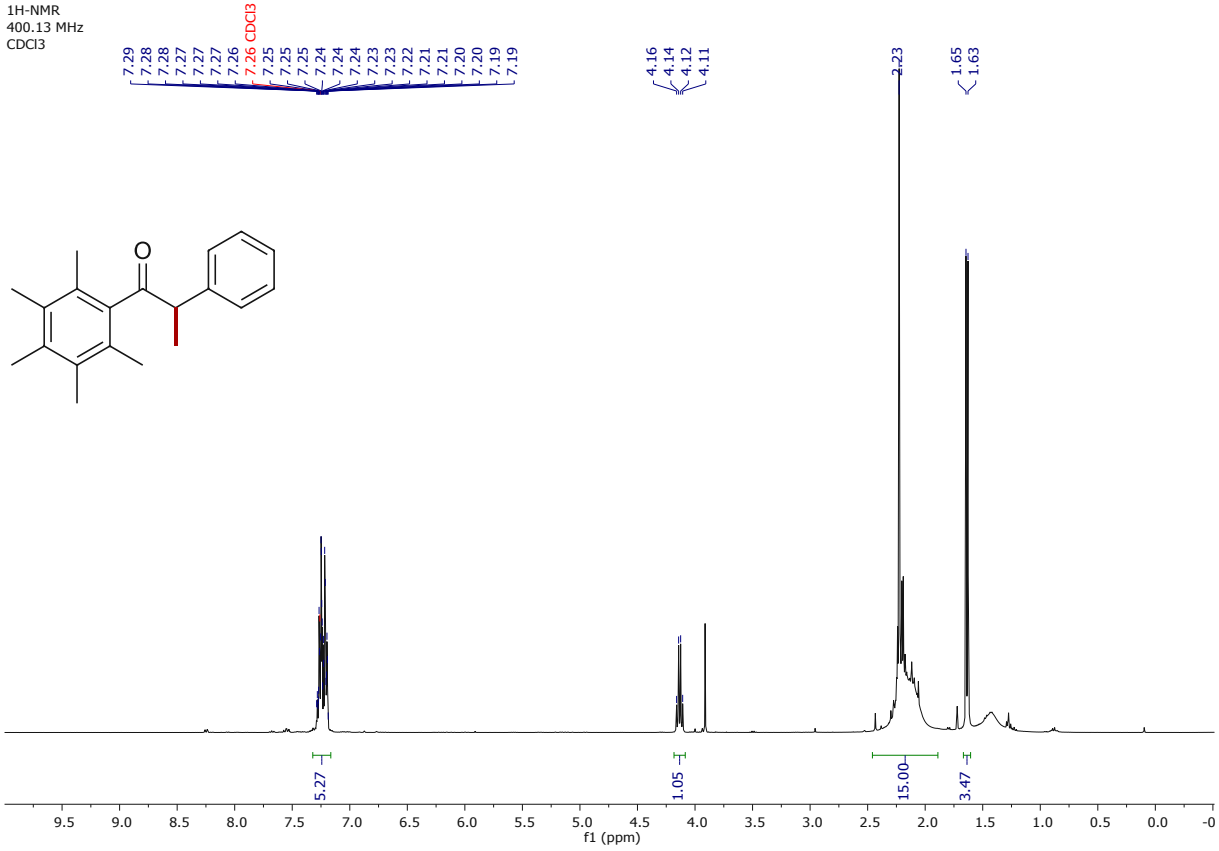


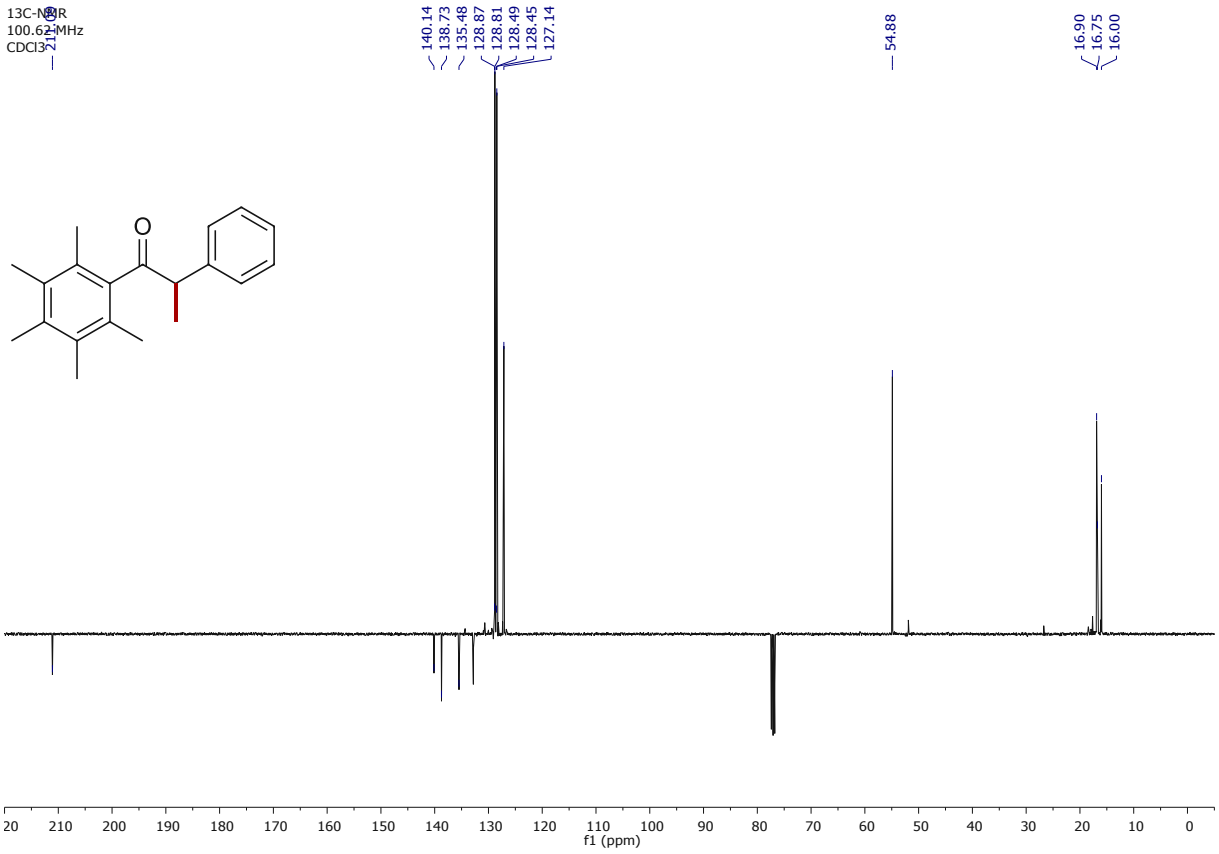
2-(4-Methylphenyl)-1-phenyl-1-propanone (3c)



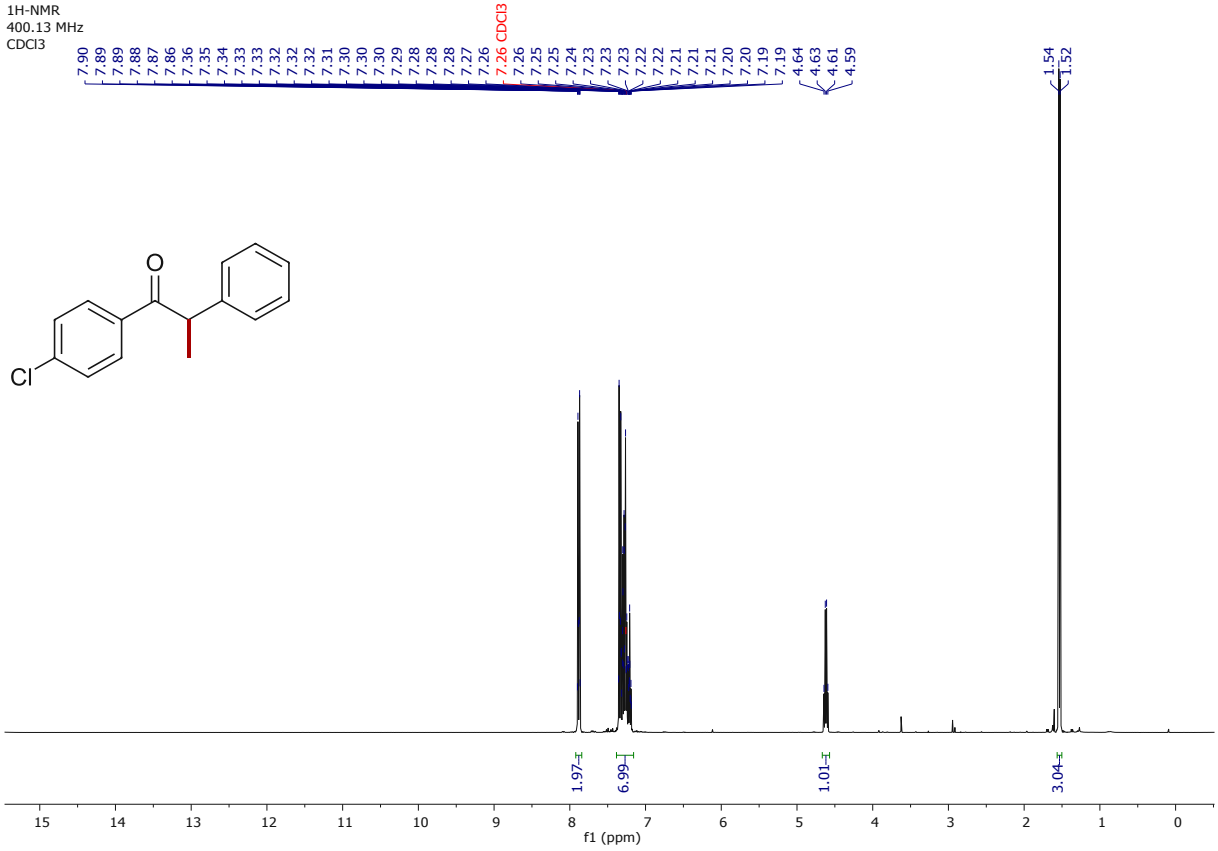


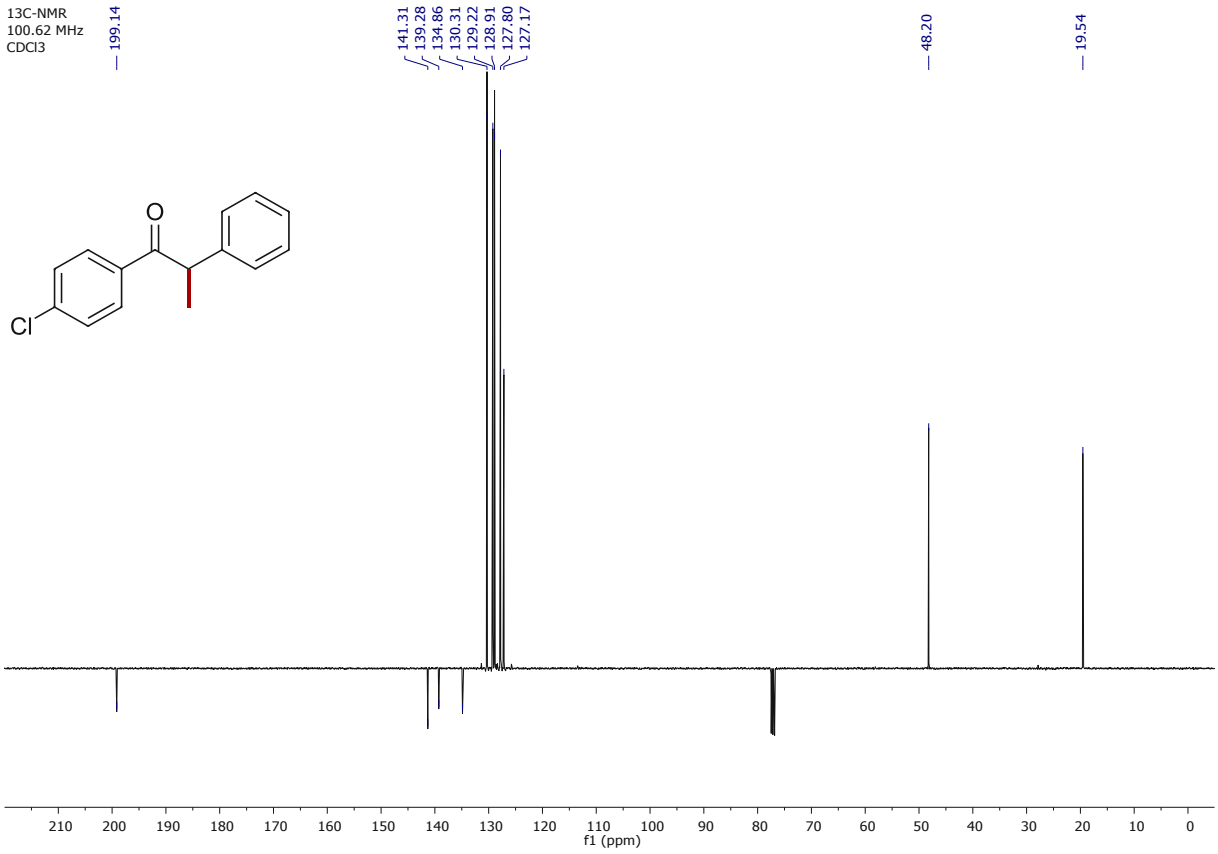
2-(2,3,4,5,6-Pentamethylphenyl)-1-phenyl-1-propanone (3d)



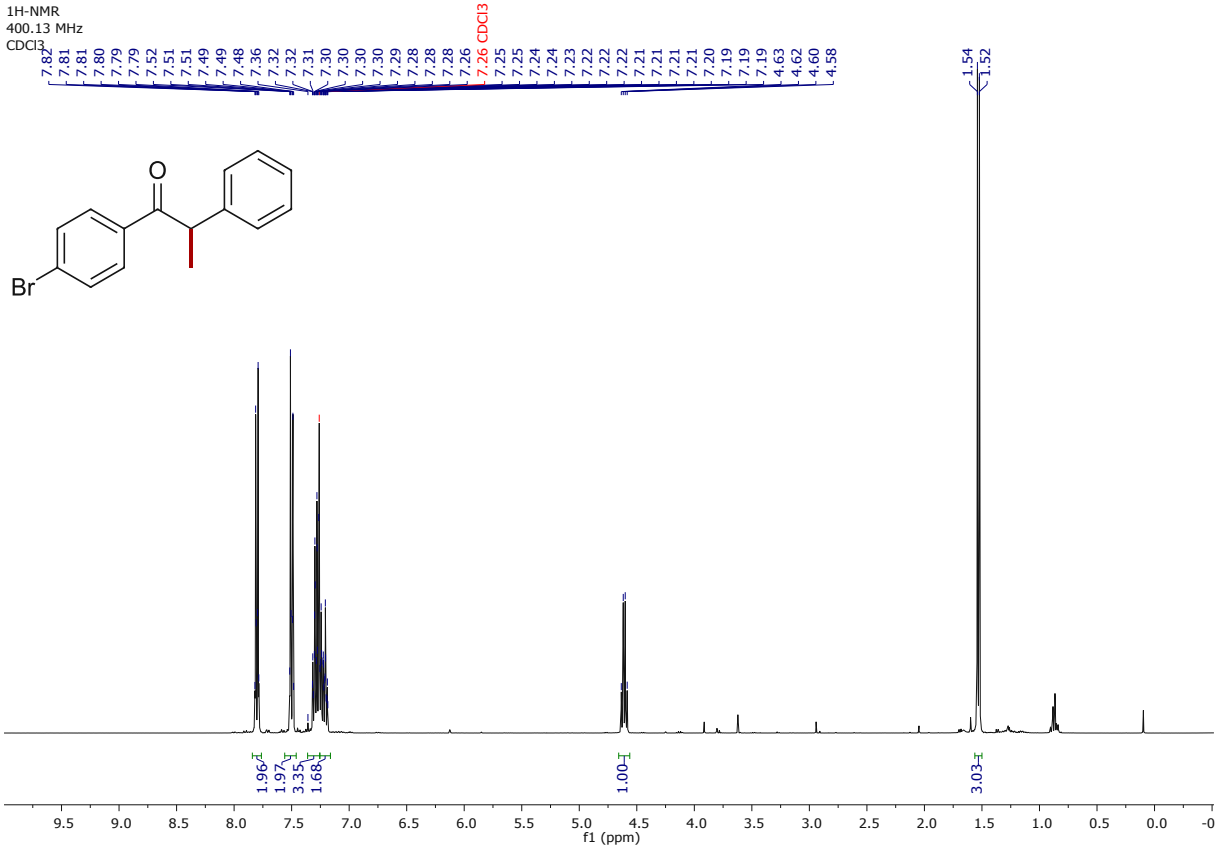


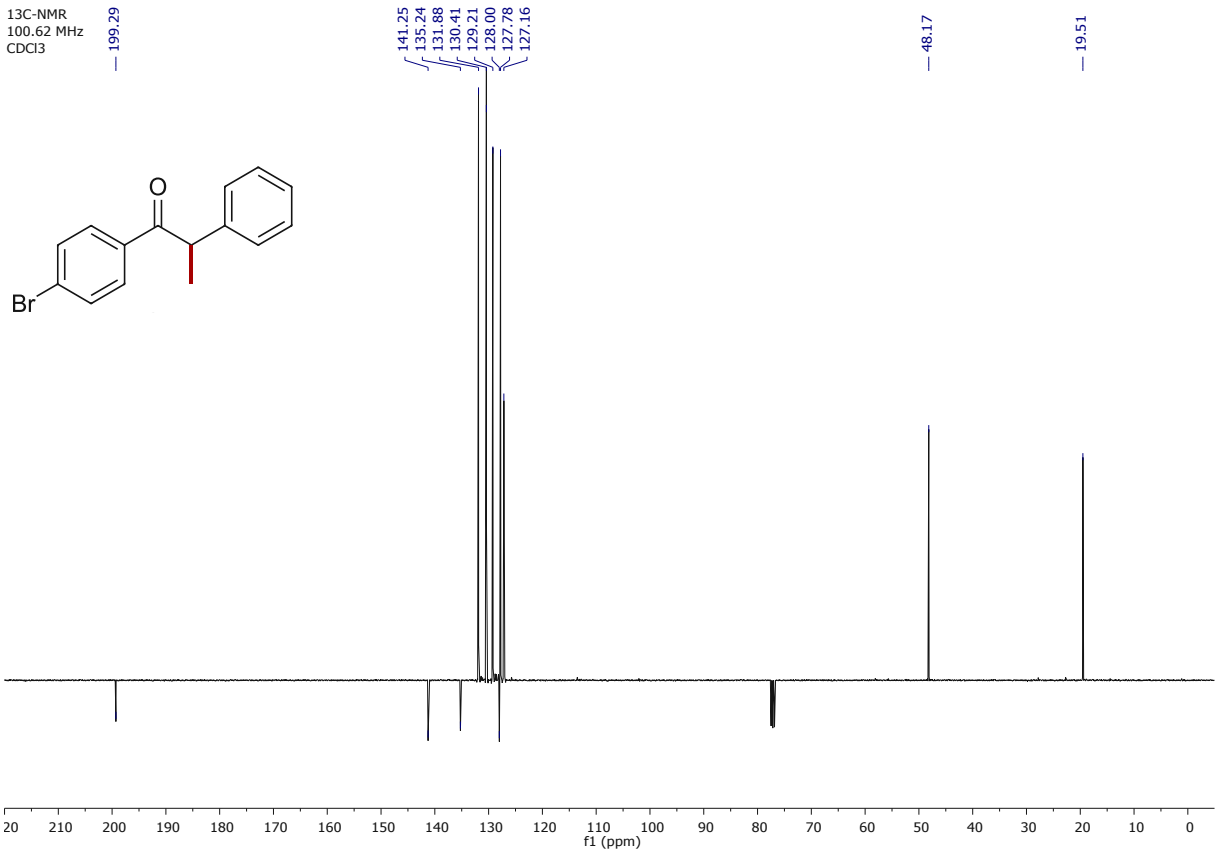
1-(4-Chlorophenyl)-2-phenyl-1-propanone (3e)



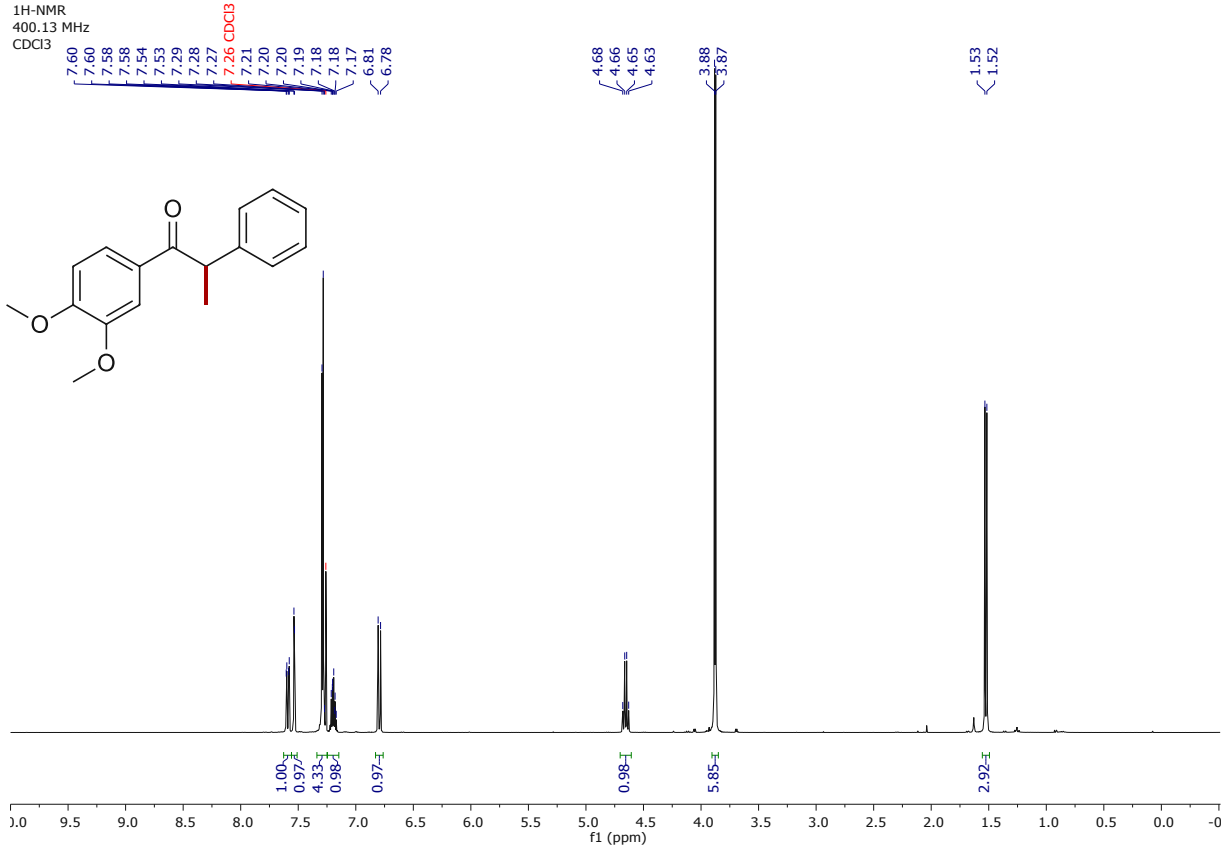


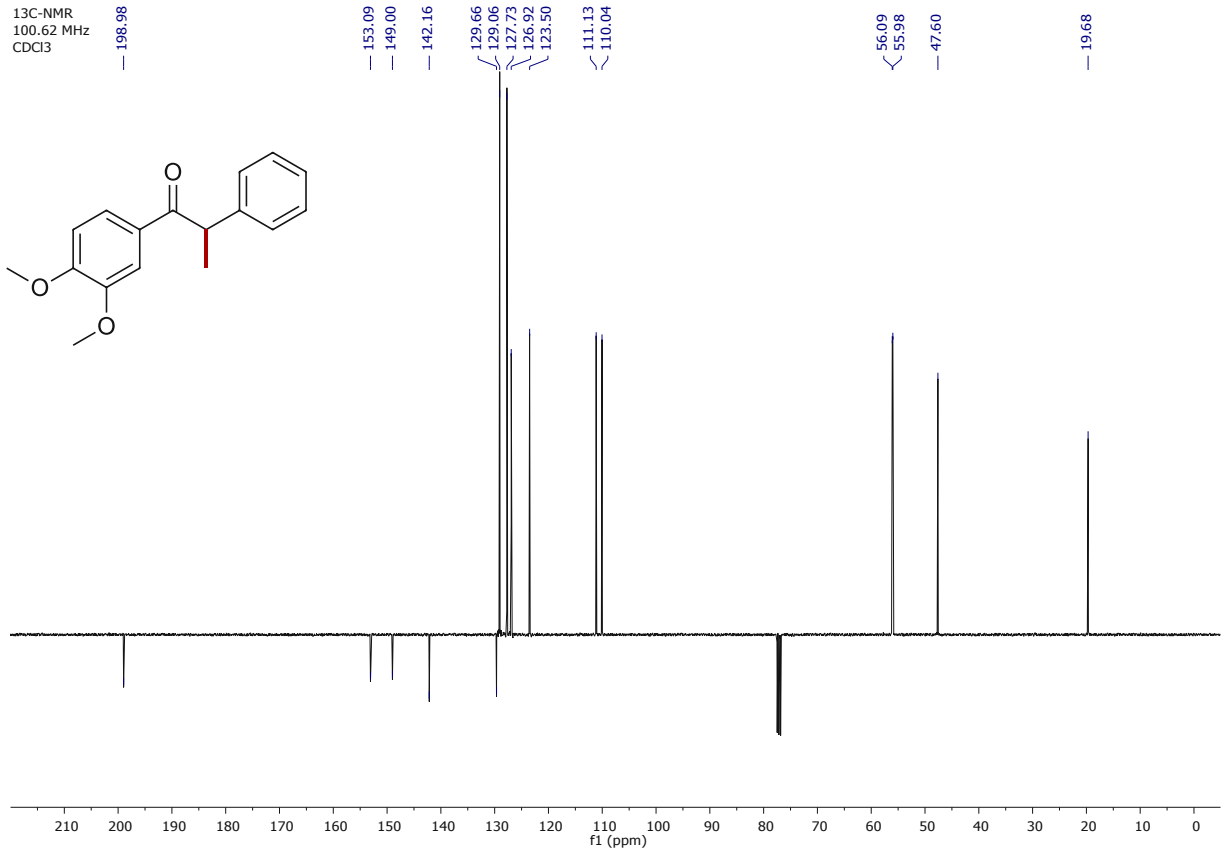
1-(4-Bromophenyl)-2-phenyl-1-propanone (3f)



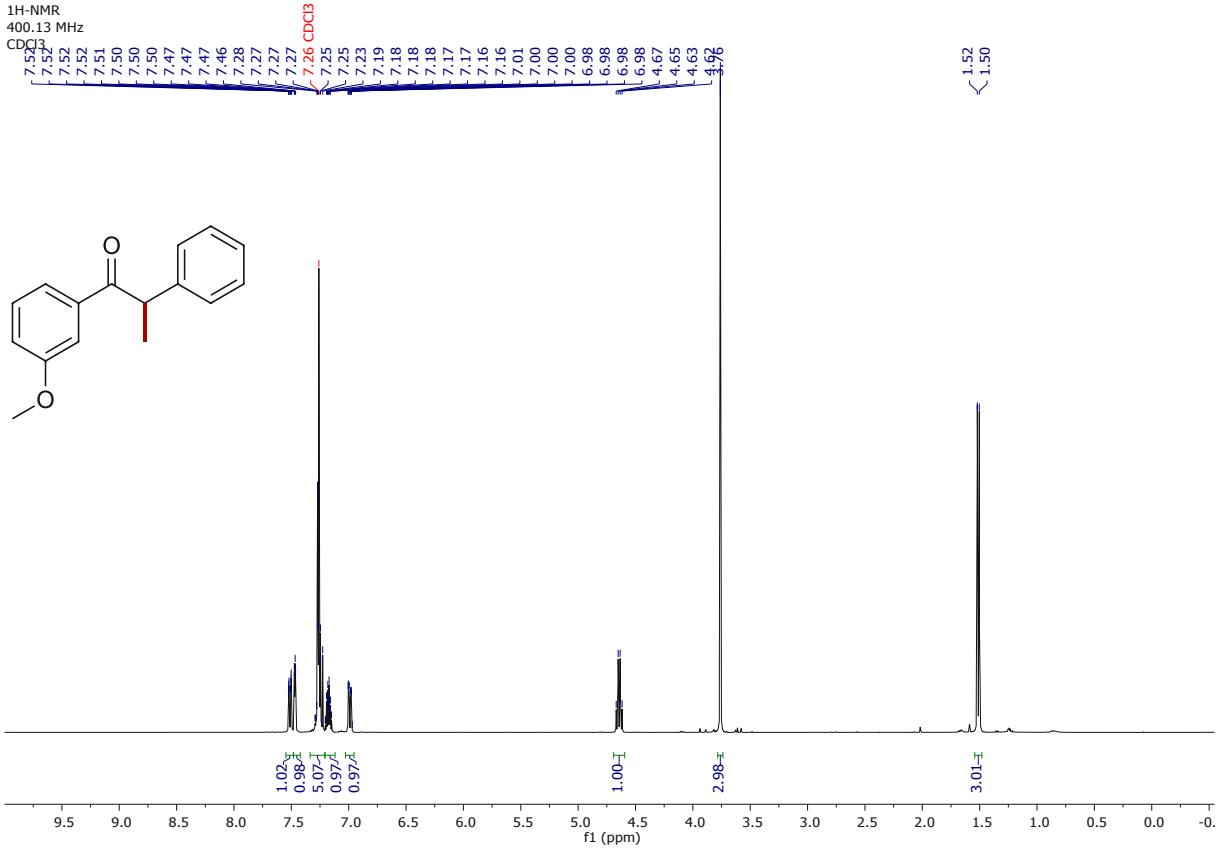


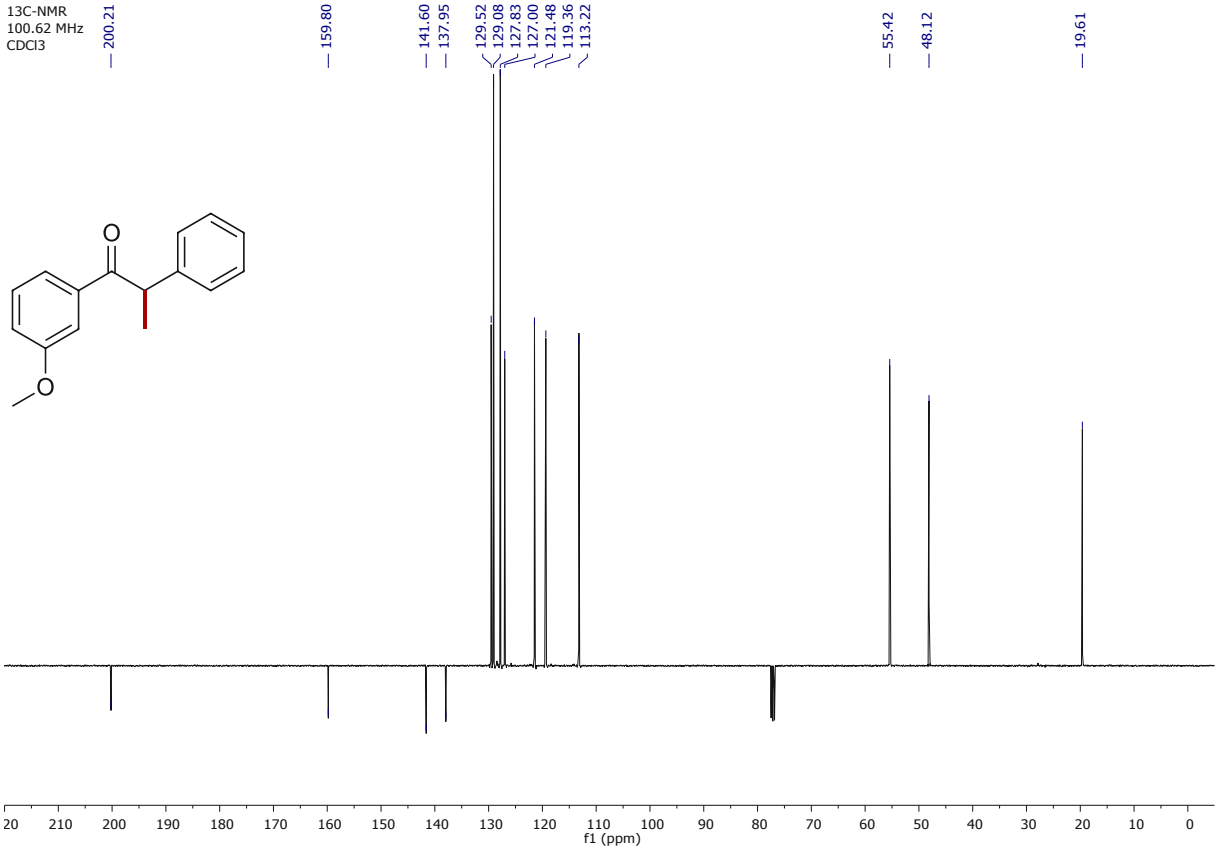
1-(3,4-Dimethoxyphenyl)-2-phenyl-1-propanone (3g)



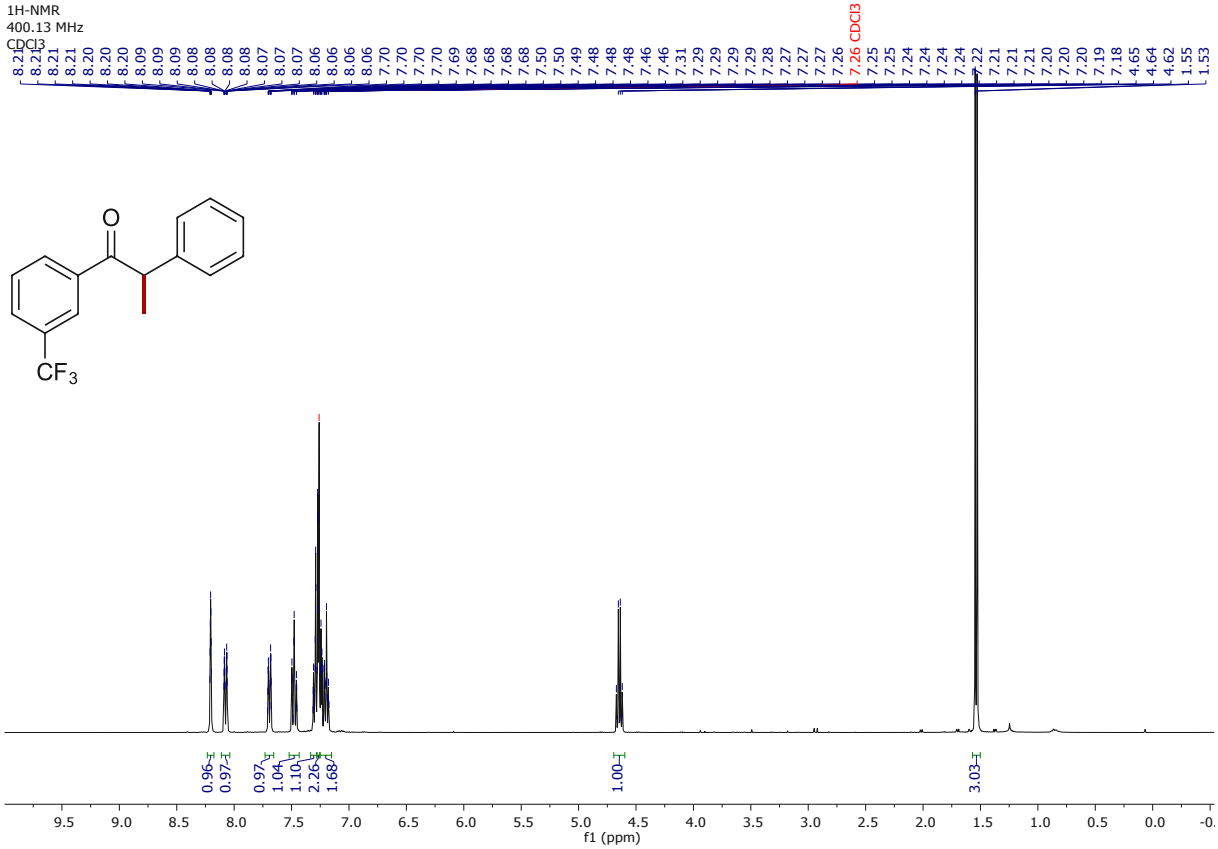


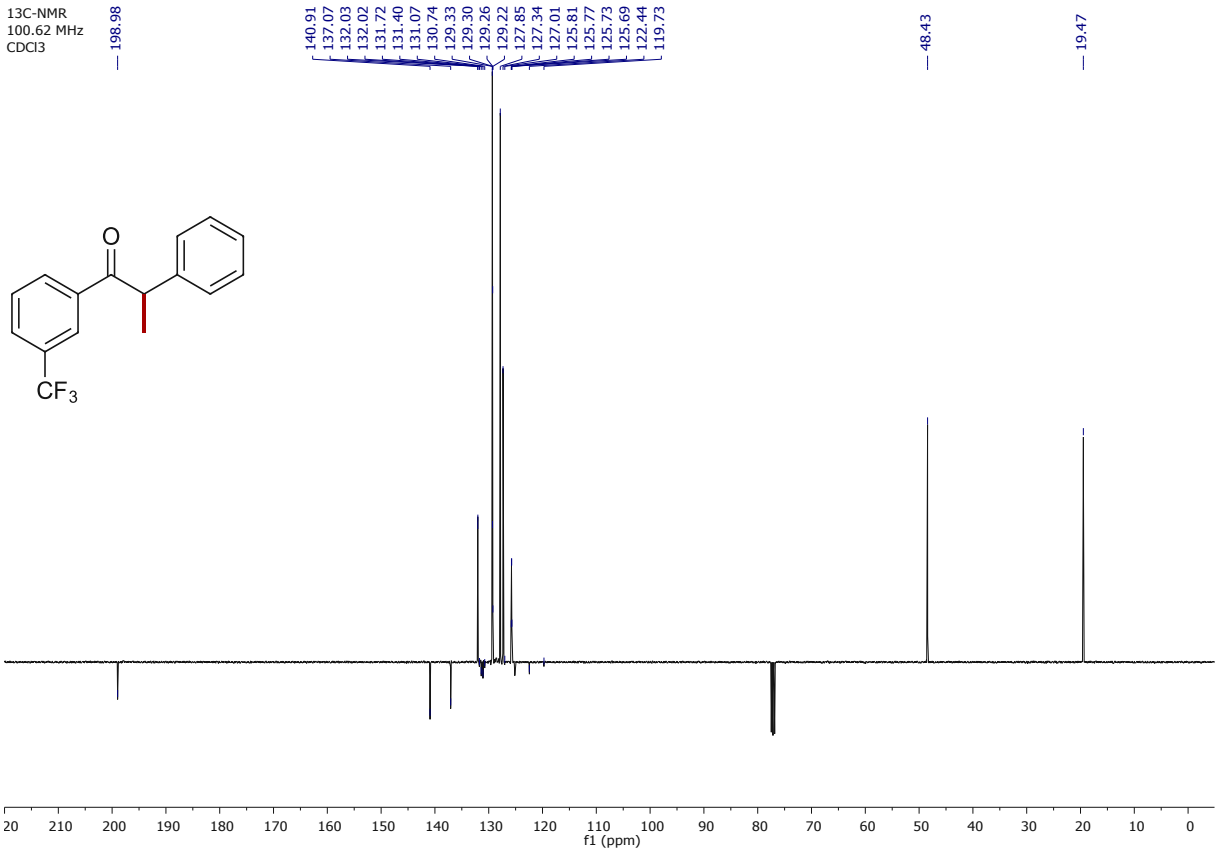
1-(3-Methoxyphenyl)-2-phenyl-1-propanone (3h)



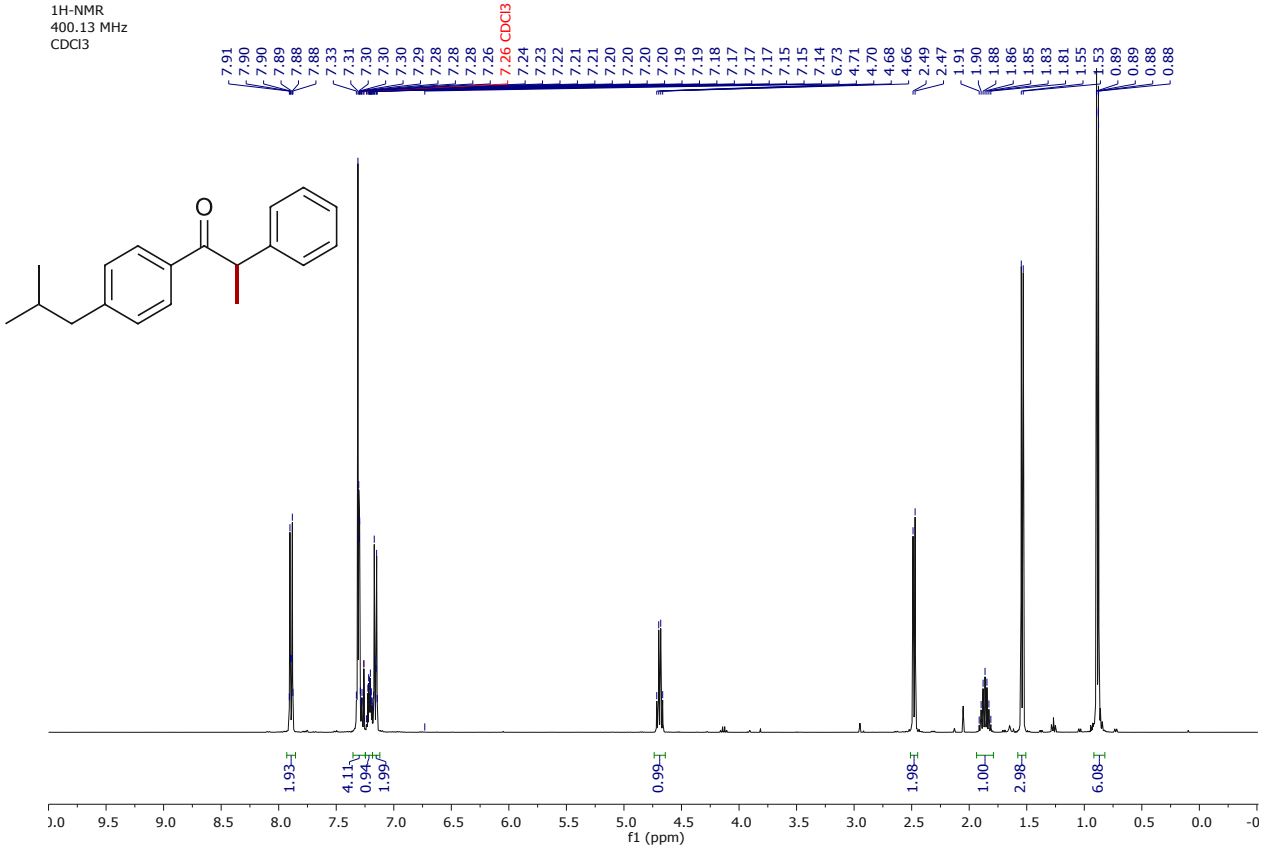


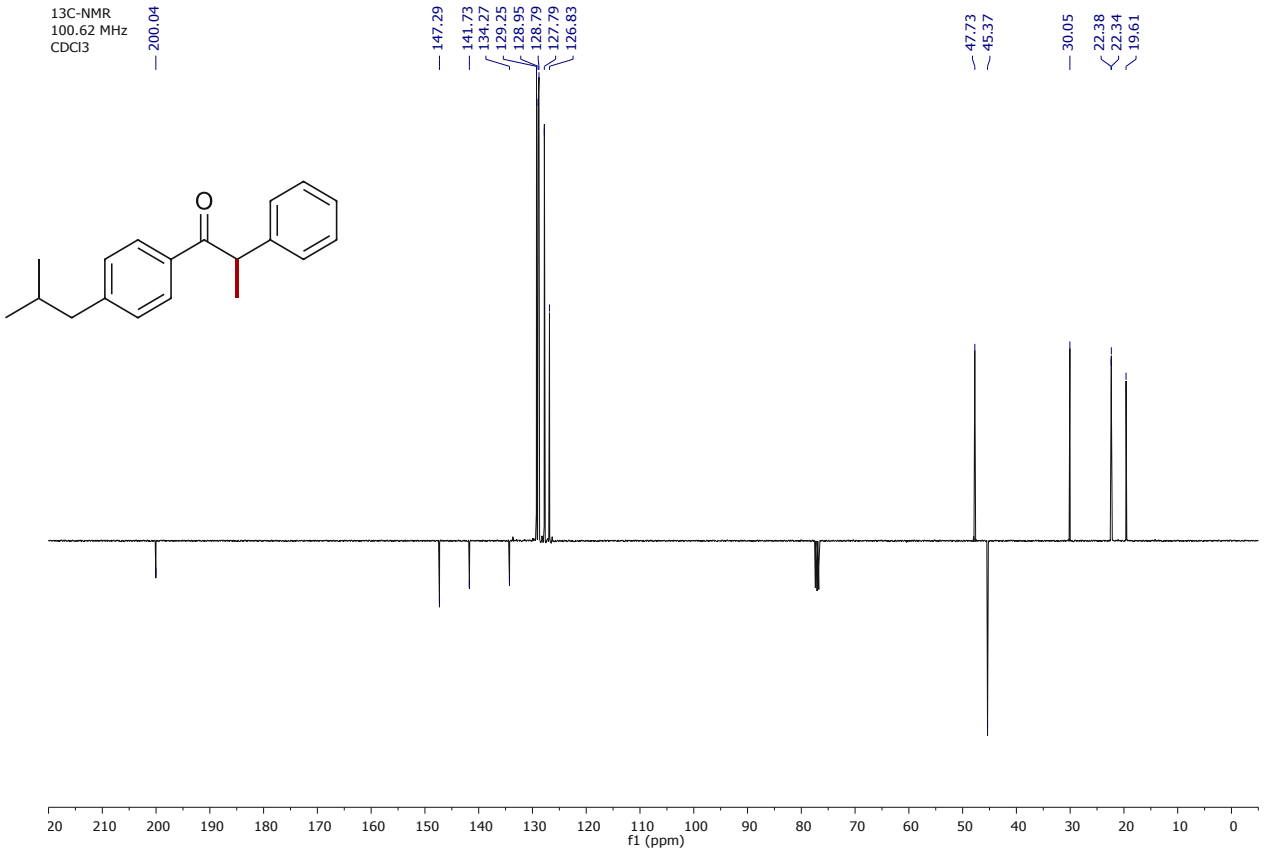
2-Phenyl-1-[3-(trifluoromethyl)phenyl]-1-propanone (3i)



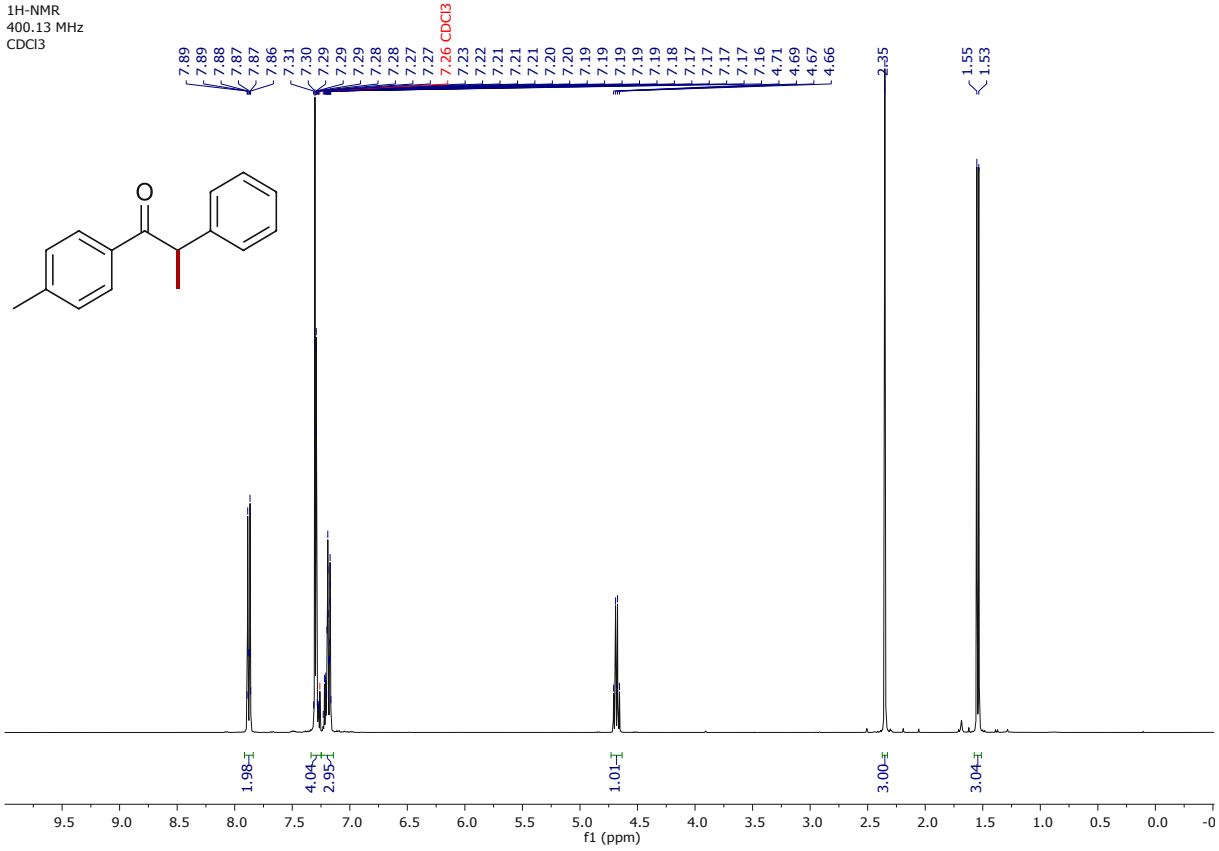


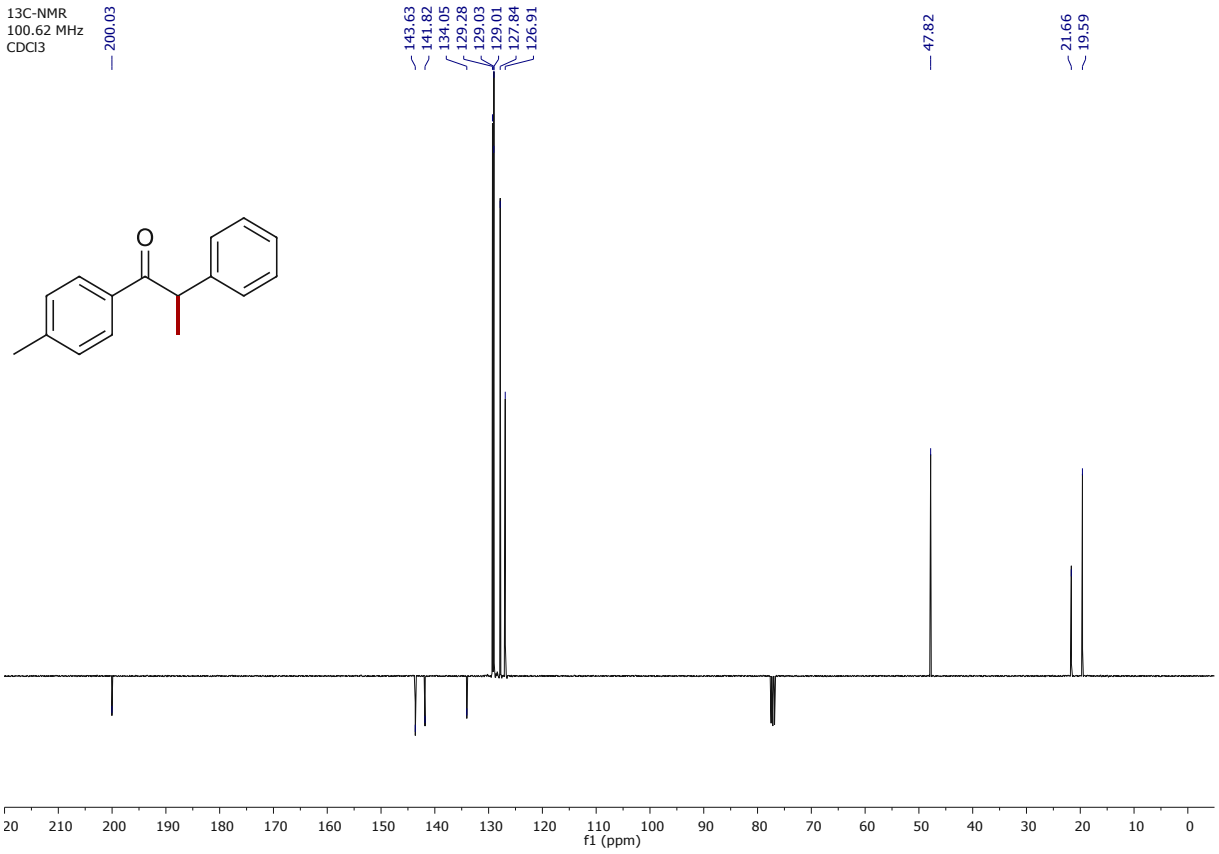
1-[4-(2-Methylpropyl)phenyl]-2-phenyl-1-propanone (3j)



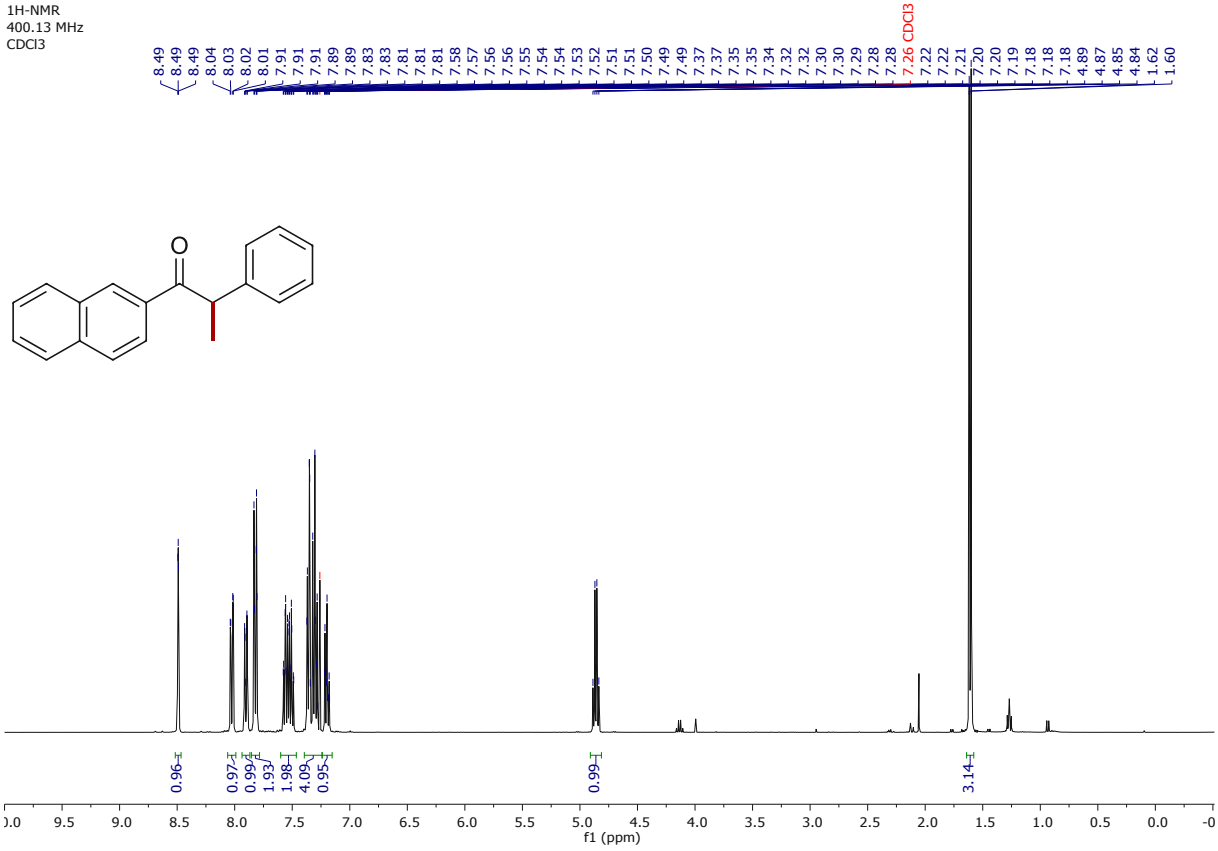


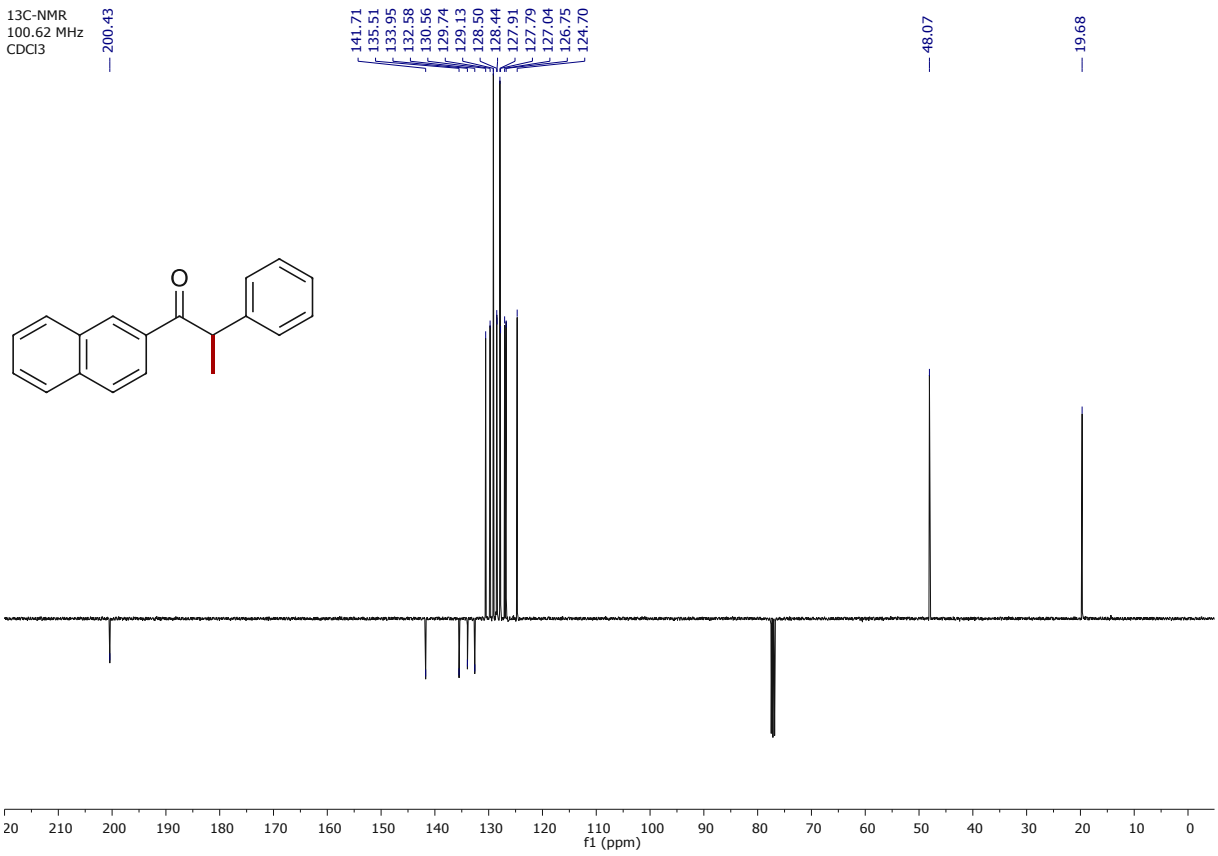
1-(4-Methylphenyl)-2-phenyl-1-propanone (3k)



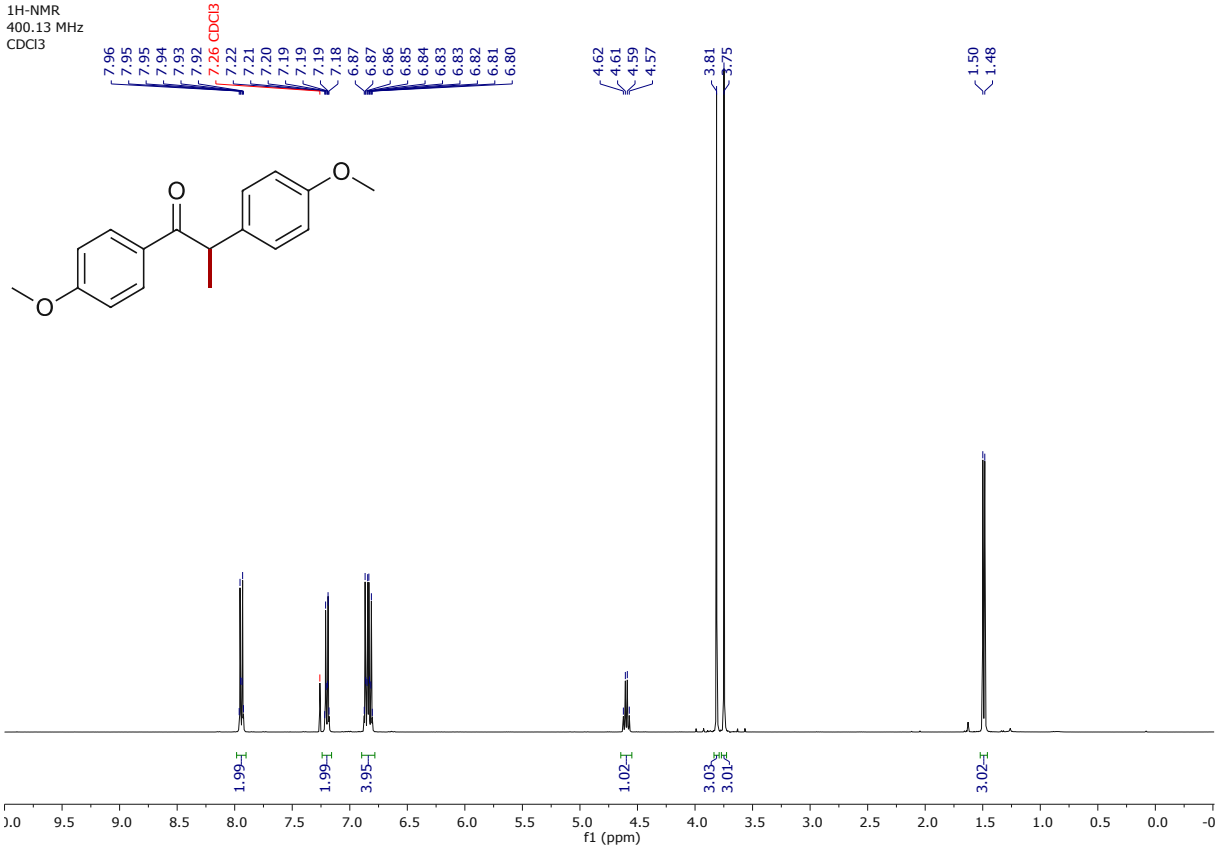


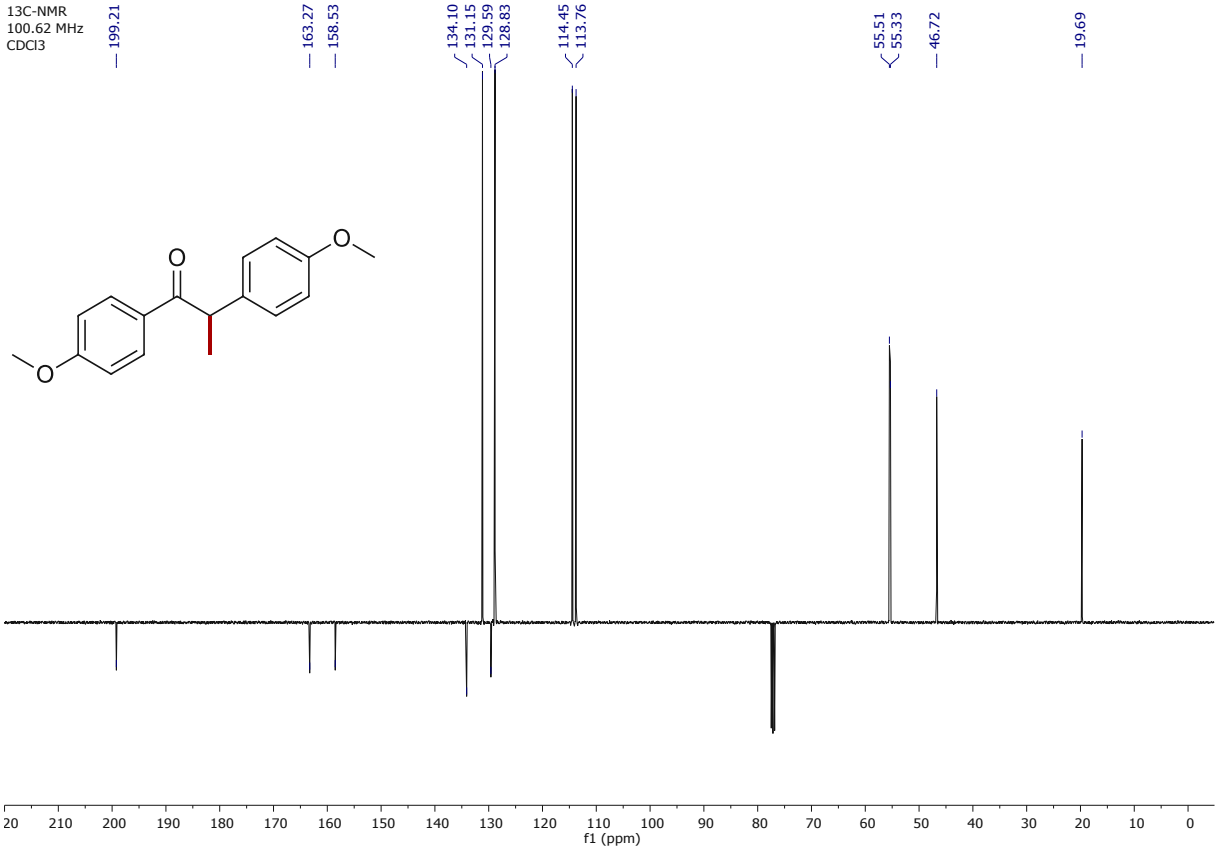
1-(2-Naphthyl)-2-phenyl-1-propanone (3l)



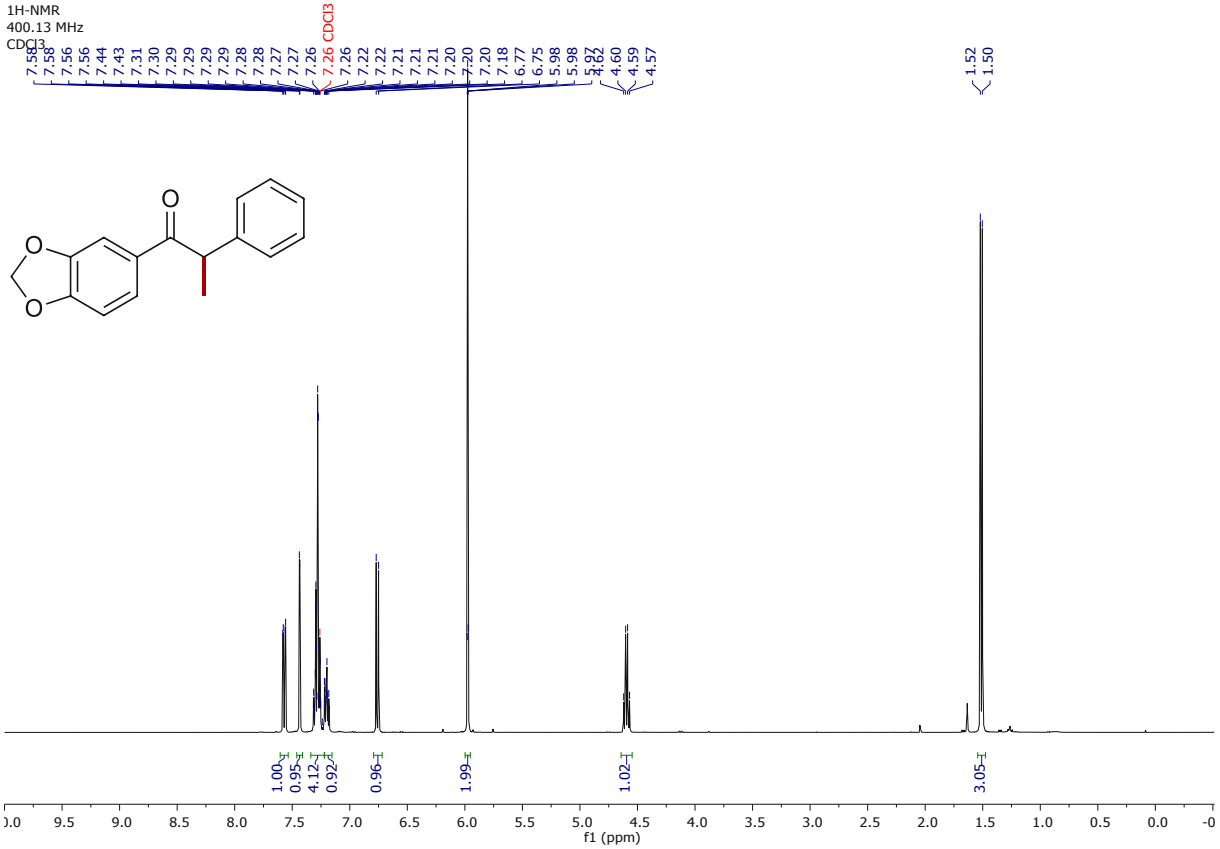


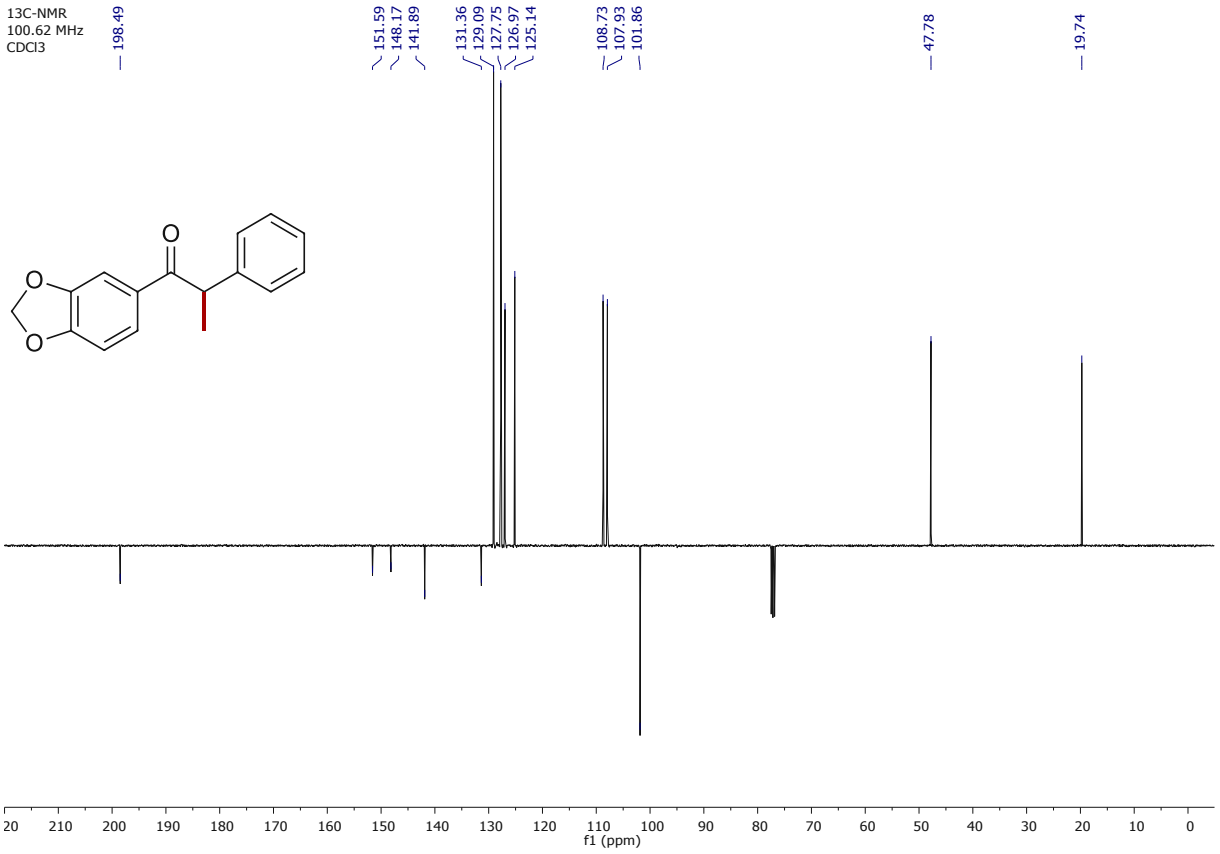
1,2-Bis(4-methoxyphenyl)-1-propanone (3m)



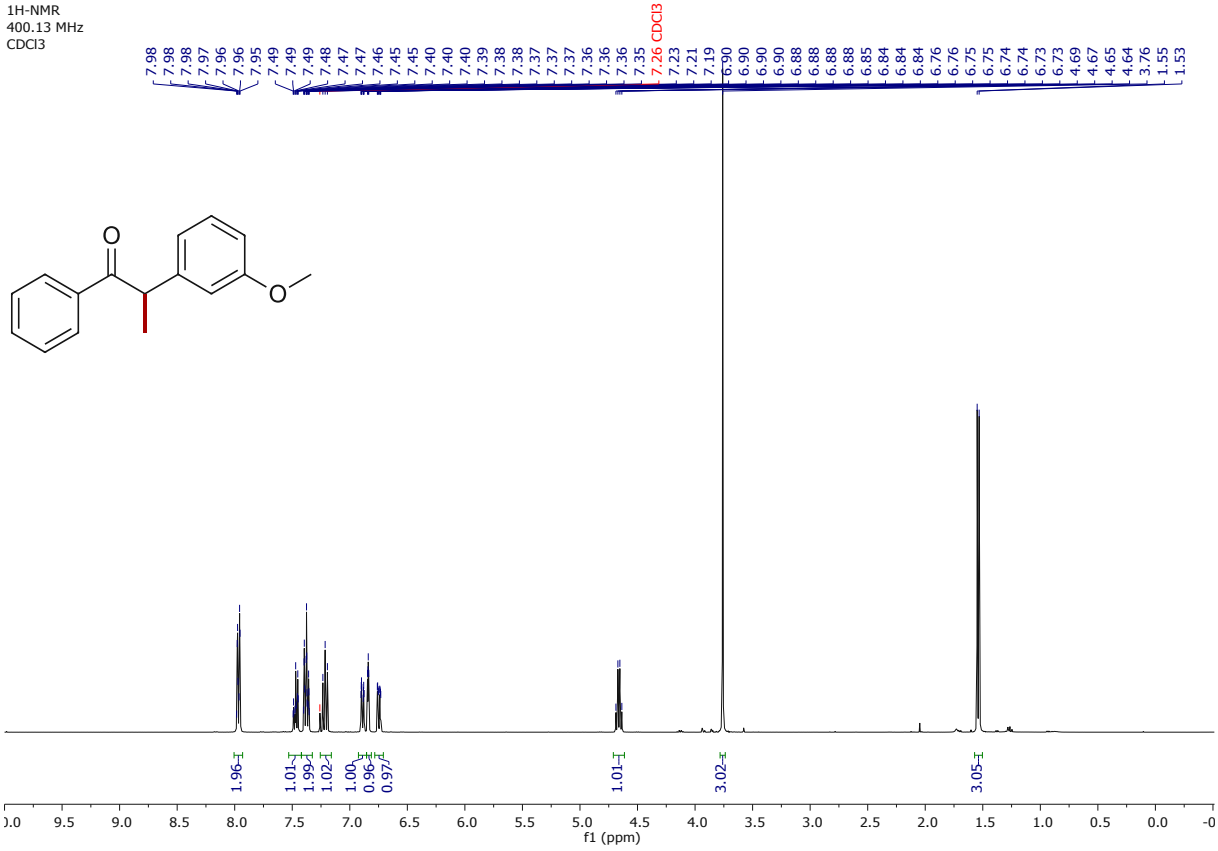


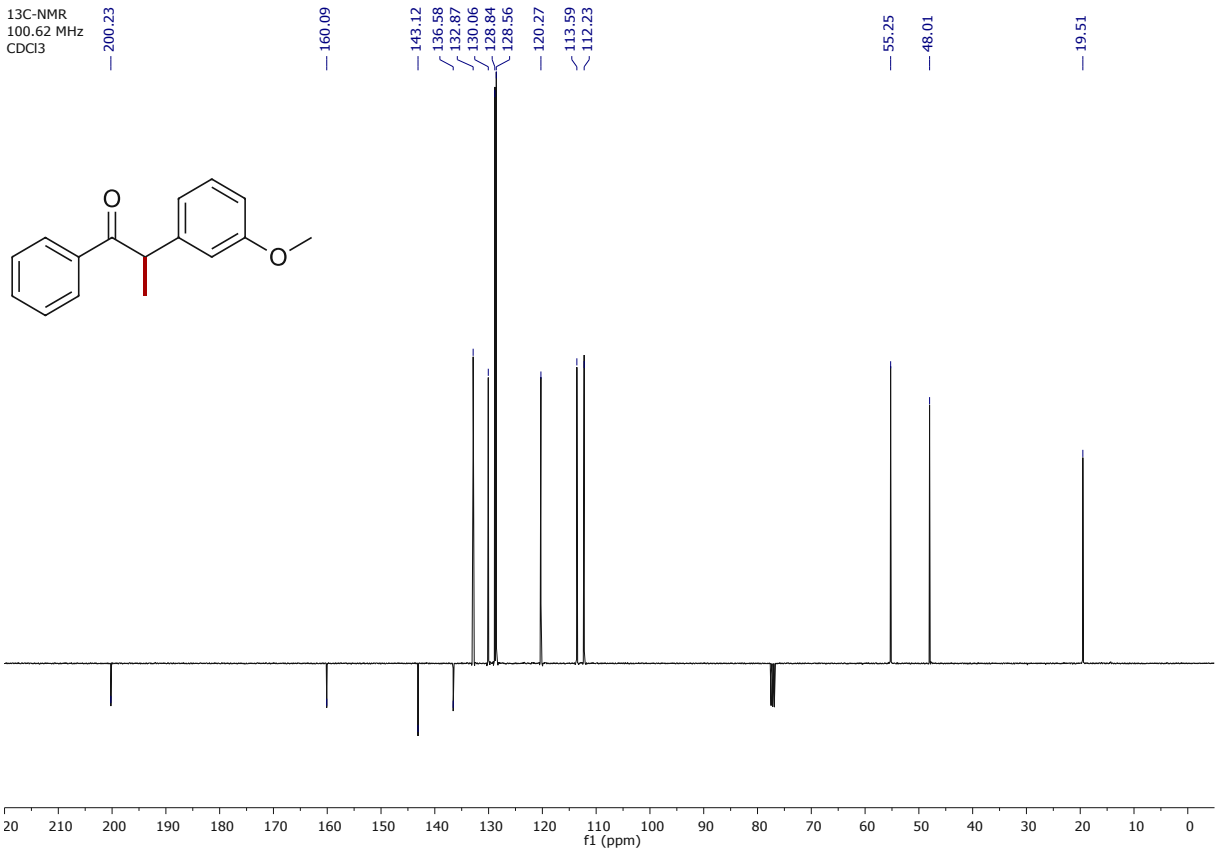
1-(2H-1,3-Benzodioxol-5-yl)-2-phenyl-1-propanone (3n)





2-(3-Methoxyphenyl)-1-phenyl-1-propanone (3o)





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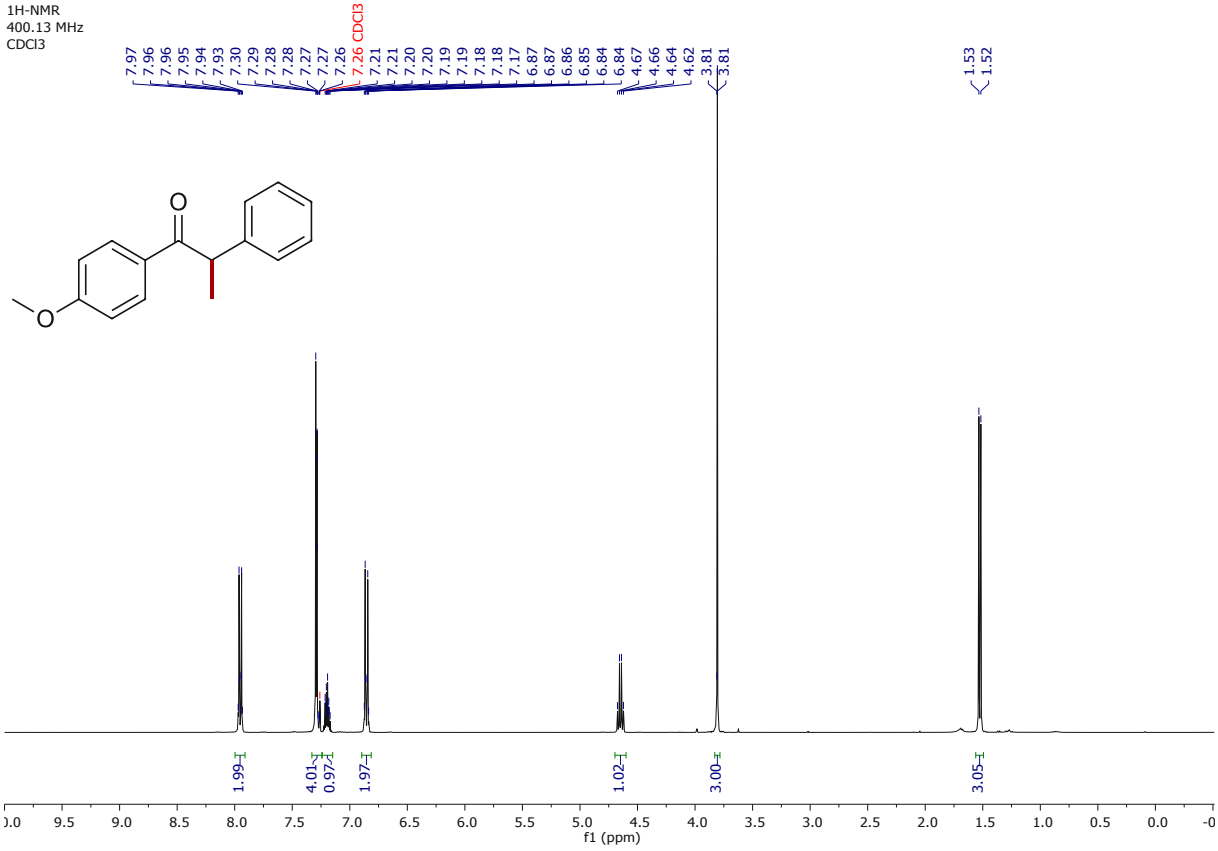

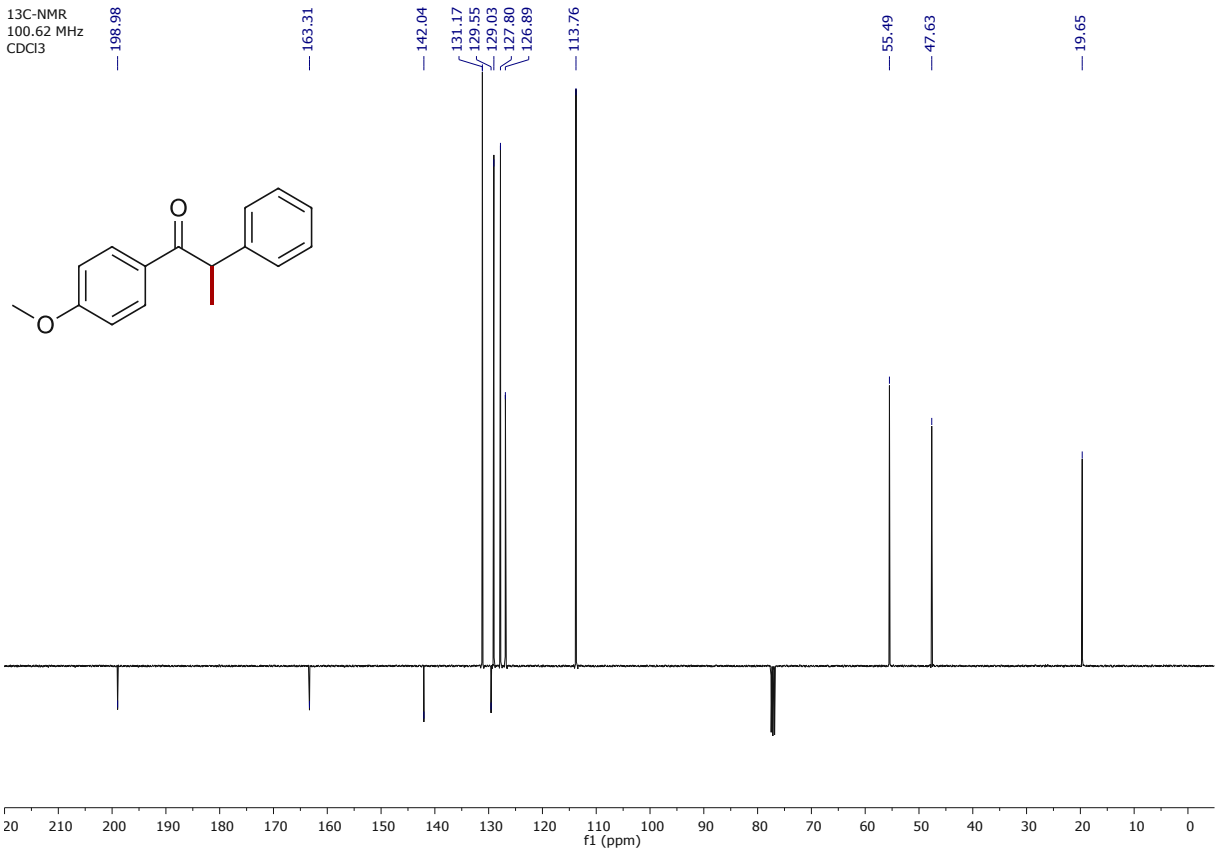

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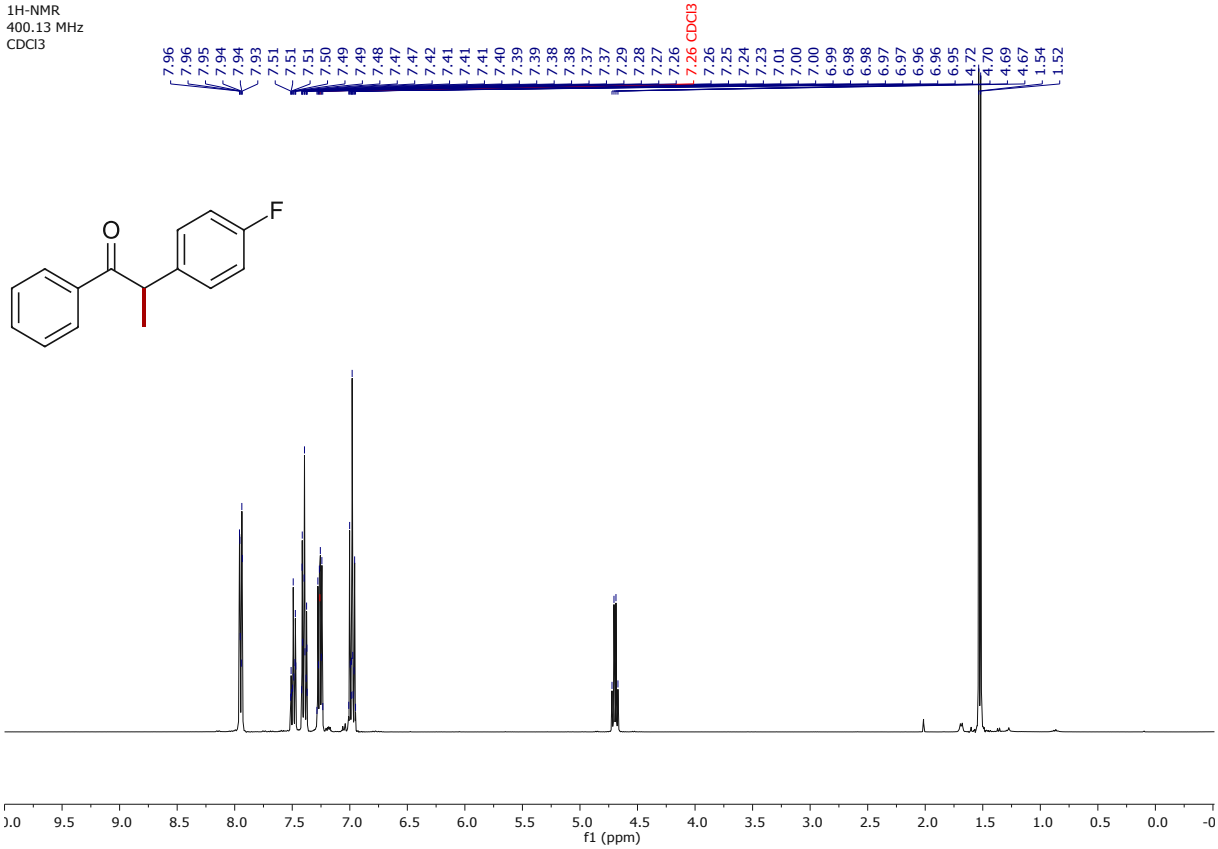

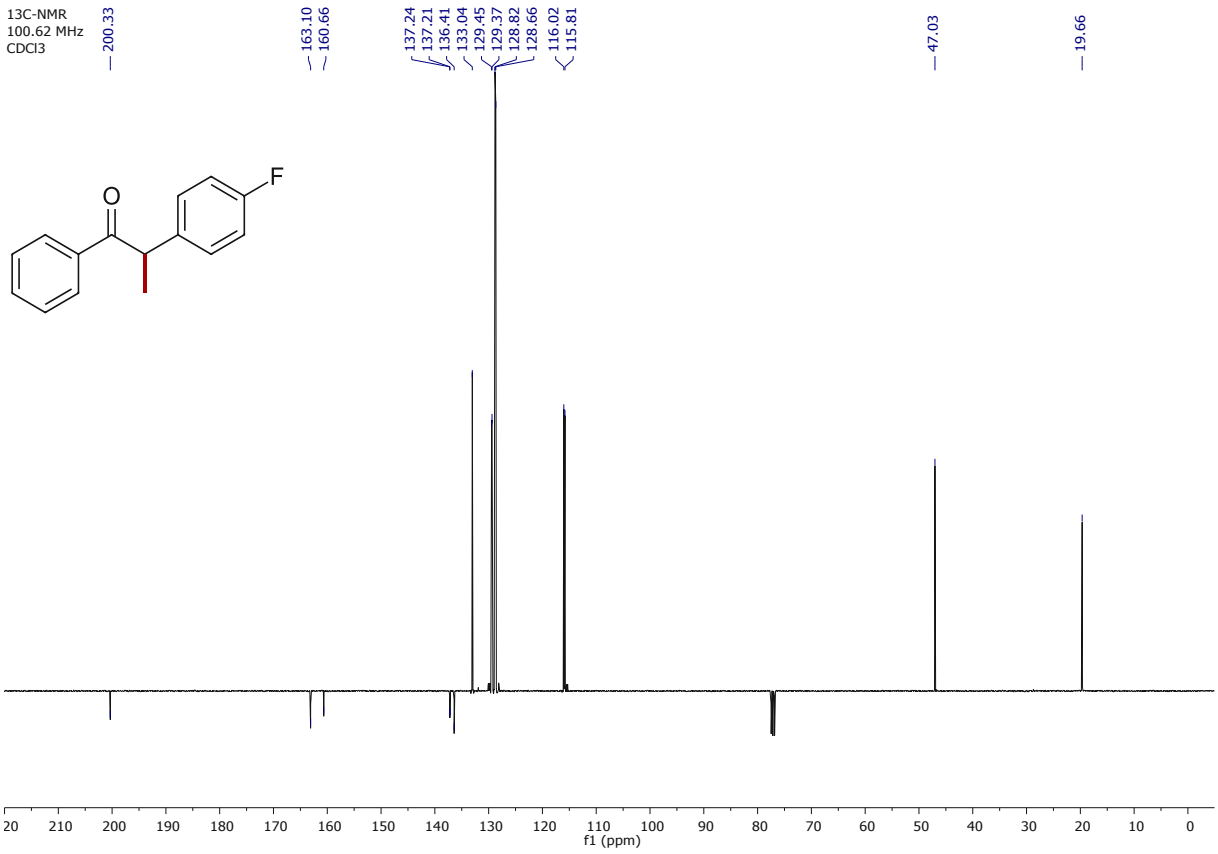

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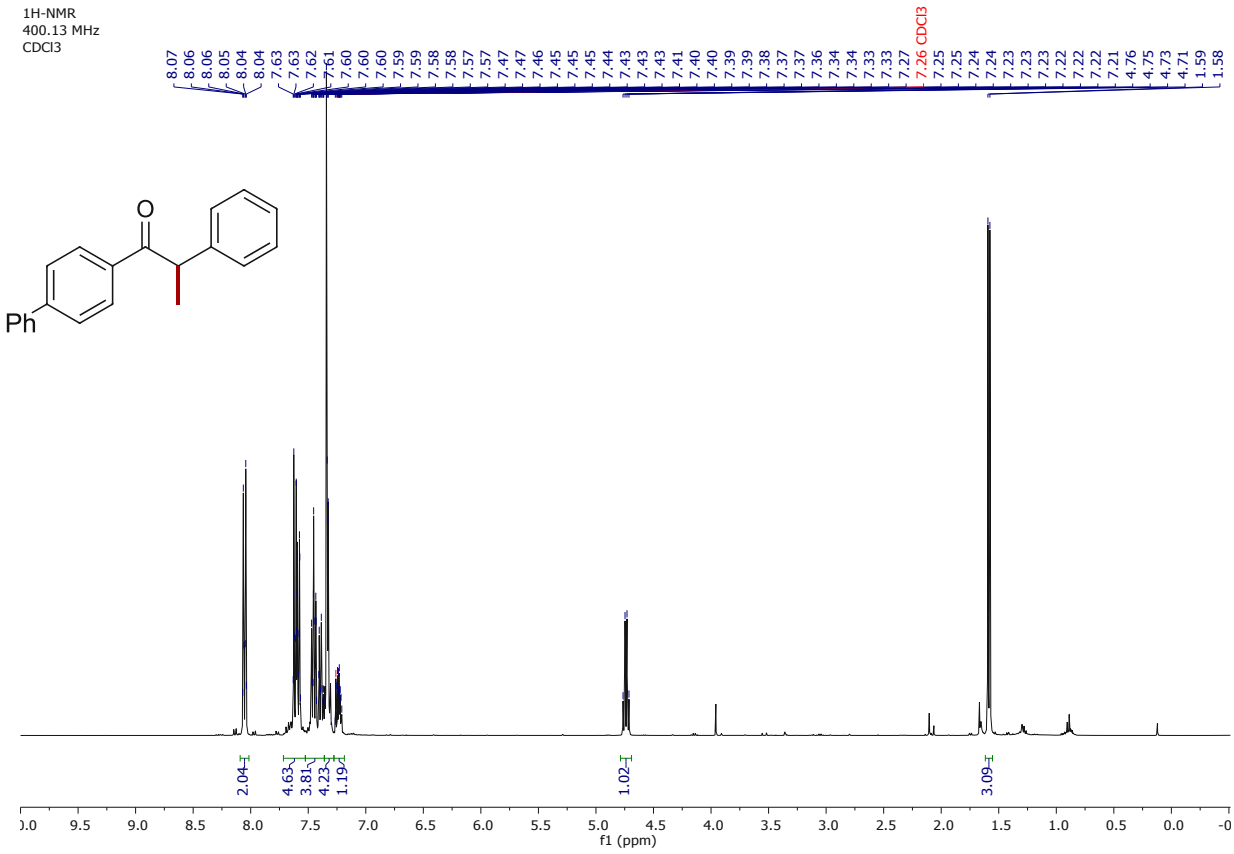

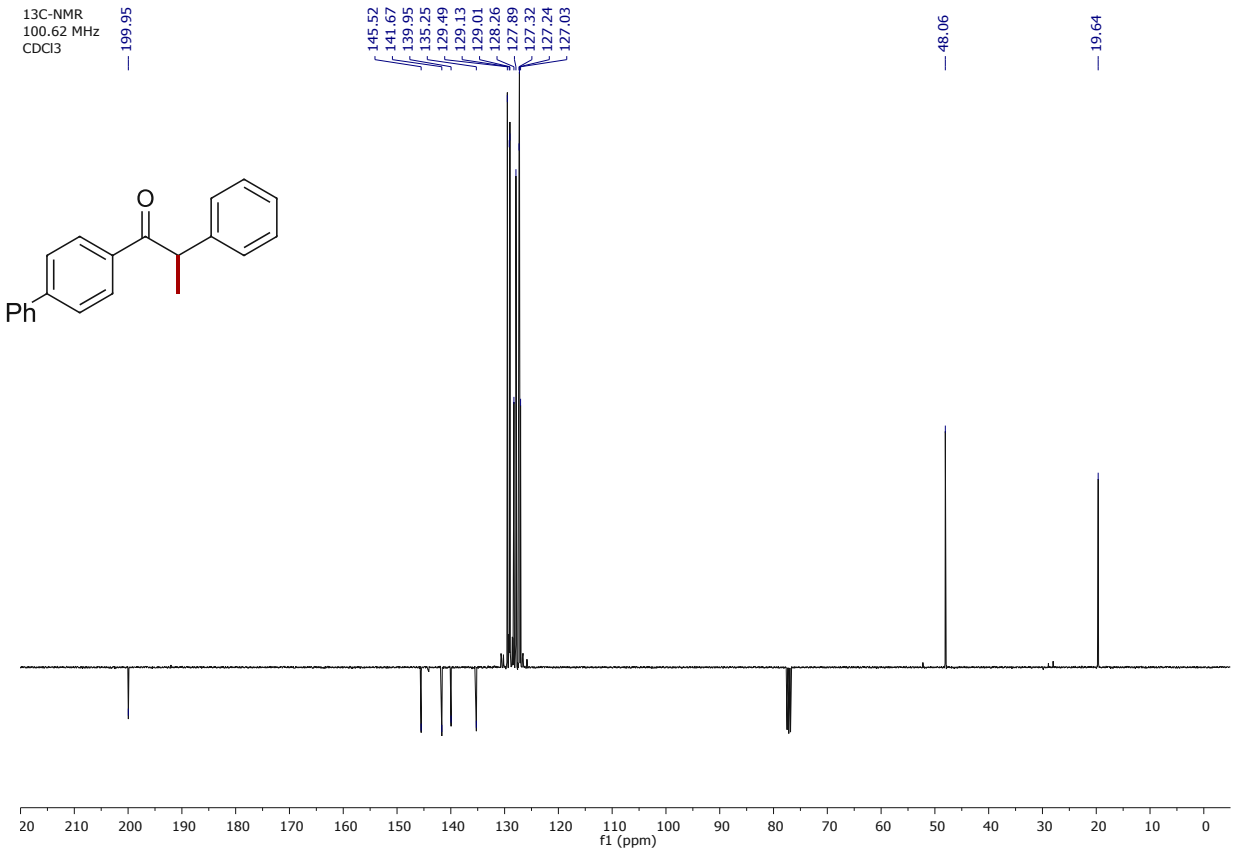

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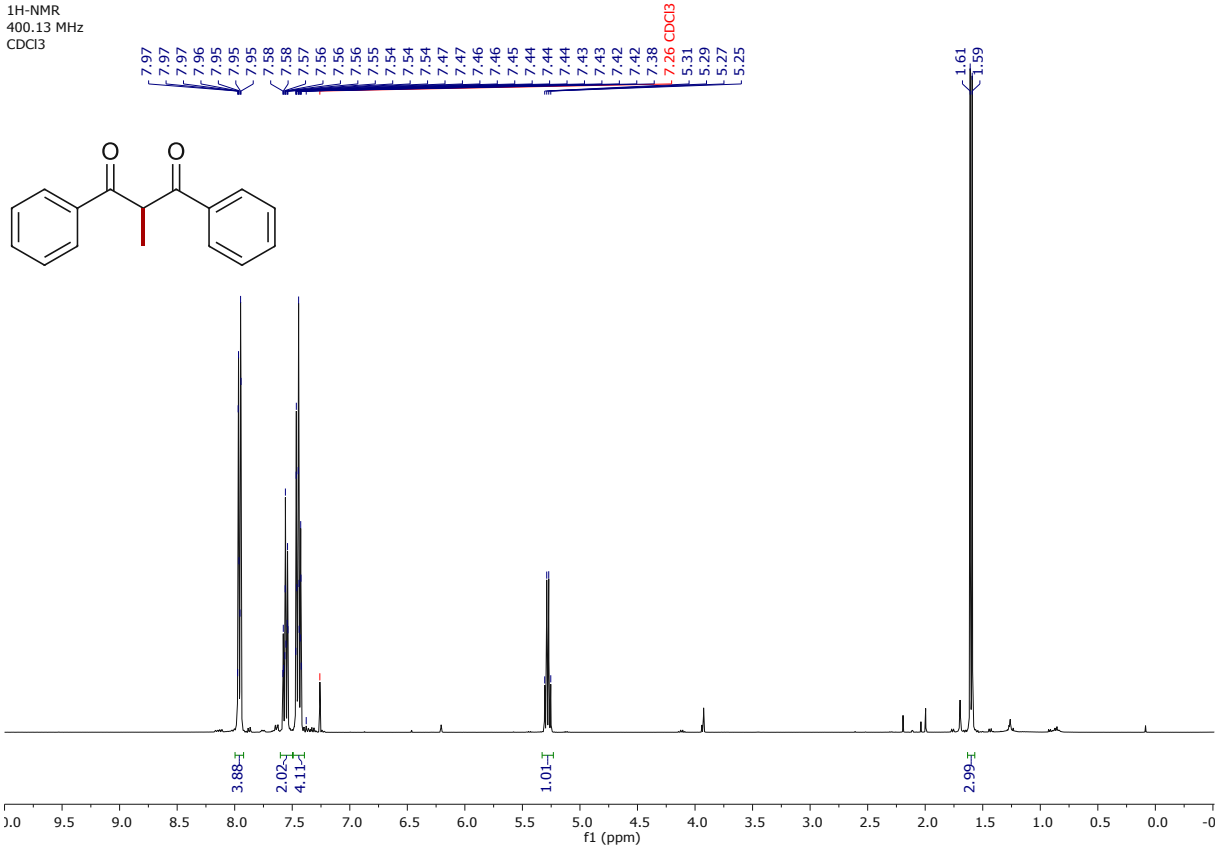
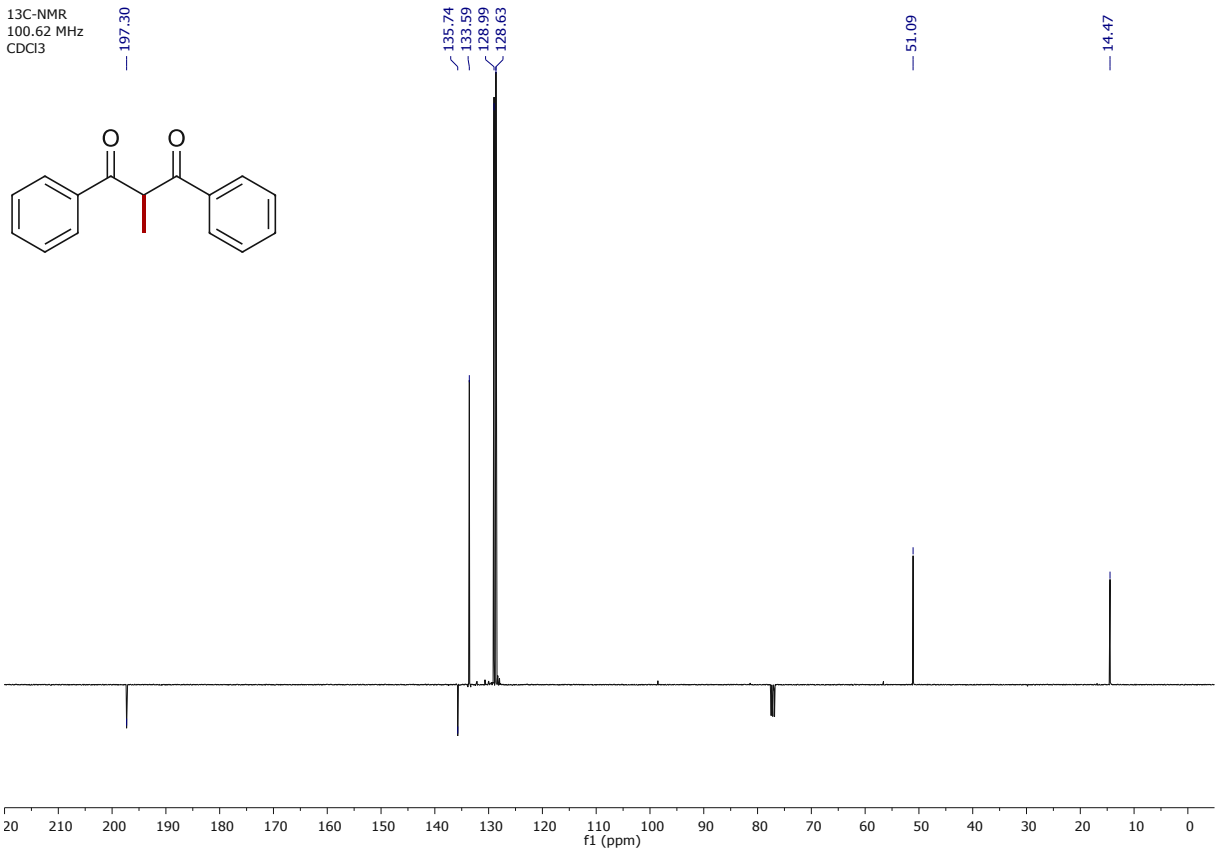
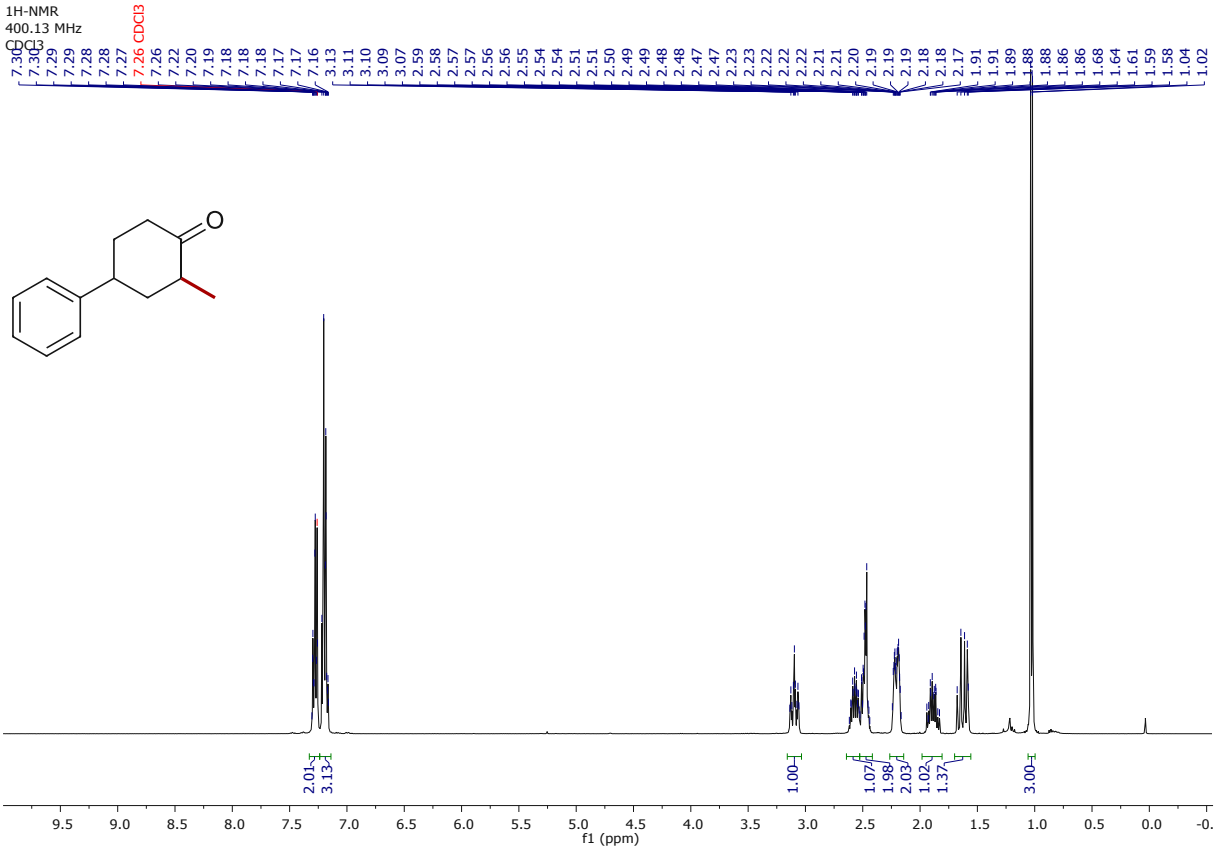
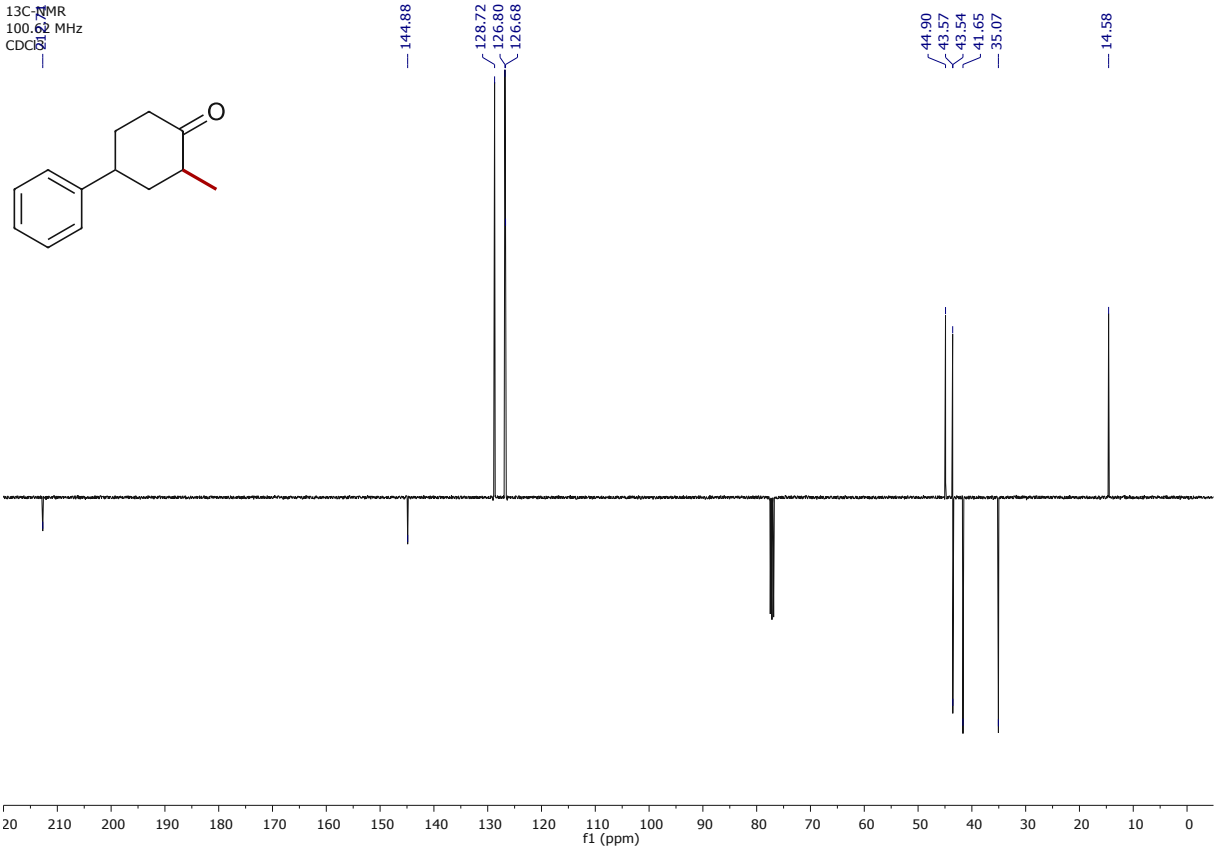


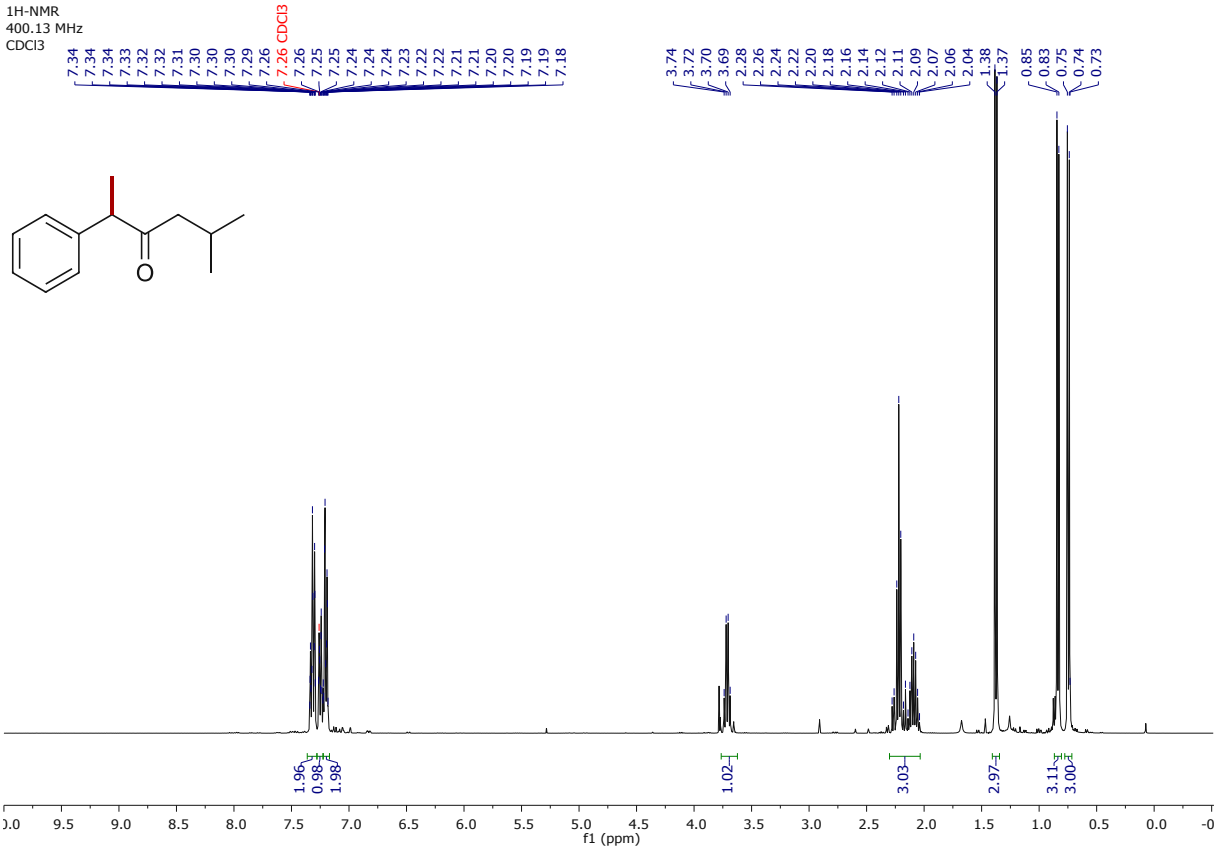


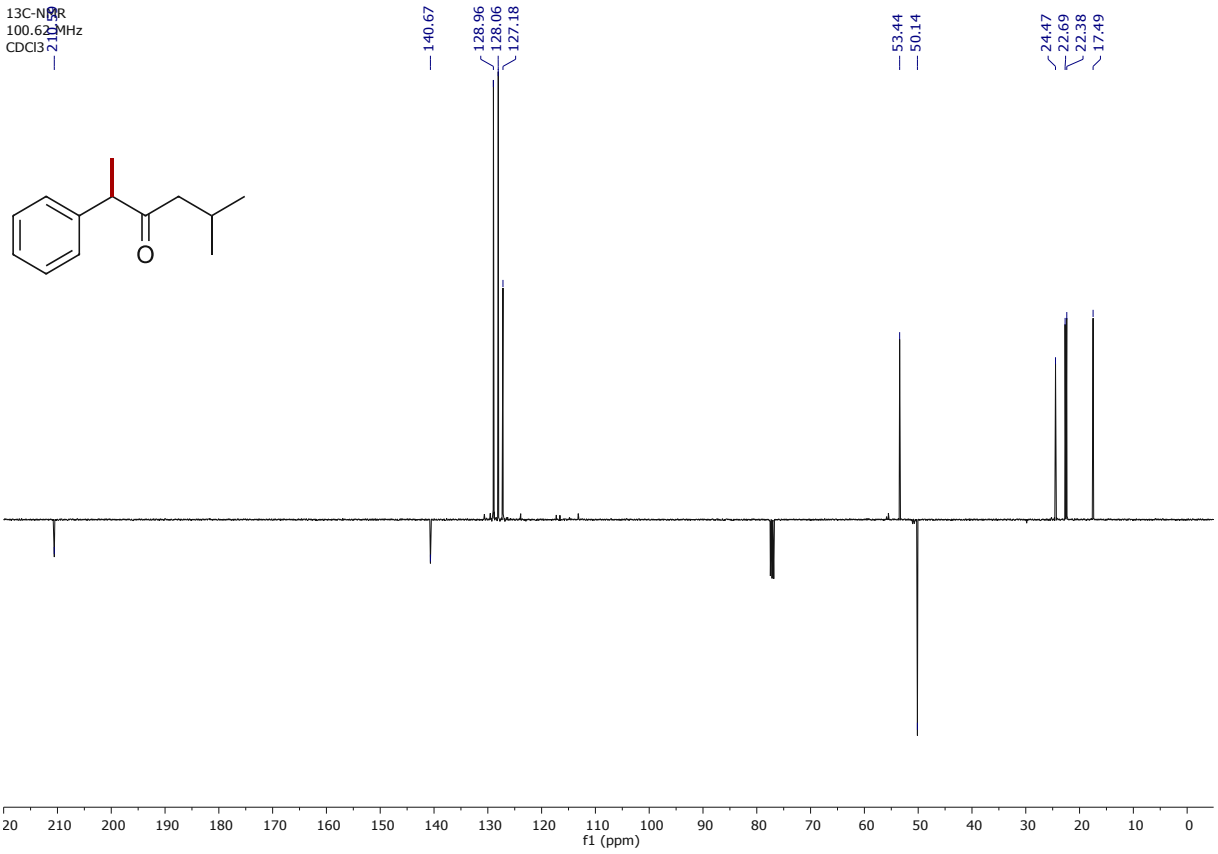
2-Methyl-4-phenylcyclohexanone (3t)



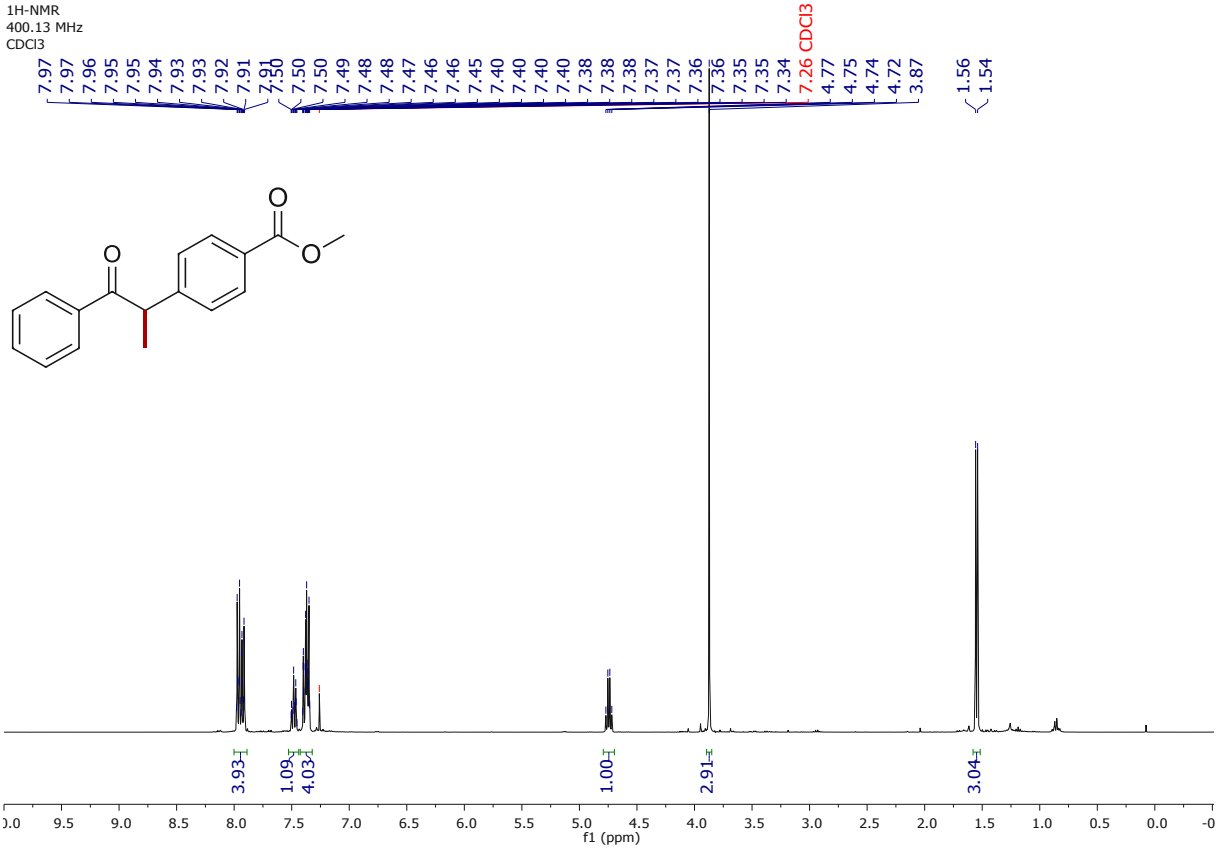


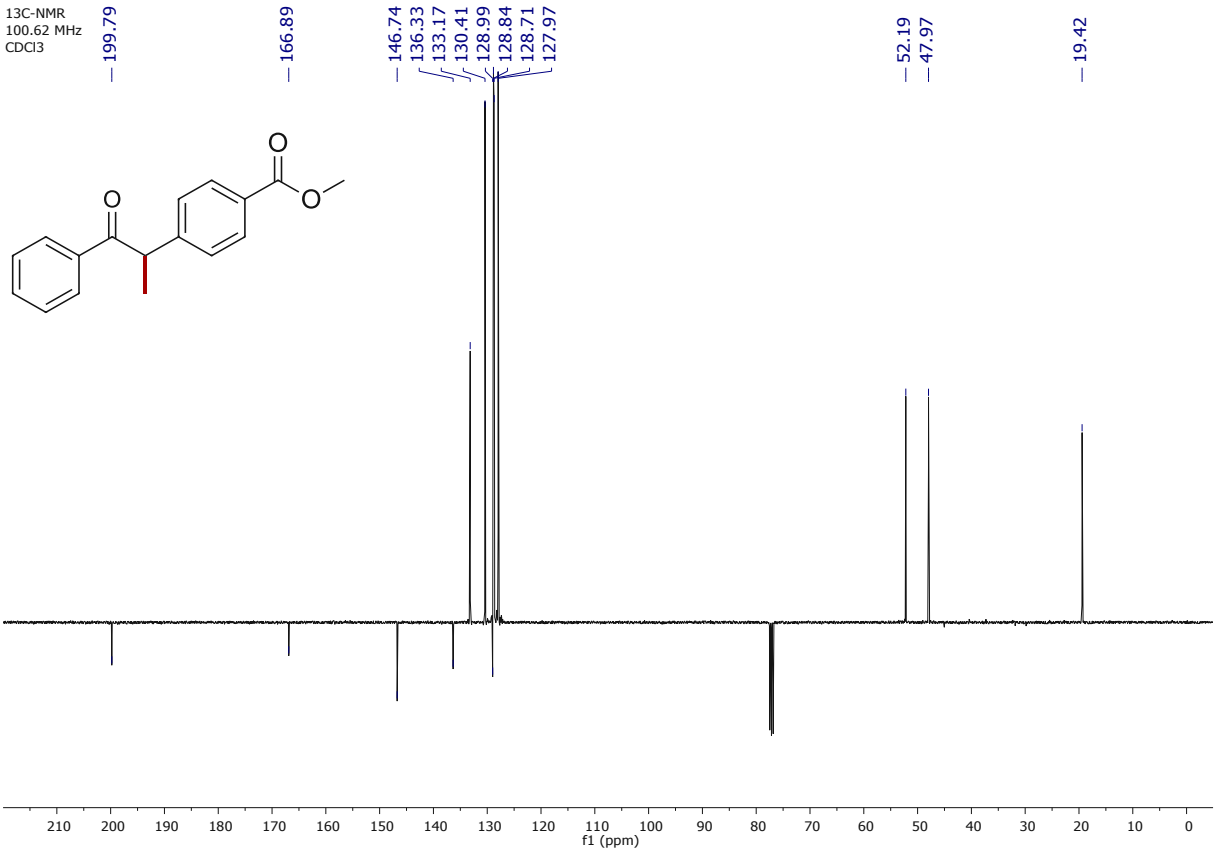
5-Methyl-2-phenyl-3-hexanone (3u)



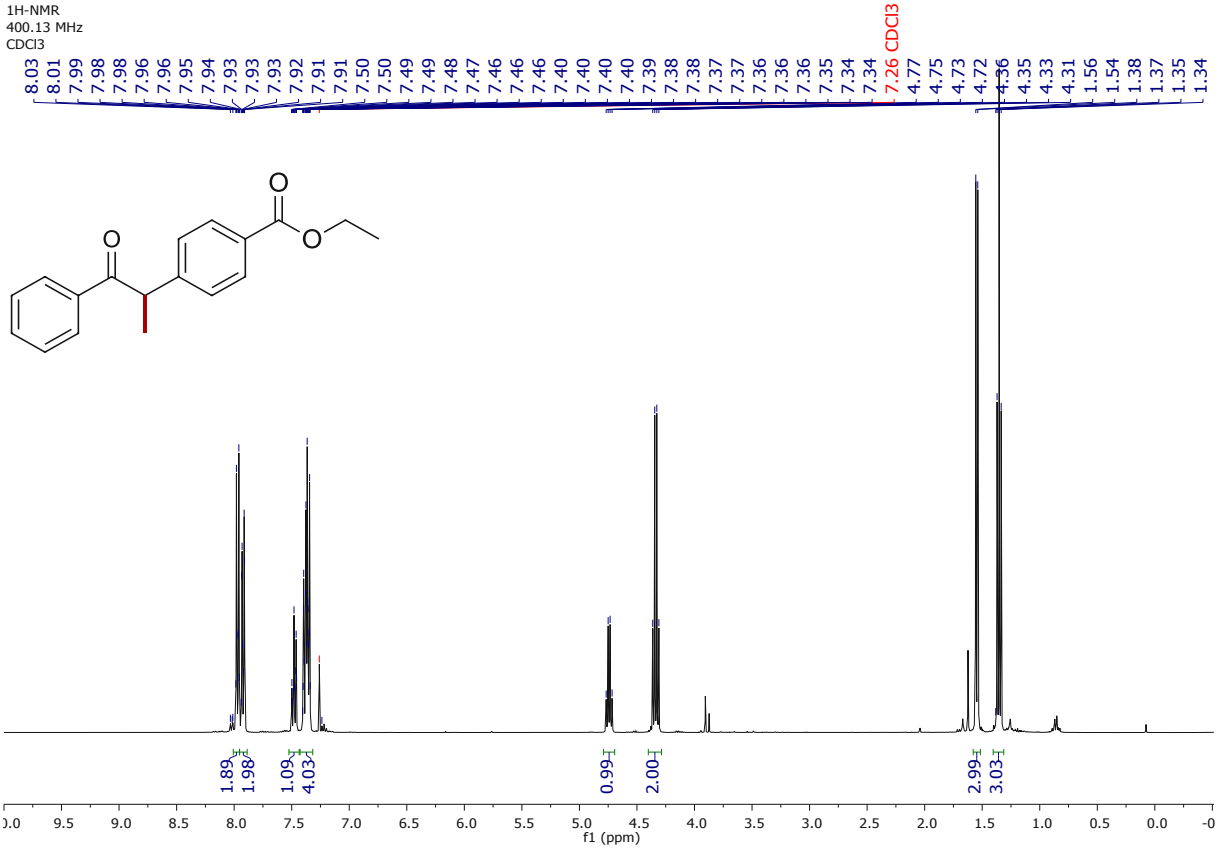


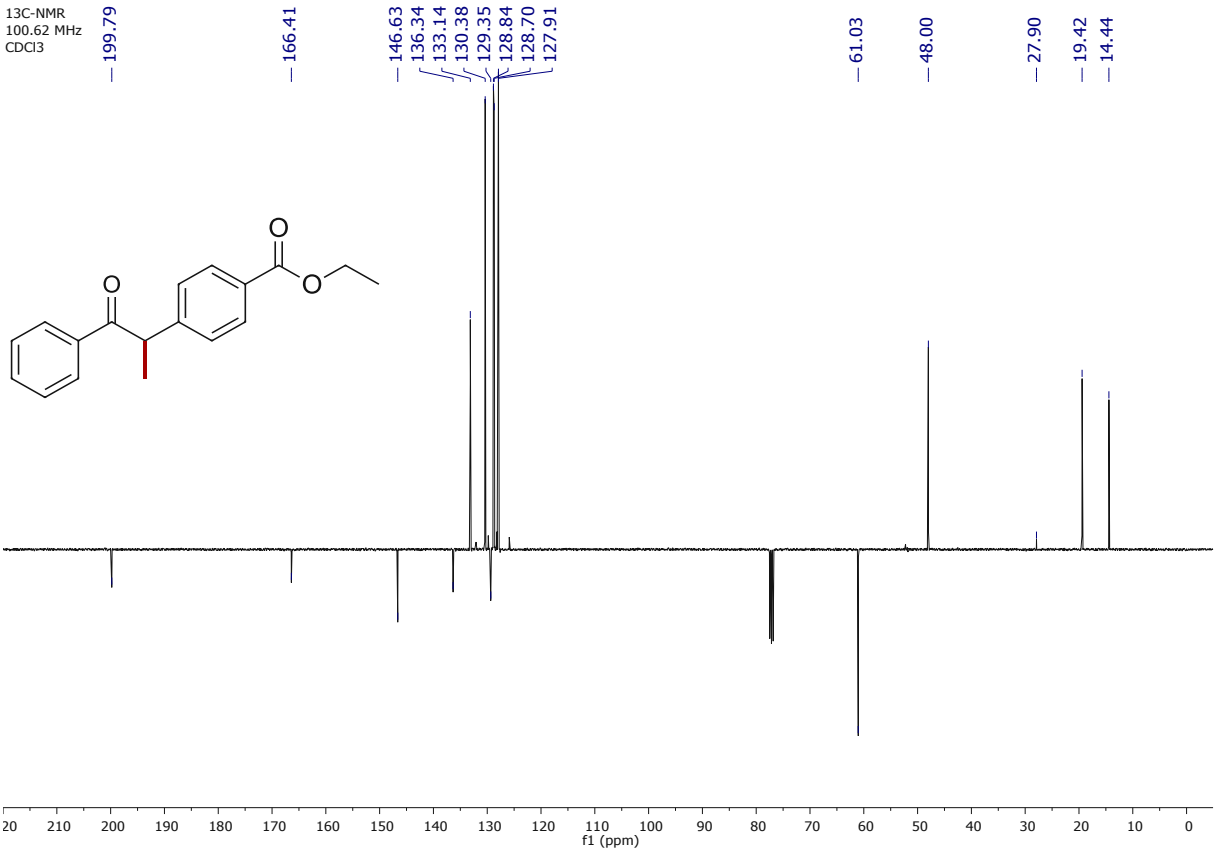
Methyl 4-(1-methyl-2-oxo-2-phenylethyl)benzoate (3v)



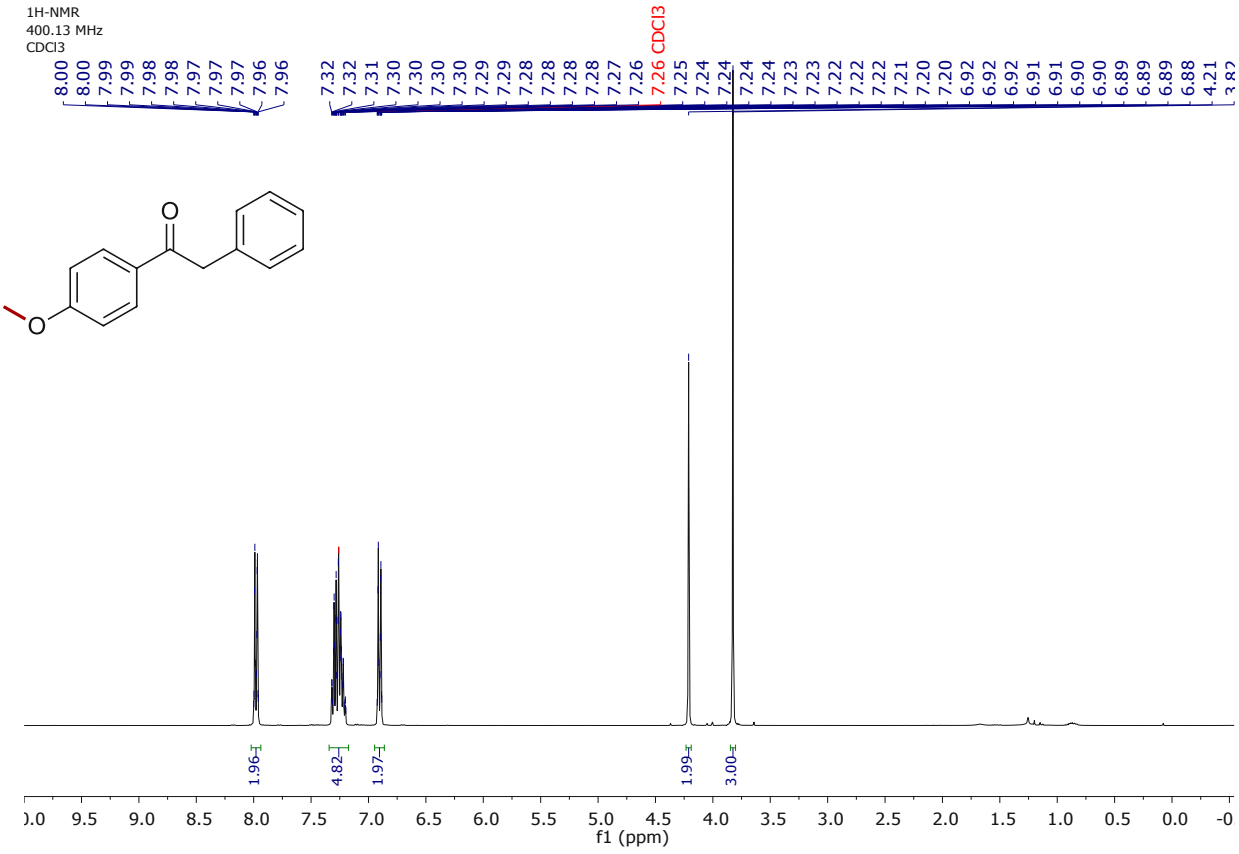


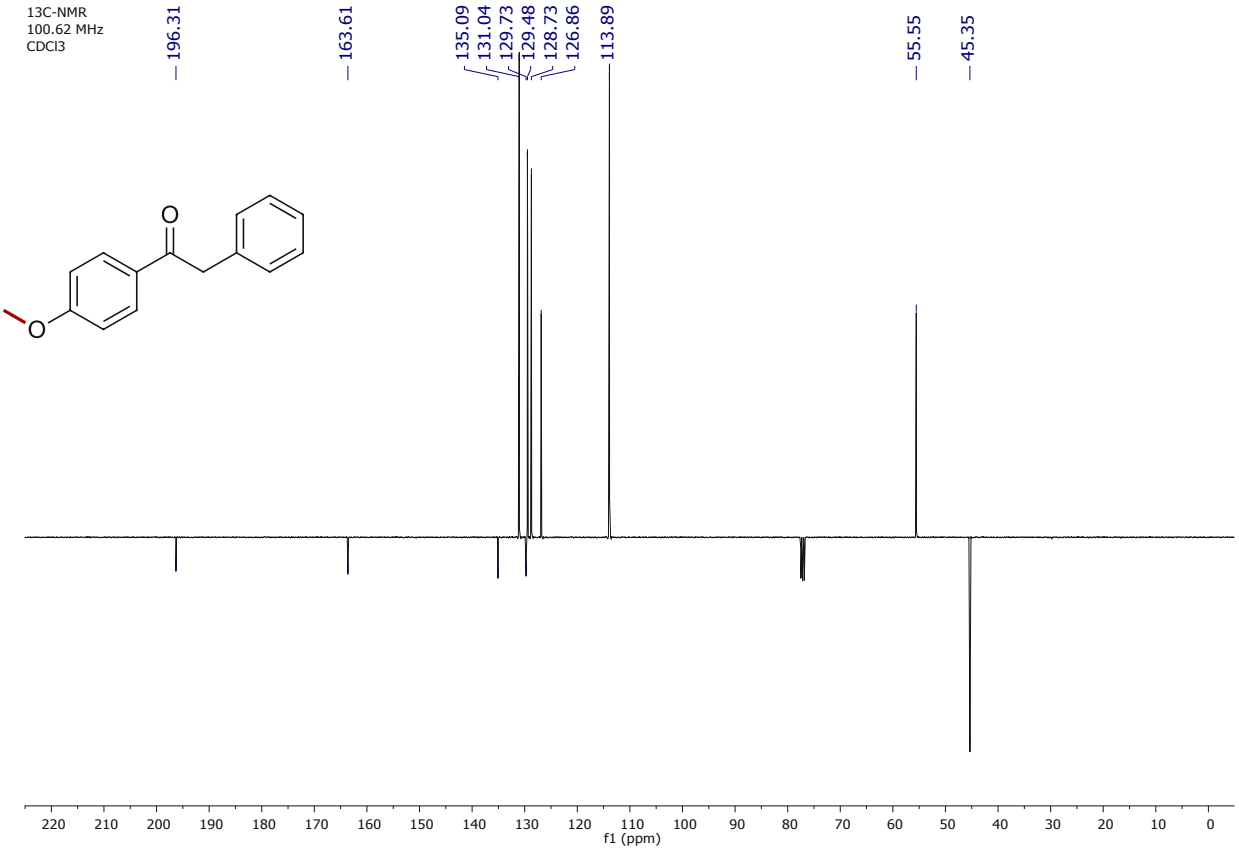
Ethyl 4-(1-methyl-2-oxo-2-phenylethyl)benzoate (3w)



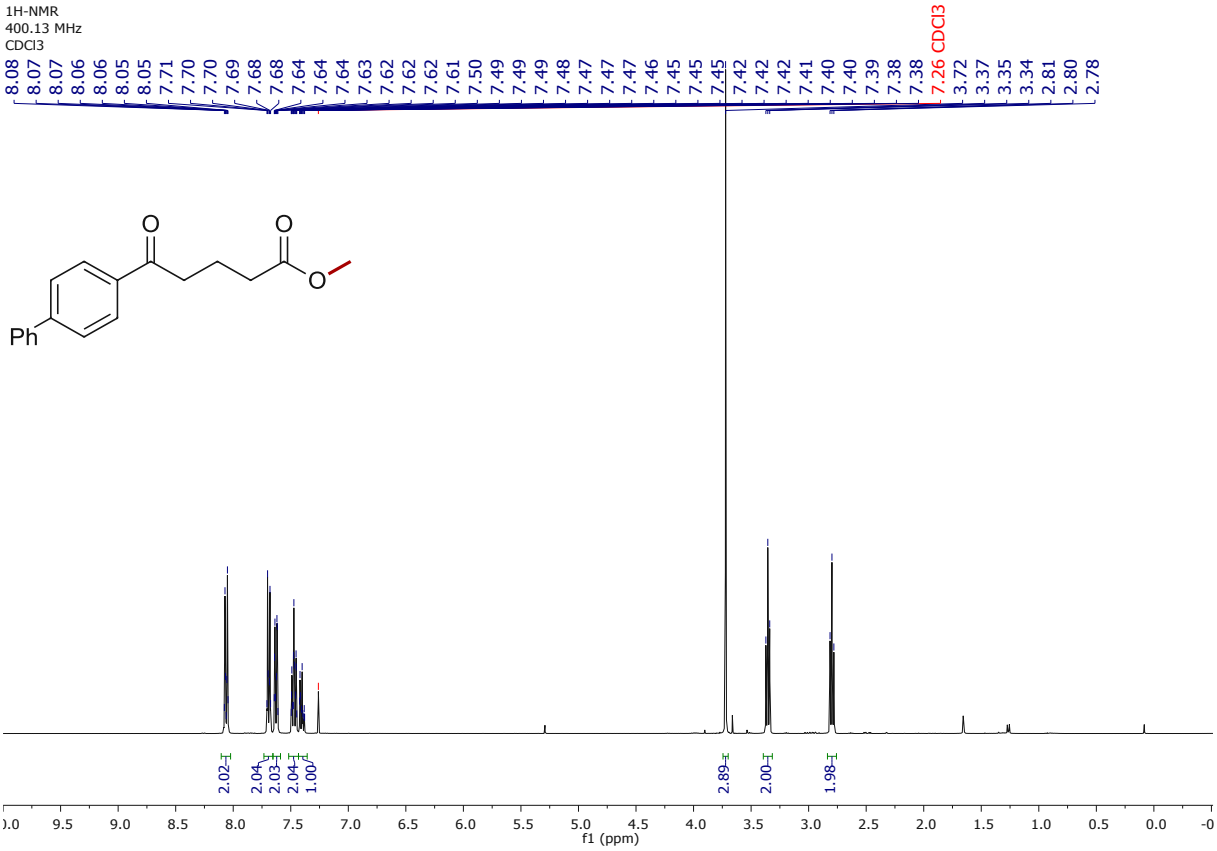


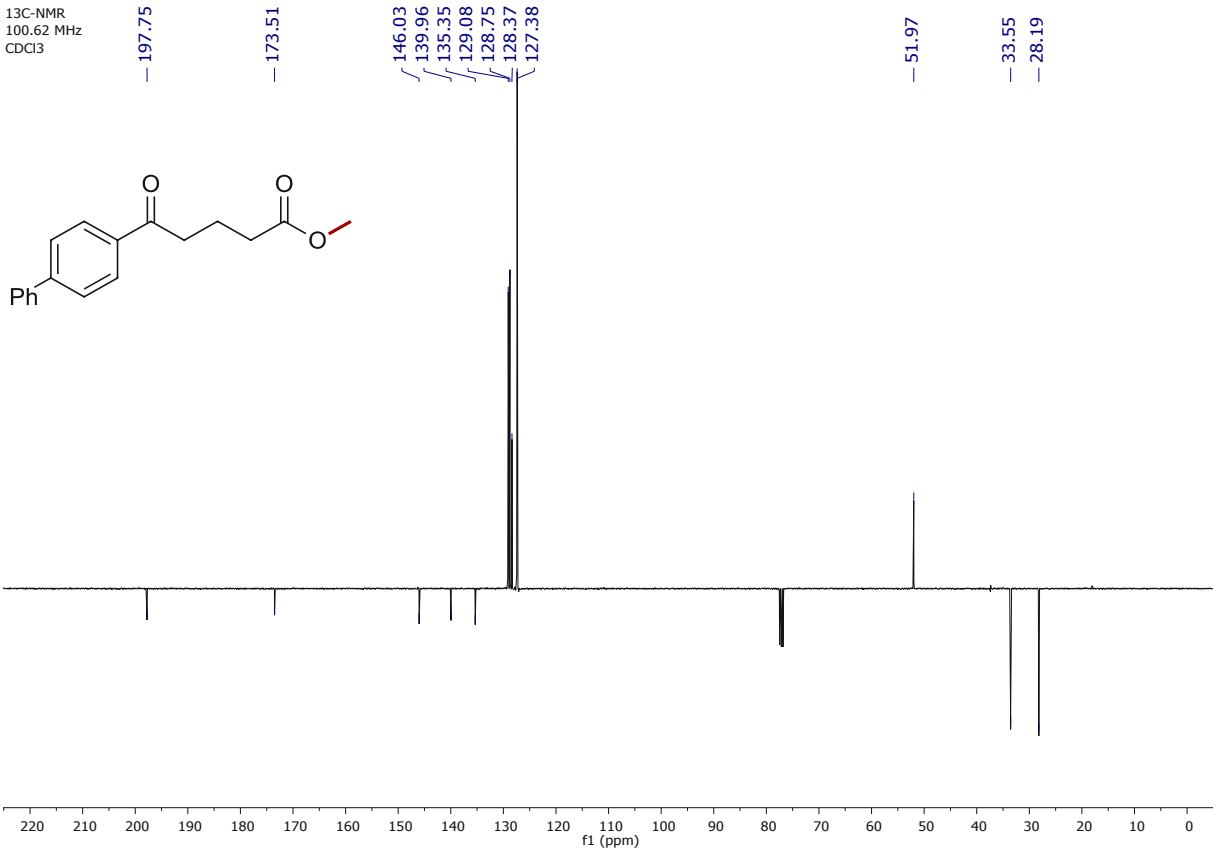
1-(4-Methoxyphenyl)-2-phenylethanone (3x)



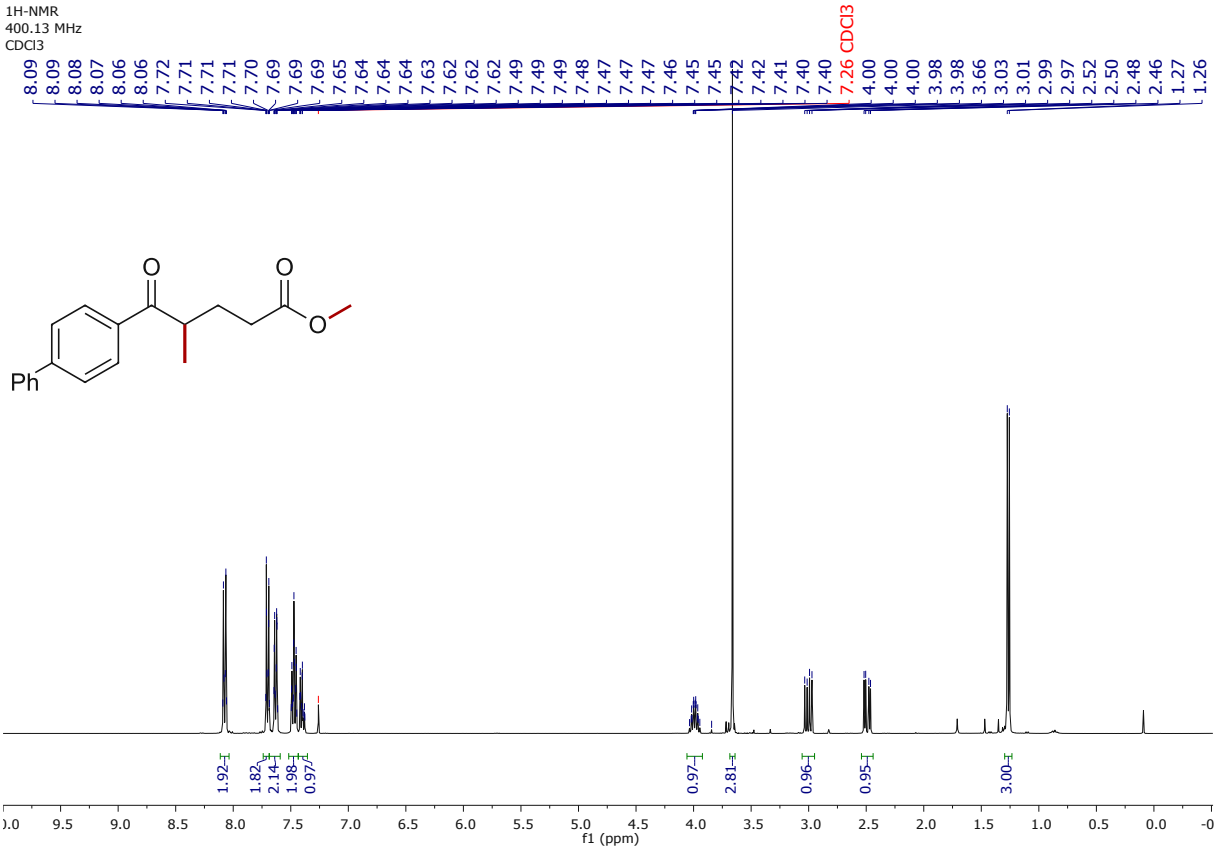


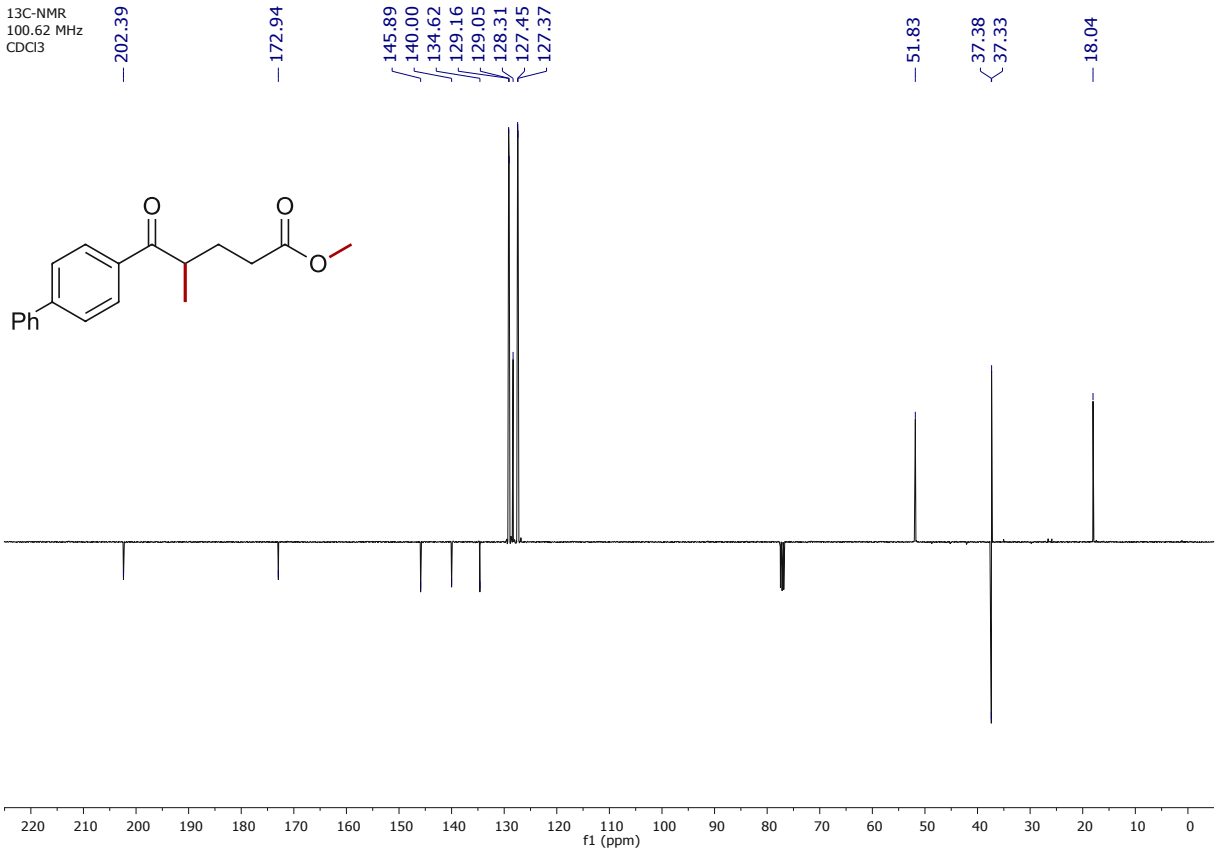
Methyl 4-(biphenyl-4-yl)-4-oxobutanoate (3y)



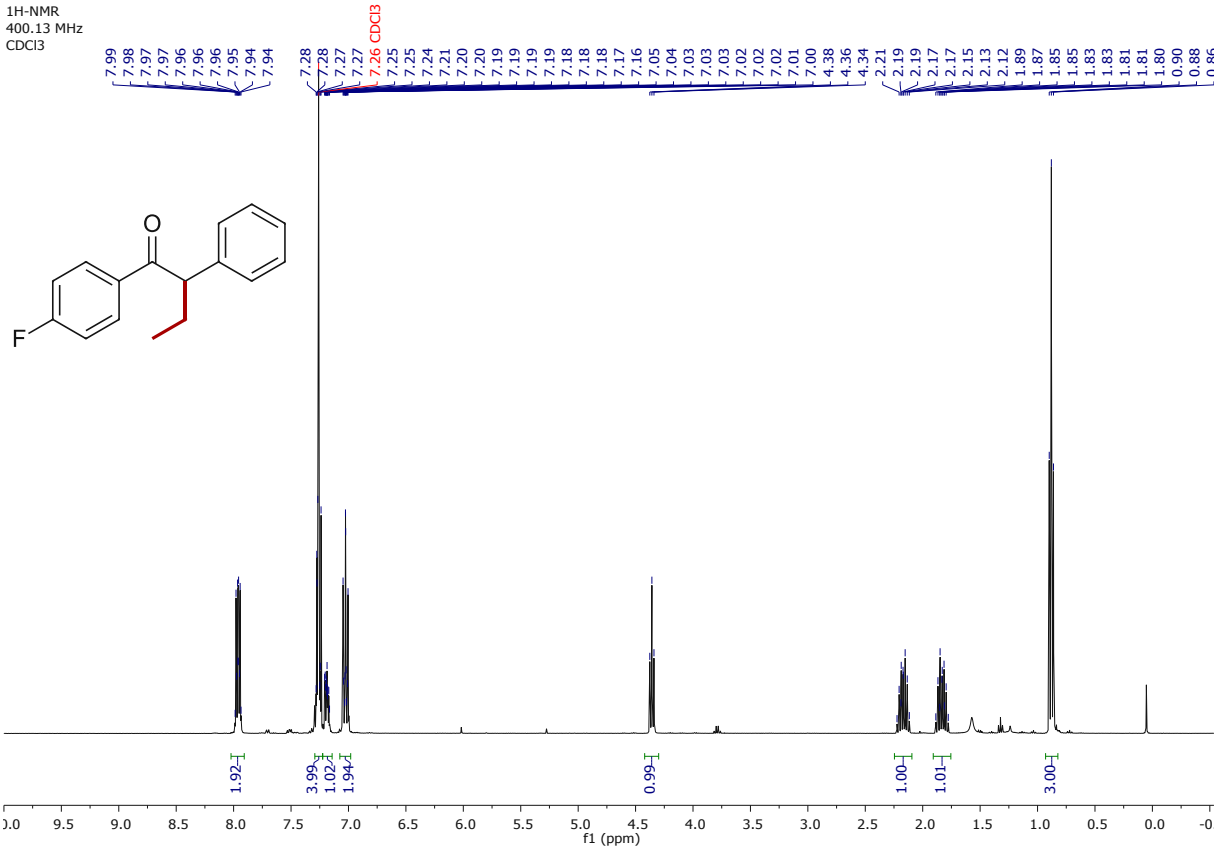


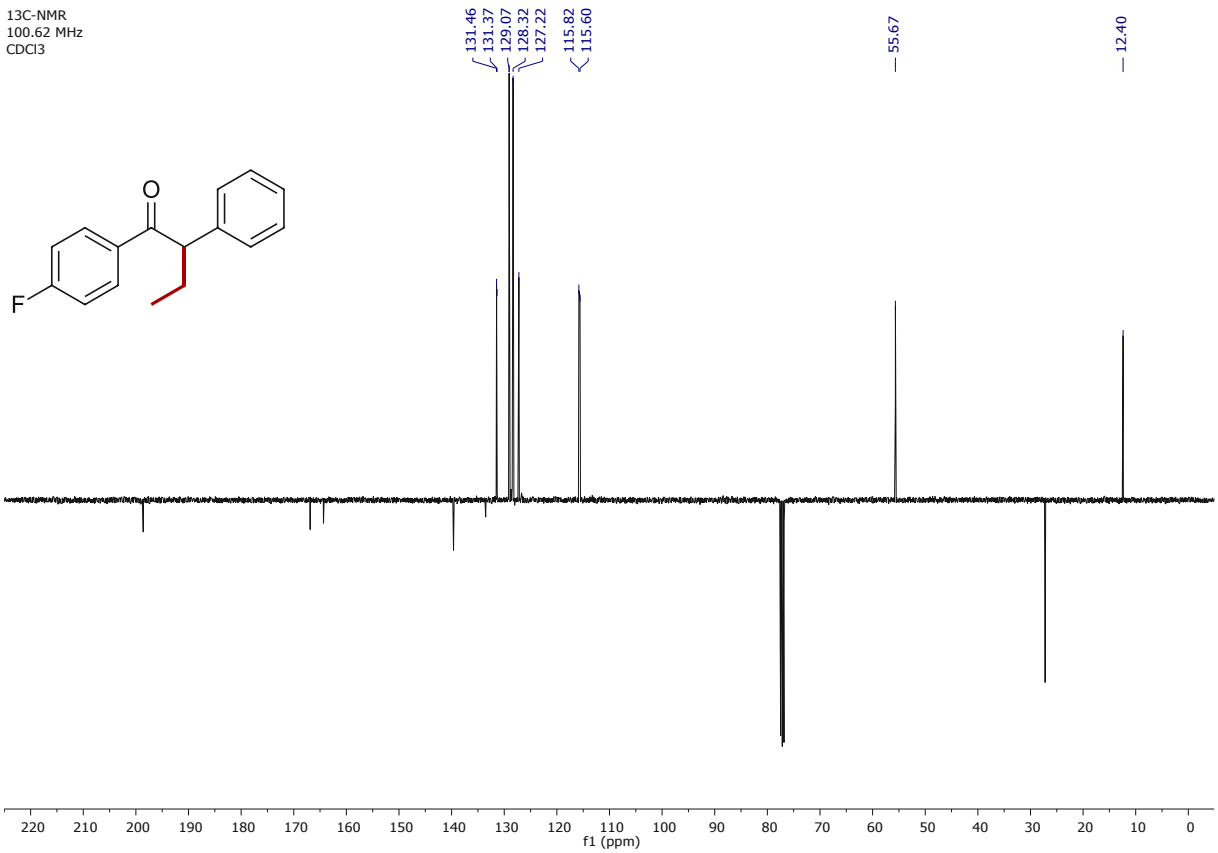
Methyl 3-methyl-4-oxo-4-(4-phenylphenyl)butanoate (3z)



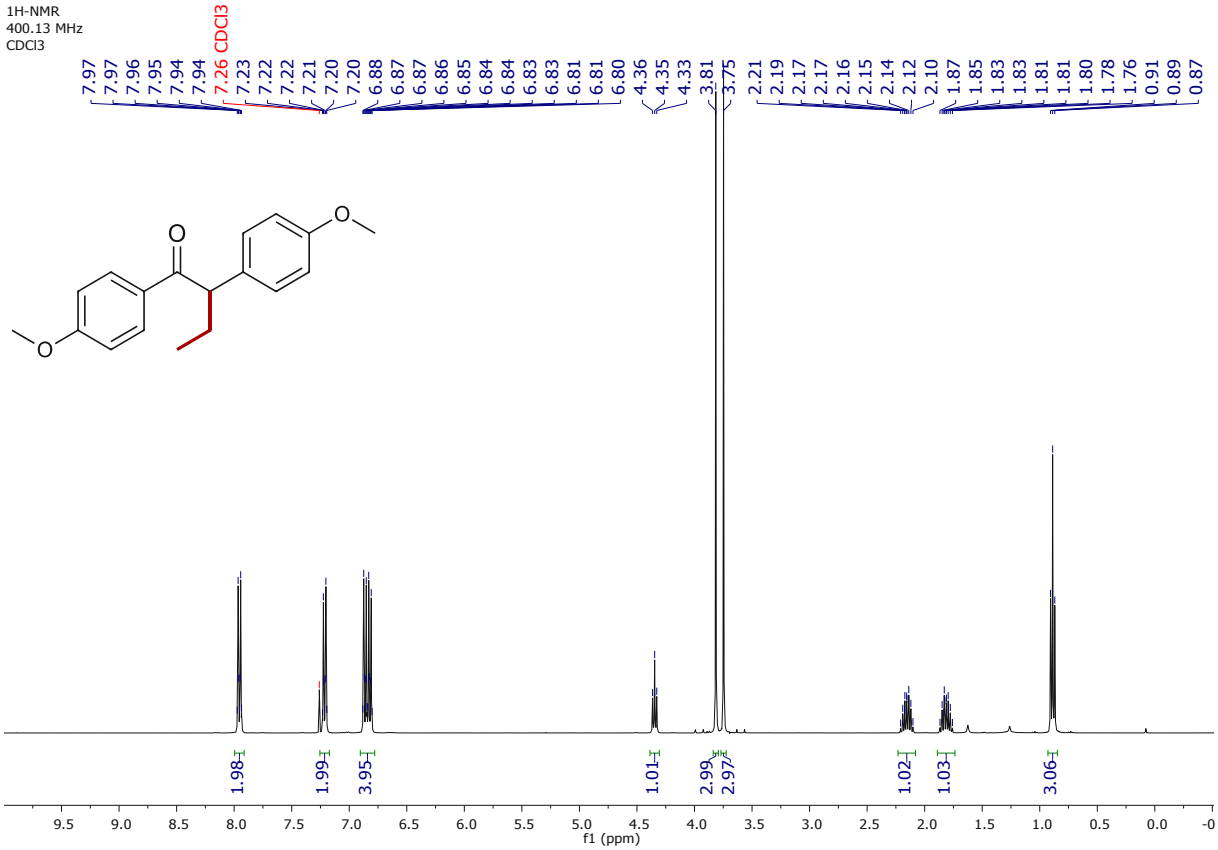


1-(4-Fluorophenyl)-2-phenyl-1-butanone (4a)

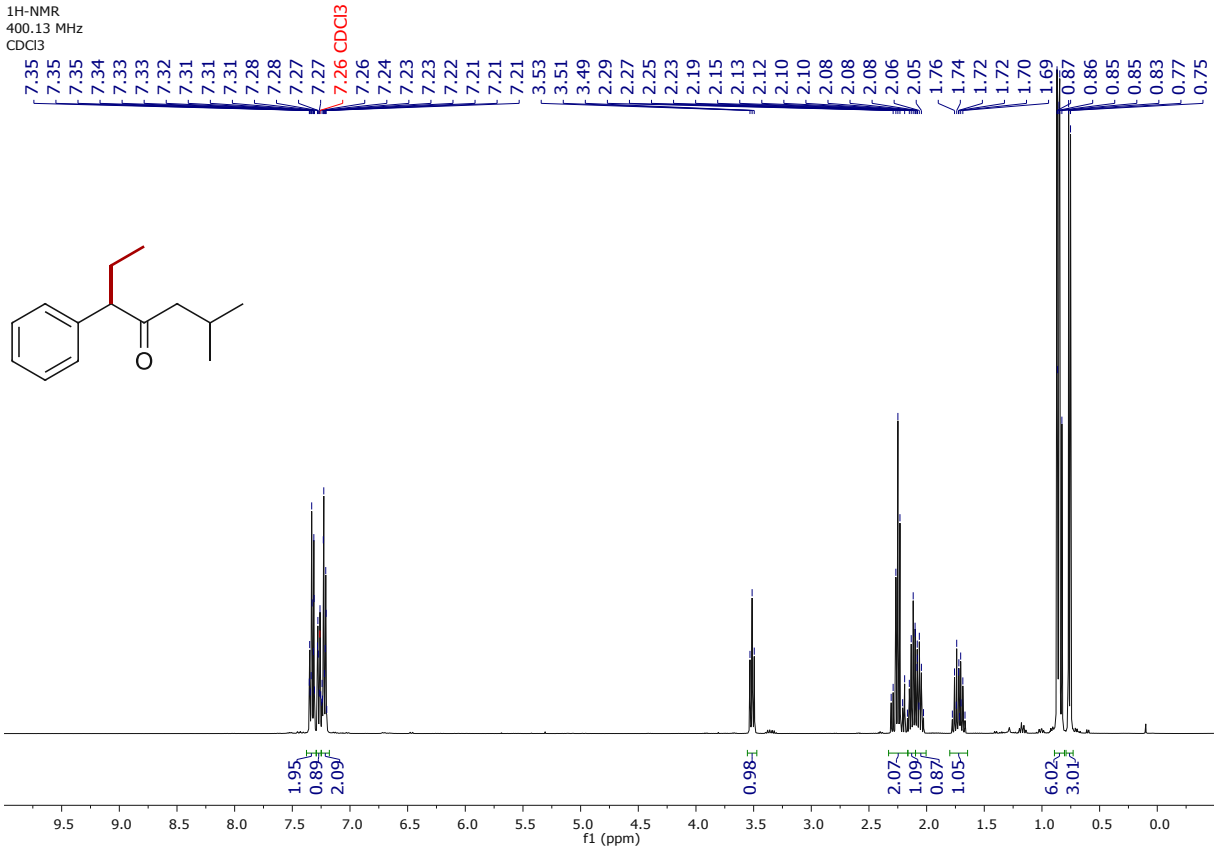


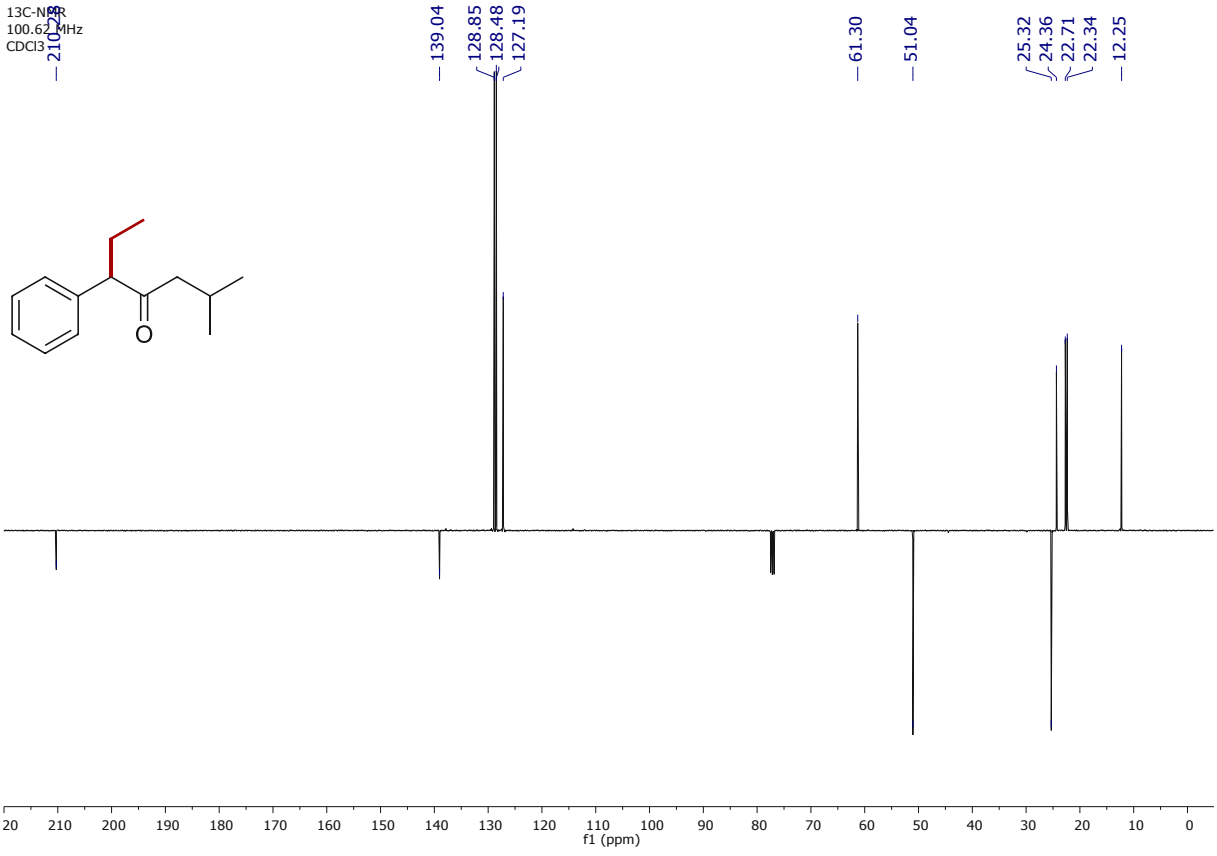


1,2-Bis(4-methoxyphenyl)-1-butanone (4b)

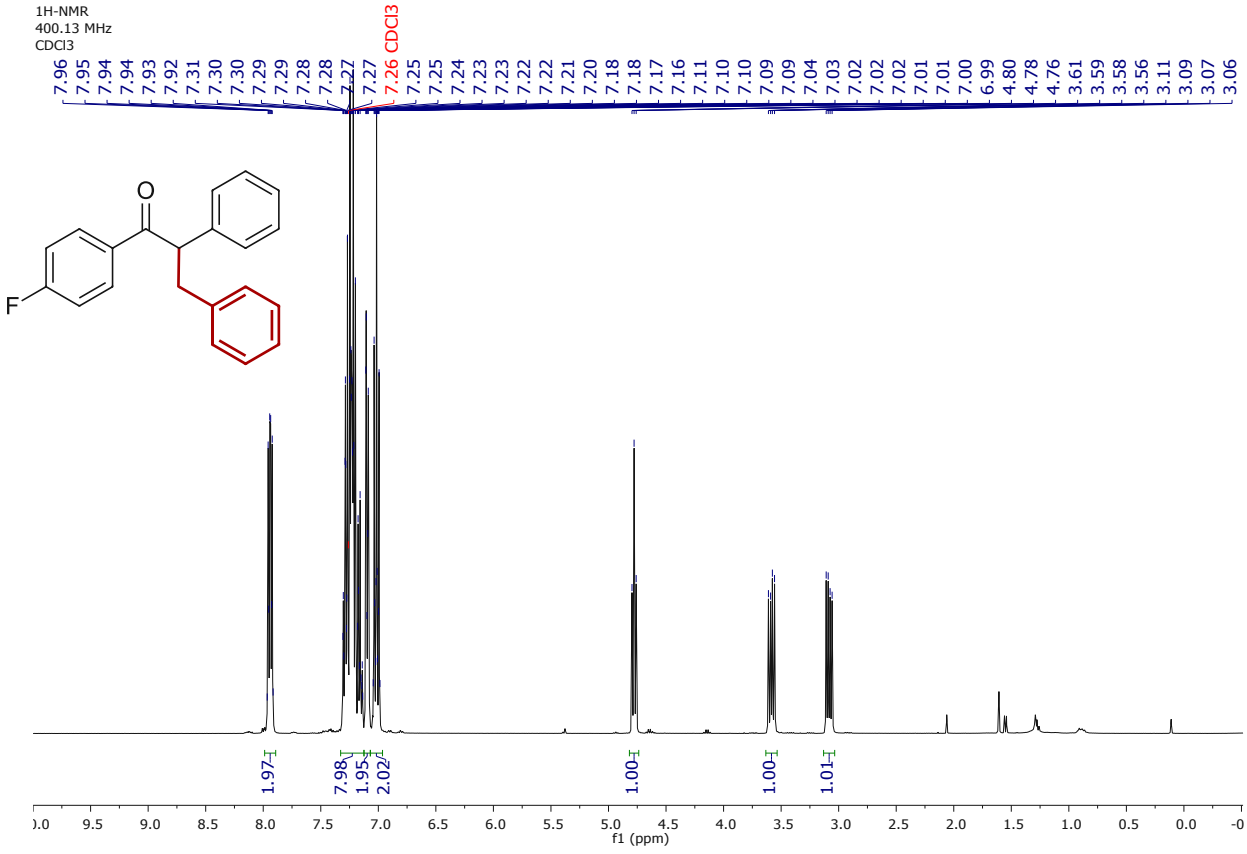


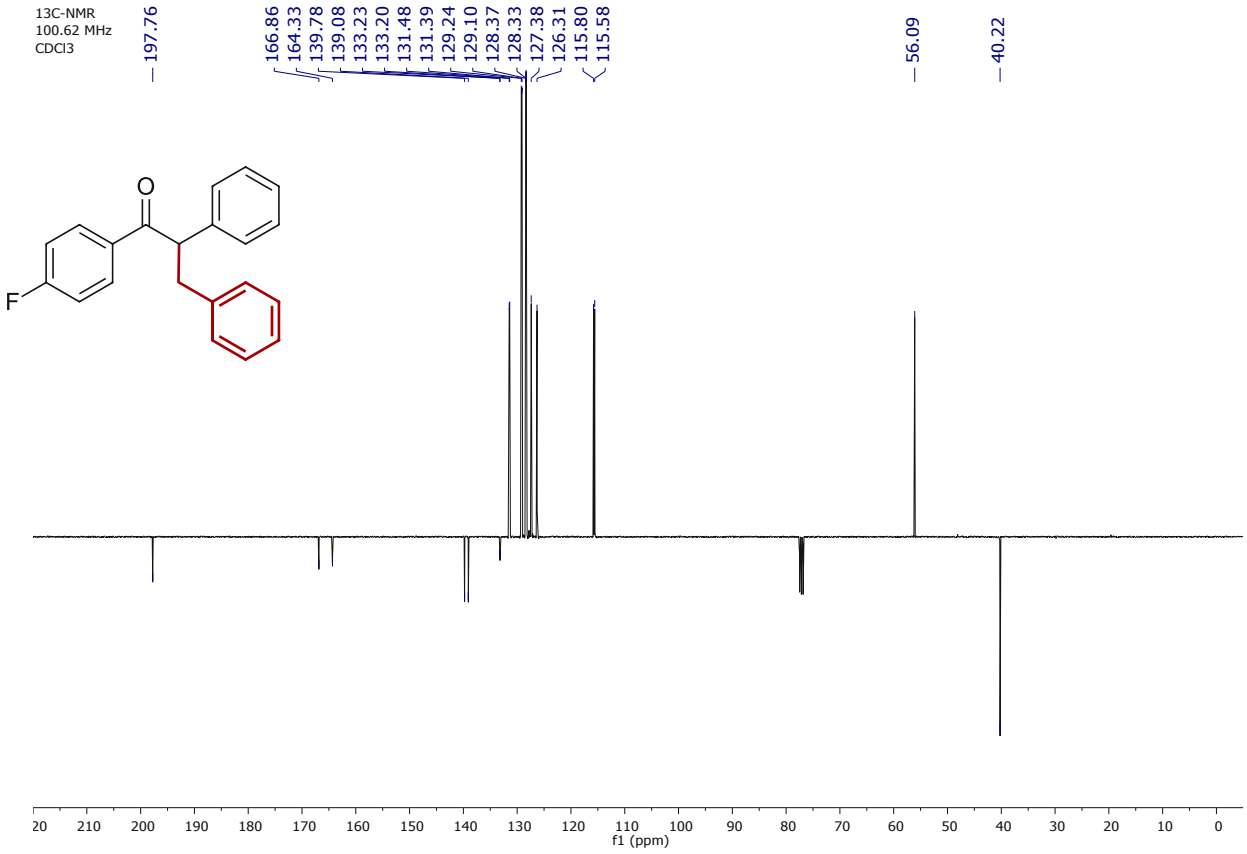
2-Methyl-5-phenyl-4-heptanone (4c)



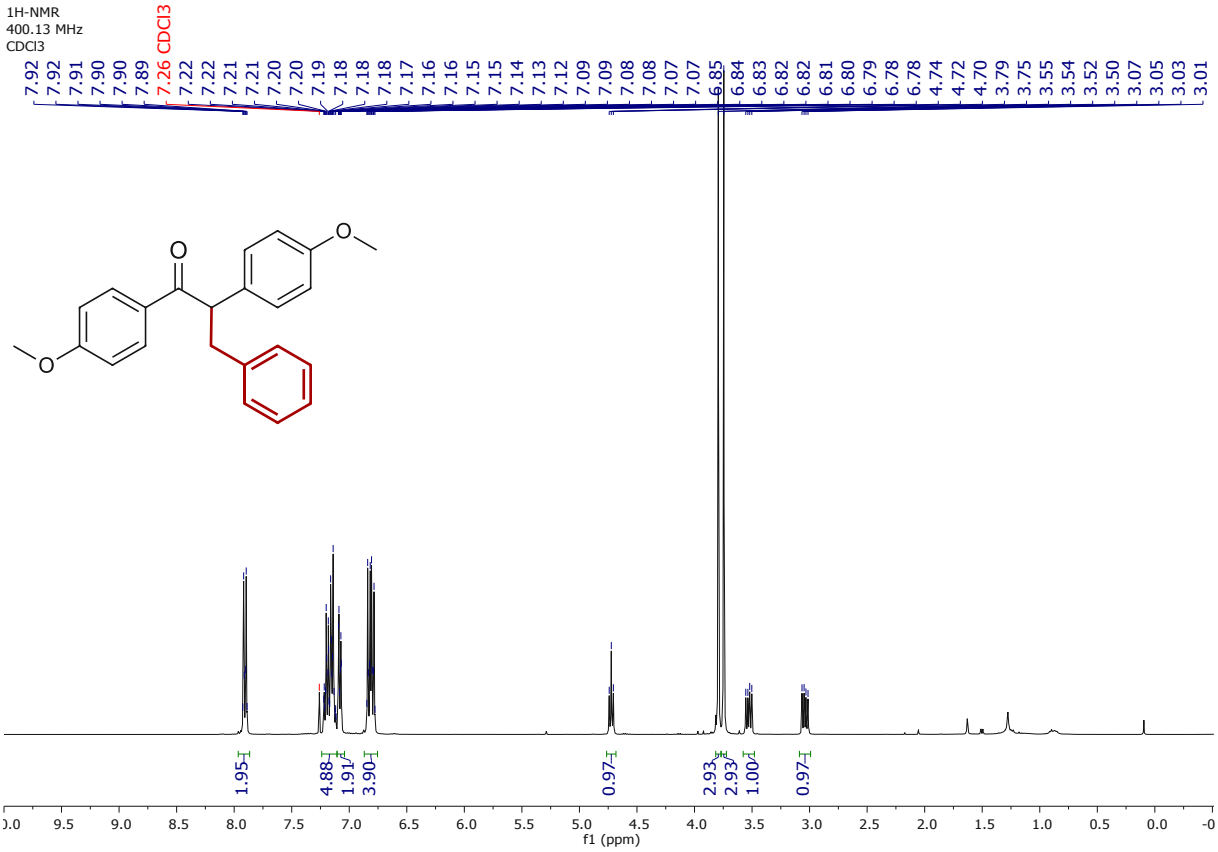


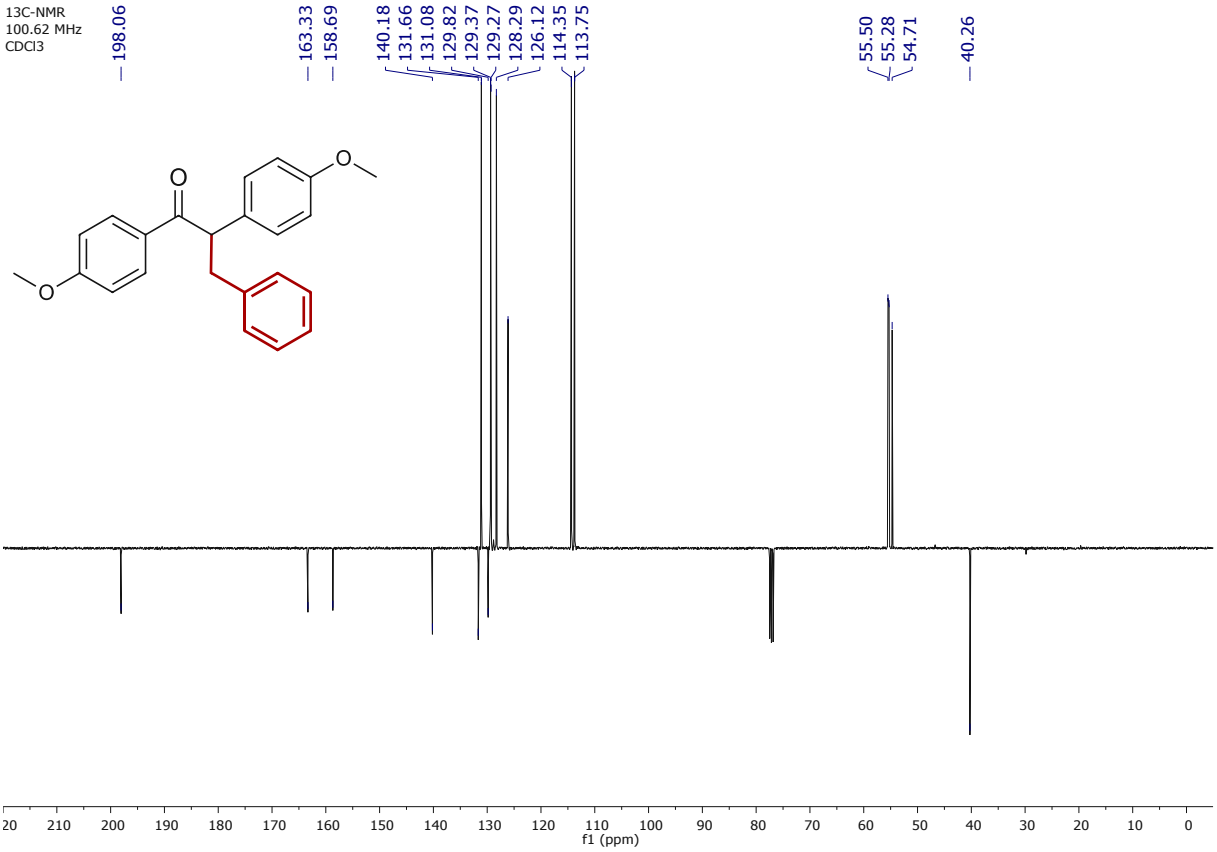
1-(4-Fluorophenyl)-2,3-diphenylpropan-1-one (5a)



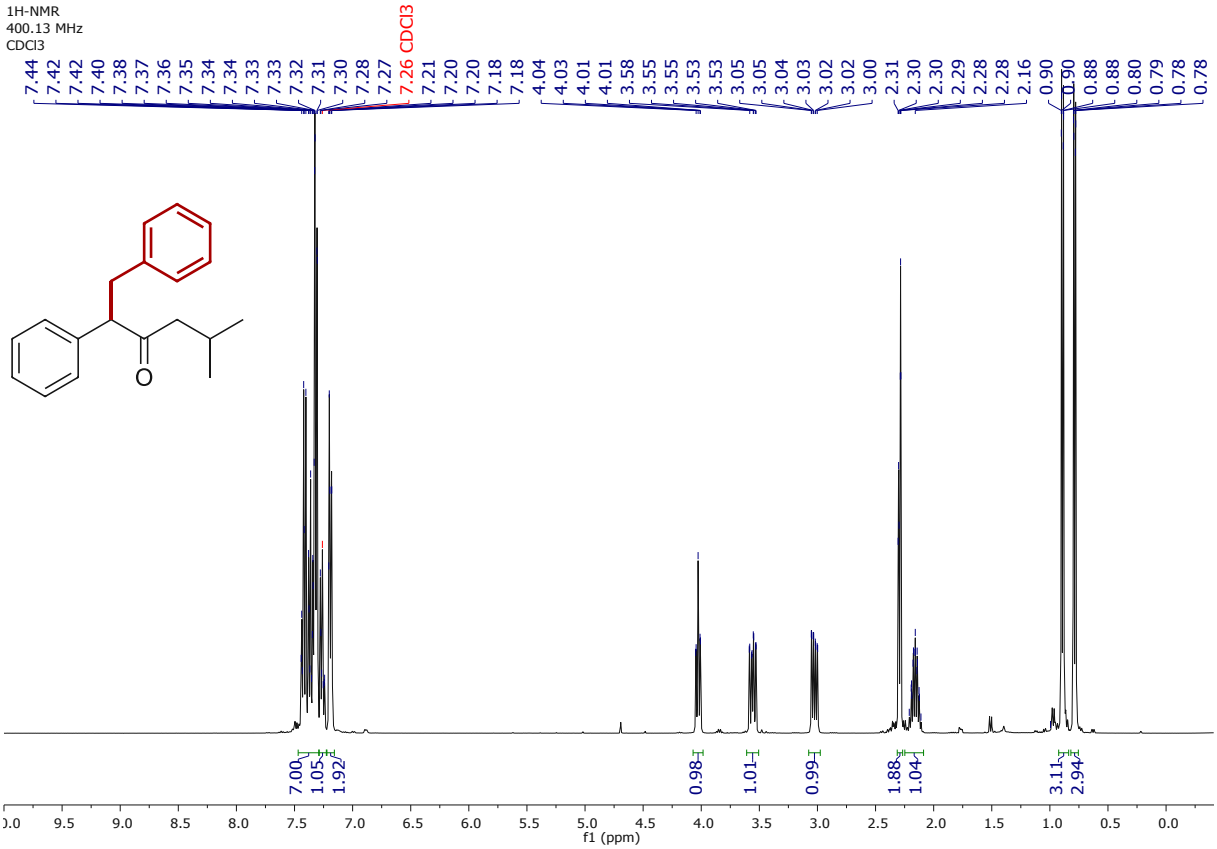


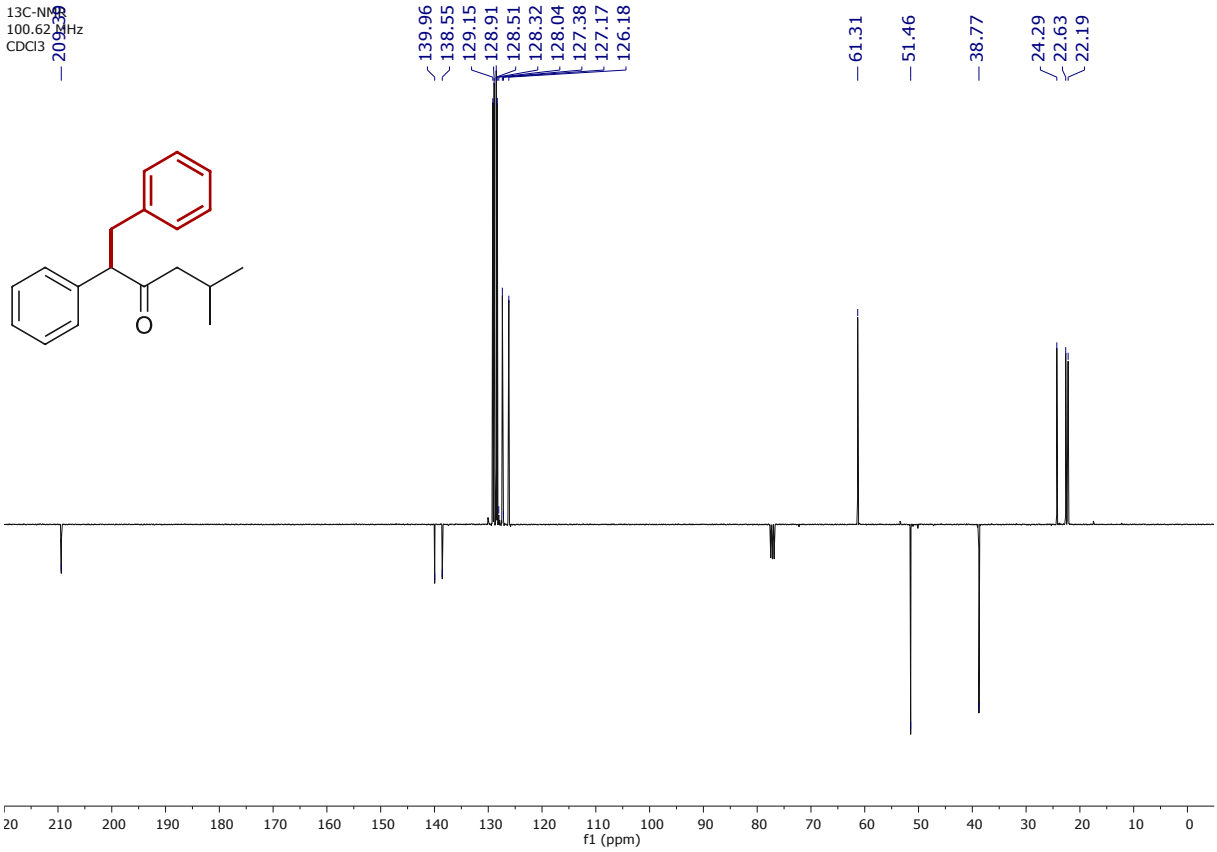
1,2-bis-(4-methoxy-phenyl)-3-phenyl-propan-1-one (5b)





5-Methyl-1,2-diphenyl-3-hexanone (5c)





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D II Manuscript 2

Johanna Templ and Michael Schnürch

A Guide for Mono-Selective N-Methylation, N-Ethylation, and N-n-Propylation of Primary Amines, Amides, and Sulfonamides and Their Applicability in Late-Stage Modification

Chem. Eur. J. 2024, e202304205. doi: 10.1002/chem.202304205

A Guide for Mono-Selective N-Methylation, N-Ethylation, and N-*n*-Propylation of Primary Amines, Amides, and Sulfonamides and Their Applicability in Late-Stage Modification of Bioactive Compounds

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Abstract: This review provides a comprehensive overview of mono-alkylation methodologies targeting crucial nitrogen moieties – amines, amides, and sulfonamides – found in organic building blocks and pharmaceuticals. Emphasizing the intersection of chemical precision with drug discovery, the central challenge addressed is achieving one-pot mono-selective short-chain N-alkylations (methylations, ethylations, and *n*-propylations), preventing undesired overalkylation. Additionally, sustainable, safe, and benign alternatives to traditional alkylating agents, including alcohols, carbon dioxide, carboxylic acids, nitriles, alkyl phosphates, quaternary ammonium salts, and alkyl carbonates, are explored. This review, categorized by the nature of the alkylating agent, aids researchers in selecting suitable methods for mono-selective N-alkylation.

