



UNICA

UNIVERSITÀ
DEGLI STUDI
DI CAGLIARI

Ph.D. DEGREE IN
Chemical Science and Technology

Cycle XXXVIII

TITLE OF THE Ph.D. THESIS

Mechanochemistry: Redefining the Paradigm of Organic Chemistry

Scientific Disciplinary Sector(s)

Organic Chemistry (CHEM-05/A)

Ph.D. Student:	Sourav Behera
Supervisor	Prof. Andrea Porcheddu (CHEM-05/A)
Co-Supervisor	Prof.ssa Tiziana Pivetta (CHEM-01/A)

Final Exam. Academic Year 2024/2025
Thesis Defence Session: February 2026

“Every experiment proves something. If it does not prove what you wanted, it proves something else.”

— Thomas Alva Edison

List of Publications During Doctoral Studies

Publications for the Thesis:

- I. S. Behera, S. K. Bera, F. Basoccu, F. Cuccu, P. Caboni, L. De Luca, A. Porcheddu. Application of Bertagnini's Salts in a Mechanochemical Approach Toward Aza-Heterocycles and Reductive Aminations via Imine Formation. *Adv. Synth. Catal.* **2024**, 366, 2035–2043.
- II. S. Behera, F. Cuccu, F. Basoccu, S. Barranco, A. Porcheddu. Mechanically processed Sardinian wool promotes C–C bond synthesis under solvent-free conditions. *RSC Sustain.* **2025**, 3, 376–382.
- III. S. Behera, D. J. Fartade, R. Mocci, M. Matta, L. De Luca, A. Porcheddu. Mechanochemistry-Driven Borrowing Hydrogen Processes for Ru-Catalyzed *N*-Alkylation: A Pathway to Enhanced Sustainability and Efficiency. *Angew. Chem. Int. Ed.* **2025**, e202508050.

Other Publications:

- I. S.K. Bera, S. Behera, L. De Luca, F. Basoccu, R. Mocci, A. Porcheddu. Unveiling the Untapped Potential of Bertagnini's Salts in Microwave-Assisted Synthesis of Quinazolinones. *Molecules.* **2024**, 29, 1986–2001.

List of Abbreviations & Pictograms

1,5-COD	1,5-Cyclooctadiene
APIs	Active Pharmaceutical Ingredients
BH	Borrowing Hydrogenation
DCM	Dichloromethane
DMA	<i>N, N</i> -dimethylacetamide
EtOAc	Ethyl acetate
EtOH	Ethanol
KIE	Kinetic Isotope Effect
LAG	Liquid Assisted Grinding
MeOH	Methanol
MI	Mass Intensity
MOF	Metal-organic Framework
OM	Olefin Metathesis
ppm	parts per million
RAM	Resonant Acoustic Mixing
rpm	revolutions per minute
SS	Stainless Steel
TBAB	Tetrabutylammonium bromide
TSE	Twin-screw Extruder
VOC	Volatile Organic Compound
	Grinding with Mortar and Pestle
	Grinding in a Planetary Mill
	Grinding in a Mixer Mill
	Mechanochemically Ground Wool/Feather Powder

Table of Contents

CHAPTER 1	1
Introduction	1
1.1. Mechanochemistry	1
1.2. Mechanochemistry: A Timeless Fundamental	1
1.3. Mechanochemical Instruments	3
1.4. Mechanochemical Parameters	6
1.4.1. Energy Parameters	6
1.4.2. Rheological Parameters	7
1.5. Mechanochemistry and the Paradigm of Organic Chemistry	8
1.6. Mechanochemistry in Catalysis	9
1.6.1. Olefin Metathesis	9
1.6.2. Negishi Cross-Coupling	12
1.6.3. Mizoroki-Heck Reaction	13
1.6.4. Suzuki-Miyaura Cross-Coupling Reaction	14
1.6.5. Buchwald-Hartwig Amination Reaction	15
1.6.6. Direct Mechanocatalysis	17
1.7. Mechanochemistry in Organometallic Reactions	18
1.7.1. Grignard Reaction	18
1.7.2. Birch Reduction	19
1.8. Mechanochemistry in Piezoelectric Organic Synthesis	21
1.9. Photomechanochemistry	22
1.10. Mechanochemical Scaling-up and Process Safety	24
1.11. Mechanochemical Literature Summary for Organic Synthesis	25
1.12. References	27
CHAPTER 2	33
Mechanochemistry: Redefining the Paradigm of Organic Chemistry	33
2.1 Aim of the Thesis	33
CHAPTER 3	34
Mechanochemistry Unveiling Reactivity of Bertagnini's Salts	34
3.1. Carbonyl Center: The Backbone of Organic Synthesis	34
3.2. Bertagnini's Salts	34
3.3. Reactivity Employing Bertagnini's Salts	34

3.4. Bertagnini's Salts and Mechanochemistry	36
3.5. Results and Discussions	36
3.5.1. Synthesis of Bertagnini's Salts	36
3.5.2. Mechanochemical Benzimidazoles from Bertagnini's Salts	37
3.5.3. Mechanochemical Synthesis of Perimidines and Dihydro-Perimidines	41
3.5.4. Mechanochemical Reductive Aminations and Hydrazone Synthesis	44
3.6. Reaction Mechanism for Mechanochemical Benzimidazole Synthesis	45
3.7. Green Metrics Calculation	46
3.8. Conclusions	53
3.9. References	54
CHAPTER 4	58
From Fleece to Bonds: Mechanochemical Wool-Mediated C–C Bond Formation	58
4.1. Sustainability in Modern Organic Synthesis: Challenges & Goals	58
4.2. Sardinian Wool: An Abundant Biopolymer at the Interface of Nature	59
4.3. From Fiber to Function: Perspectives on Wool in Literature	60
4.4. Grinding Value into Fibers: Mechanochemical Wool Processing for Reactions	61
4.5. Results and Discussions	61
4.5.1. Wool and Feather Sample Sourcing	61
4.5.2. Mechanochemical Processing of Wool and Feather Samples	62
4.5.3. FT-IR Analysis of Mechanochemically Treated Wool	62
4.5.4. SEM Analysis	64
4.5.5. Aldol Reaction	68
4.5.6. Nitro-Aldol Reaction	70
4.5.7. Knoevenagel Reaction	72
4.6. Gram-Scale Reaction and Recyclability	74
4.7. Conclusion	76
4.8. References	77
CHAPTER 5	81
Grinding Hydrogen into Action: Mechanochemical Borrowing Hydrogenation of Amines	81
5.1. The Centrality of C–N Bond Formation	81
5.2. Borrowing Hydrogenation (BH): A Sustainable Milestone	82
5.2.1. Evolution of BH Strategies in <i>N</i> -Alkylation Chemistry	82
5.3. Harnessing Mechanical Energy for BH	85

5.4. Results and Discussions	86
5.4.1. Mechanochemical BH Mediated <i>N</i> -Alkylation of Aromatic Amines.....	86
5.4.2. Mechanochemical BH for <i>N</i> -Alkylation of Aliphatic Amines and <i>N</i> -Heterocycles	91
5.5. Probing the Mechanism of Solvent-Free Mechanochemical BH	93
5.5.1. Radical Trapping Experiment	94
5.5.2. Kinetic Isotope Effect (KIE) Analysis	94
5.5.3. Hammett Analysis	98
5.5.4. Catalytic Cycle.....	100
5.6. Green Metrics.....	102
5.7. Conclusions.....	104
5.8. References.....	105
CHAPTER 6.....	110
Conclusions and Future Scope.....	110
CHAPTER 7.....	112
Experimental Section.....	112
7.1. General Information and Methodology	112
7.2. General Reaction Conditions and Characterization for Compounds in Chapter 3	114
7.2.1. Procedure for Synthesis of Benzimidazoles from Bertagnini's Salts	114
7.2.2. Procedure for Synthesis of 2,3-Dihydro-1H-perimidines from Bertagnini's Salts	114
7.2.3. Procedure for Synthesis of Perimidines from Bertagnini's Salts	114
7.2.4. Procedure for Synthesis of Secondary Amines from Bertagnini's Salts	115
7.2.5. Procedure for Synthesis of Hydrazones from Bertagnini's Salts	115
7.2.6. Procedure to Monitor Reaction Progress Over Time for Benzimidazole Synthesis	116
7.2.7. Characterization of Compounds in Chapter 3	119
7.2.8. TGA and DSC Spectra for Bertagnini's Salts in Chapter 3.....	146
7.2.9. NMR Spectra for Compounds in Chapter 3.....	153
7.3. General Reaction Conditions and Characterization for Compounds in Chapter 4	198
7.3.1. General Condition for Mechanochemical Preparation of Wool Fiber.....	198
7.3.2. General Condition for Wool Mediated Aldol Reactions	198
7.3.3. General Condition for Wool Mediated Nitro-Aldol Reactions	198
7.3.4. General Condition for Wool Mediated Knoevenagel Condensation	199
7.3.5. Procedure to Monitor Reaction Progress Over Time for Nitro-Aldol Reaction	199
7.3.6. Procedure for Gram Scale Recycling Studies of Wool Mediated Aldol Reaction	200

7.3.7. Characterization of Compounds in Chapter 4	201
7.3.8. NMR Spectra for Compounds in Chapter 4.....	218
7.4. General Reaction Conditions and Characterization for Compounds in Chapter 5	238
7.4.1. General Experimental Procedure for N-Alkylation of Aromatic Amines 3aa-3am.....	238
7.4.2. General Experimental Procedure for N-Alkylation of Aliphatic Amines 5aa-5ah	239
7.4.3. General Experimental Procedure for Synthesis of N-Heterocycles 6 and 7	239
7.4.4. General Experimental Procedure for Radical Trapping.....	240
7.4.5. General Experimental Procedures for Mechanochemical Kinetic Isotope Effect	241
7.4.6. General Experimental Procedure for Mechanochemical Hammett Analysis	249
7.4.7. Characterization of Compounds in Chapter 5	254
7.4.8. NMR Spectra for Compounds in Chapter 5.....	274
7.5. References.....	307

CHAPTER 1

Introduction

1.1. Mechanochemistry

Mechanochemistry has been recognized by the International Union of Pure and Applied Chemistry (IUPAC) as one of the most important emerging technologies, realigning organic synthesis towards sustainability.^{1,2} In this context, mechanochemistry is poised to join the lineage of transformative paradigms. The use of mechanical force as the primary driver of chemical reactivity challenges the solvent-based assumptions that have dominated synthetic chemistry for over a century. The mechanochemical paradigm is not simply “chemistry without solvent,” but rather chemistry in which the fundamental rules of molecular interaction are altered: molecular encounters occur in highly concentrated, anisotropic environments^{3,4}; energy is introduced in discrete pulses rather than continuous thermal flux; and reactivity emerges from localized mechanical stresses rather than bulk heating.⁵⁻⁷ These differences give rise to unique selectivity patterns, access to otherwise unstable intermediates, more efficient reactions, high selectivity, and a significantly reduced environmental footprint, with reactivity modes absent from solution chemistry.⁸ Moreover, mechanochemical transformations are often aligned with the 12 principles of green chemistry⁹, providing significant advantages over their solvent-based counterparts.¹⁰

One of the notable advantages of mechanochemistry over solution-based chemistry is its ability to utilize and activate insoluble reagents and materials, such as insoluble polymers, zero-valent metals, and inorganic salts. The mechanochemical energy applied through various means dissipates the aggregation of molecules, reducing the particle size and thus increasing the reactive surface area to facilitate reactivity. Thus, the utility of mechanochemistry has been elaborated in various aspects of organic and inorganic syntheses.¹¹

1.2. Mechanochemistry: A Timeless Fundamental

In the beginning, primordial elements combined and recombined to form diverse sets of organic molecules essential to sustain the base of life, such as genetic codes, metabolites, sugars, amino acids, and peptides. Amino acids, a crucial building block for life, are believed to have catalyzed the synthesis of numerous other molecules on prebiotic Earth.¹² Consequently, the successful experiments by Miller in 1953, to simulate primordial earth conditions using NH_3 , H_2O , CH_4 , and H_2 using electrical spark to form amino acids, comes as no surprise.¹³ A well-documented study shows that prebiotic Earth underwent bombardment by several extraterrestrial bodies, such as meteorites and comets, which changed the geology and delivered exogenous substances, such as amino acids, to the Earth’s crust. This can be verified by the identification of over 90 amino acids at concentrations of ppm inside these extraterrestrial bodies.¹⁴ Studies conducted under cryogenic conditions on aqueous solutions of amino acids to mimic natural comet impacts have successfully shown the oligomerization of amino acids.^{15,16} Additionally, amino acid synthesis by Bolm¹⁷ and coworkers and the oligomerization of glycine by Hernández¹⁸ and coworkers under mechanical

shear conditions support the theory that mechanical stress and shear forces could have been a part of the first energy for the initiation of life on primordial Earth (Figure 1.1. a).

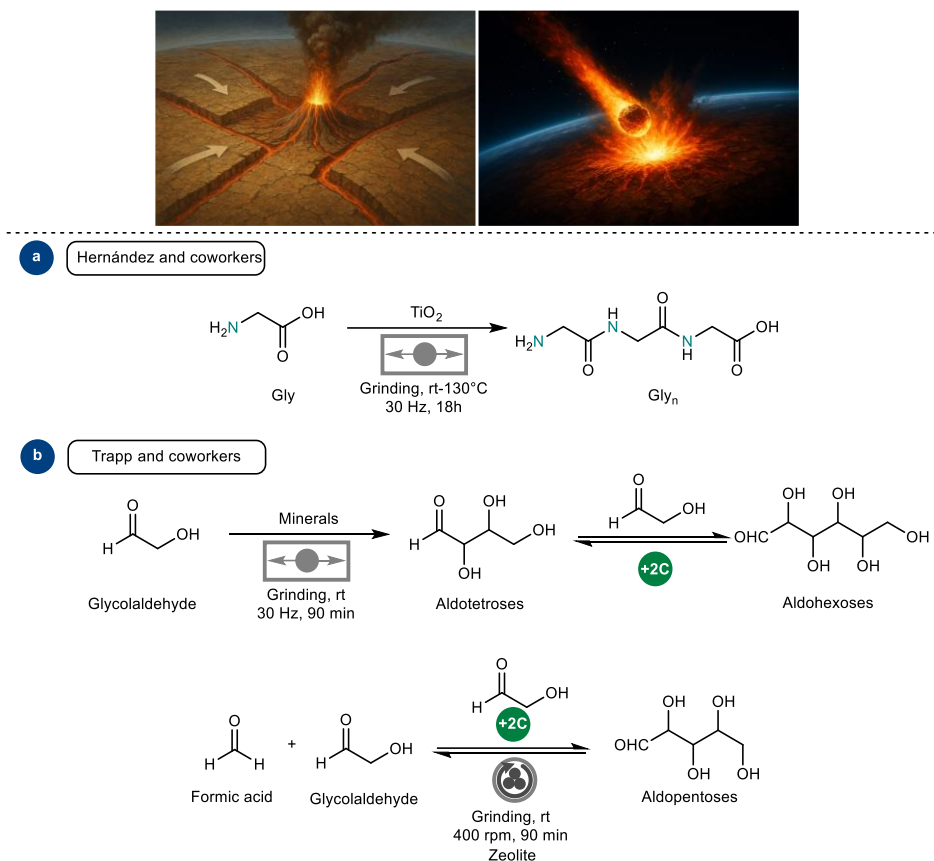


Figure 1.1.a) Oligomerization of glycine under mechanochemical conditions to simulate prebiotic earth by Hernández group; b) Mechanochemical sugar synthesis by Trapp group to simulate prebiotic earth

Simultaneously, studies based on the synthesis of sugars under prebiotic Earth conditions can be hypothesized by the formose reaction, where formaldehyde is influenced by mineral catalysis.¹⁹ In a solution-based approach to the mineral-catalyzed formose reaction, formaldehyde undergoes various steps to form glycoside analogues with some additional side reactions. Furthermore, the products formed using this approach undergo rapid deterioration in aqueous alkaline environments.^{20, 21} A mechanochemical approach, albeit slower than its solvent-based counterpart, provides more stable and non-deteriorating products.²² This shows that under prebiotic environments, such mechanical energy could have been traced back from geological events such as diagenesis, erosion, withering, movement of tectonic plates, and even meteorite showers (Figure 1.2. b). This further supports the theory of the involvement of inherent mechanochemical actions, which are the basis of early life.

Modern human civilization has acquired and flourished under the discovery of mechanical tools to aid them in their lives. The early mechanochemical applications by primitive humans can be traced back to the use of shear stress and stone impacts to ignite fire, which became the cornerstone for building a civilization and later created the basis for chemical transformations by humans

without consciousness. However, the earliest mechanochemical reaction can be dated back to 315–314 B.C. by Theophrastus of Eresus (376–286 B.C.), who was a student of Aristotle. In his book *On Stones*, or *De Lapidibus*, which is the earliest surviving scientific book on minerals, he mentioned the reduction of cinnabar (HgS) to elemental mercury by grinding the mineral inside a copper-based mortar and pestle in the presence of vinegar (Figure 1.2).²³ Although it is a remarkable mechanochemical reaction, it has been recorded as a phenomenon rather than a well-established application of mechanochemistry. Similarly, in medieval Europe, the mechanochemical reaction of Hg and elemental sulfur was performed to produce vermilion²⁴, as reported in modern literature.²⁵ Over the years, reactions have been developed through inherent mechanical treatment, although they were later substituted by thermal energy. Later, in the early 19th century, mechanochemistry saw a resurgence in applications in different aspects of organic and inorganic chemistry, thus giving birth to modern mechanochemistry.²⁶ Modern mechanochemical reactions have several applications, including pharmaceutical synthesis²⁷, catalysis^{28, 29}, organometallic reagent synthesis³⁰, photomechanochemical reactions³¹, polymer degradation^{32, 33}, and enzymatic reactions^{34, 35}. This verifies a continuum that mechanochemistry is not a tool of convenience, but rather a timeless fundamental that has existed from the beginning of nature to the modern age.

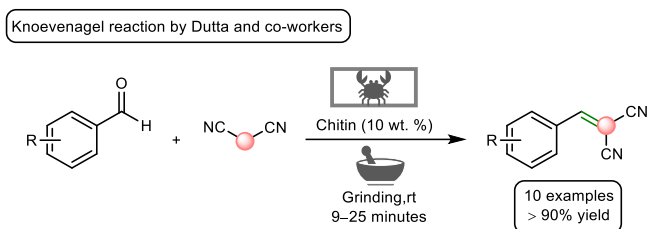


Figure 1.2. Grinding cinnabar into mercury by Theophrastus of Eresus

1.3. Mechanochemical Instruments

As described in the previous section, mechanochemical grinding using mortar and pestle for chemical transformation can be dated back thousands of years. Manual grinding of reagents is easy to set up and perform. However, this suffers from several limitations, such as non-uniform mixing, insufficient energy for transformations, and susceptibility to open environmental factors. Additionally, manual mixing is mostly susceptible to human errors, particularly for long milling times, causing infrequent reproducibility for synthesis.³⁶ A very recent study on the use of manual grinding for organic synthesis was reported by Dutta *et al.*, who successfully performed a chitin-catalyzed Knoevenagel condensation reaction using aromatic aldehydes and malononitrile.³⁷ By

grinding these compounds manually, they were able to obtain the desired Knoevenagel products with excellent yields within extremely short reaction times of up to minutes. Furthermore, in their methodology, the product was isolated through filtration using a paper filter with ethyl acetate (EtOAc), thus avoiding any additional purification steps (Scheme 1.1).



Scheme 1.1. Chitin catalyzed Knoevenagel reaction using manual grinding by Dutta and coworkers

The introduction of automated milling equipment in mechanochemistry has shaped mechanochemical reactions into a more reproducible method by implementing uniform milling environments and frequencies, along with uniform energy transfer to the reagents. In this context, ball mills have garnered significant attention for milling reagents into value-added products. The most utilized ball mills are mixer and planetary mills, which work on the same principle of transferring the kinetic energy produced by the collision of balls with each other or with the reaction vessel to the reagents, realizing seamless product formation.^{38, 39}

The most common ball milling device is a mixer mill (shaker or vibratory mill). In a general mixer mill, the reagents along with the balls are placed into a milling jar and milled horizontally at a certain frequency. This ball mill imparts kinetic energy from the collision of balls along with the jar to the reactant through compressive forces. Owing to its horizontal motion during milling, most of the energy transfer occurs at the ends of the jars. This linear motion can be avoided by using more balls to impart collision upon themselves, thus making their pathway during the milling unpredictable and imparting mechanical energy upon the reagents at every part of the milling jar and not only at the ends.³⁹ Furthermore, the simplicity of the device design allowed for the introduction of temperature probes to control the reaction temperature using an external chiller (Retsch MM–500). Additionally, for reactions at drastically lower temperatures, cryo-mills are used, which operate on the same principle as mixer mills. Some mixer mills oscillate through vertical motion rather than the conventional horizontal motion (Fritsch P-23). One profound drawback of mixer mills is the lack of up scalability of the process, as most of the jars come in the range of 5–50 mL (Figure 1.3).

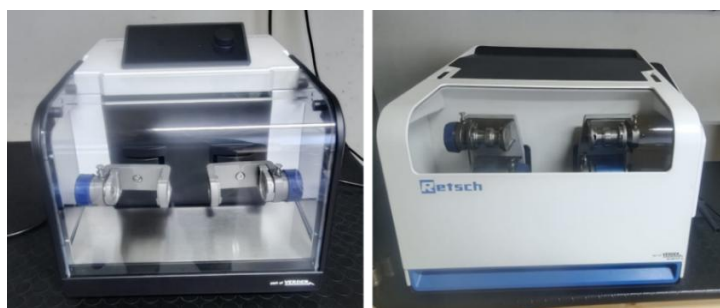


Figure 1.3. Retsch MM-400 mixer mill (left) and Retsch MM-500 mixer mill (right)

Planetary ball mills, on the other hand are ball mills, rotate across a vertical axis to impart mechanochemical energy to the reagents. In this type of mill, the rotating central platform for the jars can rotate both clockwise and counterclockwise (according to the requirement) to give rise to mechanochemical action. This complex motion gives rise to a large amount of shearing force applicable to the reactive media. These mills generally impart lower energy [approximately 1000 revolutions per minute (rpm), approximately equal to 15 Hz] compared to their mixer counterparts. Additionally, these mills generally use several balls in the reaction instead of a single ball, as in the case of a mixer mill.⁴⁰ In addition to the inherent mechanism of the mills, these mills differ from mixer mills in terms of scalability. Planetary mill jars can process reactions ranging from a few grams to a kilogram (figure 1.4).



Figure 1.4. Fritsch P7-Premium planetary mill (left) and zirconia jar for planetary mill (right)

Although ball mills are one of the most widely used devices, they lack general scalability. In practical industrial setups for the production of various value-added compounds, these limitations are the most significant drawbacks, as industries often require the large-scale preparation of chemicals. To address this issue, a continuous process milling equipment, known as a twin-screw extruder (TSE), was introduced.^{41, 42} Here, across a horizontal axis, two large screws are rotated against each other for the continuous addition of reagents and simultaneous grinding. The extruder barrels were designed such that shearing and compressive forces could be directly applied to the reagents. Additionally, these screws can be fitted with reverse screw configurations to provide additional energy to the reagents during the reaction. These screws are generally monitored using temperature probes, and thus, the overall reaction temperature can be regulated. The most notable application of TSE is in their utilization for the preparation of MOFs, which generally produce large amounts of solvent waste during their production using conventional methods.⁴³

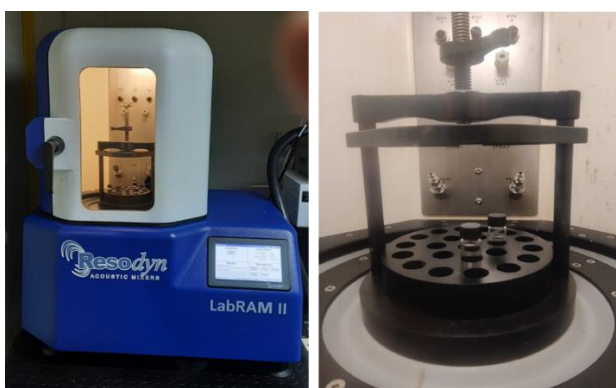


Figure 1.5. Resodyn RAM (left) and Reaction set-up assortment for RAM (right)

The mechanochemical devices discussed thus far use shear or compressive forces, leading to the generation of high amounts of energy inside the mechanochemical vessel, which can sometimes degrade sensitive chemicals. Additionally, SS jars and balls are often prone to metal leaching over time due to rusting, which can significantly impact the reaction outcomes.⁴⁴ This type of grinding media leaching can play an even more significant role in the mechanochemical catalytic process. Therefore, mixing techniques using vibration are sought after. One of the most prominent devices is Resonant Acoustic Mixing (RAM), which applies gentle vibrational forces on the reactants to facilitate reactions.^{45, 46} RAM operates on the term of g forces (acceleration due to gravity $g = 9.8 \text{ m/s}^2$), ranging from 0–100 g for vertical vibration. Owing to its ingenious design, it avoids the use of grinding media, thus avoiding any possible contamination from the mixing vessel. One of the biggest advantages of RAM over traditional ball milling techniques is the ability to perform reactions on a large scale, making it suitable for industrial applications (Figure 1.5).^{47, 48}

1.4. Mechanochemical Parameters

Performing a mechanochemical reaction is not a simple translation of solution-based reactions but often requires meticulous reaction design and parameter selection that can affect the inherent reaction in a mechanochemical process. Optimizing these parameters is essential for establishing a highly reproducible and efficient mechanochemical protocol.

1.4.1. Energy Parameters

The first category of parameters deals with the amount of energy transferred to the reagents via ball-milling. In this context, the first parameter that determines the mechanochemical energy employed is the nature of the material used for ball milling. The density, weight, and hardness of the milling jar and balls are responsible for the overall energy output of the mechanochemical reaction (Figure 1.6).^{49, 50} Generally, the ball mill jars and balls are made of stainless steel (SS), zirconia, and tungsten carbide (WC). WC with higher density (15 g/cm^3) and hardness (Mohs hardness of 9.0–9.5) generates significantly higher energy impacts compared to SS (density = 8 g/cm^3 ; Mohs hardness 5.0–6.0) and zirconia (density = 5.6 g/cm^3 ; Mohs hardness 6.5–8.5 depending upon the crystal lattice) by producing more kinetic energy to transfer to the reagents during impact. Subsequently, for reactions with lower energy requirements, Ertalyte (density = 1.4 g/cm^3 ; a plastic material) and PTFE (density = 2.2 g/cm^3 ; Mohs hardness 1.0) are preferred.



Figure 1.6. Stainless steel [SS] 10 mL ball mill jar (left) and Zirconia 10 mL ball mill jar (right)

Another key parameter for defining the overall energy during milling is the size and quantity of the balls used for the process. Balls with larger diameters generated more energy than smaller balls.^{51, 52} However, owing to the larger size of the balls, every part of the jar cannot be reached by

the ball, resulting in relatively inefficient mixing compared to the use of balls with smaller diameters. Furthermore, a large number of smaller-diameter balls can be used to increase the relative energy generation inside the mill.

The next parameter that influences the amount of energy generated during milling is the frequency at which the milling device is operated. Unlike the previous parameters, this parameter is the simplest to adjust for milling, as the devices have specific operational frequency windows. In general, mixer mills operate in the frequency range of 0–35 Hz, whereas planetary mills operate in rpm (typically 1000 rpm, approximately equal to 15 Hz). A higher value of the aforementioned translates to higher energy generation during the milling process.⁵³ In some cases, the effect of frequency significantly impacts the overall reaction outcome.

1.4.2. Rheological Parameters

Efficient energy transfer and suitable rheological conditions are crucial for successful mechanochemical transformation. Sometimes, mechanochemical reactions require the use of small amounts of liquids in the solid milling mixture to enhance the mixing of the reactants by improving the rheology, which is known as liquid-assisted grinding (LAG).⁵⁴ LAG is often described by the parameter ‘ η ’ which stands for the ratio between the amount of solvent used in μL with respect to the mg of reagent used in mg ($\mu\text{L}/\text{mg}$).⁵⁵ For the consideration of a mechanochemical reaction, the η value should be from 0 to ≤ 1 . An η value ranging from 1 to ≤ 10 is considered a slurry reaction, which is the condition between a mechanochemical reaction and a full-fledged solution-based reaction. An η factor greater than 10 is considered a solution-based reaction (Figure 1.7).⁵

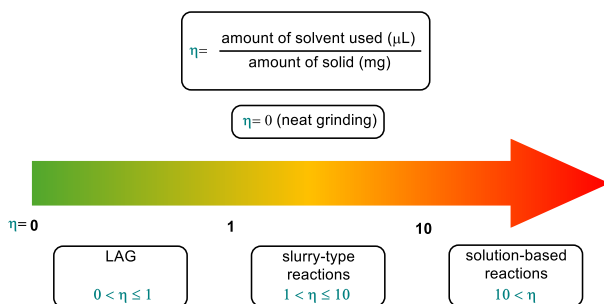


Figure 1.7. Liquid assisted grinding (LAG)

In the same context, grinding auxiliaries is another important factor to consider an efficient In the same context, grinding auxiliaries are another important factor to consider for an efficient mechanochemical protocol. The primary issue with mechanochemical reactions is the use of liquid reagents. Unlike solids, mechanochemical energy is not effectively transferred in liquids, causing serious issues in methodologies where mechanical energy is key to the reactions. To overcome this limitation, solid grinding auxiliaries are added to the reaction to improve the rheology for effective mechanochemical energy transfer in liquid reagents.^{54, 56} Additionally, mechanochemical reactions over time produce a paste-like or sticky reaction medium that can adhere to the balls, thus restricting the motion and impact generated by mechanochemical milling. For such cases, grinding auxiliaries provide a powdery texture, which helps improve homogeneity for an effective

mechanochemical strategy. The most commonly used grinding auxiliaries are silica, magnesium oxide (MgO), talcum, and alumina, and table salt (NaCl).⁵⁷

Combinedly these parameters regulate the result of any mechanochemical reaction. Extensive investigations into the underlying mechanisms of these reactions have led to the emergence of two primary, and often debated, frameworks: (i) the hot-spot theory and (ii) the mixing efficiency theory.

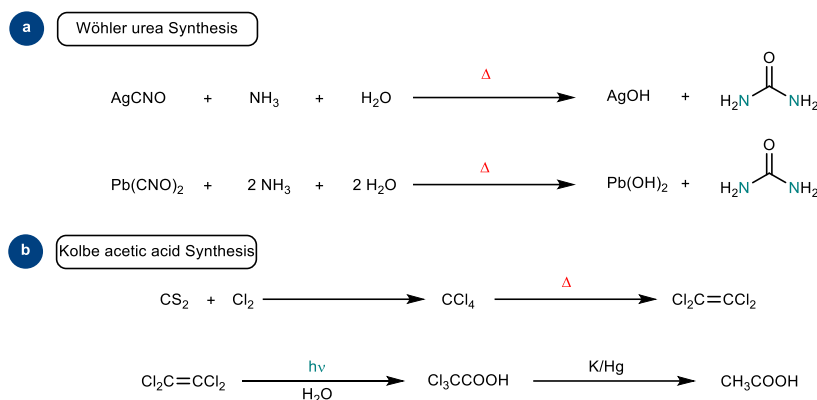
The hot-spot theory, pioneered by Bowden and Yoffe, posits that the dissipation of kinetic energy from milling impacts generates localized "micro-hotspots" with temperatures exceeding 1000 K.⁵⁸ These transient thermal spikes are thought to provide the necessary activation energy to accelerate chemical transformations. However, this model was challenged by the seminal work of Delogu and coworkers, who observed a lack of phase transitions in metals and metal oxides with relatively low temperature transitions that would be expected if such extreme temperatures were consistently reached.⁵⁹ Conversely, recent *in-situ* monitoring by Gerasimov et al. revealed that surface temperatures of milling media can indeed reach up to 600 °C, providing renewed support for the role of thermal spikes. Consequently, while the exact contribution of localized hot spots remains a subject of active debate, it is widely accepted that transient temperature increases play a significant role in enhancing reaction kinetics.

In contrast, the mixing efficiency theory suggests that the primary driver of reactivity is the mechanical deformation generated during high-energy milling.⁶⁰ This process continuously creates fresh, active surfaces and facilitates intimate contact between reagents at the molecular level. As highlighted by Boldyreva and colleagues⁶¹, this efficiency is critically dependent on the mechanical parameters of the milling setup. Despite its focus on mass transfer, the mixing efficiency model still relies heavily on thermal activation as a secondary driving force. Furthermore, this theory alone does not fully account for how mechanical stress alters the selectivity, transition states, or reaction trajectories of primary chemical processes.

To bridge these perspectives, a combined theory of mechanical bond activation (or bond rupture) has been proposed. This unified framework suggests that successful mechanochemical transformations are achieved through the direct activation or cleavage of chemical bonds via the application of mechanical force, rather than relying solely on bulk thermal or mixing effects.

1.5. Mechanochemistry and the Paradigm of Organic Chemistry

In the book *The Structure of Scientific Revolutions*, Thomas Kuhn, an American scientific philosopher and historian, described scientific revolutions as non-cumulative developmental cycles, where an older paradigm is replaced by a new one, defining the non-linear model for scientific advancements.⁶² The birth of organic chemistry exemplifies this Kuhnian theory, evolving science beyond the vitalist belief that the synthesis of organic compounds requires a 'vital force'.^{63, 64} The synthesis of urea from silver oxycyanate and aqueous ammonia mixture and acetic acid from carbon disulfide by Wöhler⁶⁵ and Kolbe⁶⁶, respectively, were the changes in basic assumptions that redefined the frontiers of known chemistry, leading to the birth of organic chemistry (Scheme 1.2). In the present day, this paradigm has been explored to give rise to many frontiers in this fascinating chemistry, such as synthesis, catalysis, and photochemistry.



Scheme 1.2. a) Urea synthesis by Wöhler (1828); b) Acetic acid synthesis by Kolbe (1845)

Over the years, numerous challenges have arisen during the study of organic chemistry, among which sustainability in chemical processes is arguably the most pressing and enduring concern. In the early 1990s, Anastas coined the term green chemistry. Green chemistry is governed by 12 fundamental principles that improve the environmental footprint by reducing toxic waste, improving the energy profile, and introducing safer alternatives during organic synthesis.⁹ In this context, mechanochemistry has emerged as one of the most important technologies for redefining the aspects of organic chemistry. The introduction of solvent-free mechanochemical synthesis has benefited several frontiers of organic chemistry in terms of environmental benefits. Furthermore, mechanochemical reactions enhance the selectivity and performance of several key organic transformations. The introduction of scalable mechanochemical devices, such as RAM, twin-screw extruders, and Dyno mills, in mechanochemical organic transformations demonstrates the revitalization of organic chemistry paradigms via this timeless technology. Selected case studies redefining organic chemistry with the help of mechanochemistry are emphasized in the subsequent part of this chapter.

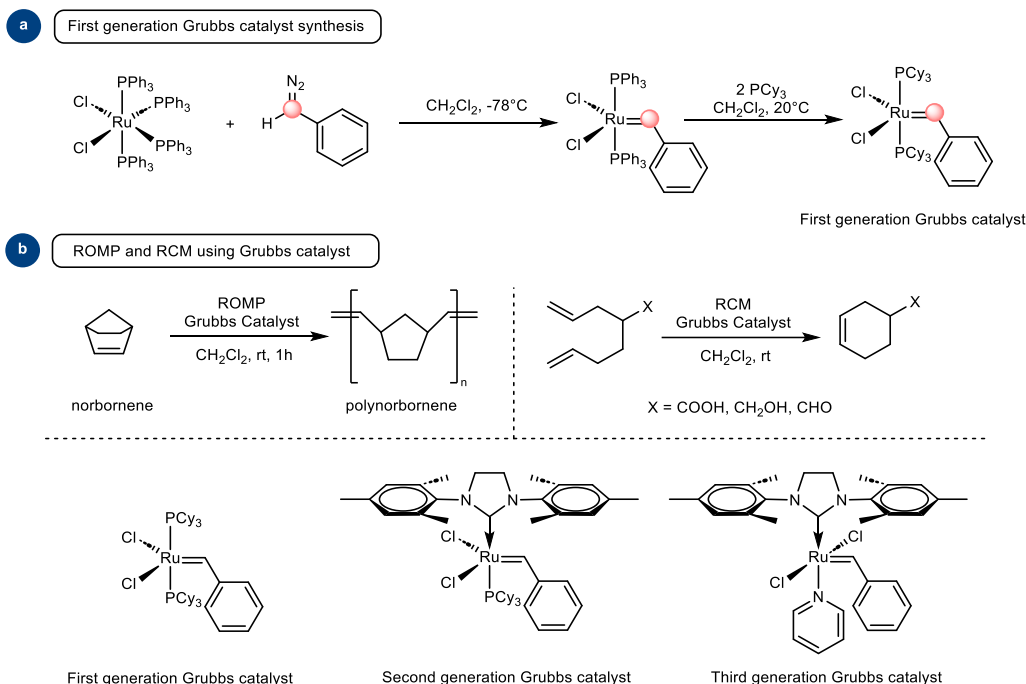
1.6. Mechanochemistry in Catalysis

The exceptional influence of metals and metal catalysts has been the focus of organic chemists in investigating transformations that are otherwise not feasible or kinetically inhibited. Several key transformations, such as C–C and C–N bond formation, to obtain value-added compounds, have been one of the most sought-after applications of metal catalysis.⁶⁷ In this regard, mechanochemical metal-catalyzed reactions have emerged as a greener and more sustainable solution. Until a few years ago, metal-mediated reactions under ball milling or mechanochemical conditions were heavily frowned upon because of moisture sensitivity, high complex decomposition rates, and instability of organometallic reagents, which are stabilized with solvents in solution-based chemistry.^{68, 69} However, efficient and more effective metal-catalyzed transformations under mechanochemical conditions prove otherwise.

1.6.1. Olefin Metathesis

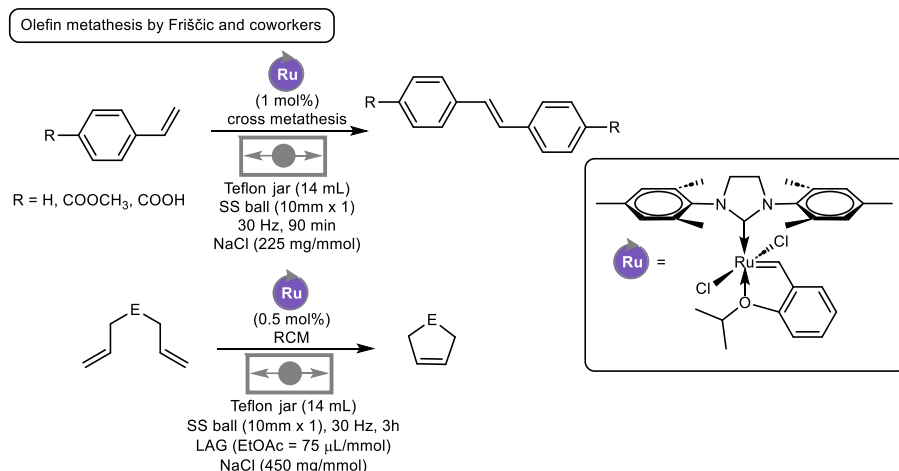
Olefin metathesis is one of the most powerful techniques known in organic chemistry for constructing C–C double bonds from alkenes.⁷⁰ In this context, molybdenum- and ruthenium-based Schrock and Grubbs catalysts have been extensively utilized in both laboratory and

industrial scales for the meticulous synthesis of polymers, medicinal compounds, and natural products.



Scheme 1.3. a) Synthesis of Grubbs first generation catalyst; b) Ring opening metathesis polymerization (ROMP) of norbornene and ring closing metathesis (RCM) using Grubbs catalyst

Utilization of Ru-based catalysts for olefin metathesis was first employed by Robert H. Grubbs in 1995 (Scheme 1.3).⁷¹ They developed a new ruthenium-based catalyst from $\text{RuCl}_2(\text{PPh}_3)_4$, phenyldiazomethane, and tricyclohexylphosphine, and utilized it in ring-opening metathesis polymerization (ROMP) and ring-closing metathesis (RCM). The catalyst used is also known as Grubbs first-generation catalyst.⁷² Subsequently, modifications in the original Grubbs type catalyst gave rise to the formation of Grubbs second and third generation catalysts. Simultaneous studies on olefin metathesis were carried out by Richard R. Schrock separately using a molybdenum-based complex catalyst.⁷³ Olefin metathesis was awarded the 2005 Nobel Prize in Chemistry to Richard R. Schrock, Robert H. Grubbs and Yves Chauvin for enabling a more sustainable methodology for pharmaceuticals, fuels, and plastics.

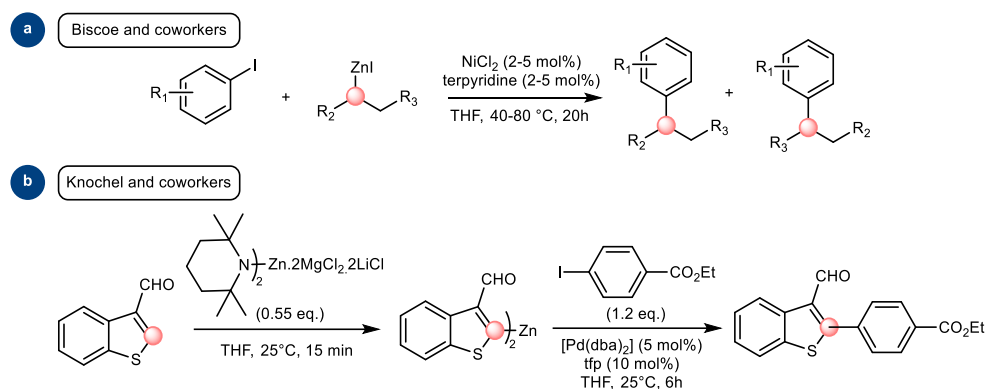


Scheme 1.4. Mechanochemical olefin metathesis reactions by Frišćić and coworkers

Based on the classics, Frišćić and coworkers modelled a mechanochemical strategy for this timeless transformation. Their methodology was translated for cross metathesis (CM) and ring-closing metathesis (RCM) under LAG conditions inside a ball mill (Scheme 1.4).⁵⁷ Furthermore, this methodology supports the reactivity of carefully selected substrates with high yields and excellent scalable transformations using commercially available Ru-based catalysts. Although olefin metathesis of solid olefins has already been explored using a solvent-free protocol, these methodologies were unable to provide any solution for RCM for these substrates, which eventually led to the mechanochemical investigation of solid olefins. Their initial screening for CM was restricted by the rheology of the reaction mixture inside the ball mill; to overcome these limitations, they employed NaCl (225 mg/mmol of substrate) as a grinding auxiliary. These modifications in the protocol provided smooth and efficient formation of CM products with solid olefins inside a ball mill within 90 min. This methodology was then translated to the RCM of solid olefins, where the combination of EtOAc (75 μ L/ mmol of substrate) as LAG and NaCl (450 mg/ mmol) as a grinding auxiliary provided the best results. In summary, this mechanochemical methodology provides a more sustainable and green approach for OM and provides products for otherwise unreactive or difficult-to-react olefins. In addition, the amount of grinding auxiliary used in these transformations is nearly quantitative (150% according to weight) compared to their solution-based counterparts (10-to-100-fold excess). This mechanochemical strategy was the precursor to other mechanochemical approaches for OM. Most notably, Grela *et al.* synthesized a modified Grubbs catalyst under mechanochemical conditions and subsequently used it in RCM under solution-based conditions.⁷⁴ The EcoScore values for the mechanochemical and solvent-based preparation of catalysts were 54 and 32, respectively, emphasizing the benefits of mechanochemistry. Altogether, the mechanochemical approach to olefin metathesis has redefined the previous paradigm. Furthermore, mechanochemical approaches have favourable outcomes in both catalyst synthesis and reactions, thus improving the sustainability and scope of olefin metathesis reactions.

1.6.2. Negishi Cross-Coupling

Negishi cross-coupling is one of the most important synthetic strategies for forming C–C bonds using an organic halide along with an organozinc compound under a Pd (0) catalyst.⁷⁵ This reaction is named after chemist Ei-chi Negishi, who was awarded the 2010 Nobel Prize in Chemistry. Organozinc reagents are generally compatible with many functional groups and easily undergo transmetalation with various transition metals, showcasing their potential in cross-coupling reactions.

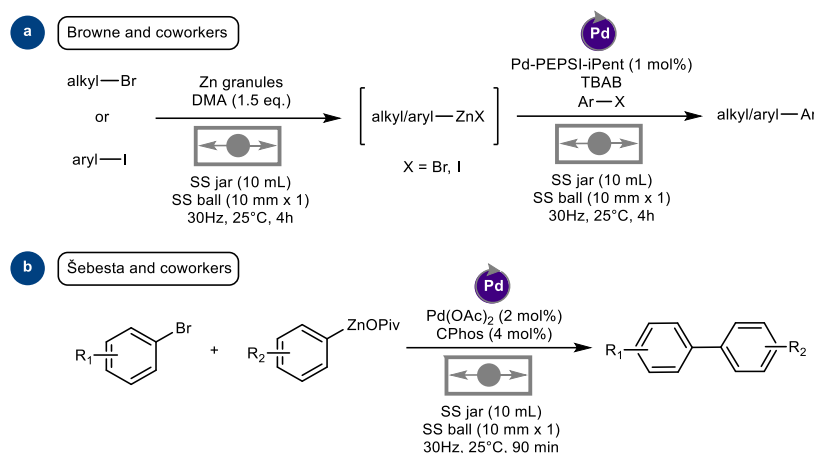


Scheme 1.5. a) Nickel catalyzed Negishi cross-coupling by Biscoe and coworkers; b) Direct zincation of C–H bonds and Negishi cross-coupling by Knochel and coworkers

Recently, this type of cross-coupling reaction has been employed using Ni-based catalysts (Scheme 1.5. a).⁷⁶ These reactions utilize highly reactive and moisture-sensitive organozinc reagents as coupling partners with organic halides; thus, they are highly moisture sensitive and usually conducted under an inert atmosphere. Zinc-based organometallic compounds are typically prepared from organolithium or organomagnesium compounds via transmetalation with Zn (II), leading to functional group incompatibility. However, the research from Knochel and coworkers provided an innovative approach to synthesize organozinc reagents from direct zincation of C–H bonds using zinc-amide bases (Scheme 1.5.b).⁷⁷ This revolutionized the innate protocol of Negishi coupling. Selection of proper solvent for this transformation is also a key factor that defines the efficacy of this methodology. Unlike other palladium catalyzed cross-coupling reactions, Negishi coupling can act on sp³, sp² and sp carbons for C–C bonds. This reaction is generally employed in the synthesis of natural product intermediates showing its strong application.

The sensitivity of organozinc reagents poses even significantly more challenging under mechanochemical conditions. In this context Browne and coworkers developed a mechanochemical Negishi cross-coupling protocol with in-situ generation of organozinc reagent from mechanochemical grinding of ethyl-4-bromobutanoate in the presence of elemental zinc (1.1 equivalent) and DMA (1.5 equivalents) for 4 hours under air (Scheme 1.6.a).⁷⁸ The reaction when quenched with acidic solution provided organozinc halide with a yield of 76%. The addition of aromatic halides, Pd-PEPSI catalyst (1 mol%) and TBAB to the mechanochemically generated organozinc reagents in a ball mill resulted in successful conversion to Negishi cross-coupling product with excellent yields up to 95%. Notably, this protocol was utilized to form a normal atmosphere stable organozinc reagents and able to form sp²–sp² bonds using both aliphatic and

aromatic organozinc reagents prepared in a one-pot condition. Inspired from this work, Šebesta and coworkers developed their own mechanochemical uptake to this fascinating reaction. Their protocol relies on the utilization of aryl-zinc pivalate reagents and aryl bromides along with palladium catalyst at room temperature resulting in excellent yields of sp^2-sp^2 Negishi cross-coupled compounds (Scheme 1.6.b).⁷⁹ Most notably, LAG of THF ($\eta = 0.3$) was crucial for their mechanochemical protocol to provide range of bi-aryl products. The reaction efficiency of this protocol was calculated by using mass intensity (MI) parameter. Mechanochemical MI valued 18.2 whereas solution-based MI was calculated to the value of 82.7, redefining the sustainability and applicability of the mechanochemical protocol.



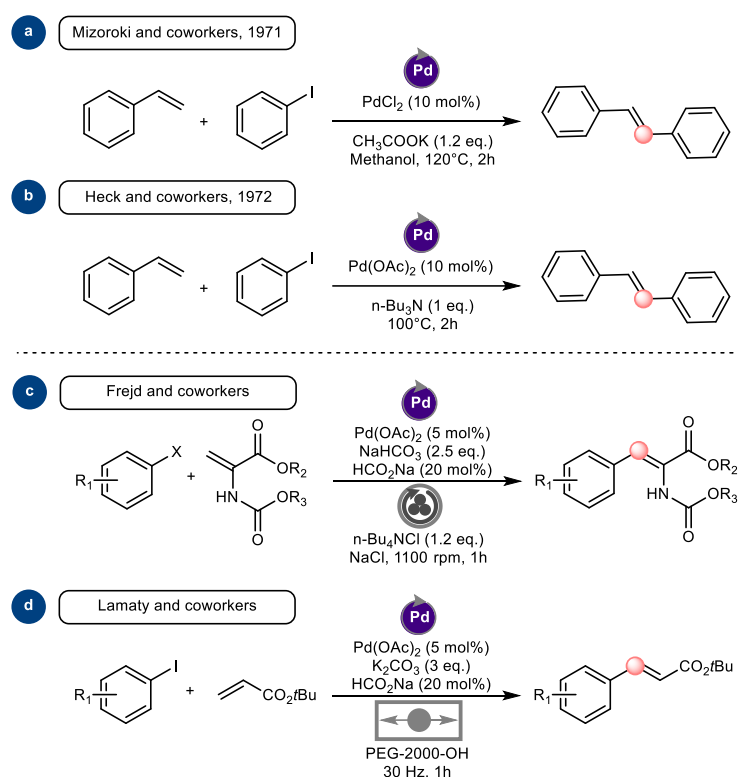
Scheme 1.6. a) Mechanochemical one-pot Negishi cross-coupling by Browne and coworkers; b) Mechanochemical Negishi cross-coupling using pivalates by Šebesta and coworkers

1.6.3. Mizoroki-Heck Reaction

Mizoroki-Heck reaction, also known as Heck reaction, is a palladium catalyzed reaction between an unsaturated halide with an alkene to form substituted alkene. The reaction first performed by Tsutomu Mizoroki *et.al.* (1971)⁸⁰ and Richard F. Heck *et.al.* (1972)⁸¹ independently, resulted in 2010 Chemistry Nobel Prize to Richard F. Heck (Scheme 1.7.a-b). The synthesis of active pharmaceutical ingredients (APIs) for medicines play an important role in such increase in the life expectancy. Because of this, efficient synthesis of drug molecules attracts the attention of researchers and industries equally. A class of drug molecules can be traced where formation of stereoselective C–C plays a crucial role. In this context, Heck reaction displays substantial use due to its stereoselective action. The inherent benefits of this innovative strategy led to the evolution of alternative Heck coupling conditions such as Heck-Jeffery.⁸²

Mechanochemistry comes into the picture when detailed analysis of this class of reactions are performed, showing the use of extensive reaction time, high reaction temperatures and use of solvents like DMF. In the attempt to develop mechanochemical counterparts of this crucial transformation, Frejd and coworkers first investigated Heck-Jeffery reaction under ball milling conditions (Scheme 1.7.c).⁸³ Their conditions used protected amino acrylates, aryl halides and tetrabutylammonium chloride in the presence of Pd catalyst to form the desired product. Tetrabutylammonium halides are solid at room temperature but act as ionic liquids in molten state

which can help in stabilization of metal centers, in this case Pd (0) species. Taking advantage of such properties Frejd and coworkers successfully performed a phase-transfer mechanochemical Heck-Jeffery reaction at room temperature. Most notably, in absence of tetrabutylammonium chloride the reaction was unable to provide any product formation. Inspired by this mechanochemical approach Lamaty and colleagues demonstrated their take on Mizoroki-Heck reaction with the use of solid polyethylene glycols (PEG-2000-OH) which are known to show stabilizing effect on metallic catalytic systems (Scheme 1.7.d).⁸⁴ They utilized iodobenzene derivatives along with tert-butyl acrylate and PEG-2000-OH under a palladium catalyzed ball milling setup. Remarkably, they were able to obtain the coupling products at room temperature and a significantly reduced time (1 h). Notably, their methodology was limited to the use of iodobenzene. These examples in the literature solidifies the claim of mechanochemistry for sustainable transformations.

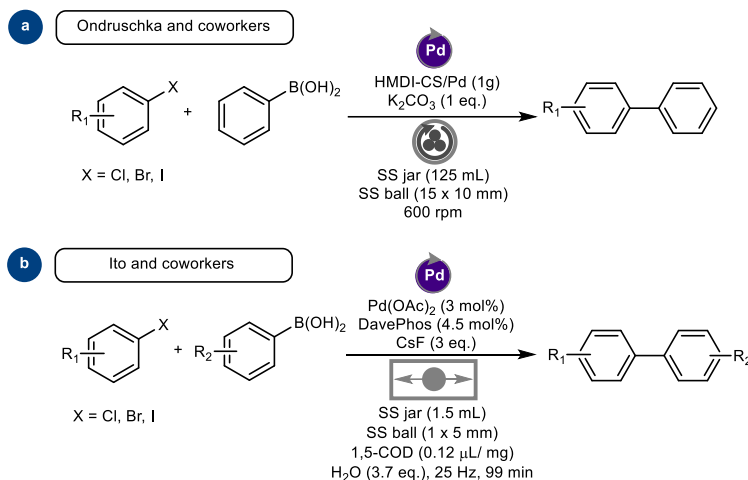


Scheme 1.7. a) Cross-coupling by Mizoroki and coworkers; b) Cross-coupling by Heck and coworkers; c) Mechanochemical phase transfer Heck-Jeffery coupling by Frejd and coworkers in planetary mill; d) Mechanochemical Heck coupling by Lamaty and coworkers in a mixer mill

1.6.4. Suzuki-Miyaura Cross-Coupling Reaction

In multistep organic synthesis, there is hardly any procedure that does not include Suzuki-Miyaura cross-coupling reaction for the synthesis of C–C bonds. This transformation was developed by Akira Suzuki and co-workers in 1979.⁸⁵ From that point onwards this reaction has seen paramount applications in every field of chemistry. For his ground-breaking work, Akira Suzuki was awarded the 2010 Nobel Prize in Chemistry. This protocol uses aryl boronic acids along with organic halides in presence of Palladium catalyst and suitable base. The role of base in this transformation is

primarily to activate the un-activated aryl boronic acid for the subsequent reaction. The key feature that separates this reaction from other C–C bond reaction is the use of milder reaction conditions, less toxic reagent and availability of boronic acids. This reaction primarily uses water as the solvent thus increasing the sustainability value of the protocol.



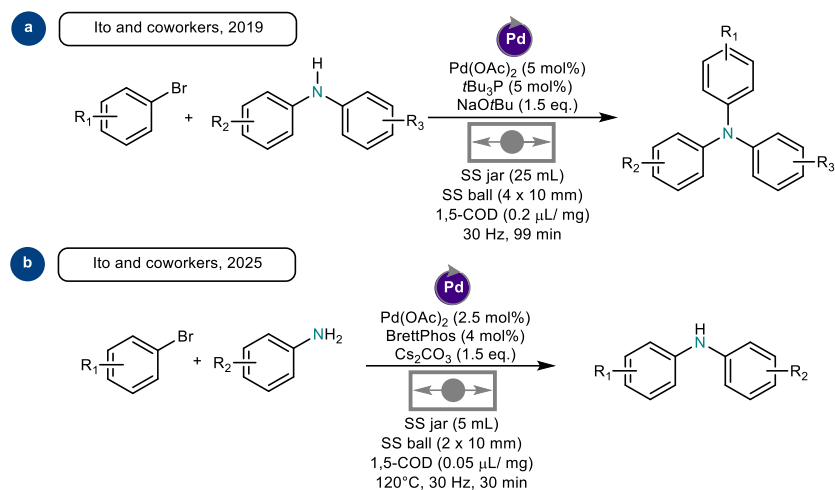
Scheme 1.8. Mechanochemical Suzuki-Miyaura cross-coupling by a) Ondruschka and coworkers; b) Ito and coworkers

Mechanochemical Suzuki-Miyaura reactions can be traced back to year 2012 by Ondruschka and coworkers where they synthesized a chitosan-based Palladium catalyst which catalyzed the coupling reaction of halobenzene with phenyl boronic acid in presence of potassium carbonate inside a planetary mill (Scheme 1.8.a).⁸⁶ This protocol was successfully able to provide products for chloro-, bromo- and iodo- benzene. Additionally, due to the heterogeneous nature of catalyst, it can be easily separated after reaction and can be re-utilized. But to the dismay, this catalyst provided substantial amount of homocoupling products in limited cases. Furthermore, the amount of homo-coupling products after each recycling setup increased. These limitations for the reaction hindered the broader applicability of this mechanochemical protocol. Later, Ito and coworkers aligned their attention to this reaction where they developed a Suzuki coupling reaction using aromatic halides and boronic acids with the use of 1,5-COD (0.12 $\mu\text{L/mg}$) as LAG and water as additive inside a mixer mill (Scheme 1.8.b).⁸⁷ This protocol was able to provide excellent yields of cross-coupled products in a short amount of time. Notably, this protocol didn't provide any homo-coupled products. While comparing with the solution-based protocol, this mechanochemical method was able to provide product at room temperature and with a higher yield and less reaction time. These advantages of mechanochemistry over solution-based chemistry make it essential for sustainable chemical synthesis.⁸⁸

1.6.5. Buchwald-Hartwig Amination Reaction

Nitrogen based molecules have been in paramount use as medicines, fertilizers, cosmetics and polymers.⁸⁹⁻⁹³ Considering their significant impact on day today life, C–N bond formation is one of the most sought-after transformations in research labs and industries. In 1983, Stephen L. Buchwald and John F. Hartwig introduced a Pd-catalyzed protocol using aryl halides and primary or secondary amines for the synthesis of aromatic amines.^{94, 95} Over the years, various palladium-

based catalysts have been developed for this remarkable transformation, while using complexes with phosphine-based ligand architecture. Revisiting the paramount importance of N-heterocyclic compounds and amines within various aspects of our day-to-day life, extensive use of this amination method has been seen across literature.

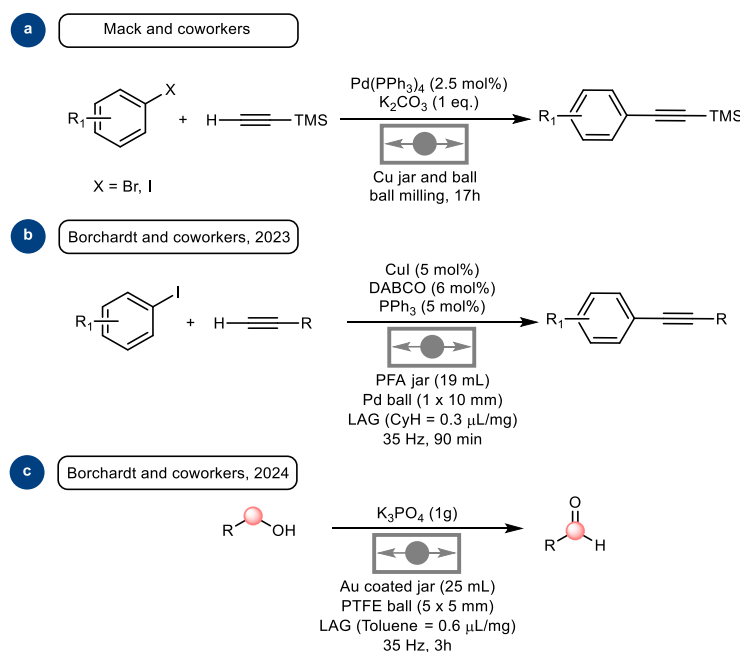


Scheme 1.9. Mechanochemical Buchwald-Hartwig amination for a) secondary amines; b) primary amines

Historically, this transformation heavily relies upon the use of solvent. In an industrial scale, fine chemical synthesis having C–N bond produces huge amount of solvent waste which significantly deteriorate the environmental profile. In this context, mechanochemical approach to this timeless reaction has attracted huge attention. Ito and coworkers proposed their version of Buchwald-Hartwig amination of solid amines and solid aryl halides at room temperature (Scheme 1.9.a).⁹⁶ While neat grinding of the starting material with catalyst failed to provide significant product yields, yet the use of LAG provided significant advantages upon this condition. Most notably, use of olefins as LAG provided significantly better yields compared to other LAG additives. Additionally, use of 1,5-COD as LAG (0.2 μL/mg) resulted in full conversion. TEM analysis defined that 1,5-COD acts an effective dispersive medium for the powdered Pd catalyst (3–5 nm) while in absence, there is counter effective aggregation of the catalyst. This study demonstrates an innovative approach to use LAG for the effective distribution of catalyst. Most notably, this protocol was reported with the use of secondary amines. Building upon their earlier research, Ito and coworkers developed another mechanochemical protocol for Buchwald-Hartwig amination of primary amines (Scheme 1.9.b).⁹⁷ The room temperature grinding of the reaction didn't provide any product formation although heating the reaction with an external heat-gun up to 120°C internal temperature proved effective for the feasible product formation. Consequently, addition of another equivalent of aryl halide resulted in formation of tertiary amines albeit with a lower conversion rate. Combinedly, mechanochemical treatment boosted the sustainability of this reaction, removed the use of inert atmosphere and improved the reaction conditions to a milder version compared to their solution-based counterpart.

1.6.6. Direct Mechanocatalysis

Mechanocatalysis provides significant advantages over their solution-based counterparts such as solvent reduction, energy efficiency, reduced reaction time and many more. However, certain limitations of these reactions cannot be properly addressed using mechanochemistry. Most importantly, catalyst recovery after mechanochemical reactions is a challenge that still needs to be addressed. The introduction of direct mechanocatalysis is the breakthrough that overcomes this limitation of mechanochemical reactions. The concept behind this remarkable technology is the use of ball milling jars or balls to be either completely made with the catalytically active metal/alloy or a thin plating of the appropriate metal over the reacting surface. This enables the direct interaction of metals by creating direct interaction of highly dispersed metal to the reactants like homogeneous catalysis and expanding reactive surface like heterogeneous catalysis.⁹⁸ These inherent qualities make direct mechanocatalysis fundamentally different from both homogeneous and heterogeneous catalysis. At first glance, this methodology encompasses both the benefits from homogeneous and heterogeneous catalysis; however, due to effective collisions inside a ball milling environment the catalytic surface can be modified by metal leaching and can introduce new reactive catalytic surface.



Scheme 1.10. Direct mechanocatalysis strategy for a) Sonogashira coupling using Cu jar and balls; b) Sonogashira coupling using a 10 mm Pd ball; c) oxidation of alcohol using gold coated jar

The application of direct mechanocatalysis for a ball milling set-up was first introduced by Mack and coworkers in 2009 (Scheme 1.10.a).⁹⁹ By utilizing a copper reaction vessel in conjunction with a co-catalyst, they successfully facilitated **Sonogashira coupling** with an efficiency comparable to traditional mechanochemical protocols mediated by copper(I) iodide (CuI). Significantly, the authors observed that substituting the copper jar with a stainless-steel vessel—even when using copper milling balls—substantially diminished product yields. This suggests that the reaction is highly dependent on the available surface area of the copper source, as the stainless-steel

configuration limited the essential contact between the copper catalyst and the alkyne substrate. Ultimately, this approach represents a significant advancement by bypassing the need for exogenous Cu(I) salts typically required in solution-based strategies. Treading on the footsteps of the previously mentioned approach, several key reactions have been demonstrated using direct mechanocatalysis. Most notably, Borchardt and coworkers have extensively researched this field. In their pursuit of direct mechanocatalysis, they have developed methodologies for several key reactions such as Sonogashira coupling with a Pd ball (Scheme 1.10.b)¹⁰⁰, oxidation of alcohols using gold coated jars (Scheme 1.10.c)¹⁰¹ and hydrogenation of organic molecules using Pd and Rh coated jars¹⁰². Most remarkably, they have also investigated the use of Pd coated twin-screw extruder for continuous Suzuki-Miyaura cross coupling reactions.¹⁰³ This signifies that beyond simple reactivity direct mechanocatalysis offers potential for a more practical technique to introduce mechanochemical benefits into industrial applications.

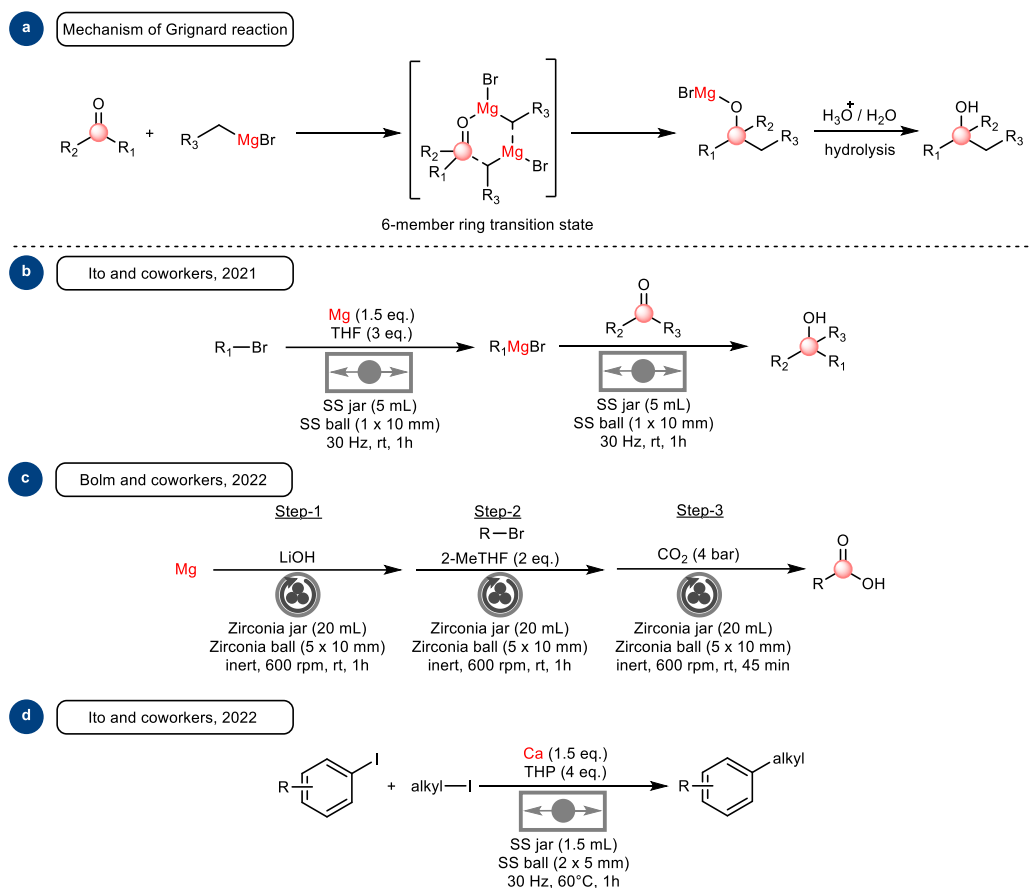
1.7. Mechanochemistry in Organometallic Reactions

Organometallic reagents and complexes are extremely reactive molecules. Synthesis, characterization and utilization of such compounds need highly controlled environments, extensively dried solvents, excess reagents, delicate temperature control and careful handling. These constraints on such molecules often result in heavy chemical waste which significantly decreases the environmental footprint. In this context, mechanochemistry shows great promise to reduce the environmental impact of these molecules in both synthesizing and applications. This section discusses the intervention of mechanochemistry in prominent organometallic reagent synthesis and subsequent reaction.

1.7.1. Grignard Reaction

Grignard reaction and reagent get their name from the French chemist Victor Grignard. It is basically a type of organomagnesium halide which can be synthesized by a reaction between an organic halide and metallic magnesium.¹⁰⁴ Primarily, the reaction of Grignard reagent with a ketone to obtain tertiary alcohol is considered Grignard reaction. Magnesium center of a Grignard reagent acts as nucleophile which interacts with the electrophilic carbonyl center. This reaction proceeds through a 6-member intermediate species to transform into tertiary alcohol after hydrolysis (Scheme 1.11.a). This remarkable reaction awarded Victor Grignard 1912 Nobel prize in Chemistry. Since the discovery of this reaction, it has been extensively used in polymer, food and fine chemical industries. However, this transformation generally utilizes extremely dry solvents, long reaction times and use of inert atmosphere. Moreover, magnesium for the synthesis of Grignard reagents is subjected to pre-activation before utilization to remove the oxide layer above the metal which also contributes to the limitations of this reaction.

In this context, mechanochemistry has emerged as the most innovative technology to revitalize this remarkable reaction. The first mechanochemical attempt to synthesize Grignard reagent was reported by Harrowfield and coworkers.¹⁰⁵ In their protocol they utilized an excess of magnesium inside a ball mill to synthesize Grignard reagent in solvent-free conditions whereas the excess metal couldn't be removed from the reaction mixture. When this Grignard reagent is utilized with ketone inside a ball mill, it provides alkenes as the major product. Subsequent investigation on Grignard reaction was carried out across multiple years.



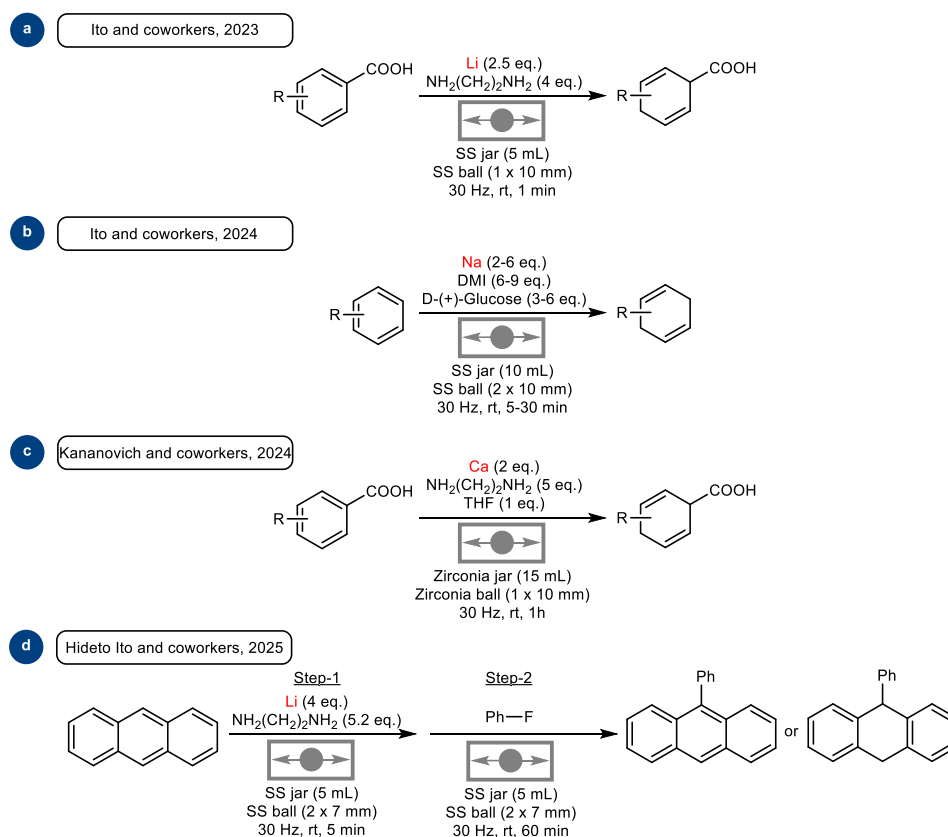
Scheme 1.11. a) Mechanism for Grignard reaction; b) Mechanochemical Grignard reaction with ketones to tertiary alcohols; c) Mechanochemical Grignard reaction with gaseous CO₂ to carboxylic acids; d) Mechanochemical Ca-based Grignard reaction

Remarkably, Ito and coworkers devised a mechanochemical production of bench stable and isolable Grignard reagent inside a ball mill using THF (3 eq.) as LAG (Scheme 1.11.b).¹⁰⁶ This reagent was then used for the successful reduction of ketones to tertiary alcohols. Later, Bolm and coworkers developed a mechanochemical Grignard reaction for reaction with gaseous carbon dioxide (CO₂) to form carboxylic acids as major product.¹⁰⁷ Additionally, this approach demonstrates the potential of mechanochemistry in use of organometallic transformations along with the use of gaseous reagents (Scheme 1.11.c). Ito and coworkers later synthesized mechanochemical heavy Grignard reagent using Calcium metal for C–C bond formation (Scheme 1.11.d).¹⁰⁸ Combinedly, these reports demonstrate that mechanochemical application reshapes Grignard reaction with elimination of solvent, synthesis of bench-stable Grignard reagent and safer reaction profile combined with significant decrease in reaction times. This proves the possible benefit of mechanochemical reaction for further applications in fine chemical synthesis using organometallics.

1.7.2. Birch Reduction

Birch Reduction is a method to obtain 1,4-cyclohexadiene derivatives from arenes using alkali metal such as sodium or lithium along with ammonia named after the chemist Arthur Birch.¹⁰⁹ This

reduction method is extremely selective in reducing the molecules as this reduction does not proceed for further reduction after 1,4-cyclohexadiene derivatives from arenes. Here, alkali metals act as single electron donors to the aromatic ring to form radical anion which then abstracts proton from alcohol to provide the reduced product. This reduction method is applicable to reduced electronegative groups such as ketones or nitro-groups. However, carboxylic acid groups and alcohols remain unaffected. This reaction generally needs inert atmosphere, low reaction temperature and critical reaction setups which limit the applicability of this method.



Scheme 1.12. a) Mechanochemical Li-mediated Birch reduction; b) Mechanochemical Na-mediated Birch reduction; c) Mechanochemical Ca-mediated Birch reduction; d) Mechanochemical Li-mediated Birch reduction for reductive arylation

Inspired by the effects of mechanochemistry to stabilize bulk reactive metals, mechanochemical Birch reductions have been conducted across the literature. In this context, Ito and coworkers developed an ammonia-free Lithium mediated Birch reduction of arenes (Scheme 1.12.a).¹¹⁰ This protocol utilized ball milling Li metal, ethylenediamine and tert-butanol as LAG at room temperature to get reduced product instantly within 1 minute. Furthermore, this mechanochemical protocol provided 10% of cyclohexene derivative as side-product. Notably, they also performed gram-scale Birch reduction to get quantitative reduction products. Later, they developed sodium and 1,3-Dimethyl-2-imidazolidinone (DMI) mediated Birch reduction of arenes using D-glucose as an additive (Scheme 1.12.b).¹¹¹ Inspired from these works, Kananovich and coworkers developed a remarkable Birch reduction protocol using group-II metals such as Mg and Ca (Scheme 1.12.c).¹¹² This protocol used Ca and ethylenediamine as reductant inside ball milling

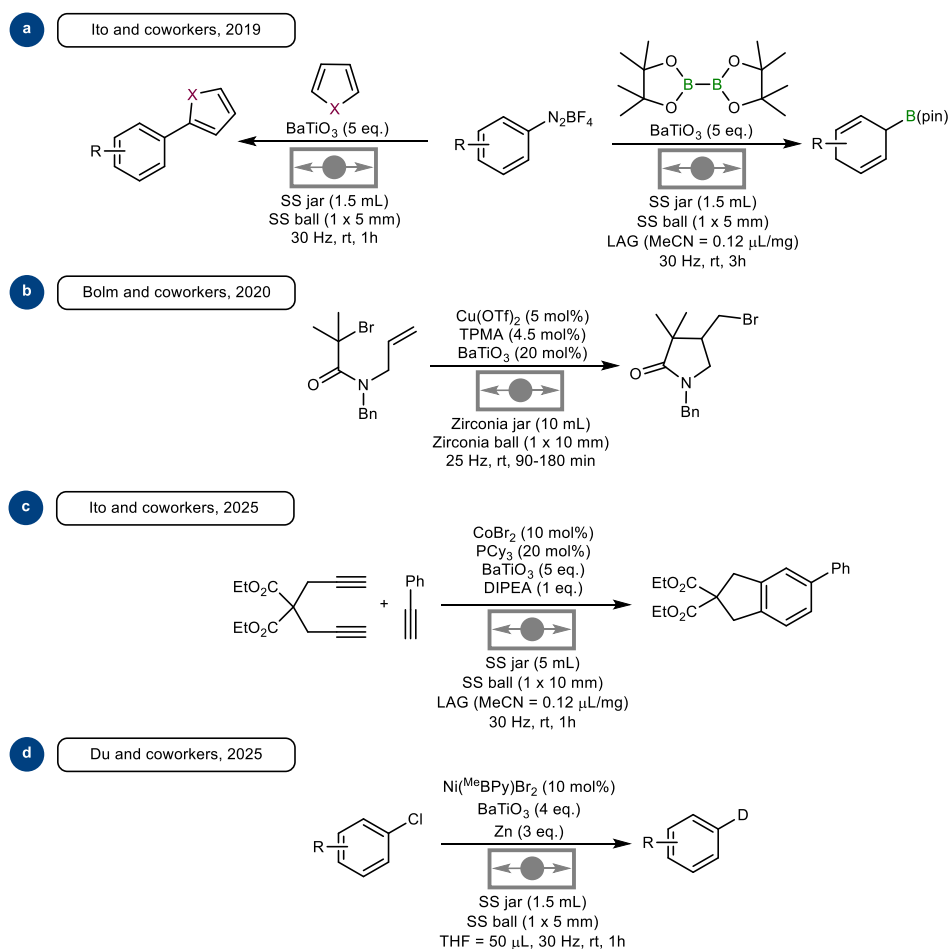
conditions with ammonium chloride as protic source. Remarkably, while Ca with EDA didn't provide any product under solution-based condition; mechanochemical reaction provided quantitative product formation showing the advantages of mechanochemistry for this type of organometallic transformation. Recently, Hideto Ito and coworkers developed lithium and ethylenediamine mediated mechanochemical Birch reductive arylation using fluorobenzene (Scheme 1.12.d).¹¹³ These reactions collectively highlight that mechanochemistry in Birch reduction can reduce solvent use, provide more stable reactive species and reduce the environmental footprint for this timeless classic.

1.8. Mechanochemistry in Piezoelectric Organic Synthesis

Photoredox chemistry has seen unprecedented rise over the past decade. A successful photochemical reaction demands the photocatalyst species having a long living phosphorescence species that can act as potent reducing agent via single electron transfer and a potent oxidizing agent then ground state of photocatalyst under photochemical conditions. Inspired by photoredox chemistry, mechanochemical equivalent of such process has been developed where the excitation of electron is performed via mechanochemical energy. Ultrasonic agitation of BaTiO₃, generates an electrochemical potential sufficient to surpass the water-splitting threshold (1.23 V) and reduce *N,N,N',N',N'',N'''*-hexamethyl[tris(aminoethyl)amine] (Me₆TREN)-ligated CuBr₂ complex ($E_{\text{red}} = -0.30\text{V}$ vs saturated calomel electrode).^{114, 115} These findings established a precedent for piezo-electrochemical activation, suggesting that the mechanical energy harnessed within a ball mill could similarly drive the redox-mediated transformation of small organic molecules in synthetic applications. In this context, Ito and co-workers first reported the use of Barium titanate as piezoelectric material under mechanochemical condition. Piezoelectric materials such as BaTiO₃ which upon application of mechanical stress produce highly polarized particles that can help in single electron transfer for small organic molecules.¹¹⁶ In their procedure, they reported piezoelectric action upon aryldiazonium salts for mechano-redox arylation and borylation. Additionally, this technique was carried out at normal atmosphere and with the utilization of LAG benefitted the reaction outcome. This reaction when performed in the presence of TEMPO (a radical scavenger), a TEMPO-trapped intermediate can be observed under NMR thus providing evidence for the mechanism. This innovative and pioneering report became the cornerstone for mechano-redox reactions. Along the way, Ito and coworkers followed this mechano-redox technology for several key reactions such as mechano-redox Cobalt catalyzed [2+2+2] cycloaddition¹¹⁷, Nickel catalyzed amination reaction¹¹⁸ and radical C–H trifluoromethylation reactions¹¹⁹.

Eventually, mechano-redox chemistry was extended by Bolm and coworkers with their utilization of BaTiO₃ mediated copper catalyzed electro-mechanochemical transfer for radical-cyclization.¹²⁰ Their methodology started with cyclization of monobromoacetamide using Cu(OTf)₂ and tris(2-pyridylmethyl)amine (TPMA) ligand under mechanochemical piezoelectric effect. Most notably, this reaction needed to be performed under argon conditions inside the milling jar and in absence of the piezoelectric material the reaction failed to provide any product formation. This reaction supports the results of Ito and coworkers regarding the broader applicability of mechano-redox chemistry. Along the way, Kramer and coworkers reported mechano-redox synthesis of aryl fluorides¹²¹; and Du and coworkers reported Nickel catalyzed dechlorination-deuteration of aryl

chlorides using BaTiO_3 .¹²² Altogether, this technology completely shifts the uses of mechanochemistry. These protocols were able to avoid solvents and provided faster and more selective reactivity of their complementary solution-based redox transformations. Although all the above-mentioned reports have been able to successfully provide solvent-free mechano-redox transformations of small organic molecules, they are limited to only use of BaTiO_3 . This limitation inspires us to analyse the piezoelectric properties of different materials and development of more mechano-redox reactions (Scheme 1.13).



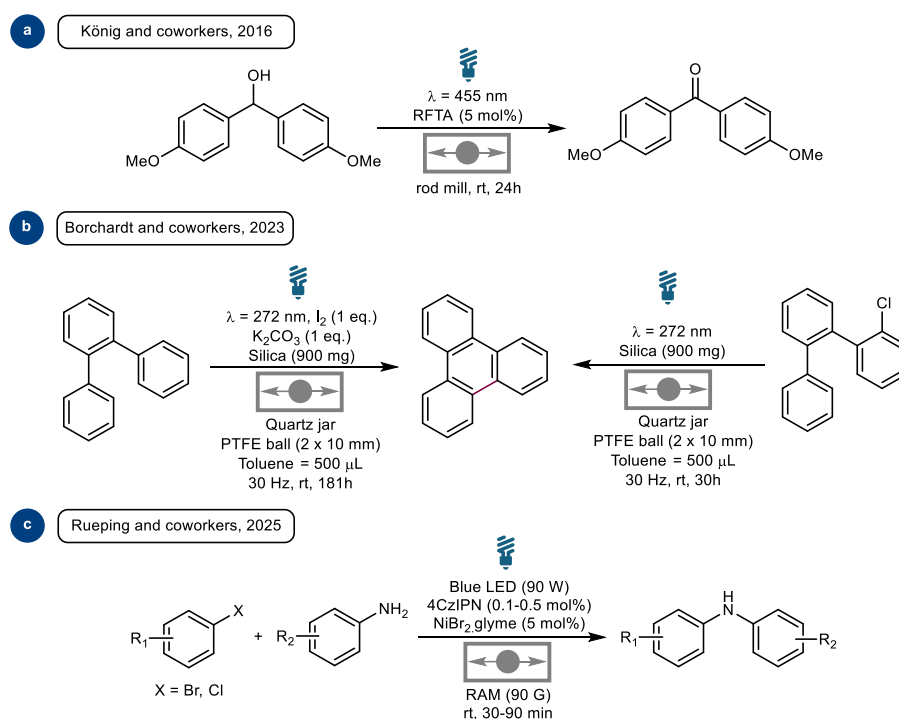
Scheme 1.13. a) Mechanochemical piezoelectric arylation of diazonium salts; b) Mechanochemical piezoelectric Cu-catalyzed cyclization; c) Mechanochemical piezoelectric Co-catalyzed [2+2+2] cycloaddition; d) Mechanochemical piezoelectric Ni-mediated dechlorination-deuteration of aryl chlorides

1.9. Photomechanochemistry

Photochemical reactions provide unique reactivity and provide access to compounds which otherwise are inaccessible by conventional means. These reactions are considered sustainable due to the use of light, but they often produce massive solvent waste due to the constraint of extreme dilution. In this context, photomechanochemistry has emerged as one of the most innovative technologies to conduct solid-state photochemical reaction by avoiding the use of solvent.³¹ Furthermore, it is a part of new mechanochemical strategies of combining different energy sources to mechanochemistry for accessing products otherwise impossible by conventional ball milling.

One of the earliest photomechanochemical transformation was introduced by König and coworkers with riboflavin tetraacetate (RFTA)-catalyzed photocatalytic oxidation of alcohols to their corresponding carbonyl compounds using a mechanical rod stirrer.¹²³ Their findings showed that the reaction proceeds through a phase-transfer into molten state revealed from the control experiment devoid of RFTA. This solvent-free approach inspired many researchers to focus on this remarkable technology. Over time photomechanochemical reactions gained immense popularity.

In this context, Borchardt and coworkers have synthesized solid-state regioselective nanographene under photomechanochemical condition. For performing this reaction, a quartz jar with PFA caps was taken in the presence of UV light ($\lambda_{\text{max}}=272$ nm).¹²⁴ In the first protocol they performed a photomechanochemical Mallory reaction with a LAG of toluene. However, the next protocol o-(2-chloro)terphenyl was milled under photomechanochemical conditions silica (900 mg/150 mg substrate) as an additive. Most notably, control experiments reveal that this transformation is primarily a photochemical reaction while mechanical mixing enables efficient mixing of substrate. Subsequently, Rueping and coworkers developed a Nickel mediated photoredox catalysis using RAM.¹²⁵ Their protocol was developed from a previous photoredox strategy from König and coworkers.¹²⁶ This strategy included the use of aryl halides and primary amines in presence of Nickel catalyst inside a RAM-based photomechanochemical set-up (90W blue LEDs) for secondary amines. Remarkably, this strategy was implemented for large scale synthesis (300 mmol) of amine products with excellent yields. Compared to traditional solution-based methods, this strategy offers superior efficiency and excellent environmental footprint. Altogether, these literature references demonstrate that photomechanochemistry provides effective solvent-free reaction, extreme regioselectivity and huge scale-up potential. (Scheme 1.14)



Scheme 1.14. a) First photomechanochemical reaction for RFTA catalyzed oxidation; b) Photomechanochemical nanographene synthesis; c) Photomechanochemical Ni-catalyzed N-alkylation

1.10. Mechanochemical Scaling-up and Process Safety

Industrial scale fine chemical synthesis and medicines at one point start inside small-scale laboratories. Hence, scaling-up practices are the end goal of a chemical reaction. Process safety and scaling-up an organic reaction for industrial scale is not a simple translation from laboratory scale but rather an intricately designed and carefully monitored protocol with several key considerations. Failing to provide those conditions can lead to unprecedented chemical waste generation, failure to provide product formation and often failure in reaction set-up. Mechanochemistry as a new and enhanced technology for laboratory scale organic synthesis has even more parameters to be considered before scaling up because of the heavy solvent-reliant instrumentations in industries.¹²⁷ Thus, conventional scale up methods are not sufficient to assess large scale mechanochemical transformations. In this regard, several key steps for scaling-up mechanochemical reactions are listed below:

- I. Equipment design and characterization methodologies are primary parameters to be considered for a mechanochemical reaction scale-up as conventional reaction set-ups are not suitable for it. Mechanochemical reactions demand the use of proper milling devices that give rise to chemical transformations. The typical devices used for laboratory-scale reaction all ball milling devices such as mixer mills or planetary mills operating at a particular frequency. Despite their operational efficacy, high-energy milling systems generate significant acoustic emissions; at industrial scales, this poses substantial occupational health and safety challenges. Furthermore, these devices come with lower-scale reaction jars which can be another big challenge for the industries to build upon. Additionally, mechanochemical reactions are harder to monitor in-situ which is essential for large-scale process build-up. In the present day, several key advancements in the field of mechanochemistry have emerged helping the scalability of the reactions. Twin-screw extruder, RAM, Dyno mills are some of the new mechanochemical devices that are designed for the up scaling of mechanochemical reactions. Additionally, in-situ monitoring techniques such as Raman spectra and in-situ solid-state NMR techniques have been developed for mechanochemical processes which can be implemented in the industrial synthesis scale.

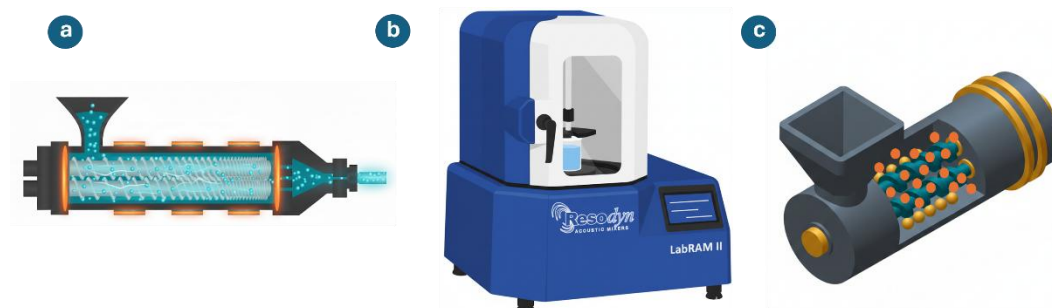


Figure 1.8. Representation of mechanochemical scale-up equipments: a) twin-screw extruder (TSE), b) resonant acoustic mixing (RAM), c) Dyno mill (bead milling technology)

- II. Heat regulation of a reaction is a benchmark standard for industries. However, mechanochemical reactions can produce tremendous amount of heat during solid-state milling of compounds. This limitation is more prominent in the use of highly reactive compounds and exothermic reactions. So, a simple large-scale synthesis of mechanochemical reactions can be a challenging task. In this regard, it is very important to provide a sink effect to a mechanochemical reaction during milling to regulate its temperature. Furthermore, the reactions using possibly explosive chemicals can be managed in smaller batches to avoid any casualties or rapid heat generation. To aid this cause, RAM can be a better option to perform mechanochemical reactions with lower energy requirements. However, for high energy requirement reactions, a proper heat sink mechanism must be introduced for milling devices to get effective temperature control.
- III. Rheological parameters are another crucial parameter to be considered during a mechanochemical reaction and process scale-up. While an effective mechanochemical reaction can be achieved easily inside a small mechanochemical vessel, for a large-scale synthesis the above cannot be achieved that easily. Furthermore, the isolable products can be extremely sticky and hard to remove from the reaction environment. In this regard, suitable technologies must be implemented for the isolation of sticky products from the vessels or from the screws and a well-defined rheology study is needed before reaction scale-up. Additionally, the use of LAG can provide significantly better results for product isolation from the vessel after reaction by providing a lubricating effect.

In addition to all the challenges, large-scale mechanochemical reactions can benefit from certain aspects of reactivity compared to the solution-based counterparts. While the removal of solvents from reactivity and purification is a huge advantage in a mechanochemical set-up, the recovery and recyclability of valuable catalysts after the reaction remain a challenge in small-scale mechanochemical reactions which utilize minimal amount of catalyst (in cases up to 0.05 mol%). Whereas industrial scale mechanochemical reactions can be relatively better for isolation of such catalyst. Furthermore, a mechanochemical transformation occurs with the use of mechanical parts in action for the reaction which can support easier repairability compared to the solution-based reaction set-ups.

Overall, with the proper instrumentations, technological advancements and deep reactivity studies scaling-up a mechanochemical reaction is a better, greener and efficient strategies for the synthesis of fine-chemicals. Recently, chemical industries such as Merck and Novartis are interested in mechanochemical scale-up reactions and are building their foundation for it.¹²⁸ Combining the above-mentioned critical parameters with the vast array of mechanochemical organic reactions for value added chemicals, mechanochemistry has emerged as an essential for redefining the paradigm and future of organic synthesis strategies.

1.11. Mechanochemical Literature Summary for Organic Synthesis

Provided detailed literature overviews of mechanochemical reactions for organic synthesis signifies the impact of modern-day mechanochemical strategies over the known solution-based paradigm. This literature study shows that mechanochemical reactions provide far more benefits

than simple reduction of solvents for a reaction but rather many of the time promotes reactivity of compounds which are unprecedented, provide stable chemical reagents and intermediates of previously unstable reagents, redefines the energy parameters by effective energy transfers to reagent, develop proficient reactions with time efficiency and most of all huge potential, technologies and availability of mechanochemical set-ups for industrial-scale use. Overall mechanochemistry in organic synthesis has not only emerged as a greener solution-based alternative but at times proved to be the only methodology to efficiently synthesize and utilize certain molecules. Hence, it's no surprise to proclaim that slowly but efficiently mechanochemistry is redefining the frontiers of organic chemistry.

1.12. References

- (1) Mechano-chemical reaction. 5.0.0 ed.; International Union of Pure and Applied Chemistry (IUPAC), 2025.
- (2) Gomollón-Bel, F. Ten Chemical Innovations That Will Change Our World: IUPAC identifies emerging technologies in Chemistry with potential to make our planet more sustainable. *Chemistry International* **2019**, *41* (2), 12-17. DOI: doi:10.1515/ci-2019-0203 (accessed 2025-10-21).
- (3) Naumov, P.; Chizhik, S.; Panda, M. K.; Nath, N. K.; Boldyreva, E. Mechanically Responsive Molecular Crystals. *Chem. Rev.* **2015**, *115* (22), 12440-12490.
- (4) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D.; Hyett, G.; Jones, W.; et al. Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.* **2012**, *41* (1), 413-447.
- (5) Do, J. L.; Friscic, T. Mechanochemistry: A Force of Synthesis. *ACS Cent. Sci.* **2017**, *3* (1), 13-19.
- (6) Carta, M.; Sanna, A. L.; Porcheddu, A.; Garroni, S.; Delogu, F. Mechanochemical effects underlying the mechanically activated catalytic hydrogenation of carbon monoxide. *Sci. Rep.* **2023**, *13* (1), 2470.
- (7) Cuccu, F.; De Luca, L.; Delogu, F.; Colacino, E.; Solin, N.; Mocci, R.; Porcheddu, A. Mechanochemistry: New Tools to Navigate the Uncharted Territory of "Impossible" Reactions. *ChemSusChem* **2022**, *15* (17), e202200362.
- (8) Dong, L.; Li, L.; Chen, H.; Cao, Y.; Lei, H. Mechanochemistry: Fundamental Principles and Applications. *Adv. Sci.* **2025**, *12* (24), e2403949.
- (9) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press, 2000. DOI: <https://doi.org/10.1093/oso/9780198506980.001.0001>.
- (10) Ardila-Fierro, K. J.; Hernandez, J. G. Sustainability Assessment of Mechanochemistry by Using the Twelve Principles of Green Chemistry. *ChemSusChem* **2021**, *14* (10), 2145-2162.
- (11) Reynes, J. F.; Leon, F.; Garcia, F. Mechanochemistry for Organic and Inorganic Synthesis. *ACS Org. Inorg. Au* **2024**, *4* (5), 432-470.
- (12) Weber, A. L.; Pizzarello, S. The peptide-catalyzed stereospecific synthesis of tetroses: a possible model for prebiotic molecular evolution. *Proc. Natl. Acad. Sci. U S A* **2006**, *103* (34), 12713-12717.
- (13) Miller, S. L. A production of amino acids under possible primitive earth conditions. *Science* **1953**, *117* (3046), 528-529.
- (14) Glavin, D. P.; McLain, H. L.; Dworkin, J. P.; Parker, E. T.; Elsila, J. E.; Aponte, J. C.; Simkus, D. N.; Pozarycki, C. I.; Graham, H. V.; Nittler, L. R.; et al. Abundant extraterrestrial amino acids in the primitive CM carbonaceous chondrite Asuka 12236. *Meteorit. Planet. Sci.* **2020**, *55* (9), 1979-2006.
- (15) Blank, J. G.; Miller, G. H.; Ahrens, M. J.; Winans, R. E. Experimental shock chemistry of aqueous amino acid solutions and the cometary delivery of prebiotic compounds. *Orig. Life Evol. Biosph.* **2001**, *31* (1-2), 15-51.
- (16) Sugahara, H.; Mimura, K. Glycine oligomerization up to triglycine by shock experiments simulating comet impacts. *Geochim. J.* **2014**, *48*, 51-62.
- (17) Bolm, C.; Mocci, R.; Schumacher, C.; Turberg, M.; Puccetti, F.; Hernandez, J. G. Mechanochemical Activation of Iron Cyano Complexes: A Prebiotic Impact Scenario for the Synthesis of alpha-Amino Acid Derivatives. *Angew. Chem. Int. Ed.* **2018**, *57* (9), 2423-2426.
- (18) Stolar, T.; Grubescic, S.; Cindro, N.; Mestrovic, E.; Uzarevic, K.; Hernandez, J. G. Mechanochemical Prebiotic Peptide Bond Formation*. *Angew. Chem. Int. Ed.* **2021**, *60* (23), 12727-12731.
- (19) Furukawa, Y.; Chikaraishi, Y.; Ohkouchi, N.; Ogawa, N. O.; Glavin, D. P.; Dworkin, J. P.; Abe, C.; Nakamura, T. Extraterrestrial ribose and other sugars in primitive meteorites. *Proc. Natl. Acad. Sci. U S A* **2019**, *116* (49), 24440-24445.
- (20) Shapiro, R. Prebiotic ribose synthesis: a critical analysis. *Orig. Life Evol. Biosph.* **1986**, *16* (3), 283-284.
- (21) Larralde, R.; Robertson, M. P.; Miller, S. L. Rates of decomposition of ribose and other sugars: implications for chemical evolution. *Proc. Natl. Acad. Sci. U S A* **1995**, *92* (18), 8158-8160.

- (22) Haas, M.; Lamour, S.; Christ, S. B.; Trapp, O. Mineral-mediated carbohydrate synthesis by mechanical forces in a primordial geochemical setting. *Commun. Chem.* **2020**, *3* (1), 140.
- (23) Takacs, L. Quicksilver from cinnabar: The first documented mechanochemical reaction? *JOM* **2000**, *52* (1), 12-13.
- (24) Miguel, C.; Pinto, J. V.; Clarke, M.; Melo, M. J. The alchemy of red mercury sulphide: the production of vermilion for medieval art. *Dyes Pigm.* **2014**, *102*, 210-217.
- (25) Marchini, M.; Montanari, G.; Casali, L.; Martelli, M.; Raggetti, L.; Baláž, M.; Baláž, P.; Maini, L. "What makes every work perfect is cooking and grinding": the ancient roots of mechanochemistry. *RSC Mechanochem.* **2024**, *1* (1), 123-129.
- (26) Takacs, L. The historical development of mechanochemistry. *Chem. Soc. Rev.* **2013**, *42* (18), 7649-7659.
- (27) Solares-Briones, M.; Coyote-Dotor, G.; Pérez-Franco, J. C.; Zermeno-Ortega, M. R.; de la O Contreras, C. M.; Canseco-González, D.; Avila-Sorrosa, A.; Morales-Morales, D.; Germán-Acacio, J. M. Mechanochemistry: A green approach in the preparation of pharmaceutical cocrystals. *Pharmaceutics* **2021**, *13* (6), 790.
- (28) Effaty, F.; Ottenwaelder, X.; Friščić, T. Mechanochemistry in transition metal-catalyzed reactions. *Curr. Opin. Green Sustain. Chem.* **2021**, *32*, 100524.
- (29) Porcheddu, A.; Colacino, E.; De Luca, L.; Delogu, F. Metal-mediated and metal-catalyzed reactions under mechanochemical conditions. *ACS Catal.* **2020**, *10* (15), 8344-8394.
- (30) Peters, D. W.; Blair, R. G. Mechanochemical synthesis of an organometallic compound: a high volume manufacturing method. *Faraday Discuss.* **2014**, *170*, 83-91.
- (31) Mele, F.; Constantin, A. M.; Porcheddu, A.; Maggi, R.; Maestri, G.; Della Ca, N.; Capaldo, L. Photomechanochemistry: harnessing mechanical forces to enhance photochemical reactions. *Beilstein J. Org. Chem.* **2025**, *21* (1), 458-472.
- (32) Zhou, J.; Hsu, T. G.; Wang, J. Mechanochemical degradation and recycling of synthetic polymers. *Angew. Chem. Int. Ed.* **2023**, *62* (27), e202300768.
- (33) He, P.; Hu, Z.; Dai, Z.; Bai, H.; Fan, Z.; Niu, R.; Gong, J.; Zhao, Q.; Tang, T. Mechanochemistry milling of waste poly (Ethylene terephthalate) into metal-organic frameworks. *ChemSusChem* **2023**, *16* (2), e202201935.
- (34) Hernández, J. G.; Ardila-Fierro, K. J.; Crawford, D.; James, S. L.; Bolm, C. Mechanoenzymatic peptide and amide bond formation. *Green Chem.* **2017**, *19* (11), 2620-2625.
- (35) Hollenbach, R.; Ochsenreither, K. Mechanoenzymatic reactions—challenges and perspectives. *ChemCatChem* **2023**, *15* (21), e202300656.
- (36) Tan, D.; Garcia, F. Main group mechanochemistry: from curiosity to established protocols. *Chem. Soc. Rev.* **2019**, *48* (8), 2274-2292.
- (37) Rachitha, S.; Yadav, A. K.; Kamali, M.; Sudarsanam, P.; Dutta, S. Mechanochemical synthesis of Knoevenagel condensation products from biorenewable furaldehydes using crustacean waste-derived chitosan as a sustainable organocatalyst. *RSC Adv.* **2025**, *15* (25), 19687-19695.
- (38) Andersen, J.; Mack, J. Mechanochemistry and organic synthesis: from mystical to practical. *Green Chem.* **2018**, *20* (7), 1435-1443.
- (39) Howard, J. L.; Cao, Q.; Browne, D. L. Mechanochemistry as an emerging tool for molecular synthesis: what can it offer? *Chem. Sci.* **2018**, *9* (12), 3080-3094.
- (40) Burmeister, C. F.; Kwade, A. Process engineering with planetary ball mills. *Chem. Soc. Rev.* **2013**, *42* (18), 7660-7667.
- (41) Bolt, R. R.; Leitch, J. A.; Jones, A. C.; Nicholson, W. I.; Browne, D. L. Continuous flow mechanochemistry: reactive extrusion as an enabling technology in organic synthesis. *Chem. Soc. Rev.* **2022**, *51* (11), 4243-4260.
- (42) Crawford, D. E.; Miskimmin, C. K.; Albadarin, A. B.; Walker, G.; James, S. L. Organic synthesis by Twin Screw Extrusion (TSE): continuous, scalable and solvent-free. *Green Chem.* **2017**, *19* (6), 1507-1518.
- (43) Crawford, D.; Casaban, J.; Haydon, R.; Giri, N.; McNally, T.; James, S. L. Synthesis by extrusion: continuous, large-scale preparation of MOFs using little or no solvent. *Chem. Sci.* **2015**, *6* (3), 1645-1649.

- (44) Basoccu, F.; Caboni, P.; Porcheddu, A. Mechanochemistry: Unravelling the impact of metal leaching in organic synthesis. *ChemSusChem* **2025**, *18* (10), e202402547.
- (45) Hope, K. S.; Ward, D.; Lloyd, H. J.; Hunter, S.; Bull, C. L.; Pulham, C. R. Putting the squeeze on energetic co-crystals: High-Pressure studies of 2 (CL-20): HMX and NQ: DNP. In *19th Seminar on New Trends in Research of Energetic Materials, Pardubice, Czech Republic*, 2016; pp 20-22.
- (46) Michalchuk, A. A.; Hope, K. S.; Kennedy, S. R.; Blanco, M. V.; Boldyreva, E. V.; Pulham, C. R. Ball-free mechanochemistry: in situ real-time monitoring of pharmaceutical co-crystal formation by resonant acoustic mixing. *Chem. Commun.* **2018**, *54* (32), 4033-4036.
- (47) Gonnet, L.; Borchers, T. H.; Lennox, C. B.; Vainauskas, J.; Teoh, Y.; Titi, H. M.; Barrett, C. J.; Koenig, S. G.; Nagapudi, K.; Frišić, T. The “ η -sweet-spot” (η max) in liquid-assisted mechanochemistry: polymorph control and the role of a liquid additive as either a catalyst or an inhibitor in resonant acoustic mixing (RAM). *Faraday Discuss.* **2023**, *241*, 128-149.
- (48) Titi, H. M.; Do, J.-L.; Howarth, A. J.; Nagapudi, K.; Frišić, T. Simple, scalable mechanosynthesis of metal–organic frameworks using liquid-assisted resonant acoustic mixing (LA-RAM). *Chem. Sci.* **2020**, *11* (29), 7578-7584.
- (49) Andersen, J.; Mack, J. Insights into Mechanochemical Reactions at Targetable and Stable, Sub-ambient Temperatures. *Angew. Chem. Int. Ed.* **2018**, *57* (40), 13062-13065.
- (50) Seo, T. Mechanochemistry-directed ligand design: Development of a high-performance phosphine ligand for palladium-catalyzed mechanochemical organoboron cross-coupling. In *Palladium-Catalyzed Mechanochemical Cross-Coupling Reactions*, Springer, 2024; pp 161-210.
- (51) Fischer, F.; Fendel, N.; Greiser, S.; Rademann, K.; Emmerling, F. Impact Is Important □ Systematic Investigation of the Influence of Milling Balls in Mechanochemical Reactions. *Org. Process Res. Dev.* **2017**, *21* (4), 655-659.
- (52) Lapshin, O.; Boldyreva, E.; Boldyrev, V. Role of mixing and milling in mechanochemical synthesis. *Russ. J. Inorg. Chem.* **2021**, *66* (3), 433-453.
- (53) Julien, P. A.; Malvestiti, I.; Frišić, T. The effect of milling frequency on a mechanochemical organic reaction monitored by in situ Raman spectroscopy. *Beilstein J. Org. Chem.* **2017**, *13* (1), 2160-2168.
- (54) Ying, P.; Yu, J.; Su, W. Liquid-assisted grinding mechanochemistry in the synthesis of pharmaceuticals. *Adv. Synth. Catal.* **2021**, *363* (5), 1246-1271.
- (55) Frišić, T. New opportunities for materials synthesis using mechanochemistry. *Journal of Materials Chemistry* **2010**, *20* (36), 7599-7605.
- (56) Hutchings, B. P.; Crawford, D. E.; Gao, L.; Hu, P.; James, S. L. Feedback Kinetics in Mechanochemistry: The Importance of Cohesive States. *Angew. Chem. Int. Ed.* **2017**, *56* (48), 15252-15256.
- (57) Do, J.-L.; Mottillo, C.; Tan, D.; Strukil, V.; Friscic, T. Mechanochemical ruthenium-catalyzed olefin metathesis. *J. Am. Chem. Soc.* **2015**, *137* (7), 2476-2479.
- (58) Bowden, F.; Yoffe, A. Fast reactions in solids, Butterworths Scientific Publications. **1958**.
- (59) Delogu, F.; Cocco, G. Weakness of the “hot spots” approach to the kinetics of mechanically induced phase transformations. *J. Alloys Compd.* **2008**, *465* (1-2), 540-546.
- (60) Butyagin, P. Y. Kinetics and nature of mechanochemical reactions. *Russ. Chem. Rev.* **1971**, *40* (11), 901.
- (61) Boldyreva, E. Mechanochemistry of inorganic and organic systems: what is similar, what is different? *Chem. Soc. Rev.* **2013**, *42* (18), 7719-7738.
- (62) Kuhn, T. S.; Hacking, I. *The structure of scientific revolutions*; University of Chicago press Chicago, 1970.
- (63) Policar, C. Bioinorganic chemistry: where from and where to? *J. Biol. Inorg. Chem.* **2025**, 1-16.
- (64) Berzelius, J. Lehrbuch der Chemie (Wöhler’s translation of Lärbok i Kemien). *Arnoldischen Buchhandlung, Dresden* **1827**, *3*, 136-139.
- (65) Wöhler, F. Ueber künstliche bildung des harnstoffs. *Annalen der Physik* **1828**, *88* (2), 253-256.
- (66) Kolbe, H. Beiträge zur Kenntniss der gepaarten Verbindungen. *Justus Liebigs Annalen der Chemie* **1845**, *54* (2), 145-188.

- (67) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Recent advances in the transition metal-catalyzed twofold oxidative C–H bond activation strategy for C–C and C–N bond formation. *Chem. Soc. Rev.* **2011**, *40* (10), 5068–5083.
- (68) Kubota, K.; Takahashi, R.; Ito, H. Mechanochemistry allows carrying out sensitive organometallic reactions in air: glove-box-and-Schlenk-line-free synthesis of oxidative addition complexes from aryl halides and palladium (0). *Chem. Sci.* **2019**, *10* (22), 5837–5842.
- (69) Porcheddu, A.; Colacino, E.; De Luca, L.; Delogu, F. Metal-Mediated and Metal-Catalyzed Reactions Under Mechanochemical Conditions Click to copy article link. *ACS Catal.* **2020**, *10* (15), 8344–8394.
- (70) Abera Tsedalu, A. A review on olefin metathesis reactions as a green method for the synthesis of organic compounds. *J. Chem.* **2021**, *2021* (1), 3590613.
- (71) Grubbs, R. H.; Miller, S. J.; Fu, G. C. Ring-closing metathesis and related processes in organic synthesis. *Acc. Chem. Res.* **1995**, *28* (11), 446–452.
- (72) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. A Series of Well-Defined Metathesis Catalysts—Synthesis of [RuCl₂(η -CHR')(PR₃)₂] and Its Reactions. *Angew. Chem. Int. Ed.* **1995**, *34* (18), 2039–2041.
- (73) Schrock, R. R. Olefin metathesis by molybdenum imido alkylidene catalysts. *Tetrahedron* **1999**, *55* (27), 8141–8153.
- (74) Mukherjee, N.; Marczyk, A.; Szczepaniak, G.; Sytniczuk, A.; Kajetanowicz, A.; Grela, K. A gentler touch: synthesis of modern ruthenium olefin metathesis catalysts sustained by mechanical force. *ChemCatChem* **2019**, *11* (21), 5362–5369.
- (75) Negishi, E.-i.; De Meijere, A. *Handbook of organopalladium chemistry for organic synthesis*; John Wiley & Sons, 2003.
- (76) Joshi-Pangu, A.; Ganesh, M.; Biscoe, M. R. Nickel-catalyzed Negishi cross-coupling reactions of secondary alkylzinc halides and aryl iodides. *Org. Lett.* **2011**, *13* (5), 1218–1221.
- (77) Wunderlich, S. H.; Knochel, P. (tmp) 2Zn· 2 MgCl₂· 2 LiCl: A Chemoselective Base for the Directed Zincation of Sensitive Arenes and Heteroarenes. *Angew. Chem. Int. Ed.* **2007**, *46* (40), 7685–7688.
- (78) Cao, Q.; Howard, J. L.; Wheatley, E.; Browne, D. L. Mechanochemical Activation of Zinc and Application to Negishi Cross-Coupling. *Angew. Chem. Int. Ed.* **2018**, *57* (35), 11339–11343.
- (79) Čarný, T.; Peňáška, T.; Andrejčák, S.; Šebesta, R. Mechanochemical Pd-Catalyzed Cross-Coupling of Arylhalides and Organozinc Pivalates. *Chem. Eur. J.* **2022**, *28* (58), e202202040.
- (80) Mizoroki, T.; Mori, K.; Ozaki, A. Arylation of olefin with aryl iodide catalyzed by palladium. *Bull. Chem. Soc. Jpn.* **1971**, *44* (2), 581–581.
- (81) Heck, R. F.; Nolley Jr, J. Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *J. Org. Chem.* **1972**, *37* (14), 2320–2322.
- (82) Jeffery, T. On the efficiency of tetraalkylammonium salts in Heck type reactions. *Tetrahedron* **1996**, *52* (30), 10113–10130.
- (83) Tullberg, E.; Peters, D.; Frejd, T. The Heck reaction under ball-milling conditions. *J. Organomet. Chem.* **2004**, *689* (23), 3778–3781.
- (84) Declerck, V.; Colacino, E.; Bantreil, X.; Martinez, J.; Lamaty, F. Poly (ethylene glycol) as reaction medium for mild Mizoroki–Heck reaction in a ball-mill. *Chem. Commun.* **2012**, *48* (96), 11778–11780.
- (85) Miyaura, N.; Yamada, K.; Suzuki, A. A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Lett.* **1979**, *20* (36), 3437–3440.
- (86) Cravotto, G.; Garella, D.; Tagliapietra, S.; Stolle, A.; Schüßler, S.; Leonhardt, S. E.; Ondruschka, B. Suzuki cross-couplings of (hetero) aryl chlorides in the solid-state. *New J. Chem.* **2012**, *36* (6), 1304–1307.
- (87) Seo, T.; Ishiyama, T.; Kubota, K.; Ito, H. Solid-state Suzuki–Miyaura cross-coupling reactions: olefin-accelerated C–C coupling using mechanochemistry. *Chem. Sci.* **2019**, *10* (35), 8202–8210.
- (88) Reynes, J. F.; García, F. Temperature-Controlled Mechanochemistry Unlocks the Nickel-Catalyzed Suzuki–Miyaura-Type Coupling of Aryl Sulfamates at Different Scales. *Angew. Chem. Int. Ed.* **2023**, *62* (2), e202215094.

- (89) Kerru, N.; Gummidi, L.; Maddila, S.; Gangu, K. K.; Jonnalagadda, S. B. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. *Molecules* **2020**, *25* (8), 1909.
- (90) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274.
- (91) Bishop-Freeman, S. C.; Shonsey, E. M.; Friederich, L. W.; Beuhler, M. C.; Winecker, R. E. Benzonatate Toxicity: Nothing to Cough At. *J. Anal. Toxicol.* **2017**, *41* (5), 461–463.
- (92) Inbaraj, J. J.; Bilski, P.; Chignell, C. F. Photophysical and photochemical studies of 2-phenylbenzimidazole and UVB sunscreen 2-phenylbenzimidazole-5-sulfonic acid. *Photochem. Photobiol.* **2002**, *75* (2), 107–116.
- (93) Syed, Y. Y. Sumatriptan/Naproxen Sodium: A Review in Migraine. *Drugs* **2016**, *76* (1), 111–121.
- (94) Hartwig, J. F. Transition metal catalyzed synthesis of arylamines and aryl ethers from aryl halides and triflates: Scope and mechanism. *Angew. Chem. Int. Ed.* **1998**, *37* (15), 2046–2067.
- (95) Yang, B. H.; Buchwald, S. L. Palladium-catalyzed amination of aryl halides and sulfonates. *J. Organomet. Chem.* **1999**, *576* (1–2), 125–146.
- (96) Kubota, K.; Seo, T.; Koide, K.; Hasegawa, Y.; Ito, H. Olefin-accelerated solid-state C–N cross-coupling reactions using mechanochemistry. *Nat. Commun.* **2019**, *10* (1), 111.
- (97) Kubota, K.; Takahashi, M.; Puccetti, F.; Ito, H. Mechanochemical Buchwald–Hartwig Cross-Coupling Reactions of Aromatic Primary Amines and Their Application to Two-Step One-Pot Rapid Synthesis of Unsymmetrical Triarylamines. *Org. Lett.* **2025**.
- (98) Hwang, S.; Gratz, S.; Borchardt, L. A guide to direct mechanocatalysis. *Chem. Commun.* **2022**, *58* (11), 1661–1671.
- (99) Fulmer, D. A.; Shearouse, W. C.; Medonza, S. T.; Mack, J. Solvent-free Sonogashira coupling reaction via high speed ball milling. *Green Chem.* **2009**, *11* (11), 1821–1825.
- (100) Pickhardt, W.; Siegfried, E.; Fabig, S.; Rappen, M. F.; Etter, M.; Wohlgemuth, M.; Gratz, S.; Borchardt, L. The Sonogashira Coupling on Palladium Milling Balls-A new Reaction Pathway in Mechanochemistry. *Angew. Chem. Int. Ed.* **2023**, *62* (27), e202301490.
- (101) Wohlgemuth, M.; Schmidt, S.; Mayer, M.; Pickhardt, W.; Graetz, S.; Borchardt, L. Solid-State Oxidation of Alcohols in Gold-Coated Milling Vessels via Direct Mechanocatalysis. *Angew. Chem. Int. Ed.* **2024**, *63* (33), e202405342.
- (102) Mayer, M.; Wohlgemuth, M.; Salome Straub, A.; Gratz, S.; Borchardt, L. Hydrogenation of Organic Molecules via Direct Mechanocatalysis. *Angew. Chem. Int. Ed.* **2025**, e202424139.
- (103) Chantrain, V.; Rensch, T.; Pickhardt, W.; Gratz, S.; Borchardt, L. Continuous Direct Mechanocatalytic Suzuki-Miyaura Coupling via Twin-Screw Extrusion. *Chem. Eur. J.* **2024**, *30* (17), e202304060.
- (104) Grignard, V. Alkyl halides & aryl halides. *Synthesis* **1900**, *130*, 1322.
- (105) Harrowfield, J. M.; Hart, R. J.; Whitaker, C. R. Magnesium and aromatics: mechanically-induced Grignard and McMurry reactions. *Aust. J. Chem.* **2001**, *54* (7), 423–125.
- (106) Takahashi, R.; Hu, A.; Gao, P.; Gao, Y.; Pang, Y.; Seo, T.; Jiang, J.; Maeda, S.; Takaya, H.; Kubota, K.; et al. Mechanochemical synthesis of magnesium-based carbon nucleophiles in air and their use in organic synthesis. *Nat. Commun.* **2021**, *12*, 6691.
- (107) Pfennig, V. S.; Vilella, R. C.; Nikodemus, J.; Bolm, C. Mechanochemical Grignard Reactions with Gaseous CO₂ and Sodium Methyl Carbonate. *Angew. Chem. Int. Ed.* **2022**, *61* (9), e202116514.
- (108) Gao, P.; Jiang, J.; Maeda, S.; Kubota, K.; Ito, H. Mechanochemically Generated Calcium-Based Heavy Grignard Reagents and Their Application to Carbon–Carbon Bond-Forming Reactions. *Angew. Chem. Int. Ed.* **2022**, *61* (41), e202207118.
- (109) Birch, A. J. The Birch reduction in organic synthesis. *Pure Appl. Chem.* **1996**, *68* (3), 553–556.
- (110) Gao, Y.; Kubota, K.; Ito, H. Mechanochemical Approach for Air-Tolerant and Extremely Fast Lithium-Based Birch Reductions in Minutes. *Angew. Chem. Int. Ed.* **2023**, *62* (21), e202217723.

- (111) Kondo, K.; Kubota, K.; Ito, H. Mechanochemistry enabling highly efficient Birch reduction using sodium lumps and d-(+)-glucose. *Chem. Sci.* **2024**, *15* (12), 4452-4457.
- (112) Nallaparaju, J. V.; Satsi, R.; Merzhyevskiy, D.; Jarg, T.; Aav, R.; Kananovich, D. G. Mechanochemical Birch Reduction with Low Reactive Alkaline Earth Metals. *Angew. Chem. Int. Ed.* **2024**, *63* (20), e202319449.
- (113) Toyama, Y.; Yagi, A.; Itami, K.; Ito, H. Birch reductive arylation by mechanochemical anionic activation of polycyclic aromatic compounds. *Nat. Commun.* **2025**, *16* (1), 5044.
- (114) Mohapatra, H.; Kleiman, M.; Esser-Kahn, A. P. Mechanically controlled radical polymerization initiated by ultrasound. *Nat. Chem.* **2017**, *9* (2), 135-139.
- (115) Matyjaszewski, K. Atom transfer radical polymerization (ATRP): current status and future perspectives. *Macromolecules* **2012**, *45* (10), 4015-4039.
- (116) Kubota, K.; Pang, Y.; Miura, A.; Ito, H. Redox reactions of small organic molecules using ball milling and piezoelectric materials. *Science* **2019**, *366* (6472), 1500-1504.
- (117) Jana, K.; Kubota, K.; Ito, H. A mechanochemical [2+ 2+ 2] cycloaddition facilitated by a cobalt (ii) catalyst and piezoelectric materials. *Chem. Sci.* **2025**.
- (118) Seo, T. Dual nickel (II)/mechanoredox catalysis: mechanical-force-driven aryl-amination reactions using ball milling and piezoelectric materials. In *Palladium-Catalyzed Mechanochemical Cross-Coupling Reactions*, Springer, 2024; pp 243-278.
- (119) Pang, Y.; Lee, J. W.; Kubota, K.; Ito, H. Solid-state radical C–H trifluoromethylation reactions using ball milling and piezoelectric materials. *Angew. Chem. Int. Ed.* **2020**, *59* (50), 22570-22576.
- (120) Schumacher, C.; Hernández, J. G.; Bolm, C. Electro-mechanochemical atom transfer radical cyclizations using piezoelectric BaTiO₃. *Angew. Chem. Int. Ed.* **2020**, *59* (38), 16357-16360.
- (121) Wang, X.; Zhang, X.; Xue, L.; Wang, Q.; You, F.; Dai, L.; Wu, J.; Kramer, S.; Lian, Z. Mechanochemical Synthesis of Aryl Fluorides by Using Ball Milling and a Piezoelectric Material as the Redox Catalyst. *Angew. Chem. Int. Ed.* **2023**, *62* (39), e202307054.
- (122) Zhang, J.; Zhang, Y.; Liu, T.; Fu, B.; Zhang, W.; Du, B. Mechanochemical Nickel-Catalyzed Dechlorination-Deuteration of Aryl Chlorides via Piezoelectric-Promoted Ar–Zn–X Intermediates. *ACS Catal.* **2025**, *15* (17), 14794-14804.
- (123) Obst, M.; König, B. Solvent-free, visible-light photocatalytic alcohol oxidations applying an organic photocatalyst. *Beilstein J. Org. Chem.* **2016**, *12* (1), 2358-2363.
- (124) Baier, D. M.; Spula, C.; Fanenstich, S.; Grätz, S.; Borchardt, L. The regioselective solid-state photo-mechanochemical synthesis of nanographenes with UV light. *Angew. Chem. Int. Ed.* **2023**, *62* (20), e202218719.
- (125) Kong, D.; Yi, L.; Nanni, A.; Rueping, M. A scalable photo-mechanochemical platform for sustainable photoredox catalysis by resonant acoustic mixing. *Nat. Commun.* **2025**, *16* (1), 3983.
- (126) Ghosh, I.; Shlapakov, N.; Karl, T. A.; Düker, J.; Nikitin, M.; Burykina, J. V.; Ananikov, V. P.; König, B. General cross-coupling reactions with adaptive dynamic homogeneous catalysis. *Nature* **2023**, *619* (7968), 87-93.
- (127) Fernandez-Bertran, J. F. Mechanochemistry: an overview. *Pure Appl. Chem.* **1999**, *71* (4), 581-586.
- (128) de la Torre, J. J. S.; Flamarique, L.; Gomollon-Bel, F.; Colacino, E. Mechanochemistry in Europe: where we come from and where we are now. *Open Research Europe* **2025**, *5*, 73.

CHAPTER 2

Mechanochemistry: Redefining the Paradigm of Organic Chemistry

2.1 Aim of the Thesis

This thesis aims to critically study and demonstrate the role of mechanochemistry for the frontiers of organic synthesis and emphasize how mechanochemistry is redefining the paradigm of organic synthesis by posing as a sustainable, efficient and versatile technology over the traditional solution-based chemistry. Through the systematic investigation of mechanochemical influences upon certain organic reactions, this work seeks to:

- I. Emphasize the critical importance of mechanochemistry to develop solvent-minimized approaches to classic organic synthesis methodologies.
- II. Explore and access the scope and limitations of substrates for a mechanochemical transformation.
- III. Activate organic materials with mechanochemical milling to be utilized for organic transformations.
- IV. Develop suitable mechanocatalytic pathways for green and sustainable synthesis of value-added products.
- V. Establish mechanistic understandings with innovative mechanochemical kinetic isotope effect and Hammett analysis.

CHAPTER 3

Mechanochemistry Unveiling Reactivity of Bertagnini's Salts

3.1. Carbonyl Center: The Backbone of Organic Synthesis

The application of aldehydes and ketones is of unequivocal paramount importance in organic synthesis. Their versatility extends across a broad spectrum¹, encompassing straightforward and intricate reactions, rendering them exceptionally adaptable tools for shaping molecular structures.² For instance, aldehydes and ketones' reactivity seamlessly fits into iminium³ and enamine⁴ catalysis, leading to the stereoselective assembly of molecular frameworks that otherwise might be inaccessible. The vital importance of these compounds is even more prominent for synthesis of nitrogen-based heterocycles^{5, 6} and amines; classes of compounds having prominent use in pharmaceutical, agricultural and food industries as both synthons and final products. These specific facets establish these compounds at the core of organic and pharmaceutical synthetic routes, where their versatile reactivity fosters the evolution of innovative and consolidated methodologies. Overall, aldehydes and ketones are the bedrock for formulating diverse reaction strategies and are essential for the ongoing progress in organic synthesis.

Even though carbonyl compounds have exceptional synergy for chemical transformations, their utilization comes with many challenges. One significant issue is that aldehydes are prone to spontaneous aerobic oxidation when repeatedly exposed to air, not to mention the self-condensation reactions of aldehydes and ketones. Moreover, low molecular weight aldehydes, being volatile, represent a substantial safety hazard for operators. As a result, addressing this issue requires taking additional measures, such as workup procedures or, in some instances, distillation, which significantly wastes time, energy, and chemicals.

3.2. Bertagnini's Salts

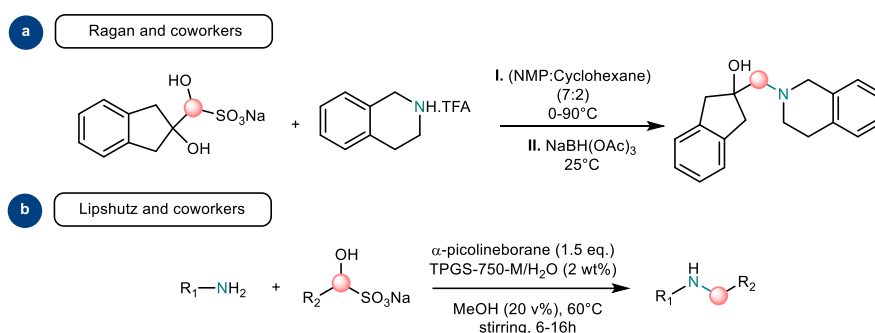
Bertagnini's salts also known as aldehyde-bisulfite adducts is a reaction between aldehyde and bisulfite salts, first discovered in early 1800s by Italian chemist Cesare Bertagnini. These salts were primarily used to isolate aldehydes from reaction mixtures as a purification technique.⁷ Although they were eventually phased out, they have recently regained interest as a solid surrogate to aldehydes in specific organic reactions. Bertagnini's salts^{8, 9} exhibit a reactivity comparable to aldehydes but are more stable against moisture and air exposure over long periods. Furthermore, these salts phase-out the problems associated with aldehydes like volatility, self-condensation affinity and possible aerial oxidation probability making them suitable for subsequent use in organic synthesis. It's worth noting that Bertagnini's salts, like many chemical compounds, can be challenging to dissolve in environmentally friendly solvents commonly used in modern applications. Consequently, using bisulfite adducts may necessitate increased solvent volumes, extended reaction times, and higher temperatures to enhance reaction outcomes.¹⁰⁻¹²

3.3. Reactivity Employing Bertagnini's Salts

The reactivity studies on the utilization of Bertagnini's salts is scarce in literature because aldehydes from these salts can only be abstracted after treatment with aqueous acid or base, conditions which

are not well tolerated by certain aldehydes or other functional groups present in it. This section briefly discusses the reactivity studies of Bertagnini's salts across literature.

One of the forefront studies on use of Bertagnini's salts was proposed by Ragan and coworkers in 2003. This research was on the synthesis and utilization of Bertagnini's salt of 2-Hydroxyindan-2-carboxaldehyde for reductive amination reaction (Scheme 3.1.a).¹³ The use of aldehydes rather than Bertagnini's salts although being suitable for laboratory scale, hampers tremendously in industrial scale reactions due to the constant challenge of aldehydes undergoing oligomerization thus providing an uncharacterized mixture of reactants. To establish a standard protocol for the reaction, Ragan and coworkers dissolved Bertagnini's salt of 2-Hydroxyindan-2-carboxaldehyde and trifluoro acetic acid salt of amine with a mixture of N-methylpyrrolidinone (NMP) and cyclohexane. After the reaction, the iminium salt was isolated and after reduction with $\text{NaBH}(\text{OAc})_3$ provided reductive amination product. However, the removal of cyclohexane and water from the reaction mixture was performed using azeotropic distillation (105°C). Later, Mani and coworkers reported reductive amination protocol using Bertagnini's salt for reactive aldehyde species using similar protocol except for the use of DCE as a solvent.¹⁴ Similarly, Lipshutz and co-workers (2021) developed a one-pot reductive amination strategy using Bertagnini's salts in water.¹⁰ Most notably, this protocol provided better reactivity than a plethora of reductive amination protocols using aldehydes (Scheme 3.1.b).

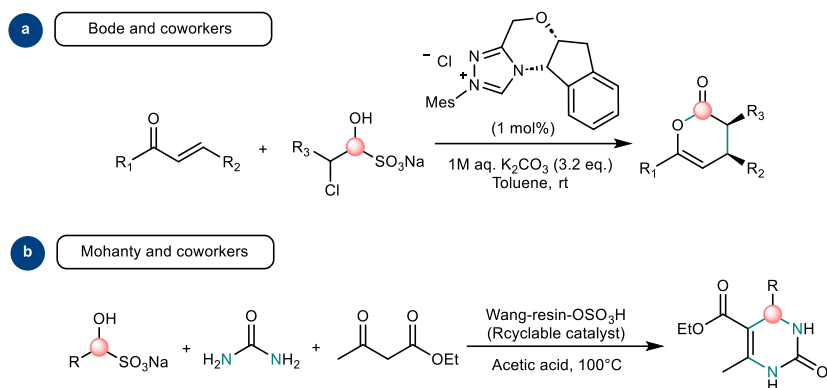


Scheme 3.1. Bertagnini's salts in reductive amination reactions

Enantioselective hetero-Diels-Alder reactions are essential for the construction of chiral heterocycles. In this context, Bode and coworkers utilized Bertagnini's salts of α -chloroaldehydes along with oxo-dienes to form chiral-NHC catalyzed enantioselective hetero-Diels-Alder products.⁸ α -chloroaldehydes are generally air and moisture sensitive and often unsafe to purify. In this regard, Bertagnini's salt of α -chloroaldehydes provide a safe, convenient and stable alternative for reactions. Most notably, Bertagnini's salt formation helped them to obtain Diels-Alder products with exceptional functional group tolerance and yields (Scheme 3.2.a). Later, Mohanty and coworkers developed an efficient synthetic route for 3,4-dihydro-2(1H)-pyrimidinones using Bertagnini's salts, urea and diones catalyzed by Wang-resin supported sulfonic acid catalyst in Acetic acid. Most notable feature of the reaction is that the sulfonic acid catalyst can be recovered and utilized multiple times for the reaction (Scheme 3.2.b).¹⁵

Although provided these limited applications in literature, Bertagnini's salts are utilized as aldehyde surrogates along with the combination of highly polar solvents which are difficult to

remove from the reaction mixture resulting in excessive energy utilization and waste generation. Recent literatures regarding utilization of Bertagnini's salts suffers from similar limitations. Thus, a more practical approach for utilization of Bertagnini's salts is needed.



Scheme 3.2. Bertagnini's salts in heterocycle synthesis reactions

3.4. Bertagnini's Salts and Mechanochemistry

Bertagnini's salts, like many chemical compounds, can be challenging to dissolve in environmentally friendly solvents commonly used in modern applications. Consequently, using bisulfite adducts may necessitate increased solvent volumes, extended reaction times, and higher temperatures to enhance the overall outcomes. In this regard, mechanochemistry¹⁶⁻¹⁹ has emerged as an efficient^{20, 21} and environmentally friendly technique²²⁻²⁵ for synthesizing valuable compounds in solid state²⁶⁻³³, entirely devoid of the need for solvents^{34, 35}. This makes it an ideal choice for both academic and industrial applications of Bertagnini's salts.³⁶⁻³⁸ This chapter discusses about the development of mechanochemical protocols for synthesis of key N-heterocycles such as benzimidazoles³⁹⁻⁴⁶, perimidines and dihydro-perimidines. Additionally, reductive amination and hydrazone synthesis under solid conditions will be discussed in the later part of the chapter.

3.5. Results and Discussions

3.5.1. Synthesis of Bertagnini's Salts

Initially, a class of Bertagnini's salts of different aldehydes were synthesized from different aldehydes. The thermal properties of Bertagnini's salts were examined before their reactivity in mechanochemistry was explored. The main aim of this preliminary investigation is to determine whether the milling process could cause the melting of Bertagnini's salts, thereby creating a molten phase that might enhance the interaction between the chemical species. Thermogravimetric analyses (TGA) of selected Bertagnini's salts were performed. It was found that the decomposition temperature for Bertagnini's salts were considerably higher than the 100–120 °C range, indicating that Bertagnini's salts remain solids throughout the mechanochemical reaction (Figure 3.1). Once this had been established, attention was directed towards mechanochemical synthesis using Bertagnini's salts.

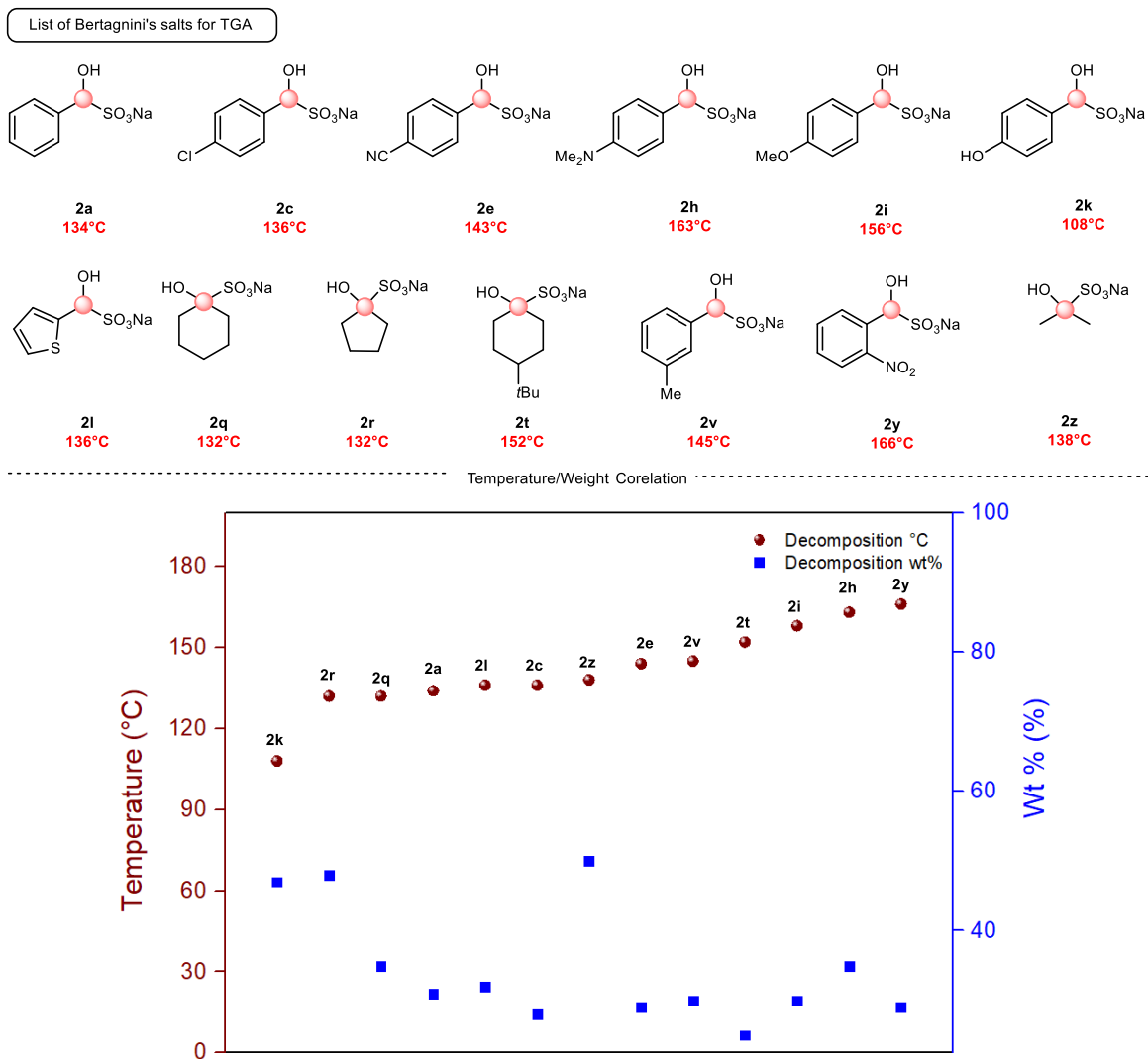
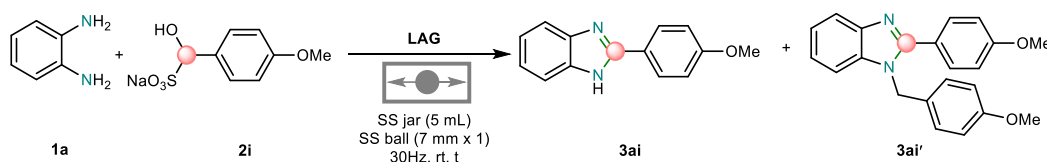


Figure 3.1. TGA analysis of Bertagnini's salts and their temperature/weight correlation

3.5.2. Mechanochemical Benzimidazoles from Bertagnini's Salts

To establish a successful mechanochemical benzimidazole synthesis protocol from Bertagnini's salts, first a 5mL stainless steel jar (SS) was charged with o-phenylenediamine (**1a**, 1 mmol), sodium hydroxy(4-methoxyphenyl)methanesulfonate (**2i**, 1.1 mmol), a LAG of methanol (80 μ L) along with a SS ball (7 mm) and milled at 30 Hz for 30 minutes using a MM-500 mixer mill. After milling, the reaction provided successful yield of desired product **3ai** (41%) along with small amount of side product **3ai'** (4%) (Table 3.1, entry 1). Increasing the reaction time to 60 minutes resulted in increase in the yield of **3ai** to 62% (Table 3.1, entry 2). Whereas best results were found when the reaction was milled for 90 minutes affording 70% isolated product of **3ai** (Table 3.1, entry 3).

Table 3.1. Screening for mechanochemical benzimidazole synthesis

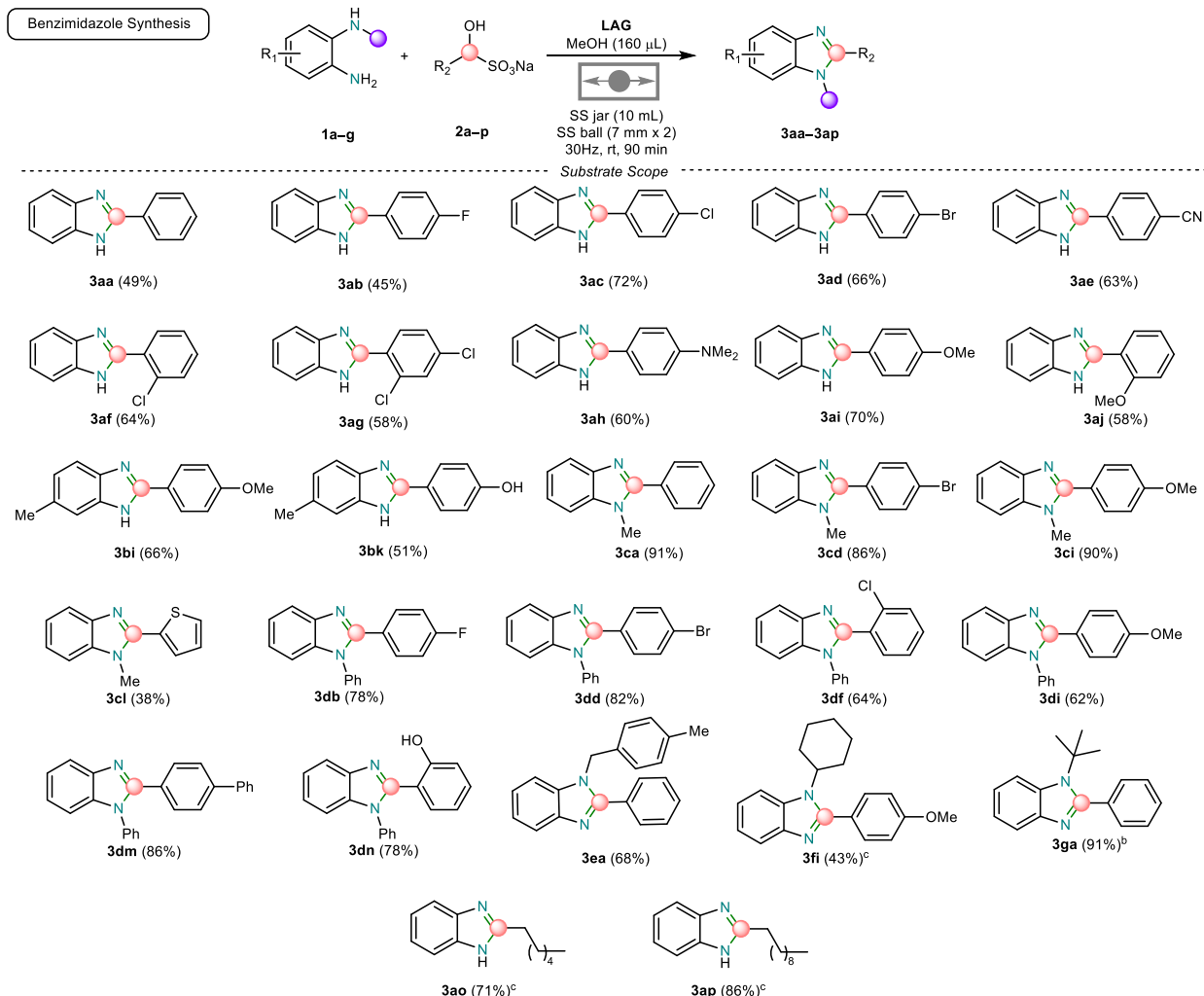
Entry	2i (eq.)	LAG (η factor)	Time (min)	Isolated Yield of 3ai (%) ^a
1	1.1	MeOH (0.4)	30	41% (3ai' : 4%) ^b
2	1.1	MeOH (0.4)	60	62% (3ai' : 5%) ^b
3	1.1	MeOH (0.4)	90	70% (3ai': 15%)^b
4	1.1	MeOH (0.4)	120	70%
5 ^c	1.1	EtOH (0.4)	90	64%
6	1.1	Acetone (0.4)	90	49%
7	1.1	<i>i</i> PrOH (0.4)	90	47%
8	2.0	MeOH (0.4)	90	69%
9 ^d	1.1	MeOH (0.4)	90	51%
10 ^e	1.1	MeOH (0.4)	90	46%
11 ^f	1.1	—	90	36%

^a Reaction Conditions: **1a** (0.50 mmol), **2i** (0.55 mmol), LAG (η = 0.4) in a 5 mL SS jar with a 7 mm SS ball milled in MM-500 Vario at 30 Hz for given time at 25°C and the yields was calculated after isolation of product; ^byields determined by ¹H NMR; ^c reaction conducted at 1 mmol scale and 70°C using a 10x4 mL SS jar with 2x7 mm SS balls milled in MM-500 Control for given time; ^d reaction performed with 1 equivalent of potassium periodide; ^e reaction performed with 1 equivalent of potassium peroxymonosulfate; ^f reaction performed without LAG

Further extension in the reaction time didn't improve the reaction outcome (Table 3.1, entry 4). When the reaction was performed at 70 °C and with a LAG of ethanol, a 64% yield of the desired product was obtained (Table 3.1, entry 5). Attempts to improve the yield of **3ai** by employing other solvents, such as acetone and *i*PrOH as LAGs, did not provide any positive results (Table 3.1, entries 6 and 7). Doubling the amount of bisulfite adduct **2i** under the standard reaction conditions also failed to provide any improvements. Contrary to general solvent-based processes⁴⁷ with aldehydes, addition of oxidants^{48, 49} failed to improve yields of **3ai** under mechanochemical conditions (Table 3.1, entries 9 and 10). Notably, in the absence of LAG, only 36% of the desired product (**3ai**) was obtained, thus confirming the essential role of a stoichiometric solvent amount in achieving efficient mechanochemical conversion (Table 3.1, entry 11). Remarkably, in ¹H NMR spectra peaks for aldehyde were not observed for mechanochemical reaction of Bertagnini's salts which is a common phenomenon under solution-based reactions of Bertagnini's salts showing the equilibrium of aldehydes with the salt.⁵⁰ In fact, it demonstrates that mechanochemical reaction of Bertagnini's salts follow different reaction dynamics.

To establish the practicability of the protocol various Bertagnini's salts were reacted with o-phenylenediamine derivatives to yield benzimidazole products. Bertagnini's salts with a halogen withdrawing group at *para*-position reacted smoothly with **1a** to provide benzimidazole products **3ab–3ad**. Bertagnini's salts with halogen substitution at different positions also reacted smoothly with **1a** to provide benzimidazole products **3af** and **3ag**. Introducing a cyano substituent at the *para* position of Bertagnini's salt resulted in a 63% yield of product **3ae**. Similarly, Bertagnini's salts

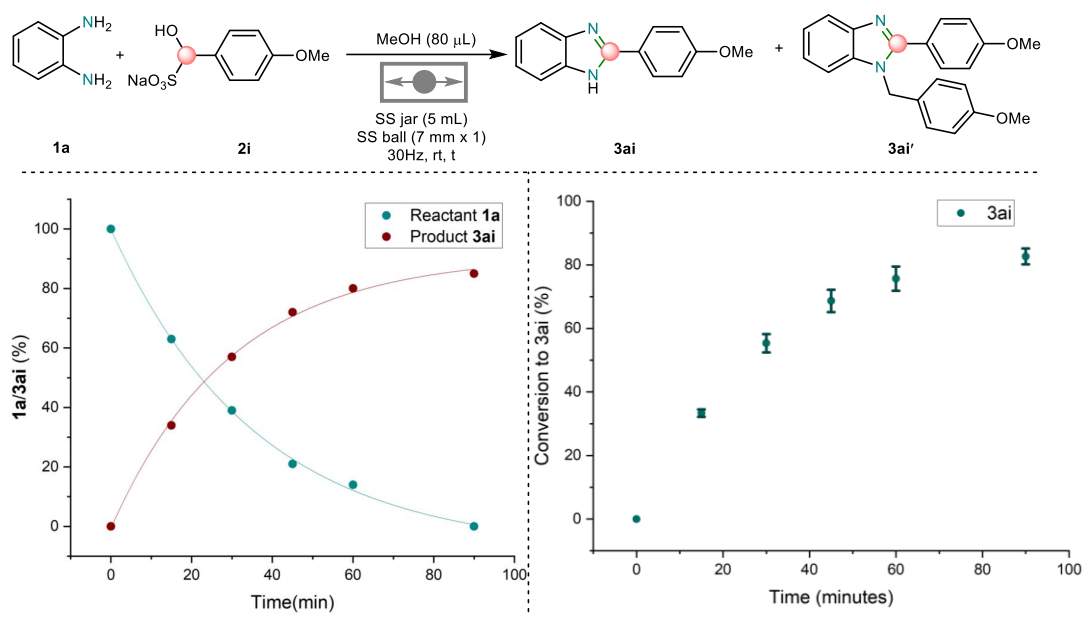
with electron donating groups reacted efficiently to provide products **3ah–3aj**. Incorporating a methyl group onto the ring of o-phenylenediamine, especially 4-methylbenzene-1,2-diamine (**1b**) reacted efficiently with Bertagnini's salts with a methoxy- and hydroxy- substituent to provide products **3bi** and **3bk** with yields of 66% and 51% respectively.



Scheme 3.3. ^a Substrate scope for benzimidazoles. Reaction conditions: **1** (1 mmol), **2** (1.1 mmol), LAG of MeOH ($\eta = 0.4$) in a 10mL SS jar with two 7 mm SS balls milled at 30 Hz in MM-500 Vario for 90 min at 25°C and yields of the products were calculated after recrystallization with EtOH; ^b reaction was milled at 30 Hz for 3h using LAG of EtOH ($\eta = 1$) at 80°C under O₂ atmosphere inside the milling jar; ^c reaction was performed at 15 Hz for 8h with LAG of MeOH ($\eta = 1$) and the yields were calculated after column chromatography

The reactivity of Bertagnini's salts with N-substituted (methyl, phenyl, 4-methylbenzyl, cyclohexyl, and tert-butyl)-phenylenediamines was further investigated (Scheme 3.3, compounds **3ca–3fi**). More favourable results were obtained with these diamine structures compared to unsubstituted o-phenylenediamines. When a thiophene-containing bisulfite adduct was reacted with N-methyl phenylenediamine (**1c**) under standard conditions, **3cl** was obtained in 38% yield. Substitution of a phenyl group on o-phenylenediamine did not hinder the synthesis of the

benzimidazole products **3db–3dn**, which were obtained in excellent to moderate yields. Incorporation of 4-methylbenzyl and cyclohexyl groups on the nitrogen of o-phenylenediamine furnished the desired products with good yields (**3ea** and **3fi**). However, insertion of a tert-butyl group on the nitrogen of o-phenylenediamine failed to deliver the cyclized product under the standard reaction conditions, affording instead the condensation product **3gi'** (Scheme 3.7.a). Notably, the target benzimidazole product **3ga** was successfully synthesized in high yield (91%) with ethanol as the Liquid-Assisted Grinding (LAG) medium ($\eta = 1.0$) at 80 °C under an O₂ atmosphere in a ball mill (30 Hz) for 3 h inside a MM-500 control mixer mill which allow the precise control over the reaction temperature.



Entry	Time (min)	Reactant (1a)	Product (3ai)	Product (3ai')
1	15 min	64%	34%	2%
2	30 min	39%	57%	4%
3	45 min	22%	72%	6%
4	60 min	15%	80%	5%
5	90 min	0%	85%	15%

Figure 3.2. Product evolution over time for mechanochemical synthesis of **3ai**. Reaction Conditions: **1a** (0.50 mmol), **2i** (0.55 mmol), LAG of MeOH ($\eta=0.4$) in a 5 mL SS jar with a 7 mm SS ball milled in MM-500 Vario for given time at 25°C and the conversion was calculated by ¹H NMR

Although extensive research has been devoted to the synthesis of 2-aryl benzimidazoles, the synthesis of 2-alkyl benzimidazoles⁵¹ under metal-free conditions at room temperature were unknown. Under the optimized conditions, the desired product could not be obtained. However, with a LAG of methanol ($\eta = 1$) combined with extended reaction time at lower milling frequency provided benzimidazole products **3ao** and **3ap** with excellent yields. The product evolution over time for product **3ai** was monitored using ¹H NMR spectroscopy to determine the viability of the protocol.

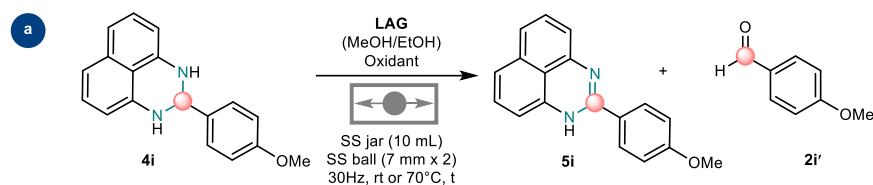
3.5.3. Mechanochemical Synthesis of Perimidines and Dihydro-Perimidines

Nitrogen-containing tricyclic heterocycles⁵², such as perimidines and 2,3-dihydro-1H-perimidines, are widely found in various natural products^{53, 54} and are known to exhibit diverse biological activities⁵⁵⁻⁵⁷, photochromic properties^{58, 59} and other distinctive features that have been exploited in different fields⁶⁰⁻⁶³. For the synthesis of these N-heterocyclic scaffolds, several traditional methods have been well documented in the literature^{64, 65}, but longer reaction times, elevated temperatures, the use of hazardous solvents, expensive reagents, and low product yields remain major drawbacks. Consequently, the development of efficient and environmentally friendly alternatives to these conventional approaches has become essential to overcome such limitations. In this context, the synthesis of 2,3-dihydro-1H-perimidines, spiro-perimidines, and perimidines from substituted bisulfite adducts with 1,8-diaminonaphthalene under mechanochemical conditions was investigated.

