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Dissertation

APPLICATION OF NON-VOLATILE REAGENTS FOR THE INTRODUCTION OF SHORT HYDROCARBON CHAINS

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

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Fakultät für Technische Chemie

von

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Ἓν οἶδα ὅτι οὐδὲν οἶδα.

Σωκράτης

All I know is that I know nothing.

Socrates

Acknowledgments

Throughout my four-year Ph.D. journey, many people have accompanied and supported me. Their guidance, advice, and encouragement, whether in the lab or during social gatherings, and events, have been crucial for my scientific and personal growth. I am deeply grateful to all who have been part of this journey.

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To my 'old' Erasmus friends, as well as to Resi who introduced me to the BSC group, and to Konsti, for making my stay in Vienna so much fun, and for sharing so many experiences throughout the years, thank you. To my cousin Stella, who has been a constant in my life since childhood, and to my friend Johanna, thank you for always being there for me, even from afar, whenever I needed to vent my stress (which happened often).

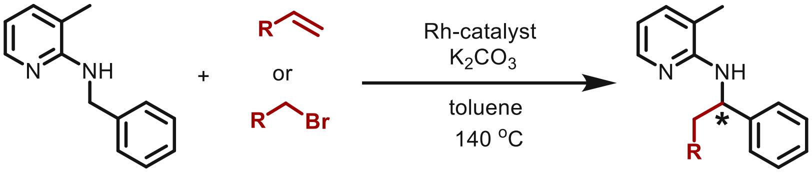
To you, Panagioti, my life partner, I couldn't be happier to have you by my side throughout this journey. Your patience and encouragement have been my anchor through the highs and lows. I am incredibly grateful for the sacrifices you've made to make this work. Thank you for always being there for me!

My biggest thank you goes to my parents! This thesis is dedicated to them and to their unfulfilled dreams. Το μεγαλύτερο ωστόσο ευχαριστώ αξίζει στους γονείς μου! Αυτή η διπλωματική εργασία είναι αφιερωμένη σε εσάς και στα δικά σας ανεκπλήρωτα όνειρα, τα οποία δε στερήσατε ποτέ από εμένα. Σας ευχαριστώ για την αγάπη, την υπομονή, την πίστη σας σε εμένα, και τη συνεχή στήριξη σε όλες τις επιλογές μου. Χωρίς εσάς δε θα είχα καταφέρει τίποτα από όλα αυτά. Τέλος, ευχαριστώ τον μεγάλο μου αδερφό, που είναι πάντα εκεί, να ακούσει και να στηρίξει.

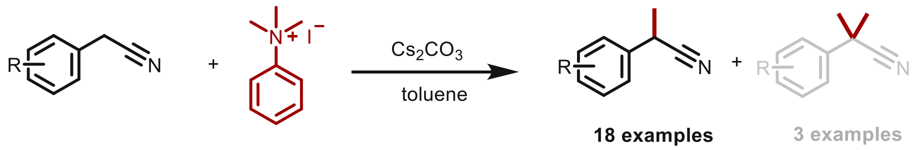
Abstract

The main objective of this thesis was to substitute gaseous reagents with solid alternatives in various transformations. Alkylations are amongst the most important yet challenging direct functionalization reactions in C-H activation chemistry. Conventional alkylating agents such as alkyl halides are inconvenient to use due to their low reactivity and the significant health hazards they pose. These agents are often highly toxic, carcinogenic, mutagenic, flammable, and corrosive. Terminal olefins have also been used as alkylating agents; however, short-chained ones (up to C5) are highly volatile, flammable, and require elaborate equipment such as autoclaves, which complicates the process. In contrast, quaternary ammonium salts provide a safer and more sustainable alternative for similar transformations overcoming these drawbacks. These solid reagents reduce health risks while being non-flammable, and non-corrosive.

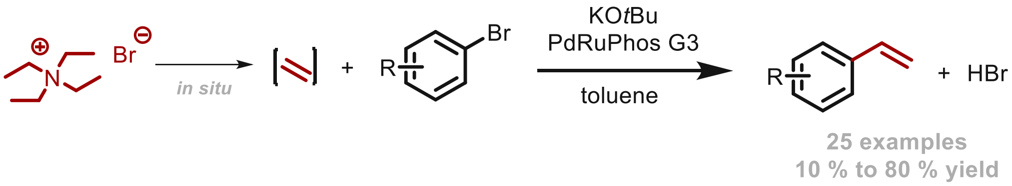
Enantioselective C-H functionalization offers a powerful tool to precisely generate new stereocenters in complex molecules in a step-and atom-economic manner, enabling late-stage modification in pharmaceutically relevant compounds. While stereoselective C-H functionalization has progressed in the past decade, enantioselective methodologies have received considerably less attention. This disparity is particularly noteworthy, and within this study, we aimed to induce enantioselectivity in our model reaction. For this purpose, the direct alkylation of benzylic amine by utilizing olefins as the alkylating agent, previously reported in our group, was used as the reference reaction.



In the first manuscript, phenyl trimethyl ammonium iodide was employed as a safer alternative methylating agent for the efficient and selective C-monomethylation of aryl acetonitriles. This methodology successfully yielded several (hetero)aryl acetonitriles as well as bioactive derivatives thereof. Additionally, selective demethylation was achieved by adjusting the reaction parameters accordingly.



In the next contribution, a convenient Heck vinylation protocol that circumvents the use of ethylene gas as a coupling partner was established. Instead, tetraethyl ammonium bromide was used as the olefin surrogate. This strategy was carried out in a one-pot reaction, under ambient atmosphere conditions, and demonstrated its efficiency across a broad range of substrates with different functionalities, yielding up to 80 % of the desired product.

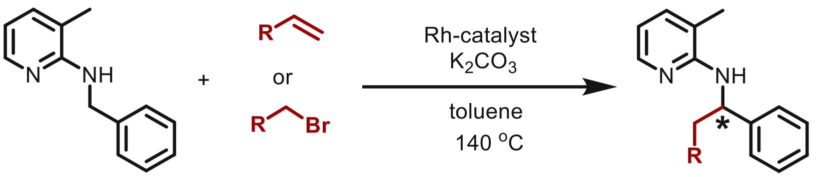


A review article highlights the importance of vinyl-containing compounds for the synthesis of complex organic molecules. It presents cutting-edge strategies for carbon, nitrogen, and oxygen vinylation reactions including both transition metal-catalyzed as well as metal-free strategies.

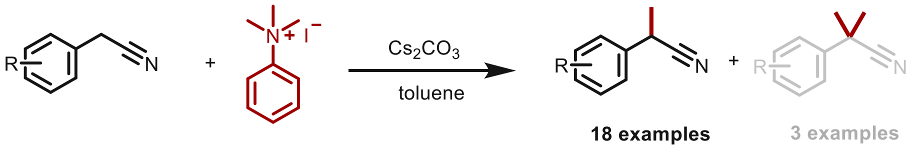
Kurzfassung

Das Hauptziel dieser Arbeit bestand darin, gasförmige Reagenzien bei verschiedenen Transformationen durch feste Alternativen zu ersetzen. Alkylierungen gehören zu den wichtigsten, aber auch schwierigsten direkten Funktionalisierungsreaktionen in der C-H-Aktivierungschemie. Herkömmliche Alkylierungsmittel wie Alkylhalogenide sind aufgrund ihrer geringen Reaktivität und der erheblichen Gesundheitsgefahren, die von ihnen ausgehen, unpraktisch in der Anwendung. Diese Mittel sind oft hochgiftig, krebserregend, erbgutverändernd, entflammbar und ätzend. Auch endständige Olefine wurden als Alkylierungsmittel verwendet; kurzkettige Olefine (bis C5) sind jedoch sehr flüchtig und entflammbar und erfordern aufwendige Geräte wie Autoklaven, was den Prozess erschwert. Im Gegensatz dazu bieten quaternäre Ammoniumsalze eine sicherere und nachhaltigere Alternative für ähnliche Umwandlungen, die diese Nachteile überwindet. Diese festen Reagenzien verringern die Gesundheitsrisiken und sind gleichzeitig nicht entflammbar und nicht korrosiv.

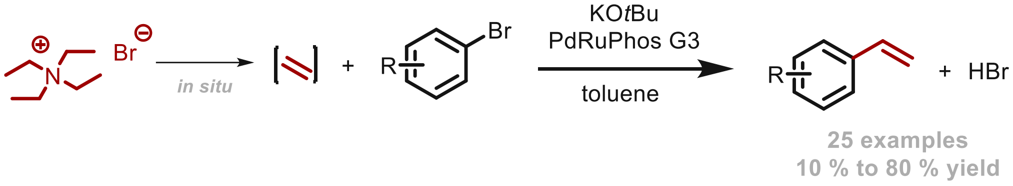
Die enantioselektive C-H-Funktionalisierung bietet ein leistungsfähiges Werkzeug zur präzisen Erzeugung neuer Stereozentren in komplexen Molekülen auf schrittweise und atomökonomische Weise und ermöglicht so eine späte Modifizierung pharmazeutisch relevanter Verbindungen. Während die stereoselektive C-H-Funktionalisierung in den letzten zehn Jahren Fortschritte gemacht hat, wurde enantioselektiven Methoden deutlich weniger Aufmerksamkeit geschenkt. Diese Diskrepanz ist besonders bemerkenswert, und im Rahmen dieser Studie haben wir versucht, Enantioselektivität in unserer Modellreaktion zu induzieren. Zu diesem Zweck wurde die direkte Alkylierung von benzylischen Aminen unter Verwendung von Olefinen als Alkylierungsmittel, über die unsere Gruppe bereits berichtet hatte, als Referenzreaktion verwendet.



Im ersten Manuskript wurde Phenyltrimethylammoniumiodid als sichereres alternatives Methylierungsmittel für die effiziente und selektive C-Monomethylierung von Arylacetonitrilen eingesetzt. Mit dieser Methode wurden mehrere (Hetero)-Arylacetonitrile sowie deren bioaktive Derivate erfolgreich hergestellt. Darüber hinaus wurde eine selektive Demethylierung erreicht, indem die Reaktionsparameter entsprechend angepasst wurden.



Im nächsten Beitrag wurde ein bequemes Heck-Vinylierungsprotokoll entwickelt, das die Verwendung von Ethylengas als Kupplungspartner umgeht. Stattdessen wurde Tetraethylammoniumbromid als Olefinsurrogat verwendet. Diese Strategie wurde in einer Eintopfreaktion unter Umgebungsatmosphäre durchgeführt und erwies sich als effizient für ein breites Spektrum von Substraten mit unterschiedlichen Funktionalitäten, wobei bis zu 80 % des gewünschten Produkts erhalten wurden.



In einem Übersichtsartikel wird die Bedeutung von vinylhaltigen Verbindungen für die Synthese komplexer organischer Moleküle hervorgehoben. Er stellt modernste Strategien für Kohlenstoff-, Stickstoff- und Sauerstoff-Vinylierungsreaktionen vor, darunter sowohl Übergangsmetall-katalysierte als auch metallfreie Strategien.

Structure of thesis

The following thesis authored by Eleni Papaplioura is composed as a cumulative dissertation comprising of three published manuscripts and one additional chapter which has not been published due to insufficient success of the corresponding project. Research papers produced during the Ph.D program are quoted as published or accepted manuscripts.

The thesis is organized as follows:

The introduction provides an overview of the relevant theoretical background and current research. The subsequent sections include the unpublished material, along with all published manuscripts as original work. It begins with a list of contributions, followed by a concise summary of each work, and a statement outlining the unique contributions. Any available supporting information is included directly following each manuscript. Lastly, the thesis concludes with a summary of findings and perspectives, followed by a list of publications derived from this work and a curriculum vitae.

Compounds are numbered per chapter.

Contents

A Introduction

The main aim of this thesis was to enable the substitution of gaseous reagents with solid alternatives. This concept was intended to be applied in three different transformations. Firstly, the aim was to design and develop a sustainable and safe alkylation reaction protocol, involving the use of solid and easy-to-handle sources of alkanes, and *in situ* generation of the required reactive coupling partners by utilizing quaternary ammonium salts as alkyl sources for C-H activation. However, the focus was mainly appointed towards the development of enantioselective reactions. To achieve this goal, several chiral ligands were evaluated for their ability to induce enantioselectivity.

In another approach, the intentional formation of ethylene *in situ* was investigated for use in Mizoroki-Heck reactions. Compounds containing styrene motifs are pivotal building blocks in organic synthesis. Hence, bypassing the need for elaborate high-pressure equipment enhances the practicality of the methodology, making it particularly appealing for applications in industry.

Additionally, quaternary ammonium salts were employed as solid, inherently safer methylating agents for late-stage methylation applications. Contrary to traditional methylating agents such as MeI and MeBr which are highly volatile and pose a greater risk of exposure due to their higher toxicity, quaternary ammonium salts offer significant advantages. They are non-toxic, non-carcinogenic, non-flammable, and non-corrosive.

The following introduction provides a comprehensive overview of the key concepts behind the desired transformations. It begins by reviewing the current state of the art in each field and emphasizes the strategies and motivation driving each project.

A I C-H Activation for Alkylation Reactions

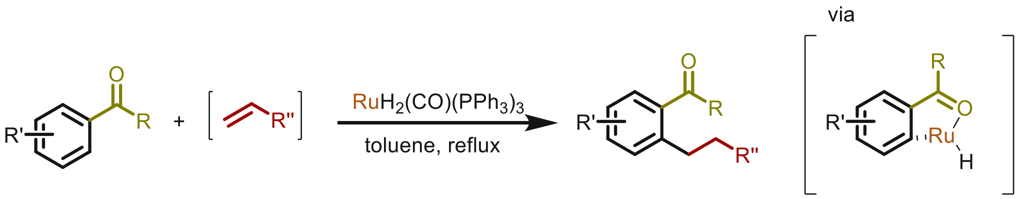
The constant urge to address energy and sustainability challenges has given rise to the concept of green chemistry. [1] According to the ‘12 Principles of Green Chemistry’, it is important to design sustainable and eco-friendly chemical processes to mitigate the environmental impact of chemical production, while improving chemical efficiency. Furthermore, safety is a crucial aspect and must be prioritized at every stage of a chemical process. Ensuring safety entails maintaining non-extreme reaction conditions, ideally utilizing ambient temperature and pressure. This approach minimizes the risk of hazardous incidents and reduces energy consumption. Furthermore, the chemicals involved, such as reaction partners, catalysts, solvents, and additives, must be non-toxic, and stable under reaction conditions.

Over the last two decades, significant advancements have been made in the field of cross-coupling reactions, particularly those mediated by metals. [2-3] Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki were awarded the Nobel Prize in 2010, for their contribution to developing palladium-catalyzed cross-coupling reactions. [4-8] However, the roots were laid in the 1970s by groundbreaking works by Kumada, Sonogashira, Stille, Tsuji, Trost, and many others. [9] While palladium-based catalysts remain preferred due to their high functional group tolerance and stability, other metals including rhodium, platinum, and iridium, as well as 3d metals like iron, nickel, copper, and cobalt also demonstrate catalytic activity, thereby expanding the toolkit available for organic syntheses. [10-11]

In particular, regarding sustainability, the C-H activation strategy has been a powerful tool in organic chemistry, allowing chemists to construct complex molecules containing C-C, C-O, and C-N bonds in an atom-economic fashion, by activating otherwise inert C-H bonds. [12] C-H activation refers to the cleavage of a stable C-H bond in organic compounds, or more specifically to the replacement of a hydrogen atom in a C-H bond with another element or functional group. [2] Unlike traditional transition metal catalysis, which requires pre-functionalized coupling partners, C-H functionalization eliminates the necessity of such pre-functionalization of at least one of the reaction partners. [13-14] Hence, this approach decreases the need for functional group introductions and consequently reduces the number of reaction steps, and minimizes environmental waste, aligning with the '12 Principles of Green Chemistry'. [1,11,13,15]

However, the abundance of C-H bonds in organic molecules and their typically low reactivity make selective functionalization of non-acidic C-H bonds a challenging and tedious process. [16-18] One way to control selectivity is through the substrate itself (innate). [19] However, the most efficient strategy to control regioselectivity in C-H activation is to perform directed reactions. [19] In this case a moiety, that is a directing group (DG) is used to bring the metal into proximity to the target C-H bond. [3,20-21] These DGs typically contain a heteroatom, which binds the transition metal to the substrate *via* agostic interactions typically forming five- or six-membered metallacycles. [3] These metallacycles serve as the intermediates and must be both thermodynamically and kinetically stable to facilitate C-H activation.[20] This coordination is considered the most critical step in the C-H activation process as it determines selectivity and therefore, the proper design of the DGs is essential. [16-18]

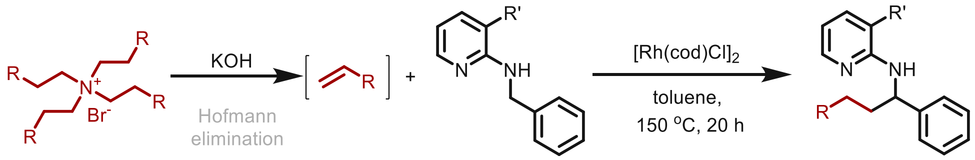
In 1993 Murai pioneered the field of transition metal-catalyzed directed C-H activation with a ketone-assisted, ruthenium-catalyzed alkylation of arenes using alkenes (Scheme 1). [22]



Scheme 1. Ketone-assisted ortho-alkylation of arenes in Murai work.

A new approach involving transient directing groups has appeared in the past decade. This method involves both the introduction and removal of the DG *in situ*, thereby facilitating C-H activation. This strategy converts weakly coordinating DGs such as ketones, into stronger ones like imines, oximes, or hydrazones. [23-25]

Our group previously employed pyridine as a directing group, to enable the direct Rh (I)-catalyzed alkylation of benzylic amines *via* C-H functionalization, using alkyl bromides and olefins as alkylating agents. Due to the inert nature of alkanes, functionalized alkanes were preferred. While halides are efficient coupling partners, with aryl halides demonstrating high effectiveness, alkyl halides pose challenges due to their significantly lower reactivity. One major challenge is the competing β-hydride elimination after oxidative addition of a metal catalyst into a C-halide bond. Additionally, the use of short alkyl chains, especially methyl and ethyl, raises concerns due to their low boiling point and high toxicity. Terminal olefins have also been reported as alkylating agents, and often alkyl halides eliminate to olefins as the real alkylating agent. However, since they remain gaseous until C4 high-pressure equipment is required, which poses safety risks, making the process inconvenient and methylation reactions cannot be carried out at all. Previous experimental findings have shown that although several alkyl bromides (ranging from C2 to C22), both linear and branched, as well as functionalized ones, were all well-tolerated, the reaction proceeded more rapidly and at lower temperatures when olefins were employed as the alkylating agents since HBr elimination to olefins is not necessary. However, in order to tackle the issue of volatile olefins, a sustainable and safe alternative involves the use of solid and easy-to-handle sources of alkanes and the *in situ* formation of the required reactive coupling partners by utilizing quaternary ammonium salts as alkylating agents *via* Hofmann elimination (Scheme 2). [26-27]



Scheme 2. Direct alkylation utilizing solid-olefin-surrogates as alkyl source.

With numerous chiral carbon-carbon (C-C) and C-heteroatom (C-X) bonds present in bioactive molecules, natural products, and materials, the concept of asymmetric C-H activation is rapidly evolving, enabling the synthesis of complex chiral compounds.[28] Up to date, significant progress has been made particularly with enantioselective C(sp^2)-H bonds which are generally more sterically accessible and acidic compared to their C(sp^3)-hybridized counterparts.[28] The two fundamental pathways to generate C(sp^2)-H stereochemistry involve i) the desymmetrization of a prochiral starting material *via* the selective C–H activation of an enantiotropic aryl C–H bond and a subsequent inter- or intramolecular functionalization, generating a molecule that possesses either central, planar or axial chirality (Figure 1); ii) the controlled addition of a coupling partner selectively to one enantiotopic face of the prochiral C–H activated bond during the migratory insertion step, directed by a chiral catalyst.[29] The limited progress in the enantioselective C(sp^3)-H activation may also be attributed to the harsh reaction conditions required for the cleavage of a C(sp^3)-H bond, and the shortage of ligands capable of facilitating enantioselective C-H activation reactions.[28] This advancement proceeds through the chemoselective desymmetrization of a prochiral starting material *via* C–H activation of an enantiotopic C(sp^3)–H bond by chiral transition metal catalysts, followed by either intra- or intermolecular functionalization, resulting in the generation of either a central or a planar chiral molecule. Alternatively, racemic mixtures can also be differentiated via kinetic resolution/ C(sp^3)-H activation. [30]

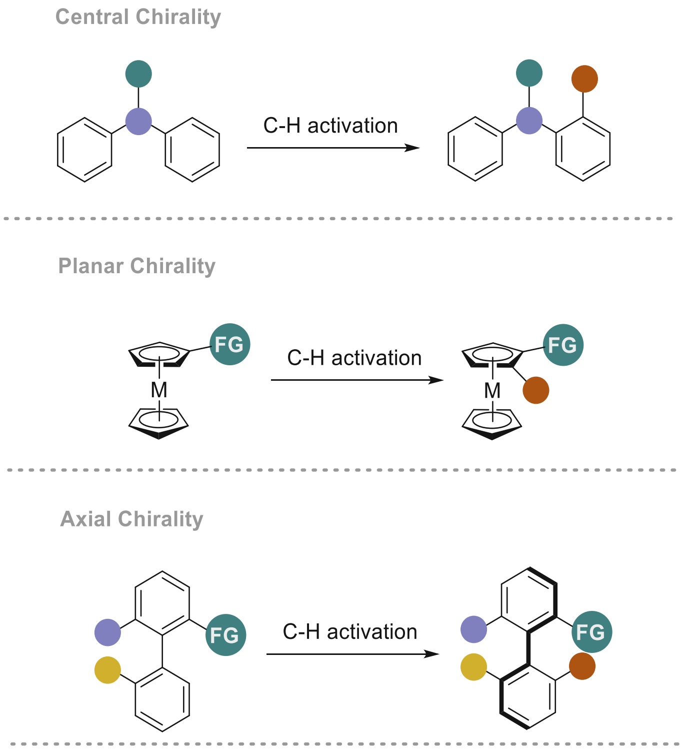


Figure 1. Nature of chirality in asymmetric C(sp^2)-H activation.

The most extensively investigated approach in asymmetric C-H activation was demonstrated by Yu and co-workers in 2008. They employed monoprotected α-amino acids (MPPA) as effective chiral ligands, along with alkyl boronic acid as the coupling partner, for Pd(II)-catalyzed enantioselective C-H activation reactions. [31] Later the same concept was successfully implemented for the enantioselective C(sp^3)–H bond activation forming *in situ* an imine intermediate between the amine moiety of the amino acid ligand and the aldehyde moiety of the substrate. Upon coordination with Pd(II), the transition state with less steric repulsion leads to the major product. [32-33]

A II Late - Stage Methylation

Alkylation reactions are fundamental processes in organic chemistry, playing a pivotal role in synthesizing a wide range of compounds across various fields, including agrochemicals, [34-38] polymer materials, [39-40] and pharmaceuticals. [41-47] Although historically, alkylation has been widely used in petrochemistry, [48-50] in recent years, its significance in medicinal chemistry has grown, especially in the late-stage modification of drug candidates [41-46,51] (Figure 2, left). Adding small alkyl groups, especially the methyl group, to an organic molecule, is critical. This modification can profoundly influence the properties and reactivity of the molecules, significantly improving their IC_{50} values compared to their precursors. [52] Extensive structure-activity relationship (SAR) studies have shown that such a modification could alter the metabolism, half-life, binding affinity, and structural conformation of the molecules, while simultaneously enhancing their lipophilicity and solubility [53-56] (Figure 2, right).

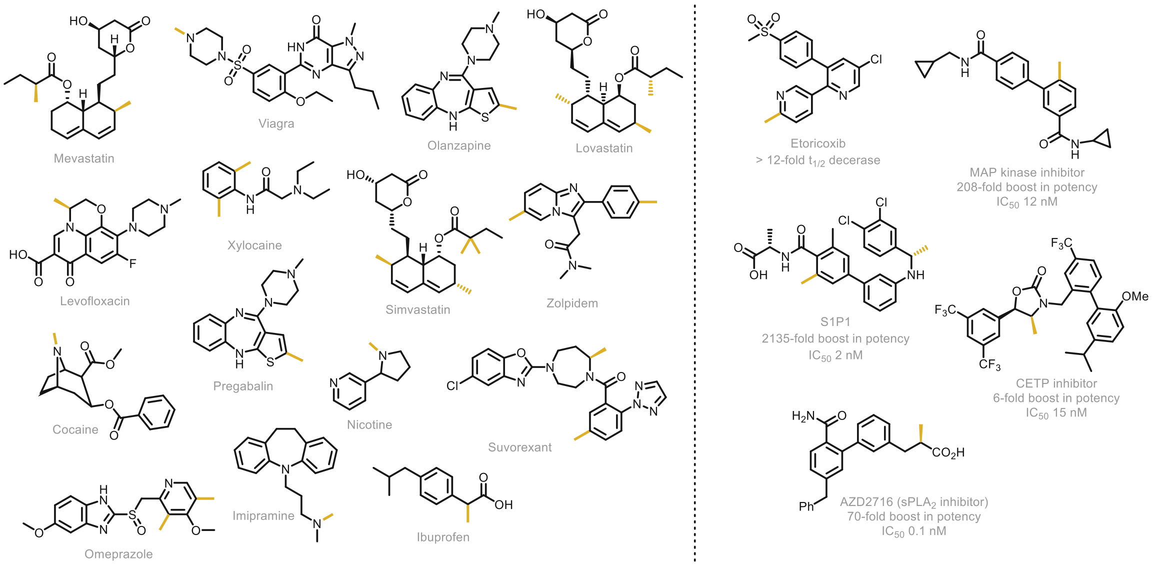


Figure 2. Representative examples of methylated drugs (left) and selected examples of profound methylation effects (right).

The importance of nitrogen-containing heterocycles in pharmaceuticals cannot be overstated. A plethora of active pharmaceuticals and active natural products contain nitrogen atoms in their scaffolds or nitrogen heterocycles in their backbones (Figure 3). [57-61] In fact, over 85 % of FDA-approved drugs currently on the market, contain nitrogen-containing heterocyclic moieties. [57] These drugs are used to address a broad spectrum of conditions, including cancer, [62-65] inflammation, [66-68] bacterial and viral infections, [69-70] diabetes, [67] or dementia. [71] In recent decades, more than 30 nitrile-containing pharmaceuticals have received FDA approval. [72-73] Research on structure-activity relationships (SAR) has shown that incorporating a nitrile group into lead compounds can significantly enhance their physicochemical and pharmacokinetic properties, bioavailability, selectivity, and binding affinity through hydrogen bonding, covalent and polar interactions, while also mitigating drug resistance. [72,74-77] This highlights the potential for continued innovation and development in this area.

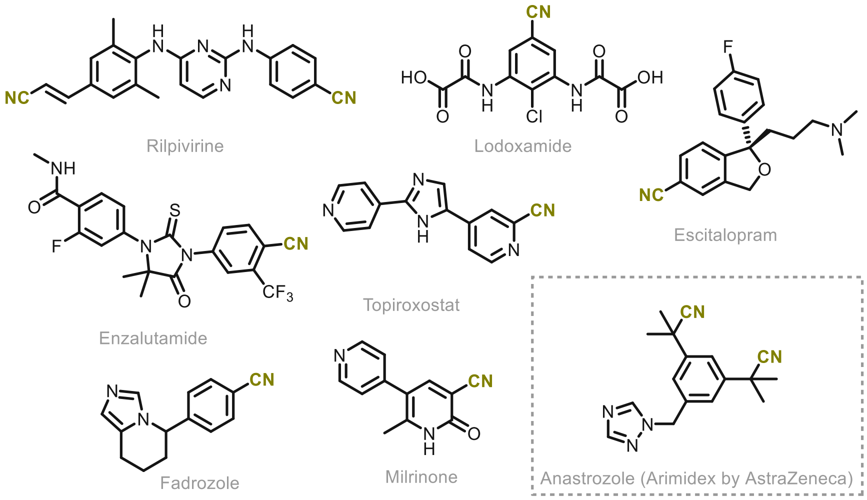


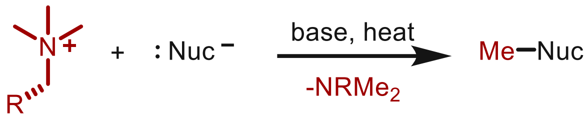
Figure 3. Representative examples of pharmaceuticals containing cyano groups.

Anastrozole, a widely used drug marketed by AstraZeneca under the trade name Arimidex, is an important treatment for breast cancer (Figure 3). Classified within the α-aryl acetonitrile drug family, it is characterized by the presence of a nitrile group attached to a quaternary carbon adjacent to an aromatic ring. These compounds are highly versatile and have been extensively researched. [78] Interestingly, the selective *C*-mono-methylation of these compounds results in the synthesis of 2-arylproprionitriles, fundamental building blocks for the development of anti-inflammatory agents such as ibuprofen, naproxen, and flurbiprofen. [79-81]

However, late-stage methylation of complex bioactive molecules remains a significant challenge in organic synthesis. [82-83] Conventional strategies for late-stage methylation often rely on transition metal catalysis (C-H methylation), necessitating highly toxic reagents and solvents. [84] Alkylation and methylation reactions, involving short alkyl chains such as methyl and ethyl, present challenges due to selectivity issues and the inconvenient handling of the highly volatile agents (e.g., MeBr, with a boiling point of 4 °C). Traditional methylating agents such as MeI or Me_2SO_4 pose significant health hazards being highly toxic, carcinogenic, and mutagenic. [85-86] Additionally, organometallic reagents employed for methylation (Me_4Sn, [87] $MeB(OH)_2$ [88-91] MeMgCl, [92]Me_3Al, [93] or Me_2Zn [94]), typically exhibit low functional group tolerance, air sensitivity, flammability, or corrosiveness, rendering them impractical for lab-scale syntheses. [95-96]

The need for novel, safer methylating agents is evident. Nitrogen salts have a long-standing history, with diazonium salts dating back to the 19th century. [97-98] In recent years, ammonium salts have been used as inexpensive phase transfer catalysts, [99-101] ionic liquids, [99,102-104] and surfactants [102]. Recent studies have demonstrated the efficiency of quaternary ammonium salts as alternative methylating agents in the selective α-methylation of aryl ketones and the mono-selective *N*-methylation of primary amides. [105-106] These solid salts pose a lower exposure compared to the volatile MeI. Additionally, they are non-carcinogenic, non-mutagenic, non-flammable, and non-corrosive, making them appealing for industrial applications. [100,107-108]

Experimental findings of these reactions suggest that the actual methylating agent is formed *via* an SN2-type reaction between the nucleophile and the methyl ammonium salt. This reaction pathway is feasible due to the positive charge and low basicity of the leaving group in quaternary ammonium salts, in the presence of a strong base and when heated. Interestingly, previous studies showed that MeI is not formed from the thermal decomposition of the methyl ammonium salts (Scheme 3). [105]



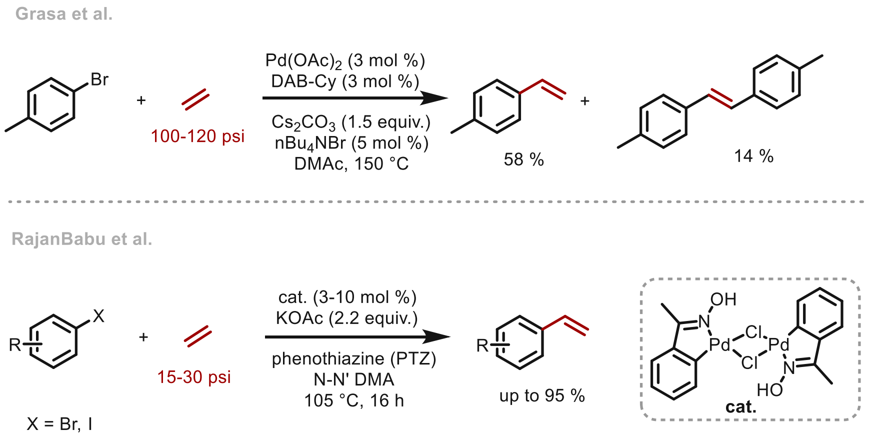
Scheme 3. Methylation reaction with a quaternary ammonium salt as methylating agent

In 2022, our group introduced the use of phenyl trimethyl ammonium iodide ($PhMe_3NI$) as an alternative methylating agent for the α-C methylation of aryl ketones. [105] In an attempt to expand on this methodology, we utilized a similar protocol using $PhMe_3NI$ as the methylating agent for the selective monomethylation of aryl acetonitriles. A detailed description can be found in Manuscript 1.

A III Efficient and Safer Vinylation Strategies

Olefins are important building blocks commonly used in organic synthesis. [109-110] They serve as key reaction partners in several transformations, including direct alkylation reactions *via* C-H functionalization [3,111-112] and in reactions like the Fujiwara-Moritani [113-114] and the Mizoroki-Heck reaction. [7,9,115-116] The Mizoroki-Heck and Fujiwara-Moritani reactions are olefination reactions, with the former belonging to cross-coupling processes and the latter to oxidative coupling methods. One common challenge associated with these reactions is their limited use in vinylation protocols because employing ethylene gas and ensuring consistent and adequate gas supply to the reaction vessel requires high-pressure equipment and specialized apparatus to control pressure and concentration adequately. [111-112] Additionally, the volatile nature of these gases raises safety concerns, as they may pose risks of leaks or accidental release.

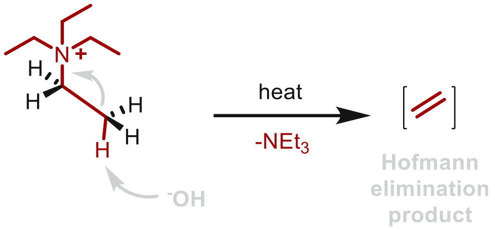
The scarce examples of similar transformations involving olefins that are gaseous at room temperature typically require pressures of above five atmospheres or very low temperatures to condense them into the reaction mixture. To the best of our knowledge, only two studies have reported the use of atmospheric or low-pressure ethylene. [117-118] (Scheme 4). Grasa et al. discovered that a $Pd(OAc)_2$/N,N′-dicyclohexyl-1,4-diazabutadiene (DAB-Cy) system effectively activates ethylene at atmospheric pressure, facilitating its reaction with 4-bromotoluene and resulting in the formation of 4-methylstyrene with a 58% yield along with 14% of the corresponding stilbene derivative (Scheme 4, top). [117] RajanBabu and Smith presented the coupling of aryl bromides or iodides with ethylene at ambient or slightly elevated pressures (15–30 psi). Utilizing catalytic amounts of a dimeric palladacycle derived from acetophenone oxime, along with phenothiazine acting as a radical inhibitor, and employing vinyl bromides as starting material, they successfully synthesized functionalized styrenes (Scheme 4, bottom). [118]



Scheme 4. Heck vinylation of aryl halides with ethylene at ambient pressure.

These factors complicate the practicability of vinylation reactions posing challenges for both efficiency and safety. Encouraged by previous studies that utilized quaternary ammonium salts as solid alternatives to gaseous olefins in C-H alkylation reactions,[27] and motivated by the significance of arylethenes as precursors for synthesizing bioactive compounds and polymers, [109-110,119] we recognized the potential for developing a safer approach for well-known transformations.

Quaternary ammonium salts are known to undergo E2-like elimination reactions under basic conditions. [120] This results in the decomposition of the quaternary ammonium moiety into a tertiary amine and olefin, whereas the least sterically hindered β-hydrogen is deprotonated preferentially (in absence of electronic effects) (Scheme 5). Motivated by this potential, we aimed to use this reaction for intentionally generating olefins *in-situ*, for example, for Heck-type reactions (aryl halide + *in-situ* formed olefin) (Manuscript 2).



Scheme 5. Base-mediated Hofmann elimination

By enabling gas substitution in small-scale studies, researchers can synthesize molecules in fewer steps, initiate the synthesis of previously avoided compounds, and create unique compounds with potential for novel applications. This approach can also positively alter the lipophilicity of medicinal compounds, enhancing their effectiveness.[119]

A IV Literature – Introduction

[1] P. Anastas,N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301-312.
[2] K. M. Altus,J. A. Love, *Commun. Chem.* **2021**, *4*, 173.
[3] C. Sambiagio,D. Schönbauer,R. Blieck,T. Dao-Huy,G. Pototschnig,P. Schaaf,T. Wiesinger,M. F. Zia,J. Wencel-Delord,T. Besset,B. U. W. Maes,M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603-6743.
[4] T. J. Colacot, *Platin. Met. Rev.* **2011**, *55*, 84-90.
[5] E.-i. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738-6764.
[6] A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722-6737.
[7] R. F. Heck,J. P. Nolley, Jr., *J. Org. Chem* **1972**, *37*, 2320-2322.
[8] N. Miyaura,A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483.
[9] C. C. C. Johansson Seechurn,M. O. Kitching,T. J. Colacot,V. Snieckus, *J. Am. Chem. Soc.* **2012**, *51*, 5062-5085.
[10] P. Gandeepan,T. Müller,D. Zell,G. Cera,S. Warratz,L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192-2452.
[11] R. Laskar,T. Pal,T. Bhattacharya,S. Maiti,M. Akita,D. Maiti, *Green Chem.* **2022**, *24*, 2296-2320.
[12] S. Dutta,P. Kumar,S. Yadav,R. D. Sharma,P. Shivaprasad,K. S. Vimaleswaran,A. Srivastava,R. K. Sharma, *Catal. Commun.* **2023**, *175*, 106615.
[13] U. Dhawa,N. Kaplaneris,L. Ackermann, *Org. Chem. Front.* **2021**, *8*, 4886-4913.
[14] F. Roudesly,J. Oble,G. Poli, *J. Mol. Catal. A: Chemical* **2017**, *426*, 275-296.
[15] T. Dalton,T. Faber,F. Glorius, *ACS Cent. Sci.* **2021**, *7*, 245-261.
[16] G. Meng,N. Y. S. Lam,E. L. Lucas,T. G. Saint-Denis,P. Verma,N. Chekshin,J. Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 10571-10591.
[17] A. Dey,S. Maity,D. Maiti, *Chem. Comm.* **2016**, *52*, 12398-12414.
[18] A. Dey,S. K. Sinha,T. K. Achar,D. Maiti, *Angew. Chem. Int. Ed.* **2019**, *58*, 10820-10843.
[19] T. Brückl,R. D. Baxter,Y. Ishihara,P. S. Baran, *Acc. Chem. Res.* **2012**, *45*, 826-839.
[20] K. Murali,L. A. Machado,R. L. Carvalho,L. F. Pedrosa,R. Mukherjee,E. N. Da Silva Júnior,D. Maiti, *Chem. Eur. J.l* **2021**, *27*, 12453-12508.
[21] S. Rej,Y. Ano,N. Chatani, *Chem. Rev.* **2020**, *120*, 1788-1887.
[22] S. Murai,F. Kakiuchi,S. Sekine,Y. Tanaka,A. Kamatani,M. Sonoda,N. Chatani, *Nature* **1993**, *366*, 529-531.
[23] P. Gandeepan,L. Ackermann, *Chem.* **2018**, *4*, 199-222.
[24] T. Bhattacharya,S. Pimparkar,D. Maiti, *RSC Adv.* **2018**, *8*, 19456-19464.
[25] C. Jacob,B. U. W. Maes,G. Evano, *Chem. Eur. J.* **2021**, *27*, 13899-13952.
[26] M. Spettel,R. Pollice,M. Schnürch, *Org. Lett.* **2017**, *19*, 4287-4290.
[27] D. Schönbauer,M. Spettel,R. Pollice,E. Pittenauer,M. Schnürch, *Org. Biomol. Chem.* **2019**, *17*, 4024-4030.
[28] Y. Zhang,J.-J. Zhang,L. Lou,R. Lin,N. Cramer,S.-G. Wang,Z. Chen, *Chem. Soc. Rev.* **2024**, *53*, 3457-3484.
[29] T. K. Achar,S. Maiti,S. Jana,D. Maiti, *ACS Catal.* **2020**, *10*, 13748-13793.
[30] T. G. Saint-Denis,R.-Y. Zhu,G. Chen,Q.-F. Wu,J.-Q. Yu, *Science* **2018**, *359*, eaao4798.
[31] B.-F. Shi,N. Maugel,Y.-H. Zhang,J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 4882-4886.
[32] F.-L. Zhang,K. Hong,T.-J. Li,H. Park,J.-Q. Yu, *Science* **2016**, *351*, 252-256.
[33] R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, Chem. Soc. Rev., 2009, 38, 3242–3272.
[34] P. Jeschke, *Eur. J. Org. Chem.* **2022**, *2022*, e202101513.
[35] C. Lamberth,S. Jeanmart,T. Luksch,A. Plant, *Science* **2013**, *341*, 742-746.

[36] D. B. Ramachary,C. Venkaiah,Y. V. Reddy,M. Kishor, *Org. Biomol. Chem.* **2009**, *7*, 2053-2062.
[37] Y. Zhu,W. Dong,W. Tang, *Advanced Agrochem.* **2022**, *1*, 125-138.
[38] S. Jeanmart,A. J. F. Edmunds,C. Lamberth,M. Pouliot,J. A. Morris, *Bioorg. Med. Chem.* **2021**, *39*, 116162.
[39] X. Hu,H. Wang,C. F. J. Faul,J. Wen,Y. Wei,M. Zhu,Y. Liao, *J. Chem. Eng.* **2020**, *382*, 122998.
[40] M. Hayashi,L. Chen, *Polym. Chem.* **2020**, *11*, 1713-1719.
[41] D. F. Nippa,K. Atz,A. T. Müller,J. Wolfard,C. Isert,M. Binder,O. Scheidegger,D. B. Konrad,U. Grether,R. E. Martin,G. Schneider, *Commun. Chem.* **2023**, *6*, 256.
[42] L. Guillemard,L. Ackermann,M. J. Johansson, *Nat. Commun.* **2024**, *15*, 3349.
[43] D. C. Blakemore,L. Castro,I. Churcher,D. C. Rees,A. W. Thomas,D. M. Wilson,A. Wood, *Nat. Chem.* **2018**, *10*, 383-394.
[44] T. Cernak,K. D. Dykstra,S. Tyagarajan,P. Vachal,S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546-576.
[45] J. H. Docherty,T. M. Lister,G. McArthur,M. T. Findlay,P. Domingo-Legarda,J. Kenyon,S. Choudhary,I. Larrosa, *Chem. Rev.* **2023**, *123*, 7692-7760.
[46] S. Y. Shim, *Chem. Eur. J.* **2023**, *29*, e202302620.
[47] F. Ospina,K. H. Schülke,S. C. Hammer, *ChemPlusChem* **2022**, *87*, e202100454.
[48] R. V. Aliyeva,Y. M. Babashova,M. J. Khamiyev,S. R. Bagirova,H. R. Azizbeyli, *Appl. Petrochem. Res.* **2021**, *11*, 65-77.
[49] A. Shokri,S. Karimi, *Russ. J. Appl. Chem.* **2021**, *94*, 1546-1559.
[50] D. Nafis,K. Detrick,R. Mehlberg, **2015**, *1*, 435-456.
[51] L. Zhang,T. Ritter, *J. Am. Chem. Soc.* **2022**, *144*, 2399-2414.
[52] Q.-Y. Li,Y. He,Y.-M. Lin,L. Gong, *Chem. Eur. J.* **2023**, *29*, e202302542.
[53] D. Aynetdinova,M. C. Callens,H. B. Hicks,C. Y. X. Poh,B. D. A. Shennan,A. M. Boyd,Z. H. Lim,J. A. Leitch,D. J. Dixon, *Chem. Soc. Rev.* **2021**, *50*, 5517-5563.
[54] E. J. Barreiro,A. E. Kümmerle,C. A. M. Fraga, *Chem. Rev.* **2011**, *111*, 5215-5246.
[55] J. Chatterjee,C. Gilon,A. Hoffman,H. Kessler, *Acc. Chem. Res.* **2008**, *41*, 1331-1342.
[56] H. Schönherr,T. Cernak, *Angew. Chem., Int. Ed.* **2013**, *52*, 12256-12267.
[57] M. M. Heravi,V. Zadsirjan, *RSC Adv.* **2020**, *10*, 44247-44311.
[58] A. Kumar,A. K. Singh,H. Singh,V. Vijayan,D. Kumar,J. Naik,S. Thareja,J. P. Yadav,P. Pathak,M. Grishina,A. Verma,H. Khalilullah,M. Jaremko,A.-H. Emwas,P. Kumar, *Pharm.* **2023**, *16*, 299.
[59] R. J. Obaid,E. U. Mughal,N. Naeem,M. M. Al-Rooqi,A. Sadiq,R. S. Jassas,Z. Moussa,S. A. Ahmed, *Process Biochem.* **2022**, *120*, 250-259.
[60] E. Vitaku,D. T. Smith,J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274.
[61] J. L. C. Sousa,H. M. T. Albuquerque,A. M. S. Silva, *Pharm.* **2023**, *16*, 1668.
[62] D. K. Lang,R. Kaur,R. Arora,B. Saini,S. Arora, *Anticancer Agents Med. Chem.* **2020**, *20*, 2150-2168.
[63] K. Taruneshwar Jha,A. Shome,Chahat,P. A. Chawla, *Bioorg. Chem.* **2023**, *138*, 106680.
[64] C. Sahu,A. Chaurasiya,P. A. Chawla, *J. Heterocycl. Chem.* **2023**, *60*, 899-928.
[65] M. Saber,Z. Ouzrour,L. Sanae,R. Salim,M. Adardour,A. Bouyahya,A. Baouid,E. M. Essassi,Y. Ramli,A. Taleb, **2023**, *22*.
[66] M. C. Egbujor,P. Tucci,U. C. Onyeije,C. N. Emeruwa,L. Saso, *Molecules* **2023**, *28*.
[67] N. Kerru,L. Gummidi,S. Maddila,K. K. Gangu,S. B. Jonnalagadda, *Molecules* **2020**, *25*.
[68] W. Wang,L. Xiong,Y. Li,Z. Song,D. Sun,H. Li,L. Chen, *Bioorg. Med. Chem.* **2022**, *56*, 116627.
[69] A. Mermer,T. Keles,Y. Sirin, *Bioorg. Chem.* **2021**, *114*, 105076.
[70] T. N. Tran,M. Henary, *Molecules* **2022**, *27*, 2700.

[71] S. Kumari,K. Maddeboina,R. D. Bachu,S. H. S. Boddu,P. C. Trippier,A. K. Tiwari, *Drug Discov. Today* **2022**, *27*, 103322.
[72] X. Wang,Y. Wang,X. Li,Z. Yu,C. Song,Y. Du, *RSC Med. Chem.* **2021**, *12*, 1650-1671.
[73] A. Kumar,B. Nehra,D. Singh,D. Kumar,P. A. Chawla, *Curr. Top. Med. Chem.* **2023**, *23*, 1277-1306.
[74] V. Bonatto,R. F. Lameiro,F. R. Rocho,J. Lameira,A. Leitão,C. A. Montanari, *RSC Med. Chem.* **2023**, *14*, 201-217.
[75] C. Scotti,J. W. Barlow, *Nat. Prod. Commun.* **2022**, *17*, 1934578X221099973.
[76] J. Wang,X. Q. Yang,N. Li,L. L. Wang, *ChemistrySelect* **2022**, *7*.
[77] L. H. Wang Jiang, *Chin. J. Chem.* **2012**, *32*, 1643-1652.
[78] F. F. Fleming,L. Yao,P. C. Ravikumar,L. Funk,B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902-7917.
[79] J.-P. Rieu,A. Boucherle,H. Cousse,G. Mouzin, *Tetrahedron* **1986**, *42*, 4095-4131.
[80] H.-M. Xia,F.-L. Zhang,T. Ye,Y.-F. Wang, *Angew. Chem., Int. Ed.* **2018**, *57*, 11770-11775.
[81] M. Selva,P. Tundo, *J. Org. Chem.* **1998**, *63*, 9540-9544.
[82] S. D. Friis,M. J. Johansson,L. Ackermann, *Nat. Chem.* **2020**, *12*, 511-519.
[83] K. Feng,R. E. Quevedo,J. T. Kohrt,M. S. Oderinde,U. Reilly,M. C. White, *Nature* **2020**, *580*, 621-627.
[84] Z. Liu,Z. Yang,X. Yu,H. Zhang,B. Yu,Y. Zhao,Z. Liu, *Org. Lett.* **2017**, *19*, 5228-5231.
[85] M. Selva,A. Perosa, *Green Chem.* **2008**, *10*, 457-464.
[86] J. Meyer,G. Schramm, *Z. anorg. allg. Chem.* **1932**, *206*, 24-30.
[87] X. Chen,J.-J. Li,X.-S. Hao,C. E. Goodhue,J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78-79.
[88] R. Giri,N. Maugel,J.-J. Li,D.-H. Wang,S. P. Breazzano,L. B. Saunders,J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510-3511.
[89] B. R. Rosen,L. R. Simke,P. S. Thuy-Boun,D. D. Dixon,J.-Q. Yu,P. S. Baran, *Angew. Chem., Int. Ed.* **2013**, *52*, 7317-7320.
[90] S. R. Neufeldt,C. K. Seigerman,M. S. Sanford, *Org. Lett.* **2013**, *15*, 2302-2305.
[91] J. A. Romero-Revilla,A. García-Rubia,R. Goméz Arrayás,M. Á. Fernández-Ibáñez,J. C. Carretero, *J. Org. Chem.* **2011**, *76*, 9525-9530.
[92] K. Graczyk,T. Haven,L. Ackermann, *Chem. Eur. J.* **2015**, *21*, 8812-8815.
[93] R. Shang,L. Ilies,S. Asako,E. Nakamura, *J. Am. Chem. Soc.* **2014**, *136*, 14349-14352.
[94] L. Ilies,S. Ichikawa,S. Asako,T. Matsubara,E. Nakamura, *ASC.* **2015**, *357*, 2175-2179.
[95] Y. Chen, *Chem. Eur. J.* **2019**, *25*, 3405-3439.
[96] S. Moulay, *Chemistry Africa* **2020**, *3*, 845-880.
[97] D. P. Hari,B. König, *Angew. Chem., Int. Ed.* **2013**, *52*, 4734-4743.
[98] F. Mo,G. Dong,Y. Zhang,J. Wang, *Org. Biomol. Chem.* **2013**, *11*, 1582-1593.
[99] F. Bureš, *Top. Curr. Chem. (Cham)* **2019**, *377*, 14.
[100] R. A. Jones, *Quaternary Ammonium Salts: Their Use in Phase-Transfer Catalysis*, Elsevier, **2000**.
[101] B. Lygo,B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518-525.
[102] P. Brown,C. Butts,R. Dyer,J. Eastoe,I. Grillo,F. Guittard,S. Rogers,R. Heenan, *Langmuir* **2011**, *27*, 4563-4571.
[103] J. Pernak,M. Smiglak,S. T. Griffin,W. L. Hough,T. B. Wilson,A. Pernak,J. Zabielska-Matejuk,A. Fojutowski,K. Kita,R. D. Rogers, *Green Chem.* **2006**, *8*, 798-806.
[104] C. I. Melo,R. Bogel-Łukasik,M. Nunes da Ponte,E. Bogel-Łukasik, *Fluid Phase Equilibria* **2013**, *338*, 209-216.
[105] J. Templ,M. Schnürch, *J. Org. Chem.* **2022**, *87*, 4305-4315.
[106] J. Templ,E. Gjata,F. Getzner,M. Schnürch, *Org. Lett.* **2022**, *24*, 7315-7319.
[107] J. D. S. Holbrey, K. , *Ionic liquids in Clean Products and Processes, Vol. 1*, Springer, **1999**.
[108] J. Templ,M. Schnürch, *Chem. Eur. J.* **2024**, *n/a*, e202400675.

[109] J. K. Stille,H. Su,P. Brechot,G. Parrinello,L. S. Hegedus, *Organometallics* **1991**, *10*, 1183-1189.
[110] K. Weissermel,H.-J. Arpe, in *Industrial Organic Chemistry*, 4th ed., John Wiley & Sons, **2003**, pp. 337-385.
[111] Z. Dong,Z. Ren,S. J. Thompson,Y. Xu,G. Dong, *Chem. Rev.* **2017**, *117*, 9333-9403.
[112] Z. Chen,B. Wang,J. Zhang,W. Yu,Z. Liu,Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107-1295.
[113] T. Kitamura,Y. Fujiwara, in *RSC Green Chem.*, RSC, **2015**, pp. 33-54.
[114] L. Zhou,W. Lu, *Chem. Eur. J.* **2014**, *20*, 634-642.
[115] R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526.
[116] T. Mizoroki,K. Mori,A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
[117] G. A. Grasa,R. Singh,E. D. Stevens,S. P. Nolan, *J. Organomet. Chem.* **2003**, *687*, 269-279.
[118] R. S. Craig,T. V. RajanBabu, *Tetrahedron* **2010**, *66*, 1102-1110.
[119] S. Jagtap, *Catalysts* **2017**, *7*, 267.
[120] A. Wrzyszczyński,M. Pietrzak,J. Bartoszewicz,H. Kozubek,G. L. Hug,B. Marciniak,J. Pączkowski, *J. Am. Chem. Soc.* **2003**, *125*, 11182-11183.

B Contributions

B I List of Contributions

Chapter 1

Enantioselective Alkylation *via* C-H Activation: Sustainable and Safe Protocol Development

Manuscript 1

Eleni Papaplioura, Johanna Templ, Nina Wildhack and Michael Schnürch

Efficient Synthesis of 2-Arylpropionitriles *via* Selective Monomethylation of Aryl Acetonitriles Using an Easy to Handle Methylation Agent

The manuscript was submitted to the European Journal of Organic Chemistry on the 20th of June 2024.

Manuscript 2

Eleni Papaplioura, Maëva Mercier, Michael E. Muratore, Tobias Biberger, Soufyan Jerhaoui and Michael Schnürch

Tetraethylammonium Salts as Solid, Easy to Handle Ethylene Precursors and Their Application in Mizoroki–Heck Coupling

J. Org. Chem. 2024, 89, 5126–5133. doi: 10.1021/acs.joc.3c02867

Manuscript 3

Eleni Papaplioura, Maëva Mercier, Soufyan Jerhaoui and Michael Schnürch

The Vinyl Group: Small but Mighty - Transition Metal Catalyzed and Non-Catalyzed Vinylation Reactions

ChemCatChem 2024, e202400513. doi: 10.1002/cctc.202400513

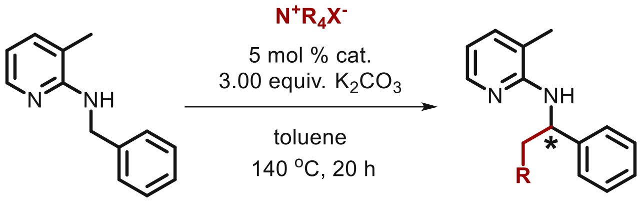
B II Context of Contributions

The following section provides a concise overview of each contribution, summarizing the main research objective and the resulting findings.

BII.1 Chapter 1

Enantioselective Alkylation *via* C-H Activation: Sustainable and Safe Protocol Development

In Chapter 1, we investigated the development of sustainable and safe alkylation reactions through C-H activation. An immediate extension of our previously reported alkylation protocol aimed to achieve enantioselectivity (Scheme BII.1). [1] Initially, our catalyst of choice was a rhodium(I) dimer with 1,5-cyclooctadiene (cod) as a ligand. While such ligands are very common in catalytic systems, chiral derivatives of cod are rare, with only a few known examples, none of which are commercially available. [2] Therefore, we attempted to synthesize a chiral cod ligand that would not racemize under the reaction conditions. Our targeted catalyst, $[Rh(S,S)\text{-obnd})Cl]_2$ (obnd = 9-oxabicyclo[3.3.1]nona-2,6-diene), was tested under standard conditions on our model substrate, but showed no stereoinduction.



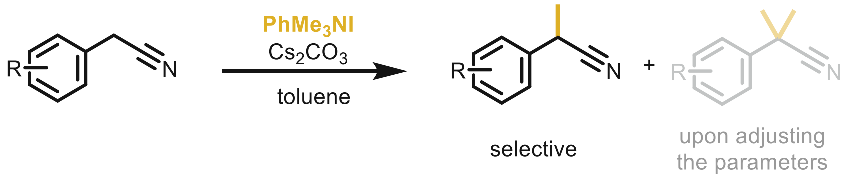
Scheme (BII.1). Enantioselective alkylation reaction evaluating chiral Rh-catalysts.

Consequently, we explored several Rh-cod-complexes bearing chiral bidentate phosphine ligands and different counterions, as well as various chiral phosphine ligands, but were unable to achieve enantioselectivity. Additionally, when we screened chiral amino acids, the outcome remained unchanged. The still elusive reaction mechanism impeded our understanding of the factors influencing stereoinduction.

BII.2 Manuscript 1

Efficient Synthesis of 2-Arylpropionitriles *via* Selective Monomethylation of Aryl Acetonitriles Using an Easy to Handle Methylation Agent

The use of quaternary ammonium salts as inherently safer and less hazardous methylating agents has been well-documented. [3] Phenyl trimethylammonium iodide, has been explored as an alternative methylating agent for C-methylation of aryl ketones, monoselective N-methylation of amides and related compounds, and N-methylation of indoles. [4, 5] Motivated by these earlier studies, we aimed to expand this established protocol to enable the selective α-C-monomethylation of (hetero)arylacetonitriles, which are important precursors in medicinal chemistry, particularly for the synthesizing key anti-inflammatory drugs. With our catalyst-free protocol, we achieved a diverse set of 18 examples, with yields reaching up to 76 %, when a mild base (Cs_2CO_3) was employed (Scheme BII.2). Further details can be found in the manuscript and its supporting information.

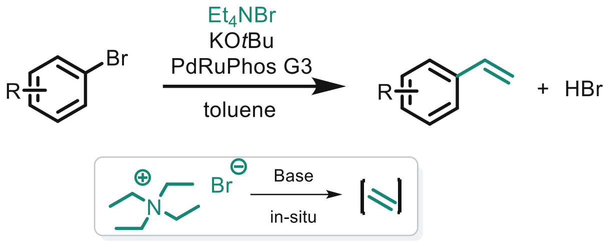


Scheme B II.2. α-C-Monomethylation of (hetero)arylacetonitriles using $PhMe_3NI$ as the methylating agent.

BII.3 Manuscript 2

Tetraethylammonium Salts as Solid, Easy to Handle Ethylene Precursors and Their Application in Mizoroki–Heck Coupling

Based on a previous project within our group, where quaternary ammonium salts served as olefin surrogates and were used as alkylating reagents *via* Hofmann elimination in the presence of a base, we realized the potential for the in-situ generation of ethylene gas from tetraethyl ammonium salts. [1] This inspired us to explore the development of safer procedures for well-established transformations. As a result, this publication marks the first investigation of using quaternary ammonium salts as solid olefin precursors in ambient atmosphere, thereby eliminating the need for ethylene gas. (Scheme B II.3)



Scheme B II.3. Heck-vinylation protocol using Et_4NBr as the olefin surrogate.

In the following manuscript, we investigated the potential for integrating conditions compatible with both Hofmann elimination and the Heck cross-coupling reaction in a one-pot reaction. Our findings revealed that, unlike most Hofmann elimination strategies that employ hydroxide bases, [1] a stronger base (KOtBu) was necessary for the reaction to proceed. We found that using Pd-Buchwald precatalysts led to significantly improved yields, while our protocol was compatible with more environmentally benign solvents (CPME), further enhancing its practicality and sustainability. Additionally, complete substrate consumption was observed in all cases, with no subsequent Heck reaction occurring that would have produced unwanted stilbenes as side products. However, achieving quantitative yields proved challenging, possibly due to the formation of polystyrene derivatives, which were not detected by GC-MS or NMR analysis due to their expected low solubility in common organic solvents. Under our reaction conditions, the facile vinylation of aryl bromides, circumventing the use of ethylene gas, and the operationally complex setups, such as gas manipulation, was possible. The study provides a diverse set of 25 examples, encompassing simple aryl bromides to heterocycles. Further details can be found in the manuscript and its supporting information.

BII.4 Manuscript 3

The Vinyl Group: Small but Mighty - Transition Metal Catalyzed and Non-Catalyzed Vinylation Reactions

This review article provides an overview of the main strategies and advancements in carbon, nitrogen, and oxygen vinylation. It focuses on the most innovative methodologies in the field, covering common transition metal-catalyzed vinylation reactions and discussing various applications. Additionally, it includes transition-metal-free vinylation strategies, highlighting their remarkable functional group tolerance and their ability to overcome selectivity challenges. This review aims to be a valuable resource for organic chemists interested in synthesizing vinyl-containing compounds, offering insights into various vinylation techniques for the efficient construction of carbon-carbon and carbon-heteroatom bonds.

B III Literature - Contributions

[1] M. Spettel,R. Pollice,M. Schnürch, *Org. Lett*. **2017**, 19, 4287-4290.

[2] C.G Newton, S.-G. Wang, C.C Oliveira, N. Cramer, *Chem. Rev*. **2017**, 117, 8908-8976.

[3] J. Templ,M. Schnürch, *Chem. Eur. J*. **2024**, n/a, e202400675.

[4] J. Templ,M. Schnürch, *J. Org. Chem*. **2022**, 87, 4305-4315.

[5] J. Templ,E. Gjata,F. Getzner,M. Schnürch, *Org. Lett*. **2022**, 24, 7315-7319.

C Statement of Contributions

Chapter 1

The applicant, **Eleni Papaplioura**, conducted the synthetic work, including reaction optimization and the design of compounds and catalysts within the project framework. The applicant also authored this chapter. Eleni Papaplioura and Michael Schnürch, contributed to the experimental design and research discussions.

Manuscript 1

The research was initiated by Johanna Templ. The applicant, **Eleni Papaplioura**, carried out the main synthetic work, including reaction optimization, compound design, and synthesis within the substrate scope, as well as experiments required for the manuscript revision. The applicant composed the manuscript. Johanna Templ and Nina Wildhack contributed to the reaction optimization. Michael Schnürch, Eleni Papaplioura, and Johanna Templ contributed to the manuscript discussion and correction.

Manuscript 2

The applicant, **Eleni Papaplioura**, carried out the synthetic work, including reaction optimization, compound design, and synthesis within the substrate scope, as well as experiments required for the manuscript revision. The manuscript was composed by the applicant. Michael Schnürch, Eleni Papaplioura, Soufyan Jerhaoui, Tobias Biberger and Michael E. Muratore contributed to the experimental design, manuscript discussion, and revisions. Maëva Mercier assisted with manuscript discussion and revisions.

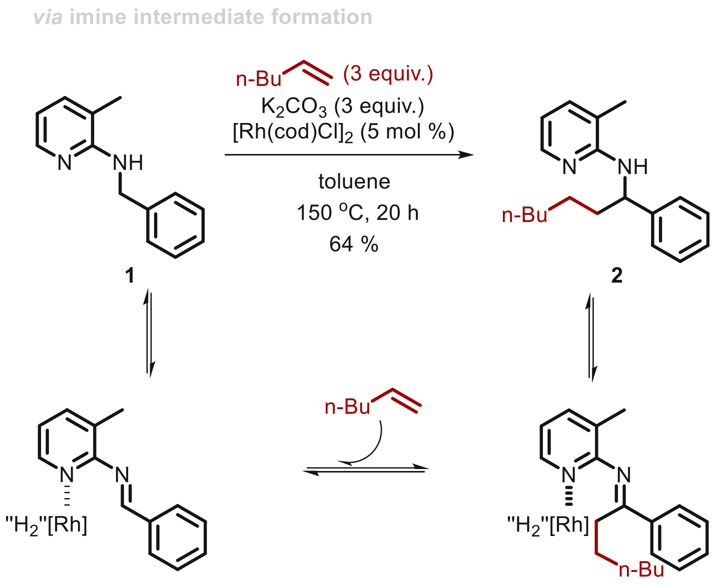
Manuscript 3

The review was composed and researched by the applicant, **Eleni Papaplioura**, with assistance from Maëva Mercier. Michael Schnürch, Eleni Papaplioura, Maëva Mercier, and Soufyan Jerhaoui contributed to the manuscript discussion and revision.

D Original Work

DI.1 Chapter 1

Previous kinetic and mechanistic investigations of a rhodium (I)-catalyzed direct C-H alkylation of benzylic amines with alkenes reveal that what initially appears to be a C(sp^3)-H activation, in fact, proceeds *via* imine intermediates, and, hence *via* C(sp^2)-H activation. [1-2] In a subsequent step, these imine intermediates are converted to the final amine product under the reaction conditions. [2] This evidence, suggests that the interconversion from an imine to an amine entails a change in hybridization from sp^2 to sp^3, a crucial step for stereochemical induction. Having established the optimized conditions for the alkylation of benzylic amines using quaternary ammonium salts as the olefin surrogates, the goal was to induce enantioselectivity in the model reaction, presumably *via* an enantioselective imine to amine reduction in the final step. [3] As a proof of concept, we began our investigations using 1-hexene, a liquid olefin, instead of a quaternary ammonium salt. This allowed focusing on the crucial final step excluding eventual negative influences of the reagents/products of the Hofmann elimination step (Scheme 1).



Scheme 1. Direct C−H Alkylation of benzylic amine **1** using alkenes.

To explore the feasibility of this concept, a model catalytic system previously employed in our projects, that is a rhodium (I) dimer bearing 1,5-cyclooctadiene (cod) ligands was employed. Such ligands are commonly used in transition metal catalysis because the metal complexes they create are typically stable to isolate, due to the chelate effect, and easy to handle (Figure 1). [4-5] Complexes bearing cod-ligands find several applications in organic synthesis including C-H arylation of BINOLs, hydrogenation of arenes, hydrosilylation, and hydroformylation reactions. [6-9]

Experimental findings revealed that cod ligands not only serve as precursors to the active catalyst, but they actively participate in the catalytic cycle. [10-16] This feature allows for the development of chiral cod ligands, which despite their potential, have been mostly overlooked in the literature and are not frequently used in catalytic systems. Nevertheless, a few bicyclic chiral dienes and several skipped ones (1,4-dienes) have already been employed in asymmetric catalysis. [12-21] Effective chiral ligands reported, include bicyclo[2.2.1]hepta-2,5-diene (nbd*), [12,22] bicyclo[2.2.2]octa-2,5-diene (bod*), [14,17-19,23-30] bicyclo[3.3.1]nona-2,6-diene (bnd*), [13,31] and bicyclo[3.3.2]deca-2,6-diene (bdd*) [13] the synthesis of which is tedious and multistep, often requiring chiral resolution. Among these, the C_2-symmetric dienes were of particular interest to us, as C_1-symmetric ones are less advantageous for enantioselective induction (Figure 1).

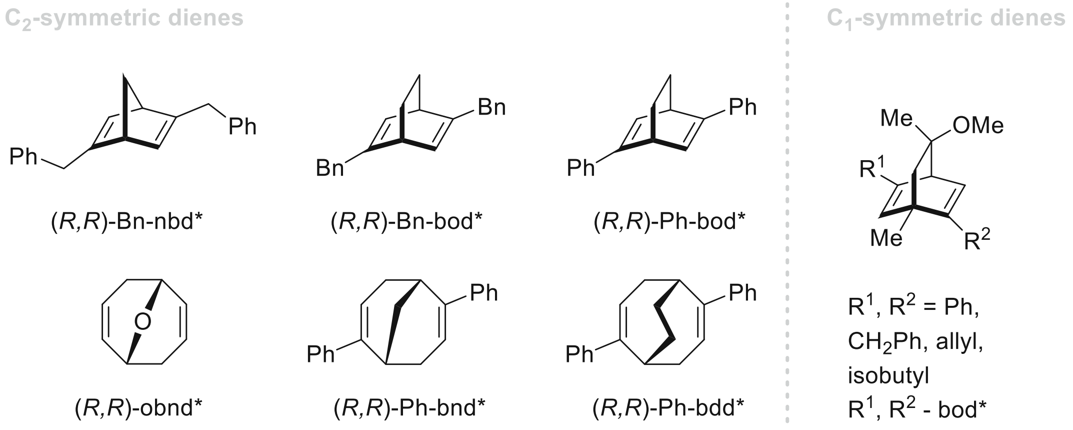
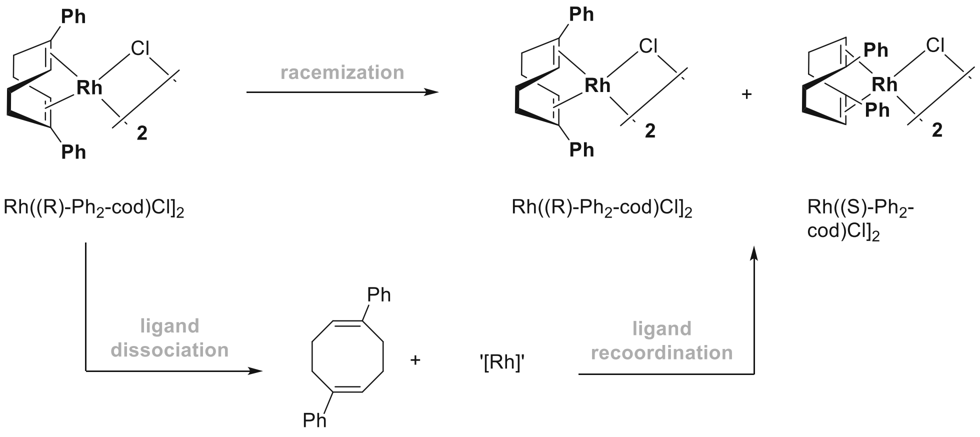


Figure 1. Chiral bicyclic dienes employed as ligands in rhodium asymmetric catalysis.

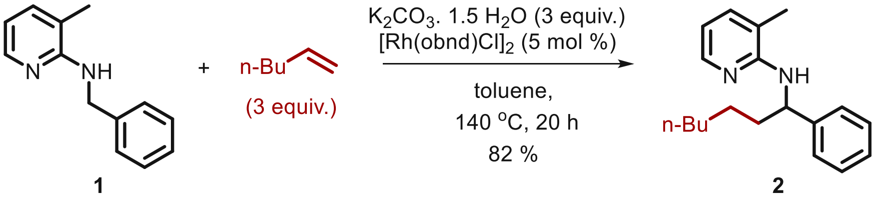
Preliminary studies conducted in our group explored the potential of the [Rh((R)-Ph$_2$-cod)Cl]$_2$ complex to induce enantioselectivity in our model substrate (Scheme 2). Encouraged by the high yields and enantioselectivities obtained in the asymmetric 1,4-addition of phenylzinc chloride to α,β-unsaturated ketones, and esters, mediated by chlorotrimethylsilane, the application of the same catalytic system to our model reaction was attempted. [32] However, despite achieving moderate conversion, no stereoinduction was observed. One possible explanation for this outcome could be the potential racemization caused by the dissociation of the Ph$_2$-cod from the Rh species, followed by the re-coordination of the ligand to the other face (Scheme 2).



Scheme 2. Racemization of the [Rh((R)-Ph$_2$-cod)Cl]$_2$ complex.

In order to prevent racemization, we decided to explore ligands bearing a bridged moiety in their backbone. Thus, we tested the 9-oxabicyclo[3.3.1]nona-2,6-diene (obnd) ligand (Figure 1). To the best of our knowledge, there is only one example in the literature that uses [Rh((R,R)-obnd)Cl]$_2$ for the silylformylation of benzaldehyde, which resulted in low yields and did not provide enantiomeric excess. [33] However, due to the ease of synthesizing the racemic form of the catalyst in only three steps, and the satisfactory results obtained in our model reaction when applied (82 % yield), we sought to develop its enantiopure complex, the total synthesis of which, has already been reported (Scheme 3). [34]

Yet, the enantiopure form ([Rh((S,S)-obnd)Cl]$_2$) of the complex, did not exhibit any stereoinduction when used under the optimized conditions on our model substrate (see Table 1, Entry 1).



Scheme 3. Direct C–H Alkylation of benzylic amine **1** using alkenes and [Rh(obnd)Cl]$_2$ as the catalyst.

Considering this result and aiming to identify potential ligands that could induce enantioselectivity, we conducted Rh(I)-catalyzed direct alkylation of our standard benzylic amine substrate, using Rh-cod-complexes bearing several chiral phosphine ligands. Phosphines are among the most prominent ligands in homogeneous metal catalysis, known for their strong metal-binding capabilities with all transition metals, a feature that promotes the catalytic reaction. By modifying the substituents attached to phosphorus, both the electronic and steric properties of the ligand can be fine-tuned, thus influencing the reactivity and selectivity of the metal center. [38-39] The first examples of chiral phosphorus ligands in homogeneous metal-catalyzed asymmetric transformations were demonstrated in the hydrogenation of C-C bonds. Since then, numerous reactions have been successfully controlled using chiral phosphine ligands. [40-50] These ligands can be categorized into three classes: monodentate, [51-54] bidentate, [39,55-56] and tridentate ligands (Figure 2). [57] Each class binds to the catalytically active center with different bite angles, influencing the overall catalytic performance. [58-59]

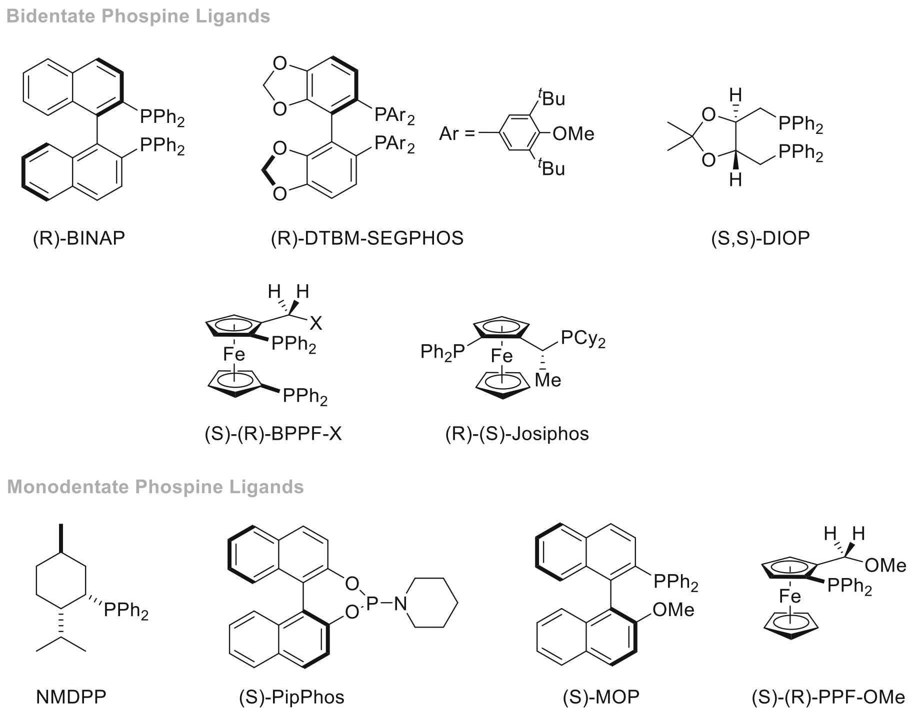
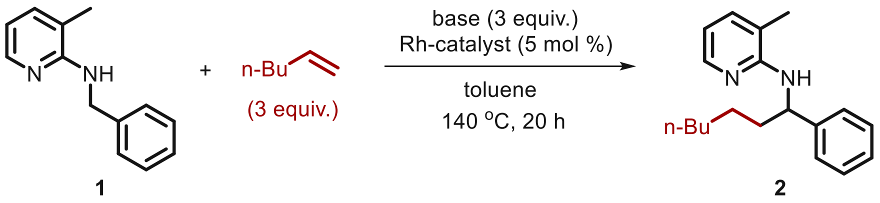


Figure 2. Selected examples of chiral monodentate and bidentate phosphine ligands.

We began our study by testing Rh-cod complexes with chiral bidentate phosphine ligands bearing various fluorinated counterions (see Table 1, Entries 2, 3, and 4). Unfortunately, neither case yielded any enantioselectivity. Therefore, we continued our screening by incorporating different chiral phosphine ligands into our standard [Rh(cod)Cl]$_2$ complex. However, these catalytic systems also exclusively produced racemic products (see Table 1, Entries 5, 6, and 7).

Table 1. Evaluation of chiral rhodium- catalysts.



Entry	Catalyst	Ligand (5 mol %)	Yield (%)	ee (%)
1[a]	$[Rh(S,S)\text{-obnd})Cl]_2$	-	18	0
2[b]	$[Rh(R,R)\text{-Me-DuPhos(cod)}]BF_4$	-	42	0
3[b]	[Rh(R,R)-*i*Pr-DuPhos(cod)]BF_4	-	23	0
4[a]	$[Rh(S)\text{-Segphos(cod)}]SbF_6$	-	traces	0
5[a]	$[Rh(cod)Cl]_2$	(R)-BINAP	14	0
6[a]	$[Rh(cod)Cl]_2$	(R)-DTBM-SEGPHOS	40	0
7[a]	$[Rh(cod)Cl]_2$	S-MOP	46	0
		(0.2 equiv.)		
8[b]	$[Rh(cod)Cl]_2$	Phthaloyl-L-isoleucine	31	0
9[b]	$[Rh(cod)Cl]_2$	Phthaloyl-L-valine	34	0
10[b]	$[Rh(cod)Cl]_2$	N,N-dimethyl-L-valine	17	0

[a] $K_2CO_3.1.5\ H_2O$ was used as the base, [b] anhydrous K_2CO_3 was used as the base.

As an alternative, we employed chiral amino acids as ligands, hoping to improve the stereoinduction profile. Over the past decades, mono-*N*-protected amino acids (MPAA) have been widely used as chiral ligands in various asymmetric C-H functionalization reactions. [60-65] In 2008, the Yu group reported the first example of enantioselective functionalization of the C-H bond using an amino acid as a chiral ligand. They achieved the asymmetric alkylation of diaryl(2-pyridyl)methane derivatives employing MPAA, demonstrating their function through the coordination of both the carboxylate and the amine moiety. [66] The low cost, ready availability, large variety of both natural and synthetic amino acids as well as their ability to coordinate to transition metals, make them excellent precursors for the synthesis of chiral ligands. [67]

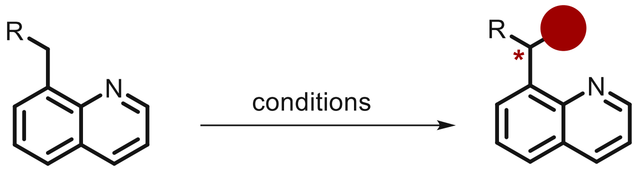
Therefore, we employed in our model reaction three different naturally occurring chiral MPAAs: phthaloyl-L-isoleucine, phthaloyl-L-valine, and N,N-dimethyl-L-valine. To our dismay, none of these ligands yielded enantioselectivity either (see Table 1, Entries 8, 9, and 10).

Our group has previously demonstrated the dependence of the initial reaction rate on the water content absorbed by the base. [2] In particular, it was found that a higher water content in the base correlates with a higher initial reaction rate. In our efforts to improve the previously reported alkylation protocol, we observed higher yields (82%) when using $[Rh(obnd)Cl]_2$, as the catalyst, and $K_2CO_3 \cdot 1.5\ H_2O$ as the base, compared to 44% yield when using anhydrous K_2CO_3 (Scheme 2). The benefits of water in C-H activation have been extensively discussed in the literature. [35-37] In our case, it was shown that the base generates the actual catalytic species, that previous experimental findings identified as $[Rh(cod)OH]_2$. [3] Nevertheless, the presence of water was not always beneficial in our transformation, since in some cases anhydrous K_2CO_3 was more efficient as shown in Table 1.

Although the plausible mechanistic pathway indicates that the substrate-rhodium complex formed, is reversibly dehydrogenated to the corresponding imine, the limited understanding of the transfer hydrogenation mechanism is a significant challenge. One possibility is that reduction - the interconversion of imine to amine - occurs *via* transfer hydrogenation onto a ligand, a common scenario with coordinated ligands in rhodium catalysis. [68-76] Alternatively, oxidative addition into the rhodium species could be involved. If the two hydrogens are directly bonded to the rhodium, the oxidative addition into the $C(sp^2)$-H bond of the imine would result in an uncommon Rh(V) system. This system has been reported in the literature in similar transformations. [77-83]

To bypass the challenge of the unknown reduction step encountered with benzylic amines, which complicates the chiral induction, we decided to shift our focus to different substrates to achieve stereoselectivity. Therefore, we selected substrates that allow for a direct C(sp^3)-H activation, avoiding the intermediate C(sp^2)-H functionalization step (Scheme 4).

Matsunaga et al. described the enantioselective C-H alkylation of 8-ethylquinolines with enones and acrolein using a rhodium (III) catalyst and a binaphthyl-based chiral carboxylic acid as ligand, achieving enantioselective C(sp^3)–H activation. [84] A few years earlier, the group of Kim, reported the rhodium (III)-catalyzed oxidative C(sp^3)–H alkylation of 8-methylquinolines with allylic alcohols in water. [85] Additionally, that same year, the Li group, demonstrated a rhodium (III)-catalyzed C(sp^3)–H bond addition to α,β-unsaturated aldehydes, yielding γ-aryl ketones and aldehydes. [86] Pentamethyl-cyclopentadienyl ligand (Cp*) has been widely used in transition metal-catalyzed C-H activation reactions due to its high reactivity, stability, and functional group tolerance. [87-90] In 2012, the groups of Cramer and Ward introduced the first chiral Cp^x ligands, and ever since, their potential has been investigated by several research groups. [91-92] However, recent studies report that enantioselectivity can be achieved by employing external chiral sources e.g. chiral carboxylic acids, without requiring a chiral Cp^x ligand. [84,93-94] Thus, we decided to incorporate such a ligand in our study, with the initial goal of developing an alkylation protocol, and next, establishing an enantioselective methodology. Moreover, quinolines are important precursors both in medicinal and industrial chemistry, which further motivated us to use this system in our efforts to develop enantioselective C(sp^3)-H activation protocols (Scheme 4). [95-97]



3: R = H
4: R = Me

3a-b: R = H
4a: R = Me

Scheme 4. Directed C-H functionalization of quinoline derivatives.