1. Introduction

Nitrogen-containing motifs, encompassing amines, amides, and sulfonamides, serve as crucial structural elements in both simple organic building blocks and complex molecules, particularly bioactive compounds and pharmaceuticals (see Scheme 1).[1] These motifs exert significant influence on pharmacological properties, engaging in diverse interactions within biological systems, thereby establishing their indispensability in drug development.[1-2] This review aims to provide a comprehensive exploration of mono-alkylation methodologies tailored for these nitrogen moieties, highlighting the importance of chemical precision and their potential application in drug discovery.[2-3]

The primary challenge addressed here revolves around accomplishing one-pot mono-selective short-chain N-alkylations (specifically methylations, ethylations, and *n*-propylations) of primary amines, amides, and sulfonamides while rigorously excluding undesired overalkylation. This overalkylation is prompted by the increased nucleophilicity of nitrogen with higher substitution levels. Noteworthy is that related reviews often exclusively focus on N-methylations[4] and may not concentrate on mono-selectivity for aliphatic short-chain alkylation of primary nitrogen moieties.[4a-c, 4e, 4f, 5]. Nevertheless, achieving a high degree of mono-selectivity in nitrogen alkylation is paramount for designing and controlling alterations in the pharmacological activity of therapeutic agents.

Additionally, this review offers valuable methods for utilizing sustainable, safe, and generally more benign alternatives (such as alcohols, carbon dioxide, carboxylic acids, nitriles, alkyl phosphates, quaternary ammonium salts, and alkyl carbonates) to traditionally applied alkylating agents like alkyl halides. The comprehensive overview of current strategies, categorized by the nature of the alkylating agent, aims to assist readers in selecting suitable methods for N-alkylation when mono-selectivity is crucial. Furthermore, it covers strategies for mono-selective N-ethylation and N-*n*-propylation, providing a well-rounded understanding of the field.

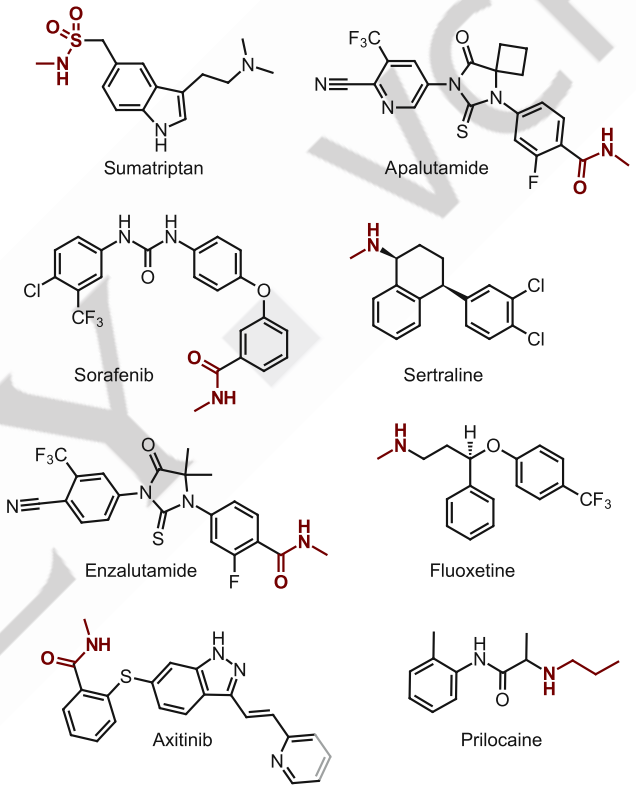


Figure 1. Examples for bioactive molecules bearing N-alkylated motifs.

Johanna Templ received her master's degree in chemistry in the field of natural product synthesis in 2019 at TU Wien. Starting her PhD in 2020 in the group of Michael Schnürch, she is currently working on substituting hazardous reagents by solid, nontoxic alternatives. Concurrently, her research focusses on the development of solvent-free mechanochemical reactions.

Prof. Michael Schnürch carried out PhD research in the field of heterocyclic and cross-coupling chemistry under the supervision of Prof. Peter Stanetty. During postdoctoral studies at the Columbia University, NY in the group of Prof. Dalibor Sames as Erwin Schrödinger fellow of the Austrian Science Fund, he investigated decarbonylative coupling reactions. After the start of his independent career, he established a research program on C-H activation chemistry and cross-dehydrogenative coupling reactions, supported by several research grants (financed by FWF, FFG, The City of Vienna, and TU Wien).

2. Amines

Amines are ubiquitous and fundamental motifs in organic chemistry, playing a central role in the synthesis of various bioactive compounds and pharmaceuticals.[3d, 6] Their significance lies in their unique reactivity and versatility, making them essential building blocks for constructing complex molecular structures. Within drug design, amines serve as key components, influencing the pharmacological activity of therapeutic agents through diverse interactions within biological systems, impacting molecular recognition and binding.[7]

N-Alkylation stands out as a transformative strategy in amine functionalization.[3d] This modification introduces a new layer of variability to amine-containing compound for precise tuning of their chemical and physical properties. The ability to precisely control the degree of alkylation is crucial in many chemical transformations. Particularly in drug development, where subtle modifications can significantly influence a compound's pharmacokinetic and pharmacodynamic properties, methods ensuring strictly mono-selective N-alkylation become not only desirable but often indispensable.

This chapter aims to provide an overview of methodologies and strategies for achieving mono-selective short-chain alkylation of amines, highlighting their applicability in late-stage modifications of bioactive compounds.

2.1. Alcohols

Alcohols present a very valuable and sustainable alternative to traditional alkylating agents, as they are inexpensive, readily available, and renewable. Giving water as the sole byproduct, their application in alkylation reactions enhances atom-efficiency and thus contributes to making chemical processes more environmentally benign.

When using alcohols as the alkylating agents, the formation of the carbon-nitrogen bond proceeds through a concept known as hydrogen autotransfer or borrowing hydrogen (see Figure 2).[8] In this process, a transition-metal mediates alcohol dehydrogenation, generating a reactive intermediate, such as an aldehyde or ketone. Subsequent condensation with an amine leads to imine formation, with water released as the sole byproduct. The intermediate metal-hydride complex [MH_2], previously formed during dehydrogenation, effectively reduces the imine species, releasing the alkylated amine, and simultaneously regenerating the catalytically active species [M]. The net N-alkylation of amines with alcohols proceeds without external hydrogen gas; instead, hydrogen is formally "borrowed" and "returned" by the active catalytic species during the reduction step.

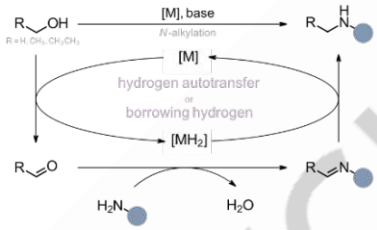


Figure 2. Simplified mechanism for metal catalyzed hydrogen autotransfer or borrowing hydrogen reactions in the alkylation of primary amines using alcohols

Conventionally, noble transition metals like ruthenium, iridium, and palladium are used in these hydrogen autotransfer-mediated N-alkylations with alcohols. Recent efforts have aimed to replace these costly transition metals with earth-abundant alternatives, such as iron, manganese, nickel, and copper. Nevertheless, a significant challenge that remains is developing catalytic systems that can operate effectively at lower temperatures, as current N-alkylation reactions with alcohols typically require high temperatures exceeding 100 °C and often involve prolonged reaction times, which in turn often requires special high-pressure equipment.

Rhodium catalysis

In 1981, Grigg and co-workers were the first to report mono-selective homogeneous transition-metal catalyzed N-methylation of primary amines with methanol, using $RhH(PPh_3)_4$ as catalyst.[9] While this early publication featured only three examples of mono-N-methylation, it unquestionably laid the foundation for subsequent advances in this field.

Ruthenium catalysis

Fifteen years after Grigg's pioneering work, Watanabe, Mitsudo, and co-workers studied the mono-selective N-ethylation on aminopyridines with ethanol under ruthenium catalysis (Figure 3, I)[10] Employing a Ru(0)(cod)(cot) catalyst, they run the reactions at 150-180 °C for 5 h in the respective alcoholic solvent, achieving outstanding selectivity for the mono-methylated, -ethylated, and -propylated products with up to 92 % yield. Only at higher temperatures (200 °C), extended reaction times (20 hours), and using $RuCl_2(PPh_3)_3$ as the catalyst, they could manipulate the degree of substitution and isolate the di-ethylated product in 70 % yield. This marked the first instance of such mono-selectivity in transition-metal-catalyzed N-alkylations, paving the way for numerous succeeding reports.

The Bhattacharjee group reported the use of $[(PPh_3)_2Ru(CH_3CN)_3Cl][BPh_4]$ catalyst for mono-alkylation of various para-substituted anilines under mild basic conditions, maintaining high mono-selectivity, though only achieving moderate yields, especially with "longer" chain alcohols like ethyl and propyl (Figure 3, II)[11]

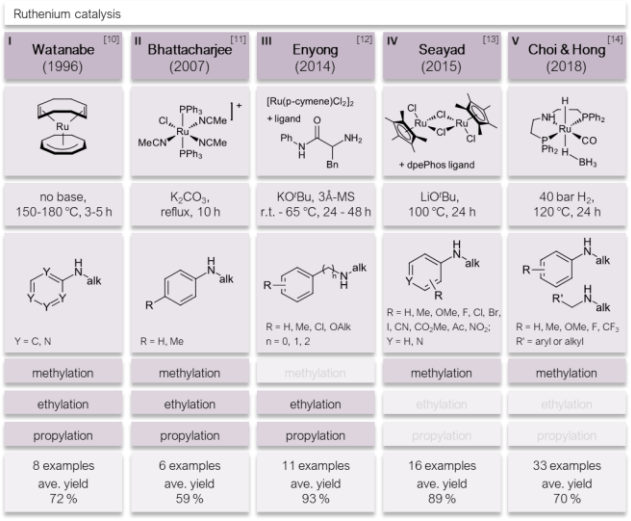
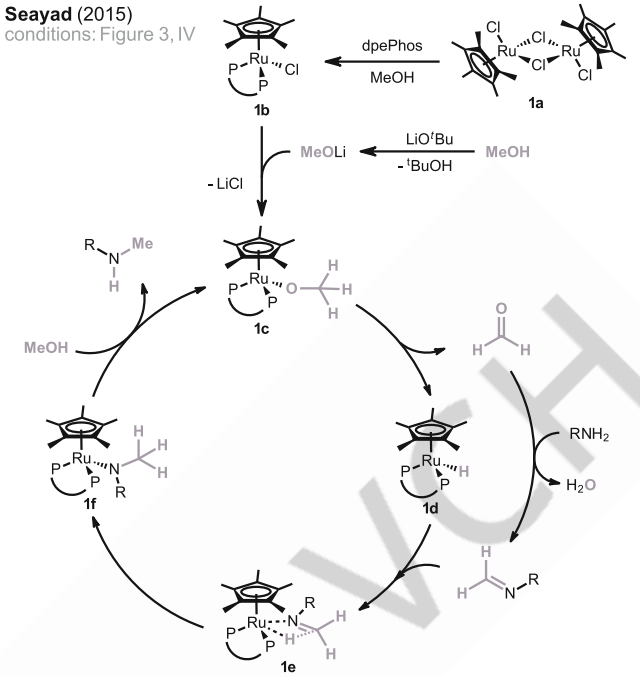


Figure 3. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under ruthenium catalysis.

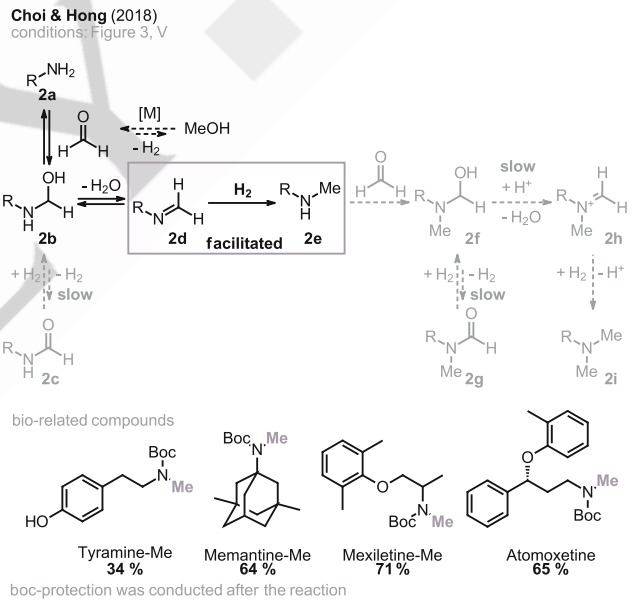
In 2014, Enyong *et al.* established a novel protocol using cheap and commercially available $[Ru(cymene)Cl_2]_2$ catalyst and a readily available amino amide ligand, enabling N-alkylation at temperatures below 70 °C (Figure 3, III).[12] This lower reaction temperature was only feasible when the respective alcohol was used as reaction solvent. In toluene with near-stoichiometric amounts of alcohol, higher temperatures up to 110 °C were required for full conversion. They successfully mono-ethylated and mono-propylated a wide range of substituted anilines and benzylamine with excellent yields of up to 98 %. Unfortunately, the absence of an example for mono-methylation left open the question whether methanol could act as an effective N-alkylating agent under these conditions.

The lack of mild and viable protocols for Ru-catalyzed N-methylation using methanol, encouraged the group of Seayad to develop a method for mono-selective N-methylation of substituted primary anilines (Figure 3, IV) and sulfonamides (see Section 4. Sulfonamides).[13] This mono-selectivity was observed for aniline-derived substrates and sulfonamides but not for aliphatic primary amines, where exclusively *N,N*-dimethylated products were obtained. They employed $[RuCp^*Cl_2]_2$ (0.5 mol%) with dpePhos ligand (1.2 mol%) as precatalytic system, which, upon activation with LiO^{t}Bu (5 mol%) generated an active Ru-methoxy complex (Scheme 1). Various substituted aniline derivatives could be mono-methylated with excellent yields ranging from 73% to 96% at 100 °C.

In 2018, Choi and Hong expanded the scope of mono-selective N-methylation under Ru-catalysis, moving beyond primarily anilines to encompass aliphatic primary amines (Figure 3, V).[14] This milestone was achieved through the deployment of pincer ligands, combined with the introduction of an H_2 atmosphere. The intent was to facilitate the formation of mono-methylated products while any further methylation of the secondary amine should be kinetically hindered (Scheme 2).



Scheme 1. Proposed catalytic cycle for the mono-N-alkylation of primary amines *via* ruthenium catalysis by the group of Seayad.[13]



Scheme 2. Proposed reaction pathway by Choi & Hong for the mono-N-methylation with alcohols using a ruthenium pincer catalyst (top) and the application of their method in a late-stage N-methylation of bio-related compounds (bottom).[14]

They hypothesized that under these reaction conditions, the intermediate charged iminium species (**2h**) formed from a secondary amine (**2e**) should have a significantly higher activation barrier compared to the lower activation barrier of an uncharged species formed from the primary amine (**2d**).

The optimal results were achieved using the pincer catalyst Ru-MACHO-BH (2 mol%; Figure 3, V) in MeOH as solvent at an H_2-pressure of 40 bar and a reaction temperature of 120 °C for 24 hours. This method yielded a wide range of mono-methylated

secondary amines with yields ranging from 34% to 99%. Notably, this method demonstrated its feasibility for the late-stage modification of several biologically relevant compounds.

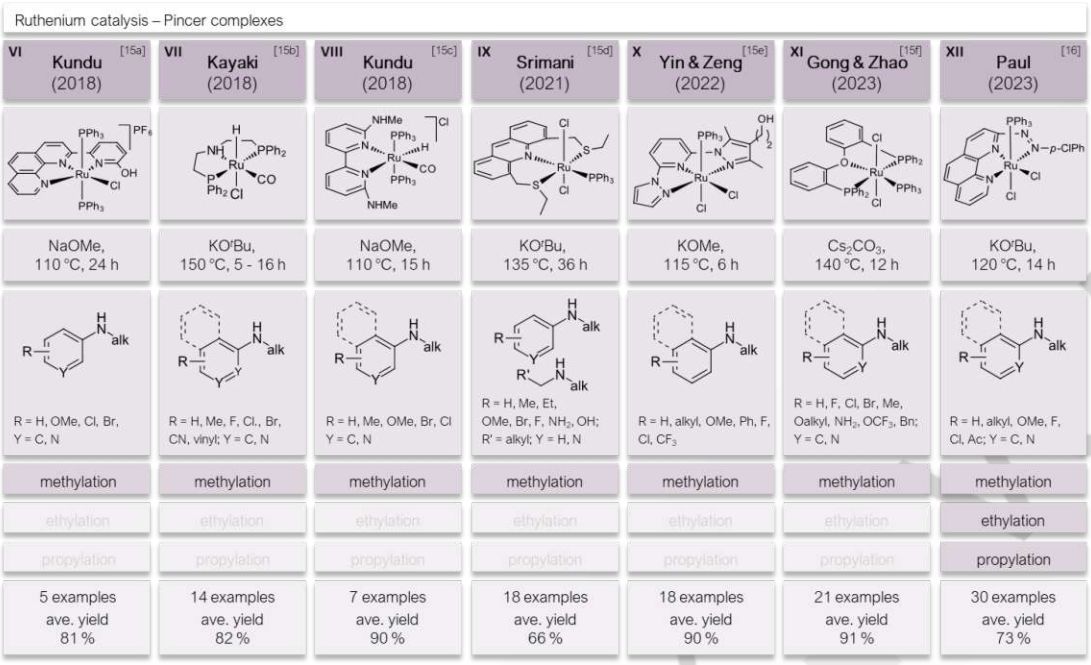


Figure 4. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under ruthenium pincer complex catalysis.

The following years, reports on using various Ru-pincer complexes for selective mono-methylation of aniline derivatives were disclosed by several groups (Figure 4, VI-XII) [15]. Most systems require strong alkoxy bases like NaOMe[15a, 15c], KOMe[15e], or KO^{t}Bu[15b, 15d] to form the catalytically active Ru-alkoxy species. Recently, Gong, Zhao and co-workers found Cs_2CO_3 as very mild base in a ruthenium POP-pincer-complex catalyzed mono-selective N-methylation protocol[15f] (Figure 4, XI). Additionally, some of those protocols could be successfully applied for mono-selective trideutero methylation of primary amines using CD_3OD[15b-f] (Scheme 3). In 2023, the group of Paul expanded the scope of Ru-pincer-complex catalyzed N-methylation towards a more general protocol for N-alkylation using C1-C10 aliphatic alcohols to mono-selectively alkylate several aniline derived substrates in up to 85 % yield. (Figure 4, XII) [16]

Figure 4, VII; 94 %; **Kayaki** (2018)[15b]
Figure 4, VIII; 85 %; **Kundu** (2018)[15c]
Figure 4, IX; 85 %; **Srimani** (2021)[15d]
Figure 4, X; 56 %; **Yin & Zeng** (2022)[15e]
Figure 4, XI; 97 %; **Gong & Zhao** (2023)[15f]

Scheme 3. N-Trideuteromethylations using CD_3OD under ruthenium pincer complex catalysis.

N-Hetrocyclic carbenes (NHCs) represent another prominent class of ligands frequently used in ruthenium-catalyzed N-alkylation reactions employing alcohols as reagents (Figure 5, XIII-XV). Numerous studies have explored these catalytic systems, with notable contributions from the groups of Rit[17] (Figure 5, XIII & XV) and Liu & Ke[18] (Figure 5, XIV). Typically, these protocols necessitate the use of a strong base such as KO^{t}Bu[18] or KOH[17] and operate at elevated temperatures surpassing 100 °C. While primary aryl amines predominantly served as substrates in these protocols, exceptions included the utilization of cyclohexylamine and benzylamine, as reported by Illam and Rit.[17b]

Yang, Li and co-workers have developed a robust bidentate, cyclometalated ruthenium complex, suitable to methylate primary amines and sulfonamides mono-selectively (Section 4 Sulfonamides) using methanol under mildly basic conditions (Cs_2CO_3), while being stable under ambient atmosphere[19] (Figure 5, XVI). The approach, executed at 120 °C for 15 hours, afforded selective mono-methylation of primary aryl amines with methanol, in yields up to 93 %. However, the same degree of mono-selectivity could not be ensured for aliphatic amines. The authors could prove that the bipyridonate ligand within the [(*p*-cymene)Ru(2,2'-bpyO)(H_2O)] system plays a crucial role in the catalytic cycle of the reaction (Scheme 4). The cycle initiates with the loss of water, leading to the formation of a vacant site on the metal center **(3b)**. Subsequent base-induced activation of methanol triggers the protonation of the ligand and simultaneous

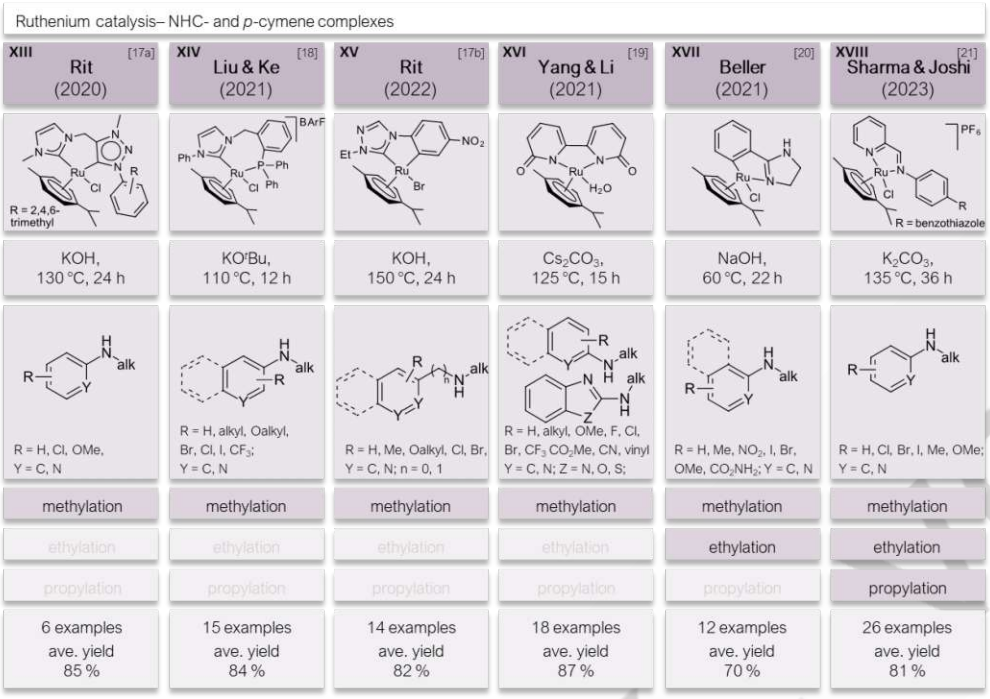


Figure 5. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under ruthenium NHC- and *p*-cymene complex catalysis.

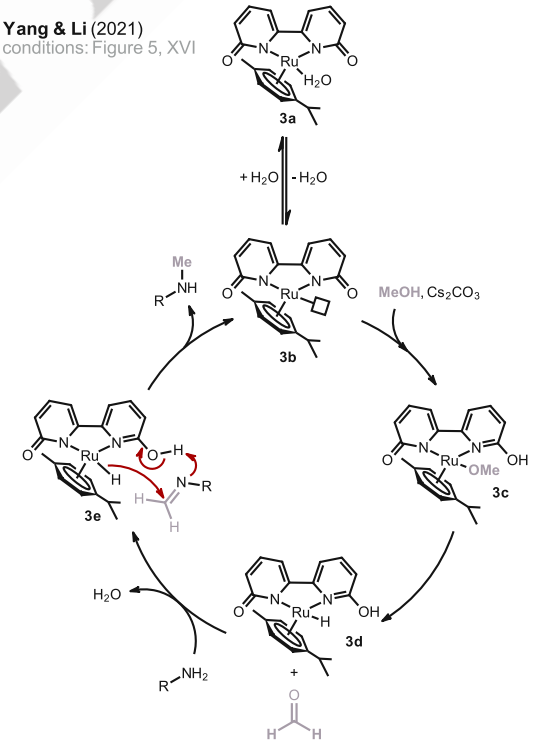
coordination of methoxy to the metal center **(3c)**. The resulting catalytic intermediate then dehydrogenates methanol to formaldehyde, which promptly combines with an amine to the corresponding imine and is hereby converted to a metal hydride species. The hydration of the imine is facilitated by the donation of the hydride coordinated to the metal center **(3e)** and the hydroxy proton of the ligand, thereby regenerating the catalytic active species **(3b)**, and liberating the desired methyl amines. In this final step, the crucial role of the oxygen species within the ligand becomes evident.

In 2021, an exceptionally mild protocol in terms of reaction temperature was devised by the group of Beller[20] (Figure 5, XVII). They used a cyclometalated Ru-complex as well which is activated by NaOH (10 mol%). This approach smoothly gave the desired mono-alkylated amines at 60 °C after 22 hours in yields up to 99 %.

Recent work of Sharma, Joshi and co-workers introduced the use of a bidentate Ru-complex for mono-selective alkylation of primary anilines and aminopyridines with C1-C3 alcohols, carried out at 135 °C for 36 hours, employing K_2CO_3 as a mild base[21] (Figure 5, XVIII).[21] High yields up to 95 % could be obtained for the targeted *N*-ethylated, and *N*-propylated products. Notably, N-methylation, could only be achieved with moderate maximum yields of 54 %.

Iridium catalysis

In addition to ruthenium, iridium complexes have emerged as versatile and highly efficient catalysts in hydrogen autotransfer mono-selective N-alkylations, using alcohols as the alkylating agent. The first report of an iridium catalyzed N-alkylation with short-chain alcohols was disclosed by the group of Kempe in 2009.[22] They reported the use of a P,N-ligand-stabilized iridium catalyst to achieve mono-selective N-alkylation of various aromatic diamines.



Scheme 4. Proposed catalytic cycle for the mono-N-alkylation of primary amines *via* ruthenium catalysis by Yang & Li indicating the crucial role of the bipyridonate ligand.[19]

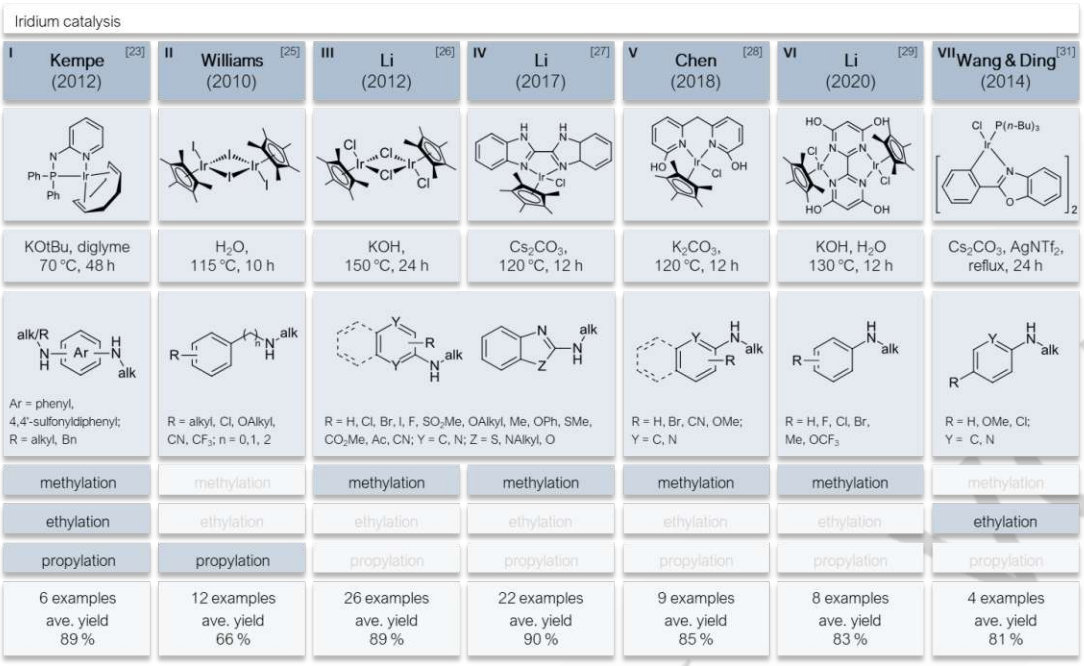
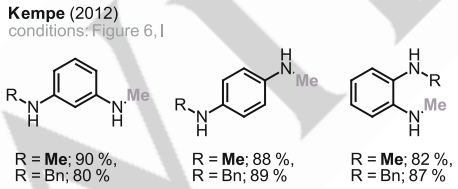


Figure 6. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under iridium catalysis.

This early report featured a single example of short-chain alkylation employing methanol, yielding 88 % of the doubly mono-methylated 2,6-diaminopyridine, facilitated by KO*t*Bu as the base at 70 °C for 48 hours.

Just three years later, the same group expanded their investigations to present a closely related protocol for the symmetric and asymmetric alkylation of diamines[23] (Figure 6, I). This innovation led to the successful synthesis of symmetric mono-N-methylated *ortho*-, *meta*-, and *para*-benzenediamines using methanol, in yields ranging from 82% to 90%, as well as unsymmetrical N-methylation of *N*-benzyl benzenediamines, in 80% to 89% yield (Scheme 5).

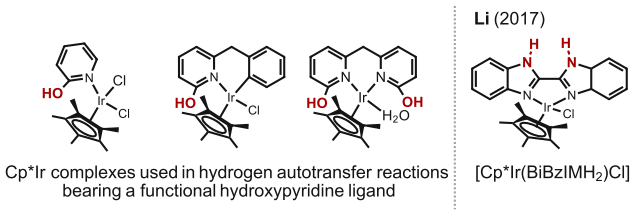


Scheme 5. Mono-N-methylation of *ortho*-, *meta*-, and *para*-benzenediamines using methanol under iridium catalysis by Kempe and co-workers.[23]

Inspired by the work of Fujita involving Cp*Ir complex catalyzed N-alkylations[24], the group of Williams reported the use of $[Cp^*IrI_2]_2$ (SCRAM™) as catalyst for mono-selective N-alkylations of various aliphatic and aromatic primary amines employing *n*-propanol and higher carbon alcohols[25] (Figure 6, II). Notably, the reactions were carried out in water at 115 °C, yielding a range of mono-*N*-propylated amines in yields up to 94 %.

In 2012, Feng Li and co-workers reported the use of a $[Cp^*IrCl_2]_2$/NaOH system for mono-N-methylation of primary arylamines (Figure 6, III) and sulfonamides (Section 4 Sulfonamides).[26] With only 0.1 mol% catalyst loading and under solvent-free conditions at 150 °C, they could successfully mono-methylate arylamines substituted at different positions on the aromatic ring in excellent yields up to 96 %. Remarkably, this protocol extended its applicability to various substituted amino-azole compounds, yielding the desired mono-*N*-methylated products with remarkable efficiency, reaching yields up to 95 %.

The group continued their work with Cp*Ir complexes for mono-selective N-alkylations with alcohols and, in 2017, published a new protocol featuring an *N,N*-bidentate Cp*Ir complex ($[Cp^*Ir(BiBzImH_2)Cl][Cl]$)[27] (Figure 6, IV). These 2,2'-bibenzimidazole ligands, containing protic hydrogen, exhibit structural tautomerism reminiscent of hydroxy pyridine ligands (Scheme 6).

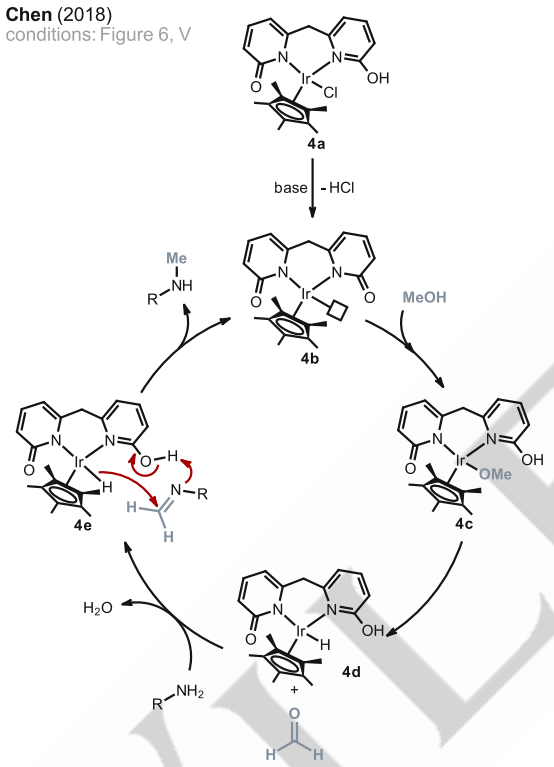


Scheme 6. Structural similarity of a 2,2'-bibenzimidazole ligand by Li and co-workers (right) to previously reported hydroxypyridine ligands (left).[27]

The reaction is characterized by low catalyst loadings of 1 mol%, the use of mild base (Cs_2CO_3, 30 mol%) and a robust catalytic system that demonstrated stability in the presence of air. Under these conditions, a range of substituted primary aryl amines was selectively mono-methylated in generally high yields between 78-95 % at 120 °C within 12 hours reaction time. Notably, mono-

selectivity was exclusively observed for primary aryl amines, with aliphatic amines inevitably undergoing full bis-methylation.

In 2018, Chen's group designed a novel, air-stable Cp*Ir catalyst with a bidentate α-hydroxybipyridine derived ligand designed for N-methylation of primary aryl amines[28] (Figure 6, V). 30 mol% of K_2CO_3 were used as mild base for catalyst activation, forming an unsaturated intermediate with a free coordination site **(4b)**, which in turn can coordinate methanol **(4c)**, and further participate in the catalytic cycle (Scheme 7). The method showed high mono-selectivity for aryl amines giving the desired products in up to 94 % yield. However, akin to previous reports on Cp*Ir catalysts, this protocol did not exhibit mono-selectivity in the N-methylation of aliphatic amines, resulting exclusively in bis-methylated products.



Scheme 7. Proposed catalytic cycle for the N-methylation of amines under iridium-catalysis by Chen and co-workers.[28]

The group of Feng Li reported two additional protocols using Cp*Ir catalysts. In 2020, they designed a water-soluble bifunctional dinuclear iridium catalyst, enabling mono-N-methylation of aryl amines and sulfonamides (Section 4 Sulfonamides), with similar substrate scope and yields (79 – 88 %) to their prior reports[26-27], under basic conditions (KOH, 1 equiv.) at 120 °C with a 12 hour reaction time[29] (Figure 6, VI). Again, mono-selectivity remained elusive for primary aliphatic amines.
Two years later, they introduced an air and moisture stable Ir-catalyst bearing a bipyridonate ligand for N-trideuteromethylation of aromatic amines with CD_3OD at 125 °C using 30 mol% KOH as base.[30] The scope for mono-N-methylation exhibited similarities to their earlier reports.[26-27, 29]

In 2014, Wang and Ding's research group investigated a different class of bidentate iridium species, specifically the benzothienyl iridium(III) complexes featuring phosphine substituents, as catalysts for the mono-N-alkylation of primary aryl amines[31] (Figure 6, VII). Interestingly, their investigation revealed a remarkable enhancement in catalytic activity when non-coordinating anions were introduced, in form of corresponding silver salts such as $AgBF_4$, $AgSbF_6$, $AgPF_6$, or $AgNTf_2$. Among these, $AgNTf_2$ exhibited the most substantial increase in reaction yield (details see Section 2.11 Trialkylamines). While their study encompassed just four examples for mono-N-ethylation of primary aromatic amines with ethanol, the scope is limited in terms of the variety of alcohols employed as alkylating agents. In this reaction Cs_2CO_3 served as the base with a catalyst loading as low as 1 mol% in conjunction with 2 mol% of $AgNTf_2$, proved to be sufficient to achieve high yields up to 86 %. The authors could show, however, that their catalytic system enabled mono-N-ethylation using triethylamine, an aspect discussed in greater detail in a subsequent section of this review (Section 2.11 Trialkylamines).

Similar to ruthenium catalysts, NHC type ligands also find applications in iridium catalyzed mono-N-alkylations using alcohols. In 2013, Li and Andersson introduced a bidentate iridium NHC-phosphine complex for the N-alkylation of primary aryl amines with alcohols[32]. However, it is important to note that this study had a primary focus on aromatic alcohols, and the sole instance involving a short, unbranched alcohol was the N-ethylation of aniline, giving the product in 94% yield. While the scope was somewhat limited, this research marked the initial step toward further advancements in employing NHC ligands in Ir-catalyzed hydrogen autotransfer protocols.
An alternative protocol utilizing iridium NHC-ligand complexes, coupled with microwave irradiation, was developed by the Crabtree research group in 2015[33] (Figure 7, VIII). Their catalytic system comprised two NHC-ligands and two CO ligands coordinated to iridium, administered in form of its BF_4 salt. Although the substrate scope was modest, comprising eight different aniline-derived substrates, mono-selective N-methylation was accomplished with yields ranging from 14 to 95 % using methanol and KOH at 120 °C under microwave irradiation for 5 h.

Fujita and co-workers screened various Cp*Ir NHC-ligand complexes for the catalytic methylation of primary aromatic amines.[34] They achieved mono-selective N-methylation using a $[Cp^*Ir(NH_3)_2][I_2]$-derived catalyst with a bis-isopropyl imidazole NHC-ligand at a loading of 0.5 mol%. K_2CO_3 (5 mol%) was employed as base (Figure 7, IX). The reaction yielded several secondary aromatic amines in high yields up to 98 %.

In 2019 and 2020, Hou and collaborators reported the synthesis and application of novel Ir $^{ABO}N,C_{(carbene)}$ complexes featuring rigid and tunable benzoxazole backbones[35] (Figure 7, X & XI).

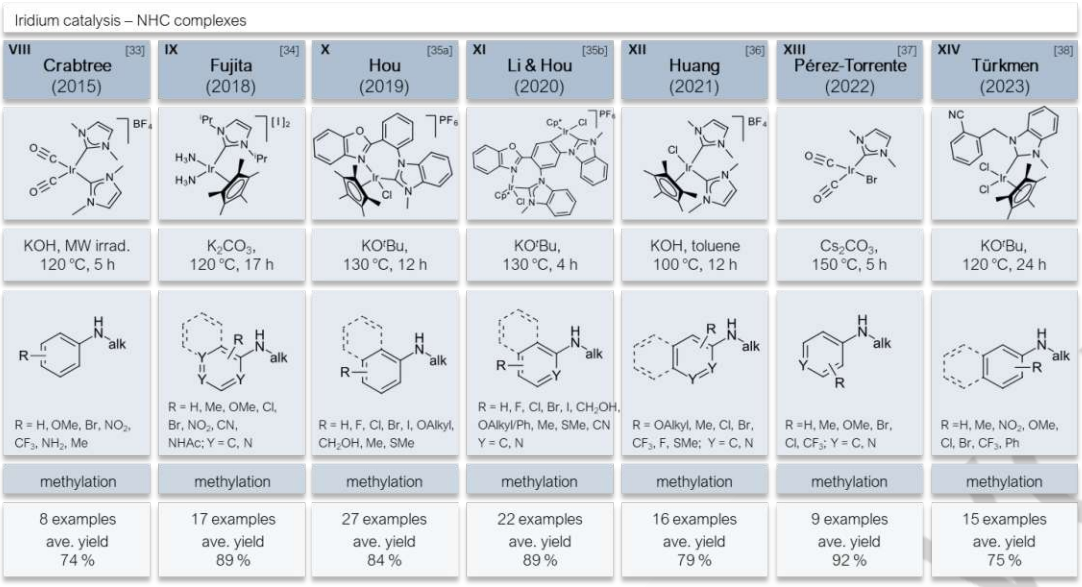
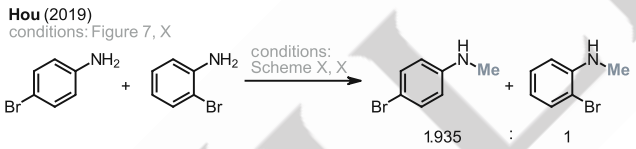


Figure 7. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under iridium NHC-catalysis.

A range of *ortho*-, *meta*-, and *para*-substituted anilines, as well as aminoquinolines, benzothiazole and sulfonamides, could be selectively N-methylated at 130 °C within reaction times of 4 or 12 hours, using KO^{t}Bu or Cs_2CO_3 as the base. Intriguingly, control experiments revealed that *para*-substituted anilines exhibited higher reactivity in this catalytic system compared to their *ortho*-substituted counterparts (Scheme 8). Assumingly, the less sterically hindered *para*-substituted imines could more readily approach the intermediate Ir-hydride complex, leading to faster hydration than *ortho*-substituted imines.



Scheme 8. Selectivity in the iridium NHC-complex catalyzed N-methylation of *ortho*- and *para*-bromo aniline by Hou and co-workers.[35a]

Additional iridium NHC-catalysts have been developed by the group of Huang (2021; Figure 7, XII),[36] Perez-Torrente (2022; Figure 7, XIII),[37] and Türkmen (2023; Figure 7, XIV)[38] all suitable for mono-N-methylation of primary aromatic amines with methanol under basic conditions.

Iridium catalysts undoubtedly represent a valuable and widely employed system for borrowing hydrogen reactions, enabling the N-alkylation of primary aromatic amines in a mono-selective manner, often characterized by high functional group tolerance, highconversion rates, and impressive turnover numbers. Nevertheless, it's worth noting that all the described protocols exhibit limitations when primary aliphatic amines are utilized as substrates, as mono-selectivity is not guaranteed in such cases.

Miscellaneous noble metal catalysis

In addition to ruthenium and iridium catalysts, which are the most commonly utilized metals for hydrogen autotransfer reactions, precious metals like palladium and rhenium have also proven efficient catalysts in the mono-selective N-alkylation of amines with alcohols.

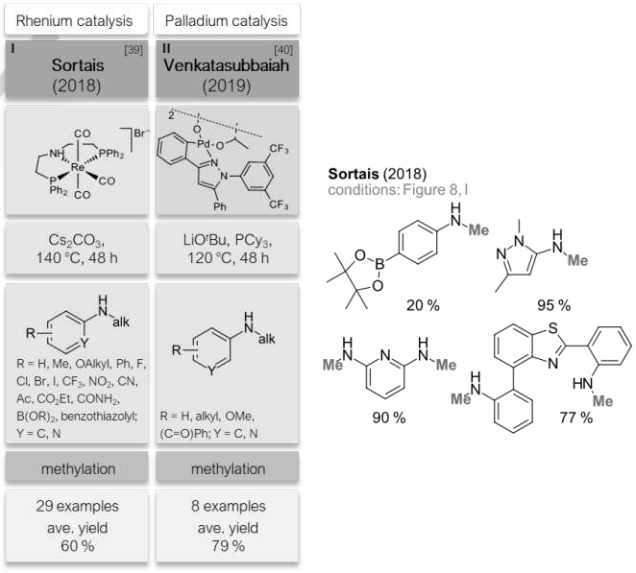


Figure 8. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under rhenium and palladium catalysis.

In 2018, the group of Sortais designed a series of cationic tricarbonyl Re(I) PNP-ligand complexes for the mono-N-methylation of aromatic amines with methanol[39] (Figure 8, I). The most effective catalytic system relied on an $NH(CH_2CH_2PPh_2)_2$ ligand and was activated by Cs_2CO_3 (5-10 mol%) as the base. This reaction took place in methanol as the solvent at 140 °C for

48 hours under an argon atmosphere, yielding a variety of N-methylated aromatic amines, including complex boronic esters, pyridinyl- and pyrazolyl-amines, and benzothiazolyl derivatives (Figure 8, right).

Palladium based catalysts are primarily employed in their heterogenous Pd/C form for hydrogen borrowing reactions. The use of a homogeneous palladium complex for N-methylation was only reported once in 2019 by Venkatasubbaiah's group[40] (Figure 8, II). They synthesized a palladacycle-phosphine complex, which, upon activation with 30 mol % LiO^{t}Bu, gave access to eight different mono-N-methylated aromatic amines in moderate to good yields.

Over the last few decades, there has been a growing trend toward the utilization of more sustainable, earth-abundant, and cost-effective non-precious metal catalysts. Multiple research groups have invested significant efforts in developing new catalytic systems containing manganese, nickel, iron, copper, and cobalt for mono-selective N-alkylation reactions with alcohols, which will be discussed further below.

Manganese catalysis

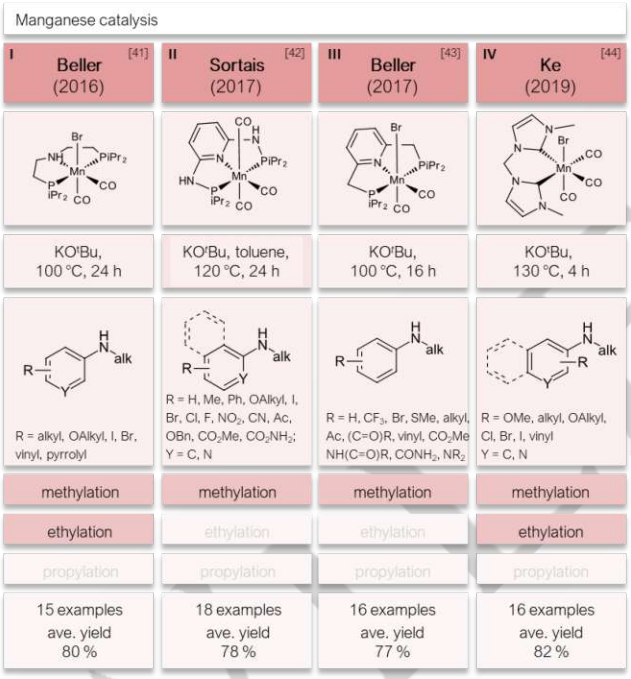
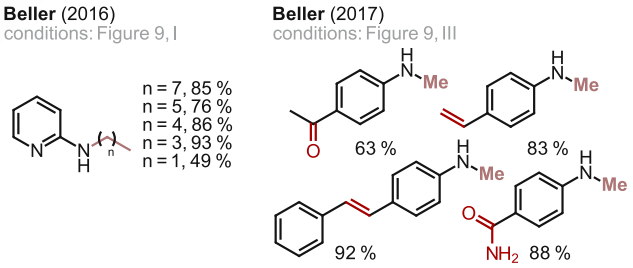


Figure 9. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under manganese catalysis.

A pioneering work in the field of manganese catalyzed N-alkylation of amines was published by Beller's group in 2016[41] (Figure 9, I). They were the first to use a defined manganese-based PNP-pincer complex to mono-selectively N-alkylate various primary amines with complex alcohols. Their protocol applied 3 mol% of the catalyst, which was activated by KO^{t}Bu to effectively partake in this hydrogen autotransfer reaction. In addition to a wide array of aromatic alcohols, short-chain, unbranched aliphatic alcohols (C1-C7) were successfully harnessed as alkylating agents. Notably, 2-aminopyridine could be ethylated and butylated in a mono-selective fashion at 80 °C in up to quantitative yields. To explore the generality of this approach using methanol as the alkylating agent, diverse primary aromatic amines were examined and could be readily N-methylated with exceptionally high yields of up to 94% at 100 °C within 24-hours reaction time.

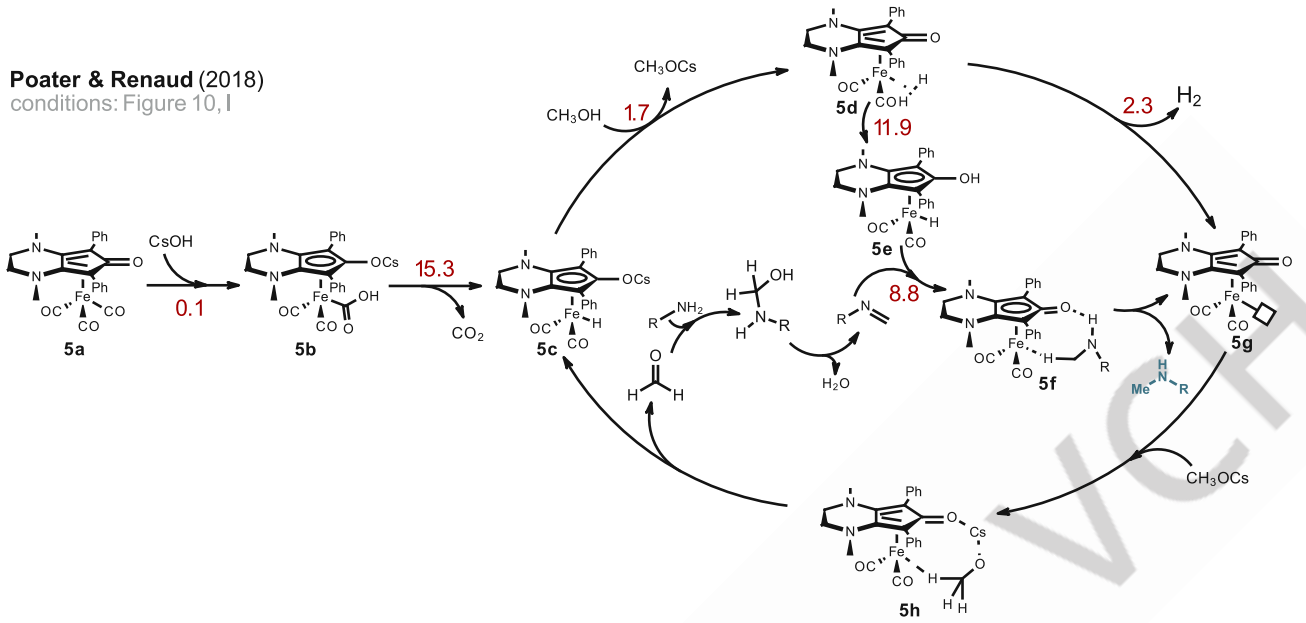
Sortais and his colleagues continued this research, revealing in 2017 a protocol for the mono-selective N-methylation of anilines using a cationic manganese PN^{3}P-pincer complex[42] (Figure 9, II). Small quantities of KO^{t}Bu (20 mol%) were essential to activate the catalytic system through N-H deprotonation. This process led to dearomatization, facilitating the decoordination of a CO ligand to generate the active catalyst. The catalyst in its active state can then dehydrogenate methanol, leading to the formation of formaldehyde. This transformation further proceeds with the creation of a metal-hydride complex, which subsequently participates in the catalytic cycle for hydrogen autotransfer reactions as previously described. Primary aromatic amines as well as sulfonamides could be readily methylated at 120 °C giving the desired products in isolated yields between 42-98 %. Interestingly, an acidic phenol substituent completely inhibited the reaction.

In the same year, the group of Beller published a second-generation pyridine-based manganese PNP-pincer complex with enhanced reactivity, even under milder conditions (100 °C instead of 120 °C) and shorter reaction times[43] (Figure 9, III). This remarkable catalytic system successfully N-methylated a diverse range of primary aromatic amines with complete mono-selectivity, giving the desired products in up to 93 % yield. Notably, anilines containing a stilbene or vinyl group could be readily methylated without affecting the double bond. Furthermore, amide and ketone functional groups remained unaltered (Scheme 9). However, nitrile substituents hampered the reaction giving only 3 % of the desired product. Interestingly, when benzyl or hexylamine were used as the substrates, the imine was the predominant product.



Scheme 9. Short-chain N-alkylations (left) under manganese catalysis and the presence of reducible groups unaltered under the given reaction conditions by the group of Beller.[41, 43]

In 2019, Ke's group developed a manganese phosphine-free catalytic system with NHC-ligands, to enable the N-alkylation of anilines with alcohols[44] (Figure 9, IV). Remarkably, this catalytic system operated at room temperature, after activation by KO^{t}Bu, when long-chain aromatic and aliphatic alcohols were employed as alkylating agents (RCH_2OH with $R \neq H$). Notably, N-ethylation of aniline could be achieved at room temperature giving the product in 70 % yield. However, for N-methylation higher temperatures (100 ° C) were still required to yield the desired mono-methylated products in 53 - 94 % yield.



Scheme 10. Proposed catalytic pathway for the iron-catalyzed N-alkylation of amines using alcohols by Poater & Renaud (the red numbers display the relative energy for transition states in kcal/mol) [45]

Iron catalysis

Iron, the most abundant transition metal in the Earth's crust, holds great promise for sustainable, non-precious metal catalysis. Recognizing the environmental benefits of iron-based catalysis, Poater, Renaud and colleagues investigated the use of iron-containing catalytic system for N-alkylation of amines with alcohols[45] (Figure 10, I). Their investigation unveiled the efficacy of an iron(0) tricarbonyl complex equipped with a cyclopentadienone ligand as catalyst in hydrogen autotransfer reactions, facilitating the N-methylation and N-ethylation of primary amines. In-depth mechanistic insights, derived from a combination of DFT calculations and experimental observations (Scheme 10), highlight the pivotal role of CsOH (10 mol%) as base in facilitating the release of a CO ligand. Additionally, the significance of H_2 pressure is emphasized, driving the equilibrium toward a catalytic intermediate responsible for the reduction of the imine to the desired alkylated amine. This phenomenon becomes apparent when considering that intermediate **5d** can follow two pathways: direct hydrogen release to intermediate **5g** or methanol-assisted indirect hydrogen cleavage toward intermediate **5e**. DFT calculations revealed that the second pathway is 9.6 kcal/mol more energy-demanding. Consequently, external hydrogen pressure could shift this equilibrium **(5d – 5g)** *via* the second pathway to intermediate **5e**, leading to the desired reduction of the imines. As observed in analogous transition-metal catalyzed N-alkylations using hydrogen borrowing strategies, mono-selective alkylation is attainable for primary aromatic amines, while overalkylation remains an issue for primary aliphatic amines. Nonetheless, the authors successfully demonstrated the adaptability of their protocol for achieving mono-N-methylation and -ethylation using alcohols at 110 °C across a range of substrates derived from anilines and aminopyridines, giving the desired products with impressive yields of up to 99% for both the methylated and ethylated species.

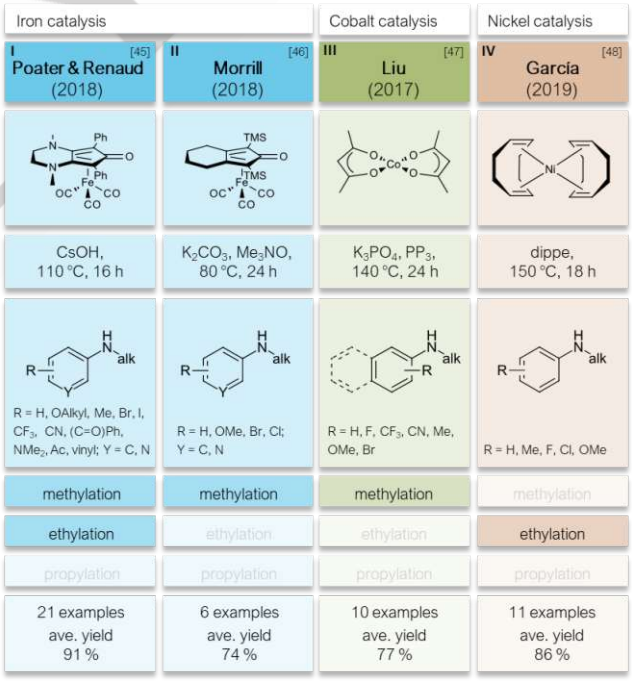


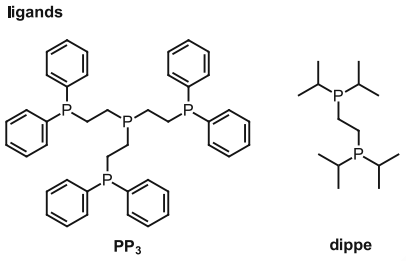
Figure 10. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under iron-, cobalt, and nickel-catalysis.

Concurrently, the Morrill group introduced a protocol employing a Knölker-type (cyclopentadienone)iron carbonyl pre-catalytic system, activated by trimethylamine *N*-oxide (4 mol%)[46] (Figure 10, II). K_2CO_3 served as the base and the reaction was performed in MeOH at a remarkably low temperature of 80 °C for 24 hours. However, it became apparent that employing a mixture of MeOH

and toluene (1:1) led to a substantial reduction in reaction yield, emphasizing the critical role of utilizing the alcohol itself as the reaction medium. While the authors concentrated primarily on the methylation of indoles and ketones, they presented only a handful of instances showcasing selective mono-methylation of primary aryl amines, resulting in yields ranging from 54 to 87%.

Cobalt-catalysis

In 2017, Zhenghui Liu *et al.* reported the successful application of a cobalt-catalyzed N-methylation of amines using methanol[47] (Figure 19, III). Their catalytic system was generated *in situ*, combining readily available $Co(acac)_2$ with the tetradentate ligand $P(CH_2CH_2PPh_2)_3$ (PP_3) (Scheme 11, left), which was then activated with K_3PO_4. The mono-methylation of aniline-derived substrates was successfully carried out at 140 °C, withyields ranging from 82% to 95%. Primary and secondary aliphatic amines, however, were found to undergo complete bis-methylation under this protocol.



Scheme 11. Ligands applied in cobalt- (left) and nickel-catalyzed (right) N-alkylation of primary amines by Liu[47] and García.[48]

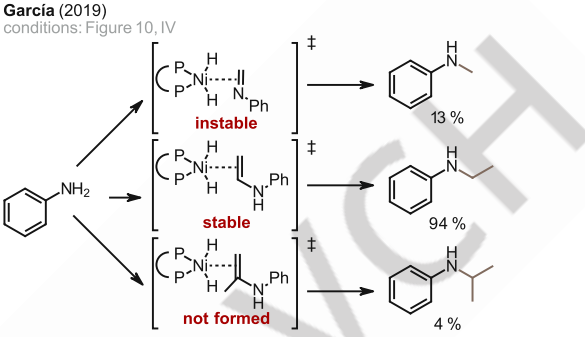
Nickel catalysis

In 2019, Medina and García described the use of a homogenous nickel catalyst for the N-alkylation of aniline derivatives using alcohols[48] (Figure 10, IV). Their catalytic system comprised a $[Ni(cod)_2]$ pre-catalyst and the dippe ligand (Scheme 11, right), forming the catalytic active species [Ni(cod)(dippe)] in situ, eliminating the need for an external base. Notably, their system exhibited good conversions when employing ethanol as the alkylating agent, while methanol or propanol resulted in maximum conversions of only 13%. They proposed a hypothesis that the imine, which forms after the dehydrogenation of methanol, might be inherently unstable, resulting in a lower selectivity towards the N-alkylated product (Scheme 12). In contrast, with 2-propanol, it appeared that the generated ketone did not lead to the formation of the corresponding iminium intermediate at all. They successfully ethylated 11 differently substituted anilines at 150 °C over an 18-hour reaction period, achieving high mono-selectivity and conversion rates ranging from 30% to quantitative yields.

Remarkable progress in Ni-catalyzed N-alkylations using short-chain aliphatic alcohols has also been achieved through heterogeneous catalytic systems such as Raney-Nickel or Ni-nanoparticles, which will be discussed in more detail below.

Heterogenous catalytic systems

Amidst the growing demand for more sustainable and eco-friendly processes, the reusability and recyclability of catalysts have become increasingly important. Unlike homogeneous catalytic systems, heterogeneous catalysts are often easier to separate and reuse, and can even be employed in fixed bed flow reactors. Over the past 15 years, numerous heterogeneous catalytic systems have been developed for efficient and selective N-alkylations using aliphatic alcohols. The catalytically active species can be immobilized on inorganic carrier materials,[49] charcoal,[50] used directly as metal nanoparticles,[51] or coordinated with organic frameworks.[52]

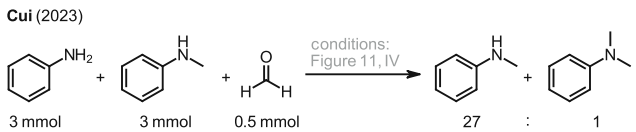


Scheme 12. Stability of potentially formed imine species in the catalytic N-alkylations of amines under nickel-catalysis by Medina & García.[48]

Immobilized metals on charcoal, such as Pd/C, are widely recognized as versatile catalysts for various hydrogenation reactions, including reductive amination, carbonyl reduction, and imine reduction, among others. It is logical to consider their potential application in N-alkylation using alcohols.

In 2019, the Natte research group introduced a protocol for mono-selective N-methylation, employing 10 mol% Pd/C and KO^{t}Bu in methanol at 130 °C[50a] (Figure 11, I). Their primary focus was on the N-methylation of nitroarenes using methanol as both C1 and H_2 source. Regarding the direct and mono-selective methylation of primary amines with methanol, only 4 examples were provided in yields between 91 % and 98 %.

However, in the same year, Guo, Hou, and co-workers expanded this limited scope to encompass a broader range of substrates[50c] (Figure 11, II). They utilized 2 mol% of Pd/C and 2 equiv. of NaO^{t}Bu at 150 °C to N-methylate 17 different aniline derivatives, achieving yields of up to 92% with 4 reactions performed on a gram scale. Again, no mono-selectivity is achieved for primary aliphatic amines.



Scheme 13. Mono-selectivity in the heterogenous Pd-catalyzed reaction of aniline by Cui applying a 1:1 mixture of mono- and bis-methylated aniline yielding primarily the mono-methylated species. [49h]

A similar catalytic system employing Pt/C, NaOH, and methanol at 150 °C for N-methylation of primary amines was reported by Siddiki, Shimizu and colleagues[50b] (Figure 11, III). In addition to achieving mono-N-methylation of primary aromatic amines (8 examples, 81 – 98 %), they successfully attained high mono-selectivity for primary aliphatic amines by applying an additional H_2 pressure of 40 bar (4 examples, 74 – 86 %).

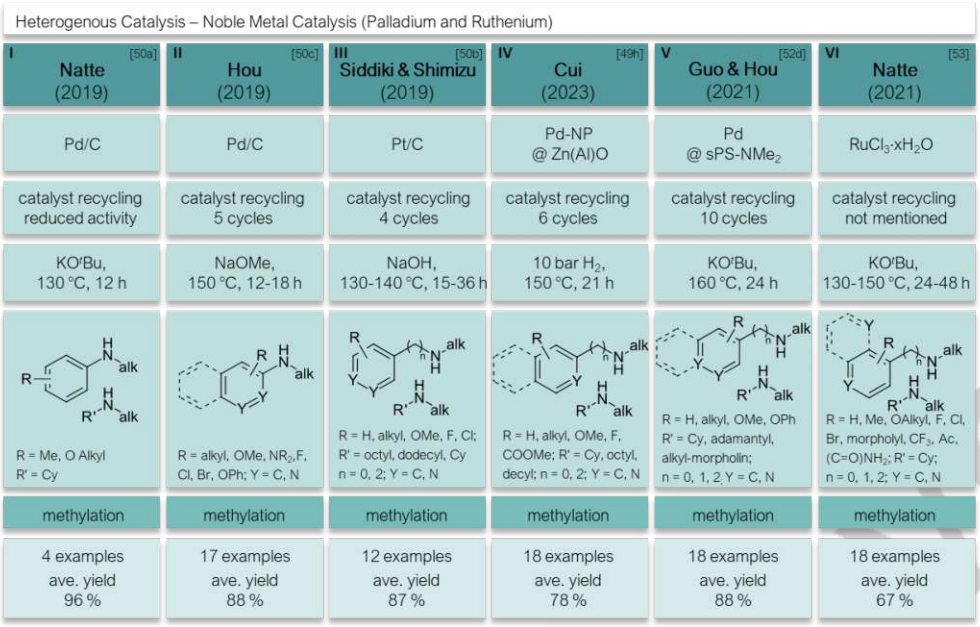
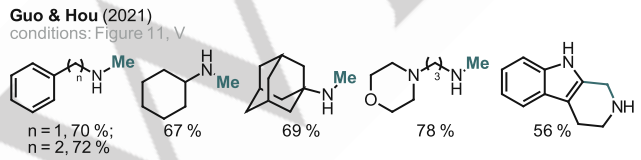


Figure 11. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under heterogenous noble metal catalysis.

Recently, the Cui research group introduced a series of heterogeneous Pd/Zn(Al)O catalysts, characterized by a Zn/Al ratio of 10:1[49h] (Figure 11, IV). These catalysts enabled the mono-selective N-methylation of primary aromatic and aliphatic amines using methanol. Importantly, this method required no additional base, as the inherent basic properties of the catalyst were sufficient to facilitate the formation of the desired amines. The authors also demonstrated the remarkable durability of their system by recycling the catalyst six times without any significant decrease in efficiency. Under an external H_2 pressure of 10 bar and a reaction temperature of 150 °C, they achieved the synthesis of several N-methylated aromatic and aliphatic secondary amines with yields ranging from 44% to 94%. The remarkable mono-selectivity of this system was demonstrated by a competitive reaction of a 1:1 mixture of aniline and N-methylaniline with formaldehyde yielding the mono- vs. bis-methylated product in a 27:1 ratio (Scheme 13).



Scheme 14. Scope of aliphatic primary amines in the N-methylation using a heterogenous Pd-nanoparticle catalyst by Guo & Hou.[52d]

In 2021, the Guo and Hou research group reported an outstanding mono-selectivity in heterogeneous Pd-catalyzed N-methylation of both aliphatic and aromatic amines, without the need for external hydrogen pressure[52d] (Figure 11, V). Their catalytic system involved Pd nanoparticles supported by syndiotactic polyaminostyrene (Pd@sPS-NMe_2), known for its high amine-adsorbing capacities. Additionally, the catalyst could be easily recovered by filtration and reused more than ten times without any loss of reactivity. They employed 2 equiv. of $NaOCH_3$ as the base and conducted the reaction at 150 °C for aromatic amines, yielding products with average yields exceeding 90%. For aliphatic amines, the reaction was carried out at 170 °C, achieving average yields greater than 70% (Scheme 14).

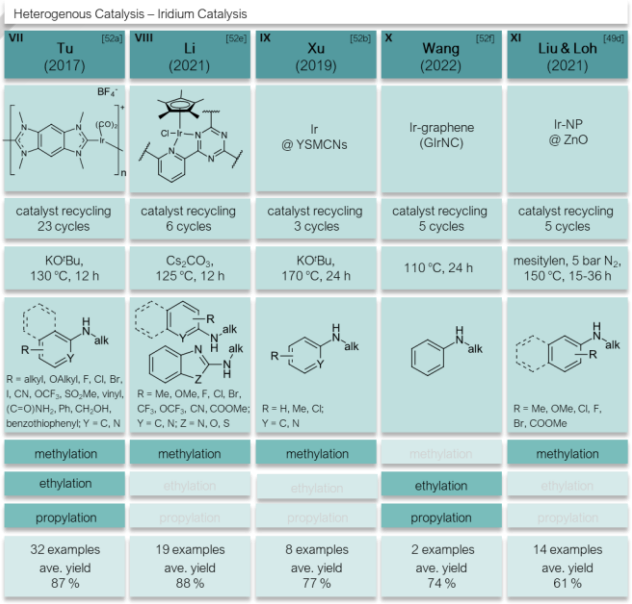
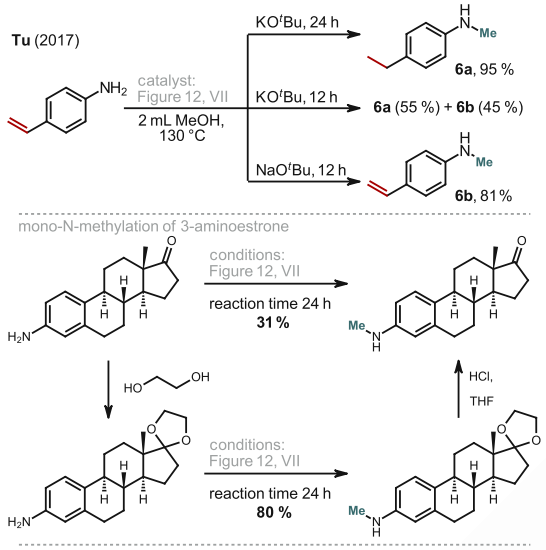


Figure 12. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under heterogenous iridium-catalysis.

In 2021, the Natte research group introduced an elegantly simple yet highly effective catalytic system for mono-N-methylation[53] (Figure 11, VI). They utilized relatively cheap and readily available

$RuCl_3 \cdot xH_2O$ as a ligand-free catalyst in the mono-selective N-methylations of primary amines. The reactions were carried out at 130-150 °C for 24-48 hours, employing KO^{t}Bu as the base in a sealed tube under ambient air conditions. This straightforward approach demonstrated its versatility, with a variety of aniline-derived substrates being successfully mono-methylated, yielding products with up to 94 %, and aliphatic primary amines achieving up to 77% yield. Upon completion of the reaction, the catalyst could be effortlessly removed *via* simple filtration.

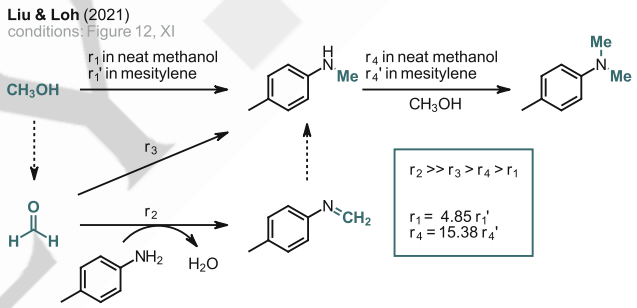


Scheme 15. Base and reaction time dependent selectivity in the *N*-methylation and vinyl reduction under heterogenous iridium-catalysis (top) and late-stage *N*-methylation by the group of Tu.[52a]

As previously mentioned, iridium stands out as a highly favored noble metal for catalytic hydrogen autotransfer reactions leading to N-C bond formation with alcohols. This trend is further reflected in the prominent presence of iridium in heterogenous catalysts for these reactions. A pioneering work in this field was made by the group of Tu in 2017[52a] (Figure 12, VII). They incorporated the active iridium metal into NHC coordination assemblies, obtaining a solid and easily prepared molecular catalyst. Impressively, this catalyst demonstrated recyclability and could be reused up to 20 times without a significant loss in reactivity. Operating with 0.5 mol% of the catalyst and 1 equiv. of KO^{t}Bu, they successfully achieved the mono-selective N-methylation of 29 different substrates derived from aniline at 130 °C within 12 hours. Interestingly, they observed that besides N-methylation, the double bond in 4-aminostyrene was reduced when using KO^{t}Bu as the base over a 24-hour reaction period. However, when they switched to NaO^{t}Bu as the base and reduced the reaction time to 12 hours, solely N-methylation occurred with the vinylic double bond being unreacted (Scheme 15, top). A remarkable demonstration of the method's applicability for late-stage modification of biologically active compounds, was the methylation of 3-aminoestrone in 31 % yield when the ketone moiety was present as a free ketone and an 80% yield when the ketone moiety was protected as an acetal (Scheme 15, bottom). Although N-ethylation and N-propylation were feasible, the yields were significantly lower, standing at 59 % and 29 %, respectively.

In 2021, Feng Li's group achieved the coordinative immobilization of catalytically active $[Cp^*IrCl_2]_2$ within a functionalized covalent triazine framework (CTF)[52e] (Figure 12, VIII). This catalyst proved to be highly efficient in the N-methylation of aromatic amines with methanol using a very mild Cs_2CO_3 base. Remarkably, the catalyst maintained its reactivity even after six consecutive recycles. Primary aromatic amines were readily methylated using only 0.5 mol% of the iridium-containing catalyst at 125 °C within a 12-hour reaction time, exclusively yielding *N*-mono-methylated products exceeding 80% yield. However, the same mono-selectivity was not observed for aliphatic amines, which resulted in the exclusive formation of di-methylated products.

The group of Xu in 2019 achieved further mono-N-alkylations of aromatic primary amines using an encapsulated Ir-nanocatalyst (Ir@YSMCNs) under basic conditions at 170 °C[52b] (Figure 12, IX). In contrast, Wang's team in 2022 utilized an iridium/graphene nanostructured catalyst under base-free conditions at 110 ° C, focusing on N-alkylations with higher carbon aldehydes (RCH_2CHO, $R \neq H$)[52f] (Figure 12, X). While the former group primarily concentrated on N-methylation, the latter group expanded the substrate scope, demonstrating successful N-ethylation and N-propylation with good yields.



Scheme 16. Kinetic studies for the mono- vs. bis-methylation of *p*-toluidine under heterogenous iridium-catalysis by Liu & Loh.[49d]

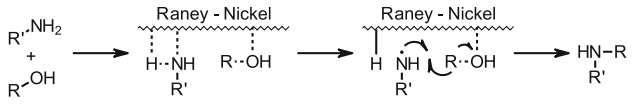
In 2021, Liu, Loh and co-workers developed a catalytic system featuring zinc oxide-supported iridium nanoparticles (Ir/ZnO)[49d] (Figure 12, XI). They fine-tuned the catalyst loading and reaction solvent to control the selectivity between mono- and bis-methylation of primary aromatic amines. Notably, higher catalyst loadings (2 mol% Ir) in neat methanol yielded *N,N*-dimethylated products, whereas using only 0.3 wt% Ir/ZnO (0.5 mol%) in mesitylene/methanol mixtures provided mono-N-methylated amines with moderate to good yields (48-83 %) at 150 °C and 5 bar N_2 pressure. Kinetic experiments were conducted to elucidate the solvent-dependent mono- vs. bis-methylation, and reaction rates for the individual steps were calculated (Scheme 16). The condensation between the *p*-toluidine and formaldehyde occurred rapidly, indicating a significantly higher rate compared to other involved steps in the reaction. Examining the initial reaction rates for each step revealed a decreasing order of $r_2 >> r_3 > r_4 > r_1$, with the activation of methanol (r_1) identified as the rate-determining step. Comparison of the initial reaction rates in neat methanol (r_1 and r_4) with those in mesitylene as the solvent (r_1' and r_4') suggested a significant reduction in the overall reactivity in the latter solvent system. Interestingly, the effective suppression of over-methylation of monomethyl amine hinted at mesitylene

potentially interfering with the active sites on the catalyst, thereby altering absorption and diffusion kinetics in this methylation reaction.

The ability to easily recover and reuse heterogeneous catalysts is a key factor in enhancing the sustainability of chemical processes. Furthermore, the substitution of precious metals with more readily available and cost-effective earth-abundant metals, like nickel, copper, or cobalt is a compelling goal.

García Ruano and colleagues introduced a well-established heterogeneous catalyst, Raney-nickel, for the purpose of mono-selective N-alkylations using alcohols, in 2009[51a] (Figure 13, XII). Their study demonstrated the successful ethylation, *n*-butylation, and *iso*-propylation of various aliphatic and aromatic primary amines, with yields reaching up to 86%. Remarkably, when methanol was used as the alkylating agent, no N-methylated products were observed. In-depth mechanistic investigations excluded a pathway involving hydrogen autotransfer and the formation of aldehyde intermediates. Instead, the authors proposed a pathway that entails radical intermediates, substantiated by the observation that the reaction was completely inhibited when TEMPO, a radical scavenger, was introduced (Scheme 17).

García Ruano (2009)
conditions: Figure 13, XII



Scheme 17. Proposed radical pathway in the N-alkylation of primary amines catalyzed with Raney-Nickel by García Ruano and co-workers.

In 2018, the Barta research group introduced a novel method utilizing in situ generated nickel nanoparticles (NiNP) from $Ni(cod)_2$ and KOH at 140 °C in cyclopentyl methyl ether (CPME)[51b] (Figure 13, XIII). The formation of NiNP as the catalytically active species was firmly substantiated through various control experiments and transmission electron microscopy (TEM). Mono-N-alkylation of aniline was successfully achieved with a range of aliphatic alcohols, yielding moderate results for N-methylation (38%) and more favourable results for N-ethylation (69%). The versatility of this method was exemplified through the N-butylation of 18 different primary amines, yielding products in the range of 25-86%. While the catalyst could be recycled, a gradual reduction in substrate conversion was observed over time.

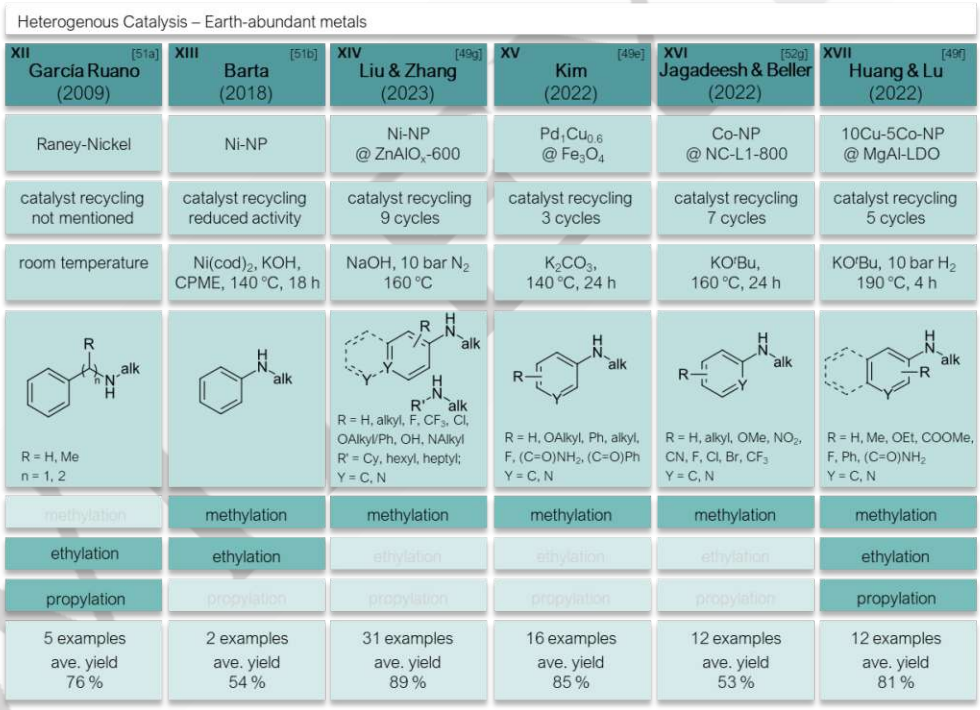
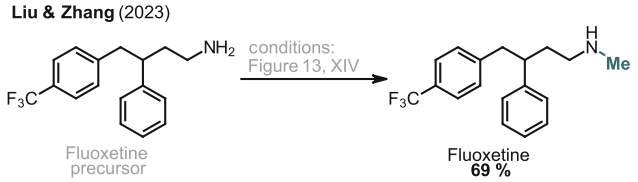


Figure 13. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under heterogenous earth-abundant metal-catalysis.

Furthermore, an innovative approach for N-methylation with methanol, employing ZnAlOx-600 supported NiNP, was recently developed by Liu, Zhang and co-worker[49g] (Figure 13, XIV). Notably, this method marked a significant advancement in Ni-catalyzed hydrogen autotransfer reactions. It not only enabled the mono-selective methylation of primary aromatic amines but also showed no undesired overalkylation with primary aliphatic amines. The reactions were conducted at 160 °C in methanol, with the addition of 25 mol % NaOH at a nitrogen pressure of 10 bar. The approach delivered an exceptionally high average isolated yield of 87% for 31 different primary amines. This methodology's remarkable effectiveness was exemplified in the final step of the synthesis of fluoxetine, a drug produced with 69% isolated yield (Scheme 18).

The Kim research group introduced a protocol for the selective N-methylation of aromatic amines using MeOH. They employed a

PdCu alloy (1:0.6 ratio) supported on Fe_3O_4, which exhibited superior catalytic activity compared to monometallic Pd and Cu catalysts[49e] (Figure 13 XV). This innovative catalyst enabled the mono-selective N-methylation of various primary aromatic amines at an average yield of 85% when using K_2CO_3 as a very mild base. A remarkable feature of this catalyst is its solid support with ferromagnetic properties, facilitating easy catalyst separation and recycling.



Scheme 18. Mono-selective N-methylation of a precursor in the final step of the synthesis of Fluoxetine under heterogenous nickel-nanoparticle catalysis by Liu, Zhang and co-workers. [49g]

In 2022, Jagadeesh, Beller and co-workers established a method for the mono-N-alkylation of amines and ammonia with alcohols, catalyzed by reusable Co-nanoparticles supported on *N*-doped carbon (Co@NC-L1-800)[52g] (Figure 13, XVI). The versatility of their new catalytic system was confirmed by N-alkylating over 100 substrates using different aromatic and aliphatic alcohols. Concerning short-chain, unbranched alcohols, they were able to selectively mono-methylate 11 different aromatic amines at 160 °C in methanol, albeit with moderate yields ranging from 24% to 67%.

In the same year, Huang, Lu, and their team developed a bimetallic catalytic system employing CuCo nanoparticles for mono-N-methylations[49f] (Figure 13, XVII). This innovative approach uses the support-dependent regulation of the degree of substitution by rationally integrating acid-base and metal sites. They obtained *N,N*-dimethylated products using Cu-Co on an Al_2O_3 support, while mono-*N*-methylated products were produced using Cu-Co on a Mg-Al layered double hydroxide (MgAl-LDO) support. Notably, no additional base was required for either system. They selectively mono-methylated a range of primary aromatic amines in MeOH at 190 °C and 10 bar H_2 pressure using 10Cu-5Co/MgAl-LDO, achieving yields of up to 95%. Remarkably, N-ethylation, N-propylation, and N-butylation were also feasible for aniline, yielding mono-alkylated products with 84-85% yields.

Heterogeneous metal-catalyzed N-alkylations with alcohols *via* hydrogen borrowing strategy usually necessitate high reaction temperatures, leading to high internal pressures. This often requires the use of specialized pressure equipment, such as autoclaves, which many small to medium-sized chemical labs lack. Therefore, finding new catalytic systems with comparable activity and performance at even lower temperatures and pressures is highly desirable. One alternative approach to provide the energy required for these reactions, even at room temperature, is the use of light irradiation. Remarkable efforts in photocatalytic mono-N-alkylations of amines with alcohols were made by Shiraishi et al. in 2013[49a] (Figure 14, XVIII). They employed a catalytic system that featured Pd nanoparticles immobilized on a photoactive TiO_2 surface in a defined ratio ($Pd_{0.3}/TiO_2$). Mechanistic investigations unveiled a tandem photocatalytic/catalytic process comprising three consecutive stages (Scheme 19). First, the alcohol is oxidized on the photoactivated TiO_2-surface (**7b**). Subsequently, the resulting aldehyde readily undergoes a condensation reaction with the amine (**7e**). Finally, the formed imine is reduced by surface hydrogen atoms on the Pd-surface (**7f**). These reactions were conducted at room temperature in the respective alcoholic solvent at 1 bar N_2 pressure under base-free conditions with $\lambda > 300$ nm. While the work presented only two examples of N-alkylation with short-chain alcohols, specifically N-ethylation (95% yield) and N-butylation (91% yield) of aniline, it highlighted the potential of photocatalysis in these catalytic systems. Similar approaches were used by the Shi research group in 2015[49b] (Figure 14, XIX), employing a Cu-Mo/TiO_2 catalyst, and the Naka research group in 2018[49c] (Figure 14, XX) using Cu/TiO_2 and Au/TiO_2 mixed systems. In both protocols, mono-selectivity in N-alkylation of primary amines was only observed for some higher alcohols (RCH_2OH, R ≠ H, CH_3). Remarkably, the latter protocol by Naka's group allowed for a solvent-controlled selectivity of the mono- vs. bis-alkylated products. For α-methyl benzylamine and undecylamine, mono-selective N-ethylation and N-propylation could be achieved when hexane was used as solvent for the reaction. In contrast, when the reactions were performed in alcoholic solvent, the *N,N*-bis-alkylated products were obtained exclusively.

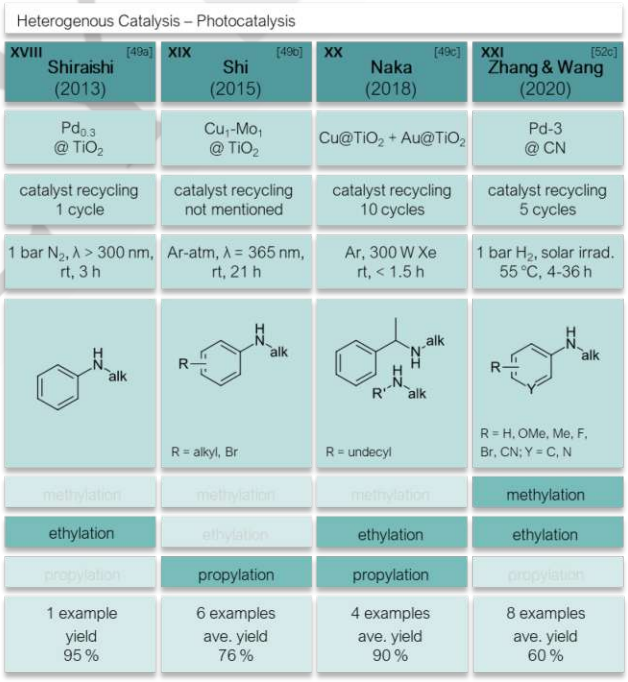
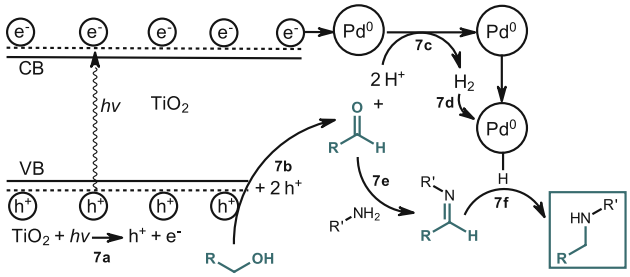


Figure 14. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under heterogenous earth-abundant metal-catalysis.

A more general photocatalytic approach for the mono-selective N-methylation of primary anilines was established by Zhang, Wang, and Gao in 2020[52c] (Figure 14, XXI). They used a Pd loaded mesoporous carbonitride (mpCN) based Mott-Schottky catalyst with a palladium to CN ratio of 3:1 (Pd-3@CN). The authors demonstrated that the primary oxidation zones of the catalyst were located at the CN, promoting aldehyde formation, while Pd nanoparticles were the primary reduction sites. Under 1 bar H_2 pressure and visible light irradiation (300 W Xenon lamp), several

primary aromatic amines could be methylated with methanol in yields up to 99 %. Mono-selectivity, however, could not be guaranteed for every substrate used within the protocol, as some para-substituted ones predominantly formed *N,N*-dimethylated products. Notably, aniline could be mono-selectively ethylated and butylated under the given reaction conditions with ethanol or *n*-butanol as the solvent.

Shiraishi (2013)



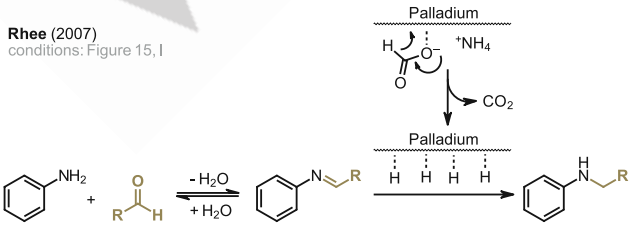
Scheme 19. Mechanism for the photocatalytic N-methylation of amines using a heterogenous TiO_2/Pd catalytic system by Shirashi *et al.* (VB = valence band; CB = conduction band)[49a]

Considering the recent progress in photocatalytic systems for N-alkylation reactions with alcohols, there is still room for improvement, especially regarding mono-selectivity when using primary aromatic and aliphatic amines. Nevertheless, these novel photocatalytic approaches offer remarkable user-friendliness and align with evolving environmental standards.

2.2. Aldehydes

The Eschweiler-Clarke reaction, a method for alkylating amines with aldehydes, has a long history in organic synthesis. However, recent developments have introduced advanced methods using aldehydes as efficient alkylating agents. These modern approaches place a strong emphasis on achieving high mono-selectivity in the alkylation of primary amines.

In 2007, the group of Rhee disclosed an innovative protocol for the reductive mono-N-alkylation of anilines using aldehydes[54] (Figure 15, I). Their method relied on a Pd/C catalyst and ammonium formate as the hydrogen source in aqueous alcoholic media (*i*-PrOH/H_2O 10:1) at room temperature (Scheme 20). While the use of formaldehyde yielded mono-N-methylated products in moderate yields (≤ 50%), the aldehydes ethanal and propanal exhibited exceptional reactivity, resulting in excellent yields exceeding 90%. Notably, the catalyst demonstrated impressive recyclability, maintaining its activity for up to 10 cycles without a significant decrease in performance.



Scheme 20. Proposed mechanistic pathway for the mono-N-alkylation of amines with aldehydes under Pd-catalysis by Rhee and co-workers.[54]

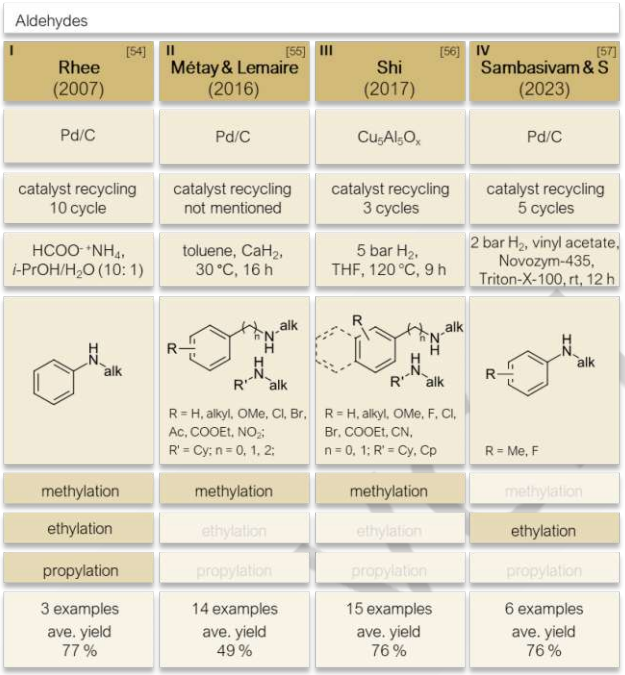


Figure 15. Methods for mono-selective N-alkylation of amines using aldehydes as alkylating agents.

In 2016, Métay, Lemaire and colleagues established a protocol which expanded the so far narrow scope for mono-N-methylation using aldehydes and, besides aryl amines, also including primary aliphatic amines[55] (Figure 15, II). In this protocol CaH_2 served as the hydrogen source, giving access to a variety of methylated amines in moderate yields (11-80 %).

Motivated by the achievements of Métay and Lemaire in the field of atom-efficient catalysis, Shi's research group endeavored to create a cost-effective and highly efficient catalytic system, with a particular focus on its potential for industrial applications[56] (Figure 15, III). Their groundbreaking protocol, developed in 2017, harnessed the atom-economical reductant H_2 under a moderate pressure of 5 bars, in conjunction with $CuAlO_x$ as a remarkably active catalyst. These reactions took place in THF at 120 °C, performing mono-selective methylation of various aromatic and aliphatic amines with good to excellent yield, using paraformaldehyde as C1 source. Notably, the authors speculated that the active species in this catalytic system might even be pure metallic copper.

In the realm of chemoenzymatic processes, an unconventional yet promising strategy for aldehyde formation and subsequent selective N-alkylation of primary amines was recently published by Ganesh, Sambasivam, and S[57] (Figure 15, IV). In this process, acetaldehyde is formed in situ from vinyl acetate, facilitated by Candida antartica Lipase-B (CALB)/Novozyme-435. Subsequently, this acetaldehyde undergoes reductive amination. Notably, this method is distinguished by its exceptionally mild reaction conditions, conducted at only 2 bars of H_2 pressure and at room temperature. The reduction of the imine is catalyzed by Pd/C. This methodology has been demonstrated to achieve mono-N-ethylation for six different aniline derivatives in up to 85 % yield, and while isopropylation is also feasible, it falls beyond the scope of this review.

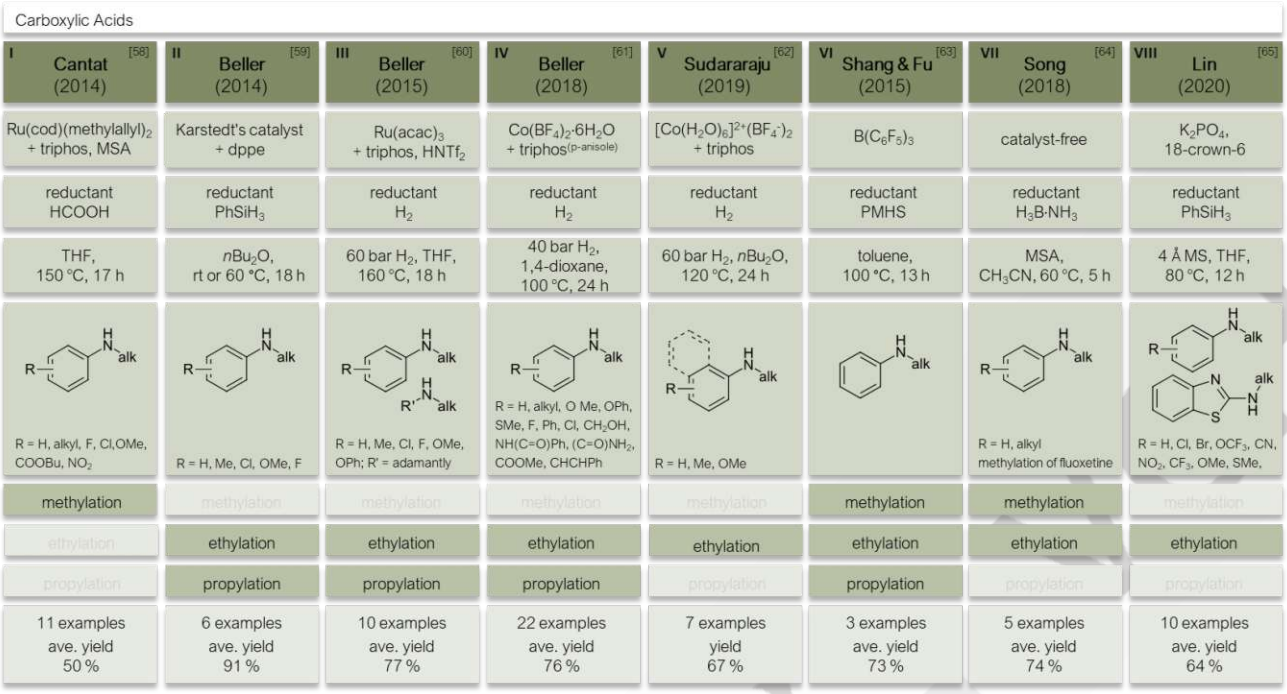


Figure 16. Methods for mono-selective N-alkylation of amines using carboxylic acids as alkylating agents.

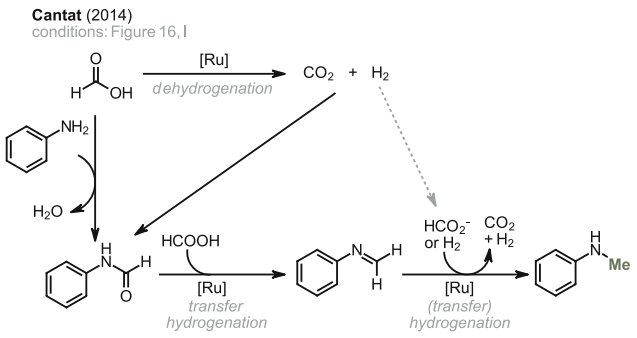
2.3. Carboxylic Acids

Carboxylic acids, due to their industrial-scale production and non-toxic nature, have the potential to serve as valuable alternatives in alkylation reactions. However, applying them in amine alkylation typically demands high temperature and pressure conditions, making them more suitable for large-scale industrial applications than small-scale laboratory setups.

In 2014, Cantat's group introduced a groundbreaking method for the direct methylation of amines using formic acid, which not only served as the carbon source but also as the hydrogen source[58] (Figure 16, I and Scheme 21 for catalytic pathway). Their catalytic system featured Ru(cod)(methylallyl)$_2$ (1 mol%) and triphos (1 mol%) in THF at 150 °C within a sealed autoclave. Importantly, distinct additives enabled control over the selectivity between mono- and bis-methylation of aniline. When adding 1.5 mol% methane sulfonic acid (MSA) a variety of mono-methylated aniline derivatives were obtained with up to 71 % yield. For the synthesis of tertiary amines HNTf$_2$ was employed as the additive.

In the same year, the group of Beller disclosed a different protocol, using higher carboxylic acids in the N-alkylation of primary amines[59] (Figure 16, II). Through systematic optimization, they identified optimal conditions for mono-selective alkylation, using commercially available Karstedt's catalyst ([Pt(CH$_2$=CHSiMe$_2$)$_2$O]) with dppe as the ligand in a 1:1 ratio. Astonishingly, this reaction could be performed at 60 °C or even at room temperature, yielding a variety of mono-alkylated aniline derivatives with up to 97% yield and exceptional mono-selectivity. However, a major drawback was the use of over-stoichiometric amounts of PhSiH$_3$ as the reducing agent.

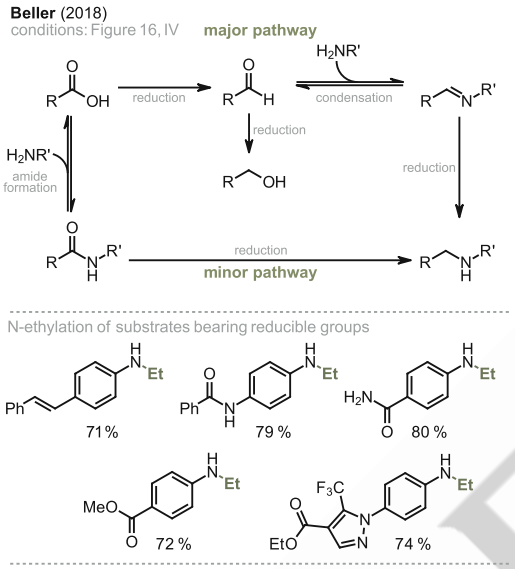
To address this limitation, the same group reported a more sustainable approach using H$_2$ as the reducing agent for amine alkylation with carboxylic acids. (RCOOH with R≠H)[60] (Figure 16, III). Ru(acac)$_3$ (2 mol%) and triphos (3 mol%) were identified as an efficient catalytic system for the reaction. The degree of alkylation (mono- vs. di-alkylation) was dependent on the amount of the additive HNTf$_2$ used. When 7.5 mol% of the additive was used, the di-alkylated product was obtained almost exclusively, while using only 2 mol% allowed for the mono-selective alkylation of various primary amines with excellent yields. However, the high temperature (160 °C) and pressure (60 bar H$_2$) required for this reaction necessitate a specialized setup.



Scheme 21. Proposed catalytic pathway for the mono-N-methylation of primary amines using formic acid as alkylating agent under ruthenium catalysis by the group of Cantat.[58]

Subsequent refinements by the Beller group introduced a protocol for alkylation of anilines under milder conditions, employing a tailored Co-catalyst, thus eliminating the need for expensive noble

metals[61] (Figure 16, IV and Scheme 22 (top) for catalytic pathway). This method also eliminated the use of air-sensitive additives such as $HNTf_2$. A wide range of anilines could be selectively mono-N-ethylated using $Co(BF_4)_2{\cdot}6H_2O$ (3 mol%) as catalyst and triphos(*p*-anisole) as ligand (6 mol%) in dioxane at 40 bar H_2 pressure and 100 °C. However, the method may not ensure mono-selectivity when using formic acid for methylation, as only secondary amines were used in this reaction. However, it is noteworthy that mono-N-ethylation and -propylation were successfully accomplished for a variety of primary aryl amines. Remarkably, substrates containing reducible groups, including amides, esters, or vinylic double bonds, could be selectively ethylated while preserving the integrity of these functional groups (Scheme 22, bottom).

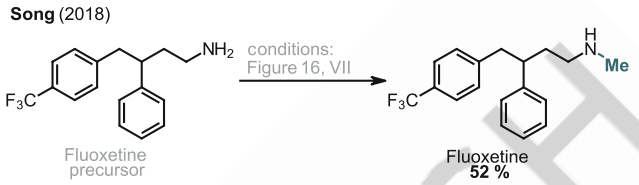


Scheme 22. Proposed catalytic pathway for the mono-N-methylation of primary amines using carboxylic acids as alkylating agent under cobalt catalysis (top) and the mono-selective N-ethylation of primary amines bearing reducible functional groups (bottom) by the group of Beller.[61]

A very similar protocol, using a $Co(BF_4)_2{\cdot}6H_2O$/triphos catalytic system at 60 bar H_2 and 120 °C, was reported by the group of Sundararaju in 2019[62] (Figure 16, V). The scope for mono-ethylation encompasses seven aniline derived substrates with moderate yields.

The first mono-selective transition-metal free N-alkylation using carboxylic acids as the alkylating agent was published in 2015 by Shang, Fu, and colleagues employing air-sensitive Lewis-acid $B(C_6F_5)_3$ as the catalyst and an excess of polymethylhydrosiloxane (PMHS) as reducing agent at 100 °C in *n*-Bu_2O[63] (Figure 16, VI). Mono-*N*-methylated aniline was obtained in a moderate yield of 62%, while the ethylation, trifluoroethylation, and propylation of primary anilines proceeded smoothly, yielding up to 81%.

In 2018, Song's group introduced a transition-metal-free approach using stoichiometric ammonia borane ($BH_3{\cdot}NH_3$) as the reductant and methane sulfonic acid (MSA) for the alkylation of various aniline derivatives[64] (Figure 16, VII). Under these conditions, aniline underwent mono-methylation with a yield of 81%. Furthermore, mono-ethylation of aniline and two of its derivatives was achieved with remarkable success, affording the product in 84% yield, all at a significantly lower reaction temperature of 60 °C compared to previously reported methods. A noteworthy accomplishment was the successful mono-methylation of the bioactive compound Fluoxetine, with an isolated yield of 52% (Scheme 23).



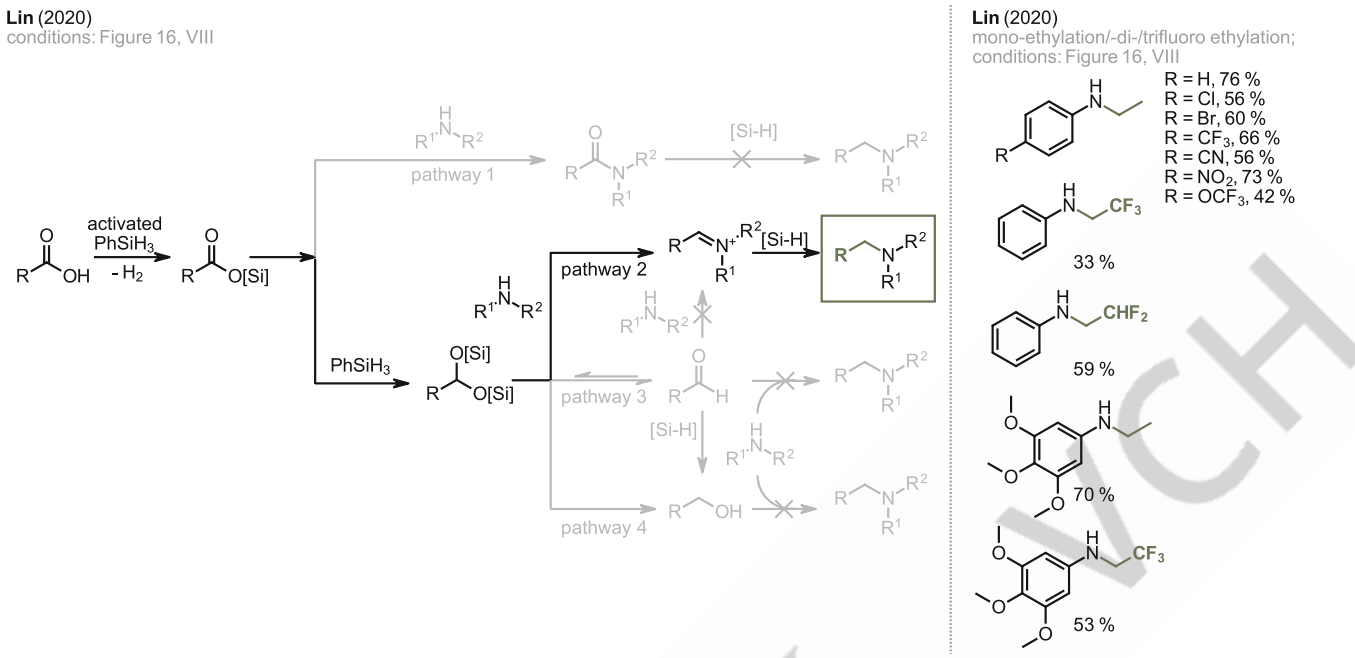
Scheme 23. Mono-selective N-methylation of a precursor in the final step of the synthesis of Fluoxetine using formic acid as methylating agent under catalyst-free conditions by Song and co-workers.[64]

A groundbreaking protocol for the reductive alkylation of primary amines using carboxylic acids was introduced by the group of Lin in 2020[65] (Figure 16, VIII). Their outstanding protocol features an air-tolerant and easy-to-handle transition-metal-free catalytic system. Phenylsilane was applied as super-stoichiometric reductant and K_2PO_4 (10 mol%) in combination with 18-crown-6 (20 mol%) was identified as an efficient catalytic system in THF at 80 °C with small amounts of molecular sieves added. This protocol achieved mono-N-ethylation, -di-, and -trifluoroethylation in moderate to good yields, up to 76%, for various aromatic primary amines (Scheme 24, bottom). The authors could prove that the reaction pathway diverged from common catalytic pathways, which directly alkylate amines using carboxylic acids and proceed *via* the reduction of a previously formed amide. Theyidentified a distinct pathway via the formation of a silyl acetal/hemiacetal, subsequent formation of an iminium intermediate and the reduction thereof (Scheme 24, top).

2.4. Carbon Dioxide

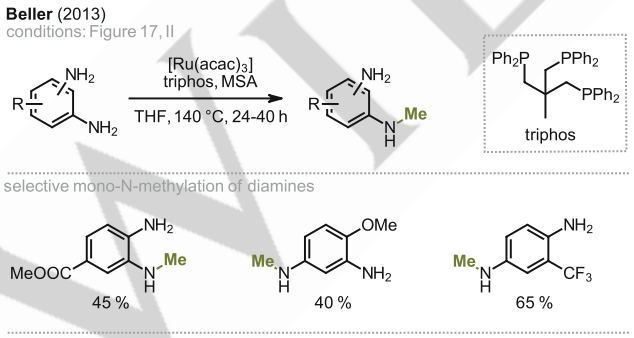
The utilization of carbon dioxide (CO_2) as an abundant and cost-effective source of C1 for the synthesis of fine chemicals has gained significant attention over recent decades. Particularly in the face of growing concerns about greenhouse gas emissions, the ability to capture and employ CO_2 in the production of high-value chemicals has become increasingly desirable. However, catalytic activation of CO_2 for a defined incorporation into molecules can be a very challenging task, driving ongoing research efforts.

In 2013, Cantat's group achieved a significant breakthrough by pioneering the use of CO_2 as a C1 source in a mono-selective N-methylation reaction[66] (Figure 17, I). They employed $IPrZnCl_2$ as the catalyst and $PhSiH_3$ as the reducing agent. This innovative approach enabled the N-methylation of several primary aryl amines at 100 °C and 1 bar CO_2 pressure within 20 hours in moderate yields. Intriguingly, with an extended reaction time of 72 hours, aniline could be selectively *N,N*-dimethylated with a yield of 79%.



Scheme 24. Proposed reaction pathway in the mono-selective N-alkylation of amines using carboxylic acids as alkylating agents and phenyl silane as reducing agent *via* the formation of a silyl acetal/hemiacetal, subsequent formation of an iminium intermediate and the reduction thereof (left) and mono-N-ethylation, -di-, and -trifluoro ethylation of aniline derivatives (right) by Lin and co-workers.[65]

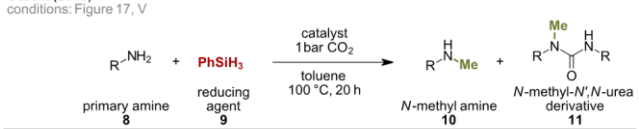
The same year, the group of Beller reported the utilization of ruthenium(III) acetylacetonate [Ru(acac)$_3$], in combination with the triphos ligand and methanesulfonic acid (MSA) as an additive, for the successful methylation of various aryl amines[67] (Figure 17, II). This method encompassed a broad scope for the methylation of secondary aryl amines and remarkably achieved mono-N-methylation for seven *para*-substituted anilines (13 - 90 % yield), three aryl diamines (40 - 65% yield, Scheme 25) and two *ortho*-substituted anilines (70 and 85 % yield) at 140 °C in THF, under 60 bars of H_2 pressure and 20 bars of CO_2 pressure.

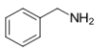
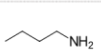
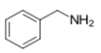
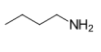


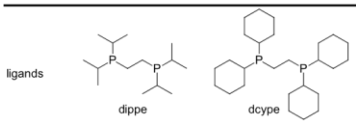
Scheme 25. Selective mono-N-methylation of various substituted diamines using carbon dioxide as the alkylating agent under ruthenium catalysis by Beller and co-workers.[67]

Just a year later, in 2014, Shi and co-workers introduced two analogous strategies for achieving mono-selective N-methylation using heterogeneous catalysts in combination with molecular hydrogen and CO_2. Their first protocol featured a $CuAlO_x$ catalyst, allowing control over the degree of methylation in primary amines through variations in reaction time and H_2 pressure. Notably, a reaction time of 48 h at 70 bar H_2 pressure led to bis-methylated amines, while a shorter reaction time of 24 h at 60 bars H_2 exclusively furnished the mono-*N*-methylated products[68] (Figure 17, III). Their subsequent method employed a Pd/$ZrCuO_x$ catalyst, demonstrating mono-selectivity for a divers variety of aryl amines at lower CO_2 and H_2 pressures of 10 bar and 25 bar, respectively[69] (Figure 17, IV).

García (2015)
conditions: Figure 17, V



entry	8	9 (equiv.)	catalyst	10 (%)	11 (%)
1		2	[(dippe)Ni(μ-H)]$_2$	11	80
			[Ni(cod)$_2$]/dcype	6	82
2		2	[(dippe)Ni(μ-H)]$_2$	9	42
			[Ni(cod)$_2$]/dcype	15	36
3		4	[(dippe)Ni(μ-H)]$_2$	66	22
			[Ni(cod)$_2$]/dcype	64	27
4		4	[(dippe)Ni(μ-H)]$_2$	45	15
			[Ni(cod)$_2$]/dcype	49	27



Scheme 26. Methylation of primary amines using carbon dioxide as alkylating agent under nickel-catalysis and the crucial role of the reducing agent for controlling the degree of substitution by García and co-workers.[70]

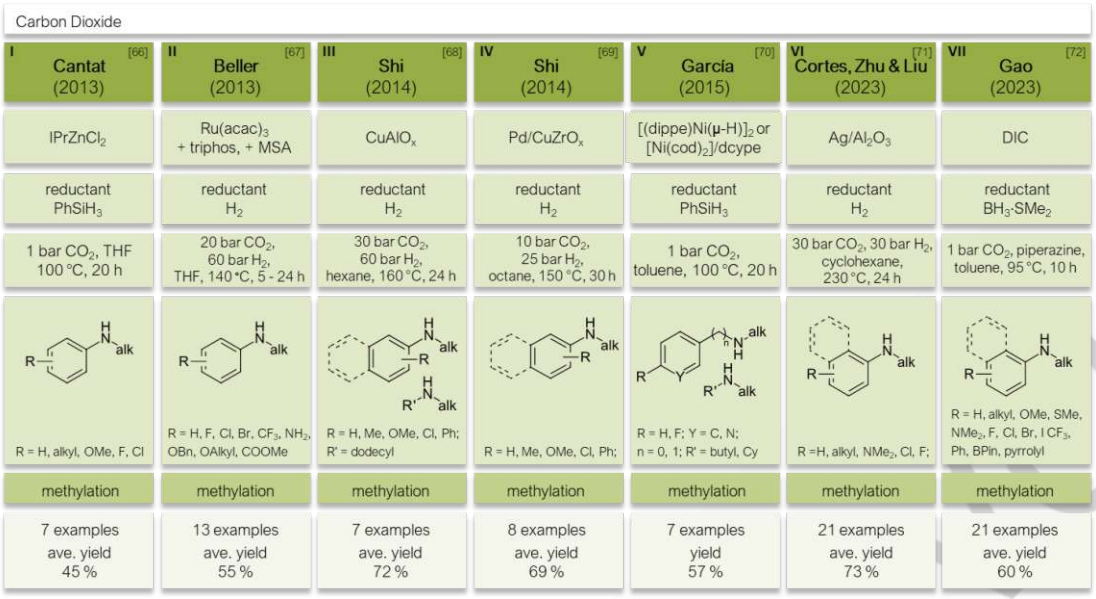
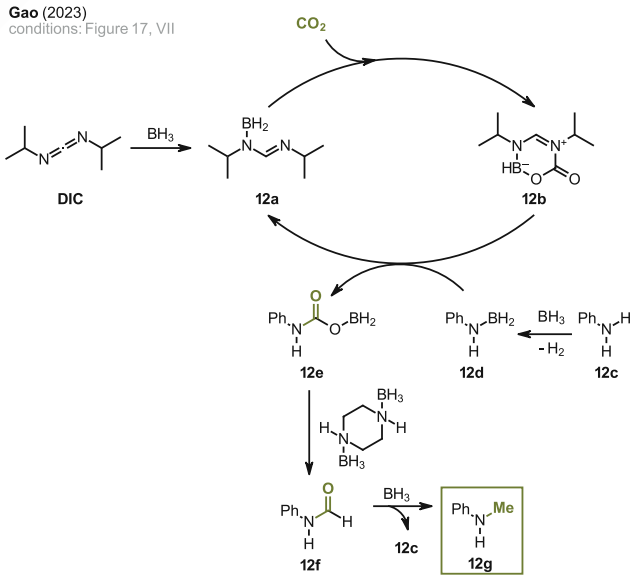


Figure 17. Methods for mono-selective N-alkylation of amines using carbon dioxide as alkylating agent.

A methylation protocol working at a remarkably low CO_2 pressure (1 atm) was disclosed by the group of Garcia in 2015[70] (Figure 17, V). The reaction was catalyzed by either $[(dippe)Ni(\mu\text{-}H)]_2$ or $[Ni(cod)_2]$/dcype (Scheme 26, bottom), which exhibited comparable performance, while $PhSiH_3$ served as the reductant. This innovative method enabled the mono-methylation of various primary aromatic and aliphatic amines in toluene at 100 °C, giving moderate product yields and selectivity. The use of four equivalents of the reducing agent was pivotal for obtaining the desired *N*-methylated products, as fewer equivalents resulted almost exclusively in *N*-methyl-*N'*,*N*-urea derivatives (Scheme 26, top).

Recently, Cortes, Zhu, Liu, and co-workers introduced a highly selective protocol for the mono-N-methylation of aniline derivatives using CO_2/H_2 as a C1 source, employing a supported Ag/Al_2O_3 catalyst[71] (Figure 17, VI). The remarkable mono-selectivity was achieved through the reversible binding of the protonated hydrogen, formed upon heterolytic dissociation of H_2 on the Ag surface, to the mono-*N*-methylated amine, thereby reducing its reactivity. A range of primary aryl amines could be methylated at 30 bars CO_2 and H_2 pressure each at 230 °C in yields up to 98 %.

Gao's group recently reported a metal-free protocol for N-methylation at a remarkably low CO_2 pressure of just 1 atm.[72] The reaction was catalyzed by *N,N'*-diisopropylcarbodiimide (DIC), with borane-trimethylamine and borane-piperazine complexes serving as the reducing agents to obtain either *N,N*-dimethylated or *N*-monomethylated products, respectively. Mechanistic insights propose the following sequence (Scheme 27): Initially, DIC undergoes hydroboration, generating an active species **2a** capable of forming a cyclic, zwitterionic intermediate through the intermolecular frustrated Lewis pair capture of CO_2 **(12b)**. A previously formed amino borane species **12d** subsequently reacts with **12b** to yield the carbamoyl borate **12e**, concurrently releasing the catalytic frustrated Lewis pair species **12a**. This species undergoes reduction by a borane-piperazine complex to form anilide **12f**, believed to be the rate-determining step. Subsequent reduction leads to the formation of the desired mono-N-methylated product **12g** and aniline **12c**. Presumably, the sterically congested interaction between the borane-piperazine complex and *N*-methyl aniline impedes a second reaction of the mono-methylated product with CO_2. Various primary aryl amines were mono-methylated in toluene at 95 °C in moderate yields ranging from 31-71 %.



Scheme 27. Proposed catalytic pathway for the mono-selective methylation of primary amines using carbon dioxide as alkylating agent catalyzed by *N,N'*-diisopropylcarbodiimine (DIC) with a borane-piperazine complex serving as the reducing agent by Gao an co-workers.[72]

2.5. Dialkyl Carbonates

Alkylations using dialkyl carbonates are considered as environmentally benign processes, releasing alcohol and CO_2 as the sole byproducts. These reagents offer affordability, wide availability, biodegradability, and nontoxicity. However, given their relatively lower reactivity compared to alkyl halides, catalytic activation becomes a necessity.

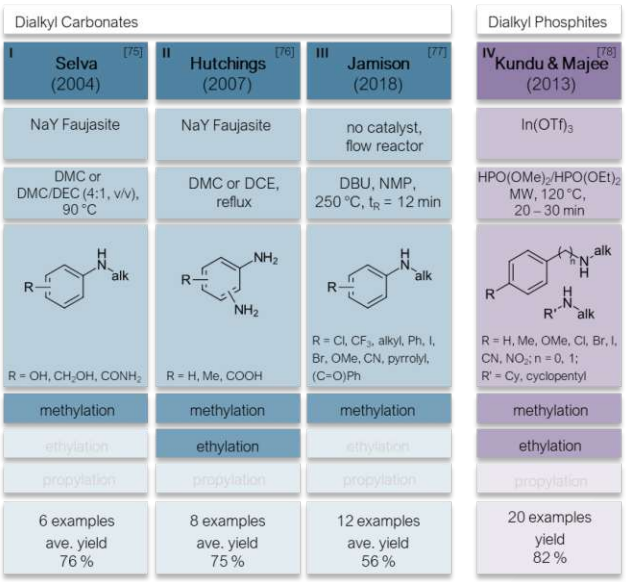
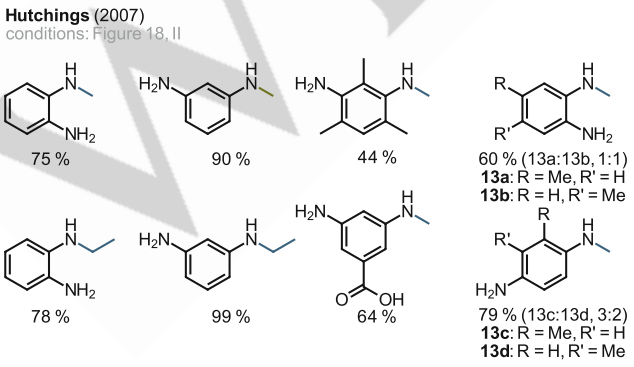


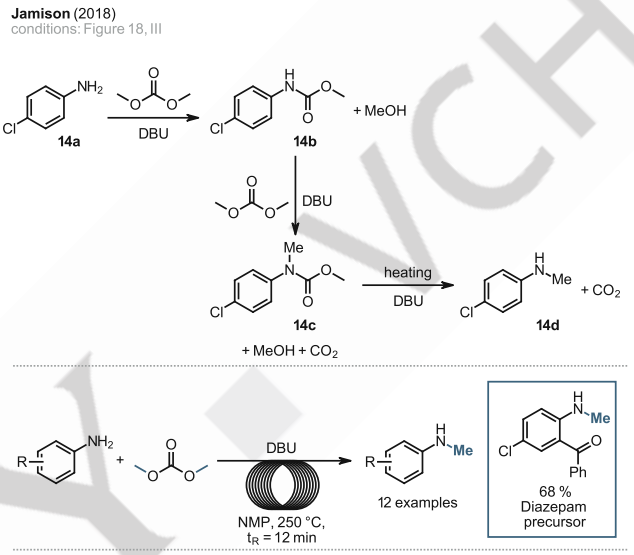
Figure 18. Methods for mono-selective N-alkylation of amines using dialkyl carbonates (I-III) and dialkyl phosphites (IV) as alkylating agent

Pioneering works by Fu and Ono[73], Tundo[74], later extended by Selva *et al.*[75], employed zeolite-type catalysts (NaY faujasite). These reports by Selva and colleagues enabled the mono-selective methylation of various primary aromatic amines at 90 °C, using dimethyl carbonate both as the solvent and C1 source, giving quantitative yields with complete mono-selectivity (Figure 18, I). Notably, several aniline-derived substrates bearing free hydroxy, amide, or carboxylic acid groups were selectively N-methylated at the amine moiety while leaving the other functional groups unaltered.



Scheme 28. Mono-selective alkylation of symmetrical and asymmetrical aryl diamines using dialkyl carbonates as alkylating agent under NaY Faujasite catalysis by Hutchings and co-workers.[76]

A similar approach using NaY zeolites and dialkyl carbonates as alkylating agents was presented in 2007 by Hutchings and co-workers, expanding the scope of previous research to arylenediamines[76] (Figure 18, II). Remarkably, under reflux conditions with the respective dialkyl carbonate as a solvent, outstanding selectivity was achieved for symmetrically substituted starting materials, yielding up to quantitative yields. For non-symmetric aryldiamines, mixtures of isomers were obtained, yet with a high degree of mono-selectivity for N-alkylation (Scheme 28).



Scheme 29. Mono-N-methylations in a flow reactor setup (bottom) *via* an *in situ* protection/deprotection approach using dimethyl carbonate as methylating agent (top) and the application in the methylation of a Diazepam precursor (bottom right) by the group of Jamison.[77]

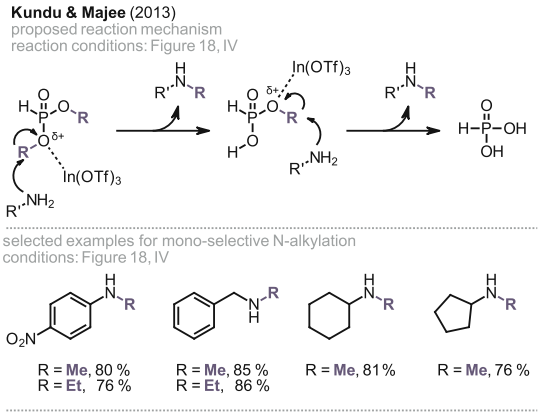
In 2018, Jamison's group introduced a modern approach to mono-N-methylation using a continuous flow setup that enabled safe reactions in superheated solvents (250 °C) under high pressure (7 bars), regulated through a backpressure control unit employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base[77] (Figure 18, III). The exceptional mono-selectivity observed in this methylation reaction is attributed to an *in situ* protection/deprotection sequence outlined in Scheme 29. Initially, the DMC forms a carbamate with the amine moiety (**14b**), facilitating a single methylation (**14c**). Subsequently, the carbamate undergoes thermal decarboxylation, ultimately yielding the desired mono-N-methylated product (**14d**). This innovative technique successfully transformed various primary aryl amides into their *N*-methyl derivatives with yields reaching up to 96%. Remarkably, this protocol enabled the synthesis of a key precursor for diazepam, specifically 5-chloro-2-(methylamino)benzophenone, in 68% yield.

2.6. Dialkyl Phosphites

In 2013, Kundu, Mitra, and Majee introduced a groundbreaking method employing dialkylphosphites as alternative alkylating agents for achieving mono-selective N-alkylation reactions of primary amines, catalyzed by indium triflate ($In(OTf)_3$).[78] The real innovation emerged when microwave irradiation was utilized to

facilitate heating under neat conditions for just 30 minutes at 120 °C, significantly enhancing mono-selectivity.

This approach demonstrated exceptional atom efficiency in alkyl transfer from the dialkyl phosphite to the amine, requiring a mere 0.6 equivalents of the alkylating agent (Scheme 30, top). This allowed for the mono-selective N-methylation and N-ethylation of a wide range of para-substituted anilines, benzylamine, and even primary aliphatic amines, such as cyclopentyl- and cyclohexylamine (Scheme 30, bottom). Impressively, this method gave high product yields, ranging from 65% to 91%.



Scheme 30. Proposed reaction mechanism for the mono-selective N-alkylation of primary amines using dialkyl phosphites under $In(OTf)_3$ catalysis (top) and selected examples (bottom) by Kundu and Majee.[78]

2.7. MeX

For decades, alkyl halides, particularly methyl iodide, have served as versatile alkylating agents for a wide array of *O-, C-,* and *N*-nucleophiles. However, controlling the degree of alkylation when using MeX with primary amines has been exceedingly challenging.

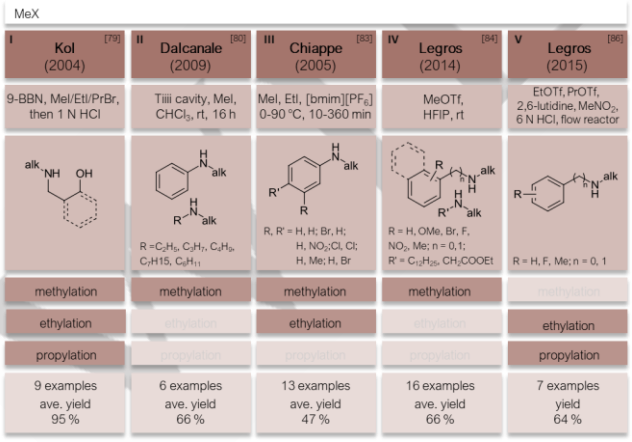
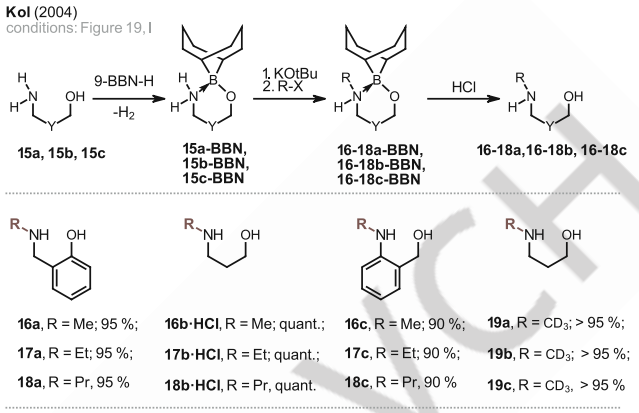


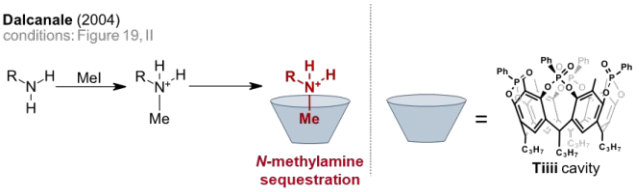
Figure 19. Methods for mono-selective N-alkylation of amines using alkyl halides or alkyl triflates as alkylating agents.

A strategy exploited by Bar-Haim and Kol in 2004, was harnessing the formation of a stable chelate complex between an γ-amino alcohol and 9-BBN[79] (Figure 19, I). The oxygen is herein covalently bound to the boron, the nitrogen in turn coordinates to the boron (Scheme 31, top). This coordination prevents an overalkylation of the nitrogen, giving solely the mono-*N*-alkylated products with the respective alkyl halides after acidic workup in over 90 % which was demonstrated for 3 different amino alcohols (Scheme 31, bottom).



Scheme 31. Mono-selective N-alkylation via the formation of a stable borane complex intermediate (top) and scope of thereof by Kol and Bar-Harim. [79]

In 2009, Yebeutchou and Dalcanale presented a distinct approach to "block" the nitrogen from undergoing further alkylation[80] (Figure 19, II). They employed a tetrabridged phosphorylated cavitand in its **iiii** configuration (**Tiiii**), known for its exceptionally high affinity for *N*-methyl ammonium salts (Scheme 32, right).[81] By an efficient sequestration of the mono-methylated intermediate further bis-methylation is hampered, leading to highly mono-selective methylation of five different aliphatic amines and aniline (Scheme 32, left). Excellent isolated yields of up to 87% were achieved using methyl iodide as the alkylating agent. However, it's worth noting that this approach may not be suitable for achieving mono-selectivity with longer alkyl groups.

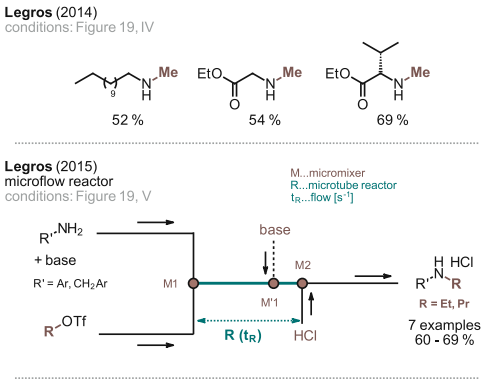


Scheme 32. Sequestration of mono-N-methylated amines (left) by a tetrabridged phosphorylated cavitand in its **iiii** configuration **(Tiiii)** (right) by Dalcanale.[80]

Building on earlier research that explored the manipulation of solute nucleophilicity with room temperature ionic liquids (IL),[82] Chiappe *et al.* introduced a protocol for the synthesis of various mono-*N*-alkylated anilines using the ionic liquid [bmim][PF_6][83] (Figure 19, III). This method yielded mono-*N*-methylated products with moderate yields of up to 60 % and mono-*N*-ethylated products with yields up to 77%.

In 2014, the Legros group made a significant discovery, finding exceptional mono-selectivity for N-methylation using MeOTf when hexafluoroisopropenol (HFIP) was employed as the reaction solvent[84] (Figure 19, IV). Their reasoning was based on previous

observations that HFIP deactivated secondary and tertiary amines but not primary amines.[85] This conclusion led them to predict that alkylation would occur in a mono-selective manner. Subsequently, they demonstrated the mono-methylation and mono-ethylation of a wide range of primary amines, achieving yields of up to 96% with the respective alkyl triflate, all at room temperature (Scheme 33, top).



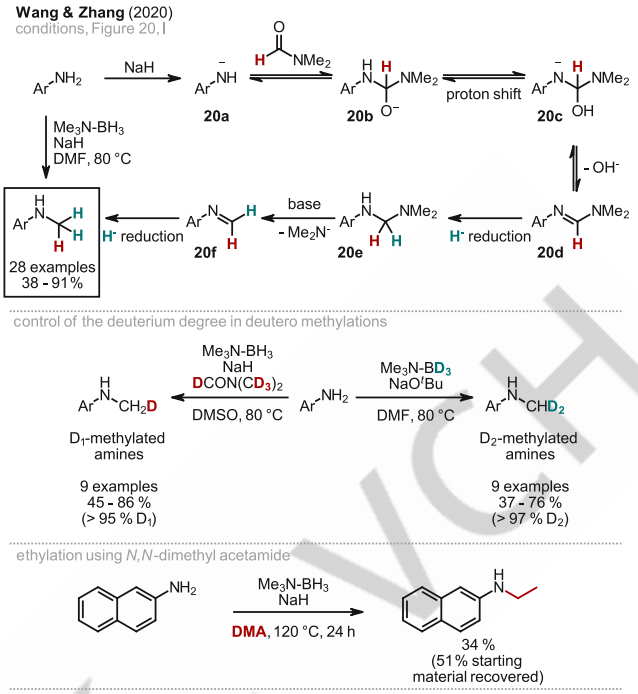
Scheme 33. Selected examples for the mono-selective N-alkylation of primary amines using alkyl triflates as alkylating agents and HFIP as reaction solvent (top) and the application of this methodology in a microflow reactor setup (bottom) by the group of Legros.[84, 86]

Furthermore, in a follow-up report, the same group optimized the reaction conditions for a flow microreactor system, expanding the scope to include mono-N-ethylations and mono-N-propylations[86] (Figure 19, V and Scheme 33, bottom).

2.8. *N,N*-Dialkyl Formamides

N,N-Dimethyl formamide (DMF) is an abundant, cheap and easy-to-handle chemical, which to date found ample utilization in various areas of organic syntheses. It is frequently used as solvent in chemical transformations, however, its application in organic synthesis additionally comprises its utilization as catalyst, stabilizer, and reagent.[87]

In 2020, the group of Wang and Zhang disclosed a protocol for a catalyst-free mono-selective methylation, and deutero-methylation using a Me_3N-BH_3/DMF system or respective deuterated analogue[88] (Figure 20, I). Their mechanistic findings could proof that the newly attached methyl group is formed by the donation of a carbon and one hydrogen atom from the formyl group of DMF, and two hydrogen atoms from the amino borane (R_3N-BH_3) (Scheme 34, top). The reaction was performed in DMF as both reagent and solvent and using NaH as the base at 80 °C. A very broad range of substrates were amenable to this approach giving the desired mono-N-methylated products in yields up to 91 %. The authors could show on one example that this approach might be also suitable for ethylation using the respective *N,N*-dimethylacetamide, however with a moderate yield of 34 % (Scheme 34, bottom). Remarkably, this approach can give access to the controlled formation of N-CH_2D, N-CHD_2, and N-CD_3 anilines by using Me_3N-BH_3/d_7-DMF, Me_3N-BD_3/DMF, and Me_3N-BD_3/d_7-DMF systems with an outstandingly efficient deuterium incorporation (>95 %) (Scheme 34, middle).



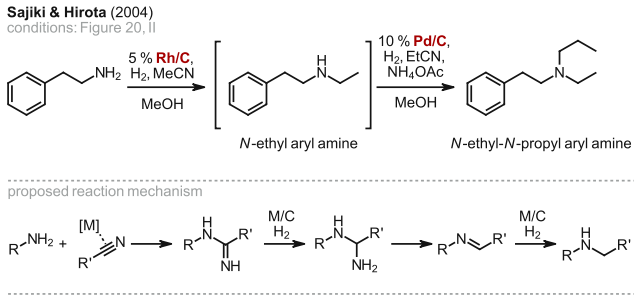
Scheme 34. Proposed reaction mechanism for the mono-selective N-methylation of primary amines using *N,N*-dimethyl formamide (DMF) as alkylating agent (top) and control of the degree of deuterium incorporation using deuterated borane and deuterated DMF (middle) and the N-ethylation using *N,N*-dimethyl acetamide by Wang and Zhang (bottom).[88]

2.9. Nitriles

Nitriles, known for their versatility and cost-effectiveness, have emerged as sustainable alkylating agents with the added environmental benefit of forming ammonia as the sole byproduct. This unique attribute positions nitriles as intriguing candidates for achieving mono-selective N-alkylation of primary amines.
To date, established strategies for mono-selective N-alkylations predominantly rely on noble metal catalysts like Pd or Rh under reducing conditions. In these reactions short and linear nitriles (RCN, R = alkyl) can be successfully applied as alkylating agents for ethylation, propylation, and butylation, respectively. However, none of these protocols allowed for methylation, presumably due to the strong coordination of $^-$CN to the catalyst, leading to blockage.[89] Additionally, the consistent observation of lower yields in alkylations with non-distilled nitriles underscores the evident necessity for prior reagent purification.

In 2004, Sajiki, Ikawa, and Hirota published a pioneering work on the mono-N-alkylation of primary aromatic and aliphatic amines with nitriles using Pd/C or Rh/C with H_2 as the reducing agent in methanol at room temperature[90] (Figure 20, II and Scheme 35, bottom for proposed reaction mechanism). Notably, the Pd/C catalyst exhibited remarkable mono-selectivity in the alkylation of anilines, yet it converted aliphatic amines quantitatively into dialkylated tertiary amines. In contrast, a transition to Rh/C exclusively furnished the desired mono-alkylated products. The combination of these two approaches offers a pathway to bis-alkylated amines, incorporating two alkyl groups with different chain lengths (Scheme 35, top). The protocol demonstrated successful ethylation, propylation, and butylation of a variety of

aromatic amines and undecylamine with high yields and outstanding mono-selectivity. In 2012, the same group further advanced their work, employing Pd/C or Rh/C catalysts in the reductive alkylation of primary amines with nitriles, significantly expanding the scope, particularly for aliphatic amines[89] (Figure 20, II).



Scheme 35. Strategy for the controlled N,N-dialkylation by sequential mono-alkylation of a primary amine using Rh/C catalysis and subsequent alkylation of the secondary amine by Pd/C catalysis (top) and proposed reaction mechanism for the mono-selective N-alkylation under metal catalysis using nitriles as alkylating agents (bottom) by Sajiki and Hirota.[90]

Hudson's group presented a similar protocol in 2005, using Pd/C and ammonium formate as the hydrogen source in aqueous methanol at room temperature for the alkylation of primary aromatic amines[91] (Figure 20, III). While achieving high mono-selectivity in the ethylation, propylation, and butylation of primary aromatic amines, the range of functional group substituents was somewhat limited to aniline, toluidines, anisidines, and cyclohexylamine.

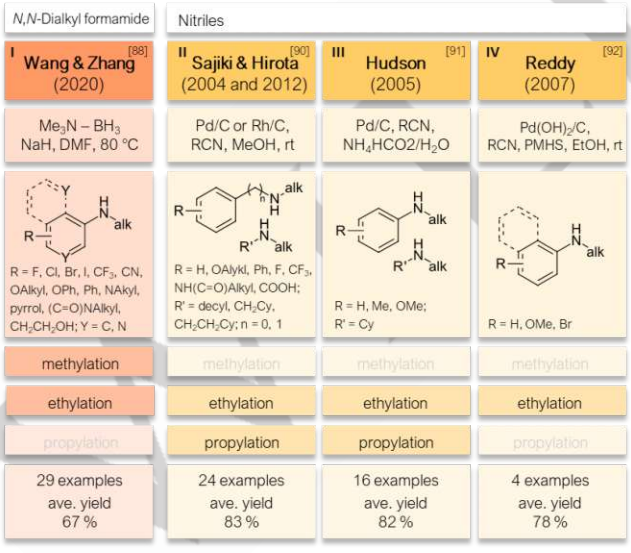


Figure 20. Methods for mono-selective N-alkylation of amines using *N,N*-dialkyl formamides (I) or nitriles (II-IV) as alkylating agents.

In 2007, Reddy et al. discovered the efficiency of polymethylhydrosiloxane (PMHS) as a reducing agent in $Pd(OH)_2$/C-catalyzed reductive N-alkylation of primary aryl amines using acetonitrile[92] (Figure 20, IV). However, with only four examples for mono-N-ethylation the scope waslittle investigated in terms of short-chain aliphatic alkylation.

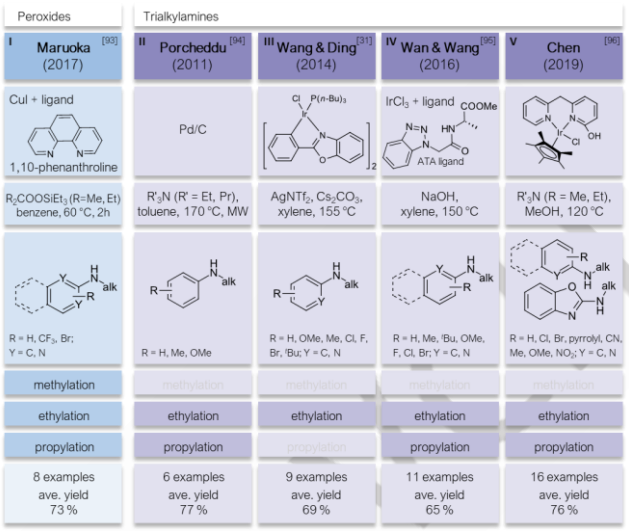


Figure 21. Methods for mono-selective N-alkylation of amines using peroxides (I) or trialkyl amines (II-V) as alkylating agents.

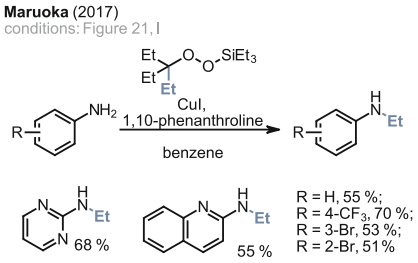
The exclusive use of noble metal catalysts in mono-selective N-alkylation using nitriles underscores the potential for further investigations to identify sustainable catalytic systems featuring earth-abundant metals.

2.10. Peroxides

The utilization of alkylsilyl peroxides as mono-selective N-alkylating agents will be further explored in the amide alkylation section, as their application in this transformation is more prevalent (Section 3 Amides).
However, in 2017, the Maruoka's group included primary aryl amines in the scope of their protocol for the mono-selective N-alkylation of primary amides and arylamides[93] (Figure 21, I). Employing CuI as an affordable and readily available catalyst, along with 1,10-phenanthroline or its derivatives as ligands, they efficiently generated alkyl radicals from alkylsilyl peroxides. This method allowed for the selective mono-ethylation of a limited selection of primary aryl amines in benzene at 50-80 °C, yielding the desired secondary amines with moderate maximum yields of 70% (Scheme 36).

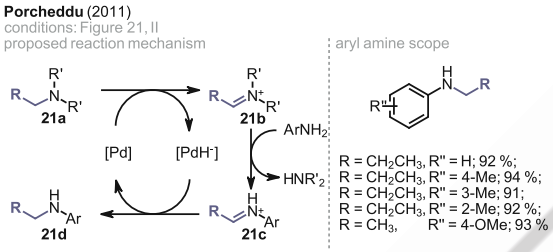
2.11 Trialkylamines

Similar to alcohols, alkylamines can engage in metal-catalyzed borrowing hydrogen reactions, generating an intermediate imine species susceptible to attack by a second amine (Scheme 37, left). However, hydrogen autotransfer reactions of amines remain less explored compared to their alcohol counterparts. Nonetheless, these net transalkylation reactions offer a valuable alternative pathway for synthesizing secondary and tertiary amines.



Scheme 36. Selected examples for the mono-selective N-ethylation using peroxides as alkylating agents by Maruoka and co-workers. [93]

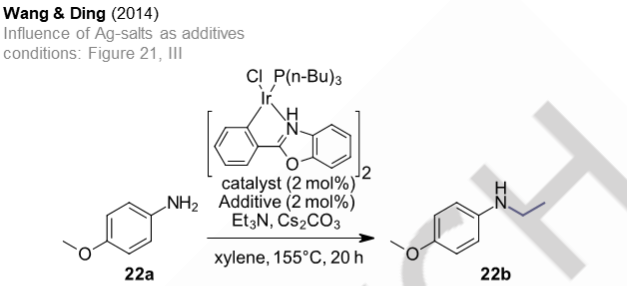
In a pioneering study in 2011, Porcheddu's group introduced the alkylation of primary aryl amines using heterogeneous Pd/C as a catalyst and tertiary amines ($(RCH_2)_3N$ with $R \neq H$)) in toluene under microwave irradiation[94] (Figure 21, II). The method allowed for mono-selective ethylation and propylation of various primary aryl amines, yielding desired products in up to 96 % (Scheme 37, right).



Scheme 37. Proposed reaction mechanism for the mono-selective N-alkylation of primary amines using trialkyl amines as the alkylating agent under palladium catalysis (left) and selected examples for N-alkylation by Porcheddu and co-workers. [94]

Wang, Ding and co-workers developed a versatile bisbenzoxazoyl iridium(III) complex designed for catalyzing hydrogen autotransfer reactions with both alcohols and tertiary amines[31] (Figure 21, III). They observed a substantial increase in yield when applying phosphine ligands and adding silver salts (e.g., $AgNTf_2$) to form an ionic complex in situ with increased activity (Scheme 38). Under mildly basic conditions (Cs_2CO_3) in xylene at 155 °C, several aryl amines underwent mono-selective ethylation using triethylamine, with yields ranging from 57% to 85%. In a subsequent study in 2016, the same group reported an Ir-based catalytic system with improved stability for the N-ethylation of primary aryl amines with triethylamine[95] (Figure 21, IV). This protocol featured $IrCl_3$ and a novel alanine triazole (ATA) ligand, employing NaOH as the base in xylene at 150 °C, resulting in mono-ethylated products with a maximum yield of 79 %.

