

**AEROBIC OXIDATION OF ALCOHOLS CATALYZED BY AN
EFFICIENT HETEROGENEOUS MIXED METAL HYDROXIDE
CATALYST**

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By

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We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.



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ABSTRACT

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M.Sc. in Chemistry

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Aerobic alcohol oxidation is one of the important reactions of organic chemistry used both in academic research and in many industries such as medicine, cosmetics and food. Aldehydes, carboxylic acids and ketones resulting from alcohol oxidation are encountered as intermediates or final products. However, some oxidation methods developed to date have drawbacks such as expensiveness, being hazardous to human health and the environment, and having low sustainability. For this reason, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ mixed metal hydroxide catalyst was developed in a collaborative work by the Ozensoy and Türkmen research groups by avoiding these drawbacks and was first used in the C-H activation reaction giving successful results. In this project, alcohol oxidation reactions were carried out using the same catalyst. Optimized reaction conditions were found by the model reaction of conversion from benzhydrol to benzophenone. Then, substrates with different electron withdrawing and donating groups attached to benzhydrol were tested along with benzyl alcohol and 1-phenylethanol derivatives. Finally, an attempt was made to obtain

information about the working mechanism of the catalyst by performing a kinetic isotope effect experiment and various control experiments.

Keywords: Aerobic alcohol oxidation, mixed metal hydroxide catalyst, benzhydrol, earth abundant metals, benzyl alcohol, 1-phenylethanol.



ÖZET

ETKİLİ BİR HETEROJEN KARIŞIK METAL HİDROKSİT KATALİZÖRÜ TARAFINDAN KATALİZLENEN ALKOLLERİN AEROBİK OKSİDASYONU

Suay Bilgin

Kimya Bölümü, Yüksek Lisans

Tez Danışmanı: Dr. Yunus Emre Türkmen

Ağustos 2024

Aerobik alkol oksidasyonu, hem akademik araştırmalarda hem de ilaç, kozmetik ve gıda gibi birçok endüstride kullanılan organik kimyanın önemli reaksiyonlarından biridir. Alkol oksidasyonunun sonucunda oluşan aldehitler, karboksilik asitler ve ketonlara akademik araştırma ve endüstride ara ürün veya son ürün olarak rastlanmaktadır. Ancak bugüne kadar geliştirilen bazı oksidasyon yöntemlerinin pahalı olması, insan sağlığına ve çevreye zarar vermesi, sürdürülebilirliğinin düşük olması gibi dezavantajları bulunmaktadır. Bu nedenle bu dezavantajlardan kaçınılarak $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ karışık metal hidroksit katalizörü Özensoy ve Türkmen araştırma grupları tarafından yapılan ortak bir çalışma kapsamında geliştirildi ve ilk olarak C-H aktivasyon reaksiyonunda kullanıldı ve başarılı sonuçlar verdi. Bu projede alkol oksidasyon reaksiyonları aynı katalizör kullanılarak gerçekleştirilmiştir. Benzhidrolden benzofenona dönüşüm model reaksiyonuyla optimize edilmiş reaksiyon koşulları bulundu. Daha sonra benzhidrole bağlı farklı elektron çekici ve verici gruplara sahip substratlar test edildi. Benzil

alkol ve 1-feniletanol türevleri de bir sonraki aşamada test edildi. Son olarak kinetik izotop etkisi deneyi ve çeşitli kontrol deneyleri yapılarak katalizörün çalışma mekanizması hakkında bilgi edinilmeye çalışıldı.

Anahtar kelimeler: Aerobik alkol oksidasyonu, karışık metal hidroksit katalizörü, benzhidrol, toprakta bol bulunan metal, benzil alkol, 1-feniletanol.



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LIST OF ABBREVIATIONS

mCPBA	<i>meta</i> -Chloroperbenzoic acid
PCC	Pyridinium chlorochromate
PDC	Pyridinium Dichromate
IBX	2-Iodoxybenzoic acid
DMP	Dess–Martin periodinane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
NCS	<i>N</i> -Chlorosuccinimide
DCU	<i>N,N'</i> -Dicyclohexylurea
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
AZADO	2-azaadamantane- <i>N</i> -oxyl
TPAP	Tetrapropylammonium perruthenate
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
HMF	5-Hydroxymethylfurfural
NMR	Nuclear magnetic resonance
EtOAc	Ethyl acetate
DCM	Dichloromethane

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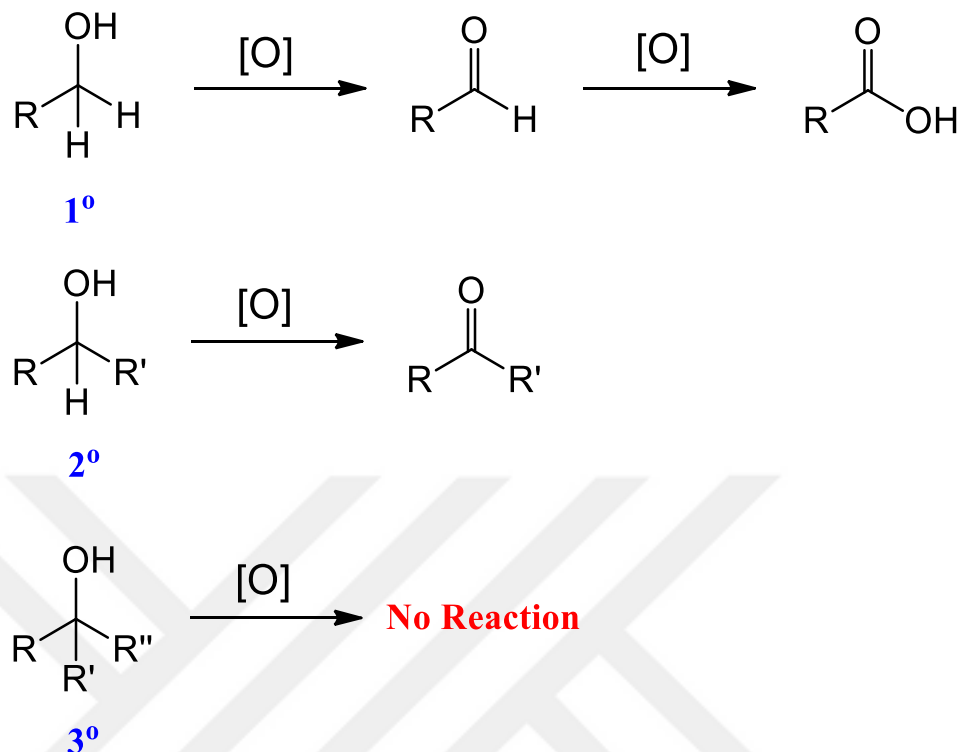


CHAPTER 1

1.1 INTRODUCTION

1.1.1 Aerobic Alcohol Oxidation

Aerobic oxidation of alcohols is one of the basic organic reactions. In addition to being a basic reaction, alcohol oxidation is frequently used in both industry and scientific research.^{1,2} Nevertheless, oxidation reactions have been a challenge, especially when synthesis in large quantities is required in industry, because of the properties of the oxidants used in the syntheses. The environmental and health hazards of traditional oxidants which are still used today can be an example of these challenges.³ Regarding this, in a study conducted by a group of scientists from different pharmaceutical companies, it was stated that common oxidation methods are avoided if possible during synthesis because these methods are not atom efficient, chemoselective and environmentally friendly.^{3,4} On the other hand, air is now known to be an ideal oxidant which offers to be used both in academia and industry.^{3,5} The reason for oxygen to arouse interest is that it is already available and abundant in the atmosphere and an environmentally friendly oxidant with a low molecular weight.⁶ Before moving on to explaining the reasons of these challenges in the oxidation reactions, let us focus on the importance of them. As a result of alcohol oxidation occurring in an oxygenated environment, three products can be obtained, depending on whether the alcohol is primary or secondary and the conditions in which the reaction takes place, as seen in **Scheme 1**. Primary alcohols can be oxidized to aldehydes and carboxylic acids, whereas secondary alcohols are oxidized to ketones. Tertiary alcohols generally do not give oxidation reactions.⁷



Scheme 1: Oxidation reactions of primary, secondary and tertiary alcohols.⁷

Aldehydes are compounds of great importance that play a role in the pharmaceutical industry and complex organic syntheses.⁸ Some of the aldehydes, which stand out with their intensely aromatic odors, oily structures and volatility, are found in essential oils that are obtained from aromatic plants by distillation or expression. However, aldehydes are very reactive compounds and although the mechanism is not fully understood, they are regarded as toxic.⁹ The simplest aromatic aldehyde, benzaldehyde, with its definitive bitter almond odor, is used in fragrances, pharmaceuticals and as flavoring agents in food. Anisaldehyde and vanillin are also used in fragrances with sweet blossom and vanilla odors, respectively (**Figure 1**).^{9–11}

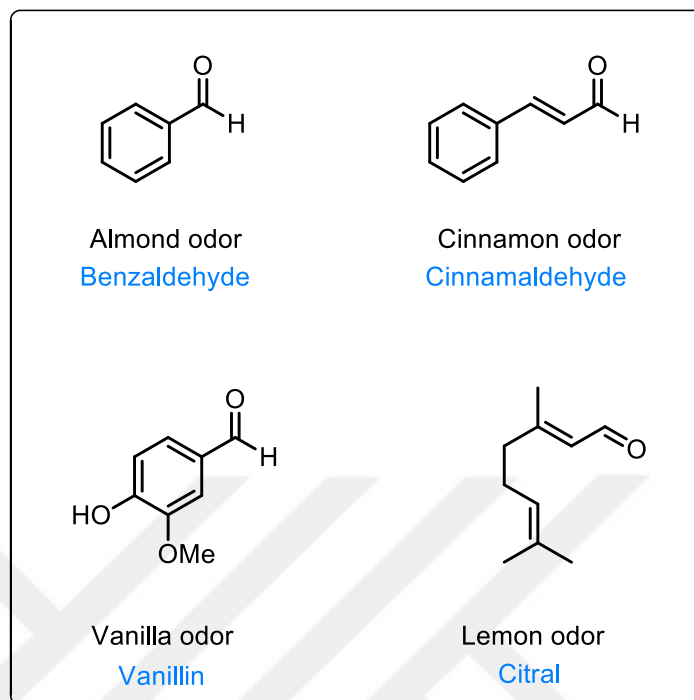


Figure 1: Aldehydes with odors.⁹⁻¹¹

Apart from the cosmetic industry, aldehydes have been used in medical therapy for many years as contributors to drug molecules.¹² Yet, this topic is still a matter of debate due to the reactivity and toxicity of aldehydes as mentioned before. Considering the alleged disadvantages, it should be noted that constant and high doses of exposure to aldehydes, combined with unhealthy living habits, are claimed to cause cardiovascular diseases or cancer.¹³ There are studies as well that explain why some drug treatment methods that were used in the past but have now been abandoned, or explain the deficiencies in these drug treatment methods that are claimed to work with incomplete scientific studies which also have now been abandoned.¹² On the other hand, containing different types of aldehydes, cinnamaldehyde has been used in stroke and proven to show enhancements in stroke patients.¹⁴ Another area of use of cinnamon oil and cinnamaldehyde is as an antimicrobial and blood pressure controlling agent as well as the kidney disorders and cancer.¹⁵ Further to these, lemongrass essential oil has been utilized to improve blood flow, balance

menstrual cycles and inhibit bacterial and fungal growth.¹⁶⁻¹⁸ In short, there are countless more favorable aldehyde uses in medicine but also leaves a question in minds. It is not known whether the use of aldehydes in industry will be reduced or precluded in the future, but it is apparent that they are used frequently at present.

Carboxylic acids, like aldehydes, are naturally occurring products and are used in different industries. The production of carboxylic acids can be synthetic or these products can be encountered as a result of biological activities as well. Many types of carboxylic acids are used in the food and polymer field or in chemical synthesis.¹⁹ In fact, to give an example for the use of carboxylic acids, in 1920, British dermatologist Arthur Whitfield reported a treatment method, named after himself, against *Tinea cruris*, a type of fungal infection. This treatment passed into the history as Whitfield's ointment (**Figure 2**).²⁰ This ointment contains 3% benzoic acid and 6% salicylic acid, and in a study conducted in AVBR Hospital in India in 2020, the use of Whitfield's ointment in treatment gave positive results. Despite the formulation and the ingredients of this ointment can be considered elementary, this effective method has been used over 100 years in medicine.²¹

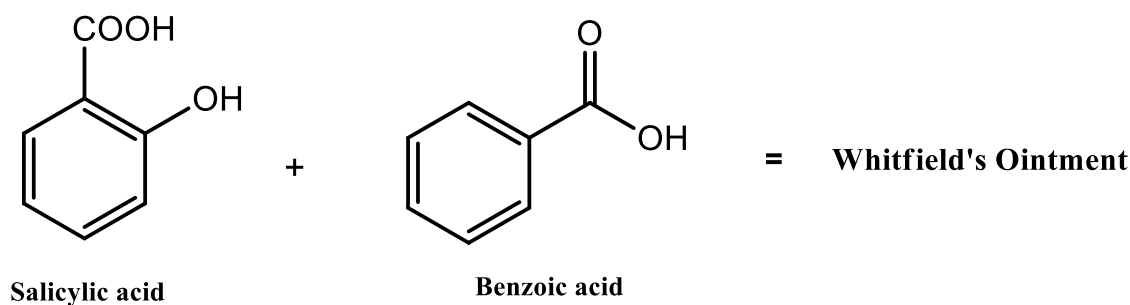


*Figure 2: Whitfield's Ointment.*²⁰

Another carboxylic acid, *p*-anisic acid or 4-methoxybenzoic acid (**Figure 3**) which is also synthesized in this project, is found in the anise plant and is used for herbal treatment, especially in some regions of Asia. It is stated in many studies that anise has many effects such as being anti-viral, anti-oxidant and anti-microbial due to the chemicals it contains. In the case of *p*-anisic acid, it is used as anti-microbial.²² At the same time, *p*-anisic acid is used as a plant-based preservative in cosmetic products and its wound healing properties have also been detected.²³ Perhaps most importantly, it should be noted that acetylsalicylic acid (ASA) (**Figure 3**), discovered by C. F. Gerhardt in 1853, known commercially as "Aspirin" was used in the treatment of many diseases and was called the most successful drug ever.²⁴⁻²⁶

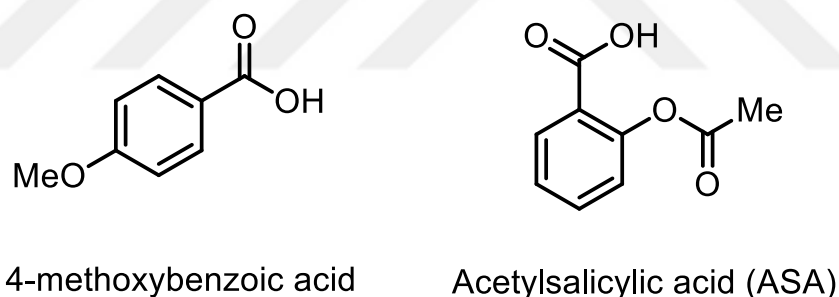
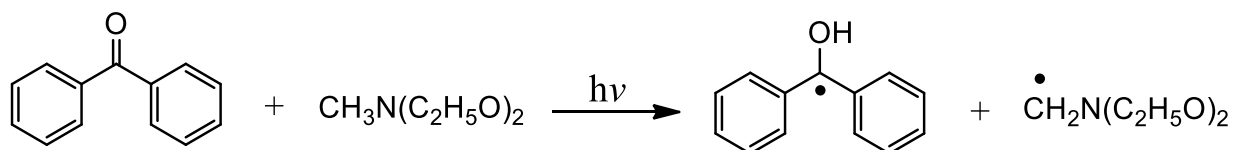


Figure 3: Structure of 4-methoxybenzoic acid and acetylsalicylic acid.^{22,24}

Aromatic ketones also form very important intermediates in the production of pharmaceuticals, agrochemicals and other industrial products such as dyes, cosmetics and so forth.²⁷ Benzophenone and its derivatives as aromatic ketones, which constitute a very important and large part of this project are widely used in industry. Starting with benzophenone itself, it is known to be a strong UV absorber used in personal care products such as sunscreens.²⁸ It is also used in flavoring, laundry and cleaning products, fragrances, plastics and coatings.²⁹ Adding different substituents

to benzophenone, its derivatives are not only used in the aforementioned industries but also used as photoinitiators (**Scheme 2**) which play a role in polymer chemistry.^{30,31}

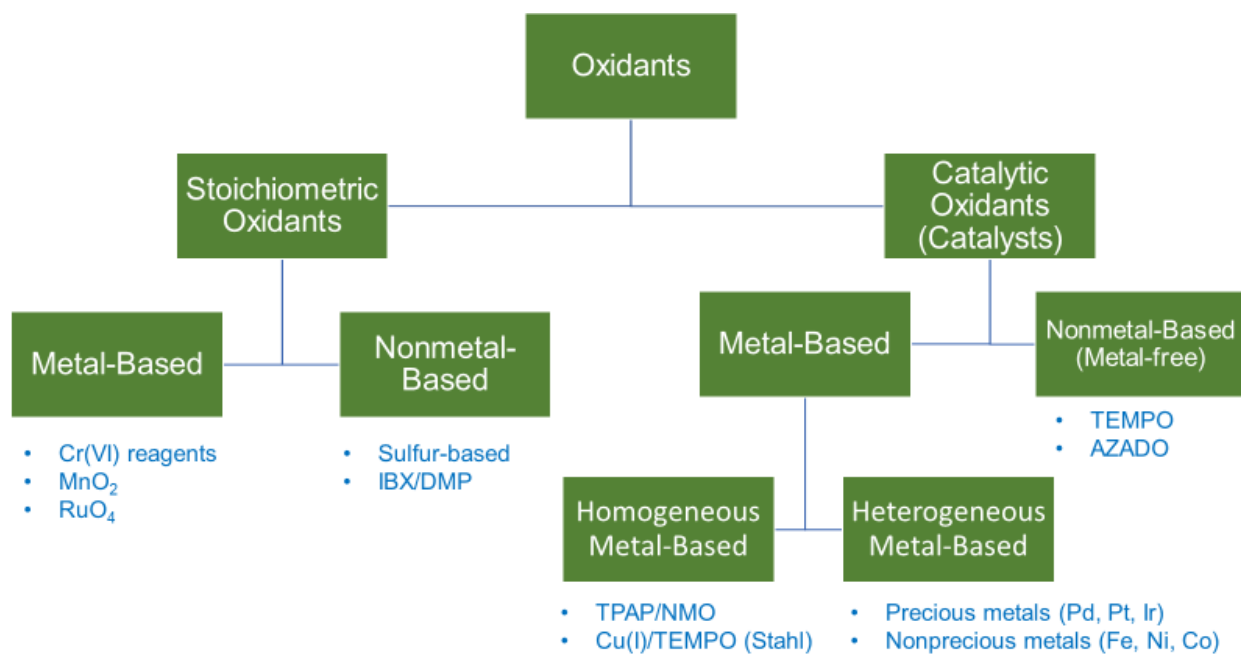


*Scheme 2: An example of benzophenone as a photoinitiator in its radical form.*³¹

As these substituents vary, benzophenone derivatives show important features that can be used as efficient treatment methods in medicine, regardless of whether they are synthetic or naturally occurring products.³²

To sum up, aldehydes, carboxylic acids and ketones are crucial both for chemical synthesis and industrial applications. Accordingly, in order to obtain these carbonyl groups, it is important to oxidize their corresponding alcohols by using a simple, environmentally friendly and low-cost method as these chemicals are needed in every field. In this way, the carbonyl products obtained are not only used in a single field but can also be combined with other synthesis methods for the fulfillment of this need.

1.1.2 Stoichiometric & Catalytic Oxidations



2

According to the definition of IUPAC, stoichiometry is the relationship between the amount of products resulting from a reaction and the amount of starting substances that react. Based on this definition, in order for a reacting substance to be a stoichiometric reagent, it is expected to be completely or partially consumed at the end of the reaction.^{33,34} As a result of this consumption of the stoichiometric reagent, waste formation is seen.³⁵ There can be a stoichiometric reagent in every reaction, so as for the oxidants which is the part that concerns this project, stoichiometric reagents are frequently used for oxidation reactions including O₂, H₂O₂, NaOCl, peroxides/hydroperoxides, *m*CPBA, KMnO₄, hypervalent iodine compounds, CrO₃ and some other metal or nonmetal-based reagents.³⁶ In order to distinguish them, stoichiometric reagents will be divided into two categories which are metal-based and metal-free stoichiometric reagents and some of the stoichiometric oxidants mentioned above will be discussed.

Catalysts are significant chemicals which reduce the activation energy (E_a) in a chemical reaction by providing a different reaction pathway and therefore facilitating it.³⁷ Catalysts can be divided into two classes regarding the phases of the reactants: homogeneous and heterogeneous. Homogeneous catalysts are in the same phase as the reactants, whereas heterogeneous ones are in a different phase.³⁸ In addition to stoichiometric oxidants, enzymes may inspire the development of catalysts for different types of reactions. Enzymes are types of proteins that catalyze the biological activities. Like all catalysts, they reduce the activation energy of the biological reaction at issue and in the absence of enzymes, the biological activities in human body for instance, would take several years.^{39,40} The field of catalysis has therefore become interesting in many different fields of science in recent years due to the desire to mimic enzymes found in natural systems from the aspect of functionality.⁴¹

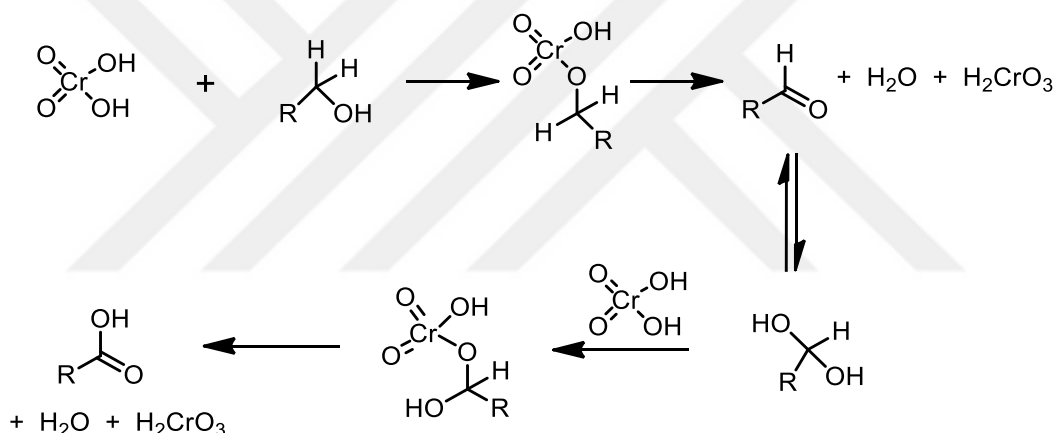
The most important feature that distinguishes catalytic reagents or catalysts from stoichiometric reagents is that catalysts are not consumed during the reaction. At the same time, catalysts provide an alternative pathway for reactions and can save energy and reagents in doing so.⁴² As mentioned above, the waste generated after the use of catalysts is less than the waste generated when using stoichiometric reagents.³⁵ For all these reasons, it can be said that catalysts are preferred over stoichiometric reagents.³⁵ At this point, catalysts should be classified as metal-based and metal-free catalysts, just like stoichiometric oxidants, but stoichiometric oxidants will be investigated first.

1.1.2.1 Metal-Based Stoichiometric Oxidations

Examples of the most commonly used metal-based stoichiometric oxidants are Cr-based PCC (pyridinium chlorochromate), PDC (pyridinium dichromate), Jones Reagent ($\text{CrO}_3/\text{H}_2\text{SO}_4$) and Collins Reagent (Dipyridine chromium(VI) oxide), while KMnO_4 , BaMnO_4 and MnO_2 can be

given as examples of Mn-based ones. In addition to these, RuO_4 and $\text{Ag}_2\text{CO}_3/\text{Celite}$ (Fétizon's reagent) are also encountered. These stoichiometric oxidants have advantages and disadvantages with different uses.

To start with the mentioned Cr-based reagents, PCC (Corey-Suggs reagent), PDC (Cornforth reagent), chromic acid (Jones reagent) and Dipyridine chromium(VI) oxide (Collins reagent), all are Cr(VI) oxidants and the reaction mechanisms are also common (**Scheme 3**).⁴³



*Scheme 3: General reaction mechanism for Cr(VI) oxidants.*⁴³

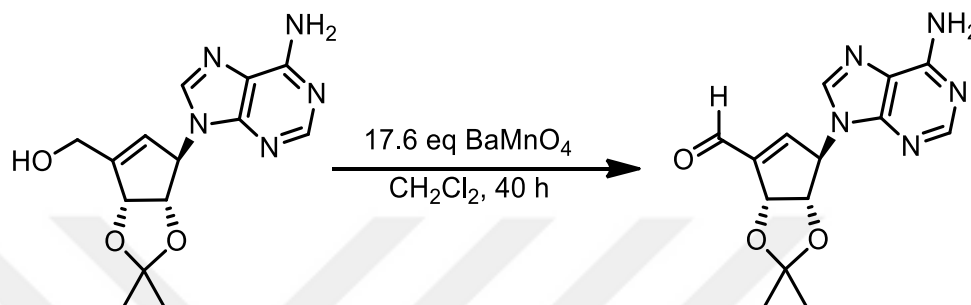
In historical order, $\text{CrO}_3/\text{H}_2\text{SO}_4$, known as the Jones reagent, was first introduced by E.R.H Jones and his colleagues in 1946. With this method, while primary and secondary alcohols are oxidized to aldehydes and ketones, aldehydes can also be further oxidized to carboxylic acids if water is present in the reaction medium. For this reason, it may be difficult to stop oxidation at the aldehyde stage.^{43–46} Following the Jones reagent is PDC, also known as the Cornforth reagent. In 1962, J.W. Cornforth presented the pyridinium salt of dichromic acid. PDC, just like Jones reagent, can oxidize primary and secondary alcohols to aldehydes and ketones in good yields, but does not

oxidize aldehydes to carboxylic acids because the reaction medium is anhydrous.^{45,47-49} After Cornforth, in 1972, J. C. Collins and W. W. Hess presented dipyridine chromium(VI) oxide. In fact, Collins reagent was developed by modifying $\text{CrO}_3 \cdot 2\text{Py}$ (Sarett reagent) by dissolving it in methylene chloride. Collins reagent also provides oxidation of primary and secondary alcohols to aldehydes and ketones with high yields. However, care should be taken when preparing Collins reagent as this complex is hygroscopic and can be explosive.^{45,50,51} Finally, in 1975, E.J. Corey and J. William Suggs developed PCC. PCC is obtained by precipitating CrO_3 with hydrochloric acid and pyridine in the presence of water. PCC, like other Cr(VI)-based oxidants, is used to oxidize alcohols to aldehydes and ketones with good yields.^{52,45,53} Although Cr(VI) oxidants are frequently used, especially in alcohol oxidation, and provide good results, they have many serious harmful effects. Cr(VI) reagents are IARC group 1 carcinogens. At short term exposure, Cr(VI) can cause skin or stomach allergies or ulceration. At long term exposure, nerve, kidney and liver damage can be observed as well as cancer or even death. Cr(VI) reagents are not only hazardous to human health but also to the environment. Therefore, The United States Environmental Protection Agency (US EPA) declared Cr(VI) reagents as one of the most threatening chemicals.⁵⁴⁻

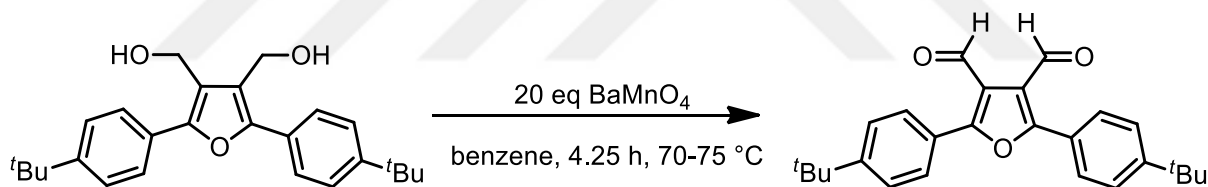
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Mn-based oxidants can be used in the oxidation of both alcohol and other functional groups due to the variable oxidation states of Mn from -3 to +7. Along with this advantage, KMnO_4 , BaMnO_4 and MnO_2 reagents are also used in oxidation reactions and are less harmful to human and environmental health than Cr(VI)-based oxidants.^{45,58,59} For example, in two different studies, BaMnO_4 was preferred over Swern and Pfitzner-Moffatt oxidation for two different reasons. While in the first study, BaMnO_4 was able to oxidize the allylic alcohol, which Swern, Pfitzner-Moffatt and PDC oxidations could not oxidize (**Scheme 4**).⁶⁰ In the other study, it was stated that BaMnO_4

was preferred over Swern for the oxidation of the diol in **Scheme 5** due to experimental convenience, although higher yields were obtained with Swern oxidation of the diol.^{61,62}