We initiated our investigation by screening reaction conditions for the alkylation of 8-ethylquinoline, using 1-hexene, and Et_4NBr as the alkylating agent. Inspired by previous work that demonstrated chirality induction using $[RhCp^*Cl_2]_2$ and a binaphthyl-based chiral carboxylic acid, [84] in similar transformations, we tested both $[RhCp^*Cl_2]_2$, and our standard $[Rh(cod)Cl]_2$, which had been previously used as a catalyst for the alkylation of benzylic amines. However, despite laborious efforts and multiple condition screenings, we did not manage to achieve any product formation. Similarly, we attempted to develop an alkylation protocol for the 8-methylquinoline, employing $[RhCp^*Cl_2]_2$, and $[Rh(cod)Cl]_2$ as catalysts, albeit using exclusively Et_4NBr as the alkylating agent. Unfortunately, no product formed in this case either. Consequently, no further investigation into enantioselectivity was attempted, before elucidating the reaction mechanisms.

Firm in our goal of developing alkylation reaction protocols for C-H activation, more substrates were tested towards that direction. Prompted by previous experimental findings, according to which compound **5** featuring a dihydrooxazole as a directing group and $[Rh(cod)Cl]_2$ as a catalyst, converted to the corresponding ethylated product in 6 days with a 29% yield, we aimed to improve this alkylation protocol and further apply our reaction conditions. [3] Unfortunately, no product formation was achieved. Similar results were obtained when 2-phenyl-2-oxazoline (**6**) was tested. Picolinamide-derived directing groups have also been employed in directed C-H alkylation reactions. [98-104] Therefore, the next substrate we tested was the N-(naphthalen-1-yl)picolinamide (**7**). Similarly, no product formed under our reaction protocol. The application of carbamates, [102,105-107] as well as the acetamides, [102,108] in the C-H functionalization reactions have also been widely studied, including both C(sp^2)-H and C(sp^3)-H bond activation and functionalization. In this context, we screened compounds **8** and **9**. Yet, none of them yielded the desired products.

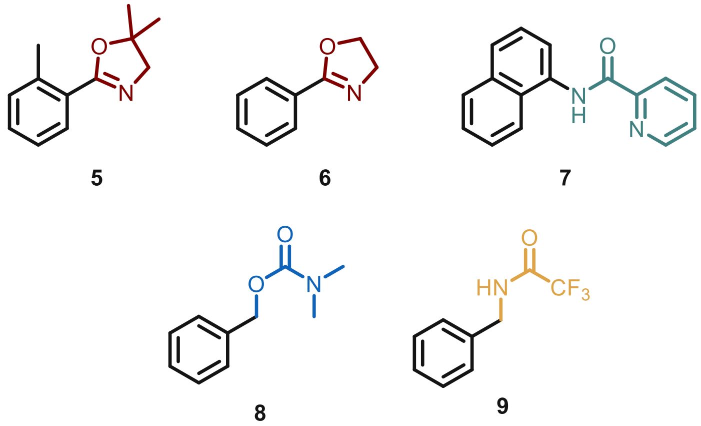


Figure 3. Unsuccessful substrates screened for directed C-H functionalization.

In conclusion, no stereoinduction was observed despite extensive efforts to achieve enantioselective transformation of benzylic amines *via* C-H activation using 1-hexene as the alkyl source and chiral rhodium-catalysts. The alkylation mechanism in this protocol remains undetermined, as DFT calculations did not reveal an energetically feasible pathway. Our investigation was based on a hypothesis grounded in logical reasoning and an educated guess. However, the lack of enantioselectivity suggests that our mechanistic assumption may be incorrect.

Additionally, the role of the solvent is not fully understood, complicating the process. During prior investigations on the alkylation of benzylic amines with alkyl bromides under rhodium catalysis, a benzylated product was formed as a side product, albeit in low yields. The formation of this product was attributed to a coupling with toluene, which was used as the solvent for the transformation. [109]

The unsuccessful attempts to achieve any alkylated product when using quinolines as substrates contributed to the realization of putting the development of an enantioselective protocol on hold until further mechanistic studies can shed light on the reaction pathway. Understanding this pathway is essential to determine whether inducing chirality is even possible in our hypotheses or not.

Lastly, the various substrates screened that did not tolerate our optimized reaction conditions led us to the conclusion that our optimized protocol is effective specifically for benzylic amines but cannot be broadly applied to the C-H activation of other substrates as is. In the course of this research project, the further development of an alkylation protocol was not feasible.

DI.2 Literature – Chapter 1

[1] A. Vasseur,I. Marek, *Nat. Protoc.* **2017**, *12*, 74-87.
[2] R. Pollice,N. Dastbaravardeh,N. Marquise,M. D. Mihovilovic,M. Schnürch, *ACS Catal.* **2015**, *5*, 587-595.
[3] D. Schönbauer,M. Spettel,R. Pollice,E. Pittenauer,M. Schnürch, *Org. Biomol. Chem.* **2019**, *17*, 4024-4030.
[4] B. Zhang,M. R. Hollerbach,S. B. Blakey,H. M. L. Davies, *Org. Lett.* **2019**, *21*, 9864-9868.
[5] B.F Straub in Organotransition Metal Chemistry. From Bonding to Catalysis, (Eds.: J. F. Hartwig),. *Angew. Chem. Int. Ed.*, ***2010***,49,pp. 7622-7622.
[6] J.-F. Yang,R.-H. Wang,Y.-X. Wang,W.-W. Yao,Q.-S. Liu,M. Ye, *Angew. Chem. Int. Ed.* **2016**, *128*.
[7] D.-W. Wang,S.-M. Lu,Y.-G. Zhou, *Tetrahedron Lett.* **2009**, *50*, 1282-1285.
[8] C. Reyes,A. Prock,W. P. Giering, *Organometallics* **2002**, *21*, 546-554.
[9] K. Hamza,J. Blum, *Eur. J. Org. Chem.* **2007**, *2007*, 4706-4710.
[10] K. D. Hesp,S. Tobisch,M. Stradiotto, *J. Am. Chem. Soc.* **2010**, *132*, 413-426.
[11] C. Cooze,R. Dada,R. J. Lundgren, *Angew. Chem. Int. Ed.* **2019**, *58*, 12246-12251.
[12] T. Hayashi,K. Ueyama,N. Tokunaga,K. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 11508-11509.
[13] Y. Otomaru,A. Kina,R. Shintani,T. Hayashi, *Tetrahedron: Asymmetry* **2005**, *16*, 1673-1679.
[14] Y. Otomaru,K. Okamoto,R. Shintani,T. Hayashi, *J. Org. Chem.* **2005**, *70*, 2503-2508.
[15] S. Helbig,S. Sauer,N. Cramer,S. Laschat,A. Baro,W. Frey, *ASC.* **2007**, *349*, 2331-2337.
[16] C.-G. Feng,Z.-Q. Wang,P. Tian,M.-H. Xu,G.-Q. Lin, *Chem. Asian J.* **2008**, *3*, 1511-1516.
[17] C. Defieber,J. F. Paquin,S. Serna,E. M. Carreira, *Org Lett* **2004**, *6*, 3873-3876.
[18] J. F. Paquin,C. Defieber,C. R. Stephenson,E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 10850-10851.
[19] J.-F. Paquin,C. R. J. Stephenson,C. Defieber,E. M. Carreira, *Org. Lett.* **2005**, *7*, 3821-3824.
[20] C. Defieber,H. Grützmacher,E. M. Carreira, *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 4482-4502.
[21] M. Nagamoto,T. Nishimura, *ACS Catal.* **2017**, *7*, 833-847.
[22] R. Shintani,K. Ueyama,I. Yamada,T. Hayashi, *Org. Lett.* **2004**, *6*, 3425-3427.
[23] N. Tokunaga,Y. Otomaru,K. Okamoto,K. Ueyama,R. Shintani,T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 13584-13585.
[24] R. Shintani,T. Kimura,T. Hayashi, *Chem. Commun.* **2005**, 3213-3214.
[25] T. Hayashi,N. Tokunaga,K. Okamoto,R. Shintani, *Chem. Lett.* **2005**, *34*, 1480-1481.
[26] R. Shintani,K. Okamoto,T. Hayashi, *Org. Lett.* **2005**, *7*, 4757-4759.
[27] R. Shintani,K. Okamoto,Y. Otomaru,K. Ueyama,T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 54-55.
[28] R. Shintani,A. Tsurusaki,K. Okamoto,T. Hayashi, *Angew. Chem. Int. Ed.* **2005**, *44*, 3909-3912.
[29] R. Shintani,K. Okamoto,T. Hayashi, *Chem. Lett.* **2005**, *34*, 1294-1295.
[30] C. Fischer,C. Defieber,T. Suzuki,E. M. Carreira, *J. Am. Chem. Soc.* **2004**, *126*, 1628-1629.
[31] Y. Otomaru,N. Tokunaga,R. Shintani,T. Hayashi, *Org. Lett.* **2005**, *7*, 307-310.
[32] A. Kina,K. Ueyama,T. Hayashi, *Org. Lett.* **2005**, *7*, 5889-5892.
[33] A. Takahashi,M. Aso,M. Tanaka,H. Suemune, *Tetrahedron* **2000**, *56*, 1999-2006.
[34] G. Bassioni,F. S. Delgado,M. Jaeggy,F. H. Köhler,S. Nogai,C. Ruiz-Pérez, *Zeitschrift für Naturforschung B* **2005**, *60*, 1143-1148.

[35] L. Jiao,T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990-12993.
[36] Z.-S. Gu,W.-X. Chen,L.-X. Shao, *J. Org. Chem.* **2014**, *79*, 5806-5811.
[37] R. de Jesus,K. Hiesinger,M. van Gemmeren, *Angew. Chem. Int. Ed.* **2023**, *62*, e202306659.
[38] P. Rojo,A. Riera,X. Verdaguer, *Coord. Chem. Rev.* **2023**, *489*, 215192.
[39] A. L. Clevenger,R. M. Stolley,J. Aderibigbe,J. Louie, *Chem. Rev.* **2020**, *120*, 6124-6196.
[40] I. Ojima, *Molecules* **2001**, *6*.
[41] E. N. Jacobsen,A. Pfaltz,H. Yamamoto, *Comprehensive Asymmetric Catalysis I - III*, Springer Berlin Heidelberg, **2000**.
[42] R. Noyori, *Asymmetric catalysis in organic synthesis*, Wiley, **1993**.
[43] W. Tang,X. Zhang, *Chem. Rev.* **2003**, *103*, 3029-3069.
[44] L. Horner,H. Büthe,H. Siegel, *Tetrahedron Lett.* **1968**, *9*, 4023-4026.
[45] W. S. Knowles,M. J. Sabacky, *Chem. Commun. (London).***1968**, 1445-1446.
[46] L. Horner,H. Siegel,H. Büthe, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942-942.
[47] T. P. Dang,H. B. Kagan, *J. Chem. Soc. D.* **1971**, 481-481.
[48] N. V. Dubrovina,A. Börner, *Angew. Chem. Int. Ed.* **2004**, *43*, 5883-5886.
[49] D. S. Glueck, *Synlett* **2020**, *32*, 875-884.
[50] T. Imamoto, *PJA-B.* **2021**, *97*, 520-542.
[51] F. Lagasse,H. B. Kagan, *Chem. Pharm. Bull. (Tokyo).* **2000**, *48*, 315-324.
[52] K. Junge,B. Hagemann,S. Enthaler,G. Oehme,M. Michalik,A. Monsees,T. Riermeier,U. Dingerdissen,M. Beller, *Angew. Chem. Int. Ed.* **2004**, *43*, 5066-5069.
[53] I. V. Komarov,A. Börner, *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1197-1200.
[54] T. Jerphagnon,J.-L. Renaud,C. Bruneau, *Tetrahedron: Asymmetry* **2004**, *15*, 2101-2111.
[55] C. Schmitz,K. Holthusen,W. Leitner,G. Franciò, *Eur. J. Org. Chem.* **2017**, *2017*, 4111-4116.
[56] L. F. B. Wilm,P. Mehlmann,F. Buß,F. Dielmann, *J. Organomet. Chem.* **2020**, *909*, 121097.
[57] P. Barbaro,C. Bianchini,G. Giambastiani,A. Togni, *Eur. J. Inorg. Chem.* **2003**, *2003*, 4166-4172.
[58] M. Kranenburg,P. C. J. Kamer,P. W. N. M. van Leeuwen,D. Vogt,W. Keim, *J. Chem. Soc., Chem. Commun.* **1995**, 2177-2178.
[59] C. F. Czauderna,A. G. Jarvis,F. J. L. Heutz,D. B. Cordes,A. M. Z. Slawin,J. I. van der Vlugt,P. C. J. Kamer, *Organometallics* **2015**, *34*, 1608-1618.
[60] C.-X. Liu,W.-W. Zhang,S.-Y. Yin,Q. Gu,S.-L. You, *J. Am. Chem. Soc.* **2021**, *143*, 14025-14040.
[61] Q. Shao,K. Wu,Z. Zhuang,S. Qian,J. Q. Yu, *Acc. Chem. Res.* **2020**, *53*, 833-851.
[62] K. M. Engle, *Pure Appl. Chem.* **2016**, *88*, 119-138.
[63] D. Parmar,R. Kumar,U. Sharma, *Org. Biomol. Chem.* **2024**, *22*, 5032-5051.
[64] K. Micskei,T. Patonay,L. Caglioti,G. Pályi, *Chem. Biodivers* **2010**, *7*, 1660-1669.
[65] J. J. Gair,B. E. Haines,A. S. Filatov,D. G. Musaev,J. C. Lewis, *Chem. Sci.* **2017**, *8*, 5746-5756.
[66] B. F. Shi,N. Maugel,Y. H. Zhang,J. Q. Yu, *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 4882-4886.
[67] Y. Titova, *Processes* **2024**, *12*, 214.
[68] K. Rafikova,N. Kystaubayeva,M. Aydemir,C. Kayan,Y. S. Ocak,H. Temel,A. Zazybin,N. Gürbüz,İ. Özdemir, *J. Organomet. Chem.* **2014**, *758*, 1-8.
[69] P. A. Akıncı,S. Gülcemal,O. N. Kazheva,G. G. Alexandrov,O. A. Dyachenko,E. Çetinkaya,B. Çetinkaya, *J. Organomet. Chem.* **2014**, *765*, 23-30.
[70] V. S. Shende,S. K. Shingote,S. H. Deshpande,N. Kuriakose,K. Vanka,A. A. Kelkar, *RSC Adv.* **2014**, *4*, 46351-46356.
[71] O. Prakash,K. N. Sharma,H. Joshi,P. L. Gupta,A. K. Singh, *Organometallics* **2014**, *33*, 983-993.

[72] O. Prakash,K. N. Sharma,H. Joshi,P. L. Gupta,A. K. Singh, *Organometallics* **2014**, *33*, 2535-2543.
[73] F. Saleem,G. K. Rao,A. Kumar,G. Mukherjee,A. K. Singh, *Organometallics* **2014**, *33*, 2341-2351.
[74] A. Nova,D. J. Taylor,A. J. Blacker,S. B. Duckett,R. N. Perutz,O. Eisenstein, *Organometallics* **2014**, *33*, 3433-3442.
[75] O. Prakash,H. Joshi,K. N. Sharma,P. L. Gupta,A. K. Singh, *Organometallics* **2014**, *33*, 3804-3812.
[76] D. Madrigal,A. L. Cooksy,R. Somanathan, *Comput. Theor. Chem.* **2012**, *999*, 105-108.
[77] S. Gangopadhyay,P. Basak,M. Drew,P. K. Gangopadhyay, *Chem. Commun.* **2010**, *46*, 7436-7438.
[78] A. C. Esqueda,S. Conejero,C. Maya,E. Carmona, *Organometallics* **2010**, *29*, 5481-5489.
[79] J. L. McBee,J. Escalada,T. D. Tilley, *J. Am. Chem. Soc.* **2009**, *131*, 12703-12713.
[80] Y. Sunada,Y. Fujimura,H. Nagashima, *Organometallics* **2008**, *27*, 3502-3513.
[81] D. Karshtedt,A. T. Bell,T. D. Tilley, *Organometallics* **2006**, *25*, 4471-4482.
[82] S. K. Brayshaw,E. L. Sceats,J. C. Green,A. S. Weller, *PNAS.* **2007**, *104*, 6921-6926.
[83] H. Nagashima,K. Tatebe,T. Ishibashi,A. Nakaoka,J. Sakakibara,K. Itoh, *Organometallics* **1995**, *14*, 2868-2879.
[84] L.-T. Huang,S. Fukagawa,M. Kojima,T. Yoshino,S. Matsunaga, *Org. Lett.* **2020**, *22*, 8256-8260.
[85] S. Kim,S. Han,J. Park,S. Sharma,N. K. Mishra,H. Oh,J. H. Kwak,I. S. Kim, *Chem. Commun.* **2017**, *53*, 3006-3009.
[86] B. Liu,P. Hu,X. Zhou,D. Bai,J. Chang,X. Li, *Org. Lette.* **2017**, *19*, 2086-2089.
[87] T. Satoh,M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212-11222.
[88] N. Kuhl,N. Schröder,F. Glorius, *ASC.* **2014**, *356*, 1443-1460.
[89] T. Piou,T. Rovis, *Ac. Chem. Res.* **2018**, *51*, 170-180.
[90] A. Peneau,C. Guillou,L. Chabaud, *Eur. J. Org. Chem.* **2018**, *2018*, 5777-5794.
[91] B. Ye,N. Cramer, *Science* **2012**, *338*, 504-506.
[92] T. K. Hyster,L. Knörr,T. R. Ward,T. Rovis, *Science* **2012**, *338*, 500-503.
[93] T. Yoshino,S. Matsunaga, *Synlett.* **2019**, *30*, 1384-1400.
[94] T. Yoshino,S. Satake,S. Matsunaga, *Chem. Eur. J.* **2020**, *26*, 7346-7357.
[95] S. M. Prajapati,K. D. Patel,R. H. Vekariya,S. N. Panchal,H. D. Patel, *RSC Adv.* **2014**, *4*, 24463-24476.
[96] W. S. Shehab,M. M. K. Amer,D. A. Elsayed,K. K. Yadav,M. H. Abdellattif, *Med. Chem. Res.* **2023**, *32*, 2443-2457.
[97] R. Kaur,K. Kumar, *Eur. J. Med. Chem.* **2021**, *215*, 113220.
[98] S. Biswas,N. R. Bheemireddy,M. Bal,B. F. Van Steijvoort,B. U. W. Maes, *J. Org. Chem.* **2019**, *84*, 13112-13123.
[99] S.-Y. Zhang,G. He,W. A. Nack,Y. Zhao,Q. Li,G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 2124-2127.
[100] Á. M. Martínez,J. Echavarren,I. Alonso,N. Rodríguez,R. Gómez Arrayás,J. C. Carretero, *Chem. Sci.* **2015**, *6*, 5802-5814.
[101] V. Rajkumar,Naveen,S. A. Babu, *ChemistrySelect* **2016**, *1*, 1207-1219.
[102] C. Sambiagio,D. Schönbauer,R. Blieck,T. Dao-Huy,G. Pototschnig,P. Schaaf,T. Wiesinger,M. F. Zia,J. Wencel-Delord,T. Besset,B. U. W. Maes,M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603-6743.
[103] T.-J. Gong,B. Xiao,Z.-J. Liu,J. Wan,J. Xu,D.-F. Luo,Y. Fu,L. Liu, *Organic Letters* **2011**, *13*, 3235-3237.
[104] C. Feng,T.-P. Loh, *Chem. Commun.* **2011**, *47*, 10458-10460.
[105] Q. Chuqiang,C. Ning,X. Jiaxi, *Prog. Chem.* **2018**, *30*, 139-155.

[106] S. S. Bera,M. S. Maji, *Org. Lett.* **2020**, *22*, 2615-2620.
[107] A. Wilsily,F. Tramutola,N. A. Owston,G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 5794-5797.
[108] J. Wang,Y. Liu,N. Han,Y. Gao,J. Luo, *Org. Biomol. Chem.* **2023**, *21*, 1878-1882.
[109] R. Pollice, *Master Thesis* **2015**.

DI.3 Experimental Part Associated to Chapter 1

General Experimental Details

Unless noted otherwise, reactants and reagents were purchased from commercial suppliers and used without further purification. The 8 mL-glass vials were sealed with Wheaton® screw caps containing a PTFE faced 14B styrene-butadiene rubber liner. All reactions were magnetically stirred and heated in a metallic reaction block. All reaction temperatures refer to external temperatures.

NMR spectra were recorded in $CDCl_3$ on a Brucker Avance UltraShield (400 MHz) or Avance III HD 600 (600 MHz) spectrometer and 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 by the following abbreviations = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

Thin Layer Chromatography (TLC) analysis was performed on precoated aluminum-backed unmodified plates (Silica gel 60 F_{254}, Merck). Compounds were visualized under UV light.

Flash column chromatography was performed using either Merck silica gel 60 (40 µm – 63 µm) by hand column or purification was performed using a TELEDYNE ISCO COMBI FLASH® COMPANION® NextGen300+ flash chromatography system with UV-Vis detector (diode array) with Macherey-Nagel Chromabond RS silica gel columns.

GC-MS analysis was performed on 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 programs: **Method A:** 2 min at 100 °C, 35 °C/min until 300 °C, 4 min at 300 °C and **Method B:** 2.5 min at 40 °C, 12 °C/min until 220 °C, 2.5 min at 220 °C.

Chiral HPLC measurements were carried out on a normal phase HPLC with a ChiralPak AS-H (250 mm x 4.6 mm ID) column on a Thermo Scientific/Dionex Ultimate 3000 HPLC using mixtures of n-hexane and i-PrOH (99.5 % to 0.5 %).

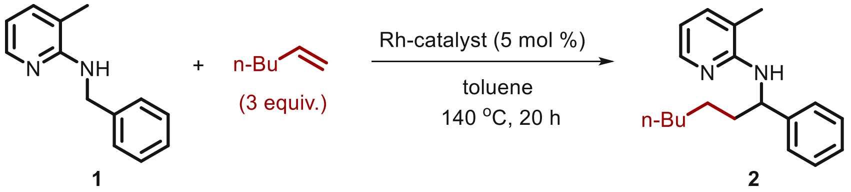
Chiral GC measurements were carried out on a Thermo Scientific Trace Dual, Restek Rtx-5, 10250). GC analysis have been performed on a Thermo Scientific Focus on

BGB5 column by using FID detector; Chiral GC measurements were performed on chiral BGB columns (BGB173 or BGB175) by using FID detector; **Determination of the enantiomeric excess** BGB175 column (110°C isotherm 90 min, 30°C /min to 220°C, 2ml/min flow): tR (*major*) = 57.0 min, tR (*minor*) = 66.2 min.

SFC measurements were performed at Johnson and Johnson Innovative Medicine, in Belgium, using an Analytical Supercritical fluid chromatography (SFC) system composed by a binary pump for delivering carbon dioxide (CO_2) and a modifier, an autosampler, a column oven, a diode array detector equipped with a high-pressure flow cell standing up to 400 bars, and a mass detector (MS). Data acquisition was performed with appropriate software. Analytical SFC-MS method used: Method code: OJ_EtOH_G2A1P1BSFC3; column: Daicel Chiralpak® AS3 column (3.0 µm, 150 x 4.6 mm); mobile phase: A: CO_2, B: EtOH + 0.2 % *i*$PrNH_2$; gradient: 10 % - 50 % B in 6 min, hold 3.5 min; flow 2.5 mL/min at 40 °C; run time: 9.5 min/130 bars.

Substrate Scope Screening for Directed-C-H Functionalization

Table 1. Optimization of the directed C-H functionalization of the benzylic amines.



Entry	Catalyst	Ligand	Base (3 equiv.)	Additive (0.2 equiv.)	Yield (%)
1	$RhCl_3$	-	$K_2CO_3.1.5H_2O$	-	0
2	$[Rh(cod)Cl]_2$	PPh_3 (1 equiv.)	$K_2CO_3.1.5H_2O$	-	0
3	$[Rh(cod)Cl]_2$	PPh_3 (10 mol %)	$K_2CO_3.1.5H_2O$	-	0
4	$[Rh(cod)Cl]_2$	PPh_3 (5 mol %)	$K_2CO_3.1.5H_2O$	-	0
5	$[Rh(cod)Cl]_2$	PPh_3 (1 mol %)	$K_2CO_3.1.5H_2O$	-	0
6	$[Rh(cod)Cl]_2$	rac-BINAP (5mol %)	$K_2CO_3.1.5H_2O$	-	28
7	$[Rh(cod)Cl]_2$	-	-	benzoic acid	0
8	$[Rh(cod)Cl]_2$	-	K_2CO_3	benzoic acid	55
9	$[Rh(cod)Cl]_2$	N,N'-dimethylglycine [a]	-	-	0
10	$[Rh(cod)Cl]_2$	N,N'-dimethylglycine [a]	K_2CO_3	-	60
11	$[Rh(cod)Cl]_2$	-	-	2,3-difluorobenzoic acid	0
12	Chiralyst P1182	-	$K_2CO_3.1.5H_2O$	-	39
13	Chiralyst P468	-	$K_2CO_3.1.5H_2O$	-	57

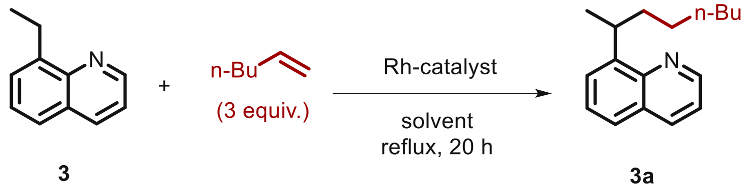
[a] 0.2 equiv. were used.

Table 2. Evaluation of the substrate scope for directed C-H functionalization. [a]

Entry	Substrate	Base (3 equiv.)	Additive (0.2 equiv.)	Yield (%)
1	4	$K_2CO_3.1.5H_2O$	-	0
2	4	-	-	0
3	4	-	2,3-difluorobenzoic acid	0
4[b]	4	$K_2CO_3.1.5H_2O$	-	0
5	5	$K_2CO_3.1.5H_2O$	-	0
6	6	$K_2CO_3.1.5H_2O$	-	0
7	6	-	2,3-difluorobenzoic acid	0
8	7	$K_2CO_3.1.5H_2O$	-	0
9	8	$K_2CO_3.1.5H_2O$	-	0
10	9	$K_2CO_3.1.5H_2O$	-	0

[a] [Rh(cod)Cl]2 (5 mol %) was used as catalyst; [b] rac-[Rh(obnd)Cl]2 (5 mol %) was used as catalyst.

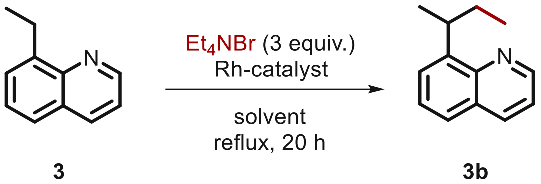
Table 3. Optimization of the directed C-H functionalization of 8-ethylquinoline using 1-hexene as the alkylating agent.



Entry	Catalyst [a]	Additive (2 equiv.)	Acid (1 equiv.)	Base (3 equiv.)	Solvent (M)	Yield (%)
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	toluene	0
2	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	H_2O	0
3	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	-	-	toluene	0
4	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	toluene	0
5	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	H_2O	0
6	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	-	K_2CO_3	toluene	0
7	$[Rh(cod)Cl]_2$	-	AcOH	-	toluene	0
8[b]	$[Rh(cod)Cl]_2$	-	-	K_2CO_3	H_2O	0

[a] $[RhCp^*Cl_2]_2$ (2.5 mol %) and $[Rh(cod)Cl]_2$ (5 mol %) were used as catalysts; [b] 6 equivalents of base were used.

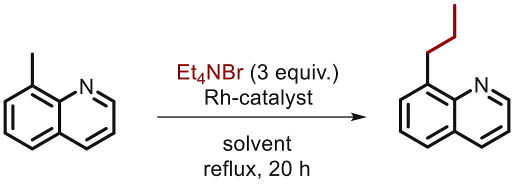
Table 4. Optimization of the directed C-H functionalization of 8-ethylquinoline using Et_4NBr as the alkylating agent.



Entry	Catalyst [a]	Additive (2 equiv.)	Acid (1 equiv.)	Base (3 equiv.)	Solvent (M)	Yield (%)
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	toluene	0
2	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	H_2O	0
3	$[RhCp^*Cl_2]_2$	-	-	K_2CO_3	H_2O	0
4	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	-	-	toluene	0
5	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	toluene	0
6	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	H_2O	0
7	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	-	K_2CO_3	toluene	0
8	$[Rh(cod)Cl]_2$	-	-	K_2CO_3	H_2O	0
9[b]	$[Rh(cod)Cl]_2$	-	-	K_2CO_3	H_2O	0
10	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	-	-	H_2O	0

[a] $[RhCp^*Cl_2]_2$ (2.5 mol %) and $[Rh(cod)Cl]_2$ (5 mol %) were used as catalysts; [b] 6 equivalents of base were used.

Table 5. Optimization of the directed C-H functionalization of 8-methylquinoline using Et_4NBr as the alkylating agent.

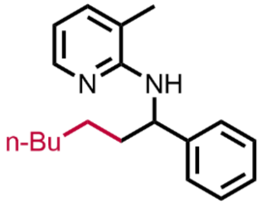


4 **4a**

Entry	Catalyst [a]	Additive (2 equiv.)	Acid (1 equiv.)	Base (3 equiv.)	Solvent (M)	Yield (%)
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	toluene	0
2	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	H_2O	0
3	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	-	-	toluene	0
4	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	-	-	H_2O	0
5	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	-	NaOH	toluene	0
6	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	-	NaOH	H_2O	0
7	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	toluene	0
8	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	AcOH	-	H_2O	0
9	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	-	-	toluene	0
10	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	-	-	H_2O	0
11	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	-	NaOH	toluene	0
12	$[Rh(cod)Cl]_2$	$Cu(OAc)_2.H_2O$	-	NaOH	H_2O	0

Synthetic Procedures

3-Methyl-N-(1-phenylheptyl)pyridin-2-amine [CAS: 210545-95-2] (2)

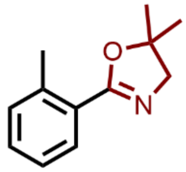


The title compound was prepared according to the literature. [1,2] In an oven-dried 8 mL vial equipped with a septum, a screw cap, and a magnetic stirring bar, were placed the solid and the non-volatile liquid materials inside the glovebox. The vial was evacuated and flushed with argon three times. N-benzyl-3-methylpyridin-2-amine (40 mg, 0.202 mmol, 1.00 equiv.), 1-hexene (52.6 mg, 0.606 mmol, 3.00 equiv.), $K_2CO_3 \cdot 1.5\ H_2O$ (100 mg, 0.606 mmol, 3.00 equiv.), and $[Rh(obnd)Cl]_2$ (8 mg, 0.01 mmol, 0.05 equiv.) were heated up to 140 °C in toluene (dry and degassed, 2 mL) for approximately 2h. Subsequently, the reaction was cooled to room temperature and the dark solid material was separated *via* filtration over Celite, and the residue was washed with DCM. The solvent was removed in *vacuo* to afford the crude material as a black oil. The crude product was further purified *via* flash column chromatography, using silica, and applying a gradient of EtOAc in LP from 0% to 10%, to obtain 47 mg (82%) of the desired compound (**2**) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 5.1, 1.8 Hz, 1H), 7.41 – 7.16 (m, 6H), 6.46 (dd, *J* = 7.1, 5.1 Hz, 1H), 5.24 (q, *J* = 7.2 Hz, 1H), 4.37 (d, *J* = 7.3 Hz, 1H), 2.11 (s, 3H), 1.96 – 1.79 (m, 2H), 1.44 – 1.19 (m, 8H), 0.87 (t, J =6.7 Hz, 3H) ppm.

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 156.3, 145.7, 144.7, 136.9, 128,5, 126.8, 126.6, 116.3, 112.6, 54.8, 37.7, 31.9, 29.4, 26.5, 22.7, 17.2, 14.2 ppm.

4,5-Dihydro-5,5-dimethyl-2-(2-methylphenyl)oxazole [CAS: 11927-60-5] (5)

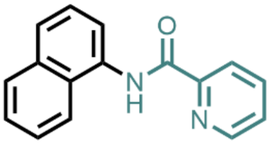


The title compound was prepared according to the literature.[3] A 100-mL sealed flask equipped with a magnetic stirring bar was charged with o-toluolaldehyde (601 mg, 5 mmol, 1 equiv.) in tertbutyl alcohol (25 mL). To this, 2-amino-2-methyl-1-propanol (527 mg, 5.5 mmol, 1.1 equiv.) was added. The reaction mixture was stirred for 30 minutes at room temperature under argon atmosphere. Subsequently, K_2CO_3 (2.07 g, 15 mmol, 3 mmol) and iodine (2.54 g, 10 mmol, 2 equiv.) were added, and the reaction mixture was stirred at 70 °C for 18 h. After 18 h, the reaction mixture was cooled to room temperature and quenched with a saturated solution of $Na_2S_2O_3$ until the iodine color almost disappeared. The crude mixture was then extracted with EtOAc and dried over Na_2SO_4. The solvent was removed in *vacuo*, and the crude product was further purified *via* flash column chromatography, using silica, (LP/EtOAC 3:1) to obtain 867 mg (92%) of the desired compound (**5**) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.31 (td, *J* = 7.6, 1.5 Hz, 1H), 7.24 – 7.17 (m, 2H), 4.06 (s, 2H), 2.56 (s, 3H), 1.39 (s, 7H) ppm.

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 162.9, 138.6, 131.1, 130.4, 129.9, 127.8, 125.6, 78.7, 68.0, 28.6, 21.5 ppm.

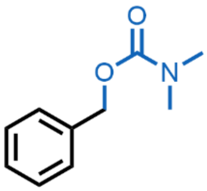
N-(naphthalen-1-yl)picolinamide [CAS: 75358-95-1] (7)



The title compound was prepared according to the literature. [4,5] A 50 mL flame-dried, two-necked round bottom flask, equipped with a magnetic stirring bar, was charged with 1-napthylamine (1.43 g, 10 mmol, 1 equiv.), picolinic acid (1.37 g, 11 mmol, 1.1 equiv.), and DMAP (0.123 g, 1 mmol, 0.1 equiv.). Dry DCM (15 mL) was added at 0 °C. Subsequently, EDCl.HCl (2.15 g, 11 mmol, 1.1 equiv.) in dry DCM (10 mL) was dropwise added to the solution under argon and the reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with water (15 mL) and extracted with DCM (3 x 10 mL). The combined organic phase was dried over Na_2SO4, filtered, and concentrated in *vacuo*. The crude product was further purified *via* flash column chromatography, using silica, (LP/EtOAC 3:1) to obtain 1.98 g (80%) of the desired compound (**7**) as a pink solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.77 (br, 1H), 8.72 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.42-8.35 (m, 2H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.98 – 7.88 (m, 2H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.62 – 7.52 (m, 4H) ppm.
^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 162.4, 150.3, 148.3, 137.9, 134.3, 132.5, 128.9, 126.7, 126.7, 126.5, 126.4, 126.2, 126.1, 125.2 122.7, 120.6, 118.8 ppm.

Benzyl N,N-dimethylcarbamate [CAS: 10507-52-5] (8)

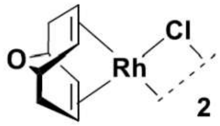


To a three-neck round bottom flask equipped with a stirring bar and a bubbler, a solution of dimethylamine (8.8 mL, 2M, 17.6 mmol, 1 equiv.) and triethylamine (4.9 mL, 35.2 mmol, 2 equiv.), in DCM (90 mL) were added at 0 °C. To this, benzyl chloroformate (3 g, 17.6 mmol, 1 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 18 h. After 18 h the reaction mixture was cooled to 0 °C and diluted with H_2O (30 mL). Aqueous HCl (3M, 30 mL) was added, and the aqueous phase was

extracted with EtOAc (2x25 mL). The combined organic layers were dried over MgSO4, filtered, and concentrated in *vacuo* to afford 2.2 g (69%) of the desired compound (**8**) as a colorless oil. The analytical data was in accordance to the literature. [6]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 5.12 (s, 2H), 2.93 (s, 6H) ppm.
^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 156.6, 137.1, 128.5, 127.9, 67.1, 36.6, 36.0 ppm.

[Rh((*S*,*S*)-obnd)Cl]$_2$



The racemic and the enantiopure form of the title compound were prepared according to the literature, and the analytical data were in accordance to the literature. [7,8,9]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.97-4.79 (m, 2H), 4.12 (s, 4H), 2.63 (m, 2H), 2.37 (m, 2H) ppm.

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 77.2, 72.5, 68.3, 38.3 ppm.

NMR Spectra

3-Methyl-N-(1-phenylheptyl)pyridin-2-amine (2)

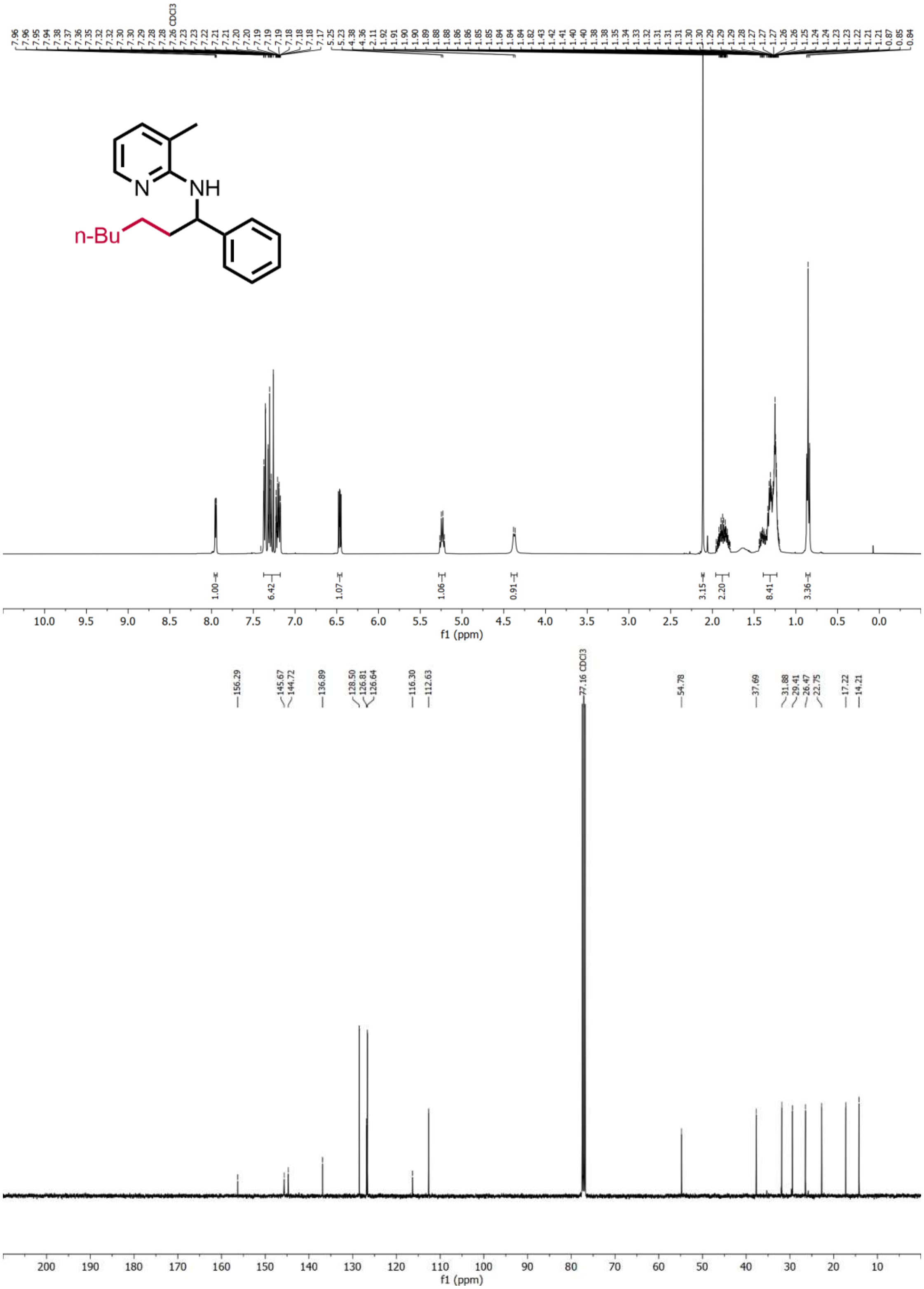


Figure 1: ^{1}H-NMR (400 MHz, $CDCl_3$) and $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) of 3-methyl-N-(1-phenylheptyl)pyridin-2-amine (2).

4,5-Dihydro-5,5-dimethyl-2-(2-methylphenyl)oxazole (5)

Figure 2: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 4,5-dihydro-5,5-dimethyl-2-(2-methylphenyl)oxazole (5).

N-(naphthalen-1-yl)picolinamide (7)

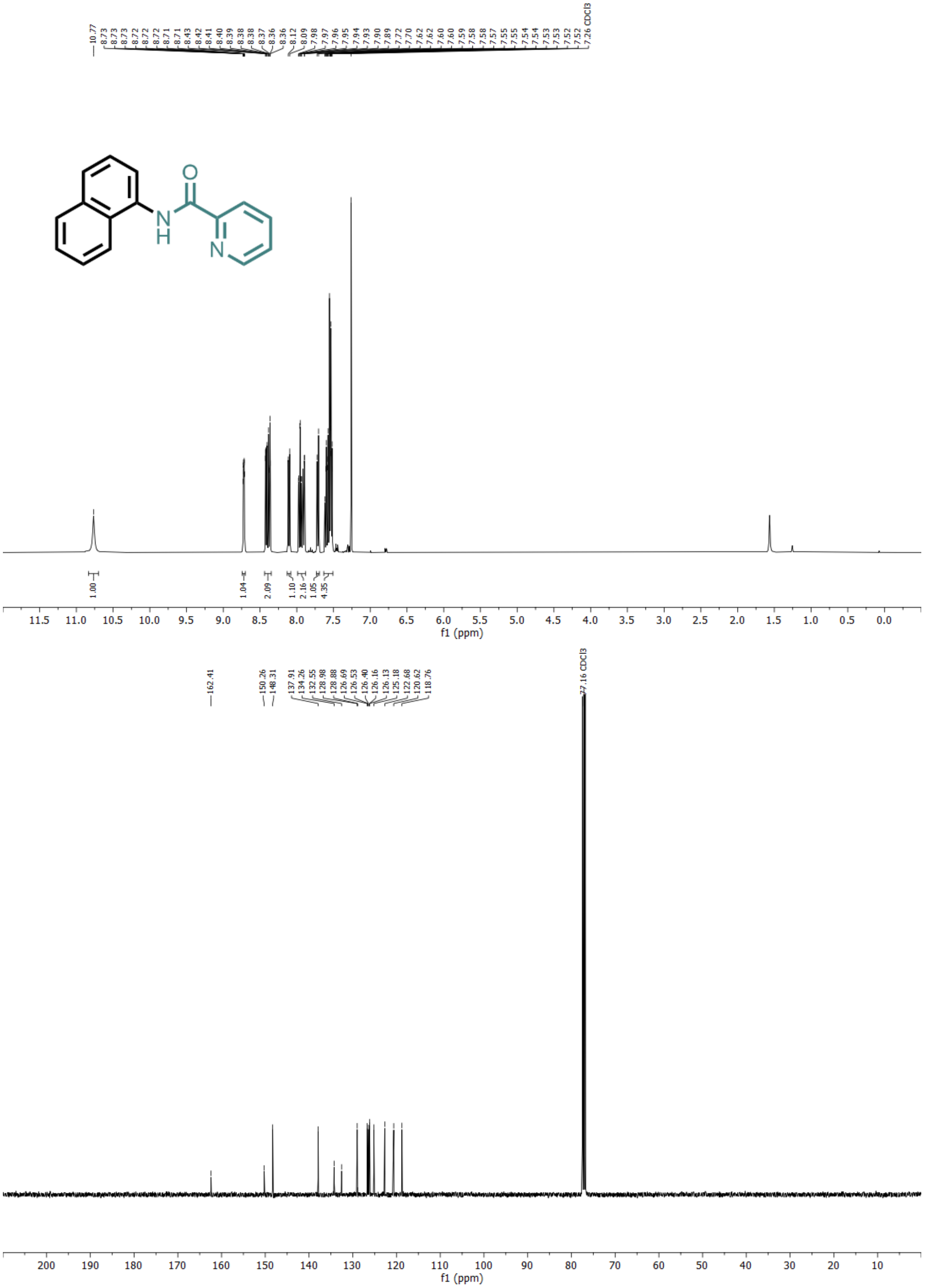


Figure 3: ^{1}H-NMR (400 MHz, $CDCl_3$) and ${}^{13}C\{{}^{1}H\}$ NMR (101 MHz, $CDCl_3$) of N-(naphthalen-1-yl)picolinamide (7).

Benzyl N,N-dimethylcarbamate (8)

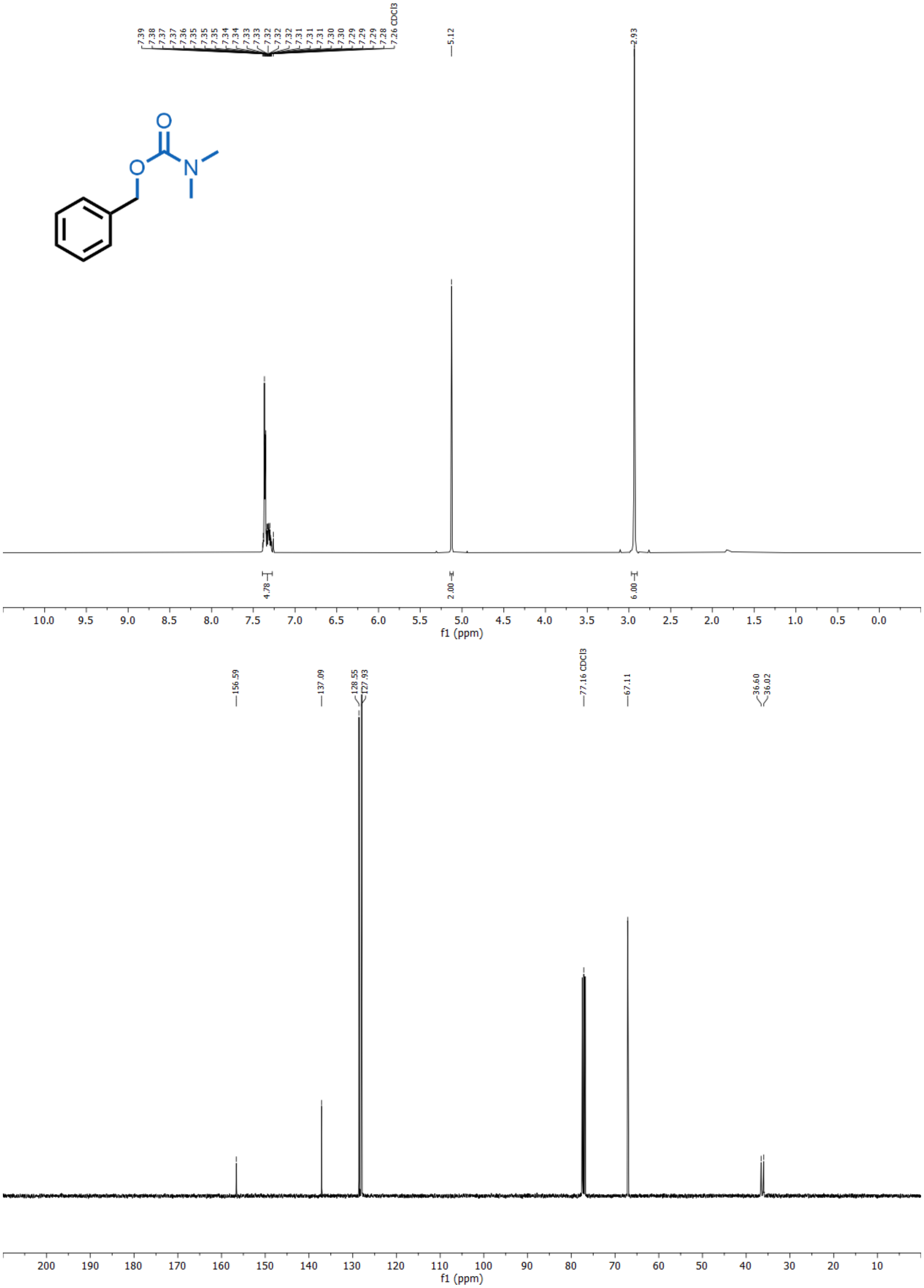


Figure 4: ^{1}H-NMR (400 MHz, $CDCl_3$) and $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) of benzyl N,N-dimethylcarbamate (8).

[Rh((*S*,*S*)-obnd)Cl]$_2$

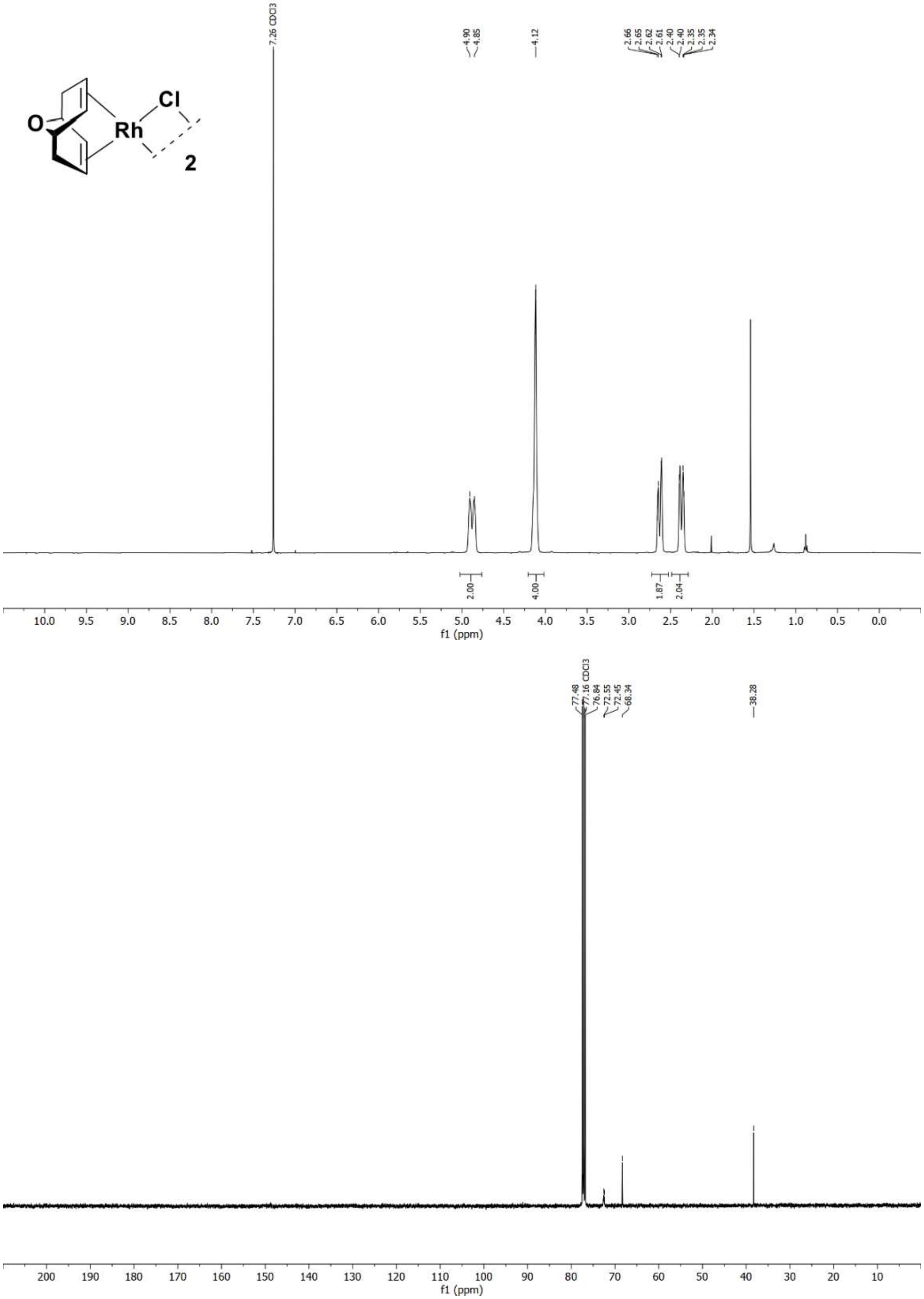
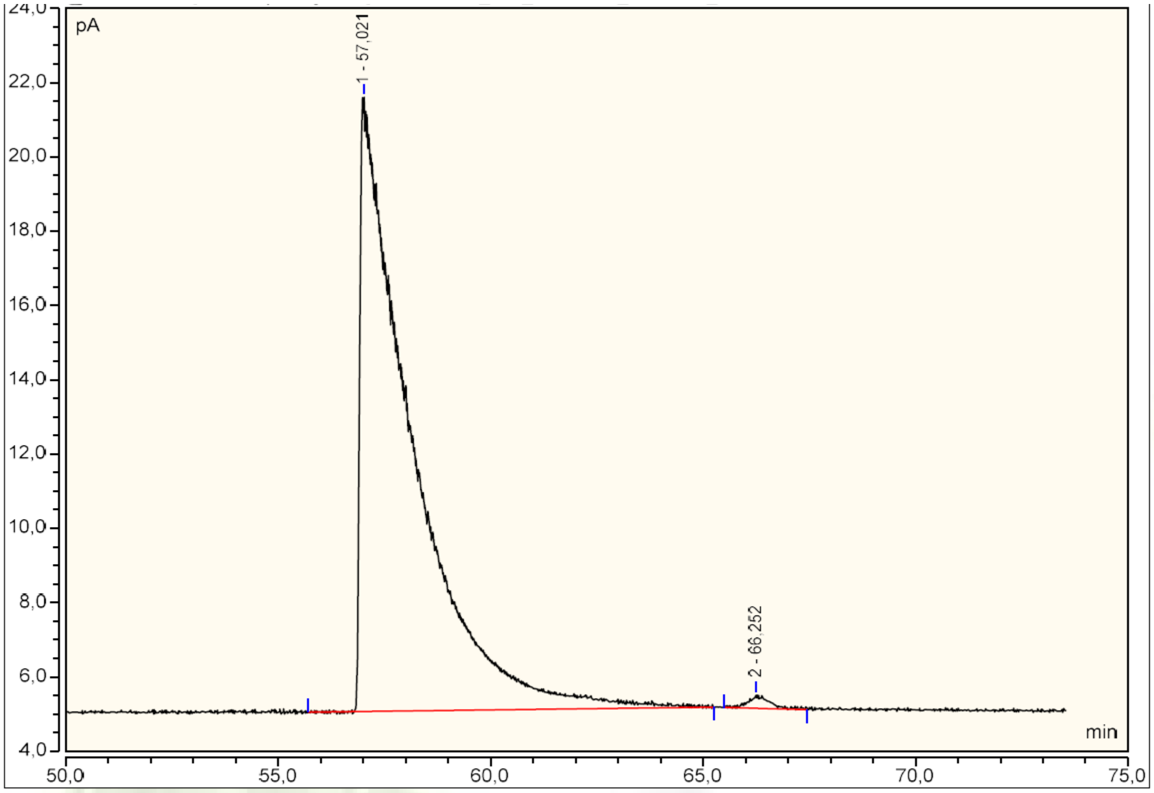
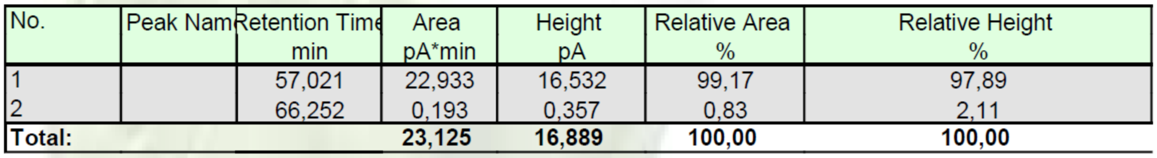


Figure 5: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of [Rh((S,S)-obnd)Cl]$_2$.

Chiral GC

[Rh((*S*,*S*)-obnd)Cl]$_2$





No.	Peak Nam	Retention Time min	Area pA*min	Height pA	Relative Area %	Relative Height %
1		57,021	22,933	16,532	99,17	97,89
2		66,252	0,193	0,357	0,83	2,11
Total:			**23,125**	**16,889**	**100,00**	**100,00**

DI.4 Literature – Experimental

[1] M. Spettel,R. Pollice,M. Schnürch, *Org. Lett.* **2017**, *19*, 4287-4290.

[2] R. Pollice,N. Dastbaravardeh,N. Marquise,M. D. Mihovilovic,M. Schnürch, *ACS Catal*. **2015**, 5, 587-595.

[3] D. Singh, G.S Kumar, M. Kapur, *J. Org. Chem*. **2019**, 84, 12881–12892.

[4] H. Zhu, S. Sun, H. Qiao, F. Yang, J. Kang, Y. Wu, Y. Wu, *Org. Lett*. **2018**, 20, 620–623.

[5] E. T. Nandres, G. I. F. Santos, D. Shabashov, O. Daugulis, *J. Org. Chem*. **2013**, 78, 9689.

[6] C. Bosset, H. Beucher, G. Bretel, E. Pasquier, L. Queguiner, C. Henry, A. Vos, J. P. Edwards, L. Meerpoel, D. Berthelot, *Org. Lett.* **2018**, *20*, 6003-6006.

[7] G. Bassioni, F. S Delgado, M. Jaeggy, F.H Kohler, S. Nogai, C. Ruiz-Perez, *Z. Naturforsch. B*, **2005**, 60, 1143-1148.

[8] A. Takahashi, M. Aso, M. Tanaka, H. Suemune, *Tetrahedron*, **2000**, 56, 1999-2006.

[9] T. Horikawa, Y. Norimine, M. Tanaka, K. Sakai, H. Suemune, *Chem. Pharm. Bull. (Tokyo),* **1998**, 46, 17‑21.

DII.1 Manuscript 1

Eleni Papaplioura, Johanna Templ, Nina Wildhack and Michael Schnürch

Efficient Synthesis of 2-Arylpropionitriles *via* Selective Monomethylation of Aryl Acetonitriles Using an Easy to Handle Methylation Agent

The manuscript was submitted to the European Journal of Organic Chemistry on the 20th of June 2024.

European Journal of Organic Chemistry

Efficient synthesis of 2-arylpropionitriles via selective monomethylation of aryl acetonitriles using an easy to handle methylation agent

--Manuscript Draft--

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	Nina Wildhack
	Michael Schnürch, Associate Prof.
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Abstract:	A convenient and safe methylation protocol employing quaternary ammonium salts (PhMe3NI) as alternative methylating agents for the selective α-methylation of arylacetonitriles is presented. This approach allows for the selective α-methylation of arylacetonitriles, overcoming the limitations of existing techniques, while offering a practical and sustainable solution for late-stage functionalization in medicinal chemistry. The straightforward and safe nature of this methodology makes it particularly well-suited for applications in drug discovery. In our report, we present a diverse set of 18 examples, achieving yields of up to 76 %.
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Do you or any of your co-authors have a conflict of interest to declare?	No
Does the research described in this manuscript include animal experiments?	No
Does the research described in this manuscript include human research participants (including for experiments with sensors or wearable technologies) or tissue samples from human subjects (including blood or sweat)?	No

Efficient synthesis of 2-arylpropionitriles via selective monomethylation of aryl acetonitriles using an easy to handle methylation agent

Eleni Papaplioura, [a] Johanna Templ, [a] Nina Wildhack, [a] Prof. Michael Schnürch *[a]

Dedication ((optional))

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Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate.))

Abstract: A convenient and safe methylation protocol employing quaternary ammonium salts ($PhMe_3NI$) as alternative methylating agents for the selective α-methylation of arylacetonitriles is presented. This approach allows for the selective α-methylation of arylacetonitriles, overcoming the limitations of existing techniques, while offering a practical and sustainable solution for late-stage functionalization in medicinal chemistry. The straightforward and safe nature of this methodology makes it particularly well-suited for applications in drug discovery. In our report, we present a diverse set of 18 examples, achieving yields of up to 76 %.

Introduction

Nitrile-containing pharmaceuticals are widely prescribed drugs, with broad bioactive potential, for treating various conditions.[1-2] Specifically, aryl acetonitriles are versatile compounds and important precursors in pharmaceutical manufacturing.[1] Anastrazole, Galopamil, and Verapamil are among the most extensively researched aryl acetonitrile-containing compounds used for the prevention and treatment of cancer and angina (Figure 1). [1] The selective *C*-mono-methylation of these compounds leads to the synthesis of α-methylphenylacetonitriles (i.e. 2-arylproprionitriles), common building blocks for the construction of anti-inflammatory drugs such as ibuprofen, naproxen, and flurbiprofen.[3-5]

The replacement of a hydrogen atom (C-H) with a methyl group (C-Me) in bioactive compounds, known as the "Magic Methyl Effect" is highly valuable in medicinal chemistry, as this modification usually enhances the potency of lead compounds by altering their pharmacodynamic, pharmacokinetic, or conformational properties.[6-9] [10] Studies on the structure-activity relationship (SAR) have shown that adding methyl groups to certain compounds significantly improve their IC_{50} values. For example, in the case of the anticancer drug tazemetostat, the incorporation of additional methyl groups in the development process resulted in a remarkable >100,000-fold enhancement in its potency.[8,11-13] However, late-stage methylation of complex bioactive molecules remains a significant challenge.[14-15] Achieving selective monomethylation is particularly difficult due to the frequent formation of dimethylated side products, the separation of which is rather laborious.[3,16-17] Traditional methylating agents, such as methyliodide, dimethylsulfate, or methyl fluorosulfonate pose significant toxicological concerns and health hazards.[16,18] Additionally, several organometallic reagents (e.g., methylboronic acid [19-22] and tetramethyltin)[23], suffer from low functional group tolerance and unfavorable physical properties (low boiling points, air sensitivity), making them impractical to handle, especially on lab-scale syntheses.[24-25] Conventional late-stage methylation strategies often involve transition metal catalysis (C-H methylation), but these methods frequently require highly toxic reagents and solvents.[26] Dimethyl carbonate and trimethyl orthoformate have also been used for the methylation of phenylacetonitriles, however, harsh reaction conditions are required.[5,27] Wang *et al.* developed a $Me_2NH\text{-}BH_3$-mediated selective α-monomethylation protocol using *N*,*N*-dimethylformamide as the methyl source.[4] Nonetheless, the formation of side products cannot be excluded, complicating the purification process. Only one year later, Xi's group described a selective monomethylation protocol employing CO_2 as the methyl source in the presence of trimethylamine-borane, yet this method required elaborate high-pressure equipment.[28]

Previous studies within our group, have highlighted the potential of quaternary ammonium salts, as safer and non-carcinogenic alternative alkylating[29] and methylating agents in organic reactions.[30-31] These salts are known to function as surfactants,[32] ionic liquids,[32-35] and phase transfer materials.[33,36-37] They also exhibit stability in air and moisture, significantly enhancing their utility in both small- and large-scale reactions.[36,38-39]

In light of the prevalence of the aryl acetonitrile moiety in various small-molecule drugs, there is a pressing need to develop advanced techniques for incorporating methyl groups, using safer reagents.[39] Therefore, this study aims to establish a selective and highly efficient metal-free protocol for the α-methylation of aryl acetonitriles by harnessing the remarkable properties of quaternary ammonium salts.

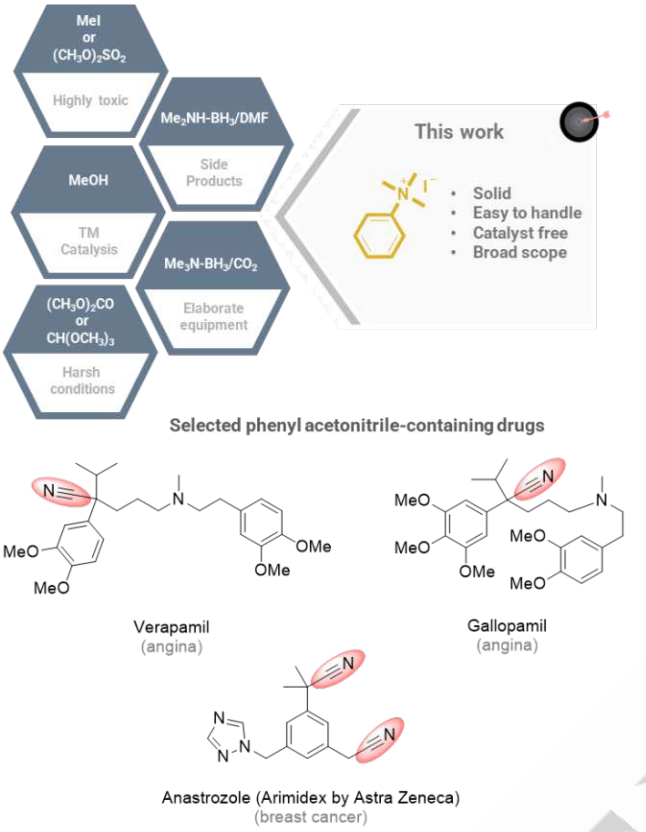


Figure 1. Strategies for the methylation of phenylacetonitriles (Top), and most prescribed nitrile-containing pharmaceuticals (Bottom).

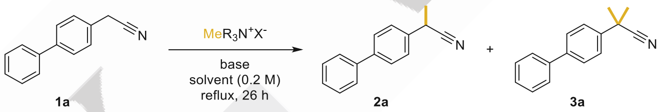
Results and Discussion

We started developing the methylation of (4-biphenyl)acetonitrile (**1a**) based on conditions optimized in a previous study from our group, which focused on the methylation of aryl ketones with quaternary ammonium salts as methylating agents (Table 1, entry 1).[30] This initial experiment showed promising results, with ~15% of the substrate recovered, 59% converted to the monomethylated product **2a**, and 13% to the dimethylated product **3a**.

Next, we examined the impact and effectiveness of various bases. Cs_2CO_3 outperformed others, yielding 71% of the desired monomethylated product **2a** (entry 2). In contrast, NaO*t*Bu favored dimethylated product **3a** with a yield of 65% (entry 3) (see complete base screening list in the SI). With Cs_2CO_3 chosen as the preferred base, we further investigated the influence of the different quaternary ammonium salts. Similar reactivity was observed for $PhMe_3NBr$ and $PhMe_3NCl$, but the overall conversion was significantly lower compared to $PhMe_3NI$ in both cases (entries 4 and 5). Tetramethylammonium salts, bearing various counter ions were practically inefficient for our purposes (entries 6 and 7) (see complete quaternary ammonium salt screening list in the SI).

To mitigate environmental impact, we tested the greener solvent alternatives *tert*-butanol (*t*-BuOH) and 2-methyl-THF (Me-THF) (Entries 8 and 9). Furthermore, trifluorotoluene (TFT) was included in the solvent screening as well (entry 10). Although similar yields and product ratios were obtained with these solvents, toluene was still superior and was selected for further substrate scope investigation (see complete solvent screening list in the SI). Finally, we determined the optimal reaction conditions to be $PhMe_3NI$ (2 equiv.) and Cs_2CO_3 (2 equiv.) in toluene (0.2 M) at 120 °C, achieving 71% yield of the desired 2-(4-biphenyl)propionitrile (**2a**) after 26 h, as determined by ^{1}H NMR quantification (entry 2). Additionally, we compared the reactivity of $PhMe_3NI$ with that of MeI and Me_2SO_4 under otherwise identical conditions. Contrary to literature reports suggesting that dimethylation typically occurs with these reagents, our protocol did not exhibit such a behavior.[3] However, when MeI was used, a significantly lower yield of 38 % of the monomethylated product was obtained (entry 11), while the use of Me_2SO_4 resulted in only negligible formation of the monomethylated product (entry 12).

Table 1. Optimization of the reaction conditions. [a]

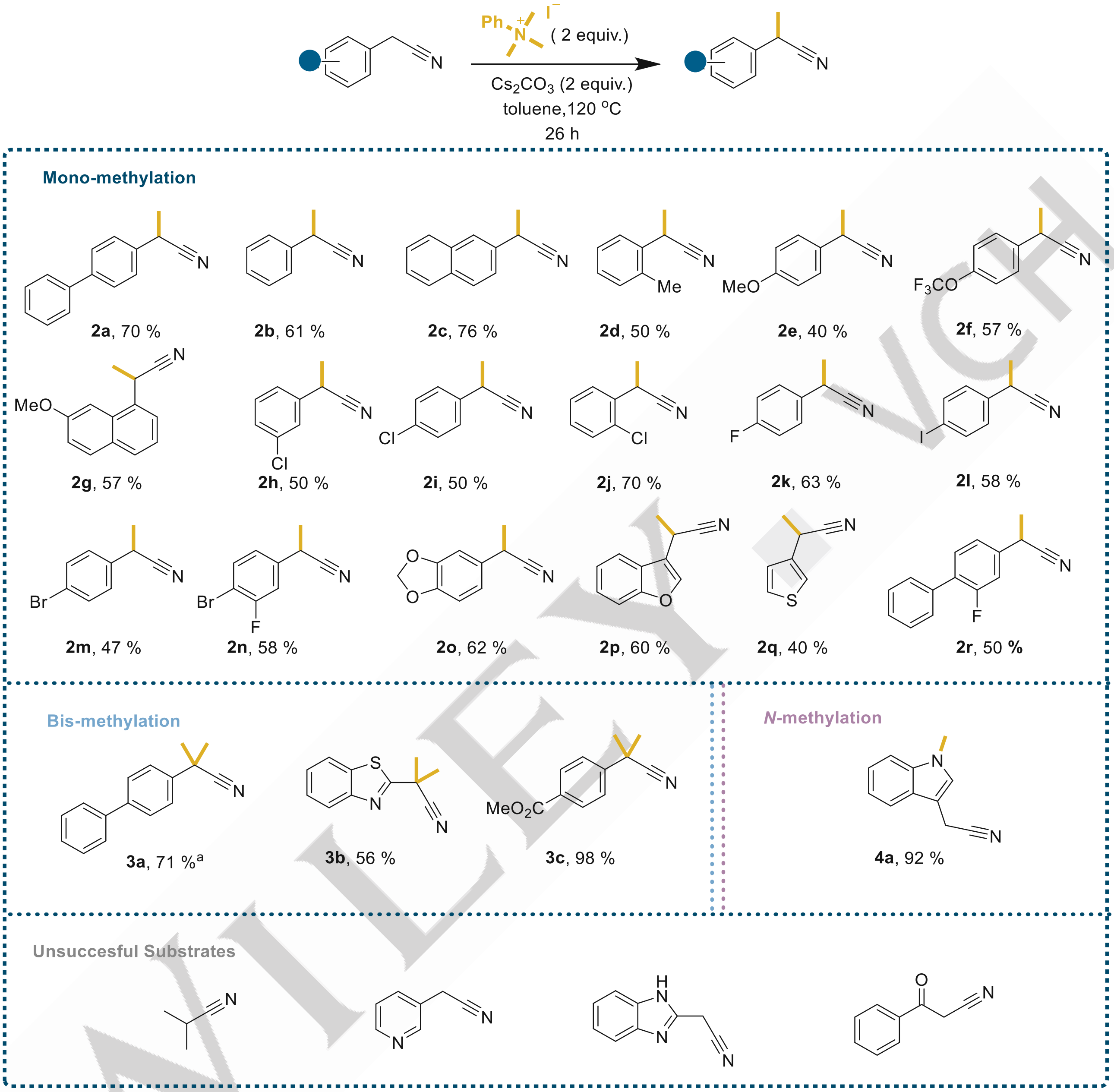


Entry	Solvent[c]	Base	Ammonium salt	Yield (%)[b]		
				1a	2a	3a
1	toluene	KOH	$PhMe_3NI$	15	59	13
2	toluene	Cs_2CO_3	$PhMe_3NI$	11	71	13
3	toluene	NaO*t*Bu	$PhMe_3NI$	0	19	65
4	toluene	Cs_2CO_3	$PhMe_3NBr$	65	13	0
5	toluene	Cs_2CO_3	$PhMe_3NCl$	59	14	0
6	toluene	Cs_2CO_3	Me_4NBr	63	8	0
7	toluene	Cs_2CO_3	Me_4NF	20	43	0
8	*t*-BuOH	Cs_2CO_3	$PhMe_3NI$	7	68	19
9	Me-THF	Cs_2CO_3	$PhMe_3NI$	11	59	10
10	TFT	Cs_2CO_3	$PhMe_3NI$	6	68	16
11	toluene	Cs_2CO_3	MeI	24	38	2
12	toluene	Cs_2CO_3	Me_2SO_4	60	3	0

[a] Reactions were performed on a 0.6 mmol scale, with base (2 equiv.) and 2 equiv. of the respective ammonium salt under Ar atmosphere; reaction time 26 h, 120 °C. [b] Yields were determined by ^{1}H NMR spectroscopy using benzyl benzoate as internal standard. [c] reflux conditions.

After identifying the best performing conditions, we explored the substrate scope with respect to aryl acetonitriles. A range of functional groups, including halides (products **2h**-**2n**) and ethers (products **2e**-**2g**), as well as heterocycles commonly found in bioactive compounds (products **2o-2q**), were tested regarding their ability to undergo monomethylation at the α-position. The desired compounds were obtained in isolated yields of up to 76%.

In all cases, stochiometric amounts of *N*,*N*-dimethylaniline were formed when using $PhMe_3NI$, which could be easily removed as its water-soluble HCl salt after a mild acidic workup.



[a] NaOtBu (2 equiv.) used as base.

Scheme 1. Scope of a-methylation of phenylacetonitriles.

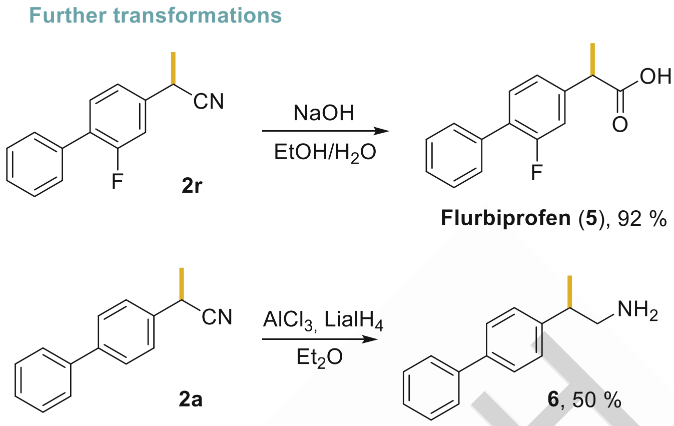
The 2-(4-biphenyl)propionitrile (**2a**) used during the optimization process was isolated with a yield of 70%, demonstrating the method's efficiency. Additionally, the unsubstituted hydrocarbons 2-phenylpropionitrile (**2b**) and 2-(2-naphthyl)propionitrile (**2c**) were obtained with yields of 61% and 76%, respectively. A slightly lower yield of 50% was observed for 2-(2-methylphenyl)propionitrile (**2d**), likely due to the increased steric hindrance and the strong electron-donating effect of the methyl group in the *ortho*-position, which might reduce the availability of the α-hydrogens for deprotonation.

An even more profound electron-donating effect was observed in the case of 2-(4-methoxyphenyl)propionitrile (**2e**) (40% isolated yield). Although the optimal stoichiometry for the methylating agent was found to be 2 equivalents of the $PhMe_3NI$ in our previous optimization studies, 3 equivalents were needed in this case to enhance product formation. A moderate yield of 57% was achieved for 2-(4-(trifluoromethoxy)phenyl)propionitrile (**2f**), as well as for 2-(7-methoxynaphth-1-yl)propionitrile (**2g**). The reaction was also applicable to substrates bearing electron-withdrawing groups. The influence of the substitution pattern on the aromatic system was examined by methylating *meta*-, *ortho*-, and *para*-chlorine-substituted phenyl acetonitriles. Moderate yields of 50% were obtained for the 2-(3-chlorophenyl)propionitrile (**2h**) and 2-(4-chlorophenyl)propionitrile (**2i**). Despite the steric hindrance of the *ortho*-substituent, significantly higher product yield (70%) was achieved for the 2-(2-chlorophenyl)propionitrile (**2j**). Aryl acetonitriles bearing different halogens at the *para*-position were also tested, with the most electron-withdrawing fluoro derivative **2k** giving the highest yield of 63%. A slightly lower yield of 58% was obtained for 2-(4-iodophenyl)propionitrile (**2l**), and a moderate yield of 47% for the bromo-substituted equivalent **2m**. The di-halogenated compound **2n** was obtained with a 58% yield, presumably due to its stronger electron-withdrawing nature. It is worth mentioning that for electron-withdrawing substrates using fewer equivalents of the ammonium salts proved efficient to avoid possible overmethylation.

Our method is not limited to substituted aryl acetonitriles but can also be applied to heterocyclic substrates frequently found in bioactive molecules such as 1,3-benzodioxole, benzofuran, and thiophene. The respective monomethylated products were formed in good to moderate yields ranging from 40% to 62% (products **2o-2q**). Additionally, we discovered that the bis-methylated product is selectively formed in the case of 2-(1,3-benzothiazol-2-yl)-2-methylpropionitrile (product **3b**). The presence of the benzothiazole ring probably increases the acidity of the benzylic position due to the stronger electron-withdrawing effect of both the nitrogen and the sulfur, resulting in selective dimethylation. More sensitive functional groups are well-tolerated, as demonstrated on the benzoate derivative. Using 3 equivalents of the ammonium salt, this derivative yielded the dimethylated product **3c** in a quantitative yield. With lower amounts of methylating agent, mixtures of mono- and demethylated product were obtained.

Furthermore, by adjusting the reaction parameters as outlined in the optimization table, the dimethylated biphenyl product **3a** can be selectively obtained using a different base, NaO*t*Bu. As expected, *N*-methylation occurred in the case of indole **4a**, however, despite further adjustments to the reaction parameters, we were unable to obtain any *C*-methylated product.[31]

Finally, we aimed to briefly showcase the utility of this protocol for late-stage methylation of bioactive molecules. Using this method, we synthesized the precursor **2r** (50%), which, after subsequent hydrolysis, yielded the anti-inflammatory drug Flurbiprofen (**5**) quantitatively. Due to the versatility of the cyano group, we further proceeded with the modifications and successfully converted 2-(4-biphenyl)propionitrile (**2a**) to its respective amine **6**.



Scheme 2. Synthesis of Flurbiprofen and reduction of 2-(4-biphenyl)propionitrile (**2a**) to the corresponding amine.

Conclusion

In conclusion, we have presented a new protocol that employs quaternary ammonium salts as effective methylating agents for the selective α-C-monomethylation of (hetero)aryl acetonitriles, important precursors for the synthesis of key anti-inflammatory drugs. Selective dimethylation can be obtained by increasing the base strength. Our research paves the way for the exploration and utilization of quaternary ammonium salts in selectively methylating complex bioactive molecules, thereby expanding the toolkit for late-stage functionalization in medicinal chemistry, and ultimately contributing to the development of powerful pharmaceutical agents. In the future, we aim to expand the scope towards ethylation and benzylation reactions of arylacetonitriles, since in analogy to our previously reported α-ethylation and α-benzylation of aryl ketones.[30]

Supporting Information

The authors have cited additional references within the Supporting Information. [[4,40-52]]

Acknowledgements

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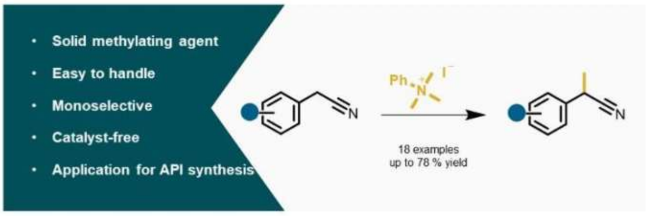
Keywords: magic methyl effect • selective α-monomethylation • phenylacetonitriles • quaternary ammonium salts • medicinal chemistry

Entry for the Table of Contents



Only one! Using a safe, easy to handle, and solid methylating agent, selective monomethylation of aryl acetonitriles is achieved. The method shows broad functional group tolerance and can be applied in the synthesis of active pharmaceutical ingredients potentially leading to compounds with increased biological activity due to the renowned magic methyl effect.