In 2019, Chen's group explored various bidentate iridium catalysts for the selective mono-N-alkylation of primary amines with trialkyl amines[96] (Figure 21, V). The exceptionally stable catalyst, active even under ambient conditions, facilitated alkylations in the presence of air. The reaction proceeded without the need for an additional base, and the use of the hydrochloric salt of the alkylating amine further enhanced the process. Despite employing methanol as the reaction solvent, hydrogen autotransfer occurred exclusively with tertiary amines, and no N-methylation by methanol was observed under the specified reaction conditions. A great range of substituted aryl amines could be mono-ethylated and -propylated in high average yields at 120 °C within 12 h reaction time.



entry	additive	Yield **22b** [%]
1	-	36
2	AgOTf	69
3	$AgBF_4$	61
4	$AgSbF_6$	73
5	$AgPF_6$	75
6	$AgNTf_2$	81

Scheme 38. Influence of silver salts as additives in iridium-catalyzed mono-selective N-ethylation of primary aryl amines using trialkyl amines as alkylating agents by Wang and Ding.[31]

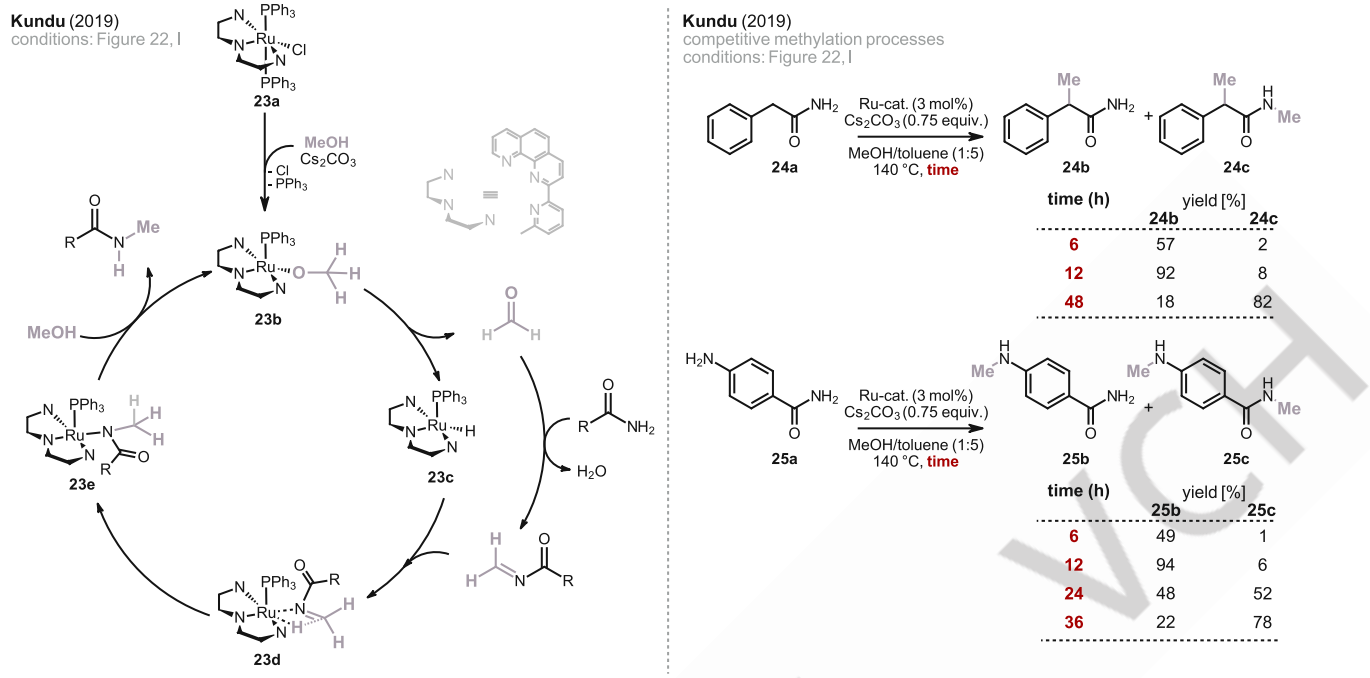
3. Amides

Amides display a fundamental structural motif in pharmaceuticals and various biologically relevant compounds. The distinctive structure of the amide group imparts crucial characteristics influencing molecular stability and interactions within biological systems.[97]

A frequently used approach for manipulating amides is through strategic N-alkylation, involving the introduction of short alkyl chains such as methyl, ethyl, or propyl.[3d] This tailored modification enhances the chemical diversity of amide-containing compounds, offering a nuanced approach to modulate their biological properties.[98] The consequences of N-alkylation can be far-reaching, influencing essential factors like solubility, lipophilicity, and overall bioavailability. As a result, the exploration of methods for amide N-alkylation emerges as a pivotal strategy for fine-tuning the properties of bioactive compounds like proteins, opening new possibilities for therapeutic applications in drug discovery and design.[99]

3.1. Alcohols

The use of alcohols as mono-selective N-alkylating agents for amines *via* a metal-catalyzed borrowing hydrogen approach is well studied (Section 2 Amines, alcohols). In contrast, only a few protocols report the use of short-chain aliphatic alcohols for the selective N-alkylation of primary amides.



Scheme 39. Proposed catalytic circle for the mono-selective N-methylation of primary aryl amides under ruthenium catalysis using alcohols as the alkylating agent (left) and time-dependent benzylic and amine methylation vs. amide methylation by Kundu and co-workers.[100]

In 2019, the group of Kundu disclosed a pioneering protocol using methanol as the C1-soure in a ruthenium (II)-catalyzed N-methylation of amides[100] (Figure 22, I). Their catalytic system featured a ruthenium-pincer complex and substoichiometric amounts of Cs_2CO_3 as the base at 140 °C in a mixed solvent system (methanol/toluene, 1:5). Remarkably, aromatic as well as aliphatic primary amides could be selectively mono-methylated in yields up to 93 %. When using phenylacetamide derivatives, however, the benzylic position was readily methylated as well, with still obtaining mono-selectivity for the nitrogen. Furthermore, NH_2 substituents on the aryl moiety underwent swift mono-methylation, and with prolonged reaction times, mono-methylation extended to the amide nitrogen. (Scheme 39, right). Extensive DFT calculations strongly suggested a pathway operating according to known hydrogen autotransfer systems (Scheme 39, left) with three main steps being dehydration of methanol **(23b→23c)**, N-methyleneamide insertion in the metal hydride complex **(23d)**, and finally, alcoholysis to release the final product **(23e→23b)**.

Three years later the same group reported an additional protocol for mono-selective N-methylation of amides with methanol and a distinct catalytic system[101] (Figure 22, II). In situ generation of an active cobalt complex obtained by combination of $CoBr_2$ and PP_3 (Scheme 10) facilitated N-methylation under basic conditions (Cs_2CO_3) at 140 °C in a 1:1 solvent mixture of MeOH/*m*-xylene. Interestingly, control experiments identified active cobalt(I) hydride [Co^I-H] as an active species, strongly suggesting its involvement in this catalytic hydrogen autotransfer process. Primary aromatic as well as aliphatic amides were readily methylated with high yields with three examples performed on a gram scale.

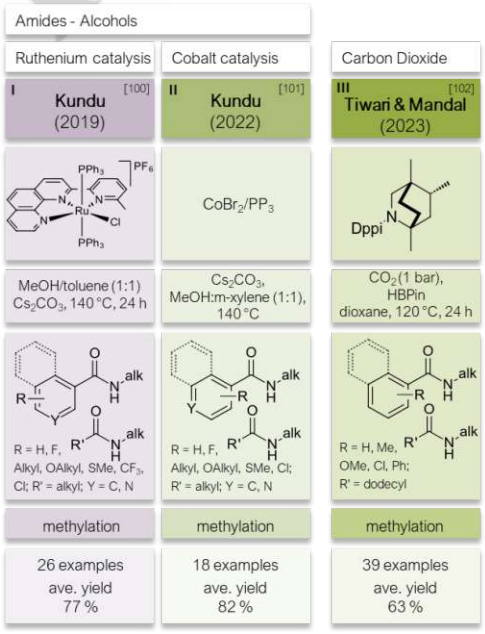
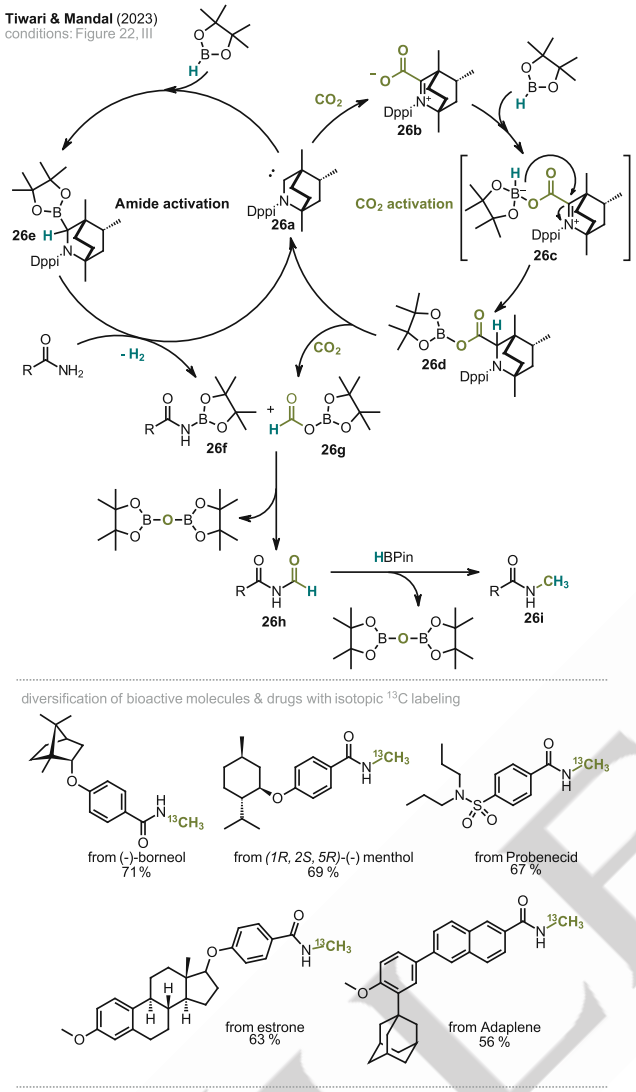


Figure 22. Methods for mono-selective N-alkylation of amides using alcohols (I-II) or carbon dioxide (III) as alkylating agents.

3.2. Carbon Dioxide

Very recently, Tiwari, Mandal and co-workers were the first to report a protocol for the catalytic methylation of primary amides using CO_2[102] (Figure 22, III). Both reactants are activated by a bicyclic (alkyl)(amino)carbene (BICAAC) having high σ-donating

and π-accepting properties. The reaction was performed in dioxane at 140 °C with an atmospheric pressure of CO_2 and 4 equivalents of pinacolborane (HBpin) as reducing agent.



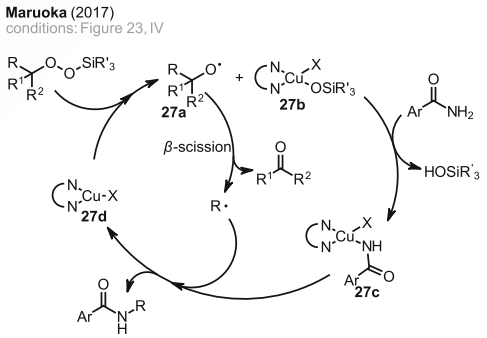
Scheme 40. Proposed reaction mechanism for the mono-selective N-methylation of primary amides using carbon dioxide as the methylating agent and the dual activation of carbon dioxide and the amide by bicyclic(alkyl)(amino)carbene (BICAAC, **A**) (top) and the application of the method for the diversification of bioactive molecules and drugs by ^{13}C-methylations (bottom) by Tiwari and co-workers. [102]

Several control experiments and DFT calculations strongly suggest a catalytic pathway operating by dual activation of the amide as well as CO_2 (Scheme 40, top). The amide activation commences *via* the activation of the pinacole borane by BICAAC **26a**. A BICAAC B-H intermediate **26e** is formed, which subsequently activates the amide *via* N-H bond borylation **(26f)** upon hydride formation and regeneration of the catalyst **26a**. On the other hand, CO_2 is activated by forming a zwitterionic adduct (BICAAC-CO_2, **26b**) which in the following reacts with the pinacolborane and undergoes a hydride transfer **(26c)** to finally liberate boron formate **26g** and regenerate the catalytic species **26a**. In the end, both activated species, the *N*-borylated amide **26f** and the boron formate **26g**, undergo formyl transfer, forming $(Bpin)_2O$ as the byproduct and an *N*-formylated product **26h**. The latter species is eventually undergoing hydroboration at the carbonyl center, generating the *N*-methylated amide **26i**. Considering this mechanistic pathway, it is clear that 4 equivalents of the pinacolborane as reducing agent are crucial.

A variety of primary aromatic, heterocyclic, and aliphatic amides readily underwent mono-N-methylation, giving the desired products in yields between 37 and 77 %. The potential applicability of this protocol in the late-stage functionalization of biologically active compounds was demonstrated in the diversification of bioactive molecules and selected drugs. Borneol, menthol, and estrone could be selectively N-methylated in up to 71 % yield. Examples for late-stage modification of drug molecules include the N-methylation of Probenecid, Adapalene, and Tocopherol. Remarkably, ^{13}C isotope labelling of these biologically important molecules could be realized using $^{13}CO_2$ (Scheme 40, bottom).

3.3. Peroxides

In the last decade, several protocols for N-methylation using different peroxides have been reported. The reaction usually proceeds *via* metal catalyzed alkyl radical formation (Scheme 41): Initially, an alkoxy radical is formed, which upon *β*-scission eventually forms an alkyl radical and the corresponding ketone from the tertiary alkoxide.[103] The amide coordinates after ligand exchange to the metal center and subsequently the alkyl radical is inducing reductive elimination of the desired N-methylated amides or sulfonamides (Section 4.2).



Scheme 41. Proposed radical reaction mechanism for the mono-selective N-alkylation of primary amides using peroxides as the alkylating agents by Marouka and co-workers.[103]

Several years later, in 2017, Li and Cai reported two protocols using di-*tert*-butyl peroxides or *tert*-butyl perbenzoate (TBPB) as methyl radical precursor[105] (Figure 23, II and III, and Scheme 42, top for peroxides). Their first method relied on $Ni(OTf)_2$ in a HOAc/water mixture[105a] whereas the following protocol featured $Fe(acac)_2$ as metal catalyst and potassium persulfate ($K_2S_2O_8$) as an additive in chlorobenzene as solvent.[105b] Both reactions operated at 120 °C. A selection of primary aryl amides and for the Ni-catalyzed protocol even primary aliphatic amides, were N-methylated mono-selectively in synthetically useful yields up to 70 %. These two methods were also applicable for the N-methylation of sulfonamides and are described as such below (Section 4.2).

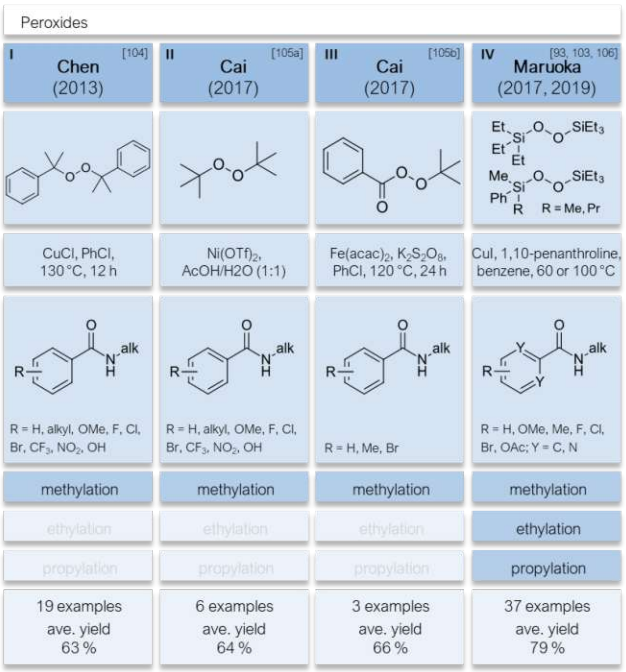
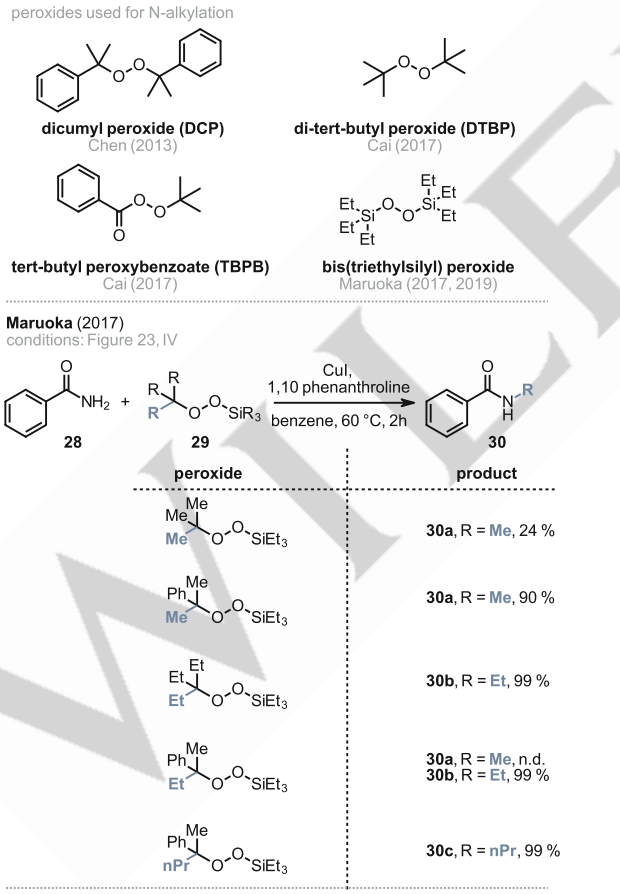


Figure 23. Methods for mono-selective N-alkylation of amides using peroxides as alkylating agents.

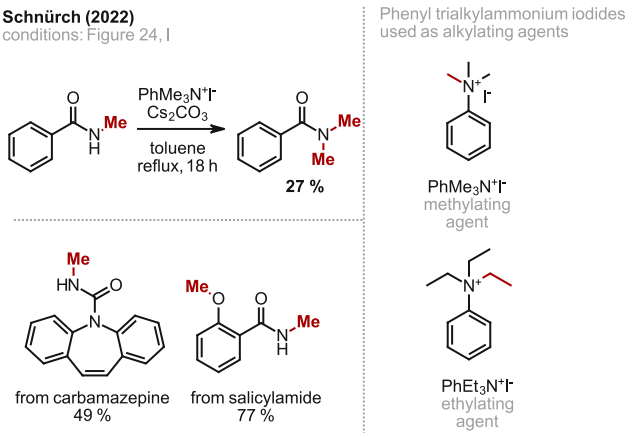


Scheme 42. Peroxides used in the mono-selective N-alkylation of primary amides (top) and the peroxide dependent alkyl transfer enabling controlled N-methylation, N-ethylation, or N-propylation by Marouka.

From 2017 to 2019, the group of Maruoka disclosed several different protocols for efficient N-alkylation of various primary amides and thus broadened the scope that was so far limited to methylation[93, 103, 106] (Figure 23, IV). Ethylation could be realized using either bis(triethylsilyl) peroxide (Scheme 42, top) or related peroxides, which formed the respective alkyl radicals with the catalytic system featuring CuI and 1,10-phenanthroline in benzene as solvent. Several primary aromatic, heteroaromatic and aliphatic amides readily underwent N-ethylation in moderate to quantitative yields. Notably, N-methylation or N-propylation were feasible using dimethyl phenyl or methyl *n*-propyl phenyl peroxides (Scheme 42, bottom).

3.4. Quaternary Ammonium Salts

Using quaternary ammonium salts as alkylating agent displays a distinct advantage, especially in comparison to traditionally applied short-chain alkylating agents like alkyl halides or dialkylsulfates: the nontoxic and solid nature of these salts makes them easy-to-handle and their application entirely safe.[107] Recently, our group investigated the use of trialkyl ammonium salts as highly mono-selective methylating and ethylating agents, respectively, in a catalyst-free protocol.[108] Trimethyl and triethyl ammonium iodides (Scheme 43, right) exhibited superior performance as alkylating agents under mildly basic conditions (Cs_2CO_3) in toluene under reflux. Several primary aromatic and aliphatic amides were N-methylated and N-ethylated in yields ranging from 59 to 92 %. Interestingly, the method could be applied in a late-stage methylation of two primary amides containing bioactive compounds, namely, carbamazepine and salicylamide, whereas the latter one was additionally *O*-methylated at the phenolic position (Scheme 43, left bottom). The outstanding mono-selectivity of this protocol was proven by reacting *N*-methyl aryl amides under the respective reaction conditions. A maximum yield of 35 % of the bis-methylated products were obtained and mainly starting material was recovered (Scheme 43, left top). These results show that even forcing a second methylation, the reaction is significantly hampered most likely by the steric congestion of the methylating agent itself.



Scheme 43. Hampered reaction for the N-methylation of secondary amides (left, top) proving the high mono-selectivity of the N-alkylation of primary amides using quaternary ammonium salts as the alkylating agents (right) and the application of the method for the late-stage methylation of bioactive compounds (left, bottom) by Schnürch and co-workers.[108]

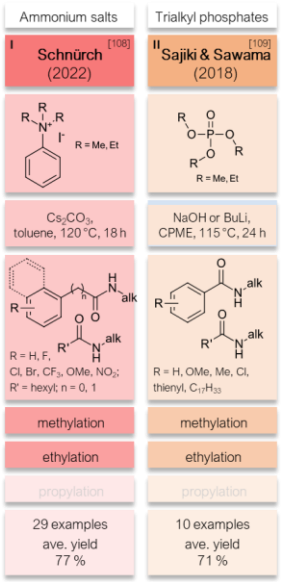


Figure 24. Methods for mono-selective N-alkylation of amides using quaternary ammonium salts (I) or trialkyl phosphates (II) as alkylating agents.

3.5. Trialkyl Phosphates

Trialkyl phosphates are to date rather underrated alkylating agents. However, they offer the great advantage of being nontoxic, relatively stable, and readily available. Besides being used as alkylating agents for alcohols or dimethylamines, Sajiki's group was the first to report their use as selective N-alkylating agents for primary amides[109] (Figure 24, II). Their catalyst-free protocol used either NaOH or *n*-BuLi as a base in cyclopentyl methyl ether (CPME) as the reaction solvent. The authors, however, did not comment on the rational for the mono-selectivity of these alkylating agents. Eventually, they could methylate several primary aryl amides and one aliphatic amide with a maximum yield of 87 %. For aniline they also proved that ethylation and butylation was feasible, but the product yield was only moderate with 54 and 61 %, respectively.

4. Sulfonamides

Sulfonamides, recognized for their pivotal role in medicinal chemistry, have become indispensable components in the development of pharmaceutically active compounds and drugs. Their prominence extends to various therapeutic applications, notably in antibacterial agents, where they exert their influence by disrupting bacterial folate synthesis through inhibition of the folic acid pathway.[110]

Concerning antibacterial activity, sulfonamides function as potent inhibitors, targeting dihydropteroate synthase, a key enzyme in the folic acid pathway. By obstructing this essential pathway, sulfonamides impede the production of folate, a vital precursor for bacterial DNA synthesis. This distinctive mode of action makes sulfonamides a cornerstone in the arsenal against bacterial infections, showcasing their importance in the field of chemotherapy.[111]

Beyond their role in antibacterial agents, sulfonamides find application in chemotherapeutic agents. Their ability to selectively target specific biological pathways makes them valuable tools in the design of drugs, where their inhibitory effects play a crucial role in modulating cellular functions.[111c, 112]

N-Alkylation of sulfonamide-containing drugs offers a versatile approach to fine-tune their properties, impacting factors such as solubility, binding affinity, and metabolic stability. This strategic modification provides chemists with a means to tailor the drug's profile for enhanced therapeutic effectiveness in specific biomedical applications.

4.1. Alcohols

Like amines and amides, sulfonamides can be readily and mono-selectively alkylated using alcohols by metal catalyzed hydrogen autotransfer with a mechanism according to the one in amide alkylation.
The protocols presented below primarily focused on the mono-selective N-alkylation of primary amines and herein further expanded their scope towards primary sulfonamides.[13, 28, 35a, 42, 46] Thus, the protocols are described in greater details within the section of amine alkylation. Reports that comprise only very few sulfonamide-containing compounds within their scope are not described in detail within this section. Only publications with a broader scope regarding selective N-alkylation of sulfonamides will be emphasized below.

In the years between 2012 to 2021, the group of Li dominated the field of mono-selective N-methylation of sulfonamides, reporting one ruthenium- and four iridium-catalyzed systems [19, 26-27, 29, 52e] (Figure 25, I-V). Their presented protocols were as well applicable for amine methylation, additionally, they encompass a variety of distinct sulfonamides within their scope.
In a publication on the mono-selective methylation of primary amines with methanol in 2012, Li *et al.* could prove that their herein described method can be also applied to sulfonamides[26] (Figure 25, I). They utilized $[Cp^*IrCl_2]_2$ as catalyst operating under basic conditions (NaOH) at 150 °C to mono-selectively methylate a variety of primary aryl sulfonamides in excellent yields between 87 and 97 %.
Subsequently, the group designed several modified Ir-catalyzed systems with increased reactivity and stability. In 2017, they introduced a bidentate 2,2'-bis-benzimidazole ligand enabling the catalytic system to operate under air with sub-stoichiometric amounts of Cs_2CO_3 as a very mild base[27] (Figure 25, II). A range of aromatic as well as aliphatic primary sulfonamides could be mono-N-methylated in outstanding yields between 89 to 96 % using methanol.
Three years later, they synthesized a novel water-soluble dinuclear iridium catalyst, allowing for N-methylation of amines and sulfonamides in water with methanol as C1-source [29] (Figure 25, III). Using KOH as the base at 130 °C several *N*-methyl sulfonamides were accessible in yields up to 93 % including non-aromatic methylsulfonamide. A few years later, they introduced an easily removable and recyclable iridium-based heterogenous catalytic system[52e] (Figure 25, IV)..

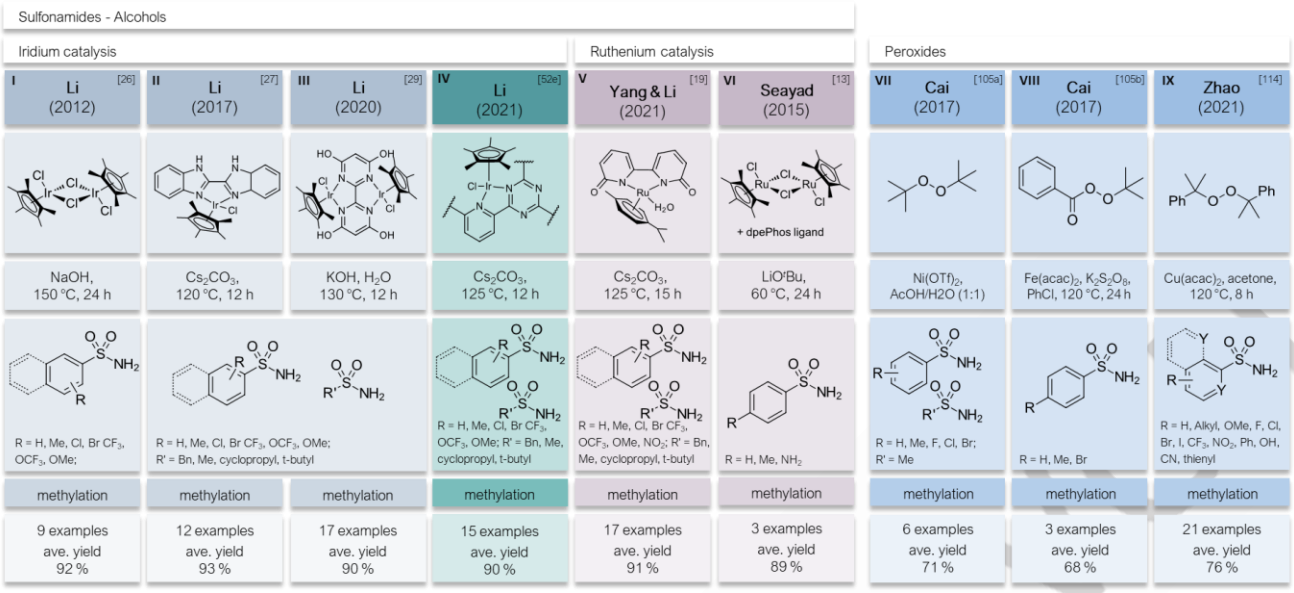
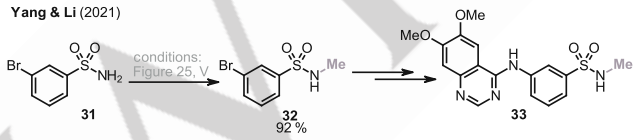


Figure 25. Methods for mono-selective N-alkylation of primary sulfonamides using alcohols (I-VI) or peroxides (VII-IX) as alkylating agents.

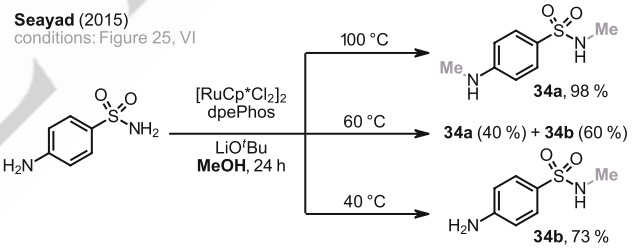
By coordinative immobilization, $[Cp^*IrCl_2]_2$ was successfully immobilized on a covalent triazine framework (CTF). The system operates in methanol as both solvent and methylating agent at 125 °C using Cs_2CO_3 as mild base. With regard to sulfonamides, their scope was similar to previous reports with yields of the N-methylated products up to 93 %.

In 2021, the group reported another distinct air-stable catalytic system suitable for mono-selective N-methylation which is based on ruthenium[19] (Figure 25, V). The crucial role of the bis-pyridonate ligand within the catalytic [(*p*-cymene)Ru(2,2'-bpyO)(H_2O)] complex is described in detail in the section of ruthenium catalyzed N-alkylation of amines with alcohols (Section 2.1). The protocol gave access to a variety of mono-N-methylated primary aromatic and aliphatic sulfonamides in up to 94 % yield. Notably, the authors applied their novel methylation protocol in the first step of a synthesis of a known kinase inhibiting compound (**33**, Scheme 44).[113]



Scheme 44. Application of the method for mono-selective N-methylation of primary sulfomamides using methanol as methylating agent under ruthenium catalysis in the first step of a known kinase inhibiting compound **c** by Yang, Li, and co-workers [19]

Even though presenting only three examples for the mono-selective N-methylation of sulfonamides, the group of Seayad made a noteworthy discovery: when using sulfanilamide and methanol under their reported $[RuCp^*Cl_2]_2$/dpePhos catalyzed conditions, the chemoselectivity for N-methylation was found to be temperature-dependent[13] (Figure 25, VI and Scheme 45). At 100 °C both the nitrogen of the amine and the sulfonamide were mono-selectively methylated. in 90 % yield. However, when the reaction was conducted at 40 °C N-methylation occurred exclusively at the sulfonamide moiety yielding 73 % of the desired product.



Scheme 45. Temperature dependent chemoselectivity in the mono-selective N-methylation of primary sulfonamides using methanol as methylating agent under ruthenium catalysis by Seayad and co-workers.[13]

4.2. Peroxides

As already mentioned previously (Section 3.3), peroxides display valuable alkylating agents for the mono-selective introduction of short-unbranched alkyl moieties on the nitrogen atom of amides and sulfonamides. The reaction pathway *via* radical formation is described more detailed above.

In 2017, Li and Cai disclosed two closely related protocols for the mono-selective N-methylation of amides and sulfonamides using either $Ni(OTf)_2$ with di-tert-butyl peroxide (DTBP)[105a] (Figure 25, VII) or $Fe(acac)_2$ with tert-butyl peroxybenzoate (TBPB) and $K_2S_2O_8$[105b] (Figure 25, VIII). The first protocol encompassed six distinct sulfonamides which could be methylated in good yields up to 74 %, whereas the latter protocol featured only three examples thereof with a maximum yield of 70 %.

Recently, Zhao, Luo, and Lian disclosed a protocol focusing exclusively on the N-methylation of sulfonamides using dicumyl

peroxide [114] (Figure 25, IX). The reaction was catalyzed by simple and readily available $Cu(acac)_2$ in acetone at 80 °C under air. A great variety of aromatic-, heteroaromatic- and benzylsulfonamides could be mono-selectively methylated in up to 90 % yield. Subjecting a mono-N-methylated sulfonamide again to the optimized reaction conditions, only 50 % of the bis-methylated product could be obtained, suggesting that the rate of a second methylation is slightly reduced.

Considering, that to date described protocols for the mono-selective short-chain N-alkylation of sulfonamides are exclusively focusing on methylation, it becomes obvious that there is a demand for novel protocols for mono-N-ethylation and N-propylation of these frequently occurring and important motifs in biologically active compounds.

5. Outlook

The mono-selective N-alkylation of primary amines, amides, and sulfonamides is a fundamental reaction in both small organic molecules and complex compounds, such as pharmaceuticals. Tailored methods that allow full control over the degree of alkylation, especially to prevent overalkylation, are often crucial. This precision is not only significant for the controlled modification of defined properties but also for waste prevention by eliminating undesired byproducts.

This comprehensive review presents several methods that can be applied to meet individual requirements. However, despite the strengths of each method, certain strategies have significant drawbacks that should prompt researchers in this field to overcome these limitations. Specifically, strategies involving the use of alcohols or gaseous reagents (e.g., CO_2) as alkylating agents under metal catalysis often require high temperatures and pressures, necessitating specialized equipment like autoclaves, which might not be readily available in every laboratory. Furthermore, these harsh conditions often limit the tolerance of functional groups in general or, considering the reductive conditions for hydrogen autotransfer reactions, alter reducible groups within a molecule (ketones, vinyl, amides, alkenes, etc.). Thus, there is a substantial demand for the development of more active catalytic systems that can operate at lower temperatures and pressures while still guaranteeing high mono-selectivity.

Concerning metal catalyzed N-alkylations, the use of catalytic systems featuring earth-abundant metals like iron, manganese, cobalt, and nickel is still underexplored. Ideally, the use of these abundant metals in a heterogeneous and easily reusable catalyst is highly desirable, especially in times of increasing demand for more environmentally friendly processes. Considering environmental concerns, the use of atom-economic and benign reagents (carboxylic acids, aldehydes, nitriles, and alcohols), or even the fixation of carbon dioxide, is highly desirable.

A second challenge in designing new methodologies for mono-selective N-alkylation is achieving precise control over chemoselectivity when different nitrogen-containing moieties are present in a single molecule. Often, primary amines are more readily alkylated compared to amides or sulfonamides. However, considering the structural complexity of the majority of bioactive compounds and pharmaceuticals, the need for highly chemo- and regioselective methods becomes apparent.

Lastly, especially concerning amine alkylation, the majority of methods only achieve mono-selectivity for aryl amines, lacking complete mono-selectivity for aliphatic amines, which are fully bis-methylated. Given the frequent occurrence of aliphatic motifs in bioactive compounds (e.g., proteins) and pharmaceuticals, the need for refinement of existing or discovery of new methodologies for mono-selective N-alkylation of aliphatic amines is evident.

We genuinely hope that this review aids researchers in choosing suitable methods for a given demand and further inspires and encourages them to find new strategies to overcome present limitations and challenges.

Acknowledgements

We thank Maximilian Wutscher for the graphical design of the frontispiece.

This work was funded by the Austrian Science Fund (FWF, Project P33064-N).

Keywords: mono-methylation • mono-ethylation • mono-propylation • chemical precision • drug discovery

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D III.1 Manuscript 3

Johanna Templ, Edma Gjata, Filippa Getzner, and Michael Schnürch

Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents

Org. Lett. 2022, 24, 40, 7315–7319. doi: 10.1021/acs.orglett.2c02766

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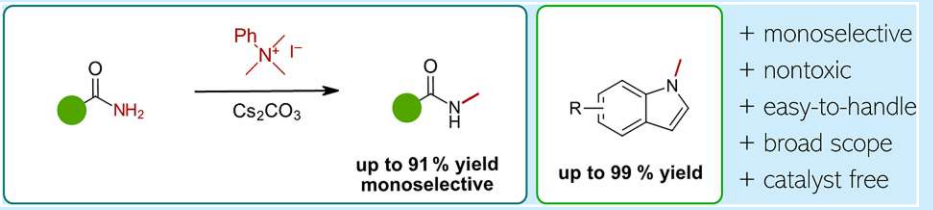


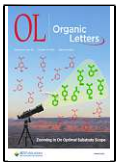
ABSTRACT: We herein report the use of phenyl trimethylammonium iodide ($PhMe_3NI$) as a safe, nontoxic, and easy-to-handle reagent for an absolutely monoselective N-methylation of amides and related compounds as well as for the N-methylation of indoles. In addition, we expanded the method to N-ethylation using $PhEt_3NI$. The ease of operational setup, high yields of ≤99%, high functional group tolerance, and especially the excellent monoselectivity for amides make this method attractive for late-stage methylation of bioactive compounds.

Nitrogen-containing compounds are privileged structures in organic chemistry. For example, among thousands of FDA-approved, small molecule drugs, more than 80% contain at least one nitrogen atom with an average of 2.3 nitrogens per drug.[1] These impressive numbers outline the importance of nitrogen-containing motifs in medicinal chemistry and drug discovery. When checking the top 200 small molecule drugs by retail sales in 2021[2] (see the bottom of Figure 1 for a selection), one notices the nitrogen atom is found in a majority of pharmaceuticals and herein appears in different structural modifications. Repeatedly occurring nitrogen-containing functionalities include amines, amides, sulfonamides, and N-heterocycles. Simple structural modifications, e.g., alkylation, of such groups often drastically change the physiological and biological properties of pharmaceutically active molecules.[3,4] Considering alkylation as a late-stage modification in bioactive compounds in general, the simplest and smallest of all alkyl groups, the methyl group, seems to have the most profound impact on altering the biological properties of a molecule.[5−7] This phenomenon is well-known as the "magic-methyl effect".[4,8,9]

Hence, new strategies for efficient and selective N-methylation of amides and related structures are of great interest.[10] However, major challenges with these specific transformations need to be considered (see Figure 1). First, traditionally applied methylating agents, such as iodomethane[11] or dimethyl sulfate,[12] often suffer from undesired properties, such as high toxicity, carcinogenicity, and volatility. Some strategies require transition metal catalysts, e.g., when using peroxides[13] or MeOH[14−16] as the single-carbon source. Still others have a relatively narrow substrate scope, which limits the broad application of the respective methylating agent, e.g., when using formaldehyde[17,18] under reductive conditions or $PO(OMe)_3$.[19] The Schoenebeck group recently reported a safe and metal-free methylation protocol using tetramethylammonium fluoride.[20] This method is characterized by a relatively broad substrate scope, including amides, N-heterocycles, and alcohols. However, this strategy lacks monoselectivity when methylating primary amides. In general, the tendency of primary amides to undergo overalkylation features the second serious challenge when searching for new N-methylation strategies.

We describe herein a novel, safe, and monoselective protocol for efficient methylation of amides using phenyl trimethylammonium iodide ($PhMe_3NI$) as the CH_3 source under mildly basic conditions, which is characterized by the ease of operational setup. In addition, we demonstrate the broad applicability of this new method by expanding the scope toward N-heterocycles, e.g., indoles, and prove its potential use in the late-stage functionalization of bioactive compounds. Furthermore, the monoselective introduction of an ethyl group

Received: August 16, 2022
Published: October 3, 2022



https://doi.org/10.1021/acs.orglett.2c02766
Org. Lett. 2022, 24, 7315−7319

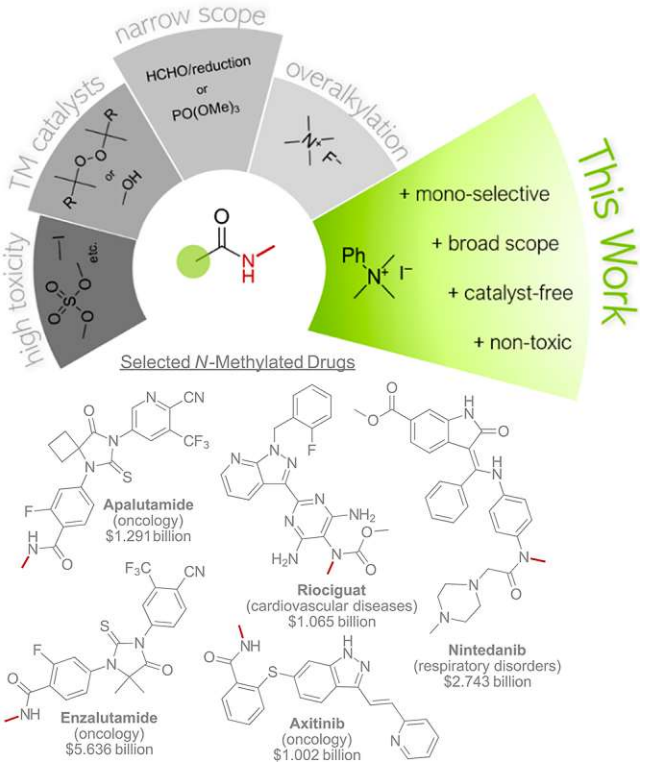


Figure 1. Strategies for the methylation of amides (top) and selected N-methylated small molecule pharmaceuticals and their retail sales in 2021 (bottom).[2]

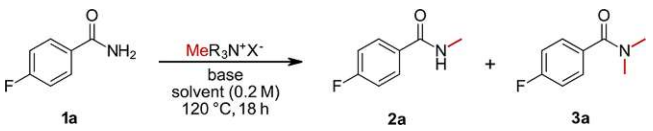
can be realized using the related quaternary ammonium salt $PhEt_3NI$.

For all optimization screenings, we used 4-fluoro benzyl amide (**1a**) as the substrate. The fluoro substituent enables facile quantification directly from the reaction solution without preceding solvent removal or workup via ^{19}F NMR using trifluoro toluene as the internal standard.

We started our investigations by building on our previous results for the selective α-C(sp^3)-methylation[21] using $PhMe_3NI$ as the methylating agent and KOH as the base in toluene at 120 °C (Table 1, entry 1). The mono-N-methylated product was obtained with a moderate yield of 56%. Other hydroxy bases showed significantly lower conversion (entries 2 and 3). Gratifyingly, we found Cs_2CO_3 as a mild base giving the mono-N-methylated product (**2a**) in 85% yield (entry 4). All other bases tested turned out to be inefficient (see the Supporting Information for details). Next, we tested different quaternary ammonium salts as the methylating agents. The tetramethylammonium halides gave lower overall yields for **2a**, with a rapid decrease in conversion from the respective fluoride to iodide salts (entries 6−9). Tetramethylammonium fluoride, which was applied for methylating secondary amides toward tertiary ones, gave a 1:1 mixture of mono- and bis-methylated products **2a** and **3a**, respectively (entry 6), and obviously lacks monoselectivity. As anticipated, the phenyl trimethylammonium halides performed best, with the phenyl trimethylammonium iodide outperforming the respective chloride and bromide (entries 4, 10, and 11). We also tested a variety of solvents that are considered to be more environmentally benign such as *t*-BuOH, cyclopentyl methyl ether (CPME),[22] and anisole.[23] Indeed, they turned out to be suitable solvents for this specific reaction; however, ∼10−20% lower yields of **2a** were obtained (entries 12−14) compared to those with toluene, which consequently remained the solvent of choice (entry 4).

In our previous publication on selective α-methylation of aryl ketones,[21] we could prove that a reaction pathway via thermal decomposition of the methylammonium salt to its respective methyl halide, which in turn could act as the actual methylating agent, can be excluded. Additionally, when the N-methylation of benzyl amide is performed with MeI under basic conditions, the N-bis-methylated product is obtained

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	ammonium salt	base	conversion (%)	yield (%)[b] 2a	3a
1	toluene	$PhMe_3NI$	KOH	81	56	19
2	toluene	$PhMe_3NI$	NaOH	43	11	7
3	toluene	$PhMe_3NI$	$LiOH·H_2O$	28	6	0
4	toluene	$PhMe_3NI$	Cs_2CO_3	91	85	5
5	toluene	$PhMe_3NI$	no base	7	0	0
6	toluene	Me_4NF	Cs_2CO_3	97	26	24
7	toluene	Me_4NCl	Cs_2CO_3	73	67	3
8	toluene	Me_4NBr	Cs_2CO_3	31	23	0
9	toluene	Me_4NI	Cs_2CO_3	8	4	0
10	toluene	$PhMe_3NCl$	Cs_2CO_3	96	78	7
11	toluene	$PhMe_3NBr$	Cs_2CO_3	99	78	11
12	*t*-BuOH[c]	$PhMe_3NI$	Cs_2CO_3	79	65	7
13	CPME	$PhMe_3NI$	Cs_2CO_3	94	74	7
14	anisole	$PhMe_3NI$	Cs_2CO_3	89	73	5

[a]Reactions were performed on a 0.35 mmol scale, with 2 equiv of the base and 2 equiv of the ammonium salt under an Ar atmosphere at 120 °C with a reaction time of 18 h. [b]Yields were determined by quantitative ^{19}F NMR using trifluoro toluene as the internal standard. [c]At 100 °C.

https://doi.org/10.1021/acs.orglett.2c02766
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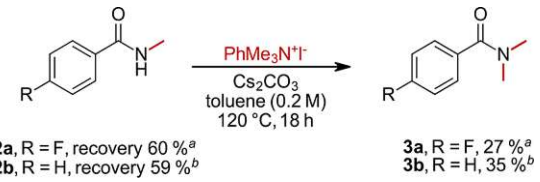
exclusively, and no monoselectivity is observed.[24] The latter results corroborate the hypothesis of a direct nucleophilic substitution mechanism rather than a pathway via thermal decomposition to MeI and even more emphasize the importance of finding novel monoselective protocols employing alternative reagents.

We performed additional experiments to demonstrate the remarkable selectivity of this new protocol. When monomethylated amides **2a** and **2b** were subjected again to the best performing reaction conditions (Table 1, entry 4), only 27% and 35% of bis-methylated products **3a** and **3b** were obtained (Scheme 1). For both reactions, mainly unreacted mono-

Scheme 1. Reaction Using Monomethylated Benzamides as Starting Materials



[a]Yield determined by quantitative ^{19}F NMR using trifluoro toluene as the internal standard. [b]Isolated yields given.

methylated starting material was recovered. This underlines the applicability of the developed reaction conditions for selective monomethylation because even when trying to enforce a second methylation, this works only poorly. These findings corroborate the hypothesis that an attachment of a sterically demanding CH_3 group makes the nitrogen less prone to further deprotonation by a weak base and alters its nucleophilicity. Therefore, a second alkylation via the bulky ammonium salt is slowed significantly.

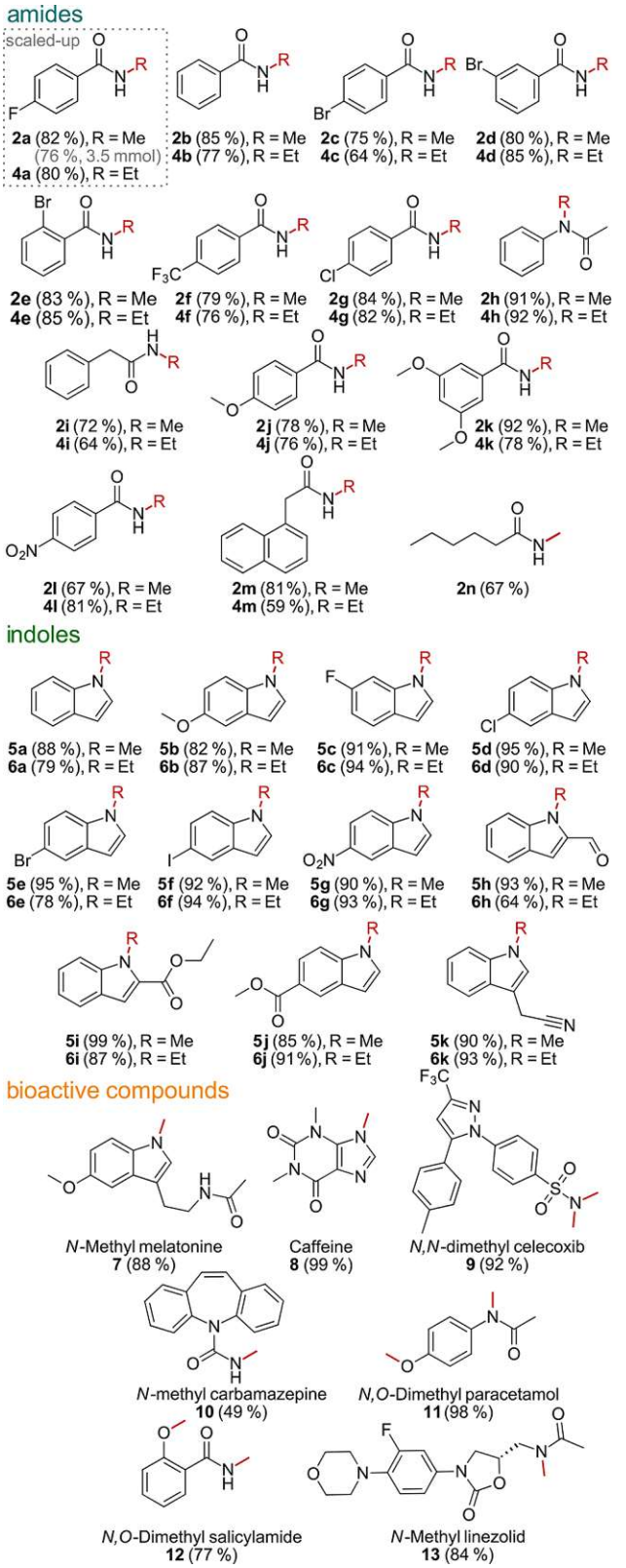
With the optimized reaction conditions in hand, we applied the N-methylation reaction to various substrates, including amides, indoles, and a variety of structurally related bioactive compounds, to demonstrate the broad applicability of our developed protocol (Scheme 2).

In all reactions, *N,N*-dimethylamine is formed as a stoichiometric byproduct from $PhMe_3NI$ after its methyl group transfer. This byproduct can be either quenched *in situ* by conversion to its water-soluble HCl salt and subsequently removed in a mild acidic workup or, for acid-sensitive compounds, easily removed via column chromatography. The obtained results are compiled in Scheme 2.

The monoalkylated amides were obtained in yields of ≤91% for the methylation (products **2a**−**2n**) and 92% for the ethylation (products **4a**−**4m**). In all cases, a variety of functional groups on the benzamide, e.g., halides (products **2a**, **2c**−**2g**, **4a**, and **4c**−**4e**), a nitro group (products **2l** and **4l**), ether (products **2j**, **2k**, **4j**, and **4k**), and fused aromatic rings (products **2m** and **4m**), were used. Interestingly, an amide functionality at a benzylic position reacted chemoselectively without substitution at the α-position (products **2i**, **4i**, **2m**, and **4m**). This method, however, is not restricted to *para*-substituted amides but can be used to methylate *ortho*- and *meta*-substituted benzamides with comparable yields (cf. **2c** and **4c** to **2d**, **2e**, **4d**, and **4e**; cf. **2j** and **4j** to **2k** and **4k**).

The aliphatic amide hexanamide could be selectively monomethylated in a moderate yield of 67% (product **2n**). No bis-methylated product could be detected in the crude reaction mixture by NMR and LC-MS analysis, but unreacted

Scheme 2. Scope of N-Methylation and N-Ethylation[a]



[a]Reactions performed on a 100 mg scale, Cs_2CO_3 (2 equiv), ammonium salt (2.5 equiv): $PhMe_3NI$ (for products **2a**−**2m**, **5a**−**5k**, and **9**−**15**), $PhEt_3NI$ (for products **4a**−**4m** and **6a**−**6k**), toluene (0.23 M), 120 °C for 16−24 h.

https://doi.org/10.1021/acs.orglett.2c02766
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starting material could be. This was also true for all other products with moderate yields. Only for products **2i** and **2m** could trace amounts (<8%) of bis-methylated species be detected via crude NMR. The reaction of *N*-acetylaniline also yielded the desired methylated and ethylated products **2h** and **4h**, showing that depending on the specific structure some secondary amides can be alkylated in excellent yields.

Because the experimental pK_a values in DMSO for **1h** (pK_a = 21.5[25]) and **2a** (pK_a = 21.5[26]) are in the same range, we hypothesize that the facile methylation of secondary amide **1h**, in comparison to the methylation of **2a** (see Scheme 1), might be caused by the lower steric demand of planar phenyl groups compared to a bulky methyl substituent directly attached to the nitrogen. Therefore, the nitrogen would be more readily approached by $PhMe_3NI$ for substrate **1h** than for **2a**. However, as the monomethylation toward secondary amides is much more demanding, we mainly focused on primary amides as starting materials. To further prove this method's applicability and ease of operational setup, we performed the methylation of **1a** on a 3.52 mmol scale, giving **2a** in a 76% isolated yield.

In addition to amides, the indole motif is considered a privileged heterocyclic structure in biologically active compounds, as well.[27−29] Hence, we tested whether indoles could be N-methylated and N-ethylated as well with our new protocol. Overall, indole-derived substances performed slightly better in this specific N-alkylation reaction than primary amides. A great range of functional groups was well tolerated, including halides (products **5c**−**5f** and **6c**−**6f**), ether (products **5b** and **6b**), nitro (products **5g** and **6g**), aldehyde (products **5h** and **6h**), esters (products **5i**, **5j**, **6i**, and **6j**), and nitrile (products **5k** and **6k**). The described methylation of selected indole derivatives with $PhMe_3NI$ under mild basic conditions gave yields as high as those of the methylation with Me_4NF performed by the group of Schönebeck.[20] In contrast to Me_4NF, however, the use of anhydrous $PhMe_3NI$ and storage of the reagent in a glovebox are not required, which makes this presented method even more convenient.

To outline the potential of this method for late-stage functionalization of bioactive molecules, we performed methylation on a selection of established pharmaceuticals. Tryptamine-derived compounds, like melatonin, are methylated exclusively at the indole nitrogen atom in 88% yield (product **7**). Upon subjecting the N-monomethylated melatonin (product **7**) again to the reaction conditions mentioned above, we could observe no further methylation at the nitrogen of the secondary amide. Theophylline can be fully methylated to give caffeine (product **8**) in quantitative yield. The sulfonamide moiety in celecoxib is fully bis-methylated in an excellent yield of 92% (product **9**). Sulfonamides exhibit significantly lower pK_a values compared to those of benzamides; hence, a monomethylated sulfonamide readily undergoes a second substitution at the nitrogen. As in carbamazepine, a urea-derived functionality is monomethylated in moderate yield (product **10**). From previous results,[21] we found hydroxy groups being readily methylated. Thus, as expected, paracetamol and salicylamide were methylated at the phenolic position and the amide moiety (products **11** and **12**), and the antibiotic linezolid can be N-methylated at the acetamide moiety with an 84% yield (product **13**).

In conclusion, we described a novel protocol for monoselective methylation and ethylation of amides, indoles, and related structures using solid, nontoxic, and easy-to-handle quaternary ammonium salts under mildly basic conditions. The method can also be applied to complex bioactive compounds and hence for late-stage modification of active pharmaceutical ingredients in drug discovery programs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02766.

Detailed procedure for quantitative ^{19}F NMR measurements, complete optimization screening data, experimental procedures, and characterization data for all compounds isolated (PDF)

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Funding

Open Access is funded by the Austrian Science Fund (FWF).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the Austrian Science Fund (FWF, Project P33064-N).

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https://doi.org/10.1021/acs.orglett.2c02766
Org. Lett. 2022, 24, 7315−7319

D III.2 Manuscript 3 – Supporting Information

Detailed procedure for quantitative ^{19}F-NMR measurements, complete optimization screening data, experimental procedures, and characterization data for all compounds isolated.

Johanna Templ, Edma Gjata, Filippa Getzner, and Michael Schnürch

Supporting Information for

Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents

Org. Lett. 2022, 24, 40, 7315–7319. doi: 10.1021/acs.orglett.2c02766

Supporting Information

Monoselective *N*-methylation of Amides, Indoles, and related Structures using Quaternary Ammonium Salts as Solid methylating Agents

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Contents

General Experimental Details

All Chemicals were purchased from commercial suppliers and, unless noted otherwise, used without further purification. The 8 mL glass vials were sealed with Wheaton® screw caps containing a PTFE faced 14B styrene-butadiene rubber liner for small-scale reaction above room temperature and heated in a metallic reaction block. All reaction temperatures refer to external temperatures.

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance UltraShield 400 at ambient temperature. Chemical Shifts (δ) are reported in ppm, using Me_4Si as internal standard. Coupling constants (*J*) are given in Hertz (Hz) and multiplicities are assigned as s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.
Quantitative ^{19}F-NMR spectra were recorded in a non-decoupled mode with a prolonged relaxation delay (d1 = 20 s), a narrowed spectral width (SW = 70 ppm), and a modified transmitter excitation frequency (O1T) to place the center of the spectrum between the peaks of interest (for details see Optimization Screening).

Thin Layer Chromatography (TLC) analysis was performed on aluminum-backed unmodified Merck silica gel 60 F_{245} plates. Visualization was realized under UV irradiation or *via* heat staining using a ceric ammonium molybdate aqueous solution. For flash column chromatography, Merck silica gel 60 (40 µm – 63 µm) was used, and purification was either done by hand-column or on a Büchi® Pure C-850 FlashPrep System.

GC-MS analysis was carried out on a Thermo Finnigan Focus GC/DSQ II with a standard capillary column RXi-5Sil MS column (30 m, 0.25 mm ID, 0.25 µm df) using the following standardized temperature program: 2 min at 100 °C, 35 °C/min until 300 °C, 4 min at 300 °C.

HR-MS analysis was performed on an Agilent 6230 LC TOFMS mass spectrometer equipped with an Agilent Dual AJS ESI-Source. The mass spectrometer was connected to a liquid chromatography system of the 1100/1200 series from Agilent Technologies, Palo Alto, CA, USA. The system consisted of a 1200SL binary gradient pump, a degasser, a column thermostat, and an HTC PAL autosampler (CTC Analytics AG, Zwingen, Switzerland). A silica-based Phenomenex C-18 Security Guard Cartridge was used as a stationary phase. Data evaluation was performed using Agilent MassHunter Qualitative Analysis B.07.00. Identification was based on peaks obtained from extracted ion chromatograms (extraction width ± 20 ppm).

General Procedures

Optimization Screening

General Procedure A:

4-Fluorobenzamide **(1a)** (50 mg, 0.352 mmol, 1 equiv), the respective ammonium salt (2 equiv), and the base (2 equiv) were placed in an 8 mL glass vial equipped with a magnetic stirring bar and a septum screw cap. *Via* a cannula, the vial was evacuated and backfilled with argon three times. Subsequently, the solvent (0.23 M) was added *via* syringe, and the evacuation and backfilling cycles were repeated under vigorous stirring so that no boiling delay occurred. The septum screw cap was replaced with a closed Wheaton® screw cap. The inhomogeneous reaction mixture was heated to 120 °C (or 100 °C for solvents with lower boiling points) in a metallic heating block for 18 h.

Sample preparation for quant. ^{19}F-NMR:
The reaction was cooled to room temperature and 100 µL of a solution of trifluorotoluene in $CHCl_3$ (52 mmol/mL) was added to the reaction mixture *via* Eppendorf® pipette. The inhomogeneous mixture was centrifuged, and 0.5 mL of the supernatant solution were transferred to an NMR tube. 0.3 mL $CDCl_3$ were added to the NMR tube, and the liquid content was homogenized thoroughly.

Quant. ^{19}F-NMR instrument parameters and processing:
NMR spectra were shimmed for $CDCl_3$ and recorded with the following changes in acquisition parameters:

- transmitter excitation frequency (O1T) = -87 ppm
- spectral width = 70 ppm
- relaxation delay = 20 s

After standard Fourier transformation, the recorded spectra were processed by MestReNova v12 software as following: [1]

- Apodization along t1: exponential 0.50 Hz
- Zero filling along t1: 512K
- Auto Phase Correction (Algorithms: Global, Selective, Metabonomics, Whitening, Min. Entropy, Baseline Optimization, Regions Analysis; Initial Phase: Zero)
- Auto Baseline Correction along t1: Ablative (5 Points, 10 Passes)

The following ^{19}F-NMR should serve as an example spectrum used for evaluation.

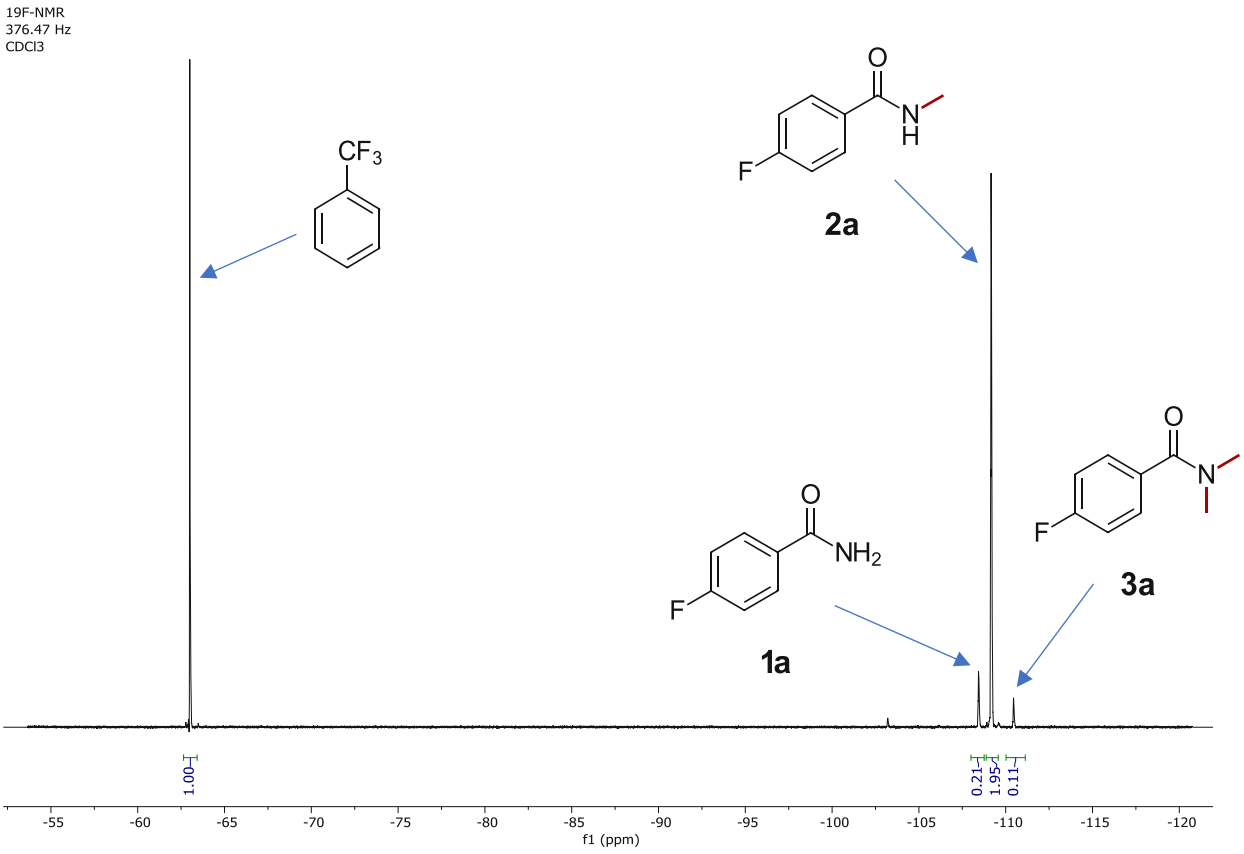


Figure S 1. example spectrum for quantitative ^{19}F NMR used for evaluation

Substrate Scope Methylation, Ethylation and Benzylation

General procedure B:

The starting material (100 mg, 1 equiv), the respective ammonium salt ($PhMe_3NI$, $PhEt_3NI$; 2.5 equiv), and Cs_2CO_3 (2 equiv) were placed in an 8 mL glass vial equipped with a magnetic stirring bar and a septum screw cap. Via a cannula, the vial was evacuated and backfilled with argon three times. Subsequently, toluene (0.23 M) was added via syringe, and the evacuation and backfilling cycles were repeated under vigorous stirring so that no boiling delay occurred. The septum screw cap was replaced with a closed Wheaton® screw cap. The inhomogeneous reaction mixture was heated to 120 °C in a metallic heating block for 15-24 h.

Work-up procedure A:

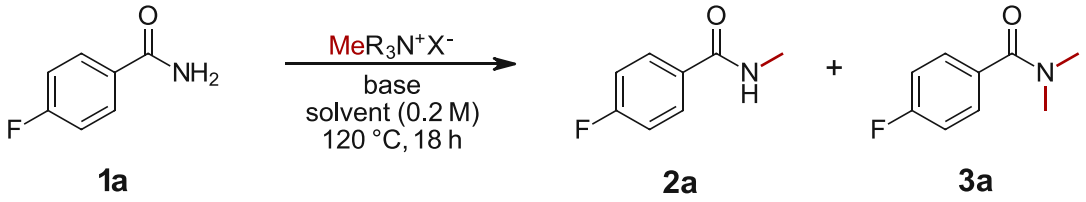
After the reaction was cooled to room temperature, 2 mL of deion. water were added, and the product was extracted 3 times with 10-15 mL EtOAc. The combined organic phases were washed once with brine, dried over Na_2SO_4, filtered, and concentrated to obtain a crude product which was further purified *via* hand column with unmodified silica gel.

Work-up procedure B:

After the reaction was cooled to room temperature 2 N HCl was added until gas evolution ceased (ca 2 mL). The product was extracted 3 times with 10-15 mL EtOAc, and the combined organic extracts were washed once twice with 3 mL 2 N HCl and once with brine, dried over Na_2SO_4, filtered and concentrated. The obtained crude product was purified *via* hand column using unmodified silica gel.

Optimization Screening for Amide *N*-Methylation

Yields, determined by quant. ^{19}F NMR, for the depicted reaction, are shown in the tables below. The following parameters were screened:



1a **2a** **3a**

Base:

Reactions were performed following the general procedure A using $PhMe_3NI$ (0.704 mmol, 2 equiv) as methylating agent, 0.704 mmol (2 equiv) of the respective base and toluene (1.5 mL, 0.23 M) as solvent at 120 °C for 18 h.

- KOH [CAS: 1310-58-3]
- NaOH [CAS: 1310-73-2]
- $LiOH \cdot H_2O$ [CAS: 1310-66-3]
- K_2CO_3 [CAS: 584-08-7]
- Cs_2CO_3 [CAS: 534-17-8]
- LiO^tBu [CAS: 1907-33-1]

- KO^{t}Bu [CAS: 865-47-4]

Table S 1. Base Screening

entry	solvent	ammonium salt	base	conversion (%)	yield (%)	
					2a	**3a**
1	toluene	$PhMe_3NI$	KOH	81	56	19
2	toluene	$PhMe_3NI$	NaOH	43	11	7
3	toluene	$PhMe_3NI$	LiOH * H_2O	28	6	0
4	toluene	$PhMe_3NI$	K_2CO_3	7	6	0
5	toluene	$PhMe_3NI$	Cs_2CO_3	91	85	5
6	toluene	$PhMe_3NI$	LiO^{t}Bu	9	2	5
7	toluene	$PhMe_3NI$	KO^{t}Bu	69	16	0
8	toluene	$PhMe_3NI$	no base	7	0	0

Ammonium Salt:

Reactions were performed following the general procedure A using Cs_2CO_3 (0.704 mmol, 2 equiv) as the base, 0.704 mmol (2 equiv) of the respective ammonium salt and toluene (1.5 mL, 0.23 M) as solvent at 120 °C for 18 h.

- Me_4NF [CAS: 373-68-2]
- Me_4NCl [CAS: 75-57-0]
- Me_4NBr [CAS: 64-20-0]
- Me_4NI [CAS: 75-58-1]
- Me_3PhNCl [CAS: 138-24-9]
- Me_3PhNBr [CAS: 16056-11-4]
- Me_3PhNI [CAS: 98-04-4]

Table S 2. Ammonium Salt Screening

entry	solvent	ammonium salt	base	conversion (%)	yield (%)	
					2a	**3a**
1	toluene	Me_4NF	Cs_2CO_3	97	26	24
2	toluene	Me_4NCl	Cs_2CO_3	73	67	3
3	toluene	Me_4NBr	Cs_2CO_3	31	23	0
4	toluene	Me_4NI	Cs_2CO_3	8	4	0
5	toluene	$PhMe_3NCl$	Cs_2CO_3	96	78	7
6	toluene	$PhMe_3NBr$	Cs_2CO_3	99	78	11
7	toluene	$PhMe_3NI$	Cs_2CO_3	95	83	6

Solvent:

Reactions were performed following the general procedure A using $PhMe_3NI$ (0.704 mmol, 2 equiv) as methylating agent and Cs_2CO_3 (0.704 mmol, 2 equiv) as base with 1.5 mL solvent (0.23 M) at respective temperatures for 18 h.

- *t*-BuOH [CAS: 75-65-0] at 100 °C

- toluene [CAS: 108-88-3] at 120 °C
- CPME [CAS: 5614-37-9] at 120 °C
- anisole [CAS: 100-66-3] at 120 °C

Table S 3. Solvent Screening

entry	solvent	ammonium salt	base	conversion (%)	yield (%)	
					2a	**3a**
1	*t*-BuOH	$PhMe_3NI$	Cs_2CO_3	79	65	7
2	toluene	$PhMe_3NI$	Cs_2CO_3	95	84	6
3	CPME	$PhMe_3NI$	Cs_2CO_3	94	74	7
4	anisole	$PhMe_3NI$	Cs_2CO_3	89	73	5

Equivalents of $PhMe_3NI$ and Cs_2CO_3

Reactions were performed following the general procedure A using $PhMe_3NI$ as methylating agent and Cs_2CO_3 as base with toluene (1.5 mL, 0.23 M) as solvent at 120 °C for 18 h.

Table S 4. Equivalents of $PhMe_3NI$ and Cs_2CO_3 Screening

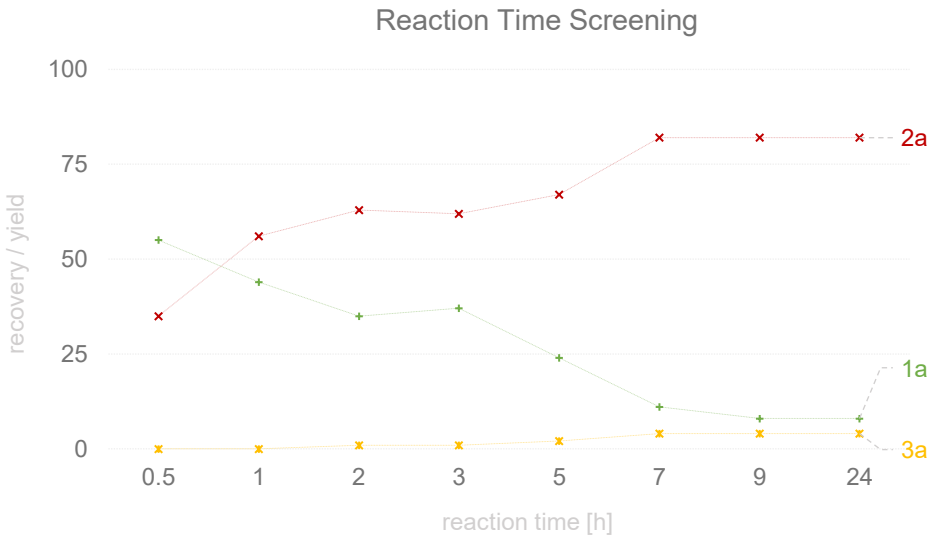
entry	solvent	$PhMe_3NI$ [mmol] (equiv)	Cs_2CO_3 [mmol] (equiv)	conversion (%)	yield (%)	
					2a	**3a**
1	toluene	0.352 (1)	0.704 (2)	74	60	2
2	toluene	0.704 (2)	0.704 (2)	92	74	4
3	toluene	1.056 (3)	0.704 (2)	98	77	8
4	toluene	0.352 (1)	0.352 (1)	55	43	1
5	toluene	0.704 (2)	0.352 (1)	66	52	1

Reaction Time:

Reactions were performed following the general procedure A using $PhMe_3NI$ (0.704 mmol, 2 equiv) as methylating agent and Cs_2CO_3 (0.704 mmol, 2 equiv) as base with toluene (1.5 mL, 0.23 M) as solvent at 120 °C for the respective reaction time.

Table S 5. Reaction Time Screening

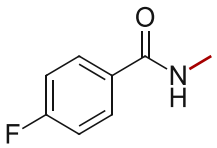
entry	time [h]	conversion (%)	yield (%)	
			2a	**3a**
1	0.5	45	35	0
2	1	56	56	0
3	2	65	63	1
4	3	63	62	1
5	5	76	67	2
6	7	89	82	4
7	9	92	82	4
8	24	92	82	4



Characterization data for all synthetic compounds

All compounds synthesized are described in the literature, except **11** and **15**. For known compounds, spectral data is in agreement with the literature.

Substrate scope methylation



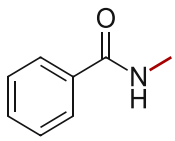
***N*-Methyl-4-fluorobenzamide[2] (2a) [CAS: 701-49-5]**

Prepared, following the general procedure from commercially available starting material with a reaction time of 20 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 88 mg (82 %) of the title compound as white crystals.

Scaled up synthesis: The synthesis of **2a** was additionally performed on a 3.52 mmol scale. The starting material (0.5 g, 3.52 mmol, 1 equiv), $PhMe_3NI$ (2.36 g, 8.80 mmol, 2.5 equiv), and Cs_2CO_3 (2.32 g, 7.04 mmol, 2 equiv) were placed in a 50 mL pressure flask equipped with a magnetic stirring bar. For degassing, the opening of the flask was temporarily covered with a septum. *Via* a cannula, the flask was evacuated and backfilled with argon three times. Subsequently, toluene (15 mL) was added *via* syringe, and the evacuation and backfilling cycles were repeated under vigorous stirring so that no boiling delay occurred. The septum screw cap was replaced with a closed screw cap. The inhomogeneous reaction mixture was heated to 120 °C in an oil bath for 20 h. After complete conversion the reaction was cooled to room temperature.
10 mL H_2O were added, and the product was extracted 4 times with 40 mL EtOAc each. The combined organic extracts were washed three times with 5 mL 2 N HCl each and once with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (50 g silica, DCM:MeOH 100:1, 30:1), yielding 407 mg (76 %) of the title compound as white crystals. Analytical data was in accordance with previous measurements.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.72 (m, 2H), 7.07 – 6.98 (m, 2H), 6.93 (bs, 1H), 2.92 (d, *J* = 4.8 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.5, 164.6 (d, *J* = 251.5 Hz), 130.8 (d, *J* = 3.2 Hz), 129.3 (d, *J* = 8.8 Hz), 115.4 (d, *J* = 21.8 Hz), 26.9.



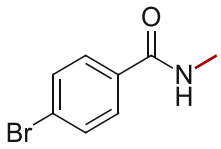
***N*-Methylbenzamide[2] (2b) [CAS: 613-93-4]**

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 75:1, 50:1), yielding 95 mg (85 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.72 (m, 2H), 7.50 – 7.41 (m, 1H), 7.41 – 7.32 (m, 2H), 6.59 (s, 1H), 2.97 (d, *J* = 4.9 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.4, 134.7, 131.3, 128.5, 126.9, 26.9.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_8H_{10}NO$: 136.0757; found: 136.0759



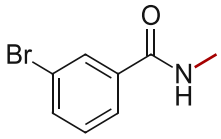
4-Bromo-*N*-methylbenzamide[2] (2c) [CAS: 27466-83-7]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 79 mg (75 %) of the title compound as slightly blue crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.58 (m, 2H), 7.57 – 7.49 (m, 2H), 6.42 (s, 1H), 2.97 (d, *J* = 4.8 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.4, 133.5, 131.8, 128.6, 126.1, 27.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for C_8H_9BrNO: 213.9862; found: 213.9868

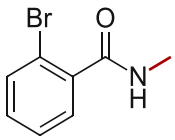


3-Bromo-*N*-methylbenzamide[3] (2d) [CAS: 49834-22-2]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1), yielding 84 mg (80 %) of the title compound as white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (t, *J* = 1.8 Hz, 1H), 7.67 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.56 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 6.80 (s, 1H), 2.96 (d, *J* = 4.8 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) 167.0, 136.6, 134.3, 130.2, 130.1, 125.6, 122.7, 27.0

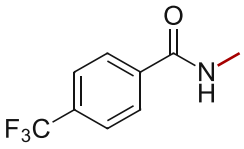


2-Bromo-*N*-methylbenzamide[4] (2e) [CAS: 61436-88-2]

Prepared, following the general procedure from commercially available starting material with a reaction time of 22 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1), yielding 87 mg (83 %) of the title compound as white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.34 – 7.20 (m, 2H), 6.17 (s, 1H), 2.97 (d, *J* = 4.9 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.4, 138.0, 133.3, 131.2, 129.5, 127.5, 119.3, 26.8.



***N*-Methyl-4-(trifluoromethyl) benzamide[3] (2f) [CAS: 65017-76-7]**

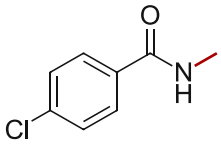
Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1), yielding 85 mg (79 %) of the title compound as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dt, *J* = 8.0, 0.8 Hz, 2H), 7.70 – 7.63 (m, 2H), 6.46 (s, 1H), 3.01 (d, *J* = 4.9 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.1, 138.0, 133.2 (q, *J* = 32.8 Hz), 127.6, 125.7 (q, *J* = 3.8 Hz), 122.4 (q, *J* = 273.4 Hz), 27.0.

^{19}F NMR$\{^1H\}$ (376 MHz, $CDCl_3$) δ -62.97.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_9F_3NO$: 204.0631; found: 204.0634



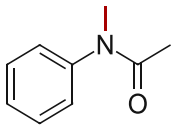
4-Chloro-*N*-methylbenzamide (2g) [2] [CAS: 6873-44-5]

Prepared, following the general procedure from commercially available starting material with a reaction time of 20 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 90 mg (84 %) of the title compound as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.65 (m, 2H), 7.40 – 7.32 (m, 2H), 6.45 (s, 1H), 2.98 (d, *J* = 4.8 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.3, 137.6, 133.0, 128.8, 128.4, 27.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for C_8H_9ClNO: 170.0367; found: 170.0369



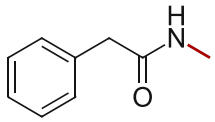
***N*-Acetyl-*N*-methylaniline[5] (2h) [CAS: 579-10-2]**

Prepared, following the general procedure from commercially available starting material with a reaction time of 20 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 50:1), yielding 97 mg (91 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.20 – 7.09 (m, 2H), 3.22 (s, 3H), 1.83 (s, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.5, 144.64, 129.7, 127.7, 127.1, 37.1, 22.4.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_{12}NO$: 150.0914; found: 150.0915



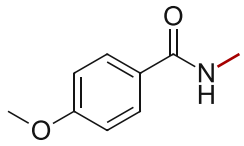
***N*-Methylphenylacetamide[6] (2i) [CAS: 6830-82-6]**

Prepared, following the general procedure from commercially available starting material with a reaction time of 16 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 80 mg (72 %) of the title compound a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.19 (m, 5H), 5.69 (s, 1H), 3.55 (s, 2H), 2.74 (d, *J* = 4.9 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.7, 135.0, 129.5, 129.0, 127.3, 43.7, 26.5.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_{12}NO$: 150.0914; found: 150.0917



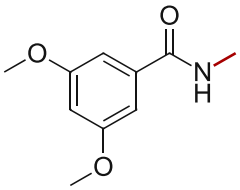
4-Methoxy-*N*-methylbenzamide[2] (2j) [CAS:3400-22-4]

Prepared, following the general procedure from commercially available starting material with a reaction time of 20 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 83 mg (78 %) of the title compound a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.69 (m, 2H), 6.90 – 6.82 (m, 2H), 6.53 (s, 1H), 3.80 (s, 3H), 2.94 (d, *J* = 4.8 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.9, 162.0, 128.7, 127.0, 113.7, 55.4, 26.8.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_{12}NO_2$: 166.0862; found: 166.0864

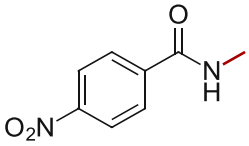


3,5-Dimethoxy-*N*-methylbenzamide[7] (2k) [CAS: 74826-21-4]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1), yielding 97 mg (92 %) of the title compound an oily liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, *J* = 2.3 Hz, 2H), 6.63 (bs, 1H), 6.54 – 6.39 (m, 1H), 3.75 (s, 6H), 2.92 (d, *J* = 4.8 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.2, 160.8, 136.9, 104.9, 103.5, 101.5, 55.5, 26.8.



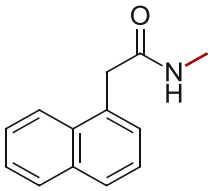
***N*-Methyl-4-nitrobenzamide[8] (2l) [CAS: 2585-23-1]**

Prepared, following the general procedure from commercially available starting material with a reaction time of 11 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1), yielding 71 mg (67 %) of the title compound as yellow solid.

^{1}H NMR (400 MHz, DMSO) δ 8.77 (s, 1H), 8.35 – 8.26 (m, 2H), 8.09 – 8.01 (m, 2H), 2.81 (d, *J* = 4.6 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 164.9, 148.9, 140.1, 128.5, 123.5, 26.3.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_8H_9N_2O_3$: 181.0608; found: 181.0611



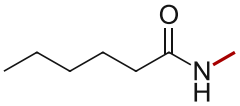
***N*-Methyl-α-naphthylacetamide (2m) [CAS:1136-81-8]**

Prepared, following the general procedure from commercially available starting material with a reaction time of 20 h. Work-up procedure A was followed (10 g silica, LP:EA 4:1, 2:3, 1:10), yielding 61 mg (58 %) of the title compound as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.91 (m, 1H), 7.91 – 7.84 (m, 1H), 7.82 (dt, *J* = 8.1, 1.2 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.45 (dd, *J* = 8.2, 6.9 Hz, 1H), 7.42 – 7.34 (m, 1H), 5.38 (s, 1H), 4.01 (s, 2H), 2.66 (d, *J* = 4.9 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.5, 134.0, 132.1, 131.2, 128.8, 128.5, 128.5, 126.9, 126.3, 125.7, 123.9, 41.7, 26.5.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{14}NO$: 200.1070; found: 200.1072

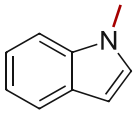


***N*-Methylhexanamide (2n)[9] [CAS: 3418-05-1]**

Prepared, following the general procedure from commercially available starting material with a reaction time of 14 h. Work-up procedure B was followed (10 g silica, DCM:MeOH 100:1), yielding 74 mg (67 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H), 2.73 (d, *J* = 4.8 Hz, 3H), 2.12 (d, *J* = 7.4 Hz, 2H), 1.63 – 1.51 (m, 2H), 1.33 – 1.16 (m, 4H), 0.83 (t, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.1, 36.6, 31.5, 26.2, 25.5, 22.4, 13.9.



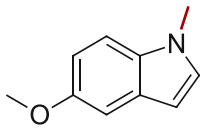
1-Methylindole (5a)[5] [CAS: 603-76-9]

Prepared, following the general procedure from commercially available starting material with a reaction time of 16 h. Work-up procedure B was followed (10 g silica, LP:EA 30:1), yielding 97 mg (88 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.39 (dq, *J* = 8.2, 0.9 Hz, 1H), 7.35 – 7.27 (m, 1H), 7.24 – 7.15 (m, 1H), 7.10 (d, *J* = 3.1 Hz, 1H), 6.57 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.83 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.8, 128.8, 128.5, 121.5, 120.9, 119.3, 109.2, 100.9, 32.8.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_{10}N$: 132.0808; found: 132.0812



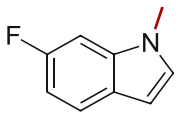
5-Methoxy-1-methylindole (5b)[5] [CAS: 2521-13-3]

Prepared, following the general procedure from commercially available starting material with a reaction time of 19 h. Work-up procedure B was followed (10 g silica, LP:EA 50:1, 40:1), yielding 89 mg (82 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 1H), 7.12 (d, *J* = 2.5 Hz, 1H), 7.03 (d, *J* = 3.1 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.42 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.87 (s, 3H), 3.77 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.1, 132.2, 129.4, 128.9, 111.9, 110.0, 102.6, 100.5, 56.0, 33.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{12}NO$: 162.0914; found: 162.0917



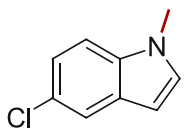
6-Fluoro-1-methylindole [5] (5c) [CAS: 441715-92-0]

Prepared, following the general procedure from commercially available starting material with a reaction time of 15 h. Work-up procedure B was followed (10 g silica, LP:EA 10:1), yielding 98 mg (91 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 1H), 7.10 – 6.98 (m, 2H), 7.01 – 6.90 (m, 1H), 6.54 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.75 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.9 (d, *J* = 237.2 Hz), 136.8 (d, *J* = 12.1 Hz), 129.3 (d, *J* = 3.8 Hz), 125.0, 121.6 (d, *J* = 10.0 Hz), 108.0 (d, *J* = 24.5 Hz), 101.1, 95.6 (d, *J* = 26.1 Hz), 32.8.

HRMS (ESI): m/z $[M+H]^+$ calcd. for C_9H_9FN: 150.0714; found: 150.0718



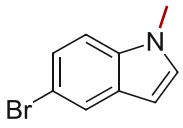
5-Chloro-1-methylindole [10] (5d) [CAS: 112398-75-1]

Prepared, following the general procedure from commercially available starting material with a reaction time of 16 h. Work-up procedure B was followed (10 g silica, LP:EA 10:1), yielding 102 mg (95 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.60 (m, 1H), 7.28 – 7.16 (m, 2H), 7.08 (d, *J* = 3.1 Hz, 1H), 6.46 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.77 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.2, 130.2, 129.5, 125.1, 121.8, 120.2, 110.3, 100.6, 33.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for C_9H_9ClN: 166.0418; found: 166.0420



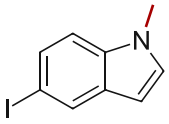
5-Bromo-1-methylindole[10] (5e) [CAS: 10075-52-2]

Prepared, following the general procedure from commercially available starting material with a reaction time of 15 h. Work-up procedure B was followed (10 g silica, LP:EA 10:1), yielding 101 mg (95 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.32 (ddd, *J* = 8.7, 1.9, 0.4 Hz, 1H), 7.19 (dt, *J* = 8.7, 0.7 Hz, 1H), 7.05 (d, *J* = 3.1 Hz, 1H), 6.45 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.76 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.4, 130.2, 130.0, 124.3, 123.3, 112.7, 110.7, 100.6, 33.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for C_9H_9BrN: 209.9913; found: 209.9914



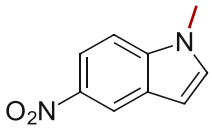
5-Iodo-1-methylindole [5] (5f) [CAS: 280563-07-7]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure B was followed (10 g silica, LP:EA 10:1), yielding 92 mg (92 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.47 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.10 (dt, *J* = 8.6, 0.7 Hz, 1H), 7.01 (d, *J* = 3.1 Hz, 1H), 6.41 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.76 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.8, 131.1, 129.8, 129.7, 129.7, 111.3, 100.3, 82.9, 33.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for C_9H_9IN: 257.9775; found: 257.9777



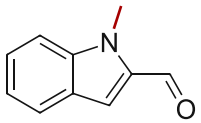
1-Methyl-5-nitroindole [11] (5g) [CAS: 29906-67-0]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure B was followed (10 g silica, LP:EA 10:1), yielding 98 mg (90 %) of the title compound as yellow crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.3 Hz, 1H), 8.10 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.31 (d, *J* = 9.1 Hz, 1H), 7.20 (d, *J* = 3.2 Hz, 1H), 6.65 (dd, *J* = 3.2, 0.8 Hz, 1H), 3.85 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 141.6, 139.5, 132.1, 127.7, 118.2, 117.2, 109.1, 103.9, 33.3.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_9N_2O_2$: 177.0659; found: 177.0661



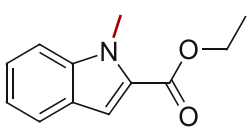
1-Methyl-2-indolecarbaldehyde [12] (5h) [CAS: 27421-51-8]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure B was followed (10 g silica, LP:EA 10:1), yielding 99 mg (93 %) of the title compound as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.74 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.48 – 7.35 (m, 2H), 7.24 (d, *J* = 0.9 Hz, 1H), 7.21 – 7.14 (m, 1H), 4.09 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 182.9, 140.9, 135.7, 126.9, 126.3, 123.4, 121.0, 117.5, 110.4, 31.6.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{10}NO$: 160.0757; found: 160.0760



Ethyl 1-methyl-2-indolecarboxylate [13] (5i) [CAS: 18450-24-3]

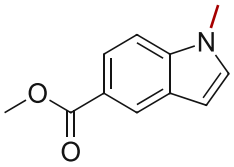
Prepared, following the general procedure from commercially available starting material with a reaction time of 23 h. Work-up procedure B was followed (10 g silica, LP:EA 30:1), yielding 106 mg (99 %) of the title compound as off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.43 – 7.29 (m, 3H), 7.21 – 7.13 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.09 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.3, 139.7, 128.1, 125.9, 125.0, 122.6, 120.6, 110.3, 110.1, 60.6, 31.6, 14.4.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{12}H_{14}NO_2$: 204.1019; found: 204.1022

Methyl 1-methyl-5-indolecarboxylate [11] (5j) [CAS: 128742-76-7]

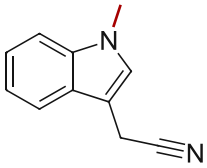


Prepared, following the general procedure from commercially available starting material with a reaction time of 23 h. Work-up procedure B was followed (10 g silica, LP:EA 30:1, 20:1, 10:1), yielding 91 mg (85 %) of the title compound as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.84 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.22 (dt, *J* = 8.7, 0.8 Hz, 1H), 7.01 (d, *J* = 3.2 Hz, 1H), 6.49 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.3, 139.2, 130.3, 128.0, 124.0, 123.0, 121.4, 108.9, 102.7, 51.9, 33.1.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{11}H_{12}NO_2$: 190.0863; found: 190.0865



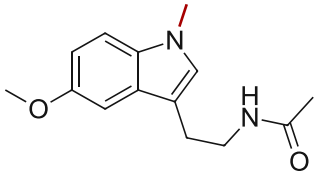
(1-Methyl-3-indolyl)acetonitrile [14] (5k) [CAS: 51584-17-9]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure B was followed (10 g silica, LP:EA 20:1, 10:1), yielding 96 mg (90 %) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.25 – 7.17 (m, 1H), 7.08 (t, *J* = 1.1 Hz, 1H), 3.81 (d, *J* = 1.1 Hz, 2H), 3.76 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.1, 127.4, 126.4, 122.4, 119.7, 118.3, 118.2, 109.7, 102.9, 32.8, 14.2.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{11}H_{11}N_2$: 171.0917; found: 171.0920



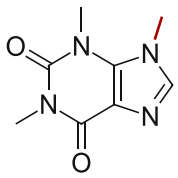
***N*-Methylmelatonine [15] (7) [CAS: 53350-25-7]**

Prepared, following the general procedure from the commercially available, bioactive compound melatonine with a reaction time of 23 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1), yielding 91 mg (88 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 8.9, 0.5 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.89 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.85 (s, 1H), 5.78 (s, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.55 (td, *J* = 6.8, 5.7 Hz, 2H), 2.91 (td, *J* = 6.8, 0.9 Hz, 2H), 1.92 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.1, 153.8, 132.5, 128.1, 127.4, 112.0, 110.9, 110.1, 100.6, 56.0, 39.9, 32.8, 25.2, 23.4.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{19}N_2O_2$: 247.1441; found: 247.1444



Caffeine (8) [CAS: 69-22-7]

Prepared, following the general procedure from commercially available Theophyllin with a reaction time of 20 h. After coolin the reaction to room temperature, 2 mL deion. water were added and the product was extracted 4 times with 10 mL DCM. The combined organic extracts were washed once with brine, dried over Na2SO4, filtered and concentrated. The crude product was purified by trituration with hexane, to obtain 100 mg (99 %) as off-white powder.

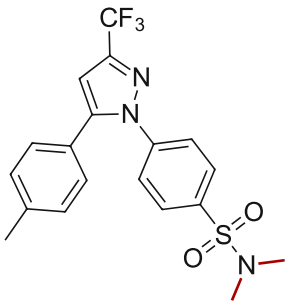
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 3.98 (s, 3H), 3.58 (s, 3H), 3.40 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.5, 151.8, 148.8, 141.5, 107.7, 33.7, 29.8, 28.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_8H_{11}N_4O_2$: 195.0877; found: 195.0879

_N,N_-Dimethyl celecoxib (9) [CAS: 2412733-30-1]

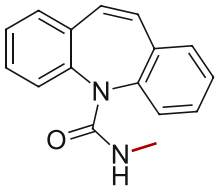
Prepared, following the general procedure from commercially available, bioactive celecoxib with a reaction time of 20 h. Work-up procedure A was followed (10 g silica, LP:EA 100:1, 70:1, 50:1, 10:1, 5:1), yielding 97 mg (92 %) of the title compound as slightly blue crystals.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.72 (m, 2H), 7.54 – 7.46 (m, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.75 (s, 1H), 2.70 (s, 6H), 2.38 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 144.2 (q, *J* = 38.5 Hz), 142.7, 139.9, 135.2, 129.8, 128.8, 128.8, 125.8, 125.7, 121.1 (q, *J* = 272.4 Hz), 106.36 (d, *J* = 2.1 Hz), 37.9, 21.4.

HRMS (ESI): m/z $[M+H]^+$ calcd. for: $C_{19}H_{19}F_3N_3O_2S$: 410.1145; found: 410.1145



_N_-Methyl carbamazepine[16] (10) [CAS: 41359-02-8]

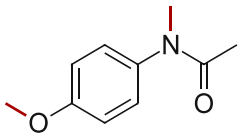
Prepared, following the general procedure from commercially available, bioactive carbamazepine with a reaction time of 16 h. Work-up procedure A was followed (10 g, LP:EA 20:1, 1:1, 1:2), yielding 50 mg (49 %) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.28 (m, 8H), 6.91 (s, 2H), 4.26 (s, 1H), 2.70 (d, *J* = 4.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9, 140.1, 135.3, 130.5, 129.6, 129.4, 129.2, 127.6, 27.3.

HRMS (ESI): m/z $[M+H]^+$ calcd. for: $C_{16}H_{15}N_2O$: 251.1179; found: 251.1179

_N,O_-Dimethyl paracetamol[5] (11) [CAS: 35813-38-8]

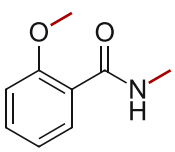


Paracetamol (100 mg, 1 equiv), $PhMe_3NI$ (2 equiv), and Cs_2CO_3 (2 equiv) were placed in an 8 mL glass vial equipped with a magnetic stirring bar and a septum screw cap. Via a cannula, the vial was evacuated and backfilled with argon three times. Subsequently, toluene (0.23 M) was added *via* syringe, and the evacuation and backfilling cycles were repeated under vigorous stirring so that no boiling delay occurred. The septum screw cap was replaced with a closed Wheaton® screw cap. The inhomogeneous reaction mixture was heated to 120 °C in a metallic heating block for 4 h. The reaction was cooled to room temperature and another 2 equiv $PhMe_3NI$, and Cs_2CO_3 each were added. The reaction was again heated up to 120 °C and stirred at respective temperature for 18 h. Work-up procedure A was followed (10 g silica, LP:EA 2:1, 1:1), yielding 116 mg (98 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 1H), 7.11 – 7.02 (m, 1H), 3.98 (s, 1H), 3.37 (s, 1H), 2.00 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 158.9, 137.6, 128.2, 114.9, 55.5, 37.4, 22.4.

_O,N_-Dimethyl salicylamide[17] (12) [CAS: 3400-35-9]

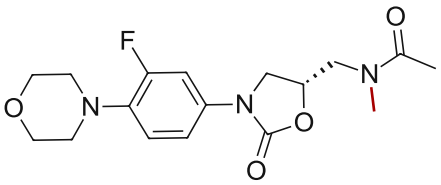


Salicylamide (100 mg, 1 equiv), $PhMe_3NI$ (2 equiv), and Cs_2CO_3 (2 equiv) were placed in an 8 mL glass vial equipped with a magnetic stirring bar and a septum screw cap. Via a cannula, the vial was evacuated and backfilled with argon three times. Subsequently, toluene (0.23 M) was added *via* syringe, and the evacuation and backfilling cycles were repeated under vigorous stirring so that no boiling delay occurred. The septum screw cap was replaced with a closed Wheaton® screw cap. The inhomogeneous reaction mixture was heated to 120 °C in a metallic heating block for 3 h. The reaction was cooled to room temperature and

another 2 equiv $PhMe_3NI$, and Cs_2CO_3 each were added. The reaction was again heated up to 120 °C and stirred at respective temperature for 17 h. Work-up procedure A was followed (10 g silica, LP:EA 2:1, 1:1), yielding 93 mg (77 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dq, *J* = 7.8, 2.1 Hz, 1H), 7.81 (s, 1H), 7.45 – 7.35 (m, 1H), 7.08 – 6.98 (m, 1H), 6.98 – 6.89 (m, 1H), 3.95 – 3.89 (m, 3H), 3.01 – 2.94 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 157.4, 132.6, 132.2, 121.5, 121.2, 111.2, 55.9, 26.5.



_N_-Methyl linezolid (13) [CAS: 3400-35-9]

Linezolid (100 mg, 1 equiv), $PhMe_3NI$ (2 equiv), and Cs_2CO_3 (2 equiv) were placed in an 8 mL glass vial equipped with a magnetic stirring bar and a septum screw cap. *Via* a cannula, the vial was evacuated and backfilled with argon three times. Subsequently, toluene (0.23 M) was added *via* syringe, and the evacuation and backfilling cycles were repeated under vigorous stirring so that no boiling delay occurred. The septum screw cap was replaced with a closed Wheaton® screw cap. The inhomogeneous reaction mixture was heated to 120 °C in a metallic heating block for 4 h. The reaction was cooled to room temperature and another 2 equiv $PhMe_3NI$, and Cs_2CO_3 each were added. The reaction was again heated up to 120 °C and stirred at respective temperature for 19 h. Work-up procedure A was followed (10 g silica, EA:MeOH 25:1), yielding 93 mg (77 %) of the title compound as a colorless oil.

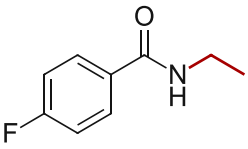
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 14.4, 2.6 Hz, 1H), 7.13 – 7.02 (m, 1H), 6.90 (t, *J* = 9.1 Hz, 1H), 4.83 (qd, *J* = 6.7, 3.1 Hz, 1H), 4.00 (t, *J* = 8.9 Hz, 1H), 3.90 (dd, *J* = 14.5, 3.2 Hz, 1H), 3.87 – 3.80 (m, 4H), 3.73 (dd, *J* = 9.2, 6.9 Hz, 1H), 3.50 (dd, *J* = 14.5, 6.4 Hz, 1H), 3.16 (s, 3H), 3.06 – 2.99 (m, 4H), 2.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 156.8, 154.4, 136.5 (d, *J* = 9.0 Hz), 133.2 (d, *J* = 10.5 Hz), 118.9 (d, *J* = 4.3 Hz), 113.9 (d, *J* = 3.5 Hz), 107.6 (d, *J* = 26.5 Hz), 72.6, 67.0, 51.1 (d, *J* = 3.2 Hz), 50.9, 48.1, 38.6, 21.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -120.2 (dd, *J* = 14.4, 9.4 Hz).

HRMS (ESI): m/z $[M+H]^+$ calcd. for: $C_{17}H_{23}FN_3O_4$: 352.1667; found: 352.1667

Substrate scope ethylation



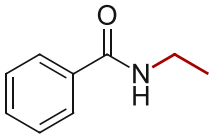
_N_-Ethyl-4-fluorobenzamide[18] (4a) [CAS: 772-18-9]

Prepared, following the general procedure from commercially available starting material with a reaction time of 12 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 94 mg (80 %) of the title compound as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.71 (m, 2H), 7.10 – 7.00 (m, 2H), 6.43 (s, 1H), 3.45 (qd, *J* = 7.3, 5.6 Hz, 2H), 1.21 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.5, 164.6 (d, *J* = 251.4 Hz), 131.0 (d, *J* = 3.2 Hz), 129.2 (d, *J* = 8.8 Hz), 115.5 (d, *J* = 21.8 Hz), 35.1, 14.9.

^{19}F{^{1}H} NMR (376 MHz) δ -108.7

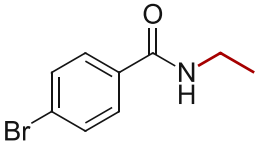


_N_-Ethylbenzamide[19] (4b) [CAS: 614-17-5]

Prepared, following the general procedure from commercially available starting material with a reaction time of 12 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 95 mg (77 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.72 (m, 2H), 7.49 – 7.41 (m, 1H), 7.41 – 7.30 (m, 2H), 6.56 (s, 1H), 3.45 (qd, *J* = 7.3, 5.6 Hz, 2H), 1.20 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.6, 134.8, 131.2, 128.5, 126.9, 34.9, 14.9.

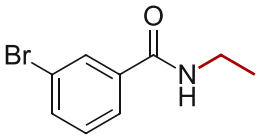


4-Bromo-_N_-ethylbenzamide[18] (4c) [CAS: 41882-25-1]

Prepared, following the general procedure from commercially available starting material with a reaction time of 12 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 71 mg (64 %) of the title compound as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 2H), 7.57 – 7.48 (m, 2H), 6.30 (s, 1H), 3.46 (qd, *J* = 7.3, 5.6 Hz, 2H), 1.23 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.6, 133.7, 131.8, 128.6, 126.0, 35.1, 14.9.

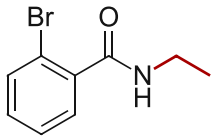


3-Bromo-_N_-ethylbenzamide[20] (4d) [CAS: 26819-10-3]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1), yielding 95 mg (85 %) of the title compound as a waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (t, *J* = 1.9 Hz, 1H), 7.66 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.57 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.25 (d, *J* = 15.7 Hz, 1H), 6.52 (s, 1H), 3.45 (qd, *J* = 7.3, 5.6 Hz, 2H), 1.22 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) 166.2, 136.8, 134.2, 130.2, 130.1, 125.5, 122.7, 35.1, 14.8.

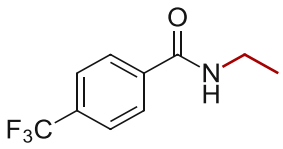


2-Bromo-_N_-ethylbenzamide[20] (4e) [CAS: 80031-02-3]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1), yielding 95 mg (85 %) of the title compound as a waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) 7.53 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.22 (td, *J* = 7.7, 1.8 Hz, 1H), 6.13 (s, 1H), 3.50 – 3.38 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) 167.6, 138.1, 133.3, 131.1, 129.4, 127.5, 119.3, 35.0, 14.7.

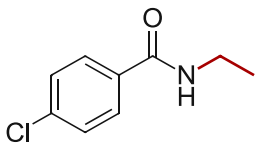


_N_-Ethyl-4-(trifluoromethyl) benzamide[21] (4f) [CAS: 1379773-10-0]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1), yielding 88 mg (76 %) of the title compound as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.9 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 6.59 (s, 1H), 3.47 (qd, *J* = 7.3, 5.6 Hz, 2H), 1.23 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.4, 138.1, 133.1 (q, *J* = 32.8 Hz), 127.4, 125.6 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.6 Hz), 35.2, 14.8.

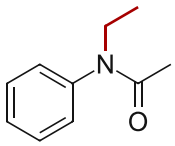


4-Chloro-_N_-ethylbenzamide[19] (4g) [CAS: 26930-17-6]

Prepared, following the general procedure from commercially available starting material with a reaction time of 12 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 95 mg (82 %) of the title compound as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 2H), 7.39 – 7.30 (m, 2H), 6.46 (s, 1H), 3.44 (qd, *J* = 7.3, 5.6 Hz, 2H), 1.21 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.5, 137.5, 133.2, 128.7, 128.4, 35.1, 14.9.

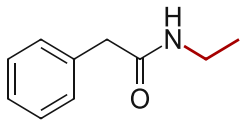


_N_-Ethylacetanilide[22] (4h) [CAS: 529- 65-7]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 50:1), yielding 108 mg (92 %) of the title compound as slightly blue oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H), 7.34 – 7.26 (m, 1H), 7.16 – 7.08 (m, 2H), 3.71 (q, *J* = 7.1 Hz, 2H), 1.78 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.9, 142.9, 129.6, 128.2, 127.8, 43.8, 22.8, 13.0.

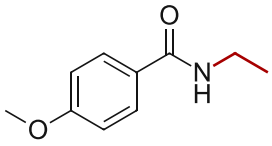


_N_-Ethylphenylacetamide[6] (4i) [CAS: 5465-00-9]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 50:1), yielding 77 mg (64 %) of the title compound a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.09 (m, 6H), 5.66 (s, 1H), 3.54 (s, 2H), 3.23 (qd, *J* = 7.3, 5.6 Hz, 2H), 1.05 (t, *J* = 7.3 Hz, 3H)

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 135.1, 129.4, 128.9, 127.2, 43.8, 34.5, 14.7.

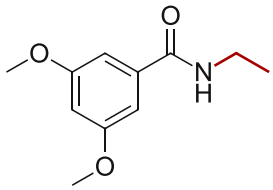


_N_-Ethyl-4-methoxybenzamide[23] (4j) [CAS: 7403-41-0]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 90 mg (76 %) of the title compound as amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.06 (s, 1H), 3.84 (s, 3H), 3.48 (qd, *J* = 7.2, 5.6 Hz, 2H), 1.24 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.0, 162.1, 128.7, 127.2, 113.8, 55.5, 34.9, 15.1.

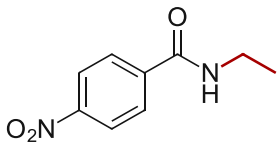


_N_-Ethyl-3,5-dimethoxbenzamide (4k) [CAS: 120301-09-9]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1), yielding 88 mg (78 %) of the title compound an amorphous solid..

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, *J* = 2.3 Hz, 2H), 6.56 – 6.50 (m, 1H), 6.33 (s, 1H), 3.82 – 3.74 (m, 6H), 3.44 (qd, *J* = 7.2, 5.9 Hz, 2H), 1.21 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.3, 160.9, 137.1, 104.8, 103.4, 55.6, 35.0, 14.9.

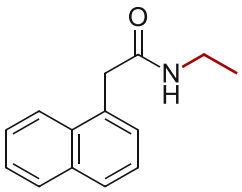


_N_-Ethyl-4-nitrobenzamide[24] (4l) [CAS: 50445-50-6]

Prepared, following the general procedure from commercially available starting material with a reaction time of 11 h. Work-up procedure A was followed (10 g silica, DCM:MeOH 100:1, 50:1), yielding 93 mg (81 %) of the title compound as yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.9 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H), 6.63 (s, 1H), 3.48 (qd, *J* = 7.3, 5.6 Hz, 2H), 1.24 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.5, 149.5, 140.4, 128.2, 123.8, 35.4, 14.7.

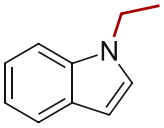


_N_-Ethyl-α-naphthylacetamide (4m) [CAS: 1140-55-2]

Prepared, following the general procedure from commercially available starting material with a reaction time of 12 h. Work-up procedure A was followed (10 g silica, LP:EA 4:1, 2:3, 1:10), yielding 66 mg (59 %) of the title compound as a colorless waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.91 (m, 1H), 7.91 – 7.84 (m, 1H), 7.84 – 7.75 (m, 1H), 7.58 – 7.49 (m, 2H), 7.49 – 7.36 (m, 2H), 5.36 (s, 1H), 4.00 (s, 2H), 3.16 (qd, *J* = 7.2, 5.7 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 134.0, 132.1, 131.3, 128.8, 128.5, 128.4, 126.8, 126.2, 125.7, 123.9, 41.9, 34.5, 14.7.

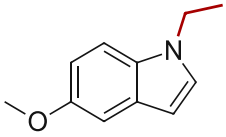


1-Ethylindole[25] (6a) [CAS: 10604-59-8]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure B was followed (10 g silica, LP:EA 30:1), yielding 97 mg (79 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.68 (m, 1H), 7.48 – 7.41 (m, 1H), 7.36 – 7.17 (m, 3H), 6.64 – 6.57 (m, 1H), 4.23 (q, *J* = 7.3 Hz, 2H), 1.54 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.7, 128.7, 127.0, 121.4, 121.0, 119.3, 109.3, 101.1, 41.0, 15.5.

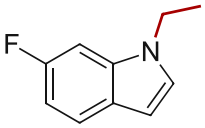


1-Ethyl-5-methoxyindole[25] (6b) [CAS: 46182-32-5]

Prepared, following the general procedure from commercially available starting material with a reaction time of 21 h. Work-up procedure B was followed (10 g silica, LP:EA 50:1), yielding 103 mg (87 %) of the title compound as a waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.9 Hz, 1H), 7.25 (dd, *J* = 9.5, 2.8 Hz, 2H), 7.04 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.57 (d, *J* = 3.2 Hz, 1H), 4.27 (q, *J* = 7.3 Hz, 2H), 4.00 (s, 3H), 1.59 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.0, 131.1, 129.0, 127.5, 111.8, 110.0, 102.6, 100.6, 55.9, 41.1, 15.5.



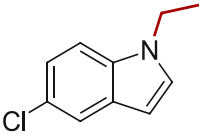
1-Ethyl-5-fluoroindole (6c) [CAS: 613684-38-1]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure B was followed (10 g silica, LP:EA 30:1), yielding 111 mg (94 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.6, 5.4 Hz, 1H), 7.12 (d, *J* = 3.2 Hz, 1H), 7.09 – 6.99 (m, 1H), 6.96 – 6.84 (m, 1H), 6.51 (dd, *J* = 3.2, 0.9 Hz, 1H), 4.12 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.8 (d, *J* = 236.9 Hz), 135.8 (d, *J* = 12.0 Hz), 127.5 (d, *J* = 3.6 Hz), 125.1, 121.7 (d, *J* = 10.2 Hz), 108.0 (d, *J* = 24.6 Hz), 101.3, 95.7 (d, *J* = 26.2 Hz), 41.2, 15.3.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -121.3

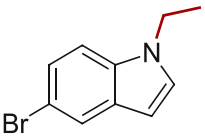


5-Chloro-1-ethylindole[25] (6d) [CAS: 112194-57-7]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure B was followed (10 g silica, LP:EA 30:1), yielding 104 mg (90 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 1H), 7.32 – 7.22 (m, 1H), 7.22 – 7.10 (m, 2H), 6.45 (dd, *J* = 3.2, 0.8 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.2, 129.7, 128.4, 125.0, 121.7, 120.3, 110.3, 100.8, 41.2, 15.5.

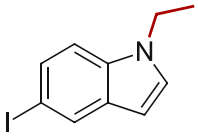


5-Bromo-1-ethylindole[26] (6e) [CAS: 195253-49-7]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure B was followed (10 g silica, LP:EA 30:1), yielding 88 mg (78 %) of the title compound as an amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (t, *J* = 2.3 Hz, 1H), 7.28 – 7.13 (m, 2H), 7.07 (d, *J* = 3.2 Hz, 1H), 6.48 – 6.28 (m, 1H), 4.08 (q, *J* = 7.3 Hz, 2H), 1.40 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.4, 130.4, 128.2, 124.2, 123.4, 112.6, 110.8, 100.7, 41.2, 15.4.

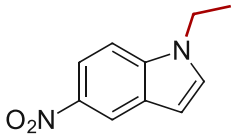


1-Ethyl-5-iodoindole (6f) [CAS: 2413600-46-9]

Prepared, following the general procedure from commercially available starting material with a reaction time of 17 h. Work-up procedure B was followed (10 g silica, LP:EA 30:1), yielding 100 mg (94 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.7 Hz, 1H), 7.46 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.13 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.08 (d, *J* = 3.2 Hz, 1H), 6.43 (dd, *J* = 3.1, 0.9 Hz, 1H), 4.14 (q, *J* = 7.3 Hz, 2H), 1.46 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.8, 131.3, 129.8, 129.6, 127.9, 111.3, 100.5, 82.8, 41.2, 15.4.

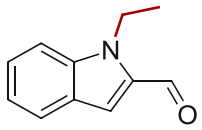


1-Ethyl-5-nitroindole (6g) [CAS: 193977-99-0]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure B was followed (10 g silica, LP:EA 30:1), yielding 109 mg (93 %) of the title compound as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.2 Hz, 1H), 8.09 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.34 (dt, *J* = 9.1, 0.7 Hz, 1H), 7.27 (s, 1H), 6.66 (dd, *J* = 3.3, 0.9 Hz, 1H), 4.22 (q, *J* = 7.3 Hz, 2H), 1.49 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 141.5, 138.6, 130.3, 127.8, 118.3, 117.1, 109.1, 104.0, 41.6, 15.4.

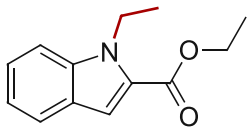


1-Ethyl-2-indolecarbaldehyde (6h) [CAS: 40913-43-7]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure B was followed (10 g silica, LP:EA 10:1), yielding 74 mg (64 %) of the title compound as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.75 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.26 (d, *J* = 0.5 Hz, 1H), 7.19 (dt, *J* = 8.0, 3.9 Hz, 1H), 4.62 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ182.6, 139.9, 135.1, 126.9, 126.5, 123.5, 120.9, 117.9, 110.4, 39.7, 15.6.

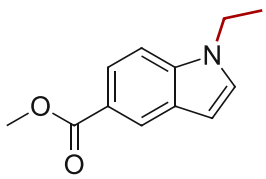


Ethyl 1-ethyl-2-indolecarboxylate[27] (6i) [CAS: 40913-41-5]

Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure B was followed (10 g silica, LP:EA 30:1), yielding 100 mg (87 %) of the title compound as off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.35 (dq, *J* = 8.5, 1.0 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.15 – 7.06 (m, 1H), 4.58 (q, *J* = 7.1 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.41 – 1.32 (m, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.0, 138.7, 127.3, 126.1, 124.9, 122.7, 120.5, 110.4, 110.3, 60.5, 39.6, 15.70, 14.4.

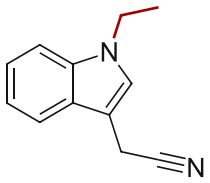


Methyl 1-ethyl-5-indolecarboxylate (6j) [CAS: 1205532-00-8]

Prepared, following the general procedure from commercially available starting material with a reaction time of 14 h. Work-up procedure B was followed (10 g silica, DCM:MeOH 100:1), yielding 105 mg (91 %) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.93 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.34 (dt, *J* = 8.7, 0.8 Hz, 1H), 7.16 (d, *J* = 3.2 Hz, 1H), 6.60 (dd, *J* = 3.2, 0.9 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 3.94 (s, 3H), 1.45 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.3, 138.2, 128.5, 128.1, 124.0, 122.7, 121.3, 108.9, 102.7, 51.8, 41.1, 15.4.



(1-Ethyl-3-indolyl)acetonitrile (6k) [CAS: 851041-59-3]

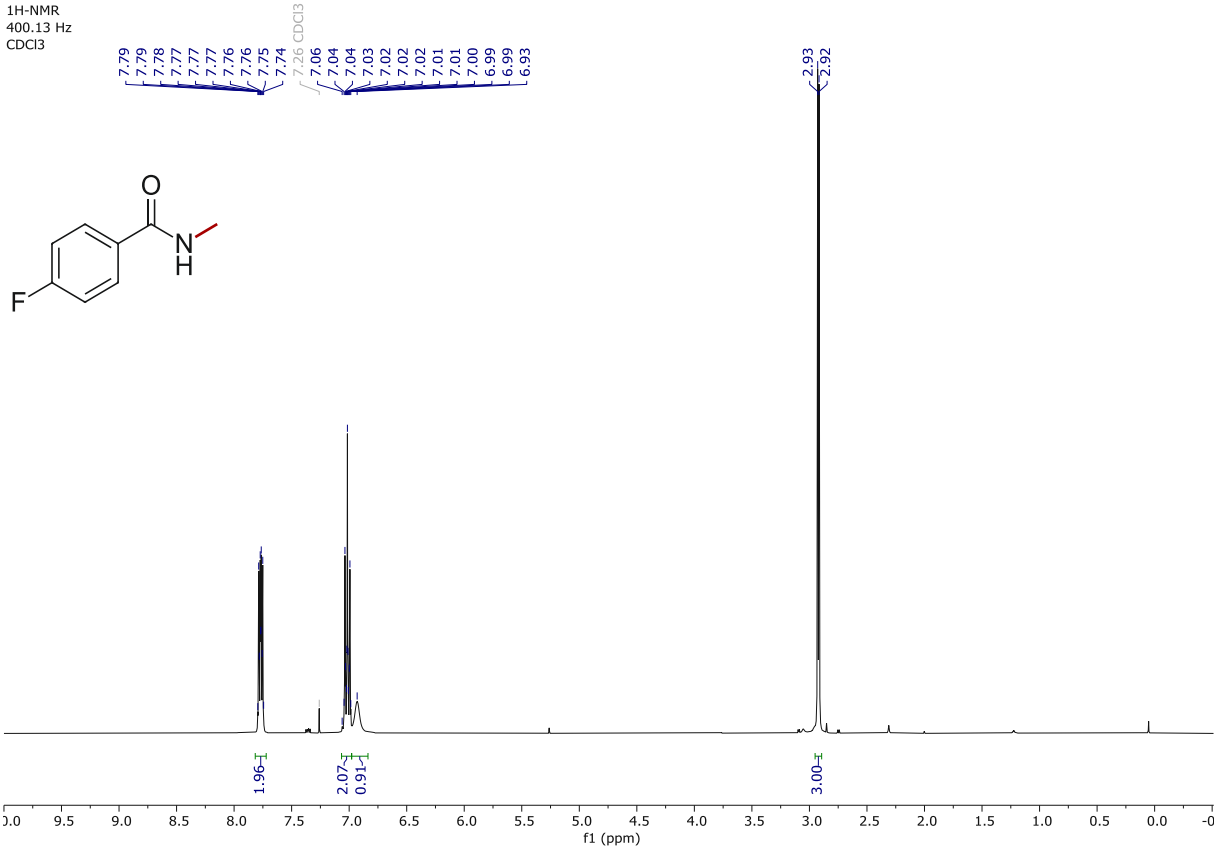
Prepared, following the general procedure from commercially available starting material with a reaction time of 18 h. Work-up procedure B was followed (10 g silica, LP:EA 40:1, 20:1, 10:1), yielding 108 mg (93 %) of the title compound as a yellow oil.

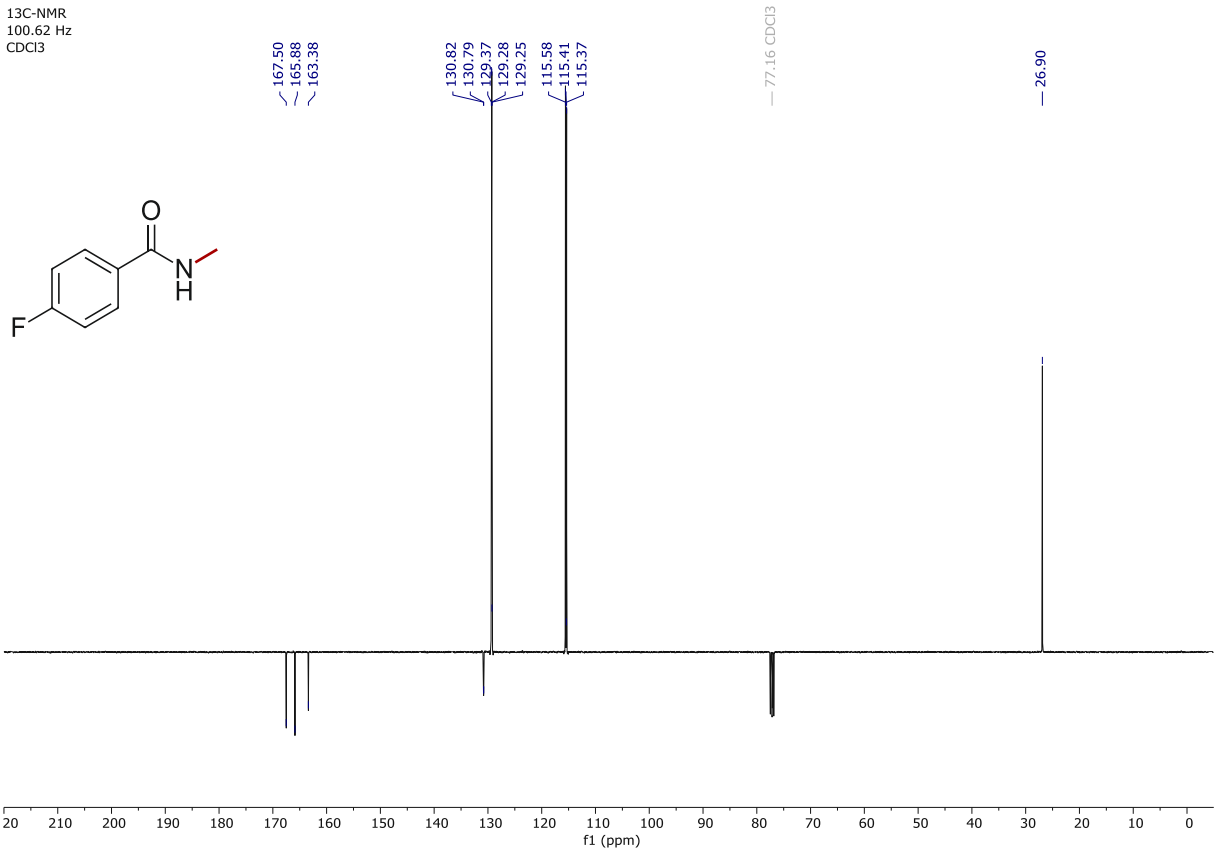
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.50 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.46 – 7.37 (m, 1H), 7.37 – 7.28 (m, 1H), 7.26 (d, *J* = 1.1 Hz, 1H), 4.25 (q, *J* = 7.3 Hz, 2H), 3.92 (d, *J* = 1.1 Hz, 2H), 1.58 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.1, 126.5, 125.6, 122.2, 119.6, 118.3, 118.2, 109.7, 103.0, 40.9, 15.4, 14.2.

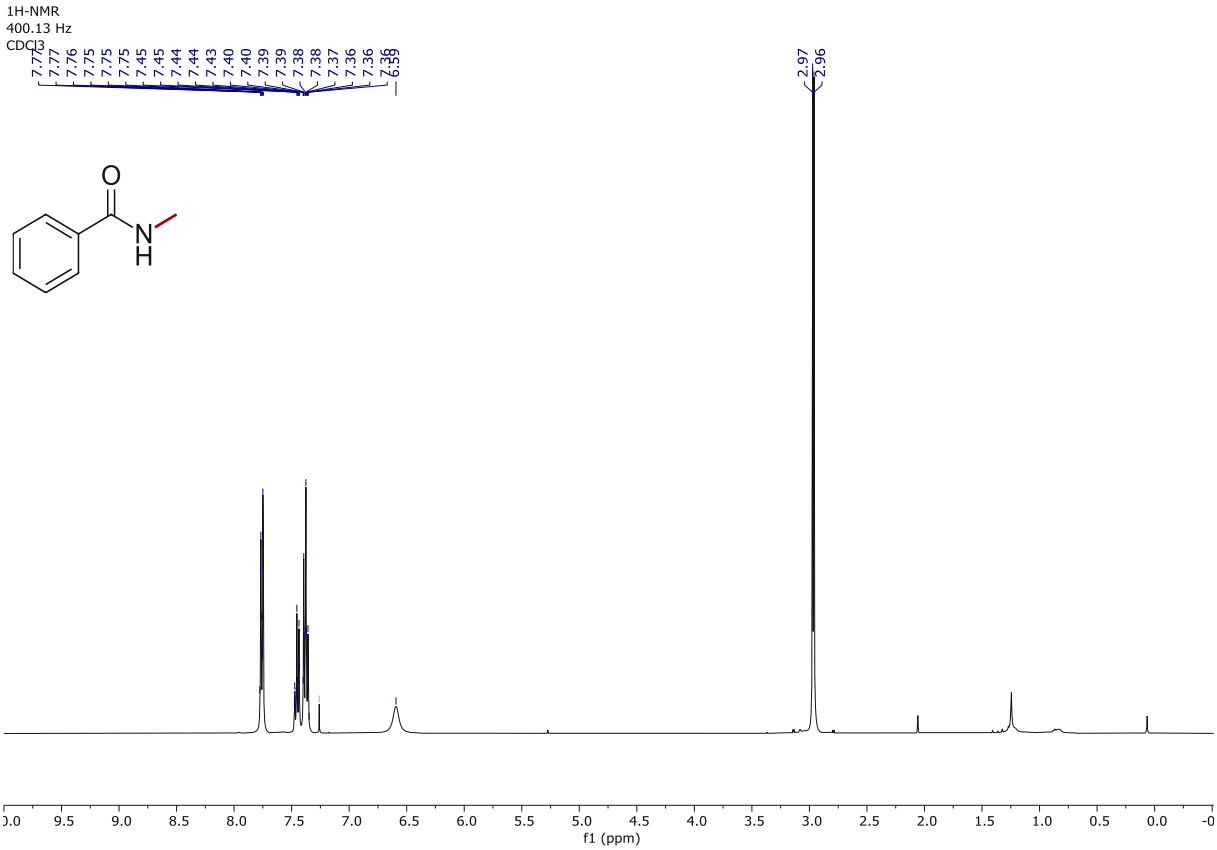
NMR-Spectra

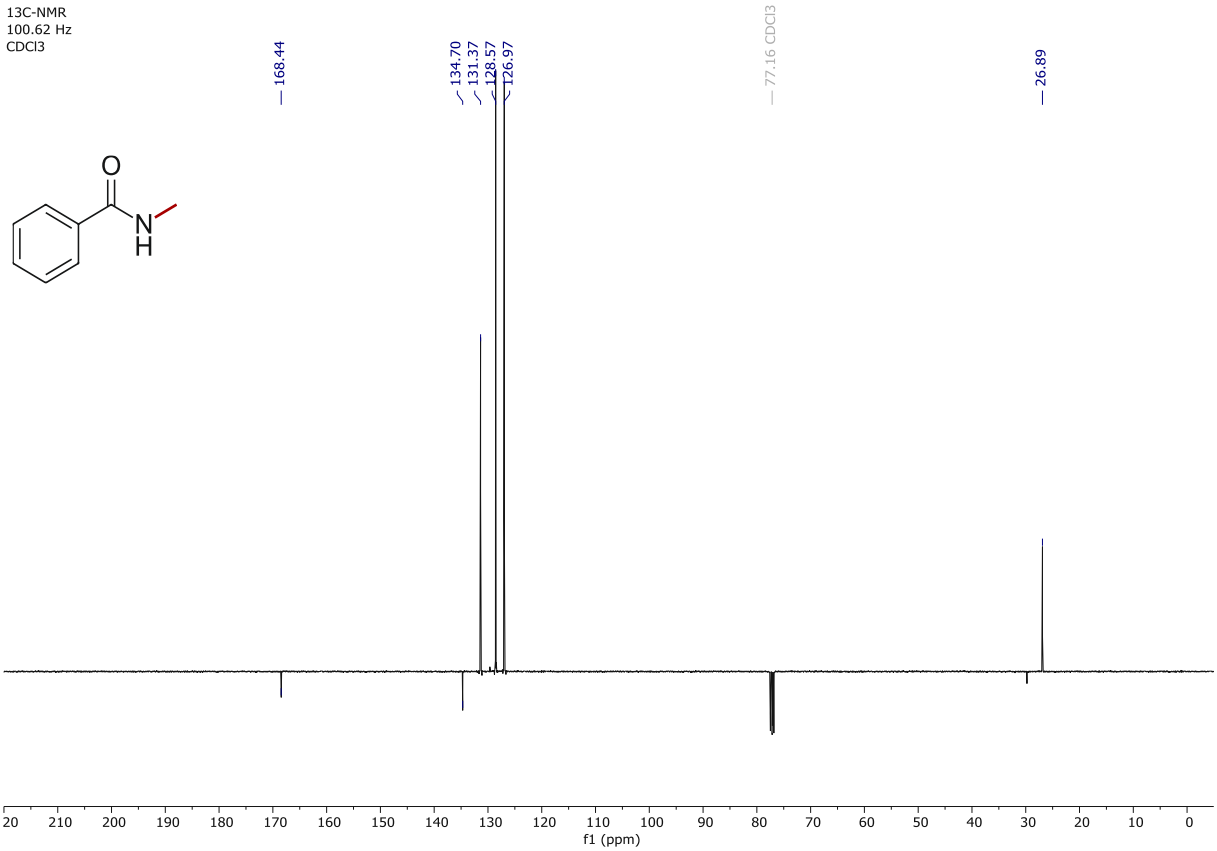
N-Methyl -4-fluorobenzamide (2a)



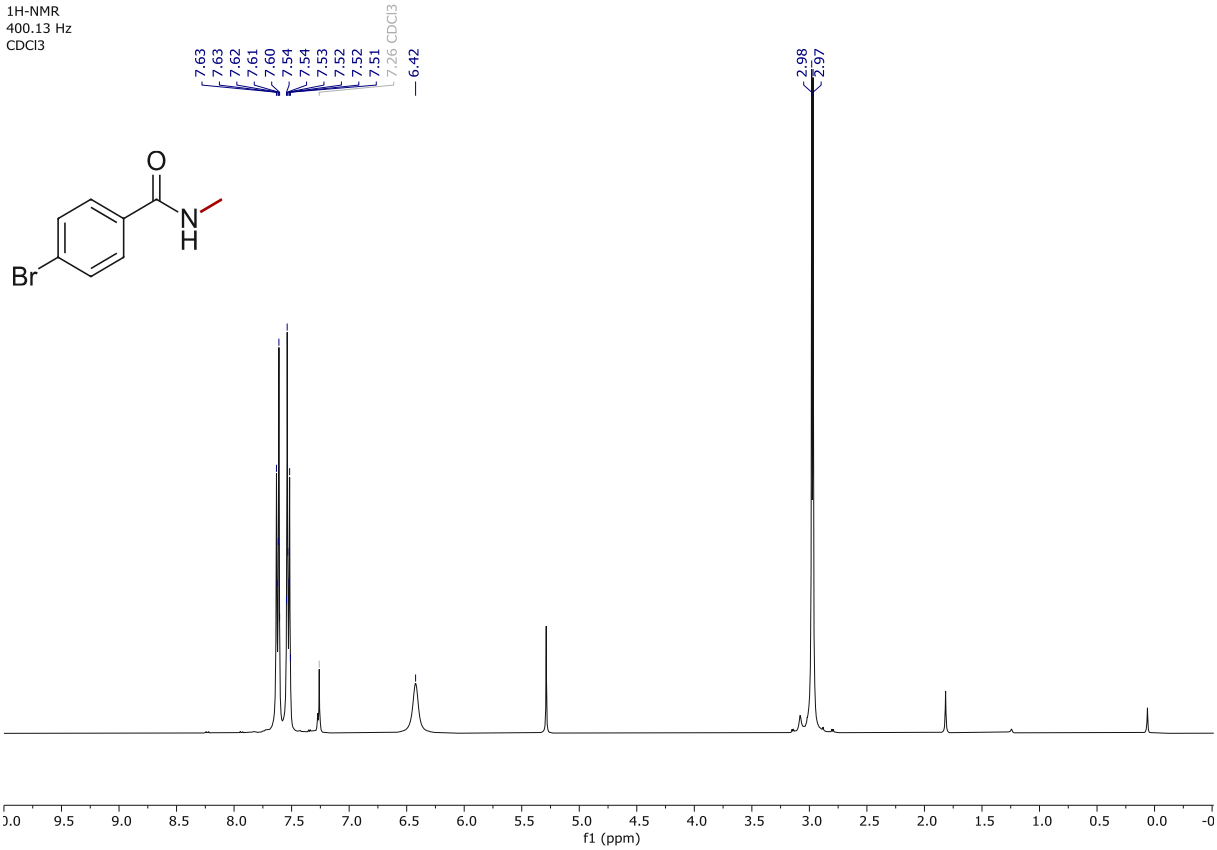


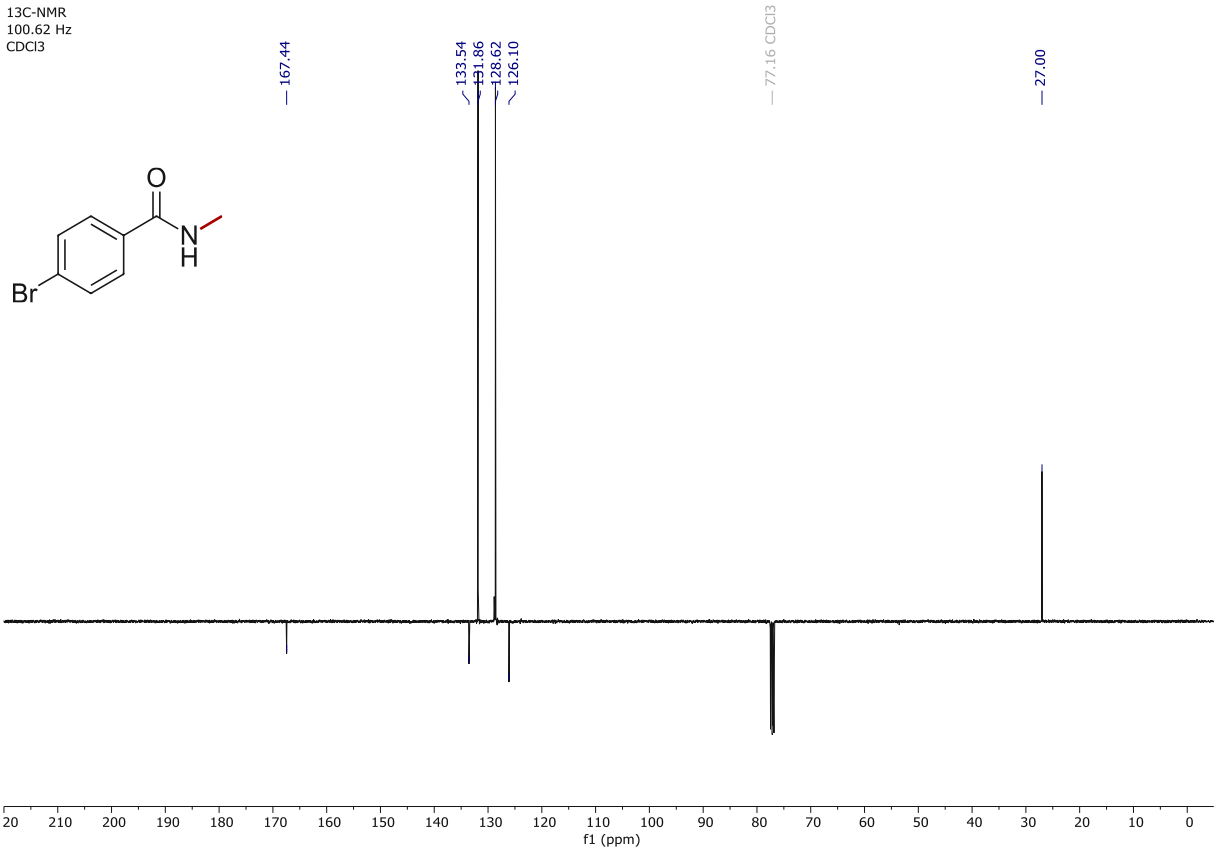
N-Methylbenzamide (2b)



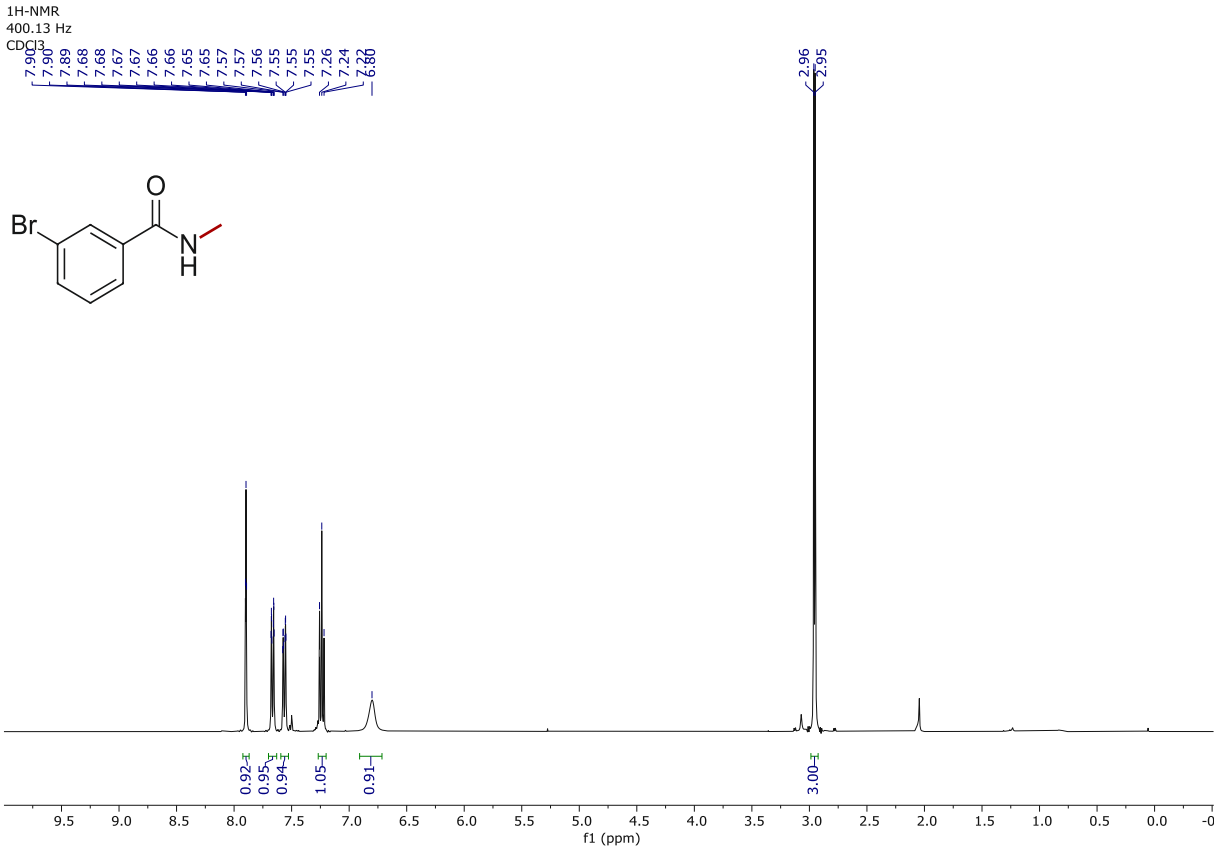


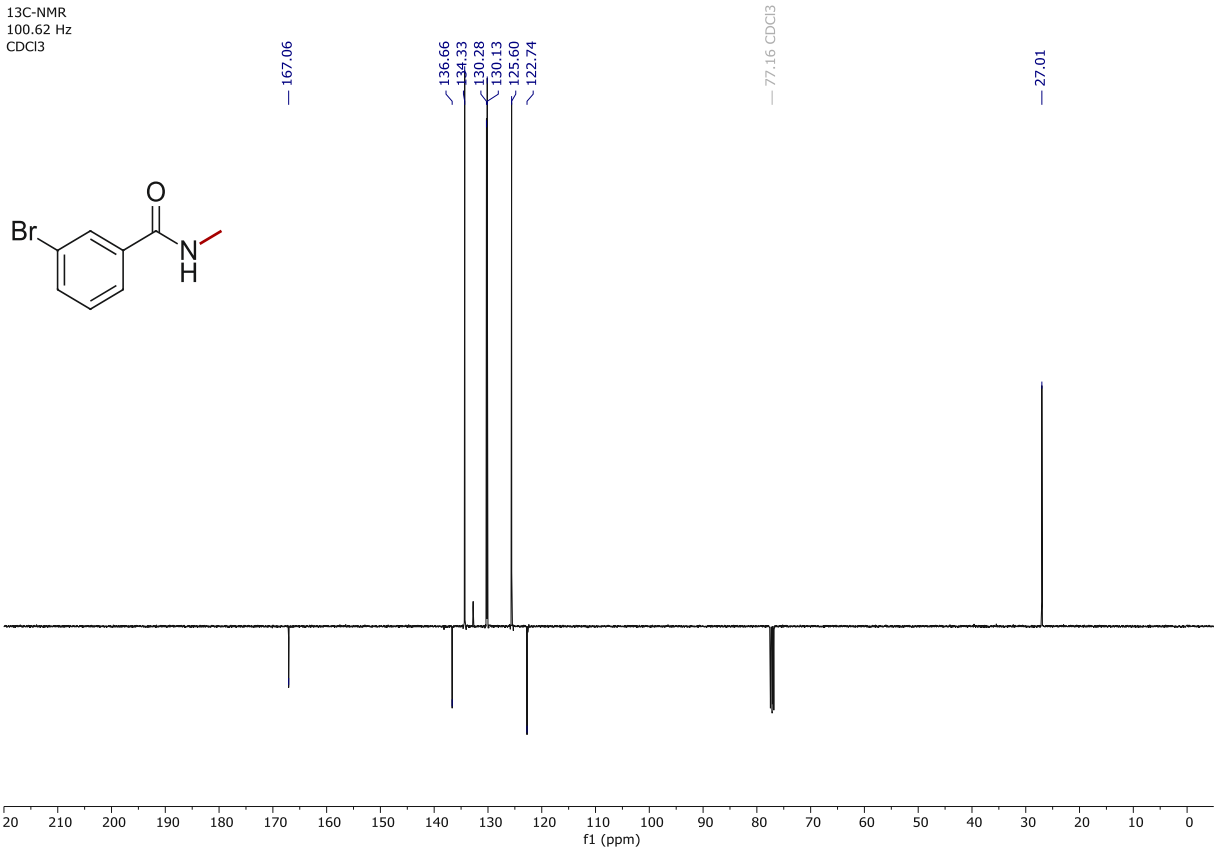
N-Methyl-4-bromobenzamide (2c)



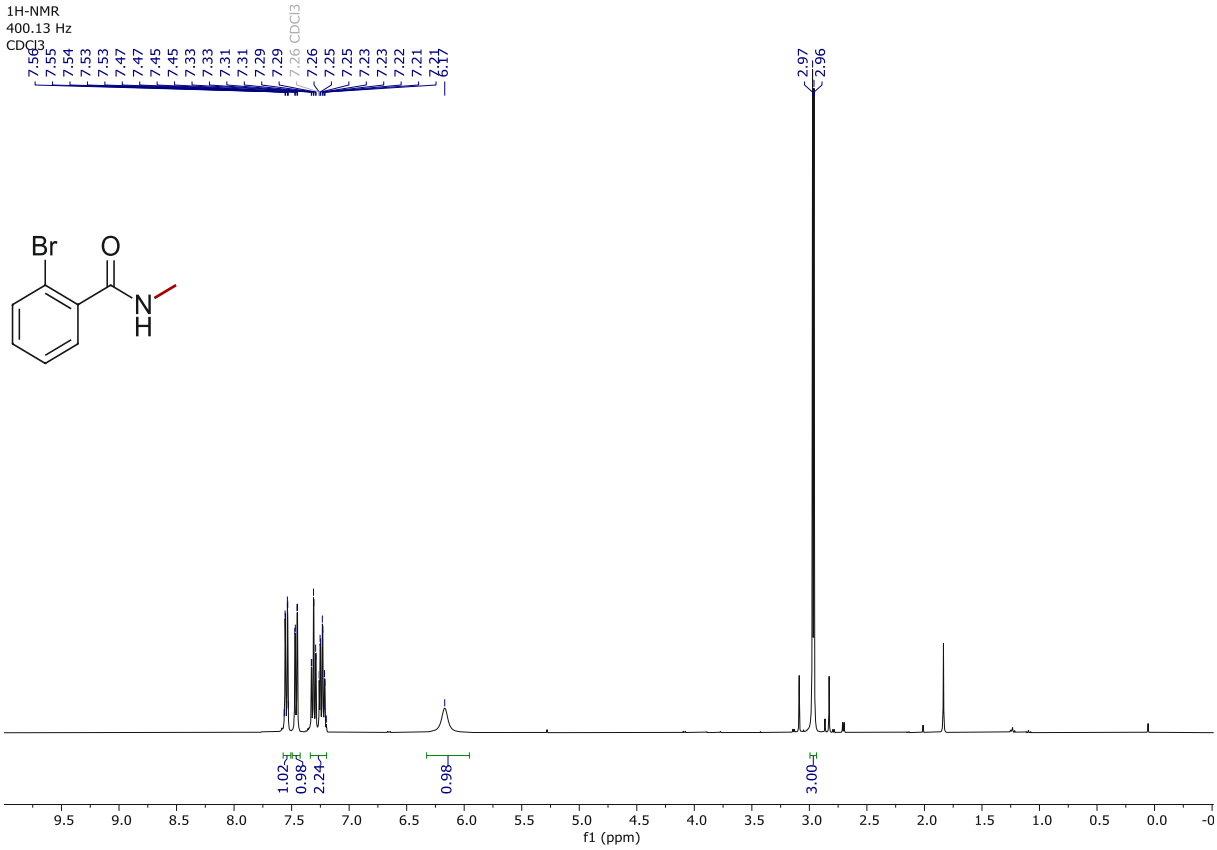


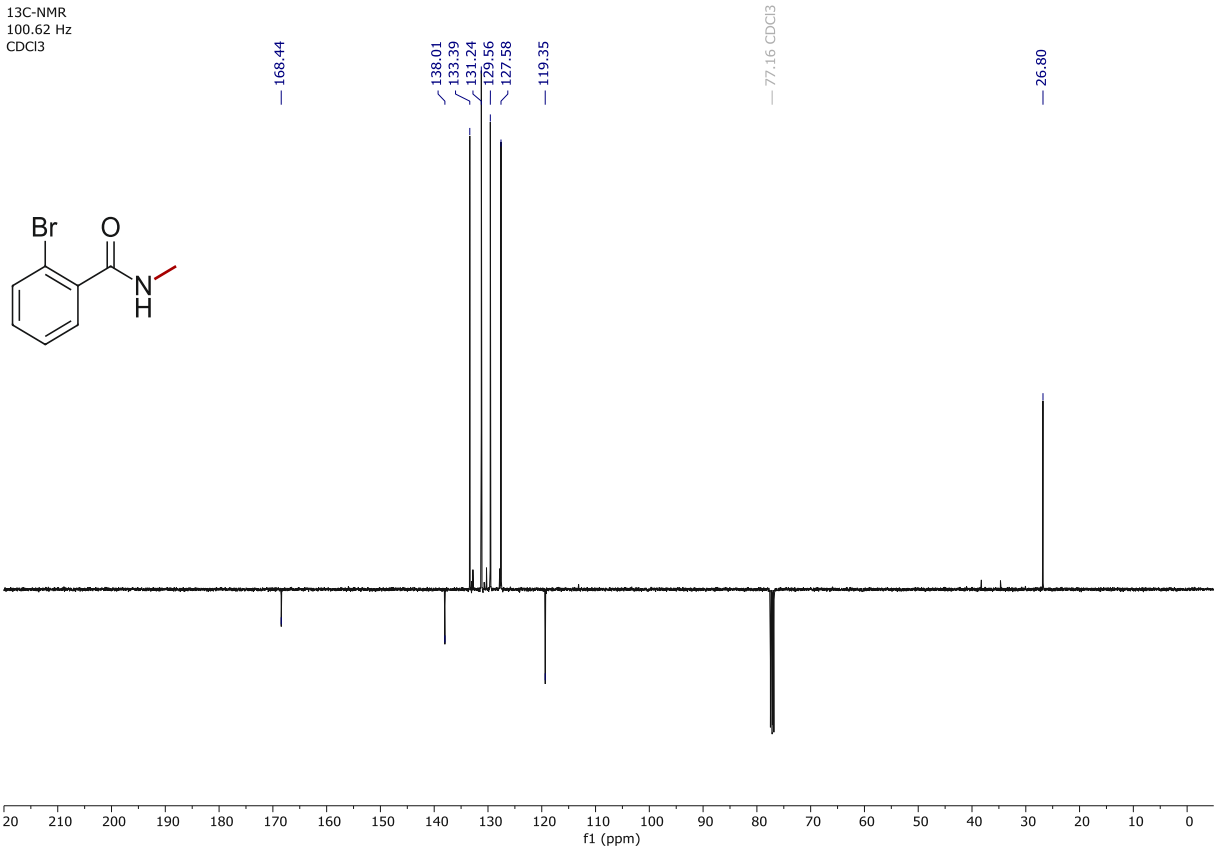
3-Bromo-*N*-methylbenzamide (2d)



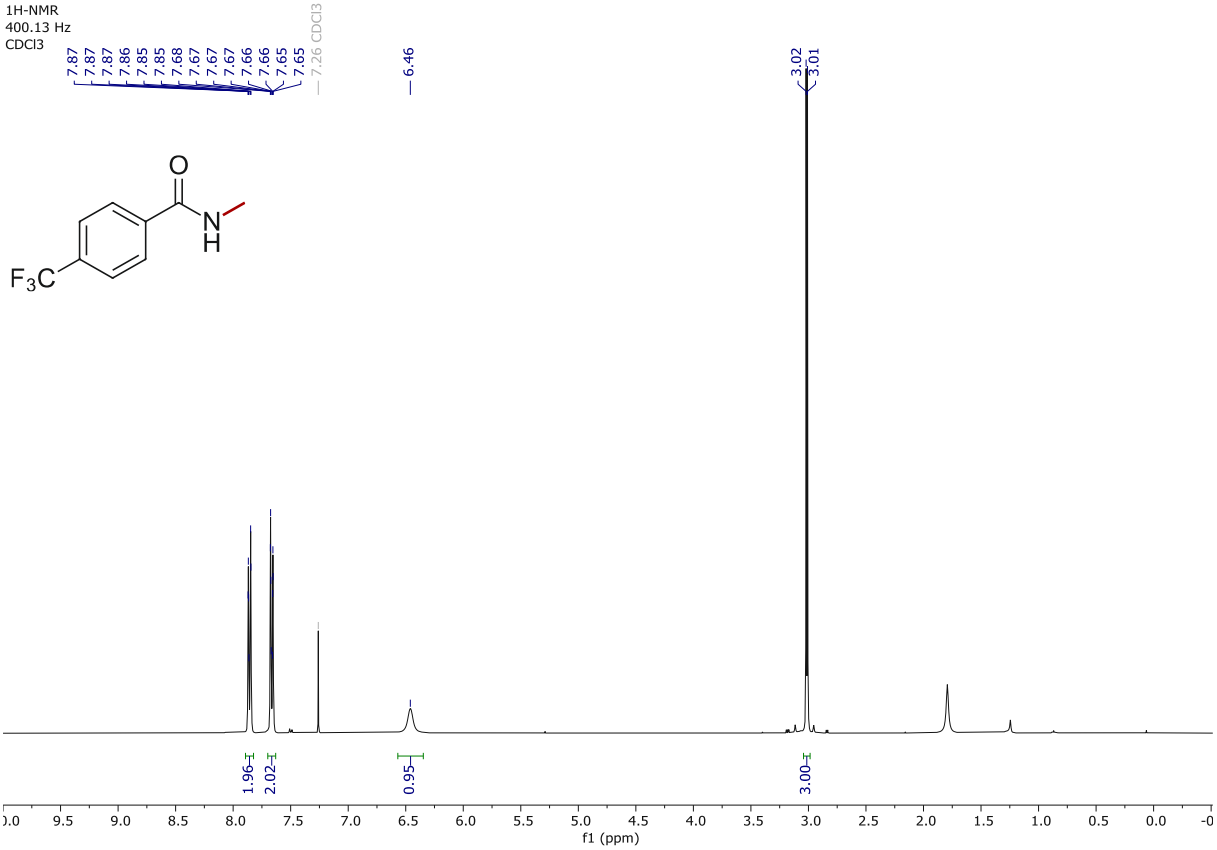


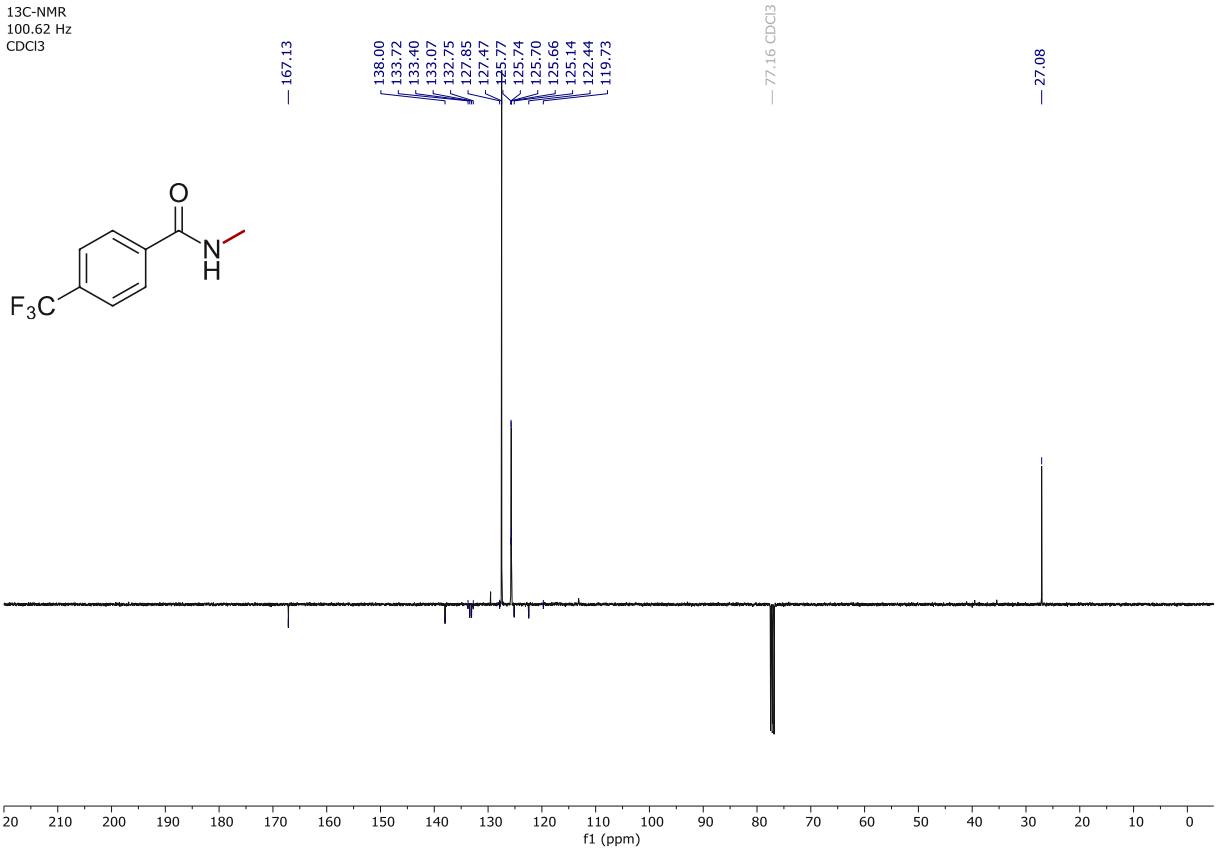
2-Bromo-*N*-methylbenzamide (2e)

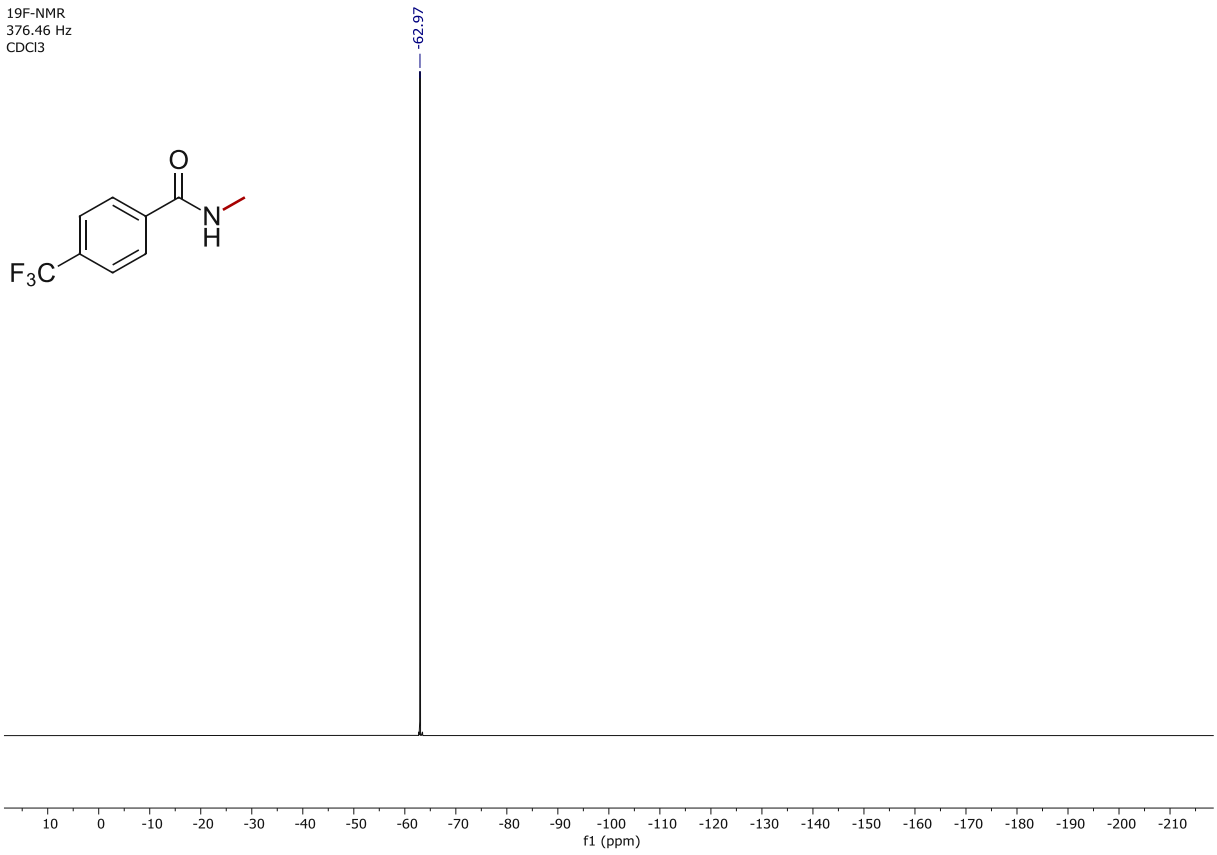




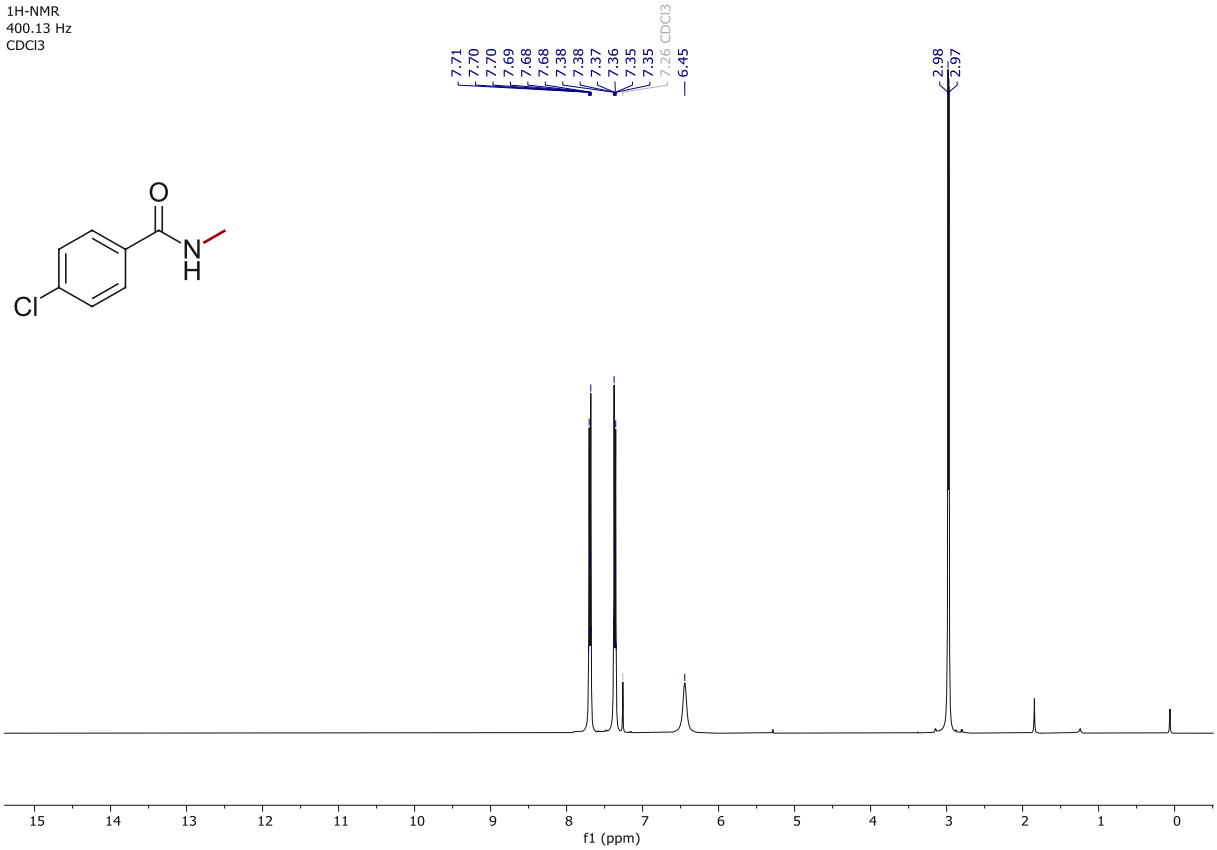
N-Methyl-4-(trifluoromethyl)benzamide (2f)

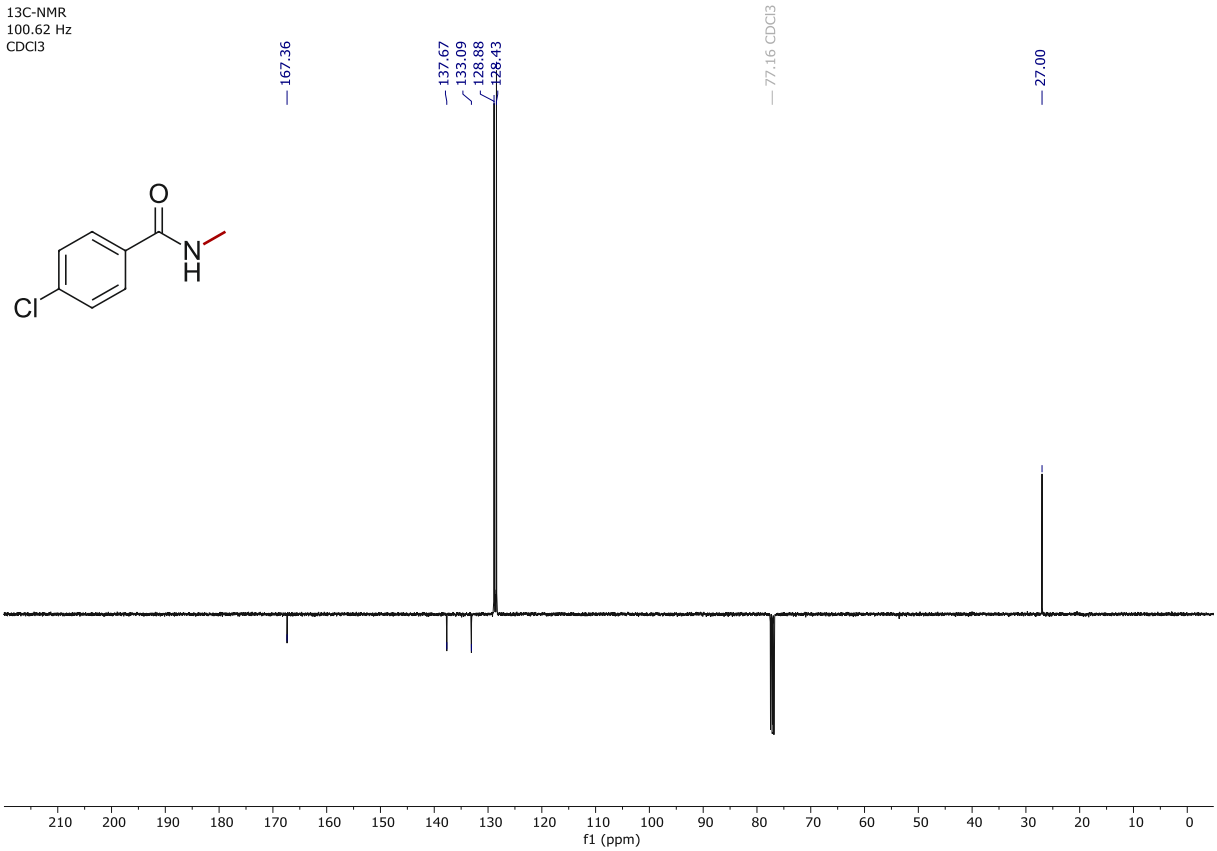




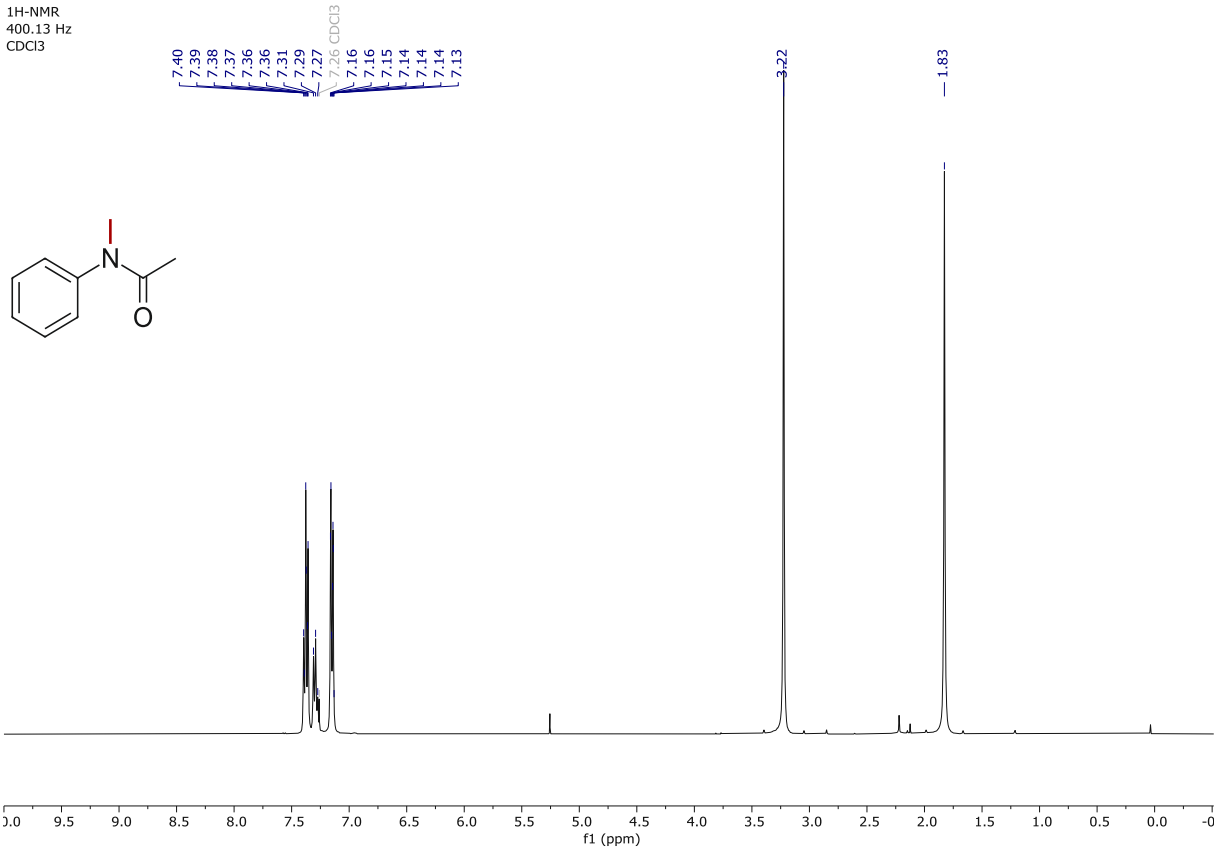


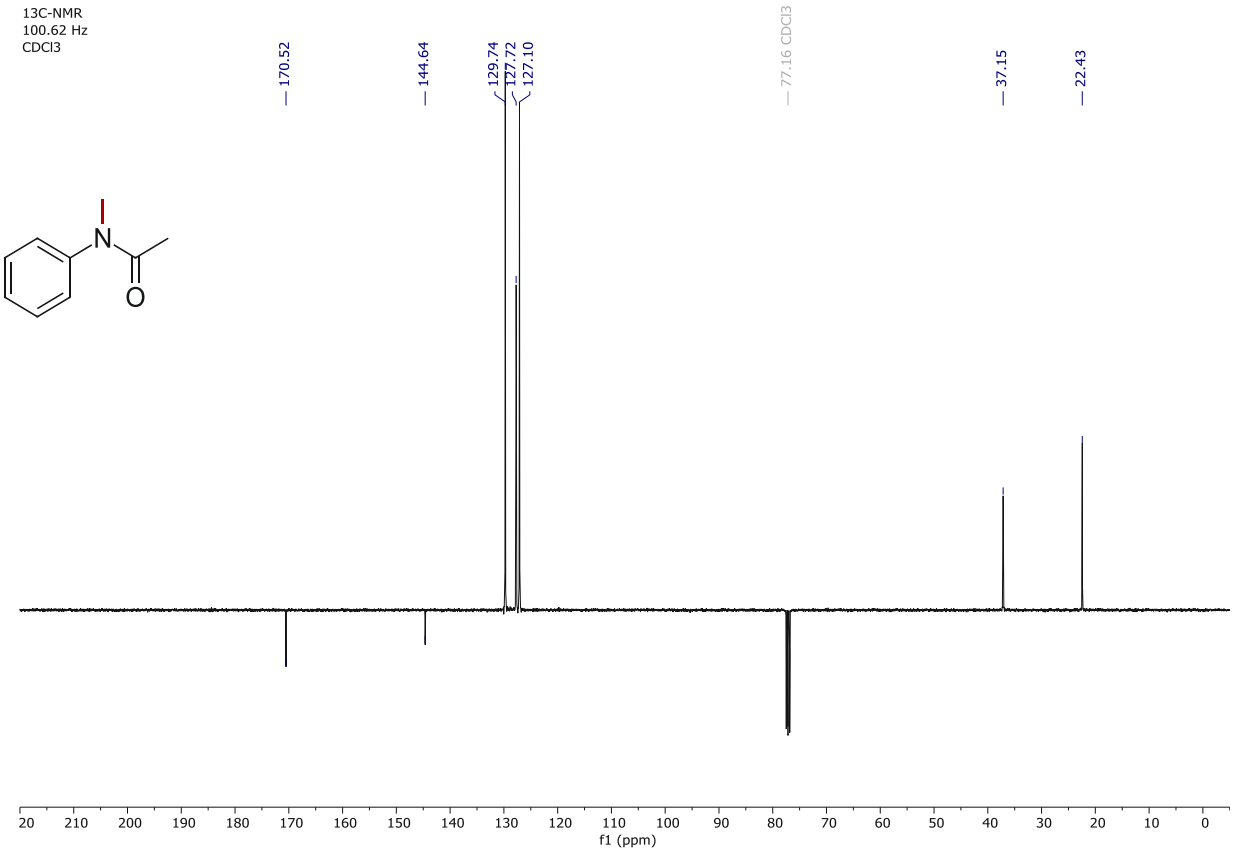
4-Chloro-*N*-methylbenzamide (2g)



