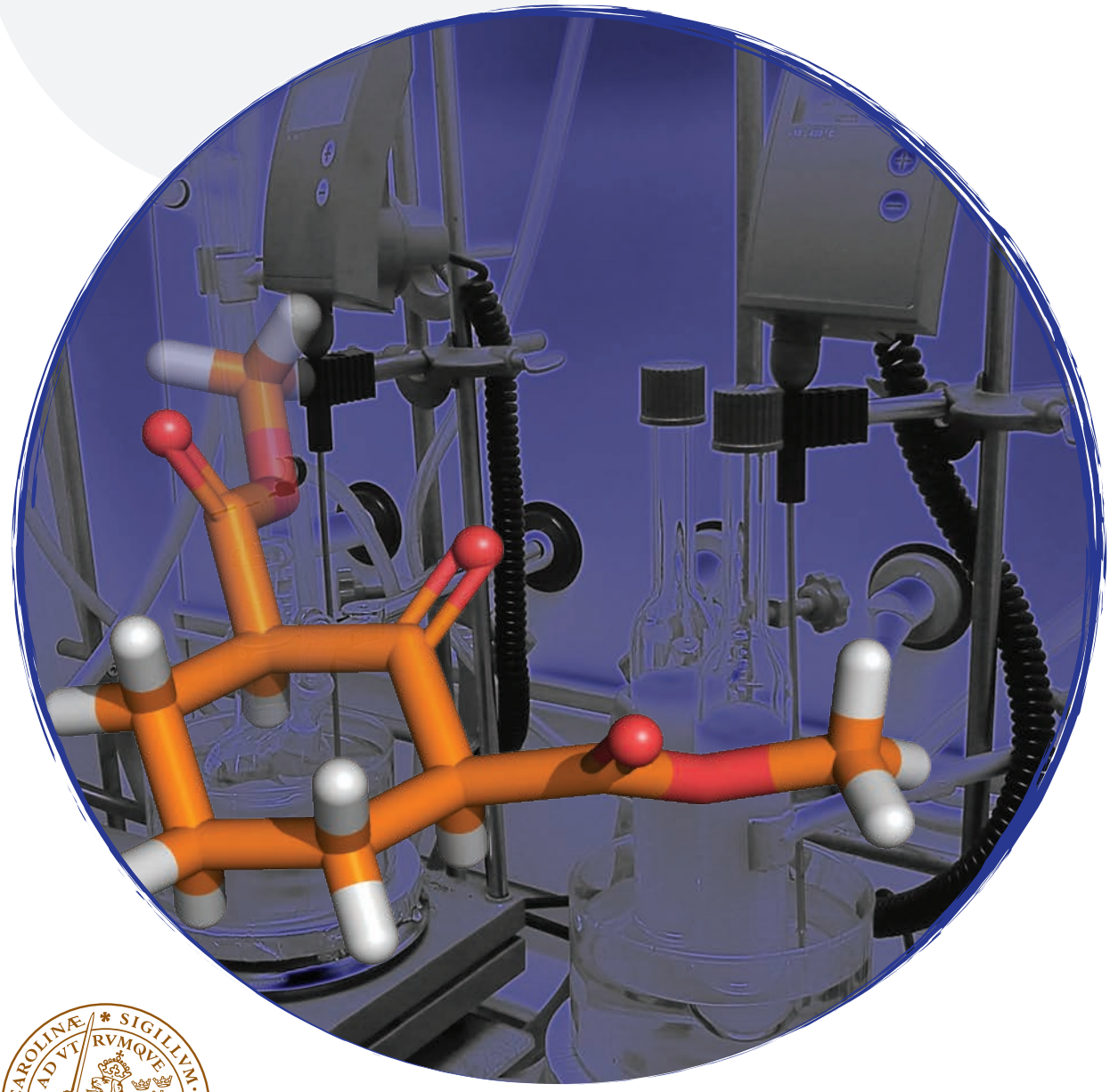
C-F activation

Towards the synthesis of a fluorinated diphosphine compound for the study of C-F activation



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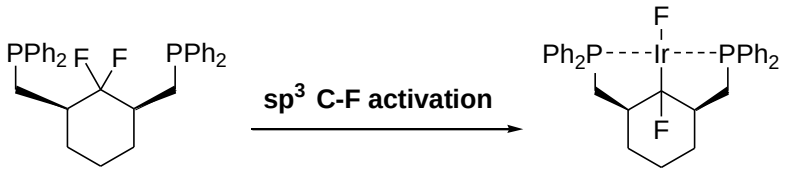
The aim of this thesis is to develop a method for the selective cleavage of a carbon fluorine bond with a transition metal. The main focus is directed towards the synthesis of a gem-difluoro, syn-diphosphine compound **XX**. When treated with iridium the metal should bind to the phosphines which keeps it close enough to the carbon fluorine bond to break it and form what is known as a PC(F)P pincer type product like **XX** which would represent an entirely new class of coordination compounds.



XX **XX**

Two synthetic reaction pathways were examined for the synthesis of the gem-difluoro compound **XX**. The first attempt was a three-step synthesis outgoing from a known cyclization of an acetonedicarboxylate followed by a fluorination reaction. The result of this proposed synthetic pathway was not successful and leading to design another synthetic reaction route which was a seven step reaction sequence where we selectively mask parts of the molecule that can cause side reactions at various points. Unfortunately this route led to the formation of a related vinyl fluoride compound rather than the desired **XX**.

In conclusion, the desired gem-difluoro compound **XX** for as not reached via the two examined strategies and towards a molecular vehicle for the study of sp^3 C-F activation further investigations are required.

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II. Abbreviations

L	Ligand
M	Metal
NBE	Norbornene
PMA	Phosphomolybdic acid
TFA	Trifluoroacetic acid

III. Abstract

The Wendt group at LU has recently developed a new class of sp^3 pincer type ligands through the selective C-H bond activation which introduced a rare example of PC(sp^3)P pincer Pd(II) complex.

In the present study, we aim to obtain insight into the selective cleavage of the sp^3 C-F bond by insertion of iridium metal. We are particularly interested in performing this reactivity on a gem-diflouro, syn-diphosphine structure for studying sp^3 C-F bond activation to generate an entirely new class of coordination compounds.

1. Introduction

1.1. C-F bond activation via metal complexes

An interesting area of research that has recently attracted inorganic and organometallic chemists is the coordination and activation of fluorocarbons by transition metal complexes. In general fluorocarbon compounds are reluctant to coordinate to metal centers and resistant to chemical attack thus this activation reminds a challenging goal due to the high strength of these bonds and also small size and high electronegativity of the fluorine atom.

Fluorine is much more electronegative than carbon. That means that fluorine attracts the bonding pair of electrons much more strongly than carbon. The bond length is on the order of 1.35Å versus 1.0 Å for C-H bond thus this is the strongest and relatively short single bond in organic chemistry. The short length of the bond can also be attributed to the ionic character between the partial charges on carbon and fluorine. Moreover, the potency of the fluorine atom to act as both a δ-acceptor and a π-donor make the C-F bond with great strength. Thus selective cleavage of this bond by insertion of transition metals represents a significant challenge.

Transition metals are employed as catalyst in several industrial processes including the conversion of hydrocarbons, such as olefin hydrogenation, hydroformylation and polymerizations.[1] Interaction of the transition metal with the fluorocarbon may ultimately lead to the cleavage of the robust carbon fluorine bonds.

The work on C-F bond activation at transition metal complexes would be seen in the broad context of the multiple applications of fluorinated organic molecules such as pharmaceuticals, pesticides, catalysts, polymers, refrigerants, solvents, liquid crystals, etc.[2]

Unfortunately, examples of carbon fluorine bond activation by metal complexes are rare. Several factors have contributed to the lack of this study. The one reason can be the instability of combination of a low-valent metal center and a fluoride ion. Another factor can be contributed to the deficiency of convenience ways to build fluoro ligands. Most starting materials used for synthesizing organometallics are more readily available and more easily handled as chloro or bromo derivatives, but working with elemental fluorine and hydrogen fluoride are major limitations to synthesis organo fluoro compounds.

It can be classified the fundamental process of intermolecular C-F bond activation in the following six categories:

1. Oxidative addition of fluorocarbon

   $[M] + R\text{-}F \longrightarrow R\text{-}[M]\text{-}F$

2. M-C bond formation with HF elimination

   $H\text{-}[M] + R\text{-}F \longrightarrow R\text{-}[M] + H\text{-}F$

3. M-C bond formation with fluorosilan elimination

   $R_3Si\text{-}[M] + R\text{-}F \longrightarrow R\text{-}[M] + R_3Si\text{-}F$

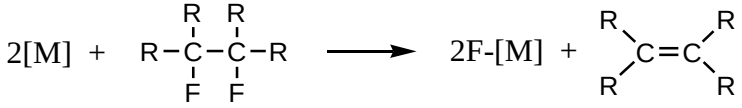
4. Hydrodefluorination of fluorocarbon with M-F bond formation

   $[M] + R\text{-}F \longrightarrow F\text{-}[M] + R\text{-}H$

5. Nucleophile attack on fluorocarbon

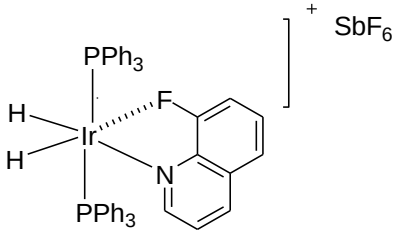
   $[M]^- + R\text{-}F \longrightarrow R\text{-}[M] + F^-$

6. Defluorination of fluorocarbon



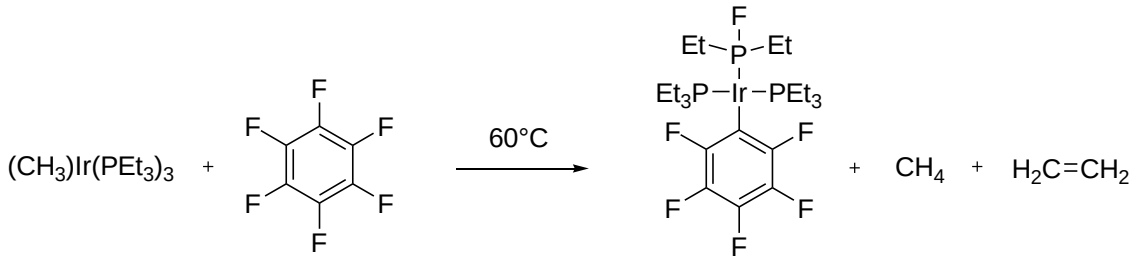
Early transition metals such as Ti, Zr, and Hf have been shown to be efficient reagents for C-F transformation. In particular, metalloocene zirconium dihydride complexes have been deeply studied by Jones and Eisenstein.[3] But oxidative addition reactions are not common with these complexes because they are normally d^0 species, which cannot be oxidized.