Institute and/or researcher Twitter usernames: @biosynchem, @papaplioura, @TemplJohanna, @Schnuerchlab

[1] F. F. Fleming,L. Yao,P. C. Ravikumar,L. Funk,B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902-7917.
[2] C. Scotti,J. W. Barlow, *Nat. Prod. Commun.* **2022**, *17*, 1934578X221099973.
[3] J.-P. Rieu,A. Boucherle,H. Cousse,G. Mouzin, *Tetrahedron* **1986**, *42*, 4095-4131.
[4] H.-M. Xia,F.-L. Zhang,T. Ye,Y.-F. Wang, *Angew. Chem., Int. Ed.* **2018**, *57*, 11770-11775.
[5] M. Selva,P. Tundo, *J. Org. Chem.* **1998**, *63*, 9540-9544.
[6] E. J. Barreiro,A. E. Kümmerle,C. A. M. Fraga, *Chem. Rev.* **2011**, *111*, 5215-5246.
[7] D. Illuminati,A. Fantinati, *Pharmaceuticals* **2024**, *17*, 563.
[8] H. Schönherr,T. Cernak, *Angew. Chem., Int. Ed.* **2013**, *52*, 12256-12267.
[9] D. Aynetdinova,M. C. Callens,H. B. Hicks,C. Y. X. Poh,B. D. A. Shennan,A. M. Boyd,Z. H. Lim,J. A. Leitch,D. J. Dixon, *Chem. Soc. Rev.* **2021**, *50*, 5517-5563.
[10] J. Lian,J. Wang,H. F. Sun,D. Z. Lin,H. Liu, *Yao Xue Xue Bao* **2013**, *48*, 1195-1208.
[11] P. S. M. Pinheiro,L. S. Franco,C. A. M. Fraga, *Pharmaceuticals (Basel)* **2023**, *16*.
[12] K. W. Kuntz,J. E. Campbell,H. Keilhack,R. M. Pollock,S. K. Knutson,M. Porter-Scott,V. M. Richon,C. J. Sneeringer,T. J. Wigle,C. J. Allain,C. R. Majer,M. P. Moyer,R. A. Copeland,R. Chesworth, *J. Med. Chem.* **2016**, *59*, 1556-1564.
[13] S. M. Hoy, *Drugs* **2020**, *80*, 513-521.
[14] S. D. Friis,M. J. Johansson,L. Ackermann, *Nat. Chem.* **2020**, *12*, 511-519.
[15] K. Feng,R. E. Quevedo,J. T. Kohrt,M. S. Oderinde,U. Reilly,M. C. White, *Nature* **2020**, *580*, 621-627.
[16] M. Selva,A. Perosa, *Green Chem.* **2008**, *10*, 457-464.
[17] M. Selva,C. A. Marques,P. Tundo, *J. Chem. Soc.* **1994**, 1323-1328.
[18] J. Meyer,G. Schramm, *Z. anorg. allg. Chem.* **1932**, *206*, 24-30.
[19] R. Giri,N. Maugel,J.-J. Li,D.-H. Wang,S. P. Breazzano,L. B. Saunders,J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510-3511.
[20] B. R. Rosen,L. R. Simke,P. S. Thuy-Boun,D. D. Dixon,J.-Q. Yu,P. S. Baran, *Angew. Chem., Int. Ed.* **2013**, *52*, 7317-7320.
[21] S. R. Neufeldt,C. K. Seigerman,M. S. Sanford, *Org. Lett.* **2013**, *15*, 2302-2305.
[22] J. A. Romero-Revilla,A. García-Rubia,R. Goméz Arrayás,M. Á. Fernández-Ibáñez,J. C. Carretero, *J. Org. Chem.* **2011**, *76*, 9525-9530.
[23] X. Chen,J.-J. Li,X.-S. Hao,C. E. Goodhue,J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78-79.
[24] Y. Chen, *Chem. Eur. J.* **2019**, *25*, 3405-3439.
[25] S. Moulay, *Chemistry Africa* **2020**, *3*, 845-880.
[26] Z. Liu,Z. Yang,X. Yu,H. Zhang,B. Yu,Y. Zhao,Z. Liu, *Org. Lett.* **2017**, *19*, 5228-5231.
[27] J. Molleti,G. D. Yadav, *J. Mol. Catal.* **2017**, *438*, 66-75.
[28] X. Zhang,S. Wang,C. Xi, *J. Org. Chem.* **2019**, *84*, 9744-9749.
[29] J. Templ,M. Schnürch, *Angew. Chem., Int. Ed.* **2024**, *63*, e202314637.
[30] J. Templ,M. Schnürch, *J. Org. Chem.* **2022**, *87*, 4305-4315.
[31] J. Templ,E. Gjata,F. Getzner,M. Schnürch, *Org. Lett.* **2022**, *24*, 7315-7319.
[32] P. Brown,C. Butts,R. Dyer,J. Eastoe,I. Grillo,F. Guittard,S. Rogers,R. Heenan, *Langmuir* **2011**, *27*, 4563-4571.
[33] F. Bureš, *Top Curr Chem (Cham)* **2019**, *377*, 14.
[34] J. Pernak,M. Smiglak,S. T. Griffin,W. L. Hough,T. B. Wilson,A. Pernak,J. Zabielska-Matejuk,A. Fojutowski,K. Kita,R. D. Rogers, *Green Chem.* **2006**, *8*, 798-806.
[35] C. I. Melo,R. Bogel-Łukasik,M. Nunes da Ponte,E. Bogel-Łukasik, *Fluid Phase Equilibria* **2013**, *338*, 209-216.
[36] R. A. Jones, *Quaternary Ammonium Salts: Their Use in Phase-Transfer Catalysis*, Elsevier, **2000**.
[37] B. Lygo,B. I. Andrews, *Accounts of Chemical Research* **2004**, *37*, 518-525.
[38] J. D. S. Holbrey, K. , *Ionic liquids in Clean Products and Processes, Vol. 1*, Springer, **1999**.
[39] J. Templ,M. Schnürch, *Chem. Eur. J.* **2024**, *n/a*, e202400675.
[40] I. T. Schiefer, S. Abdul-Hay, H. Wang, M. Vanni, Z. Qin, G. R. J. Thatcher, *J. Med. Chem.* **2011**, *54*, 2293-2306.
[41] T. Frejd, T. Klingstedt, *Synthesis* **1987**, *1987*, 40-42.
[42] M. de Greef, B. Breit, *Angew. Chem., Int. Ed.* **2009**, *48*, 551-554.
[43] M. Ettaoussi, A. Sabaouni, B. Pérès, E. Landagaray, O. Nosjean, J. A. Boutin, D.-H. Caignard, P. Delagrange, P. Berthelot, S. Yous, *ChemMedChem* **2013**, *8*, 1830-1845.
[44] Y. Huang, Y. Yu, Z. Zhu, C. Zhu, J. Cen, X. Li, W. Wu, H. Jiang, *J. Org. Chem.* **2017**, *82*, 7621-7627.
[45] T. Betke, P. Rommelmann, K. Oike, Y. Asano, H. Gröger, *Angew. Chem. Int. Ed.* **2017**, *56*, 12361-12366.
[46] R. Wang, C.-Y. Wang, P. Liu, K.-J. Bian, C. Yang, B.-B. Wu, X.-S. Wang, *Science Advances* **2023**, *9*, eadh5195.
[47] J. Guin, G. Varseev, B. List, *J. Am. Chem. Soc.* **2013**, *135*, 2100-2103.
[48] R. Shang, D.-S. Ji, L. Chu, Y. Fu, L. Liu, *Angew. Chem. Int. Ed.* **2011**, *50*, 4470-4474.
[49] A. Klapars, J. H. Waldman, K. R. Campos, M. S. Jensen, M. McLaughlin, J. Y. L. Chung,R. J. Cvetovich, C.-y. Chen, *J. Org. Chem.* **2005**, *70*, 10186-10189.
[50] K. J. Hock, A. Knorrscheidt, R. Hommelsheim, J. Ho,M. J. Weissenborn, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2019**, *58*, 3630-3634.
[51] G. Cavallini, E. Massarini, D. Nardi, R. D´Ambrosio *J. Am. Chem. Soc.* **1956**, *79*, 3514-3517.
[52] J.-P. Rieu, A. Boucherle, H. Cousse, G. Mouzin *Tetrahedron*, **1986**, *42*, 4095-4131

DII.2 Manuscript 1 – Supporting Information

A concise summary of the detailed procedure for quantitative ^{1}H-NMR measurements, including complete optimization screening data, experimental details, and characterization data for all isolated compounds.

Eleni Papaplioura, Johanna Templ, Nina Wildhack and Michael Schnürch

Supporting Information for

Efficient Synthesis of 2-Arylpropionitriles *via* Selective Monomethylation of Aryl Acetonitriles Using an Easy to Handle Methylation Agent

The manuscript was submitted to the European Journal of Organic Chemistry on the 20th of June 2024.

Supporting Information

Efficient Synthesis of 2-Arylpropionitriles *via* Selective Monomethylation of Aryl Acetonitriles Using an Easy to Handle Methylation Agent

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General Experimental Details

Unless noted otherwise, reactants and reagents were purchased from commercial suppliers and used without further purification. The 8 mL brown-glass vials were sealed with Wheaton® screw caps containing a PTFE faced 14B styrene-butadiene rubber liner. All reactions were magnetically stirred and heated in a metallic reaction block. All reaction temperatures refer to external temperatures.

NMR spectra were recorded in $CDCl_3$ or d_8-toluene on a Brucker Avance UltraShield (400 MHz) or Avance III HD 600 (600 MHz) spectrometer and 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 by the following abbreviations = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

Thin Layer Chromatography (TLC) analysis was performed on precoated aluminum-backed unmodified plates (Silica gel 60 F_{254}, Merck). Compounds were visualized under UV light.

Flash column chromatography was performed using either Merck silica gel 60 (40 µm – 63 µm) by hand column or purification was performed using a TELEDYNE ISCO COMBI FLASH® COMPANION® NextGen300+ flash chromatography system with UV-Vis detector (diode array) with Macherey-Nagel Chromabond RS silica gel columns.

GC-MS analysis was performed on 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 programs: **Method A:** 2 min at 100 °C, 35 °C/min until 300 °C, 4 min at 300 °C and **Method B:** 2.5 min at 40 °C, 12 °C/min until 220 °C, 2.5 min at 220 °C.

General Experimental Procedures

Reaction Optimization Screening

General Procedure A

In an 8-mL glass vial equipped with a magnetic stirring bar, were added the 4-biphenylacetonitrile (0.3 mmol, 1 equiv.), the respective ammonium salt (1-3 equiv.), and the respective base (1-3 equiv.). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. Subsequently, the respective solvent (0.2 M) was added *via* syringe, and evacuation and backfilling with argon were repeated three times under vigorous stirring to prevent any boiling delay. Next, the septum screw cap was replaced with a Wheaton® screw cap, and the vial was sealed tightly. The reaction mixture was heated to 120 °C, in a metallic block for 20-48 h. After a certain reaction time, the reaction mixture was cooled to room temperature. 2N HCl (5 mL) was added, and the resulting mixture was extracted three times with Et_2O (5 mL each). The combined organic phases were washed twice with 2N HCl (1 mL) each and dried over Na_2SO_4, filtered, and concentrated in *vacuo*.

Sample preparation for ^{1}H-NMR quantification:

After workup procedure (see General Procedure A) and solvent evaporation, 100 µL of a solution of benzylbenzoate in $CDCl_3$ (48 mmol/mL) was added to the crude product *via* Hamilton syringe. 1 mL of $CDCl_3$ was added to dissolve the crude product fully. The solution was transferred to an NMR tube and measured on a Bruker 400 MHz NMR machine with the following instrument parameters:

- transmitter excitation frequency (O1T) = 7.2 ppm
- spectral width = 15.62 ppm
- relaxation delay = 15 s

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

- 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)

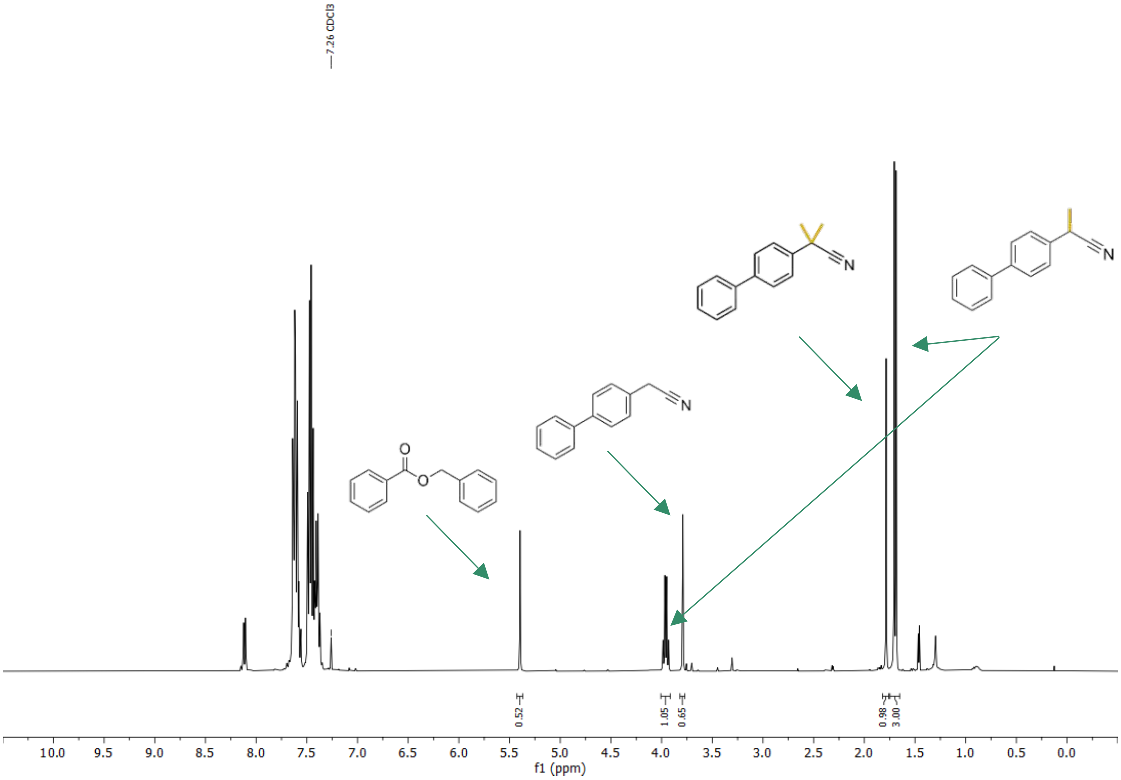


Figure 1: ^{1}H-NMR used as an example for quantification.

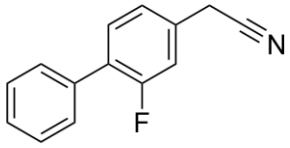
Substrate Scope Screening

General Procedure B

In an 8-mL glass vial equipped with a magnetic stirring bar, were added the respective acetonitrile starting material (0.6 mmol, 1 equiv.), trimethylphenyl ammonium iodide (2 equiv.), and Cs_2CO_3 (2 equiv.). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. Subsequently, toluene (0.2 M) was added *via* syringe, and evacuation and backfilling with argon were repeated three times under vigorous stirring to prevent any boiling delay. Next, the septum screw cap was replaced with a Wheaton® screw cap, and the vial was sealed tightly. The reaction mixture was heated to 120 °C, in a metallic block for 26 h. After 26 h the reaction mixture was cooled to room temperature. 2N HCl (5 mL) was added, and the resulting mixture was extracted three times with Et_2O (5 mL each). The combined organic phases were washed twice with 2N HCl (1 mL) each and dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The obtained crude product was purified *via* hand column using unmodified silica gel and a mixture of pentane and Et_2O as eluent.

Flurbiprofen precursor synthesis [1]

2-(3-Fluoro-4-phenylphenyl)acetonitrile (7)



4-Bromo-3-fluorophenylacetonitrile (863 mg, 4 mmol, 1 equiv.), phenylboronic acid (975 mg, 8 mmol, 2 equiv.), tetrabutylammonium bromide (1.45 g, 4.4 mmol, 1.1 equiv.), and $Pd(OAc)_2$ (135 mg, 0.6 mmol, 15 mol%) were suspended in 20 mL of a 2 M Na_2CO_3 aqueous solution. 20 mL toluene were added, and the reaction mixture was heated to reflux temperatures *via* an oil bath for 4 hours. Subsequently, the reaction was cooled to room temperature and 10 mL 2 N HCl were added, and the resulting mixture was filtered over a short plug of celite and washed with EtOAc. The organic phase was separated, and the aqueous phase was extracted twice with EtOAc. The combined organic phases were washed twice with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was further purified *via* flash column chromatography (50 g silica, LP:EtOAc 5:1) to obtain 427 mg (51%) of the desired compound (**7**) as a yellow solid.

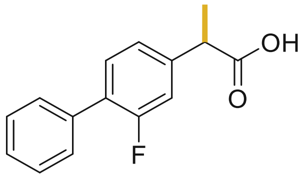
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54-7.32 (m, 6H), 7.18-7.07 (m, 2H), 3.74 (s, 2H) ppm.

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 159.8 (d, J = 249.8 Hz), 135, 131.6 (d, J = 4.0 Hz), 131.1 (d, J = 8.1 Hz), 129.03 (d, J = 3.0 Hz), 128.7, 128.1, 124.0 (d, J = 3.7 Hz), 116 (d, J = 24.6 Hz), 23.2 ppm.

^{19}F-NMR (376 MHz, $CDCl_3$) δ -116.4.

Nitrile reductions

2-(3-Fluoro-4-phenylphenyl)propanoic acid (Flurbiprofen) (5) [CAS: 5104-49-4][2]



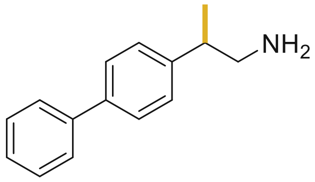
The title compound was prepared according to the literature from 2-(3-fluoro-4-phenylphenyl)propionitrile (**2r**). A 100-mL sealed flask equipped with a magnetic stirring bar, was charged with 2-fluoro-α-methyl[1,1'-biphenyl]-4-acetonitrile (45.1 mg, 0.2 mmol, 1 equiv.) and NaOH (480 mg, 12 mmol, 60 equiv.). EtOH (1.5 mL) and water (6 mL) were added, and the reaction mixture was heated to 120 °C for 5 h. After 5 h, the reaction mixture was cooled to room temperature. 1M H_2SO_4 was added to acidify the crude mixture, which was subsequently extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The obtained crude product was purified *via* hand column using unmodified silica gel and a mixture of pentane and Et_2O as eluent (10:1) to yield 45 mg of the product as a white solid: 92 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (dt, *J* = 8.1, 1.5 Hz, 2H), 7.48 – 7.34 (m, 4H), 7.22 – 7.12 (m, 2H), 3.79 (q, *J* = 7.2 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 180.0, 159.8 (d, *J* = 248.5 Hz), 141.1 (d, *J* = 7.5 Hz), 135.6, 131.0 (d, *J* = 3.9 Hz), 129.1 (d, *J* = 2.9 Hz), 128.6, 128.4 (d, *J* = 13.5 Hz), 127.9, 123.8 (d, *J* = 3.4 Hz), 115.5 (d, *J* = 23.7 Hz), 45.0, 18.2.

^{19}F-NMR (376 MHz, $CDCl_3$) δ -117.4.

2-(4-Phenylphenyl)propan-1-amine (6) [CAS: 20375-54-6]



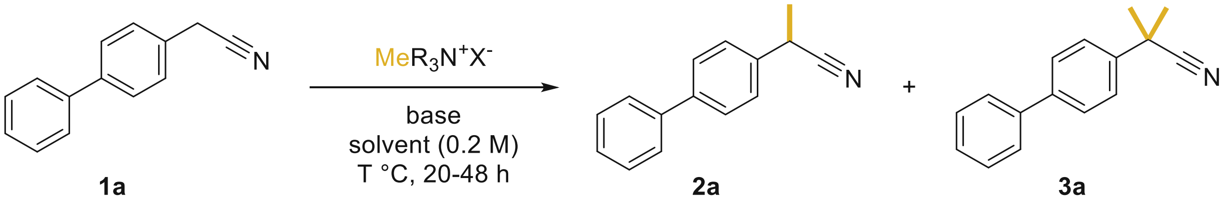
The title compound was prepared according to the literature[3] from 2-biphenyl-4-yl-propanenitrile (**2a**). A solution of aluminum chloride (13.7 mg, 0.362 mmol, 2.5 equiv.) in ether Et_2O (0.20 mL) was added to a stirring suspension of $LiAlH_4$ (49.2 mg, 0.362 mmol, 2.5 equiv.) in Et_2O (0.20 mL), and the reaction mixture was stirring for 5 minutes. Subsequently, a solution of **2a** (30 mg, 0.145 mmol, 1 equiv.) in ether Et_2O (0.20 mL) was added and the stirring was continued for 1 h. After 1 h, the reaction mixture was cooled down to 0 °C and water (0.30 mL) was added dropwise. The aqueous phase was extracted twice with Et_2O (0.40 mL). To the aqueous phase Et_2O (0.40 mL), and conc. aqueous NH_3 (0.40 mL) were added, and the reaction mixture was stirred for 20 minutes. Next, the precipitate was filtered off and the phases were separated. The process was repeated twice, and the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. No additional purification was required. The title compound was obtained with 50 % yield (15 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 4H), 7.47 – 7.40 (m, 2H), 7.37 – 7.27 (m, 3H), 2.90 (d, *J* = 6.9 Hz, 2H), 2.81 (q, *J* = 6.8 Hz, 1H), 1.30 (d, *J* = 6.8 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 144.2, 141.1, 139.5, 128.9, 127.9, 127.4, 127.2, 127.2, 127.2, 49.6, 43.3, 19.5.

Optimization Screening for Methylation Reaction

The reaction below was chosen as the model reaction and yields were determined by quant. ^{1}H-NMR spectroscopy for the crude reaction mixtures using benzyl benzoate as internal standard. We examined the following parameters: quaternary ammonium salt, base, solvent, reagent equivalents, and reaction time.



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

Reactions were performed according to the general procedure A using PhMe$_3$NI (2 equiv.), the respective base (2 equiv.), and toluene (0.2 M) at reflux conditions for 26 h.

Table 1: Base screening:

Entry	Base variation	Yield (%)		
		1a	**2a**	**3a**
1	no base	94	0	0
2	K_2CO_3	85	0	0
3	Cs_2CO_3	11	71	13
4	NaOH	27	55	5
5	KOH	15	59	13
6	NaO*t*Bu	0	19	65

Reactions were performed according to the general procedure A using the respective methylating agent (2 equiv.), Cs_2CO_3 (2 equiv.), and toluene (0.2 M) at reflux conditions for 20 h.

Table 2: Methylation agent screening:

Entry	Methylating agent variation	Yield (%)		
		1a	**2a**	**3a**
1	Me_4NF	20	43	11
2	Me_4NCl	68	4	0
3	Me_4NBr	63	8	0
4	$PhMe_3NCl$	59	14	0
5	$PhMe_3NBr$	65	13	0
6	$PhMe_3NI$	28	35	2
7[a]	$PhMe_3NI$	1	51	7
8	MeI	24	38	2
9[b]	MeI	48	19	0
10	Me_2SO_4	60	3	0
11[b]	Me_2SO_4	51	2	0

[a] 26 h. [b] (1 equiv.) of the methylating agent was used.

Comparison between PhMe$_3$I and MeI/Me$_2$SO$_4$

Standard methylating reagents such as MeI and Me_2SO_4 were tested under the identical reaction conditions using Cs_2CO_3 as base (Table 2, entries 8-11). It has to be mentioned, that typically stronger bases are reported in literature for benzylic cyanides and hence, it could be expected, that these reactions would be less efficient in presence of Cs_2CO_3. For example, **1a** has been methylated using MeI as methylating agent and $NaNH_2$ as base giving 63% of **2a** accompanied by an unspecified amount of **3a**.[13,14] Indeed, using 1 equiv. of MeI, only 19% of **2a** and 48% remaining starting material **1a** were observed, with no demethylated product **3a** (Table 2, entry 9). Increasing the amount of MeI to 2 equiv. led to 38% **2a**, 24% **1a** and minimal formation of **3a** (2%) (Table 2, entry 8). Me_2SO_4 was even less suitable as methylating agent under our standard conditions, forming only 3% of **2a** with 2 equiv. methylating agent and 2% with 1 equiv. and mainly starting material remaining (Table 2, entries 10 & 11).

Reactions were performed according to the general procedure A using $PhMe_3NI$ (2 equiv.), Cs_2CO_3 (2 equiv.), and the respective solvent (0.2 M) at reflux conditions for 26 h.

Table 3: Solvent screening:

Entry	Solvent variation	Yield (%) **1a**	 **2a**	 **3a**
1	*t*-BuOH	7	68	19
2	Me-THF	11	59	10
3	ACN	0	52	40
4	THF	20	63	10
5	TFT	6	68	16
6	heptane	33	55	4
7	toluene	11	71	13

Reactions were performed according to the general procedure A using $PhMe_3NI$ (x equiv.), Cs_2CO_3 (x equiv.), and toluene (0.2 M) at reflux conditions for 26 h.

Table 4: Reagent equivalents screening:

Entry	Base variation (equiv.)	Ammonium salt variation (equiv.)	Yield (%) **1a**	 **2a**	 **3a**
1	1	1	48	40	1
2	1	2	31	58	4
3	1	3	42	34	1
4	2	1	36	58	3
5	2	2	15	70	8
6	2	3	5	70	18
7	3	1	43	48	2
8	3	1.5	8	69	15
9	3	2	2	65	30
10	3	3	0	50	41

Reactions were performed according to the general procedure A using $PhMe_3NI$ (2 equiv.), Cs_2CO_3 (2 equiv.), and toluene (0.2 M) at reflux conditions.

Table 5: Reaction time screening:

Entry	Reaction time variation	Yield (%) **1a**	 **2a**	 **3a**
1	26	11	71	13
2	36	5	68	18

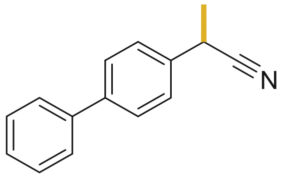
3	48	6	67	17

Characterization data for all synthetic compounds

All synthesized compounds are described in the literature. The spectra were in agreement with the literature values.

Substrate Scope

2-Biphenyl-4-yl-propanenitrile (2a)[4] [CAS: 54321-43-6]



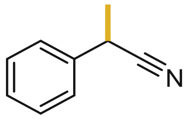
The title compound was prepared according to general procedure B from commercially available starting material. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1, 60:1) to yield 145 mg of the product as a white solid: 70 %.

The title compound was also prepared on a 3 mmol scale as follows:
In a 50 mL round bottom flask equipped with a magnetic stirring bar, were added 4-biphenylacetonitrile (3 mmol, 1 equiv.), $PhMe_3NI$ (1.61 g, 6 mmol, 2 equiv.) and Cs_2CO_3 (1.97 g, 6 mmol, 2 equiv.). The flask was closed with a septum, and using a cannula, it was evacuated and backfilled with argon three times. Subsequently, toluene (15 mL, 0.2 M) was added *via* syringe, and evacuation and backfilling with argon were repeated three times under vigorous stirring to prevent any boiling delay. The reaction mixture was heated to 120 °C in an oil bath. After 26 h, the reaction mixture was cooled to room temperature. 2N HCl (15 mL) was added, and the resulting mixture was extracted three times with Et_2O (25 mL each). The combined organic phases were washed twice with 2N HCl (5 mL) each and dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The crude residue was purified *via* column chromatography. Analytical data were in accordance with the previous findings.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.55 (m, 4H), 7.52 – 7.36 (m, 5H), 3.96 (q, *J* = 7.3 Hz, 1H), 1.70 (d, *J* = 7.3 Hz, 3H).7.44 – 7.25 (m, 5 H), 3.90 (q, *J* = 7.3 Hz, 1H), 1.65 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 141.1, 140.3, 136.1, 128.9, 127.9, 127.7, 127.2, 127.1, 121.6, 31.0, 21.5.

2-Phenylpropionitrile (2b)[2] [CAS: 1823-91-2]

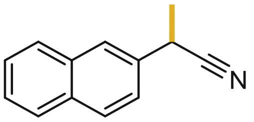


The title compound was prepared according to general procedure B from commercially available starting material. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1, 60:1) to yield 48 mg of the product as a pale-yellow oil: 61 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.25 (m, 5 H), 3.90 (q, *J* = 7.3 Hz, 1H), 1.65 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 137.2, 129.2, 128.1, 126.8, 121.7, 31.3, 21.5.

2-(2-Naphthyl)propionitrile (2c)[2] [CAS: 22250-78-8]

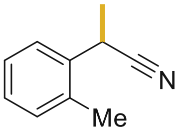


The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 1 equivalent trimethylphenyl ammonium iodide was used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1) to yield 83 mg of the product as a pale-yellow solid: 76 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 4H), 7.57 – 7.48 (m, 2H), 7.43 (dd, *J* = 8.5, 1.9 Hz, 1H), 4.07 (q, *J* = 7.3 Hz, 1H), 1.74 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 134.4, 133.4, 132.9, 129.3, 128.0, 127.8, 126.8, 126.6, 125.7, 124.5, 121.7, 31.5, 21.5.

2-(2-Methylphenyl)propionitrile (2d)[2] [CAS: 58422-60-9]

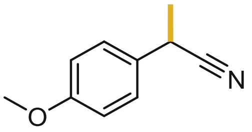


The title compound was prepared according to general procedure B from commercially available starting material. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1) to yield 44 mg of the product as a pale-yellow oil: 51 %.

^{1}H-NMR (400 MHz, $CDCl_3$) 7.40 – 7.34 (m, 1H), 7.21 – 7.08 (m, 3H), 3.96 (q, *J* = 7.2 Hz, 1H), 2.28 (s, 2H), 1.53 (d, *J* = 7.2 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 135.3, 134.8, 131.1, 128.2, 127.1, 126.7, 121.9, 28.2, 20.1, 19.1.

2-(4-Methoxyphenyl)propionitrile (2e)[4] [CAS: 31007-06-4]

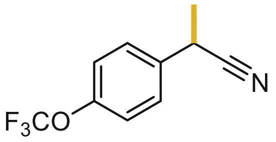


The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 3 equivalents trimethylphenyl ammonium iodide and 3 equivalents Cs_2CO_3 were used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1, 50:1, 30:1) to yield 39 mg of the product as a colorless oil: 40 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 6.93 – 6.88 (m, 2H), 3.85 (q, *J* = 7.3 Hz, 1H), 3.81 (s, 3H), 1.62 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 159.4, 129.2, 127.9, 121.9, 114.6, 55.5, 30.6, 21.6.

2-(4-(Trifluoromethoxy)phenyl)propionitrile (2f)[2] [CAS: 1096868-23-3]



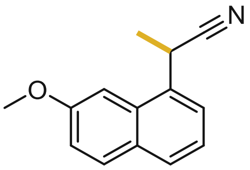
The title compound was prepared according to general procedure B from commercially available starting material. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1) to yield 74 mg of the product as a yellow oil: 57 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 2H), 7.29 – 7.20 (m, 2H), 3.92 (q, *J* = 7.3 Hz, 1H), 1.66 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 149.0, 135.8, 128.4, 121.8, 121.2, 119.2, 30.8, 21.5.

^{19}F-NMR (376 MHz, $CDCl_3$) δ -57.9.

2-(7-Methoxynaphth-1-yl) propionitrile (2g)[5] [CAS: 259866-21-2]

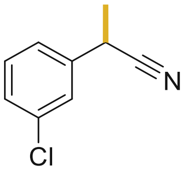


The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 1.5 equivalents of trimethylphenyl ammonium iodide were used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1, 50:1, 30:1) to yield 70 mg of the product as a yellow solid: 55 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.8, 0.7 Hz, 1H), 7.77 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.36 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.24 – 7.18 (m, 2H), 4.53 (q, *J* = 7.2 Hz, 1H), 3.97 (s, 3H), 1.81 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 158.5, 131.2, 131.1, 131.0, 129.6, 128.8, 125.4, 123.4, 121.9, 118.5, 101.4, 55.5, 28.5, 20.1.

2-(3-Chlorophenyl)propionitrile (2h)[6] [CAS: 14271-35-3]

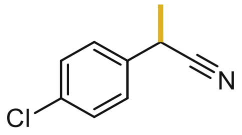


The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 1 equivalent trimethylphenyl ammonium iodide was used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1) to yield 50 mg of the product as a colorless oil: 50 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 4H), 3.88 (q, *J* = 7.3 Hz, 1H), 1.64 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 139.0, 135.1, 130.6, 128.5, 127.1, 125.1, 121.0, 31.0, 21.4.

2-(4-Chlorophenyl)propionitrile (2i)[7] [CAS: 2184-88-5]

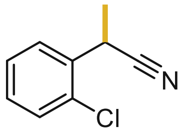


The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 1 equivalent trimethylphenyl ammonium iodide was used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1) to yield 51 mg of the product as a colorless oil: 51 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 4H), 3.88 (q, *J* = 7.3 Hz, 1H), 1.63 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 135.6, 134.2, 129.4, 128.2, 121.2, 30.8, 21.5.

2-(2-Chlorophenyl)propionitrile (2j)[6] [CAS: 75920-46-6]

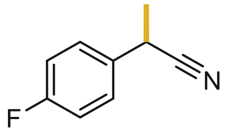


The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 1.5 equivalents of trimethylphenyl ammonium iodide were used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1) to yield 70 mg of the product as a colorless oil: 70 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.40 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.31 (dtd, *J* = 23.5, 7.7, 1.8 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 1H), 1.63 (d, *J* = 7.2 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 134.9, 132.6, 130.2, 129.6, 128.4, 127.9, 121.1, 29.0, 20.1.

2-(4-Fluorophenyl)propionitrile (2k)[2] [CAS: 51965-61-8]



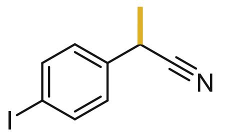
The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 1.5 equivalents of trimethylphenyl ammonium iodide were used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1, 50:1, 30:1) to yield 56 mg of the product as a colorless oil: 63 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 2H), 7.13-7.03 (m, 2H), 3.89 (q, *J* = 7.3 Hz, 1H), 1.63 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 162.5 (d, *J* = 247.2 Hz), 133.0 (d, *J* = 3.3 Hz), 128.6 (d, *J* = 8.4 Hz), 116.2 (d, *J* = 21.9 Hz), 30.7, 21.6.

^{19}F-NMR (376 MHz, $CDCl_3$) δ -113.9.

2-(4-Iodophenyl)propionitrile (2l)[8] [CAS: 442513-17-9]

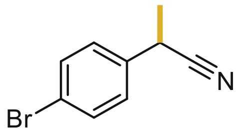


The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 1.5 equivalents of trimethylphenyl ammonium iodide were used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et$_2$O 100:1, 70:1, 60:1) to yield 90 mg of the product as a yellow oil: 58 %.

^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.76 – 7.69 (m, 2H), 7.15 – 7.07 (m, 2H), 3.85 (q, *J* = 7.3 Hz, 1H), 1.63 (d, *J* = 7.3 Hz, 3H)

^{13}C{1H} NMR (101 MHz, CDCl$_3$) δ 138.3, 136.8, 128.7, 121.1, 93.7, 31.0, 21.4.

2-(4-Bromophenyl)propionitrile (2m)[2] [CAS: 42186-06-1]

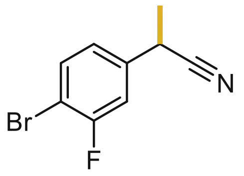


The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 1.5 equivalents of trimethylphenyl ammonium iodide were used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et$_2$O 100:1, 70:1) to yield 60 mg of the product as a yellow oil: 47 %.

^{1}H-NMR (400 MHz, CDCl$_3$) 7.56 – 7.51 (m, 2H), 7.29 – 7.22 (m, 2H), 3.88 (q, *J* = 7.3 Hz, 1H), 1.64 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, CDCl$_3$) δ 136.2, 132.4, 128.5, 122.2, 121.1, 30.9, 21.4.

2-(4-Bromo-3-fluorophenyl)propionitrile (2n) [CAS: 1823790-62-0]



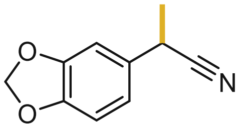
The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 1 equivalent trimethylphenyl ammonium iodide was used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et$_2$O 100:1, 70:1, 50:1, 30:1) to yield 79 mg of the product as a yellow oil: 57 %.

^{1}H-NMR (400 MHz, CDCl$_3$) δ 757 (ddd, *J* = 9.6, 7.5, 2.2 Hz, 1H), 7.18-7.11 (m, 1H), 7.08-7.02 (m, 2H), 3.88 (q, *J* = 7.3 Hz, 1H), 1.64 (d, *J* = 7.3 Hz, 2H).

^{13}C{1H} NMR (101 MHz, CDCl$_3$) δ 159.4 (d, *J* = 249.1 Hz), 138.7, 123.7 (d, *J* = 3.6 Hz), 115.3 (d, *J* = 23.9 Hz), 108.95 (d, *J* = 21.2 Hz), 30.8, 21.2.

^{19}F-NMR (376 MHz, CDCl$_3$) δ -105.28.

2-(Benzo[d][1,3]dioxol-5-yl)propionitrile (2o)[2] [CAS: 67301-74-0]

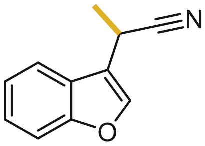


The title compound was prepared according to general procedure B from commercially available starting material. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1, 50:1) to yield 65 mg of the product as a yellow oil: 62 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 – 6.79 (m, 3H), 5.98 (s, 2H), 3.81 (q, *J* = 7.3 Hz, 1H), 1.61 (d, *J* = 7.2 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 148.4, 147.5, 130.9, 121.7, 120.2, 108.7, 107.3, 101.5, 31.1, 21.7.

2-(Benzofuran-3-yl)propionitrile (2p) [CAS: 1538391-46-6]

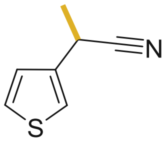


The title compound was prepared according to general procedure B from commercially available starting material. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1, 50:1, 30:1) to yield 61 mg of the product as a colorless oil: 60 %.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddd, *J* = 7.6, 1.4, 0.8 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.41 – 7.28 (m, 2H), 4.09 (q, *J* = 7.2 Hz, 1H), 1.77 (d, *J* = 7.2 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 155.8, 141.8, 125.5, 125.3, 123.2, 120.5, 119.4, 117.0, 112.1, 21.8, 18.9.

2-(Thiophen-3-yl)propionitrile (2q)[9] [CAS: 188908-91-0]

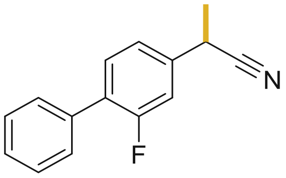


The title compound was prepared according to general procedure B from commercially available starting material. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1, 50:1) to yield 33 mg of the product as a yellow oil: 40 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.07 (dd, *J* = 5.0, 1.4 Hz, 1H), 3.99 (q, *J* = 7.2 Hz, 1H), 1.66 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 137.1, 127.3, 126.1, 121.9, 121.5, 26.7, 20.4.

2-(3-Fluoro-4-phenylphenyl)propionitrile (2r)[10] [CAS: 74648-00-3]



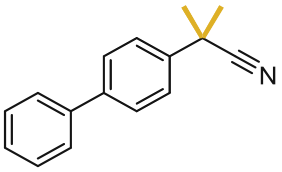
The title compound was prepared according to general procedure B from 2-fluorobiphenyl-4-acetonitrile (**5**) starting material. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1, 50:1) to yield 68 mg of the product as a white solid: 50 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 8.1, 1.5 Hz, 2H), 7.50 – 7.43 (m, 3H), 7.43 – 7.37 (m, 1H), 7.25 – 7.15 (m, 2H), 3.94 (q, *J* = 7.3 Hz, 1H), 1.69 (d, *J* = 7.3 Hz, 3H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 159.9 (d, *J* = 249.8 Hz), 138.3 (d, *J* = 7.7 Hz), 135.1 (d, *J* = 1.4 Hz), 131.6 (d, *J* = 4.0 Hz), 129.1 (d, *J* = 3.0 Hz), 128.9, 128.7, 128.1, 122.8 (d, *J* = 3.6 Hz), 121.1, 114.8 (d, *J* = 24.5 Hz), 30.8, 21.3.

^{19}F-NMR (376 MHz, $CDCl_3$) δ -116.3.

2-Methyl-2-(4-phenylphenyl)propionitrile (3a)[10] [CAS: 92962-22-6]

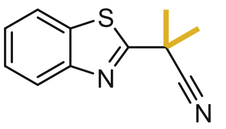


The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 2 equivalents NaO*t*Bu were used as the base. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1) to yield 94 mg of the product as a yellow solid: 71 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.53 (m, 6H), 7.50-7.43 (m, 2H), 7.41-7.34 (m, 1H), 1.78 (s, 6H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 140.9, 140.5, 140.4, 128.9, 127.7, 127.7, 127.2, 125.7, 124.6, 37.1, 29.3.

2-(1,3-Benzothiazol-2-yl)-2-methylpropionitrile (3b)[11] [CAS: 66277-05-2]

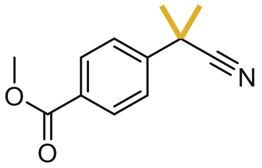


The title compound was prepared according to general procedure B from commercially available starting material. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 70:1, 50:1, 10:1) to yield 68 mg of the product as a pale-yellow oil: 56 %.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.52 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 1.94 (s, 6H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.1, 152.9, 135.0, 126.6, 125.8, 123.6, 122.3, 121.8, 38.0, 28.3.

Methyl 4-(2-cyanopropan-2-yl)benzoate (3c)[4] [CAS: 129488-73-9]

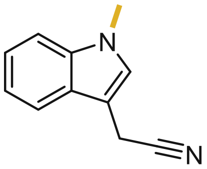


The title compound was prepared according to general procedure B from commercially available starting material, with the deviation that 3 equivalents of trimethylphenyl ammonium iodide were used. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 100:1, 70:1, 50:1) to yield 111 mg of the product as a yellow oil: 98 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.02 (m, 2H), 7.58 – 7.54 (m, 2H), 3.93 (s, 3H), 1.75 (s, 6H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 166.5, 146.4, 130.4, 129.9, 125.3, 124.0, 52.5, 37.5, 29.1

2-(1-Methylindol-3-yl)acetonitrile (4a)[12] [CAS: 51584-17-9]



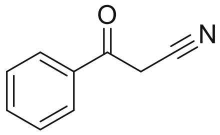
The title compound was prepared according to general procedure B from commercially available starting material. The crude residue was purified *via* column chromatography (10 g silica, pentane: Et_2O 10:1, 5:1, 2:1) to yield 94 mg of the product as a brown oil: 92 %.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.37 – 7.26 (m, 2H), 7.18 (ddt, J = 7.9, 6.8, 1.0 Hz, 1H), 7.09 (s, 1H), 3.83 (s, 2H), 3.78 (s, 3H) ppm.

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 137.0, 127.3, 126.4, 122.4, 119.7, 118.2, 118.1, 109.6, 102.9, 32.8, 14.3 ppm.

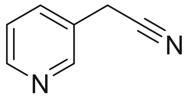
Unsuccessful Substrates

3-Oxo-3-phenylpropanenitrile [CAS: 614-16-4]



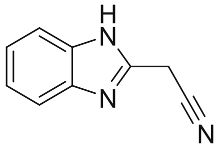
Following the general procedure B, the title compound was subjected to reaction conditions, and no product formed according to NMR analysis. Deviating to 1 equivalent of trimethylphenyl ammonium iodide no product formed according to NMR analysis either.

2-Pyridin-3-ylacetonitrile [CAS: 6443-85-2]



Following the general procedure B, the title compound was subjected to reaction conditions, and no product formed according to NMR analysis. Deviating to 3 equivalents of trimethylphenyl ammonium iodide and 3 equivalents of Cs_2CO_3 no product formed according to NMR analysis either. An aqueous workup procedure was also attempted.

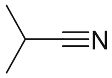
2-(1H-Benzimidazol-2-yl)acetonitrile [CAS: 4414-88-4]



Following the general procedure B, the title compound was subjected to reaction conditions, and no product formed according to NMR analysis. Deviating to 3 equivalents of trimethylphenyl ammonium iodide and 3 equivalents of Cs_2CO_3 no product formed according to NMR analysis either.

Following the general procedure B, the title compound was subjected to reaction conditions with the deviation that 2 equivalents NaO*t*Bu were used as the base. No product formed according to NMR analysis.

2-Methylpropanenitrile [CAS: 78-82-0]



Following the general procedure B, the title compound was subjected to reaction conditions, and no product formed according to NMR analysis.

NMR-Spectra of isolated compounds

2-Biphenyl-4-yl-propanenitrile (2a)

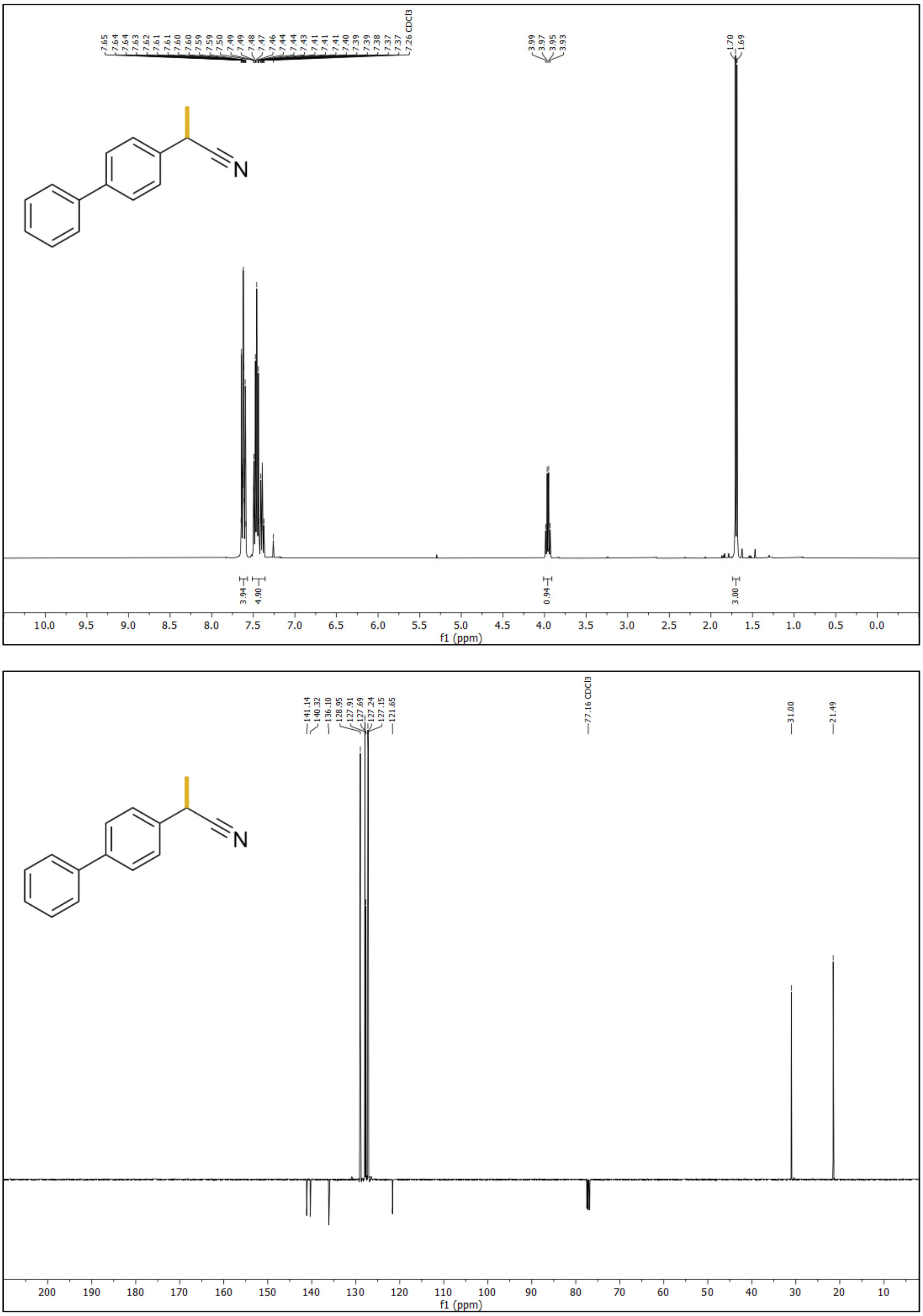


Figure 2: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-biphenyl-4-yl-propanenitrile (2a).

2-Phenylpropionitrile (2b)

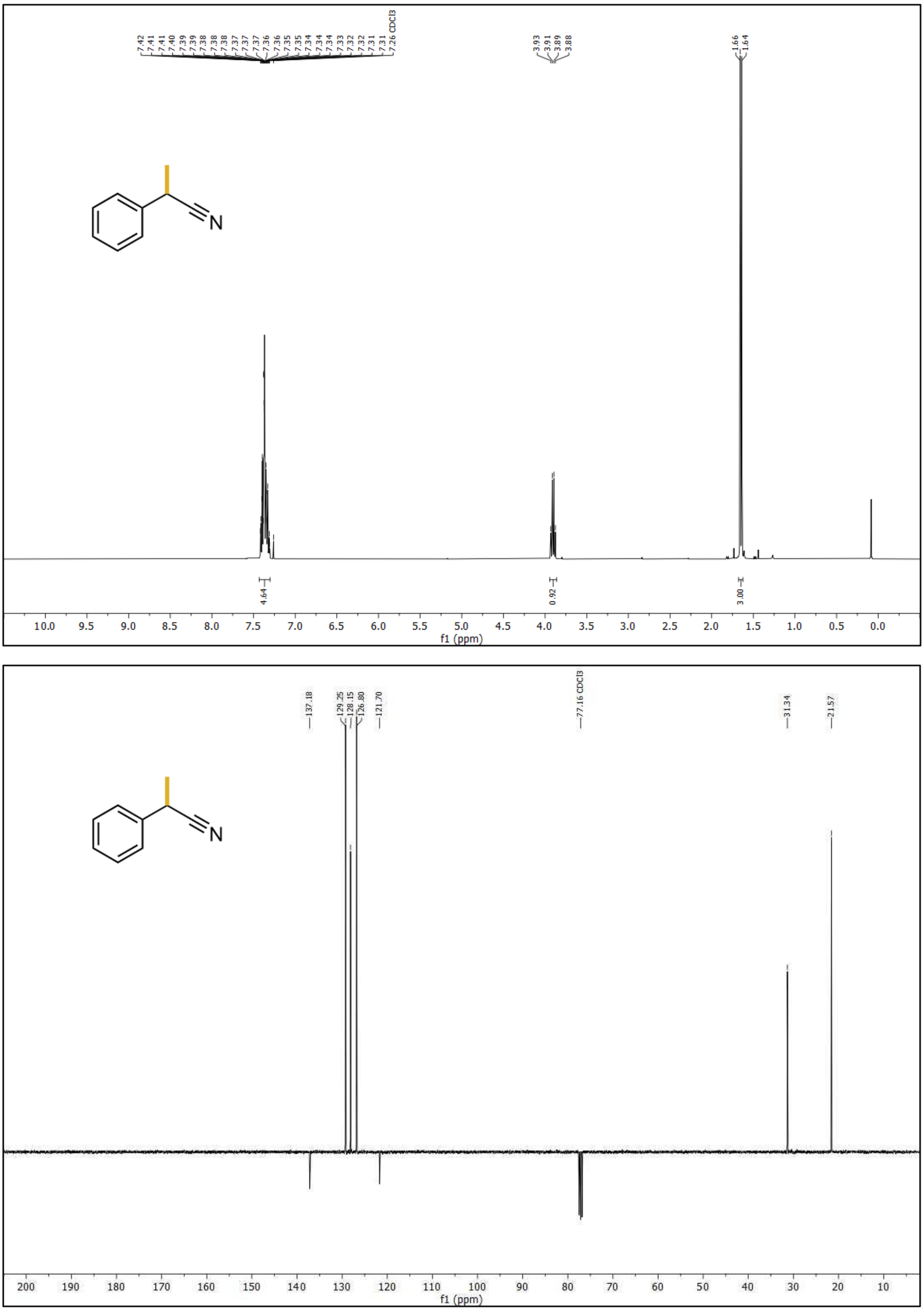


Figure 3: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-phenylpropionitrile (2b).

2-(2-Naphthyl)propionitrile (2c)

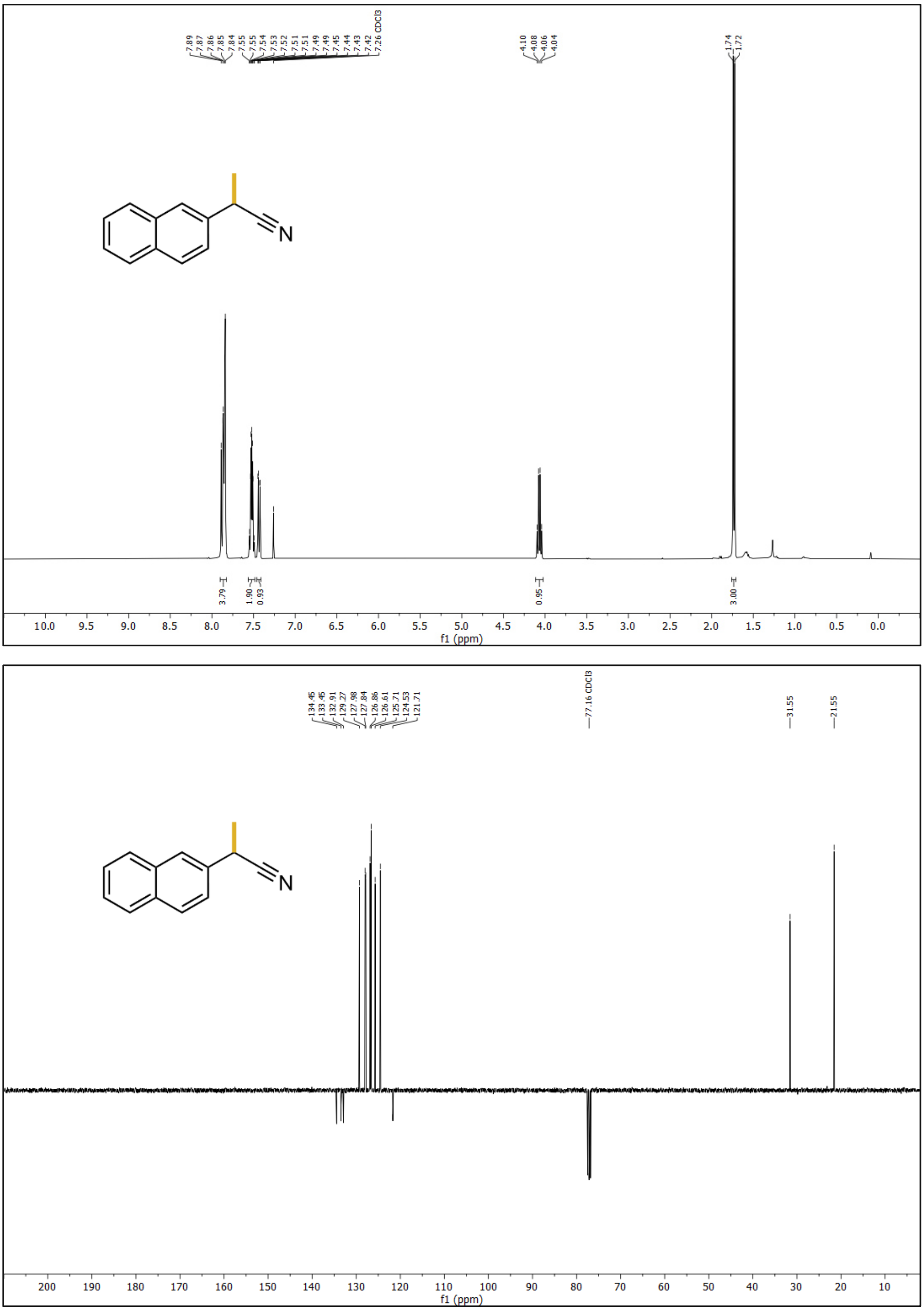
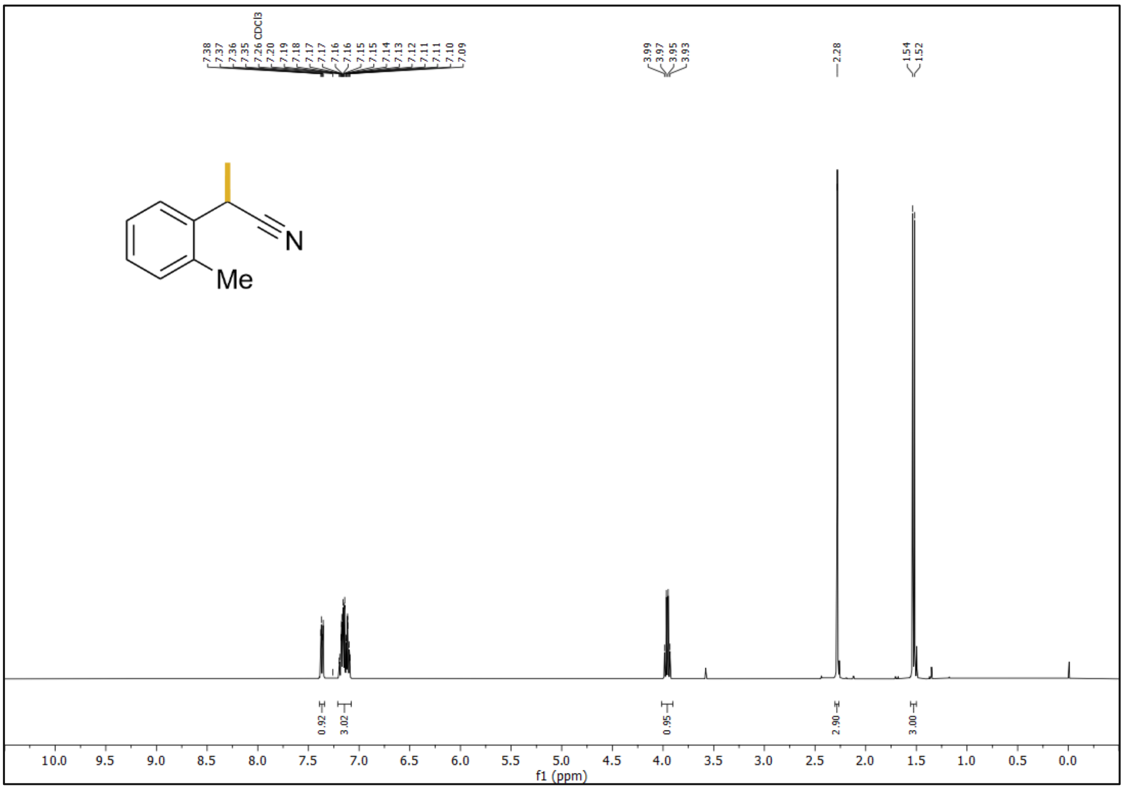


Figure 4: ^{1}H-NMR (400 MHz, $CDCl_3$) and $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) of 2-(2-naphthyl)propionitrile (2c).

2-(2-Methylphenyl)propionitrile (2d)



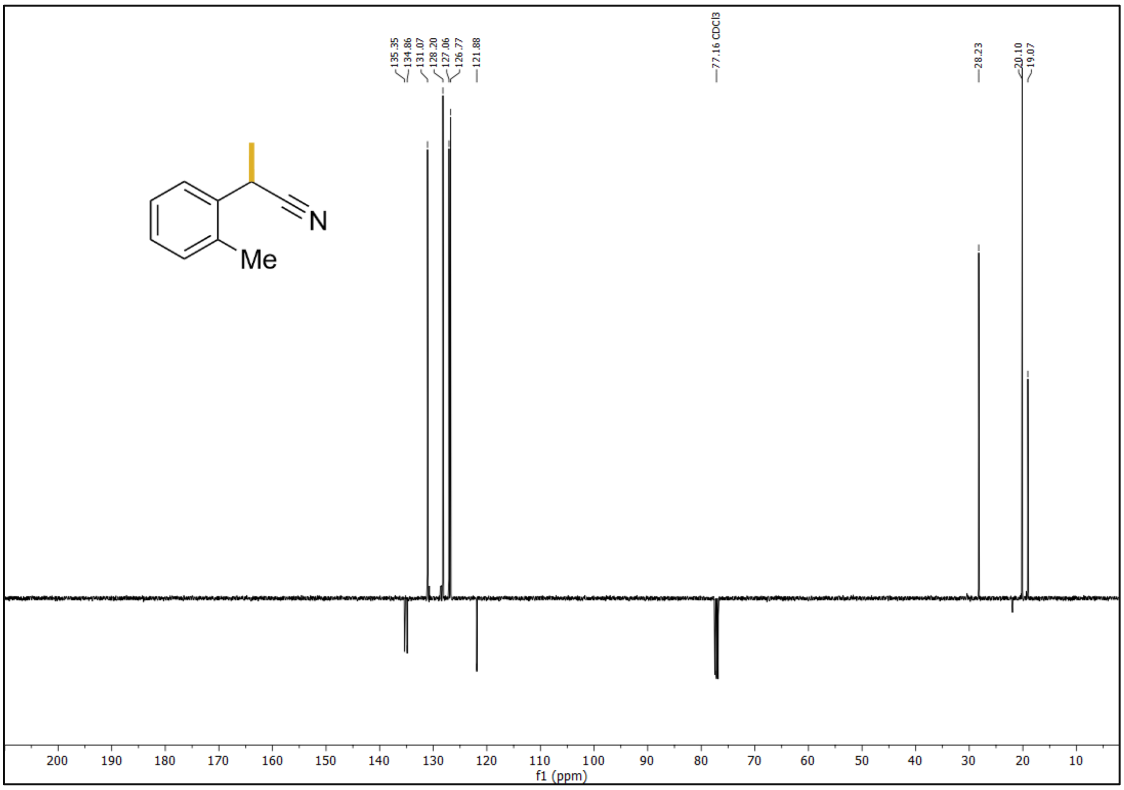


Figure 5: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-(2-methylphenyl)propionitrile (2d).

2-(4-Methoxyphenyl)propionitrile (2e)

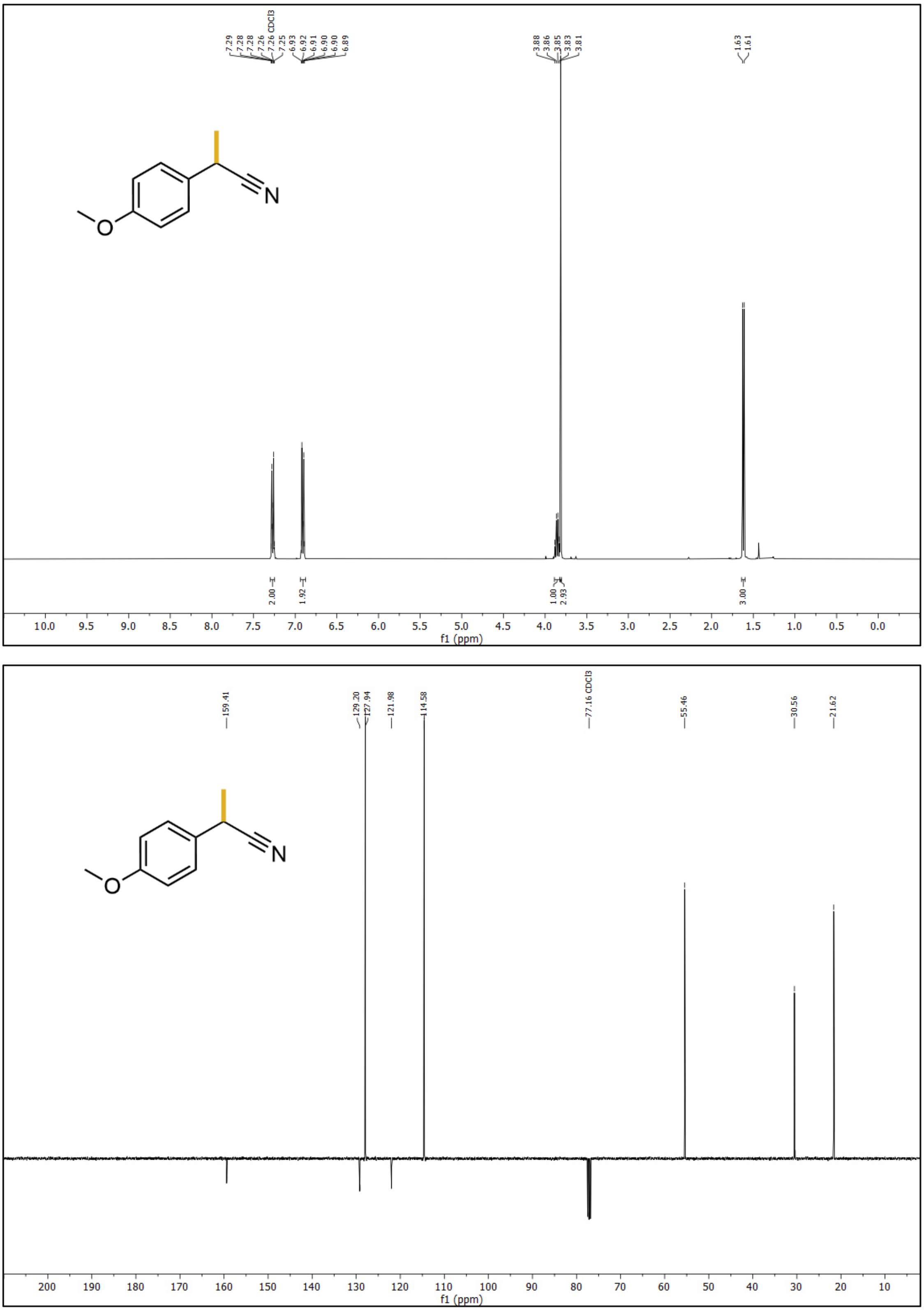
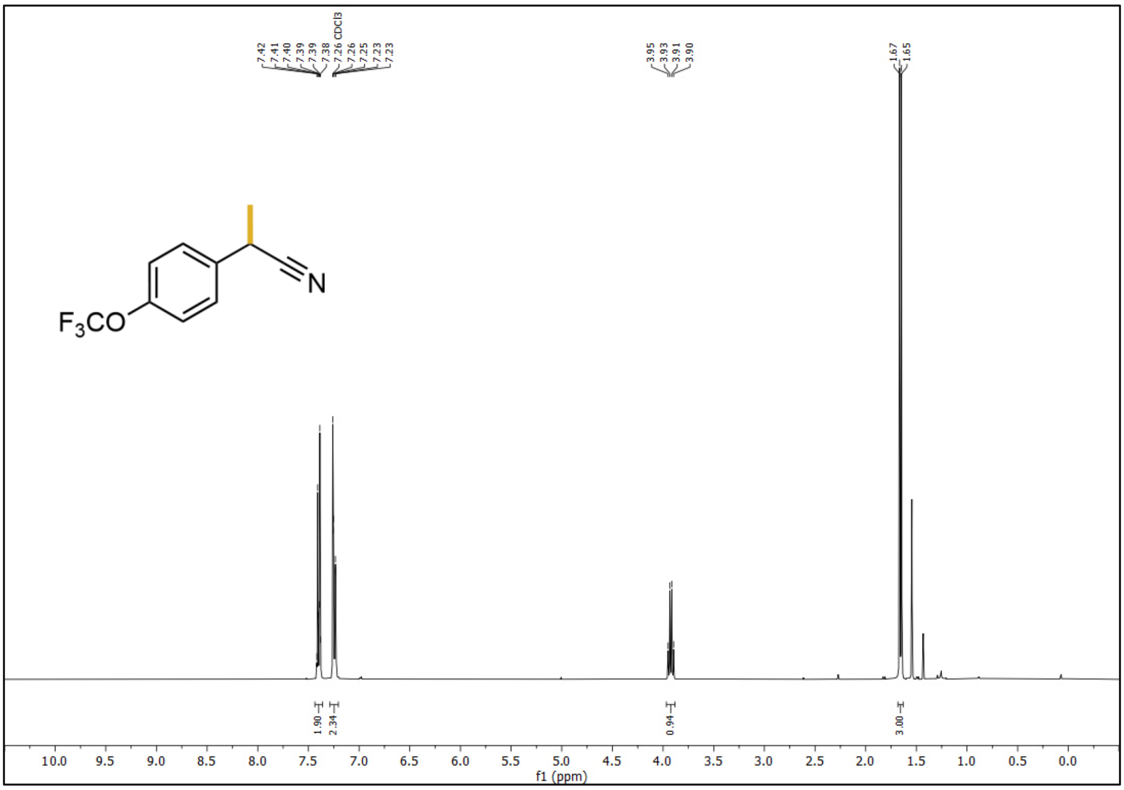
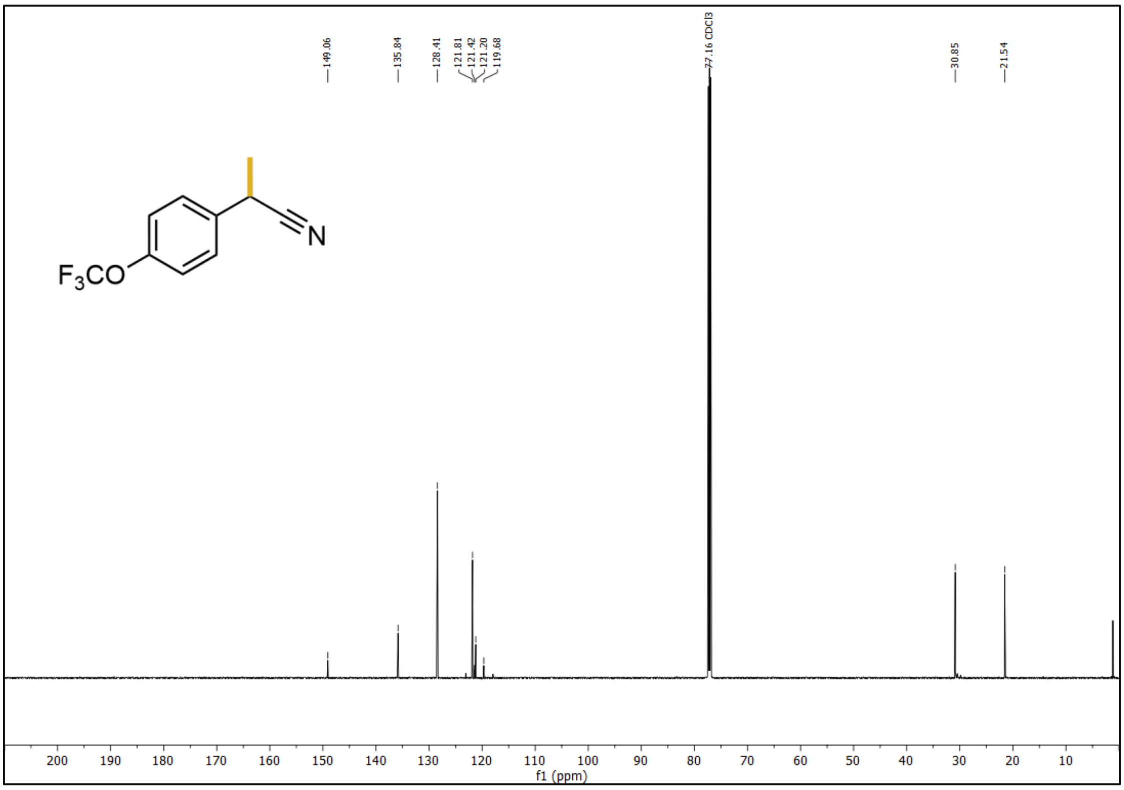


Figure 6: ¹H-NMR (400 MHz, CDCl$_3$) and ¹³C{1H} NMR (101 MHz, CDCl$_3$) of 2-(4-methoxyphenyl)propionitrile (2e).

2-(4-(Trifluoromethoxy)phenyl)propionitrile (2f)





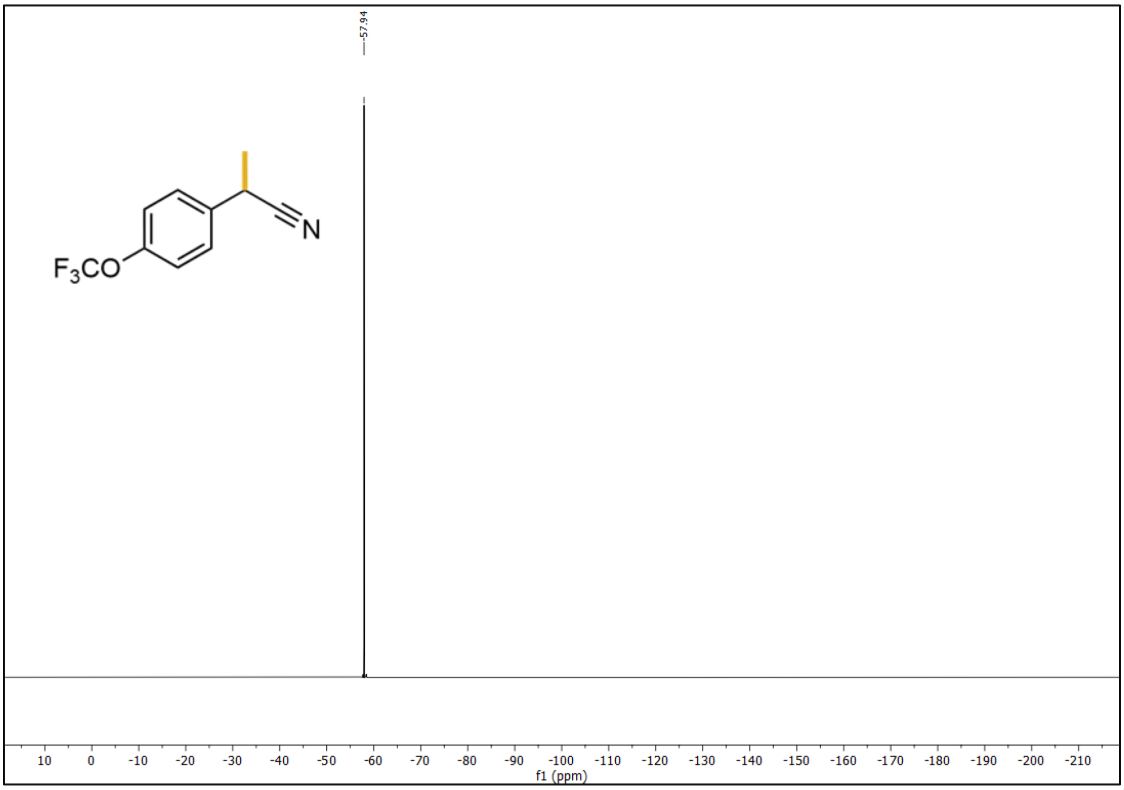


Figure 7: ^{1}H-NMR (400 MHz, CDCl$_3$), ^{13}C{1H} NMR (101 MHz, CDCl$_3$) and ^{19}F-NMR (376 MHz, CDCl$_3$) of 2-(4-(trifluoromethoxy)phenyl)propionitrile (2f).

2-(7-Methoxynaphth-1-yl) propionitrile (2g)

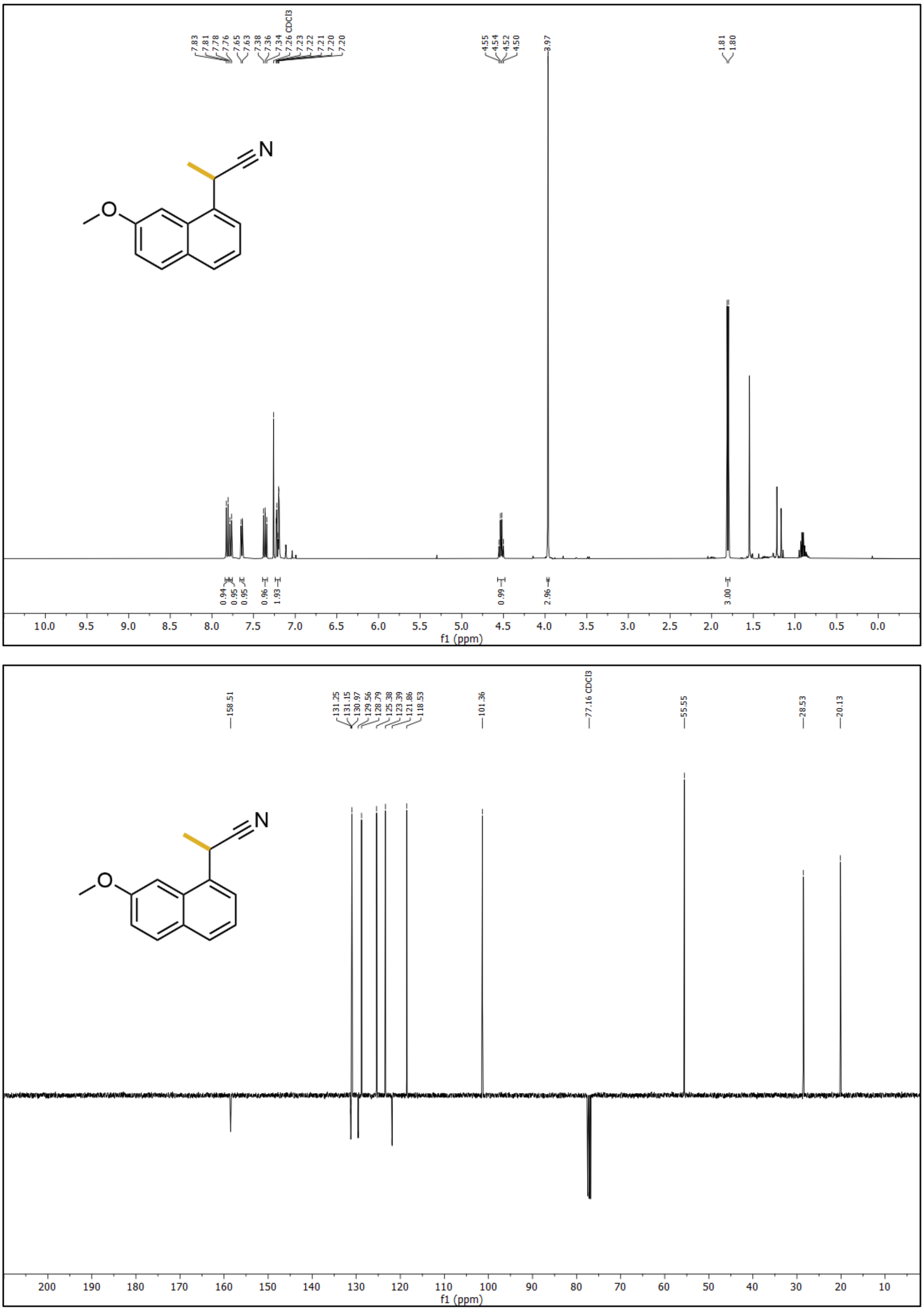


Figure 8: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-(7-methoxynaphth-1-yl) propionitrile (2g).

2-(3-Chlorophenyl)propionitrile (2h)

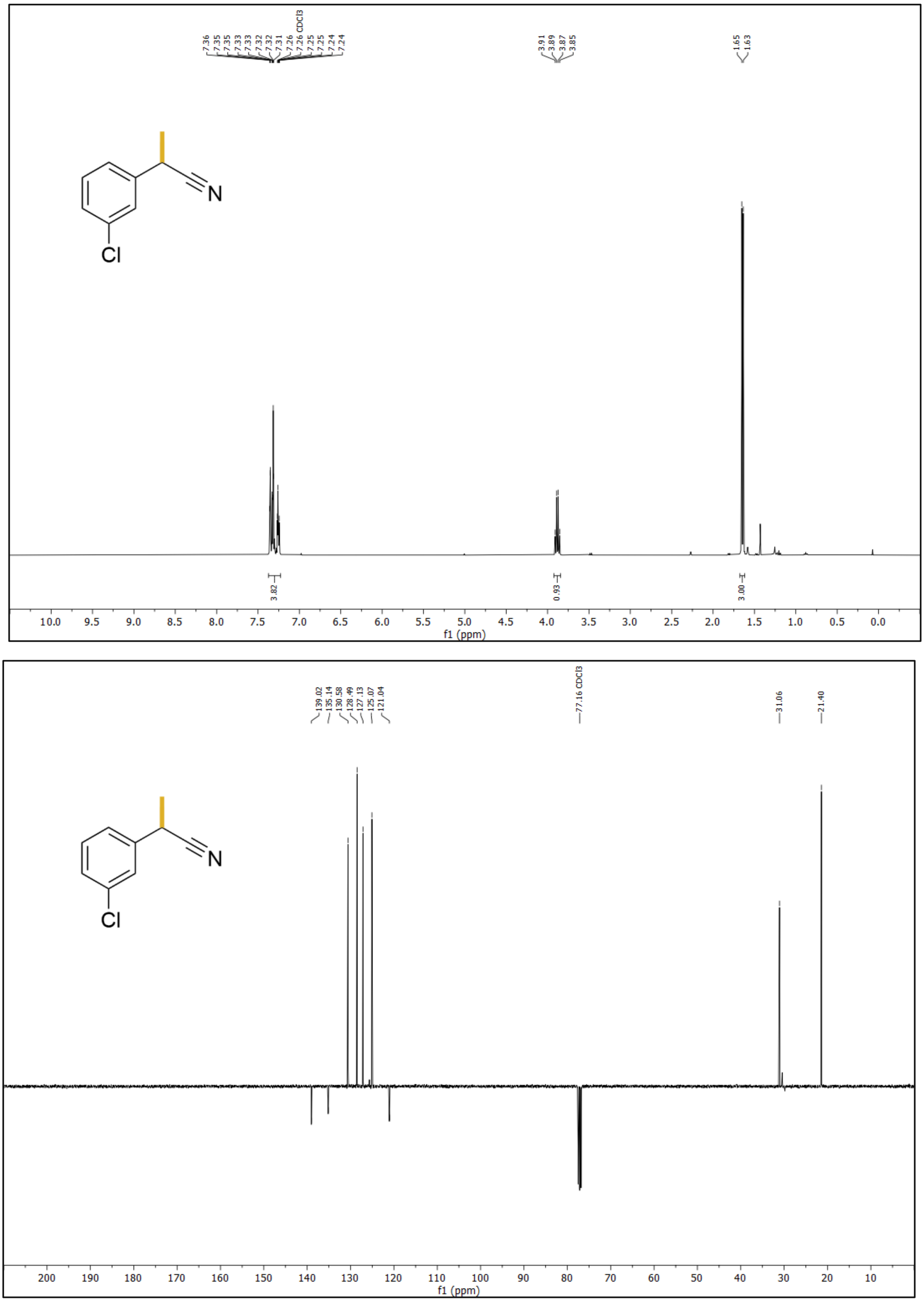


Figure 9: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C{1H} NMR (101 MHz, $CDCl_3$) 2-(3-chlorophenyl)propionitrile (2h).