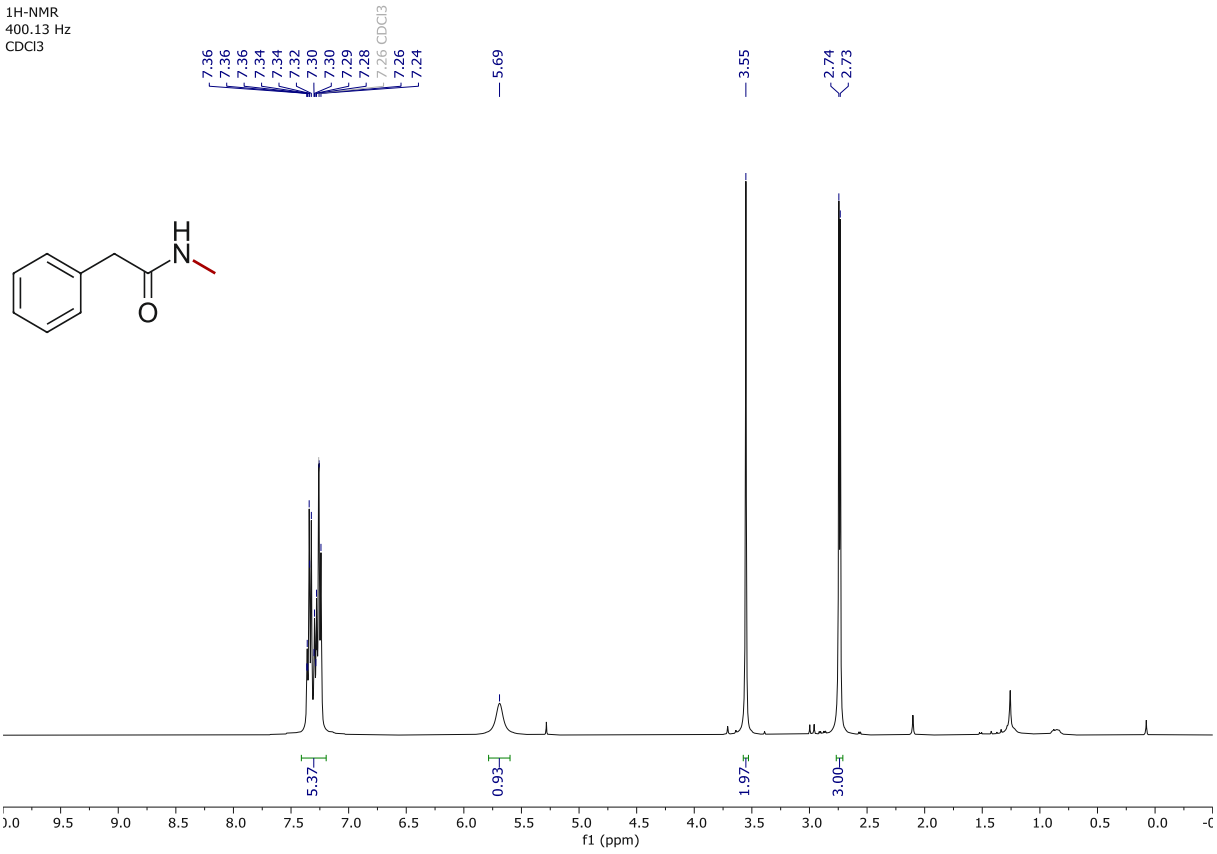


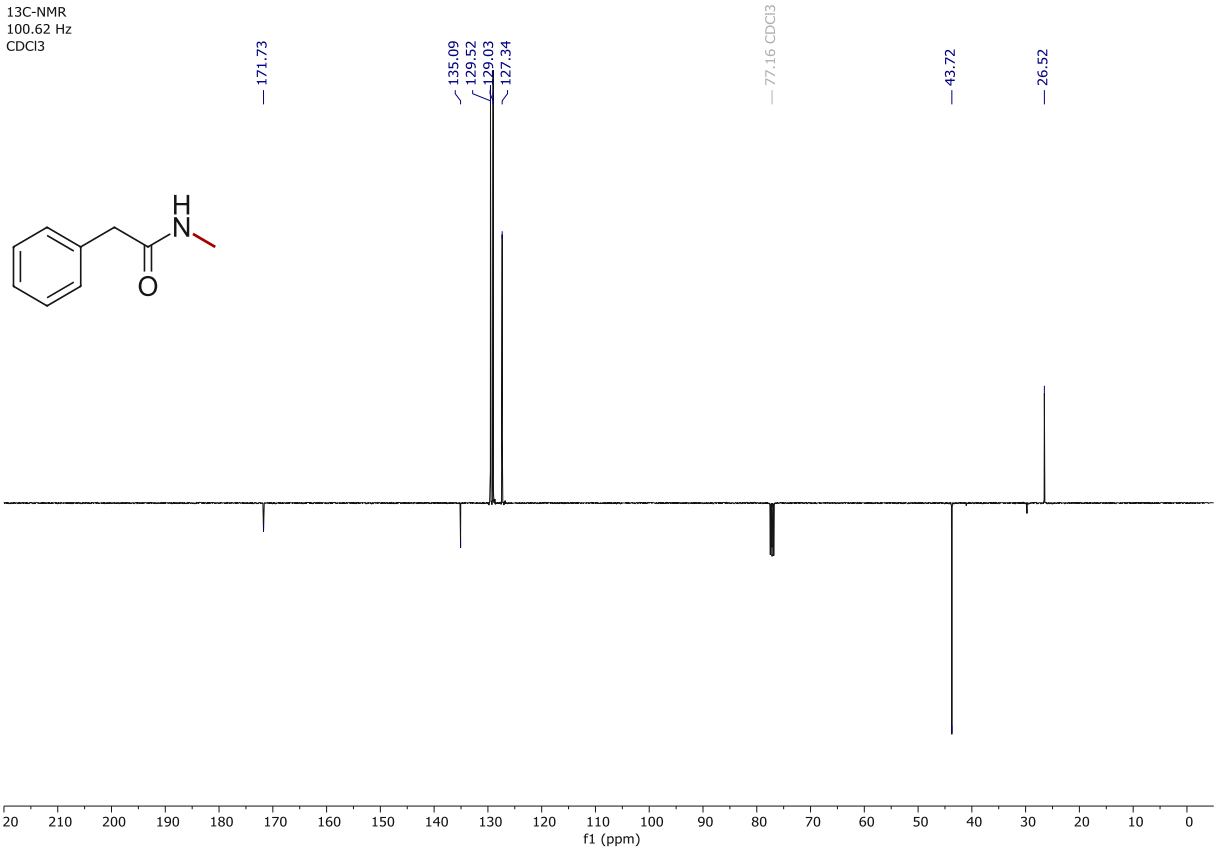
N-Acetyl-*N*-methylaniline (2h)



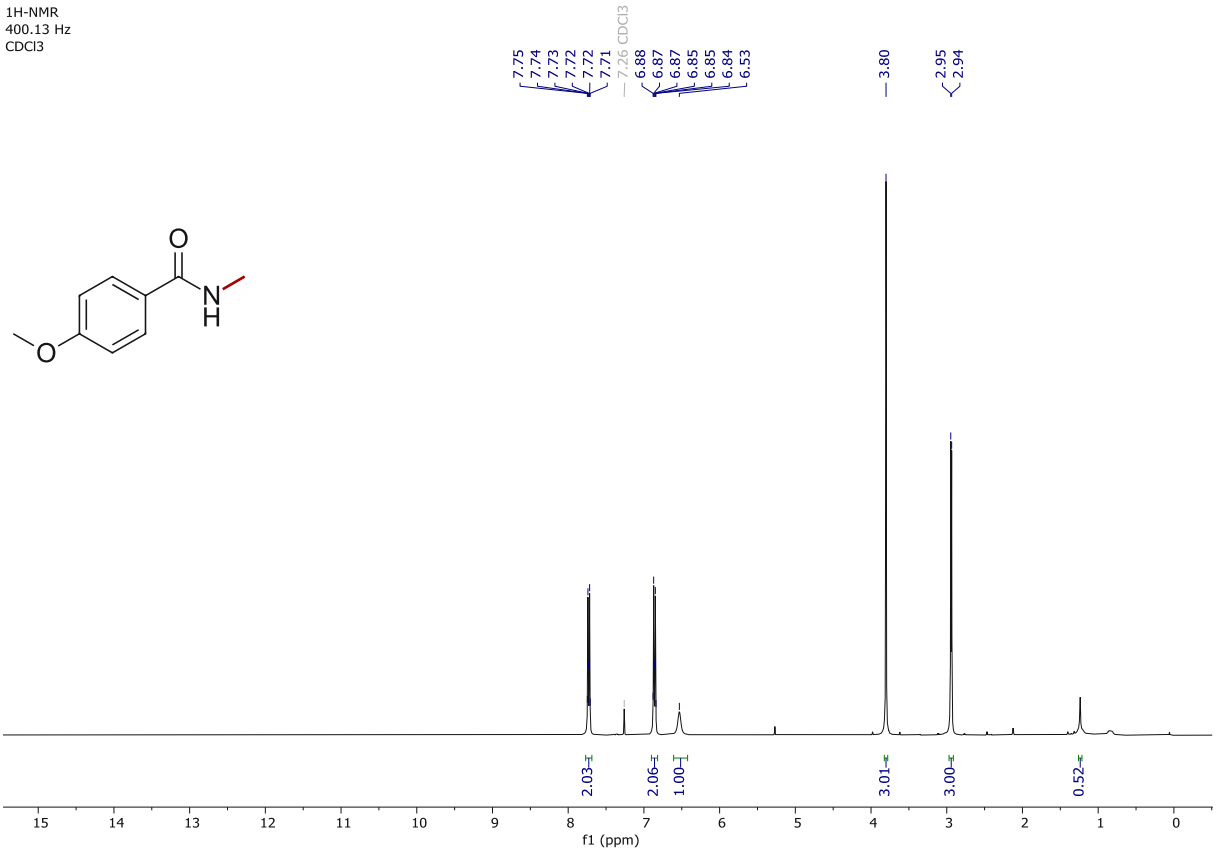


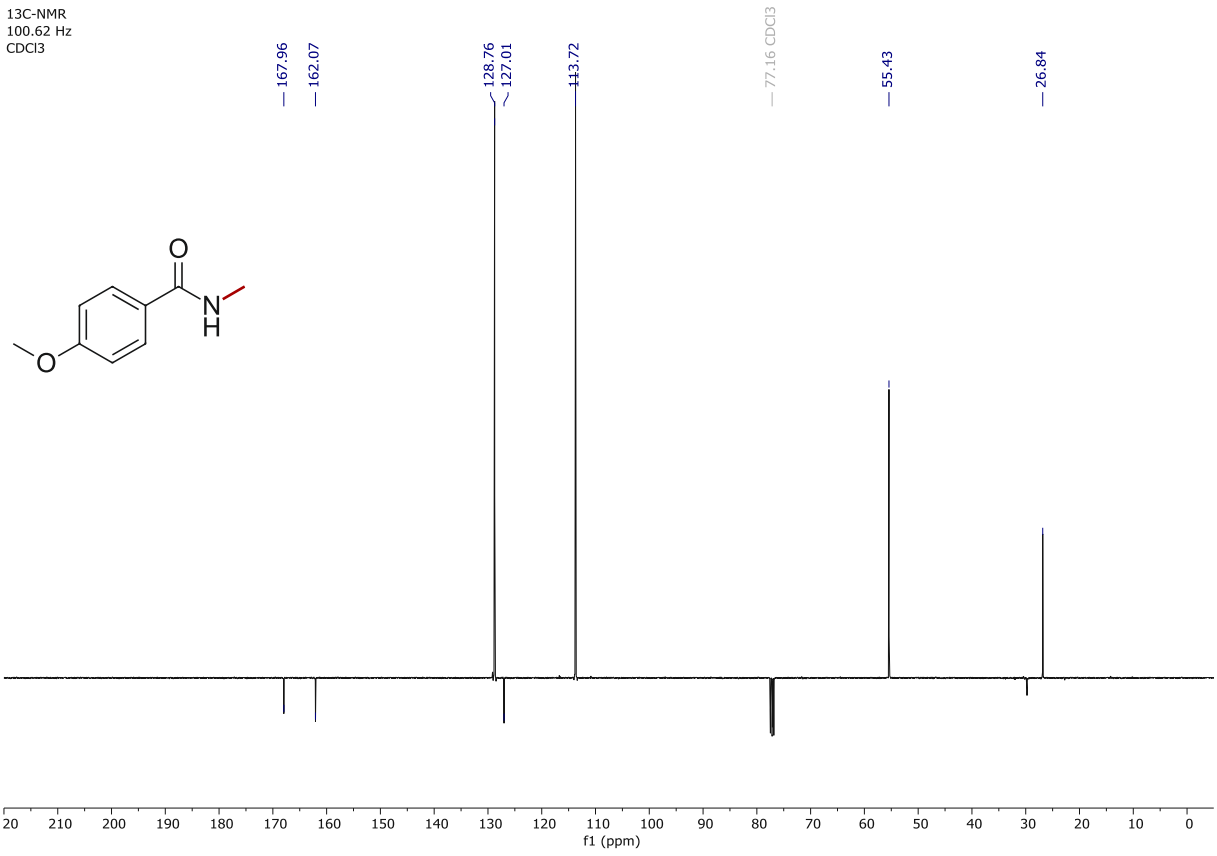
N-Methylphenylacetamide (2i)



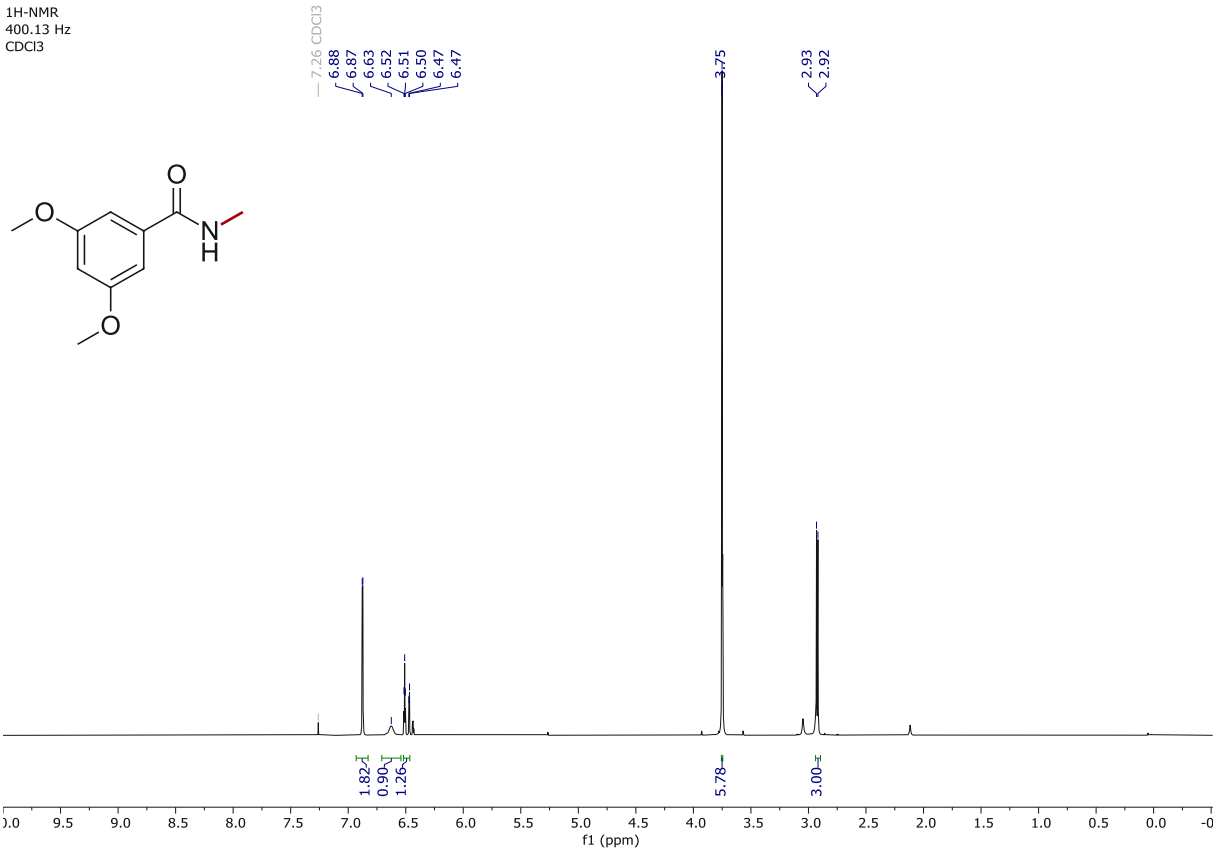


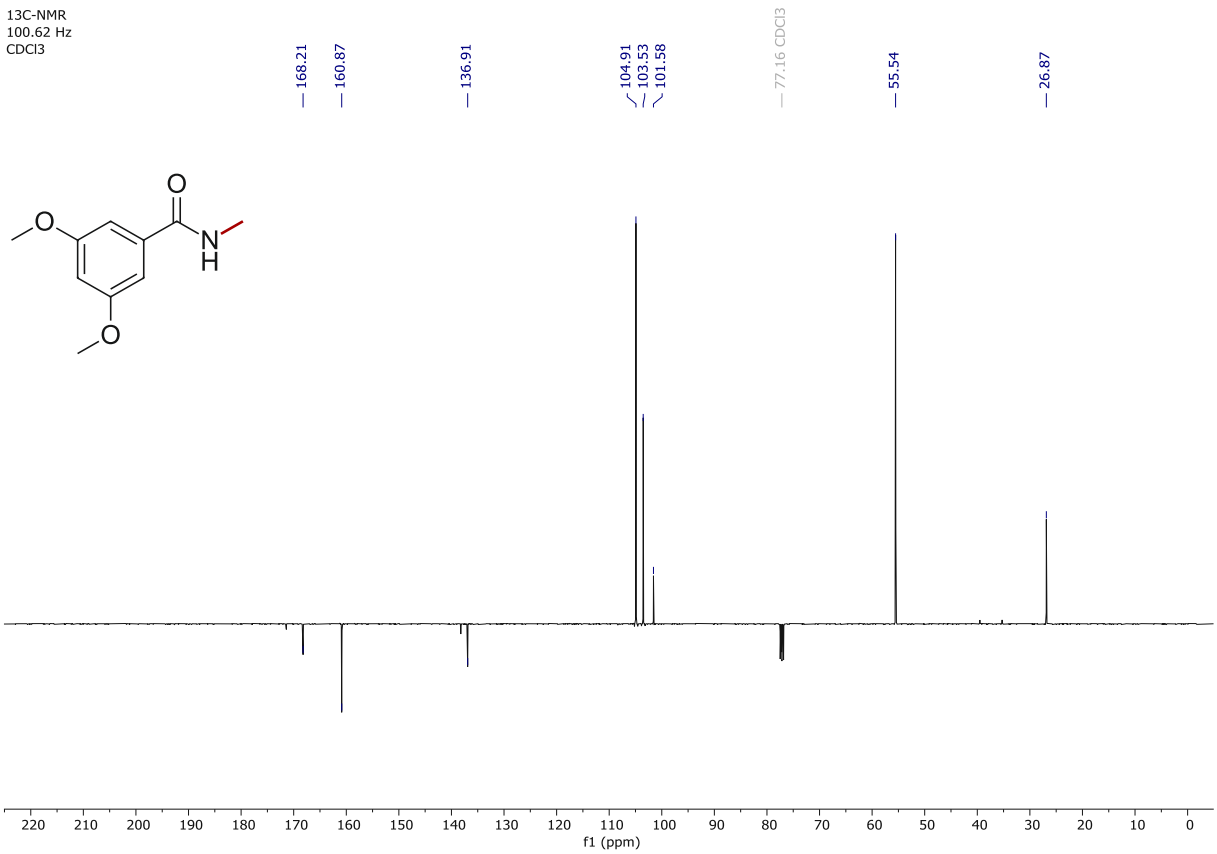
4-Methoxy-*N*-methylbenzamide (2j)



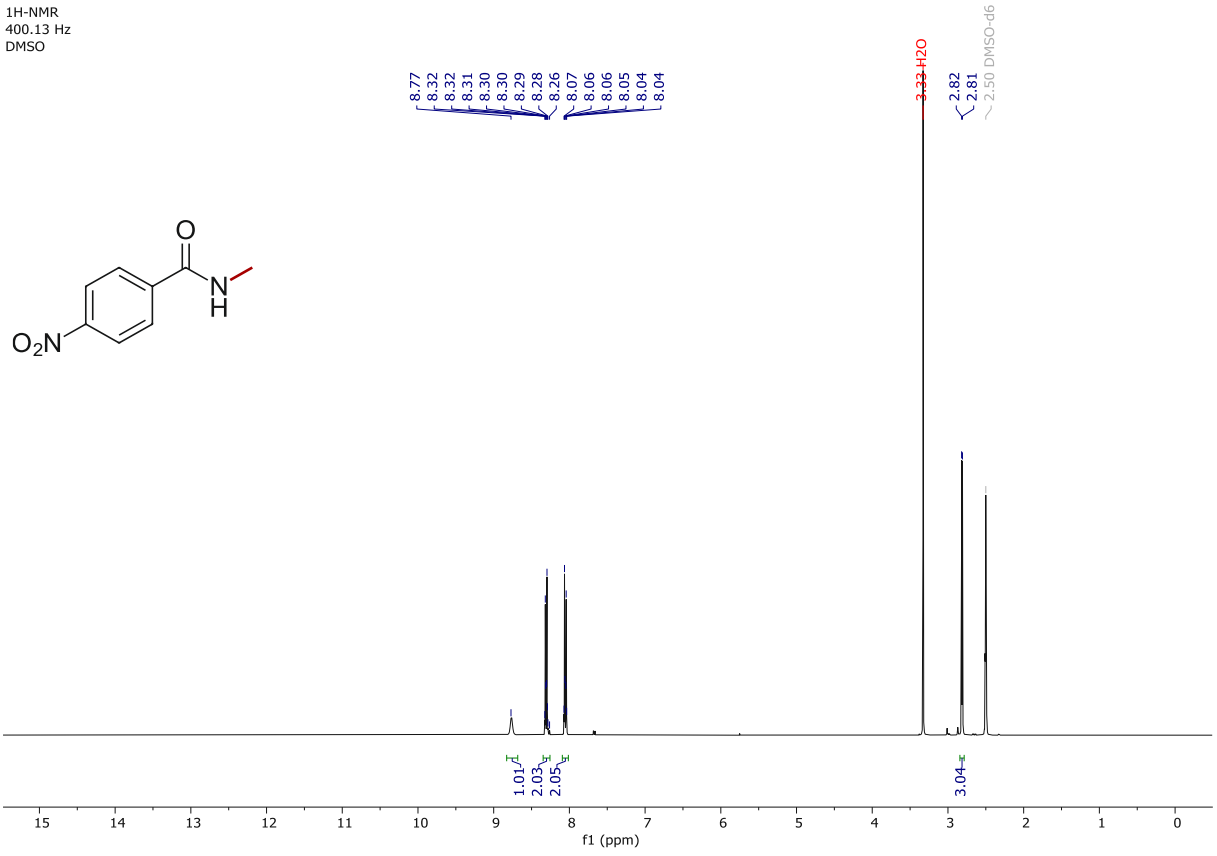


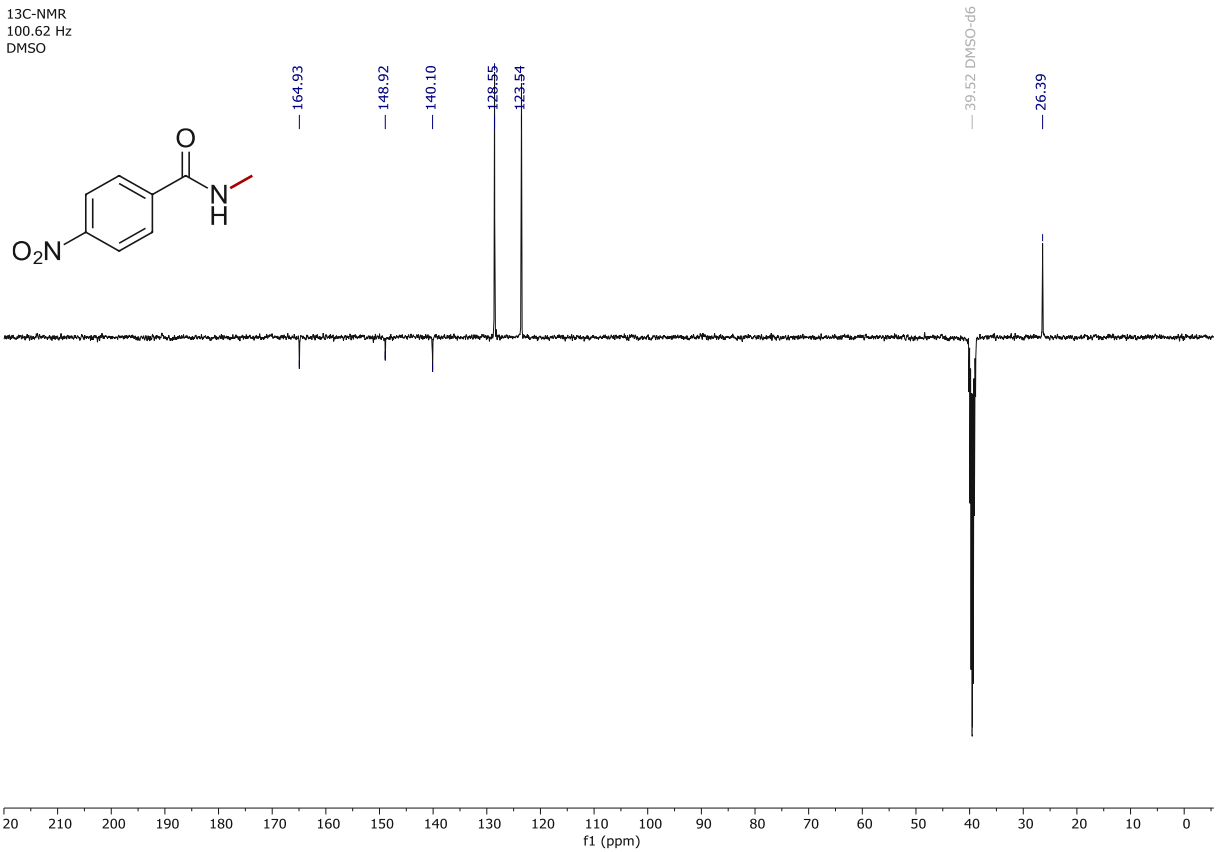
3,5-Dimethoxy-*N*-methylbenzamide (2k)



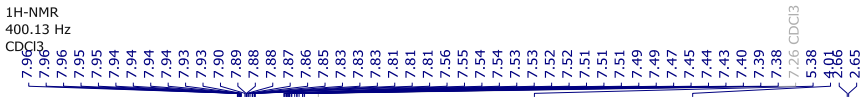


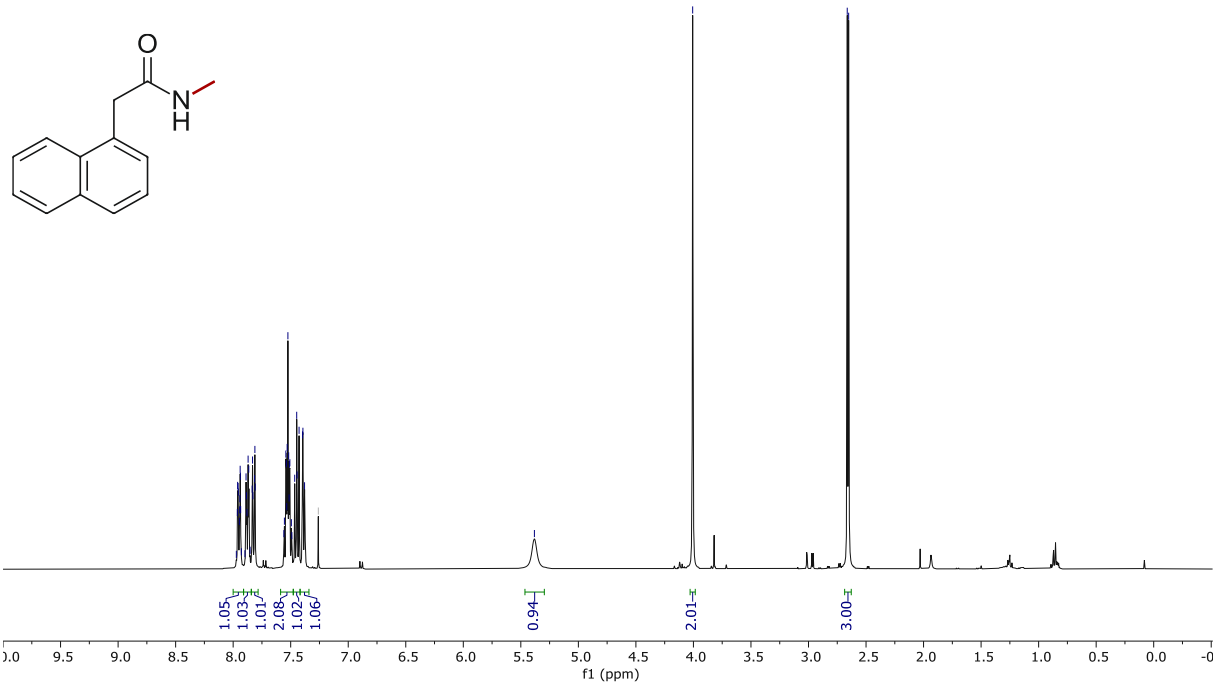
N-Methyl-4-nitrobenzamide (2l)

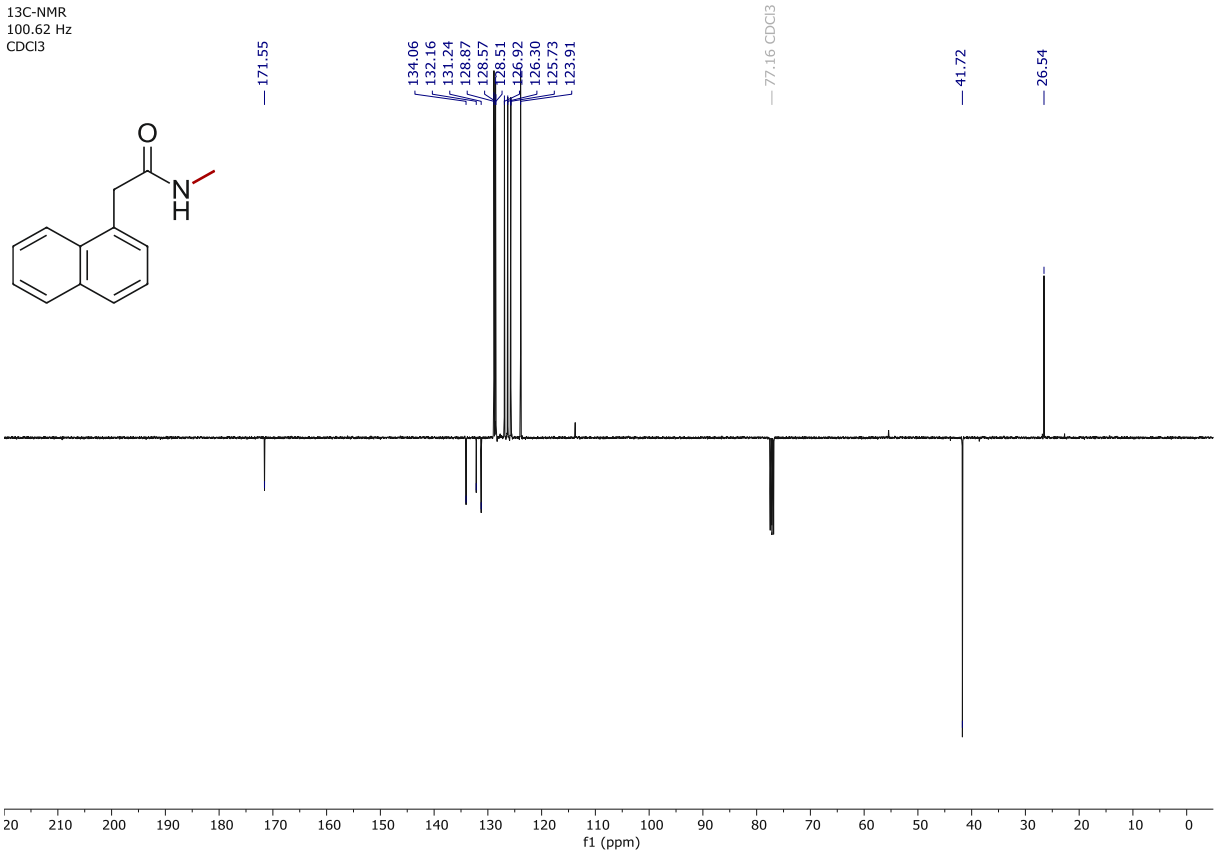




N-Methyl-α-naphthylacetamide (2m)

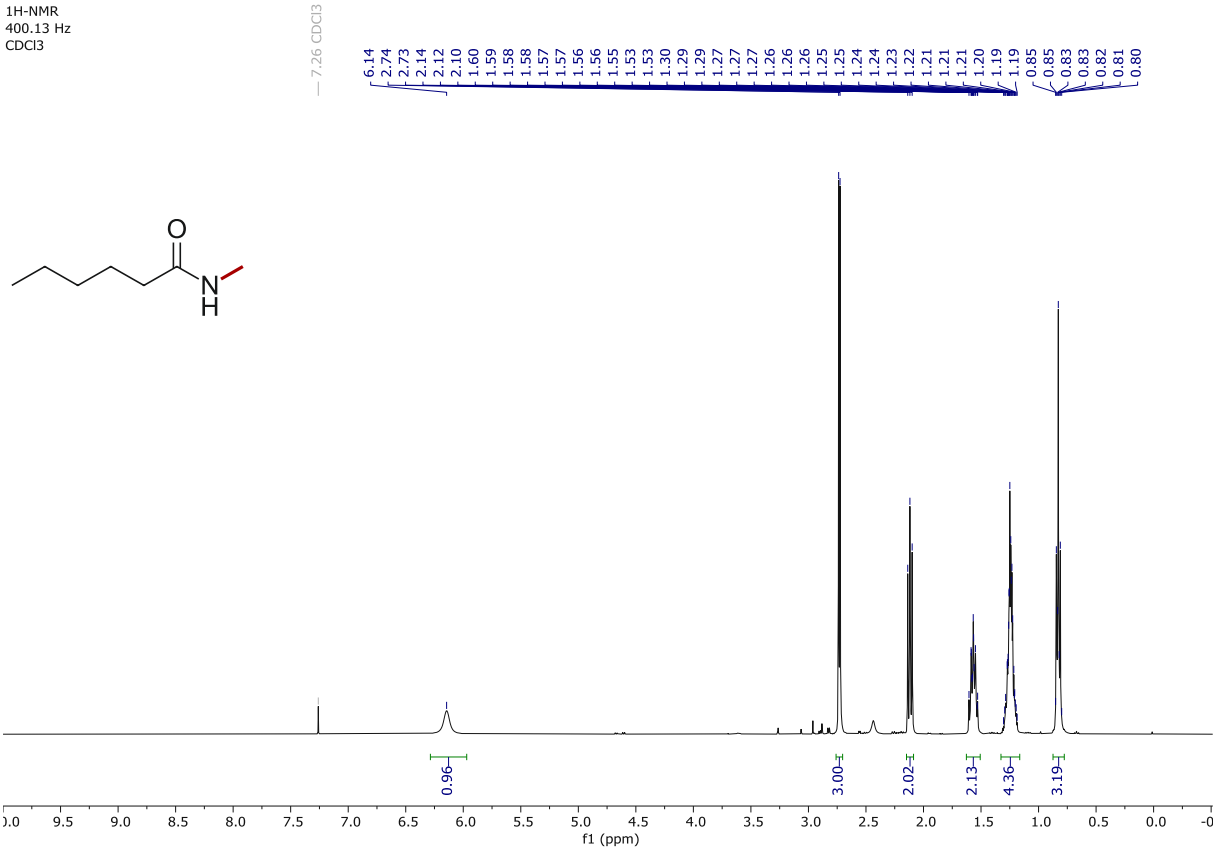




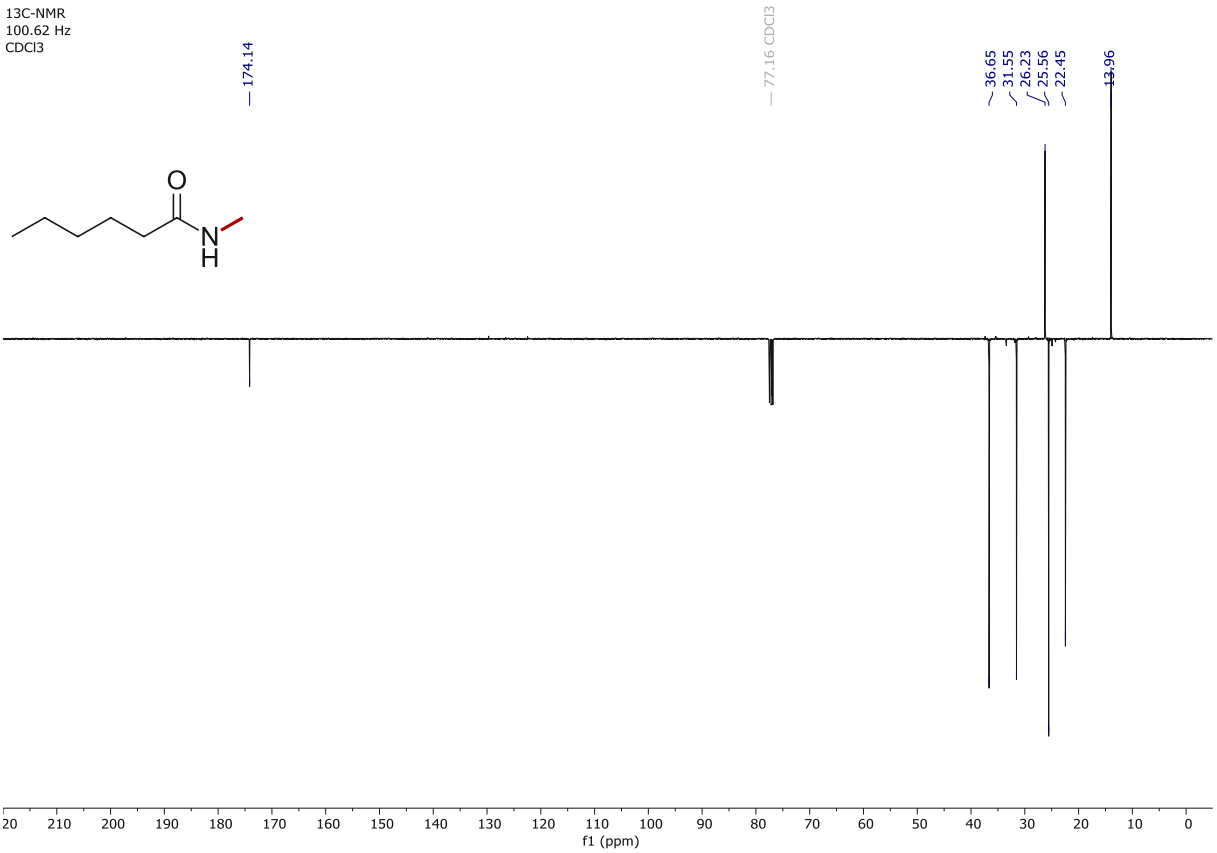


N-Methylhexanamide (2n)

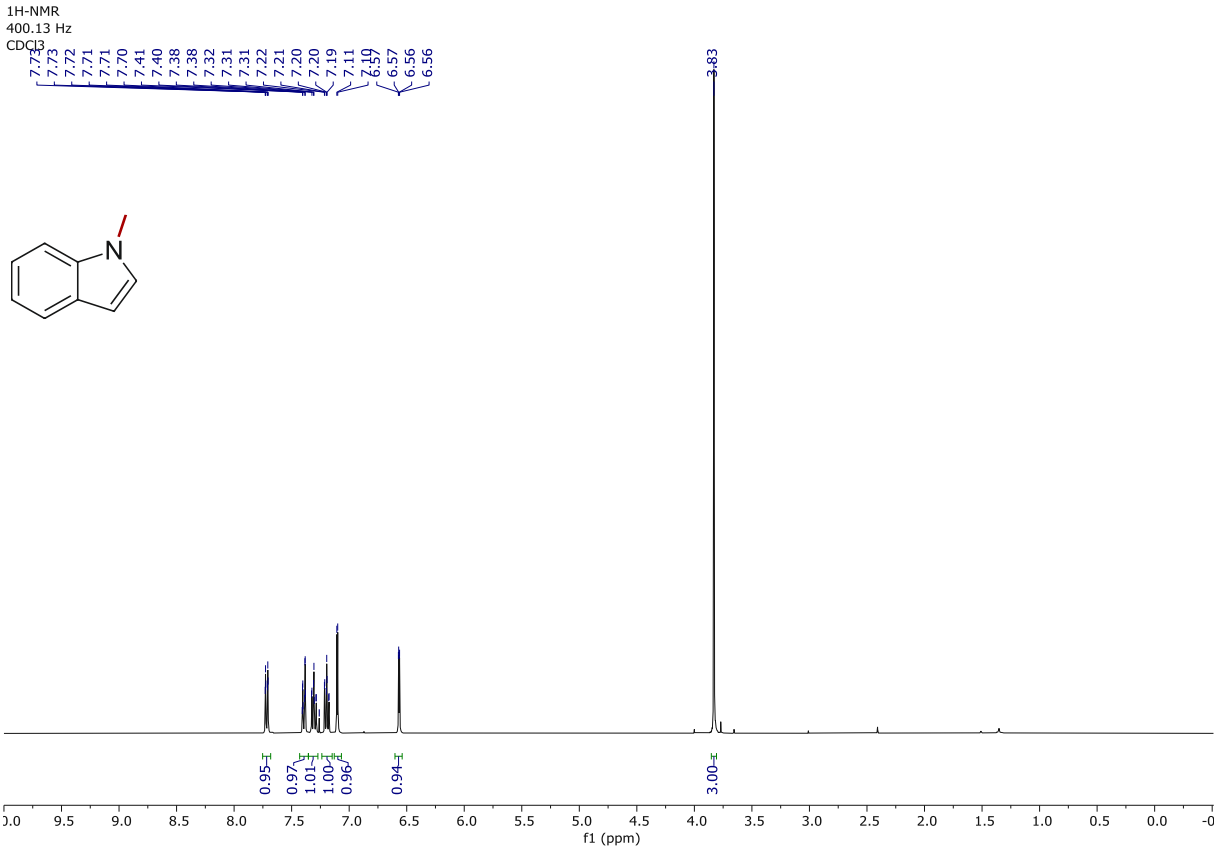
1H-NMR
400.13 Hz
CDCl3

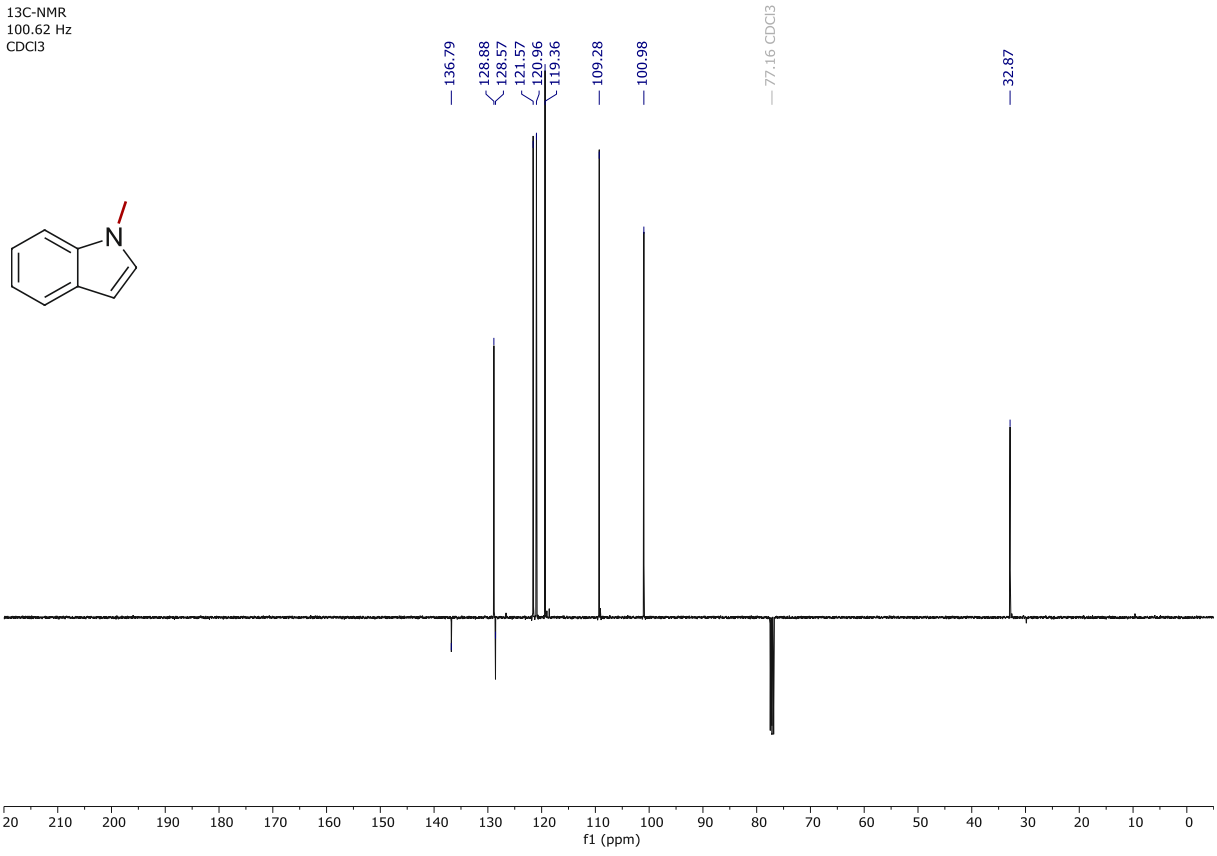


13C-NMR
100.62 Hz
CDCl3

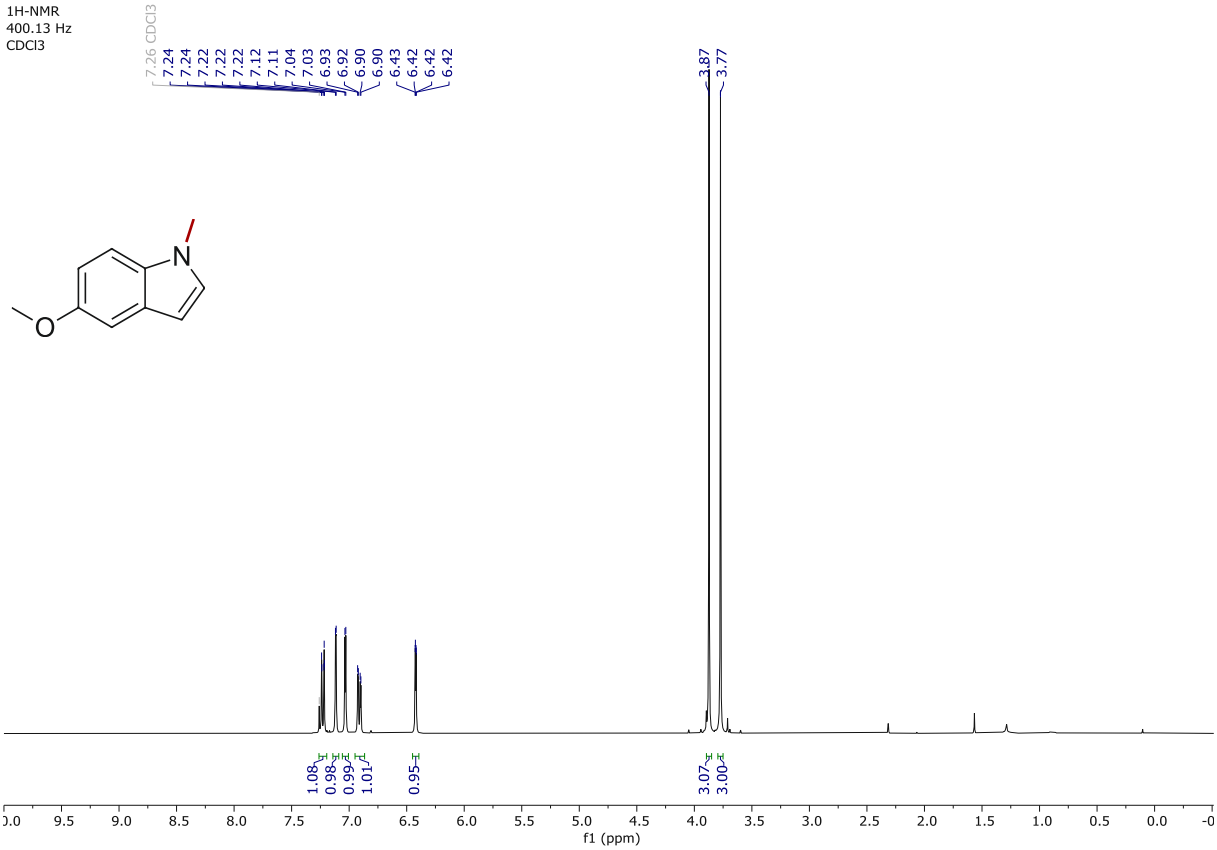


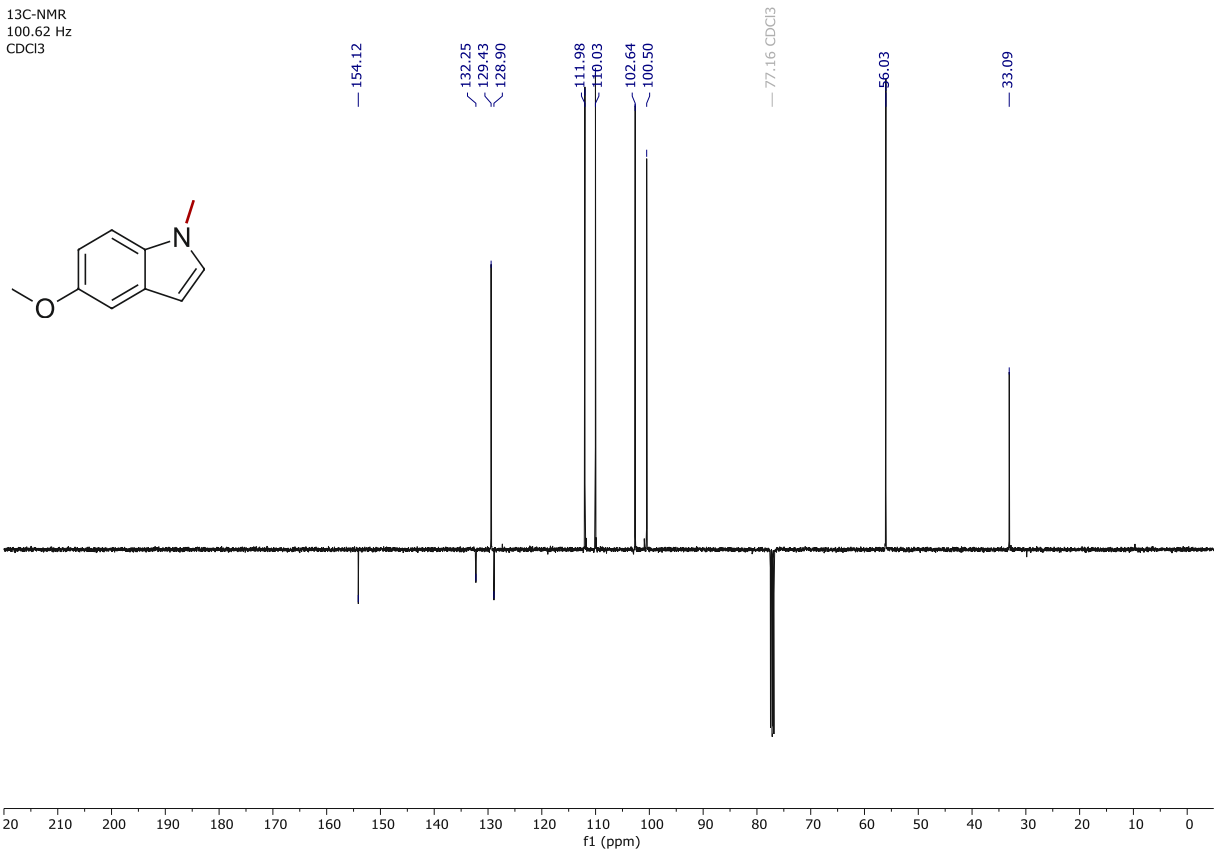
1-Methylindole (5a)



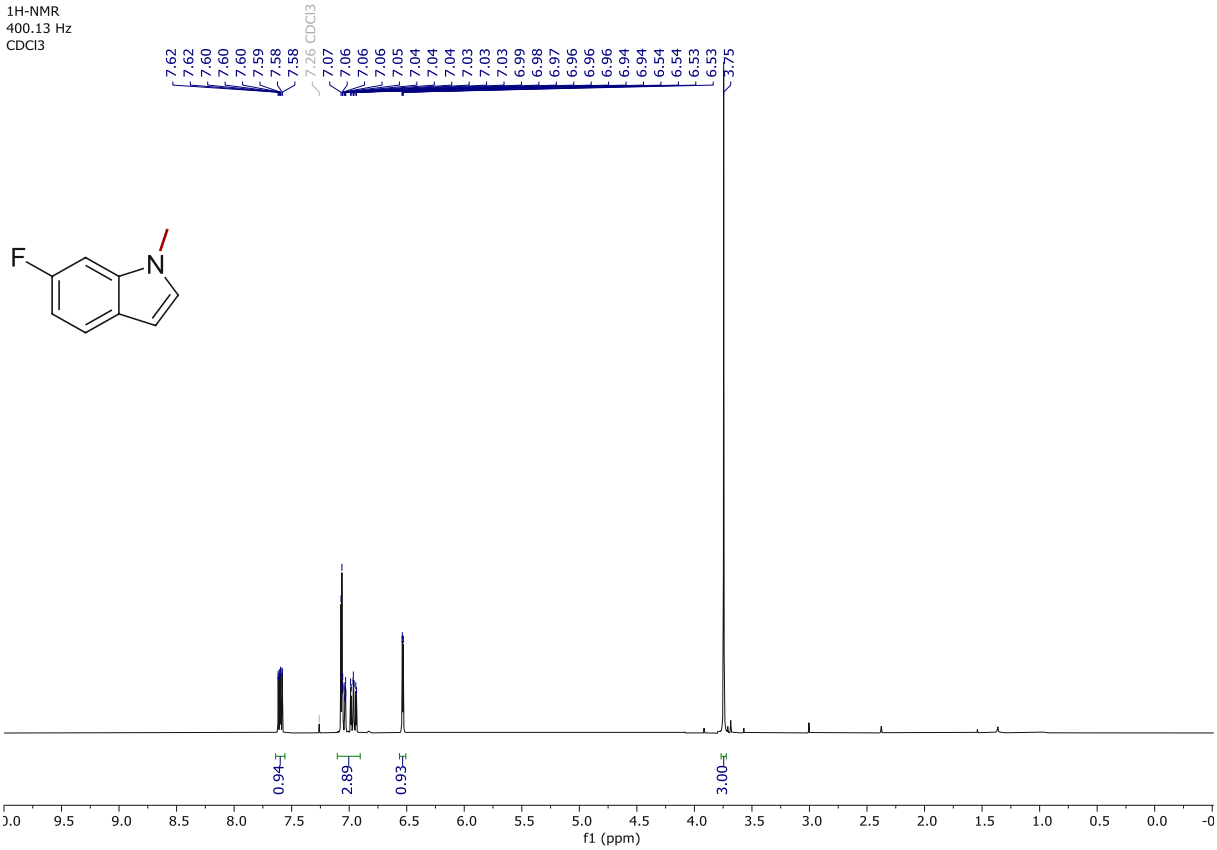


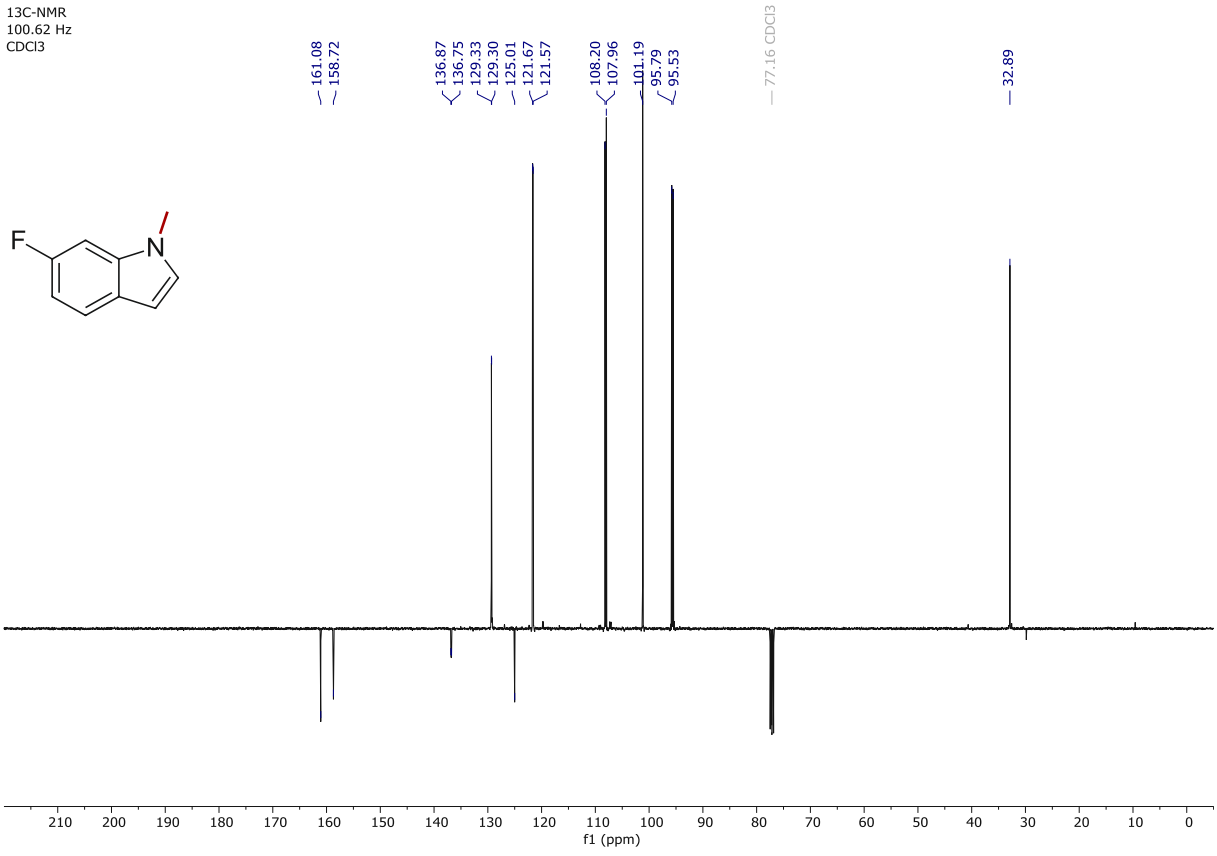
5-Methoxy-1-methylindole (5b)



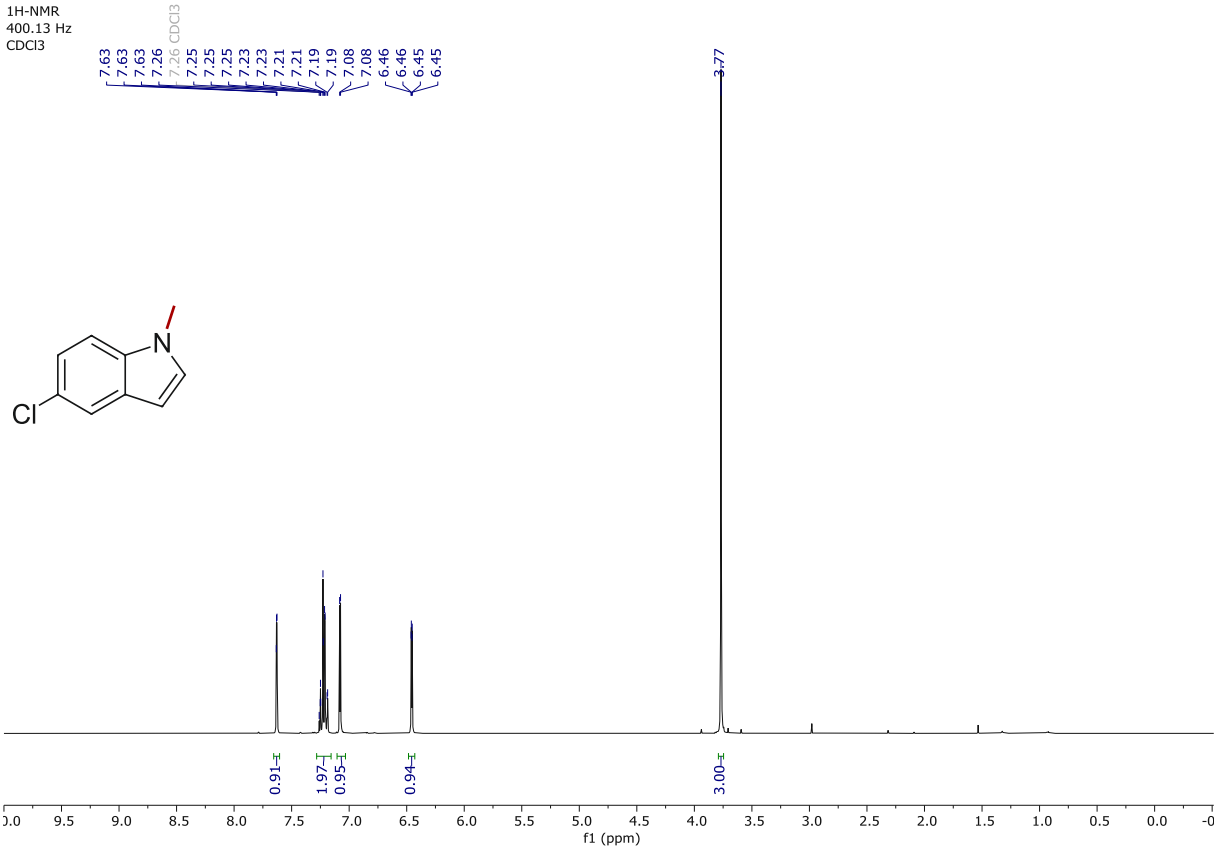


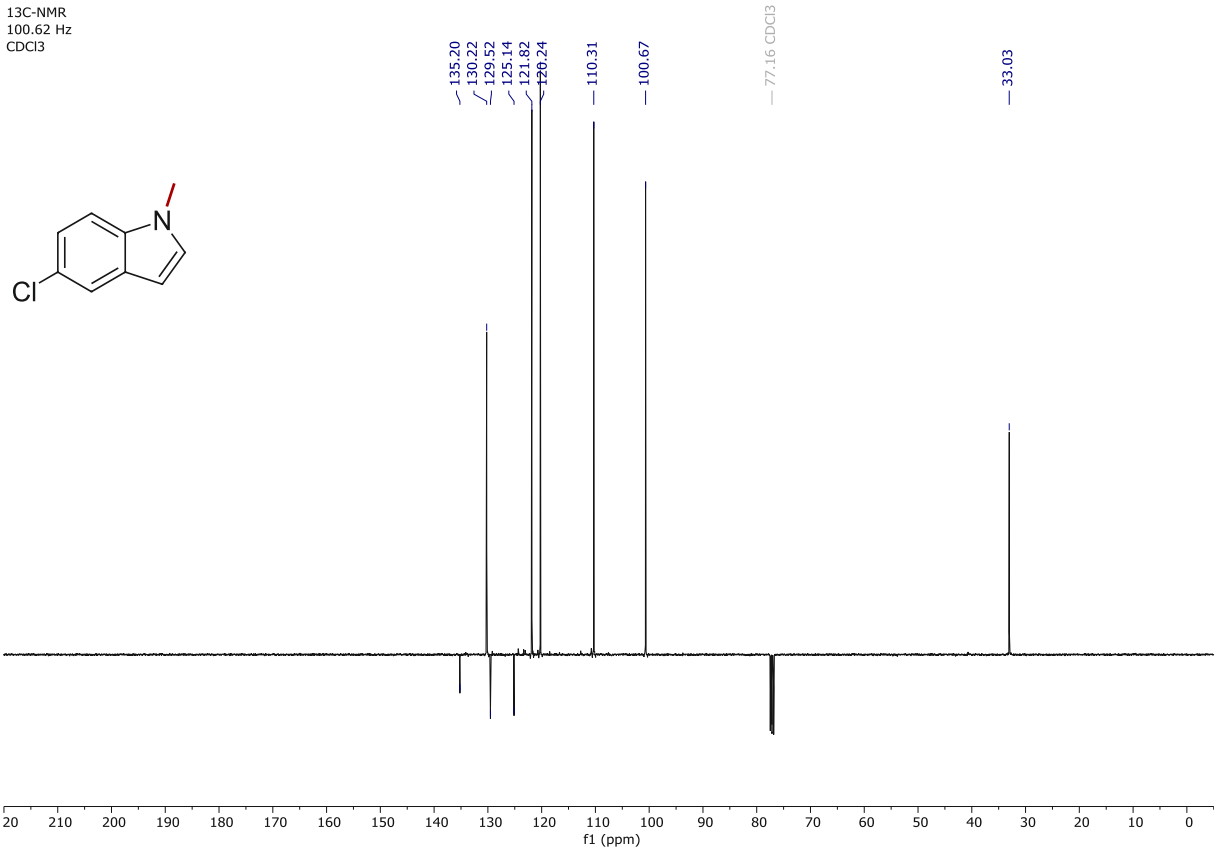
6-Fluoro-1-methylindole (5c)



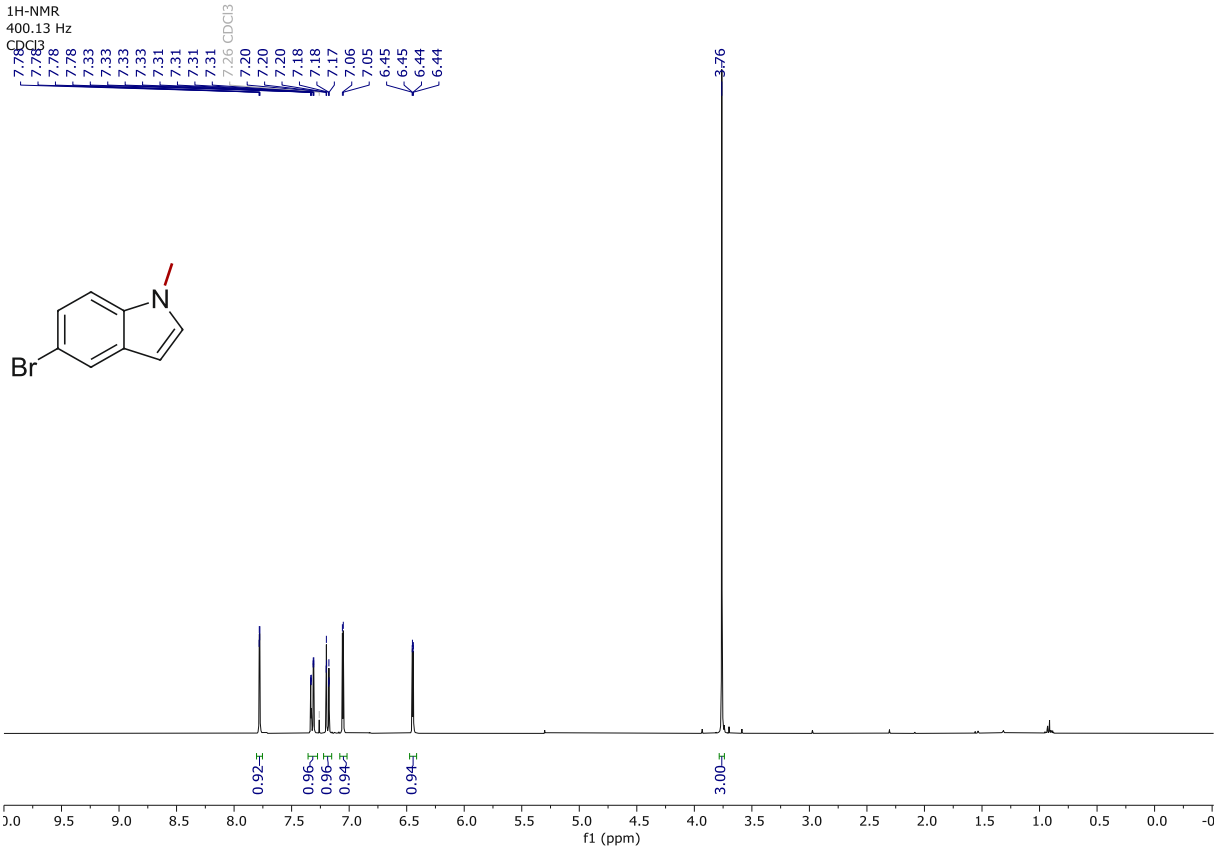


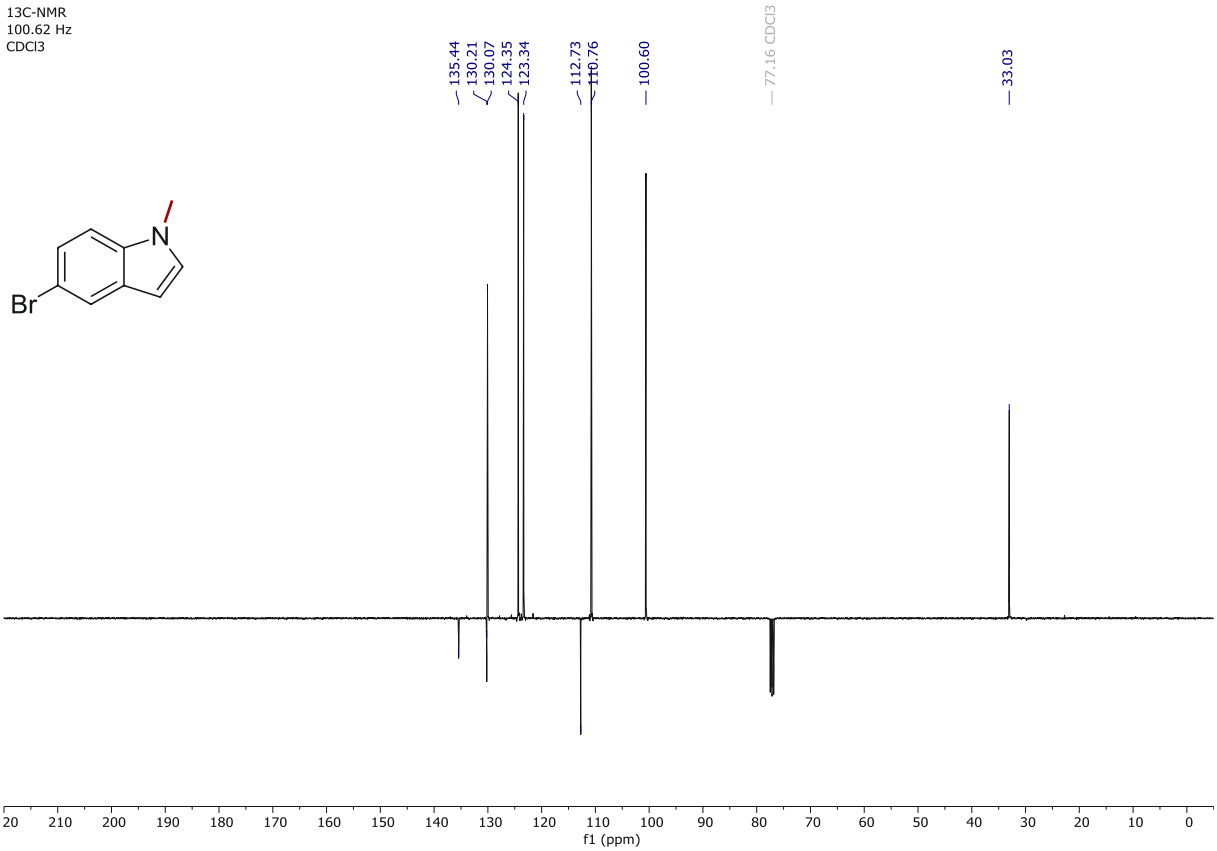
5-Chloro-1-methylindole (5d)



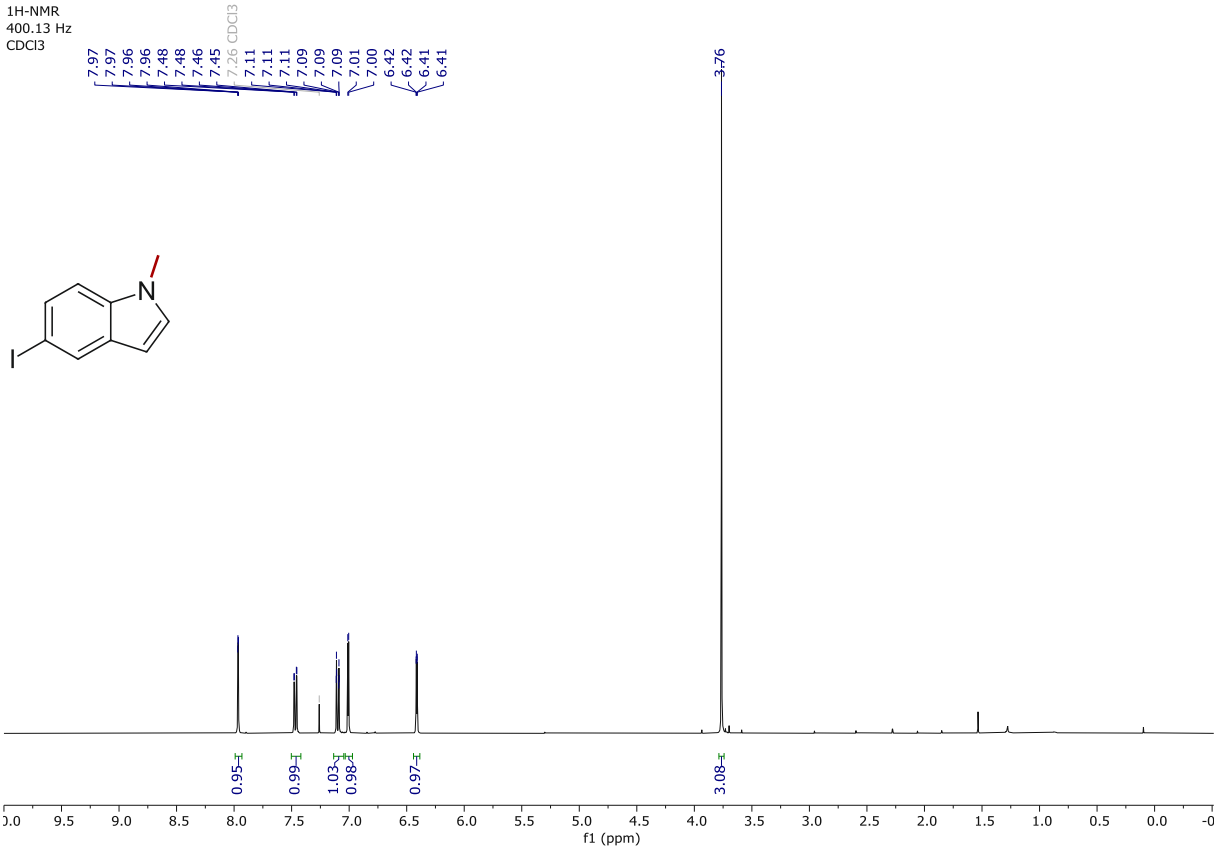


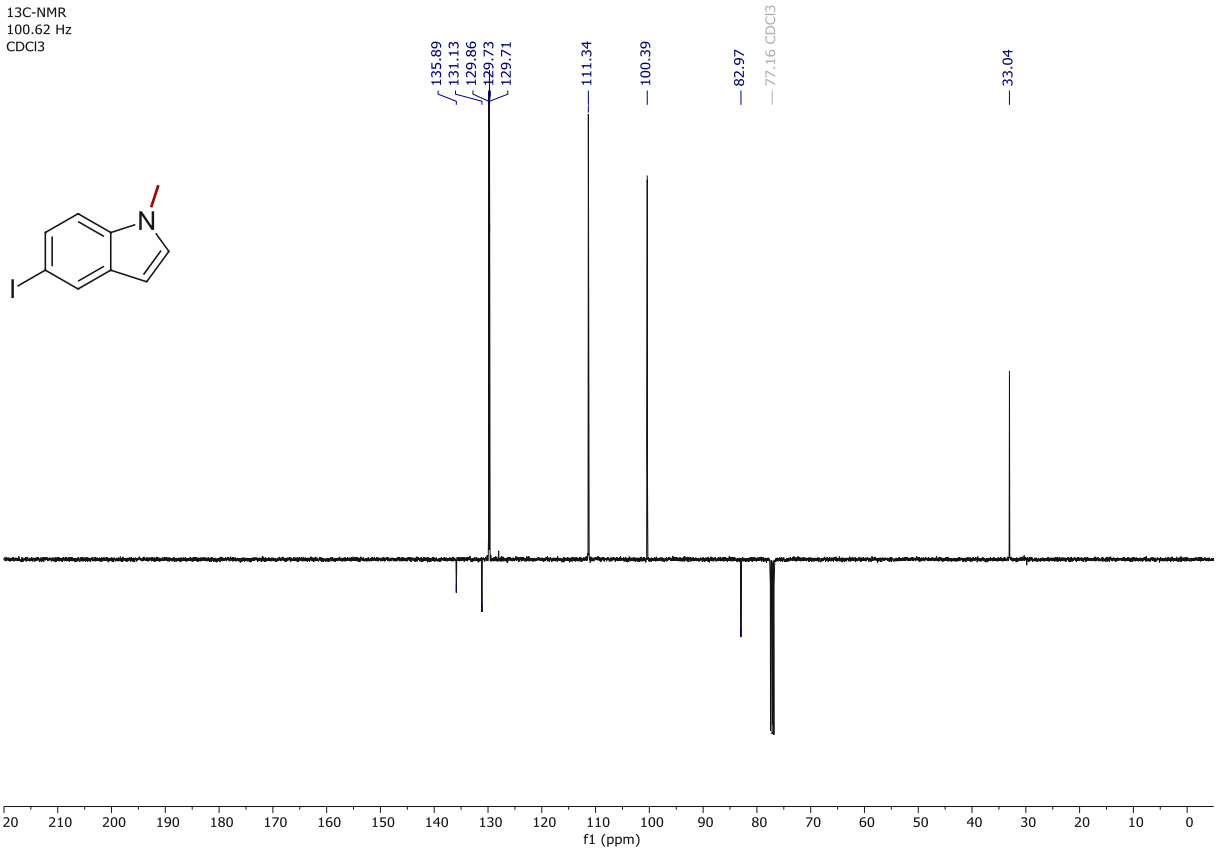
5-Bromo-1-methylindole (5e)



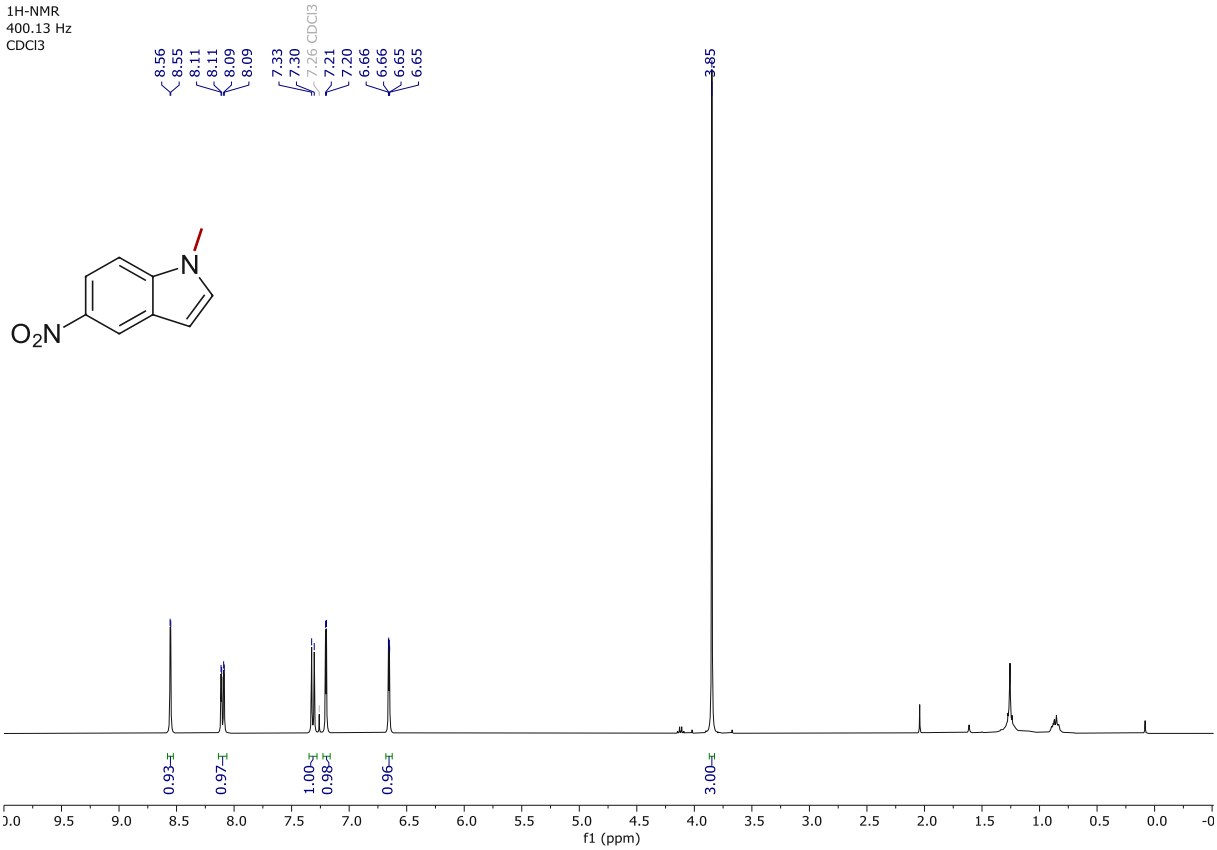


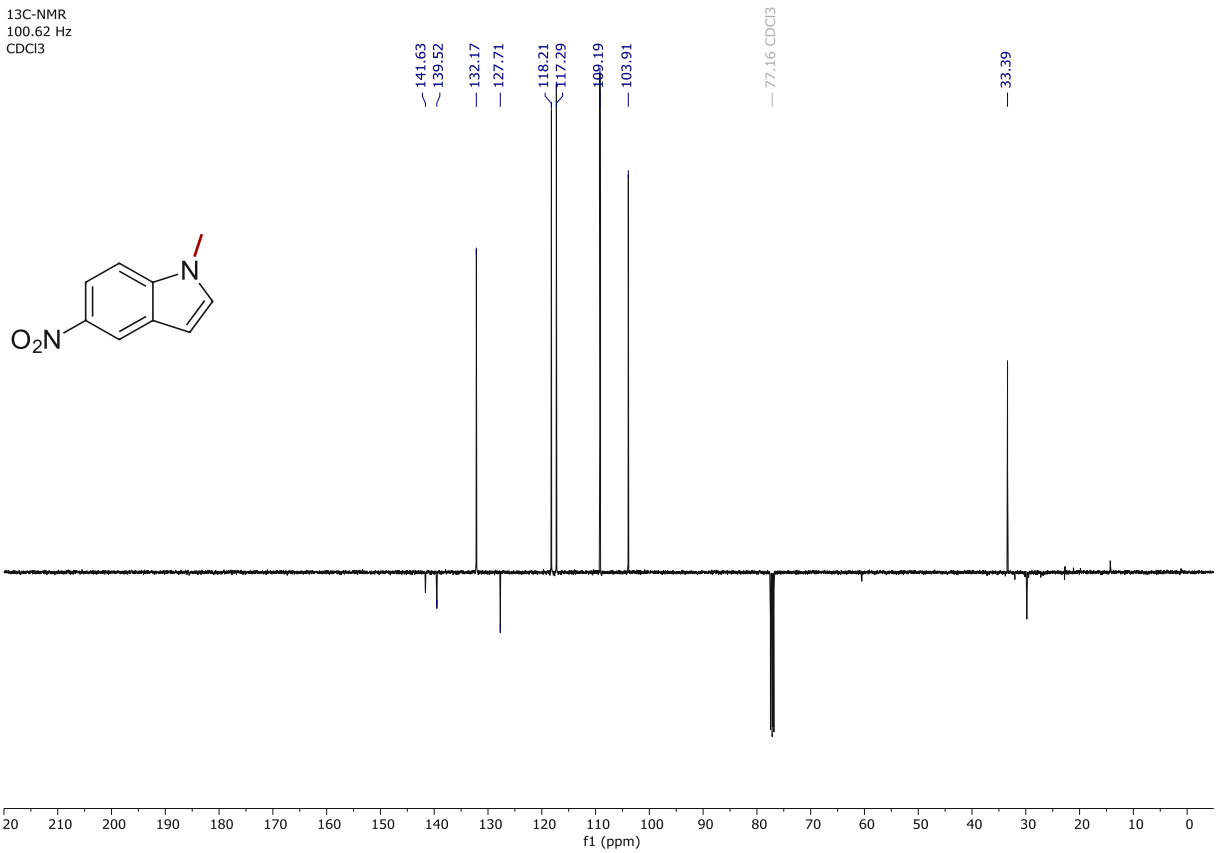
5-Iodo-1-methylindole (5f)



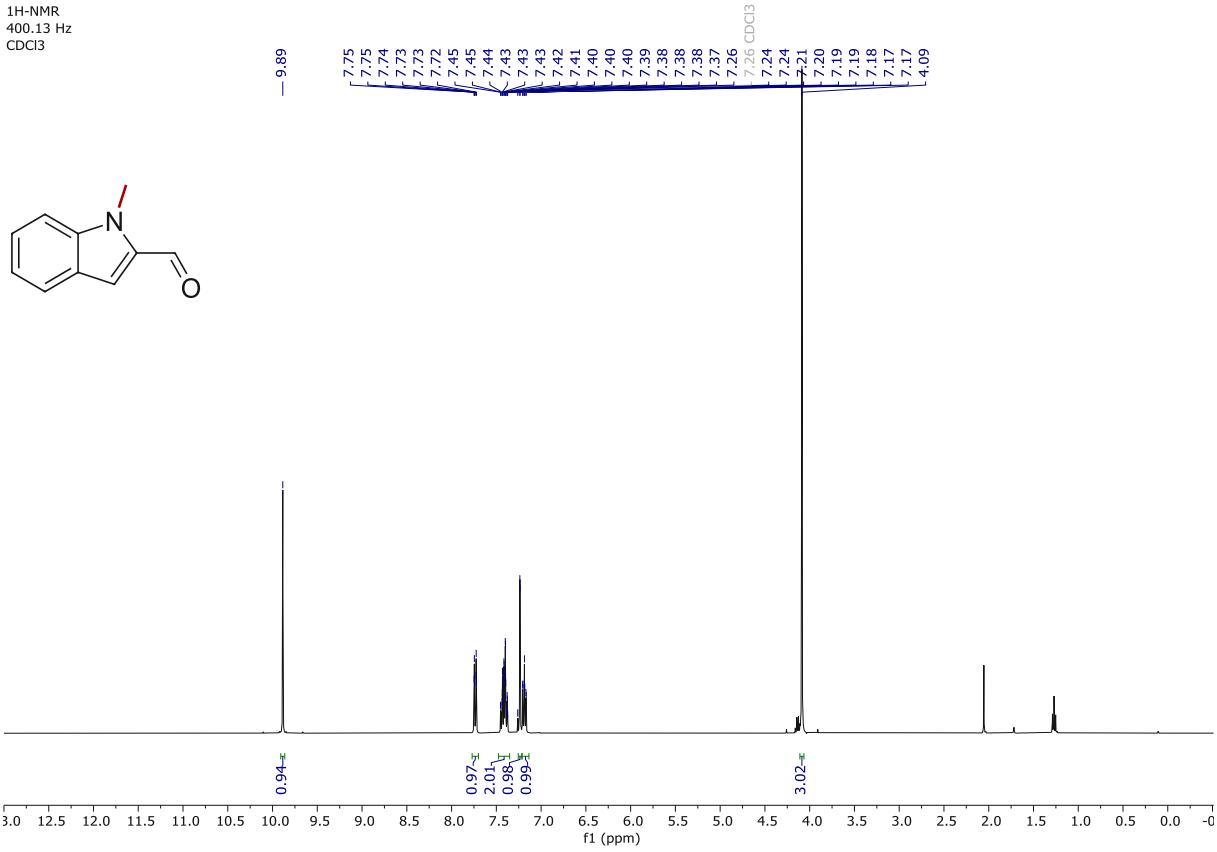


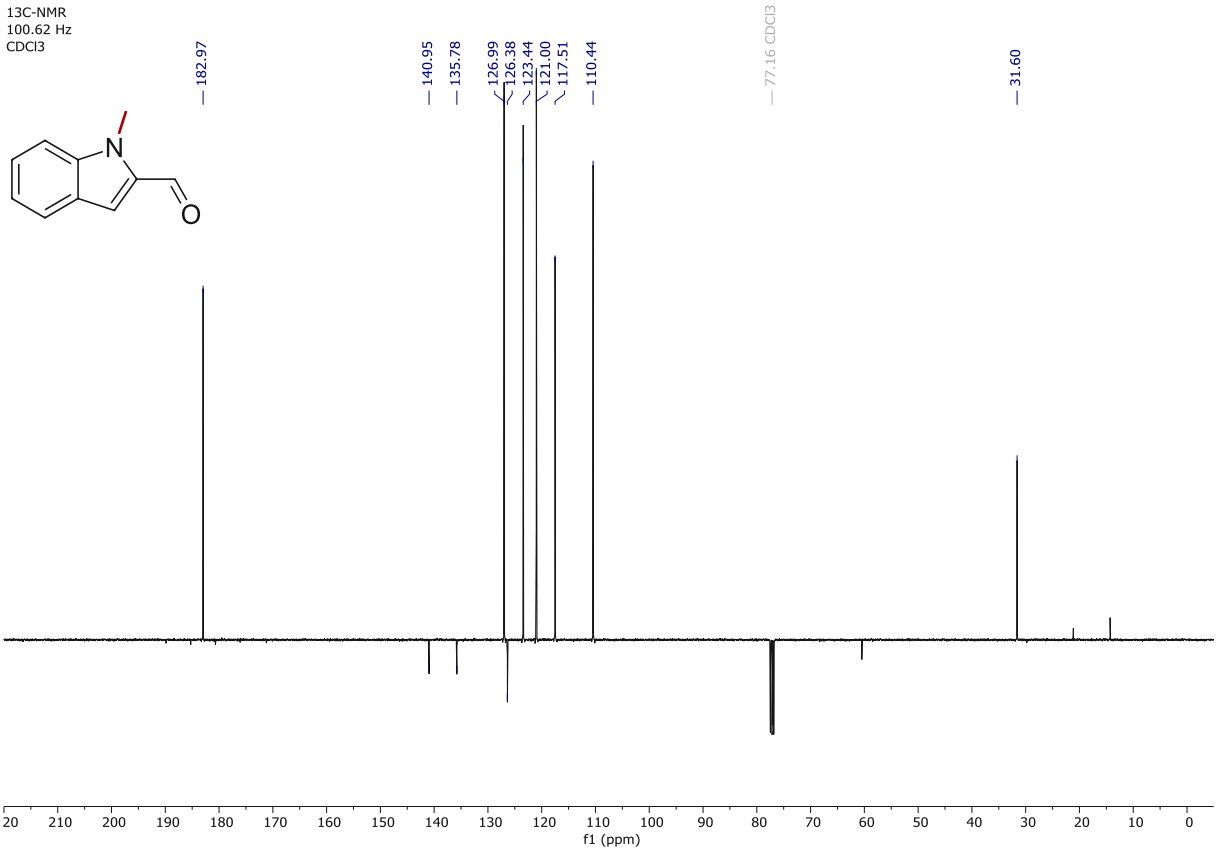
1-Methyl-5-nitroindole (5g)



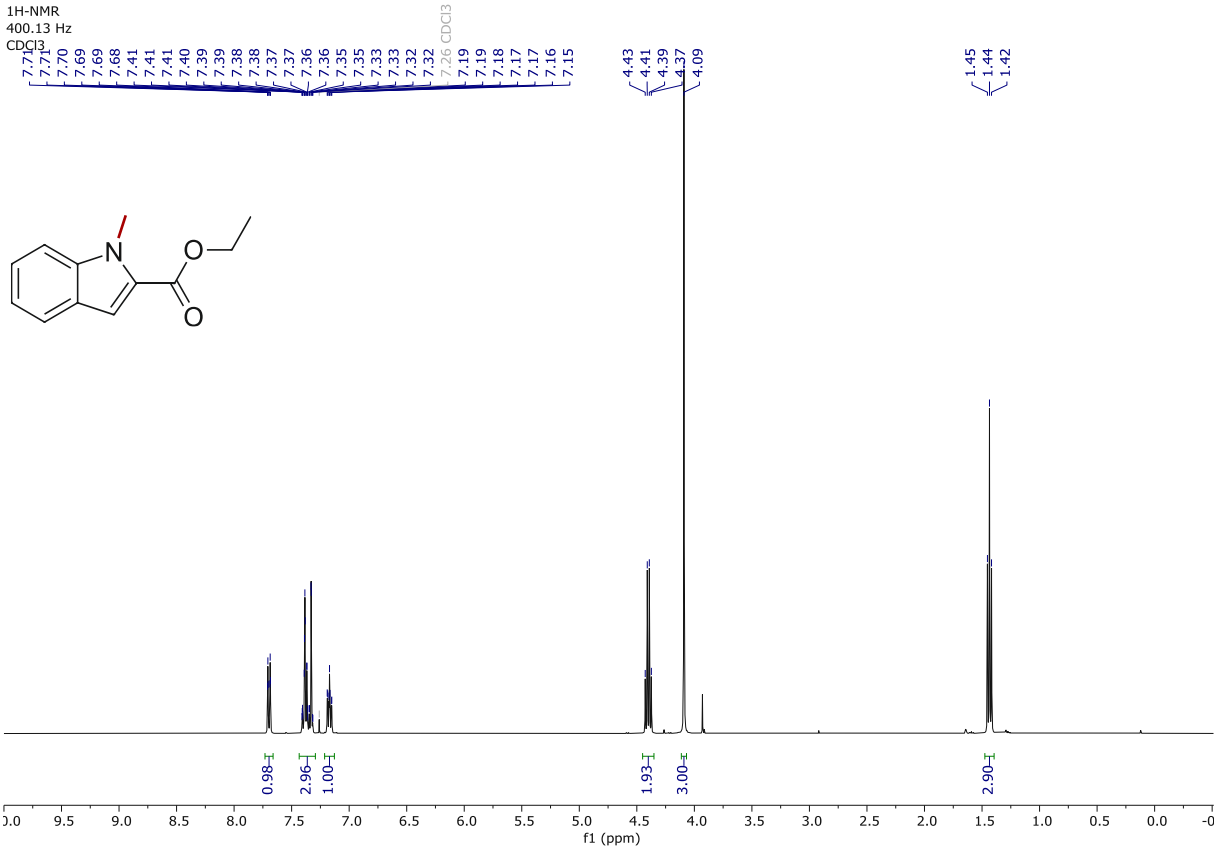


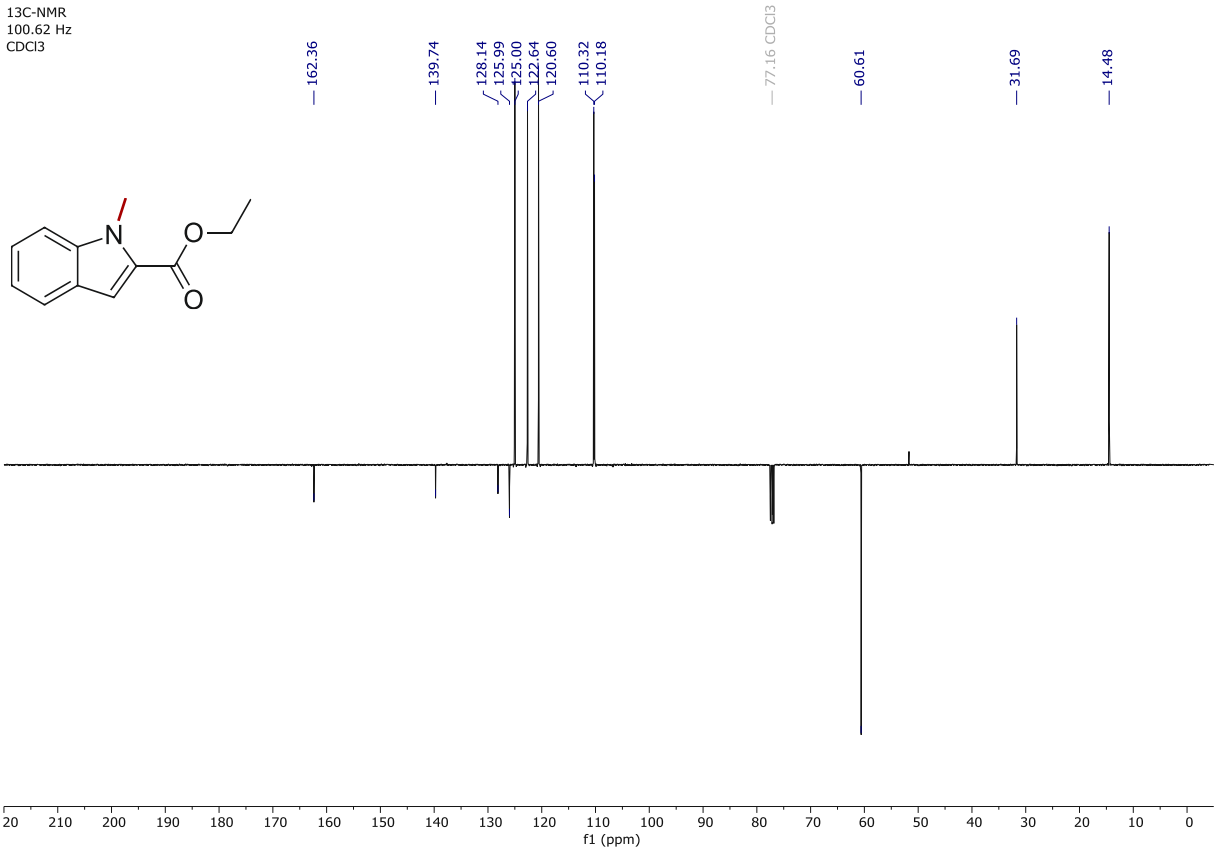
1-Methyl-2-indolecarbaldehyde (5h)



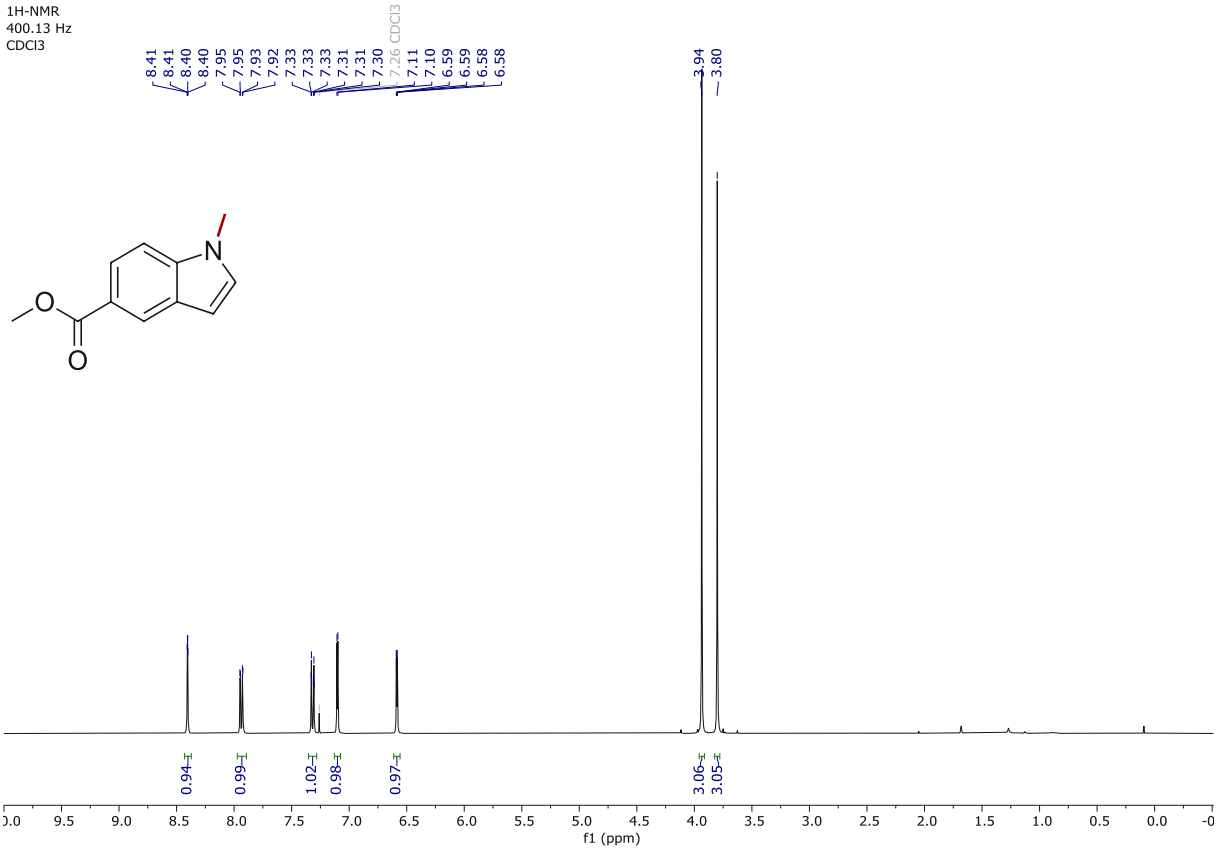


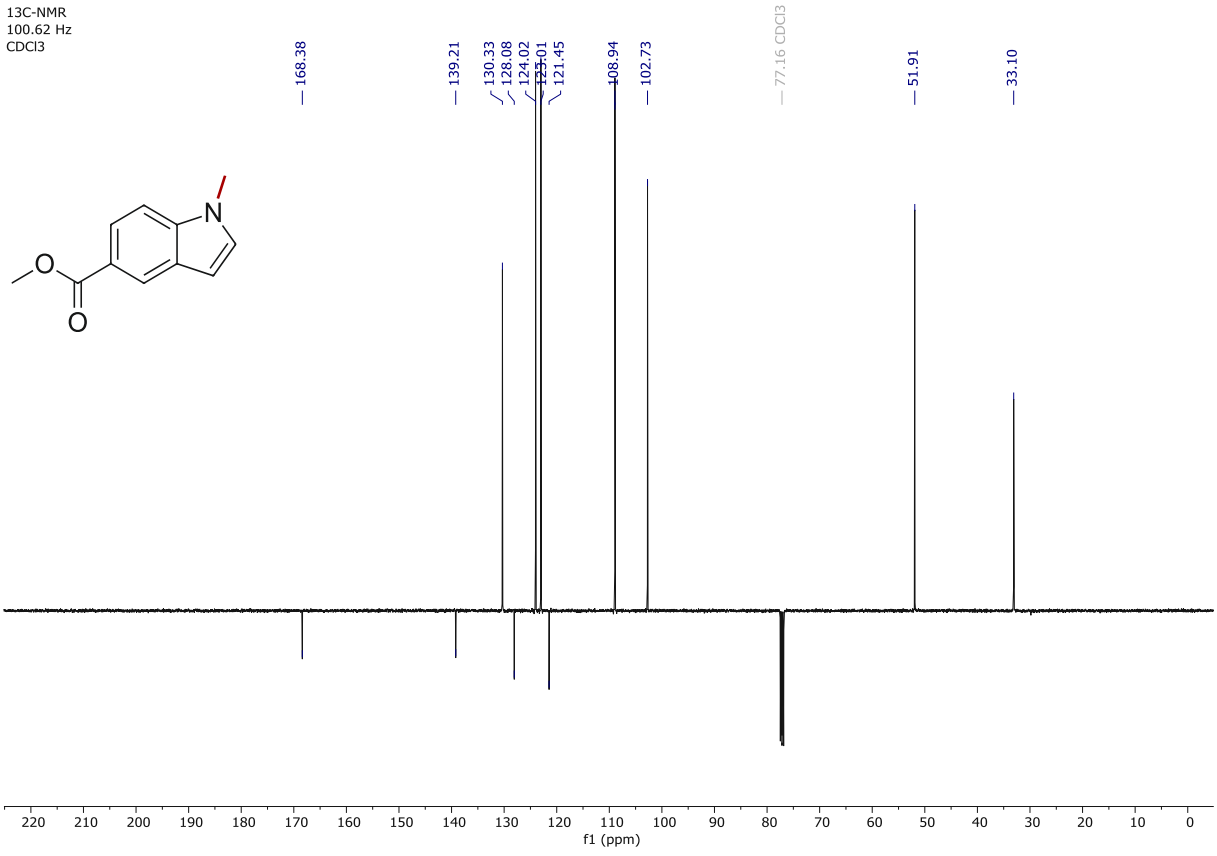
Ethyl 1-methyl-2-indolecarboxylate (5i)



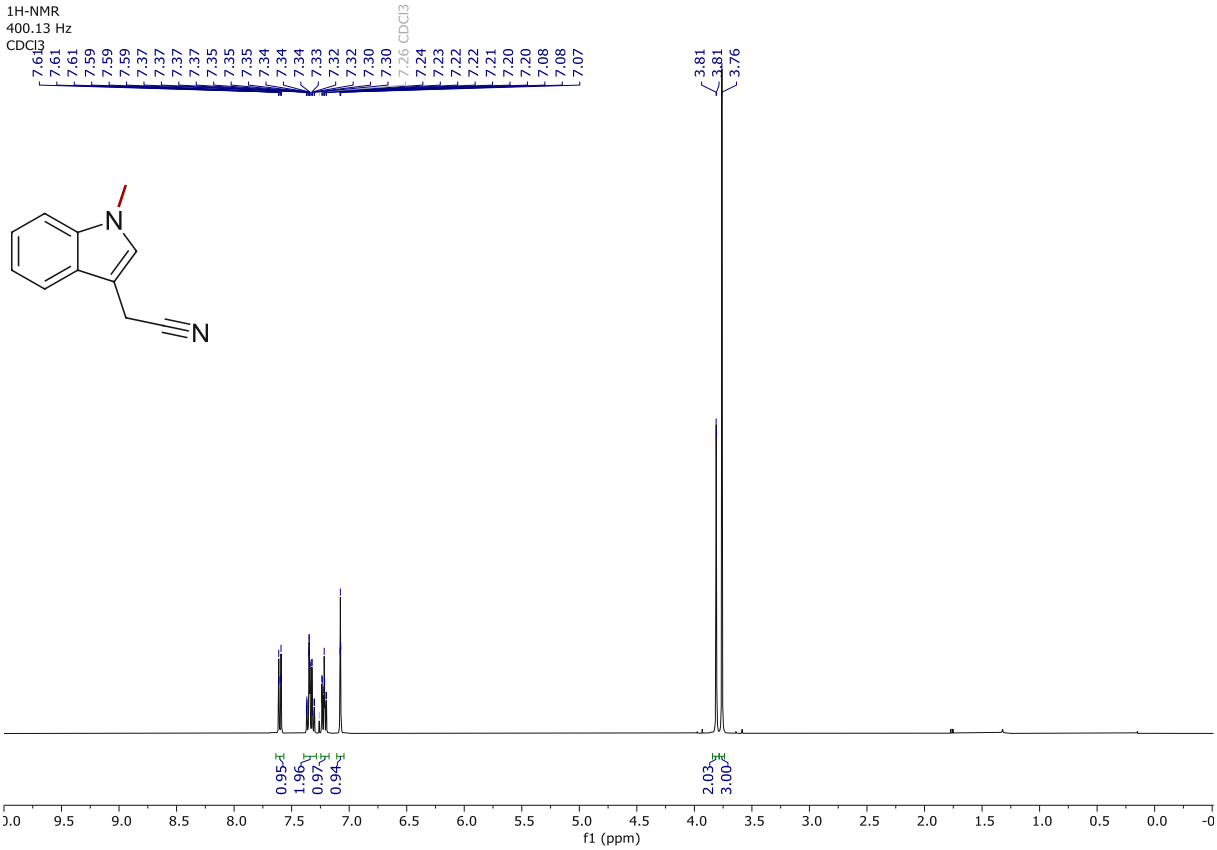


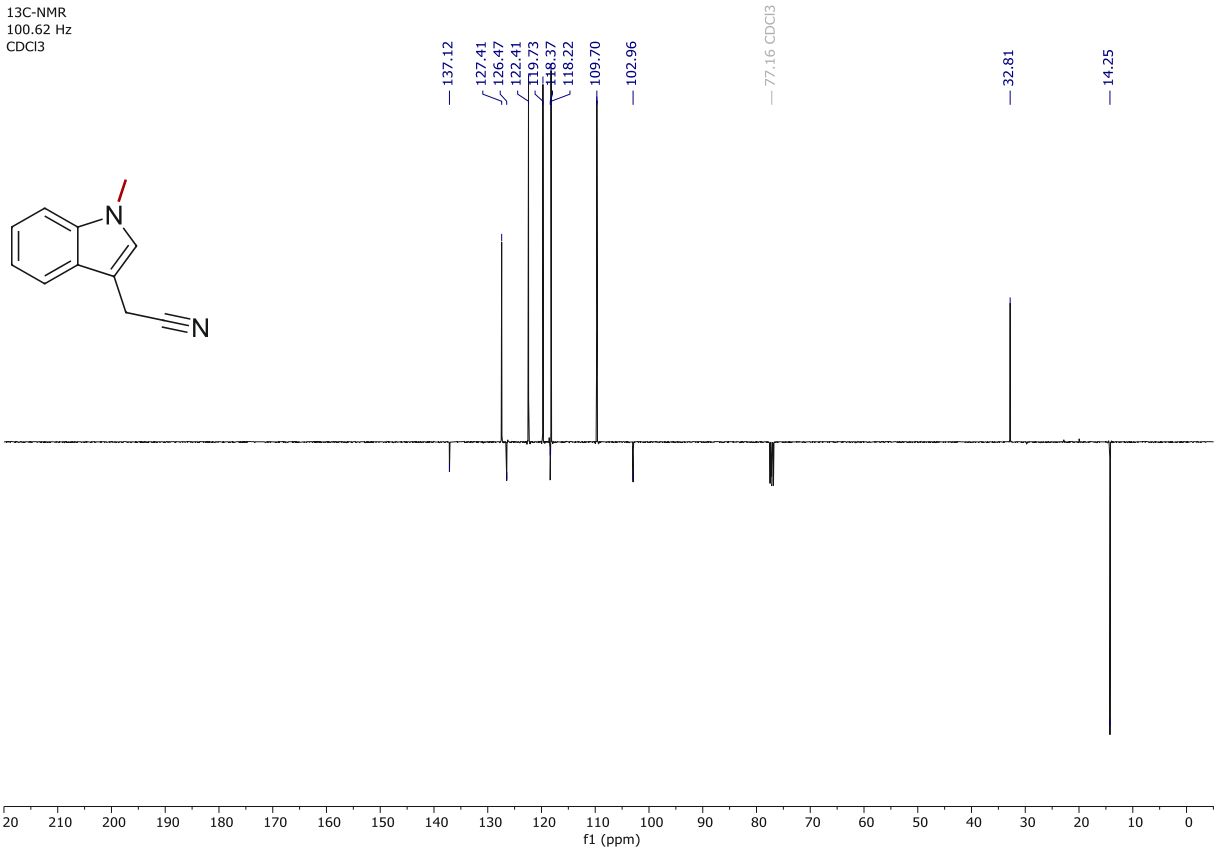
Methyl 1-methyl-5-indolecarboxylate (5j)



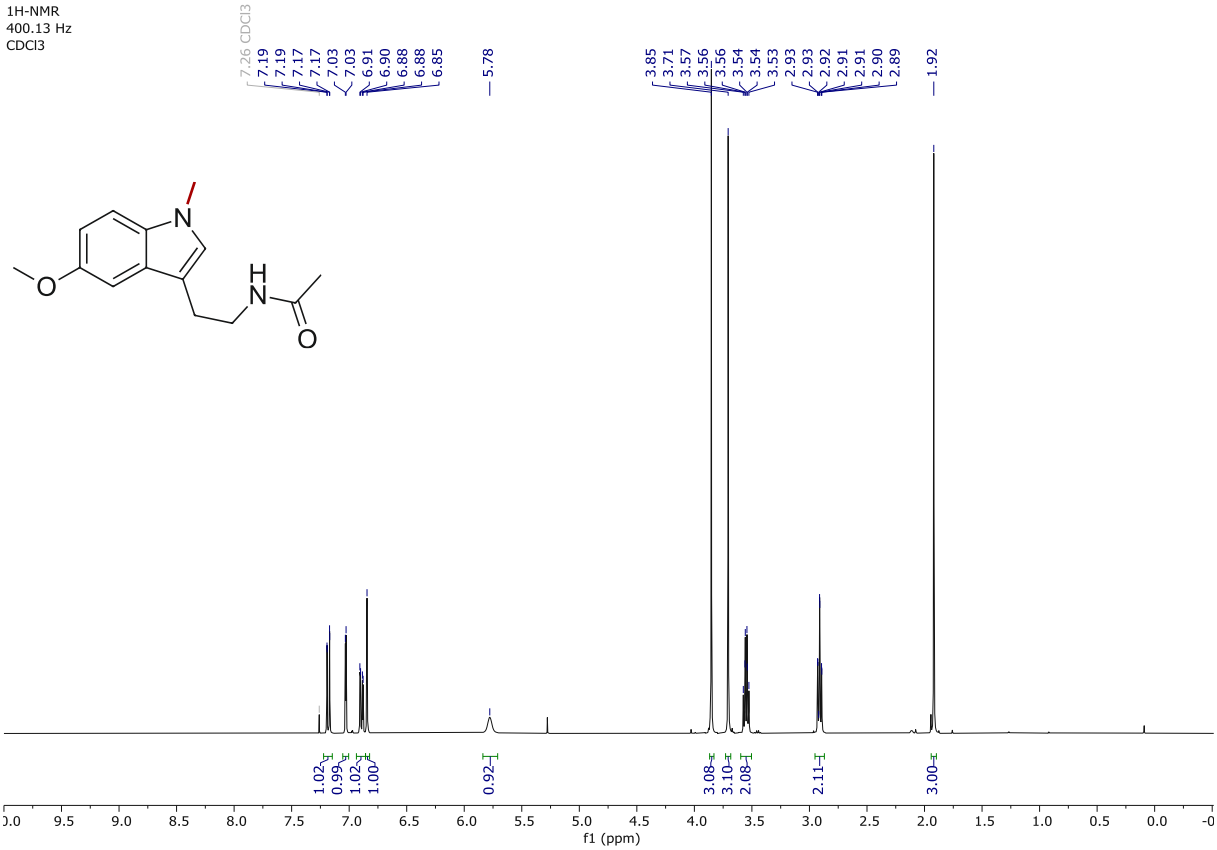


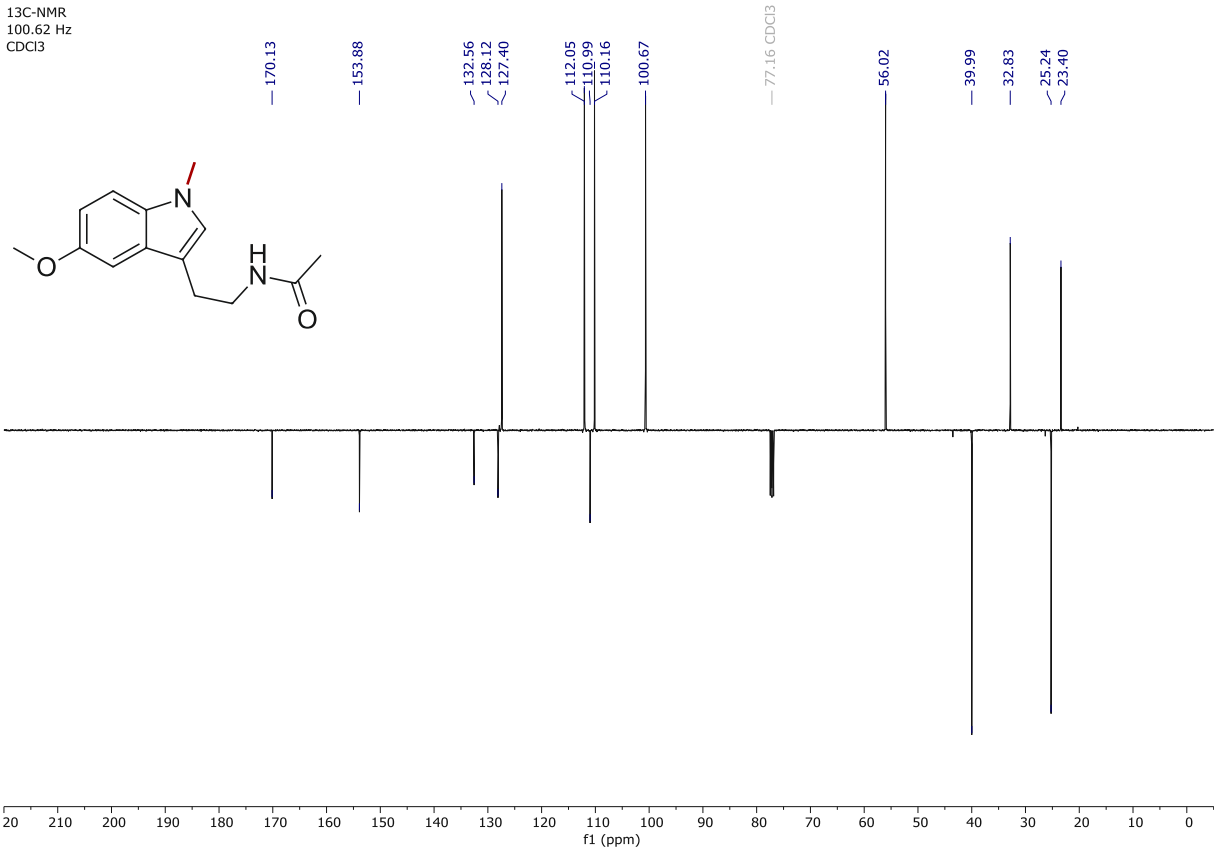
(1-Methyl-3-indolyl)acetonitrile (5k)



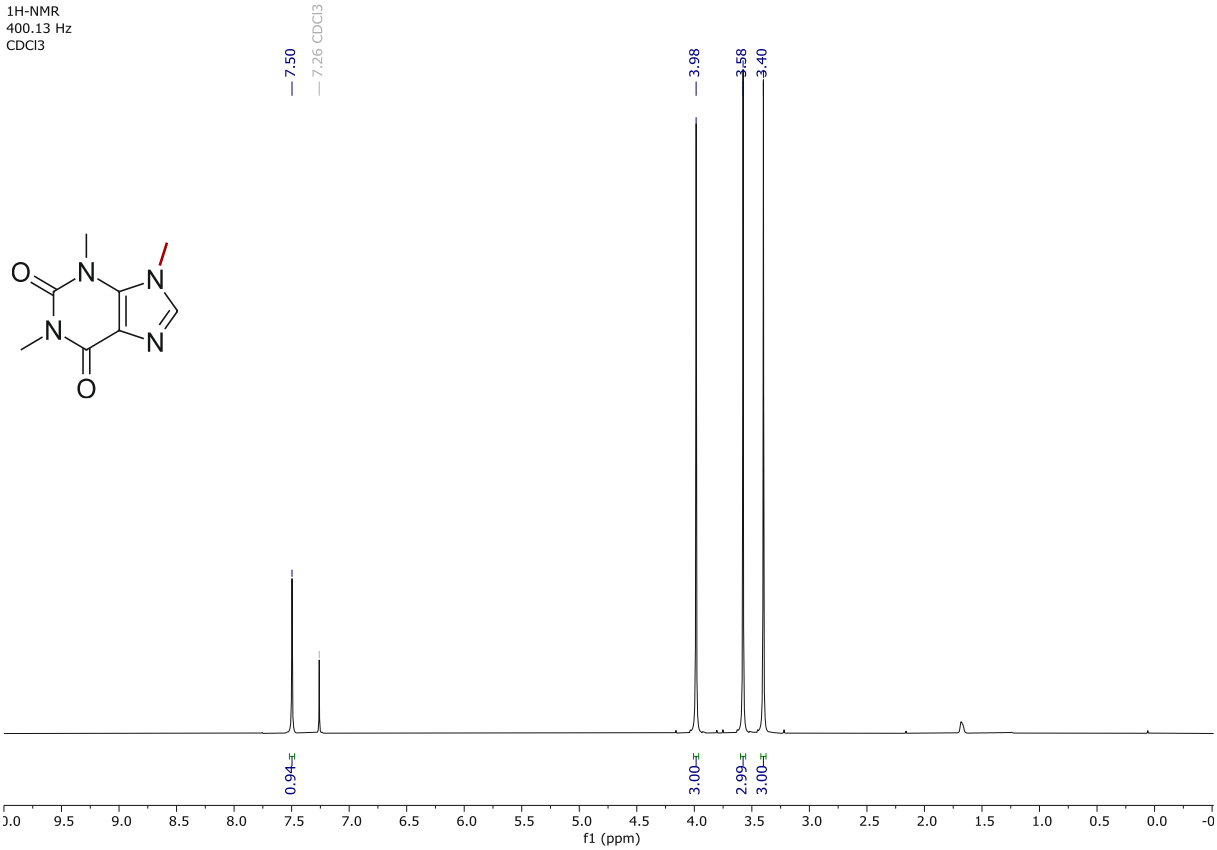


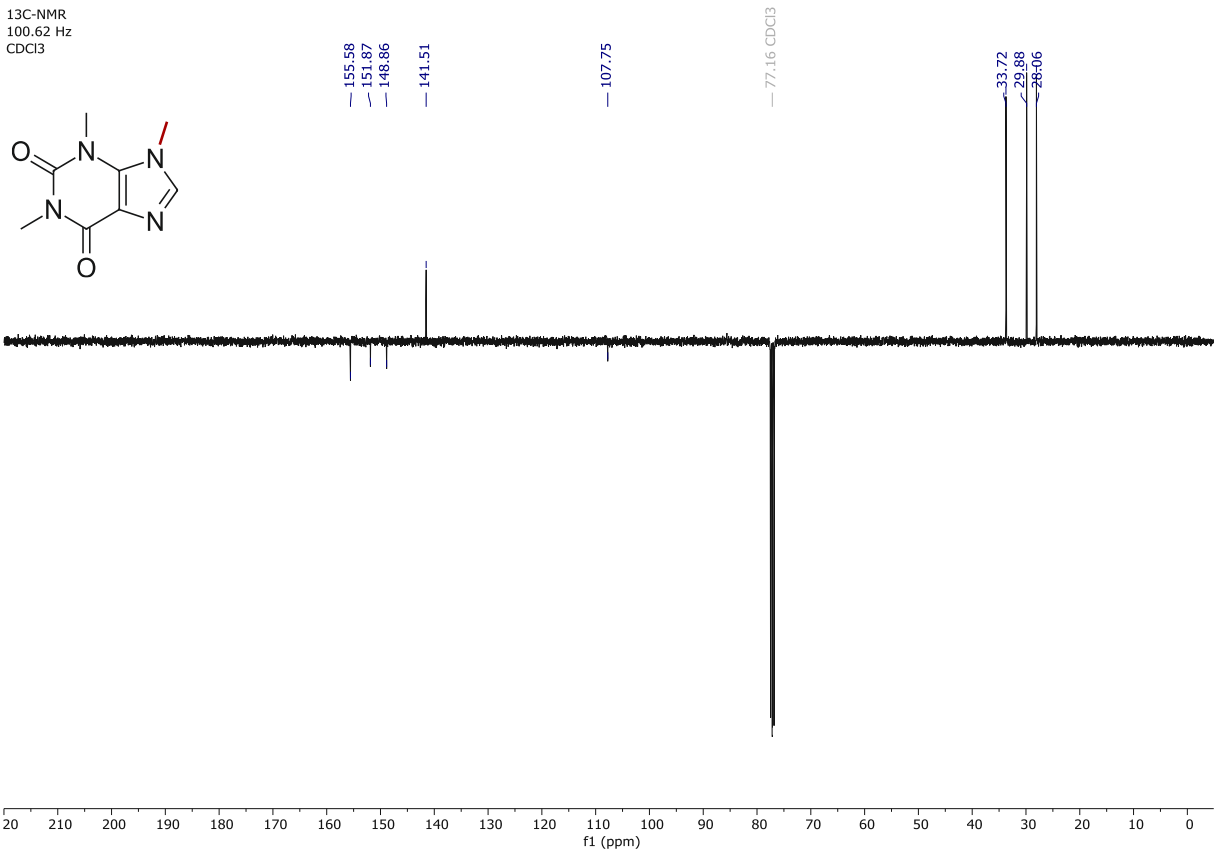
N-Methylmelatonine (9)



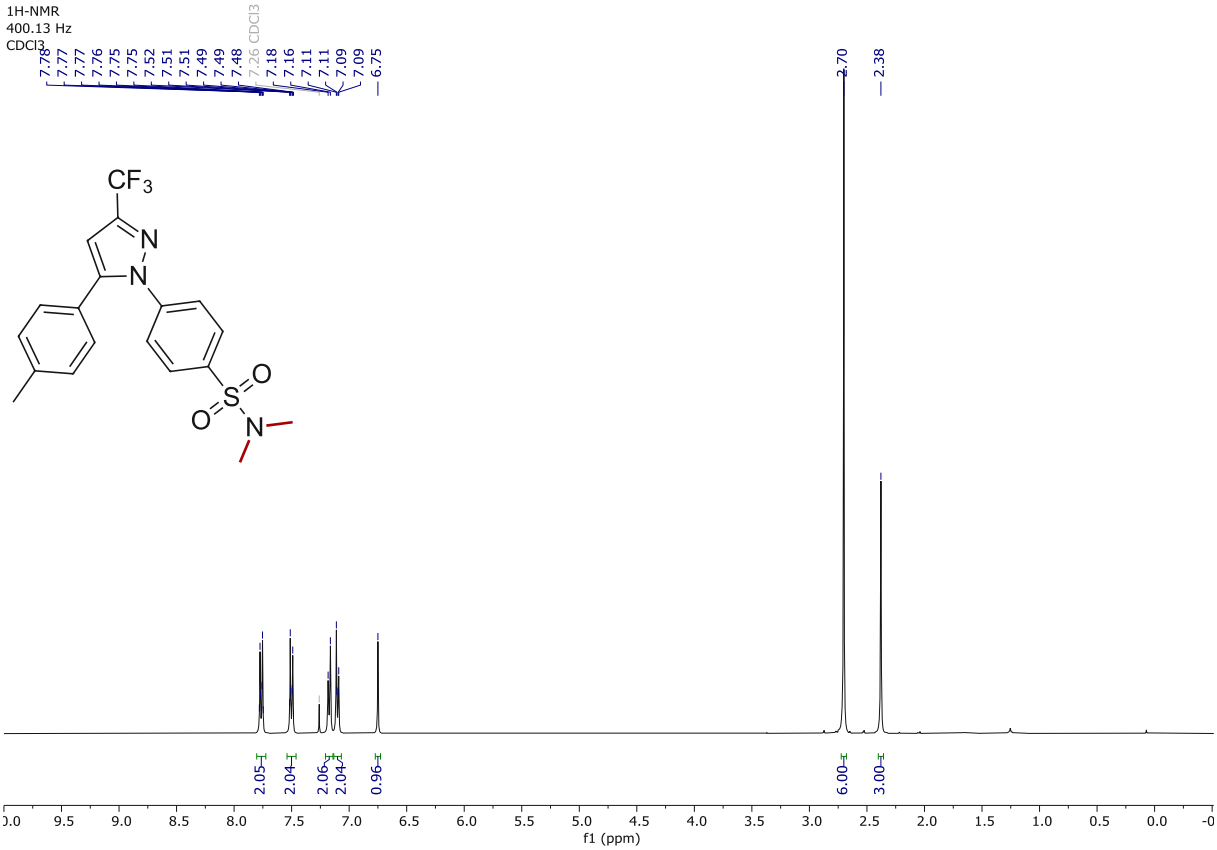


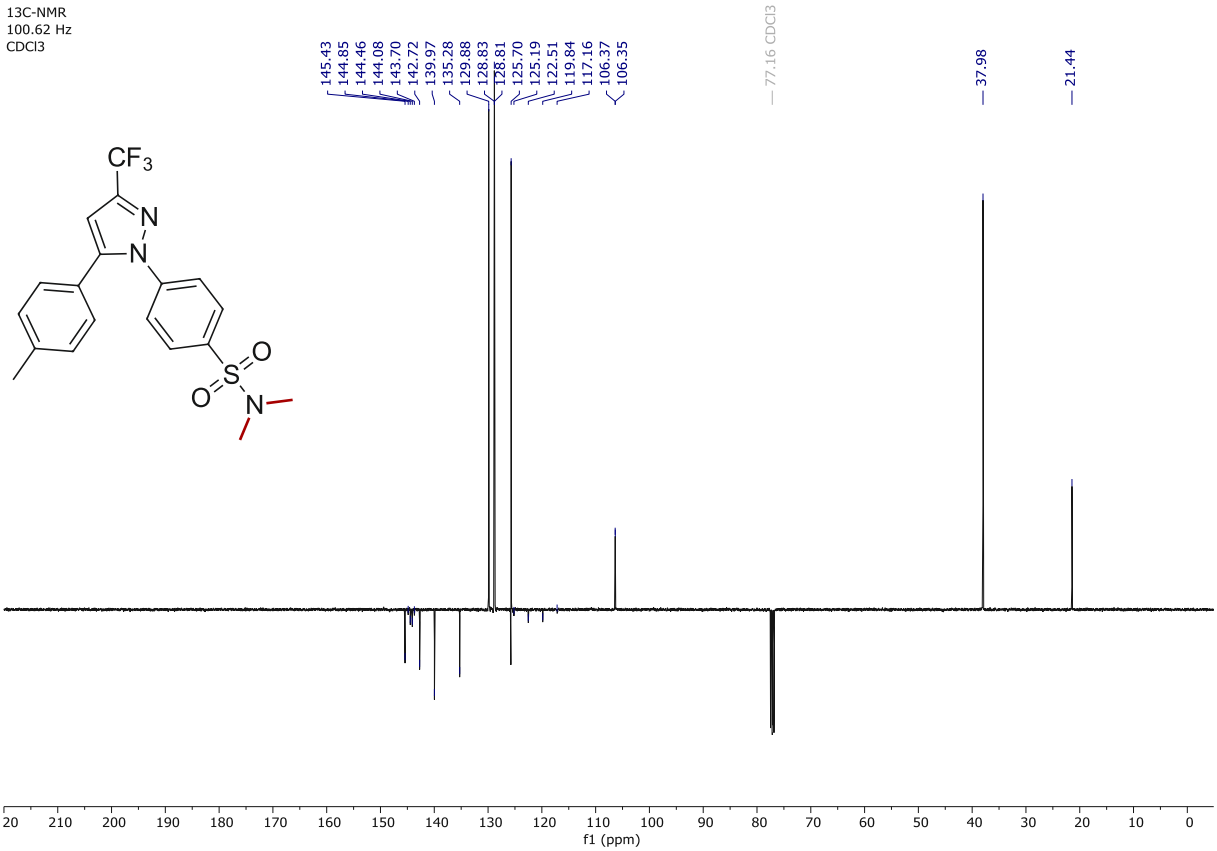
Caffeine (10)



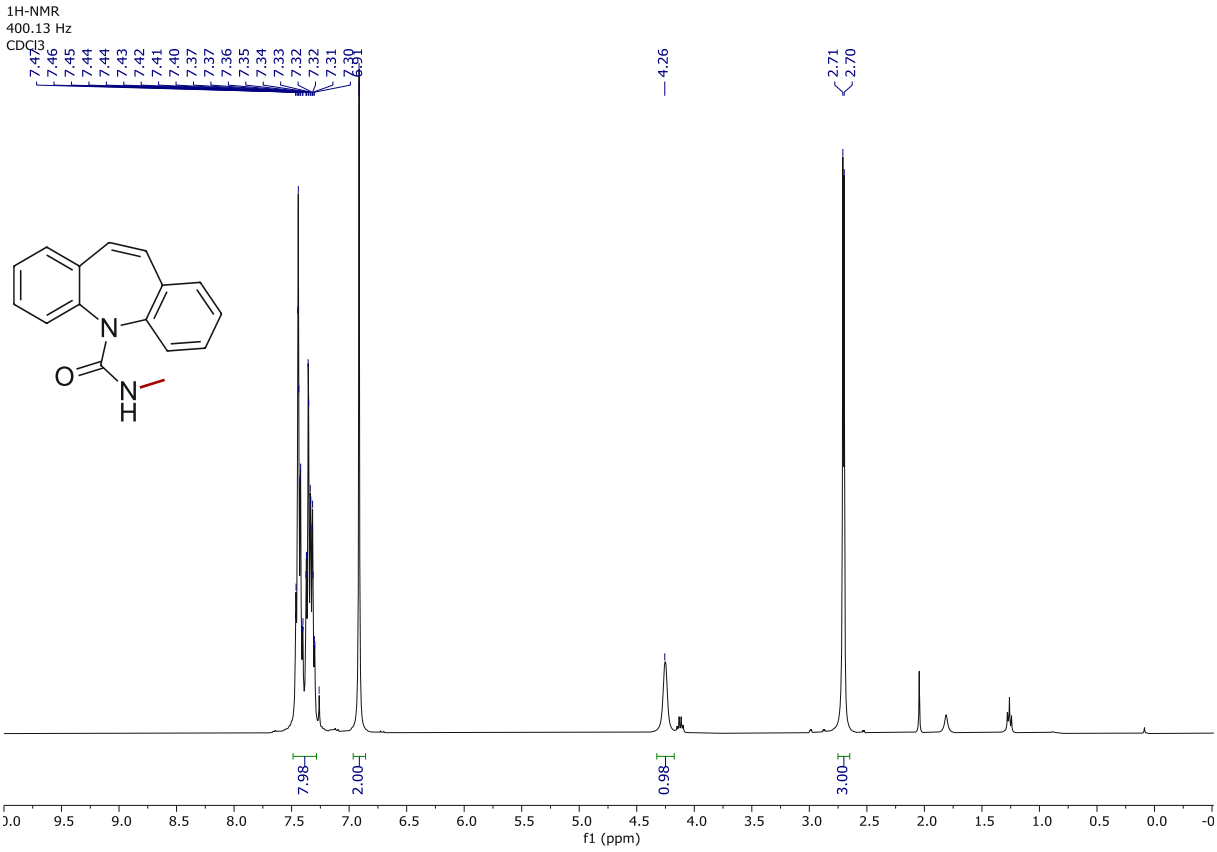


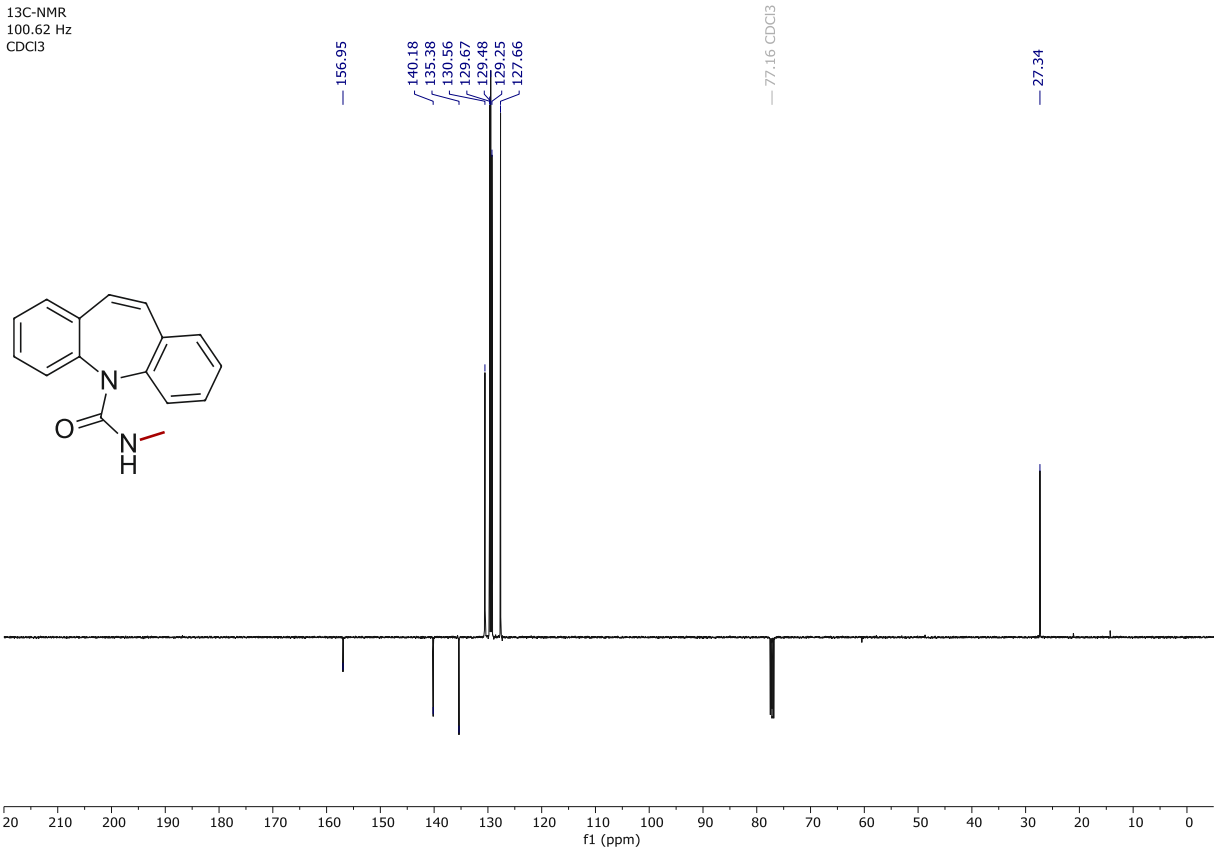
N,N-Dimethyl celecoxib (11)



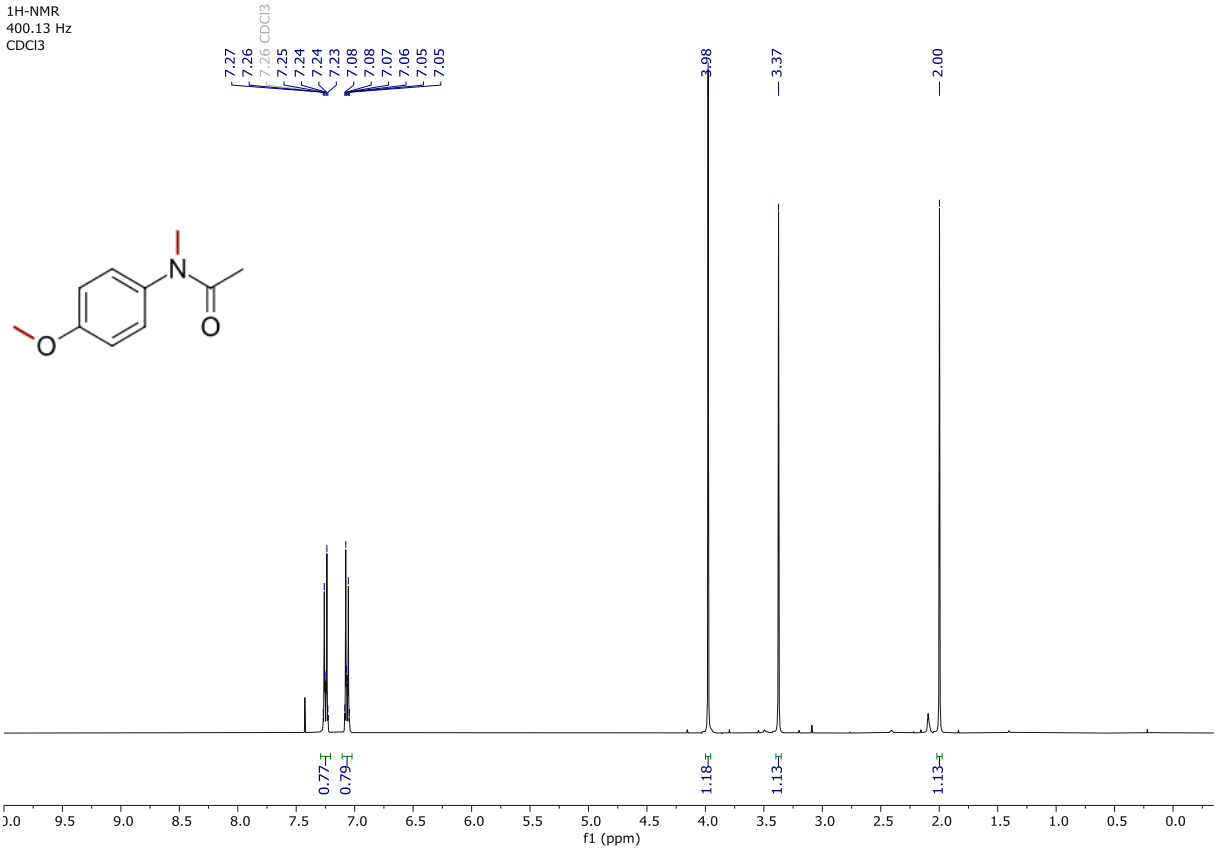


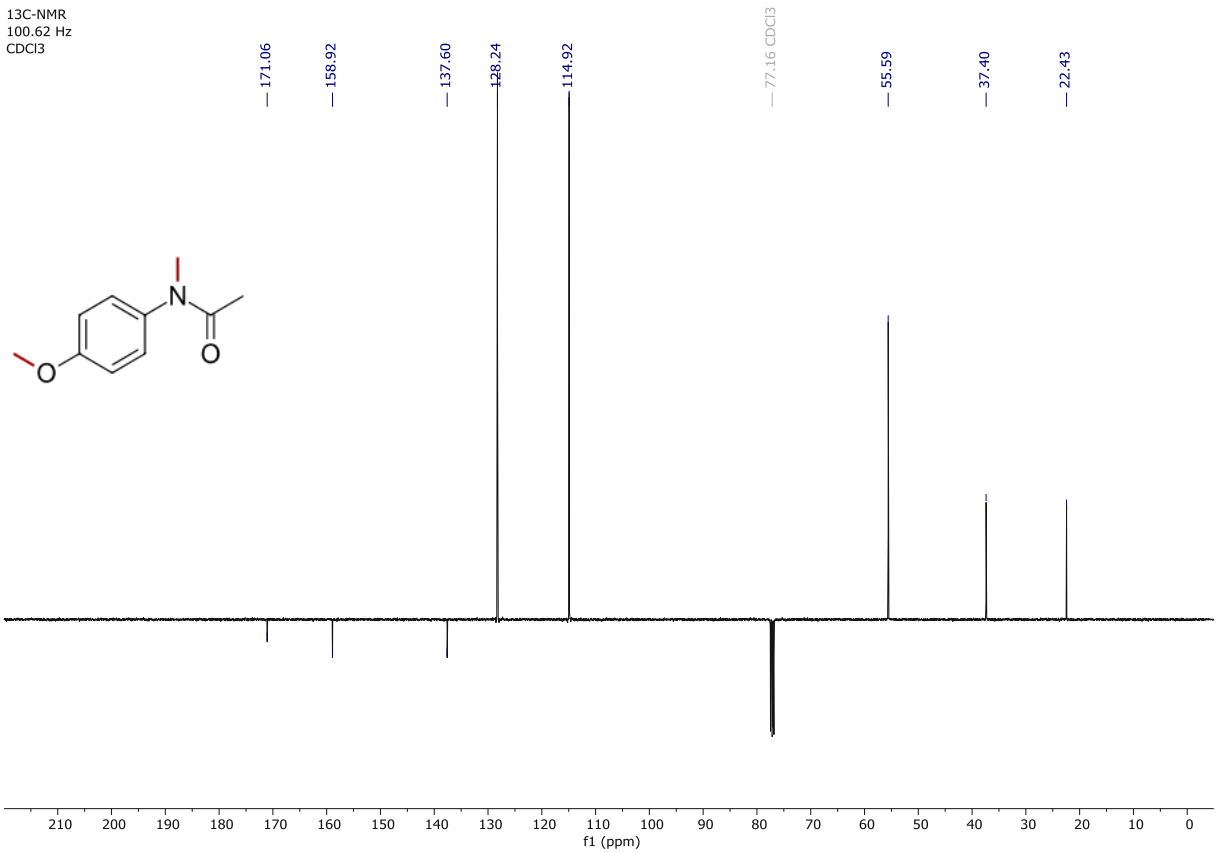
N-Methyl carbamazepine (12)



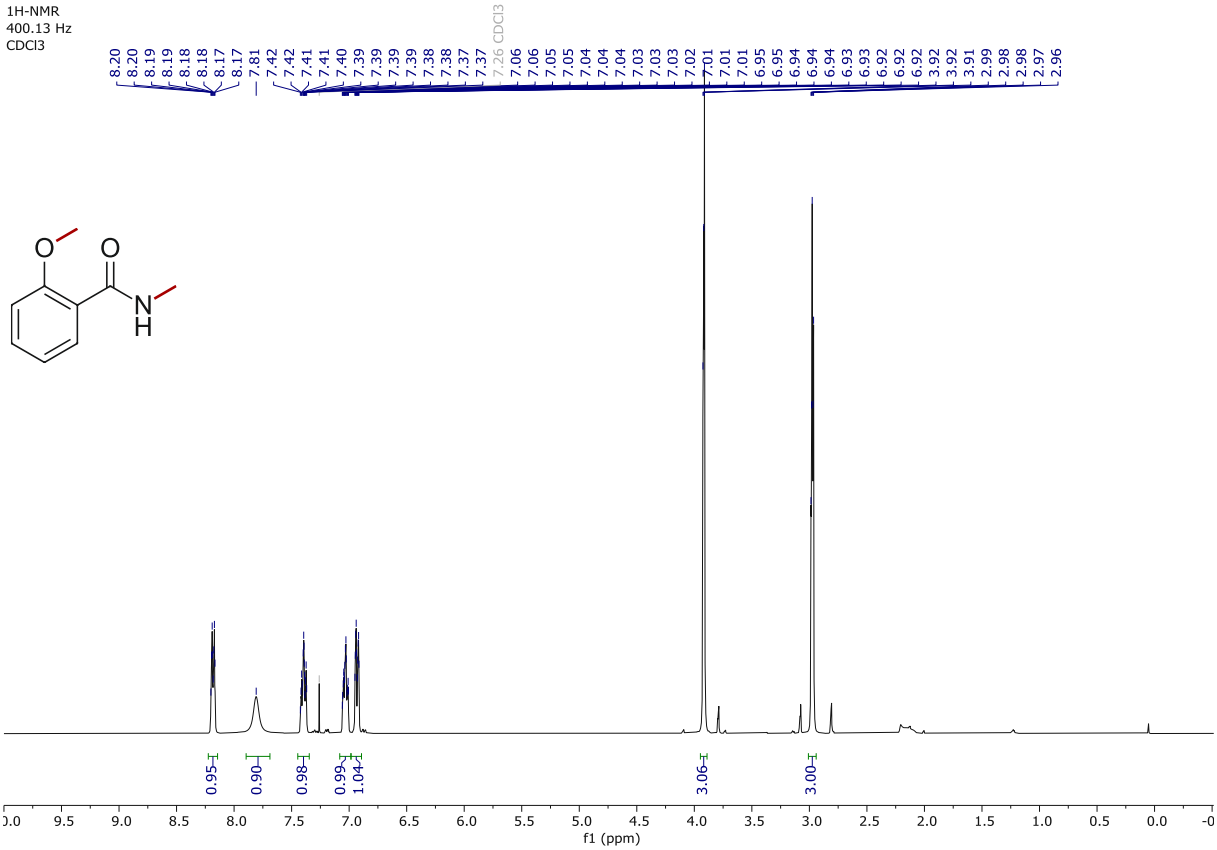


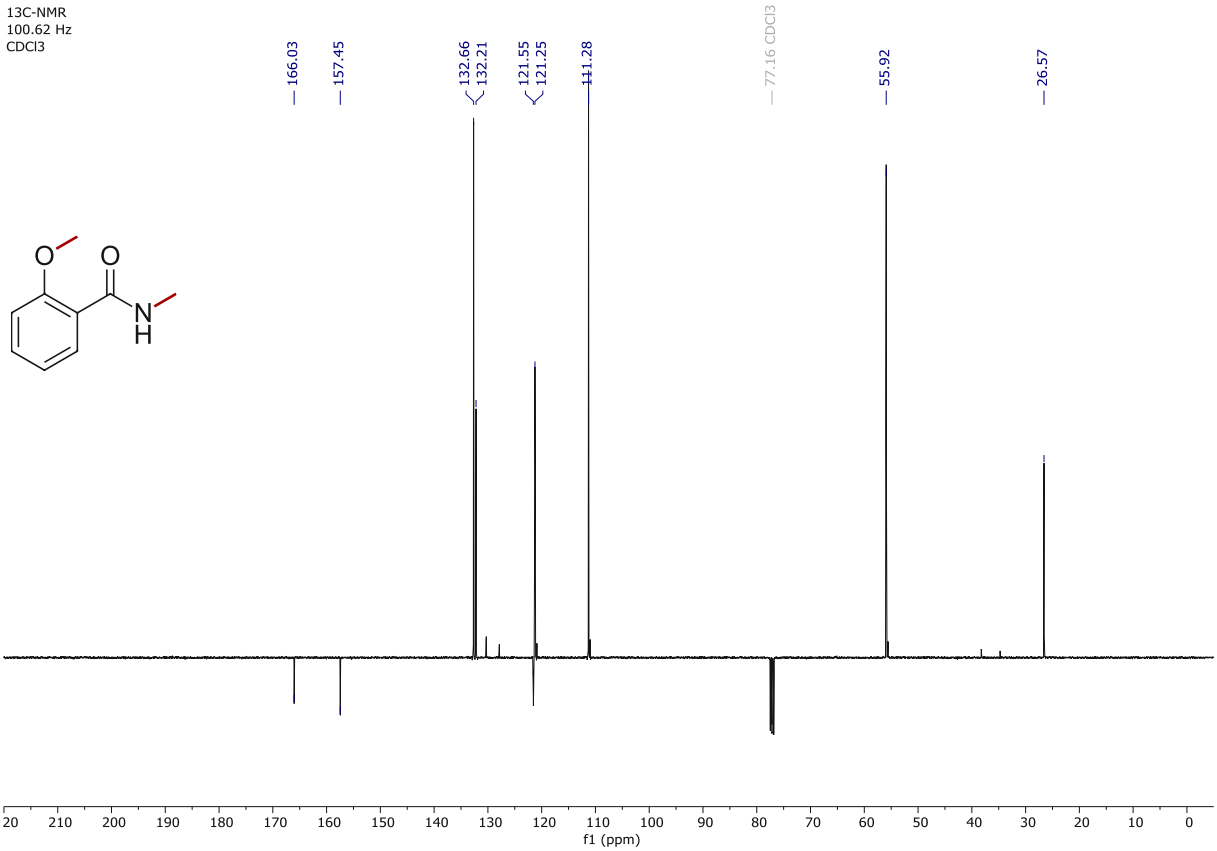
O,N-Dimethyl paracetamol (13)



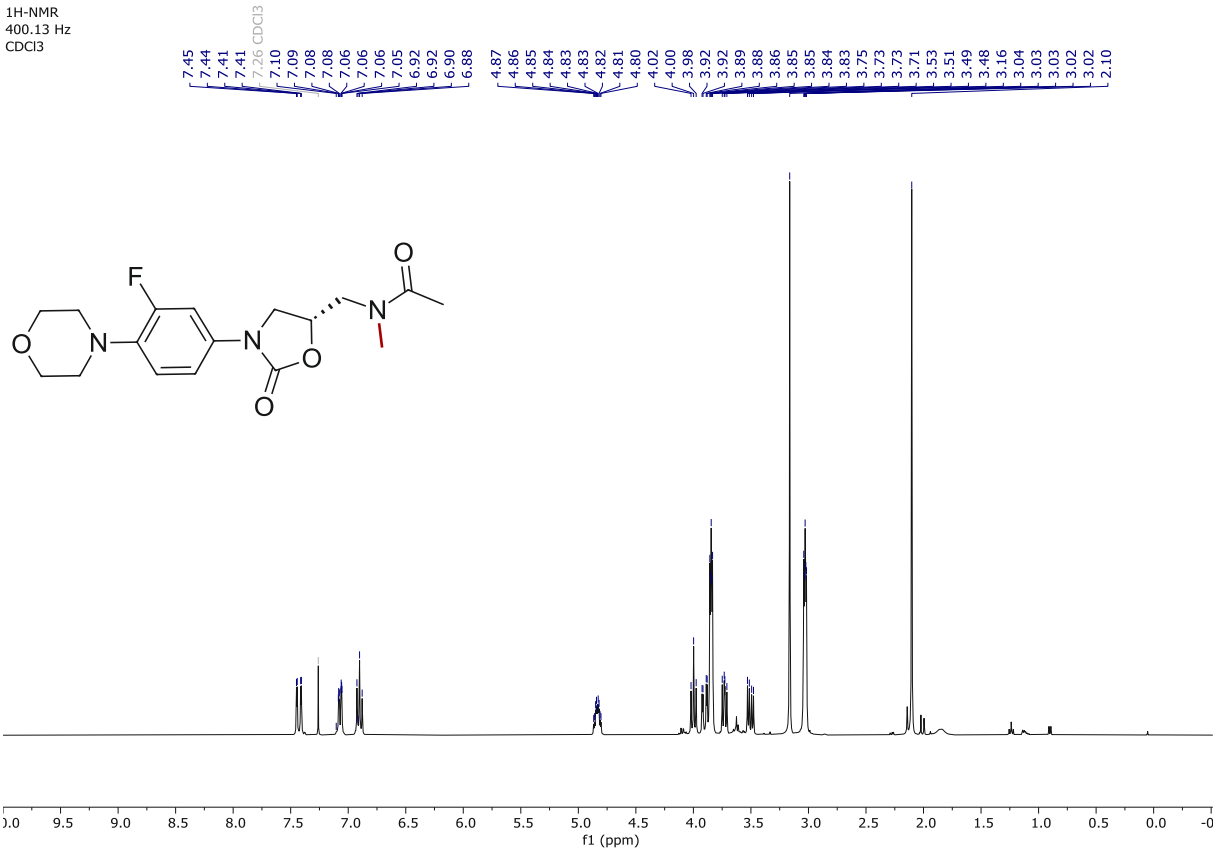


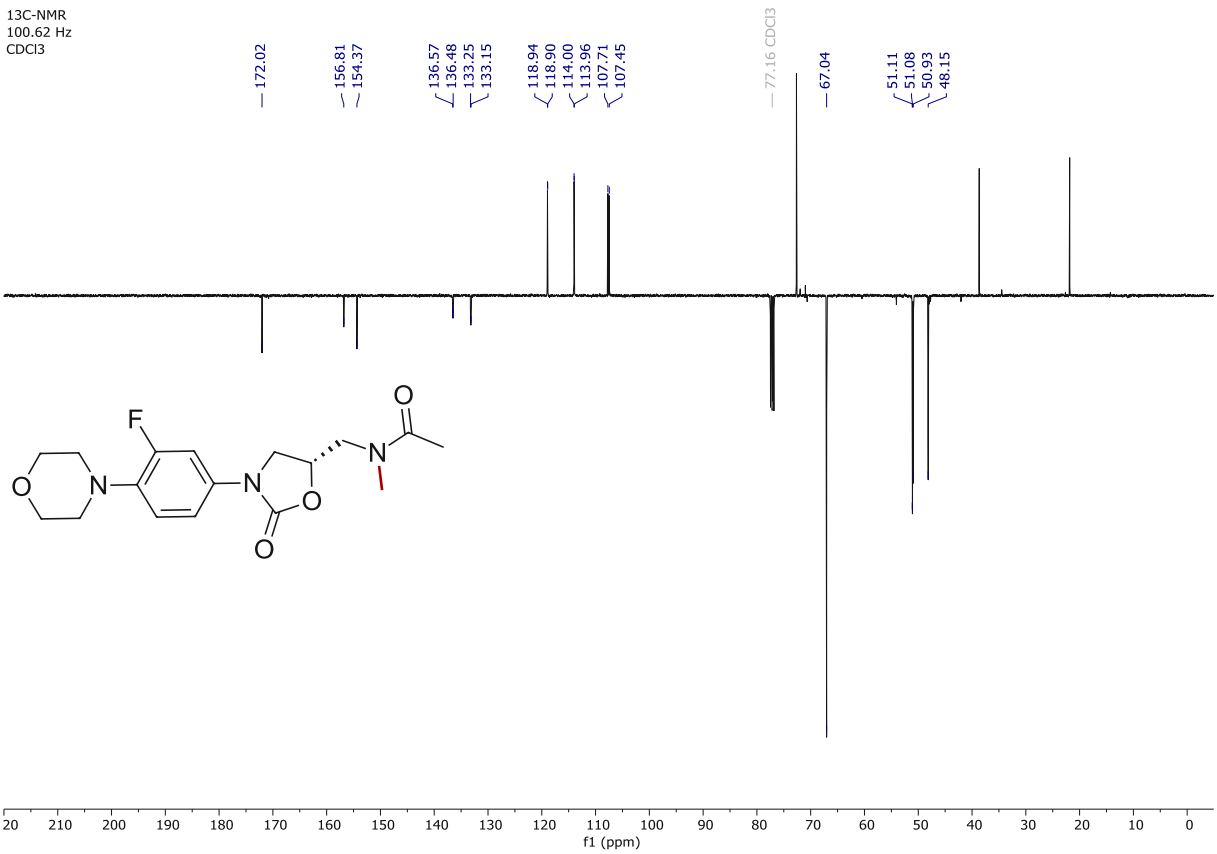
O,N-Dimethyl salicylamide (14)

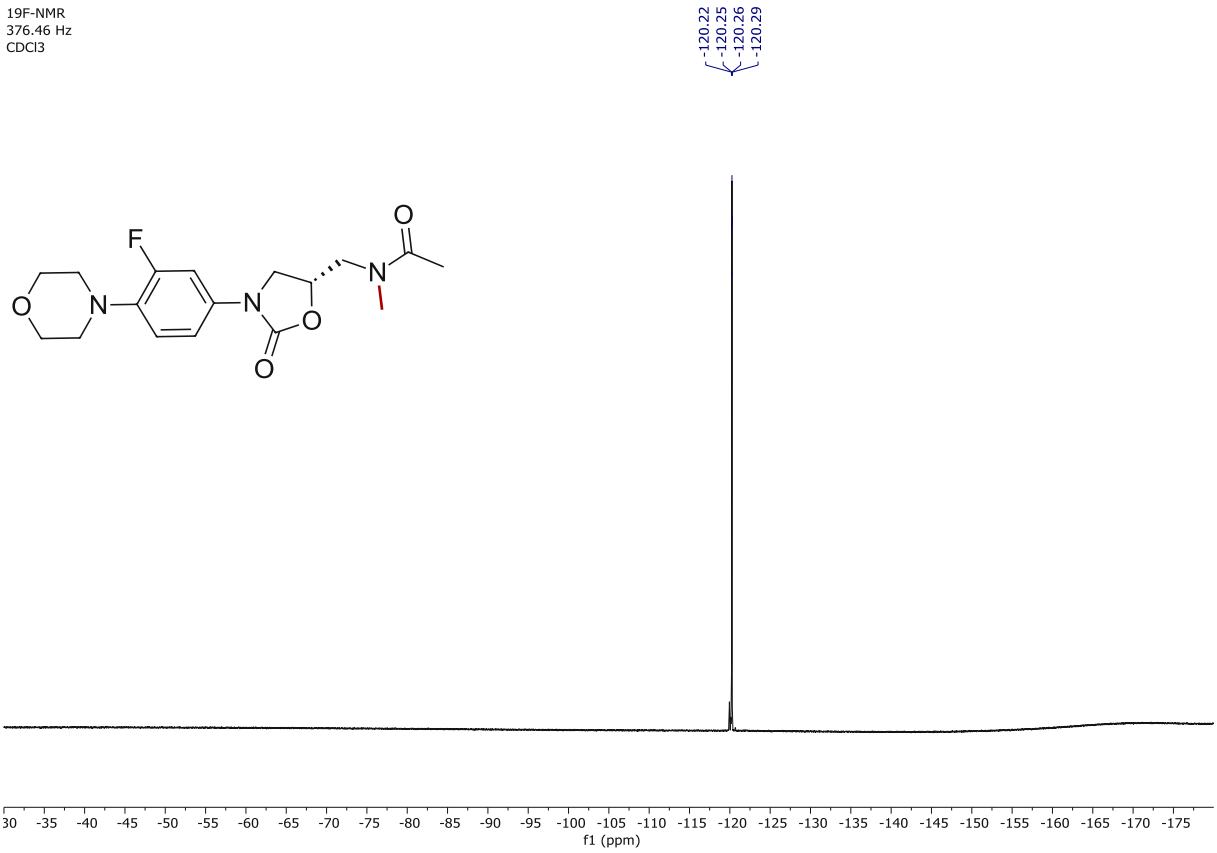




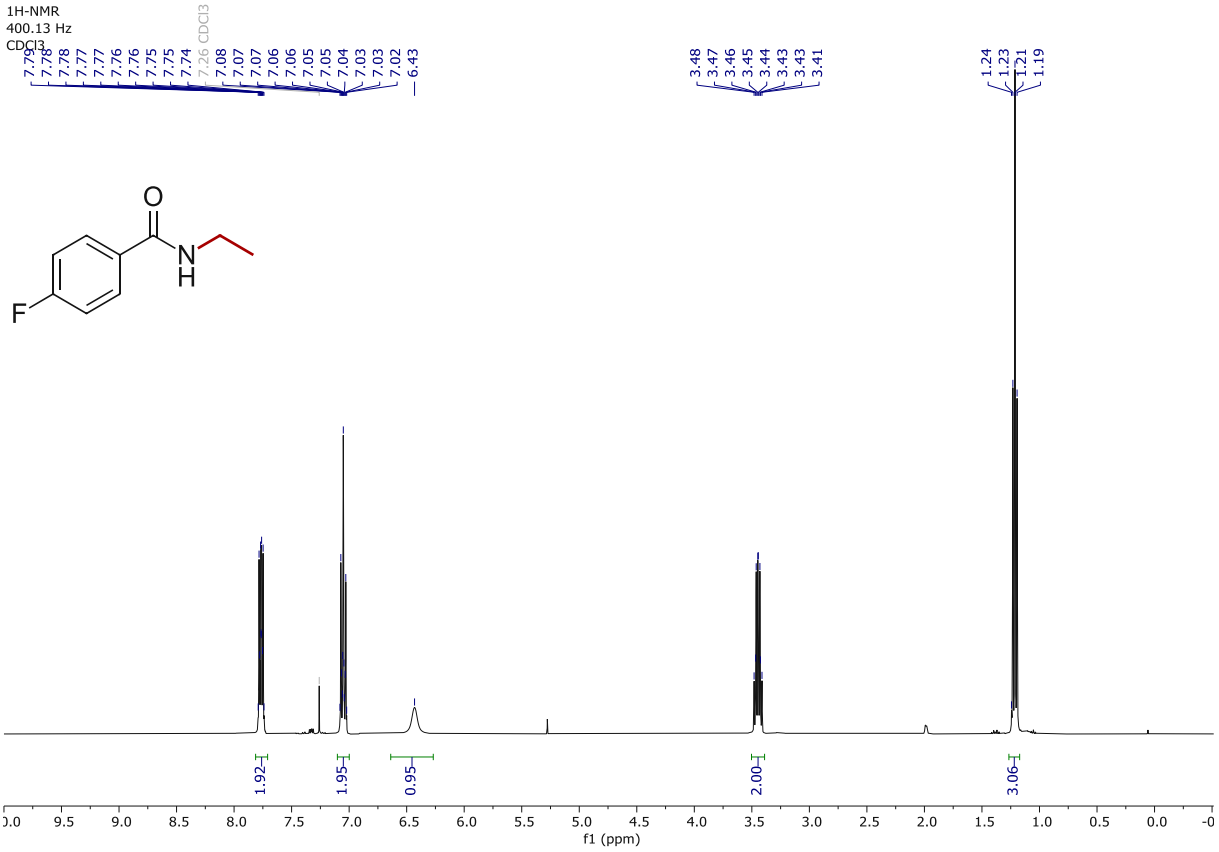
N-Methyl linezolid (15)