Scheme 4: Allylic alcohol oxidation with BaMnO₄.⁶⁰

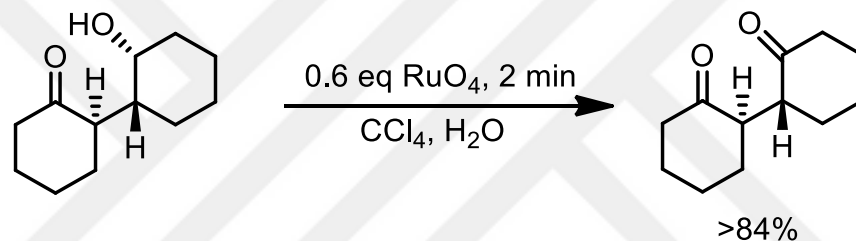


Scheme 5: Aromatic diol oxidation with BaMnO₄.^{61,62}

However, the most notable disadvantage is that the equivalents of both BaMnO₄ and MnO₂ are extremely high. As can be seen in the synthesis article of Marshall and Eidam, in order to oxidize 4-triisopropylsilyl-3-butyne-2-ol to its ketone analogue, MnO₂ was used in 336.9 mmol whereas the alcohol was used in 25.6 mmol.⁶³

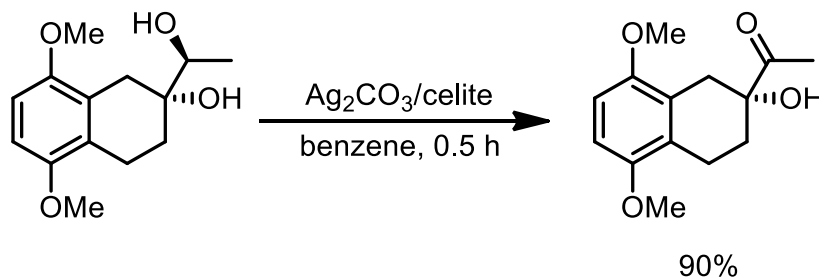
Known as a very strong oxidizing agent, RuO₄ is a highly volatile and chemically toxic solid. Ru element was discovered by Karl Karlovich Klaus which is one of the rarest elements in the earth and has no natural role. In addition to its chemical toxicity, due to an isotope of Ru, RuO₄ is also known as a radiotoxic agent and has been responsible for most of the radioactive pollution.^{64–66}

How reactive RuO_4 is can be considered in two ways: firstly, when looking at the reaction conditions of RuO_4 , it is seen that it is used in highly halogenated solvents because it can be flammable when reacting violently with organic solvents⁴⁵, and secondly, in the study of Berkowitz and Rylander in 1958, after stating that even very hindered primary and secondary alcohols are oxidized to carboxylic acids and ketones,⁶⁷ another study observed that alcohol oxidation was completed within minutes (**Scheme 6**).⁶⁸



*Scheme 6: Mild and quick oxidation with excess RuO_4 .*⁶⁸

Finally, if Fétizon's reagent is considered, it can be seen that Fétizon's reagent gives good results, especially in the oxidation of lactols to lactones and in the monooxidation of some symmetric diols.^{45,58} In the following example (**Scheme 7**), the use of Fétizon's reagent gave an α -hydroxyketone in 90% yield where Collins, PCC, PDC, Jones, Moffatt and Corey-Kim oxidations were unsuccessful.⁶⁹ The most important drawback of Fétizon's reagent may be its high price.⁴⁵



Scheme 7: Oxidation with Fétizon's reagent.⁶⁹

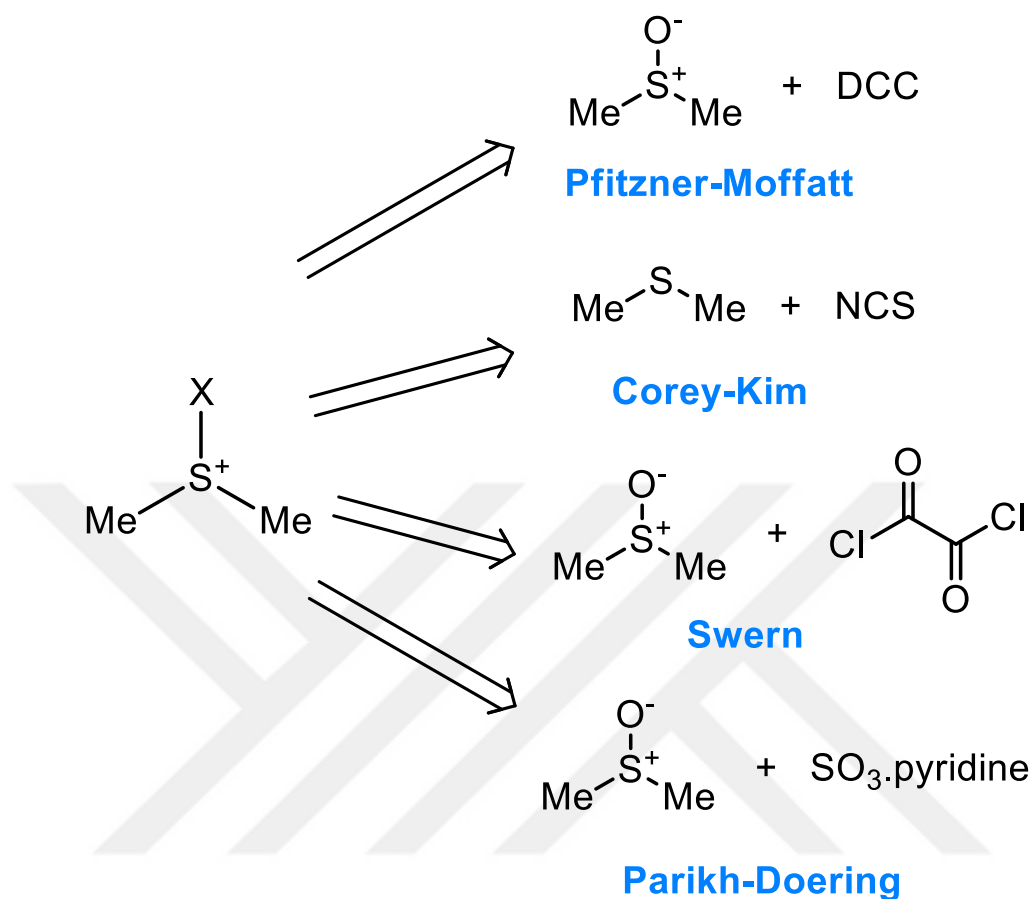
1.1.2.2 Nonmetal-Based Stoichiometric Oxidations

As well as metal-based stoichiometric oxidants, nonmetal-based stoichiometric oxidants are also frequently used. Some stoichiometric oxidants that can be examples of this group are: peroxy acids, sulfonium based oxidants, IBX (2-Iodoxybenzoic acid) and DMP (Dess-Martin periodinane).

Organic and inorganic peroxy acids containing the -OOH group have many uses. While the most well-known inorganic peroxy acid is peroxysulfuric acid (Caro's acid), two of the most common peroxides in organic synthesis are *m*CPBA and peracetic acid.⁷⁰ For example, Baeyer-Villiger oxidation synthesizes esters or lactones from ketones with the use of peroxy acids. In this case, the peroxy acid may also be *m*CPBA.⁷¹ *m*CPBA can be used in the oxidation of carbonyl compounds, alkynes, olefins, amines and imines, and many more due to its great reactivity.⁷² Despite having so many uses, *m*CPBA is shock sensitive, flammable, hygroscopic and explosive beyond 85% purity. It has also been reported to cause serious damage when it comes into contact with skin, hair or eyes.^{71,73}

DMS (Dimethyl sulfide) and DMSO (Dimethyl sulfoxide), which are sulfonium based oxidants and are widely used especially in the oxidation of primary and secondary alcohols (**Scheme 8**),

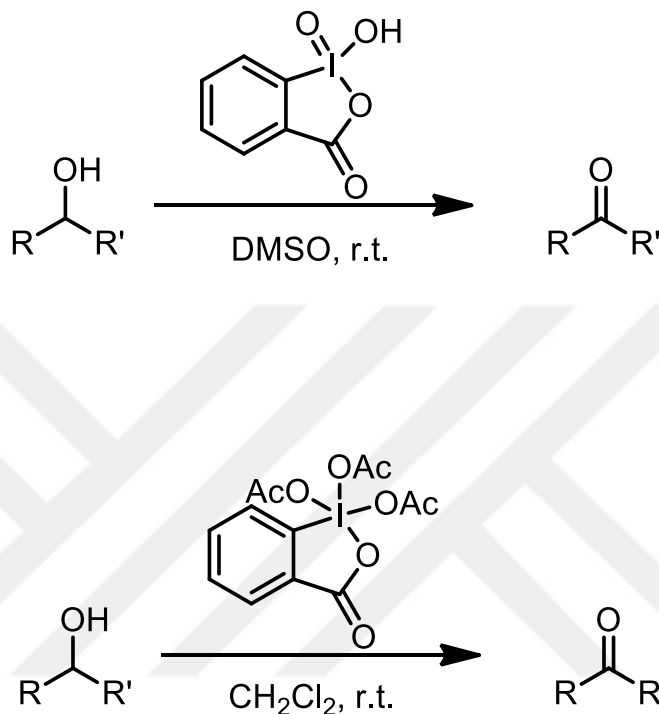
appear in Swern, Pfitzner-Moffatt, Parikh-Doering and Corey-Kim oxidations and all require different activating reagents such as DCC (*N,N'*-Dicyclohexylcarbodiimide), SO₃.pyridine, NCS (*N*-Chlorosuccinimide) and oxalyl chloride in order to activate DMSO or Me₂S.⁷⁴⁻⁷⁹ The unpleasant odor of Me₂S, low reaction temperature (-60 °C) of Swern oxidation and the release of toxic HCl and CO gases in a possible interaction of oxalyl chloride with water are the featured drawbacks.⁷⁴⁻⁷⁹ In Parikh-Doering and Corey-Kim oxidation, Me₂S gas may be released, similar to Swern oxidation, and at the same time, both SO₃ and pyridine are harmful to human health and the environment.^{80,81} It has also been reported that NCS is harmful to the aquatic environment.⁸² DCC, on the other hand, which is also used to activate DMSO in the Pfitzner-Moffatt oxidation, forms a urea derivative by-product called DCU (Dicyclohexylurea) at the end of the oxidation. The low solubility of DCU in organic solvents makes it difficult to separate it from the reaction medium.^{83,84}



Scheme 8: Named sulfonium-based oxidation reactions.⁵⁸

DMP and IBX are hypervalent iodine compounds that are involved in the oxidation of primary and secondary alcohols to aldehydes and ketones (**Scheme 9**).⁸⁵ In fact, although IBX has been known for 130 years, due to its low solubility in many organic solvents, it began to be used less frequently than Dess-Martin periodinane, as Daniel Benjamin Dess and James Cullen Martin modified IBX in 1983.^{86,87} Other reasons why IBX is less used include its low atomic economy, being potentially explosive, irritant, and expensive for high-scale reactions. The reasons why DMP is more advantageous than IBX are its features such as its ability to oxidize in a shorter time and under milder reaction conditions and its higher chemoselectivity. However, in addition to all these

advantages that DMP has over IBX, DMP also has low atom economy, can be explosive, and is expensive.⁸⁸⁻⁹¹



Scheme 9: Oxidation with IBX and DMP.⁴⁵

In this section where, stoichiometric reagents/oxidants are mentioned and exemplified, the number of these oxidants can be increased further. After explaining the general properties of stoichiometric oxidants and classifying them, catalytic reagents/oxidants will be discussed next.

1.1.2.3 Nonmetal-Based (Metal-free) Catalytic Oxidations

Catalysts that do not contain metal are called organic catalysts, and the field that studies these catalysts is called organocatalysis. These organic catalysts also increase the reaction rate, just like metal-based catalysts.^{92,93} Among the organic catalysts, the most commonly used ones in alcohol oxidation can be listed as TEMPO, AZADO and 1-Me-AZADO or other AZADO derivatives (**Figure 4**). In addition to these organic catalysts, a stoichiometric oxidant (also known as a

terminal oxidant) such as O_2 or NaOCl is generally used.^{58,94-96} It has been reported that the difference of TEMPO compared to AZADO derivatives is limited to primary alcohols. At the same time, it has been observed in a study that 1-Me-AZADO oxidizes alcohols with very high yields even under very low catalytic loading conditions.⁹⁴ The most obvious advantage that TEMPO has over AZADO and its derivatives is its relatively low price, considering that it is used in catalytic quantities, since AZADO is sold in lower quantities at a much higher price.^{97,98}

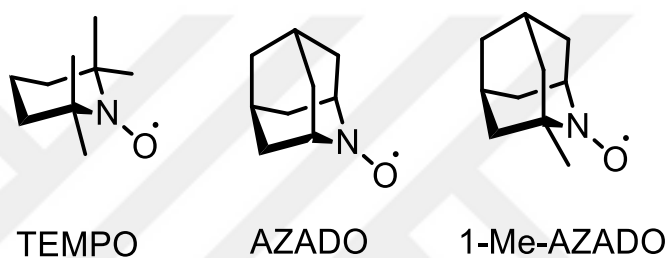


Figure 4: Structures of TEMPO, AZADO and 1-Me-AZADO.⁵⁸

1.1.2.4 Metal-Based Catalytic Oxidations

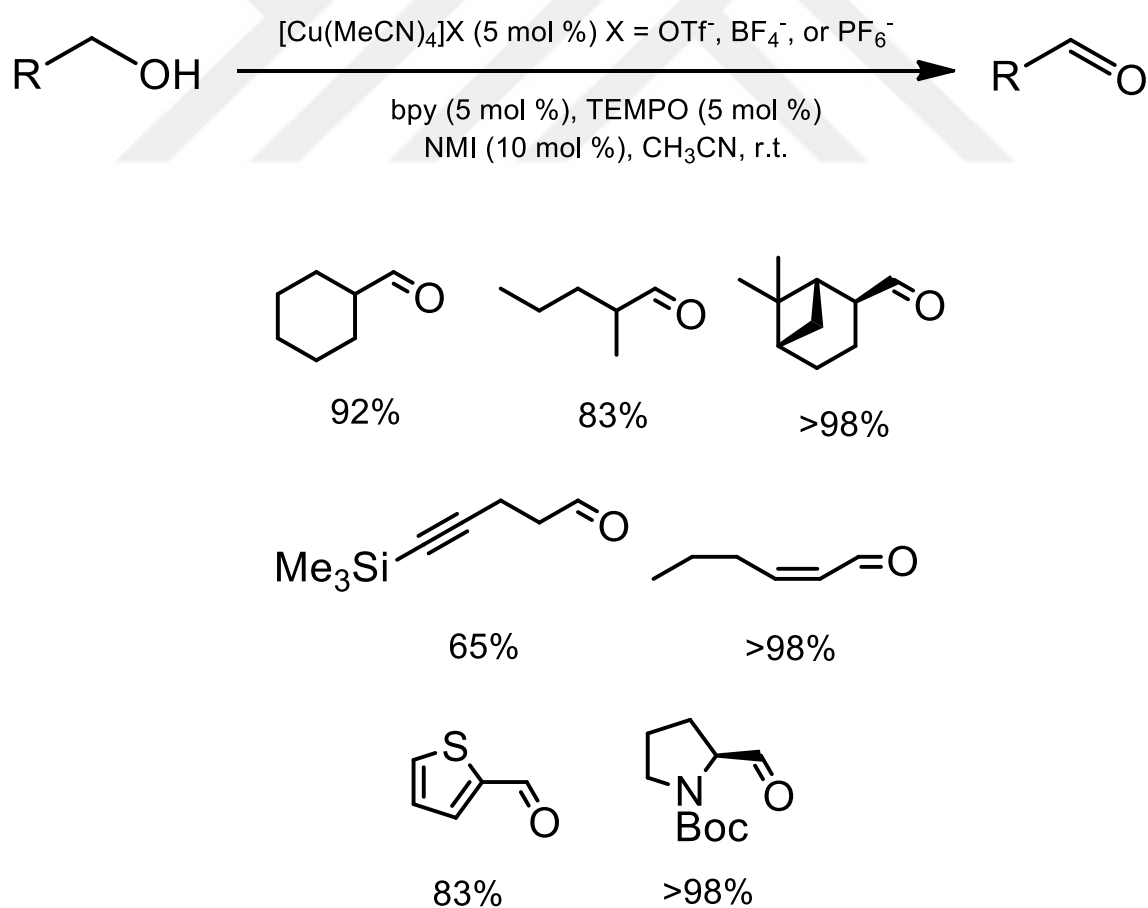
Metal-based heterogeneous catalysts adsorb different molecules separately, and after these molecules react on the surface of the catalyst, the molecules of the resulting products are desorbed.^{99,100} Metals can be found in different sizes such as single atoms, clusters or nanoparticles, and they can be used in many heterogeneous catalytic reactions due to the properties of each metal such as different particle size, shape, chemical composition or interactions with the solvent.¹⁰¹ Thanks to these different properties and therefore different uses, a broad range of reactions have been developed. Since there are many and important reactions in which metal-based catalysts are used, it is necessary to detail and exemplify this section, not just restrict it to alcohol oxidation at the beginning. For example, in the process developed by Fischer-Tropsch in 1925 and named after it, hydrocarbons are expected to be obtained as a result of the reaction of H_2 and CO ,

but since the reaction would be difficult to occur without a catalyst, Fe or Co was used as a catalyst in this process.^{100,102} Another reaction in which Fe is used is the Haber-Bosch process. In this process, developed by Haber and Bosch in 1909, ammonia was produced as a result of hydrogenation of inert N₂ gas using an iron catalyst.^{100,103} As a matter of course, the development of metal catalysts did not stop in the 20th century and continues today. Not only metals such as iron, nickel and cobalt, but also precious metals such as palladium, platinum, rhodium or ruthenium have been used as catalysts. While Pd catalysts are used in important reactions such as C-H activation, Suzuki-Miyaura coupling and Heck coupling, the Rh-based catalyst developed by Wilkinson is used in the homogeneous hydrogenation of acetylene and olefins.^{104–106} Many examples of metal-based catalysts can also be seen when the use of this catalyst is limited to alcohol oxidation. Studies in which primary and secondary alcohols are oxidized to aldehyde and ketone, respectively, as a result of the use of homogeneous TPAP (tetrapropylammonium perruthenate) with NMO (*N*-methylmorpholine *N*-oxide) and Stahl's oxidation (Copper(I)/TEMPO) are important examples of this.^{107,108} After the homogeneous metal-based catalysts, the precious and nonprecious metal-based heterogeneous catalysts mentioned above will be explained.

1.1.2.4.1 Homogeneous Metal-Based Catalytic Oxidations

Although there are many homogeneous metal-based catalysts for different types of reactions in the literature, TPAP/NMO and Copper(I)/TEMPO can be shown as the most suitable examples for alcohol oxidation. Since the homogeneous catalyst was defined before, it would be appropriate to point out that these two catalysts can be dissolved in organic solvents and therefore they are homogeneous as they are in the same phase with the reactants. The use of RuO₄ as a stoichiometric oxidant and its drawbacks were mentioned previously. The TPAP/NMO catalyst was also

mentioned for the first time in the Ley-Griffith oxidation.¹⁰⁹ This catalyst is more soluble in organic solvents than RuO₄ and can be seen as a milder version of RuO₄. Additionally, the catalyst can be recovered by adding terminal oxidant at the end of the reaction.¹¹⁰ Thanks to TPAP/NMO, primary and secondary alcohols can be oxidized to aldehydes and ketones, respectively.⁵⁸ The disadvantage of TPAP is that it is high priced even though it is used in catalytic amounts.¹¹¹ The other example will be the work of Stahl et al., in 2011, in which primary alcohols and diols without protecting groups were oxidized in a very wide substrate scope using the (bpy)Cu(I)/TEMPO catalyst system and molecular oxygen, and in 2013, they revealed the mechanism of this oxidation (**Scheme 10**).^{108,112}



*Scheme 10: Stahl oxidation with different substrates.*¹⁰⁸

1.1.2.4.2 Heterogeneous Metal-Based Catalytic Oxidations

Elements such as Ru, Pd, Pt and Ir are called precious metals, and these metals are used as catalysts in various reactions including alcohol oxidation.^{113,114} Pd(OAc)₂, one of the Pd catalysts, showed excellent results in a study, especially in the oxidation of benzylic alcohols with only 0.05 mmol of use.¹¹⁵ Pt catalysts are also used in alcohol oxidation. For example, in the study of Kon et al., Pt black-SiO₂ catalyst oxidized (E)-cinnamyl alcohol and many other types of alcohols in a flow reactor system in the presence of H₂O₂.¹¹⁶ The same good results can be seen for Ru-based catalysts. In the work of Zou et al., it can be seen that benzylic alcohols with different substituents are oxidized with very high yields in a short time and at room temperature with the Ru(III)-based catalyst they synthesized.¹¹⁷ Finally, the Ir-based IrNP@NiO (Iridium catalyst on NiO) catalyst oxidized alcohols to which alkyl, aryl and heteroaryl groups were attached to carboxylic acids.¹¹⁸ Although precious metal catalysts provide such good results in the areas where they are used, they have some disadvantages. First of all, considering the current reserves of these metals, it is predicted that they will be consumed within 50-100 years.¹¹⁹ Therefore, elements such as rhodium, palladium, ruthenium and iridium, which were frequently used in the past in catalyst synthesis, have now begun to be avoided due to being expensive, toxic and having limited source and access. As an alternative, transition metals such as iron, nickel, cobalt and manganese, which do not have these disadvantages, that is, are less harmful to the environment, are less expensive and are easier to access due to their abundance, have begun to be used with an increasing interest.¹²⁰⁻¹²² The transition metals mentioned here and others are called earth-abundant metals as a whole and according to geochemical studies, within the scope of transition metals, iron is the most abundant whereas manganese is the third one (**Figure 5**).^{123,124} For the reasons mentioned above, the field of green chemistry or green catalysis is constantly evolving. With the intention of having a rough

idea on why and how it has been evolved until now, this case can be considered: In Anastas and Kirchoff's publication in June 2002, it is remarked that with the green chemistry applications becoming prevalent starting from then, “fundamental scientific methods” that can protect human health and the environment and be economic at the same time, have begun to be used. In the “History” section of the article, it is understood that the aim of these actions in the United States, is to prevent an environmental problem from existing in the first place, rather than to solve it after arising, and thus to maintain a more sustainable life.¹²⁵

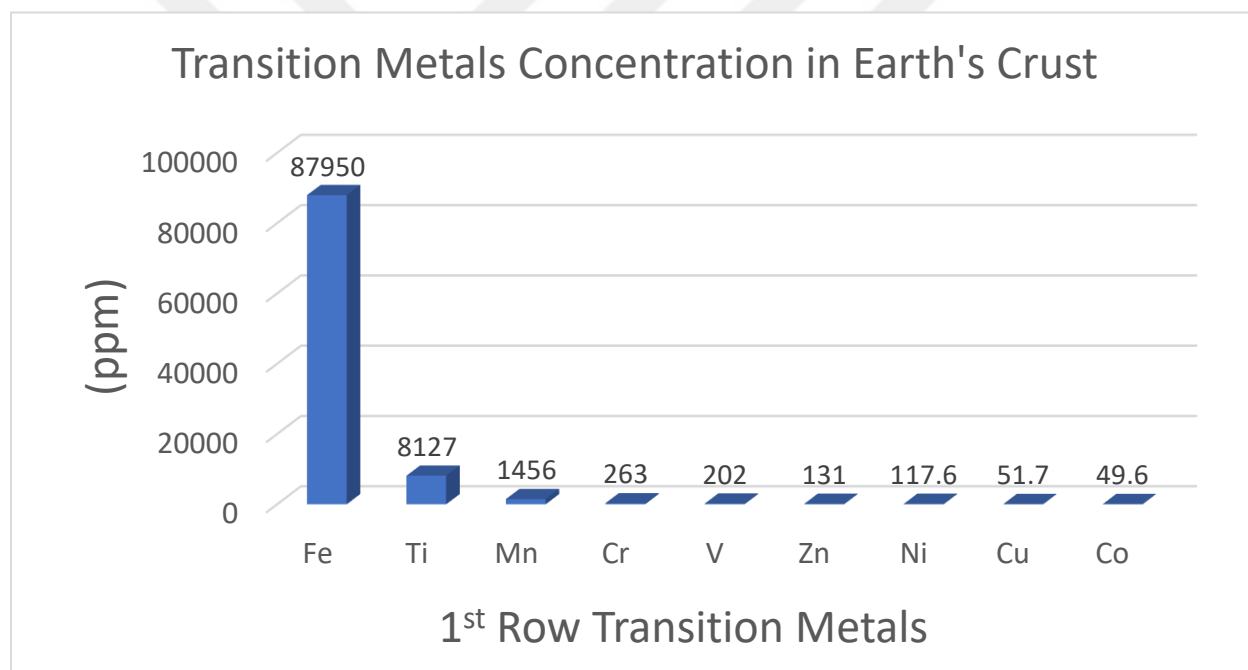


Figure 5: Abundance of 1st Row Transition Metals.^{123,124}

Apart from their practical and environmental features, according to Bullock et al. the use of these transition metals has also useful chemical features, claiming that these transition metals have good reactivity profiles, corresponding to their electronic structures, thermochemical and kinetical features.¹²⁶ These nonprecious metal-based catalysts do not have to be synthesized solely by single metal-ligand interaction. For example, there are also mixed metal hydroxide catalysts synthesized

by the combination of divalent and trivalent metals.¹²⁷ Mixed metal hydroxide catalysts are composed of two or more metals with hydroxides. These catalysts can be encountered in different fields such as electrochemistry or organic chemistry. Analyzing the working principle of these catalysts can be challenging, although the mixed metals are stated to increase the performance of the catalyst due to their multiple oxidation states, when compared to their single metal analogues.^{128–132} Catalysts where nonprecious metals are used with a ligand or as mixed metal hydroxide can be exemplified respectively. Ni, one of the nonprecious metals, oxidized benzyl alcohol derivatives and benzhydrol derivatives with good yields when used as a Ni-alumina catalyst.¹³³ In another example, aerobic alcohol oxidation to carboxylic acid is done with a Fe-based catalyst.¹³⁴ Co-based Co@NC catalyst was also used in the oxidative esterification reaction.¹³⁵ In addition to all these examples, our research group used LaMnO₃ perovskite¹³⁶ and Ni_{0.6}Mn_{0.4}(OH)_y¹³⁷ catalysts, which were synthesized in the collaboration study with Ozensoy Research Group carried out in previous years, in C-H activation and alcohol oxidation. These catalysts, which were synthesized without the problems such as sustainability, cost, and toxicity encountered in precious metal catalysts, were also used in the C-H and alcohol oxidation reactions without using a very costly system such as the flow reactor. Similarly, in the current work, the preparation of Fe_{0.6}Mn_{0.4}(OH)_x catalyst was performed by Ozensoy research group using the earth abundant metals Fe and Mn. The properties of this synthesized catalyst and its results in C-H activation were revealed in the M.Sc. theses of Erdivan¹³⁸ and Calikyilmaz¹³⁹. In this project, we investigated the oxidation of benzylic alcohols, 1-phenylethanol derivatives and benzhydrol derivatives using the Fe_{0.6}Mn_{0.4}(OH)_x catalyst. We also tried to gather information about the reaction mechanism through control experiments and a kinetic isotope effect experiment. The oxidation results of this mixed metal hydroxide catalyst to the mentioned alcohols will be

discussed in the results and discussion section. To conclude, from the point of organic reactions requiring catalysts, overuse of precious metals is only one problem which is being tried to be solved by developing different methods/catalysts by using earth abundant metals and our study also focuses on the solution of this problem and aims to contribute.