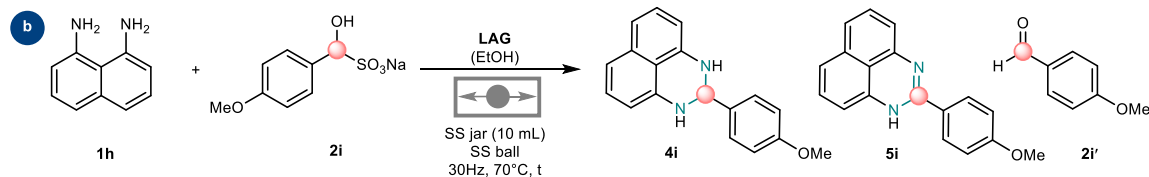
Based upon the previously optimised reaction condition for benzimidazole synthesis, Reaction of Bertagnini's salt **2a** with 1,8-diaminonaphthalene (**1h**) at room temperature afforded the cyclized product **4a** in 89% yield within 30 minutes. Introduction of electron-withdrawing groups (–F, –Cl, –Br) on the aromatic ring of the bisulfite adduct gave the corresponding products (**4b–4d**) in good yields. Likewise, Bertagnini's salts bearing electron-donating groups (–NMe₂ and –OMe) were transformed into the corresponding cyclized derivatives (**4h** and **4i**) in 81% and 85% yields, respectively (Scheme 3.4). The synthetic potential of the procedure was further expanded by employing bisulfite adducts of cyclic ketones under room-temperature mechanochemical conditions. Notably, the formation of Bertagnini's salts derived from cyclic ketones has remained unexplored in the literature. Under these conditions, the reaction of the bisulfite adduct of cyclohexanone with **1h** afforded **4q** in 98% yield within 3h (Scheme 3.4). Similarly, Bertagnini's salts derived from cyclopentanone and cycloheptanone afforded the desired cyclized products (**4r** and **4s**) in 86% and 67% yields, respectively (Scheme 3.4). In addition, bisulfite adducts of cyclohexanone bearing p-tert-butyl and phenyl substituents were well tolerated, yielding products **4t** and **4u** in 47% and 59% yields, respectively (Scheme 3.4).

To get access to perimidines, introduction of oxidants was employed under mechanochemical conditions. During the evaluation of reaction conditions for optimization, 2,3-dihydro-1H-perimidine (**4i**) was employed as the model substrate. Numerous oxidants were tested, but none proved efficacious. Additionally, changing the amount and dimensions of balls failed to provide any significant product formation. Instead, a one-pot synthesis approach was adopted using 1,8-diaminonaphthalene and bisulfite adducts at varying temperatures.⁶⁶⁻⁶⁸ The best result (85% yield, Scheme 2) for perimidine **5i** was obtained by employing one equivalent of 1,8-diaminonaphthalene and 1.1 equivalents of 4-methoxy bisulfite at 70 °C for 3 h inside a MM-500 control mixer mill.

Table 3.2. Screening for mechanochemical perimidine synthesis from dihydro-perimidine



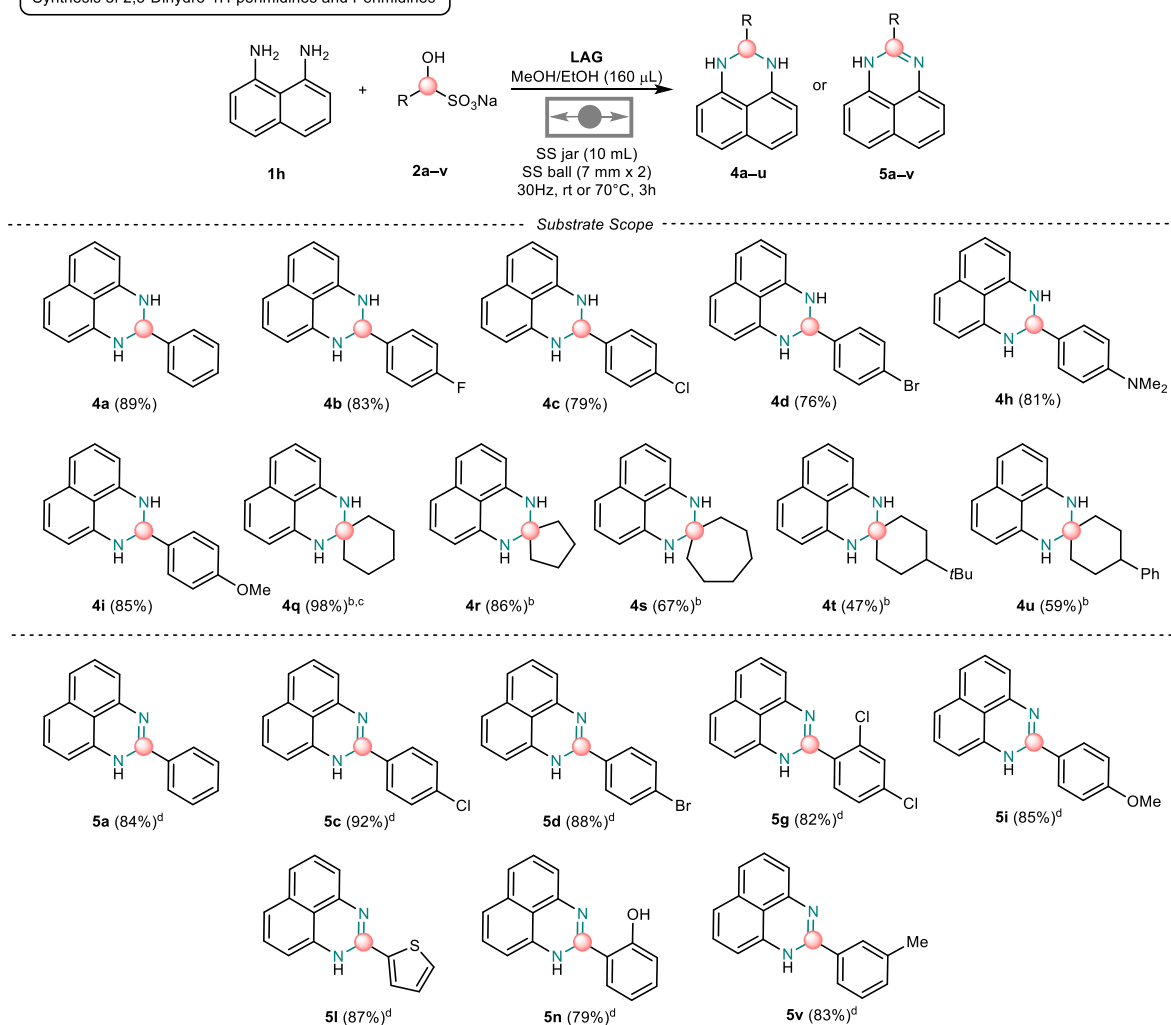
Entry	LAG (η factor)	Time (min)	Temp (°C)	Oxidant (eq.)	4i	5i	2i'	Size of balls
1	—	120 min	rt	UHP (1)	90%	—	10%	(7 mm x 1)
2	H ₂ O (0.3)	120 min	rt	UHP (1)	88%	—	12%	(7 mm x 1)
3 ^b	—	120 min	rt	UHP (1)	100%	—	—	(7 mm x 1)
4	MeOH (0.3)	60 min	rt	Oxone (1)	88%	—	12%	(7 mm x 2)
5 ^{c,d}	MeOH (0.3)	120 min	rt	Oxone (1)	—	51%	49%	(7 mm x 2)
6 ^c	H ₂ O (0.3)	120 min	rt	Sodium Percarbonate (1)	86%	—	14%	(7 mm x 1)
7	—	120 min	rt	DDQ (1)	97%	—	3%	(7 mm x 1)
8	MeOH (0.3)	120 min	rt	Oxone (1)	96%	—	4%	(7 mm x 1)
9 ^{b,d}	MeOH (0.3)	120 min	rt	Oxone (1)	66%	21%	13%	(7 mm x 2)
10 ^e	MeOH (0.3)	60 min	70°C	UHP (1)	26%	57%	17%	(7 mm x 1)(10 mm x 1)
11 ^e	MeOH (0.3)	60 min	70°C	—	49%	51%	—	(7 mm x 1)(10 mm x 1)



Entry	LAG (η factor)	Time (min)	Temp (°C)	Oxidant (eq.)	4i	5i	2i'	Size of balls
12 ^{e,f}	EtOH (0.3)	240 min	70°C	—	—	67%	33%	(7 mm x 1)(10 mm x 1)
13 ^{e,f}	EtOH (0.3)	180 min	70°C	—	74%	26%	—	(7 mm x 1)(5 mm x 1)
14 ^{e,f}	EtOH (0.3)	120 min	70°C	—	22%	78%	—	(7 mm x 1)(5 mm x 1)
15 ^{e,f}	EtOH (0.3)	120 min	70°C	—	—	42%	—	(5 mm x 3)
16 ^{e,f}	EtOH (0.4)	180 min	70°C	—	—	92%	8%	(7 mm x 2)
17 ^{e,f,g}	EtOH (0.3)	180 min	70°C	—	—	85%	15%	(7 mm x 2)

^a Reaction Conditions: **1h** (0.50 mmol), **2i** (0.55 mmol), LAG (η= 0.3) in a 5 mL SS jar with SS balls milled in MM-500 Vario at 30 Hz for given time and temperature, the conversion was calculated via ¹H NMR; ^b 0.02 eq. of TEMPO were added; ^c 2.00 eq. of NaHSO₄ anhydrous were added; ^d reaction was run by using 1.00 mmol of **1h** with a 10 mL SS jar; ^e reaction was run on a 1.0 mmol scale using a Retsch-MM500 Control ball mill in a (4 x 10) mL SS jar; ^f one pot process using **1h** and **2i** as starting materials; ^g the reaction was conducted at 20 Hz

Synthesis of 2,3-Dihydro-1H-perimidines and Perimidines

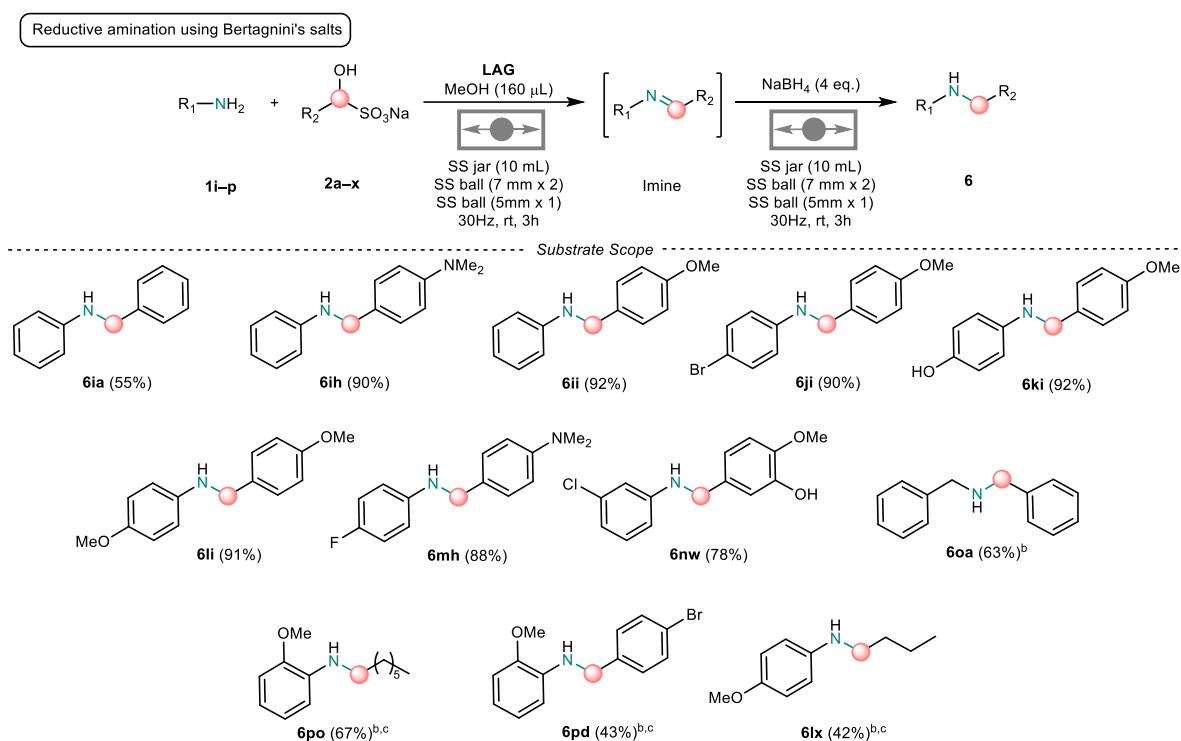


Scheme 3.4. ^a Substrate scope for synthesis of dihydro perimidines and perimidines. Reaction conditions: **1h** (1 mmol), **2** (1.1 mmol), LAG of MeOH ($\eta = 0.4$) in a 10 mL SS jar with two 7 mm SS balls milled at 30 Hz in MM-500 Vario for 30 min at 25°C and yields of the products were calculated after recrystallization with EtOH; ^b reaction was milled at 30 Hz for 3h and yield was calculated after column chromatography; ^c No column chromatography was needed; ^d The reaction was performed at 70°C with a LAG of ethanol and a milling frequency of 30 Hz for 3h. Yield was calculated after recrystallization with ethanol

Using the optimized reaction conditions, a range of perimidines was synthesized by introducing different electron-donating and electron-withdrawing groups at the bisulfite adduct moiety, affording products (**5a–5v**) in moderate to excellent yields. Efficient formation of **5a** (84% yield) was achieved from the unsubstituted bisulfite adduct and 1,8-diaminonaphthalene (Scheme 3.4). Bertagnini's salts bearing electron-withdrawing groups (such as –Cl and –Br) were efficiently converted into the corresponding cyclized products (**5c–5g**) in moderate yields. By contrast, bisulfite adducts containing methyl, methoxy and hydroxyl substituents afforded **5v**, **5i** and **5n** in 83%, 85% and 79% yields, respectively (Scheme 3.4). Interestingly, thiophene-containing bisulfite adducts were transformed into the corresponding perimidine (**5l**) in 87% yield.

3.5.4. Mechanochemical Reductive Aminations and Hydrazone Synthesis

To showcase the versatility of Bertagnini's salts, the reactivity of other nucleophiles was analysed. In reductive aminations, an aldehyde is reacted with an amine to form a transient imine, which is subsequently reduced to the corresponding secondary amine.^{69, 70} This method is extensively employed for the selective functionalization of primary amines, thereby avoiding polyalkylation of the nitrogen moiety. Reductive amination of bisulfite adducts with amines has previously been achieved using 2-picoline borane as a reducing agent in methanol and under α -picoline–borane aqueous micellar catalysis at 60°C. However, these processes require hazardous organic solvents, detrimental surfactants, expensive reducing agents, and precise temperature control. Moreover, the combination of surfactants and water can lead to contamination of drinking water, which must then be distilled to restore purity, making such procedures unsustainable on an industrial scale.



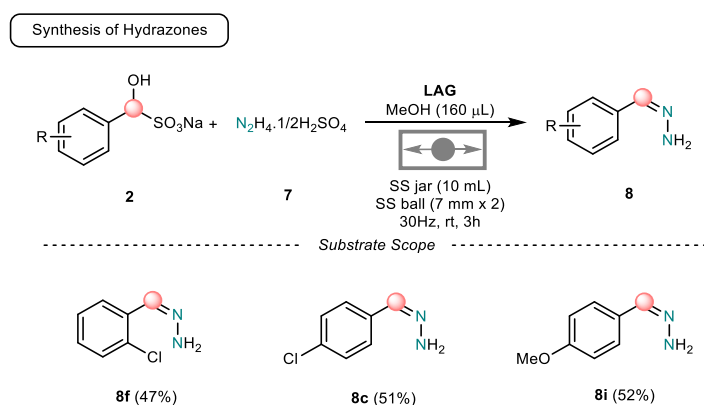
Scheme 3.5. ^a Substrate scope for mechanochemical reductive amination. Reaction conditions: **1** (1 mmol), **2** (1.1 mmol), LAG of MeOH ($\eta = 0.4$) in a 10 mL SS jar with two 7 mm and a 5 mm SS balls milled at 30 Hz in MM-500 Vario for 3 h at 25°C, after that the ball mill jar was opened and NaBH₄ (4 eq.) was added followed by another 3 h milling at 30 Hz; ^b yield was calculated after column chromatography; ^c reaction was performed using MeOH ($\eta = 1$) at 15 Hz for 6 hrs and 2 hrs for the reducing step

In this regard, reductive amination of Bertagnini's salts was demonstrated using NaBH₄ as a hydride source under mechanochemical conditions at room temperature. The reaction was carried out in a two-step, one-pot process, wherein the first step consisted of the mechanochemical synthesis of imines over 3 h, followed by reduction with NaBH₄ for an additional 3 h. Upon completion, the final reaction mixture was treated with a minimal volume of ethyl acetate, enabling efficient recovery of the secondary amine in high yield without chromatographic purification.

Various substituted bisulfite adducts were then evaluated with electron-deficient and electron-rich amines (Scheme 3.5). Reactions of aniline (**1i**) with unsubstituted (**2a**) and N,N-disubstituted (**2h**) bisulfite adducts afforded **6ia** and **6ih** in 55% and 90% yields, respectively. Introduction of a methoxy substituent at the *para*-position of the aromatic ring in bisulfite adducts, followed by reaction with different anilines, afforded the corresponding secondary amines (**6ii–6li**) in 90–92% yields (Scheme 3.5). Furthermore, 4-fluoroaniline (**1m**) afforded the desired product (**6mh**) in 88% yield when reacted with corresponding Bertagnini's salt (**2h**).

Interestingly, the bisulfite-adduct of vanillin (**2w**) reacted with 3-chloroaniline (**1n**) to furnish the desired product **6nw** in 78% yield. Under the standard conditions, benzylamine (**1o**) displayed comparable reactivity, providing the derivative **6oa** in modest yield. Moreover, 2-methoxyaniline (**1p**) reacted with bisulfite-adducts of heptanal (**2o**) and 4-bromobenzaldehyde (**2d**) to yield **6po** and **6pd** in 67% and 43% yields, respectively. Notably, even the bisulfite-adduct of a butyraldehyde, a VOC reagent (**2x**); coupled with 4-methoxyaniline (**1l**) to deliver the product **6lx** in 42% yield.

The scope of the research was expanded to include the synthesis of hydrazones, thereby enabling exploration of Bertagnini's salts as powerful synthetic tools (Scheme 3.6). Hydrazones constitute a crucial structural motif in numerous heterocyclic scaffolds⁷¹ and are well known for their diverse biological activities⁷² in specific medical contexts⁷³. Under mechanochemical conditions, Bertagnini's salts and hydrazine hemisulfate were employed to afford hydrazones within 3 hours. This approach provided access to hydrazones under mild conditions with a straightforward purification process. Chloro-substituted bisulfite adducts afforded compounds **8f** and **8c** in 47% and 51% yields, respectively. In addition, introduction of a methoxy group at the *para*-position of the bisulfite adduct (**2i**) afforded the corresponding hydrazone (**8i**) in 52% yield.

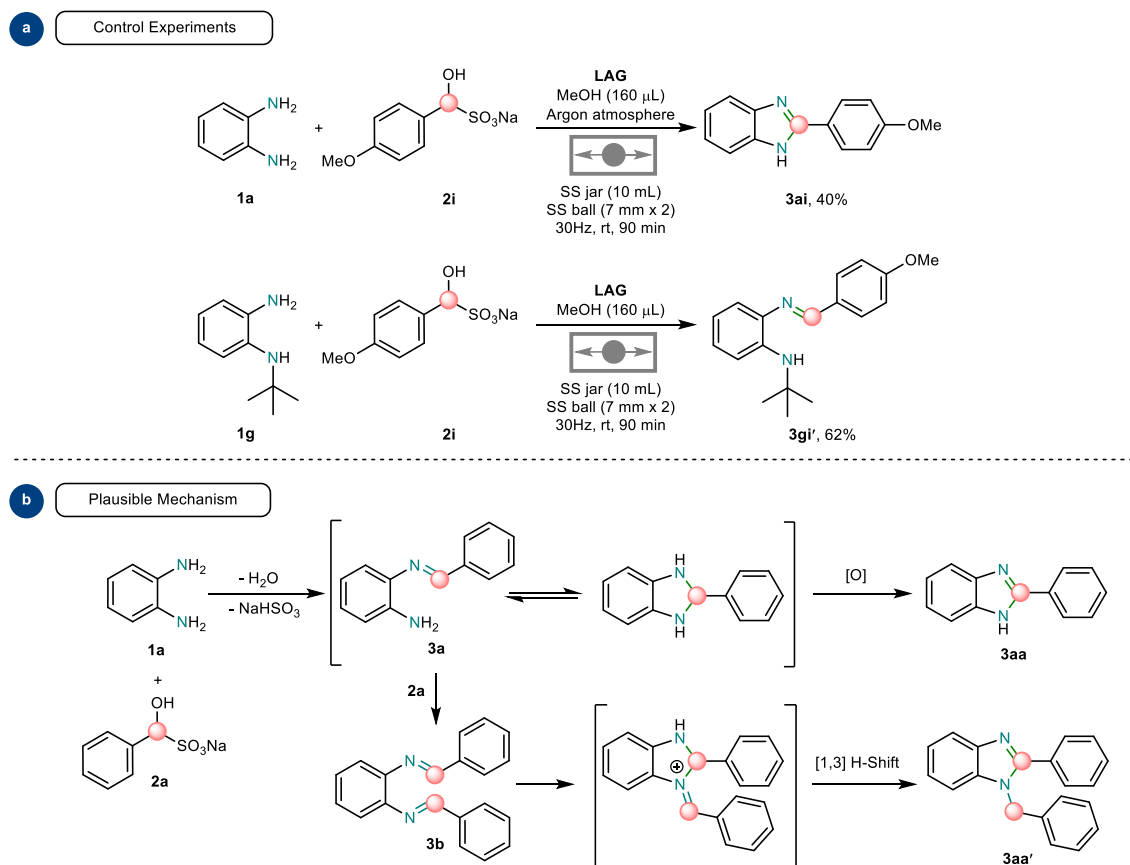


Scheme 3.6. ^a Substrate scope for mechanochemical synthesis of hydrazones. Reaction conditions: **2** (1.1 mmol), **7** (1 mmol), LAG of MeOH ($\eta = 0.4$) in a 10mL SS jar with two 7 mm SS balls milled at 30 Hz in MM-500 Vario for 3h at 25°C, yield was calculated after isolation

3.6. Reaction Mechanism for Mechanochemical Benzimidazole Synthesis

To verify the role of oxygen in the reaction mechanism⁷⁴, the reaction was carried out under an argon atmosphere at the standard conditions, resulting in a lower yield of the expected product **3ai**

(Scheme 3.7.a). Furthermore, when the reaction was conducted with *tert*-butyl-substituted *o*-phenylenediamine (**1g**) under the standard conditions, the condensation imine product (**3gi'**) was isolated in 62% yield (Scheme 3.7.a). Based on the control experiments and literature precedent, a plausible reaction mechanism for the synthesis of benzimidazoles is proposed in Scheme 3.7.b. In the first step, nucleophilic attack of the amine on the carbon center of the bisulfite adduct affords the mono-imine (**3a**), which undergoes intramolecular cyclization to generate the dihydroimidazole intermediate. The aromatized product (**3aa**) is then obtained via aerial oxidation, with the gain in aromaticity serving as the primary driving force. With extended reaction times, the di-imine (**3b**) is formed, which subsequently delivers the *N*-alkylated benzimidazoles (**3aa'**) through intramolecular cyclization followed by a [1,3]-H shift.



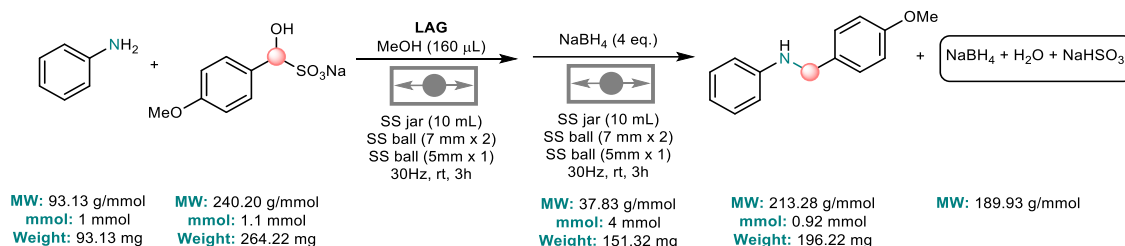
Scheme 3.7.a) Control experiments for synthesis of benzimidazoles. Reaction conditions: **1a** (1 mmol), **2i** (1.1 mmol), LAG of MeOH ($\eta = 0.4$) in a 10mL SS jar with two 7 mm SS balls milled at 30 Hz in MM-500 Vario under inert atmosphere for 90 minutes at 25°C and **1g** reacted with **2i** at normal atmosphere, yield was calculated after isolation; **b)** plausible reaction mechanism for benzimidazole synthesis from Bertagnini's salts under mechanochemical condition

3.7. Green Metrics Calculation

This section describes the green chemistry metrics for the mechanochemical methodologies for synthesis of benzimidazoles, dihydro-perimidines and reductive aminations compared to a previously reported, solution-based approaches. Specifically, a quantitative and qualitative

evaluations by measuring the E-factor and eco-scale values have been conducted using Ecoscale calculator. This analysis determined that mechanochemical reactions using Bertagnini's salt significantly improve the environmental footprint. For reductive amination procedure mechanochemical E-factor was 20.4 whereas solution-based procedure has an E-factor of 937.7. Similarly, for benzimidazole (30.61 vs 399.36) and dihydro-perimidine synthesis (18.22 vs 1972.23) mechanochemical E-factors were significantly better. In EcoScore values, mechanochemical procedure performed equally well otherwise better than solution-based analogues.

Calculation of the Green Chemistry Metrics for the Mechanochemical Preparation of **6fi**



Work up: filtration with 4 mL EtOAc (3608 mg)

$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{213.28}{93.13 + 240.20 + 37.83 + 32.04} \times 100 = 53\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{24.02 + 63.36 + 113.49 + 189.93 + 3608.00}{196.22} = 20.4$$

$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{196.22}{93.13 + 264.22 + 112.92 + 151.32} \times 100 = 32\%$$

The Eco-scale Score for the Mechanochemical Preparation of Secondary Amine **6fi**

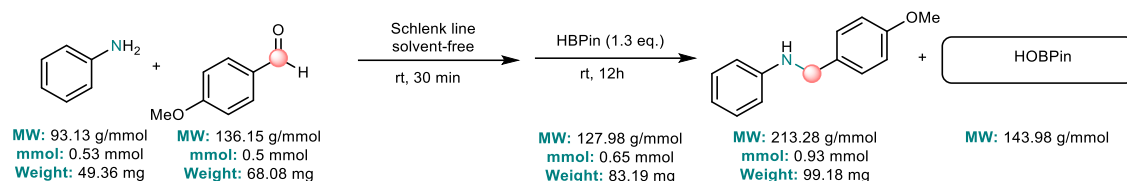
EcoScale: 100 – sum of penalty points

Table 3.3. Calculation of Ecoscale score for the mechanochemical preparation of amine **6fi**^a

Reagents	MF	MW	mmol	Weight (g)	Eq.
Aniline	C ₆ H ₇ N	93.13	1.00	0.093	1.00
α-Toluenesulfonic acid, α-hydroxy-p-methoxy-, monosodium salt	C ₈ H ₁₀ O ₅ NaS	241.21	1.10	0.265	1.10
Sodium borohydride	NaBH ₄	37.83	4.00	0.151	4.00
Products	MF	MW	mmol	Weight (g)	Eq.
(4-Methoxy-benzyl)-phenylamine (6fi)	C ₁₄ H ₁₅ NO	213.28	0.92	0.196	92%

Entry	Parameters	Penalty Points
1	Yield (92%)	-4
2	Price/availability	-13
3	Safety	-15
4	Technical set-up (Unconventional activation technique)	-2
5	Room temperature (< 24h)	-1
6	Work-up and purification	0
	EcoScale score	65

Calculation of the Green Chemistry Metrics for the in-solution preparation of 6fi



* V. K. Pandey, S. Bauri, and A. Rit *Org. Biomol. Chem.* **2020**, 18, 20, 3853-3857.⁷⁵

Due to the absence of data, the quantity of ethyl acetate/hexane used for purifying the desired product has been postulated via flash column chromatography on silica gel (NO DATA). All the factors that contributed to the waste calculation were considered in the following way:

The amount of silica and solvents used for purifying the organic mixture is ascribable to the data reported in the literature (W. C. Still, M. Kahn, and A. Mitra *J. Org. Chem.* **1978**, 43, 14, 2923-2925).⁷⁶ We chose as a model a 10 mm diameter column and a 7:3 mixture of Hexane:EtOAc because it allows a $\Delta R_f \approx 0.2$. The theoretical quantity of eluent necessary for the purifying step is 100 mL, so the relative amounts of EtOAc and Hexane are 30 mL and 70 mL, respectively. By exploiting their densities, this procedure's waste can be easily calculated.

Work up: column chromatography with EtOAc (27060 mg), hexane (45850 mg) and silica (20000 mg)

$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{213.28}{93.12 + 136.15 + 127.98} \times 100 = 60\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{2.80 + 19.20 + 71.99 + 92910}{99.18} = 937.7$$

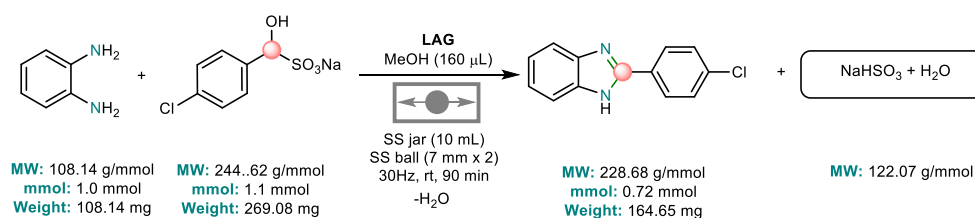
$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{99.18}{49.36 + 68.08 + 83.19} \times 100 = 49\%$$

Table 3.4. Calculation of Ecoscale score for solution-based preparation of amine **6fi**^a

Reagents	MF	MW	mmol	Weight (g)	Eq.
Aniline	C ₆ H ₇ N	93.13	0.53	0.049	1.05
p-Anisaldehyde	C ₈ H ₈ O ₂	136.15	0.50	0.068	1.00
Pinacolborane	C ₆ H ₁₃ BO ₂	37.83	0.65	0.083	1.30
Products	MF	MW	mmol	Weight (g)	Eq.
(4-Methoxy-benzyl)-phenyl-amine (6ii)	C ₁₄ H ₁₅ NO	213.28	0.47	0.099	93%

Entry	Parameters	Penalty Points
1	Yield (92%)	-3
2	Price/availability	-8
3	Safety	-10
4	Technical set-up (Inert atmosphere)	-1
5	Room temperature (< 24h)	-1
6	Work-up and purification	-10
	EcoScale score	67

Calculation of the Green Chemistry Metrics for the Mechanochemical Preparation of **3ac**



Work up: filtration using methanol (3960 mg) and recrystallization with ethanol (789 mg)

$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{228.68}{108.14 + 244.62 + 16} \times 100 = 62\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{24.46 + 126.72 + 4749 + 122.07 + 18.01}{164.65} = 30.61$$

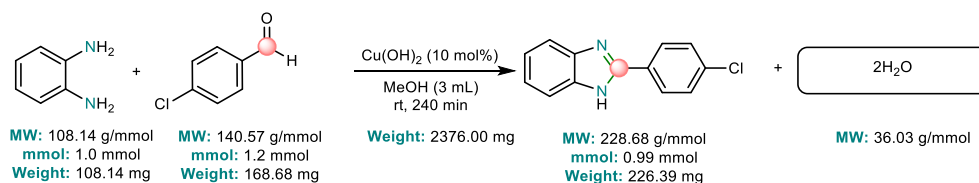
$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{164.65}{108.14 + 269.08 + 16} \times 100 = 42\%$$

Table 3.5. Calculation of Ecoscale score for mechanochemical preparation of **3ac**^a

Reagents	MF	MW	mmol	Weight (g)	Eq.
o-Phenyldiamine	C ₆ H ₈ N ₂	108.14	1.00	0.108	1.00
Alpha-Toluenesulfonic acid, alpha-hydroxy-p-chloro-, monosodium salt	C ₇ H ₇ ClO ₄ SNa	244.62	1.10	0.269	1.10
Products	MF	MW	mmol	Weight (g)	Eq.
2-(4-Chlorophenyl)benzimidazole (3ac)	C ₁₃ H ₉ N ₂ Cl	228.68	0.72	0.1647	72%

Entry	Parameters	Penalty Points
1	Yield (72%)	-14
2	Price/availability	-5
3	Safety	-5
4	Technical set-up (Unconventional activation technique)	-2
5	Room temperature (< 24h)	-1
6	Work-up and purification	-1
	EcoScale score	72

Calculation of the Green Chemistry Metrics for the in-solution preparation of **3ac**



* M. A. Chari, D. Shobha and S. Malayalama *Int. J. Org. Chem.* **2013**, 3, 4, 243-250.⁷⁷

Due to the absence of data, it has been postulated the quantity of ethyl acetate/hexane used for purifying via column chromatography on silica gel (NO DATA) the desired product. All the factors that contributed to the waste calculation were considered in the following way:

The quantity of solvents used for purifying the organic mixture is ascribable to the data reported in the literature (W. C. Still, M. Kahn, and A. Mitra *J. Org. Chem.* **1978**, 43, 14, 2923-2925).⁷⁶ We chose as a model a 10 mm diameter column and a 9:1 mixture of Hexane:EtOAc as reported in the paper ($\Delta R_f \approx 0.2$). The theoretical quantity of eluent necessary for the purifying step is 100 mL, so the relative amount of EtOAc and Hexane is 10 mL and 90 mL, respectively. By exploiting their densities, it can be easily calculated the amount of waste for this procedure.

Work up: column chromatography with EtOAc (9020 mg), hexane (58950 mg) and silica (20000 mg)

$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{228.68}{108.14 + 140.57 + 16} \times 100 = 86\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{28.11 + 2376.00 + 36.03 + 87970.00}{226.39} = 399.36$$

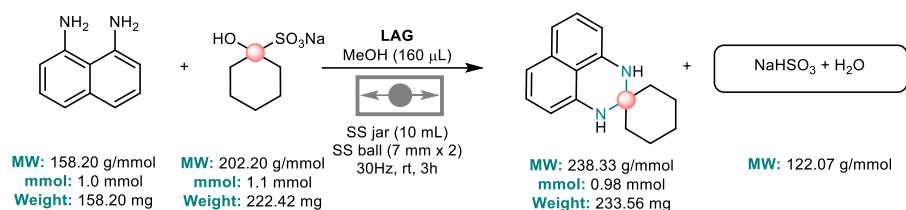
$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{226.39}{108.14 + 168.68 + 16} \times 100 = 77\%$$

Table 3.6. Calculation of Ecoscale score solution-based preparation of **3ac**^a

Reagents	MF	MW	mmol	Weight (g)	Eq.
o-Phenyldiamine	C ₆ H ₈ N ₂	108.14	1.00	0.108	1.00
p-Chlorobenzaldehyde	C ₇ H ₅ ClO	140.57	1.20	0.168	1.10
Products	MF	MW	mmol	Weight (g)	Eq.
2-(4-Chlorophenyl)benzimidazole (3ac)	C ₁₃ H ₉ N ₂ Cl	228.68	0.99	0.2264	99%

Entry	Parameters	Penalty Points
1	Yield (99%)	-1
2	Price/availability	-10
3	Safety	-10
4	Technical set-up (Common set-up)	0
5	Room temperature (< 24h)	-1
6	Work-up and purification	-10
	EcoScale score	68

Calculation of the Green Chemistry Metrics for the Mechanochemical Preparation of **4q**



Work up: filtration with methanol (3960 mg)

$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{238.33}{158.20 + 202.20} \times 100 = 66\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{20.22 + 152.25 + 3960.00 + 104.06 + 18.02}{233.56} = 18.22$$

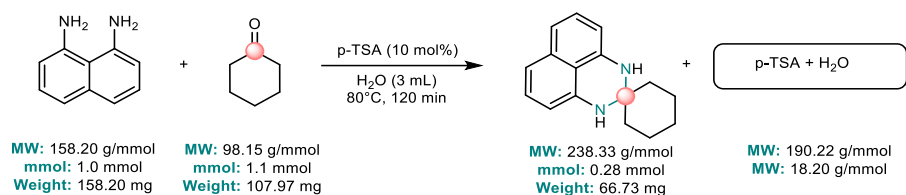
$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{233.56}{158.20 + 222.42} \times 100 = 61\%$$

Table 3.7. Calculation of Ecoscale score for mechanochemical preparation of **4q**^a

Reagents	MF	MW	mmol	Weight (g)	Eq.
1,8-Diaminonaphthalene	C ₁₀ H ₁₀ N ₂	158.2028	1.00	0.1582	1.00
Cyclohexanesulfonic acid, 1-hydroxy-, sodium salt	C ₆ H ₁₁ O ₄ SNa	202.1998	1.10	0.2224	1.10
Products	MF	MW	mmol	Weight (g)	Eq.
1',3'-Dihydrospiro[cyclohexane-1,2'-perimidine] (4q)	C ₁₆ H ₁₈ N ₂	238.33	0.98	0.2336	98%

Entry	Parameters	Penalty Points
1	Yield (98%)	-1
2	Price/availability	-5
3	Safety	0
4	Technical set-up (Unconventional activation technique)	0
5	Room temperature (< 24h)	-1
6	Work-up and purification	0
	EcoScale score	93

Calculation of the Green Chemistry Metrics for the in-solution preparation of 4q



* N. A. Harry, T. Shilpa, S. M. Ujwaldev and G. Anilkumar *J. Heterocycl. Chem.* **2021**, 58, 1, 375-381.⁷⁸

Due to the absence of data, it has been postulated the quantity of ethyl acetate/hexane used for purifying via column chromatography on silica gel (NO DATA) the desired product. All the factors that contributed to the waste calculation were considered in the following way:

The quantity of solvents used for purifying the organic mixture is ascribable to the data reported in the literature (W. C. Still, M. Kahn, and A. Mitra *J. Org. Chem.* **1978**, 43, 14, 2923-2925).⁷⁶ We chose as a model a 10 mm diameter column and a 9:1 mixture of Hexane:EtOAc as reported in the paper ($\Delta R_f \approx 0.2$). The theoretical quantity of eluent necessary for the purifying step is 100 mL, so the relative amounts of EtOAc and Hexane are 10 mL and 90 mL, respectively. By exploiting their densities, this procedure's waste can be easily calculated.

Work up: extraction with EtOAc (40590 mg) column chromatography with EtOAc (9020 mg), hexane (58950 mg) and silica (20000 mg)

$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{66.73}{158.20 + 98.15} \times 100 = 93\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{9.82 + 40590.00 + 3000.00 + 18.02 + 19.02 + 87970.00}{66.73} = 1972.23$$

$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{66.73}{158.20 + 107.97} \times 100 = 25\%$$

Table 3.8. Calculation of Ecoscale score for solution-based preparation of **4q**^a

Reagents	MF	MW	mmol	Weight (g)	Eq.
1,8-diaminonaphthalene	C ₁₀ H ₁₀ N ₂	158.2028	1.00	0.1582	1.00
Cyclohexanone	C ₆ H ₁₀ O	98.14	1.10	0.2224	1.10
p-toluensulphonic acid	C ₇ H ₁₀ SO ₄	190.22	0.10	0.0190	0.10
Products	MF	MW	mmol	Weight (g)	Eq.
1',3'-Dihydrospiro[cyclohexane-1,2'-perimidine] (4q)	C ₁₆ H ₁₈ N ₂	238.33	0.28	0.0667	28%

Entry	Parameters	Penalty Points
1	Yield (98%)	-36
2	Price/availability	-5
3	Safety	0
4	Technical set-up (Common set-up)	0
5	Room temperature (< 24h)	-3
6	Work-up and purification	-10
	EcoScale score	46

^aValues calculated using the eco scale calculator software available at the link:

<http://ecoscale.cheminfo.org/calculator>

3.8. Conclusions

In the past, Bertagnini's salts were commonly employed as reagents for the removal or purification of aldehydes and ketones from crude reaction mixtures. Owing to their general insolubility in organic solvents, their application in organic synthesis has remained relatively underexplored, and their efficacy has often been inconsistent. More recently, Bertagnini's salts have been applied in mechanochemistry as solid surrogates for aldehydes and ketones. In this context, the limitations arising from poor solubility are eliminated, thereby providing new opportunities for synthetic utilization. The present study demonstrates that Bertagnini's salts can successfully replace liquid carbonyl compounds in classical reactions involving aldehydes or ketones. By overcoming disadvantages such as the need for column chromatography and laborious workup procedures, this strategy affords the desired products in yields ranging from 38–91%. Bertagnini's salts with electron-donating and withdrawing groups reacted efficiently to provide the desired heterocyclic products, however bulky groups on the diamine severely hampers the efficient product formation. Moreover, the potential of this class of compounds is highlighted through their application in mechanochemical processes for the preparation of perimidine rings under thermal methods, as well as through the introduction of bisulfite adducts of ketones, which considerably enhanced the reactivity of these compounds.

3.9. References

- (1) Amistadi-Revol, H.; Liu, S.; Prévost, S. C–H Functionalization of Aldehydes and Ketones with Transient Directing Groups: Recent Developments. *Eur. J. Org. Chem.* **2023**, 26 (31), e202300582.
- (2) Yuan, Z.; Liao, J.; Jiang, H.; Cao, P.; Li, Y. Aldehyde catalysis—from simple aldehydes to artificial enzymes. *RSC Adv.* **2020**, 10 (58), 35433-35448.
- (3) Erkkilä, A.; Majander, I.; Pihko, P. M. Iminium catalysis. *Chem. Rev.* **2007**, 107 (12), 5416-5470.
- (4) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric enamine catalysis. *Chem. Rev.* **2007**, 107 (12), 5471-5569.
- (5) Doraghi, F.; Mohaghegh, F.; Qareaghaj, O. H.; Larijani, B.; Mahdavi, M. Synthesis of N-, O-, and S-heterocycles from aryl/alkyl alkynyl aldehydes. *RSC Adv.* **2023**, 13 (20), 13947-13970.
- (6) Arcadi, A.; Morlacci, V.; Palombi, L. Synthesis of Nitrogen-Containing Heterocyclic Scaffolds through Sequential Reactions of Aminoalkynes with Carbonyls. *Molecules* **2023**, 28 (12), 4725.
- (7) Bertagnini, C. Ueber die Verbindungen einiger flüchtigen Oele mit den zweifach-schwefligsauren Alkalien. *Justus Liebigs Annalen der Chemie* **1853**, 85 (2), 179-196.
- (8) He, M.; Beahm, B. J.; Bode, J. W. Chiral NHC-catalyzed oxodiene Diels–Alder reactions with α -chloroaldehyde bisulfite salts. *Org. Lett.* **2008**, 10 (17), 3817.
- (9) Mohanty, S.; Roy, A. K.; Reddy, S.; Kumar, K. P. V.; Karmakar, A. C. Reaction pathway of POCl₃-mediated Knoevenagel condensation of bisulfite adducts with 2, 4-thiazolidinedione. *Phosphorus Sulfur Silicon Relat. Elem.* **2016**, 191 (6), 857-866.
- (10) Li, X.; Iyer, K. S.; Thakore, R. R.; Leahy, D. K.; Bailey, J. D.; Lipshutz, B. H. Bisulfite addition compounds as substrates for reductive aminations in water. *Org. Lett.* **2021**, 23 (18), 7205-7208.
- (11) Betti, M.; Genesio, E.; Marconi, G.; Sanna Coccone, S.; Wiedenau, P. A scalable route to the SMO receptor antagonist SEN826: Benzimidazole synthesis via enhanced in situ formation of the bisulfite–aldehyde complex. *Org. Process Res. Dev.* **2014**, 18 (6), 699-708.
- (12) Khosropour, A. R.; Khodaei, M. M.; Beygzadeh, M. Highly convenient one-pot conversion of aryl acylals or aryl aldehyde bisulfites into dihydropyrimidones using BI (NO₃) 3· 5H₂O. *Heteroatom Chemistry: An International Journal of Main Group Elements* **2007**, 18 (6), 684-687.
- (13) Ragan, J. A.; am Ende, D. J.; Brenek, S. J.; Eisenbeis, S. A.; Singer, R. A.; Tickner, D. L.; Teixeira, J. J.; Vanderplas, B. C.; Weston, N. Safe execution of a large-scale ozonolysis: preparation of the bisulfite adduct of 2-hydroxyindan-2-carboxaldehyde and its utility in a reductive amination. *Org. Process Res. Dev.* **2003**, 7 (2), 155-160.
- (14) Pandit, C. R.; Mani, N. S. Expedient reductive amination of aldehyde bisulfite adducts. *Synthesis* **2009**, 2009 (23), 4032-4036.
- (15) Kumar K. Pavithran, V.; Rao, V. S.; Jaganmohan, C.; Mohanty, S.; Kumar, J.; Rao Battula, V.; Kalyani, K.; Kallam, S. R. An efficient synthesis of 3, 4-dihydro-2 (1H)-pyrimidinones from aldehyde bisulfite adducts using recyclable wang resin supported sulfonic acid catalyst. *Lett. Org. Chem.* **2022**, 19 (6), 463-470.
- (16) Howard, J. L.; Cao, Q.; Browne, D. L. Mechanochemistry as an emerging tool for molecular synthesis: what can it offer? *Chem. Sci.* **2018**, 9.
- (17) Friscic, T.; Mottillo, C.; Titi, H. M. Mechanochemistry for Synthesis. *Angew. Chem. Int. Ed.* **2020**, 59 (3), 1018-1029.
- (18) Boldyreva, E. Mechanochemistry of inorganic and organic systems: what is similar, what is different? *Chem. Soc. Rev.* **2013**, 42 (18), 7719-7738.
- (19) O'Neill, R. T.; Boulatov, R. The many flavours of mechanochemistry and its plausible conceptual underpinnings. *Nat. Rev. Chem.* **2021**, 5 (3), 148-167.
- (20) Fantozzi, N.; Volle, J. N.; Porcheddu, A.; Virieux, D.; Garcia, F.; Colacino, E. Green metrics in mechanochemistry. *Chem. Soc. Rev.* **2023**, 52 (19), 6680-6714.
- (21) Egorov, I. N.; Santra, S.; Kopchuk, D. S.; Kovalev, I. S.; Zyryanov, G. V.; Majee, A.; Ranu, B. C.; Rusinov, V. L.; Chupakhin, O. N. Ball milling: an efficient and green approach for asymmetric organic syntheses. *Green Chem.* **2020**, 22 (2), 302-315.

- (22) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D.; Hyett, G.; Jones, W.; et al. Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.* **2012**, *41* (1), 413-447.
- (23) Ardila-Fierro, K. J.; Hernandez, J. G. Sustainability Assessment of Mechanochemistry by Using the Twelve Principles of Green Chemistry. *ChemSusChem* **2021**, *14* (10), 2145-2162.
- (24) Gao, Y.; Kubota, K.; Ito, H. Mechanochemical Approach for Air-Tolerant and Extremely Fast Lithium-Based Birch Reductions in Minutes. *Angew. Chem.* **2023**, *135* (21), e202217723.
- (25) Seo, T. Mechanochemistry-directed ligand design: Development of a high-performance phosphine ligand for palladium-catalyzed mechanochemical organoboron cross-coupling. In *Palladium-Catalyzed Mechanochemical Cross-Coupling Reactions*, Springer, 2024; pp 161-210.
- (26) Bera, S. K.; Bhanja, R.; Mal, P. DDQ in mechanochemical C–N coupling reactions. *Beilstein J. Org. Chem.* **2022**, *18* (1), 639-646.
- (27) Bera, S. K.; Mal, P. Mechanochemical-cascaded C–N cross-coupling and halogenation using N-bromo- and N-chlorosuccinimide as bifunctional reagents. *J. Org. Chem.* **2021**, *86* (20), 14144-14159.
- (28) Mishra, A. K.; Moorthy, J. N. Mechanochemical catalytic oxidations in the solid state with in situ-generated modified IBX from 3, 5-di-tert-butyl-2-iodobenzoic acid (DTB-IA)/Oxone. *Org. Chem. Front.* **2017**, *4* (3), 343-349.
- (29) Weng, Y.; Lan, T.; Sun, C.; Yang, T.; Su, W.; Xie, Y. Mechanochemical palladium-catalyzed C (sp²)–H homocoupling of N-arylcarbamates: synthesis of 2, 2'-biaryldiamines. *Org. Chem. Front.* **2018**, *5* (13), 2103-2107.
- (30) Estévez, V.; Villacampa, M.; Menéndez, J. C. Concise synthesis of atorvastatin lactone under high-speed vibration milling conditions. *Org. Chem. Front.* **2014**, *1* (5), 458-463.
- (31) Hernández, J. G.; Ardila-Fierro, K. J.; Barišić, D.; Geneste, H. Multi-faceted reactivity of N-fluorobenzenesulfonimide (NFSI) under mechanochemical conditions: fluorination, fluorodemethylation, sulfonylation, and amidation reactions. *Beilstein J. Org. Chem.* **2022**, *18* (1), 182-189.
- (32) Banerjee, M.; Bhosle, A. A.; Chatterjee, A.; Saha, S. Mechanochemical synthesis of organic dyes and fluorophores. *J. Org. Chem.* **2021**, *86* (20), 13911-13923.
- (33) Jang, B. J.; Zhao, Q.; Baek, J. H.; Seo, J. M.; Jeon, J. P.; Kweon, D. H.; Han, G. F.; Xu, C.; Baek, J. B. Direct Synthesis of Fluorinated Carbon Materials via a Solid-State Mechanochemical Reaction Between Graphite and PTFE. *Adv. Funct. Mater.* **2023**, *33* (47), 2306426.
- (34) Constable, D. J.; Jimenez-Gonzalez, C.; Henderson, R. K. Perspective on solvent use in the pharmaceutical industry. *Org. Process Res. Dev.* **2007**, *11* (1), 133-137.
- (35) Crawford, D. E.; Miskimmin, C. K.; Albadarin, A. B.; Walker, G.; James, S. L. Organic synthesis by Twin Screw Extrusion (TSE): continuous, scalable and solvent-free. *Green Chem.* **2017**, *19* (6), 1507-1518.
- (36) Do, J. L.; Friscic, T. Mechanochemistry: A Force of Synthesis. *ACS Cent. Sci.* **2017**, *3* (1), 13-19.
- (37) Galant, O.; Cerfeda, G.; McCalmont, A. S.; James, S. L.; Porcheddu, A.; Delogu, F.; Crawford, D. E.; Colacino, E.; Spataro, S. Mechanochemistry can reduce life cycle environmental impacts of manufacturing active pharmaceutical ingredients. *ACS Sustain. Chem. Eng.* **2022**, *10* (4), 1430-1439.
- (38) Ying, P.; Yu, J.; Su, W. Liquid-assisted grinding mechanochemistry in the synthesis of pharmaceuticals. *Adv. Synth. Catal.* **2021**, *363* (5), 1246-1271.
- (39) Bera, S. K.; Boruah, P. J.; Parida, S. S.; Paul, A. K.; Mal, P. A Photochemical Intramolecular C–N Coupling Toward the Synthesis of Benzimidazole-Fused Phenanthridines. *J. Org. Chem.* **2021**, *86* (14), 9587-9602.
- (40) Liu, J.; Zhang, N.; Yue, Y.; Liu, G.; Liu, R.; Zhang, Y.; Zhuo, K. One-pot synthesis of benzimidazo [1, 2-f] phenanthridines by cascade palladium-catalyzed N-arylation and intramolecular C–H coupling. *Eur. J. Org. Chem.* **2013**, *2013* (34), 7683-7687.
- (41) Yadav, G.; Ganguly, S. Structure activity relationship (SAR) study of benzimidazole scaffold for different biological activities: A mini-review. *Eur. J. Med. Chem.* **2015**, *97*, 419-443.
- (42) Sondhi, S. M.; Rajvanshi, S.; Johar, M.; Bharti, N.; Azam, A.; Singh, A. K. Anti-inflammatory, analgesic and antiamebic activity evaluation of pyrimido [1, 6-a] benzimidazole derivatives synthesized

by the reaction of ketoisothiocyanates with mono and diamines. *Eur. J. Med. Chem.* **2002**, 37 (10), 835-843.

(43) Barreca, M. L.; Rao, A.; De Luca, L.; Iraci, N.; Monforte, A.-M.; Maga, G.; De Clercq, E.; Pannecouque, C.; Balzarini, J.; Chimirri, A. Discovery of novel benzimidazolones as potent non-nucleoside reverse transcriptase inhibitors active against wild-type and mutant HIV-1 strains. *Bioorg. Med. Chem. Lett.* **2007**, 17 (7), 1956-1960.

(44) Ranjan, N.; Story, S.; Fulcrand, G.; Leng, F.; Ahmad, M.; King, A.; Sur, S.; Wang, W.; Tse-Dinh, Y.-C.; Arya, D. P. Selective inhibition of Escherichia coli RNA and DNA topoisomerase I by Hoechst 33258 derived mono- and bisbenzimidazoles. *J. Med. Chem.* **2017**, 60 (12), 4904-4922.

(45) Nardi, M.; Cano, N. C. H.; Simeonov, S.; Bence, R.; Kurutos, A.; Scarpelli, R.; Wunderlin, D.; Procopio, A. A review on the green synthesis of benzimidazole derivatives and their pharmacological activities. *Catalysts* **2023**, 13 (2), 392.

(46) Pardeshi, V. A. S.; Chundawat, N. S.; Pathan, S. I.; Sukhwal, P.; Chundawat, T. P. S.; Singh, G. P. A review on synthetic approaches of benzimidazoles. *Synth. Commun.* **2021**, 51 (4), 485-513.

(47) Zhang, R.; Qin, Y.; Zhang, L.; Luo, S. Oxidative synthesis of benzimidazoles, quinoxalines, and benzoxazoles from primary amines by ortho-quinone catalysis. *Org. Lett.* **2017**, 19 (20), 5629-5632.

(48) Hu, Z.; Zhao, T.; Wang, M.; Wu, J.; Yu, W.; Chang, J. I2-mediated intramolecular C–H amidation for the synthesis of N-substituted benzimidazoles. *J. Org. Chem.* **2017**, 82 (6), 3152-3158.

(49) Bera, S. K.; Alam, M. T.; Mal, P. C–N Coupling via Antiaromatic Endocyclic Nitrenium Ions. *J. Org. Chem.* **2019**, 84 (18), 12009-12020.

(50) Kissane, M. G.; Frank, S. A.; Renner, G. A.; Ley, C. P.; Alt, C. A.; Stroud, P. A.; Vaid, R. K.; Boini, S. K.; McKee, L. A.; Vicenzi, J. T. Counterion effects in the preparation of aldehyde–bisulfite adducts. *Tetrahedron Lett.* **2013**, 54 (48), 6587-6591.

(51) Zhang, C.; Zhang, L.; Jiao, N. Catalyst free approach to benzimidazoles using air as the oxidant at room temperature. *Green Chem.* **2012**, 14 (12), 3273-3276.

(52) Bera, S. K.; Mal, P. Regiodivergent C–N Coupling of Quinazolinones Controlled by the Dipole Moments of Tautomers. *Org. Lett.* **2022**, 24 (17), 3144-3148.

(53) Kumar, V.; Mahajan, M. P. Pyrimidine and Imidazole. *Heterocycles in Natural Product Synthesis* **2011**, 507-533.

(54) Harry, N. A.; Ujwaldev, S. M.; Aneja, T.; Anilkumar, G. A comprehensive overview of perimidines: Synthesis, chemical transformations, and applications. *Curr. Org. Chem.* **2021**, 25 (2), 248-271.

(55) Fernández-Gijón, C. A.; Olvera-Mancilla, J.; Le Lagadeec, R.; Barba-Behrens, N.; Rico-Bautista, H.; Toscano, R. A.; Alexandrova, L. 2-Substituted perimidines: Zwitterionic tautomerism in solid state, substituent effect on their crystal packing and biological activity. *J. Mol. Struct.* **2022**, 1252, 132056.

(56) Nagasundaram, N.; Govindhan, C.; Sumitha, S.; Sedhu, N.; Raguvaran, K.; Santhosh, S.; Lalitha, A. Synthesis, characterization and biological evaluation of novel azo fused 2, 3-dihydro-1H-perimidine derivatives: In vitro antibacterial, antibiofilm, anti-quorum sensing, DFT, in silico ADME and Molecular docking studies. *J. Mol. Struct.* **2022**, 1248, 131437.

(57) Herbert, J. M.; Woodgate, P. D.; Denny, W. A. Potential antitumor agents. 53. Synthesis, DNA binding properties, and biological activity of perimidines designed as minimal DNA-intercalating agents. *J. Med. Chem.* **1987**, 30 (11), 2081-2086.

(58) Norikane, Y.; Davis, R.; Tamaoki, N. Photochromism of a spiroperimidine compound in polymer matrices. *New J. Chem.* **2009**, 33 (6), 1327-1331.

(59) Davis, R.; Tamaoki, N. Novel photochromic spiroheterocyclic molecules via oxidation of 1, 8-diaminonaphthalene. *Org. Lett.* **2005**, 7 (8), 1461-1464.

(60) Sahiba, N.; Agarwal, S. Recent advances in the synthesis of perimidines and their applications. *Top. Curr. Chem.* **2020**, 378 (4), 44.

(61) Zhang, H.-J.; Wang, X.-Z.; Cao, Q.; Gong, G.-H.; Quan, Z.-S. Design, synthesis, anti-inflammatory activity, and molecular docking studies of perimidine derivatives containing triazole. *Bioorg. Med. Chem. Lett.* **2017**, 27 (18), 4409-4414.

- (62) Zhou, D.-C.; Lu, Y.-T.; Mai, Y.-W.; Zhang, C.; Xia, J.; Yao, P.-F.; Wang, H.-G.; Huang, S.-L.; Huang, Z.-S. Design, synthesis and biological evaluation of novel perimidine o-quinone derivatives as non-intercalative topoisomerase II catalytic inhibitors. *Bioorg. Chem.* **2019**, *91*, 103131.
- (63) Kim, S.-H.; Kim, J.-H.; Cui, J.-Z.; Gal, Y.-S.; Jin, S.-H.; Koh, K. Absorption spectra, aggregation and photofading behaviour of near-infrared absorbing squarylium dyes containing perimidine moiety. *Dyes Pigm.* **2002**, *55* (1), 1-7.
- (64) Schwob, T.; Ade, M.; Kempe, R. A Cobalt Catalyst Permits the Direct Hydrogenative Synthesis of 1H-Perimidines from a Dinitroarene and an Aldehyde. *ChemSusChem* **2019**, *12* (13), 3013-3017.
- (65) Zhang, B.; Li, J.; Zhu, H.; Xia, X.-F.; Wang, D. Novel recyclable catalysts for selective synthesis of substituted perimidines and aminopyrimidines. *Catal. Lett.* **2023**, *153* (8), 2388-2397.
- (66) Félix, G.; Fabregue, N.; Leroy, C.; Métro, T.-X.; Chen, C.-H.; Laurencin, D. Induction-heated ball-milling: a promising asset for mechanochemical reactions. *Phys. Chem. Chem. Phys.* **2023**, *25* (35), 23435-23447.
- (67) Rensch, T.; Fabig, S.; Grätz, S.; Borchardt, L. Mechanochemically-Assisted Synthesis of Polyimides. *ChemSusChem* **2022**, *15* (1), e202101975.
- (68) Kong, D.; Ma, D.; Wu, P.; Bolm, C. Mechanochemical Solvent-Free N-Sulfonylations of Sulfoximines and Sulfonimidamides. *ACS Sustain. Chem. Eng.* **2022**, *10* (9), 2863-2867.
- (69) Murugesan, K.; Senthamarai, T.; Chandrashekhar, V. G.; Natte, K.; Kamer, P. C.; Beller, M.; Jagadeesh, R. V. Catalytic reductive aminations using molecular hydrogen for synthesis of different kinds of amines. *Chem. Soc. Rev.* **2020**, *49* (17), 6273-6328.
- (70) Afanasyev, O. I.; Kuchuk, E.; Usanov, D. L.; Chusov, D. Reductive amination in the synthesis of pharmaceuticals. *Chem. Rev.* **2019**, *119* (23), 11857-11911.
- (71) Wahbeh, J.; Milkowski, S. The use of hydrazones for biomedical applications. *SLAS Technol.* **2019**, *24* (2), 161-168.
- (72) Verma, G.; Marella, A.; Shaquiquzzaman, M.; Akhtar, M.; Ali, M. R.; Alam, M. M. A review exploring biological activities of hydrazones. *J. Pharm. Bioallied Sci.* **2014**, *6* (2), 69-80.
- (73) Cheng, Y.; Dai, Q.; Morshed, R. A.; Fan, X.; Wegscheid, M. L.; Wainwright, D. A.; Han, Y.; Zhang, L.; Auffinger, B.; Tobias, A. L. Blood-brain barrier permeable gold nanoparticles: an efficient delivery platform for enhanced malignant glioma therapy and imaging. *Small* **2014**, *10* (24), 5137-5150.
- (74) Jiang, Y.-q.; Jia, S.-h.; Li, X.-y.; Sun, Y.-m.; Li, W.; Zhang, W.-w.; Xu, G.-q. An efficient NaHSO₃-promoted protocol for chemoselective synthesis of 2-substituted benzimidazoles in water. *Chem. Pap.* **2018**, *72* (5), 1265-1276.
- (75) Pandey, V. K.; Bauri, S.; Rit, A. Catalyst-and solvent-free efficient access to N-alkylated amines via reductive amination using HBpin. *Org. Biomol. Chem.* **2020**, *18* (20), 3853-3857.
- (76) Still, W. C.; Kahn, M.; Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **1978**, *43* (14), 2923-2925.
- (77) Chari, M. A.; Shobha, D.; Malayalama, S. Synthesis of multifunctionalised 2-substituted benzimidazoles using copper (II) hydroxide as efficient solid catalyst. *Int. J. Org. Chem.* **2013**, *2013*.
- (78) Harry, N. A.; Shilpa, T.; Ujwaldev, S. M.; Anilkumar, G. A novel eco-friendly on-water protocol for the synthesis of 2, 2-disubstituted 2, 3-dihydro-1 H-perimidines. *J. Heterocycl. Chem.* **2021**, *58* (1), 375-381.

From Fleece to Bonds: Mechanochemical Wool-Mediated C–C Bond Formation

4.1. Sustainability in Modern Organic Synthesis: Challenges & Goals

In recent decades, environmental safety and preservation have emerged as pressing global priorities, driven by the relentless and often harmful impact of human activity. Climate change, deforestation, and pollution are just a few of the cascading challenges that have resulted from these actions. Addressing such complex issues calls for urgent, coordinated strategies that not only mitigate human impact but also promote sustainable practices and restore ecological balance. Around the world, governments, organizations, and communities are taking meaningful steps to tackle these problems. In the chemical sciences, this growing awareness has fuelled the rise of green chemistry¹⁻⁸, an approach guided by twelve core principles⁹⁻¹¹ designed to reduce the environmental footprint of chemical processes (Figure 4.1). Among these principles, the use of renewable feedstock stands out as a key priority.¹²⁻¹⁶ Today, most organic compounds and solvents still come from fossil fuels, raising serious concerns about long-term sustainability given their finite availability. As a result, plant- and animal-based wastes are increasingly being explored as renewable feedstocks, offering the potential to improve recyclability, reduce dependence on non-renewable resources^{17, 18}, and move the chemical industry toward a more sustainable future.¹⁹

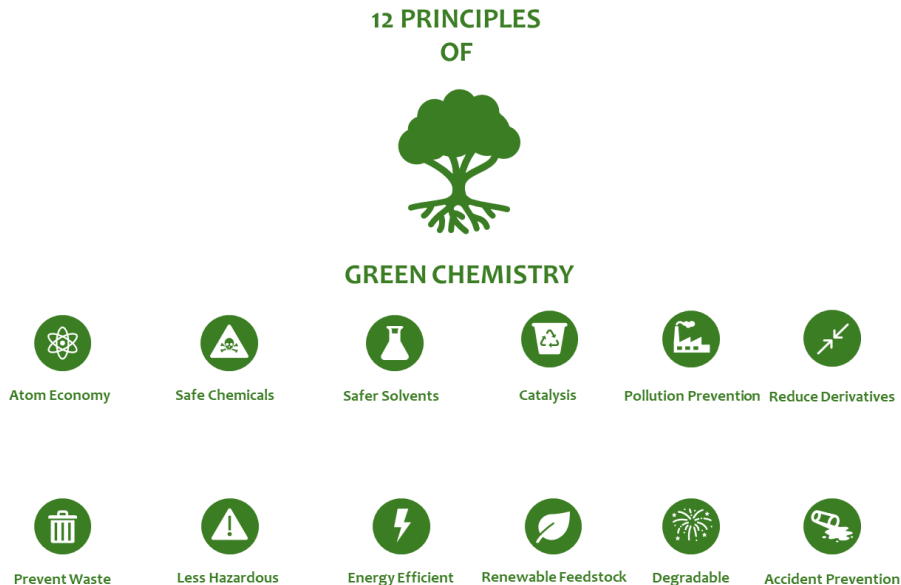


Figure 4.1. 12 Principles of Green Chemistry

The scale of the challenge is immense. According to the Global Waste Management Outlook (GWMO), the world generated approximately 2.1 billion tons of municipal solid waste in 2020.²⁰ This waste stemmed largely from households, agriculture, industry, and construction. Against this backdrop, transforming waste into value-added products is essential. Doing so requires a

combination of effective waste-reduction strategies, innovative recycling technologies, and strong policies that encourage sustainable consumption and production. Agriculture produces vast amounts of plant and livestock waste each year. Over time, researchers and industries have developed a variety of methods to convert these resources into useful products, delivering both environmental and socio-economic benefits.²¹⁻²⁶ Within this context, the principles of the circular economy central to the European Union's sustainability agenda offer a valuable framework. This model promotes sharing, reusing, repairing, refurbishing, and recycling materials to extend product life cycles and reduce environmental impact, helping to close the loop between waste generation and resource use.²⁷⁻²⁹

4.2. Sardinian Wool: An Abundant Biopolymer at the Interface of Nature

Wool, a natural polymer obtained from sheep, is widely valued across the textile, construction, and biomedical industries for its distinctive mechanical and physical properties.^{30, 31} Its primary constituent is the protein keratin (up to 95%), a biopolymer composed of 18 amino acids such as glycine, alanine, cystine, proline, and serine.³²⁻³⁴ Among these, cystine plays a particularly important role due to its sulfur content, which contributes significantly to the structural integrity of the fiber (Figure 4.2). Higher cystine levels increase the sulfur content of wool, enhancing its resistance to physical and chemical treatments and improving its overall physicommechanical performance.³⁴ However, certain sheep breeds yield low-quality fleece that lacks the fineness, strength, or uniformity required for high-value textile applications. EC Regulation 1069/2009 and EU Regulation 142/2011 impose strict sanitary requirements for the disposal of wool biomass³⁵⁻³⁷, posing significant challenges, particularly in Sardinia, where sheep farming and sheep-derived products play a vital economic role.³⁸⁻⁴¹ Due to the predominance of dairy breeds, much of the fleece produced in Sardinia is of low quality for textile applications, leading to considerable volumes of wool waste. Under current regulations, such waste incurs substantial disposal costs, making its valorization both an environmental necessity and a socio-economic priority for the region.^{42, 43}

In this context, chemical processes play a crucial role in the valorization of wool waste. Wool, primarily composed of amino acids, exhibits excellent binding affinities for metal cation centres.^{32, 33, 44, 45} This is further supported by the isoelectric point of wool, which ranges between pH 4.5 and 5, indicating a strong affinity for cationic species.³⁴ This property is particularly desirable for constructing metal support for various reactions. Subsequently, wool-derived keratin powder has been directly used for nitroaldol condensation reactions, as demonstrated by Díaz *et al.* However, their procedure was limited by the utilization of toxic solvents and reagents, such as TBAB, which reduces the green aspect of their methodology.^{46, 47} A reliable and environmentally friendly method for wool valorization is therefore required. Additionally, determining the exact amount of keratin in wool samples are subjected to sample source which can limit the practicability of wool mediated chemical reaction. Thus, wool occur as a challenging reagent for chemical transformations.



Figure 4.2. Wool: its source and composition

4.3. From Fiber to Function: Perspectives on Wool in Literature

Across literature, the catalytic potential of wool has been only sparingly explored. One of the earliest studies was reported by Díaz and co-workers (Figure 4.3.a), who demonstrated the nitroaldol (Henry) reaction between aromatic aldehydes and nitromethane using keratin derived from wool. The wool powder used in their work was commercially purchased and described only as “keratin powder from wool,” leaving it unclear whether it had been obtained by physical, chemical, or combined processing.⁴⁶ They proposed that the catalytic activity originated from amino acid residues in keratin, thus establishing a sustainable protocol for the Henry reaction. However, their procedure was limited by the utilization of toxic solvents and reagents, such as TBAB, which reduces the green aspect of their methodology. In subsequent years, Emanuelsson and co-workers also showed that wool fibers could catalyse the Henry reaction using a spinning mesh disc reactor (SMDR).⁴⁸

Building on these findings, other efforts were directed toward designing wool-based catalysts. A notable example was reported by Faroghi and co-workers, who prepared a solid acid catalyst by oxidizing the S–S bonds in wool with KMnO_4 to generate sulfonic acid ($-\text{SO}_3\text{H}$) functionalities (Figure 4.3.b).⁴⁹ This modified fiber was successfully applied to the synthesis of 3,4-dihydroquinoxalin-2-amine and 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives, all obtained in excellent yields. This work exemplifies an innovative and environmentally friendly application of wool in solid acid catalysis. Furthermore, other studies have employed wool as a catalyst or as a support for enzymes⁵⁰ and metal catalysts^{51–54} in various transformations. In such cases, wool-infused catalysts were not only easy to separate from the reaction mixture but also enhanced reactivity compared to the unsupported catalysts, by acting simultaneously as both a support and a ligand. Despite these promising demonstrations, the catalytic utility of wool remains underexplored, leaving significant opportunities for further investigation.

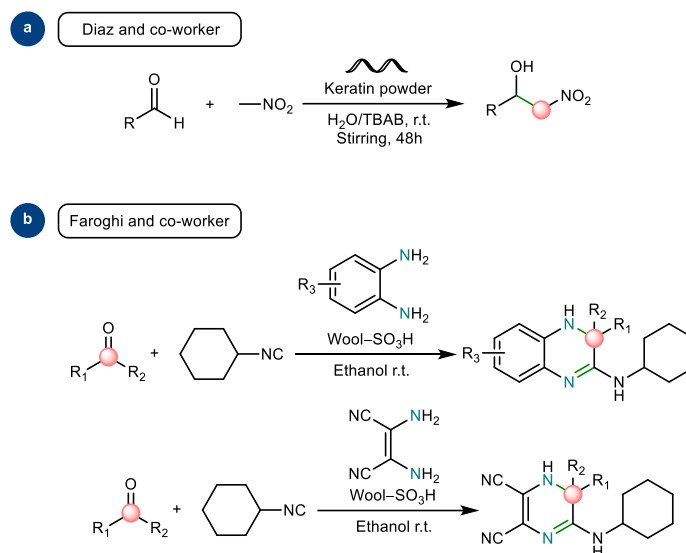


Figure 4.3. Work by a) Diaz and co-workers; b) Faroghi and co-workers

4.4. Grinding Value into Fibers: Mechanochemical Wool Processing for Reactions

The exceptional work of Díaz and co-workers on keratin powder-mediated Henry reactions demonstrates that the catalytic activity arises from the free amino groups present in amino acids. These intrinsic functionalities, typically responsible for base catalysis, highlight the untapped potential of protein-derived materials as natural organo-catalysts. In native wool, however, most free amine groups from amino acids are inaccessible within peptide bonds, which restricts the potential of the catalyst. Mechanochemical treatment through ball milling provides a solution to this limitation by reducing the fiber size, thus exposing additional amino acid residues with their free amine groups and increasing the surface area for reactants to bind with the catalyst.⁵⁵⁻⁵⁷ As free amino acids⁵⁸⁻⁶² are known to effectively promote a wide range of base-catalyzed reactions, including aldol and Knoevenagel condensations, we focused on valorizing wool powder as a sustainable, amino acid-derived catalytic material for these transformations, thereby bridging biopolymer valorization with green mechanochemistry.⁶³⁻⁶⁶

4.5. Results and Discussions

4.5.1. Wool and Feather Sample Sourcing

White wool fibers were collected from Ittiri, a town in the northern region of Sardinia, and black wool was sourced from Guspini, located inland on the island. Chicken feathers were obtained from Concimi-Bio, and the wool was obtained from Sechi Farm, which adheres to strict animal welfare standards. Shearing, a humane and necessary practice, was carried out without causing distress to the animals; in fact, it is essential for their health, as unshorn sheep are prone to parasitic infections and heat stress during Sardinia's hot summers, conditions that can become life threatening. All fibers were obtained in their raw form and subsequently subjected to mechanochemical treatment in our laboratory.

4.5.2. Mechanochemical Processing of Wool and Feather Samples

To ensure their suitability for mechanochemical valorization, wool and feather samples underwent careful purification and preparation. The raw fibers were first thoroughly washed with tap water and soap to remove hydrophilic impurities, followed by successive rinses with heptane and acetone to eliminate residual hydrophobic contaminants. Furthermore, acidified wool was prepared by soaking wool in a 10% HCl solution for 2 days. After several washing cycles, the cleaned fibers were dried either under an infrared lamp or in an oven overnight, yielding pristine starting material. The long fibers obtained from both untreated and acid-treated sources were finely cut to produce short wool fibers (WF) and feather fibers (FF), which were subsequently ball-milled. Optimal grinding conditions were achieved using a planetary ball mill, where 3.00 g of cut fibers were processed in a 20 mL zirconia jar containing zirconia balls (5 mm $\times$ 35, m_{tot} = 13.75 g), affording fine powders. Through this procedure, black wool powder (BWP), white wool powder (WWP), and feather powder (FP) were successfully obtained, providing well-defined biopolymer powders as renewable catalytic materials. Acidified white wool powder (WWP.HCl) and acidified black wool powder (BWP.HCl) were prepared using similar methods.

4.5.3. FT-IR Analysis of Mechanochemically Treated Wool

Fourier-transform infrared (FT-IR) spectroscopy was used to evaluate the secondary structures of wool samples subjected to various mechanical and chemical treatments. Spectrum A (Figure 4.4A) corresponds to black wool fibers, powders, and acid-treated powders, while Spectrum B (Figure 4.4B) represents the corresponding white wool samples.⁶⁷ In Spectrum A, all black wool specimens—including fibers (BWF), powders (BWP), and powders treated with 10% HCl (BWP(HCl))—exhibited a characteristic amide I band at 1657 cm^{-1} , which was assigned to the C=O stretching vibrations of α -helical structures. A pronounced band at 1543 cm^{-1} , attributed to amide II vibrations (N–H bending coupled with C–N stretching), and an additional band at 1635 cm^{-1} , characteristic of β -pleated sheet structures⁶⁷, were consistently observed. The persistence of these signals across all treatments demonstrates that neither mechanochemical processing (ball milling) nor acidic conditions disrupt the intrinsic secondary structure of the black wool keratin. Comparable features were identified in Spectrum B for the white wool samples, with α -helical⁶⁸ and β -sheet structures evident at 1540 and 1635 cm^{-1} , respectively. Thus, both black and white wool exhibit remarkable resistance to structural alterations under the applied mechanical and chemical treatments, underscoring the robustness of keratin's secondary architecture and demonstrating the effectiveness of milling in reducing the particle size of the wool samples.

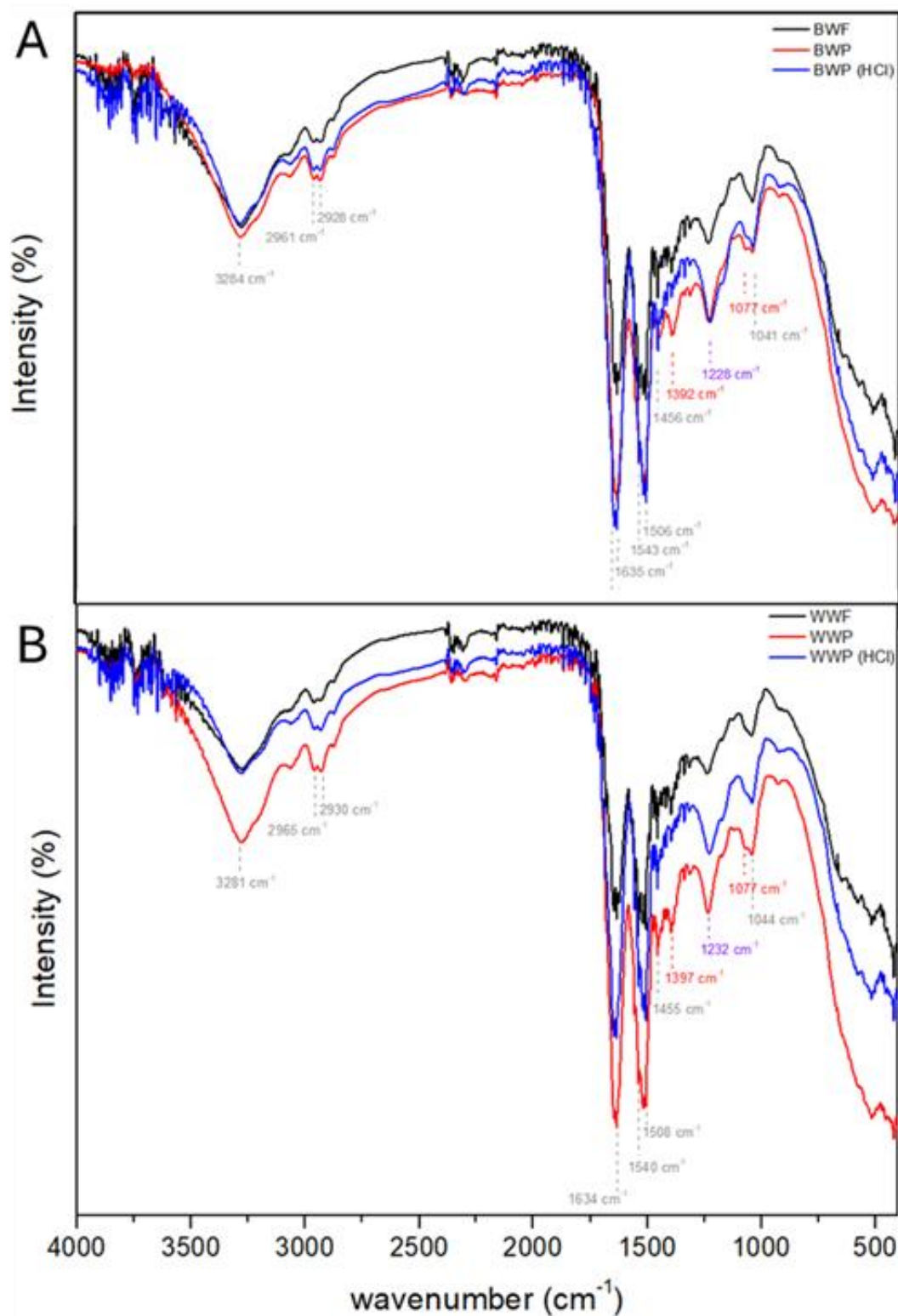


Figure 4.4. FT-IR spectra of wool samples; Spectrum A: black wool fibre (BWF), black wool powder (BWP) and acid treated black wool powder (BWP(HCl)); Spectrum B: white wool fibre (WWF), white wool powder (WWP) and acid treated white wool powder (WWP(HCl))

4.5.4. SEM Analysis

SEM–EDX analysis was conducted on WWF, WWP, WWP(HCl), BWF, BWP, and BWP(HCl) to investigate the morphological alterations induced by mechanical and chemical treatments. Low-magnification images ($\leq 250\ \mu\text{m}$) revealed fragmented fiber particles with roughened surfaces (Figure 4.5). In the powdered samples, distinct longitudinal features remained visible, indicating the partial retention of the fibrous architecture despite milling. Notably, acid-treated samples (WWP(HCl) and BWP(HCl)) exhibited similar pronounced granular roughness with traces of the original fibrous network (Figure 4.6). The heterogeneous morphologies, characterized by cracks and granular domains, confirmed that ball milling promoted significant fiber breakage and surface roughening. These modifications are expected to increase the surface area and expose reactive sites on keratin, thereby enhancing chemical accessibility while preserving the overall fibrous framework, which is consistent with the FT-IR analysis. Comparative SEM–EDX analyses of WWP, WWP(HCl), BWP, and BWP(HCl) revealed that the elemental compositions of both white and black wool powders remained largely unchanged after acid treatment. The major constituents (C, N, O, and S) were preserved, confirming that the keratin framework is chemically stable under the applied conditions of this study. However, in the acid-treated samples, a detectable chlorine signal was observed, most likely arising from residual HCl.

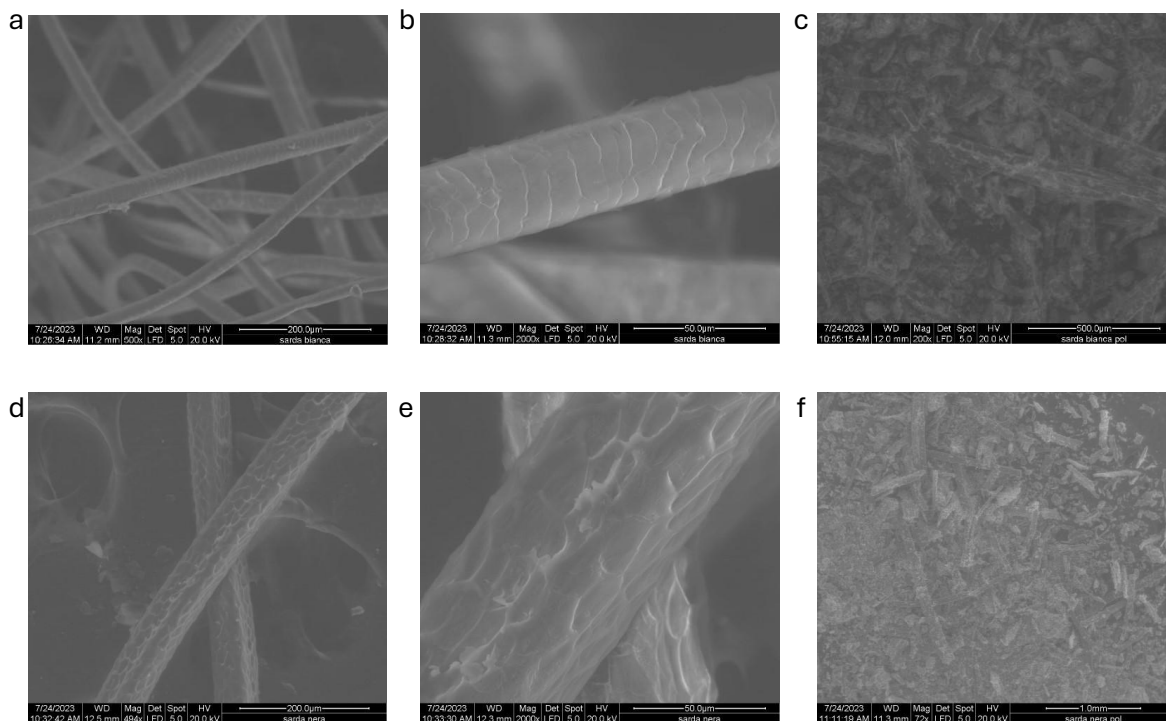


Figure 4.5. SEM images for wool samples before and after the treatment, a) White Wool Fiber (WWF); b) White Wool Fiber (WWF) – magnification; c) White Wool Powder (WWP); d) Black Wool Fiber (BWF); e) Black Wool Fiber (BWF)– magnification; f) Black Wool Powder (BWP)

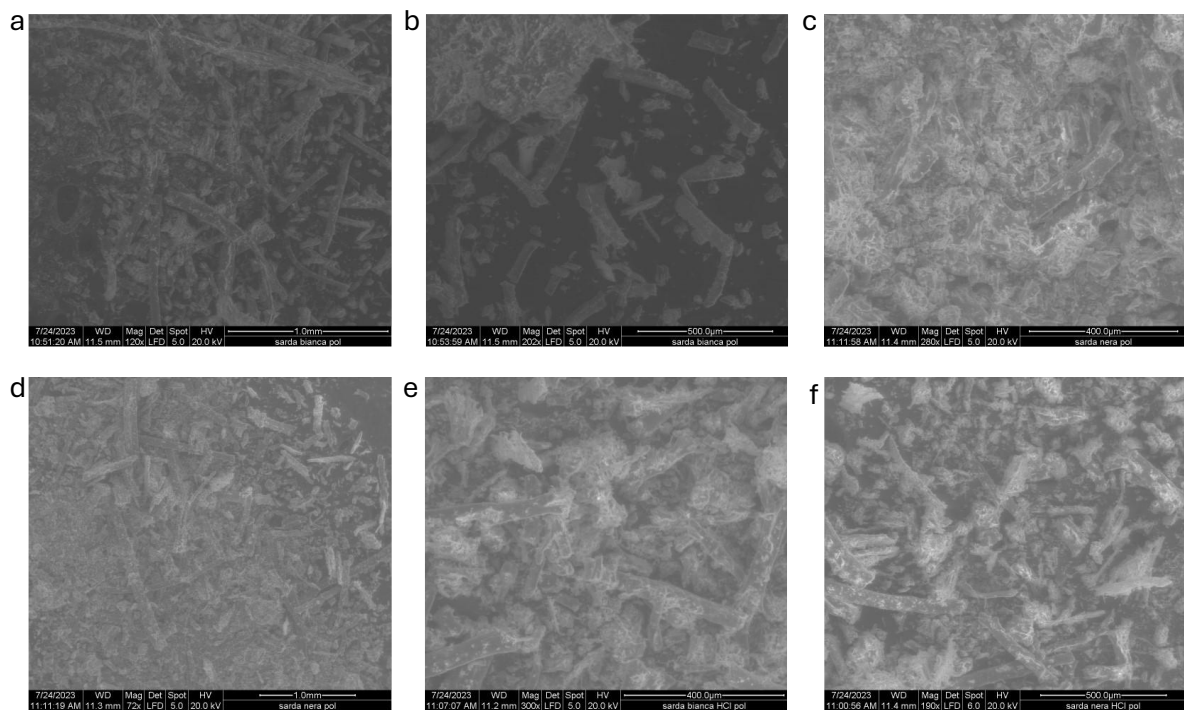


Figure 4.6. SEM images for wool powder samples with and without HCl treatment, a) White Wool Powder (WWP); b) White Wool Powder (WWP) – magnification; c) White Wool Powder-HCl (WWP-HCl); d) Black Wool Fiber (BWP); e) Black Wool Powder (BWP) – magnification; f) Black Wool Powder- HCl (BWP-HCl)

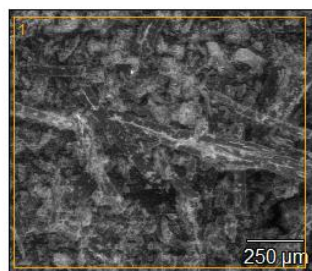
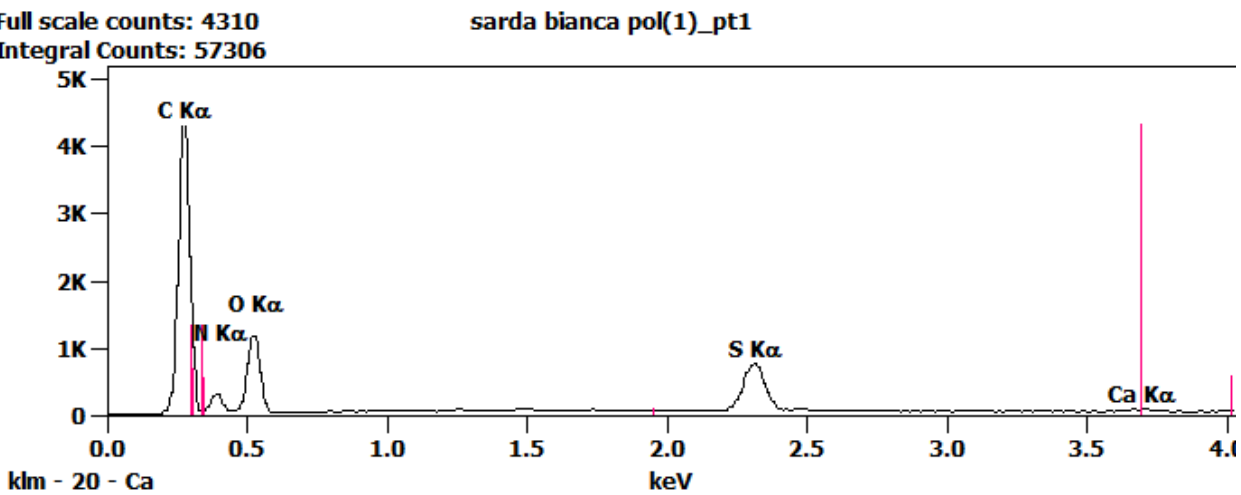


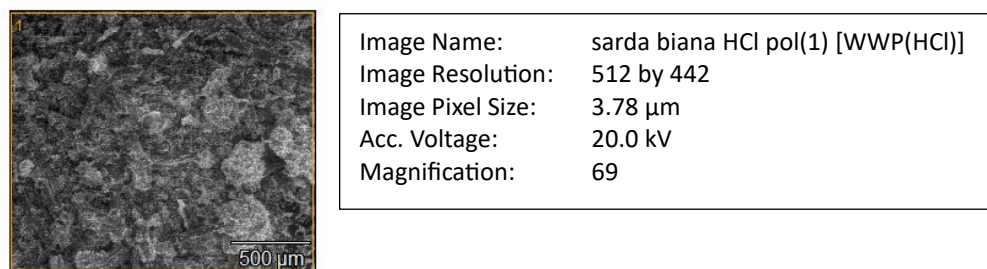
Image Name:	sarda bianca pol(1) [WWP]
Image Resolution:	512 by 442
Image Pixel Size:	2.61 µm
Acc. Voltage:	20.0 kV
Magnification:	100

Full scale counts: 4310
Integral Counts: 57306



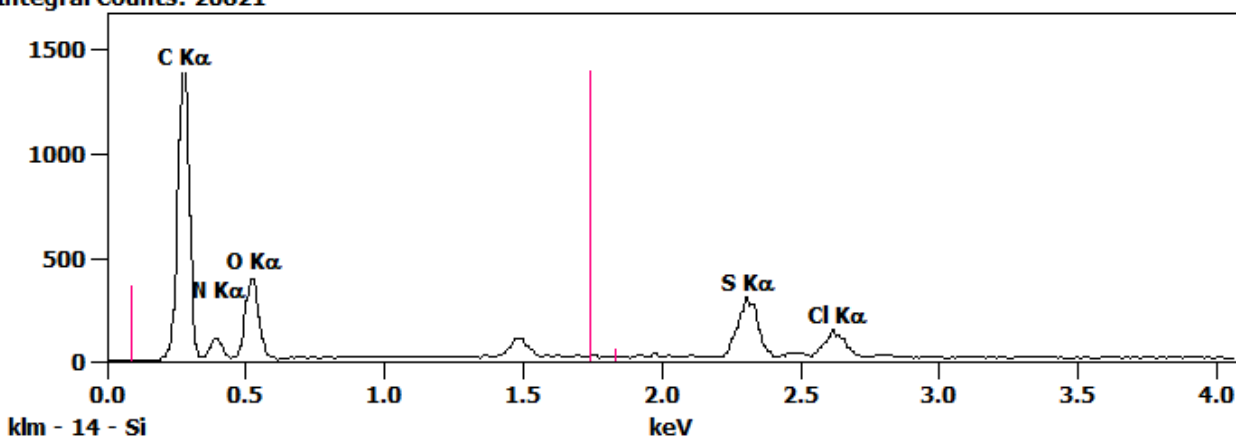
Element	WWP	WWP	WWP	WWP
	Line type	Weight %	Atom %	Atom % err
C K (C)	K	44.9	51.3	0.4
N K (C)	K	21.7	21.3	2.7
O K (C)	K	30.4	26.1	0.5
S K	K	2.6	1.1	0.0
Ca K	K	0.4	0.1	0.0
		100.0	100.0	

Figure 4.7. SEM-EDX analysis for white wool powder (WWP)



Full scale counts: 1395
Integral Counts: 20821

sarda biana HCl pol(1)_pt1



Element	WWP(HCl)	WWP(HCl)	WWP(HCl)	WWP(HCl)
	Line type	Weight %	Atom %	Atom % err
C K (C)	K	39.8	46.0	0.5
N K (C)	K	28.4	28.1	2.2
O K (C)	K	28.1	24.4	0.7
S K	K	2.4	1.1	0.0
Cl K	K	1.2	0.5	0.0
		100.0	100.0	

Figure 4.8. SEM-EDX analysis for white wool powder treated in HCl [WWP(HCl)]

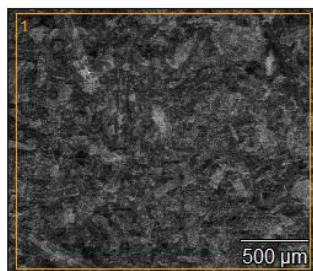
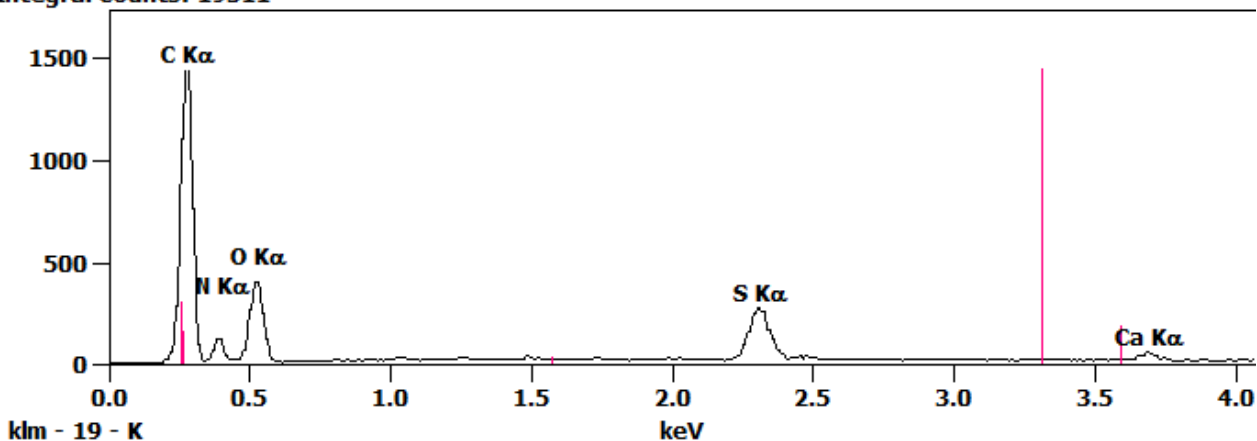


Image Name: sarda nera pol(1) [BWP]
 Image Resolution: 512 by 442
 Image Pixel Size: 4.42 μm
 Acc. Voltage: 20.0 kV
 Magnification: 59

Full scale counts: 1439
 Integral Counts: 19511

sarda nera pol(1)_pt1



Element	BWP	BWP	BWP	BWP
	Line type	Weight %	Atom %	Atom % err
C K (C)	K	43.2	49.7	0.6
N K (C)	K	23.1	22.8	4.4
O K (C)	K	30.3	26.1	0.8
S K	K	2.7	1.2	0.0
Ca K	K	0.6	0.2	0.0
		100.0	100.0	

Figure 4.9. SEM-EDX analysis for black wool powder (BWP)

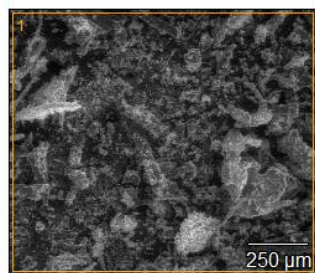
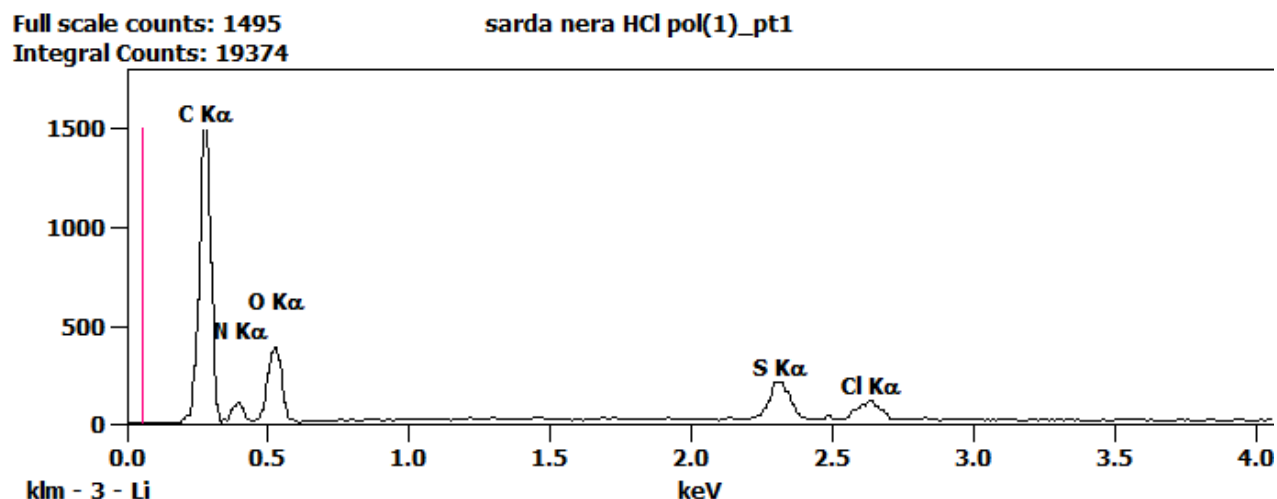


Image Name: sarda nera HCl pol(1) [BWP(HCl)]
 Image Resolution: 512 by 442
 Image Pixel Size: 2.51 μm
 Acc. Voltage: 20.0 kV
 Magnification: 104



Element	BWP(HCl)	BWP(HCl)	BWP(HCl)	BWP(HCl)
	Line type	Weight %	Atom %	Atom % err
C K (C)	K	41.2	47.3	0.5
N K (C)	K	28.1	27.6	2.2
O K (C)	K	27.8	23.9	0.7
S K	K	1.7	0.7	0.0
Cl K	K	1.1	0.4	0.0
		100.0	100.0	

Figure 4.10. SEM-EDX analysis for black wool powder treated in HCl [BWP(HCl)]

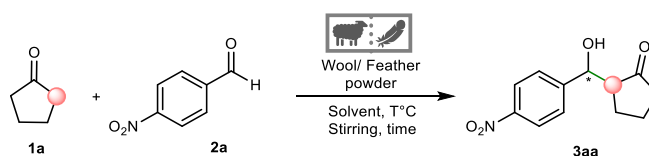
4.5.5. Aldol Reaction

The catalytic efficacy of wool was initially evaluated by a model transformation. The aldol addition between cyclopentanone (**1a**) and 4-nitrobenzaldehyde (**2a**) was selected to obtain the corresponding aldol product (**3aa**) in the presence of white wool powder. The optimal conditions were determined to be **2a** (0.2 mmol), **1a** (1.00 mmol), 98 μ L of water, and 50 mg of white wool powder (WWP), which was gently stirred at room temperature for seven days. Under these conditions, the reaction was successfully carried out, and the aldol product was obtained in 98% yield (Table 4.1, entry 1). Deviations from the standard conditions were also studied.

The stoichiometric ratio for the aldol reaction was initially fine-tuned, and it was found that the reaction proceeded efficiently with a tenfold excess of **1a** (entry 2, Table 4.1). Interestingly, halving this amount did not significantly diminish the yield, allowing a 1:5 ratio of **2a** to **1a** to be adopted as the standard to minimize waste (entry 1, Table 4.1). Further reductions in the quantity of **2a** resulted in markedly lower yields than those under the optimized conditions. Notably, when the amount of WWP was decreased from 50 mg to 25 mg, the conversion to **3aa** dropped dramatically from 98% to 47% (entry 3, Table 4.1), indicating that 50 mg of WWP was the minimum required to achieve efficient catalysis for this transformation. Comparable results were obtained when WWP was replaced with black wool powder (BWP) or chicken feather powder (FP), further supporting the role of keratin powder in the reaction (entries 4 and 5, Table 4.1).

When WWP(HCl) was employed instead of WWP, the yield of **3aa** decreased dramatically (entry 6, Table 4.1), indicating that ionizable nitrogen-containing side chains play a pivotal role in the reaction, further supporting an enamine-mediated catalytic pathway. Shortening the reaction time from seven to four days also led to a marked decrease in conversion, with the yield of **3aa** decreasing to 61% (entry 7, Table 4.1). The reaction in the presence of WWF instead of WWP resulted in significantly lower yields than WWP (entry 8, Table 4.1), suggesting the significance of the mechanical treatment of wool fibers. This effect can be attributed to the increased surface area and abundance of active sites generated upon grinding the keratin fibers, while the primary and secondary protein structures remain largely intact, as confirmed by the FT-IR spectra and SEM analysis of the treated samples (Figure 4.4 to 4.6). Finally, the analysis of different solvent conditions and a controlled temperature of 40 °C did not provide any significant advantage (entries 9-13, Table 4.1), likely due to the hydrophilic-hydrophobic balance between the wool powder and reagents.

Table 4.1. Screening for wool mediated aldol reaction

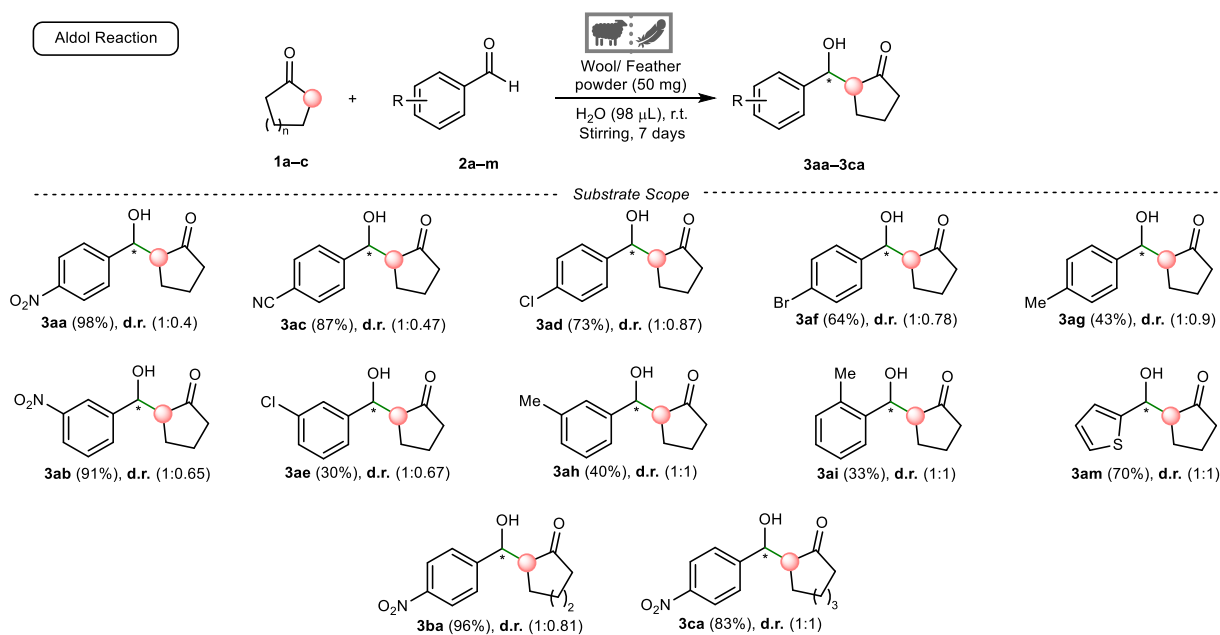


Entry	Deviation from Standard Conditions	NMR Conversion
1	None	98% ^{a, b}
2	10 mmol of 1a	99% ^b
3	25mg of WWP instead of 50mg of WWP	47% ^b
4	50 mg of BWP instead of WWP	93% ^{b, c}
5	FP instead of WWP	95% ^{b, d}
6	50 mg of WWP(HCl) instead of WWP	23% ^b
7	4 days of reaction time instead of 7 days	61% ^b
8	50 mg of WWF instead of WWP	7% ^b
9	1 mL of H ₂ O instead of 98 μL of H ₂ O	58% ^b
10	98 μL of DMSO instead of H ₂ O	—
11	98 μL of EtOH instead of H ₂ O	—
12	98 μL of EtOAc instead of H ₂ O	12% ^b
13	40°C instead of rt	80% ^b
14	No WWP ^e	—

^a Reaction Conditions: **2a** (0.20 mmol), **1a** (1.00 mmol), water (98 μL), and 50 mg of white wool powder were gently stirred at r.t. for 7 days; NMR conversion was calculated using trimethoxybenzene as an internal standard; ^b approximate diastereoisomer ratio (*anti/syn* = 0.4:1); ^c approximate diastereoisomer ratio (*anti/syn* = 0.5:1); ^d approximate diastereoisomer ratio (*anti/syn* = 0.5:1); ^e the reaction was monitored for 10 days.

The efficacy of the protocol was verified by extending the substrate scope of the wool powder-mediated aldol reaction (Scheme 4.1). Aldehydes with electron-withdrawing groups **2a–f** reacted efficiently with cyclopentanone **1a** to give the desired products. For instance, *para*-substituted aldehydes with nitro (**2a**) and nitrile (**2c**) groups afforded excellent yields of 98% and 87%, respectively. Benzaldehydes with *para*-halogen substituents (**2d** and **2f**) provided moderate to good yields of 73% and 64%, respectively. In contrast, an electron-donating group at the *para*-

position (**2 g**) resulted in a significantly lower yield of 43% compared to its electron-withdrawing analogues. The positional effect of substituent groups on the benzaldehyde ring from para- to meta- position yielded comparable yields. However, for aldehyde **2e**, a significant drop in yield was observed compared to its *para*-substituted counterpart (**2d**). Similarly, *ortho*-methyl substitution (**2i**) led to a reduced yield of 33% compared to para- and meta-isomers. The reaction of **1a** with a heteroaryl aldehyde (**2m**) also proceeded smoothly, affording the product in an excellent yield of 70%. Changing the ketone to cyclohexanone (**1b**) and cycloheptanone (**1c**) with **2a** resulted in smooth conversion to products **3ba** and **3ca** with yields of 96% and 83%, respectively. The reactions performed with black wool powder (BWP) and feather powder (FP) resulted in similar yields and diastereomeric ratios. Notably, for benzaldehydes **2a** and **2i**, an inverted diastereomeric ratio (syn/anti = 1:0.6) was obtained using black wool powder (BWP) instead of white wool powder (WWP).

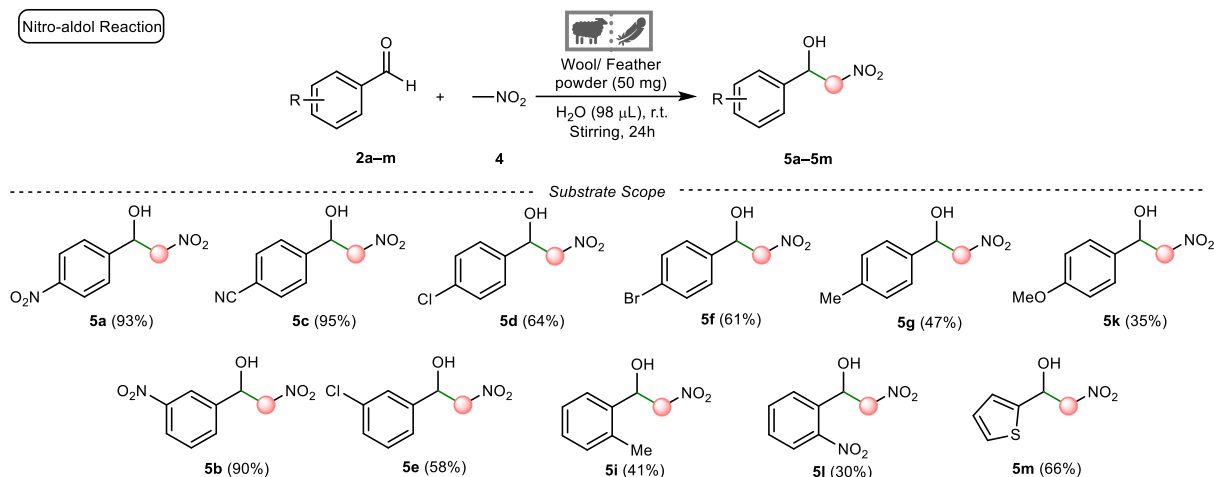


Scheme 4.1. Substrate scope for wool-mediated aldol reaction. Reaction conditions: **1** (1.00 mmol), **2** (0.2 mmol), water (98 µL), and 50 mg of white wool powder were gently stirred at r.t. for 7 days, and the yields of the products were calculated after filtration through a paper filter using ethyl acetate (EtOAc) and concentrated under reduced pressure.

4.5.6. Nitro-Aldol Reaction

Following the successful synthesis of aldol products using wool powder, efforts were made to extend the methodology to the nitro-aldol reaction (Henry reaction). Based on the findings from the wool powder-mediated aldol reaction, initial reaction screening for the Henry reaction was carried out using 4-nitro benzaldehyde (**2a**) and nitromethane (**4**) as model substrates in the presence of white wool powder (WWP). Initial screening was carried out with **2a** (0.2 mmol), **4** (2.0 mmol), 98 µL of water, and 50 mg of white wool powder (WWP) and the reaction progress was monitored using TLC. The optimal conditions were determined to be **2a** (0.2 mmol), **4** (2.0 mmol), 98 µL of water, and 50 mg of white wool powder (WWP), which was gently stirred at room

temperature for 24h. Additionally, with the decrease in WWP from 50mg to 25mg failed to provide full conversion to the product.



Scheme 4.2. Substrate scope for the wool-mediated Henry reaction. Reaction conditions: **4** (2.00 mmol), **2** (0.2 mmol), water (98 μ L), and 50 mg of white wool powder were gently stirred at r.t. for 24h and yields of the products were calculated after filtration through a paper filter using ethyl acetate (EtOAc) and concentrating under reduced pressure.

With the optimization conditions established, nitroaldol reaction proceeded efficiently with aldehydes bearing electron-withdrawing groups (Scheme 4.2). *Para*-substituted benzaldehydes containing electron-withdrawing substituents (**2a-f**) afforded excellent yields (61–93%). In contrast, *para*-substituted aldehydes with electron-donating groups (**2g** and **2k**) yielded noticeably lower yields. Analysis of the positional effects showed that moving the substituents from the *para* to the *meta* position resulted in comparable yields, whereas *ortho*-substitution significantly decreased the efficiency, yielding only 41% (**5i**) and 30% (**5l**). Interestingly, heteroaromatic aldehyde **2m** reacted smoothly with **4** to furnish the nitro-aldol product in a good yield of 66%. Black wool and chicken feather powders were also used to assess the products, and comparable outcomes were obtained. The product evolution over time for the nitro-aldol reaction using aldehyde **2a** was monitored until the completion of the reaction, as determined by GC-MS (Figure 4.11).

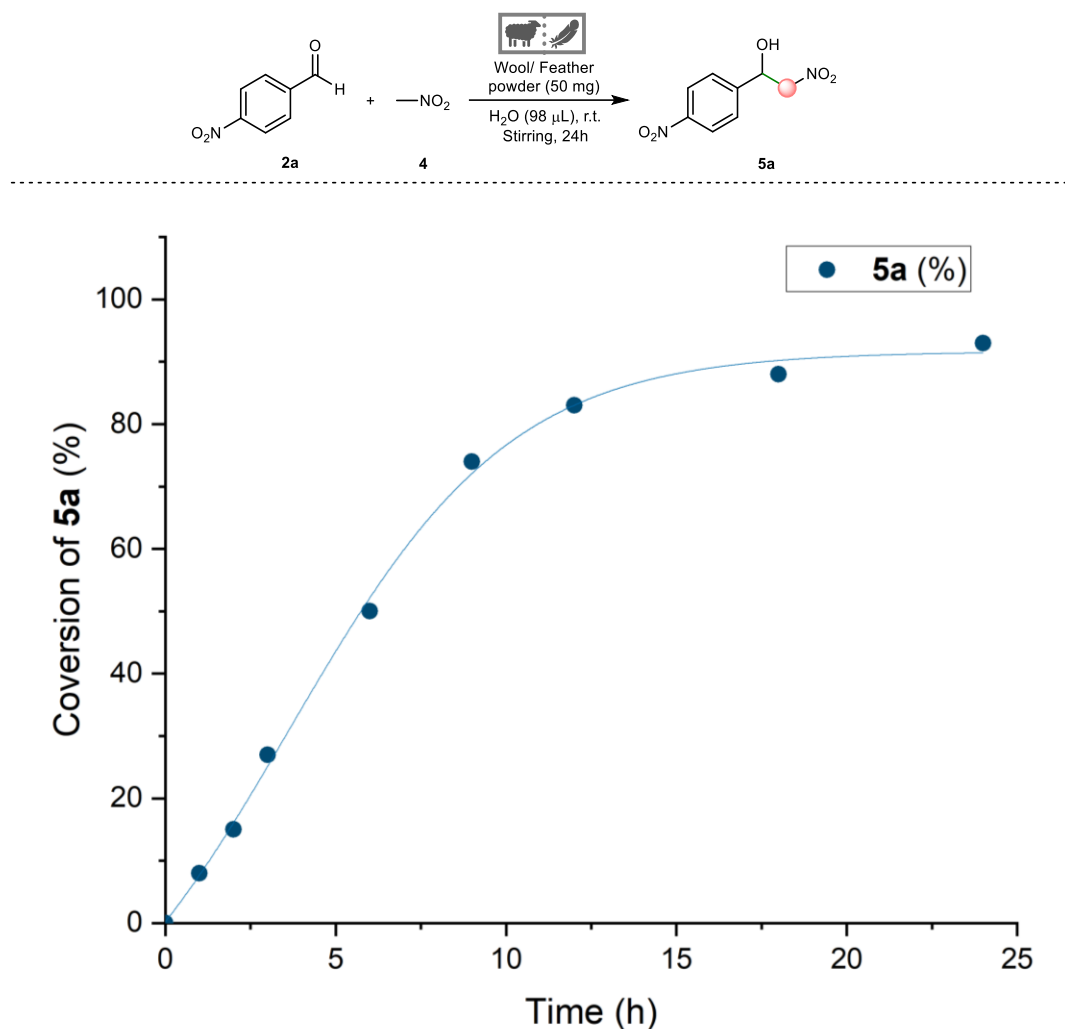
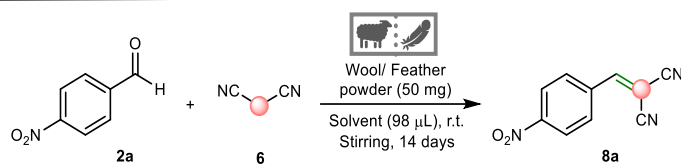


Figure 4.11. Product evolution over-time for **5a**, determined through GC-MS

4.5.7. Knoevenagel Reaction

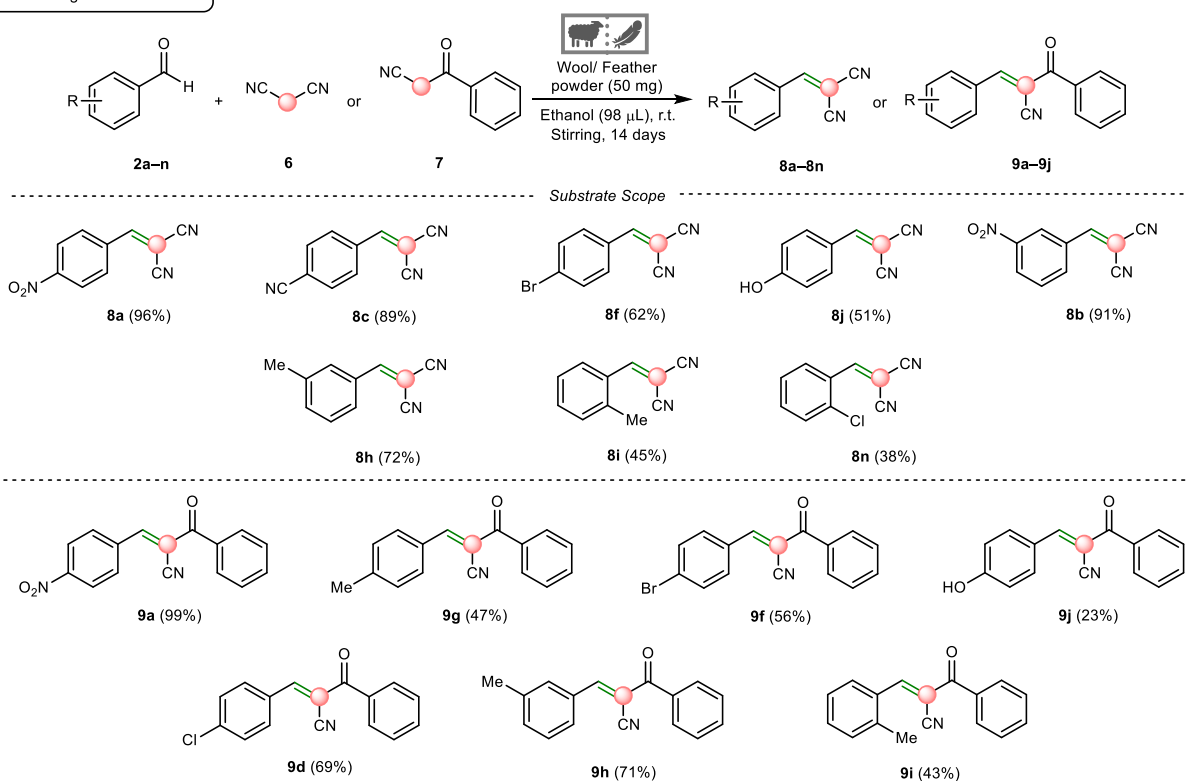
Building upon our pre-established optimized conditions for aldol and nitro-aldol reactions, we shifted our focus to wool powder-mediated Knoevenagel reactions using 4-nitro benzaldehyde (**2a**) and dicyanomalonate (**6**) as model substrates along with WWP. To circumvent purification by column chromatography, a stoichiometric amount of **2a** (0.2 mmol), **6** (0.2 mmol), 98 μ L of water, and 50 mg of white wool powder (WWP) were gently stirred at room temperature for 14 days to obtain the Knoevenagel product. Unfortunately, a very low yield of the Knoevenagel product (8%) was observed in the NMR spectra, which can be attributed to the final dehydration process associated with the formation of Knoevenagel products (entry 1, Table 4.2). Therefore, a series of solvents were screened using the same methodology. Excellent yields of Knoevenagel products were observed in the presence of alcoholic solvents, with absolute ethanol delivering the best result (entry 6, Table 4.2), affording the Knoevenagel product with a 98% yield in NMR.

Table 4.2. Solvent screening for wool mediated Knoevenagel reaction

Entry	Solvent Selection	NMR Conversion ^a
1	Distilled H ₂ O	08%
2	n-Hexane	23%
3	Toluene	20%
4	EtOAc	73%
5	MeOH	96%
6	Absolute EtOH	98%
7	2-MeTHF	58%

^a Reaction Conditions: **2a** (0.20 mmol), **6** (0.20 mmol), solvent (98 μ L), and 50 mg of white wool powder were gently stirred at r.t. for 7 days, NMR Conversion was calculated using trimethoxy benzene as internal standard

Knoevenagel Condensation



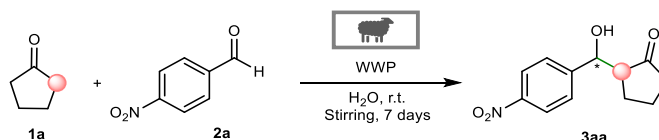
Scheme 4.3. Substrate scope for the wool-mediated Knoevenagel reaction. Reaction conditions: **2a-n** (0.2 mmol), **6** or **7** (0.2 mmol), absolute ethanol (98 μ L), and 50 mg of white wool powder were gently stirred at r.t. for 14 days and yields of the products were calculated after filtration through a paper filter using ethyl acetate (EtOAc) and concentrating under reduced pressure.

Based on the optimized reaction conditions, the efficacy of the protocol was further verified by extending the substrate scope (Scheme 4.3). Benzaldehyde derivatives with electron withdrawing groups at *para*-position (**2a-f**) reacted efficiently with dicyanomalonate (**6**) to prove excellent yields, whereas aldehyde with –OH substitution at *para*-position provided significantly less yield of Knoevenagel product (51%). Similar to previous observations regarding the positional effect of substitutions in wool powder-mediated aldol and nitro-aldol reactions, *meta*-substituted aldehydes provided comparable yields of Knoevenagel products. Similarly, *ortho*-substituted aldehydes reacted poorly compared to their *para*- and *meta*-substituted counterparts. Aldehydes **2i** and **2n** yielded 45% and 38% of the product, respectively, when reacted with **6**. A similar trend was observed when dicyanomalonate (**6**) was substituted with benzoylacetonitrile (**7**). Overall, a broad scope of benzaldehyde derivatives (**2a–n**) furnished the Knoevenagel products in yields ranging from excellent (96%) to moderate (38%), with *meta*-substituted substrates performing comparably to their *para*-substituted counterparts and *ortho*-substituted substrates showing consistently diminished reactivity.

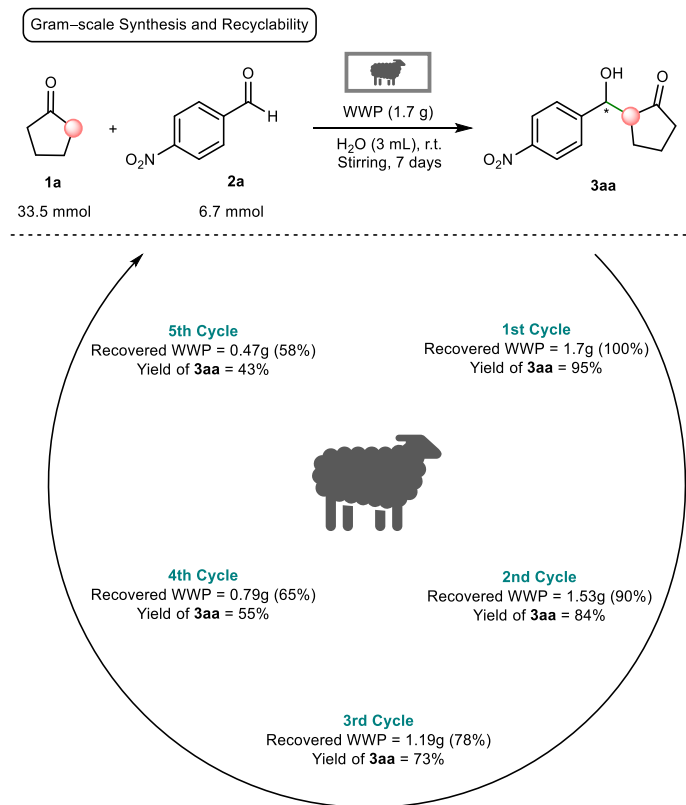
4.6. Gram–Scale Reaction and Recyclability

The recyclability of wool powder is a critical parameter for evaluating the sustainability and practical utility of wool-mediated aldol, Henry, and Knoevenagel reactions. Reusable catalytic systems not only minimize waste generation and operational costs but also align with the principles of green chemistry by reducing the reliance on non-renewable resources. To demonstrate this, a recyclability study was performed using WWP for gram-scale aldol reactions. For the reaction cycles, 4–nitrobenzaldehyde (6.7 mmol) along with cyclopentanone (33.5 mmol) and WWP (1.7 g) was used, and the recovered WWP was used for the next reaction cycle up to five reaction cycles (Scheme 4.4). This study confirmed that WWP can be successfully recycled to promote aldol product formation across multiple runs (Figure 4.12). Furthermore, the linear relationship between the yield of aldol product **3aa** and the progressive mass of WWP during recovery suggests that both the material integrity and effective quantity of wool powder play a decisive role in governing the reaction outcome (Figure 4.13, $R^2=0.99905$).

Table 4.3. Gram–scale reaction recycling experiments



Entry	Cycle	Recovered WWP (%)	Isolated Yield ^a
1	1 st Cycle	100%	95%
2	2 nd Cycle	90%	90%
3	3 rd Cycle	78%	73%
4	4 th Cycle	65%	55%
5	5 th Cycle	58%	43%



Scheme 4.4. Reaction conditions: **1a** (33.5 mmol), **2a** (6.7 mmol), water (3 mL), and 1.7 g of white wool powder were gently stirred at r.t. for 7 days and yields of the products were calculated after filtration through a paper filter using ethyl acetate (EtOAc) and concentrating under reduced pressure.

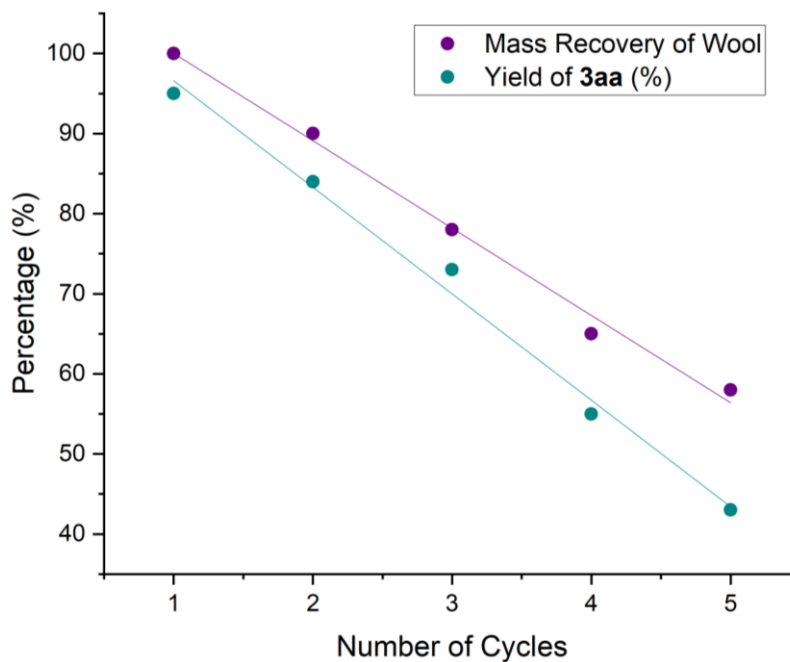


Figure 4.12. Mass of recovered WWP with respect to number of cycles for the product formation of **3aa**

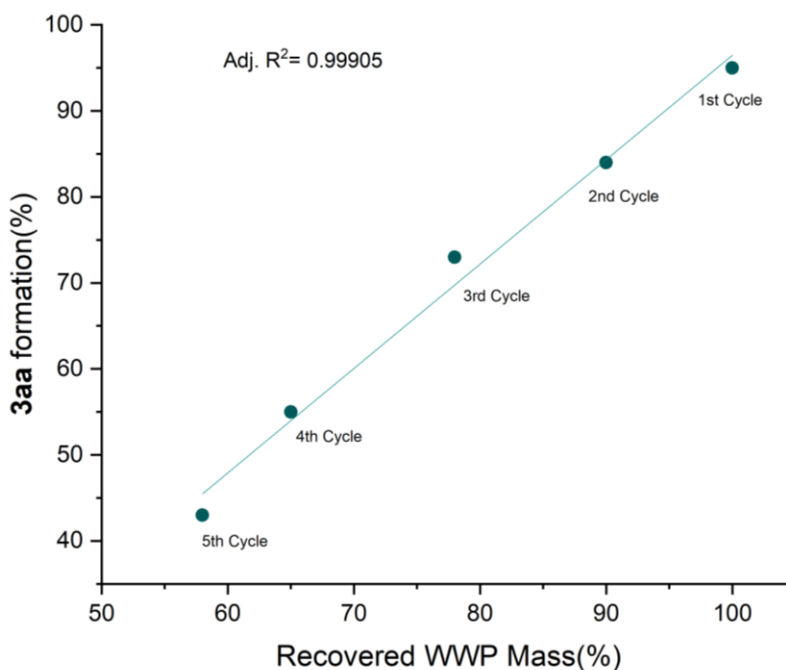


Figure 4.13. Comparison between recovered WWP over 5 cycles and yield % of product **3aa**

4.7. Conclusion

This chapter demonstrates the potential of Sardinian wool as a renewable and sustainable catalytic medium for diverse organic transformations. Owing to its keratin content and abundance of functional groups, wool offers distinct advantages in heterogeneous catalysis, as evidenced by its efficacy in promoting aldol, nitro-aldol, and Knoevenagel reactions under optimized conditions. Our studies revealed that stoichiometry, catalytic support composition, and mechanical processing critically influence catalytic performance, while FT-IR and SEM-EDX analyses confirmed that the structural integrity of wool was largely preserved across treatments. Comparative studies on chicken feathers further emphasize the broader applicability of keratin-based biomaterials. Beyond their chemical relevance, these findings highlight the economic and environmental significance of valorizing locally sourced wool, transforming an agricultural waste stream into a functional material that directly supports the principles of circular economy. Importantly, the application of mechanochemical treatment has proven pivotal in enhancing the catalytic properties of wool, illustrating its potential as a powerful tool for biopolymer valorization. Whereas the conventional paradigm regards such residues as disposable waste, mechanochemistry offers an alternative pathway that not only facilitates the controlled degradation of complex biomaterials but also redefines them as valuable resources for sustainable organic synthesis. Thus, the mechanochemical activation of wool waste represents a paradigm shift in how waste is perceived, managed, and integrated into chemical value chains, opening a new frontier for green chemistry and circular resource utilization.

4.8. References

- (1) Ratti, R. Industrial applications of green chemistry: Status, Challenges and Prospects. *SN Appl. Sci.* **2020**, 2 (2), 263.
- (2) Eilks, I.; Rauch, F. Sustainable development and green chemistry in chemistry education. *Chemistry Education Research and Practice* **2012**, 13 (2), 57-58.
- (3) Dunn, P. J. The importance of green chemistry in process research and development. *Chem. Soc. Rev.* **2012**, 41 (4), 1452-1461.
- (4) Kirchhoff, M. M. Promoting sustainability through green chemistry. *Resour. Conserv. Recycl.* **2005**, 44 (3), 237-243.
- (5) Cioc, R. C.; Ruijter, E.; Orru, R. V. Multicomponent reactions: advanced tools for sustainable organic synthesis. *Green Chem.* **2014**, 16 (6), 2958-2975.
- (6) Anastas, P. T.; Lankey, R. L. Sustainability through green chemistry and engineering. ACS Publications, 2002.
- (7) Karpudewan, M.; Ismail, Z.; Roth, W.-M. Ensuring sustainability of tomorrow through green chemistry integrated with sustainable development concepts (SDCs). *Chemistry Education Research and Practice* **2012**, 13 (2), 120-127.
- (8) Anastas, P.; Eghbali, N. Green chemistry: principles and practice. *Chem. Soc. Rev.* **2010**, 39 (1), 301-312.
- (9) Erythropel, H. C.; Zimmerman, J. B.; de Winter, T. M.; Petitjean, L.; Melnikov, F.; Lam, C. H.; Lounsbury, A. W.; Mellor, K. E.; Janković, N. Z.; Tu, Q. The Green ChemisTREE: 20 years after taking root with the 12 principles. *Green Chem.* **2018**, 20 (9), 1929-1961.
- (10) Jessop, P. G.; Trakhtenberg, S.; Warner, J. The twelve principles of green chemistry. ACS Publications, 2009.
- (11) Casti, F.; Basoccu, F.; Mocci, R.; De Luca, L.; Porcheddu, A.; Cuccu, F. Appealing renewable materials in green chemistry. *Molecules* **2022**, 27 (6), 1988.
- (12) Clark, J. H.; Budarin, V.; Deswarte, F. E.; Hardy, J. J.; Kerton, F. M.; Hunt, A. J.; Luque, R.; Macquarrie, D. J.; Milkowski, K.; Rodriguez, A. Green chemistry and the biorefinery: a partnership for a sustainable future. *Green Chem.* **2006**, 8 (10), 853-860.
- (13) Gallezot, P. Process options for converting renewable feedstocks to bioproducts. *Green Chem.* **2007**, 9 (4), 295-302.
- (14) Höfer, R.; Bigorra, J. Biomass-based green chemistry: sustainable solutions for modern economies. *Green Chem. Lett. Rev.* **2008**, 1 (2), 79-97.
- (15) Gude, V. G.; Martinez-Guerra, E. Green chemistry with process intensification for sustainable biodiesel production. *Environ. Chem. Lett.* **2018**, 16 (2), 327-341.
- (16) Dimitratos, N.; Lopez-Sanchez, J. A.; Hutchings, G. J. Green catalysis with alternative feedstocks. *Top. Catal.* **2009**, 52 (3), 258-268.
- (17) Yayayürük, A. E.; Yayayürük, O. Applications of green chemistry approaches in environmental analysis. *Anal. Chem.* **2019**, 15 (7), 745-758.
- (18) Varma, R. S. Green chemistry with microwave energy. In *Innovations in Green Chemistry and Green Engineering: Selected Entries from the Encyclopedia of Sustainability Science and Technology*, Springer, 2012; pp 115-156.
- (19) Hidalgo, D.; Corona, F.; Martín-Marroquín, J. M.; Gómez, M.; Aguado, A.; Antolín, G. Integrated and sustainable system for multi-waste valorization. *Environ. Eng. Manag. J.* **2014**, 13 (10), 2467-2475.
- (20) <https://www.unep.org/ietc/resources/report/global-waste-management-outlook-2024> (accessed 23/10/2025).
- (21) Sadhukhan, J.; Martinez-Hernandez, E. Material flow and sustainability analyses of biorefining of municipal solid waste. *Bioresour. Technol.* **2017**, 243, 135-146.
- (22) Kothari, R.; Singh, A.; Pandey, A.; Tyagi, V.; Egamberdieva, D.; Bellingrath-Kimura, S. D.; Arora, N. K. Valorization of bio-waste material: Future dimensions for path towards sustainability. *Environ. Sustain.* **2021**, 4 (2), 199-200.

- (23) Caldeira, C.; Vlysidis, A.; Fiore, G.; De Laurentiis, V.; Vignali, G.; Sala, S. Sustainability of food waste biorefinery: A review on valorisation pathways, techno-economic constraints, and environmental assessment. *Bioresour. Technol.* **2020**, *312*, 123575.
- (24) Jin, Q.; Yang, L.; Poe, N.; Huang, H. Integrated processing of plant-derived waste to produce value-added products based on the biorefinery concept. *Trends Food Sci. Technol.* **2018**, *74*, 119-131.
- (25) Kwan, T. H.; Hu, Y.; Lin, C. S. K. Techno-economic analysis of a food waste valorisation process for lactic acid, lactide and poly (lactic acid) production. *J. Clean. Prod.* **2018**, *181*, 72-87.
- (26) Marcelino, S.; Gaspar, P. D.; Paco, A. Sustainable waste management in the production of medicinal and aromatic plants—A systematic review. *Sustainability* **2023**, *15* (18), 13333.
- (27) Ben-Othman, S.; Jõudu, I.; Bhat, R. Bioactives from agri-food wastes: Present insights and future challenges. *Molecules* **2020**, *25* (3), 510.
- (28) Hepburn, C.; Adlen, E.; Beddington, J.; Carter, E. A.; Fuss, S.; Mac Dowell, N.; Minx, J. C.; Smith, P.; Williams, C. K. The technological and economic prospects for CO₂ utilization and removal. *Nature* **2019**, *575* (7781), 87-97.
- (29) Huang, Z.; Grim, R. G.; Schaidle, J. A.; Tao, L. The economic outlook for converting CO₂ and electrons to molecules. *Energy Environ. Sci.* **2021**, *14* (7), 3664-3678.
- (30) Bouagga, T.; Harizi, T.; Sakli, F.; Zoccola, M. Correlation between the mechanical behavior and chemical, physical and thermal characteristics of wool: A study on Tunisian wool. *J. Nat. Fibers* **2020**.
- (31) Ballagh, K. O. Acoustical properties of wool. *Appl. Acoust.* **1996**, *48* (2), 101-120.
- (32) Rajabinejad, H.; Zoccola, M.; Patrucco, A.; Montarsolo, A.; Rovero, G.; Tonin, C. Physicochemical properties of keratin extracted from wool by various methods. *Text. Res. J.* **2018**, *88* (21), 2415-2424.
- (33) Cardamone, J. M. Investigating the microstructure of keratin extracted from wool: Peptide sequence (MALDI-TOF/TOF) and protein conformation (FTIR). *J. Mol. Struct.* **2010**, *969* (1-3), 97-105.
- (34) Shavandi, A.; Silva, T. H.; Bekhit, A. A.; Bekhit, A. E.-D. A. Keratin: dissolution, extraction and biomedical application. *Biomater. Sci.* **2017**, *5* (9), 1699-1735.
- (35) Batrićević, A.; Paunović, N. Waste disposal in the European Union: Normative framework and practice. *Strani pravni život* **2017**, *61* (4), 107-122.
- (36) Vehlow, J.; Bergfeldt, B.; Visser, R.; Wilén, C. European Union waste management strategy and the importance of biogenic waste. *J. Mater. Cycle Waste Manag.* **2007**, *9* (2), 130-139.
- (37) Väntsi, O.; Kärki, T. Mineral wool waste in Europe: a review of mineral wool waste quantity, quality, and current recycling methods. *J. Mater. Cycle Waste Manag.* **2014**, *16* (1), 62-72.
- (38) Wang, D.; Tang, Y.-T.; Long, G.; Higgitt, D.; He, J.; Robinson, D. Future improvements on performance of an EU landfill directive driven municipal solid waste management for a city in England. *Waste Management* **2020**, *102*, 452-463.
- (39) Bhavsar, P.; Zoccola, M.; Patrucco, A.; Montarsolo, A.; Mossotti, R.; Rovero, G.; Giansetti, M.; Tonin, C. Superheated water hydrolysis of waste wool in a semi-industrial reactor to obtain nitrogen fertilizers. *ACS Sustain. Chem. Eng.* **2016**, *4* (12), 6722-6731.
- (40) Vagnoni, E.; Carrino, C.; Dibenedetto, N.; Pieragostini, E.; Consenti, B. The enhancement of native sheep's wool: Three case studies from some Italian regions. *Small Rumin. Res.* **2016**, *135*, 85-89.
- (41) Atzori, A. S.; Bayer, L.; Molle, G.; Arca, P.; Franca, A.; Vannini, M.; Cocco, G.; Usai, D.; Duce, P.; Vagnoni, E. Sustainability in the Sardinian sheep sector: A systems perspective, from good practices to policy. *Integr. Environ. Assess.* **2022**, *18* (5), 1187-1198.
- (42) Iacovidou, E.; Ohandja, D.-G.; Voulvoulis, N. Food waste disposal units in UK households: The need for policy intervention. *Sci. Total Environ.* **2012**, *423*, 1-7.
- (43) Banterle, A.; Marchini, A.; Mathijs, E.; Russo, C.; Zylbersztajn, D. Agricultural and Food Economics: A new journal for a changing world. *Agric. Food Econ.* **2013**, *1*, 1-2.
- (44) Ross, R.; Fairbridge, C.; MacCallum, J. Carbon fibres as supports for transition metal catalysts in hydrocarbon oxidation reactions. *Carbon* **1985**, *23* (2), 209-213.
- (45) Durkin, D. P.; Ye, T.; Larson, E. G.; Haverhals, L. M.; Livi, K. J.; De Long, H. C.; Trulove, P. C.; Fairbrother, D. H.; Shuai, D. Lignocellulose fiber-and welded fiber-supports for palladium-based catalytic

hydrogenation: a natural fiber welding application for water treatment. *ACS Sustain. Chem. Eng.* **2016**, *4* (10), 5511-5522.

(46) Häring, M.; Pettignano, A.; Quignard, F.; Tanchoux, N.; Diaz Diaz, D. Keratin protein-catalyzed nitroaldol (henry) reaction and comparison with other biopolymers. *Molecules* **2016**, *21* (9), 1122.

(47) Tobiszewski, M.; Bystrzanowska, M. Monetary values estimates of solvent emissions. *Green Chem.* **2020**, *22* (22), 7983-7988.

(48) Shivaprasad, P.; Jones, M. D.; Patterson, D. A.; Emanuelsson, E. A. C. Process intensification of catalysed henry reaction using copper-wool catalyst in a spinning mesh disc reactor. *Chem. Eng. Process. Process Intensif.* **2017**, *122*, 550-559.

(49) Shaabani, A.; Hezarkhani, Z.; Faroghi, M. T. Wool-SO₃H and nano-Fe₃O₄@ wool as two green and natural-based renewable catalysts in one-pot isocyanide-based multicomponent reactions. *Monatsh. Chem.* **2016**, *147* (11), 1963-1973.

(50) Opwis, K.; Straube, T.; Kiehl, K.; Gutmann, J. S. Various strategies for the immobilization of biocatalysts on textile carrier materials. *CHEMICAL ENGINEERING* **2014**, *38*.

(51) McNeil, S. J.; Sunderland, M. R.; Leighs, S. J. The utilisation of wool as a catalyst and as a support for catalysts. *Appl. Catal. Gen.* **2017**, *541*, 120-140.

(52) Ghadamgahi, S.; Johnston, J. H.; Fonseca-Paris, C. Ecofriendly Palladium on Wool Nanocatalysts for Cyclohexene Hydrogenation. *Nanomaterials* **2018**, *8* (8), 621.

(53) Yin, M.-Y.; Yuan, G.-L.; Huang, M.-Y.; Jiang, Y.-Y. Catalytic behavior of a Wool-Pd complex in asymmetric hydrogenation of diacetone alcohol and 3-methyl-2-butanone. *J. Mol. Catal. A Chem.* **1999**, *147* (1-2), 89-92.

(54) Xue, L.; Jia, B.; Tang, L.; Ji, X. F.; Huang, M. Y.; Jiang, Y. Y. Asymmetric hydration of alkenes catalyzed by wool-palladium complex. *Polym. Adv. Technol.* **2004**, *15* (6), 346-349.

(55) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D.; Hyett, G.; Jones, W.; et al. Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.* **2012**, *41* (1), 413-447.

(56) Bolt, R. R.; Leitch, J. A.; Jones, A. C.; Nicholson, W. I.; Browne, D. L. Continuous flow mechanochemistry: reactive extrusion as an enabling technology in organic synthesis. *Chem. Soc. Rev.* **2022**, *51* (11), 4243-4260.

(57) Porcheddu, A.; Mocci, R.; Brindisi, M.; Cuccu, F.; Fattuoni, C.; Delogu, F.; Colacino, E.; D'Auria, M. V. Mechanochemical Fischer indolisation: an eco-friendly design for a timeless reaction. *Green Chem.* **2022**, *24* (12), 4859-4869.

(58) Chignell, C.; Han, S.; Mouithys-Mickalad, A.; Sik, R.; Stadler, K.; Kadiiska, M. EPR studies of in vivo radical production by 3, 3', 5, 5'-tetrabromobisphenol A (TBBPA) in the Sprague-Dawley rat. *Toxicol. Appl. Pharmacol.* **2008**, *230* (1), 17-22.

(59) List, B.; Lerner, R. A.; Barbas, C. F. Proline-catalyzed direct asymmetric aldol reactions. *J. Am. Chem. Soc.* **2000**, *122* (10), 2395-2396.

(60) Kumar, P.; Dwivedi, N. Proline catalyzed α -aminooxylation reaction in the synthesis of biologically active compounds. *Acc. Chem. Res.* **2013**, *46* (2), 289-299.

(61) Wang, Y.; Wang, Y.; Liu, L.; Sang, K.; Zhang, C.; Satoh, T. Asymmetric aldol reaction catalyzed by amino acid tetrapeptides (l-Pro-l-Pro-l-Phe-l-Phe-OMe). *React. Chem. Eng.* **2023**, *8* (8), 2022-2028.

(62) Rout, S. K.; Wunnava, S.; Krepl, M.; Cassone, G.; Šponer, J. E.; Mast, C. B.; Powner, M. W.; Braun, D. Amino acids catalyse RNA formation under ambient alkaline conditions. *Nat. Commun.* **2025**, *16* (1), 5193.

(63) Vasconcelos, A. A.; Gatti, L. C. P.; de Mescouto, V. A.; De Oliveira, A. D. N.; Melchiorre, M.; Noronha, R. C. R.; Luque, R.; Esposito, R.; Nascimento, L. A. S. d. Mechanochemistry in Waste Valorization: Advances in the Synthesis of Catalysts, Polymers, and Functional Materials. *Catalysts* **2025**, *15* (9), 897.

(64) Aydonat, S.; Hergesell, A. H.; Seitzinger, C. L.; Lennarz, R.; Chang, G.; Sievers, C.; Meisner, J.; Vollmer, I.; Göstl, R. Leveraging mechanochemistry for sustainable polymer degradation. *Polym. J.* **2024**, *56* (4), 249-268.

- (65) Klok, H.-A.; Herrmann, A.; Göstl, R. Force ahead: emerging applications and opportunities of polymer mechanochemistry. ACS Publications: 2022; Vol. 2, pp 208-212.
- (66) Jicsinszky, L.; Bucciol, F.; Chaji, S.; Cravotto, G. Mechanochemical degradation of biopolymers. *Molecules* **2023**, 28 (24), 8031.
- (67) Surewicz, W. K.; Mantsch, H. H.; Chapman, D. Determination of protein secondary structure by Fourier transform infrared spectroscopy: a critical assessment. *Biochemistry* **1993**, 32 (2), 389-394.
- (68) Lyman, D. J.; Murray-Wijelath, J.; Feughelman, M. Effect of temperature on the conformation of extended α -keratin. *Appl. Spectrosc.* **2001**, 55 (5), 552-554.

Grinding Hydrogen into Action: Mechanochemical Borrowing Hydrogenation of Amines

5.1. The Centrality of C–N Bond Formation

Nitrogen-based compounds, particularly *N*-alkylated amines and heterocycles, are indispensable as intermediates and final products in the synthesis of diverse drugs, agrochemicals, and advanced functional materials, highlighting their exceptional versatility and significance in driving modern chemical and pharmaceutical innovation.^{1–5} These molecules serve as the backbone of numerous therapeutic agents, exhibiting critical properties such as antihypertensive, anti-inflammatory, antitumor, and antimigraine effects, as well as providing relief from chronic respiratory infections (Figure 4.1). Considering their crucial importance in healthcare and medicine, the development of effective C–N bond strategies remain a highly sought-after objective in synthetic chemistry.^{6–10}

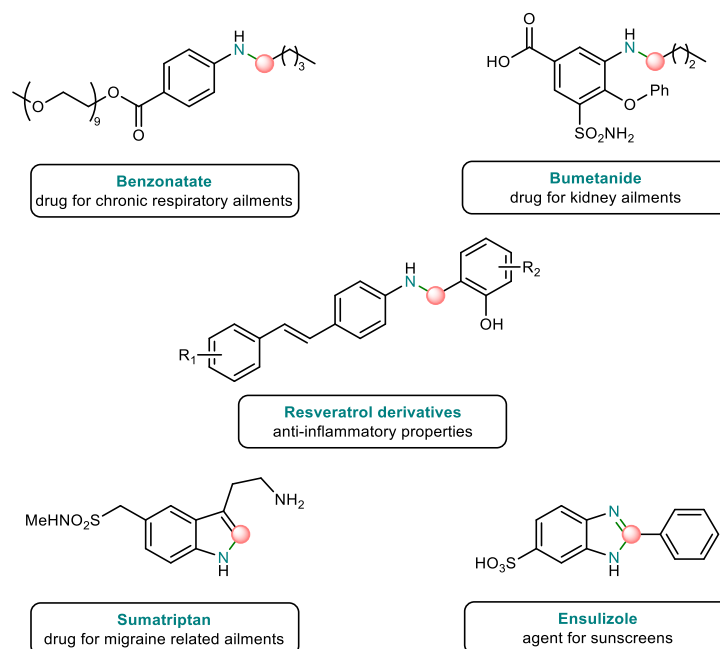


Figure 5.1. Pharmaceutically relevant *N*-alkylated amines and *N*-heterocycles

Despite their indispensable utility, conventional *N*-alkylation protocols face significant limitations, primarily because of their reliance on hazardous alkyl halides.^{11–14} This dependency results in poor atom economy, formation of undesired side products, and generation of substantial stoichiometric waste, which compromise safety and undermine both the efficiency and sustainability of the process.¹⁵ In response, the use of alcohols as alkylating agents has attracted considerable interest owing to their easy accessibility, cost-effectiveness, and favourable environmental profiles^{16, 17}, which include their origin from biomass feedstocks^{18, 19}. However, their application remains limited by their inherently low electrophilicity.

5.2. Borrowing Hydrogen (BH): A Sustainable Milestone

The pioneering work of Watanabe²⁰ and Grigg²¹ paved the way for the use of alcohols as alkylating agents for *N*-heterocycle synthesis and *N*-alkylation using metal catalysis. Their work initiated the development of the borrowing hydrogen (BH) strategy, which has since emerged as a cornerstone of sustainable catalytic organic synthesis (Figure 5.2.a).²²⁻²⁷ The BH reaction involves the initial dehydrogenation of an alcohol to generate a reactive carbonyl intermediate, which then undergoes nucleophilic attack by the hydride donor. The hydrogen atoms removed during the dehydrogenation step are subsequently returned *in-situ* via [M–H₂] species, producing water as the sole byproduct and completing a closed-loop catalytic cycle with minimal waste (Figure 5.2. b). On a commercial scale, BH strategies eliminate the need for external hydrogen gas, thereby avoiding the safety risks and logistical challenges associated with pressurized hydrogen gas cylinders.^{28, 29} These methods not only improve operational safety and broaden the scope of synthetic transformations but also offer a more sustainable alternative for C–N bond formation.

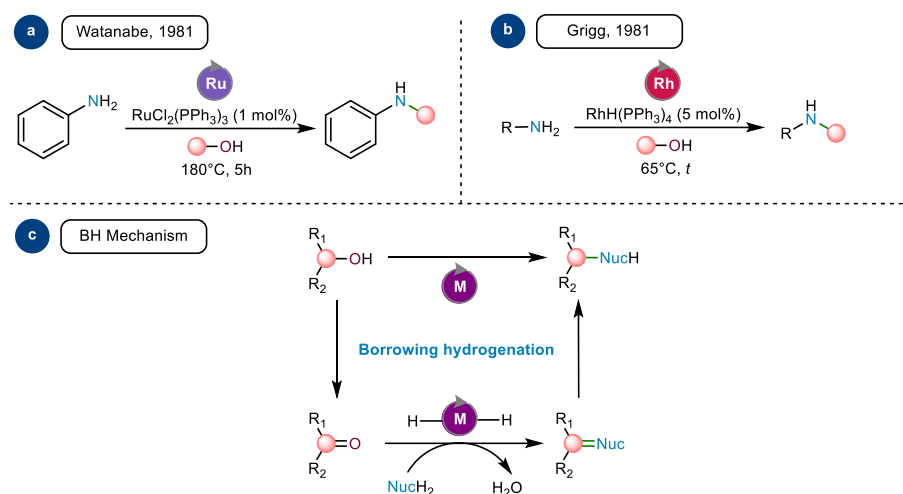
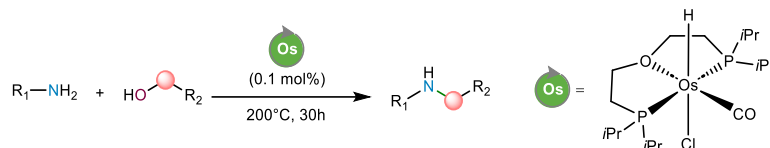


Figure 5.2. a) BH reaction by Watanabe and co-workers; b) BH reaction by Grigg and co-workers; c) Reaction mechanism of BH

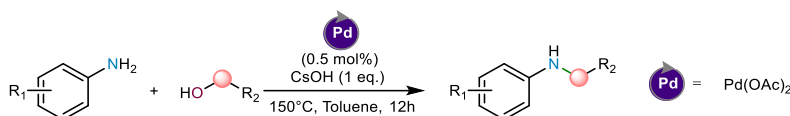
5.2.1. Evolution of BH Strategies in *N*-Alkylation Chemistry

The remarkable advantages and broad applicability of BH reactions have spurred extensive studies on the development of efficient homogeneous catalytic systems using various noble metal complexes for the *N*-alkylation of amines, leading to several key improvements over classical approaches.^{25, 30} After the resurgence of the BH strategy in the early 2000s, Gusev *et al.* developed an osmium-catalyzed BH strategy for amines under base-free and low catalyst loading conditions.³¹ Remarkably, their methodology enabled the *N*-alkylation of amines with both aromatic and aliphatic amines and alcohols, delivering high yields. However, one of the drawbacks of their methodology is the use of extremely high temperature (200 °C) for an extended period of 30 h, which makes this process very energy-intensive (Scheme 5.1).



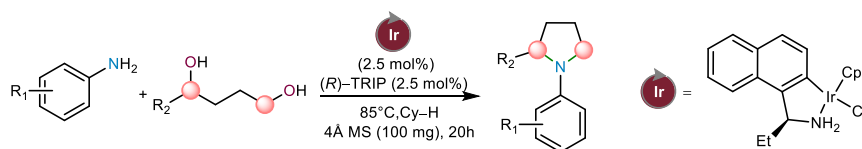
Scheme 5.1. Gusev and co-workers' methodology for Osmium catalyzed BH reaction for *N*-alkylation of amines

During the same period, Ramón *et al.* developed a palladium salt-catalyzed methodology for *N*-alkylation, in which the BH transformation was promoted by the addition of a stoichiometric amount of CsOH as the base in toluene.³² Moreover, their methodology was utilized for the *N*-alkylation of amides and sulfonamides. Although this strategy represented a significant improvement over previous attempts, it still required high temperature (150°C), hydrocarbon solvent (toluene), and long reaction time (12h). Additionally, the methodology was effective only for aromatic amines and alcohols, thereby limiting its applicability (Scheme 5.2).