2-(4-Chlorophenyl)propionitrile (2i)

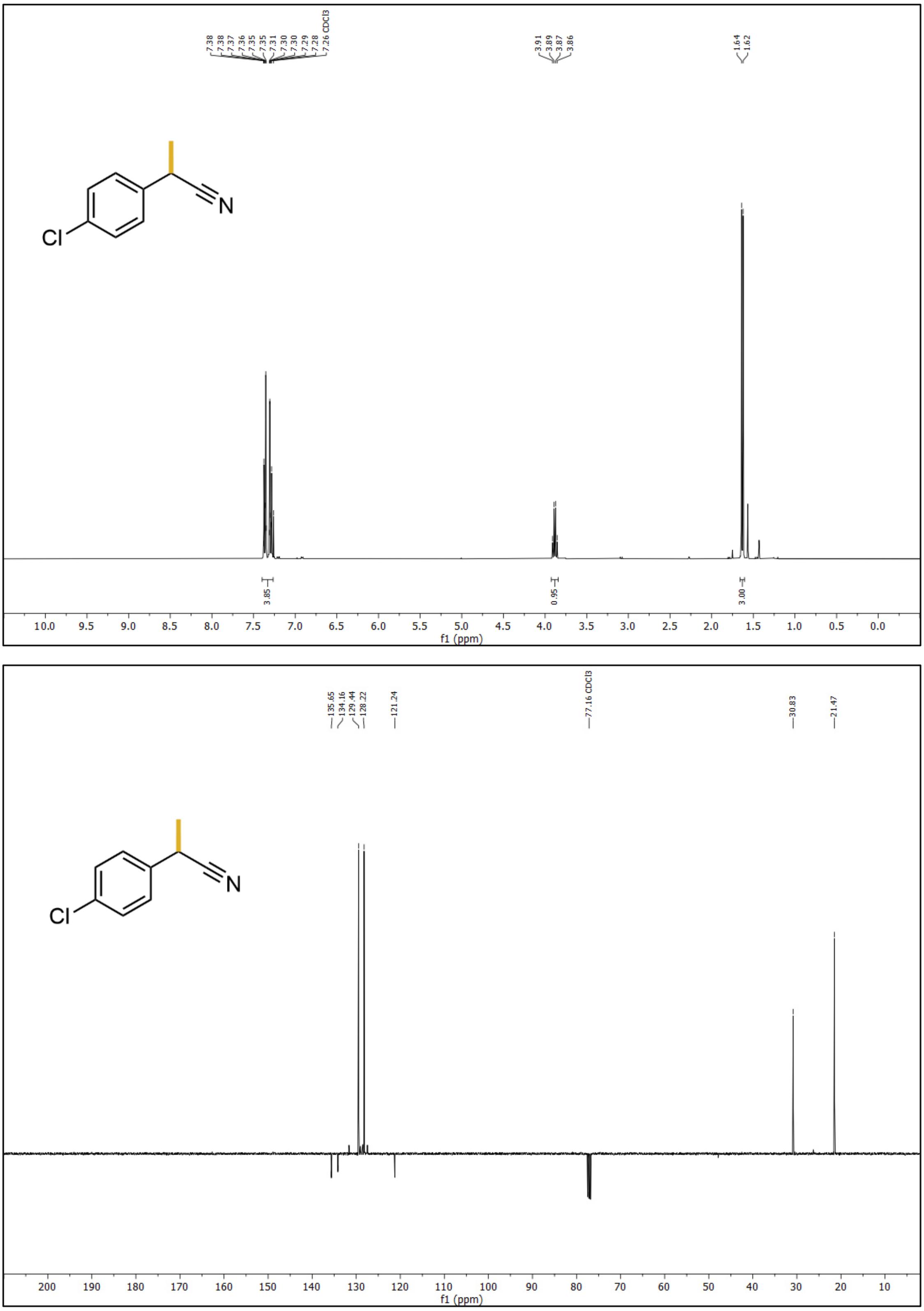


Figure 10: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-(4-chlorophenyl)propionitrile (2i).

2-(2-Chlorophenyl)propionitrile (2j)

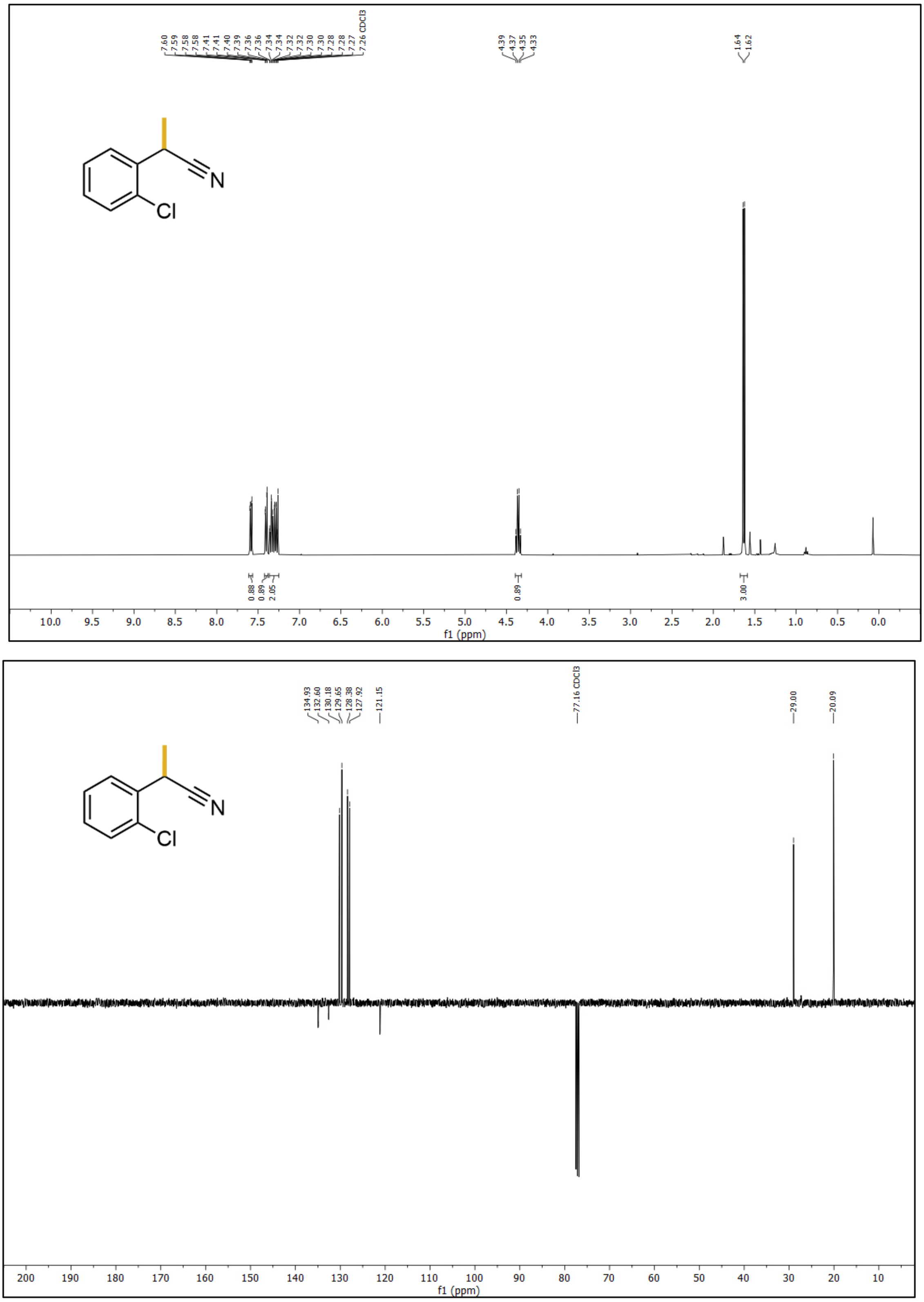
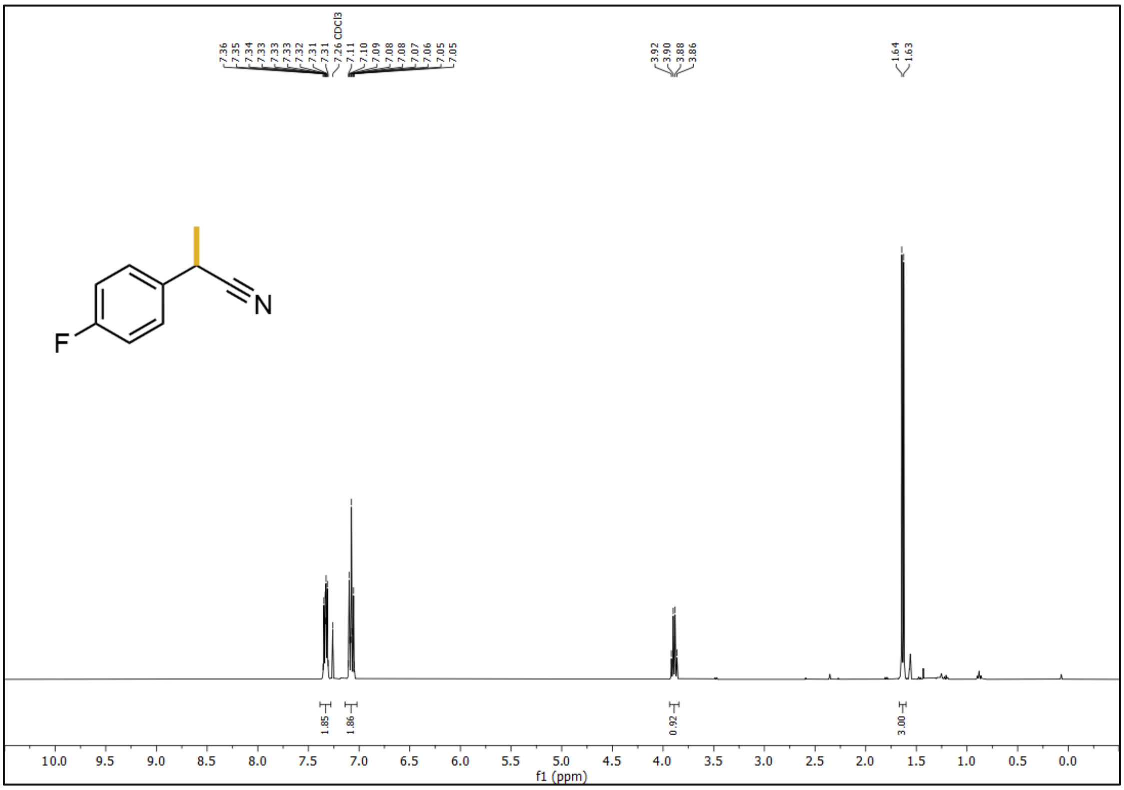
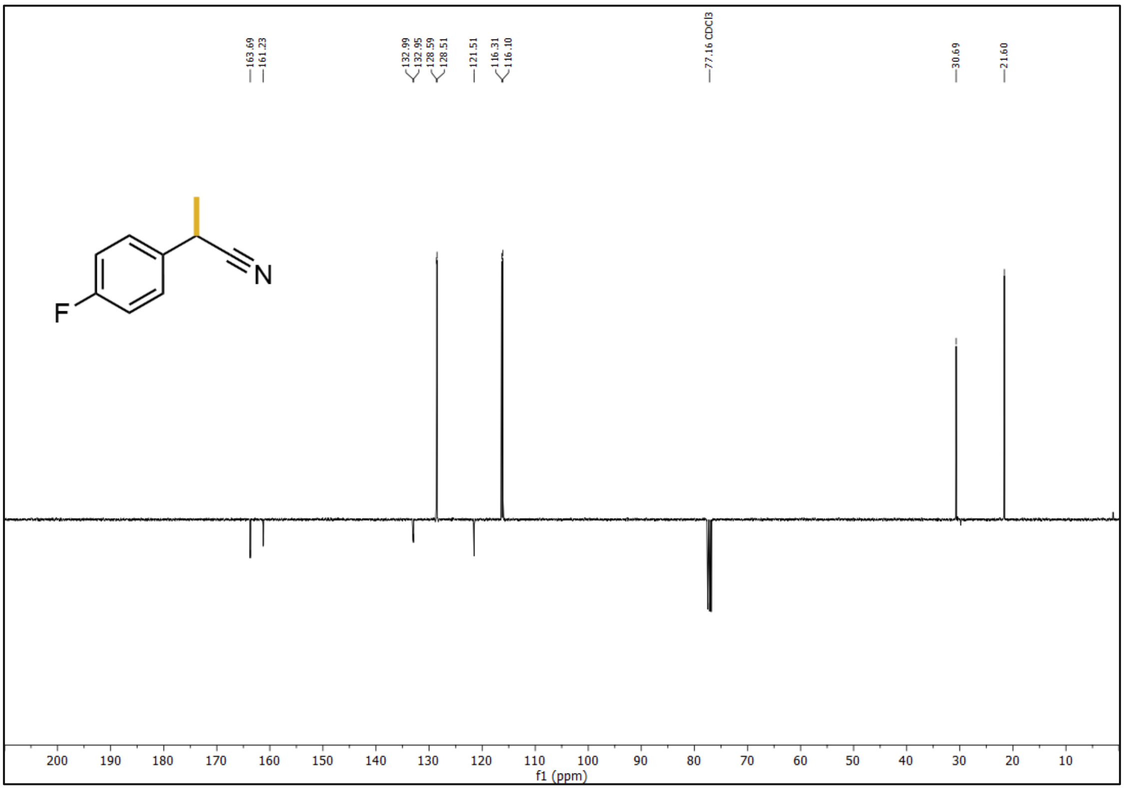


Figure 11: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-(2-chlorophenyl)propionitrile (2j).

2-(4-Fluorophenyl)propionitrile (2k)





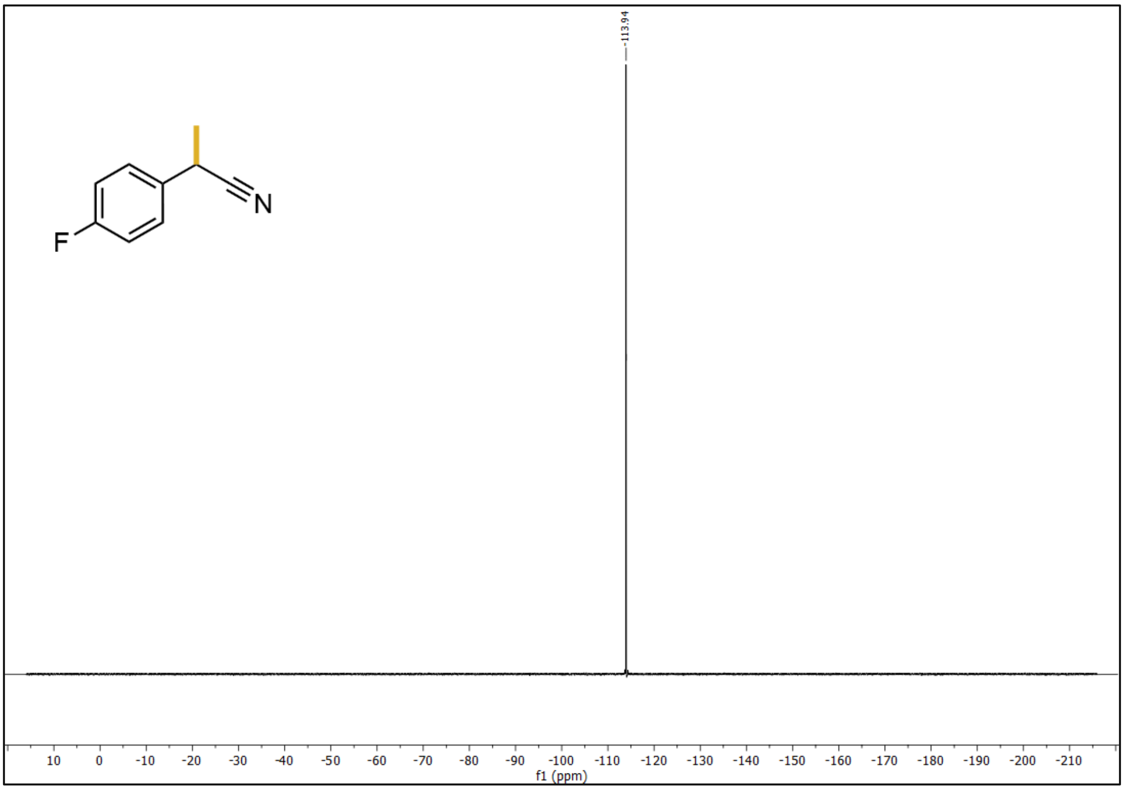


Figure 12: ^{1}H-NMR (400 MHz, CDCl$_3$), ^{13}C{1H} NMR (101 MHz, CDCl$_3$) and ^{19}F-NMR (376 MHz, CDCl$_3$) of 2-(4-fluorophenyl)propionitrile (2k).

2-(4-Iodophenyl)propionitrile (2l)

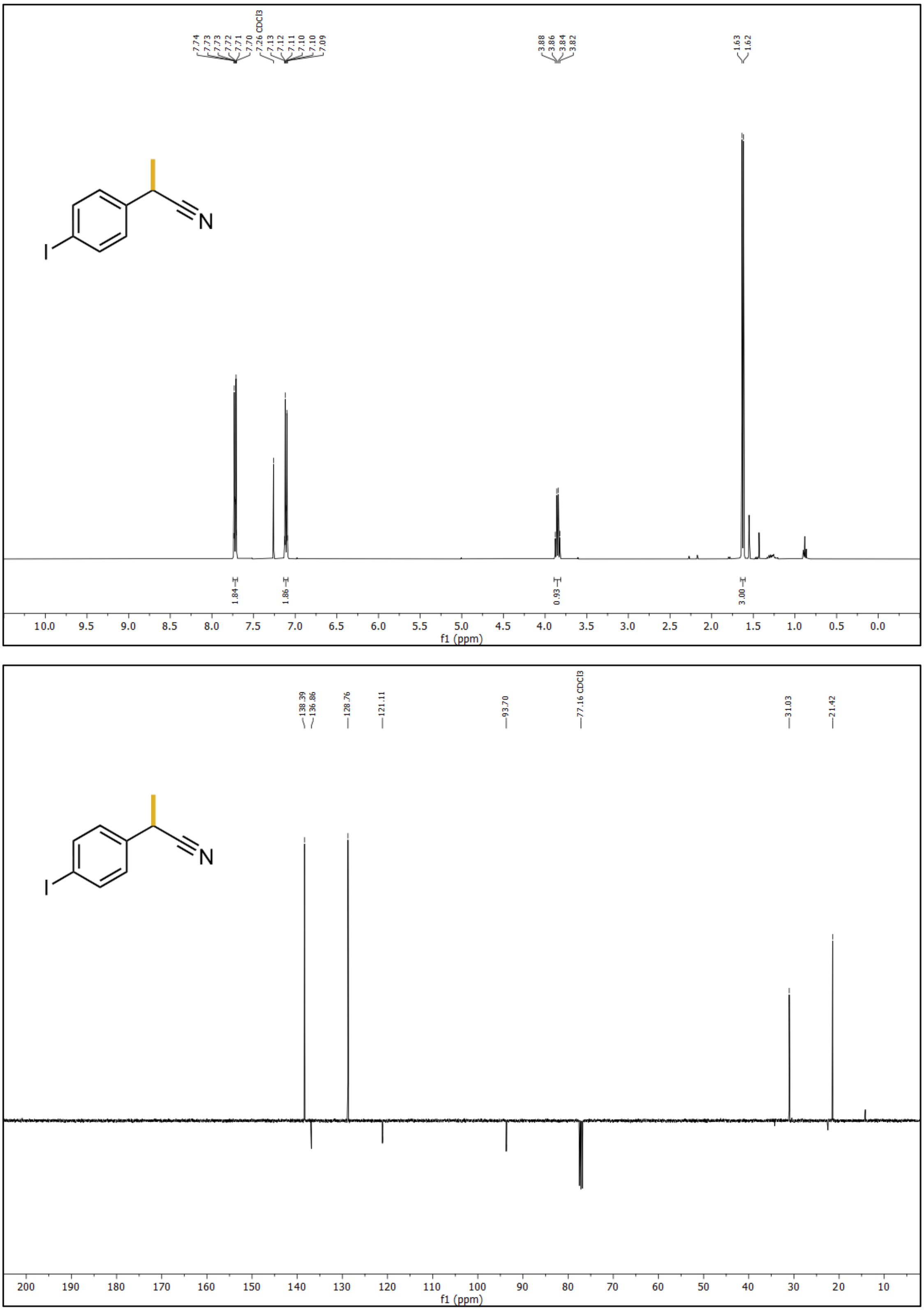


Figure 13: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-(4-iodophenyl)propionitrile (2l).

2-(4-Bromophenyl)propionitrile (2m)

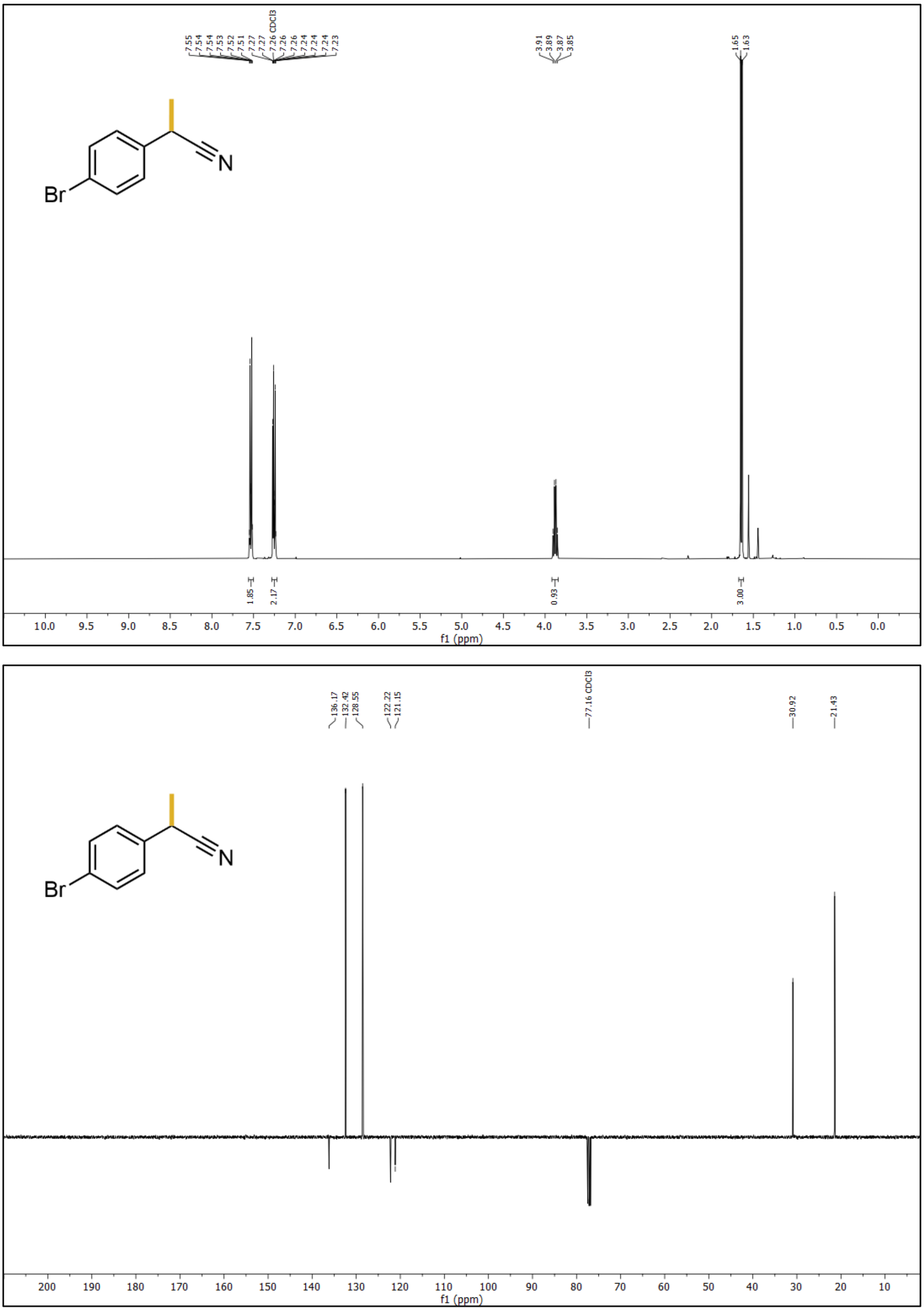
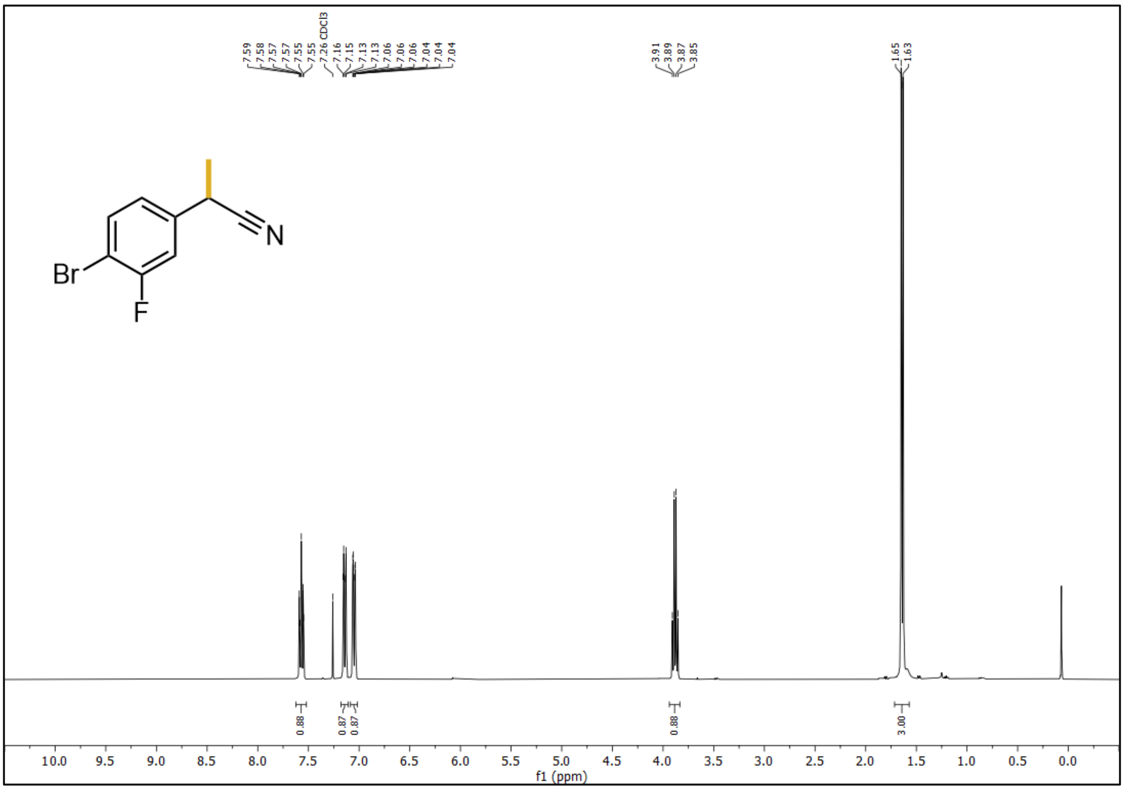
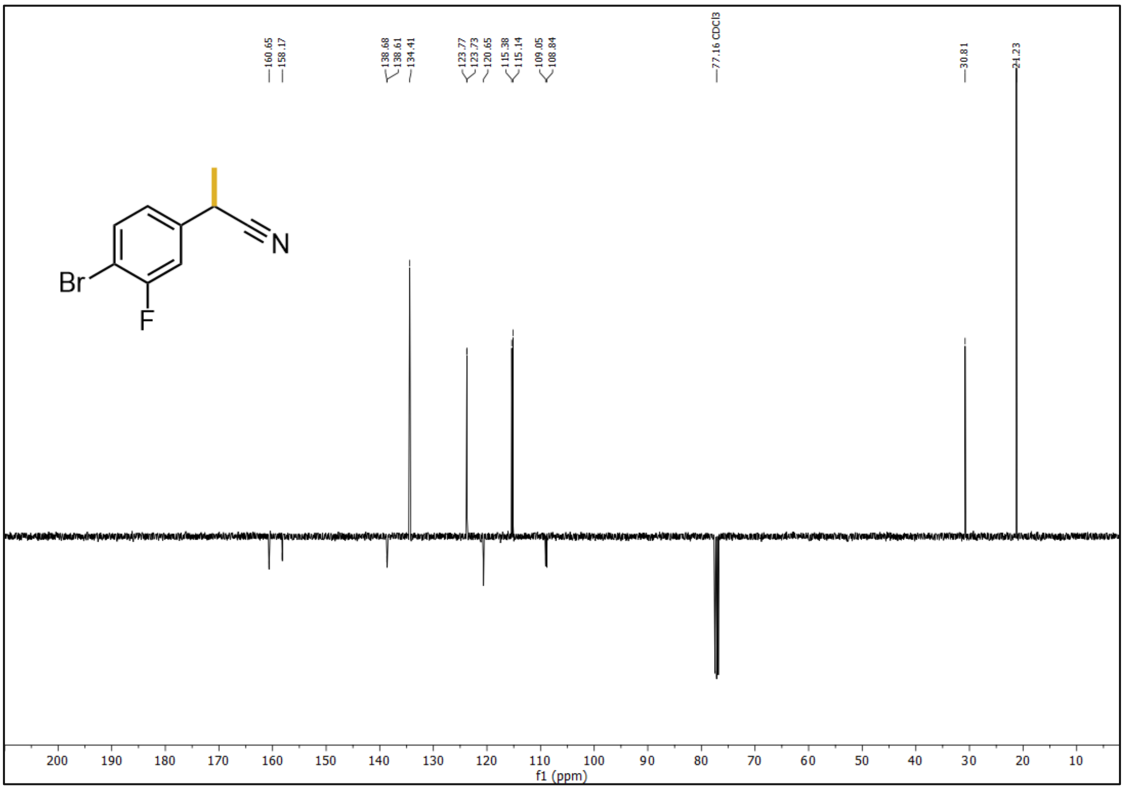


Figure 14: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-(4-bromophenyl)propionitrile (2m).

2-(4-Bromo-3-fluorophenyl)propionitrile (2n)





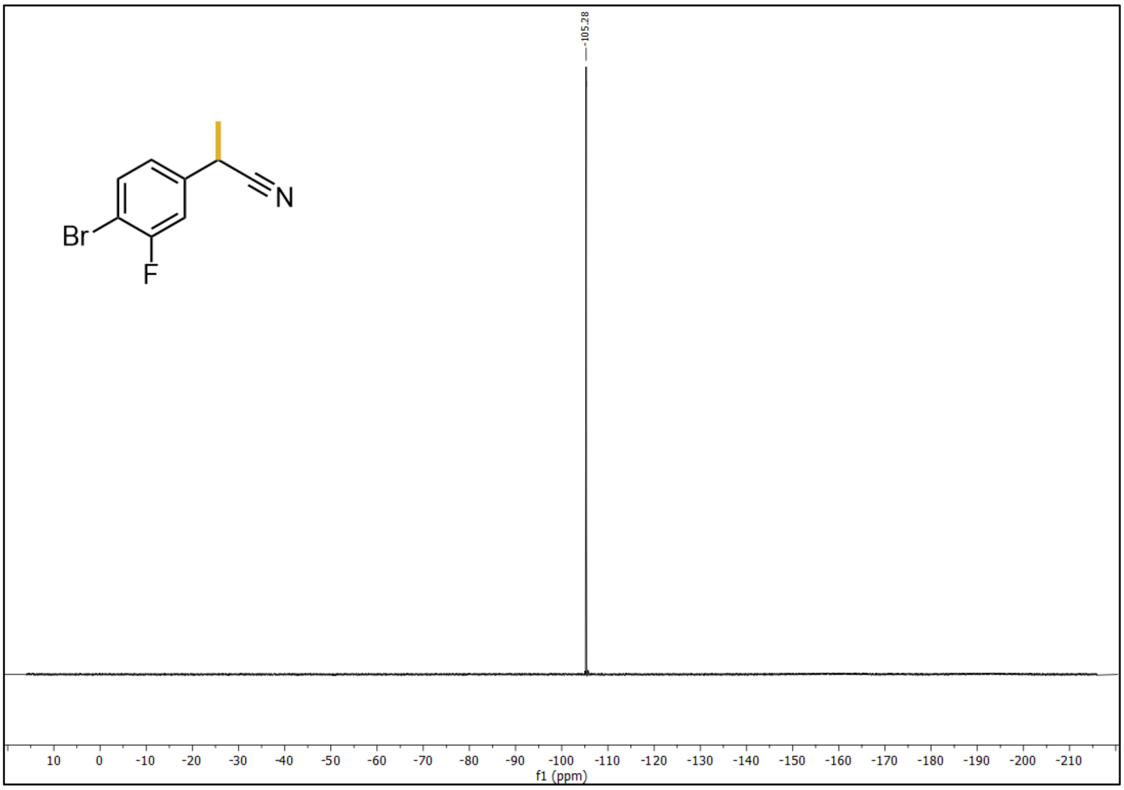


Figure 15: ^{1}H-NMR (400 MHz, $CDCl_3$), ^{13}C{1H} NMR (101 MHz, $CDCl_3$) and ^{19}F of 2-(4-bromo-3-fluorophenyl)propionitrile (2n).

2-(Benzo[d][1,3]dioxol-5-yl)propionitrile (2o)

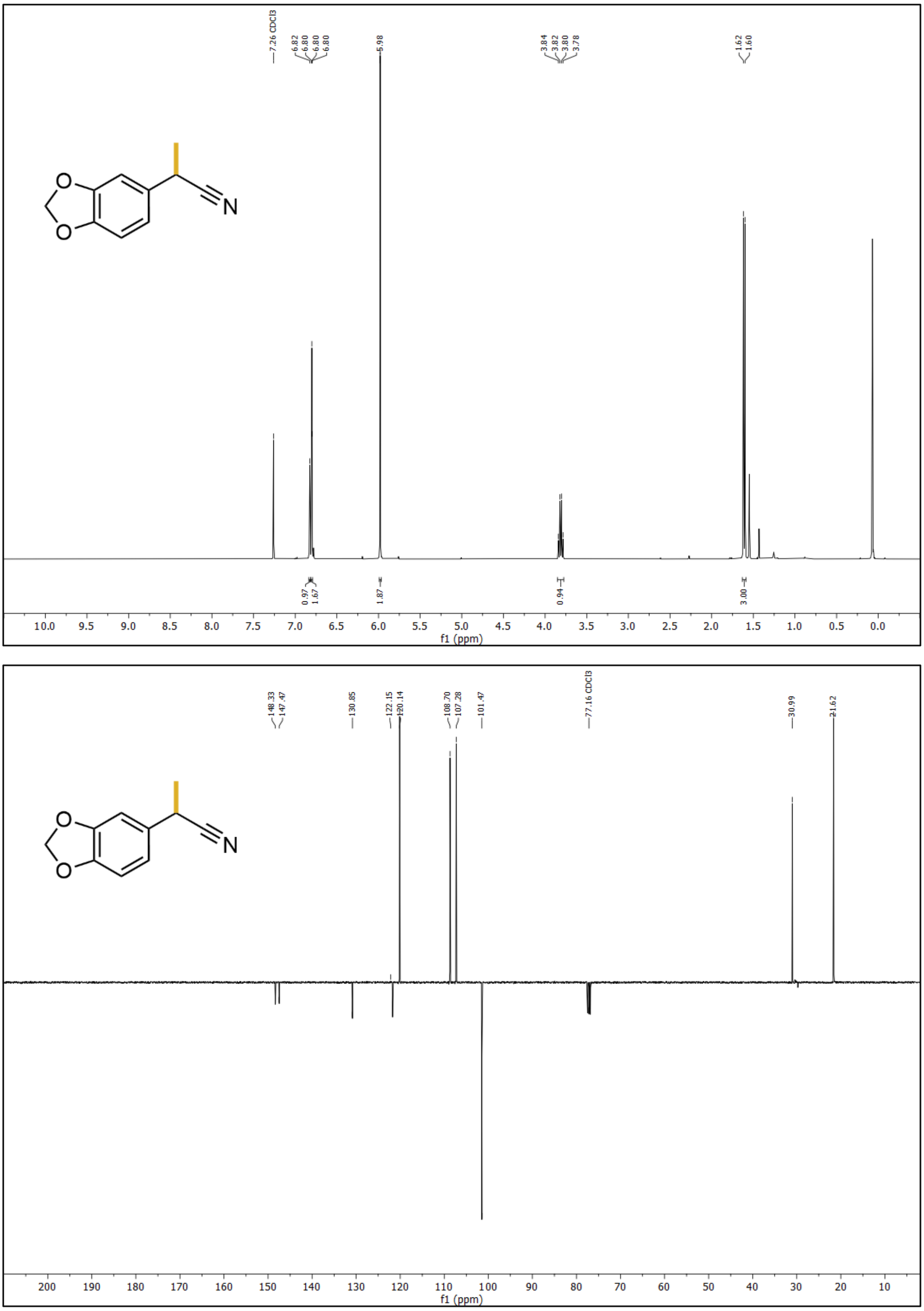
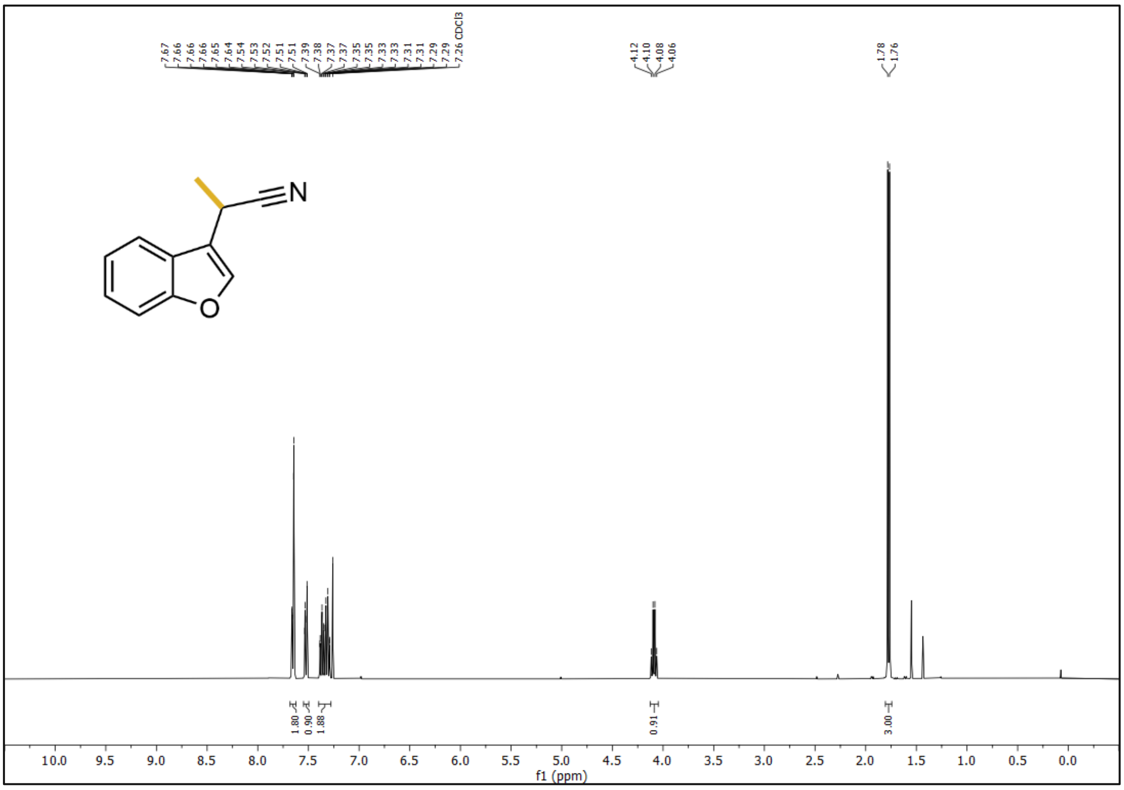


Figure 16: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-(benzo[d][1,3]dioxol-5-yl)propionitrile (2o).

2-(Benzofuran-3-yl)propionitrile (2p)



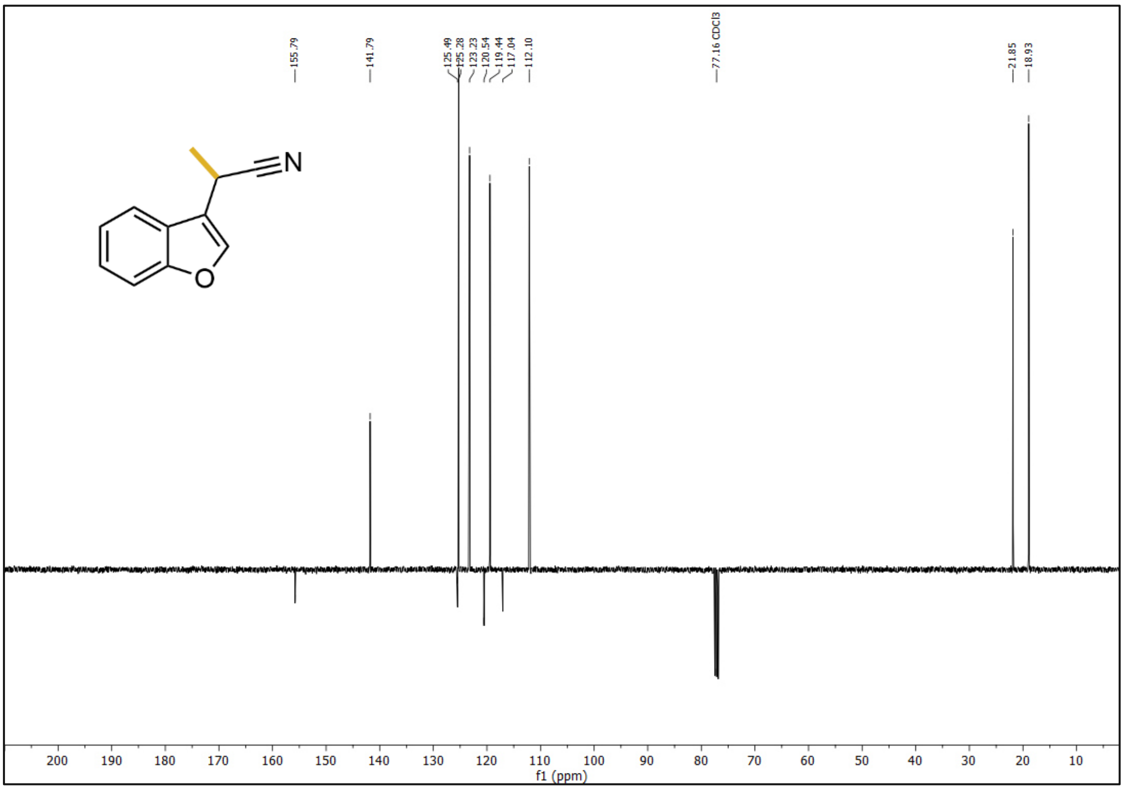


Figure 17: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C{1H} NMR (101 MHz, $CDCl_3$) of 2-(benzofuran-3-yl)propionitrile (2p).

2-(Thiophen-3-yl)propionitrile (2q)

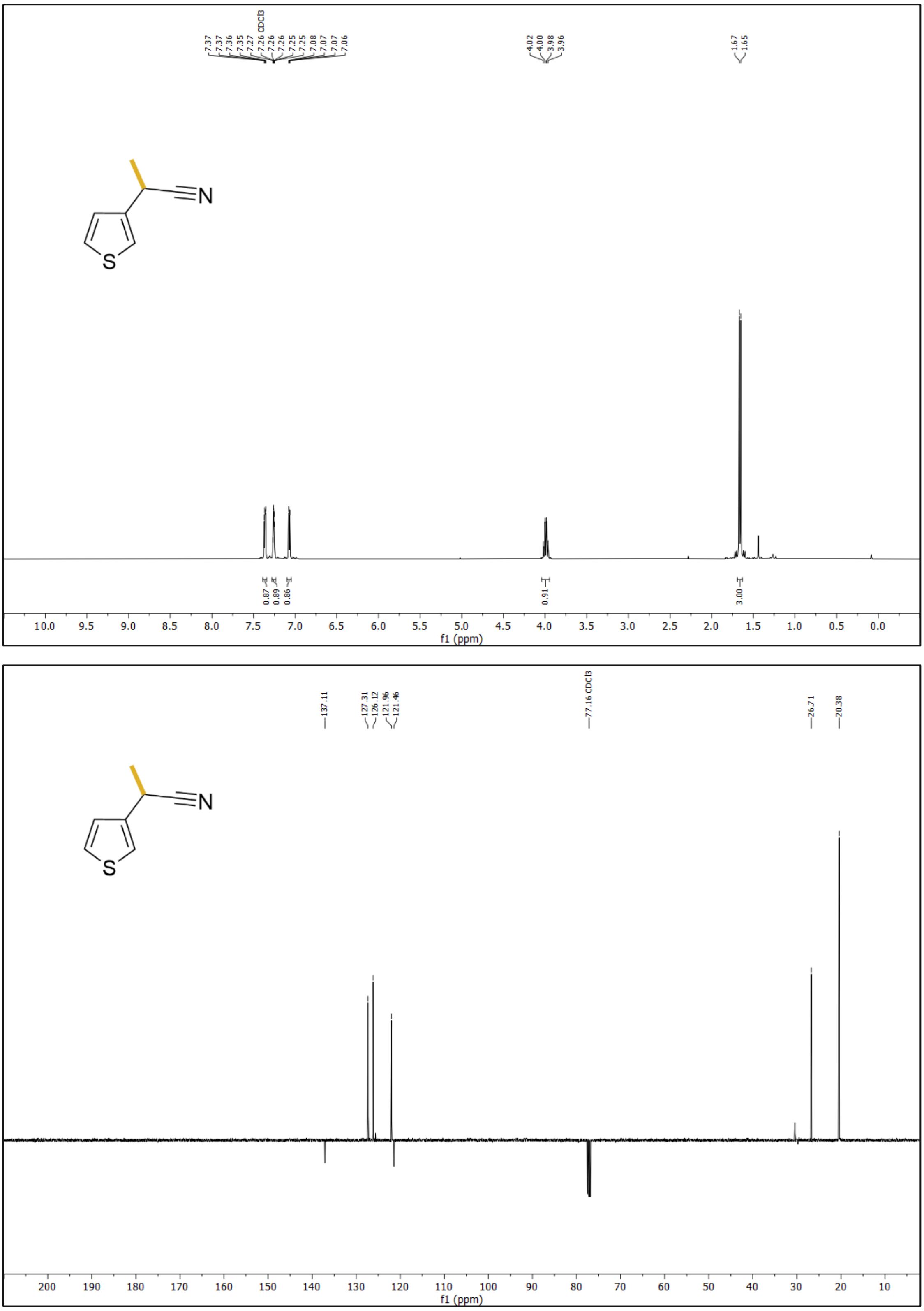
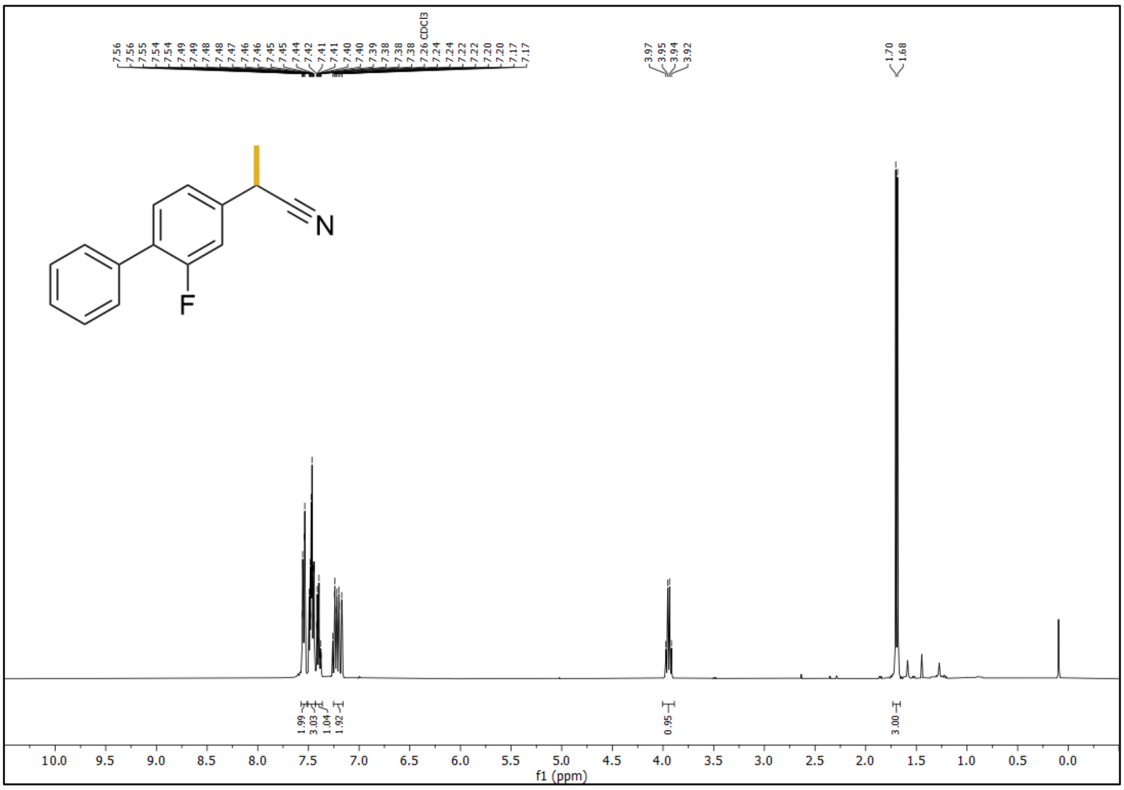
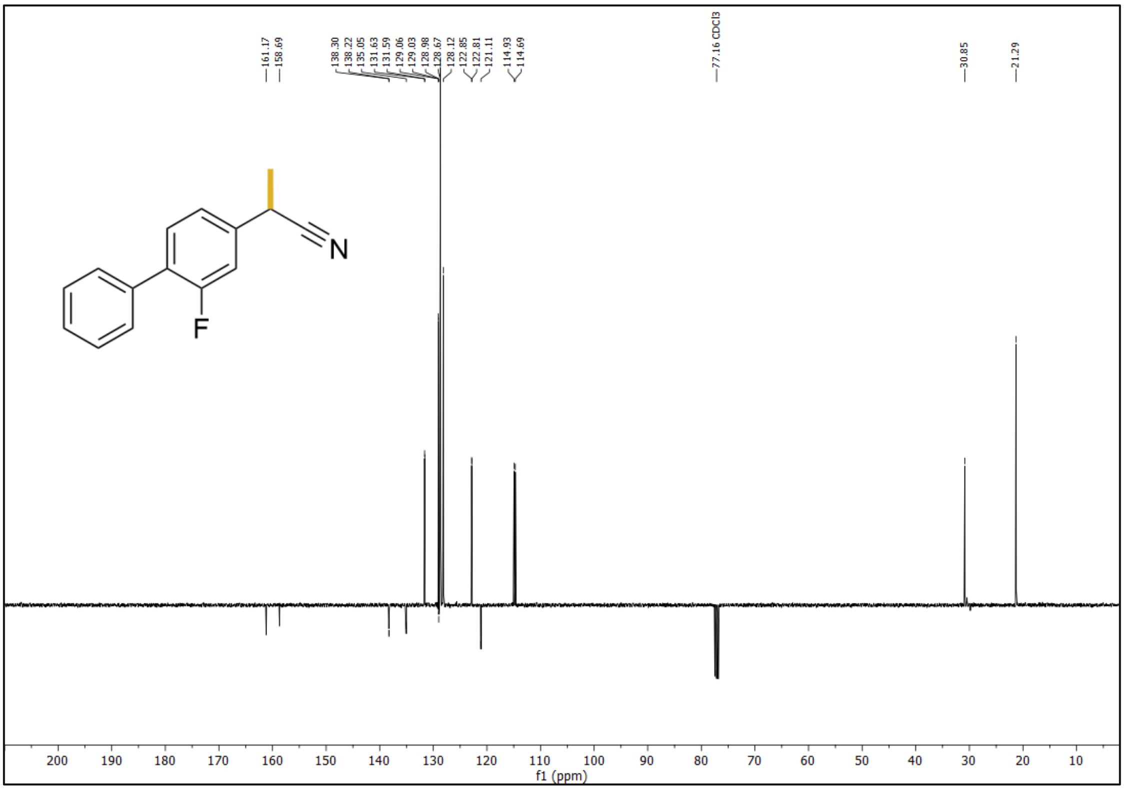


Figure 18: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-(thiophen-3-yl)propionitrile (2q).

2-(3-Fluoro-4-phenylphenyl)propionitrile (2r)





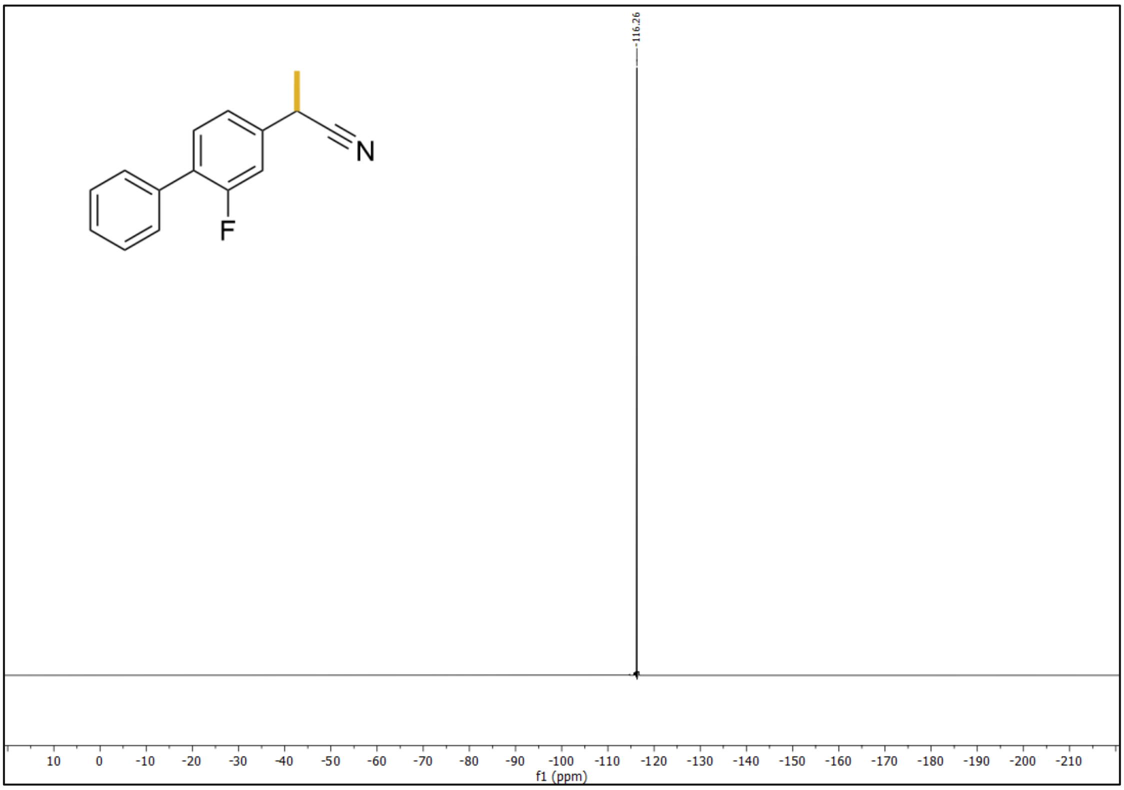


Figure 19: ^{1}H-NMR (400 MHz, CDCl$_3$), ^{13}C{1H} NMR (101 MHz, CDCl$_3$) and ^{19}F-NMR (376 MHz, CDCl$_3$) of 2-(3-fluoro-4-phenylphenyl)propionitrile (2r).

2-Methyl-2-(4-phenylphenyl)propionitrile (3a)

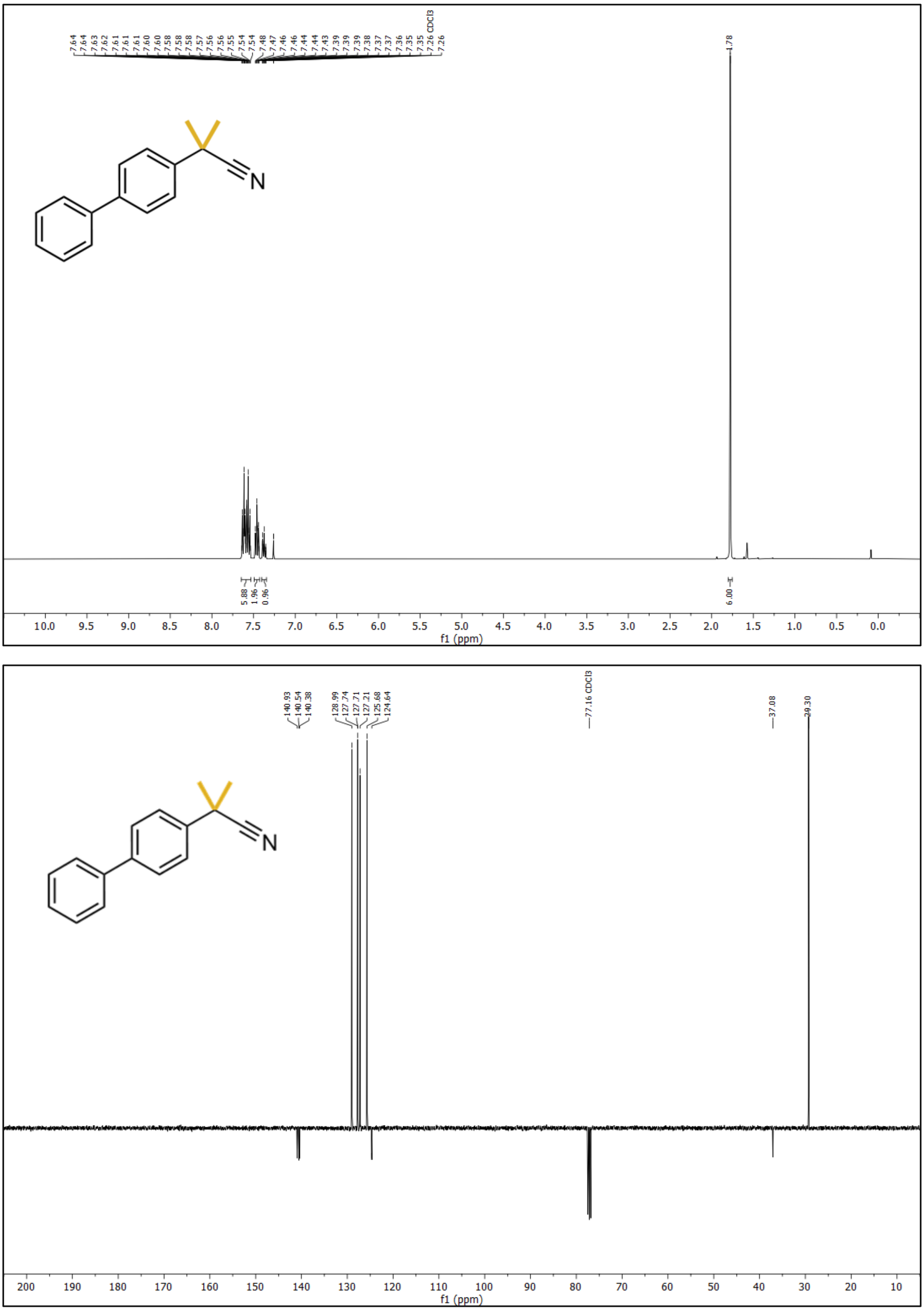


Figure 20: ^{1}H-NMR (400 MHz, $CDCl_3$) and $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) of 2-methyl-2-(4-phenylphenyl)propionitrile (3a).

2-(1,3-Benzothiazol-2-yl)-2-methylpropionitrile (3b)

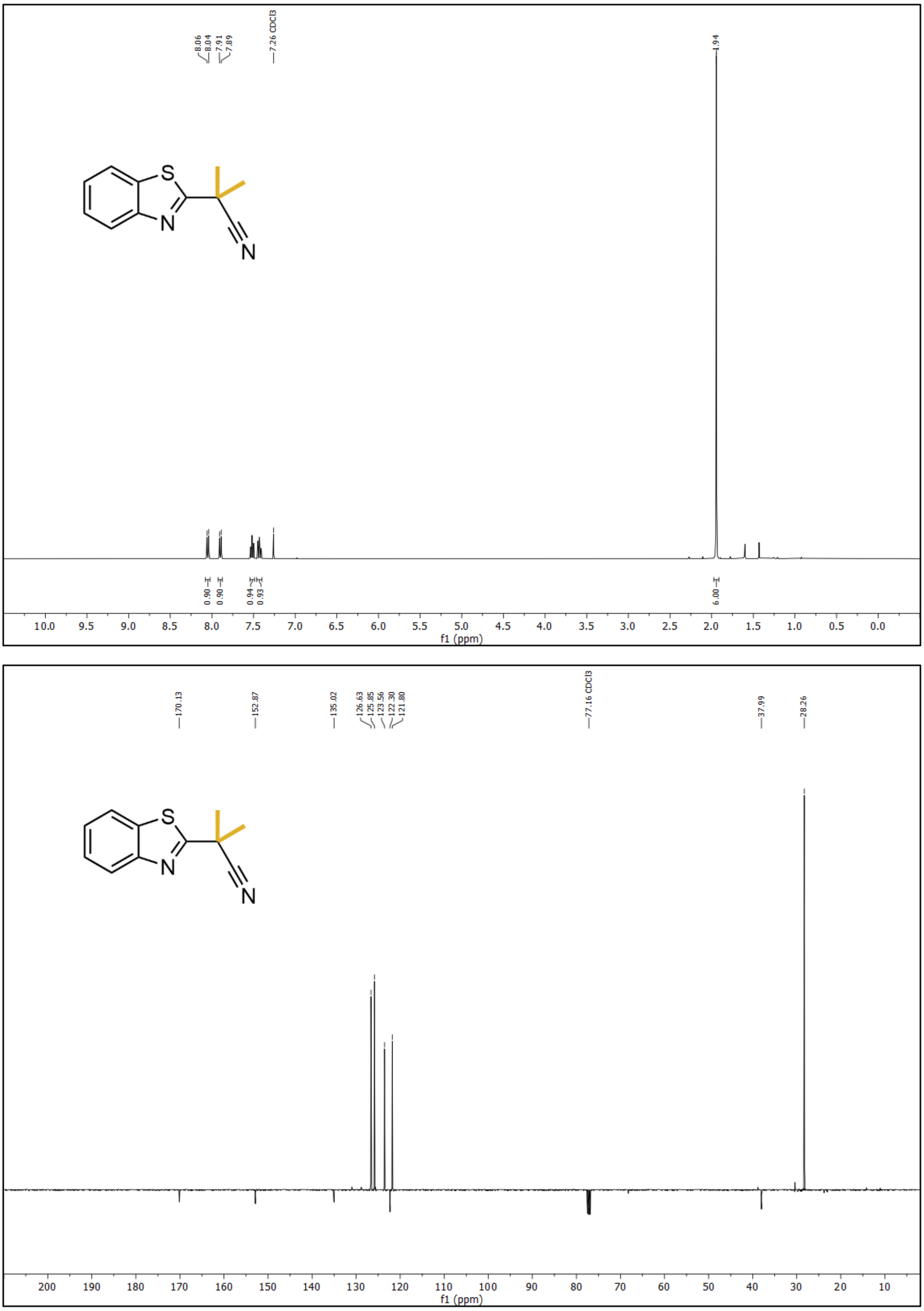


Figure 21: ¹H-NMR (400 MHz, CDCl₃) and ¹³C{1H} NMR (101 MHz, CDCl₃) of 2-(1,3-benzothiazol-2-yl)-2-methylpropionitrile (3b).

Methyl 4-(2-cyanopropan-2-yl)benzoate (3c)

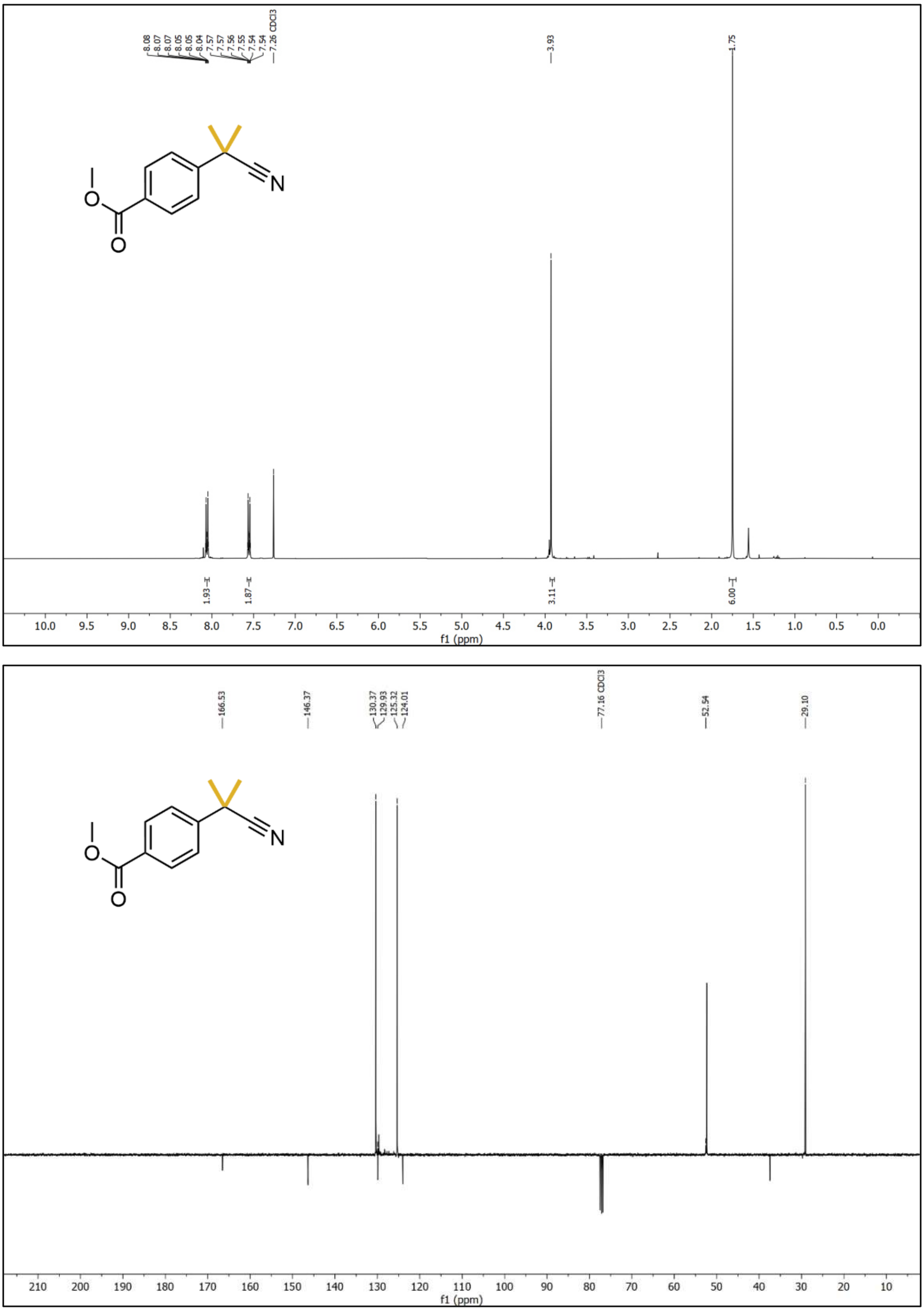


Figure 22: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C{1H} NMR (101 MHz, $CDCl_3$) of methyl methyl 4-(2-cyanopropan-2-yl)benzoate (3c).

2-(1-Methylindol-3-yl)acetonitrile (4a)

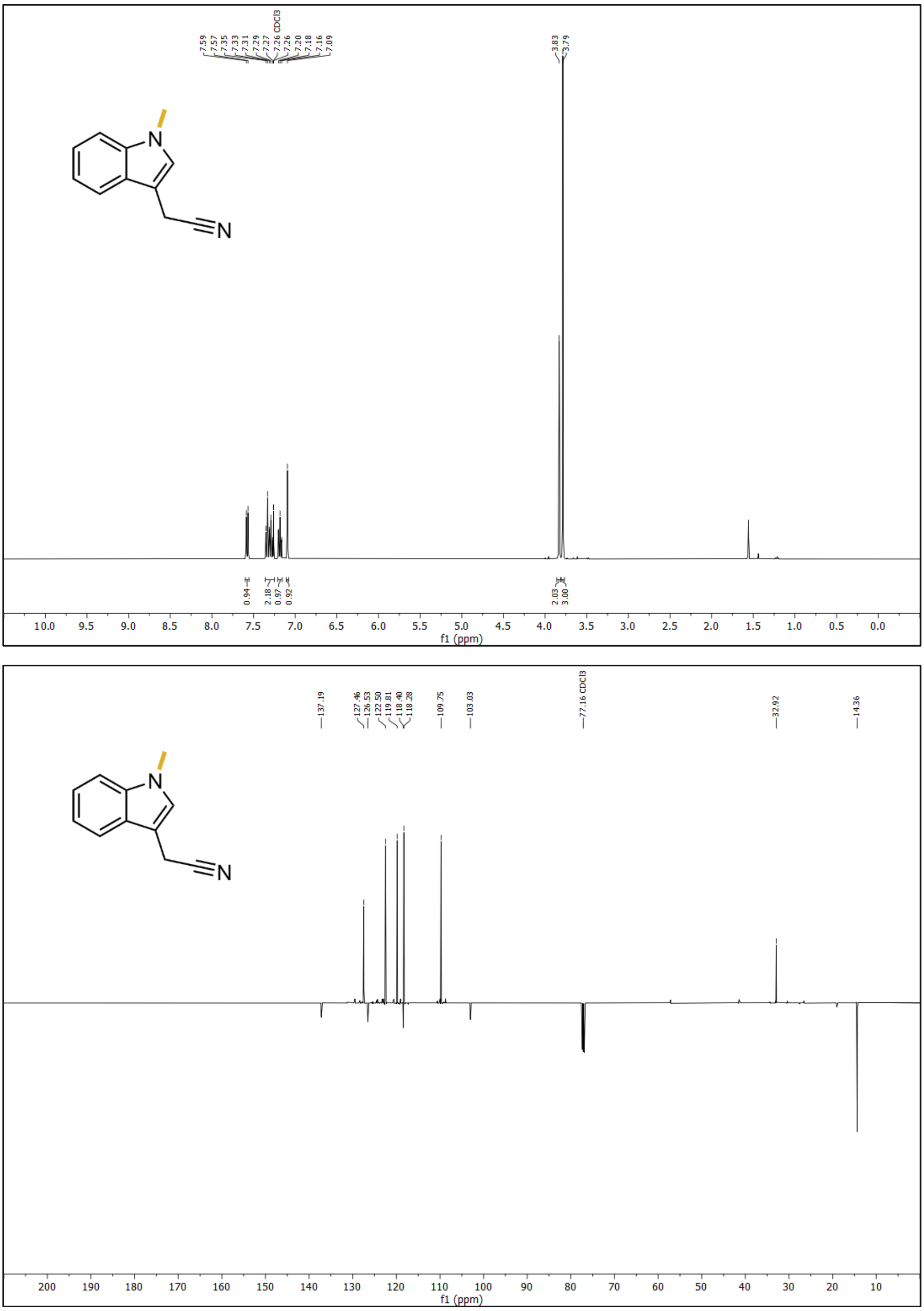
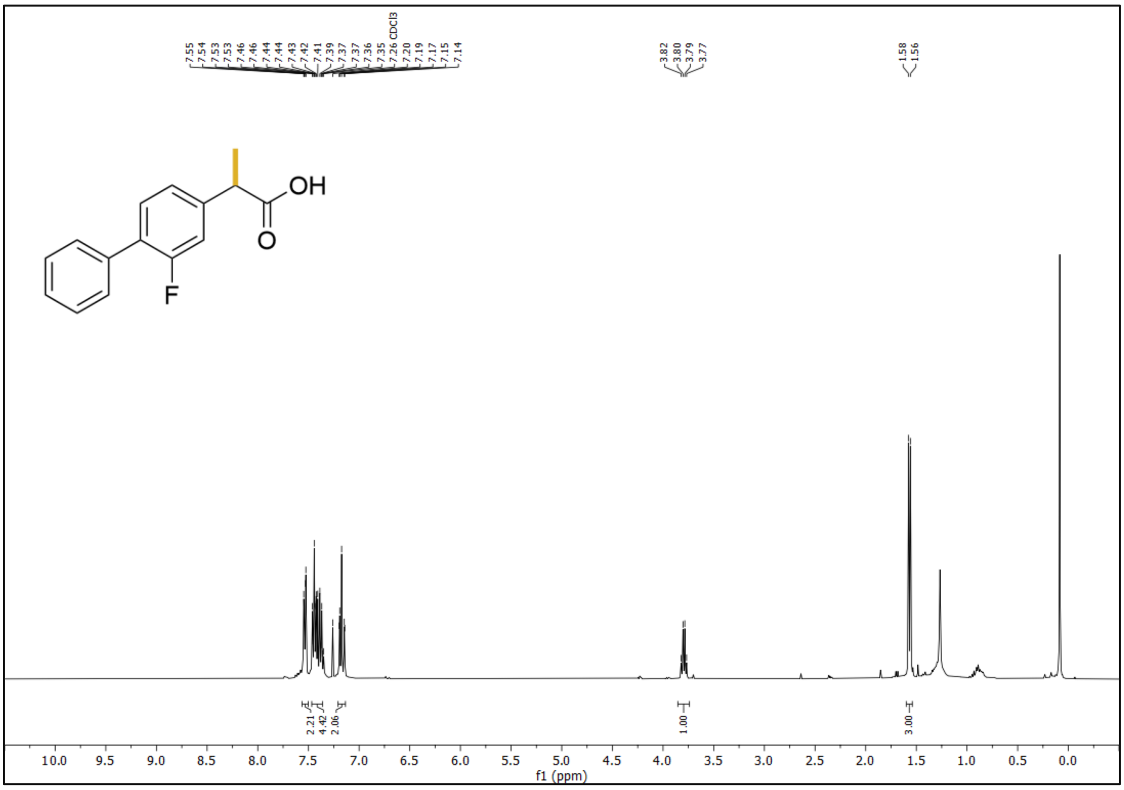
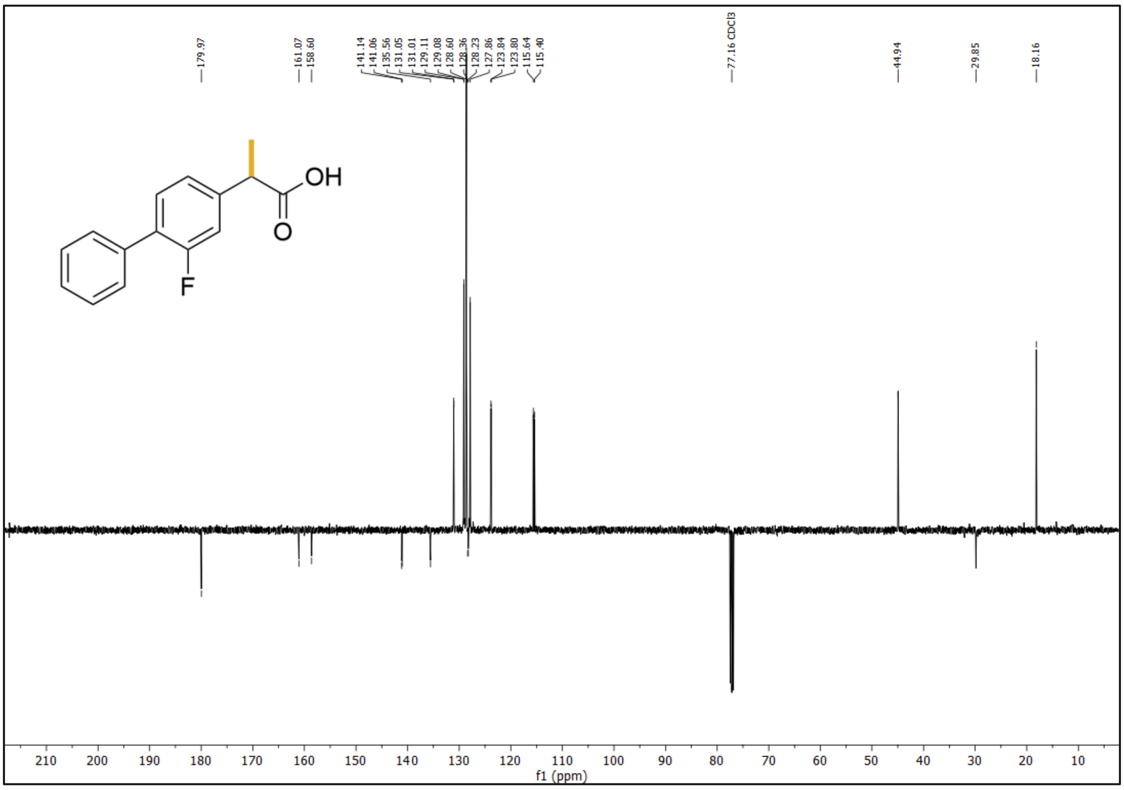


Figure 23: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-(1-methylindol-3-yl)acetonitrile (4a).

2-(3-Fluoro-4-phenylphenyl)propanoic acid (Flurbiprofen) (5)





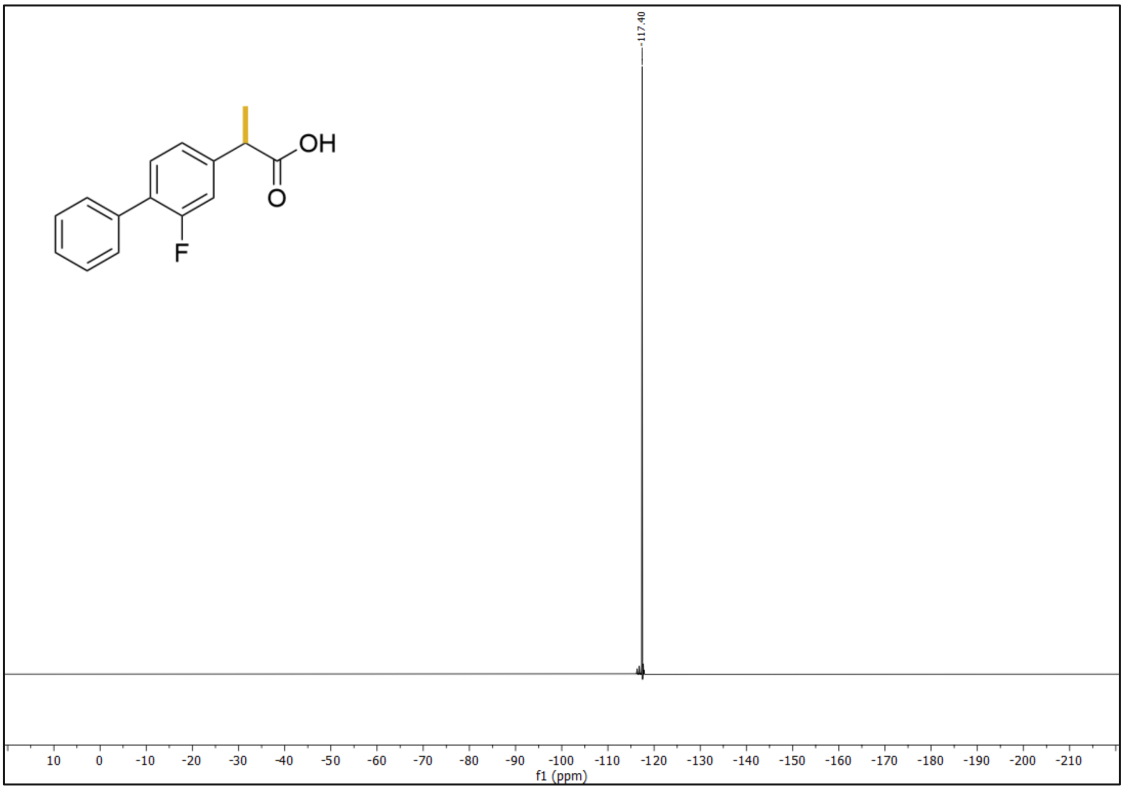


Figure 24: ^{1}H-NMR (400 MHz, CDCl$_3$), ^{13}C{1H} NMR (101 MHz, CDCl$_3$) and ^{19}F-NMR (376 MHz, CDCl$_3$) of 2-(3-fluoro-4-phenylphenyl)propanoic acid (Flurbiprofen) (5).