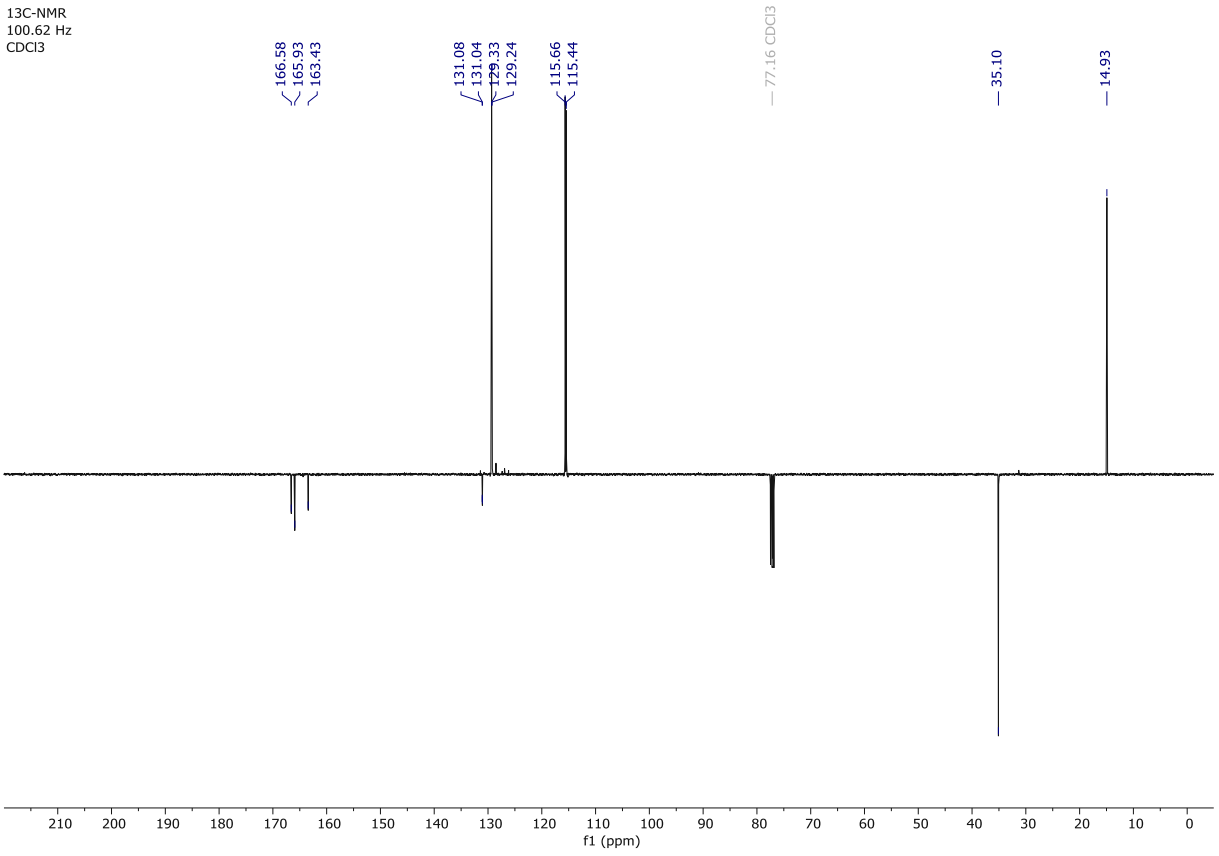




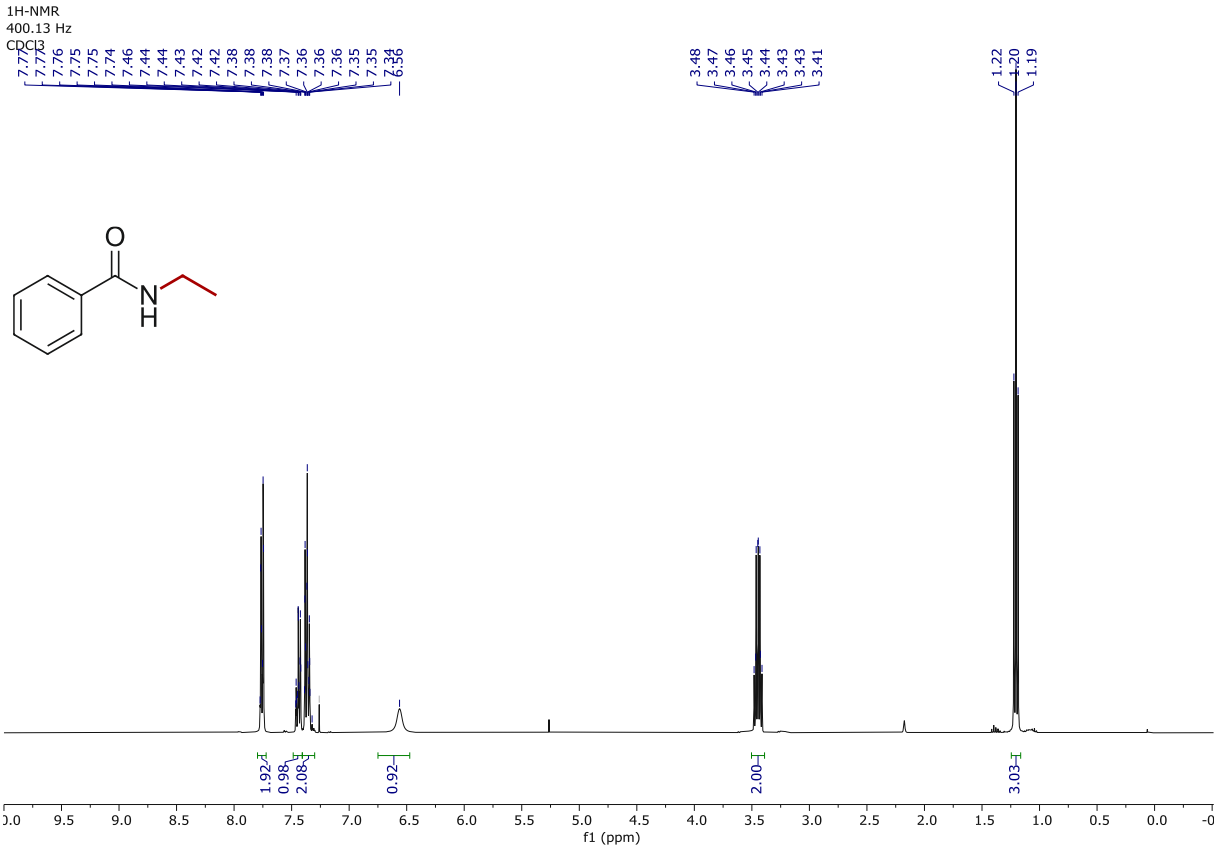


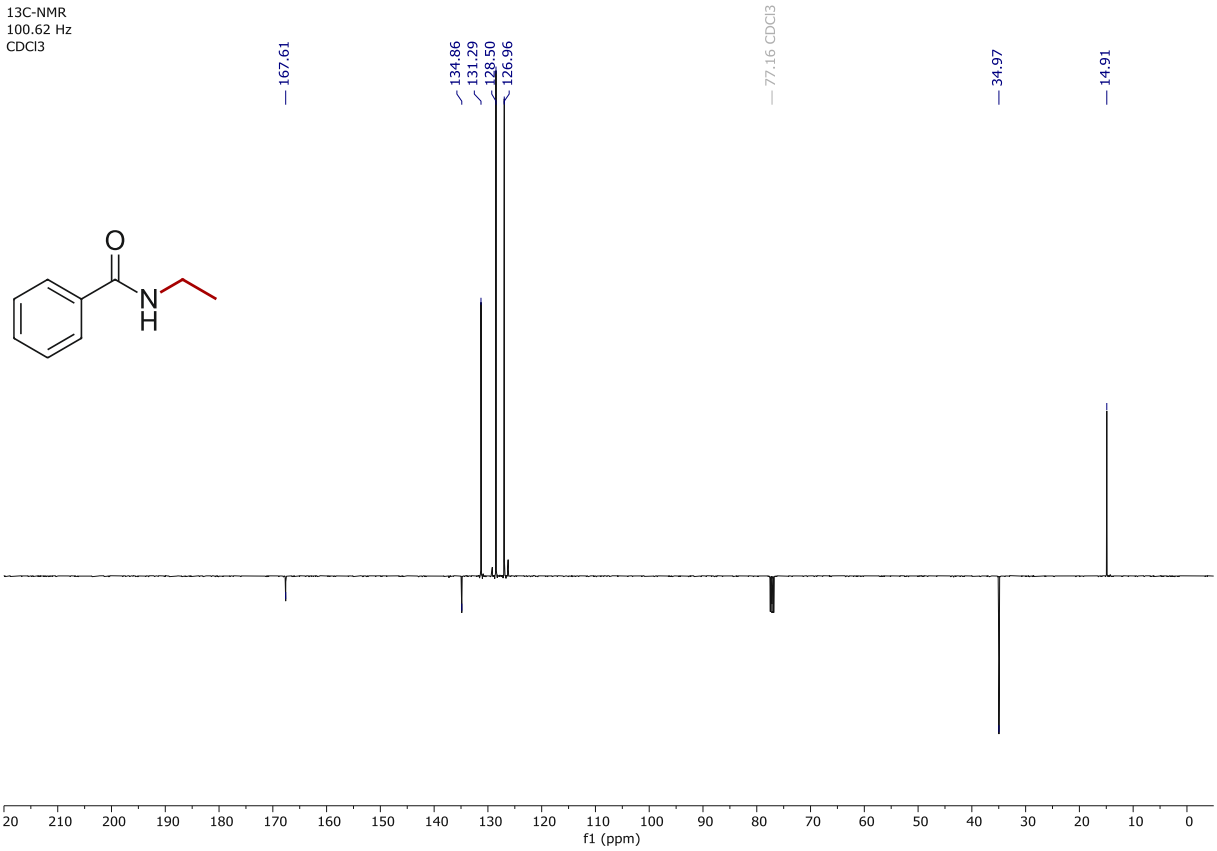
N-Ethyl-4-fluorobenzamide (4a)



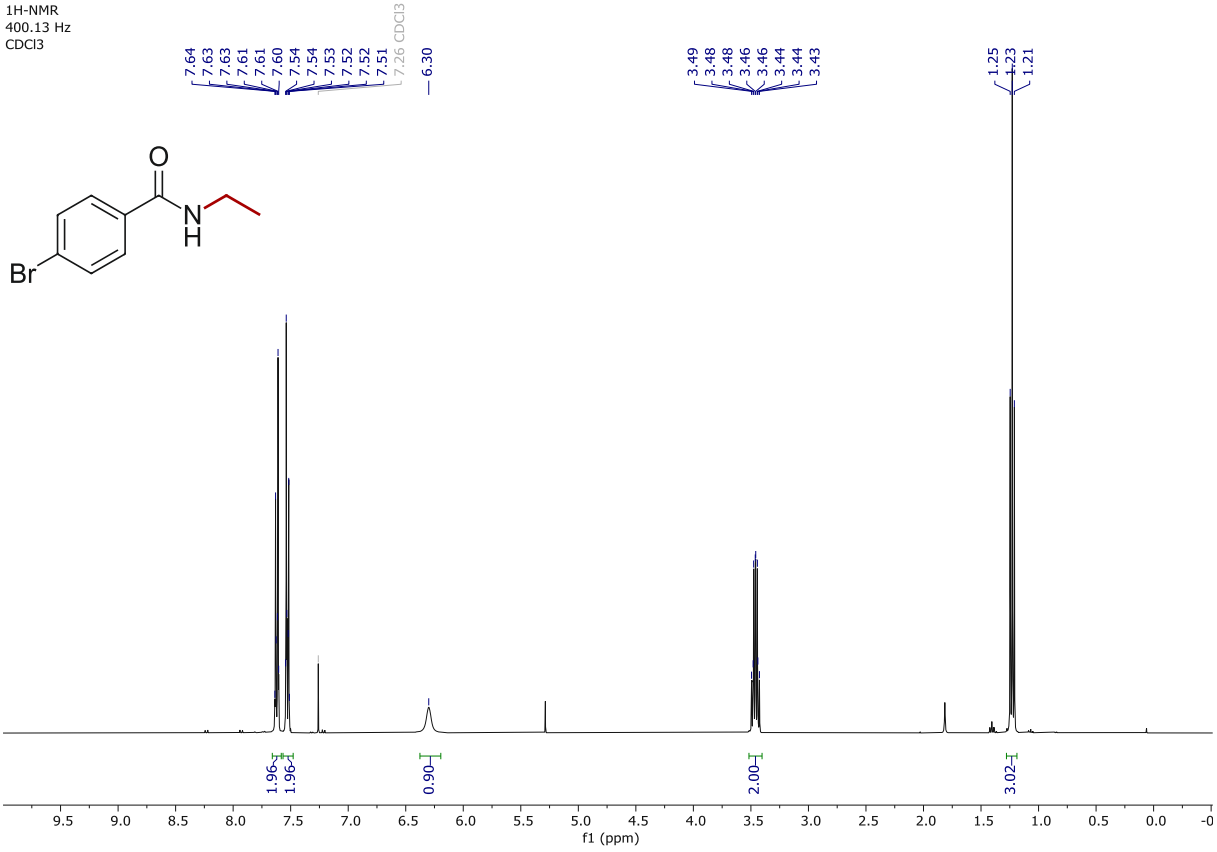


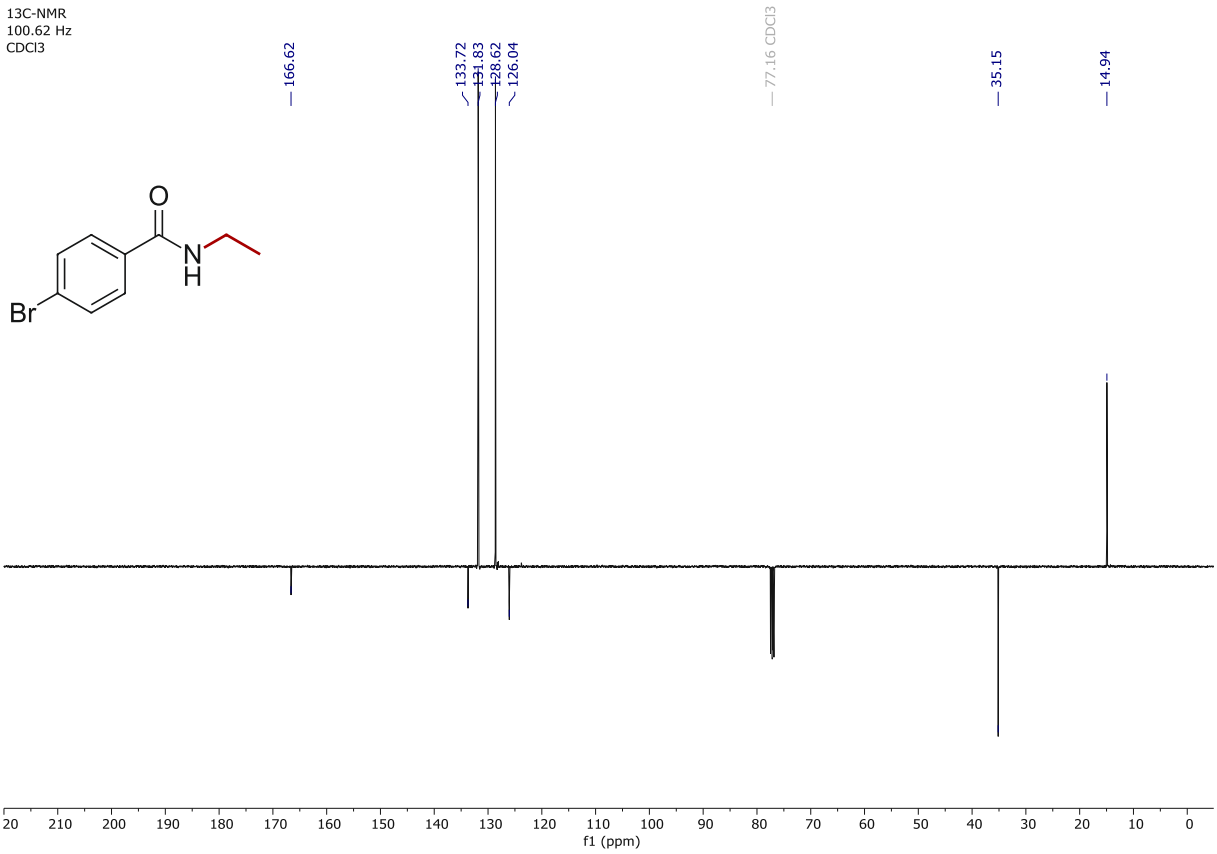
N-Ethylbenzamide (4b)



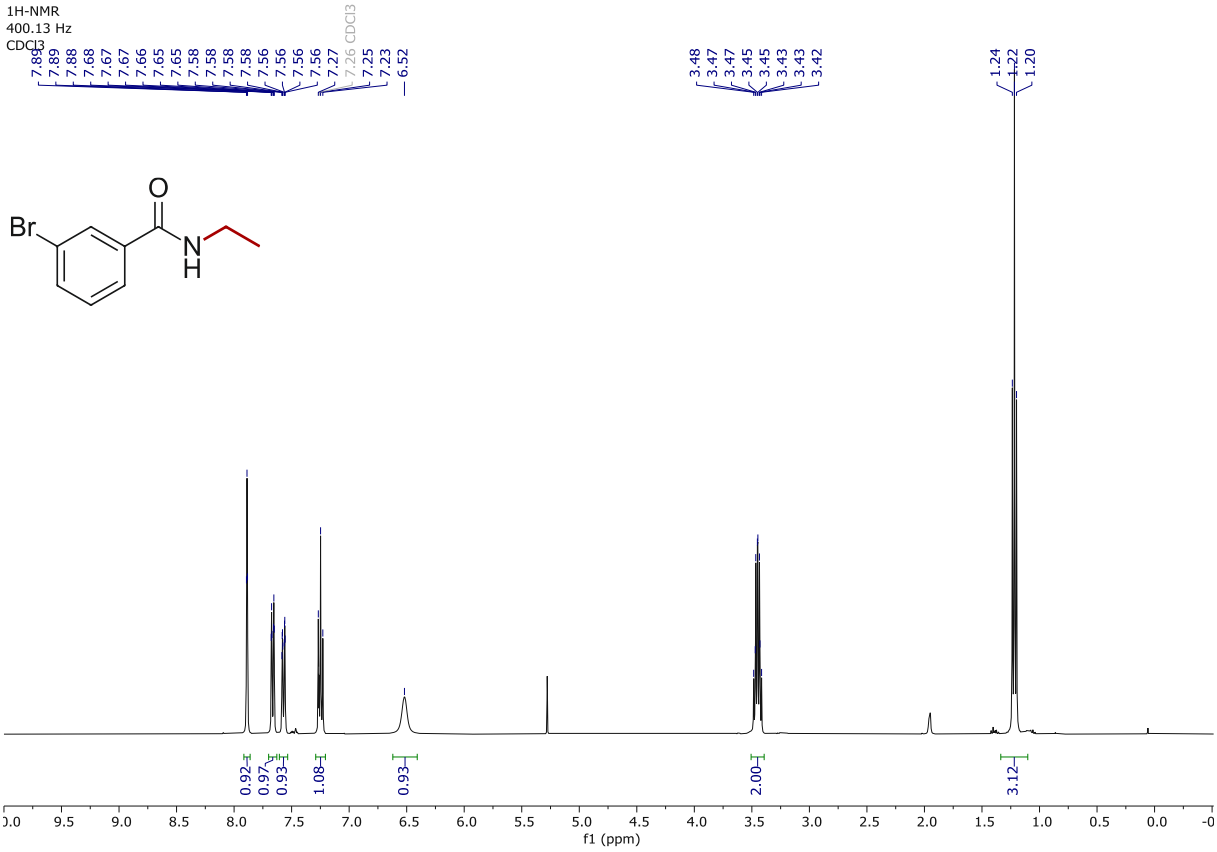


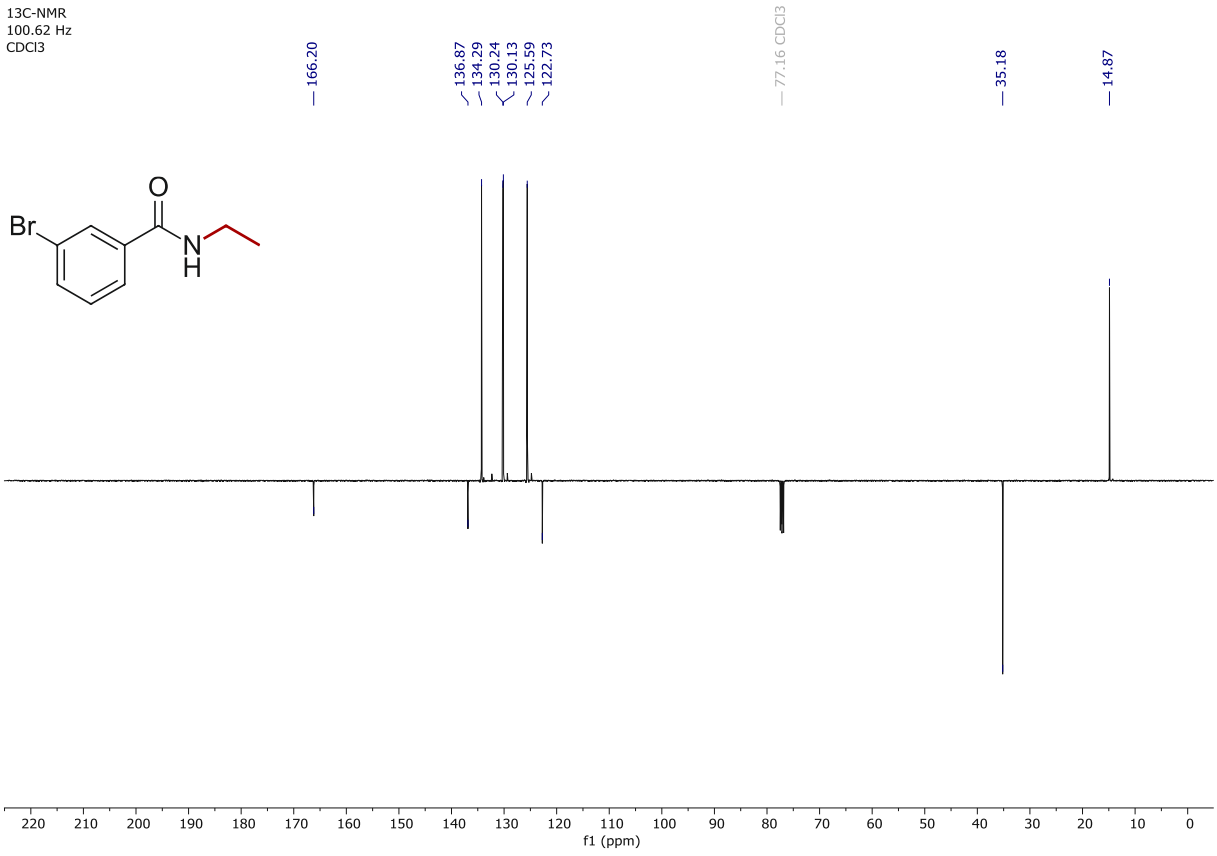
4-Bromo-*N*-ethylbenzamide (4c)



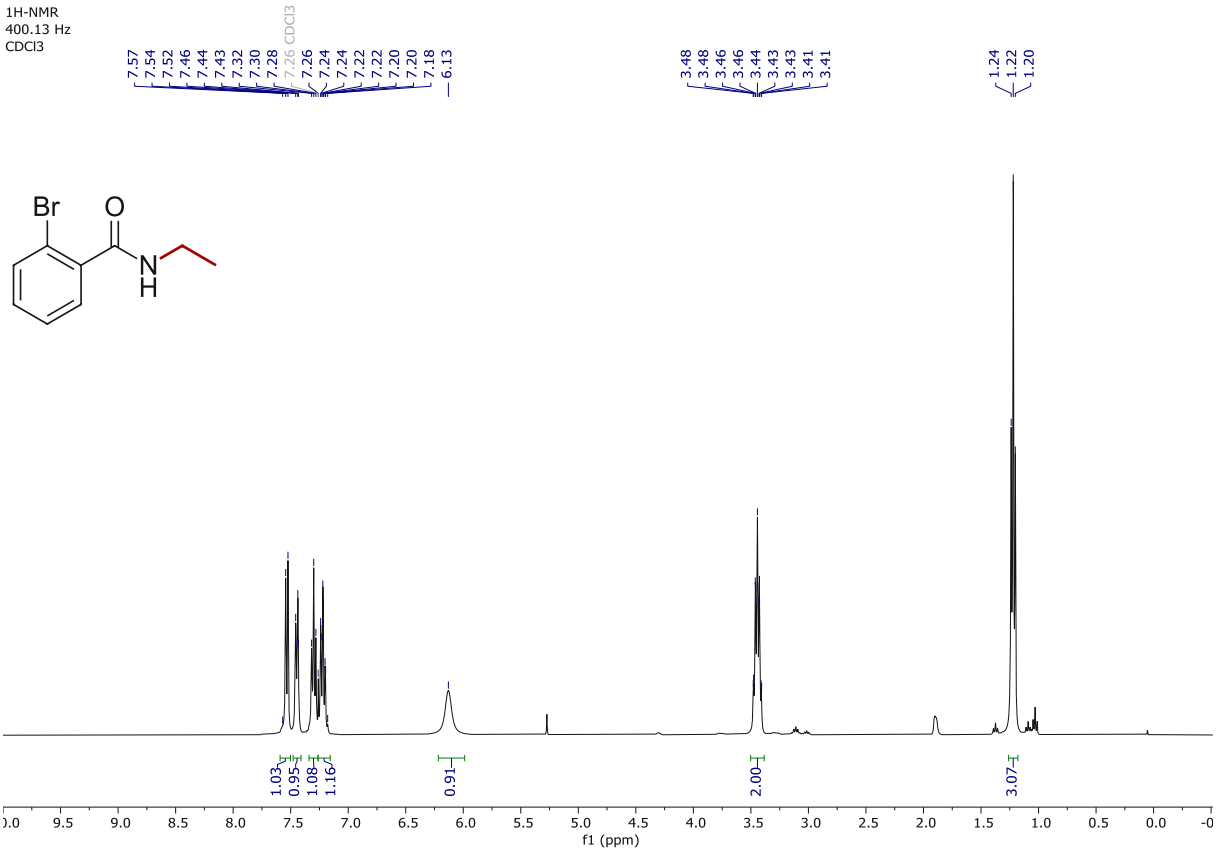


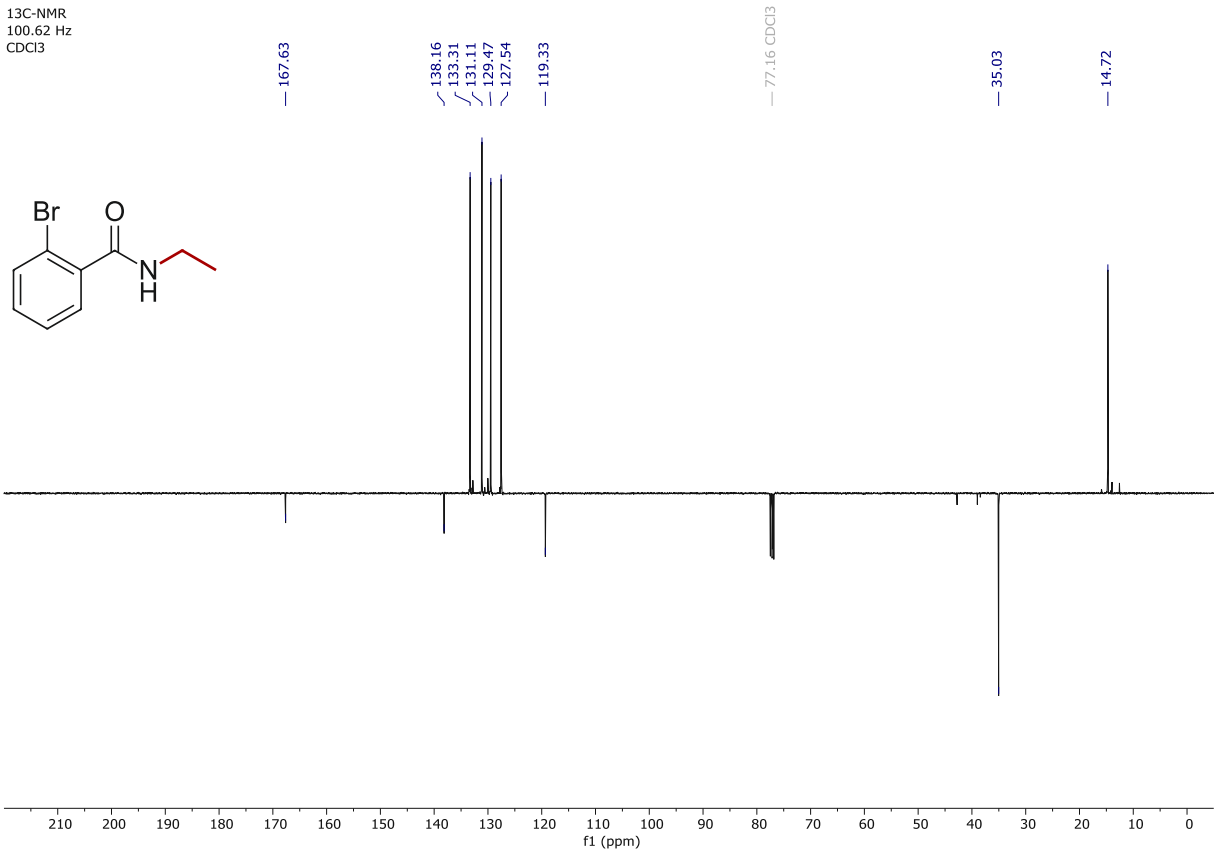
3-Bromo-*N*-ethylbenzamide (4d)



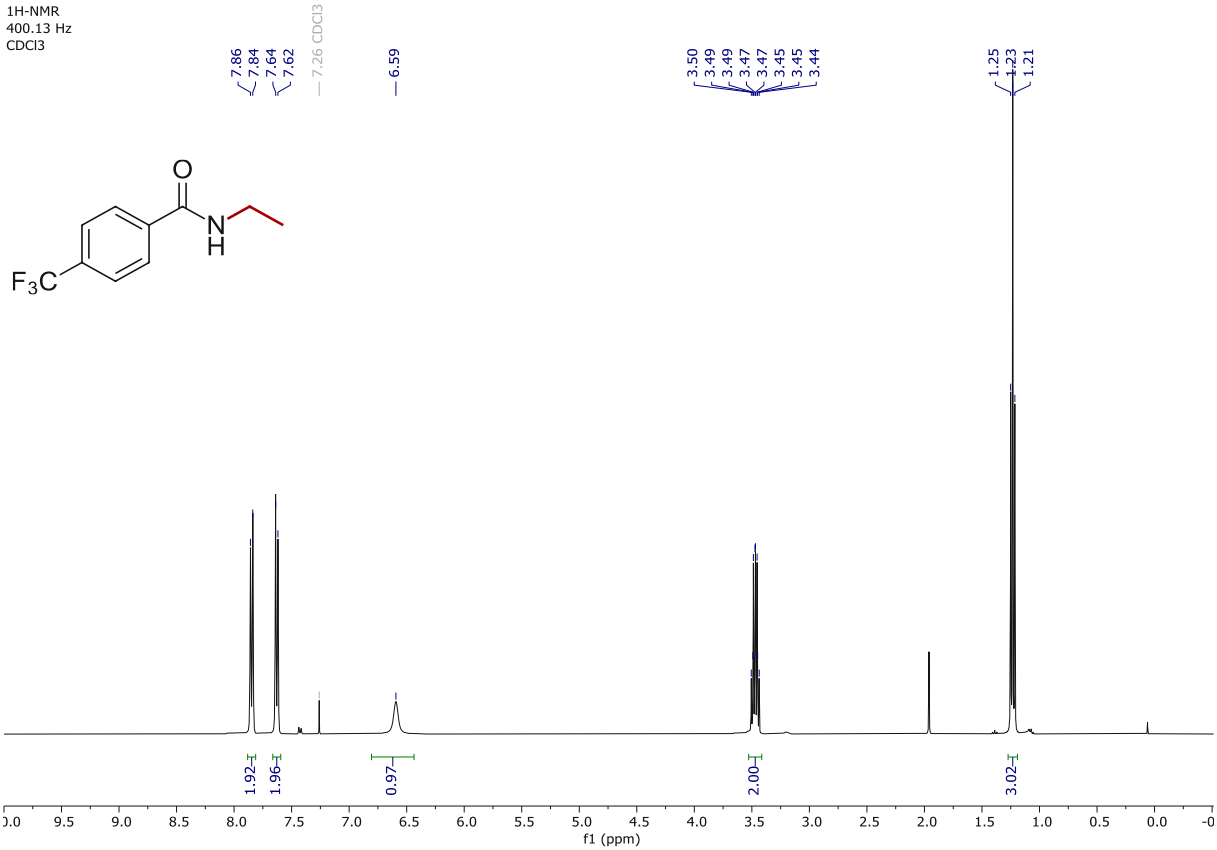


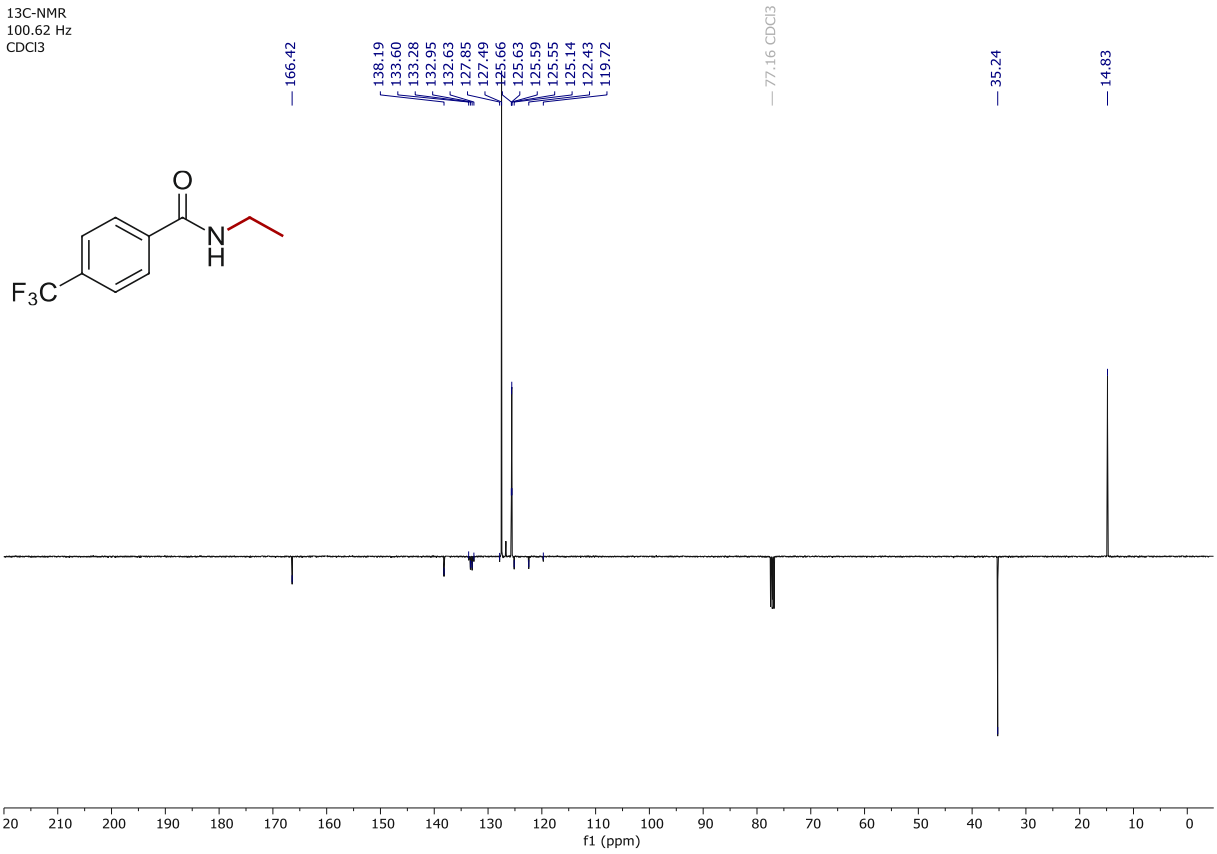
2-Bromo-*N*-ethylbenzamide (4e)





N-Ethyl-4-(trifluoromethyl) benzamide (4f)





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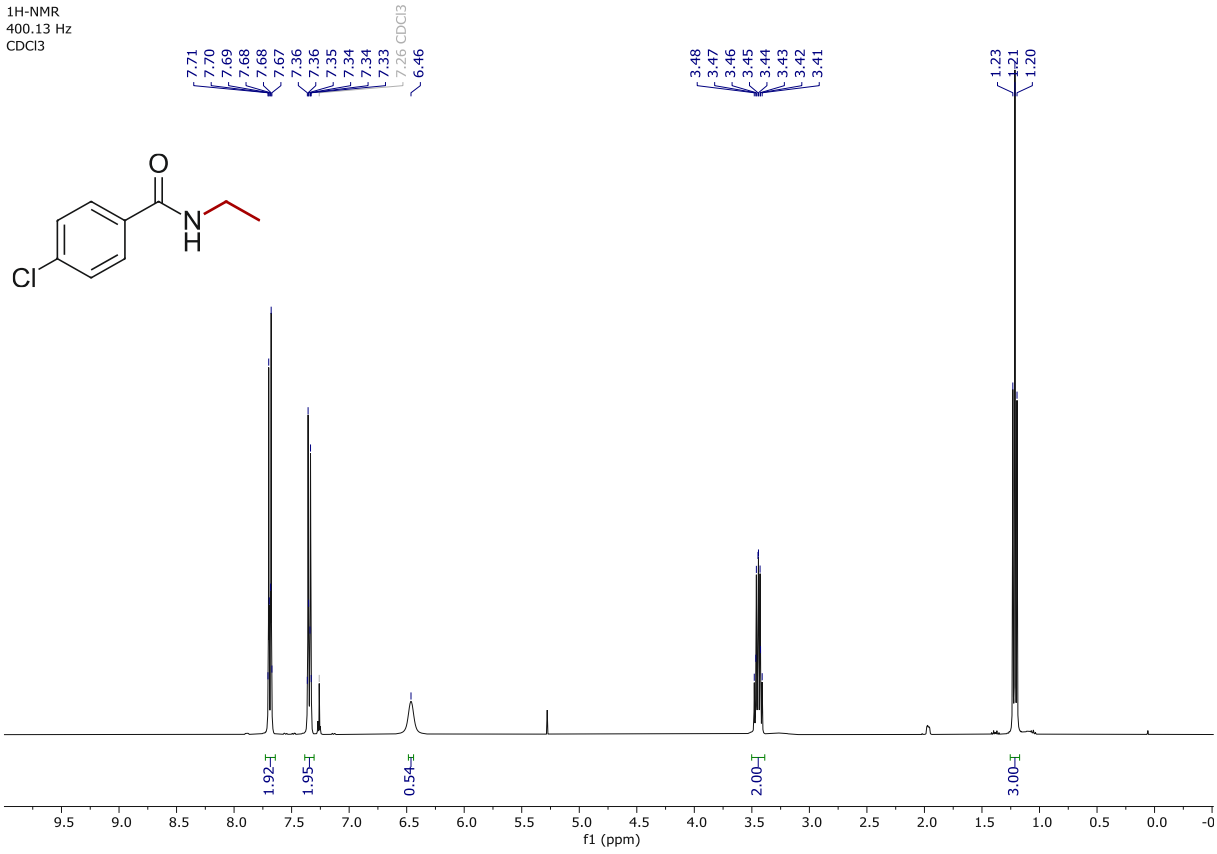

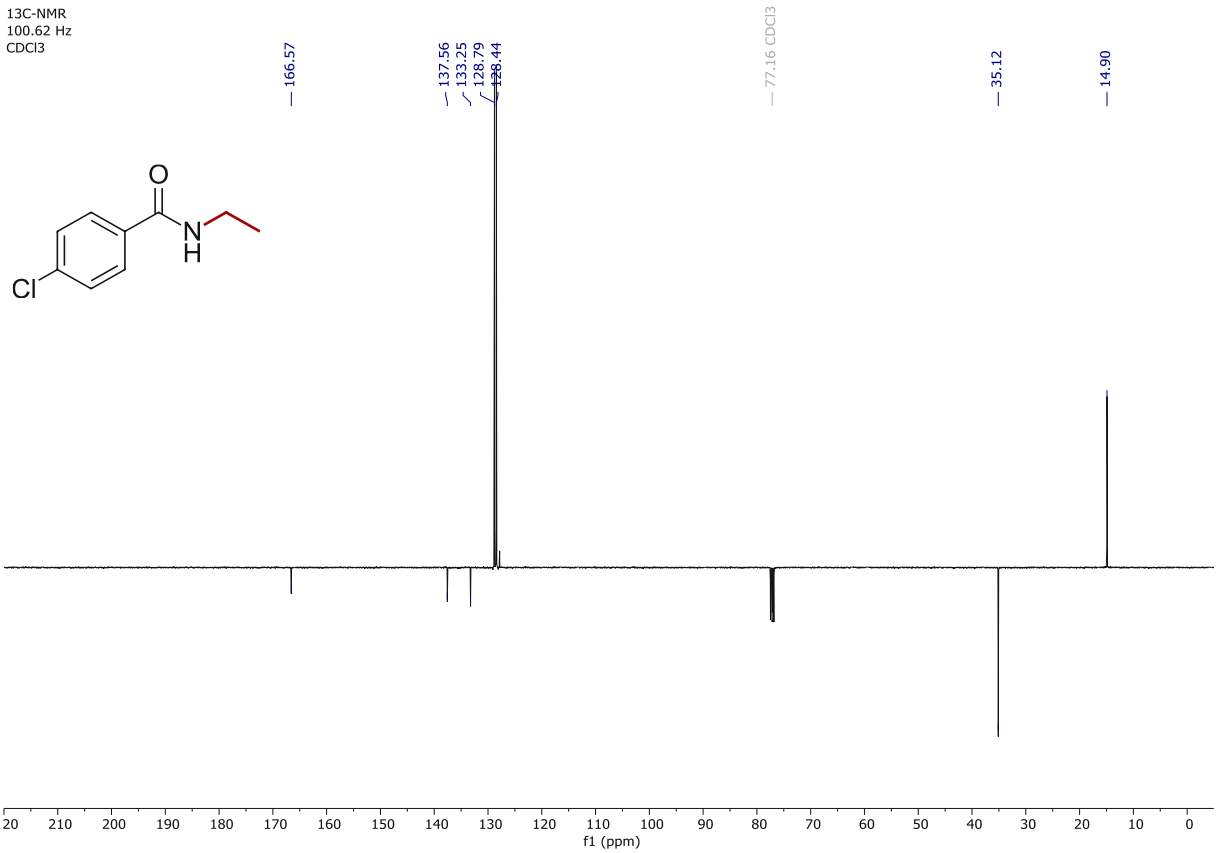

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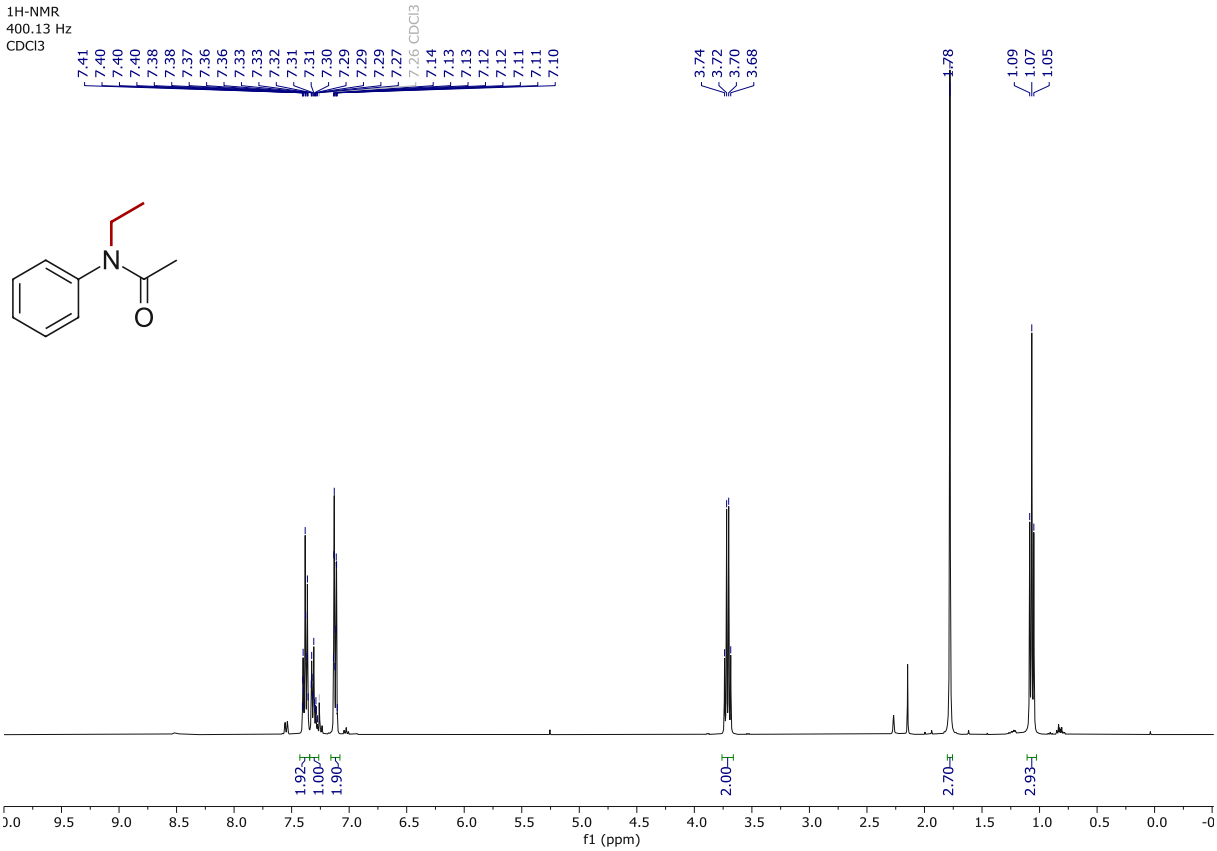
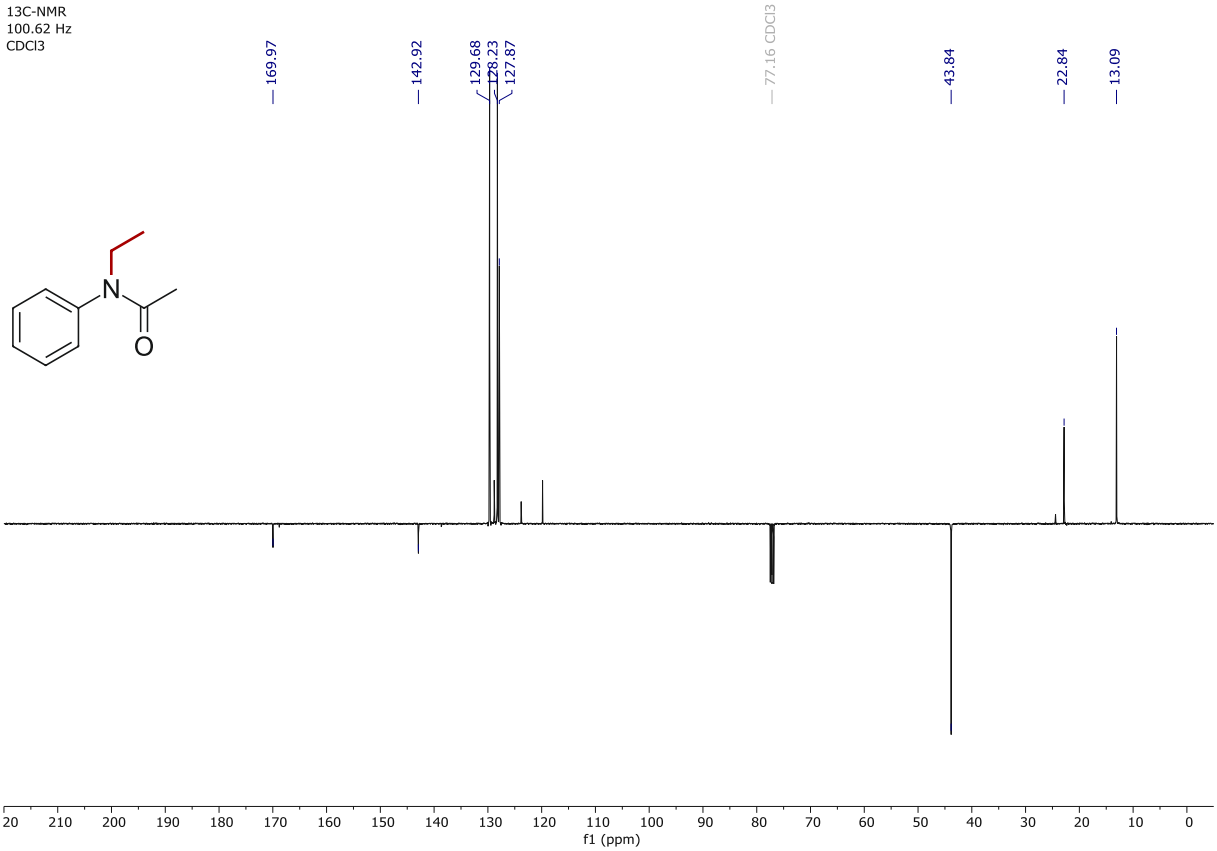
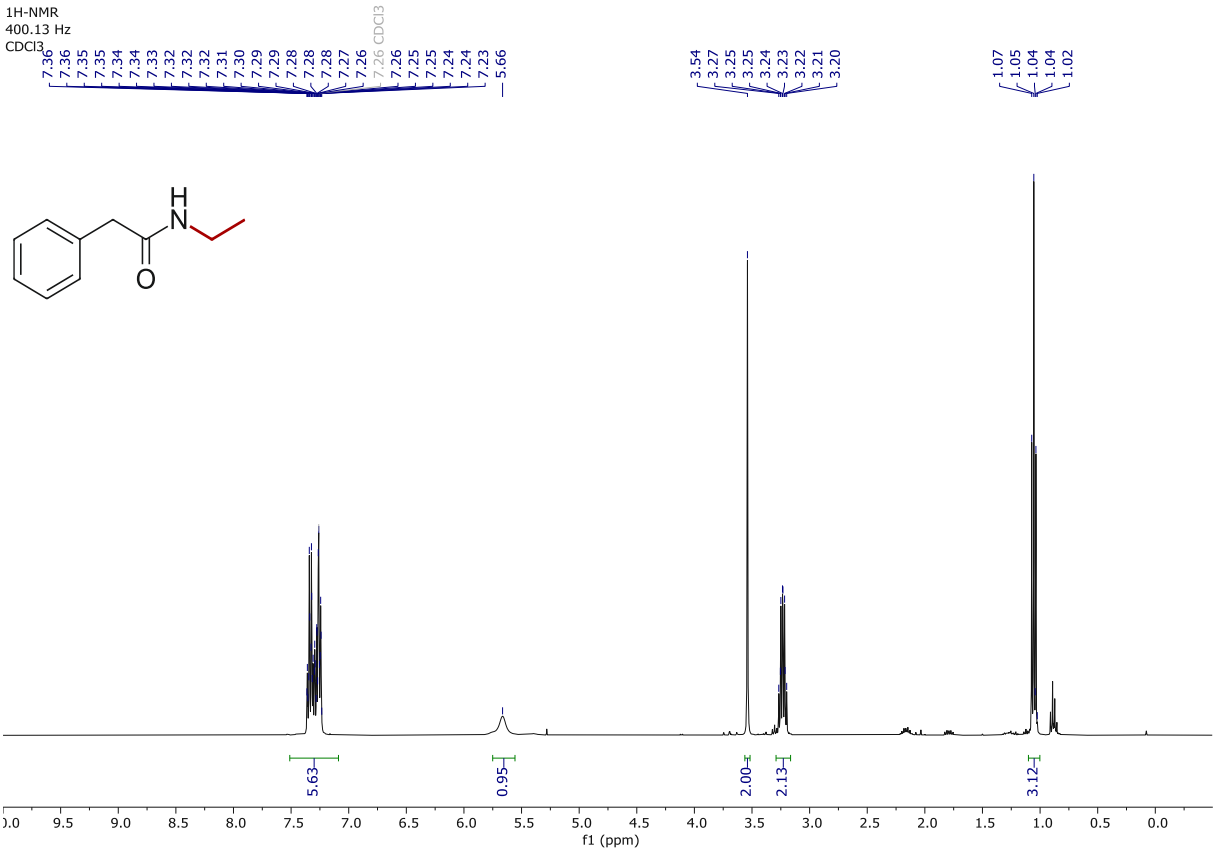
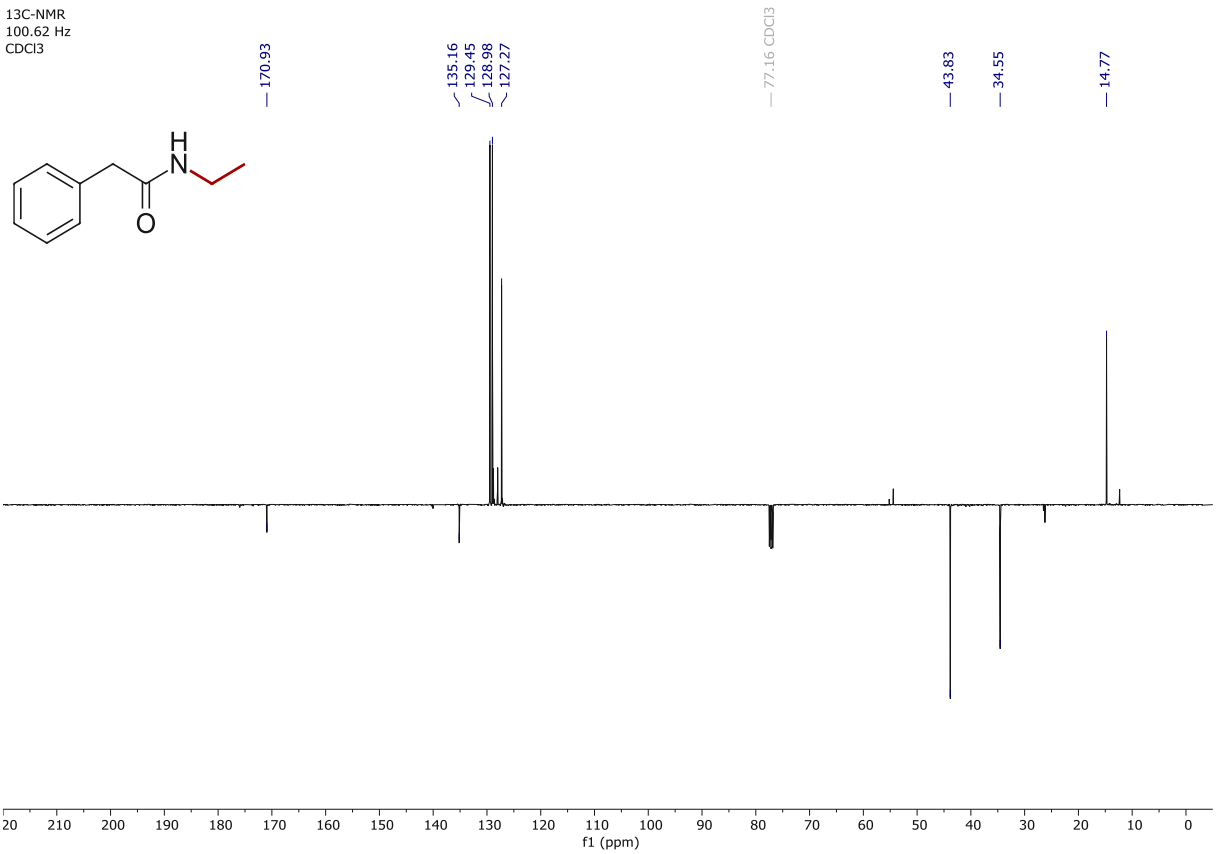




N-Ethylphenylacetamide (4i)





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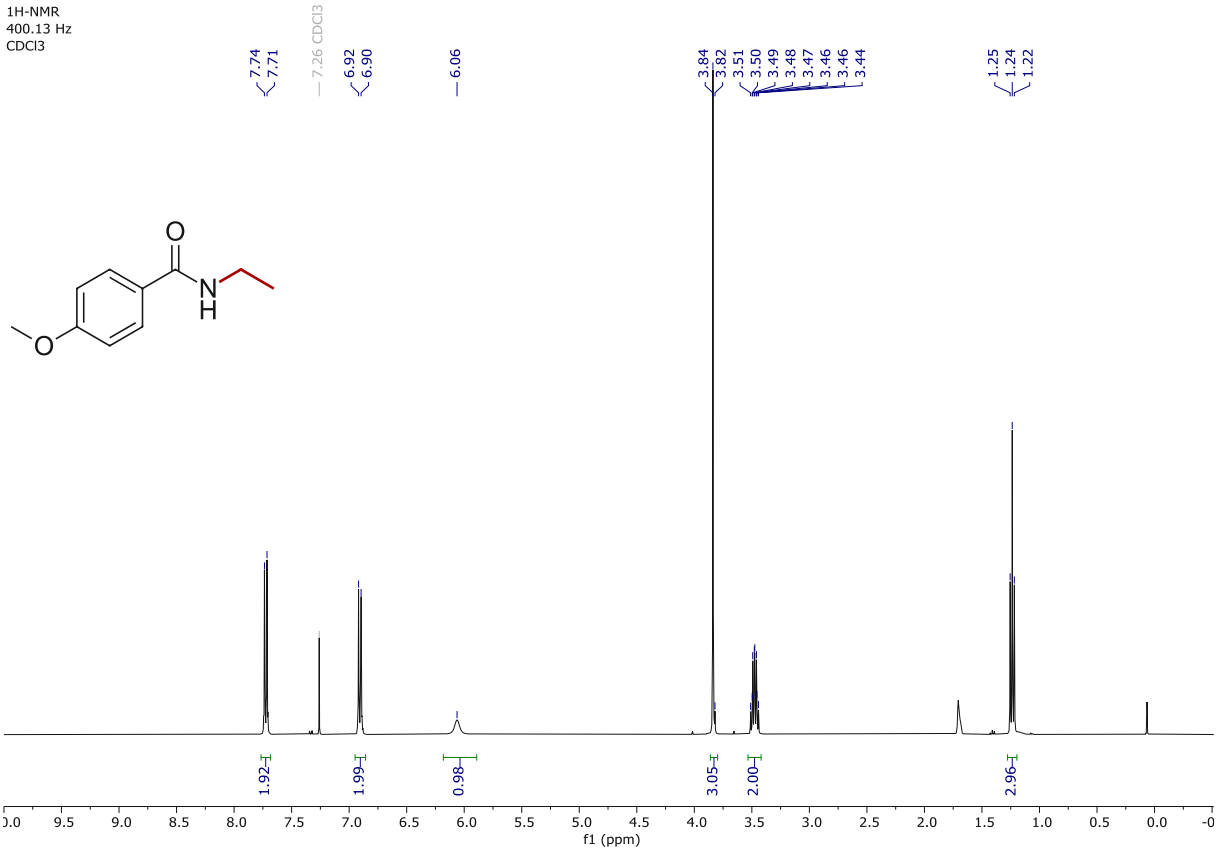

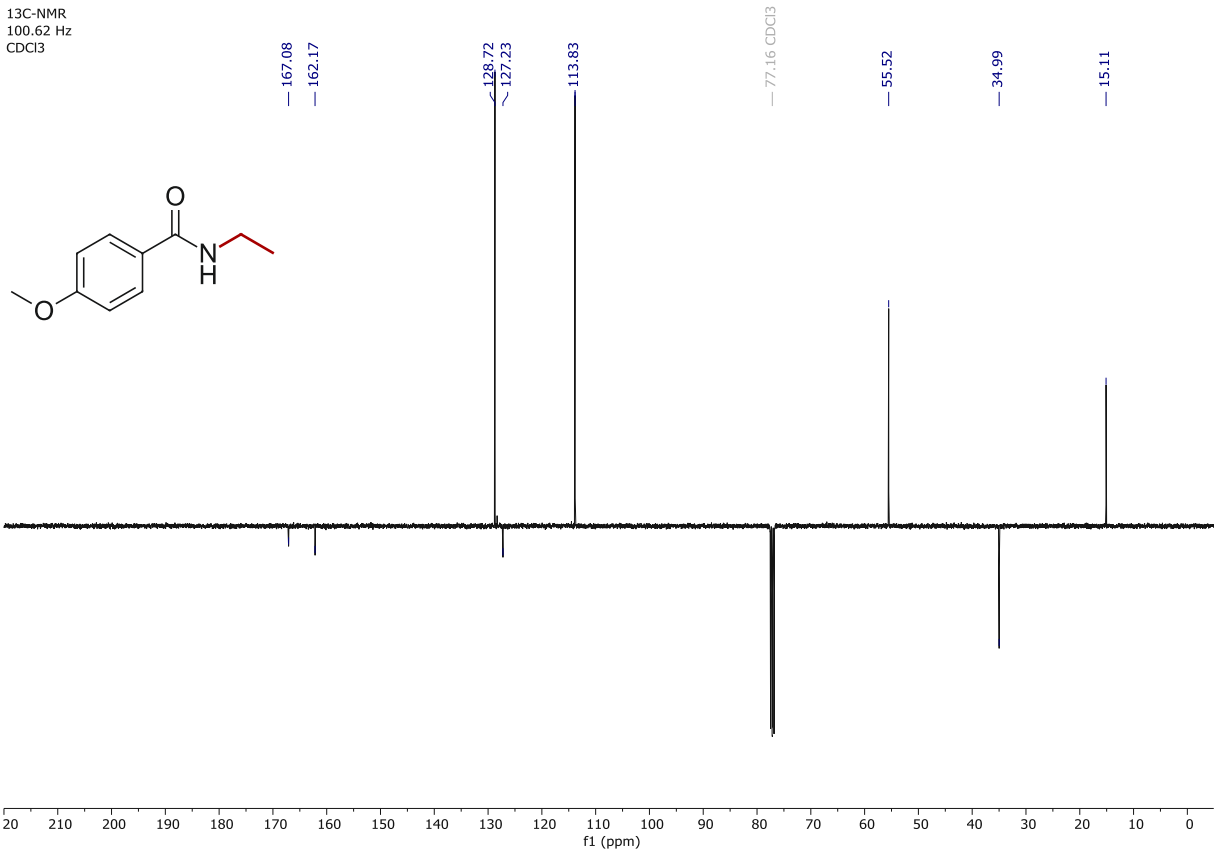

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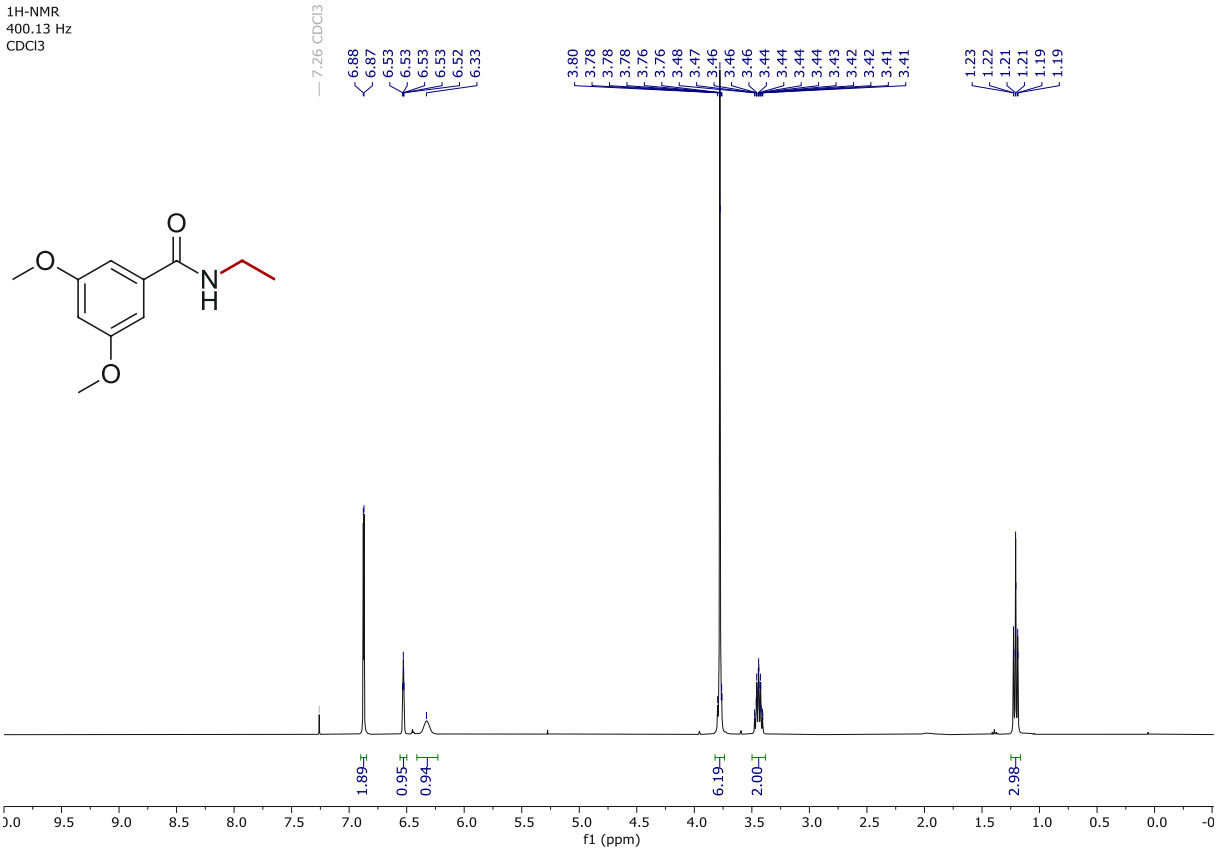
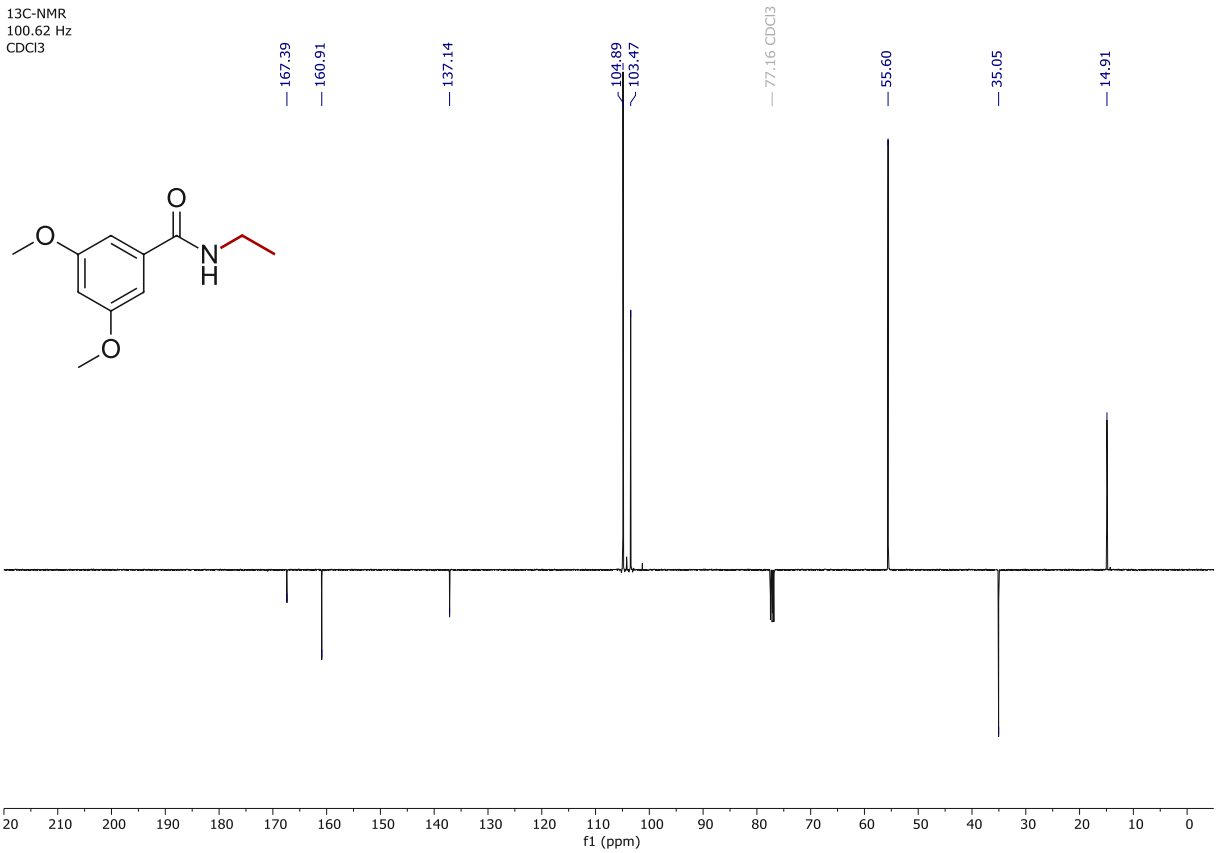
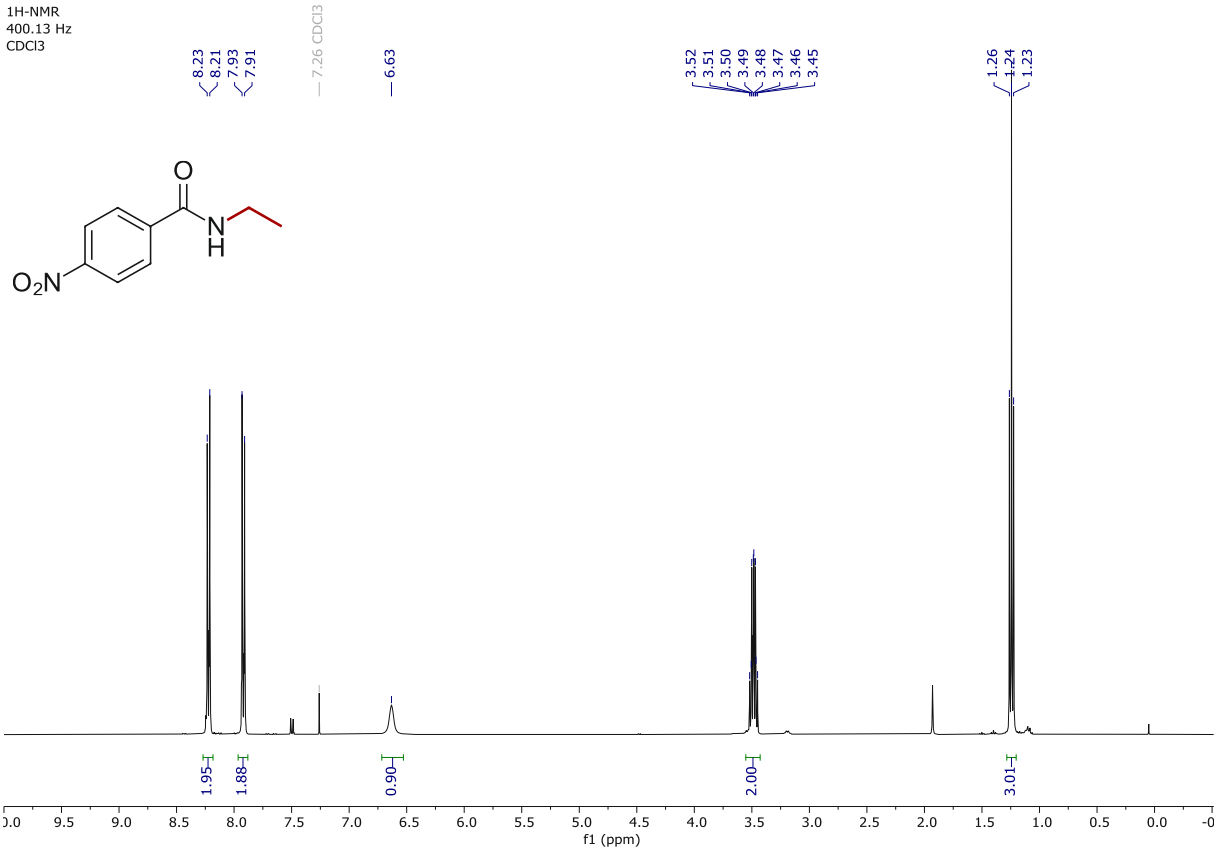
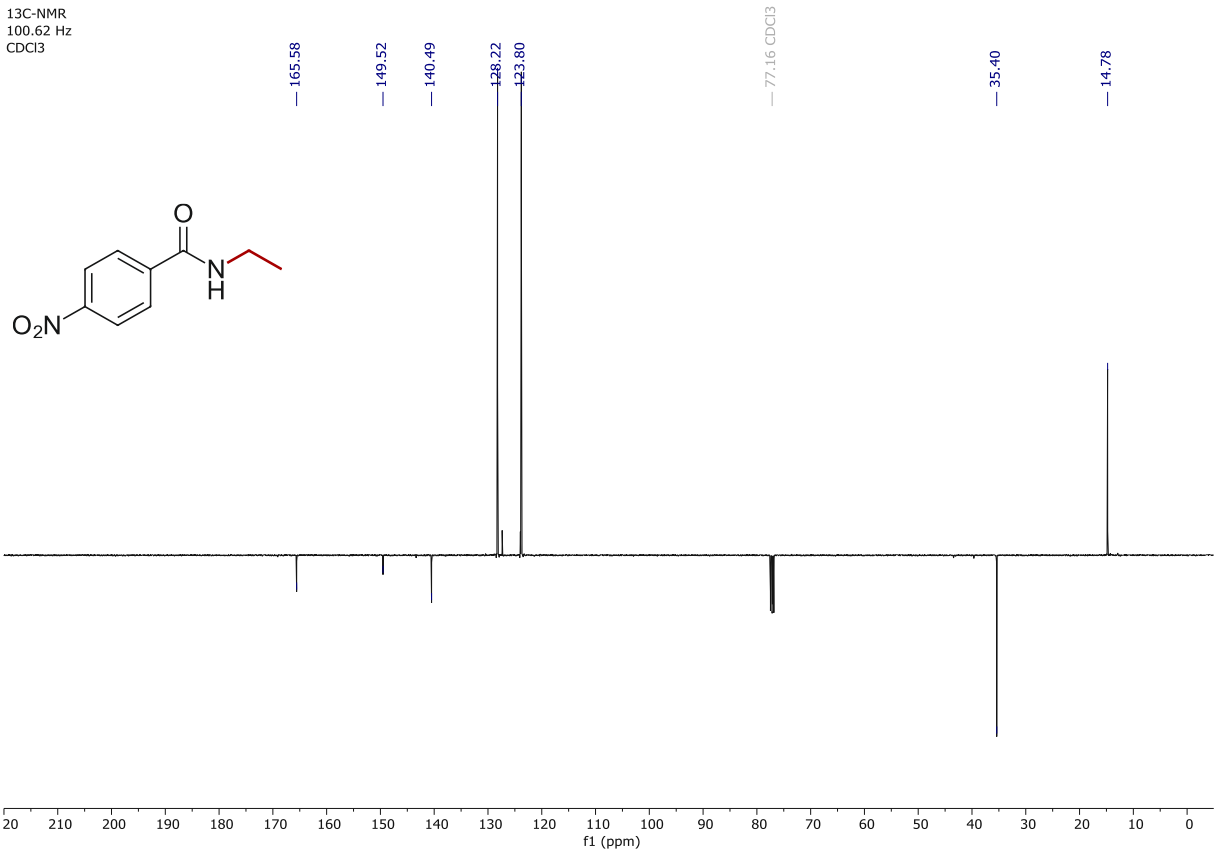


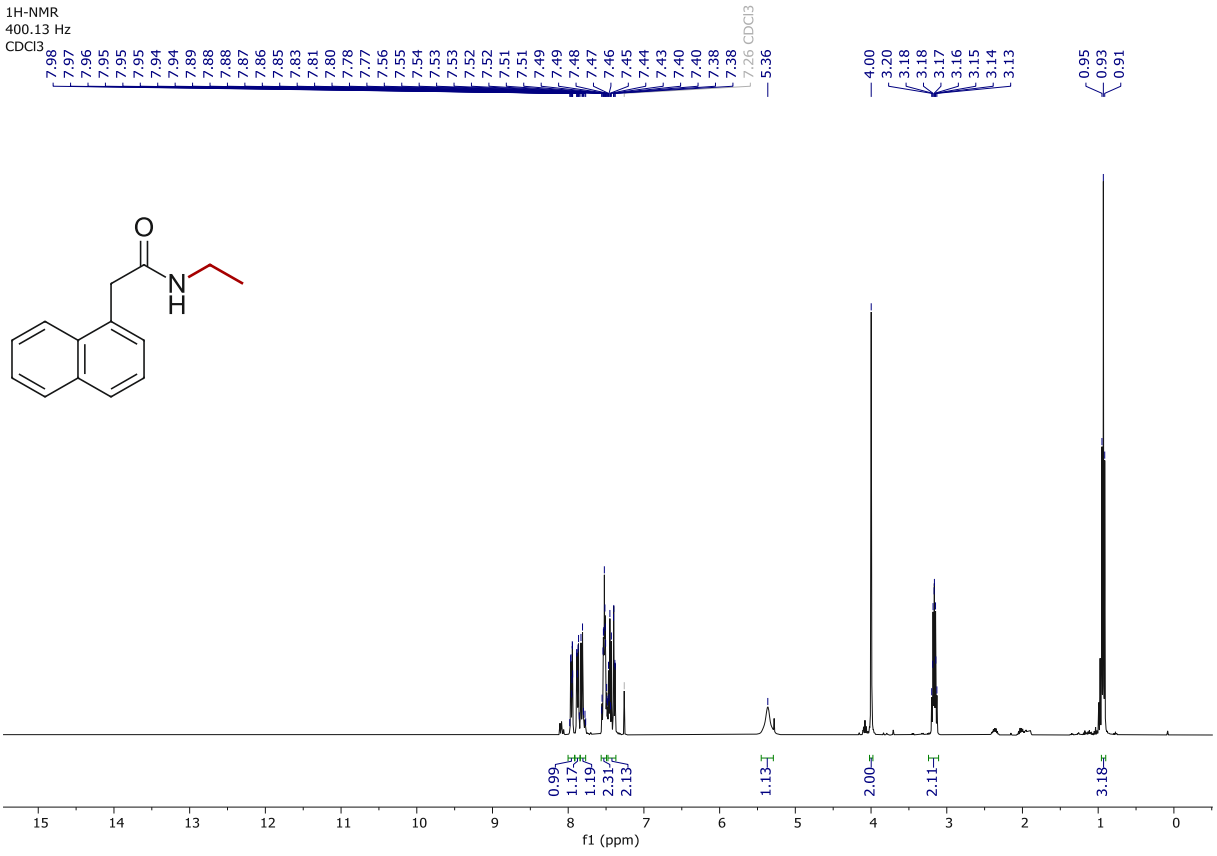


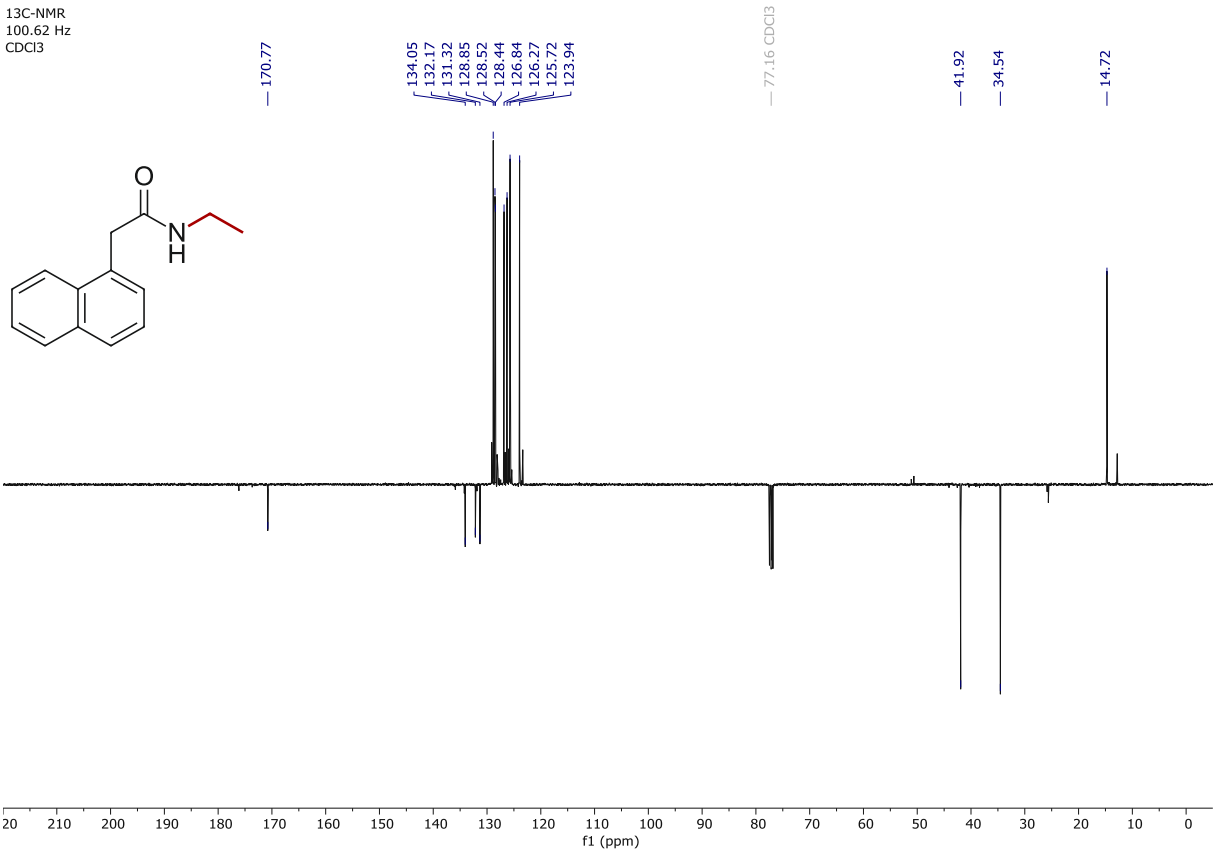
_N_-Ethyl-4-nitrobenzamide (4l)



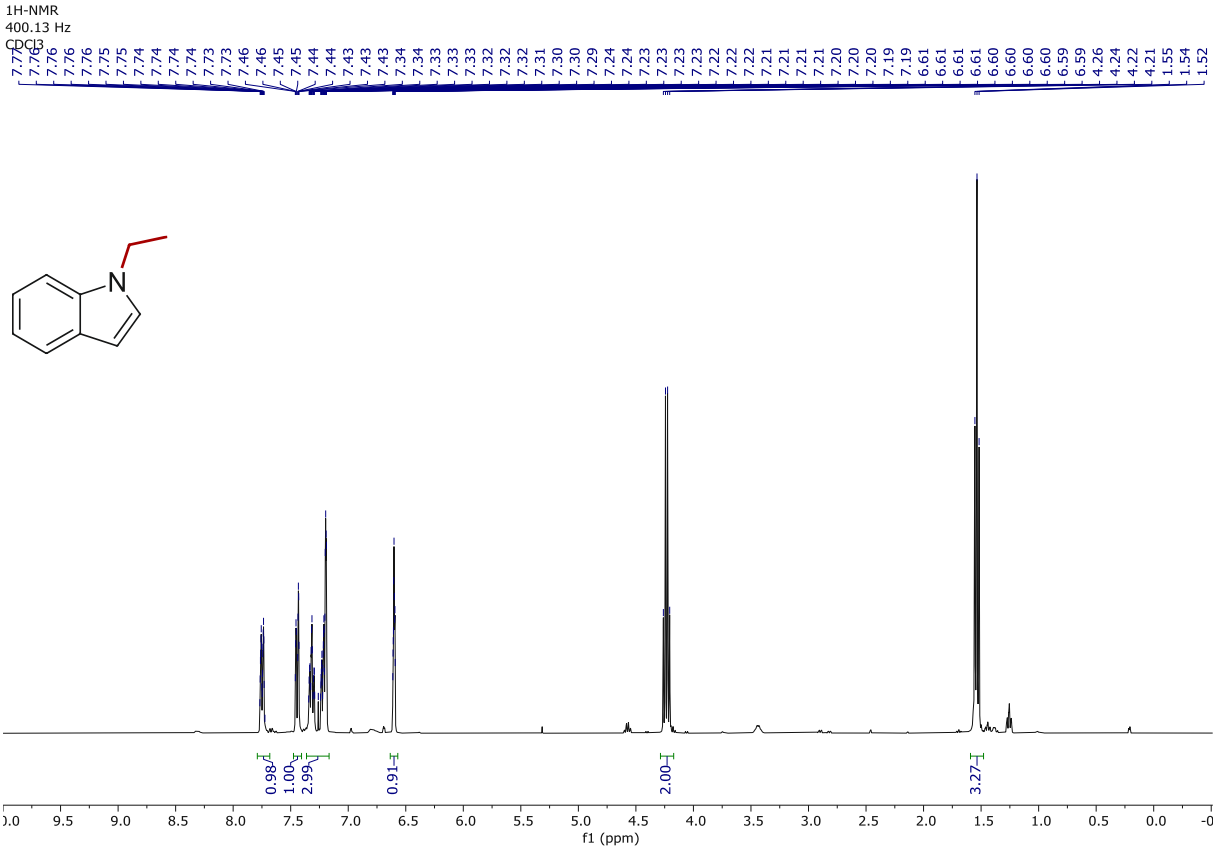


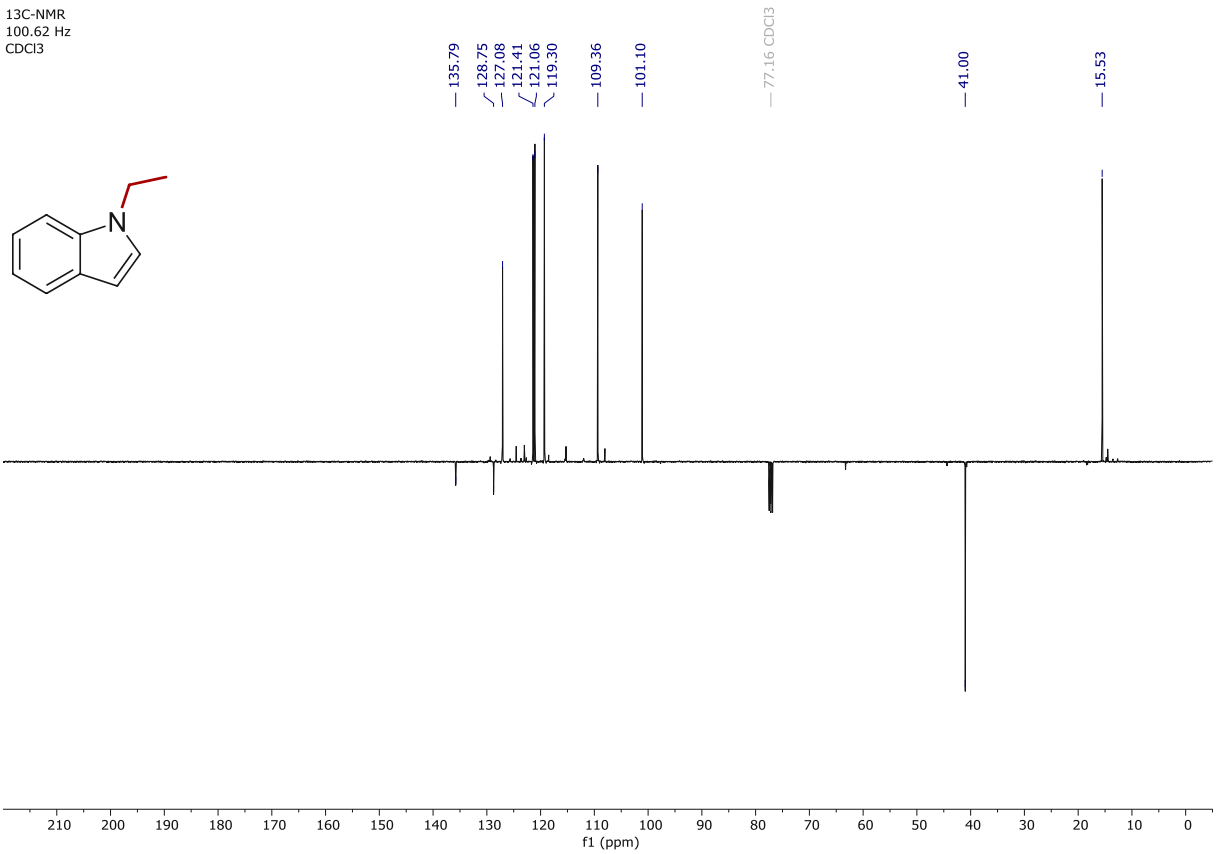
N-Ethyl-α-naphthylacetamide (4m)



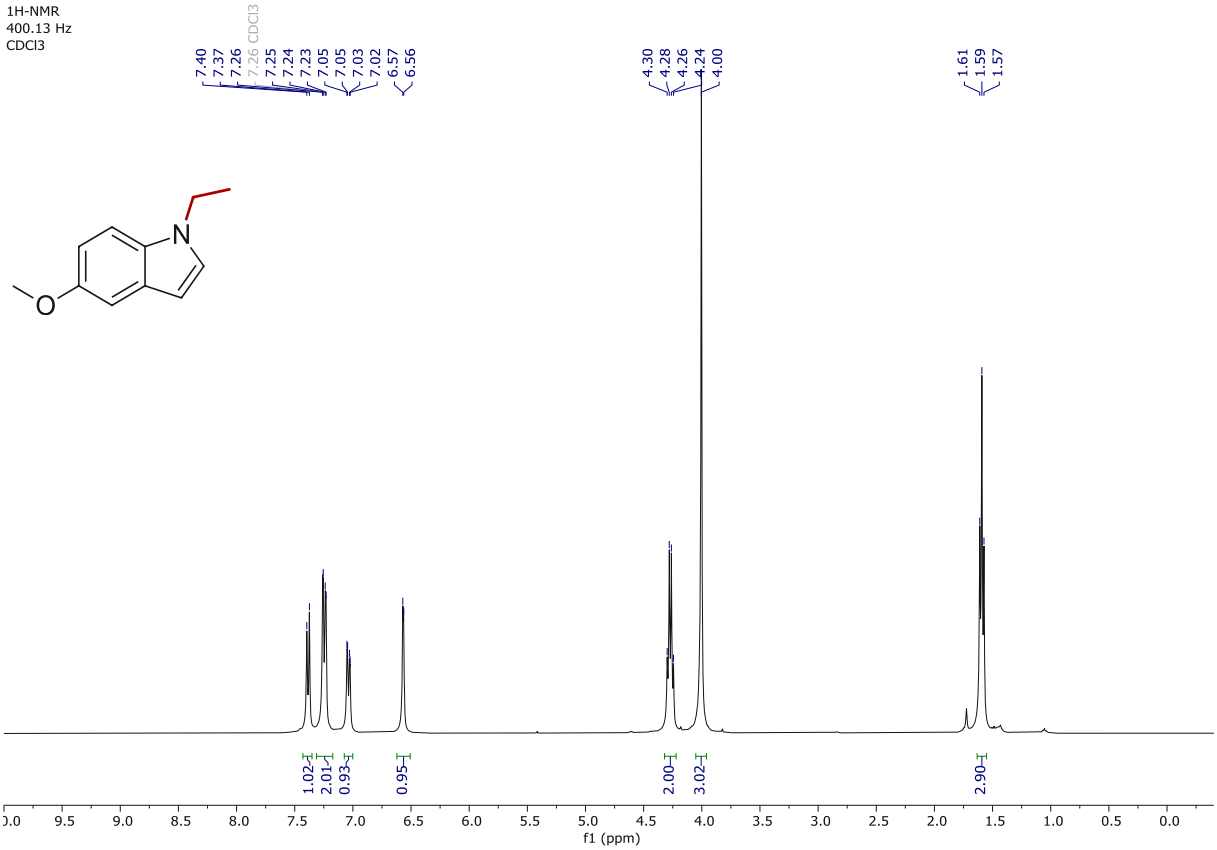


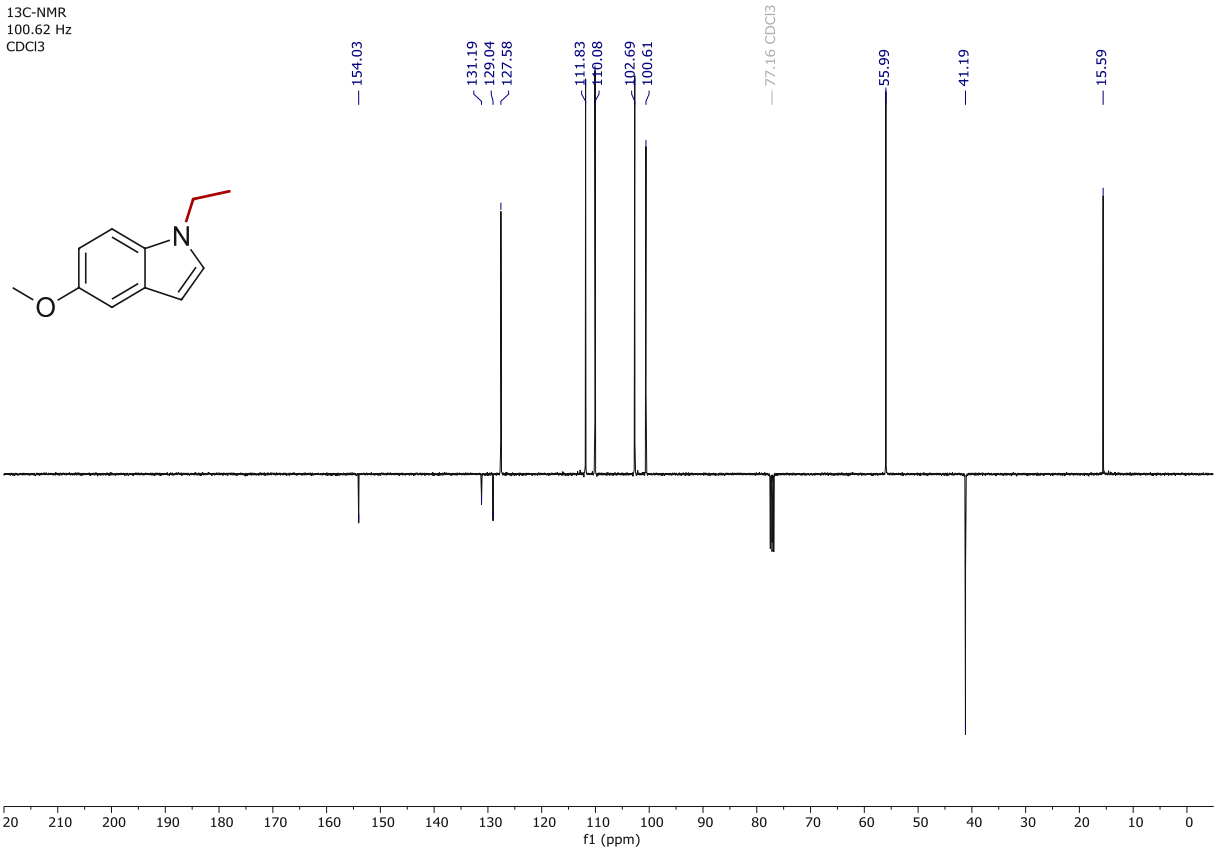
1-Ethylindole (6a)



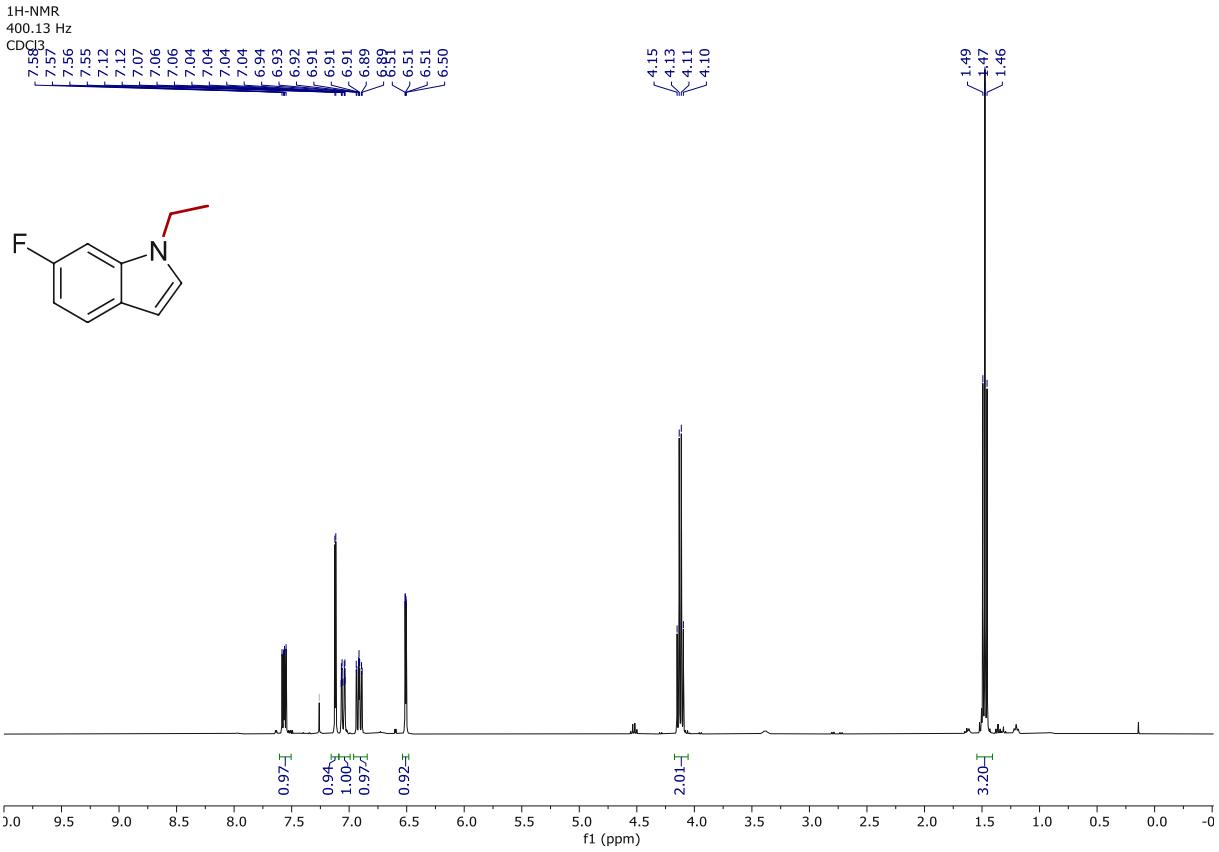


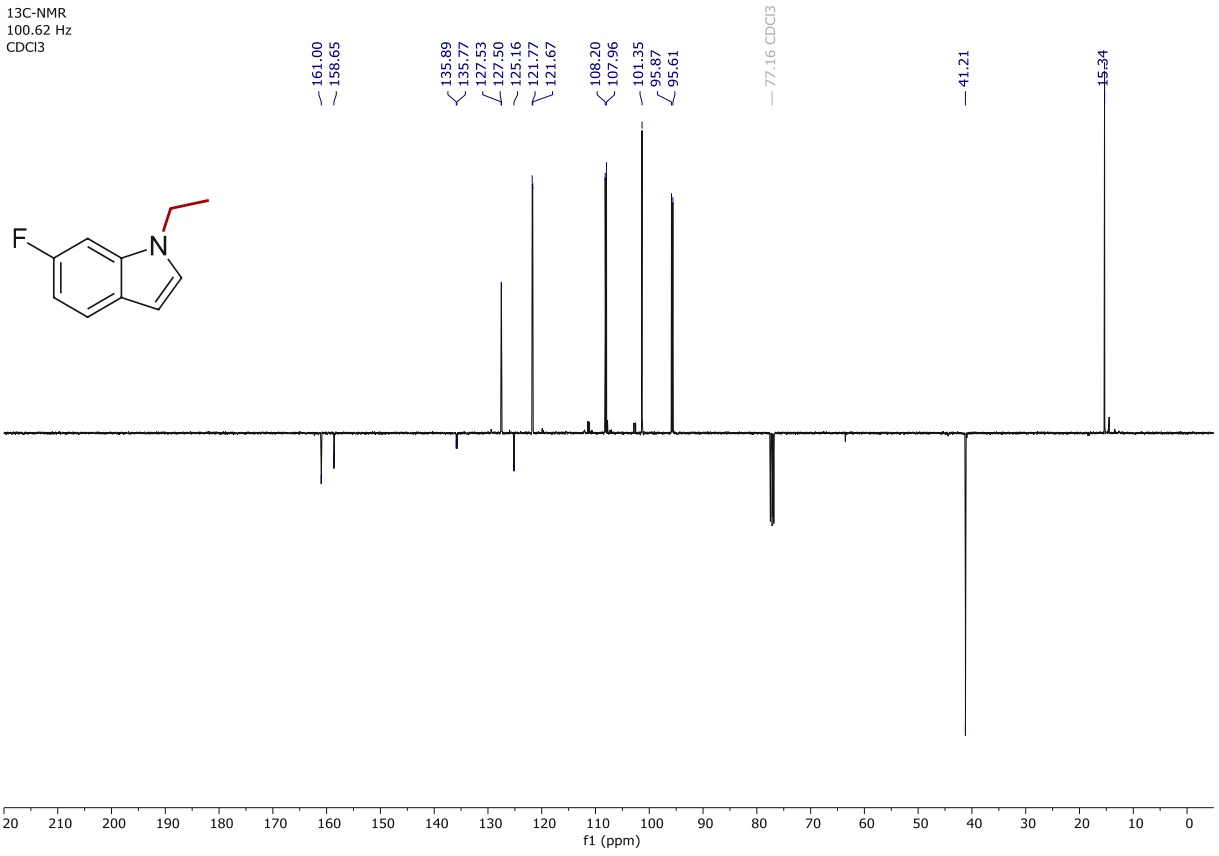
1-Ethyl-5-methoxyindole (6b)



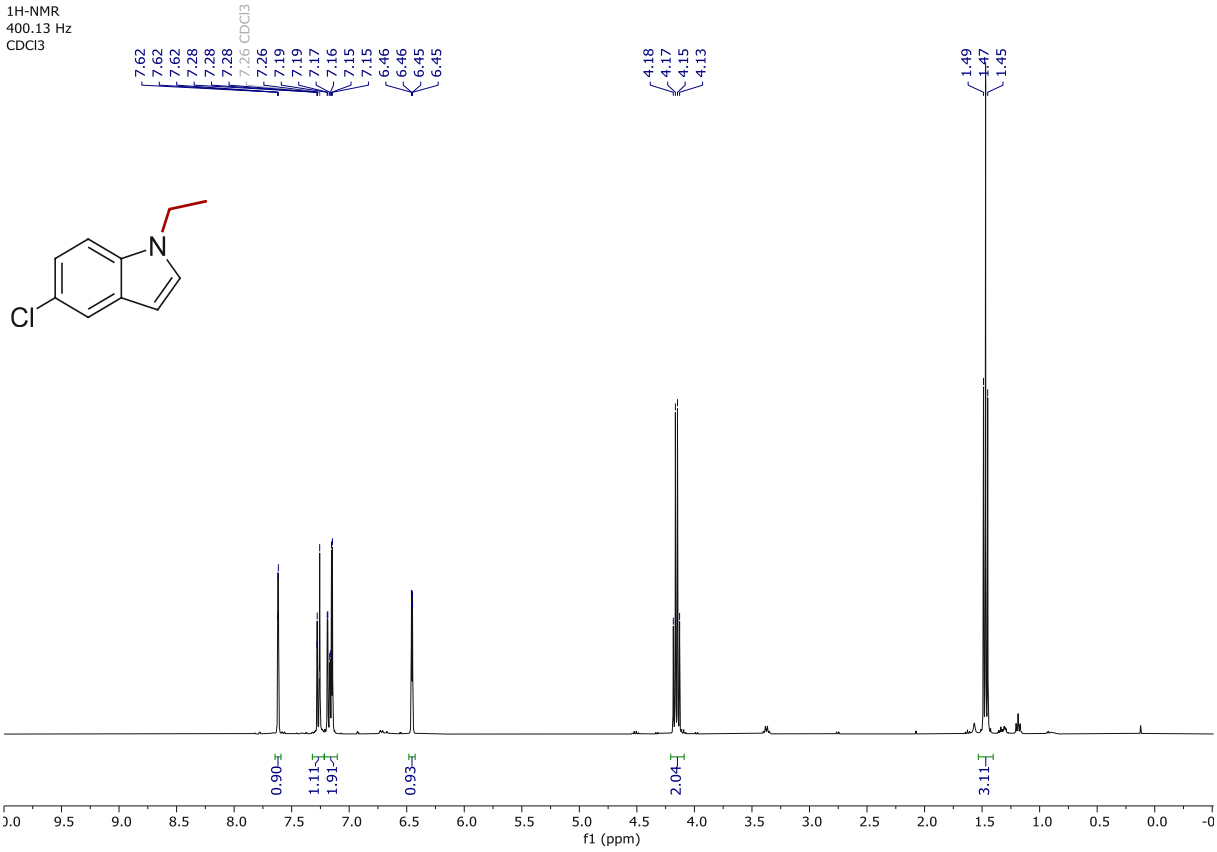


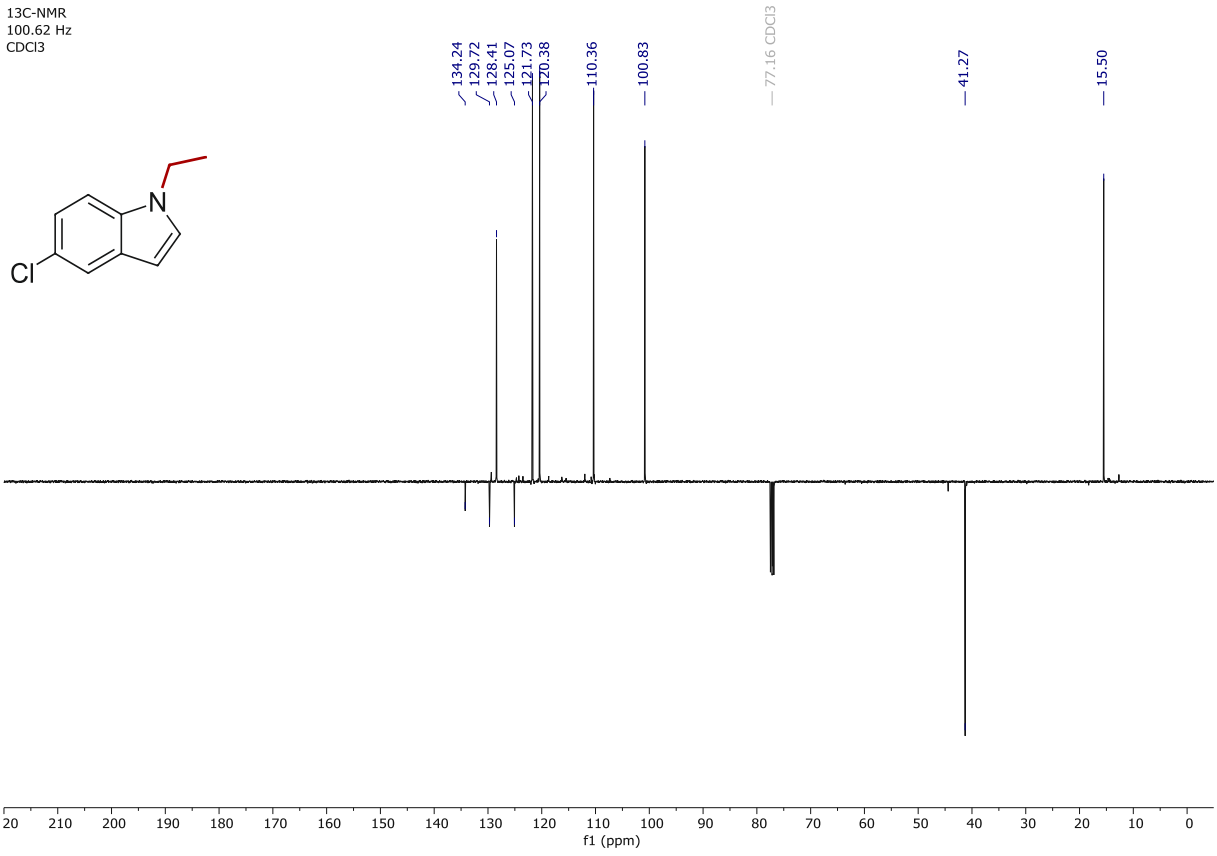
1-Ethyl-5-fluoroindole (6c)



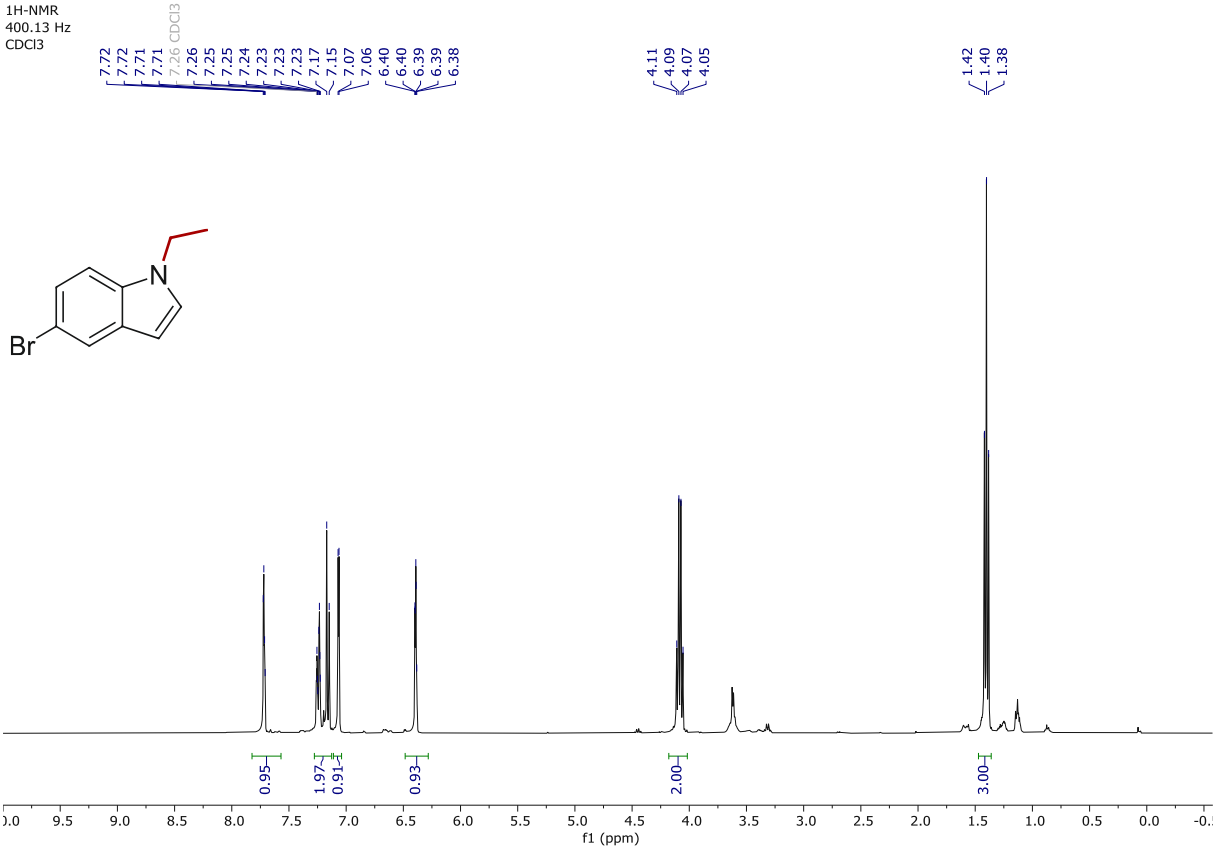


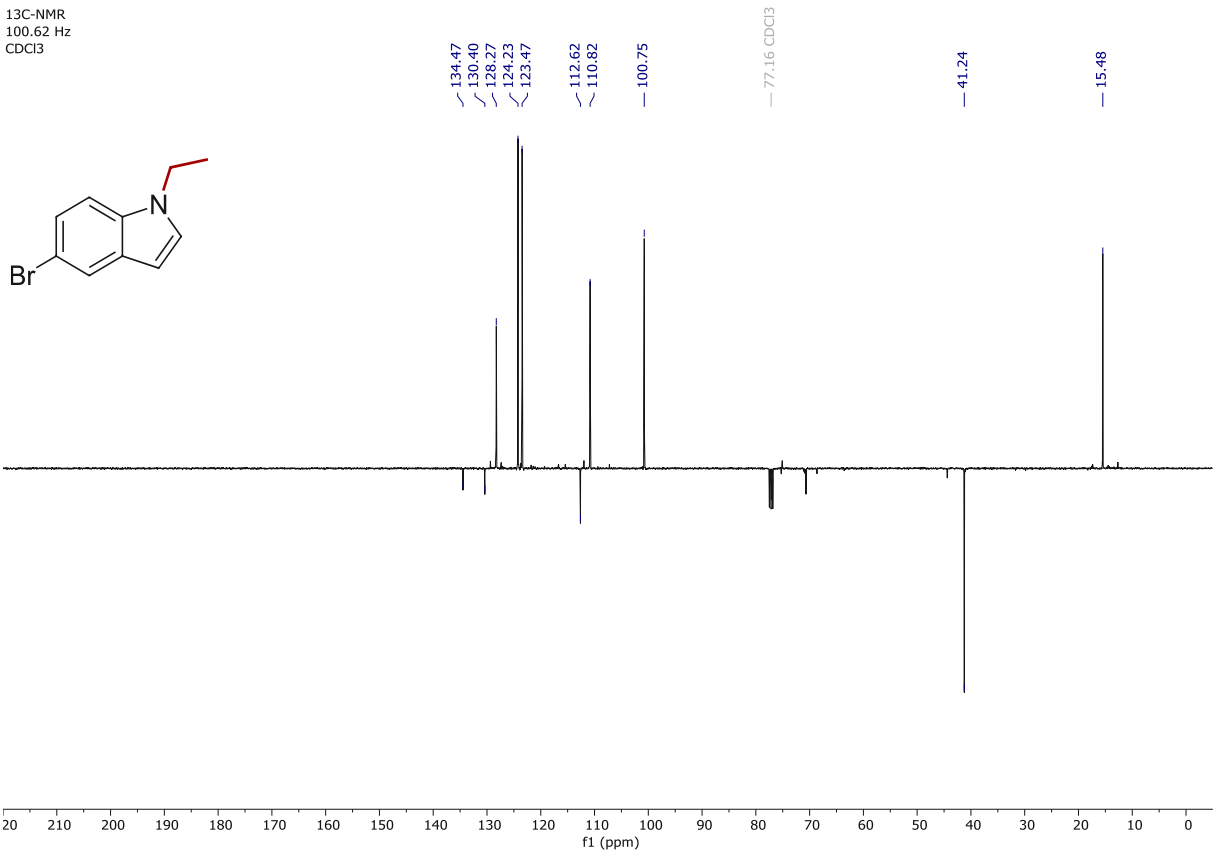
5-Chloro-1-ethylindole (6d)



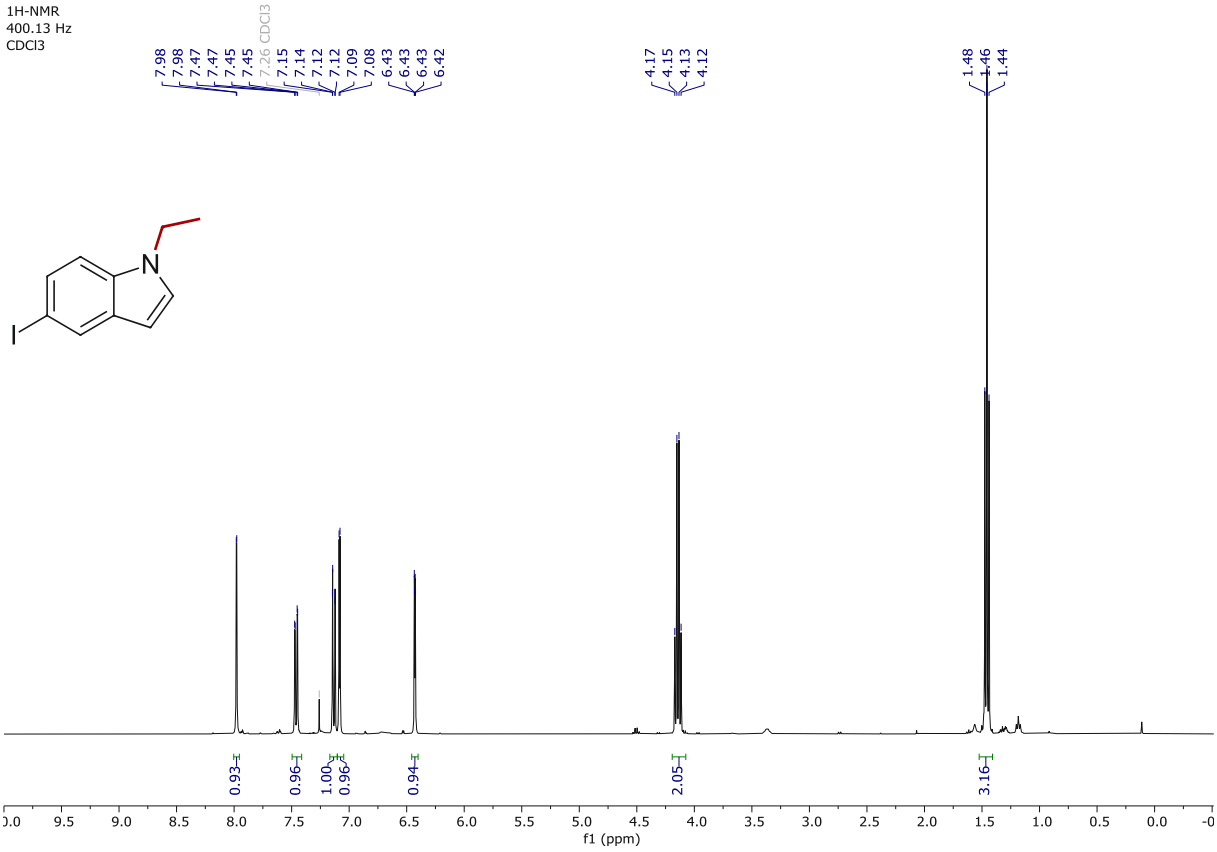


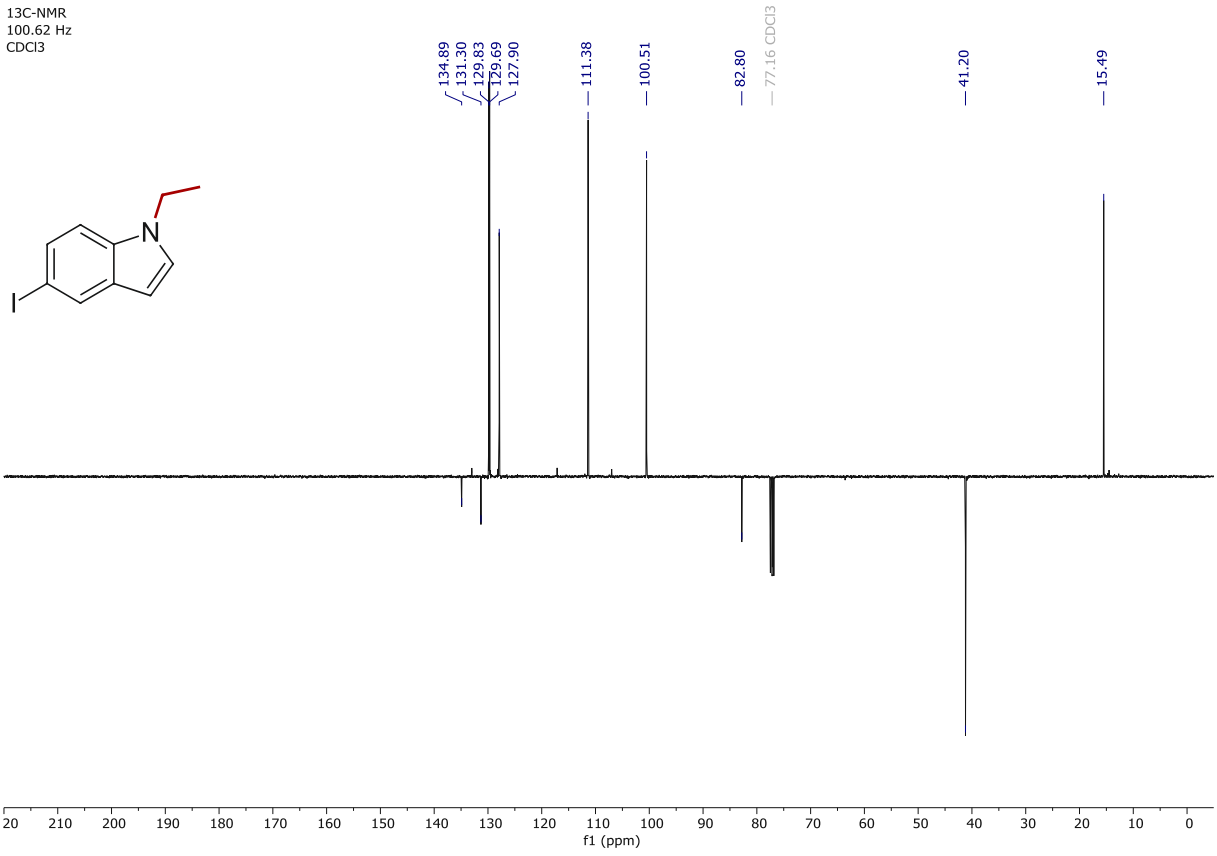
5-Bromo-1-ethylindole (6e)





1-Ethyl-5-iodoindole (6f)





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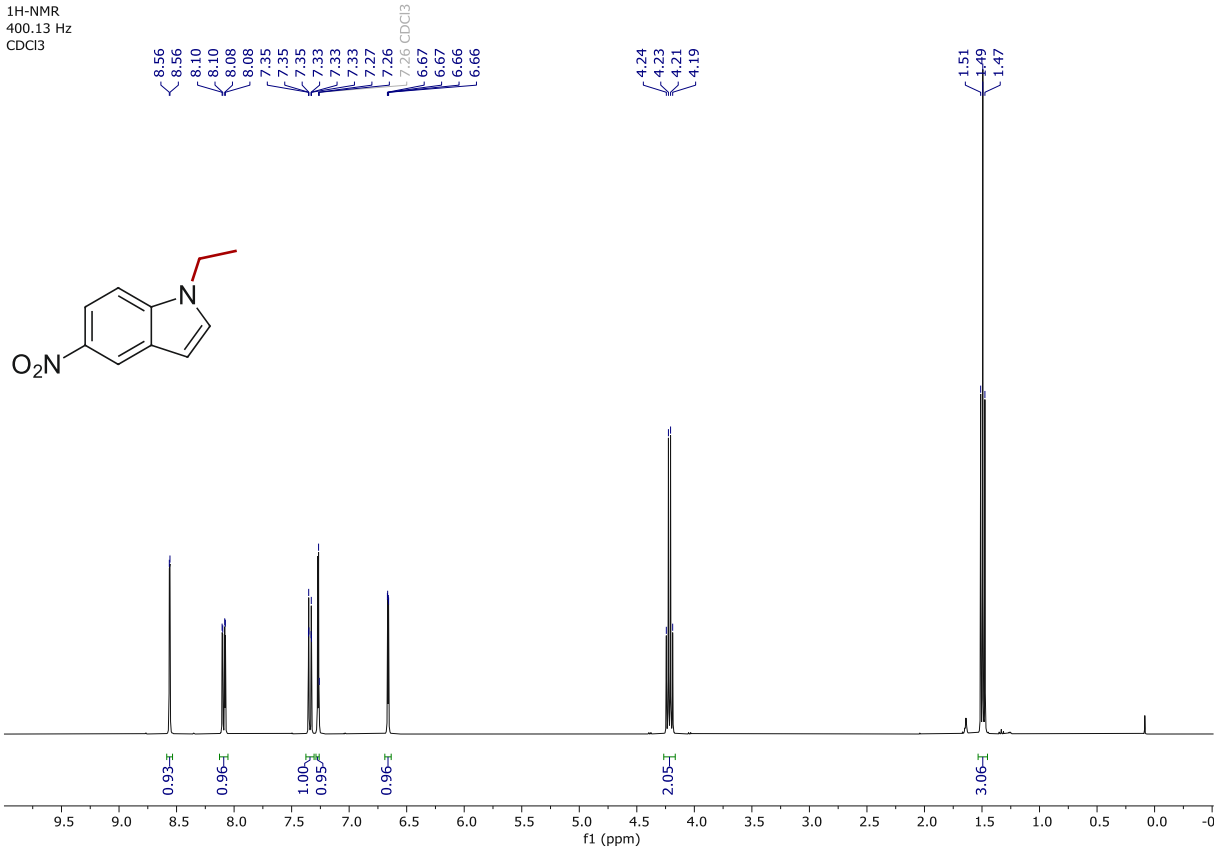
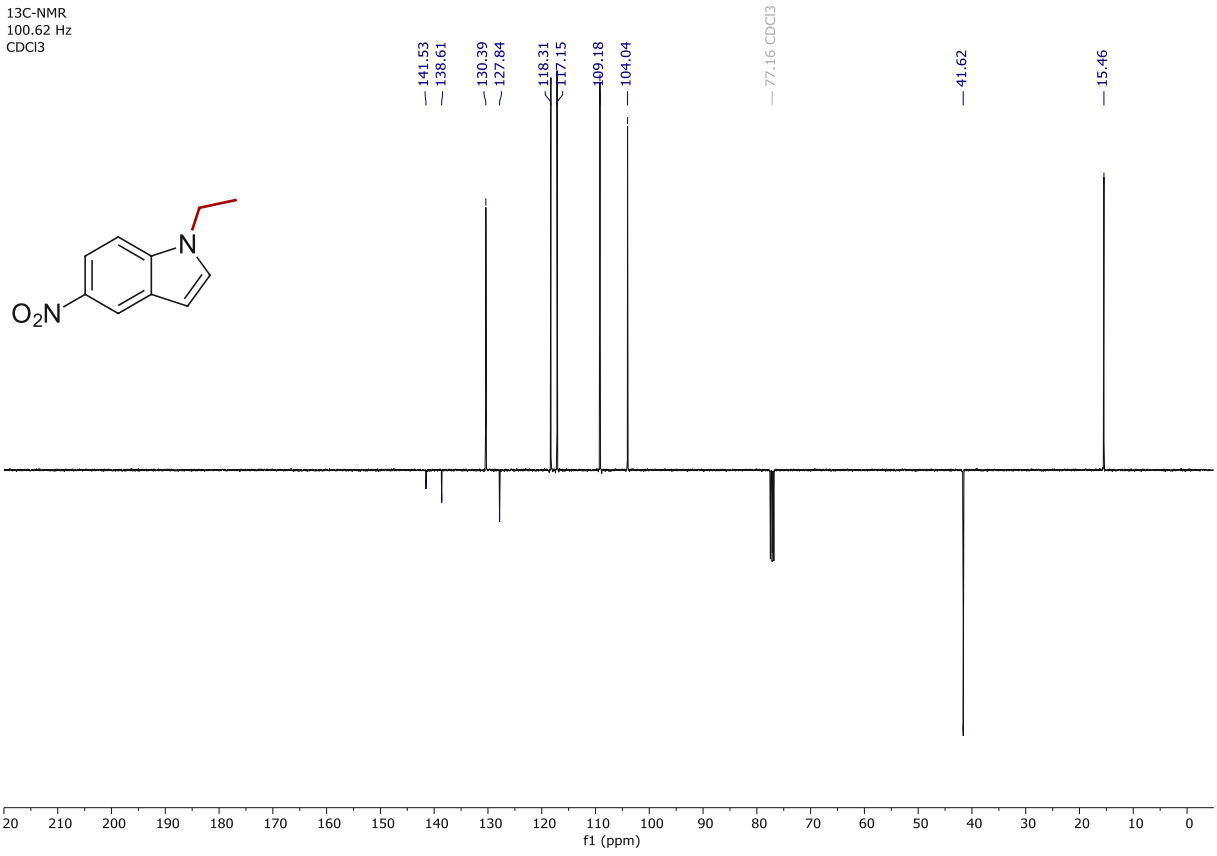
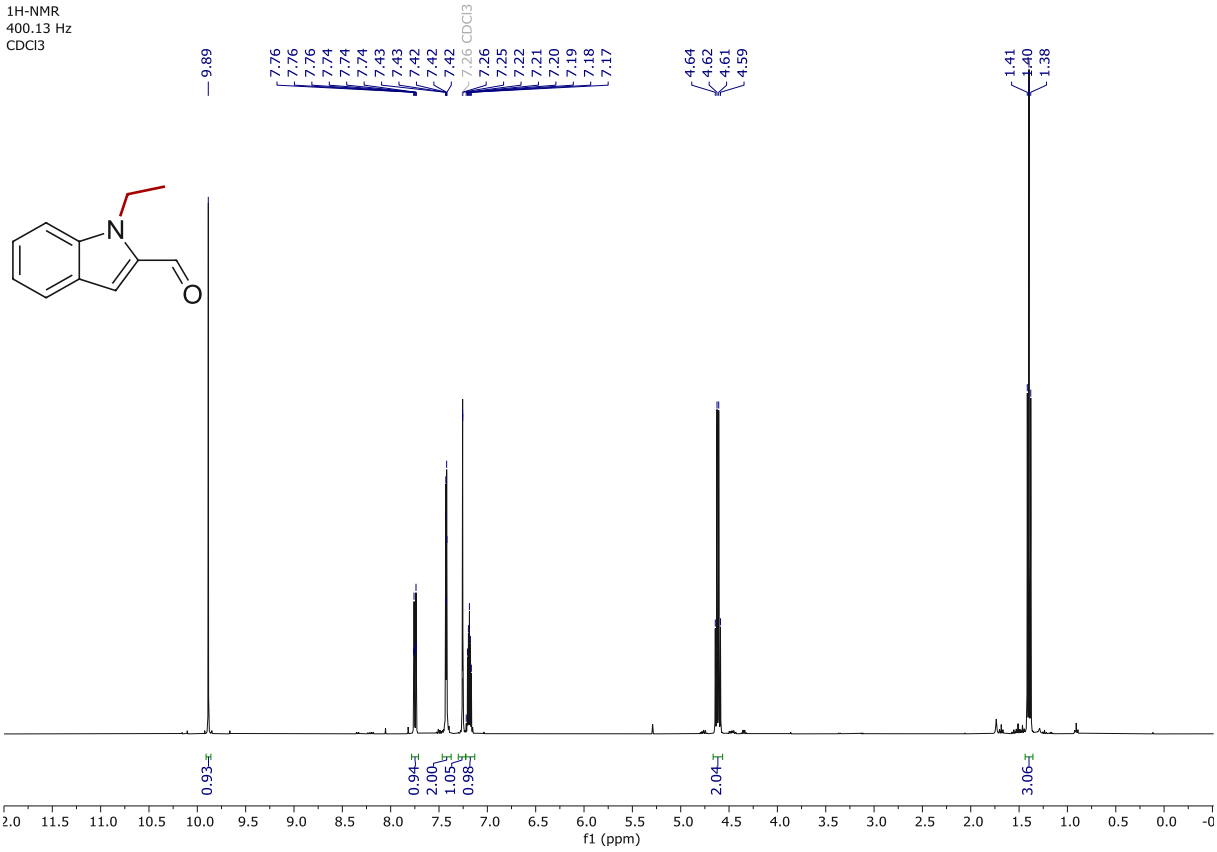
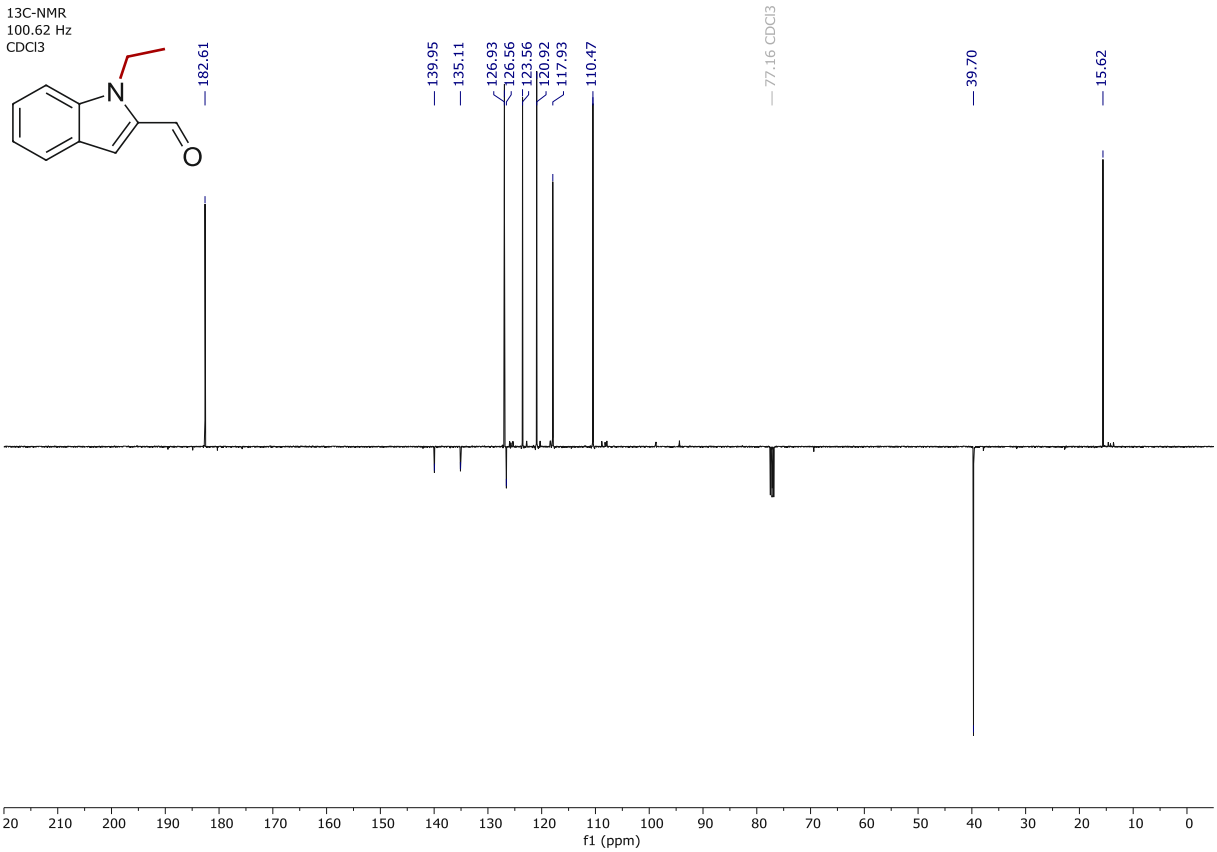


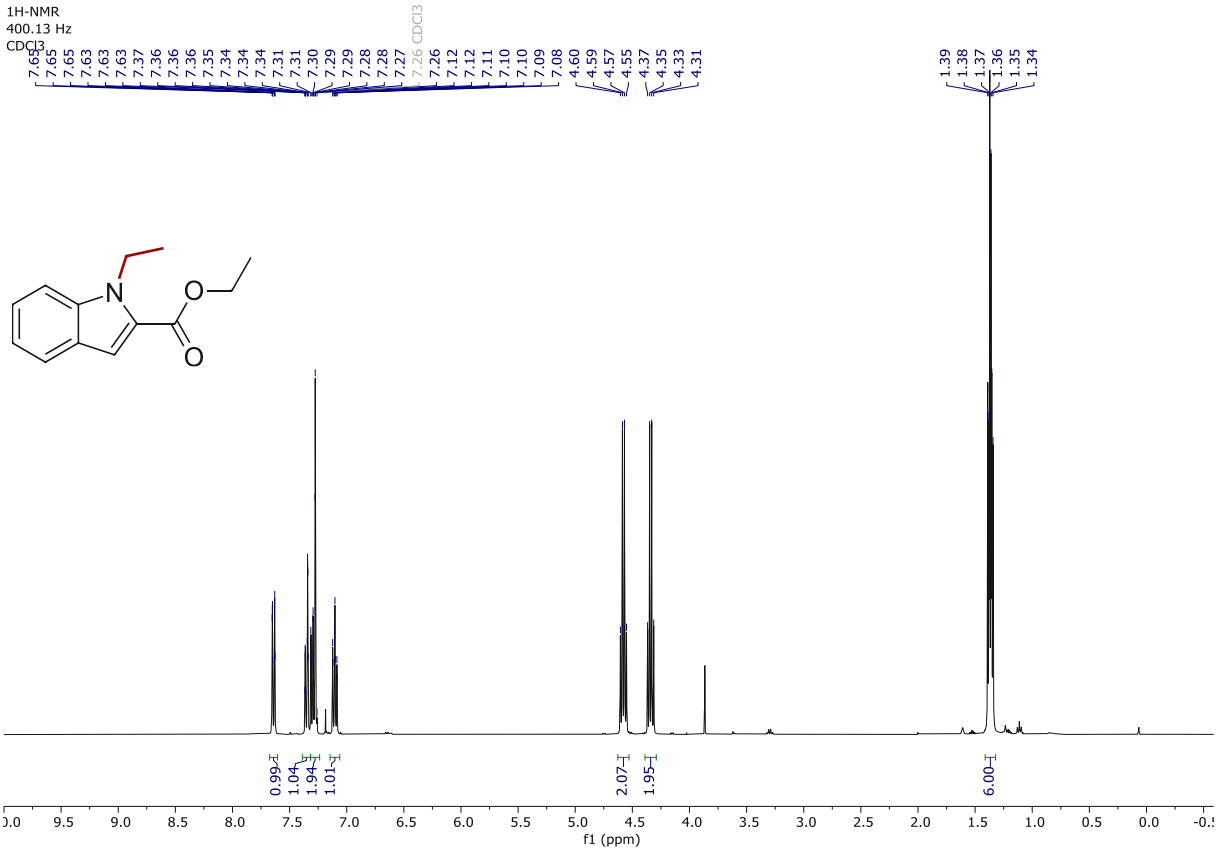


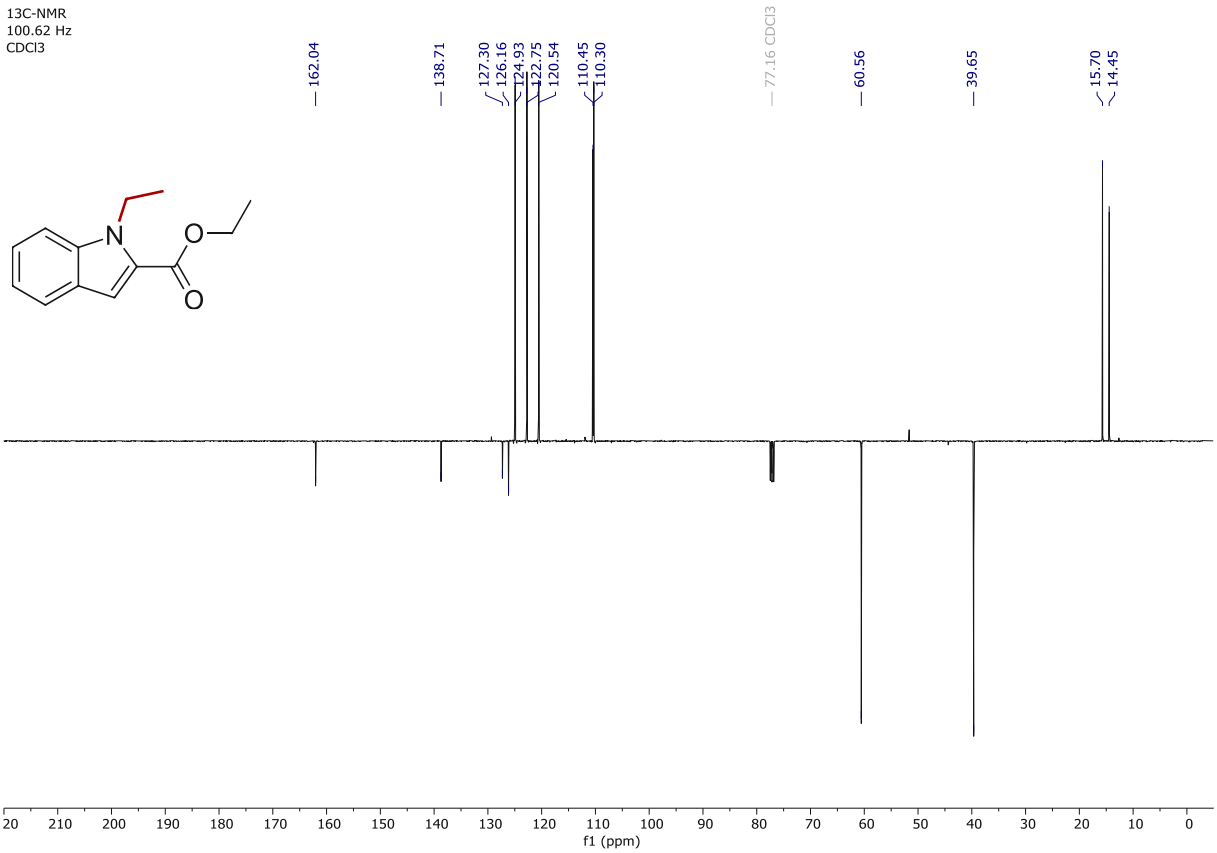
1-Ethyl-2-indolecarbaldehyde (6h)



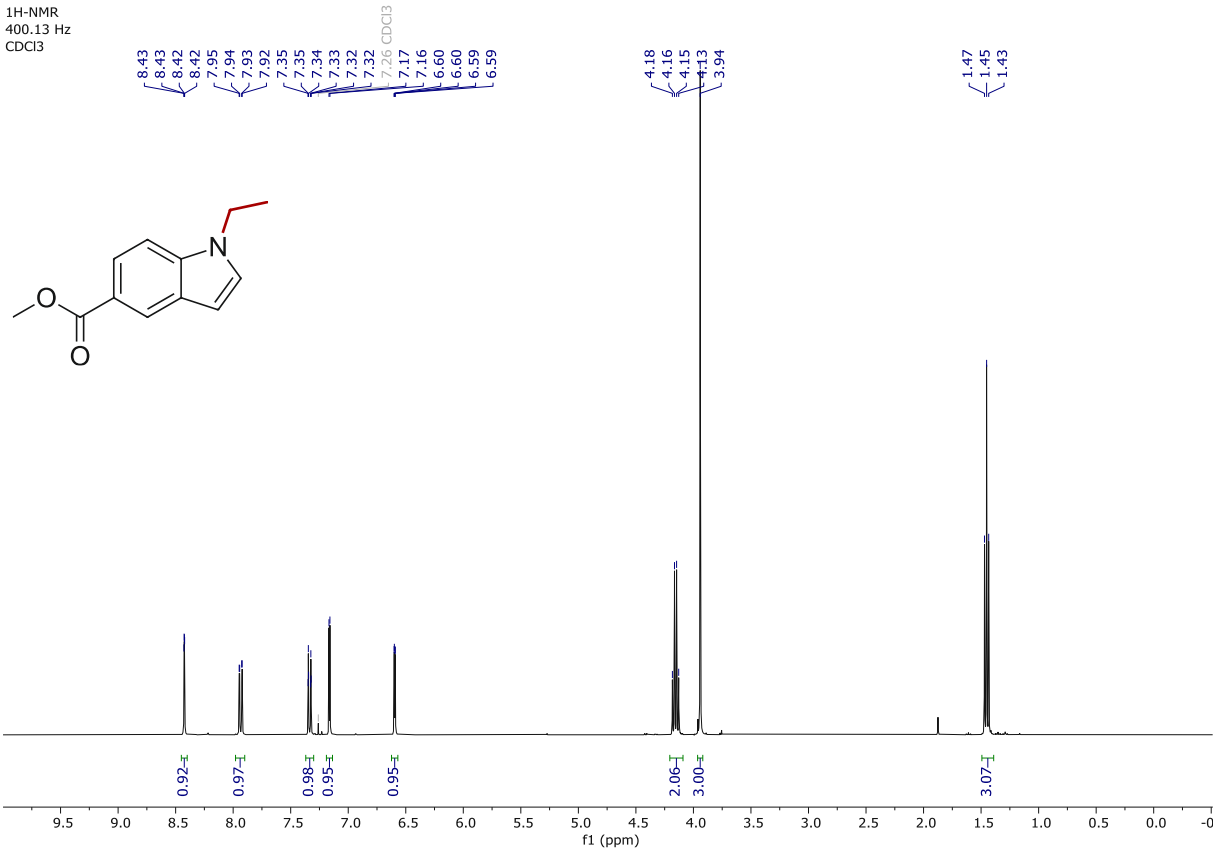


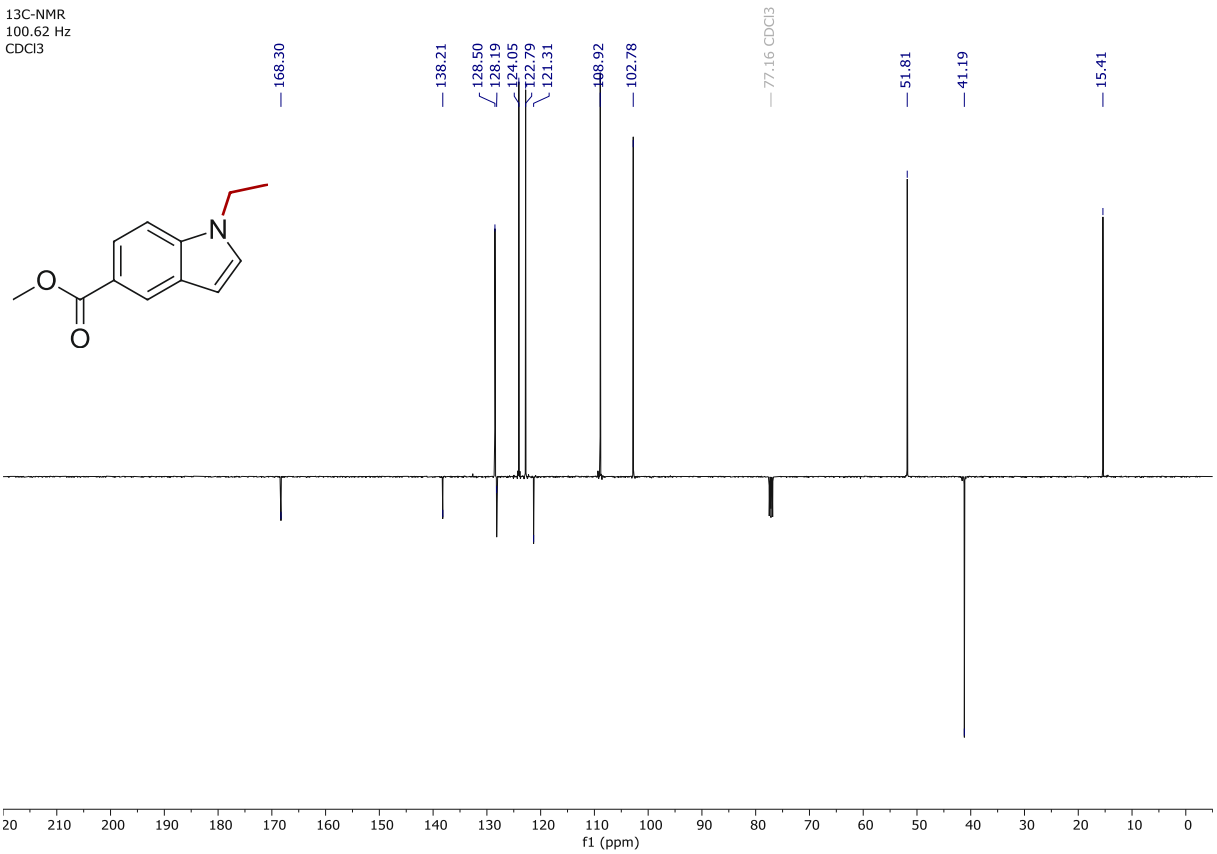
Ethyl 1-ethyl-2-indolecarboxylate (6i)



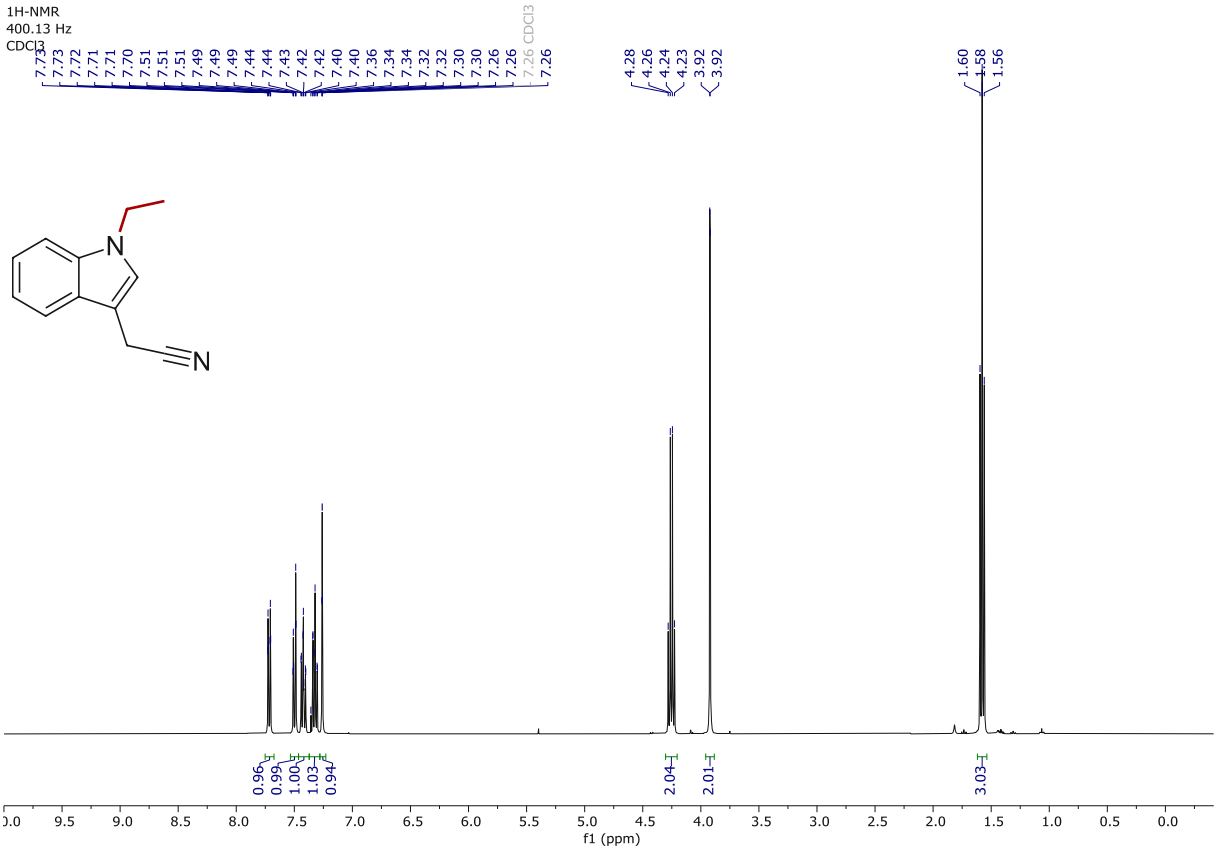


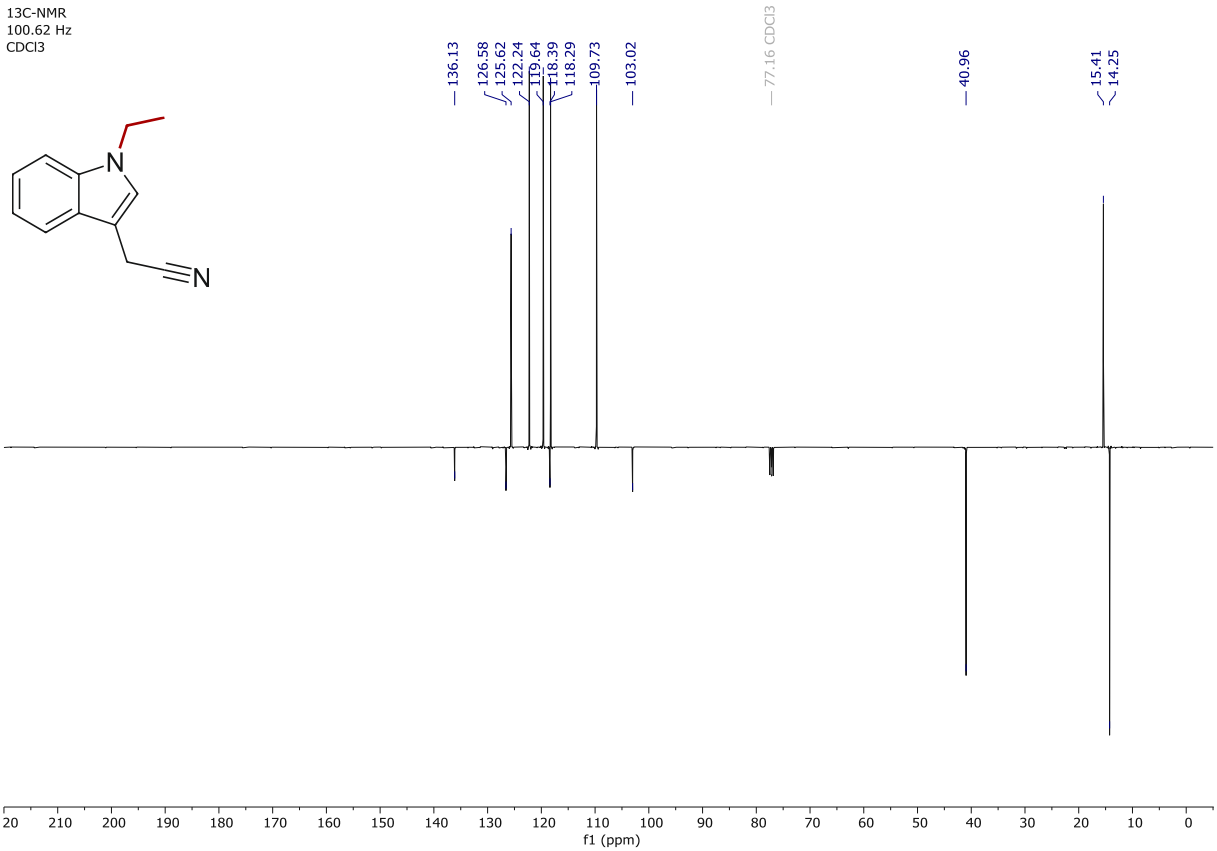
Methyl 1-ethyl-5-indolecarboxylate (6j)





(1-Ethyl-3-indolyl)acetonitrile (6k)





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Johanna Templ and Michael Schnürch

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Angew. Chem. Int. Ed. 2024, 63, e202314637. doi: 10.1002/anie.202314637

How to cite: *Angew. Chem. Int. Ed.* **2024**, *63*, e202314637
doi.org/10.1002/anie.202314637

Mechanochemistry

Allylation of *C*-, *N*-, and *O*-Nucleophiles via a Mechanochemically-Driven Tsuji–Trost Reaction Suitable for Late-Stage Modification of Bioactive Molecules

*Johanna Templ and Michael Schnürch**

Abstract: We present the first solvent-free, mechanochemical protocol for a palladium-catalyzed Tsuji–Trost allylation. This approach features exceptionally low catalyst loadings (0.5 mol %), short reaction times (< 90 min), and a simple setup, eliminating the need for air or moisture precautions, making the process highly efficient and environmentally benign. We introduce solid, nontoxic, and easy-to-handle allyl trimethylammonium salts as valuable alternative to volatile or hazardous reagents. Our approach enables the allylation of various *O*-, *N*-, and *C*-nucleophiles in yields up to 99 % even for structurally complex bioactive compounds, owing to its mild conditions and exceptional functional group tolerance.

In recent years, mechanochemistry has emerged as a revolutionary tool in modern synthetic chemistry.[1] Especially en route to more sustainable and environmentally benign chemical processes, mechanochemical transformations are privileged,[2] since this approach offers a unique advantage: the ability to conduct conventional synthetic reactions without the need for solvents coupled with rapid reaction kinetics. These unique features make mechanochemistry highly attractive for both industrial applications[3] and fundamental research across diverse fields, including material science, inorganic chemistry, and organic chemistry.[1a,2c,d,4]

In the past few years, significant efforts have been made to devising more economical protocols for palladium-catalyzed reactions employing ball milling setups that rely solely on mechanical force for energy input.[5] To date, mechanochemical adaptions of various fundamental Pd-catalyzed reactions, such as the Negishi,[6] Mizoroki–Heck,[7] Suzuki–Miyaura,[8] Buchwald–Hartwig,[9] Sonogashira,[10] a C–S coupling[11] and C–H arylation[12] have been successfully established. To further enrich this "green" toolbox, we present a novel and solvent-free protocol for a mechanochemical palladium-catalyzed Tsuji–Trost allylation of *O*-, *N*-, and *C*-nucleophiles using a ball mill reactor (Figure 1).

Our endeavor prioritized the development of an environmentally benign and entirely safe process, aligning with the principles of green chemistry.

In the Tsuji–Trost reaction, the presence of a leaving group in the allylic position of the substrate is crucial.[13] Numerous protocols have been developed for various leaving groups, encompassing halides, carbonates, acetates,

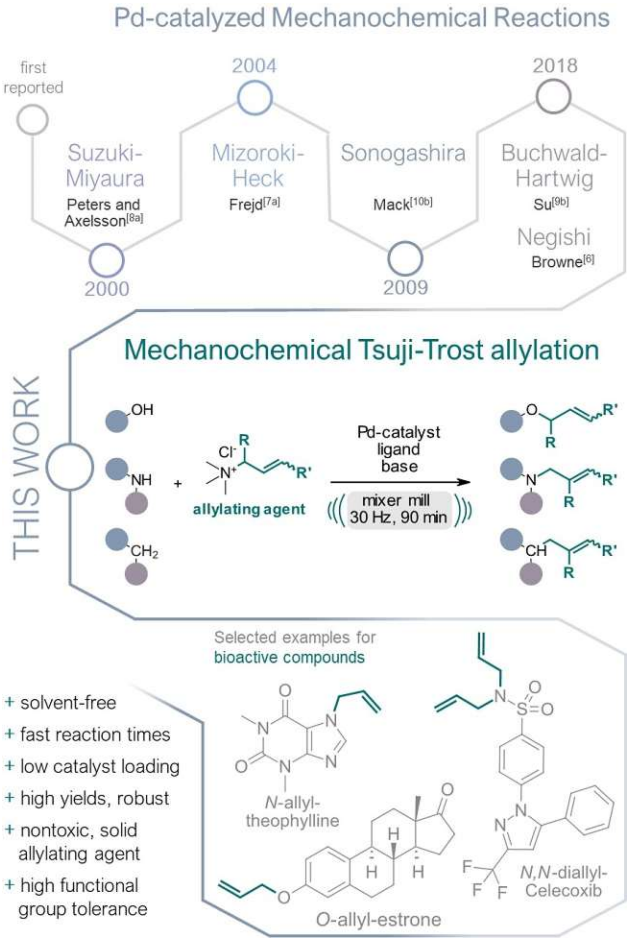

Figure 1. Pd-catalyzed mechanochemical reactions according to their first appearance in literature (top) and the mechanochemical Tsuji–Trost allylation (middle) with an outline of potential application in late-stage functionalization of bioactive compounds (bottom).

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hydroxy groups, and amides.[14] Notably, quaternary ammonium moieties in allylic positions are seldomly employed as leaving groups with only limited examples documented in literature.[15] Nevertheless, harnessing these quaternary ammonium salts as the allyl source presents a distinctive advantage, especially when considering the potential hazards and toxicity associated with traditionally applied allylating agents, such as allyl chloride or bromide. Quaternary ammonium salts are nontoxic and pose significantly fewer health and safety risks. Moreover, their solid nature drastically simplifies the handling. Consequently, they represent a valuable and sustainable alternative to hazardous reagents.[16]

The allylic trimethylammonium chlorides employed in this protocol solely release gaseous trimethylamine as the leaving group, obviating the need for an additional by-product separation step. This feature can be particularly advantageous in the pharmaceutical industry[17] or when the product is intended for use in subsequent reactions without further purification.

Building upon our prior research involving ammonium salts as solid alkylating agents,[16,18] we initiated our current investigation using allyl trimethylammonium chloride as the allylating agent (**II**), paired with 4-hydroxybiphenyl (**I**) serving as the nucleophile. Based on mechanistic considerations[19] of the catalytic cycle for Tsuji–Trost allylation, where a leaving group elimination prompts the formation of an η_3 π-allyl-Pd^{II} complex, we commenced our optimization studies (see Figure 2) by selecting a known and robust catalytic system of $[Pd(allyl)Cl]_2$ (**cat 1**) with cheap *rac*-[2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] (*rac*-BINAP) ligand (**L1**).[20] Initially, 30 mol % of Cs_2CO_3 were added, aligning with precedent literature recommendations[20–21] and the allylated product was obtained in 42 % yield (entry A2). Increasing the amount of base to 1.1 equiv. drastically increased the yield of **1** to 77 % and even 93 % when 2 equiv. were used. As no significant difference in yields could be observed when using Cs_2CO_3 or K_2CO_3 as the base, we continued our studies with the latter cheaper base (cf. entry A4 and A5). Through systematic optimization, we achieved a remarkable reduction of catalyst and ligand loadings to as little as 0.5 mol % and 1 mol % (entry B4), respectively, and reduction of the milling time to as short as 90 min, while still attaining an excellent yield of 97 % (entry C3). Excluding both the catalyst and the ligand (entry B5) or the ligand only (entry B6), no or only 5 % product formation could be observed. These findings prove that the reaction requires the catalytic system to operate, distinctively from a conventional nucleophilic substitution mechanism. Finally, we conducted a reaction in toluene (0.5 M) at 60 °C with a comparable reaction time of 90 min (entry C5). Only 19 % product formation could be observed, underscoring the typically accelerated reaction kinetics inherent to mechanochemical reactions.[2b]

We initiated our scope evaluation by testing various nucleophiles (Scheme 1), including *O*-, *N*-, and *C*-nucleophiles, with commercially available allyl trimethylammonium chloride (**II**) under the optimized reaction conditions (Figure 2, entry C3). The choice between potassium or cesium carbonate as the base depended on the specific reaction's yield. For most substrates, pure allylated product was obtained solely through silica filtration (for further details see the SI). Phenol nucleophiles consistently delivered excellent yields ranging from 61 % to 99 % (**1**–**13**, **17**, **18**, and **21**) independent of their substitution pattern. Electron-donating (**1**, **2**, **8**–**11**, and **17**) and electron-withdrawing (**4**–**6**, **12**, **13**) groups as well as combinations thereof (**5** and **7**), were tolerated at various positions on the aryl ring. Aliphatic (**15**, **16**, and **20**) and allylic (**19**) alcohols also readily underwent allylation, with yields reaching 96 %.