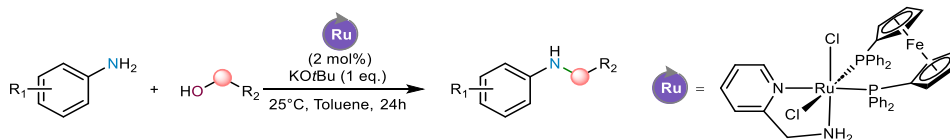
Scheme 5.2. Ramón and co-workers' take on Palladium catalyzed BH for *N*-alkylation

Enantioconvergent synthesis has garnered significant attention in the past decade. However, enantioconvergent *N*-alkylation has remained a challenging aspect of BH chemistry and has only recently begun to gain traction. In this context, Zhao *et al.* developed a base-free iridium-catalyzed BH transformation for the annulation of racemic 1,4-diols and amines to access chiral *N*-heterocycles with a TRIP ligand in cyclohexane.³³ Although promising, this methodology suffers from the use of hydrocarbon solvents, very long reaction time (20h) and moderately high temperature requirements (Scheme 5.3).



Scheme 5.3. Iridium catalyzed enantioconvergent BH by Zhao and co-workers

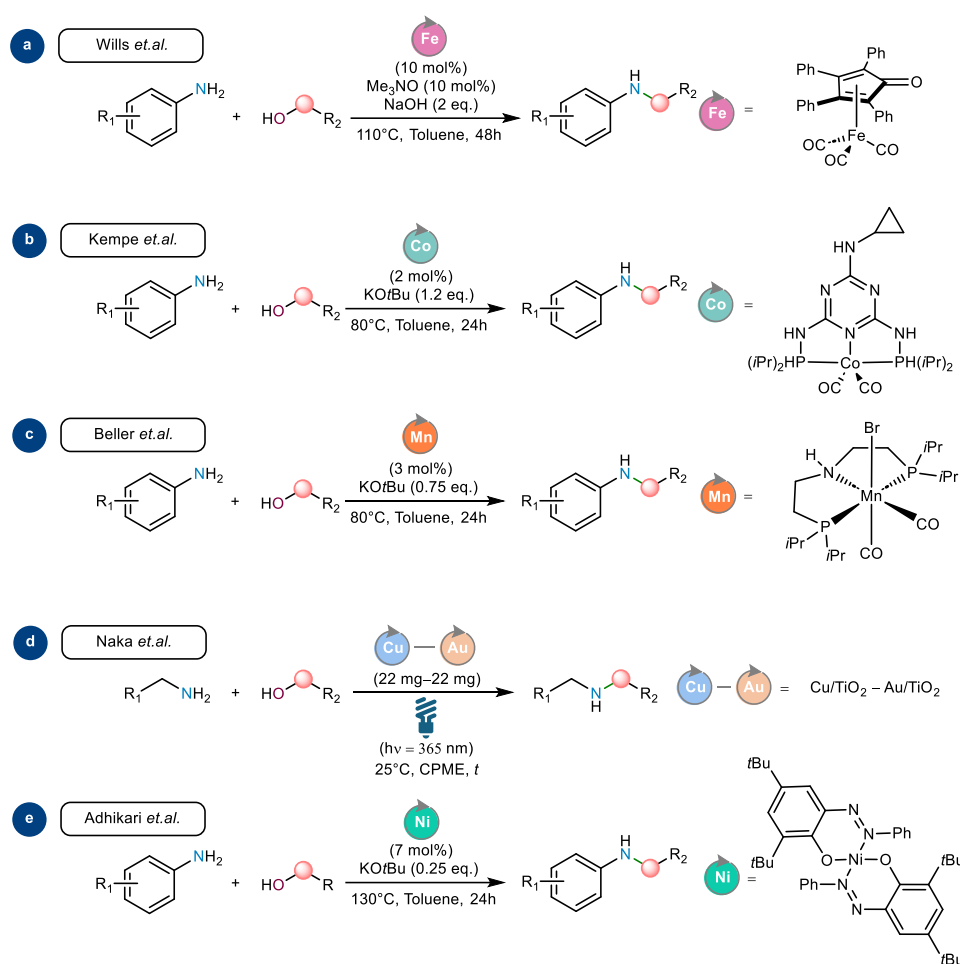
In this context, room-temperature BH transformation has been largely unexplored in the literature. In our previous attempt to develop a sustainable and practical BH methodology, we established a room-temperature Ru-catalyzed protocol for the *N*-alkylation of amines in toluene.³⁴ However, high catalyst loading (2 mol%), long reaction time (24h) and the use of hydrocarbon solvents (toluene) remain significant unaddressed limitations (Scheme 5.4). Additionally, this methodology is only applicable to aromatic amines and cannot be used to obtain products from aliphatic amines.



Scheme 5.4. Porcheddu *et.al.* in room temperature Ruthenium catalyzed BH for *N*-alkylation of aromatic amines.

Recently, first-row transition metal catalysts have been reported in the literature for demonstrating BH transformations, albeit requiring higher catalyst loadings, harsher reaction conditions, and other operational limitations (Scheme 5.5).^{6, 24, 35, 36} One of the foremost studies was conducted by Wills *et al.* using an iron-based catalyst in toluene for the *N*-alkylation of amines (Scheme 5.5. a).³⁷ However, this methodology utilizes a very high catalyst loading (7 mol%), extended reaction time (48h), excess NaOH as the base (2 equivalents), and elevated reaction temperature (110°C). Furthermore, this protocol uses toluene as a solvent and is only applicable to aromatic amines and benzyl alcohols, demonstrating some concerning drawbacks in practical implementation. In the same year, Kempe *et al.* developed a cobalt-catalyzed protocol for the same reaction in toluene with a lower catalyst loading.³⁸ The drawbacks of this protocol are the use of a moderately high temperature (80°C) for an extended period (24h) and limited reactivity with only aromatic amines (Scheme 5.5. b). Additionally, the Co-based catalyst used in this protocol is not commercially available, making the protocol less accessible to the broader scientific community. Building upon previous attempts, a remarkable protocol was developed by Beller *et al.* using a manganese-based pincer complex in toluene (Scheme 5.5. c).⁶ Consequently, this method was modified to synthesize *N*-methylated amines and indole. However, this method is only applicable to aromatic amines. Additionally, moderately high temperature (80°C), use of toluene, and an extended reaction time (24h) further increased the drawbacks. Subsequently, a photochemical approach for *N*-alkylation of amines was established by Naka and co-workers (Scheme 5.5. d).³⁹ They developed Cu- and Au-infused TiO₂ as photocatalysts for *N*-alkylated amines in CPME under a Xe-lamp ($\lambda=365$ nm). Although the reaction is carried out at room temperature, several significant drawbacks limit its application, such as the use of an inert atmosphere, excess reagents (in cases up to 2500 equivalents of alcohol compared to amine), and in certain instances, very long reaction times (up to 16h). Furthermore, this method is only applicable to aliphatic amines. Meanwhile, Adhikari *et al.* used a nickel-based catalyst for BH-mediated *N*-alkylated amines in toluene for a range of substrates (Scheme 5.5. e).⁴⁰ However, their procedure is limited to aromatic amines. Furthermore, the requirement of high catalyst loading (7 mol%), elevated reaction temperature (130°C) for an extended time (24h) and the use of hydrocarbon solvents are drawbacks of this method.

Consequently, Ru- and Ir-based complexes remain the most widely adopted for BH processes, encompassing a favourable balance between efficiency, sustainability, and practical feasibility.^{30, 34, 41, 42} These limitations in various attempts at BH-mediated *N*-alkylation encourage further improvement in such a transformative approach.^{22, 28, 43-46}



Scheme 5.5. Different approaches in BH for *N*-alkylated amines using first-row transition metal catalyst

5.3. Harnessing Mechanical Energy for BH

As laboratories and industries increasingly shift toward greener practices, a safer, milder, and more energy-efficient BH methodology represents a significant achievement. In this regard, mechanochemistry has emerged as a groundbreaking platform that offers solvent-free conditions and exceptional energy efficiency.⁴⁷⁻⁵⁰ Rapidly gaining prominence, this transformative approach is redefining the manner, in which chemical reactions are conducted.⁵¹⁻⁵⁴ Mechanocatalysis is a specialized subset of catalysis in which mechanical force directly drives catalytic transformations.⁵⁵⁻⁶² This strategy has enabled a wide array of landmark reactions, including Suzuki–Miyaura^{63, 64} and Negishi cross-couplings⁶⁵, Mizoroki–Heck reactions⁶⁶, olefin metathesis⁶⁷, and Buchwald–Hartwig aminations⁶⁸, often surpassing the limitations associated with conventional solution-based methods.⁶⁹ Under mechanochemical conditions, the application of mechanical force induces unconventional energy transfer pathways, profoundly affecting the reaction kinetics, mechanistic trajectories, and interfacial phenomena. These effects frequently diverge from those observed in solution-phase chemistry, thereby opening new avenues for reactivity and selectivity. Mechanocatalysis is increasingly recognized as a powerful and versatile tool for sustainable chemical innovation.

This chapter discusses the first solid-state mechanochemical ball-milling approach for BH reactions, enabling the solvent-free synthesis of *N*-alkylated amines and heterocycles at ambient temperature with minimal catalyst loading, using a commercially available Ru-based catalyst.⁷⁰⁻⁷³ This advancement enhances sustainability and operational efficiency. Beyond synthetic methodologies, this chapter delves into mechanistic investigations through kinetic isotope effect (KIE) analysis and Hammett studies, providing deeper insights into the underlying reaction pathway.

5.4. Results and Discussions

5.4.1. Mechanochemical BH Mediated *N*-Alkylation of Aromatic Amines

To develop an efficient mechanochemical BH methodology, an initial screening was conducted using a series of commercially available transition metal catalysts, with a primary focus on Ru-based pincer complexes known for their proven efficacy in transfer hydrogenation and acceptorless dehydrogenation reactions (Figure 5.3).^{73, 74} The initial catalyst screening for the room-temperature mechanochemical BH reaction was performed in a 10 mL zirconia milling jar containing a single 10 mm zirconia ball (2.87 g). The reaction mixture consisted of *p*-anisidine (**1a**, 1.0 mmol), *n*-pentanol (**2a**, 1.0 mmol), and potassium *tert*-butoxide (KO*t*Bu, 2.0 mmol). Milling was conducted for 4 h at 30 Hz using a Retsch MM-500 Vario ball mill (Table 5.1).

Among the evaluated catalysts, the ruthenium complexes bearing phosphine ligand frameworks exhibited the highest performance. Notably, Ru-MACHO (**[Ru]-1**) exhibited the highest catalytic efficiency under mechanochemical BH conditions (entry 1, Table 5.1). In contrast, Ru-MACHO-BH (**[Ru]-2**) exhibited reduced activity (entry 2, Table 5.1). Interestingly, *cis*-[RuCl₂(dppf)(ampy)] (**[Ru]-3**), which was previously reported to facilitate BH reactions at room temperature in solution, achieved good conversion under ball-milling conditions (entry 3, Table 5.1). Conversely, the Milstein catalyst (**[Ru]-4**) and RuCl₂[(*R*)-xylbinap][(R)-daipen] (**[Ru]-6**), despite their well-documented efficacy in the dehydrocoupling reactions of alcohols and amines, showed limited reactivity in the mechanochemical setup (entries 4 and 6, Table 5.1) which could be attributed to lack of solvent-based stabilization of the catalyst under mechanochemical conditions.⁷⁵ Other tested catalysts provided only poor to moderate conversions under similar conditions. In contrast, the use of first-row transition metal catalysts resulted in no observable product formation under mechanochemical conditions (Table 5.1).

Building upon the promising performance of Ru-MACHO, the impact of reducing its catalyst loading from 2 mol% to 0.05 mol% was investigated. Under these conditions, complete conversion was still achievable, albeit requiring an extended milling time of 6h instead of 4 h (entry 2, Table 5.2). The influence of the base-to-alcohol ratio on the reaction outcome was monitored for further refinements. Reducing the loading of KO*t*Bu from 2.0 to 1.0 equivalent had no detrimental effect on the yield (entry 3, Table 5.2). However, further reduction significantly impaired the reaction efficiency, and using 0.5 equivalents of base resulted in a yield of only 50% (entry 4, Table 5.2). These findings are consistent with those observed in solution-phase systems, where the base concentration plays a critical role in modulating the formation rate of the alkoxide intermediate and the overall reaction kinetics.⁷⁶

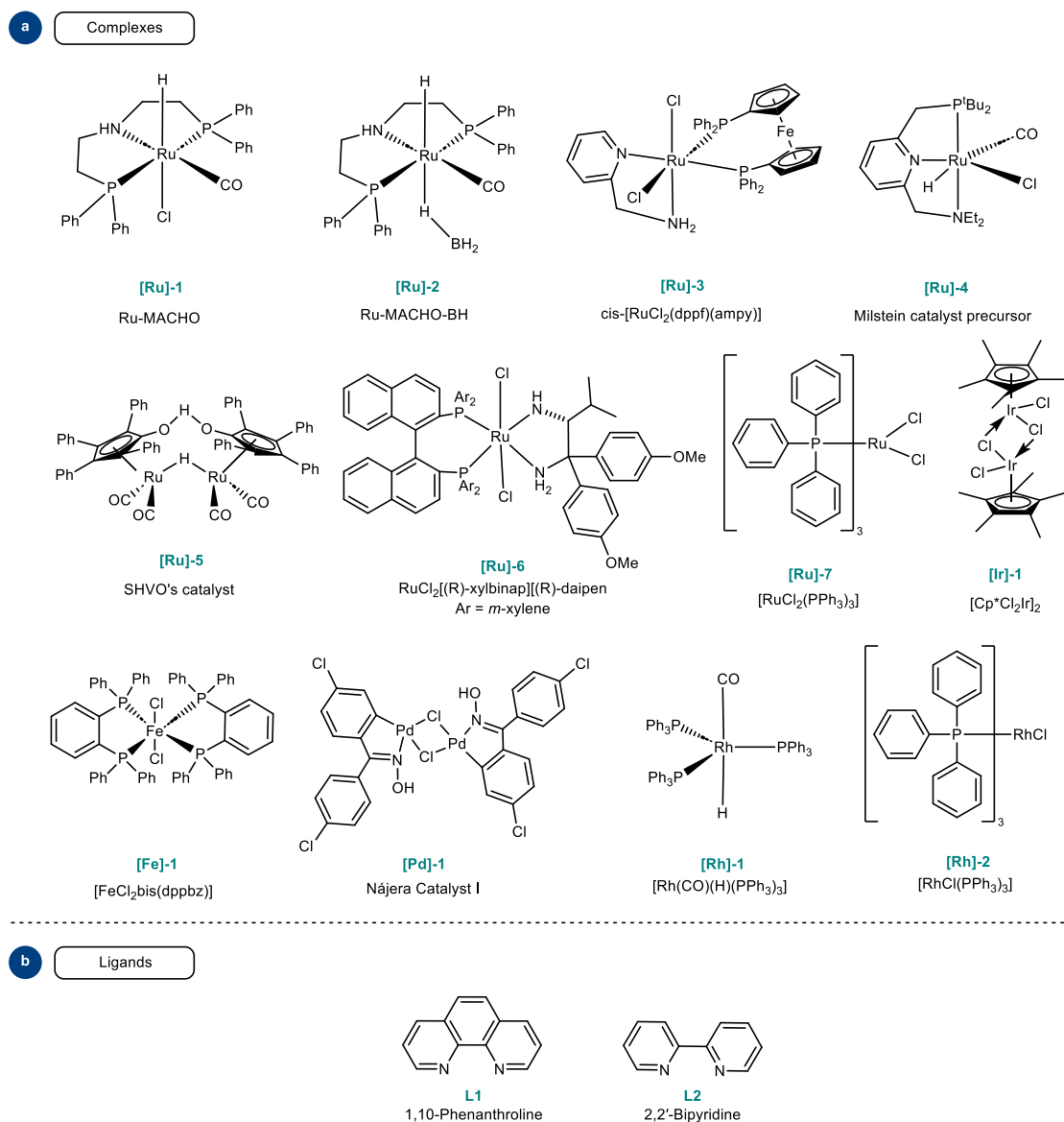
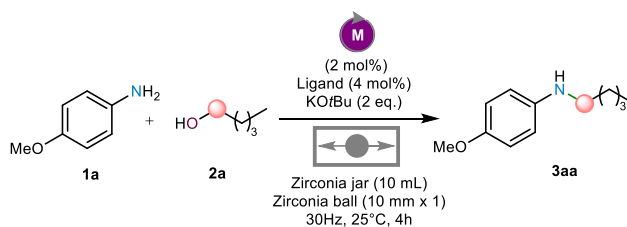


Figure 5.3. Complexes and ligands for catalyst screening of *N*-alkylation using mechanochemical BH strategy

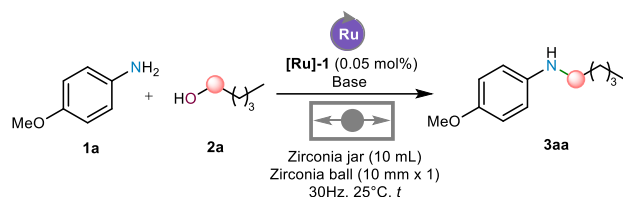
The methodology was successfully scaled up under standard milling conditions, affording the product in excellent yield (entry 5, Table 5.2). Under these optimized conditions, a turnover number (TON) exceeding 2000 and a turnover frequency (TOF) of 0.0936 s⁻¹ were achieved, demonstrating the high efficiency of the catalyst.⁷⁷ When the milling frequency was reduced to 15 Hz, product formation was still observed, albeit at a lower yield (entry 6, Table 5.2). The choice of base was found to be critical for the mechanochemical transformation. The substitution of KOtBu with sodium methoxide (NaOMe) led to a significant decrease in the yield (26%) and the formation of a 5% *N*-methylated byproduct (entry 7, Table 4.2). Weaker bases, such as potassium hydroxide (KOH) and potassium carbonate (K₂CO₃), failed to promote the reaction (entries 8– and 9, respectively, Table 4.2).

Table 5.1. Catalyst Screening for Mechanochemical *N*-alkylation of amines with BH strategy

Entry	Complex/Metal Salt	Ligand	Conversion of 3aa ^{a,b}
1	[Ru]-1	—	98%
2	[Ru]-2	—	65%
3	[Ru]-3	—	73%
4	[Ru]-4	—	34%
5	[Ru]-5	—	Trace
6	[Ru]-6	—	40%
7	[Ru]-7	—	—
8	[Ir]-1	—	—
9	[Fe]-1	—	Trace
10	[Pd]-1	—	10%
11	[Rh]-1	—	7%
12	[Rh]-2	—	Trace
13	Co ₂ (CO) ₈	—	—
14	Ni(acac) ₂	L1	—
15	NiCl ₂	L1	—
16	NiCl ₂	L2	—
17	Fe ₃ O ₄	—	—
18	dppf	—	Trace
19	Co(acac) ₂	L1	—

^a Reaction Conditions: **1a** (1 mmol), **2a** (1 mmol), KOtBu (2 mmol), complex/metal salt (2 mol%), ligand (4 mol%) in a 10 mL zirconia jar with a 10 mm zirconia ball milled in MM-500 Vario for 4 hours at 25 °C; ^b conversion determined by GC-MS

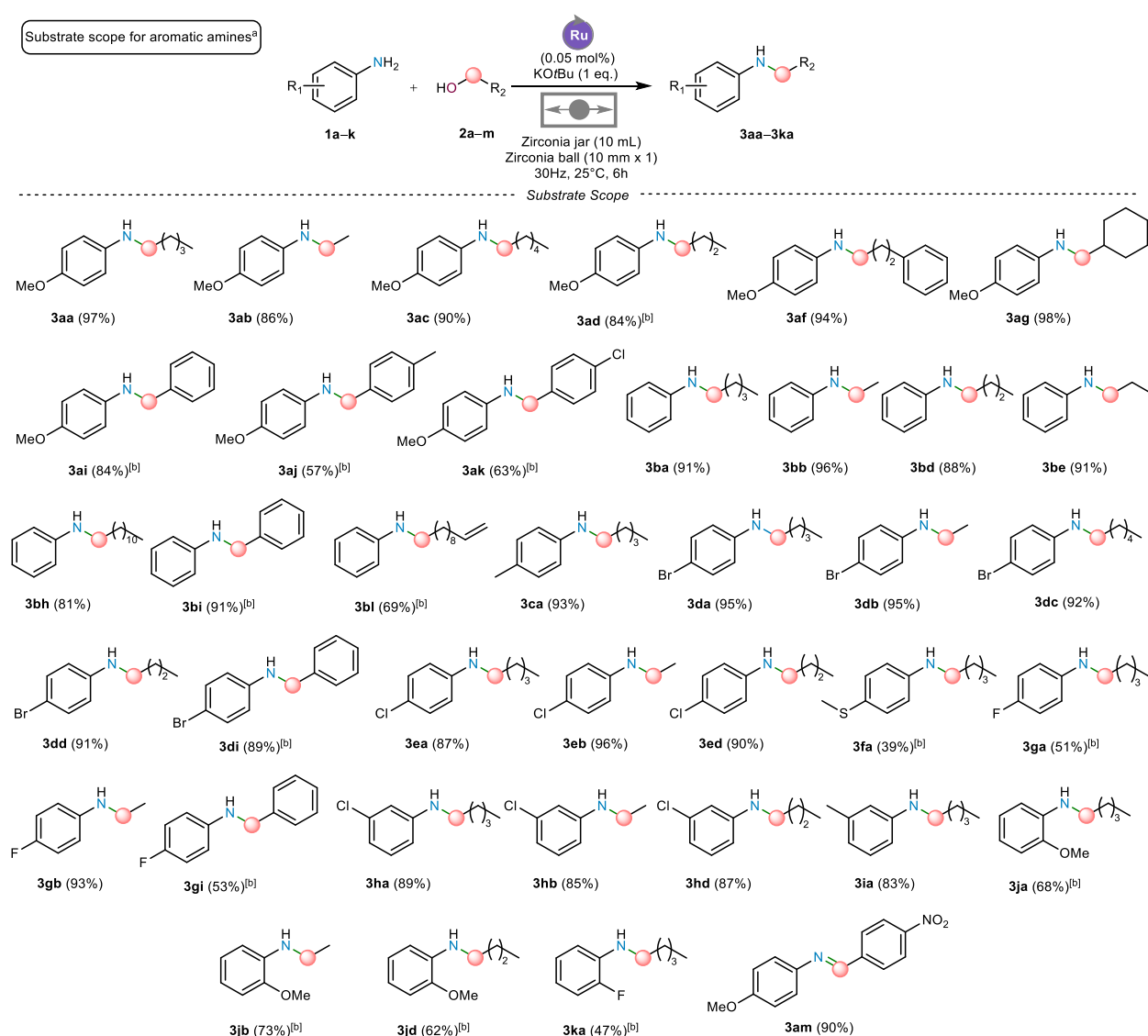
A series of control experiments conducted in toluene confirmed the pivotal role of the mechanochemical approach in enabling a highly efficient and rapid BH reaction. Under solvent-based conditions, only 16% yield was obtained after 6 h (entry 10, Table 5.2), and 51% after 24 h of stirring (entry 11, Table 5.2). Even at a mildly elevated temperature of 40 °C for over 12 h, the yield increased only marginally to 58% (entry 12, Table 5.2). Additionally, a neat control experiment performed under conventional conditions exhibited poor reproducibility and sluggish kinetics (entry 13, Table 5.2). These results highlight the distinct advantages of mechanochemical methodology over traditional solution-based protocols, demonstrating that enhanced performance arises not from an alternative reaction pathway but from significantly improved kinetics, offering superior efficiency and reproducibility.

Table 5.2. Reaction optimization for *N*-alkylation of aromatic amines with BH strategy

Entry	Ru-MACHO (mol%)	Base (eq.)	Time (h)	Conversion of 3aa ^{a,b}
1	0.05 mol%	KOtBu (2 eq.)	4h	82%
2	0.05 mol%	KOtBu (2 eq.)	6h	94%
3	0.05 mol%	KOtBu (1 eq.)	6h	94%
4	0.05 mol%	KOtBu (0.5 eq.)	6h	50%
5 ^c	0.05 mol%	KOtBu (1 eq.)	6h	99%
6 ^d	0.05 mol%	KOtBu (1 eq.)	6h	76%
7	0.05 mol%	NaOMe (1 eq.)	6h	26%
8	0.05 mol%	KOH (1 eq.)	6h	—
9	0.05 mol%	K ₂ CO ₃ (1 eq.)	6h	—
10 ^e	0.05 mol%	KOtBu (1 eq.)	6h	16%
11 ^e	0.05 mol%	KOtBu (1 eq.)	24h	51%
12 ^f	0.05 mol%	KOtBu (1 eq.)	12h	58%
13 ^g	0.05 mol%	KOtBu (2 eq.)	24h	67%

^a Reaction Conditions: **1a** (1 mmol), **2a** (1 mmol), Base, Ru-MACHO (0.05 mol%) in a 10mL zirconia jar with a 10 mm zirconia ball milled in MM-500 Vario for given time at 25°C; ^b conversion determined by GC-MS; ^c reaction conducted with **1a** and **2a** at 4 mmol scale; ^d reaction performed at 15 Hz; ^e reaction performed in toluene (1 M) at solution based condition; ^f reaction in toluene (1 M) at 40°C; ^g neat stirring reaction

The versatility of the catalytic system was evaluated by extending the substrate scope to various aromatic amines and alcohols (Scheme 5.6). The alkylation of *p*-anisidine (**1a**) with ethanol yielded product **3ab** in a high yield, and elongation of the alkyl chain had no adverse effect on reactivity, providing products **3ac** and **3ad** in excellent yields. Reactions with 3-phenylpropan-1-ol and cyclohexylmethanol proceeded smoothly, furnishing **3af** and **3ag** in excellent yields. *Para*-substituted benzyl alcohols, regardless of their electronic properties, delivered the desired products in satisfactory yields: 57% for **3aj** (*p*-methyl) and 63% for **3ak** (*p*-chloro). Aniline underwent efficient alkylation with a broad range of alcohols, furnishing products **3ba–3bh** in high yield. The reaction with benzyl alcohol produced **3bi** in excellent yield, accompanied by a minor imine byproduct. Importantly, no reduction of the C=C double bond was observed when alcohol **2l** was employed, yielding **3bl** in 69% yield, highlighting the selectivity of the process.



Scheme 5.6. ^a Substrate scope for aromatic amines. Reaction conditions: **1a** (4 mmol), **2a** (4 mmol), KOtBu (1 eq.), Ru-MACHO (0.05 mol%) in a 10 mL zirconia jar with a 10 mm zirconia ball milled in MM-500 Vario for 6 h at 25 °C and yields of the products were calculated after extraction with 20 mL of ethyl acetate (EtOAc) and concentrating under reduced pressure; ^b yield calculated after column chromatography

p-Toluidine and *p*-bromoaniline reacted effectively, affording **3ca** and **3da–3dd** in excellent yields. The reaction of *p*-bromoaniline with benzyl alcohol also proceeded efficiently, yielding **3di** alongside minor imine formation. Similarly, *p*-chloroaniline produced products **3ea–3ed** with high selectivity and yield. Notably, electron-deficient anilines exhibited superior reactivity compared to their electron-rich counterparts, indicating a significant electronic effect. 4-(Methylthio)-*N*-pentylaniline (**1f**) furnished product **3fa** in a satisfactory yield of 39%, despite the potential for sulfur-induced catalyst deactivation. *p*-Fluoroaniline yielded products **3ga** and **3gi** in moderate yields of 51% and 53%, respectively. Anilines bearing *meta*-substituents, such as *m*-chloro and *m*-methyl groups, did not significantly affect the reaction efficiency, and **3ha**, **3hb**, **3hd**, and **3ia** were obtained in good yields. In contrast, *ortho*-methoxy substitution introduced steric hindrance,

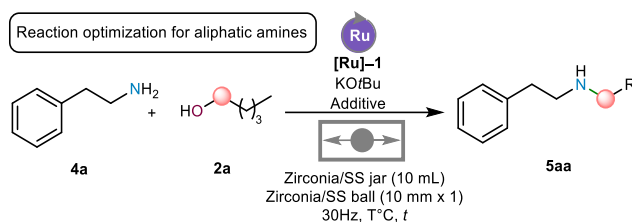
resulting in moderately reduced yields for **3ja**, **3jb** and **3jd**. However, this steric effect was less pronounced in **3ka**, where the yield remained comparable to that of the *para*-substituted analogue. Importantly, nitro groups were tolerated without any reduction. However, the reaction between **1a** and 4-nitrobenzyl alcohol (**2m**) stalled at the imine intermediate **3am**, suggesting that the catalytic system could not facilitate the final hydrogenation step.

5.4.2. Mechanochemical BH for *N*-Alkylation of Aliphatic Amines and *N*-Heterocycles

Following the successful *N*-alkylation of primary aromatic amines via the mechanochemical BH strategy, efforts were made to extend the substrate scope to include aliphatic amines. However, the optimized conditions developed for aromatic substrates were ineffective for aliphatic amines. To address this limitation, systematic screening was performed to adjust the reaction parameters and enhance the versatility of the catalytic system. Initially, 2-phenylethylamine (**4a**, 1.0 mmol) was reacted with *n*-pentanol (**2a**, 2.0 mmol) using **[Ru]-1** (0.05 mol%) and KO*t*Bu (1.0 mmol) under standard conditions, but no product was formed. Subsequent attempts to increase the catalyst and base loadings, extend the milling time, or perform the reaction under an inert atmosphere also failed to yield the desired product (entries 1–5, Table 5.3).

This limitation was overcome by milling a mixture of 2-phenylethylamine (**4a**, 1.0 mmol), *n*-pentanol (**2a**, 2.0 mmol), **[Ru]-1** (1 mol%), and KO*t*Bu (3.0 mmol) in a 10 mL stainless-steel (SS) jar with a single 10 mm SS ball (3.6 g) using a Fritsch P-23 mill. External heating to 80 °C was applied using a heat-gun, and the temperature was monitored using an IR-thermometer.⁷⁸ Notably, the over-all milling temperature remained constant, although slightly elevated temperature was noted on the jar surface directly facing the heat-gun. Under these conditions, the *N*-alkylated product was obtained in 28% yield after 6 h of milling (entry 7, Table 5.3). Extending the milling time to 12 h resulted in a 90% product yield (entry 8, Table 5.3). Reducing the catalyst loading markedly decreased the yield (entry 9, Table 5.3), whereas lowering the base loading to 2 mmol caused a moderate drop in product formation (76 %) (entry 10, Table 5.3). However, adding MgO (200 mg per mmol of amine) while reducing KO*t*Bu to 1.0 mmol restored the yield to 96%, indicating efficient formation of the product. A solution-phase control experiment was conducted by heating **4a** (2.0 mmol), **2a** (2.0 mmol), **[Ru]-1** (5 mol%), and KO*t*Bu (2.0 mmol) in toluene (1 mL) at 130 °C for 48 h, with no observable product formation (entry 12, Table 5.3).

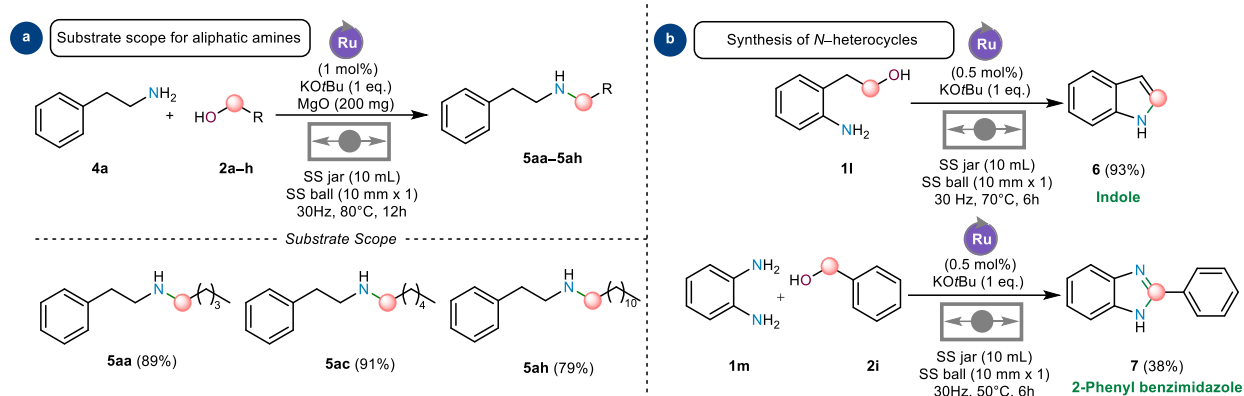
This significant contrast highlights the essential role of mechanical activation in enabling BH reactivity under solvent-free conditions in this study. The solvent-free nature of mechanochemistry maximizes the reactant concentration and collision efficiency, whereas mechanical forces ensure uniform catalyst dispersion and enhance active site accessibility. In addition, the localized heat generated during milling provides the activation energy required for the reaction. Together, these factors emphasize the unique advantages of mechanochemistry in overcoming the limitations of traditional solution-based methods, enabling more efficient hydrogen transfer during these transformations. Applying this methodology under similar conditions yielded compounds **5ac** and **5ah** using hexanol and dodecanol, respectively, with excellent yields (Scheme 5.7). a).

Table 5.3. Reaction optimization for *N*-alkylation of aliphatic amines with BH strategy

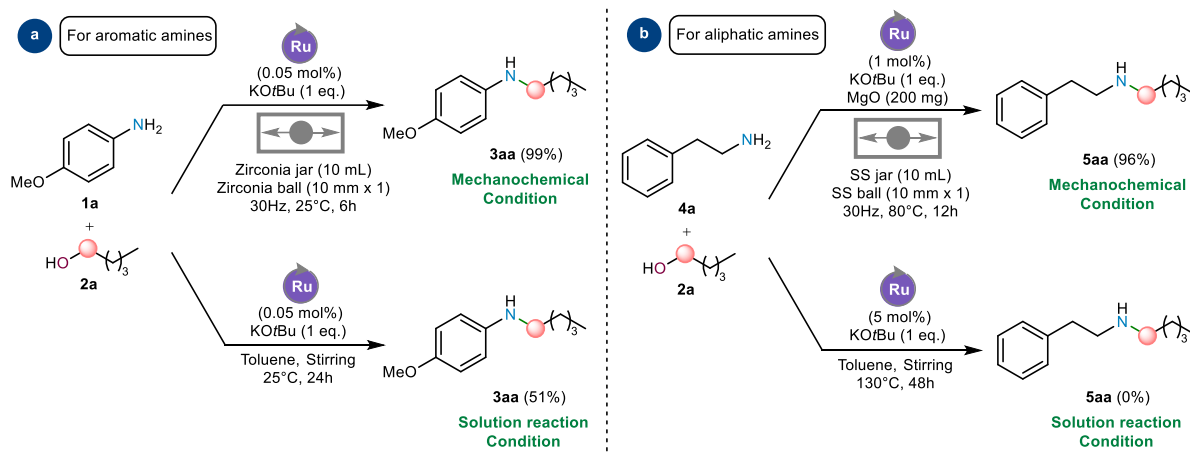
Entry	[Ru]-1 (mol%)	KOtBu (eq.)	Additive	Time (h)	Temperature (°C)	Milling jar/ball	Conv. of 3aa ^{a,b}
1	0.05 mol%	1 eq.	—	6h	25°C	ZrO ₂ /ZrO ₂	—
2	1 mol%	1 eq.	—	6h	25°C	ZrO ₂ /ZrO ₂	—
3	1 mol%	2 eq.	—	6h	25°C	ZrO ₂ /ZrO ₂	—
4	1 mol%	2 eq.	—	10h	25°C	ZrO ₂ /ZrO ₂	—
5 ^c	1 mol%	2 eq.	—	10h	25°C	ZrO ₂ /ZrO ₂	—
6	1 mol%	3 eq.	—	8h	25°C	SS/SS	—
7	1 mol%	3 eq.	—	6h	80°C	SS/SS	28%
8	1 mol%	3 eq.	—	12h	80°C	SS/SS	90%
9	0.1 mol%	3 eq.	—	12h	80°C	SS/SS	22%
10	1 mol%	2 eq.	—	12h	80°C	SS/SS	76%
11 ^d	1 mol%	1 eq.	MgO (200 mg)	12h	80°C	SS/SS	96%
12 ^e	5 mol%	1 eq.	—	48h	130°C	—	—

^a Reaction conditions: **4a** (1.0 mmol, 1 eq.), **2a** (2.0 mmol, 2 eq.), KOtBu, and **[Ru]-1** were placed in a 10 mL jar with a 10 mm ball (Stainless steel {SS} or Zirconia) and milled at 30 Hz in Fritsch P-23/MM-500 Vario for the given time and temperature; ^b All the conversions are determined by ¹H NMR; ^c Reaction conducted under N₂; ^d Milling additive (200 mg per mmol of **4a**); ^e Reaction performed under solution condition in toluene (2 M) with 5 mol% **[Ru]-1** at 130°C for 48h

Traditional aza-heterocycle synthesis typically relies on multistep processes, making BH particularly attractive and valuable for this purpose. Accordingly, we applied BH to synthesize indole (**6**) and 2-phenylbenzimidazole (**7**) (Scheme 5.7.b). Initial experiments using 2-aminophenethyl alcohol (**11**) at 25 °C did not yield the desired indole (**6**). This limitation was overcome by milling **11** (1.0 mmol), KOtBu (1.0 mmol), and **[Ru]-1** (0.5 mol%) in a 10 mL stainless-steel (SS) jar with a single 10 mm SS ball on a Fritsch P-23 mill, applying external heating at 70 °C for 6h with a heat-gun and monitored using an external IR-thermometer. Under these conditions, complete conversion was achieved, affording indole (**6**) as the sole product in a 93% yield (Scheme 5.7b). Additionally, milling o-phenylenediamine (**1m**) with benzyl alcohol (**2i**) at 50 °C produced 2-phenylbenzimidazole (**7**) in a 38% yield (Scheme 5.7.b).



Scheme 5.7. a) Substrate scope for *N*-alkylation of aliphatic amines; b) BH mediated *N*-heterocycle synthesis; yields of the products are calculated after isolation.



Scheme 5.8. Reaction comparison between mechanochemical vs solvent-based approach for *N*-alkylation of amines via BH methodology catalysed by Ru-MACHO; a) aromatic amines; b) aliphatic amines

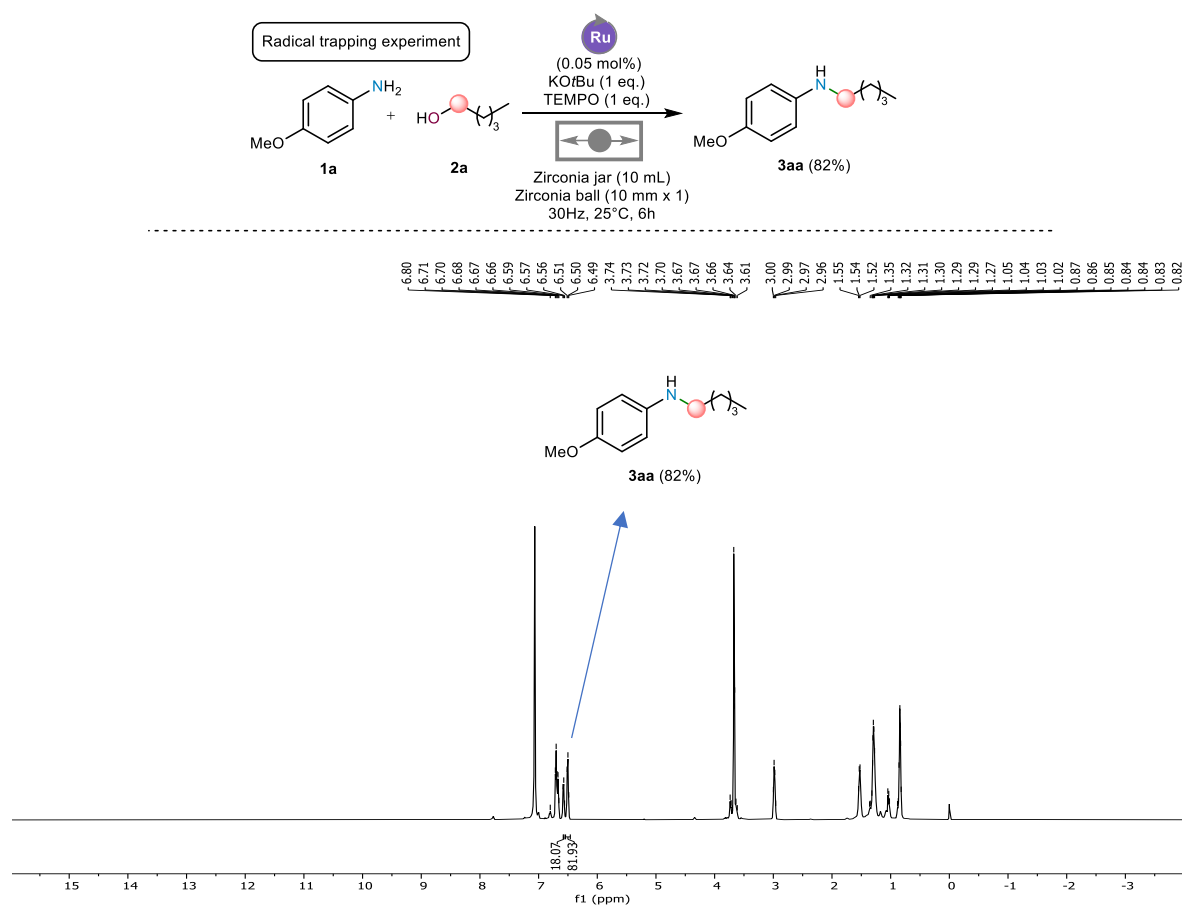
5.5. Probing the Mechanism of Solvent-Free Mechanochemical BH

Mechanistic studies in mechanochemistry pose significant challenges owing to the complex, heterogeneous, and dynamic nature of solid-state reactions. Unlike solution-based processes, which allow intermediates to be easily monitored in real time, mechanochemical transformations occur with continuous mechanical energy input, making direct observation inherently challenging.⁷⁹ The lack of standardized *in-situ* techniques complicates the identification of transient species and reaction pathways. Moreover, localized heating, shear forces, and variable reactant mixing introduce unpredictable effects on reactivity, hindering the development of definitive mechanistic models.⁸⁰ These challenges are particularly pronounced in borrowing hydrogenation reactions, where multiple catalytic steps, including dehydrogenation, condensation, and re-hydrogenation, occur via transient intermediates, such as metal-hydride species and imines or enones, which remain elusive under mechanochemical conditions. Despite these obstacles,

elucidating the reaction mechanisms in mechanochemistry is vital for rational catalyst design, reaction optimization, and the advancement of sustainable, solvent-free methodologies.

5.5.1. Radical Trapping Experiment

To determine whether mechanochemical BH proceeds via a radical pathway, an *in-situ* radical-trapping experiment was conducted. Here, using p-anisidine (**1a**, 4.0 mmol), n-pentanol (**2a**, 4.0 mmol), and KO^tBu (4.0 mmol) in the presence of the radical trapping agent TEMPO (4.0 mmol) were milled under standardized optimized reaction conditions. The formation of product **3aa** with an 82% conversion in ¹H NMR, even in the presence of TEMPO, suggests that the reaction does not follow a radical-mediated pathway (Scheme 5.9).

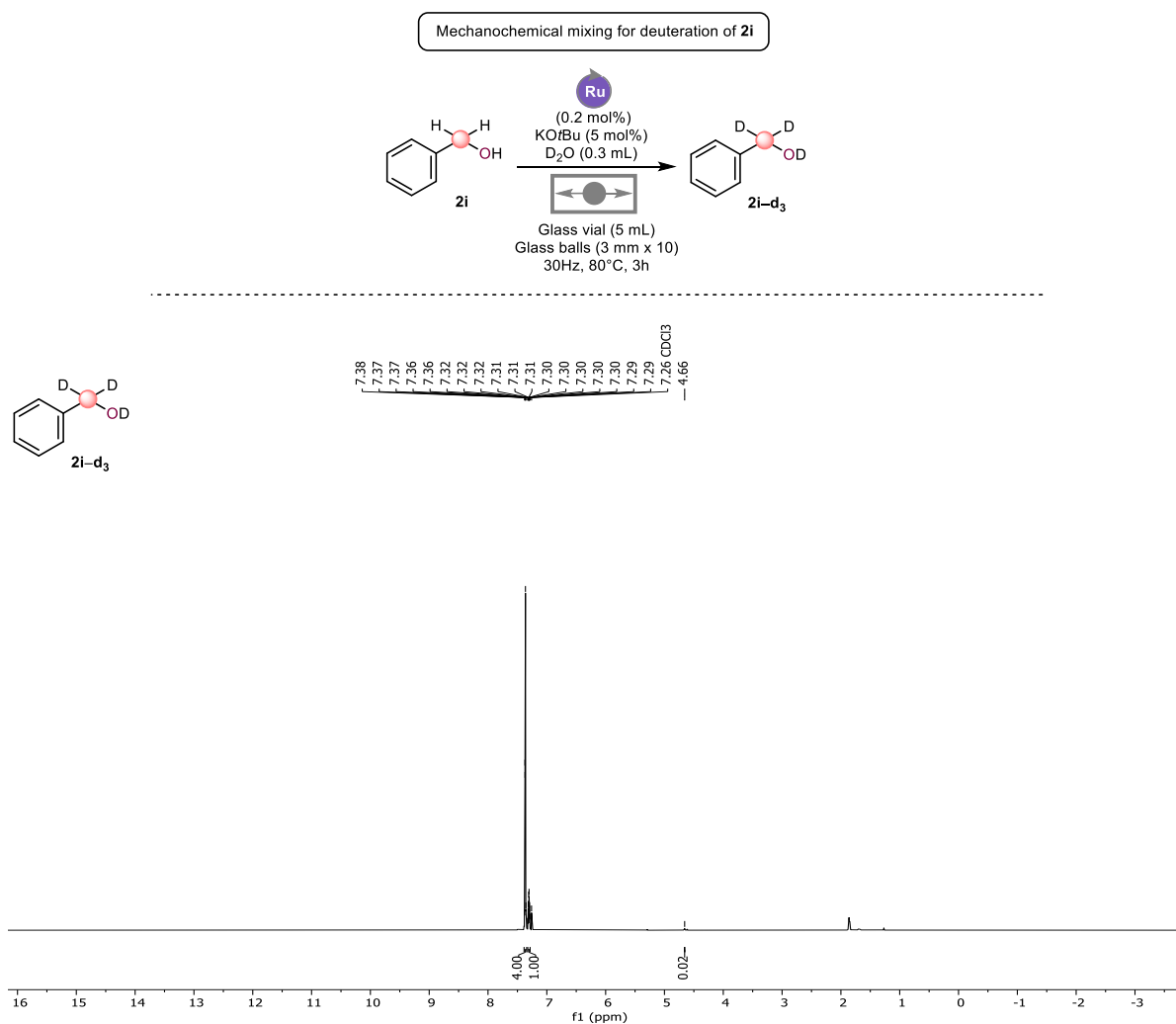


Scheme 5.9. Radical trapping experiment for mechanochemical BH reaction using TEMPO as the radical trapping agent

4.5.2. Kinetic Isotope Effect (KIE) Analysis

Further mechanistic insights were obtained through deuterium isotope labelling experiments, which led to the development of a milder and more efficient strategy for synthesizing benzyl alcohol-d₃ (**2i-d₃**). In this approach, D₂O was employed as the deuterium source in the presence of Ru-MACHO as a catalyst under mechanochemical mixing conditions, a method previously reported for isotopic incorporation in solutions (Figure 5.4). Upon optimization of the reaction conditions, the required amount of D₂O was reduced from 1 mL to 300 μL per mmol, thereby

enhancing the efficiency and sustainability.⁸¹ This refined protocol enabled the effective conversion of benzyl alcohol **2i** to benzyl alcohol-d₃ (**2i-d₃**). The final product (**2i-d₃**) was obtained with approximately 99% di-deuteration at the benzyl position, whereas only trace amounts of the non-deuterated product **2i** were detected. High isotopic enrichment was thus achieved while minimizing excess reagent consumption, as confirmed by NMR spectroscopy (Scheme 5.10) and high-resolution mass spectrometry (HRMS) (ESI) m/z calc. for C₇H₅D₂O [M-H]⁻: 109.0628, found: 109.0619.



Scheme 5.10. Deuteration of benzyl alcohol **2i** with D₂O by a Ru-catalysed mechanochemical BH methodology

To gain a deeper understanding of the mechanochemical hydrogen borrowing (BH) processes, Kinetic Isotope Effect (KIE) investigations were conducted using benzyl alcohol-d₃ (**2i-d₃**), which was synthesized through an optimized strategy based on the principles of BH. This analysis aimed to elucidate the relative rates of alcohol oxidation and imine reduction. We employed quantitative ¹H NMR spectroscopy, utilizing ethylene carbonate as an internal standard, to monitor the reactions between benzyl alcohol (**2i**) or benzyl alcohol-d₃ (**2i-d₃**) and p-anisidine (**1a**) (Scheme 5.11). The alcohol concentration was measured over time, which conforms to the following equation:

$$\ln \left(\frac{[C]_0}{[C]_t} \right) = kt$$

$[C]_0$ and $[C]_t$ represent the concentrations of alcohol at times 0 and t, respectively. The decay rates of the concentrations of benzyl alcohol (**2i**) and benzyl alcohol- d_3 (**2i-d₃**) exhibited similar trends; however, the reaction rate was faster for benzyl alcohol (**2i**). This difference can be attributed to the altered vibrational frequency of the isotopes caused by the mass difference between ^1H and D. The magnitude of the kinetic isotope effect (KIE) is determined by the nature of the isotopic substitution and the involvement of the bond in the rate-determining step (rds) of the reaction:

$$KIE = \frac{k_H}{k_D}$$

where k_H and k_D are the rate constants for the reactions involving ^1H and D, respectively.⁸² The calculated low KIE value of 1.27 ± 0.09 with an R^2 value of 0.97 (Figure 5.5) suggests that the rds is not the alcohol oxidation step (Table 5.4).⁸³ During the reduction of the *in-situ* formed imine, the reducing agent [**Ru1-H₂**] cleaved the Ru-H bond. The lower force constant of the Ru-H bond compared to that of the C-H bonds results in a KIE, albeit a smaller one. The low KIE observed ruled out not only alcohol oxidation but also imine reduction as the rds.

From the substrate scope, the isolation of compound **3am** as an imine without further reduction to the corresponding amine suggests that imine formation is not the rds. This conclusion was further supported by ^1H NMR spectroscopy, which revealed no peaks for aldehydes, confirming the absence of intermediate oxidation products. In summary, the low KIE value, along with these observations, strongly suggests that the rate-determining step likely involves the coordination of the [**Ru1-H₂**] species with an imine intermediate.⁸³

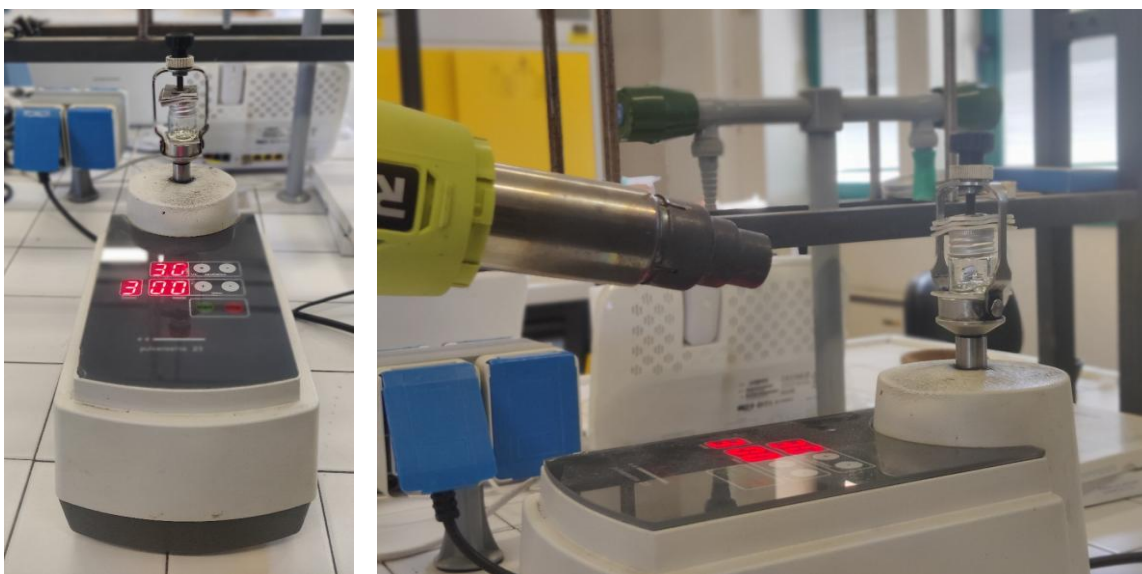
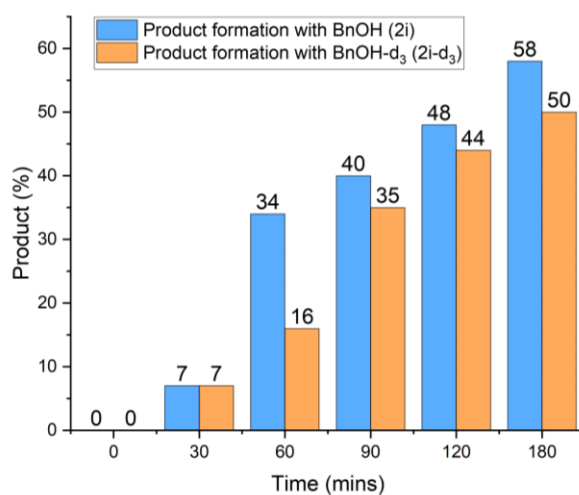
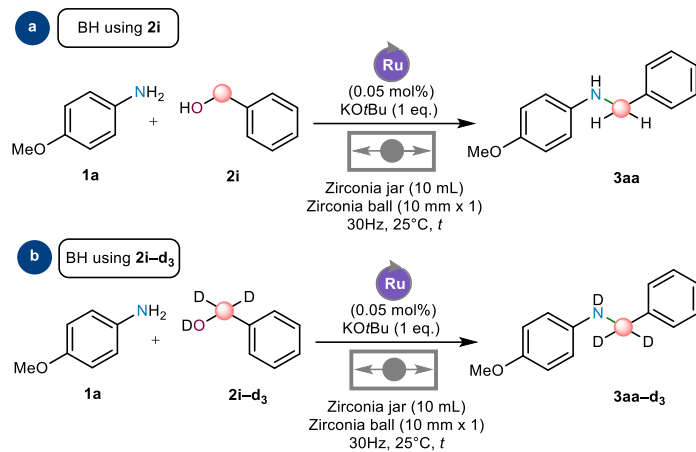


Figure 5.4. Deuteration experiment set-up



Scheme 5.11. Kinetic isotope effect analysis of mechanochemical BH for N-alkylation of aromatic amines using; a) benzyl alcohol (**2i**); b) benzyl alcohol-d₃ (**2i-d₃**)

Table 5.4. KIE analysis for N-alkylation of aromatic amines with BH strategy

Time (s)	[C _{2i}]	ln([C _{2i(0)}]/ [C _{2i(t)}])	[C _{2i-d3}]	ln([C _{2i-d3(0)}]/ [C _{2i-d3(t)}])
0	1	0	1	0
1800	0.65	0.43078	0.75	0.28768
3600	0.44	0.82098	0.68	0.38566
5400	0.36	1.02165	0.41	0.8916
7200	0.29	1.23787	0.37	0.99425
9000	0.22	1.51413	0.3	1.20397

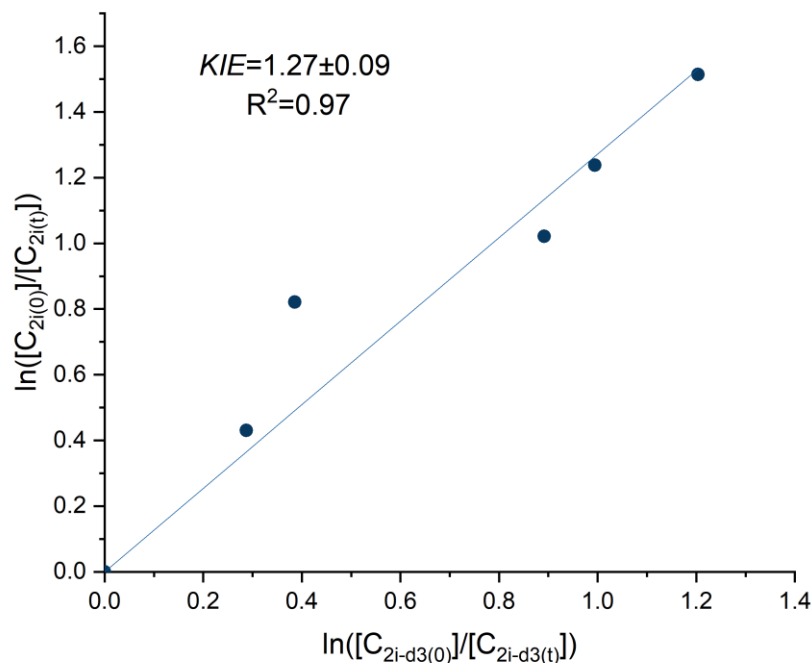


Figure 5.5. Kinetic isotope effect (KIE) analysis with benzyl alcohol 2i and benzyl alcohol- d_3 (2i- d_3) with the plot of $\ln([C_{2i-d3(0)}]/[C_{2i-d3(t)}])$ vs $\ln([C_{2i(0)}]/[C_{2i(t)}])$; KIE= 1.27 ± 0.09 ($R^2 = 0.97$).

5.5.3. Hammett Analysis

Non-competitive Hammett studies were performed using a series of *para*-substituted anilines with electron-donating and electron-withdrawing groups to further investigate the step-determining selectivity in the mechanochemical borrowing hydrogenation process.⁸⁴⁻⁸⁷ The reactions between pentanol (**2a**) and *para*-substituted aniline derivatives (**1a–e**) were closely monitored using quantitative ^1H NMR spectroscopy, with ethylene carbonate as the internal standard for accurately measuring the aniline concentrations over time. The results revealed a clear trend in reactivity based on the electronic nature of substituent. Anilines with electron-withdrawing groups at the *para* position (e.g., **1d–e**) exhibited significantly higher reactivity than their electron-donating counterparts (e.g., **1a**, **1c**). *p*-Bromoaniline demonstrated the highest activity among the tested derivatives, whereas *p*-anisidine showed the lowest reactivity. Hammett analysis provided quantitative insights into the electronic effects of substituents on the reaction mechanism, correlating reaction kinetics or equilibria with substituent constants (σ). This study highlights the intricate interplay between the electronic structure and chemical reactivity by establishing this relationship.

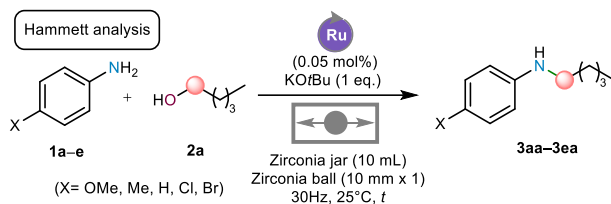
This relationship is mathematically described by the Hammett equation:

$$\log\left(\frac{k_X}{k_H}\right) = \rho\sigma$$

where k_X and k_H are the rate constants (or equilibrium constants) for the substituted and unsubstituted compounds, respectively; σ is the substituent constant representing the electronic

effect of the substituent, and ρ is the reaction constant reflecting the sensitivity of the reaction to these electronic effects.

Table 5.5. Hammett analysis for *N*-alkylation of aromatic amines with BH strategy



Time (s)	$\ln([C_{\text{Br}(0)}]/[C_{\text{Br}(t)}])$	$\ln([C_{\text{Cl}(0)}]/[C_{\text{Cl}(t)}])$	$\ln([C_{\text{H}(0)}]/[C_{\text{H}(t)}])$	$\ln([C_{\text{Me}(0)}]/[C_{\text{Me}(t)}])$	$\ln([C_{\text{OMe}(0)}]/[C_{\text{OMe}(t)}])$
0	0	0	0	0	0
600	0.35667	0.34249	0.30111	0.22314	0.07257
1200	0.63488	0.57982	—	0.37106	0.18633
1800	1.04982	—	0.8916	0.56212	0.34249
2400	1.51413	1.42712	1.20397	0.71335	0.4943
3000	1.96611	1.77196	1.34707	0.94161	0.63488
3600	2.52573	2.30259	1.51413	1.10866	0.75502

The Hammett plot for the mechanochemical hydrogen borrowing (BH) reaction was constructed by correlating $\log(k_X/k_H)$ with the substituent constants (σ). This plot exhibited a strong linear relationship ($R^2 = 0.98$) and a reaction constant (ρ) of 0.92 ± 0.05 (Table 5.6.). A positive ρ value indicates the development of a partial positive charge in the transition state, suggesting an electron-deficient environment (Figure 5.6.b). These findings are consistent with insights from Kinetic Isotope Effect (KIE) studies, reinforcing the conclusion that the coordination between the $[\text{Ru1-H}_2]$ species and imine represent an irreversible step in the reaction mechanism. Under mechanochemical BH conditions, the ground-state energy of $[\text{Ru1-H}_2]$ and the energy barrier associated with the transition state owing to the interaction of $[\text{Ru1-H}_2]$ with the imine are critical factors to consider. Notably, the ground-state energies of the various anilines significantly affected the reaction rate. Although electron-rich anilines are inherently more reactive, their strong coordination ability paradoxically impedes the reaction by slowing the overall reaction rate. This finding highlights the importance of electronic factors, as the enhanced binding affinity of electron-rich anilines outweighs their intrinsic reactivity under mechanochemical BH conditions.

Table 5.6. Hammett Analysis

Entry	X	Substituent Constant (σ)	$\log(k_X/k_H)$
1	Br	0.232	0.20605
2	Cl	0.227	0.16466
3	H	0	0
4	Me	-0.17	-0.15321
5	OMe	-0.268	-0.29329

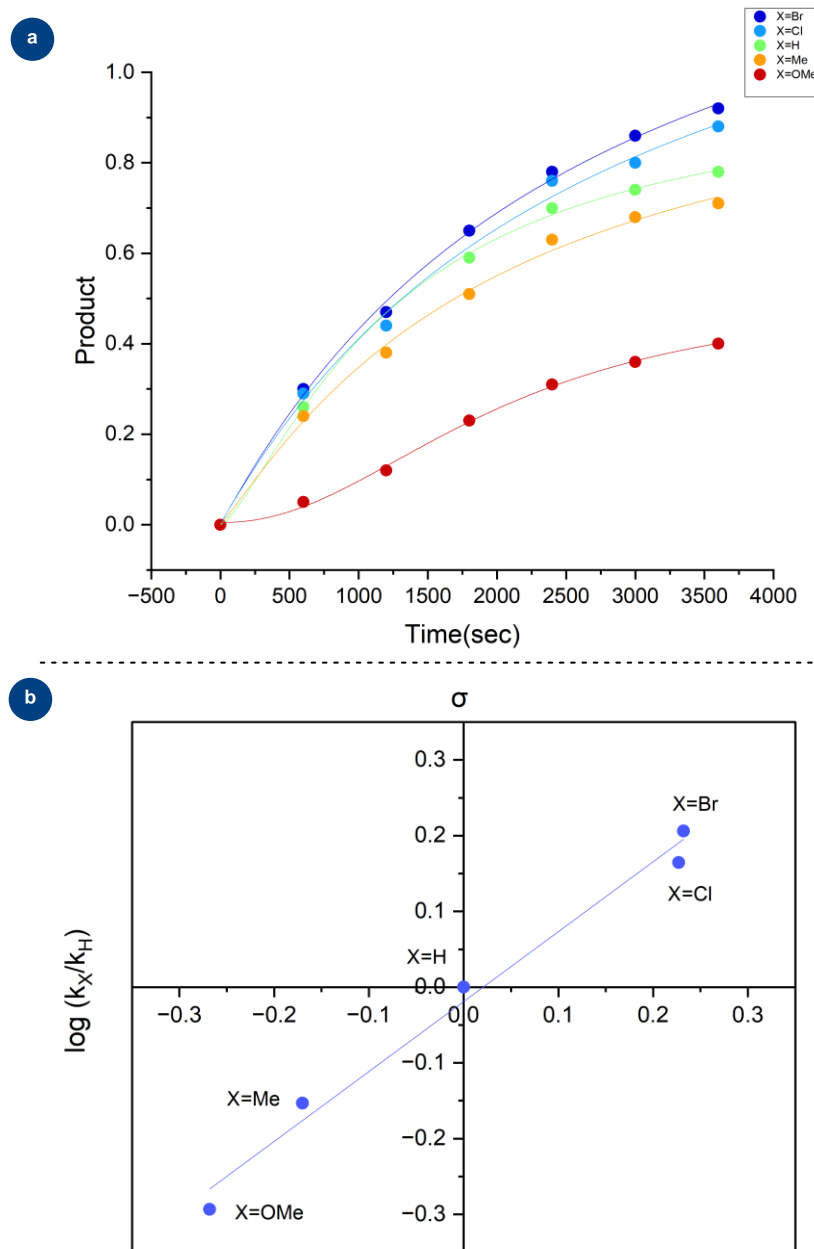
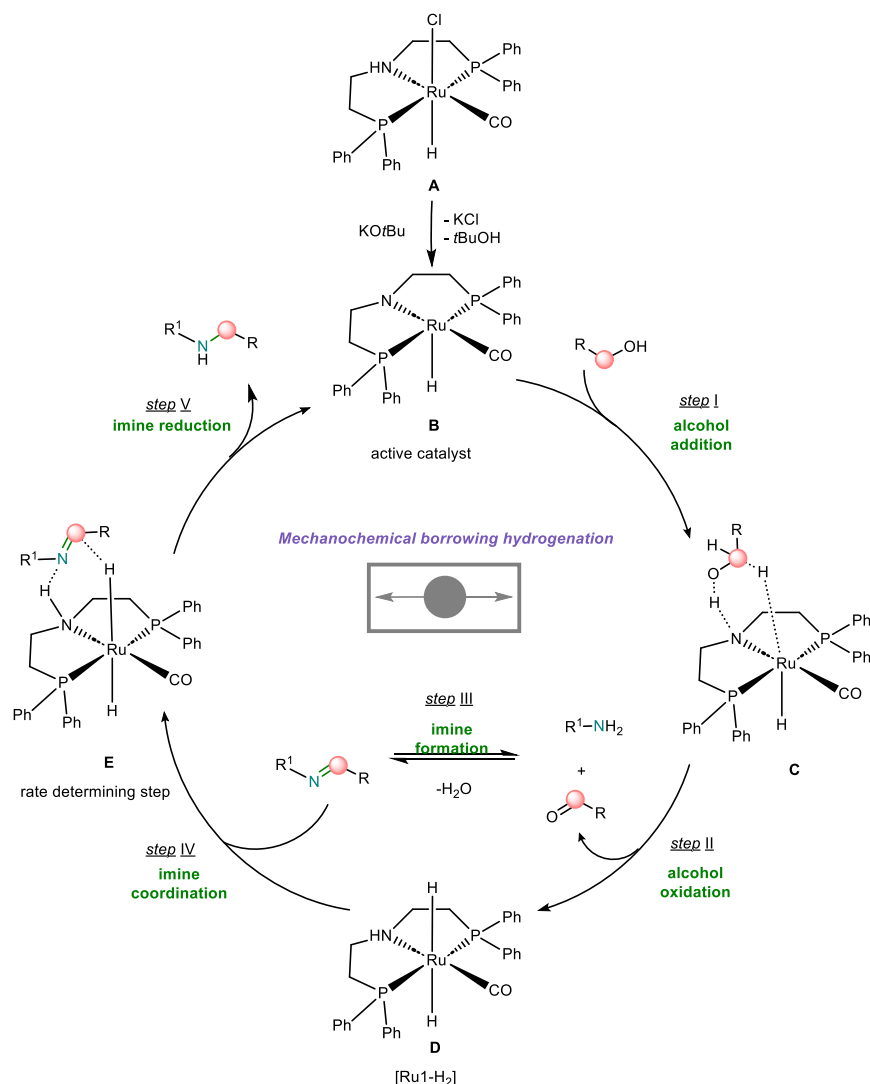


Figure 5.6. Hammett analysis; a) Product evolution with different *para*-substituted anilines (**1a–e**) and pentanol (**2a**); b) Hammett plot for *para*-substituted anilines; Hammett slope = 0.92 ± 0.05 ($R^2 = 0.98$)

5.5.4. Catalytic Cycle

Based on the comprehensive experimental results outlined above, a plausible reaction mechanism for the observed outcomes was proposed (Scheme 5.12). Initially, in the presence of KO*t*Bu, the Ru-MACHO complex (Scheme 5.12, species **A**) is activated by mechanical milling, leading to the formation of the active catalyst (Scheme 5.12, species **B**). In the first step of the catalytic cycle (step I), alcohol coordination with the activated catalyst was observed. This coordination is

followed by alcohol oxidation, resulting in the formation of the corresponding aldehyde via a ruthenium–hydride complex [**Ru1–H₂**] (Scheme 5.12, species **D**).



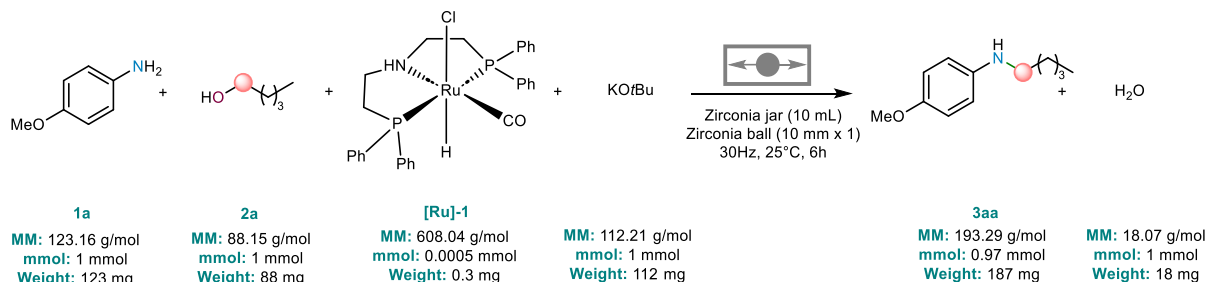
Scheme 5.12. Plausible reaction mechanism for mechanochemical BH reaction

In a parallel reaction pathway (step III), the aldehyde produced in step II reacts with an amine species, yielding the corresponding imine and byproduct water. This reaction is subsequently followed by the coordination of the imine species to the ruthenium–hydride complex [**Ru1–H₂**] (Scheme 5.12, species **E**), preparing the system for imine reduction. Kinetic isotope effect (Figure 5.5) studies combined with Hammett analysis (Figure 5.6.b) suggest that the coordination of the imine to the catalyst constitutes the rate-determining step (rds) of the catalytic cycle. Following the effectively irreversible formation of complex **E**, the imine was reduced, affording the secondary amine product. Notably, inhibition of the reaction by the secondary amine product was not observed, which suggests that strong interactions with the ruthenium center might not have formed at any stage of the catalytic cycle.

5.6. Green Metrics

This section describes the green chemistry metrics for the mechanochemical borrowing hydrogenation methodology compared to a previously reported solution-based approach³⁴ employing a Ru-based catalyst at room temperature. Specifically, a quantitative and qualitative evaluations by measuring the E-factor⁸⁸ and eco-scale⁸⁹ values have been conducted using Ecoscale calculator.

Calculation of the green metrics for the mechanochemical preparation of 3aa:

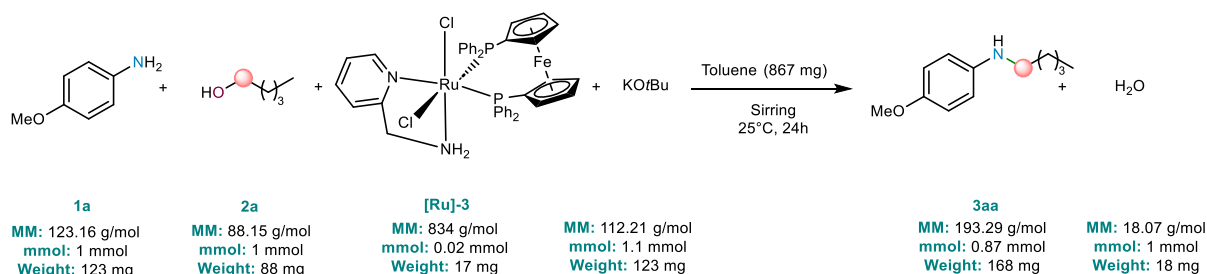


$$\text{Environmental factor (E)} = \frac{\text{mass of total waste}}{\text{mass of desired product}} = \frac{(123+88+0.3+112-187)\text{mg}}{187\text{ mg}} = \frac{136\text{ mg}}{187\text{ mg}} = 0.7$$

Work-up: filtration through celite (1000 mg) using EtOAc (4510 mg)

$$\text{E (after work-up and purification)} = \frac{(4510+1000+136)\text{ mg}}{187\text{ mg}} = \frac{5646\text{ mg}}{187\text{ mg}} = 30$$

Calculation of the green metrics for the solution-based preparation of 3aa:



$$\text{Environmental factor (E)} = \frac{\text{mass of total waste}}{\text{mass of desired product}} = \frac{(123+88+17+123+867-168)\text{mg}}{168\text{ mg}} = \frac{1050\text{ mg}}{168\text{ mg}} = 6.3$$

Work-up: column chromatography with n-hexane (59490 mg), EtOAc (9020 mg) and silica (20000 mg)

$$\text{E (after work-up and purification)} = \frac{(59490+9020+20000+1050)\text{ mg}}{168\text{ mg}} = \frac{89560\text{ mg}}{168\text{ mg}} = 533$$

The results show that the mechanochemical procedure outperforms the analogous procedure in solution, achieving an E-factor of 30 compared to 533 and an eco-scale value of 70 versus 52.5.

Notably, the high E-factor in solution-based methods largely stems from the need for solvents and chromatographic purification.

Eco-scale score for the mechanochemical preparation of amine **3aa**

EcoScale: 100 – sum of penalty points

Table 5.7. Calculation of Ecoscale score for the mechanochemical preparation of amine **3aa**^a

Reagents	MF	MW	mmol	Weight (g)	Eq.
p-Anisidine	C ₇ H ₉ NO	123.15	1.0	0.123	1.0
1-Pentanol	C ₅ H ₁₂ O	88.15	1.0	0.088	1.0
Potassium tert-butoxide	C ₄ H ₉ KO	112.21	1.0	0.112	1.0
Ru-MACHO	C ₂₉ H ₃₀ ClNOP ₂ Ru	607.03	0.0005	0.0003	0.0005
Products	MF	MW	mmol	Weight (g)	Eq.
4-methoxy-N-pentylaniline (3aa)	C ₁₂ H ₁₉ NO	193.29	0.97	0.193	97%

Entry	Parameters	Penalty Points
1	Yield (97%)	-2
2	Price/availability	-5
3	Safety	-20
4	Technical set-up (Unconventional activation technique)	-2
5	Room temperature (< 24h)	-1
6	Work-up and purification	0
	EcoScale score	70

Eco-scale score for the solution-based preparation of amine **3aa**

Table 5.8. Calculation of Ecoscale score for the solution-based preparation of amine **3aa**^a

Reagents	MF	MW	mmol	Weight (g)	Eq.
p-Anisidine	C ₇ H ₉ NO	123.15	1.0	0.123	1.0
1-Pentanol	C ₅ H ₁₂ O	88.15	1.0	0.088	1.0
Potassium tert-butoxide	C ₄ H ₉ KO	112.21	1.1	0.123	1.1
cis-[RuCl ₂ (ampy)(dppf)]	C ₄₀ H ₃₆ Cl ₂ FeN ₂ P ₂ Ru	834.50	0.017	0.02	0.02
Toluene	C ₇ H ₈	92.14	0.866	9.4	9.4
Products	MF	MW	mmol	Weight (g)	Eq.
4-methoxy-N-pentylaniline (3aa)	C ₁₂ H ₁₉ NO	193.29	0.168	0.87	87%

Entry	Parameters	Penalty Points
1	Yield (97%)	-6.5
2	Price/availability	-5
3	Safety	-25
4	Technical set-up (Unconventional activation technique)	0
5	Room temperature (< 24h)	-1
6	Work-up and purification	-10
	EcoScale score	52.5

^a Values calculated using the eco scale calculator software available at the link:

<http://ecoscale.cheminfo.org/calculator>

5.7. Conclusions

This chapter presents a mechanochemical strategy for borrowing hydrogen (BH) to synthesize N-alkylated amines and heterocycles under direct, solvent-free, and efficient conditions. By harnessing ball milling alongside a ruthenium-based catalyst, our approach effectively addresses the challenges associated with solution-phase syntheses, including the use of toxic reagents and the need for high temperatures, while achieving nearly quantitative conversion of various primary amines and alcohol substrates. Kinetic isotope effect (KIE) studies and Hammett analyses underscore the crucial role of substrate-derived hydrogen in the reaction, distinguishing it from conventional methods. Furthermore, this methodology allows the synthesis of various heterocycles, including indoles and benzimidazoles, showcasing its versatility. Mechanochemical ball milling has emerged as a more sustainable alternative to traditional methods, making it well-suited for pharmaceutical, agrochemical, and fine-chemical applications. Operating under mild, solvent-free conditions aligns with current sustainability goals. Ongoing research will continue to deepen our understanding of and expand the applications of this innovative approach in synthetic chemistry.

5.8. References

- (1) Kerru, N.; Gummidi, L.; Maddila, S.; Gangu, K. K.; Jonnalagadda, S. B. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. *Molecules* **2020**, *25* (8), 1909.
- (2) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274.
- (3) Bishop-Freeman, S. C.; Shonsey, E. M.; Friederich, L. W.; Beuhler, M. C.; Winecker, R. E. Benzonatate Toxicity: Nothing to Cough At. *J. Anal. Toxicol.* **2017**, *41* (5), 461–463.
- (4) Inbaraj, J. J.; Bilski, P.; Chignell, C. F. Photophysical and photochemical studies of 2-phenylbenzimidazole and UVB sunscreen 2-phenylbenzimidazole-5-sulfonic acid. *Photochem. Photobiol.* **2002**, *75* (2), 107–116.
- (5) Syed, Y. Y. Sumatriptan/Naproxen Sodium: A Review in Migraine. *Drugs* **2016**, *76* (1), 111–121.
- (6) Elangovan, S.; Neumann, J.; Sortais, J. B.; Junge, K.; Darcel, C.; Beller, M. Efficient and selective N-alkylation of amines with alcohols catalysed by manganese pincer complexes. *Nat. Commun.* **2016**, *7*, 12641.
- (7) Porcheddu, A.; Mocci, R.; Brindisi, M.; Cuccu, F.; Fattuoni, C.; Delogu, F.; Colacino, E.; D'Auria, M. V. Mechanochemical Fischer indolisation: an eco-friendly design for a timeless reaction. *Green Chem.* **2022**, *24* (12), 4859–4869.
- (8) Yin, H. N.; Wang, P. C.; Liu, Z. Recent advances in biocatalytic C–N bond-forming reactions. *Bioorg. Chem.* **2024**, *144*, 107108.
- (9) Bariwal, J.; Van der Eycken, E. C–N bond forming cross-coupling reactions: an overview. *Chem. Soc. Rev.* **2013**, *42* (24), 9283–9303.
- (10) Guo, W.; Zhao, M.; Tan, W.; Zheng, L.; Taao, K.; Fan, X. Developments towards synthesis of N-heterocycles from amidines via C–N/C–C bond formation. *Org. Chem. Front.* **2019**, *6* (13), 2120–2141.
- (11) Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. Survey of GMP Bulk Reactions Run in a Research Facility between 1985 and 2002. *Org. Process Res. Dev.* **2005**, *9* (3), 253–258.
- (12) Hernández, J. G.; Turberg, M.; Schiffrs, I.; Bolm, C. Mechanochemical Strecker Reaction: Access to α -Aminonitriles and Tetrahydroisoquinolines under Ball-Milling Conditions. *Chem. Eur. J.* **2016**, *22* (41), 14513–14517.
- (13) Guin, A. K.; Pal, S.; Chakraborty, S.; Chakraborty, S.; Paul, N. D. N-Alkylation of Amines by C1–C10 Aliphatic Alcohols Using A Well-Defined Ru(II)-Catalyst. A Metal-Ligand Cooperative Approach. *J. Org. Chem.* **2023**, *88* (9), 5944–5961.
- (14) Templ, J.; Schnürch, M. A Guide for Mono-Selective N-Methylation, N-Ethylation, and N-n-Propylation of Primary Amines, Amides, and Sulfonamides and Their Applicability in Late-Stage Modification. *Chem. Eur. J.* **2024**, *30* (26), e202304205.
- (15) Xu, Q.; Xie, H.; Zhang, E.-L.; Ma, X.; Chen, J.; Yua, X.-C.; Li, H. Selective catalytic Hofmann N-alkylation of poor nucleophilic amines and amides with catalytic amounts of alkyl halides. *Green Chem.* **2016**, *18*, 3940–3944.
- (16) Ruscic, B. Active Thermochemical Tables: Sequential Bond Dissociation Enthalpies of Methane, Ethane, and Methanol and the Related Thermochemistry. *J. Phys. Chem. A* **2015**, *119* (28), 7810–7837.
- (17) Williams, M. T. J.; Cardona, L. A.; Bolm, C. Mechanochemical Mitsunobu Reactions. *Adv. Synth. Catal.* **2024**, *366* (10), 2220–2225.
- (18) Bull, S. R. Renewable alternative fuels: Alcohol production from lignocellulosic biomass. *Renew. Energy* **1994**, *5*, 799–806.
- (19) Schubert, T. Production routes of advanced renewable C1 to C4 alcohols as biofuel components – a review. *Biofuels, Bioprod. Bioref.* **2020**, *14* (4), 845–878.
- (20) Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. The ruthenium catalyzed N-alkylation and N-heterocyclization of aniline using alcohols and aldehydes. *Tetrahedron Lett.* **1981**, *22* (18), 2667–2670.
- (21) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. Transition metal-catalysed N-alkylation of amines by alcohols. *Chem. Commun.* **1981**, *22* (12), 611–612.

- (22) Hamid, M. H.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J.; Williams, J. M. Ruthenium-catalyzed N-alkylation of amines and sulfonamides using borrowing hydrogen methodology. *J. Am. Chem. Soc.* **2009**, *131* (5), 1766-1774.
- (23) Bahn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. Synthesis of primary amines from secondary and tertiary amines: ruthenium-catalyzed amination using ammonia. *Chem. Eur. J.* **2011**, *17* (17), 4705-4708.
- (24) Denjean, A. E. F.; Nova, A.; Balcells, D. Borrowing Hydrogen Mechanism in Amine Alkylation by Single Atom Nickel Catalysts. *ACS Catal.* **2024**, *14* (15), 11332–11342.
- (25) Reed-Berendt, B. G.; Latham, D. E.; Dambatta, M. B.; Morrill, L. C. Borrowing Hydrogen for Organic Synthesis. *ACS Cent. Sci.* **2021**, *7* (4), 570-585.
- (26) Corma, A.; Navas, O.; Sabater, M. J. Advances in One-Pot Synthesis through Borrowing Hydrogen Catalysis. *Chem. Rev.* **2018**, *118* (4), 1410–1459.
- (27) Alexandridis, A.; Quintard, A. Enantioselective Borrowing Hydrogen: A Modern Tool to Construct Enantioenriched Molecules. *ChemCatChem* **2024**, *16* (24), e202400902.
- (28) Ji, J.; Huo, Y.; Dai, Z.; Chen, Z.; Tu, T. Manganese-Catalyzed Mono-N-Methylation of Aliphatic Primary Amines without the Requirement of External High-Hydrogen Pressure. *Angew. Chem. Int. Ed.* **2024**, *63* (13), e202318763.
- (29) Mehr, A. S.; Phillips, A. D.; Brandon, M. P.; Pryce, M. T.; Carton, J. G. Recent challenges and development of technical and technoeconomic aspects for hydrogen storage, insights at different scales; A state of art review. *Int. J. Hydrogen Energy* **2024**, *70*, 786-815.
- (30) Podyacheva, E.; Afanasyev, O. I.; Vasilyev, D. V.; Chusov, D. Borrowing Hydrogen Amination Reactions: A Complex Analysis of Trends and Correlations of the Various Reaction Parameters. *ACS Catal.* **2022**, *12* (12), 7142–7198.
- (31) Bertoli, M.; Choualeb, A.; Lough, A. J.; Moore, B.; Spasyuk, D.; Gusev, D. G. Osmium and ruthenium catalysts for dehydrogenation of alcohols. *Organometallics* **2011**, *30* (13), 3479-3482.
- (32) Martinez-Asencio, A.; Yus, M.; Ramon, D. J. Palladium (II) acetate as catalyst for the N-alkylation of aromatic amines, sulfonamides, and related nitrogenated compounds with alcohols by a hydrogen autotransfer process. *Synthesis* **2011**, *2011* (22), 3730-3740.
- (33) Liu, Y.; Diao, H.; Hong, G.; Edward, J.; Zhang, T.; Yang, G.; Yang, B.-M.; Zhao, Y. Iridium-catalyzed enantioconvergent borrowing hydrogen annulation of racemic 1, 4-diols with amines. *J. Am. Chem. Soc.* **2023**, *145* (9), 5007-5016.
- (34) Mocci, R.; Atzori, L.; Baratta, W.; De Luca, L.; Porcheddu, A. N-Alkylation of aromatic amines with alcohols by using a commercially available Ru complex under mild conditions. *RSC Adv.* **2023**, *13* (49), 34847-34851.
- (35) Polidano, K.; Allen, B. D. W.; Williams, J. M. J.; Morrill, L. C. Iron-Catalyzed Methylation Using the Borrowing Hydrogen Approach. *ACS Catal.* **2018**, *8* (7), 6440-6445.
- (36) Wei, D.; Yang, P.; Yu, C.; Zhao, F.; Wang, Y.; Peng, Z. N-Alkylation of Amines with Alcohols Catalyzed by Manganese(II) Chloride or Bromopentacarbonylmanganese(I). *J. Org. Chem.* **2021**, *86* (3), 2254-2263.
- (37) Rawlings, A. J.; Diorazio, L. J.; Wills, M. C–N bond formation between alcohols and amines using an iron cyclopentadienone catalyst. *Org. Lett.* **2015**, *17* (5), 1086-1089.
- (38) Rosler, S.; Ertl, M.; Irrgang, T.; Kempe, R. Cobalt-Catalyzed Alkylation of Aromatic Amines by Alcohols. *Angew. Chem. Int. Ed.* **2015**, *54* (50), 15046-15050.
- (39) Wang, L. M.; Morioka, Y.; Jenkinson, K.; Wheatley, A. E. H.; Saito, S.; Naka, H. N-Alkylation of functionalized amines with alcohols using a copper-gold mixed photocatalytic system. *Sci. Rep.* **2018**, *8* (1), 6931.
- (40) Bains, A. K.; Kundu, A.; Yadav, S.; Adhikari, D. Borrowing Hydrogen-Mediated N-Alkylation Reactions by a Well-Defined Homogeneous Nickel Catalyst. *ACS Catal.* **2019**, *9* (10), 9051–9059.
- (41) Li, J. Q.; Andersson, P. G. Room temperature and solvent-free iridium-catalyzed selective alkylation of anilines with alcohols. *Chem. Commun.* **2013**, *49* (55), 6131-6133.

- (42) Shen, D.; Poole, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. Hydrogen-borrowing and interrupted-hydrogen-borrowing reactions of ketones and methanol catalyzed by iridium. *Angew. Chem. Int. Ed.* **2015**, *54* (5), 1642-1645.
- (43) Enyong, A. B.; Moasser, B. Ruthenium-catalyzed N-alkylation of amines with alcohols under mild conditions using the borrowing hydrogen methodology. *J. Org. Chem.* **2014**, *79* (16), 7553-7563.
- (44) Yamaguchi, K.; He, J.; Oishi, T.; Mizuno, N. The "Borrowing Hydrogen Strategy" by Supported Ruthenium Hydroxide Catalysts: Synthetic Scope of Symmetrically and Unsymmetrically Substituted Amines. *Chem. Eur. J.* **2010**, *16* (24), 7199-7207.
- (45) Bhatt, S.; Rana, M.; Sharma, A. K.; Joshi, H. Ruthenium Complexes of Bidentate N,N-Ligand as Catalyst for Selective N-Alkylation of Amines with Alcohols. *Asian J. Org. Chem.* **2023**, *12*, e202300158.
- (46) Cruz, S. L.; Rivera-García, M. T.; Woodward, J. J. Review of Toluene Actions: Clinical Evidence, Animal Studies, and Molecular Targets. *J. Drug Alcohol Res.* **2014**, *3*, 235840.
- (47) Cuccu, F.; De Luca, L.; Delogu, F.; Colacino, E.; Solin, N.; Mocci, R.; Porcheddu, A. Mechanochemistry: New Tools to Navigate the Uncharted Territory of "Impossible" Reactions. *ChemSusChem* **2022**, *15* (17), e202200362.
- (48) Rodríguez, B.; Bruckmann, A.; Rantanen, T.; Bolm, C. Solvent-Free Carbon-Carbon Bond Formations in Ball Mills. *Adv. Synth. Catal.* **2007**, *349*, 2213 – 2233.
- (49) Sander, M.; Fabig, S.; Borchardt, L. The Transformation of Inorganic to Organic Carbonates: Chasing for Reaction Pathways in Mechanochemistry. *Chem. Eur. J.* **2023**, *29* (7), e202202860.
- (50) Reynes, J. F.; Leon, F.; Garcia, F. Mechanochemistry for Organic and Inorganic Synthesis. *ACS Org. Inorg. Au* **2024**, *4* (5), 432-470.
- (51) Yong, T.; Bati, G.; Garcia, F.; Stuparu, M. C. Mechanochemical transformation of planar polyarenes to curved fused-ring systems. *Nat. Commun.* **2021**, *12* (1), 5187.
- (52) Howard, J. L.; Cao, Q.; Browne, D. L. Mechanochemistry as an emerging tool for molecular synthesis: what can it offer? *Chem. Sci.* **2018**, *9*.
- (53) Fantozzi, N.; Volle, J. N.; Porcheddu, A.; Virieux, D.; Garcia, F.; Colacino, E. Green metrics in mechanochemistry. *Chem. Soc. Rev.* **2023**, *52* (19), 6680-6714.
- (54) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D.; Hyett, G.; Jones, W.; et al. Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.* **2012**, *41* (1), 413-447.
- (55) Hwang, S.; Gratz, S.; Borchardt, L. A guide to direct mechanocatalysis. *Chem. Commun.* **2022**, *58* (11), 1661-1671.
- (56) Porcheddu, A.; Colacino, E.; De Luca, L.; Delogu, F. Metal-Mediated and Metal-Catalyzed Reactions Under Mechanochemical Conditions. *ACS Catal.* **2020**, *10* (15), 8344-8394.
- (57) Ke, J.; van Bonn, P.; Bolm, C. Mechanochemical difluoromethylations of ketones. *Beilstein J. Org. Chem.* **2024**, *20*, 2799-2805.
- (58) Tan, D.; Garcia, F. Main group mechanochemistry: from curiosity to established protocols. *Chem. Soc. Rev.* **2019**, *48* (8), 2274-2292.
- (59) Chantrain, V.; Rensch, T.; Pickhardt, W.; Gratz, S.; Borchardt, L. Continuous Direct Mechanocatalytic Suzuki-Miyaura Coupling via Twin-Screw Extrusion. *Chem. Eur. J.* **2024**, *30* (17), e202304060.
- (60) Williams, M. T. J.; Morrill, L. C.; Browne, D. L. Nickel-Catalyzed Intramolecular Alkene Difunctionalization by Ball-Milling. *Adv. Synth. Catal.* **2023**, *365* (9), 1477-1484.
- (61) Pontini, L.; Leitch, J. A.; Browne, D. L. Mechanochemical Simmons-Smith cyclopropanation via ball-milling-enabled activation of zinc(0). *Green Chem.* **2023**, *25*, 4319-4325.
- (62) Nicholson, W. I.; Howard, J. L.; Magri, G.; Seastram, A. C.; Khan, A.; Bolt, R. R. A.; Morrill, L. C.; Richards, E.; Browne, D. L. Ball-Milling-Enabled Reactivity of Manganese Metal*. *Angew. Chem. Int. Ed.* **2021**, *60* (43), 23128-23133.
- (63) Seavill, P. W. Suzuki-Miyaura mechanochemistry. *Nat. Synth.* **2023**, *2*, 307.
- (64) Reynes, J. F.; García, F. Temperature-Controlled Mechanochemistry Unlocks the Nickel-Catalyzed Suzuki-Miyaura-Type Coupling of Aryl Sulfamates at Different Scales. *Angew. Chem.* **2023**, *135* (2), e202215094.

- (65) Cao, Q.; Howard, J. L.; Wheatley, E.; Browne, D. L. Mechanochemical activation of zinc and application to Negishi cross-coupling. *Angew. Chem.* **2018**, *130* (35), 11509-11513.
- (66) Yang, X.; Wu, C.; Su, W.; Yu, J. Mechanochemical C–X/C–H Functionalization: An Alternative Strategic Access to Pharmaceuticals. *Eur. J. Org. Chem.* **2022**, (8), e202101440.
- (67) Do, J.-L.; Mottillo, C.; Tan, D.; Strukil, V.; Friscic, T. Mechanochemical ruthenium-catalyzed olefin metathesis. *J. Am. Chem. Soc.* **2015**, *137* (7), 2476-2479.
- (68) Kubota, K.; Seo, T.; Koide, K.; Hasegawa, Y.; Ito, H. Olefin-accelerated solid-state C–N cross-coupling reactions using mechanochemistry. *Nat. Commun.* **2019**, *10* (1), 111.
- (69) Hickenboth, C. R.; Moore, J. S.; White, S. R.; Sottos, N. R.; Baudry, J.; Wilson, S. R. Biasing reaction pathways with mechanical force. *Nature* **2007**, *446* (7134), 423-427.
- (70) Subaramanian, M.; Sivakumar, G.; Landge, V. G.; Kumar, R.; Natte, K.; Jagadeesh, R. V.; Balaraman, E. General and selective homogeneous Ru-catalyzed transfer hydrogenation, deuteration, and methylation of functional compounds using methanol. *J. Catal.* **2023**, *425*, 386-405.
- (71) Yang, L.; Guo, X.; Ren, Y.; Gu, R.; Chen, Z.-X.; Zeng, G. Mechanistic Insight into Acceptorless Dehydrogenation of Methanol to Syngas Catalyzed by MACHO-Type Ruthenium and Manganese Complexes: A DFT Study. *Inorg. Chem.* **2023**, *62* (48), 19516–19526.
- (72) Kuriyama, W.; Matsumoto, T.; Ogata, O.; Ino, Y.; Aoki, K.; Tanaka, S.; Ishida, K.; Kobayashi, T.; Sayo, N.; Saito, T. Catalytic Hydrogenation of Esters. Development of an Efficient Catalyst and Processes for Synthesising (R)-1,2-Propanediol and 2-(l-Menthoxy)ethanol. *Org. Process Res. Dev.* **2012**, *16* (1), 166-171.
- (73) Pinheiro, D. L. J.; Nielsen, M. Base-Free Synthesis of Furfurylamines from Biomass Furans Using Ru Pincer Complexes. *Catalysts* **2021**, *11* (5), 558.
- (74) Ogata, O.; Nara, H.; Mitsuhiro, F.; Matsumura, K.; Kayaki, Y. N-Monomethylation of Aromatic Amines with Methanol via PNHP-Pincer Ru Catalysts. *Org. Lett.* **2018**, *20* (13), 3866–3870.
- (75) Luo, J.; Zhou, Q. Q.; Montag, M.; Ben-David, Y.; Milstein, D. Acceptorless dehydrogenative synthesis of primary amides from alcohols and ammonia. *Chem. Sci.* **2022**, *13* (13), 3894-3901.
- (76) Das, K.; Nandi, P. G.; Islam, K.; Srivastava, H. K.; Kumar, A. N-Alkylation of Amines Catalyzed by a Ruthenium–Pincer Complex in the Presence of in situ Generated Sodium Alkoxide. *Eur. J. Org. Chem.* **2019**, (40), 6855-6866.
- (77) Kozuch, S.; Martin, J. M. L. “Turning Over” Definitions in Catalytic Cycles. *ACS Catal.* **2012**, *2* (12), 2787–2794.
- (78) Takahashi, R.; Hu, A.; Gao, P.; Gao, Y.; Pang, Y.; Seo, T.; Jiang, J.; Maeda, S.; Takaya, H.; Kubota, K. Mechanochemical synthesis of magnesium-based carbon nucleophiles in air and their use in organic synthesis. *Nat. Commun.* **2021**, *12* (1), 6691.
- (79) Quaranta, C.; d’Anciaes Almeida Silva, I.; Moos, S.; Bartalucci, E.; Hendrickx, L.; Fahl, B. M. D.; Pasqualini, C.; Puccetti, F.; Zobel, M.; Bolm, C.; et al. Molecular Recognition in Mechanochemistry: Insights from Solid-State NMR Spectroscopy. *Angew. Chem. Int. Ed.* **2024**, *63* (43), e202410801.
- (80) Michalchuk, A. A. L.; Emmerling, F. Time-Resolved In Situ Monitoring of Mechanochemical Reactions. *Angew. Chem. Int. Ed.* **2022**, *61* (21), e202117270.
- (81) Chatterjee, B.; Gunanathan, C. Ruthenium Catalyzed Selective α - and α,β -Deuteration of Alcohols Using D₂O. *Org. Lett.* **2015**, *17*, 4794–4797.
- (82) Hermann, G. N.; Becker, P.; Bolm, C. Mechanochemical Iridium(III)-Catalyzed C–H Bond Amidation of Benzamides with Sulfonyl Azides under Solvent-Free Conditions in a Ball Mill. *Angew. Chem. Int. Ed.* **2016**, *55* (11), 3781-3784.
- (83) Bartoszewicz, A.; Miera, G. G.; Marcos, R.; Norrby, P.-O.; Martín-Matute, B. Mechanistic Studies on the Alkylation of Amines with Alcohols Catalyzed by a Bifunctional Iridium Complex. *ACS Catal.* **2015**, *5* (6), 3704–3716.
- (84) Fristrup, P.; Turskya, M.; Madsen, R. Mechanistic investigation of the iridium-catalysed alkylation of amines with alcohols. *Org. Biomol. Chem.* **2012**, *10*, 2569.
- (85) Vugrin, L.; Carta, M.; Delogu, F.; Halasz, I. Extending the Hammett correlation to mechanochemical reactions. *Chem. Commun.* **2023**, *59* (12), 1629-1632.

- (86) Barbee, M. H.; Kouznetsova, T.; Barrett, S. L.; Gossweiler, G. R.; Lin, Y.; Rastogi, S. K.; Brittain, W. J.; Craig, S. L. Substituent Effects and Mechanism in a Mechanochemical Reaction. *J. Am. Chem. Soc.* **2018**, *140* (40), 12746-12750.
- (87) Lukin, S.; Tireli, M.; Stolar, T.; Barisic, D.; Blanco, M. V.; di Michiel, M.; Uzarevic, K.; Halasz, I. Isotope Labeling Reveals Fast Atomic and Molecular Exchange in Mechanochemical Milling Reactions. *J. Am. Chem. Soc.* **2019**, *141* (3), 1212-1216.
- (88) Tobiszewski, M.; Marc, M.; Galuszka, A.; Namiesnik, J. Green Chemistry Metrics with Special Reference to Green Analytical Chemistry. *Molecules* **2015**, *20* (6), 10928-10946.
- (89) Gałuszka, A.; Migaszewski, Z. M.; Konieczka, P.; Namieśnik, J. Analytical Eco-Scale for assessing the greenness of analytical procedures. *Trends Anal. Chem.* **2012**, *37*, 61-72.

Conclusions and Future Scope

This thesis demonstrates the importance of mechanochemistry in modern organic synthesis. At the core of this thesis, it is verified that mechanochemistry generates advantages in organic transformations beyond simple solvent reduction but rather reconfigures the organic transformative potential. Furthermore, through a broad literature overview, this study emphasizes the potential of mechanochemistry through reactions, mechanistic investigations, and the introduction of innovative technologies. The shift from classical to mechanochemical reactions offers far-reaching implications for sustainability, efficiency, and creativity in molecular design. The key conclusions derived from this thesis are as follows:

- I. Mechanochemistry has emerged as a transformative technology for the reactivity of insoluble compounds, such as Bertagnini's salts, into value-added compounds with pharmaceutical relevance, such as benzimidazoles, dihydro perimidines, perimidines, secondary amines, and hydrazones, by the reduction and elimination of solvents during the reaction and purification steps. Additionally, our research mentioned recrystallization techniques for the purification of the synthesized compounds to align with the goal of green chemistry principles by reducing the amount of solvents used. Overall, our work demonstrates the potential of Bertagnini's salts for application in organic reactions as solid aldehyde surrogates, which bypass disadvantages such as volatility, aerial oxidation potential, and self-condensation tendencies inherent to aldehydes.
- II. The mechanochemical treatment of wool into powder promotes the reactivity of wool fibers for amino acid-catalyzed reactions, such as aldol reactions, nitro-aldol reactions, and Knoevenagel condensation. Moreover, wool waste was transformed into a sustainable catalytic material for organic transformations, minimizing waste generation and operational costs.
- III. Mechanochemistry redefined borrowing hydrogenation strategies for the direct, solvent-free, and efficient synthesis of secondary amines and N-heterocycles. Ball milling enabled Ru-catalyzed borrowing hydrogen with enhanced reactivity, room temperature operations, solvent-free conditions, and avoided the utilization of toxic reagents. Additionally, detailed studies have revealed the benefits of mechanochemistry by enabling reactions of aliphatic amines that are not possible under solvent-based reaction conditions. Through detailed studies on the mechanism, the mechanochemical protocol was verified as a practical and efficient technology for industrial-scale synthesis.
- IV. The mechanochemical kinetic isotope effect (KIE) and Hammett analyses have enabled the broader application of such fundamental organic tools to describe the reaction pathway and rate-determining state of the reactions. This highlights the potential of mechanochemistry to go beyond simple synthetic utility and provides a platform for mechanistic explorations.

Overall, mechanochemistry effectively enables solvent-less synthesis strategies, redefines the parameters of organic chemistry by elevating the potential of insoluble compounds for reactions, valorizes waste biopolymers into valuable catalytic media, and enables catalytic reactivities

beyond the horizons of solvent-based protocols. Moreover, emerging technologies within mechanochemical strategies enable efficient mechanistic studies to elucidate the core of solid-state reactions. In addition, emerging devices and reaction technologies strengthen the stand of mechanochemistry as a practical synthetic approach for organic synthesis in industries.

The works presented in this thesis demonstrate that mechanochemistry should no longer be framed merely as a “greener substitute” for solution synthesis. It is increasingly recognized as a complementary, and frequently superior, synthetic paradigm that expands chemical accessibility, delivering transformations, selectivities, and solid forms that can be difficult or impractical to achieve in solution. Building on these findings, several avenues of future research emerge that have the potential to further redefine how organic chemistry is conceived, practiced, and scaled:

- I. A primary frontier lies in the synthesis of substrates traditionally deemed "unreactive" due to poor solubility in organic solvents. Mechanochemistry bypasses the thermodynamic and kinetic limitations imposed by the liquid phase, allowing for the direct transformation of insoluble precursors. Future research should focus on mapping the reactivity of these "recalcitrant" substrates to access novel chemical space and products that are fundamentally inaccessible via solution chemistry.
- II. A critical and yet under-reported aspect of mechanochemical reactions is the challenges affiliated with milling-media attrition. While majority of mechanochemical transformations are reported using SS jars, the underlying effect of metal leaching is a very undermined concept. A possibility towards more effective organic synthesis in mechanochemistry can be related to the influential effect of metals. For high-purity sectors, such as the pharmaceutical industry, the presence of these trace metals necessitates intensive downstream purification, which often requires the organic solvents that mechanochemistry seeks to eliminate. Thus, deep understanding in this regard is beneficial. In this regard, innovative technologies like RAM can provide a milling-media free mechanochemical environment.
- III. Despite the synthetic efficacy, the black box nature of mechanochemical set-up hinders the *in-situ* monitoring of the reactions. This problem is more severe in case of mechanocatalysis where small changes can deactivate the catalytic species. Thus, future research on *in-situ* mechanochemical reaction monitoring seems promising.
- IV. Additionally, scalability experiments in mechanochemistry are often challenging requiring potentially critical set-ups and technically sound reaction monitoring procedures. Research on scalable techniques can be instrumental for the practical viability of mechanochemistry.

In summary, mechanochemistry offers more than incremental improvements in efficiency or sustainability—it compels a re-examination of long-held assumptions in organic chemistry. Continued exploration of its unique reactivity, mechanisms, and applications has the potential to redefine not only how reactions are performed, but how chemical reactivity itself is understood.

CHAPTER 7

Experimental Section

7.1. General Information and Methodology

Commercially available reagents and solvents were purchased from Acros, Alfa-Aesar, Carlo Erba, Merck and TCI-Europe, and used as received without further purifications. For chapter 4, all the wool samples were collected from the Sardinian province of Italy. White wool fibers were collected from the city of Ittiri in the northern region of Sardinia, while black wool fibers were obtained from Guspini, a town in the Sardinian inland. The wool was procured from the Sechi farm, ensuring full compliance with animal welfare standards. Chicken feathers were obtained from the Concimi-Bio company. All the wool fibers and chicken feathers were obtained as raw materials and then treated in our laboratory. All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck) with suitable eluent, and compounds were visualized under UV light (254 nm) or using iodine vapor chamber. The eluents were technical grade. Mechanochemical reactions were conducted using a Retsch MM500 Vario, Fritsch-P7 Premium (room temperature reaction), Retsch MM500 Control and Fritsch Pulverisette-23 (heating reactions) apparatus. The reagents were milled using a zirconia grinding jar (10 mL) or stainless-steel jar (10 mL) with balls with $\phi = 10$ mm, 5 mm, 7 mm of the same material or the combination of thereof, if otherwise not stated in the parameters. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 600 MHz NMR spectrometer at 298K unless otherwise specified. Chemical shifts were reported in parts per million (ppm, δ value), and the residual solvent peak was used as internal reference: in proton (chloroform δ 7.26; dimethyl sulfoxide δ 2.50) or in carbon (chloroform δ 77.16; dimethyl sulfoxide δ 39.52). Data are reported as follows: chemical shift δ , multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and combination of thereof), coupling constants (J) in hertz (Hz) and integration. Samples were analyzed using an Agilent 5977B MS interfaced to the GC 7890B equipped with a DB-5ms column (J & W), injector temperature at 230 °C, detector temperature at 280 °C, helium carrier gas flow rate of 1 mL/min. The GC oven temperature program was 100 °C initial temperature with a 4 min hold-time and ramping at 15 °C/min to a final temperature of 270 °C with 7 min hold time. One μL of each sample was injected in split (1:20) mode. After a solvent delay of 3 minutes, mass spectra were acquired in full scan mode using 2.28 scans/s with a 50–500 amu mass range. Retention times of different compounds were determined by injecting pure compounds under identical conditions. High resolution mass spectra (HRMS) were recorded on LTQ Orbitrap Elite (ThermoFischer) instrument (ESI). The temperature for reactions was monitored using POWERFIX Profi (IAN 279816) infrared (IR) thermometer, with $P_{\text{max}} < 1$ mW; λ : 650nm; measuring range: -50 to +380°C. All the experiments were carried out in duplicate to ensure the reproducibility of the experimental data. Yields refer to pure, isolated materials unless otherwise stated.



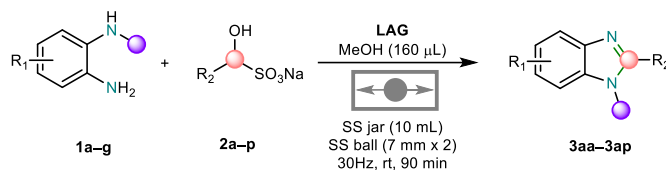
Mechanochemical instrumentations for room temperature reactions: a) MM-500 Vario mixer mill, b) stainless-steel (SS) jar (10 mL), c) zirconia jar (10 mL), d) Fritsch-P7 Premium planetary mill, e) planetary mill jar (zirconia, 20 mL).



Mechanochemical instrumentations for high temperature reactions: f) MM-500 Control mixer mill, g) stainless-steel (SS) jar (4 x 10 mL), h) Fritsch Pulverisette-23, i) stainless-steel (SS) jar (10 mL) for Fritsch Pulverisette-23.

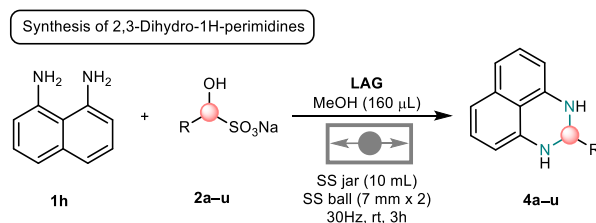
7.2. General Reaction Conditions and Characterization for Compounds in Chapter 3

7.2.1. Procedure for Synthesis of Benzimidazoles from Bertagnini's Salts



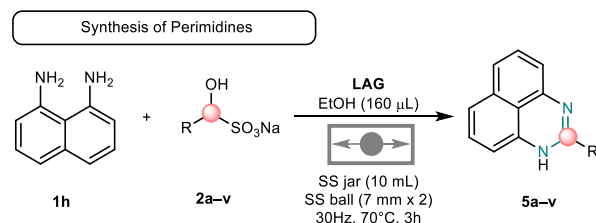
A 10 mL stainless steel jar equipped with two stainless steel milling balls (7 mm diameter, 2.67 g) was filled with o-phenylenediamines **1** (1.00 mmol), bisulfite adducts **2** (1.10 mmol), and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the products (**3aa-3ea**). However, the products **3ao**, **3fi** and **3ap** were isolated after column chromatography. For the bisulfite adducts of aliphatic aldehyde, the reactions were performed at 15 Hz for 8 hours (using methanol, η = 1) under room temperature conditions, and the product yield was calculated after column chromatography. In this context, the product (**3ga**) was prepared using ethanol (η factor= 1.0) at 80 °C under an O₂ atmosphere in the MM-500 control ball mill (30 Hz) for 3 hours.

7.2.2. Procedure for Synthesis of 2,3-Dihydro-1H-perimidines from Bertagnini's Salts



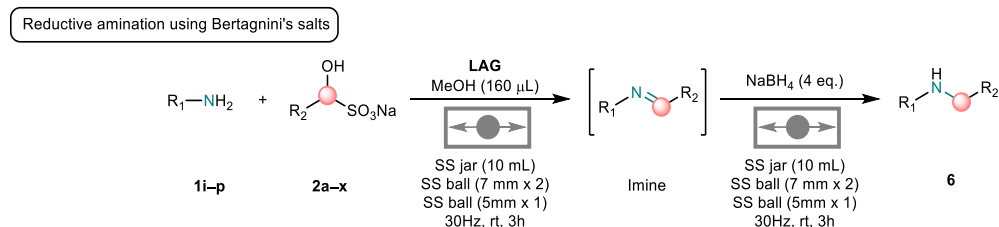
A 10 mL stainless steel jar equipped with two stainless steel milling balls (7 mm diameter, 2.67 g) was filled with 1,8-diaminonaphthalene **1h** (1.00 mmol), bisulfite adducts **2** (1.10 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the products (**4a-4i**). However, the product **4q** was isolated after extraction with methanol and concentration under high vacuum. Additionally, products column chromatography was needed for purification of products **4r-4u**.

7.2.3. Procedure for Synthesis of Perimidines from Bertagnini's Salts



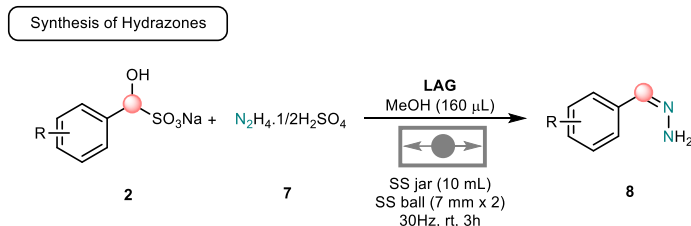
A 10 mL stainless steel jar equipped with two stainless steel milling balls (7 mm diameter, 2.67 g) was filled with 1,8-diaminonaphthalene **1h** (1.00 mmol), bisulfite adducts **2** (1.10 mmol), and ethanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 180 min at 30 Hz and 70 °C inside a MM-500 control mixer mill. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the products (**5a–5v**).

7.2.4. Procedure for Synthesis of Secondary Amines from Bertagnini's Salts



A 10 mL stainless steel jar equipped with two stainless steel milling balls (7 mm diameter, 2.67 g) and one stainless steel ball (5 mm diameter, 0.803 g) was filled with aniline **1i-p** (1.00 mmol), bisulfite adducts **2** (1.10 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 180 minutes at 30 Hz. At the end of the reaction, an additional refill of NaBH₄ (4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. A further aqueous workup was made to remove the inorganic sub-products whenever necessary. Lastly, the solvent was removed under reduced pressure to afford the pure secondary amine **6**. However, the yields of products **6oa**, **6po**, **6pd**, and **6lx** were calculated after column chromatography, and the reaction was performed using MeOH (η = 1) at 15 Hz for 6 hrs and 2 hrs for the reducing step. For the bisulfite adduct of aliphatic aldehydes (**2o**, **2x**) and the electron-deficient group containing aldehyde (**2d**), the reactions were performed using MeOH (η = 1) at 15 Hz for 6 hrs and 2 hrs for the reducing step. They delivered the products **6po**, **6lx** and **6pd**, respectively.

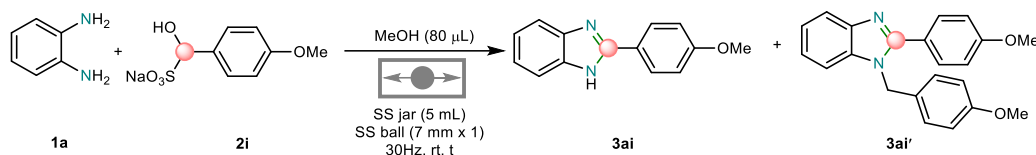
7.2.5. Procedure for Synthesis of Hydrazones from Bertagnini's Salts



A 10 mL stainless steel jar equipped with two stainless steel milling balls (7 mm diameter, 2.67 g) was filled with bisulfite adducts **2** (1.10 mmol), hydrazine hemisulfate **7** (1.00 mmol, 81.1 mg), and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 180 minutes at 30 Hz. At the end of the reaction, the crude product was recovered

with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure hydrazone **8**.

7.2.6. Procedure to Monitor Reaction Progress Over Time for Benzimidazole Synthesis



A 5 mL stainless-steel jar equipped with a stainless-steel milling ball (7 mm diameter) was filled with o-phenylenediamines **1a** (1.00 mmol), bisulfite adduct **2i** (1.10 mmol), and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reactions were conducted at 30 Hz for time ranging from 15 minutes to 90 minutes. The reaction mixtures were extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and ^1H NMR was recorded in DMSO- d_6 .

Entry	Time (min)	Reactant (1a)	Product (3ai)	Product (3ai')
1	15 min	64%	34%	2%
2	30 min	39%	57%	4%
3	45 min	22%	72%	6%
4	60 min	15%	80%	5%
5	90 min	0%	85%	15%

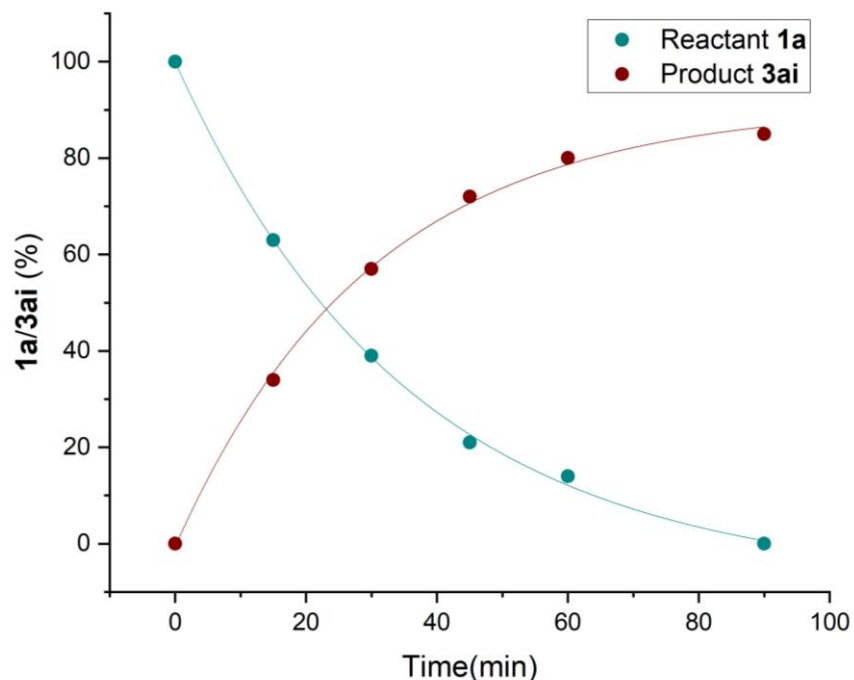
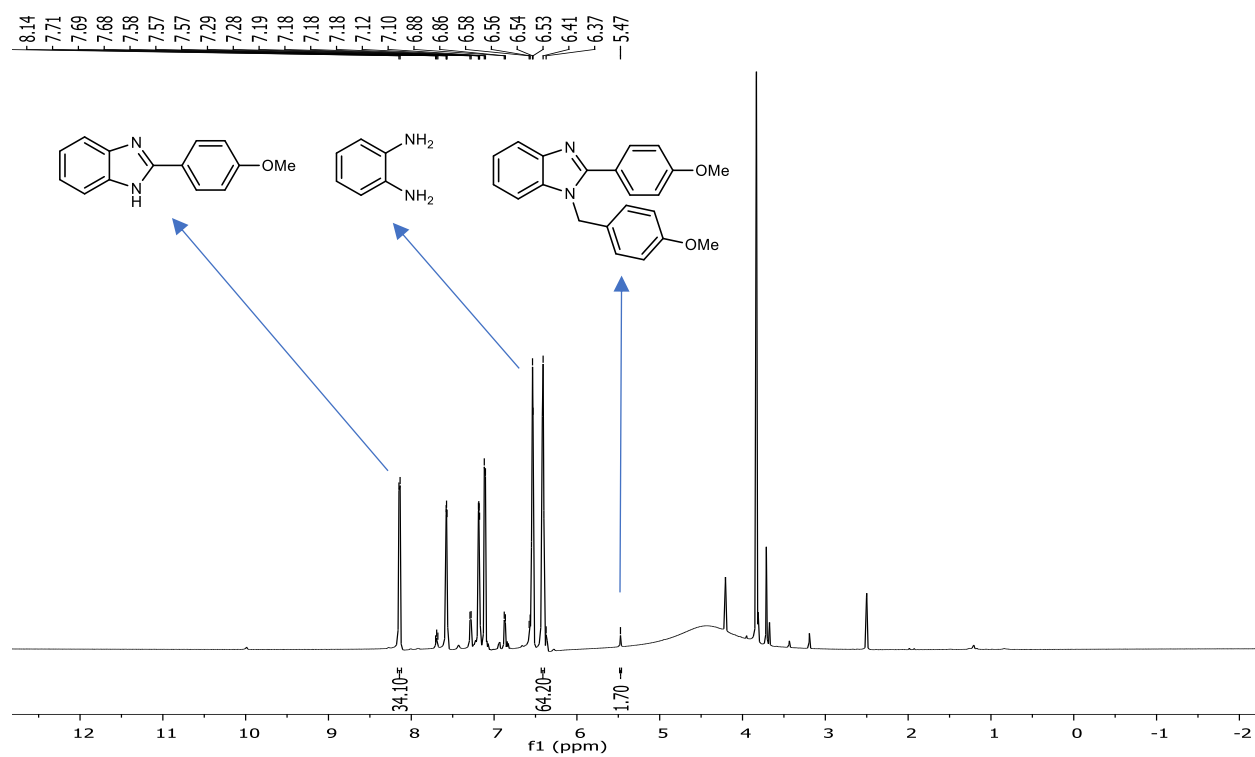
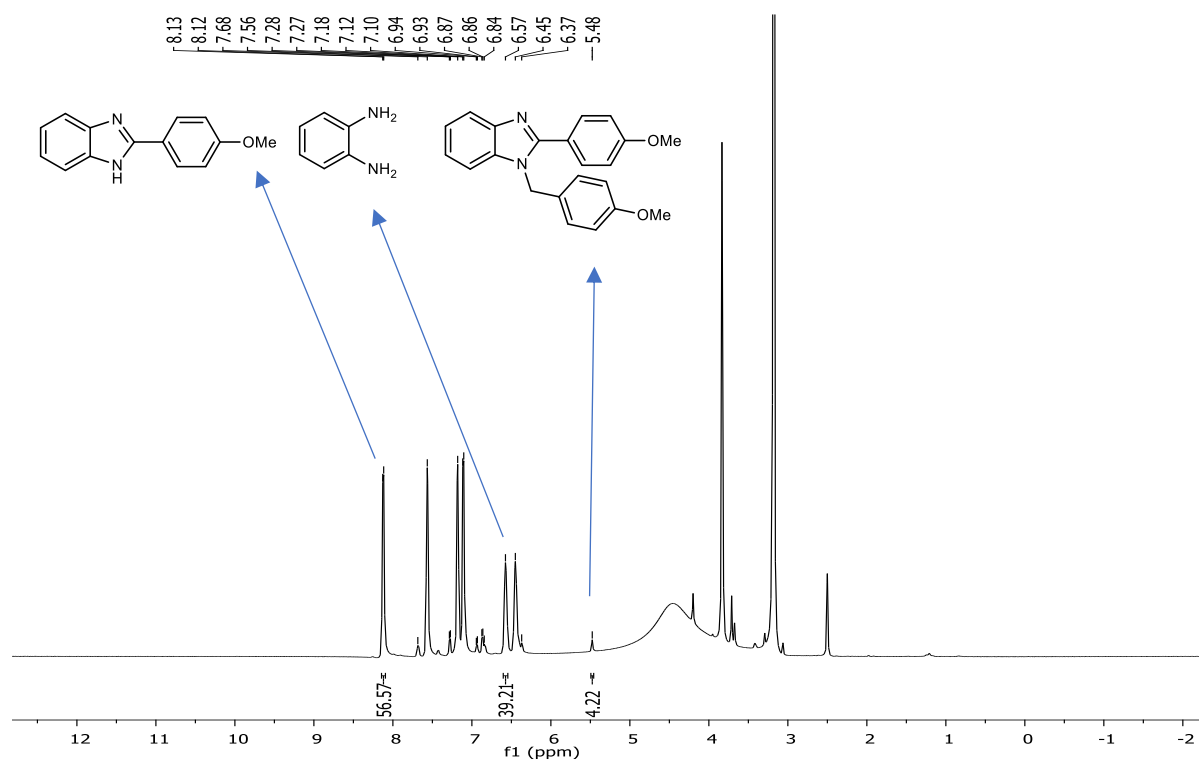


Figure 7.1. Product evolution over time for synthesis of benzimidazole **3ai** and **3ai'** from Bertagnini's salt **2i** monitored using ^1H NMR in DMSO- d_6 .

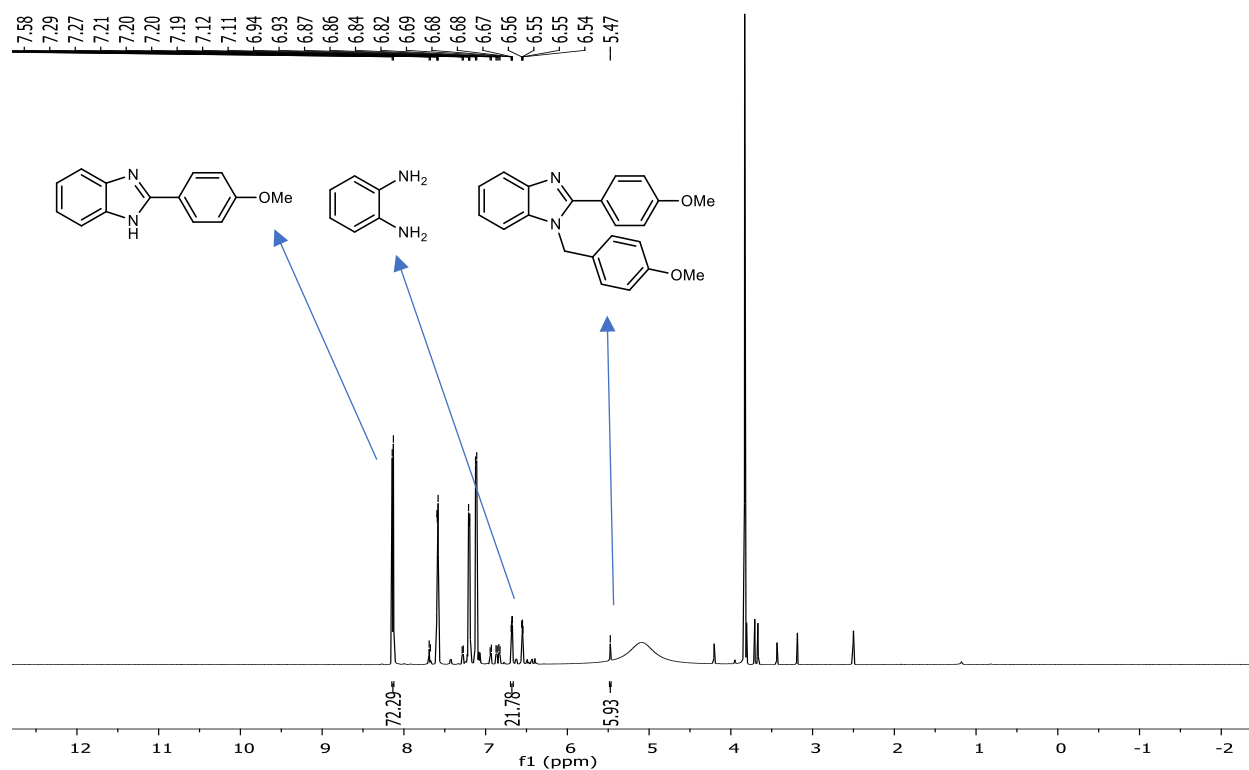
¹H NMR (600 MHz, DMSO-d₆): Entry 1 (15 mins)



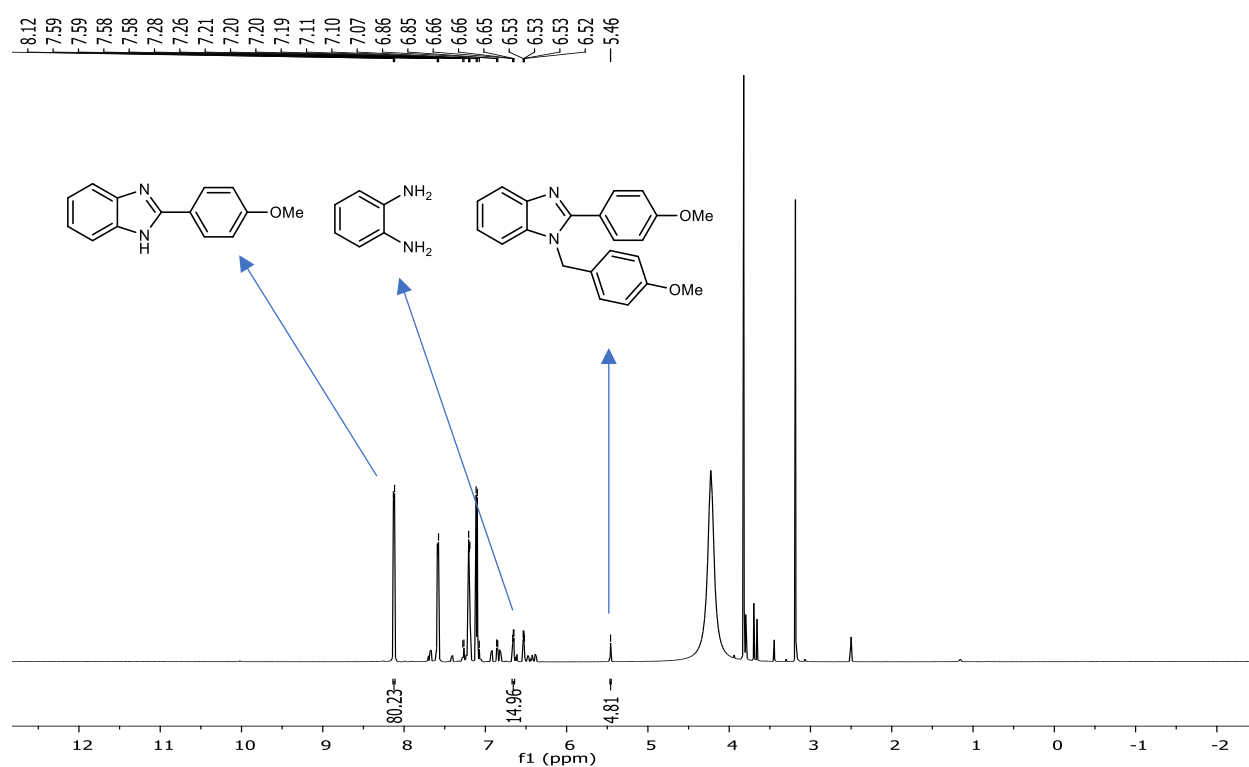
¹H NMR (600 MHz, DMSO-d₆): Entry 2 (30 mins)



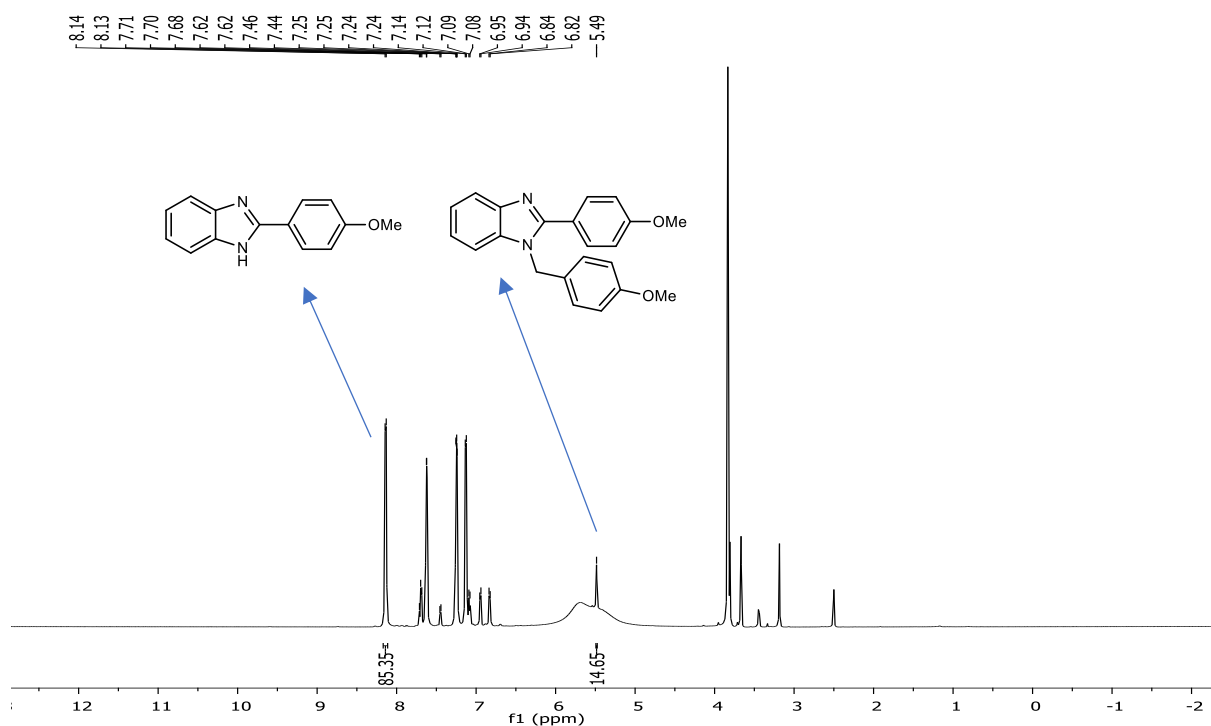
¹H NMR (600 MHz, DMSO-d₆): Entry 3 (45 mins)



¹H NMR (600 MHz, DMSO-d₆): Entry 4 (60 mins)

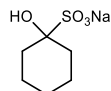


¹H NMR (600 MHz, DMSO-d₆): Entry 5 (90 mins)



7.2.7. Characterization of Compounds in Chapter 3

7.2.7.1. Spectral Data for Bertagnini's Salts

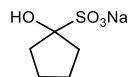


Sodium 1-hydroxycyclohexane-1-sulfonate (q): The compound was synthesized according to the previously reported in the literature¹, white solid, yield 86% (174 mg).

¹H NMR (600 MHz, DMSO-d₆) δ 4.25 (s, 1H), 1.70 (d, J = 13.2 Hz, 2H), 1.65 – 1.58 (m, 2H), 1.52 (d, J = 12.6 Hz, 1H), 1.45 (d, J = 8.4 Hz, 4H), 1.10 – 1.00 (m, 1H).

¹³C NMR (151 MHz, DMSO-d₆) δ 83.5, 31.7, 25.4, 21.5.

FTIR $\tilde{\nu}$ max = 3420, 3310, 2932, 1190, 1088, 982, 647 cm⁻¹.

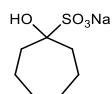


Sodium 1-hydroxycyclopentane-1-sulfonate (r): The title compound was synthesized according to the previously reported in the literature¹, white solid, yield 81% (150 mg).

¹H NMR (600 MHz, DMSO-d₆) δ 4.69 (s, 1H), 2.11 – 2.04 (m, 2H), 1.61 (t, J = 11.4 Hz, 2H), 1.57 – 1.49 (m, 4H).

¹³C NMR (151 MHz, DMSO-d₆) δ 130.7, 74.2, 62.4.

FTIR $\tilde{\nu}_{\text{max}}$ = 3253, 3019, 2949, 1211, 1165, 1073, 1012, 648 cm^{-1} .

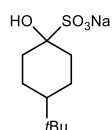


Sodium 1-hydroxycycloheptane-1-sulfonate (s): The title compound was synthesized according to the previously reported in the literature¹, white solid, yield 76% (164 mg).

¹H NMR (600 MHz, DMSO- d_6) δ 4.24 (d, J = 10.8 Hz, 1H), 2.02 - 1.96 (m, 2H), 1.73 – 1.67 (m, 2H), 1.49 (s, 6H), 1.45 – 1.39 (m, 2H).

¹³C NMR (151 MHz, DMSO- d_6) δ 87.2, 35.9, 29.7, 22.5.

FTIR $\tilde{\nu}_{\text{max}}$ = 3301, 2914, 1211, 1170, 1054, 999, 696, 617 cm^{-1} .

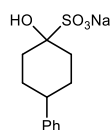


Sodium 4-(tert-butyl)-1-hydroxycyclohexane-1-sulfonate (t): The title compound was synthesized according to the previously reported in the literature¹, white solid, yield 78% (201 mg).

¹H NMR (600 MHz, DMSO- d_6) δ 4.33 (s, 1H), 1.79 (s, 1H), 1.77 (s, 1H), 1.63 (dd, J = 18.6, 8.4 Hz, 2H), 1.47 (d, J = 12.0 Hz, 2H), 1.21 (q, J = 12.0 Hz, 2H), 0.92 - 0.85 (m, 1H), 0.82 (s, 9H).

¹³C NMR (151 MHz, DMSO- d_6) δ 83.4, 47.1, 32.1, 27.5, 22.2.

FTIR $\tilde{\nu}_{\text{max}}$ = 2951, 2865, 1362, 1211, 1186, 1073, 721, 644 cm^{-1} .



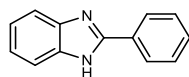
Sodium 1-hydroxy-4-phenylcyclohexane-1-sulfonate (u): The title compound was synthesized according to the previously reported in the literature¹, white solid, yield 87% (242 mg).

¹H NMR (600 MHz, DMSO- d_6) δ 7.26 (t, J = 7.2 Hz, 2H), 7.20 (d, J = 7.2 Hz, 2H), 7.15 (d, J = 6.6 Hz, 1H), 4.47 (s, 1H), 2.41 (t, J = 12.0 Hz, 1H), 1.89 – 1.79 (m, 4H), 1.74 – 1.63 (m, 2H), 1.57 (d, J = 11.4 Hz, 2H).

¹³C NMR (151 MHz, DMSO- d_6) δ 147.5, 128.2, 126.6, 125.7, 82.9, 43.0, 32.0, 29.2.

FTIR $\tilde{\nu}_{\text{max}}$ = 3537, 3463, 3359, 1179, 1157, 968, 698, 658 cm^{-1} .

7.2.7.2. Spectral Data for Benzimidazoles

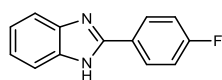


2-Phenyl-1*H*-benzo[d]imidazole (3aa): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2a** (231 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3aa** as white solid, yield 49% (95 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.19 (s, 1H), 8.17 (s, 1H), 7.64 (s, 2H), 7.58 (t, J = 6.6 Hz, 2H), 7.54 (d, J = 6.6 Hz, 1H), 7.27 (s, 2H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 150.8, 138.0, 130.5, 129.1, 128.9, 126.7, 122.8, 114.9.

Spectroscopic data are in agreement with those reported earlier.²

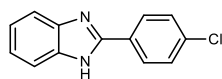


2-(4-Fluorophenyl)-1*H*-benzo[d]imidazole (3ab): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2b** (251 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3ab** as white solid, yield 45% (96 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.24 (s, 2H), 7.65 (s, 2H), 7.45 (s, 2H), 7.28 (s, 2H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 163.3 (d, J = 247.8 Hz), 149.9, 138.0, 129.1 (d, J = 7.6 Hz), 125.5, 122.8, 116.2 (d, J = 22.0 Hz), 114.9.

Spectroscopic data are in agreement with those reported earlier.²

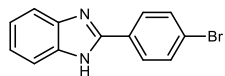


2-(4-Chlorophenyl)-1*H*-benzo[d]imidazole (3ac): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2c** (269 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3ac** as white solid, yield 72% (165 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 12.99 (s, 1H), 8.20 (s, 1H), 8.18 (s, 1H), 7.63 (s, 1H), 7.61 (d, J = 7.3 Hz, 2H), 7.62 – 7.55 (m, 3H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 160.83, 150.15, 134.49, 129.06, 129.04, 128.14, 122.30, 118.23.

Spectroscopic data are in agreement with those reported earlier.²

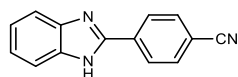


2-(4-Bromophenyl)-1H-benzo[d]imidazole (3ad): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2d** (318 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3ad** as white solid, yield 66% (180 mg).

^1H NMR (600 MHz, DMSO- d_6) δ 8.15 (s, 1H), 8.14 (s, 1H), 7.74 (s, 1H), 7.73 (s, 1H), 7.62 (dd, J = 6.0, 3.0 Hz, 2H), 7.20 (dd, J = 6.0, 3.0 Hz, 2H).

^{13}C NMR (151 MHz, DMSO- d_6) δ 150.3, 139.4, 131.9, 129.4, 128.4, 123.2, 122.3, 115.3.

Spectroscopic data are in agreement with those reported earlier.²

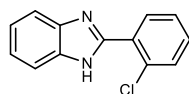


4-(1H-Benzo[d]imidazol-2-yl)benzonitrile (3ae): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2e** (258.5 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3ae** as white solid, yield 63% (138 mg).

^1H NMR (600 MHz, DMSO- d_6) δ 13.27 (s, 1H), 8.35 (s, 2H), 7.97 (s, 2H), 7.66 (s, 2H), 7.24 (s, 2H).

^{13}C NMR (151 MHz, DMSO- d_6) δ 149.4, 145.2, 134.2, 132.9, 130.9, 129.8, 128.6, 127.0, 122.7, 118.6, 111.8, 109.5.

Spectroscopic data are in agreement with those reported earlier.²

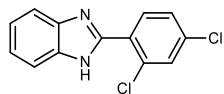


2-(2-Chlorophenyl)-1H-benzo[d]imidazole (3af): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2f** (269 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3af** as white solid, yield 64% (147 mg).

^1H NMR (600 MHz, DMSO- d_6) δ 12.70 (s, 1H), 7.90 (dd, J = 7.2, 1.8 Hz, 1H), 7.65 (t, J = 7.8 Hz, 3H), 7.55 (dd, J = 7.2, 6.0 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.24 (dd, J = 6.0, 3.0 Hz, 2H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 148.9, 142.1, 132.7, 132.1, 131.7, 131.3, 130.8, 130.4, 130.2, 129.7, 127.5, 122.4.

Spectroscopic data are in agreement with those reported earlier.²

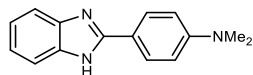


2-(2,4-Dichlorophenyl)-1H-benzo[d]imidazole (3ag): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2g** (307 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3ag** as white solid, yield 58% (153 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 12.76 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.84 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 3H), 7.25 (s, 2H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 147.44, 137.03, 135.91, 133.50, 132.86, 130.02, 127.90, 127.13, 123.45, 115.25.

Spectroscopic data are in agreement with those reported earlier.³

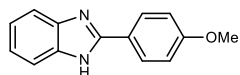


4-(1H-Benzo[d]imidazol-2-yl)-N,N-dimethylaniline (3ah): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2h** (278.5 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3ah** as white solid, yield 60% (142 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.01 (s, 1H), 8.00 (s, 1H), 7.57 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.23 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.87 (s, 1H), 6.85 (s, 1H), 3.01 (s, 6H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 151.9, 151.4, 136.8, 128.1, 122.6, 114.1, 113.9, 111.8, 39.7 (×2).

Spectroscopic data are in agreement with those reported earlier.⁴



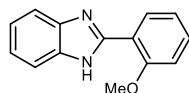
2-(4-Methoxyphenyl)-1H-benzo[d]imidazole (3ai): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2i** (264 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then,

the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3ai** as white solid, yield 70% (157 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.12 (s, 1H), 8.11 (s, 1H), 7.58 (s, 2H), 7.20 (s, 2H), 7.13 (s, 1H), 7.12 (s, 1H), 3.84 (s, 3H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 160.9, 151.2, 138.7, 128.2, 122.3, 122.2, 122.2, 121.9, 121.9, 114.7, 114.5, 55.4.

Spectroscopic data are in agreement with those reported earlier.²

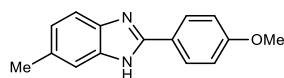


2-(2-Methoxyphenyl)-1H-benzo[d]imidazole (3aj): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2j** (264 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3aj** as white solid, yield 58% (130 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 12.13 (s, 1H), 8.33 (s, 1H), 7.62 (s, 2H), 7.48 (s, 1H), 7.26 - 7.08 (m, 4H), 4.02 (s, 3H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 156.7, 149.0, 142.6, 134.7, 131.2, 129.7, 121.9, 121.4, 120.8, 118.3, 118.1, 112.0, 111.9, 55.7.

Spectroscopic data are in agreement with those reported earlier.⁵

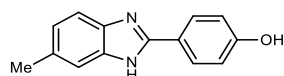


2-(4-Methoxyphenyl)-6-methyl-1H-benzo[d]imidazole (3bi): The compound was synthesized with general procedure 7.2.1. **1b** (122 mg, 1.0 mmol), **2i** (264 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3bi** as white solid, yield 66% (158 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.09 (d, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.34 (s, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 1H), 3.84 (s, 3H), 2.42 (s, 3H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 160.9, 150.6, 145.5, 137.8, 136.4, 131.8, 128.2, 123.9, 121.3, 114.5, 113.9, 55.4, 21.3.

Spectroscopic data are in agreement with those reported earlier.⁶

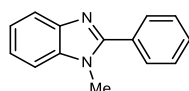


4-(6-Methyl-1*H*-benzo[d]imidazol-2-yl)phenol (3bk): The compound was synthesized with general procedure 7.2.1. **1b** (122 mg, 1.0 mmol), **2k** (248.6 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3bk** as white solid, yield 51% (114 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 10.08 (s, 1H), 7.99 (s, 1H), 7.98 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.36 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 6.93 (s, 1H), 2.43 (s, 3H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 159.7, 150.9, 136.2, 131.7, 128.4, 123.9, 119.6, 115.8, 115.6, 114.3, 113.8, 21.3.

Spectroscopic data are in agreement with those reported earlier.⁷

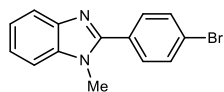


1-Methyl-2-phenyl-1*H*-benzo[d]imidazole (3ca): The compound was synthesized with general procedure 7.2.1. **1c** (122 mg, 1.0 mmol), **2a** (231 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3ca** as white solid, yield 91% (190 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.76 – 7.69 (m, 1H), 7.54 (q, J = 8.4 Hz, 5H), 7.28 – 7.25 (m, 1H), 7.25 – 7.21 (m, 2H), 3.72 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 152.6, 142.9, 136.7, 131.9, 130.9, 129.2, 124.4, 123.1, 122.7, 119.9, 109.8, 31.7.

Spectroscopic data are in agreement with those reported earlier.⁸

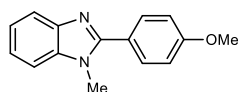


2-(4-Bromophenyl)-1-methyl-1*H*-benzo[d]imidazole (3cd): The compound was synthesized with general procedure 7.2.1. **1c** (122 mg, 1.0 mmol), **2d** (318 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3cd** as white solid, yield 86% (248 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.82 (d, J = 7.2 Hz, 1H), 7.67 (q, J = 8.4 Hz, 4H), 7.40 (d, J = 7.2 Hz, 1H), 7.36 – 7.30 (m, 2H), 3.87 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 152.8, 143.1, 136.8, 132.1, 131.1, 129.3, 124.5, 123.2, 122.8, 120.1, 109.8, 31.9.

Spectroscopic data are in agreement with those reported earlier.⁹

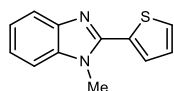


2-(4-Methoxyphenyl)-1-methyl-1H-benzo[d]imidazole (3ci): The compound was synthesized with general procedure 7.2.1. **1c** (122 mg, 1.0 mmol), **2i** (264 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3ci** as white solid, yield 90% (214 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.80 (s, 1H), 7.71 (d, J = 7.2 Hz, 2H), 7.40 – 7.27 (m, 3H), 7.04 (d, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 160.9, 153.9, 143.1, 136.7, 130.9, 122.7, 122.6, 122.4, 119.7, 114.3, 109.6, 55.5, 31.8.

Spectroscopic data are in agreement with those reported earlier.¹⁰

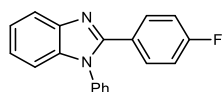


1-Methyl-2-(thiophen-2-yl)-1H-benzo[d]imidazole (3cl): The compound was synthesized with general procedure 7.2.1. **1c** (122 mg, 1.0 mmol), **2l** (237.8 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3bi** as white solid, yield 38% (82 mg).

¹H NMR (600 MHz, DMSO- d_6) δ 7.81 (d, J = 5.4 Hz, 1H), 7.79 (d, J = 3.6 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.4, 5.4 Hz, 2H), 7.23 (t, J = 7.8 Hz, 1H), 4.02 (s, 3H).

¹³C NMR (151 MHz, DMSO- d_6) δ 147.3, 142.3, 136.6, 132.5, 129.3, 128.3, 128.1, 122.5, 122.1, 118.7, 110.4, 31.6.

Spectroscopic data are in agreement with those reported earlier.¹¹



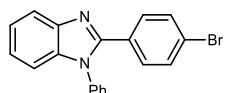
2-(4-Fluorophenyl)-1-phenyl-1H-benzo[d]imidazole (3db): The compound was synthesized with general procedure 7.2.1. **1d** (184 mg, 1.0 mmol), **2b** (251 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the

reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3bi** as white solid, yield 78% (225 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 7.79 (d, *J* = 7.8 Hz, 1H), 7.61 – 7.51 (m, 5H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.22 – 7.16 (m, 3H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 162.7 (d, *J* = 247.9 Hz), 150.9, 142.5, 137.0, 136.3, 131.4 (d, *J* = 8.7 Hz), 130.1, 128.9, 127.5, 126.4 (d, *J* = 3.1 Hz), 123.4, 122.8, 119.4, 115.5 (d, *J* = 21.9 Hz), 110.4.

Spectroscopic data are in agreement with those reported earlier.¹²

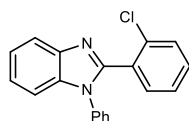


2-(4-Bromophenyl)-1-phenyl-1*H*-benzo[d]imidazole (3dd): The compound was synthesized with general procedure **7.2.1**. **1d** (184 mg, 1.0 mmol), **2d** (318 mg, 1.1 mmol) and methanol (η factor = 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3dd** as white solid, yield 82% (286 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.32 (m, 3H), 7.28 (q, *J* = 8.4 Hz, 4H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.14 (s, 1H), 7.13 (s, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 151.2, 142.9, 137.3, 136.8, 131.6, 130.9, 130.1, 128.9, 128.8, 127.4, 124.1, 123.7, 123.2, 119.9, 110.5.

Spectroscopic data are in agreement with those reported earlier.¹³

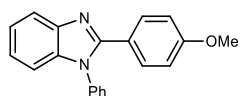


2-(2-Chlorophenyl)-1-phenyl-1*H*-benzo[d]imidazole (3df): The compound was synthesized with general procedure **7.2.1**. **1d** (184 mg, 1.0 mmol), **2f** (269 mg, 1.1 mmol) and methanol (η factor = 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3df** as white solid, yield 64% (195 mg).

¹H NMR (600 MHz, CDCl₃ + DMSO-*d*₆) δ 7.79 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 6.6 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 3H), 7.26 (d, *J* = 7.2 Hz, 4H), 7.24 – 7.19 (m, 2H), 7.17 (s, 1H), 7.15 (s, 1H).

¹³C NMR (151 MHz, CDCl₃ + DMSO-*d*₆) δ 150.4, 142.7, 135.8, 135.6, 133.9, 132.3, 130.9, 130.0, 129.5, 129.3, 128.0, 126.5, 126.4, 123.5, 122.8, 119.9, 110.5.

Spectroscopic data are in agreement with those reported earlier.¹²

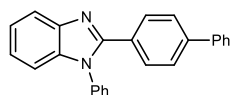


2-(4-Methoxyphenyl)-1-phenyl-1H-benzo[d]imidazole (3di): The compound was synthesized with general procedure 7.2.1. **1d** (184 mg, 1.0 mmol), **2i** (264 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3di** as white solid, yield 62% (187 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.90 (s, 1H), 7.54 (s, 5H), 7.35 (s, 3H), 7.26 (s, 2H), 6.85 (s, 2H), 3.83 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 160.6, 152.5, 143.2, 137.6, 137.4, 131.0, 130.0, 128.6, 127.6, 123.1, 122.9, 122.5, 119.7, 113.9, 110.4, 55.4.

Spectroscopic data are in agreement with those reported earlier.¹⁴

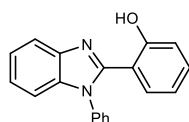


2-([1,1'-Biphenyl]-4-yl)-1-phenyl-1H-benzo[d]imidazole (3dm): The compound was synthesized with general procedure 7.2.1. **1d** (184 mg, 1.0 mmol), **2m** (315 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3dm** as white solid, yield 86% (298 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 7.81 (s, 1H), 7.69 (s, 4H), 7.64 – 7.56 (m, 5H), 7.50 – 7.41 (s, 4H), 7.38 (s, 1H), 7.35 – 7.26 (m, 2H), 7.19 (s, 1H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 151.5, 142.6, 140.9, 138.9, 137.2, 136.5, 130.2, 129.6, 129.0, 128.9, 128.8, 127.9, 127.6, 126.7, 126.5, 123.4, 122.8, 119.4, 110.5.

Spectroscopic data are in agreement with those reported earlier.¹⁵



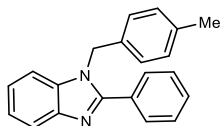
2-(1-Phenyl-1H-benzo[d]imidazol-2-yl)phenol (3dn): The compound was synthesized with general procedure 7.2.1. **1d** (184 mg, 1.0 mmol), **2n** (248.6 mg, 1.1 mmol) and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then,

the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3dn** as white solid, yield 68% (195 mg).

¹H NMR (600 MHz, CDCl₃) δ 13.53 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 5.4 Hz, 3H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.14 – 7.07 (m, 2H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.54 (t, *J* = 7.2 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 159.8, 150.9, 140.2, 137.3, 136.7, 131.5, 130.5, 129.7, 128.1, 127.4, 123.9, 123.6, 118.8, 118.2, 118.1, 112.5, 110.5.