2-(4-Phenylphenyl)propan-1-amine (6)

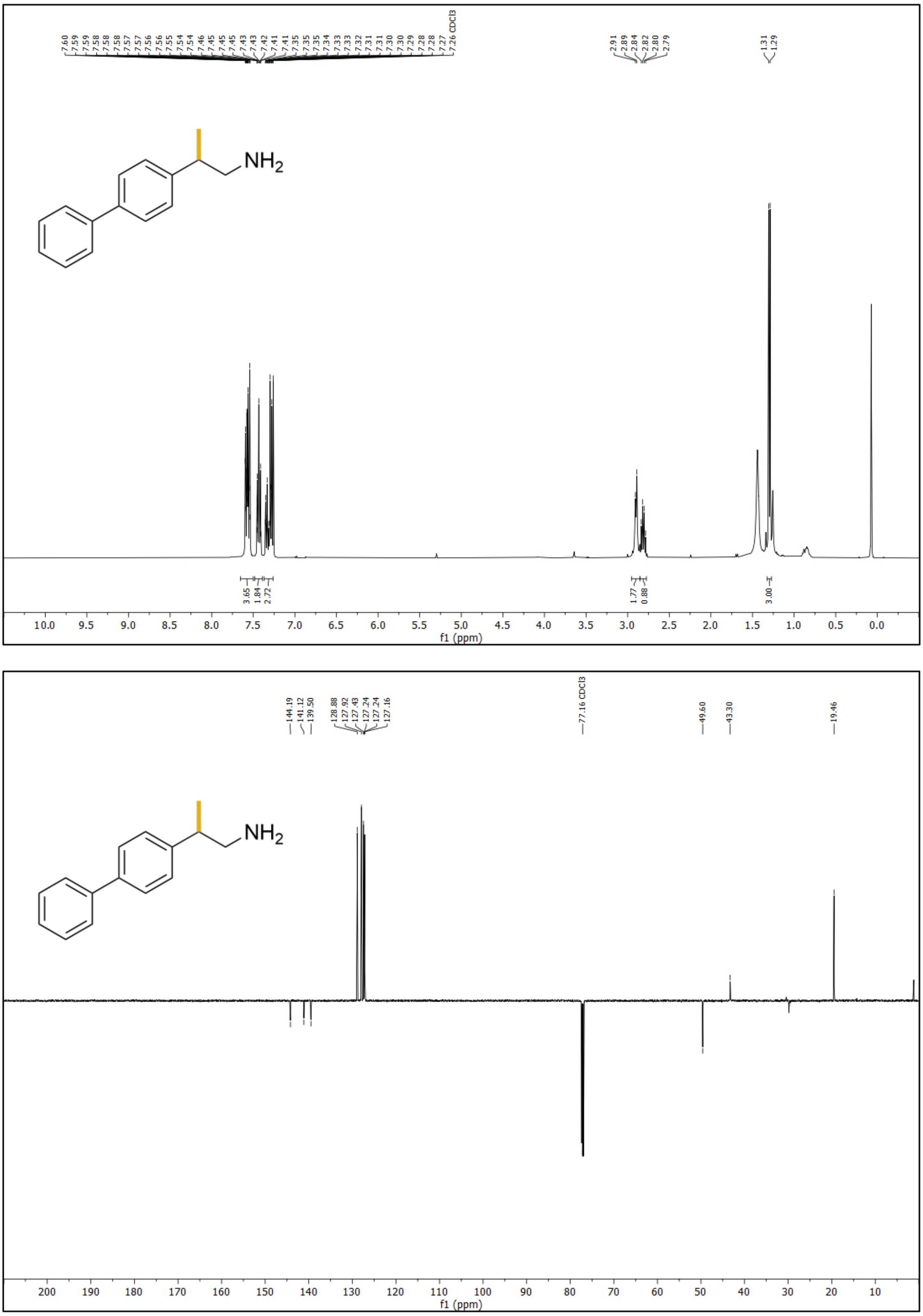
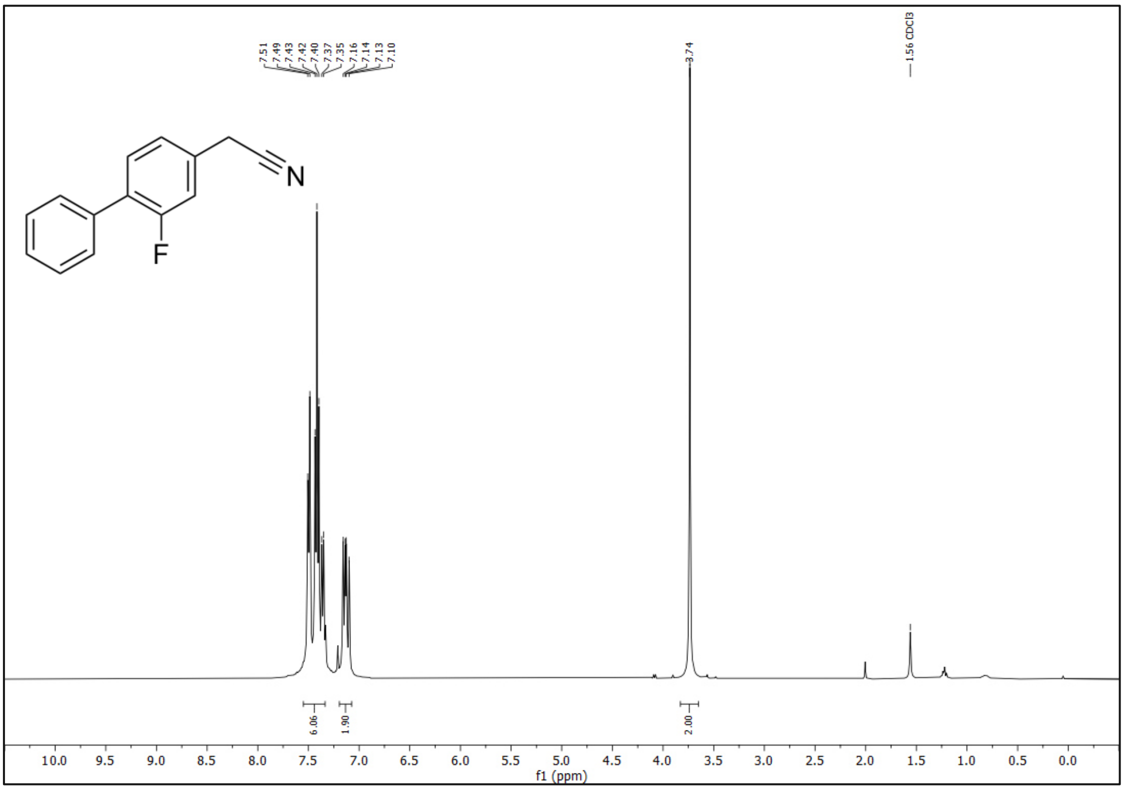
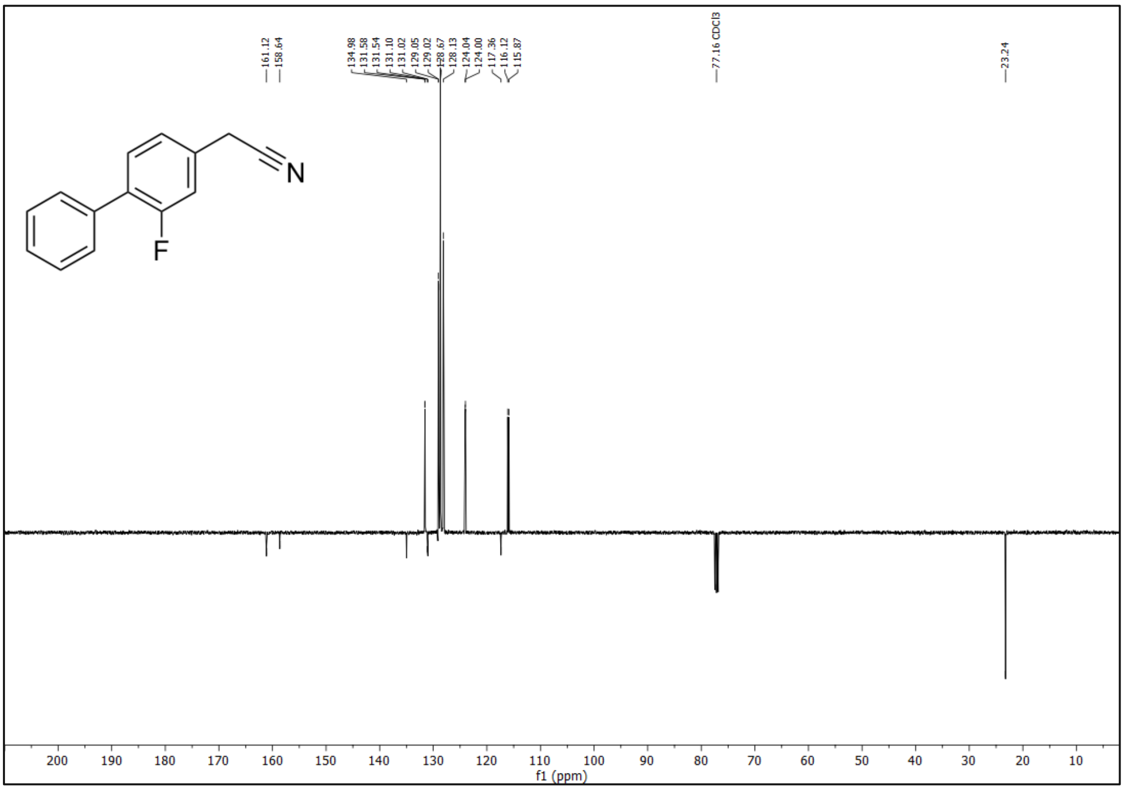


Figure 25: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-(4-phenylphenyl)propan-1-amine (6).

2-(3-Fluoro-4-phenylphenyl)acetonitrile (7)





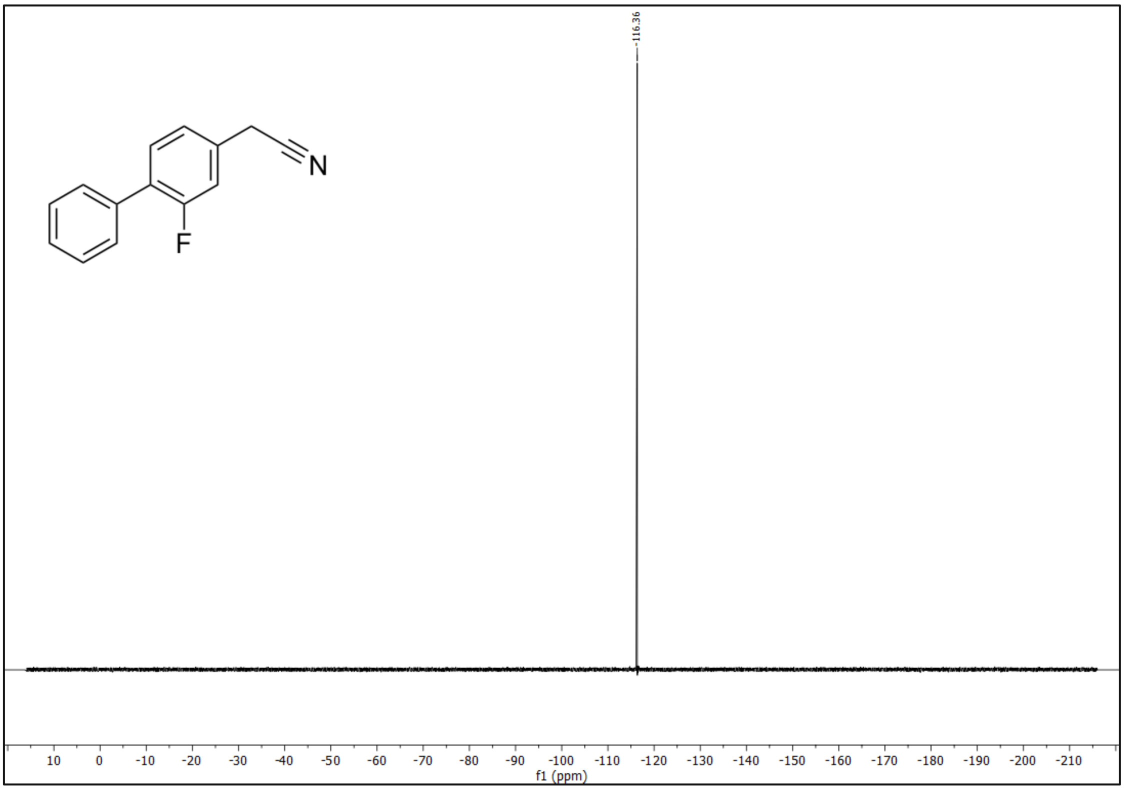


Figure 26: ^{1}*H-NMR (400 MHz, CDCl*$_3$*),* ^{13}*C{1H} NMR (101 MHz, CDCl*$_3$*) and* ^{19}*F-NMR (376 MHz, CDCl*$_3$*) of 2-(3-fluoro-4-phenylphenyl)acetonitrile (7).*

References

[1] I. T. Schiefer, S. Abdul-Hay, H. Wang, M. Vanni, Z. Qin, G. R. J. Thatcher, *J. Med. Chem.* **2011**, *54*, 2293-2306.

[2] H.-M. Xia, F.-L. Zhang, T. Ye, Y.-F. Wang, *Angew. Chem., Int. Ed.* **2018**, *57*, 11770-11775.

[3] T. Frejd, T. Klingstedt, *Synthesis* **1987**, *1987*, 40-42.

[4] M. de Greef, B. Breit, *Angew. Chem., Int. Ed.* **2009**, *48*, 551-554.

[5] M. Ettaoussi, A. Sabaouni, B. Pérès, E. Landagaray, O. Nosjean, J. A. Boutin, D.-H. Caignard, P. Delagrange, P. Berthelot, S. Yous, *ChemMedChem* **2013**, *8*, 1830-1845.

[6] Y. Huang, Y. Yu, Z. Zhu, C. Zhu, J. Cen, X. Li, W. Wu, H. Jiang, *J. Org. Chem.* **2017**, *82*, 7621-7627.

[7] T. Betke, P. Rommelmann, K. Oike, Y. Asano, H. Gröger, *Angew. Chem. Int. Ed.* **2017**, *56*, 12361-12366.

[8] R. Wang, C.-Y. Wang, P. Liu, K.-J. Bian, C. Yang, B.-B. Wu, X.-S. Wang, *Science Advances* **2023**, *9*, eadh5195.

[9] J. Guin, G. Varseev, B. List, *J. Am. Chem. Soc.* **2013**, *135*, 2100-2103.

[10] R. Shang, D.-S. Ji, L. Chu, Y. Fu, L. Liu, *Angew. Chem. Int. Ed.* **2011**, *50*, 4470-4474.

[11] A. Klapars, J. H. Waldman, K. R. Campos, M. S. Jensen, M. McLaughlin, J. Y. L. Chung,R. J. Cvetovich, C.-y. Chen, *J. Org. Chem.* **2005**, *70*, 10186-10189.

[12] K. J. Hock, A. Knorrscheidt, R. Hommelsheim, J. Ho,M. J. Weissenborn, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2019**, *58*, 3630-3634.

[13] G. Cavallini, E. Massarini, D. Nardi, R. D´Ambrosio *J. Am. Chem. Soc.* **1956**, *79*, 3514-3517.

[14] J.-P. Rieu, A. Boucherle, H. Cousse, G. Mouzin *Tetrahedron*, **1986**, *42*, 4095-4131.

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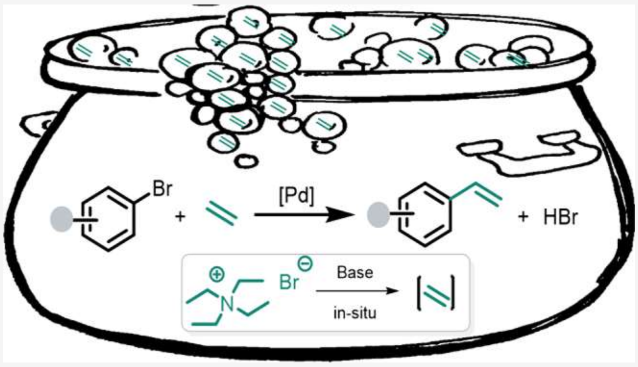
ABSTRACT: In this study, we introduce a convenient Heck vinylation protocol that eliminates the requirement for ethylene gas as a coupling partner. In contrast to traditional methodologies, quaternary ammonium salts can serve as solid olefin precursors under ambient atmosphere conditions. The practicality of this method, distinguished by its convenience and safety in a one-pot reaction, renders it appealing for applications in research and discovery context.



Arylethenes are powerful precursors in organic synthesis, used for the preparation of a broad variety of compounds with widespread pharmaceutical[1] applications and synthetic uses.[2] The versatility of the alkene moiety makes them excellent substrates for constructing more complex molecules. Notable transformations utilizing olefins include the Mizoroki–Heck reaction,[3−6] the Fujiwara–Moritani reaction,[7,8] and direct alkylation reactions through C–H functionalization.[9−11] However, in this type of transformation, ethylene and other gaseous olefins are often avoided, primarily for practical and safety reasons. Although Heck reported on the use of ethylene as a coupling partner as early as 1968, its application has not been significantly developed since then.[4] Conventional methodologies usually require high pressure of the olefin,[12−19] and thus elaborate high-pressure equipment such as autoclaves or flow-chemistry reactors are needed (Figure 1). However, flow chemistry is not considered to be a standard laboratory technique and still requires ethylene pressures of >15 bar.[20,21] To the best of our knowledge, only two papers have reported the use of ethylene at atmospheric or low pressure, but these intriguing results were not further explored.[22,23] In a continuing research program dedicated to substituting gaseous or volatile reagents with easy-to-handle solids, we demonstrated that quaternary ammonium salts can be used as alkyl sources in direct C–H functionalization reactions.[24,25] Herein, we describe our efforts to convert these reagents into convenient surrogates for ethylene in vinylation reactions. Substituting gaseous precursors with solid precursors not only simplifies and makes experimental setups safer but also improves the practicality and applicability of these reactions in small-scale experiments, typically encountered in academic research and medicinal chemistry programs.

We initiated our investigations with the vinylation of 2-bromo-6-methoxynapthalene **1**, a key precursor for the synthesis of naproxen[26] and nabumeton[27] through the Heck reaction. Initially, we employed Et_4NBr as the olefin surrogate, KO*t*Bu as the base, and a Pd/phosphine ligand complex as the catalytic system in toluene as solvent. $Pd(OAc)_2/(o\text{-Tol})_3P$ is the most commonly used catalytic system for such reactions, as originally described by Heck in 1978.[28] Under these conditions, only a minimal amount of the corresponding styrene **2** was produced after 18 h at 100 °C (Table 1, entry 1). In the subsequent step, it was explored whether the presence of 1 wt % H_2O at a higher temperature of 120 °C would enhance the desired transformation, as described in the literature.[29] Indeed, compound **2** was obtained in an improved yield of 31% (entry 2). Other Pd(0) and Pd(II) sources showed lower conversions (entries 3 and 4). By employing PdXPhos G4, a Buchwald precatalyst, we achieved a substantial improvement in yield, reaching 54% (entry 5). Additionally, we examined the impact of various quaternary ammonium salts as ethylene surrogates in the reaction. We tested Et_4NPF_6, Et_4NBF_4, Et_4NCl, and Et_4NI, all of which resulted in moderate yields

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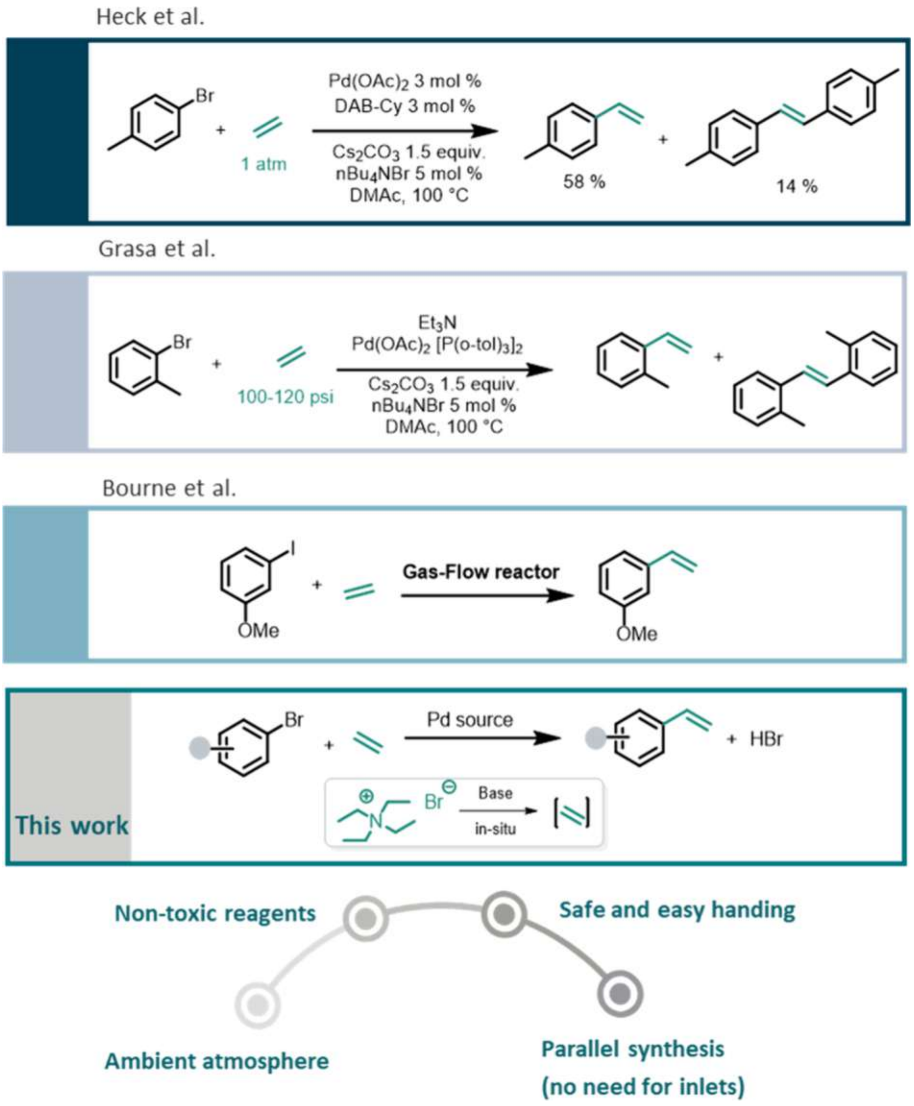

Figure 1. Strategies for Mizoroki–Heck coupling.

ranging from 40% to 50%, whereas PhEt$_3$NI proved to be ineffective. Therefore, Et$_4$NBr was chosen as the preferred olefin source for further investigation (see the complete quaternary ammonium salt screening list in the Supporting Information (SI)). Next, we conducted a screen of various bases. Although hydroxide bases are known to facilitate Hofmann elimination,[24] when subjected to our reaction conditions, KOH only led to low conversion (entry 6), and no product was formed when employing an organic base such as DBU (entry 7) (see complete base screening list in the SI). Since styrene is prone to polymerization at temperatures exceeding 100 °C,[30] lower temperatures were tested. This can have a second beneficial effect: the effective increase of the ethylene concentration due to its higher solubility at lower temperatures.[31] Reducing the temperature from 120 to 100 °C significantly improved the reaction performance (entry 8). Lowering the temperature is known to be detrimental to the yield of the Hofmann elimination and prevented us from further decreasing the temperature in this methodology. Furthermore, additional precatalysts were tested at the optimal temperature of 100 °C. PdPePPSI, an NHC-type precatalyst (entry 9), formed the desired product in only 20% yield. Finally, when PdRuPhos G3 and PdJosiphos SL-J009-1 G3 were used, product **2** was obtained with a yield of 82% and 79%, respectively (entries 10 and 11) (see complete catalyst screening list in the SI). Due to the higher cost of the latter, we found the optimal conditions to be Et$_4$NBr (8 equiv), KO*t*Bu (8 equiv), PdRuPhos G3 (10 mol %), in toluene (0.2 M) at 100 °C for 18 h. To address environmental concerns, we explored greener solvent alternatives, such as cyclopentylmethyl ether (CPME) and 2-methyl-THF (Me-THF). To our delight, CPME demonstrated efficiency comparable to toluene in the specific reaction, albeit with only about ~7% lower yield. For the investigation of a scope with volatile substrates, we decided, for practical reasons, to retain toluene as the solvent.

With the optimized conditions established, we investigated the vinylation of various substrates, including compounds bearing electron-withdrawing or electron-donating groups, as well as heterocycles often encountered in bioactive compounds, and dihalogenated substrates (Scheme 1). Due to the highly volatile nature of the products, the yields reported below were determined by quantitative ^{1}H NMR spectroscopy, unless otherwise specified. Aryl bromides bearing a trifluoromethyl group at different positions of the aryl ring were all tolerated, with the *meta*-derivative yielding 71% of the corresponding product **4**, while a notably lower yield was observed for the

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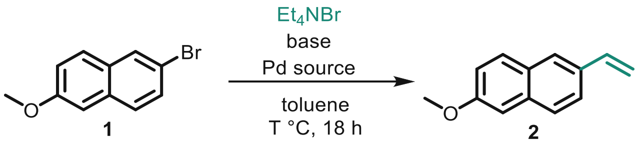
Table 1. Optimization of the Reaction Conditions[a]



Entry	Base	Pd source	Temp (°C)	Yield (%)[b]
1	KO*t*Bu	$Pd(OAc)_2$ + (*o*-Tol)$_3$P	100	trace
2	KO*t*Bu	$Pd(OAc)_2$ + 1 wt % H_2O	120	31
3	KO*t*Bu	$Pd_2(dba)_3$	120	25
4	KO*t*Bu	$Pd(PPh_3)_4$	120	28
5	KO*t*Bu	PdXPhos G4	120	54
6	KOH	PdXPhos G4	120	20
7	DBU	PdXPhos G4	120	-
8	KO*t*Bu	PdXPhos G4	100	77
9	KO*t*Bu	PdPEPPSI	100	20
10	KO*t*Bu	PdRuPhos G3	100	82
11	KO*t*Bu	PdJosiphos SL-J009-1 G3	100	79

[a]Reactions were performed on a 0.2 mmol scale, with 8.0 equiv of ammonium salt, 8.0 equiv of base, and 10 mol % catalyst; reaction time: 18 h. [b]Yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures using 1,3,5-trimethoxybenzene as internal standard.

ortho-analogue **6** likely due to steric hindrance.[32] Interestingly, the carboxylic acid moiety was also tolerated in the vinylation reaction to give product **7**, but to our surprise, that was not the case for the corresponding methyl- and *tert*-butyl- ester analogue that did not undergo the reaction. Additionally, nitro, nitrile, and aldehyde moieties were not tolerated. The reaction was also applicable to substrates bearing substituents with electron-donating properties. We systematically screened aryl bromides with methoxy functionalities (products **8**, **9**, and **10**), yielding 50% for the *meta*- and *para*-analogues and 31% for the *ortho* analogue, again presumably due to steric hindrance. Similarly, compounds with ethyl substituents (products **12**, **13**, and **14**) afforded yields of up to 60% for the ortho derivative. The 4-vinyl *Boc*-protected aniline **15** was also formed with a moderate yield of 40%. The 4-vinyl dimethylaniline **11** and the 4-vinylphenol **16** were both obtained, albeit in lower yields.

It is worth noting that we observed complete substrate consumption in all cases and there was no formation of the corresponding stilbene side product, which may have formed by a subsequent Heck reaction with the desired product. However, we did not achieve quantitative yields in any case. Polystyrene-derivatives are most likely formed,[32] but could not be detected *via* GC-MS or NMR analysis possibly due to their (expected) low solubility in common organic solvents. Additionally, we explored heteroaromatic compounds related to bioactive molecules, producing the corresponding vinylated products in moderate to high yields. It should be noted that the lower isolated yields in contrast to the ^{1}H NMR yields were attributed to the volatility of the respective compounds upon purification. We were delighted to find that various nitrogen-containing heterocycles, compounds with diverse chemical properties, and vast applications, particularly in medicinal chemistry, were compatible with our methodology. Compounds including pyridine, indazole, or (iso)quinoline motifs, were tested using our novel protocol. 1-Methyl-6-vinyl-1*H*-indazole **17** and 1-methoxy-6-vinylisoquinoline **18** were obtained with a 66% and 68% yield respectively, while 3-vinylquinoline **19** was formed in 57% yield. An extended reaction time of up to 40 h was required for the complete conversion of 3-bromopyridine into desired product **20**. Similar reactivity was observed for heteroarenes such as 4-bromobenzofuran and 5-bromobenzothiophene yielding 74% and 70% of the corresponding products **21** and **22**, respectively.

Furthermore, 2-vinyl-6-fluoronapthalene **23** was also tolerated and formed in a yield of 77%. The presence of the free NH group in 6-bromo-1*H*-indazole **24** appeared to be problematic for the reaction to proceed, whereas 3-bromo-1,5-naphthyridine **25**, 6-bromoquinoxaline **26**, and 3-bromo-1,8-naphthyridine **27** surprisingly did not undergo the transformation (for the complete heterocycle scope screening, see the SI). Finally, the selected substrate for optimizing this protocol, 2-bromo-6-methoxynapthalene, gave the respective vinylated product **2** with an isolated yield of 82%. Increasing the scale in this example from 0.2 mmol to intermediate scales of 0.4 and 0.6 mmol and eventually to 1 mmol scale led to a constant decrease in yield as follows: 71%, 65%, and 37%, respectively.

In conclusion, we have presented a novel protocol for the facile vinylation of aryl bromides, utilizing tetraethylammonium salts as surrogates for gaseous olefins in a one-pot reaction conducted under an ambient atmosphere. We have successfully demonstrated this methodology with a diverse set of 25 examples, ranging from simple aryl bromides to heterocycles, providing vinyl(hetero)arenes in chemical yields ranging from 10% to 80%. It is important to note that this represents just the initial phase toward achieving a convenient Heck reaction. Further efforts are in progress to identify conditions that will enable a broader scope. Moreover, the applicability and practicality of this transformation make it well-suited for use in a discovery medicinal chemistry context where operationally complex reaction setups, such as the manipulation of gases, are not common practice.

■ EXPERIMENTAL SECTION

Unless noted otherwise, the reactants and reagents were purchased from commercial suppliers and used without further purification. The 4 mL brown-glass vials were sealed with Wheaton screw caps containing a PTFE faced 14B styrene-butadiene rubber liner. All reactions were magnetically stirred and heated in a metallic reaction block. All reaction temperatures refer to external temperatures.

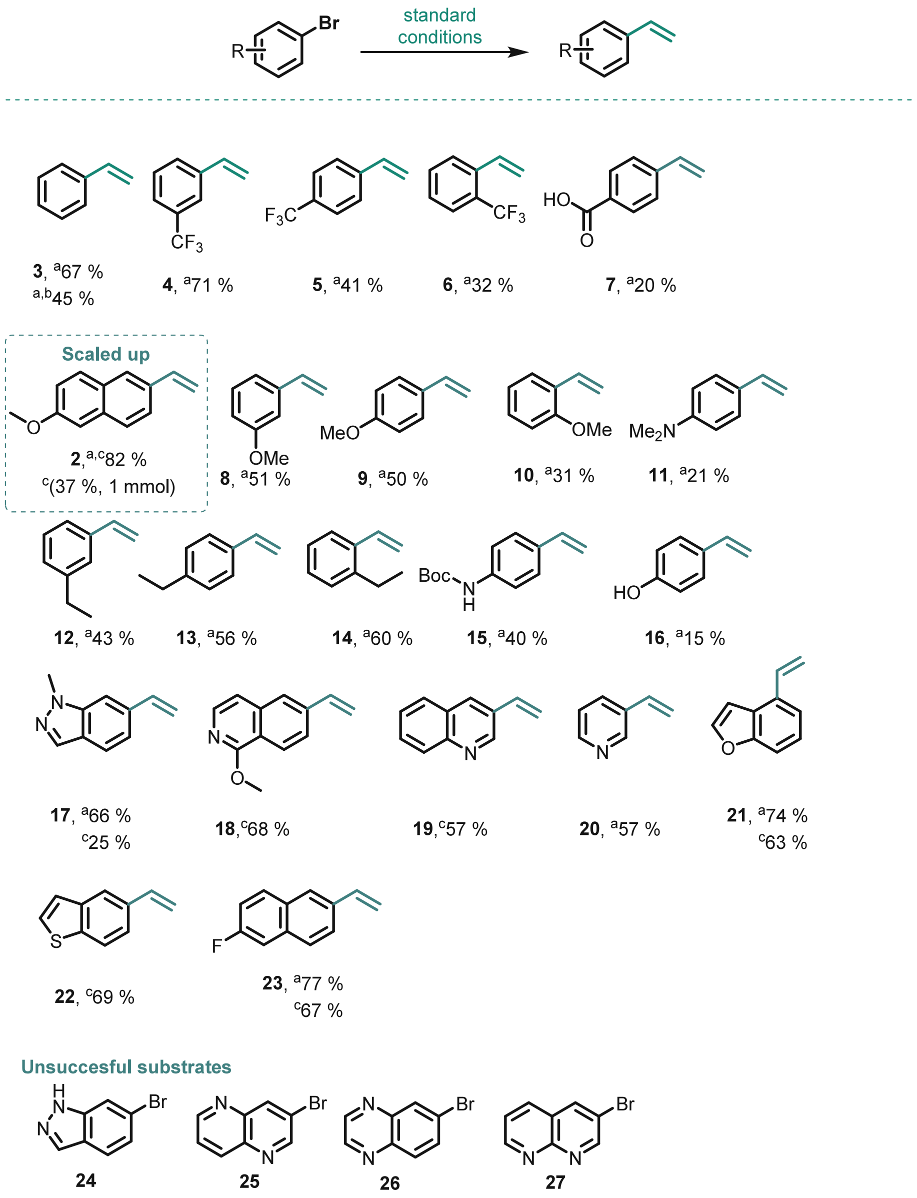
NMR spectra were recorded in $CDCl_3$ or d_8-toluene on a Bruker Avance UltraShield (400 MHz) or Avance III HD 600 (600 MHz) spectrometer, and chemical shifts (δ) are reported in ppm, using Me_4Si as internal standard. Coupling constants (J) are given in hertz (Hz), and multiplicities are assigned by the following abbreviations = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

Thin Layer Chromatography (TLC) analysis was performed on precoated aluminum-backed unmodified plates (Silica gel 60 F_{254}, Merck). Compounds were visualized under UV light.

Flash column chromatography was performed using either Merck silica gel 60 (40 μm−63 μm) by hand column, or purification was performed using a TELEDYNE ISCO COMBI FLASH COMPANION NextGen300+ flash chromatography system with a UV−vis detector (diode array) with Macherey-Nagel Chromabond RS silica gel columns.

GC-MS analysis was performed 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 programs: **Method A:** 2 min at 100 °C, 35 °C/min until 300 °C, 4 min at 300 °C and **Method B:** 2.5 min at 40 °C, 12 °C/min until 220 °C, 2.5 min at 220 °C.

Scheme 1. Scope of Vinylation Couplings



Reactions were performed on a 0.2 mmol scale, Et_4NBr (8 equiv), KO*t*Bu (8 equiv), PdRuPhos G3 (10 mol %) toluene (0.2 M), 100 °C for 18−40 h. [a]Yields were determined by ^1H NMR spectroscopy of the crude reaction mixtures using 1,3,5-trimethoxybenzene as internal standard. [b]Iodobenzene was used as starting material instead of bromobenzene. [c]Isolated yields.

HR-MS data were recorded using a Thermo Scientific Orbitrap Elite hybrid ion trap/orbitrap spectrometer system with an Ultimate 3000 series LPG-3400XRS pump system. Mass calibration was performed using the Pierce LTQ Velos ESI positive ion calibration solution from Thermo Scientific (lot PF200011, product no. 88323).

Reaction Optimization Screening. The optimization of reaction conditions was carried out following general procedure A (see the SI for details). Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

General Procedure A. To a 4 mL brown vial equipped with a magnetic stirring bar and a Wheaton screw cap were added 2-bromo-6-methoxynapthalene (**1**) (48.4 mg, 0.2 mmol, 1 equiv), the respective ammonium salt (8 equiv), the base (8 equiv), and the catalyst (amount as specified in the optimization table). Subsequently, solvent (0.2 M) was added via syringe, and the reaction mixture was heated to 120 °C, or to 100 and 80 °C, depending on the corresponding solvent in a metallic block for 18−36 h respectively. For the sample preparation for ^1H NMR quantification, the reaction mixture was cooled to room temperature and filtered over Celite in a syringe filter. The filter cake was washed with EtOAc, and the volatiles were removed in vacuo. 1,3,5-Trimethoxybenzene (0.2 mmol, 1 equiv) was added, and the crude mixture was dissolved in 0.5 mL of $CDCl_3$ and transferred to an NMR tube. The recorded spectra were processed by MestReNova v14 software.

General Procedure B. To a 4 mL brown vial equipped with a magnetic stirring bar and a Wheaton screw cap were added the starting material (0.2 mmol, 1 equiv), Et_4NBr (8 equiv), KO*t*Bu (8 equiv), and PdRuPhos G3 (10 mol %). Subsequently, d_8-toluene (0.2 M) was added *via* syringe, and the reaction mixture was heated to 100 °C in a metallic block for 18−36 h. The reaction mixture was cooled down to room temperature and filtered in a syringe filter. The filter cake was washed with d_8-toluene, and 1,3,5-trimethoxybenzene (0.2 mmol, 1 equiv) was added to the crude reaction mixture. To an NMR tube was transferred 0.5 mL of the reaction solution, and the recorded spectra were processed by MestReNova v14.

General Procedure C. To a 4 mL brown vial equipped with a magnetic stirring bar and a Wheaton screw cap were added the starting material (0.2 mmol, 1 equiv), Et_4NBr (8 equiv), KO*t*Bu (8 equiv), and PdRuPhos G3 (10 mol %). Subsequently, toluene (0.2 M) was added *via* a syringe, and the reaction mixture was heated to 100 °C, in a metallic block for 18−36 h. Workup Procedure 1: The reaction mixture was cooled down to room temperature and filtered in a syringe filter. The filter cake was washed with EtOAc, and the volatiles were removed in *vacuo*. Workup Procedure 2: The reaction mixture was cooled down to room temperature and filtered in a syringe filter, and toluene was removed in *vacuo*. The crude mixture was redissolved in DCM, and water was added (HCl 1 M was added for neutralization). The aqueous phase was extracted with DCM (5×), the combined organic extracts were dried over Na_2SO_4, and the volatiles were removed in *vacuo*. 1,3,5-Trimethoxybenzene (0.2 mmol, 1 equiv) was added, and the crude mixture was dissolved in 0.5 mL of $CDCl_3$ and transferred to an NMR tube. The recorded spectra were processed by MestReNova v14 software. The crude residue was purified either *via* manual column chromatography using unmodified silica or by using an automated purification system.

General Procedure D. To a 4 mL brown vial equipped with a magnetic stirring bar and a Wheaton screw cap were added the starting material (0.2 mmol, 1 equiv), Et_4NBr (8 equiv), KO*t*Bu (8 equiv), and PdXPhos G (10 mol %). Subsequently, toluene (0.2 M) was added *via* syringe, and the reaction mixture was heated to 100 °C in a metallic block for 18−20 h. Workup Procedure 1: The reaction mixture was cooled down to room temperature and filtered in a syringe filter. The filter cake was washed with EtOAc, and the volatiles were removed in *vacuo*. 1,3,5-Trimethoxybenzene (0.2 mmol, 1 equiv) was added, and the crude mixture was dissolved in 0.5 mL of $CDCl_3$ and transferred to an NMR tube. The recorded spectra were processed by MestReNova v14 software. The crude residue was purified either *via* manual column chromatography using unmodified silica or using an automated purification system.

General Procedure E. To a 4 mL brown vial equipped with a magnetic stirring bar and a Wheaton screw cap were added the starting material (0.2 mmol, 1 equiv), Et_4NBr (8 equiv), KO*t*Bu (8 equiv), and PdXPhos G4 (10 mol %). Subsequently, d_8-toluene (0.2 M) was added *via* syringe, and the reaction mixture was heated to 100 °C in a metallic block for 18 h. The reaction mixture was cooled down to room temperature and filtered in a syringe filter. The filter cake was washed with d_8-toluene, and 1,3,5-trimethoxybenzene (0.2 mmol, 1 equiv) was added to the crude reaction mixture. To an NMR tube was transferred 0.5 mL of the reaction solution, and the recorded spectra were processed by MestReNova v14.

2-Vinyl-6-methoxynaphthalene[33] (2). The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as a white solid. ^1H NMR yield (based on the integration of peaks at 6.09 and 5.80 ppm): 82%. Isolated yield: (30 mg, 81%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77−7.67 (m, 3H), 7.60 (dd, J = 8.8, 1.6 Hz, 1H), 7.19−7.09 (m, 2H), 6.85 (dd, J = 17.6, 10.8 Hz, 1H), 5.82 (dd, J = 17.6, 0.9 Hz, 1H), 5.28 (dd, J = 10.8, 0.9 Hz, 1H), 3.92 (s, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ: 157.9, 137.1, 134.5, 133.1, 129.7, 129.1, 127.1, 126.3, 123.9, 119.1, 113.2, 106.0, 55.5. Compound **2** was also prepared on a 0.4 mmol scale as described above: ^1H NMR yield (based on the integration of peaks at 6.09 and 5.80 ppm): 71%, on a 0.6 mmol scale: ^1H NMR yield (based on the integration of peaks at 6.09 and 5.80 ppm): 65%, and on a 1 mmol scale (1 equiv) using Et_4NBr (8 equiv), KO*t*Bu (8 equiv), and PdRuPhos G3 (10 mol %). Isolated yield: (68 mg, 37%, 0.148 mmol).

Styrene[34] (3). The title compound was prepared according to general procedure B from commercially available starting materials with a reaction time of 20 h. From bromobenzene [CAS 108-86-1]: ^1H NMR yield (based on the integration of peaks at 6.10 and 5.58 ppm): 67%, and from iodobenzene [CAS 591-50-4]: ^1H NMR yield (based on the integration of peaks at 6.10 and 5.59 ppm): 45%.

1-(Trifluoromethyl)-3-vinylbenzene[35] (4). The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.19 and 5.49 ppm): 71%.

1-(Trifluoromethyl)-4-vinylbenzene[35] (5). The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.47 ppm): 41%. The title compound was also prepared according to general procedure E from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.47 ppm): 9%.

1-(Trifluoromethyl)-2-vinylbenzene[36] (6). The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 40 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.48 ppm): 32%.

4-Vinylbenzoic Acid[37] (7). The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.57 ppm): 20%. The title compound was also prepared according to general procedure E from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.57 ppm): 31%.

1-Methoxy-3-vinylbenzene[38] (8). The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.78 ppm): 51%. The title compound was prepared according to general procedure E from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.78 ppm): 51%.

1-Methoxy-4-vinylbenzene[39] (9). The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 40 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.54 ppm): 50%.

1-Methoxy-2-vinylbenzene[38] (10). The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 40 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.71 ppm): 31%.

***N*,*N*-Dimethyl-4-vinylaniline[40] (11).** The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.57 ppm): 21%.

1-Ethyl-3-vinylbenzene (12). The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.67 ppm): 43%.

1-Ethyl-4-vinylbenzene[35] (13). The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.63 ppm): 56%.

1-Ethyl-2-vinylbenzene[41] (14). The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.63 ppm): 60%.

***tert*-Butyl (4-Vinylphenyl)carbamate[42] (15).** The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 20 h. ^1H NMR yield (based on the integration of peaks at 6.13 and 5.68 ppm): 40%.

4-Vinylphenol[43] (16). The title compound was prepared according to general procedure B from a commercially available starting material with a reaction time of 18 h. ^1H NMR yield (based on the integration of peaks at 6.15 and 5.61 ppm): 15%.

1-Methyl-6-vinyl-1*H*-indazole (17). The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as a white solid. ^1H NMR yield (based on the integration of peaks at 6.09 and 5.86 ppm): 66%. Isolated yield: (8 mg, 25%). Decomposition observed over time, and upon applying high vacuum. The title compound was also prepared according to general procedure D from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. ^{1}H NMR yield (based on the integration of peaks at 6.09 and 5.84 ppm): 56%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 (d, J = 1.0 Hz, 1H), 7.66 (dt, J = 8.4, 0.6 Hz, 1H), 7.35−7.27 (m, 2H), 6.91−6.80 (m, 1H), 5.86 (dd, J = 17.5, 0.8 Hz, 1H), 5.34 (dd, J = 10.9, 0.8 Hz, 1H), 4.07 (s, 3H). ^{13}C{1H} NMR (101 MHz, CDCl$_3$) δ 140.5, 137.3, 136.1, 132.8, 123.8, 121.1, 118.9, 114.7,107.1, 35.6. HRMS (ESI/q-TOF): m/z [M + H]$^+$ calcd. for $C_{10}H_{10}N_2$+H$^+$: 159.0922; found: 159.0915.

1-Methoxy-6-vinylisoquinoline (18). The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as a colorless oil. ^{1}H NMR yield (based on the integration of peaks at 6.09 and 5.92 ppm): 68%. Isolated yield: (25 mg, 68%, 91% purity). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.21−8.14 (m, 1H), 7.98 (d, J = 5.9 Hz, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.17 (dd, J = 5.9, 0.9 Hz, 1H), 6.86 (dd, J = 17.6, 10.9 Hz, 1H), 5.93 (dd, J = 17.6, 0.8 Hz, 1H), 5.42 (dd, J = 10.9, 0.8 Hz, 1H), 4.13 (s, 3H). ^{13}C{1H} NMR (150 MHz, CDCl3) δ 161.0, 140.3, 139.5, 138.3, 136.5, 124.5, 124.3, 124.2, 119.3, 116.4, 115.1, 53.8. HRMS (ESI/Orbitrap): m/z [M + H]$^+$ calcd. for $C_{12}H_{11}NO$ +H$^+$: 186.0919; found: 186.0913.

3-Vinylquinoline[44] (19). The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as pale-yellow oil. Isolated yield: (18 mg, 57%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.03 (d, J = 2.2 Hz, 1H), 8.11−8.05 (m, 2H), 7.81 (dd, J = 8.2, 1.4 Hz, 1H), 7.68 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.54 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 6.88 (dd, J = 17.7, 11.0 Hz, 1H), 5.99 (dd, J = 17.8, 0.6 Hz, 1H), 5.47 (dd, J = 11.0, 0.6 Hz, 1H). ^{13}C{1H} NMR (101 MHz, CDCl$_3$) δ 149.3, 147.8, 133.9, 132.6, 130.5, 129.4, 129.4, 128.1, 128.0, 127.1, 116.5.

3-Vinylpyridine[39] (20). The title compound was prepared according to general procedure B from a commercially available starting material with a reaction time of 40 h. ^{1}H NMR yield (based on the integration of peaks at 6.09 and 5.49 ppm): 57%.

4-Vinylbenzofuran (21). The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica by using pentane to give the product as a colorless oil. ^{1}H NMR yield (based on the integration of peaks at 6.09 and 5.88 ppm): 74%. Isolated yield: (18 mg, 63%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 (d, J = 2.3 Hz, 1H), 7.43 (dt, J = 8.1, 1.0 Hz, 1H), 7.35 (dt, J = 7.5, 0.8 Hz, 1H), 7.31−7.24 (m, 1H), 7.07−6.99 (m, 1H), 6.97 (dd, J = 2.2, 1.0 Hz, 1H), 5.88 (dd, J = 17.7, 1.1 Hz, 1H), 5.42 (dd, J = 11.1, 1.1 Hz, 1H). ^{13}C{1H} NMR (101 MHz, CDCl$_3$) δ: 155.4, 145.3, 134.6, 131.2, 125.7, 124.4, 120.2, 115.8, 110.8, 105.3. HRMS (ESI/Orbitrap): m/z [M + H]$^+$ calcd. for $C_{10}H_8O$+H$^+$: 145.0653; found: 145.0647.

5-Vinylbenzo[*b*]thiophene[39] (22). The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as a yellow solid. ^{1}H NMR yield (based on the integration of peaks at 6.09 and 5.80 ppm): 70%. Isolated yield: (22 mg, 69%).^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86−7.78 (m, 2H), 7.52−7.41 (m, 2H), 7.32 (dd, J = 5.4, 0.8 Hz, 1H), 6.84 (dd, J = 17.6, 10.9 Hz, 1H), 5.81 (dd, J = 17.6, 0.9 Hz, 1H), 5.28 (dd, J = 10.9, 0.9 Hz, 1H). ^{13}C{1H} NMR (101 MHz, CDCl$_3$) δ: 140.1, 139.3, 137.1, 134.2, 127.0, 124.1, 122.6, 122.3, 121.8, 113.6.

2-Vinyl-6-fluoronaphthalene (23). The title compound was prepared according to general procedure C from a commercially available starting material with a reaction time of 18 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as a colorless oil. ^{1}H NMR yield (based on the integration of peaks at 6.09 and 5.86 ppm): 77%. Isolated yield: (23 mg, 67%).^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 (dd, J = 9.0, 5.6 Hz, 1H), 7.73 (dd, J = 5.0, 3.5 Hz, 2H), 7.65 (dd, J = 8.6, 1.7 Hz, 1H), 7.41 (dd, J = 9.8, 2.6 Hz, 1H),7.29−7.19 (m, 1H), 6.86 (dd, J = 17.6, 10.9 Hz, 1H), 5.85 (d, J = 17.6 Hz, 1H), 5.33 (d, J = 10.6 Hz, 1H). ^{13}C{1H} NMR (151 MHz, CDCl$_3$) δ 161.6, 160.0, 136.7, 134.5, 133.9, 130.5 (d, J = 9.2 Hz), 127.6 (d, J = 5.3 Hz), 126.3, 124.4, 116.8 (d, J = 25.4 Hz), 114.3, 111.1 (d, J = 20.5 Hz). ^{19}F-NMR (376 MHz, CDCl$_3$) δ −114.6.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c02867.

Experimental details, characterization data and spectra of novel compounds as well as spectra for NMR-quantification of literature known volatile compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Stille, J. K.; Su, H.; Brechot, P.; Parrinello, G.; Hegedus, L. S. Platinum-Catalyzed Asymmetric Hydroformylation of Olefins with

(−)-BPPM/SnCl2-based Catalyst Systems. *Organometallics.* **1991**, *10* (4), 1183−1189.

(2) Weissermel, K.; Arpe, H.-J. Benzene Derivatives. In *Industrial Organic Chemistry*, 4th ed.; John Wiley & Sons: 2003; pp 337−385.

(3) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *J. Am. Chem. Soc.* **2012**, *51* (21), 5062−5085.

(4) Heck, R.; Acylation, F. Methylation, and Carboxyalkylation of Olefins by Group VIII Metal Derivatives. *J. Am. Chem. Soc.* **1968**, *90* (20), 5518−5526.

(5) Mizoroki, T.; Mori, K.; Ozaki, A. Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *Bull. Chem. Soc. Jpn.* **1971**, *44* (2), 581.

(6) Heck, R. F.; Nolley, J. P., Jr. Palladium-Catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides. *J. Org. Chem.* **1972**, *37* (14), 2320−2322.

(7) Kitamura, T.; Fujiwara, Y. Dehydrogenative Heck-Type Reactions: The Fujiwara-Moritani Reaction. In *RSC Green Chem.*, Royal Society of Chemistry, **2014**; pp 33−54.

(8) Zhou, L.; Lu, W. Towards Ideal Synthesis: Alkenylation of Aryl C-H Bonds by a Fujiwara−Moritani Reaction. *Chem.—Eur. J.* **2014**, *20* (3), 634−642.

(9) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. Transition-Metal-Catalyzed C-H Alkylation Using Alkenes. *Chem. Rev.* **2017**, *117* (13), 9333−9403.

(10) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. Transition Metal-Catalyzed C−H Bond Functionalizations by the Use of Diverse Directing Groups. *Org. Chem. Front.* **2015**, *2* (9), 1107−1295.

(11) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A Comprehensive Overview of Directing Groups Applied in Metal-Catalysed C−H Functionalisation Chemistry. *Chem. Soc. Rev.* **2018**, *47* (17), 6603−6743.

(12) Plevyak, E. J.; Heck, R. F. Palladium-Catalyzed Arylation of Ethylene. *J. Org. Chem.* **1978**, *43* (12), 2454−2456.

(13) Bräse, S.; Rümper, J.; Voigt, K.; Albecq, S.; Thurau, G.; Villard, R.; Waegell, B.; de Meijere, A. Synthesis of o-Dialkenylbenzenes and Indenes Using Heck and Oxypalladation Reactions. *Eur. J. Org. Chem.* **1998**, *1998* (4), 671−678.

(14) Atla, S. B.; Kelkar, A. A.; Puranik, V. G.; Bensch, W.; Chaudhari, R. V. NC Palladacycles in the Heck Arylation of Ethylene: Synthesis, Structure and Their Reactivity. *J. Organomet. Chem.* **2009**, *694* (5), 683−690.

(15) Kormos, C. M.; Leadbeater, N. E. Preparation of Nonsymmetrically Substituted Stilbenes in a One-Pot Two-Step Heck Strategy Using Ethene as a Reagent. *J. Org. Chem.* **2008**, *73* (10), 3854−3858.

(16) Southard, G. E.; Murray, G. M. Synthesis of Vinyl-Substituted *β*-Diketones for Polymerizable Metal Complexes. *J. Org. Chem.* **2005**, *70* (22), 9036−9039.

(17) Schnyder, A.; Aemmer, T.; Indolese, A. F.; Pittelkow, U.; Studer, M. First Application of Secondary Phosphines as Supporting Ligands for the Palladium-Catalyzed Heck Reaction: Efficient Activation of Aryl Chlorides. *Adv. Synth. Catal.* **2002**, *344* (5), 495−498.

(18) Kayaki, Y.; Noguchi, Y.; Ikariya, T. Enhanced Product Selectivity in the Mizoroki−Heck Reaction Using a Supercritical Carbon Dioxide−Liquid Biphasic System. *ChemComm.* **2000**, *22*, 2245−2246.

(19) DeVries, R. A.; Mendoza, A. Synthesis of High-Purity o- and p-Vinyltoluenes by the Heck Palladium-Catalyzed Arylation Reaction. *Organometallics.* **1994**, *13* (6), 2405−2411.

(20) Bourne, S. L.; O'Brien, M.; Kasinathan, S.; Koos, P.; Tolstoy, P.; Hu, D. X.; Bates, R. W.; Martin, B.; Schenkel, B.; Ley, S. V. Flow Chemistry Syntheses of Styrenes, Unsymmetrical Stilbenes and Branched Aldehydes. *ChemCatChem.* **2013**, *5* (1), 159−172.

(21) Bourne, S. L.; Koos, P.; O'Brien, M.; Martin, B.; Schenkel, B.; Baxendale, I. R.; Ley, S. V. The Continuous-Flow Synthesis of Styrenes Using Ethylene in a Palladium-Catalysed Heck Cross-Coupling Reaction. *Synlett.* **2011**, *2011* (18), 2643−2647.

(22) Grasa, G. A.; Singh, R.; Stevens, E. D.; Nolan, S. P. Catalytic Activity of Pd(II) and Pd(II)/DAB-R Systems for the Heck Arylation of Olefins. *J. Organomet. Chem.* **2003**, *687* (2), 269−279.

(23) Smith, C. R.; RajanBabu, T.V. Low Pressure Vinylation of Aryl and Vinyl Halides via Heck−Mizoroki Reactions Using Ethylene. *Tetrahedron.* **2010**, *66* (5), 1102−1110.

(24) Spettel, M.; Pollice, R.; Schnürch, M. Quaternary Ammonium Salts as Alkylating Reagents in C−H Activation Chemistry. *Org. Lett.* **2017**, *19* (16), 4287−4290.

(25) Schönbauer, D.; Spettel, M.; Pollice, R.; Pittenauer, E.; Schnürch, M. Investigations of the Generality of Quaternary Ammonium Salts as Alkylating Agents in Direct C−H Alkylation Reactions: Solid Alternatives for Gaseous Olefins. *Org. Biomol. Chem.* **2019**, *17* (16), 4024−4030.

(26) Ammar, Y. A.; Salem, M. A.; Fayed, E. A.; Helal, M. H.; El-Gaby, M. S. A.; Thabet, H. K. Naproxen Derivatives: Synthesis, Reactions, and Biological Applications. *Synth. Commun.* **2017**, *47* (15), 1341−1367.

(27) Viviano, M.; Glasnov, T. N.; Reichart, B.; Tekautz, G.; Kappe, C. O. A Scalable Two-Step Continuous Flow Synthesis of Nabumetone and Related 4-Aryl-2-butanones. *Org. Process Res. Dev.* **2011**, *15* (4), 858−870.

(28) Ziegler, C. B., Jr.; Heck, R. F. Palladium-Catalyzed Vinylic Substitution with Highly Activated Aryl Halides. *J. Org. Chem.* **1978**, *43* (15), 2941−2946.

(29) Tao, L.-M.; Li, Q.-G.; Liu, W.-Q.; Zhou, Y.; Zhou, J.-F. Water-Promoted Palladium-Catalysed Heck Cross-Coupling Reactions of Aryl Halides with Alkenes in TBAB. *J. Chem. Res.* **2011**, *35* (3), 154−156.

(30) Khuong, K. S.; Jones, W. H.; Pryor, W. A.; Houk, K. N. The Mechanism of the Self-Initiated Thermal Polymerization of Styrene. Theoretical Solution of a Classic Problem. *J. Am. Chem. Soc.* **2005**, *127* (4), 1265−1277.

(31) Stevens, K. A.; Smith, Z. P.; Gleason, K. L.; Galizia, M.; Paul, D. R.; Freeman, B. D. Influence of Temperature on Gas Solubility in Thermally Rearranged (TR) Polymers. *J. Membr. Sci.* **2017**, *533*, 75−83.

(32) Saha, S.; Baker, G. L. Substituent Effects in Surface-Initiated ATRP of Substituted Styrenes. *Appl. Surf. Sci.* **2015**, *359*, 911−916.

(33) Richmond, E.; Moran, J. Ligand Control of E/Z Selectivity in Nickel-Catalyzed Transfer Hydrogenative Alkyne Semireduction. *J. Org. Chem.* **2015**, *80* (13), 6922−6929.

(34) An, N.; Ainembabazi, D.; Reid, C.; Samudrala, K.; Wilson, K.; Lee, A. F.; Voutchkova-Kostal, A. Microwave-Assisted Decarbonylation of Biomass-Derived Aldehydes Using Pd-Doped Hydrotalcites. *ChemSusChem.* **2020**, *13* (2), 312−320.

(35) Jiang, Y.; Fang, W.-Y.; Rakesh, K. P.; Qin, H.-L. Copper-Catalyzed Mild Desulfonylation of Vinyl Sulfonyl Molecules. *Org. Chem. Front.* **2020**, *7* (13), 1696−1702.

(36) Aukland, M. H.; Talbot, F. J. T.; Fernández-Salas, J. A.; Ball, M.; Pulis, A. P.; Procter, D. J. An Interrupted Pummerer/Nickel-Catalysed Cross-Coupling Sequence. *Angew. Chem., Int. Ed.* **2018**, *57* (31), 9785−9789.

(37) Liu, K.-J.; Jiang, S.; Lu, L.-H.; Tang, L.-L.; Tang, S.-S.; Tang, H.-S.; Tang, Z.; He, W.-M.; Xu, X. Bis(methoxypropyl) Ether-Promoted Oxidation of Aromatic Alcohols into Aromatic Carboxylic Acids and Aromatic Ketones with O_2 Under Metal- and Base-Free Conditions. *Green Chem.* **2018**, *20* (13), 3038−3043.

(38) Wang, C.; Gong, S.; Liang, Z.; Sun, Y.; Cheng, R.; Yang, B.; Liu, Y.; Yang, J.; Sun, F. Ligand-Promoted Iridium-Catalyzed Transfer Hydrogenation of Terminal Alkynes with Ethanol and Its Application. *ACS Omega.* **2019**, *4* (14), 16045−16051.

(39) Gordillo, Á.; de Jesús, E.; López-Mardomingo, C. Consecutive Palladium-Catalyzed Hiyama−Heck Reactions in Aqueous Media

Under Ligand-Free Conditions. *ChemComm.* **2007**, No. 39, 4056–4058.

(40) Zhang, X.; Jiang, Y.; Fei, H. UiO-Type Metal–Organic Frameworks with NHC or Metal–NHC Functionalities for N-Methylation Using CO2 as The Carbon Source. *ChemComm.* **2019**, *55* (79), 11928–11931.

(41) Denmark, S. E.; Butler, C. R. Vinylation of Aryl Bromides Using an Inexpensive Vinylpolysiloxane. *Org. Lett.* **2006**, *8* (1), 63–66.

(42) Falk, A.; Cavalieri, A.; Nichol, G. S.; Vogt, D.; Schmalz, H.-G. Enantioselective Nickel-Catalyzed Hydrocyanation Using Chiral Phosphine-Phosphite Ligands: Recent Improvements and Insights. *Adv. Synth. Catal.* **2015**, *357* (14–15), 3317–3320.

(43) Lafaye, K.; Nicolas, L.; Guérinot, A.; Reymond, S.; Cossy, J. Lewis Basicity Modulation of N-Heterocycles: A Key for Successful Cross-Metathesis. *Org. Lett.* **2014**, *16* (19), 4972–4975.

(44) Akram, M. O.; Shinde, P. S.; Chintawar, C. C.; Patil, N. T. Gold(I)-Catalyzed Cross-Coupling Reactions of Aryldiazonium Salts with Organostannanes. *Org. Biomol. Chem.* **2018**, *16* (16), 2865–2869.

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DIII.2 Manuscript 2 – Supporting Information

A concise summary of the detailed procedure for quantitative ^{1}H-NMR measurements, including complete optimization screening data, experimental details, characterization data for all isolated compounds, and NMR spectra for the quantification of literature known volatile compounds.

Eleni Papaplioura, Maëva Mercier, Michael E. Muratore, Tobias Biberger, Soufyan Jerhaoui and Michael Schnürch

Supporting Information for

Tetraethylammonium Salts as Solid, Easy to Handle Ethylene Precursors and Their Application in Mizoroki–Heck Coupling

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Supporting Information

Tetraethylammonium salts as solid, easy to handle ethylene precursors and their application in Mizoroki-Heck coupling.

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Abbreviation	**Definition**
TEA	Triethylamine
TMB	1,3,5-Trimethoxybenzene
SM	Starting material
IS	Internal standard

General Experimental Details

Unless noted otherwise, reactants and reagents were purchased from commercial suppliers and used without further purification. The 4 mL brown-glass vials were sealed with Wheaton® screw caps containing a PTFE faced 14B styrene-butadiene rubber liner. All reactions were magnetically stirred and heated in a metallic reaction block. All reaction temperatures refer to external temperatures.

NMR spectra were recorded in $CDCl_3$ or d_8-toluene on a Brucker Avance UltraShield (400 MHz) or Avance III HD 600 (600 MHz) spectrometer and 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 by the following abbreviations = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

Thin Layer Chromatography (TLC) analysis was performed on precoated aluminum-backed unmodified plates (Silica gel 60 F_{254}, Merck). Compounds were visualized under UV light.

Flash column chromatography was performed using either Merck silica gel 60 (40 µm – 63 µm) by hand column or purification was performed using a TELEDYNE ISCO COMBI FLASH® COMPANION® NextGen300+ flash chromatography system with UV-Vis detector (diode array) with Macherey-Nagel Chromabond RS silica gel columns.

GC-MS analysis was performed on 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 programs: **Method A:** 2 min at 100 °C, 35 °C/min until 300 °C, 4 min at 300 °C and **Method B:** 2.5 min at 40 °C, 12 °C/min until 220 °C, 2.5 min at 220 °C.

HR-MS data were recorded using a Thermo Scientific Orbitrap Elite hybrid ion trap/orbitrap spectrometer system with an Ultimate 3000 series LPG-3400XRS pump system. Mass calibration was performed using the Pierce LTQ Velos ESI positive ion calibration solution from Thermo Scientific (lot PF200011, product no. 88323).

General Experimental Procedures

Reaction Optimization Screening

General Procedure A

In a 4-mL brown vial equipped with a magnetic stirring bar and a Wheaton® screw cap, were added 2-bromo-6-methoxynapthalene (**1**) (48.4 mg, 0.2 mmol, 1 equiv.), the respective ammonium salt (8 equiv.), the base (8 equiv.), and the catalyst (x mol %). Subsequently, solvent (0.2 M) was added *via* syringe, and the reaction mixture was heated to 120 °C, or to 100 °C and 80 °C, depending on the corresponding solvent in a metallic block for 18-36 h respectively.

Sample preparation for ^{1}H-NMR quantification:

The reaction mixture was cooled down to room temperature and filtered over celite in a syringe filter. The filter cake was washed with EtOAc and the volatiles removed in *vacuo*. 1,3,5-Trimethoxybenzene (0.2 mmol, 1 equiv.) was added, and the crude mixture was dissolved in 0.5 mL $CDCl_3$ and transferred to an NMR tube. The recorded spectra were processed by MestReNova v14 software.

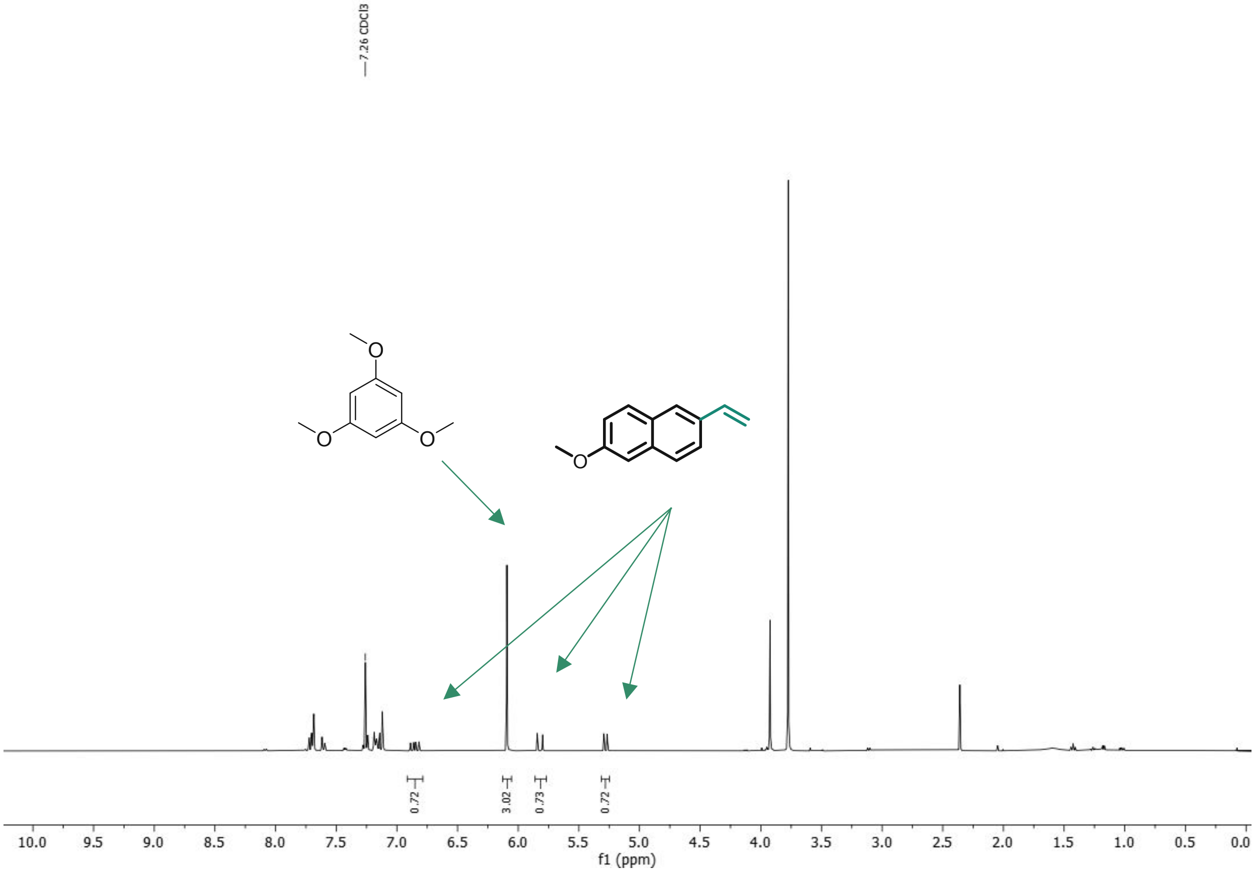


Figure S1: ^{1}H-NMR used as an example for quantification.

Substrate Scope Screening

General Procedure B

In a 4-mL brown vial equipped with a magnetic stirring bar and a Wheaton® screw cap, were added the starting material (0.2 mmol, 1 equiv.), Et_4NBr (8 equiv.), KO*t*Bu (8 equiv.), and PdRuPhos G3 (10 mol %). Subsequently, d_8-toluene (0.2 M) was added *via* syringe, and the reaction mixture was heated to 100 °C, in a metallic block for 18-36 h.

Sample preparation for ^{1}H-NMR quantification:

The reaction mixture was cooled down to room temperature and filtered in a syringe filter. The filter cake was washed with d_8-toluene and 1,3,5-trimethoxybenzene (0.2 mmol, 1 equiv.) was added to the crude reaction mixture. In an NMR tube were transferred 0.5 mL of the reaction solution and the recorded spectra were processed by MestReNova v14.

General Procedure C

In a 4-mL brown vial equipped with a magnetic stirring bar and a Wheaton® screw cap, were added the starting material (0.2 mmol, 1 equiv.), Et_4NBr (8 equiv.), KO*t*Bu (8 equiv.), and PdRuPhos G3 (10 mol %). Subsequently, toluene (0.2 M) was added *via* syringe, and the reaction mixture was heated to 100 °C, in a metallic block for 18-36 h.

- Workup Procedure 1: The reaction mixture was cooled down to room temperature and filtered in a syringe filter. The filter cake was washed with EtOAc and the volatiles removed in *vacuo*.
- Workup Procedure 2: The reaction mixture was cooled down to room temperature and filtered in a syringe filter and toluene was removed in *vacuo*. The crude mixture was redissolved in DCM and water was added (HCl 1M was added for neutralization). The aqueous phase was extracted with DCM (x 5), the combined organic extracts dried over Na_2SO_4 and the volatiles removed in *vacuo*.

Sample preparation for ^{1}H-NMR quantification:

1,3,5-Trimethoxybenzene (0.2 mmol, 1 equiv.) was added, and the crude mixture was dissolved in 0.5 mL $CDCl_3$ and transferred to an NMR tube. The recorded spectra were processed by MestReNova v14 software. The crude residue was purified either *via* manual column chromatography using unmodified silica or using an automated purification system.

General Procedure D

In a 4-mL brown vial equipped with a magnetic stirring bar and a Wheaton® screw cap, were added the starting material (0.2 mmol, 1 equiv.), Et_4NBr (8 equiv.), KO*t*Bu (8 equiv.), and PdXPhos G (10 mol %). Subsequently, toluene (0.2 M) was added *via* syringe, and the reaction mixture was heated to 100 °C, in a metallic block for 18-20 h.

- Workup Procedure 1: The reaction mixture was cooled down to room temperature and filtered in a syringe filter. The filter cake was washed with EtOAc and the volatiles removed in *vacuo*.

Sample preparation for ^{1}H-NMR quantification:

1,3,5-Trimethoxybenzene (0.2 mmol, 1 equiv.) was added, and the crude mixture was dissolved in 0.5 mL $CDCl_3$ and transferred to an NMR tube. The recorded spectra were processed by MestReNova v14 software. The crude residue purified either *via* manual column chromatography using unmodified silica or using an automated purification system.

General Procedure E

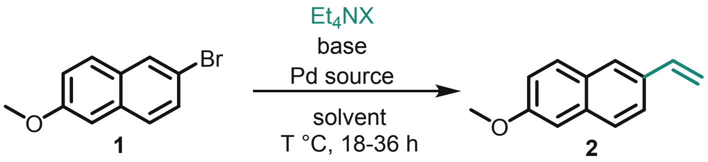
In a 4-mL brown vial equipped with a magnetic stirring bar and a Wheaton® screw cap, were added the starting material (0.2 mmol, 1 equiv.), Et_4NBr (8 equiv.), KO*t*Bu (8 equiv.), and PdXPhos G4 (10 mol %). Subsequently, d_8-toluene (0.2 M) was added *via* syringe, and the reaction mixture was heated to 100 °C, in a metallic block for 18 h.

Sample preparation for ^{1}H-NMR quantification:

The reaction mixture was cooled down to room temperature and filtered in a syringe filter. The filter cake was washed with d_8-toluene and 1,3,5-trimethoxybenzene (0.2 mmol, 1 equiv.) was added to the crude reaction mixture. In an NMR tube were transferred 0.5 mL of the reaction solution and the recorded spectra were processed by MestReNova v14.

Optimization Screening

The reaction below was chosen as the model reaction and yields were determined by quant. ^{1}H-NMR spectroscopy for the crude reaction mixtures using 1,3,5- trimethoxybenzene as internal standard. We examined the following parameters: quaternary ammonium salt, base, Pd source/ loading, solvent, temperature, reaction time.



Reactions were performed according to the general procedure A using Et_4NBr (1.6 mmol, 8 equiv.) as the olefin surrogate, the respective base (1.6 mmol, 8 equiv.), PdXPhos G4 (5 or 10 mol %) as the catalyst and toluene (1 mL, 0.2 M) at 120 °C for 18 h.

Table S1: Base screening:

Entry	Ammonium salt	Solvent	Base	Pd source	Yield (%)
1	Et_4NBr	Toluene	KOH	PdXPhos G4 (10 mol %)	20
2	Et_4NBr	Toluene	KOH	PdXPhos G4 (5 mol %)	31
3	Et_4NBr	Toluene	DBU	PdXPhos G4 (10 mol %)	-
4	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4 (5 mol %)	44
5	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4 (10 mol %)	54
6	Et_4NBr	Toluene	KOTMS	PdXPhos G4 (10 mol %)	48

Reactions were performed according to the general procedure A using the respective ammonium salt (1.6 mmol, 8 equiv.) as the olefin surrogate, KO*t*Bu as the base (1.6 mmol, 8 equiv.), PdXPhos G4 (10 mol %) as the catalyst and toluene (1 mL, 0.2 M) at 120 °C for 18 h.

Table S2: Quaternary ammonium salt screening:

Entry	Ammonium salt	Solvent	Base	Pd source	Yield (%)
1	Et_4NCl	Toluene	KO*t*Bu	PdXPhos G4	53
2	Et_4NI	Toluene	KO*t*Bu	PdXPhos G4	49
3	Et_4NPF_6	Toluene	KO*t*Bu	PdXPhos G4	48
4	Et_4NBF_4	Toluene	KO*t*Bu	PdXPhos G4	44
5	$PhEt_3NI$	Toluene	KO*t*Bu	PdXPhos G4	8

Reactions were performed according to the general procedure A using Et_4NBr (1.6 mmol, 8 equiv.) as the olefin surrogate, KO*t*Bu as the base (1.6 mmol, 8 equiv.), the respective catalyst (10 mol %) and toluene (1 mL, 0.2 M) at 120 °C.

Table S3: Catalyst screening, temperature, reaction times and loadings:

Entry	Ammonium salt	Solvent	Base	Pd source	Temp. °C	Time	Yield (%)
1	Et_4NBr	Toluene	KO*t*Bu	$PdOAc_2$ /$(o\text{-}Tol)_3P$ (40 mol %)	100	18	trace
2	Et_4NBr	Toluene	KO*t*Bu	$Pd(OAc)_2$ /1 wt % H_2O	120	20	31
3	Et_4NBr	Toluene	KO*t*Bu	$Pd(OAc)_2$ /1 wt % H_2O	120	72	47
4	Et_4NBr	Toluene	KO*t*Bu	$Pd(OAc)_2$/ PPh_3 (20 mol %)	120	20	29
5	Et_4NBr	Toluene	KO*t*Bu	$Pd(OAc)_2$/ PCy_3 (20 mol %)	120	20	25
6	Et_4NBr	Toluene	KO*t*Bu	$PdCl_2$	120	20	0
7	Et_4NBr	Toluene	KO*t*Bu	$PdCl_2$ / PPh_3 (20 mol %)	120	20	43
8	Et_4NBr	Toluene	KO*t*Bu	$PdCl_2(PPh_3)_2$	120	20	18
9	Et_4NBr	Toluene	KO*t*Bu	$Pd_2(dba)_3$	120	20	25
10	Et_4NBr	Toluene	KO*t*Bu	$Pd(PPh_3)_4$	120	20	28
11	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4	120	18	54
12	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4	100	18	77
13	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4/ 1 wt % H_2O	120	20	44
14	Et_4NBr	Toluene	KO*t*Bu	PdSPhos G3	100	18	73
15	Et_4NBr	Toluene	KO*t*Bu	PdBINAP G4	100	18	27
16	Et_4NBr	Toluene	KO*t*Bu	Pd CataCXium A G3	100	18	53
17	Et_4NBr	Toluene	KO*t*Bu	PdBrettPhos G4	100	18	26
18	Et_4NBr	Toluene	KO*t*Bu	PdCPhos G3	100	18	53
19	Et_4NBr	Toluene	KO*t*Bu	$Pd(dppf)Cl_2$	100	18	13
20	Et_4NBr	Toluene	KO*t*Bu	$(Ataphos)_2PdCl_2$	100	18	-
21	Et_4NBr	Toluene	KO*t*Bu	PdXanpthos G3	100	18	27
22	Et_4NBr	Toluene	KO*t*Bu	PdPEPPSI	100	18	20
23	Et_4NBr	Toluene	KO*t*Bu	PdRuPhos G3	100	18	82
24	Et_4NBr	Toluene	KO*t*Bu	PdJosiphos SL-J009-1 G3	100	18	79
25	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4 (10 mol %)	120	6	50
26	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4 (5 mol %)	120	9	48

Reactions were performed according to the general procedure A using Et_4NBr (1.6 mmol, 8 equiv.) as the olefin surrogate, KO*t*Bu as the base (1.6 mmol, 8 equiv.), PdXPhos G4 (10 mol %) as the catalyst, and the respective solvent (1 mL, 0.2 M) for 20-48 h.

Table S4: Solvent screening:

Entry	Ammonium salt	Solvent	Base	Pd source	Temp. °C	Time	Yield (%)
1	Et_4NBr	Me-THF	KO*t*Bu	PdXPhos G4	80	20	-
2	Et_4NBr	Me-THF	KO*t*Bu	PdXPhos G4	80	48	-
3	Et_4NBr	CPME	KO*t*Bu	PdXPhos G4	100	20	70
4	Et_4NBr	CPME	KO*t*Bu	PdXPhos G4	100	48	71

Reactions were performed according to the general procedure A using Et_4NBr (1.6 mmol, 8 equiv.) as the olefin surrogate, KO*t*Bu as the base (1.6 mmol, 8 equiv.), PdXPhos G4 (10 mol %) as the catalyst, the respective polymerization inhibitor and toluene as the solvent (1 mL, 0.2 M) at 100-120 °C for 20 h.

Table S5: Polymerization inhibitors screening:

Entry	Ammonium salt	Solvent	Base	Pd source	Temp. °C	Yield (%)
1	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4/10 mol % cod	120	55
2	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4/BHT (1 equiv.)	100	75
3	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4/ 1 wt % 4-*tert*-butylcatechol	100	75

Reactions were performed according to the general procedure A using Et_4NBr (1.6 mmol, 8 equiv.) as the olefin surrogate, KO*t*Bu as the base (1.6 mmol, 8 equiv.), PdXPhos G4 (x mol %) as the catalyst, and toluene as the solvent (1 mL, 0.2 M) at 120 °C for 20 h.

Table S6: Catalyst equivalents screening:

Entry	Ammonium salt	Solvent	Base	Pd source	Yield (%)
1	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4 (5 mol %)	44
2	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4 (15 mol %)	46
3	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4 (20 mol %)	43

Table S7: Control experiments screening:

Entry	Ammonium salt	Solvent	Base	Pd source	Additive	Yield (%)
1	Et_4NBr	Toluene	KO*t*Bu	PdRuPhos G3	styrene (1 equiv.)	80
2	Et_4NBr	Toluene	KO*t*Bu	PdXPhos G4	styrene (1 equiv.)	44
3	Et_4NBr	Toluene	KO*t*Bu	PdRuPhos G3 (10 mol %)	Et_3N	83

Table S8: NMR quantification calculations of volatile products 3-16 & 20:

Entry	Product	SM (mmol)	IS (mmol)	Integral of one vinylic proton (product)	Integral of aromatic protons IS (three protons)	Yield (%)
1	**3** (X=Br)	0.2	0.2	0.67	3.00	67
2	**3** (X=I)	0.2	0.2	0.45	3.00	45
3	**4**	0.2	0.190	0.75	3.00	71
4	**5**	0.2	0.193	0.43	3.00	41
5	**6**	0.2	0.2	0.32	3.00	32
6	**7**	0.2	0.2	0.20	3.00	20
7	**8**	0.2	0.196	0.52	3.00	51
8	**9**	0.2	0.193	0.52	3.00	50
9	**10**	0.2	0.190	0.33	3.00	31
10	**11**	0.21	0.188	0.23	3.00	21
11	**12**	0.2	0.188	0.46	3.00	43
12	**13**	0.2	0.21	0.54	3.00	56
13	**14**	0.2	0.2	0.60	3.00	60
14	**15**	0.2	0.2	0.40	3.00	40
15	**16**	0.2	0.2	0.15	3.00	15
16	**20**	0.2	0.2	0.57	3.00	57

CO-Ware reactor

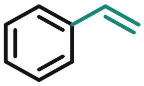
In a two-chamber reactor (CO-Ware) equipped with two stirring bars at each chamber were added: **Chamber 1**: Et_4NBr (8 equiv.), KOH (8 equiv.) and toluene (1 mL), **Chamber 2**: Starting material (0.2 mmol, 1 equiv.), KO*t*Bu (8 equiv.),PdXPhos G4 (5 mol%) and toluene (0.2 M, 1 mL), and the reaction mixture was heated to 120 °C in a metallic block for 20 h. No product formation was observed.

Characterization data for all synthetic compounds

All synthesized compounds are described in the literature, except for **18**, **19**, **22** and **25**. In the case of already known compounds, the spectra were in agreement with literature values.

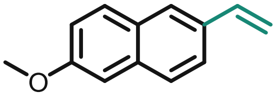
Substrate Scope

Styrene (3)[1] [CAS 100-42-5]



The title compound was prepared according to general procedure B from commercially available starting materials with a reaction time of 20 h. From bromobenzene **[CAS 108-86-1]:** ^{1}H-NMR yield (based on the integration of peaks at 6.10 and 5.59 ppm): 67 %, and from iodobenzene **[CAS 591-50-4]:** ^{1}H-NMR yield (based on the integration of peaks at 6.10 and 5.59 ppm): 45 %

2-Vinyl-6-methoxynaphthalene (2)[2] [CAS: 63444-51-9]



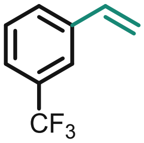
The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as a white solid. ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.80 ppm): 82 %. Isolated yield: (30 mg, 81 %).

^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.77 – 7.67 (m, 3H), 7.60 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.19 – 7.09 (m, 2H), 6.85 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.82 (dd, *J* = 17.6, 0.9 Hz, 1H), 5.28 (dd, *J* = 10.8, 0.9 Hz, 1H), 3.92 (s, 3H).

^{13}C{1H} NMR (101 MHz, CDCl$_3$) δ 157.9, 137.1, 134.5, 133.1, 129.7, 129.1, 127.1, 126.3, 123.9, 119.1, 113.2, 106.0, 55.5.

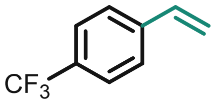
Compound (**2**) was also prepared on a 0.4 mmol scale as described above: ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.80 ppm): 71 %, on a 0.6 mmol scale: ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.80 ppm): 65 %, and on a 1 mmol scale (1 equiv.) using Et$_4$NBr (8 equiv.), KO*t*Bu (8 equiv.), and PdRuPhos G3 (10 mol %).: Isolated yield: (68 mg, 37 %, 0.148 mmol).

1-(Trifluoromethyl)-3-vinylbenzene (4)[3] [CAS: 402-24-4]



The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.10 and 5.49 ppm): 71 %.

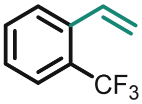
1-(Trifluoromethyl)-4-vinylbenzene (5)[3] [CAS: 402-50-6]



The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.47 ppm): 41 %.

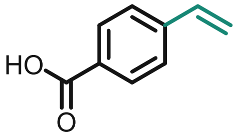
The title compound was also prepared according to general procedure E from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.47 ppm): 9 %.

1-(Trifluoromethyl)-2-vinylbenzene (6)[4] [CAS: 395-45-9]



The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 40 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.48 ppm): 32 %.

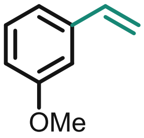
4-Vinylbenzoic acid (7)[5] [CAS: 1075-49-6]



The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.57 ppm): 20 %.