1.1.3 The Aim of the Project

The structure and properties of the $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ mixed metal hydroxide catalyst synthesized by Ozensoy Research Group and its use in C-H activation were discussed in the M.Sc. theses of Erdivan¹³⁸ and Çalıkyılmaz¹³⁹. The aim of this project is to use the same catalyst and observe its effect on aerobic alcohol oxidation reactions. The catalyst contains the earth abundant metals Fe and Mn with hydroxide and it has been stated that this type of mixed metal hydroxide catalysts has an increased efficiency on the reaction due to their multiple oxidation states.¹²⁶ Thus, this catalyst, which was developed using metals that are not harmful to human health and the environment, are inexpensive and have less risk of depletion in nature than precious metals, was used in aerobic alcohol oxidation after C-H activation.

For this purpose, a model reaction was first chosen to find out under what conditions these oxidation reactions would be carried out, and this model reaction is the oxidation of benzhydrol to benzophenone. Using this model reaction, factors such as temperature, solvent type, and catalyst amount were tested, provided that the amount of benzhydrol was kept constant. After the optimized reaction conditions were determined as a result of the experiments, benzhydrol derivatives with different electron withdrawing and donating substituents were oxidized using this catalyst. In the second stage, benzyl alcohol and its derivatives and 1-phenylethanol and its derivatives were reacted under the same conditions. In the last stage, kinetic isotope effect experiment and various control experiments were carried out to obtain information about the function of this catalyst in

aerobic alcohol oxidation, that is, the mechanism of the reaction. As a result of the study, it was seen that the structure of the alcohol, the amount of catalyst, temperature and the type of solvent also affected the result of oxidations.



1.2 RESULTS & DISCUSSION

1.2.1 Optimized Reaction Conditions for Benzhydrol and Derivatives

In the first part of this work, we focused on the optimization of the reaction conditions for the catalytic oxidation of benzhydrol (**1a**) to benzophenone (**2a**) using the $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ mixed metal hydroxide catalyst. The amount of catalyst used in this transformation as well as the temperature and time parameters were examined. While optimizing the reaction conditions required for the conversion of the benzhydrol model molecule to benzophenone, the optimized conditions for the conversion of the fluorene molecule to fluorenone in the previous C-H activation study were taken into consideration, and all of the reactions below were carried out twice and the average conversion was calculated with each trial's conversion (**Table 1**). Accordingly, it was first tested at 90 °C with 15 mg catalyst for 24 h, giving 91% conversion (entry 1). Afterwards, when the amount of catalyst and time were kept the same and the temperature was increased to 100 °C, the conversion was found to be >99% (entry 2). Later, in order to investigate the effect of the amount of the catalyst, the reaction was again carried out at 100 °C and for 24 h with 12 mg of catalyst instead of 15 mg per 0.5 mmol of substrate. As a result of this experiment, it was seen that the conversion decreased from >99% to 96% (entry 3). In the 4th experiment, it was observed that when the time was decreased from 24 h to 8 h, the conversion decreased to 82% while the catalyst amount was 15 mg and the temperature was 100 °C. The 5th experiment gave the same positive results as the 2nd experiment in which the only variable was the temperature increased from 100 °C to 110 °C. In the 6th experiment, the amount of catalyst was reduced to 10 mg but the temperature was increased to 110 °C and the result was 87% conversion. In the last two experiments (entries 7 and 8), the amount of catalyst was 15 mg and the temperature was 110 °C,

but the reaction time was 16 and 8 h, respectively. Although the conversion rate was >99% in both experiments, it is not known whether 8 or 16 h of reaction time will be sufficient when different substituents are attached to benzhydrol. Therefore, 24 h was chosen as the safest time. In addition, if these experiments are carried out in academia or industry, the experiment duration of 8 and 16 h may not be preferred since the removal of the catalyst and the isolation and characterization of the pure substance after the end of the experiment will take a long time. In other words, 24 h was considered to be the most appropriate time for the researcher to effectively use the time during the experiment and the following procedure afterwards. Again, when different substituents were added to benzhydrol, 100 °C was found to be insufficient, so we decided to run the experiments at 110 °C. As a result, the best reaction conditions were determined as 15 mg catalyst, 110 °C temperature and 24 h, excluding only benzhydrol and 4,4'-difluorobenzhydrol which were reacted at 100 °C.

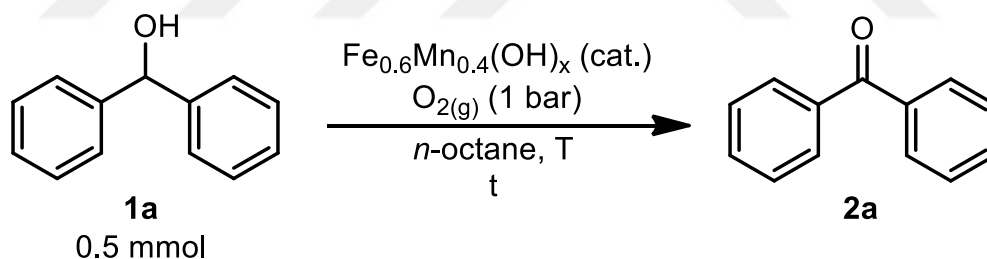


Table 1: Optimization of the reaction conditions for benzhydrol (1). *

Entry	Catalyst amount (mg)	Temperature (°C)	Time (h)	Conversion 1 (%)	Conversion 2 (%)	Average Conversion (%)
1	15	90	24	93	89	91
2	15	100	24	>99	>99	>99
3	12	100	24	93	99	96
4	15	100	8	71	93	82
5	15	110	24	>99	>99	>99
6	10	110	24	96	78	87
7	15	110	16	>99	>99	>99
8	15	110	8	>99	>99	>99

*Each experiment was performed separately twice with 2 mL of *n*-octane as solvent per 0.5 mmol of substrate.

1.2.2 Catalytic Oxidation of Benzhydrol, Benzyl Alcohol and 1-Phenylethanol

Derivatives

After the reaction conditions were optimized for the benzhydrol molecule, other benzhydrol derivatives were also examined under the same conditions except temperature and solvent. The temperature was kept at 100 °C for some substrates and 110 °C for others (**Table 2**). In addition, while the solvent used under the optimized condition was *n*-octane, chlorobenzene as a more polar solvent was used as the solvent instead of *n*-octane in some substrates that had solubility problems. When deciding to use *n*-octane and chlorobenzene as solvents, it was considered that the boiling points of both solvents were higher than the temperature at which the reaction took place. After reacting benzhydrol (**1a**) at 100 °C and in *n*-octane, 90% yield was obtained by column chromatography (Table 2, entry 1). Then, electron donating groups such as -CH₃ (**2b**), -OMe (**2c**) and -NMe₂ (**2d**) attached to benzhydrol in para position symmetrically were tested, and after column chromatography, 76%, 99% and 70% yields were obtained, respectively (entries 2-4). Additionally, when compound **2b** was reacted in chlorobenzene instead of *n*-octane, it was observed that it gave 99% conversion (entry 2). This reaction was tested only once due to lack of material. Here, an isolation problem also occurred in the derivative of benzhydrol with -NMe₂ (**2d**) attached to both sides, as can be seen in the table below (**Table 2**), that is, while the conversion percentage from alcohol to ketone was 93% on average, the yield obtained as a result of column chromatography dropped to 70%. The reason for this loss is that we encountered solubility problem both during isolation by column chromatography and characterization by ¹H-NMR of the compound **2d** - also known as Michler's ketone -. Again, >99% conversion and 99% yield were

obtained when the electron donor -CH_3 (**2e**) group attached to benzhydrol was in the ortho position with respect to the alcohol group (entry 5).

After testing the effect of electron-donating groups, reactions have also been tried with electron withdrawing groups. Initially, the derivative of benzhydrol with the -F group (**2f**) added symmetrically on both sides and the -Cl derivative (**2g**) added to benzhydrol from one side were tested. The isolated product yields obtained with these two electron-withdrawing groups were >99% and 97%, respectively (entries 6 and 7). After testing the symmetrical and unsymmetrical positioning of the electron-withdrawing groups, the effect of the -CF_3 group, which is also electron-withdrawing and asymmetric, but is attached to benzhydrol from different positions, was tested. When testing -CF_3 groups, the conversion from alcohol to ketone could not be calculated because the peaks in the $^1\text{H-NMR}$ spectrum had a broad appearance. Therefore, the isolated product yield values obtained directly after column chromatography were calculated without calculating the conversion percentage. Accordingly, based on the alcohol group of benzhydrol, the -CF_3 groups in the ortho (**2h**), meta (**2j**) and para (**2i**) positions have different yields. The yields obtained for ortho, meta and para positions are 53%, 98% and 72%, respectively (entries 8-10). The -CF_3 group is an electron withdrawing group and withdraws electrons most effectively from ortho and para positions. For this reason, the benzhydrol derivative with the -CF_3 group at the meta position is relatively the most electron rich among these three benzhydrols, and it provided the oxidation product **2j** with the highest yield (98%). Likewise, benzhydrols with the -CF_3 groups at the ortho and para positions are relatively electron deficient leading to lower reaction yields (53% and 72%, respectively).

When the derivatives of benzhydrol with electron-withdrawing and donating groups are examined, it is seen that they are oxidized with very high yields, except for two derivatives with the -CF_3

group attached (**2h** and **2i**). Therefore, it can be said that a wide substrate scope is obtained when oxidizing benzhydrol derivatives to benzophenone derivatives.

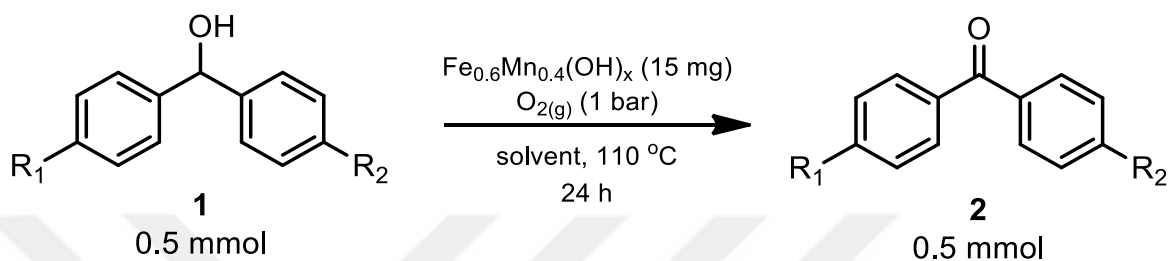
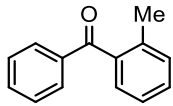
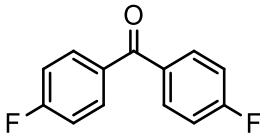
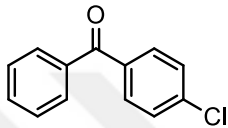
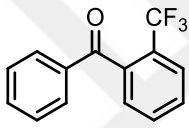
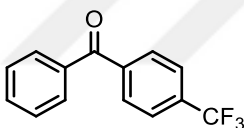
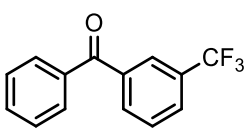


Table 2: Catalytic oxidation of substituted benzhydrol derivatives.

Entry	Product	Solvent (2 mL)	Conversion 1 (%)	Conversion 2 (%)	Average Conversion (%)	Yield (%)
1	2a	<i>n</i> -octane (100 °C)	>99	>99	>99	90
2	2b	<i>n</i> -octane	77	65	71	76
		chlorobenzene	>99	-	-	-
3	2c	chlorobenzene	>99	>99	>99	>99
4	2d	chlorobenzene	92	94	93	70

5	 2e	<i>n</i> -octane	>99	>99	>99	99
6	 2f	<i>n</i> -octane (100 °C)	>99	>99	>99	>99
7	 2g	chlorobenzene	>99	>99	>99	97
8	 2h	chlorobenzene	-	-	-	53 ^a
9	 2i	chlorobenzene	-	-	-	72 ^b
10	 2j	chlorobenzene	-	-	-	98 ^c

^a This experiment was performed twice and the yields were 52% and 54%. ^b This experiment was performed twice and the yields were 68% and 75%. ^c This experiment was performed twice and the yields were 99% and 97%.

The benzhydrol derivatives that were tested in the previous section as substrates were all doubly-benzylic secondary alcohols. Next, we sought to investigate the oxidation of mono-benzylic secondary alcohols using the newly developed catalytic alcohol oxidation method. To this end, 1-phenylethanol derivatives were also reacted under the same conditions. When 1-phenylethanol (**3**) is oxidized, it forms acetophenone product (**4**), which is a volatile substance with an intense odor.

Therefore, CH₂Cl₂ and *n*-pentane were used as mobile phases when performing column chromatography of such volatile substances. While acetophenone was obtained with 82% yield (Table 3, entry 1), the apocynin (**6**) was obtained in only 18% yield (entry 2). The reason for this low yield is thought to be that the other -OH group in the aromatic ring may also be oxidized and a quinone derivative may be formed. The compound ethyl benzoylformate (**8**) was isolated next in 14% yield (entry 3). When ethyl mandelate (**7**) was oxidized to ethyl benzoylformate (**8**) with 15 mg of catalyst, an aldehyde peak was observed in the ¹H-NMR spectrum, which made us think that this compound may have undergone a C-C bond cleavage presumably after a potential hydrolysis of the ethyl ester. When this compound was synthesized with 20 mg of catalyst, no aldehyde peak was observed and 14% yield was obtained (entry 3). The last 1-phenylethanol derivative obtained was 2-chloroacetophenone (**10**) and the yield of this compound was very low (3%; entry 4). It is thought that since the chlorine atom is electronegative, it withdraws the electron from the carbon to which it is bonded and makes this carbon open to nucleophilic attack. For compounds **6**, **8** and **10**, multiple spots were observed in TLC analysis. In this section, the menthol compound was tested last as substrate, but menthol (**11**) was not oxidized to menthone (**12**). For this reason, it is possible to say that this oxidation method has a limited scope for non-doubly-benzylic secondary alcohols. Overall, it can be concluded that the success of our methodology increases with the number of benzylic positions in the substrates. In other words, doubly-benzylic secondary alcohols work better than mono-benzylic secondary alcohols whereas menthol as a non-benzylic secondary alcohol did not get oxidized with our method. Reactive intermediates such as radicals or carbocations are well-known to be stabilized at the benzylic positions. Even though the mechanism is uncertain, this type of stabilization of intermediates at the benzylic position may explain the observed reactivity trend.

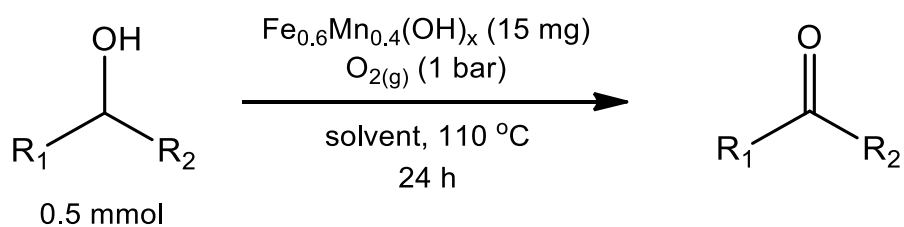
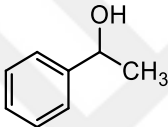
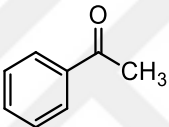
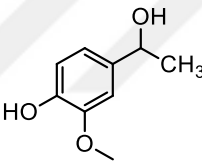
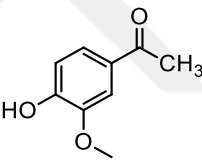
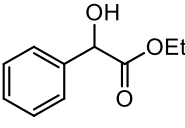
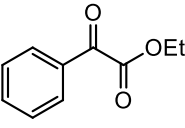
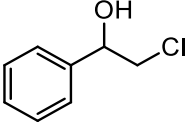
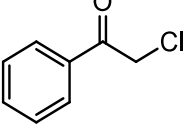
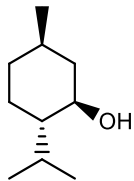
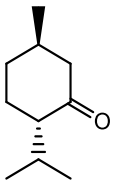


Table 3: Catalytic oxidation of 1-Phenylethanol and derivatives.

Entry	Substrate	Solvent (2 mL)	Product	Yield (%)
1	 3	<i>n</i> -octane	 4	82
2	 5	chlorobenzene	 6	18
3	 7	chlorobenzene	 8	14 ^a
4	 9	chlorobenzene	 10	3

5	 11	chlorobenzene	 12	-
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^a 20 mg of catalyst per 0.5 mmol of substrate was used in this experiment.

In the next phase of our work, the catalytic oxidation of benzylic primary alcohols was examined. When the oxidation of unsubstituted benzyl alcohol (**13a**) was tested at 110 °C in *n*-octane as solvent, benzaldehyde (**14a**) was isolated in 92% yield (Table 4, entry 1). Similarly, the oxidation of 4-methylbenzyl alcohol (**13b**) proceeded smoothly to afford 4-methylbenzaldehyde (**14b**) in 82% yield (entry 2). We should mention that in both of these reactions, oxidation stopped at the aldehyde stage in both compounds. However, when a stronger electron donating methoxy group was present, 4-methoxybenzaldehyde (**14c**) was obtained in 74% yield along with the formation of 4-methoxybenzoic acid (**14c'**) in 24% yield as a result of further oxidation (entry 3). 4-nitrobenzaldehyde (**14d**), which contains the electron-withdrawing -NO₂ group, was obtained in 72% yield at 110 °C, while this yield increased to 84% at 130 °C (entries 4 and 5). This may indicate that the oxidation in the presence of electron withdrawing group -NO₂ required higher temperatures in order to obtain higher yields. To summarize, benzyl alcohol derivatives with electron donating groups were oxidized in higher yields whereas the derivative with electron withdrawing group was oxidized in lower yield.

5-hydroxymethyl furfural (HMF) is one of the most valuable chemicals obtained from biomass as the chemicals obtained from biomass provide an alternative to fossil-based chemicals. As a result of the oxidation of HMF, while 2,5-furandicarboxylic acid obtained is an alternative for petroleum-based polyesters, 2,5-furandicarboxaldehyde is considered as an alternative for petroleum-based

polyimine vitrimers.^{140,141} In our work, 2,5-furandicarboxaldehyde (**16**) was obtained under 3 different conditions. In the first condition, 15% yield was obtained with 15 mg catalyst at 110 °C, 26% yield was obtained with 15 mg catalyst at 130 °C, and 55% yield was obtained with 50 mg catalyst at 130 °C.

Finally, in this project, two drug molecules, fexofenadine (**17**) and chloramphenicol (**18**), were tried to be oxidized, but no reaction was observed in either of them.

As a result, successful results were obtained in primary benzylic alcohols and benzhydrol derivatives, but no results were obtained in large molecules such as drug molecules due to the fact that other functional groups may inhibit the catalyst activity. On the other hand, 1-phenylethanol derivatives were not as successful as benzyl alcohol or benzhydrol derivatives except for the parent 1-phenylethanol (**3**).

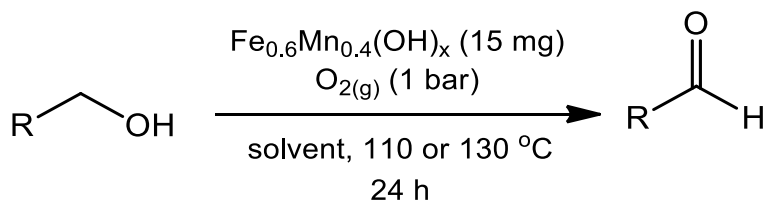
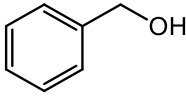
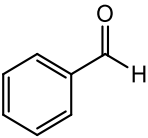
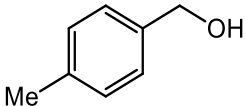
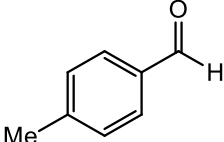
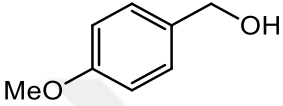
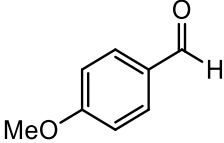
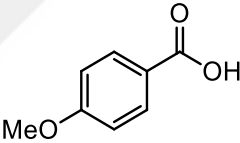
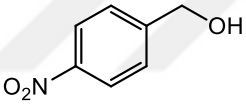
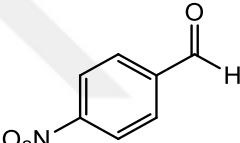
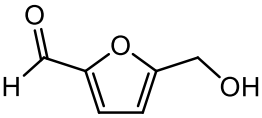
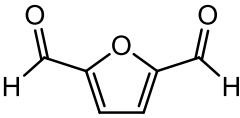
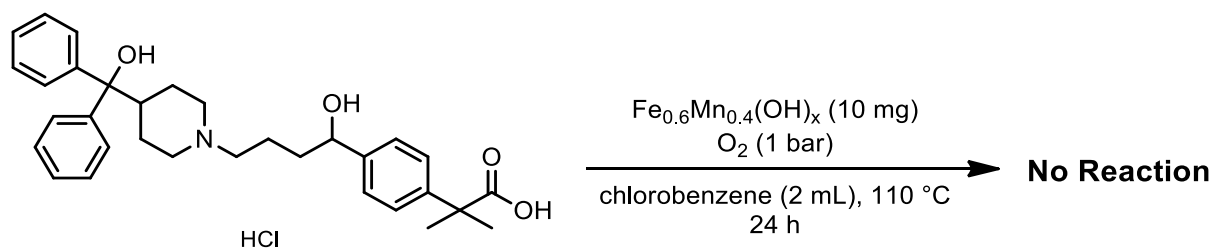


Table 4: Catalytic oxidation of benzyl alcohol derivatives and HMF.

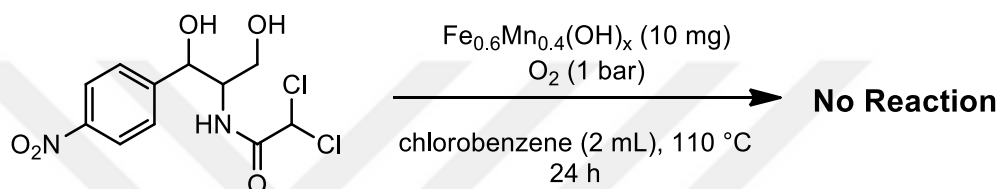
Entry	Substrate	Temperature (°C)	Solvent	Product	Yield (%)
1	 13a	110	n-octane	 14a	92

2	 13b	110	<i>n</i> -octane	 14b	82
3	 13c	110	chlorobenzene	 14c +  14c'	74 (14c) + 24 (14c')
4	 13d	110	chlorobenzene	 14d	72
5		130			84
6	 15	110	chlorobenzene	 16	15
7		130	chlorobenzene		26
8		130 ^a	chlorobenzene		55

^a 50 mg of catalyst per 0.5 mmol of substrate was used in this experiment.



Fexofenadine (17)
0.25 mmol



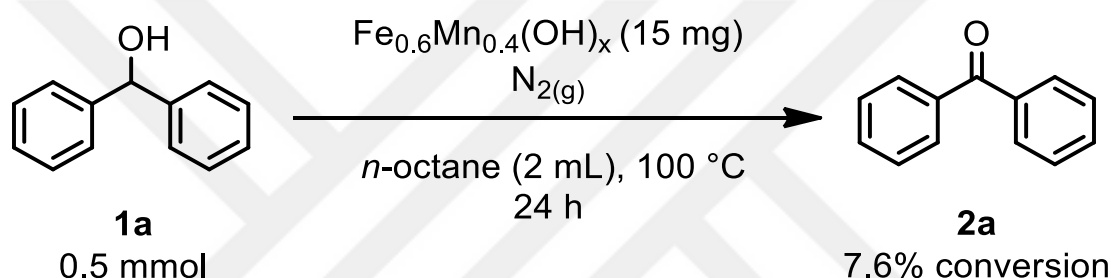
Chloramphenicol (18)
0.25 mmol

1.2.3 Control Experiments & Mechanistic Studies

1.2.3.1 Effect of Deoxygenation

In the first control experiment, the effect of oxygen on the reaction outcome was investigated. The experiment of the conversion from benzhydrol (**1a**) to benzophenone (**1b**) was repeated again under optimized reaction conditions but, in this instance, in an oxygen-free and inert atmosphere to understand whether the molecular oxygen used in the experimental procedure had an effect on the experimental results (**Scheme 11**). For the conduct of this experiment, an experimental procedure from a previous study was followed.¹³⁶ Molecular oxygen was removed from the reaction medium using the "freeze-pump-thaw" technique as in this procedure. Following this method, molecular oxygen was removed from the reaction medium and the reaction was carried out under N_2 gas instead. The result was checked by ^1H -NMR spectroscopy and as a result of the

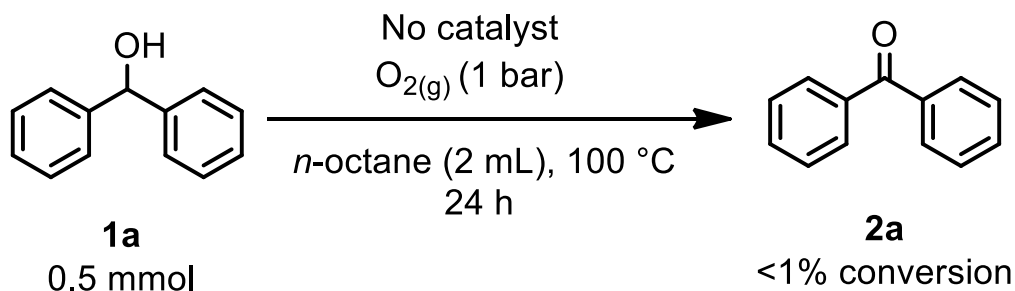
analysis, it was determined that benzhydrol was converted to benzophenone with only 7.6% conversion in an oxygen-free environment. This 7.6% conversion may have occurred due to the small amount of oxygen remaining in the solvent or oxygen leaking into the reaction medium from outside. However, as a result of this experiment, the significance of the presence of oxygen as the stoichiometric oxidant along with the catalyst for the alcohol oxidation is seen.



*Scheme 11: Effect of $\text{O}_{2(g)}$ on the catalytic oxidation of benzhydrol (**1a**) to benzophenone (**2a**).*

1.2.3.2 Effect of the Catalyst

In the second control experiment, the effect of the catalyst was investigated. In other words, it was aimed to test whether only molecular oxygen would act as an oxidant by itself, without using any catalyst in the reaction medium, and whether benzhydrol would be oxidized to benzophenone under the optimized reaction conditions (**Scheme 12**). Consequently, the optimized experimental procedure was followed exactly, only without the use of the catalyst. As a result of this experiment, it was observed that benzhydrol did not convert to benzophenone without the use of the catalyst, which shows that molecular oxygen is not sufficient for oxidation and the catalyst is necessary.



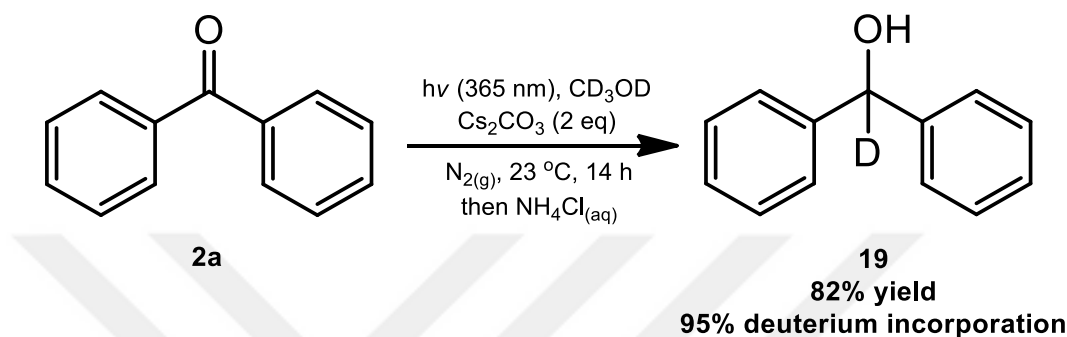
Scheme 12: Effect of the catalyst on the catalytic oxidation of benzhydrol (1a) to benzophenone (2a).