Spectroscopic data are in agreement with those reported earlier.¹⁴

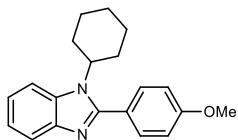


1-(4-Methylbenzyl)-2-phenyl-1H-benzo[d]imidazole (3ea): The compound was synthesized with general procedure **7.2.1**. **1e** (212.3 mg, 1.0 mmol), **2a** (231 mg, 1.1 mmol) and methanol (η factor = 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product **3ea** as white solid, yield 68% (102 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.69 (t, *J* = 1.8 Hz, 1H), 7.49 – 7.43 (m, 3H), 7.32 – 7.29 (m, 1H), 7.25 – 7.20 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 5.42 (d, *J* = 7.2 Hz, 2H), 2.34 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 154.3, 143.3, 137.6, 136.2, 133.5, 130.3, 130.0, 129.9, 129.4, 128.9, 126.1, 123.1, 122.8, 120.1, 110.7, 48.3, 21.2.

Spectroscopic data are in agreement with those reported earlier.¹⁶



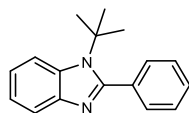
1-Cyclohexyl-2-(4-methoxyphenyl)-1H-benzo[d]imidazole (3fi): The compound was synthesized with general procedure **7.2.1**. **1f** (190.3 mg, 1.0 mmol), **2i** (264 mg, 1.1 mmol) and methanol (η factor = 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo. The product yield was calculated after column chromatography to afford the product **3fi** as yellow liquid, yield 43% (131 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 7.82 – 7.78 (m, 1H), 7.65 – 7.63 (m, 1H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.56 (d, *J* = 3.0 Hz, 1H), 7.23 – 7.14 (m, 2H), 7.13 (s, 1H), 7.12 (d, *J* = 3.0 Hz, 1H), 4.31 -

4.23 (m, 1H), 3.86 (s, 3H), 2.32 – 2.25 (m, 2H), 1.86 (t, $J = 15.6$ Hz, 4H), 1.65 (d, $J = 12.6$ Hz, 1H), 1.41 – 1.32 (m, 1H), 1.31 – 1.23 (m, 2H).

^{13}C NMR (151 MHz, DMSO- d_6) δ 160.1, 153.0, 143.2, 133.5, 130.6, 122.9, 121.6, 121.2, 119.2, 114.0, 112.7, 56.4, 55.2, 30.5, 25.4, 24.4.

Spectroscopic data are in agreement with those reported earlier.¹⁷

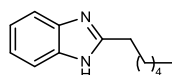


1-(Tert-butyl)-2-phenyl-1H-benzo[d]imidazole (3ga): The compound was synthesized with general procedure 7.2.1. **1g** (164.3 mg, 1.0 mmol), **2a** (231 mg, 1.1 mmol) and ethanol (η factor= 1.0) at 80 °C under an O₂ atmosphere in ball mill (30 Hz) for 3 hours. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo. The product yield was calculated after column chromatography to afford the product **3ga** as white solid, yield 91% (114 mg).

^1H NMR (600 MHz, CDCl₃) δ 7.81 – 7.77 (m, 1H), 7.72 (dd, $J = 6.6, 2.4$ Hz, 1H), 7.47 (d, $J = 7.8$ Hz, 2H), 7.45 – 7.37 (m, 3H), 7.30 – 7.24 (m, 2H), 1.61 (s, 9H).

^{13}C NMR (151 MHz, CDCl₃) δ 153.5, 143.1, 135.7, 134.9, 129.7, 129.1, 127.8, 122.1, 121.9, 120.1, 114.7, 59.0, 31.5.

Spectroscopic data are in agreement with those reported earlier.¹⁸

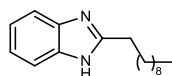


2-Hexyl-1H-benzo[d]imidazole (3ao): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2o** (240 mg, 1.1 mmol) and methanol (η factor= 1.0). The vessel was closed, and the mechanochemical reaction was conducted for 8h at 15 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo, and the yield was calculated after column chromatography as white solid, yield 71% (71 mg).

^1H NMR (600 MHz, DMSO- d_6) δ 7.49 – 7.37 (m, 2H), 7.10-7.07 (m, 2H), 2.79 (t, $J = 7.8$ Hz, 2H), 1.79 – 1.69 (m, 2H), 1.35 – 1.30 (m, 2H), 1.28- 1.25 (m, 4H), 0.84 (t, $J = 6.0$ Hz, 3H).

^{13}C NMR (151 MHz, DMSO- d_6) δ 155.1, 139.3, 120.9, 114.2, 30.9, 28.4, 28.2, 27.4, 21.9, 13.8.

Spectroscopic data are in agreement with those reported earlier.¹⁹



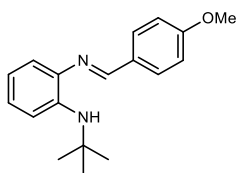
2-Decyl-1H-benzo[d]imidazole (3ap): The compound was synthesized with general procedure 7.2.1. **1a** (108 mg, 1.0 mmol), **2p** (302 mg, 1.1 mmol) and methanol (η factor= 1.0). The vessel

was closed, and the mechanochemical reaction was conducted for 8h at 15 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo, and the yield was calculated after column chromatography as white solid, yield 86% (105 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 7.47 – 7.42 (m, 2H), 7.13 – 7.06 (m, 2H), 2.78 (t, *J* = 7.2 Hz, 2H), 1.78 – 1.70 (m, 2H), 1.33 – 1.27 (s, 4H), 1.26 – 1.17 (m, 10H), 0.84 (t, *J* = 6.6 Hz, 3H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 155.2, 121.1, 31.3, 29.0, 28.9, 28.8, 28.7, 28.7, 28.5, 27.6, 22.1, 14.0.

Spectroscopic data are in agreement with those reported earlier.²⁰



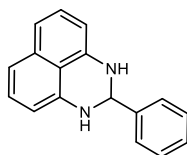
(E)-N-(Tert-butyl)-2-((4-methoxybenzylidene)amino)aniline (3gi'): The compound was synthesized with general procedure 7.2.1. **1g** (164.3 mg, 1.0 mmol), **2i** (264 mg, 1.1 mmol) and methanol (*η* factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 90 minutes at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo. The product yield was calculated after column chromatography to afford the product **3gi'** as yellow solid, yield 62% (87 mg).

¹H NMR (600 MHz, CDCl₃) δ 8.45 (s, 1H), 7.90 – 7.79 (m, 2H), 7.13 – 7.09 (m, 1H), 7.03 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.99 (s, 1H), 6.98 (dd, *J* = 9.0, 1.8 Hz, 1H), 6.70 (td, *J* = 7.8, 1.2 Hz, 1H), 3.88 (s, 3H), 1.44 (s, 9H).

¹³C NMR (151 MHz, CDCl₃) δ 162.2, 156.7, 142.5, 138.6, 130.4, 129.9, 127.1, 116.9, 116.8, 114.3, 55.5, 51.2, 30.2.

Spectroscopic data are in agreement with those reported earlier.²¹

7.2.7.3. Spectral Data for 2,3-Dihydro-1H-perimidines

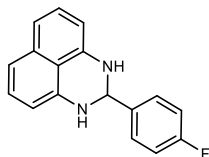


2-Phenyl-2,3-dihydro-1H-perimidine (4a): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2a** (231 mg, 1.1 mmol), and methanol (*η* factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as yellow solid, yield 89% (219 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.60 (d, *J* = 3.6 Hz, 2H), 7.43 (s, 3H), 7.30 – 7.15 (m, 4H), 6.48 (s, 1H), 6.47 (s, 1H), 5.40 (s, 1H), 4.40 (s, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 142.2, 140.2, 134.9, 129.7, 128.9, 128.0, 126.9, 117.9, 113.6, 105.9, 68.4.

Spectroscopic data are in agreement with those reported earlier.²²

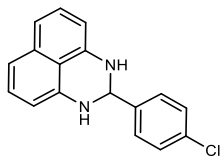


2-(4-Fluorophenyl)-2,3-dihydro-1H-perimidine (4b): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2b** (251 mg, 1.1 mmol), and methanol (η factor = 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as yellow solid, yield 83% (219 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.58 (dd, *J* = 7.8, 6.0 Hz, 2H), 7.30 – 7.16 (m, 4H), 7.10 (t, *J* = 8.4 Hz, 2H), 6.50 (s, 1H), 6.49 (s, 1H), 5.41 (s, 1H), 4.45 (s, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 163.5 (d, *J* = 248.2 Hz), 142.1, 136.1 (d, *J* = 3.1 Hz), 134.9, 129.9 (d, *J* = 8.4 Hz), 127.0, 118.1, 115.9 (d, *J* = 21.5 Hz), 113.5, 106.0, 67.8.

Spectroscopic data are in agreement with those reported earlier.²³

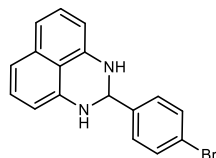


2-(4-Chlorophenyl)-2,3-dihydro-1H-perimidine (4c): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2c** (269 mg, 1.1 mmol), and methanol (η factor = 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as yellow solid, yield 79% (222 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.59 (s, 1H), 7.58 (s, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 7.34 – 7.23 (m, 4H), 6.56 (s, 1H), 6.55 (s, 1H), 5.45 (s, 1H), 4.50 (s, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 141.9, 138.8, 135.5, 134.9, 129.5, 129.2, 127.0, 118.2, 113.5, 106.1, 67.8.

Spectroscopic data are in agreement with those reported earlier.²²

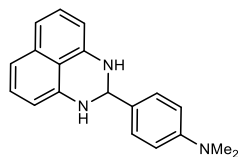


2-(4-Bromophenyl)-2,3-dihydro-1H-perimidine (4d): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2d** (318 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as yellow solid, yield 76% (247 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.61 (s, 1H), 7.60 (s, 1H), 7.55 (s, 1H), 7.53 (s, 1H), 7.33 – 7.19 (m, 4H), 6.57 (s, 1H), 6.56 (s, 1H), 5.46 (s, 1H), 4.50 (s, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 141.89, 139.29, 135.00, 132.16, 129.77, 127.03, 123.76, 118.27, 113.54, 106.13, 67.89.

Spectroscopic data are in agreement with those reported earlier.²⁴

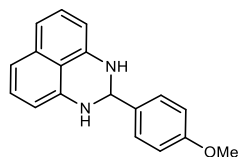


4-(2,3-Dihydro-1H-perimidin-2-yl)-N,N-dimethylaniline (4h): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2h** (278.5 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as yellow solid, yield 81% (235 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.52 (s, 1H), 7.51 (s, 1H), 7.30 – 7.26 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.80 (s, 1H), 6.79 (s, 1H), 6.52 (s, 1H), 6.51 (s, 1H), 5.40 (s, 1H), 4.51 (s, 2H), 3.02 (s, 6H).

¹³C NMR (151 MHz, CDCl₃) δ 151.6, 142.8, 135.1, 128.9, 127.7, 126.9, 117.7, 113.6, 112.4, 105.7, 68.3, 40.7 ($\times 2$).

Spectroscopic data are in agreement with those reported earlier.²⁵



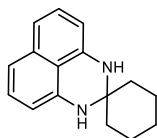
2-(4-Methoxyphenyl)-2,3-dihydro-1H-perimidine (4i): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2i** (264 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at

30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as yellow solid, yield 85% (235 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.58 (s, 1H), 7.57 (s, 1H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.98 (s, 1H), 6.97 (s, 1H), 6.53 (s, 1H), 6.52 (s, 1H), 5.43 (s, 1H), 4.50 (s, 2H), 3.86 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 160.7, 142.4, 135.1, 132.5, 129.3, 127.0, 117.9, 114.3, 113.6, 105.9, 68.1, 55.5.

Spectroscopic data are in agreement with those reported earlier.²⁵

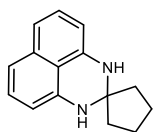


1'H,3'H-Spiro[cyclohexane-1,2'-perimidine] (4q): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2q** (222.4 mg, 1.1 mmol), and methanol (η factor = 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo to afford the product as white solid, yield 98% (234 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.29 (s, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.52 (d, *J* = 6.6 Hz, 2H), 4.43 (s, 2H), 1.78 (s, 4H), 1.64 (s, 4H), 1.54 (s, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 140.1, 134.8, 127.2, 117.2, 113.6, 106.1, 65.5, 37.1, 25.4, 22.5.

Spectroscopic data are in agreement with those reported earlier.²⁶

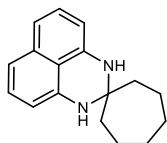


1'H,3'H-Spiro[cyclopentane-1,2'-perimidine] (4r): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2r** (207 mg, 1.1 mmol), and methanol (η factor = 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by column chromatography to afford the product as black solid, yield 86% (193 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.25 (t, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.52 (d, *J* = 7.2 Hz, 2H), 4.20 (s, 2H), 1.86 (d, *J* = 6.6 Hz, 4H), 1.80 (d, *J* = 6.6 Hz, 4H).

¹³C NMR (151 MHz, CDCl₃) δ 141.0, 134.9, 126.9, 117.5, 114.0, 106.6, 76.2, 39.4, 23.1.

Spectroscopic data are in agreement with those reported earlier.²⁵



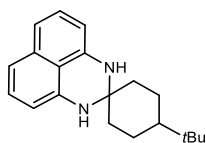
1'H,3'H-Spiro[cycloheptane-1,2'-perimidine] (4s): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2s** (238 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by column chromatography to afford the product as R_f = 0.50 (hexane/ethyl acetate 9:1), black solid, yield 67% (169 mg).

^1H NMR (600 MHz, CDCl_3) δ 7.24 (t, J = 7.8 Hz, 2H), 7.17 (s, 1H), 7.15 (s, 1H), 6.53 (s, 1H), 6.52 (s, 1H), 4.29 (s, 2H), 2.00 – 1.92 (m, 4H), 1.65 (s, 4H), 1.57 (d, J = 4.2 Hz, 4H).

^{13}C NMR (151 MHz, CDCl_3) δ 139.8, 134.7, 127.1, 117.4, 113.8, 106.5, 69.8, 40.4, 29.4, 22.1.

FTIR $\tilde{\nu}$ max = 2939, 2360, 2160, 1585, 1364, 813 cm^{-1} .

HRMS: calculated for $\text{C}_{17}\text{H}_{21}\text{N}_2$: 253.1705 $[\text{M}+\text{H}]^+$; found: 253.1708.



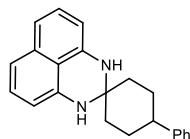
4-(Tert-butyl)-1'H,3'H-spiro[cyclohexane-1,2'-perimidine] (4t): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2t** (284 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by column chromatography to afford the product as R_f = 0.50 (hexane/ethyl acetate 9:1); black solid, yield 47% (138 mg).

^1H NMR (600 MHz, CDCl_3) δ 7.26 -7.22 (m, 2H), 7.17 – 7.12 (m, 2H), 6.54 (d, J = 7.2 Hz, 1H), 6.48 (d, J = 7.2 Hz, 1H), 4.29 (brs, 2H), 2.17 (d, J = 12.0 Hz, 2H), 1.75 (d, J = 13.2 Hz, 2H), 1.38 (td, J = 13.2, 3.0 Hz, 2H), 1.29 – 1.26 (m, 1H), 1.22 (d, J = 11.4 Hz, 1H), 1.10 (d, J = 12.0 Hz, 1H), 0.92 (s, 9H).

^{13}C NMR (151 MHz, CDCl_3) δ 140.5, 139.7, 134.8, 127.2, 127.1, 117.2, 117.1, 113.6, 106.4, 105.9, 65.3, 47.5, 37.2, 32.5, 27.7, 23.3.

FTIR $\tilde{\nu}$ max = 3031, 2941, 2371, 2348, 1586, 1362, 814 cm^{-1} .

HRMS: calculated for $\text{C}_{20}\text{H}_{27}\text{N}_2$: 295.2169 $[\text{M}+\text{H}]^+$; found: 295.2178.



4-Phenyl-1'*H*,3'*H*-Spiro[cyclohexane-1,2'-perimidine] (4u): The compound was synthesized with general procedure 7.2.2. **1h** (158 mg, 1.0 mmol), **2u** (306 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 30 min at 30 Hz. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by column chromatography to afford the product as R_f =0.50 (hexane/ethyl acetate 9:1), black solid, yield 59% (185 mg).

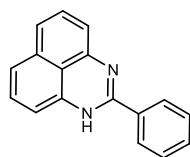
¹H NMR (600 MHz, CDCl₃) δ 7.32 (t, J = 7.2 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H), 7.21 (dd, J = 9.6, 4.8 Hz, 3H), 7.16 (dd, J = 7.8, 5.4 Hz, 2H), 6.58 (d, J = 7.2 Hz, 1H), 6.51 (d, J = 7.2 Hz, 1H), 4.74 (brs, 2H), 2.64 – 2.56 (m, 1H), 2.23 (d, J = 12.0 Hz, 2H), 1.91 (d, J = 12.6 Hz, 2H), 1.72 (td, J = 13.2, 2.4 Hz, 2H), 1.58 (td, J = 13.2, 3.6 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 145.9, 140.0, 139.3, 134.7, 128.5, 127.1, 126.7, 126.4, 117.5, 117.4, 117.3, 113.6, 106.8, 106.2, 65.1, 43.2, 36.9, 29.9.

FTIR $\tilde{\nu}$ max = 2979, 2341, 1540, 1507, 1043, 927, 814 cm⁻¹.

HRMS: calculated for C₂₂H₂₃N₂: 315.1861 [M+H]⁺; found: 315.1866.

7.2.7.4. Spectral Data for Perimidines

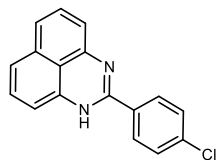


2-Phenyl-1*H*-perimidine (5a): The compound was synthesized with general procedure 7.2.3. **1h** (158 mg, 1.0 mmol), bisulfite adducts **2a** (231 mg, 1.1 mmol), and ethanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 180 min at 30 Hz and 70 °C. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as yellow solid, yield 84% (205 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.85 (s, 1H), 7.83 (s, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.26 (s, 1H), 7.18 (s, 2H), 7.13 (s, 1H), 7.11 (s, 1H), 6.59 (s, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 152.7, 145.3, 135.6, 134.2, 131.3, 129.0, 128.6, 128.4, 126.3, 122.7, 122.0, 120.1, 120.0, 114.9, 105.4.

Spectroscopic data are in agreement with those reported earlier.²⁷

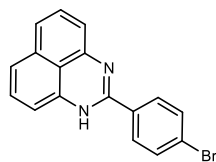


2-(4-Chlorophenyl)-1H-perimidine (5c): The compound was synthesized with general procedure **7.2.3**. **1h** (158 mg, 1.0 mmol), bisulfite adducts **2c** (269 mg, 1.1 mmol), and ethanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 180 min at 30 Hz and 70 °C. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as yellow solid, yield 92% (256 mg).

¹H NMR (600 MHz, DMSO- d_6) δ 10.68 (s, 1H), 8.04 (s, 1H), 8.03 (s, 1H), 7.60 (s, 1H), 7.59 (s, 1H), 7.17 (d, J = 6.6 Hz, 1H), 7.12 (s, 1H), 7.06 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 6.0 Hz, 1H), 6.54 (d, J = 6.0 Hz, 1H).

¹³C NMR (151 MHz, DMSO- d_6) δ 151.7, 144.8, 138.4, 135.8, 135.1, 132.2, 128.9, 128.7, 128.5, 128.0, 121.6, 119.5, 117.9, 114.1, 102.9.

Spectroscopic data are in agreement with those reported earlier.²⁷

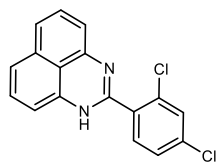


2-(4-Bromophenyl)-1H-perimidine (5d): The compound was synthesized with general procedure **7.2.3**. **1h** (158 mg, 1.0 mmol), bisulfite adducts **2d** (318 mg, 1.1 mmol), and ethanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 180 min at 30 Hz and 70 °C. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as yellow solid, yield 88% (284 mg).

¹H NMR (600 MHz, DMSO- d_6) δ 10.68 (s, 1H), 7.97 (s, 1H), 7.96 (s, 1H), 7.75 (s, 1H), 7.73 (s, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 7.2 Hz, 1H), 6.53 (d, J = 7.2 Hz, 1H).

¹³C NMR (151 MHz, DMSO- d_6) δ 151.8, 144.8, 138.3, 135.0, 132.5, 131.4, 128.9, 128.8, 128.0, 124.6, 121.6, 119.5, 117.9, 114.1, 102.9.

Spectroscopic data are in agreement with those reported earlier.²⁷



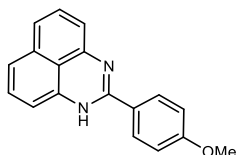
2-(2,4-Dichlorophenyl)-1*H*-perimidine (5g): The compound was synthesized with general procedure 7.2.3. **1h** (158 mg, 1.0 mmol), bisulfite adducts **2g** (307 mg, 1.1 mmol), and ethanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 180 min at 30 Hz and 70 °C. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as R_f = 0.70 (hexane/ethyl acetate 7:3), yellow solid, yield 82% (258 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.78 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.23 – 7.06 (m, 4H), 6.85 (s, 1H), 6.23 (s, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 151.3, 144.1, 137.1, 135.6, 132.4, 132.2, 131.9, 130.3, 129.3, 128.0, 127.7, 127.6, 122.0, 121.2, 119.7, 115.8, 102.5.

FTIR $\tilde{\nu}$ max = 2358, 1540, 1051, 820, 770 cm⁻¹.

HRMS: calculated for C₁₇H₁₁Cl₂N₂: 313.0299 [M+H]⁺; found: 313.0312.

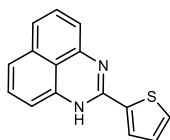


2-(4-Methoxyphenyl)-1*H*-perimidine (5i): The compound was synthesized with general procedure 7.2.3. **1h** (158 mg, 1.0 mmol), bisulfite adducts **2i** (264 mg, 1.1 mmol), and ethanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 180 min at 30 Hz and 70 °C. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as white solid, yield 85% (233 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.83 (s, 1H), 7.82 (s, 1H), 7.26 (s, 2H), 7.17 (s, 2H), 7.11 (s, 1H), 7.10 (s, 1H), 6.99 (s, 1H), 6.97 (s, 1H), 6.58 (s, 1H), 3.86 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 162.2, 153.4, 152.1, 135.6, 131.1, 128.7, 127.9, 126.4, 124.7, 121.8, 119.8, 119.8, 118.8, 114.3, 55.6.

Spectroscopic data are in agreement with those reported earlier.²⁸



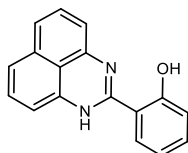
2-(Thiophen-2-yl)-1*H*-perimidine (5l): The compound was synthesized with general procedure 7.2.3. **1h** (158 mg, 1.0 mmol), bisulfite adducts **2l** (237.8 mg, 1.1 mmol), and ethanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 180 min at 30 Hz and 70 °C. The reaction mixture was extracted with 5 mL of methanol at the end of the

reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as white solid, yield 87% (218 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.63 (s, 1H), 7.30 (d, *J* = 4.8 Hz, 1H), 6.99 – 6.88 (m, 4H), 6.87 (s, 1H), 6.86 (s, 1H), 6.44 (s, 2H).

¹³C NMR (151 MHz, CDCl₃+DMSO-*d*₆) δ 150.8, 148.4, 143.7, 138.5, 135.1, 129.3, 129.2, 127.9, 127.9, 127.2, 126.8, 126.7, 121.6, 118.7, 118.6.

Spectroscopic data are in agreement with those reported earlier.²⁹

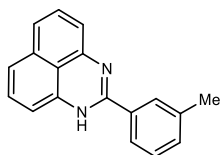


2-(1*H*-Perimidin-2-yl)phenol (5n): The compound was synthesized with general procedure **7.2.3**. **1h** (158 mg, 1.0 mmol), bisulfite adducts **2n** (248.6 mg, 1.1 mmol), and ethanol (*η* factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 180 min at 30 Hz and 70 °C. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as white solid, yield 79% (206 mg).

¹H NMR (600 MHz, DMSO-*d*₆) δ 14.79 (s, 1H), 10.69 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.97 – 6.89 (m, 2H), 6.70 (s, 1H), 6.69 (s, 1H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 161.2, 154.7, 137.0, 134.8, 133.3, 128.8, 128.5, 128.3, 126.2, 121.0, 120.2, 118.8, 118.0, 112.8, 112.6, 104.2.

Spectroscopic data are in agreement with those reported earlier.²⁸



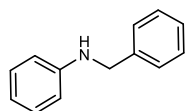
2-(*m*-Tolyl)-1*H*-perimidine (5v): The compound was synthesized with general procedure **7.2.3**. **1h** (158 mg, 1.0 mmol), bisulfite adducts **2v** (246.6 mg, 1.1 mmol), and ethanol (*η* factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted for 180 min at 30 Hz and 70 °C. The reaction mixture was extracted with 5 mL of methanol at the end of the reaction. Then, the extracted reaction mixture was evaporated to dryness in vacuo and purified by recrystallization with ethanol to afford the product as yellow solid, yield 83% (214 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.68 (s, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.26 (s, 1H), 7.17 (s, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.72 (s, 2H), 2.41 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 152.9, 147.7, 139.9, 138.9, 135.6, 134.1, 132.1, 128.9, 127.3, 127.1, 123.3, 123.2, 121.9, 119.9, 114.4, 21.5.

Spectroscopic data are in agreement with those reported earlier.²⁷

7.2.7.5. Spectral Data for Reductive Amination

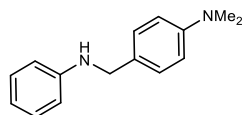


N-Benzylaniline (6ia): The compound was synthesized with general procedure 7.2.4. **1i** (93 mg, 1.0 mmol), bisulfite adducts **2a** (231 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 180 minutes at 30 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure secondary amine as pale-yellow liquid, yield 55% (100 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.39 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.19 (t, J = 7.2 Hz, 2H), 6.73 (t, J = 7.2 Hz, 1H), 6.66 (s, 1H), 6.65 (s, 1H), 4.34 (s, 2H), 4.06 (s, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 148.2, 139.5, 129.4, 128.8, 127.7, 127.4, 117.8, 113.0, 48.5.

Spectroscopic data are in agreement with those reported earlier.³⁰

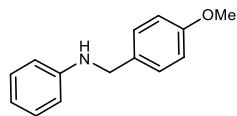


N,N-Dimethyl-4-((phenylamino)methyl)aniline (6ih): The compound was synthesized with general procedure 7.2.4. **1i** (93 mg, 1.0 mmol), bisulfite adducts **2h** (278.5 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 180 minutes at 30 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure secondary amine as pale-yellow liquid, yield 90% (204 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.30 (d, J = 8.4 Hz, 2H), 7.23 (t, J = 7.8 Hz, 2H), 6.79 – 6.74 (m, 3H), 6.70 (d, J = 7.8 Hz, 2H), 4.25 (s, 2H), 3.87 (br, 1H), 2.99 (s, 6H).

¹³C NMR (151 MHz, CDCl₃) δ 150.1, 148.5, 129.3, 128.8, 127.2, 117.4, 112.9, 48.0, 40.8 (×2).

Spectroscopic data are in agreement with those reported earlier.³¹

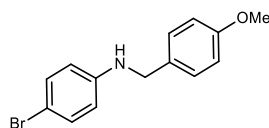


N-(4-Methoxybenzyl)aniline (6ii): The compound was synthesized with general procedure 7.2.4. **1i** (93 mg, 1.0 mmol), bisulfite adducts **2i** (264 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 180 minutes at 30 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure secondary amine as pale-yellow liquid, yield 92% (196 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.32 (s, 1H), 7.31 (s, 1H), 7.21 (dt, J = 9.6, 4.8 Hz, 2H), 6.91 – 6.89 (m, 1H), 6.89 – 6.87 (m, 1H), 6.80 (t, J = 7.2 Hz, 1H), 6.74 (s, 1H), 6.73 (s, 1H), 4.28 (s, 2H), 3.81 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 159.1, 146.9, 130.5, 129.4, 129.3, 118.8, 114.1, 55.4, 48.7.

Spectroscopic data are in agreement with those reported earlier.³²

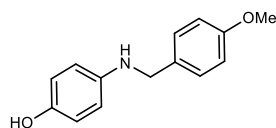


4-Bromo-N-(4-methoxybenzyl)aniline (6ji): The compound was synthesized with general procedure 7.2.4. **1j** (172 mg, 1.0 mmol), bisulfite adducts **2i** (264 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 180 minutes at 30 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure secondary amine as pale-yellow liquid, yield 90% (263 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.27 (s, 1H), 7.25 (s, 1H), 7.24 (s, 1H), 7.23 (s, 1H), 6.89 (s, 1H), 6.87 (s, 1H), 6.51 (s, 1H), 6.50 (s, 1H), 4.22 (s, 2H), 4.06 (br, 1H), 3.80 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 159.1, 147.2, 132.1, 130.9, 128.9, 114.6, 114.3, 109.3, 55.5, 47.9.

Spectroscopic data are in agreement with those reported earlier.³³



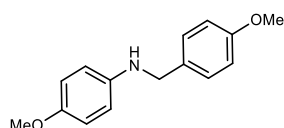
4-((4-Methoxybenzyl)amino)phenol (6ki): The compound was synthesized with general procedure 7.2.4. **1k** (109 mg, 1.0 mmol), bisulfite adducts **2i** (264 mg, 1.1 mmol), and methanol

(η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 180 minutes at 30 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure secondary amine as pale-yellow liquid, yield 92% (211 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.29 (s, 1H), 7.28 (s, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 8.4 Hz, 2H), 4.31 (br, 1H), 4.20 (s, 2H), 3.80 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 158.9, 147.9, 142.7, 131.8, 129.0, 116.3, 114.5, 114.2, 55.5, 48.9.

Spectroscopic data are in agreement with those reported earlier.³⁴

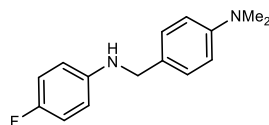


4-Methoxy-N-(4-methoxybenzyl)aniline (6li): The compound was synthesized with general procedure 7.2.4. **1l** (123 mg, 1.0 mmol), bisulfite adducts **2i** (264 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 180 minutes at 30 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure secondary amine as pale-yellow liquid, yield 91% (222 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.29 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 8.4 Hz, 2H), 4.21 (s, 2H), 3.81 (s, 3H), 3.75 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 158.9, 152.4, 142.5, 131.7, 129.0, 115.1, 114.4, 114.1, 55.9, 55.4, 48.9.

Spectroscopic data are in agreement with those reported earlier.³⁵



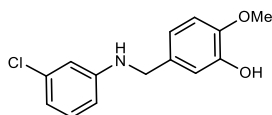
4-(((4-Fluorophenyl)amino)methyl)-N,N-dimethylaniline (6mh): The compound was synthesized with general procedure 7.2.4. **1m** (111 mg, 1.0 mmol), bisulfite adducts **2h** (278.5 mg, 1.1 mmol), and methanol (η factor= 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 180 minutes at 30 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure secondary amine as R_f = 0.40 (hexane/ethyl acetate 7:3), white solid, yield 88% (215 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.93 (t, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.64 – 6.58 (m, 2H), 4.21 (s, 2H), 3.83 (br, 1H), 2.99 (s, 6H).

¹³C NMR (151 MHz, CDCl₃) δ 155.9 (d, *J* = 234.6 Hz), 150.2, 144.9, 128.8, 126.9, 115.7 (d, *J* = 22.3 Hz), 113.7 (d, *J* = 7.4 Hz), 112.9, 48.7, 40.8 (×2).

FTIR $\tilde{\nu}$ max = 3390, 2919, 2850, 1606, 1506, 1207, 1105, 1063, 806, 772 cm⁻¹.

HRMS: calculated for C₁₅H₁₆FN₂: 243.1298 [M-H]⁺; found: 243.1298.



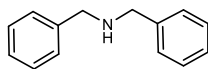
4-(((3-Chlorophenyl)amino)methyl)-2-methoxyphenol (6nw): The compound was synthesized with general procedure 7.2.4. **1n** (127.5 mg, 1.0 mmol), bisulfite adducts **2w** (282 mg, 1.1 mmol), and methanol (*η* factor = 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 180 minutes at 30 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure secondary amine as R_f = 0.70 (hexane/ethyl acetate 1:1), pale pink solid, yield 78% (206 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.07 (t, *J* = 7.8 Hz, 1H), 6.93 – 6.88 (m, 1H), 6.87 – 6.82 (m, 2H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.62 (s, 1H), 6.50 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.61 (s, 1H), 4.21 (d, *J* = 4.8 Hz, 2H), 4.04 (s, 1H), 3.87 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 149.4, 146.9, 145.1, 135.1, 130.7, 130.3, 120.6, 117.5, 114.6, 112.6, 111.3, 110.3, 56.1, 48.2.

FTIR $\tilde{\nu}$ max = 3347, 2232, 2118, 1906, 1595, 1455, 1126, 987, 941, 817 cm⁻¹.

HRMS: calculated for C₁₄H₁₃ClNO₂: 262.0635 [M-H]⁺; found: 262.0641.

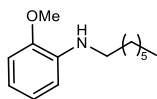


Dibenzylamine (6oa): The compound was synthesized with general procedure 7.2.4. **1o** (107 mg, 1.0 mmol), bisulfite adducts **2a** (231 mg, 1.1 mmol), and methanol (*η* factor = 0.4). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 180 minutes at 30 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 180 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure and purified using column chromatography to afford the pure secondary amine as pale-yellow liquid, yield 63% (125 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.36 (d, *J* = 9.6 Hz, 3H), 7.34 (s, 4H), 7.20 – 7.17 (m, 3H), 4.02 (d, *J* = 5.4 Hz, 1H), 4.00 (d, *J* = 5.4 Hz, 1H), 3.86 (s, 1H), 3.80 (d, *J* = 6.0 Hz, 1H), 3.78 (d, *J* = 6.0 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 134.5, 129.8, 129.0, 128.8, 58.7.

Spectroscopic data are in agreement with those reported earlier.³⁶



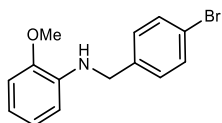
***N*-Heptyl-2-methoxyaniline (6po):** The compound was synthesized with general procedure 7.2.4. **1p** (123 mg, 1.0 mmol), bisulfite adducts **2o** (240 mg, 1.1 mmol), and methanol (η factor= 1.0). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 6h at 15 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 120 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure and purified using column chromatography to afford the pure secondary amine as pale-yellow liquid, yield 67% (74 mg).

¹H NMR (600 MHz, CDCl₃) δ 6.88 (t, J = 7.8 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.65 (t, J = 7.8 Hz, 1H), 6.61 (d, J = 7.8 Hz, 1H), 4.17 (s, 1H), 3.85 (s, 3H), 3.12 (t, J = 7.2 Hz, 2H), 1.69 – 1.62 (m, 2H), 1.46 – 1.38 (m, 2H), 1.38 – 1.28 (m, 5H), 0.90 (t, J = 6.6 Hz, 4H).

¹³C NMR (151 MHz, CDCl₃) δ 146.9, 138.7, 121.5, 116.2, 109.9, 109.5, 55.5, 43.9, 31.9, 29.7, 29.3, 27.4, 22.8, 14.2.

HRMS: calculated for C₁₄H₂₄NO: 222.1852 [M-H]⁺; found: 222.1843.

Spectroscopic data are in agreement with those reported earlier.³⁷

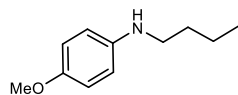


***N*-(4-Bromobenzyl)-2-methoxyaniline (6pd):** The compound was synthesized with general procedure 7.2.4. **1p** (123 mg, 1.0 mmol), bisulfite adducts **2d** (318 mg, 1.1 mmol), and methanol (η factor= 1.0). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 6h at 15 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 120 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure and purified using column chromatography to afford the pure secondary amine as pale-yellow liquid, yield 43% (127 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.46 (d, J = 7.8 Hz, 2H), 7.27 (s, 2H), 6.84 – 6.79 (m, 2H), 6.70 (t, J = 7.8 Hz, 1H), 6.54 (d, J = 7.8 Hz, 1H), 4.70 (s, 1H), 4.33 (s, 2H), 3.87 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 146.9, 138.8, 137.9, 131.8, 129.2, 121.4, 120.9, 117.1, 110.3, 109.6, 55.6, 47.6.

Spectroscopic data are in agreement with those reported earlier.³⁸



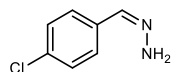
N-Butyl-4-methoxyaniline (6lx): The compound was synthesized with general procedure 7.2.4. **1l** (123 mg, 1.0 mmol), bisulfite adducts **2x** (194 mg, 1.1 mmol), and methanol (η factor= 1.0). The vessel was then closed, and the mechanochemical reaction was conducted, ranging from 6h at 15 Hz. At the end of the reaction, an additional refill of NaBH₄ (151.32 mg, 4.00 mmol) was made, and the mechanochemical reaction was run for 120 min at a frequency of 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure and purified using column chromatography to afford the pure secondary amine as pale-yellow liquid, yield 42% (38 mg).

¹H NMR (600 MHz, CDCl₃) δ 6.78 (d, J = 8.4 Hz, 2H), 6.59 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H), 3.07 (t, J = 7.2 Hz, 2H), 1.63 – 1.54 (m, 2H), 1.43 (dd, J = 14.4, 7.2 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 152.2, 142.9, 115.1, 114.2, 56.0, 44.9, 31.9, 20.5, 14.1.

Spectroscopic data are in agreement with those reported earlier.³⁹

7.2.7.6. Spectral Data for Hydrazones

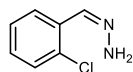


(Z)-(4-Chlorobenzylidene)hydrazine (8c): The compound was synthesized with general procedure 7.2.5. **2c** (269 mg, 1.1 mmol), hydrazine hemisulfate **7** (81.1 mg, 1.0 mmol), and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 180 minutes at 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure hydrazone as pale-yellow solid, yield 51% (79 mg).

¹H NMR (600 MHz, CDCl₃) δ 8.61 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 161.2, 137.5, 132.6, 129.9, 129.3.

Spectroscopic data are in agreement with those reported earlier.⁴⁰

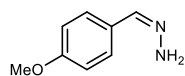


(Z)-(2-Chlorobenzylidene)hydrazine (8f): The compound was synthesized with general procedure 7.2.5. **2f** (269 mg, 1.1 mmol), hydrazine hemisulfate **7** (81.1 mg, 1.0 mmol), and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 180 minutes at 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure hydrazone as pale-yellow solid, yield 47% (73 mg).

¹H NMR (600 MHz, CDCl₃) δ 9.09 (s, 1H), 8.22 (d, J = 6.0 Hz, 1H), 7.53 – 7.30 (m, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 159.2, 136.0, 132.3, 131.6, 130.2, 128.5, 127.2.

Spectroscopic data are in agreement with those reported earlier.⁴¹



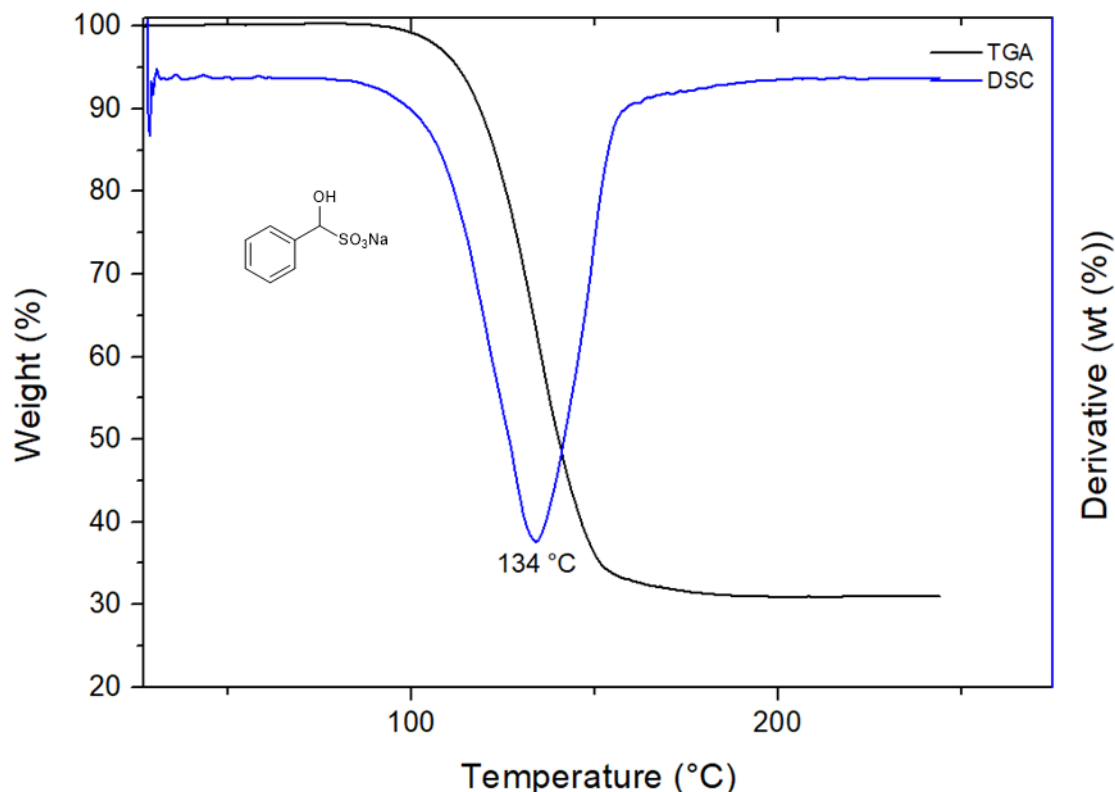
(Z)-(4-Methoxybenzylidene)hydrazine (8i): The compound was synthesized with general procedure 7.2.5. **2i** (264 mg, 1.1 mmol), hydrazine hemisulfate **7** (81.1 mg, 1.0 mmol), and methanol (η factor= 0.4). The vessel was closed, and the mechanochemical reaction was conducted for 180 minutes at 30 Hz. At the end of the reaction, the crude product was recovered with 4 mL of EtOAc. Lastly, the solvent was removed under reduced pressure to afford the pure hydrazone as pale-yellow solid, yield 52% (78 mg).

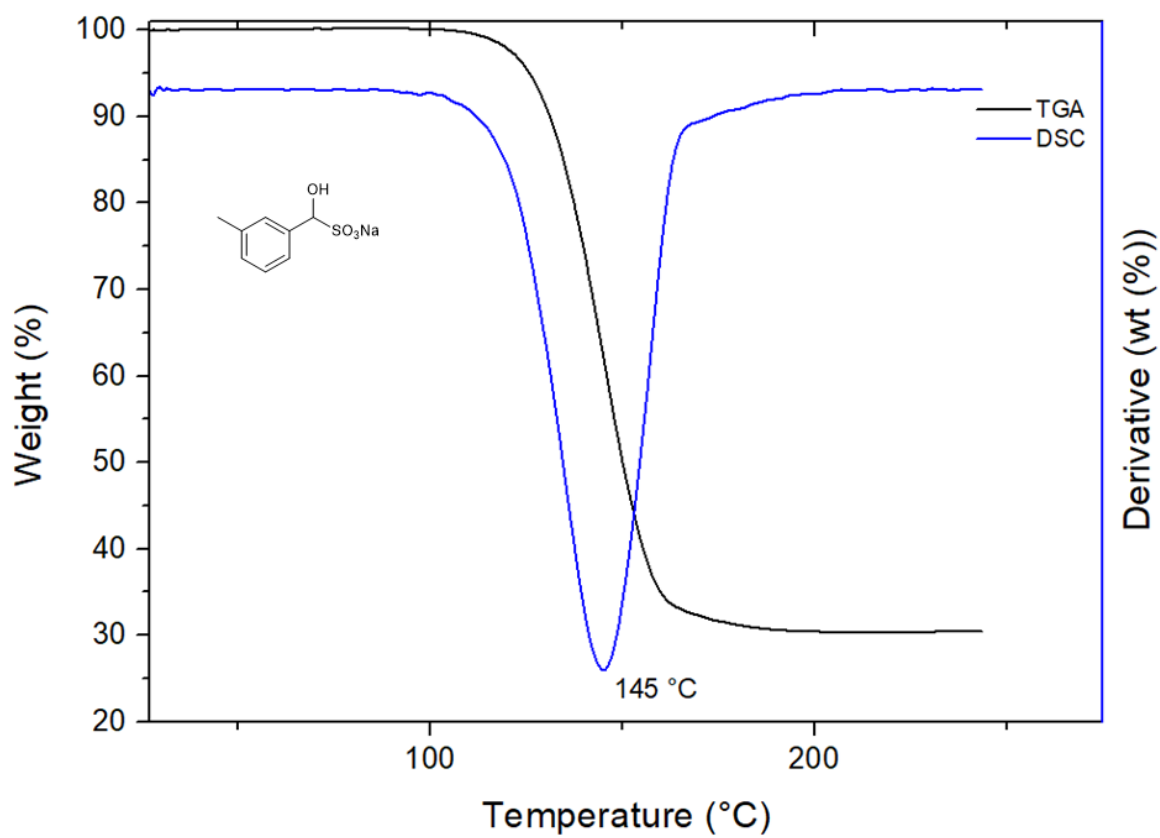
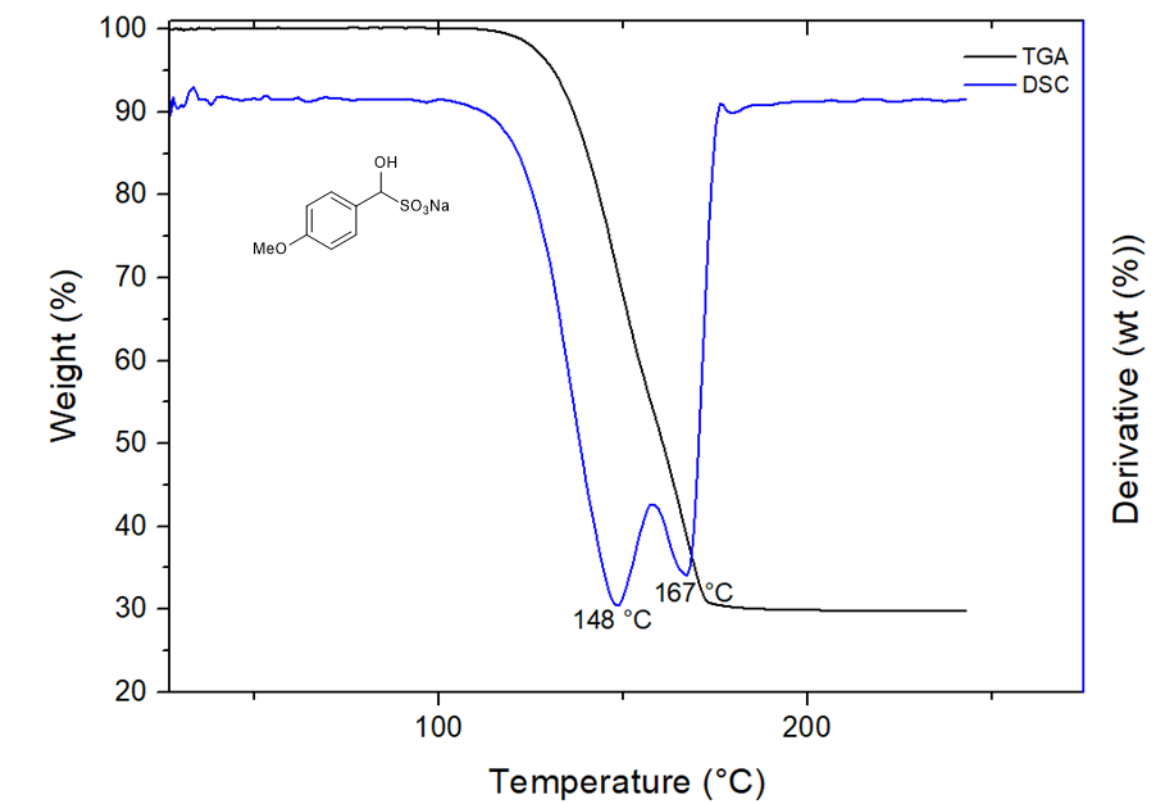
^1H NMR (600 MHz, CDCl_3) δ 8.61 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 3.87 (s, 3H).

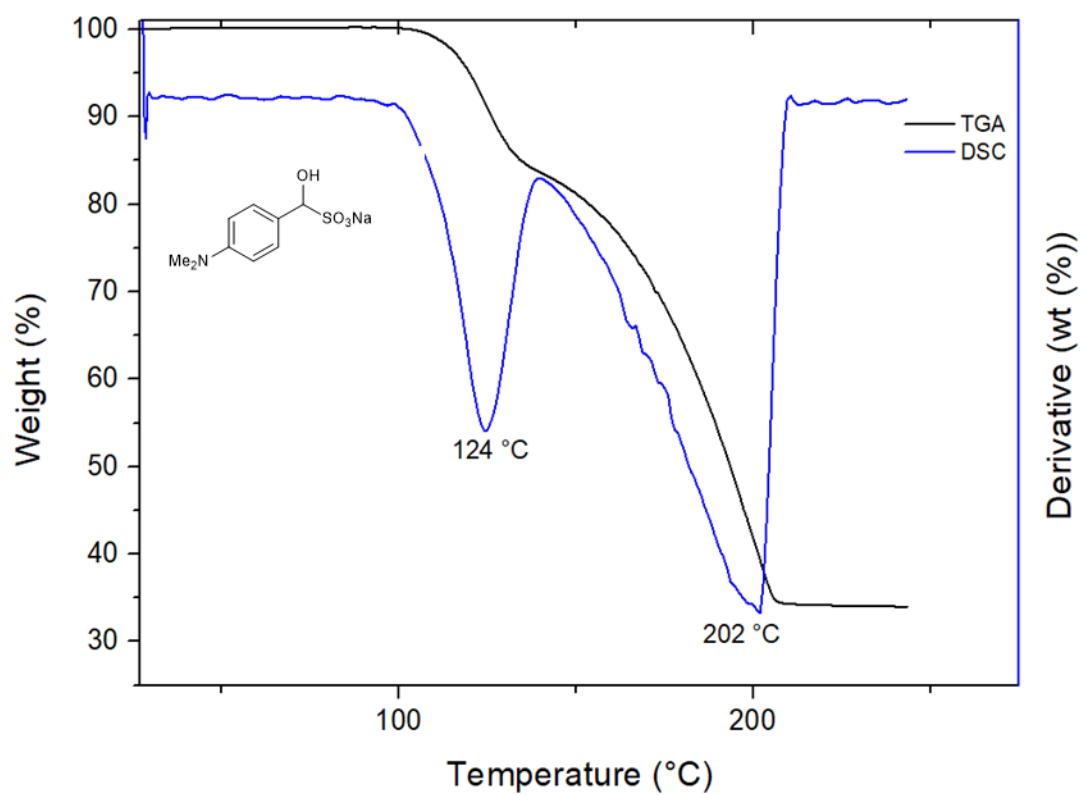
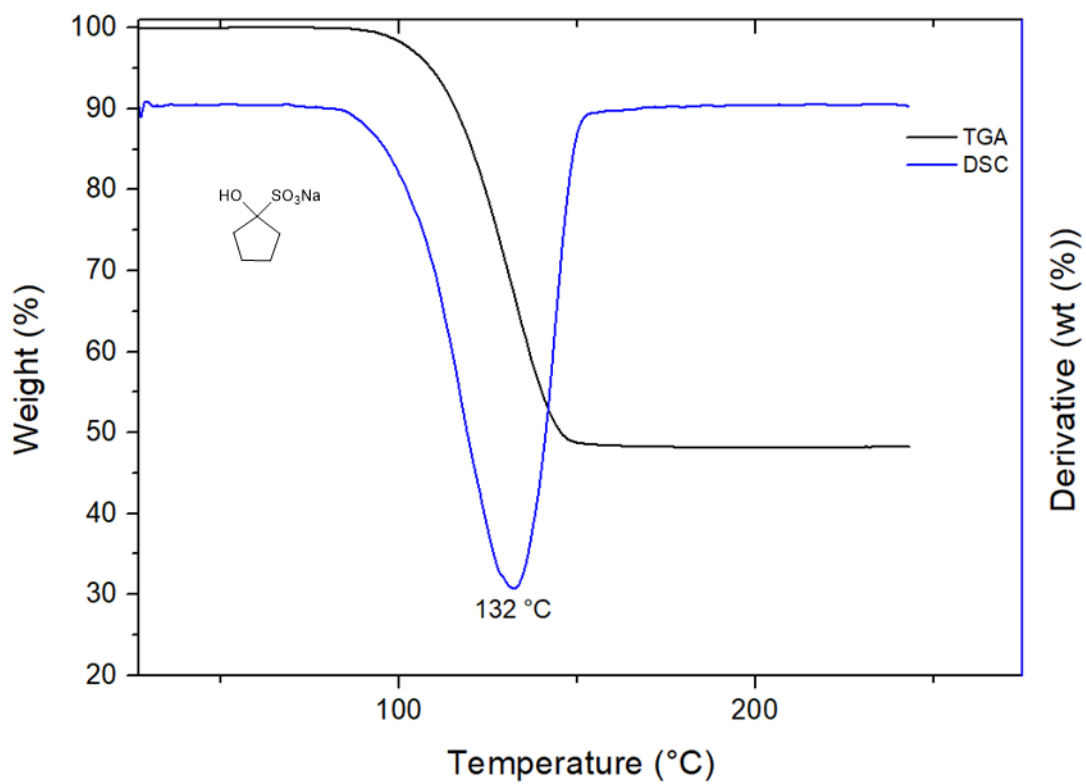
^{13}C NMR (151 MHz, CDCl_3) δ 162.2, 161.2, 130.3, 127.2, 114.4, 55.6.

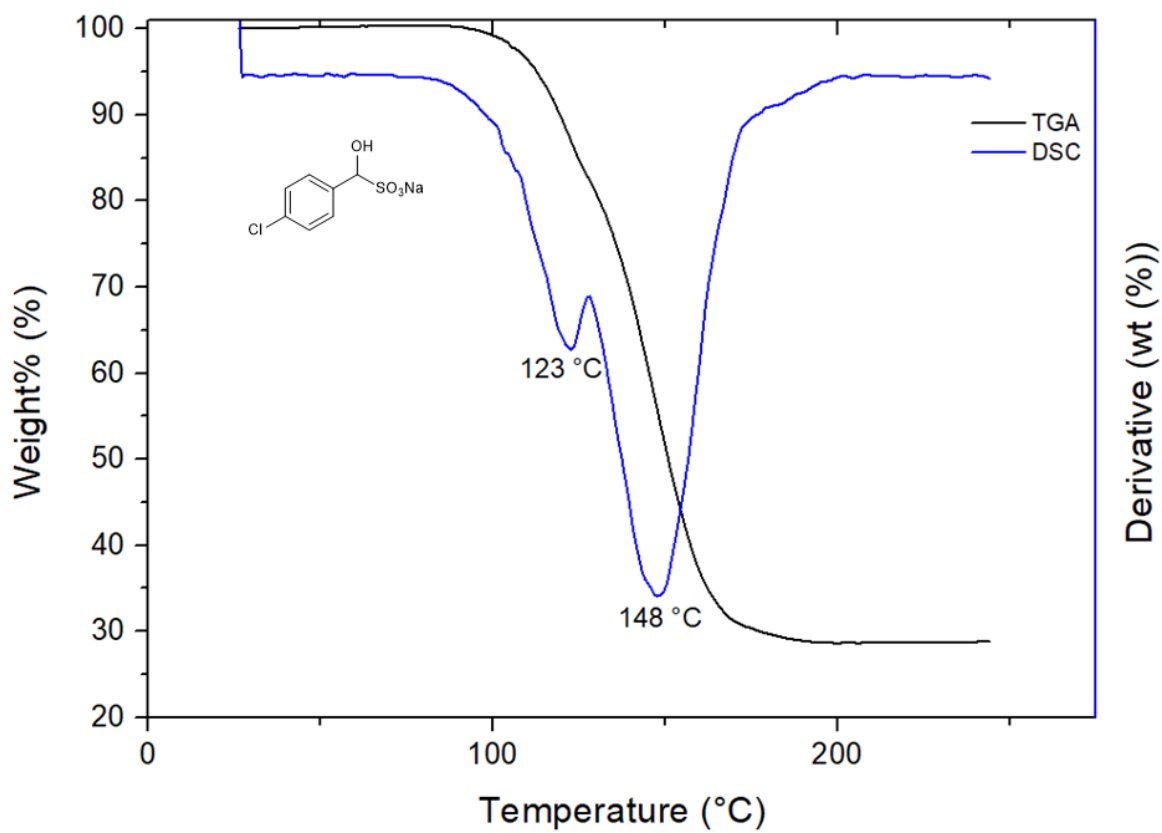
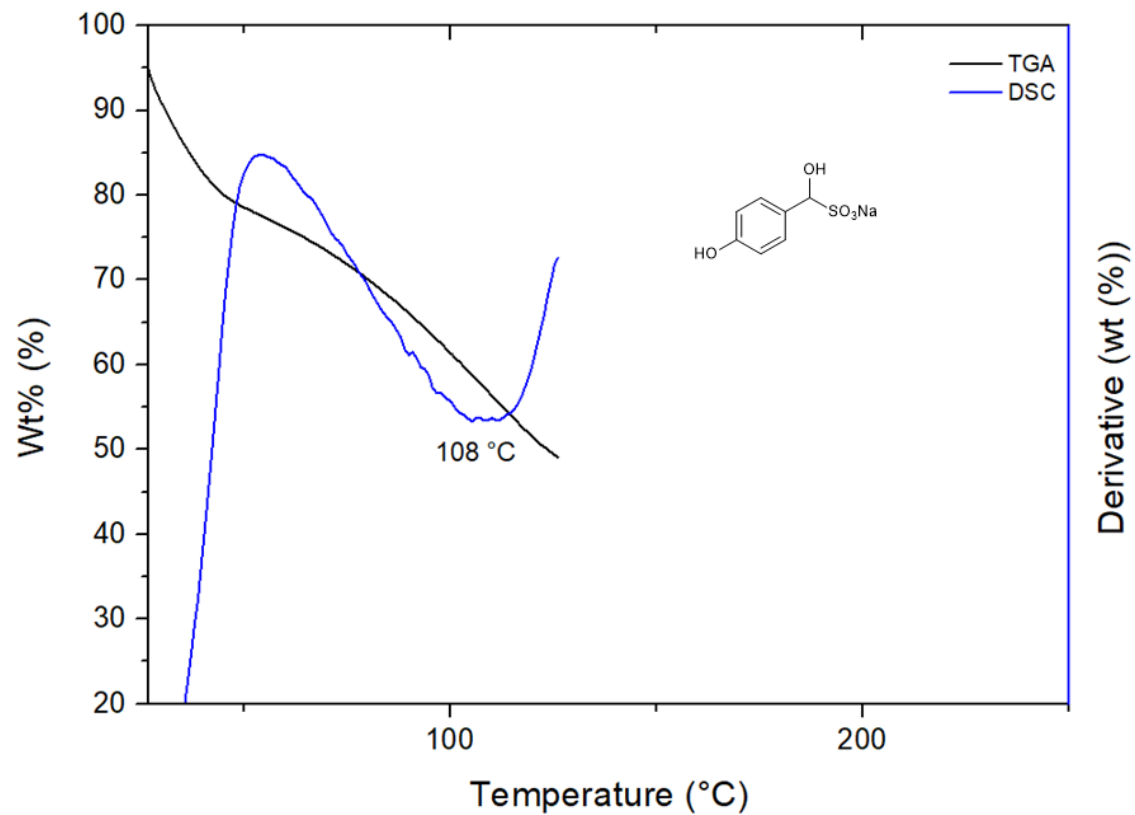
Spectroscopic data are in agreement with those reported earlier.⁴²

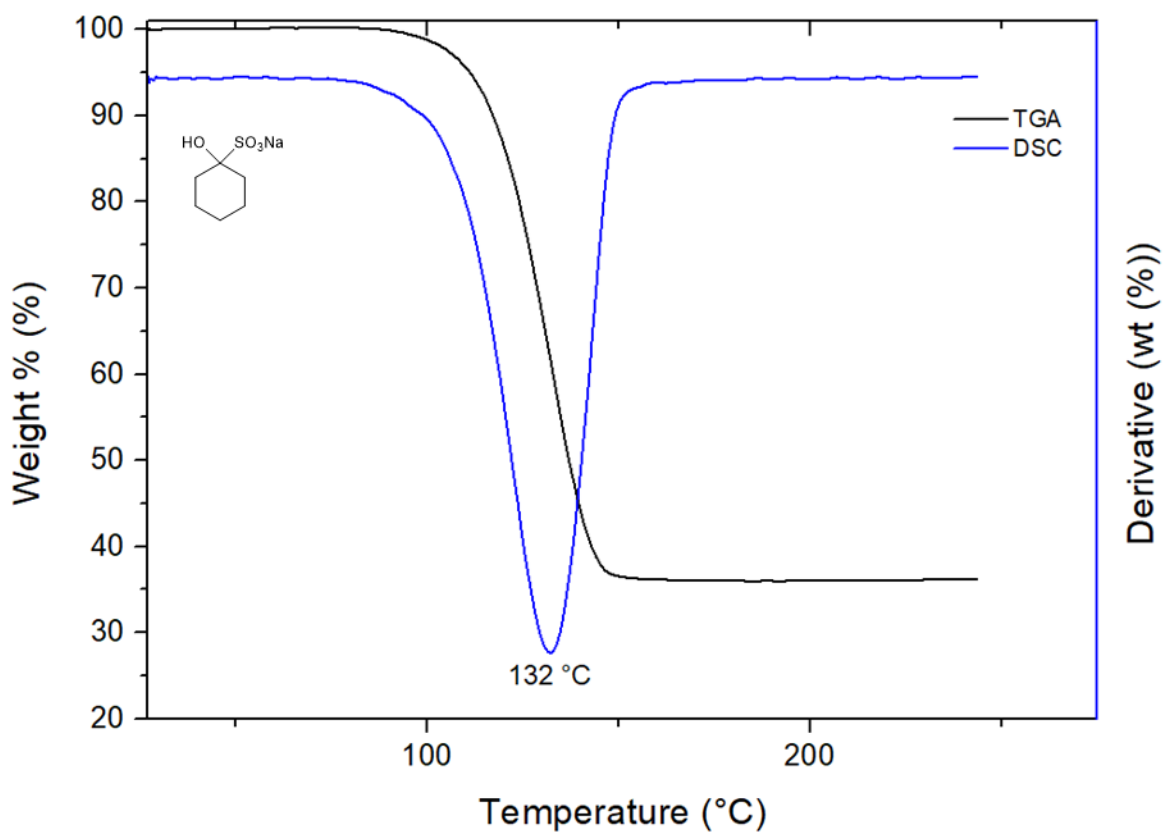
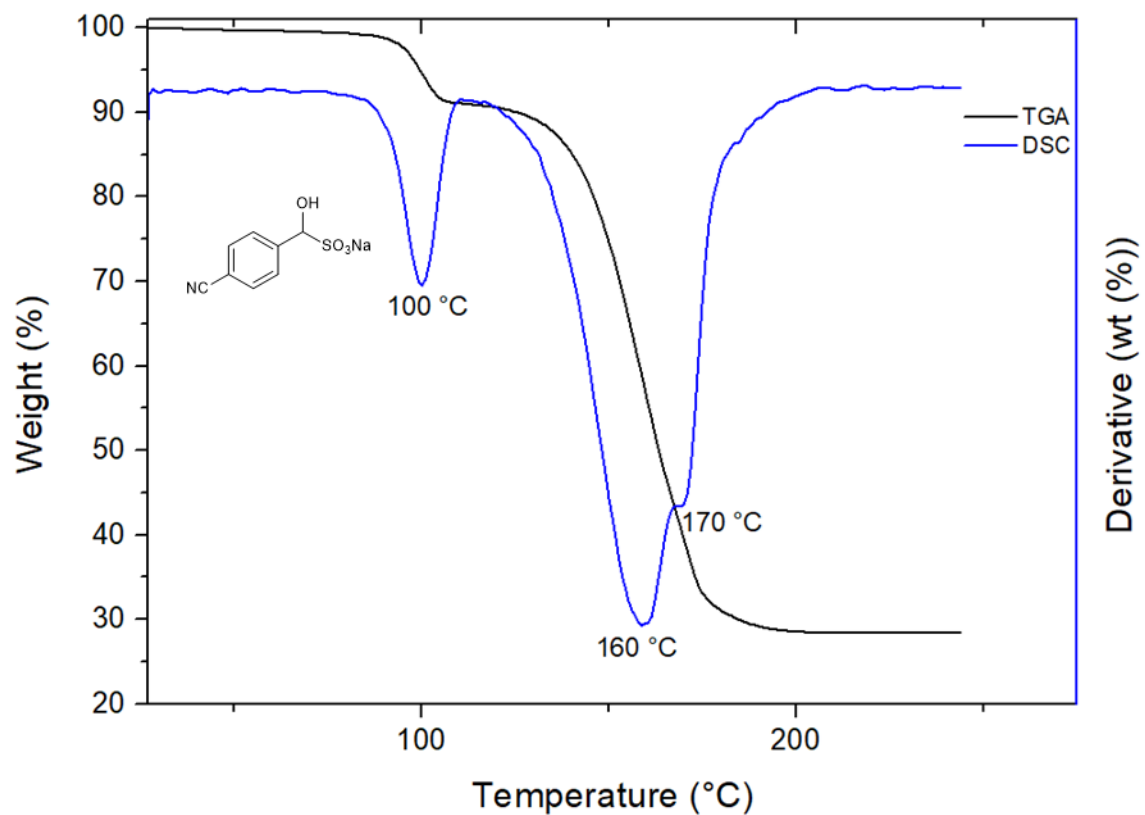
7.2.8. TGA and DSC Spectra for Bertagnini's Salts in Chapter 3

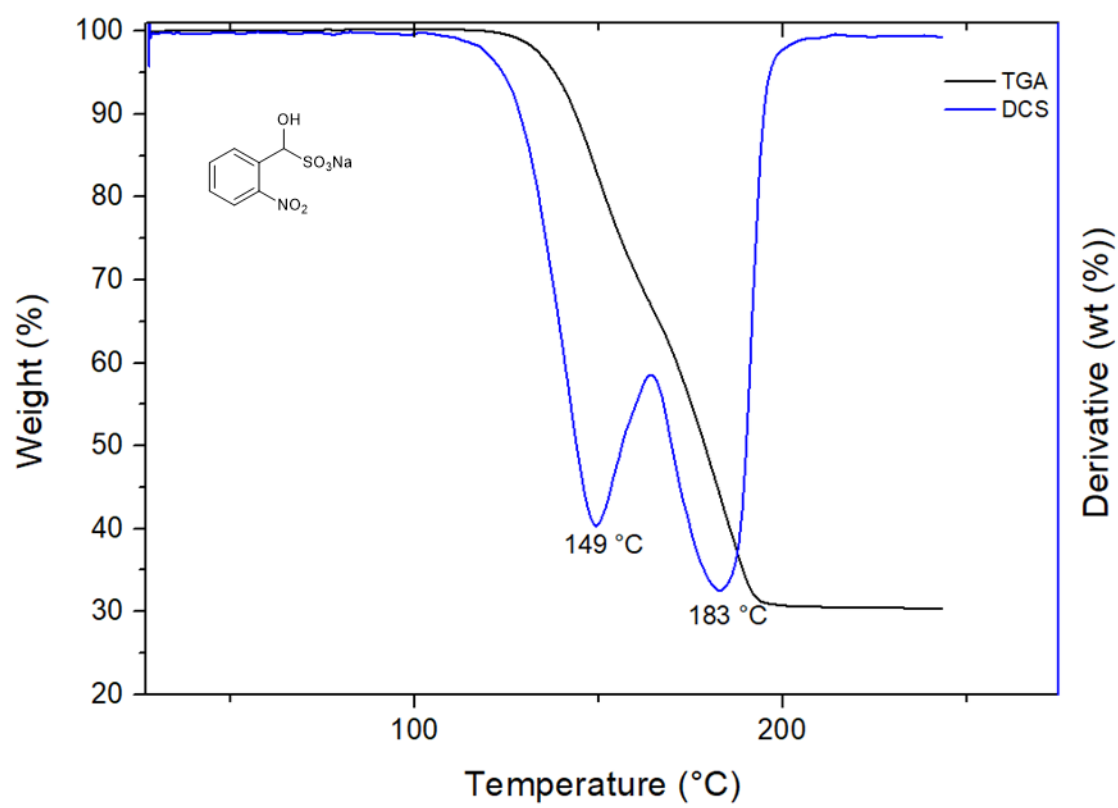
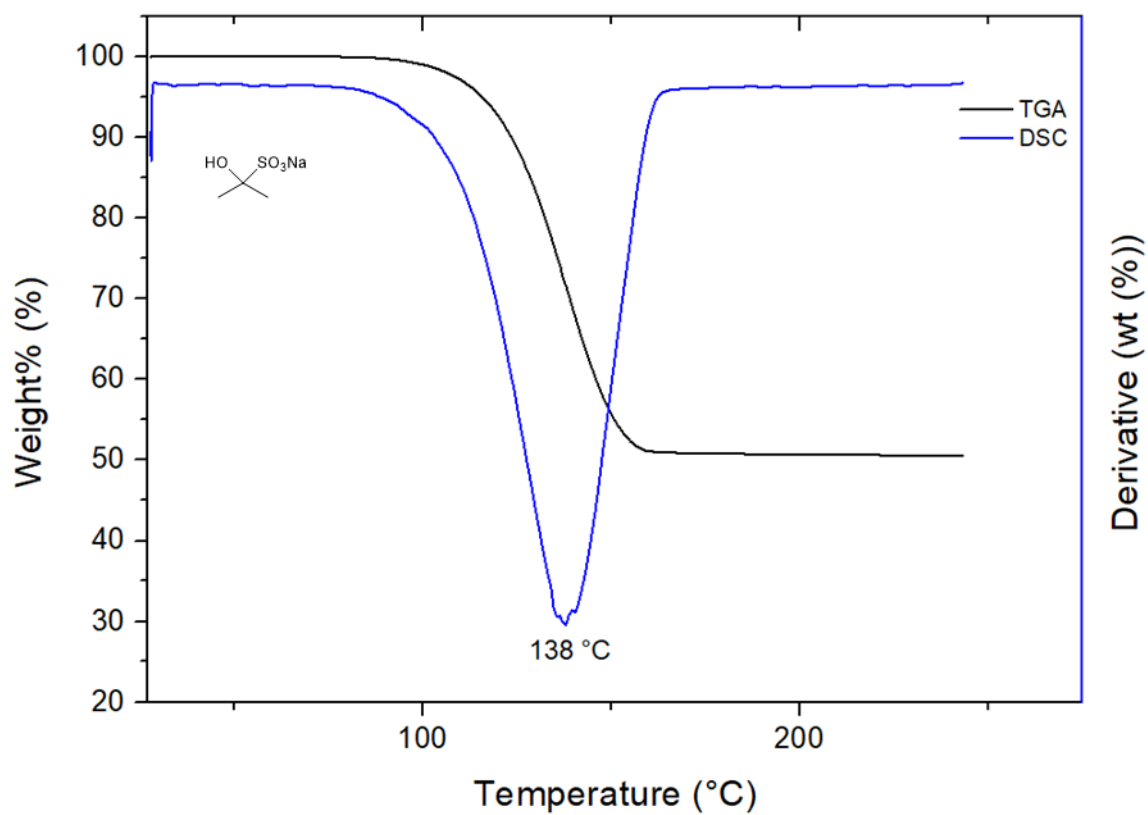


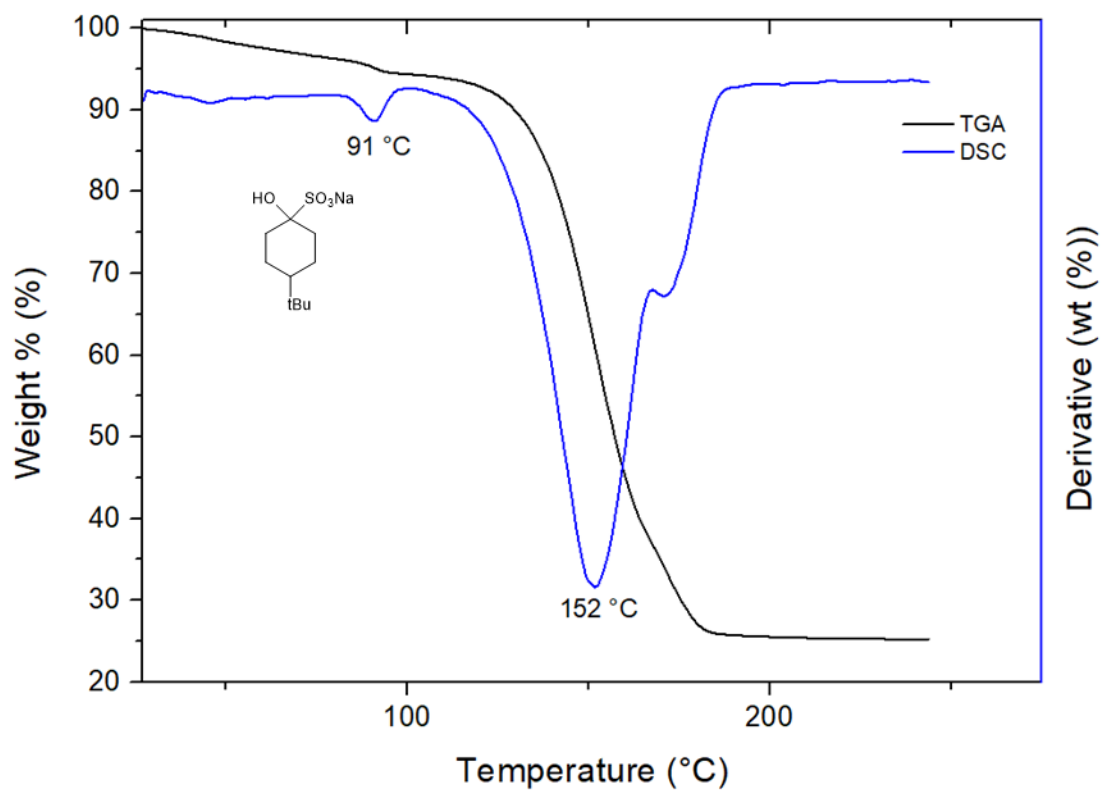
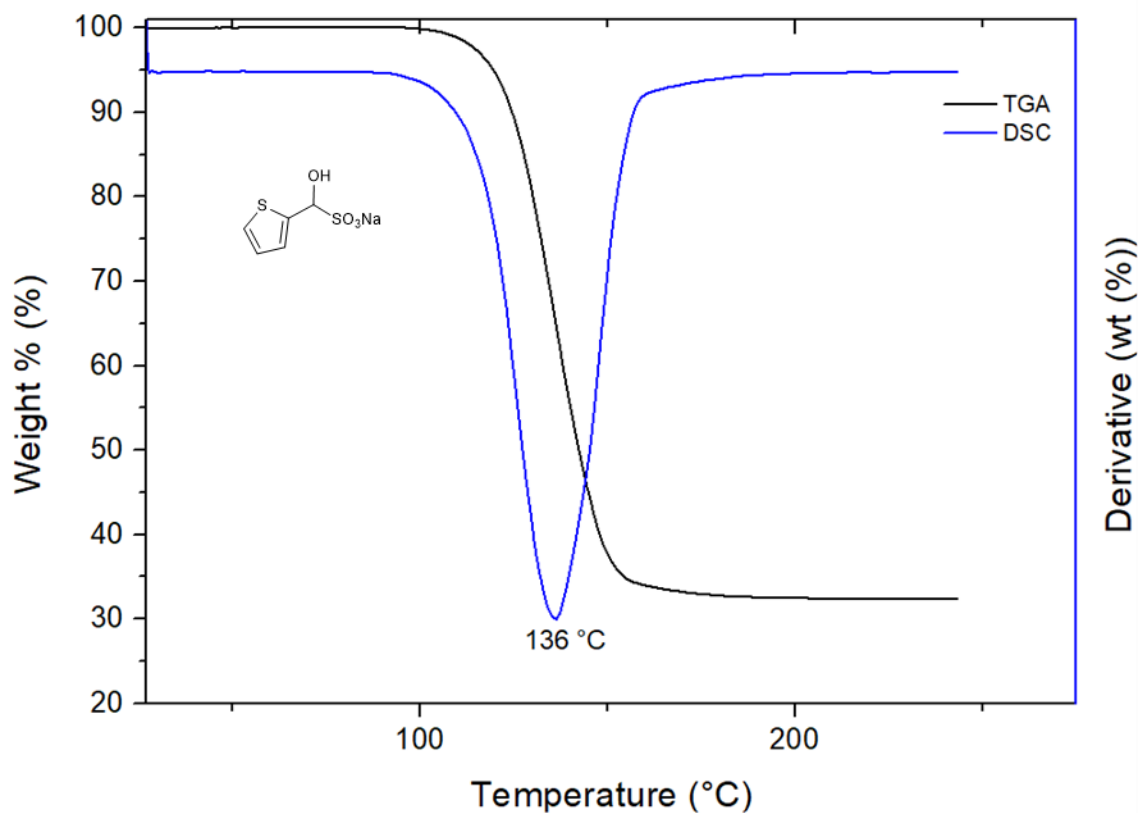






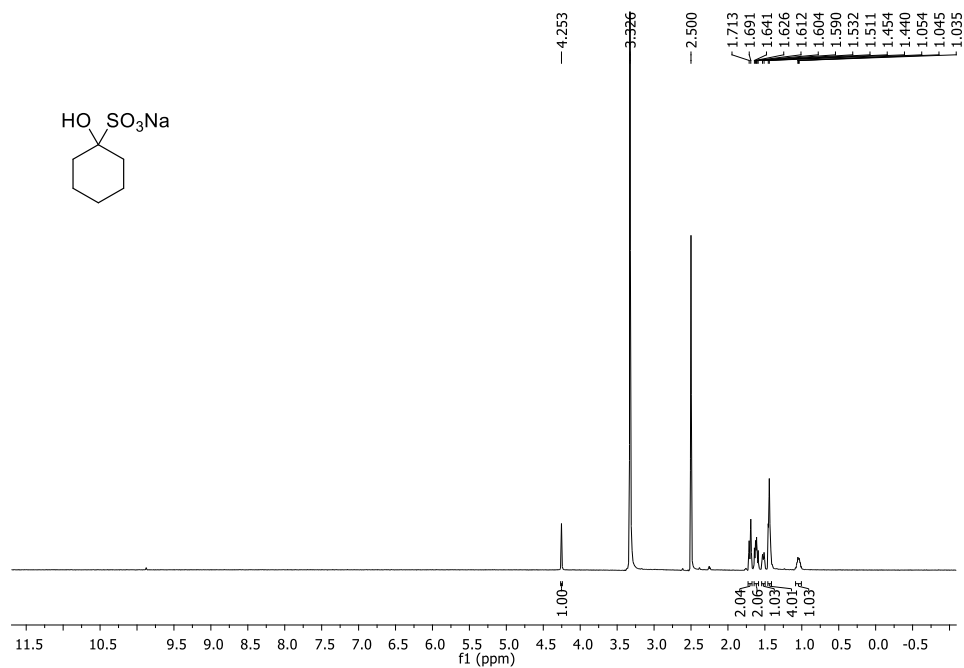




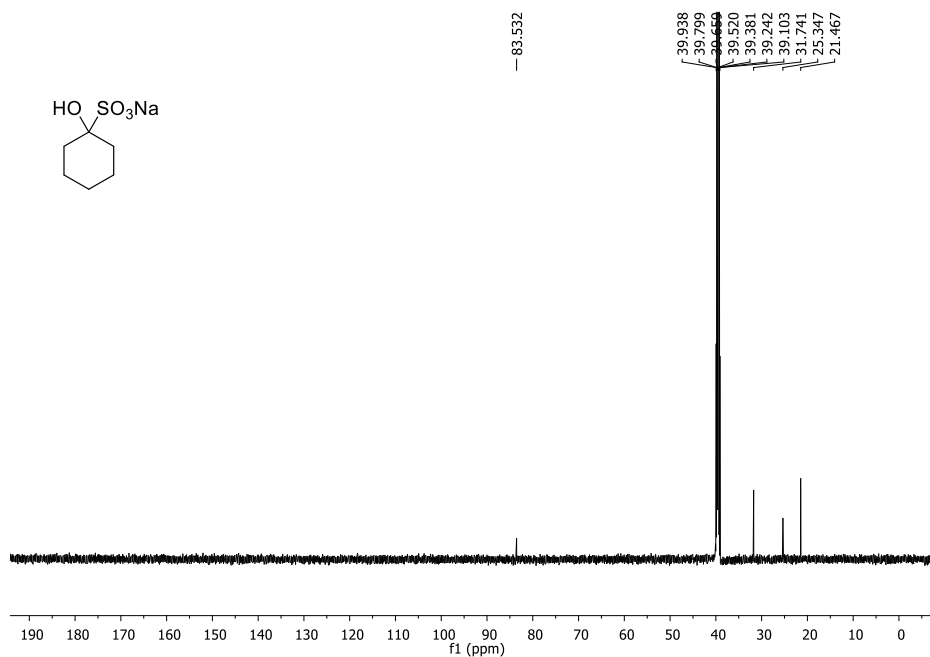


7.2.9. NMR Spectra for Compounds in Chapter 3

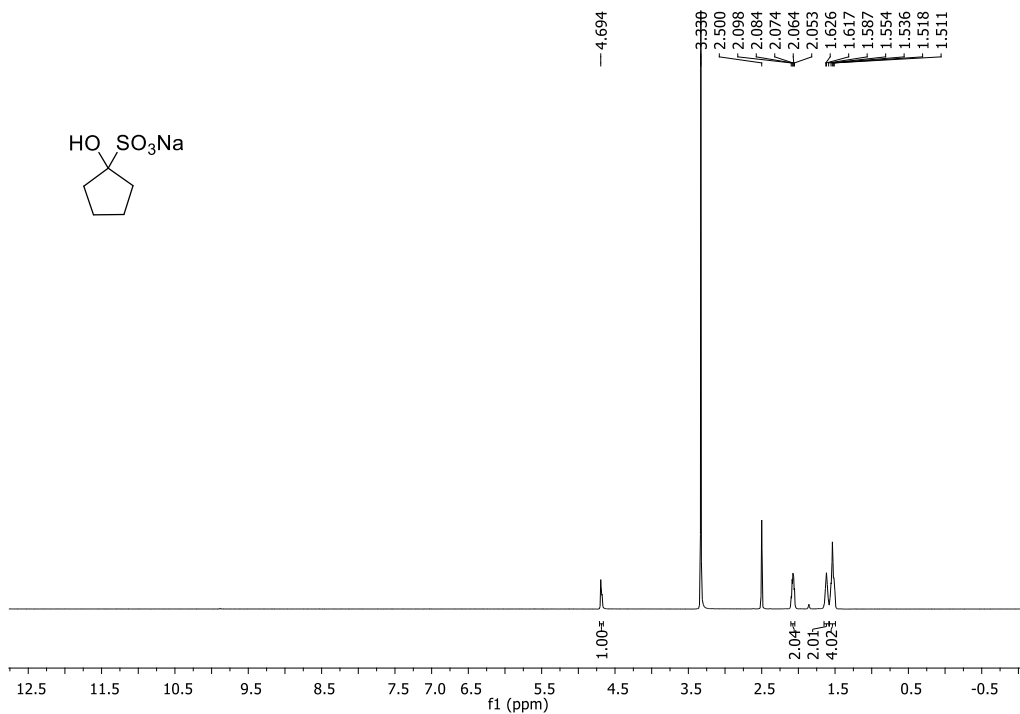
^1H NMR (600 MHz, DMSO- d_6) spectrum of **Sodium 1-hydroxycyclohexane-1-sulfonate (q)**



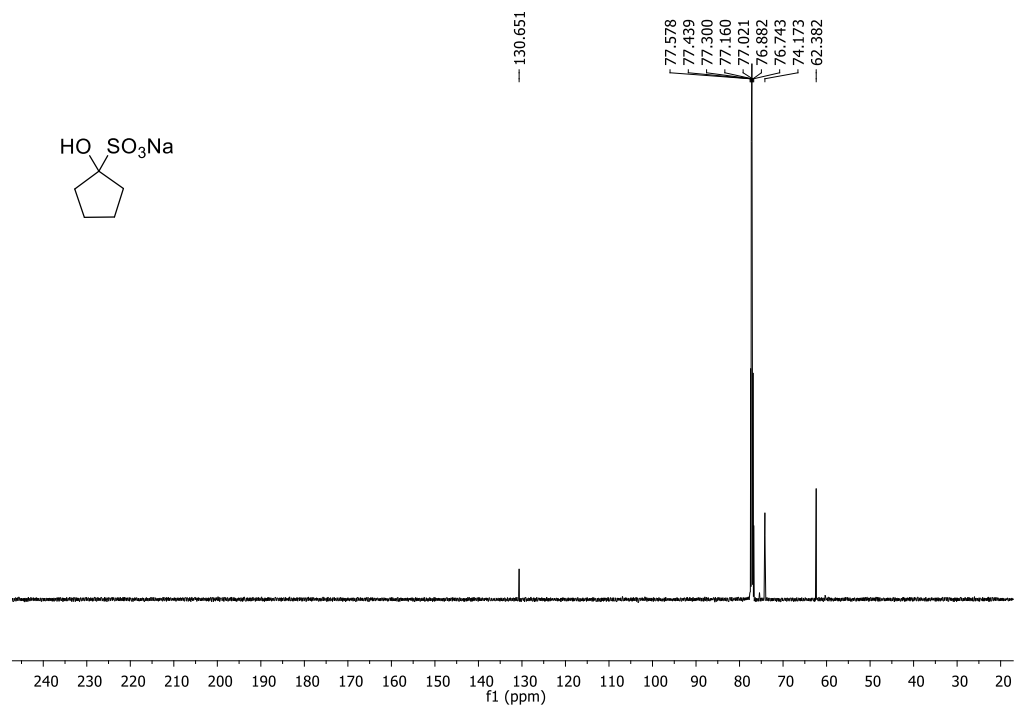
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of **Sodium 1-hydroxycyclohexane-1-sulfonate (q)**



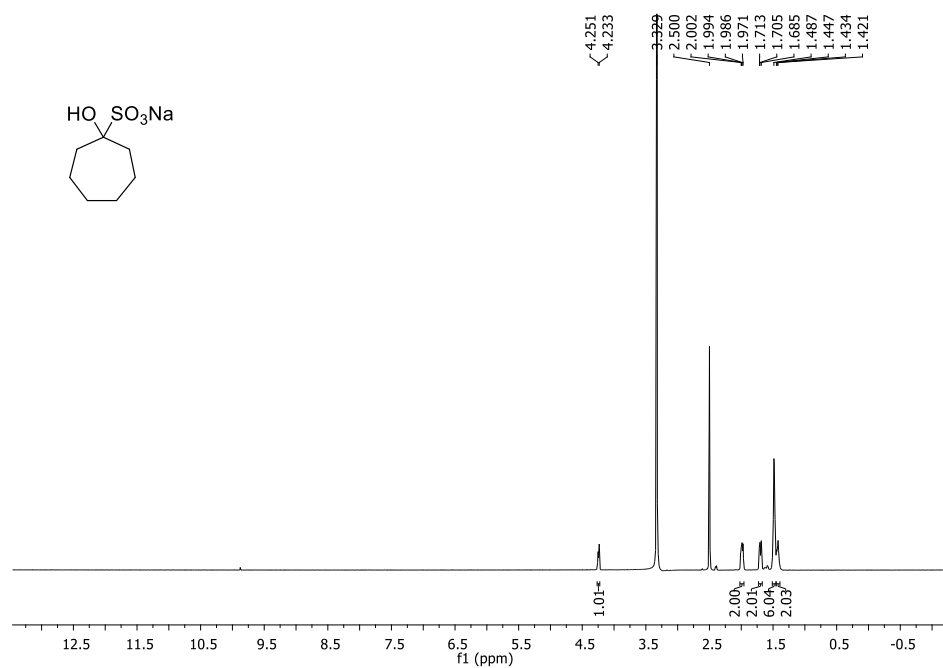
^1H NMR (600 MHz, DMSO- d_6) spectrum of **Sodium 1-hydroxycyclopentane-1-sulfonate (r)**



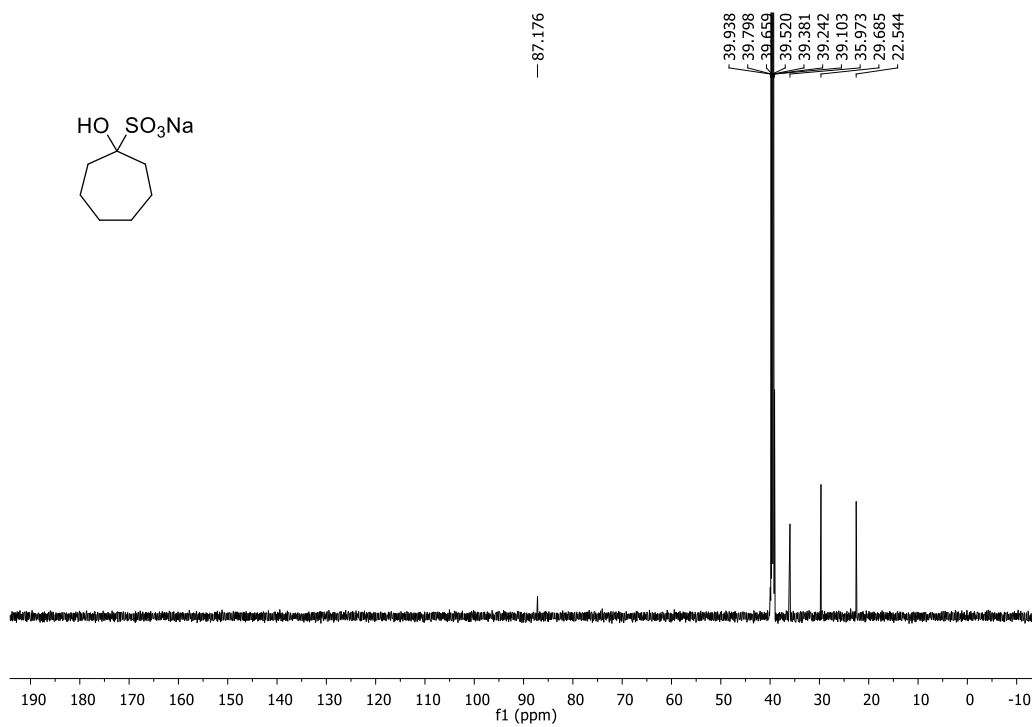
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of Sodium 1-hydroxycyclopentane-1-sulfonate (r)



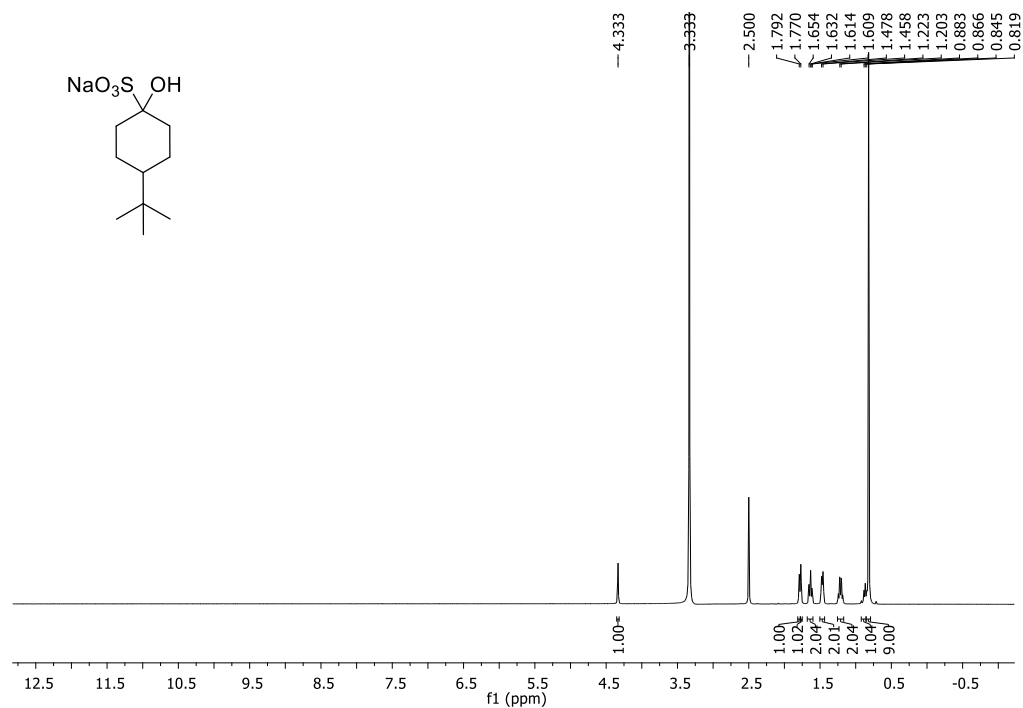
^1H NMR (600 MHz, DMSO- d_6) spectrum of Sodium 1-hydroxycycloheptane-1-sulfonate (s)



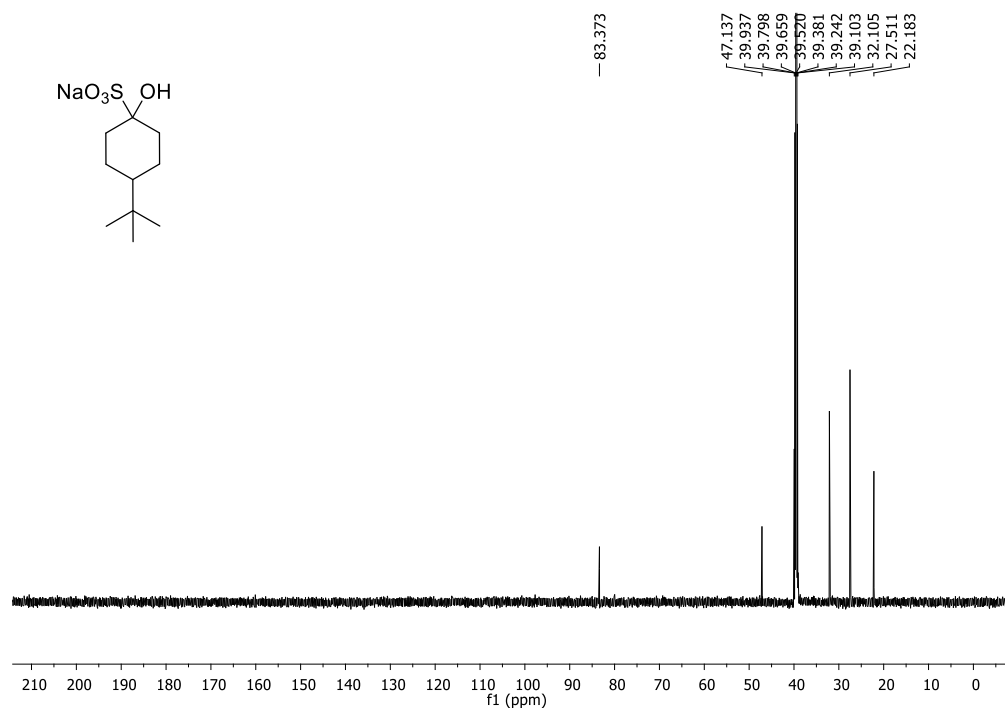
^{13}C NMR (151 MHz, DMSO-d_6) spectrum of **Sodium 1-hydroxycycloheptane-1-sulfonate (s)**



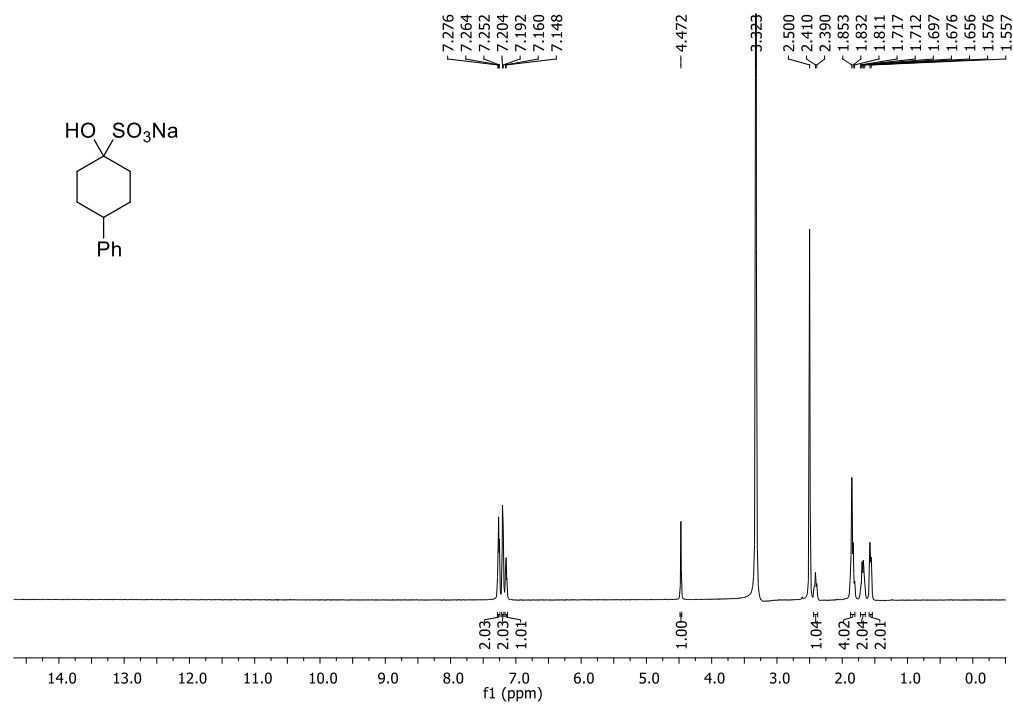
^1H NMR (600 MHz, DMSO- d_6) spectrum of **Sodium 4-(*tert*-butyl)-1-hydroxycyclohexane-1-sulfonate (t)**



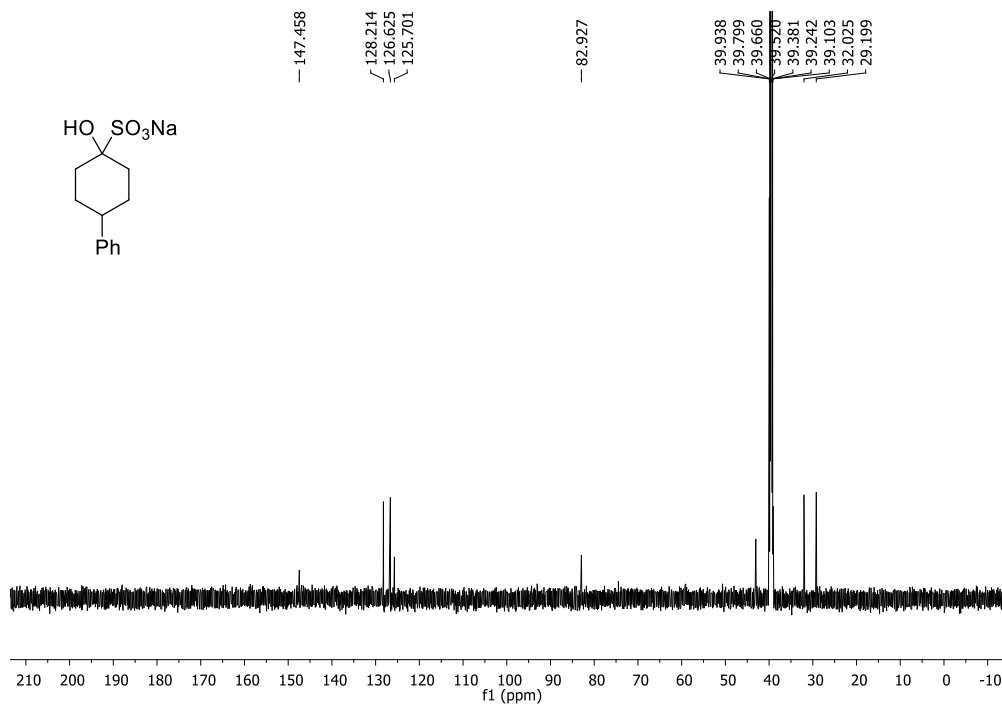
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of **Sodium 4-(*tert*-butyl)-1-hydroxycyclohexane-1-sulfonate (t)**



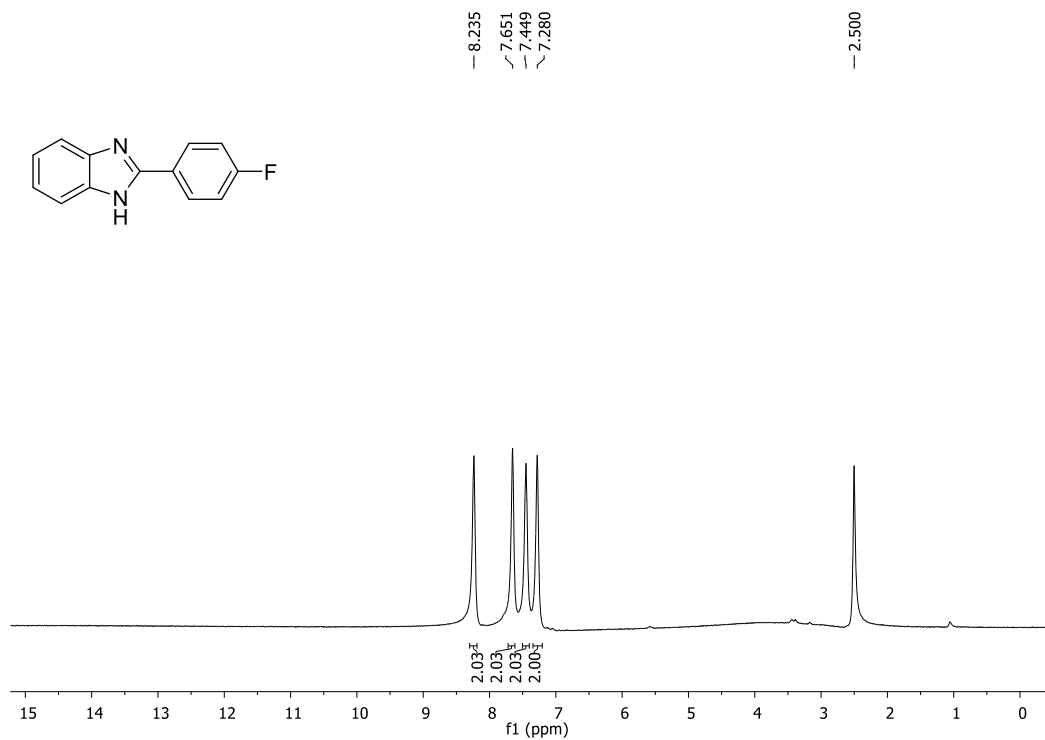
¹H NMR (600 MHz, DMSO-d₆) spectrum of **Sodium 1-hydroxy-4-phenylcyclohexane-1-sulfonate (u)**



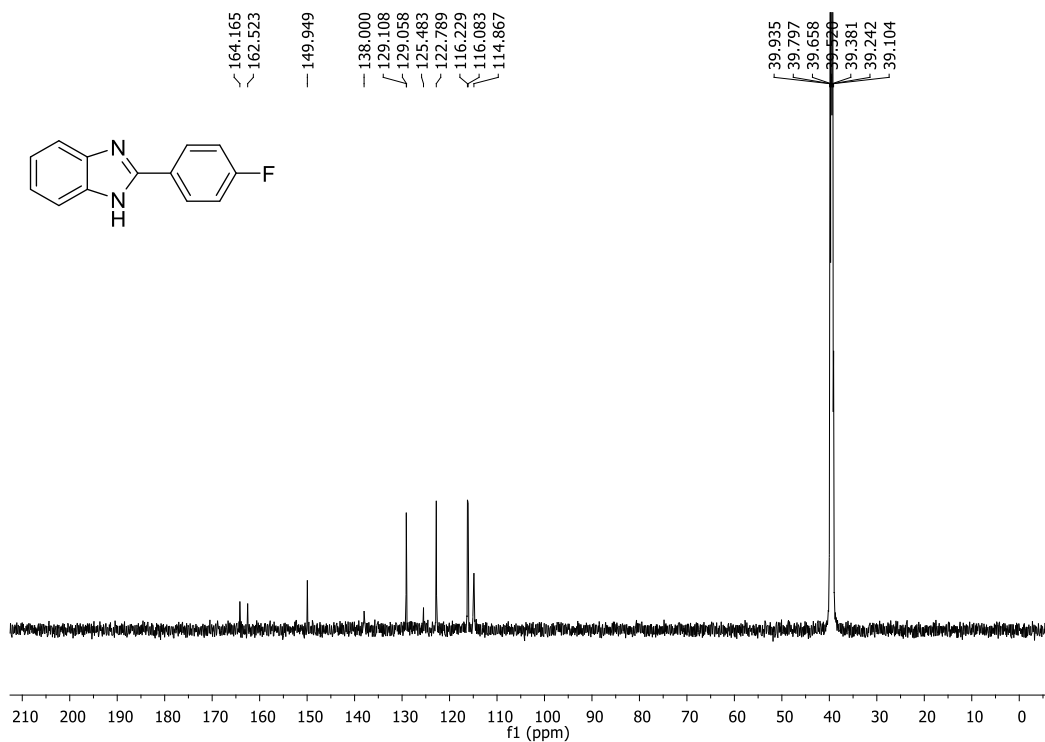
¹³C NMR (151 MHz, DMSO-d₆) spectrum of **Sodium 1-hydroxy-4-phenylcyclohexane-1-sulfonate (u)**



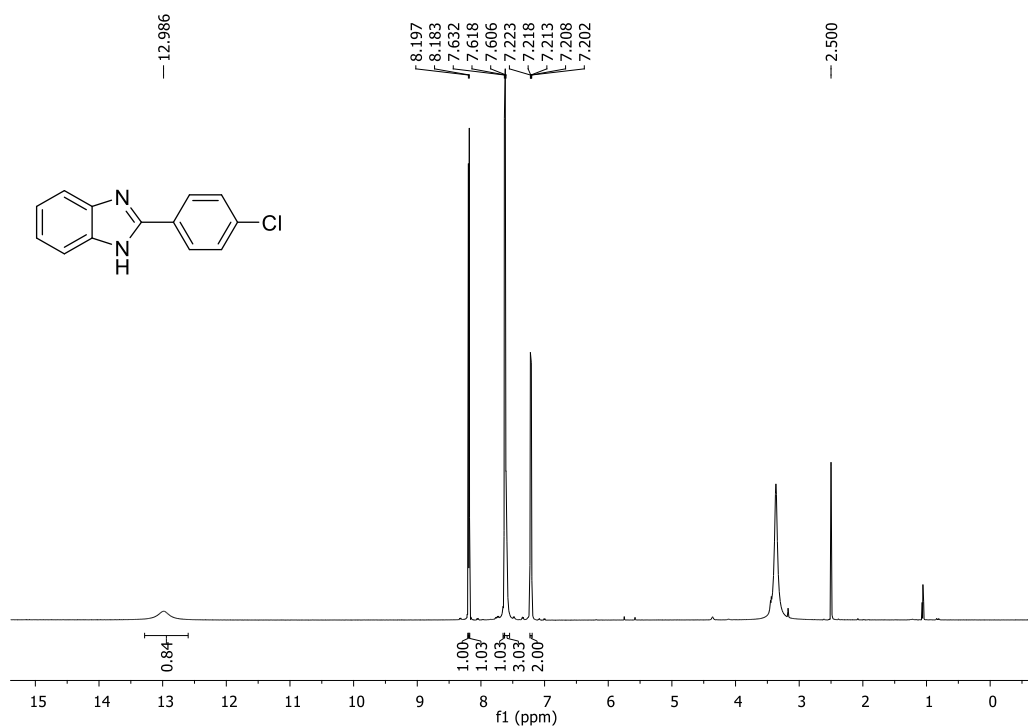
^1H NMR (600 MHz, DMSO- d_6) spectrum of **2-(4-Fluorophenyl)-1H-benzo[d]imidazole (3ab)**



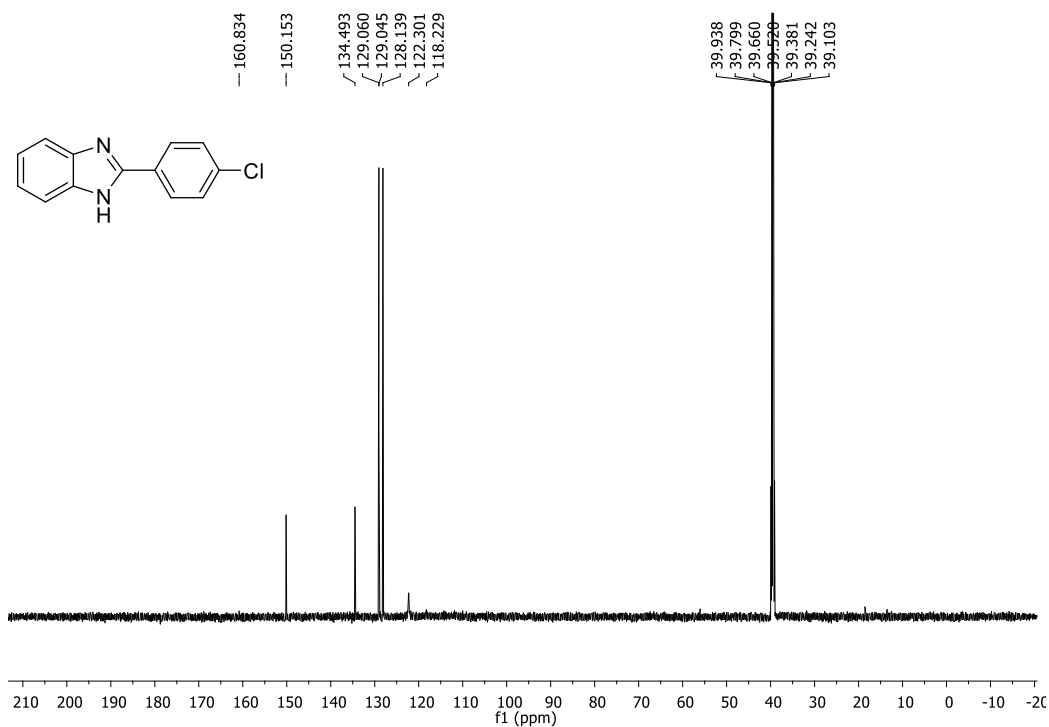
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of **2-(4-Fluorophenyl)-1H-benzo[d]imidazole (3ab)**



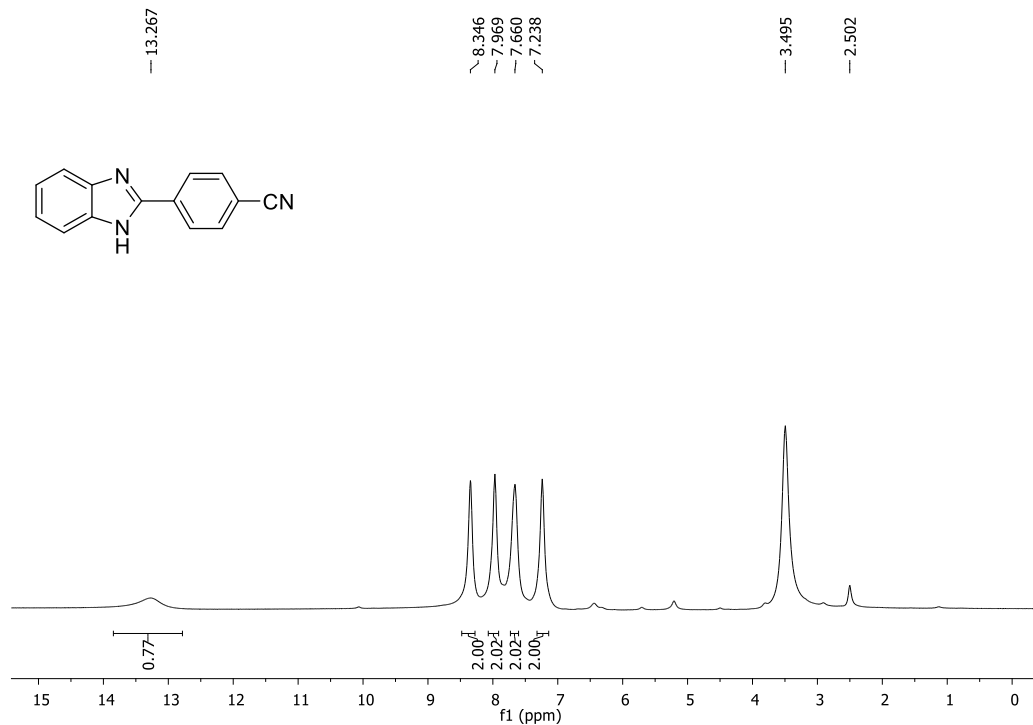
^1H NMR (600 MHz, DMSO- d_6) spectrum of **2-(4-Chlorophenyl)-1H-benzo[d]imidazole (3ac)**



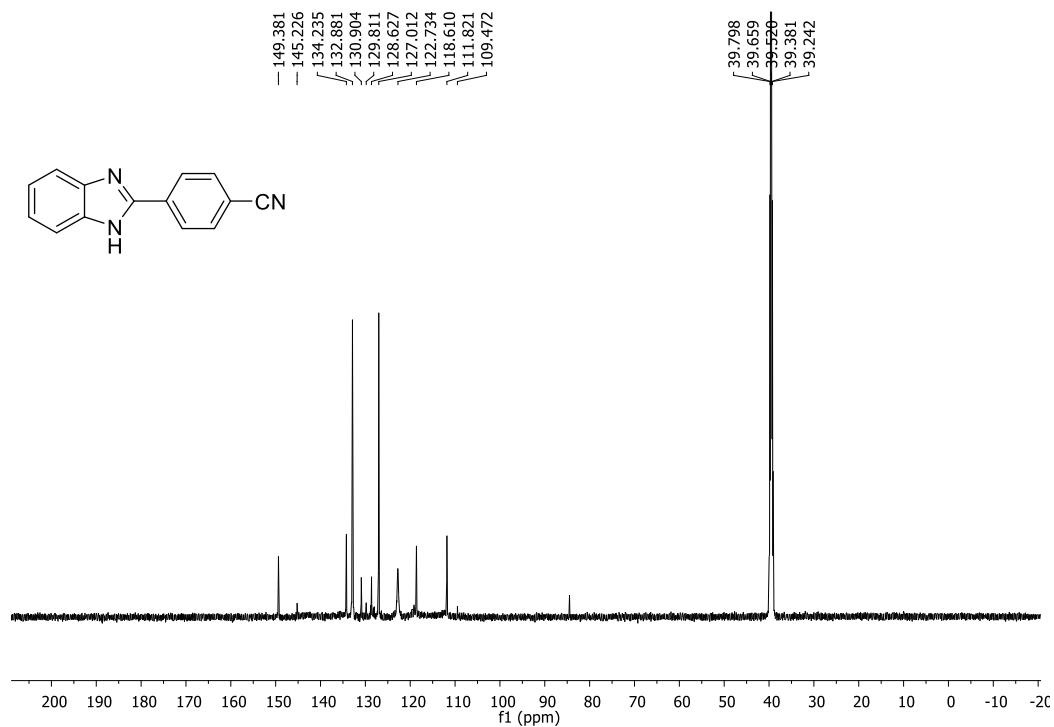
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of **2-(4-Chlorophenyl)-1H-benzo[d]imidazole (3ac)**



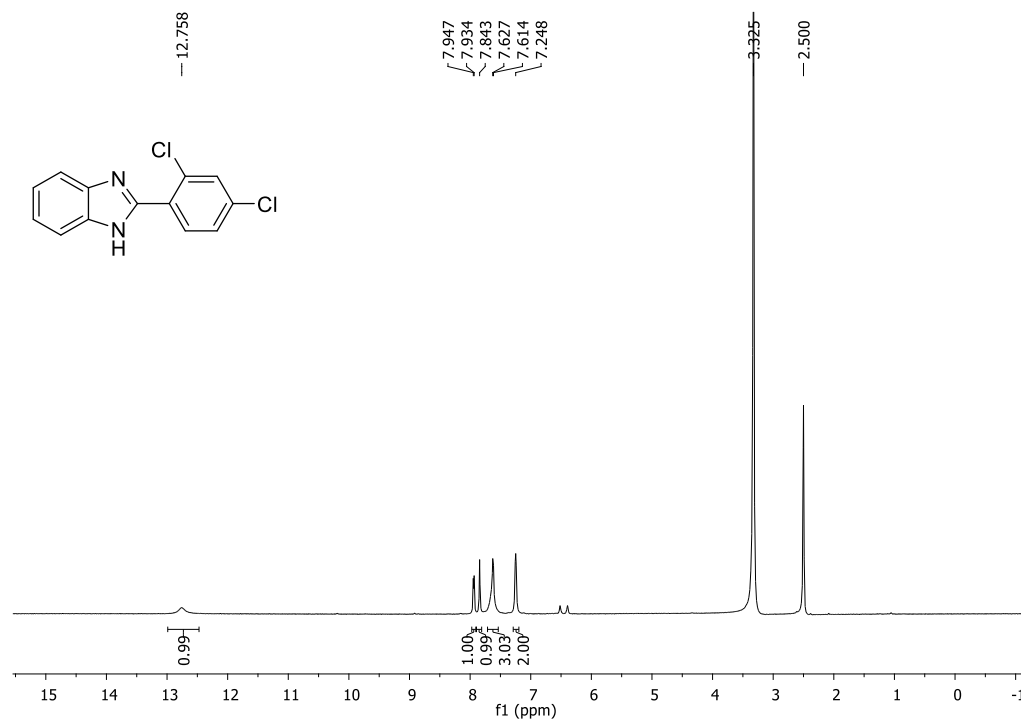
^1H NMR (600 MHz, DMSO- d_6) spectrum of **4-(1*H*-Benzo[d]imidazol-2-yl)benzonitrile (3ae)**



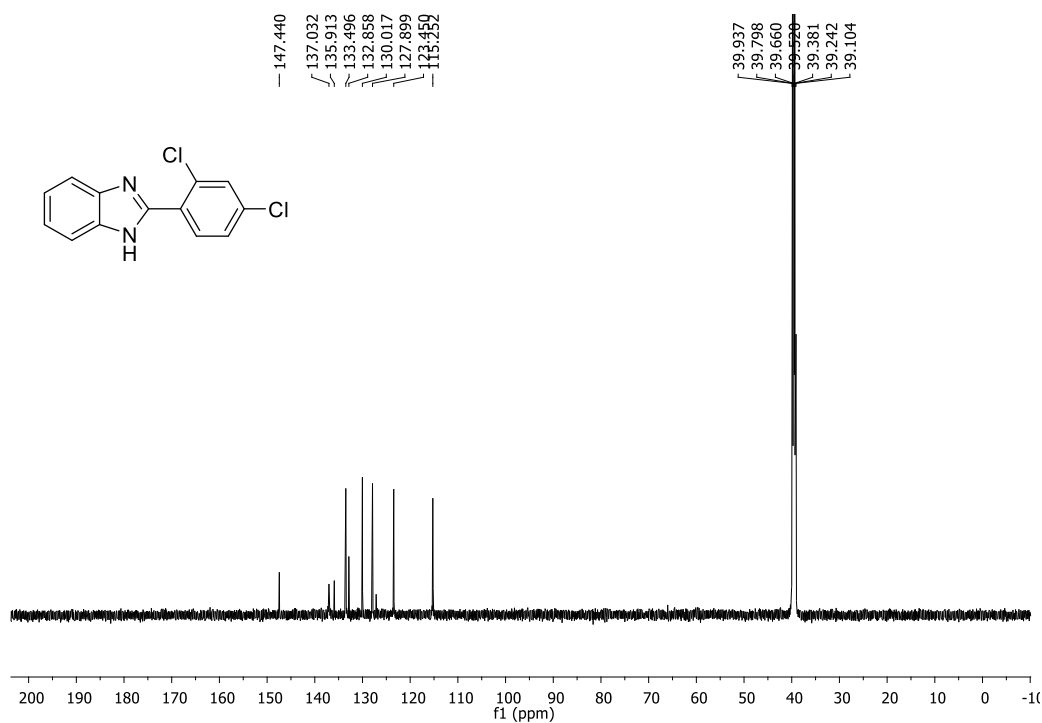
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of **4-(1*H*-Benzo[d]imidazol-2-yl)benzonitrile (3ae)**



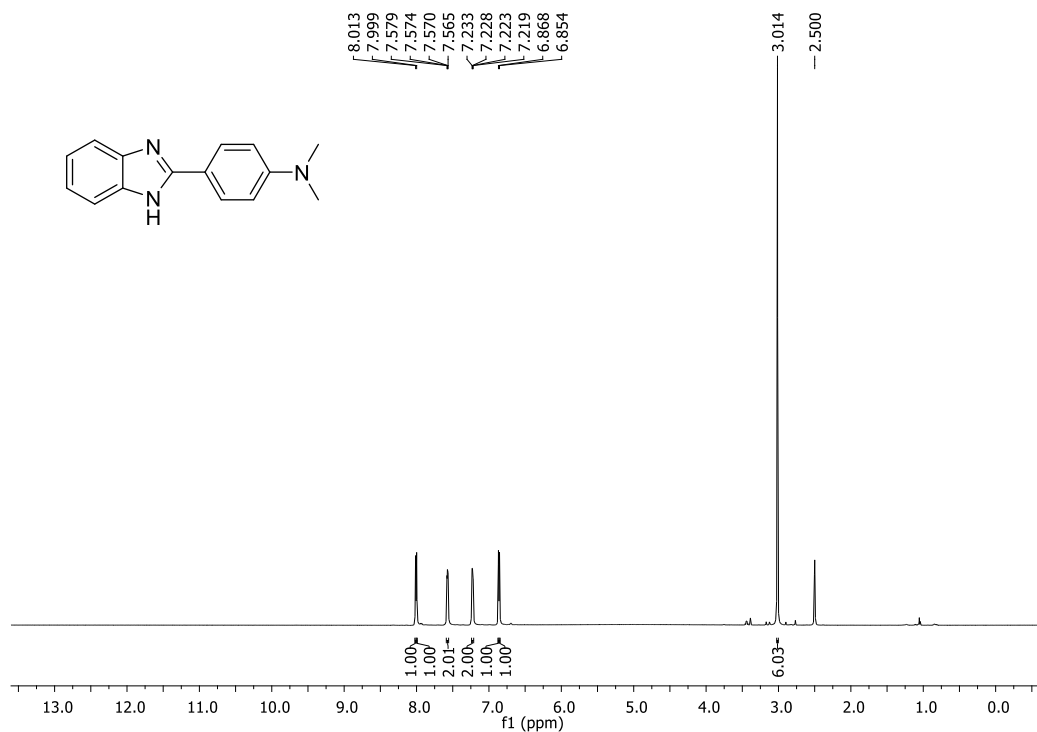
¹H NMR (600 MHz, DMSO-d₆) spectrum of **2-(2,4-Dichlorophenyl)-1H-benzo[d]imidazole (3ag)**



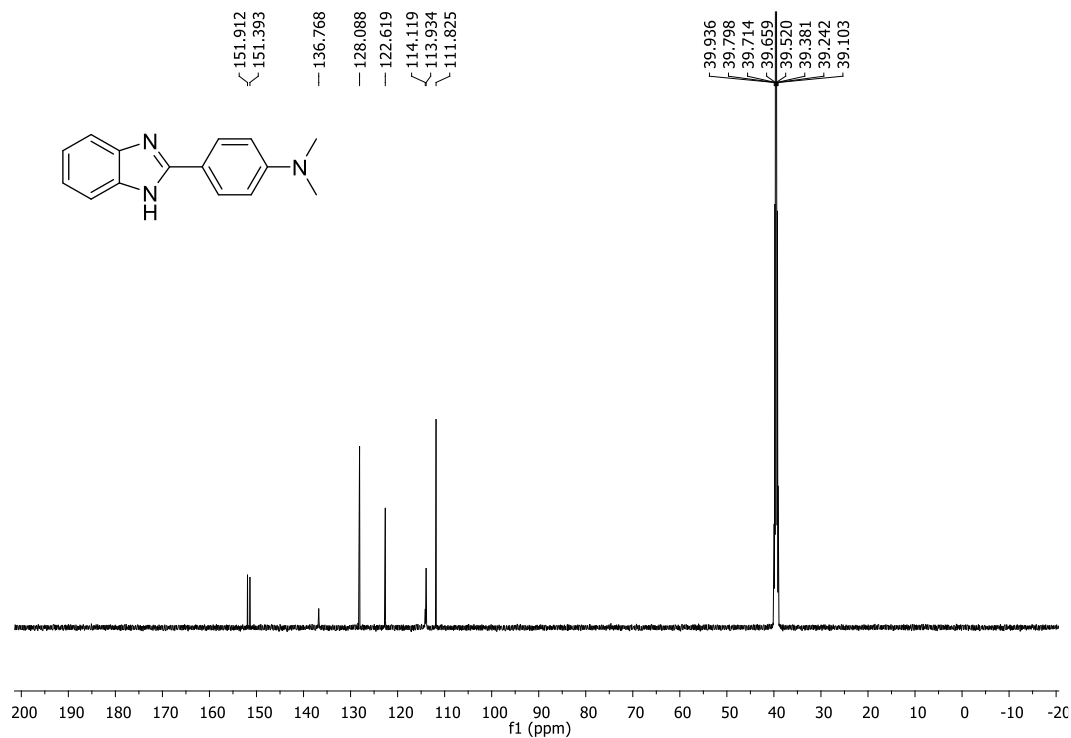
¹³C NMR (151 MHz, DMSO-d₆) spectrum of **2-(2,4-Dichlorophenyl)-1H-benzo[d]imidazole (3ag)**



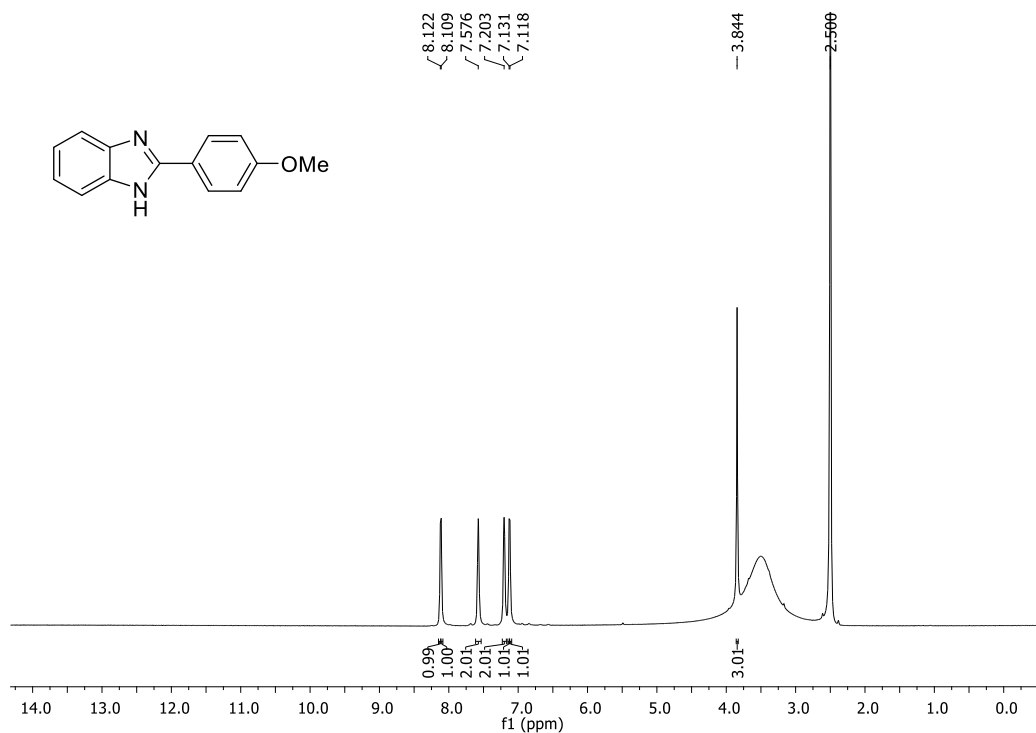
¹H NMR (600 MHz, DMSO-d₆) spectrum of **4-(1*H*-Benzo[d]imidazol-2-yl)-*N,N*-dimethylaniline (3ah)**



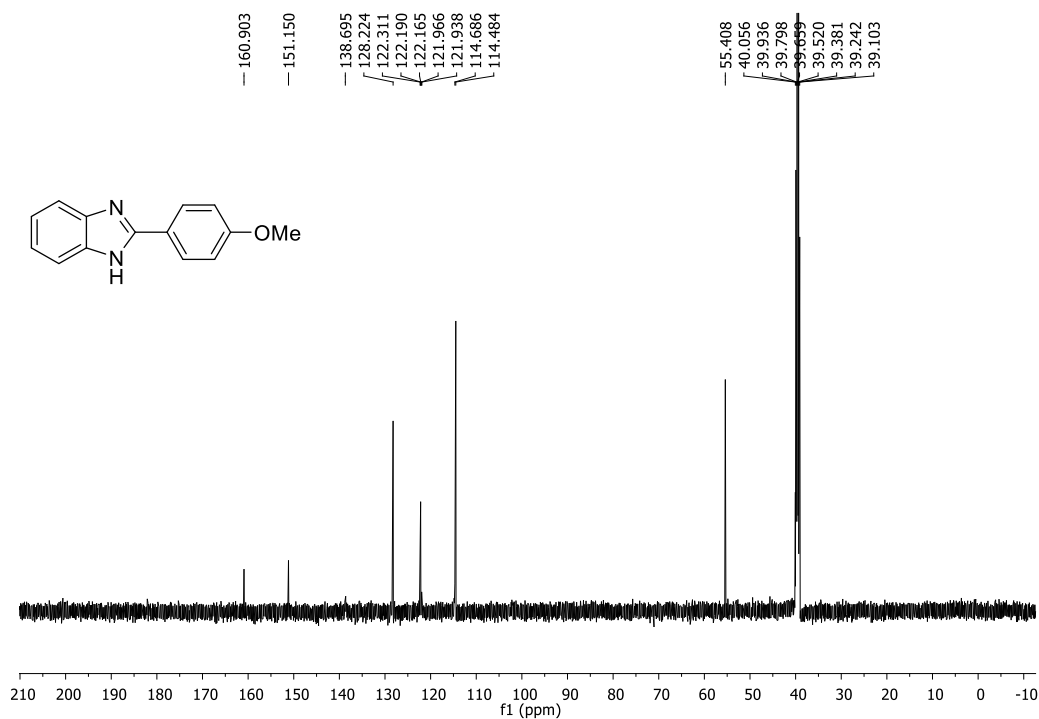
¹³C NMR (151 MHz, DMSO-d₆) spectrum of **4-(1*H*-Benzo[d]imidazol-2-yl)-*N,N*-dimethylaniline (3ah)**



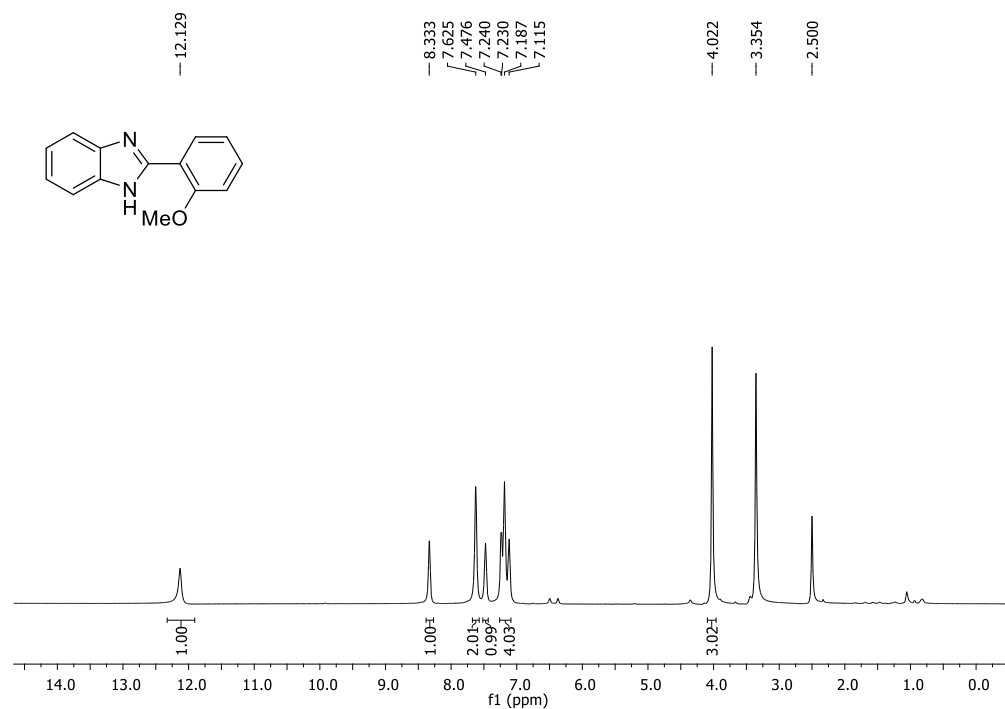
^1H NMR (600 MHz, DMSO-d_6) spectrum of **2-(4-Methoxyphenyl)-1H-benzo[d]imidazole (3ai)**



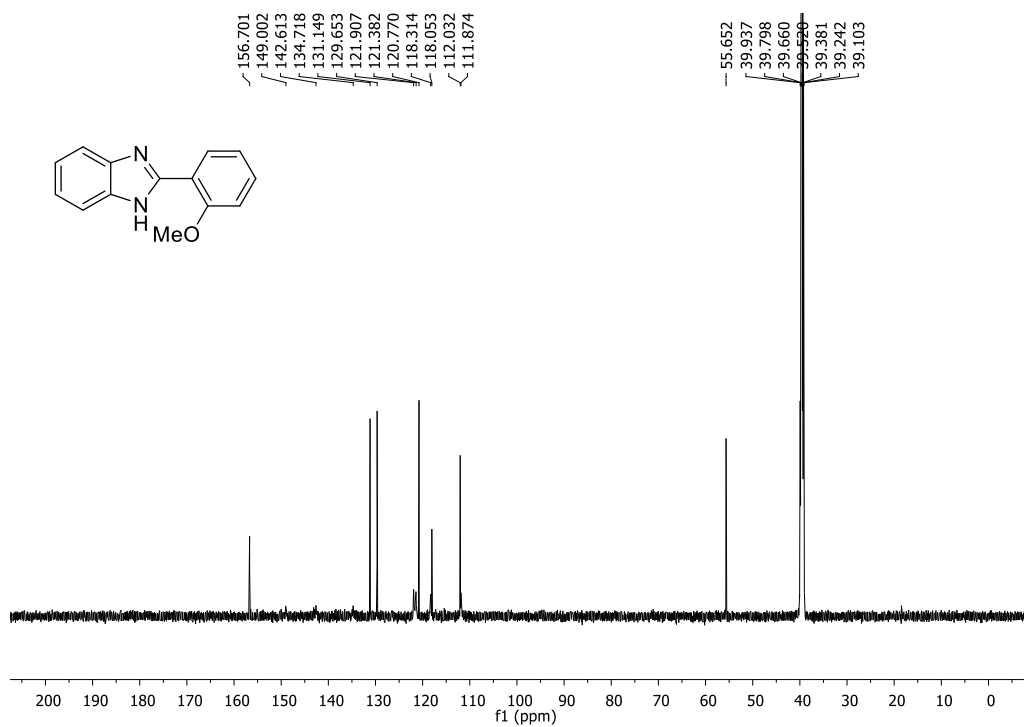
^{13}C NMR (151 MHz, DMSO-d_6) spectrum of **2-(4-Methoxyphenyl)-1H-benzo[d]imidazole (3ai)**



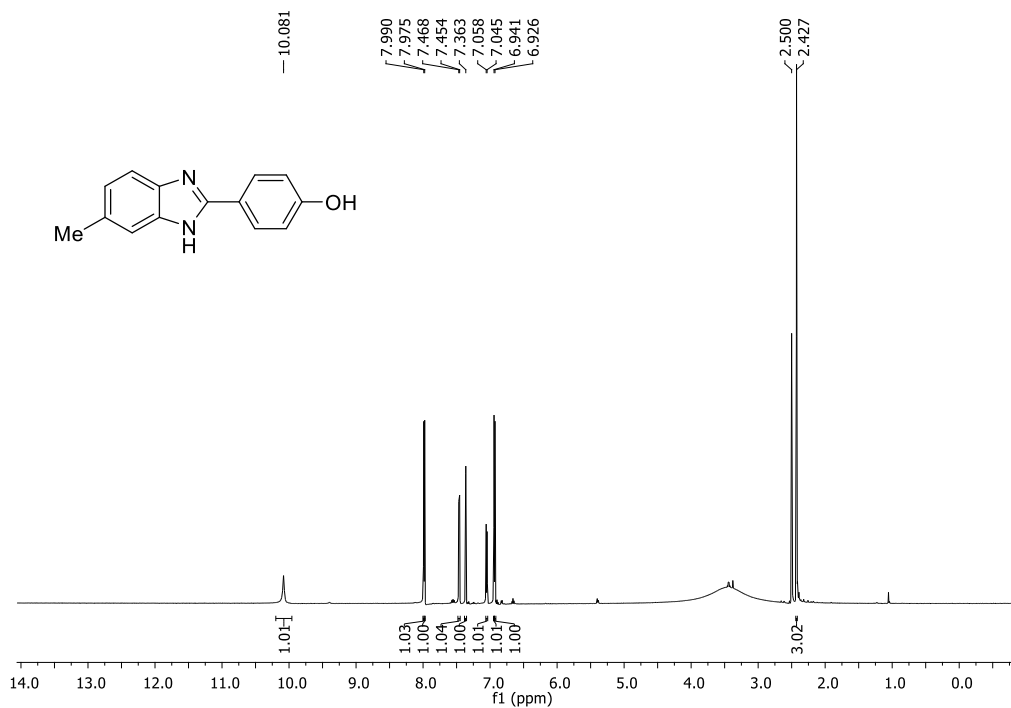
¹H NMR (600 MHz, DMSO-d₆) spectrum of **2-(2-Methoxyphenyl)-1H-benzo[d]imidazole (3aj)**



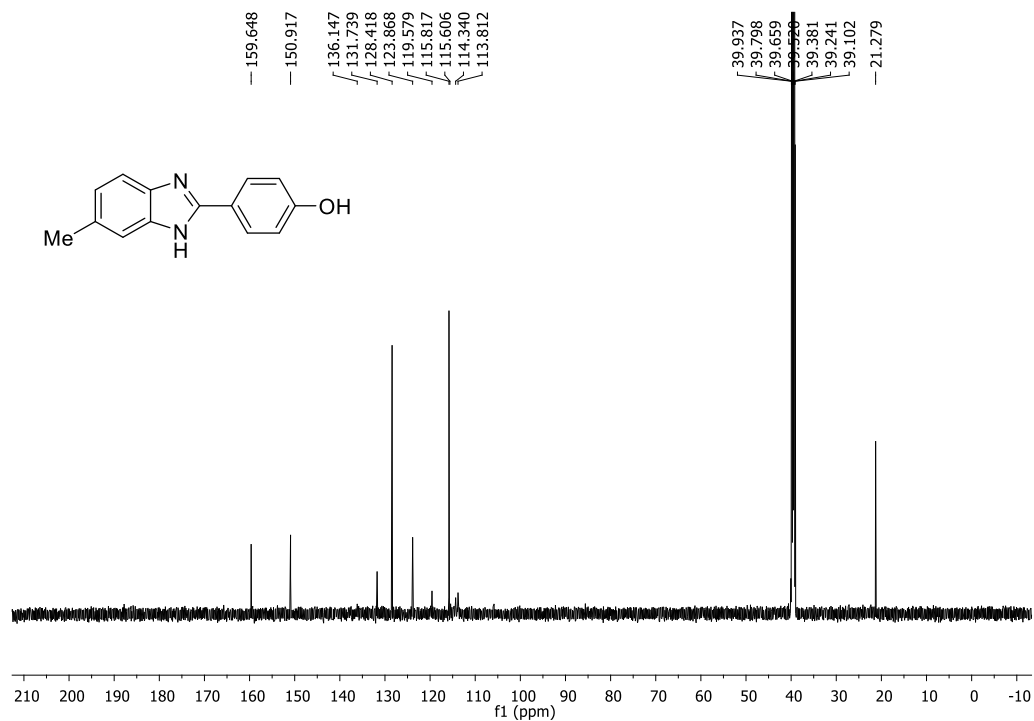
¹³C NMR (151 MHz, DMSO-d₆) spectrum of **2-(2-Methoxyphenyl)-1H-benzo[d]imidazole (3aj)**



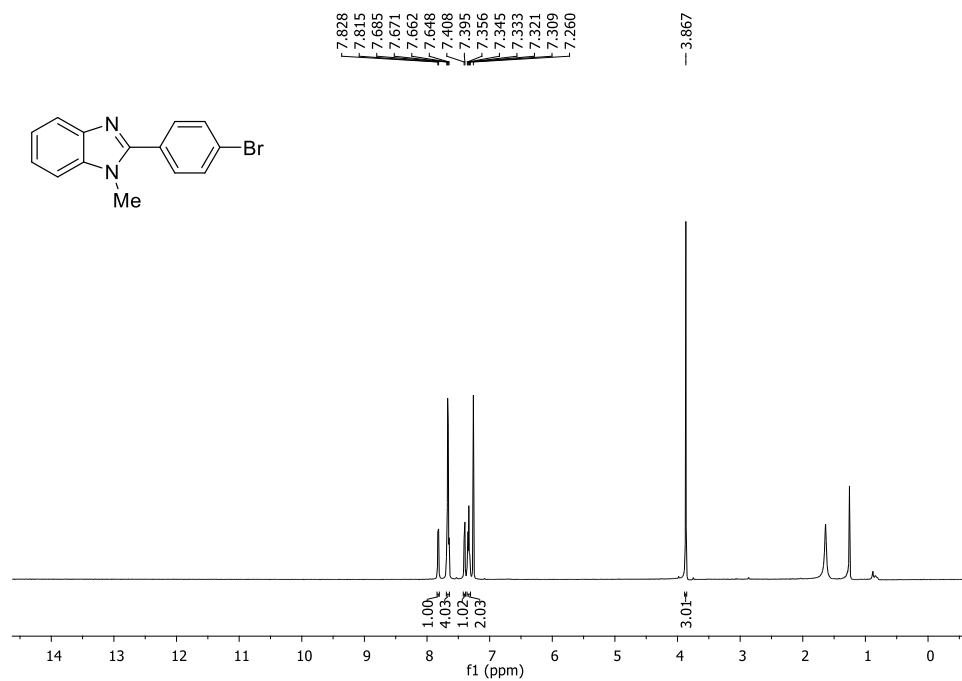
¹H NMR (600 MHz, DMSO-d₆) spectrum of **4-(6-Methyl-1*H*-benzo[d]imidazol-2-yl)phenol (3bk)**



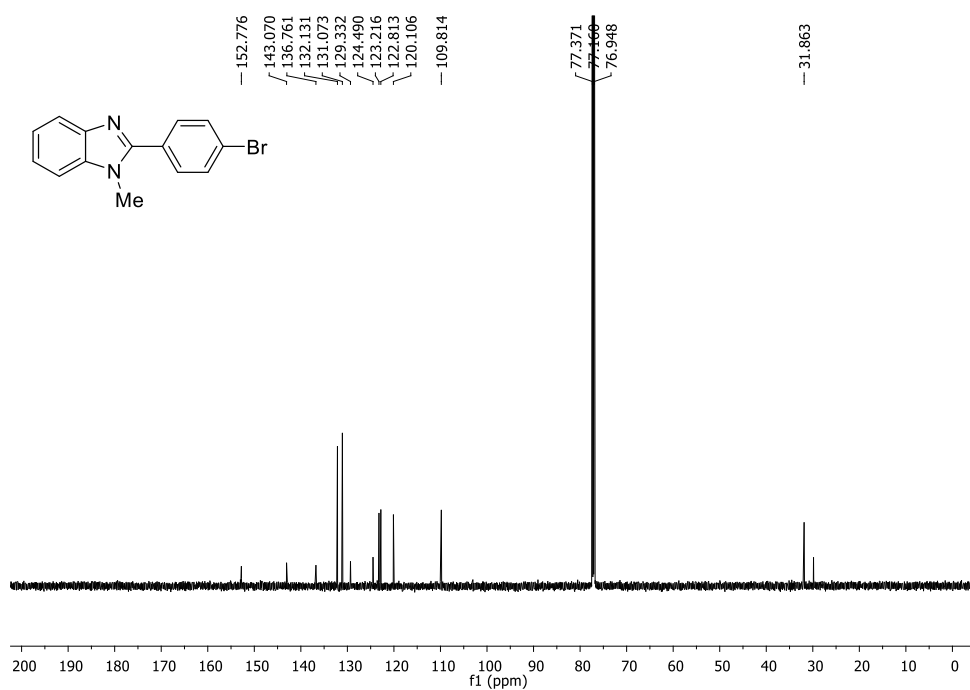
¹³C NMR (151 MHz, DMSO-d₆) spectrum of **4-(6-Methyl-1*H*-benzo[d]imidazol-2-yl)phenol (3bk)**



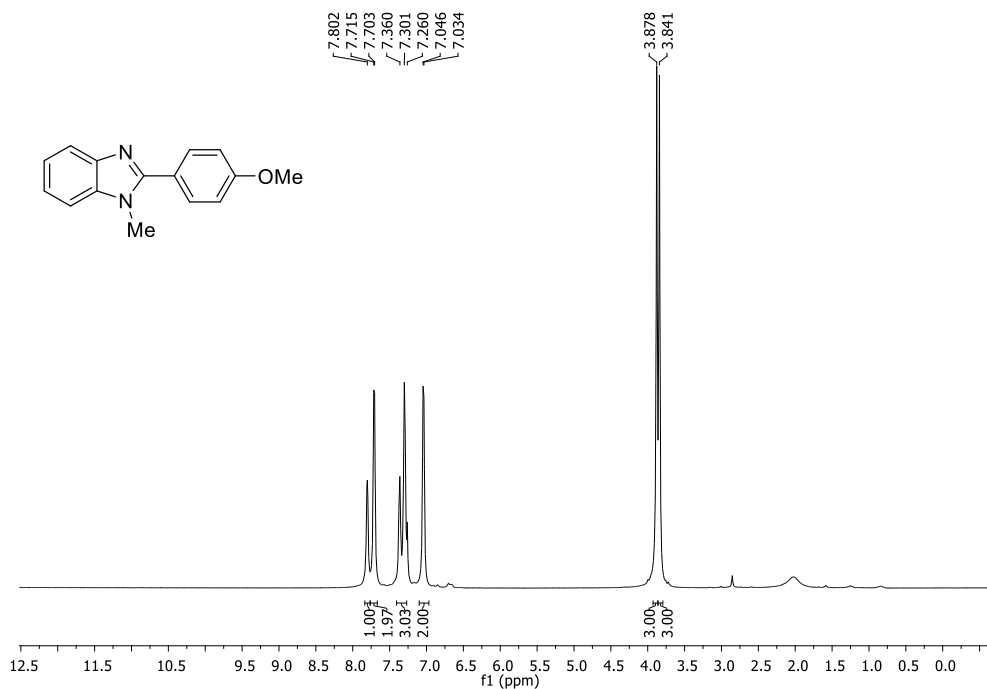
^1H NMR (600 MHz, CDCl_3) spectrum of **2-(4-Bromophenyl)-1-methyl-1H-benzo[d]imidazole (3cd)**



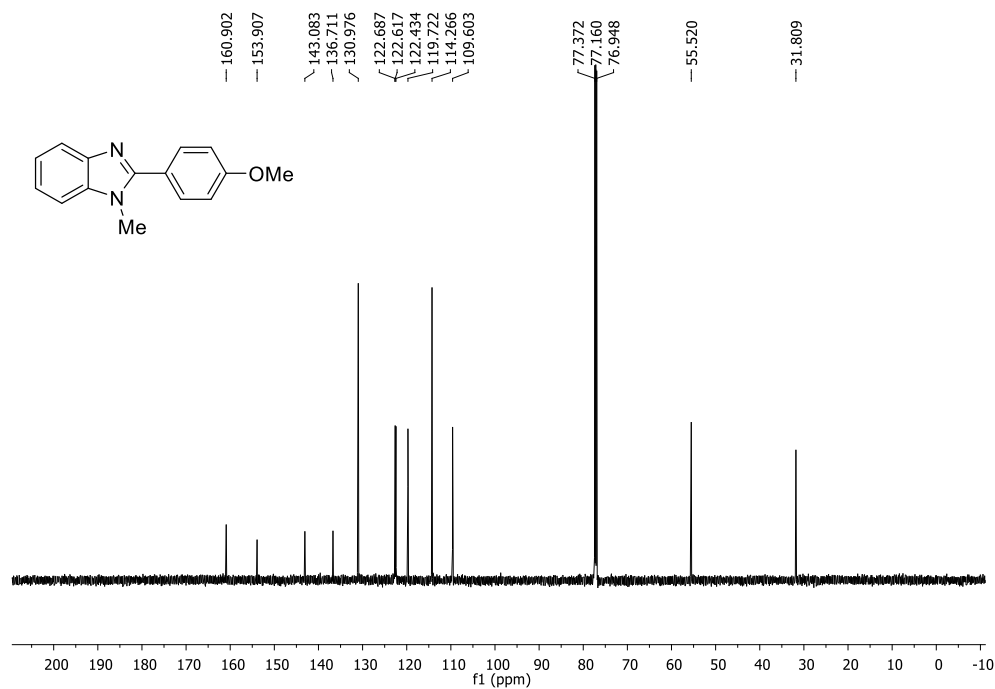
^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-(4-Bromophenyl)-1-methyl-1H-benzo[d]imidazole (3cd)**



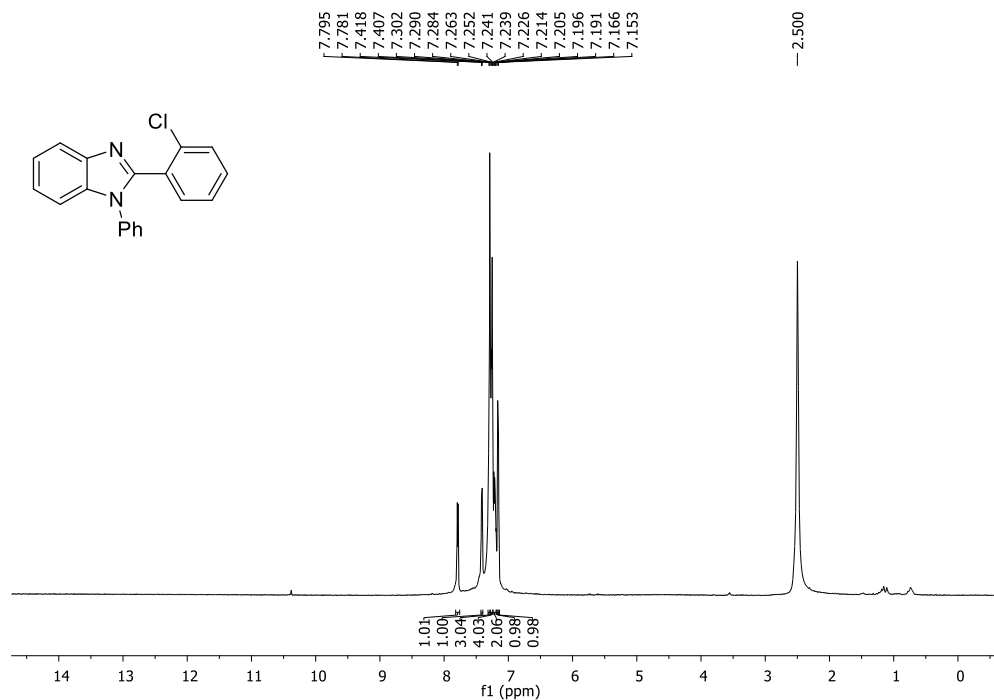
¹H NMR (600 MHz, CDCl₃) spectrum of **2-(4-Methoxyphenyl)-1-methyl-1H-benzo[d]imidazole (3ci)**