One of the first examples of fluorocarbon coordination to the transition metal was reported in 1987 by Richards and associates.[4] However it was Crabtree and co-workers[5] who have shown the first example of chelation of C-F bond to Iridium to form an 8-fluoroquinoline complex, scheme 1.



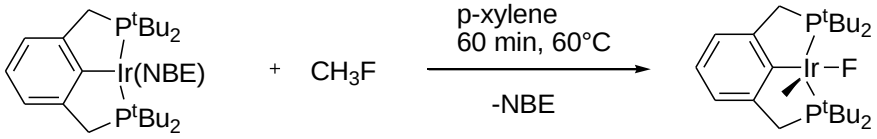
Scheme 1. 8-fluoroquinoline iridium complex

Early studies by Milstein and co-workers[6] illustrated that thermolysis of $(CH_3)Ir(PEt_3)_3$ in hexafluorobenzene at 60ºC afforded $Ir(PEt_3)_2(PEt_2F)(C_6F_5)$. In this unique transformation, a strong C-F and a P-C bond are cleaved and a P-F bond is formed, Scheme 2.



Scheme 2. Formation of $Ir(PEt_3)_2(PEt_2F)(C_6F_5)$

In 2011 Goldman and co-workers[7] reported an oxidative addition of C-F bond to Iridium via initial C-H bond activation, scheme 3. In this reaction the pincer-liganded iridium complex acts as a precursor to insert the C-F bond. In proposed reaction mechanism, the reaction proceeds via addition of the C-H bond followed by α-F migration.



Scheme 3. Addition of fluoromethane to the (PCP)Ir(NBE) complex

Too many studies have been reported on mediated C-F activation with different transition metal complexes (e.g. Pt, Pd, Ru) but here we were only focused on iridium mediated C-F bond activation.

1.2. Fluorine molecules in life science

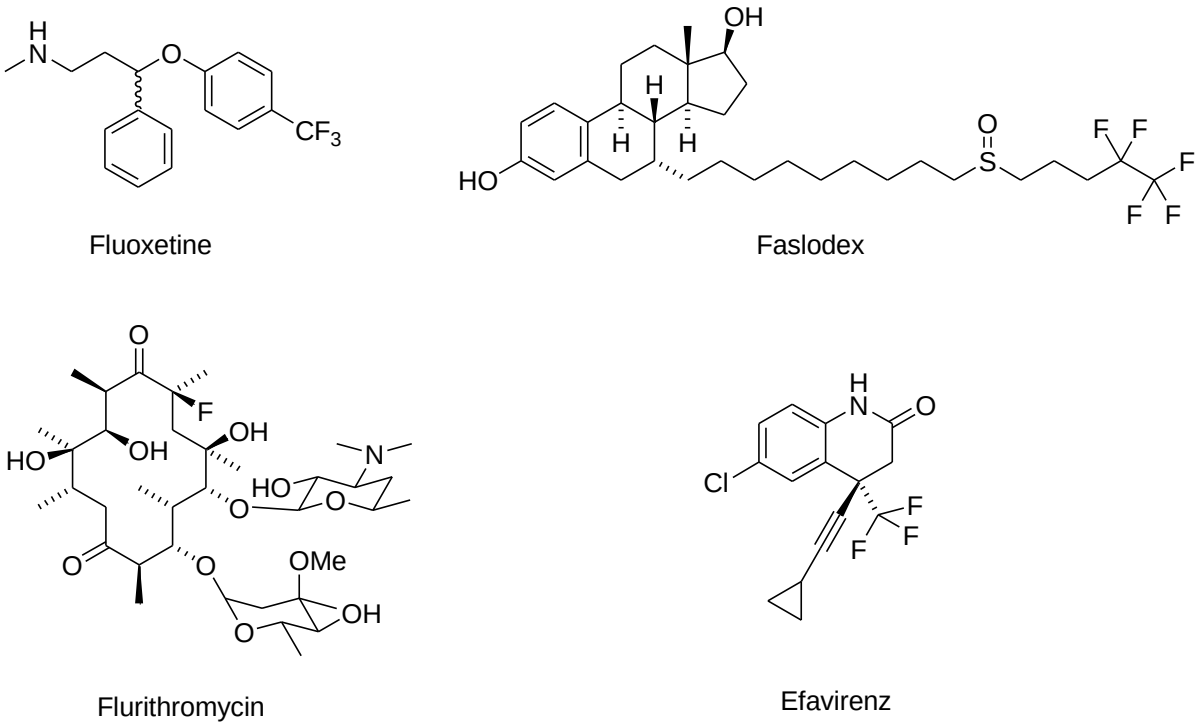
Fluorinated molecules are valuable in a wide range of user for instance, pharmaceutical, agrochemicals, imaging agents[8] and a new series of compound such as fluoropolymers.

1.2.1. Fluorine in pharmaceutical

It has become evident that fluorinated compounds have a significant proof in medicinal chemistry and will perform a continuing role in providing lead compounds for therapeutic applications. Interestingly there are 20-25% of drugs on the market today contains at least one fluorine atom.[9]

One of the earliest synthetic fluorinated drugs is 5-fluorouracil, an antineoplastic agent which was synthesised in 1957.[10] Since the present of 5-fluorouraci, fluorine substitution is commonly used in medicinal chemistry to improve metabolic stability, bioavailability and protein-ligand interactions.

Fluorine drugs illustrated the wide range of disease area, these include Fluoxetine antidepressant, Faslodex anticancer, Flurithromycin antibacterial and Efavirenz antiviral, scheme 4.



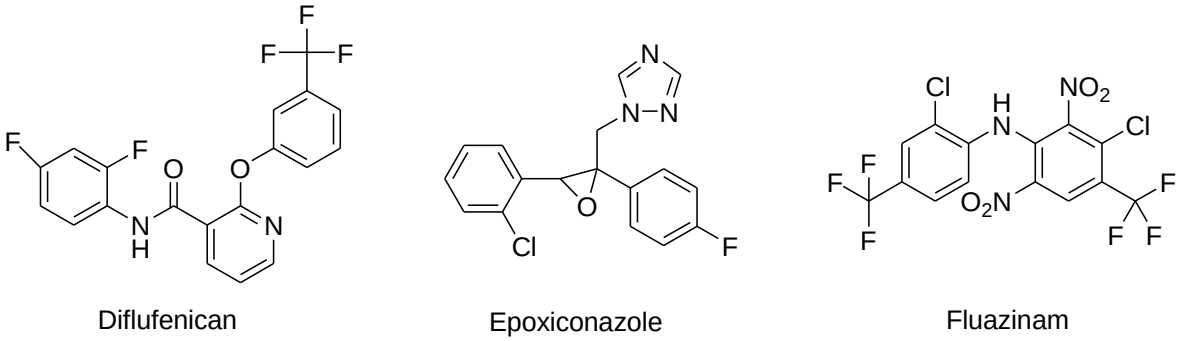
Scheme 4. Example of fluorine drugs

Fluorinated compounds are mainly synthesized in modern medicinal chemistry and have led to a large number of highly effective drugs.

1.2.2. Fluorine in agrochemicals

It has been shown that the fluorine is one of the main active chemical ingredients in 700 total agrochemical products. The importance of fluorine in agro products can be imputed to the well-known physicochemical effects on agricultural products properties like toxicology, solubility, polarity and also penetration. The incorporation of fluorine into agrochemicals for modern crop protection has the benefits like; high and reliable biological activity, high selectivity, good crop tolerance and low toxicity to beneficial organisms.

Fluorinated aromatic compounds are a very important class of agrochemical compounds, Scheme 5.[11]



Scheme 5. Example of fluorinated agrochemicals

1.2.3. Fluoropolymers

Fluorinated polymers have achieved a great success due to their unique combination of properties in thermoplastics, elastomers, membranes and coatings. The major commercial products include the homopolymers and copolymers, such as tetrafluoroethylene (TFE), chlorotrifluroethylene (CTFE) and probably the most important one is polytetrafluoroethylene (PTFE) which is widely used in chemical process industry.

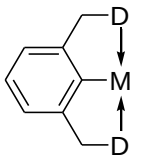
Although fluoropolymers represent only about 0.1% of all plastics, but trends to use them are being increased dramatically because of their outstanding performance characteristics.

1.3 Pincer complexes

In the recent years the development of complexes with having a pincer type ligand structure has attracted considerable attention. Now a days these complexes are designed and synthesized not just for their unique structure but for the multiple applications of these compounds. They are widely used as robust catalysis and successfully appeared in medicinal chemistry.

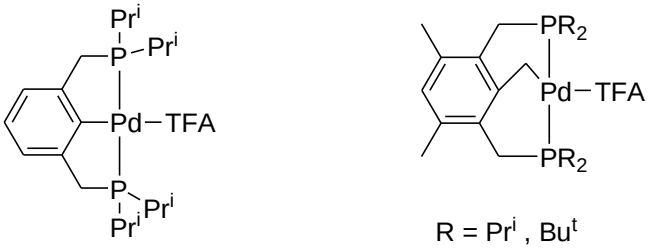
In 1976 Moulton and Shaw synthesized the first pincer type ligand.[12] These complexes revealed an extraordinary thermal stability thus enable them to be potentially used in homogeneous catalysis.

The pincer complexes consist of a metallic center and a pincer type ligand containing donor atoms which enable them to coordinate as a tridented ligand. It is believed that the δ-metal bond is responsible for the unique stability of these complexes. Moreover, the donor atoms allow the fine tuning of the steric and electronic properties.