1.2.3.3 Kinetic Isotope Effect

Kinetic isotope effect experiments are one of the most useful tools when investigating the chemical kinetics of a reaction. In a kinetic isotope effect experiment, one atom of the reactant is replaced with its heavier isotope and so a decrease in the rate of this chemical reaction is observed. By this way, either a primary or a secondary kinetic isotope effect is found. In a primary kinetic isotope effect, the bond involving the isotope is broken and this breakage is directly the rate-determining step whereas in a secondary isotope effect, the bond breakage involving the isotope does not affect the rate-determining step. For instance, considering the exchange of H atom with its heavier isotope D (C-H replaces with C-D in this case), the reason for this decrease can be explained as follows: when hydrogen atom is replaced with deuterium, as deuterium is heavier than hydrogen, a reduction will be seen in the zero-point energy of the bond which means the activation energy for C-D bond will be higher than that for C-H bond. When the ratio $k_{\text{C-H}}/k_{\text{C-D}} > 1$, it is called a normal kinetic isotope effect and when $k_{\text{C-H}}/k_{\text{C-D}} < 1$, it is called an inverse kinetic isotope effect.^{142–}

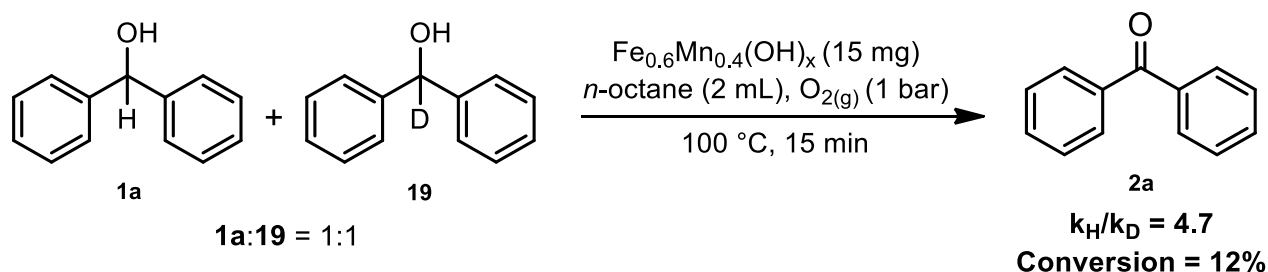
¹⁴⁵ In this study, kinetic isotope effect was investigated through benzhydrol molecule by replacing the C-H in the benzylic position with C-D. For this purpose, deuterated benzhydrol was synthesized first. However, the resulting product contained deuterium bonded to both carbon and oxygen. Therefore, in order to prevent the exchange between O-D and O-H resulting from the

small amount of water in air or in the reaction medium, the resulting molecule was treated with $\text{NH}_4\text{Cl}_{(\text{aq})}$ (**Scheme 13**). The desired compound containing deuterium only at the carbon atom was obtained (**19**).



*Scheme 13: Synthesis of deuterated benzhydrol (**19**).*

Afterwards, the compounds shown were reacted in a 1:1 ratio and the reaction was terminated after 15 min (**Scheme 14**). According to the ^1H -NMR analysis performed as a result of the reaction, the conversion from these compounds to the benzophenone compound was determined to be 12%. Again, as a result of this analysis, the ratio of the consumption rate of compound **1** to the consumption rate of compound **19** was found to be 4.7. R. Stewart reported that the $k_{\text{H}}/k_{\text{D}}$ ratio was 6.6 when the oxidation of benzhydrol (**1a**) was carried out with MnO_4^- in water and at 25°C . In another study, Mansoor et al., reported the $k_{\text{H}}/k_{\text{D}}$ ratio as 5.86 when they oxidized benzhydrol (**1a**) with triethylammonium chlorochromate in DMSO and at 40°C .^{146,147} Aside from the change of solvent and oxidant, it is seen that the $k_{\text{H}}/k_{\text{D}}$ ratio decreases with increasing temperature. Finally, in Wiberg's article, it was stated that the maximum isotope effect ($k_{\text{H}}/k_{\text{D}}$) for the C-H bond at 100°C could be 4.7.¹⁴⁶ Based on all these data, it can be concluded that the primary (1°) kinetic isotope effect is observed in this work. According to this effect, breaking the C-H bond is proposed to be the rate-determining step in the developed catalytic alcohol oxidation reaction.



Scheme 14: Kinetic isotope effect in the catalytic oxidation of benzhydrol (1a).

1.2.3.4 Spent Catalyst Experiment

The purpose of this experiment was to see whether the catalyst would oxidize the alcohol to ketone for a second time after it was used, separated from the reaction mixture, and dried without any additional treatment. For this purpose, benzhydrol was oxidized to benzophenone in 24 h with 15 mg of catalyst and O_2 gas in 2 mL of *n*-octane. The catalyst was then separated from the reaction mixture and dried in the oven at 60 °C for 12 h. At the end of 12 h, it was observed that some white powder remained on the catalyst taken from the oven, and this white powder was thought to be benzophenone stuck to the catalyst. Thereupon, the reaction was carried out again at 100 °C for 24 h with 0.53 mmol benzhydrol, 16 mg spent catalyst and 2.1 mL *n*-octane. As a result of the reaction, ^1H -NMR analysis revealed that the conversion from benzhydrol to benzophenone was 6.7%. According to this result, it was understood that the reaction almost did not occur, and the 6.7% that occurred could be due to benzophenone that was already stuck to the catalyst. Thus, it was concluded that oxidation did not occur when the catalyst was used for the second time without any additional treatment. This shows that the active sites of the catalyst lose their function after the first use.

1.3 CONCLUSION

The aim of this project was to test the $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst, which was developed in a collaborative project by the Ozensoy and Türkmen research groups and contains Fe and Mn metals that are cheap and abundant in soil, and are not harmful to human and environmental health, in aerobic alcohol oxidation reactions. For this purpose, first of all, the oxidation reaction of benzhydrol (**1a**) to benzophenone (**2a**) was chosen as a model reaction, and thanks to the optimization of this model reaction, it was decided under what conditions the next alcohol oxidations would continue. These conditions were determined as 15 mg catalyst per 0.5 mmol substrate, 110 °C temperature and 24 h of reaction time. However, it was observed that changing the amount of catalyst, temperature or solvent gave better results in some substrates. At the same time, possible reasons for oxidations resulting in low yields depending on the structure of the substrate were explained. While higher yields were obtained in benzhydrol derivatives and benzyl alcohol derivatives, these yields could not be obtained in 1-phenylethanol derivatives except for the parent 1-phenylethanol (**3**).

In order to obtain insight about the working mechanism of this catalyst, some control experiments and kinetic isotope effect experiments were carried out. According to the kinetic isotope effect experiment, it was determined that the rate determining step was the breaking of the C-H bond (1° KIE). According to the results of the control experiments, it was understood that in the absence of either molecular oxygen or catalyst in the reaction environment, the reaction took place very little or not at all. In addition, when the catalyst was isolated from the reaction medium and dried after the first oxidation, it was observed that the reaction did not occur when used for the second time.

CHAPTER 2

2.1 EXPERIMENTAL SECTION

2.1.1 Materials and Methods

All solution-phase catalytic oxidation reactions were carried out in oven-dried glassware at 1 bar of oxygen gas. The photochemical experiment was performed in a commercial UV gel nail dryer (Beurer) equipped with four 9-W UV lamps (365 nm). Thin-layer chromatography (TLC) using aluminum-backed plates pre-coated with silica gel (Silicycle, Silica Gel 60 F₂₅₄) was used for monitoring the reactions. For TLC visualization, UV light (254 nm) and KMnO₄ solutions were used. For the purification by flash column chromatography, Silicycle 40-63 μ m (230-400 mesh) flash silica gel was used. NMR spectra were recorded using a Bruker NMR spectrometer at 400 MHz for ¹H-NMR spectra and 100 MHz for ¹³C-NMR spectra. Calibrations were done from internal standard TMS (0 ppm) or residual solvent signals (chloroform at 7.26 ppm for ¹H spectra and at 77.16 ppm and for ¹³C spectra) ¹H-NMR data are reported as follows: chemical shift (parts per million, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double of doublet, m = multiplet, app = apparent), coupling constant (Hz) and integration.

Since some of the products obtained in this work are volatile, DCM and *n*-pentane, which are easy to remove due to their low boiling points, were used as eluents in their purification by column

chromatography. In addition, these solvents were removed carefully under reduced pressure to minimize loss of products.

2.1.2 Reaction Procedures for Chapter 1

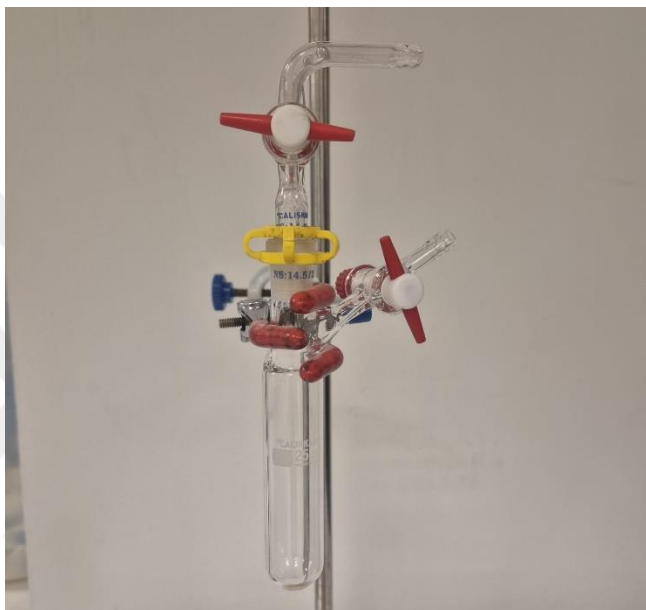
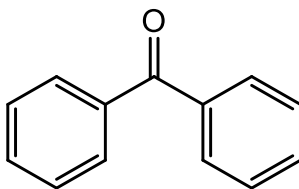


Figure 6: The setup used for the catalytic oxidation reactions.



Benzophenone (2a). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and benzhydrol (92.1 mg, 0.50 mmol), respectively. 2 mL of *n*-octane was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 100 °C for 24 h. At the end of 24 h, the reaction mixture was filtered through a pad of Celite using EtOAc to

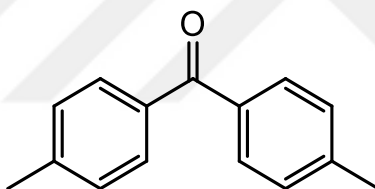
remove the catalyst. EtOAc and *n*-octane were evaporated under reduced pressure. Purification was performed by flash column chromatography (1:5 = EtOAc:hexanes) and as a result, pure benzophenone was obtained as a white solid (82 mg, 90% yield). The NMR data are in agreement with the data reported in the literature.¹⁴⁸

$R_f = 0.84$ (1:3 = EtOAc:hexanes)

TLC Visualization: UV active; stains very slowly with KMnO₄ solution

¹H NMR (400 MHz; CDCl₃) δ : 7.79 (4H, d, $J = 8.1$ Hz), 7.61-7.53 (2H, m), 7.46 (4H, t, $J = 7.6$ Hz).

¹³C{¹H} NMR (100 MHz; CDCl₃) δ : 196.7, 137.7, 132.5, 130.1, 128.3.



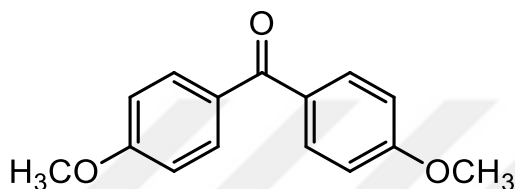
4,4'-Dimethylbenzophenone (2b). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, Fe_{0.6}Mn_{0.4}(OH)_x catalyst (15 mg), and 4,4'-dimethylbenzhydrol (106.14 mg, 0.50 mmol), respectively. 2 mL of *n*-octane was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O₂ (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. At the end of 24 h, the reaction mixture was filtered through a pad of Celite using EtOAc to remove the catalyst. EtOAc and *n*-octane were evaporated under reduced pressure. Purification was performed by flash column chromatography (only hexanes) and as a result, 4,4'-dimethylbenzophenone was obtained as a pale-yellow solid (80 mg, 76% yield). The NMR data are in agreement with the data reported in the literature.¹⁴⁸

$R_f = 0.89$ (1:3 = EtOAc:hexanes)

TLC Visualization: UV active; stains very slowly with KMnO_4 solution

^1H NMR (400 MHz; CDCl_3) δ : 7.71 (4H, d, $J = 8.1$ Hz), 7.27 (4H, d, $J = 8.0$ Hz), 2.43 (6H, s).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz; CDCl_3) δ : 196.3, 143.0, 135.3, 130.3, 129.0, 21.7.



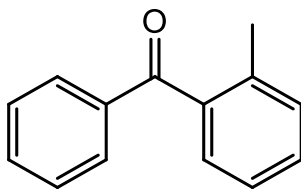
4,4'-Dimethoxybenzophenone (2c). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 4,4'-dimethoxybenzhydrol (122.1 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. At the end of 24 h, the reaction mixture was filtered through a pad of Celite using EtOAc to remove the catalyst. Chlorobenzene and EtOAc were evaporated under reduced pressure. Purification was performed by flash column chromatography (only hexanes) and as a result, 4,4'-dimethoxybenzophenone was obtained as a pale-yellow solid (120.8 mg, >99%). The NMR data are in agreement with the data reported in the literature.¹⁴⁹

$R_f = 0.63$ (1:3 = EtOAc:hexanes)

TLC Visualization: UV active; stains very slowly with KMnO_4 solution

^1H NMR (400 MHz; CDCl_3) δ : 7.76 (4H, d, $J = 8.6$ Hz), 6.93 (4H, d, $J = 8.5$ Hz), 3.84 (6H, s).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz; CDCl_3) δ : 194.4, 162.8, 132.2, 130.7, 113.4, 55.5.



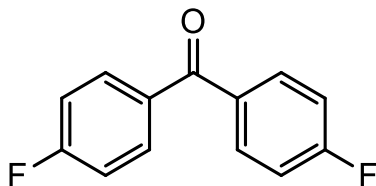
2-Methylbenzophenone (2e). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 2-methylbenzhydrol (99.13 mg, 0.50 mmol), respectively. 2 mL of *n*-octane was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. At the end of 24 h, the reaction mixture was filtered through a pad of Celite using EtOAc to remove the catalyst. EtOAc and *n*-octane were evaporated under reduced pressure. Purification was performed by flash column chromatography (hexanes only) and as a result, 2-methylbenzophenone was obtained as a yellow oil (98 mg, 99%). The NMR data are in agreement with the data reported in the literature.¹⁴⁸

R_f = 0.76 (1:3 = EtOAc:hexanes)

TLC Visualization: UV active; stains very slowly with KMnO_4 solution

^1H NMR (400 MHz; CDCl_3) δ : 7.81 (2H, d, J = 8.1 Hz), 7.58 (1H, t, J = 7.9 Hz), 7.45 (2H, t, J = 7.6 Hz), 7.42-7.36 (1H, m), 7.33-7.23 (3H, m), 2.34 (3H, s).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz; CDCl_3) δ : 198.8, 138.8, 137.9, 136.9, 133.3, 131.2, 130.4, 130.3, 128.6, 125.4, 20.1 (11 signals were observed out of 12 expected signals).



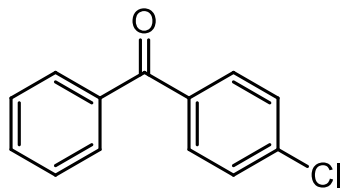
4,4'-Difluorobenzophenone (2f). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 4,4'-difluorobenzhydrol (110.11 mg, 0.50 mmol), respectively. 2 mL of *n*-octane was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 100 °C for 24 h. At the end of 24 h, the reaction mixture was filtered through a pad of Celite using EtOAc to remove the catalyst. EtOAc and *n*-octane were evaporated under reduced pressure. Purification was performed by flash column chromatography (hexanes then EtOAc) and as a result, 4,4'-difluorobenzophenone was obtained as a white solid (108 mg, >99%). The NMR data are in agreement with the data reported in the literature.¹⁵⁰

$R_f = 0.76$ (1:3 = EtOAc:hexanes)

TLC Visualization: UV active; stains very slowly with KMnO_4 solution

^1H NMR (400 MHz; CDCl_3) δ : 7.78 (4H, dd, $J = 7.3, 5.4$ Hz), 7.12 (4H, t, $J = 8.4$ Hz).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz; CDCl_3) δ : 193.5, 165.5 (d, $J_{\text{C-F}} = 254.4$ Hz), 133.8 (d, $J_{\text{C-F}} = 3.0$ Hz), 132.6 (d, $J_{\text{C-F}} = 9.0$ Hz), 115.6 (d, $J_{\text{C-F}} = 21.9$ Hz)



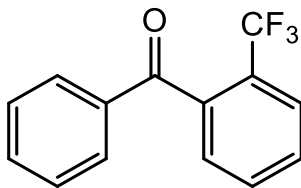
4-chlorobenzophenone (2g). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 4-chlorobenzhydrol (109 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. At the end of 24 h, the reaction mixture was filtered through a pad of Celite using EtOAc to remove the catalyst. Chlorobenzene and EtOAc were evaporated under reduced pressure. Purification was performed by flash column chromatography (hexanes only) and as a result, 4-chlorobenzophenone was obtained as a white solid (105 mg, 97%). The NMR data are in agreement with the data reported in the literature.¹⁴⁹

$R_f = 0.89$ (1:3 = EtOAc:hexanes)

TLC Visualization: UV active; stains very slowly with KMnO_4 solution

^1H NMR (400 MHz; CDCl_3) δ : 7.75-7.71 (4H, m), 7.56 (1H, t, $J = 7.4$ Hz), 7.47-7.41 (4H, m).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz; CDCl_3) δ : 195.3, 138.8, 137.2, 135.8, 132.6, 131.4, 129.9, 128.6, 128.4.

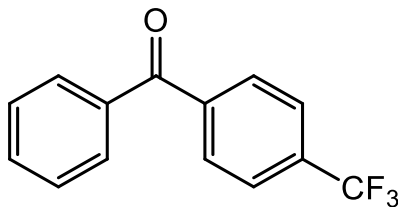


2-(Trifluoromethyl)benzophenone (2h). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 2-(trifluoromethyl)benzhydrol (126.3 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. At the end of 24 h, the reaction mixture was filtered through a pad of Celite using EtOAc to remove the catalyst. Chlorobenzene and EtOAc were evaporated under reduced pressure. Purification was performed by flash column chromatography (hexanes only) and as a result, 2-(trifluoromethyl)benzophenone was obtained as a white solid (66.5 mg, 53%). The NMR data are in agreement with the data reported in the literature.¹⁵¹

$R_f = 0.82$ (1:3 = EtOAc:hexanes)

TLC Visualization: UV active; stains very slowly with KMnO_4 solution

^1H NMR (400 MHz; CDCl_3) δ : 7.89 (2H, d, $J = 8.1$ Hz), 7.81 (2H, d, $J = 7.5$ Hz), 7.75 (2H, d, $J = 8.1$ Hz), 7.63 (1H, t, $J = 7.4$ Hz), 7.51 (2H, t, $J = 7.6$ Hz).



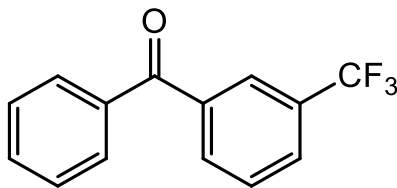
4-(Trifluoromethyl)benzophenone (2i). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 4-(trifluoromethyl)benzhydrol (126.3 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. At the end of 24 h, the reaction mixture was filtered through a pad of Celite using EtOAc to remove the catalyst. Chlorobenzene and EtOAc were evaporated under reduced pressure. Purification was performed by flash column chromatography (hexanes only) and as a result, 4-(trifluoromethyl)benzophenone was obtained as a white solid (89.5 mg, 72%). The NMR data are in agreement with the data reported in the literature.¹⁴⁸

$R_f = 0.84$ (1:3 = EtOAc:hexanes)

TLC Visualization: UV active; stains very slowly with KMnO_4 solution

^1H NMR (400 MHz; CDCl_3) δ : 7.89 (2H, d, $J = 8.1$ Hz), 7.80 (2H, d, $J = 7.9$ Hz), 7.75 (2H, d, $J = 8.1$ Hz), 7.62 (1H, t, $J = 7.4$ Hz), 7.50 (2H, t, $J = 7.6$ Hz).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz; CDCl_3) δ : 195.6, 140.9, 136.8, 134.0, 133.6, 133.2, 130.3, 130.2, 128.6, 125.5 (q, $J_{\text{C-F}} = 3.6$ Hz).



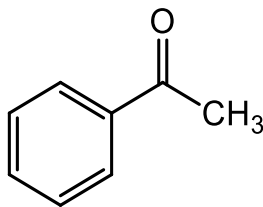
3-(Trifluoromethyl)benzophenone (2j). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 3-(trifluoromethyl)benzhydrol (126.3 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. At the end of 24 h, the reaction mixture was filtered through a pad of Celite using EtOAc to remove the catalyst. Chlorobenzene and EtOAc were evaporated under reduced pressure. Purification was performed by flash column chromatography (hexanes only) and as a result, 3-(trifluoromethyl)benzophenone was obtained as a white solid (122.7 mg, 98%). The NMR data are in agreement with the data reported in the literature.¹⁴⁸

$R_f = 0.82$ (1:3 = EtOAc:hexanes)

TLC Visualization: UV active; stains very slowly with KMnO_4 solution

^1H NMR (400 MHz; CDCl_3) δ : 8.07 (1H, s), 7.97 (1H, d, $J = 7.6$ Hz), 7.84 (1H, d, $J = 7.7$ Hz), 7.79 (2H, d, $J = 8.0$ Hz), 7.62 (2H, t, $J = 7.0$ Hz), 7.50 (2H, t, $J = 7.6$ Hz).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz; CDCl_3) δ : 195.2, 138.4, 136.9, 133.2, 133.1, 131.2, 130.9, 130.1, 129.1, 128.9 (q, $J_{\text{C-F}} = 3.5$ Hz), 128.7, 126.8 (q, $J_{\text{C-F}} = 3.6$ Hz), 123.8 (q, $J_{\text{C-F}} = 272.8$ Hz).

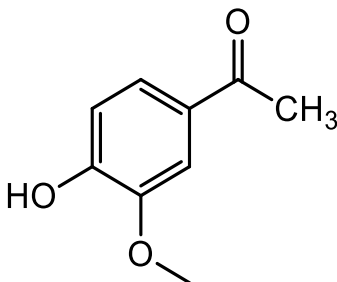


Acetophenone (4). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 1-phenylethanol (61.1 mg, 0.50 mmol), respectively. 2 mL of *n*-octane was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. Right after 24 h, the reaction mixture was directly loaded to column, and purification was performed by flash column chromatography (1:1 = DCM:pentane), and as a result, acetophenone was obtained as a yellow liquid (49.4 mg, 82% yield). The NMR data are in agreement with the data reported in the literature.¹⁵²

$R_f = 0.55$ (1:1 = DCM:pentane)

TLC Visualization: UV active; does not stain with KMnO_4 solution

$^1\text{H-NMR}$: 7.96 (2H, d, $J = 7.9$ Hz), 7.57 (1H, t, $J = 7.3$ Hz), 7.46 (2H, t, $J = 7.7$ Hz), 2.60 (3H, s).



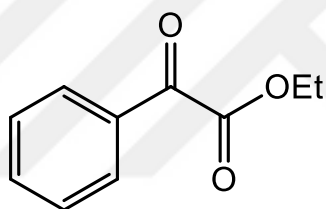
4-Methoxy-3-hydroxyacetophenone (6). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 1-(4-hydroxy-3-methoxyphenyl)ethanol (84.1 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk

flask. After the Schlenk flask was closed, O₂ (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. Right after 24 h, the reaction mixture was directly loaded to column, and purification was performed by flash column chromatography (1:2 = EtOAc:hexanes), and as a result, 4-Methoxy-3-hydroxyacetophenone was obtained as a white solid (14.7 mg, 18% yield). The NMR data are in agreement with the data reported in the literature.¹⁵³

R_f = 0.34 (1:3 = EtOAc:hexanes)

TLC Visualization: UV active; stains with KMnO₄ solution

¹H-NMR: 7.57–7.54 (2H, m), 6.97 (1H, d, *J* = 8.7 Hz), 6.19 (1H, s), 3.97 (3H, s), 2.58 (3H, s).

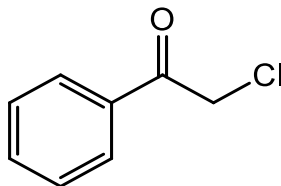


Ethyl benzoylformate (8). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, Fe_{0.6}Mn_{0.4}(OH)_x catalyst (20 mg), and ethyl mandelate (90.1 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O₂ (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. Right after 24 h, the reaction mixture was directly loaded to column, and purification was performed by flash column chromatography (1:7 = EtOAc:hexanes), and as a result, ethyl benzoylformate was obtained as a yellow solid (12.5 mg, 14% yield). The NMR data are in agreement with the data reported in the literature.¹⁵⁴

R_f = 0.87 (1:7 = EtOAc:hexanes)

TLC Visualization: UV active; stains slowly with KMnO₄ solution

¹H-NMR: 8.01 (2H, d, $J = 7.3$ Hz), 7.66 (1H, t, $J = 7.4$ Hz), 7.52 (2H, t, $J = 7.7$ Hz), 4.46 (2H, q, $J = 7.1$ Hz), 1.43 (3H, t, $J = 7.1$ Hz).

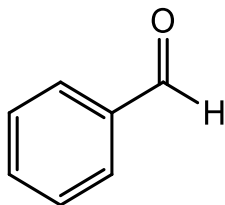


2-Chloroacetophenone (10). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 2-chloro-1-phenylethanol (78.3 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. Right after 24 h, the reaction mixture was directly loaded to column, and purification was performed by flash column chromatography (1:1 = DCM:pentane), and as a result, 2-chloroacetophenone was obtained as a yellow solid (2.5 mg, 3% yield). The NMR data are in agreement with the data reported in the literature.¹⁵²

$R_f = 0.79$ (1:1 = DCM:pentane)

TLC Visualization: UV active; stains slowly with KMnO_4 solution

¹H-NMR: 7.99 (2H, d, $J = 8.0$ Hz), 7.64 (1H, d, $J = 7.5$ Hz), 7.53 (2H, t, $J = 7.6$ Hz), 4.74 (1H, s).



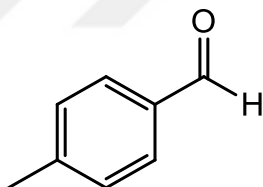
Benzaldehyde (14a). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and benzyl alcohol (54.1 mg, 0.50 mmol), respectively. 2

mL of *n*-octane was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O₂ (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. Right after 24 h, the reaction mixture was directly loaded to column, and purification was performed by flash column chromatography (1:1 = DCM:pentane), and as a result, pure benzaldehyde was obtained (48.7 mg, 92% yield). The NMR data are in agreement with the data reported in the literature.¹⁵⁵

R_f = 0.77 (1:1 = DCM:pentane)

TLC Visualization: UV active; does not stain with KMnO₄ solution

¹H NMR (400 MHz; CDCl₃) δ: 10.03 (1H, s), 7.89 (2H, d, *J* = 7.2 Hz), 7.66 – 7.61 (1H, m), 7.54 (2H, t, *J* = 7.3 Hz).

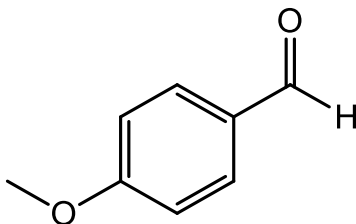


4-Methylbenzaldehyde (14b). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, Fe_{0.6}Mn_{0.4}(OH)_x catalyst (15 mg), and 4-methylbenzyl alcohol (61.1 mg, 0.50 mmol), respectively. 2 mL of *n*-octane was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O₂ (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. Right after 24 h, the reaction mixture was directly loaded to column, and purification was performed by flash column chromatography (1:1 = DCM:pentane), and as a result, pure 4-methylbenzaldehyde was obtained (49.3 mg, 82% yield). The NMR data are in agreement with the data reported in the literature.¹⁵⁵

R_f = 0.79 (1:1 = DCM:pentane)

TLC Visualization: UV active; does not stain with KMnO_4 solution

$^1\text{H-NMR}$: 9.97 (1H, s), 7.78 (2H, d, $J = 8.1$ Hz), 7.34 (2H, d, $J = 7.9$ Hz), 2.44 (3H, s).