The title compound was also prepared according to general procedure E from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.57 ppm): 31 %.

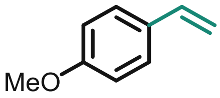
1-Methoxy-3-vinylbenzene (8)[6] [CAS: 626-20-0]



The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.78 ppm): 51 %.

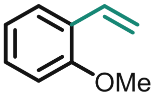
The title compound was prepared according to general procedure E from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.78 ppm): 51 %.

1-Methoxy-4-vinylbenzene (9)[7] [CAS: 637-69-4]



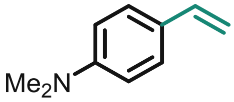
The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 40 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.54 ppm): 50 %.

1-Methoxy-2-vinylbenzene (10)[6] [CAS: 612-15-7]



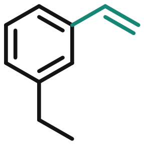
The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 40 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.71 ppm): 31 %.

***N*,*N*-Dimethyl-4-vinylaniline (11)[8] [CAS: 2039-80-7]**



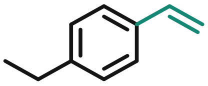
The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.57 ppm): 21 %.

1-Ethyl-3-vinylbenzene (12) [CAS: 7525-62-4] Spectral data were obtained from Enamine Ltd.



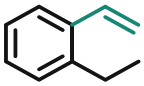
The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.67 ppm): 43 %.

1-Ethyl-4-vinylbenzene (13)[3] [CAS: 3454-07-7]



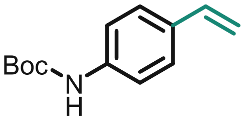
The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.63 ppm): 56 %.

1-Ethyl-2-vinylbenzene (14)[9] [CAS: 7564-63-8]



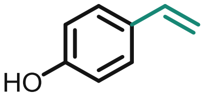
The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.54 ppm): 60 %.

tert-Butyl (4-vinylphenyl)carbamate (15)[10] [CAS: 57295-14-4]



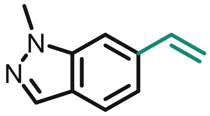
The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 20 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.68 ppm): 40 %.

4-Vinylphenol (16)[11] [CAS: 2628-17-3]



The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 18 h. ^{1}H-NMR yield (based on the integration of peaks at 6.15 and 5.61 ppm): 15 %.

1-Methyl-6-vinyl-1*H*-indazole (17)



The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as white solid. ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.86 ppm): 66 %. Isolated yield: (8 mg, 25 %). Decomposition observed over time, and upon applying high vacuum.

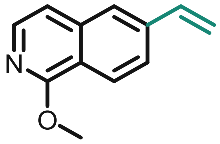
The title compound was also prepared according to general procedure D from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.84 ppm): 56 %.

^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.93 (d, J = 1.0 Hz, 1H), 7.66 (dt, J = 8.4, 0.6 Hz, 1H), 7.35 – 7.27 (m, 2H), 6.91 – 6.80 (m, 1H), 5.86 (dd, J = 17.5, 0.8 Hz, 1H), 5.34 (dd, J = 10.9, 0.8 Hz, 1H), 4.07 (s, 3H).

^{13}C{1H} NMR (101 MHz, CDCl$_3$) δ 140.5, 137.3, 136.1, 132.8, 123.8, 121.1, 118.9, 114.7,107.1, 35.6.

HRMS (ESI/q-TOF): *m/z* [M+H]$^+$ calcd. for $C_{10}H_{10}N_2+H^+$: 159.0922; found: 159.0915.

1-Methoxy-6-vinylisoquinoline (18)



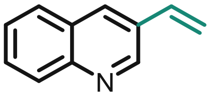
The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as a colorless oil. ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.92 ppm): 68 %. Isolated yield: (25 mg, 68 %, 91 % purity).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.14 (m, 1H), 7.98 (d, *J* = 5.9 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.17 (dd, *J* = 5.9, 0.9 Hz, 1H), 6.86 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.93 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.42 (dd, *J* = 10.9, 0.8 Hz, 1H), 4.13 (s, 3H).

^{13}C{1H} NMR (150 MHz, CDCl3) δ 161.0, 140.3, 139.5, 138.3, 136.5, 124.5, 124.3, 124.2, 119.3, 116.4, 115.1, 53.8.

HRMS (ESI/Orbitrap): *m/z* [M+H]$^+$ calcd. for $C_{12}H_{11}NO+H^+$: 186.0919; found:186.0913.

3-Vinylquinoline (19)[12] [CAS: 67752-31-2]

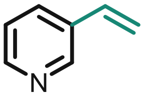


The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as pale-yellow oil. Isolated yield: (18 mg, 57 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 2.2 Hz, 1H), 8.11 – 8.05 (m, 2H), 7.81 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.68 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.54 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 6.88 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.99 (dd, *J* = 17.8, 0.6 Hz, 1H), 5.47 (dd, *J* = 11.0, 0.6 Hz, 1H).

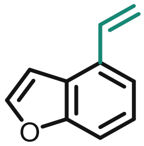
^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 149.3, 147.8, 133.9, 132.6, 130.5, 129.4, 129.4, 128.1, 128.0, 127.1, 116.5.

3-Vinylpyridine (20)[7] [CAS: 1121-55-7]



The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 40 h. ^{1}H-NMR yield (based on the integration of peaks at 6.13 and 5.53 ppm): 57 %.

4-Vinylbenzofuran (21) [CAS: 1337879-41-0]



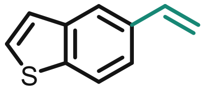
The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as a colorless oil. ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.88 ppm): 74 %. Isolated yield: (18 mg, 63 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.3 Hz, 1H), 7.43 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.35 (dt, *J* = 7.5, 0.8 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.07 – 6.99 (m, 1H), 6.97 (dd, *J* = 2.2, 1.0 Hz, 1H), 5.88 (dd, *J* = 17.7, 1.1 Hz, 1H), 5.42 (dd, *J* = 11.1, 1.1 Hz, 1H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 155.4, 145.3, 134.6, 131.2, 125.7, 124.4, 120.2, 115.8, 110.8, 105.3.

HRMS (ESI/Orbitrap): *m/z* [M+H]$^+$ calcd. for $C_{10}H_8O+H^+$: 145.0653; found: 145.0647.

5-Vinylbenzo[*b*]thiophene (22)[7] [CAS: 1033775-44-8]

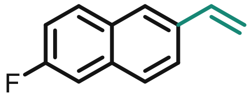


The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as yellow solid. ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.80 ppm): 70 %. Isolated yield: (22 mg, 69 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.52 – 7.41 (m, 2H), 7.32 (dd, *J* = 5.4, 0.8 Hz, 1H), 6.84 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.81 (dd, *J* = 17.6, 0.9 Hz, 1H), 5.28 (dd, *J* = 10.9, 0.9 Hz, 1H).

^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 140.1, 139.3, 137.1, 134.2, 127.0, 124.1, 122.6, 122.3, 121.8, 113.6.

2-Vinyl-6-fluoronaphthalene (23) [CAS: 1638155-81-3]



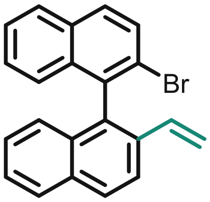
The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 18 h, following Workup Procedure 1. The crude residue was filtered over a short plug of silica using pentane to give the product as a colorless oil. ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.86 ppm): 77 %. Isolated yield: (23 mg, 67 %).

^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.78 (dd, *J* = 9.0, 5.6 Hz, 1H), 7.73 (dd, *J* = 5.0, 3.5 Hz, 2H), 7.65 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.41 (dd, *J* = 9.8, 2.6 Hz, 1H),7.29 – 7.19 (m, 1H), 6.86 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.85 (d, *J* = 17.6 Hz, 1H), 5.33 (d, *J* = 10.6 Hz, 1H).

^{13}C{1H} NMR (151 MHz, CDCl$_3$) δ 161.6, 160.0, 136.7, 134.5, 133.9, 130.5 (d, *J* = 9.2 Hz), 127.6 (d, *J* = 5.3 Hz), 126.3, 124.4, 116.8 (d, *J* = 25.4 Hz), 114.3, 111.1 (d, *J* = 20.5 Hz).

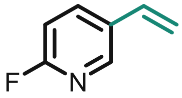
^{19}F-NMR (376 MHz, CDCl$_3$) δ -114.6.

2-Bromo-2'-vinyl-1,1'-binaphthalene (28)



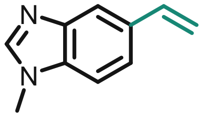
The title compound was prepared according to general procedure C from commercially available starting material with a reaction time of 20 h and 36 h, following Workup Procedure 1. ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.83 ppm): for 20 h: 14 %, incomplete conversion; for 36 h: 20 %, incomplete conversion.

5-Vinyl-2-fluoropyridine (29)[11] [CAS 1133879-66-9]



The title compound was prepared according to general procedure B from commercially available starting material with a reaction time of 20 h. ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.39 ppm): for 20 h: 33 %, incomplete conversion; for 36 h: 12 %, incomplete conversion.

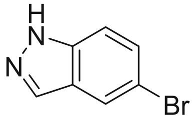
1-Methyl-5-vinyl-1*H*-benzo[*d*]imidazole (30)



The title compound was prepared according to general procedure D from commercially available starting material, with a reaction time of 18 h following Workup Procedure 1. ^{1}H-NMR yield (based on the integration of peaks at 6.09 and 5.76 ppm): 30 %.

Unsuccessful Substrates

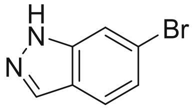
5-Bromo-1*H*-indazole [CAS: 53857-57-1]



Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

Following the general procedure D, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

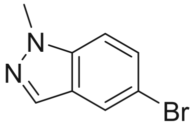
6-Bromo-1*H*-indazole [CAS: 79762-54-2]



Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

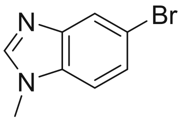
Following the general procedure D, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

5-Bromo-1-methyl-1*H*-indazole [CAS: 465529-57-1]



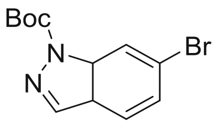
Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 20 h. After Workup Procedure 1, no product formed according to NMR analysis.

5-Bromo-1-methyl-1*H*-benzo[*d*]imidazole [CAS 53484-15-4]



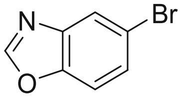
Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

tert-Butyl 6-bromo-1*H*-indazole-1-carboxylate [CAS 147621-26-9]



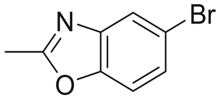
Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 20 h. After Workup Procedure 1, no product formed according to NMR analysis.

5-Bromobenzo[*d*]oxazole [CAS: 132244-31-6]



Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

5-Bromo-2-methylbenzo[*d*]oxazole [CAS: 5676-56-2]

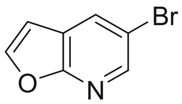


Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h.

Workup procedure 1: No product formation according to NMR analysis.

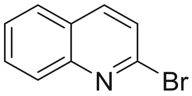
Workup procedure 2: No product formation according to NMR analysis.

5-Bromofuro[2,3-*b*]pyridine [CAS 220957-39-1]



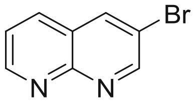
Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

2-Bromoquinoline [CAS 2005-43-8]



Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

3-Bromo-1,8-naphthyridine [CAS 17965-78-5]

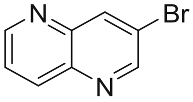


Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h.

Workup procedure 1: No product formation according to NMR analysis.

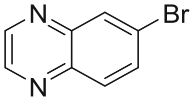
Workup procedure 2: No product formation according to NMR analysis.

3-Bromo-1,5-naphthyridine [CAS 17965-71-8]



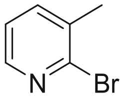
Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

6-Bromoquinoxaline [CAS50998-17-9]



Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

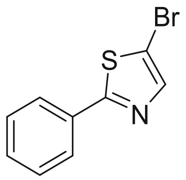
2-Bromo-3-methylpyridine [CAS 3430-17-9]



Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

Following the general procedure E, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

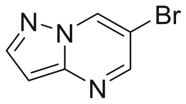
5-Bromo-2-phenylthiazole [CAS 53715-67-6]



Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

Following the general procedure D, the title compound was subjected to the reaction conditions with a reaction time of 18 h. After Workup Procedure 1, no product formed according to NMR analysis.

6-Bromopyrazolo[1,5-*a*]pyrimidine [CAS 705263-10-1]

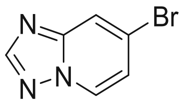


Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h.

Workup procedure 1: No product formation according to NMR analysis.

Workup procedure 2: No product formation according to NMR analysis.

7-Bromo-[1,2,4]triazolo[1,5-*a*]pyridine [CAS 1053655-66-5]

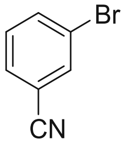


Following the general procedure C, the title compound was subjected to the reaction conditions with a reaction time of 18 h.

Workup procedure 1: No product formation according to NMR analysis.

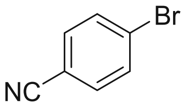
Workup procedure 2: No product formation according to NMR analysis.

3-Bromobenzonitrile [CAS 6952-59-6]



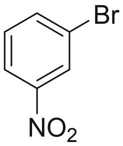
Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

4-Bromobenzonitrile [CAS 623-00-7]-886



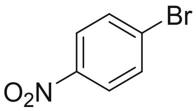
Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

1-Bromo-3-nitrobenzene [CAS 585-79-5]



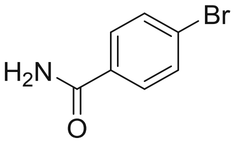
Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

1-Bromo-4-nitrobenzene [CAS 586-78-7]



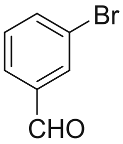
Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

4-Bromobenzamide [CAS698-67-9]



Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

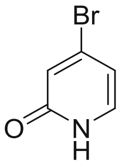
3-Bromobenzaldehyde [CAS 3132-99-8]



Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

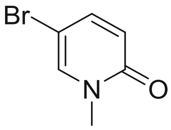
Following the general procedure E, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

4-Bromopyridin-2(1*H*)-one [36953-37-4]



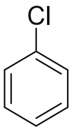
Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

5-Bromo-1-methylpyridin-2-one [CAS: 81971-39-3]



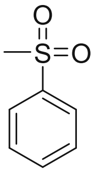
Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

Chlorobenzene [CAS 108-90-7]



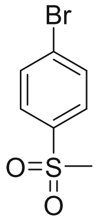
Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

Methyl phenyl sulfone [CAS 3112-85-4]



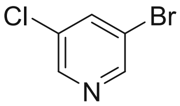
Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

4-Bromophenyl methyl sulfone [CAS 3466-32-8]



Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

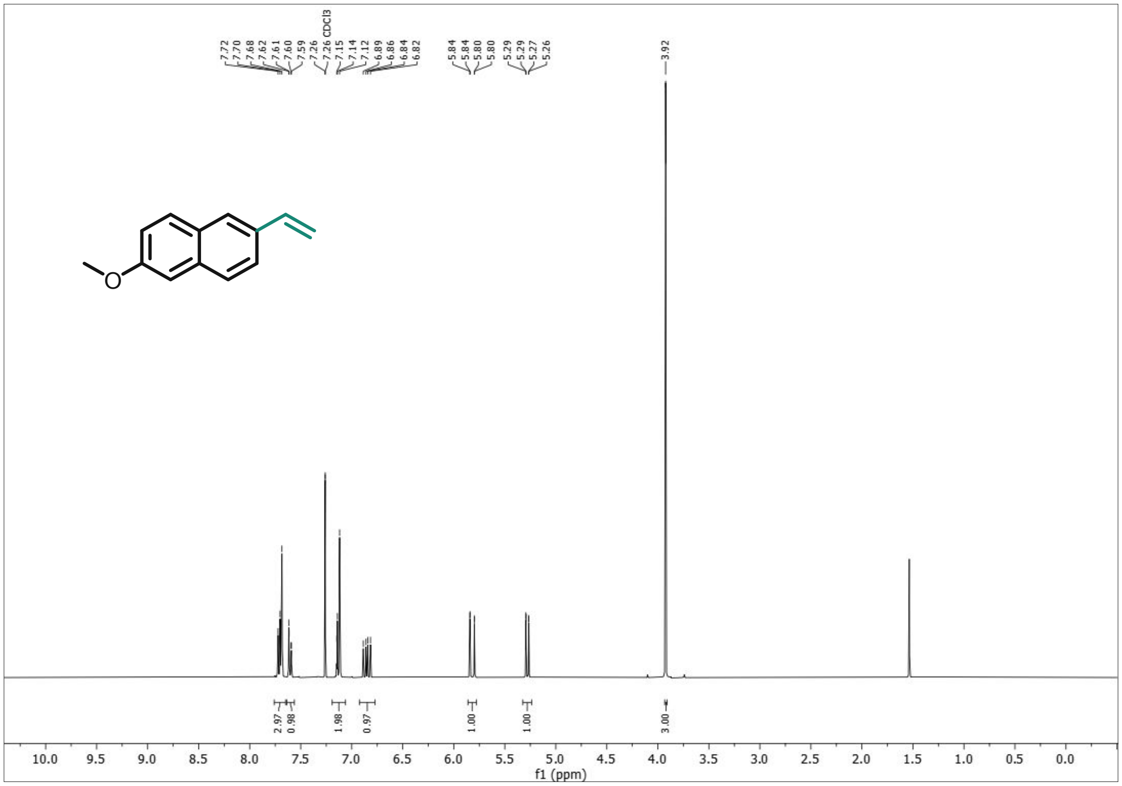
3-Bromo-5-chloropyridine [CAS 5140-72-7]



Following the general procedure B, the title compound was subjected to the reaction conditions with a reaction time of 18 h. No product formation according to NMR analysis.

NMR-Spectra of isolated compounds

2-Vinyl-6-methoxynaphthalene (2)



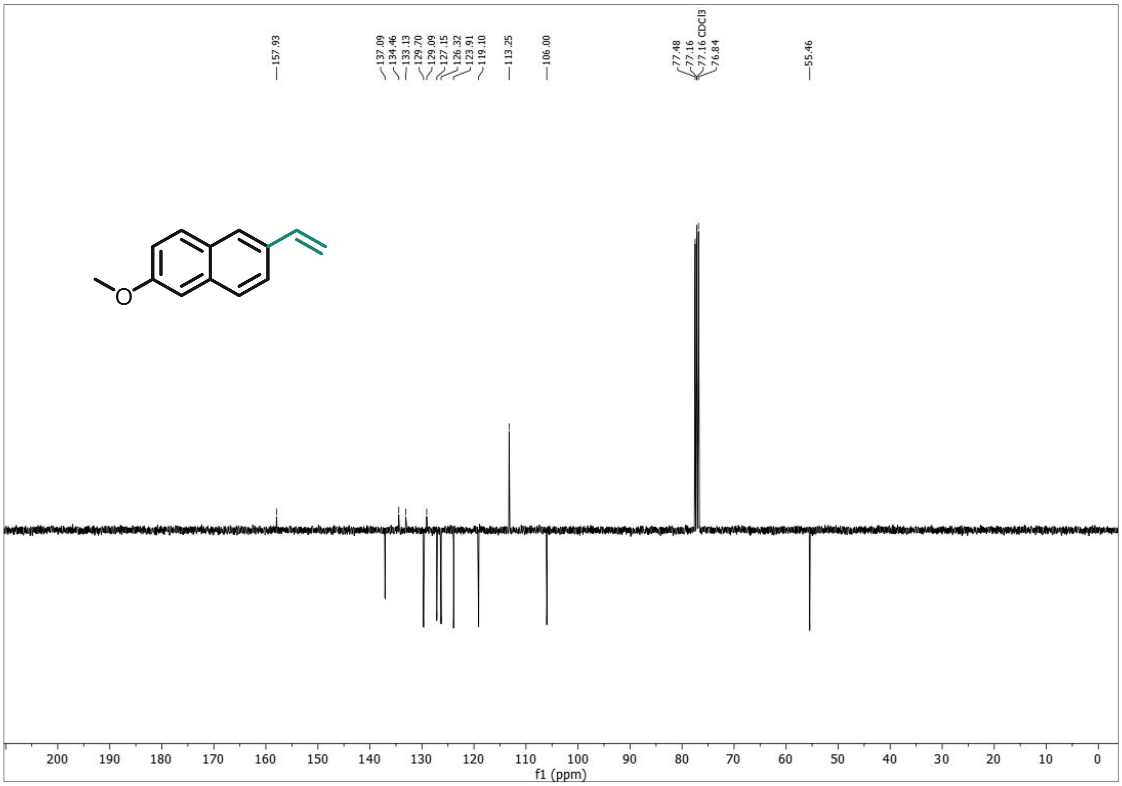


Figure S2: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 2-vInyl-6-methoxynapththalene (2).

1-Methyl-6-vinyl-1*H*-indazole (17)

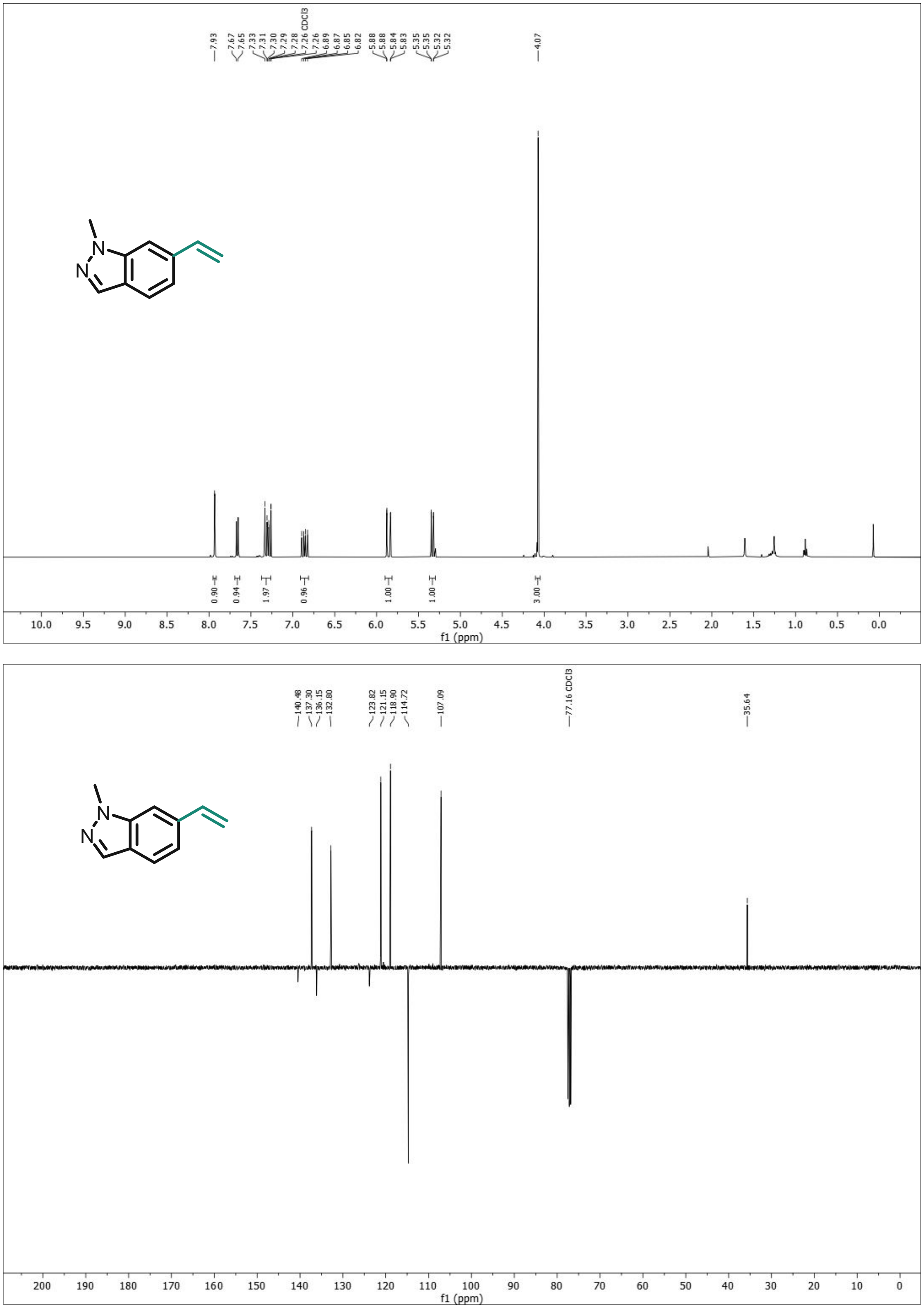


Figure S3: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 1-methyl-6-vinyl-1H-indazole (17).

1-Methoxy-6-vinylisoquinoline (18)

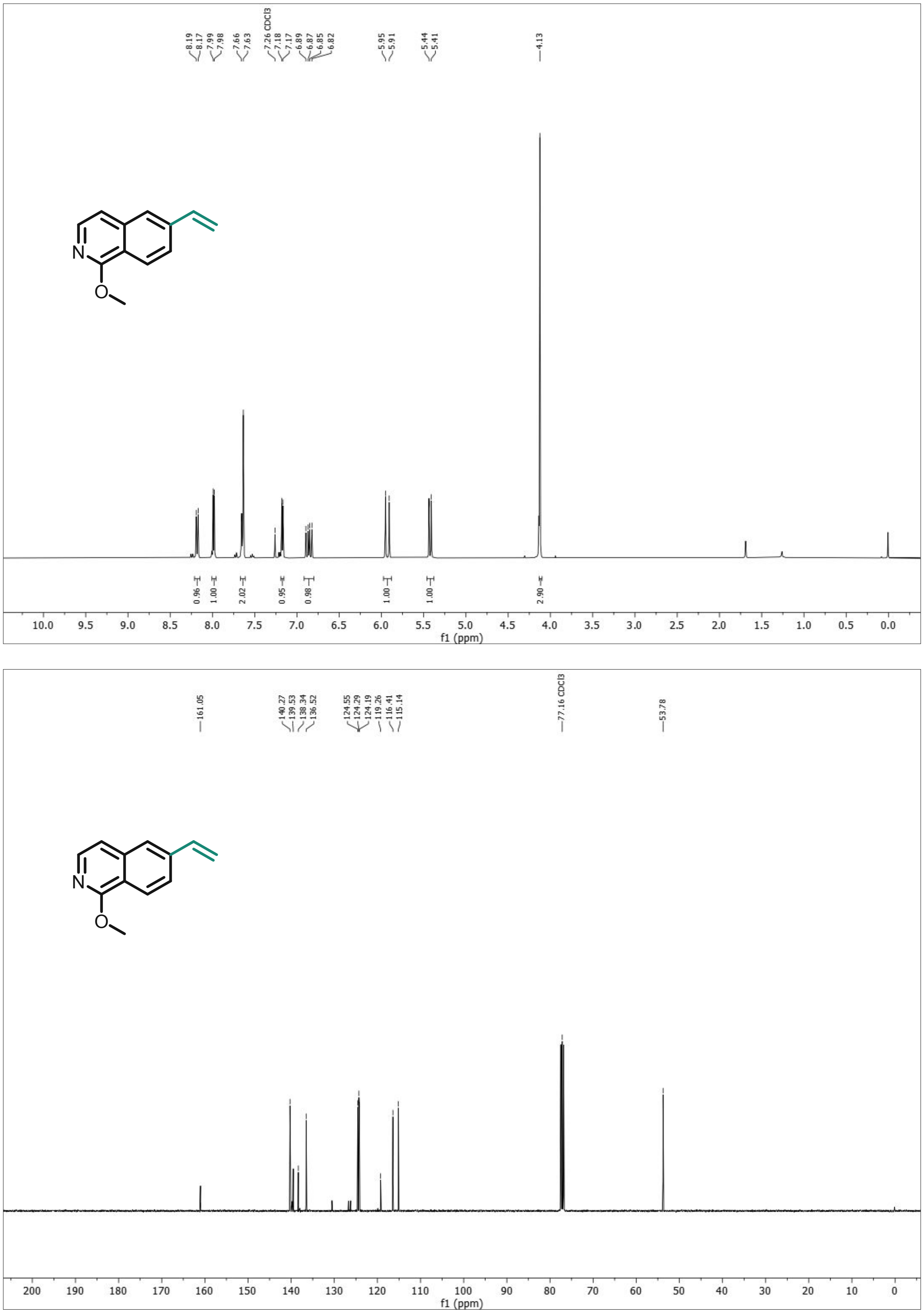


Figure S4: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C{1H} NMR (101 MHz, $CDCl_3$) of 1-methoxy-6-vinylquinoline (18).

3-Vinylquinoline (19)

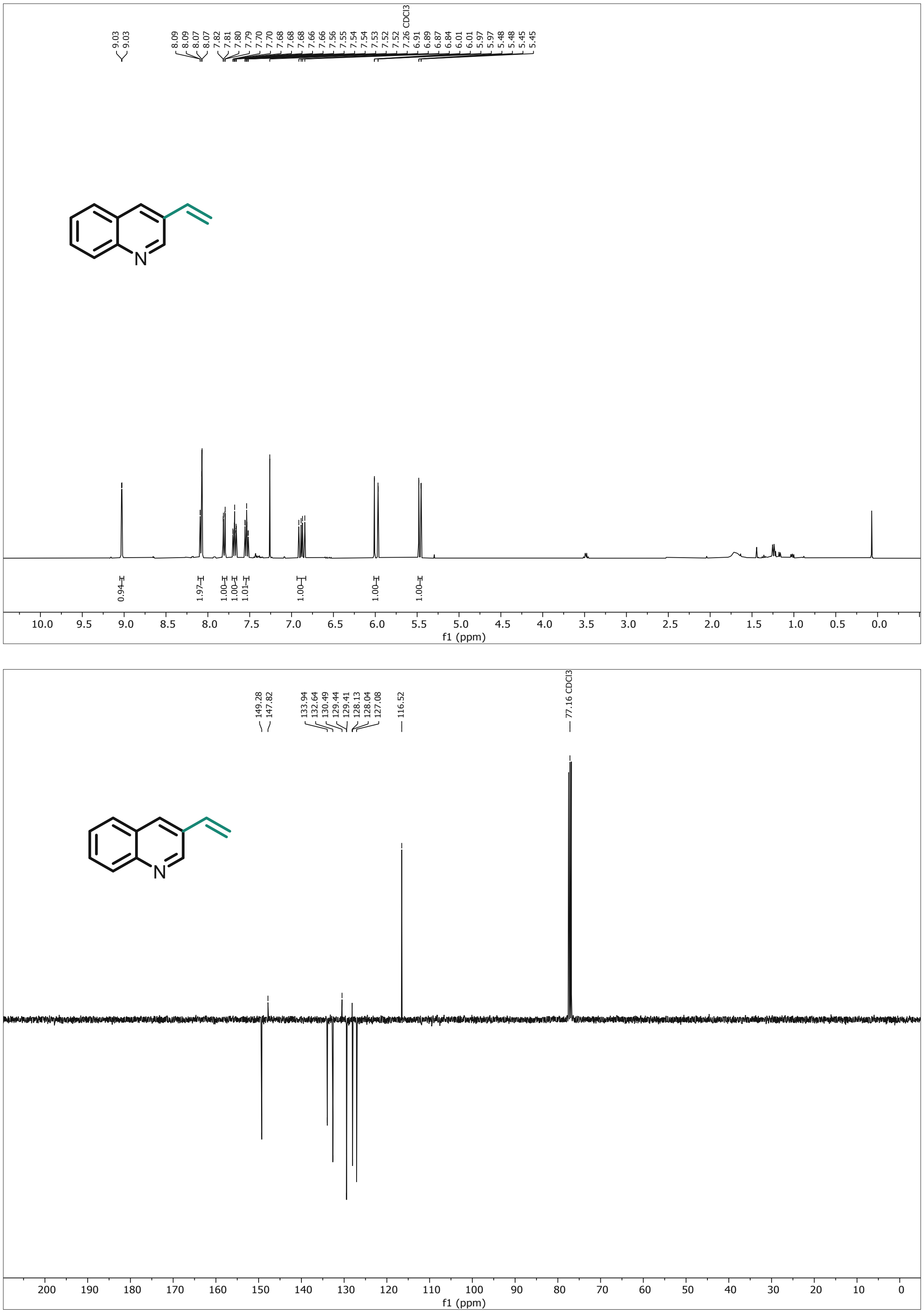
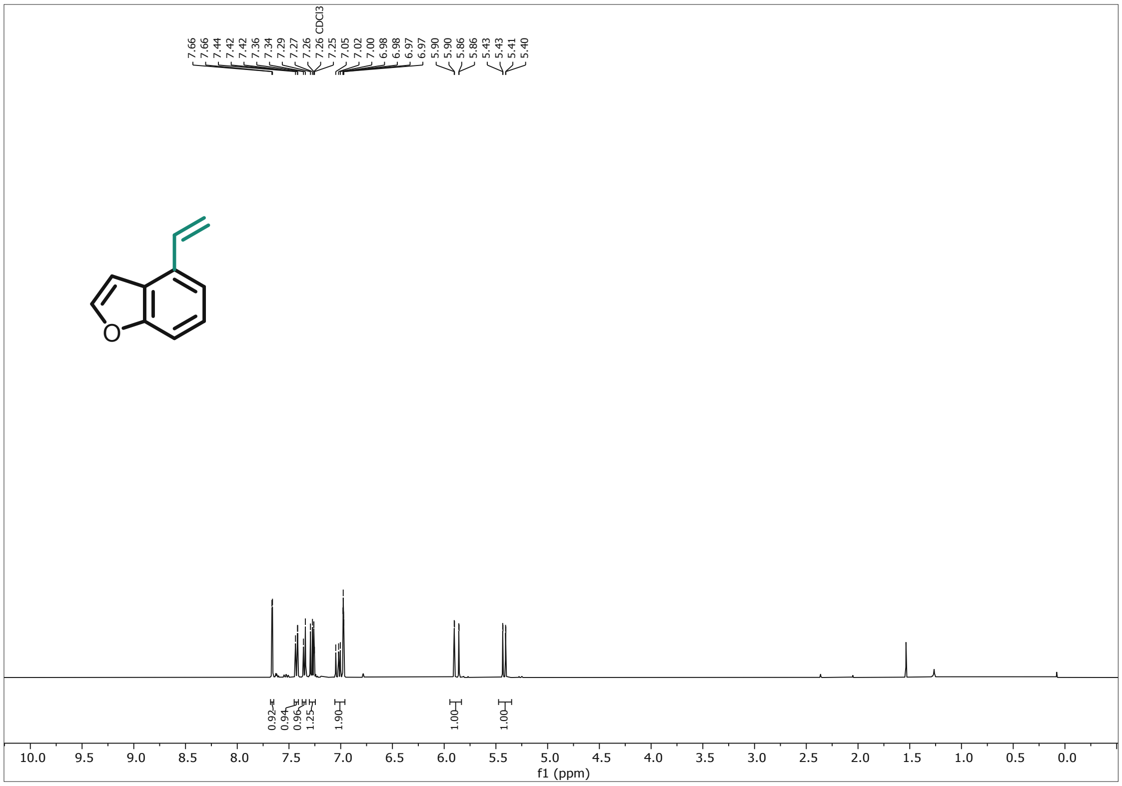


Figure S5: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 3-vinylquinoline (19).

4-Vinylbenzofuran (21)



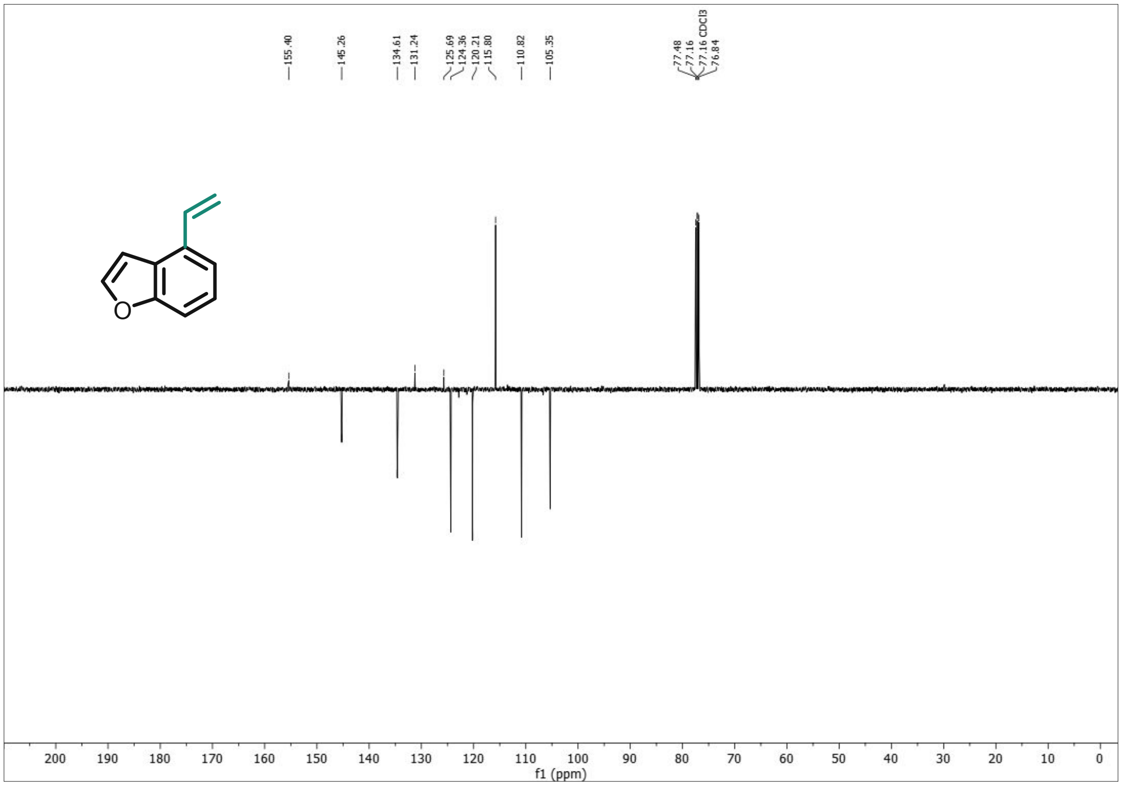


Figure S6: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C{1H} NMR (101 MHz, $CDCl_3$) of 4-vinylbenzofuran (21).

5-Vinylbenzo[*b*]thiophene (22)

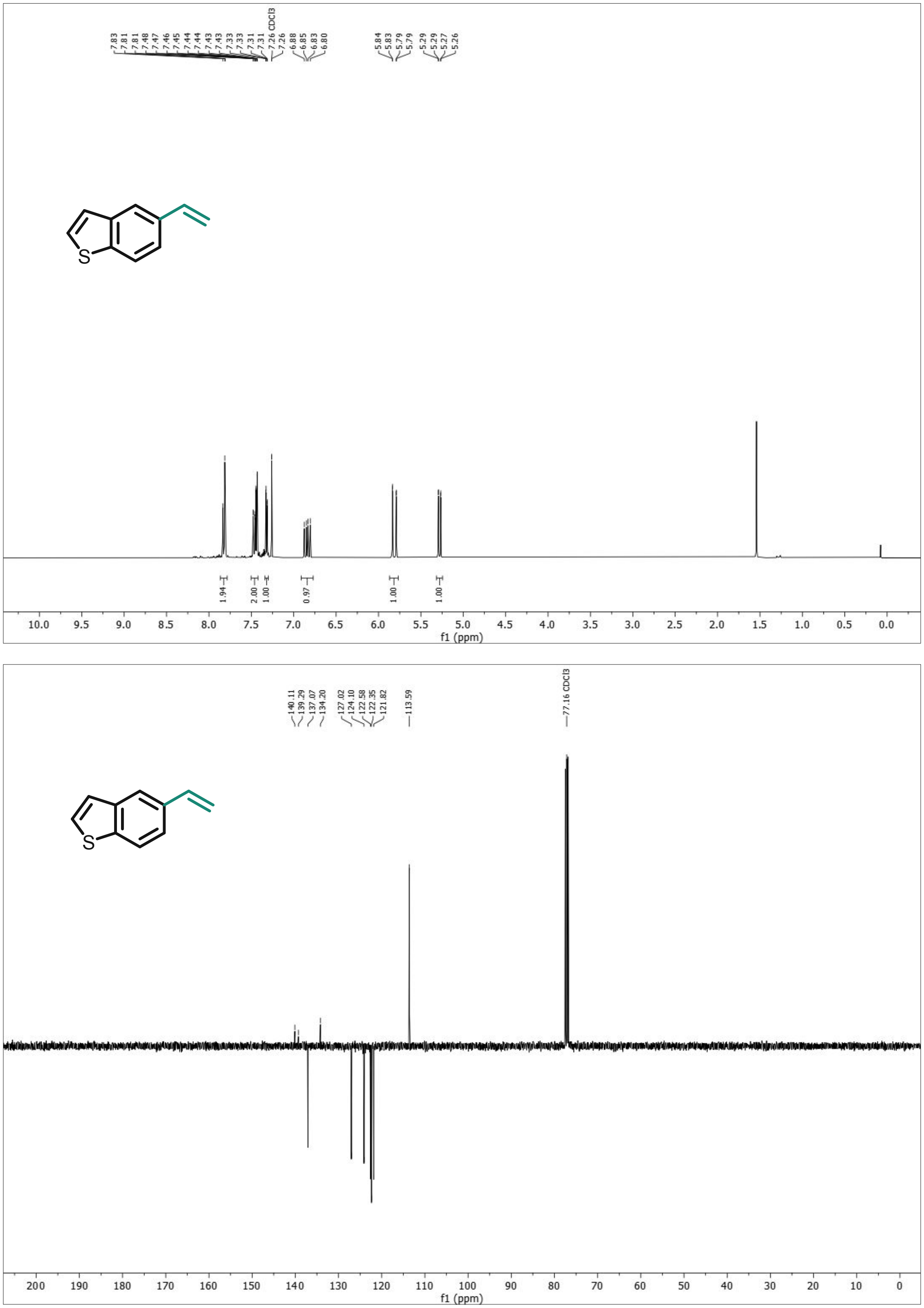
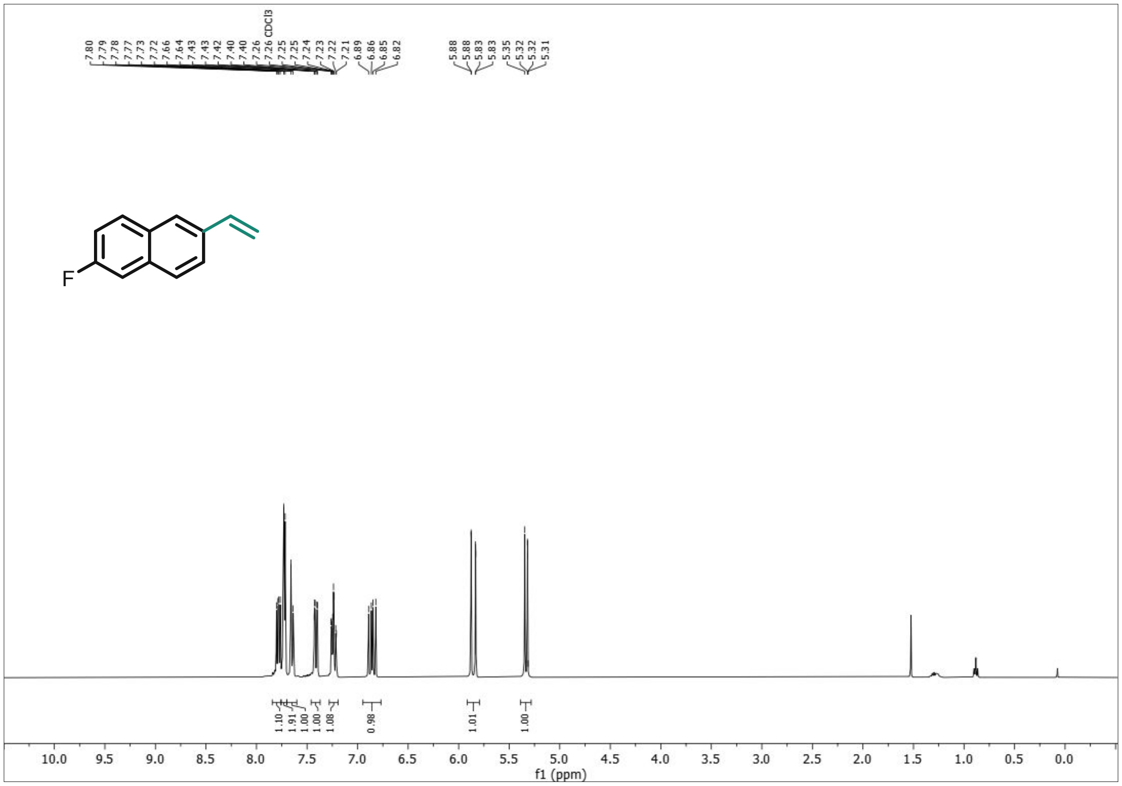
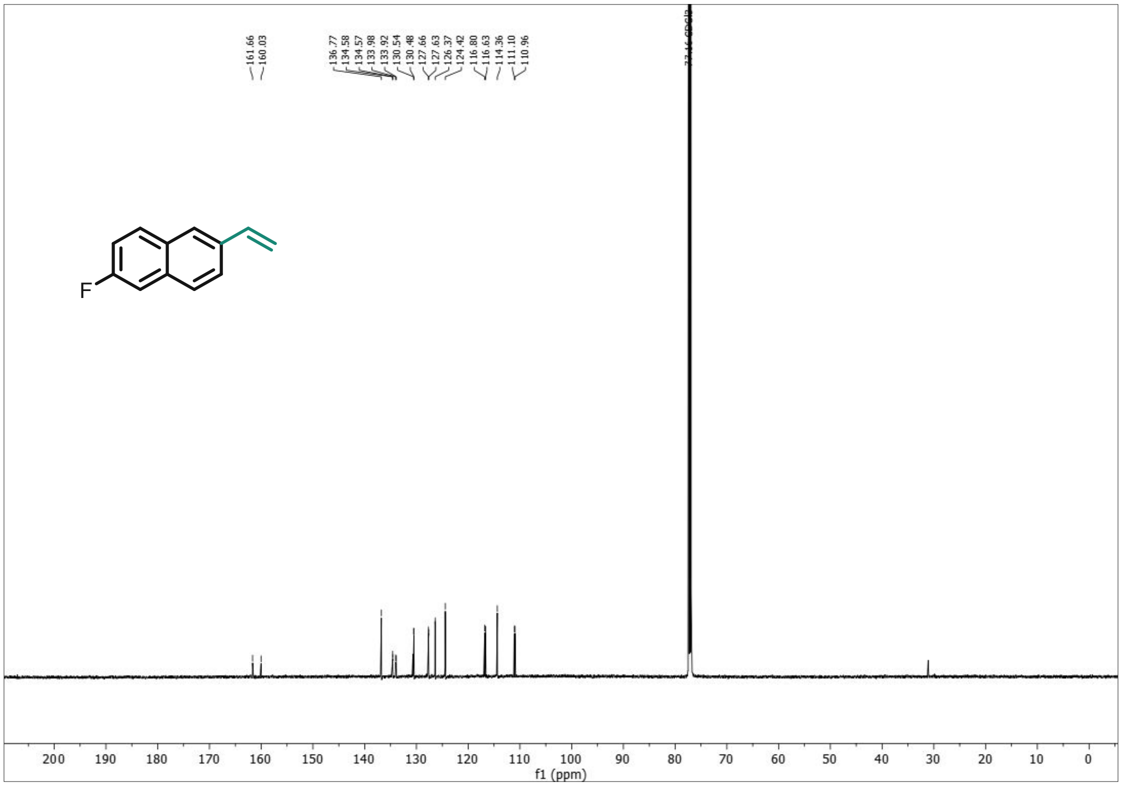


Figure S7: ^{1}H-NMR (400 MHz, CDCl$_3$) and ^{13}C{1H} NMR (101 MHz, CDCl$_3$) of 5-vinyl-benzo[b]thiophene (22).

2-Vinyl-6-fluoronaphthalene (23)





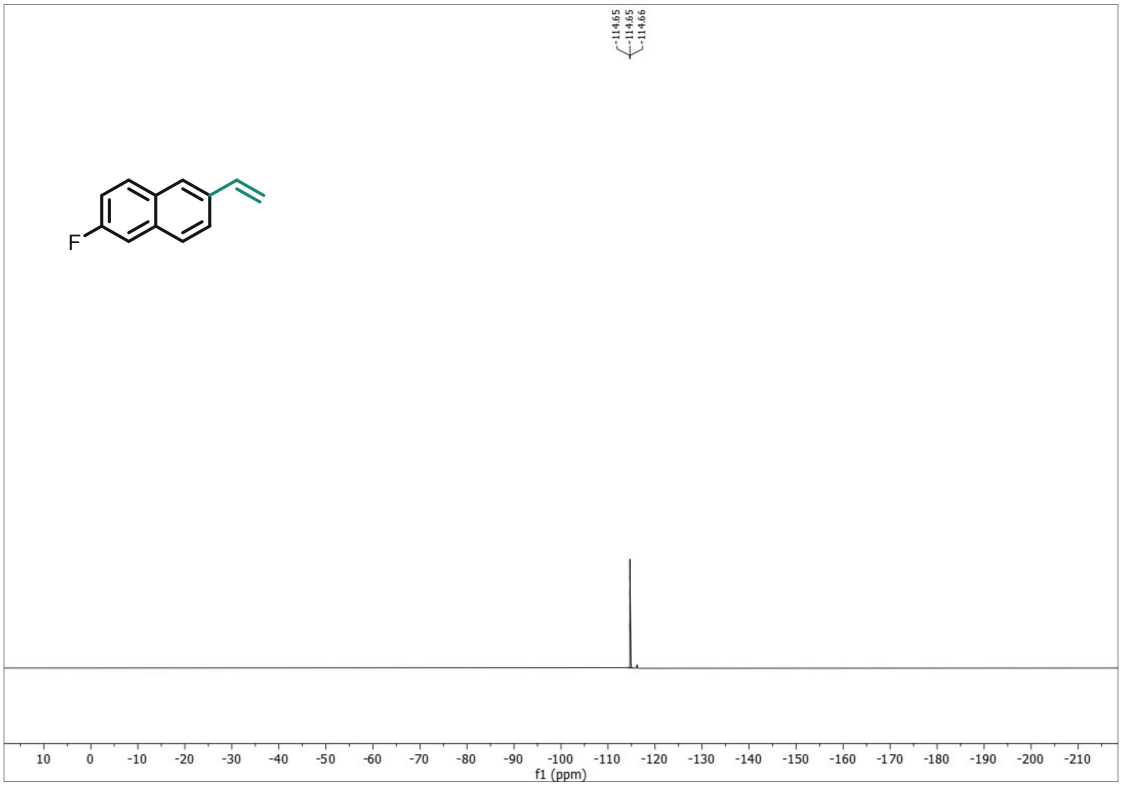


Figure S8: ^{1}H-NMR (400 MHz, CDCl$_3$) ^{13}C{1H} NMR (101 MHz, CDCl$_3$) and ^{19}F-NMR (376 MHz, CDCl$_3$) of 2-vinyl-6-fluoronapthalene (23).

NMR-Spectra of volatile compounds for quantification

For quantification only the vinylic protons (not overlapping with other peaks of the crude mixture) of the corresponding product and the aromatic protons of the internal standard were integrated and used for the calculation of the yield.

Styrene (3)

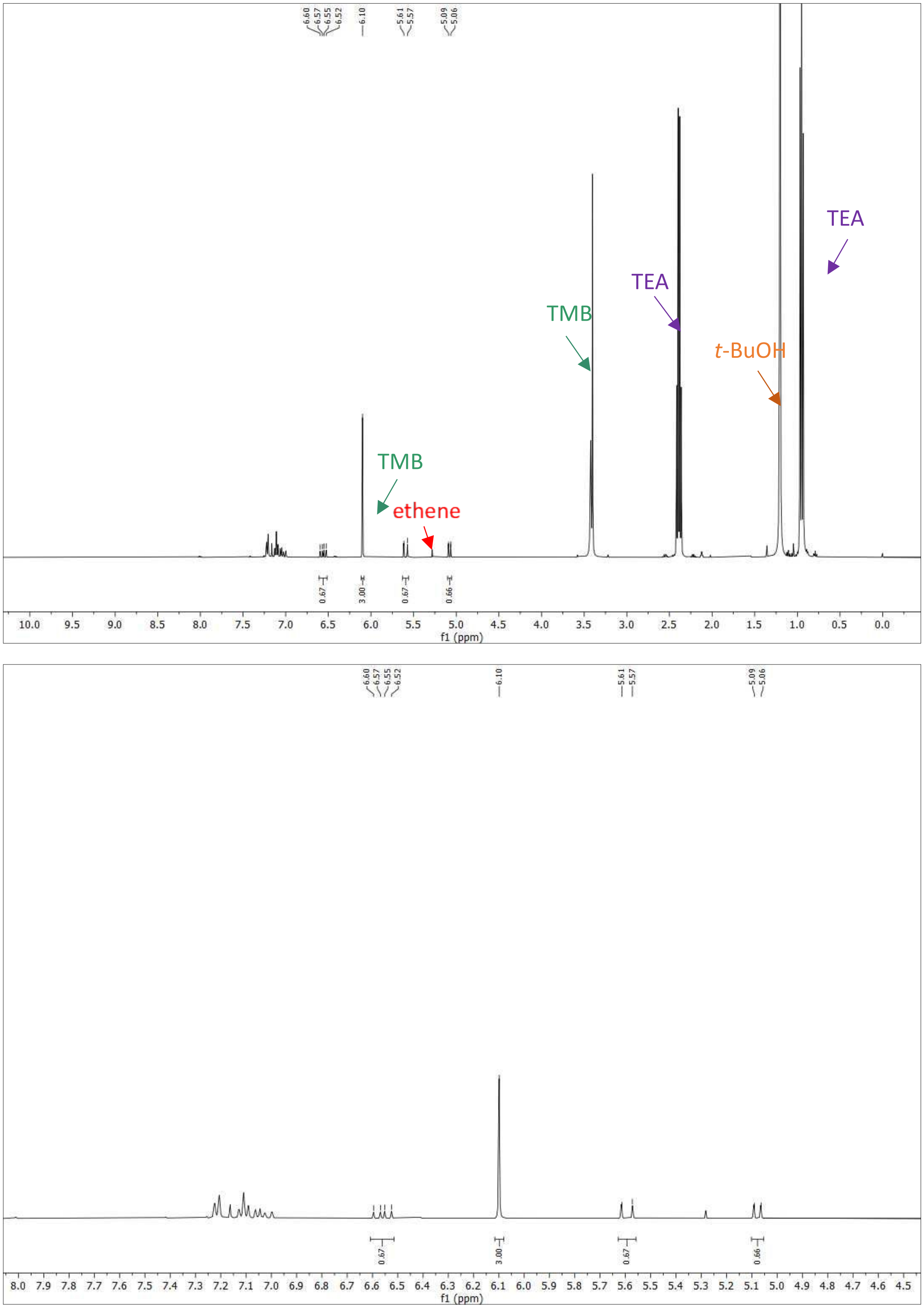


Figure S9: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of styrene (3) when X=Br.

Styrene (3)

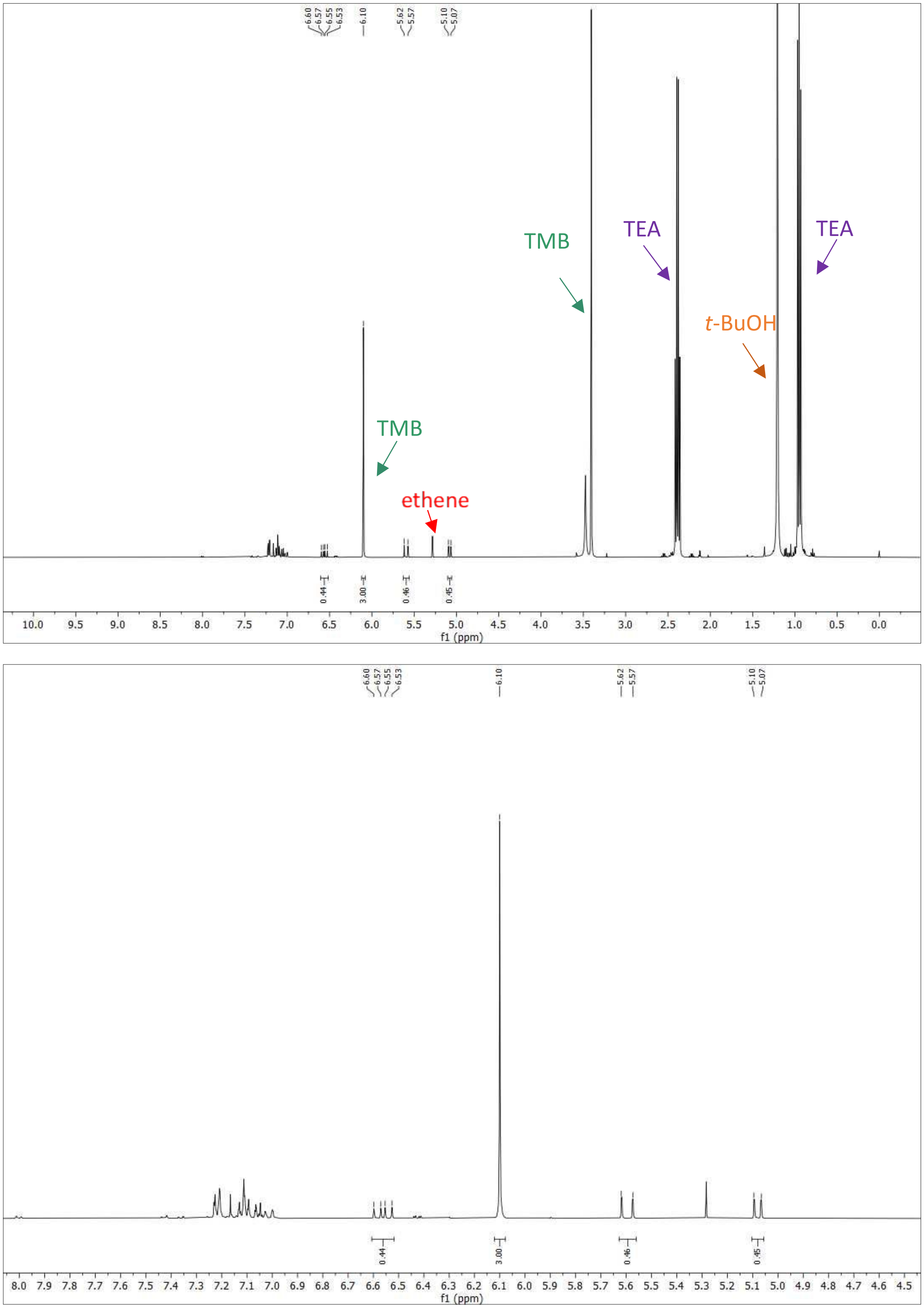


Figure S10: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of styrene (3) when X=I.

1-(Trifluoromethyl)-3-vinylbenzene (4)

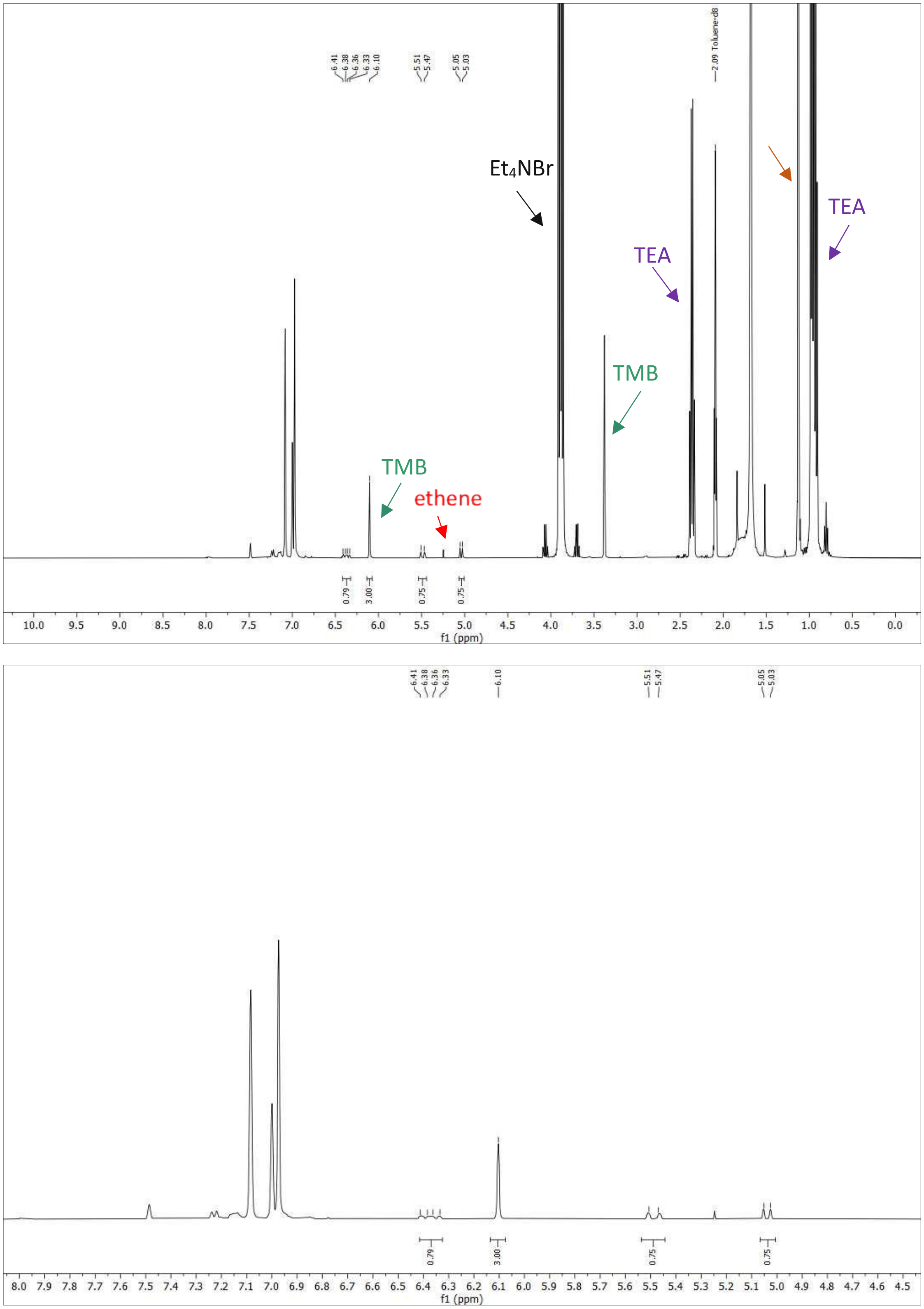


Figure S11: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 1-(trifluoromethyl)-3-vinylbenzene (4).

1-(Trifluoromethyl)-4-vinylbenzene (5)

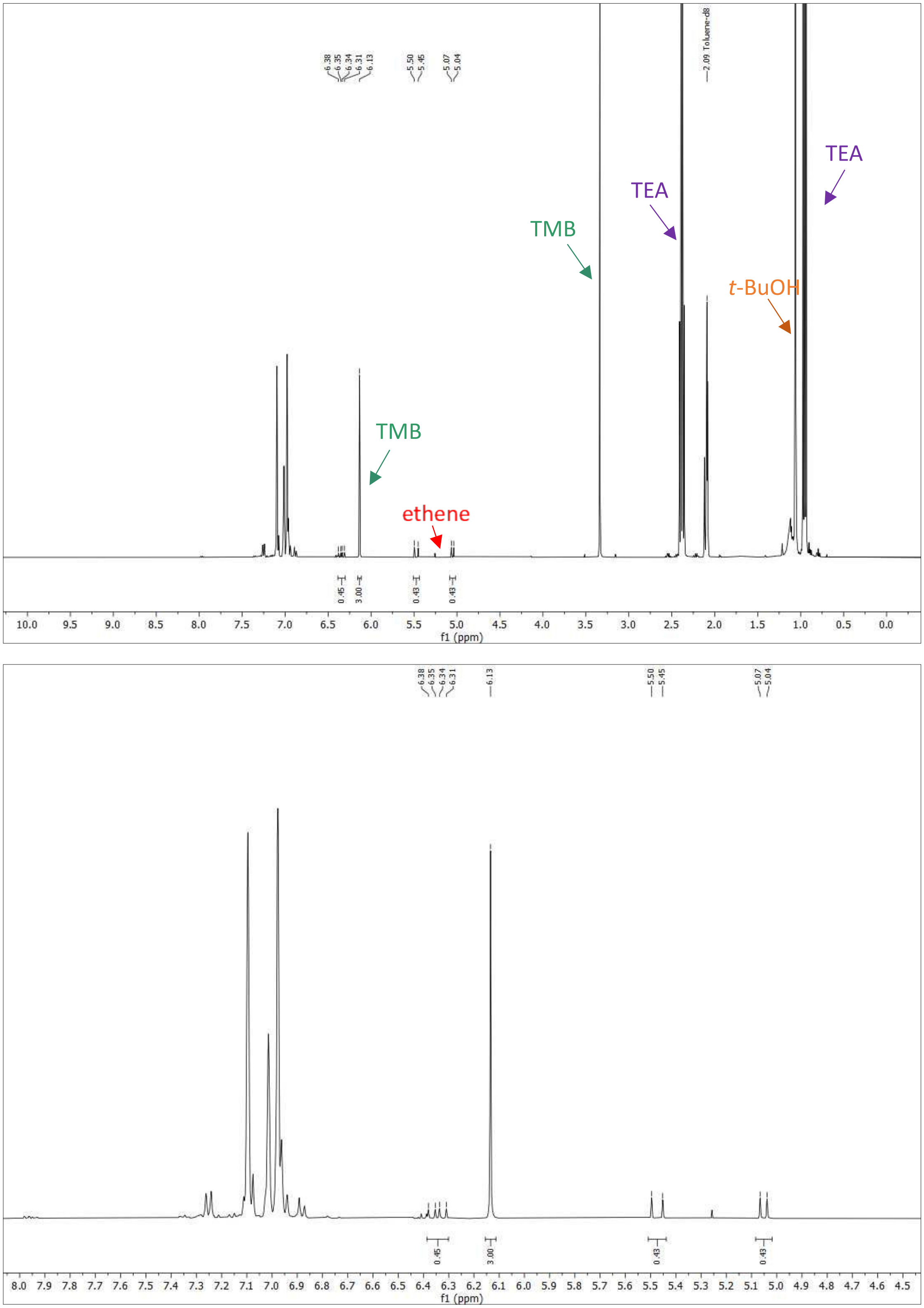


Figure S12: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 1-(trifluoromethyl)-4-vinylbenzene (5).

1-(Trifluoromethyl)-2-vinylbenzene (6)

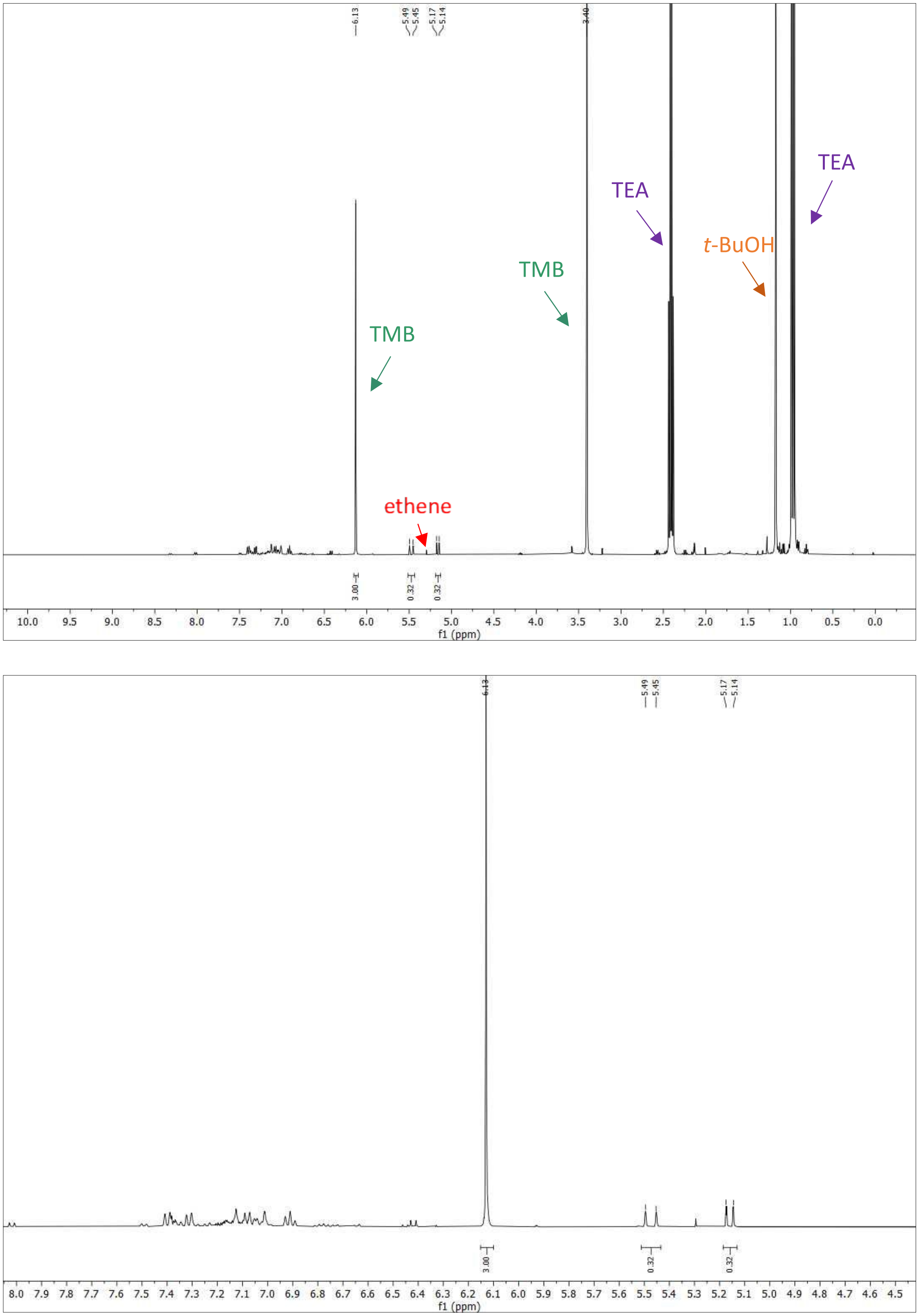


Figure S13: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 1-(trifluoromethyl)-2-vinylbenzene (6).

4-vinylbenzoic acid (7)

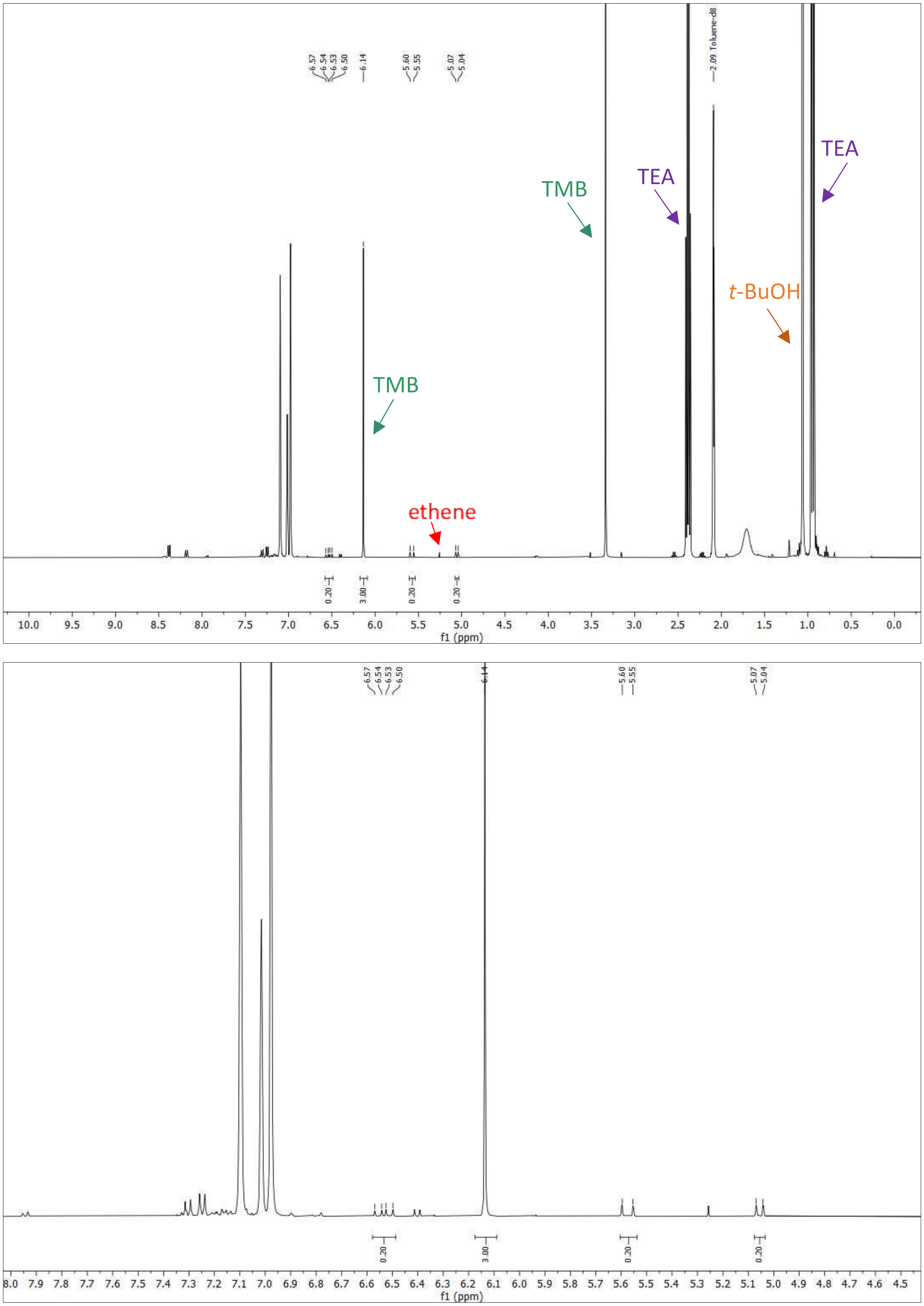


Figure S14: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 4-vinylbenzoic acid (7).

1-Methoxy-3-vinylbenzene (8)

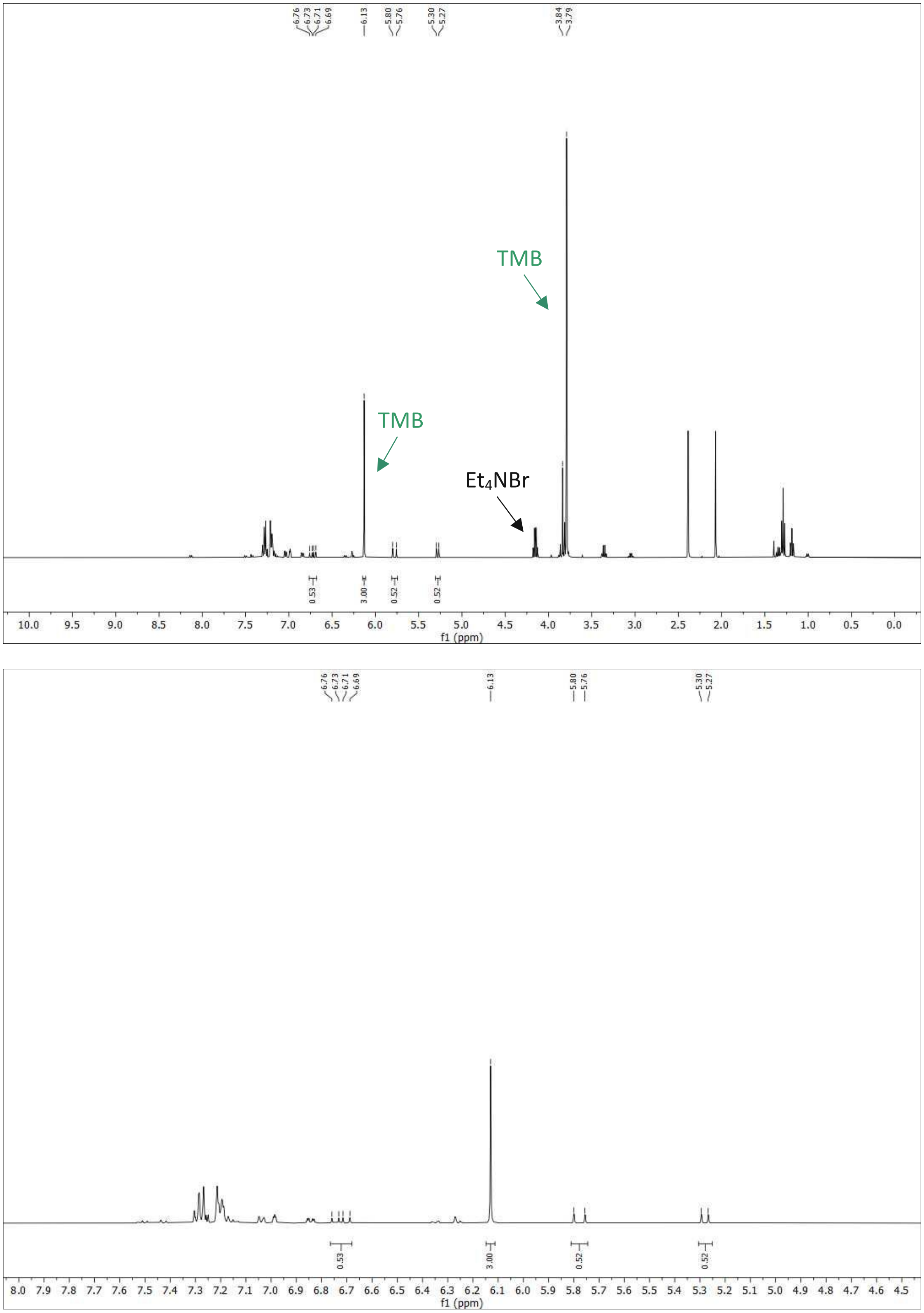


Figure S15: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 1-methoxy-3-vinylbenzene (8).

1-Methoxy-4-vinylbenzene (9)

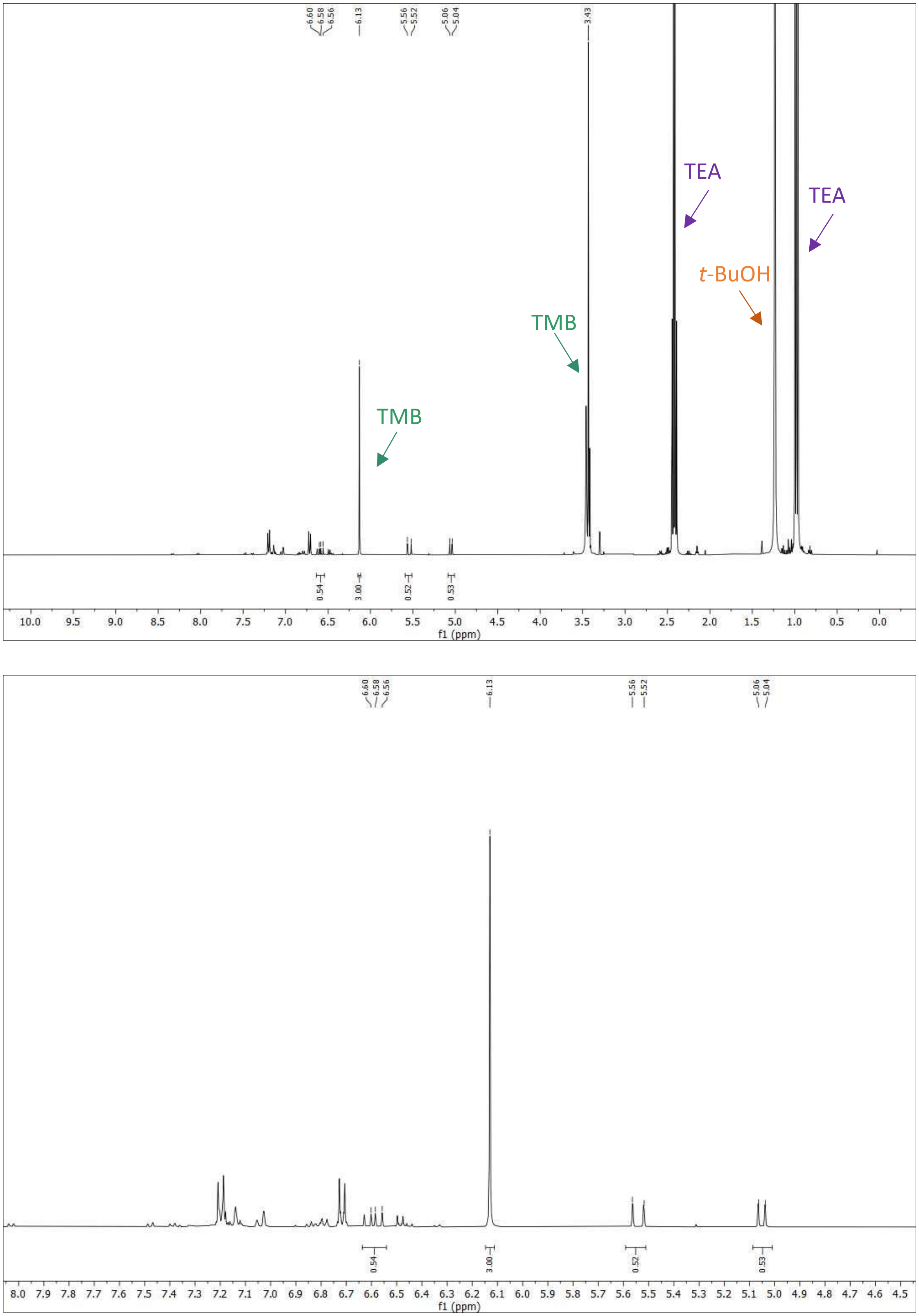


Figure S16: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 1-methoxy-4-vinylbenzene (9).