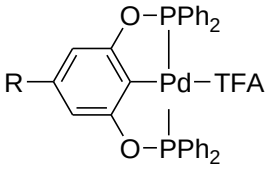
D = donor atom; O,S,N,P
M= metallic center

Milstein and co-workers were one of the pioneers of applying Pd-PCP pincer complexes in Heck coupling reaction as a catalyst.[6]



Scheme 6. Milstein's catalysts

One the other hand, Pd(II) complexes having phosphinito PCP pincer ligands have been successfully used in the Suzuki type couplings by Bedford and coworkers.[13]

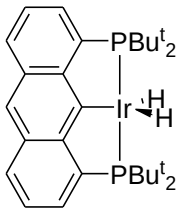


R = H, Me

Scheme 7. Bedford's catalyst

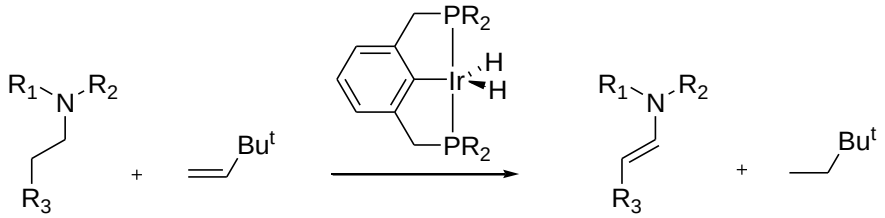
The high thermal stability of these complexes led to the researchers to the use of PCP pincer complexes as catalyst in the dehydrogenation of alkanes. Thus in 1998, Jensen and co-workers reported the use of the dihydride rhodium complex $RhH_2\{C_6H_3\text{-}2,6\text{-}(CH_2PBu^t_2)_2\}$ in the dehydrogenation of cyclooctane.[14]

In 2001, Kaska and co-workers have reported a rigid PCP pincer system based on antracene backbone. This complex has demonstrated catalytic activity in the dehydrogenation of alkanes at temperature as high as 250ºC without decomposition.[15]



Scheme 8. Kaska's catalyst

Goldman and co-workers[16] have recently reported the use of these same species for the catalytic dehydrogenation of a wide variety of tertiary amines to enamines in good yields, scheme 9.

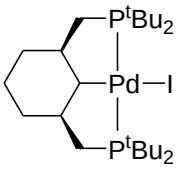


Scheme 9. Transfer-dehydrogenation of tertiary amines catalysed by Ir-PCP pincer complex.

1.3.1. Aliphatic pincer complexes

In the large majority of cases the PCP backbone consists of an aromatic ring and only a few complexes with an aliphatic backbone have been reported, and catalytic properties of such compounds have generally not been examined. Among them it can be mentioned Milstein[6] and Wendt's catalyst.[17] According to their investigations there might be an increased electron density on the metal center, caused by coordination of an sp^3 carbon instead of an sp^2 carbon, and resulting in increase in catalytic activity of such complexes.

The aliphatic pincer complex synthesized by Wendt was examined in the Heck reaction, which shows a highly active catalyst.

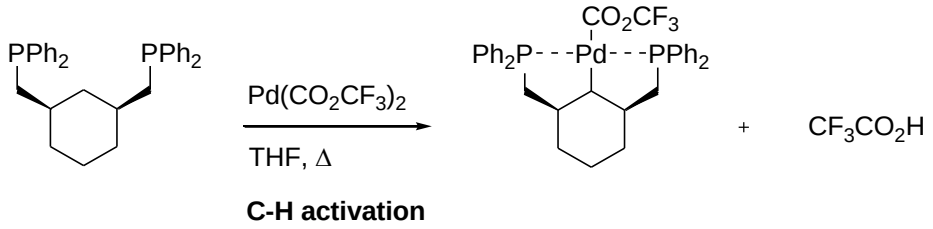


Scheme 10. Wendt's catalyst

In general, the chemistry of pincer ligands has shown a long period of development and will continue to grow. The future catalytic studies will probably be desired to development of new type of pincer complexes.

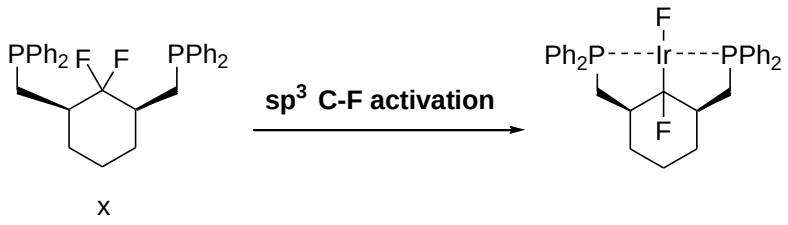
2. Results and Discussion

The Wendt group at LU has recently developed a new class of sp^3 pincer type ligands through the selective C-H bond activation which introduced a rare example of PC(sp^3)P pincer Pd(II) complex, scheme 11.



Scheme 11. Selective C-H bond activation by Wendt's catalyst.

In the present study, we aim to obtain insight into the selective cleavage of the sp^3 C-F bond by insertion of iridium metal. We are particularly interested in performing this reactivity on a gem-diflouro, syn-diphosphine structure for studying sp^3 C-F bond activation to generate an entirely new class of coordination compounds, scheme 12.

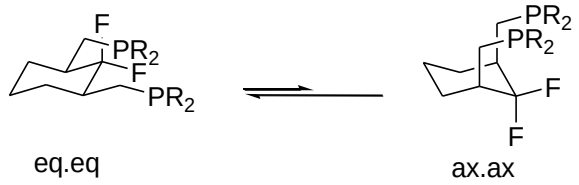


Scheme 12. Proposed C-F activation

2.1. Computational studies

One of the most important aspects in this work is the geometry of the intermediate **x** to metalated pincer complex by Iridium metal. We have to take into consideration the possibility of the ligand to coordinate in an appropriate position. For this reason a computational study was carried out with three different programs which are shown in table 1.

The results indicate that the energy of the equatorial configuration of corresponding cyclohexene is lower than the axial one, scheme 13, Therefore the equatorial configuration will be more stable, and allow to insertion of the metal to the C-F bond whereas the metal is linked by phosphine groups.



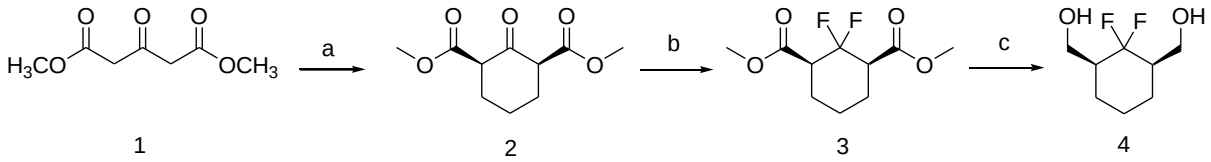
Scheme 13. Two possible configuration of the cyclohexene.

Table 1. Computational data

	Quantum Mechanic (Kcal/mol)	Molecular Mechanics (Kcal/mol)	T1 Heat of Formation (Kcal/mol)
Equatorial	-1275.51841	271.98	-634.45
Axial	-1275.50981	282.31	-621.56
Different Energy (Δ)	5.3965	2.47	3.08

2.2. Ligand Synthesis

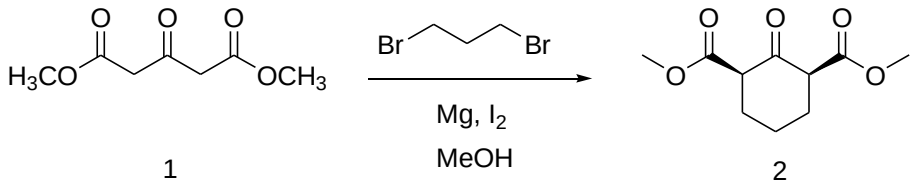
It was suggested a three-step synthesis of key intermediate **4** which is shown in scheme 14**.** In this pathway cyclohexanone **2** is made using McCarty producer[18] followed by fluorination and reduction to form the gem-difluoride compound **4**.



Scheme 14. Proposed synthesis of 4.
Reagents: (a) 1,3-diboromopropane, $Mg(OMe)_2$; (b) Deoxofluor, CH_2Cl_2 ; (c) DIBAL, CH_2Cl_2.

2.2.1. Cyclization

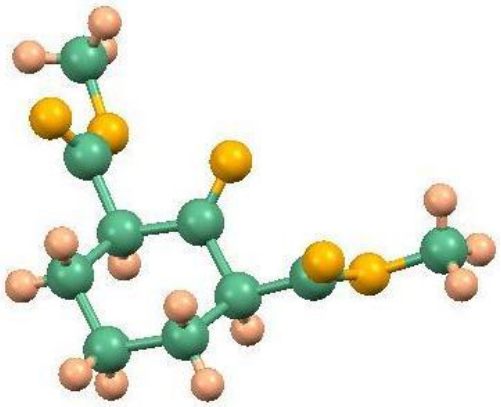
Compound **2** was synthesised according to the McCarty procedure from 1,3-dibromopropane and $Mg(OMe)_2$. Product was obtained in 33% yield, scheme 15.



Scheme 15. Cyclization step

The compound was approved by the ^{1}H-NMR, ^{13}C-NMR and X-ray data. The crystal structure of compound **2** is shown in scheme 16.

According to the crystal structure two ester groups are sited in equatorial position and formed a C_S symmetric structure.



Scheme 16. Crystal structure of compound 2.

2.2.2. Fluorination

In the next step to the synthesis compound **3** several reactions were examined using two different reagents. Deoxofluoro and Xtalfluor-E reagents were found to act as efficient fluorinating reagents. Xtalfluor-E is a crystalline fluorinating agent that is more easily handled and significantly more stable than Deoxofluor and other analogues. Unlike Deoxofluoro, Xtalfluor-E does not generate highly corrosive free-HF and therefore can be used in standard borosilicate vessels. When used in combination with promoters such as $Et_3N.3HF$, Xtalfluor-E reagent effectively converts carbonyls to gem-difluorides.

All reagents and reaction conditions examined are summarized in Table 1.