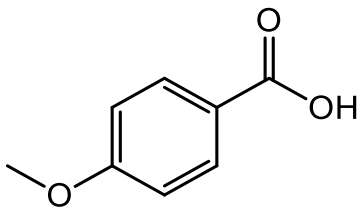


4-Methoxybenzaldehyde (14c). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 4-methoxybenzyl alcohol (69.1 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. Right after 24 h, the reaction mixture was directly loaded to column, and purification was performed by flash column chromatography (1:4 = EtOAc:hexanes), and as a result, pure 4-methoxybenzaldehyde was obtained (50.7 mg, 74% yield). The NMR data are in agreement with the data reported in the literature.¹⁵⁵

$R_f = 0.53$ (1:4 = EtOAc:hexanes)

TLC Visualization: UV active; does not stain with KMnO_4 solution

$^1\text{H-NMR}$: 9.89 (1H, s), 7.84 (2H, d, $J = 8.8$ Hz), 7.01 (2H, d, $J = 8.7$ Hz), 3.89 (3H, s).

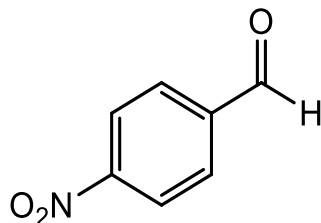


4-Methoxybenzoic acid (14c'). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 4-methoxybenzyl alcohol (69.1 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O_2 (1 bar) was filled by the sidearm. The reaction was stirred at 110 °C for 24 h. Right after 24 h, the reaction mixture was directly loaded to column, and purification was performed by flash column chromatography (1:1 = EtOAc:hexanes + 1% acetic acid), and as a result, 4-methoxybenzoic acid was obtained as a white solid (18 mg, 24% yield). The NMR data are in agreement with the data reported in the literature.¹⁵⁶

$R_f = 0.63$ (1:1 = EtOAc:hexanes)

TLC Visualization: UV active; does not stain with KMnO_4 solution

$^1\text{H-NMR}$: 8.10 (2H, d, $J = 8.6$ Hz), 6.98 (2H, d, $J = 8.7$ Hz), 3.91 (3H, s).



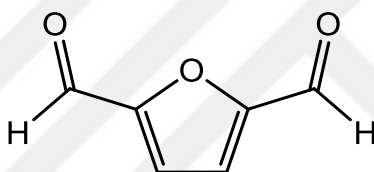
4-nitrobenzaldehyde (14d). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, $\text{Fe}_{0.6}\text{Mn}_{0.4}(\text{OH})_x$ catalyst (15 mg), and 4-nitrobenzyl alcohol (76.6 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask.

After the Schlenk flask was closed, O₂ (1 bar) was filled by the sidearm. The reaction was stirred at 130 °C for 24 h. Right after 24 h, the reaction mixture was directly loaded to column, and purification was performed by flash column chromatography (1:1 = EtOAc:hexanes), and as a result, 4-nitrobenzaldehyde was obtained as a white solid (63.4 mg, 84% yield). The NMR data are in agreement with the data reported in the literature.¹⁵⁷

R_f = 0.84 (1:1 = EtOAc:hexanes)

TLC Visualization: UV active; stains slowly with KMnO₄ solution

¹H-NMR: 10.18 (1H, s), 8.41 (2H, d, *J* = 8.7 Hz), 8.10 (2H, d, *J* = 8.8 Hz).



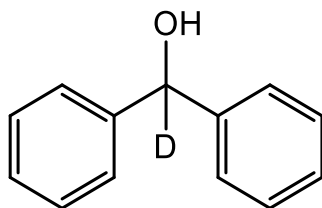
2,5-Furandicarboxaldehyde (16). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, Fe_{0.6}Mn_{0.4}(OH)_x catalyst (50 mg), and 5-hydroxymethylfurfural (63.1 mg, 0.50 mmol), respectively. 2 mL of chlorobenzene was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O₂ (1 bar) was filled by the sidearm. The reaction was stirred at 130 °C for 24 h. Right after 24 h, the reaction mixture was directly loaded to column, and purification was performed by flash column chromatography (1:1 = EtOAc:hexanes), and as a result, 2,5-furandicarboxaldehyde was obtained as a yellow solid (34.2 mg, 55% yield). The NMR data are in agreement with the data reported in the literature.¹⁵⁸

R_f = 0.66 (1:1 = EtOAc:hexanes)

TLC Visualization: UV active; stains rapidly with KMnO₄ solution

¹H-NMR: 9.85 (2H, s), 7.35 (2H, s).

2.1.3 Kinetic Isotope Effect Experiment Details



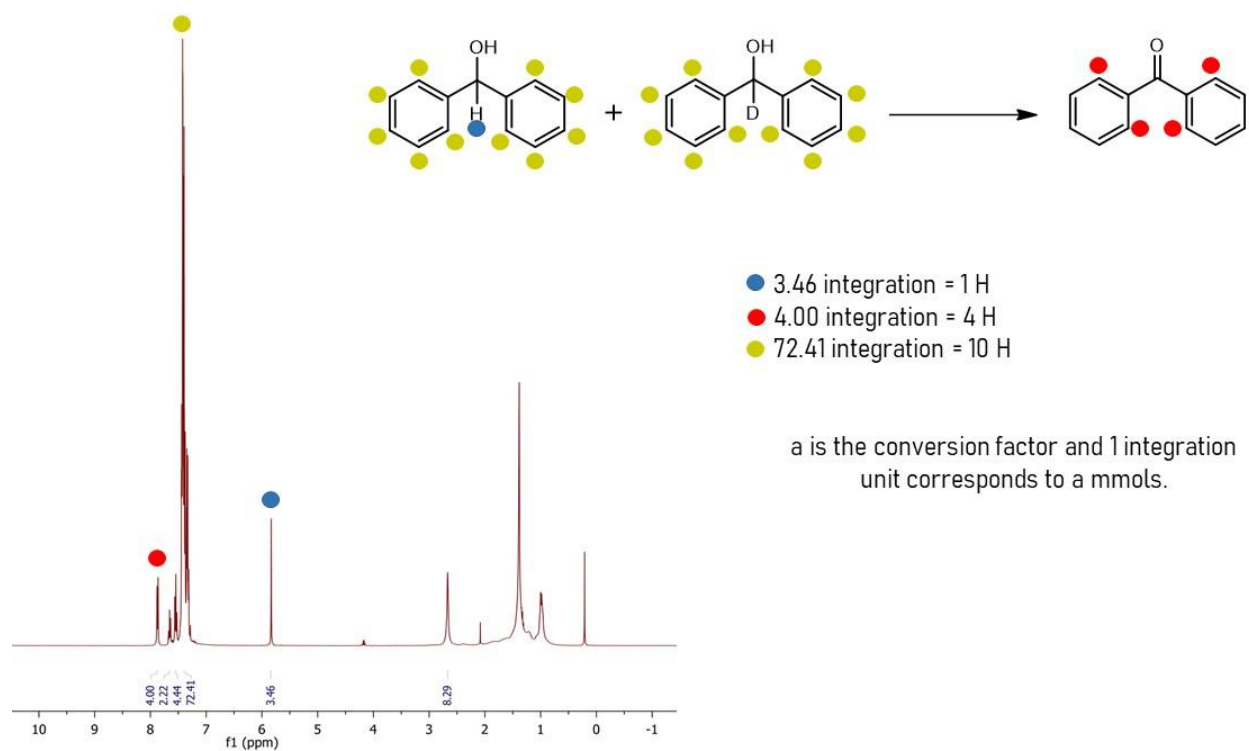
19

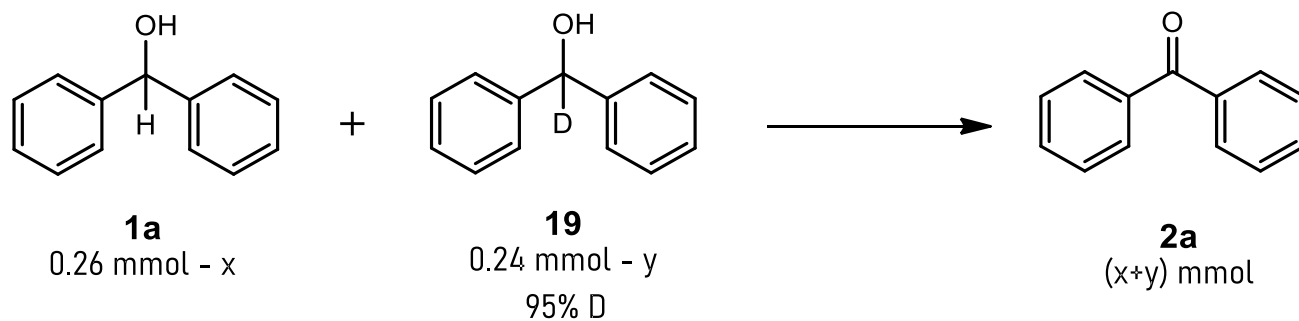
In an oven-dried quartz test tube, a stir bar, benzophenone (111.0 mg, 0.60 mmol), Cs₂CO₃ (2 eq, 391.3 mg, 1.2 mmol), and 1.5 mL CD₃OD were added, respectively. Then the lid of the quartz test tube was connected to a previously N_{2(g)} filled balloon with a pipe and a syringe needle (1 mL). The reaction mixture in the quartz test tube was placed into the UV Gel Nail Dryer (365 nm, 36 W) and irradiated for 14 h. At the end of 14 h, the reaction mixture was quenched with saturated NH₄Cl solution (5 mL), then extracted with EtOAc (3x10 mL) and distilled water (3x10 mL). Purification was performed by flash column chromatography (SiO₂, EtOAc:hexanes = 1:19, then 1:9) and as a result, compound **19** was obtained (92.8 mg, 95% deuterium incorporation, 83% yield). The NMR data are in agreement with the data reported in the literature.¹⁵⁹

¹H NMR (400 MHz; CDCl₃) δ: 7.46 – 7.30 (10H, m), 2.53 (1H, s).

Benzophenone (2a). An oven-dried 25 mL Schlenk flask was loaded with a stir bar, Fe_{0.6}Mn_{0.4}(OH)_x catalyst (15 mg), **1a** (46.1 mg, 0.25 mmol) and **19** (46.3 mg, 0.25 mmol), respectively. 2 mL of *n*-octane was added by washing the walls of the Schlenk flask. After the Schlenk flask was closed, O₂ (1 bar) was filled by the sidearm. The reaction was stirred at 100 °C for 15 min. At the end of 15 min, the reaction mixture was filtered through a pad of Celite using

EtOAc to remove the catalyst. EtOAc and *n*-octane were evaporated under reduced pressure. Conversion was directly calculated via ^1H -NMR.





(1) $x + y = a$
 (2) $0.26 - x = 3.46 * a$
 (3) $0.5 - x - y = 7.24 * a$

$0.25 \text{ mmol} \times 0.95 = 0.24 \text{ mmol}$

$0.25 \text{ mmol} + (0.25 \times 0.05) = 0.26 \text{ mmol}$

Solving the equations (1), (2) and (3) together:

$0.5 = 8.24 * a$

$a = 0.0607$

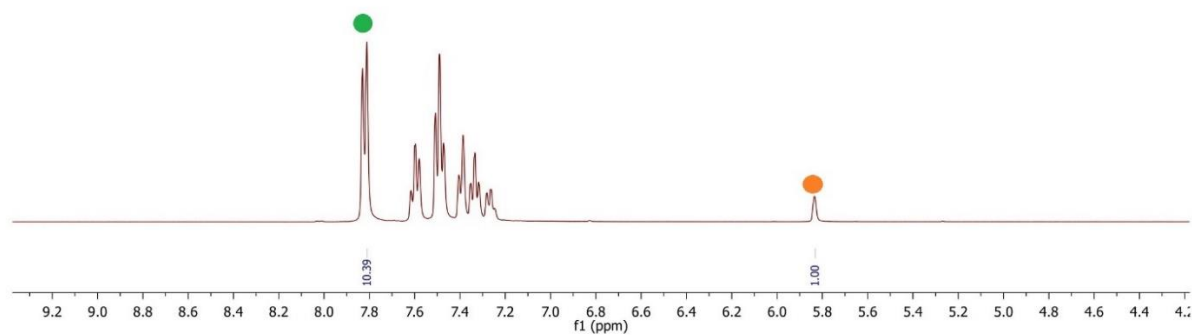
$x = 0.050 \text{ mmol}$

$y = 0.0107 \text{ mmol}$

$$\frac{k_H}{k_D} = \frac{x}{y} = 4.67$$

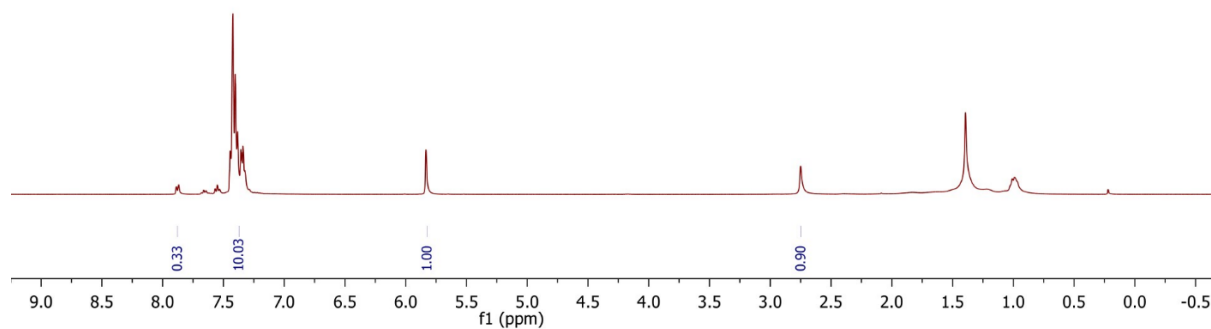
$$\frac{x + y}{0.5} = \frac{a}{0.5} = 12\% \text{ conversion}$$

Examples on Calculating the % Conversion Value in the Oxidation of Benzhydrol (1) Compound to Benzophenone (2) Product:



$$10.39/4 = 2.6$$

$$\text{Conversion} = [2.6/(1+2.6)] \times 100 = 72\%$$



$$0.33/4 = 0.083$$

$$\text{Conversion} = [0.083/(1+0.083)] \times 100 = 7.6\%$$

NMR SPECTRA

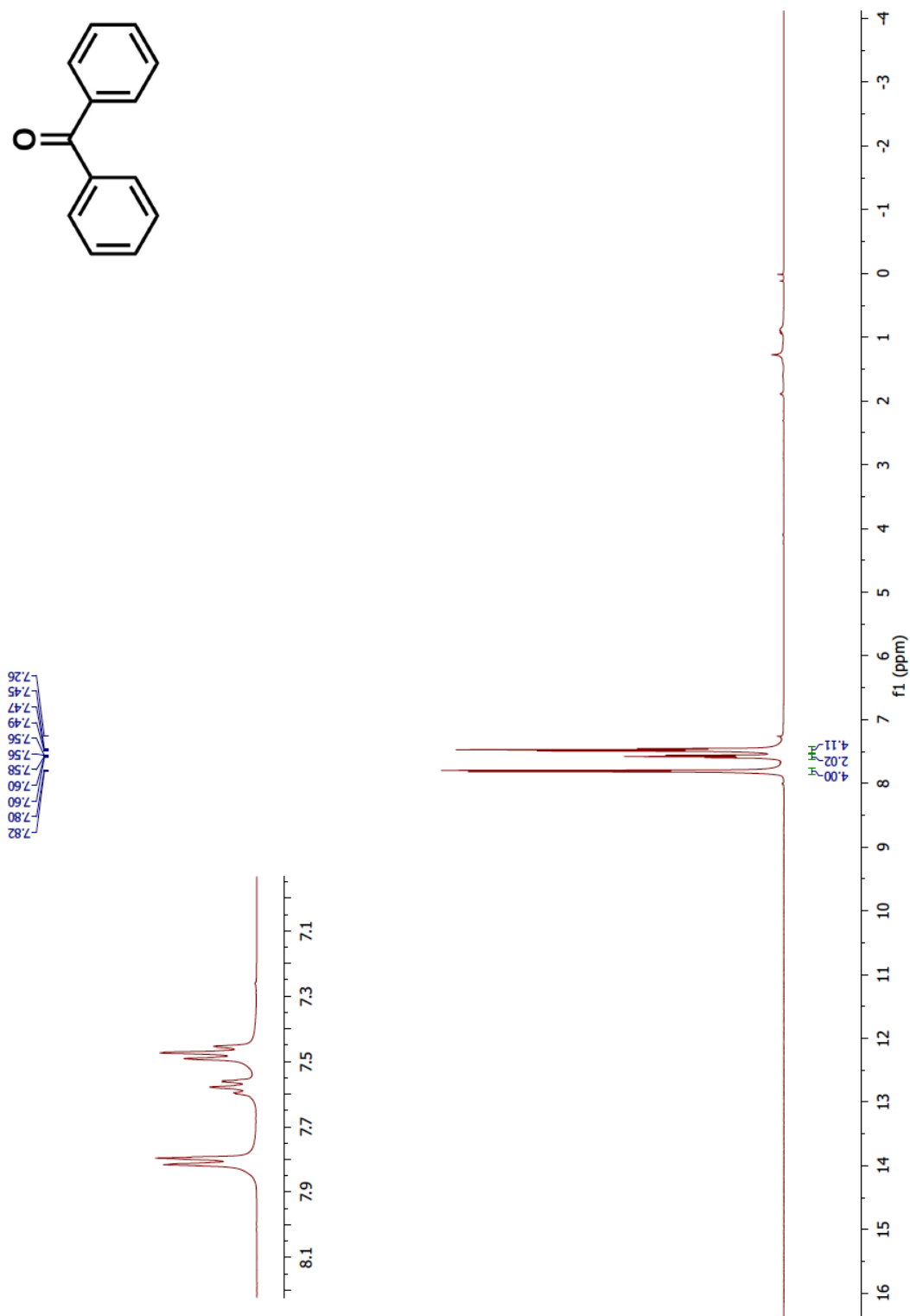


Figure 7: ¹H-NMR spectrum of **2a** in CDCl₃.

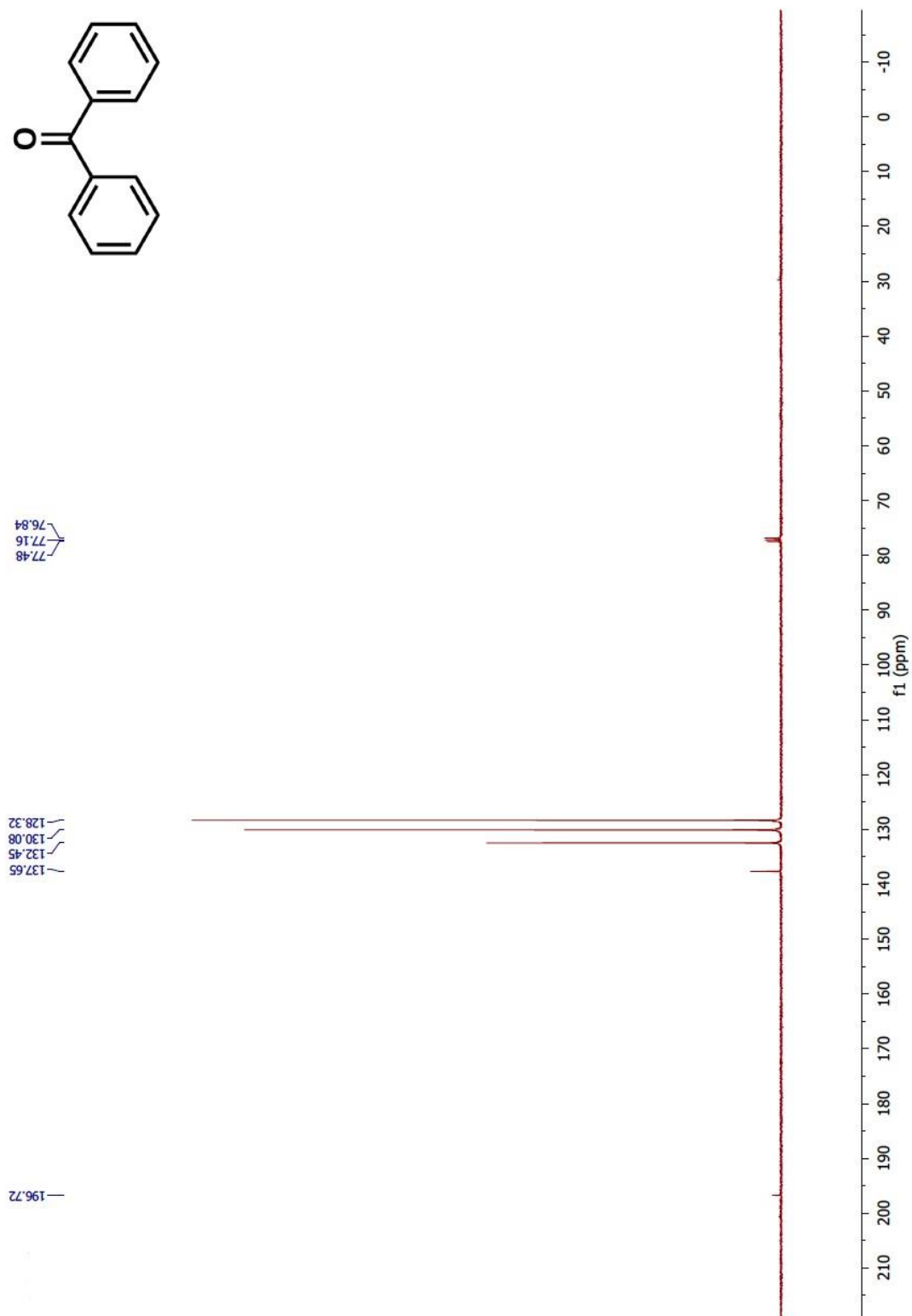


Figure 8: ^{13}C -NMR spectrum of **2a** in CDCl₃.

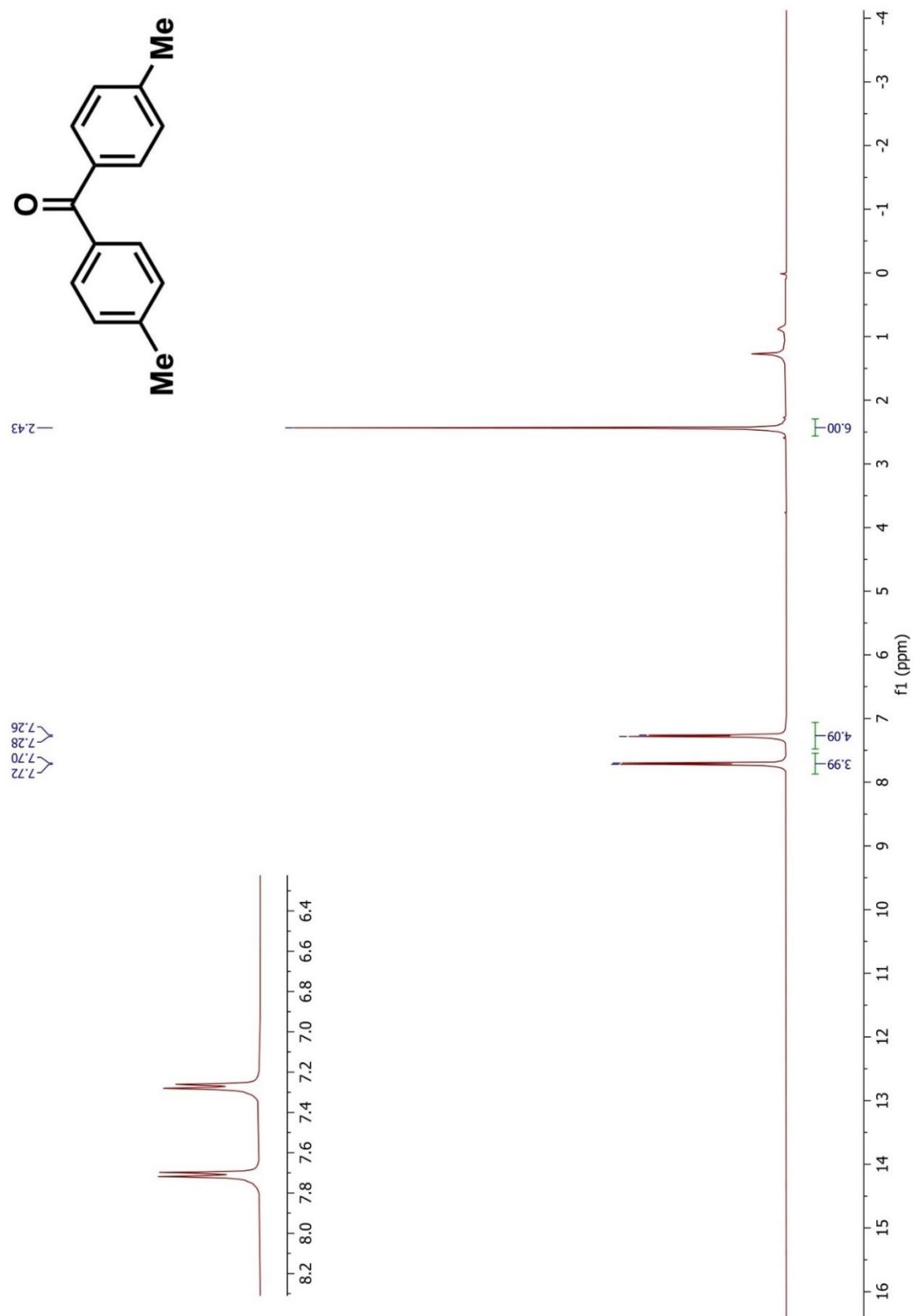


Figure 9: ¹H-NMR spectrum of **2b** in CDCl₃.

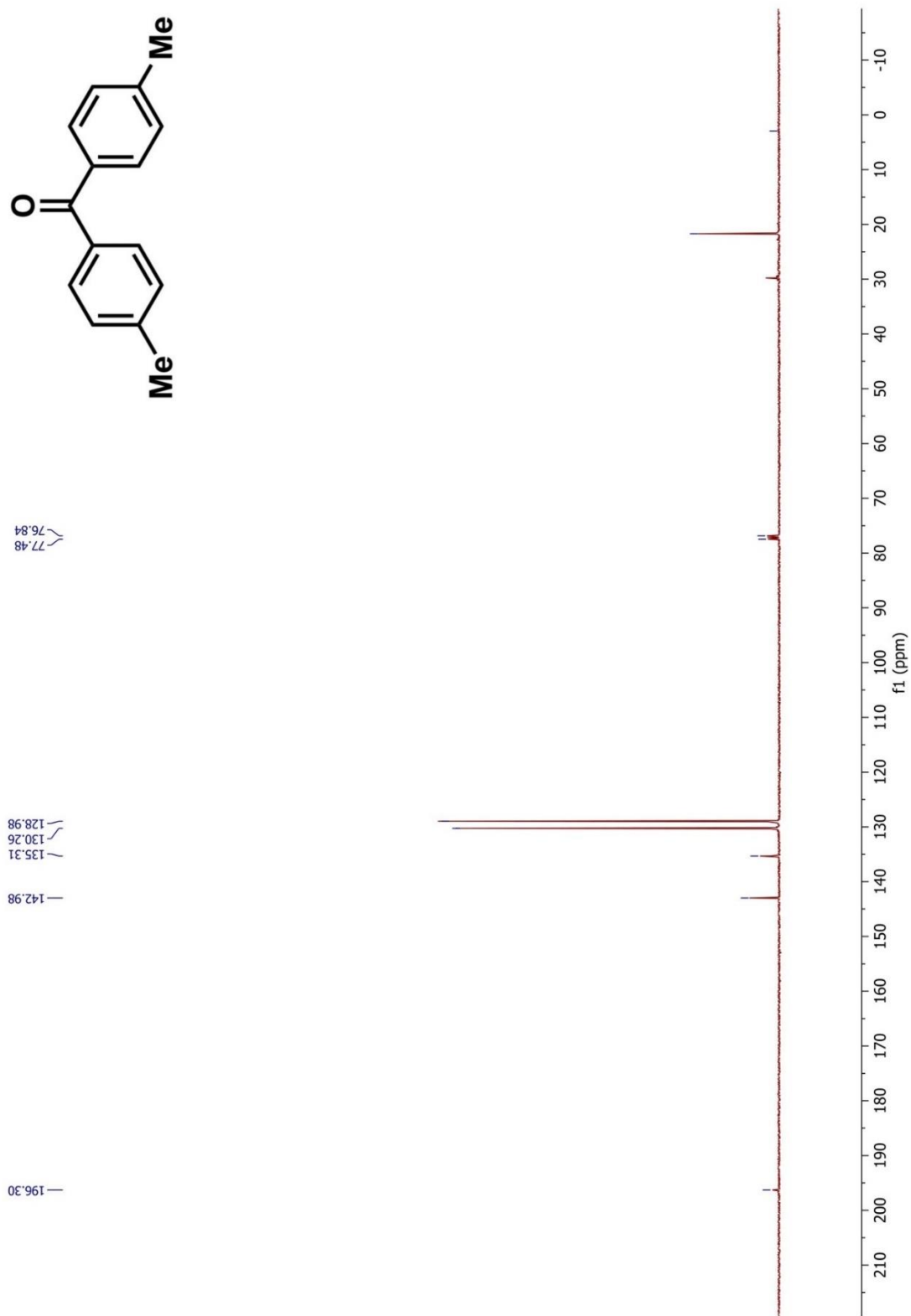


Figure 10: ^{13}C -NMR spectrum of **2b** in CDCl₃.