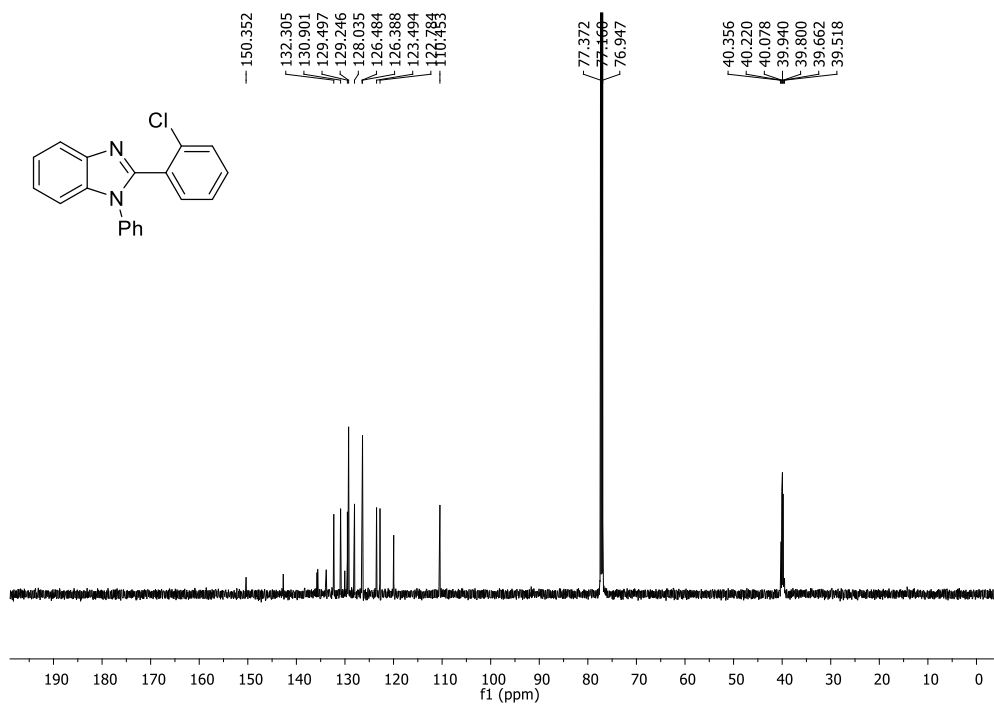
¹³C NMR (151 MHz, CDCl₃) spectrum of **2-(4-Methoxyphenyl)-1-methyl-1H-benzo[d]imidazole (3ci)**



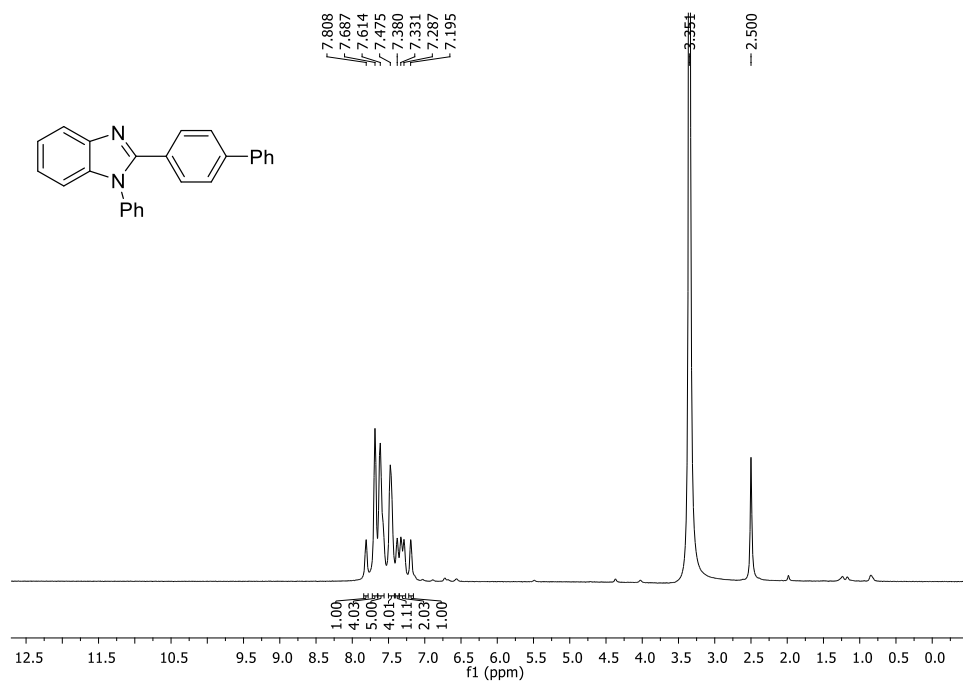
^1H NMR (600 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$) spectrum of **2-(2-Chlorophenyl)-1-phenyl-1H-benzo[d]imidazole (3df)**



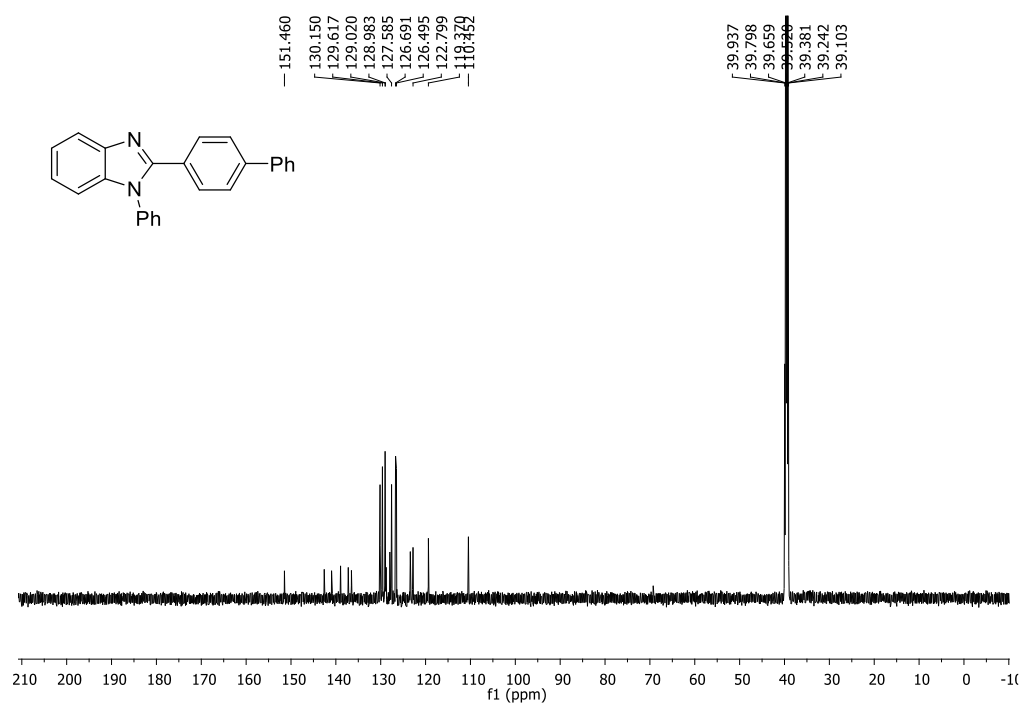
^{13}C NMR (151 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$) spectrum of **2-(2-Chlorophenyl)-1-phenyl-1H-benzo[d]imidazole (3df)**



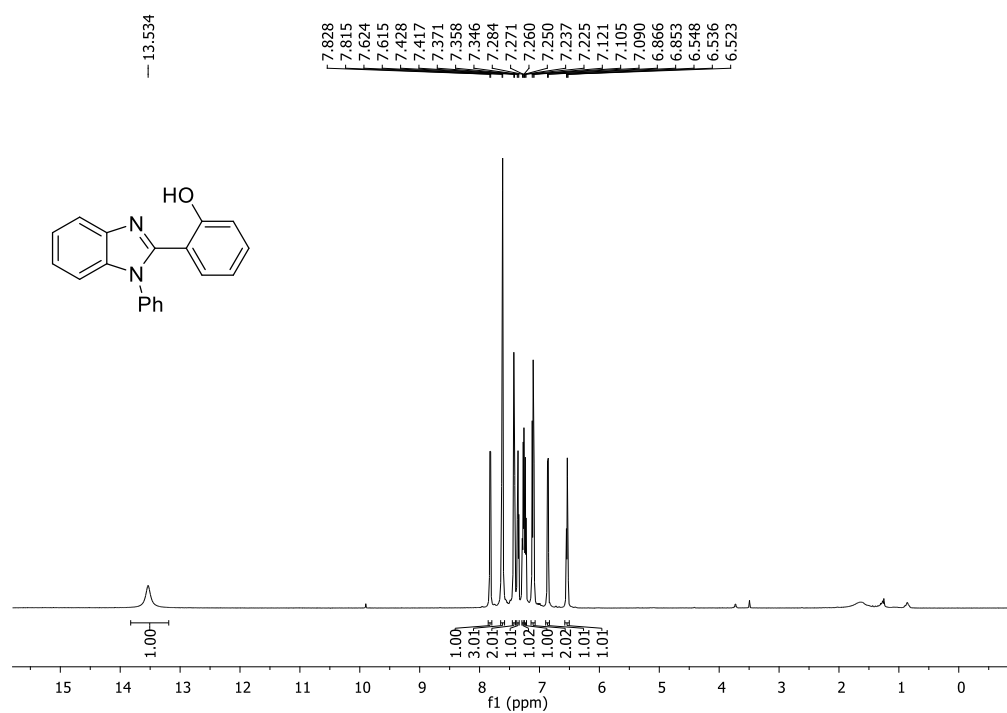
¹H NMR (600 MHz, DMSO-d₆) spectrum of 2-([1,1'-Biphenyl]-4-yl)-1-phenyl-1*H*-benzo[d]imidazole (3dm)



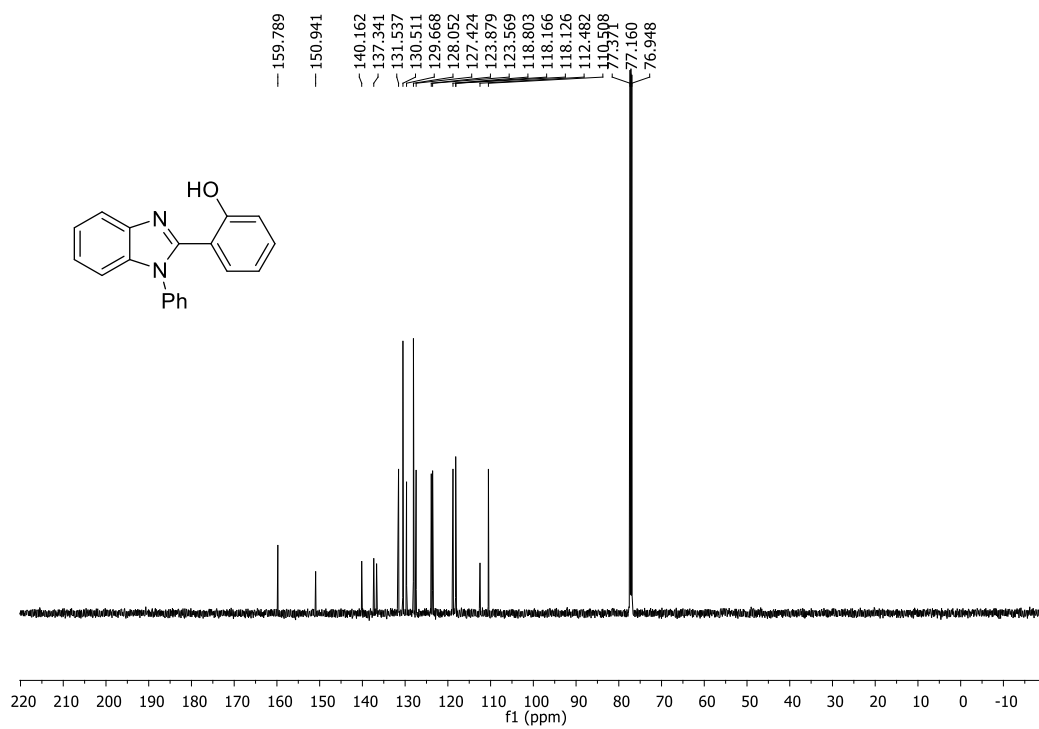
¹³C NMR (151 MHz, DMSO-d₆) spectrum of 2-([1,1'-Biphenyl]-4-yl)-1-phenyl-1*H*-benzo[d]imidazole (3dm)



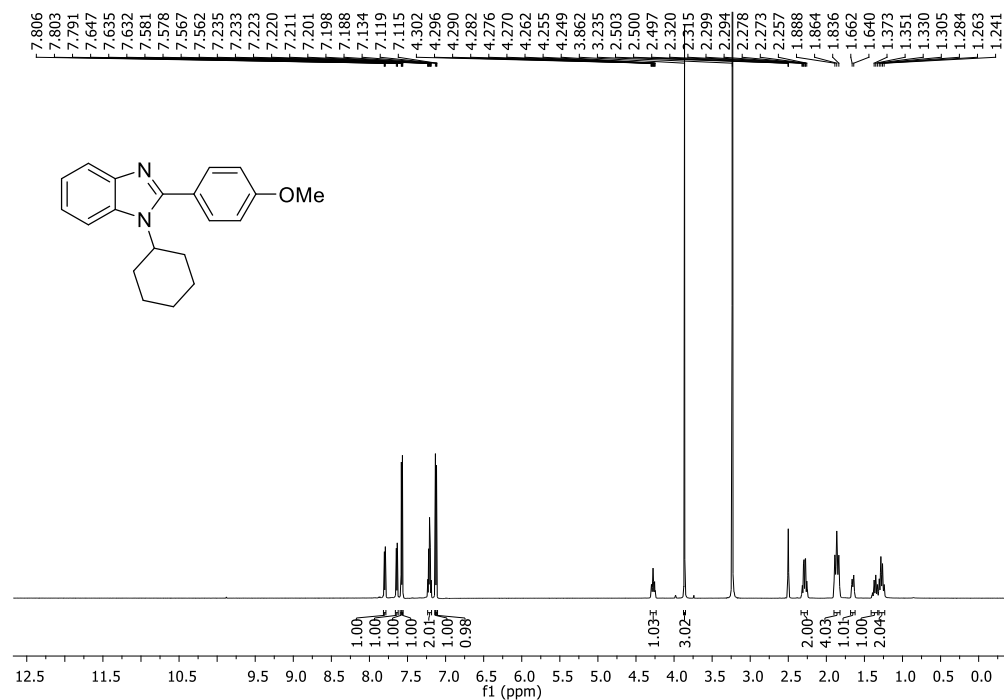
^1H NMR (600 MHz, CDCl_3) spectrum of **2-(1-Phenyl-1H-benzo[d]imidazol-2-yl)phenol (3dn)**



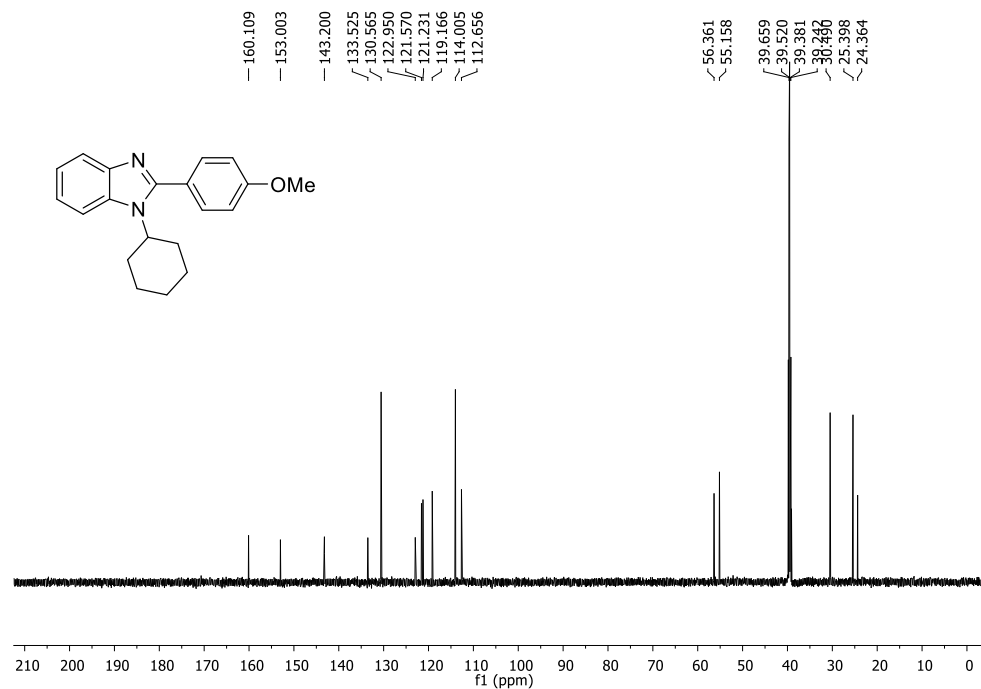
^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-(1-Phenyl-1H-benzo[d]imidazol-2-yl)phenol (3dn)**



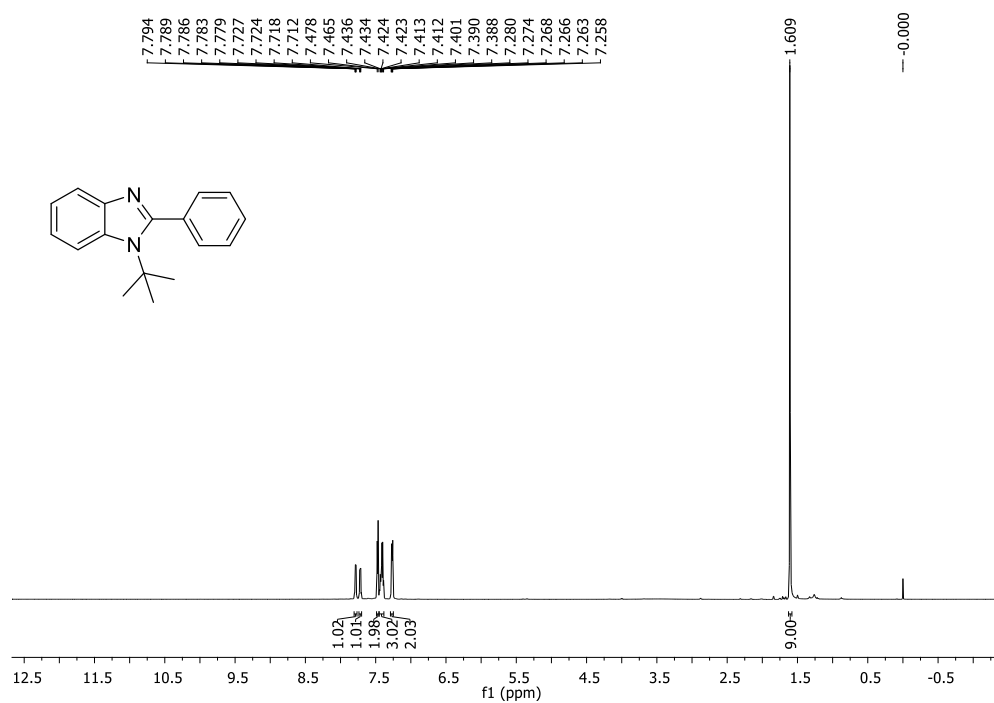
¹H NMR (600 MHz, DMSO-d₆) spectrum of **1-Cyclohexyl-2-(4-methoxyphenyl)-1H-benzo[d]imidazole (3fi)**



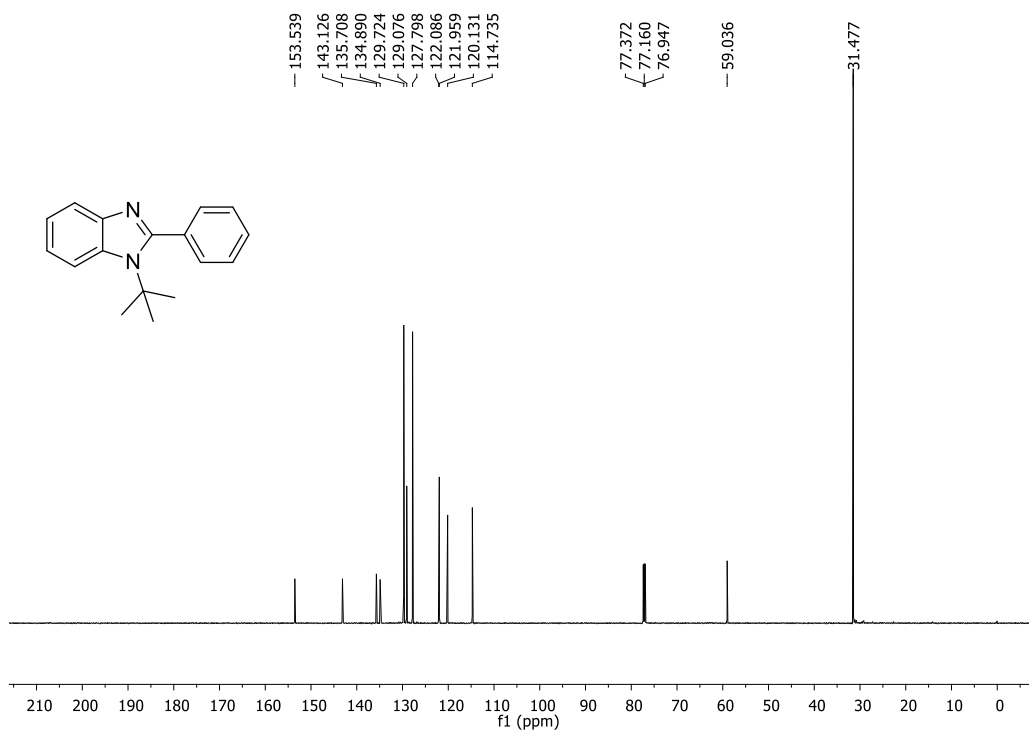
¹³C NMR (151 MHz, DMSO-d₆) spectrum of **1-Cyclohexyl-2-(4-methoxyphenyl)-1H-benzo[d]imidazole (3fi)**



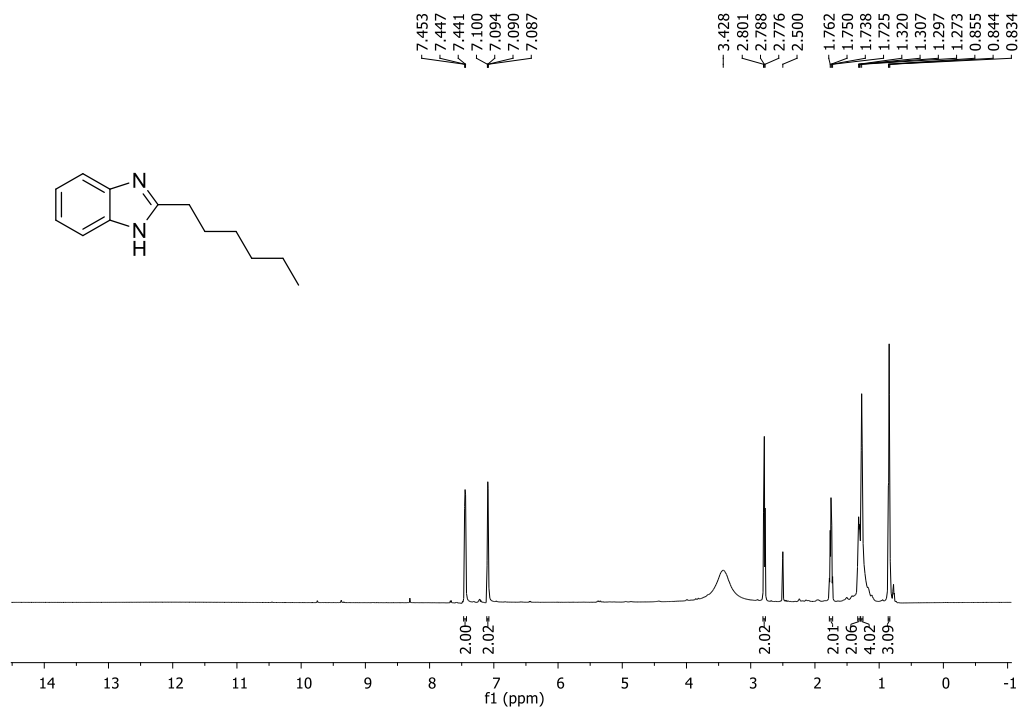
^1H NMR (600 MHz, CDCl_3) spectrum of **1-(Tert-butyl)-2-phenyl-1H-benzo[d]imidazole (3ga)**



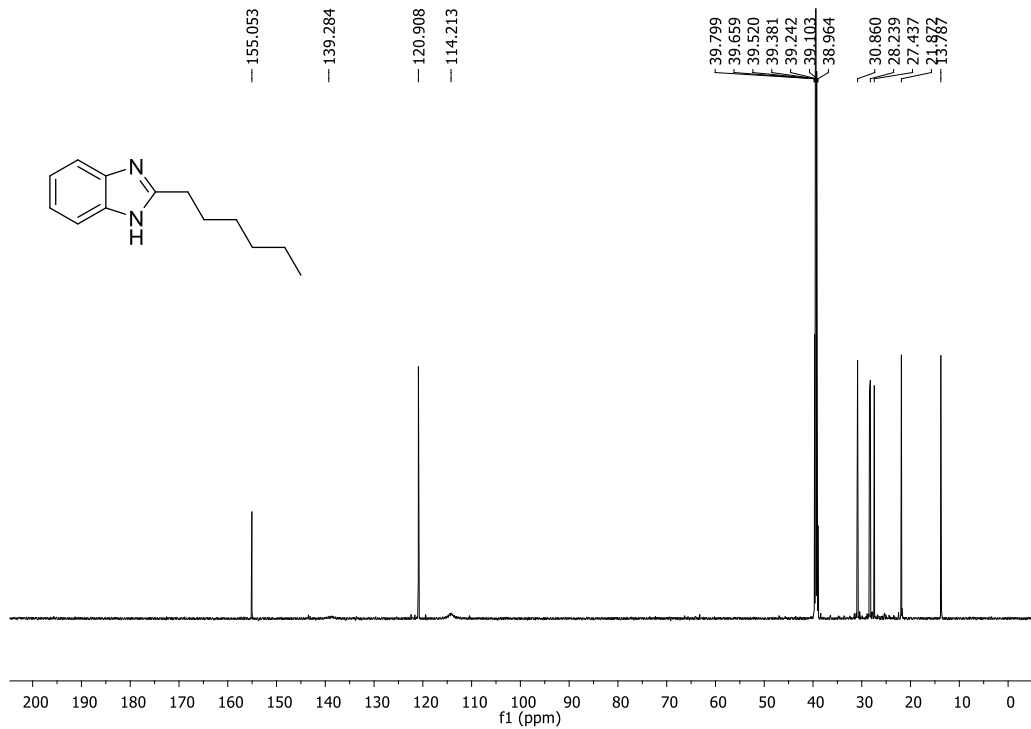
^{13}C NMR (151 MHz, CDCl_3) spectrum of **1-(Tert-butyl)-2-phenyl-1H-benzo[d]imidazole (3ga)**



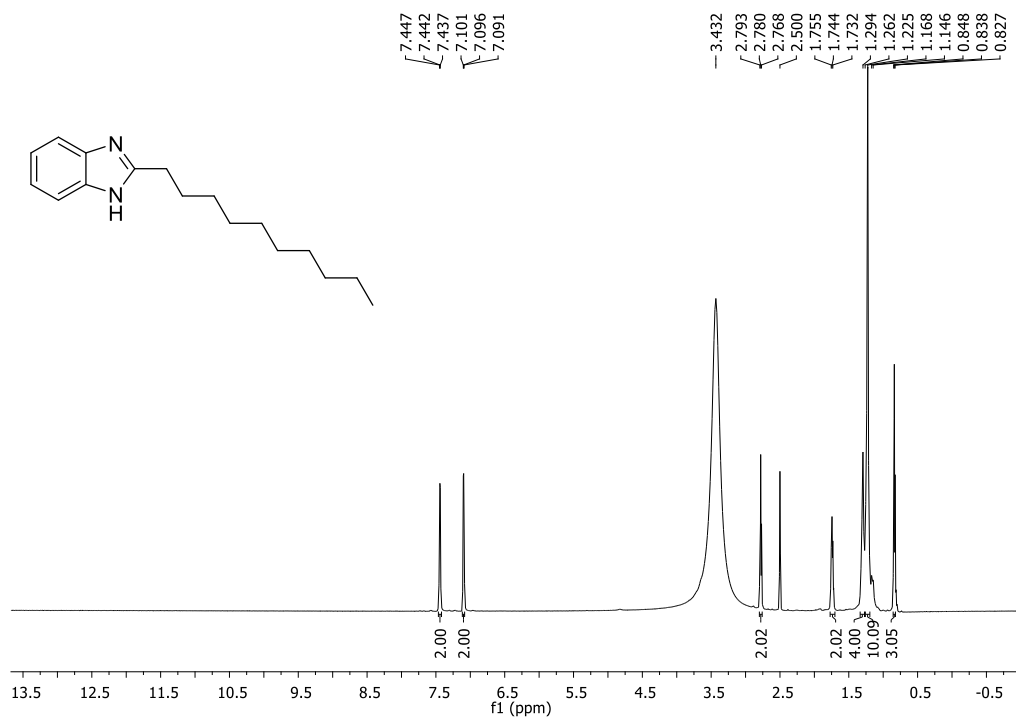
^1H NMR (600 MHz, DMSO- d_6) spectrum of **2-Hexyl-1H-benzo[d]imidazole (3ao)**



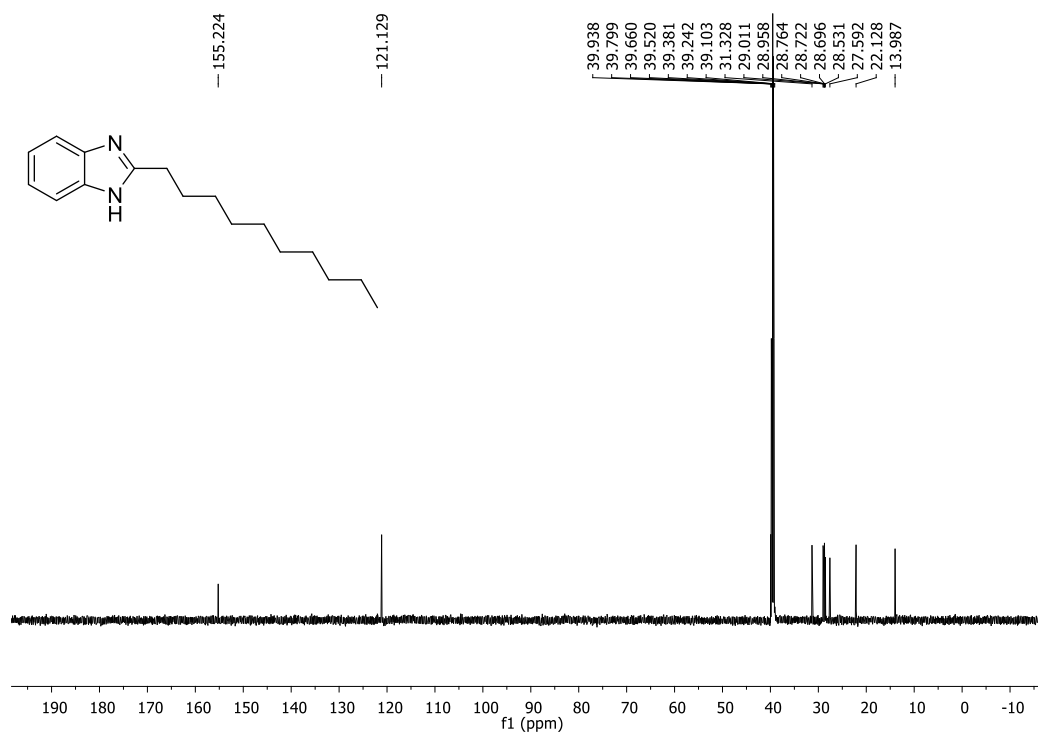
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of **2-Hexyl-1H-benzo[d]imidazole (3ao)**



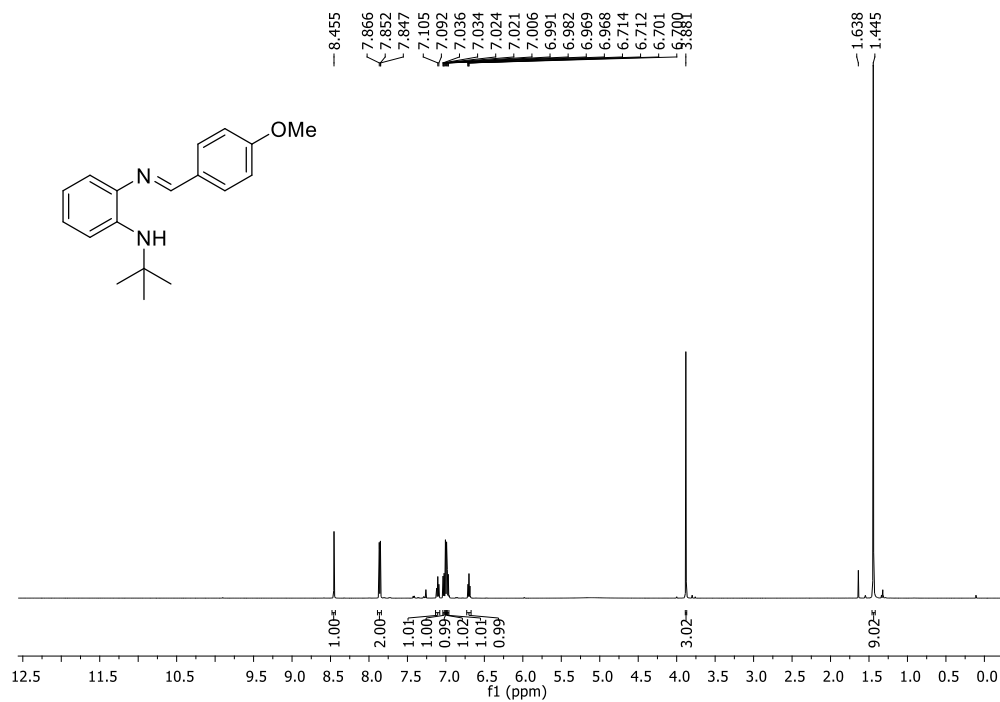
^1H NMR (600 MHz, DMSO- d_6) spectrum of **2-Decyl-1H-benzo[d]imidazole (3ap)**



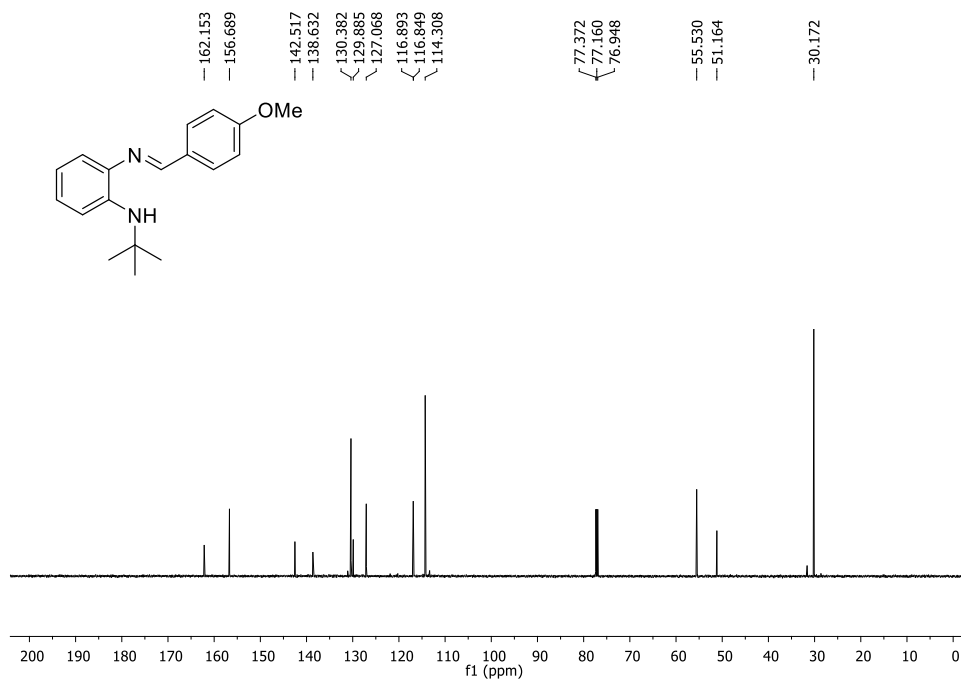
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of **2-Decyl-1H-benzo[d]imidazole (3ap)**



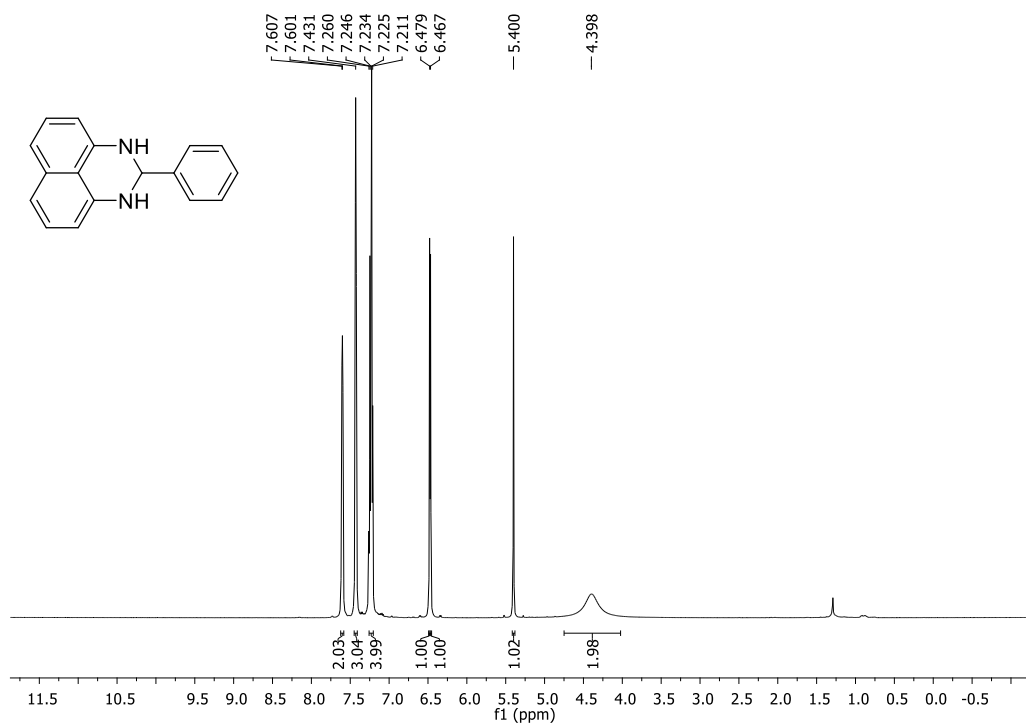
¹H NMR (600 MHz, CDCl₃) spectrum of (E)-N-(Tert-butyl)-2-((4-methoxybenzylidene)amino)aniline (3ga')



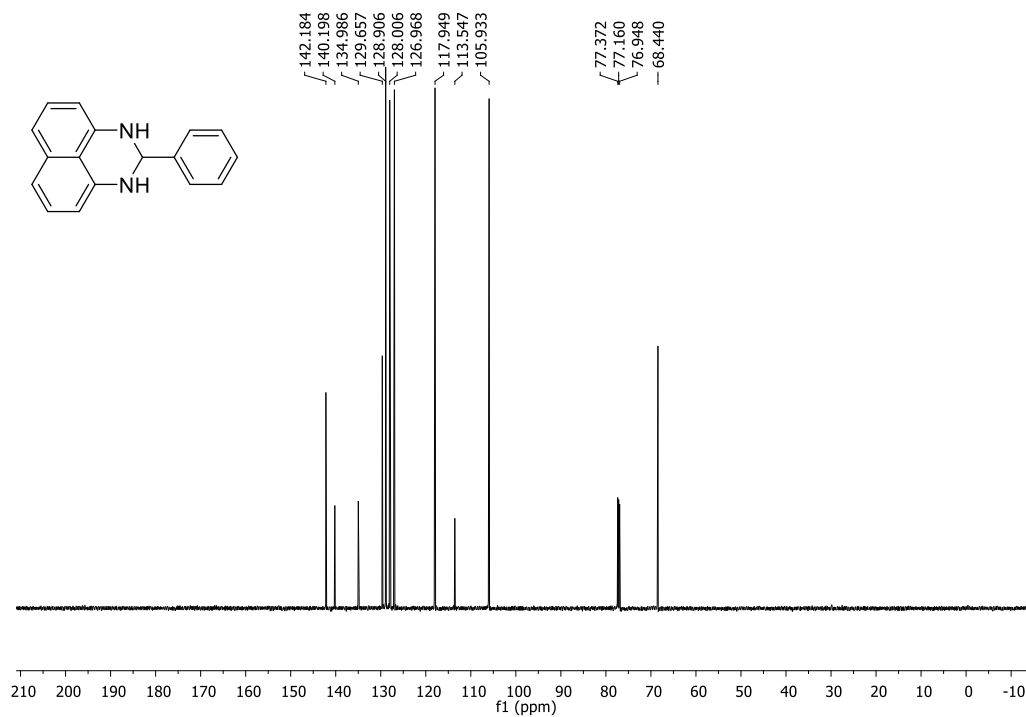
¹³C NMR (151 MHz, CDCl₃) spectrum of (E)-N-(Tert-butyl)-2-((4-methoxybenzylidene)amino)aniline (3ga')



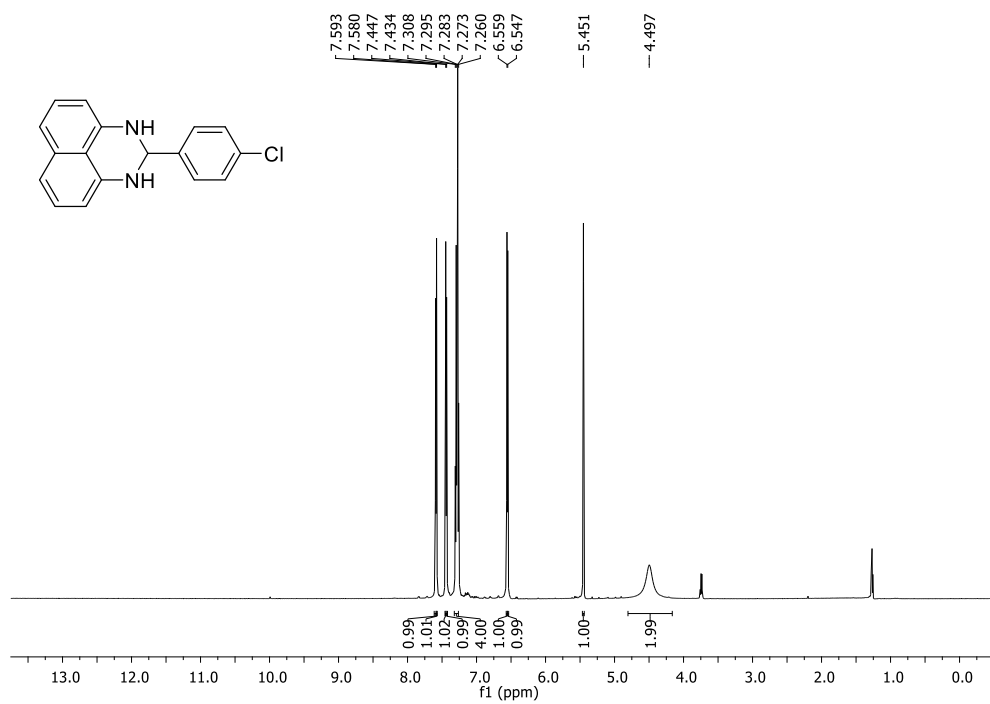
^1H NMR (600 MHz, CDCl_3) spectrum of **2-Phenyl-2,3-dihydro-1H-perimidine (4a)**



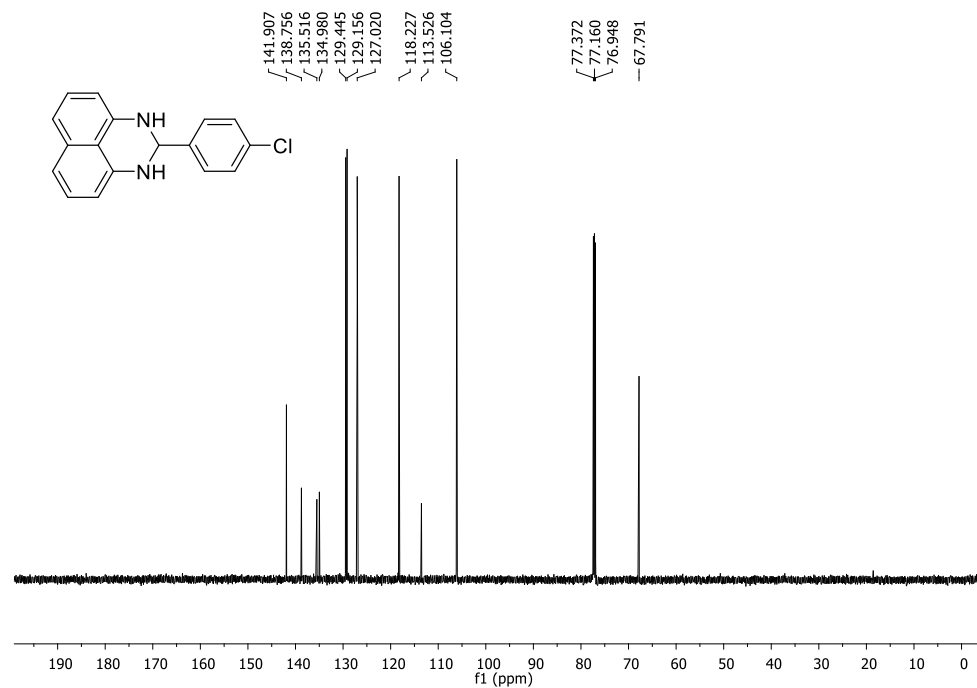
^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-Phenyl-2,3-dihydro-1H-perimidine (4a)**



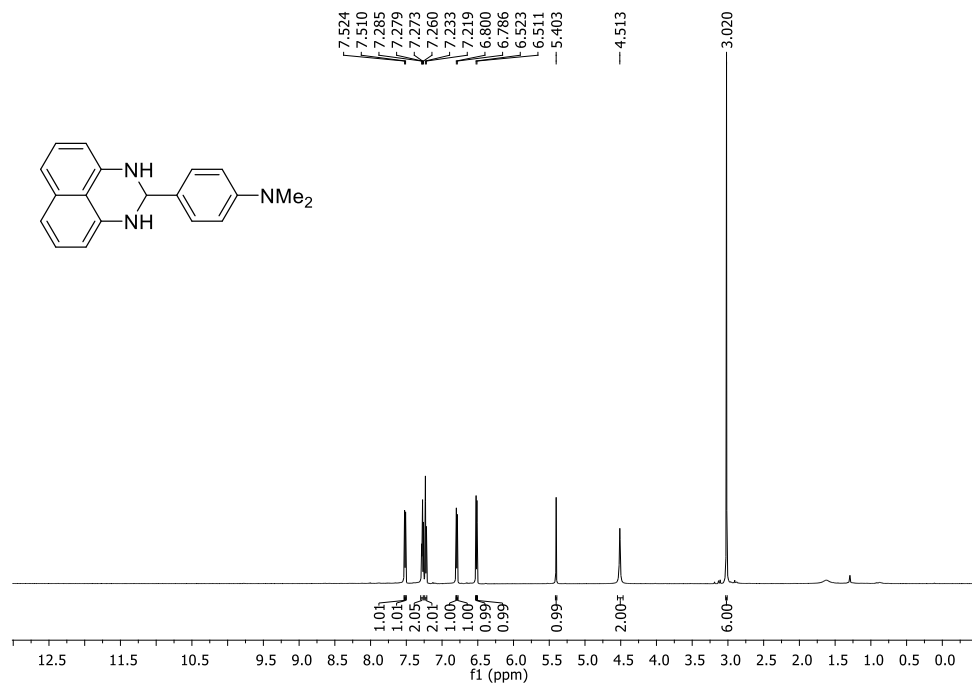
^1H NMR (600 MHz, CDCl_3) spectrum of **2-(4-Chlorophenyl)-2,3-dihydro-1H-perimidine (4c)**



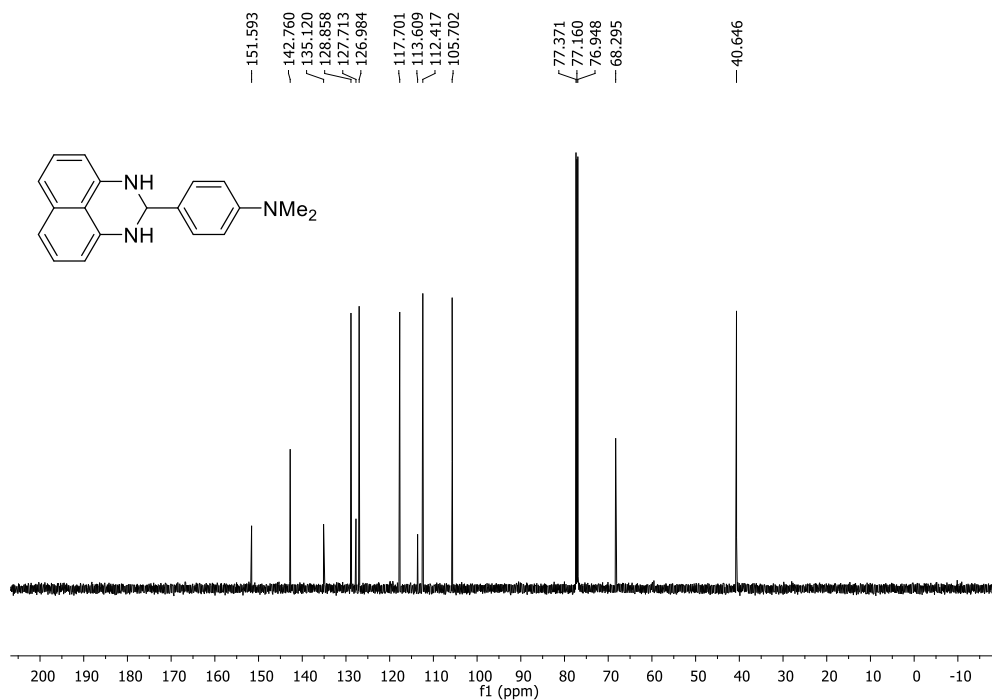
^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-(4-Chlorophenyl)-2,3-dihydro-1H-perimidine (4c)**



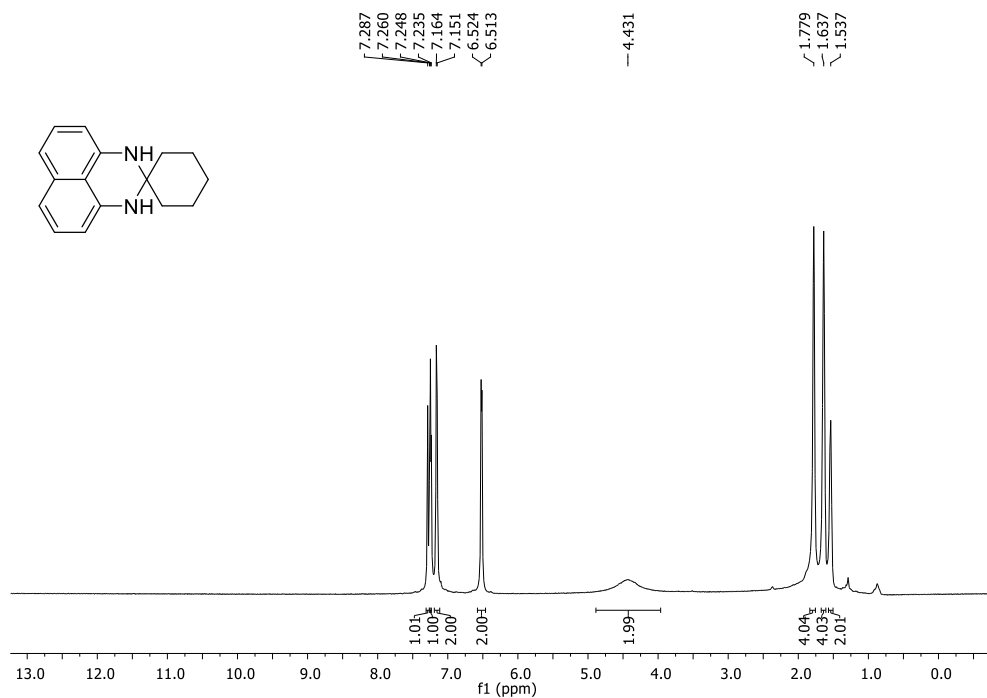
¹H NMR (600 MHz, CDCl₃) spectrum of **4-(2,3-Dihydro-1*H*-perimidin-2-yl)-*N,N*-dimethylaniline (4h)**



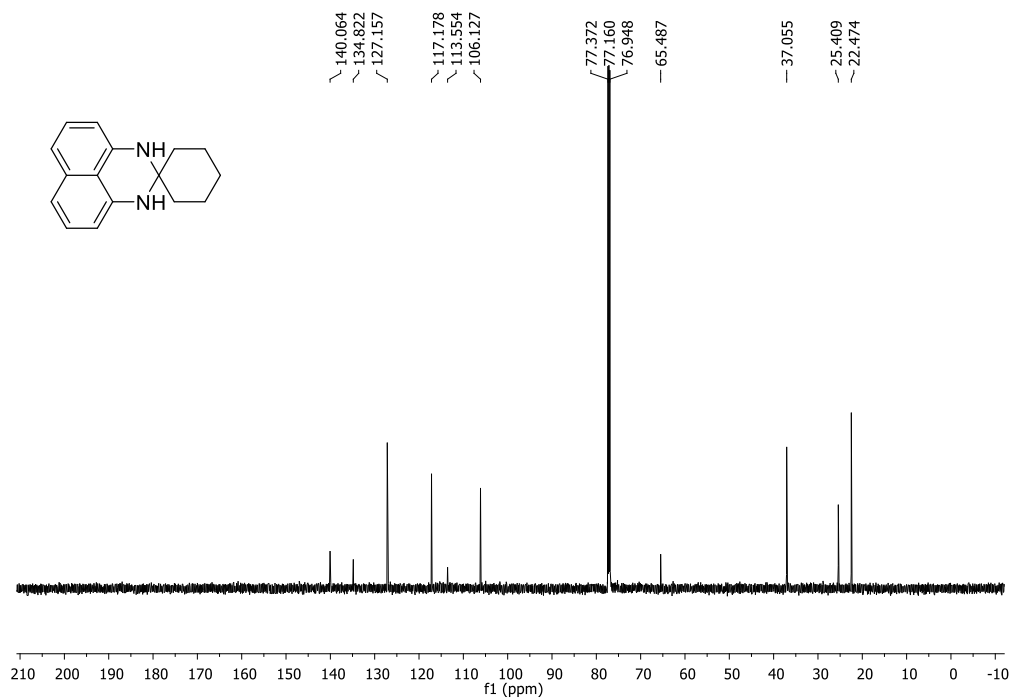
¹³C NMR (151 MHz, CDCl₃) spectrum of **4-(2,3-Dihydro-1*H*-perimidin-2-yl)-*N,N*-dimethylaniline (4h)**



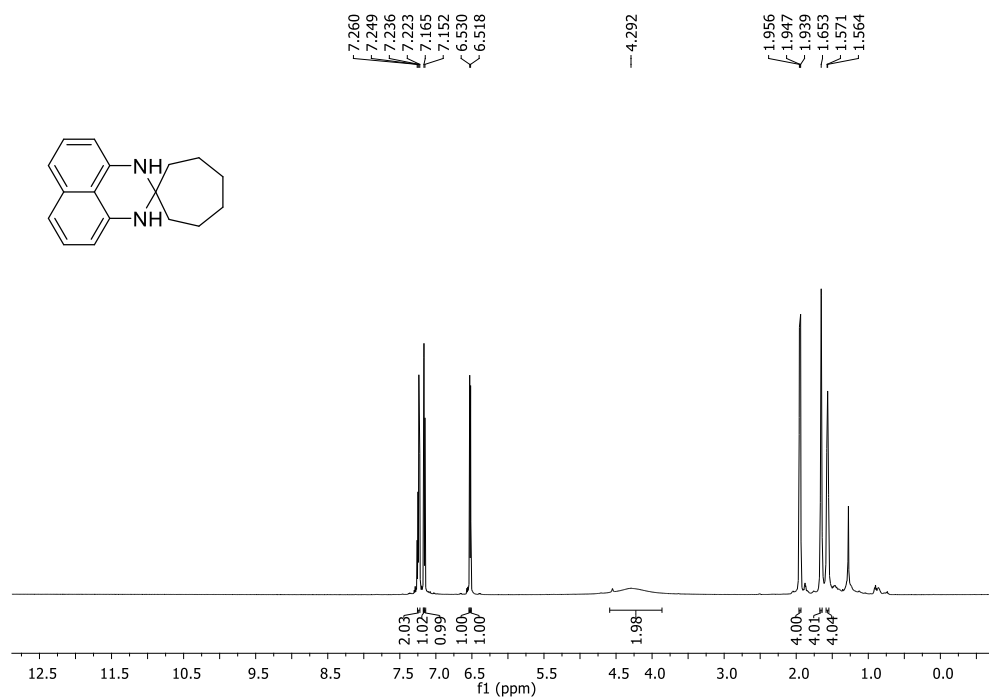
^1H NMR (600 MHz, CDCl_3) spectrum of **1'*H*,3'*H*-Spiro[cyclohexane-1,2'-perimidine] (4q)**



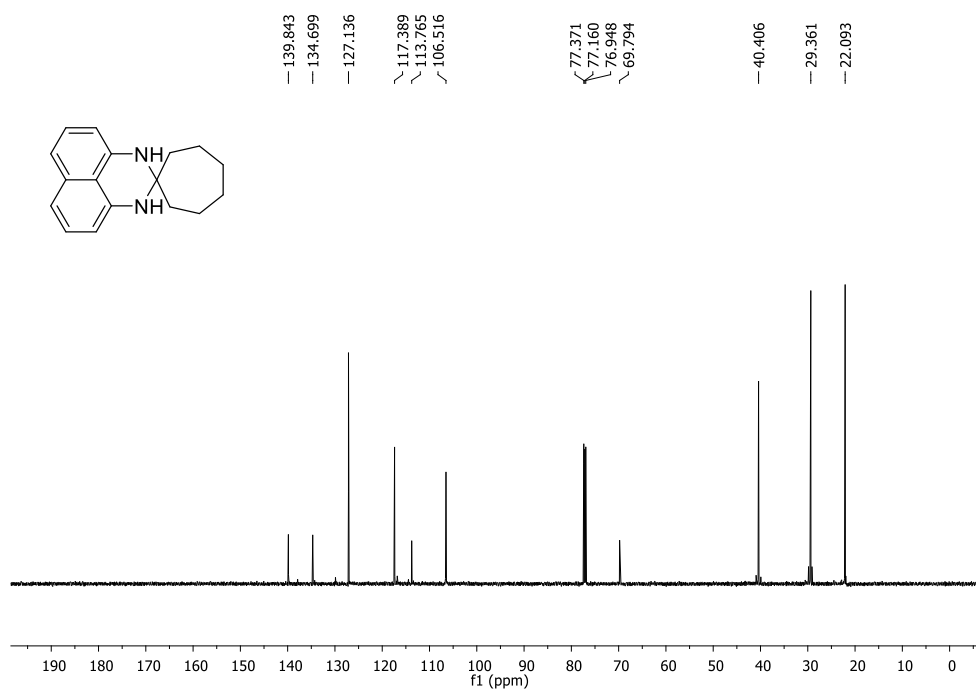
^{13}C NMR (151 MHz, CDCl_3) spectrum of **1'*H*,3'*H*-Spiro[cyclohexane-1,2'-perimidine] (4q)**



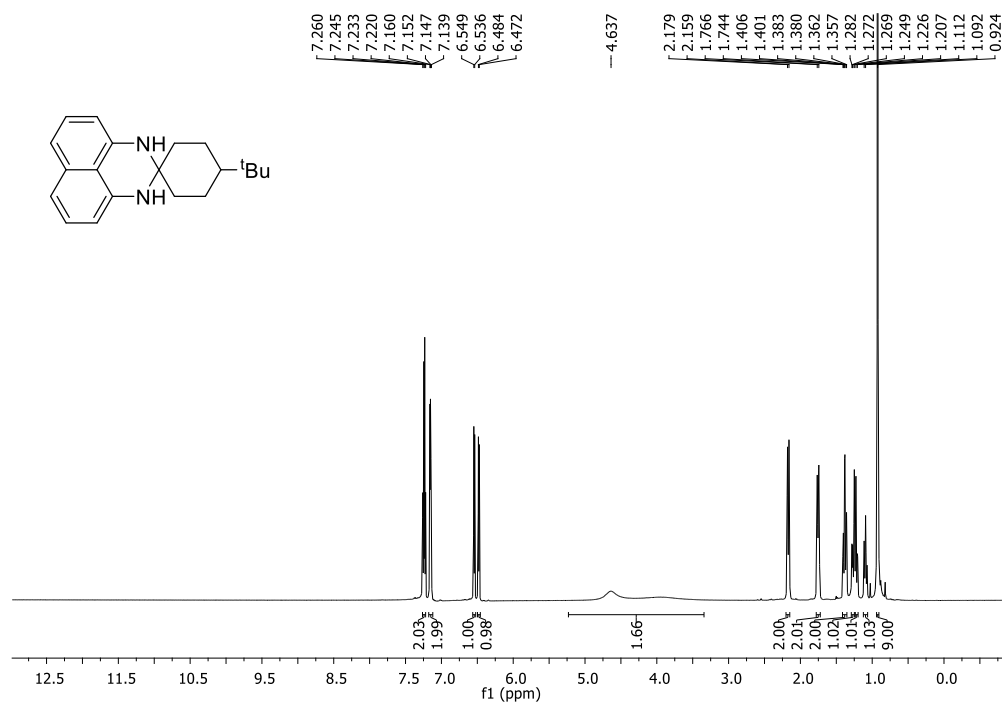
^1H NMR (600 MHz, CDCl_3) spectrum of **1'*H*,3'*H*-Spiro[cycloheptane-1,2'-perimidine] (4s)**



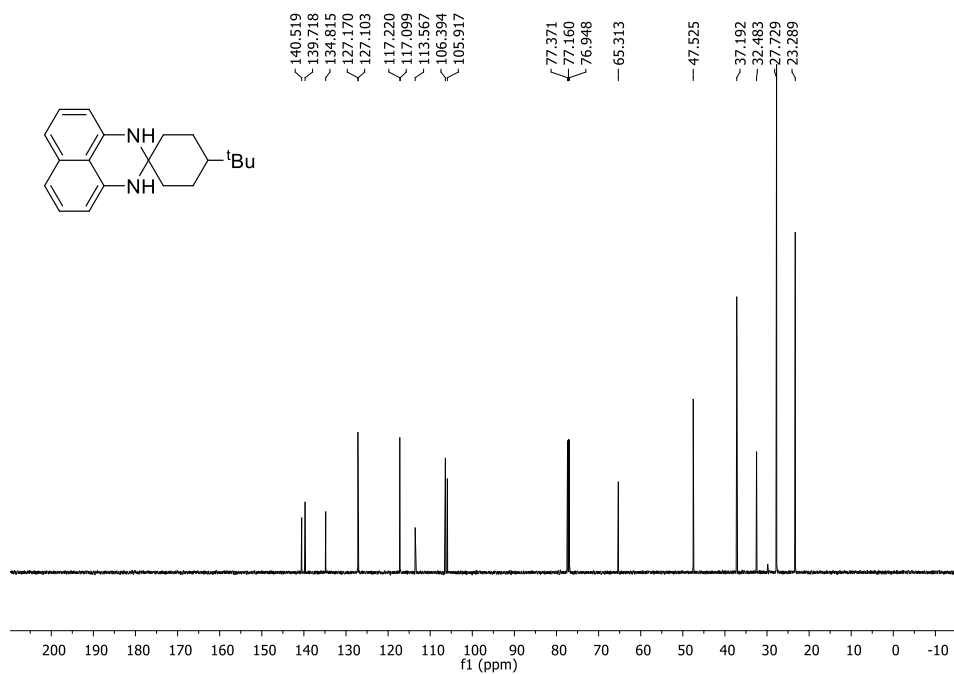
^{13}C NMR (151 MHz, CDCl_3) spectrum of **1'*H*,3'*H*-Spiro[cycloheptane-1,2'-perimidine] (4s)**



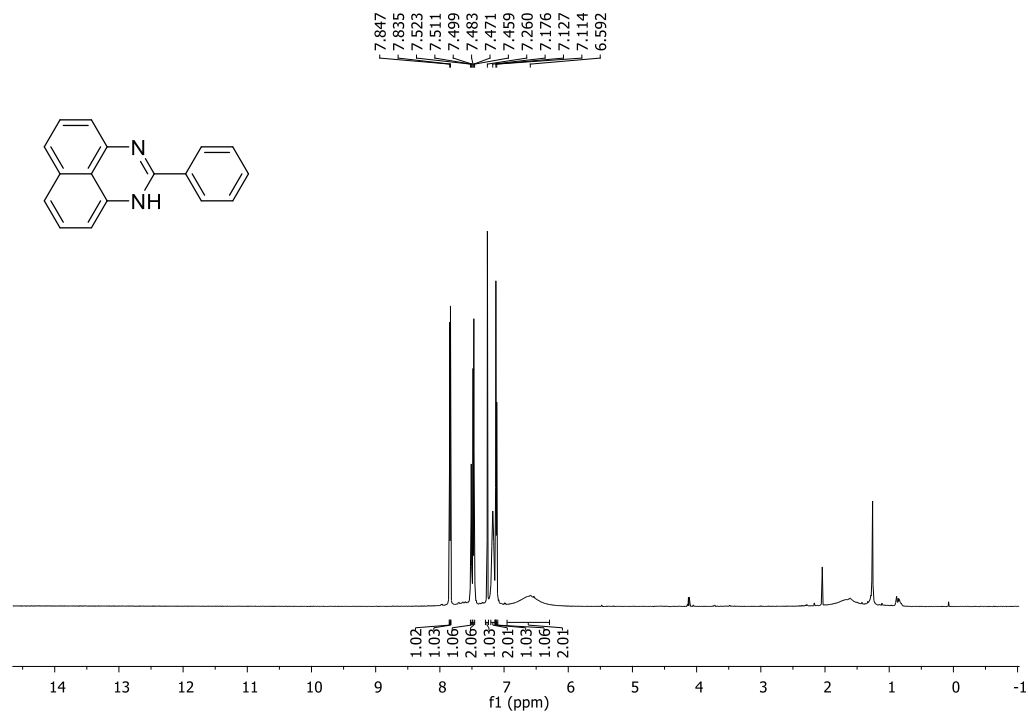
^1H NMR (600 MHz, CDCl_3) spectrum of **4-(Tert-butyl)-1'*H*,3'*H*-spiro[cyclohexane-1,2'-perimidine] (4t)**



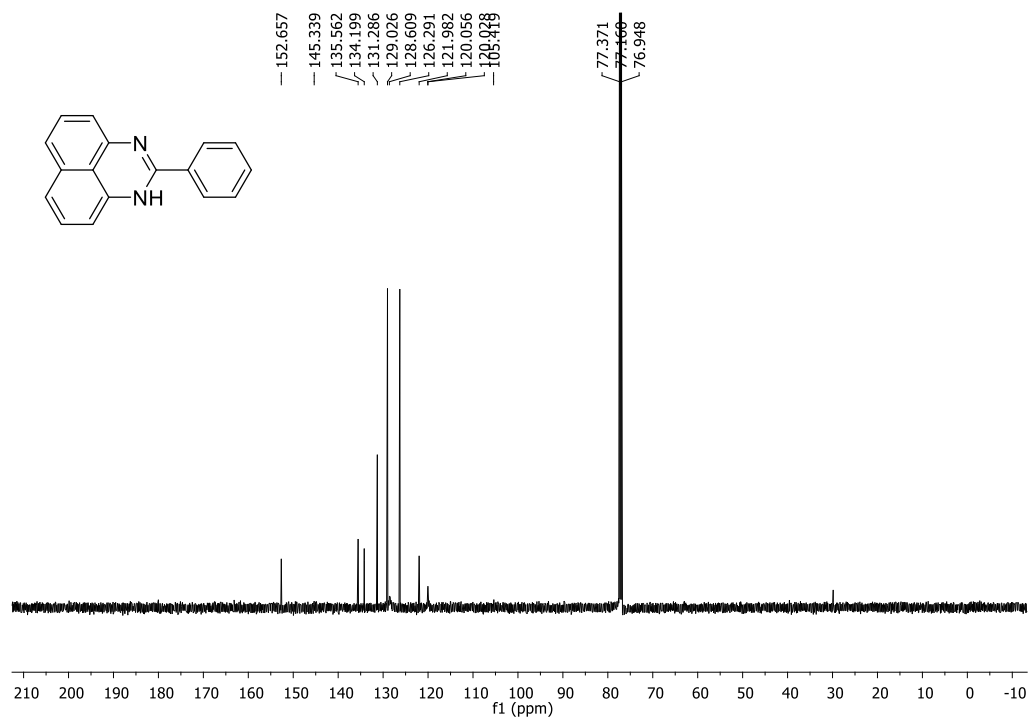
^{13}C NMR (151 MHz, CDCl_3) spectrum of **4-(Tert-butyl)-1'*H*,3'*H*-spiro[cyclohexane-1,2'-perimidine] (4t)**



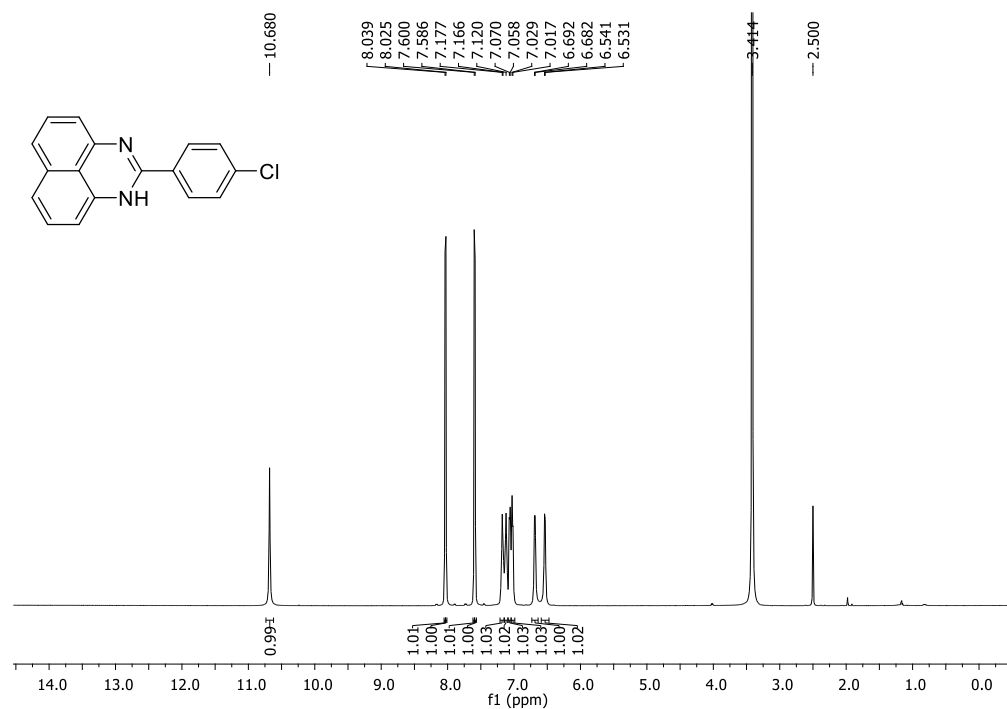
¹H NMR (600 MHz, CDCl₃) spectrum of **2-Phenyl-1H-perimidine (5a)**



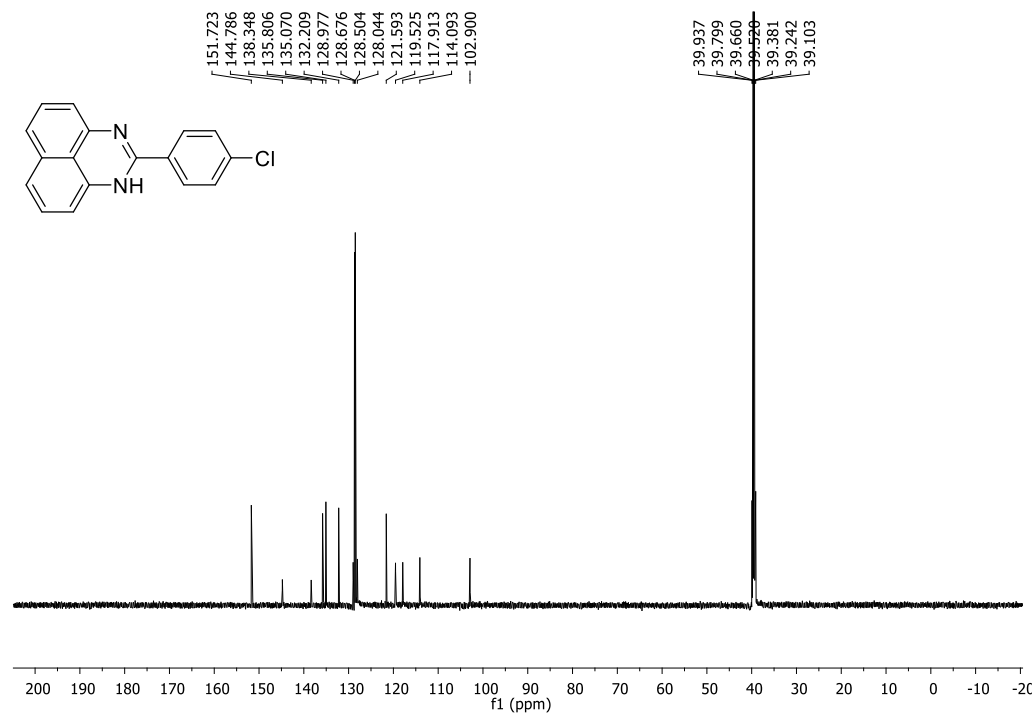
¹³C NMR (151 MHz, CDCl₃) spectrum of **2-Phenyl-1H-perimidine (5a)**



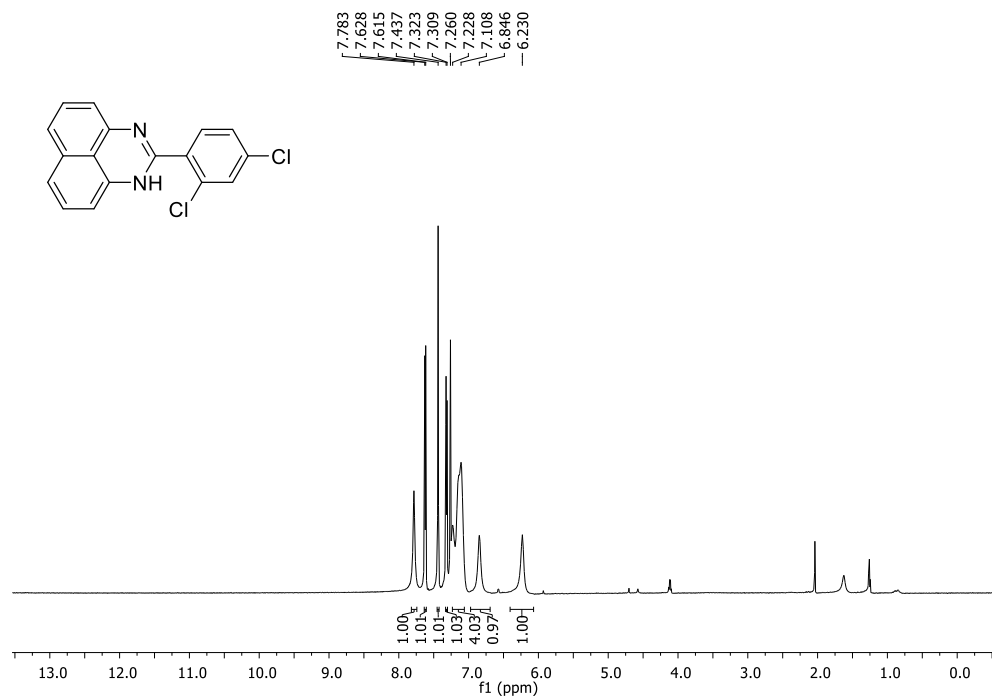
^1H NMR (600 MHz, DMSO- d_6) spectrum of **2-(4-Chlorophenyl)-1H-perimidine (5c)**



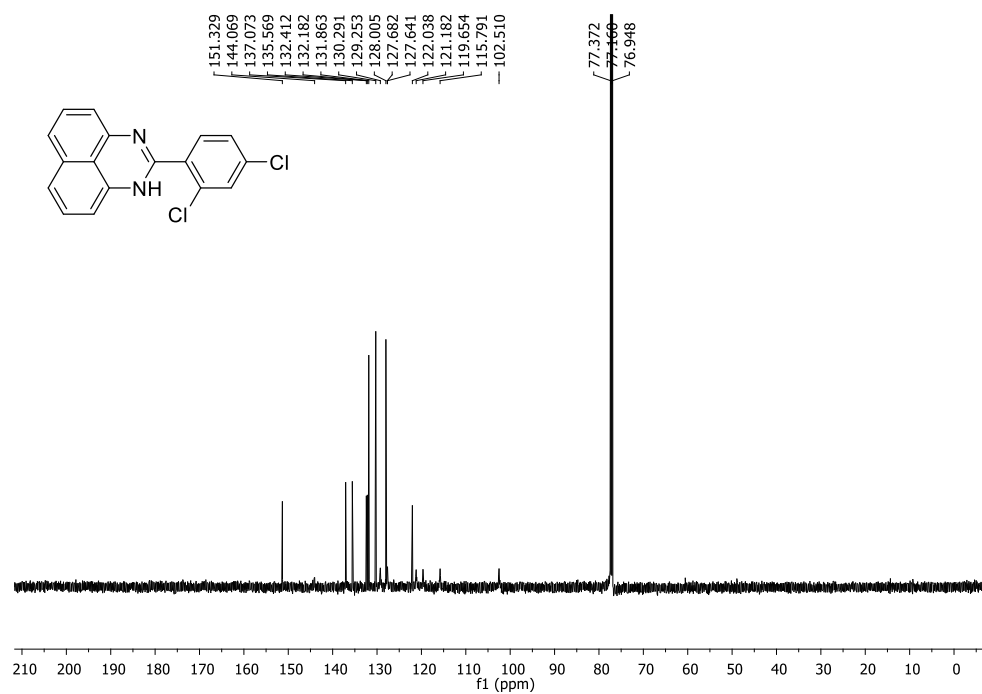
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of **2-(4-Chlorophenyl)-1H-perimidine (5c)**



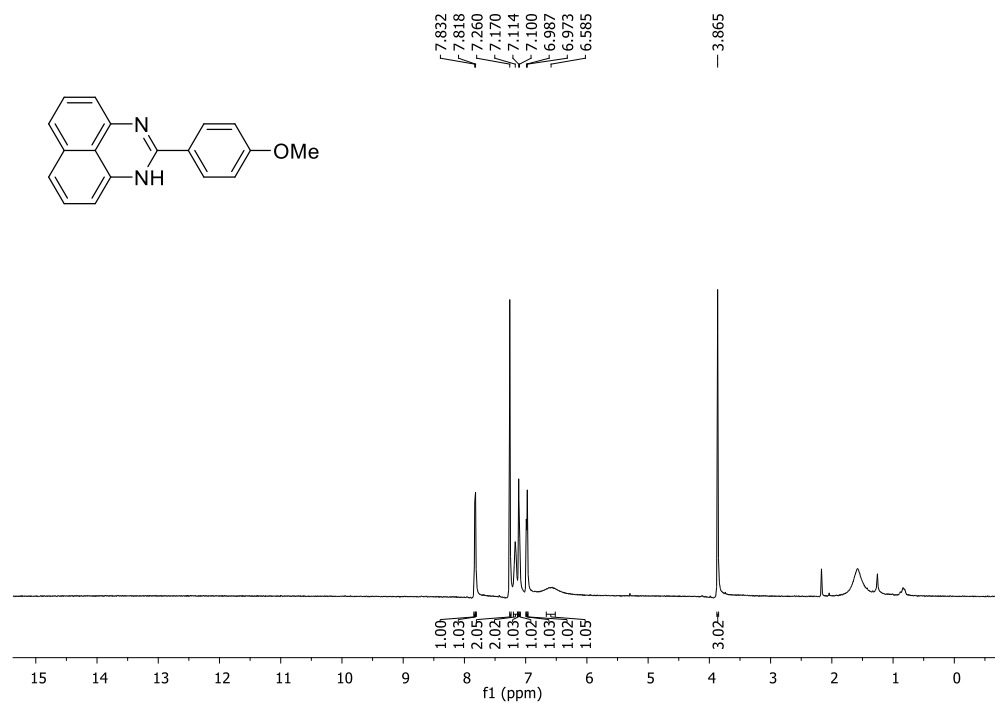
^1H NMR (600 MHz, CDCl_3) spectrum of **2-(2,4-Dichlorophenyl)-1*H*-perimidine (5g)**



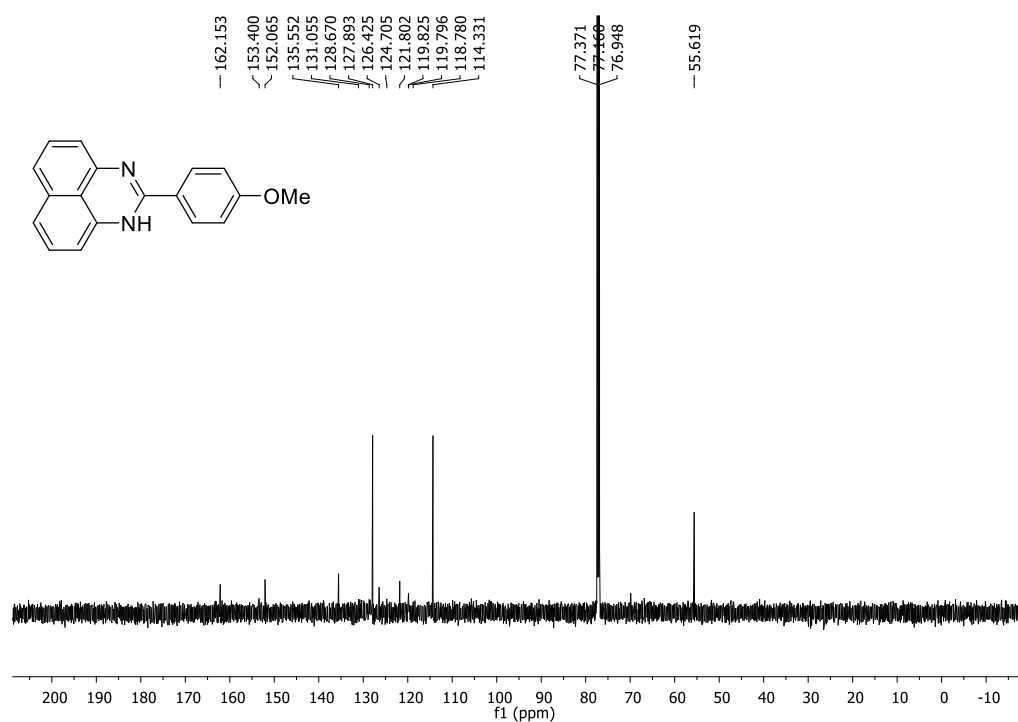
^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-(2,4-Dichlorophenyl)-1*H*-perimidine (5g)**



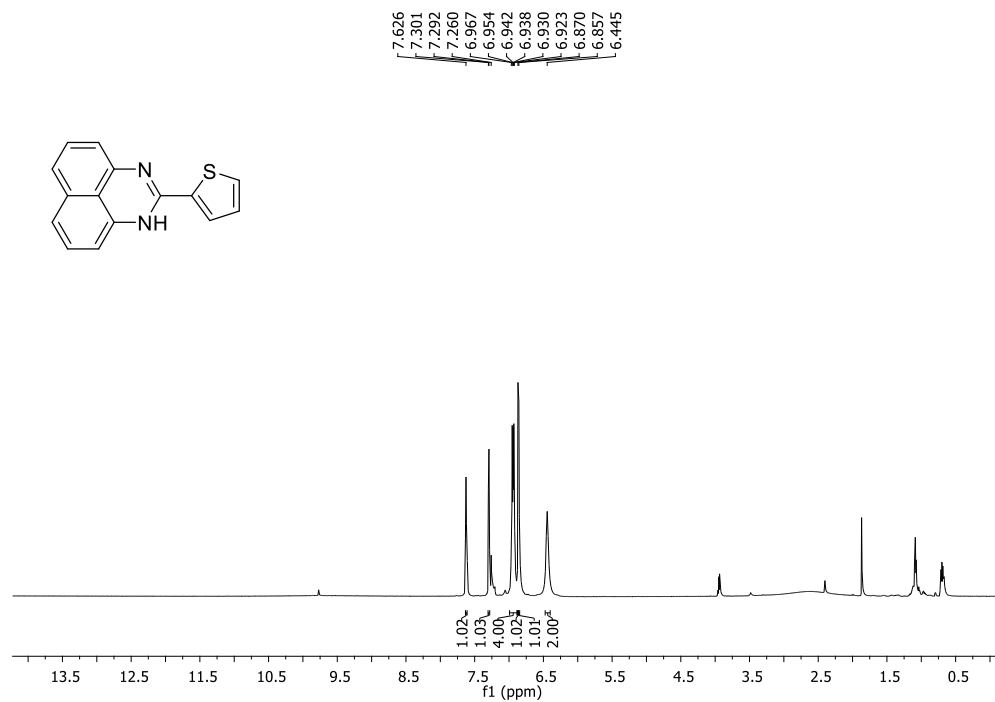
^1H NMR (600 MHz, CDCl_3) spectrum of **2-(4-Methoxyphenyl)-1H-perimidine (5i)**



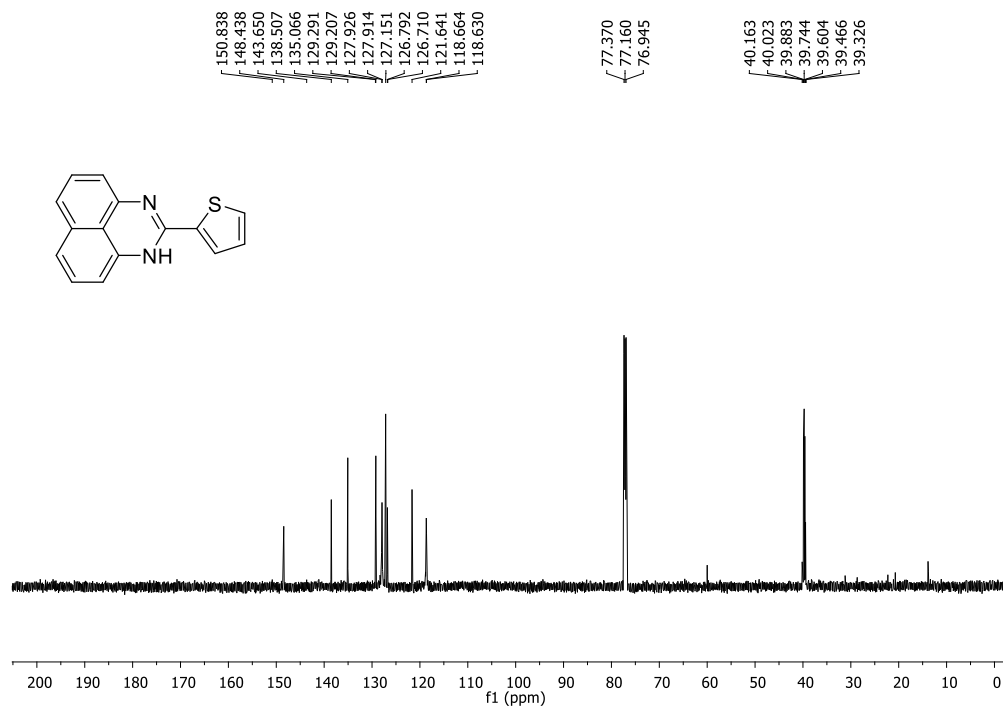
^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-(4-Methoxyphenyl)-1H-perimidine (5i)**



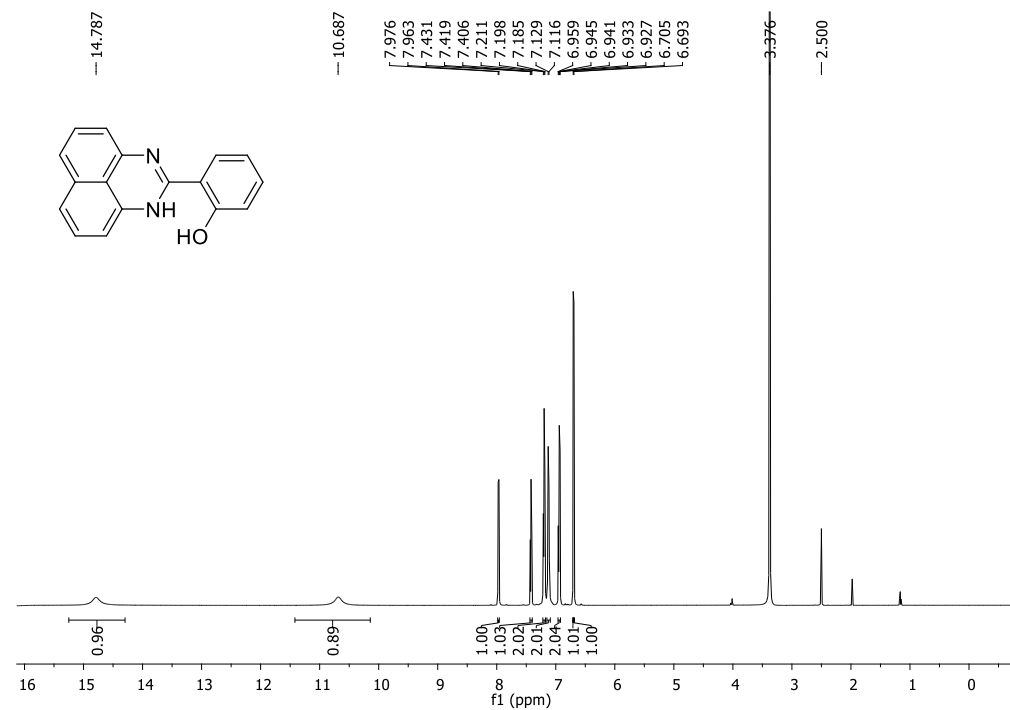
^1H NMR (600 MHz, CDCl_3) spectrum of **2-(Thiophen-2-yl)-1H-perimidine (5l)**



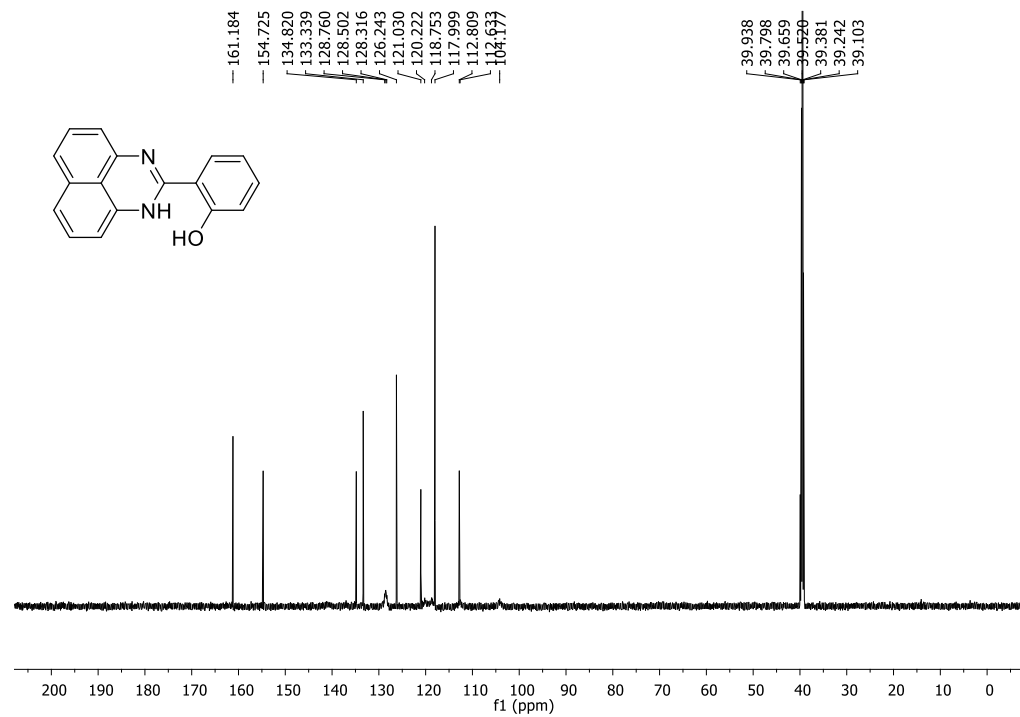
^{13}C NMR (151 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$) spectrum of **2-(Thiophen-2-yl)-1H-perimidine (5l)**



¹H NMR (600 MHz, DMSO-d₆) spectrum of **2-(1*H*-perimidin-2-yl)phenol (5n)**



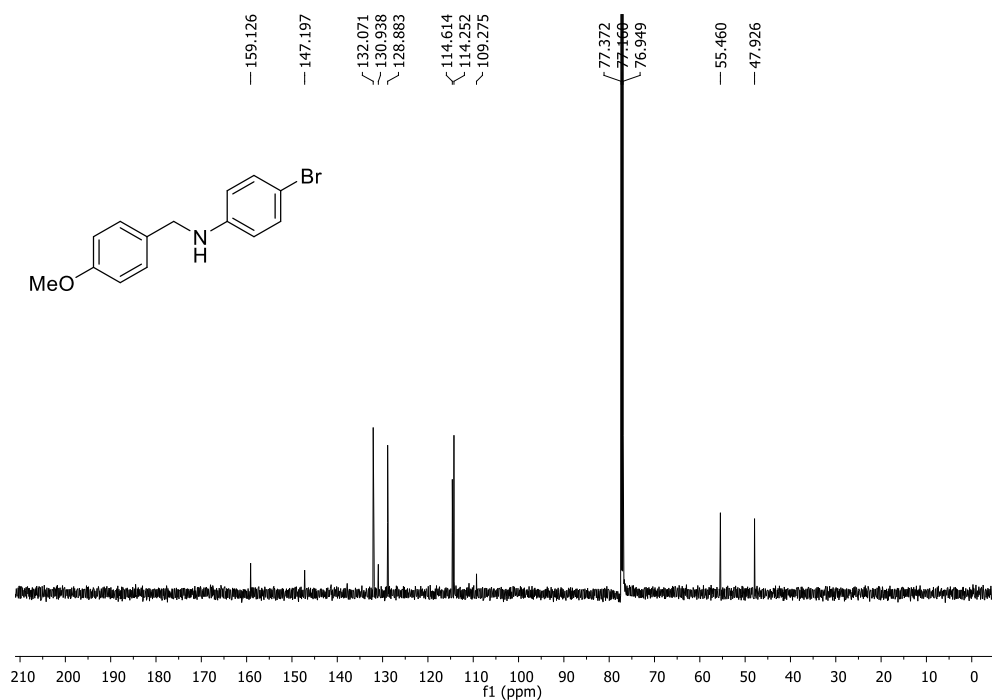
¹³C NMR (151 MHz, DMSO-d₆) spectrum of **2-(1*H*-perimidin-2-yl)phenol (5n)**



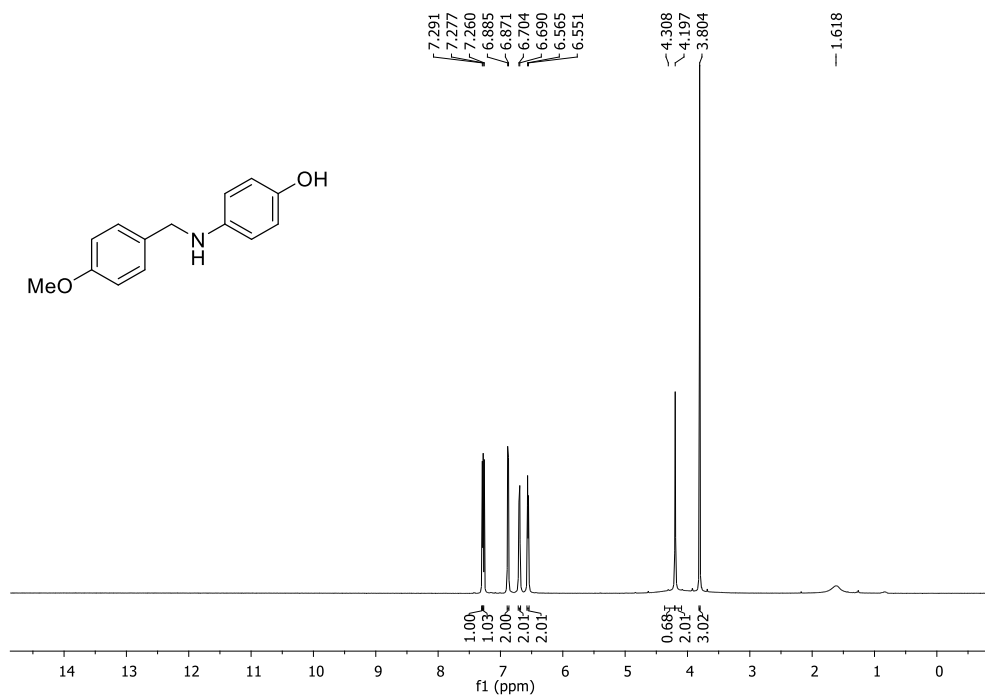
^1H NMR (600 MHz, CDCl_3) spectrum of **4-Bromo-*N*-(4-methoxybenzyl)aniline (6ji)**



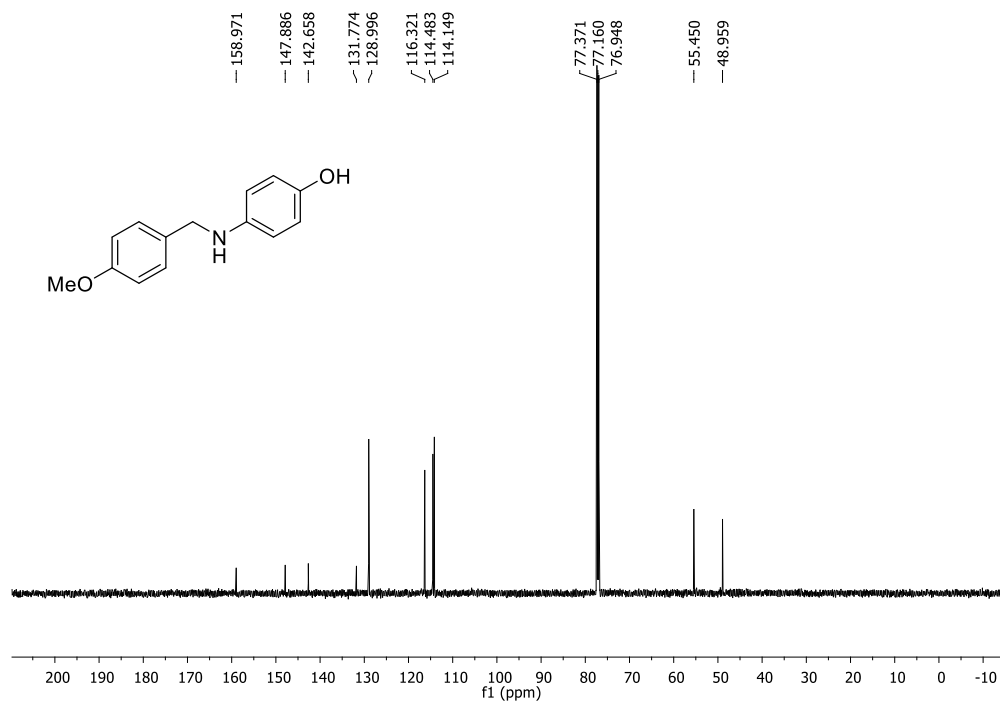
^{13}C NMR (151 MHz, CDCl_3) spectrum of **4-Bromo-*N*-(4-methoxybenzyl)aniline (6ji)**



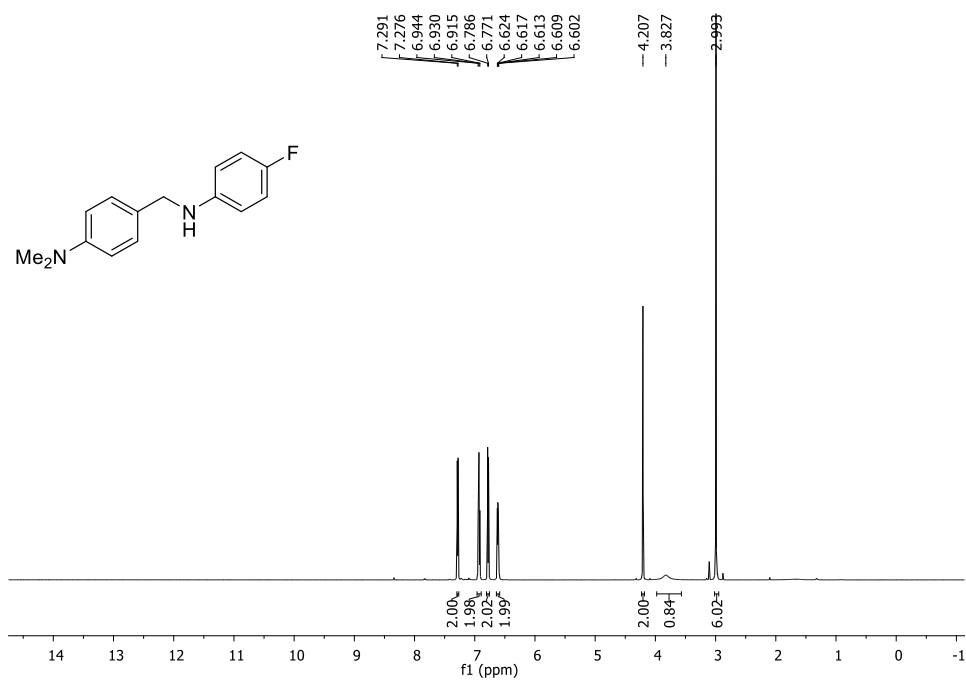
^1H NMR (600 MHz, CDCl_3) spectrum of 4-((4-Methoxybenzyl)amino)phenol (6li)



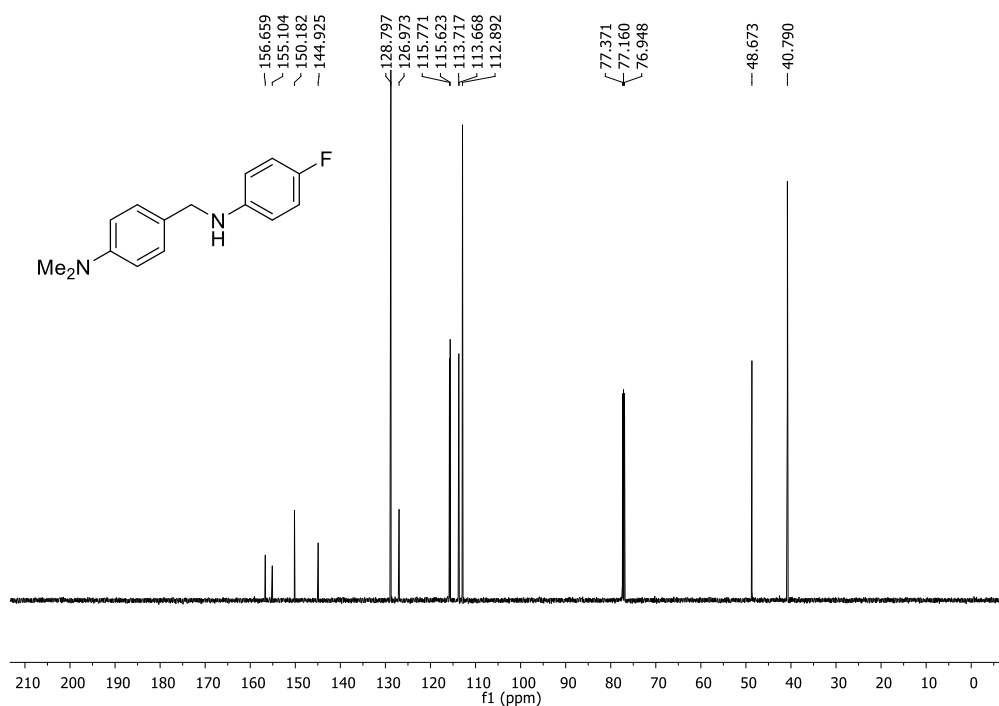
^{13}C NMR (151 MHz, CDCl_3) spectrum of 4-((4-Methoxybenzyl)amino)phenol (6li)



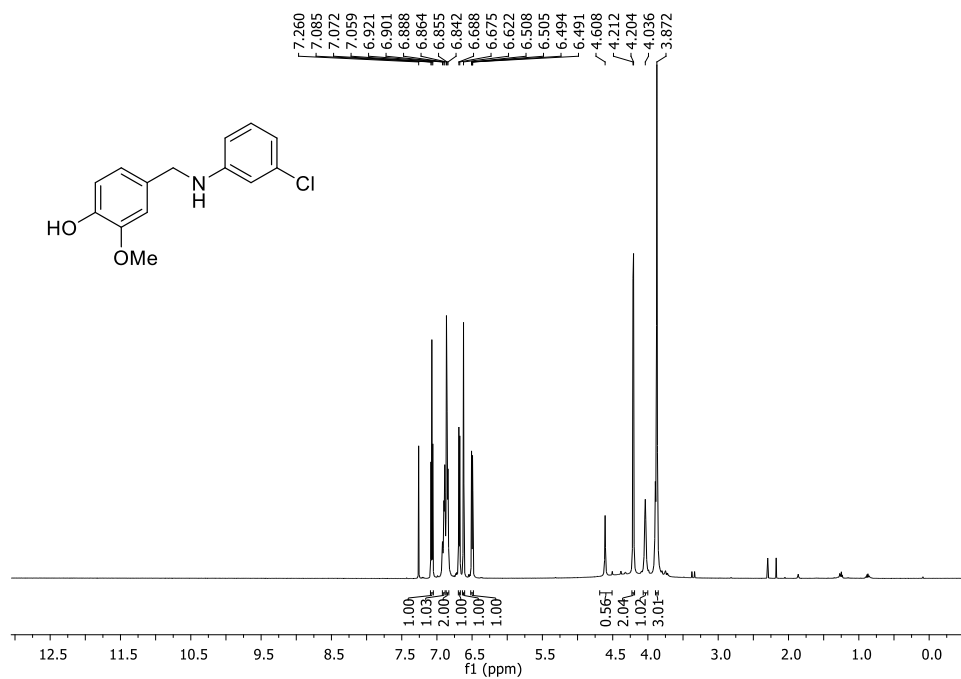
^1H NMR (600 MHz, CDCl_3) spectrum of 4-(((4-Fluorophenyl)amino)methyl)-*N,N*-dimethylaniline (6mh)



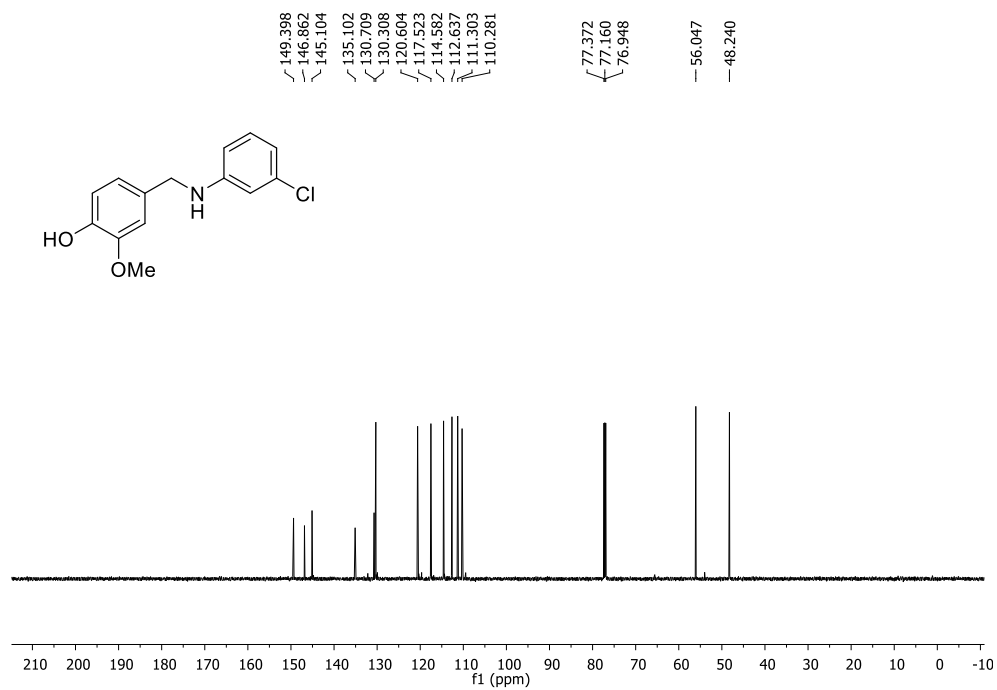
^{13}C NMR (151 MHz, CDCl_3) spectrum of 4-(((4-Fluorophenyl)amino)methyl)-*N,N*-dimethylaniline (6mh)



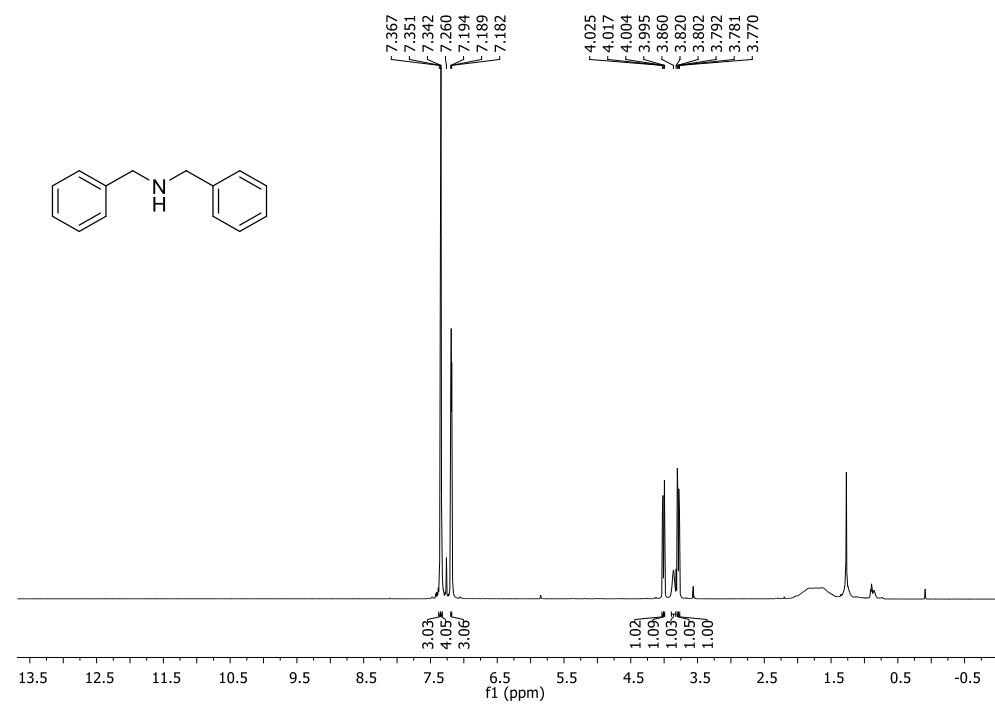
¹H NMR (600 MHz, CDCl₃) spectrum of 4-(((3-Chlorophenyl)amino)methyl)-2-methoxyphenol (6nw)



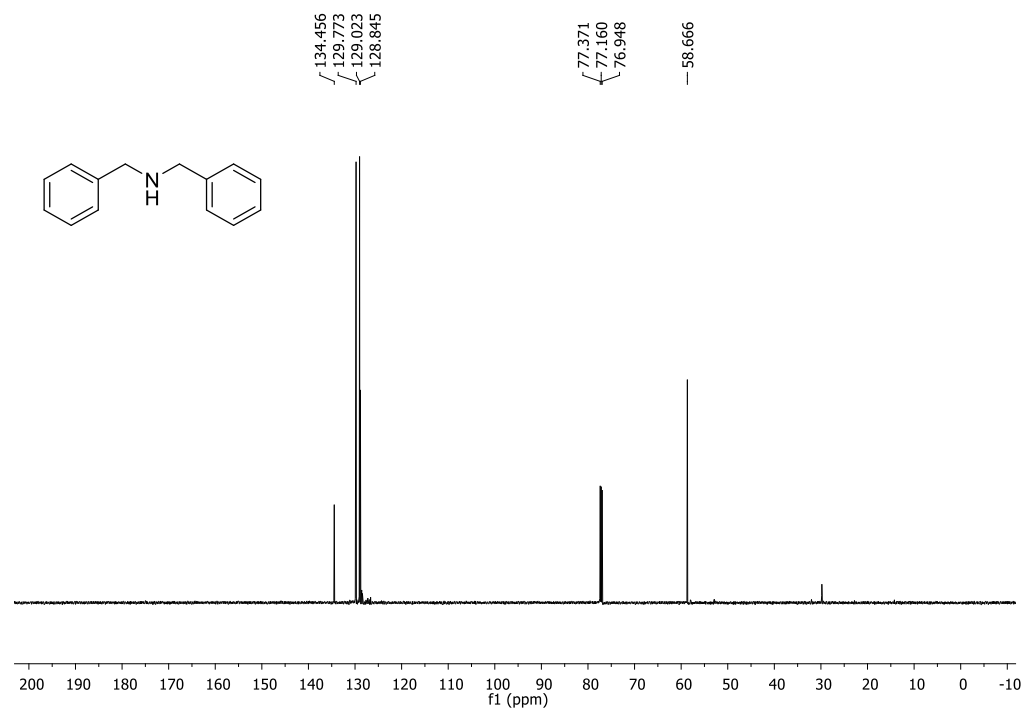
¹³C NMR (151 MHz, CDCl₃) spectrum of 4-(((3-Chlorophenyl)amino)methyl)-2-methoxyphenol (6nw)



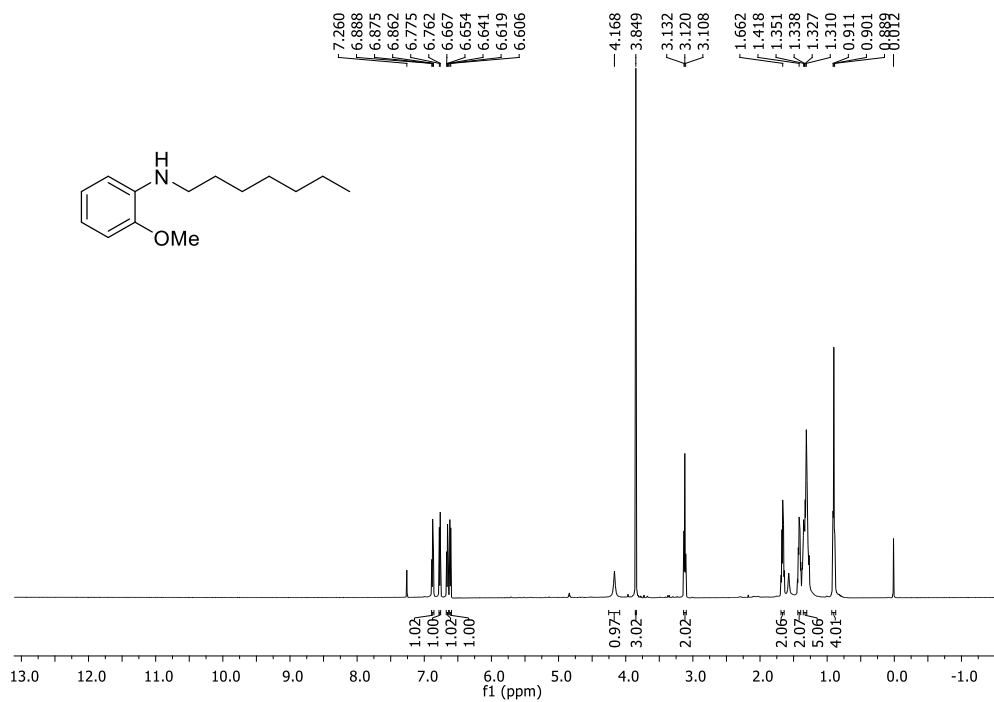
^1H NMR (600 MHz, CDCl_3) spectrum of **Dibenzylamine (60a)**



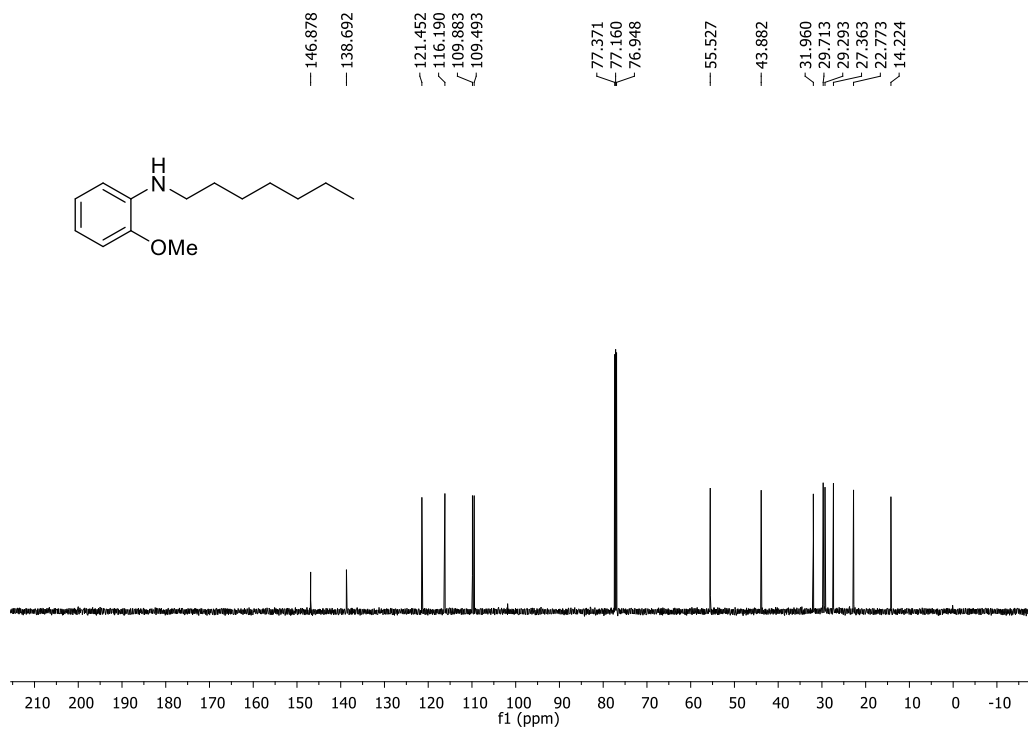
^{13}C NMR (151 MHz, CDCl_3) spectrum of **Dibenzylamine (60a)**



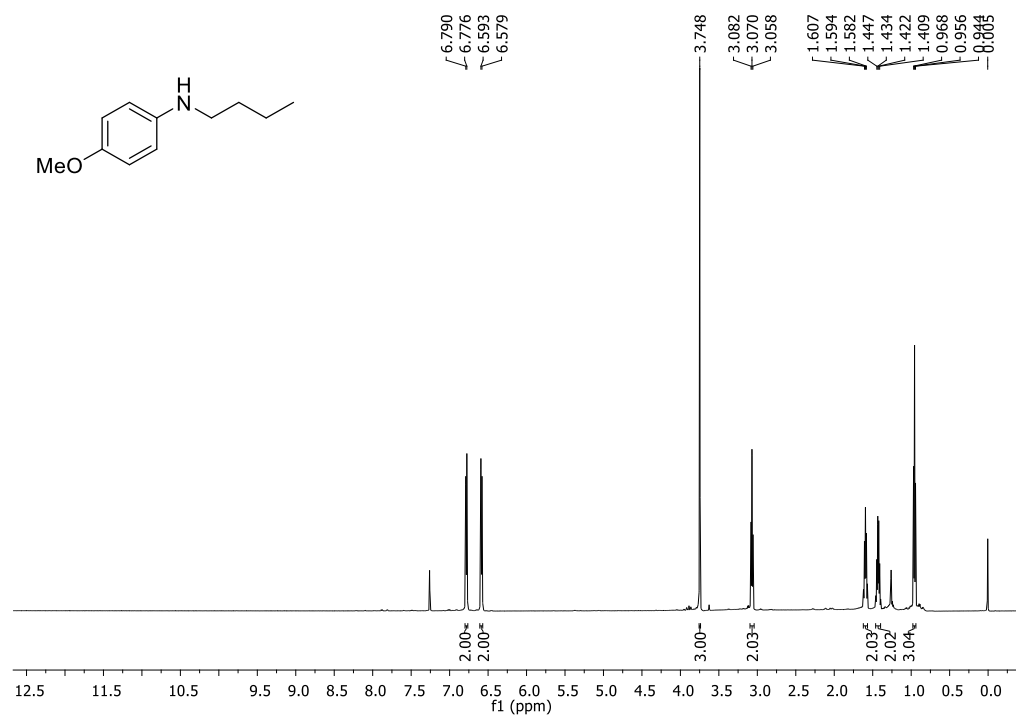
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-Heptyl-2-methoxyaniline (6po)



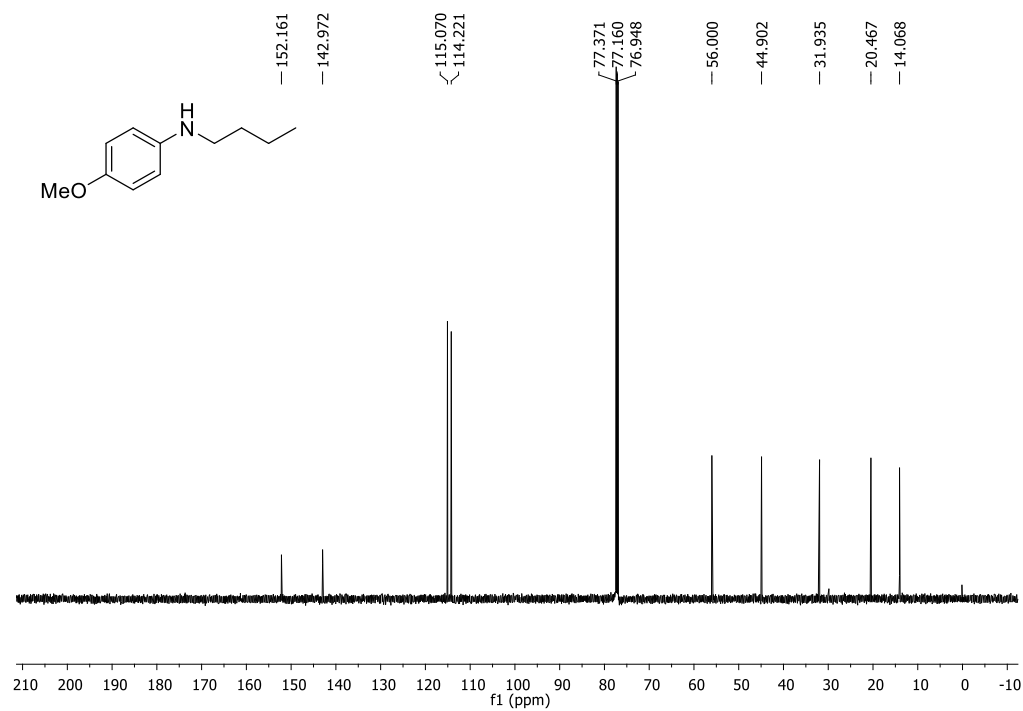
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-Heptyl-2-methoxyaniline (6po)



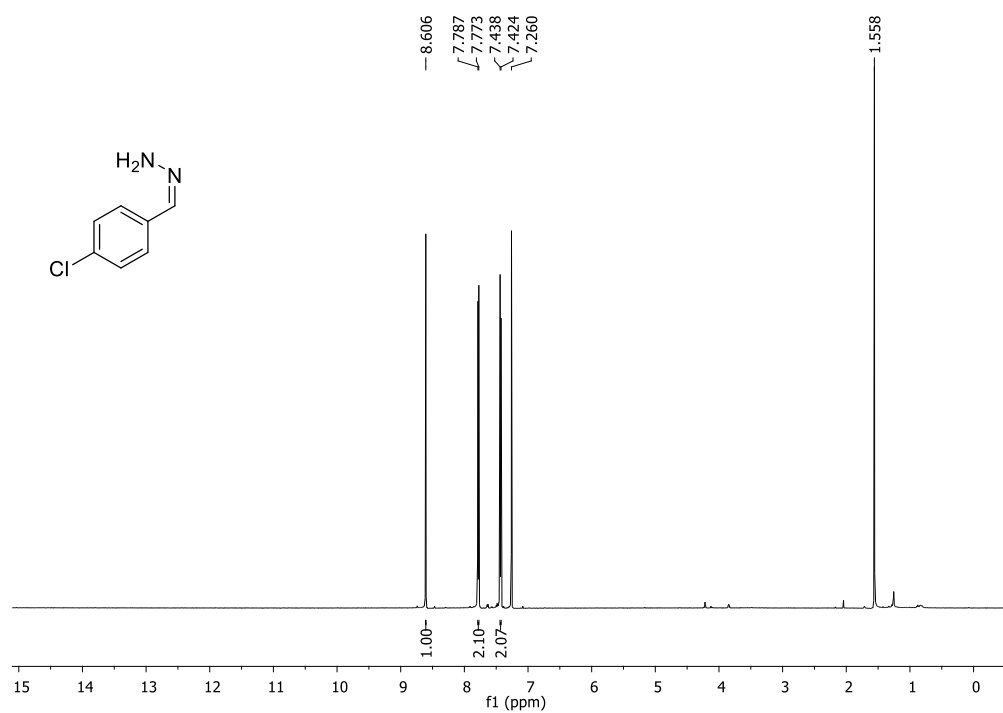
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-Butyl-4-methoxyaniline (**6ix**)



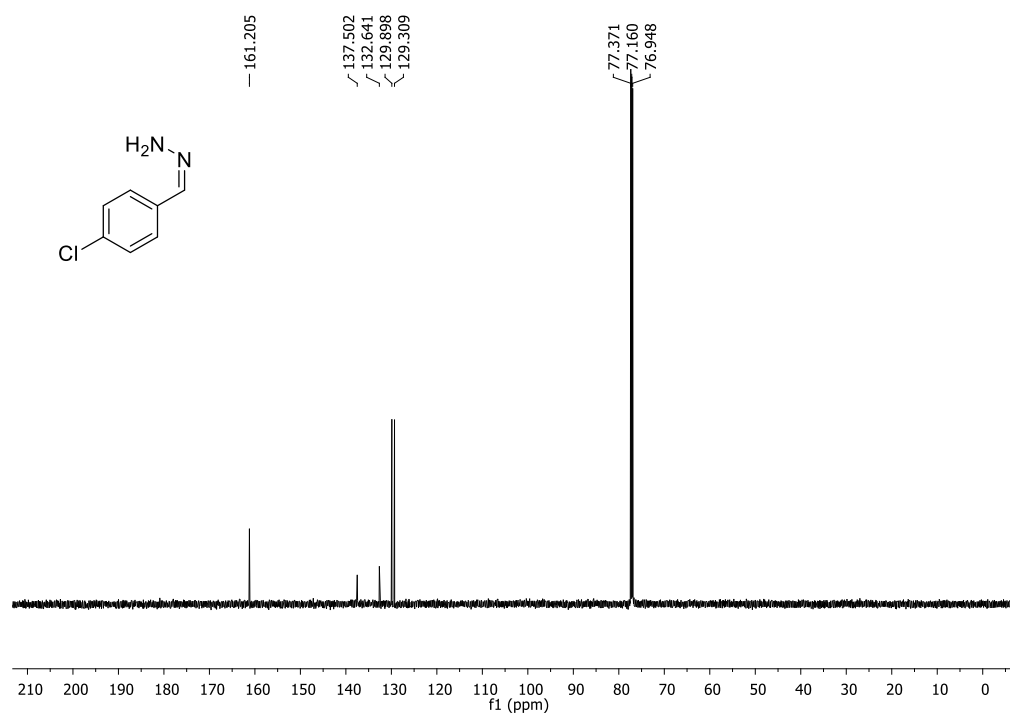
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-Butyl-4-methoxyaniline (**6ix**)



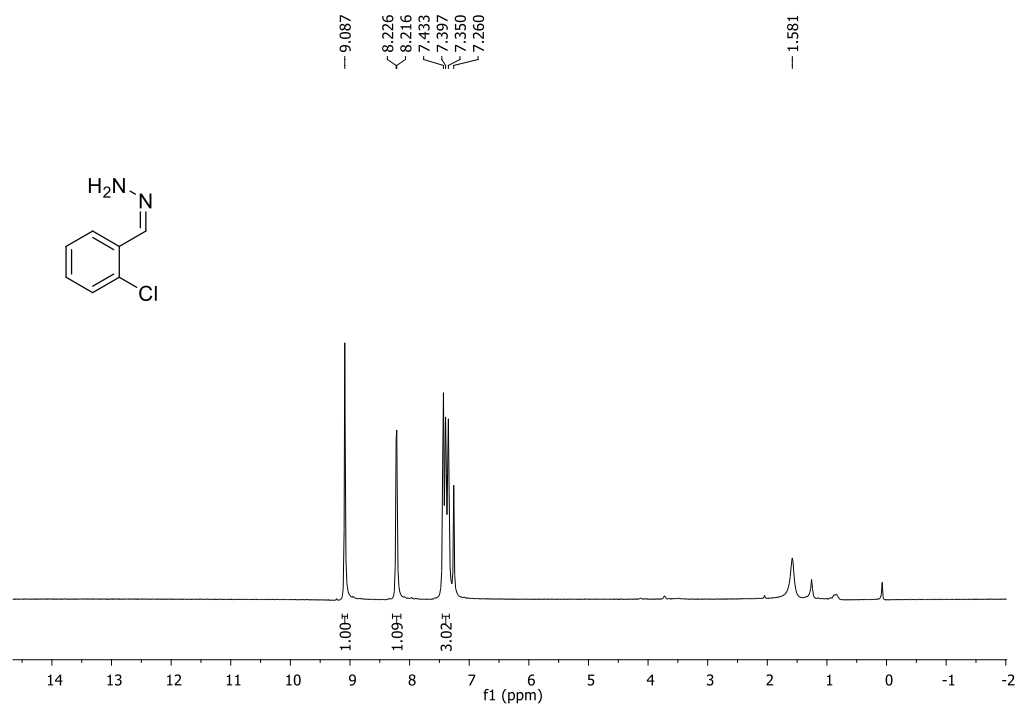
^1H NMR (600 MHz, CDCl_3) spectrum of (Z)-(4-Chlorobenzylidene)hydrazine (8c)



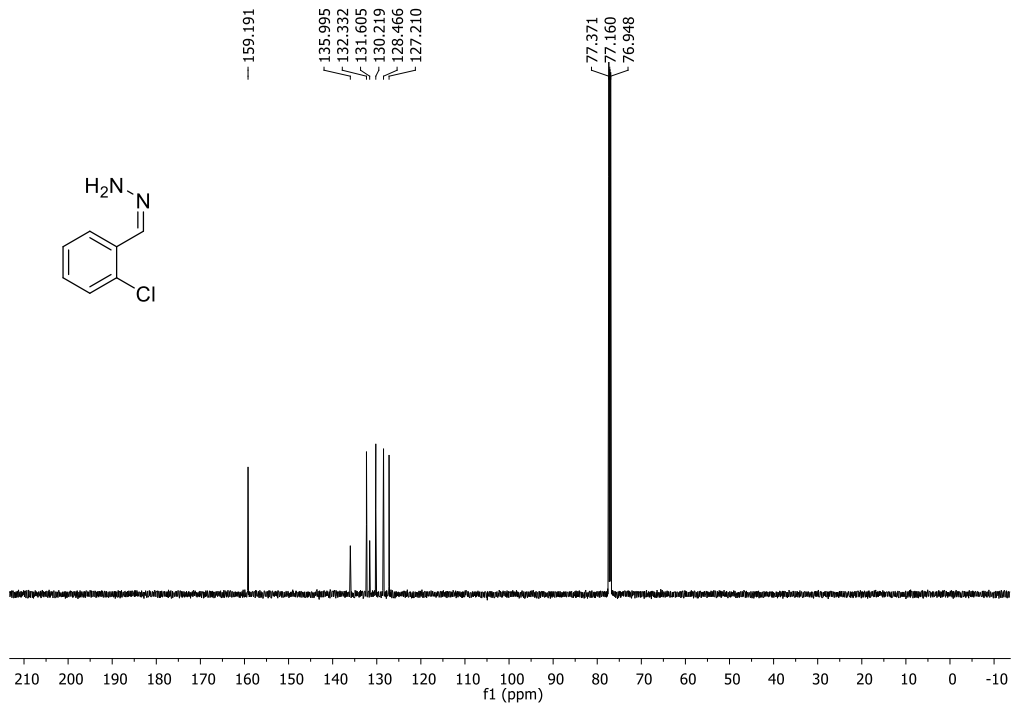
^{13}C NMR (151 MHz, CDCl_3) spectrum of (Z)-(4-Chlorobenzylidene)hydrazine (8c)



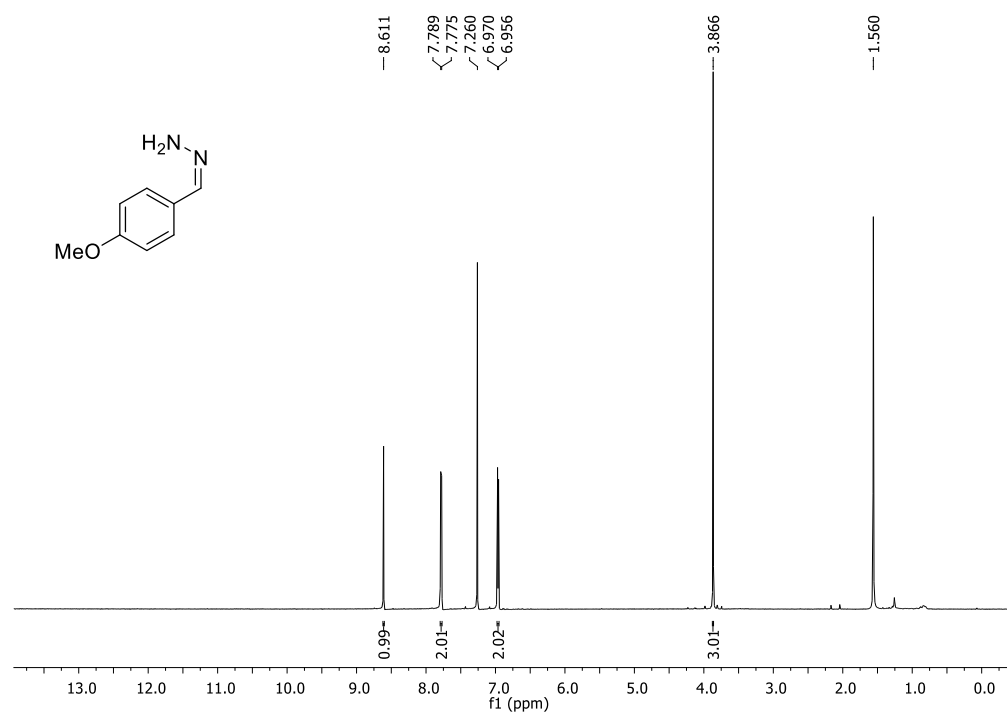
^1H NMR (600 MHz, CDCl_3) spectrum of **(Z)-(2-Chlorobenzylidene)hydrazine (8f)**



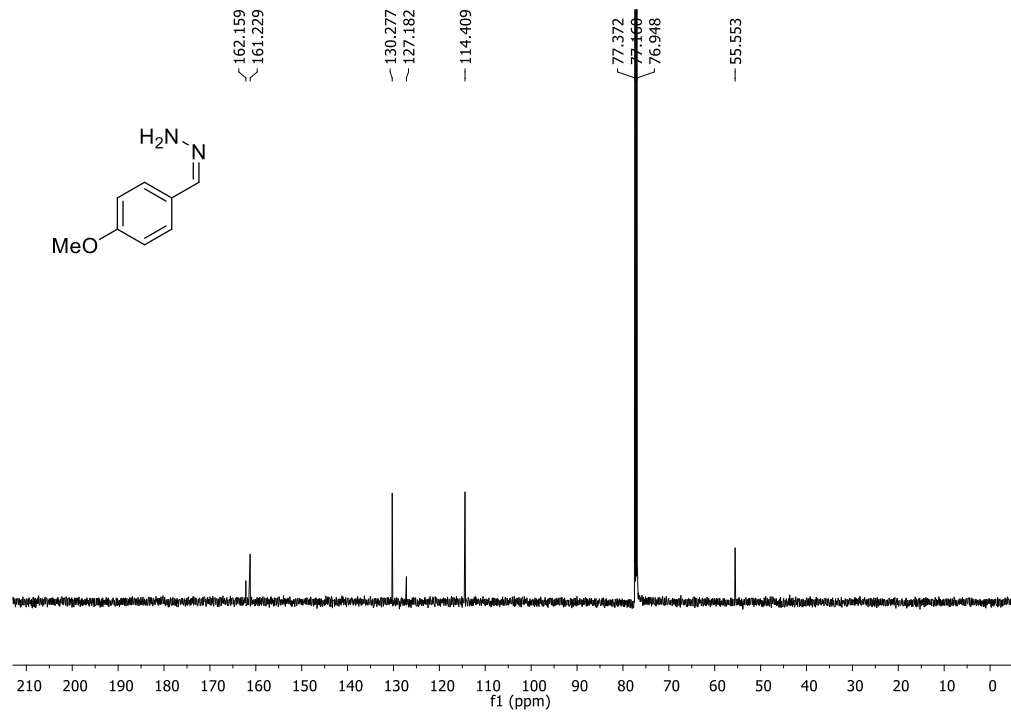
^{13}C NMR (151 MHz, CDCl_3) spectrum of **(Z)-(2-Chlorobenzylidene)hydrazine (8f)**



¹H NMR (600 MHz, CDCl₃) spectrum of (Z)-(4-Methoxybenzylidene)hydrazine (8i)



¹³C NMR (151 MHz, CDCl₃) spectrum of (Z)-(4-Methoxybenzylidene)hydrazine (8i)



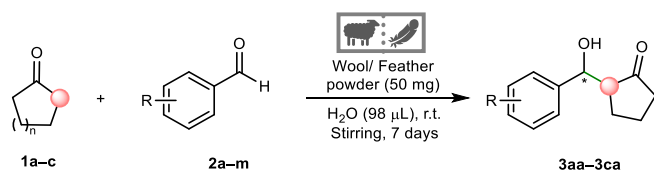
7.3. General Reaction Conditions and Characterization for Compounds in Chapter 4

7.3.1. General Condition for Mechanochemical Preparation of Wool Fiber



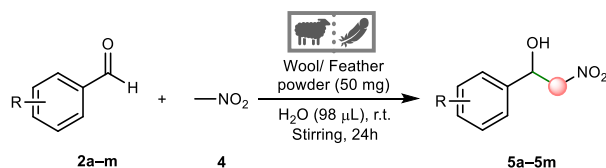
The raw materials were thoroughly rinsed and washed with tap water and soap to eliminate hydrophilic impurities. Afterward, the fibers were rinsed with heptane and then with acetone to remove the hydrophobic impurities. After several washes, the fibers have been dried overnight inside an oven. To prepare the acidic wool samples, 10 g of washed wool fibers were placed inside a beaker containing 500 mL of HCl solution (10%) and left untouched for 72 hours. Afterward, the treated fibers were washed with regular tap water and dried overnight in an oven. The dried long fibers have been finely cut into 1 cm pieces to obtain the desired wool fibers (WF) size. The cut fibers were ground with ball mills using zirconia jars and balls. The best results in terms of finer powder were achieved using the Fritsch-P7 Premium planetary ball mill (3.00 g of cut fiber inside a 20 mL zirconia jar with 35 balls with diameter $\Phi = 5$ mm and $m_{\text{tot}} = 13.75$ g at 1000 rpm for 20 minutes). After grinding, black wool powder (BWP) and white wool powder (WWP) have been obtained. Wool powders were also obtained from the hydrochloric acid-treated wool fibers (BWP(HCl) and WWP(HCl)) using the same ball milling methodology. After the wool samples were subjected to FT-IR and SEM-EDX analysis.

7.3.2. General Condition for Wool Mediated Aldol Reactions



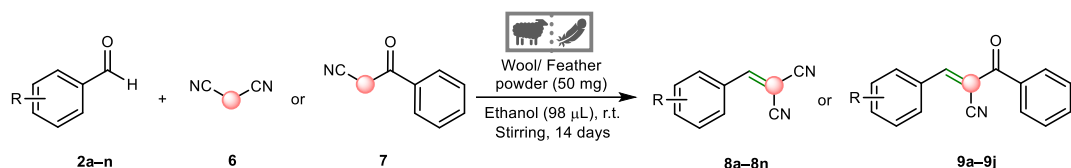
Inside a 4 mL glass vial with a magnetic stirrer, aldehyde (0.20 mmol), ketone (5 equiv.), and 50 mg of wool powder were placed in 98 μL of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pure products.

7.3.3. General Condition for Wool Mediated Nitro-Aldol Reactions



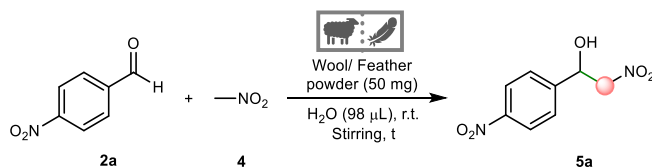
Inside a 4 mL glass vial equipped with a magnetic stirrer, aromatic aldehyde (0.20 mmol), nitromethane (10 equiv.), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pure products.

7.3.4. General Condition for Wool Mediated Knoevenagel Condensation



Inside a 4 mL glass vial equipped with a magnetic stirrer, aldehyde (0.20 mmol), malononitrile or benzoyl acetonitrile (0.20 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pure products.

7.3.5. Procedure to Monitor Reaction Progress Over Time for Nitro-Aldol Reaction



Inside a 4 mL glass vial equipped with a magnetic stirrer, aromatic aldehyde (0.20 mmol), nitromethane (10 equiv.), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. The reaction was gently stirred for given time and the product evolution was monitored using GC-MS till the completion of the reaction.

Entry	Time (h)	Conversion to 5a (%)
1	0	0
2	1	8
3	2	15
4	3	27
5	6	50
6	9	74
7	12	83
8	18	88
9	24	93

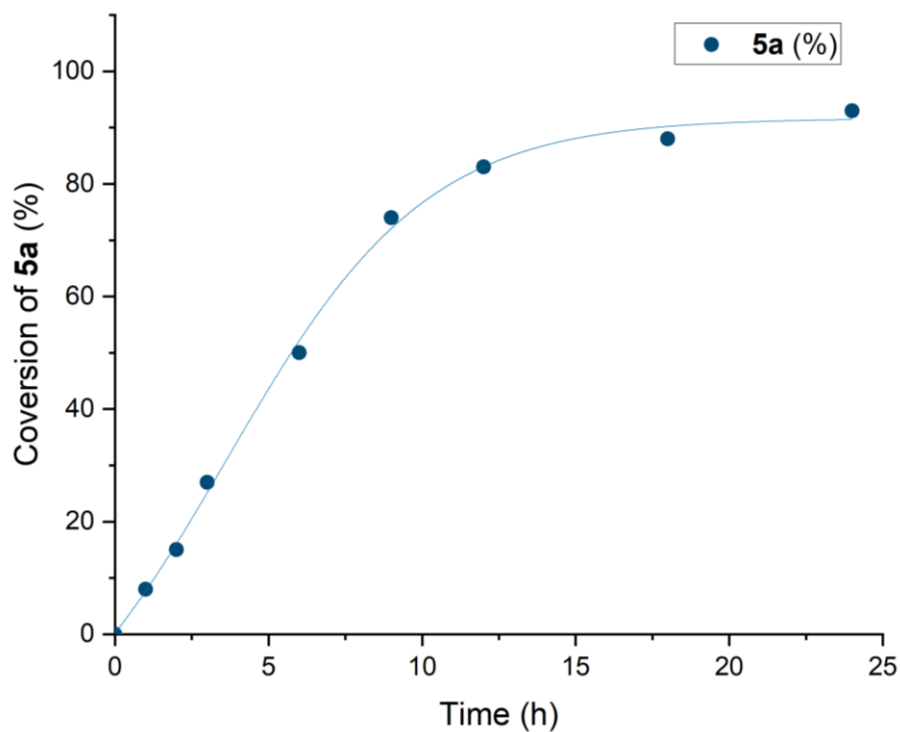
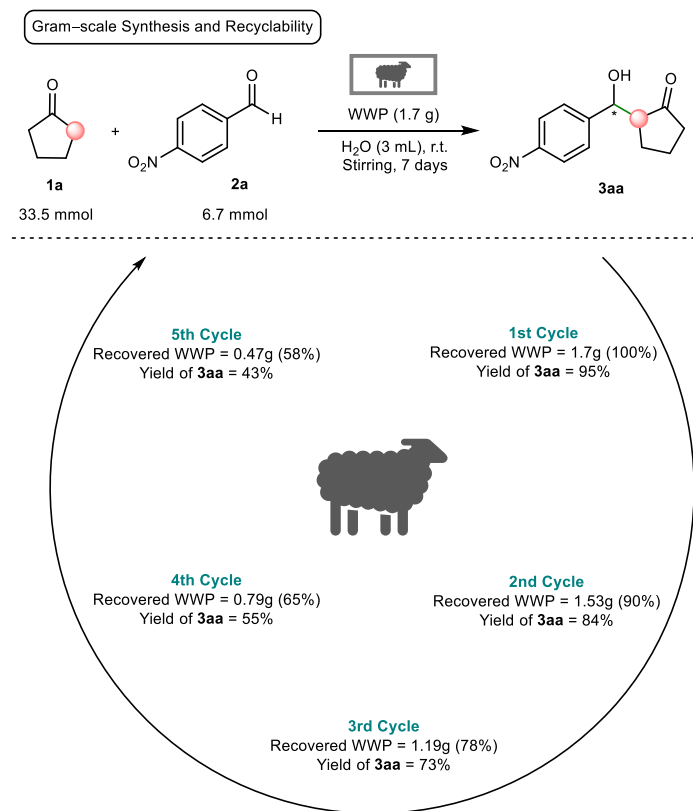


Figure 7.2. Product evolution over time for wool mediated Nitro-aldol product **5a**.

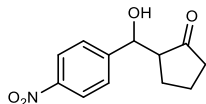
7.3.6. Procedure for Gram Scale Recycling Studies of Wool Mediated Aldol Reaction



Inside a 50 mL glass vial with a magnetic stirrer, aldehyde (6.7 mmol), ketone (5 equiv.), and 1.7 g of wool powder were placed in 3 mL of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt on a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pure products. The wool powder was then thoroughly washed with water and acetone, dried overnight at 50 °C and then reused.

7.3.7. Characterization of Compounds in Chapter 4

7.3.7.1. Spectral Data for Wool Mediated Aldol Reactions



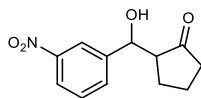
2-(hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one (3aa): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2a** (30 mg, 0.2 mmol), **1a** (84 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μ L of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellow solid (45.3 mg, 96%).

M.P.: 95 °C.

¹H NMR (600 MHz, CDCl₃, mixture of diastereoisomers, syn/anti ratio: 70/30), ¹H NMR (600 MHz, CDCl₃) δ 8.26 – 8.15 (m, 2H), 7.51 (t, J = 7.0 Hz, 2H), 5.42 – 4.82 (m, diastereoisomeric proton, 1H), 2.49 – 2.32 (m, 2H), 2.29 – 2.09 (m, diastereoisomeric proton, 1H), 2.04 – 1.91 (m, 2H), 1.78 – 1.64 (m, 2H).

¹³C NMR (151 MHz, CDCl₃, mixture of diastereoisomers) δ 219.78 (diastereoisomeric C=O is missing), 150.4, 148.7, 147.7, 147.3, 127.5, 126.5, 123.8, 123.7, 74.5, 70.5, 56.2, 55.2, 39.1, 38.7, 26.9, 22.5, 20.5, 20.4.

Spectroscopic data are in agreement with those reported earlier.⁴³



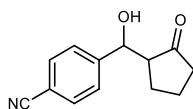
2-(hydroxy(3-nitrophenyl)methyl)cyclopentan-1-one (3ab): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2b** (30 mg, 0.2 mmol), **1a** (84 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μ L of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellow solid (37.0 mg, 91%).

M.P.: 102 °C.

¹H NMR (600 MHz, CDCl₃) δ 8.22 (m, 1H), 8.17 – 8.10 (m, 1H), 7.70 – 7.64 (m, 1H), 7.52 (m, 1H), 5.41 – 4.83 (d, *J* = 9.2 Hz, *diastereoisomeric proton*, 1H), 2.52 – 2.35 (m, 2H), 2.33 – 2.12 (m, *diastereoisomeric proton*, 1H), 2.11 – 1.83 (m, 2H), 1.80 – 1.69 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 222.4, 219.7, 148.5, 145.1, 143.8, 132.8, 131.8, 129.7, 129.6, 129.5, 123.1, 122.4, 121.7, 120.8, 74.6, 70.4, 56.2, 55.2, 39.1, 38.7, 27.0, 22.6, 20.5, 20.4.

Spectroscopic data are in agreement with those reported earlier.⁴³



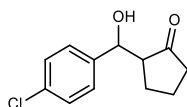
4-(hydroxy(2-oxocyclopentyl)methyl)benzonitrile (3ac): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2c** (26 mg, 0.2 mmol), **1a** (84 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μL of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the off-white solid (39.9 mg, 87%).

M.P.: 112-113 °C.

¹H NMR (600 MHz, CDCl₃, *mixture of diastereoisomers, syn/anti ratio: 68/32*) δ 7.61 (dd, *J* = 8.1, 5.9 Hz, 2H), 7.44 (dd, *J* = 8.1, 5.9 Hz, 2H), 5.35 – 4.75 (m, *diastereoisomeric proton*, 1H), 2.45 – 2.28 (m, 2H), 2.27 – 2.08 (m, *diastereoisomeric proton*, 1H), 2.07 – 1.88 (m, 2H), 1.76 – 1.63 (m, 2H).

¹³C NMR (151 MHz, CDCl₃, *mixture of diastereoisomers*) δ 219.9, 207.7, 148.5, 148.4, 146.7, 132.3, 132.2, 127.3, 126.3, 118.8, 118.7, 111.7, 111.0, 74.5, 70.5, 56.1, 55.1, 39.0, 38.6, 26.7, 22.4, 20.4.

Spectroscopic data are in agreement with those reported earlier.⁴³



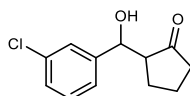
2-((4-chlorophenyl)(hydroxy)methyl)cyclopentan-1-one (3ad): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2d** (28 mg, 0.2 mmol), **1a** (84 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μL of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellow oil (27.2 mg, 61%).

¹H NMR (600 MHz, CDCl₃, *mixture of diastereoisomers, syn/anti ratio: 58:42*) δ 7.27 (dd, *J* = 8.8, 4.9 Hz, 2H), 7.25 – 7.20 (dd, 8.8, 4.9 Hz, 2H), 5.24 – 4.64 (m, *diastereoisomeric proton*, 1H),

2.42 – 2.30 (m, 2H), 2.24 – 2.05 (m, *diastereoisomeric proton*, 1H), 2.04 – 1.89 (m, 2H), 1.78 – 1.60 (m, 2H).

¹³C NMR (151 MHz, CDCl₃, *mixture of diastereoisomers*) δ 208.10, (*diastereoisomeric C=O is missing*), 141.4, 140.1, 131.7, 129.1, 128.7, 128.6, 128.1, 127.1, 74.7, 70.9, 70.8, 56.2, 55.4, 39.3, 38.8, 27.0, 22.8, 20.5.

Spectroscopic data are in agreement with those reported earlier.⁴³

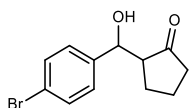


2-((3-chlorophenyl)(hydroxy)methyl)cyclopentan-1-one (3ae): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2e** (28 mg, 0.2 mmol), **1a** (84 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μL of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellowish oil (28.9 mg, 65%).

¹H NMR (600 MHz, CDCl₃, *mixture of diastereoisomers, syn/anti ratio: 60:40*) δ 7.37 – 7.34 (m, 1H), 7.32 – 7.26 (m, 1H), 7.24 (m, 1H), 7.20 (m, 1H), 5.30 – 5.26 (m, *diastereoisomeric proton*, 1H), 2.48 – 2.32 (m, 2H), 2.29 – 2.10 (m, *diastereoisomeric proton*, 1H), 2.08 – 1.95 (m, 2H), 1.82 – 1.65 (m, 2H).

¹³C NMR (151 MHz, CDCl₃, *mixture of diastereoisomers*) δ 208.0, (*diastereoisomeric C=O is missing*), 145.1, 143.6, 134.5, 134.5, 129.8, 129.7, 128.3, 127.5, 126.8, 125.9, 124.9, 123.8, 74.8, 70.8, 56.2, 55.3, 39.2, 38.8, 27.0, 22.7, 20.5, 20.4.

Spectroscopic data are in agreement with those reported earlier.⁴³



2-((4-bromophenyl)(hydroxy)methyl)cyclopentan-1-one (3af): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2f** (37 mg, 0.2 mmol), **1a** (84 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μL of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the off-white solid (16.9 mg, 31%).