Table 1. Fluorination of ketone with Deoxofluoro and XtalFluor-E reagents.

Entry	SM	Reagent (eq.)	Additive (eq.)	Additive (eq.)	Solvent	T°C	Time (h)	Product
1[19]	2	Deoxofluoro (1.7)	MeOH (0.2)	-	DCM	r.t	4 day	No*
2[20]	2	Deoxofluoro (3)	TEA.3HF (4)	-	DCM	r.t	9 day	No*
3[20]	2	Xtalfluor-E (3)	TEA.3HF (4)	TEA (2)	DCM	r.t	5 day	No*
4[20]	2	Xtalfluor-E (1.5)	TEA.3HF (2)	-	DCM	r.t	4 day	No*
5[20]	2	Xtalfluor-E (1.5)	TEA.3HF	-	DCE	reflux	3 day	No*

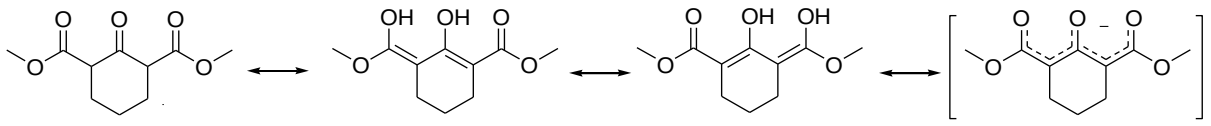
* The product was not detected by ^{1}H-NMR and GC-MS.

The first reaction was conducted in CH_2Cl_2 at room temperature in the present of 0.2 equiv. of MeOH. After 4 days stirring the desired product was not afforded.

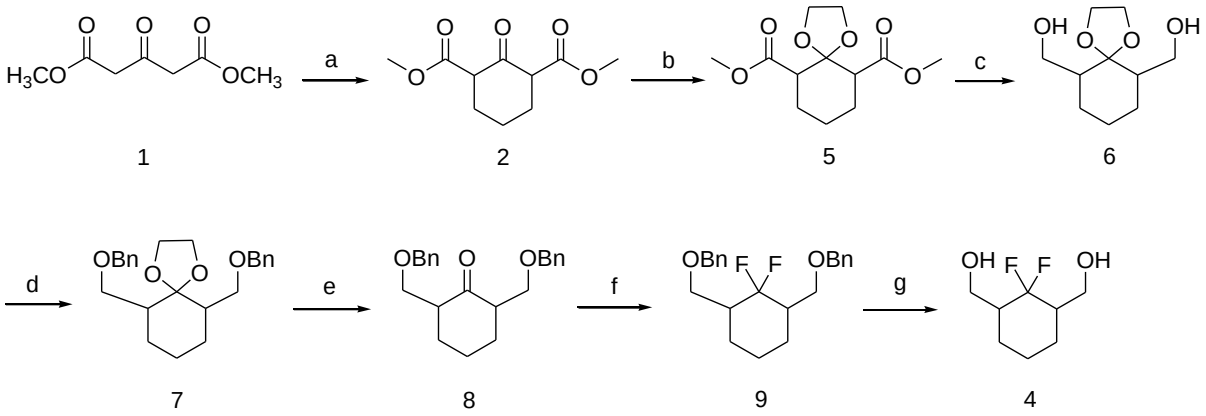
The second reaction was performed with the mild HF source, $Et_3N.3HF$ instead of MeOH as a promoter but then again was not successful.

In the next third reactions the fluorinating reagent was replaced by Xtalfluor-E. Ultimately, no conversion was observed.

In summary, results of these investigations have shown that compound **2** was not converted to the desired gem-difluor compound using these reagents and conditions. The reason can be attributed to the conjugated system of compound **2**.



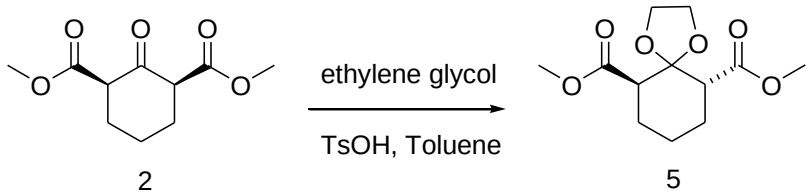
In order to synthesis the intermediate **4** a new route was planned which is outlined in scheme 17.



Scheme 17. A new proposed synthetic route
Reagents and Conditions: (a) 1,3-diboromopropane, $Mg(OMe)_2$; (b) ethylene glycol, TsOH, Toluene, reflux, 3hr ; (c) $LiBH_4$, THF ; (d) NaH, BnBr, THF, reflux ; (e) TsOH, THF:H_2O, reflux.

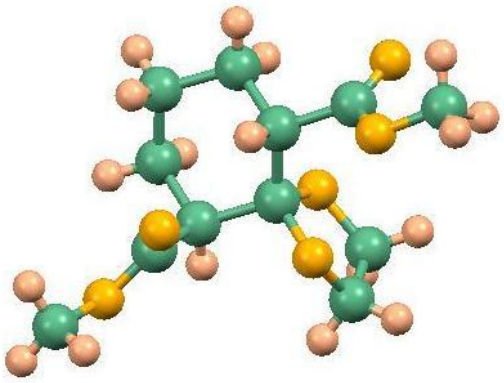
2.2.3. Protection of Ketone

A common example of a protecting group is the use of an ethylene ketal to mask a carbonyl group and protect it for the next step of the reaction. By adding ethylene glycol and catalytic amount of *p*-toluene sulfonic acid to the reaction mixture, certain amount of water is removed by using Dean-Stark water separator. After workup, the crude product was purified by flash chromatography and the ketal was afforded in 47% yield.



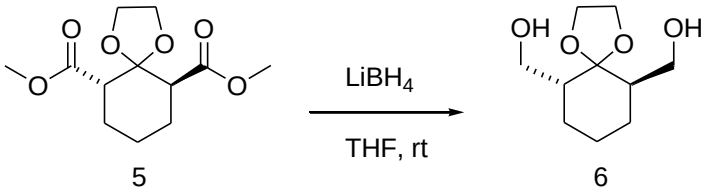
Compound **5** was characterized by NMR spectroscopy (^1H, ^{13}C) and X-ray data. The crystal structure of this compound is shown in scheme 18.

According to the crystal structure one ester is located in axial and the other one is in equatorial position and formed a C_2 symmetric structure. Therefore during the protection step compound **2** was epimerized and symmetry was changed to C_2. Moreover, the integral traces show the syn-geometry structure was not formed and there is only one epimer.



Scheme 18. Crystal structure of compound 5.

2.2.4. Reduction of Ester

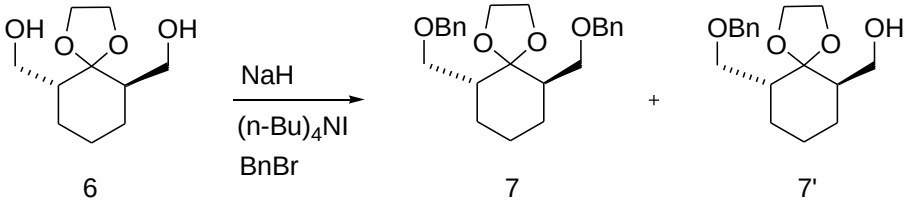


Once the reactive ketone moiety has been masked two ester groups can be reduced. The ester is reduced using $LiBH_4$ in THF to give the corresponding primary alcohol **6** in 70% yield, but the reaction required five days to be completed**.** The ^{1}H-NMR spectroscopic analysis of this compound exhibits two broad peaks at 2.6 and 2.2 ppm, which is typical for hydroxyl group and confirms the C_2 symmetry structure. Furthermore, two different signals for the stereo genic centers in ^{13}C-NMR prove this structure.

2.2.5. Protection of Alcohol

There are many protecting groups for alcohols, but among them benzyl ether is simple and quite useful example that can be formed readily by the reaction of an alcohol with benzyl bromide under basic conditions.

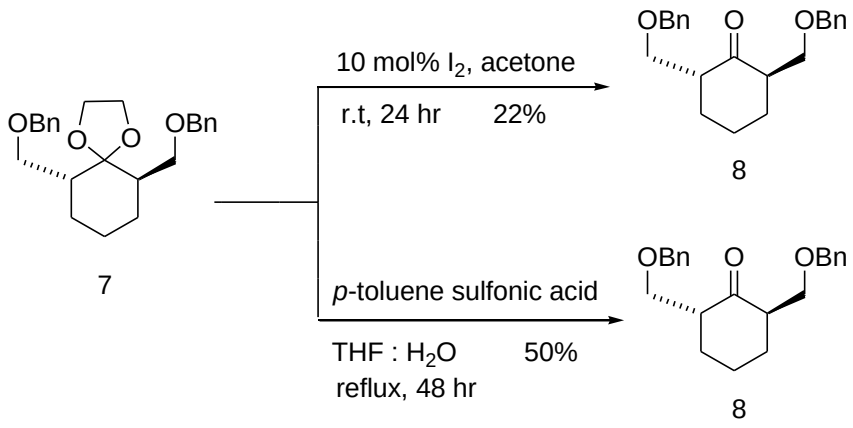
In this step NaH as a base and $(n\text{-}Bu)_4NI$ as a catalyst were added to the alcohol **6**, in dry THF. Benzyl bromide was added to the reaction mixture and refluxed it for 3 days. After workup, the crude product was purified by flash chromatography thus affording product **7**, as colorless oil in 28 % yield. Formation of the by-product **7´** would cause a low yield of the reaction which can be justified by the steric hindered of ketal.



Compound **7** also indicates the C_2 symmetry which is justified by two different carbon signals at 40 and 42 ppm for the stereo-genic centers.

2.2.6. Ketal hydrolysis

Ketals are stable but can be converted back to ketones through acid catalyzed hydrolysis. Hydrolysis is the breakage of a bond by reaction with water. The synthetic routes that were attempted for the hydrolysis are outlined in scheme 19.



Scheme 19. Ketal Hydrolysis

Two different reaction condition were examined one was ketal catalyzed by molecular iodine in acetone, and the second one was using *p*-toluene sulfonic acid in the present of THF and water which was more productive thus preferred the second pathway. Through this reaction the structure symmetry not showing any changes and indicates the C_2 symmetry.