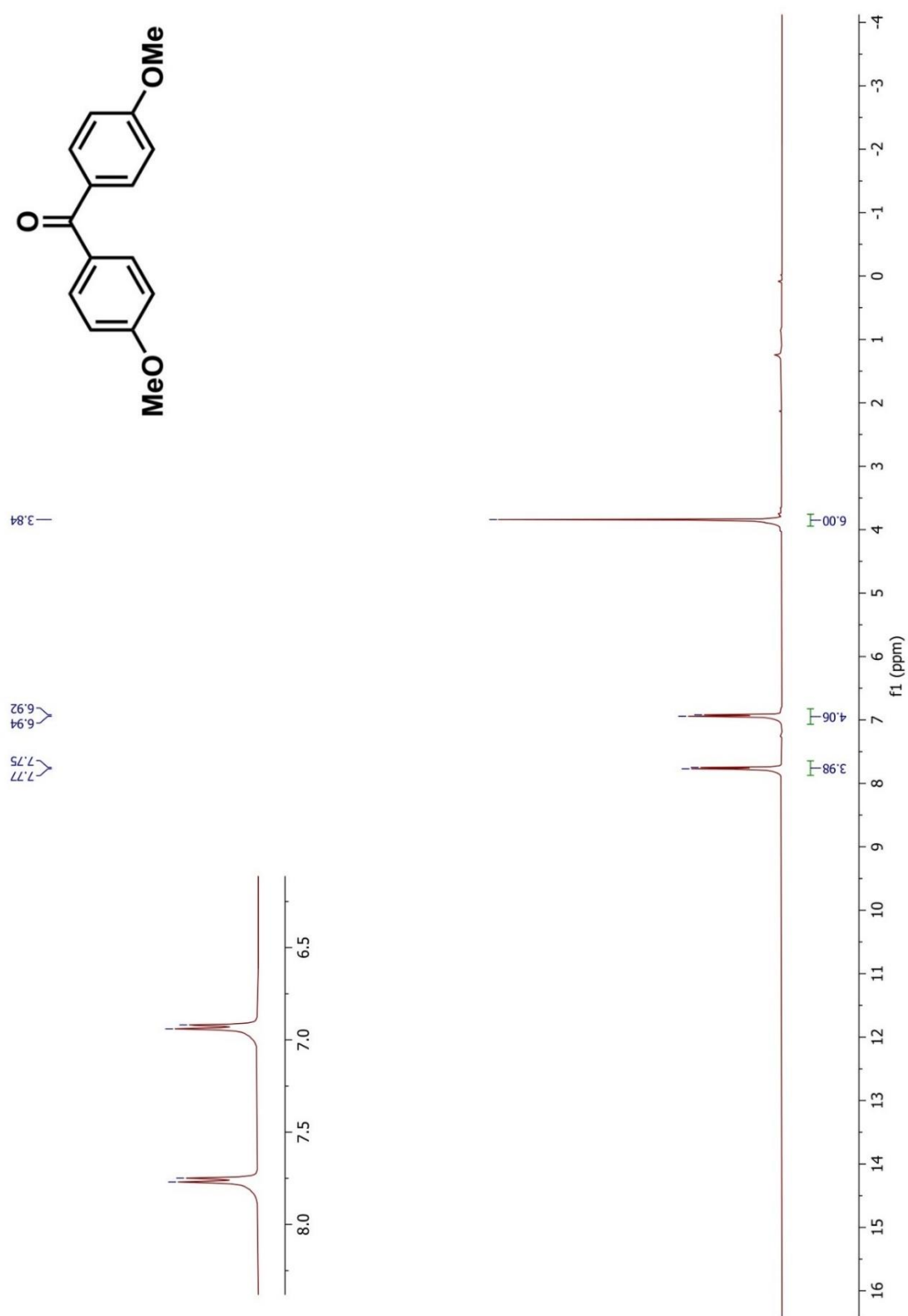


Figure 11: ^1H -NMR spectrum of **2c** in CDCl_3 .

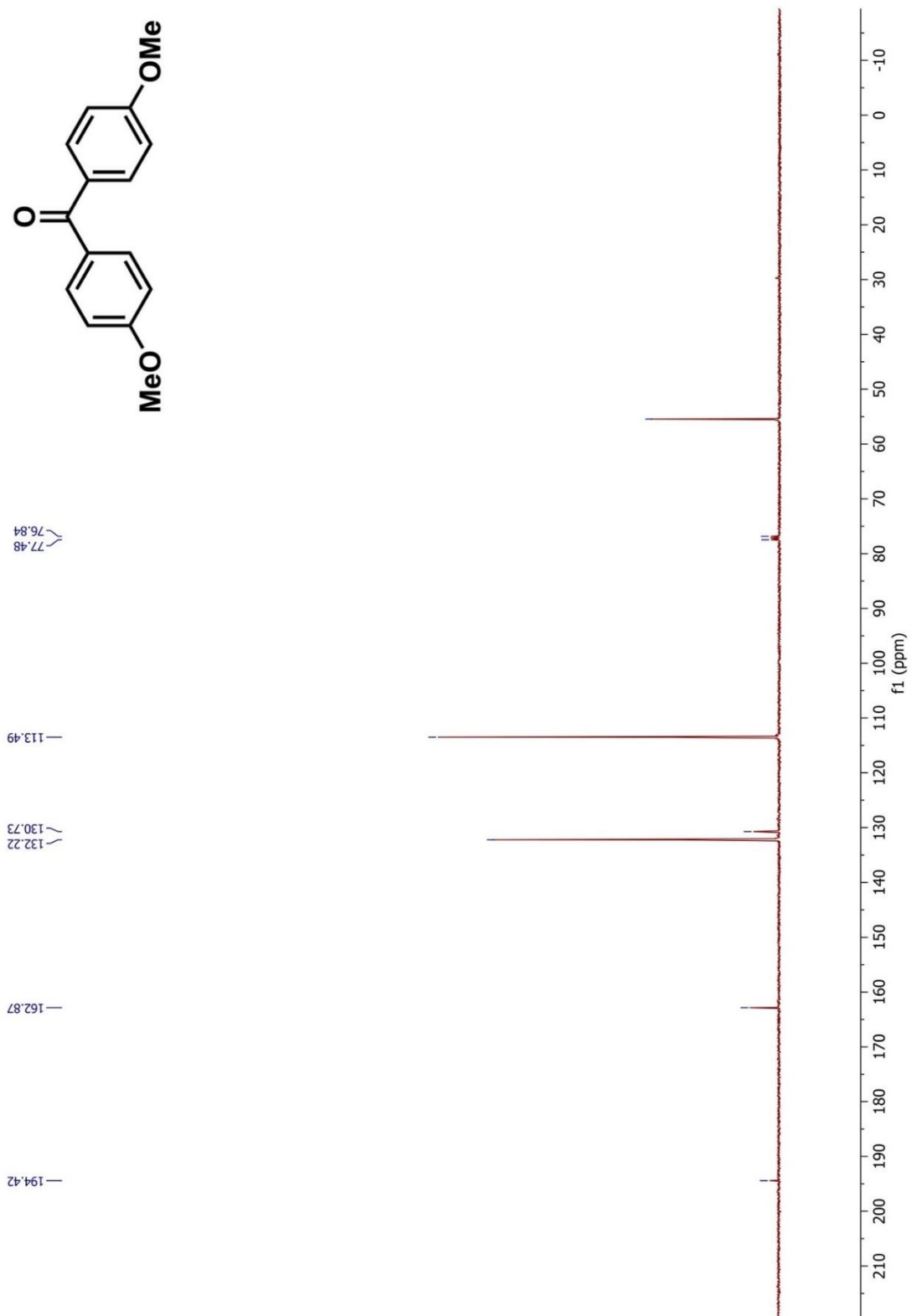


Figure 12: ^{13}C -NMR spectrum of **2c** in CDCl₃.

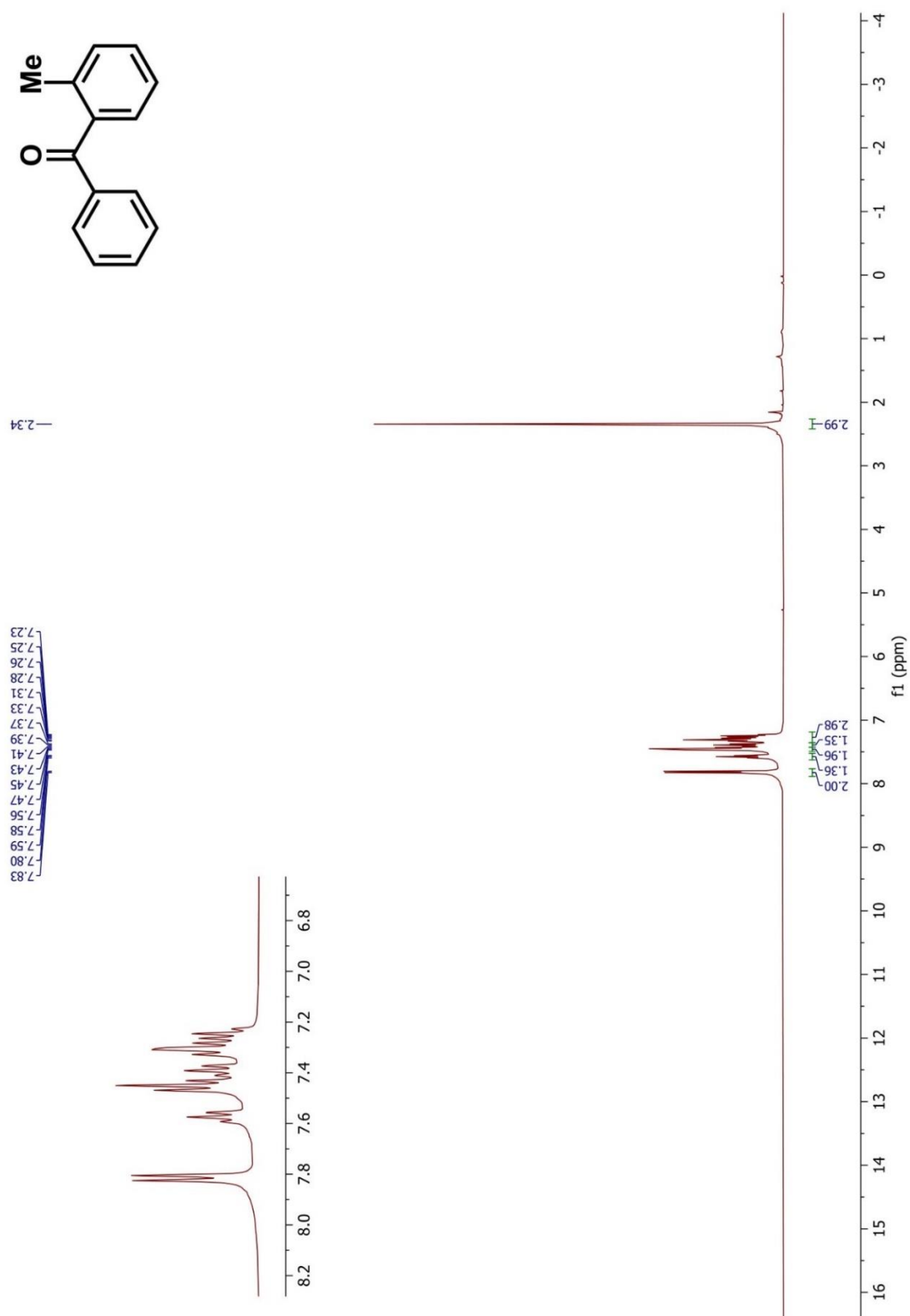


Figure 13: ^1H -NMR spectrum of **2e** in CDCl_3 .

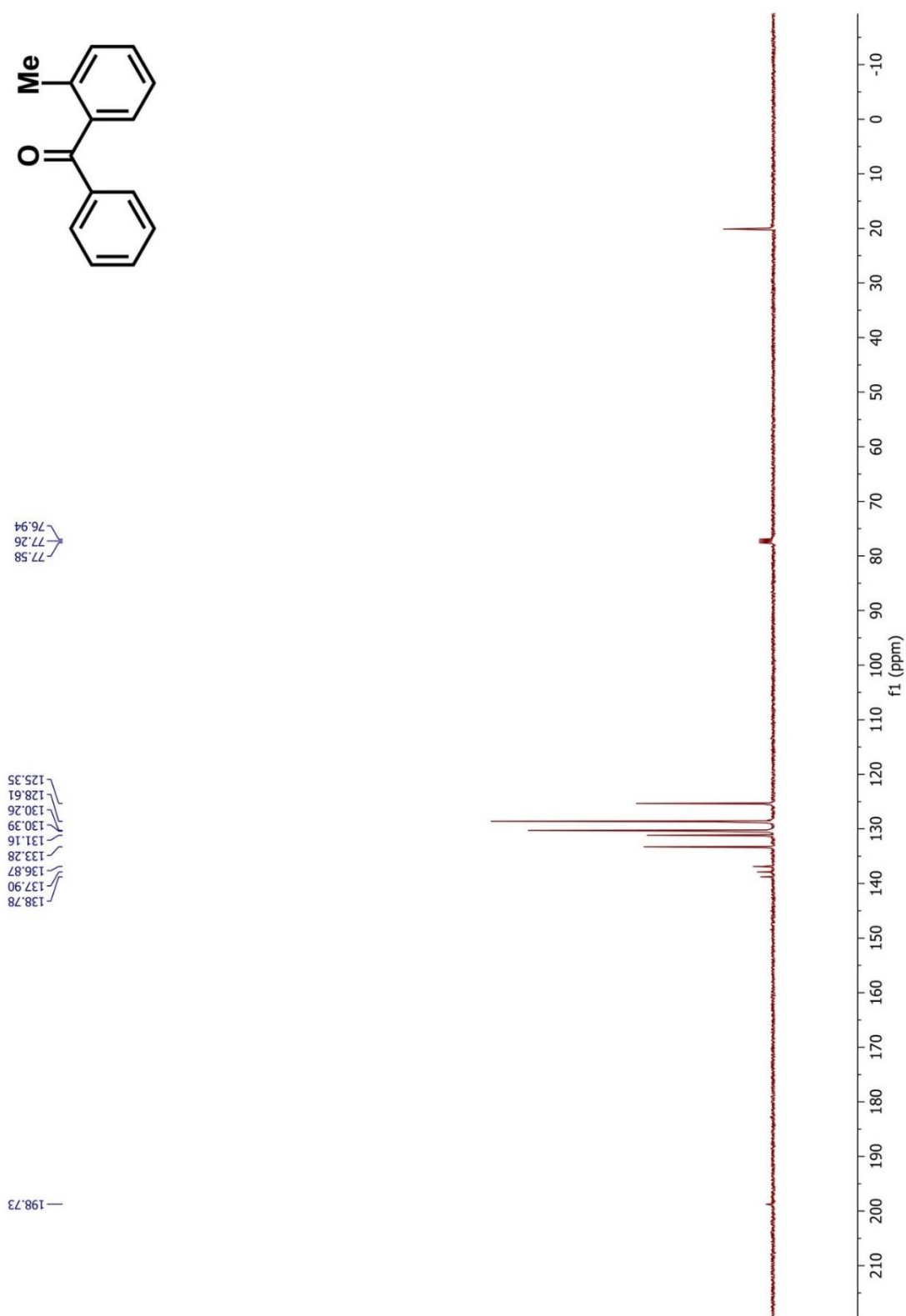


Figure 14: ^{13}C -NMR spectrum of **2e** in CDCl_3 .

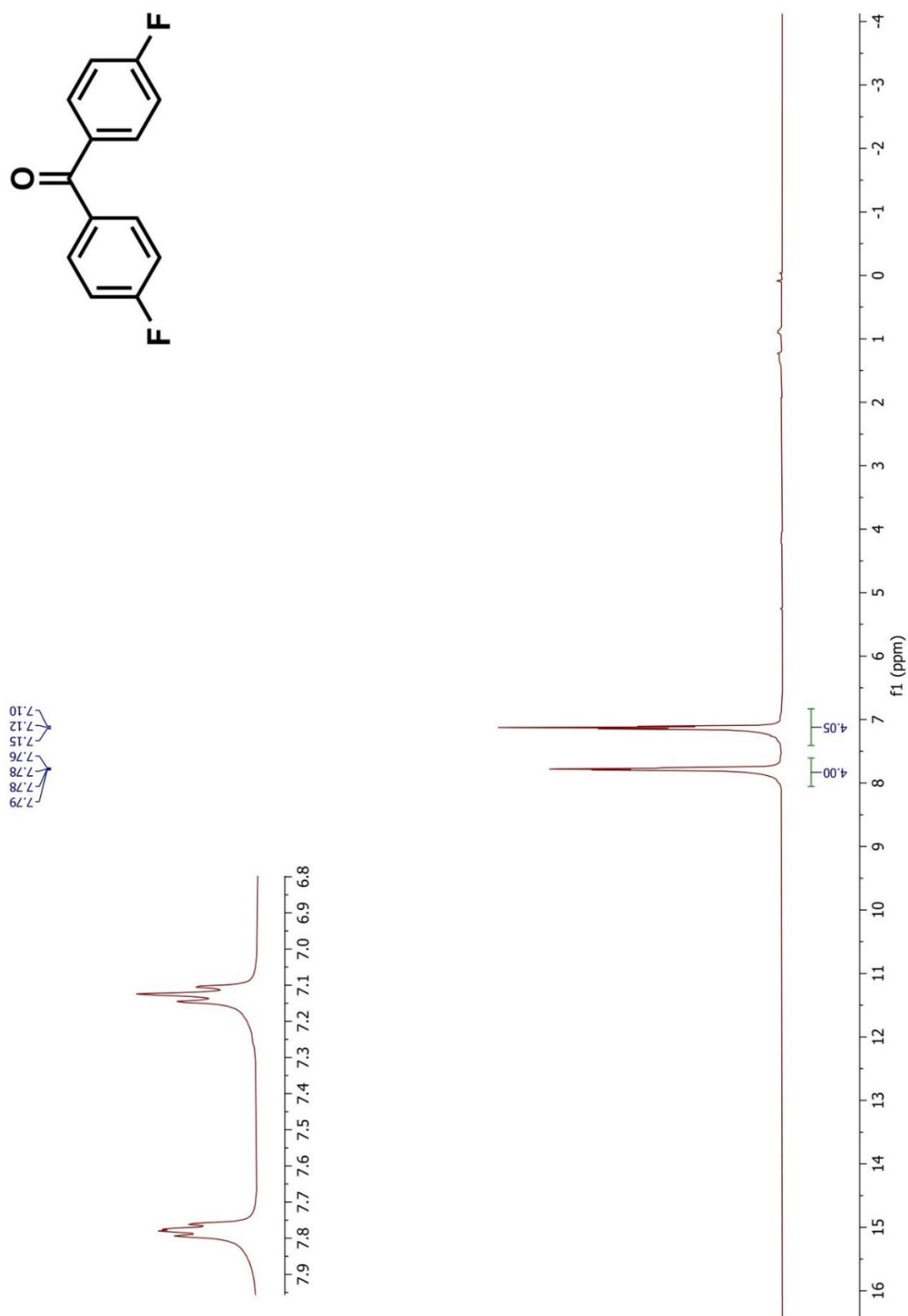


Figure 15: ¹H-NMR spectrum of **2f** in CDCl₃.



Figure 16: ^{13}C -NMR spectrum of **2f** in CDCl₃.

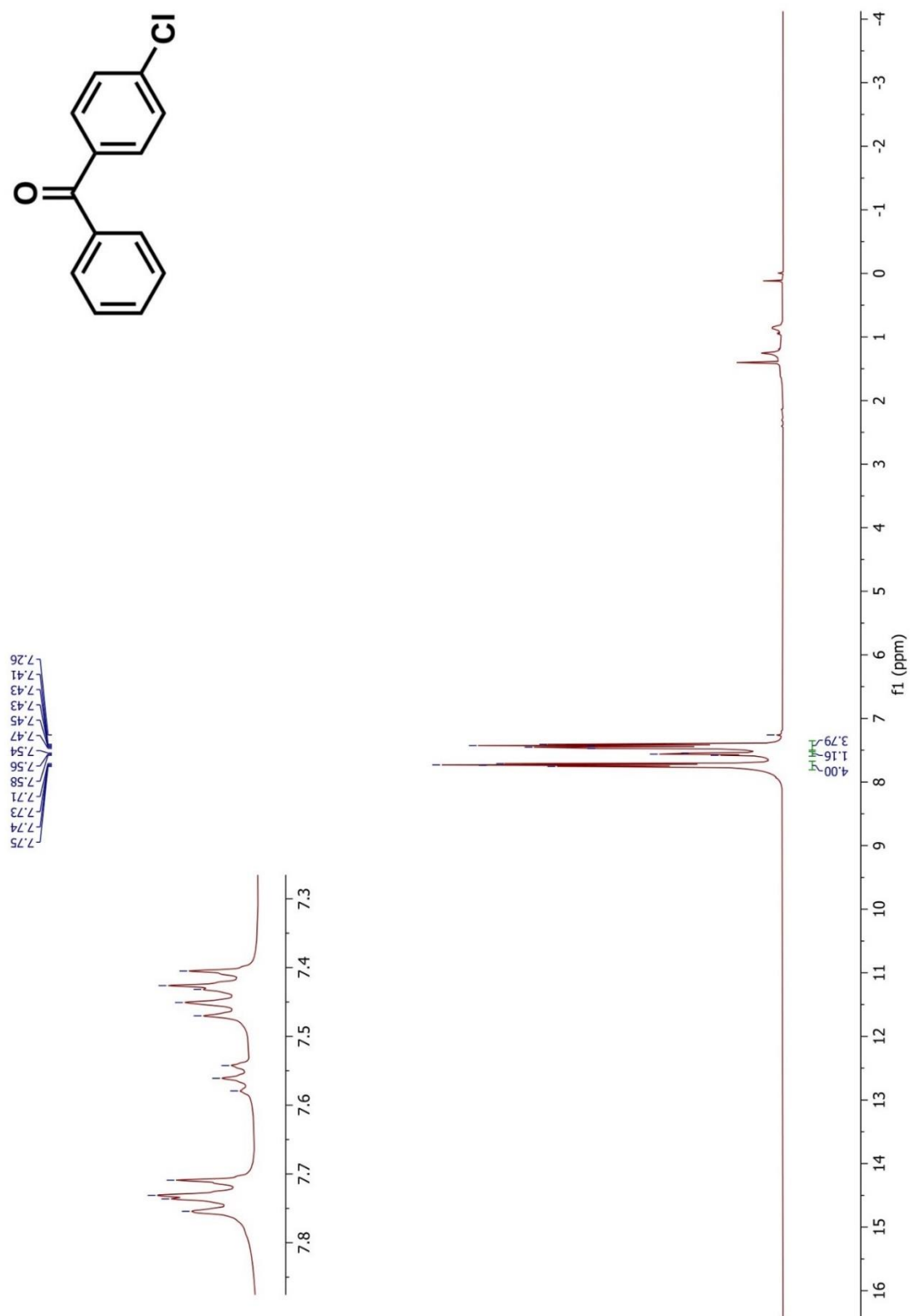


Figure 17: ¹H-NMR spectrum of **2g** in CDCl₃.

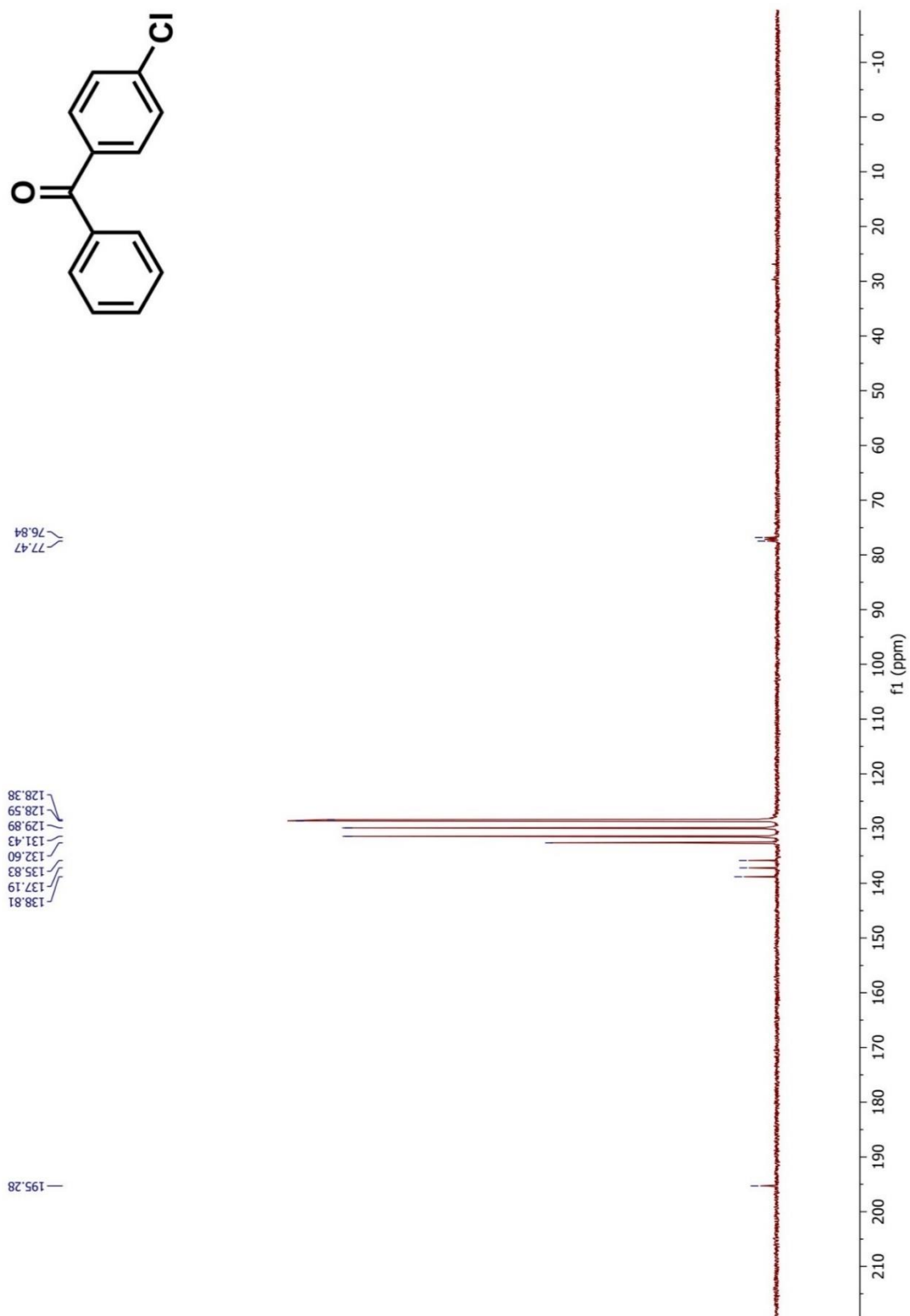


Figure 18: ^{13}C -NMR spectrum of **2g** in CDCl_3 .