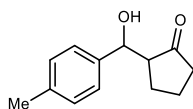
M.P.: 99 °C.

¹H NMR (600 MHz, CDCl₃, *mixture of diastereoisomers, syn/anti ratio: 56:44*) δ 7.44 (dd, *J* = 7.1, 1.4 Hz, 2H), 7.19 (ddd, *J* = 7.1, 1.4 Hz, 2H), 5.23 – 4.65 (m, *diastereoisomeric proton*, 1H),

2.42 – 2.30 (m, 2H), 2.26 – 2.07 (m, *diastereoisomeric proton*, 1H), 2.05 – 1.88 (m, 2H), 1.79 – 1.64 (m, 2H).

¹³C NMR (151 MHz, CDCl₃, *mixture of diastereoisomers*) δ 208.0, (*diastereoisomeric C=O is missing*), 141.9, 140.5, 131.6, 131.4, 128.3, 127.4, 121.8, 121.0, 74.6, 70.8, 56.1, 55.2, 39.2, 38.7, 26.9, 22.6, 20.4, 20.4.

Spectroscopic data are in agreement with those reported earlier.⁴³

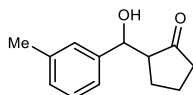


2-(hydroxy(p-tolyl)methyl)cyclopentan-1-one (3ag): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2g** (24 mg, 0.2 mmol), **1a** (84 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μL of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellow oil (17.6 mg, 43%).

¹H NMR (600 MHz, CDCl₃) δ 7.22 (dd, *J* = 7.9, 5.6 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 5.26 (m, *diastereoisomeric proton*, 1H), 2.47 – 2.39 (m, 2H), 2.34 (s, 3H), 2.28 – 2.10 (m, *diastereoisomeric proton*, 1H), 2.07 – 1.88 (m, 2H), 1.87 – 1.66 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 208.3, (*diastereoisomeric C=O is missing*), 142.9, 132.7, 131.4, 128.9, 127.3, 126.4, 123.8, 122.7, 75.3, 71.6, 56.2, 55.4, 39.3, 38.9, 37.9, 29.5, 27.1, 22.9, 21.6, 20.6.

Spectroscopic data are in agreement with those reported earlier.⁴³

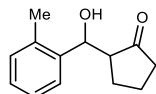


2-(hydroxy(m-tolyl)methyl)cyclopentan-1-one (3ah): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2h** (24 mg, 0.2 mmol), **1a** (84 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μL of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellow oil (16.3 mg, 40%).

¹H NMR (600 MHz, CDCl₃, *mixture of diastereoisomers, syn/anti ratio: 50:50*) δ 7.38 – 7.28 (dd, 15.6, 7.6 Hz, 1H), 7.22 (td, *J* = 15.6, 7.6 Hz, 1H), 7.15 (dd, *J* = 15.6, 7.6 Hz, 1H), 7.12 – 7.05 (dd, 15.6, 7.6 Hz, 1H), 5.27 – 4.64 (m, *diastereoisomeric proton*, 1H), 2.47 – 2.39 (m, 2H), 2.35 (s, 3H), 2.28 – 2.10 (m, *diastereoisomeric proton*, 1H), 2.06 – 1.90 (m, 2H), 1.87 – 1.61 (m, 2H).

¹³C NMR (151 MHz, CDCl₃, mixture of diastereoisomers) δ 208.3, (diastereoisomeric C=O is missing) 142.8, 141.4, 132.6, 131.3, 130.2, 128.8, 128.3, 128.1, 127.2, 126.3, 123.8, 122.6, 75.3, 71.6, 56.2, 55.3, 39.2, 38.8, 37.8, 29.4, 27.1, 22.8, 20.5, 20.4.

Spectroscopic data are in agreement with those reported earlier.⁴³

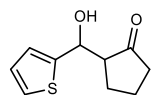


2-(hydroxy(o-tolyl)methyl)cyclopentan-1-one (3ai): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2i** (24 mg, 0.2 mmol), **1a** (84 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μL of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the colourless oil (13.5 mg, 33%).

¹H NMR (600 MHz, CDCl₃) δ 7.55 – 7.46 (m, 1H), 7.27 – 7.23 (m, 2H), 7.18 (m, 1H), 5.30 – 4.68 (m, diastereoisomeric proton, 1H), 2.48 – 2.42 (m, 2H), 2.37 (s, 3H), 2.30 – 2.12 (m, diastereoisomeric proton, 1H), 2.09 – 1.99 (m, 2H), 1.92 – 1.66 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 208.27, 196.50, 139.78, 139.74, 136.99, 135.11, 132.46, 130.81, 130.59, 129.48, 129.12, 129.05, 126.52, 125.56, 75.04, 71.57, 56.10, 55.34, 39.25, 37.79, 29.37, 22.91, 21.48, 21.08, 20.52, 20.18.

Spectroscopic data are in agreement with those reported earlier.⁴³

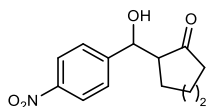


2-(hydroxy(thiophen-2-yl)methyl)cyclopentan-1-one (3am): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2m** (22.4 mg, 0.2 mmol), **1a** (84 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μL of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the colourless paste (33.5, 85).

¹H NMR (600 MHz, CDCl₃, mixture of diastereoisomers, syn/anti ratio: 50:50; inseparable mixture with elimination product) δ 7.27 (m, 1H), 6.97 – 6.94 (m, 2H), 5.49 – 5.01 (m, diastereoisomeric proton, 1H), 2.44 – 2.32 (m, 2H), 2.26 – 2.16 (m, diastereoisomeric proton, 1H), 2.02 – 1.88 (m, 2H), 1.82 – 1.71 (m, 2H).

¹³C NMR (151 MHz, CDCl₃, mixture of diastereoisomers) δ 207.8, (diastereoisomeric C=O is missing), 130.1, 129.6, 128.1, 126.8, 126.5, 125.3, 124.7, 124.6, 124.0, 71.4, 68.9, 56.0, 55.9, 39.3, 38.9, 27.1, 23.5, 20.7.

Spectroscopic data are in agreement with those reported earlier.⁴⁴



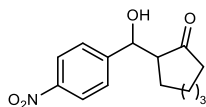
2-(hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (3ba): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2a** (30 mg, 0.2 mmol), **1b** (98 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μ L of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the off-white solid (47.2 mg, 96%).

M.P.: 98 °C.

¹H NMR (600 MHz, CDCl₃, mixture of diastereoisomers, syn/anti ratio: 55/45) δ 8.18 (dd, J = 8.7, 3.6 Hz, 2H), 7.49 (dd, J = 8.7, 3.6 Hz, 2H), 5.48 – 4.88 (m, diastereoisomeric proton, 1H), 2.60 (m, 1H), 2.50 – 2.44 (m, 1H), 2.36 (m, 2H), 2.12 – 2.05 (m, diastereoisomeric proton, 1H), 1.73 – 1.49 (m, 6H).

¹³C NMR (151 MHz, CDCl₃, mixture of diastereoisomers) δ 214.9, 214.2, 149.3, 148.5, 147.7, 147.1, 128.0, 126.7, 123.7, 123.5, 74.1, 70.2, 57.3, 56.9, 42.8, 42.7, 30.9, 27.9, 27.7, 26.0, 24.8, 24.7.

Spectroscopic data are in agreement with those reported earlier.⁴³



2-(hydroxy(4-nitrophenyl)methyl)cycloheptan-1-one (3ca): The compound was synthesized with general procedure 7.3.2. Inside a 4 mL glass vial with a magnetic stirrer, **2a** (30 mg, 0.2 mmol), **1c** (112 mg, 1.0 mmol), and 50 mg of wool powder were placed in 98 μ L of distilled water. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the off-white solid (43.9 mg, 83%).

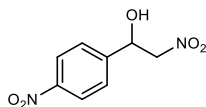
M.P.: 121-123 °C.

¹H NMR (600 MHz, CDCl₃) δ 8.18 (ddd, J = 8.8, 3.7, 1.6 Hz, 2H), 7.49 (ddd, J = 8.8, 3.7, 1.6 Hz, 2H), 5.47 – 4.89 (m, diastereoisomeric proton, 1H), 2.60 (qd, J = 17.1, 8.6 Hz, 1H), 2.51 – 2.44 (qd, J = 17.1, 8.6 Hz, 1H), 2.36 (qt, J = 17.1, 8.6 Hz, 2H), 2.14 – 2.06 (m, diastereoisomeric proton, 1H), 1.76 – 1.46 (m, 6H).

¹³C NMR (151 MHz, CDCl₃) δ 214.9, 214.2, 149.3, 148.5, 147.7, 147.1, 128.0, 126.7, 123.7, 123.5, 74.1, 70.2, 57.3, 56.9, 42.8, 42.7, 30.9, 29.2, 27.9, 27.7, 26.0, 24.8, 24.8.

Spectroscopic data are in agreement with those reported earlier.⁴³

7.3.7.2. Spectral Data for Wool Mediated Nitro–Aldol Reactions

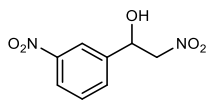


2-nitro-1-(4-nitrophenyl)ethan-1-ol (5a): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2a** (30 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellow oil (36.5 mg, 93%).

¹H NMR (600 MHz, DMSO) δ 8.23 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 5.44 (m, 1H), 4.97 – 4.60 (m, 2H), 3.35 (bs, 1H).

¹³C NMR (151 MHz, DMSO) δ 148.0, 147.1, 127.6, 123.4, 81.2, 69.1.

Spectroscopic data are in agreement with those reported earlier.⁴⁵

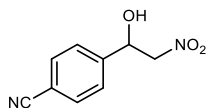


2-nitro-1-(3-nitrophenyl)ethan-1-ol (5b): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2b** (30 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pale orange oil (35.3 mg, 90%).

¹H NMR (600 MHz, CDCl₃) δ 8.26 (m, 1H), 8.16 (m, 1H), 7.72 – 7.68 (m, 1H), 7.55 (m, 1H), 5.54 (m, 1H), 4.59 – 4.49 (m, 2H), 3.10 (bs, 1H).

¹³C NMR (151 MHz, DMSO) δ 142.8, 136.9, 133.0, 129.9, 122.8, 121.0, 81.2, 68.8.

Spectroscopic data are in agreement with those reported earlier.⁴⁵



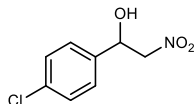
4-(1-hydroxy-2-nitroethyl)benzonitrile (5c): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2b** (26 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was

monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the colourless oil (31.9 mg, 83%).

¹H NMR (600 MHz, DMSO) δ 7.85 (dt, J = 8.0, 4.1 Hz, 1H), 7.66 (dt, J = 8.0, 4.1 Hz, 2H), 5.37 (m, 1H), 4.96 – 4.55 (m, 2H), 3.34 (bs, 1H).

¹³C NMR (151 MHz, DMSO) δ 146.0, 132.3, 127.3, 118.7, 110.7, 81.2, 69.3.

Spectroscopic data are in agreement with those reported earlier.⁴⁵

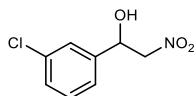


1-(4-chlorophenyl)-2-nitroethan-1-ol (5d): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2d** (28 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the colourless oil (25.8 mg, 64%).

¹H NMR (600 MHz, CDCl₃) δ 7.40 – 7.37 (m, 2H), 7.37 – 7.34 (m, 2H), 5.46 (m, 1H), 4.58 (m, 1H), 4.50 (m, 1H).

¹³C NMR (151 MHz, CDCl₃) 146.0, 132.3, 127.3, 118.7, 110.7, 81.2, 69.3.

Spectroscopic data are in agreement with those reported earlier.⁴⁵

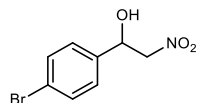


1-(3-chlorophenyl)-2-nitroethan-1-ol (5e): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2e** (28 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pale-yellow oil (23.4 mg, 58%).

¹H NMR (600 MHz, DMSO) δ 7.52 (t, J = 1.5 Hz, 1H), 7.41 (dt, J = 7.7, 1.5 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.34 (dd, J = 7.7, 1.5 Hz, 1H), 6.28 – 6.23 (m, 1H), 5.33 (dd, J = 9.7, 3.4 Hz, 1H), 4.89 (dd, J = 12.6, 3.4 Hz, 1H), 4.61 (dd, J = 12.6, 9.7 Hz, 1H).

¹³C NMR (151 MHz, DMSO) 146.0, 132.3, 127.3, 118.7, 110.7, 81.2, 69.3.

Spectroscopic data are in agreement with those reported earlier.⁴⁵

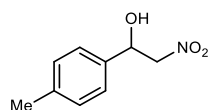


1-(4-bromophenyl)-2-nitroethan-1-ol (5f): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2f** (37 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellowish oil (30.1 mg, 61%).

^1H NMR (600 MHz, CDCl_3) δ 7.55 – 7.54 (m, 2H), 7.41 – 7.40 (m, 2H), 5.30 – 5.27 (m, 1H), 4.86 – 4.84 (m, 1H), 4.59 – 4.56 (m, 1H).

^{13}C NMR (151 MHz, CDCl_3) 137.1, 132.5, 131.0, 128.8, 83.2, 70.4.

Spectroscopic data are in agreement with those reported earlier.⁴⁵

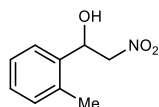


2-nitro-1-(p-tolyl)ethan-1-ol (5g): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2g** (24 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pale-yellow oil (17.2 mg, 47%).

^1H NMR (600 MHz, DMSO) δ 7.85 – 7.83 (m, 1H), 7.30 – 7.28 (m, 1H), 7.17 (d, J = 7.8 Hz, 2H), 6.03 (s, 1H), 5.23 (dd, J = 9.9, 3.5 Hz, 1H), 4.79 (dd, J = 12.4, 3.5 Hz, 1H), 4.54 (dd, J = 12.4, 9.8 Hz, 1H), 2.28 (s, 3H).

^{13}C NMR (151 MHz, DMSO) δ 167.8, 143.5, 138.0, 137.6, 82.4, 70.3, 21.6.

Spectroscopic data are in agreement with those reported earlier.⁴⁵



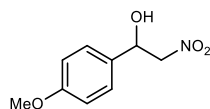
2-nitro-1-(o-tolyl)ethan-1-ol (5i): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2i** (24 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using

AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellow oil (14.9 mg, 83%).

¹H NMR (600 MHz, CDCl₃) δ 7.25 – 7.21 (m, 3H), 7.11 – 7.08 (m, 1H), 4.75 (m, 3H), 2.46 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 136.3, 134.5, 130.8, 128.6, 126.7, 125.6, 80.2, 67.9, 18.8.

Spectroscopic data are in agreement with those reported earlier.⁴⁵

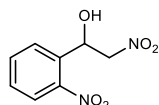


1-(4-methoxyphenyl)-2-nitroethan-1-ol (5k): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2k** (27 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μL of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the colourless oil (13.9 mg, 35%).

¹H NMR (600 MHz, CDCl₃) δ 7.16 – 7.12 (m, 2H), 6.91 – 6.88 (m, 2H), 4.77 – 4.71 (m, 3H), 3.80 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 160.1, 128.5, 125.8, 115.0, 55.3, 41.2.

Spectroscopic data are in agreement with those reported earlier.⁴⁵

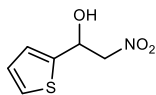


1-(2-nitrophenyl)-2-nitroethan-1-ol (5l): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2l** (30 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μL of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pale orange paste (12.7 mg, 30%).

¹H NMR (600 MHz, DMSO) δ 8.06 – 8.04 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.92 – 7.90 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.82 – 7.80 (td, *J* = 7.8, 1.4 Hz, 1H), 7.63 – 7.60 (ddd, *J* = 8.4, 7.8, 1.4 Hz, 1H), 6.38 (dd, *J* = 4.9, 1.2 Hz, 1H), 5.80 – 5.78 (ddd, *J* = 9.5, 4.9, 2.8 Hz, 1H), 4.98 – 4.95 (ddd, *J* = 12.9, 2.8, 1.2 Hz, 1H), 4.62 – 4.58 (dd, *J* = 12.9, 9.5 Hz, 1H).

¹³C NMR (151 MHz, DMSO) δ 147.7, 136.0, 134.4, 129.9, 129.6, 124.9, 81.4, 66.6.

Spectroscopic data are in agreement with those reported earlier.⁴⁵



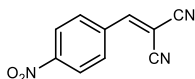
2-nitro-1-(thiophen-2-yl)ethan-1-ol (5m): The compound was synthesized with general procedure 7.3.3. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2m** (22.4 mg, 0.2 mmol), **4** (122 mg, 2.0 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of distilled water. Upon completion, the reaction mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 1:1). The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellowish oil (22.9 mg, 66%).

^1H NMR (600 MHz, CDCl_3) δ 7.34 (dd, $J = 5.1, 1.1$ Hz, 1H), 7.07 (dt, $J = 3.6, 1.1$ Hz, 1H), 7.02 (dd, $J = 5.1, 3.6$ Hz, 1H), 5.73 (dd, $J = 9.3, 3.2$ Hz, 1H), 4.72 (dd, $J = 13.4, 9.3$ Hz, 1H), 4.62 (dd, $J = 13.4, 3.2$ Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 141.4, 135.6, 134.7, 133.9, 132.2, 131.7, 129.0, 127.4, 126.3, 125.2, 80.9, 67.3.

Spectroscopic data are in agreement with those reported earlier.⁴⁶

7.3.7.3. Spectral Data for Wool Mediated Knoevenagel Reaction



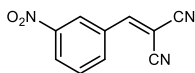
2-(4-nitrobenzylidene)malononitrile (8a): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2a** (30 mg, 0.2 mmol), **6** (13.2 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellowish solid (38.3 mg, 96%).

M.P.: 164-165 $^{\circ}\text{C}$.

^1H NMR (600 MHz, CDCl_3) δ 8.10 (m, 3H), 8.04 (s, 1H), 7.92 (m, 2H), 7.83 – 7.79 (m, 3H), 7.70 – 7.66 (m, 2H), 7.55 (m, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 187.7, 152.4, 135.7, 135.1, 134.0, 132.9, 131.0, 129.4, 128.9, 117.7, 116.0, 113.5.

Spectroscopic data are in agreement with those reported earlier.⁴⁷



2-(3-nitrobenzylidene)malononitrile (8b): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2b** (30 mg, 0.2 mmol), **6** (13.2 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute

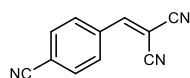
ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the white solid (36.3 mg, 91%).

M.P.: 105 °C.

¹H NMR (600 MHz, CDCl₃) δ 8.66 (d, *J* = 2.3 Hz, 1H), 8.47 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.32 (d, *J* = 8.2 Hz, 1H), 7.89 (s, 1H), 7.79 (t, *J* = 8.2 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 157.1, 148.8, 134.9, 132.1, 131.1, 128.4, 125.7, 112.8, 111.8, 87.0.

Spectroscopic data are in agreement with those reported earlier.⁴⁷



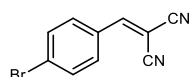
2-(4-cyanobenzylidene)malononitrile (8c): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2c** (26 mg, 0.2 mmol), **6** (13.2 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μL of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the off-white solid (31.9 mg, 89%).

M.P.: 157-158 °C.

¹H NMR (600 MHz, CDCl₃) δ 8.02 – 7.97 (m, 2H), 7.84 (s, 1H), 7.84 – 7.79 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 157.4, 134.4, 133.3, 130.8, 117.4, 117.4, 112.9, 111.8.

Spectroscopic data are in agreement with those reported earlier.⁴⁷



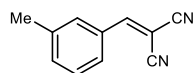
2-(4-bromobenzylidene)malononitrile (8f): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2f** (37 mg, 0.2 mmol), **6** (13.2 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μL of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pale brownish solid (32.8 mg, 62%).

M.P.: 163 °C.

¹H NMR (600 MHz, CDCl₃) δ 7.78 – 7.76 (dd, *J* = 8.6, 1.8 Hz, 2H), 7.71 (s, 1H), 7.70 – 7.68 (dd, *J* = 8.6, 1.8 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 158.4, 133.1, 131.8, 129.9, 129.7, 113.4, 112.3, 83.6.

Spectroscopic data are in agreement with those reported earlier.⁴⁷



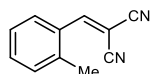
2-(3-methylbenzylidene)malononitrile (8h): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2h** (24 mg, 0.2 mmol), **6** (13.2 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the white solid (26.1 mg, 72%).

M.P.: 136-137 °C.

¹H NMR (600 MHz, CDCl₃) δ 7.75 – 7.71 (m, 2H), 7.68 (s, 1H), 7.46 – 7.41 (m, 2H), 2.43 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 160.3, 139.8, 135.7, 131.4, 131.1, 129.6, 128.0, 113.9, 112.7, 82.5, 21.4.

Spectroscopic data are in agreement with those reported earlier.⁴⁷



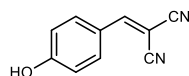
2-(2-methylbenzylidene)malononitrile (8i): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2i** (24 mg, 0.2 mmol), **6** (13.2 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the white solid (16.3 mg, 45%).

M.P.: 105 °C.

¹H NMR (600 MHz, CDCl₃) δ 8.10 (s, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 2.45 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 158.3, 139.9, 134.3, 131.5, 130.1, 128.4, 127.2, 113.9, 112.6, 84.2, 19.9.

Spectroscopic data are in agreement with those reported earlier.⁴⁷



2-(4-hydroxybenzylidene)malononitrile (8j): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2j** (24.4 mg, 0.2 mmol),

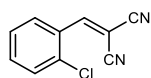
6 (13.2 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pale yellow solid (18.5 mg, 51%).

M.P.: 184 °C.

¹H NMR (600 MHz, CDCl₃) 7.91 – 7.89 (m, 2H), 7.65 – 7.62 (m, 2H), 7.01 (s, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 161.7, 158.9, 133.7, 130.6, 124.5, 116.8, 116.3, 114.4.

Spectroscopic data are in agreement with those reported earlier.⁴⁷



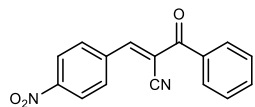
2-(2-chlorobenzylidene)malononitrile (8n): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2n** (28 mg, 0.2 mmol), **6** (13.2 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the white solid (15.3 mg, 38%).

M.P.: 91-92 °C.

¹H NMR (600 MHz, CDCl₃) δ 8.27 (s, 1H), 8.18 (m, 1H), 7.58 – 7.53 (m, 2H), 7.48 – 7.42 (m, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 156.1, 136.4, 135.1, 130.7, 129.5, 129.1, 127.8, 113.2, 111.9, 85.8.

Spectroscopic data are in agreement with those reported earlier.⁴⁷



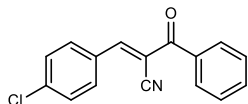
2-benzoyl-3-(4-nitrophenyl)acrylonitrile (9a): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2a** (30 mg, 0.2 mmol), **7** (29 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pale-brown solid (57.8 mg, 99%).

M.P.: 115-117 °C.

¹H NMR (600 MHz, CDCl₃) δ 8.02 (s, 1H), 7.99 – 7.96 (m, 2H), 7.90 (m, 2H), 7.67 – 7.63 (m, 1H), 7.56 – 7.52 (m, 2H), 7.52 – 7.49 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 188.5, 153.8, 139.6, 135.6, 133.5, 132.2, 131.1, 130.2, 130.0, 129.7, 129.3, 129.1, 128.7, 128.4, 116.7, 110.5.

Spectroscopic data are in agreement with those reported earlier.⁴⁸



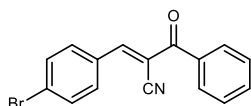
2-benzoyl-3-(4-chlorophenyl)acrylonitrile (9d): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2d** (28 mg, 0.2 mmol), **7** (29 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μL of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pale yellowish solid (38.2 mg, 69%).

M.P.: 89-90 °C.

¹H NMR (600 MHz, CDCl₃) δ 8.00 (s, 1H), 7.91 – 7.88 (m, 4H), 7.69 – 7.66 (m, 2H), 7.66 – 7.63 (m, 2H), 7.56 – 7.52 (m, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 188.9, 154.3, 136.0, 134.0, 133.1, 132.6, 132.4, 131.2, 131.0, 129.7, 129.1, 128.7, 117.1, 111.0.

Spectroscopic data are in agreement with those reported earlier.⁴⁸



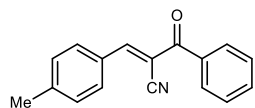
2-benzoyl-3-(4-bromophenyl)acrylonitrile (9f): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2f** (37 mg, 0.2 mmol), **7** (29 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μL of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the pale brownish solid (35.8 mg, 56%).

M.P.: 103.

¹H NMR (600 MHz, CDCl₃) δ 7.99 (s, 1H), 7.90 – 7.86 (m, 4H), 7.65 (m, 3H), 7.53 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 188.6, 154.1, 135.7, 133.7, 132.8, 130.7, 129.4, 129.2, 128.8, 128.4, 116.8, 110.8.

Spectroscopic data are in agreement with those reported earlier.⁴⁸



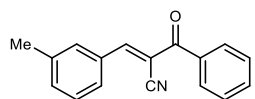
2-benzoyl-3-(p-tolyl)acrylonitrile (9g): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2g** (24 mg, 0.2 mmol), **7** (29 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellow solid (25.3 mg, 47%).

M.P.: 95 °C.

^1H NMR (600 MHz, CDCl_3) δ 8.03 (s, 1H), 7.95 – 7.92 (m, 2H), 7.89 – 7.86 (m, 2H), 7.63 – 7.61 (dd, J = 8.4, 7.8 Hz, 1H), 7.52 (ddd, J = 8.4, 7.8, 1.8 Hz, 2H), 7.32 (dd, J = 7.8, 1.8 Hz, 2H), 2.44 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 189.3, 155.7, 144.9, 136.1, 133.3, 131.4, 130.2, 129.4, 129.3, 128.7, 117.2, 109.0, 22.0.

Spectroscopic data are in agreement with those reported earlier.⁴⁸

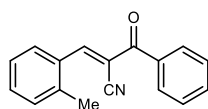


2-benzoyl-3-(m-tolyl)acrylonitrile (9h): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2h** (24 mg, 0.2 mmol), **7** (29 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellowish paste (35.4 mg, 71%).

^1H NMR (600 MHz, CDCl_3) δ 8.03 (s, 1H), 7.90 – 7.86 (dd, J = 14.1, 7.7 Hz, 3H), 7.81 (s, 1H), 7.66 – 7.62 (ddd, 14.1, 7.7, 1.8 Hz, 1H), 7.53 (td, J = 7.7, 1.8 Hz, 2H), 7.43 – 7.39 (m, 2H), 2.43 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 189.3, 156.0, 139.4, 136.0, 134.5, 133.5, 131.9, 129.5, 129.4, 128.8, 128.4, 117.1, 110.1, 21.5.

Spectroscopic data are in agreement with those reported earlier.⁴⁸

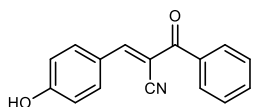


2-benzoyl-3-(o-tolyl)acrylonitrile (9i): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2i** (24 mg, 0.2 mmol), **7** (29 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the yellow paste (21.4 mg, 43%).

^1H NMR (600 MHz, CDCl_3) δ 8.37 (s, 1H), 8.24 – 8.22 (d, J = 7.8 Hz, 1H), 7.94 – 7.89 (m, 2H), 7.67 – 7.62 (m, 1H), 7.55 – 7.52 (t, J = 7.8 Hz, 2H), 7.46 – 7.43 (t, J = 7.6 Hz, 1H), 7.37 – 7.35 (t, J = 7.6 Hz, 1H), 7.31 – 7.30 (d, J = 7.6 Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 189.1, 154.0, 139.8, 136.0, 133.6, 132.9, 131.2, 131.1, 129.5, 128.8, 128.7, 126.9, 116.8, 111.8, 20.0.

Spectroscopic data are in agreement with those reported earlier.⁴⁸



2-benzoyl-3-(4-hydroxyphenyl)acrylonitrile (9j): The compound was synthesized with general procedure 7.3.4. Inside a 4 mL glass vial equipped with a magnetic stirrer, **2j** (24.4 mg, 0.2 mmol), **7** (29 mg, 0.2 mmol), and 50 mg of wool powder were placed in the presence of 98 μ L of absolute ethanol. The mixture was gently stirred, and the reaction progress was monitored using TLC (Heptane/AcOEt 5:1) upon completion. The product was recovered by implementing simple filtration using AcOEt with a paper filter. After that, the solvent was evaporated under reduced pressure to obtain the off-white solid (12.2 mg, 23%).

M.P.: 123 $^{\circ}\text{C}$.

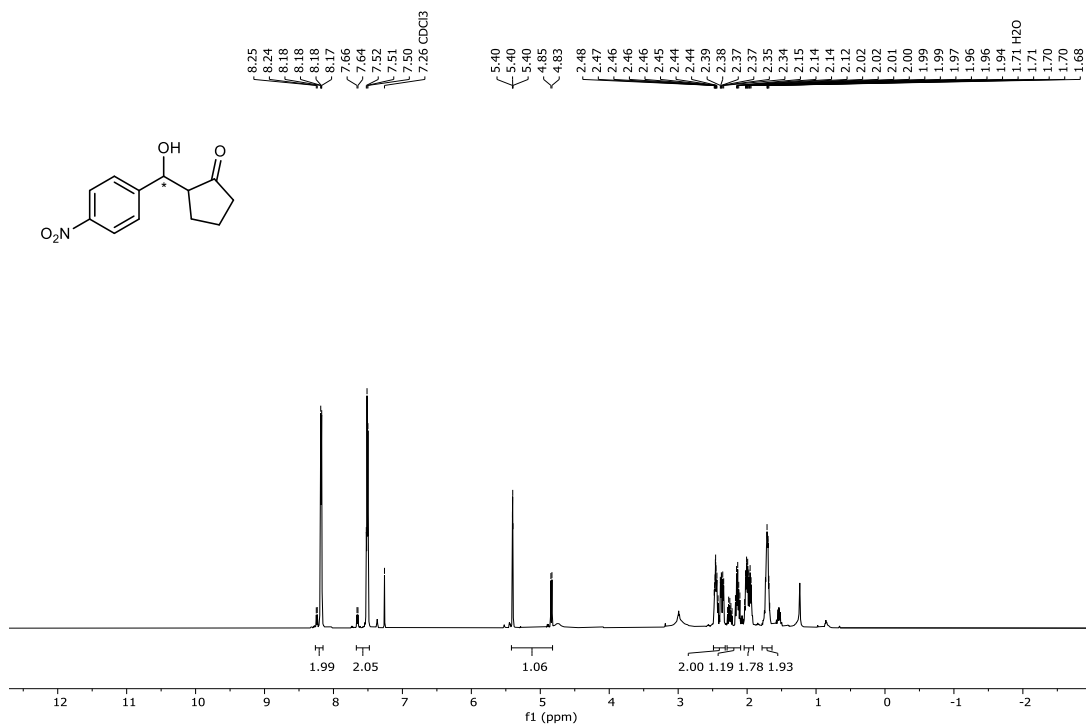
^1H NMR (600 MHz, CDCl_3) δ 8.03 (s, 1H), 8.01 (m, 2H), 7.93 (m, 1H), 7.87 (m, 2H), 7.53 (m, 2H), 6.95 (m, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 191.4, 155.3, 151.0, 149.2, 143.9, 143.5, 142.6, 134.1, 133.1, 129.2, 128.6, 116.5.

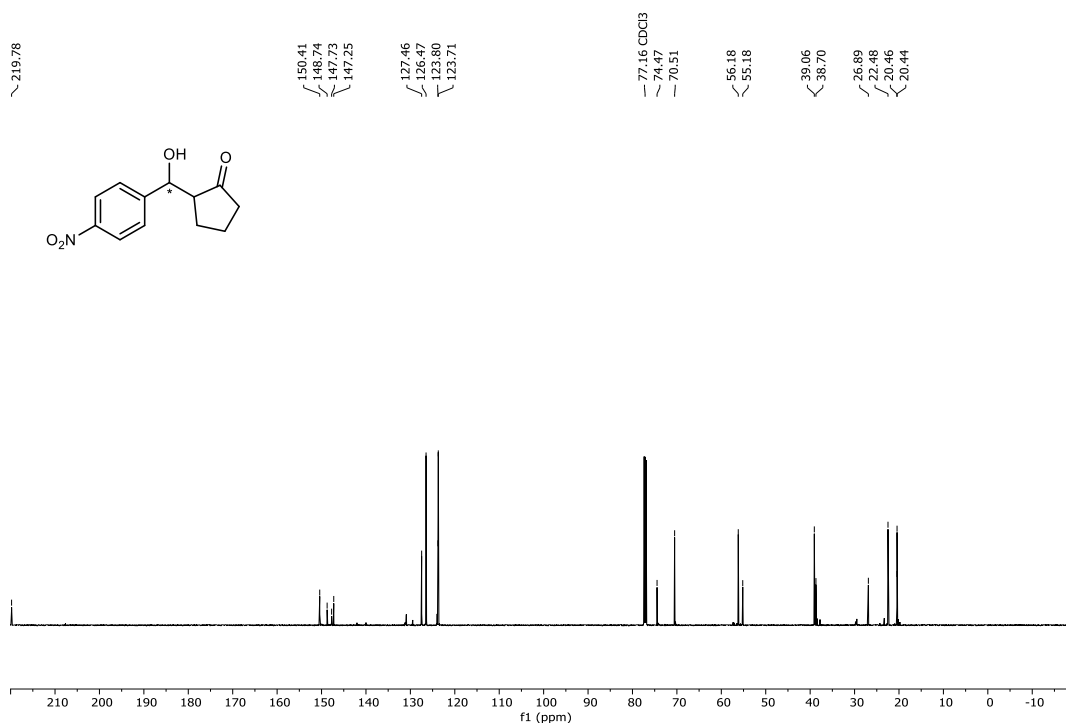
Spectroscopic data are in agreement with those reported earlier.⁴⁸

7.3.8. NMR Spectra for Compounds in Chapter 4

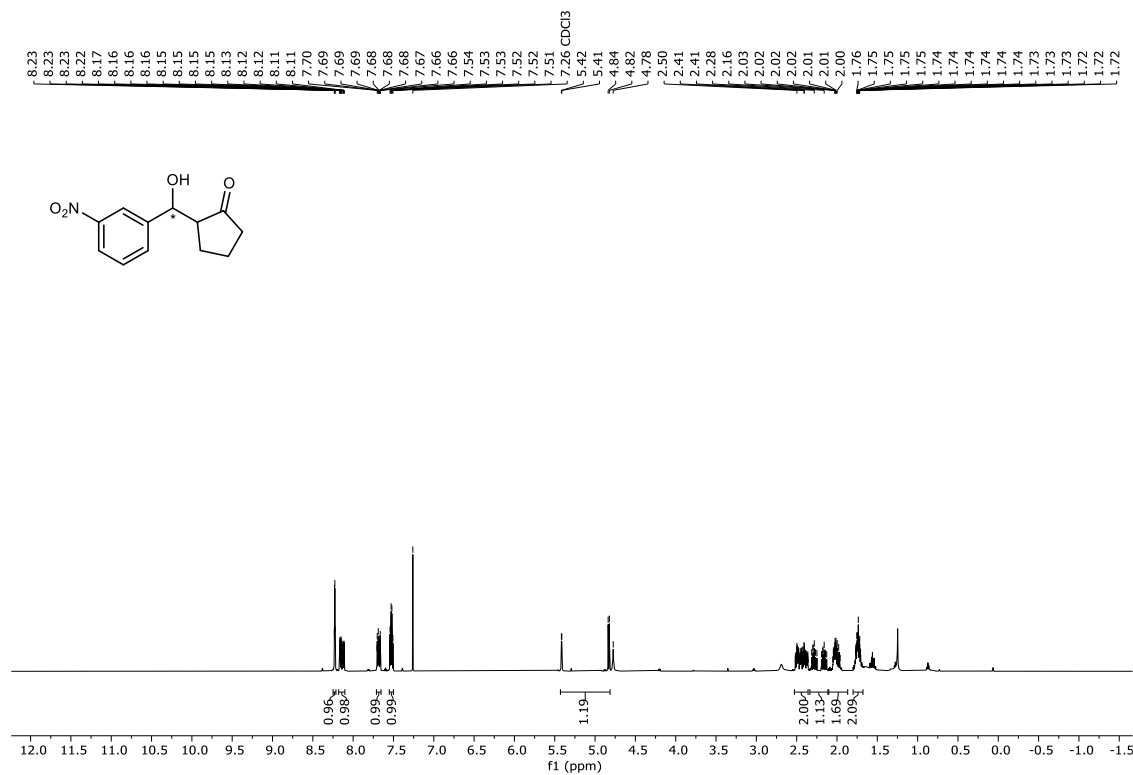
^1H NMR (600 MHz, CDCl_3) spectrum of 2-(hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one (3aa)



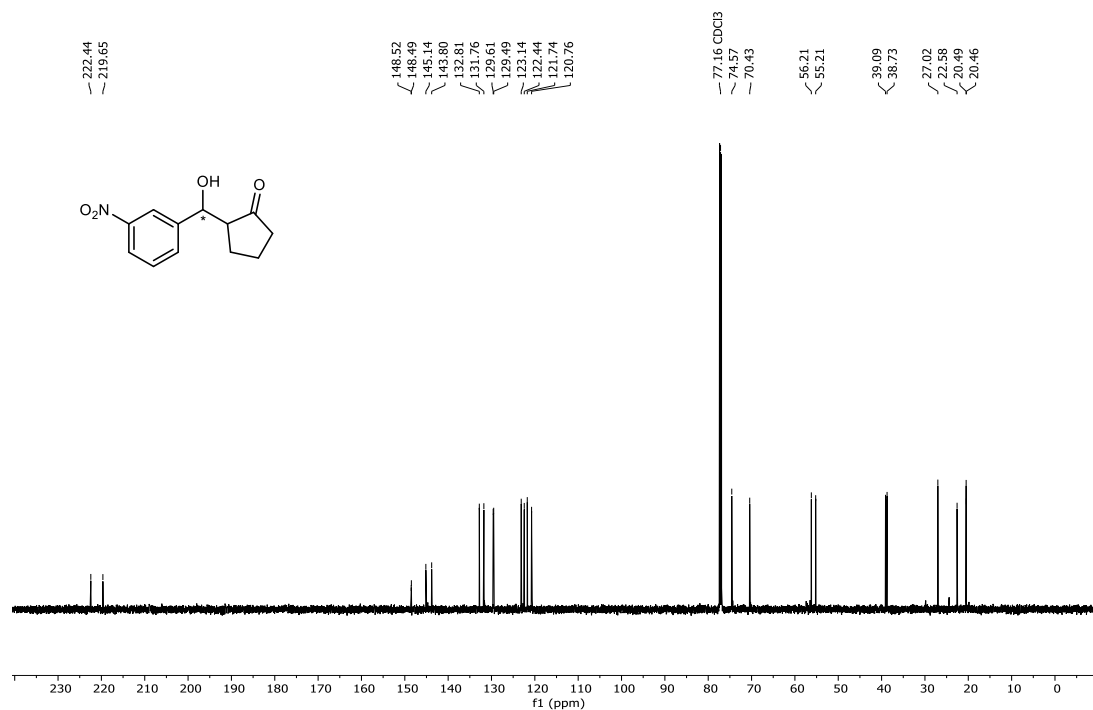
^{13}C NMR (151 MHz, CDCl_3) spectrum of 2-(hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one (3aa)



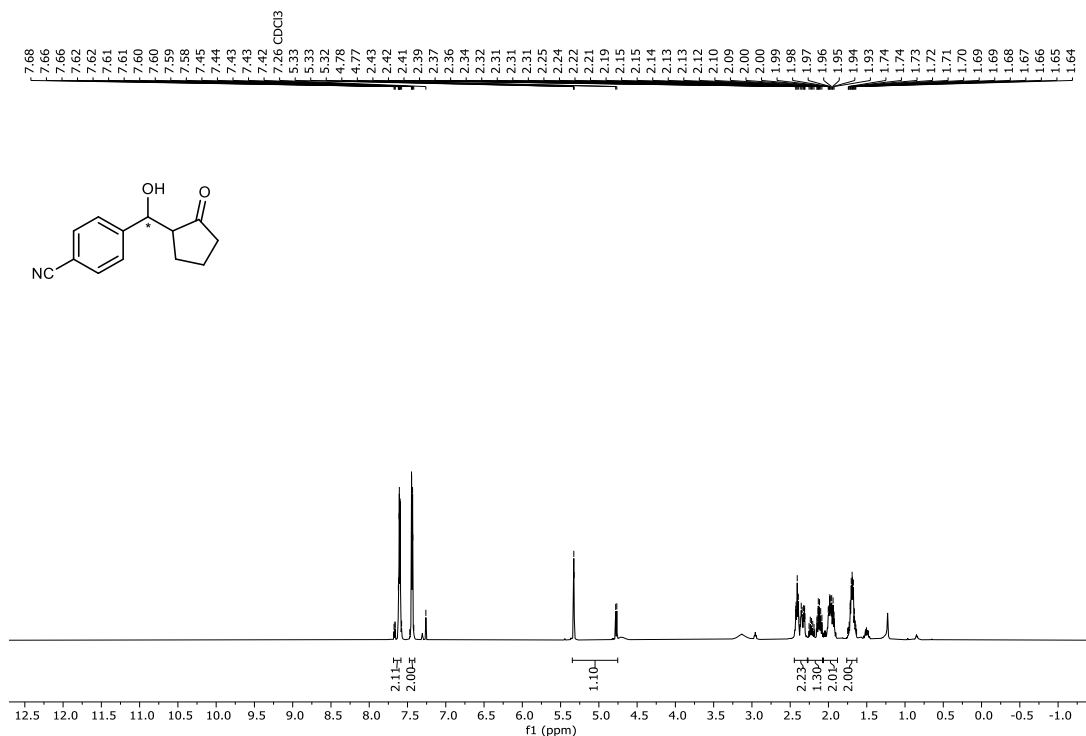
¹H NMR (600 MHz, CDCl₃) spectrum of **2-(hydroxy(3-nitrophenyl)methyl)cyclopentan-1-one (3ab)**



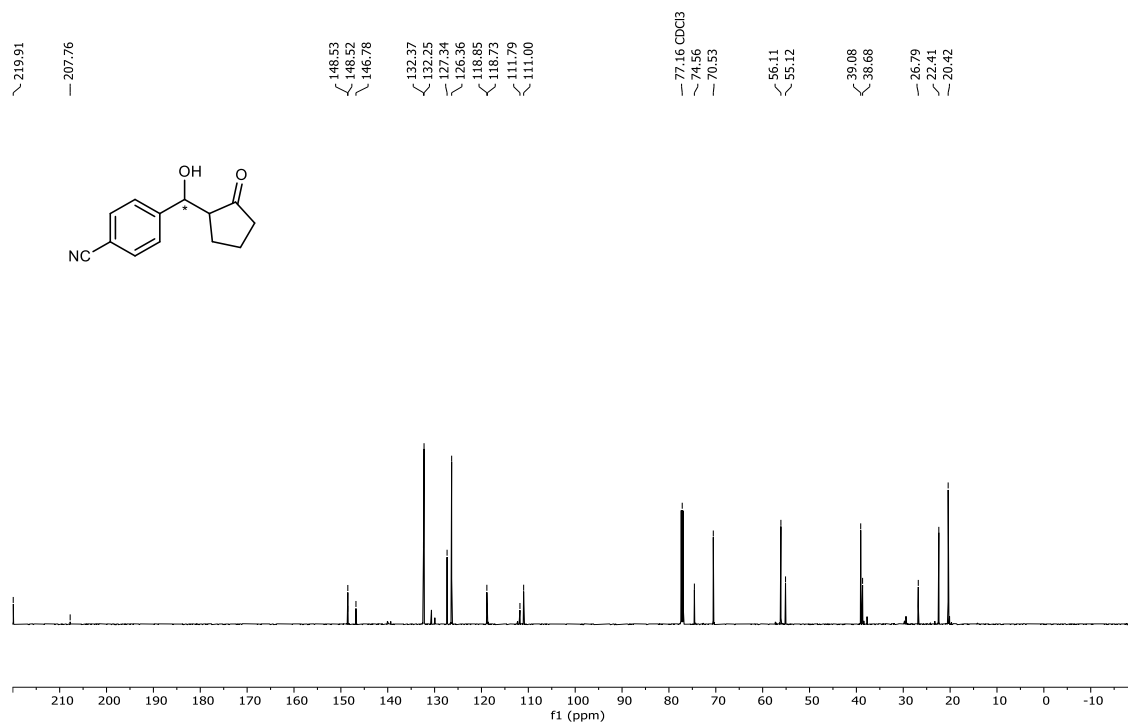
¹³C NMR (151 MHz, CDCl₃) spectrum of **2-(hydroxy(3-nitrophenyl)methyl)cyclopentan-1-one (3ab)**



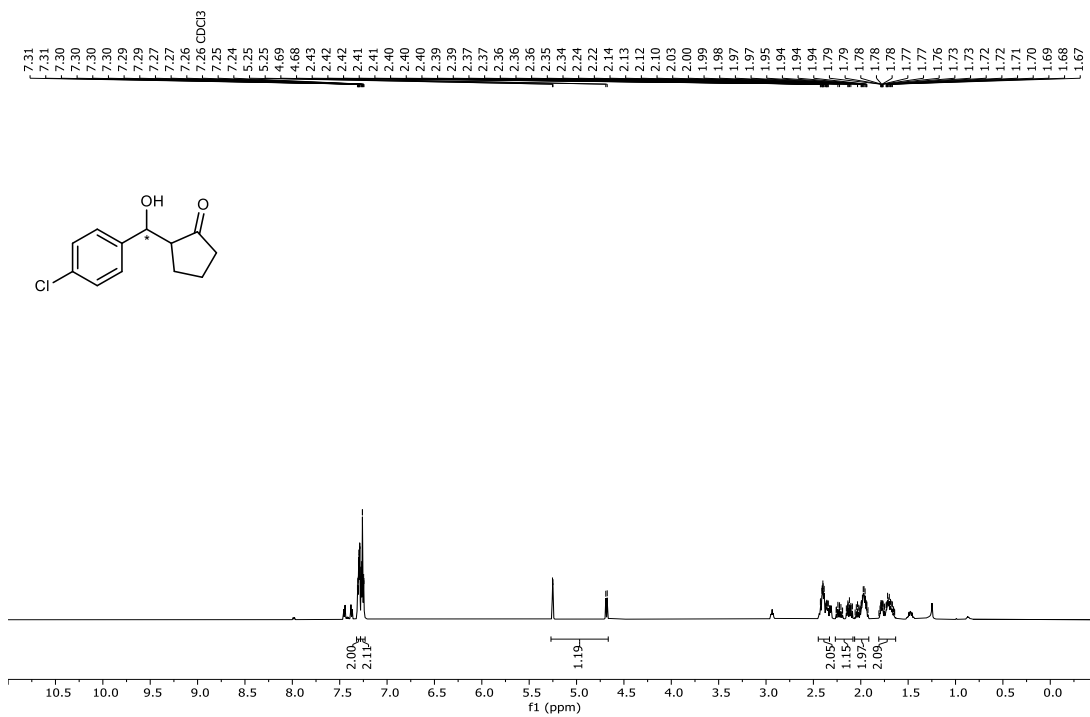
¹H NMR (600 MHz, CDCl₃) spectrum of 4-(hydroxy(2-oxocyclopentyl)methyl)benzonitrile (3ac)



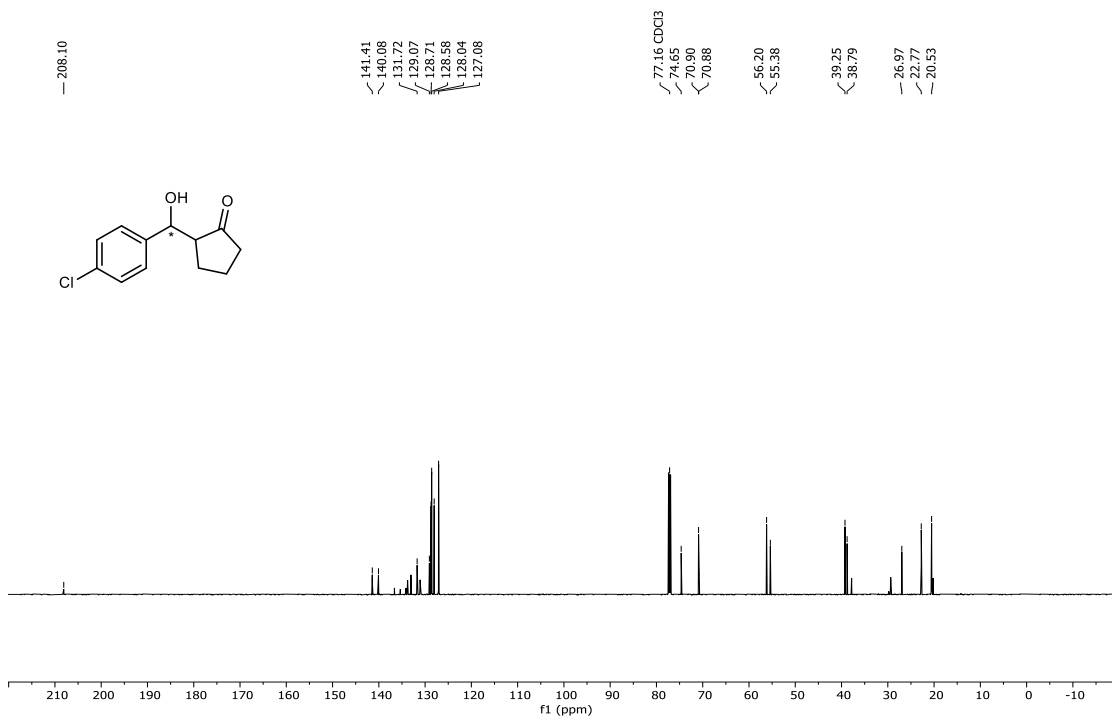
¹³C NMR (151 MHz, CDCl₃) spectrum of 4-(hydroxy(2-oxocyclopentyl)methyl)benzonitrile (3ac)



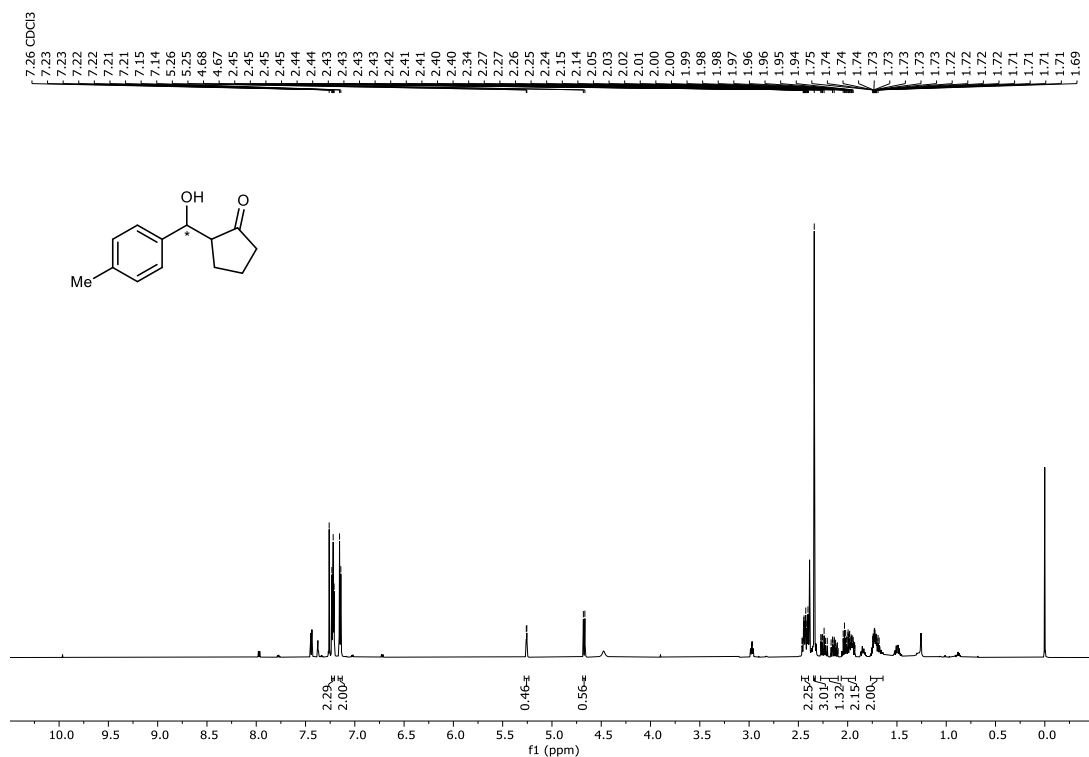
¹H NMR (600 MHz, CDCl₃) spectrum of **2-((4-chlorophenyl)(hydroxy)methyl)cyclopentan-1-one (3ad)**



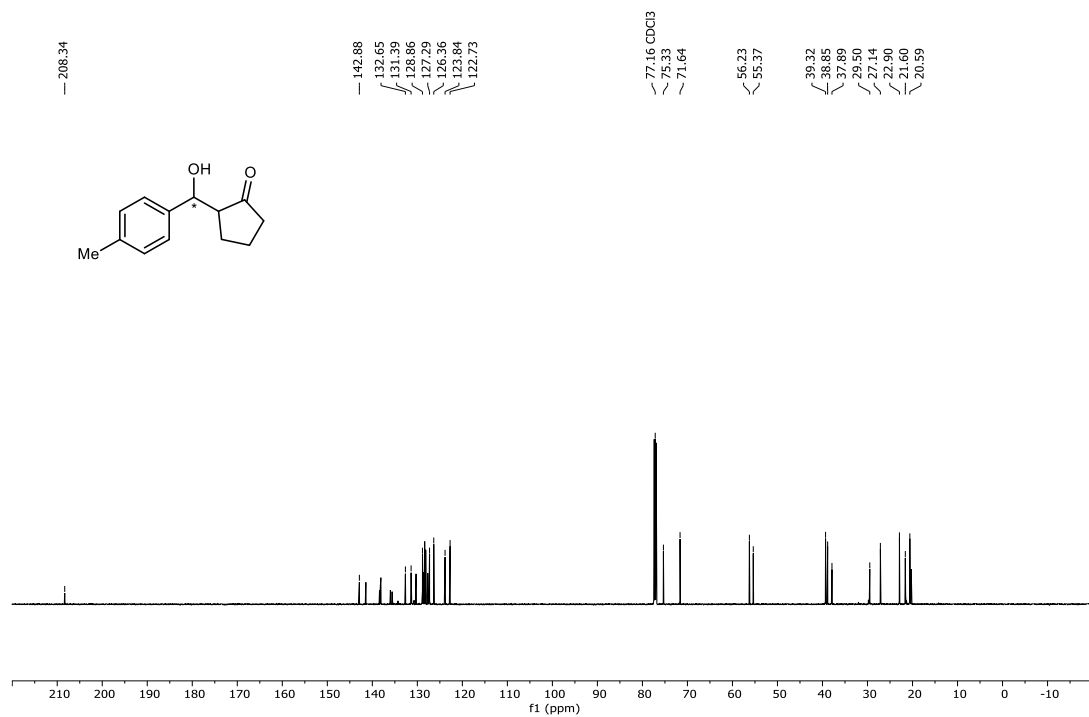
¹³C NMR (151 MHz, CDCl₃) spectrum of **2-((4-chlorophenyl)(hydroxy)methyl)cyclopentan-1-one (3ad)**



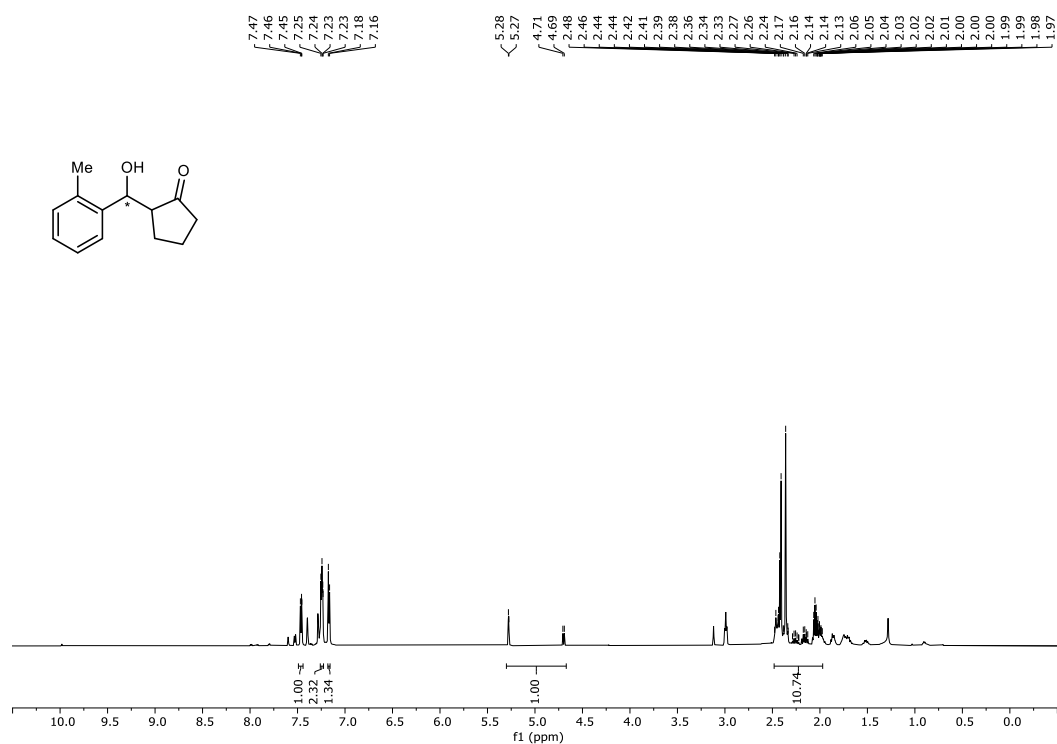
¹H NMR (600 MHz, CDCl₃) spectrum of **2-(hydroxy(p-tolyl)methyl)cyclopentan-1-one (3ag)**



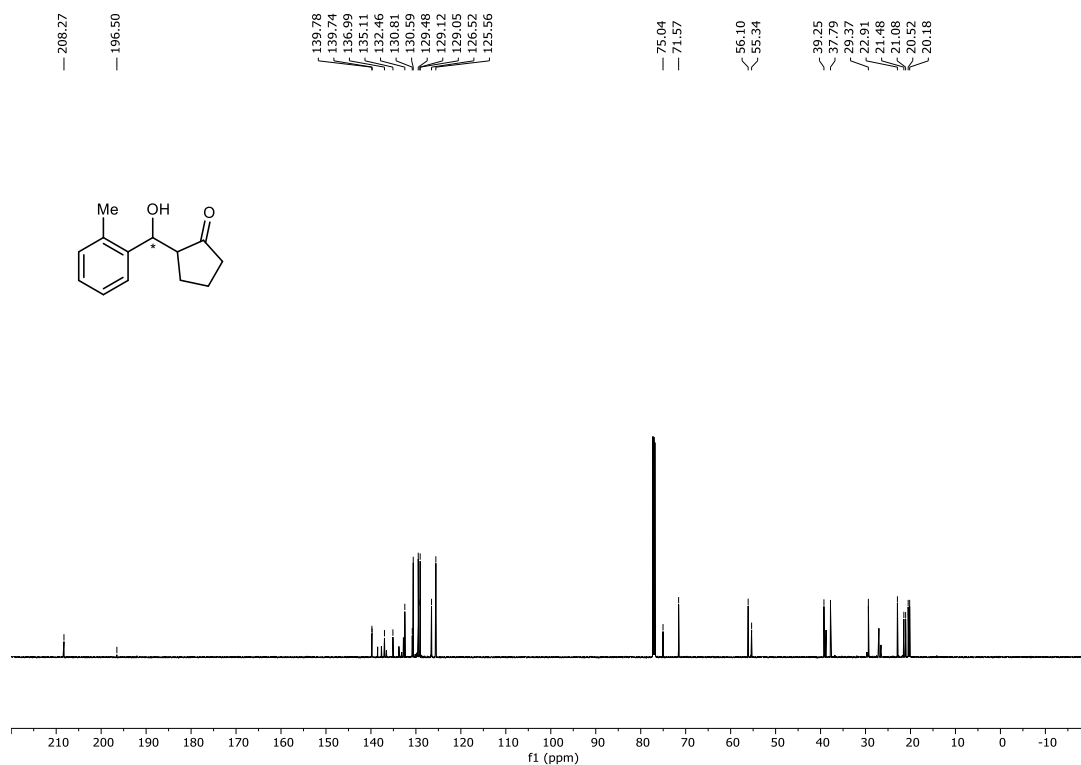
¹³C NMR (151 MHz, CDCl₃) spectrum of **2-(hydroxy(p-tolyl)methyl)cyclopentan-1-one (3ag)**



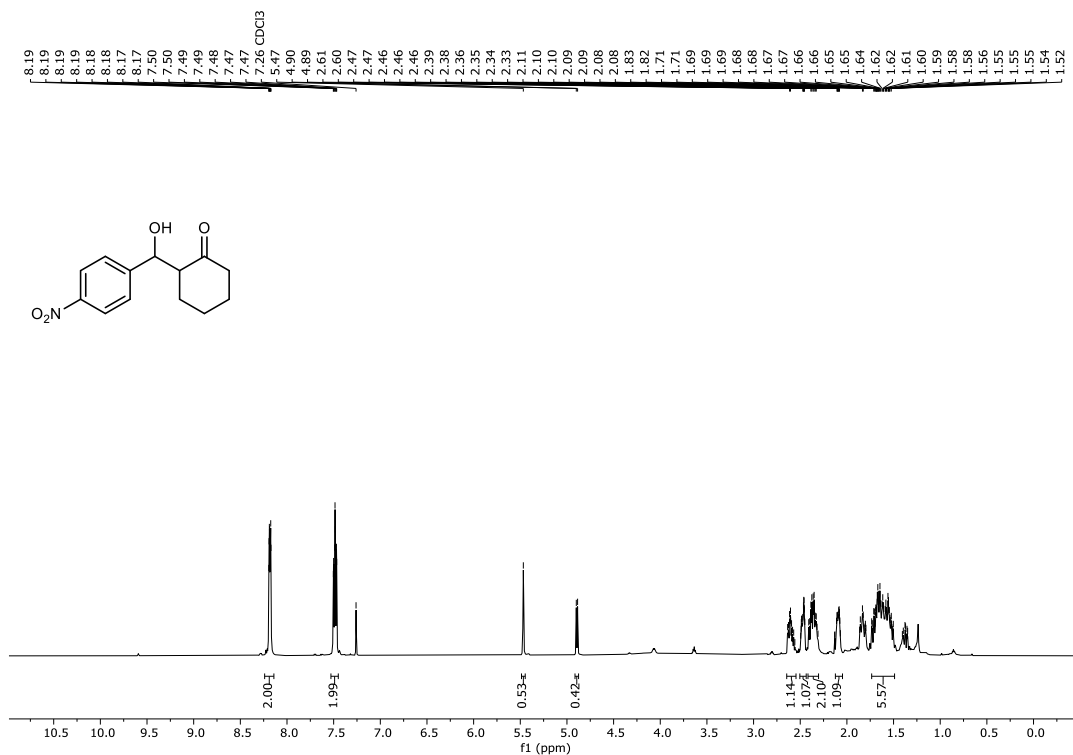
¹H NMR (600 MHz, CDCl₃) spectrum of 2-(hydroxy(o-tolyl)methyl)cyclopentan-1-one (3ai)



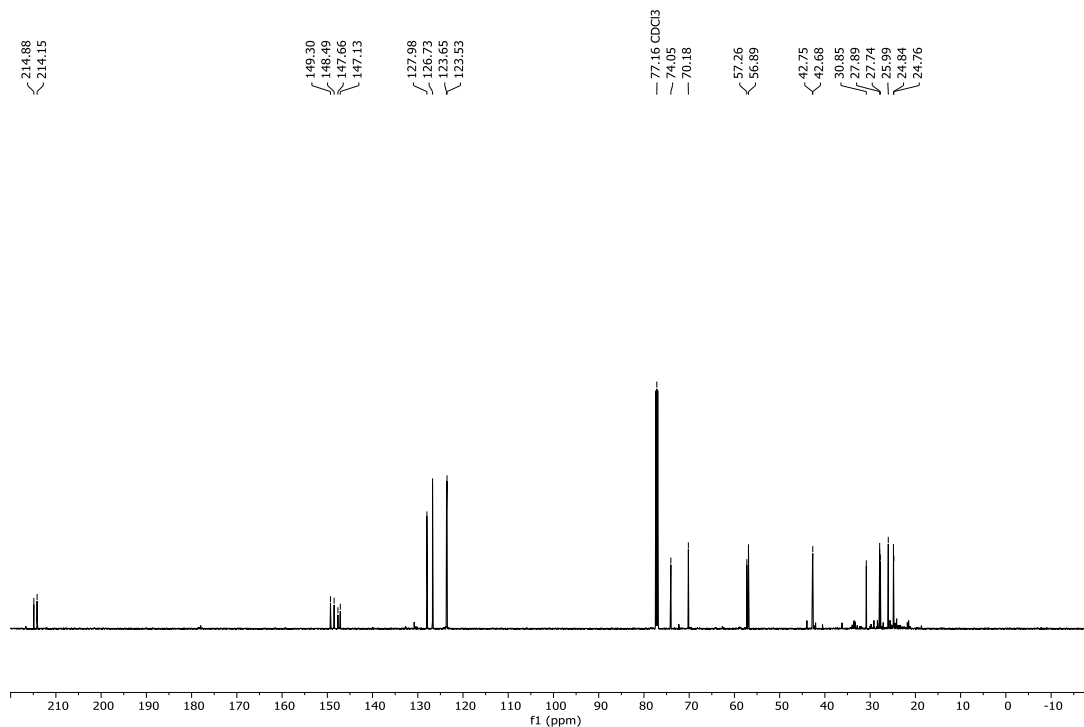
¹³C NMR (151 MHz, CDCl₃) spectrum of 2-(hydroxy(o-tolyl)methyl)cyclopentan-1-one (3ai)



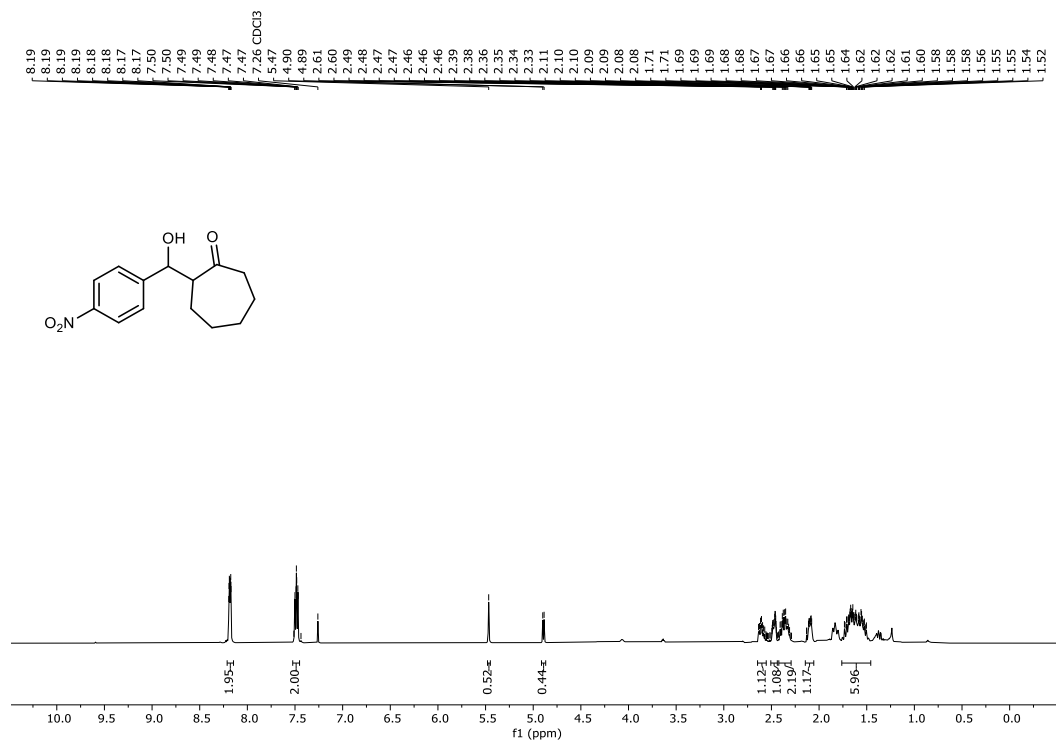
¹H NMR (600 MHz, CDCl₃) spectrum of 2-(hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (3ba)



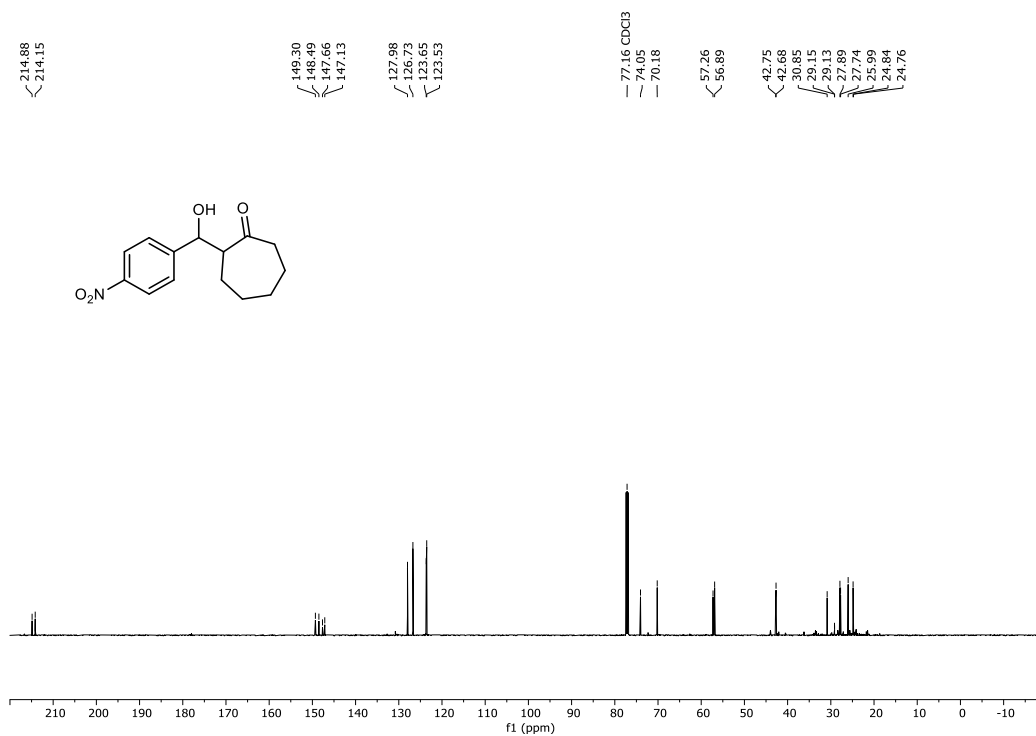
¹³C NMR (151 MHz, CDCl₃) spectrum of 2-(hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (3ba)



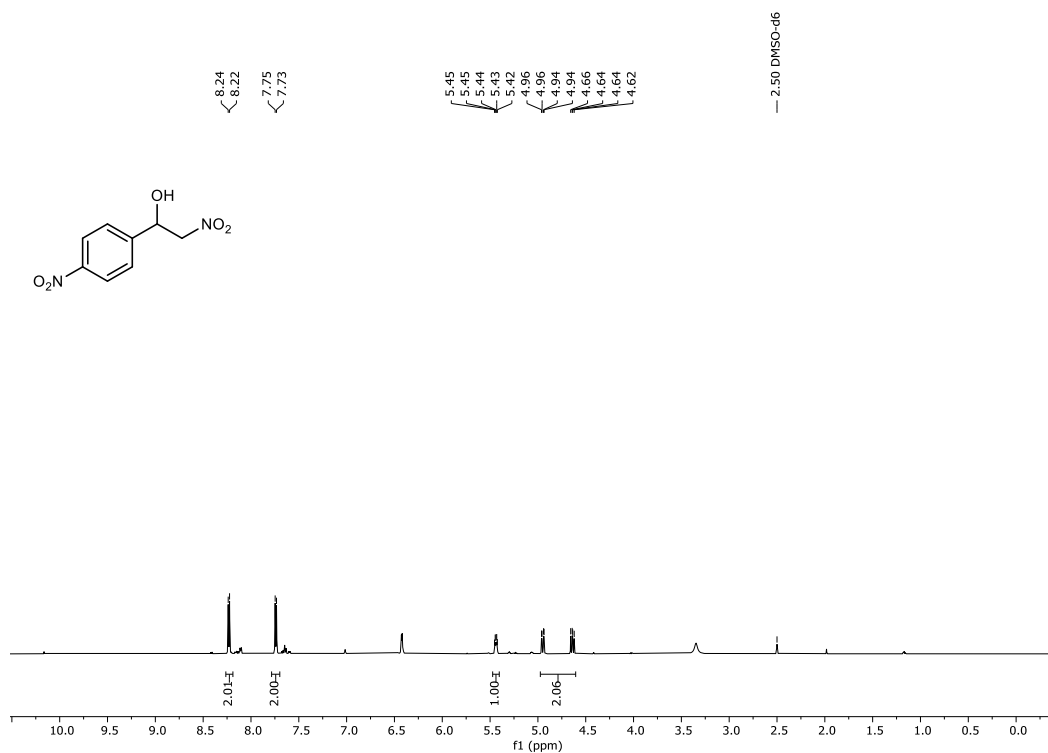
^1H NMR (600 MHz, CDCl_3) spectrum of 2-(hydroxy(4-nitrophenyl)methyl)cycloheptan-1-one (3ca)



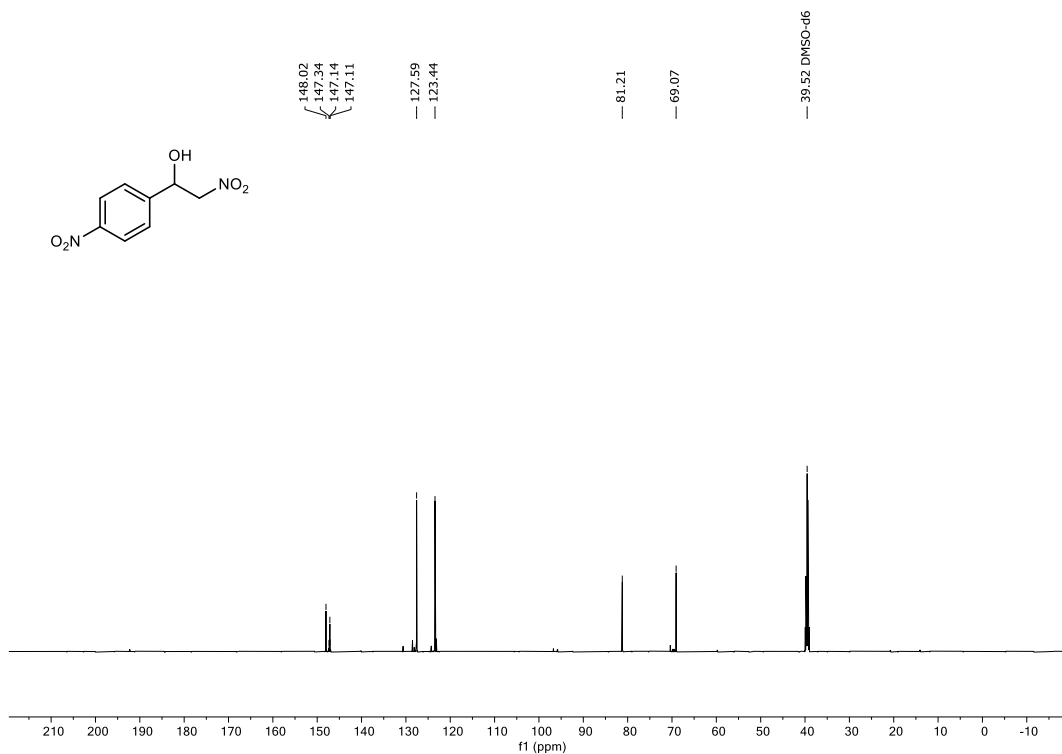
^{13}C NMR (151 MHz, CDCl_3) spectrum of 2-(hydroxy(4-nitrophenyl)methyl)cycloheptan-1-one (3ca)



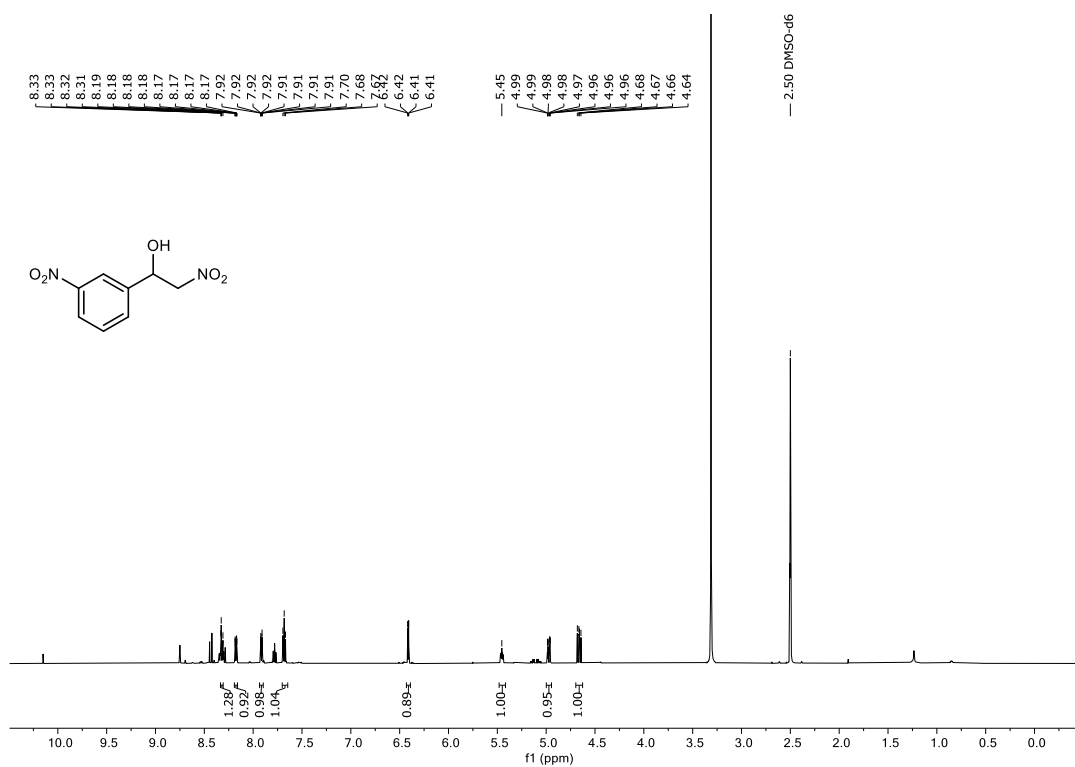
^1H NMR (600 MHz, DMSO- d_6) spectrum of **2-nitro-1-(4-nitrophenyl)ethan-1-ol (5a)**



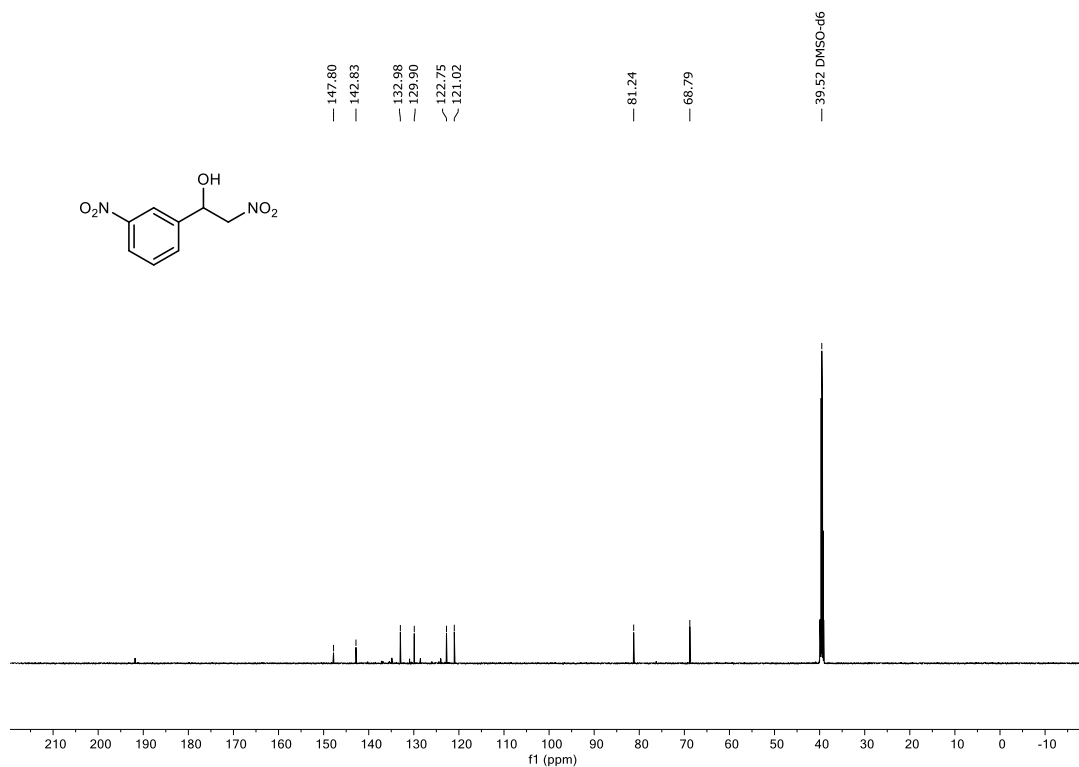
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of **2-nitro-1-(4-nitrophenyl)ethan-1-ol (5a)**



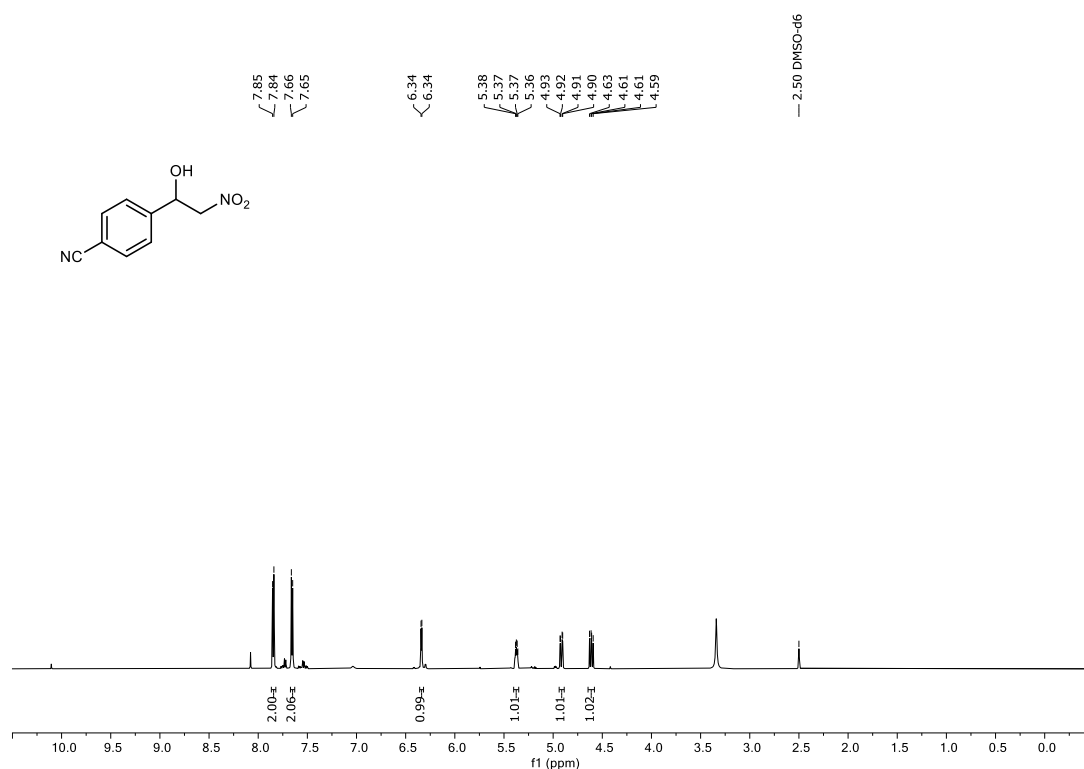
^1H NMR (600 MHz, DMSO- d_6) spectrum of **2-nitro-1-(3-nitrophenyl)ethan-1-ol (5b)**



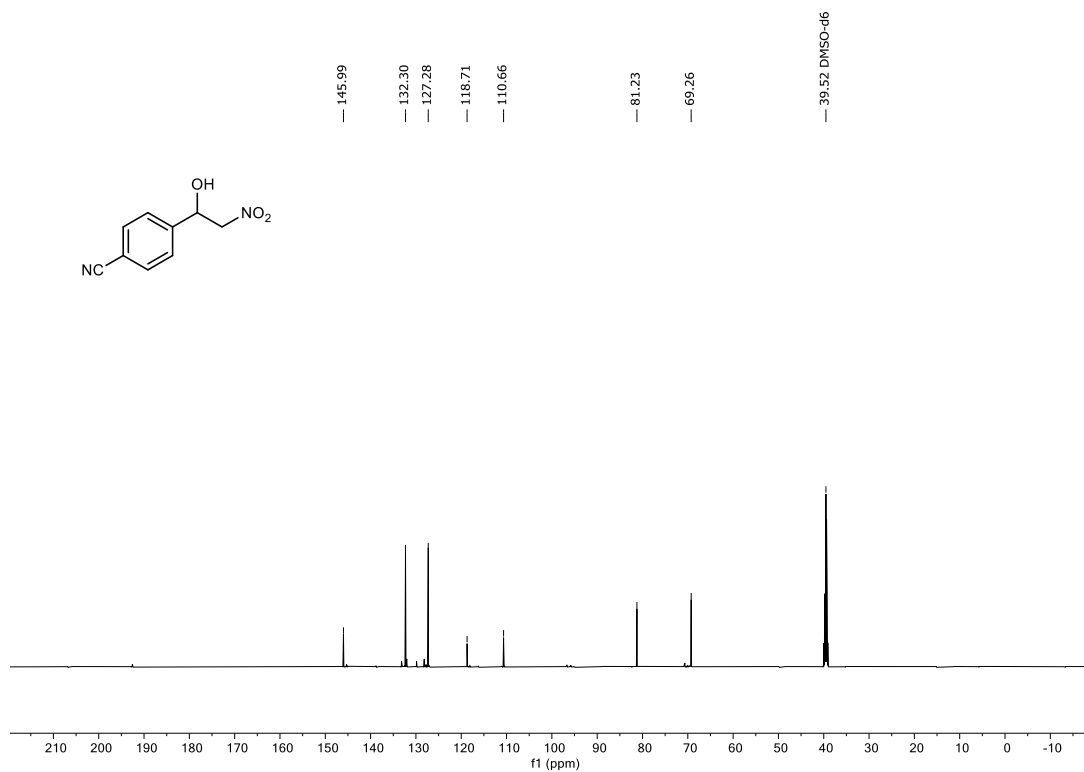
^{13}C NMR (151 MHz, DMSO- d_6) spectrum of **2-nitro-1-(3-nitrophenyl)ethan-1-ol (5b)**



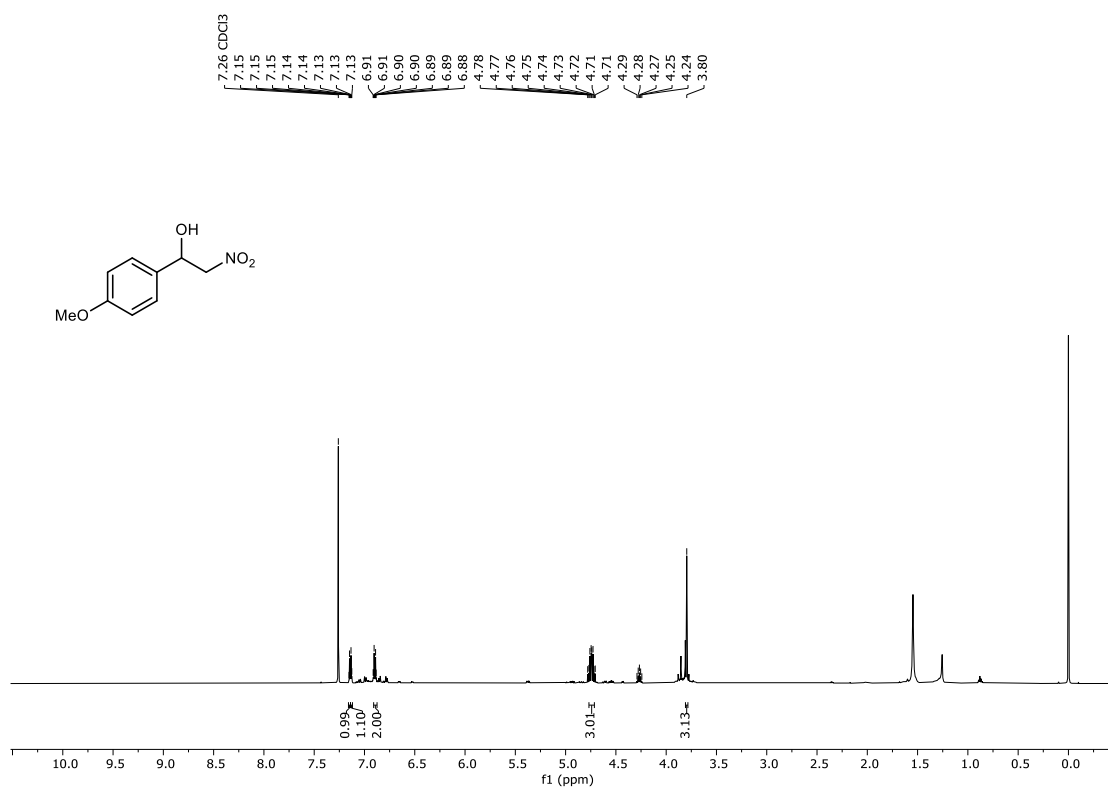
¹H NMR (600 MHz, DMSO-d₆) spectrum of **4-(1-hydroxy-2-nitroethyl)benzonitrile (5c)**



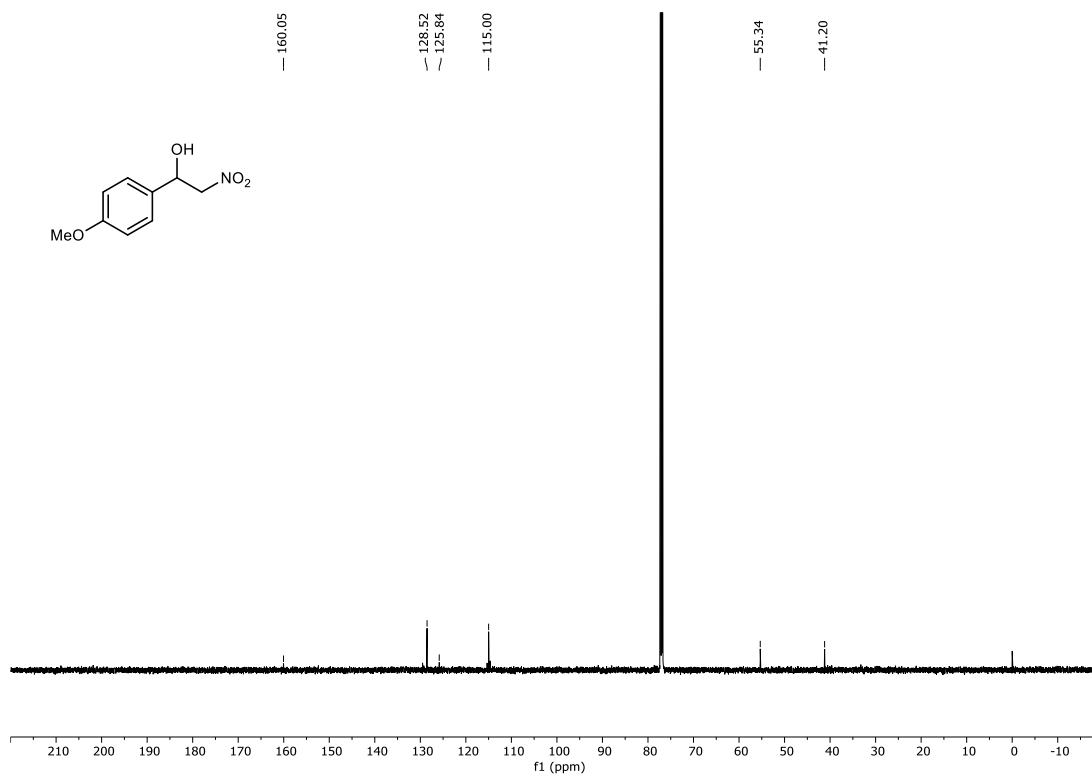
¹³C NMR (151 MHz, DMSO-d₆) spectrum of **4-(1-hydroxy-2-nitroethyl)benzonitrile (5c)**



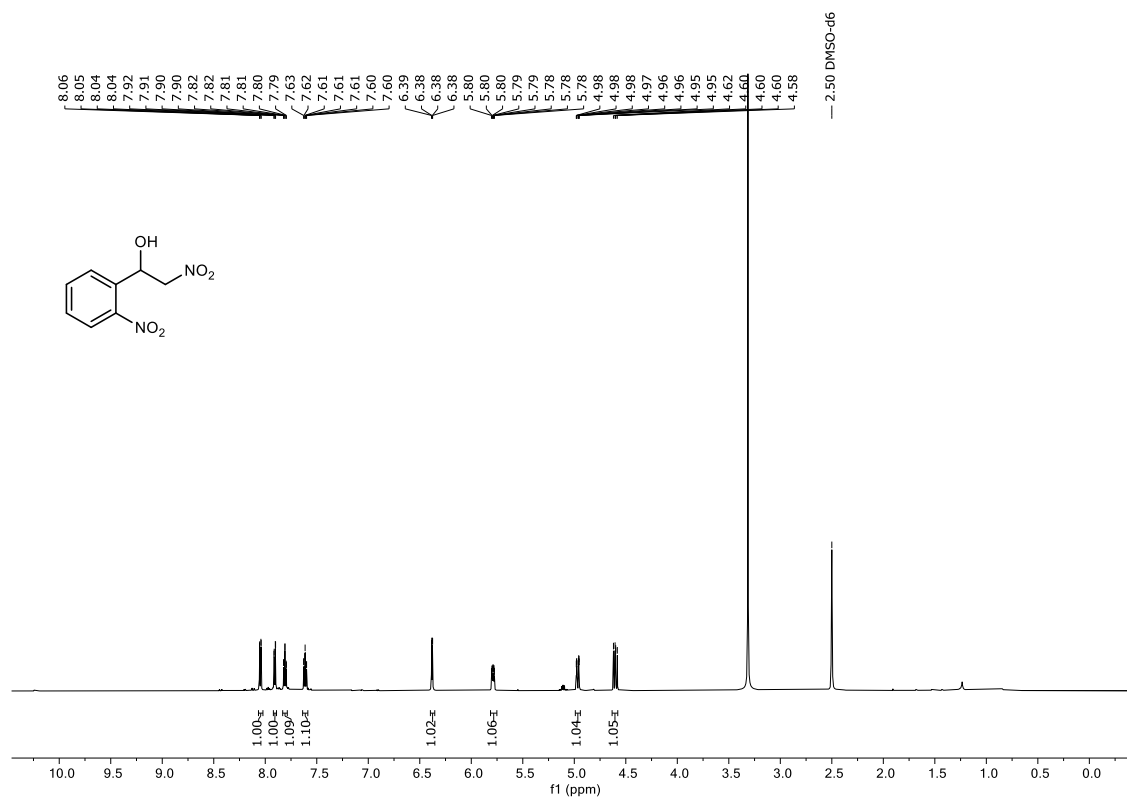
^1H NMR (600 MHz, CDCl_3) spectrum of **1-(4-methoxyphenyl)-2-nitroethan-1-ol (5k)**



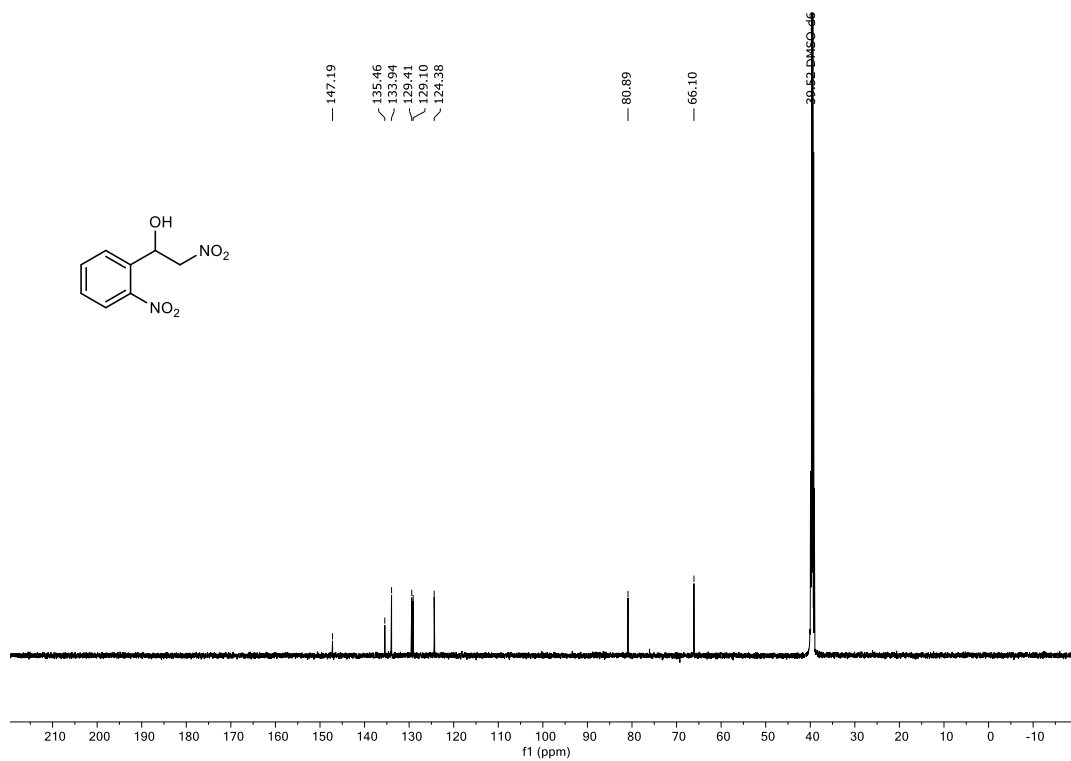
^{13}C NMR (151 MHz, CDCl_3) spectrum of **1-(4-methoxyphenyl)-2-nitroethan-1-ol (5k)**



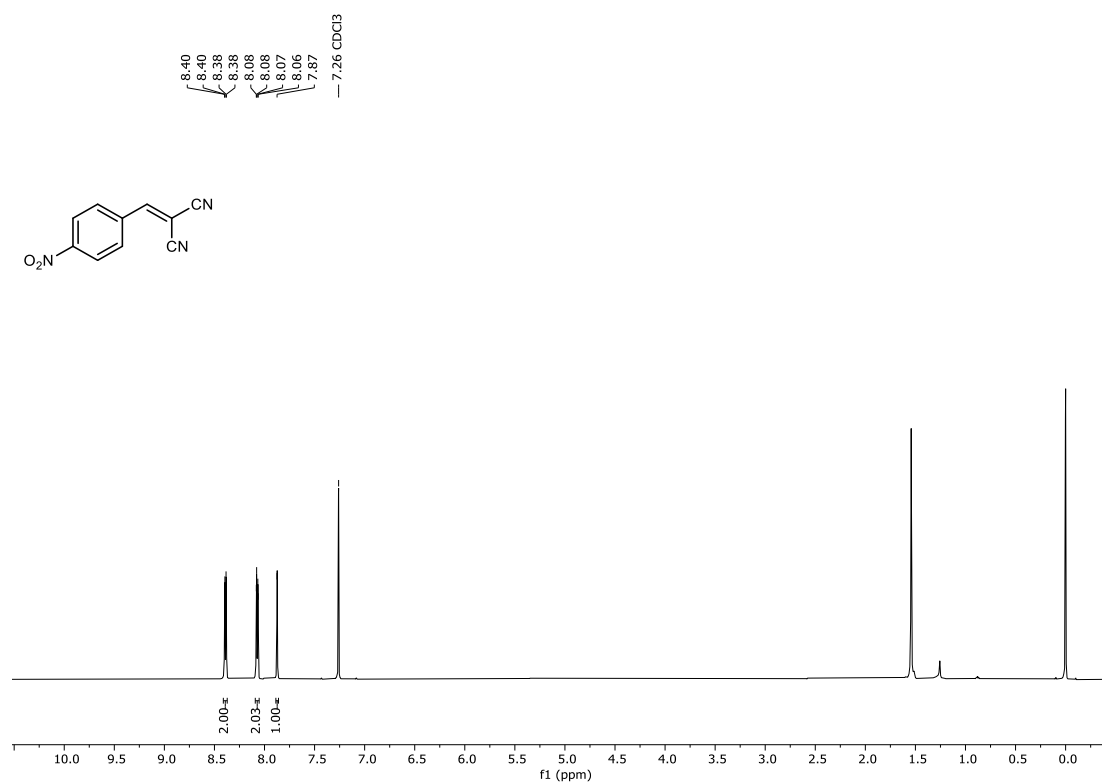
¹H NMR (600 MHz, DMSO-d₆) spectrum of 1-(2-nitrophenyl)-2-nitroethan-1-ol (5l)



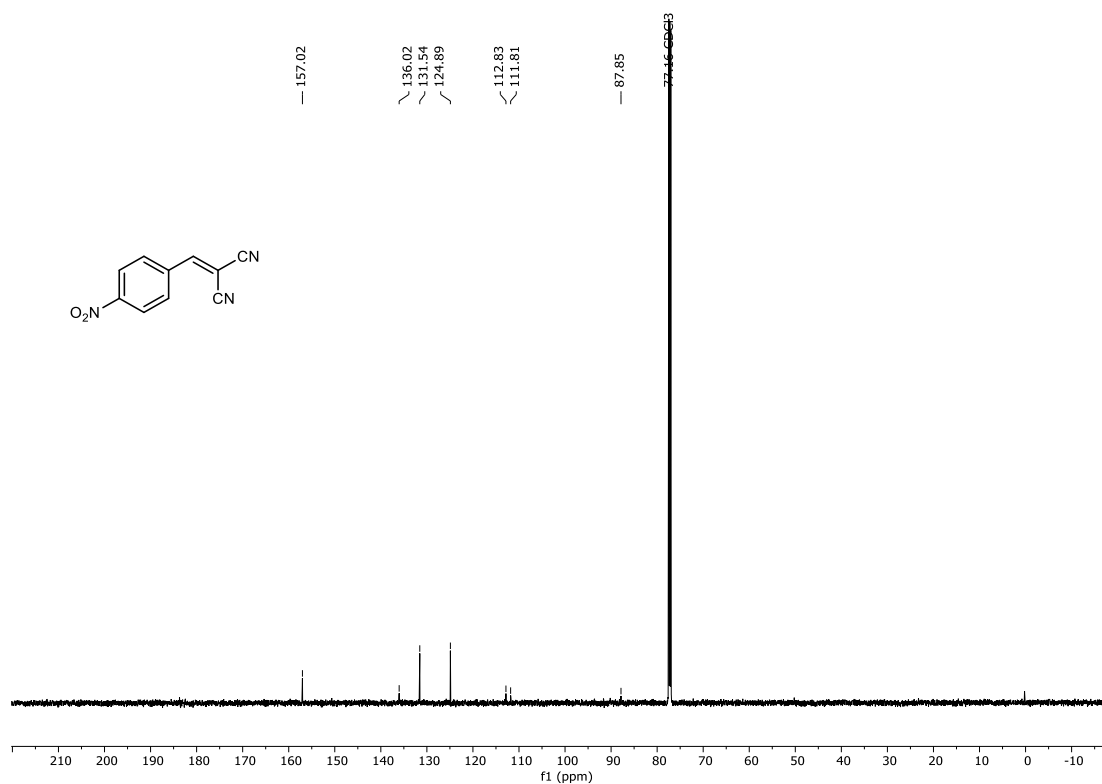
¹³C NMR (151 MHz, DMSO-d₆) spectrum of 1-(2-nitrophenyl)-2-nitroethan-1-ol (5l)



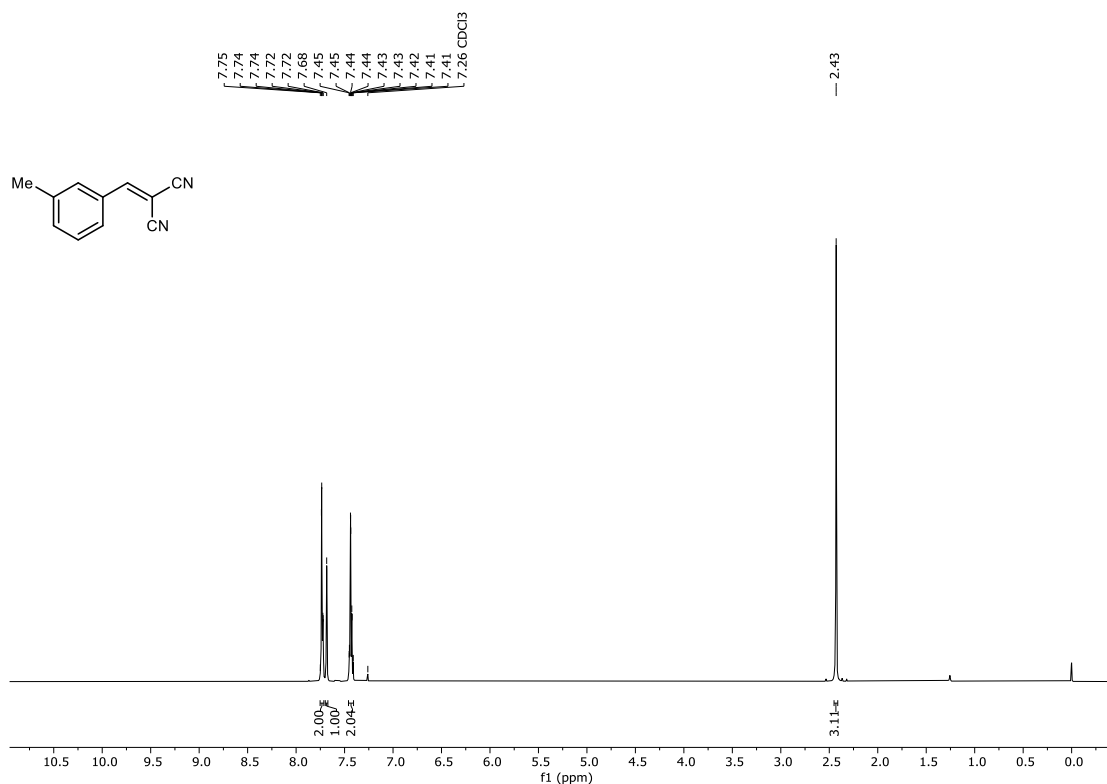
^1H NMR (600 MHz, CDCl_3) spectrum of 2-(4-nitrobenzylidene)malononitrile (**8a**)



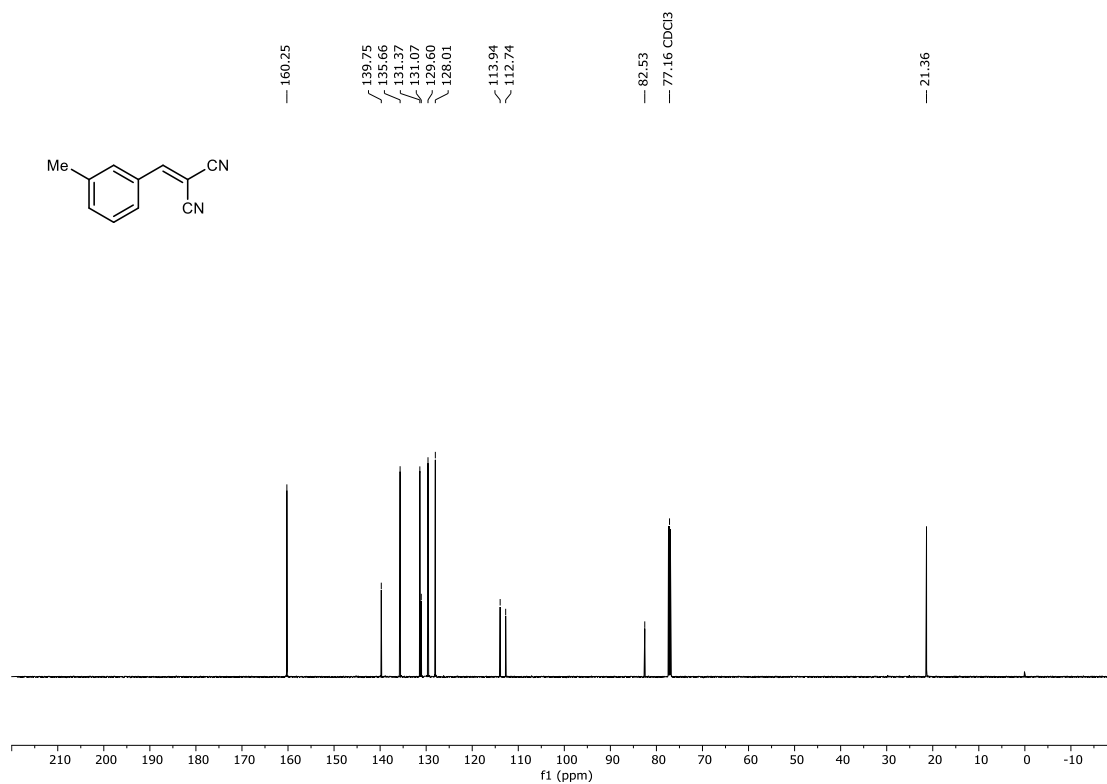
^{13}C NMR (151 MHz, CDCl_3) spectrum of 2-(4-nitrobenzylidene)malononitrile (**8a**)



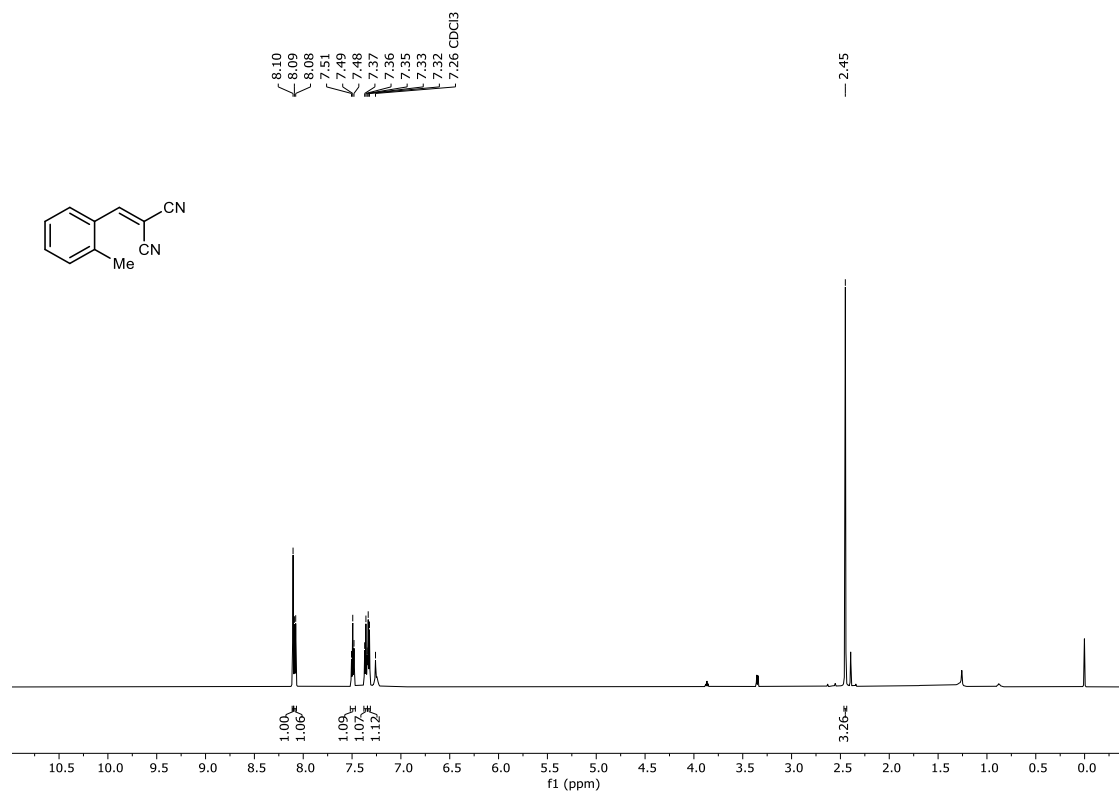
¹H NMR (600 MHz, CDCl₃) spectrum of **2-(3-methylbenzylidene)malononitrile (8h)**



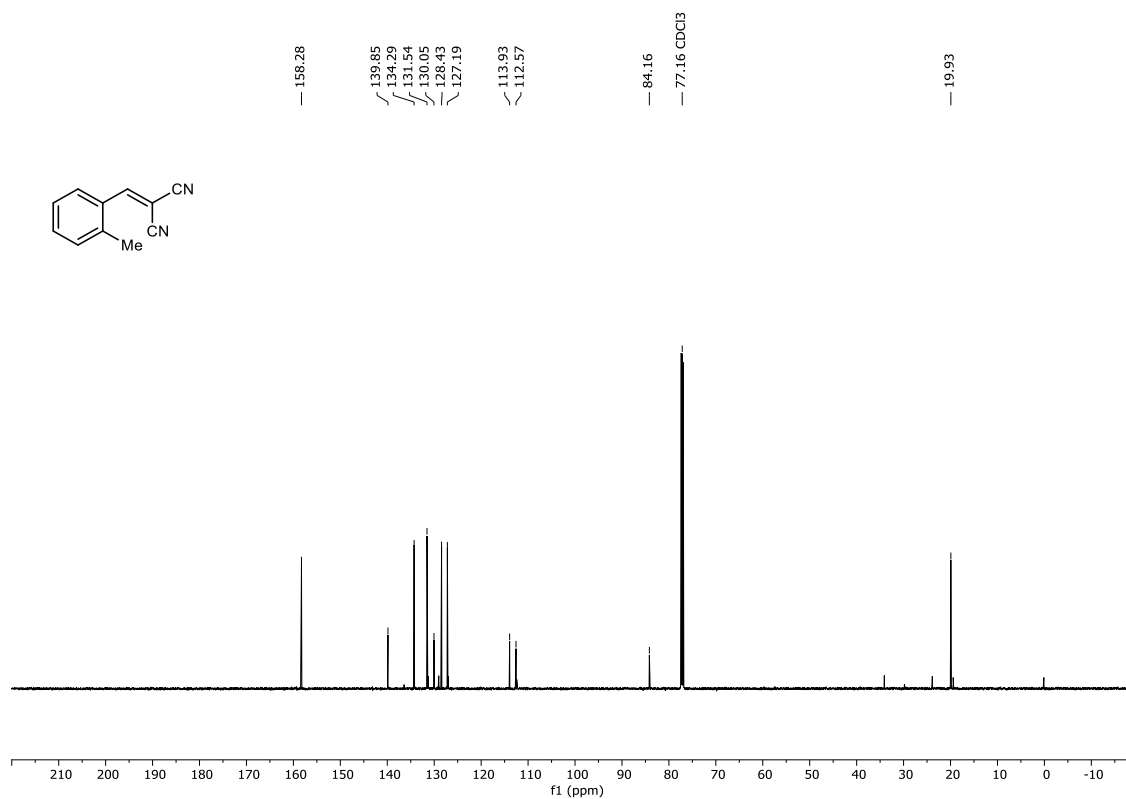
¹³C NMR (151 MHz, CDCl₃) spectrum of **2-(3-methylbenzylidene)malononitrile (8h)**



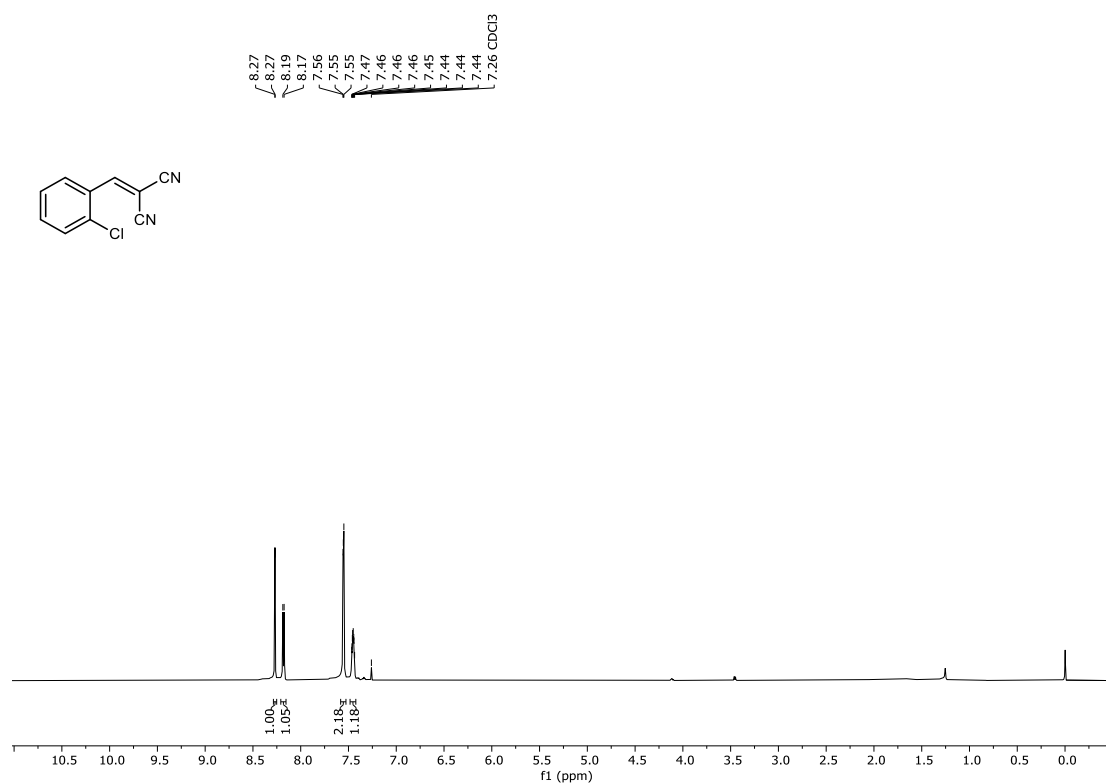
^1H NMR (600 MHz, CDCl_3) spectrum of **2-(2-methylbenzylidene)malononitrile (8i)**



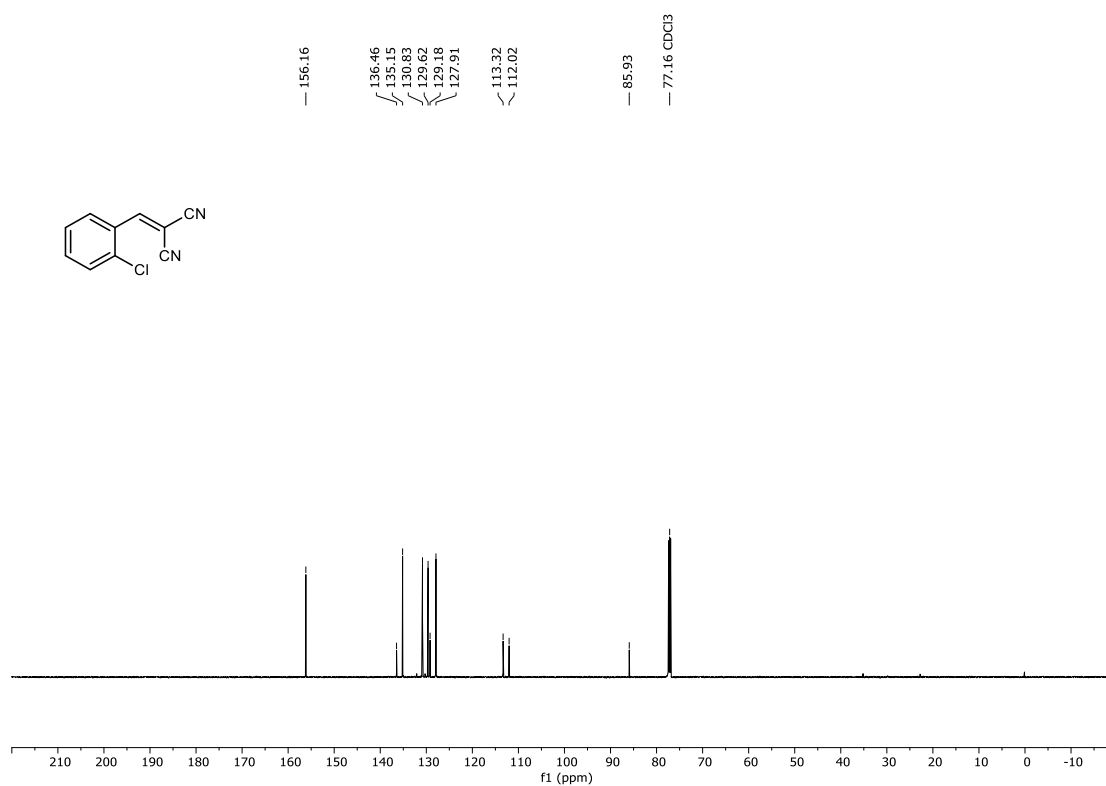
^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-(2-methylbenzylidene)malononitrile (8i)**



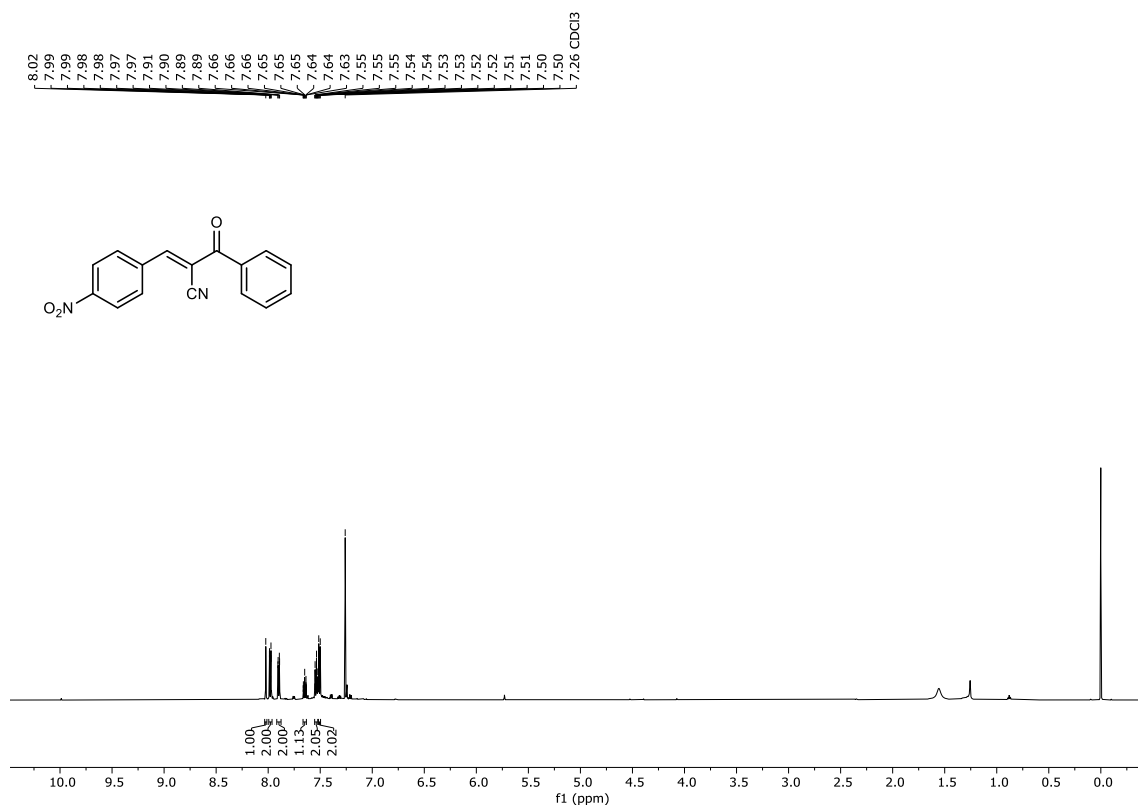
^1H NMR (600 MHz, CDCl_3) spectrum of **2-(2-chlorobenzylidene)malononitrile (8n)**



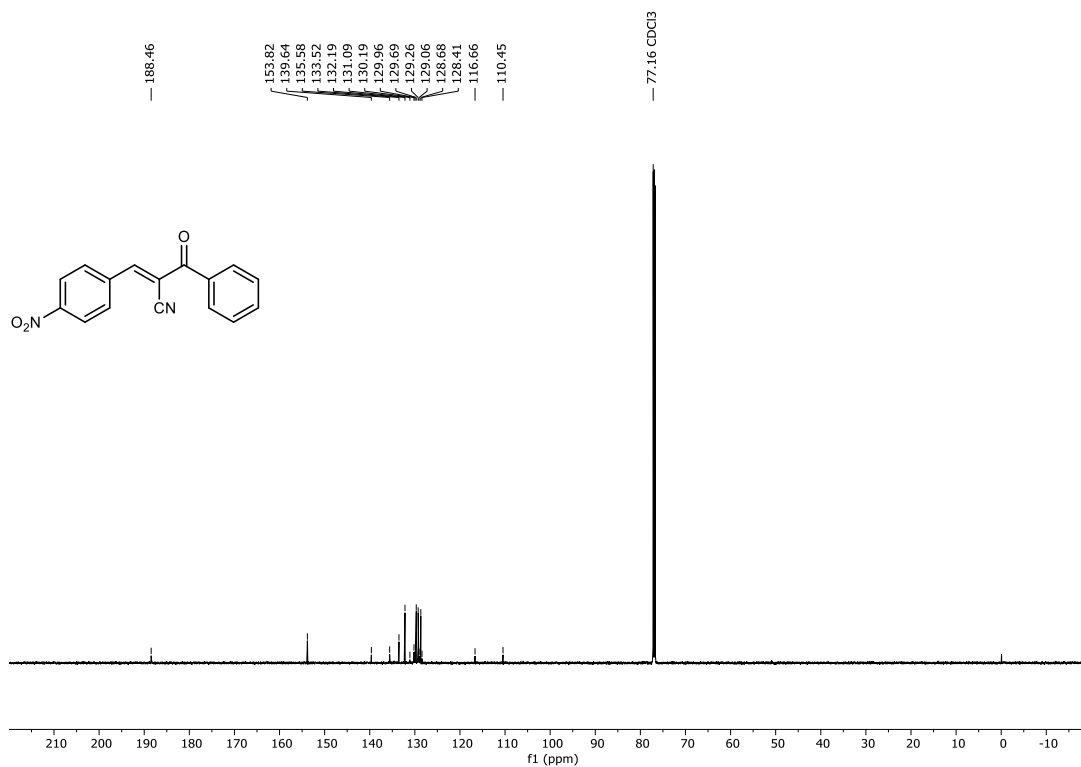
^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-(2-chlorobenzylidene)malononitrile (8n)**



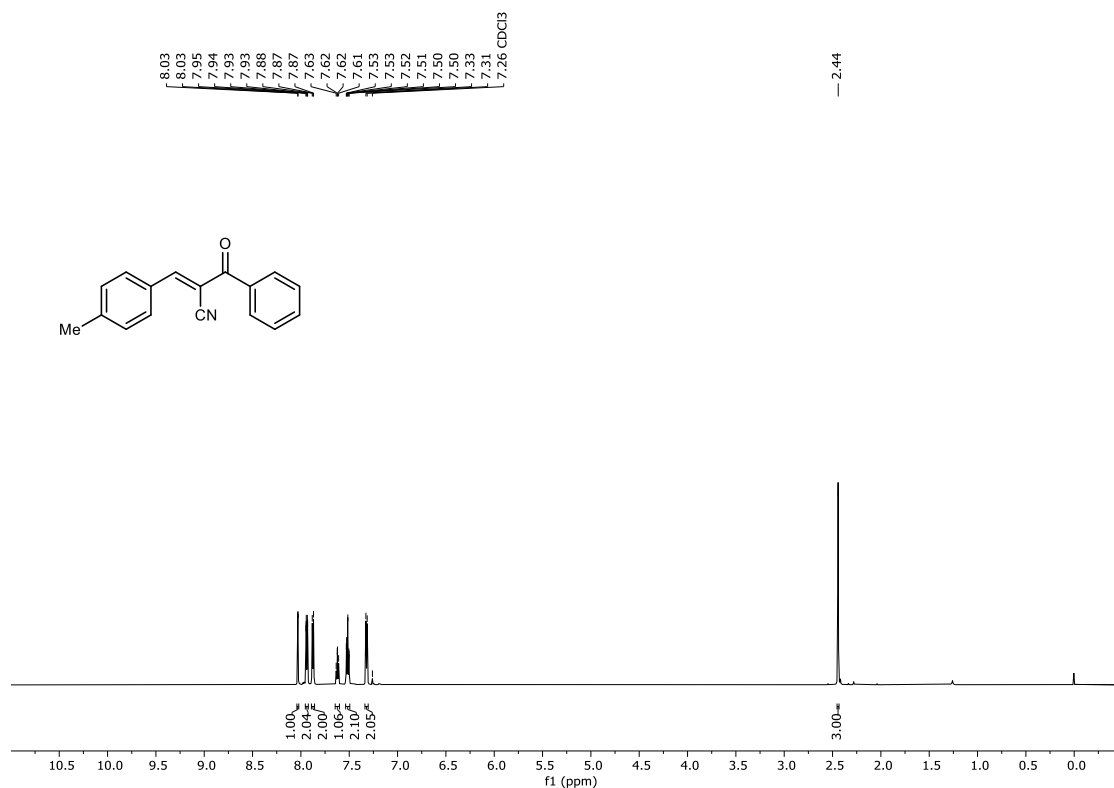
^1H NMR (600 MHz, CDCl_3) spectrum of **2-benzoyl-3-(4-nitrophenyl)acrylonitrile (9a)**



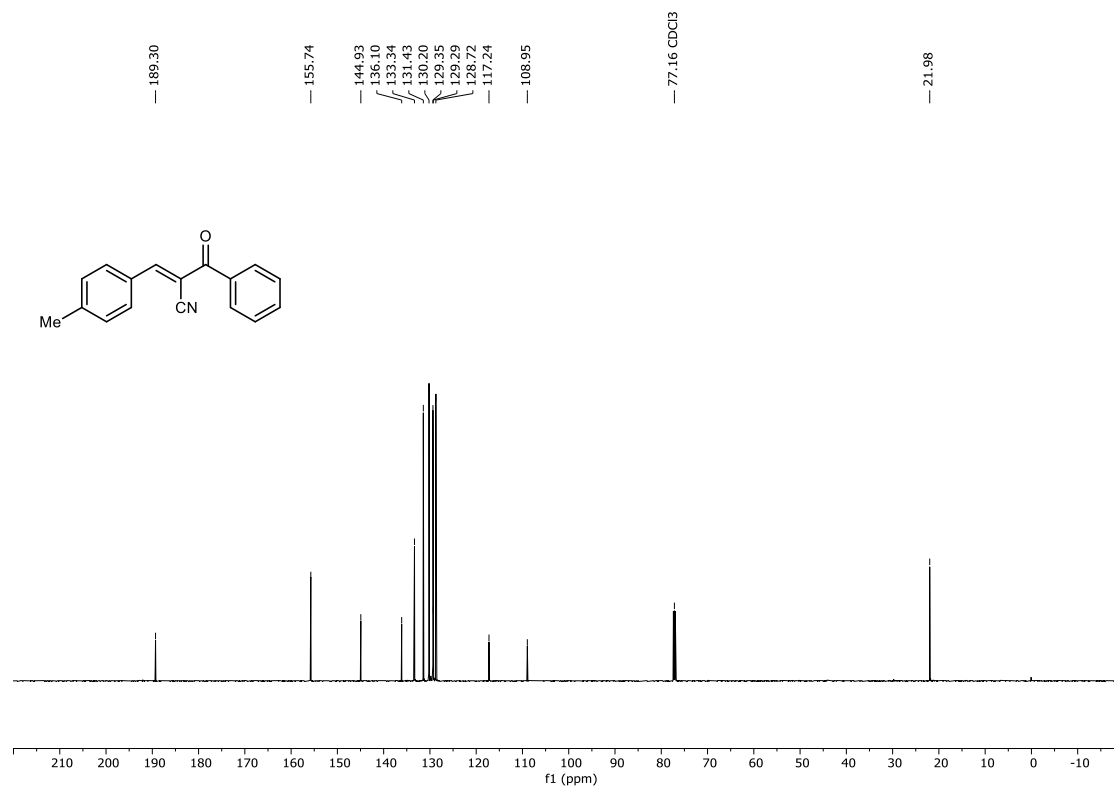
^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-benzoyl-3-(4-nitrophenyl)acrylonitrile (9a)**



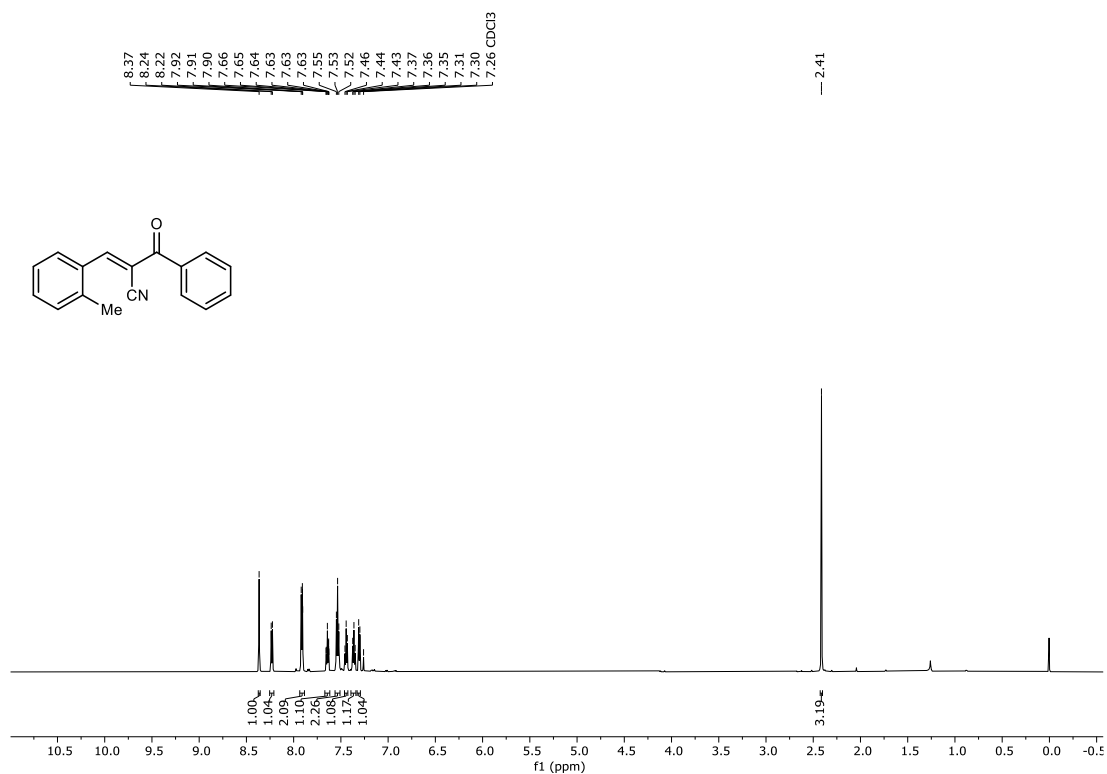
^1H NMR (600 MHz, CDCl_3) spectrum of **2-benzoyl-3-(p-tolyl)acrylonitrile (9g)**



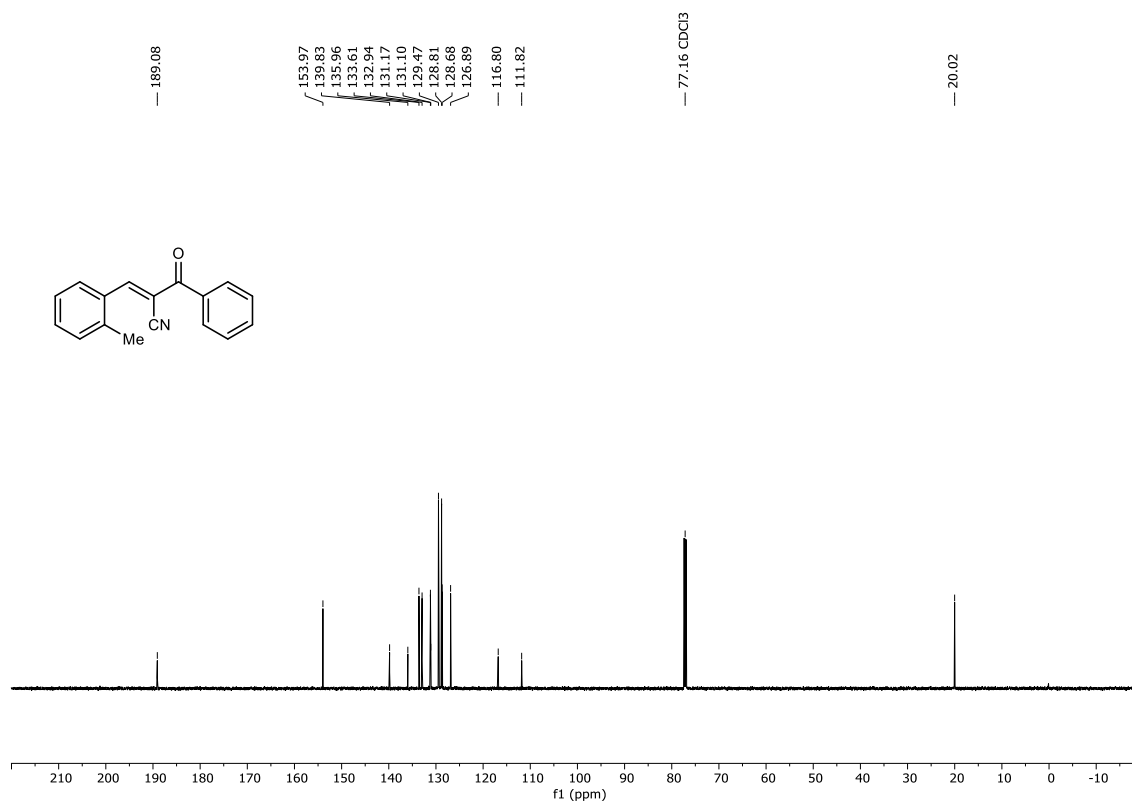
^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-benzoyl-3-(p-tolyl)acrylonitrile (9g)**



^1H NMR (600 MHz, CDCl_3) spectrum of **2-benzoyl-3-(o-tolyl)acrylonitrile (9i)**

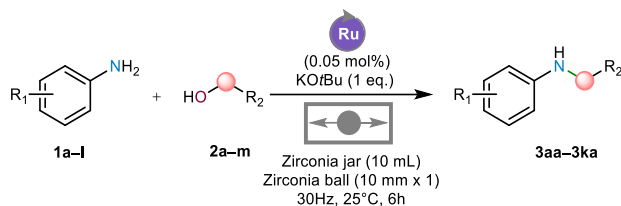


^{13}C NMR (151 MHz, CDCl_3) spectrum of **2-benzoyl-3-(o-tolyl)acrylonitrile (9i)**



7.4. General Reaction Conditions and Characterization for Compounds in Chapter 5

7.4.1. General Experimental Procedure for N-Alkylation of Aromatic Amines 3aa-3am

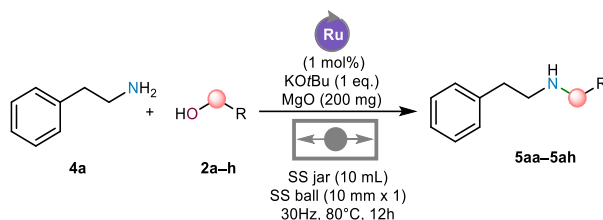


Aromatic amine (**1a-k**, 4 mmol), primary alcohol (**2a-m**, 4 mmol), potassium *tert*-butoxide (KOtBu, 4 mmol) and Ru-MACHO catalyst (0.05 mol%, 1.2 mg) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball ($\phi = 10$ mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum. $^1\text{H-NMR}$ and ^{13}C spectrometry confirmed the structure of the compounds. Where necessary, further purification can be achieved by column chromatography (*n*-hexane/EtOAc: 9/1, v/v).

Note: Internal reaction temperature of jar before (24.9°C) and after (25.7°C) mechanochemical borrowing hydrogenation with *p*-anisidine (4 mmol), pentanol (4 mmol), potassium *tert*-butoxide (KOtBu, 1 mmol), [Ru]-1 in a 10mL zirconia jar with a 10 mm zirconia ball milled in MM-500 Vario for given time at 25°C for 6h was monitored to verify that the reaction primarily proceeds through mechanochemical grinding and the internal temperature of the reaction does not rise significantly.⁴⁹

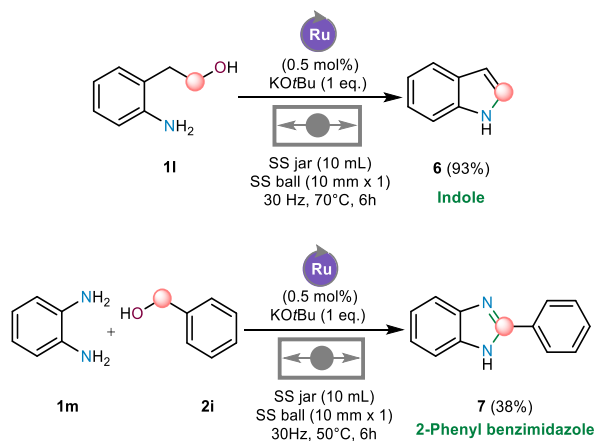


7.4.2. General Experimental Procedure for N-Alkylation of Aliphatic Amines 5aa-5ah



Aliphatic amine (1 mmol), primary alcohol (2 mmol), potassium *tert*-butoxide (KOtBu, 1 mmol), Ru-MACHO catalyst (1 mol%, 6 mg) and MgO (200 mg) were loaded into a stainless-steel grinding jar (10 mL) equipped with 1 ball ($\phi = 10$ mm, m 3.6g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill Fritsch P-23 for 12 hours. The reaction jar was heated to an external temperature of 80°C using a heat-gun and maintained as such for the whole course of the reaction.⁴⁹ Then, the reaction jar was cooled down to room temperature, and the reaction progress was monitored by TLC (hexane/EtOAc: 8/2). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (1.0 g) with 20 mL of EtOAc and then dried using sodium sulfate and the resultant filtrate was evaporated under high vacuum. The further purification the compound was achieved using column chromatography (*n*-hexane:EtOAc 8:2 v/v). ¹H-NMR and ¹³C spectrometry confirmed the structure of the compounds.

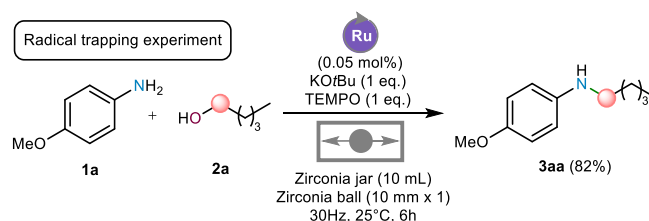
7.4.3. General Experimental Procedure for Synthesis of N-Heterocycles 6 and 7



Amine (1 mmol), alcohol (1 mmol), potassium *tert*-butoxide (1 mmol) and Ru-MACHO catalyst (0.5 mol%, 3 mg) were loaded into a stainless-steel grinding jar (10 mL) equipped with 1 ball ($\phi = 10$ mm, m 3.6g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill Fritsch P-23 for 6 hours at an appropriate temperature using a heat-gun. Then, the reaction jar was cooled down to room temperature, and the reaction progress is monitored by TLC (hexane/EtOAc: 7/3). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum. ¹H-NMR and ¹³C spectrometry confirmed the structure of the compound.

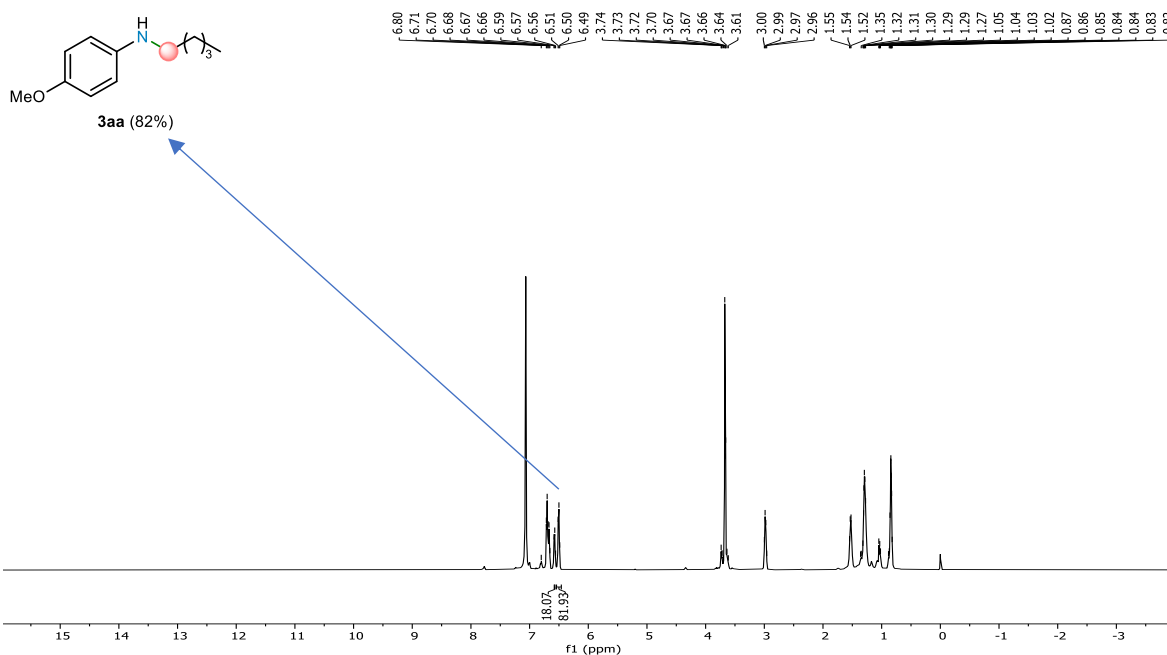
Note: In case of indole **6**, the product was obtained without any further purification, while in the case of 2-phenyl benzimidazole **7**, the pure product is isolated by column chromatography (*n*-hexane/EtOAc: 7:3 v/v).

7.4.4. General Experimental Procedure for Radical Trapping



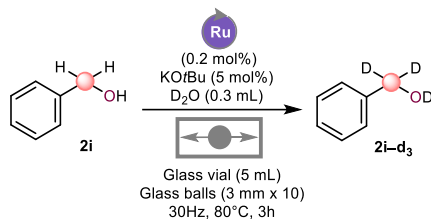
p-Anisidine (**1a**, 4 mmol), pentanol (**2a**, 4 mmol), potassium tert-butoxide (KO*t*Bu, 4 mmol), Ru-MACHO catalyst (0.05 mol%, 1.2 mg) and TEMPO (4 mmol, 625 mg) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at a frequency of 30Hz in a shaker mill MM-500 vario at room temperature for 6 hours. After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum.

¹H NMR (600 MHz, CDCl₃) for mechanochemical radical trapping for N-alkylation of aromatic amines using TEMPO



7.4.5. General Experimental Procedures for Mechanochemical Kinetic Isotope Effect

7.4.5.1. General Experimental Procedure for Synthesis of Deuterated Benzyl Alcohol



Alcohol (1 mmol), potassium *tert*-butoxide (5 mol%), D₂O (300 μ L) and Ru-MACHO catalyst (0.2 mol%, 1.2 mg) were loaded into a glass vial (5 mL) equipped with 10 balls (ϕ = 3 mm) of the same material. The jar was purged with argon gas, sealed and milled at 30Hz in a shaker mill Fritsch P-23 for 3 hours at the temperature of 80°C using a heat-gun (Figure 7.3). Then, the reaction jar was cooled down to room temperature. After completion of the reaction, the resulting reaction mixture was extracted by separating funnel using DCM (3x2 mL) **without addition of any further water**. The DCM layer was then dried using sodium sulfate and the resultant filtrate was evaporated under high vacuum. ¹H-NMR and ¹³C spectrometry confirmed the deuteriation of the alcohol to **2i-d₃** up to 99%.⁵⁰

¹H NMR (600 MHz, CDCl₃) δ 7.37 (d, J = 4.8 Hz, 4H), 7.33 – 7.28 (m, 1H).

HRMS (ESI) m/z calc. for C₇H₅D₂O [M-H]⁻: 109.0628, found: 109.0619.

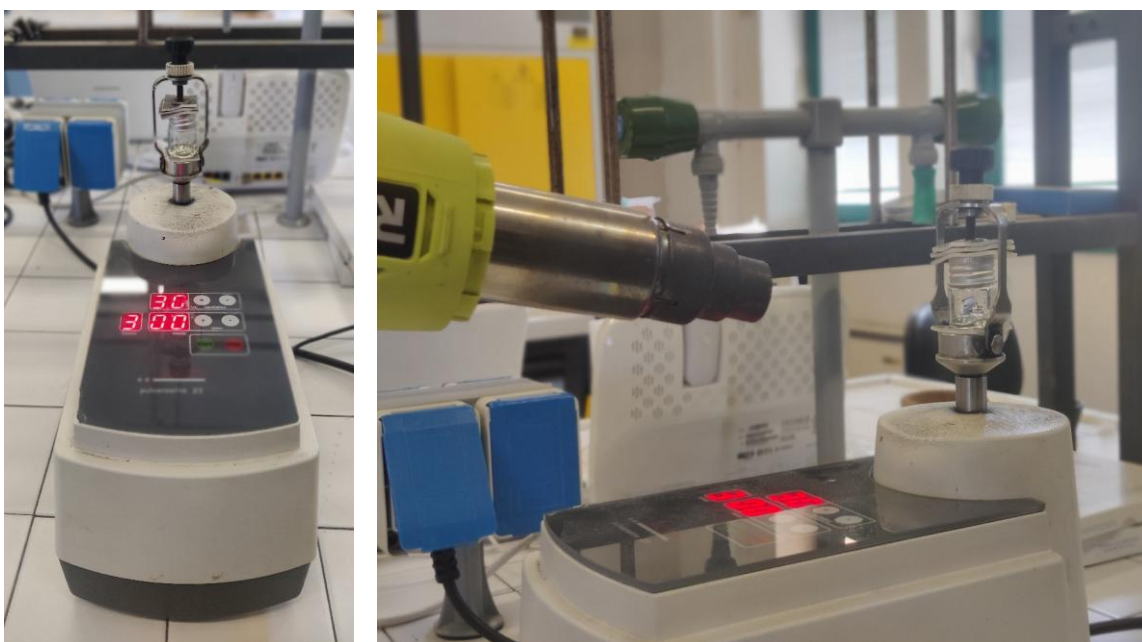
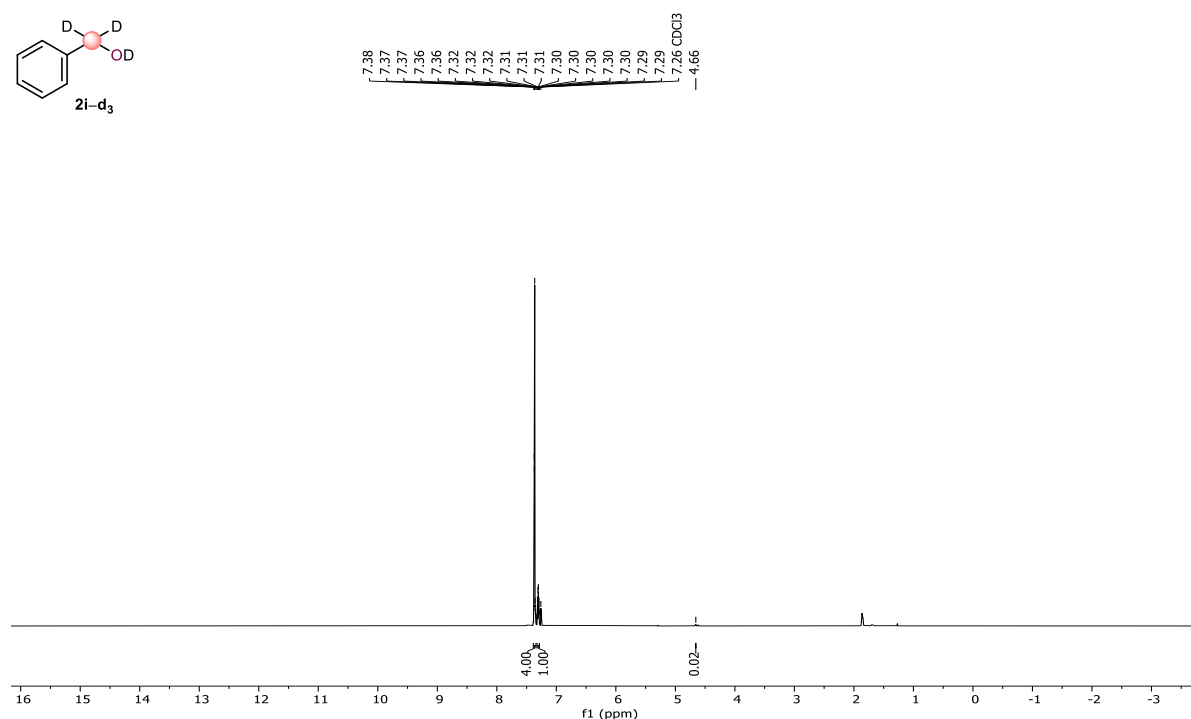
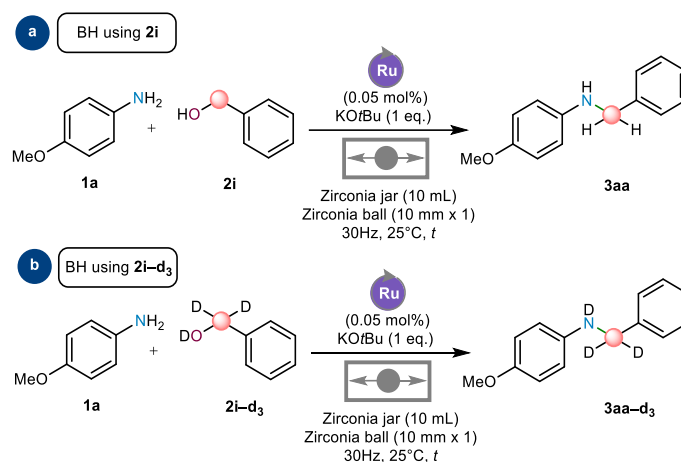


Figure 7.3. Deuteriation experiment set-up

¹H NMR (600 MHz, CDCl₃) for mechanochemical deuteration of benzyl alcohol (2i)



7.4.5.2. General Experimental Procedure for Kinetic Isotope Effect Analysis



p-Anisidine (**1a**, 4 mmol), benzyl alcohols (**2i**/ **2i-d₃**, 4 mmol), potassium tert-butoxide (KOtBu, 4 mmol) and Ru-MACHO catalyst (0.05 mol%, 1.2 mg) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30Hz in a shaker mill MM-500 vario at room temperature. All the reaction experiments were carried out separately with an interval of 30 minutes from time ranging from 0 minutes to 150 minutes. After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite with 20 mL of EtOAc. The filtrates were evaporated under high vacuum. The products were then subjected to quantitative ¹H-NMR spectrometry using ethylene carbonate (2 mmol, 176 mg) as an internal standard in CDCl₃. The reaction coefficients (*k*) were measured and plotted. Finally, the *KIE* is measured by

the formula k_H/k_D obtainable from the slope between $\ln([C_{2i-d3(0)}]/[C_{2i-d3(t)}])$ and $\ln([C_{2i(0)}]/[C_{2i(t)}])$, where $[C_{2i-d3(0)}]$ and $[C_{2i-d3(t)}]$ are the initial concentration and concentration at time ' t ' of **2i-d₃** respectively; while $[C_{2i(0)}]$ and $[C_{2i(t)}]$ represents the initial concentration and concentration at time ' t ' of **2i** respectively (Table 7.1; Figure 7.5).