2.2.7. Fluorination

The final reaction step in the ligand synthesis was fluorination step. Two synthetic strategies were attempted which are outlined in table 2.

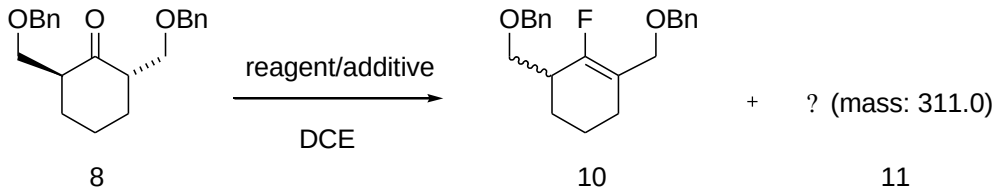


Table 2. Fluorination of ketone with deoxofluoro and Xtalfluor-E reagents.

Entry	Reagent (eq)	Additive (eq)	Solvent	Tº C	Time	Product
1	Deoxofluoro (10)	TEA.3HF (5)	DCE	rt	72 h	10 + 11
2	Xtalfluor-E (5)	TEA.3HF (5)	DCE	rt → reflux	48 h	10 + 11

The results of this investigation have shown that fluorination of compound **8** are prone to elimination. In fact fluorinating predominantly lead to vinyl fluoride **10** and one unknown side product **11**.

3. Conclusion and Future Work

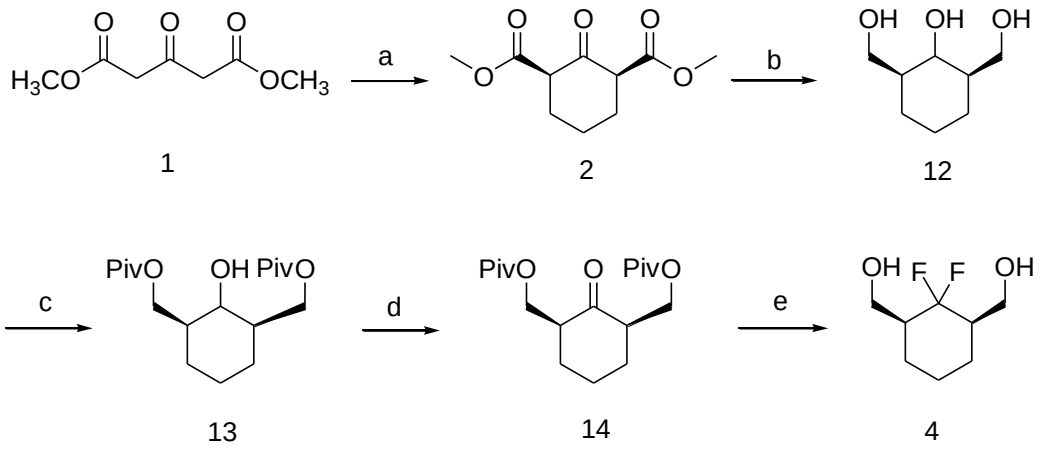
In summery our attempt to synthesis a gem-difluoro compound was not successful. Compound **8** did not undergo fluorination and instead the elimination fluoro compound was formed. Synthesis of the pincer ligand consist of 7 steps which start with cyclization of dimethylacetonedicarboxylate to afford compound **2** and for further reaction it was needed to protect the ketone group to allow the reduction of esters to alcohols by $LiBH_4$ in THF as the common reducing agent. The yield of this reaction however could probably be improved. There is the possibility to use other reducing agents such as $LiAlH_4$ or milder one like DIBAL. The next step, protecting the alcohol was so problematic cause of formation of by-product therefore this step needs further optimization. Finally removing the ketal although seems to be done easily but spend a lot of time in low yield. We attempted to change the reaction condition by using I_2 as a catalyst to improve the yield but did not work properly. The final reaction to fluorination of ketone needs the biggest amount of work. Here we used two different reagents, Deoxofluoro and Xtalfluor-E a new series of fluorination reagent. Two methods were carried out at room temperature and reflux condition. The results of both were not the gem-difluoro compound and instead the elimination compound was given in addition of an unknown compound.

Evidence indicates that compound **8** is not reactive toward the fluorination therefore it is required to design a new route to form this compound mainly in syn-geometry which is essential for the metal insertion.

3.1. Plans and Ideas

Based on the results of this work synthesis of the key intermediate **4** is not achievable by this method and further investigation is required.

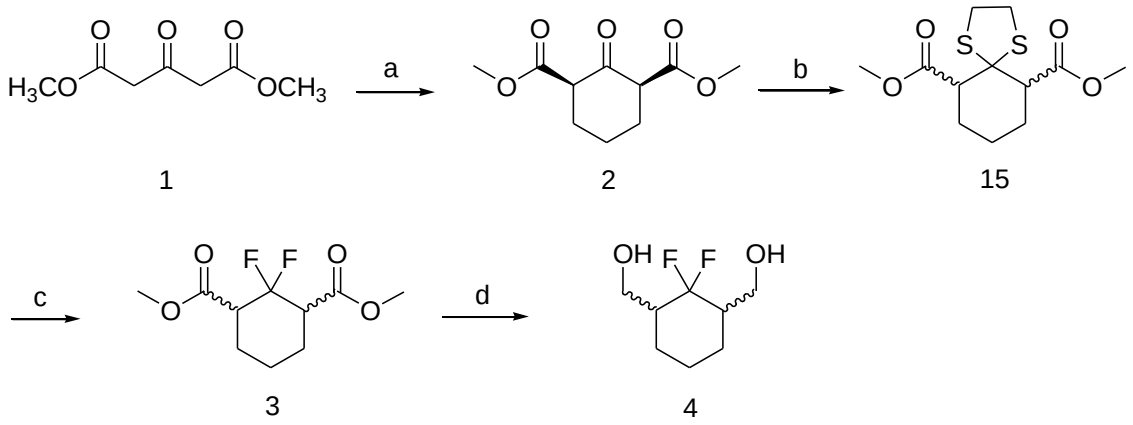
As mentioned before formation of compound **8** with C_S symmetry is one of the important tasks in this project otherwise the insertion of metal to C-F bond would not be possible, here we suggest a new procedure to prepare the specific structure to fluorination, scheme 20.



Scheme 20. A new proposed synthetic route.
Reagents (a) 1,3-diboromopropane, $Mg(OMe)_2$; (b) LAH, THF, rt ; (c) PivCl, Pyridine, DCM ; (d) Dess-Martin periodinane, DCM ; (e) Fluorination.

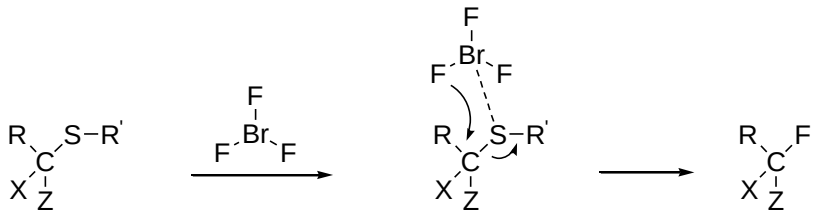
In this sequence, compound **12** was made after reduction of compound **2** followed by selective acylation and oxidation. The structure **14** will be provided in order to fluorination.

The second method for the preparation of our gem-difluoro compound can be a four-step synthesis method which is depicted in scheme 21.



Scheme 21. A new proposed synthetic route.
Reagents: (a) 1,3-diboromopropane, $Mg(OMe)_2$; (b) Ethan-1,2-dithiol/H^+ ; (C) BrF_3, CH_2Cl_2 ; (d) DIBAL, CH_2Cl_2.

The methodology behind this idea will be the possible reaction between bromide in BrF_3 as a soft acid with sulfur atom as a soft base and make the position where fluoride near the potential site react with carbon and result a gem-difluoro structure.[19]



Scheme 21. The complexation of BrF_3 with soft heteroatoms.

One challenging work in this procedure is preparation of BrF_3 and also handling it. BrF_3 is tends to react with water and other oxygenated organic solvents such as acetone or THF. Moreover working with fluorine gas and making BrF_3 is a tricky work.

4. Acknowledgements

I would like to express my deep gratitude to my supervisor Prof. Ola F. Wendt for his support and inspiration. Special thanks should be given to Dr. Daniel Strand, my research project supervisor for his professional guidance and valuable support.

I wish to thank all the people who help me and create such a nice atmosphere at the department of organic chemistry.

Finally, I would like to thank my family, my parents and my brother, without their help this degree would not have been possible.