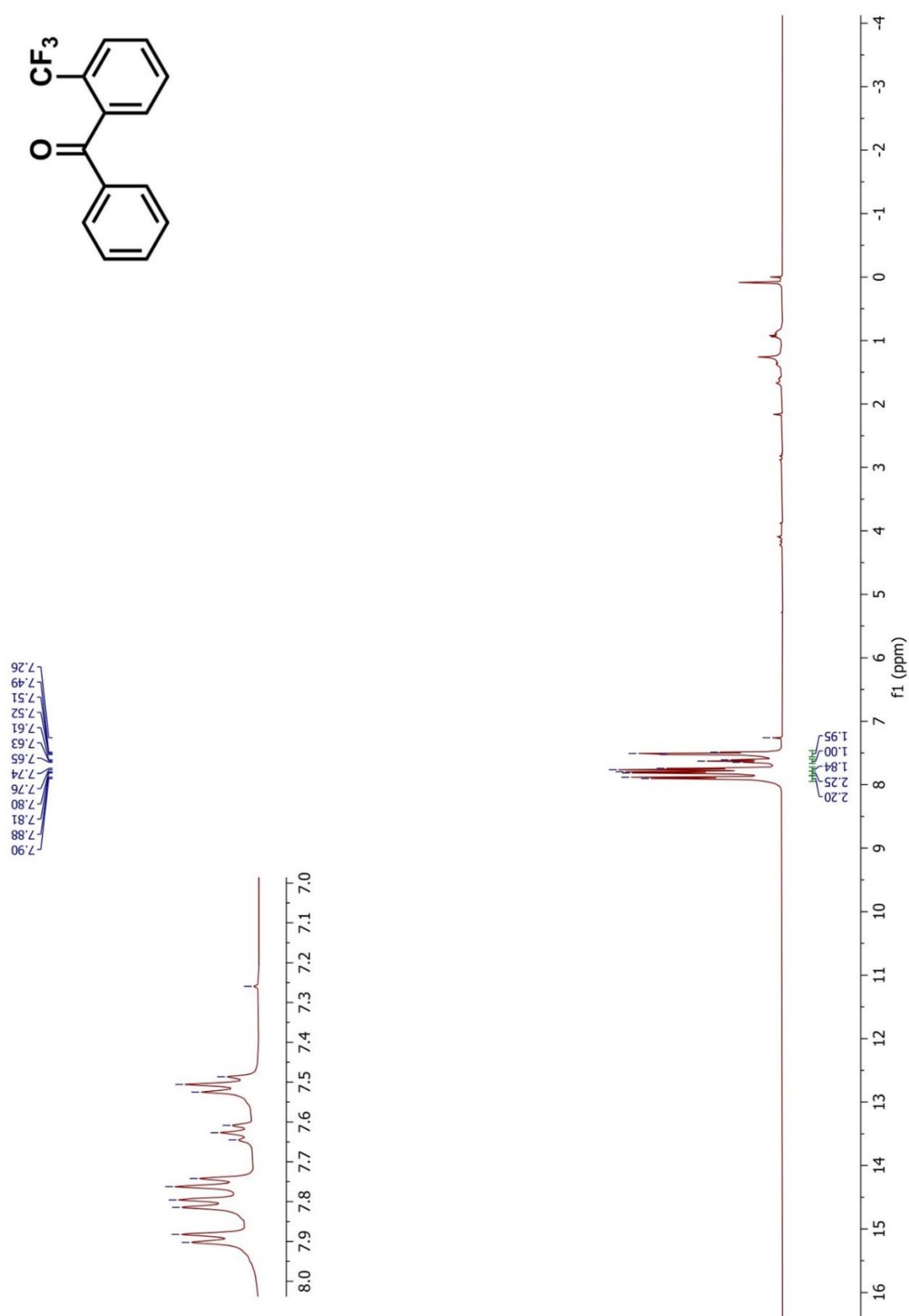


Figure 19: ^1H -NMR spectrum of **2h** in CDCl₃.

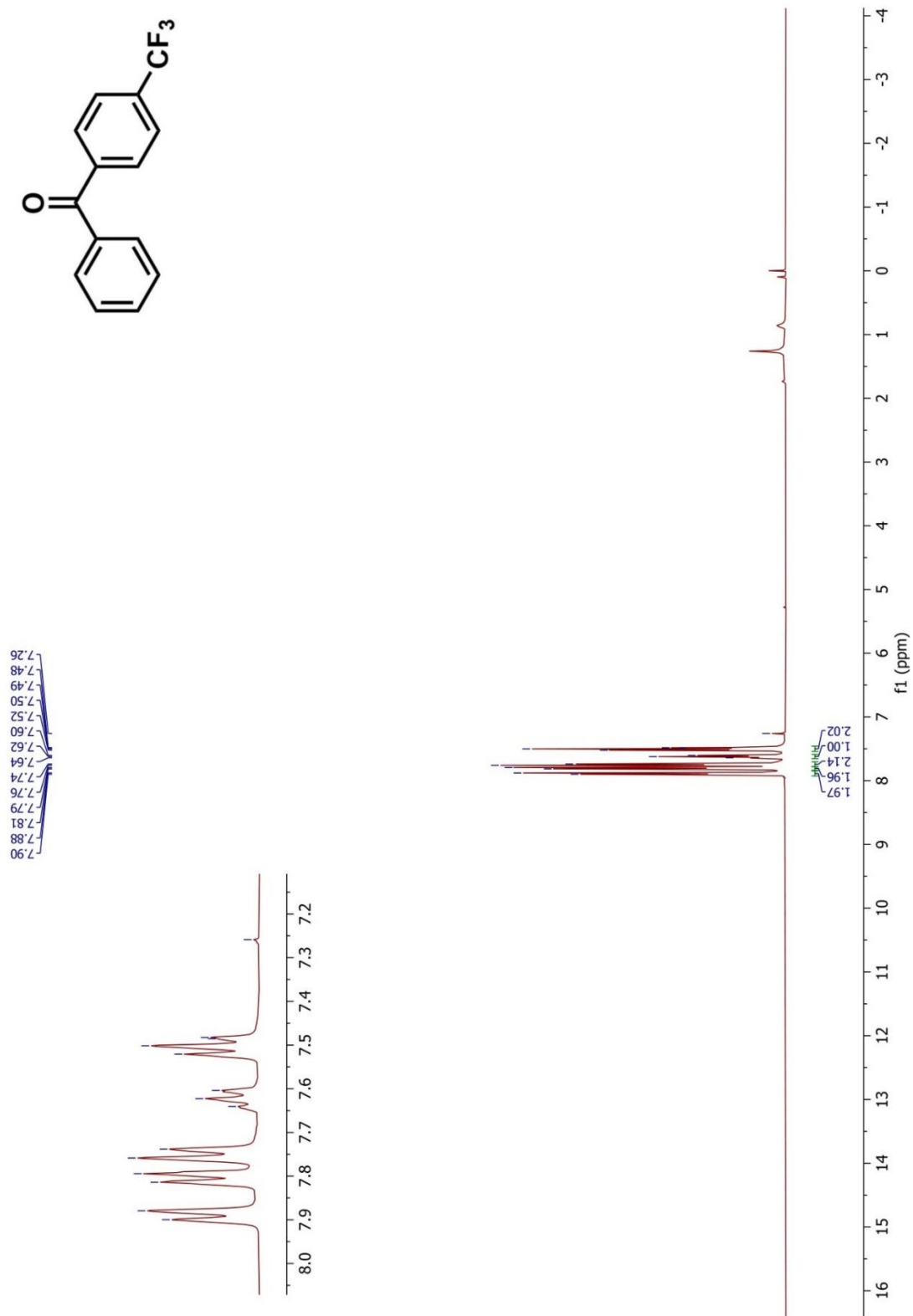


Figure 20: ^1H -NMR spectrum of **2i** in CDCl₃.

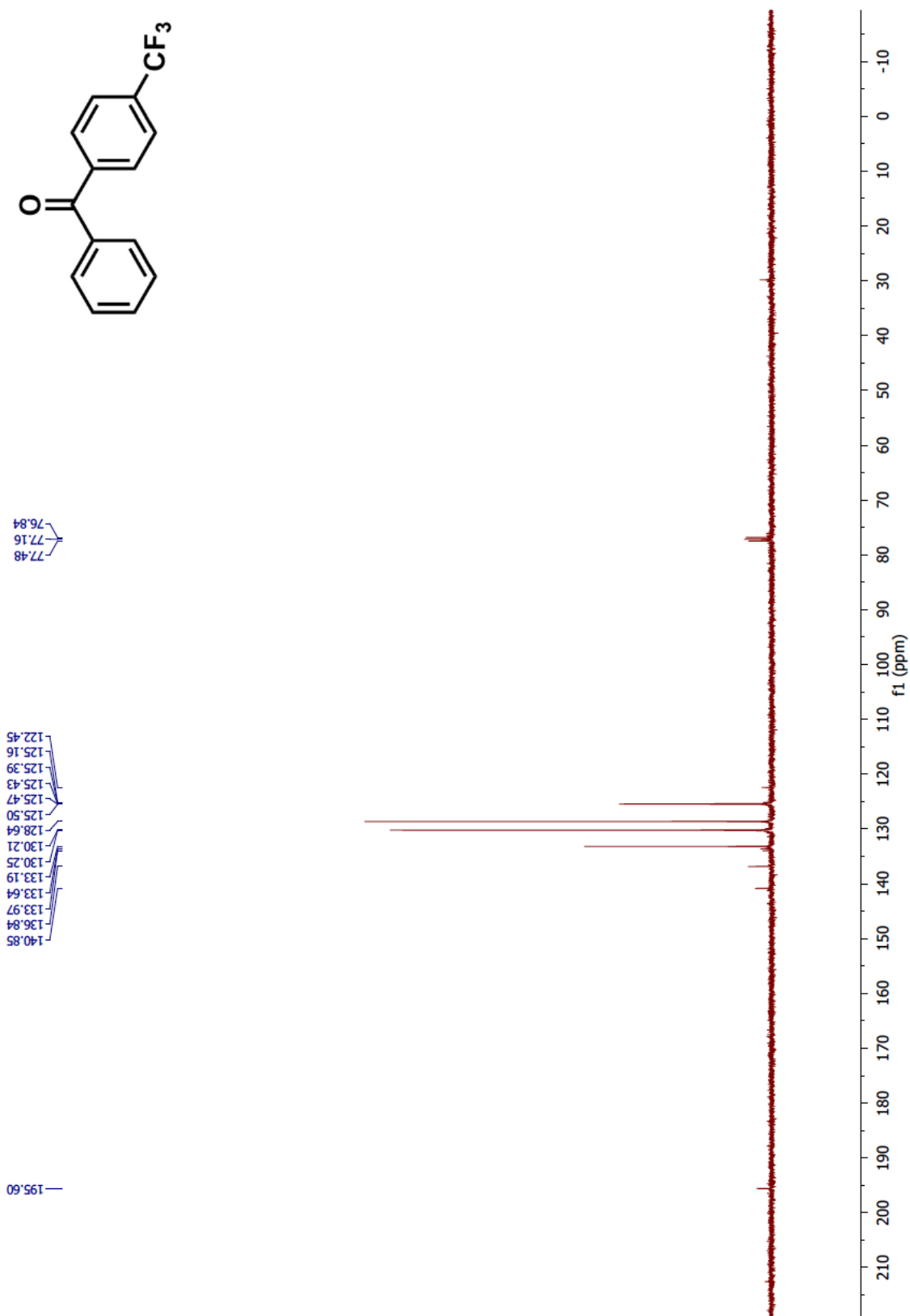


Figure 21: ^{13}C -NMR spectrum of **2i** in CDCl_3 .

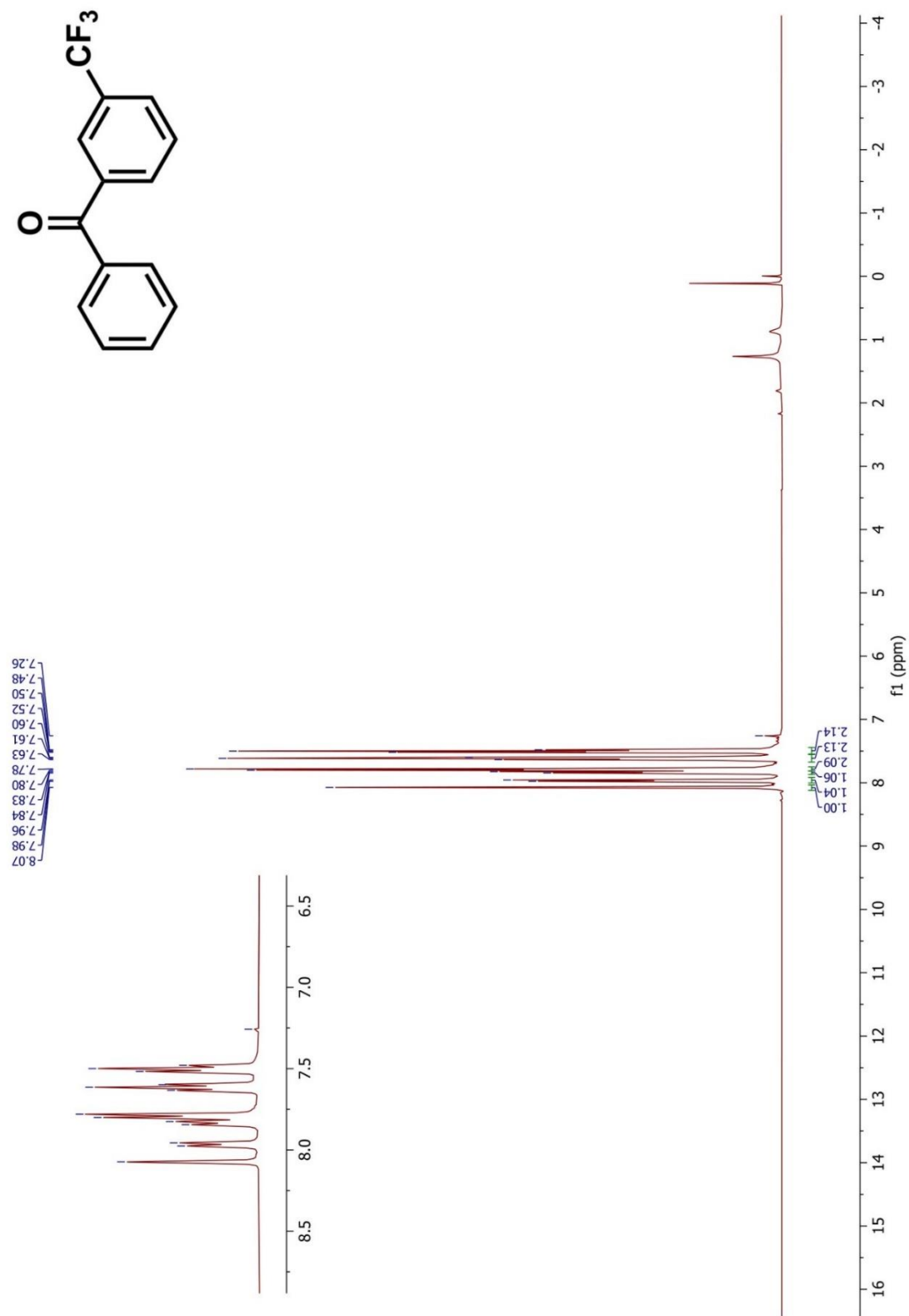


Figure 22: ¹H-NMR spectrum of **2j** in CDCl₃.

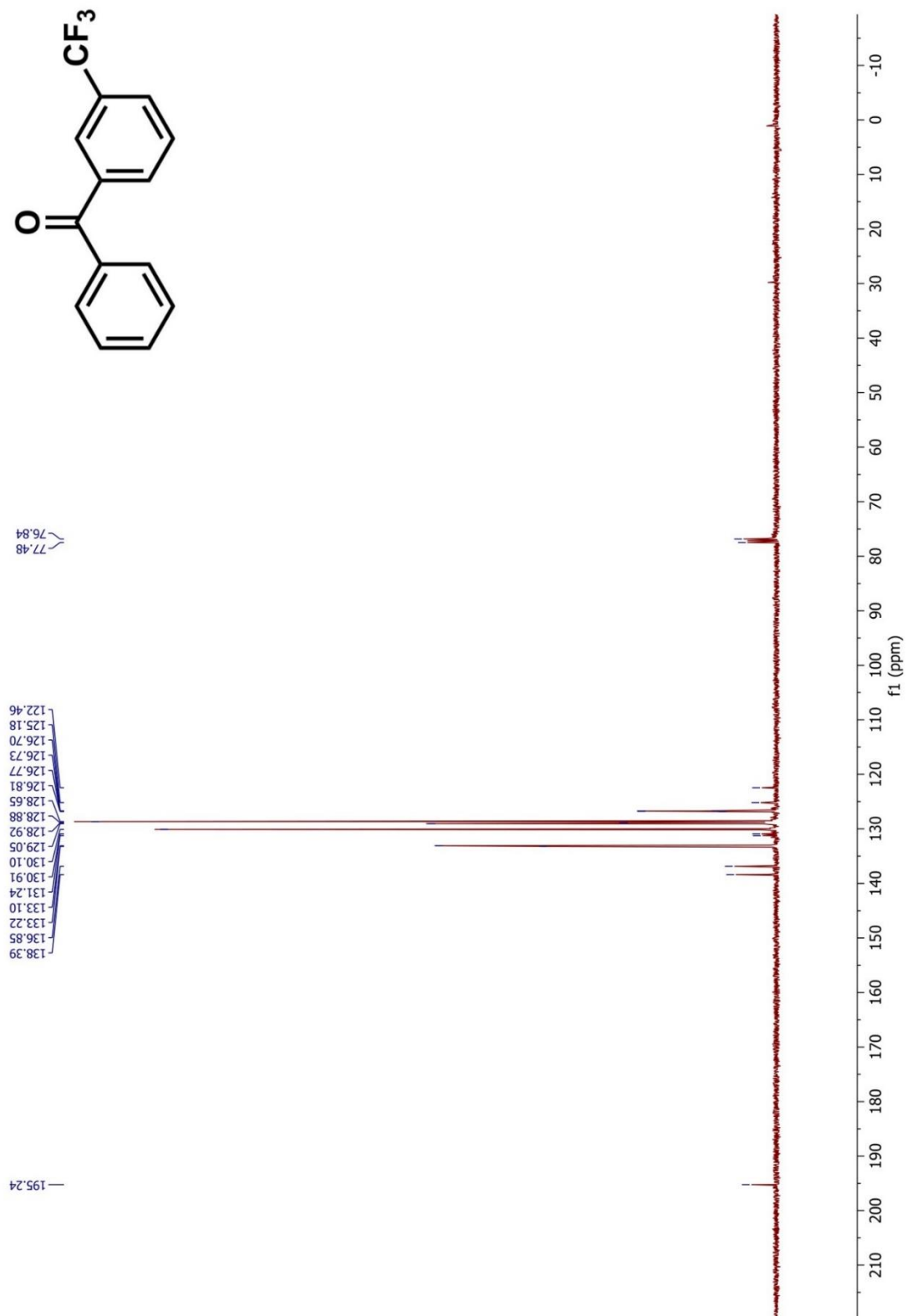


Figure 23: ¹³C-NMR spectrum of **2j** in CDCl₃.

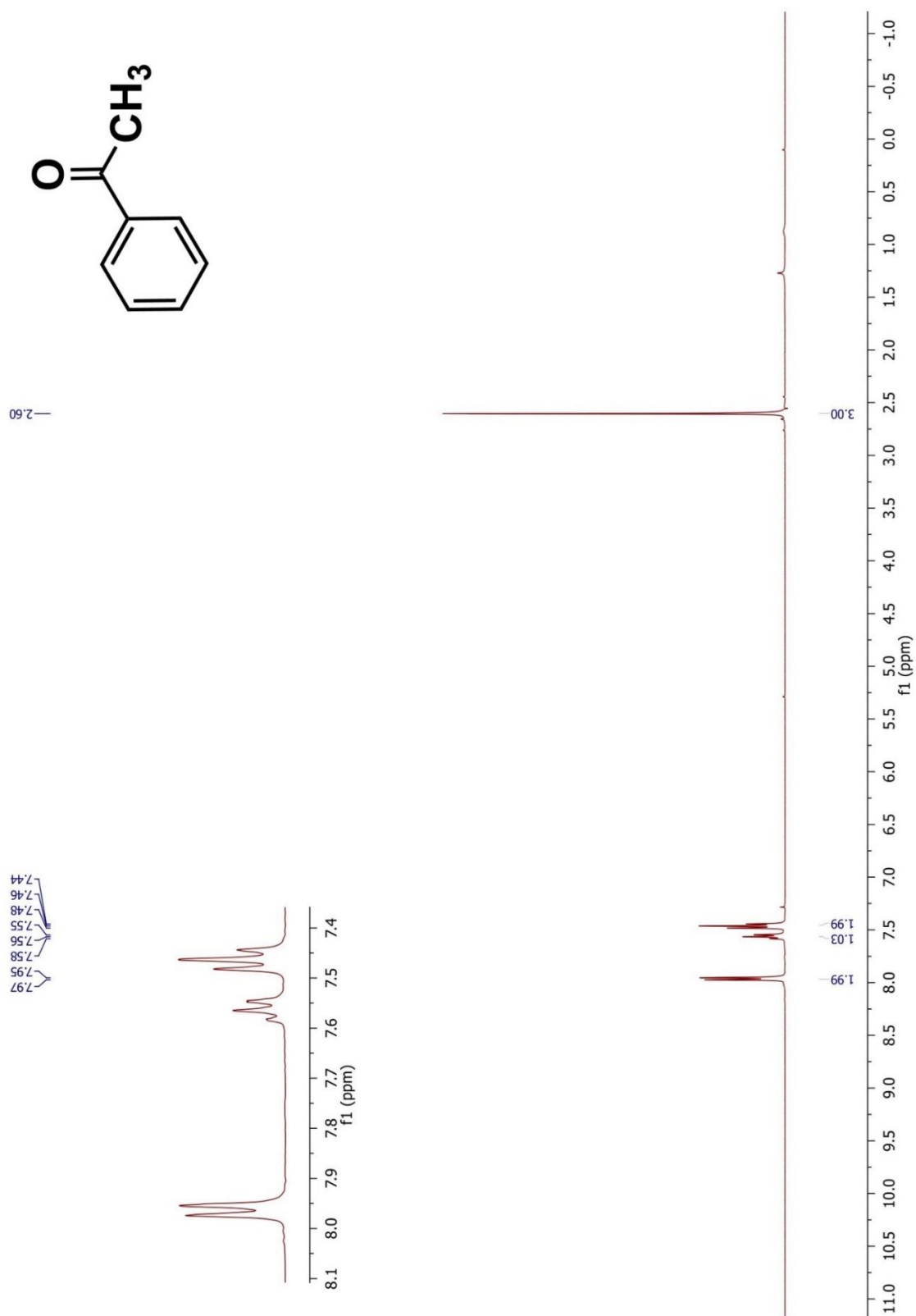


Figure 24: ^1H -NMR spectrum of **4** in CDCl_3 .

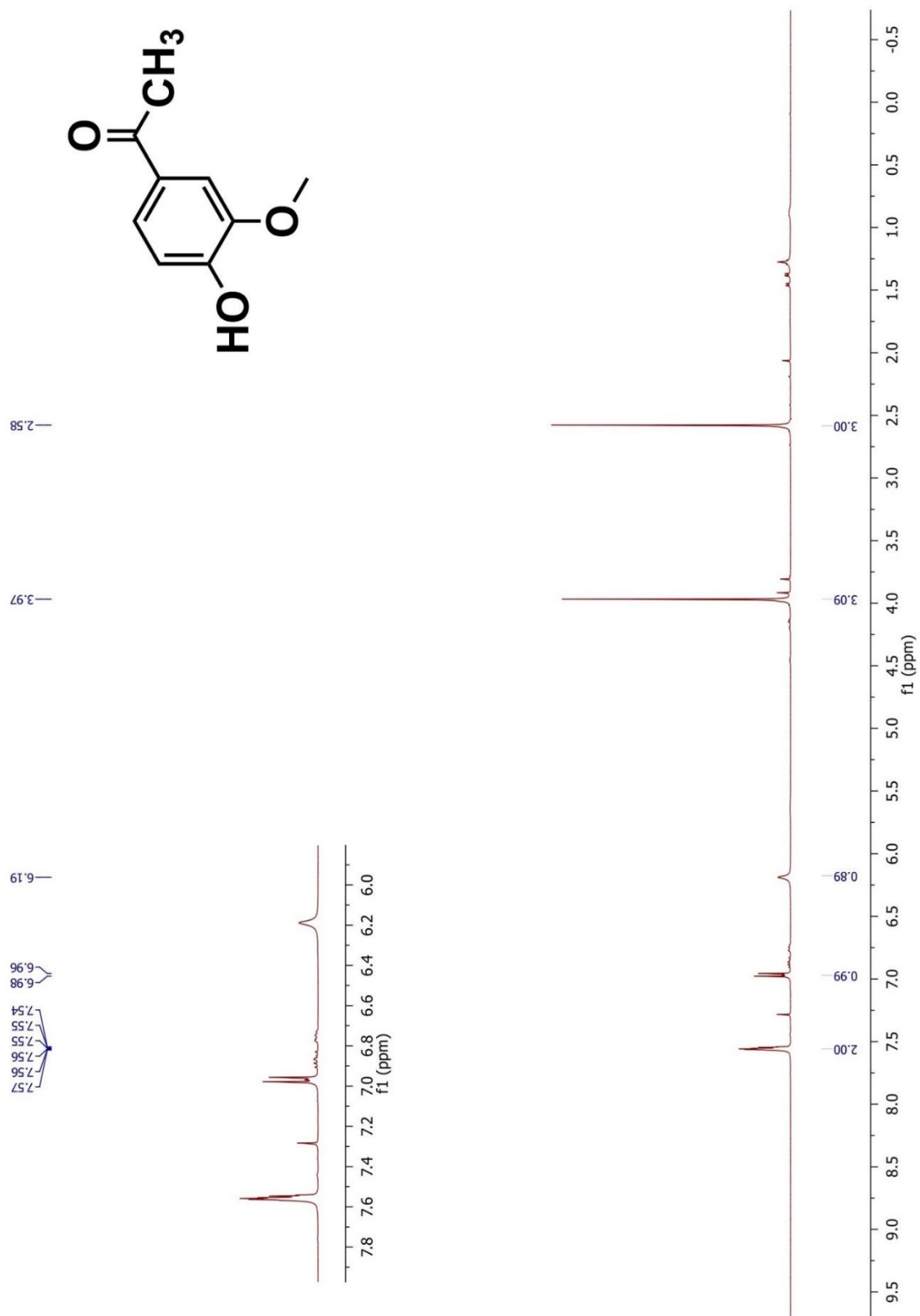


Figure 25: ^1H -NMR spectrum of **6** in CDCl_3 .

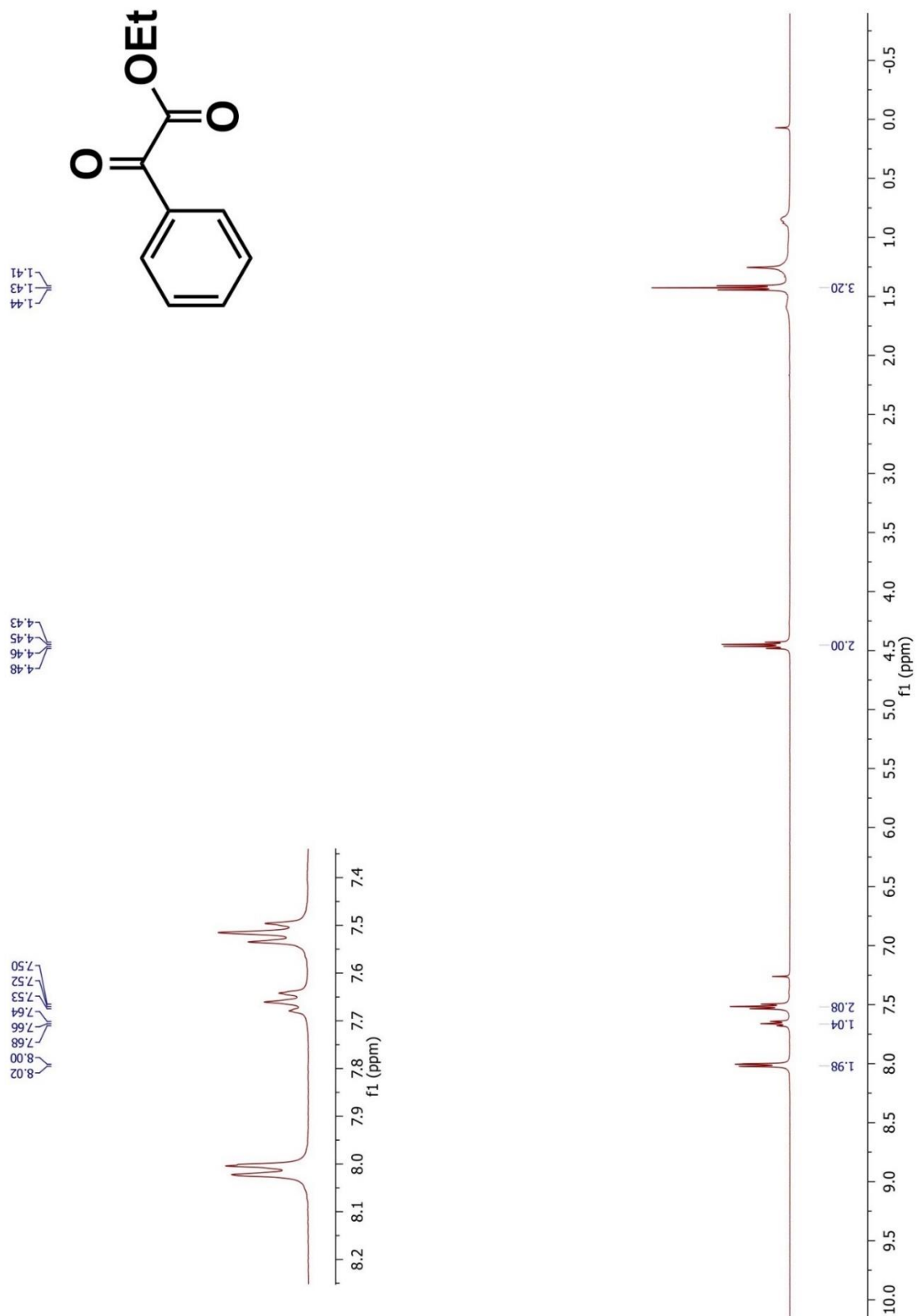


Figure 26: ^1H -NMR spectrum of **8** in CDCl_3 .