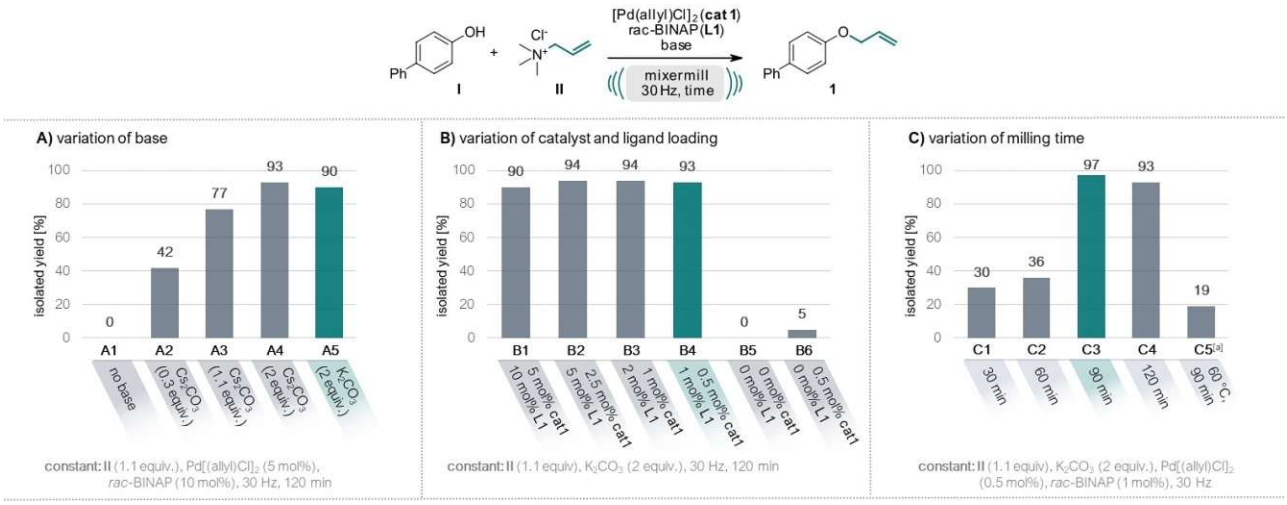
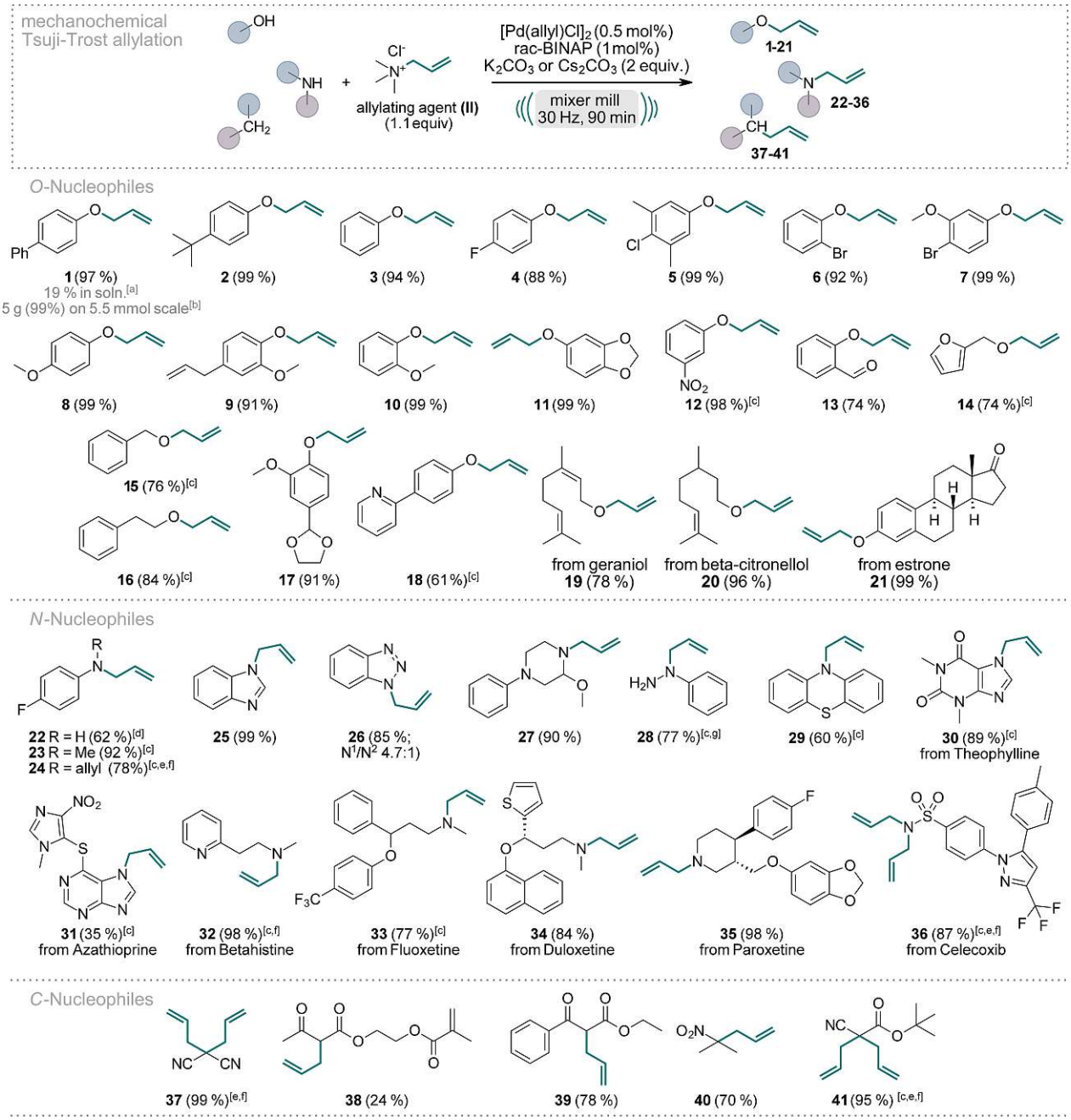


Figure 2. Optimization of the reaction conditions for the mechanochemical Tsuji–Trost allylation. Reactions were performed on a 0.5 mmol scale under air in an IST636 mixer mill, using a Teflon milling jar (7 mL) and two ZrO_2 milling balls (one with 7 mm diameter, one with 10 mm diameter, see Supporting Information for details) at a frequency of 30 Hz. Allyl trimethylammonium chloride (**II**) was used as allylating agent and 4-hydroxybiphenyl (**I**) as nucleophile, $[Pd(allyl)Cl]_2$ as catalyst (**cat 1**) and *rac*-BINAP as ligand (**L 1**). Full table see SI. [a] Reaction performed in toluene (0.5 M) at 60 °C with a reaction time of 90 min.



Scheme 1. Scope of the Pd-catalyzed, mechanochemical Tsuji–Trost reaction of *O*-, *N*-, and *C*-nucleophiles. Reactions were performed on a 0.5 mmol scale under air in an IST636 mixer mill, using a Teflon milling jar (7 mL) and two ZrO_2 milling balls (one with 7 mm diameter, one with 10 mm diameter, see Supporting Information for details) with a milling time of 90 minutes at a frequency of 30 Hz. If not stated otherwise, K_2CO_3 was used as the base. Isolated yields are shown. [a] Reaction performed in toluene (0.5 M) at 60 °C with a reaction time of 90 min. [b] Reaction was performed on a 5.5 mmol scale using 2 Teflon milling jars (25 mL) each equipped with two 12.7 mm ZrO_2 milling balls. [c] Cs_2CO_3 was used as the base. [d] No base. [e] 2.5 equiv. of **II**. [f] 3 equiv. of the base were used. [g] 1 equiv. of **II**, 1 mol% $Pd[(allyl)Cl]_2$, 2 mol% *rac*-BINAP.

Even the complex bioactive compound estrone was quantitatively allylated (**21**). To underscore the robustness and practicality of this approach, we conducted the synthesis of product **1** on a 1 g scale. The reaction scale-up involved an increase of the dimensions of the milling vessels and the milling balls, yet the reaction yielded comparable results, with silica filtration sufficing to obtain pure product **1** in a quantitative yield of 1.15 g.

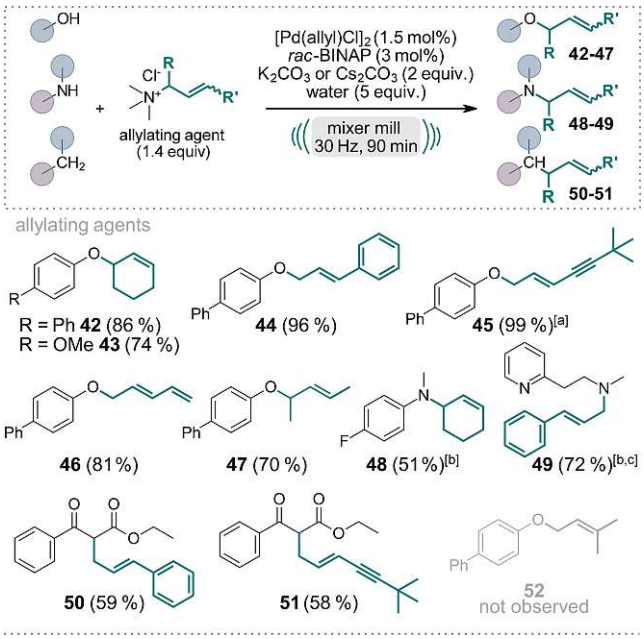
Given the significance of nitrogen-containing motifs in biologically active compounds, we next focused on *N*-nucleophiles, particularly in small molecule drugs and frequently encountered motifs thereof.[22] Aniline derivatives could be mono- or bis-allylated (**22**–**24**). However, primary amines showed diminished yields due to the challenging prevention of over-alkylation (**22**). Secondary amines, on

the other hand, gave excellent allylation yields without overalkylation concerns (**23**, **27**, **32**–**35**).

Nitrogen containing heterocycles are important motifs due to their presence in numerous biologically active compounds. Gratifyingly, our protocol allowed efficient allylation of many *N*-heterocyclic systems, both aromatic and aliphatic ones. Benzotriazole gave a high overall yield of 85 % (**26**), with the allylation occurring predominantly at the N^1-position, and to some extent at position N^2 at a 4.75 : 1 ratio. Notably, column chromatography easily separated these two isomers. Other *N*-heterocyclic compounds were allylated with excellent yields, including benzimidazole towards product **25** and Theophylline giving product **30**. Unfortunately, bioactive Azathioprine could be allylated only in a modest yield of 35 % (**31**), likely due to its steric congestion. Phenylhydrazine was exclusively allylated at the N^1-position, consistent with recent literature reports[23] (product **28**). The sulfonamide moiety in Celecoxib was fully bis-allylated as its high nucleophilicity hampers a mono-selective reaction (**36**). This mild protocol successfully facilitated the allylation of several complex *N*-containing small molecule drugs (**30**–**36**), highlighting its potential in late-stage modifications.

C-nucleophiles bearing electron-withdrawing groups in alpha-position could be mono-allylated, giving products **38**–**40**, or fully converted to the bis-allylated products (**37** and **41**) with yields up to 99 %. Notably, in the case of product **39**, the competitive byproduct formed via *O*-allylation of the enolate was significantly reduced when K_2CO_3 was employed as the base, rather than Cs_2CO_3.

Subsequently, we explored the versatility of substituted allyl ammonium salts (Scheme 2) with *O*-, *N*-, and *C*-nucleophiles (**42**–**51**). These salts can be readily derived from the respective allyl chlorides by reacting with Me_3N solution. Initially, when employing the freshly synthesized and recrystallized ammonium salt from cinnamyl chloride, the yield of product **44** did not exceed 20 %. However, as others have calculated, we made the noteworthy discovery that the addition of water significantly accelerated the reaction.[24] Specifically, when we conducted the reaction with 4-hydroxybiphenyl as the nucleophile and dried cinnamyl trimethylammonium chloride as the allylating agent, only 6 % of product **44** was obtained when additional molecular sieves were added to the milling vessel. In contrast, when 2 equivalents of water were added, the yield of **44** increased to 63 %, and upon the addition of 5 equivalents of water, the reaction proceeded with complete conversion, and an isolated yield of 96 %. This water-mediated enhancement of reaction rates was consistently observed with all other synthesized allyl ammonium salts employed in this protocol. Alternatively, the acceleration of the reaction by addition of water might be due to the effect of liquid assisted grinding,[25] or a combination of both factors. Interestingly, when employing terminal allyl ammonium compounds, exclusively linear products were obtained with moderate to excellent yields (**44**–**46**, **49**–**51**). To ensure a cleaner reaction, we slightly increased the catalyst loading to 1.5 mol % since it resulted in the exclusive formation of the trans-isomer. Due to competing

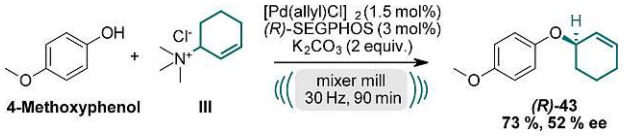


Scheme 2. Scope of the Pd-catalyzed, mechanochemical Tsuji–Trost reaction employing various substituted allyl trimethylammonium salts as allylating agents. Reactions were performed on a 0.5 mmol scale under air in an IST636 mixer mill, using a Teflon milling jar (7 mL) and two ZrO_2 milling balls (one with 7 mm diameter, one with 10 mm diameter, see Supporting Information for details) with a milling time of 90 minutes at a frequency of 30 Hz. If not stated otherwise, K_2CO_3 was used as the base. Isolated yields are shown. [a] 2 mol % of Pd[(allyl)Cl]$_2$ and 4 mol % *rac*-BINAP were used. [b] Cs_2CO_3 was used as the base. [c] 3 equiv. of base were used.

bis-allylation, yields for the *C*-allylated products **50** and **51** were diminished. Interestingly, the 3,3-dimethylallyl trimethylammonium chloride did not give the desired product **52** but only starting material was recovered, assumingly due to steric hindrance upon Pd-allyl complex formation and subsequent nucleophilic attack.

This novel reaction, employing allyl trimethylammonium chloride as the allylating agent, achieves an exceptional level of selectivity, yielding only a single product. This is in stark contrast to using the corresponding allyl chloride directly under the conditions outlined. For example, using cinnamyl chloride instead of cinnamyl trimethylammonium chloride under the reaction conditions described in Scheme 2, the crude NMR reveals a complex mixture of products and starting material. Conversely, when alternative cinnamyl trimethylammonium chloride is utilized, the reaction yields pure product **44** after simple silica filtration.

Prompted by our results, we explored the potential for enantioselective reactions using chiral ligands (Scheme 3, for further details see SI). Several enantioselective reactions using ball milling conditions are already established under organocatalytic conditions.[26] In contrast, metal-catalyzed mechanochemical reactions have received only limited attention so far. Employing a chiral (*R*)-BINAP ligand, we achieved an enantiomeric excess (***ee***) of 28 % under the described conditions. Gratifyingly, using a chiral (*R*)-5,5′-bi-



Scheme 3. Enantioselective reaction towards **(*R*)-43** using chiral (*R*)-SEGPHOS ligand.

(diphenylphosphino)-4,4′-bi-1,3-benzodioxole ((*R*)-SEGPHOS) ligand, we obtained compound **(*R*)-43** in a yield of 73 % with a moderate ***ee*** of 52 %. Further investigations to improve the *ee*-values are currently underway in our laboratories.

In summary, we have established a solvent-free, robust, and high-yielding protocol for a palladium-catalyzed mechanochemical Tsuji–Trost allylation. This method offers an easy setup without the need for air or moisture precautions, very low catalyst and ligand loading, very mild reaction conditions, short reaction times, and high conversion rates. The outstanding functional group tolerance allows clean and mild late-stage allylation of complex bioactive compounds. This study underscores the underappreciated potential of solid, nontoxic allyl ammonium salts as allylating agents in Tsuji–Trost reactions, offering a valuable and environmentally friendly alternative to traditional hazardous allylation reactions.

Supporting Information

Complete optimization screening data, experimental procedures, and characterization data for all compounds isolated.

The authors have cited additional references within the Supporting Information.[20, 27–56]

Acknowledgements

This work was funded by the Austrian Science Fund (FWF, Project P33064-N). The authors acknowledge TU Wien Bibliothek for financial support through its Open Access Funding Programme.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Ammonium Salts · Ball Milling · Green Chemistry · Mechanochemistry · Solvent Free

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Manuscript received: September 29, 2023
Accepted manuscript online: November 6, 2023
Version of record online: November 29, 2023

D IV.2 Manuscript 4 – Supporting Information

Complete optimization screening data, experimental procedures, and characterization data for all compounds isolated.

Johanna Templ and Michael Schnürch

Supporting Information for

Allylation of *C*-, *N*-, and *O*-Nucleophiles *via* a Mechanochemically-Driven Tsuji–Trost Reaction Suitable for Late-Stage Modification of Bioactive Molecules

Angew. Chem. Int. Ed. 2024, 63, e202314637. doi: 10.1002/anie.202314637

Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

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*J. Templ, M. Schnürch**

Allylation of *C-, N-,* and *O*-Nucleophiles *via* a Mechanochemically-Driven Tsuji-Trost Reaction Suitable for Late-Stage Modification of Bioactive Molecules

Supporting Information

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General Experimental Details

All Chemicals were purchased from commercial suppliers and, unless noted otherwise, used without further purification.

For small-scale reactions at a 0.5 mmol scale in solution, the used 8 mL glass vials were sealed with Wheaton® screw caps containing a PTFE faced 14B styrene-butadiene rubber liner for small-scale reaction above room temperature and heated in a metallic reaction block. All reaction temperatures refer to external temperatures.

Mechanochemical reactions were conducted in an IST636 mixer mill, using a Teflon milling jar (7 mL) and 2 ZrO_2 milling balls (one with 7 mm diameter, one with 10 mm diameter) at a frequency of 30 Hz under ambient conditions without external heating. Reaction vessels were purchased from InSolido Technologies.

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance UltraShield 400 at ambient temperature. Chemical Shifts (δ) are reported in ppm. Coupling constants (J) are given in Hertz (Hz) and multiplicities are assigned as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), td (triplet of doublets), and dt (doublet of triplets).

Column chromatography was performed on standard manual glass columns using Merck silica gel 60 (40 µm – 63 µm). Thin Layer Chromatography (TLC) analysis was performed on aluminum-backed unmodified Merck silica gel 60 F_{245} plates. Visualization was realized under UV irradiation or via heat staining using a ceric ammonium molybdate aqueous solution.

HR-MS analysis was performed using HTC PAL system auto sampler, an Agilent 1100/1200 HPLC and Agilent 6230 AJS ESI-TOF mass spectrometer. Data evaluation was performed using Agilent MassHunter Qualitative Analysis B.07.00. Identification was based on peaks obtained from extracted ion chromatograms (extraction width ± 20 ppm).

Chiral HPLC measurements were carried out on a DIONEX UPLC equipped with a photodiode array (PDA) plus detector (190–360 nm), using CHIRALCEL OD column (0.46 cm diameter, 25 cm length)

General Procedures

General Procedure A – Optimization screening

4-Hydroxybiphenyl (I) (85 mg, 0.5 mmol, 1 equiv.), allyl trimethylammonium chloride (II), the respective base (K_2CO_3 or Cs_2CO_3), $Pd[(allyl)Cl]_2$, and *rac*-BINAP were placed in a 7 mL Teflon milling jar, equipped with two ZrO_2 milling balls, one with 7 mm diameter, one with 10 mm diameter. The two different sizes of milling balls were chosen, since it was observed that two 7 mm milling balls got stuck relatively quickly in the milling process. The closed vessel was mounted into the holding station of the mixer mill and milling was conducted at 30 Hz for the indicated time. After the reaction, the crude material was washed out with dichloromethane (DCM), filtered over a short plug of silica in cotton-stuffed Pasteur pipette, eluted with small amounts of DCM (2-4 mL) and the solvent was subsequently removed under reduced pressure. The residue was purified *via* column chromatography (dry load on celite, 5 g silica, LP:EA 50:1).

General Procedure B – synthesis of the allyl trimethyl ammonium salts

Procedure B1 – chlorination of allylic alcohol groups

To a stirred solution of the respective allylic alcohol (1 equiv.) in pentane (1.5 M) was added concentrated hydrochloric acid (3 equiv., 37 %) under vigorous stirring at 0 °C. As soon as the addition of the acid was completed, the reaction was allowed to warm to room temperature and stirred for the a given time. 5 mL of water were added, and product was extracted 3 times with each 20-30 mL pentane. The combined organic extracts were washed 4 times with each 10-20 mL sat. $NaHCO_3$ solution, once with brine, dried over Na_2SO_4, filtered and concentrated at 50 °C water bath temperature and atmospheric pressure. The crude product was used for the next step without further purification and with small amounts of pentane still present. *It is important to note that no acid should be present in the crude mixture to prevent a formation of trimethylamine hydrochloride salt in the subsequent quaternization step.*

Procedure B2 – quaternary ammonium salt formation from the respective allyl chloride derivative

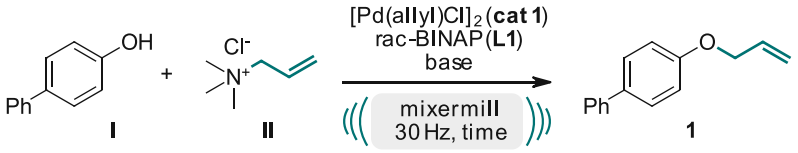
Either commercially available allylic chlorides were used directly or the crude reaction mixtures from the previous chlorination step (procedure B1) were used without further purification.
A round bottom flask was charged with the allylic chloride and a 4.2 M solution of trimethylamine in EtOH (2.5 equiv.) was added dropwise *via* a syringe at 0 °C. The reaction was stirred for 18 hours at room temperature. Subsequently, all volatiles were evaporated under reduced pressure. The obtained off-white solid was dispersed in pentane, filtered, washed several times with pentane and finally dried *in vacuo* to obtain the quaternary allylic ammonium chloride. *It has to be noted that the ammonium salts are highly hygroscopic and suction filtration should be conducted fast without any prolonged exposal to air.*

General Procedure C – for the preparation of the nucleophile scope:

A Teflon milling jar (7 mL) equipped with two ZrO_2 milling balls, one with 7 mm diameter, one with 10 mm diameter, was charged with the respective nucleophile (0.5 mmol, 1 equiv.), the allyl trimethylammonium chloride (76 mg, 0.55 mmol, 1.1 equiv.), $Pd[(allyl)Cl]_2$ (0.95 mg, 0.5 mol%), *rac*-BINAP (3.11 mg, 1 mol%), and either K_2CO_3 (138 mg, 1 mmol, 2 equiv.) or Cs_2CO_3 (329 mg, 1 mmol, 2 equiv.). The two different sizes of milling balls were chosen, since it was observed that two 7 mm milling balls got stuck relatively quickly in the milling process. *The choice of base will be specified within the respective compound characterization section.* The closed vessel was mounted into the holding station of the mixer mill and milling was conducted at 30 Hz for 90 minutes. After the reaction, the crude material was washed out with dichloromethane (DCM), filtered over a short plug of silica in a cotton-stuffed Pasteur pipette, eluted with small amounts of DCM (2-4 mL) and the solvent was subsequently removed under reduced pressure. If not stated otherwise, no further purification step was needed.

General Procedure D – for the preparation of the allylating agent scope:

A Teflon milling jar (7 mL) equipped with two ZrO_2 milling balls (one with 7 mm diameter, one with 10 mm diameter) was charged with the respective nucleophile (0.5 mmol, 1 equiv.), the respective allyl ammonium chloride (0.7 mmol, 1.4 equiv.), $Pd[(allyl)Cl]_2$ (2.7 mg, 1.5 mol%), *rac*-BINAP (9.5 mg, 3 mol%), and either K_2CO_3 (138 mg, 1 mmol, 2 equiv.) or Cs_2CO_3 (329 mg, 1 mmol, 2 equiv.). The two different sizes of milling balls were chosen, since it was observed that two 7 mm milling balls got stuck relatively quickly in the milling process. Subsequently, water was added *via* an Eppendorf® pipette (45 µL, 5 equiv.) *The choice of base will be specified within the respective compound characterization section.* The closed vessel was mounted into the holding station of the mixer mill and milling was conducted at 30 Hz for 90 minutes. After the reaction, the crude material was washed out with dichloromethane (DCM), filtered over a short plug of silica in a cotton-stuffed Pasteur pipette, eluted with small amounts of DCM (2-4 mL) and the solvent was subsequently removed under reduced pressure. If not stated otherwise, no further purification step was needed.



Base:

Reactions were performed following the general procedure A, using K_2CO_3 or Cs_2CO_3 as the base, allyl trimethylammonium chloride (76 mg, 0.55 mmol, 1.1 equiv.), Pd[(allyl)Cl]$_2$ (4.57 mg, 5 mol%), *rac*-BINAP (15.6 mg, 10 mol%) with a milling time of 120 minutes. Isolated yields are shown.

Table 1. Optimization of reaction parameters - base

entry	base	base equivalents	yield [%]
1	no base	-	0
2	Cs_2CO_3	0.3	42
3	Cs_2CO_3	1.1	77
4	Cs_2CO_3	2	93
5	K_2CO_3	2	90

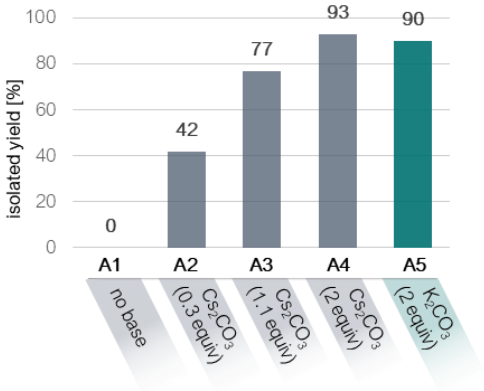


Figure 1. Optimization of reaction parameters - base

Catalyst and ligand loading:

Reactions were performed following the general procedure A, using K_2CO_3 (138 mg, 1 mmol, 2 equiv.) as the base, allyl trimethylammonium chloride (76 mg, 0.55 mmol, 1.1 equiv.), Pd[(allyl)Cl]$_2$, *rac*-BINAP with a milling time of 120 minutes. Isolated yields are shown.

Table 2. Optimization of reaction parameters – catalyst and ligand loading

entry	Pd[(allyl)Cl]$_2$ [mol%]	*rac*-BINAP [mol%]	yield [%]
1	5	10	90
2	2.5	5	94
3	1	2	94
4	0.5	1	93
5	-	-	0
6	0.5	-	5

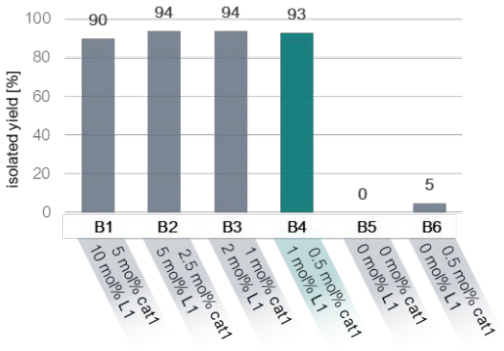


Figure 2. Optimization of reaction parameters - catalyst and ligand loading

Milling time:

Reactions were performed following the general procedure A, using K_2CO_3 (138 mg, 1 mmol, 2 equiv.) as the base, allyl trimethylammonium chloride (76 mg, 0.55 mmol, 1.1 equiv.), Pd[(allyl)Cl]$_2$ (0.91 mg, 0.5 mol%), *rac*-BINAP (3.11 mg, 1 mol%). The milling time is given in the table below. Isolated yields are shown.

Table 3. Optimization of reaction parameters – milling time

entry	milling time [min]	yield [%]
1	30	30
2	60	36
3	90	97
4	120	93

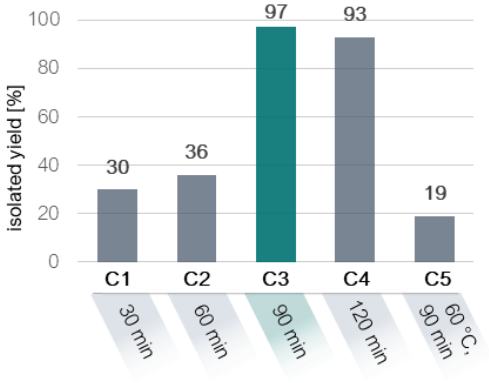


Figure 3. Optimization of reaction parameters - milling time

Chiral ligand screening:

Reactions were performed, following the general procedure D from commercially available 4-methoxyphenol with the deviation that the chiral ligand was varied (3 mol %). The enantiomers were separated using CHIRALCEL OD column eluting with 99.5:0.5 heptane:iso-propanol at 1.0 mL/min. Retention times for racemic mixture: **(R)-43** 10.87 min; **(S)-43** 13.70 min. The absolute configurations of the major isomers were assigned based on reported data in literature. [27] The detailed chromatograms and a detailed procedure for the reaction using (R)-SEGPHOS as the ligand are attached at the end of the document.

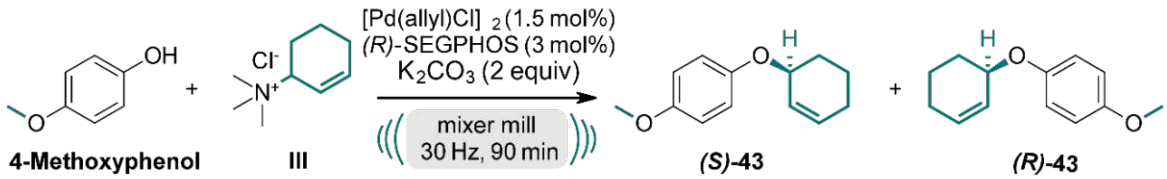


Table 4. Optimization of Reaction Conditions – chiral ligand screening

entry	ligand	CAS number ligand	***(R)*-43 rel. [%]**	***(S)*-43 rel. [%]**	***ee*** [%]
1	*rac*-BINAP	98327-87-8	50	50	-
2	*(R)*-BINAP	76189-55-4	36	64	28
3	*(S)*-tol-BINAP	100165-88-6	61	39	22
4	*(S,S)*-DACH-phenyl-Trost	169689-05-8	46	54	8
5	*(R)*-SEGPHOS	244261-66-3	76	24	52

Control Experiments

Reactions in solution:

An 8 mL glass vial was charged with 4-hydroxybiphenyl (85 mg, 0.5 mmol, 1 equiv.), the allyl trimethylammonium chloride (76 mg, 0.55 mmol, 1.1 equiv.), $Pd[(allyl)Cl]_2$ (0.95 mg, 0.5 mol%), *rac*-BINAP (3.11 mg, 1 mol%), and either K_2CO_3 (138 mg, 1 mmol, 2 equiv.) and 1 mL toluene (p.A. grade) was added. The vial was closed and stirred at room temperature (control 1) or 60 °C (control 2) for 90 minutes. After the reaction, the crude reaction mixture was filtered over a short plug of silica in a cotton-stuffed Pasteur pipette, eluted with small amounts of DCM (2-4 mL) and the solvent was subsequently removed under reduced pressure. The residue was purified *via* column chromatography (dry load on celite, 5 g silica, LP:EA 50:1). Only product and residual starting material were obtained.

Table 5. Control experiments – reactions in solution

experiment	solvent	reaction time [min]	temperature [°C]	yield [%]
control 1	toluene	90	25	4
control 2	toluene	90	60	19

Reaction using allyl bromide as the allylating agent:

A Teflon milling jar (7 mL) equipped with two ZrO_2 milling balls (one with 7 mm diameter, one with 10 mm diameter) was charged with the 4-hydroxybiphenyl (85 mg, 0.5 mmol, 1 equiv.), allyl bromide (66 mg, 0.55 mmol, 1.1 equiv.), Cs_2CO_3 (247 mg, 0.75 mmol, 1.5 equiv.), once with $Pd[(allyl)Cl]_2$ (0.95 mg, 5 mol%), *rac*-BINAP (3.11 mg, 10 mol%) (control 3), and once without any catalyst and ligand (control 4). The closed vessel was mounted into the holding station of the mixer mill and milling was conducted at 30 Hz for 0 minutes. After the reaction, the crude material was washed out with dichloromethane (DCM), filtered over a short plug of silica in a cotton-stuffed Pasteur pipette, eluted with small amounts of DCM (2-4 mL) and the solvent was subsequently removed under reduced pressure.

Table 6. Control experiments – reactions using allyl bromide as the allylating agent

experiment	$Pd[(allyl)Cl]_2$ [mol%]	*rac*-BINAP [mol%]	reaction time [min]	yield [%]
control 3	5	10	120	93
control 4	-	-	120	91

Reaction using cinnamyl chloride instead of cinnamyl trimethylammonium chloride:

A Teflon milling jar (7 mL) equipped with two ZrO_2 milling balls (one with 7 mm diameter, one with 10 mm diameter) was charged with the 4-hydroxybiphenyl (85 mg, 0.5 mmol, 1 equiv.), cinnamyl chloride (88 mg, 0.55 mmol, 1.1 equiv.), Cs_2CO_3 (247 mg, 0.75 mmol, 1.5 equiv.), once with $Pd[(allyl)Cl]_2$ (0.95 mg, 1 mol%), *rac*-BINAP (3.11 mg, 2 mol%). The closed vessel was mounted into the holding station of the mixer mill and milling was conducted at 30 Hz for 90 minutes. After the reaction, the crude material was washed out with dichloromethane (DCM), filtered over a short plug of silica in a cotton-stuffed Pasteur pipette, eluted with small amounts of DCM (2-4 mL) and the solvent was subsequently removed under reduced pressure to obtain 119 mg of a crude brown oil. Crude NMR showed the formation of multiple products and starting material.

The NMR spectra shows the crude reaction mixture after silica filtration when cinnamyl chloride is used as allylating agent (top spectrum, blue) and when cinnamyl trimethylammonium chloride is used as the allylating agent (bottom spectrum, red) in the reaction.

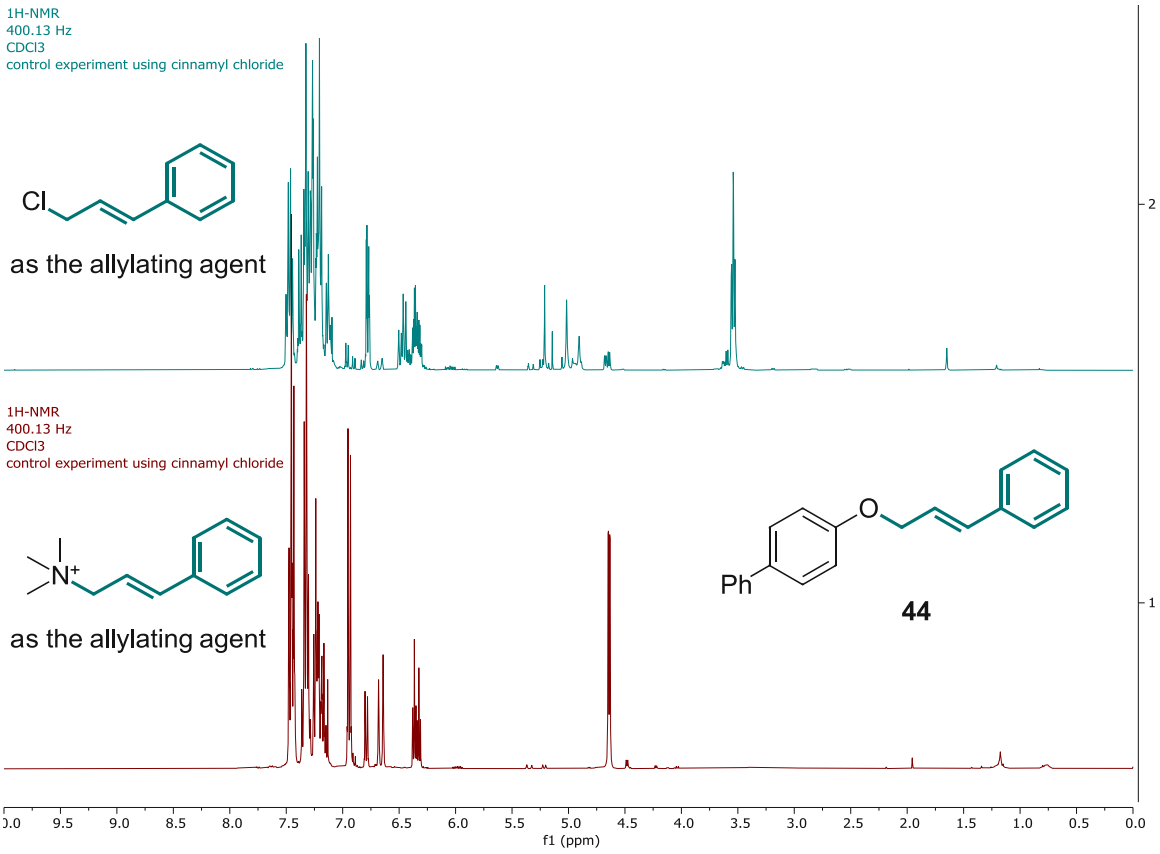
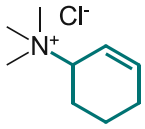


Figure 4. NMR of the crude reaction mixtures after silica filtration. Top spectrum (blue): cinnamyl chloride is used as the allylating agent; bottom spectrum (red): allyl trimethylammonium chloride is used as the allylating agent. The bottom spectrum shows full conversion and solely product formation (cf. NMR-spectrum of compound 44)

2-Cyclohexen-1-yltrimethylammonium chloride **(III)**



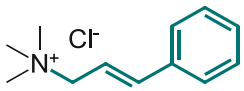
The allylic chloride intermediate was prepared according to the general procedure B1 from commercially available 2-cyclohexen-1-ol (5.17 g, 5.2 mL, 50 mmol, 1 equiv.) and conc. HCl (12.7 mL, 37 %, 3 equiv.) for 18 h. The crude product was subsequently reacted with a solution of trimethylamine in EtOH (30 mL, 2.5 equiv., 4.2 M). The title compound was obtained as a white powder (6.9 g, 79 %)

^{1}H NMR (400 MHz,) δ 6.31 – 6.21 (m, 1H), 5.81 (dt, *J* = 10.5, 2.1 Hz, 1H), 4.48 (ddt, *J* = 8.8, 5.6, 2.8 Hz, 1H), 3.39 (d, *J* = 1.5 Hz, 9H), 2.33 – 2.22 (m, 1H), 2.05 (dt, *J* = 6.2, 3.4 Hz, 2H), 1.97 – 1.86 (m, 1H), 1.79 – 1.57 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 118.7, 70.7, 50.7, 24.3, 23.4, 20.6.

HRMS (ESI): m/z $[M]^+$ calcd. for $C_9H_{18}N$: 140.1434; found: 140.1437.

(3-Phenyl-2-propenyl)trimethylammonium chloride **(IV)**



Prepared according to procedure B2 from commercially available cinnamyl chloride (3.2 g, 2.9 mL, 20 mmol, 1 equiv.) with a solution of trimethylamine in EtOH (4.2 mL, 2.5 equiv., 4.2 M). The title compound was obtained as a white powder (41.5 g, 99 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dq, *J* = 7.4, 2.5 Hz, 2H), 7.31 – 7.20 (m, 3H), 7.01 (d, *J* = 15.6 Hz, 1H), 6.23 (dt, *J* = 15.5, 7.7 Hz, 1H), 4.54 (d, *J* = 7.7 Hz, 2H), 3.39 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 134.6, 129.5, 128.9, 127.3, 114.4, 67.8, 52.7.

HRMS (ESI): m/z $[M]^+$ calcd. for $C_{12}H_{18}N$: 176.1434; found:176.1435.

(6,6-Dimethyl-2-hepten-4-ynyl)trimethylammonium chloride **(V)**

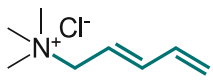
Prepared according to procedure B2 from commercially available 1-chloro-6,6-dimethyl-2-hepten-4-yne (1.12 g, 1.24 mL, 7 mmol, 1 equiv.) with a solution of trimethylamine in EtOH (12 mL, 2.5 equiv., 4.2 M). The title compound was obtained as a white powder (4.04 g, 95 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (dt, *J* = 15.4, 1.0 Hz, 1H), 5.97 (dt, *J* = 15.5, 7.8 Hz, 1H), 4.45 (dd, *J* = 7.7, 1.0 Hz, 2H), 3.40 (s, 9H), 1.23 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 125.7, 125.3, 104.6, 75.9, 67.3, 52.8, 30.7, 28.2.

HRMS (ESI): m/z $[M]^+$ calcd. for $C_{12}H_{22}N$: 180.1747; found: 180.1749.

2,4-Pentadienyltrimethylammonium chloride **(VI)**



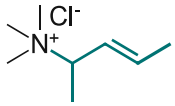
The allylic chloride intermediate was prepared according to the general procedure B1 from commercially available 1,4-pentadien-3-ol (841, 0.97 mL, 10 mmol, 1 equiv.) and conc. HCl (2.6 mL, 37 %, 3 equiv.) for 2 h. The crude product was subsequently reacted with a solution of trimethylamine in EtOH (6 mL, 2.5 equiv., 4.2 M). The title compound was obtained as an off-white powder (840 mg, 52 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (dd, *J* = 15.1, 10.6 Hz, 1H), 6.32 (dt, *J* = 17.0, 10.3 Hz, 1H), 5.71 (dt, *J* = 15.3, 7.8 Hz, 1H), 5.38 (d, *J* = 16.9 Hz, 1H), 5.29 (d, *J* = 10.1 Hz, 1H), 4.40 (d, *J* = 7.8 Hz, 2H), 3.36 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 134.7, 123.1, 118.1, 67.6, 52.7.

HRMS (ESI): m/z $[M]^+$ calcd. for $C_8H_{16}N$: 126.1277; found: 126.1279.

(1-Methyl-2-butenyl)trimethylammonium chloride **(VII)**



The allylic chloride intermediate was prepared according to the general procedure B1 from commercially available 3-penten-2-ol (1.7 g, 2 mL, 19 mmol, 1 equiv.) and conc. HCl (4.8 mL, 37 %, 3 equiv.) for 18 h. The crude product was subsequently reacted with a solution of trimethylamine in EtOH (11 mL, 2.5 equiv., 4.2 M). The title compound was obtained as a white powder (1.42 g, 46 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (dq, *J* = 15.1, 6.6 Hz, 1H), 5.38 (ddq, *J* = 15.0, 9.3, 1.7 Hz, 1H), 4.55 (dq, *J* = 9.3, 6.7 Hz, 1H), 3.33 – 3.27 (m, 9H), 1.76 (dd, *J* = 6.6, 1.7 Hz, 3H), 1.46 (d, *J* = 6.7 Hz, 3H).

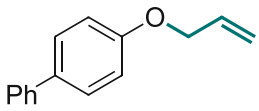
^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2 123.2, 72.3, 50.7, 44.9, 18.3, 15.5.

HRMS (ESI): m/z $[M]^+$ calcd. for $C_8H_{18}N$: 128.1434; found: 128.1435.

Nucleophile Scope

O-Nucleophiles

4-Allyloxy-biphenyl **(1)** [CAS: 20281-44-1]



Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a white solid (120 mg, 97 %).

Analytical data is in accordance with literature [28]

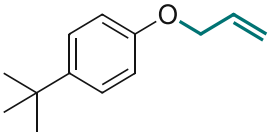
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 – 7.55 (m, 4H), 7.48 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.42 – 7.33 (m, 1H), 7.10 – 7.02 (m, 2H), 6.22 – 6.08 (m, 1H), 5.51 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.38 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.63 (dt, *J* = 5.3, 1.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 140.9, 134.0, 133.4, 128.8, 128.2, 126.81, 126.77, 115.1, 68.9.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{15}H_{15}O$: 211.1118; found: 211.1115.

Scale up synthesis: The synthesis of 1 was additionally performed on a 5.5 mmol scale in two separate Teflon milling vessels (25 mL) each equipped with two ZrO_2 milling balls (12.7 mm). Each vessel was charged with 4-hydroxybiphenyl (468 mg, 2.75 mmol, 1 equiv.), allyl trimethylammonium chloride (419 mg, 3.03 mmol, 1.1 equiv.), K_2CO_3 (760 mg, 5.5 mmol, 2 equiv.), $Pd[(allyl)Cl]_2$ (5.03 mg, 0.013 mmol, 0.5 mol%), and *rac*-BINAP (17.7, 0.03 mmol, 1 mol%). The closed vessel was mounted into the holding station of the mixer mill and milling was conducted at 30 Hz for 90 minutes. After the reaction, the reaction mixtures of both milling vessels were combined and the crude material was washed out with dichloromethane (DCM), filtered over a short plug of silica in cotton-stuffed Pasteur pipette, eluted with DCM (30 mL) and the solvent was subsequently removed under reduced pressure. Without any further purification, the title compound was obtained as white solid in quantitative yields (1.15 g, 99 %). Analytical data was in accordance with previous measurements.

Allyl 4-(tert-butyl)phenylether **(2)** [CAS: 24806-16-4]

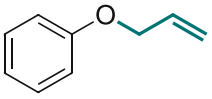


Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (94 mg, 99 %)
Analytical data is in accordance with literature[29]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.28 (m, 2H), 6.92 – 6.84 (m, 2H), 6.15 – 6.01 (m, 1H), 5.43 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.29 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.54 (dt, *J* = 5.3, 1.6 Hz, 2H), 1.32 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 143.6, 133.7, 126.3, 117.6, 114.3, 69.0, 34.2, 31.7.

Allyl phenyl ether **(3)** [CAS: 1746-13-0]

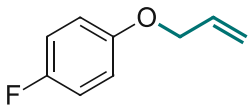


Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (63 mg, 94 %).
Analytical data is in accordance with literature[30]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.27 (m, 2H), 7.03 – 6.91 (m, 3H), 6.16 – 6.02 (m, 1H), 5.44 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.31 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.56 (dt, *J* = 5.3, 1.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 133.5, 129.6, 121.0, 117.7, 114.9, 68.8.

1-(Allyloxy)-4-fluorobenzene **(4)** [CAS: 13990-72-2]



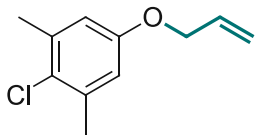
Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as yellow oil (67 mg, 88 %)
Analytical data is in accordance to literature[31]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03 – 6.92 (m, 2H), 6.90 – 6.81 (m, 2H), 6.12 – 5.98 (m, 1H), 5.41 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.29 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.50 (dt, *J* = 5.3, 1.6 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.4 (d, *J* = 238.3 Hz), 154.8 (d, *J* = 2.1 Hz), 133.3, 117.9, 116.0 (d, *J* = 9.3 Hz), 115.8 (d, *J* = 5.8 Hz), 69.6.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -123.94.

5-(allyloxy)-2-chloro-1,3-dimethylbenzene **(5)** [CAS: 93589-80-1]

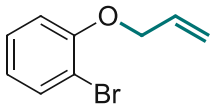


Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (98 mg, 99 %).
Analytical data is in accordance with literature[32]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.67 (s, 2H), 6.12 – 5.98 (m, 1H), 5.41 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.29 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.50 (dt, *J* = 5.3, 1.6 Hz, 2H), 2.36 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 137.2, 133.3, 126.5, 117.7, 114.9, 69.0, 21.1.

1-(Allyloxy)-2-bromobenzene **(6)** [CAS: 60333-75-7]

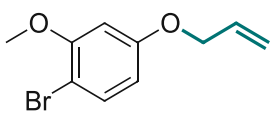


Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a slightly yellow oil (99 mg, 92 %)
Analytical data is in accordance with literature[33]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.29 – 7.20 (m, 1H), 6.90 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.84 (td, *J* = 7.6, 1.4 Hz, 1H), 6.15 – 6.01 (m, 1H), 5.50 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.32 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.62 (dt, *J* = 5.0, 1.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.04, 133.5, 132.7, 128.5, 122.1, 117.8, 113.7, 112.4, 69.7.

1-Bromo-2-methoxy-4-allyloxybenzene **(7)** [CAS: 200336-42-1]



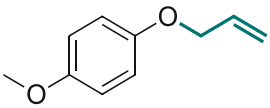
Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (120 mg, 99 %)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.7 Hz, 1H), 6.52 (d, *J* = 2.7 Hz, 1H), 6.40 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.11 – 5.97 (m, 1H), 5.41 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.30 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.51 (dt, *J* = 5.3, 1.6 Hz, 2H), 3.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 156.7, 133.2, 133.0, 118.1, 106.9, 102.7, 100.8, 69.2, 56.2.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{12}BrO_2$: 243.0015; found: 243,0015.

1-(Allyloxy)-4-methoxybenzene **(8)** [CAS: 13391-35-0]

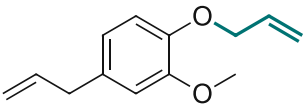


Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (81 mg, 99 %).
Analytical data is in accordance with literature[32]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.91 – 6.79 (m, 4H), 6.13 – 5.99 (m, 1H), 5.41 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.49 (dt, *J* = 5.3, 1.6 Hz, 2H), 3.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 152.9, 133.8, 117.6, 115.9, 114.7, 69.6, 55.8.

4-Allyl-1-(allyloxy)-2-methoxybenzene **(9)** [CAS: 4125-45-5]



Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (93 mg, 91 %).

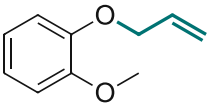
Analytical data is in accordance with literature[34]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.82 (d, *J* = 8.0 Hz, 1H), 6.75 – 6.65 (m, 2H), 6.16 – 6.03 (m, 1H), 6.02 – 5.90 (m, 1H), 5.39 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.4 Hz, 1H), 5.13 – 5.07 (m, 1H), 5.07 – 5.02 (m, 1H), 4.59 (dt, *J* = 5.4, 1.5 Hz, 2H), 3.87 (s, 3H), 3.34 (dt, *J* = 6.7, 1.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 146.5, 137.8, 133.7, 133.2, 120.5, 117.9, 115.8, 113.8, 112.4, 70.2, 56.0, 39.9.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{17}O_2$: 205.1223; found: 205,1224

1-(Allyloxy)-2-methoxybenzene **(10)** [CAS: 4125-43-3]



Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (82 mg, 99%).

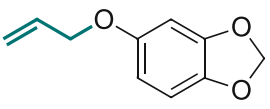
Analytical data is in accordance with literature[35]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.98 – 6.83 (m, 4H), 6.17 – 6.03 (m, 1H), 5.41 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.29 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.62 (dt, *J* = 5.5, 1.5 Hz, 2H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 148.1, 133.5, 121.3,0 120.8, 117.9, 113.7, 111.8, 69.9, 55.9.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{13}O_2$: 165.0910; found: 165.0911

O-Allyl-sesamol **(11)** [CAS: 19202-22-3]



Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a slightly yellow oil (88 mg, 99 %).

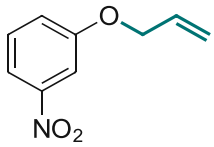
Analytical data is in accordance with literature. [36]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.70 (d, *J* = 8.5 Hz, 1H), 6.52 (d, *J* = 2.5 Hz, 1H), 6.34 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.11 – 5.97 (m, 1H), 5.91 (s, 2H), 5.40 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.46 (dt, *J* = 5.4, 1.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 148.3, 141.8, 133.5, 117.7, 108.0, 106.1, 101.2, 98.4, 69.9.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{11}O_3$: 179.0703; found: 179.0702

1-Allyloxy-3-nitrobenzene **(12)** [CAS: 58621-55-9]



Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as slightly yellow oil (88 mg, 98 %).

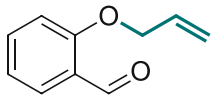
Analytical data is in accordance with literature. [37]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 – 7.77 (m, 1H), 7.73 (t, *J* = 2.3 Hz, 1H), 7.42 (t, *J* = 8.2 Hz, 1H), 7.27 – 7.20 (m, 1H), 6.11 – 5.97 (m, 1H), 5.44 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.34 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.61 (dt, *J* = 5.3, 1.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 149.3, 132.2, 130.0, 122.00, 118.6, 116.0, 109.2, 69.4.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_{10}NO_3$: 180.0655; found: 180.0656

2-(Allyloxy)benzaldehyde **(13)** [CAS: 28752-82-1]



Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as yellow oil (60 mg, 74 %).

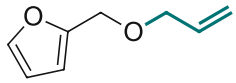
Analytical data is in accordance with literature. [38]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.53 (d, *J* = 0.8 Hz, 1H), 7.83 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.56 – 7.48 (m, 1H), 7.06 – 6.92 (m, 2H), 6.14 – 6.00 (m, 1H), 5.45 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.33 (dq, *J* = 10.6, 1.5 Hz, 1H), 4.65 (dt, *J* = 5.2, 1.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6, 161.0, 135.9, 132.5, 128.5, 121.0, 118.2, 113.0, 69.3.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{11}O_2$: 163.0754; found 163.0754

Allyl furfuryl ether **(14)** [CAS: 113505-00-3]



Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as yellow oil (51 mg, 74 %).

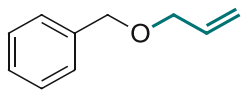
Analytical data is in accordance with literature. [39]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.37 – 6.28 (m, 2H), 5.99 – 5.85 (m, 1H), 5.35 – 5.25 (m, 1H), 5.21 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.46 (s, 2H), 4.02 (dt, *J* = 5.7, 1.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 142.9, 134.5, 117.6, 110.4, 109.4, 71.1, 63.9.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_8H_{11}O_2$: 139.0754; found: 139.0751

Benzyl allyl ether **(15)** [CAS: 14593-43-2]



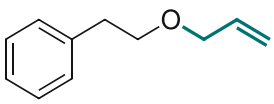
Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (56 mg, 76 %).

Analytical data is in accordance with literature. [40]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.27 (m, 5H), 6.06 – 5.92 (m, 1H), 5.34 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.23 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.55 (s, 2H), 4.06 (dt, *J* = 5.6, 1.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 134.9, 128.5, 127.8, 127.7, 117.2, 72.2, 71.3.

2-(2-propenyloxy)ethylbenzene **(16)** [CAS: 14289-65-7]



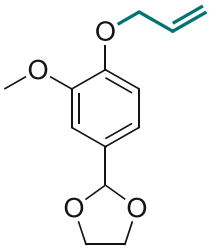
Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (68 mg, 84 %).

Analytical data is in accordance with literature. [41]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.24 (m, 2H), 7.24 – 7.14 (m, 3H), 5.98 – 5.83 (m, 1H), 5.25 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.16 (dq, *J* = 10.4, 1.4 Hz, 1H), 3.99 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.65 (t, *J* = 7.3 Hz, 2H), 2.91 (t, *J* = 7.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 135.0, 129.0, 128.5, 126.3, 116.9, 72.0, 71.4, 36.5.

2-[4-(Allyloxy)-3-methoxyphenyl]-1,3-dioxolane (**17**)



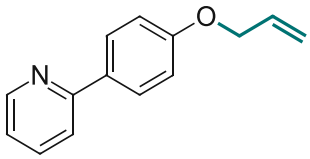
Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (107 mg, 91 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.96 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.14 – 6.00 (m, 1H), 5.74 (s, 1H), 5.39 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.61 (dt, *J* = 5.4, 1.5 Hz, 2H), 4.17 – 4.07 (m, 2H), 4.07 – 3.96 (m, 2H), 3.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 148.9, 133.3, 130.7, 119.3, 118.1, 113.0, 109.6, 103.8, 70.0, 65.3, 56.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for C13H17O4: 237.1122; found: 237.1125

2-(4-(allyloxy)phenyl)pyridine **(18)** [CAS: 1623748-79-7]



Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. The crude product was purified *via* column chromatography (6 g, silica, pentane:EtOAc 10:1 – 9:1) to obtain the title compound as a white solid (64 mg, 61 %).

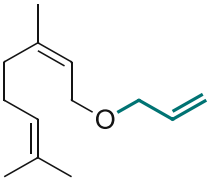
Analytica data is in accordance with literature. [42]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 – 8.62 (m, 1H), 7.98 – 7.90 (m, 2H), 7.74 – 7.67 (m, 1H), 7.66 (dt, *J* = 8.1, 1.3 Hz, 1H), 7.20 – 7.12 (m, 1H), 7.05 – 6.97 (m, 2H), 6.15 – 6.01 (m, 1H), 5.44 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.30 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.59 (dt, *J* = 5.3, 1.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 157.2, 149.7, 136.8, 133.2, 132.3, 128.3, 121.5, 119.9, 117.9, 115.0, 69.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{14}NO$: 212.1070; found: 212.1077

(E)-1-(Allyloxy)-3,7-dimethylocta-2,6-diene **(19)** [CAS: 35534-61-3]



Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as colorless oil (76 mg, 78 %).

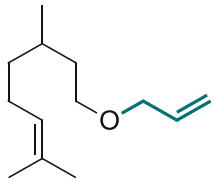
Analytical data is in accordance with literature. [43]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.00 – 5.85 (m, 1H), 5.36 (tq, *J* = 6.8, 1.3 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dq, *J* = 10.3, 1.3 Hz, 1H), 5.12 – 5.06 (m, 1H), 3.99 (d, *J* = 6.8 Hz, 2H), 3.96 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.15 – 2.07 (m, 2H), 2.06 – 2.00 (m, 2H), 1.67 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 135.2, 131.8, 124.1, 120.9, 117.0, 71.1, 66.7, 39.7, 26.5, 25.8, 17.8, 16.6

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{23}O$: 195.1743; found: 195.1742

O-Allyl citronellol **(20)** [CAS: 139694-24-9]



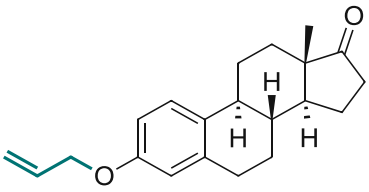
Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (94 mg, 96 %).

Analytical data is in accordance with literature. [44]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.99 – 5.81 (m, 1H), 5.25 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.15 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.13 – 5.04 (m, 1H), 3.95 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.51 – 3.37 (m, 2H), 2.06 – 1.88 (m, 2H), 1.71 – 1.50 (m, 8H), 1.46 – 1.27 (m, 2H), 1.21 – 1.09 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 131.2, 124.9, 116.7, 71.9, 68.8, 37.4, 36.8, 29.7, 25.8, 25.6, 19.7, 17.7.

3-Allyloxy estrone **(21)** [CAS: 1624-67-5]



Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as yellow oil (155 mg, 99 %).

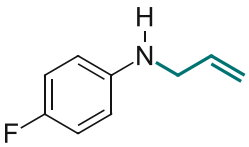
Analytical data is in accordance with literature. [45]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (dd, *J* = 8.7, 1.1 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.69 – 6.62 (m, 1H), 6.12 – 5.98 (m, 1H), 5.41 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.51 (dt, *J* = 5.3, 1.6 Hz, 2H), 2.93 – 2.82 (m, 2H), 2.56 – 2.45 (m, 1H), 2.44 – 2.32 (m, 1H), 2.32 – 1.89 (m, 6H), 1.69 – 1.36 (m, 7H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 221.1, 156.8, 137.9, 133.7, 132.3, 126.4, 117.6, 114.9, 112.5, 68.9, 50.6, 48.2, 44.1, 38.5, 36.0, 31.7, 29.8, 26.7, 26.0, 21.7, 14.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{21}H_{27}O_2$: 311.2006; found: 311.2010

N-Allyl-4-fluoroaniline **(22)** [CAS: 83164-79-8]



Prepared following the general procedure C with the deviation that no base was used. The crude product was purified *via* column chromatography (dry load, pentane:Et_2O 95:5). The title compound was obtained as yellow oil (47 mg, 62 %) along with small amounts of the bis-allylated compound **24** (10 mg, 11 %).

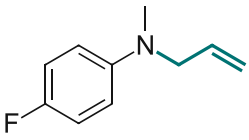
Analytical data is in accordance with literature. [46]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.94 – 6.83 (m, 2H), 6.61 – 6.51 (m, 2H), 6.02 – 5.88 (m, 1H), 5.28 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dq, *J* = 10.3, 1.5 Hz, 1H), 3.74 (dt, *J* = 5.4, 1.7 Hz, 2H), 3.71 – 3.55 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (d, *J* = 234.9 Hz), 144.5, 135.5, 116.5, 115.8 (d, *J* = 22.3 Hz), 113.9 (d, *J* = 7.4 Hz), 47.3.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_{11}FN$: 152.0870; found: 152.0867

N-Allyl-4-fluoro-*N*-methylaniline **(23)** [CAS: 1687753-93-0]



Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as a slightly yellow oil (76 mg, 92 %)

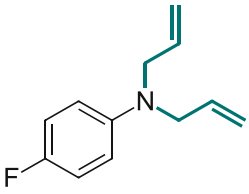
Analytical data is in accordance with literature.[47]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.00 – 6.89 (m, 2H), 6.72 – 6.63 (m, 2H), 5.91 – 5.77 (m, 1H), 5.23 – 5.13 (m, 2H), 3.91 – 3.85 (m, 2H), 2.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (d, *J* = 235.0 Hz), 146.4, 133.9, 116.6, 115.5 (d, *J* = 22.0 Hz), 113.9 (d, *J* = 7.3 Hz), 56.2, 38.7

^{19}F NMR (376 MHz, Chloroform-*d*) δ -129.26.

N,N-diallyl-4-fluoroaniline **(24)** [83164-94-7]



Prepared, following the general procedure C from commercially available starting material with the deviation that 2.5 equivalents of allyl trimethylammonium chloride were used and 3 equivalents of Cs_2CO_3 as the base. The crude product was purified *via* column chromatography (5 g silica, pentane:Et_2O, 100:1) to obtain the title compound as slightly yellow oil (75 mg, 78 %).

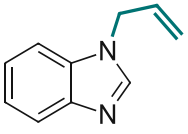
Analytical data is in accordance with literature. [48]

^{1}H NMR (400 MHz, Chloroform-d) δ 6.95 – 6.84 (m, 2H), 6.68 – 6.58 (m, 2H), 5.99 – 5.65 (m, 2H), 5.22 – 5.12 (m, 4H), 3.88 (dt, J = 4.9, 1.7 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (d, *J* = 234.8 Hz), 145.5, 134.2, 116.3, 115.5 (d, *J* = 22.0 Hz), 113.7 (d, *J* = 7.2 Hz), 53.5.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{12}H_{15}FN$: 192.1183; found: 192.1183.

1-Allylbenzimidazole **(25)** [CAS: 19018-22-5]



Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (79 mg, 99 %).

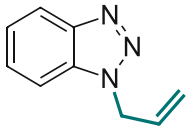
Analytical data is in accordance with literature.[49]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 2.1 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.32 – 7.13 (m, 3H), 5.97 – 5.82 (m, 1H), 5.23 – 5.15 (m, 1H), 5.13 – 5.03 (m, 1H), 4.69 – 4.62 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 143.0, 133.9, 132.0, 123.0, 122.2, 120.4, 118.6, 110.0, 47.4.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{11}N_2$: 159.0917; found: 159.0917

1-Allylbenzotrialzole **(26)** [CAS: 52298-91-6]



Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base The crude product was purified *via* column chromatography (6 g silica, LP:EA 10:1 – 2:1) to obtain the title compound (N^1-allylbenzotriazole) (56 mg, 70 %) and the N^2-allylbenzotriazole (12 mg, 15 %) as a colorless oil. The overall yield of the allylated benzotriazole was 68 mg (85 %) with a ratio of N^1/N^2 4.7:1.

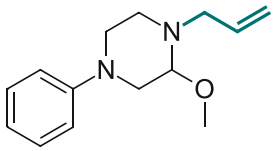
Analytical data was in accordance with literature. [20]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.51 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.40 – 7.31 (m, 1H), 6.13 – 5.99 (m, 1H), 5.32 (dt, *J* = 10.2, 1.2 Hz, 1H), 5.30 – 5.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 133.0, 131.3, 127.4, 124.0, 120.2, 119.4, 109.8, 51.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_{10}N_3$: 160.0869; found: 160.0872

1-Allyl-4-(2-methoxy-phenyl)-piperazine **(27)** [CAS: 6322-40-3]



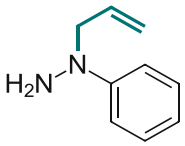
Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as yellow oil (104 mg, 90 %)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.05 – 6.88 (m, 3H), 6.85 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.98 – 5.84 (m, 1H), 5.22 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.19 – 5.13 (m, 1H), 3.85 (s, 3H), 3.19 – 2.98 (m, 6H), 2.66 (t, *J* = 4.7 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 141.5, 135.2, 122.9, 121.0, 118.3, 118.1, 111.3, 62.0, 55.4, 53.4, 50.7.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{21}N_2O$: 233.1648; found: 233.1651

N-Allyl-N-phenylhydrazine **(28)** [CAS: 31928-39-9]



Prepared, following the general procedure C from commercially available starting material with the deviation that 1 equivalent allyl trimethylammonium chloride was used, 1 mol% of $Pd[(allyl)Cl]_2$, and 2 mol% *rac*-BINAP. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as brown oil (57 mg, 77 %).

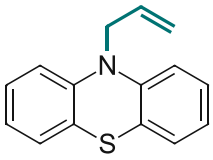
Analytical data is in accordance with literature. [50]

^{1}H NMR (400 MHz, Chloroform-d) δ 7.51 – 7.42 (m, 2H), 7.24 (s, 2H), 7.01 (t, J = 7.3 Hz, 1H), 6.16 – 6.02 (m, 1H), 5.53 – 5.43 (m, 2H), 4.23 (d, J = 5.9 Hz, 2H), 3.80 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5, 132.8, 129.1, 118.7, 118.6, 113.8, 59.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_{13}N_2$: 149.1073; found: 149.1078

N-Allylphenothiazine **(29)** [CAS: 20962-92-9]



Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. The crude product was purified *via* column chromatography (dry load, 6 g, silica, pentane:Et_2O 50:1) to obtain the title compound as a colorless oil (72 mg, 60 %).

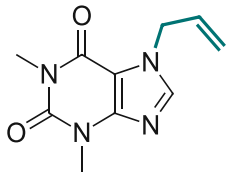
Analytical data is in accordance with literature.[51]

^{1}H NMR (400 MHz, Chloroform-d) δ 7.08 (dd, J = 8.3, 6.7 Hz, 4H), 6.93 – 6.80 (m, 4H), 6.07 – 5.94 (m, 1H), 5.38 – 5.24 (m, 2H), 4.48 (dt, J = 4.2, 2.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 133.3, 127.3, 126.9, 123.2, 122.5, 117.6, 115.4, 51.4.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{15}H_{14}NS$: 240.0841; found: 240.0838

7-Allyl-1,3-dimethylxanthine **(30)** [CAS: 61444-26-6]



Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as a white solid (98 mg, 89 %).

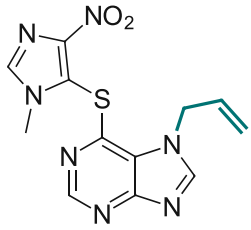
Analytical data is in accordance with literature.[52]

^{1}H NMR (400 MHz, Chloroform-d) δ 7.55 (s, 1H), 6.11 – 5.96 (m, 1H), 5.31 (dq, J = 10.2, 1.2 Hz, 1H), 5.23 (dq, J = 17.0, 1.3 Hz, 1H), 4.93 (dt, J = 5.9, 1.5 Hz, 2H), 3.58 (s, 3H), 3.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 151.8, 148.9, 140.8, 132.2, 119.5, 107.0, 49.1, 29.9, 28.1.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{13}N_4O_2$: 221.1033; found: 221.1035

N-allyl azathioprine **(31)**



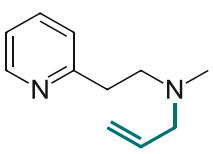
Prepared, following the general procedure C from commercially available starting material with the deviation that short pad silica filtration was conducted using EtOAc:MeOH 10:1 as eluent. Cs_2CO_3 was used as the base. The crude material was purified *via* column chromatography (5 g silica, EtOAc:MeOH 20:1, 10:1) to obtain the title compound as a colorless oil (57 mg, 35 %).

^{1}H NMR (400 MHz, Chloroform-d) δ 8.54 (s, 1H), 8.01 (s, 1H), 7.74 (s, 1H), 6.07 – 5.93 (m, 1H), 5.31 (dq, J = 10.3, 1.2 Hz, 1H), 5.22 (dq, J = 17.0, 1.4 Hz, 1H), 4.85 (dt, J = 5.8, 1.5 Hz, 2H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 152.1, 149.9, 144.1, 138.1, 131.2, 131.1, 119.9, 119.1, 116.9, 46.1, 33.3.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{12}H_{12}N_7O_2S$: 318.0768; found: 318.0772

N-Allylbetahistine **(32)**



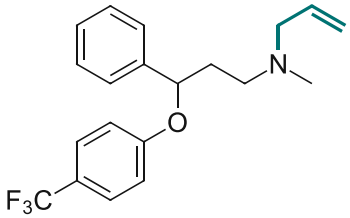
Prepared, following the general procedure C from commercially available starting material with the deviation that 3 equivalents of. Cs_2CO_3 were used as the base, and the short pad silica filtration was conducted using DCM:MeOH 10:1 as the eluent. Without further purification, the title compound was obtained as a slightly yellow oil (86 mg, 98 %).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.46 (m, 1H), 7.57 (td, *J* = 7.7, 1.9 Hz, 1H), 7.16 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.12 – 7.04 (m, 1H), 5.92 – 5.77 (m, 1H), 5.21 – 5.07 (m, 2H), 3.06 (dt, *J* = 6.6, 1.3 Hz, 2H), 3.00 – 2.92 (m, 2H), 2.83 – 2.73 (m, 2H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 149.4, 136.4, 135.7, 123.3, 121.2, 117.7, 61.0, 57.2, 42.1, 36.3.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{11}H_{17}N_2$: 177.1386; found 177.1383

N-Allyl fluoxetine **(33)** [123604-97-7]



Prepared, following the general procedure C from commercially available starting material. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as a yellow oil (134 mg, 77 %)

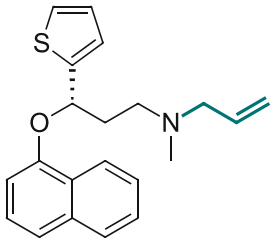
^{1}H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.40 (m, 2H), 7.40 – 7.31 (m, 4H), 7.31 – 7.21 (m, 1H), 6.96 – 6.88 (m, 2H), 5.81 (ddt, J = 16.7, 10.2, 6.5 Hz, 1H), 5.30 (dd, J = 8.3, 4.8 Hz, 1H), 5.16 (dq, J = 17.1, 1.6 Hz, 1H), 5.12 – 5.06 (m, 1H), 3.00 (ddt, J = 6.5, 5.1, 1.3 Hz, 2H), 2.56 (ddt, J = 12.5, 7.9, 6.8 Hz, 1H), 2.46 (ddd, J = 12.5, 8.0, 5.5 Hz, 1H), 2.28 – 2.13 (m, 4H), 2.06 – 1.93 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 141.4, 135.8, 128.9, 127.9, 126.8 (q, *J* = 3.7 Hz), 126.0, 122.8 (q, *J* = 32.6 Hz), 117.5, 115.9, 78.6, 61.1, 53.3, 42.2, 36.7.

^{19}F NMR (376 MHz, Chloroform-d) δ -61.51.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{20}H_{23}NOS$: 350.1726; found: 350.1727

N-Allyl duloxetine **(34)**



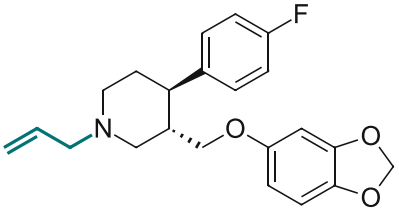
Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a slightly yellow oil (141 mg, 84 %)

^{1}H NMR (400 MHz, Chloroform-d) δ 8.31 – 8.22 (m, 1H), 7.73 – 7.64 (m, 1H), 7.44 – 7.32 (m, 2H), 7.32 – 7.26 (m, 1H), 7.22 – 7.14 (m, 1H), 7.11 (dd, J = 5.0, 1.2 Hz, 1H), 6.97 (dt, J = 3.4, 1.0 Hz, 1H), 6.84 (dd, J = 5.0, 3.5 Hz, 1H), 6.82 – 6.75 (m, 1H), 5.79 – 5.64 (m, 2H), 5.04 (dq, J = 17.1, 1.6 Hz, 1H), 5.00 – 4.92 (m, 1H), 2.91 (dt, J = 6.5, 1.3 Hz, 2H), 2.58 – 2.43 (m, 2H), 2.43 – 2.29 (m, 1H), 2.16 (s, 3H), 2.15 – 2.05 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 145.6, 135.8, 134.7, 127.6, 126.6, 126.4, 126.3, 125.9, 125.3, 124.8, 124.7, 122.4, 120.6, 117.5, 107.2, 74.8, 61.2, 53.3, 42.3, 36.9.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{21}H_{24}NOS$: 338.1573; found 338.1571

N-Allyl paroxetine **(35)**



Prepared, following the general procedure C from commercially available starting material with the deviation that the short pad silica filtration was conducted using DCM:MeOH 20:1 as the eluent. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a red oil (180 mg, 98 %).

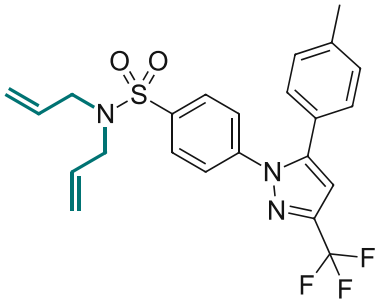
^{1}H NMR (400 MHz, Chloroform-d) δ 7.21 – 7.11 (m, 2H), 7.01 – 6.91 (m, 2H), 6.61 (d, J = 8.5 Hz, 1H), 6.34 (d, J = 2.5 Hz, 1H), 6.12 (dd, J = 8.5, 2.5 Hz, 1H), 6.01 – 5.84 (m, 3H), 5.30 – 5.13 (m, 2H), 3.57 (dd, J = 9.4, 2.9 Hz, 1H),

3.45 (dd, J = 9.4, 6.9 Hz, 1H), 3.31 – 3.22 (m, 1H), 3.15 – 3.00 (m, 3H), 2.47 (td, J = 11.2, 5.1 Hz, 1H), 2.27 – 2.14 (m, 1H), 2.10 – 1.96 (m, 2H), 1.94 – 1.76 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6 (d, *J* = 244.2 Hz), 154.5, 148.2, 141.6, 139.8 (d, *J* = 3.2 Hz), 135.2, 128.9 (d, *J* = 7.8 Hz), 118.1, 115.5 (d, *J* = 21.1 Hz), 107.9, 105.7, 101.2, 98.1, 69.7, 62.3, 57.6, 54.1, 44.2, 42.3, 34.5.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{22}H_{25}FNO_3$: 370.1813; found: 370.1811.

N,N-Diallyl celecoxib **(36)**



Prepared, following the general procedure C from commercially available starting material with the deviation that 2.5 equivalents of allyl trimethylammonium chloride, and 3 equivalents of Cs_2CO_3 were used. The crude product was purified *via* column chromatography (10 g silica, pentane:EtOAc 20:1, 10:1) to obtain the title compound as colorless oil (201 mg, 87 %)

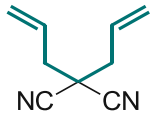
^{1}H NMR (400 MHz, Chloroform-d) δ 7.85 – 7.77 (m, 2H), 7.50 – 7.42 (m, 2H), 7.20 – 7.13 (m, 2H), 7.13 – 7.05 (m, 2H), 6.74 (s, 1H), 5.66 – 5.51 (m, 2H), 5.20 – 5.10 (m, 4H), 3.81 (dt, J = 6.3, 1.4 Hz, 4H), 2.38 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 144.2 (q, *J* = 38.5 Hz), 142.4, 140.2, 139.9, 132.2, 129.8, 128.8, 128.3, 125.8, 125.7, 121.2 (q, *J* = 269.1 Hz), 119.5, 106.3, 49.4, 21.4.

^{19}F NMR (376 MHz, Chloroform-d) δ -62.42.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{23}H_{23}F_3N_3O_2S$: 462.1458; found: 462.1453.

2,2-Diallylmalononitrile **(37)** [CAS: 90557-34-9]



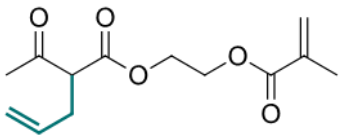
Prepared, following the general procedure C from commercially available starting material with the deviation that 2.5 equivalents of allyl trimethylammonium chloride were used. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a yellow oil (73 mg, 99 %) yellow oil

Analytical data is in accordance with literature. [53]

^{1}H NMR (400 MHz, Chloroform-d) δ 5.97 – 5.82 (m, 2H), 5.48 – 5.36 (m, 4H), 2.68 (dt, J = 7.3, 1.1 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 128.5, 123.5, 115.0, 41.0, 37.4.

2-(Isopropenylcarbonyloxy)ethyl 2-acetyl-4-pentenoate **(38)**



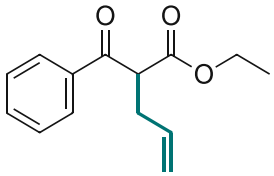
Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. The crude product was purified *via* column chromatography (6 g, silica, pentane:EtOAc 30:1 – 10:1) to obtain the title compound as a yellow oil (37 mg, 24 %)

^{1}H NMR (400 MHz, Chloroform-d) δ 6.11 (dq, J = 2.0, 1.1 Hz, 1H), 5.81 – 5.66 (m, 1H), 5.60 (p, J = 1.6 Hz, 1H), 5.09 (dq, J = 17.1, 1.6 Hz, 1H), 5.04 (dq, J = 10.2, 1.3 Hz, 1H), 4.46 – 4.30 (m, 4H), 3.56 (t, J = 7.4 Hz, 1H), 2.67 – 2.53 (m, 2H), 2.23 (s, 3H), 1.94 (dd, J = 1.6, 1.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1, 169.2, 167.1, 136.0, 134.2, 126.3, 117.8, 63.1, 62.2, 59.2, 32.3, 29.3, 18.4.

HRMS (ESI): m/z $[M+Na]^+$ calcd. for $C_{13}H_{18}NaO_5$: 277.1046; found: 277.1047

Ethyl 2-benzoylpent-4-enoate **(39)** [CAS: 63202-75-5]



Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. The crude product was purified *via* column chromatography (6 g, silica, pentane:Et_2O 100:1 – 30:1) to obtain the title compound as colorless oil (91 mg, 78 %).

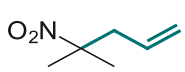
Analytical data is in accordance with literature.[54]

^{1}H NMR (400 MHz, Chloroform-d) δ 8.03 – 7.95 (m, 2H), 7.62 – 7.53 (m, 1H), 7.52 – 7.42 (m, 2H), 5.89 – 5.74 (m, 1H), 5.11 (dq, J = 17.1, 1.5 Hz, 1H), 5.03 (dq, J = 10.2, 1.3 Hz, 1H), 4.39 (t, J = 7.2 Hz, 1H), 4.14 (qd, J = 7.1, 2.0 Hz, 2H), 2.83 – 2.67 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6, 169.5, 136.3, 134.6, 133.6, 128.8, 128.7, 117.5, 61.6, 54.0, 33.1, 14.1.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{17}O_3$: 233.1172; found: 233.1170

4-Methyl-4-nitro-1-pentene **(40)** [CAS: 81500-64-3]



Prepared, following the general procedure C from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (45 mg, 70 %).

Analytical data is in accordance with literature. [55]

^{1}H NMR (400 MHz, Chloroform-d) δ 5.76 – 5.61 (m, 1H), 5.22 – 5.10 (m, 2H), 2.64 (dd, J = 7.5, 1.4 Hz, 2H), 1.59 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 131.2, 120.5, 87.9, 5.12, 25.6.

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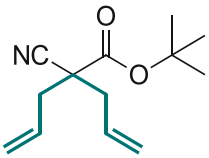
tert-Butyl 2-allyl-2-cyano-4-pentenoate **(41)**



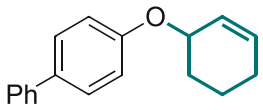
Prepared, following the general procedure C from commercially available starting material with the deviation that 2.5 equivalents of allyl trimethylammonium chloride were used. Cs_2CO_3 was used as the base. Without further purification, the title compound was obtained as a colorless oil (105 mg, 95 %).

^{1}H NMR (400 MHz, Chloroform-d) δ 5.89 – 5.74 (m, 2H), 5.28 – 5.18 (m, 4H), 2.66 – 2.55 (m, 2H), 2.55 – 2.44 (m, 2H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 130.8, 120.8, 118.9, 84.3, 49.8, 40.9, 28.0.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{20}NO_2$: 222.1489; found: 222.1486

3-(4-Biphenylyloxy)cyclohexene **(42)**



Prepared, following the general procedure D from commercially available starting material. K_2CO_3 was used as the base. The crude material was purified *via* column chromatography (dry load, 5 g silica, pentane:EtOAc 50:1) to obtain the title compound as a white solid (108 mg, 86 %).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.63 – 7.51 (m, 4H), 7.49 – 7.40 (m, 2H), 7.37 – 7.29 (m, 1H), 7.08 – 7.00 (m, 2H), 6.03 (dtd, J = 10.1, 3.6, 1.2 Hz, 1H), 5.94 (dq, J = 10.1, 2.3 Hz, 1H), 4.92 – 4.83 (m, 1H), 2.26 – 1.83 (m, 5H), 1.76 – 1.62 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 141.0, 133.8, 132.4, 128.8, 128.3, 126.8, 126.7, 126.4, 116.2, 71.1, 28.4, 25.2, 19.1.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{18}H_{19}O$: 251.1430; found 251.1431

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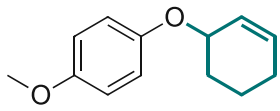
p-(2-Cyclohexen-1-yloxy)methoxybenzene **(43)** [CAS: 175735-18-9]



Prepared, following the general procedure D from commercially available starting material. K_2CO_3 was used as the base. The crude material was purified *via* column chromatography (dry load, 5 g silica, pentane:EtOAc 80:1) to obtain the title compound as a colorless oil (75 mg, 74 %)

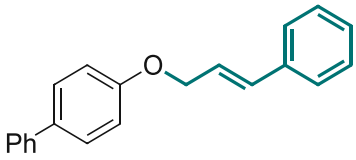
Analytical data is in accordance with literature.[1a]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 – 6.78 (m, 4H), 6.00 – 5.91 (m, 1H), 5.87 (dq, *J* = 10.0, 2.3 Hz, 1H), 4.72 – 4.63 (m, 1H), 3.77 (s, 3H), 2.20 – 1.77 (m, 5H), 1.71 – 1.55 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 152.0, 132.0, 126.8, 117.5, 114.8, 72.1, 55.8, 28.5, 25.3, 19.1.

HRMS (ESI): m/z $[M+Na]^+$ calcd. for $C_{13}H_{16}NaO_2$: 227.1043; found: 227.1048.

(E)-Cinnamyl 1,1'-biphenyl ether **(44)** [CAS: 2410719-96-7]



Prepared, following the general procedure D from commercially available starting material. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as a slightly yellow oil (137 mg, 96 %).

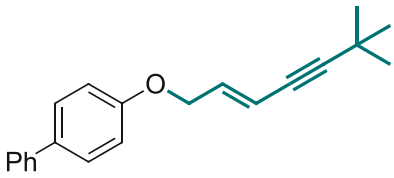
Analytical data is in accordance with literature. [56]

^{1}H NMR (400 MHz, Chloroform-d) δ 7.61 – 7.51 (m, 4H), 7.48 – 7.38 (m, 4H), 7.38 – 7.26 (m, 4H), 7.09 – 7.01 (m, 2H), 6.77 (dt, J = 16.0, 1.6 Hz, 1H), 6.46 (dt, J = 16.0, 5.8 Hz, 1H), 4.76 (dd, J = 5.8, 1.5 Hz, 2H).

^{13}C NMR (101 MHz, CDCl3) δ 158.3, 140.9, 136.5, 134.1, 133.2, 128.8, 128.7, 128.3, 128.0, 126.8, 126.8, 126.7, 124.5, 115.2, 68.8.

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 140.9, 136.6, 134.1, 133.2, 128.9, 128.8, 128.3, 128.1, 126.9, 126.8, 126.7, 124.6, 115.2, 68.9

4-[(E)-6,6-Dimethyl-2-hepten-4-ynyloxy]biphenyl **(45)**



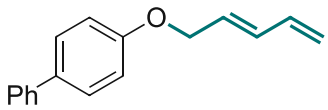
Prepared, following the general procedure D from commercially available starting material with the deviation that 2 mol% of $Pd[(allyl)Cl]_2$ and 4 mol% of *rac*-BINAP were used. K_2CO_3 was used as the base. Without further purification, the title compound was obtained as yellow solid (144 mg, 99 %).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.61 – 7.49 (m, 4H), 7.43 (t, J = 7.7 Hz, 2H), 7.36 – 7.27 (m, 1H), 7.02 – 6.94 (m, 2H), 6.24 (dt, J = 15.9, 5.5 Hz, 1H), 5.88 (dt, J = 15.9, 1.7 Hz, 1H), 4.61 (dd, J = 5.5, 1.7 Hz, 2H), 1.27 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 140.9, 135.9, 134.2, 128.9, 128.3, 126.9, 126.8, 115.1, 113.5, 100.3, 76.8, 68.0, 31.1, 28.1.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{21}H_{23}O$: 291.1743; found: 291.1742

4-biphenylyl 2,4-pentadienyl ether **(46)** [CAS: 103993-00-6]



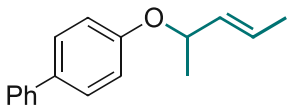
Prepared, following the general procedure D from commercially available starting material. K_2CO_3 was used as the base. The crude material was purified *via* column chromatography (5 g silica, pentane:Et_2O 100:1) to obtain the title compound as white solid (96 mg, 81 %)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.60 – 7.50 (m, 4H), 7.47 – 7.39 (m, 2H), 7.36 – 7.29 (m, 1H), 7.05 – 6.96 (m, 2H), 6.49 – 6.33 (m, 2H), 6.02 – 5.90 (m, 1H), 5.35 – 5.23 (m, 1H), 5.23 – 5.12 (m, 1H), 4.63 (d, J = 5.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 140.9, 136.2, 134.1, 133.9, 128.9, 128.5, 128.3, 126.9, 126.8, 118.4, 115.2, 68.3.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{17}H_{17}O$: 237.1274; found: 237.1276

4-[(E)-1-Methyl-2-butenyloxy]biphenyl **(47)**



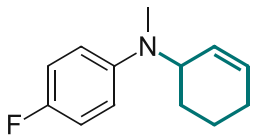
Prepared, following the general procedure D from commercially available starting material. K_2CO_3 was used as the base. The crude material was purified *via* column chromatography (5 g silica, pentane:EtOAc 80:1) to obtain the title compound as a colorless oil (83 mg, 70 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2H), 7.57 – 7.50 (m, 2H), 7.45 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.38 – 7.29 (m, 1H), 7.06 – 6.96 (m, 2H), 5.86 – 5.73 (m, 1H), 5.62 (ddq, *J* = 15.4, 6.5, 1.6 Hz, 1H), 4.85 (p, *J* = 6.4 Hz, 1H), 1.84 – 1.72 (m, 3H), 1.48 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 141.0, 133.7, 132.3, 128.8, 128.1, 127.5, 126.8, 126.7, 116.4, 74.6, 21.7, 17.9.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{17}H_{19}O$: 239.1430; found: 239.1435.

N-2-Cyclohexen-1-yl-N-methyl(p-fluorophenyl)amine **(48)**



Prepared, following the general procedure D from commercially available starting material. Cs_2CO_3 was used as the base. The crude material was purified *via* column chromatography (5 g silica, pentane:Et_2O 95:5) to obtain the title compound as yellow oil (52 mg, 51 %)

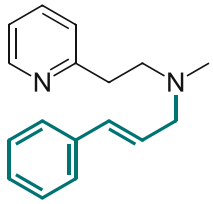
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 – 6.88 (m, 2H), 6.78 – 6.62 (m, 2H), 5.96 – 5.84 (m, 1H), 5.68 – 5.59 (m, 1H), 4.39 – 4.29 (m, 1H), 2.74 (s, 3H), 2.04 (dq, *J* = 5.5, 2.8 Hz, 2H), 1.88 – 1.73 (m, 2H), 1.72 – 1.50 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (d, *J* = 235.2 Hz), 146.7, 130.8, 130.0, 115.6 (d, *J* = 21.9 Hz), 114.5 (d, *J* = 7.1 Hz), 56.2, 33.0, 25.1, 21.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -129.20.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{17}FN$: 206.1340; found: 206.1336.

N-Methyl[2-(2-pyridyl)ethyl][*(E)*-3-phenyl-2-propenyl]amine **(49)**



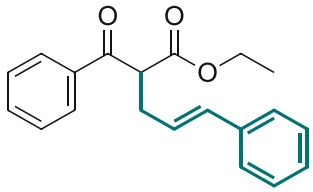
Prepared, following the general procedure D from commercially available starting material with the deviation that 3 equivalents of Cs_2CO_3 were used as the base and silica filtration was conducted using DCM:MeOH 20:1 as eluent.. The crude material was purified *via* column chromatography (5 g silica, DCM:MeOH 10:1) to obtain the title compound as yellow oil (91 mg, 72 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.64 (td, *J* = 7.6, 1.9 Hz, 1H), 7.47 – 7.33 (m, 4H), 7.33 – 7.20 (m, 2H), 7.16 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 6.58 (dt, *J* = 16.0, 1.5 Hz, 1H), 6.34 (dt, *J* = 15.9, 6.7 Hz, 1H), 3.31 (dd, *J* = 6.7, 1.4 Hz, 2H), 3.08 (dd, *J* = 9.4, 6.2 Hz, 2H), 2.98 – 2.87 (m, 2H), 2.43 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 149.3, 137.1, 136.4, 132.6, 128.5, 127.4, 127.3, 126.3, 123.2, 121.3, 60.2, 57.2, 42.1, 36.3.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{17}H_{21}N_2$: 253.1700; found: 253.1697.

Ethyl [(E)-3-phenyl-2-propenyl]benzoylacetate **(50)**



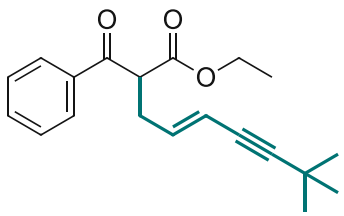
Prepared, following the general procedure D from commercially available starting material. K_2CO_3 was used as the base. The crude material was purified *via* column chromatography (5 g silica, pentane:Et_2O 100:1, 50:1, 20:1, 10:1) to obtain the title compound as a colorless oil (91 mg, 59 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.95 (m, 2H), 7.65 – 7.54 (m, 1H), 7.53 – 7.42 (m, 2H), 7.33 – 7.24 (m, 4H), 7.23 – 7.16 (m, 1H), 6.49 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.20 (dt, *J* = 15.7, 7.2 Hz, 1H), 4.46 (dd, *J* = 7.6, 6.8 Hz, 1H), 4.16 (qd, *J* = 7.1, 2.7 Hz, 2H), 3.01 – 2.83 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6, 169.5, 137.2, 136.3, 133.7, 132.8, 128.9, 128.8, 128.6, 127.5, 126.3, 126.2, 61.6, 54.5, 32.5, 14.2.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{20}H_{21}O_3$: 309.1485; found: 309.1485.

Ethyl *(E)*-2-benzoyl-8,8-dimethyl-4-nonen-6-ynoate **(51)**

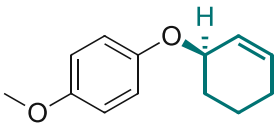


Prepared, following the general procedure D from commercially available starting material. K_2CO_3 was used as the base. The crude material was purified *via* column chromatography (5 g silica, pentane:Et_2O 70:1, 50:1, 20:1, 10:1) to obtain the title compound as a colorless oil (90 mg, 58 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.91 (m, 2H), 7.58 (tq, *J* = 6.9, 1.7 Hz, 1H), 7.52 – 7.42 (m, 2H), 5.99 (dt, *J* = 15.7, 7.3 Hz, 1H), 5.57 (dt, *J* = 15.7, 1.5 Hz, 1H), 4.35 (t, *J* = 7.2 Hz, 1H), 4.13 (qd, *J* = 7.1, 1.3 Hz, 2H), 2.84 – 2.68 (m, 2H), 1.22 – 1.11 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 169.2, 138.0, 136.1, 133.7, 128.9, 128.8, 113.2, 98.4, 77.1, 61.7, 54.0, 32.2, 31.1, 27.9, 14.1.

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{20}H_{25}O_3$: 313.1798; found: 313.1799.



***(R)*-43**

(R)-Cyclohex-2-enyl 4'-methoxyphenyl ether ***(R)*-43** [CAS: 854735-43-6]

Prepared, following the general procedure D from commercially available starting material with the deviation that *(R)*-SEGPHOS (CAS: 244261-66-3) was used as the ligand. K_2CO_3 was used as the base. The crude material was purified *via* column chromatography (dry load on celite, 5 g silica, pentane:Et_2O 80:1) to obtain the enantioenriched titlecompound as a colorless oil (74 mg, 73 %, 52 % ee).

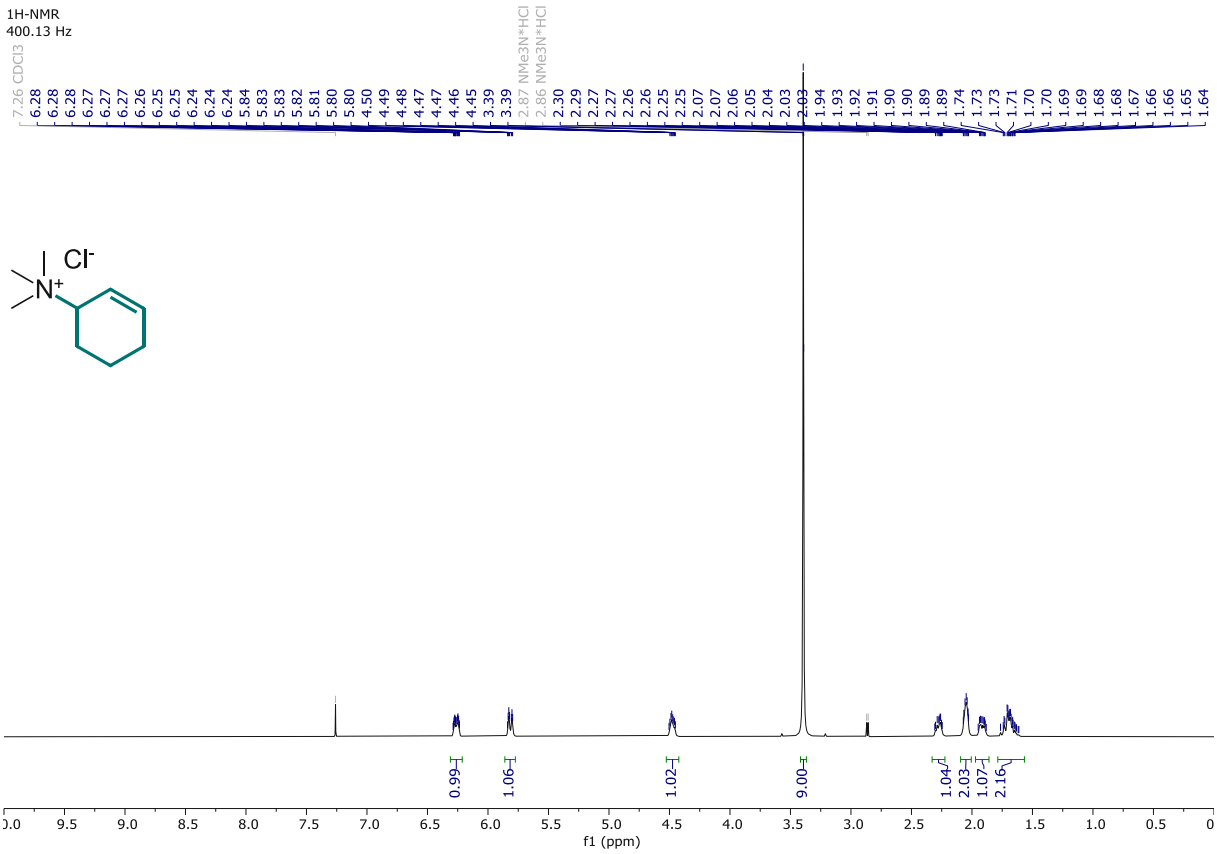
NMR-Spectra matched with the spectra obtained for rac-**43**.

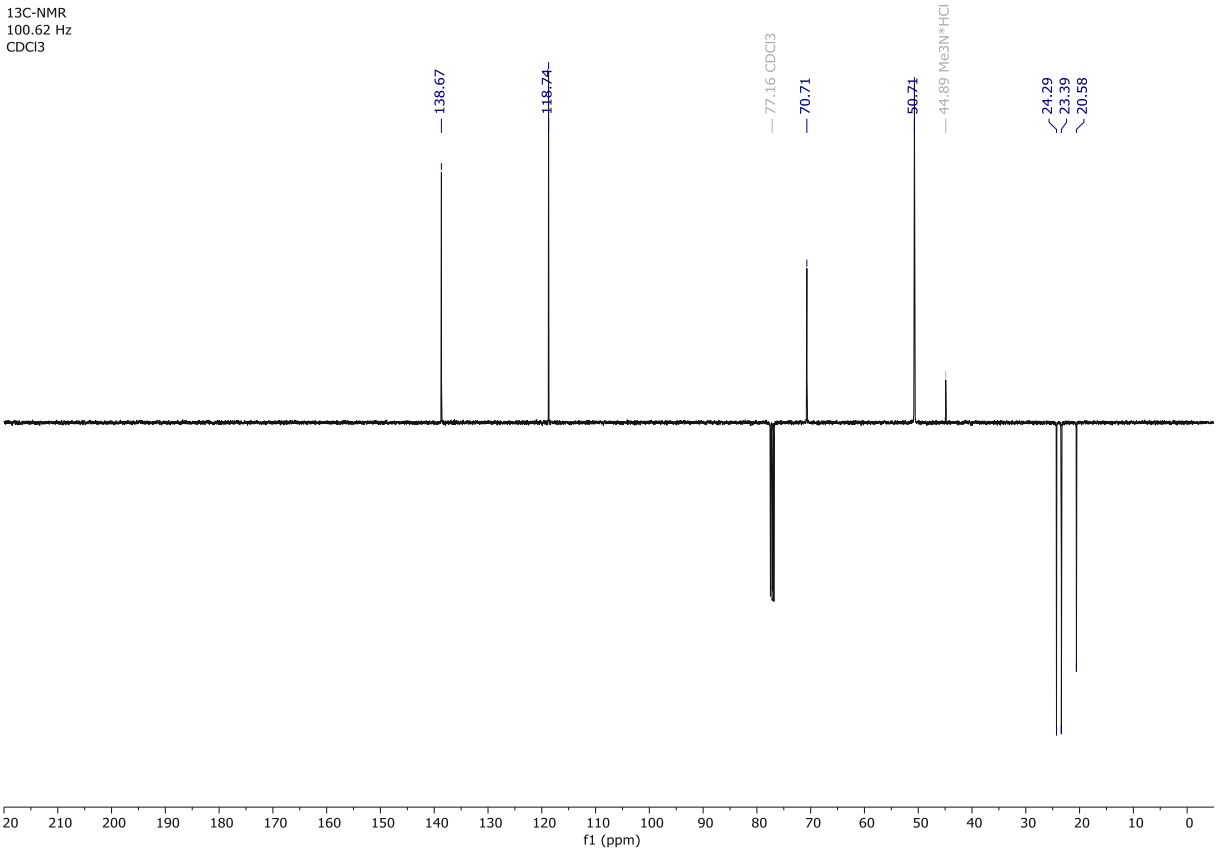
$[\alpha]_D^{20}$ +63.84 (c = 1.0, $CHCl_3$)

The enantiomers were separated using CHIRALCEL OD column eluting with 99.5:0.5 heptane:iso-propanol at 1.0 mL/min. Retention times for racemic mixture: ***(R)*-43** 10.87 min; ***(S)*-43** 13.70 min. Retention times major isomer *(R)* 10.89 min; minor isomer *(S)* 13.64 min. The absolute configurations of the major isomers were assigned based on reported data in literature. [27]

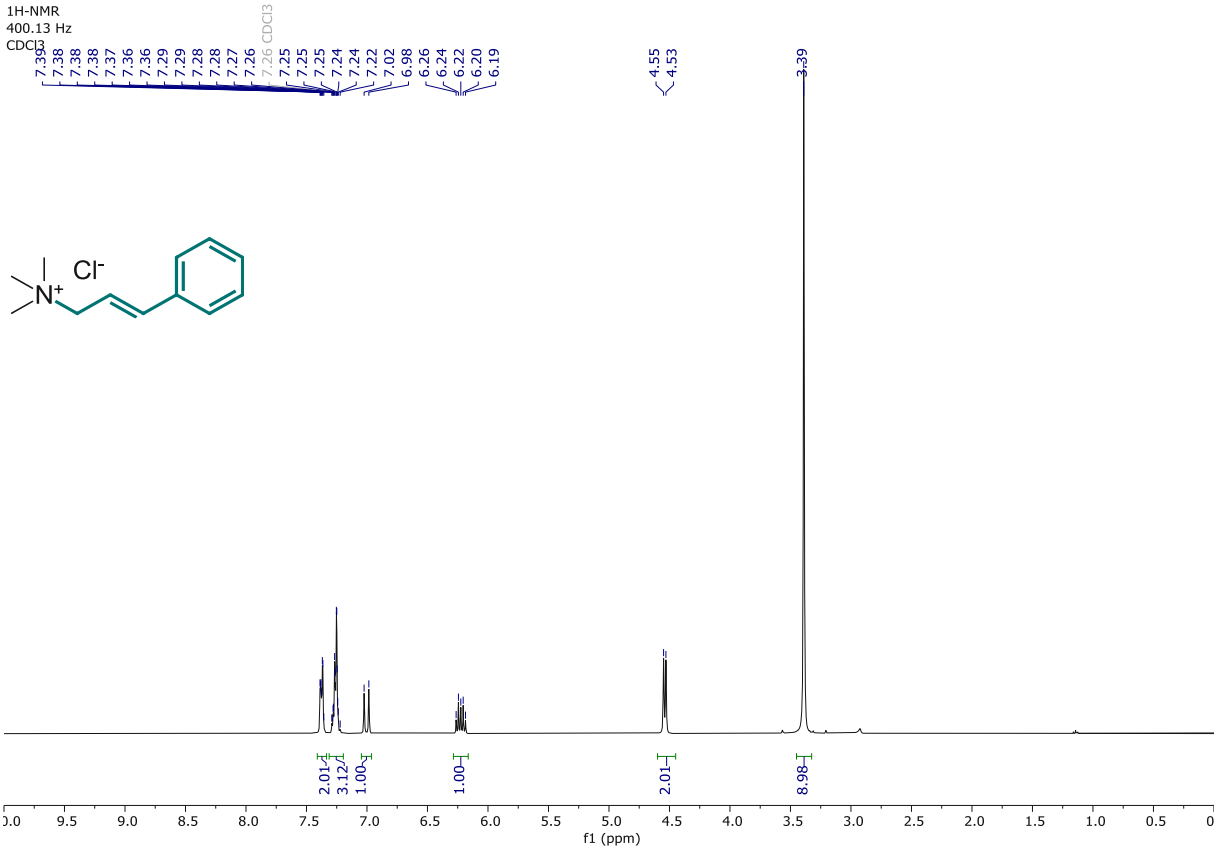
NMR-Spectra

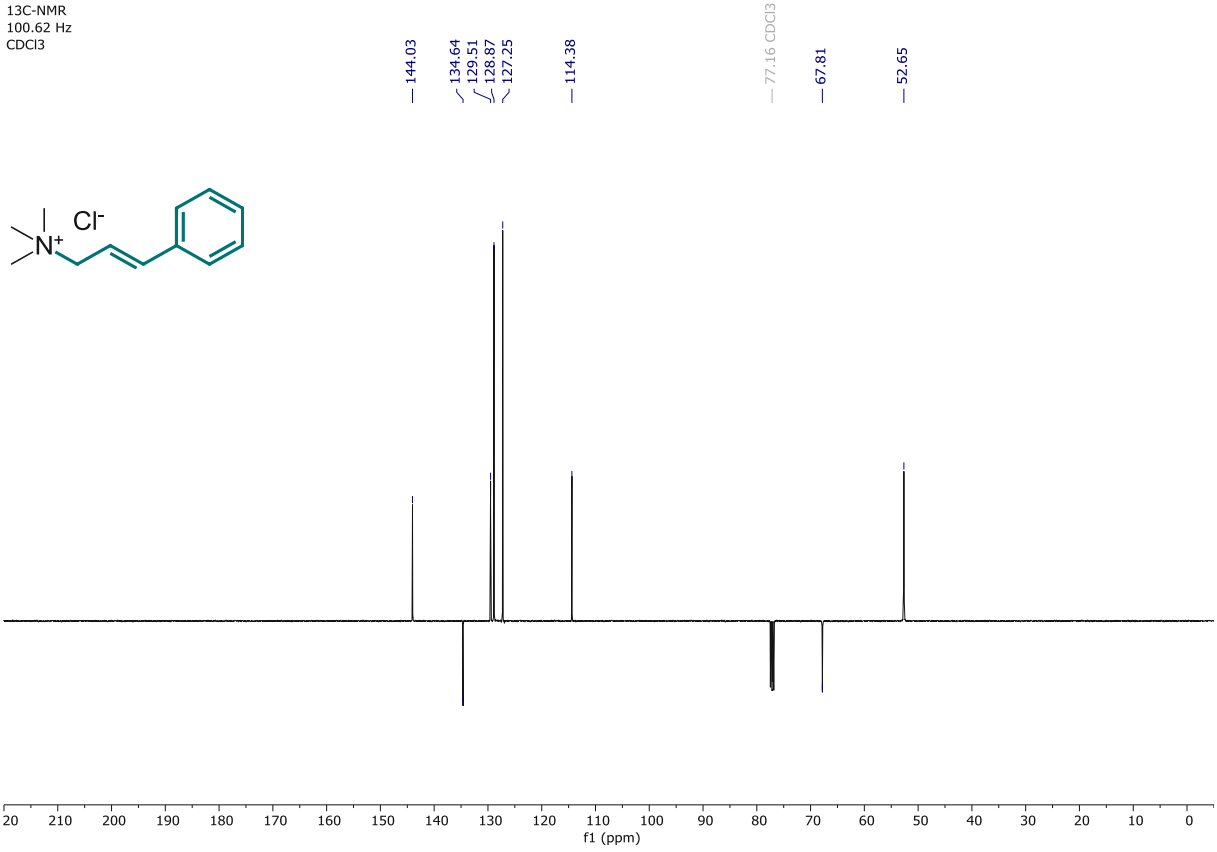
2-Cyclohexen-1-yltrimethylammonium chloride **(III)**



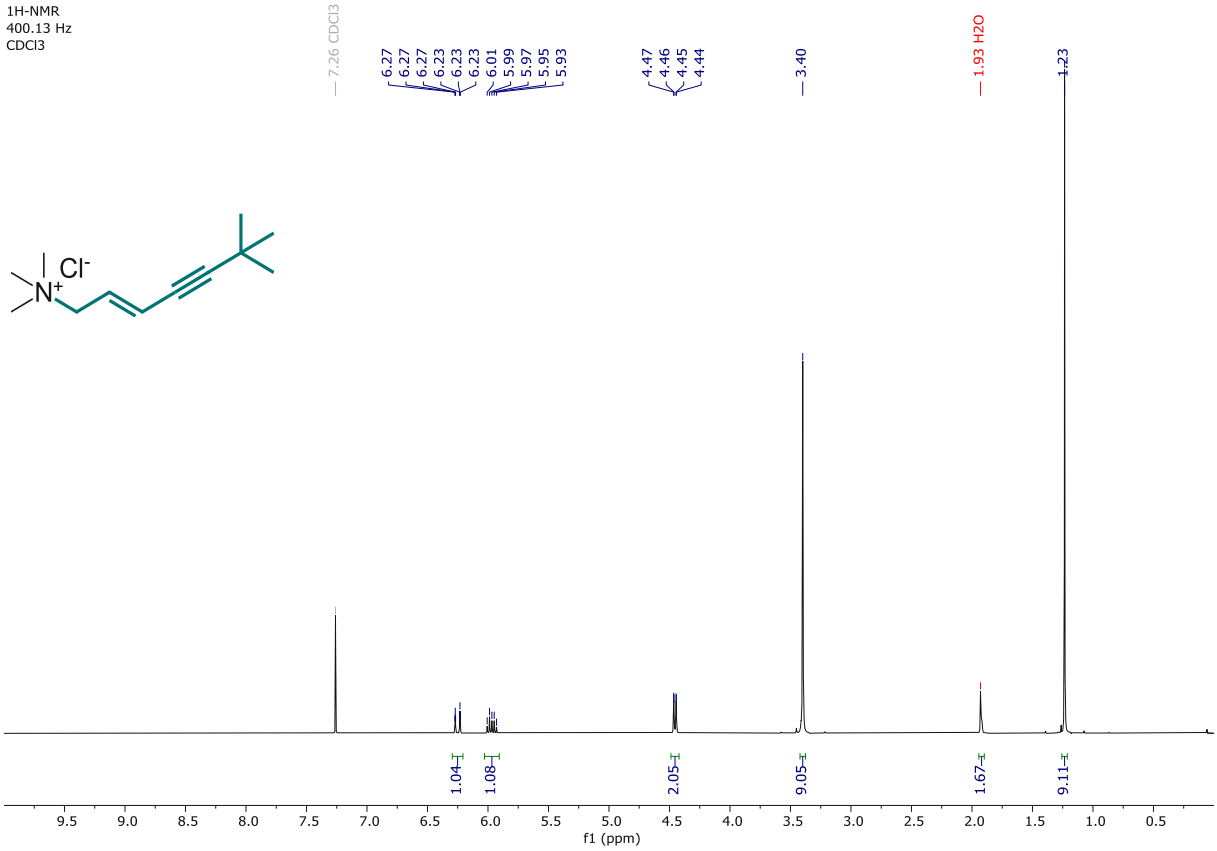


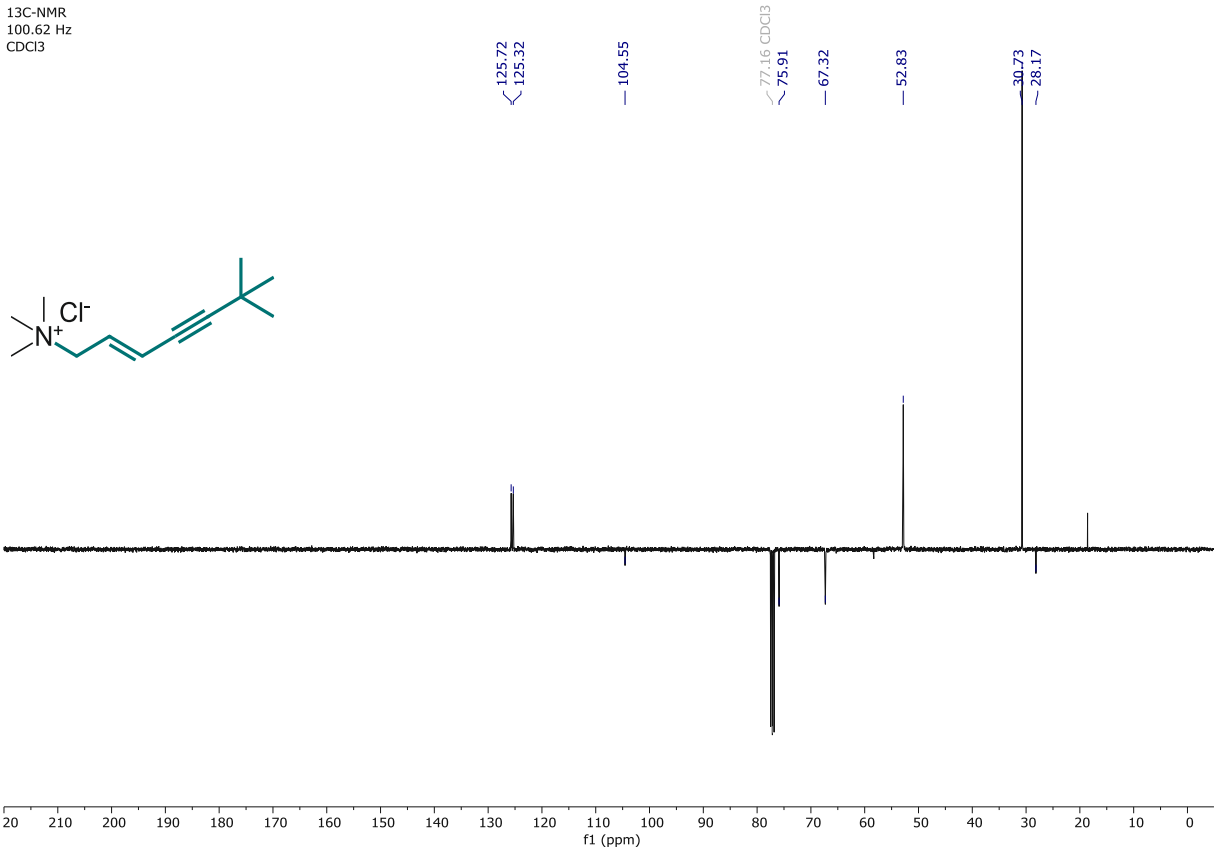
(3-Phenyl-2-propenyl)trimethylammonium chloride **(IV)**



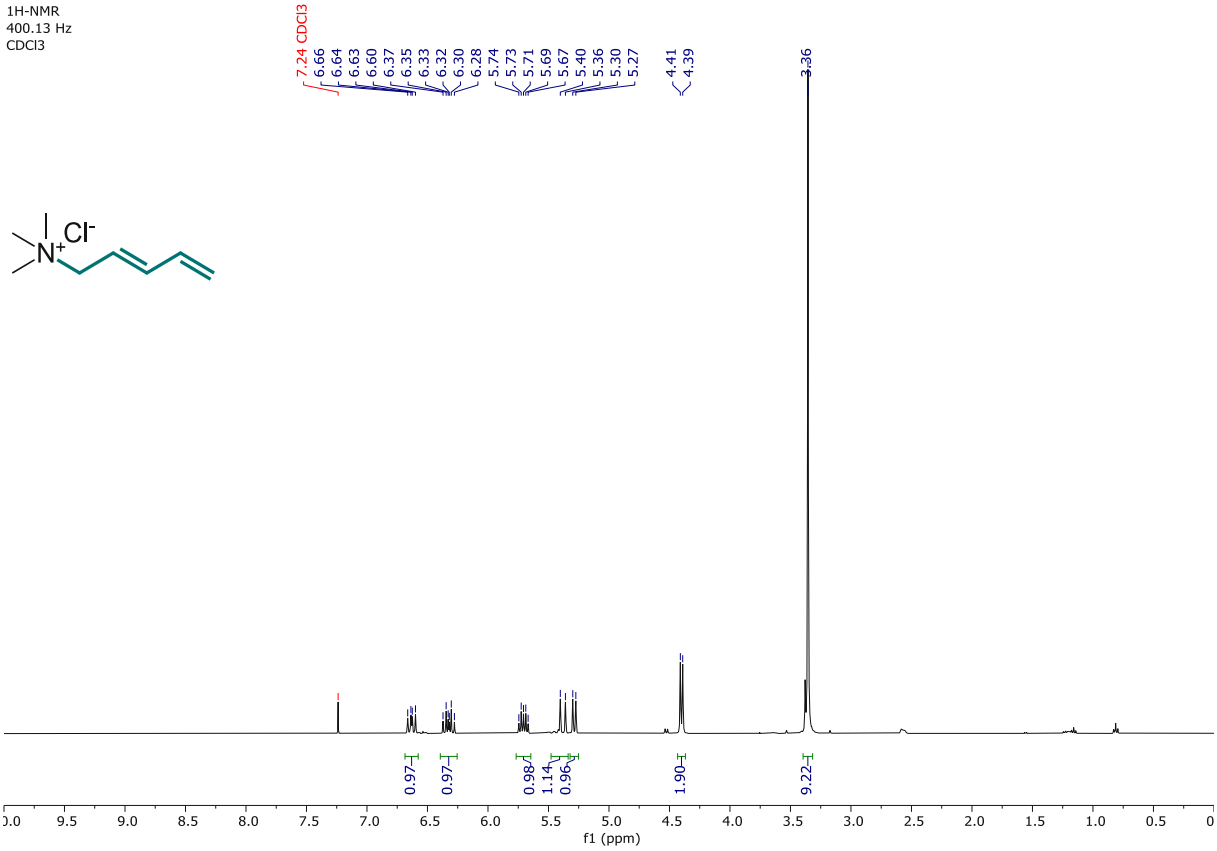


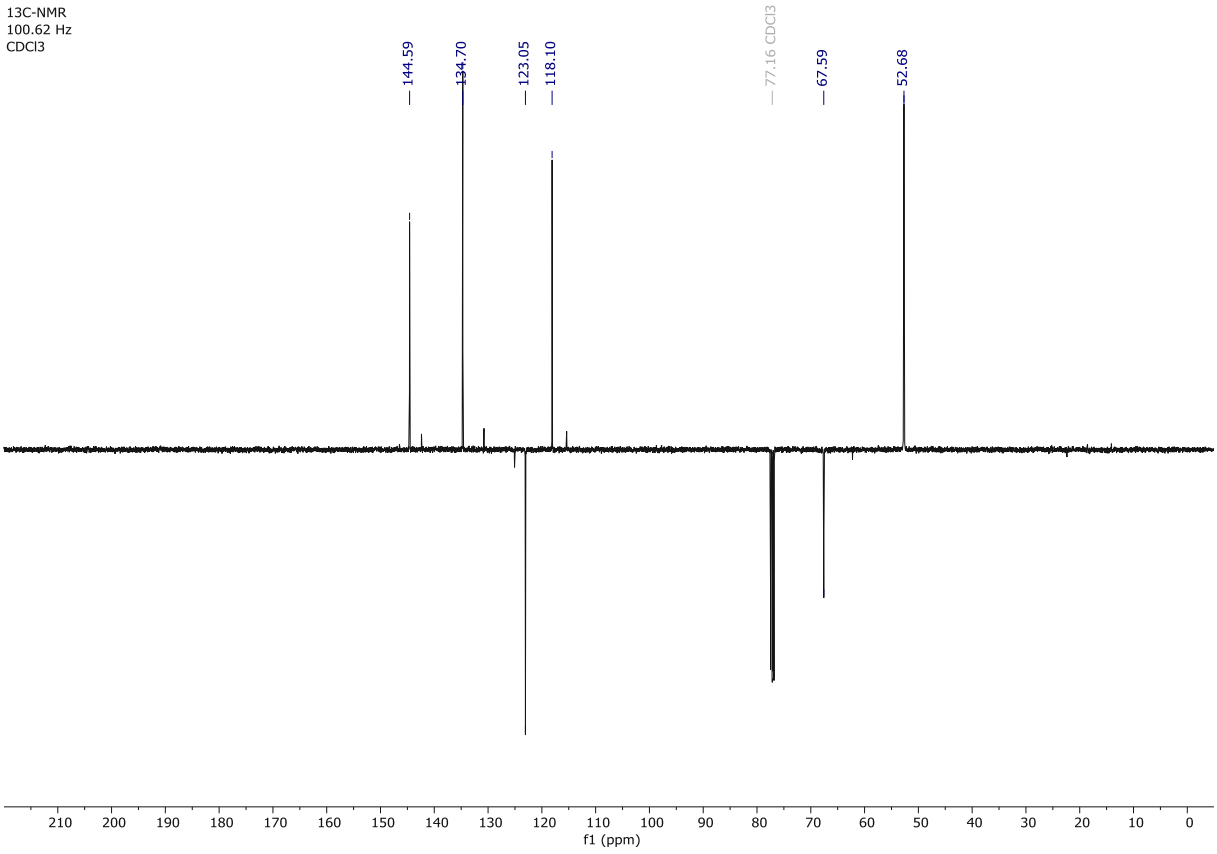
(6,6-Dimethyl-2-hepten-4-ynyl)trimethylammonium chloride **(V)**



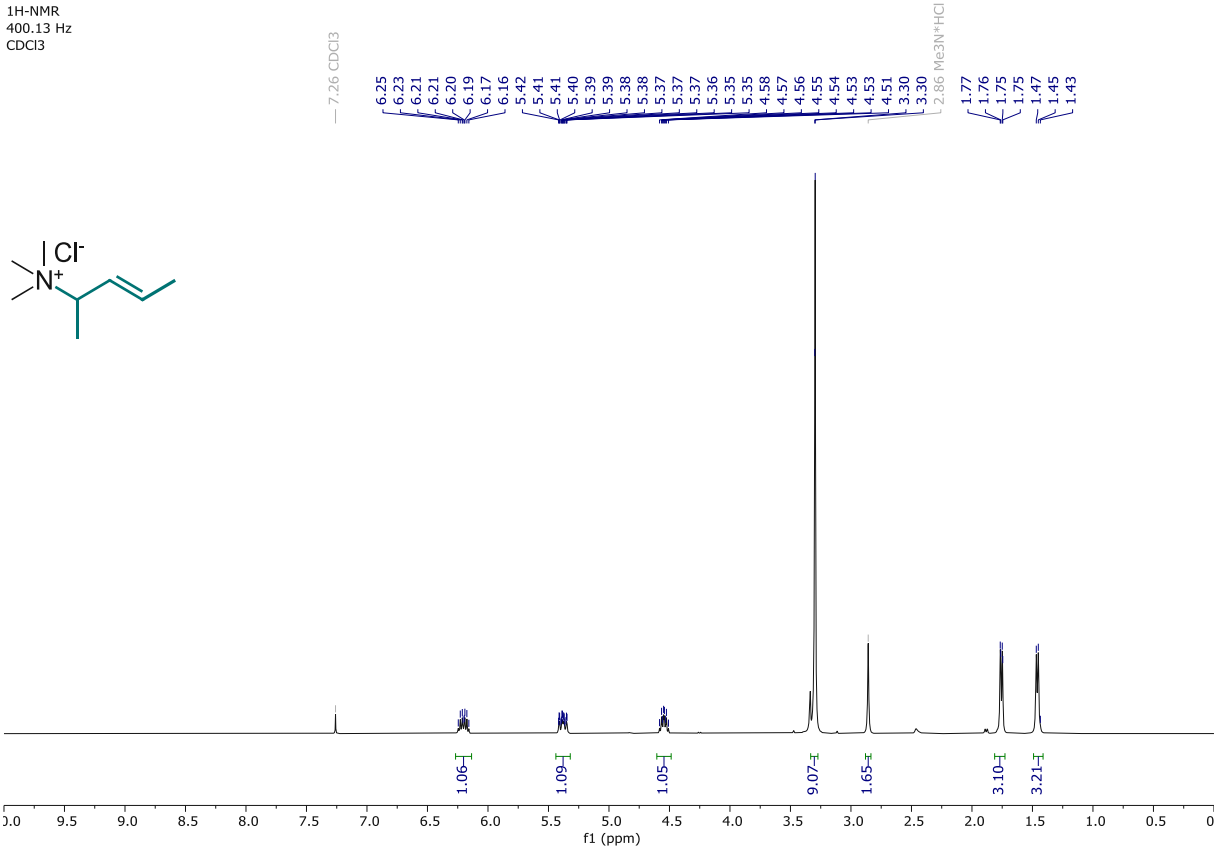


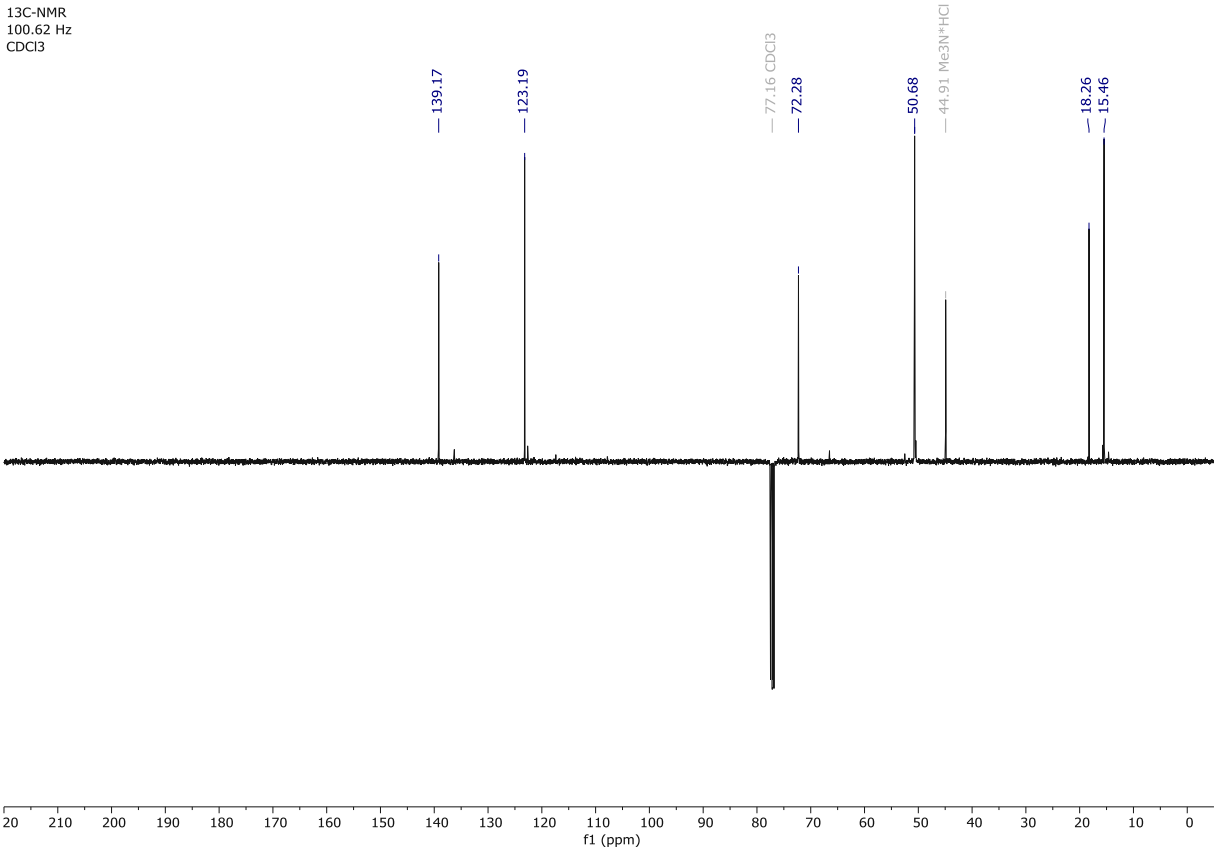
2,4-Pentadienyltrimethylammonium chloride **(VI)**



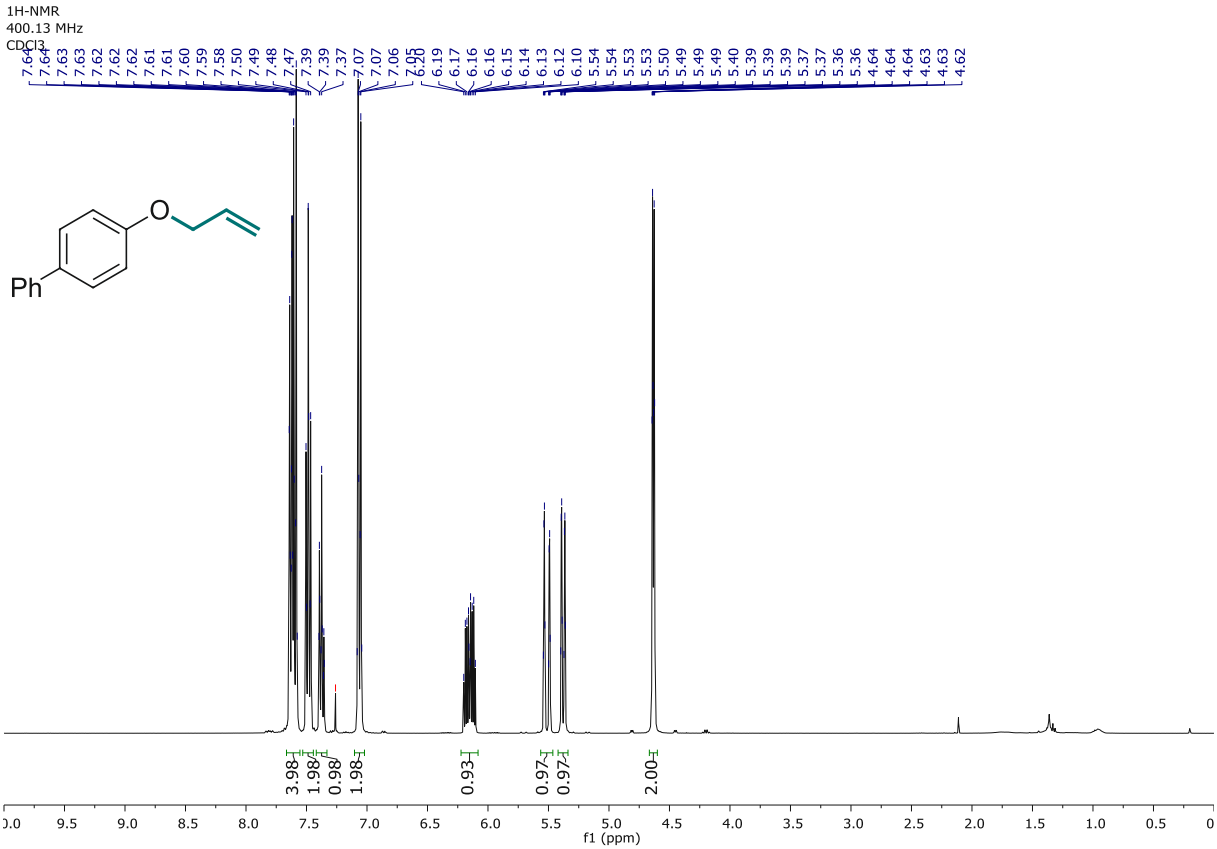


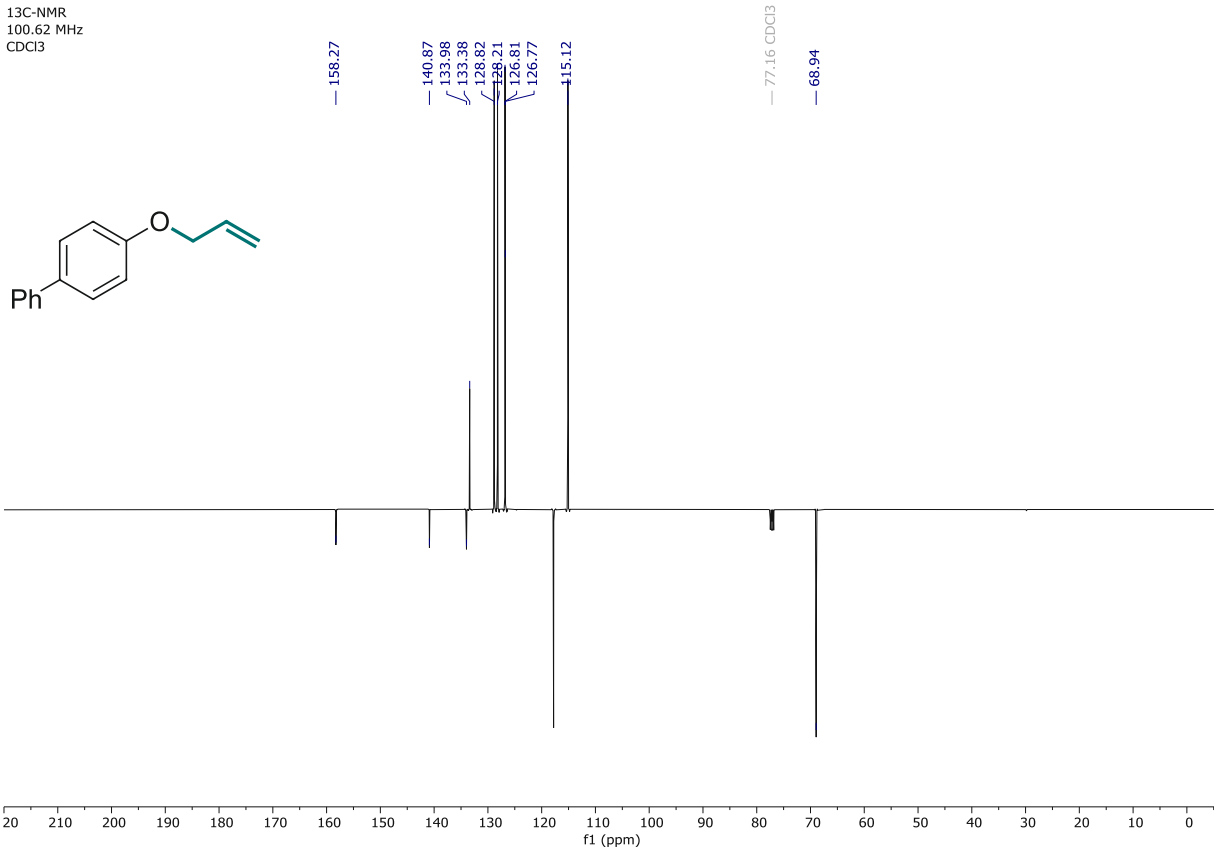
(1-Methyl-2-butenyl)trimethylammonium chloride **(VII)**



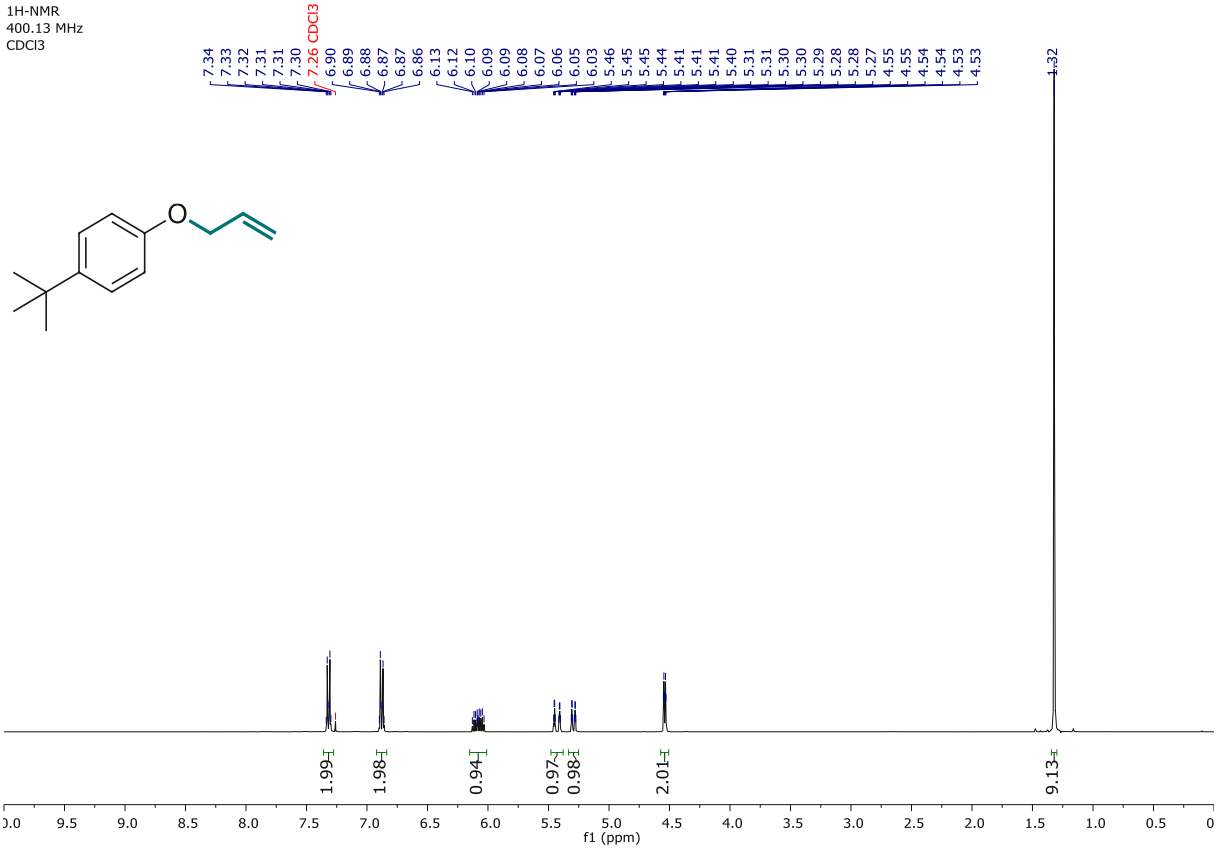


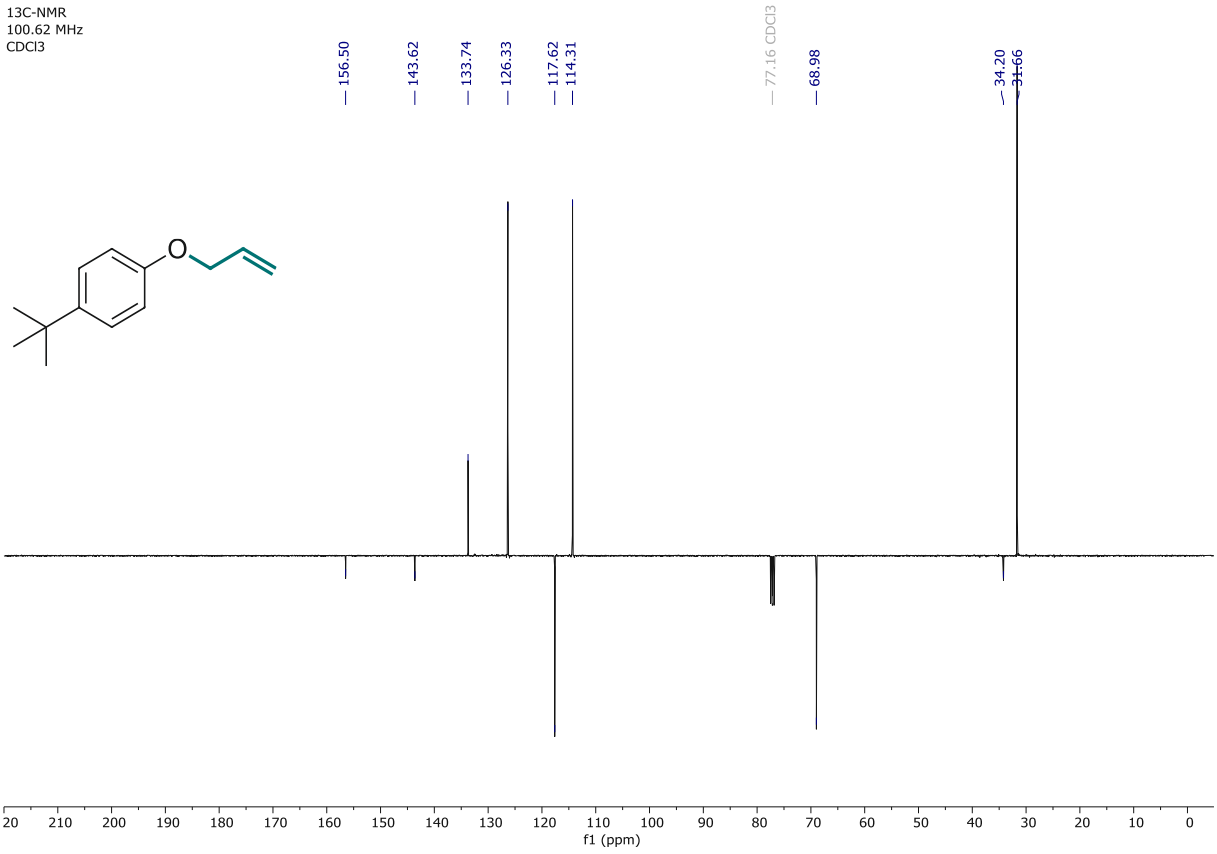
4-Allyloxy-biphenyl (**1**)



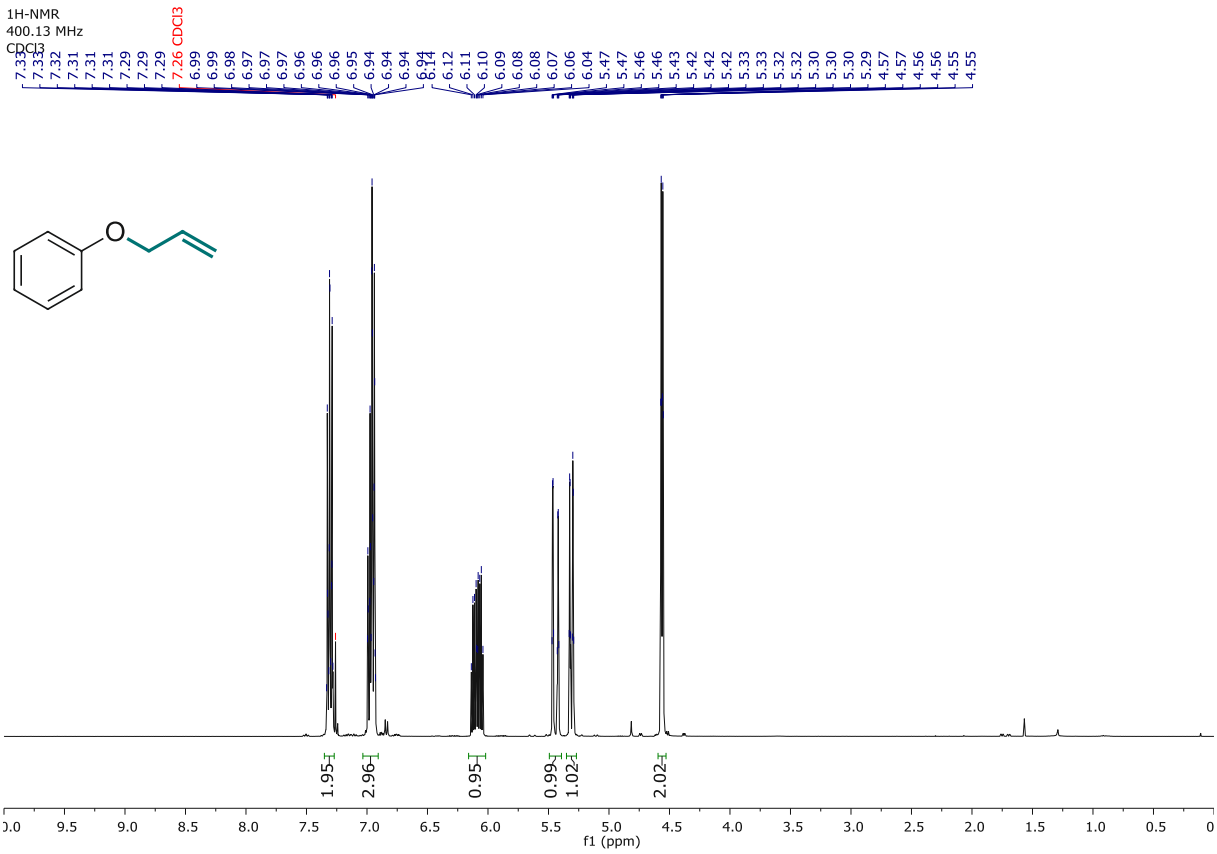


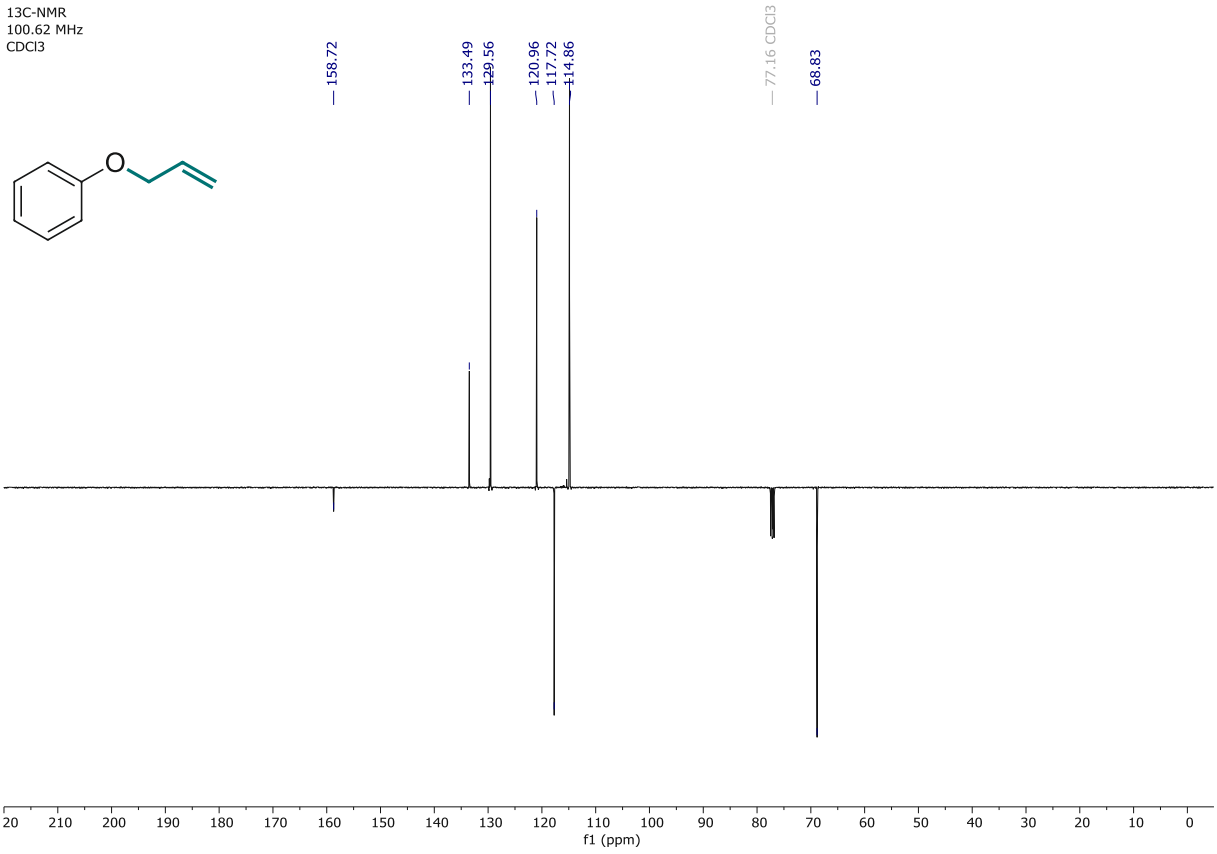
Allyl 4-(tert-butyl)phenyl ether **(2)**



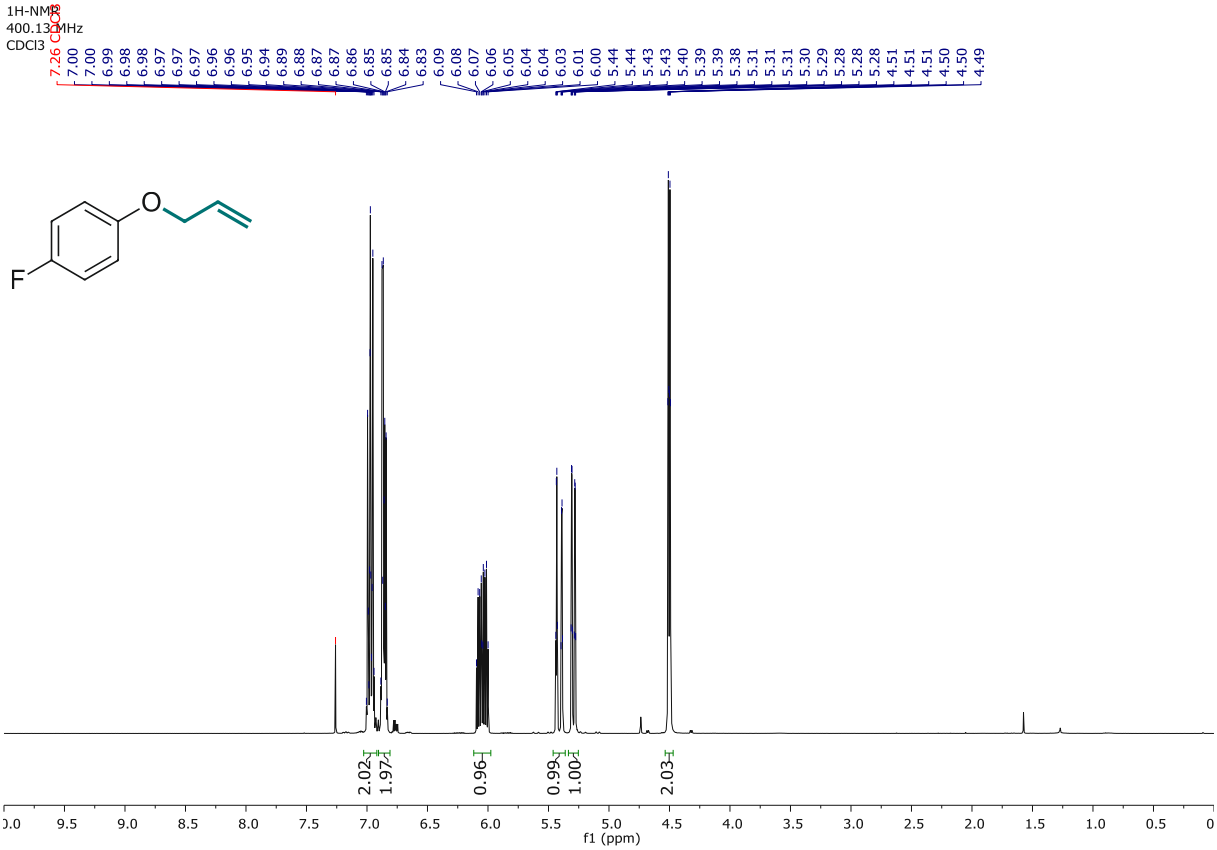


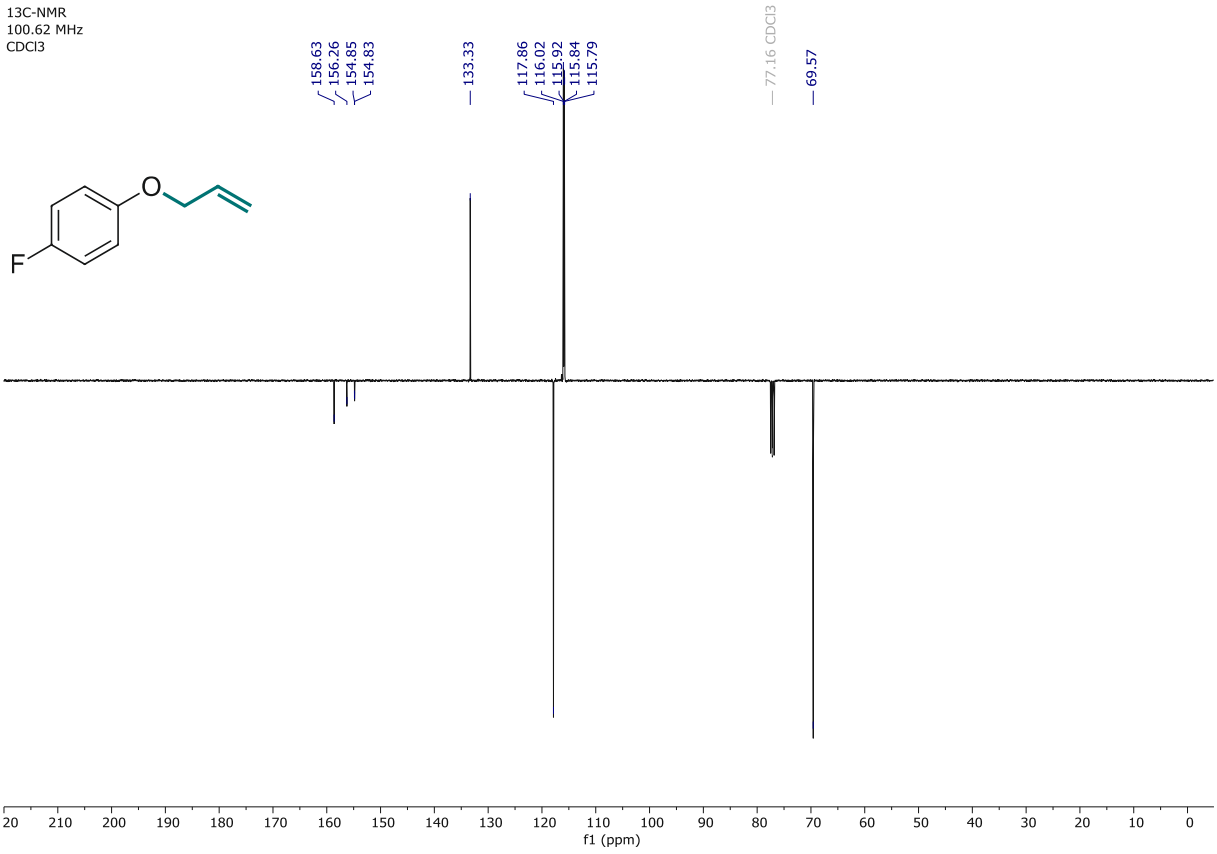
Allyl phenyl ether **(3)**

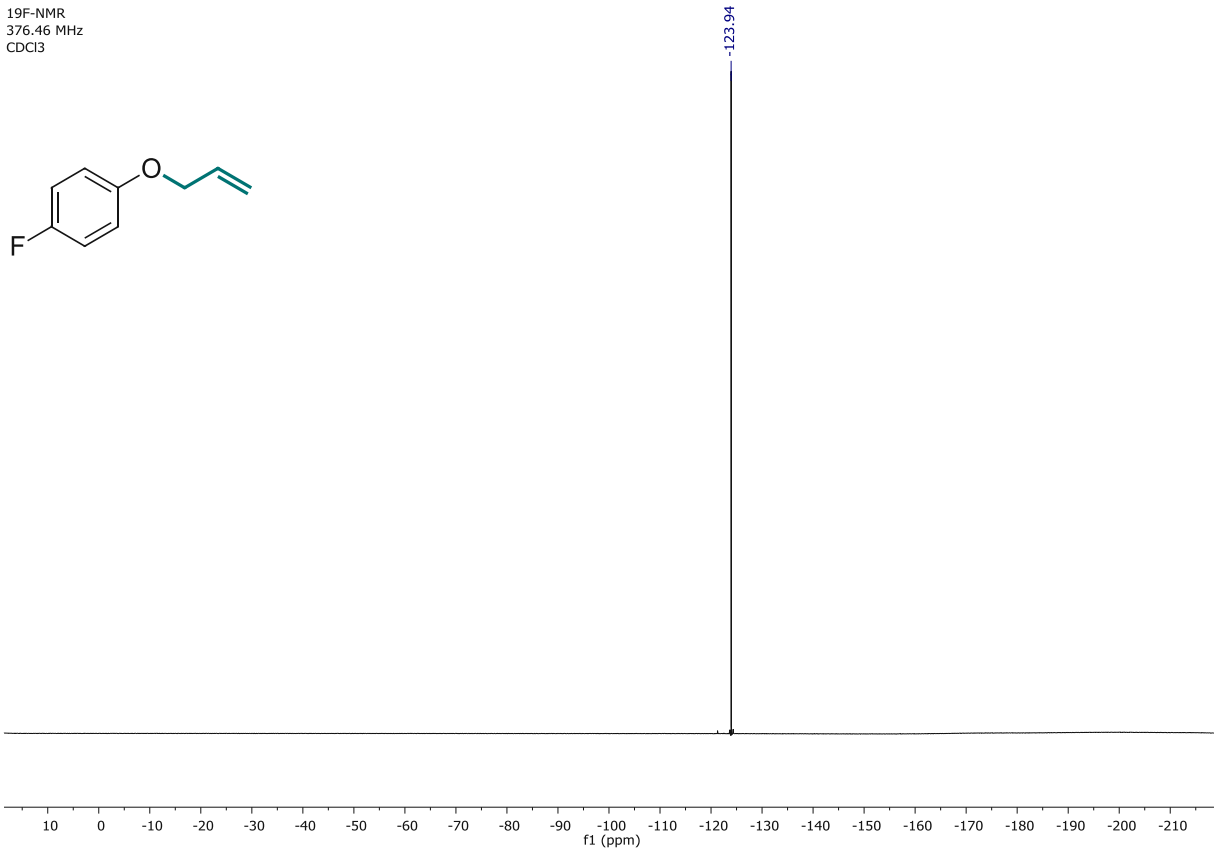




1-(Allyloxy)-4-fluorobenzene **(4)**

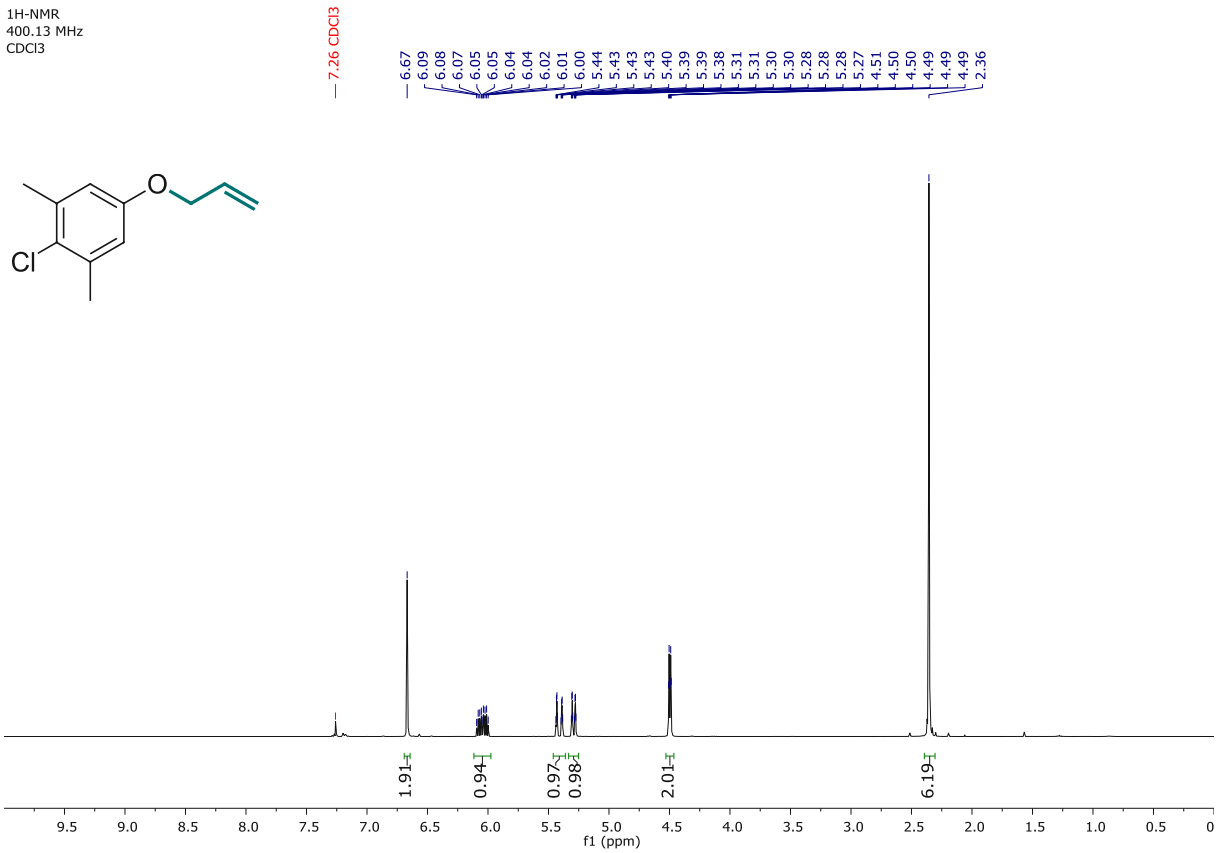




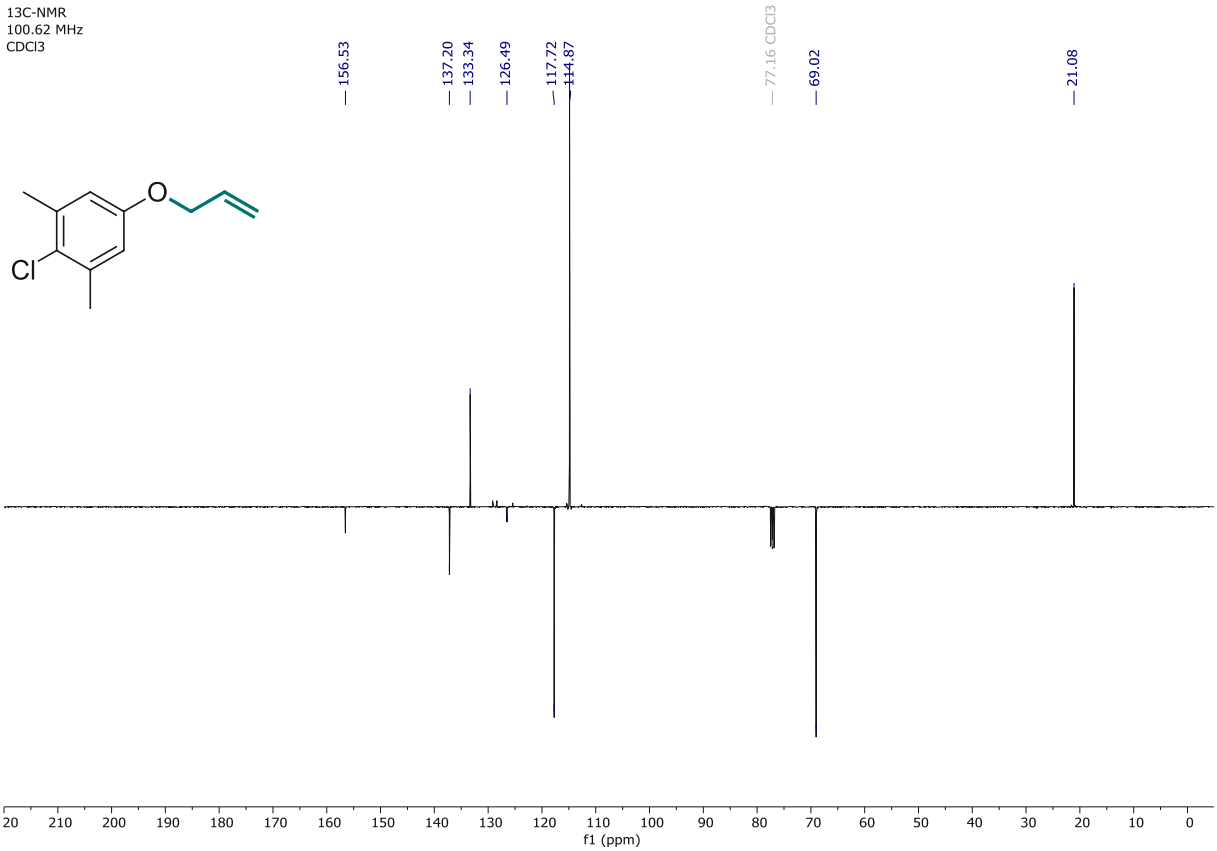


5-(allyloxy)-2-chloro-1,3-dimethylbenzene **(5)**

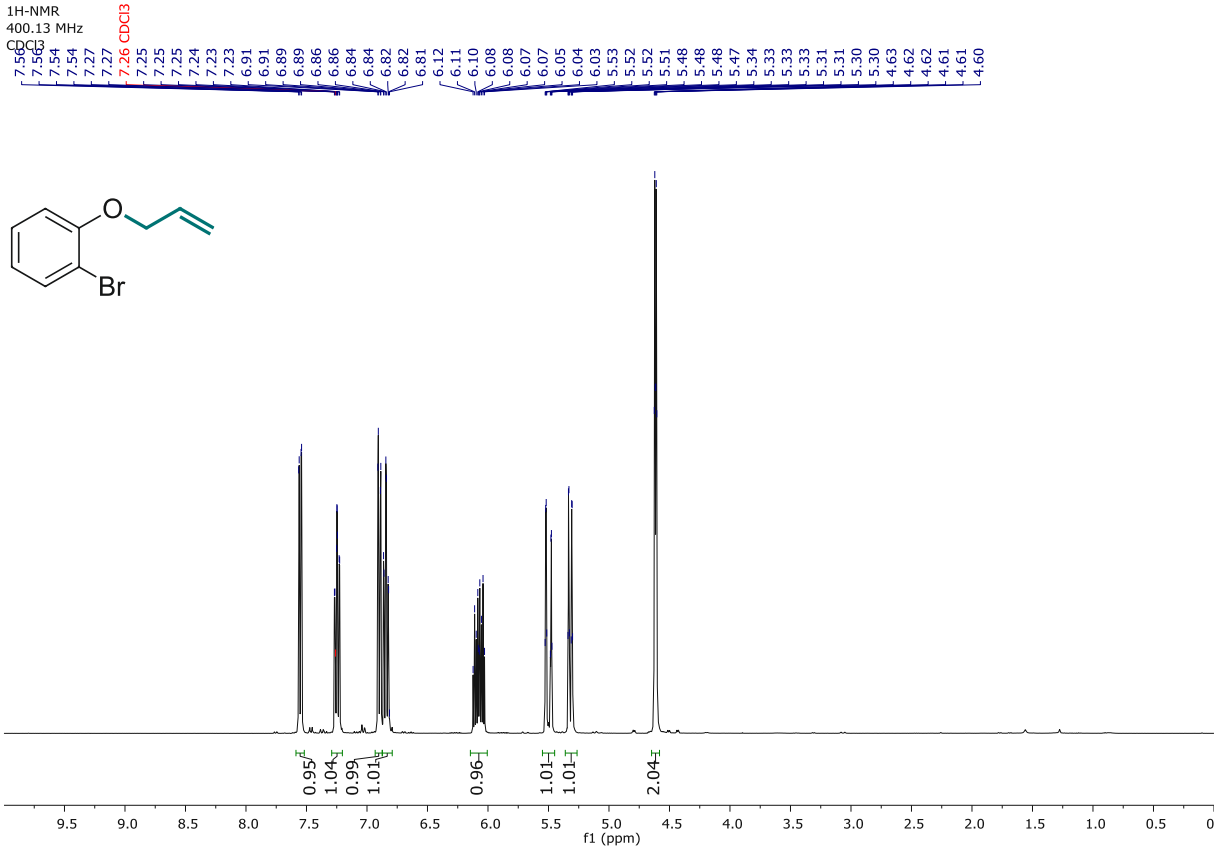
1H-NMR
400.13 MHz
CDCl3

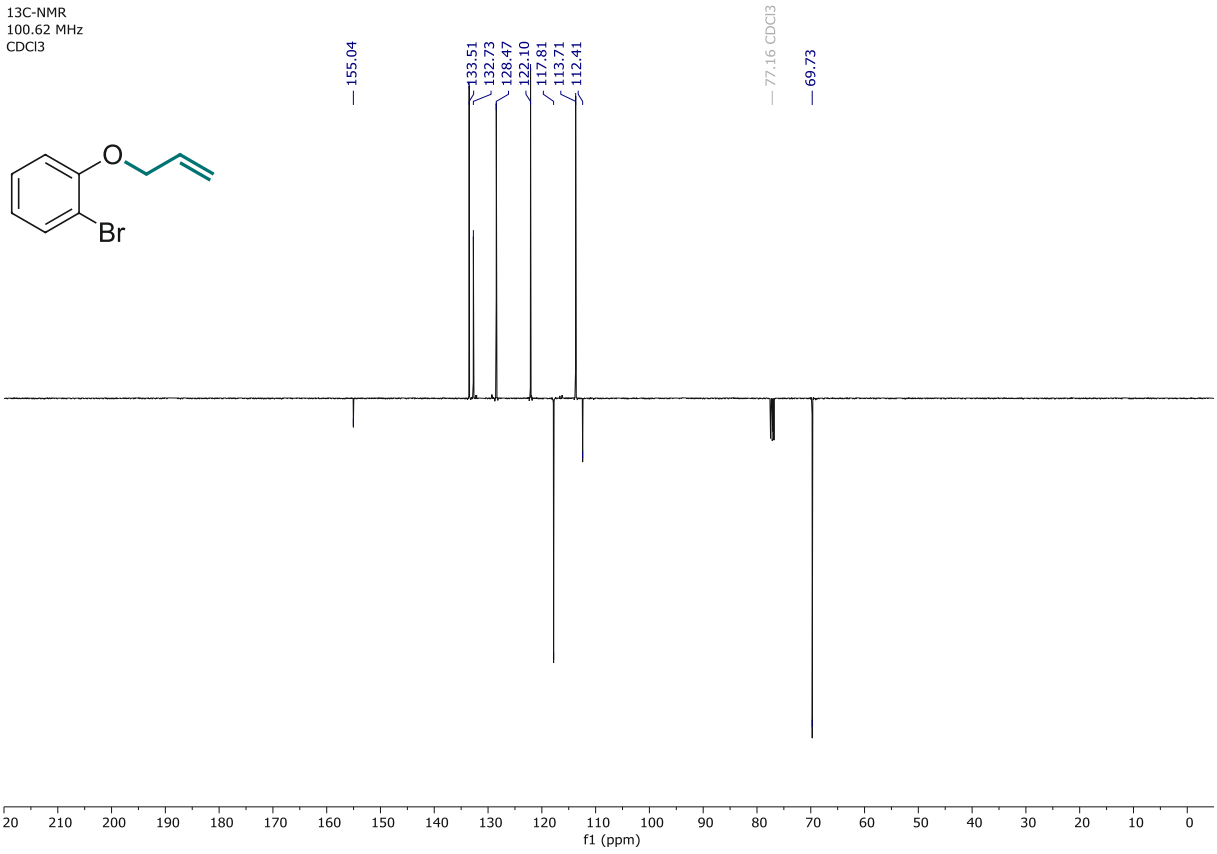


13C-NMR
100.62 MHz
CDCl3

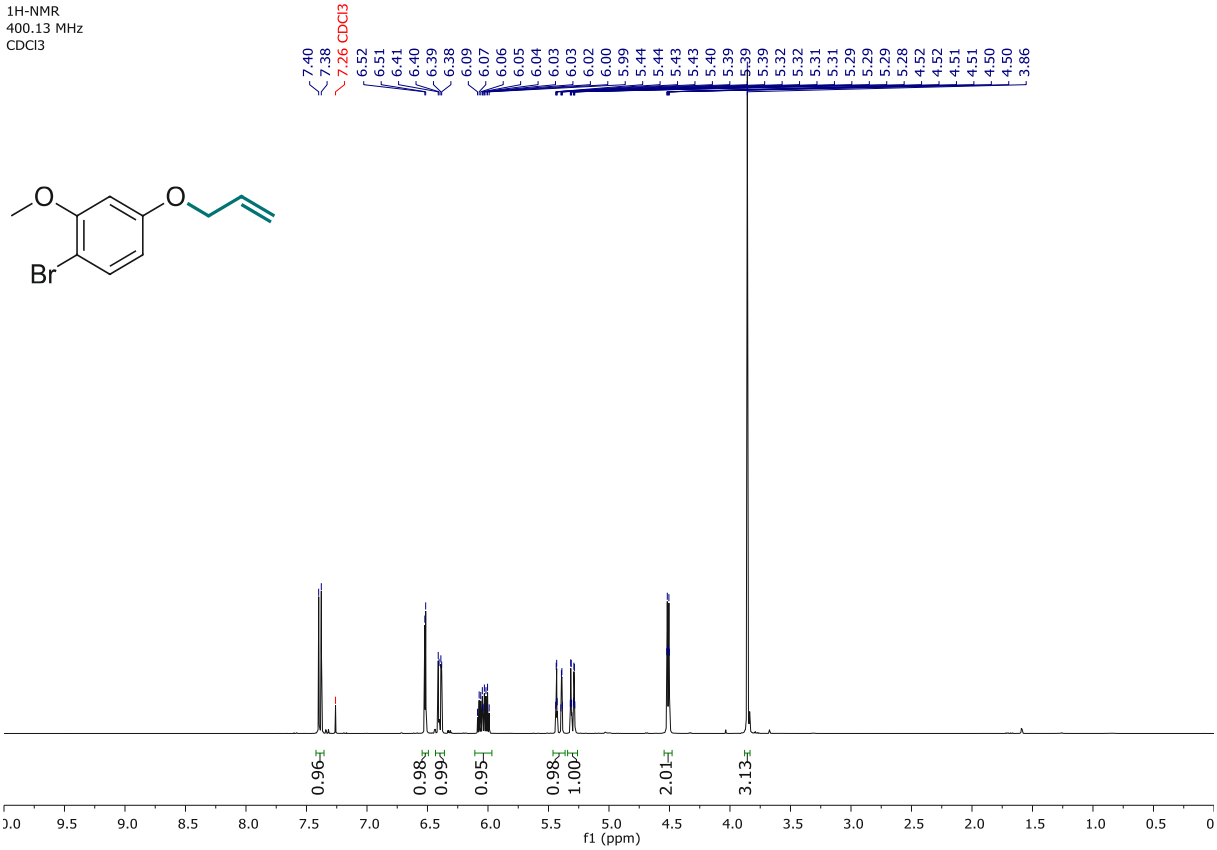


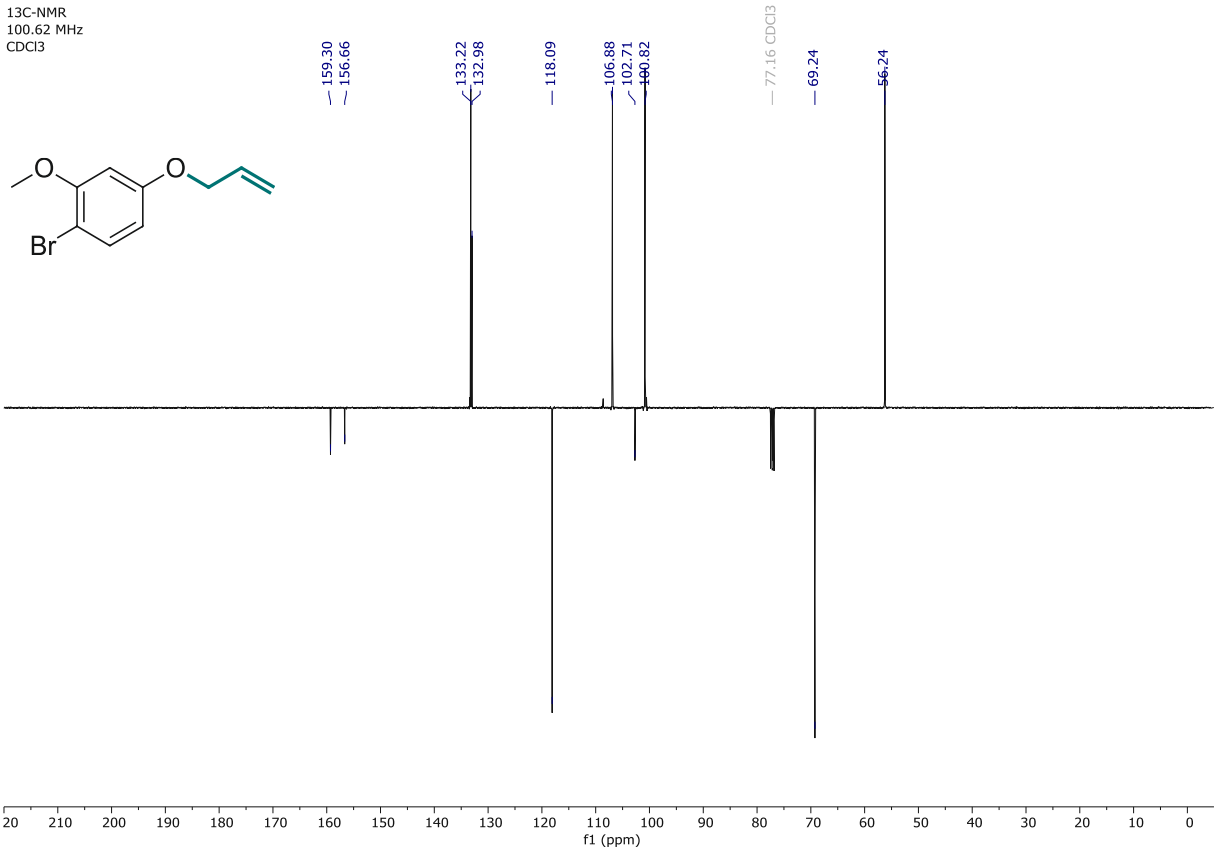
1-(Allyloxy)-2-bromobenzene **(6)**



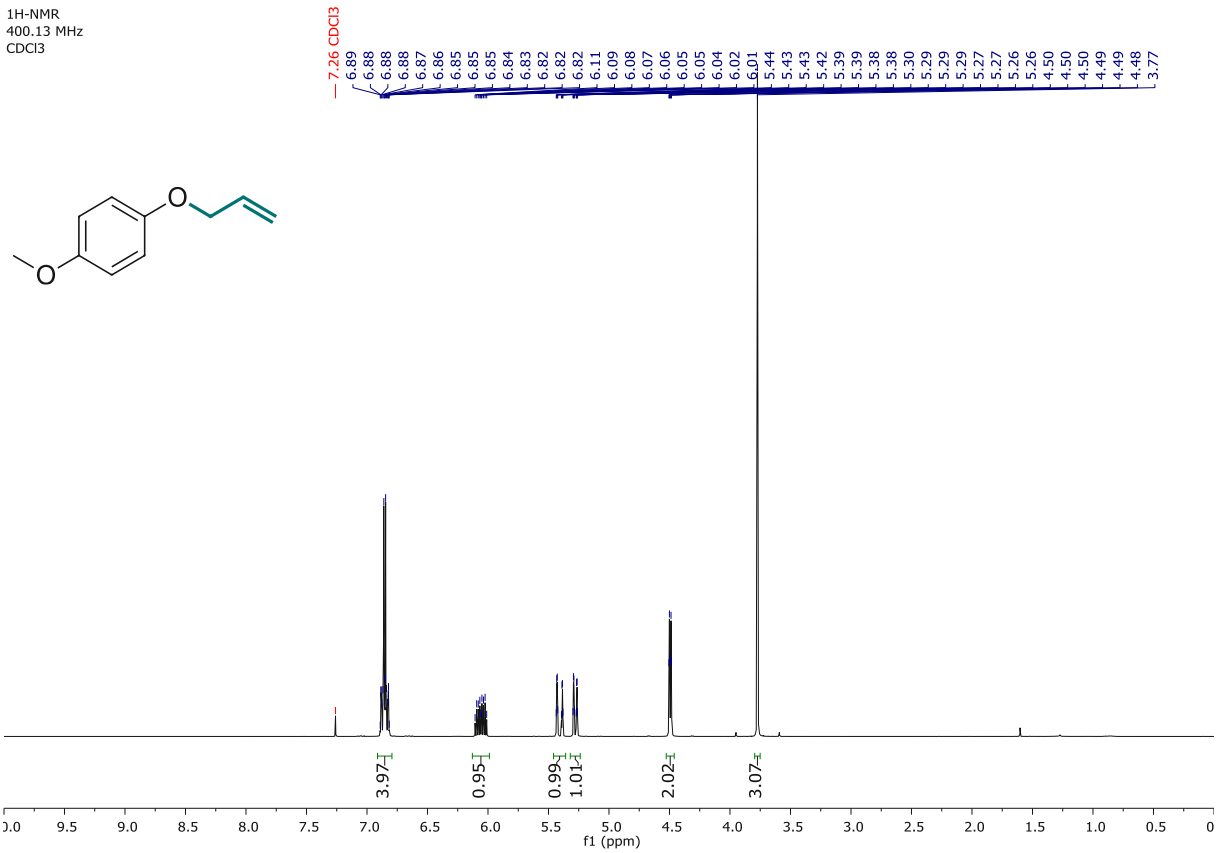


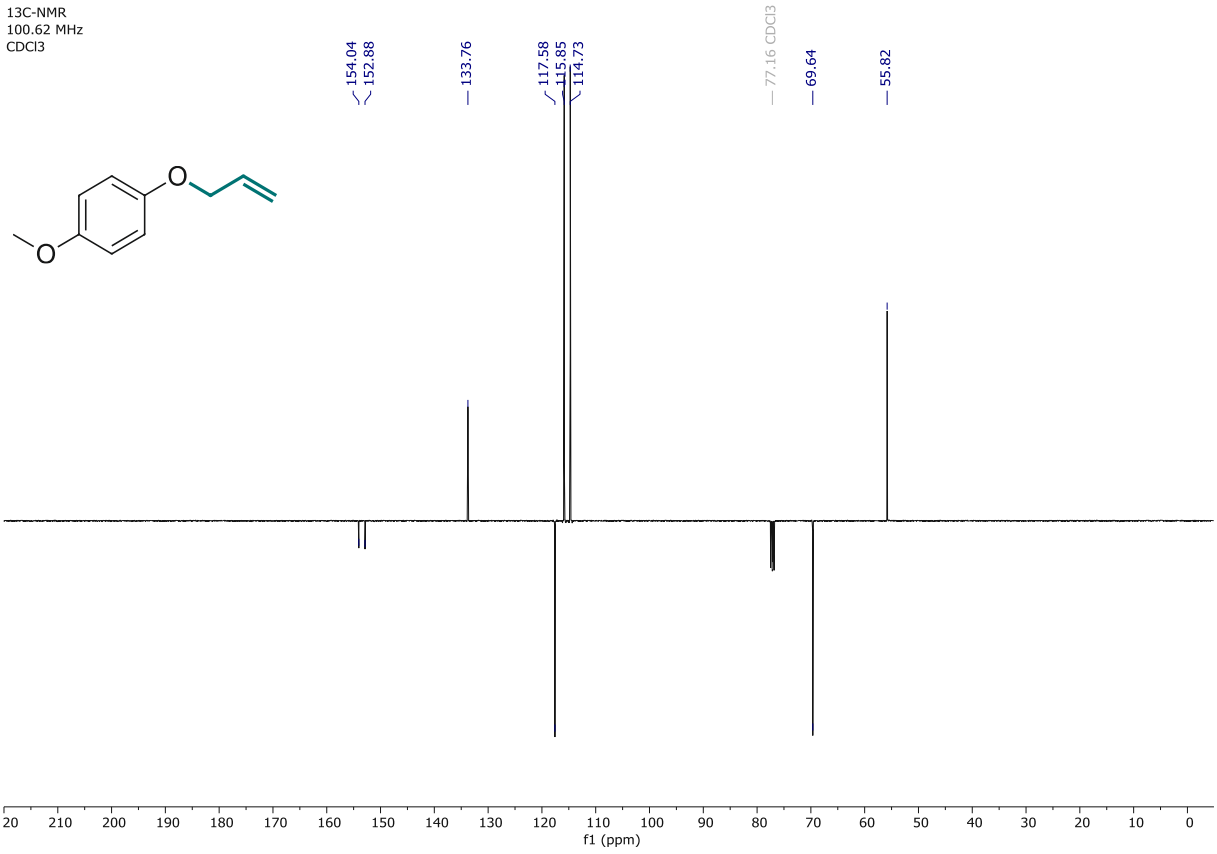
1-Bromo-2-methoxy-4-allyloxybenzene **(7)**