5. References

1. Gary O. Spessard; Gary L. Miessler. "*Organometallic Chemistry*" Oxford, **2010**, 2nd Edition, p 350-384.
2. (a) Kenneth L. Kirk. "Fluorination in Medicinal Chemistry: Methods, Strategies, and Recent Developments." *Organic Process Research & Development* **2008**, *12*, 305-321; (b) Klaus Muller, Christoph Faeh and. Francois Diederich, "Flurine in Pharmacuticals: Looking Beyond Intuition" *Science* **2007**, *317*, 1881-1886; (c) Hans-Joachim Bohm, David Banner and Martin Stahl, "Fluorine in Medicinal Chemistry" *ChemBioChem* **2004**, *5*, 637-643.
3. Bredley M. Kraft and William D. Jones. "Mechanistic investigation of vinylic carbone-fluorine bond activation of perfluorinated cycloalkenes using $Cp^*_2ZrH_2$ and Cp^*_2ZrHF" *J. Fluorine Chem*istry **2010**, *13*, 1122-1132.
4. Rosa Maria Catala, and Hugo Torrens. "A C–F–Ru interaction in a complex: preparation and X-ray structure of $[Ru\{SC_6F_4(F\text{-}2)\}(SC_6F_5)_2(PMe_2Ph)_2]$" *J. Chem. Soc., Chem. Commun.*, **1987**, 261.
5. Robert J. Kulawiec and Robert H. Crabtree. " Chelation of a C-F Bond to Iridium in an 8-fluoroquinoline Complex" *Inorg. Chem.*, **1987**, *26*, 2559-2561.
6. Ofer Blum, Felix Frolow and David Milstein. "C-F Bond Activation by Iridium (I). A unique process involving P-C Bond cleavage, P-F Bond Formation and Net Retention of Oxidation State" *J. Chem. Soc., Chem. Commun.*, **1991**, 258-259.
7. Jong Choi, David Y. Wang and Alan S. Goldman. "Net Oxidative Addition of $C(sp^3)$-F Bonds to Iridium via Initial C-H Bond Activation" *Science*, **2011**, *332*, 1545.
8. Simon M. Ametamey, Michael Honer, and Pius August Schubiger "Molecular Imaging with PET" *Chem. Rev.*, **2008**, *108*, 1501–1516.
9. Sophie Purser and Veronique Gouverneur. "Fluorine in medical chemistry" *Chem. Soc. Rev.*, **2008**, *37*, p 237-432.
10. Charles Heidelberger and J. Scheiner. "Fluorinated Pyrimidines, A New Class of Tumour-Inhibitory Compounds" *Nature*, **1957**, *179*, 663.
11. Blake D. Key and Craig S. Criddle "Fluorinated Organic in the Biosphere" *Environmental Science and Technology*, **1997**, *31*, p 2445-22454.
12. Christopher J. Moulton and Bernard L. Shaw. "Transition Metal-Carbon Bonds. Complexes of Nickel, Palladium, Platinium, Rhodium and Iridium with the Tridentate Ligand 2,6-Bis[(di-t-butylphosphino)methyl]phenyl" *J.C.S. Chem. Comm.*, **1974**, 918.
13. Robin B. Bedford and Samantha L. Welch. "Palladium bis(phosphinite) PCP –pincer complexes and their application as catalysts in the Suzuki reaction." *New. J. Chem.*, **2000**, *24*, 745-747.
14. Do W. Lee. William C. Kaska and Craig M. Jensen. "Mechanistic Features of Iridium Pincer Complex Catalyzed Hydrocarbon Dehydrogenation Reaction." *Organometallic*, Vol. *17*, No. 1, **1998**.
15. Matthias W. Haenel and Michael B. Hall. "Thermally stable Homogeneous Catalysts for Alkane Dehydrogenation." *Angew. Chem. Int. Ed.*, **2001**, *40*, No. 19.
16. Xiawei Zhang and Alan S. Goldman. "Novel synthesis of enamenes by iridium catalyzed dehydrogenation of tertiary amines." *Chem. Commun.*, **2003**, 2000-2061.

17. Sven Sjövall, Ola F. Wendt and Carlaxel Anderson. "Synthesis, characterisation and catalytic investigation of new type of PC(sp^3)P pincer Pd(II) complex" *J. Chem. Soc., Dalton Trans*, **2002**, 1396-1400.
18. F. F. Blicke and F. J. McCarty *"*Disubstitution of Cycloalkanones in the Mannish Reaction*" J. Org. Chem.*, **1959**, *24*, 1069-1076.
19. Gauri S. Ll and Hansong cheng. "Bis(2-mthyoxyl)aminosulfur Trifluoride: Anew Broad-Spectrum Deoxofluorinating Agent with Enhanced Thermal Stability" *J.Org. Chem*., **1999**, *64*, No.19, 7048-7057.
20. Aleandre L Heureux, Francis Beaulieu and Michel Couturier. "Aminodifluorosulfinium Salts: Selective Fluorination Reagents with Enhanced Thermal Stability and Ease of Handling" *J. Org. Chem*., **2010**, *75*, No. 10, 3401-3411.
21. Or. Cohen and Shlomo Rozen. "A general rout for the synthesis of β,β-difluorocarboxylic acids." *Tetrahedron,* **2008,** 64, 5362-5364.

Supporting information

Towards the synthesis of a fluorinated diphosphine compound for the study of C-F activation

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1. Experimental

1.1. General Methods

All reactions were carried out in oven-dried glassware under nitrogen atmosphere. Mixtures were concentrated using a *Heidolph* rotary evaporator.

Reactants and reagents were purchased by *Sigma Aldrich*, *Alfa Aesar*, *ABCR* or *Acros Organics* and used without further purification. Solvents for extraction and chromatography were of technical grade.

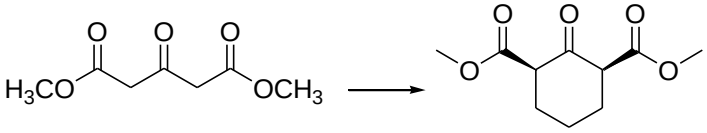
Reactions were followed by TLC using aluminum -backed plates (*Merck* $60F_{254}$ silica gel) and visualized with UV (252 nm) and/or PMA. Preparative chromatography was performed using gel (*Acros* 40-60 µm, 60 Å) columns or a flash purification system (*Biotage Isolera One*).

NMR Spectra were recorded on *Bruker Ulrashield 400 plus* (^{1}H-resonance: 400 MHz, ^{13}C-resnance: 101 MHz and ^{19}F-resonance: 376 MHz). Spectra were processed using MestReNova (version 6.1.0-6267). Chemical shifts are given in ppm downfield from $SiMe_4$ using the residual solvent peak as reference (^{1}H-NMR: $CDCl_3$: δ 7.26 ppm; acetone: δ 2.05 ppm; ^{13}C-NMR: $CDCl_3$: δ 77.16 ppm; acetone: δ 29.84, 206.26 ppm). ^{1}H spectra are reported as followed: chemical shift (δ, ppm), multiplicity (s = single, bs = broad singlet, d = doublet, t = triplet, q = quartet, sept = septet, dd = doublet of doublets, dt = doublet of triplet, m = multiplet, app. = appears as) coupling constant (Hz) and integration. ^{13} C spectra are reported in chemical shifts.

Mass spectra were recorded on a *Micromass Q-TOF* spectrometer. The ionization was ensued by electrospray ionization (ESI). Detected masses are given in *m/z* (Mass per charge).

IR spectra were recorded using a *Bruker AlPHA-P* spectrometer. The Location of the absorption bands are given in wave numbers (cm^{-1}) and intensities are described as s = strong, m = medium, w = weak and br = broad.

1.2. Synthesis of Dimethyl-2-oxocyclohexan-1,3-dicarboxylate (2)



1 2

For the mechanism see 1 in the Appendix.

In a 250 ml round-bottomed flask a mixture of magnesium (1.21 g, 0.05 g.atom, 1 eq) and iodine (0.125 g, 4 mmol, 0.1 eq), and 100 ml of dry methanol was stirred at room temperature for 1 hr. Then it was refluxed for 4 hour on an oil bath. The mixture was cooled and placed in a pressure bottle and dimethyl acetone dicarboxylate (4.37 g, 25 mmol, 1 eq) was added to the mixture. The reaction mixture was heated for 1 h then 1,3-dibromopropane (5.0 g, 25 mmol, 1 eq) was added and the mixture was heated for 24 h. The solvent was removed and the residue was mixed with 50 ml of concentrated (50 wt%) hydrochloric acid. The product was extracted with diethyl ether and the solvent was removed then the oily residue was dissolved in 50 ml methanol and refluxed to dissolve the residue. The solution was cooled in the refrigerator for 24 h. The white precipitate was filtered to give 1.765 g (8.2 mmol) of dimethyl-2-oxocyclohexan-1,3-dicarboxylate **2**.

Yield: 33%

^{1}H-NMR: (400MHz, $CDCl_3$) δ: 3.74 (s, 6H), 3.44 (dd, *J* = 6.8, 2H), 2.27-1.98 (m, 4H), 1.76-1.66 (m, 2H) ppm.

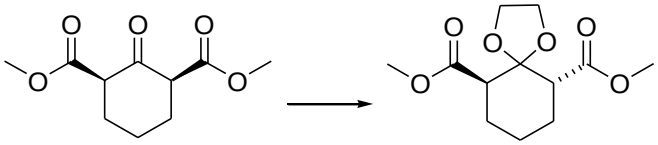
^{13}C-NMR: (101 MHz, $CDCl_3$) δ: 172.5, 169.3, 57.3, 52.3, 52.2, 51.6, 45.5, 30.0, 26.2, 22.7, 22.2, ppm.

*One carbonyl signal is missing in ^{13}C spectra.

IR: ($CHCl_3$, film): 1700 (s), 1750 (s), 1200 (m), 1300 (m), 1350 (m) cm^{-1}.

Mp: 136ºC

1.3. Synthesis of Dimethyl -1,4-dioxosparo[4,5]decane-6,10-dicarboxylate (5)



2 5

For the mechanism see 2 in the Appendix.

In a 100 ml round- bottomed flask is equipped with a Dean-Stark water separator compound **2** (0.5 g, 2.5 mmol, 1 eq) was dissolved in 10 ml Toluene. Ethylene glycol (1.6 g, 25.7 mmol, 10 eq) and catalytic amount of *p*-toluene sulfonic acid were added to the solution. The

reaction mixture was stirred and heated at reflux. Water that separates during the reaction is periodically removed and refluxing is continued until water separation ceases (3h). The reaction mixture was washed with 10 ml $NHCO_3$ and 10 ml of water. The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified with flash chromatography (20 g silica 60, petroleum ether/ethyl acetate: 6.25%), which gave 0.30 g (1.18 mmol) color less oil of dimethyl -1,4-dioxosparo[4,5]decane-6,10-dicarboxylate **5**.

Yield: 46%

R_f: 0.3 in 6.25% petroleum ether/ethyl acetate.

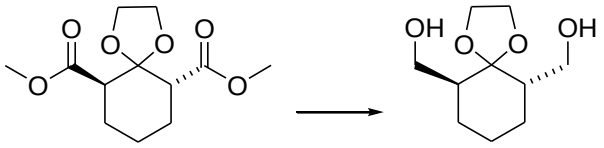
^{1}H-NMR: (400MHz, $CDCl_3$) δ: 4.0-3.8 (m, 4H), 3.69 (s, 6H), 3.17 (t, 2H), 2.6 (dd, *J* = 8, 2H), 2.0-1.8 (m, 2H) ppm.