Figure 27: ¹H-NMR spectrum of **10** in CDCl₃.

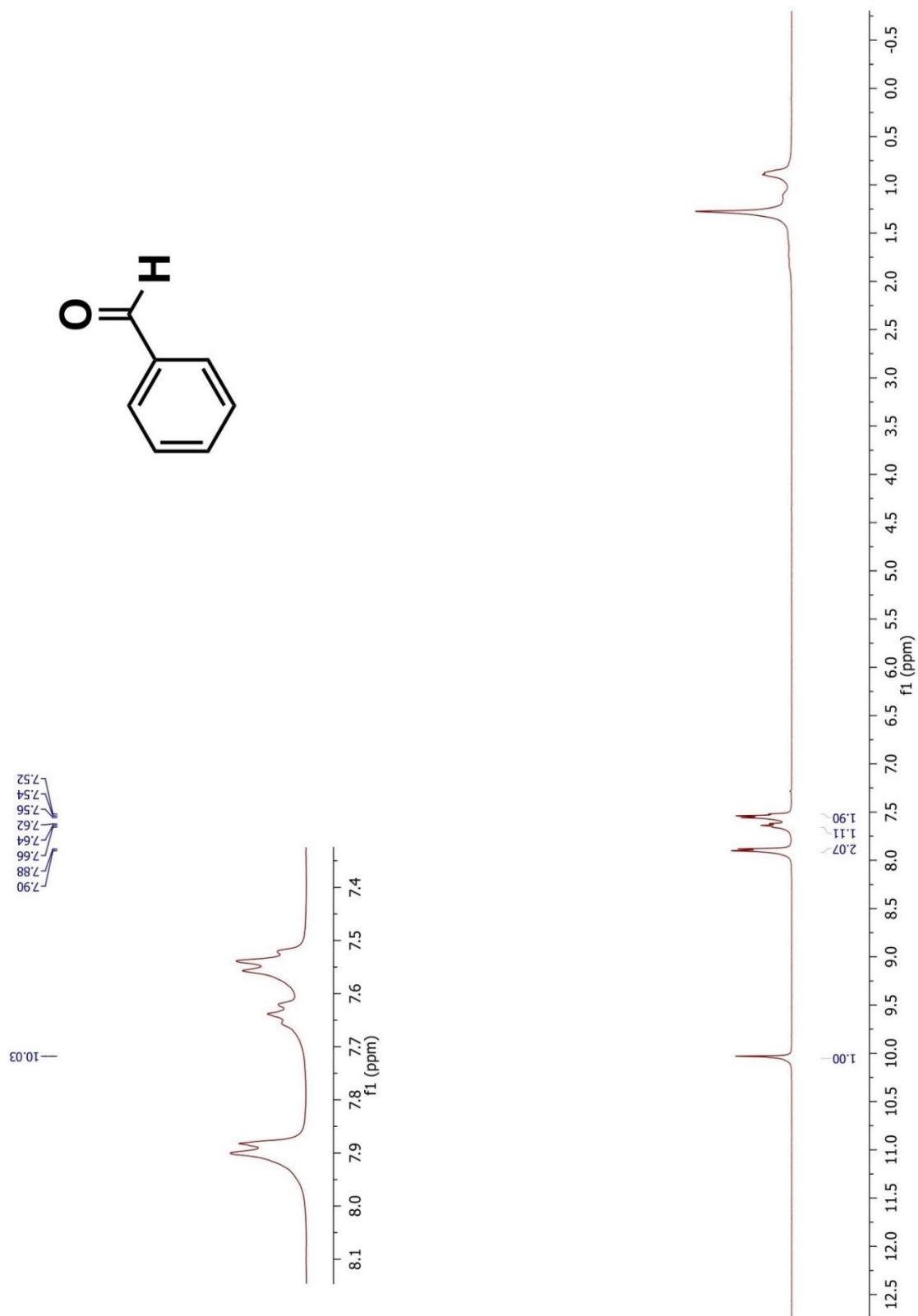


Figure 28: ^1H -NMR spectrum of **14a** in CDCl_3 .

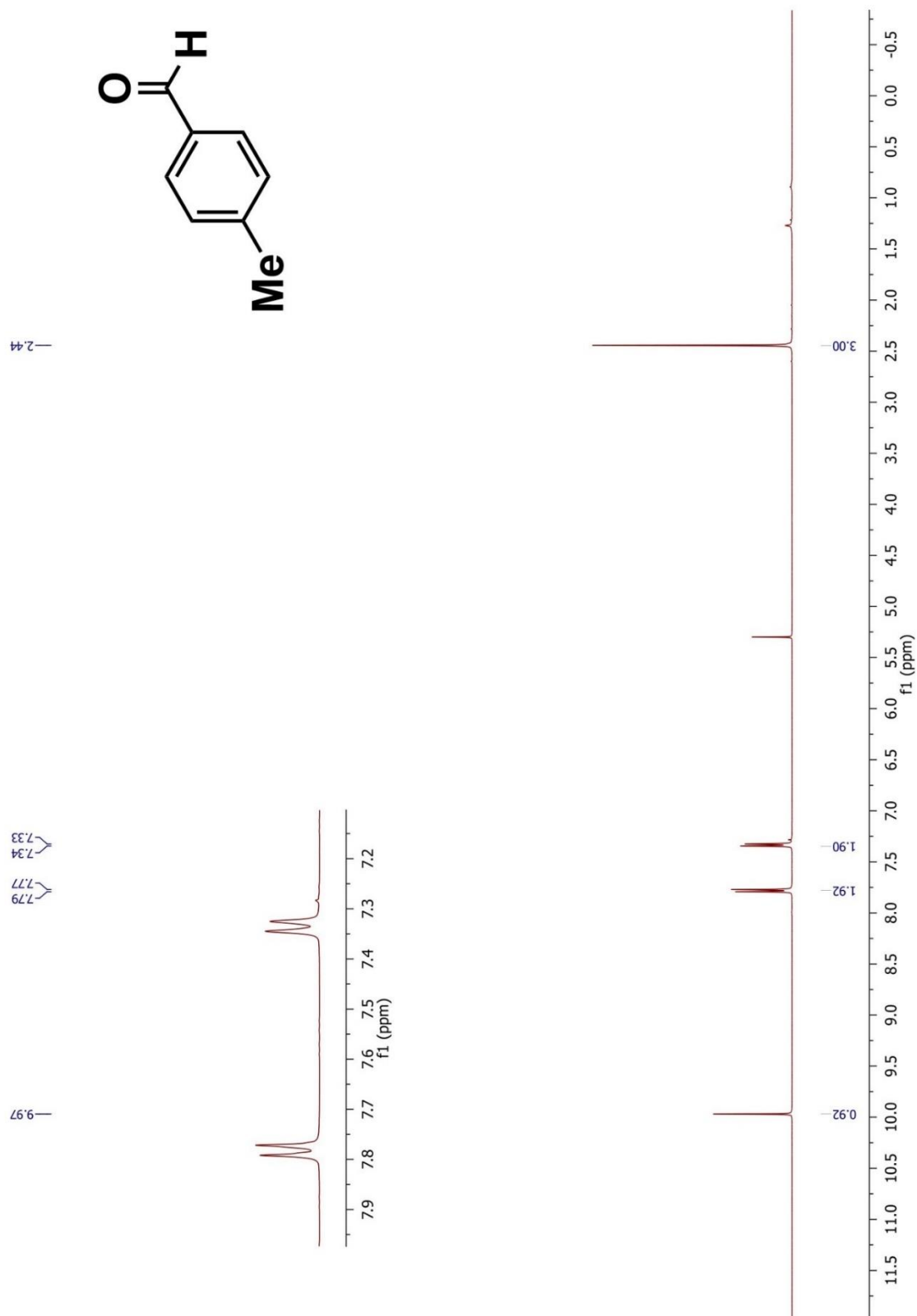


Figure 29: ^1H -NMR spectrum of **14b** in CDCl₃.

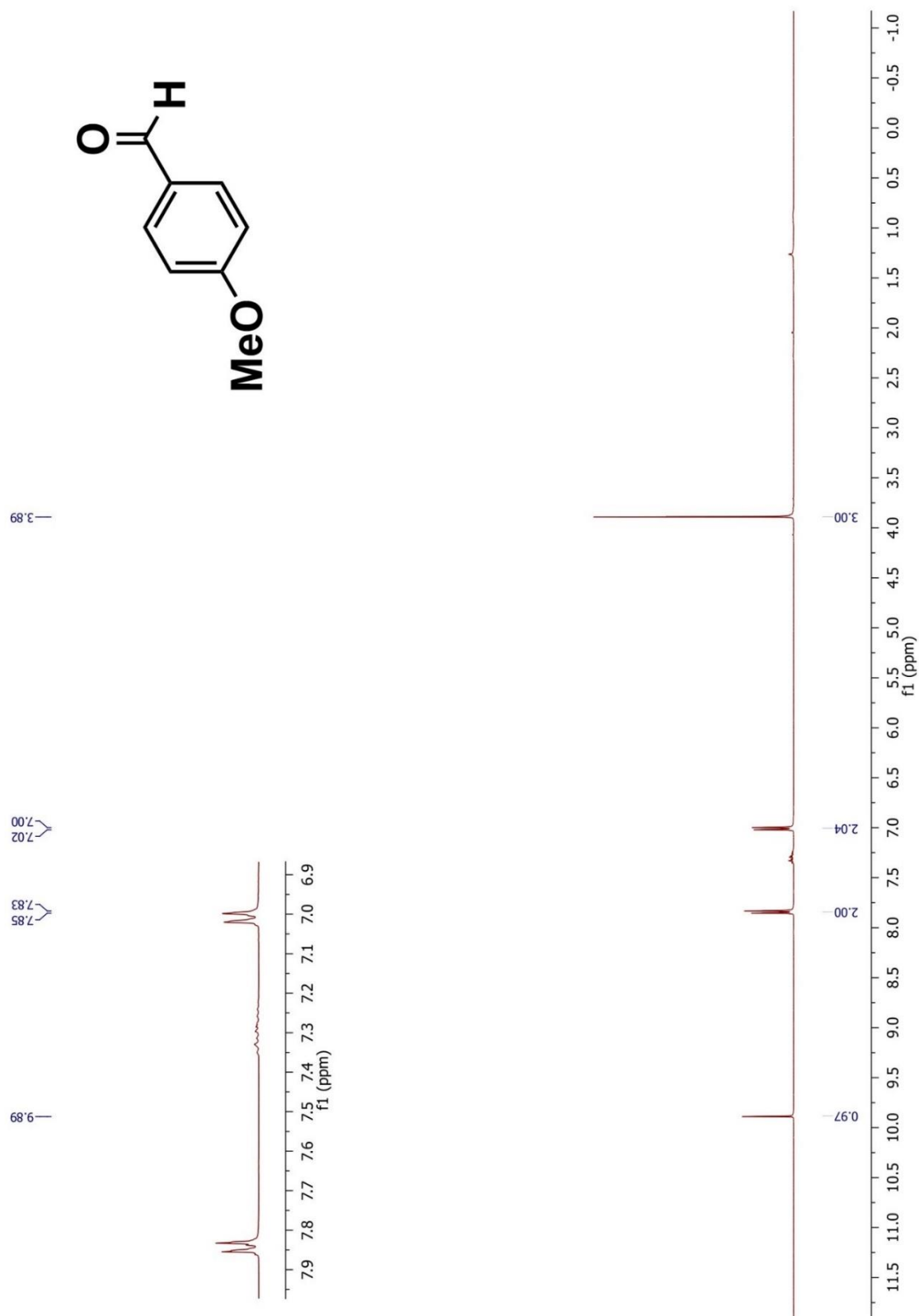


Figure 30: ^1H -NMR spectrum of **14c** in CDCl₃.

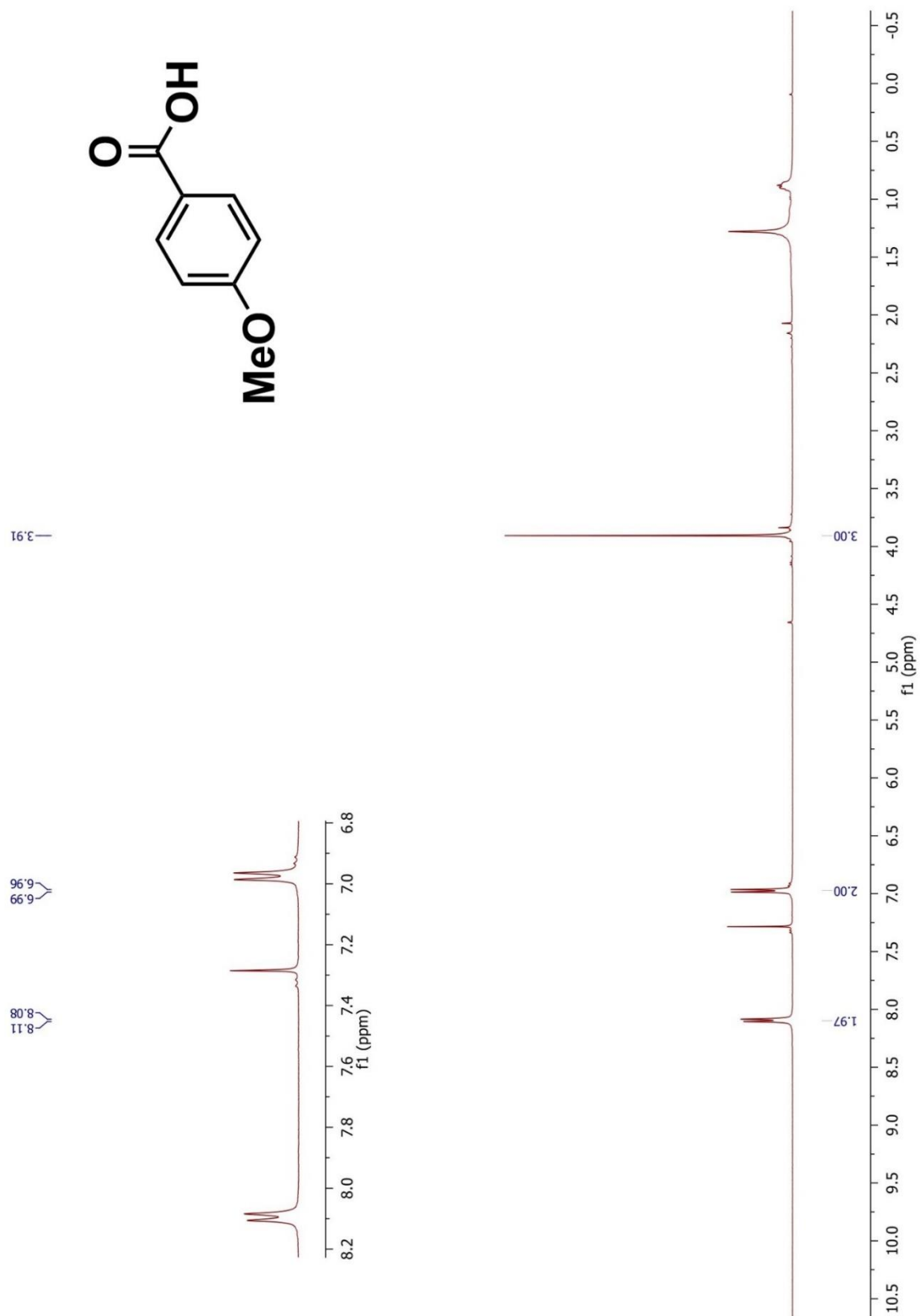


Figure 31: ¹H-NMR spectrum of **14c'** in CDCl₃.

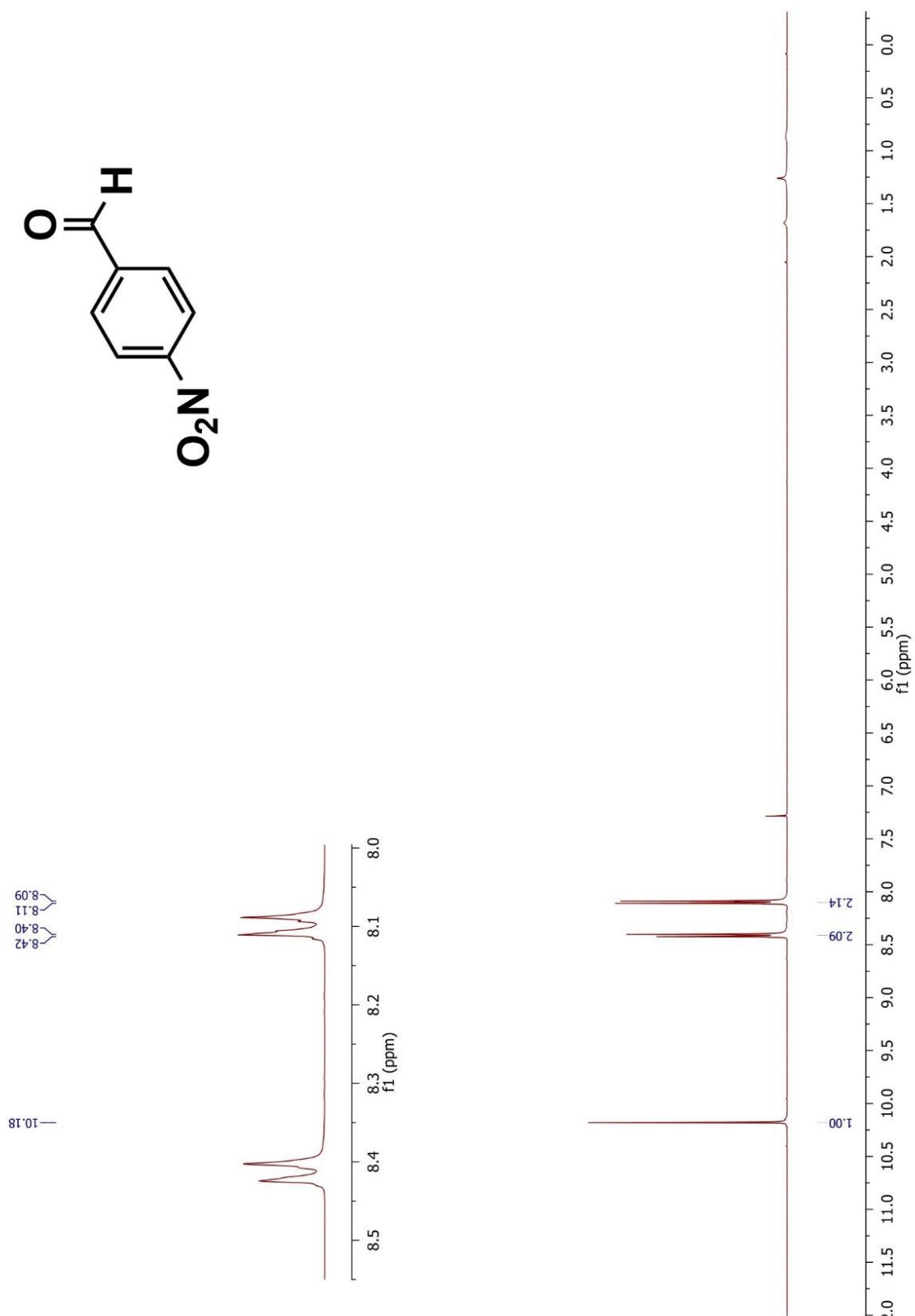


Figure 32: ¹H-NMR spectrum of **14d** in CDCl₃.

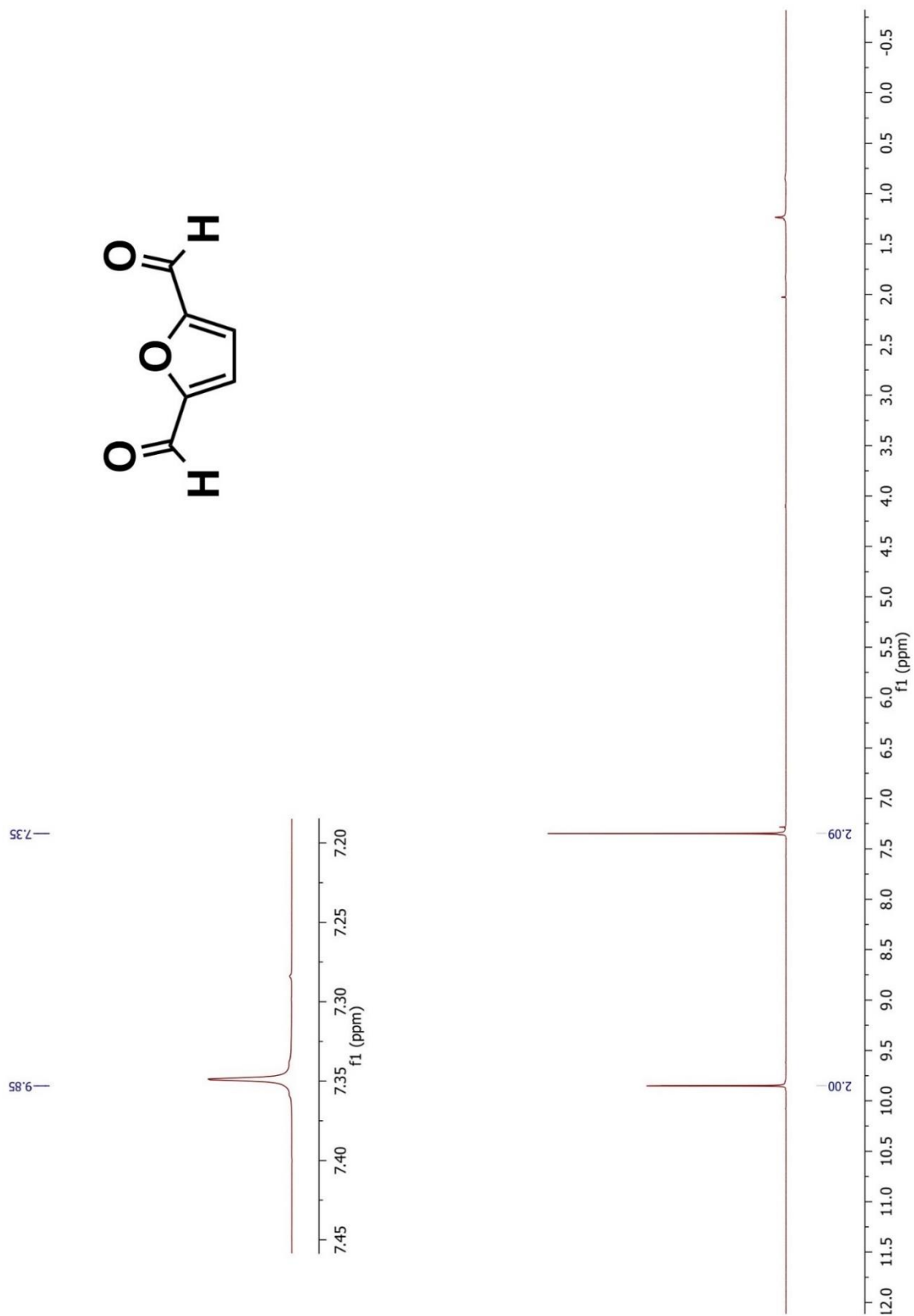


Figure 33: $^1\text{H-NMR}$ spectrum of **16** in CDCl_3 .

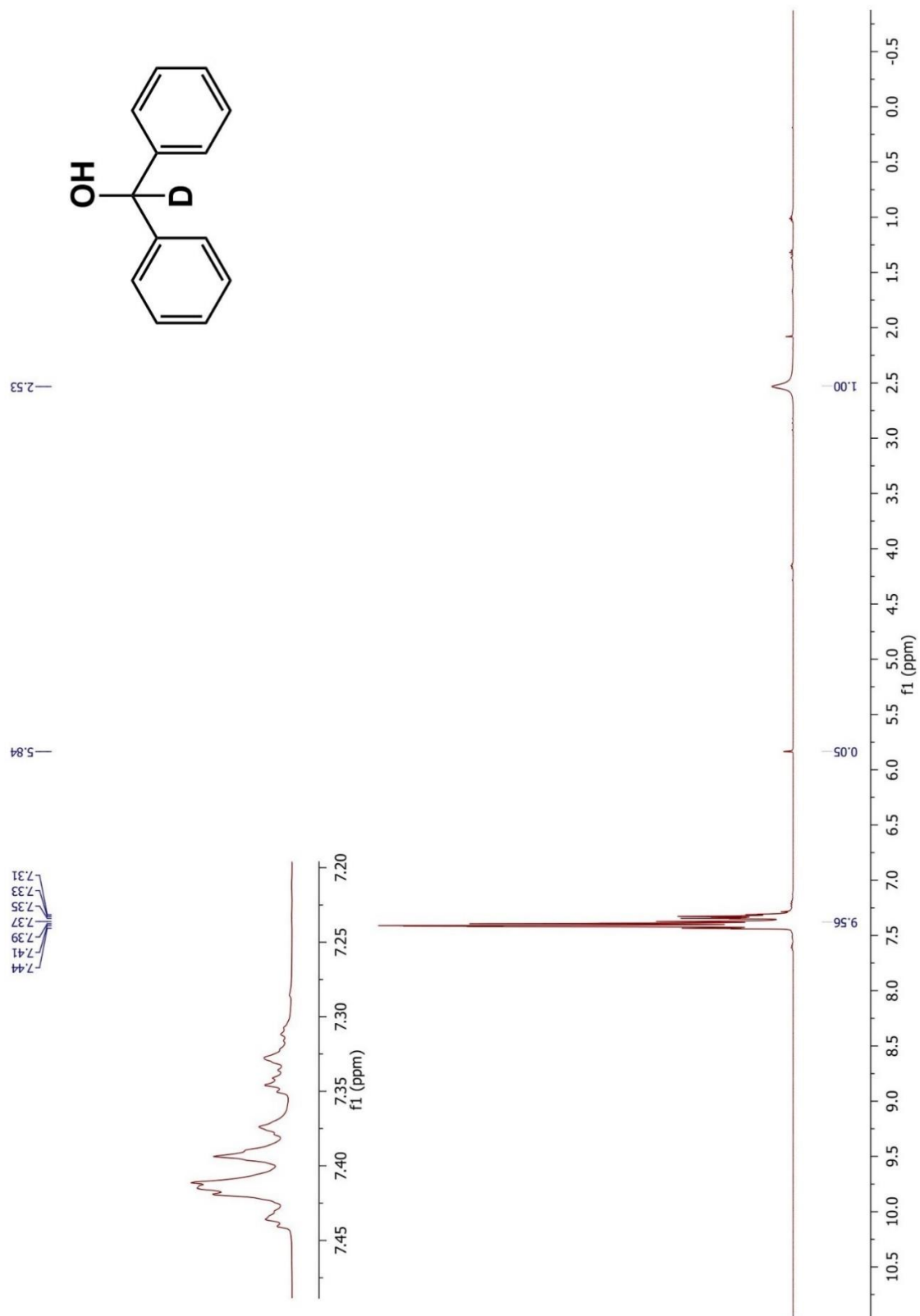


Figure 34: ^1H -NMR spectrum of **19** in CDCl_3 .

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