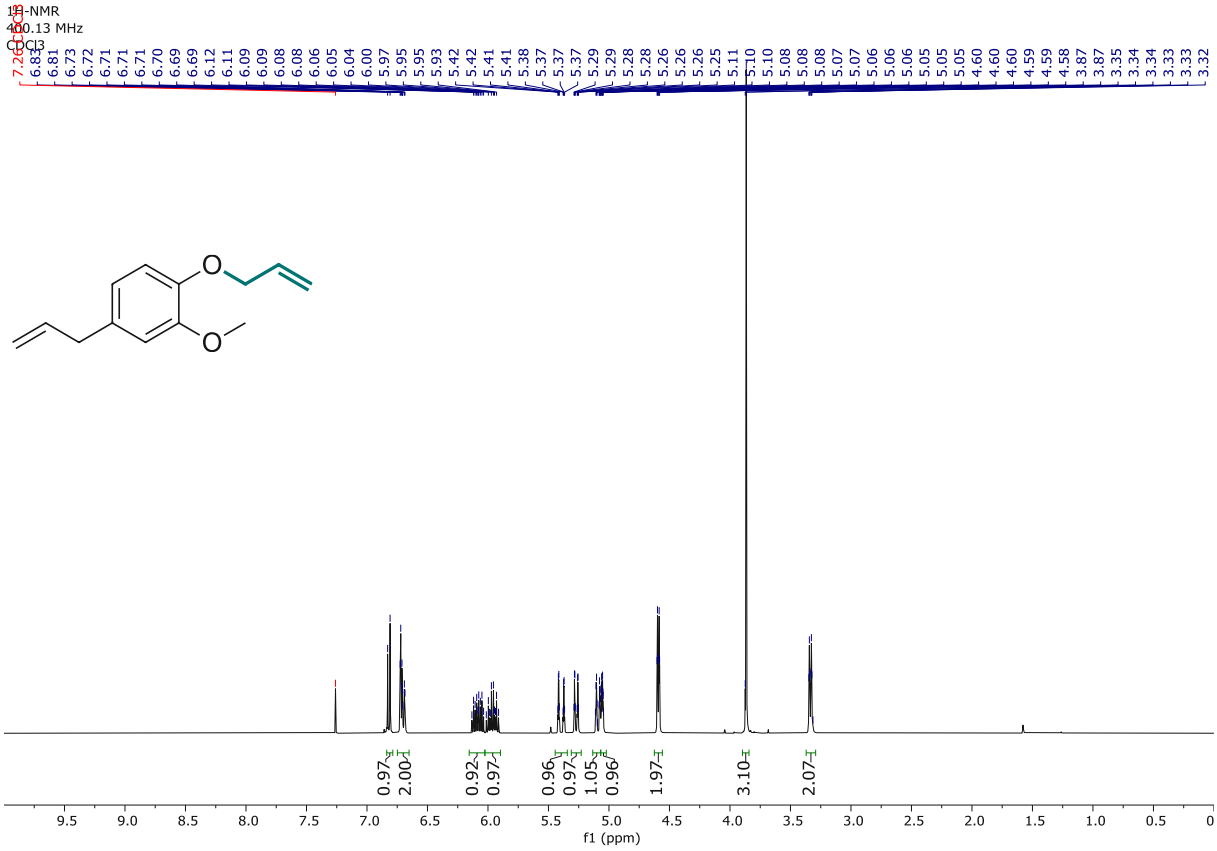


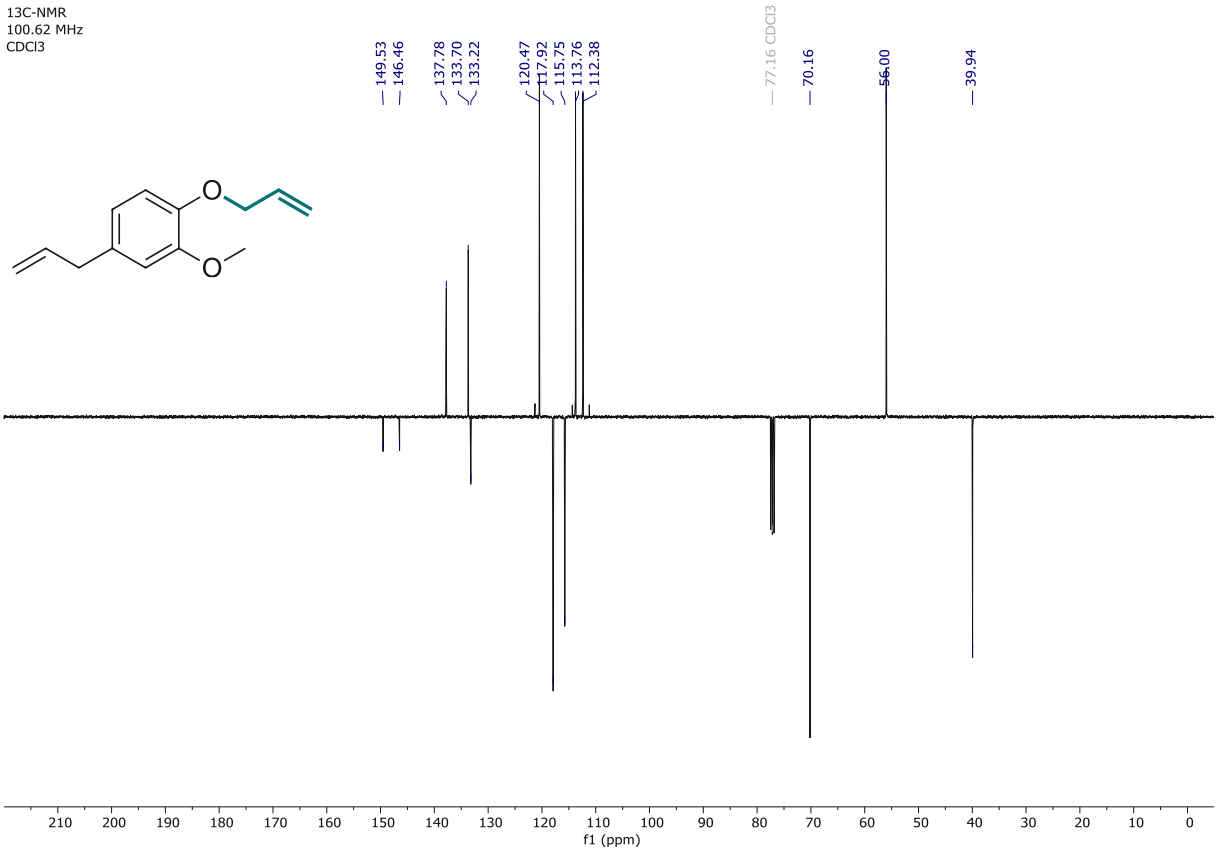
1-(Allyloxy)-4-methoxybenzene **(8)**



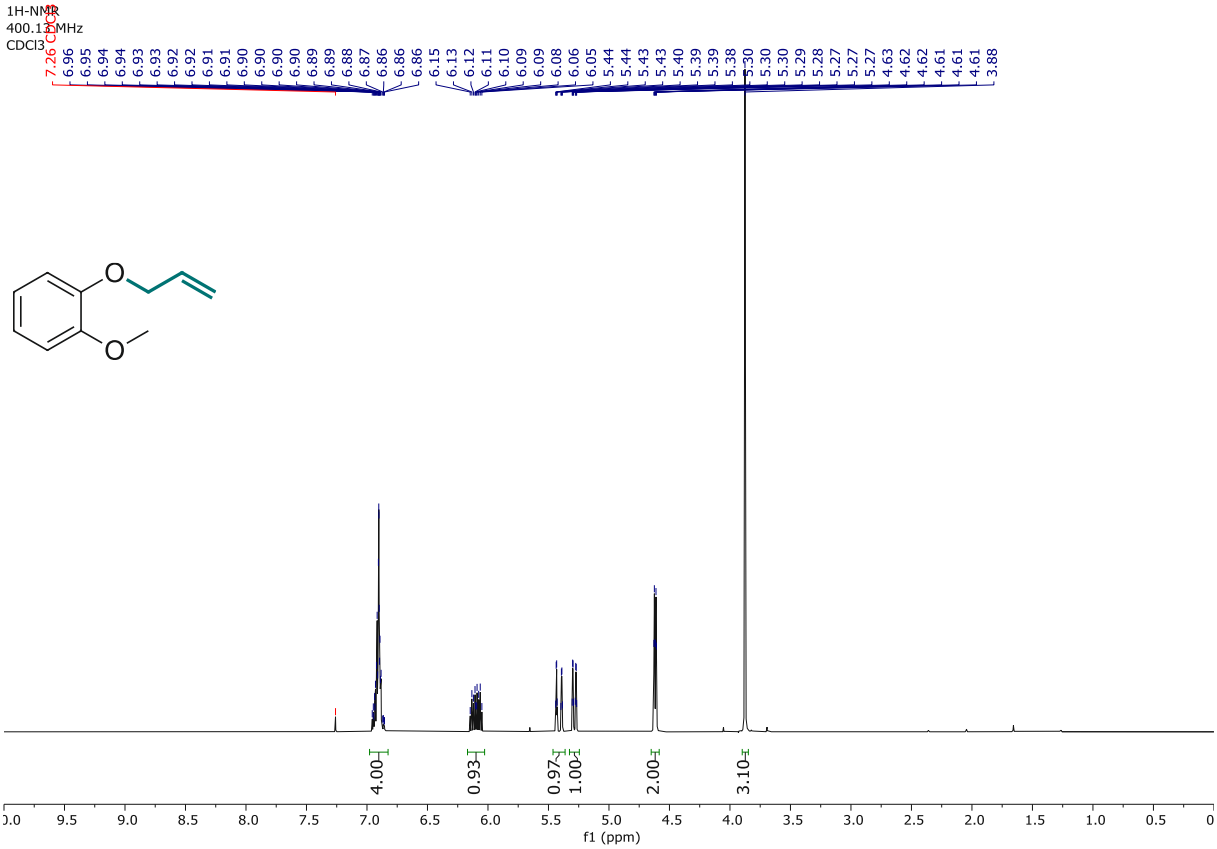


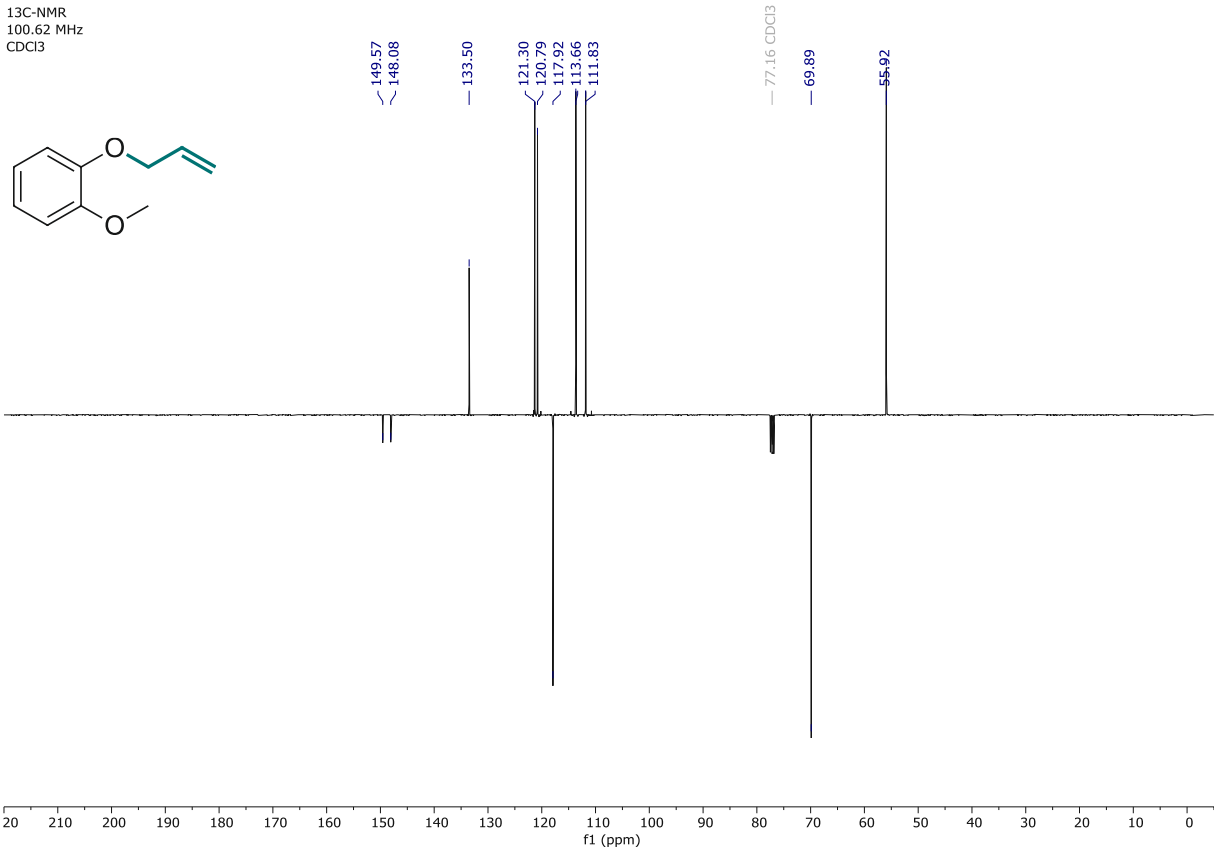
4-Allyl-1-(allyloxy)-2-methoxybenzene **(9)**



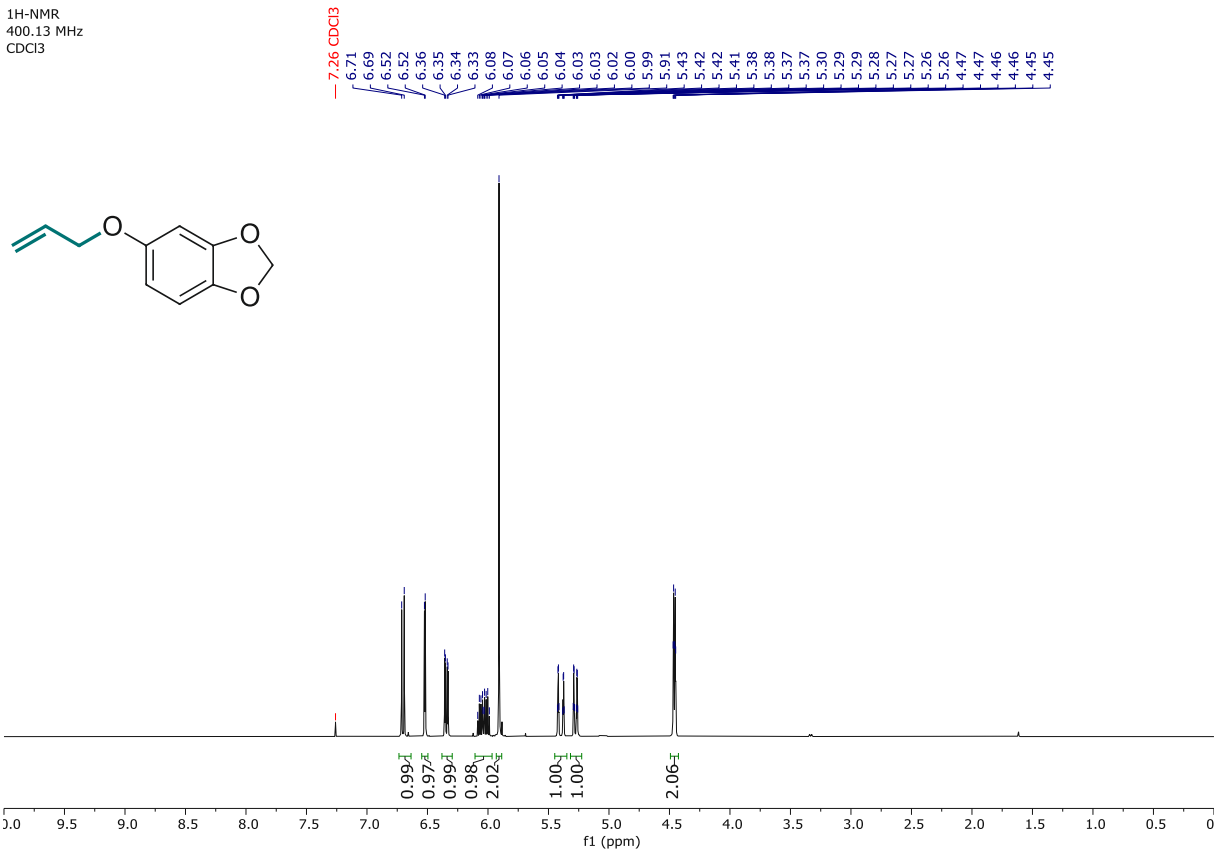


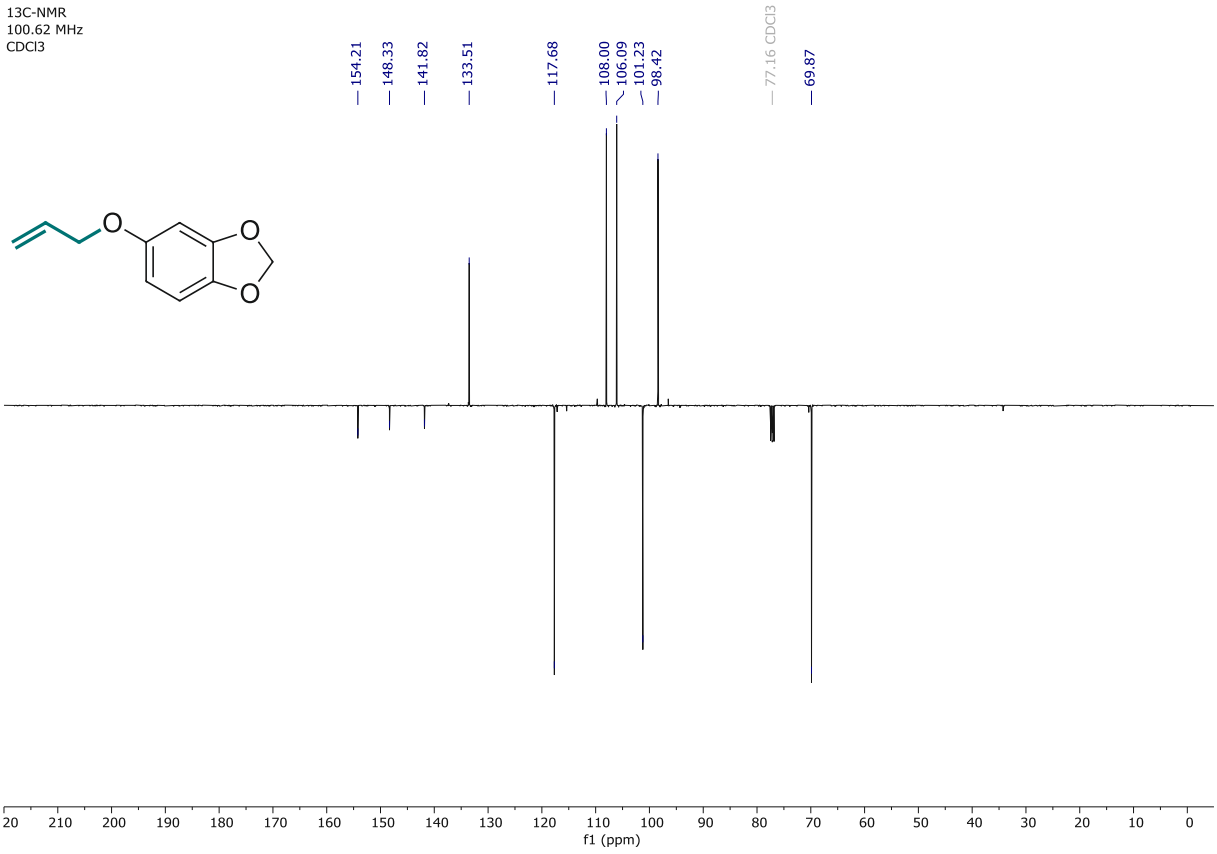
1-(Allyloxy)-2-methoxybenzene **(10)**



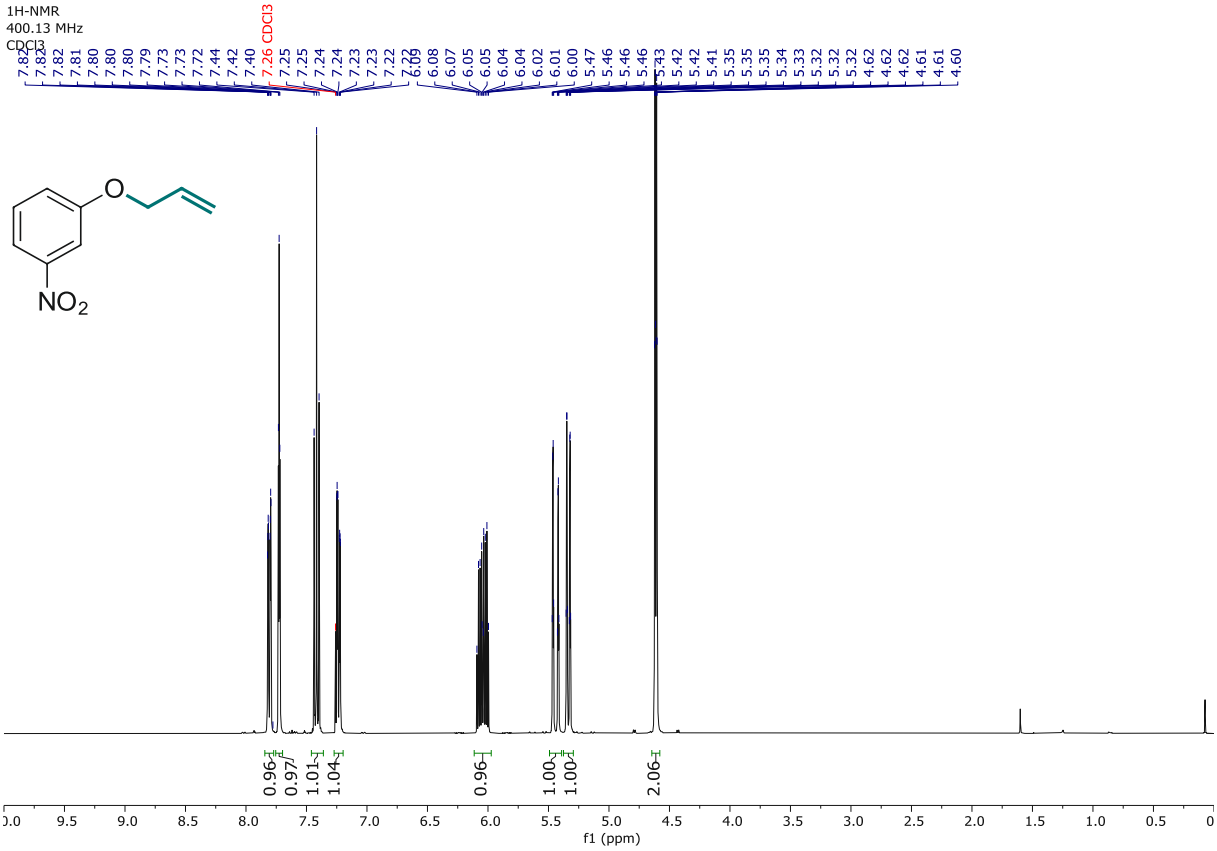


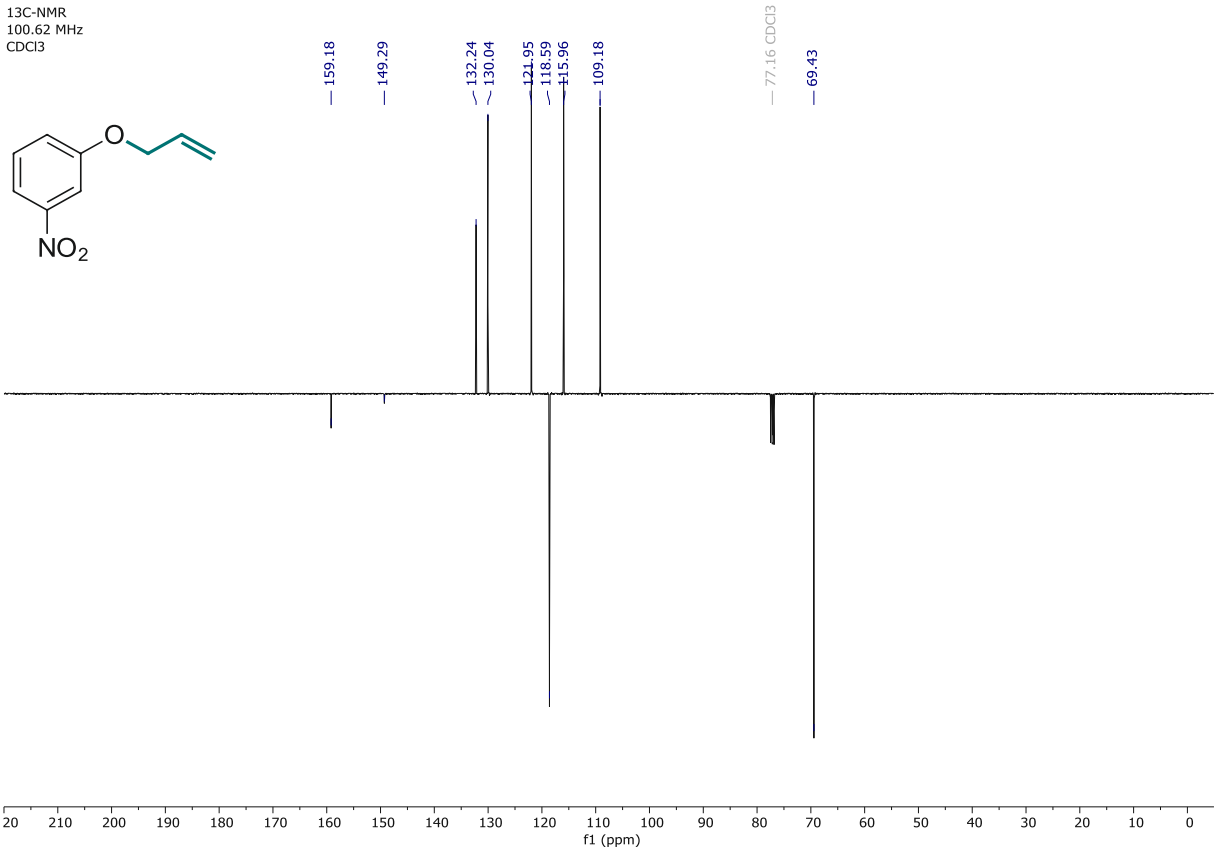
O-Allyl-sesamol **(11)**



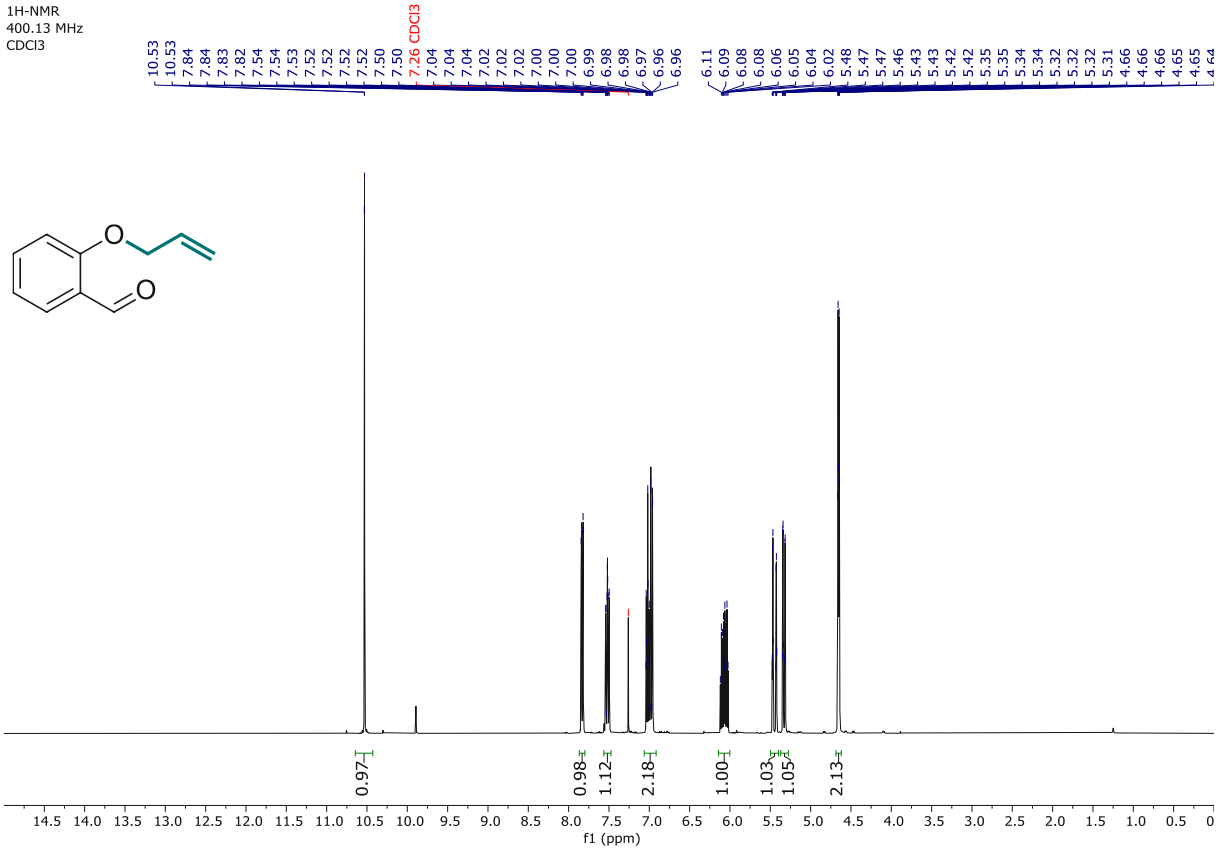


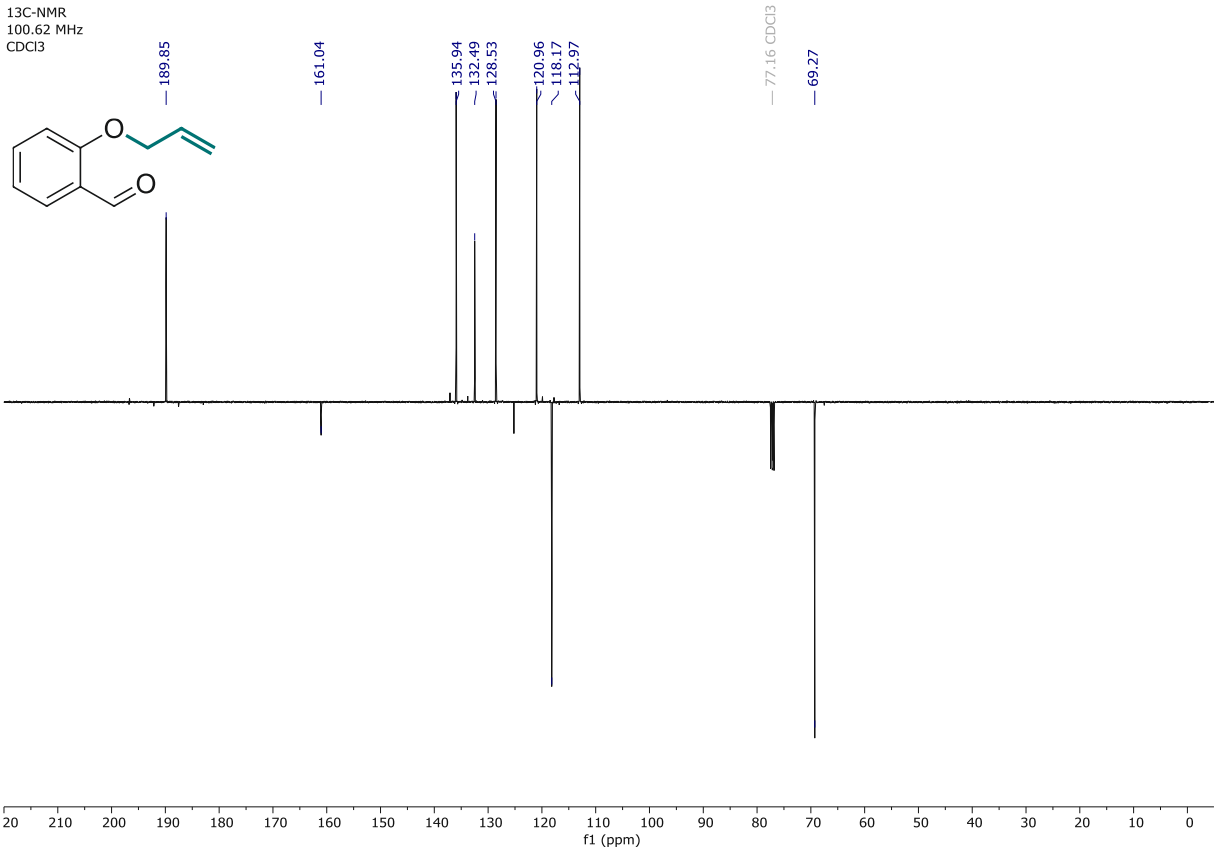
1-Allyloxy-3-nitrobenzene **(12)**



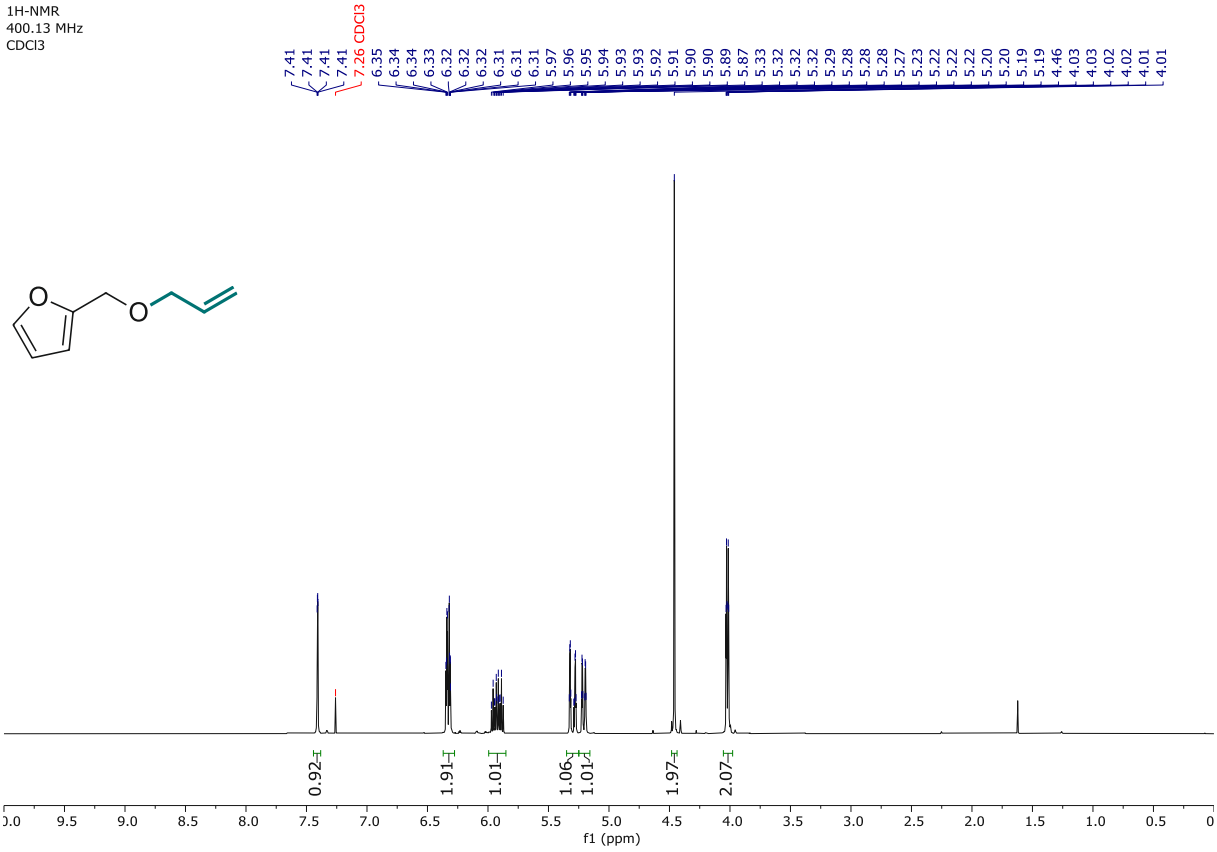


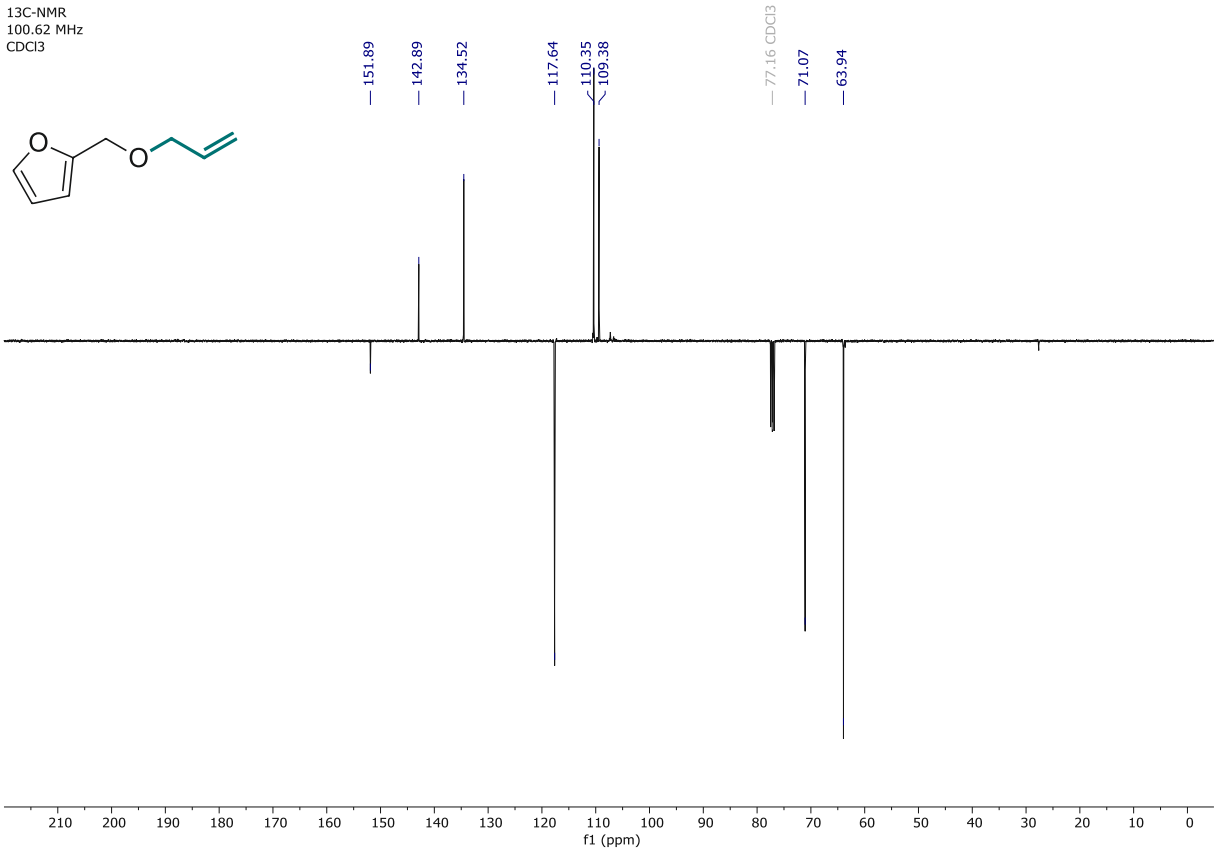
2-(Allyloxy)benzaldehyde **(13)**



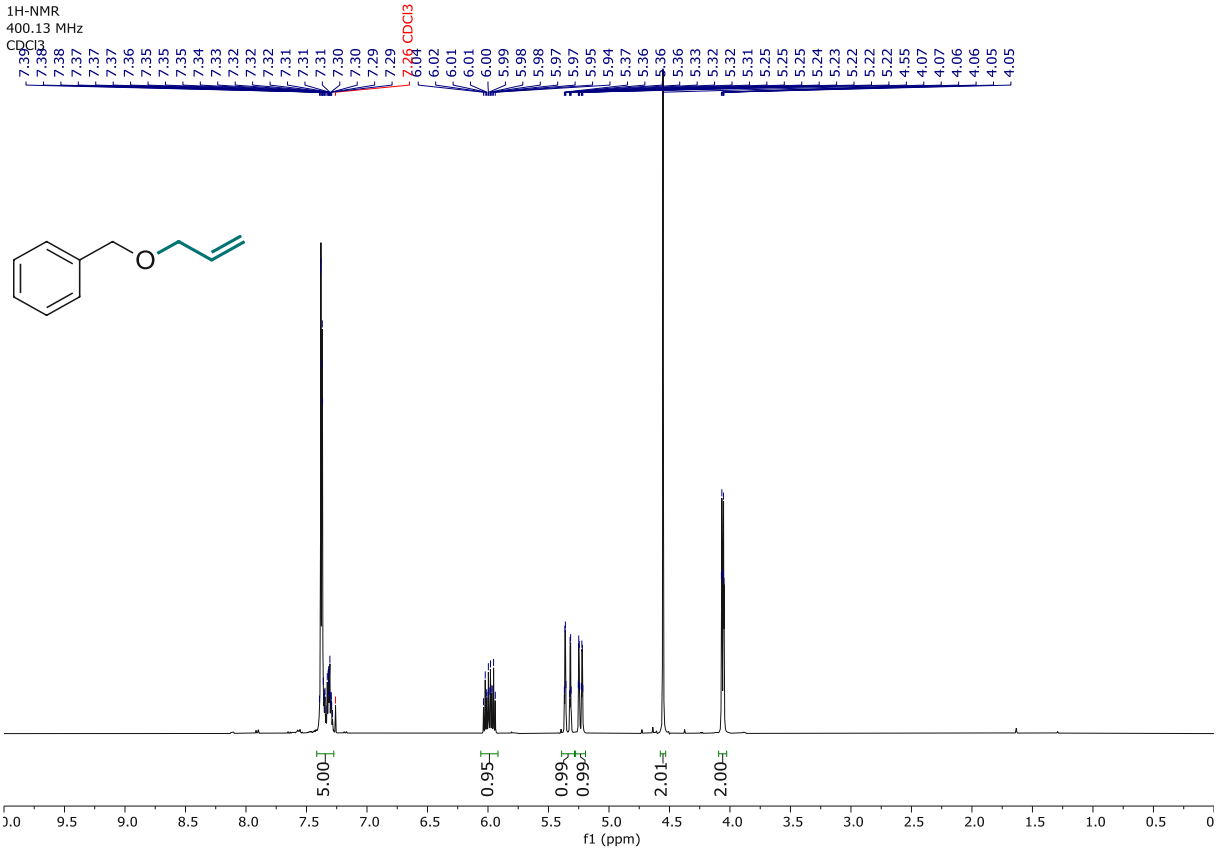


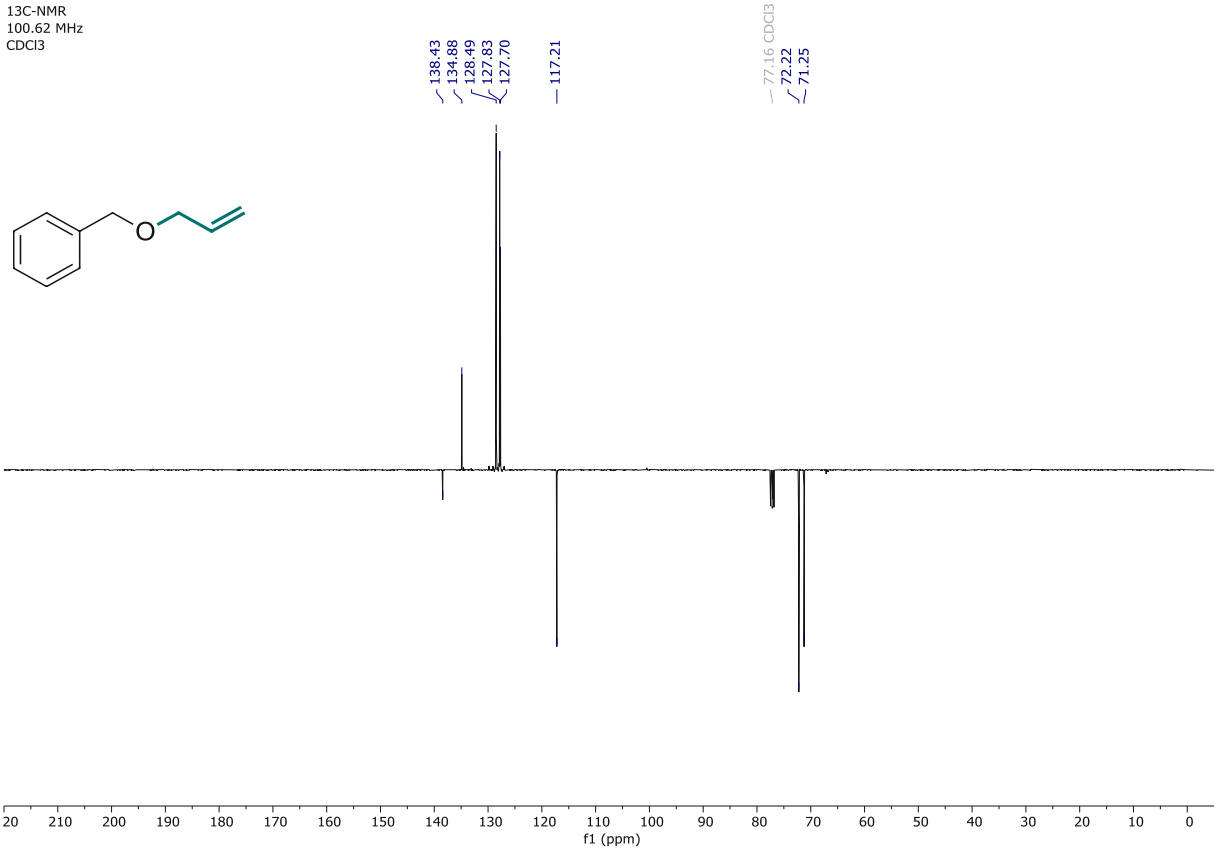
Allyl furfuryl ether **(14)**



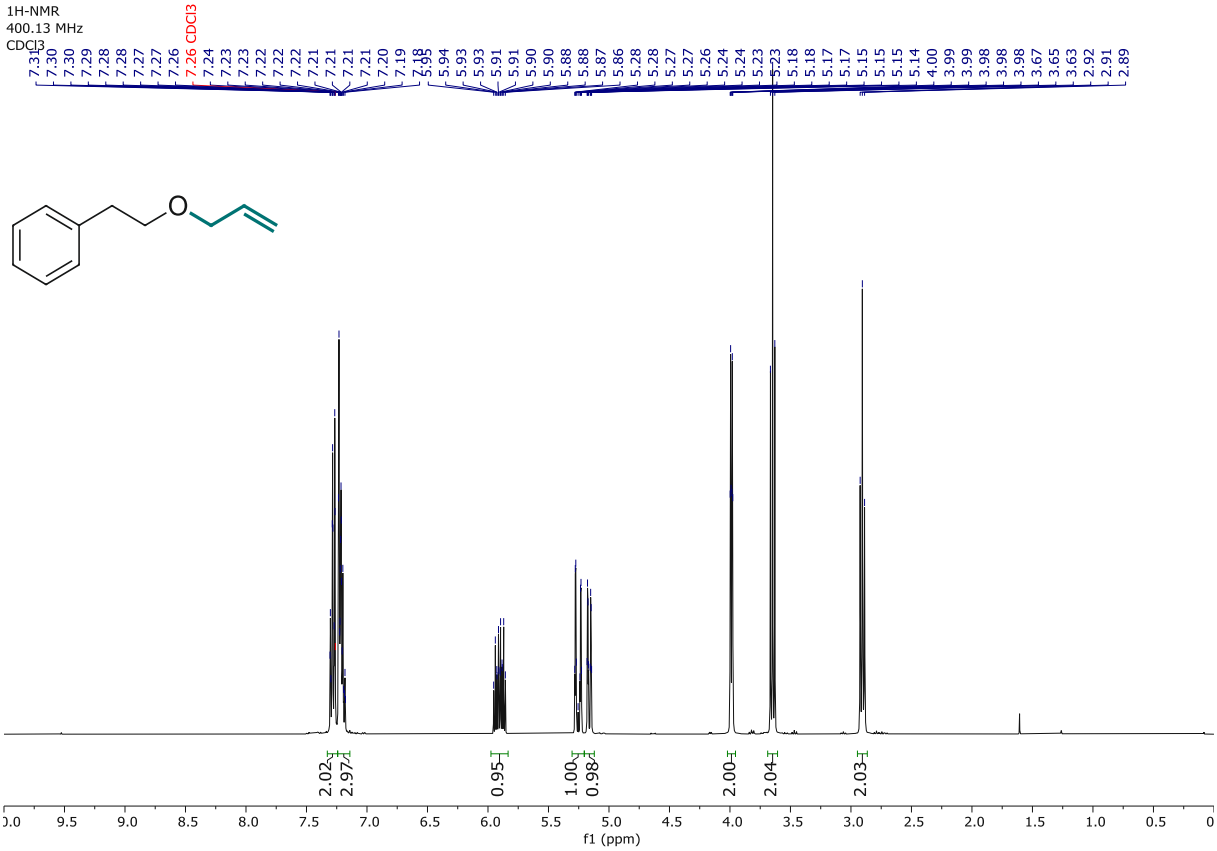


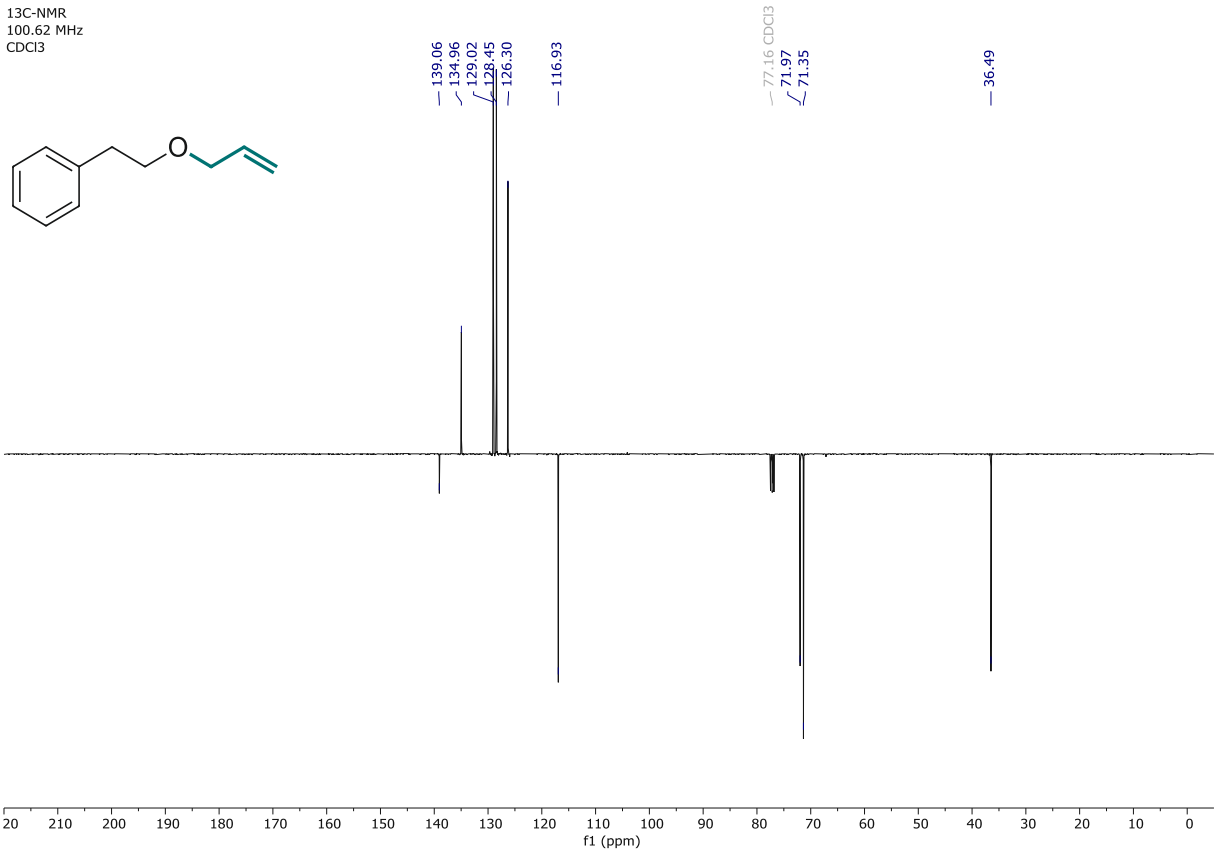
Benzyl allyl ether **(15)**



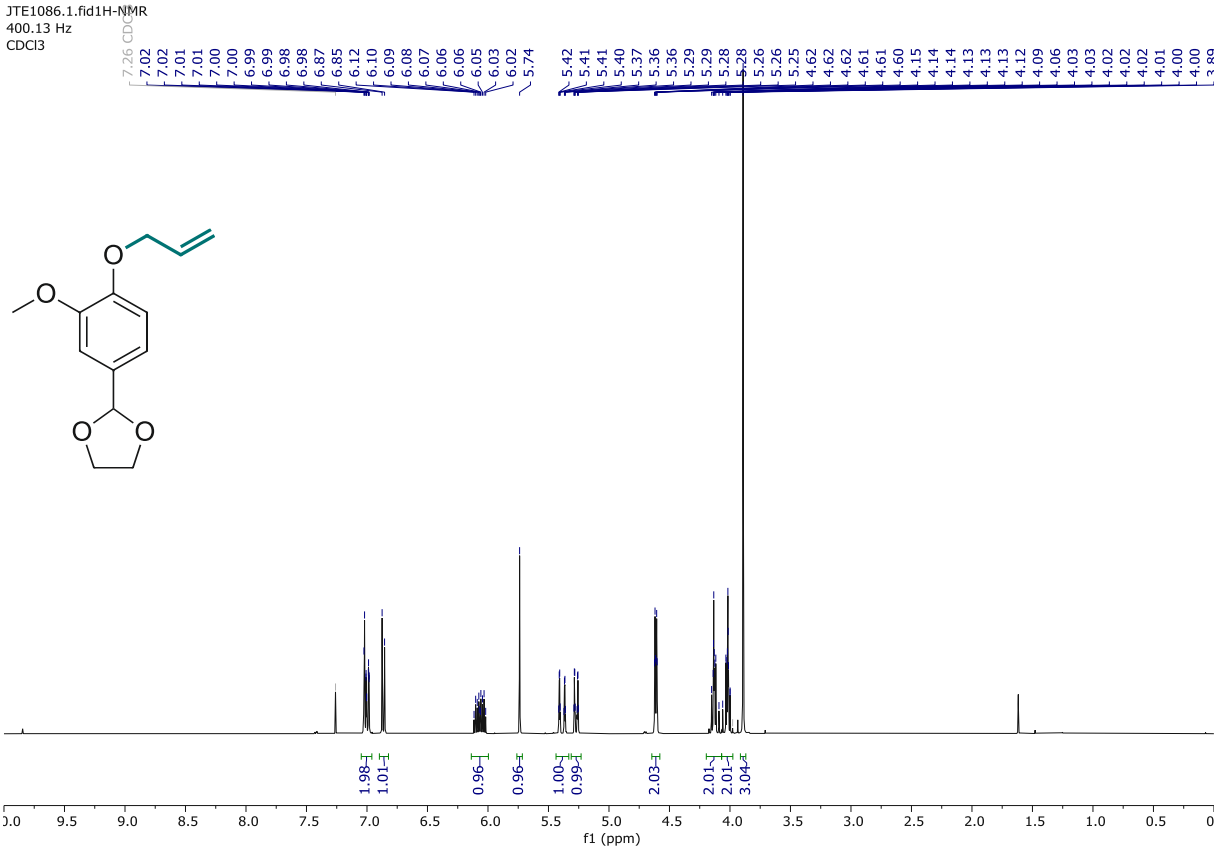


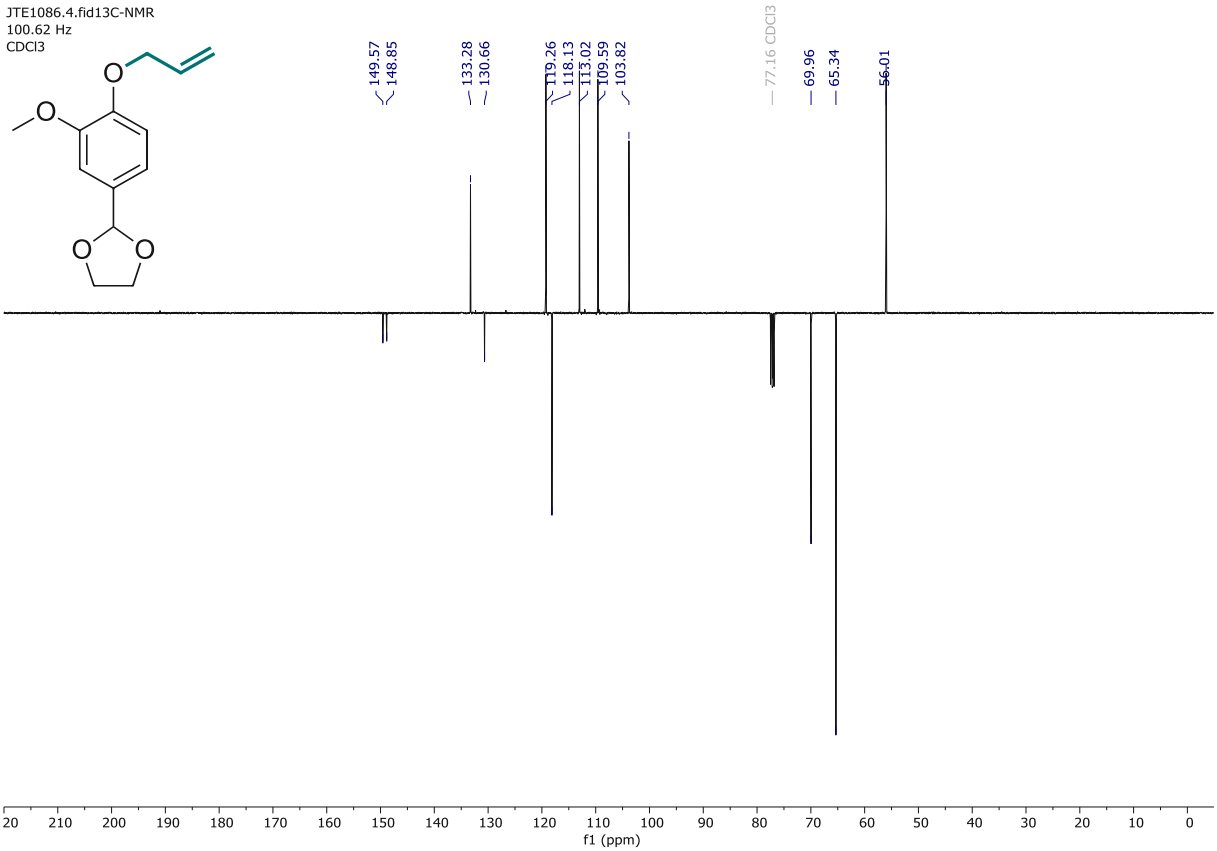
2-(2-propenyloxy)ethylbenzene **(16)**



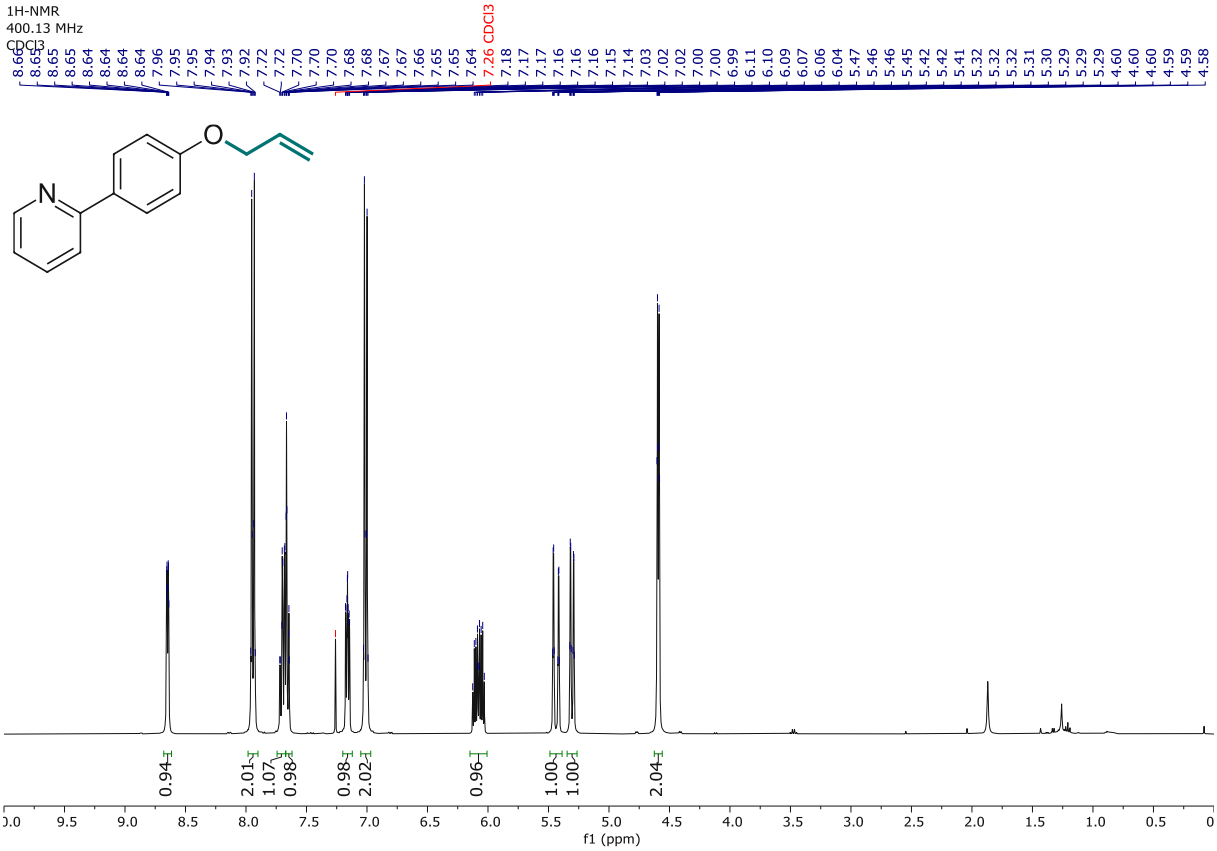


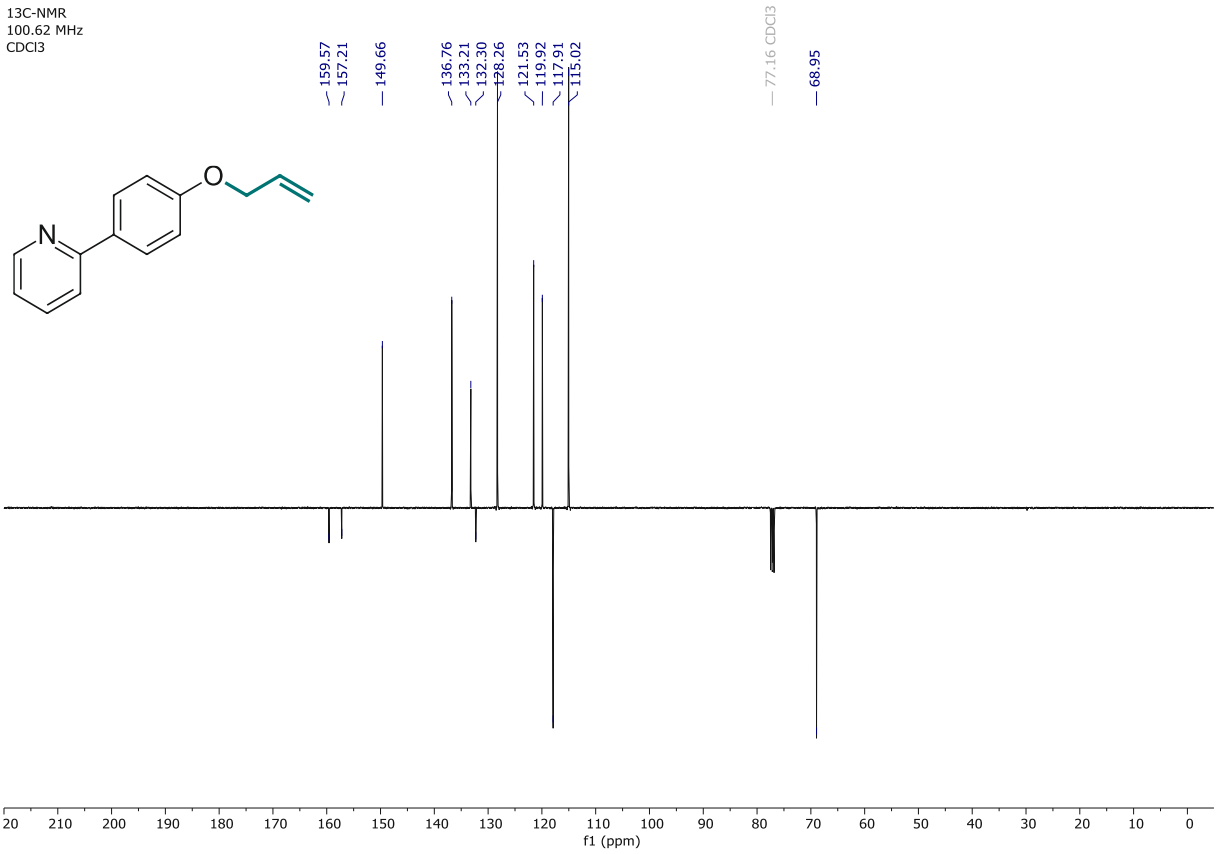
2-[4-(Allyloxy)-3-methoxyphenyl]-1,3-dioxolane (**17**)



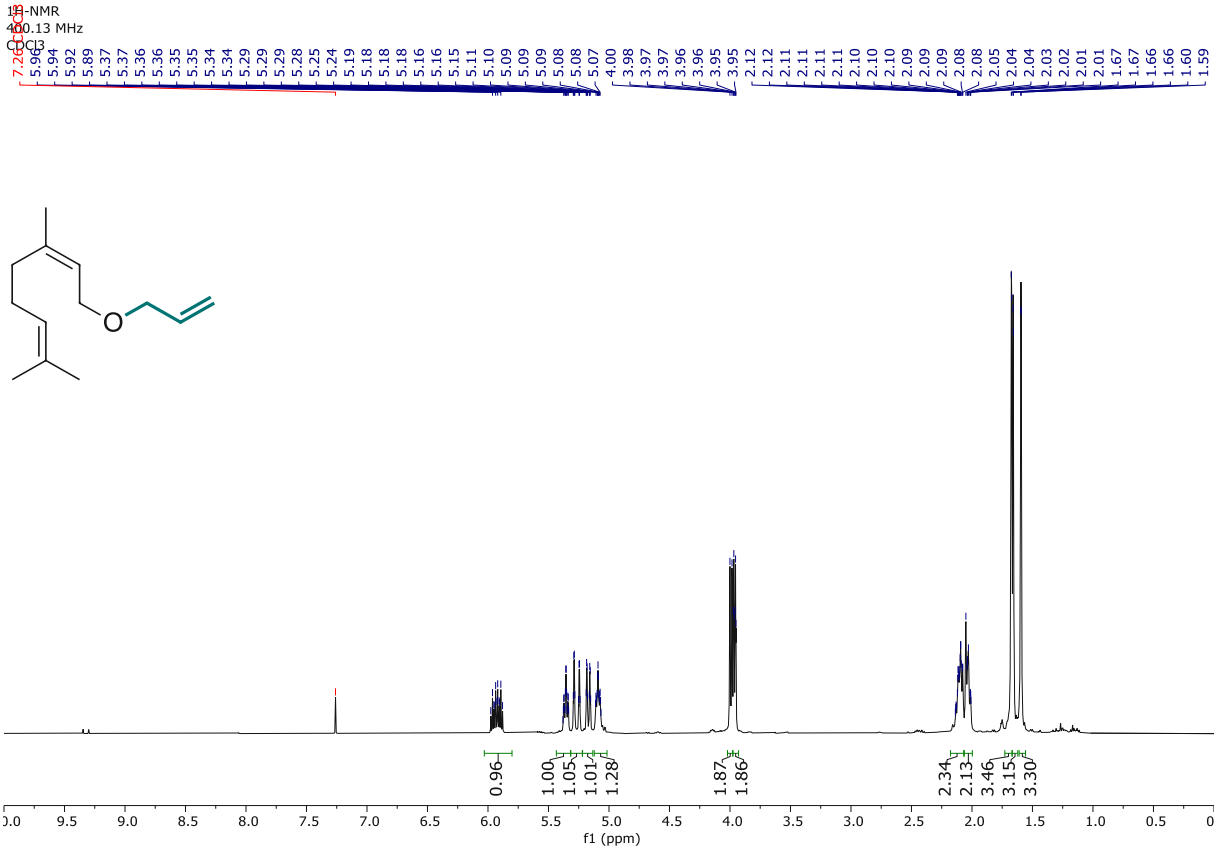


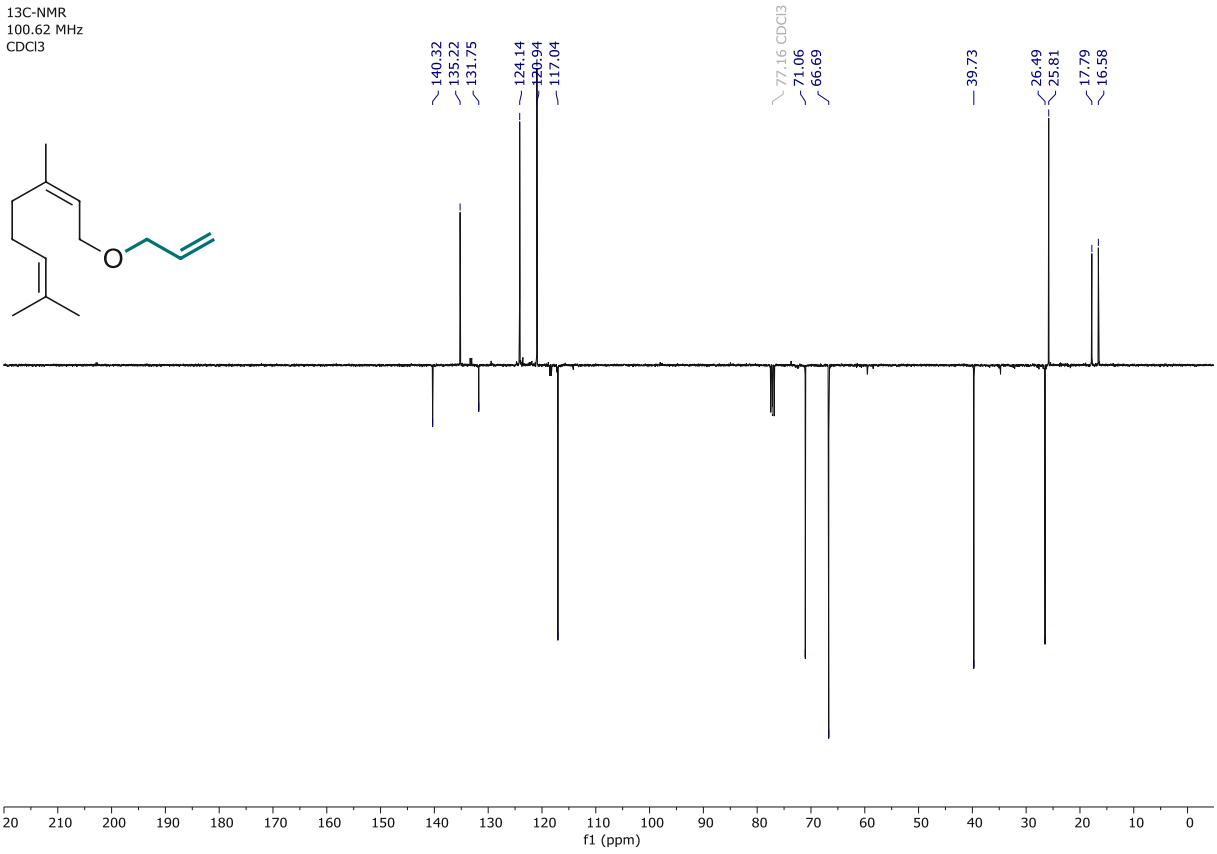
2-(4-(allyloxy)phenyl)pyridine **(18)**



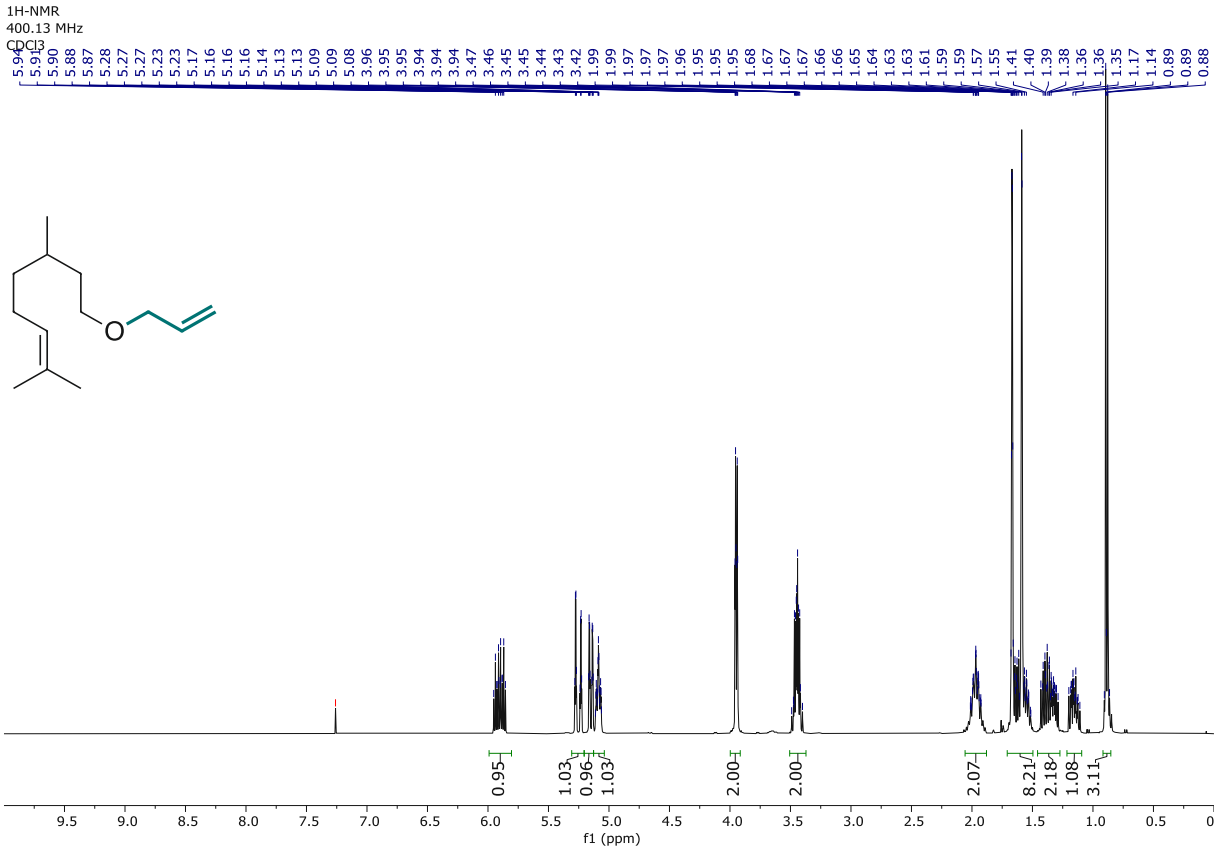


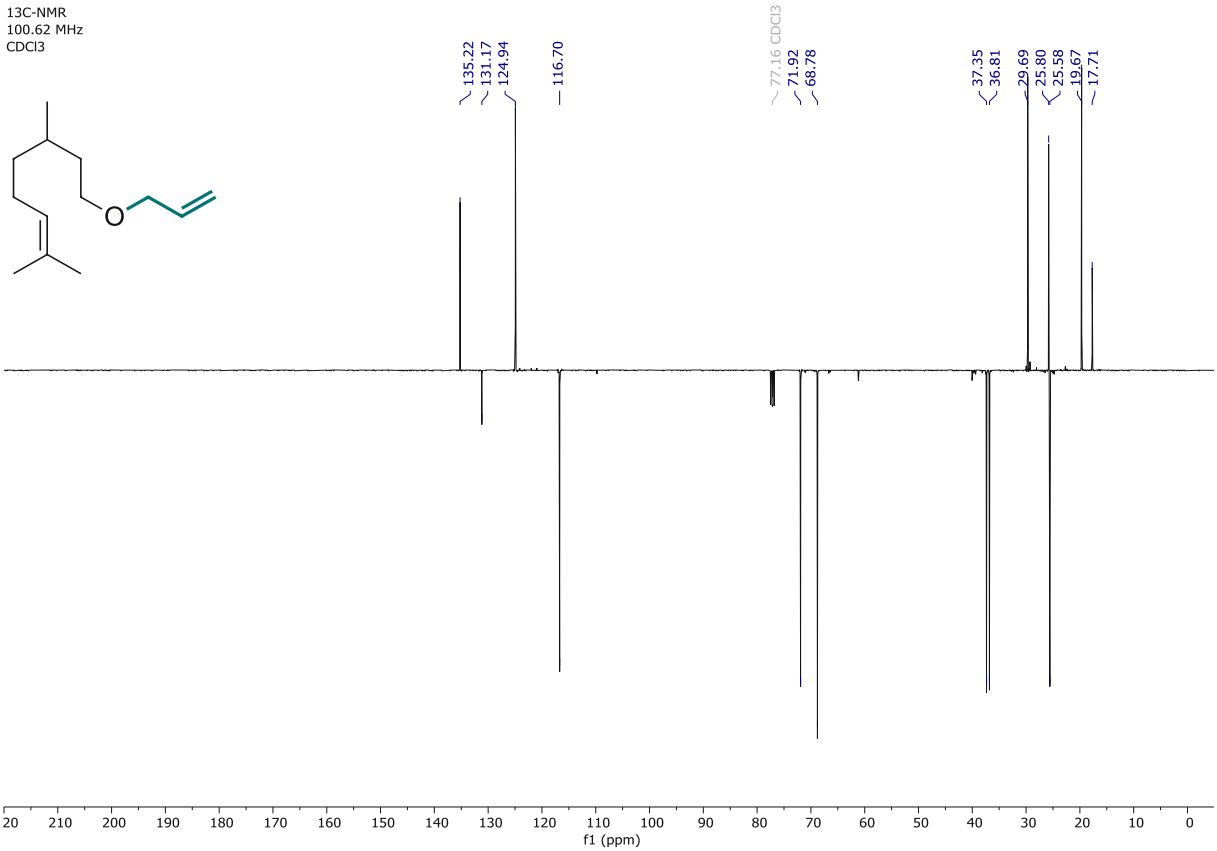
(E)-1-(Allyloxy)-3,7-dimethylocta-2,6-diene **(19)**



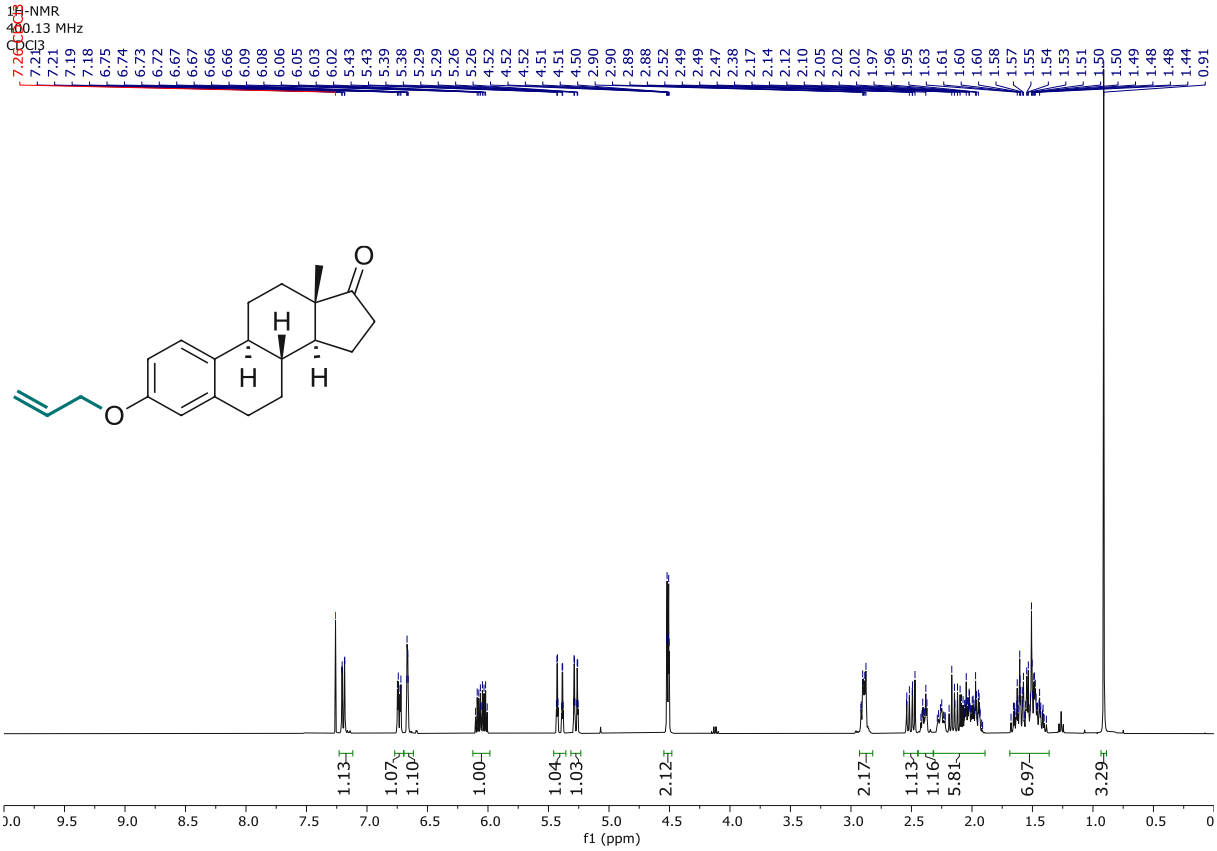


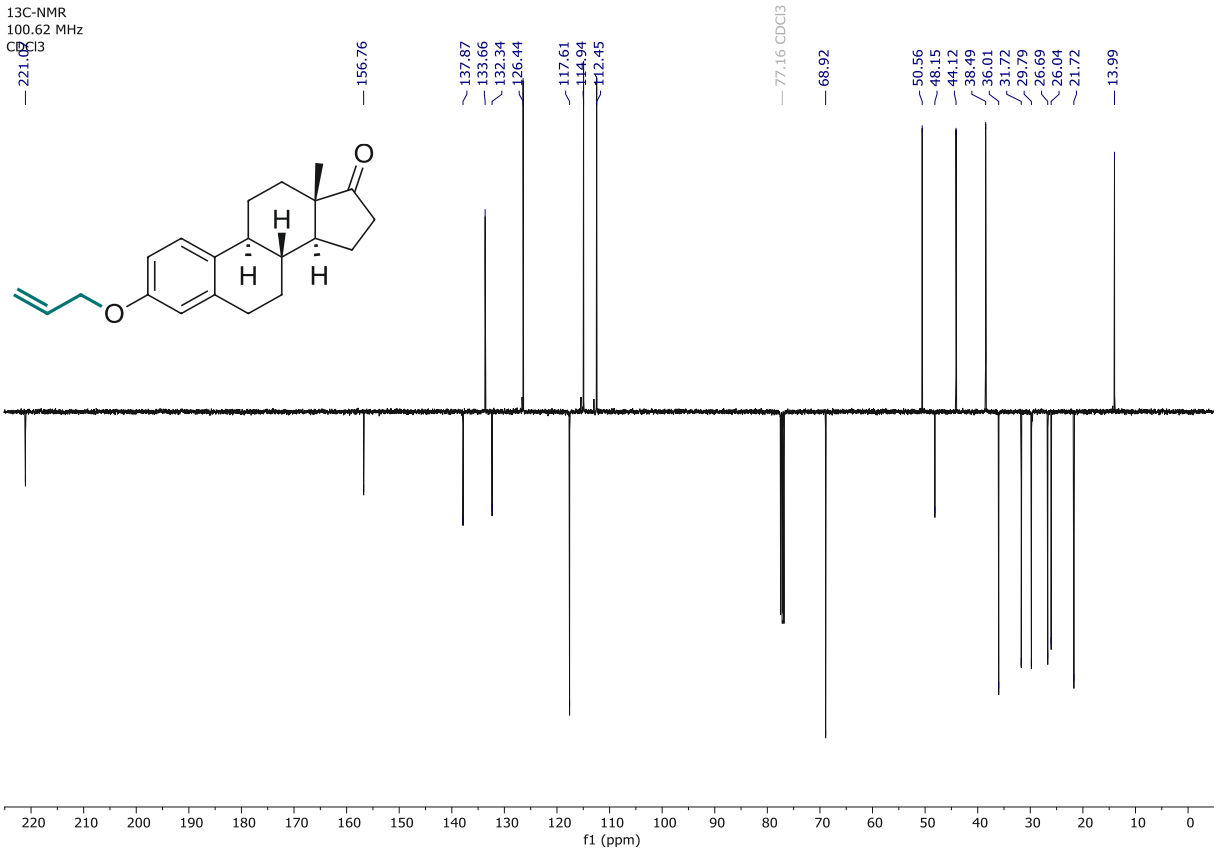
O-Allyl citronellol **(20)**



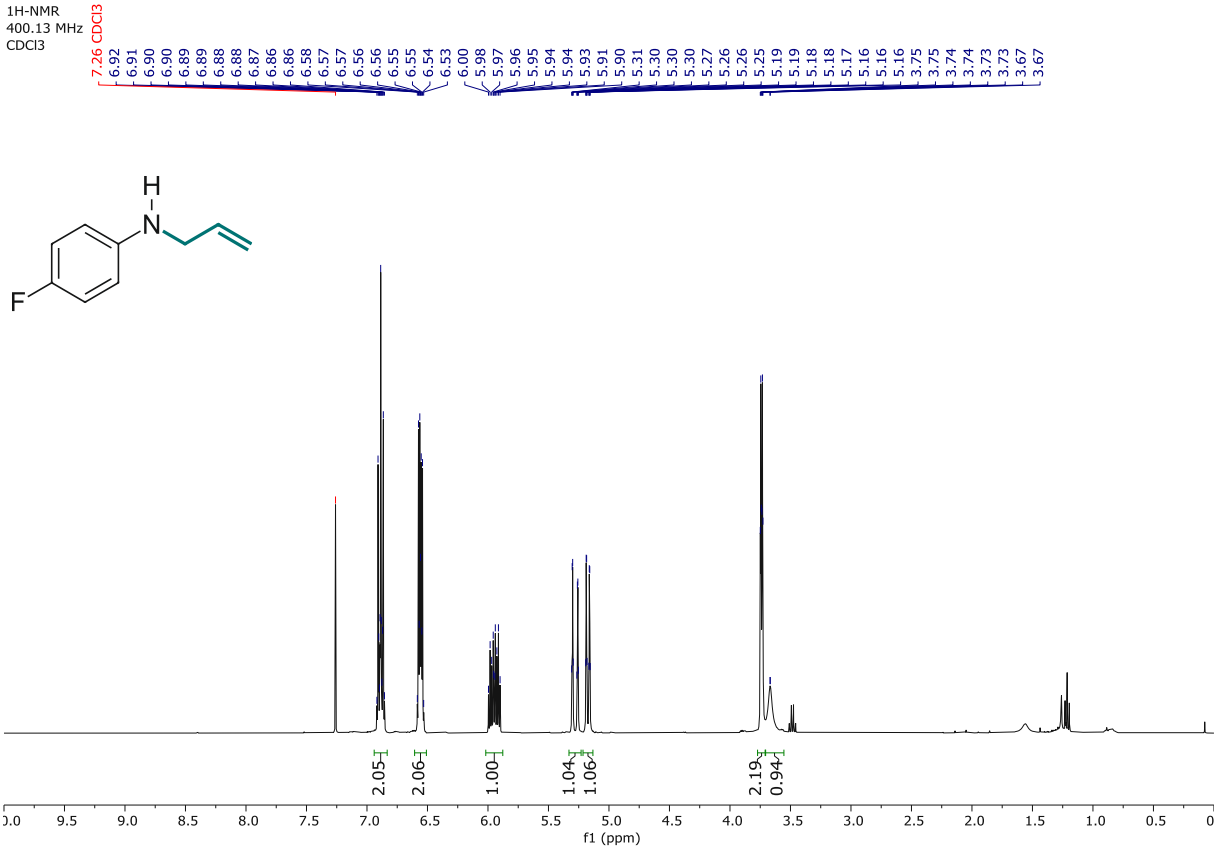


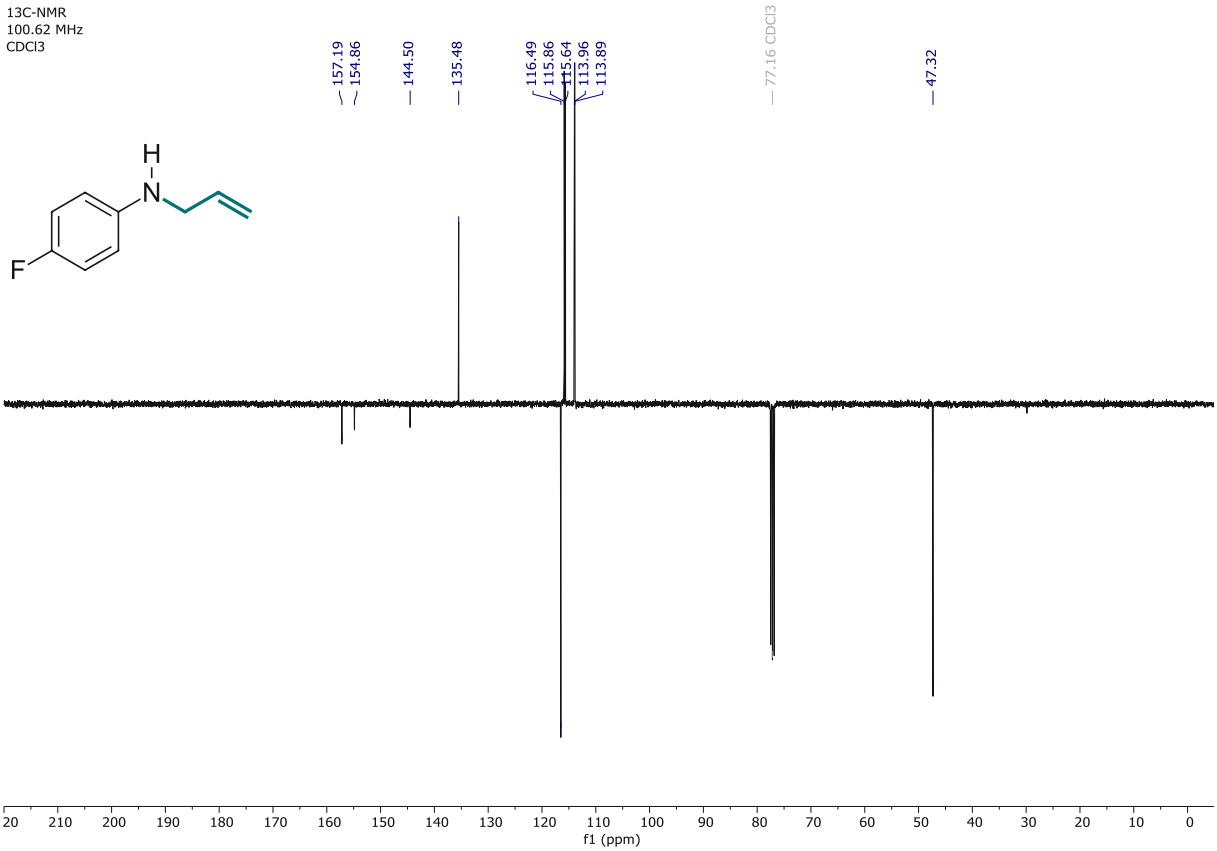
3-allyloxy estrone **(21)**



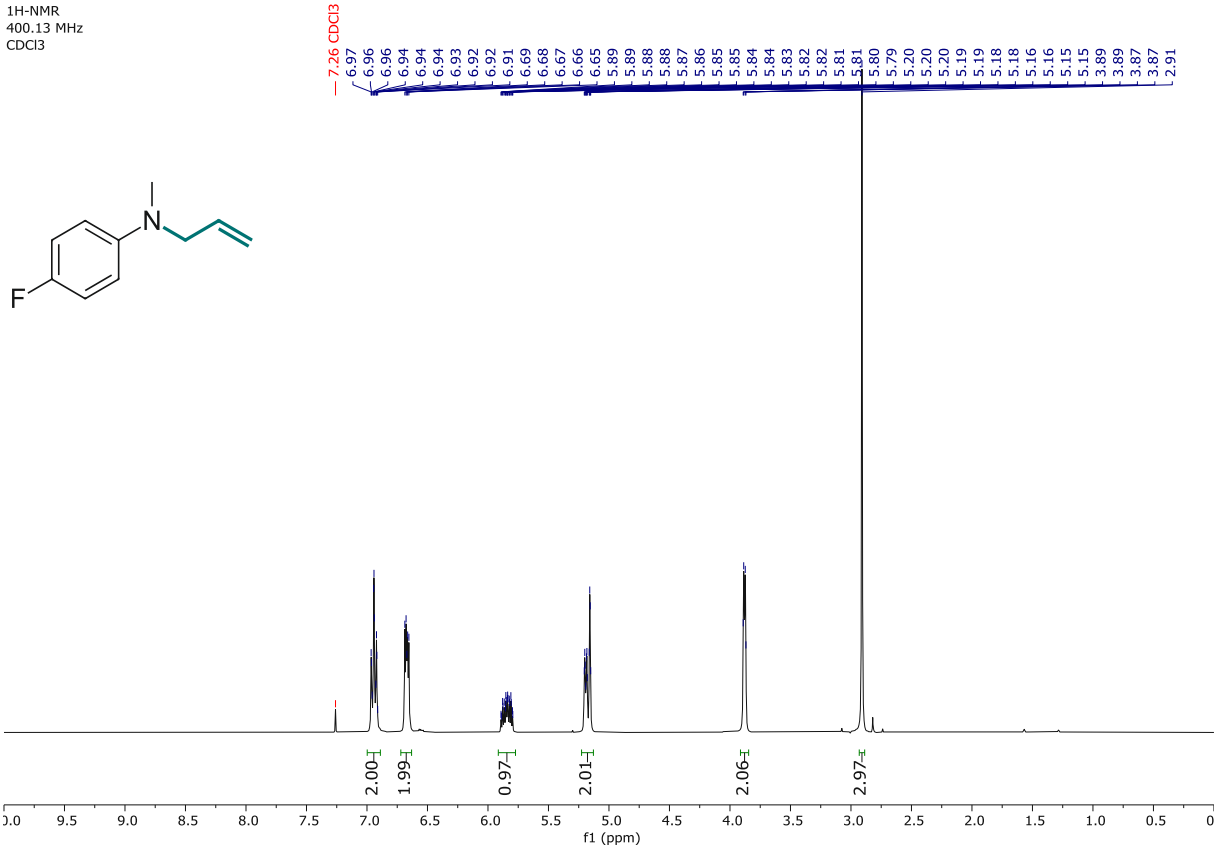


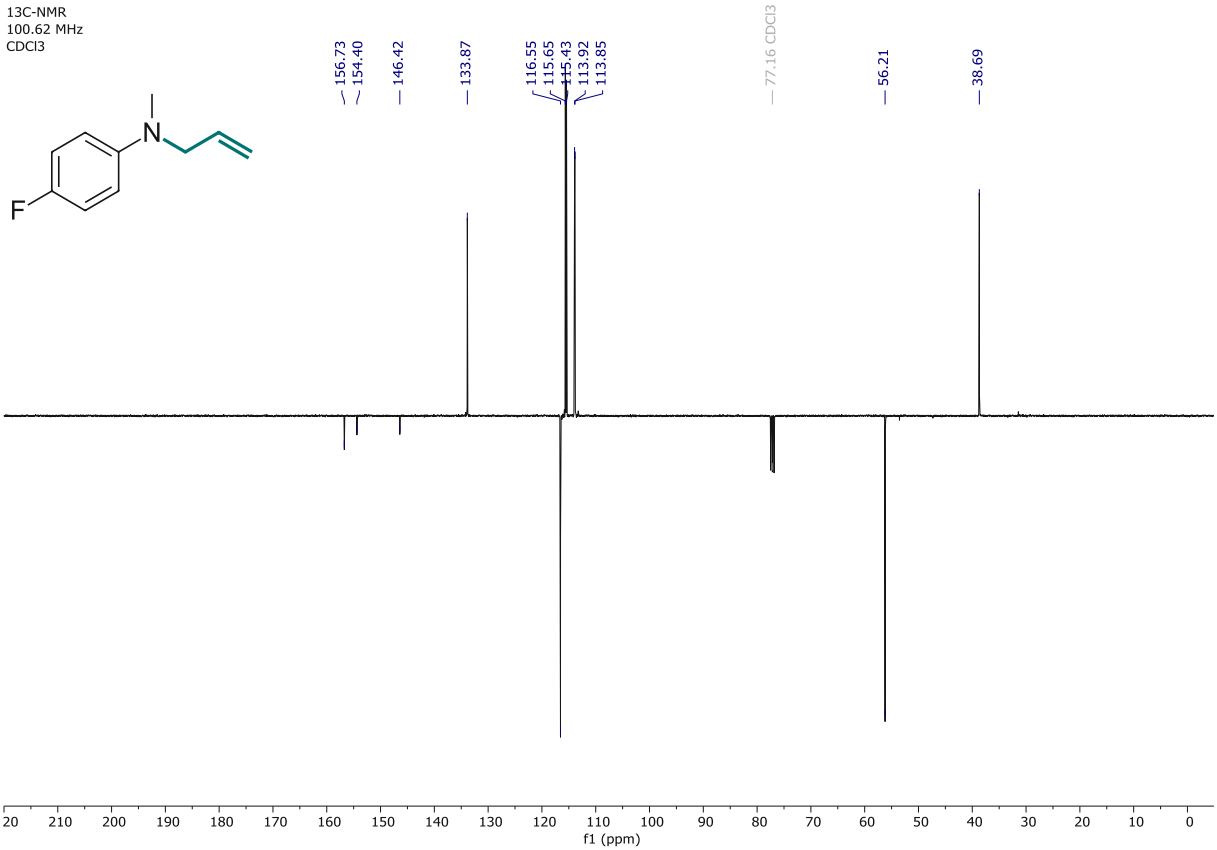
N-Allyl-4-fluoroaniline **(22)**

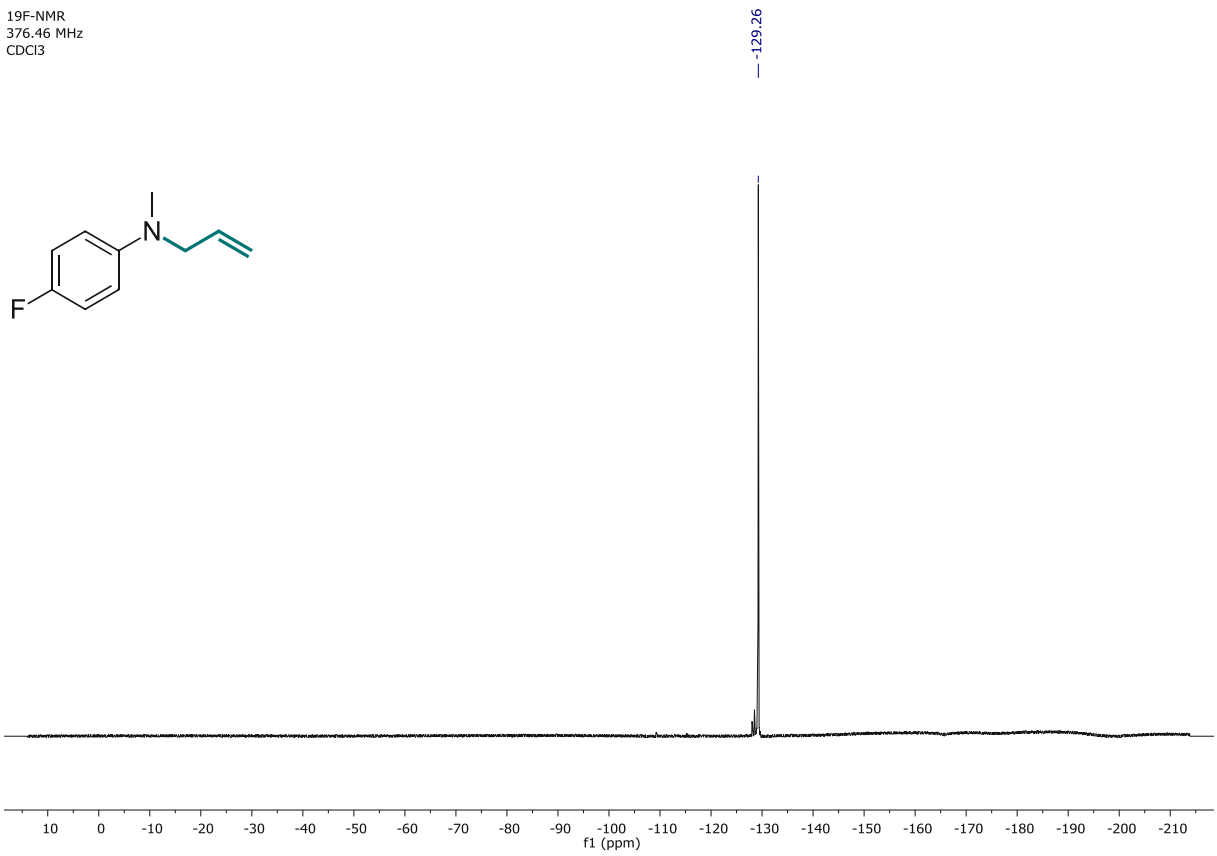




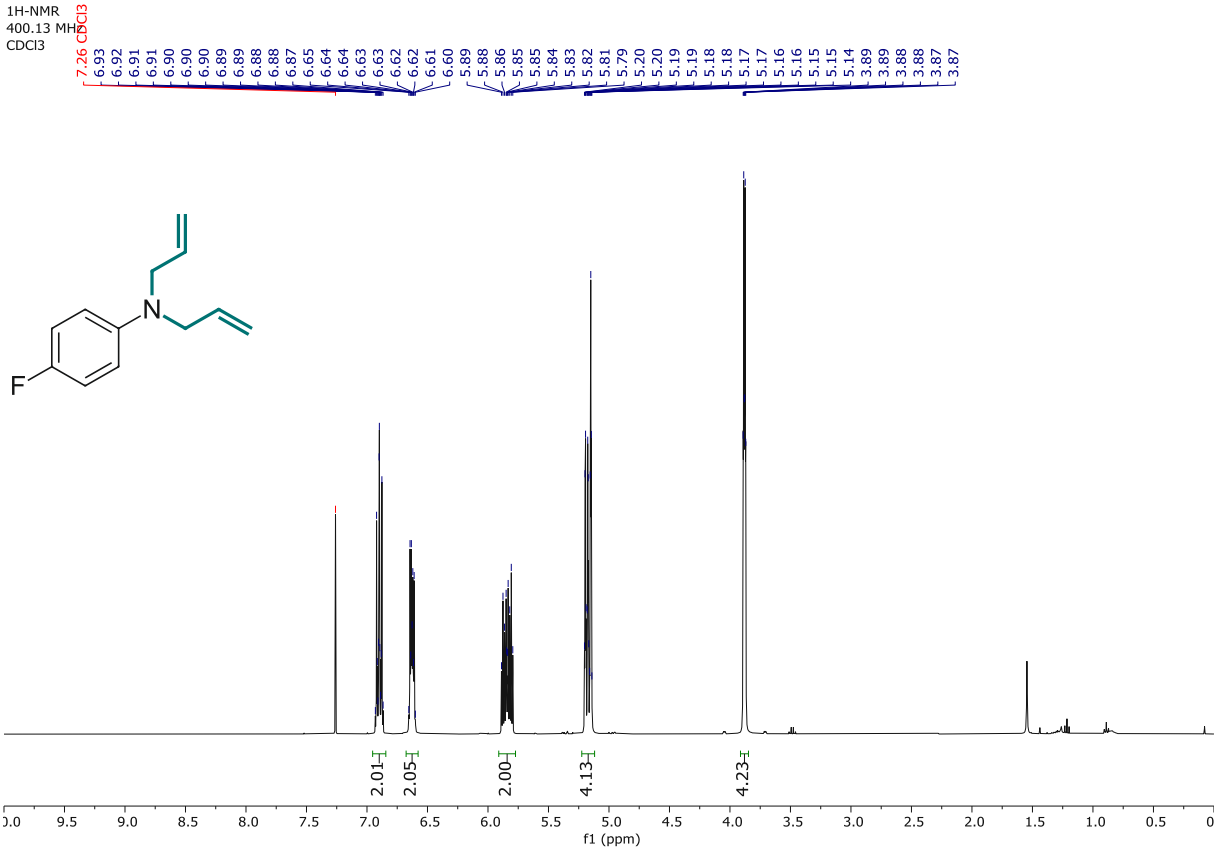
N-Allyl-4-fluoro-*N*-methylaniline **(23)**

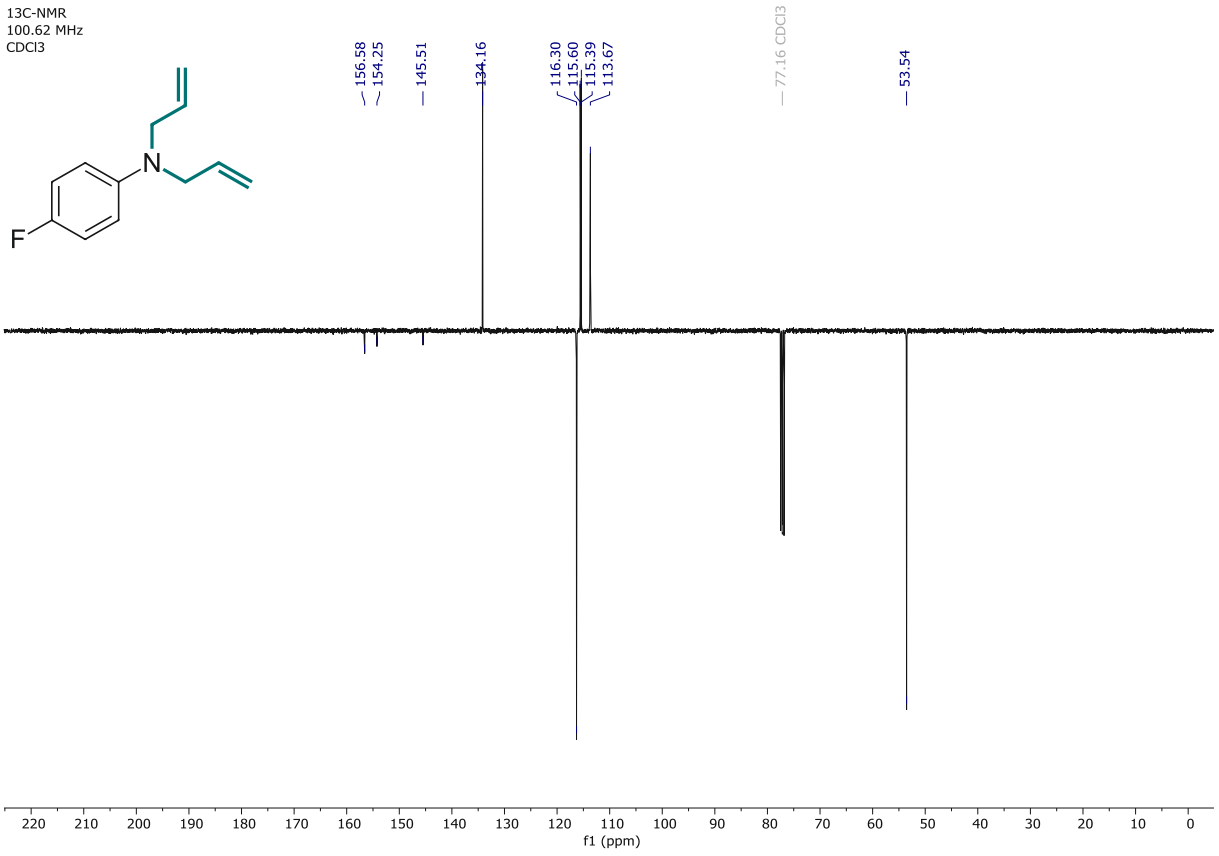




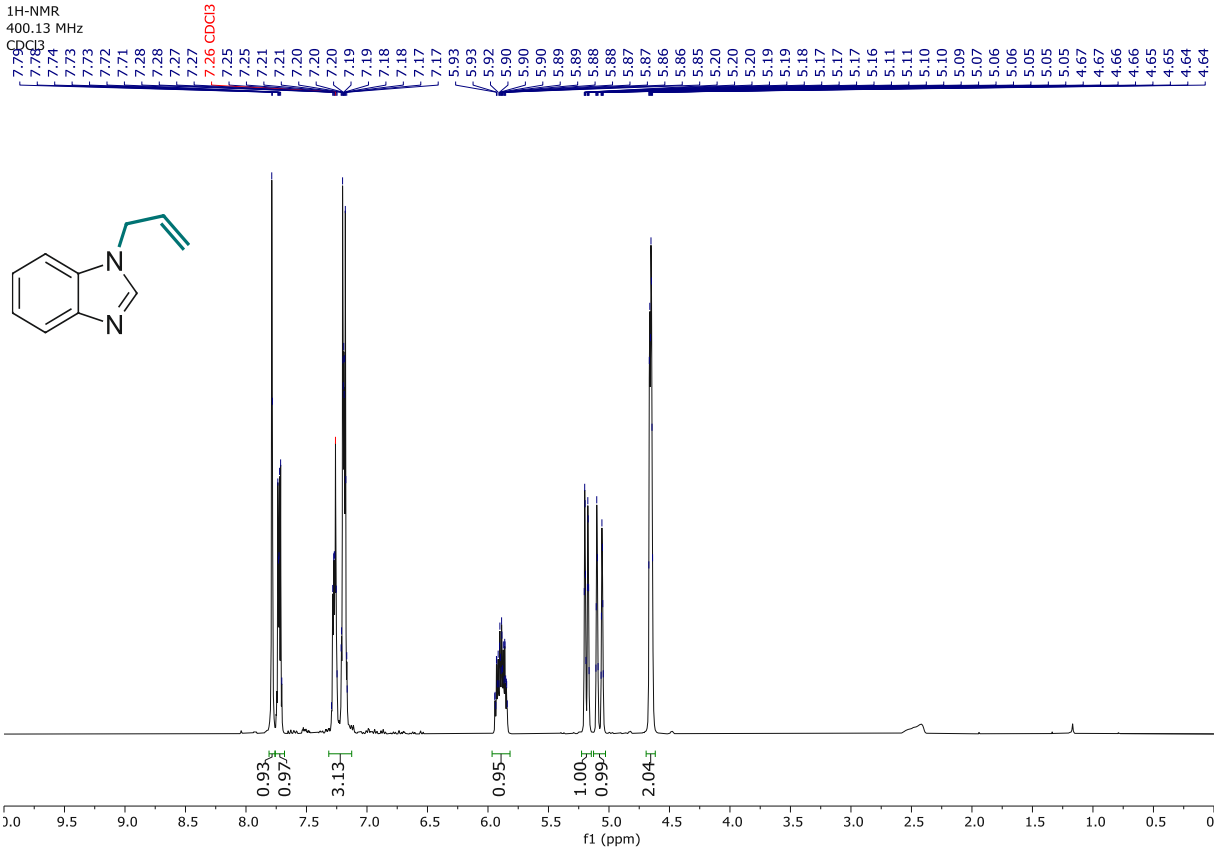


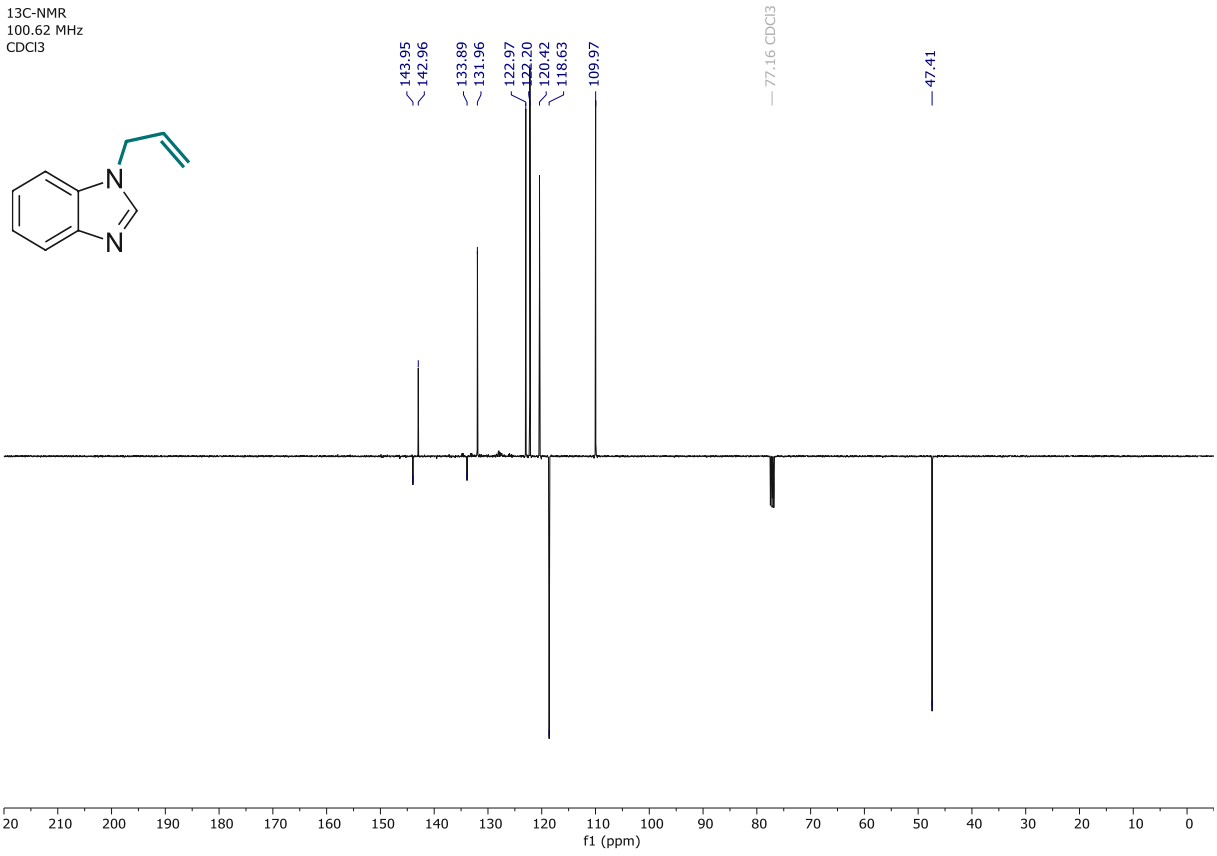
N,N-diallyl-4-fluoroaniline **(24)**



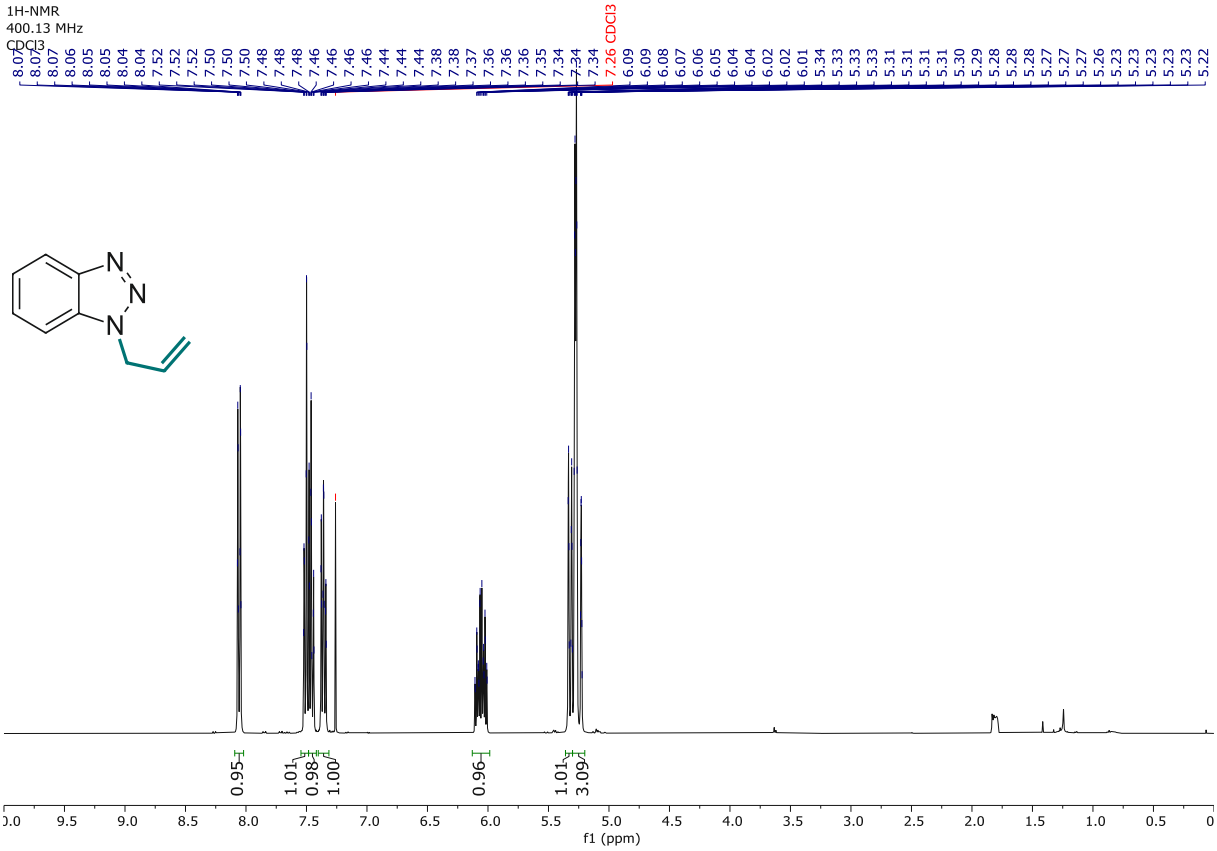


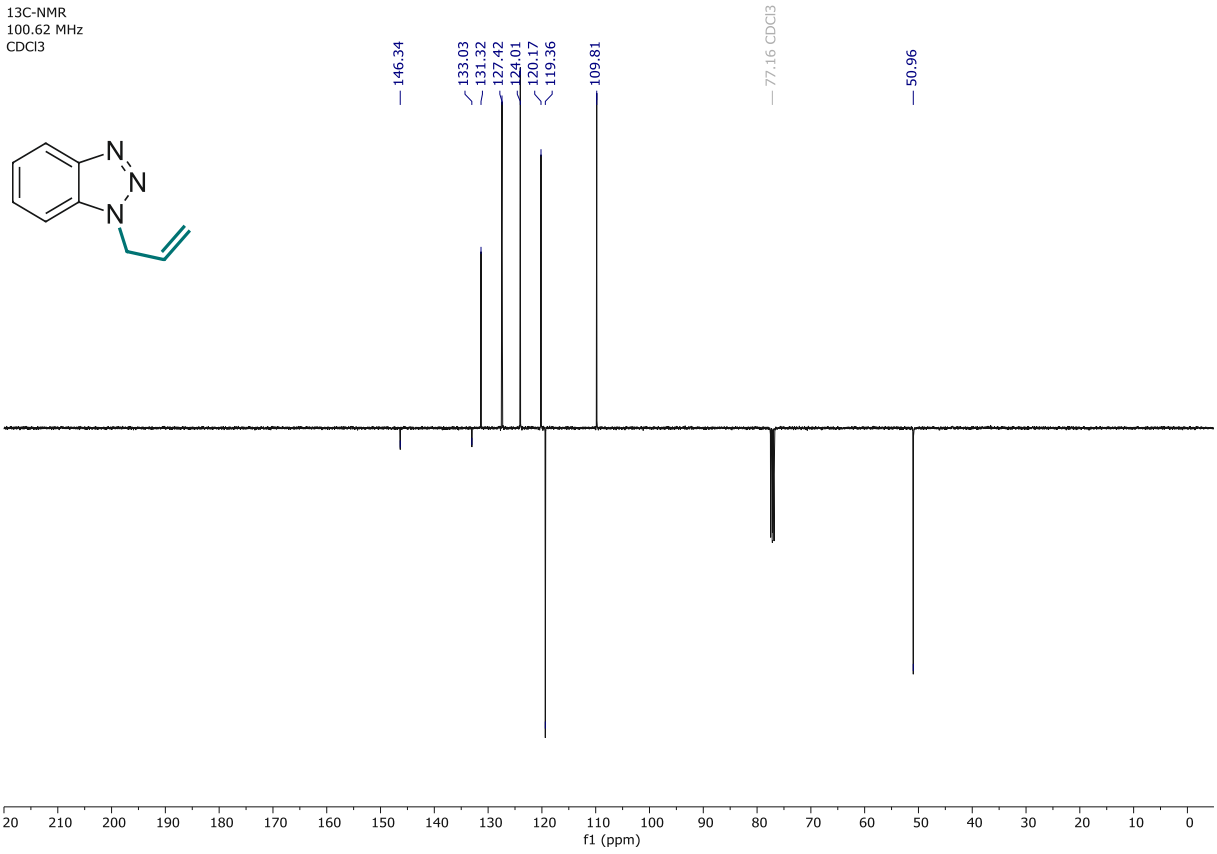
1-Allylbenzimidazole **(25)**



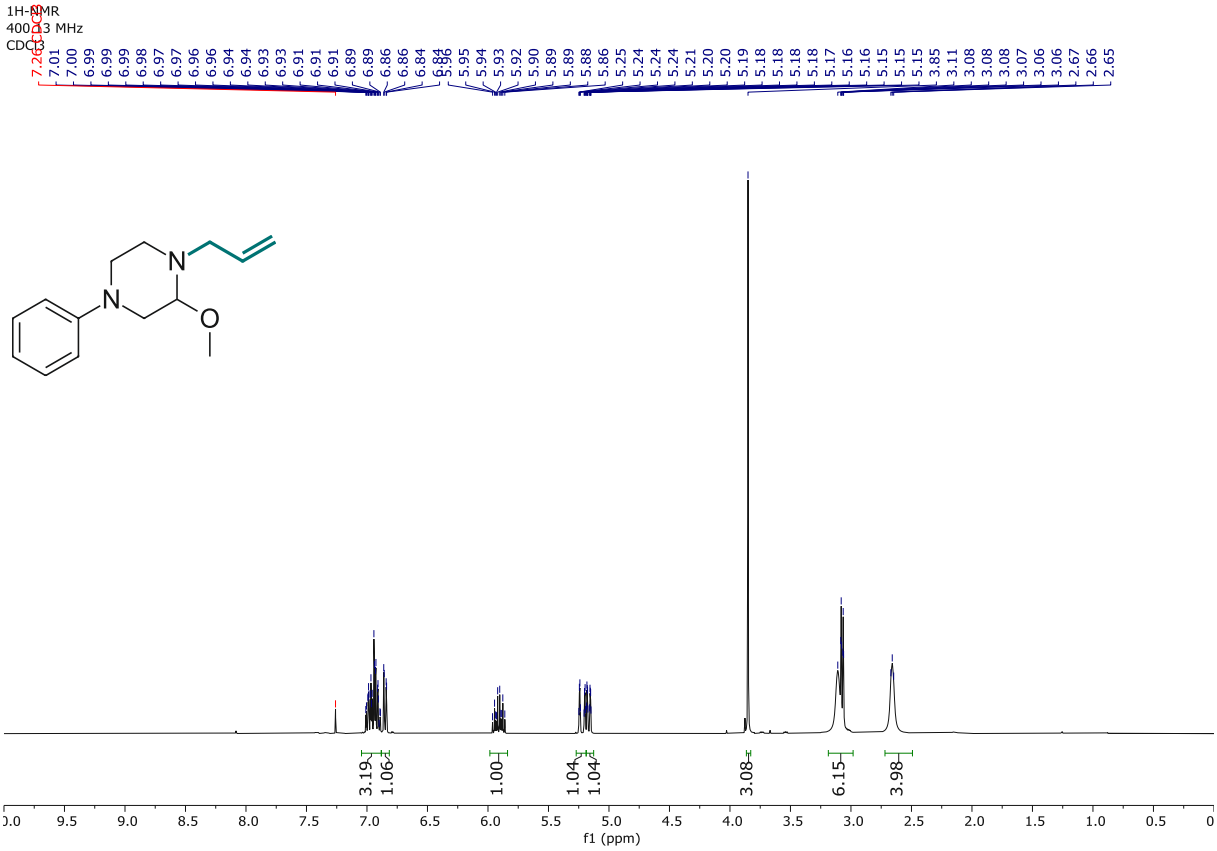


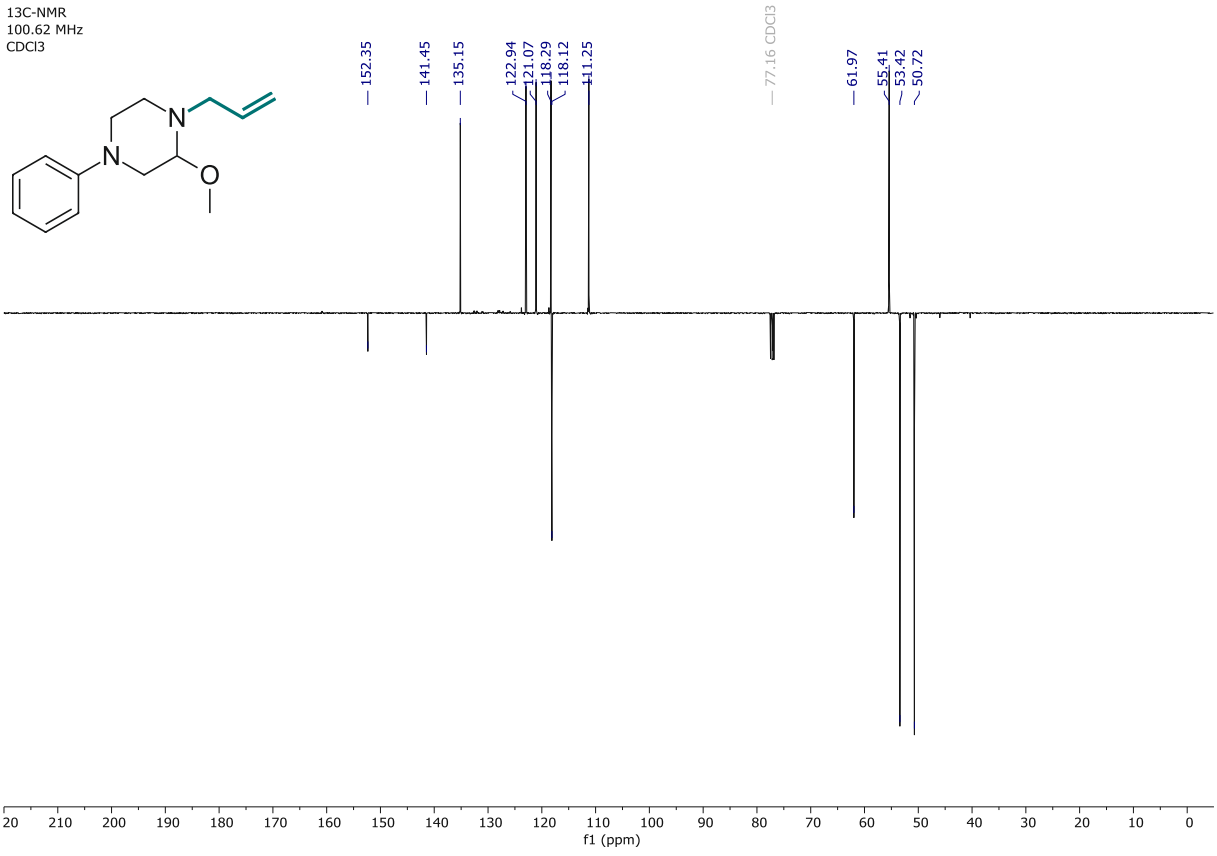
1-Allylbenzotriazole **(26)**



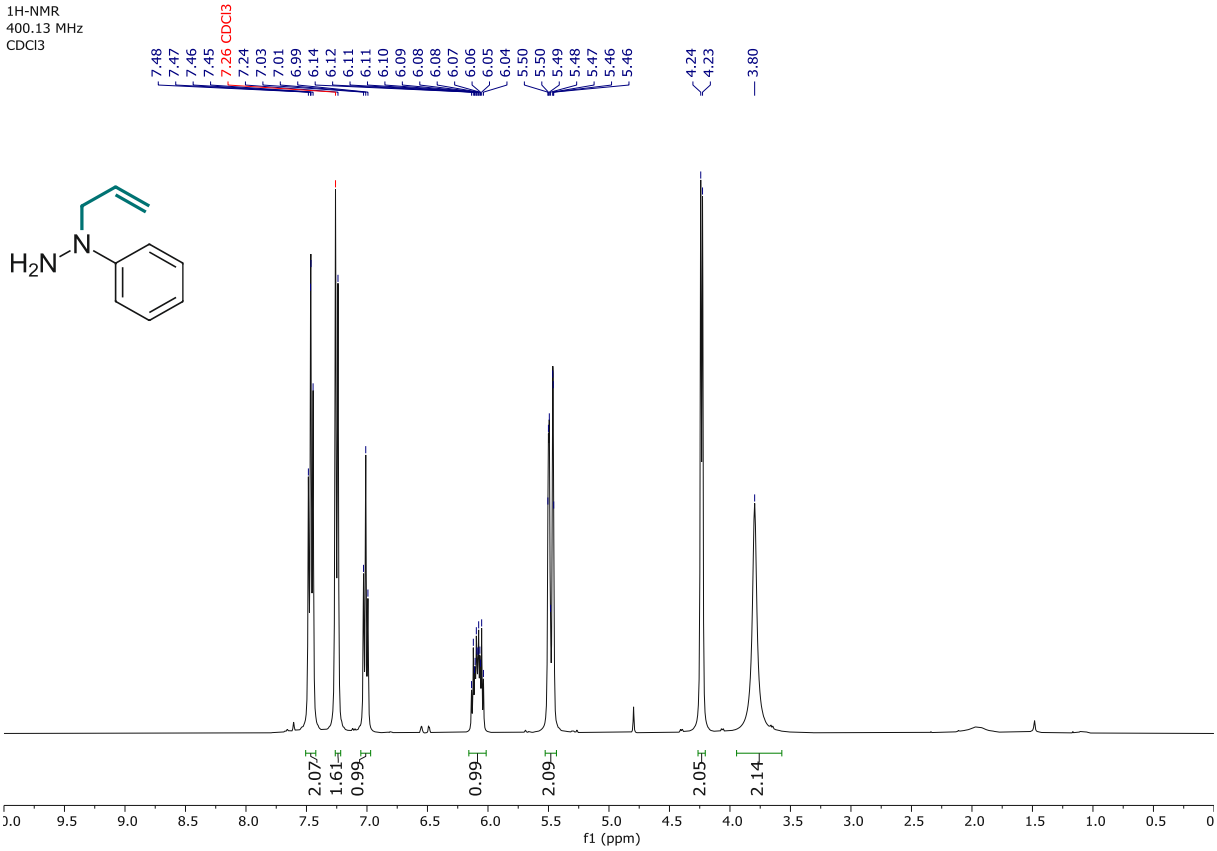


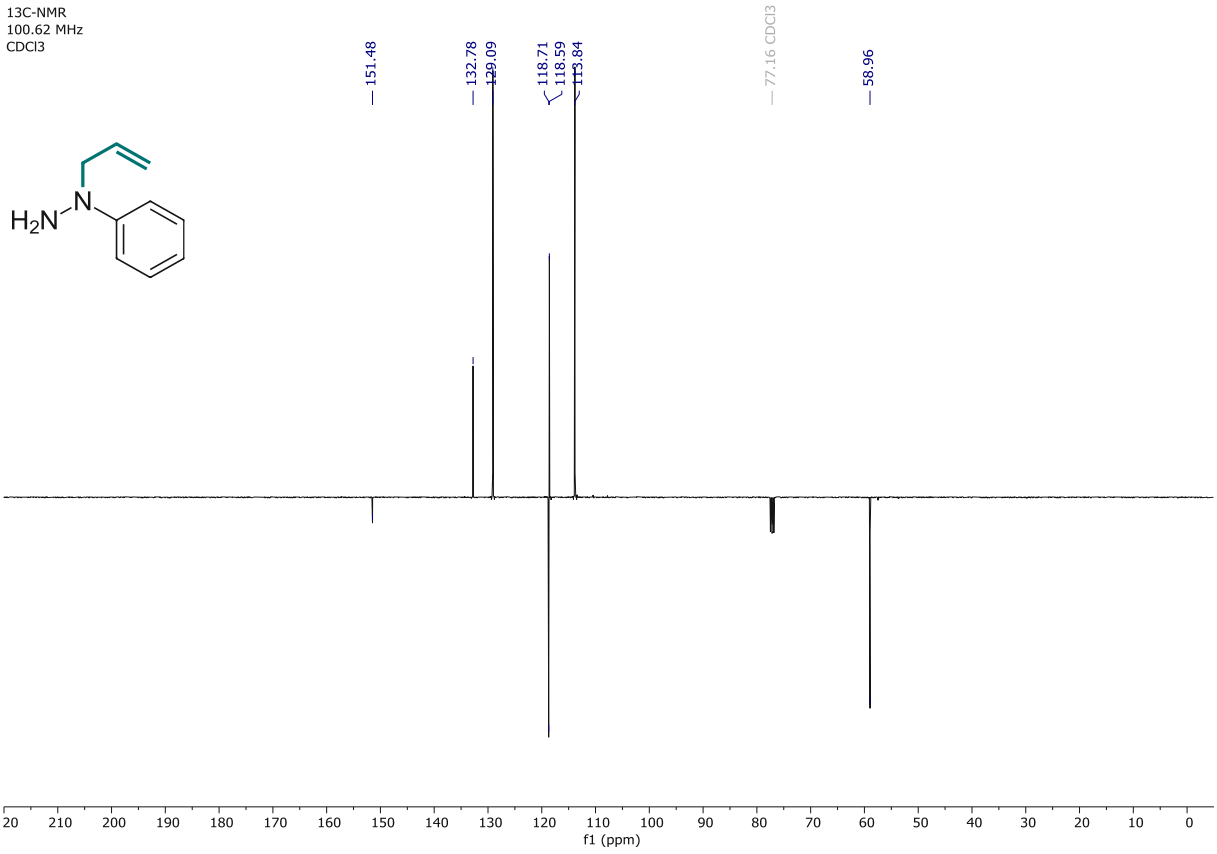
1-Allyl-4-(2-methoxy-phenyl)-piperazine **(27)**