^{13}C-NMR: (101 MHz, $CDCl_3$) δ: 66.2, 65.1, 52.1, 51.8, 51.7, 47.5, 27.1, 26.6, 23.5, 19.8 ppm.

*Two carbonyl signals are missing in ^{13}C spectra.

IR: ($CHCl_3$, film): 1727 (s), 1434 (m), 1161 (s) cm^{-1}.

1.4. Synthesis of 1,4-dioxosparo[4,5]decane-6,10-dihydroxymethyl (6)



5 6

For the mechanism see 3 in the Appendix.

In a 100 ml round-bottomed flask equipped with a N_2 inlet tube, compound **5** (0.15 g, 0.6 mmol, 1 eq) was dissolved in dry THF. Then $NaBH_4$ (0.1 g, 5 mmol, 8 eq) was added. The reaction mixture was stirred at room temperature until the reaction was completed based on TLC monitoring. Upon completion of the reaction the mixture was quenched using aqueous saturated NH_4Cl. The product was extracted with 3 × 30 ml CH_2Cl_2. The combined organic phases were dried using anhydrous Na_2SO_4, filtered, and the solvent was evaporated to afford the corresponding pure alcohol 0.08 g, (0.41 mmol).

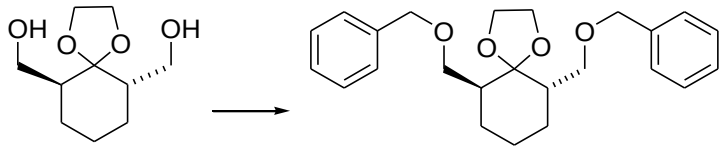
Yield: 70%

^{1}H-NMR: (400MHz, $CDCl_3$) δ: 4.6-4.0 (m, 4H), 3.88-3.83 (m, 2H), 3.7-3.6 (m, 2H), 3.55-3.52 (m, 2H), 2.6 (s, OH), 2.07-2.03 (m, 2H), 1.83-1.79 (m, 2H), 1.72-1.41 (m, 2H) ppm.

^{13}C-NMR: (101 MHz, $CDCl_3$) δ: 114.2, 114.0, 66.9, 66.1, 64.5, 63.3, 48.8, 42.0, 29.6, 27.2, 26.7, 24.5 ppm.

IR: ($CHCl_3$, film): 3350 (br), 1950 (m), 1500 (s) cm^{-1}.

1.5. Synthesis of 1,4-dioxosparo[4,5]decane-6,10-dibenzyloxymethyl (7)



6 7

For the mechanism see 4 in the Appendix.

The diol **6** (0.35 g, 1.76 mmol, 1 eq) and 20 ml THF was placed in a 250 ml 2-necked round-bottomed flask equipped with a N_2 inlet tube and degassed by Nitrogen cycles. NaH (0.21 g, 5.2 mmol, 3 eq) and $(n\text{-}Bu)_4NI$ (0.32 g, 0.88 mmol, 0.5 eq) were added to the solution. The reaction mixture was cooled to 0ºC on an ice bath. After 1 h the ice bath was removed. Benzyl bromide (1.2 g, 7.0 mmol, 4 eq) is slowly was introduced via syringe and the resulting suspension is stirred at reflux for 3 days. The reaction is carefully quenched by slow addition of aqueous saturated $NHCO_3$. The aqueous layer is repeatedly extracted with diethyl ether. The combined organic phases were dried using anhydrous Na_2SO_4, filtered, and the solvent was evaporated then the residue is purified by flash chromatography (20 g silica 60, petroleum ether/ethyl acetate: 12.5%), which gave 0.19 g (0.49 mmol) color less oil of 1,4-dioxosparo[4,5]decane-6,10-dibenzyloxymethyl, **7**.

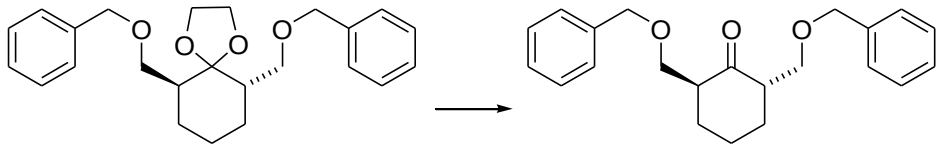
Yield: 28%

^{1}H-NMR: (400MHz, $CDCl_3$) δ: 7.3-7.2 (m, 10H), 4.50 (t, 2H), 4.54 (t, 2H), 4.01-3 (m, 4H), 3.85 (t, 1H), 3.64 (dd, *J = 9*, 2H), 3.5-3.4 (m, 1H) ppm.

^{13}C-NMR: (101 MHz, $CDCl_3$) δ: 138.5, 128.4, 128.3, 128.2, 127.7, 127.6, 127.5, 112.3, 73.2, 73.0, 70.3, 69.0, 64.5, 64.3, 63.7, 62.7, 42.7, 40.9, 30.2, 26.8, 26.7, 26.2, 19.9 ppm.

IR: ($CHCl_3$, film): 2906 (m), 2843 (m), 1050 (s), 1083 (s), cm^{-1}.

1.6. Synthesis of 2,6-bis((benzyloxy)methyl) cyclohexanone (8)



7 8

For the mechanism see 5 in the Appendix.

In a 100 ml round-bottomed flask, Compound **7** (0.019 g, 0.05 mmol, 1 eq) was dissolved in 3 ml THF and 1.5 ml H_2O, catalytic amount of TsOH was added to the reaction mixture, and refluxed it for 48 hours. The reaction was quenched by adding $NHCO_3$. The product was extracted with 3 × 30 ml CH_2Cl_2. The combined organic phases were dried using $MgSO_4$, filtered, and the solvent was evaporated then the residue is purified by flash chromatography

(20 g silica 60, petroleum ether/ethyl acetate: 6.25%), which gave 0.018 g (0.05 mmol) color less oil of 2,6-bis((benzyloxy)methyl) cyclohexanone, **8**.

Yield: 50%

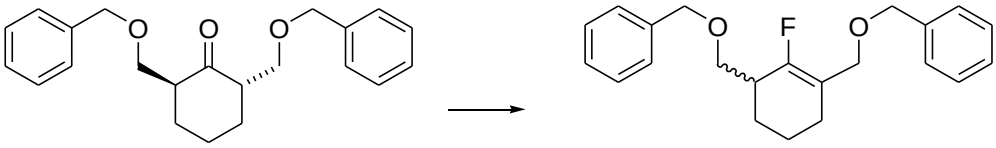
^{1}H-NMR: (400MHz, $CDCl_3$) δ: 7.33 (m, 10H), 4.52 (s, 4H), 3.6-3.5 (m,4H), 1.7-1.68 (m, 2H), 0.88-0.83 (m, 6H) ppm.

^{13}C-NMR: (101 MHz, $CDCl_3$) δ: 128.4, 127.7, 127.6, 73.0, 70.3, 62.7, 30.2, 29.7, 26.7 ppm.

*One carbonyl signal is missing in ^{13}C spectra.

IR: ($CHCl_3$, film): 2923 (m), 1700 (m) cm^{-1}.

1.7. Synthesis of 1-(((3-((benzyloxy)methyl)-2-fluorocyclohex-2-enyl)methoxy)methyl)benzene (10)



8 10

Procedure one: In a 50 ml round-bottomed flask equipped with a N_2 inlet tube and degassed by Nitrogen cycles, compound **8** (0.013 g, 0.03 mmol, 1 eq) was dissolved in 2ml dichloroethane. Deoxofluoro (0.06 g, 0.3 mmol, 10 eq) and triethylamine trihydrofluoride (0.02 g, 0.12 mmol, 5 eq) were added to the reaction mixture drop wisely. The reaction mixture was stirred at room temperature for 72 h. The reaction is carefully quenched by slow addition of aqueous saturated $NHCO_3$. The aqueous layer is repeatedly extracted with dichloromethane. The combined organic phases were dried using anhydrous Na_2SO_4, filtered, and the solvent was evaporated. NMR of the crude mixture and GC-MS did not show the desired product, **9**. Instead compound **10** was given.

Procedure two: In a 50 ml round-bottomed flask equipped with a N_2 inlet tube and degassed by Nitrogen cycles, compound **8** (0.015 g, 0.04 mmol, 1 eq) was dissolved in 2ml dichloroethane. Xtalfluoro-E (0.05g, 0.2 mmol, 5 eq) was added to the reaction mixture. After 1 hr, triethylamine trihydrofluoride (0.04 g, 0.22 mmol, 5 eq) was added to the reaction mixture drop wisely. The reaction mixture was stirred at room temperature for 24 h then refluxed it for 24 h. The reaction is carefully quenched by slow addition of aqueous saturated $NHCO_3$. The aqueous layer is repeatedly extracted with dichloromethane. The combined organic phases were dried using anhydrous Na_2SO_4, filtered, and the solvent was evaporated and the residue is purified by flash chromatography (20 g silica 60, petroleum ether/ethyl acetate: 3.13%), which gave 2 mg (0.005 mmol) of compound **10**.

Yield: 14%

HRMS-ESI (m/z): $[M+H]^+$; 341.1.