Table 7.1. KIE analysis for *N*-alkylation of aromatic amines with BH strategy

Time (s)	$[C_{2i}]$	$\ln([C_{2i(0)}]/[C_{2i(t)}])$	$[C_{2i-d3}]$	$\ln([C_{2i-d3(0)}]/[C_{2i-d3(t)}])$
0	1	0	1	0
1800	0.65	0.43078	0.75	0.28768
3600	0.44	0.82098	0.68	0.38566
5400	0.36	1.02165	0.41	0.8916
7200	0.29	1.23787	0.37	0.99425
9000	0.22	1.51413	0.3	1.20397

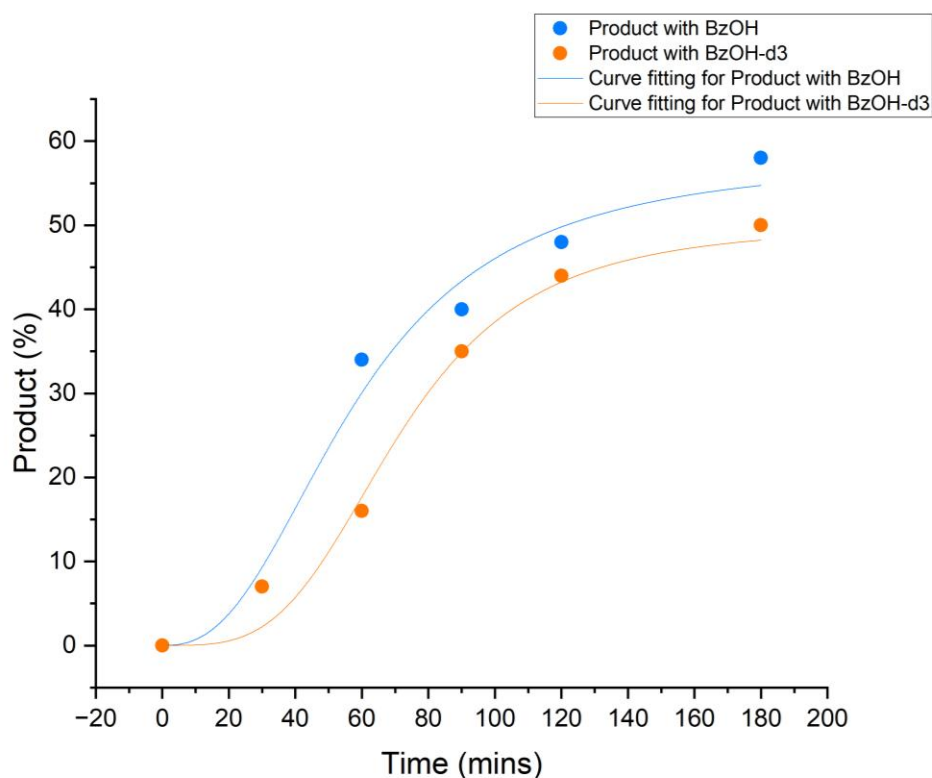


Figure 7.4. Product evolution of **3ai** and **3ai-d₃** with respect to time

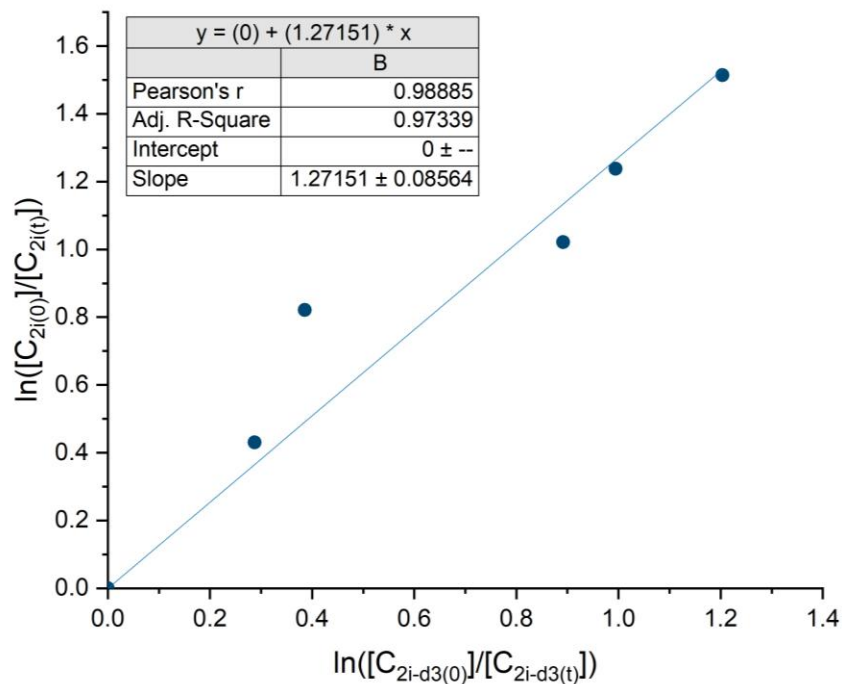


Figure 7.5. $\ln([C_{2i-d3(0)}]/[C_{2i-d3(t)}])$ vs $\ln([C_{2i(0)}]/[C_{2i(t)}])$ plot to find the value of $KIE = 1.27 \pm 0.09$ ($R^2 = 0.97$)

NMR Spectra for KIE

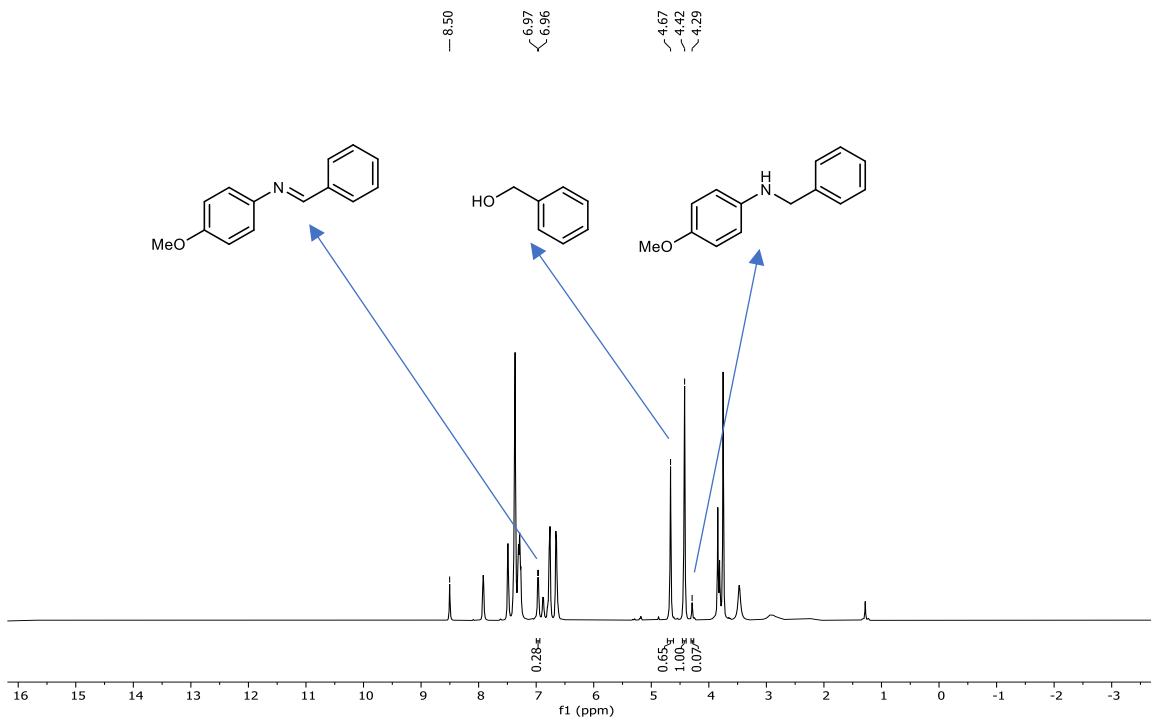


Figure 7.6. Quantitative $^1\text{H-NMR}$ for **3ai**, $t=30$ minutes with ethylene carbonate as internal standard

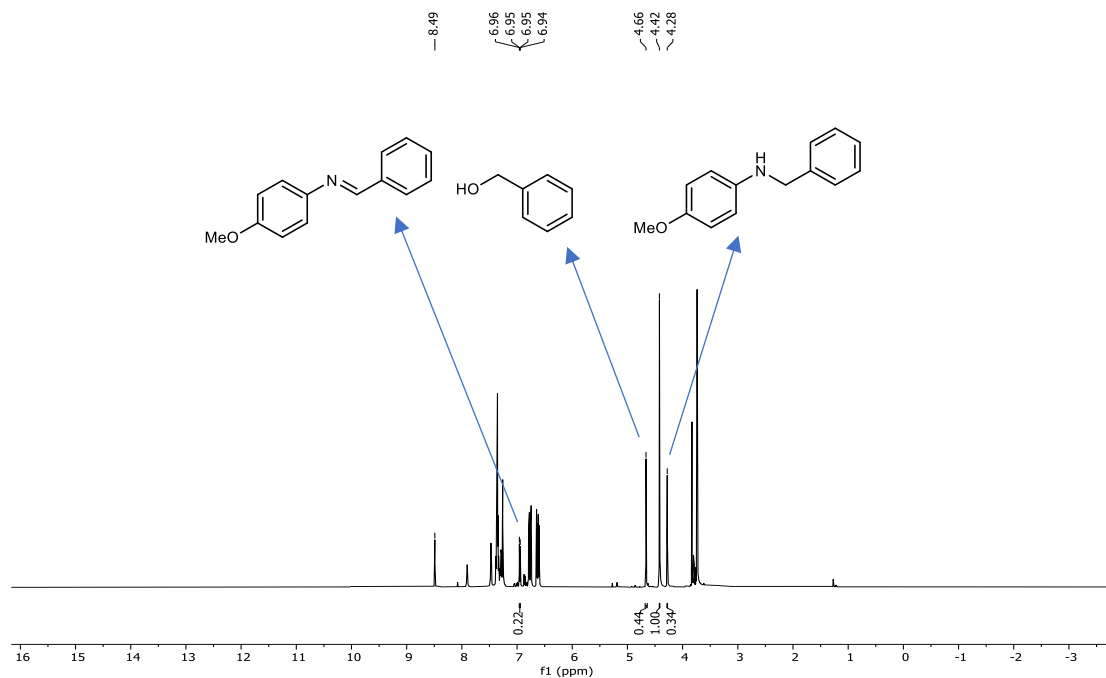


Figure 7.7. Quantitative ^1H -NMR for **3ai**, $t=60$ minutes with ethylene carbonate as internal standard

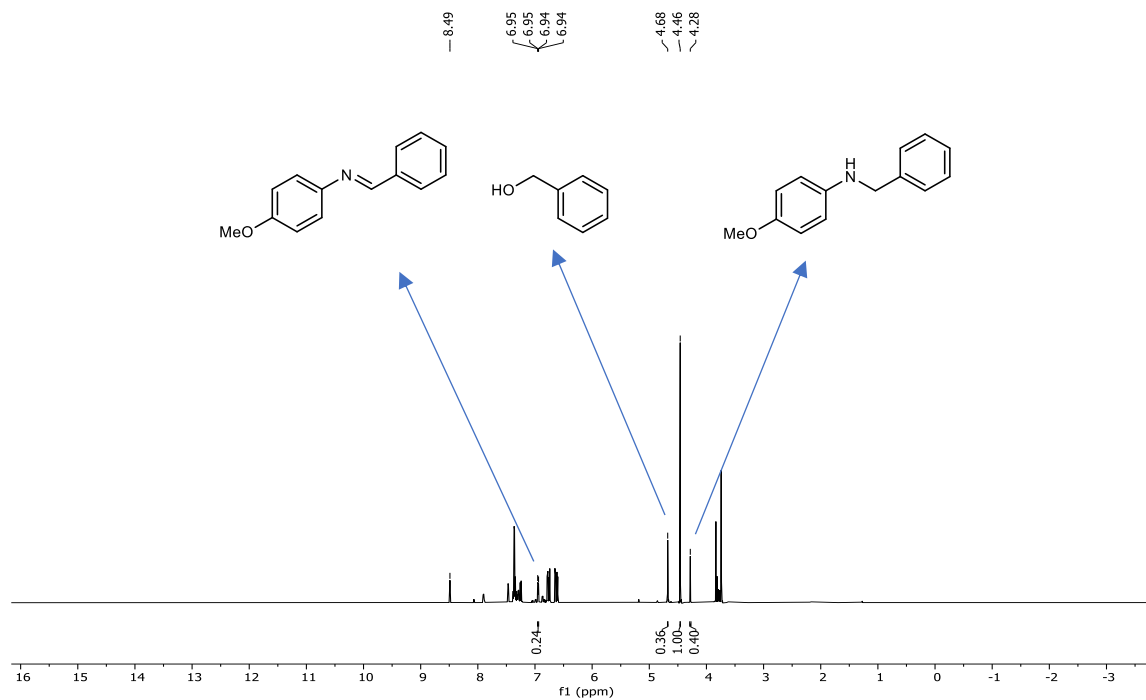


Figure 7.8. Quantitative ^1H -NMR for **3ai**, $t=90$ minutes with ethylene carbonate as internal standard

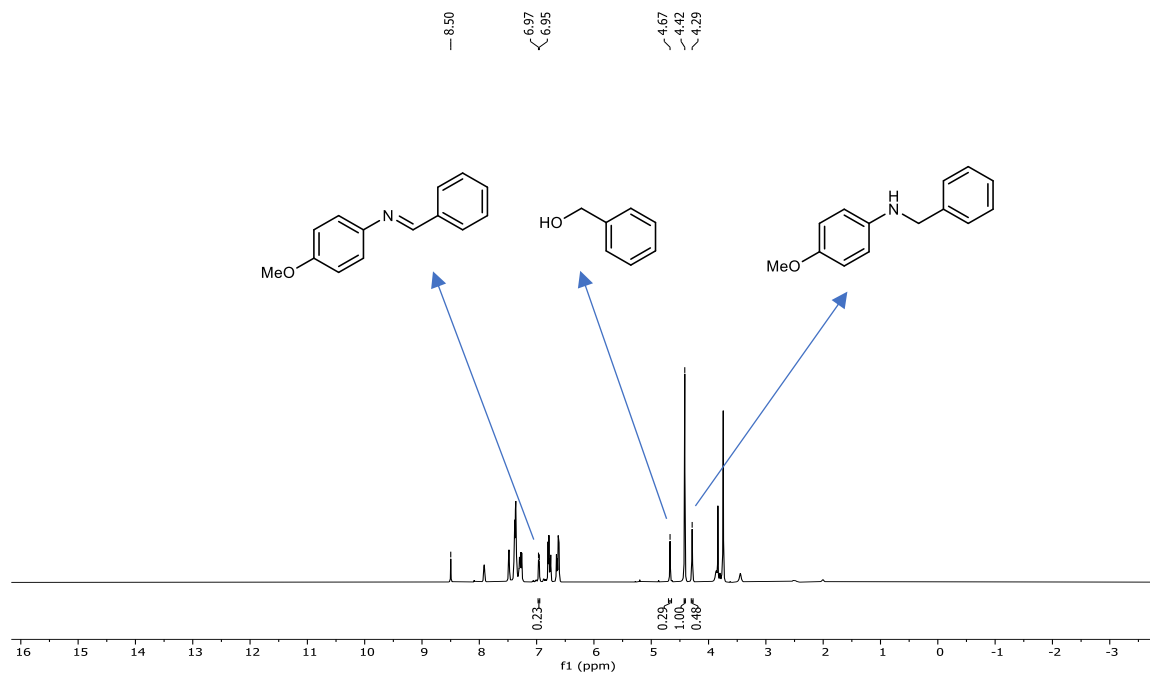


Figure 7.9. Quantitative ^1H -NMR for **3ai**, $t=120$ minutes with ethylene carbonate as internal standard

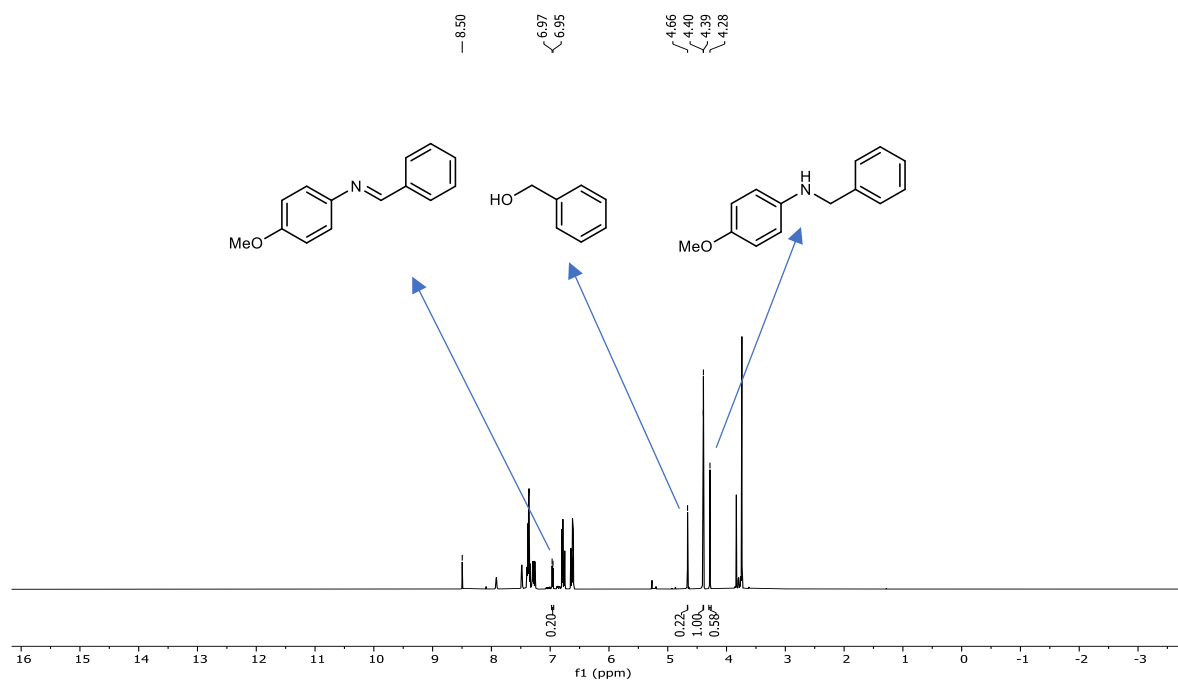


Figure 7.10. Quantitative ^1H -NMR for **3ai**, $t=150$ minutes with ethylene carbonate as internal standard

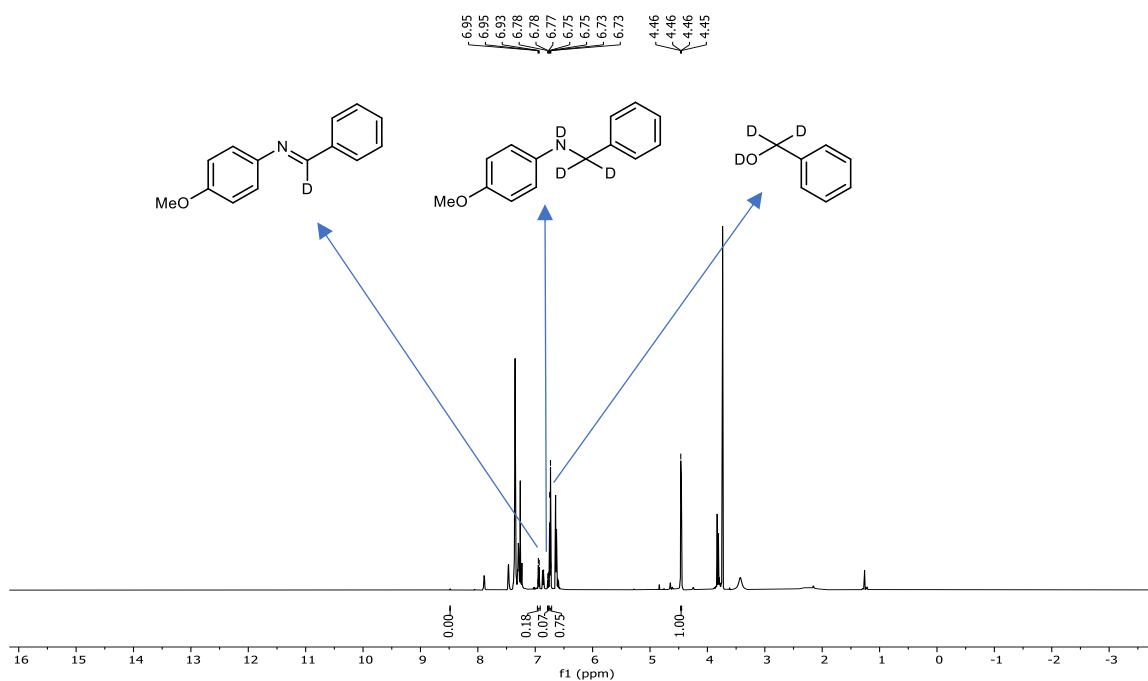


Figure 7.11. Quantitative ^1H -NMR for **3ai-d₃**, $t=30$ minutes with ethylene carbonate as internal standard

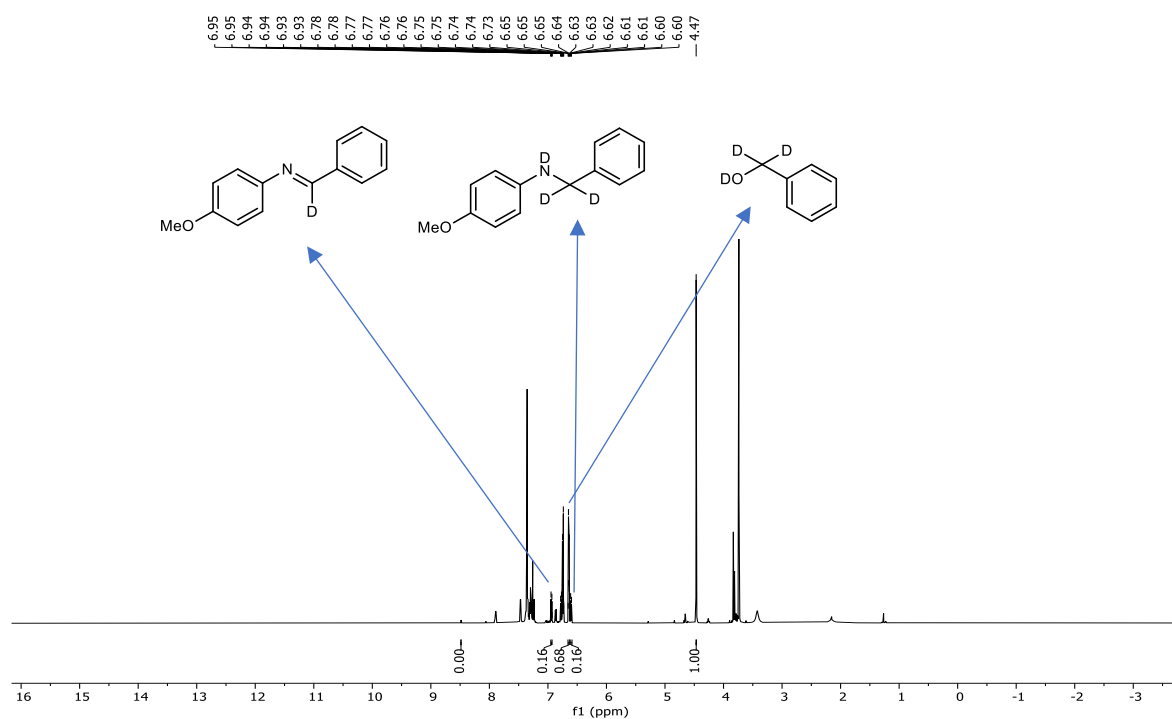


Figure 7.12. Quantitative ^1H -NMR for **3ai-d₃**, $t=60$ minutes with ethylene carbonate as internal standard

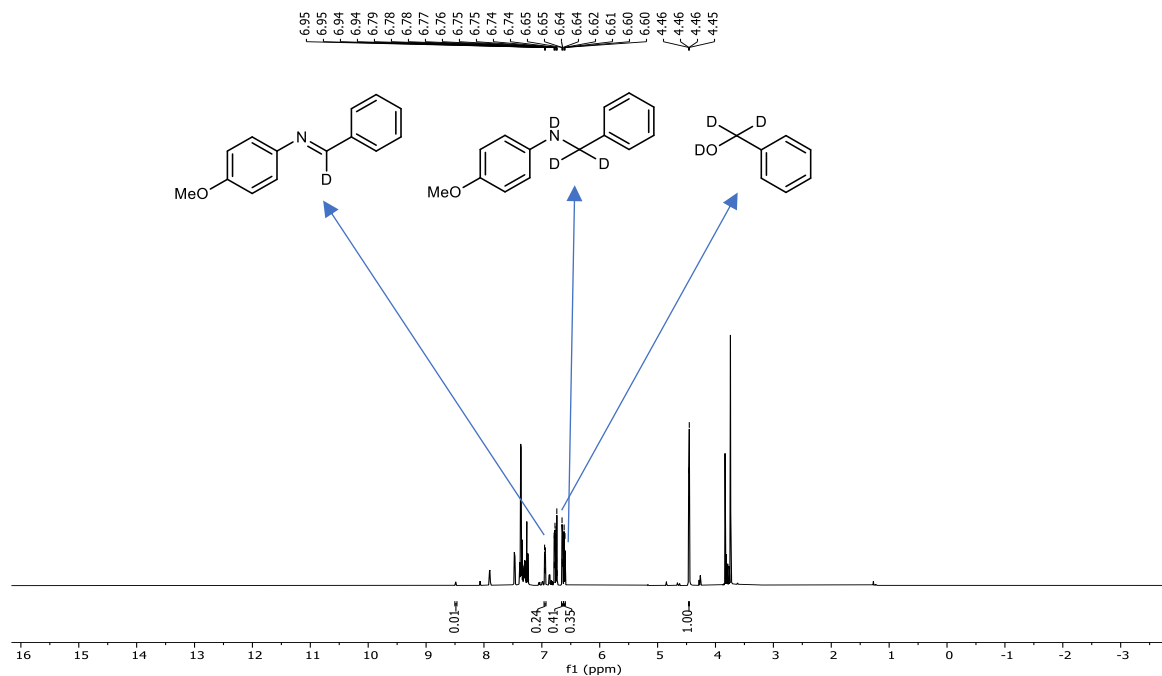


Figure 7.13. Quantitative ^1H -NMR for **3ai-d₃**, $t=90$ minutes with ethylene carbonate as internal standard

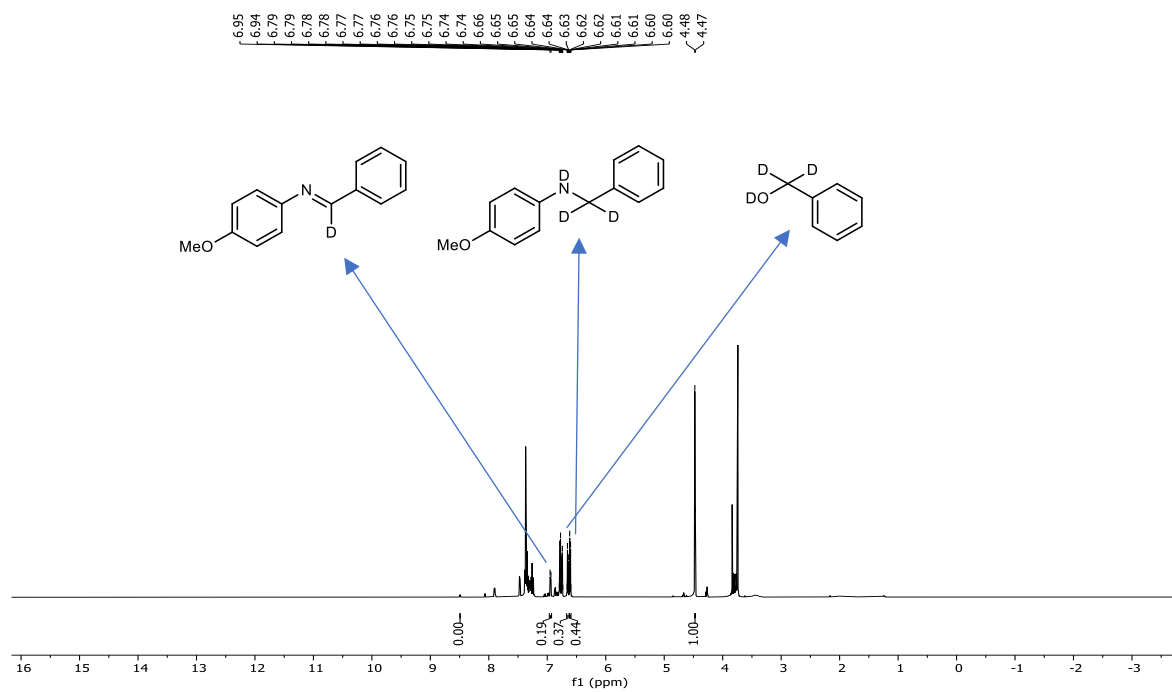


Figure 7.14. Quantitative ^1H -NMR for **3ai-d₃**, $t=120$ minutes with ethylene carbonate as internal standard

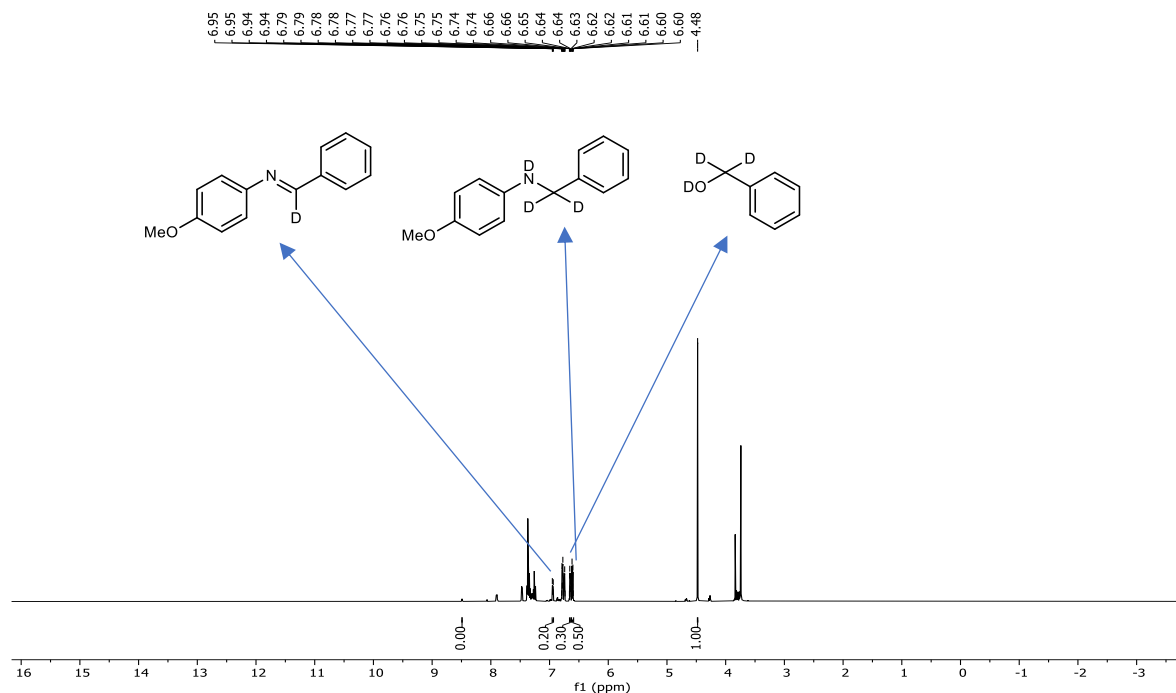
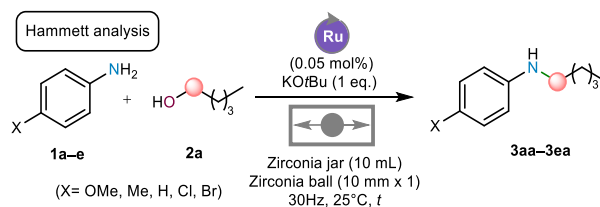


Figure 7.15. Quantitative ^1H -NMR for **3ai-d₃**, $t=150$ minutes with ethylene carbonate as internal standard

7.4.6. General Experimental Procedure for Mechanochemical Hammett Analysis



Amine (**1a-e**, 4 mmol), pentanol (**2a**, 4 mmol), potassium *tert*-butoxide (KOtBu, 4 mmol) and Ru-MACHO catalyst (0.05 mol%, 1.2 mg) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball ($\phi = 10$ mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 Vario at room temperature. All the reaction experiments were carried out separately with an interval of 10 minutes from time ranging from 0 minutes to 60 minutes. After completion of the reactions, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum. The products were then subjected to quantitative ^1H -NMR spectrometry using ethylene carbonate (2 mmol, 176 mg) as an internal standard in CDCl_3 . The reaction rate constants (k) were calculated and $\log(k_X/k_H)$ were plotted against substituent constants (σ) to analyze the dependency of the substituent groups on anilines upon the product formation (Figure 7.22).

Time (s)	[C _{X=Br}]	[C _{X=Cl}]	[C _{X=H}]	[C _{X=Me}]	[C _{X=OMe}]
0	1	1	1	1	1
600	0.70	0.71	0.74	0.80	0.93
1200	0.53	0.56	–	0.69	0.83
1800	0.35	–	0.41	0.57	0.71
2400	0.22	0.24	0.30	0.49	0.61
3000	0.14	0.17	0.26	0.39	0.53
3600	0.08	0.10	0.22	0.33	0.47

Time (s)	$\ln([C_{Br(0)}]/[C_{Br(t)}])$	$\ln([C_{Cl(0)}]/[C_{Cl(t)}])$	$\ln([C_{H(0)}]/[C_{H(t)}])$	$\ln([C_{Me(0)}]/[C_{Me(t)}])$	$\ln([C_{OMe(0)}]/[C_{OMe(t)}])$
0	0	0	0	0	0
600	0.35667	0.34249	0.30111	0.22314	0.07257
1200	0.63488	0.57982	–	0.37106	0.18633
1800	1.04982	–	0.8916	0.56212	0.34249
2400	1.51413	1.42712	1.20397	0.71335	0.4943
3000	1.96611	1.77196	1.34707	0.94161	0.63488
3600	2.52573	2.30259	1.51413	1.10866	0.75502

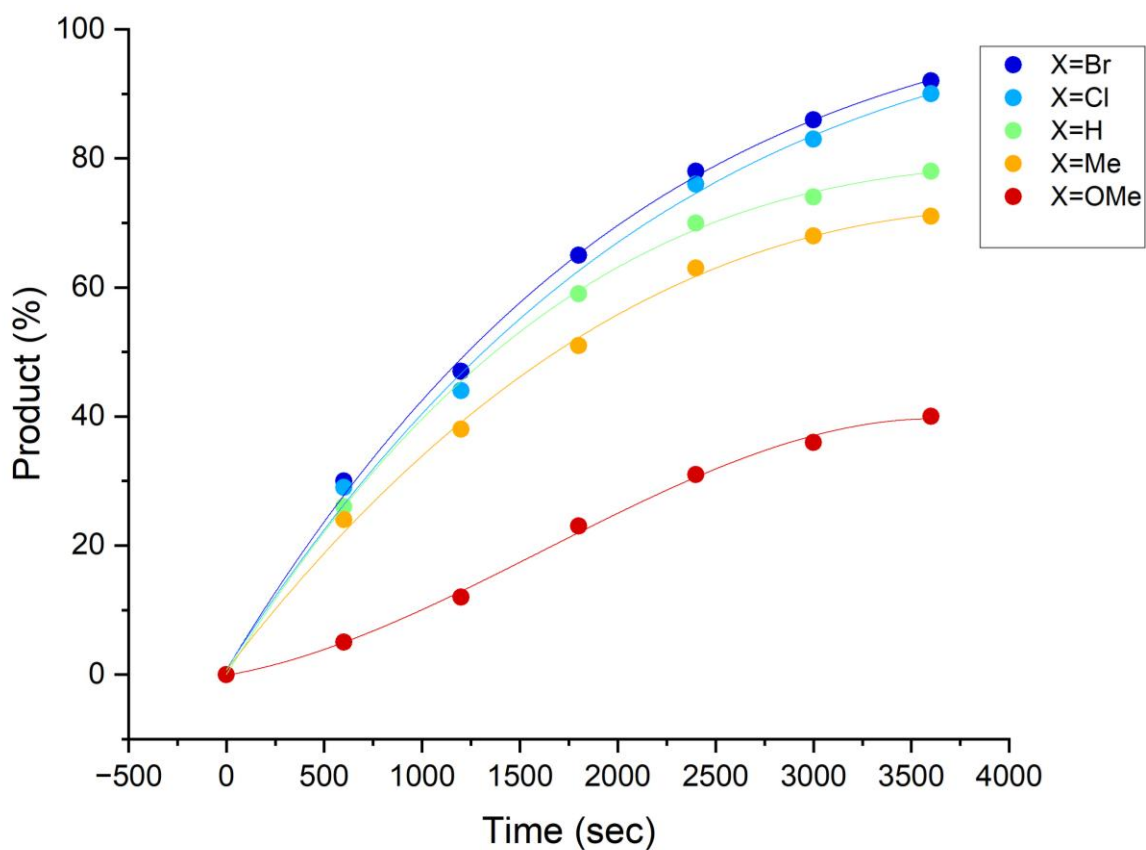


Figure 7.16. Product evolution over time for Hammett plot for different substituents in aniline

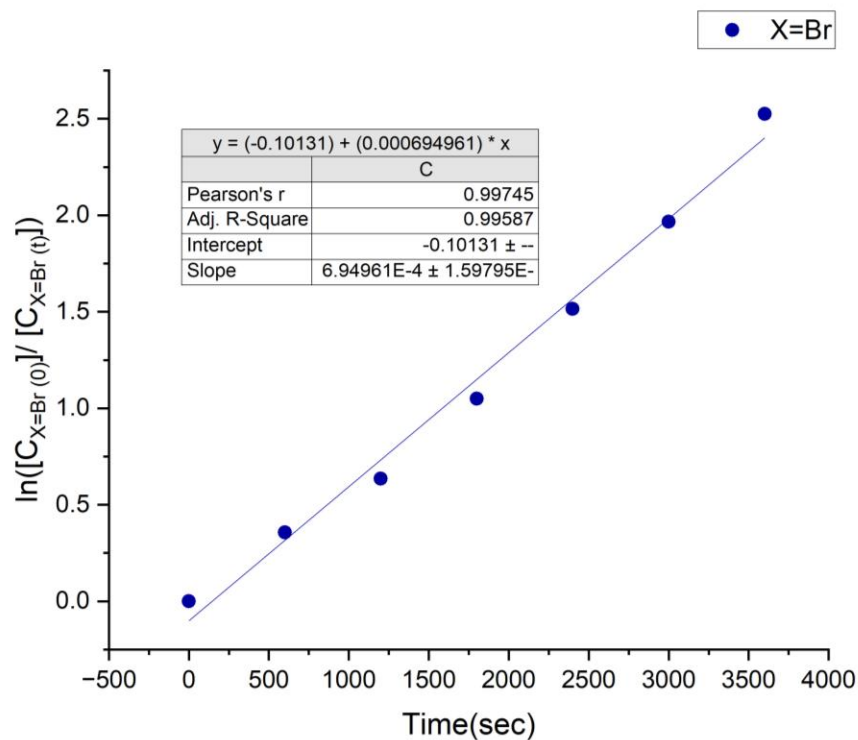


Figure 7.17. Plot between $\ln([C_{X=Br(0)}]/[C_{X=Br(t)}])$ vs time to get $k_{X=Br}$

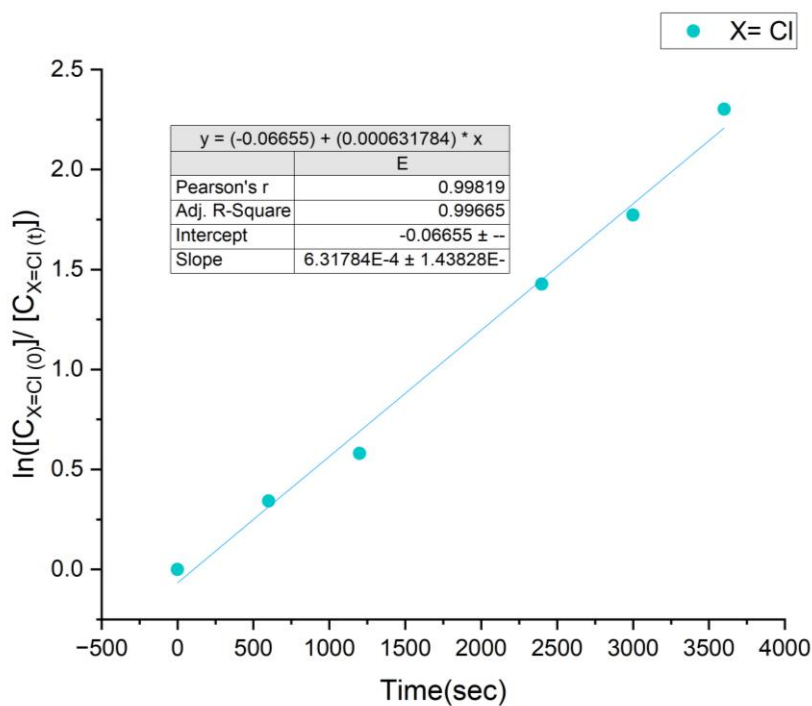


Figure 7.18. Plot between $\ln([C_{X=Cl(0)}]/[C_{X=Cl(t)}])$ vs time to get $k_{X=Cl}$

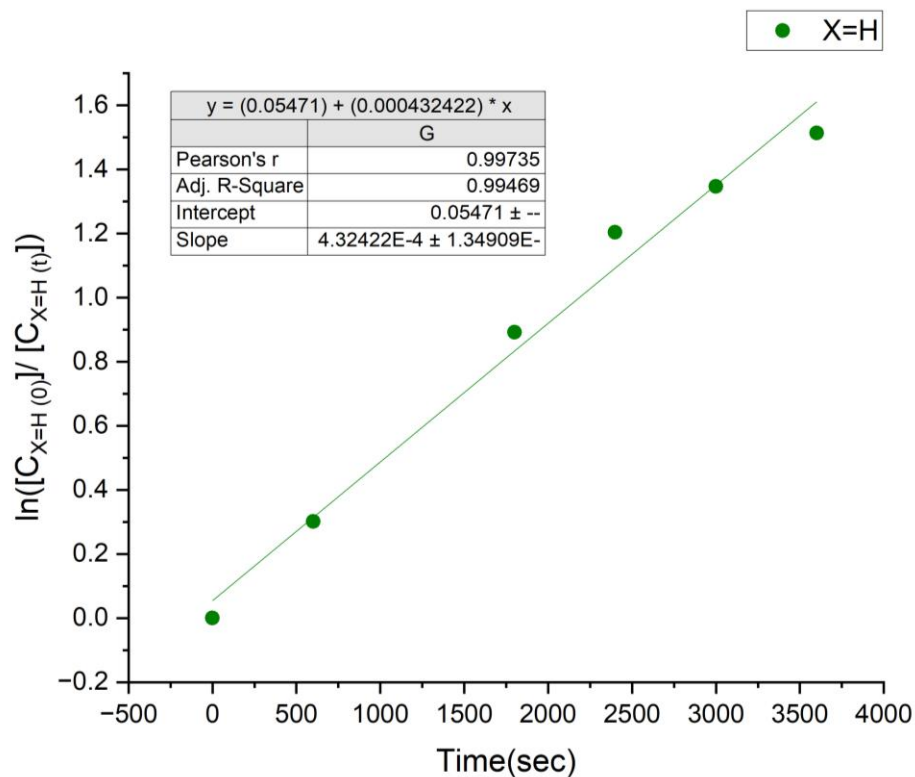


Figure 7.19. Plot between $\ln([C_{X=H(0)}]/[C_{X=H(t)}])$ vs time to get $k_{X=H}$

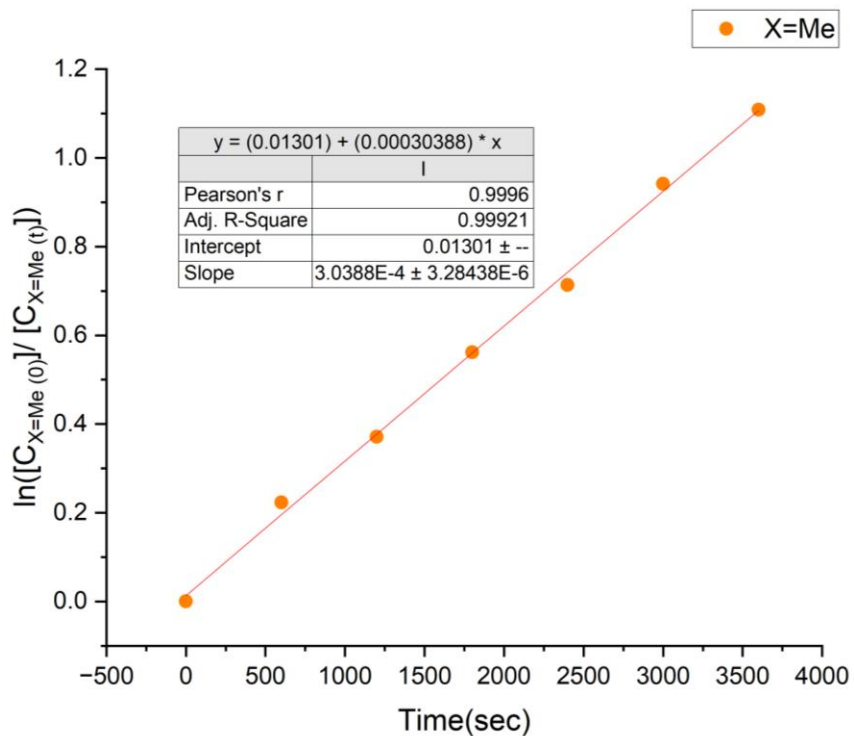


Figure 7.20. Plot between $\ln([C_{X=Me(0)}]/[C_{X=Me(t)}])$ vs time to get $k_{X=Me}$

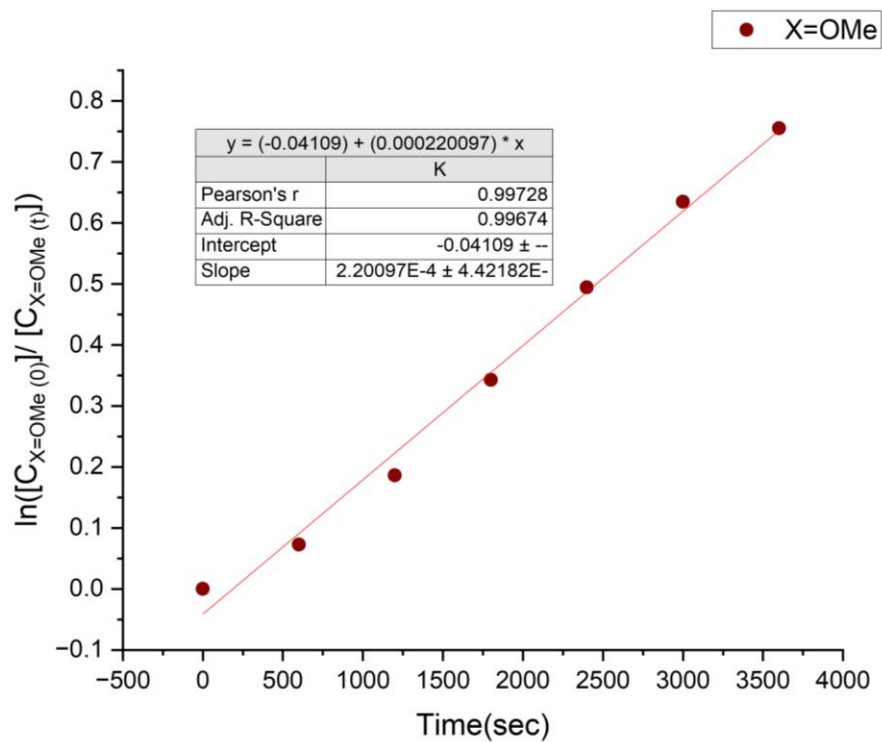


Figure 7.21. Plot between $\ln([C_{X=OMe(0)}]/[C_{X=OMe(t)}])$ vs time to get $k_{X=OMe}$

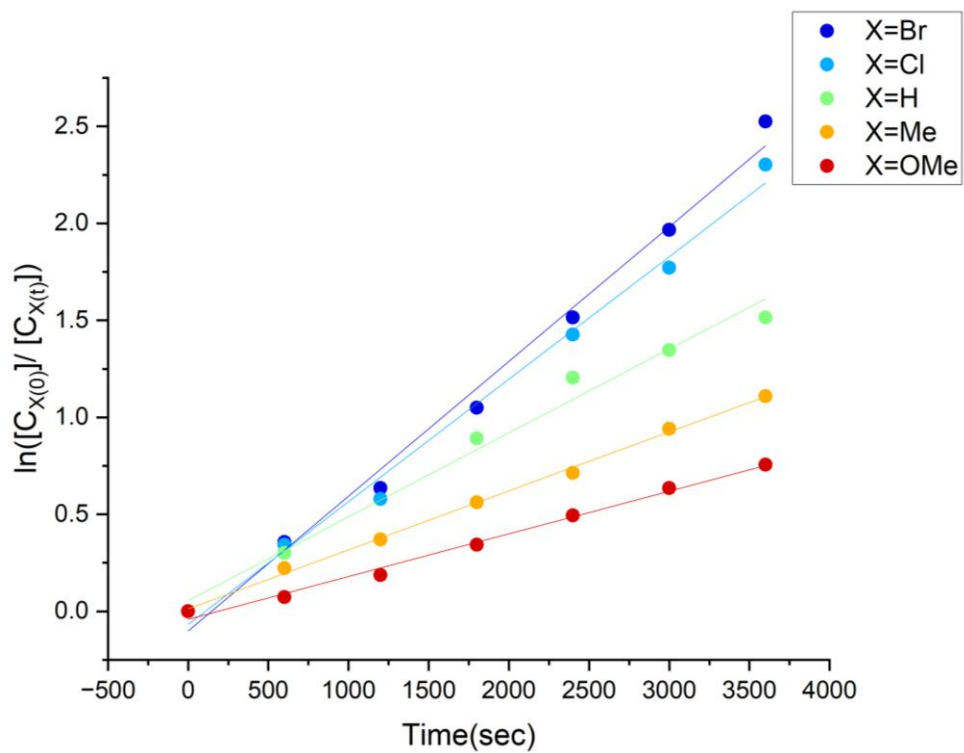


Figure 7.22. Plot between $\ln([C_{X(0)}]/[C_{X(t)}])$ vs time for $X=Br, Cl, H, Me, OMe$

Entry	X	Substituent Constant (σ)	$\log(k_X/k_H)$
1	Br	0.232	0.20605
2	Cl	0.227	0.16466
3	H	0	0
4	Me	-0.17	-0.15321
5	OMe	-0.268	-0.29329

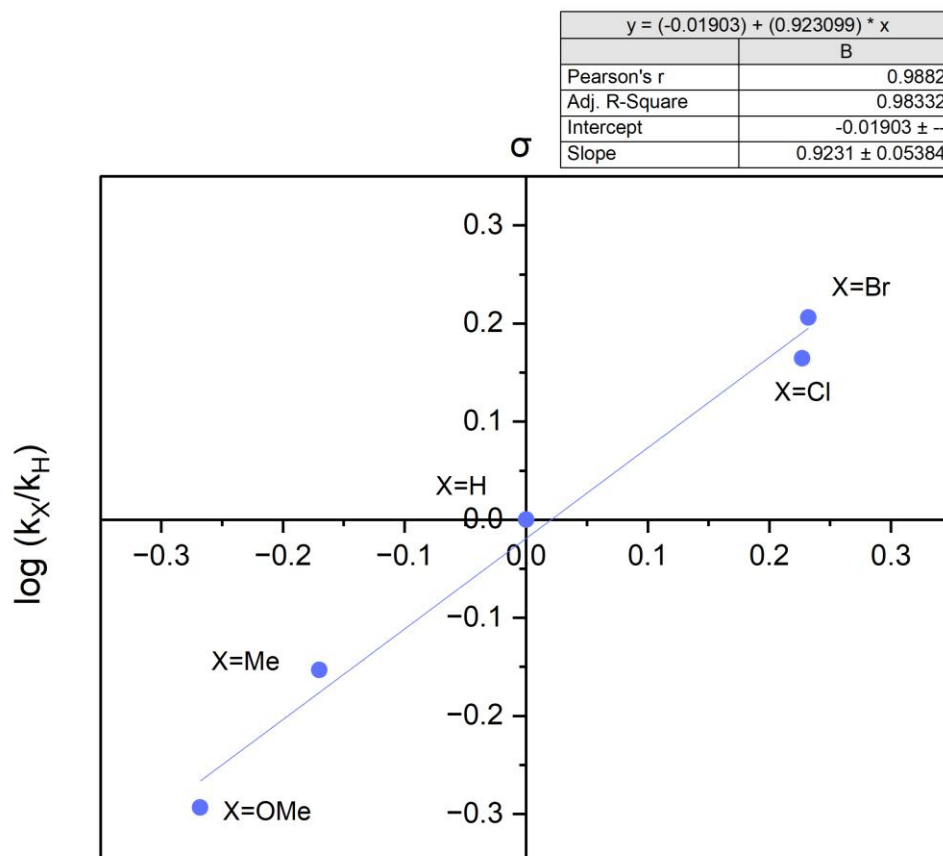
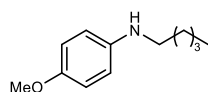


Figure 7.22. Hammett plot between $\log(k_X/k_H)$ with substituent constants (σ) where X=Br, Cl, H, Me, OMe; Hammett slope = 0.92 ± 0.05 ($R^2 = 0.98$)

7.4.7. Characterization of Compounds in Chapter 5

7.4.7.1. Spectral Data for N-Alkylation of Aromatic Amines



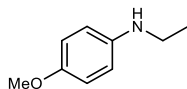
4-methoxy-N-pentylaniline (3aa): The compound was synthesized with general procedure 7.4.1. **1a** (492 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball ($\phi = 10$ mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered

using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield pale yellow oil, Yield: 749 mg, 97%.

¹H NMR (600 MHz, CDCl₃) δ 6.82 – 6.76 (m, 2H), 6.62 – 6.57 (m, 2H), 3.75 (s, 3H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.62 (dq, *J* = 11.1, 6.6 Hz, 2H), 1.46 – 1.27 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 152.3, 142.8, 115.0, 114.3, 55.9, 45.2, 29.5, 29.5, 22.6, 14.1.

Spectroscopic data are in agreement with those reported earlier.⁵¹

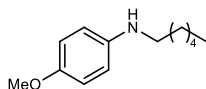


***N*-ethyl-4-methoxyaniline (3ab):** The compound was synthesized with general procedure 7.4.1. **1a** (492 mg, 4 mmol), **2b** (184 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (φ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield colourless oil, Yield: 522 mg, 86%.

¹H NMR (600 MHz, CDCl₃) δ 6.79 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 3.13 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 152.7, 141.9, 115.0, 115.0, 55.9, 40.2, 14.8.

Spectroscopic data are in agreement with those reported earlier.⁵²

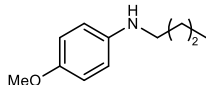


***N*-hexyl-4-methoxyaniline (3ac):** The compound was synthesized with general procedure 7.4.1. **1a** (492 mg, 4 mmol), **2c** (408 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (φ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 743 mg, 90%.

¹H NMR (600 MHz, CDCl₃) δ 6.81 – 6.75 (m, 2H), 6.61 – 6.55 (m, 2H), 3.75 (s, 3H), 3.06 (t, *J* = 7.2 Hz, 2H), 1.60 (p, *J* = 7.3 Hz, 2H), 1.47 – 1.36 (m, 2H), 1.35 – 1.29 (m, 4H), 0.97 – 0.83 (m, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 152.1, 143.0, 115.1, 114.2, 56.0, 45.2, 31.8, 29.8, 27.0, 22.8, 14.2.

Spectroscopic data are in agreement with those reported earlier.⁵³

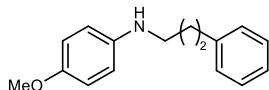


N-butyl-4-methoxyaniline (3ad): The compound was synthesized with general procedure 7.4.1. **1a** (492 mg, 4 mmol), **2d** (296 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 602 mg, 84%.

¹H NMR (600 MHz, CDCl₃) δ 6.94 – 6.74 (m, 2H), 6.66 – 6.47 (m, 2H), 3.75 (s, 3H), 3.07 (t, J = 7.1 Hz, 2H), 1.59 (dtd, J = 8.8, 7.4, 5.9 Hz, 2H), 1.47 – 1.37 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 152.2, 143.0, 115.1, 114.2, 56.0, 44.9, 31.9, 20.5, 14.1.

Spectroscopic data are in agreement with those reported earlier.⁵⁴

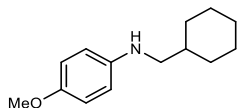


4-methoxy-N-(3-phenylpropyl)aniline (3af): The compound was synthesized with general procedure 7.4.1. **1a** (492 mg, 4 mmol), **2f** (545 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 906 mg, 94%.

¹H NMR (600 MHz, CDCl₃) δ 7.30 (dd, J = 8.4, 6.8 Hz, 2H), 7.24 – 7.18 (m, 3H), 6.81 – 6.74 (m, 2H), 6.59 – 6.50 (m, 2H), 3.75 (s, 3H), 3.12 (t, J = 7.0 Hz, 2H), 2.74 (t, J = 7.6 Hz, 2H), 1.95 (dq, J = 8.7, 7.1 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 152.2, 142.8, 141.9, 128.6, 128.5, 126.1, 115.1, 114.3, 56.0, 44.6, 33.6, 31.3.

Spectroscopic data are in agreement with those reported earlier.⁵⁵

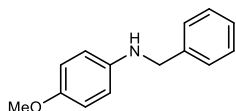


***N*-(cyclohexylmethyl)-4-methoxyaniline (3ag):** The compound was synthesized with general procedure 7.4.1. **1a** (492 mg, 4 mmol), **2g** (457 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield colourless oil, Yield: 858 mg, 98%.

¹H NMR (600 MHz, CDCl₃) δ 6.83 – 6.74 (m, 2H), 6.60 – 6.54 (m, 2H), 3.75 (s, 3H), 2.91 (d, J = 6.7 Hz, 2H), 1.90 – 1.78 (m, 2H), 1.77 – 1.71 (m, 2H), 1.68 (dddd, J = 12.1, 4.7, 3.1, 1.5 Hz, 1H), 1.56 (dddd, J = 14.5, 11.3, 6.8, 3.2 Hz, 1H), 1.31 – 1.15 (m, 3H), 0.98 (qd, J = 12.0, 3.4 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 152.0, 143.1, 115.1, 114.1, 56.0, 51.8, 37.78, 31.5, 26.8, 26.1.

Spectroscopic data are in agreement with those reported earlier.⁵⁶

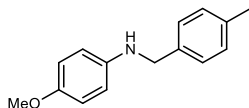


***N*-benzyl-4-methoxyaniline (3ai):** The compound was synthesized with general procedure 7.4.1. **1a** (492 mg, 4 mmol), **2i** (432 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 716 mg, 84%.

¹H NMR (600 MHz, CDCl₃) δ 7.43 – 7.35 (m, 4H), 7.32 – 7.28 (m, 1H), 6.83 – 6.77 (m, 2H), 6.63 (dd, J = 8.6, 1.5 Hz, 2H), 4.31 (s, 2H), 3.77 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 152.3, 142.6, 139.8, 128.7, 127.6, 127.3, 115.0, 114.2, 55.9, 49.3.

Spectroscopic data are in agreement with those reported earlier.⁵⁷



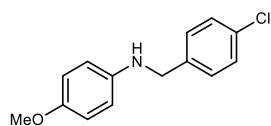
4-methoxy-*N*-(4-methylbenzyl)aniline (3aj): The compound was synthesized with general procedure 7.4.1. **1a** (492 mg, 4 mmol), **2j** (488 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in

a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 520 mg, 57%.

¹H NMR (600 MHz, CDCl₃) δ 7.18 (t, *J* = 3.9 Hz, 3H), 7.07 (d, *J* = 7.7 Hz, 2H), 6.73 – 6.67 (m, 2H), 6.56 – 6.51 (m, 2H), 4.16 (s, 2H), 3.67 (s, 3H), 2.27 (s, 3H), 1.50 (br, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 152.3, 142.7, 136.9, 136.7, 129.4, 127.7, 115.1, 114.3, 56.0, 49.2, 21.2.

Spectroscopic data are in agreement with those reported earlier.⁵⁸

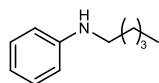


***N*-(4-chlorobenzyl)-4-methoxyaniline (3ak):** The compound was synthesized with general procedure 7.4.1. **1a** (492 mg, 4 mmol), **2k** (570 mg, 4 mmol), KO^{*t*}Bu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 624 mg, 63%.

¹H NMR (600 MHz, CDCl₃) δ 7.30 (s, 4H), 6.81 – 6.73 (m, 2H), 6.62 – 6.53 (m, 2H), 4.26 (s, 2H), 3.74 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 152.5, 142.2, 138.4, 132.3, 128.9, 128.9, 115.1, 114.3, 56.9, 48.7.

Spectroscopic data are in agreement with those reported earlier.⁵⁹

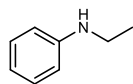


***N*-pentylaniline (3ba):** The compound was synthesized with general procedure 7.4.1. **1b** (372 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^{*t*}Bu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 594 mg, 91%.

¹H NMR (600 MHz, CDCl₃) δ 7.20 (ddt, *J* = 9.5, 7.4, 2.2 Hz, 2H), 6.71 (tt, *J* = 7.3, 1.0 Hz, 1H), 6.63 (dt, *J* = 8.8, 1.6 Hz, 2H), 3.61 (br, 1H), 3.30 – 2.99 (m, 2H), 1.79 – 1.53 (m, 2H), 1.44 – 1.36 (m, 4H), 0.95 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 148.7, 129.3, 117.2, 112.8, 44.1, 29.5, 29.4, 22.6, 14.2.

Spectroscopic data are in agreement with those reported earlier.⁶⁰

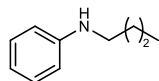


N-ethylaniline (3bb): The compound was synthesized with general procedure 7.4.1. **1b** (372 mg, 4 mmol), **2b** (184 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 465 mg, 96%.

¹H NMR (600 MHz, CDCl₃) δ 7.22 – 7.14 (m, 2H), 6.71 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.65 – 6.57 (m, 2H), 3.54 (br, 1H), 3.17 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 148.6, 129.3, 117.3, 112.9, 38.6, 15.0.

Spectroscopic data are in agreement with those reported earlier.⁶¹

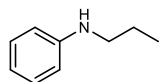


N-butylaniline (3bd): The compound was synthesized with general procedure 7.4.1. **1b** (372 mg, 4 mmol), **2d** (296 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 527 mg, 88%.

¹H NMR (600 MHz, CDCl₃) δ 7.21 – 7.16 (m, 2H), 6.70 (tt, *J* = 7.3, 1.0 Hz, 1H), 6.65 – 6.57 (m, 2H), 3.60 (br, 1H), 3.13 (t, *J* = 7.1 Hz, 2H), 1.62 (tt, *J* = 8.7, 7.0 Hz, 2H), 1.50 – 1.38 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 148.7, 129.3, 117.2, 112.8, 43.8, 31.8, 20.4, 14.0.

Spectroscopic data are in agreement with those reported earlier.⁶²

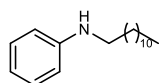


N-propylaniline (3be): The compound was synthesized with general procedure 7.4.1. **1b** (372 mg, 4 mmol), **2e** (240 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 493 mg, 91%.

¹H NMR (600 MHz, CDCl₃) δ 7.23 – 7.16 (m, 2H), 6.71 (tt, J = 7.4, 1.1 Hz, 1H), 6.65 – 6.60 (m, 2H), 3.63 (br, 1H), 3.10 (t, J = 7.1 Hz, 2H), 1.66 (h, J = 7.3 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 148.6, 129.3, 117.2, 112.8, 45.9, 22.9, 11.8.

Spectroscopic data are in agreement with those reported earlier.⁶³

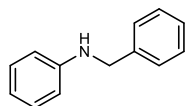


N-dodecylaniline (3bh): The compound was synthesized with general procedure 7.4.1. **1b** (372 mg, 4 mmol), **2h** (745 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 847 mg, 81%.

¹H NMR (600 MHz, CDCl₃) δ 7.19 – 7.14 (m, 2H), 6.69 (t, J = 7.3 Hz, 1H), 6.63 – 6.58 (m, 2H), 3.10 (t, J = 7.1 Hz, 2H), 1.62 (p, J = 7.2 Hz, 2H), 1.44 – 1.36 (m, 2H), 1.28 (d, J = 9.2 Hz, 16H), 0.89 (t, J = 6.9 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 148.7, 129.4, 117.2, 112.9, 44.2, 32.1, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 27.3, 22.8, 14.3.

Spectroscopic data are in agreement with those reported earlier.⁶³



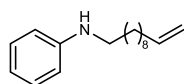
N-benzylaniline (3bi): The compound was synthesized with general procedure 7.4.1. **1b** (372 mg, 4 mmol), **2i** (432 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m

2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 667 mg, 91%.

¹H NMR (600 MHz, CDCl₃) δ 7.43 – 7.35 (m, 4H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 2H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 2H), 4.36 (s, 2H), 4.05 (br, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 148.3, 139.6, 129.4, 128.8, 127.6, 127.3, 117.7, 113.0, 48.4.

Spectroscopic data are in agreement with those reported earlier.⁶⁴

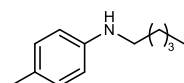


N-(undec-10-en-1-yl)aniline (3bl): The compound was synthesized with general procedure 7.4.1. **1b** (372 mg, 4 mmol), **2l** (681 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (φ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 676 mg, 69%.

¹H NMR (600 MHz, CDCl₃) δ 7.21 – 7.13 (m, 2H), 6.69 (td, *J* = 7.3, 1.4 Hz, 1H), 6.61 (dt, *J* = 7.4, 1.2 Hz, 2H), 5.83 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 3.63 (br, 1H), 3.11 (t, *J* = 7.1 Hz, 2H), 2.11 – 1.99 (m, 2H), 1.62 (p, *J* = 7.2 Hz, 2H), 1.40 (h, *J* = 6.8 Hz, 4H), 1.35 – 1.30 (m, 8H).

¹³C NMR (151 MHz, CDCl₃) δ 148.6, 139.3, 129.3, 117.3, 114.3, 112.9, 44.2, 44.2, 33.9, 29.7, 29.7, 29.6, 29.2, 29.1, 27.3.

Spectroscopic data are in agreement with those reported earlier.⁶⁵

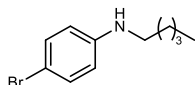


4-methyl-N-pentylaniline (3ca): The compound was synthesized with general procedure 7.4.1. **1c** (428 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (φ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 658 mg, 93%.

¹H NMR (600 MHz, CDCl₃) δ 7.11 – 6.97 (m, 2H), 6.63 – 6.48 (m, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 1.71 – 1.56 (m, 2H), 1.39 (h, *J* = 2.9 Hz, 4H), 1.03 – 0.85 (m, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 146.3, 129.8, 126.5, 113.1, 44.6, 29.5, 29.4, 22.6, 20.5, 14.2.

Spectroscopic data are in agreement with those reported earlier.⁶⁶

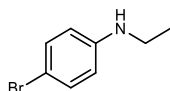


4-bromo-*N*-pentylaniline (3da): The compound was synthesized with general procedure 7.4.1. **1d** (688 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 920 mg, 95%.

¹H NMR (600 MHz, CDCl₃) δ 7.33 – 7.24 (m, 2H), 6.59 – 6.43 (m, 2H), 3.65 (br, 1H), 3.09 (t, *J* = 7.2 Hz, 2H), 1.64 (p, *J* = 7.4 Hz, 2H), 1.41 (dt, *J* = 7.3, 3.8 Hz, 4H), 1.02 – 0.90 (m, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 147.6, 131.9, 114.3, 108.5, 44.0, 29.4, 29.2, 22.6, 14.1.

Spectroscopic data are in agreement with those reported earlier.⁶⁶

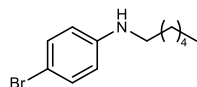


4-bromo-*N*-ethylaniline (3db): The compound was synthesized with general procedure 7.4.1. **1d** (688 mg, 4 mmol), **2b** (184 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 801 mg, 95%.

¹H NMR (600 MHz, CDCl₃) δ 7.26 – 7.19 (m, 2H), 6.53 – 6.43 (m, 2H), 3.57 (br, 1H), 3.12 (q, *J* = 7.0 Hz, 2H), 1.25 (td, *J* = 7.1, 1.2 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 147.5, 132.0, 114.4, 108.81, 38.61, 14.84.

Spectroscopic data are in agreement with those reported earlier.⁶⁷

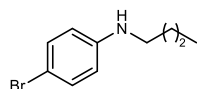


4-bromo-*N*-hexylaniline (3dc): The compound was synthesized with general procedure 7.4.1. **1d** (688 mg, 4 mmol), **2c** (408 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 942 mg, 92%.

¹H NMR (600 MHz, CDCl₃) δ 7.27 – 7.11 (m, 2H), 6.58 – 6.29 (m, 2H), 3.65 (br, 1H), 3.06 (t, J = 7.2 Hz, 2H), 1.60 (p, J = 7.3 Hz, 2H), 1.39 (dq, J = 8.9, 6.8 Hz, 2H), 1.35 – 1.30 (m, 4H), 0.94 – 0.88 (m, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 147.6, 132.0, 114.4, 108.7, 44.2, 31.7, 29.5, 26.9, 22.7, 14.2.

Spectroscopic data are in agreement with those reported earlier.⁵³

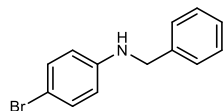


4-bromo-*N*-butylaniline (3dd): The compound was synthesized with general procedure 7.4.1. **1d** (688 mg, 4 mmol), **2d** (296 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 828 mg, 91%.

¹H NMR (600 MHz, CDCl₃) δ 7.33 – 7.12 (m, 2H), 6.51 – 6.39 (m, 2H), 3.62 (br, 1H), 3.07 (t, J = 7.1 Hz, 2H), 1.72 – 1.53 (m, 2H), 1.43 (dt, J = 14.9, 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 147.6, 131.0, 114.3, 108.6, 43.8, 31.6, 20.4, 14.0.

Spectroscopic data are in agreement with those reported earlier.⁶⁸



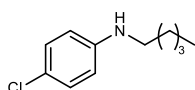
***N*-benzyl-4-bromoaniline (3di):** The compound was synthesized with general procedure 7.4.1. **1d** (688 mg, 4 mmol), **2i** (432 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ =

10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 933 mg, 89%.

¹H NMR (600 MHz, CDCl₃) δ 7.35 (d, *J* = 4.4 Hz, 4H), 7.31 – 7.27 (m, 1H), 7.26 – 7.22 (m, 2H), 6.55 – 6.48 (m, 2H), 4.31 (s, 2H), 4.10 (br, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 147.2, 139.0, 132.1, 128.8, 127.5, 127.5, 114.6, 109.3, 48.4.

Spectroscopic data are in agreement with those reported earlier.⁶⁹

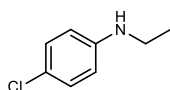


4-chloro-*N*-pentylaniline (3ea): The compound was synthesized with general procedure 7.4.1. **1e** (510 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 688 mg, 87%.

¹H NMR (600 MHz, CDCl₃) δ 7.17 – 7.00 (m, 2H), 6.71 – 6.36 (m, 2H), 3.65 (br, 1H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.80 – 1.53 (m, 2H), 1.42 – 1.30 (m, 4H), 1.05 – 0.83 (m, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 147.2, 129.1, 121.7, 113.9, 44.3, 29.4, 29.3, 22.6, 14.2.

Spectroscopic data are in agreement with those reported earlier.⁷⁰

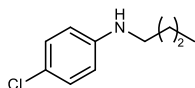


4-chloro-*N*-ethylaniline (3eb): The compound was synthesized with general procedure 7.4.1. **1e** (510 mg, 4 mmol), **2b** (184 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 597 mg, 96%.

¹H NMR (600 MHz, CDCl₃) δ 7.18 – 7.01 (m, 2H), 6.60 – 6.41 (m, 2H), 3.55 (br, 1H), 3.12 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 147.1, 129.1, 121.8, 113.9, 38.7, 14.9.

Spectroscopic data are in agreement with those reported earlier.⁷¹

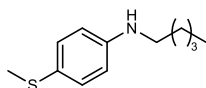


N-butyl-4-chloroaniline (3ed): The compound was synthesized with general procedure 7.4.1. **1e** (510 mg, 4 mmol), **2d** (296 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 660 mg, 90%.

¹H NMR (600 MHz, CDCl₃) δ 7.17 – 7.05 (m, 2H), 6.56 – 6.43 (m, 2H), 3.60 (br, 1H), 3.08 (t, *J* = 7.1 Hz, 2H), 1.69 – 1.54 (m, 2H), 1.42 (dt, *J* = 14.6, 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 147.2, 129.1, 121.7, 113.8, 43.9, 31.7, 20.4, 14.0.

Spectroscopic data are in agreement with those reported earlier.⁷²

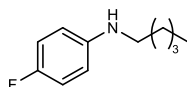


4-(methylthio)-N-pentylaniline (3fa): The compound was synthesized with general procedure 7.4.1. **1f** (557 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 326 mg, 39%.

¹H NMR (600 MHz, CDCl₃) δ 7.24 – 7.20 (m, 2H), 6.67 – 6.46 (m, 2H), 3.70 (br, 1H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.62 (ddt, *J* = 14.4, 10.2, 5.8 Hz, 2H), 1.37 (h, *J* = 4.0 Hz, 4H), 1.01 – 0.87 (m, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 147.5, 131.8, 124.0, 113.4, 44.1, 29.4, 29.3, 22.6, 19.4, 14.1.

Spectroscopic data are in agreement with those reported earlier.⁷³

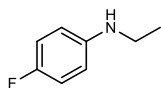


4-fluoro-*N*-pentylaniline (3ga): The compound was synthesized with general procedure 7.4.1. **1g** (444 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 340 mg, 51%.

¹H NMR (600 MHz, CDCl₃) δ 7.09 – 6.76 (m, 2H), 6.63 – 6.38 (m, 2H), 3.06 (t, J = 7.1 Hz, 2H), 1.62 (tt, J = 8.8, 6.1 Hz, 2H), 1.45 – 1.32 (m, 4H), 1.02 – 0.83 (m, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 155.8 (d, J = 234.4 Hz), 145.0 (d, J = 1.6 Hz), 115.7 (d, J = 22.2 Hz), 113.6 (d, J = 7.5 Hz), 44.8, 29.5, 29.4, 22.6, 14.2.

Spectroscopic data are in agreement with those reported earlier.⁷³

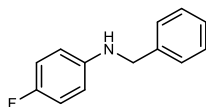


***N*-ethyl-4-fluoroaniline (3gb):** The compound was synthesized with general procedure 7.4.1. **1g** (444 mg, 4 mmol), **2b** (184 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 517 mg, 93%.

¹H NMR (600 MHz, CDCl₃) δ 7.07 – 6.75 (m, 2H), 6.54 (ddd, J = 9.0, 4.4, 0.9 Hz, 2H), 3.12 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 155.9 (d, J = 234.6 Hz), 144.9, 115.7 (d, J = 22.4 Hz), 113.7 (dd, J = 7.3, 3.5 Hz), 39.3, 15.0.

Spectroscopic data are in agreement with those reported earlier.⁷⁴



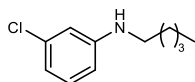
***N*-benzyl-4-fluoroaniline (3gi):** The compound was synthesized with general procedure 7.4.1. **1g** (444 mg, 4 mmol), **2i** (432 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC

(hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 426 mg, 53%.

¹H NMR (600 MHz, CDCl₃) δ 7.42 – 7.33 (m, 4H), 7.31 – 7.27 (m, 1H), 6.95 – 6.81 (m, 2H), 6.62 – 6.53 (m, 2H), 4.30 (s, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 156.9, 155.39, 144.5, 139.3, 128.2 (d, *J* = 174.7 Hz), 127.5, 115.8 (d, *J* = 22.2 Hz), 113.9 (d, *J* = 7.3 Hz), 49.1.

Spectroscopic data are in agreement with those reported earlier.⁶⁰

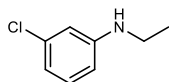


3-Chloro-*N*-pentylaniline (3ha): The compound was synthesized with general procedure 7.4.1. **1h** (510 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 703 mg, 89%.

¹H NMR (600 MHz, CDCl₃) δ 7.06 (t, *J* = 8.0 Hz, 1H), 6.65 (dd, *J* = 7.9, 2.0 Hz, 1H), 6.57 (t, *J* = 2.1 Hz, 1H), 6.46 (dd, *J* = 8.2, 2.3 Hz, 1H), 3.69 (br, 1H), 3.08 (t, *J* = 7.2 Hz, 2H), 1.62 (dq, *J* = 9.6, 7.1 Hz, 2H), 1.38 (tt, *J* = 6.2, 2.9 Hz, 4H), 0.94 (td, *J* = 5.8, 2.3 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 149.8, 135.2, 130.3, 117.0, 112.3, 111.1, 43.9, 29.4, 29.2, 22.6, 14.1.

Spectroscopic data are in agreement with those reported earlier.⁷³

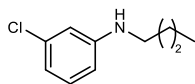


3-Chloro-*N*-ethylaniline (3hb): The compound was synthesized with general procedure 7.4.1. **1h** (510 mg, 4 mmol), **2b** (184 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 529 mg, 85%.

¹H NMR (600 MHz, CDCl₃) δ 7.07 (t, *J* = 8.0 Hz, 1H), 6.66 (ddd, *J* = 7.8, 2.0, 0.9 Hz, 1H), 6.57 (t, *J* = 2.2 Hz, 1H), 6.46 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H), 3.64 (br, 1H), 3.14 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 149.6, 135.1, 130.3, 117.1, 112.3, 111.2, 38.4, 14.8.

Spectroscopic data are in agreement with those reported earlier.⁷¹

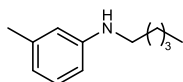


N-Butyl-3-chloroaniline (3hd): The compound was synthesized with general procedure 7.4.1. **1h** (510 mg, 4 mmol), **2d** (296 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 639 mg, 87%.

¹H NMR (600 MHz, CDCl₃) δ 7.06 (t, *J* = 8.0 Hz, 1H), 6.65 (ddd, *J* = 7.9, 2.0, 0.9 Hz, 1H), 6.57 (t, *J* = 2.1 Hz, 1H), 6.46 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H), 3.68 (br, 1H), 3.09 (t, *J* = 7.1 Hz, 2H), 1.84 – 1.52 (m, 2H), 1.43 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 149.8, 135.1, 130.2, 116.9, 112.3, 111.2, 43.6, 31.6, 20.4, 14.0.

Spectroscopic data are in agreement with those reported earlier.⁷¹

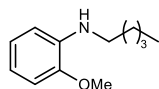


3-methyl-N-pentylaniline (3ia): The compound was synthesized with general procedure 7.4.1. **1i** (428 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield yellow oil, Yield: 588 mg, 83%.

¹H NMR (600 MHz, CDCl₃) δ 7.08 (t, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 7.4 Hz, 1H), 6.44 (d, *J* = 8.2 Hz, 2H), 3.55 (br, 1H), 3.11 (t, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 1.69 – 1.56 (m, 2H), 1.47 – 1.33 (m, 4H), 0.94 (td, *J* = 6.8, 2.7 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 148.7, 139.1, 129.2, 118.2, 113.6, 110.0, 44.1, 29.45, 29.5, 22.6, 21.8, 14.2.

Spectroscopic data are in agreement with those reported earlier.⁶⁹

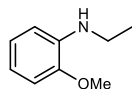


2-methoxy-*N*-pentylaniline (3ja): The compound was synthesized with general procedure 7.4.1. **1j** (492 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 526 mg, 68%.

¹H NMR (600 MHz, CDCl₃) δ 6.89 (tt, J = 7.6, 1.3 Hz, 1H), 6.78 (dd, J = 8.0, 1.6 Hz, 1H), 6.67 (tt, J = 7.8, 1.4 Hz, 1H), 6.63 (dt, J = 7.8, 1.4 Hz, 1H), 4.18 (br, 1H), 3.86 (s, 3H), 3.18 – 3.08 (m, 2H), 1.68 (p, J = 6.8 Hz, 2H), 1.49 – 1.36 (m, 4H), 0.95 (td, J = 7.0, 1.4 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 146.9, 138.7, 121.4, 116.2, 109.8, 109.5, 55.5, 43.8, 29.6, 29.4, 22.7, 14.2.

Spectroscopic data are in agreement with those reported earlier.⁷⁰

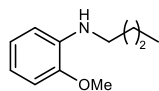


***N*-ethyl-2-methoxyaniline (3jb):** The compound was synthesized with general procedure 7.4.1. **1j** (492 mg, 4 mmol), **2b** (184 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 442 mg, 73%.

¹H NMR (600 MHz, CDCl₃) δ 6.94 (td, J = 7.6, 1.4 Hz, 1H), 6.83 (dd, J = 7.9, 1.4 Hz, 1H), 6.73 (td, J = 7.7, 1.5 Hz, 1H), 6.68 (dd, J = 7.8, 1.5 Hz, 1H), 4.17 (s, 1H), 3.90 (s, 3H), 3.23 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 146.8, 138.5, 121.4, 116.3, 109.9, 109.4, 55.4, 38.2, 14.9.

Spectroscopic data are in agreement with those reported earlier.⁵²

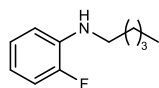


N-butyl-2-methoxyaniline (3jd): The compound was synthesized with general procedure 7.4.1. **1j** (492 mg, 4 mmol), **2d** (296 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 445 mg, 62%.

¹H NMR (600 MHz, CDCl₃) δ 6.92 (tdd, J = 8.6, 2.7, 1.4 Hz, 1H), 6.81 (dq, J = 7.9, 1.5 Hz, 1H), 6.73 – 6.61 (m, 2H), 4.22 (s, 1H), 3.96 – 3.73 (m, 3H), 3.18 (ddd, J = 9.4, 5.6, 2.0 Hz, 2H), 1.69 (dtdd, J = 9.4, 7.3, 5.6, 3.0 Hz, 2H), 1.50 (ttdd, J = 9.6, 7.3, 4.0, 2.1 Hz, 2H), 1.02 (dtd, J = 7.4, 4.4, 2.2 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 146.8, 138.6, 121.4, 116.1, 109.8, 109.4, 55.4, 43.5, 31.8, 20.5, 14.0.

Spectroscopic data are in agreement with those reported earlier.⁵²

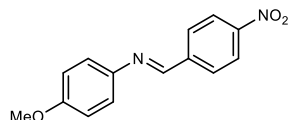


2-fluoro-N-pentylaniline (3ka): The compound was synthesized with general procedure 7.4.1. **1k** (444 mg, 4 mmol), **2a** (352.6 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield yellow oil, Yield: 340 mg, 47%.

¹H NMR (600 MHz, CDCl₃) δ 7.05 – 6.91 (m, 2H), 6.70 (ddd, J = 9.2, 8.0, 1.6 Hz, 1H), 6.61 (tdd, J = 7.7, 4.9, 1.6 Hz, 1H), 3.86 (s, 1H), 3.15 (t, J = 7.1 Hz, 2H), 1.67 (dq, J = 9.3, 7.0 Hz, 2H), 1.51 – 1.28 (m, 4H), 0.95 (t, J = 7.0 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 151.7 (d, J = 237.8 Hz), 137.1 (d, J = 11.6 Hz), 124.7 (d, J = 3.4 Hz), 116.3 (d, J = 6.9 Hz), 114.4 (d, J = 18.5 Hz), 112.1 (d, J = 3.6 Hz), 43.7, 29.4, 29.3, 22.6, 14.1.

Spectroscopic data are in agreement with those reported earlier.⁶⁹

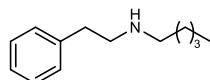


(E)-N-(4-methoxyphenyl)-1-(4-nitrophenyl)methanimine (3am): The compound was synthesized with general procedure 7.4.1. **1a** (492 mg, 4 mmol), **2m** (612 mg, 4 mmol), KO^tBu (448 mg, 4 mmol) and Ru-MACHO (1.2 mg, 0.05 mol%) were loaded into a zirconium dioxide grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 2.87 g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill MM-500 vario at room temperature, for 6 hours. The reaction was monitored by TLC (hexane/EtOAc: 9/1). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (4g) with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield orange solid, Yield: 921 mg, 90%.

¹H NMR (600 MHz, CDCl₃) δ 8.58 (s, 1H), 8.31 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 8.7 Hz, 2H), 7.35 – 7.28 (m, 2H), 6.99 – 6.94 (m, 2H), 3.85 (s, 3H).

Spectroscopic data are in agreement with those reported earlier.⁷⁵

7.4.7.2. Spectral Data for N-Alkylation of Aliphatic Amines

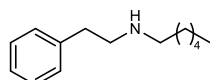


N-phenethylpentan-1-amine (5aa): The compound was synthesized with general procedure 7.4.2. **4a** (121 mg, 1 mmol), **2a** (176.3 mg, 2 mmol), KO^tBu (112 mg, 1 mmol), Ru-MACHO (6 mg, 1.0 mol%) and MgO (200 mg) were loaded into a stainless-steel grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 3.6g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill Fritsch P-23 for 12 hours. The reaction jar was heated to an external temperature of 80°C using a heat-gun and maintained as such for the whole course of the reaction. Then, the reaction jar was cooled down to room temperature, and the reaction progress was monitored by TLC (hexane/EtOAc: 8/2). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (1.0 g) with 20 mL of EtOAc and then dried using sodium sulfate and the resultant filtrate was evaporated under high vacuum. The further purification the compound was achieved using column chromatography to yield colourless liquid, Yield: 170 mg, 89%.

¹H NMR (600 MHz, CDCl₃) δ 7.29 (dd, J = 8.3, 6.9 Hz, 2H), 7.21 (d, J = 7.4 Hz, 3H), 2.93 – 2.86 (m, 2H), 2.82 (t, J = 6.8 Hz, 2H), 2.61 (t, J = 7.4 Hz, 2H), 1.47 (p, J = 7.4 Hz, 2H), 1.34 – 1.25 (m, 4H), 0.88 (t, J = 7.1 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 140.2, 128.8, 128.6, 126.2, 51.3, 50.0, 36.5, 29.8, 29.7, 22.7, 14.1.

Spectroscopic data are in agreement with those reported earlier.⁷⁶

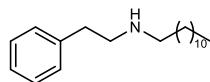


N-phenethylhexan-1-amine (5ac): The compound was synthesized with general procedure 7.4.2. **4a** (121 mg, 1 mmol), **2c** (204 mg, 2 mmol), KO^tBu (112 mg, 1 mmol), Ru-MACHO (6 mg, 1.0 mol%) and MgO (200 mg) were loaded into a stainless-steel grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 3.6g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill Fritsch P-23 for 12 hours. The reaction jar was heated to an external temperature of 80°C using a heat-gun and maintained as such for the whole course of the reaction. Then, the reaction jar was cooled down to room temperature, and the reaction progress was monitored by TLC (hexane/EtOAc: 8/2). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (1.0 g) with 20 mL of EtOAc and then dried using sodium sulfate and the resultant filtrate was evaporated under high vacuum. The further purification the compound was achieved using column chromatography to yield colourless liquid, Yield: 186 mg, 91%.

¹H NMR (600 MHz, CDCl₃) δ 7.33 – 7.27 (m, 2H), 7.23 – 7.18 (m, 3H), 2.89 (td, J = 6.9, 1.2 Hz, 2H), 2.82 (dd, J = 8.3, 6.7 Hz, 2H), 2.64 – 2.58 (m, 2H), 1.52 – 1.43 (m, 2H), 1.28 (dddd, J = 11.1, 8.8, 7.0, 2.2 Hz, 6H), 0.87 (t, J = 6.9 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 140.2, 128.8, 128.6, 126.3, 51.3, 50.0, 36.4, 31.9, 30.0, 27.1, 22.72, 14.1.

Spectroscopic data are in agreement with those reported earlier.⁷⁷



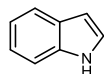
N-phenethyldodecan-1-amine (5ah): The compound was synthesized with general procedure 7.4.2. **4a** (121 mg, 1 mmol), **2h** (372.7 mg, 2 mmol), KO^tBu (112 mg, 1 mmol), Ru-MACHO (6 mg, 1.0 mol%) and MgO (200 mg) were loaded into a stainless-steel grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 3.6g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill Fritsch P-23 for 12 hours. The reaction jar was heated to an external temperature of 80°C using a heat-gun and maintained as such for the whole course of the reaction. Then, the reaction jar was cooled down to room temperature, and the reaction progress was monitored by TLC (hexane/EtOAc: 8/2). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite (1.0 g) with 20 mL of EtOAc and then dried using sodium sulfate and the resultant filtrate was evaporated under high vacuum. The further purification the compound was achieved using column chromatography to yield colourless liquid, Yield: 227 mg, 79%.

¹H NMR (600 MHz, CDCl₃) δ 7.31 – 7.27 (m, 2H), 7.23 – 7.18 (m, 3H), 2.89 (ddd, J = 7.5, 6.6, 1.3 Hz, 2H), 2.83 (dd, J = 8.5, 6.7 Hz, 2H), 2.65 – 2.59 (m, 2H), 1.48 (t, J = 7.3 Hz, 2H), 1.35 – 1.20 (m, 18H), 0.88 (t, J = 7.0 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 140.1, 128.8, 128.6, 126.2, 51.2, 49.9, 36.3, 32.0, 30.0, 29.8, 29.7 (3C), 29.6, 29.5, 27.4, 22.8, 14.2.

Spectroscopic data are in agreement with those reported earlier.⁷⁸

7.4.7.3. Spectral Data for N-Heterocycles

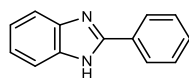


1H-Indole (6): The compound was synthesized with general procedure 7.4.3. **11** (121 mg, 1.0 mmol), KO^tBu (112 mg, 1.0 mmol) and Ru-MACHO (3 mg, 0.5 mol%) were loaded into a stainless-steel grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 3.6g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill Fritsch P-23 for 6 hours at an appropriate temperature using a heat-gun. Then, the reaction jar was cooled down to room temperature, and the reaction progress is monitored by TLC (hexane/EtOAc: 7/3). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum to yield white solid, Yield: 109 mg, 93%.

¹H NMR (600 MHz, CDCl₃) δ 7.89 (s, 1H), 7.57 (dq, J = 7.9, 0.9 Hz, 1H), 7.25 (dq, J = 8.2, 1.0 Hz, 1H), 7.11 (ddd, J = 8.2, 6.2, 1.2 Hz, 1H), 7.07 – 7.00 (m, 2H), 6.46 (ddd, J = 3.1, 2.0, 1.0 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 135.9, 127.9, 124.3, 122.1, 120.8, 119.9, 111.2, 102.7.

Spectroscopic data are in agreement with those reported earlier.⁷³



2-phenyl-1H-benzimidazole (7): The compound was synthesized with general procedure 7.4.3. **1m** (108 mg, 1.0 mmol), **2i** (108 mg, 1.0 mmol), KO^tBu (112 mg, 1.0 mmol) and Ru-MACHO (3 mg, 0.5 mol%) were loaded into a stainless-steel grinding jar (10 mL) equipped with 1 ball (ϕ = 10 mm, m 3.6g) of the same material. The jar was sealed and milled at 30 Hz in a shaker mill Fritsch P-23 for 6 hours at an appropriate temperature using a heat-gun. Then, the reaction jar was cooled down to room temperature, and the reaction progress is monitored by TLC (hexane/EtOAc: 7/3). After completion of the reaction, the resulting reaction mixture was filtered using a sintered vacuum funnel through a small bed of celite with 20 mL of EtOAc. The filtrate was then evaporated under high vacuum and purified with column chromatography to yield white solid, Yield: 73 mg, 38%.

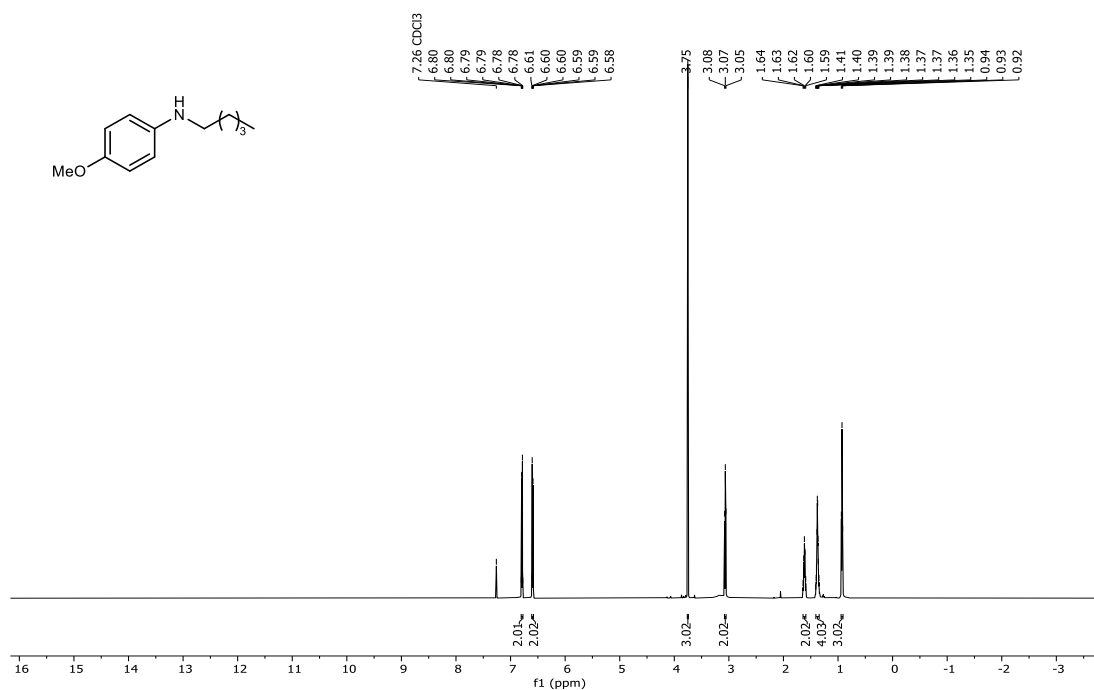
¹H NMR (600 MHz, DMSO) δ 8.18 (d, J = 7.6 Hz, 2H), 7.67 – 7.62 (m, 2H), 7.58 (t, J = 7.5 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.30 – 7.24 (m, 2H).

¹³C NMR (151 MHz, DMSO) δ 150.8, 138.0, 130.5, 129.1, 128.9, 126.7, 122.8, 114.9.

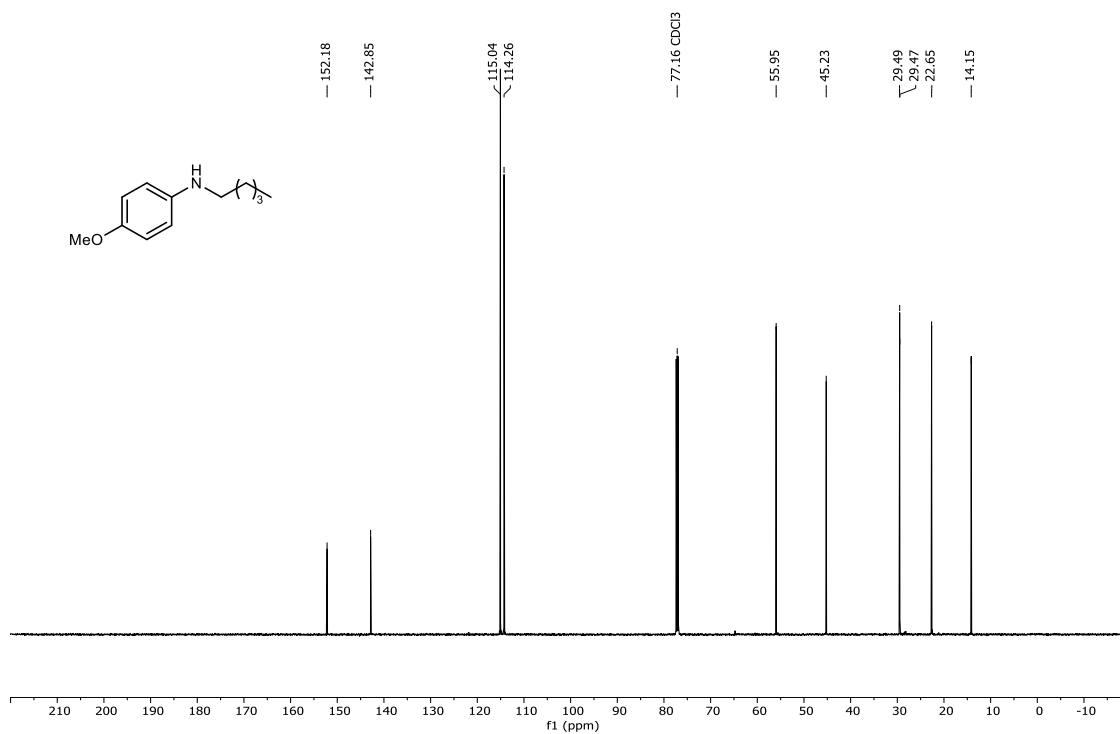
Spectroscopic data are in agreement with those reported earlier.⁷⁹

7.4.8. NMR Spectra for Compounds in Chapter 5

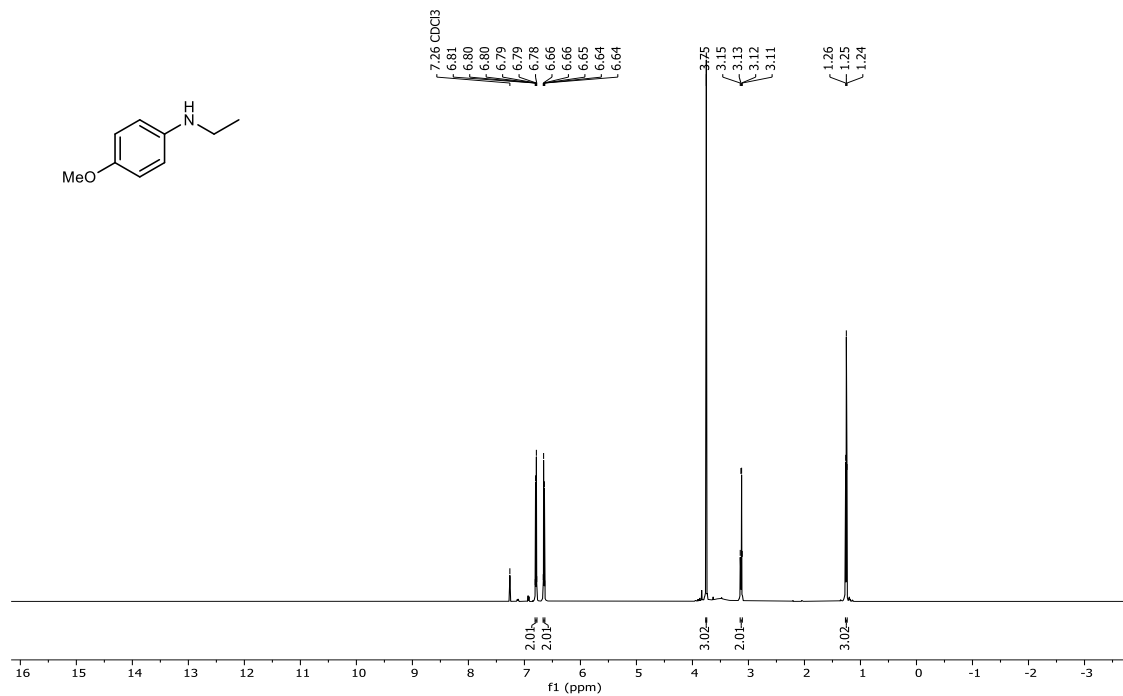
^1H NMR (600 MHz, CDCl_3) spectrum of **4-methoxy-*N*-pentylaniline (3aa)**



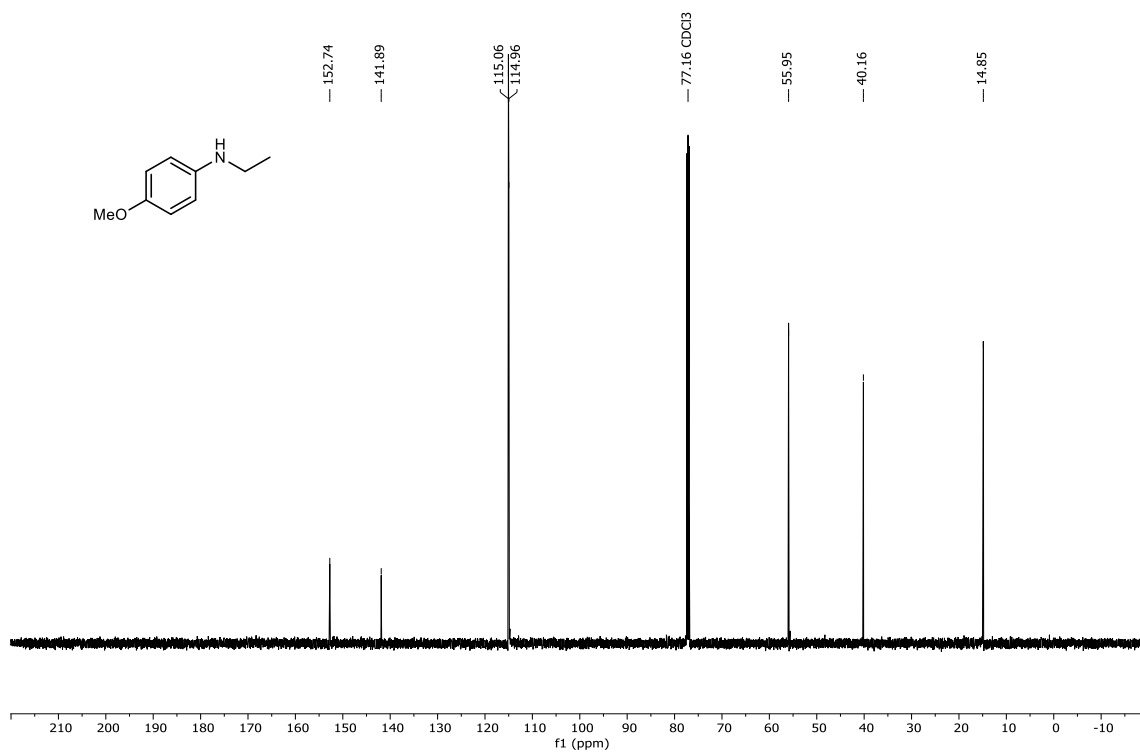
^{13}C NMR (151 MHz, CDCl_3) spectrum of **4-methoxy-*N*-pentylaniline (3aa)**



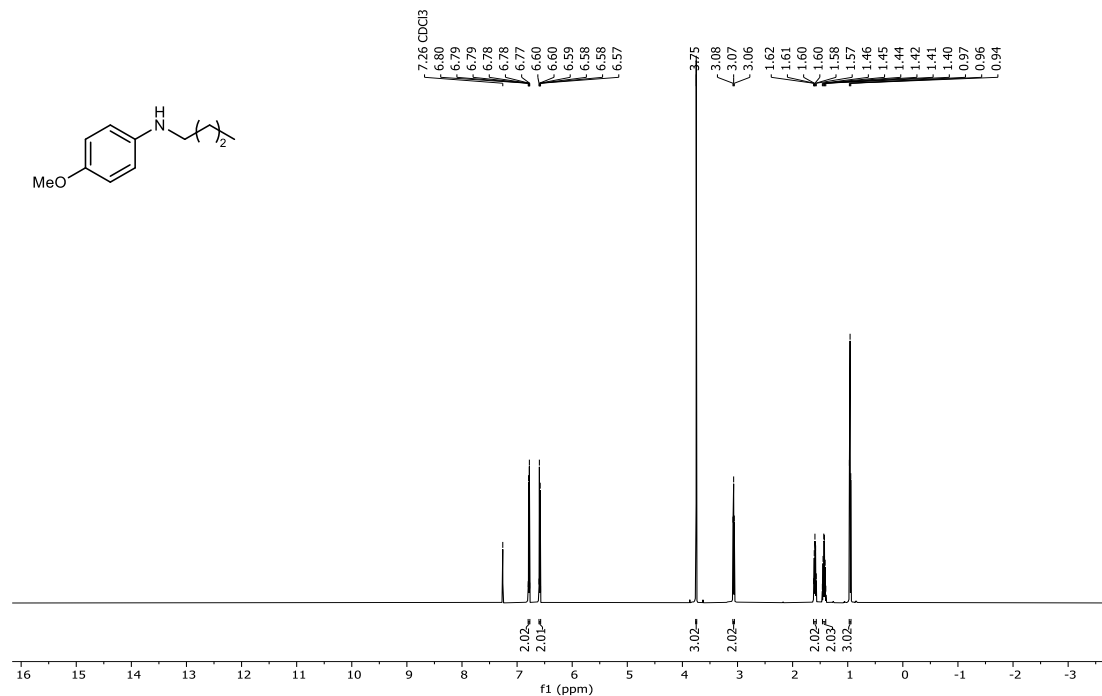
¹H NMR (600 MHz, CDCl₃) spectrum of *N*-ethyl-4-methoxyaniline (**3ab**)



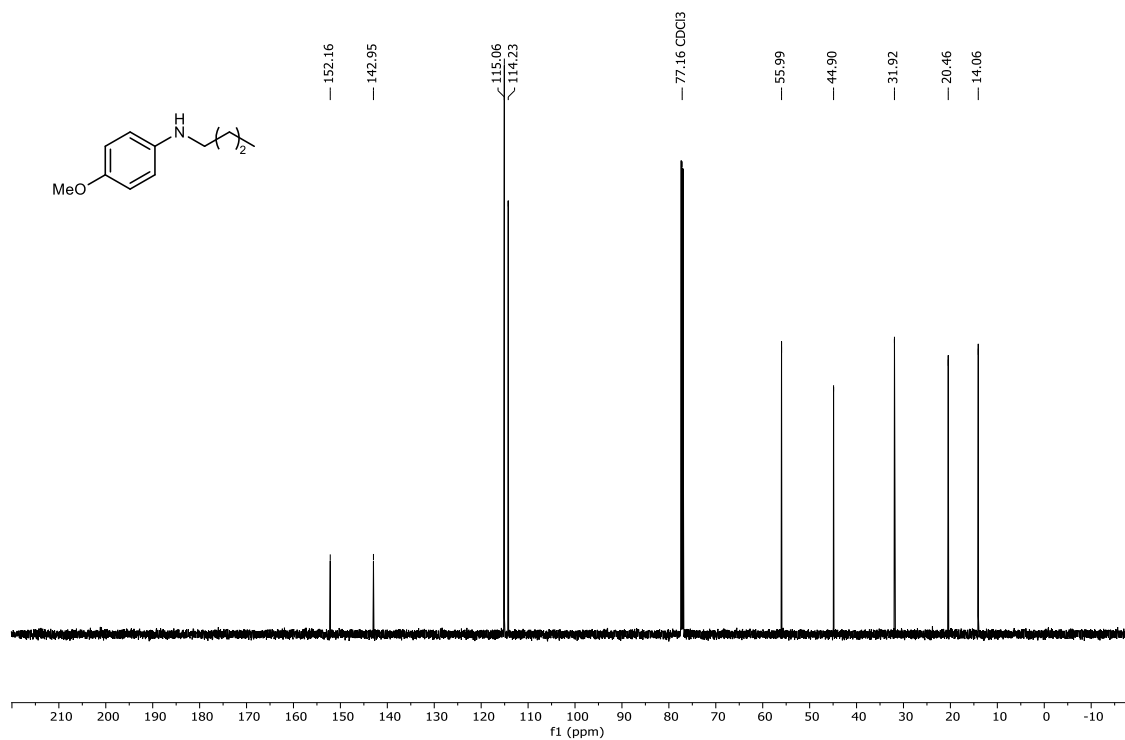
¹³C NMR (151 MHz, CDCl₃) spectrum of *N*-ethyl-4-methoxyaniline (**3ab**)



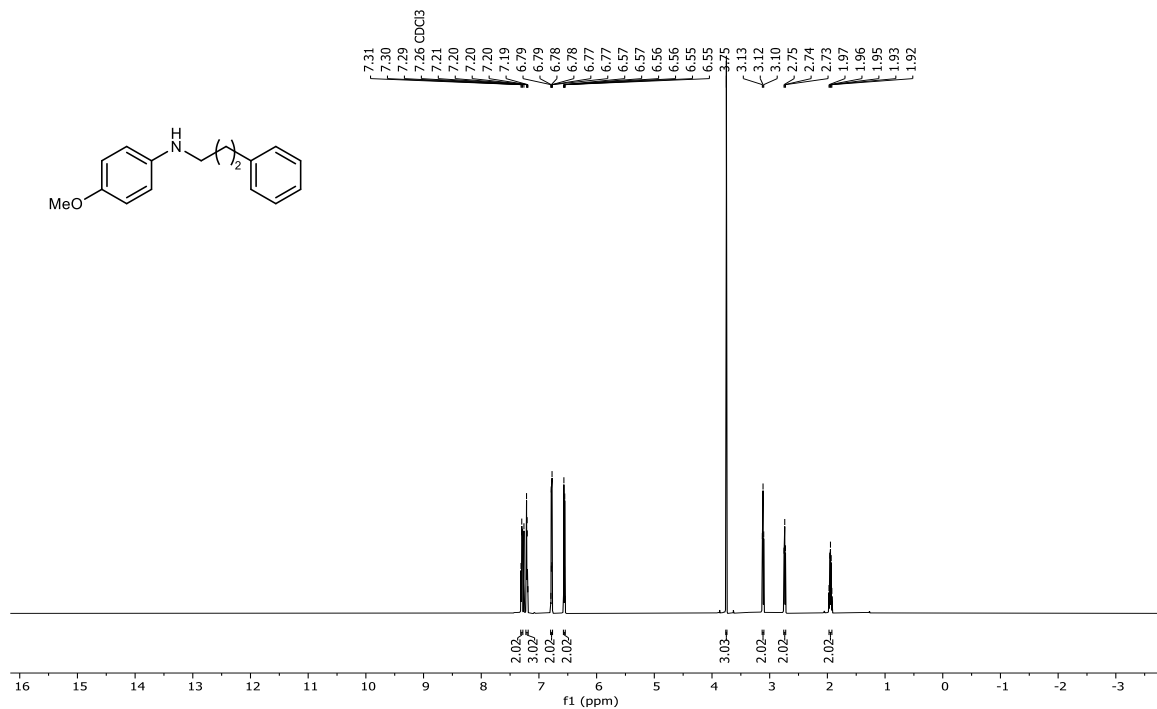
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-butyl-4-methoxyaniline (**3ad**)



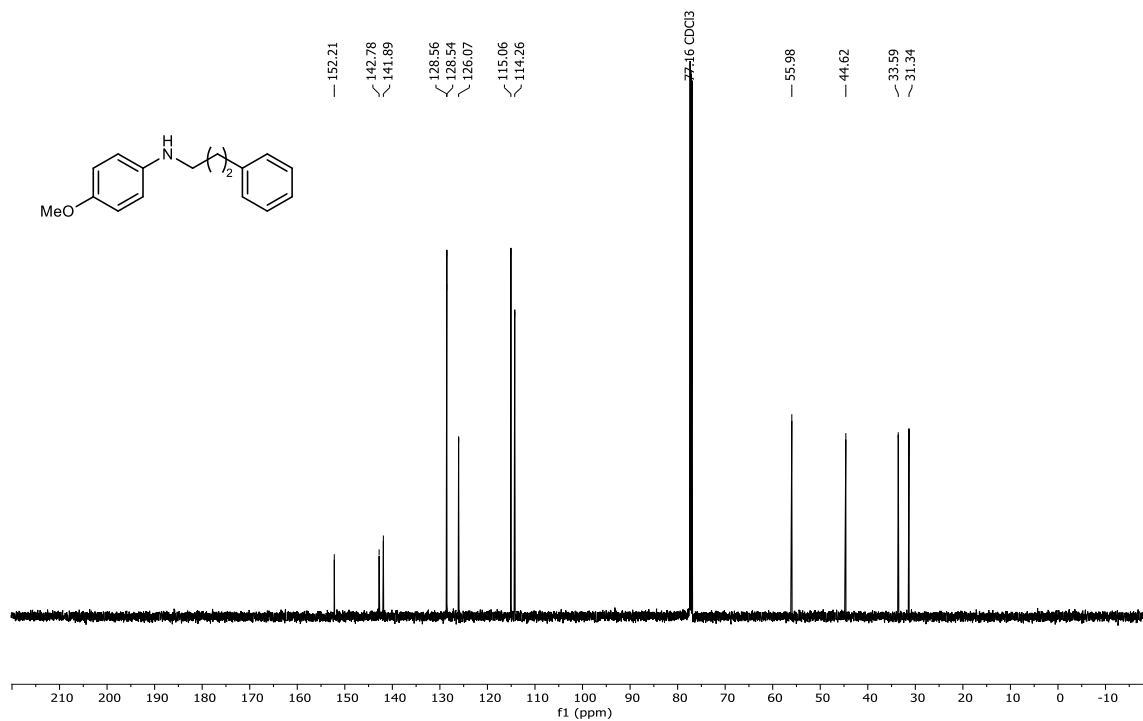
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-butyl-4-methoxyaniline (**3ad**)



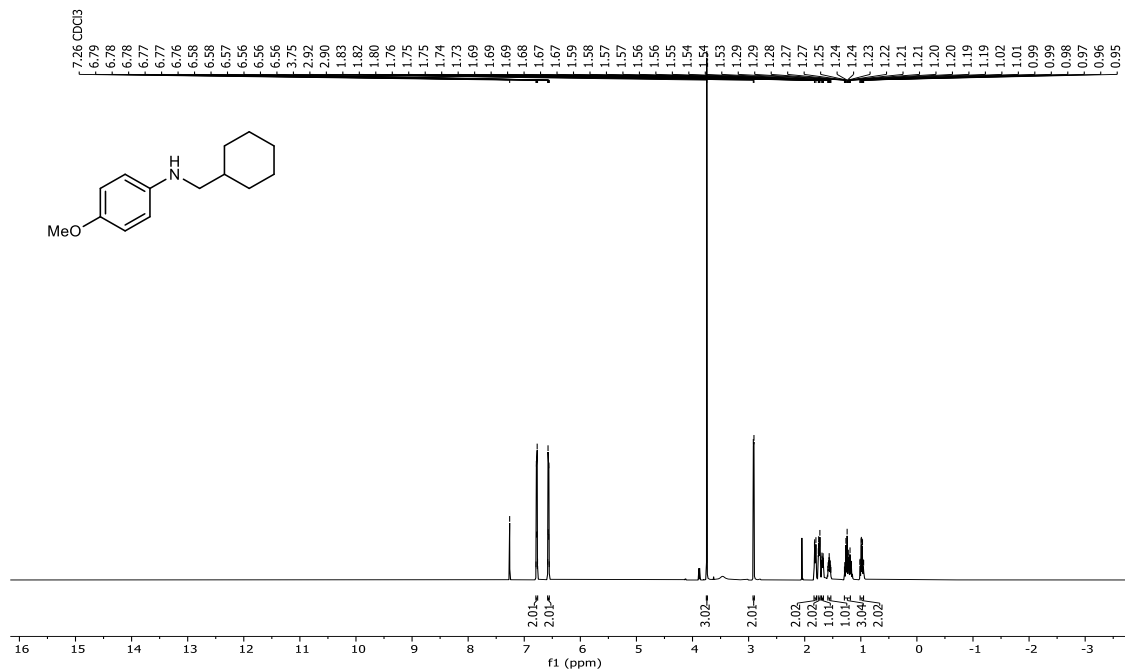
^1H NMR (600 MHz, CDCl_3) spectrum of **4-methoxy-*N*-(3-phenylpropyl)aniline (3af)**



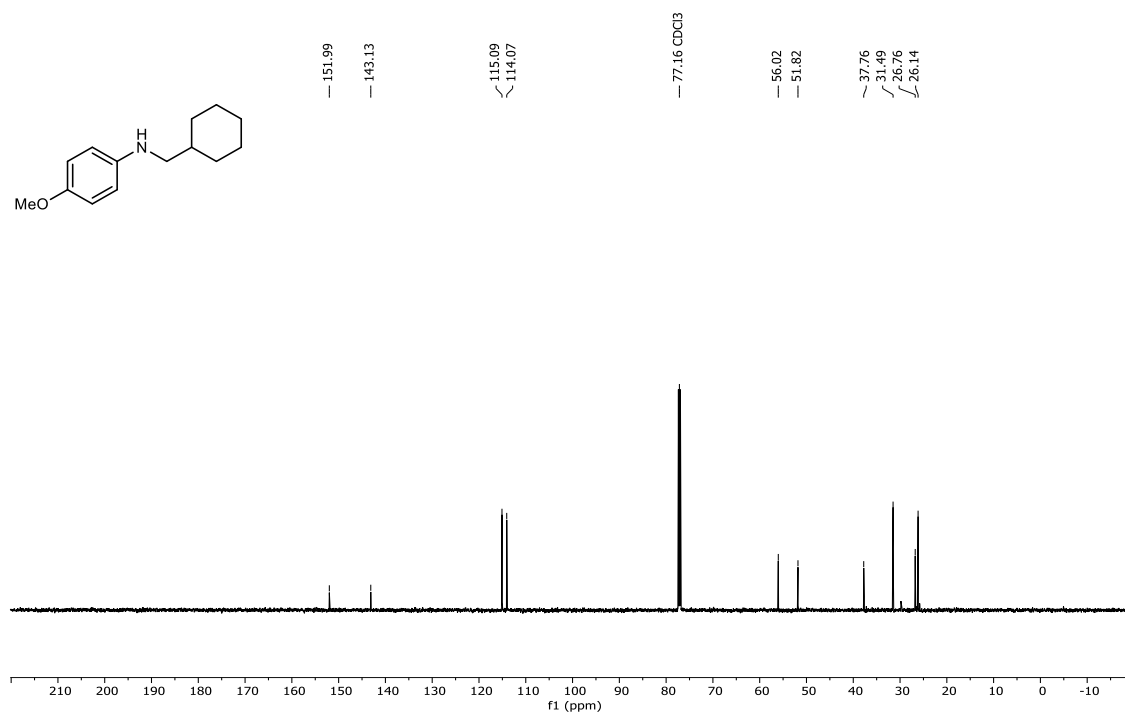
^{13}C NMR (151 MHz, CDCl_3) spectrum of **4-methoxy-*N*-(3-phenylpropyl)aniline (3af)**



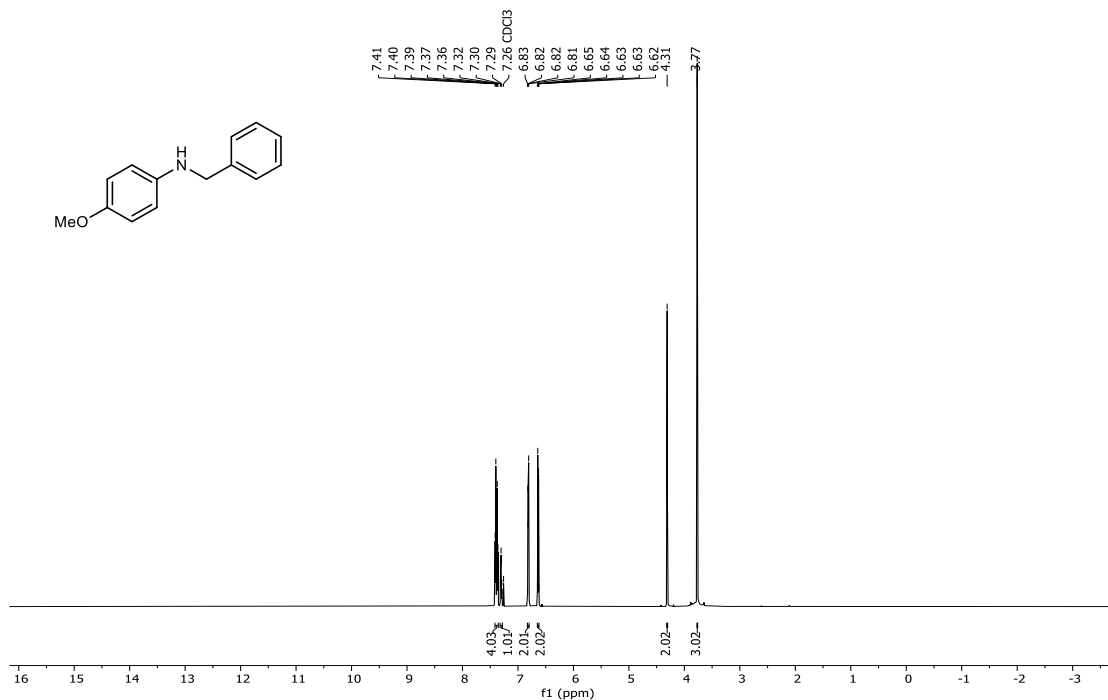
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-(cyclohexylmethyl)-4-methoxyaniline (**3ag**)



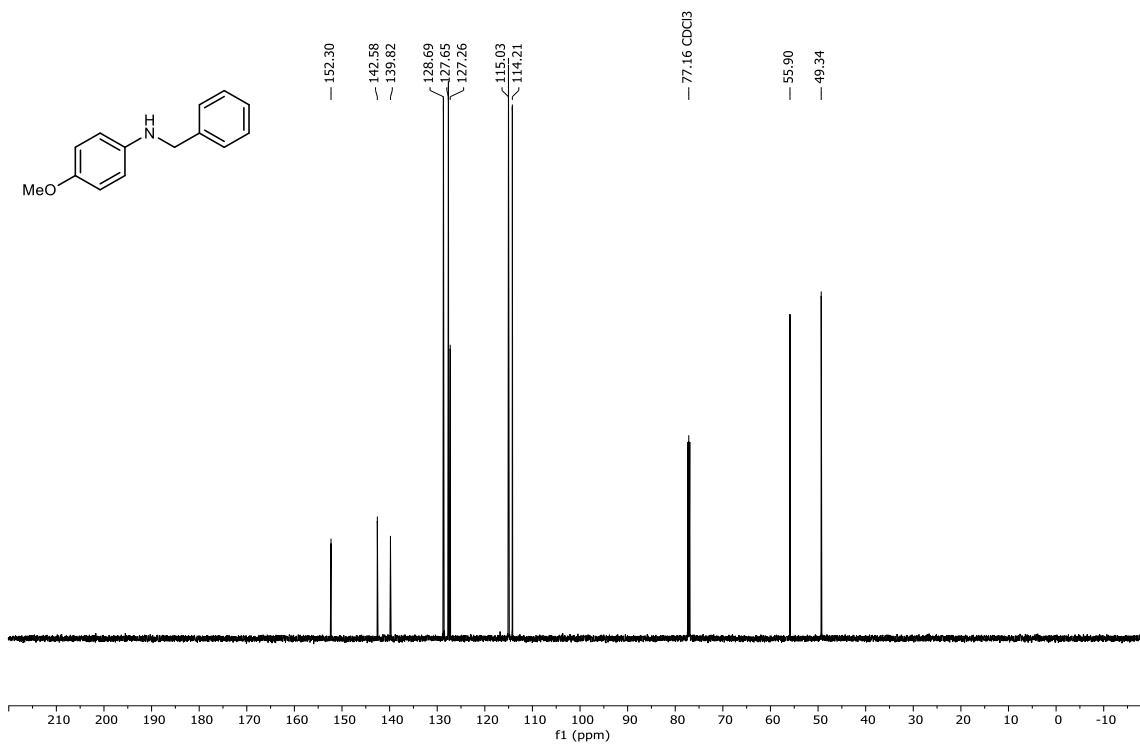
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-(cyclohexylmethyl)-4-methoxyaniline (**3ag**)



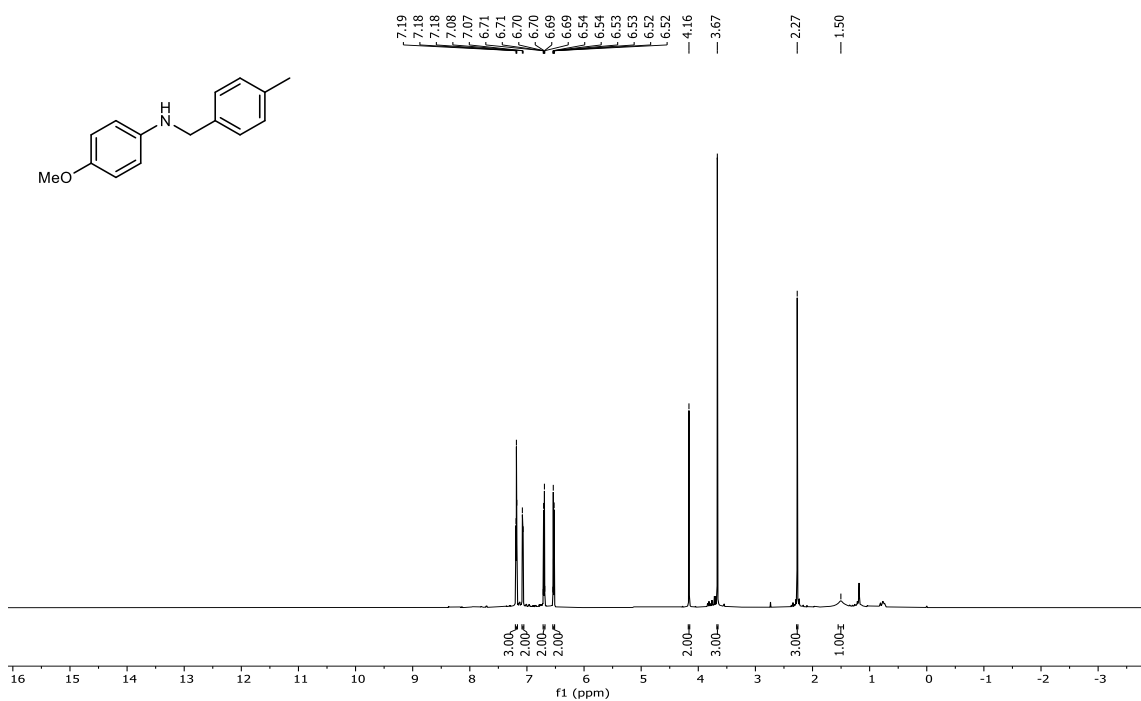
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-benzyl-4-methoxyaniline (**3ai**)



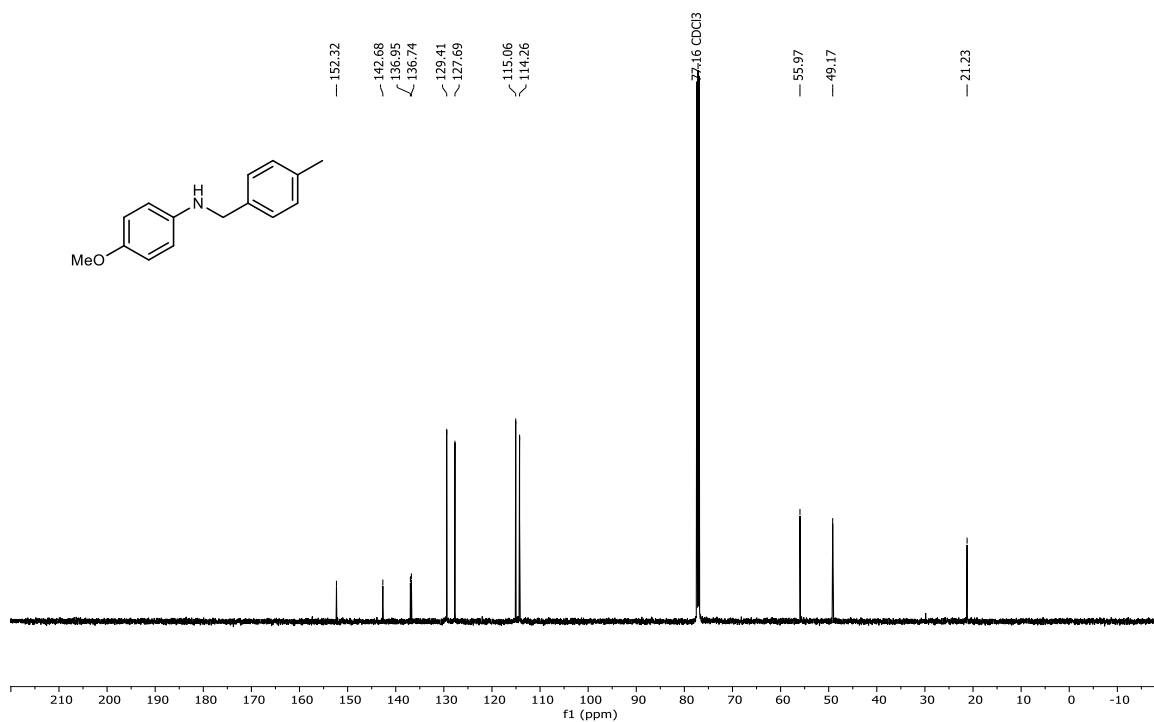
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-benzyl-4-methoxyaniline (**3ai**)



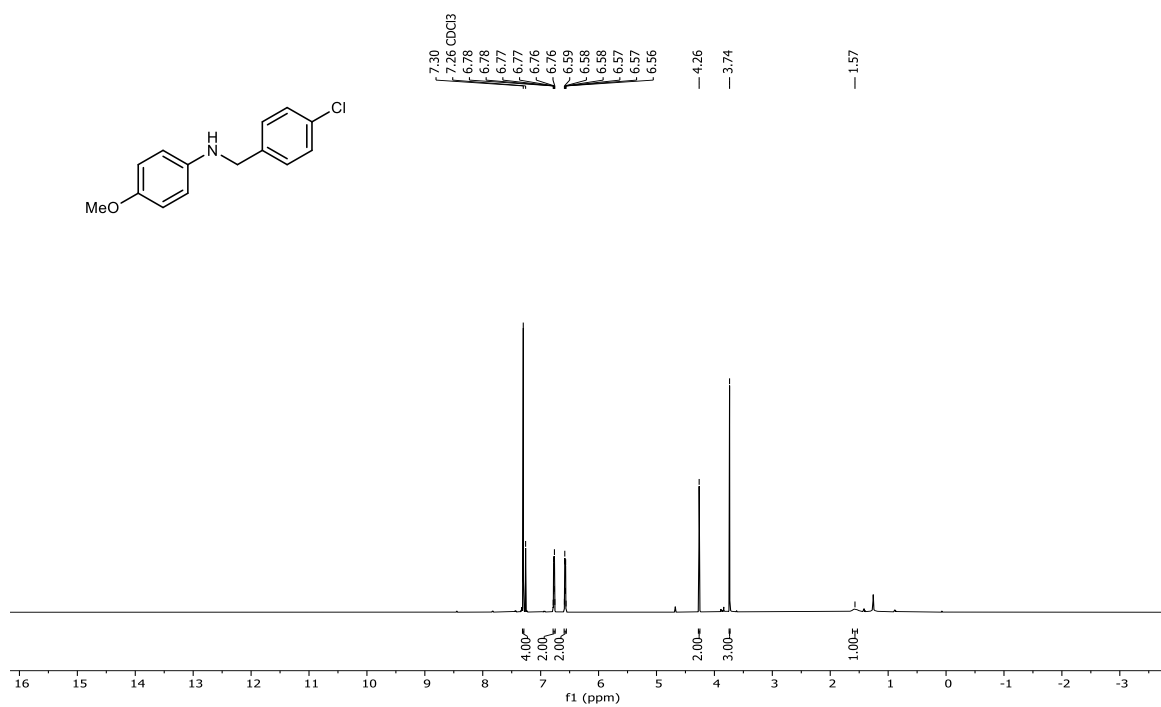
¹H NMR (600 MHz, CDCl₃) spectrum of **4-methoxy-*N*-(4-methylbenzyl)aniline (3aj)**



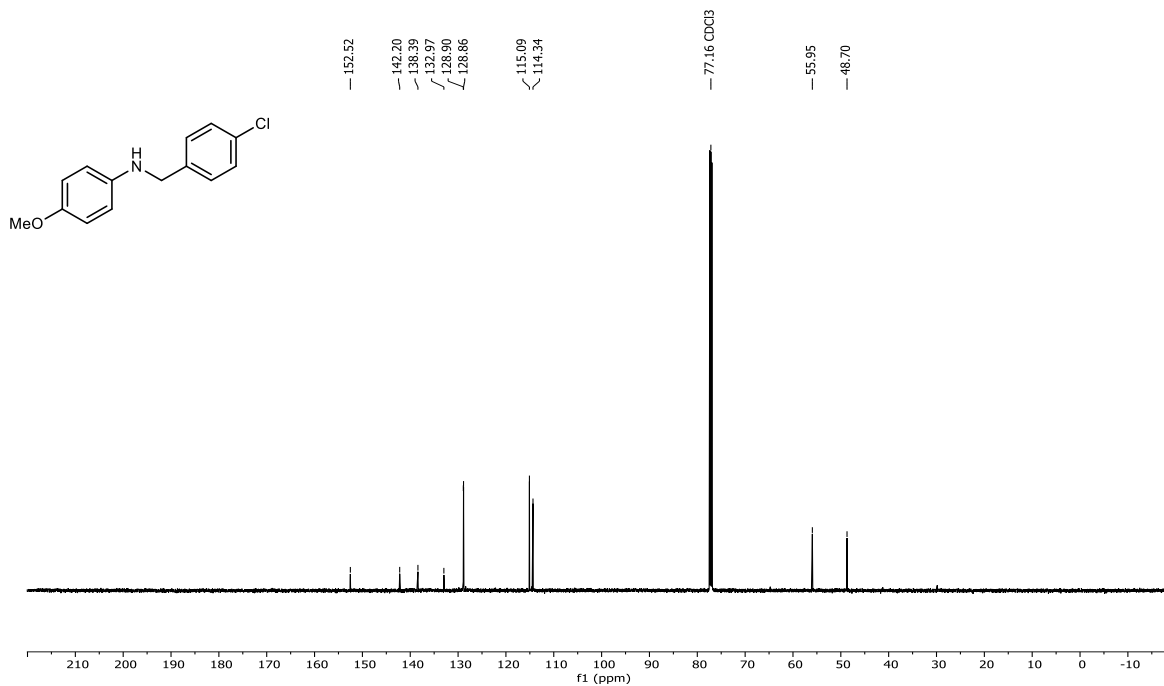
¹³C NMR (151 MHz, CDCl₃) spectrum of **4-methoxy-*N*-(4-methylbenzyl)aniline (3aj)**



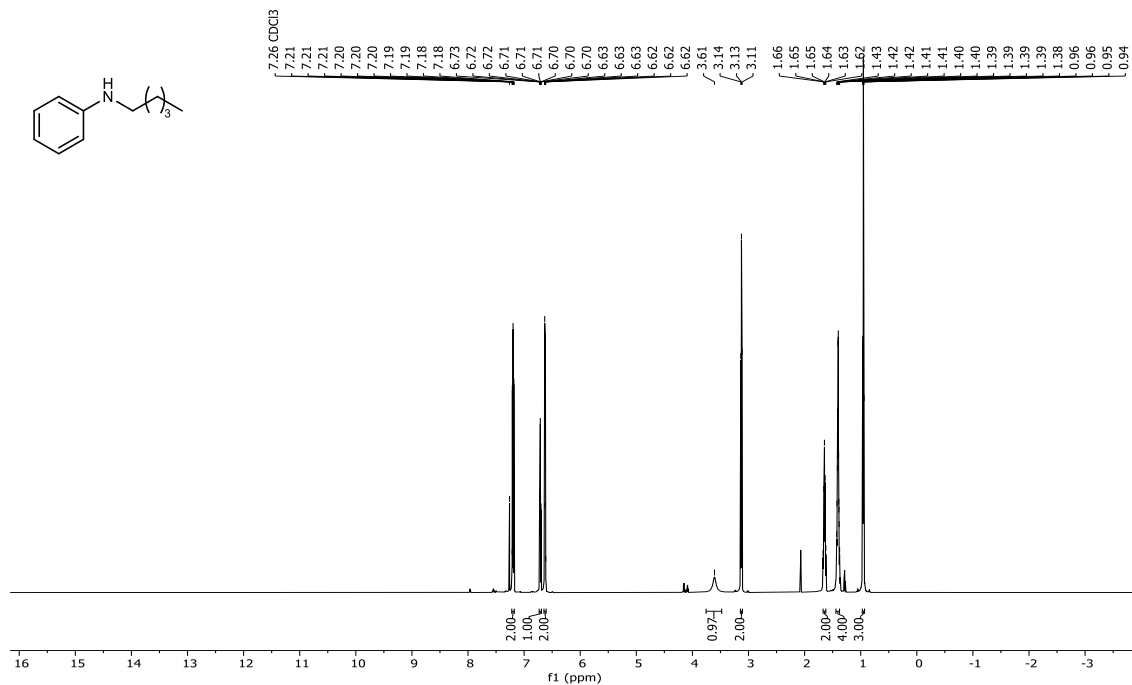
¹H NMR (600 MHz, CDCl₃) spectrum of *N*-(4-chlorobenzyl)-4-methoxyaniline (3ak)



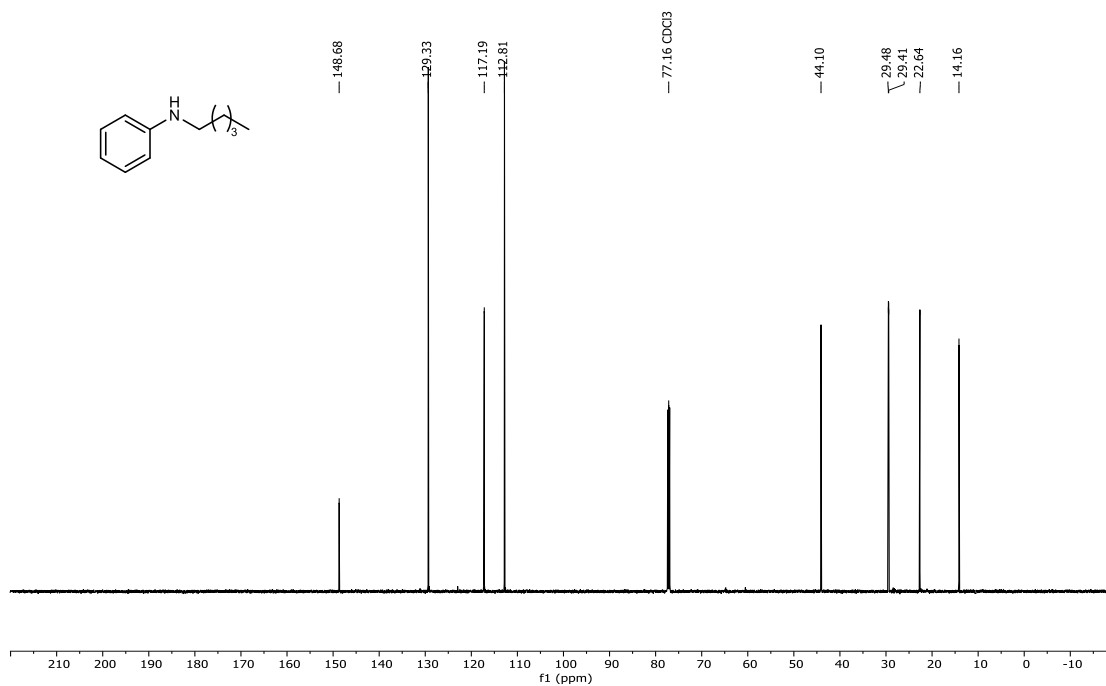
¹³C NMR (151 MHz, CDCl₃) spectrum of *N*-(4-chlorobenzyl)-4-methoxyaniline (3ak)



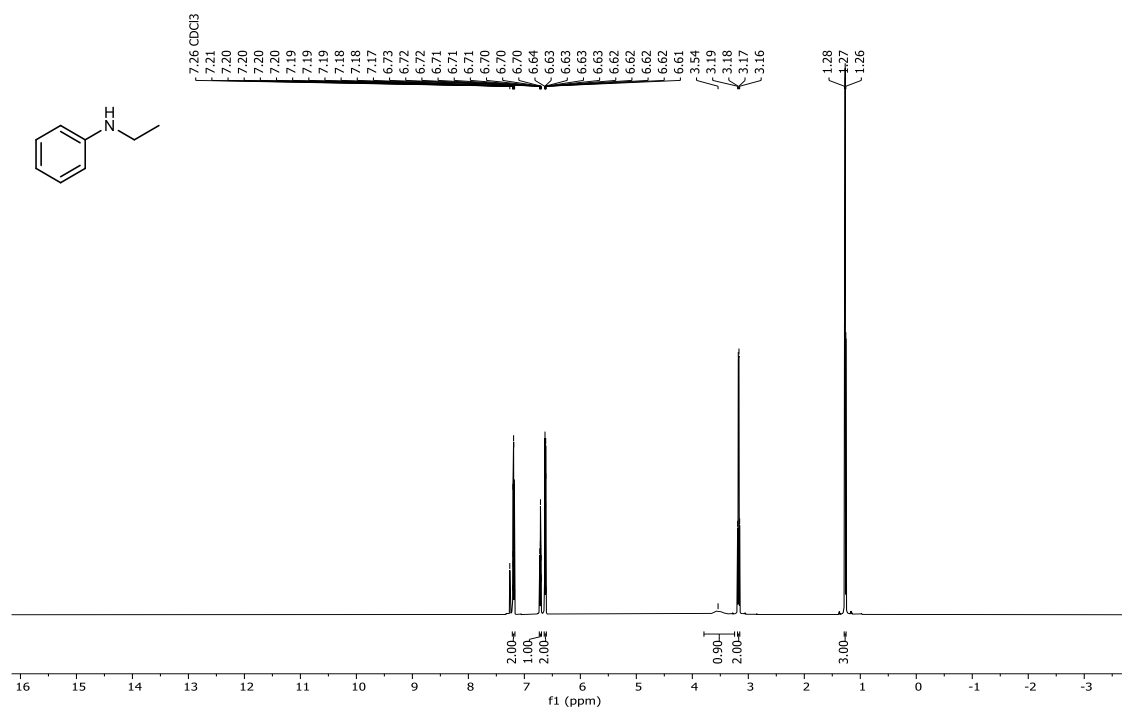
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-pentylaniline (**3ba**)



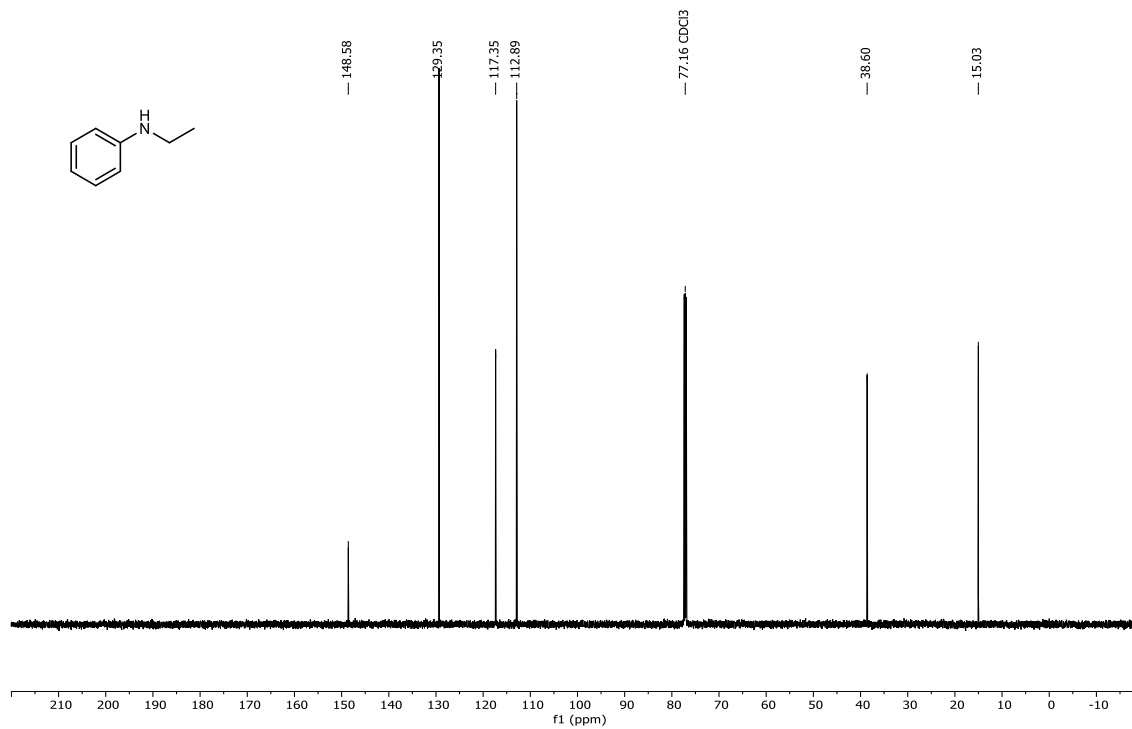
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-pentylaniline (**3ba**)



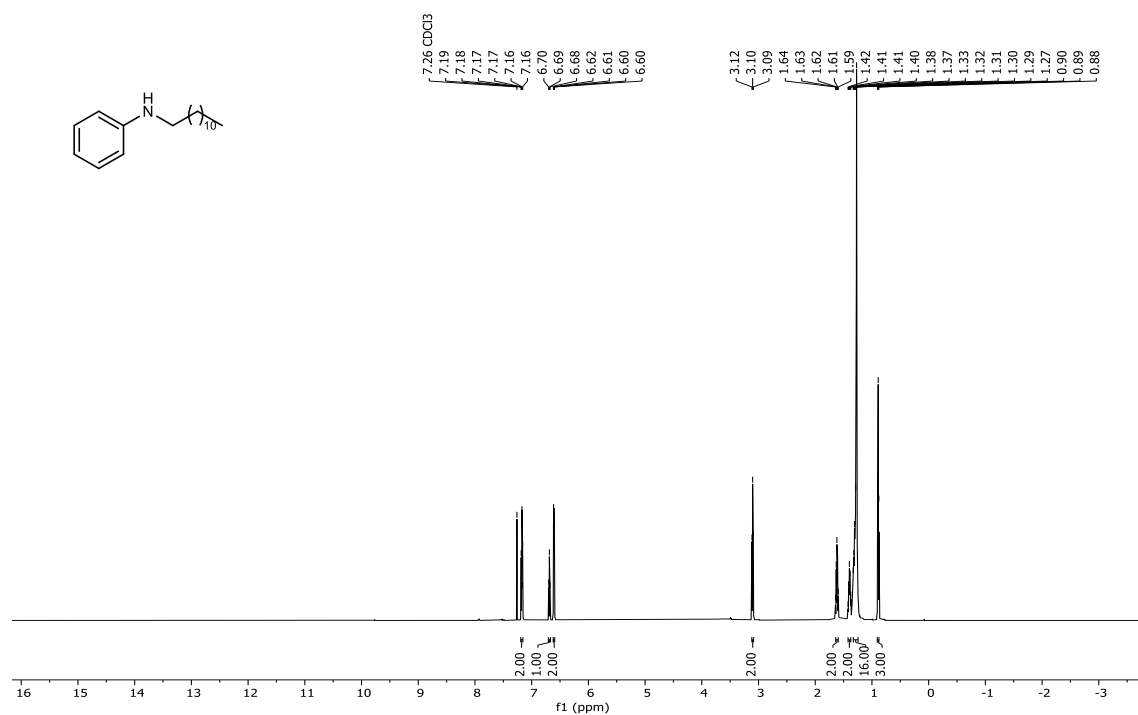
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-ethylaniline (**3bb**)



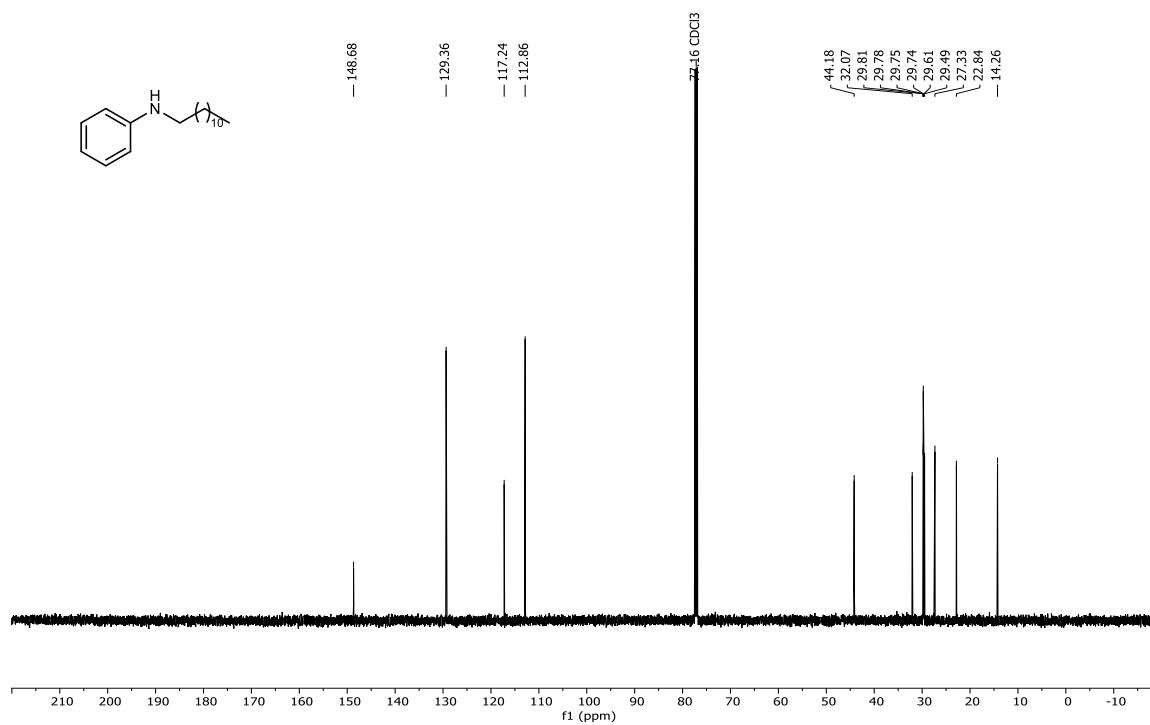
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-ethylaniline (**3bb**)