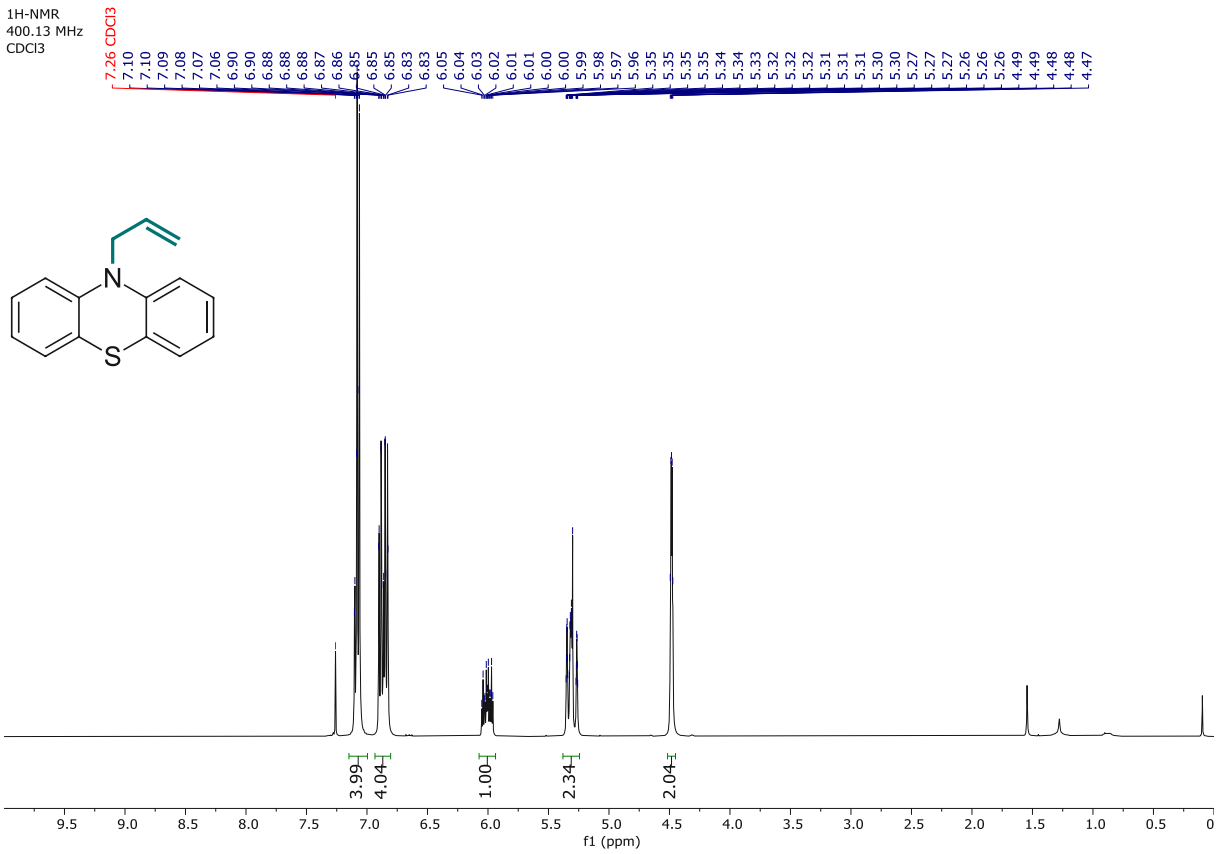


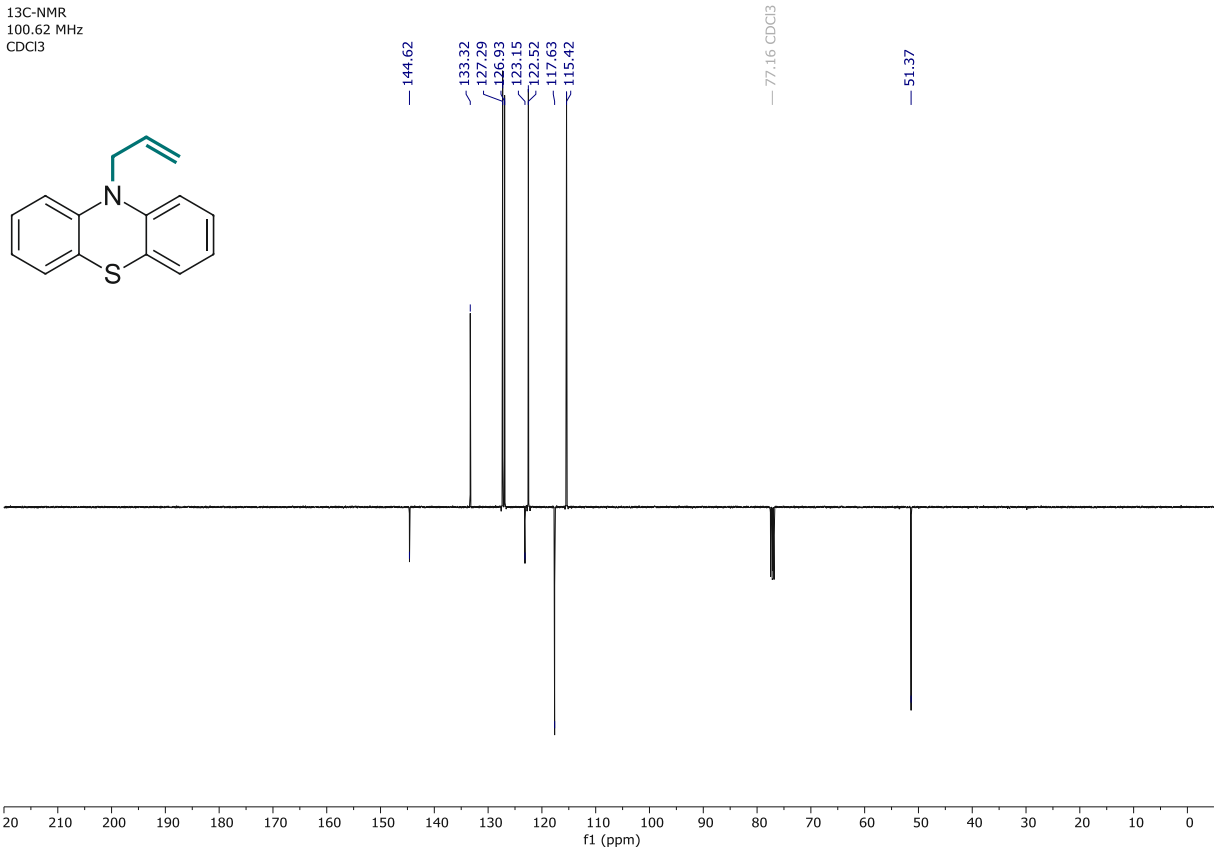
N-Allyl-N-phenylhydrazine **(28)**



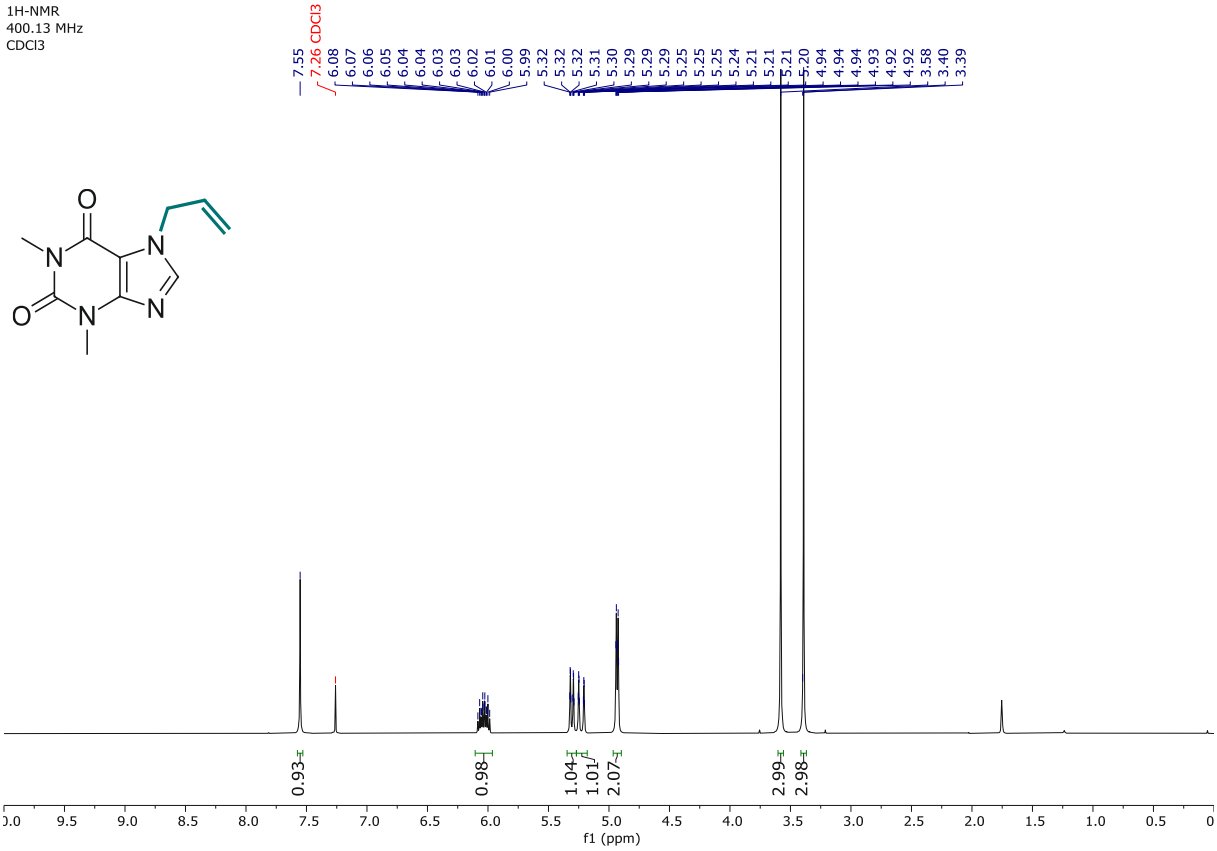


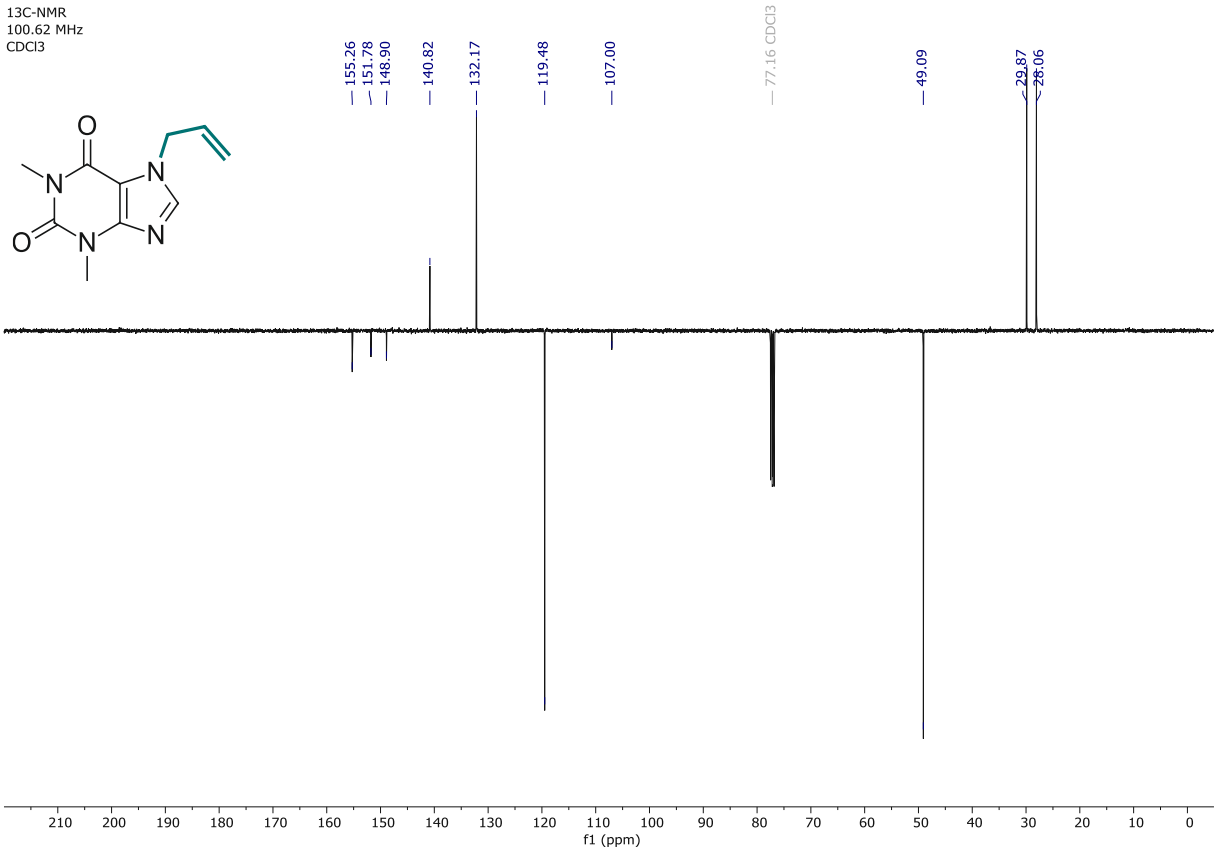
N-Allylphenothiazine **(29)**



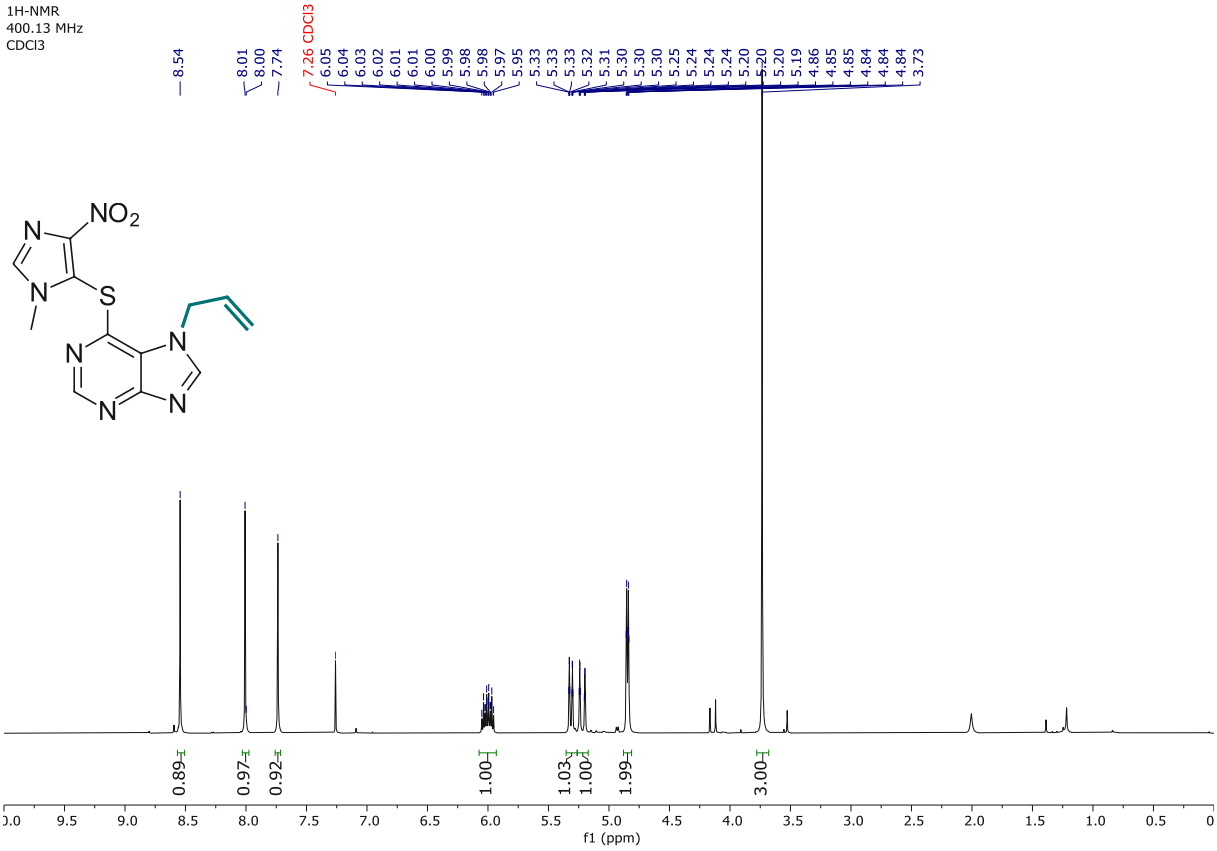


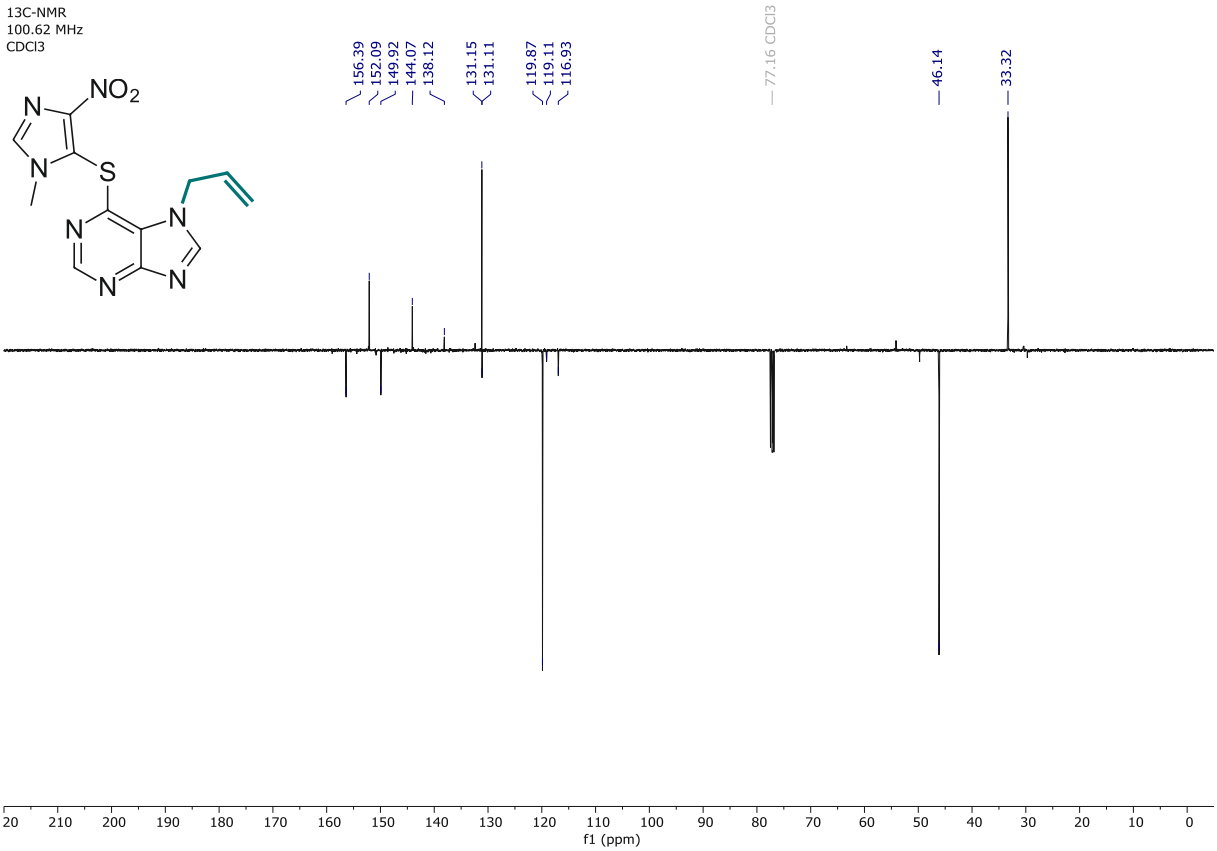
7-Allyl1,3-dimethylxanthine **(30)**



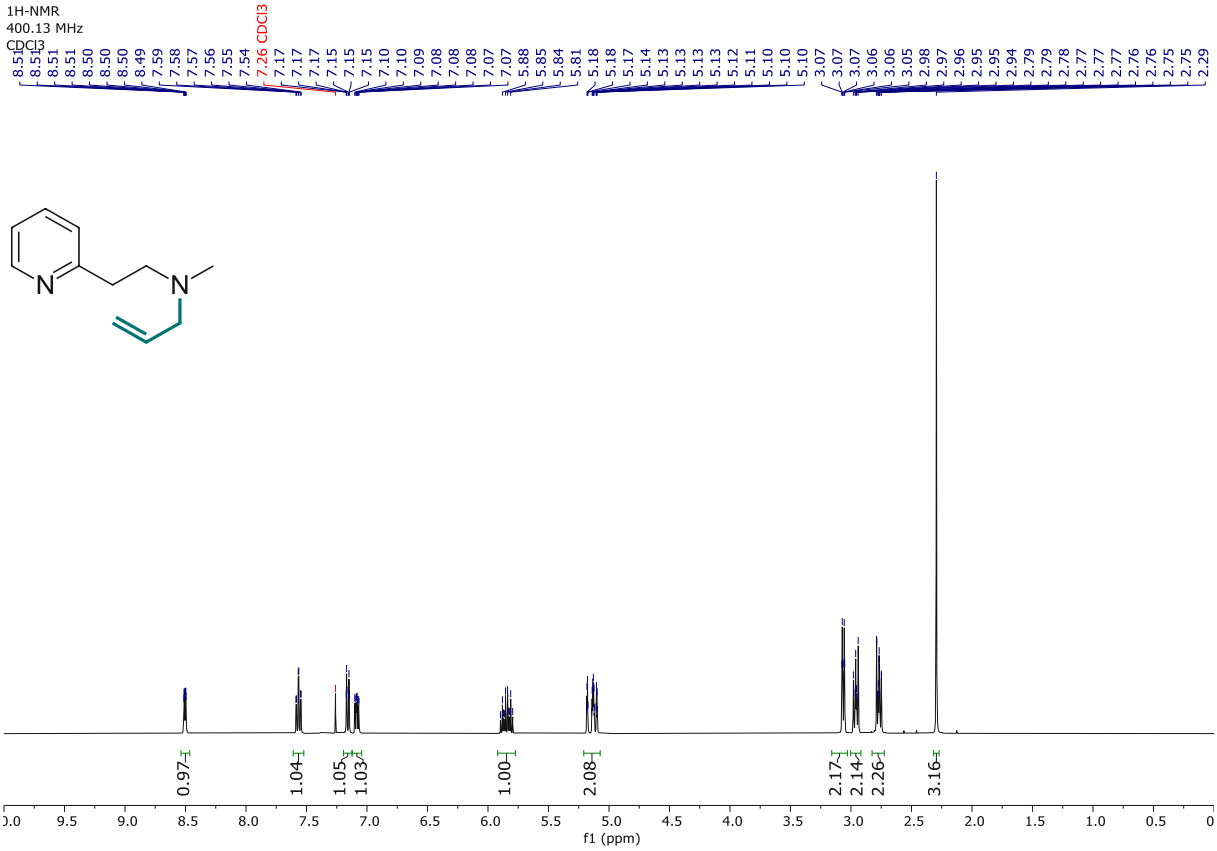


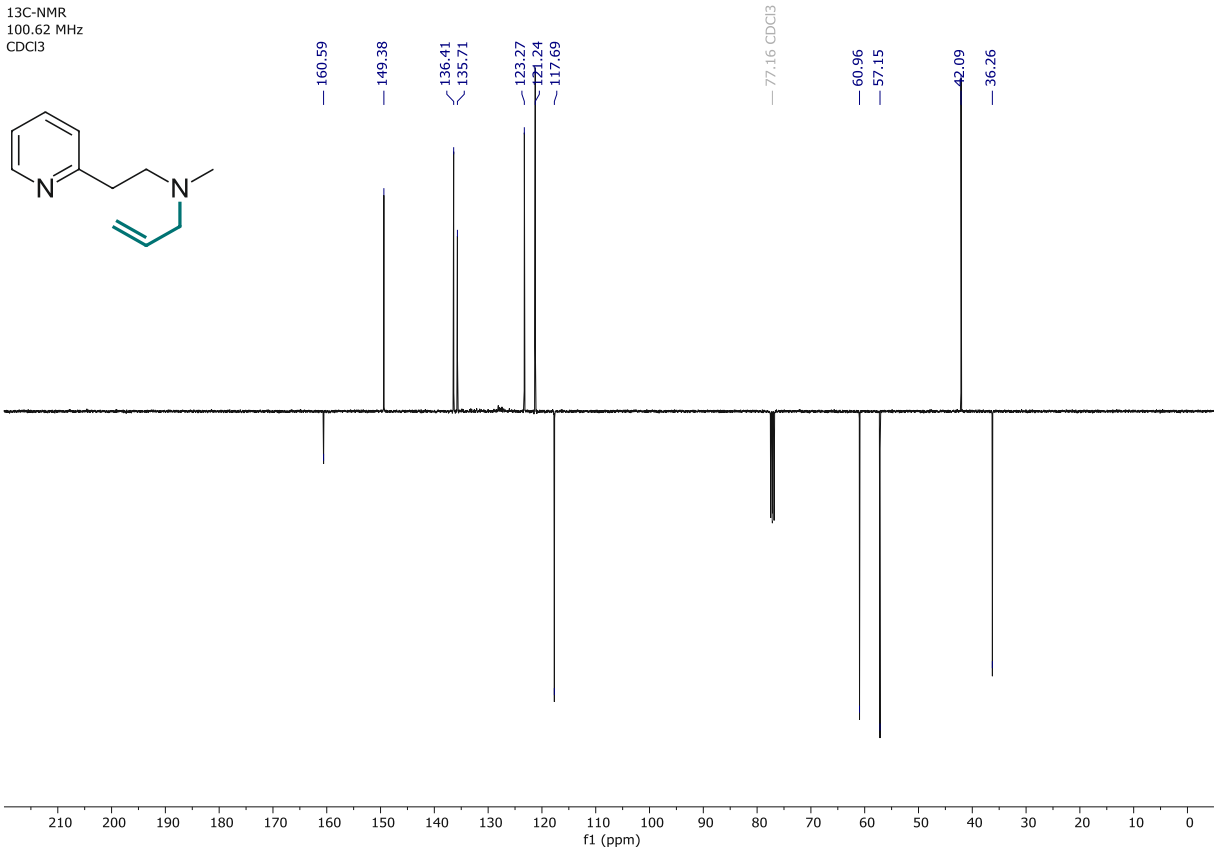
N-allyl azathioprine **(31)**



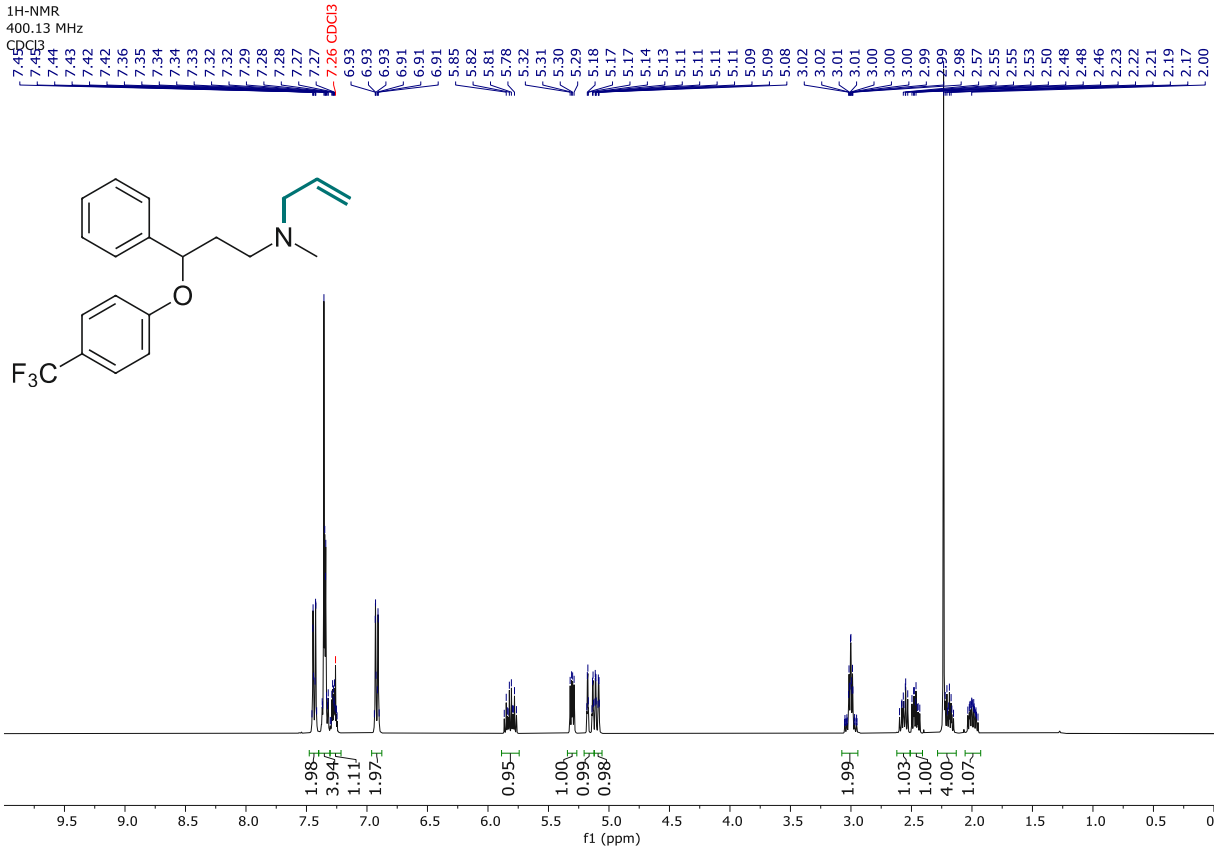


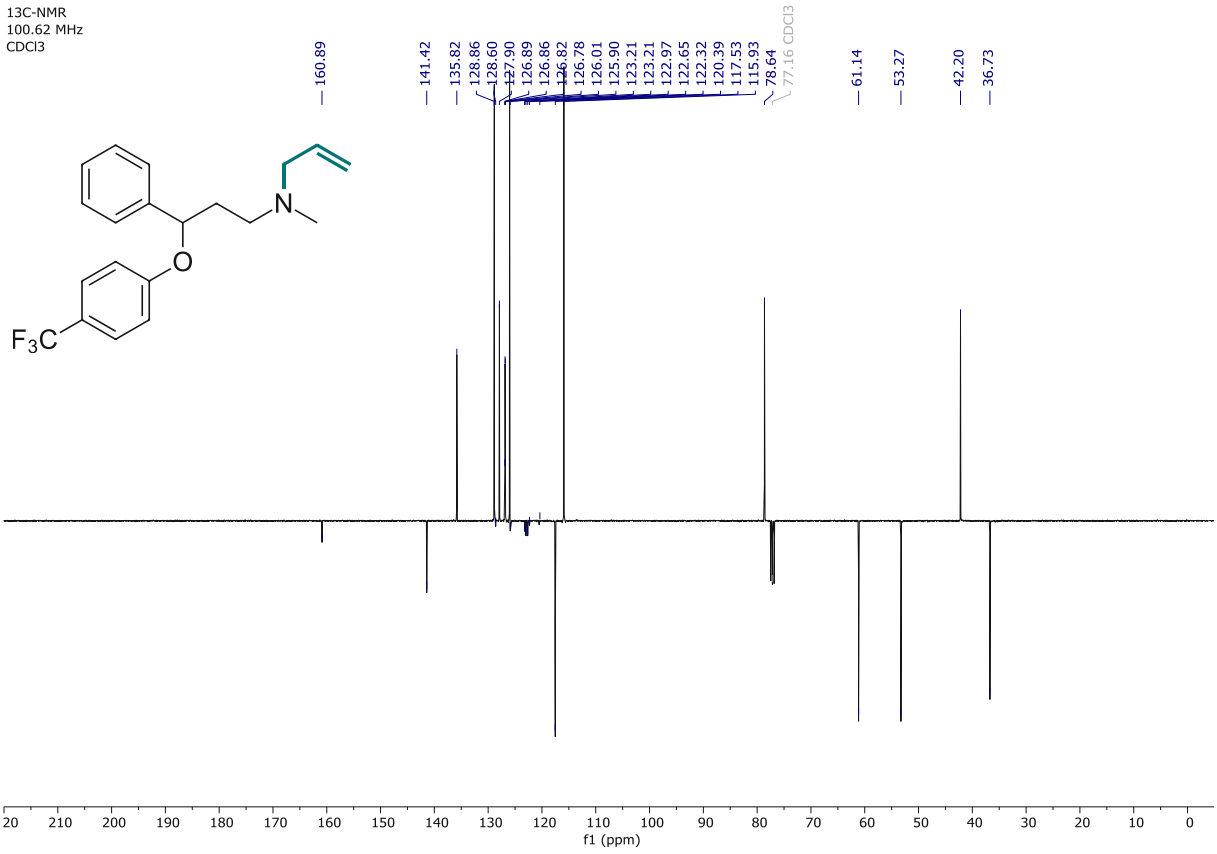
N-Allyl betahistine **(32)**



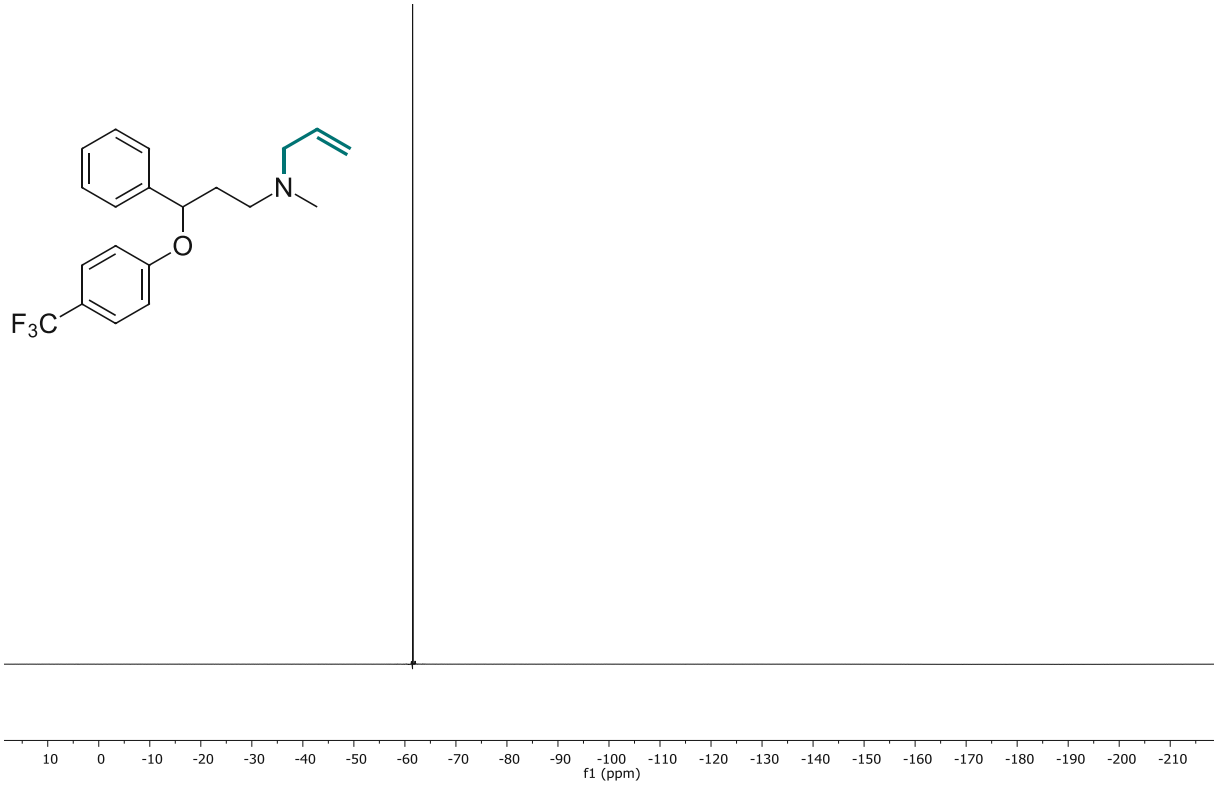


N-Allyl fluoxetine **(33)**

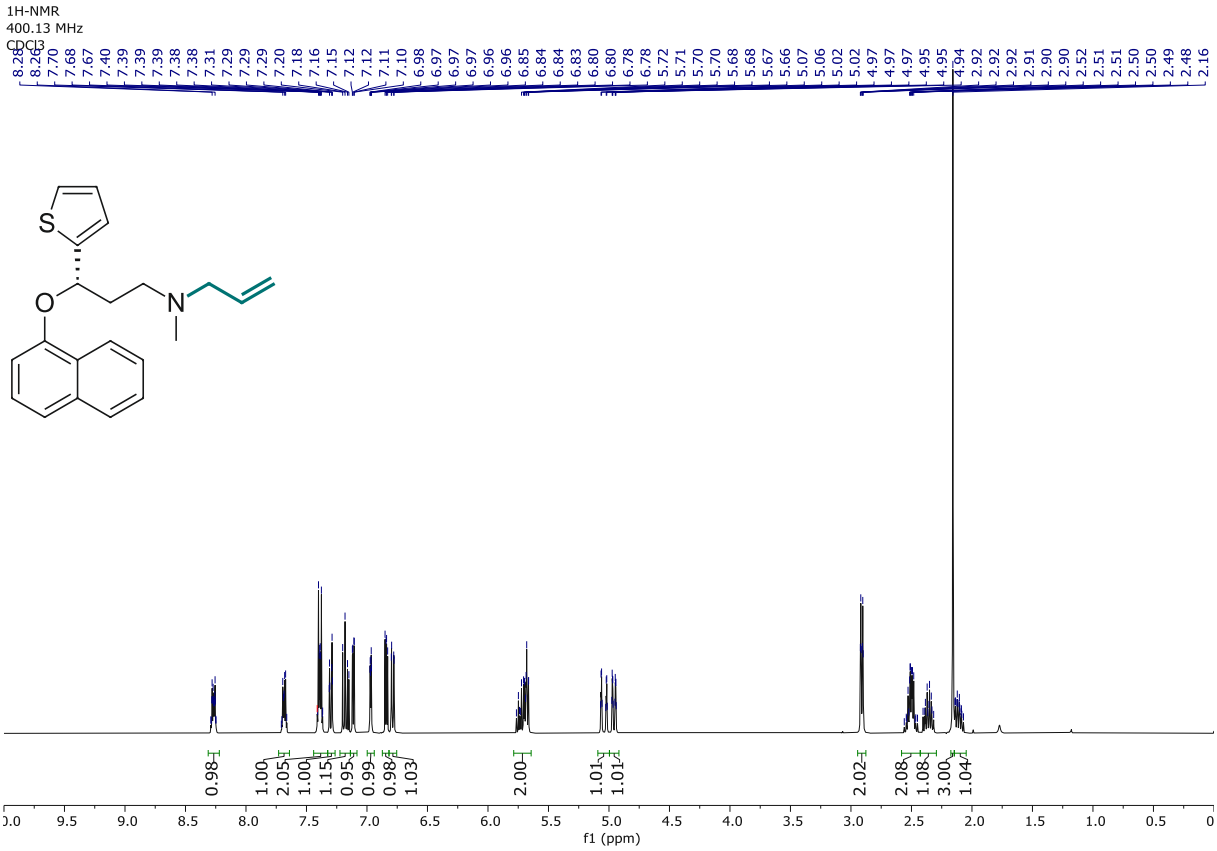


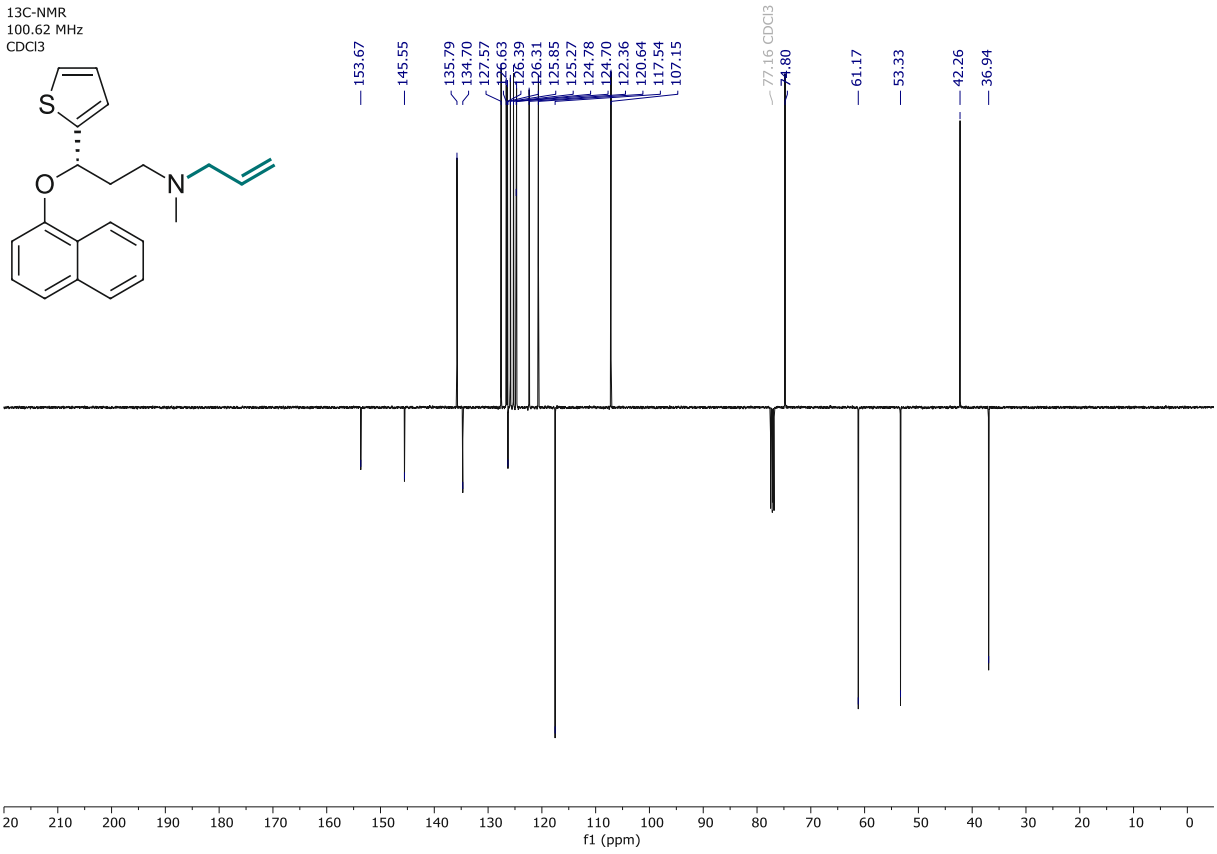


19F-NMR
376.46 MHz
CDCl3

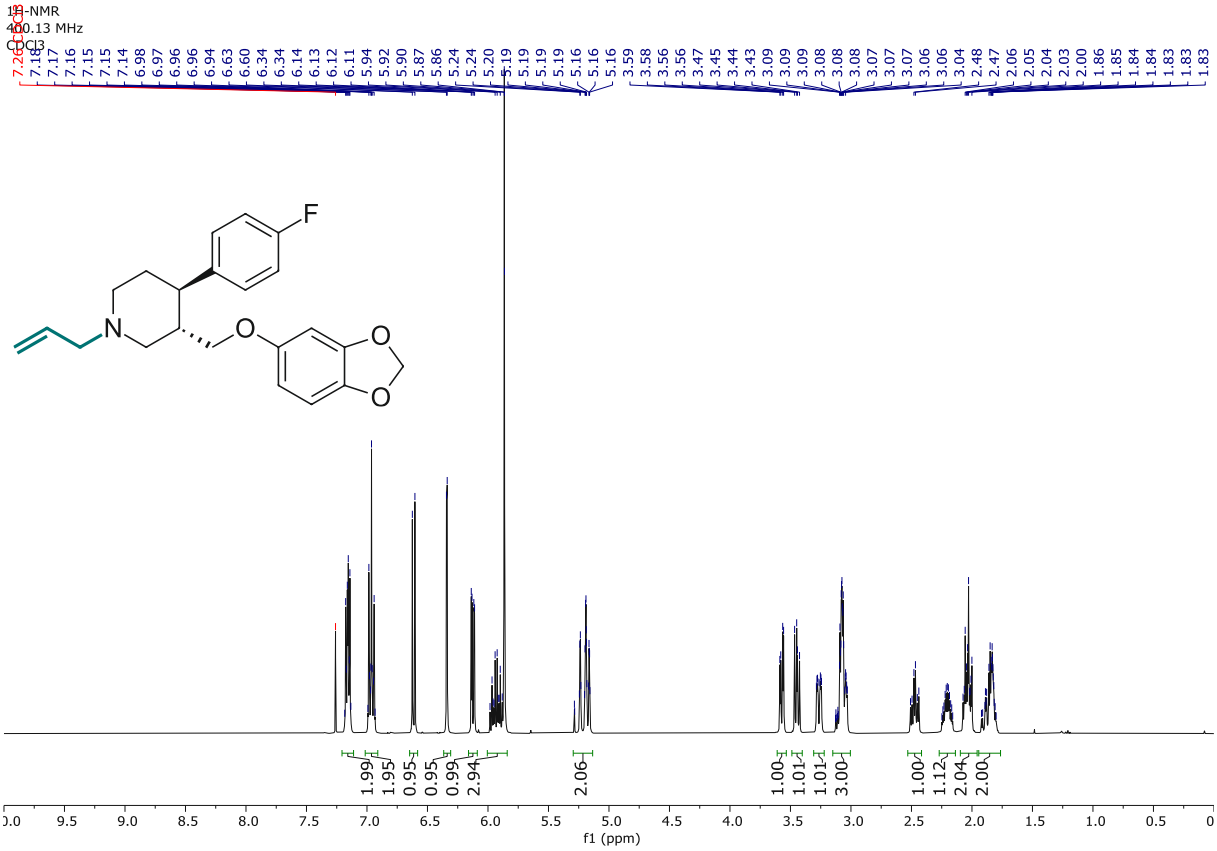


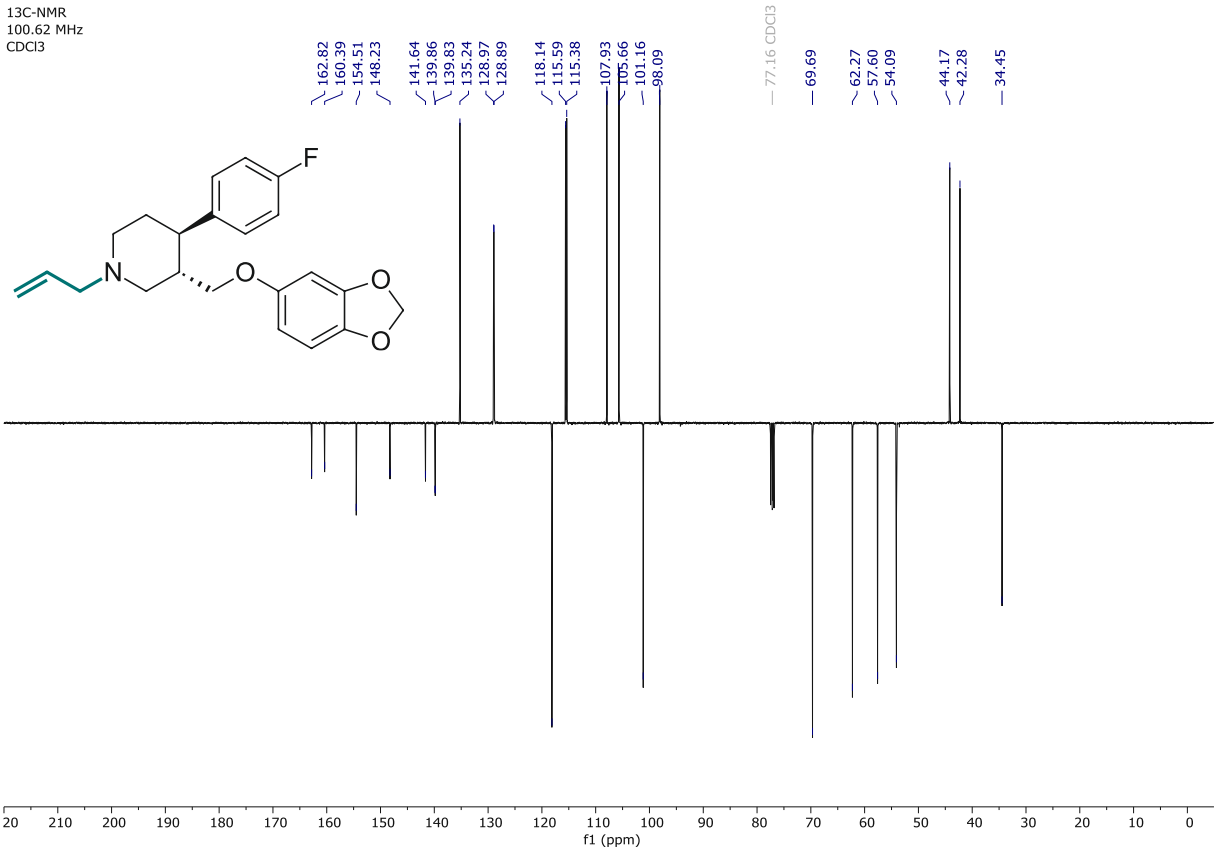
N-Allyl duloxetine **(34)**



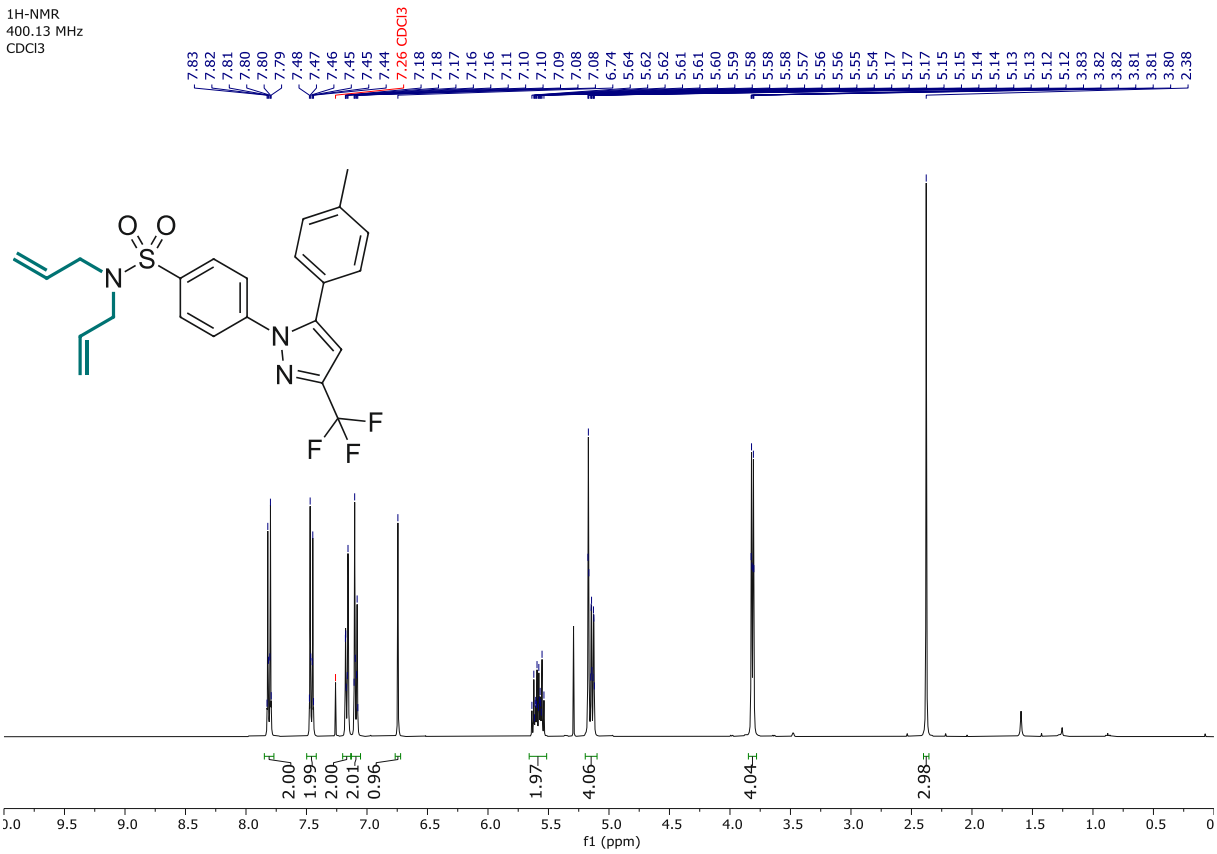


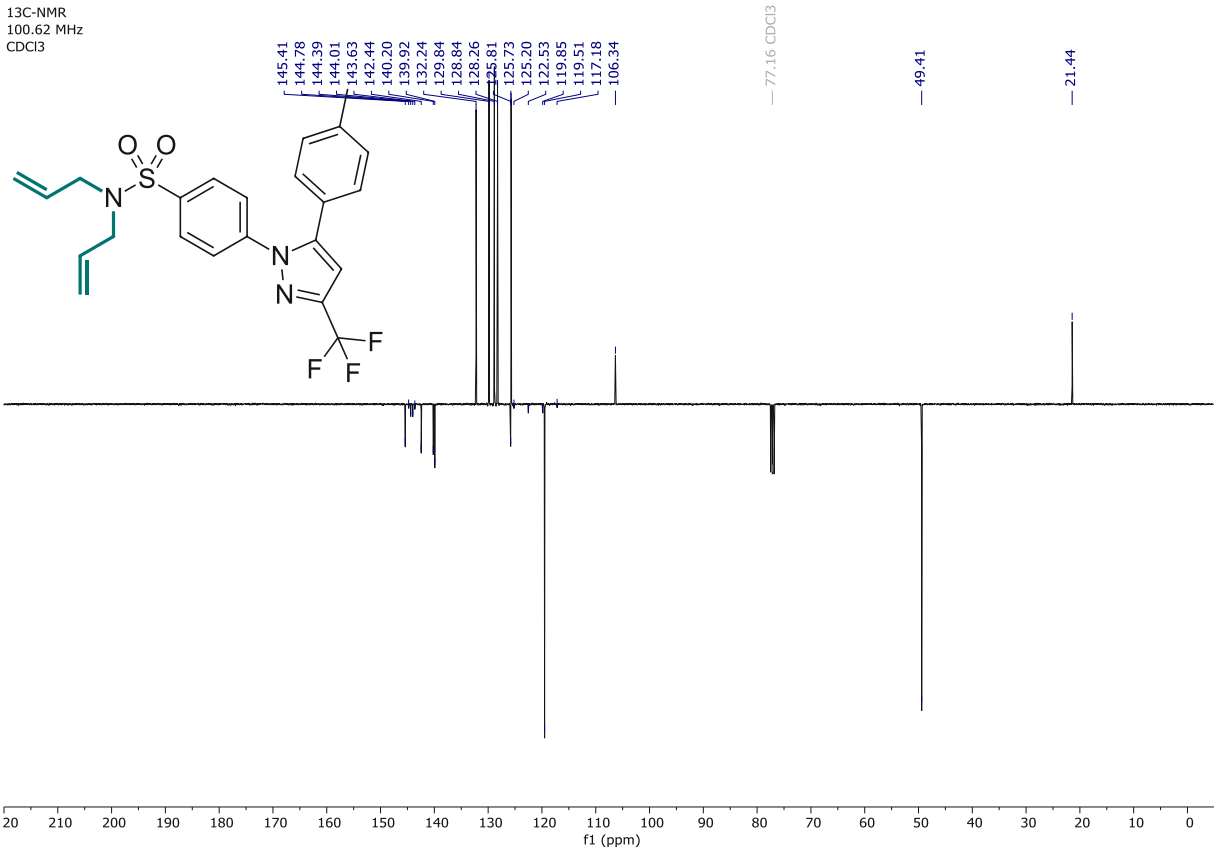
N-Allyl paroxetine **(35)**

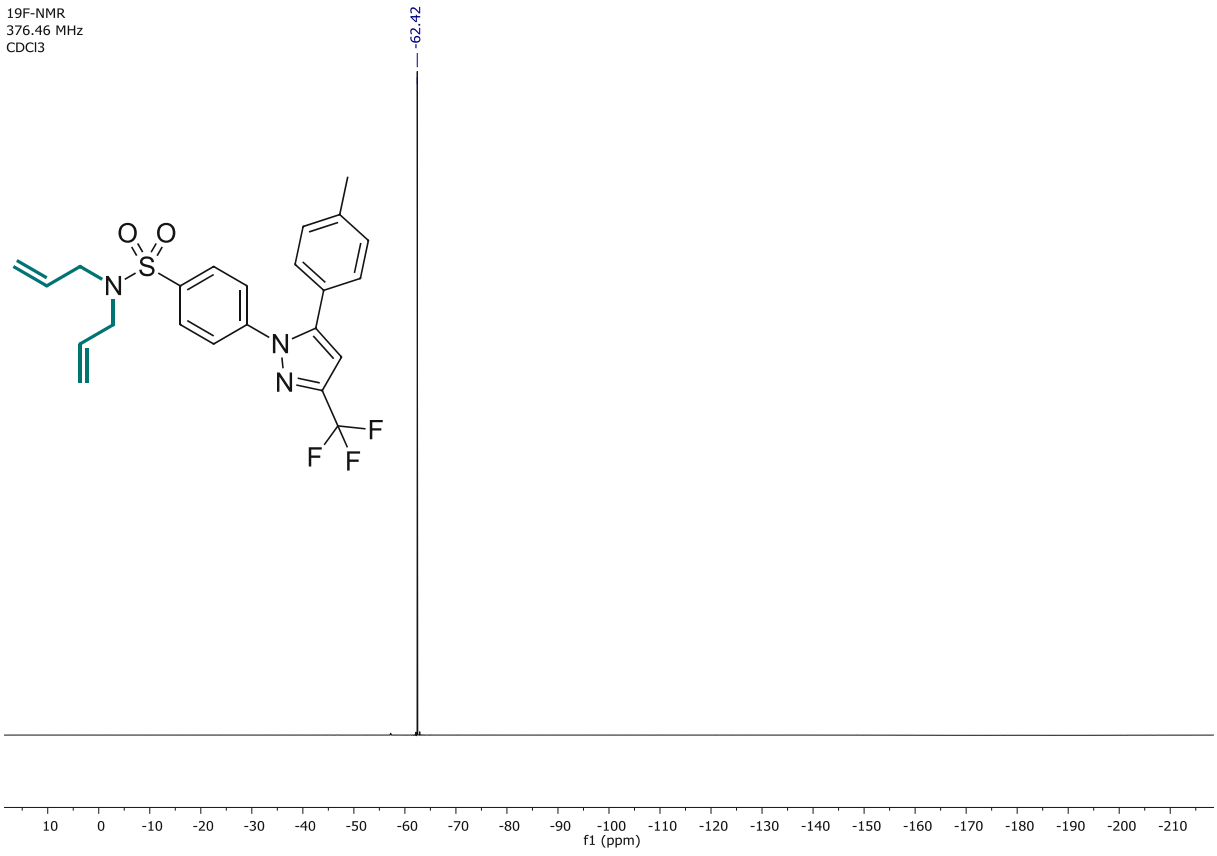




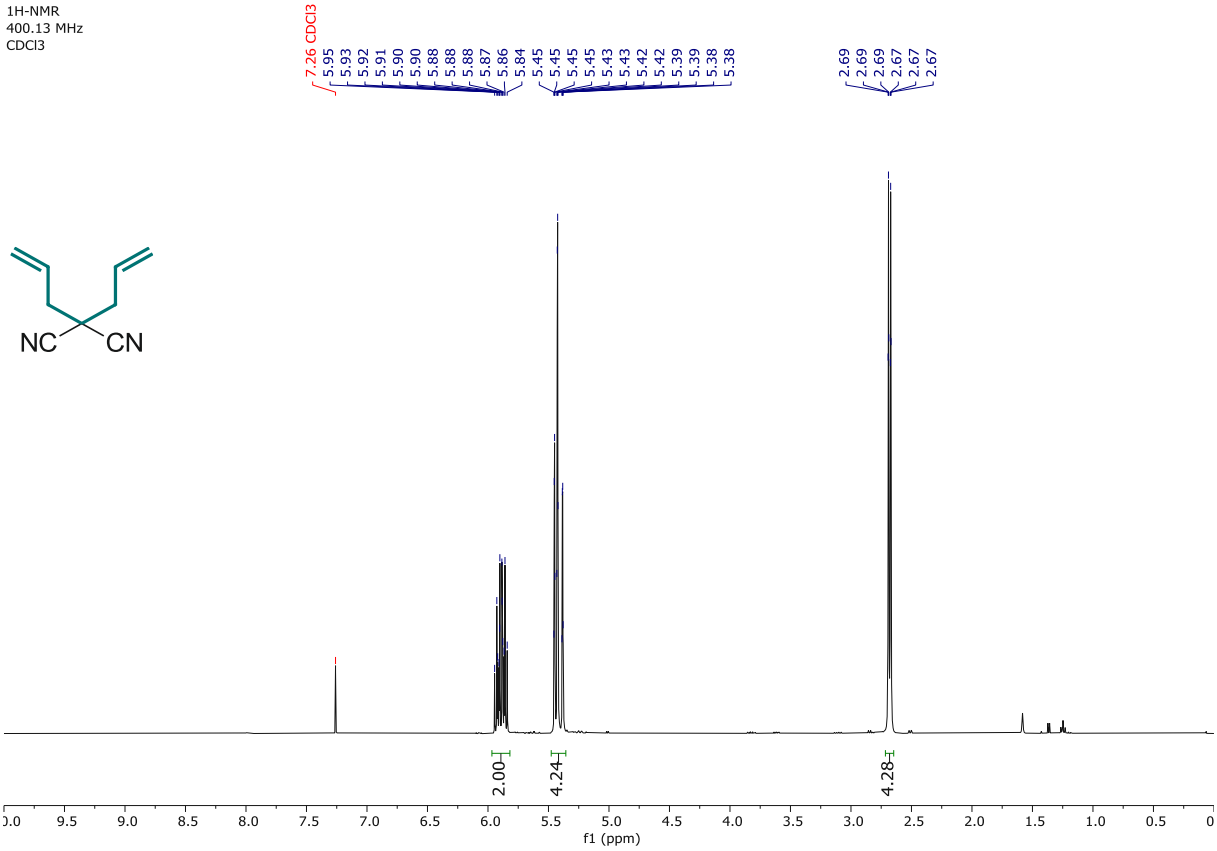
N,N-Diallyl celecoxib **(36)**

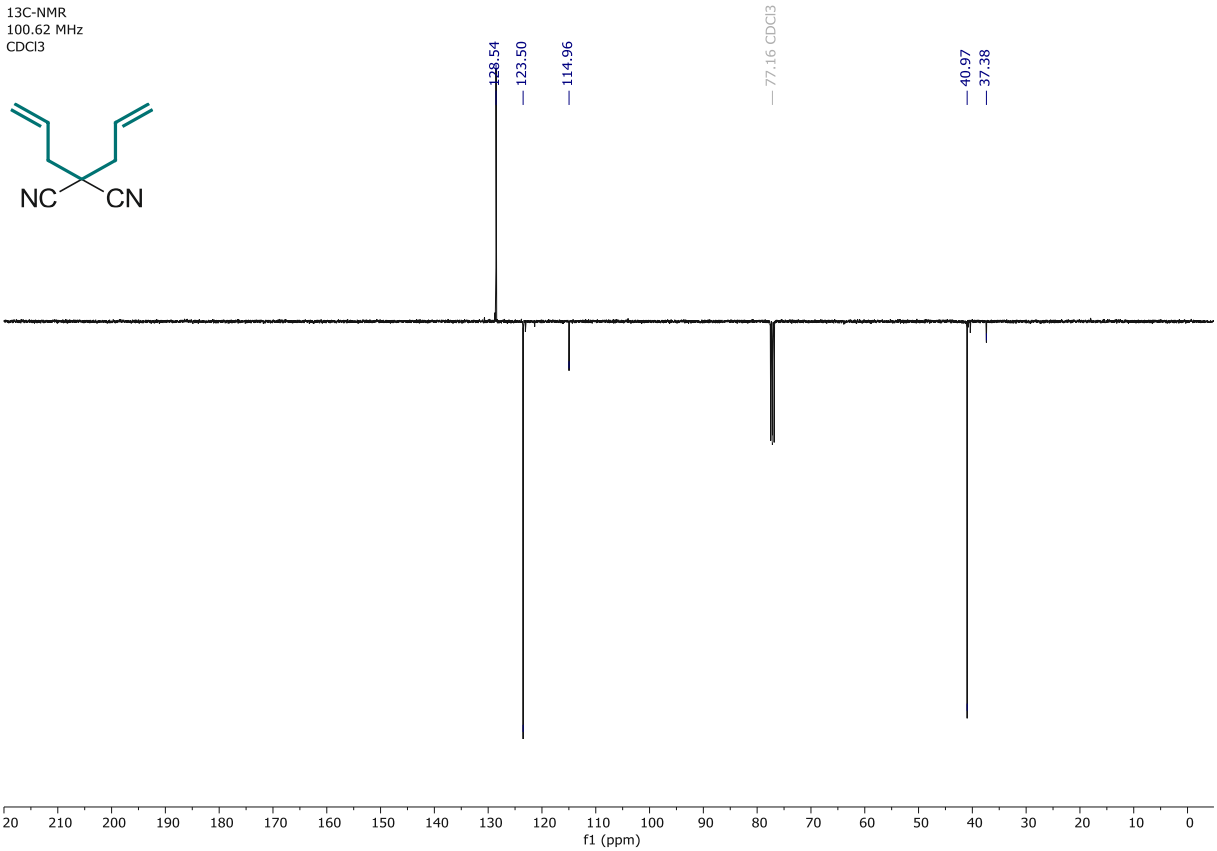




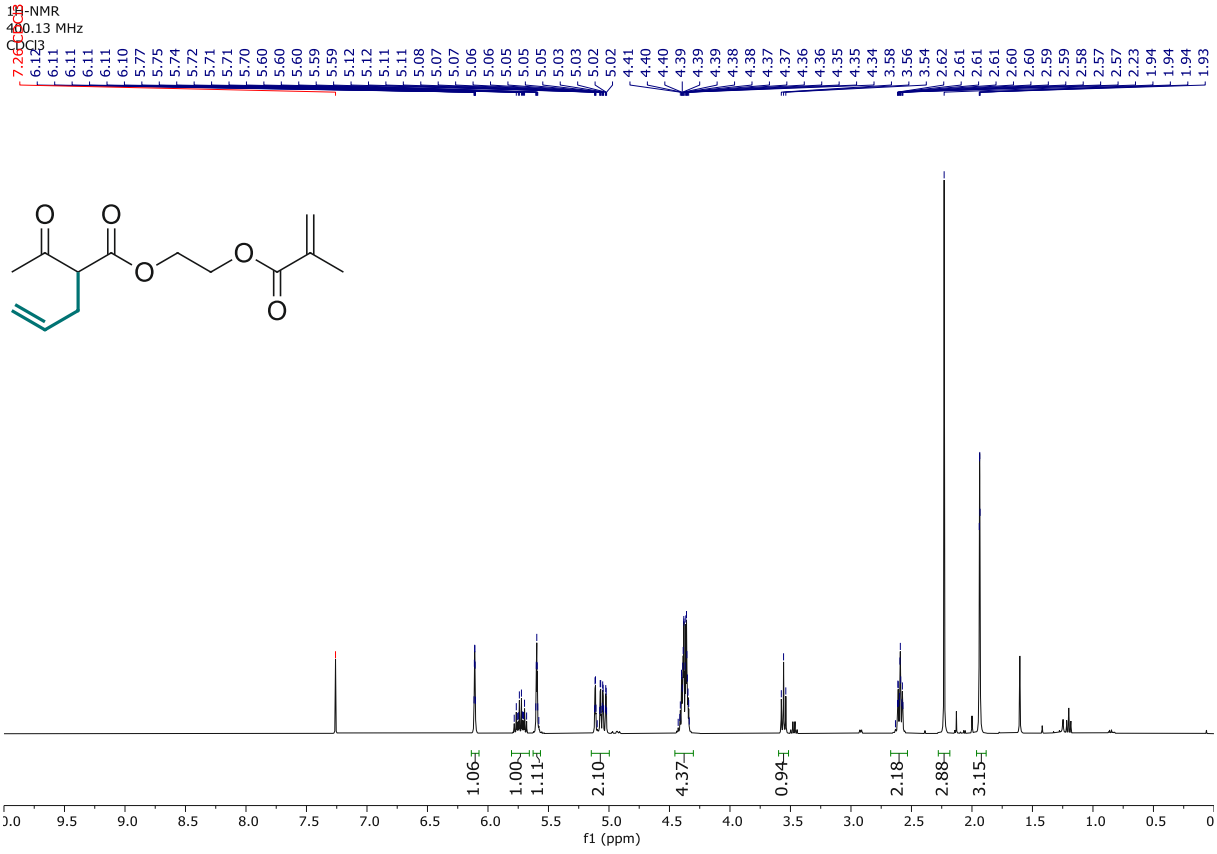


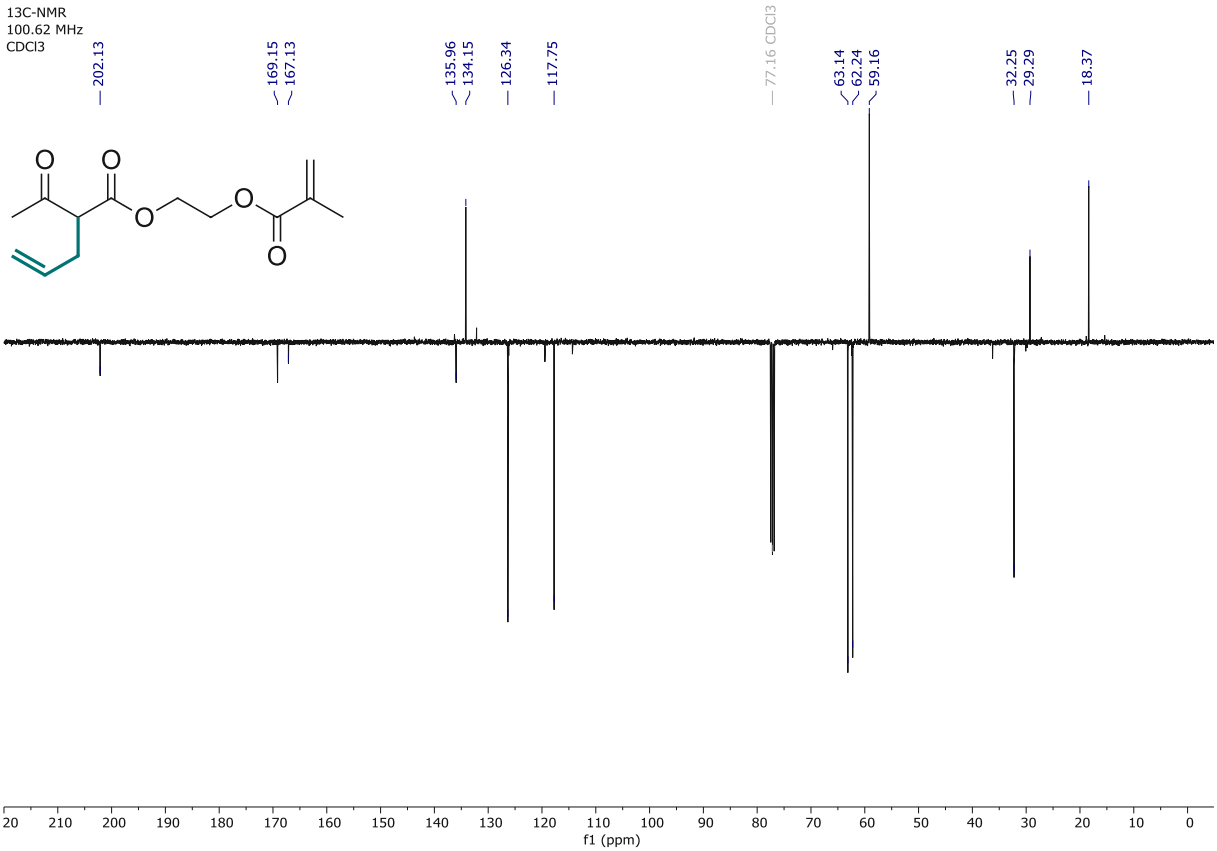
2,2-Diallylmalononitrile **(37)**



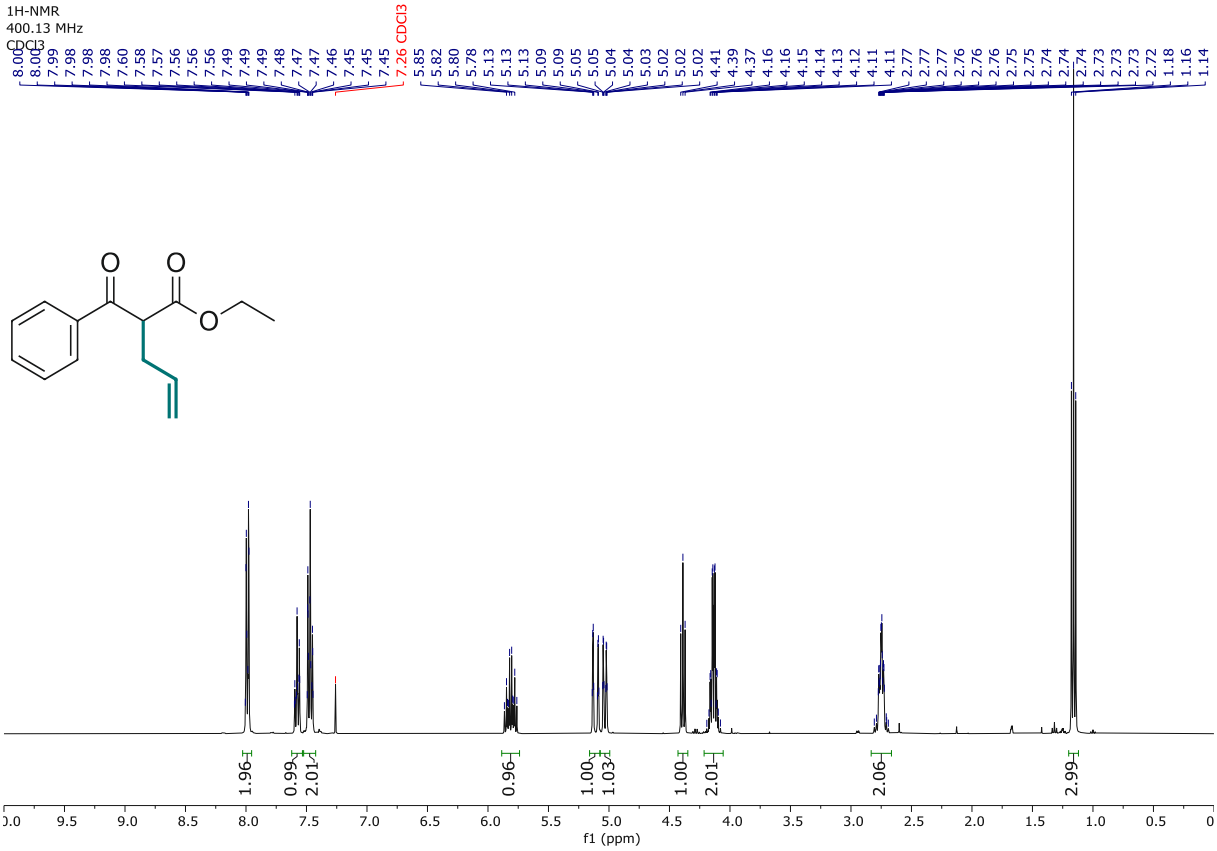


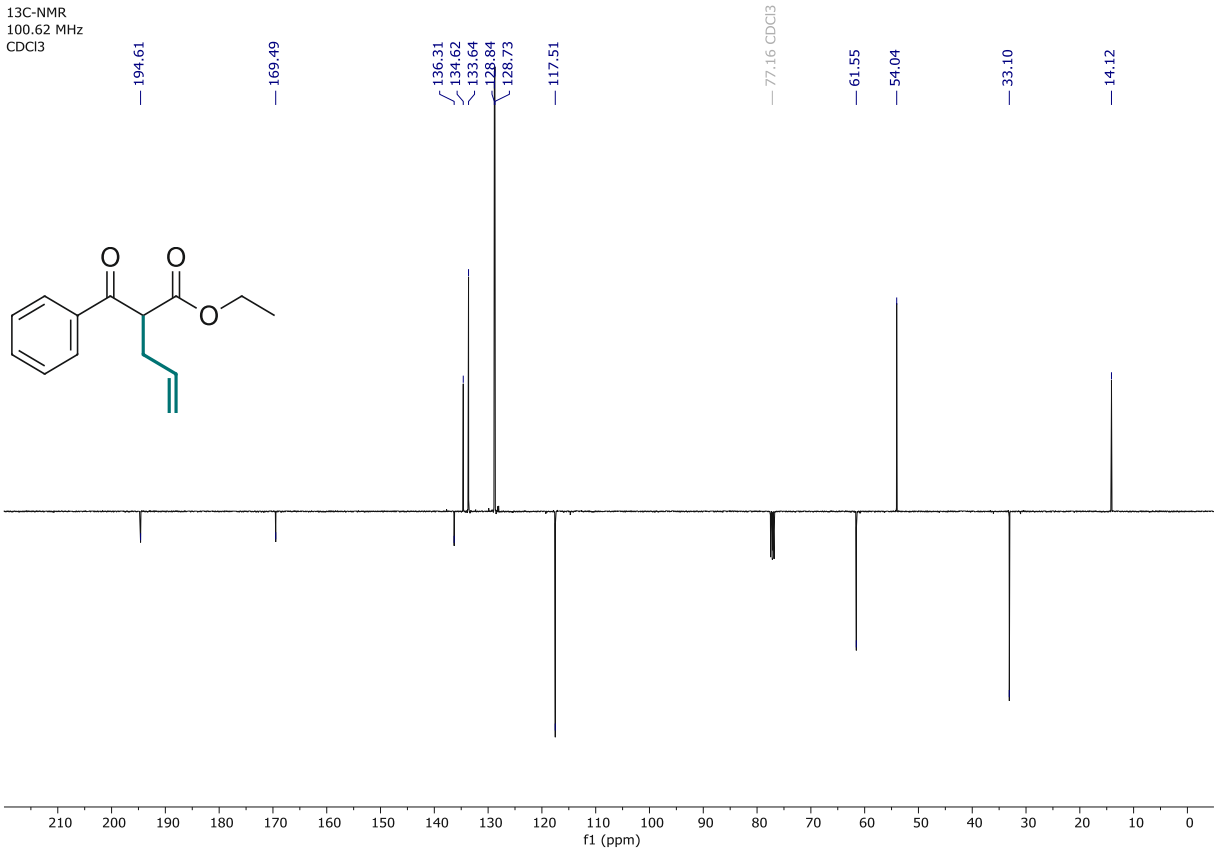
2-(Isopropenylcarbonyloxy)ethyl 2-acetyl-4-pentenoate **(38)**



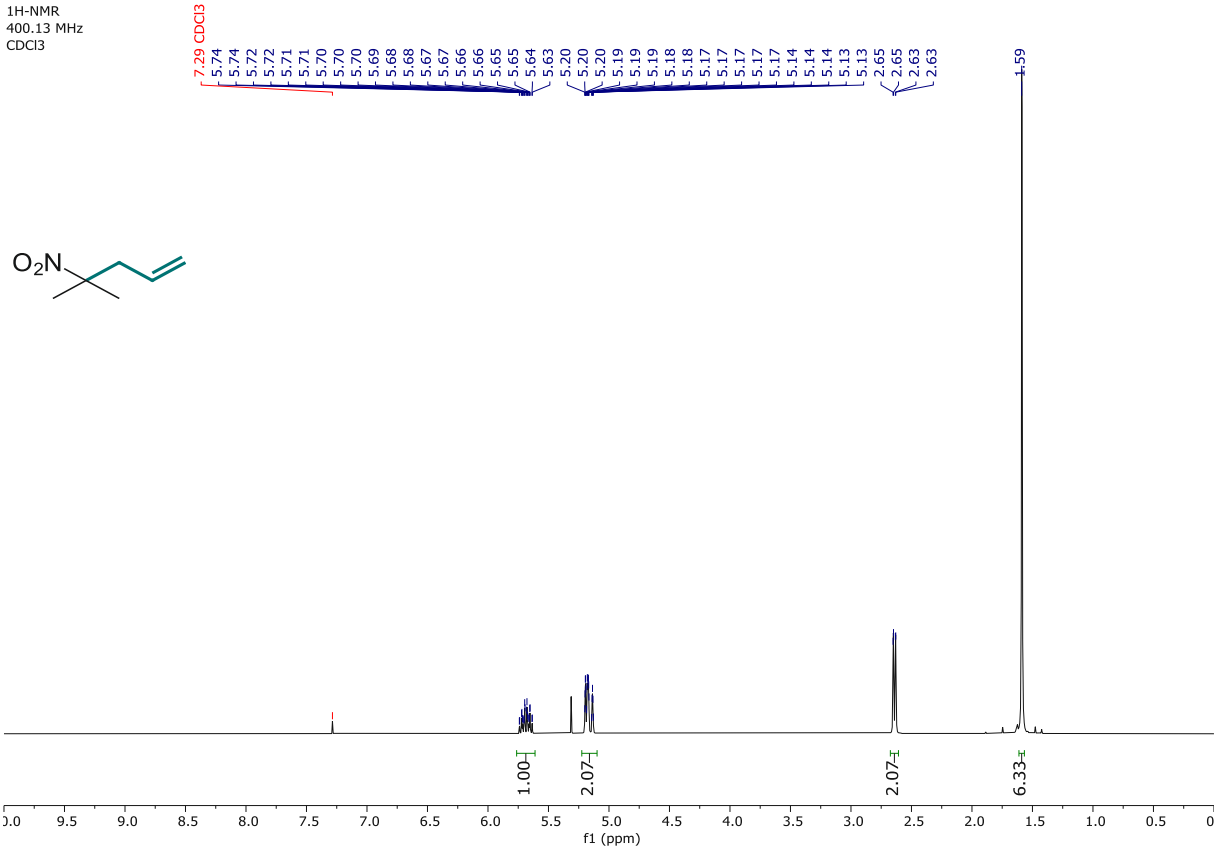


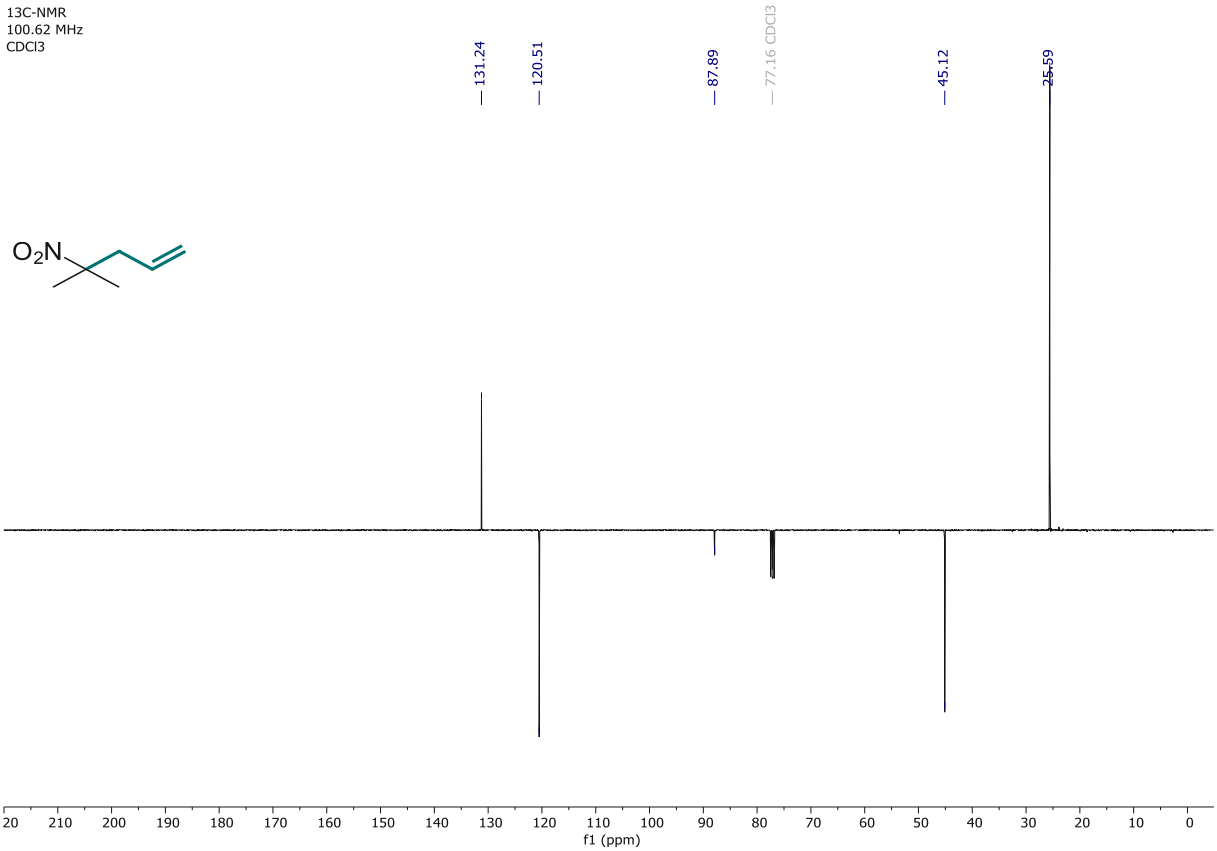
Ethyl 2-benzoylpent-4-enoate **(39)**



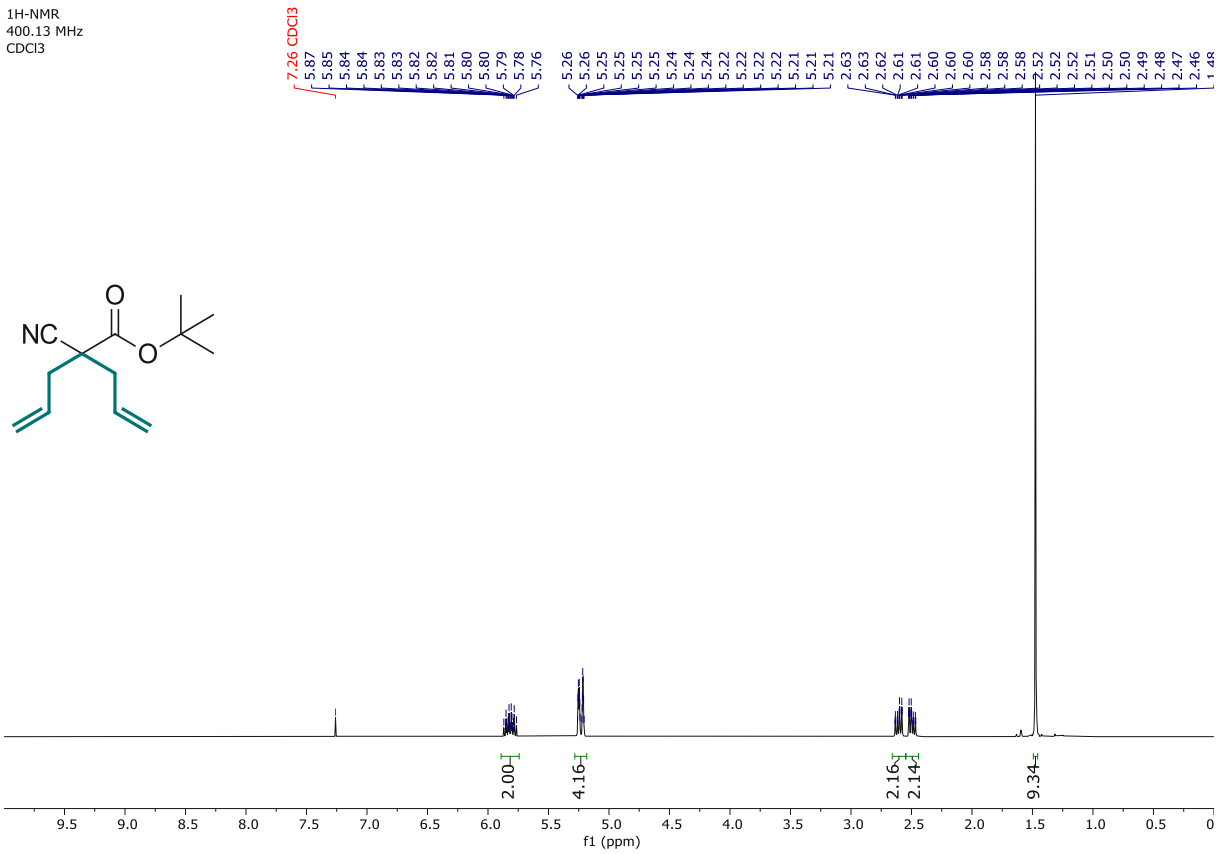


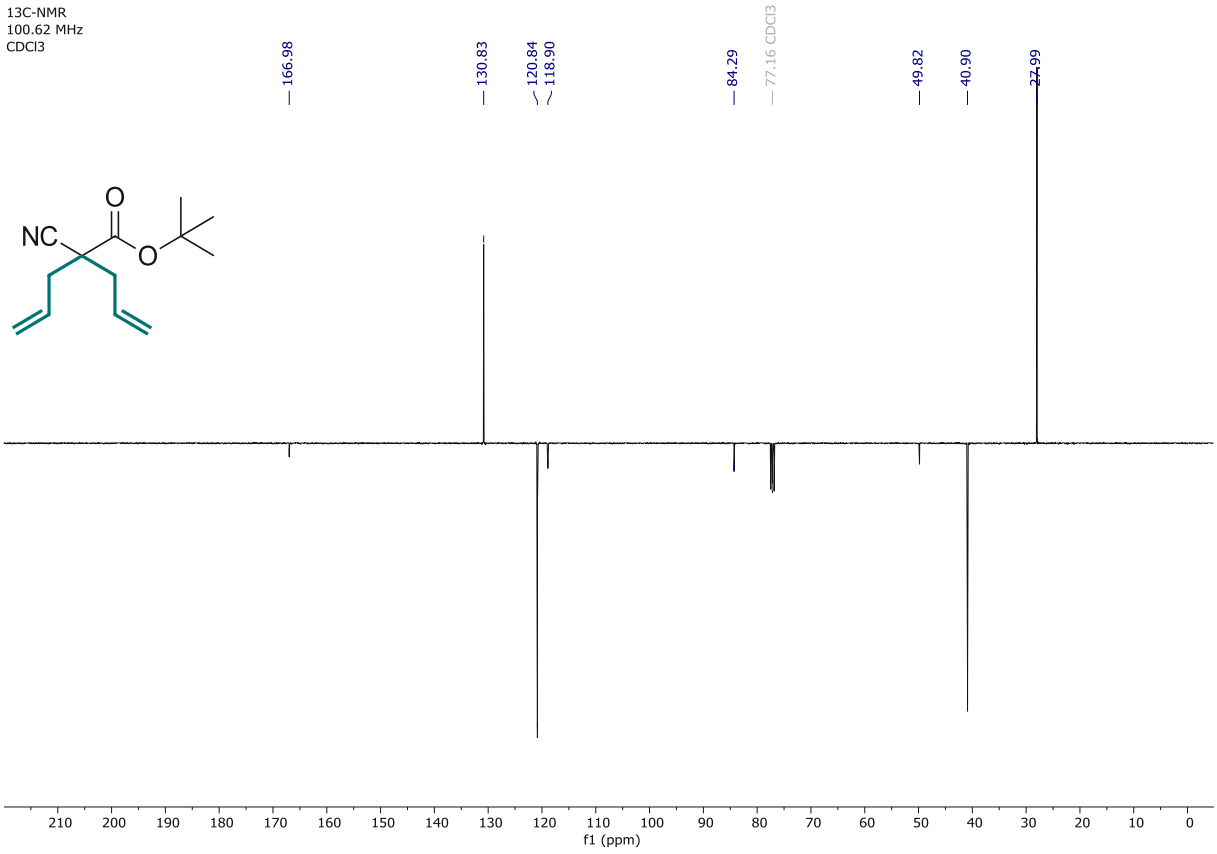
4-Methyl-4-nitro-1-pentene **(40)**



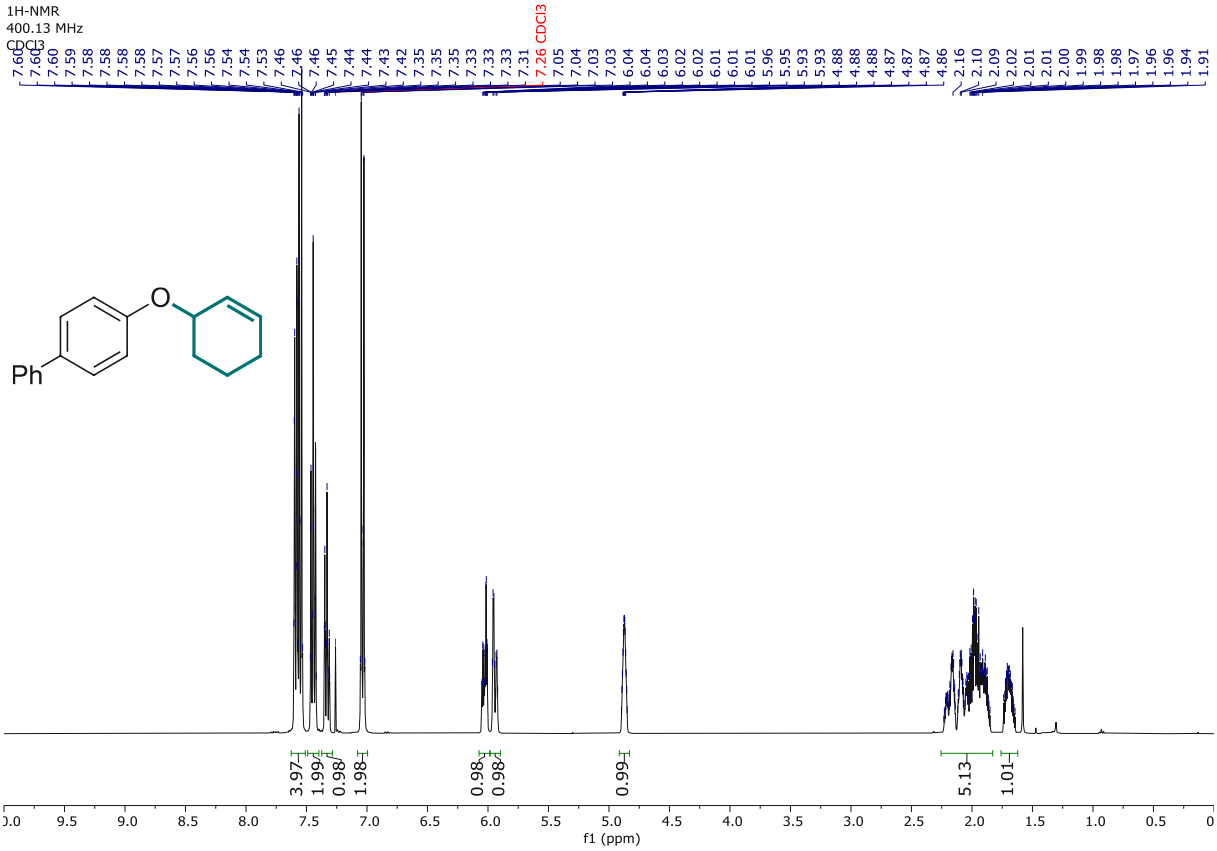


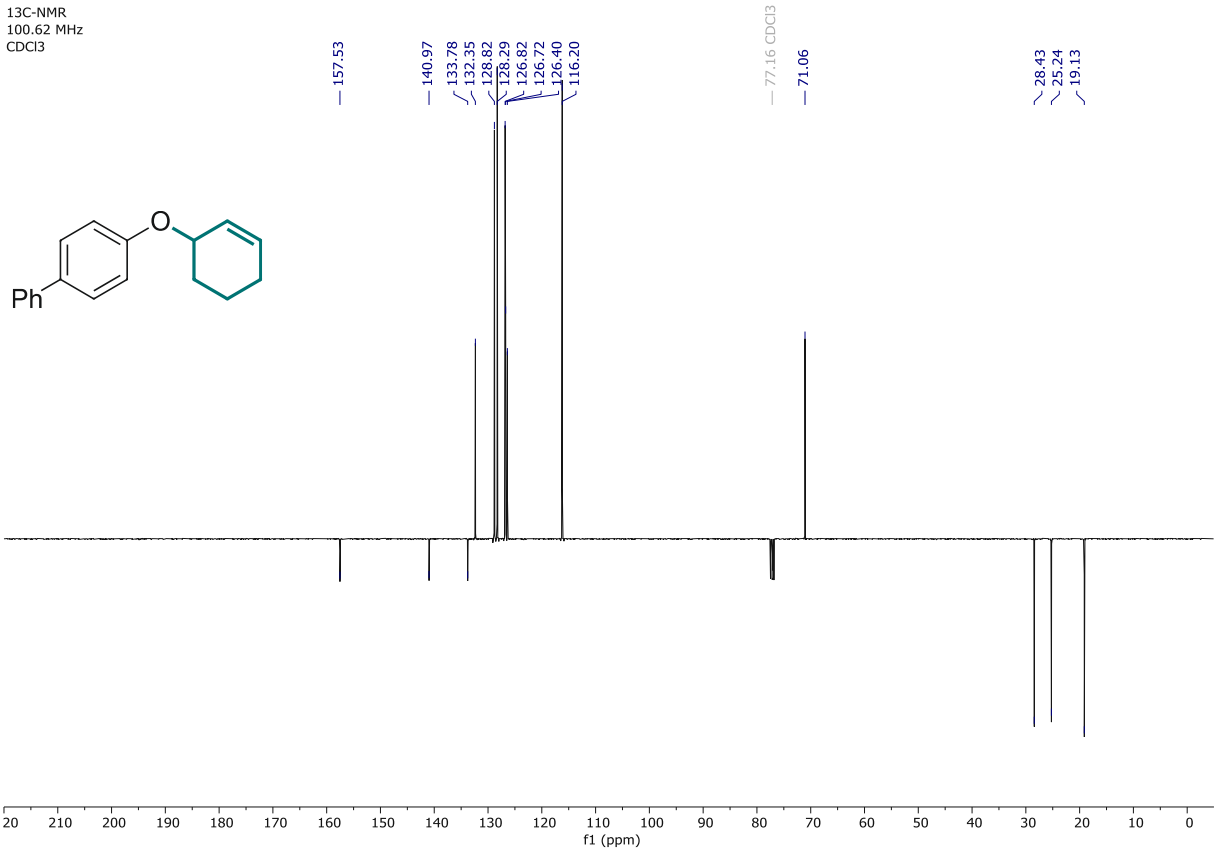
tert-Butyl 2-allyl-2-cyano-4-pentenoate **(41)**



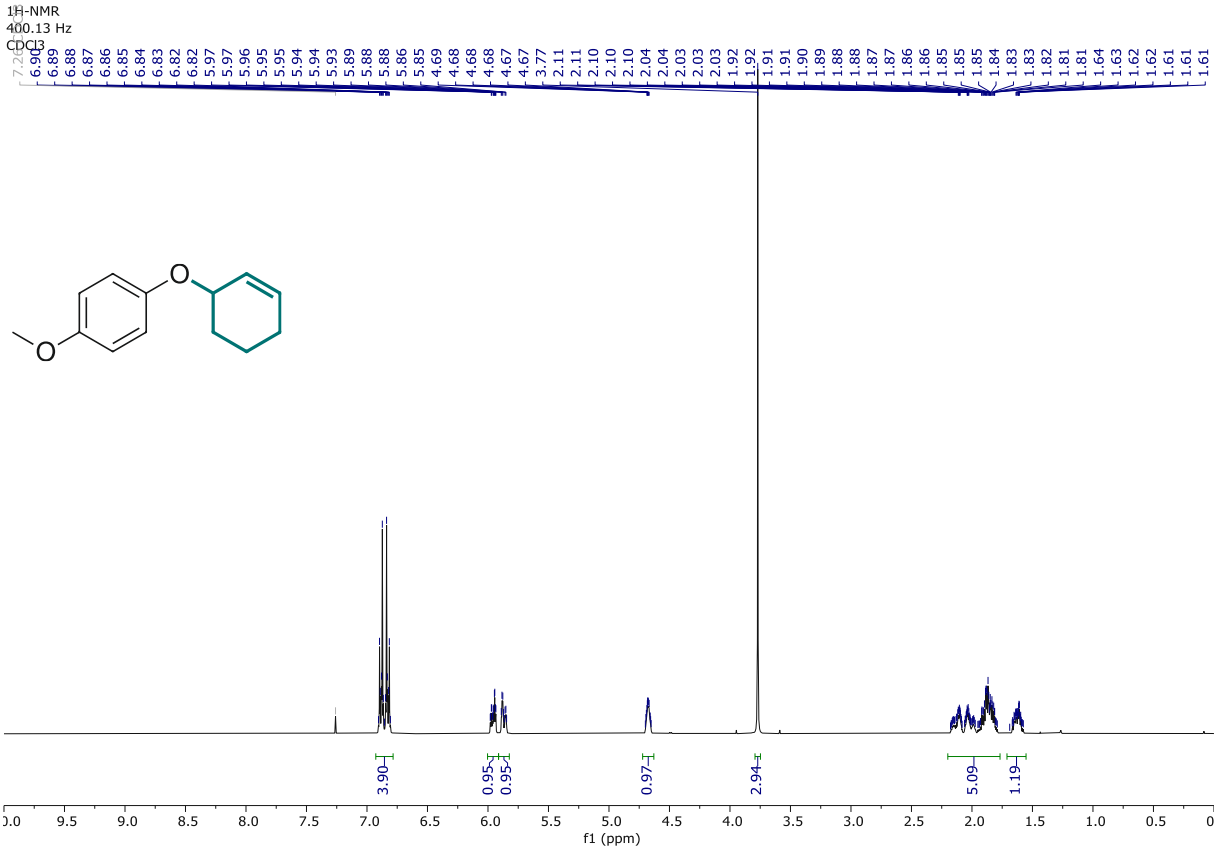


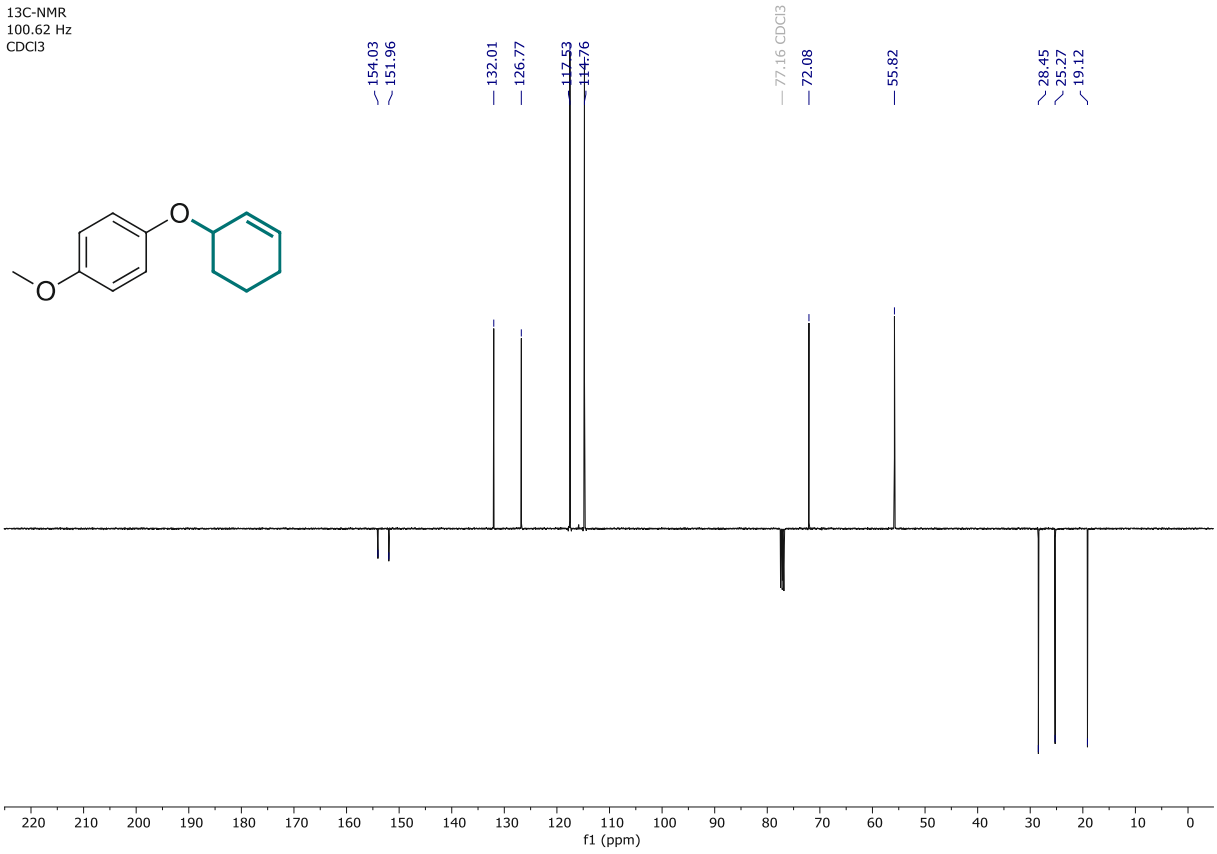
3-(4-Biphenylyloxy)cyclohexene **(42)**



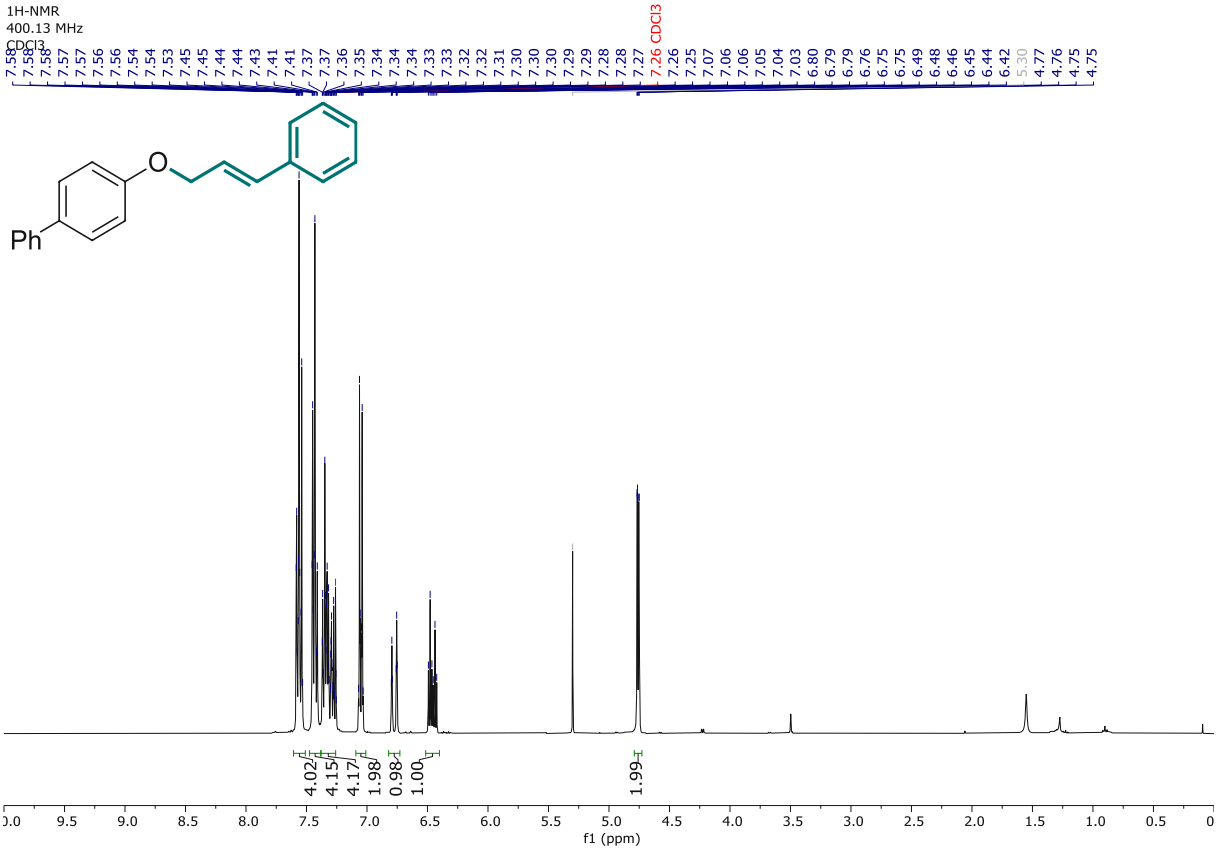


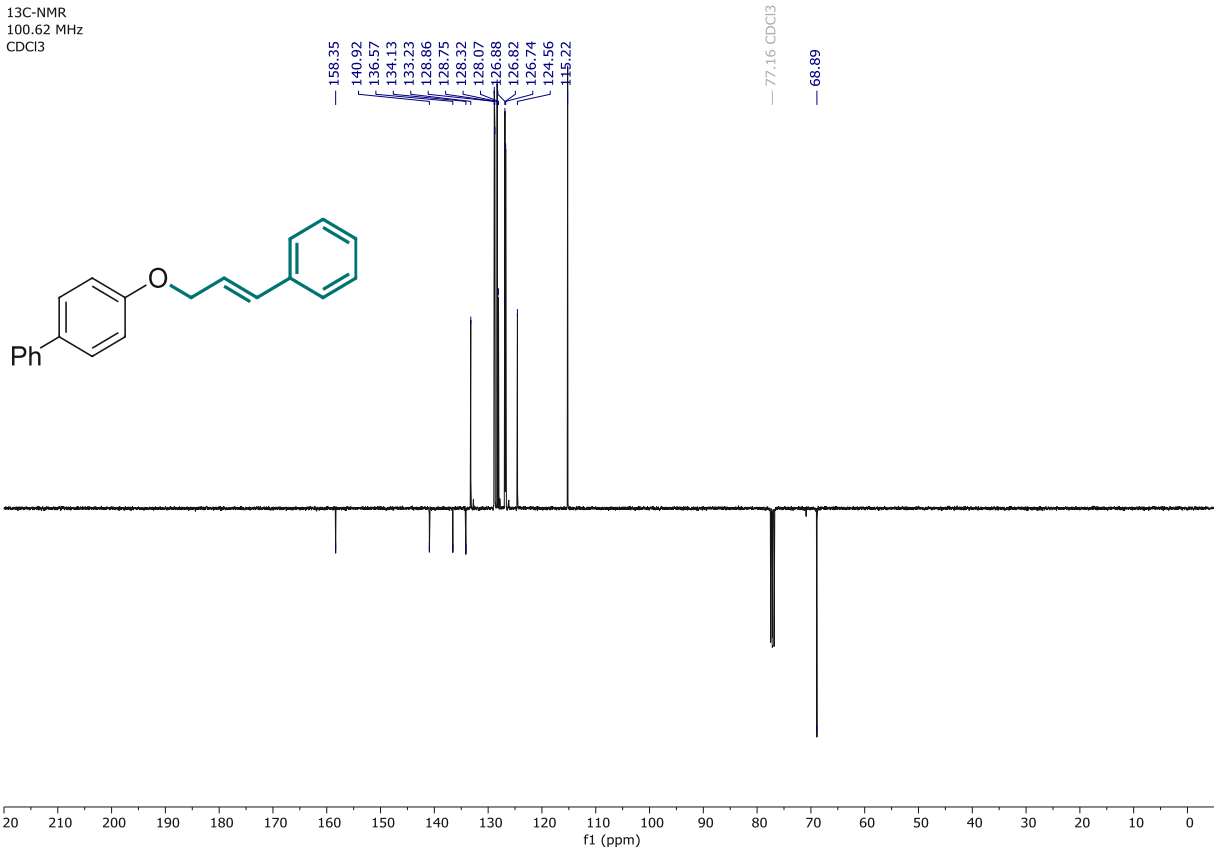
p-(2-Cyclohexen-1-yloxy)methoxybenzene **(43)**



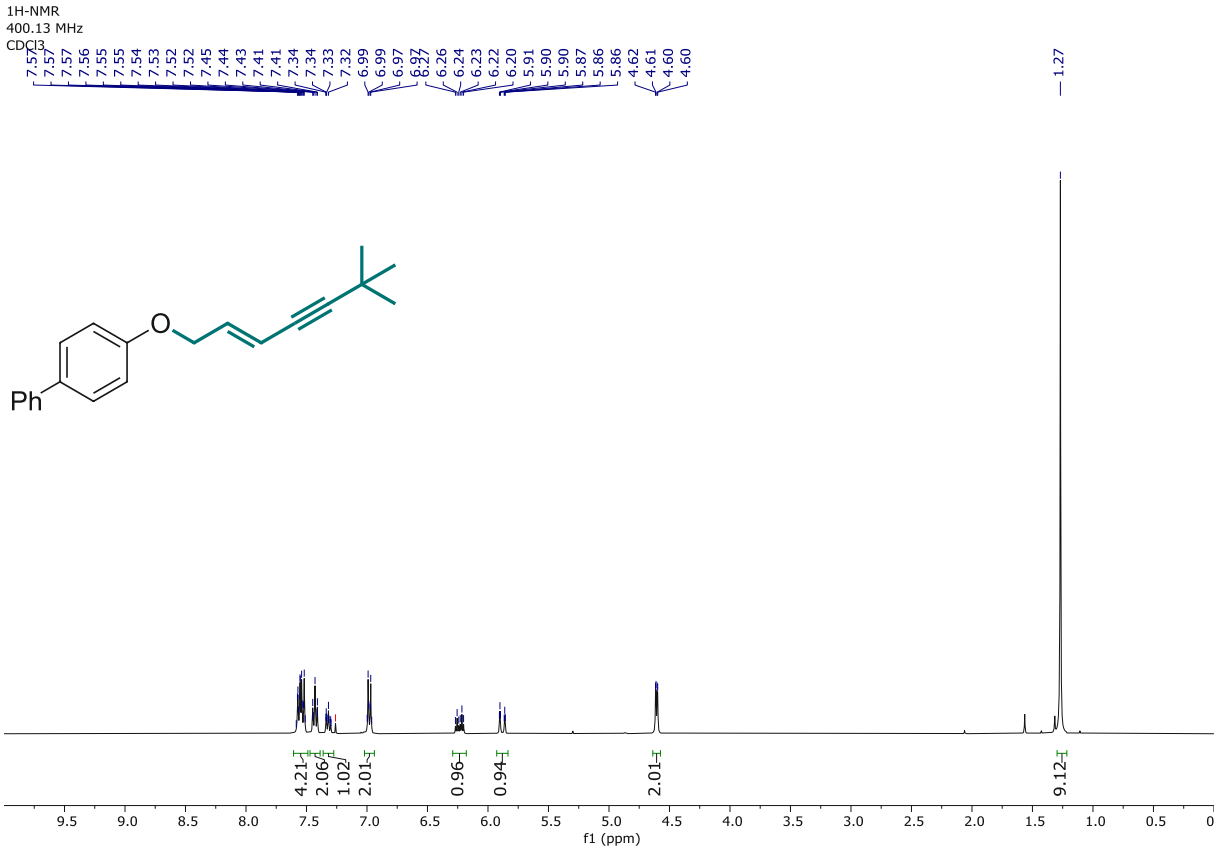


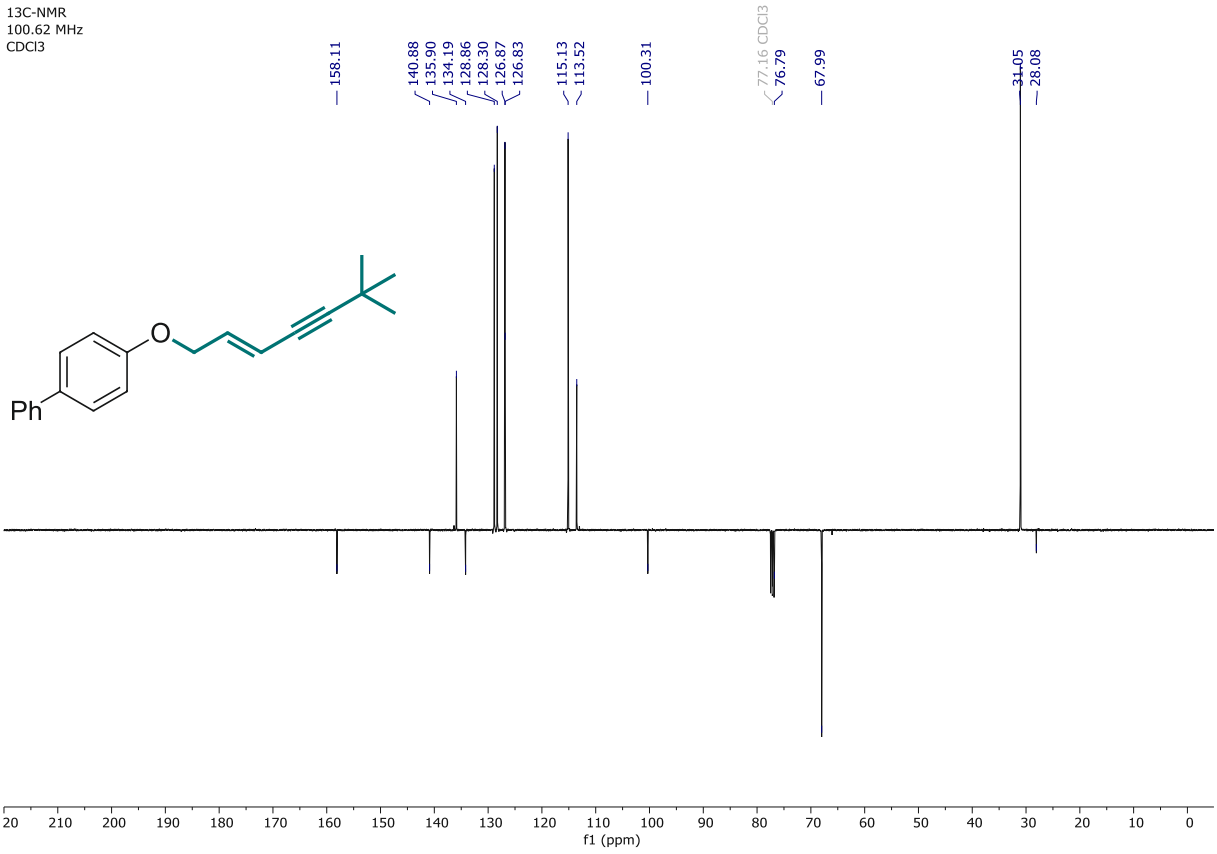
(E)-Cinnamyl 1,1'-biphenyl ether **(44)**



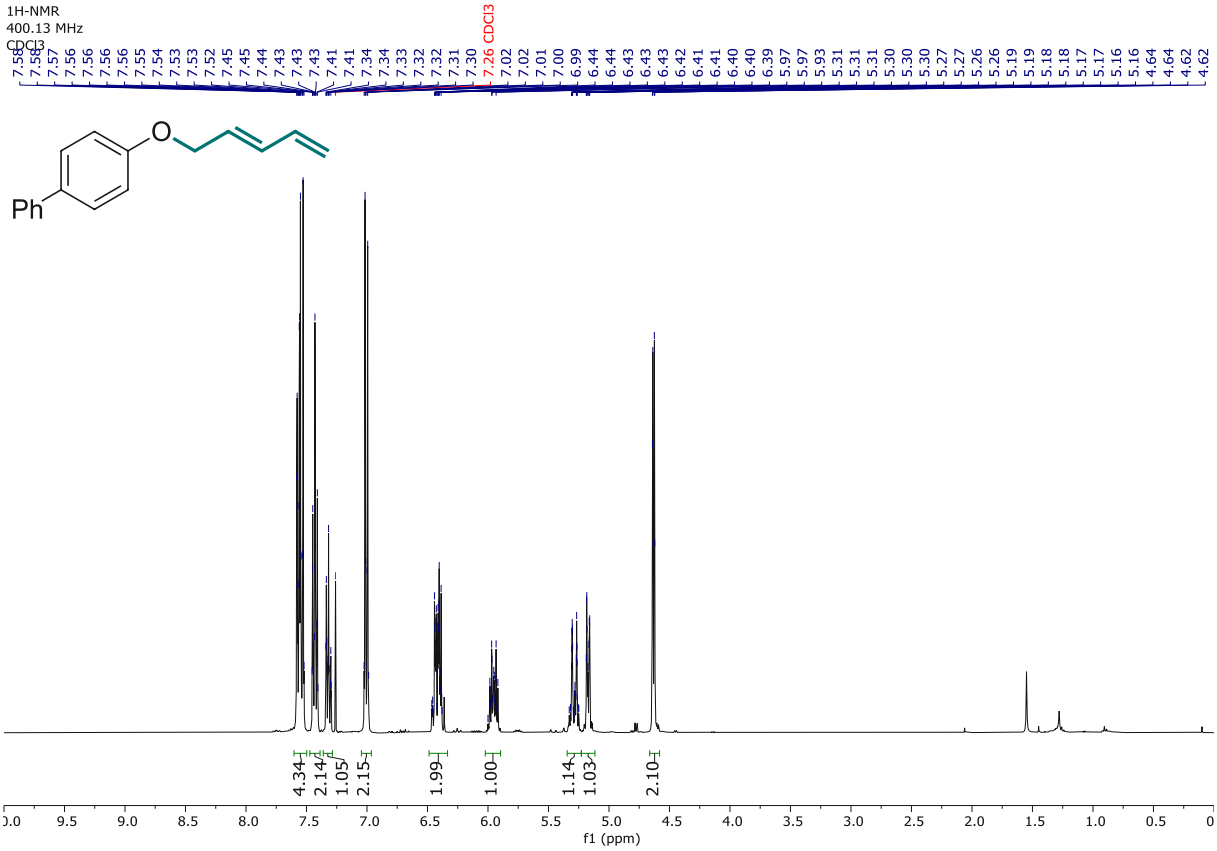


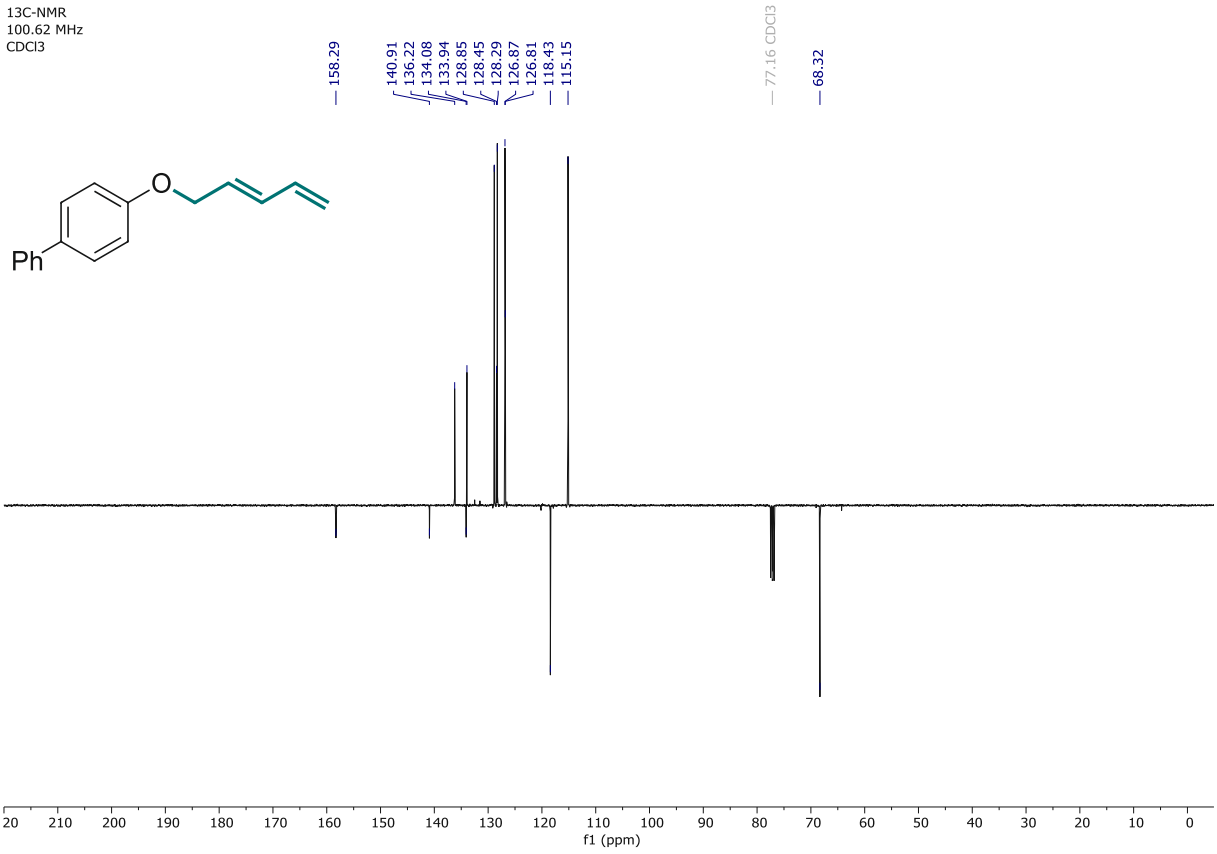
4-[(E)-6,6-Dimethyl-2-hepten-4-ynyloxy]biphenyl **(45)**



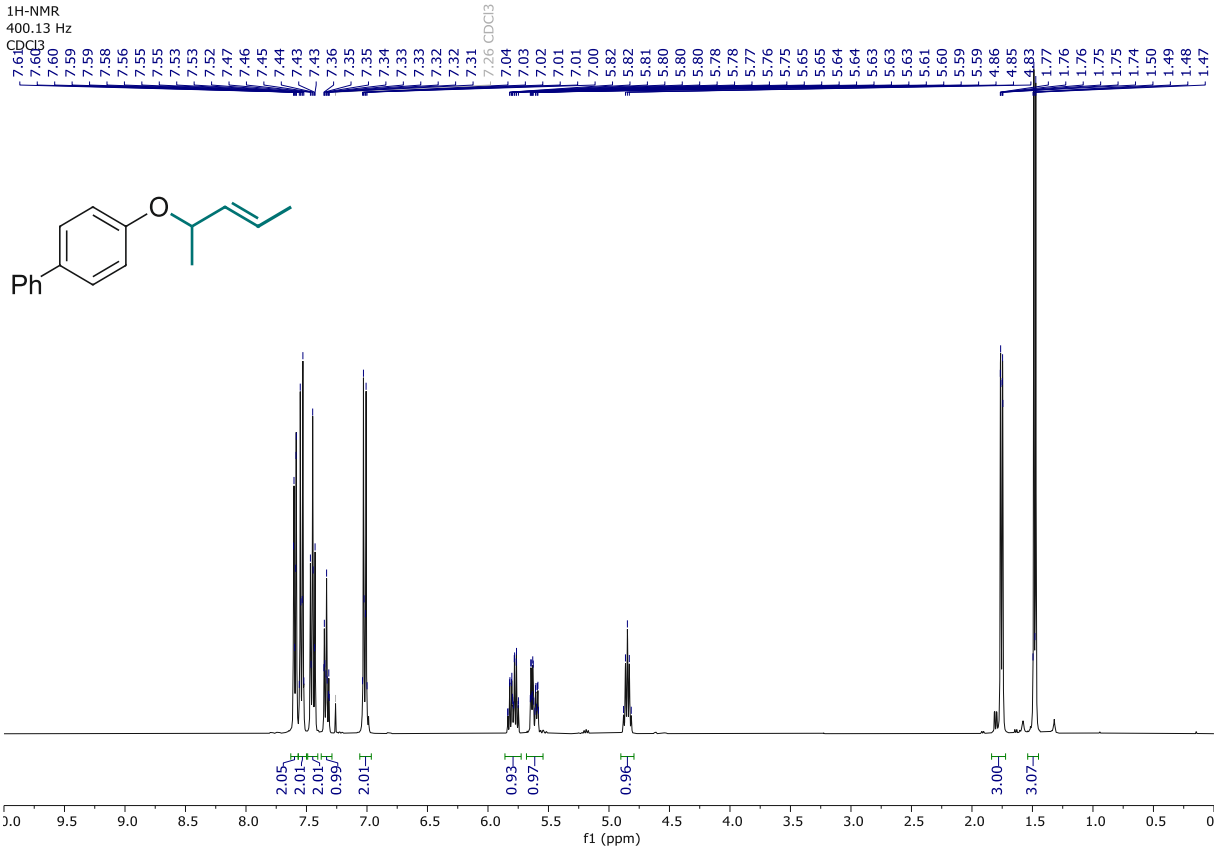


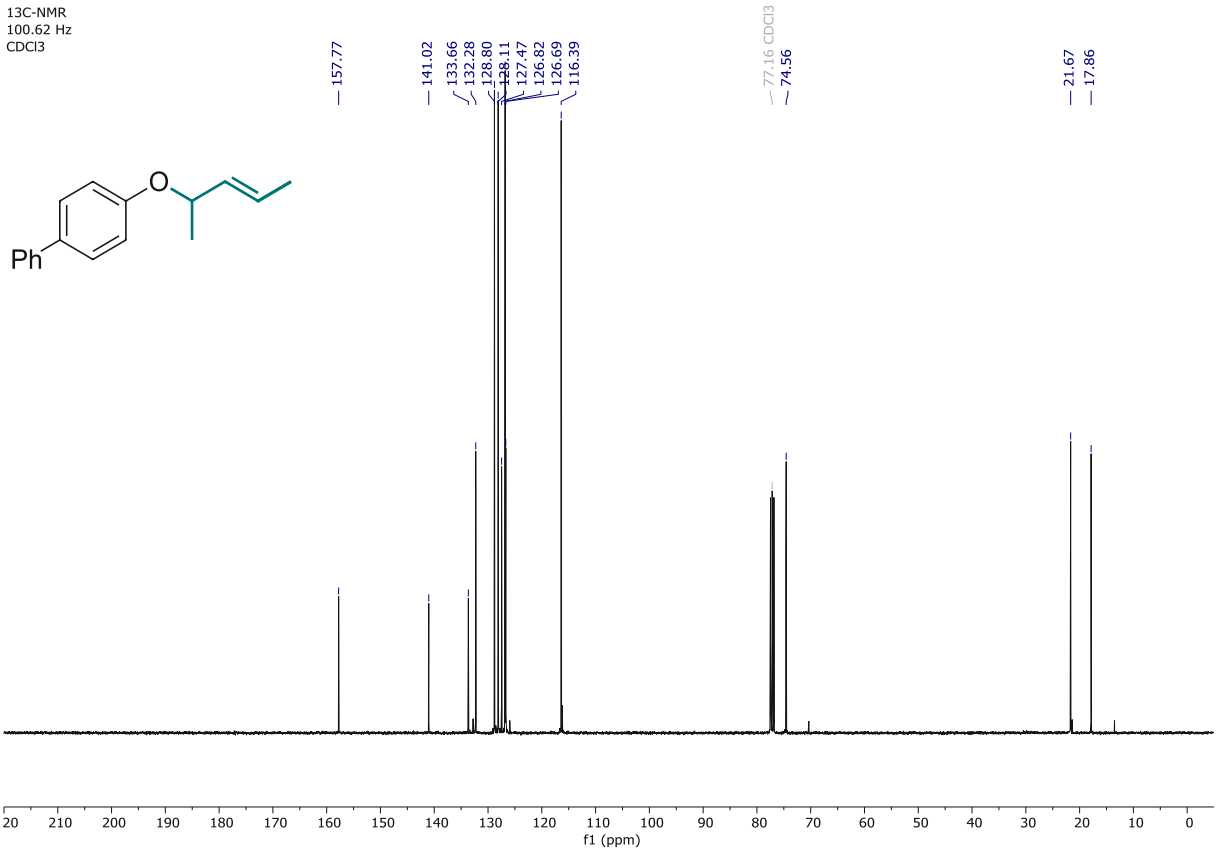
4-biphenylyl 2,4-pentadienyl ether **(46)**



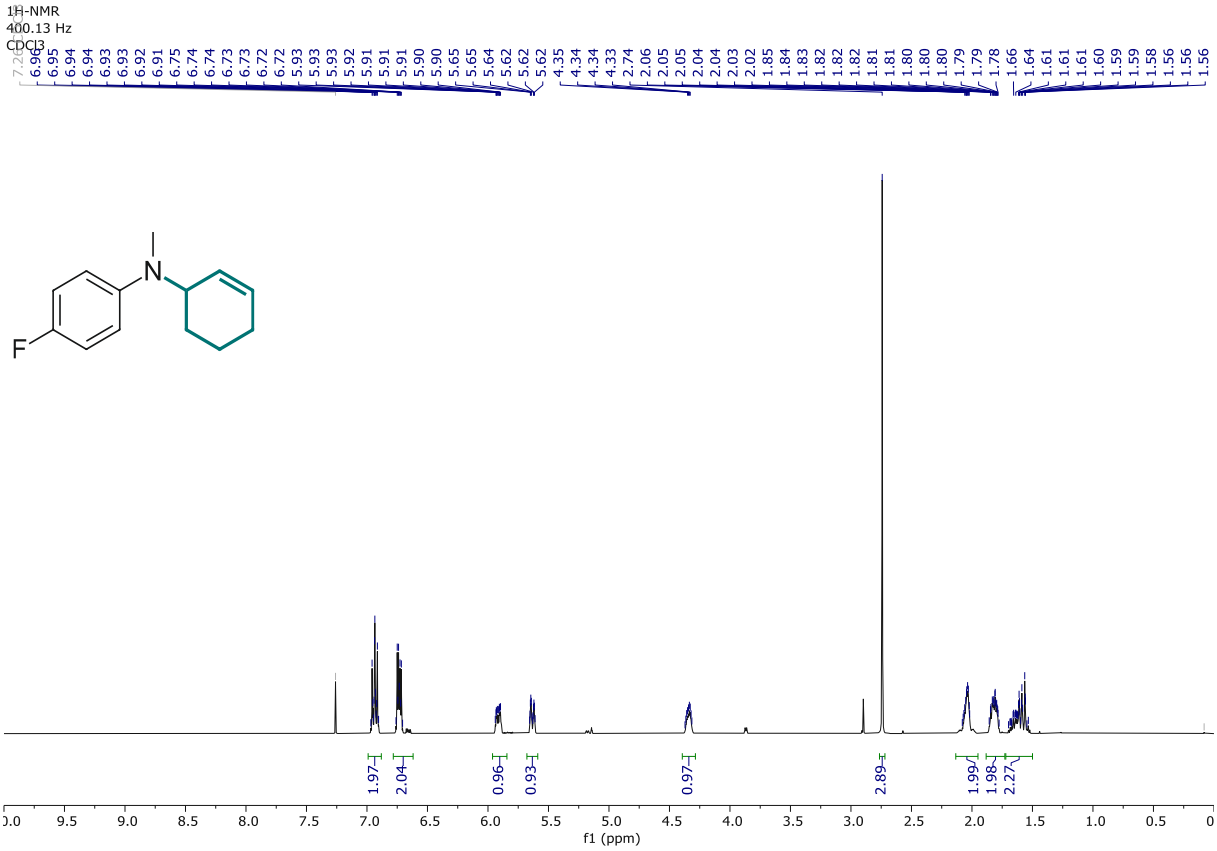


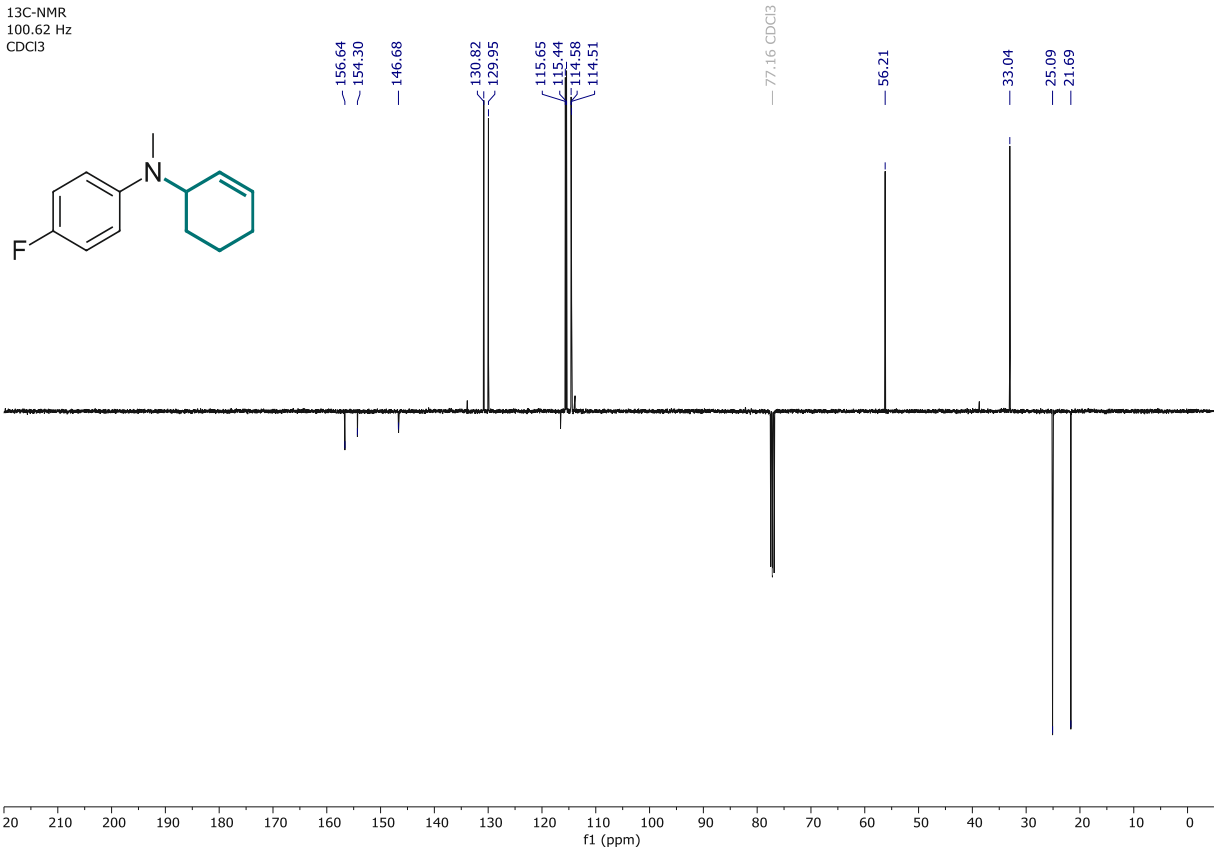
4-[(E)-1-Methyl-2-butenyloxy]biphenyl **(47)**

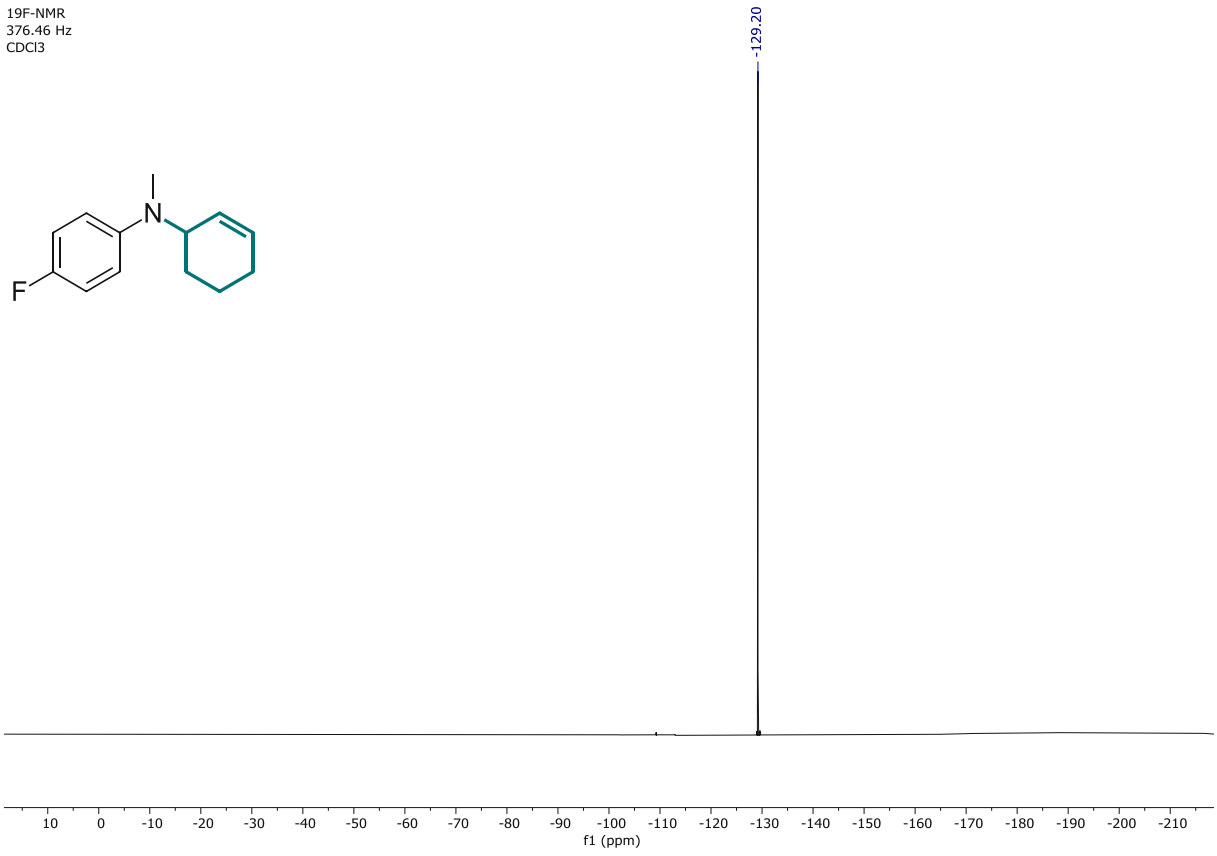




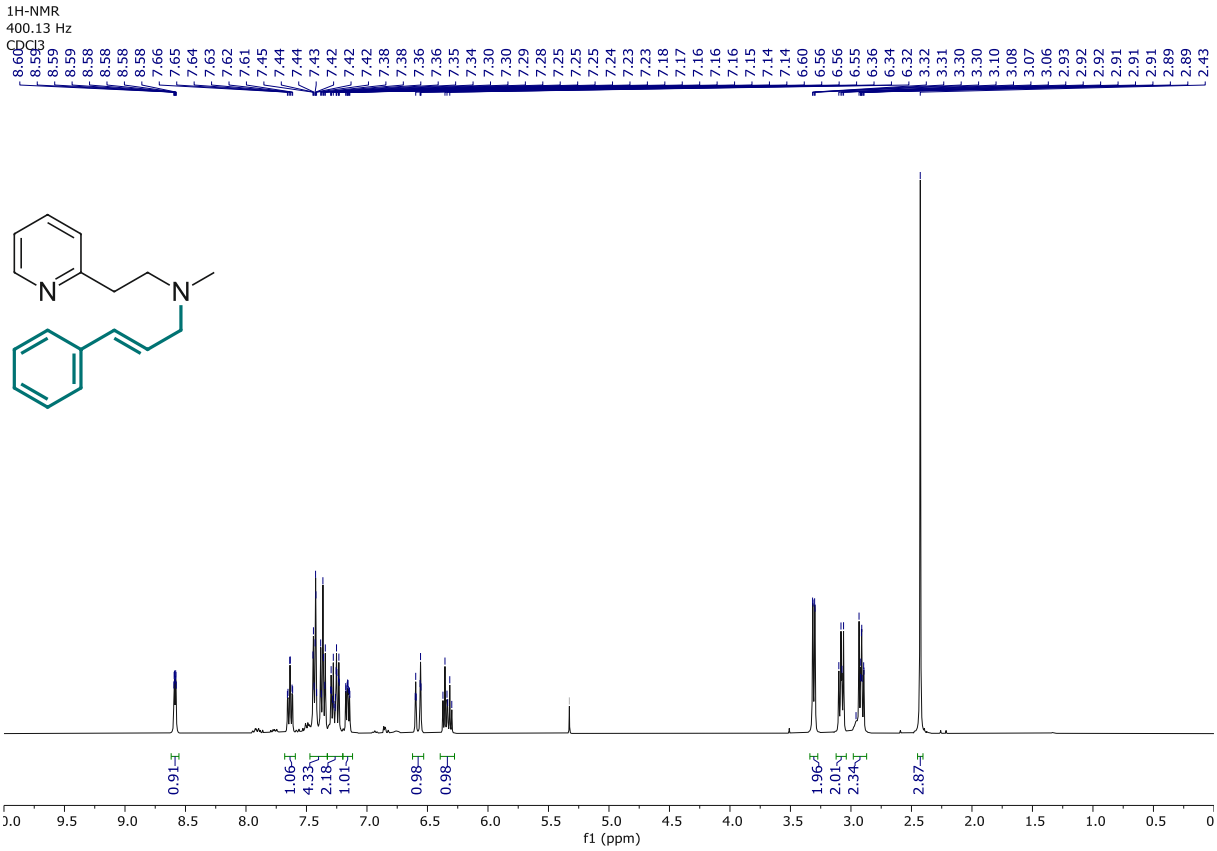
N-2-Cyclohexen-1-yl-N-methyl(p-fluorophenyl)amine **(48)**

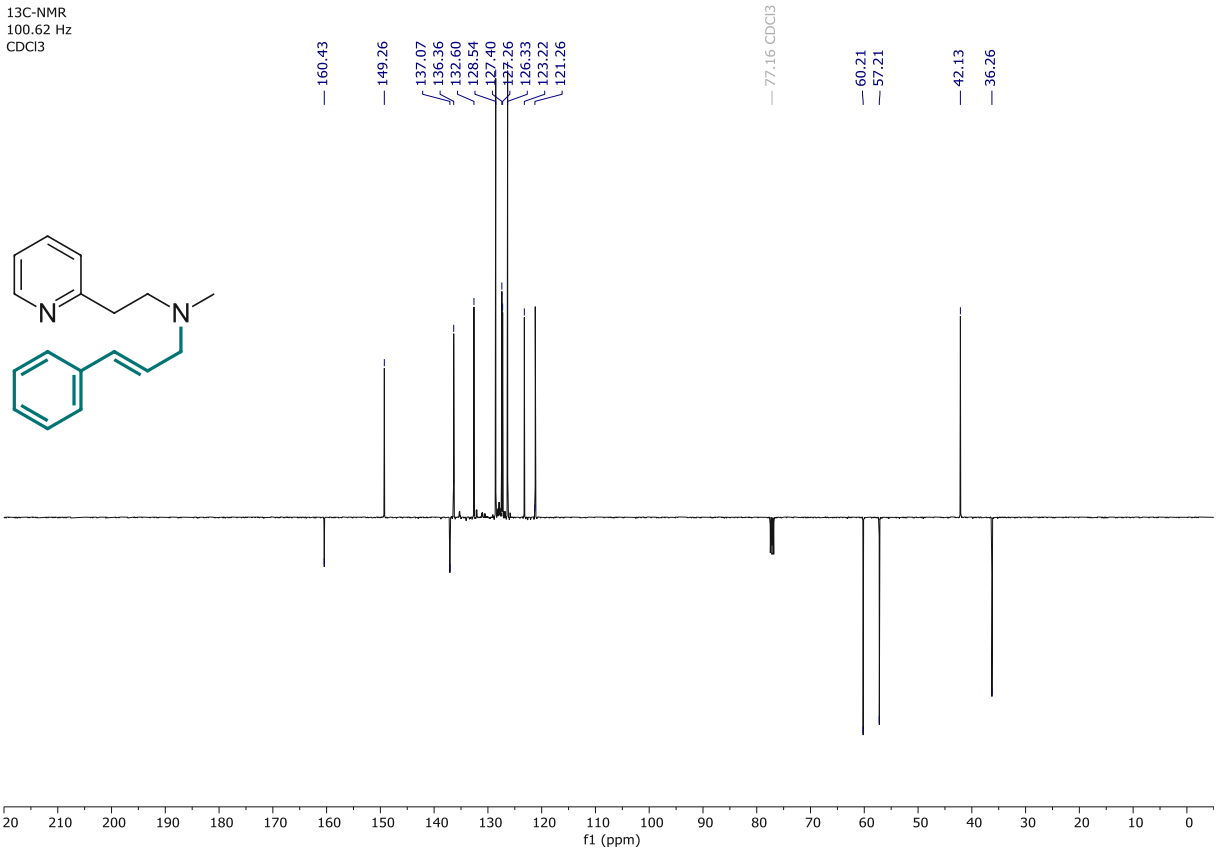




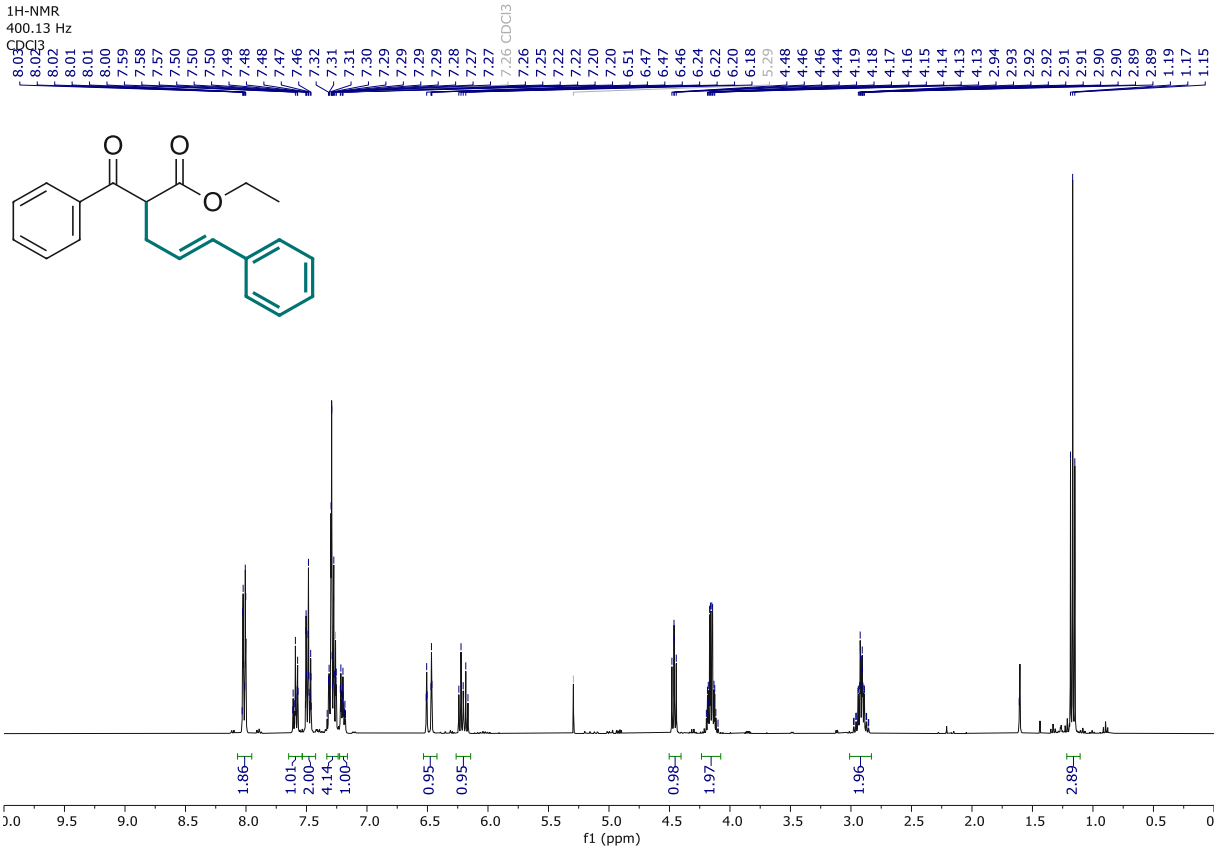


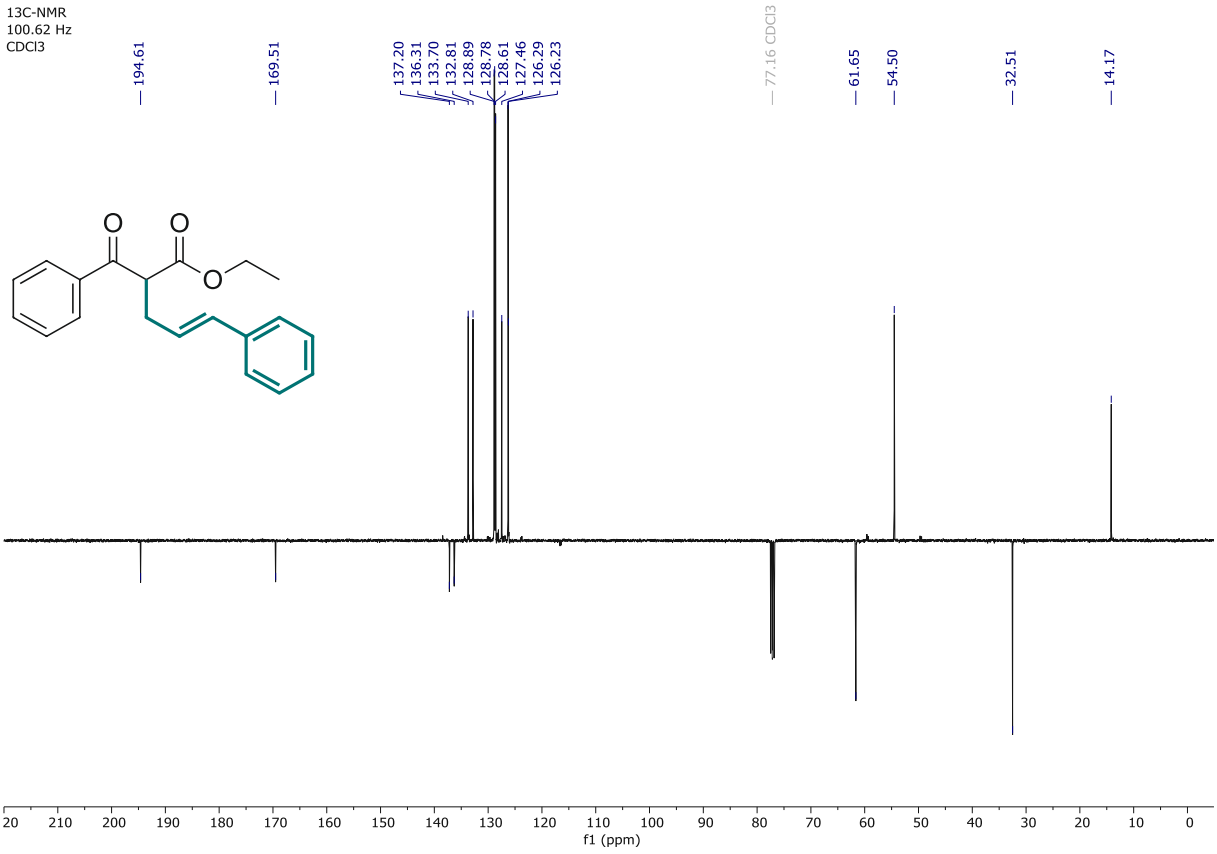
N-Methyl[2-(2-pyridyl)ethyl][(E)-3-phenyl-2-propenyl]amine **(49)**



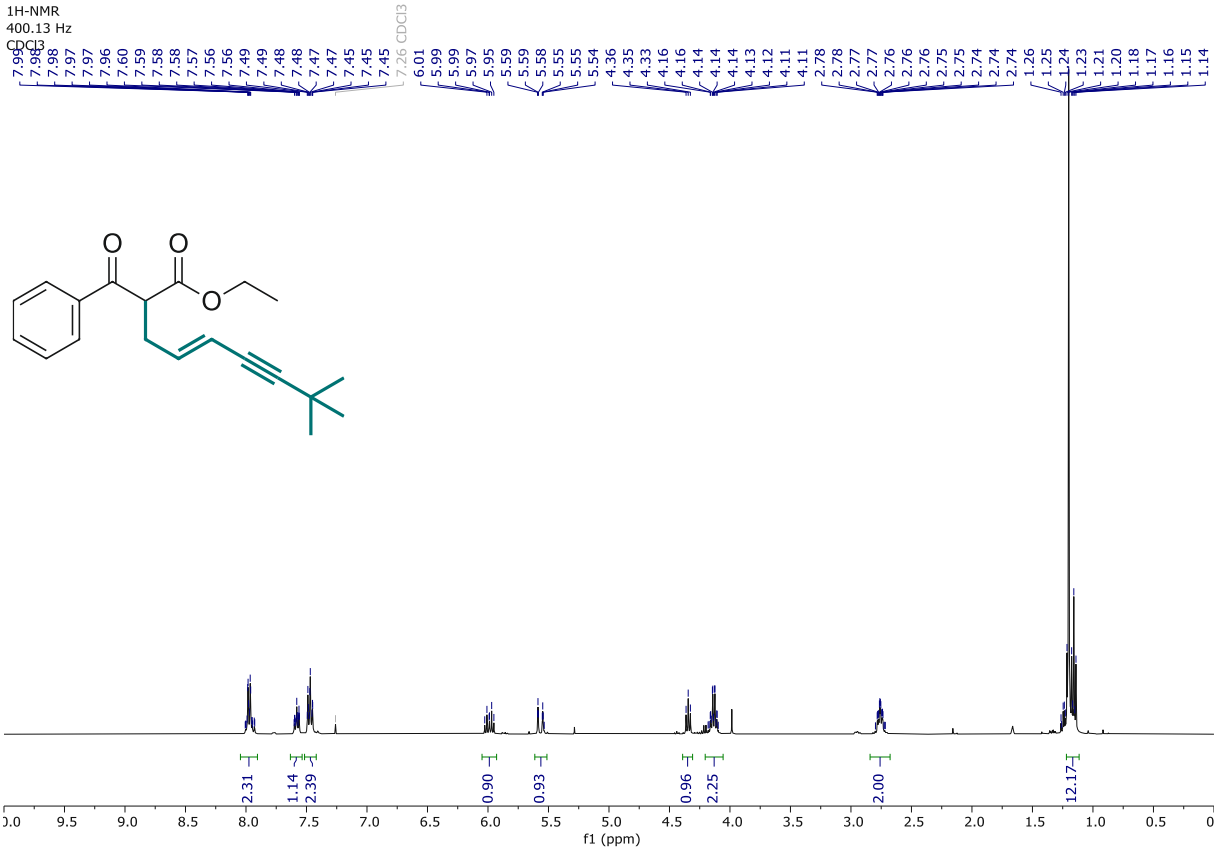


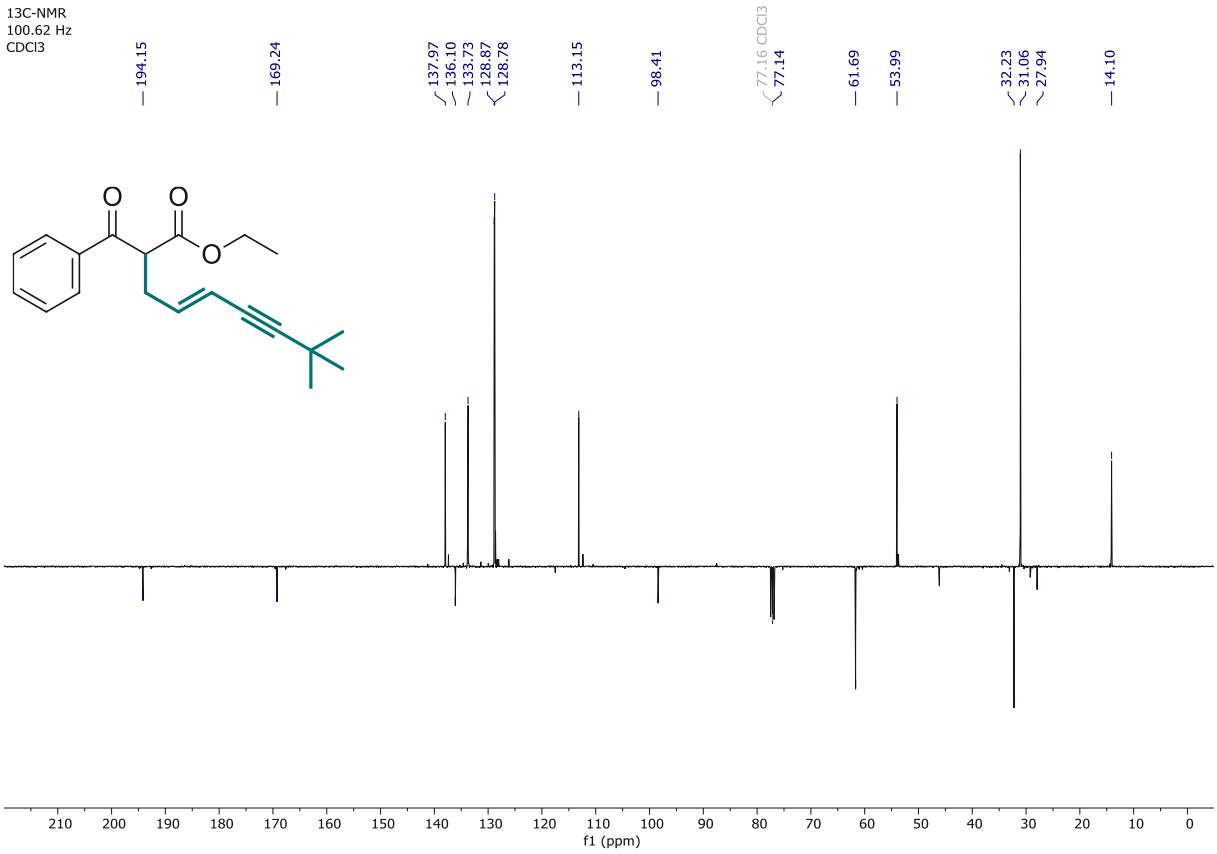
Ethyl [(E)-3-phenyl-2-propenyl]benzoylacetate **(50)**





Ethyl *(E)*-2-benzoyl-8,8-dimethyl-4-nonen-6-ynoate **(51)**





Chromatograms for Chiral HPLC for the synthesis of (R)-/(S)-42 grouped by ligands used.

rac-BINAP

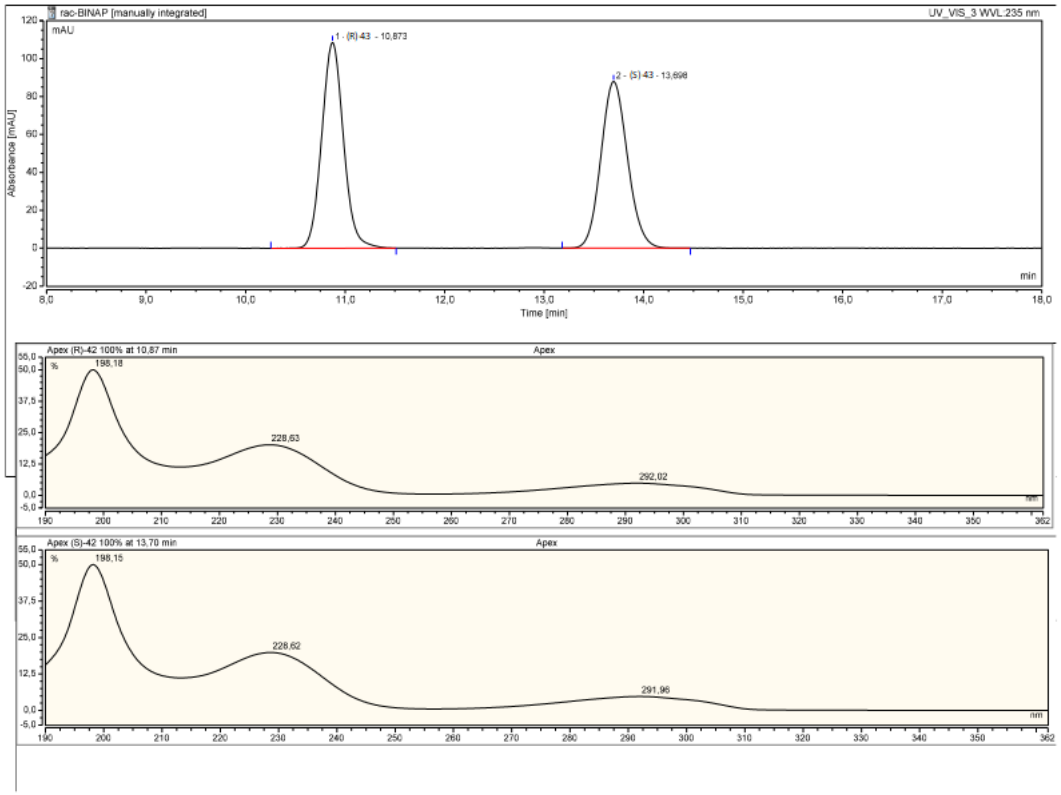
Chromatogram and Results

Injection Name:	**rac-BINAP**	*Run Time (min):*	**30,00**
Injection Volume:	**1,00**	*Channel:*	**UV_VIS_3**
Column:	**OD-2**	*Wavelength:*	**254,0**

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1	(R)-43	10,873	27,498	108,504	50,20	55,24	n.a.
2	(S)-43	13,698	27,281	87,920	49,80	44,76	n.a.
Total:			**54,779**	**196,424**	**100,00**	**100,00**	

Chromatogram



***(R)*-BINAP**

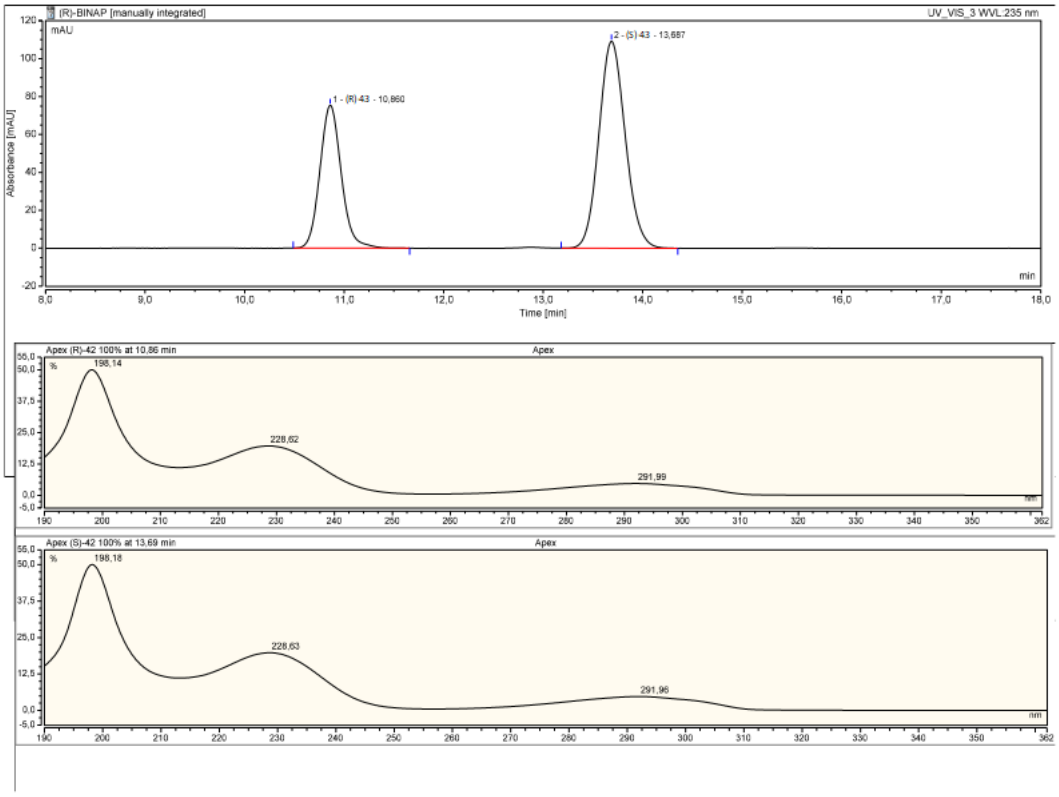
Chromatogram and Results

Injection Name:	**(R)-BINAP**	*Run Time (min):*	**30,00**
Injection Volume:	**1,00**	*Channel:*	**UV_VIS_3**
Column:	**OD-2**	*Wavelength:*	**254,0**

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1	(R)-43	10,860	18,764	75,350	35,89	40,83	n.a.
2	(S)-43	13,687	33,512	109,218	64,11	59,17	n.a.
Total:			**52,277**	**184,568**	**100,00**	**100,00**	

Chromatogram



***(S)*-tol-BINAP**

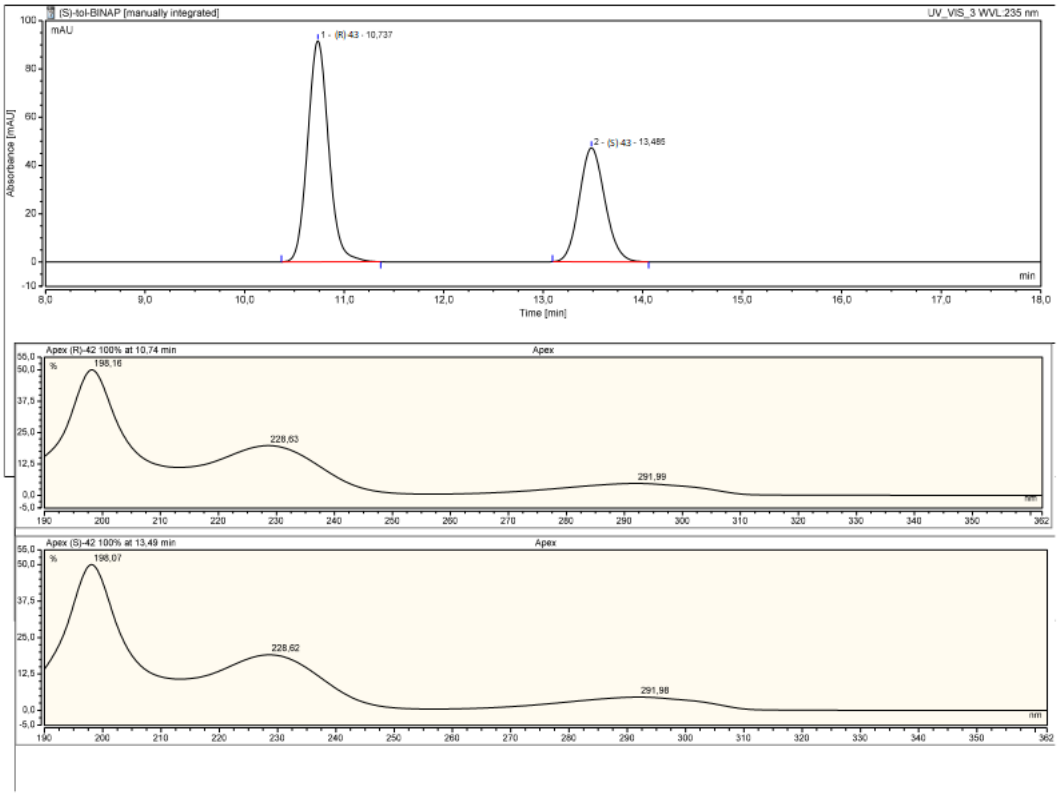
Chromatogram and Results

Injection Name:	**(S)-tol-BINAP**	*Run Time (min):*	**30,00**
Injection Volume:	**1,00**	*Channel:*	**UV_VIS_3**
Column:	**OD-2**	*Wavelength:*	**254,0**

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1	(R)-43	10,737	22,360	91,582	61,32	66,00	n.a.
2	(S)-43	13,485	14,106	47,173	38,68	34,00	n.a.
Total:			**36,466**	**138,755**	**100,00**	**100,00**	

Chromatogram



(1S,2S)-DACH Trost

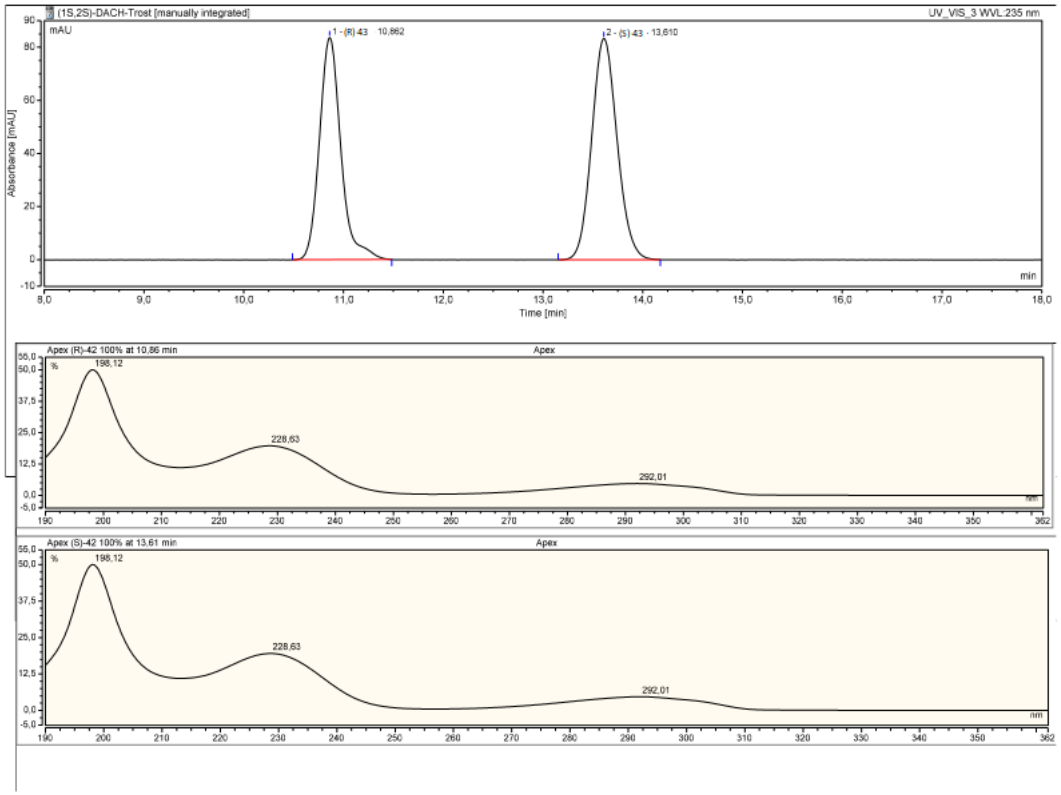
Chromatogram and Results

Injection Name:	**(1S,2S)-DACH-Trost**	*Run Time (min):*	**30,00**
Injection Volume:	**1,00**	*Channel:*	**UV_VIS_3**
Column:	**OD-2**	*Wavelength:*	**254,0**

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1	(R)-43	10,862	20,903	83,716	45,93	50,11	n.a.
2	(S)-43	13,610	24,608	83,337	54,07	49,89	n.a.
Total:			**45,511**	**167,053**	**100,00**	**100,00**	

Chromatogram



(R)-SEGPHOS

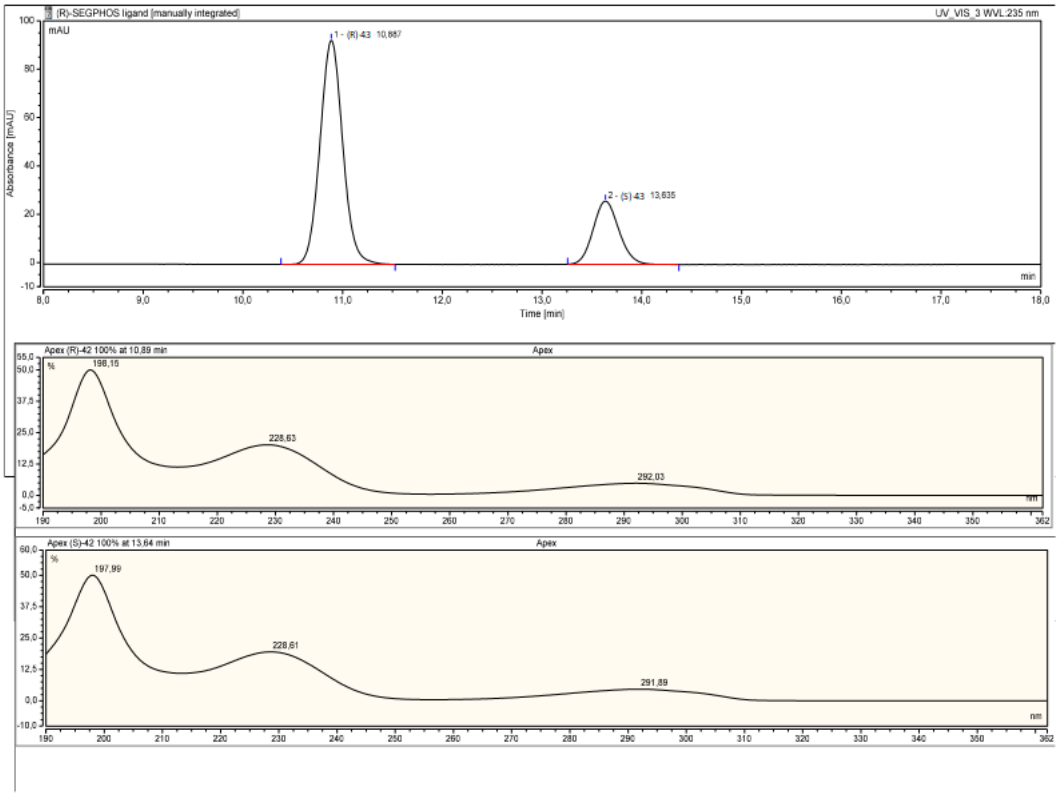
Chromatogram and Results

Injection Name:	**(R)-SEGPHOS ligand**	*Run Time (min):*	**30,00**
Injection Volume:	**1,00**	*Channel:*	**UV_VIS_3**
Column:	**OD-2**	*Wavelength:*	**254,0**

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1	(R)-43	10,887	24,543	92,664	75,82	78,01	n.a.
2	(S)-43	13,635	7,826	26,124	24,18	21,99	n.a.
Total:			**32,369**	**118,788**	**100,00**	**100,00**	

Chromatogram



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E Conclusion and Perspective

Throughout this pre-doctoral research, we investigated the use of quaternary ammonium salts (QAS) as solid reagents in hydrocarbonylation reactions, a relatively unexplored and unconventional approach in organic synthesis. In contrast to traditionally applied alkylating agents like MeI or dimethylsulfate, QAS offer several advantages, including being easy-to-handle solids and exhibiting non-toxic, non-cancerogenic, non-mutagenic, non-flammable, and non-corrosive properties.

Our findings revealed that phenyl trimethylammonium iodide serves as a promising alternative methylating agent, enabling highly mono-selective α-C-methylation reactions of aryl ketones and N-methylation reactions of primary amides. This method holds potential for late-stage methylations of bioactive compounds. Additionally, we successfully utilized allyl-containing ammonium salts in a mechanochemically driven Tsuji-Trost reaction, facilitating the synthesis of various allylated nucleophiles, including complex pharmaceuticals. This solvent-free approach not only enables rapid and highly selective reactions but also contributes to environmental sustainability. However, the enantiomeric excess of the palladium-catalyzed reaction using chiral ligands was moderate at 52 %, indicating room for improvement and further investigation.

An important consideration moving forward is the synthesis of these QAS, which currently involves alkyl halides, diminishing their attractiveness for industrial applications. Developing efficient and environmentally benign synthetic routes for QAS is therefore crucial. Moreover, the mechanism of alkylation reactions using QAS remains incompletely understood, necessitating further elucidation.

Despite these challenges, the vast natural abundance of chiral amines, such as amino acids, presents an exciting opportunity. Converting these compounds into chiral ammonium species and utilizing them in reactions with efficient chirality transfer holds immense potential for accessing novel enantiomerically enriched compounds. Additionally, the

possibility of replacing noble-metal catalysts with earth-abundant alternatives could further enhance the sustainability of these transformations.

In conclusion, our research underscores the potential of QAS as versatile reagents in organic synthesis, offering opportunities for the development of efficient and sustainable methodologies. Continued investigation into QAS-based reactions, mechanistic studies, and synthetic strategies is essential for unlocking their full potential in the pursuit of novel chemical transformations and the synthesis of complex molecules.

F Appendix

F I Publications Resulting from This Thesis

Journal Articles

Johanna Templ and Michael Schnürch

Selective α-Methylation of Aryl Ketones Using Quaternary Ammonium Salts as Solid Methylating Agents

J. Org. Chem. 2022, 87, 6, 4305 – 4315. doi: 10.1021/acs.joc.1c03158

Johanna Templ and Michael Schnürch

A Guide for Mono-Selective N-Methylation, N-Ethylation, and N-*n*-Propylation of Primary Amines, Amides, and Sulfonamides and Their Applicability in Late-Stage Modification

Chem. Eur. J. 2024, e202304205. doi: 10.1002/chem.202304205

Johanna Templ, Edma Gjata, Filippa Getzner, and Michael Schnürch

Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents

Org. Lett. 2022, 24, 40, 7315–7319. doi: 10.1021/acs.orglett.2c02766

Johanna Templ and Michael Schnürch

Allylation of *C*-, *N*-, and *O*-Nucleophiles *via* a Mechanochemically-Driven Tsuji–Trost Reaction Suitable for Late-Stage Modification of Bioactive Molecules

Angew. Chem. Int. Ed. 2024, 63, e202314637. doi: 10.1002/anie.202314637

Johanna Templ and Michael Schnürch

Strategies for using Quaternary Ammonium Salts as Alternative Reagents in Aliphatic Hydrocarbonylations

Chem. Eur. J., submitted manuscript (feb 2024)

Conference Talks

European Meeting on C-H Activation – Lisbon, Portugal, Jan 2024
Johanna Templ and Michael Schnürch
"Mashing up Tsuji-Trost Allylation - a mechanochemical approach"
Oral Communication

ISOS 2023 - Corbella Summer School – Gargnano, Italy, June 2023
Oral Communication as Full Fellowship Holder
Johanna Templ, Edma Gjata, Filippa Getzner, and Michael Schnürch
"Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents"
Oral Communication as Full Fellowship Holder

Blue Danube Smposium on Heterocyclic Chemistry – Bratislava, Slovakia, Aug 22
Johanna Templ, Edma Gjata, Filippa Getzner, and Michael Schnürch
"Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents"
Oral Communication

FemChem Scientific Workshop – Vienna, Austria, Sept 22
Johanna Templ, Edma Gjata, Filippa Getzner, and Michael Schnürch
"Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents"
Oral Communication

19th Austrian Chemistry Days – Vienna, Austria, Sept 22
Johanna Templ, Edma Gjata, Filippa Getzner, and Michael Schnürch
"Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents"
Oral Communication

Poster Presentations

22nd ESOC – Ghent, Belgium, July 2023
Johanna Templ and Michael Schnürch
"Mashing up Tsuji-Trost Allylation - a mechanochemical approach"
Poster Presentation

Johanna Templ and Michael Schnürch
8th EuChemS – Lisbon, Portugal, Sept 2022
"Quaternary Ammonium Salts as Solid Methylating Agents"
Poster Presentation

B II Curriculum Vitae

JOHANNA TEMPL

Ph.D. student - Technical Chemistry

organic chemistry | methodology | metal catalysis | mechanochemistry

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EDUCATION

Ph. D. - Technical Chemistry — 2020 - ongoing
TU Wien - Institute of Applied Synthetic Chemistry (Austria)

Extension programme - Digital Skills — 2022 - ongoing
TU Wien (Austria)

MSc. - Technical Chemistry — 2017 - 2019
TU Wien - Institute of Applied Synthetic Chemistry (Austria)

Thesis:
"Towards the Total Synthesis of Euphosalicin"

BSc. - Technical Chemistry — 2013 - 2017
TU Wien - Institute of Applied Synthetic Chemistry (Austria)

Thesis:
"Development of Novel Enzym Substrates to Indicate Mucopolysaccharidosis in Newborn"

WORK EXPERIENCE

Short Scientific Stay at the Noel Research Group — Jan-Mar, 2023
University of Amsterdam, Amsterdam (Netherlands)

Photoredox Catalysis

Lectures in Basic Chemistry Courses — 2019 - 2022
Sigmund Freud University, Vienna (Austria)

Chemistry Lectures for Med-Students in their first Semester

Supervision of Laboratory Courses — 2016 - 2022
TU Wien, Vienna (Austria)

Supervision in practical Laboratory Courses for Bachelor's program in Technical Chemistry

PUBLICATIONS

Strategies for Using Quaternary Ammonium Salts as Alternative Reagents in Aliphatic Hydrocarbonylation — Feb 2024
Johanna Templ and Michael Schnürch

Chem. Eur. J. **submitted manuscript**

LANGUAGE

German — native

English — fluent

Italian — basic

SKILLS

LaTeX

Python

Driving License — B

A Guide for Mono-Selective N-Methylation, N-Ethylation, and N-n-Propylation of Primary Amines, Amides, and Sulfonamides and Their Applicability in Late-Stage Modification — Feb 2024
Johanna Templ and Michael Schnürch

Chem. Eur. J. **2024**, e202304205

Allylation of C-, N-, and O-Nucleophiles via a Mechanochemically-Driven Tsuji-Trost Reaction Suitable for Late-Stage Modification of Bioactive Molecules — Nov 2023
Johanna Templ and Michael Schnürch

Angew. Chem. Int. Ed. **2024**, 63, e202314637

Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents — Oct 2022
Johanna Templ, Edma Gjata, Filippa Getzner and Michael Schnürch

Org. Lett. **2022**, 24, 40, 7315–7319.

Selective α-Methylation of Aryl Ketones Using Quaternary Ammonium Salts as Solid Methylating Agents — March 2022
Johanna Templ and Michael Schnürch

J. Org. Chem. **2022**, 87, 6, 4305–4315.

PRESENTATIONS & CONFERENCES

European Meeting on C-H Activation - Lisbon — Jan 2024
Oral Communication

Mashing up Tsuji-Trost Allylation - a mechanochemical approach

22nd ESOC - Ghent — July 2023
Poster Presentation

Mashing up Tsuji-Trost Allylation - a mechanochemical approach

ISOS 2023 - Corbella Summer School — June 2023
Oral Communication as Full Fellowship Holder

Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents

Blue Danube Symposium on Heterocyclic Chemistry — Aug 2022
Oral Communication

8th EuChemS - Lisbon — Sept 2022
Poster Presentation

Quaternary Ammonium Salts as Solid Methylating Agents

FemChem Scientific Workshop — Sept 2022
Oral Communication

19th Austrian Chemistry Days — Sept 2022
Oral Communication

21st ESOC - Vienna July 2019

Poster Presentation

Towards the Total Synthesis of Euphosalicin and Pepluanin A - Route to a Highly Oxygenated Cyclopentane Key Intermediate

HONORS AND AWARDS

- **"Best Oral Communication"**, *European Meeting on C-H Activation, Jan 2024*
  "Mashing Up Tsuji-Trost Allylation - a mechanochemical approach"
- **"Participation Fellowship"**, *ISOS 2023 - Corbella Summer School, June 2023*
  "Monoselective N-Methylation of Amides, Indoles, and Related Structures Using Quaternary Ammonium Salts as Solid Methylating Agents"
- **"Christiana Hörbiger Preis"**, *private scholarship, Oct 2022*
  for short term scientific stays abroad
- **"Leistungsstipendium"**, *merit scholarship, Dec 2018*
  for excellence in studies of the Federal Ministry of Science and Research, Austria
- **"Förderungsstipendium"**, *promotion scholarship, Nov 2019*
  of the Federal Ministry of Science and Research, Austria
- **"Poster Prize"**, *21st ESOC - Vienna, July 2019*
  Poster Prize sponsored by the Royal Society of Chemistry
- **"Leistungsabzeichen"**, *bronze and silver medal of honor for violoncello of the Federal Music School of Upper Austria, Austria*