1-Methoxy-2-vinylbenzene (10)

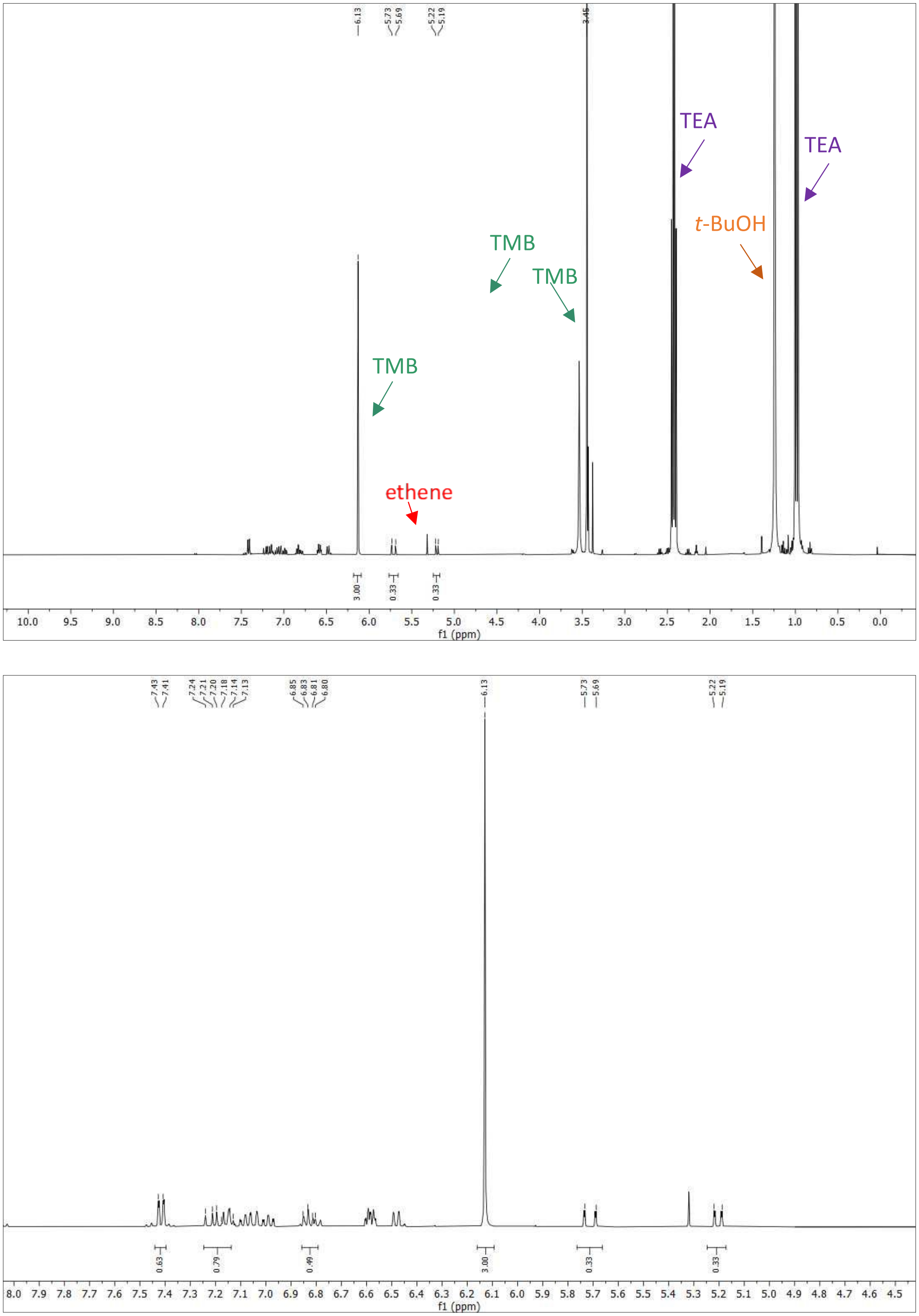


Figure S17: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 1-methoxy-2-vinylbenzene (10).

N,N-Dimethyl-4-vinylaniline (11)

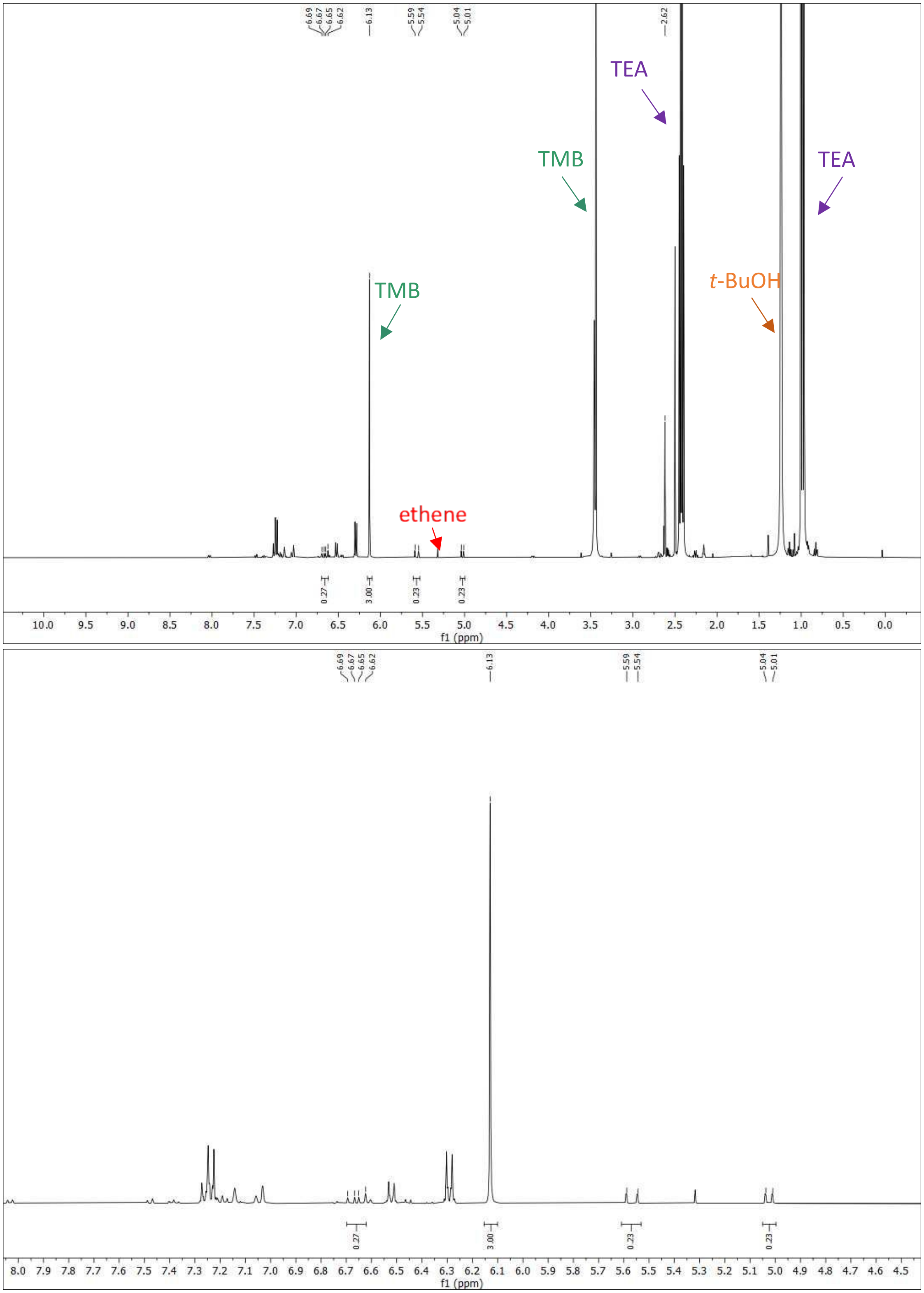


Figure S18: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of N,N-dimethyl-4-vinylaniline (11).

1-Ethyl-3-vinylbenzene (12)

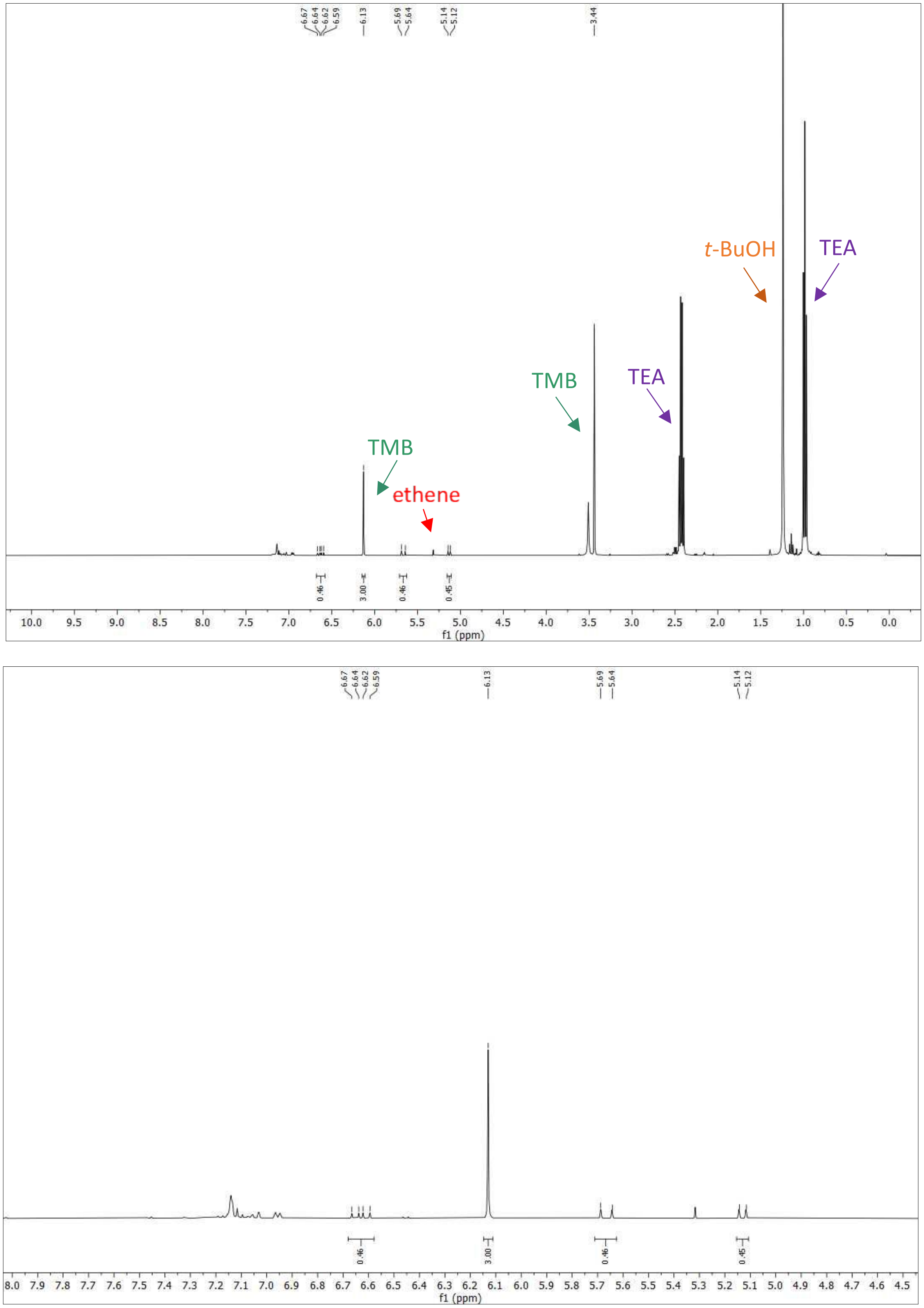
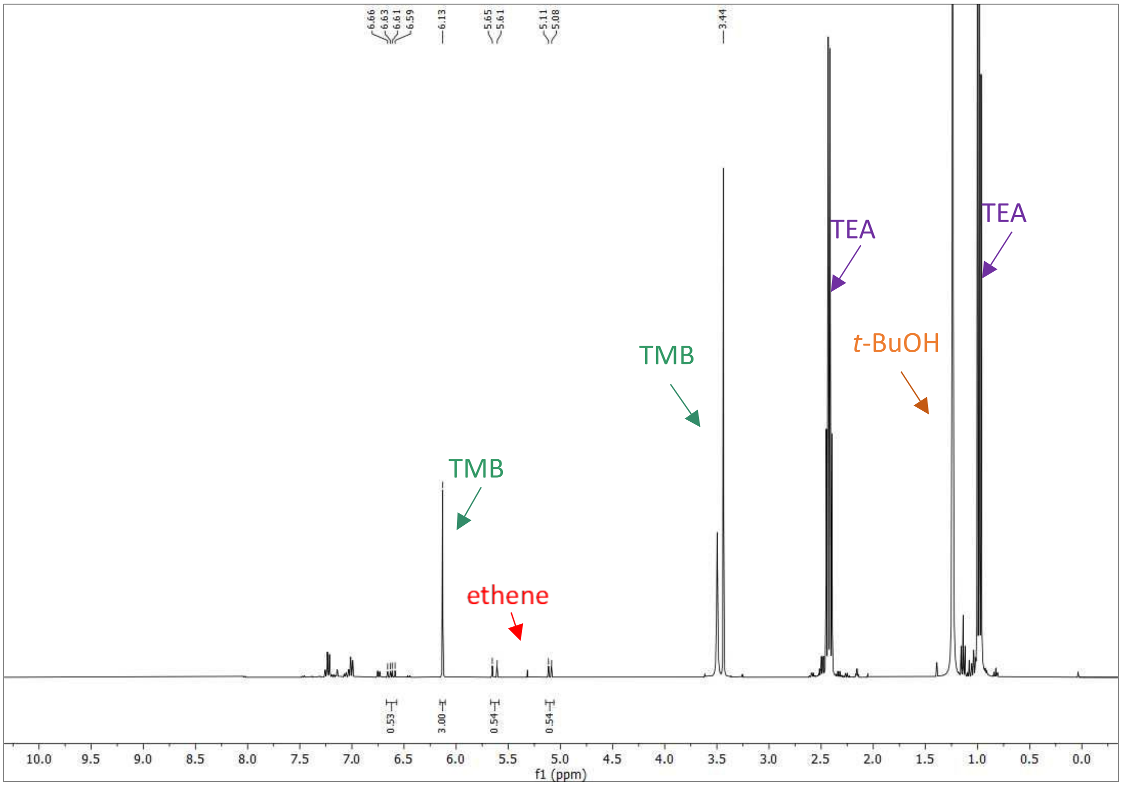


Figure S19: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 1-ethyl-3-vinylbenzene (12).

1-Ethyl-4-vinylbenzene (13)



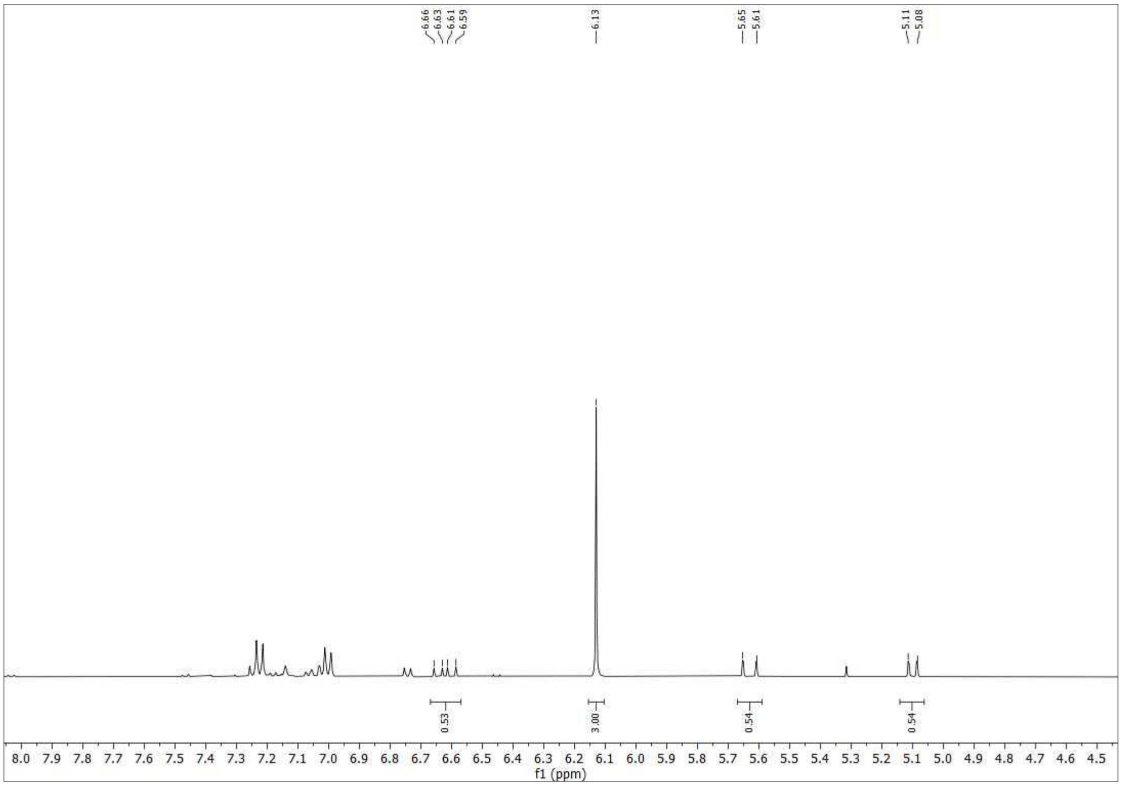


Figure S20: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 1-ethyl-4-vinylbenzene (13).

1-Ethyl-2-vinylbenzene (14)

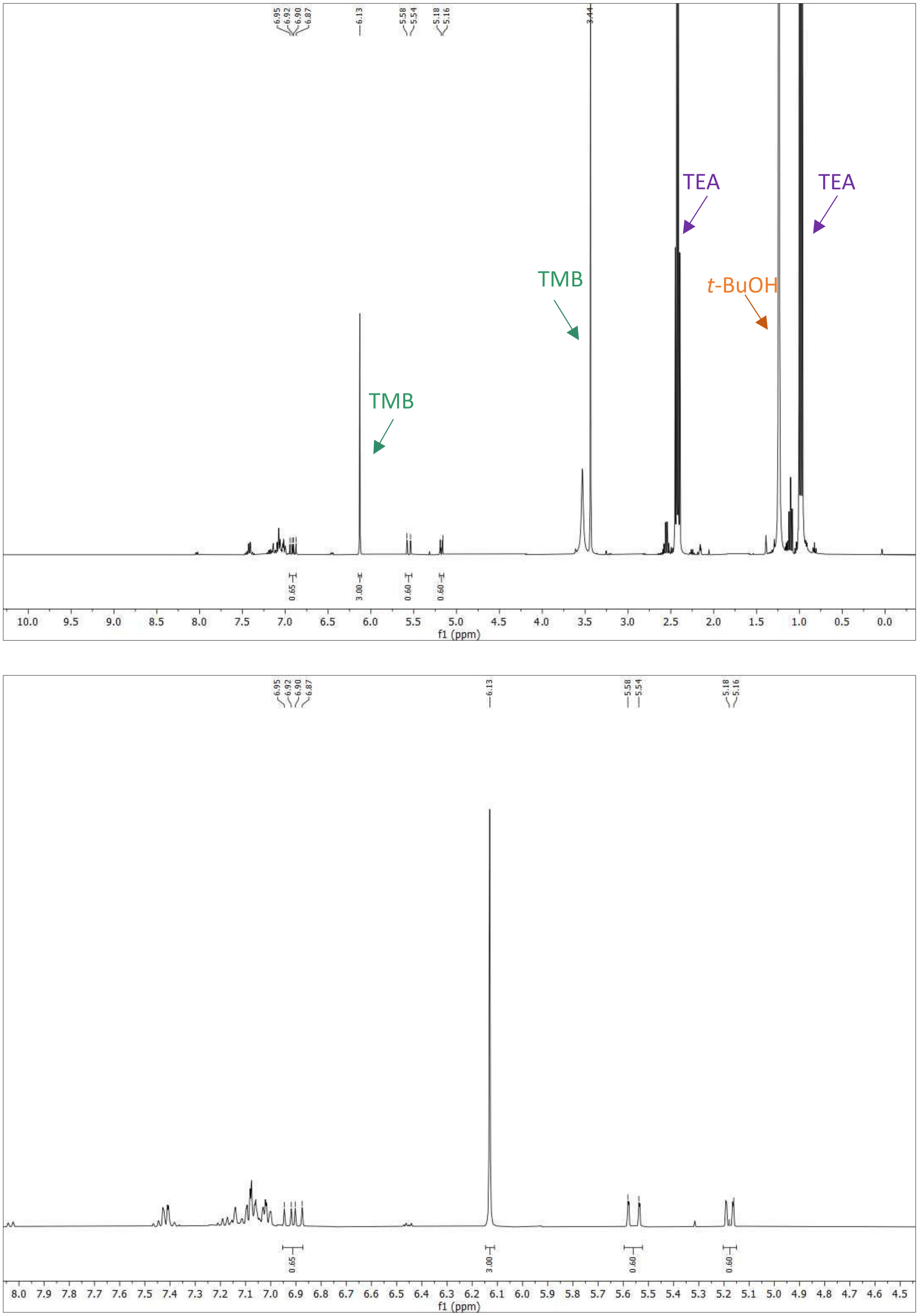


Figure S21: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 1-ethyl-2-vinylbenzene (14).

tert-Butyl (4-vinylphenyl)carbamate (15)

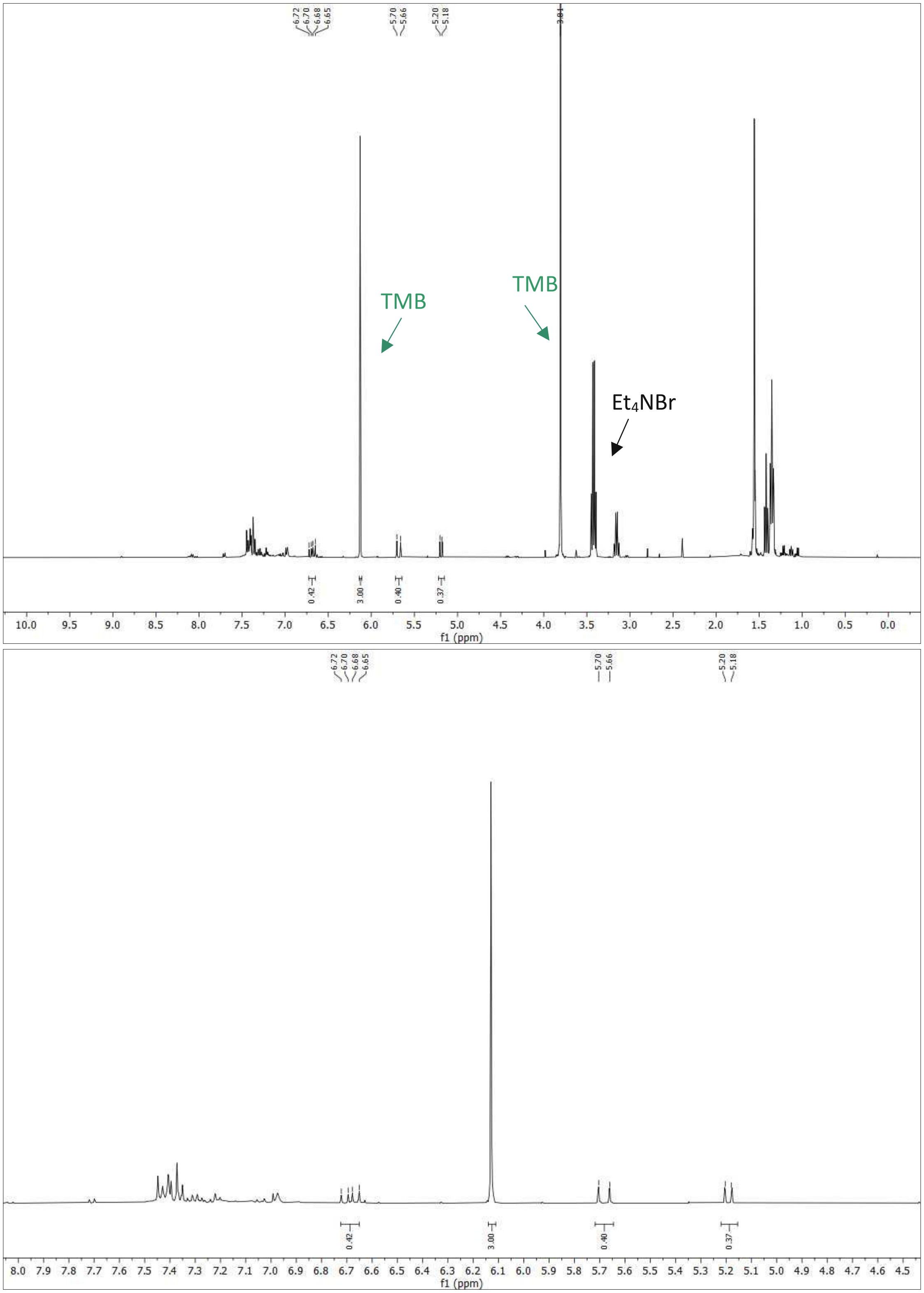


Figure S22: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of tert-butyl (4-vinylphenyl)carbamate (15).

4-Vinylphenol (16)

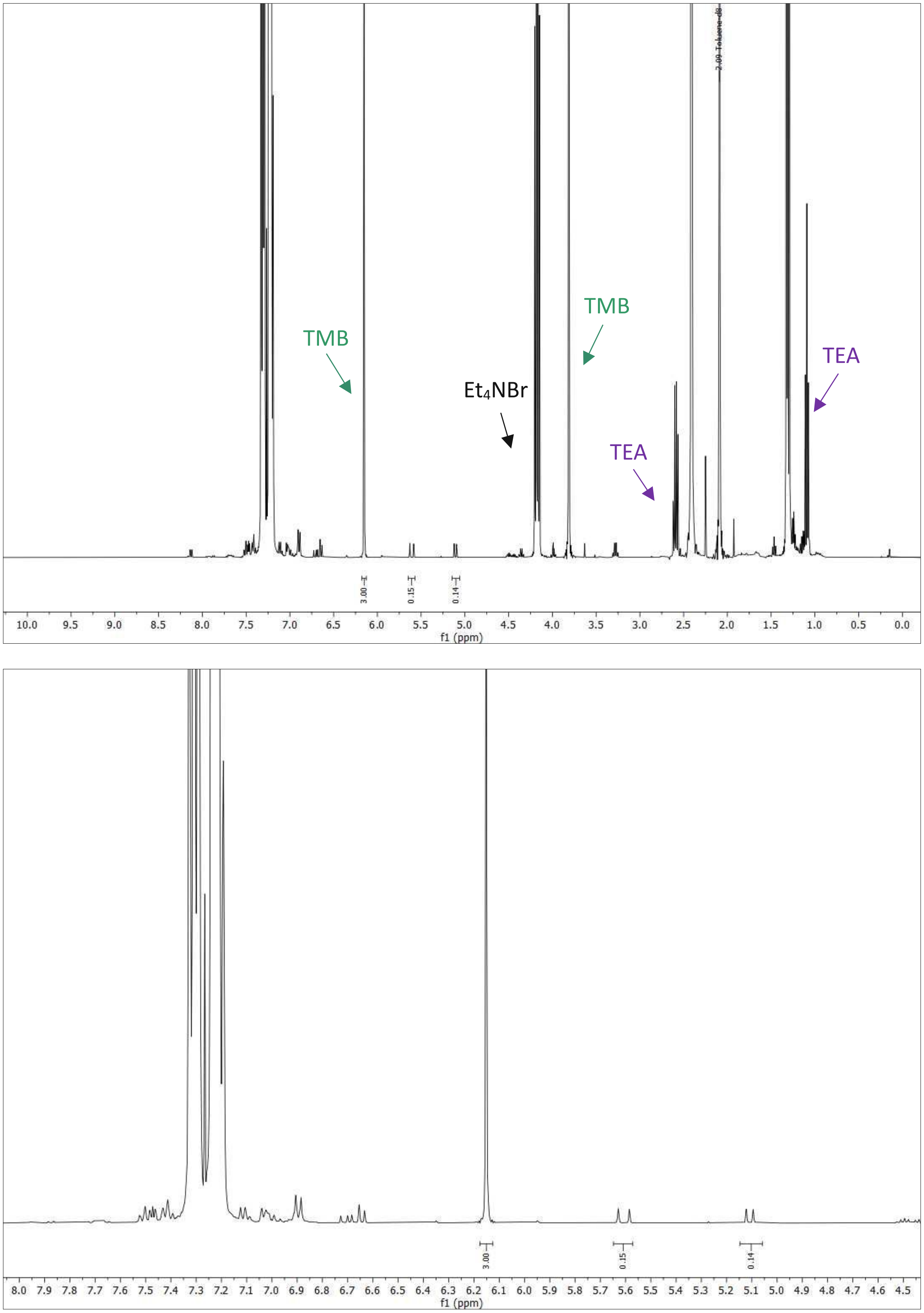


Figure S23: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 4-vinylphenol (16).

3-Vinylpyridine (20)

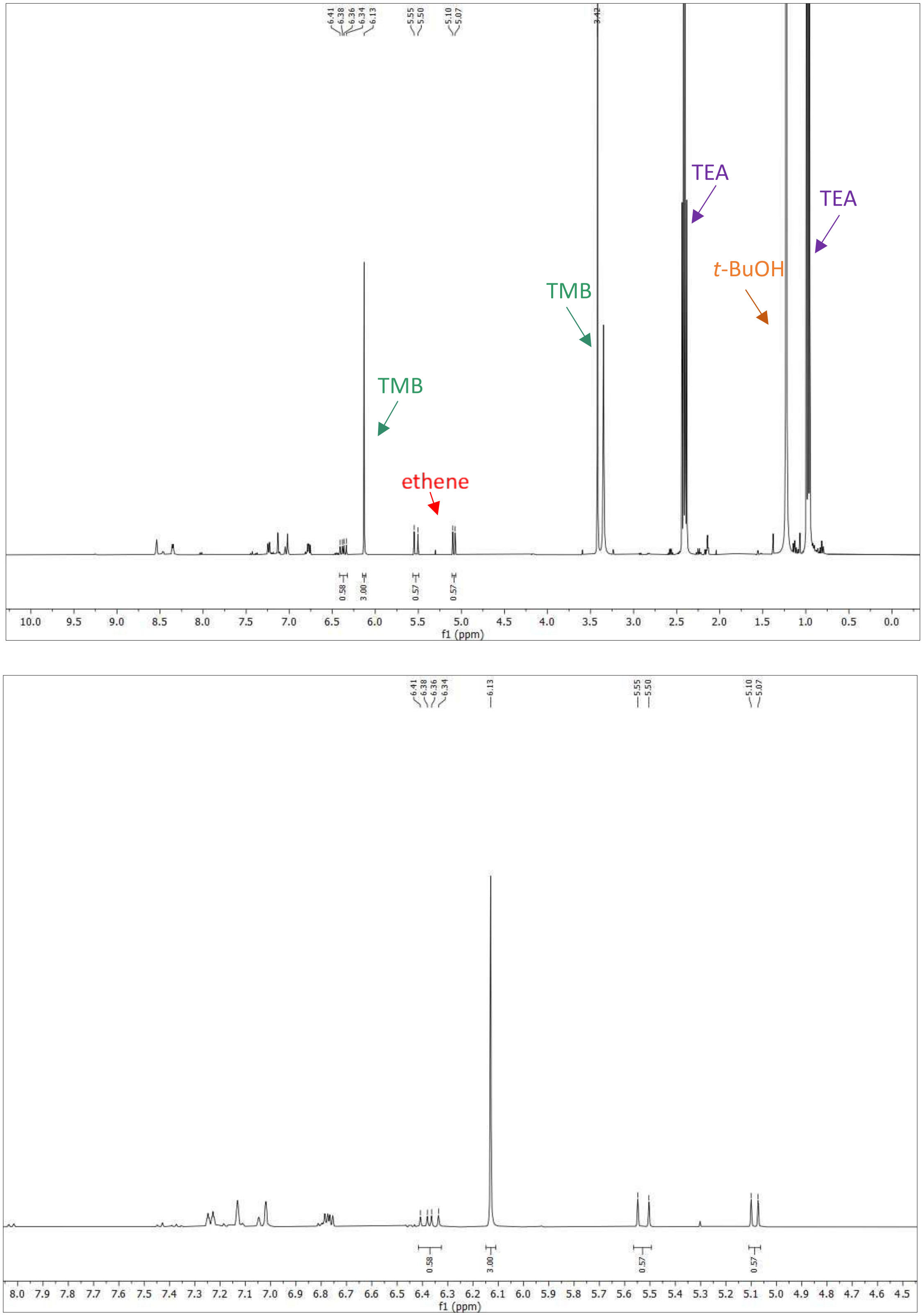


Figure S24: ^{1}H-NMR (400 MHz, C_7D_8) used for quantification of 3-vinylpyridine (20).

References

(1) An, N.; Ainembabazi, D.; Reid, C.; Samudrala, K.; Wilson, K.; Lee, A. F.; Voutchkova-Kostal, A. Microwave-Assisted Decarbonylation of Biomass-Derived Aldehydes Using Pd-Doped Hydrotalcites. *ChemSusChem.* **2020**, *13* (2), 312-320. DOI: 10.1002/cssc.201901934.

(2) Richmond, E.; Moran, J. Ligand Control of E/Z Selectivity in Nickel-Catalyzed Transfer Hydrogenative Alkyne Semireduction. *J. Org. Chem.* **2015**, *80* (13), 6922-6929. DOI: 10.1021/acs.joc.5b01047.

(3) Jiang, Y.; Fang, W.-Y.; Rakesh, K. P.; Qin, H.-L. Copper-Catalyzed Mild Desulfonylation of Vinyl Sulfonyl Molecules. *Org. Chem. Front.* **2020**, *7* (13), 1696-1702. DOI: 10.1039/D0QO00468E.

(4) Aukland, M. H.; Talbot, F. J. T.; Fernández-Salas, J. A.; Ball, M.; Pulis, A. P.; Procter, D. J. An Interrupted Pummerer/Nickel-Catalysed Cross-Coupling Sequence. *Angew. Chem., Int. Ed.* **2018**, *57* (31), 9785-9789. DOI: 10.1002/anie.201805396.

(5) Liu, K.-J.; Jiang, S.; Lu, L.-H.; Tang, L.-L.; Tang, S.-S.; Tang, H.-S.; Tang, Z.; He, W.-M.; Xu, X. Bis(methoxypropyl) Ether-Promoted Oxidation of Aromatic Alcohols into Aromatic Carboxylic Acids and Aromatic Ketones with O_2 Under Metal- and Base-Free Conditions. *Green Chem*. **2018**, *20* (13), 3038-3043. DOI: 10.1039/C8GC00223A.

(6) Wang, C.; Gong, S.; Liang, Z.; Sun, Y.; Cheng, R.; Yang, B.; Liu, Y.; Yang, J.; Sun, F. Ligand-Promoted Iridium-Catalyzed Transfer Hydrogenation of Terminal Alkynes with Ethanol and Its Application. *ACS Omega*. **2019**, *4* (14), 16045-16051. DOI: 10.1021/acsomega.9b02191.

(7) Gordillo, Á.; de Jesús, E.; López-Mardomingo, C. Consecutive Palladium-Catalyzed Hiyama–Heck Reactions in Aqueous Media Under Ligand-Free Conditions. *ChemComm*. **2007**, (39), 4056-4058. DOI: 10.1039/B707583A

(8) Zhang, X.; Jiang, Y.; Fei, H. UiO-Type Metal–Organic Frameworks with NHC or Metal–NHC Functionalities for N-Methylation Using CO_2 as The Carbon Source. *ChemComm*. **2019**, *55* (79), 11928-11931. DOI: 10.1039/C9CC06659D.

(9) Denmark, S. E.; Butler, C. R. Vinylation of Aryl Bromides Using an Inexpensive Vinylpolysiloxane. *Org. Lett*. **2006**, *8* (1), 63-66. DOI: 10.1021/ol052517r.

(10) Falk, A.; Cavalieri, A.; Nichol, G. S.; Vogt, D.; Schmalz, H.-G. Enantioselective Nickel-Catalyzed Hydrocyanation Using Chiral Phosphine-Phosphite Ligands: Recent Improvements and Insights. *Adv. Synth. Catal*. **2015**, *357* (14-15), 3317-3320. DOI: 10.1002/adsc.201500644.

(11) Lafaye, K.; Nicolas, L.; Guérinot, A.; Reymond, S.; Cossy, J. Lewis Basicity Modulation of N-Heterocycles: A Key for Successful Cross-Metathesis. *Org. Lett*. **2014**, *16* (19), 4972-4975. DOI: 10.1021/ol502016h.

(12) Akram, M. O.; Shinde, P. S.; Chintawar, C. C.; Patil, N. T. Gold(I)-Catalyzed Cross-Coupling Reactions of Aryldiazonium Salts with Organostannanes. *Org. Biomol. Chem.* **2018**, *16* (16), 2865-2869. DOI: 10.1039/C8OB00630J.

D IV Manuscript 3

The Vinyl Group: Small but Mighty - Transition Metal Catalyzed and Non-Catalyzed Vinylation Reactions

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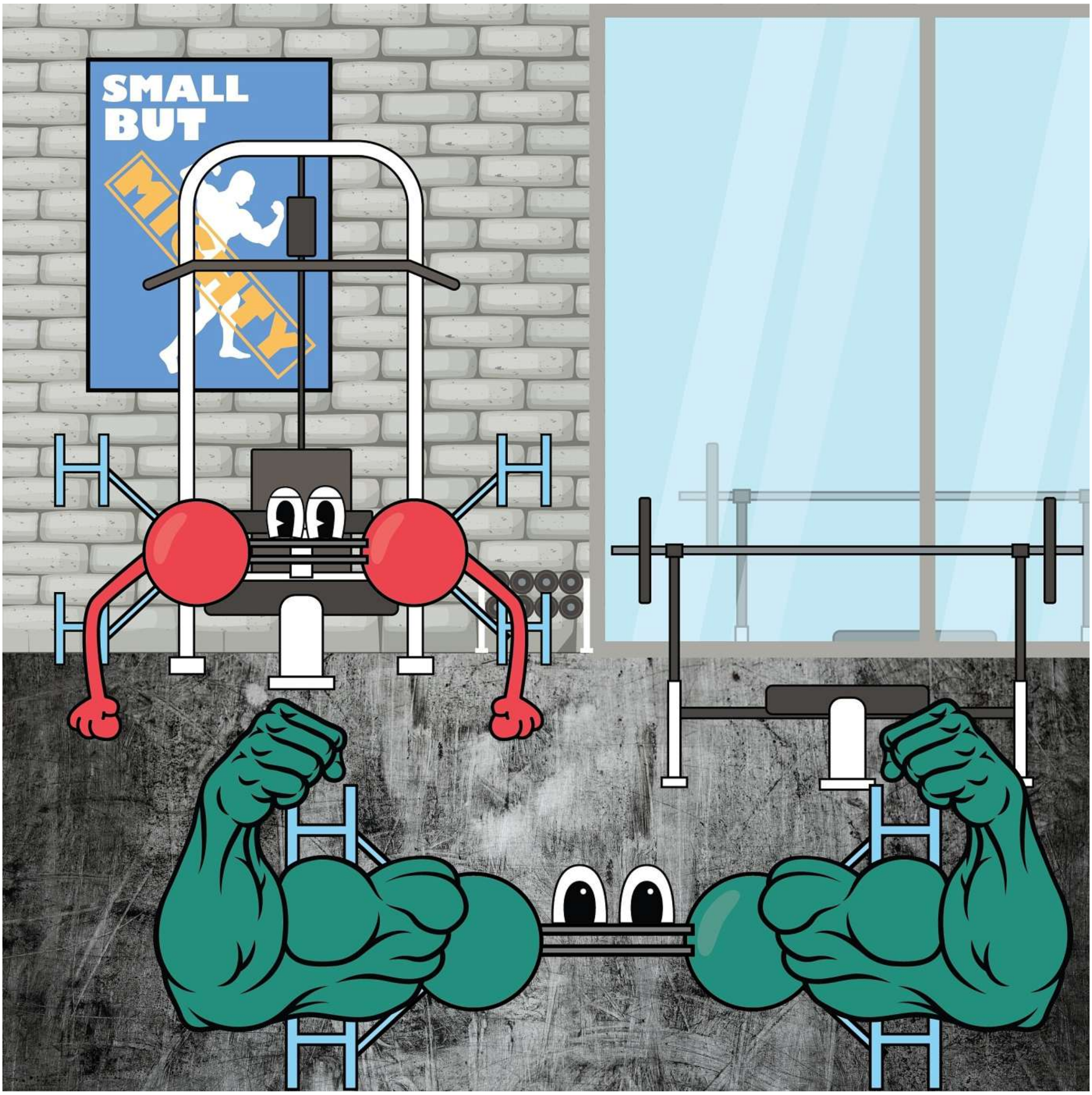
The Vinyl Group: Small but Mighty – Transition Metal Catalyzed and Non-Catalyzed Vinylation Reactions

Eleni Papaplioura,[a] Maëva Mercier,[b] Soufyan Jerhaoui,[b] and Michael Schnürch*[a]



Transition metal catalysis allows for the efficient and selective introduction of vinyl moieties onto organic molecules and offers a versatile approach to synthesizing complex organic molecules. Nonetheless, few transition-metal free vinylation reactions have also been reported, exhibiting exceptional functional group tolerance and circumventing selectivity issues. This review provides an overview of carbon, nitrogen and oxygen vinylation, presenting innovative strategies and key advancements in the field. Hence, it will serve as a valuable resource for organic chemists who are interested in the synthesis of vinyl-containing compounds. By understanding the diverse strategies involved in vinylation, readers will gain insights into harnessing this powerful synthetic methodology for the efficient construction of carbon-carbon and carbon-heteroatom bonds.

1. Introduction

Despite being one of the smallest units containing solely carbon and hydrogen, the importance of the vinyl group should not be underestimated. It is present in a significant number of fine chemicals, pharmaceuticals, and agrochemicals.[1] Characteristic examples of vinyl-containing bioactive compounds or examples in which a vinylated compound is a key intermediate are depicted in Figure 1. Consequently, the introduction of a vinyl group is of continuing interest in synthetic organic chemistry.[2]

Metal-catalyzed vinylation reactions have emerged as valuable tools in organic synthesis for the direct introduction of vinyl groups into organic molecules, thus facilitating the synthesis of complex organic compounds with diverse functional groups. Various transition metal catalysts have been employed to promote vinylation reactions, such as palladium, rhodium, ruthenium, iridium, nickel, cobalt, and copper, which will be treated comprehensively in the subsequent sections.

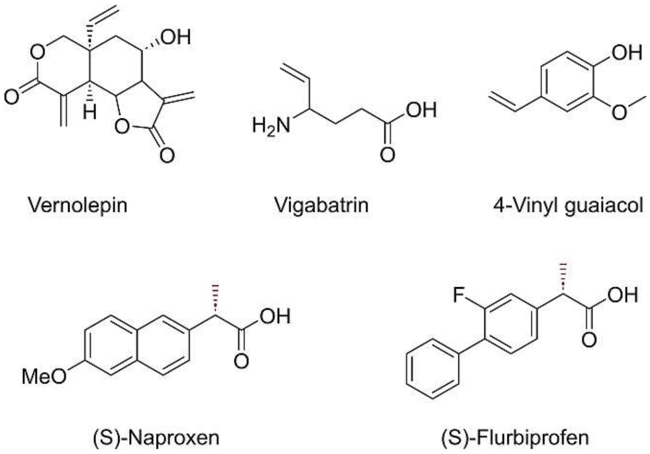
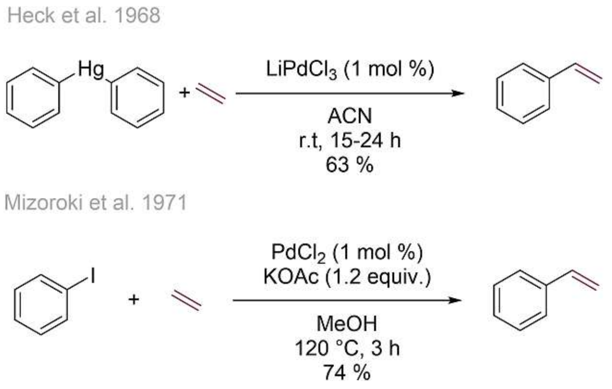


Figure 1. Bioactive compounds containing a vinyl group or having a vinylated compound as precursor.

Already in 1968 Heck reported on the olefination of arylmercury reagents, including an example using diphenylmercury and ethylene to form styrene (Scheme 1).[3] Shortly thereafter, a more practical method for aryl-olefination in general, also applicable for vinylation was disclosed, now generally known as the Mizoroki-Heck reaction.[4] This versatile methodology, which typically takes advantage of aryl halides in combination with olefins under palladium catalysis, was pioneered by Tsutomu Mizoroki, who first reported the reaction in 1971,[5] and Richard Heck, who independently published similar findings in 1972.[6] Ei-ichi Negishi further contributed to the development of the reaction, leading to its widespread use in the synthesis of natural products, pharmaceuticals, and materials.[7] It allows the coupling of vinyl halides with various nucleophilic partners through a carbon-heteroatom or carbon-carbon bond formation.[2b]

In the past twenty years, significant advancements have been made in metal-catalyzed vinylation reactions. Nickel catalysis has proved effective for vinylation of aryl and alkyl halides, enabling direct $C(sp^2)–C(sp^3)$ bond formation (see section 2.5). Rhodium and ruthenium catalysts have emerged as powerful tools for C–H bond functionalization, facilitating the direct vinylation of C–H bonds (see sections 2.2 and 2.3). Iridium catalysis stands out in vinylation chemistry, offering numerous advantages such as a wide functional group tolerance, mild reaction conditions, and high efficiency and selectivity (see sections 3.3 and 4.2). These advancements render iridium catalysts particularly attractive for synthesizing complex molecules through late-stage functionalization. The advent of iridium catalysis adds a new dimension to vinylation chemistry,



Scheme 1. The Mizoroki-Heck cross-coupling reaction reported in the early 70 s.

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expanding the possibilities for efficient and versatile synthetic routes. In addition, cobalt catalysts provide an appealing alternative, as they are both, air-stable and relatively cheap (see section 2.4).

Besides *C*-vinylation reactions, *N*- and *O*-vinylation also hold significant importance in organic synthesis. This is due to the utility of vinyl ethers and esters as synthons in polymer synthesis, drug discovery, and various other applications.[8] Additionally, their capability to undergo Claisen rearrangement, a pivotal step in the synthesis of natural products and complex compounds, further underscores their significance. Similarly, *N*-vinylated products find applications in the polymer and biomedical industry, owing to their biocompatibility and thermoplastic features.[9] Consequently, transition metal-catalyzed vinylation but also non-catalyzed *N*-vinylation (see section 3.4) and *O*-vinylation (see section 4.4) are a crucial class of reactions.

Classical vinylation methodologies involve amongst others elimination reactions, Wittig reactions, and the use of vinyl-Grignard reagents. Elimination reactions represent a classical method for vinylation, involving the removal of a leaving group from a precursor molecule to generate a vinyl group. For instance, alkyl halides treated with a strong hydroxy base (e.g. KOH, NaOH) undergo dehydrohalogenation leading to the formation of C–C double bonds, which, depending on the substrate, could be a vinyl group as well. The Wittig reaction plays a pivotal role in vinylation, particularly through the transformation of carbonyl groups. Last but not least, vinyl magnesium halides, such as vinyl magnesium bromide, can readily undergo reaction with a variety of electrophiles, including carbonyl compounds and alkyl halides, to yield vinylated products. These classical approaches are not covered in this review since they have been covered extensively elsewhere and are typically content already in an organic chemistry 1 lecture at university level.

The present mini-review discusses significant *C*-, *N*- and *O*-vinylation examples from 2002 onwards, focusing on catalysts, reagents, and intriguing applications. The review is structured first according to the vinylated center (C, N, or O) and within the chapter according to the metal catalyst. The *N*- and *O*-vinylation sections are each concluded with a non-catalyzed section. Alternatively, a structure according to the vinylation reagent was considered, which would have had its benefits. However, we decided for the aforementioned structure and provide at the beginning a table of the applied vinylation reagents in literature associated with a brief list of pros and cons (Table 1). In this way, the reader can quickly look up the properties of a vinylation reagent at a single location in the review.

2. C-Vinylation

Modern *C*-vinylation is undeniably a more challenging transformation than *N*- and *O*-vinylation, with a high potential for innovation and creativity. Cross-coupling reactions are the

Eleni Papaplioura received her master's degree in chemistry in the field of natural product synthesis (Elite program of the Network of Excellence Bavaria), from the University of Regensburg (Germany) in 2019, under the supervision of Prof. Oliver Reiser. Starting her PhD in 2020 in the group of Prof. Michael Schnürch, her doctoral studies focus on the" Sustainable and safe C-H activation for large-scale production" within the Chair, a Marie Curie funded ITN PhD project. Currently, she is working on substituting toxic gaseous reagents for safer, non-toxic solid alternatives.

Maëva obtained her master's degree in organic chemistry from the University of Montpellier (France) in 2015. She worked in the UK for 5 years, first joining RedX Pharma, a biotech company near Manchester, and then Sygnature Discovery, a CRO located in Nottingham. She joined Johnson & Johnson as a medicinal chemist at the end of 2020 in the Discovery Chemistry department, working on small molecule oncology programs.

Soufyan graduated his Ph.D. in organic chemistry from the University of Strasbourg in 2018, under the supervision of Prof Colobert and Dr Djukic. During his Ph.D. studies, he used chiral sulfoxide moieties to develop new strategies for asymmetric C(sp^3)-H bond activation. He joined the Discovery Chemistry department at Johnson & Johnson in 2019 where he initially worked in the oncology field. He subsequently took on higher responsibilities in the neuroscience space and then in the peptide field. Soufyan also plays a significant role in the implementation and advancement of LiveDesign, a data analysis and idea generation tool designed for medicinal chemists.

Michael Schnürch has received his PhD in 2005 from TU Wien. He was then Post-Doc with Prof. Dalibor Sames at the Columbia University in New York City. After his return, he completed his habilitation in 2013. He was promoted to privatdozent and in 2016 to Associate Professor for Organometallic Chemistry, a position he still holds. In 2024 he became head of institute of the Institute of Applied Synthetic Chemistry at TU Wien. His research interests are located in the field of medicinal chemistry, C–H activation, the substitution of gaseous reagents for solid alternatives, green chemistry, and mechanochemistry.

Review
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Table 1. Overview of Vinylation Reagents.

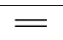
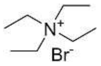
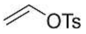
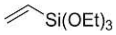
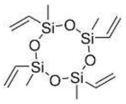
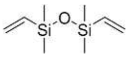
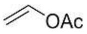
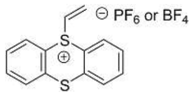
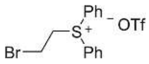
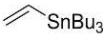
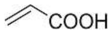
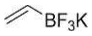
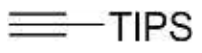
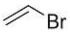
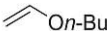
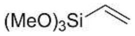
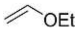
Vinylation Reagent[a]	Metal	Advantages	Disadvantages
 Ethylene	Pd, Rh	atom efficiency	toxic, flammable, non-selective, gas
 Tetraethylammonium bromide	Pd, Rh, Ru	solid, easy to handle, low toxicity	harmful to aquatic life
 Vinyl tosylate	Pd	stable	toxic, expensive, prone to polymerization
 Triethoxyvinylsilane	Pd, Rh	low toxicity, green	byproduct formation, careful storage
 1,3,5,7-tetravinyl-1,3,5,7-tetramethyl- cyclotetrasi-loxane (D_4^V)	Pd	stable, high coupling efficiency	all vinyl silane reagents require activation via a F-source
 Divinyltetramethyldisiloxane (DVDS)	Pd	low toxicity	flammable
 Vinyl acetate	Pd, Rh, Co, Ir, Au	easy to handle, versatile	flammable, moderately toxic
 Pinacol vinyl borate	Pd, Rh	easy to handle	stability, storage issues, expensive
 Vinyl thianthrenium salt (VTT)	Pd, non-catalytic	easy to handle	expensive, non- atom efficient
 (2-Bromoethyl)diphenyl-sulfonium triflate	Pd	stable, non-volatile, easy to handle	expensive
 Tributyl(vinyl)tin	Pd, Rh	easy to handle	high metal toxicity
 Acrylic acid	Rh	green	low reactivity
 Potassium vinyltrifluoroborate	Rh, Cu	safe, easy to handle	Expensive
 Vinyl butyrate	Ru	stable, low toxicity	expensive
 TIPS acetylene	Co	easy to handle, more stable than TMS acetylene	expensive, low boiling point
 Vinyl bromide	Pd	highly reactive	toxic, flammable, gas
 Butyl vinyl ether	Pd	green	highly flammable
			

Table 1. continued

Vinylation Reagent[a]	Metal	Advantages	Disadvantages
Vinyltrimethoxysilane	Cu	easy to handle	highly flammable
 Ethoxyethene	Au	green	low boiling point
CaC_2 Calcium carbide	Non-catalytic	easy to handle, atom efficiency	highly toxic, corrosive, environmental concerns

[a] All vinylation reagents are commercially available.

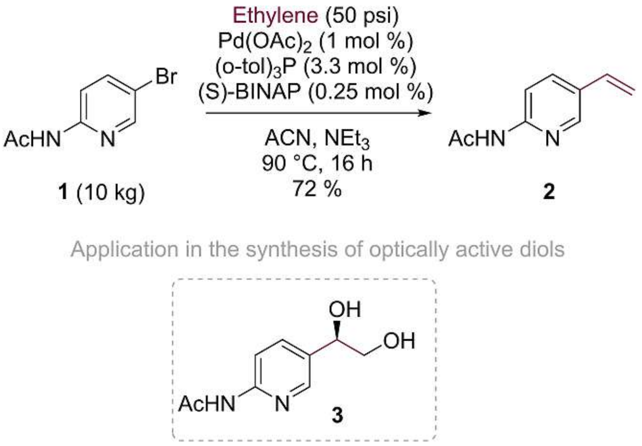
safest option for such a transformation, but oxidative Heck-type reactions are rapidly gaining traction, owing to the exponential interest for C–H activation methods in the past 20 years.

2.1. Pd-Catalyzed C-Vinylation

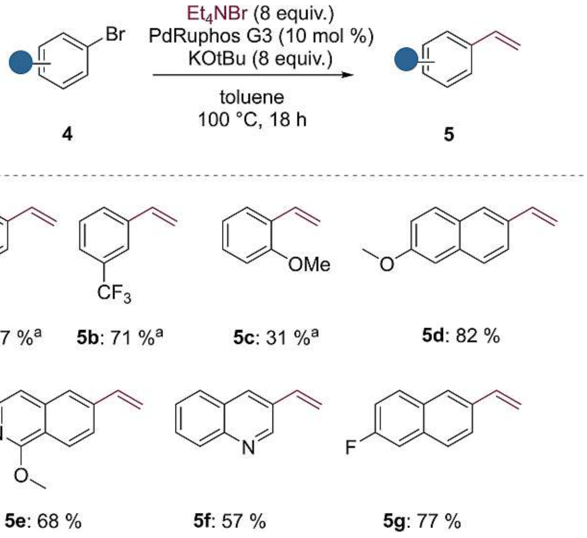
Since the discovery of Pd-catalyzed cross-coupling reactions, palladium emerged as the most reliable metal in many fields of catalysis and remains the most frequently applied metal in *C*-vinylation reactions.[10] From an economical and sustainability point of view, substituting palladium for non-precious metal alternatives is desirable. However, it is commonly the case that simple catalyst precursors, such as $Pd(OAc)_2$, can be used and compete economically with 3d metals, which often need more elaborate ligands.

Raggon et al.[11] disclosed a novel synergistic effect among phosphine ligands in a Heck coupling, facilitating the production of 2-acetamido-5-vinylpyridine on a multikilogram scale (Scheme 2). In this study, 3% tri(*O*-tolyl)phosphine ($P(O\text{-tol})_3$) and 0.25% 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) were added to achieve yields of approximately 70% for both laboratory- and large-scale experiments. Ethylene was used as the vinyl source at a moderate pressure of 50 psi. Interestingly, when ($P(O\text{-tol})_3$) and (BINAP) were tested individually for their efficacy in promoting the reaction, they did not exhibit the same level of effectiveness as when they were combined. However, no mechanistic studies providing an explanation for this empirical finding were undertaken. Inconstant yields ranging from 37% to 66% were observed in the absence of BINAP, likely due to the rapid formation of Pd^0, while lower yields as of 57% were noted in the absence of the ($P(O\text{-tol})_3$). Furthermore, the purity of the ($P(O\text{-tol})_3$) was found to be critical, significantly impacting reaction times. This methodology was employed for the synthesis of optically active diol **3**, an important synthon for the synthesis of pharmaceutically active compounds, such as anorectic agents, starting from the readily available 2-amino-5-bromopyridine.[12]

Only recently, our group presented a novel protocol for the facile vinylation of aryl bromides eliminating the need for ethylene gas as a coupling partner (Scheme 3).[13] Quaternary ammonium salts were utilized as solid olefin precursors under ambient atmosphere conditions, offering convenience and safety in a one-pot reaction setup. A diverse array of vinyl (hetero)arenes with yields ranging from 10% to 80% were obtained, highlighting the versatility of this methodology. The practicability and applicability of this transformation render it suitable for use in research and discovery contexts, particularly in medicinal chemistry where complex gas reaction setups are



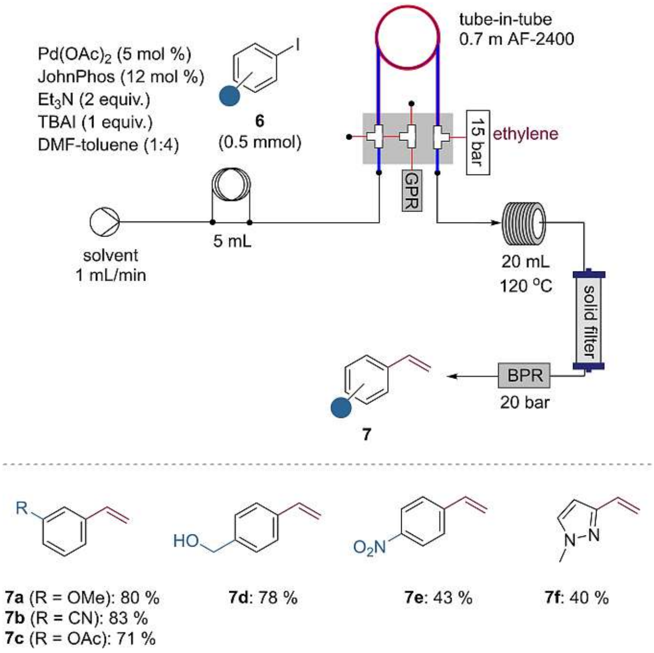
Scheme 2. Large-scale Heck vinylation of 2-acetaminO-5-brompyridine.



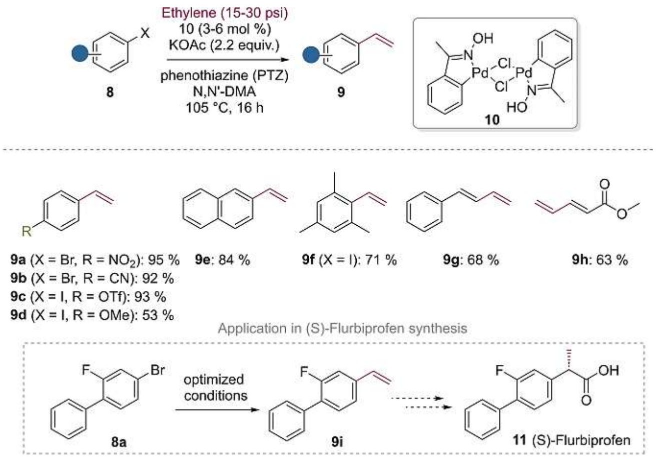
Scheme 3. Mizoroki-Heck coupling using tetraethylammonium bromide as ethylene precursor. ^{a}NMR yields.

not commonly employed. Compound **5d** surely could thus serve as a precursor for the synthesis of Naproxen (Figure 1).

One of the challenges of Mizoroki-Heck type reactions is the generation and use of ethylene gas to access functionalized styrenes. In a pioneering work in 2011,[14] Ley and co-workers disclosed an elegant flow set-up using a tube-in-tube gas-liquid reactor, allowing the use of ethylene (Scheme 4). The outer tube is a standard polytetrafluoroethylene (PTFE) tubing containing the gas (shown in red). The inner tube is a semi-permeable Teflon AF-2400 membrane from which the gas permeates and reaches the liquid phase, (shown in blue). It allows for the continuous generation of homogeneous solutions of gas. They used a palladium catalyzed system with the bulky (2-biphenyl)di-*tert*-butylphosphine (JohnPhos) as optimal ligand and employed tetrabutylammonium iodide (TBAI) as additive. A mixture of DMF and toluene was found to be the optimal system allowing to dissolve properly all the starting materials. Their scope included various functional groups such as nitrile **7b**, free alcohol **7d** and nitro **7e**. Continuing their work from 2011[14] and 2013[15] Polyzos and co-workers[16] discussed the utility of these reactors in processing reactive gases and developed further tandem processes, for example a tandem Heck-Heck sequence, and a tandem Heck-hydroformylation sequence.



Scheme 4. Flow set-up for the synthesis of styrenes using ethylene gas. GPR: gas pressure regulator, BPR: back pressure regulator.

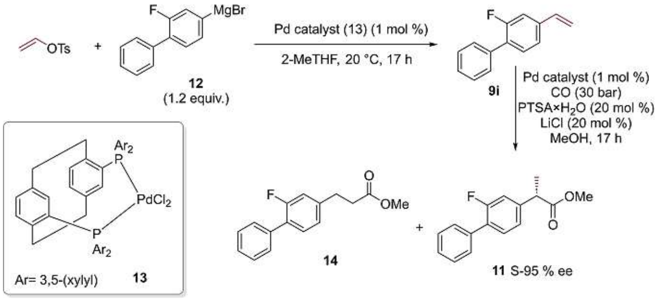


Scheme 5. Low pressure Heck vinylation of aryl halides with ethylene.

RajanBabu and Smith[17] presented an interesting example of the Mizoroki-Heck coupling between aryl bromides or iodides and ethylene at ambient or slightly elevated pressure (15-30 psi) (Scheme 5). Employing catalytic amounts of a dimeric palladacycle derived from acetophenone oxime, phenothiazine acting as a radical inhibitor, and vinyl bromides as starting material, the authors produced functionalized styrenes **9**. They claim this palladacycle-mediated coupling showed improved stability of the catalyst in comparison to classical phosphine complexes,[11] better activity at higher temperatures, and most importantly, suitability for use at ambient pressure conditions. Optimization studies were conducted to prevent the tandem Heck process (i.e. stilbene formation) as well as styrene polymerization.

Clarke and Harkness introduced an alternative highly enantioselective two-step synthesis of (*S*)-Flurbiprofen methyl ester, a prodrug of (*S*)-Flurbiprofen which is renowned for its anti-inflammatory properties, starting from commercially available 2-fluoro-1,1'-biphenyl.[18] The success of this synthesis hinged on the application of a specific catalyst, [PdCl$_2$((*S*)-xylyl-phanephos)], which facilitated the asymmetric methoxycarbonylation of **9i** (Scheme 6), yielding the desired product **11** with high enantioselectivity.

Taking inspiration from the previously reported Hiyama coupling conducted in an aqueous system,[19] Gordillo et al.[20] investigated a ligand-free, Pd-catalyzed vinylation of 4-iodobenzoic acid with triethoxy(vinyl)silanes in water. A pH above 12 allowed the reaction to proceed smoothly in water, with the rapid hydrolysis of triethoxyvinylsilane forming the water-soluble silanolate derivative. Mechanistic studies revealed that styrenes are predominantly formed via the Heck coupling mechanism, followed by a Pd-catalyzed hydrodesilylation, as opposed to a direct Hiyama coupling mechanism. The authors demonstrated that the hydride species produced in the Heck



Scheme 6. Synthesis of (*S*)-Flurbiprofen methyl ester using [PdCl$_2$((*S*)-xylyl-phanephos)].

reaction are transferred to the silyl olefins rather than to NaOH, either intra- or inter-molecularly (Scheme 7). This study significantly contributes to the understanding of the mechanism behind this environmentally sustainable transformation.

Further thorough mechanistic investigations[21] by the same group revealed the presence of competing reaction pathways, however, a detailed discussion goes beyond the scope of this review.

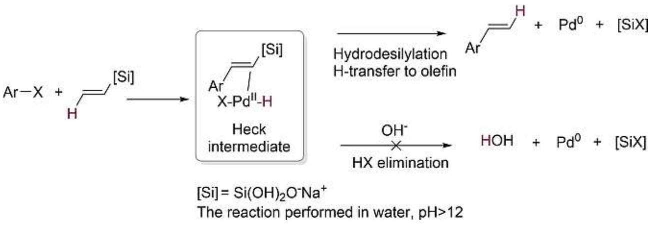
In 2008, Denmark and Butler[22] reported a Design of Experiment (DoE) optimization study of the palladium-catalyzed coupling of aryl iodides and organosilanes. Mild fluoride-free conditions were found using $Pd(dba)_2$ in DMF, 1,3-divinyltetramethyldisiloxane (DVDS) as the vinyl donor, in the presence of potassium trimethylsilanolate as a silanolate activator. Additionally, they adapted these conditions to aryl bromides, demonstrating the method's potential for synthesizing substituted styrenes.

In 2018, Yang et al.[23] developed a rare example of a Pd-catalyzed Hiyama vinylation of non-activated aryl bromides and chlorides under mild conditions. Using inexpensive 1,3,5,7-tetravinyl-1,3,5,7-tetramethyl-cyclotetrasiloxane (D_4^V) or DVDS as vinyl donor, tetrabutylammonium fluoride (TBAF) as activating agent and $Pd(OAc)_2$/Xphos/**17** as the catalytic system (Scheme 8). Utilization of electron-rich sterically hindered phosphine ligands was crucial for the reaction to proceed at room temperature. A good functional group compatibility was exhibited, including substrates bearing both electron withdrawing and donating groups. The methodology was suitable for preparative-gram scale experiments, while the resulting vinyl pyridines formed in this transformation can be easily polymerized and used for nuclear reprocessing, underlying the potential utility of the reaction in the synthesis of highly relevant materials.[24] Studies revealed that different electronic substituents on the vinyl pyridines, embedded in silica beads influence the americium/curium (Am/Cm) selectivity and their separation thereof.

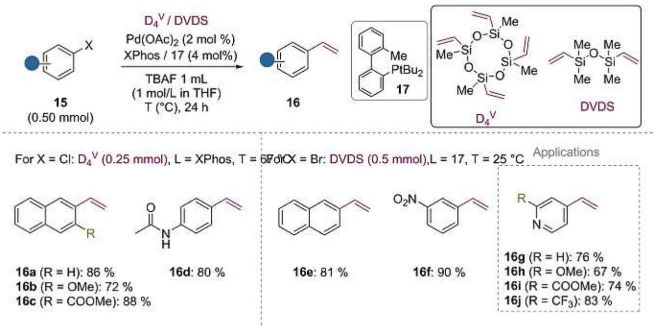
Lindh and colleagues[25] reported on the Pd-catalyzed vinylation of arylboronic acids and aryltrifluoroborates employing vinyl acetate as the olefin surrogate (Scheme 9). Their novel oxidative Heck reaction proceeded without the need for a base or oxidants when microwave irradiation was applied under air. A broad substrate scope was screened and tolerated. According to the proposed mechanistic studies, the reaction progresses via a Pd^{II} hydride species facilitating the release of ethylene, which undergoes oxidative arylation to form the desired styrene product **19**. Mass spectrometry analysis helped to confirm the formation of the styrene from arylation of ethylene rather than vinyl acetate.

Indazoles, commonly found in pharmaceutical compounds,[26] gained significant attention in research. The Gajardo group[27] used microwave-assisted conditions to perform a Suzuki cross-coupling to obtain *C*-3 vinylated unprotected indazoles using pinacol vinyl boronate. Both Boc-protected (not shown) and unprotected indazoles **20** were tested, investigating the influence of electronic properties of the *C*-5 substituent (Scheme 10). Only the *C*-3 vinylated product **21** was obtained in all cases, with no observed byproducts.

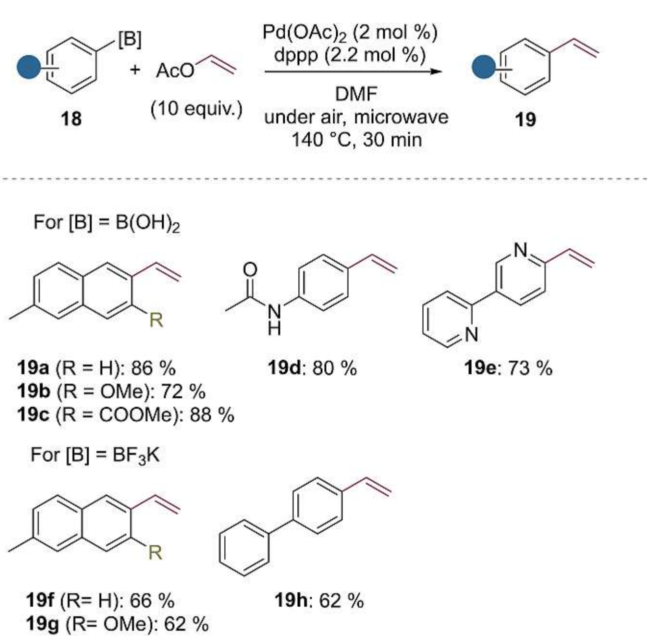
Ritter's group developed in 2021 an innovative vinyl thianthrenium electrophile reagent (VTT), that can be prepared directly from ethylene.[28] This reagent is a bench-stable, non-hygroscopic, crystalline solid and the only vinylating reagent which can be directly synthesized in one step from ethylene under ambient pressure. It can be easily synthesized and stored without decomposition for at least one year. It also demonstrates a desirable safety profile, as it does not decompose at



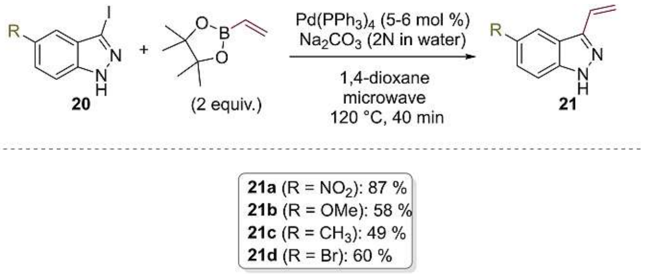
Scheme 7. Proposed pathway for the Heck desilylation reaction.



Scheme 8. Pd-catalyzed vinylation of aryl halides using organosilicon reagents.



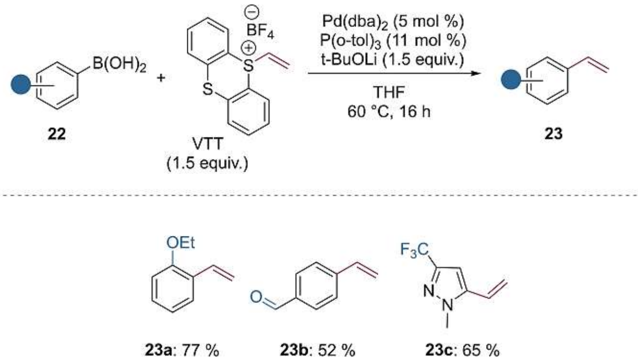
Scheme 9. Vinylation of arylboronic acids with aryltrifluoroborates and vinyl acetate.



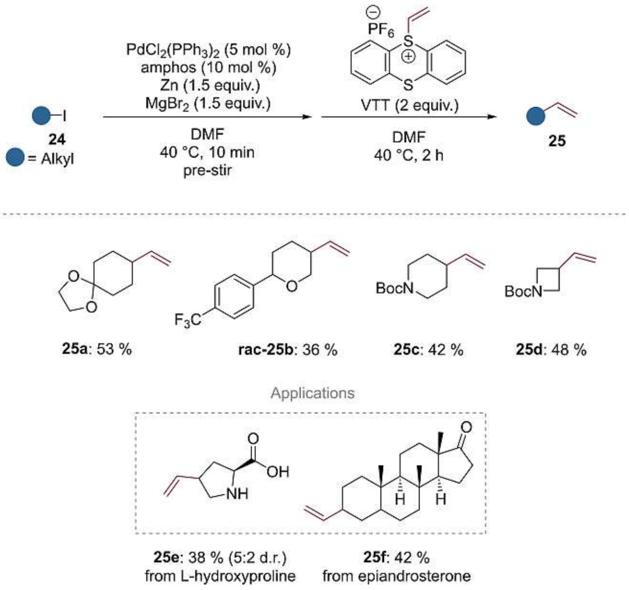
Scheme 10. Vinylation reaction of unprotected 5-substituted-3-iodoindazoles.

temperatures lower than 280 °C. Moreover, it undergoes fast oxidative addition to Pd, thus making it suitable for cross-coupling reactions such as Suzuki-type vinylation (Scheme 11).

An example of palladium catalyzed reductive vinylation of alkyl iodides was disclosed by the same group a few years later.[29] In this methodology, VTT was employed in the presence of zinc, affording the vinylated compounds **25** (Scheme 12). The typical formation of butadiene through vinyl homocoupling was circumvented with the dropwise addition of the vinyl thianthrenium salt. The process involves in situ formation of an alkyl zinc intermediate, which engages in reductive cross-coupling with alkyl iodides. This mechanism prevents the buildup of the AmphosPd^{II}(vinyl) intermediate (Amphos = bis(di-*tert*-butyl)-4-dimethylaminophenylphosphine, that typically forms after oxidative addition, reducing the undesired homocoupling to form butadiene. Optimization studies emphasized the important contributions of Amphos, and magnesium bromide, and demonstrated that vinyl bromide can also be used as the vinylating agent. A potential function of magnesium bromide could be to facilitate the formation of a zincate complex, thereby assisting in the transmetalation by weakening the Zn–C bond. However, vinyl bromides gaseous state makes it impractical, especially for large-scale applications. Moreover, this protocol facilitates the straightforward synthesis of 4-vinyl-*L*-proline **25e**, a crucial synthon for α-helical peptides, while compound **25f**, a steroid bearing a vinyl group at the C17 position, has the potential to enhance cytotoxicity against human colon cancer cells.[30]



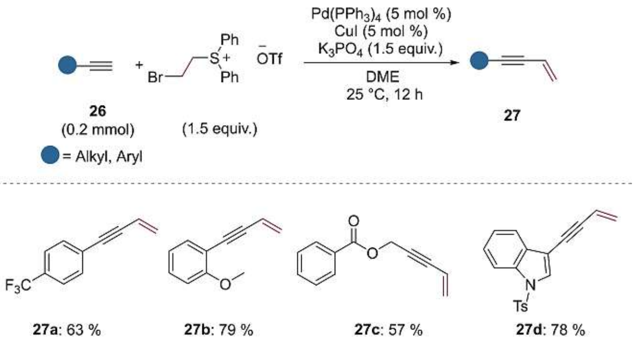
Scheme 11. Suzuki-type vinylation with VTT.



Scheme 12. Reductive cross-coupling of vinyl thianthrenium salt (VTT) and alkyl iodides.

Ming et al.[31] developed a Sonogashira-type coupling between terminal alkynes and the readily available (2-bromoethyl)diphenylsulfonium triflate under dual Pd/Cu catalysis, to afford 1,3-enynes (Scheme 13). The utilization of (2-bromoethyl)diphenylsulfonium) triflate as a vinylation reagent, serving as a precursor for diphenyl(vinyl)sulfonium through successive elimination in the presence of Pd/Cu catalysts, offers several advantages. It is a crystalline solid which exhibits high stability, non-volatility, and ease of storage and handling, allowing for large-scale applications. What is more, it offers specific C_{vinyl}-S bond rather than C_{aryl}-S bond cleavage, mild reaction conditions and good functional group tolerance.[32] The process was tested with different aromatic and aliphatic terminal alkynes bearing both electron-withdrawing and -donating groups, resulting in the formation of the corresponding 1,3-enynes **27** in moderate to high yields.

Monofluorinated alkenes, often encountered in natural products, are key building blocks in organic chemistry, with high potential as peptide isosteres in pharmaceutical applications.[33] Following earlier work on Pd-catalyzed *C*-F bond functionalization of tetrasubstituted *gem*-difluoroalkenes, the Tsui group[34] developed a methodology for the *C*-F bond



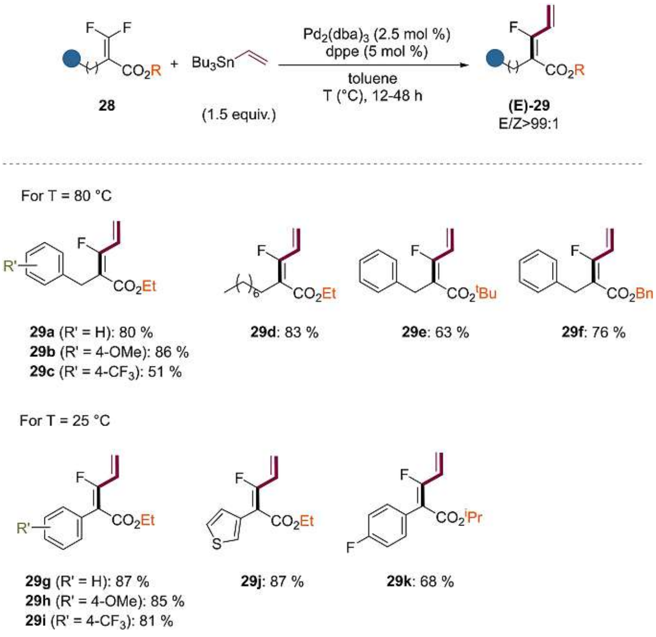
Scheme 13. Pd/Cu-catalyzed vinylation of terminal alkynes.

vinylation of similar substrates. Monofluorinated 1,3-dienes were formed via a Stille-type cross coupling reaction employing Pd^0, dppe as a ligand and tributyl(vinyl)tin as the vinylation reagent with excellent diastereomeric ratios (>99:1 *E/Z*) (Scheme 14). The broad scope of this work includes aryls bearing diverse electron withdrawing and electron donating moieties. The same protocol could be extended to allylation when tributyl(allyl)tin is used as the allylation reagent. A key drawback of this method is the vinylation reagent, due to the high toxicity associated with tin metal.[35]

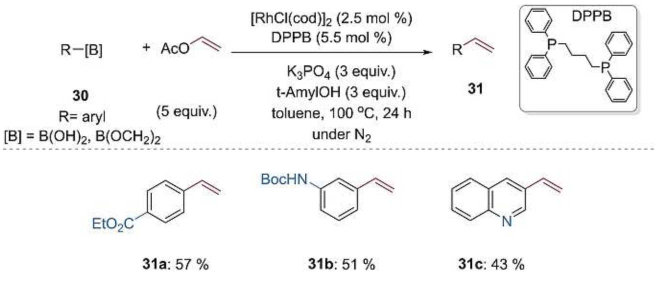
2.2. Rh-Catalyzed C-Vinylation

More recently, rhodium and to a lesser extent ruthenium (see section 2.3) became successful transition metals to catalyze vinylation reactions, particularly for oxidative Heck-type couplings, with the first examples published less than 15 years ago. Rhodium in particular shows attractive features such as low catalyst loadings and high functional group tolerance.

In 2009,[36] given the emerging success of vinyl acetate, an easy-to-handle vinylic electrophile, as a coupling partner for organometallic compounds, Yu and Kuwano published a method for Rh-catalyzed vinylation via cross coupling of organoboron compounds **30** (Scheme 15). Several metal complexes were explored, $[RhCl(cod)]_2$ (cod: 1,5-cyclooctadiene) was found to be the most effective catalyst. The choice of 1,4-bis(diphenylphosphino)butane (DPPB) as ligand and the use of ethylene glycol boronic esters instead of typical boronates were key to suppress protodeboronation. This method is very similar to the one reported by Larhed's group[25] (Scheme 9) which employs Pd instead of Rh. The method with Pd uses the same type of bidentate phosphine ligand, 1,3-bis(diphenylphosphino)propane (DPPP) and is slightly more advantageous as it does not require any base or additives and the reaction can be performed under air.



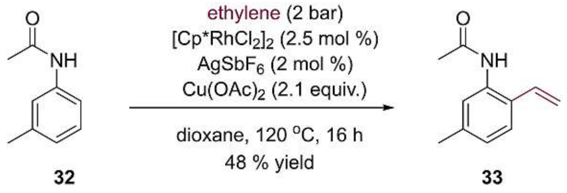
Scheme 14. Stereoselective synthesis of monofluorinated 1,3-dienes.



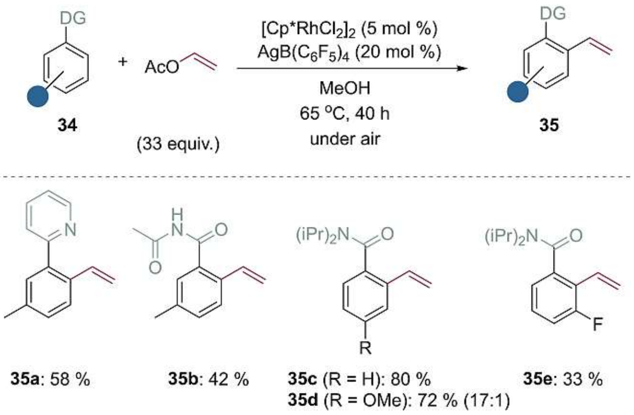
Scheme 15. Rh-catalyzed cross coupling.

Inspired by progress in oxidative Heck reactions under palladium[37] and rhodium catalysis,[38] Patureau and Glorius published in 2010 a Rh-catalyzed, group-directed cross-dehydrogenative coupling (CDC) between ethylene and acetanilides (Scheme 16).[39] Acetanilides are easy to prepare and can be hydrolyzed to the corresponding anilines. The reaction required relatively low ethylene pressure (2 bar) and proved selective for the less sterically hindered *ortho* position. The authors focused mainly on olefins and only one example of vinylation was reported (**33**), nonetheless highlighting the future opportunities offered by this method for the synthesis of styrene derivatives, and potential applications for natural product synthesis.