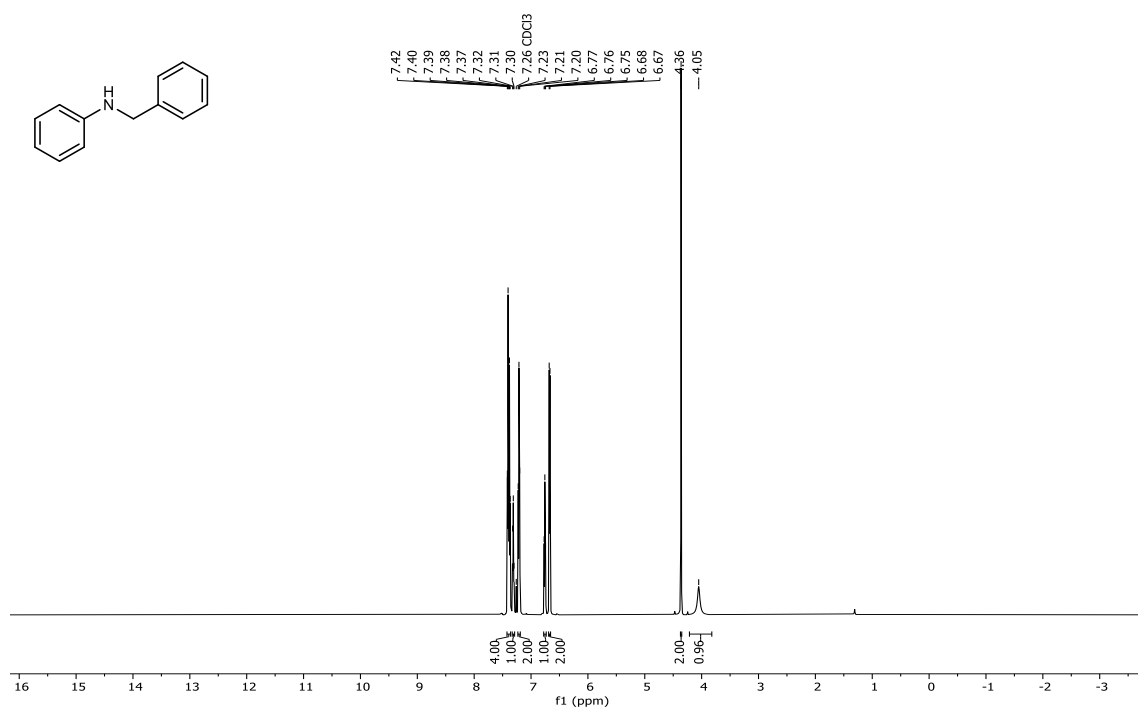
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-dodecylaniline (**3bh**)



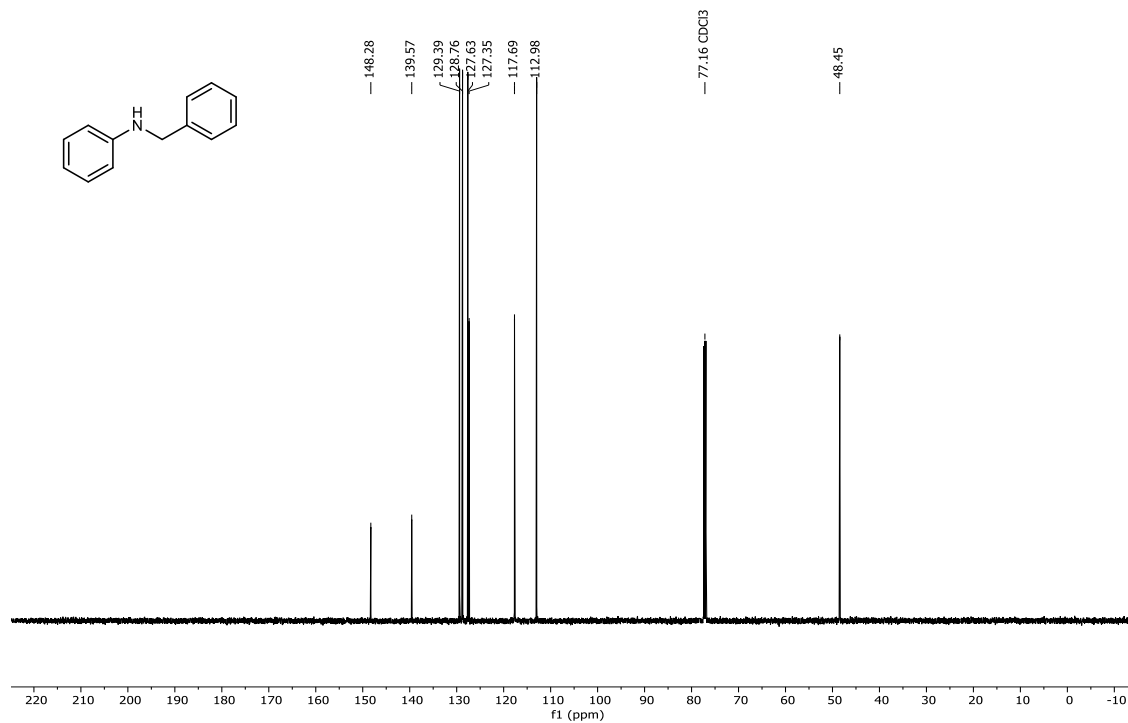
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-dodecylaniline (**3bh**)



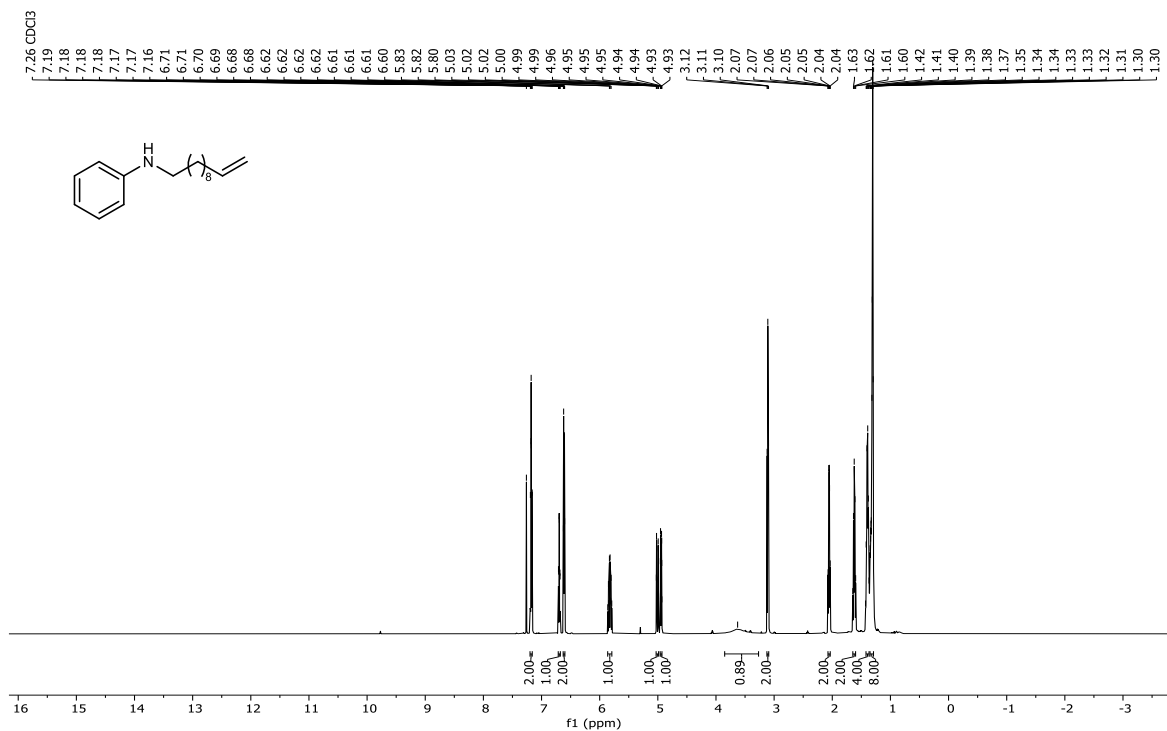
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-benzylaniline (**3bi**)



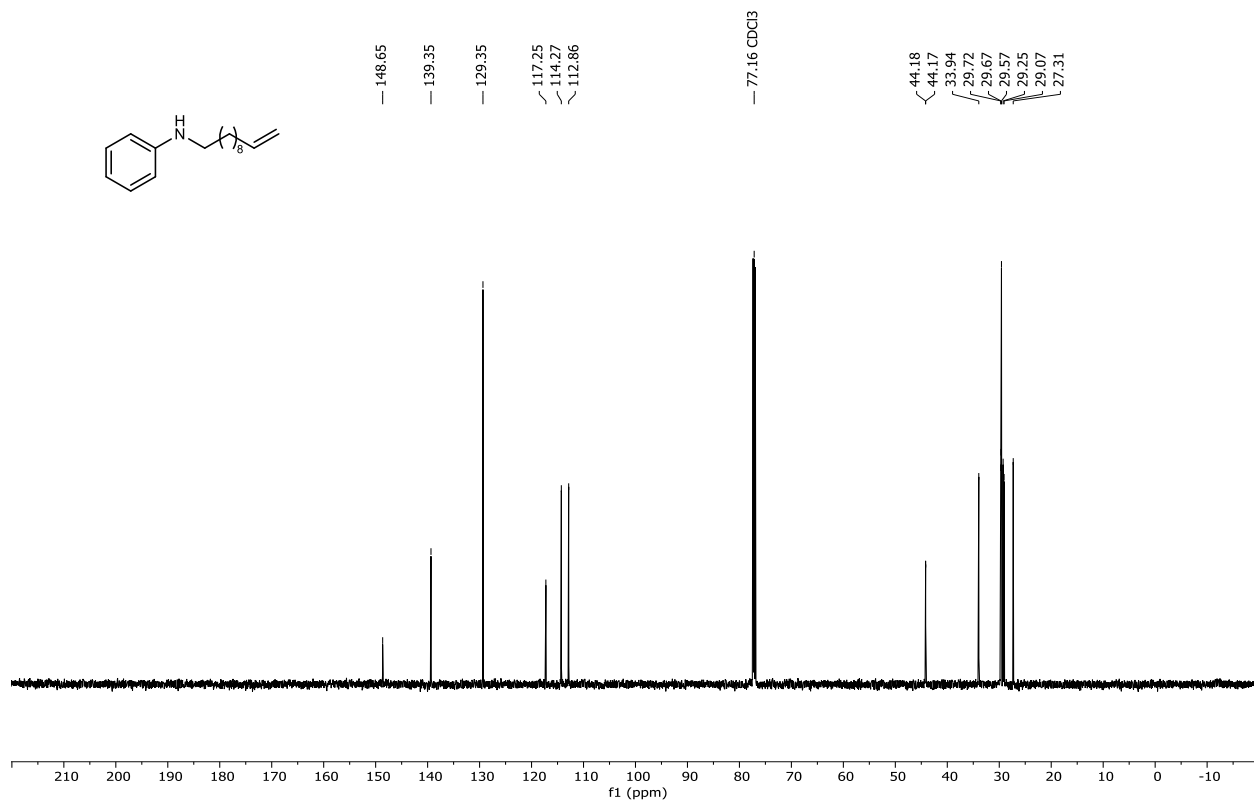
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-benzylaniline (**3bi**)



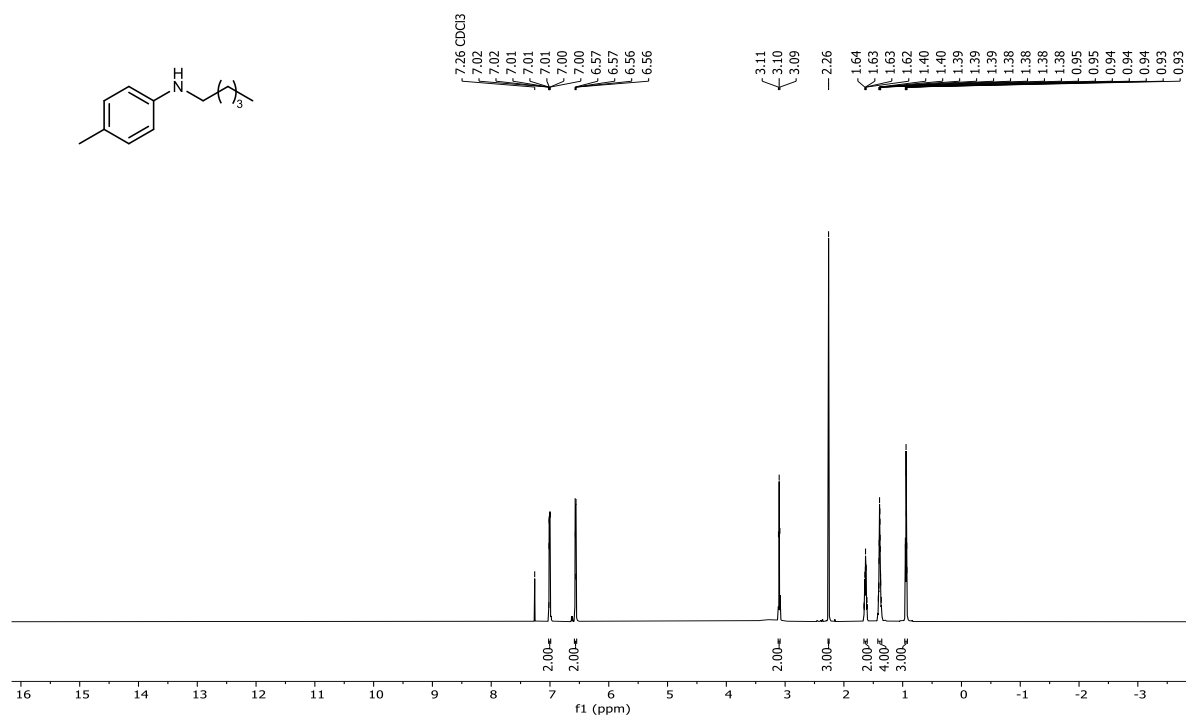
¹H NMR (600 MHz, CDCl₃) spectrum of *N*-(undec-10-en-1-yl)aniline (3bl)



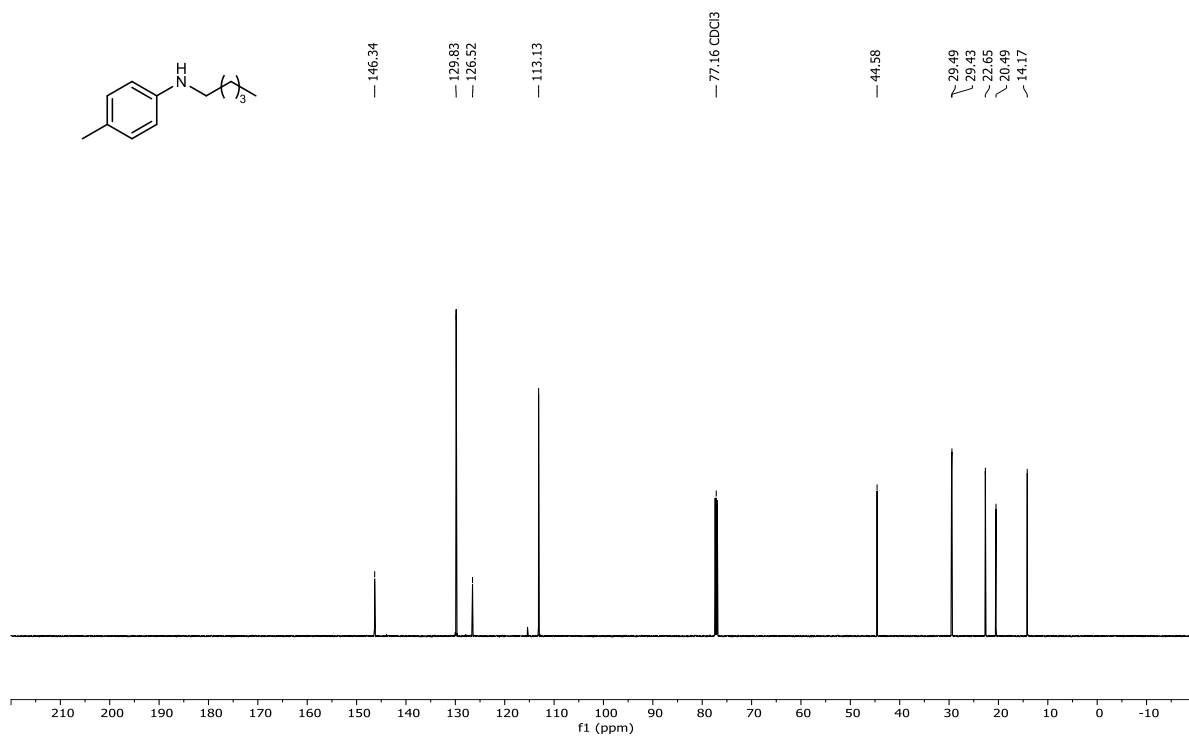
¹³C NMR (151 MHz, CDCl₃) spectrum of *N*-(undec-10-en-1-yl)aniline (3bl)



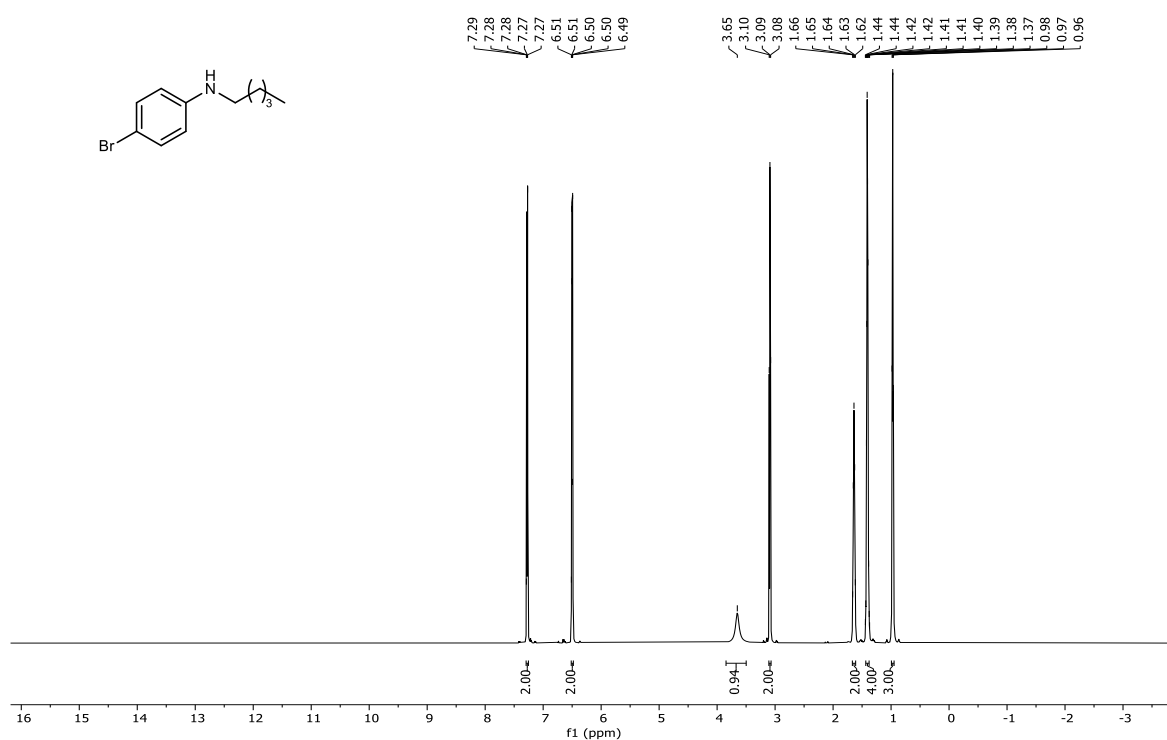
¹H NMR (600 MHz, CDCl₃) spectrum of **4-methyl-N-pentylaniline (3ca)**



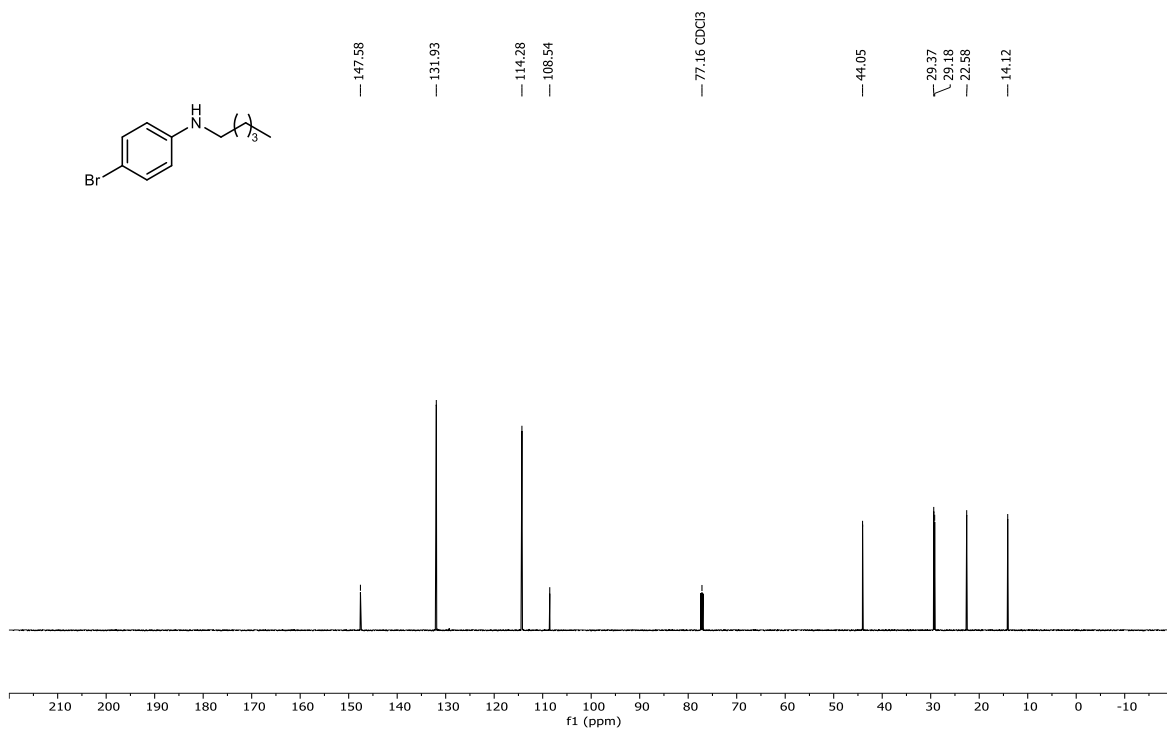
¹³C NMR (151 MHz, CDCl₃) spectrum of **4-methyl-N-pentylaniline (3ca)**



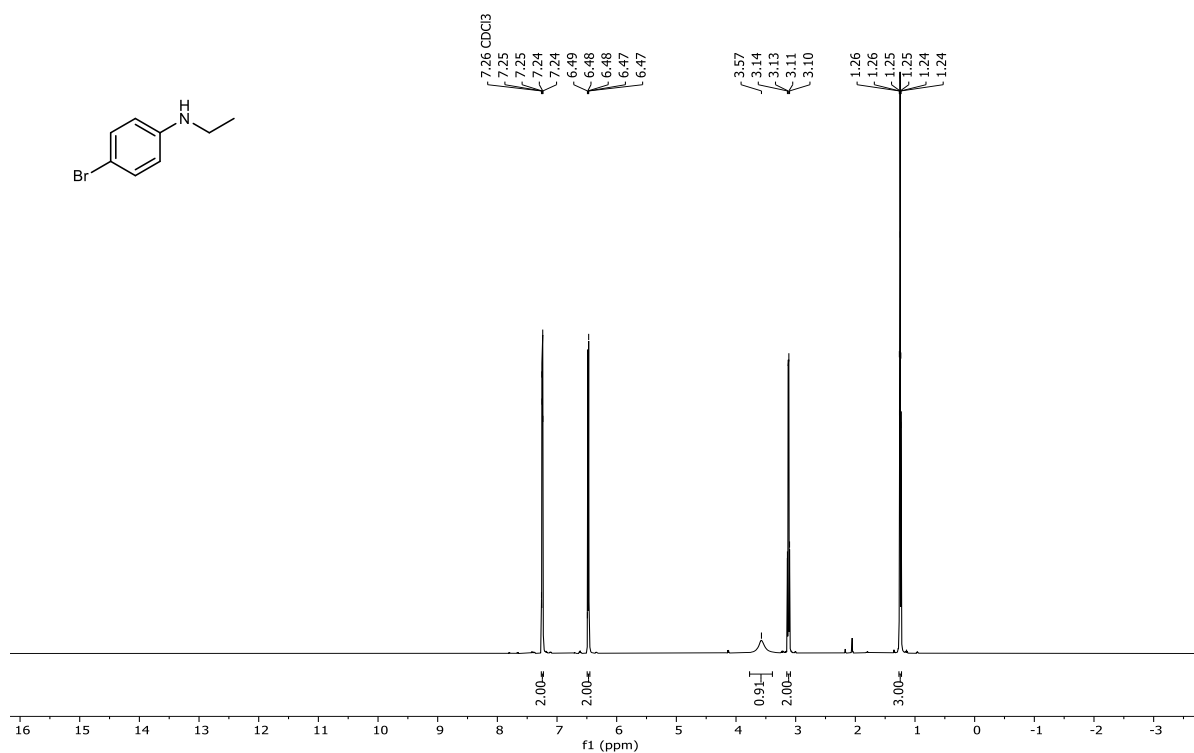
^1H NMR (600 MHz, CDCl_3) spectrum of **4-bromo-*N*-pentylaniline (3da)**



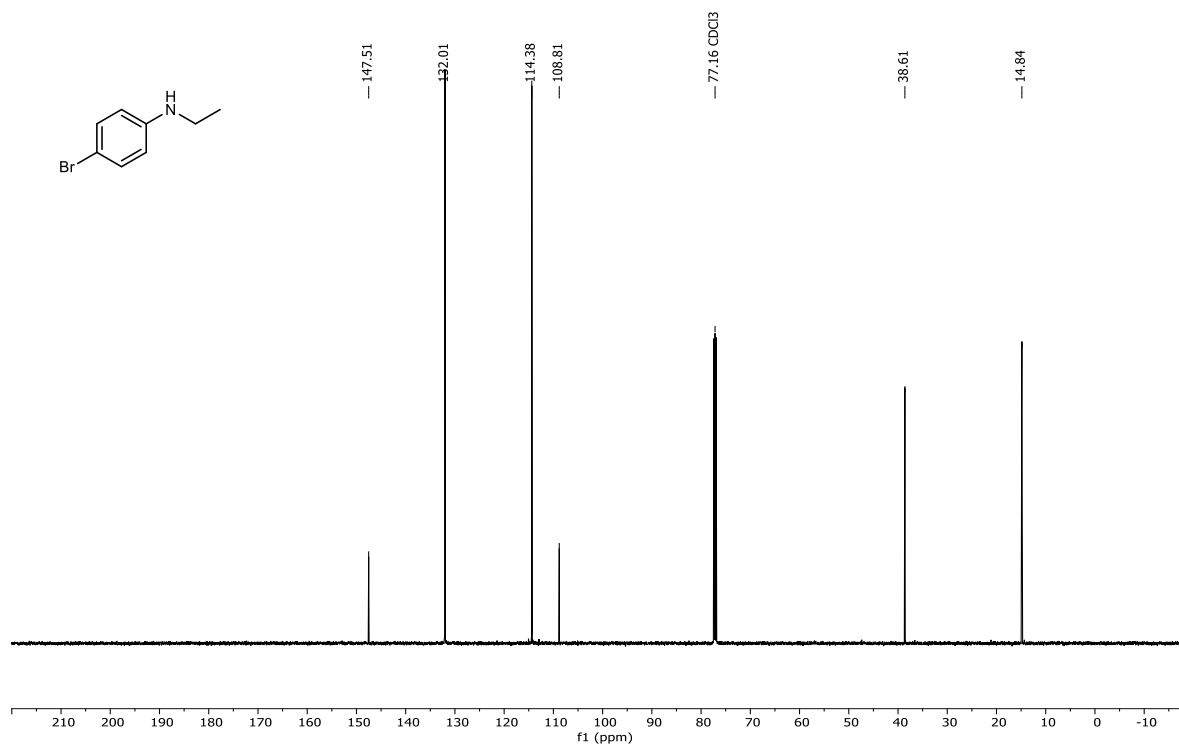
^{13}C NMR (151 MHz, CDCl_3) spectrum of **4-bromo-*N*-pentylaniline (3da)**



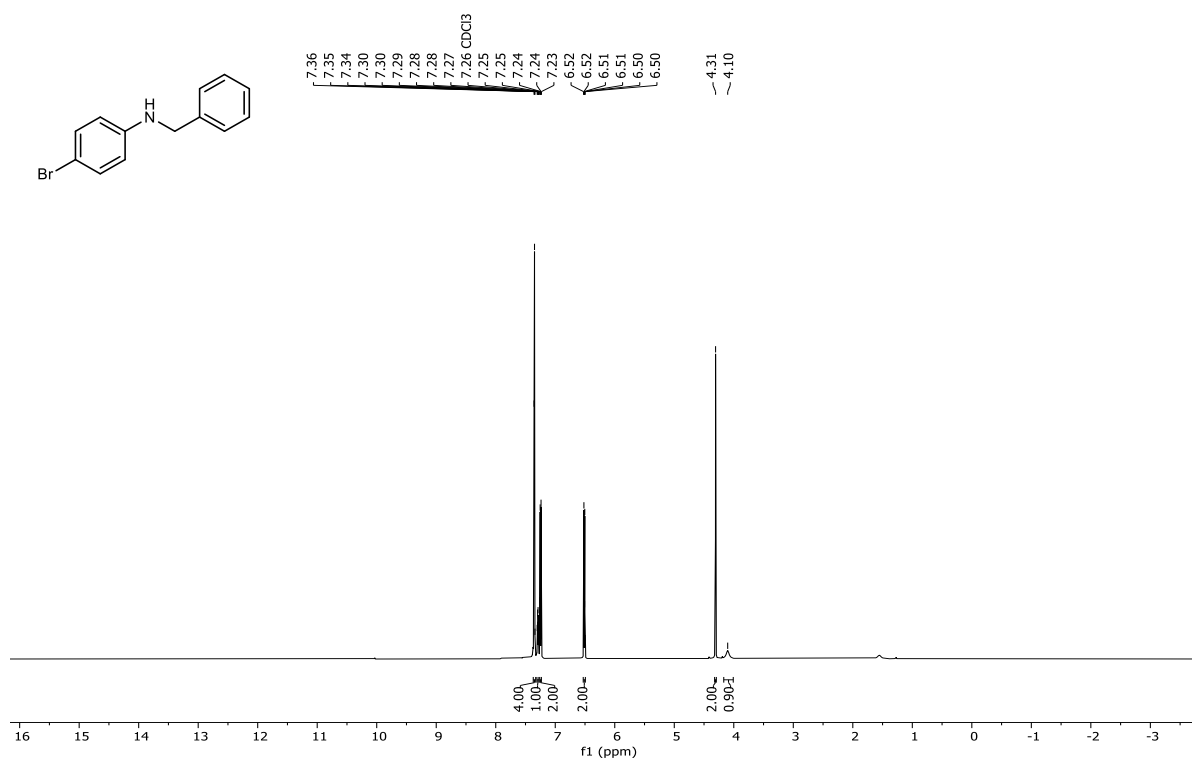
^1H NMR (600 MHz, CDCl_3) spectrum of **4-bromo-*N*-ethylaniline (3db)**



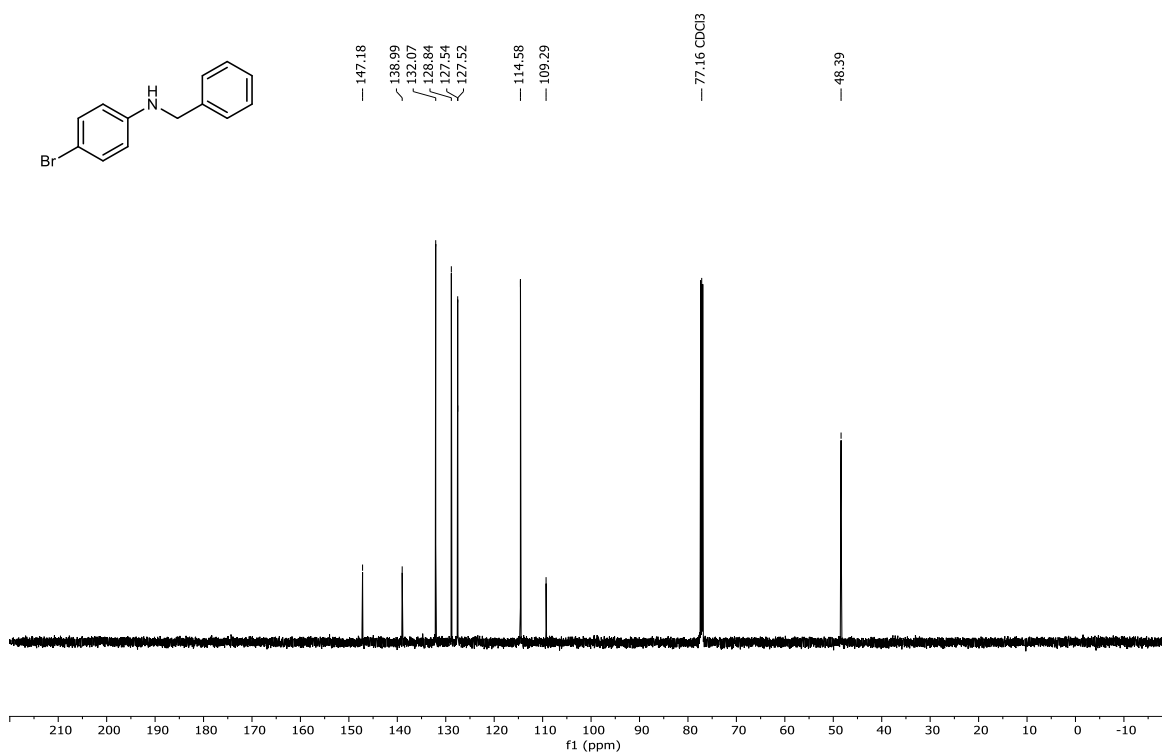
^{13}C NMR (151 MHz, CDCl_3) spectrum of **4-bromo-*N*-ethylaniline (3db)**



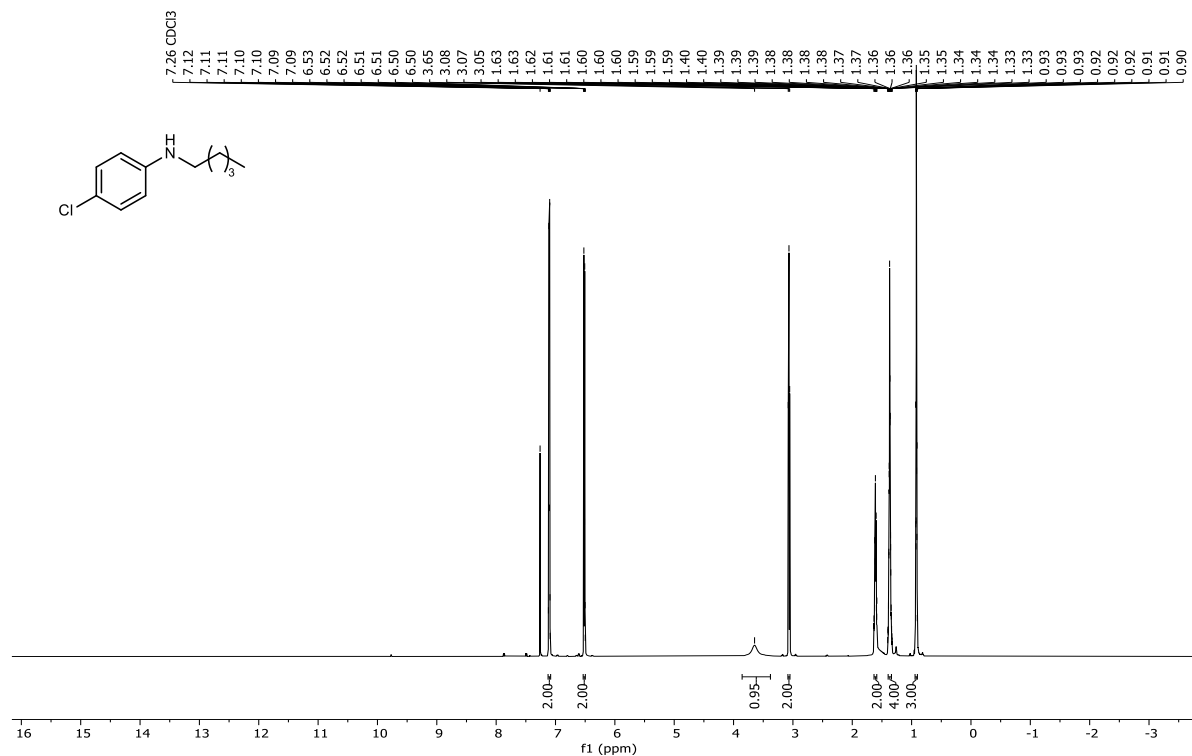
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-benzyl-4-bromoaniline (3di)



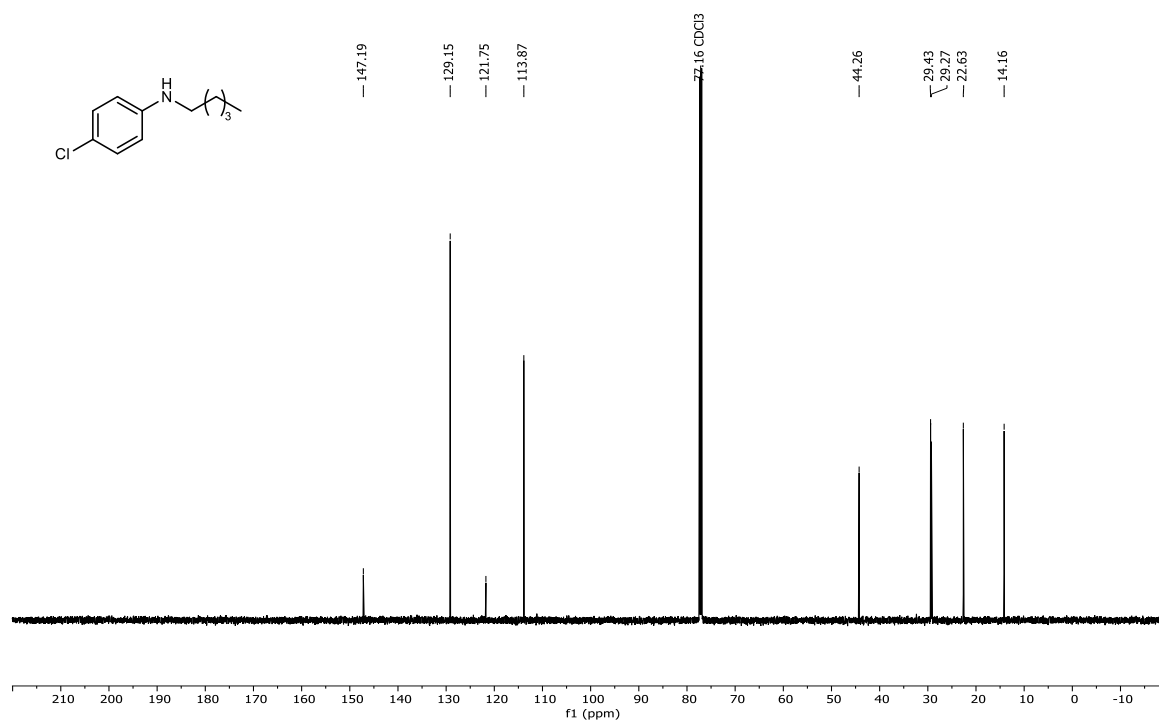
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-benzyl-4-bromoaniline (3di)



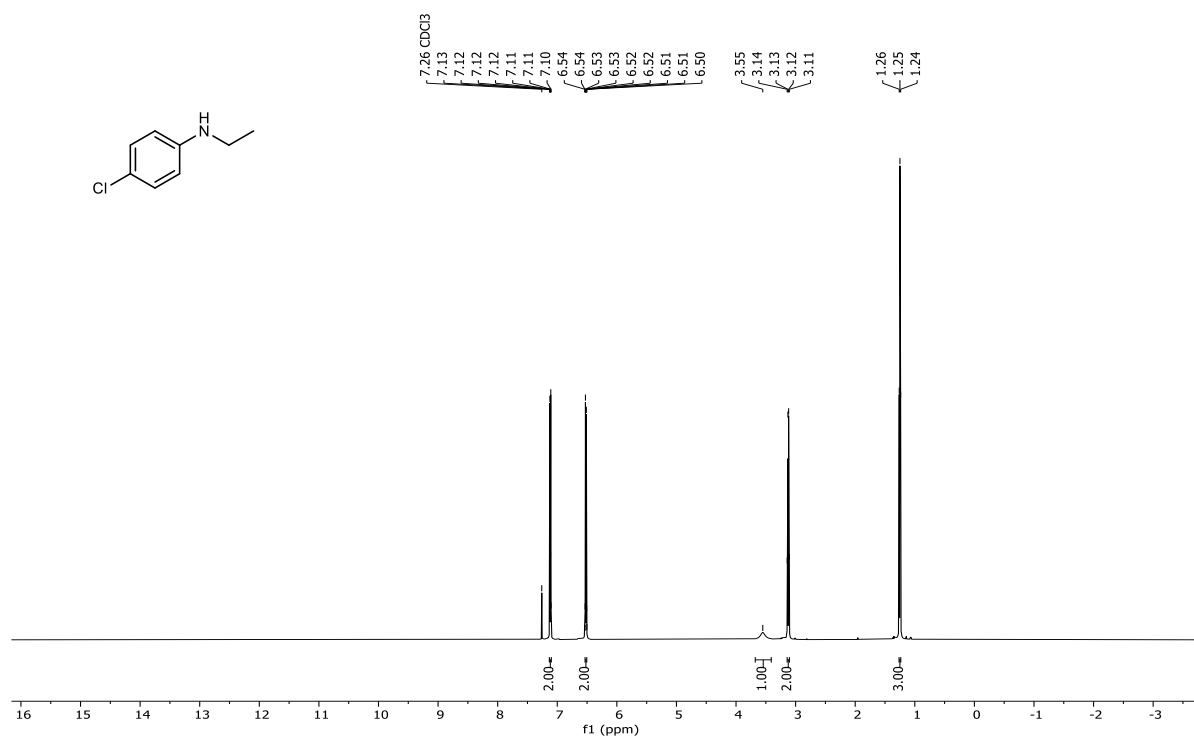
¹H NMR (600 MHz, CDCl₃) spectrum of **4-chloro-*N*-pentylaniline (3ea)**



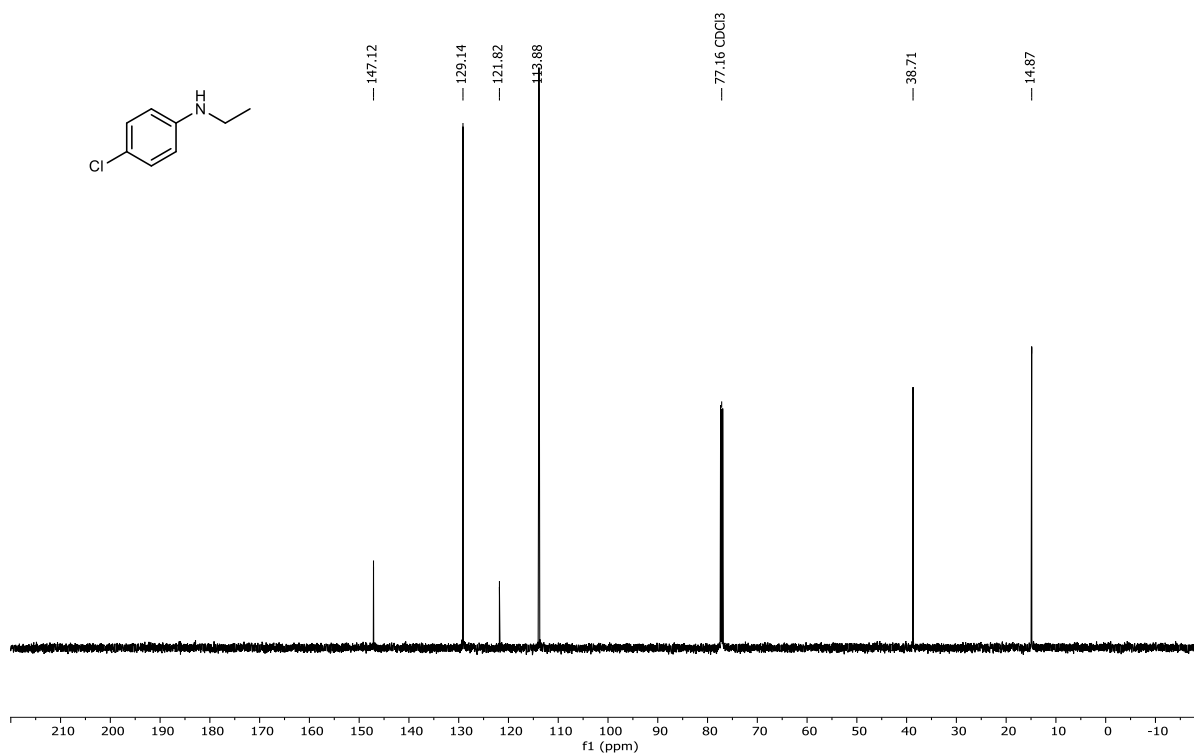
¹³C NMR (151 MHz, CDCl₃) spectrum of **4-chloro-*N*-pentylaniline (3ea)**



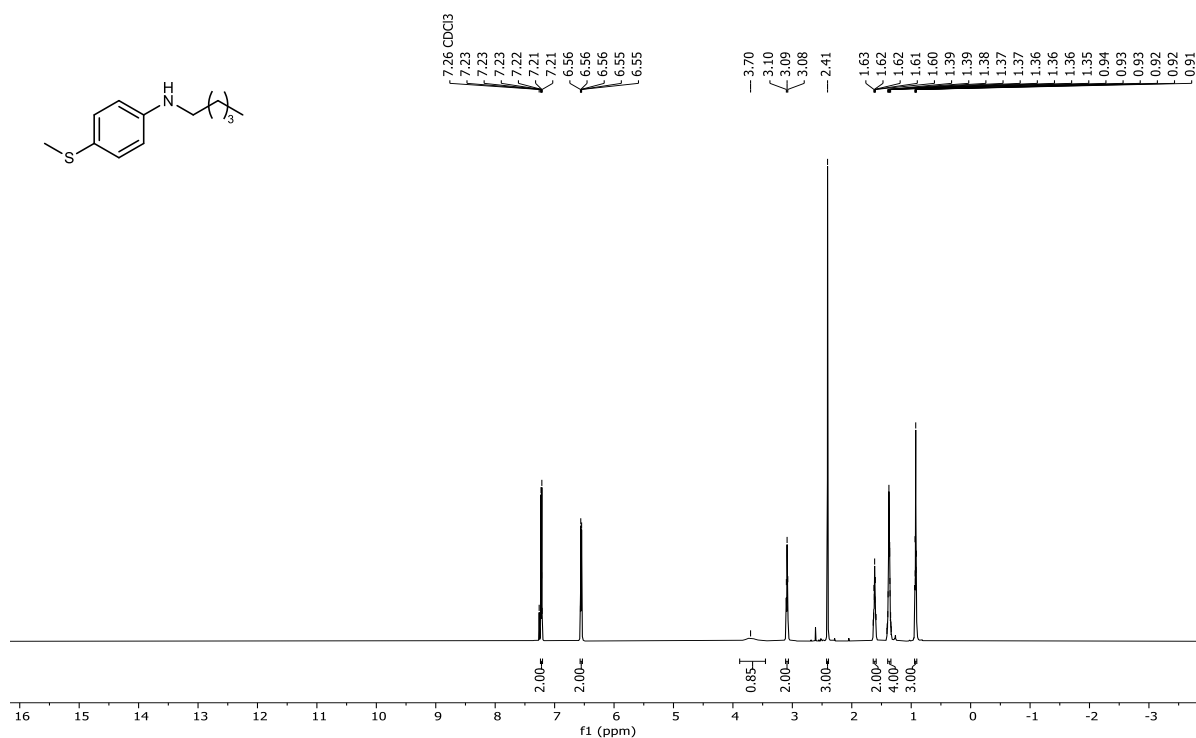
¹H NMR (600 MHz, CDCl₃) spectrum of **4-chloro-*N*-ethylaniline (3eb)**



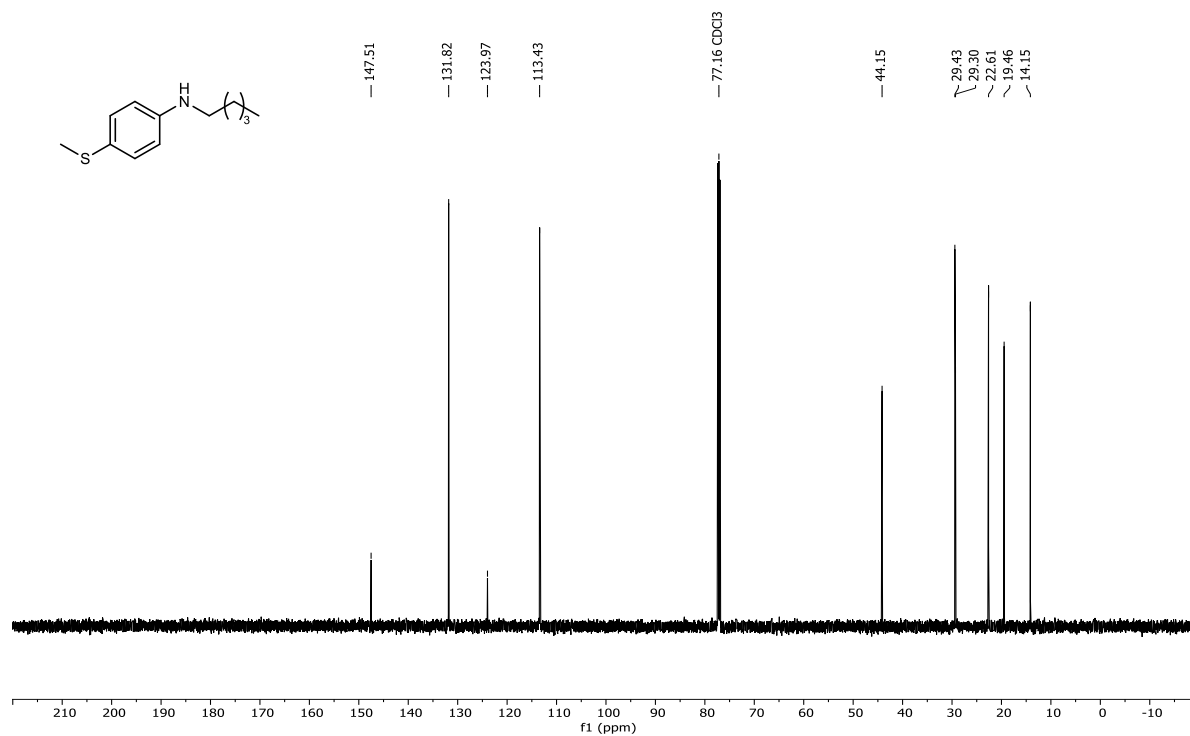
¹³C NMR (151 MHz, CDCl₃) spectrum of **4-chloro-*N*-ethylaniline (3eb)**

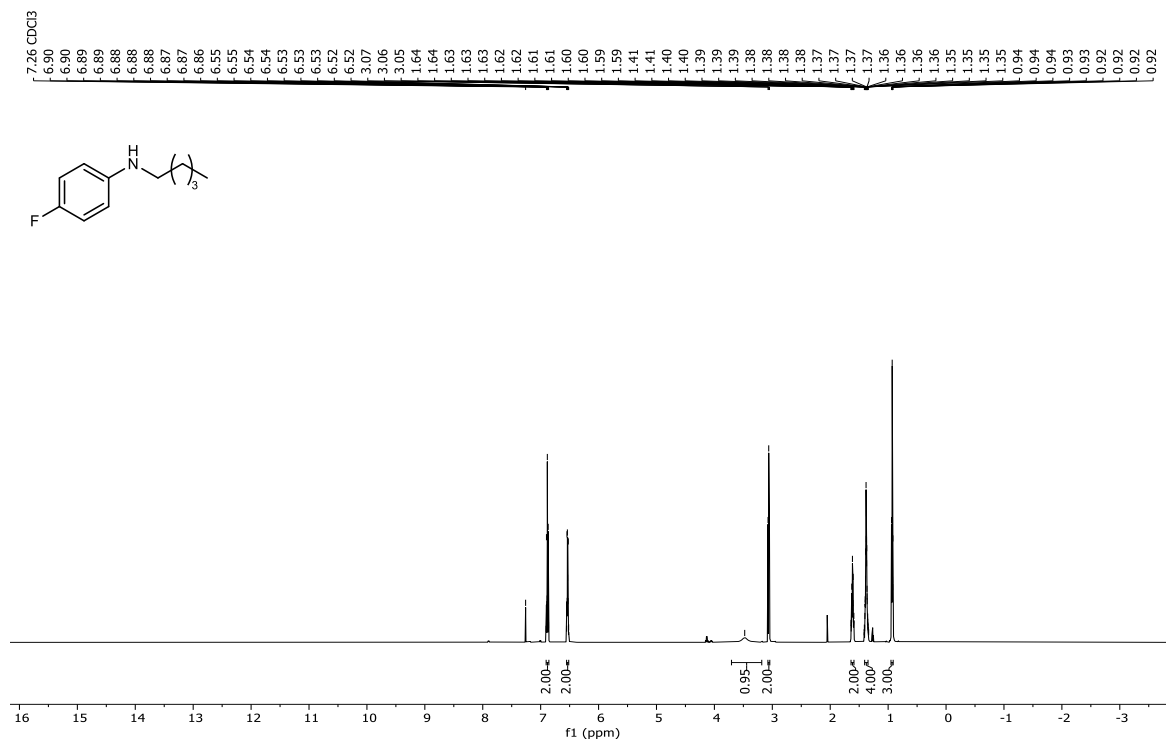


^1H NMR (600 MHz, CDCl_3) spectrum of 4-(methylthio)-*N*-pentylaniline (3fa)

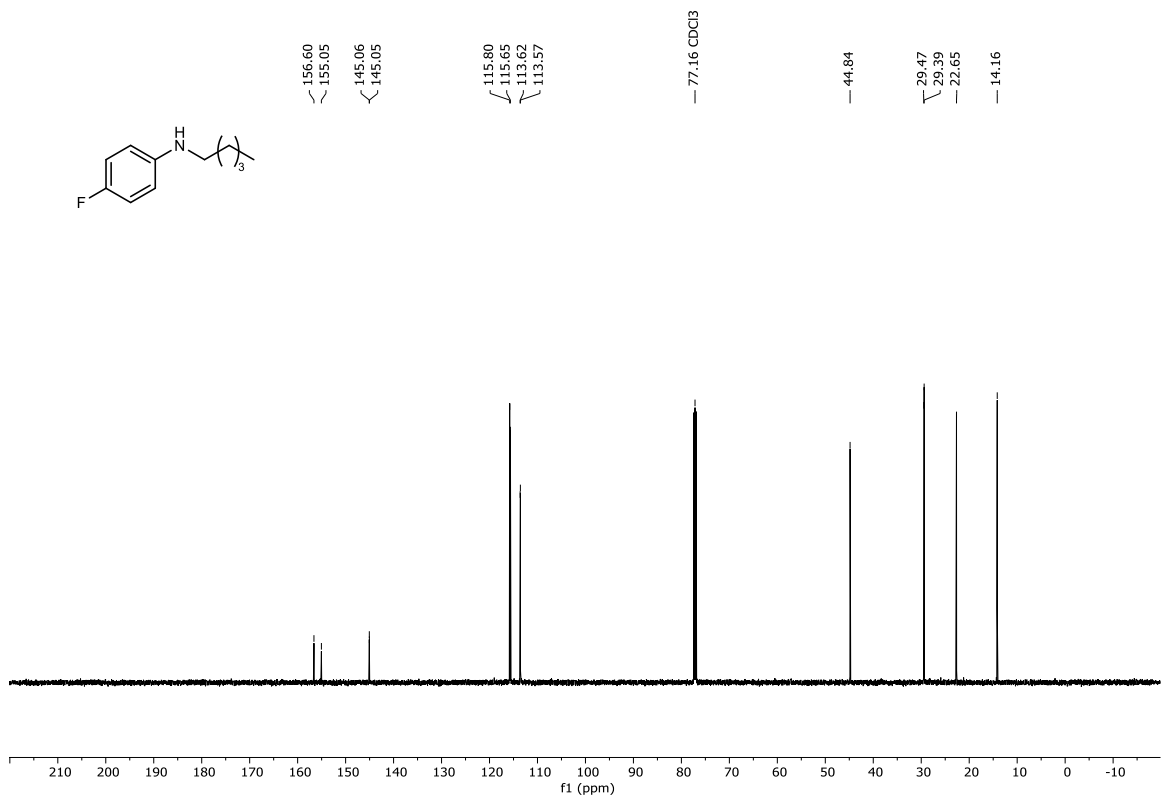


^{13}C NMR (151 MHz, CDCl_3) spectrum of 4-(methylthio)-*N*-pentylaniline (3fa)

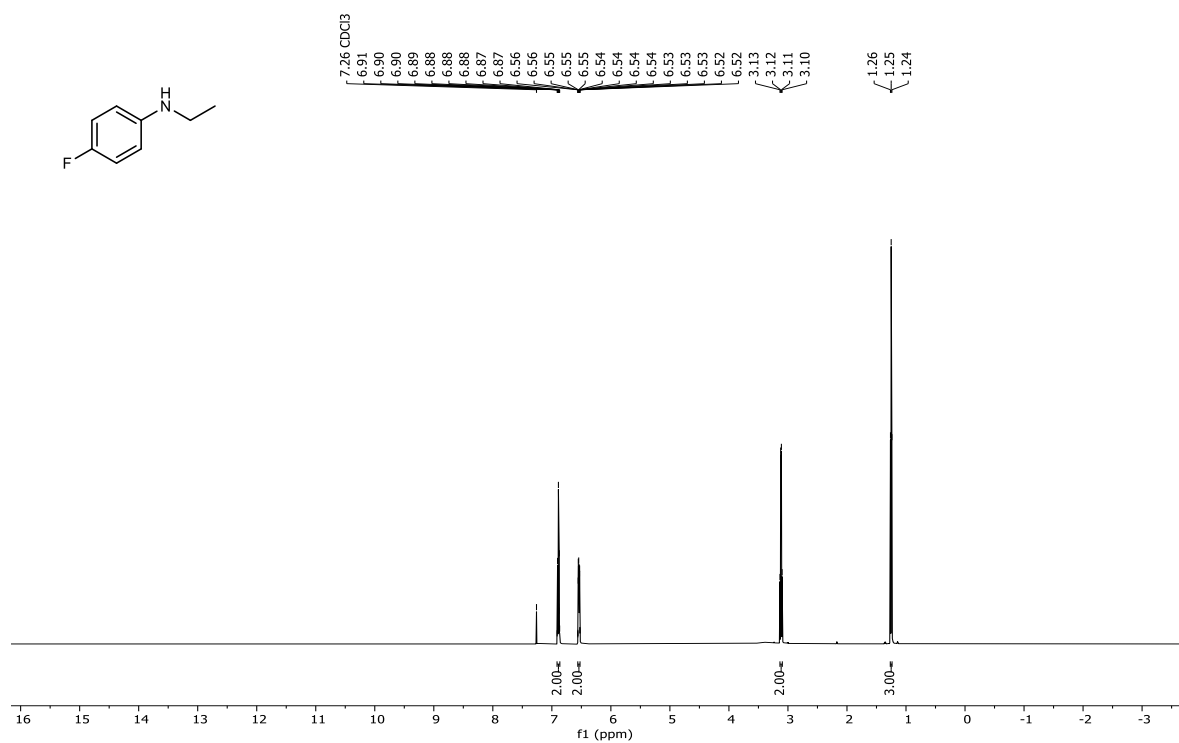


¹H NMR (600 MHz, CDCl₃) spectrum of **4-fluoro-*N*-pentylaniline (3ga)**

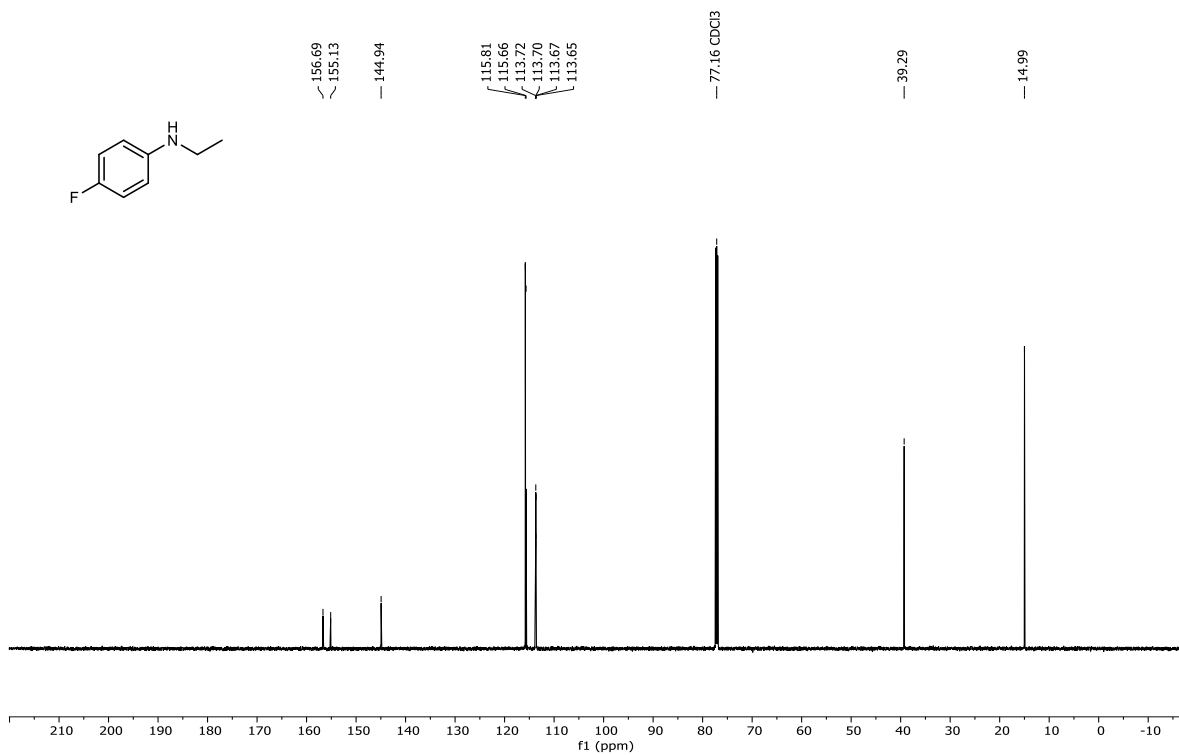
¹³C NMR (151 MHz, CDCl₃) spectrum of **4-fluoro-N-pentylaniline (3ga)**



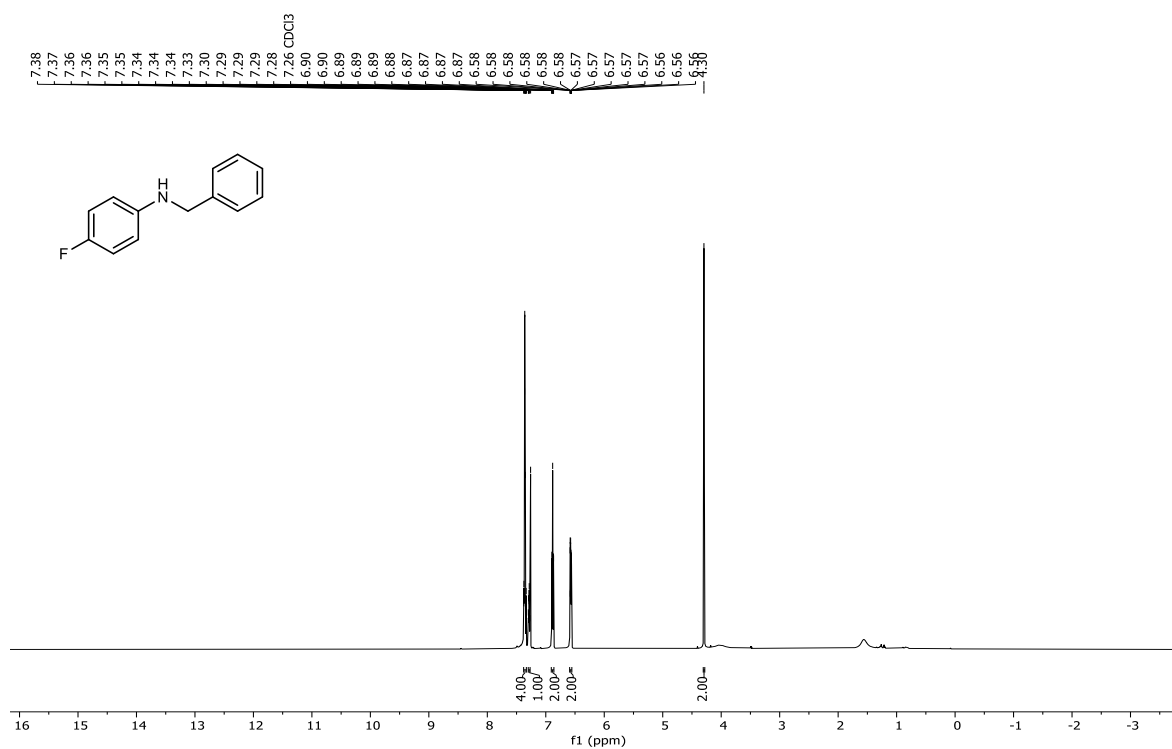
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-ethyl-4-fluoroaniline (**3gb**)



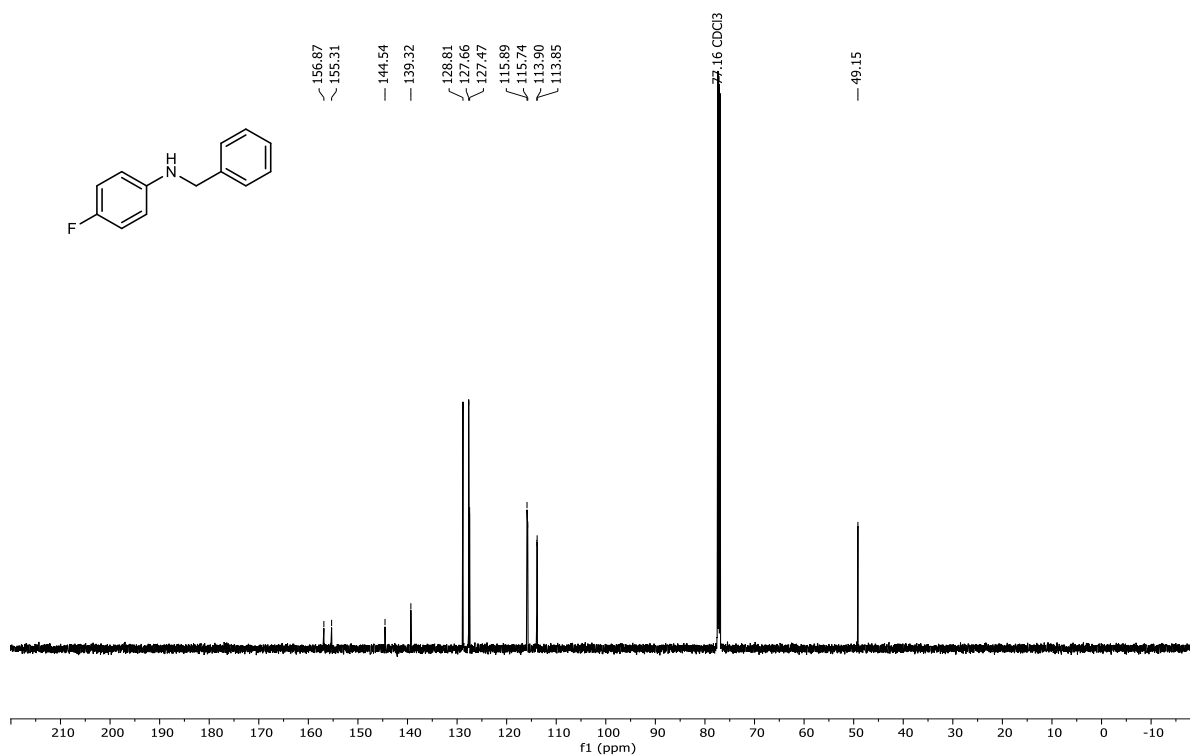
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-ethyl-4-fluoroaniline (**3gb**)



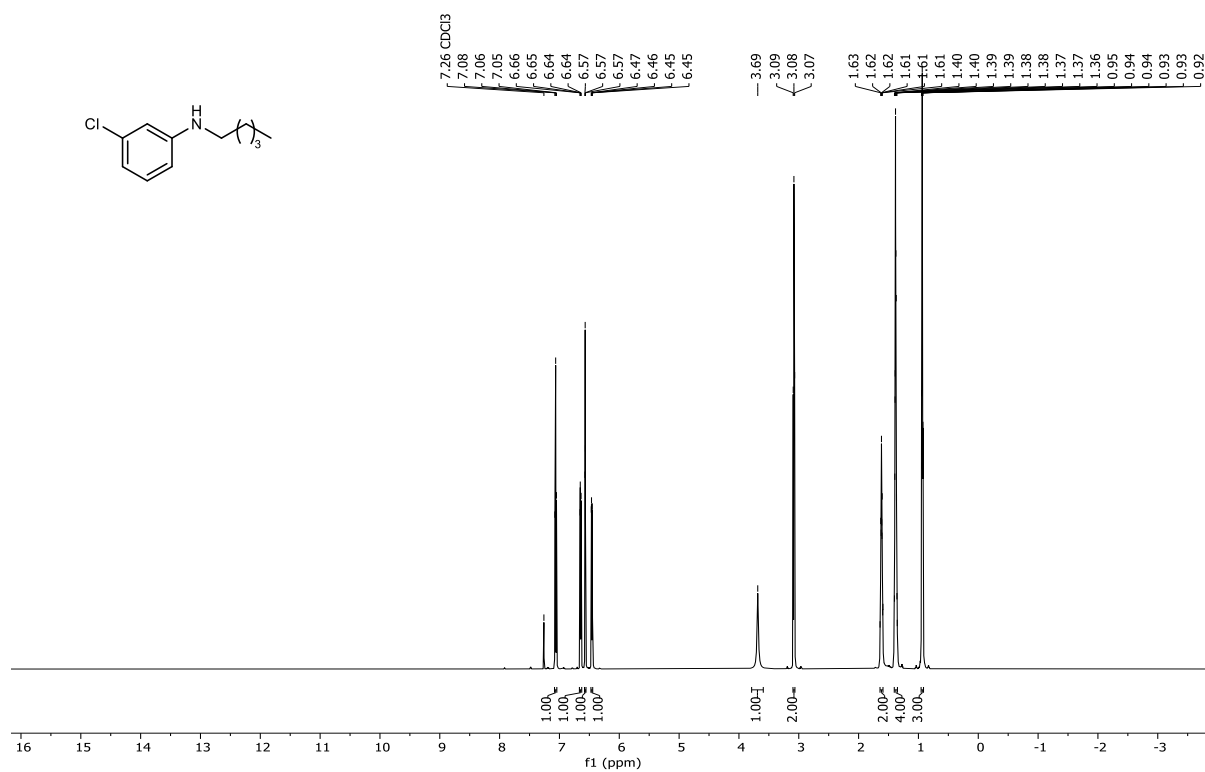
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-benzyl-4-fluoroaniline (**3gi**)



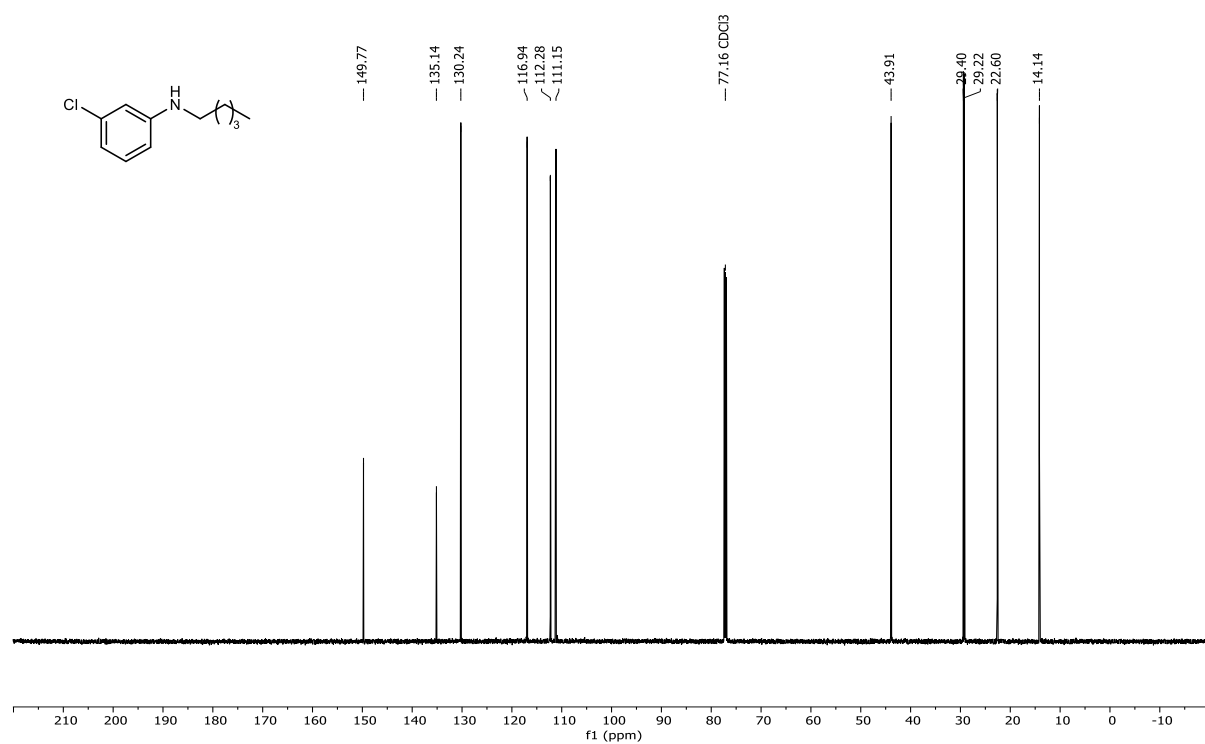
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-benzyl-4-fluoroaniline (**3gi**)



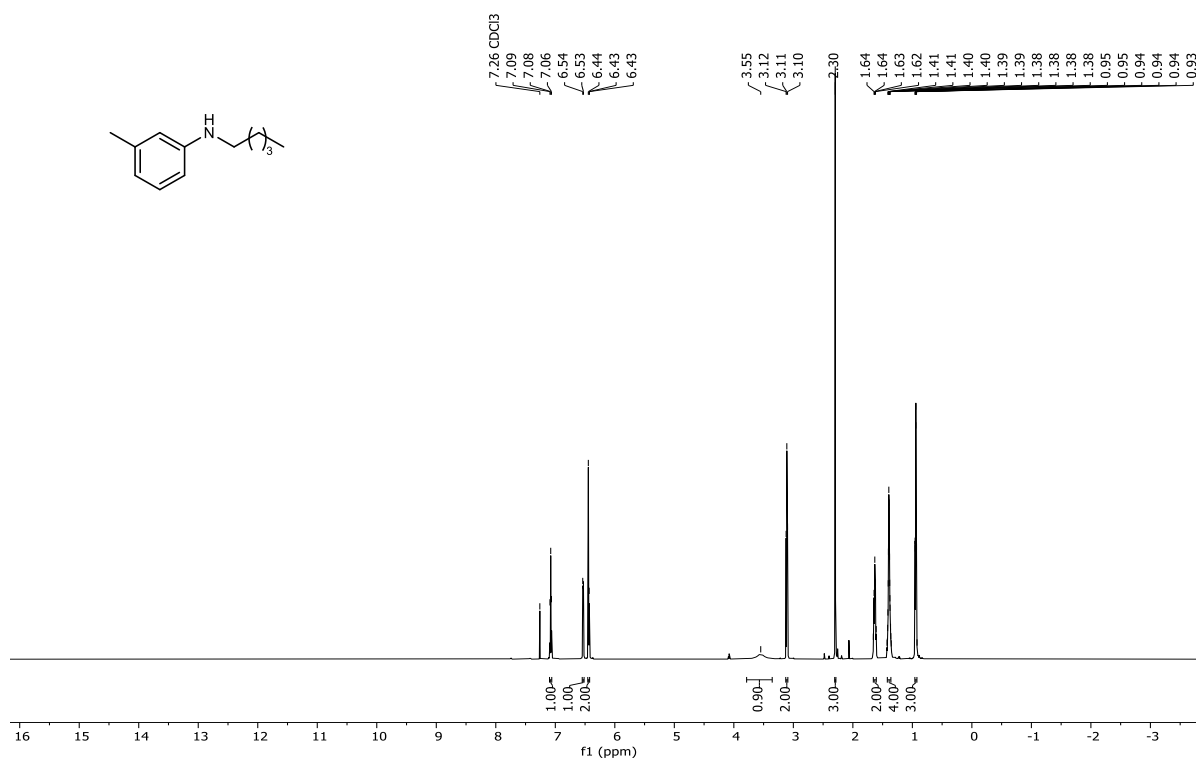
^1H NMR (600 MHz, CDCl_3) spectrum of **3-chloro-*N*-pentylaniline (3ha)**



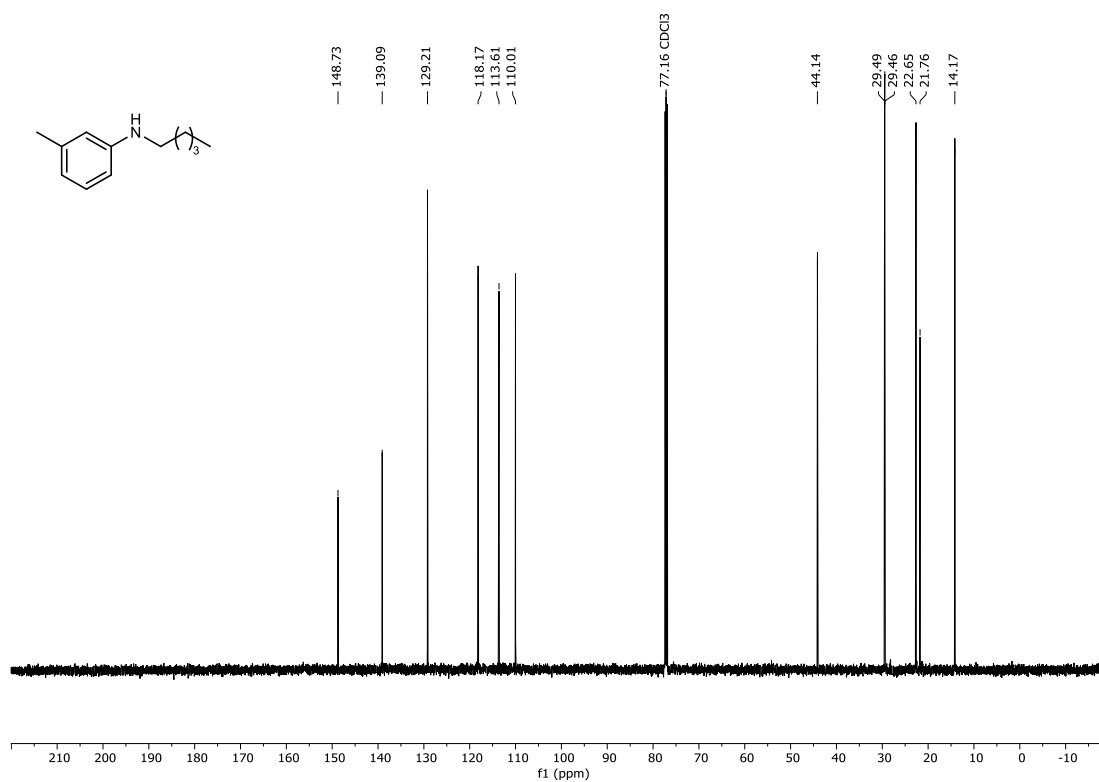
^{13}C NMR (151 MHz, CDCl_3) spectrum of **3-chloro-*N*-pentylaniline (3ha)**



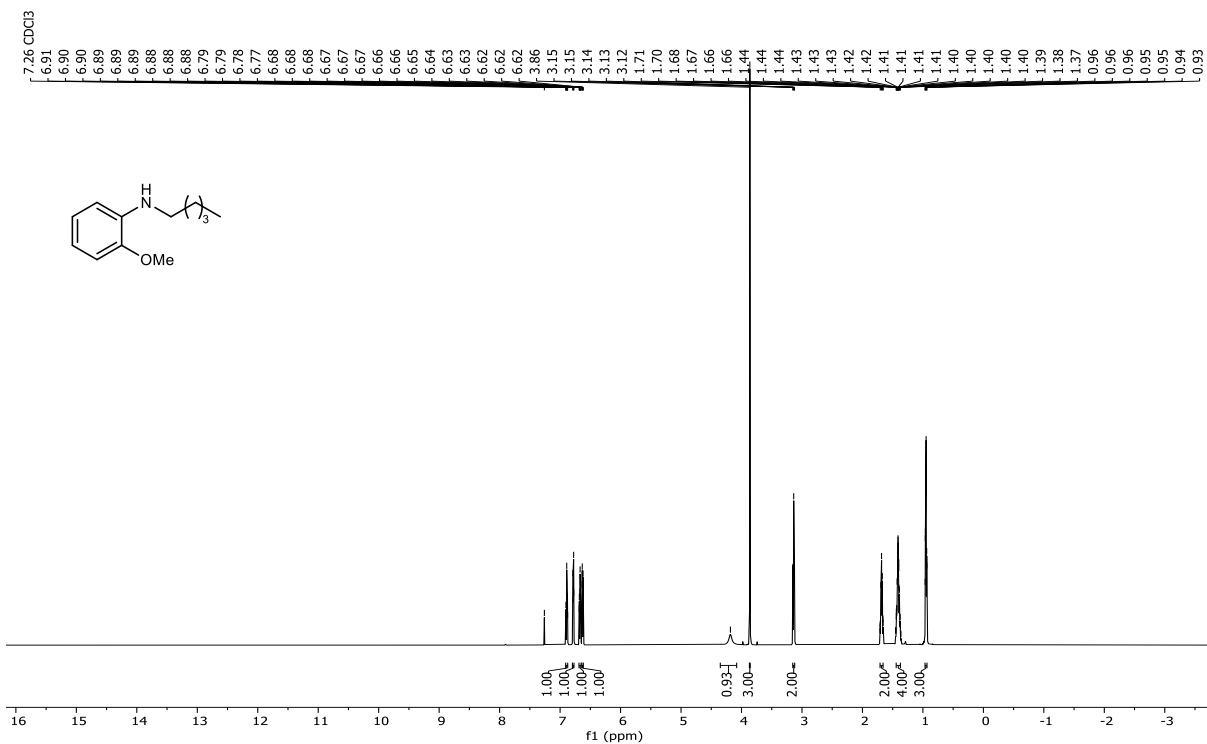
^1H NMR (600 MHz, CDCl_3) spectrum of **3-methyl-N-pentylaniline (3ia)**



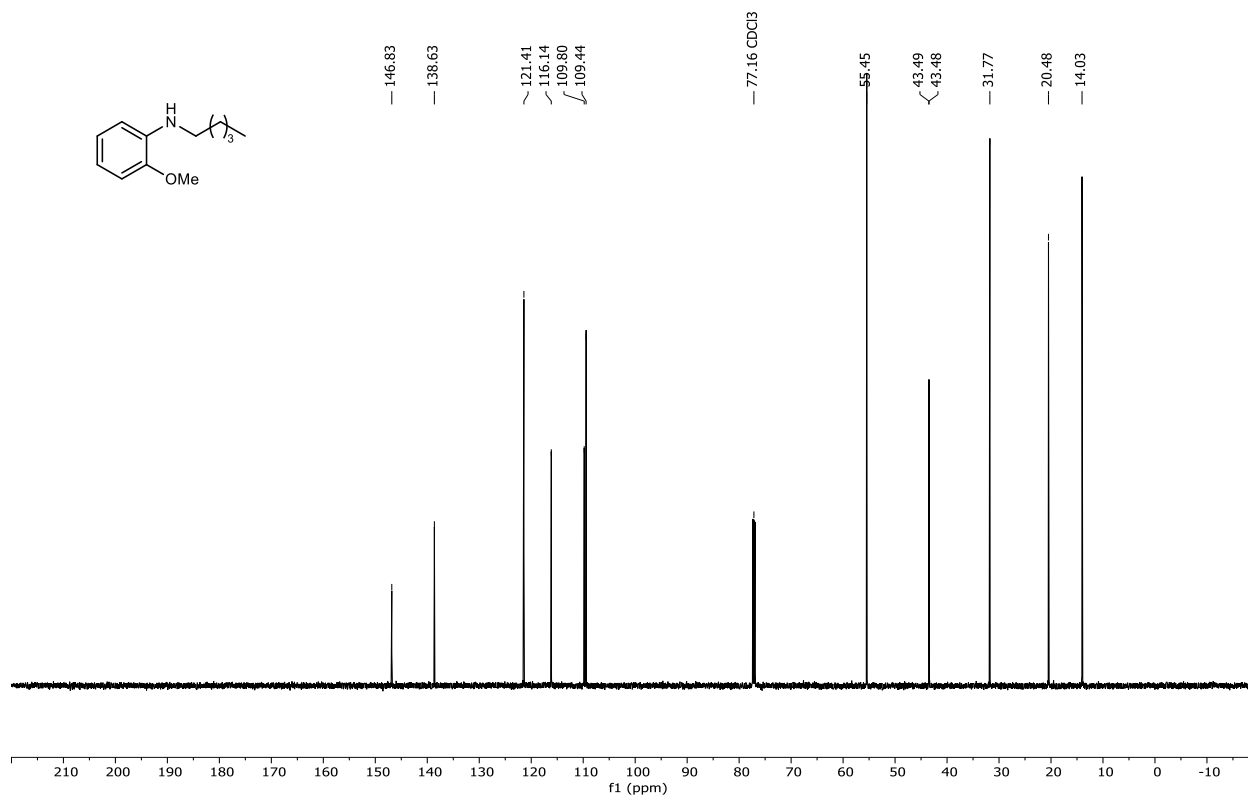
^{13}C NMR (151 MHz, CDCl_3) spectrum of **3-methyl-N-pentylaniline (3ia)**



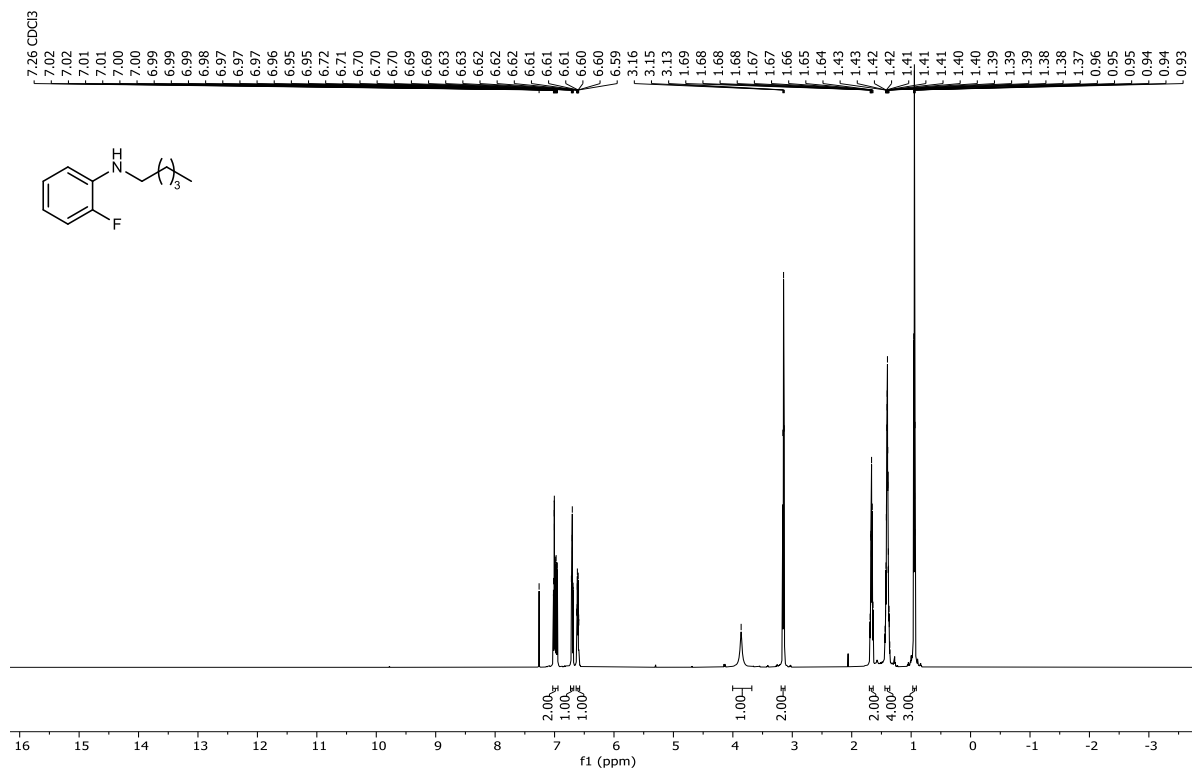
¹H NMR (600 MHz, CDCl₃) spectrum of **2-methoxy-*N*-pentylaniline (3ja)**



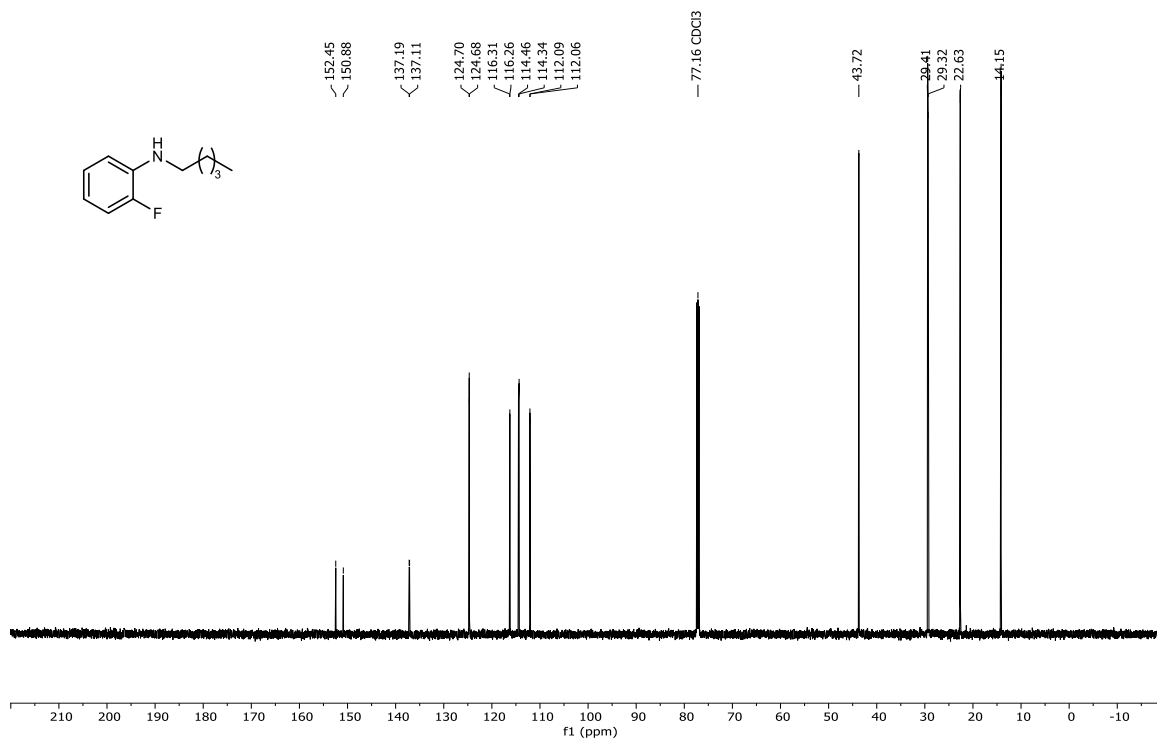
¹³C NMR (151 MHz, CDCl₃) spectrum of **2-methoxy-*N*-pentylaniline (3ja)**



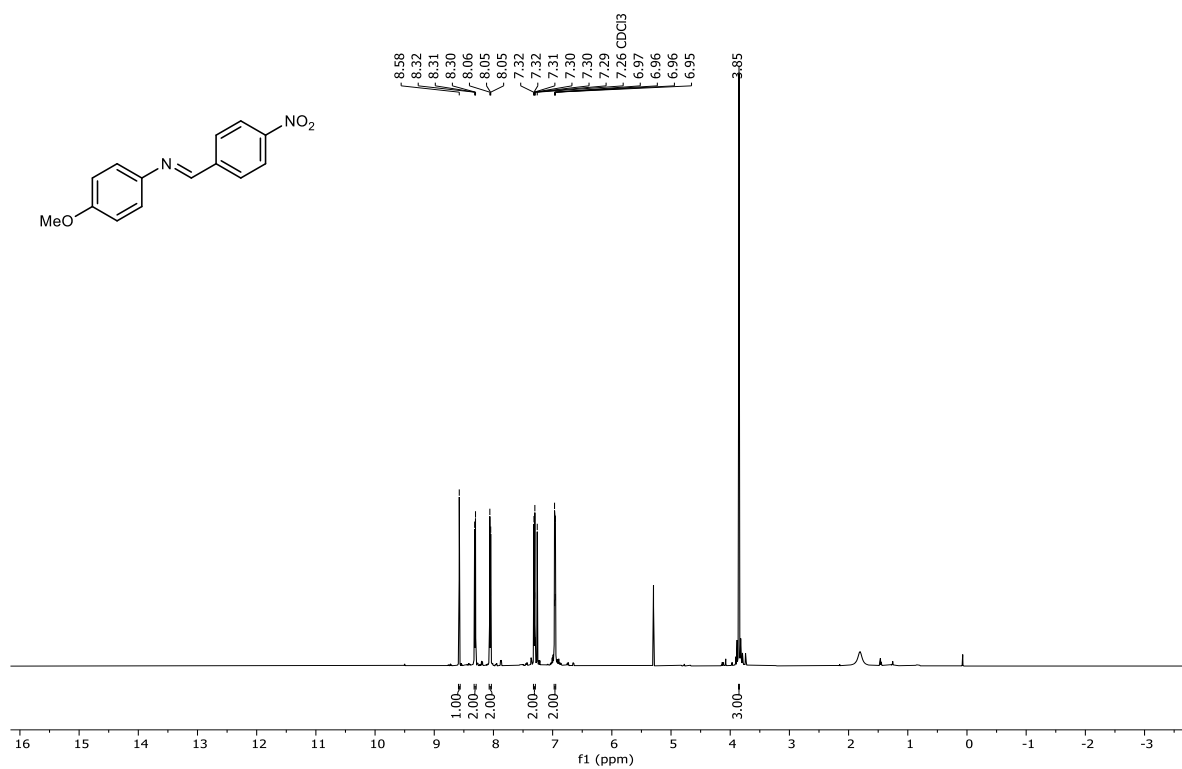
¹H NMR (600 MHz, CDCl₃) spectrum of **2-fluoro-N-pentylaniline (3ka)**



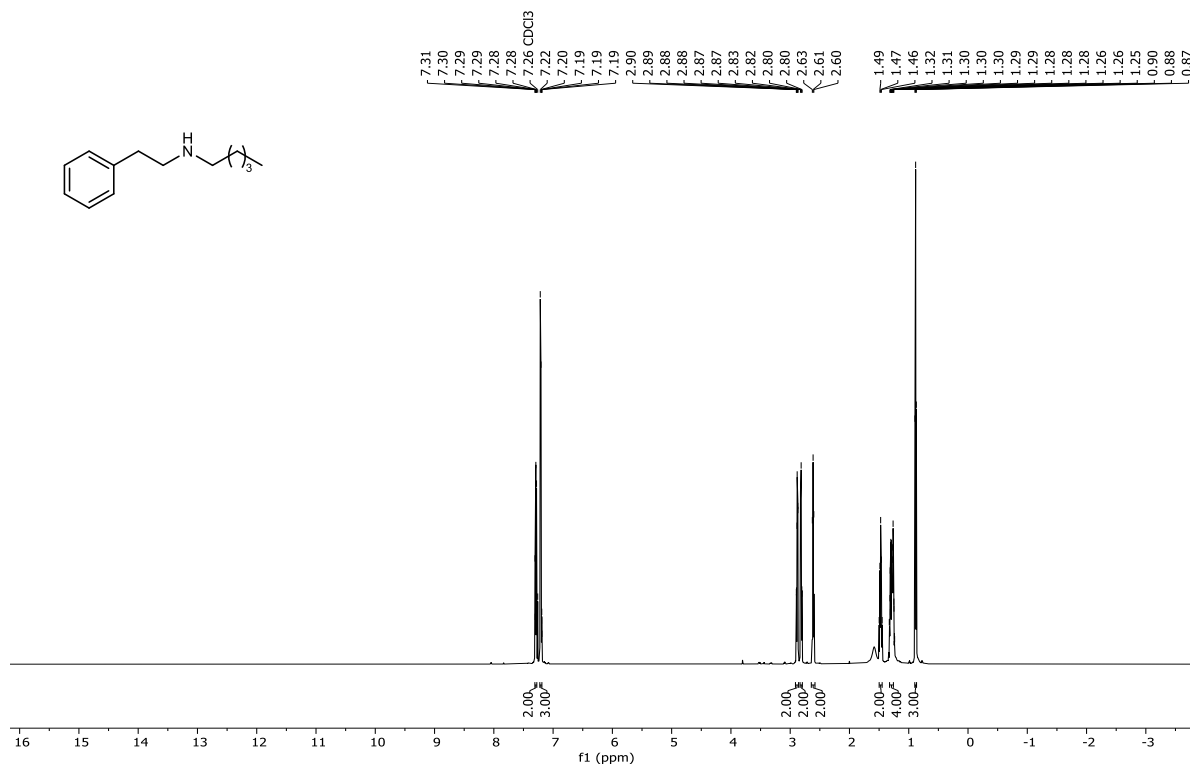
¹³C NMR (151 MHz, CDCl₃) spectrum of **2-fluoro-N-pentylaniline (3ka)**



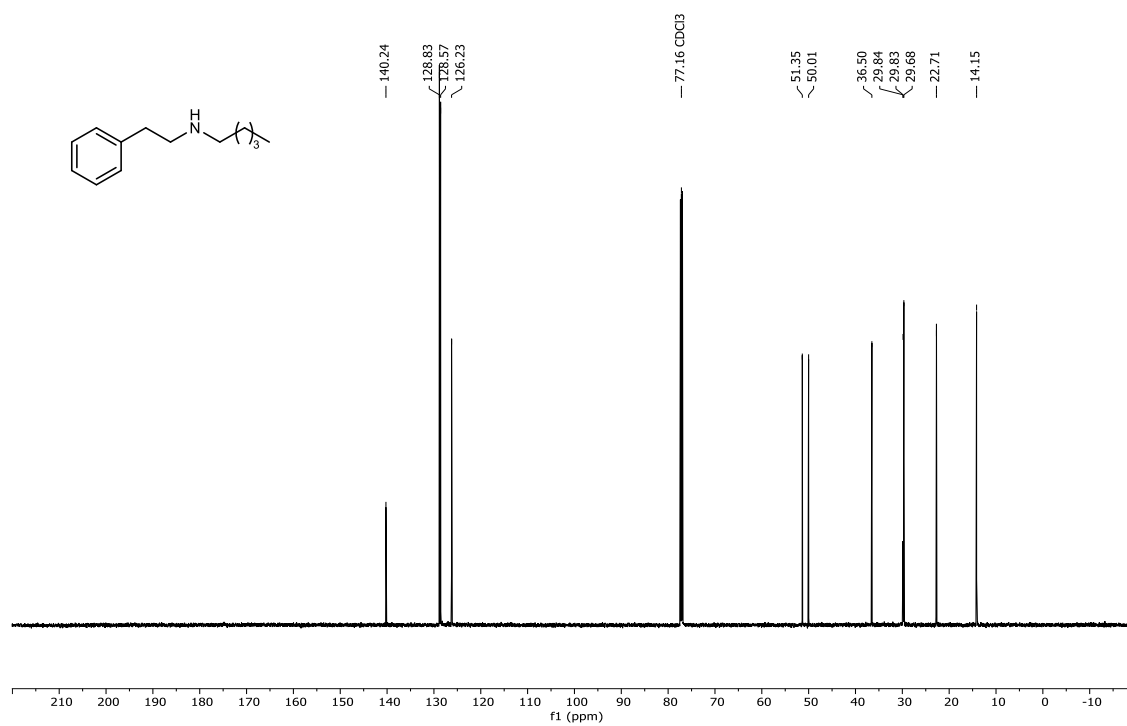
¹H NMR (600 MHz, CDCl₃) spectrum of (E)-N-(4-methoxyphenyl)-1-(4-nitrophenyl)methanimine (3am)



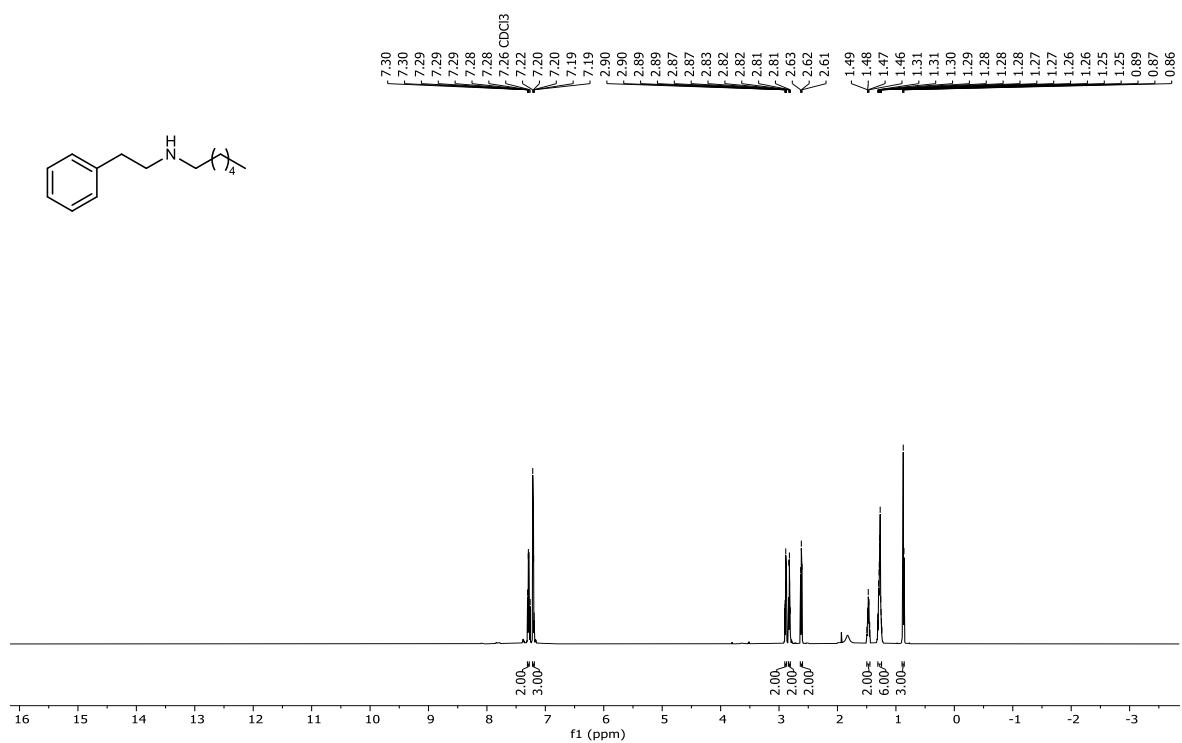
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-phenethylpentan-1-amine (**5aa**)



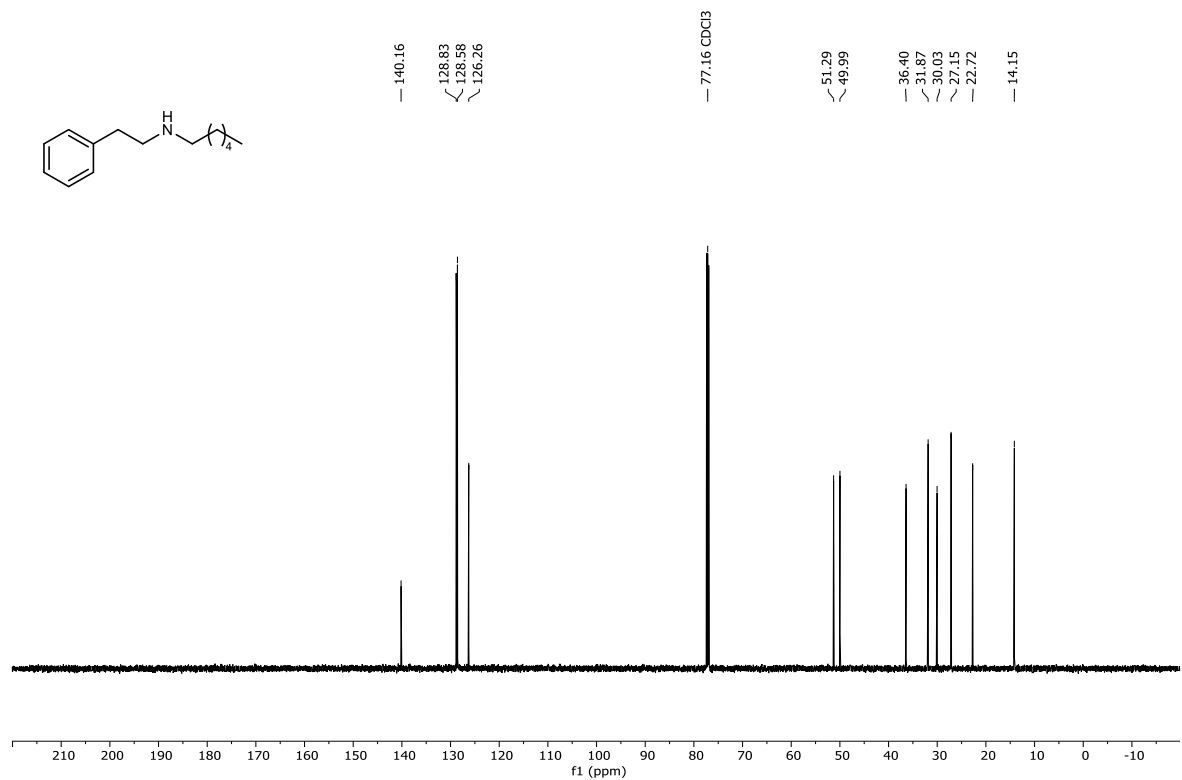
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-phenethylpentan-1-amine (**5aa**)



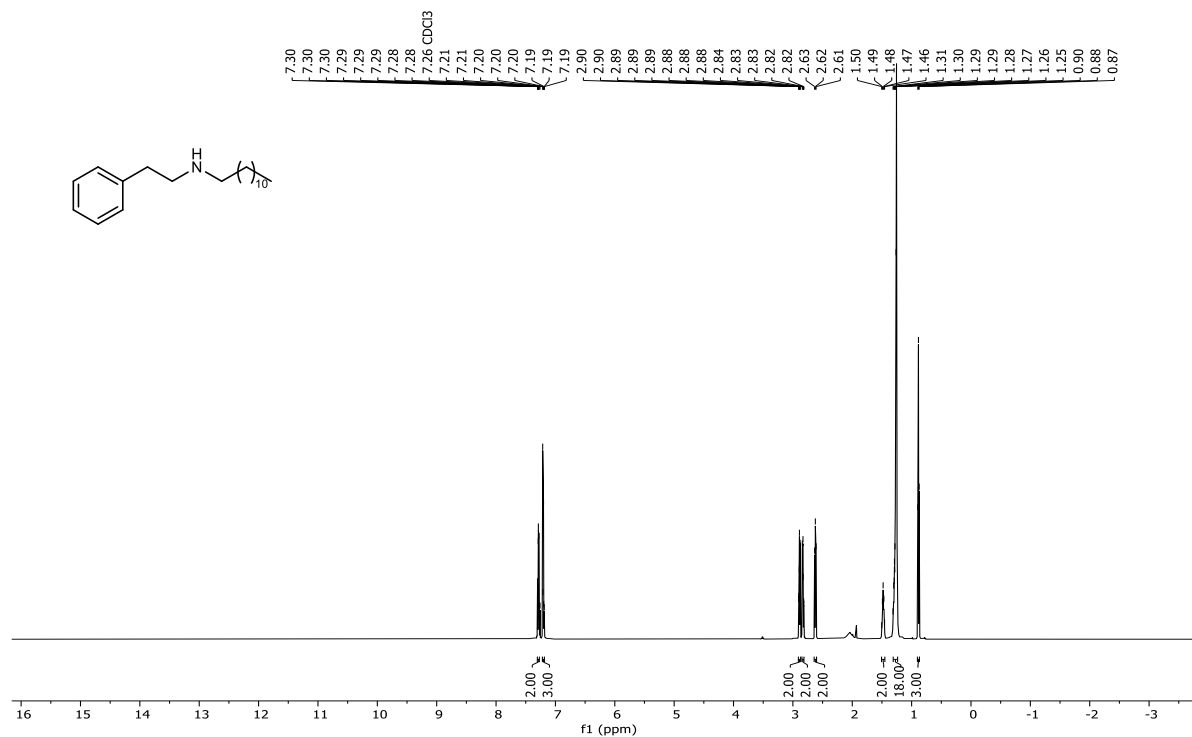
^1H NMR (600 MHz, CDCl_3) spectrum of *N*-phenethylhexan-1-amine (**5ac**)



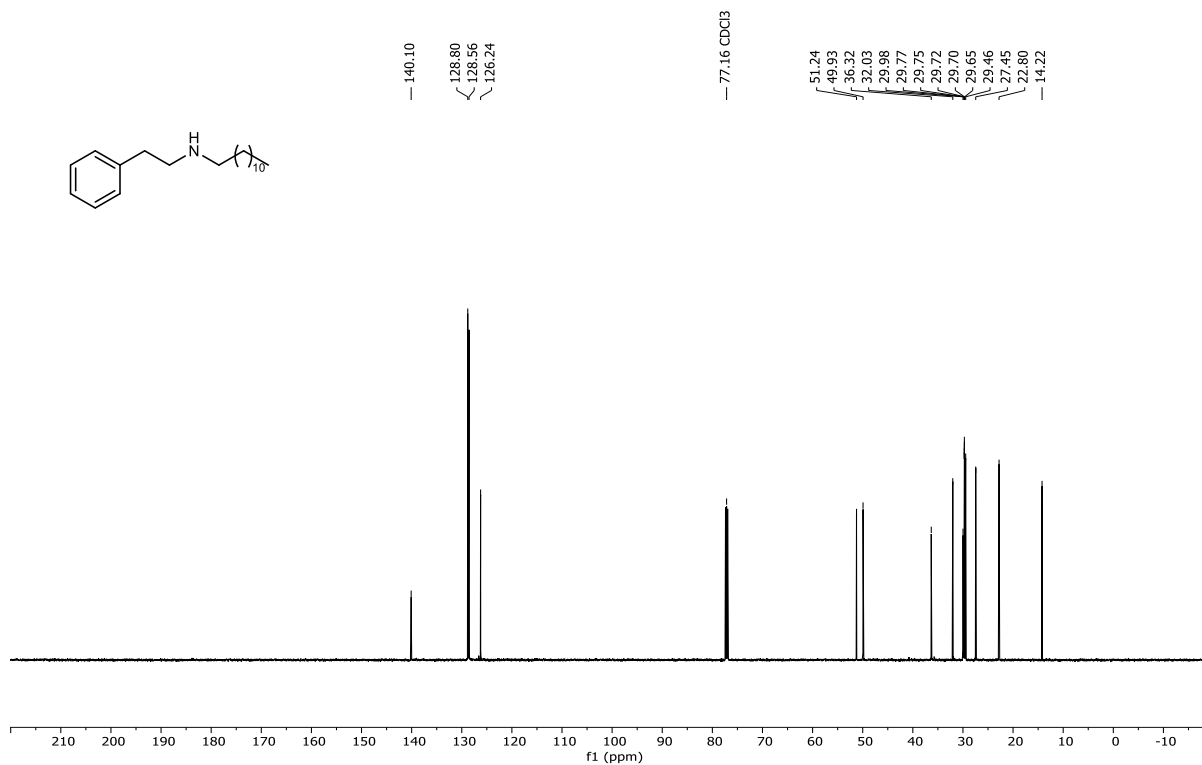
^{13}C NMR (151 MHz, CDCl_3) spectrum of *N*-phenethylhexan-1-amine (**5ac**)



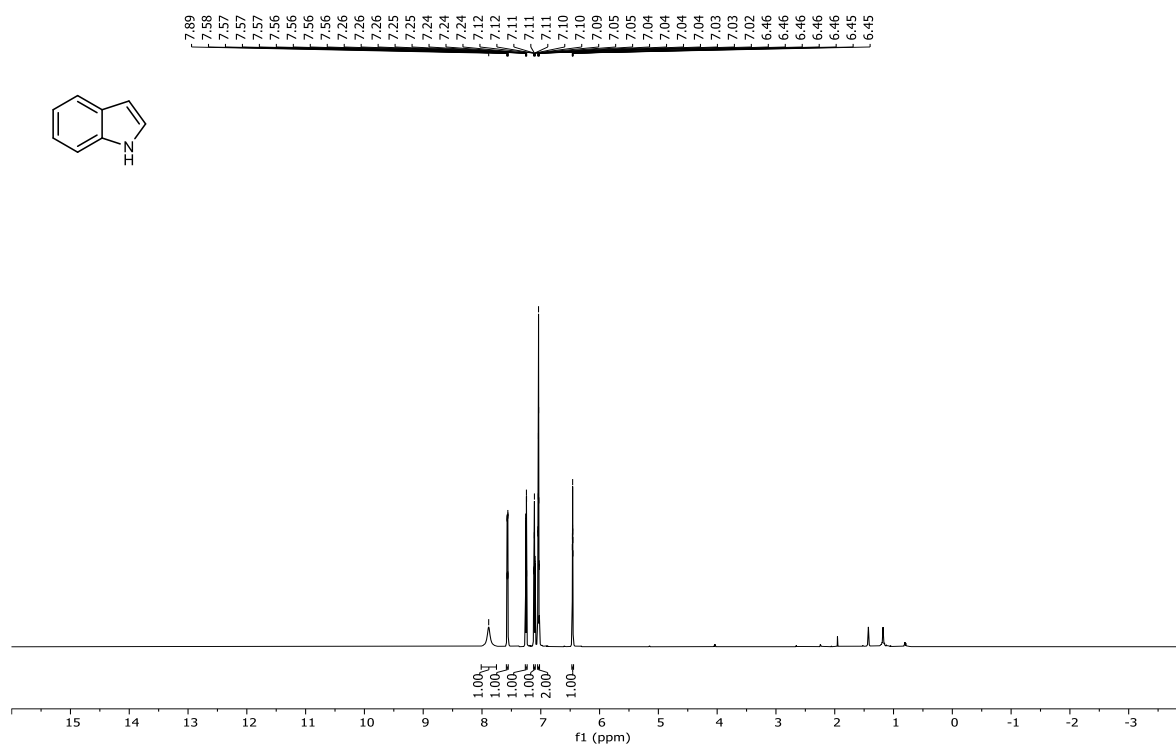
¹H NMR (600 MHz, CDCl₃) spectrum of *N*-phenethyldodecan-1-amine (**5ah**)



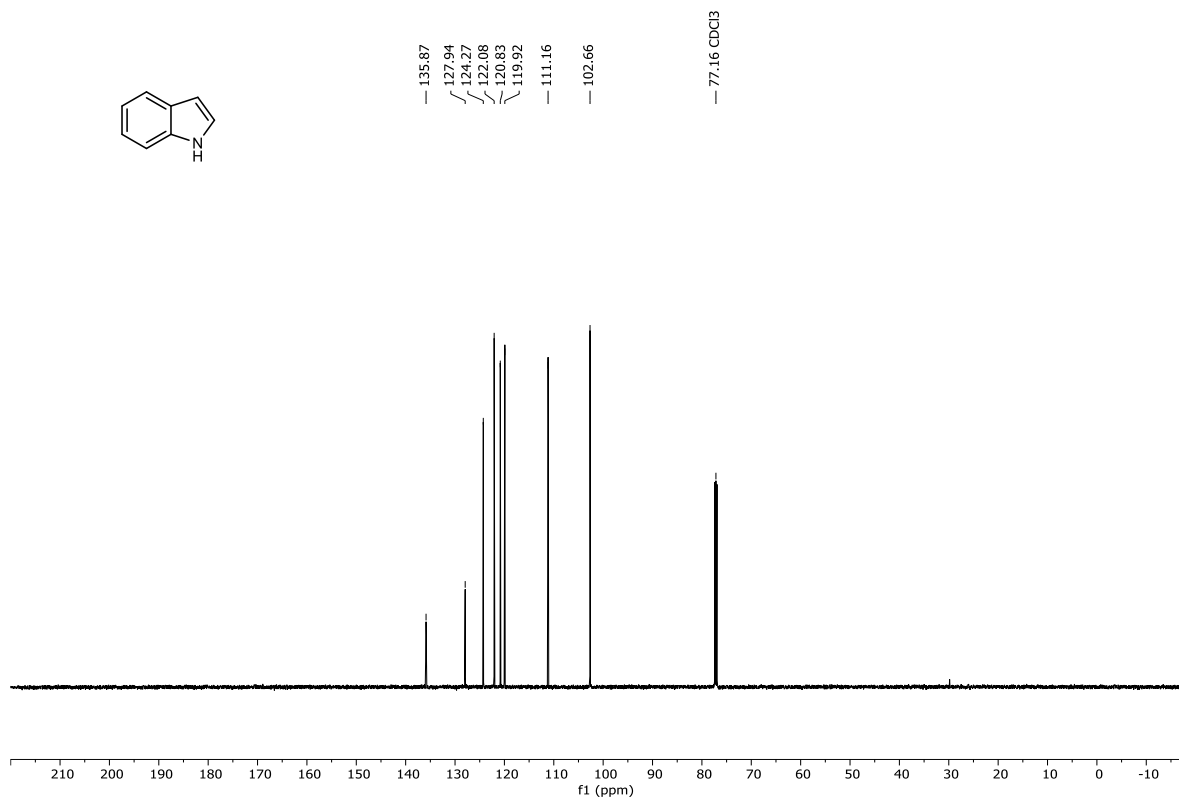
¹³C NMR (151 MHz, CDCl₃) spectrum of *N*-phenethyldodecan-1-amine (**5ah**)



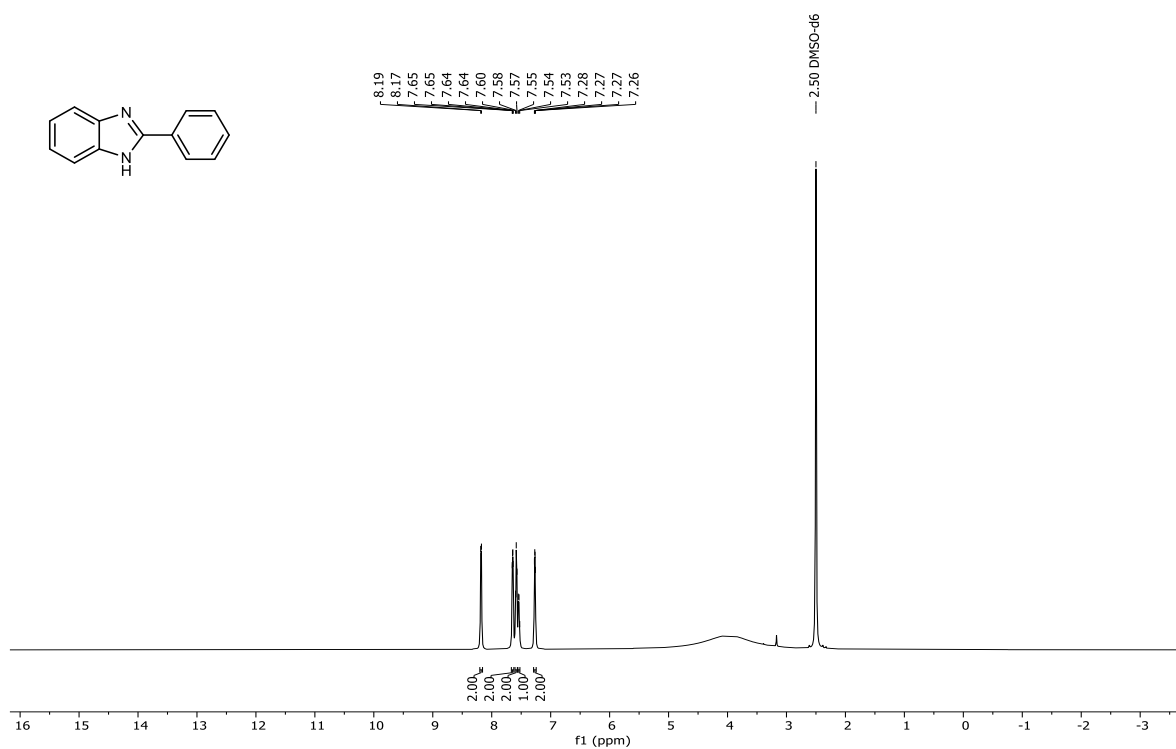
^1H NMR (600 MHz, CDCl_3) spectrum of **1H-Indole (6)**



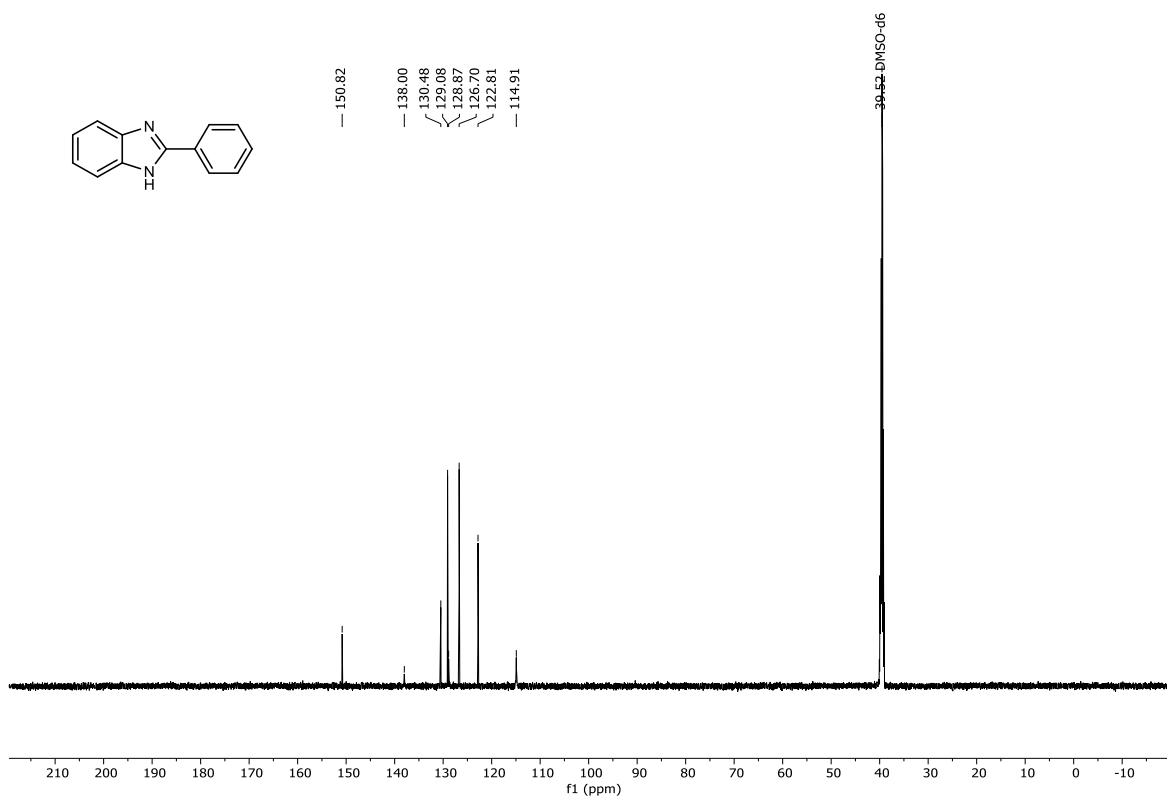
^{13}C NMR (151 MHz, CDCl_3) spectrum of **1H-Indole (6)**



¹H NMR (600 MHz, CDCl₃) spectrum of **2-phenyl-1H-benzimidazole (7)**



¹³C NMR (151 MHz, CDCl₃) spectrum of **2-phenyl-1H-benzimidazole (7)**



7.5. References

- (1) Kissane, M. G.; Frank, S. A.; Renner, G. A.; Ley, C. P.; Alt, C. A.; Stroud, P. A.; Vaid, R. K.; Boini, S. K.; McKee, L. A.; Vicenzi, J. T. Counterion effects in the preparation of aldehyde–bisulfite adducts. *Tetrahedron Lett.* **2013**, *54* (48), 6587–6591.
- (2) An, W.-K.; Zheng, S.-J.; Zhang, H.-X.; Shang, T.-T.; Wang, H.-R.; Xu, X.-J.; Jin, Q.; Qin, Y.; Ren, Y.; Jiang, S. s-Tetrazine-functionalized hyper-crosslinked polymers for efficient photocatalytic synthesis of benzimidazoles. *Green Chem.* **2021**, *23* (3), 1292–1299.
- (3) Narang, U.; Yadav, K. K.; Bhattacharya, S.; Chauhan, S. M. Cobalt (II) Phthalocyanine Catalyzed One-Pot Synthesis of 2-Substituted Benzimidazoles, Benzothiazoles and Benzoxazoles from Substituted Benzyl Alcohols. *ChemistrySelect* **2017**, *2* (24), 7135–7140.
- (4) Kim, Y.; Kumar, M. R.; Park, N.; Heo, Y.; Lee, S. Copper-catalyzed, one-pot, three-component synthesis of benzimidazoles by condensation and C–N bond formation. *J. Org. Chem.* **2011**, *76* (23), 9577–9583.
- (5) Bano, K.; Kisan, D. A.; Panda, T. K. Facile Synthesis of Benzimidazole and Benzothiazole Compounds Mediated by a Zinc Precatalyst Supported by an Iminopyrrole-Morpholine Ligand. *Eur. J. Inorg. Chem.* **2022**, *2022* (10), e202200023.
- (6) Xu, Z.; Wang, D. S.; Yu, X.; Yang, Y.; Wang, D. Tunable triazole-phosphine-copper catalysts for the synthesis of 2-aryl-1H-benzo [d] imidazoles from benzyl alcohols and diamines by Acceptorless dehydrogenation and borrowing hydrogen reactions. *Adv. Synth. Catal.* **2017**, *359* (19), 3332–3340.
- (7) Savall, B. M.; Fontimayor, J. R.; Edwards, J. P. Selective phenol alkylation for an improved synthesis of 2-arylbenzimidazole H4 receptor ligands. *Tetrahedron Lett.* **2009**, *50* (21), 2490–2492.
- (8) Zhang, R.; Qin, Y.; Zhang, L.; Luo, S. Oxidative synthesis of benzimidazoles, quinoxalines, and benzoxazoles from primary amines by ortho-quinone catalysis. *Org. Lett.* **2017**, *19* (20), 5629–5632.
- (9) Chakrabarty, M.; Mukherji, A.; Mukherjee, R.; Arima, S.; Harigaya, Y. A Keggin heteropoly acid as an efficient catalyst for an expeditious, one-pot synthesis of 1-methyl-2-(hetero) arylbenzimidazoles. *Tetrahedron Lett.* **2007**, *48* (30), 5239–5242.
- (10) Gu, Z.-S.; Chen, W.-X.; Shao, L.-X. N-heterocyclic carbene-palladium (II)-1-methylimidazole complex-catalyzed direct C–H bond arylation of (Benz) imidazoles with aryl chlorides. *J. Org. Chem.* **2014**, *79* (12), 5806–5811.
- (11) Baars, H.; Beyer, A.; Kohlhepp, S. V.; Bolm, C. Transition-metal-free synthesis of benzimidazoles mediated by KOH/DMSO. *Org. Lett.* **2014**, *16* (2), 536–539.
- (12) Secci, D.; Bolasco, A.; D'Ascenzio, M.; Della Sala, F.; Yáñez, M.; Carradori, S. Conventional and microwave-assisted synthesis of benzimidazole derivatives and their in vitro inhibition of human cyclooxygenase. *J. Heterocycl. Chem.* **2012**, *49* (5), 1187–1195.
- (13) Debeaux, M.; Thesen, M. W.; Schneidenbach, D.; Hopf, H.; Janietz, S.; Krüger, H.; Wedel, A.; Kowalsky, W.; Johannes, H. H. Charge-Transporting Polymers based on Phenylbenzimidazole Moieties. *Adv. Funct. Mater.* **2010**, *20* (3), 399–408.
- (14) Nardi, M.; Bonacci, S.; Herrera Cano, N.; Oliverio, M.; Procopio, A. The highly efficient synthesis of 1, 2-disubstituted benzimidazoles using microwave irradiation. *Molecules* **2022**, *27* (5), 1751.
- (15) Sharma, R.; Abdullaha, M.; Bharate, S. B. Metal-Free Ionic-Liquid-Mediated Synthesis of Benzimidazoles and Quinazolin-4 (3H)-ones from Benzylamines. *Asian J. Org. Chem.* **2017**, *6* (10), 1370–1374.
- (16) Xie, C.; Han, X.; Gong, J.; Li, D.; Ma, C. One-pot strategy of copper-catalyzed synthesis of 1, 2-disubstituted benzimidazoles. *Org. Biomol. Chem.* **2017**, *15* (27), 5811–5819.
- (17) Karuvalam, R. P.; Haridas, K. R.; Sajith, A. M.; Pakkath, R.; Bhaskaran, S.; Padusha, M. S. A.; Bakulev, V. A.; Joy, M. N. Suzuki-miyaura coupling under microwave enhanced conditions: Synthesis of 2-(hetero) aryl benzimidazoles. **2020**.
- (18) Qi, S.-L.; Liu, Y.-P.; Li, Y.; Luan, Y.-X.; Ye, M. Ni-catalyzed hydroarylation of alkynes with unactivated β -C (sp²)–H bonds. *Nat. Commun.* **2022**, *13* (1), 2938.

- (19) Zhang, C.; Zhang, L.; Jiao, N. Catalyst free approach to benzimidazoles using air as the oxidant at room temperature. *Green Chem.* **2012**, *14* (12), 3273-3276.
- (20) Barasa, L.; Yoganathan, S. An efficient one-pot conversion of carboxylic acids into benzimidazoles via an HBTU-promoted methodology. *RSC Adv.* **2018**, *8* (62), 35824-35830.
- (21) Ma, D.; Ji, X.; Wu, Z.; Cheng, C.; Zhou, B.; Zhang, Y. Synthesis of Benzimidazoles through Palladium-Catalyzed Amination of 2-Iodobenzimines with Diaziridinone. *Adv. Synth. Catal.* **2019**, *361* (4), 739-746.
- (22) Sahiba, N.; Sethiya, A.; Soni, J.; Agarwal, S. Metal free sulfonic acid functionalized carbon catalyst for green and mechanochemical synthesis of perimidines. *ChemistrySelect* **2020**, *5* (42), 13076-13080.
- (23) Pal, A.; Das, K. M.; Thakur, A. Microwave-Assisted Synthesis of E-Aldimines, N-Heterocycles, and H₂ by Dehydrogenative Coupling of Benzyl Alcohol and Aniline Derivatives Using CoCl₂ as a Catalyst. *J. Org. Chem.* **2023**, *88* (13), 8955-8968.
- (24) Mannarsamy, M.; Nandeshwar, M.; Muduli, G.; Prabusankar, G. Highly active cyclic zinc (II) thione catalyst for C–C and C–N bond formation reactions. *Chem. Asian J.* **2022**, *17* (18), e202200594.
- (25) Harry, N. A.; Cherian, R. M.; Radhika, S.; Anilkumar, G. A novel catalyst-free, eco-friendly, on water protocol for the synthesis of 2, 3-dihydro-1H-perimidines. *Tetrahedron Lett.* **2019**, *60* (33), 150946.
- (26) Zhang, J.; Zhang, S. Bismuth (III) chloride-promoted efficient synthesis of perimidine derivatives under ambient conditions. *Synth. Commun.* **2007**, *37* (15), 2615-2624.
- (27) Schwob, T.; Ade, M.; Kempe, R. A Cobalt Catalyst Permits the Direct Hydrogenative Synthesis of 1H-Perimidines from a Dinitroarene and an Aldehyde. *ChemSusChem* **2019**, *12* (13), 3013-3017.
- (28) Amrollahi, M.; Ashayeri-Harati, F. Magnetic Graphene Oxide Bearing ZrO₂ as a New Composite Catalyst for the Synthesis of 1 H-Perimidines. *Org. Prep. Proced. Int.* **2020**, *52* (4), 282-289.
- (29) Maquestiau, A.; Berte, L.; Mayence, A.; Eynde, J.-J. V. An improved one-pot method for the preparation of 2-substituted 1H-perimidines. *Synth. Commun.* **1991**, *21* (21), 2171-2180.
- (30) Bohigues, B.; Rojas-Buzo, S.; Moliner, M.; Corma, A. Coordinatively unsaturated Hf-MOF-808 prepared via hydrothermal synthesis as a bifunctional catalyst for the tandem N-alkylation of amines with benzyl alcohol. *ACS Sustain. Chem. Eng.* **2021**, *9* (47), 15793-15806.
- (31) Zhou, P.; Zhang, Z. One-pot reductive amination of carbonyl compounds with nitro compounds by transfer hydrogenation over Co–Nx as catalyst. *ChemSusChem* **2017**, *10* (9), 1892-1897.
- (32) Hoshimoto, Y.; Kinoshita, T.; Hazra, S.; Ohashi, M.; Ogoshi, S. Main-group-catalyzed reductive alkylation of multiply substituted amines with aldehydes using H₂. *J. Am. Chem. Soc.* **2018**, *140* (23), 7292-7300.
- (33) Sousa, S. C.; Fernandes, A. C. Efficient and highly chemoselective direct reductive amination of aldehydes using the system silane/oxorhenium complexes. *Adv. Synth. Catal.* **2010**, *352* (13), 2218-2226.
- (34) Gupta, P.; Kour, M.; Paul, S.; Clark, J. H. Ionic liquid coated sulfonated carbon/silica composites: novel heterogeneous catalysts for organic syntheses in water. *RSC Adv.* **2014**, *4* (15), 7461-7470.
- (35) Hernández-Juárez, M.; López-Serrano, J.; Lara, P.; Morales-Cerón, J. P.; Vaquero, M.; Álvarez, E.; Salazar, V.; Suárez, A. Ruthenium (II) Complexes Containing Lutidine-Derived Pincer CNC Ligands: Synthesis, Structure, and Catalytic Hydrogenation of C≡N bonds. *Chem. Eur. J.* **2015**, *21* (20), 7540-7555.
- (36) Furukawa, S.; Suzuki, R.; Komatsu, T. Selective activation of alcohols in the presence of reactive amines over intermetallic PdZn: efficient catalysis for alcohol-based N-alkylation of various amines. *ACS Catal.* **2016**, *6* (9), 5946-5953.
- (37) Pintado-Sierra, M.; Rasero-Almansa, A. M.; Corma, A.; Iglesias, M.; Sánchez, F. Bifunctional iridium-(2-aminoterephthalate)–Zr-MOF chemoselective catalyst for the synthesis of secondary amines by one-pot three-step cascade reaction. *J. Catal.* **2013**, *299*, 137-145.
- (38) Jiménez, M. V.; Fernández-Tornos, J.; González-Lainez, M.; Sánchez-Page, B.; Modrego, F. J.; Oro, L. A.; Pérez-Torrente, J. J. Mechanistic studies on the N-alkylation of amines with alcohols catalysed by iridium (I) complexes with functionalised N-heterocyclic carbene ligands. *Catal. Sci. Technol.* **2018**, *8* (9), 2381-2393.
- (39) Wahba, A. E.; Hamann, M. T. Reductive N-alkylation of nitroarenes: a green approach for the N-alkylation of natural products. *J. Org. Chem.* **2012**, *77* (10), 4578-4585.

- (40) Poh, J. S.; Makai, S.; von Keutz, T.; Tran, D. N.; Battilocchio, C.; Pasau, P.; Ley, S. V. Rapid Asymmetric Synthesis of Disubstituted Allenes by Coupling of Flow-Generated Diazo Compounds and Propargylated Amines. *Angew. Chem. Int. Ed.* **2017**, *56* (7), 1864-1868.
- (41) Teng, Q.-H.; Lu, F.-L.; Wang, K.; Zhou, L.-Y.; Li, D.-P. Chemodivergent Photocatalyzed Heterocyclization of Hydrazones and Isothiocyanates for the Selectivity Synthesis of 2-Amino-1, 3, 4-thiadiazoles and 1, 2, 4-Triazole-3-thiones. *J. Org. Chem.* **2023**, *88* (11), 7104-7116.
- (42) Cao, D.; Pan, P.; Zeng, H.; Li, C.-J. Umpolung cross-coupling of polyfluoroarenes with hydrazones via activation of C–F bonds. *Chem. Commun.* **2019**, *55* (63), 9323-9326.
- (43) Rani, R.; Peddinti, R. K. Camphor-10-sulfonamide-based prolinamide organocatalyst for the direct intermolecular aldol reaction between ketones and aromatic aldehydes. *Tetrahedron: Asym.* **2010**, *21* (7), 775-779.
- (44) Ikishima, H.; Sekiguchi, Y.; Ichikawa, Y.; Kotsuki, H. Synthesis of (–)-(5R, 6S)-6-acetoxylhexadecanolide based on l-proline-catalyzed asymmetric aldol reactions. *Tetrahedron* **2006**, *62* (2-3), 311-316.
- (45) Sharma, S.; Kumar, M.; Bhatt, V.; Nayal, O. S.; Thakur, M. S.; Kumar, N.; Singh, B.; Sharma, U. Vasicine from *Adhatoda vasica* as an organocatalyst for metal-free Henry reaction and reductive heterocyclization of o-nitroacylbenzenes. *Tetrahedron Lett.* **2016**, *57* (45), 5003-5008.
- (46) Gao, N.; Chen, Y.-L.; He, Y.-H.; Guan, Z. Highly efficient and large-scalable glucoamylase-catalyzed Henry reactions. *RSC Adv.* **2013**, *3* (37), 16850-16856.
- (47) Mahmoudi, H.; Malakooti, R. Mn-grafted imine-functionalized mesoporous SBA-15 as an efficient catalyst for Knoevenagel condensation under mild conditions. *React. Kinet. Mech. Catal.* **2014**, *113* (1), 241-255.
- (48) Kao, T.-T.; Syu, S.-e.; Jhang, Y.-W.; Lin, W. Preparation of tetrasubstituted furans via intramolecular Wittig reactions with phosphorus ylides as intermediates. *Org. Lett.* **2010**, *12* (13), 3066-3069.
- (49) Takahashi, R.; Hu, A.; Gao, P.; Gao, Y.; Pang, Y.; Seo, T.; Jiang, J.; Maeda, S.; Takaya, H.; Kubota, K.; et al. Mechanochemical synthesis of magnesium-based carbon nucleophiles in air and their use in organic synthesis. *Nat. Commun.* **2021**, *12*, 6691.
- (50) Chatterjee, B.; Gunanathan, C. Ruthenium Catalyzed Selective α - and α,β -Deuteration of Alcohols Using D₂O. *Org. Lett.* **2015**, *17*, 4794-4797.
- (51) Xie, X.; Zhang, T. Y.; Zhang, Z. Synthesis of bulky and electron-rich MOP-type ligands and their applications in palladium-catalyzed C–N bond formation. *J. Org. Chem.* **2006**, *71* (17), 6522-6529.
- (52) Nacario, R.; Kotakonda, S.; Fouchard, D. M.; Tillekeratne, L. V.; Hudson, R. A. Reductive monoalkylation of aromatic and aliphatic nitro compounds and the corresponding amines with nitriles. *Org. Lett.* **2005**, *7* (3), 471-474.
- (53) Hollmann, D.; Bahn, S.; Tillack, A.; Beller, M. A general ruthenium-catalyzed synthesis of aromatic amines. *Angew. Chem. Int. Ed.* **2007**, *46* (43), 8291-8294.
- (54) Watson, A. J.; Maxwell, A. C.; Williams, J. M. Borrowing hydrogen methodology for amine synthesis under solvent-free microwave conditions. *J. Org. Chem.* **2011**, *76* (7), 2328-2331.
- (55) Wei, Y.; Zhao, C.; Xuan, Q.; Song, Q. An expedient and novel strategy for reductive amination by employing H₂O as both a hydrogen source and solvent via B₂(OH)₄/H₂O systems. *Org. Chem. Front.* **2017**, *4* (12), 2291-2295.
- (56) Braun, C.; Nieger, M.; Bräse, S.; Schafer, L. L. Planar-Chiral [2.2] Paracyclophane-Based Pyridonates as Ligands for Tantalum-Catalyzed Hydroaminoalkylation. *ChemCatChem* **2019**, *11* (21), 5264-5268.
- (57) Jaladi, A. K.; Kim, H.; Lee, J. H.; Shin, W. K.; Hwang, H.; An, D. K. Lithium diisobutyl-tert-butoxyaluminum hydride (LDBBA) catalyzed hydroboration of alkynes and imines with pinacolborane. *New J. Chem.* **2019**, *43* (42), 16524-16529.
- (58) Maytum, H. C.; Francos, J.; Whatrup, D. J.; Williams, J. M. 1, 4-Butanediol as a Reducing Agent in Transfer Hydrogenation Reactions. *Chem. Asian J.* **2010**, *5* (3), 538-542.
- (59) Fleischer, S.; Zhou, S.; Junge, K.; Beller, M. An Easy and General Iron-catalyzed Reductive Amination of Aldehydes and Ketones with Anilines. *Chem. Asian J.* **2011**, *6* (9), 2240-2245.

- (60) Kato, H.; Shibata, I.; Yasaka, Y.; Tsunoi, S.; Yasuda, M.; Baba, A. The reductive amination of aldehydes and ketones by catalytic use of dibutylchlorotin hydride complex. *Chem. Commun.* **2006**, (40), 4189-4191.
- (61) Fu, M. C.; Shang, R.; Cheng, W. M.; Fu, Y. Boron-catalyzed N-alkylation of amines using carboxylic acids. *Angew. Chem. Int. Ed.* **2015**, 54 (31), 9042-9046.
- (62) Bartoszewicz, A.; Marcos, R.; Sahoo, S.; Inge, A. K.; Zou, X.; Martín-Matute, B. A Highly Active Bifunctional Iridium Complex with an Alcohol/Alkoxide-Tethered N-Heterocyclic Carbene for Alkylation of Amines with Alcohols. *Chem. Eur. J.* **2012**, 18 (45), 14510-14519.
- (63) Hollmann, D.; Bähn, S.; Tillack, A.; Beller, M. N-Dealkylation of aliphatic amines and selective synthesis of monoalkylated aryl amines. *Chem. Commun.* **2008**, (27), 3199-3201.
- (64) Kallmeier, F.; Fertig, R.; Irrgang, T.; Kempe, R. Chromium-Catalyzed Alkylation of Amines by Alcohols. *Angew. Chem. Int. Ed.* **2020**, 59 (29), 11789-11793.
- (65) Sakai, N.; Takeoka, M.; Kumaki, T.; Asano, H.; Konakahara, T.; Ogiwara, Y. Indium-catalyzed reduction of secondary amides with a hydrosiloxane leading to secondary amines. *Tetrahedron Lett.* **2015**, 56 (46), 6448-6451.
- (66) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. CuBr/rac-BINOL-catalyzed N-arylations of aliphatic amines at room temperature. *J. Org. Chem.* **2007**, 72 (2), 672-674.
- (67) Barbero, M.; Cadamuro, S.; Dughera, S.; Ghigo, G. Reactions of Arenediazonium o-Benzenedisulfonimides with Aliphatic Triorganoindium Compounds. Wiley Online Library: 2008.
- (68) Kubo, T.; Katoh, C.; Yamada, K.; Okano, K.; Tokuyama, H.; Fukuyama, T. A mild inter- and intramolecular amination of aryl halides with a combination of CuI and CsOAc. *Tetrahedron* **2008**, 64 (49), 11230-11236.
- (69) Elangovan, S.; Neumann, J.; Sortais, J. B.; Junge, K.; Darcel, C.; Beller, M. Efficient and selective N-alkylation of amines with alcohols catalysed by manganese pincer complexes. *Nat. Commun.* **2016**, 7, 12641.
- (70) Yan, T.; Feringa, B. L.; Barta, K. Iron catalysed direct alkylation of amines with alcohols. *Nat. Commun.* **2014**, 5, 5602.
- (71) Sorribes, I.; Cabrero-Antonino, J. R.; Vicent, C.; Junge, K.; Beller, M. Catalytic N-alkylation of amines using carboxylic acids and molecular hydrogen. *J. Am. Chem. Soc.* **2015**, 137 (42), 13580-13587.
- (72) Song, G.; Li, Q.; Song, J.; Nong, D.-Z.; Dong, J.; Li, G.; Fan, J.; Wang, C.; Xue, D. Light-Promoted Efficient Generation of Fe(I) to Initiate Amination. *ACS Catal.* **2024**, 14 (7), 4968-4974.
- (73) Mocci, R.; Atzori, L.; Baratta, W.; De Luca, L.; Porcheddu, A. N-Alkylation of aromatic amines with alcohols by using a commercially available Ru complex under mild conditions. *RSC Adv.* **2023**, 13 (49), 34847-34851.
- (74) Sajiki, H.; Ikawa, T.; Hirota, K. Reductive and catalytic monoalkylation of primary amines using nitriles as an alkylating reagent. *Org. Lett.* **2004**, 6 (26), 4977-4980.
- (75) Bennett, J. S.; Charles, K. L.; Miner, M. R.; Heuberger, C. F.; Spina, E. J.; Bartels, M. F.; Foreman, T. Ethyl lactate as a tunable solvent for the synthesis of aryl aldimines. *Green Chem.* **2009**, 11 (2), 166-168.
- (76) Guisado, C.; Waterhouse, J. E.; Price, W. S.; Jorgensen, M. R.; Miller, A. D. The facile preparation of primary and secondary amines via an improved Fukuyama-Mitsunobu procedure. Application to the synthesis of a lung-targeted gene delivery agent. *Org. Biomol. Chem.* **2005**, 3 (6), 1049-1057.
- (77) Liu, B.; Roisnel, T.; Carpentier, J.-F.; Sarazin, Y. When bigger is better: intermolecular hydrofunctionalizations of activated alkenes catalyzed by heteroleptic alkaline Earth complexes. *Angew. Chem. Int. Ed.* **2012**, 51 (20), 4943-4946.
- (78) Buil, M. L.; Esteruelas, M. A.; Lopez, A. M.; Mateo, A. C. Preparation of Half-Sandwich Alkyl-Titanium (IV) Complexes Stabilized by a Cyclopentadienyl Ligand with a Pendant Phosphine Tether and Their Use in the Catalytic Hydroamination of Aliphatic and Aromatic Alkynes. *Organometallics* **2006**, 25 (17), 4079-4089.

(79) Prokopcova, H.; Kappe, C. O. Palladium (0)-catalyzed, copper (I)-mediated coupling of boronic acids with cyclic thioamides. selective carbon– carbon bond formation for the functionalization of heterocycles. *J. Org. Chem.* **2007**, 72 (12), 4440-4448.

Acknowledgements

First and foremost, I would like to express my deepest gratitude to Prof. Andrea Porcheddu for his invaluable guidance, continuous support, and encouragement throughout every stage of my PhD. His insightful discussions, evening brainstorming sessions, and occasional coffee breaks have not only enriched my scientific growth but have also shaped me personally. I am deeply grateful for his patience, advice, and trust in my abilities.

I sincerely thank the Department of Chemical and Geological Sciences, University of Cagliari, for giving me the opportunity to pursue my doctoral studies. My heartfelt appreciation also goes to Concimi Biologici for their partial financial support of my PhD scholarship.

I extend my warmest thanks to all my colleagues and friends from the GREET Lab— Shyamal, Francesco, Rita, Dipak, Federico, Andrea, Pietro, Irfan, Astha, Roberto and Ricardo whose direct or indirect contributions have been essential for the completion of this thesis. This work would not have been possible without your collaboration, support, and friendship. As a team, we have learned to overcome any challenge together. In particular, I would like to express my special thanks to Shyamal and Francesco, who have been instrumental in shaping me into the researcher I am today. Your guidance and constant support, especially during the early stages of my PhD, have meant a lot to me. I am also grateful to Rita for her friendship, countless lunch breaks, laughter, and for “babysitting” me on many occasions. My sincere thanks go to Dipak for his advice, humour, and the many conversations that made each day brighter. It has truly been an honour to be part of this group, and I wish everyone great success in their future endeavours. You all made this PhD journey not only productive but also enjoyable.

My sincere gratitude also goes to Prof. Carsten Bolm for welcoming me into his laboratory at RWTH Aachen University and for his constant support during my stay. I would like to thank all the group members for their help and kindness. A special mention goes to Calo, whose friendship, collaboration, and shared laughter made my time there memorable. I am also thankful to Michael sensei for all the laughs and life altering insights (and of course graphs at 5.02), and to Leonie, Sam, Sodeeq, and Antonia for their discussions and friendship. Special thanks to Ganesh and Dipankar for the parties and trips that added so much joy. I look forward to sharing more good times together in the future.

Beyond the lab, I want to express my gratitude to my friends in Cagliari Fede, Stef, Perry, Chiara, Vik, Sara, Sara, Fra, Mau, and Sonia, for their friendship and companionship, which made my PhD life much easier and more enjoyable. My heartfelt thanks to Fede and Stef for all the conversations, dinners, and laughter we shared. You have all given me memories from the past three years that I will always cherish.

I also wish to thank the lunch group Saswati, Aditya, Hardik, Athar, Amit, and Dukhishyam for the lively lunches, discussions, and laughter that always reminded me of home. My special thanks go to Devi and Saswati for their warmth and friendship, and for treating me like family.

My appreciation also goes to Michela, who began as a student and became a wonderful friend. I wish you all the success in your career and to Alessia for her friendship, our lunches, and for being my Prague tour guide!

Thanks also to my flatmates Margaux, Gianluca, Alessandro, Michela, and Carlotta for making my stay comfortable and pleasant throughout this journey.

Finally, I want to express my deepest gratitude to my friends back in India Jyoti, Sambit, Debashish, Haresh, Chandan, and Nihar for being part of my life's journey from childhood until now. A special thanks to Madan for still being such a great friend and for all our unforgettable Formula 1 discussions that always brightened my weekends. I also want to thank H.S. Behera sir and I.P. Sahu sir for their guidance, help and nurturing, during my schooling years.

And most importantly, I owe everything to Rahul and my parents, whose unconditional love, sacrifices, and encouragement have been the foundation of all my achievements.

There are many more people whose names I might not have mentioned but who have been part of my life in one way or another. To all of you, thank you for your presence, your kindness, and your support.

This publication (communication/thesis/article, etc.) was produced while attending the PhD programme in Chemical Sciences and Technologies at the University of Cagliari, Cycle XXXVIII, with the support of a scholarship co-financed by the Ministerial Decree no. 352 of 9th April 2022, based on the NRRP - funded by the European Union - NextGenerationEU - Mission 4 "Education and Research", Component 2 "From Research to Business", Investment 3.3, and by the company Concimi Biologici S.r.l.