In 2015, Otley and Ellman reported a method using a Rh^{III} catalyst for the synthesis of styrenes via group-directed C–H activation (Scheme 17).[40] Double ortho-vinylation was observed during the reaction optimization of the 2-phenylpyridine substrate (not shown), therefore *meta*-substituted substrate



Scheme 16. Selective vinylation via oxidative Heck coupling.



Scheme 17. Rh^{III}-catalyzed C–H vinylation to access functionalized styrenes. In parenthesis, isolated ratio of single to double C–H activation product.

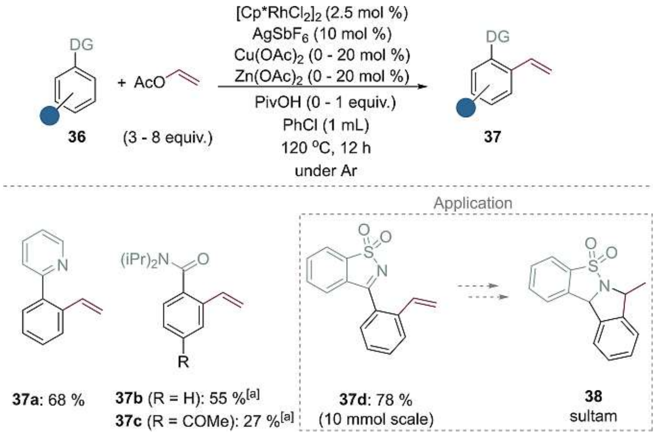
35 a was utilized to prevent over-vinylation successfully. The same strategy was employed to explore different amide directing groups (DGs), with **35 b** as an example. The arene scope with an amide DG was extended to other substrates at various positions showing high selectivity for mono-vinylated products (**35 c** and **35 d**). The *ortho* directing effect[41] is well known for strongly electronegative substituents, as observed for the *meta*-fluorinated substrate **35 e**. This methodology offered the possibility of mild vinylation at 65 °C under air, despite a large excess of vinyl acetate.

The same year, Wei's group[42] reported a similar Rh^{III}-catalyzed C–H vinylation (Scheme 18). PivOH, $Cu(OAc)_2$ and $Zn(OAc)_2$ were found to be key additives for yield improvement, despite their precise role remaining unclear. A range of aryls combined with various DGs (pyridine (**37 a**), azoles, amides (**37 b** and **37 c**) and cyclic *N*-sulfonyl ketimine (**37 d**) were explored. The attractiveness of the method was demonstrated by its application for the synthesis of pharmaceutically relevant sultam **38**.[43] This method is a better alternative compared to the work of Otley and Ellman (Scheme 17)[40] in terms of substrate diversity and selective mono-vinylation. Nevertheless, the general setup is more complex with the need for inert atmosphere, additives, and high temperature.

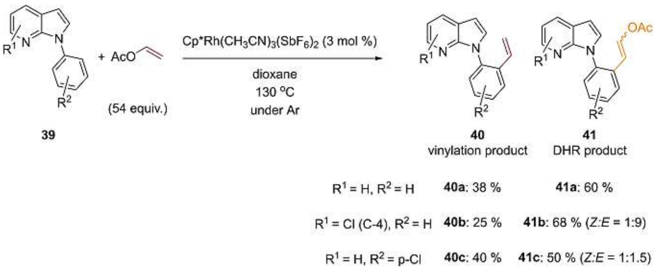
Li et al.[44] conducted a study on the use of a Rh^{III} catalyst for C–H activation using 7-azaindoles and different electron-donating olefins (Scheme 19). With a large excess of vinyl acetate, both the expected vinylation products **40** and dehydrogenative Heck-type reaction (DHR) products **41** were obtained. The ratio of vinylation to DHR product varied based on the specific substrate and each product could be separated by normal phase purification.

Cheng's group[45] reported a method using Rh^{III}-catalyzed DG-assisted C–H activation of *N*-methoxybenzamides or *N*-phenoxyacetamides with vinylstannanes (Scheme 20). A variety of functional groups at the *para* position as well as mono- and bis-substituted aromatic moieties were explored (**43 a** to **43 c**). For the *meta*-methoxy, *meta*-chloro and *meta*-bromo *N*-methoxibenzamide substrates (not shown), a regioisomeric mixture of *ortho*-vinylated products was obtained. Two hetero arenes (furan **43 d** and thiophene **43 e**) were successfully applied. A reaction with *N*-phenoxyacetamides **44** also proceeded well, with in situ cleavage of the DG, to give the corresponding 2-vinylphenols **45**. Application in the synthesis of the important alkaloid thalactamine[46] **46** and oxepine[47] **47** containing a 7-membered ring demonstrated the usefulness of this simple and mild method.

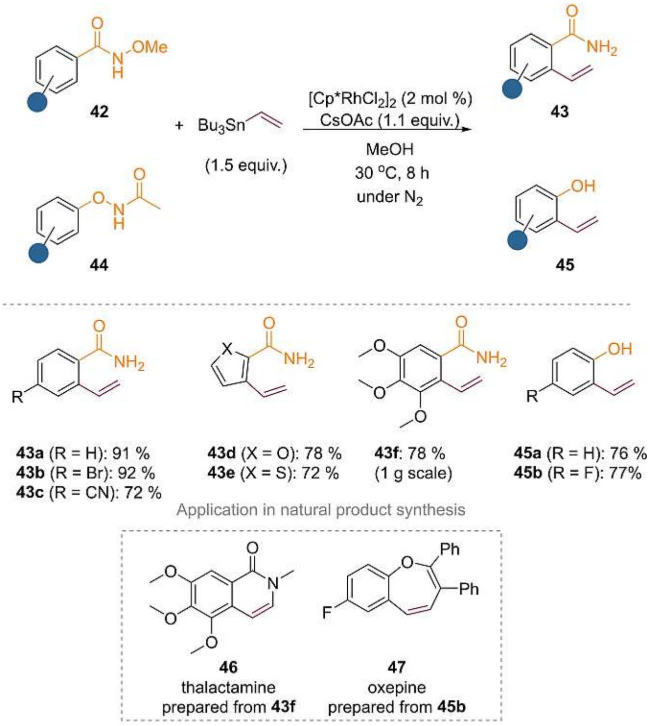
Xu et al.[48] published a chelation-assisted Rh^{I}-catalyzed decarbonylative C–H vinylation of arenes with acrylic acid (Scheme 21, Method **A**). DPPP as ligand was found critical for the reaction to proceed. Pyrimidyl-protected indoles with mostly variations at the *C*-5 and *C*-3 position were explored (**49 a** to **49 d**), with subsequent cleavage of the DG with sodium ethoxide[49] to obtain the vinylated indole **50**. Numerous aryl pyridines (**51**) and 6-arylpurine systems (**52**) were also successfully obtained. Despite the high temperature, this method uses a highly atom efficient vinylation reagent and offers a broad substrate scope. Vinylation of pyrimidyl-protected indole systems was studied by Wang et al. as well,[50] in their case using potassium vinyltrifluoroborate (Scheme 21, Method **B**). Simple



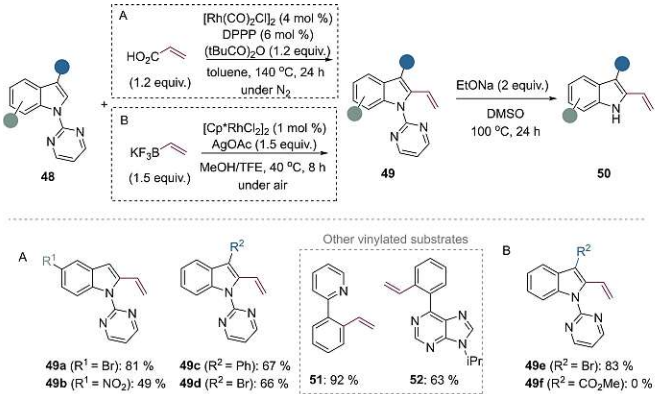
Scheme 18. Synthesis of styrenes via C–H activation. [a]Without $Cu(OAc)_2$, $Zn(OAc)_2$, and PivOH.



Scheme 19. Synthesis of 7-azaindole derivatives.



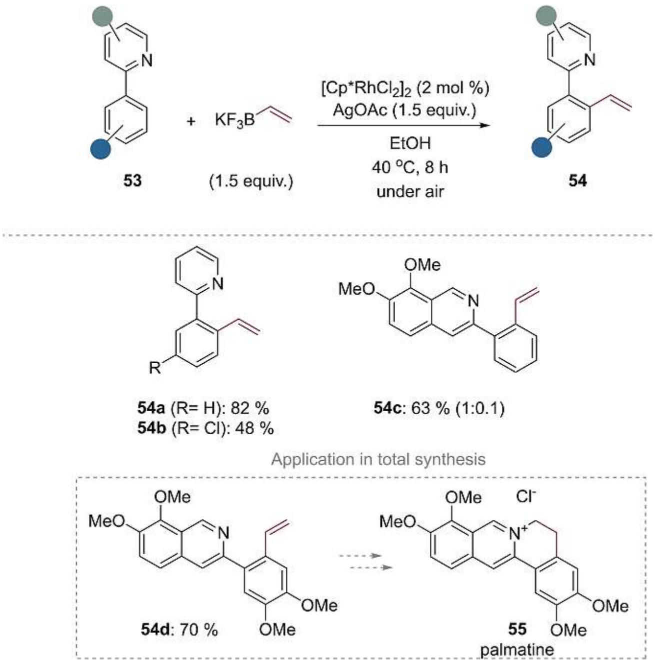
Scheme 20. Synthesis of 2-vinylbenzamides and 2-vinylphenols.



Scheme 21. Direct *C*-2 vinylation of indoles.

mild reaction conditions were required but substitution at the *C*-3 position (**49e** and **49f**) was critical for the success of the reaction.

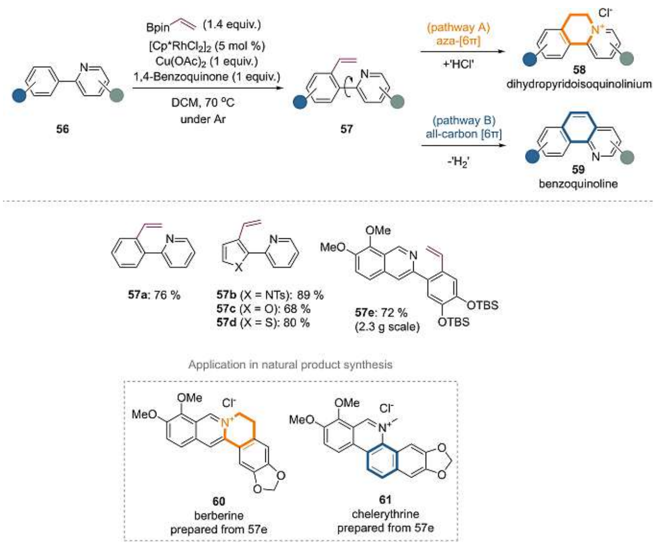
In 2020, Wu's group[51] reported a Rh^{III}-catalyzed *ortho* vinylation of 2-aryl pyridines with potassium vinyltrifluoroborate (Scheme 22), with conditions almost identical to Wang's protocol (method B, Scheme 21).[50] Wu's method was successfully applied to seven 2-aryl pyridines (two shown, **54a** and **54b**), 3-phenylisoquinoline **54c** and subsequently a more complex 3-arylisoquinoline **54d**, an intermediate in the synthesis of the alkaloid palmatine **55**. The protocol developed allowed a short and efficient synthetic route to palmatine in four steps from commercially available materials, compared to the classical method which is three steps starting from the related alkaloid berberine.[52]



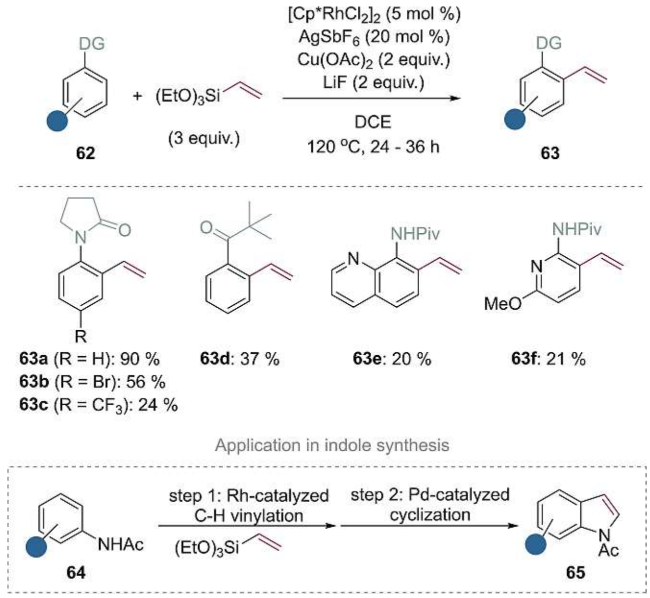
Scheme 22. Synthesis of pyridinyl styrene derivatives. In parenthesis, ^{1}H NMR ratio of single to double C–H activation product.

Jiang et al.[53] published an elegant two-step methodology to access dihydropyridoisoquinoliniums **58** or benzoquinolines **59** via C–H vinylation, followed by switchable 6π electrocyclizations (Scheme 23). The first part of their work focused on the C–H vinylation step via Rh^{III}-catalyzed oxidative coupling of readily available 2-phenylpyridines and pinacol vinyl borate. In total, fifty-two pyridinyl styrene derivatives (**57a** to **57e**) were obtained in moderate to high yields. The reaction was mostly selective towards mono-vinylation and tolerated a wide range of functional groups. The second part of the paper investigated the second step with two distinct pathways: aza-6 π electrocyclization (pathway A) and all carbon-6 π electrocyclization (pathway B). Density Functional Theory (DFT) calculations revealed that pathway A was much more kinetically favorable than B under thermal conditions. Therefore, an 'HCl' source and thermal conditions should favor A, and the absence of an 'HCl' source and photochemical conditions should favor B. This was confirmed experimentally, after optimization of the reaction conditions for each pathway on the model substrate **57a**, a quite impressive scope was reported with overall less success for the all carbon-6 π electrolization pathway. The power of this divergent methodology was demonstrated with the synthesis of two alkaloids berberine **60** and chelerythrine **61** from a common intermediate **57e**. Potential application of this protocol for the synthesis of palmatine **55** discussed above in Wu's paper[51] (Scheme 22) comes to mind evidently.

Shi's group[54] published a Rh^{III}-catalyzed oxidative vinylation of arenes using vinyltriethoxysilane as the vinyl source (Scheme 24). Other readily available vinyl silanes, such as DVDS and D$_4^V$, were found ineffective for this transformation. Various aryls and different DGs (pyrrolidinones, pivalamides, amides and ketones) were explored (**63a** to **63d**). Interestingly, quinoline **62e** and pyridines **62f** were successfully vinylated, albeit in lower yields. To demonstrate the utility of this method, it was applied to a two-step sequence for the synthesis of *N*-acylindoles **65**. This method is almost identical to the one



Scheme 23. Synthesis of dihydropyridoisoquinoliniums and benzoquinolines.

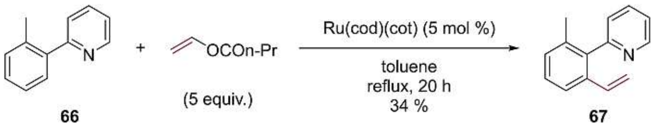


Scheme 24. Vinylation of arenes and heteroarene.

reported by Wei[42] (Scheme 16) and differs only in terms of vinylating agent. Compared to vinyl acetate used in Wei's method, organovinylsilanes usually require a fluoride source for activation, which can limit the functional group tolerance of the reaction.

2.3. Ru-Catalyzed C-Vinylation

Kakiuchi et al.[55] reported a rare example of Ru-catalyzed *ortho* vinylation of arylpyridine under halogen-free reaction conditions (Scheme 25). The substrate employed was 2-(2-tolyl)pyridine **66** and vinyl butyrate as the vinyl source. The reaction was conducted in the presence of catalytic amounts of Ru(cod)(cot) (cod: cyclooctadiene, cot: 1,3,5-cyclooctatriene), resulting in the formation of the corresponding vinyl pyridine **67** in 34% yield. The focus of their work was the introduction of longer alkene chains for alkenylation products, which were obtained in higher yields. This highlights again the difficulty in introducing specifically a simple vinyl unit. Compared to rhodium (see section 2.2), the use of ruthenium as a transition metal for catalyzed *ortho* vinylation via C–H activation is much less explored.



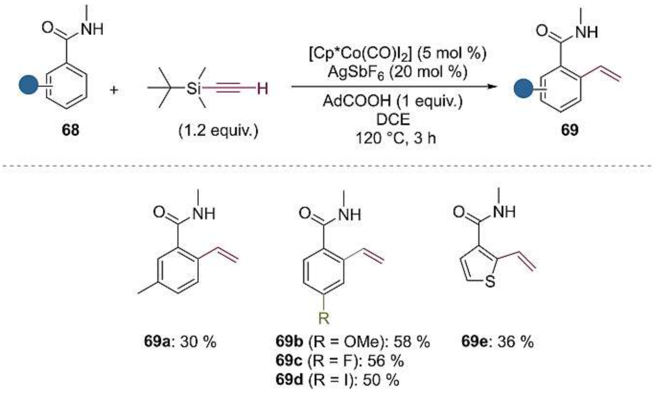
Scheme 25. Ruthenium-catalyzed *ortho* vinylation of an arylpyridine derivative.

2.4. Co-Catalyzed C-Vinylation

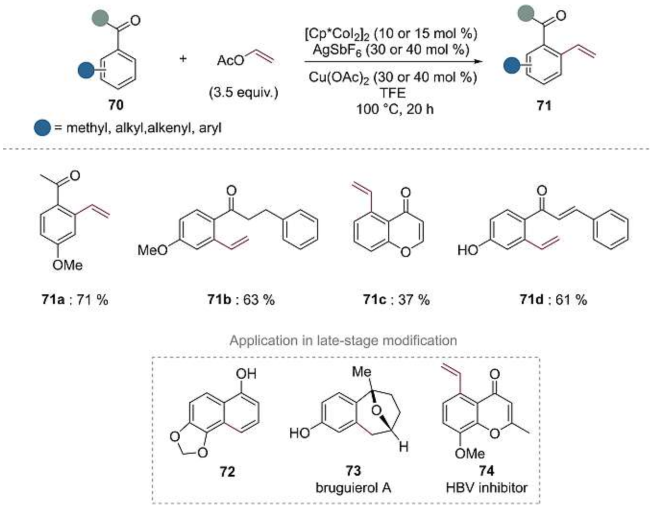
While the use of precious metals is predominant, 3d metals such as cobalt and nickel (see sections 2.4 and 2.5) for *C*-vinylation are gaining traction. From a sustainability standpoint, unlike precious 4d and 5d metals, 3d metals are abundant in nature, making them attractive and more cost-effective metals. Additionally, 3d metals exhibit lower toxicity levels compared to noble metals and are therefore ideal candidates for pharmaceutical and agricultural-related applications.[56] Furthermore, as industries aim for greener chemical processes, their utilization promises innovation while expanding the scope of synthetic chemistry.

In 2018, Muniraj and coworkers[57] successfully developed an air-stable and cost effective Co^{III}-catalyzed method for the desilylative direct *ortho*-vinylation of secondary *N*-methyl benzamide derivatives (Scheme 26). Mechanistic studies provided valuable insights, highlighting the significance of the [SbF$_6$]$^-$ in the desilylation process. Upon identifying optimal reaction conditions, the authors explored the scope of benzamide derivatives **68**, resulting in modest yields in most cases for the respective products **69**. This methodology offers a versatile approach for the synthesis of *ortho*-vinylated secondary *N*-methyl benzamides.

Maji and coworkers[58] reported on a novel Co^{III}-catalyzed ketone-directed C–H vinylation using vinyl acetate to obtain a wide range of 2-vinyl aromatic ketones (Scheme 27). This method operates efficiently without the need for installing a leaving group on the aromatic ketone **70**, utilizing a cost-effective and stable Co catalyst. While optimization studies showed that the best yields were achieved using a fluorinated solvent, specifically 2,2,2-trifluoroethanol (TFE), the reaction also proceeded neat by using a large excess of vinyl acetate. Various acetophenones and benzophenones carrying substituents with different electronic properties tolerated the reaction conditions. When subjected to the protocol, chalcones underwent vinylation of the aromatic C–H bond selectively rather than the olefinic one (**71 d**). The significance of this methodology was demonstrated by its application in the syntheses of α-naphthol **72** and natural product bruguierol A **73**, and the late-stage vinylation of an HBV inhibitor towards **74**. These examples



Scheme 26. Direct vinylation of secondary benzamides.

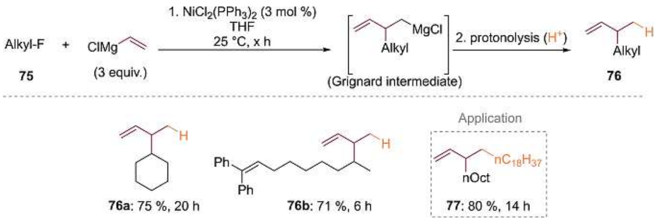


Scheme 27. Ketone-directed C–H vinylation of acetophenones, diarylketones and chromones.

highlight the potential for late-stage C–H vinylation of bioactive vinyl ketones.

2.5. Ni-Catalyzed C-Vinylation

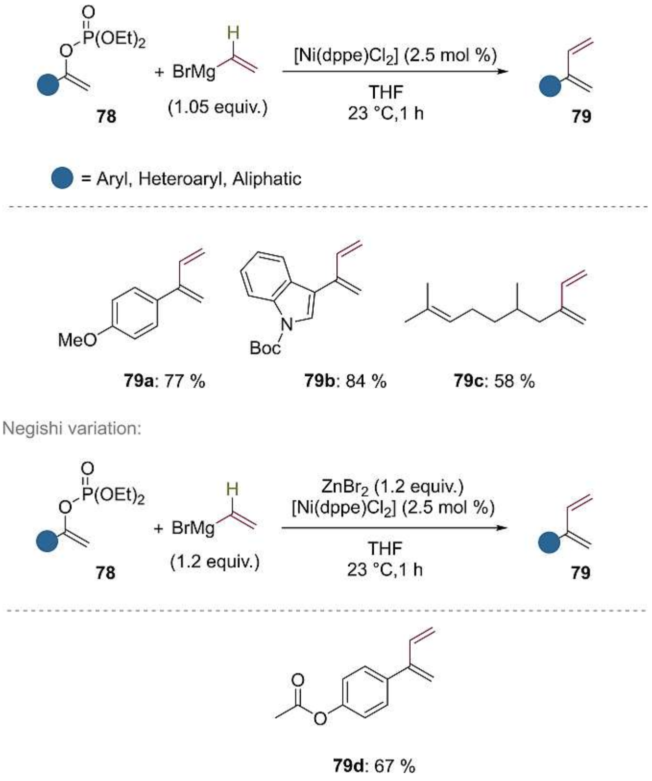
Terao et al. described a novel dimerization cross coupling reaction of alkyl fluorides with vinyl Grignard reagents facilitated by nickel catalysis (Scheme 28).[59] Overall, one equivalent of the vinyl-Grignard reagent gets alkylated by the alkyl fluoride and vinylated by a second equivalent of the vinyl-Grignard reagent. A plausible reaction pathway was proposed, with two different possibilities to form the Grignard intermediate, but further studies would be required to fully elucidate the mechanism. Given the inherent inert nature of the C-F bond, the study showed that alkyl fluorides **75** proved to be superior alkylating agents, with exclusive reactivity in the desired transformation, compared to the corresponding chlorides, bromides or iodides which are prone to side reactions. This study also demonstrated the introduction of secondary alkyl groups, albeit requiring prolonged reaction times. Subsequently, a Ni-catalyzed cross-coupling reaction with alkyl halides could facilitate further alkylation, achieving the regioselective incorporation of two distinct alkyl groups.



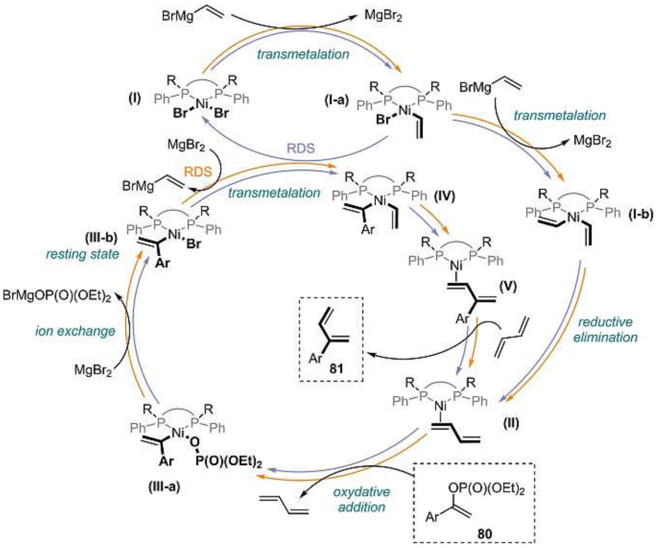
Scheme 28. Ni-Catalyzed dimerization of vinyl Grignard reagents using alkyl fluorides.

In 2018, the group of Mazet[60] published their study presenting a Ni-catalyzed Kumada vinylation for the preparation of 2-substituted 1,3-dienes (Scheme 29). These dienes serve as important organic synthons for the preparation of fine chemicals, polymers, and natural products.[61] The authors identified two nickel pre-catalysts, [(dppe)NiBr$_2$] and [(dmpe)NiBr$_2$], capable of operating under mild conditions, utilizing readily available enol phosphates and commercially available vinyl magnesium bromide. This study stands out due to the otherwise tedious incorporation of a vinyl derivative, low catalyst loading and remarkable functional group tolerance, affording the corresponding products **79** with yields between 61 % to 90 %. Furthermore, this approach allows the preparation of more substituted conjugated 1,3-dienes with high stereo control (not shown). For more sensitive functional groups such as esters (**79 d**) and nitriles, a Negishi variant was developed. An additional highlight of this transformation lies in its scalability, as demonstrated by a multikilogram-scale experiment.

A few years later, the same group focused on the mechanistic investigation of the Ni-catalyzed Kumada vinylation of enol phosphates with vinyl magnesium bromide.[62] Through a combination of experimental findings from stochiometric organometallic synthesis, structural analysis, reaction monitoring, radical-clock experiments and kinetic investigations, the authors concluded that the two biphosphine catalysts [(dppe)NiBr$_2$] and [(dmpe)NiBr$_2$] operated via two proposed plausible distinct catalytic pathways (Scheme 30). Although they both involve similar Ni^0/Ni^{II} intermediates, there are



Scheme 29. Ni-catalyzed cross-coupling of vinyl phosphates and vinyl magnesium reagents.



Scheme 30. Proposed catalytic cycles for Ni-catalyzed vinylation of enol phosphates using [(dppe)NiBr$_2$] (R = phenyl, orange path) and [(dmpe)NiBr$_2$] (R = methyl, blue path).

variations in the order of the elementary steps and the interaction between reactive species. Starting the investigation with the [(dppe)NiBr$_2$], it was found that the activation of the pre-catalyst precedes the Initiation of a conventional catalytic cycle, involving oxidative addition/transmetalation and reductive elimination steps. Notably, mechanistic investigation studies on the [(dmpe)NiBr$_2$] complex unveiled that the transmetalation step occurs between two nickel intermediates. A nickel species formed during pre-catalyst activation interacts with an α-styrenyl Ni^{II} intermediate generated in the sequence of elementary steps. This discovery holds significance and aims to the development of promising catalysts for vinylation reactions in the future.

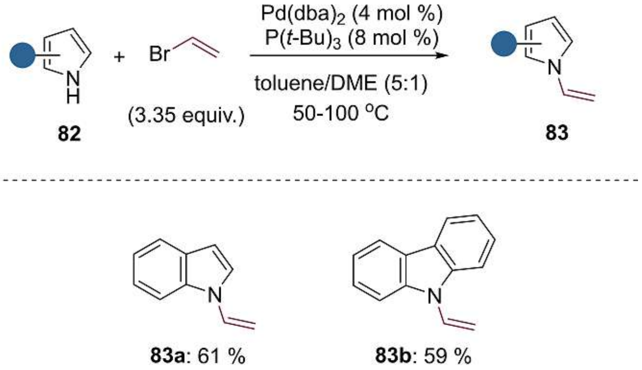
3. N-Vinylation

As for *C*-vinylation, Pd is an obvious choice for transition metal-catalyzed N-vinylation. However, selectivity towards N-vinylation versus *C*-vinylation is a concern for halide-containing substrates, limiting the possibilities for N-vinylation of more complex substrates. Copper is an equally key transition metal for this chapter, and scope limitations can also be explained by the versatility of this metal in catalysis. Finally, iridium has emerged more recently for N-vinylation reactions, an interesting prospect due to the very low catalyst loadings reported. Alternatively, well established and more recent non-catalytic methods can also be used (see section 3.4) and circumvent selectivity or functional group tolerance limitations.

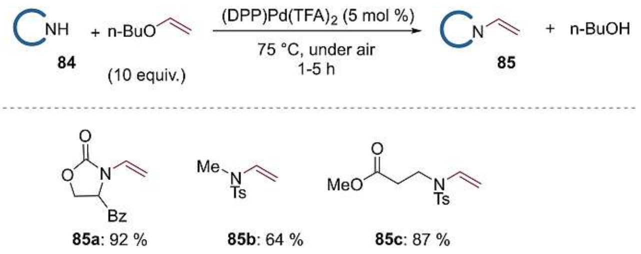
3.1. Pd-Catalyzed N-Vinylation

Back in 2002, the group of Voskoboynikov[63] reported a Pd-catalyzed vinylation of azoles and phenothiazine, one of the earliest examples of Pd-catalyzed N-vinylation (Scheme 31). They found that the choice of ligand was crucial for successful results and the most active catalytic system was Pd(dba)$_2$/P(*t*-Bu)$_3$. Only two examples (**83 a** and **83 b**) of free vinylation were reported. In case of *Z*- or *E*-bromo-alkenes (not shown), the reaction was stereospecific yielding the corresponding *Z*- and *E*-enamines with full retention of configuration. Despite the use of vinyl bromide, this method was seen as an attractive alternative to existing ones and provided an appealing route for enamines that could not be prepared by routine condensation of amines with aldehydes or ketones.

A novel approach for the synthesis of enamides was described by Stahl and co-workers,[64] involving the Pd^{II}-catalyzed vinyl transfer from vinyl ethers to N-nucleophiles (Scheme 32). Addressing common challenges encountered in Pd^0-cross coupling reactions, the authors opted for Pd^{II} catalysts for this transformation. Drawing inspiration from their previous investigation on transfer vinylation using alcohols and 1,10-phenanthroline ligands, they found that (DPP)Pd(TFA)$_2$, (DPP: 4,7-diphenyl-1,10-phenanthroline) exhibited the highest catalytic activity.[65] The reaction was compatible with various nucleophiles including amides (not shown), carbamates (**85 a**) and sulfonamides (**85 b** and **85 c**), affording good to excellent product yields. Although dibutyl acetal emerged as a byproduct from the catalyzed addition of butanol to butyl vinyl ether



Scheme 31. Catalytic *N*-vinylation of azoles.



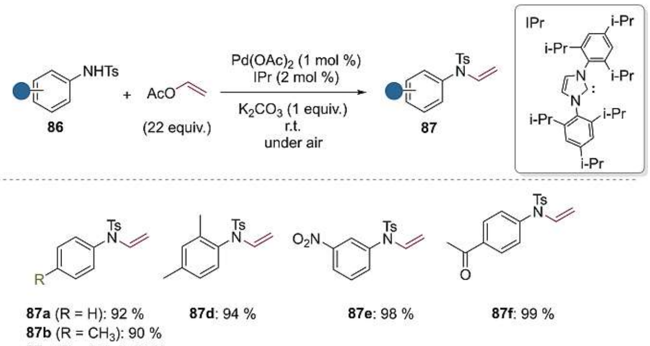
Scheme 32. Formation of various enamides via Pd^{II}-catalyzed transfer vinylation.

(BVE), its occurrence was effectively suppressed by adding an excess of BVE.

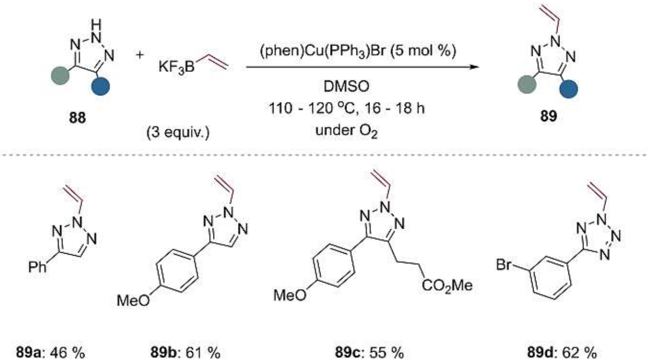
A Pd-catalyzed synthesis of enamides at room temperature and under air was reported by Guo's group.[66] They utilized a $Pd(OAc)_2$/carbene catalyst system with vinyl acetate as the vinyl source, successfully producing terminal enamides **87** from various substituted sulfonamides (**86a** to **86f**) and acrylamides (not shown). Substrates featuring electron-withdrawing groups demonstrated enhanced efficiency compared to those with electron-donating groups. This approach established a novel methodology for palladium-catalyzed C-N bond formation reactions and gave remarkably high yields (Scheme 33).

3.2. Cu-Catalyzed N-Vinylation

In the first examples of Cu promoted N-vinylation, a stochiometric amount of Cu was required for the reaction to proceed.[67] Later on, two publications from the group of Belyakov reported an efficient method for N-vinylation of aryl carboxamides,[67a] nucleobases, nucleosides and 5-membered N-heterocycles[67b] using one equivalent of Cu^{II} acetate, trimethoxyvinylsilane as the vinyl source and TBAF. The same year, Batey and Bolshan[61] published a method for Cu-catalyzed N-vinylation of amides with potassium alkenyl trifluoroborate salts, with a single example of free vinyl formation.



Scheme 33. Synthesis of sulfonamides and acrylamides via Pd^{II}-catalyzed *N*-vinylation.



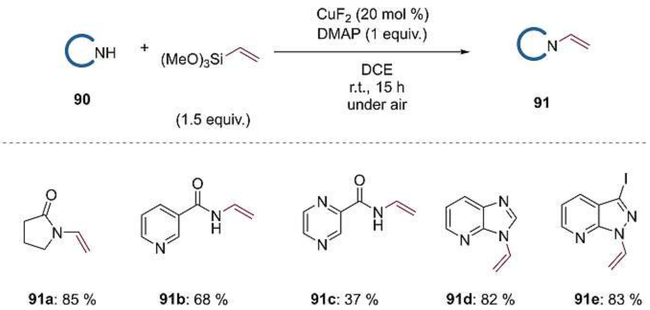
Scheme 34. Copper catalyzed N2-Vinylation of triazoles and tetrazoles.

Motornov et al.[68] published in 2019 a Cu^{I}-catalyzed Chan-Lam coupling method for N2-vinylation of electron-deficient azoles using potassium vinyl trifluoroborate as the vinyl source (Scheme 34). This method allowed low catalyst loading (5 mol %) and base-free conditions. A mixture of N2/N1-product was obtained with an NMR ratio from 5:1 for monosubstituted triazoles (**89a** and **89b**) to >30:1 for bulky disubstituted triazoles (**89c**). The major N2 product was easily separated by normal phase purification. For the tetrazole example, the vinylation afforded the 2-vinylated tetrazole **89d** exclusively.

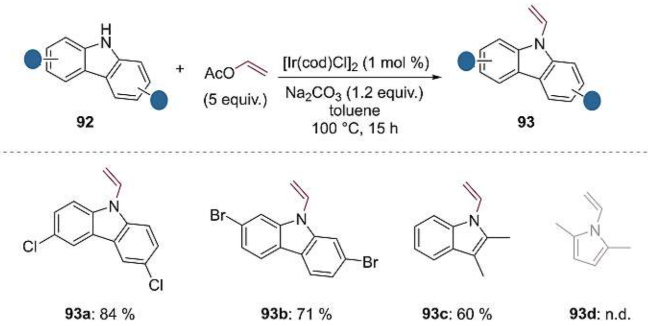
Das' group[9] reported a Cu^{II} fluoride/DMAP-catalyzed method for the N-vinylation of amides and azoles with vinyltrimethoxysilane (Scheme 35). Mechanistic studies showed that $[Cu(DMAP)_4Cl_2]$ was the catalytically active species, demonstrating the dual function of DMAP as a base and ligand and the dual function of Cu^{II} fluoride as a catalyst and fluoride source for the cleavage of trimethoxysilane. Different azoles and a range of amides, including carbamate, succinimide, hydantoin and pyridine were explored (**91a** to **91e**). This procedure runs under mild reaction conditions and shows a decent functional group tolerance, but the stochiometric use of toxic DMAP can reduce its attractiveness.

3.3. Ir-Catalyzed N-Vinylation

A practical method for the synthesis of vinylcarbazoles, using vinyl acetate as the vinyl source under iridium catalysis has been reported by the group of Obora (Scheme 36).[69] *N*-Vinylcarbazoles, besides being important synthons in medicinal



Scheme 35. *N*-Vinylation of amides and azoles.



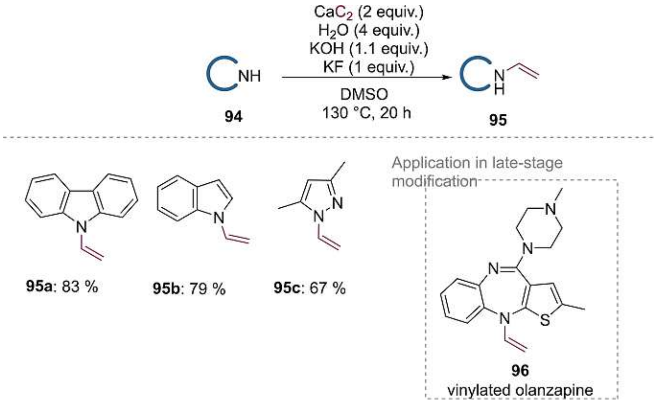
Scheme 36. Iridium-catalyzed vinylation of carbazole derivatives using vinyl acetate, and selected examples. (n.d.: not detected by GC/MS)

and organic chemistry, also act as monomers to produce poly(*N*-vinylcarbazoles), compounds with various applications in electroluminescent devices.[70] Given that the substitution pattern significantly impacts photoconductivity properties of the materials, scaffolds with different halogens (**93 a** and **93 b**) were systematically screened. However, attempting to extend the present protocol to other azole derivatives proved challenging, with lower success rates, especially for less substituted pyrroles, and only indole **93 c** was obtained with a moderate 60 % yield.

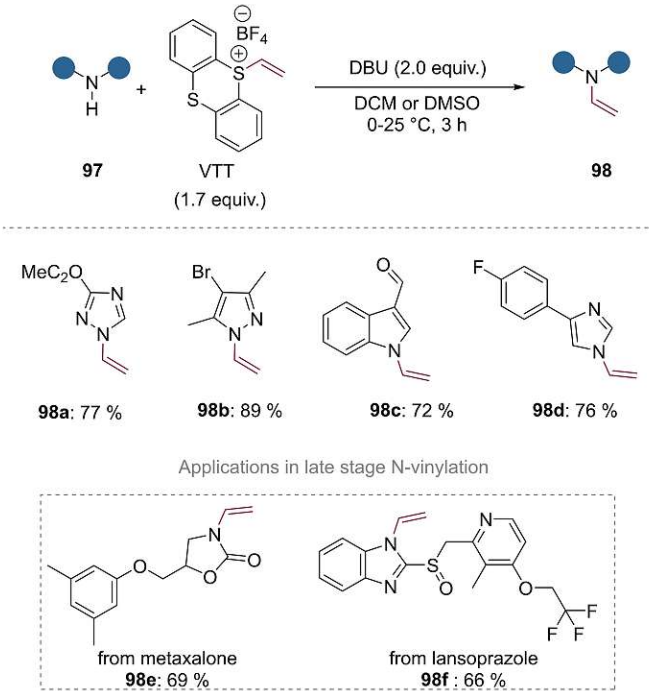
3.4. Non-Catalyzed N-Vinylation

Ananikov's group[71] introduced a novel approach for the vinylation of secondary amines using calcium carbide (CaC_2), an inorganic vinylation reagent, to form a range of *N*-vinyl derivatives (Scheme 37). Their process eliminated the need for high-pressure equipment for acetylene use, demonstrating high efficiency towards various substrates including pyrrole, pyrazole, indoles, aryl amines, and carbazoles (**95 a** to **95 c**). Subsequently, the obtained vinylated compounds were subjected to both radical and cationic polymerization techniques, successfully synthesizing both linear and cross-linked polymers from substrates containing carbazole and bicarbazole moieties. What is more, they achieved late-stage modification of olanzapine **96**, an antipsychotic drug, highlighting the methodology's potential in the fields of both material chemistry and drug development.

Ritter's group,[28] who developed and employed the VTT salt in cross-coupling reactions such as Suzuki-type vinylations for the synthesis of styrenes and carbocycles (see Pd-catalyzed *C*-Vinylation section 2.1), extended its application to a non-catalyzed N-vinylation protocol (Scheme 38). This protocol could tolerate various polar groups on nitrogen-containing heterocycles, as well as aryl halides (**98 b**) and aldehyde groups (**98 c**). The usefulness of the protocol was demonstrated by application in late-stage functionalization to obtain **98 e** and **98 f**. Two examples in particular, halide containing **98 b** and aldehyde containing **98 c**, highlight the complementary of this method with metal-catalyzed N-vinylation and N-vinylation using CaC_2.



Scheme 37. *N*-vinylation of secondary amines.



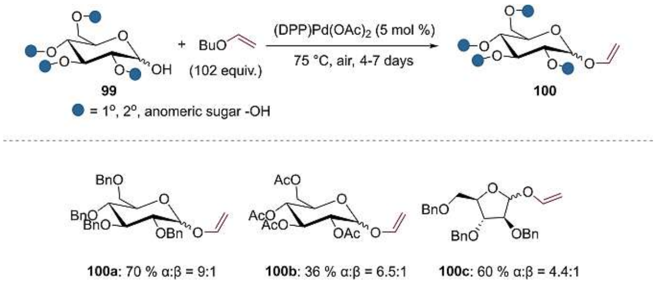
Scheme 38. Non-catalyzed vinylation of *N*-heterocycles.

4. O-Vinylation

Concerning transition metal-catalyzed O-vinylation, Pd catalysis predominantly facilitates transfer vinylation, demonstrating a relatively broad scope and good functional group tolerance. These reactions can be conducted under air, effectively suppressing acetal formation. A more sustainable approach involves the use of iridium, which requires even lower catalyst loading, utilizing a bio-derived solvent eventually and which shows high tolerance, particularly for more sterically hindered substrates. Notably, to the best of our knowledge, only one research group has reported on gold-catalyzed O-trans vinylation between alcohols or carboxylic acids and vinyl acetates under relatively mild conditions.

4.1. Pd-Catalyzed O-Vinylation

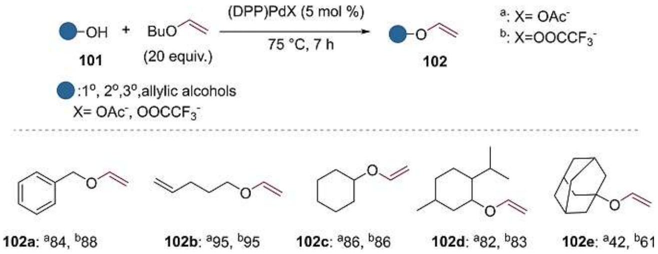
In 2002, Schlaf[65a] developed a novel methodology for the synthesis of vinylated sugars via Pd-catalyzed transfer vinylation. Protected monosaccharides **99** with a single free hydroxyl group were utilized as substrates, employing vinyl butyl ether as both solvent and reagent, and $Pd(OAc)_2$/DPP as the optimal catalytic system (Scheme 39). Through optimization of the reaction conditions, the authors identified DPP as the optimal ligand, while efforts to use other vinyl sources besides vinyl ethers proved to be unsuccessful in obtaining the desired



Scheme 39. Pd^{II}-catalyzed transfer vinylation of protected monosaccharides.

product. Steric availability of the oxygen bearing the vinyl carbon was found to be vital for promoting the reaction. Primary and secondary hydroxyl groups, as well as pyranose and furanose anomeric positions were all successfully vinylated. The reaction tolerated various protecting groups, including acetal, benzyl, silyl ether, and acetates, albeit with slightly reduced yields. Extensive mechanistic studies uncovered the sensitivity of the catalytic system to deactivation and formation of Pd black, when moisture was excluded. This undesired side reaction could be prevented by carrying the reaction under air.

In 2003, again Schlaf[65b] presented a novel method for synthesizing allyl and alkyl vinyl ethers using an in situ formed, air-stable Pd catalyst (Scheme 40). Building on the prior success of $Pd(OAc)_2$/1,10-phenanthroline or 2,2′-bipyridyl catalytic systems in facilitating the transfer vinylation of sugars,[65a] the authors reexamined the catalytic system by substituting the acetate counterion with trifluoroacetate.[65a] Employing (DPP)Pd$(TFA)_2$ as the catalyst and commercially available butyl vinyl ether as both solvent and reagent, they explored this modified system **101** with various primary, secondary, and tertiary alcohols. Mechanistic studies showed that the exchange of acetate for trifluoroacetate did not directly affect the equilibrium position (the chemical equilibrium of reactants and products), but did impact the reaction time, leading to shorter reaction times until equilibrium was reached. The authors attributed this observation to the coordinating ability of the counterion. The less coordinating ability of trifluoroacetate resulted in the equilibrium favoring the formation of the corresponding vinyl ether. However, simultaneously the formation of acetals as byproduct is favored in these cases, which was suppressed by the addition of NEt_3. The study also highlighted the sensitivity of the reaction to steric effects, allowing only simple ethenyl to be tolerated. However, the reaction did tolerate remote C–C double bonds in alcohol substrates and allyl alcohol, though phenols proved incompatible with the process.

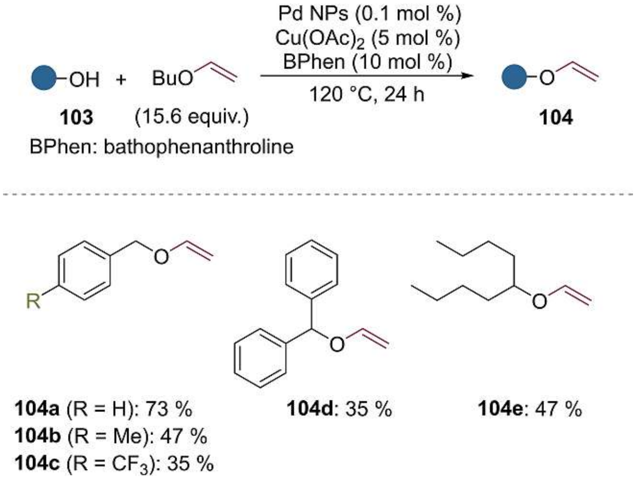


Scheme 40. Synthesis of allyl and alkyl vinyl ethers under Pd-catalysis. GC yields reported in %.

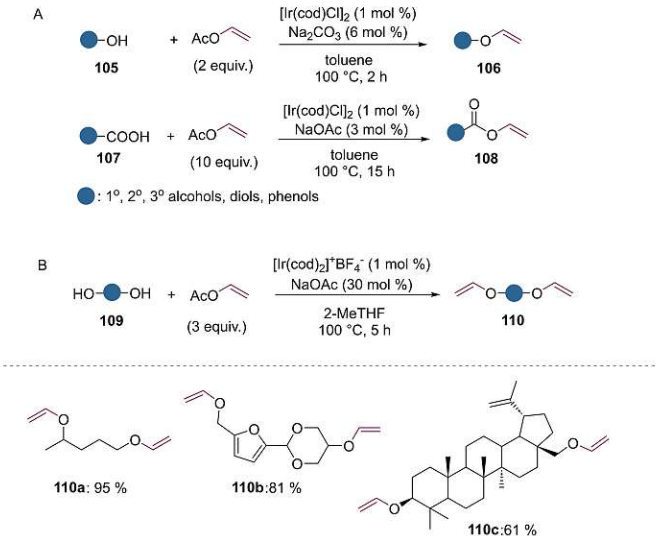
Recently, the group of Obora[72] reported on the transfer vinylation of alcohols from vinyl ethers catalyzed by *N,N′*-DMF-stabilized palladium nanoparticles (NP) and bathophenanthroline (Scheme 41). Although, catalytic systems, employing Pd$(OAc)_2$ and phenanthroline derivatives, offer advantages such as complex stability and the suppression of the acetal formation, these transformations typically suffer from low recyclability and require high catalyst loading due to the deactivation of the metal complex catalyst. In this study, employing palladium nanoparticles and bathophenanthroline, the authors utilized low catalyst loadings (0.05–0.10 mol %) and achieved catalyst recycling. Transmission Electron Microscopy (TEM) and Dynamic Light Scattering (DLS) revealed that the yield and selectivity of the transformation was highly dependent on the nature and amount of ligand. Moreover, additives such as $Cu(OAc)_2$ and bathophenanthroline were found to prevent nanoparticle aggregation in *N*-butyl vinyl ether. Primary and secondary alcohols **103** were subjected to the reaction scope, with electron-rich benzyl alcohols affording products **104** with moderate yields, while electron-deficient benzyl alcohols showed lower efficacy. Good tolerance was observed for aliphatic and allylic alcohols, while five catalyst recycling experiments were conducted, demonstrating high turnover numbers (3.1 x 10^3). However, accumulation of residual copper salts and loss of catalyst in the extraction step decreased the efficiency after several rounds of recycling.

4.2. Ir-Catalyzed O-Vinylation

Driven by the need to produce biodegradable polymers sustainably, Ishii[73] developed an innovative catalytic method for the synthesis of valuable vinyl ethers using readily available vinyl acetate and alcohols **105** (Scheme 42, **A**). Iridium com-



Scheme 41. Transfer vinylation of alcohols from vinyl ether, catalyzed by Pd NPs.



Scheme 42. A) Synthesis of vinyl ethers and vinyl esters under iridium catalysis by Ishii et al. B) Synthesis of bio-based (bis)-vinyl ethers under iridium catalysis.

plexes demonstrated notable efficiency, with $[Ir(cod)Cl]_2$ emerging as the most effective in selectively forming vinyl ethers **106** without the formation of any acetal byproducts. This catalytic system proved suitable for synthesizing both secondary and tertiary vinyl ethers, while high turnover numbers were observed.

Transvinylation between carboxylic acids **107** and vinyl acetates catalyzed by $[IrCl(cod)]_2$ in the presence of NaOAc, was successfully conducted by the same group to yield various vinyl esters **108** with high to excellent selectivity (Scheme 42, **A**).[8b]

The method developed by Ishii and coworkers for the synthesis of vinyl ethers employing $[IrCl(cod)]_2$ and vinyl acetate, stands as one of the best protocols to date. Nonetheless, their use of toluene, a non-renewable solvent, stoichiometric amounts of base, and the formation of acetals as byproducts leave room for improvement. Spiegelberg et al.[74] have introduced an advanced protocol for synthesizing bio-based (bis)-vinyl ethers, employing $[Ir(cod)_2]^+BF_4^-$ as the catalyst, sub-stochiometric amounts of base (NaOAc) and 2-MeTHF as a bio-derived solvent (Scheme 42, **B**). The protocol also showed exceptional selectivity towards vinylation of diols **109** containing both primary and secondary -OH groups. The transfer vinylation protocol demonstrated tolerance for a variety of aliphatic diols, furan-based diols, phenols, bio-derived alcohols, and even more sterically demanding substrates, while the feasibility of gram-scale vinylation indicates its significance in synthesizing bio-based vinyl ethers, suitable for potential applications in CASE (coatings, adhesives, sealants, and elastomers). Mechanistic studies underscored the importance of both basicity and solvent polarity in influencing reaction selectivity and suppressing acetal formation. Finally, DFT calculations revealed the necessity of the carbonyl group of the vinyl acetate in forming a six-membered cyclic intermediate, serving as the active catalytic species.

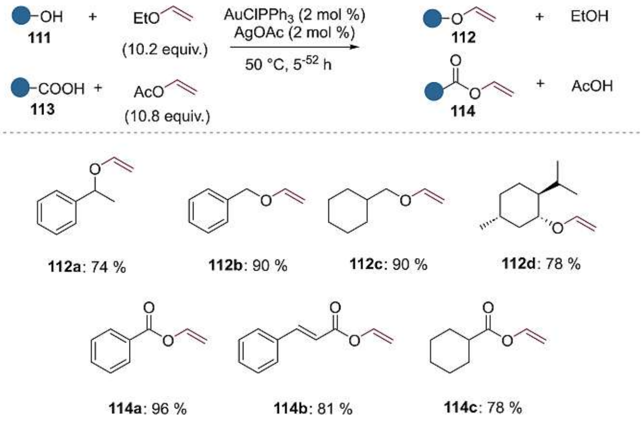
4.3. Au-Catalyzed O-Vinylation

Nakamura and Tokunaga[8a] developed the first Au^I complexes catalyzing vinylation of alcohols and carboxylic acids with vinyl ethers and esters respectively (Scheme 43). Optimization studies revealed that the $AuClPPh_3$/ AgOAc catalytic system proved to be the most efficient one, effectively suppressing acetal formation. Primary, secondary, and tertiary alcohols **111** were all tolerated with primary alcohols exhibiting excellent conversion to the corresponding vinyl ethers **112** with yields $>90\%$. Secondary alcohols, while giving somewhat lower yields, still produced the desired products in the range of 64% to 90%, albeit with an extended reaction time. Tertiary alcohols displayed comparatively lower reactivities, and silanol derivatives were inert in the reaction protocol. Attempts to employ a vinyl source other than ethyl vinyl ether were generally unsuccessful, except for vinyl acetate, which yielded the corresponding product with a 20% yield. The methodology was further extended to carboxylic acids **113**, demonstrating good yields (78-96%) in the formation of the respective vinyl esters **114**.

4.4. Non-Catalyzed O-Vinylation

Transition metal-free O-vinylation reactions have also been reported, especially for the vinylation of alcohols. The group of Zhang[75] developed a green and safe methodology for the direct vinylation of natural alcohols, including polyols and phenols, employing calcium carbide. Notably, the study revealed that the presence of electron-donating groups on phenols enhances efficiency, making this methodology particularly promising for potential applications in the synthesis of valuable compounds from renewable resources such as biomass.

The same year, the group of Wacharasindhu[76] presented a transition metal-free vinylation of activated phenols, employing calcium carbide as the acetylene precursor. This approach yielded phenyl vinyl ethers in satisfactory yields, particularly for electron-rich phenols.

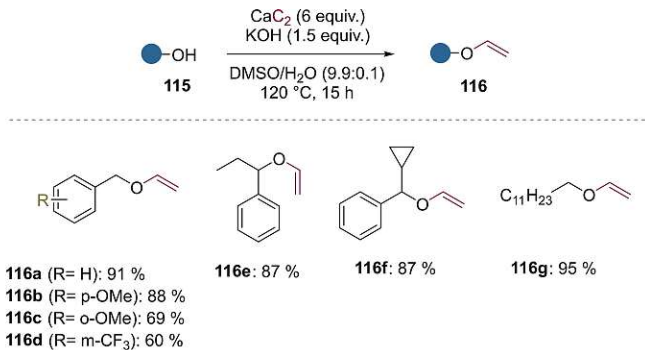


Scheme 43. Au^I-catalyzed transfer vinylation of alcohols and carboxylic acids.

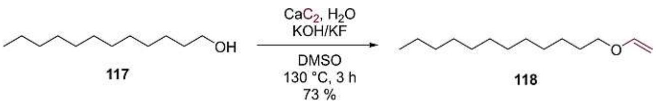
Similarly, Matake[77] and colleagues synthesized vinyl ethers from alcohols using calcium carbide as the acetylene source, albeit under superbasic catalytic conditions (KOH/DMSO) (Scheme 44). Primary and secondary alcohols **115** were successfully vinylated with this easy-to-handle protocol, underscoring the potential of this methodology for both academia and industry applications as an alternative to the Favorskii-Reppe reaction.[78]

Ananikov and co-workers[79] used calcium carbide as ethylene source to synthesize vinyl ether of carbohydrates, which were then polymerized to new materials. They utilized electron microscopy and a focused ion beam to examine the intrinsic organization of cavities within the polymers. The materials showed promising properties for applications such as encapsulation and controlled release. Overall, the study presents a cost-efficient and environmentally friendly approach to creating innovative materials using biobased monomers.

Feringa and co-workers[80] developed a sustainable alternative to petrochemical-based materials and processes in the field of biobased chemicals and synthesis methods. Specifically, the paper focused on the use of renewable resources and greener synthetic procedures to produce polymers and coatings, which are widely used in society. They also used calcium carbide in addition to a base to introduce the vinyl group on 1-dodecanol **117** and subsequently using it for polymerization reactions (Scheme 45). The study explored the efficiency of a new photosensitizer in generating singlet oxygen, a crucial step in the synthesis of biobased polymers. The goal was to reduce dependence on fossil fuels and minimize emission of greenhouse gases. The paper highlighted the importance of integrated approaches that consider biobased reagents, sustainable catalysis, and biodegradable solvents in achieving a more sustainable process.



Scheme 44. Vinylation of alcohols with calcium carbide as the source of acetylene.



Scheme 45. Vinylation of 1-dodecanol.

5. Summary and Outlook

This review delved into the world of vinylation reactions, highlighting the diverse approaches that exist, each reflecting the many possibilities for constructing a vinyl bond.

As a first observation, important advancements aided at bypassing the need for ethylene. Nowadays, a range of vinyl sources are readily available, stable, and easy to handle solids or liquids, while their reactivities vary, making the selection of the vinylation reagent a crucial element in designing a particular transformation. Amongst them, vinyl acetate is the most versatile reagent, found in several TM-catalyzed methods, with different metals, for standard cross couplings and oxidative couplings. Nonetheless, ethylene remains the most atom economic reagent, the increased accessibility of which along with a deeper understanding about flow chemistry can reignite the interest for this gas in research labs.

In terms of transformation, oxidative coupling via C–H activation stands out as the most efficient and therefore greener method for forming a new vinyl bond. As the sustainability aspect is of growing importance for industries in designing new processes, the field of C–H activation holds promise for a greener future. However, major limitations still need to be overcome. For instance, C–H activation vinylations require a DG, which often necessitates additional steps for their instalment and cleavage. Some methods allow for an in-situ cleavage of the DG but this is not universally applicable. Additionally, most C–H activation vinylations suffer from moderate selectivity, leading to either a mixture of mono and di-vinylation products or a regioisomeric mixture of ortho-vinylated products. Another obvious limitation is the ortho position selectivity for activation, giving less freedom for more distant C–H activation vinylation.

To address environmental concerns, the substitution of precious metals with 3d ones was also mentioned as a strategy. However, significant progress remains to be seen to enable 3d metals to replace Pd (and to a lesser extent Rh) on those grounds. A simple example can be catalyst loading, which is typically much lower for precious metals.

Finally, N- and O-vinylations have received less attention and are regarded as less attractive transformations compared to C-vinylation for pharmaceutical applications, although they are valuable for polymers and biomaterial applications. One notable advancement in N-vinylation reactions is the transition from stoichiometric to catalytic amounts of copper. Additionally, the VTT salt developed by Ritter's group presents another interesting non-catalytic approach for N-vinylation, albeit being a non-atom efficient method. CaC_2 has been widely used for both N- and O-vinylation, offering a complementary method despite its harsh reaction conditions.

As an outlook, considering the rising popularity of electrochemistry and photochemistry in recent years, it would be intriguing to explore methods applying those principles.

By critically analyzing the knowledge and expertise presented in this mini review, we believe that the utilization of vinylation reactions would address current challenges of modern synthetic chemistry, enabling the efficient construction of complex organic molecules. Finally, our aim for this work is to inspire continued research and innovation in the field, driving forward the frontiers of synthetic chemistry.

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Conflict of Interests

The authors declare no conflict of interest.

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[1] S. Jagtap, *Catalysts* **2017**, *7*, 267.
[2] a) T. Tobrman, *Chemistry* **2023**, *5*, 2288–2321; b) S. E. Denmark, C. R. Butler, *Chem. Commun.*. **2009**, *1*, 20–33.
[3] R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526.
[4] R. F. Heck, *Palladium-Catalyzed Vinylation of Organic Halides*, Wiley, New York, **1982**, pp. 345–390.
[5] T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **2006**, *44*, 581–581.
[6] R. F. Heck, J. P. Nolley Jr., *J. Org. Chem.* **1972**, *37*, 2320–2322.
[7] E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821–1823.
[8] a) A. Nakamura, M. Tokunaga, *Tetrahedron Lett.* **2008**, *49*, 3729–3732; b) H. Nakagawa, Y. Okimoto, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett.* **2003**, *44*, 103–106.
[9] K. Mondal, S. Patra, P. Halder, N. Mukhopadhyay, P. Das, *Org. Lett.* **2023**, *25*, 1235–1240.
[10] a) *Metal-Catalyzed Cross-Coupling Reactions and More*, (Eds.: A. de Meijere, S. Bräse, M. Oestreich), Wiley-VCH Verlag GmbH & Co. KGaA, **2013**; b) *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.: E.-i. Negishi), John Wiley & Sons, Inc., **2002**.
[11] J. W. Raggon, W. M. Snyder, *Org. Process Res. Dev.* **2002**, *6*, 67–69.
[12] a) R. L. W. Dow, (Pfizer Products Inc.), Vol. 920864 A; b) B. C. Vanderplas, K. M. DeVries, D. E. Fox, J. W. Raggon, M. W. Snyder, F. J. Urban, *Org. Process Res. Dev.* **2004**, *8*, 583–586.
[13] E. Papaplioura, M. Mercier, M. E. Muratore, T. Biberger, S. Jerhaoui, M. Schnürch, *J. Org. Chem.* **2024**, *89*, 5126–5133.
[14] S. L. Bourne, P. Koos, M. O'Brien, B. Martin, B. Schenkel, I. R. Baxendale, S. V. Ley, *Synlett* **2011**, 2643–2647.
[15] S. L. Bourne, M. O'Brien, S. Kasinathan, P. Koos, P. Tolstoy, D. X. Hu, R. W. Bates, B. Martin, B. Schenkel, S. V. Ley, *ChemCatChem* **2013**, *5*, 159–172.
[16] M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349–362.
[17] R. S. Craig, T. V. RajanBabu, *Tetrahedron* **2010**, *66*, 1102–1110.
[18] a) G. J. Harkness, M. L. Clarke, *Eur. J. Org. Chem.* **2017**, *2017*, 4859–4863; b) S. S. Adams, K. F. McCullough, J. S. Nicholson, *Arzneim.-Forsch.* **1975**, *25*, 1786–1791.
[19] L. Liu, Y. Zhang, Y. Wang, *J. Org. Chem.* **2005**, *70*, 6122–6125.
[20] A. Gordillo, E. de Jesús, C. López-Mardomingo, *J. Am. Chem. Soc.* **2009**, *131*, 4584–4585.
[21] A. Gordillo, M. A. Ortuño, C. López-Mardomingo, A. Lledós, G. Ujaque, E. de Jesús, *J. Am. Chem. Soc.* **2013**, *135*, 13749–13763.
[22] S. E. Denmark, C. R. Butler, *J. Am. Chem. Soc.* **2008**, *130*, 3690–3704.
[23] C.-T. Yang, J. Han, J. Liu, Y. Li, F. Zhang, H.-Z. Yu, S. Hu, X. Wang, *Chem. Eur. J.* **2018**, *24*, 10324–10328.
[24] M. Draye, M. Lemaire, R. Chevillotte, R. Chomel, P. Doutreluingne, J. Foos, A. Guy, *Sep. Sci. Technol.* **1995**, *30*, 1245–1257.
[25] J. Lindh, J. Sävmarker, P. Nilsson, P. J. R. Sjöberg, M. Larhed, *Chem. Eur. J.* **2009**, *15*, 4630–4636.
[26] A. Schmidt, A. Beutler, B. Snovydovych, *Eur. J. Org. Chem.* **2008**, *2008*, 4073–4095.
[27] G. Vera, B. Diethelm, C. A. Terraza, G. RecabarreN-Gajardo, *Molecules* **2018**, *23*, 2051.
[28] F. Juliá, J. Yan, F. Paulus, T. Ritter, *J. Am. Chem. Soc.* **2021**, *143*, 12992–12998.
[29] B. Lansbergen, S. Tewari, I. Tomczyk, M. Seemann, H. L. Buchholz, M. Rippegarten, D. C. Cieminski, F. Juliá, T. Ritter, *Angew. Chem. Int. Ed.* **2023**, e202313659.
[30] a) J. Wang, Y. Zhang, H. Liu, Y. Shang, L. Zhou, P. Wei, W. B. Yin, Z. Deng, X. Qu, Q. Zhou, *Nat. Commun.* **2019**, *10*, 3378; b) H. Abas, P. Blencowe, J. L. Brookfield, L. A. Harwood, *Chem. Eur. J.* **2023**, *29*, e202301066.
[31] X. X. Ming, S. Wu, Z. Y. Tian, J. W. Song, C. P. Zhang, *Org. Lett.* **2021**, *23*, 6795–6800.
[32] a) M. Mondal, S. Chen, N. J. Kerrigan, *Molecules* **2018**, *23*, 738; b) J. V. Matlock, V. K. Aggarwal, E. M. McGarrigle, *(2-Bromoethyl)diphenylsulfonium Trifluoromethanesulfonate*, John Wiley & Sons Ltd., **2016**.
[33] a) M. Drouin, J.-D. Hamel, J.-F. Paquin, *Synthesis* **2018**, *50*, 881–955 ; b) H. Yanai, T. Taguchi, *Eur. J. Org. Chem.* **2011**, *2011*,5939–5954.
[34] M. Li, Y. Wang, G. C. Tsui, *Org. Lett.* **2021**, *23*, 8072–8076.
[35] K. S. Egorova, V. P. Ananikov, *Organometallics* **2017**, *36*, 4071–4090.
[36] J.-Y. Yu, R. Kuwano, *Angew. Chem. Int. Ed.* **2009**, *48*, 7217–7220.
[37] a) M. D. Boele, G. P. van Strijdonck, A. H. de Vries, P. C. Kamer, J. G. de Vries, P. W. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587; b) J.-R. Wang, C.-T. Yang, L. Liu, Q.-X. Guo, *Tetrahedron Lett.* **2007**, *48*, 5449–5453.
[38] N. Umeda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 7094–7099.
[39] F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9982–9983.
[40] K. D. Otley, J. A. Ellman, *Org. Lett.* **2015**, *17*, 1332–1335.
[41] B. L. Tóth, A. Monory, O. Egyed, A. Domján, A. Bényei, B. Szathury, Z. Novák, A. Stirling, *Chem. Sci.* **2021**, *12*, 5152–5163.
[42] S.-T. Mei, K. Jiang, N.-J. Wang, L. Shuai, Y. Yuan, Y. Wei, *Eur. J. Org. Chem.* **2015**, *2015*, 6135–6140.
[43] S. Debnath, S. Mondal, *Eur. J. Org. Chem.* **2018**, *2018*, 933–956.
[44] S.-S. Li, C.-Q. Wang, H. Lin, X.-M. Zhang, L. Dong, *Org. Biomol. Chem.* **2016**, *14*, 229–237.
[45] S. Prakash, K. Muralirajan, C.-H. Cheng, *Chem. Commun.* **2015**, *51*, 13362–13364.
[46] B. D. Krane, M. Shamma, *J. Nat. Prod.* **1982**, *45*, 377–384.
[47] K. R. Sokol, T. Magauer, *Synthesis* **2021**, *53*, 4187–4202.
[48] J. Xu, C. Chen, H. Zhao, C. Xu, Y. Pan, X. Xu, H. Li, L. Xu, B. Fan, *Org. Chem. Front.* **2018**, *5*, 734–740.
[49] L. Zhang, X. Xue, C. Xu, Y. Pan, G. Zhang, L. Xu, H. Li, Z. Shi, *ChemCatChem* **2014**, *6*, 3069–3074.
[50] C. N. Zhou, H. H. Xie, Z. A. Zheng, Y. C. Xiao, G. Li, Y. H. Shen, W. M. Peng, L. Wang, *Chemistry* **2018**, *24*, 5469–5473.
[51] S. Lv, R. Nie, L. Guo, Y. Zheng, Y. Liu, L. Guo, Y. Wu, *Pharmaceutical Fronts* **2020**, *02*, e94–e99.
[52] J. Yue, H. Wang, Y. Zhang, X. Jian, *Chin. J. Med. Chem.* **2015**, *25*, 453–456.
[53] X. Jiang, Z. Zeng, Y. Hua, B. Xu, Y. Shen, J. Xiong, H. Qiu, Y. Wu, T. Hu, Y. Zhang, *J. Am. Chem. Soc.* **2020**, *142*, 15585–15594.
[54] J. Zhou, X. Li, G. Liao, B.-F. Shi, *Chin. J. Chem.* **2018**, *36*, 1143–1146.
[55] Y. Matsuura, M. Tamura, T. Kochi, M. Sato, N. Chatani, F. Kakiuchi, *J. Am. Chem. Soc.* **2007**, *129*, 9858–9859.
[56] P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192–2452.
[57] N. Muniraj, K. R. Prabhu, *Adv. Synth. Catal.* **2018**, *360*, 3579–3584.
[58] M. R. Sk, M. S. Maji, *Org. Chem. Front.* **2020**, *7*, 19–24.
[59] J. Terao, H. Watabe, N. Kambe, *J. Am. Chem. Soc.* **2005**, *127*, 3656–3657.
[60] D. Fiorito, S. Folliet, Y. Liu, C. Mazet, *ACS Catal.* **2018**, *8*, 1392–1398.
[61] M. De Paolis, I. Chataigner, J. Maddaluno in *Stereoselective Alkene Synthesis* (Ed.: J. Wang), Springer Berlin Heidelberg, Berlin, Heidelberg, **2012**, pp. 87–146.
[62] P.-A. Poisson, G. Tran, C. Besnard, C. Mazet, *ACS Catal.* **2021**, *11*, 15041–15050.
[63] A. Y. Lebedev, V. V. Izmer, D. N. Kazyul'kin, I. P. Beletskaya, A. Z. Voskoboynikov, *Org. Lett.* **2002**, *4*, 623–626.
[64] J. L. Brice, J. E. Meerdink, S. S. Stahl, *Org. Lett.* **2004**, *6*, 1845–1848.

[65] a) S. Handerson, M. Schlaf, *Org. Lett.* **2002**, *4*, 407–409; b) M. Bosch, M. Schlaf, *J. Org. Chem.* **2003**, *68*, 5225–5227.

[66] J. Xu, Y. Fu, B. Xiao, T. Gong, Q. Guo, *Tetrahedron Lett.* **2010**, *51*, 5476–5479.

[67] a) P. Arsenyan, A. Petrenko, S. Belyakov, *Tetrahedron Lett.* **2008**, *49*, 5255–5257; b) P. Arsenyan, A. Petrenko, E. Paegle, S. Belyakov, *Mendeleev Commun.* **2011**, *21*, 326–328.

[68] V. Motornov, G. V. Latyshev, Y. N. Kotovshchikov, N. V. Lukashev, I. P. Beletskaya, *Adv. Synth. Catal.* **2019**, *361*, 3306–3311.

[69] J. Kimura, S. Nakamichi, S. Ogawa, Y. Obora, *Synlett* **2017**, *28*.

[70] F. Bekkar, F. Bettahar, I. Moreno, R. Meghabar, M. Hamadouche, E. Hernáez, J. L. Vilas-Vilela, L. Ruiz-Rubio, *Polymer* **2020**, *12*, 2227.

[71] K. S. Rodygin, A. S. Bogachenkov, V. P. Ananikov, *Molecules* **2018**, *23*, 648.

[72] K. Tabaru, M. Nakatsuji, S. Itoh, T. Suzuki, Y. Obora, *Org. Biomol. Chem.* **2021**, *19*, 3384–3388.

[73] Y. Okimoto, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2002**, *124*, 1590–1591.

[74] B. Spiegelberg, H. Jiao, R. Grauke, C. Kubis, A. Spannenberg, A. Brandt, A. Taden, H. Beck, S. Tin, J. G. de Vries, *Adv. Synth. Catal.* **2022**, *364*, 1251–1263.

[75] S. P. Teong, A. Y. H. Chua, S. Deng, X. Li, Y. Zhang, *Green Chem.* **2017**, *19*, 1659–1662.

[76] E. Rattanangkool, T. Vilaivan, M. Sukwattanasinitt, S. Wacharasindhu, *Eur. J. Org. Chem.* **2016**, *2016*, 4347–4353.

[77] R. Matake, Y. Adachi, H. Matsubara, *Green Chem.* **2016**, *18*, 2614–2618.

[78] a) A. Favorsky, *Zh. Russ. Fiz.-Khim. O-va.* **1905**, *37*, 643–645; b) A. Favorsky, *Bull. Soc. Chim. Fr.* **1907**, *2*, 1087–1088.

[79] K. S. Rodygin, I. Werner, V. P. Ananikov, *ChemSusChem* **2018**, *11*, 292–298.

[80] J. G. H. Hermens, T. Freese, G. Alachouzos, M. L. Lepage, K. J. Van den Berg, N. Elders, B. L. Feringa, *Green Chem.* **2022**, *24*, 9772–9780.

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REVIEW

This review highlights innovative strategies and key advancements in carbon, nitrogen, and oxygen vinylation. Categorized by the type of vinylation and whether or not it is catalyzed, it serves as a valuable resource for organic chemists, offering insights into diverse vinylation techniques for the construction of carbon-carbon and carbon-heteroatom bonds.

*E. Papaplioura, M. Mercier, Dr. S. Jerhaoui, Prof. M. Schnürch**

1 – 22

The Vinyl Group: Small but Mighty – Transition Metal Catalyzed and Non-Catalyzed Vinylation Reactions

E Conclusion and Perspective

This thesis covers three separate yet conceptually related projects with the shared goal to substitute gaseous reagents for solid alternatives. In the first chapter, we focused on developing sustainable and safe alkylation reactions through C-H activation, with a primary emphasis on achieving enantioselectivity. Several attempts towards enantioselective induction were conducted during this study, which were ultimately unsuccessful, as no stereoinduction was obtained in any case. This may be due to an incorrect hypothesis of the reaction mechanism (a Rh-catalyzed reduction as the final step). Unfortunately, extensive efforts to elucidate the mechanism *via* DFT calculations (carried out by Prof. Andras Stirling, Hungarian Academy of Science) were unsuccessful and the underlying mechanism remains elusive. Nonetheless, those failures lay the groundwork for further mechanistic investigation, since certain pathways can be ruled out. Elucidating the reaction mechanism should provide valuable insights into what hinders a stereoselective outcome of the reaction and whether enantioselectivity is possible in this context at all.

Throughout these studies, we investigated the application of quaternary ammonium salts as solid alternatives in various reactions, emphasizing their advantages over conventional alkylating and methylating agents, which are typically highly toxic and pose significant health risks upon exposure. Quaternary ammonium salts are solid, bench-stable, and easy to handle reagents, offering non-toxic, and non-corrosive properties. Our findings demonstrated that similar to how tetraalkylammonium salts can replace olefins, ethylene can be intentionally formed *in situ* and used for Heck-type reactions. This approach eliminates the need for ethylene gas and the complex equipment typically required, thereby simplifying the entire process and enhancing its suitability for applications in e.g. drug development, where high-throughput experimentation is desired, typically not possible with an autoclave setup. Further research to identify conditions that will enable a broader substrate scope will fully harness the potential of this innovative chemical process.

Quaternary ammonium salts were also employed in methylation reactions. Specifically, phenyl trimethylammonium iodide served as an alternative methylating agent for the selective α-C-monomethylation of (hetero)aryl acetonitriles, important precursors for the synthesis of key anti-inflammatory drugs.

In conclusion, this research has highlighted the versatility of quaternary ammonium salts and their potential as inherently safer alternative reagents for developing sustainable methodologies. This sets the stage for further exploitation of these reagents in the synthesis of complex compounds, including chiral molecules, and to enable late-stage functionalization in medicinal chemistry and large-scale production. To overcome the limitations regarding stereoselectivity and in some instances limited substrate scope, further mechanistic investigations will be essential.

F Appendix

F I Publications Resulted from This Thesis

Journal Articles

Eleni Papaplioura, Johanna Templ, Nina Wildhack and Michael Schnürch

Efficient Synthesis of 2-Arylpropionitriles via Selective Monomethylation of Aryl Acetonitriles Using an Easy to Handle Methylation Agent

Eur. J. Org. Chem., submitted manuscript (June 2024)

Eleni Papaplioura, Maëva Mercier, Michael E. Muratore, Tobias Biberger, Soufyan Jerhaoui and Michael Schnürch

Tetraethylammonium Salts as Solid, Easy to Handle Ethylene Precursors and Their Application in Mizoroki–Heck Coupling

J. Org. Chem. 2024, 89, 5126–5133. doi: 10.1021/acs.joc.3c02867

Eleni Papaplioura, Maëva Mercier, Soufyan Jerhaoui and Michael Schnürch

The Vinyl Group: Small but Mighty - Transition Metal Catalyzed and Non-Catalyzed Vinylation Reactions

ChemCatChem 2024, e202400513. doi: 10.1002/cctc.202400513

Conference Talks

FemChem Scientific Workshop, Vienna, Austria, February 2024

Eleni Papaplioura and Michael Schnürch

"Substituting Gaseous Reagents for Solid Alternatives"

Oral Communication

European Meeting on C-H Activation - Lisbon, Portugal, January 2024

Eleni Papaplioura and Michael Schnürch

"Tetraethylammonium Salts as Solid, Easy to Handle Ethylene Precursors and Their Application in Mizoroki–Heck Coupling"

Oral Communication

Chair Scientific Workshop, Warsaw, Poland, September 2023

Eleni Papaplioura and Michael Schnürch

"Tetraethylammonium Salts as Solid, Easy to Handle Ethylene Precursors and Their Application in Mizoroki–Heck Coupling"

Oral Communication

Chair Industrial Workshop, Strasbourg, France, April 2023

Eleni Papaplioura and Michael Schnürch

"Tetraethylammonium Salts as Solid, Easy to Handle Ethylene Precursors and Their Application in Mizoroki–Heck Coupling"

Oral Communication

Chair Scientific Workshop, Vienna, Austria, February 2023

Eleni Papaplioura and Michael Schnürch

"Tetraethylammonium Salts as Solid, Easy to Handle Ethylene Precursors and Their Application in Mizoroki–Heck Coupling"

Oral Communication

Poster Presentations

MolTag Closing Event, Vienna, Austria, September 2023

Eleni Papaplioura and Michael Schnürch

"Substituting Gaseous Reagents for Solid Alternatives"

F II Curriculum Vitae

Eleni Papaplioura

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EDUCATION

Ph.D - Technical Chemistry 2020 - ongoing
TU Wien, Institute of Applied Synthetic Chemistry, Austria
Marie - Curie Fellowship | CHAIR ITN

M.Sc. - Advanced Synthesis and Catalysis 2017 - 2019
University of Regensbourg, Germany
Elite Network of Bavaria | SynCat
Thesis: “Synthesis of tricyclic gamma-butyrolactone bioactive compounds”

Erasmus + Placement 2016- 2016
TU Wien, Institute of Applied Synthetic Chemistry, Austria

B.Sc. - Chemistry 2011 - 2016
University of Ioannina, Ioannina, Greece
Thesis: “Application of chemiluminescence in the analysis of wastewaters.”

WORK EXPERIENCE

Ph.D Candidate/ Marie-Curie Fellowship | CHAIR ITN 2020 - ongoing
BSC Group, TU Wien, Austria

Research Intern 2023-2023
Boehringer Ingelheim RCV, Vienna, Austria

Research Intern 2022-2023
Johnson & Johnson, Beerse, Belgium

Research Scholar 2018-2018
University of North Carolina, Chapel Hill, USA

LANGUAGES

Greek | Native

English | IELTS 7

German | Goethe B1

SKILLS

HPLC

UPLC-MS

CG / GC-MS

1D and 2D NMR

TLC

MS Office

ChemDraw

MestreNova

ELN

SciFinder / Reaxys

Driving Licence B

PUBLICATIONS

Efficient Synthesis of 2-Arylpropionitriles via Selective Monomethylation of Aryl Acetonitriles Using a Non-Toxic, Easy to Handle Methylation Agent — June 2024

Eleni Papaplioura, Johanna Templ, Nina Wildhack, Michael Schnürch

J. Org. Chem., submitted

The Vinyl Group: Small but Mighty - Transition Metal Catalyzed and Non-Catalyzed Vinylation Reactions — May 2024

Eleni Papapliora, Maëva Mercier, Soufyan Jerhaoui, Michael Schnürch

ChemCatChem 2024, e202400513

Tetraethylammonium Salts as Solid, Easy to Handle Ethylene Precursors and Their Application in Mizoroki–Heck Coupling — March 2024

Eleni Papapliora, Maëva Mercier, Michael E. Muratore, Tobias Biberger, Soufyan Jerhaoui, Michael Schnürch

J Org Chem 2024, 89, 7, 5126–5133

Investigation of Leoligin Derivatives as NF-κB Inhibitory Agents — December 2021

Thomas Linder , Eleni Papaplioura , Diyana Ogurlu , Sophie Geyrhofer, Scarlet Hummelbrunner, Daniel Schachner , Atanas G. Atanasov, Marko D. Mihovilovic , Verena M. Dirsch, Michael Schnürch

Biomedicines 2022, 10(1), 62

Design and Synthesis of a Compound Library Exploiting 5-Methoxyleoligin as Potential Cholesterol Efflux Promoter — Febrruary 2020

Thomas Linder, Sophie Geyrhofer, Eleni Papaplioura, Limei Wang, Atanas G. Atanasov, Hermann Stuppner, Verena M. Dirsch, Michael Schnürch, Marko D. Mihovilovic

Molecules 25(3):662

A silver-coated copper wire as inexpensive drug eluting stent model: determination of the relative releasing properties of leoligin and derivatives — November 2020

Laszlo Czollner, Eleni Papaplioura, Thomas Linder, Rongxia Liu, Yuanfang Li, Atanas G. Atanasov, Verena M. Dirsch, Michael Schnürch, Marko D. Mihovilovic

Monatsh Chem 154, 1317–1326 (2023)