1.8. Crystallography

Dimethyl-2-oxocyclohexan-1,3-dicarboxylate (2)

Crystal data

$C_{12}H_{18}O_6$	F(000) = 276
M_r = 258.26	D_x = 1.336 Mgm^{-3}
Monoclinic, Pc	λ = 0.71073 Å
Hall Symbol: P-2yc	Cell Parameters from 1887 reflection
a = 8.6243 (9) Å	θ = 2.7–28.6 º
b = 7.3203 (6) Å	μ= 0.11 mm^{-1}
c = 10.1704 (9) Å	T = 293 K
V = 641.79 (10) $Å^3$	Plate, colorless
Z = 2	0.3 × 0.3 × 0.4

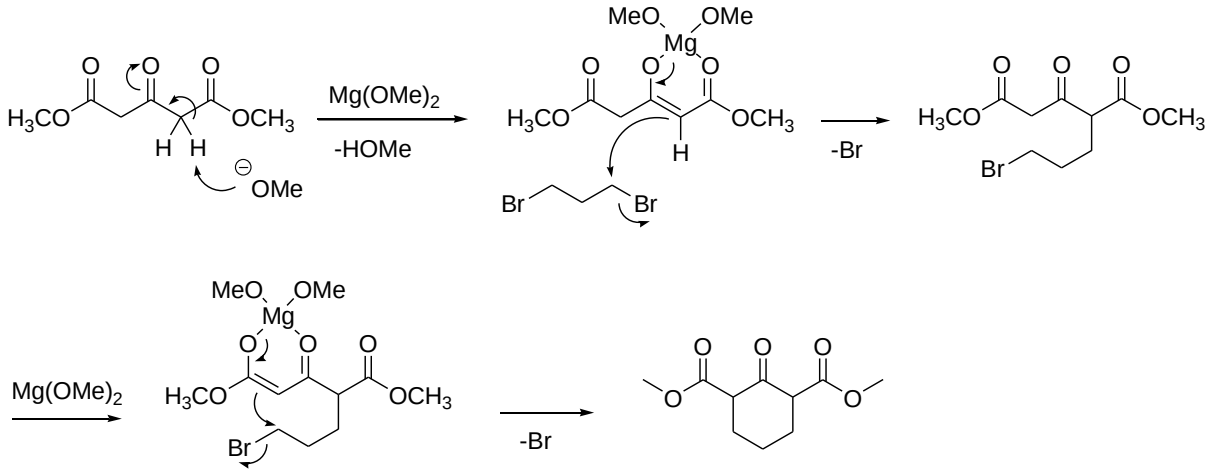
Dimethyl -1,4-dioxosparo[4,5]decane-6,10-dicarboxylate (5)

Crystal data

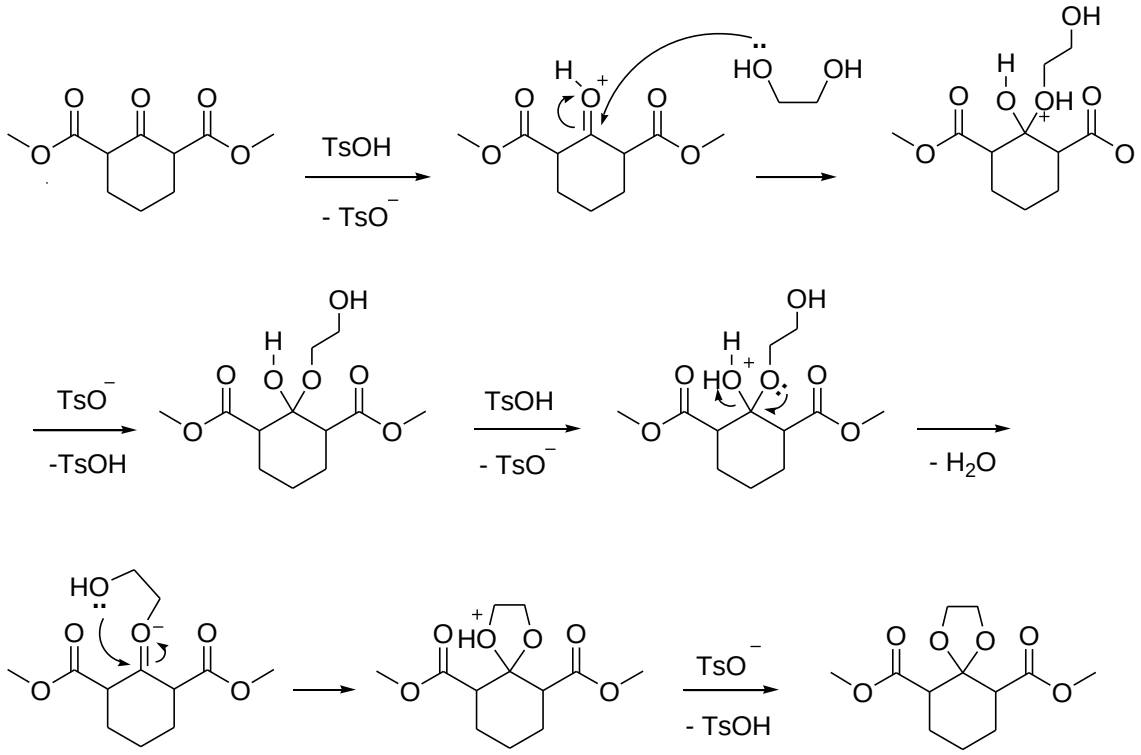
$C_{10}H_{14}O_5$	F(000) = 456
M_r = 2.14.21	D_x = 1.336 Mgm^{-3}
a = 19.914 (4) Å	λ = 0.71073 Å
b = 4.7547 (5) Å	μ= 0.108 mm^{-1}
c = 11.7644 (18) Å	T = 293 (2) K
V = 1065.0 (3) $Å^3$	Z = 4

2. Appendix

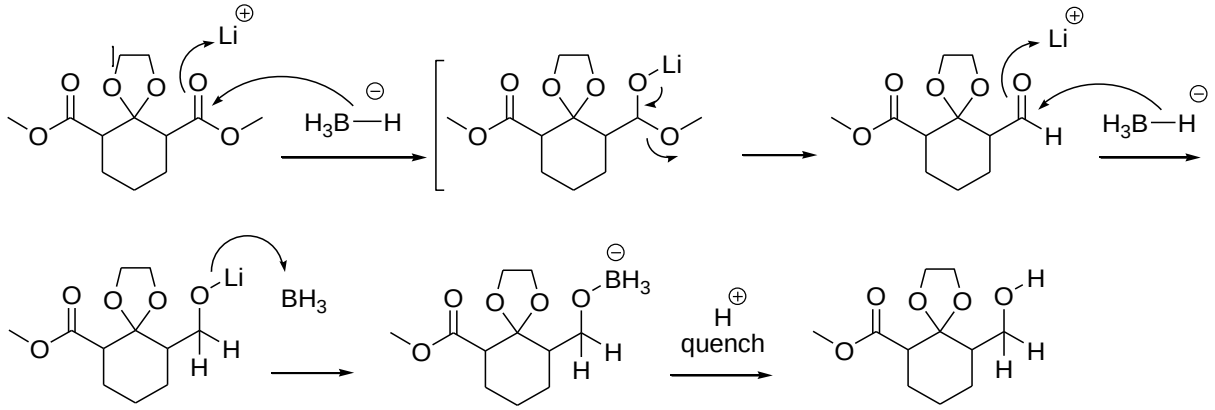
2.1. Cyclization



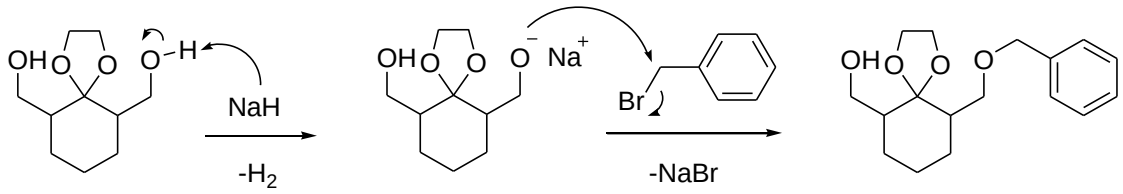
2.2. Ketone protection



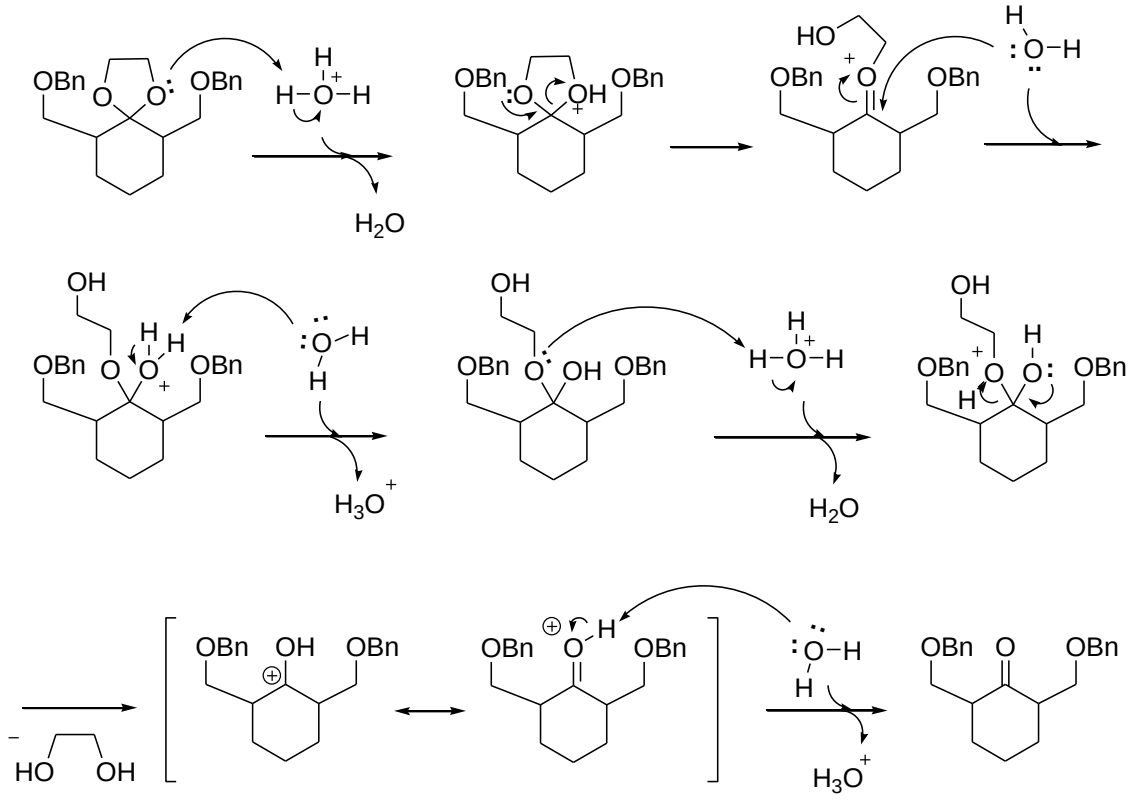
2.3. Reduction of ester



2.4. Alcohol protection

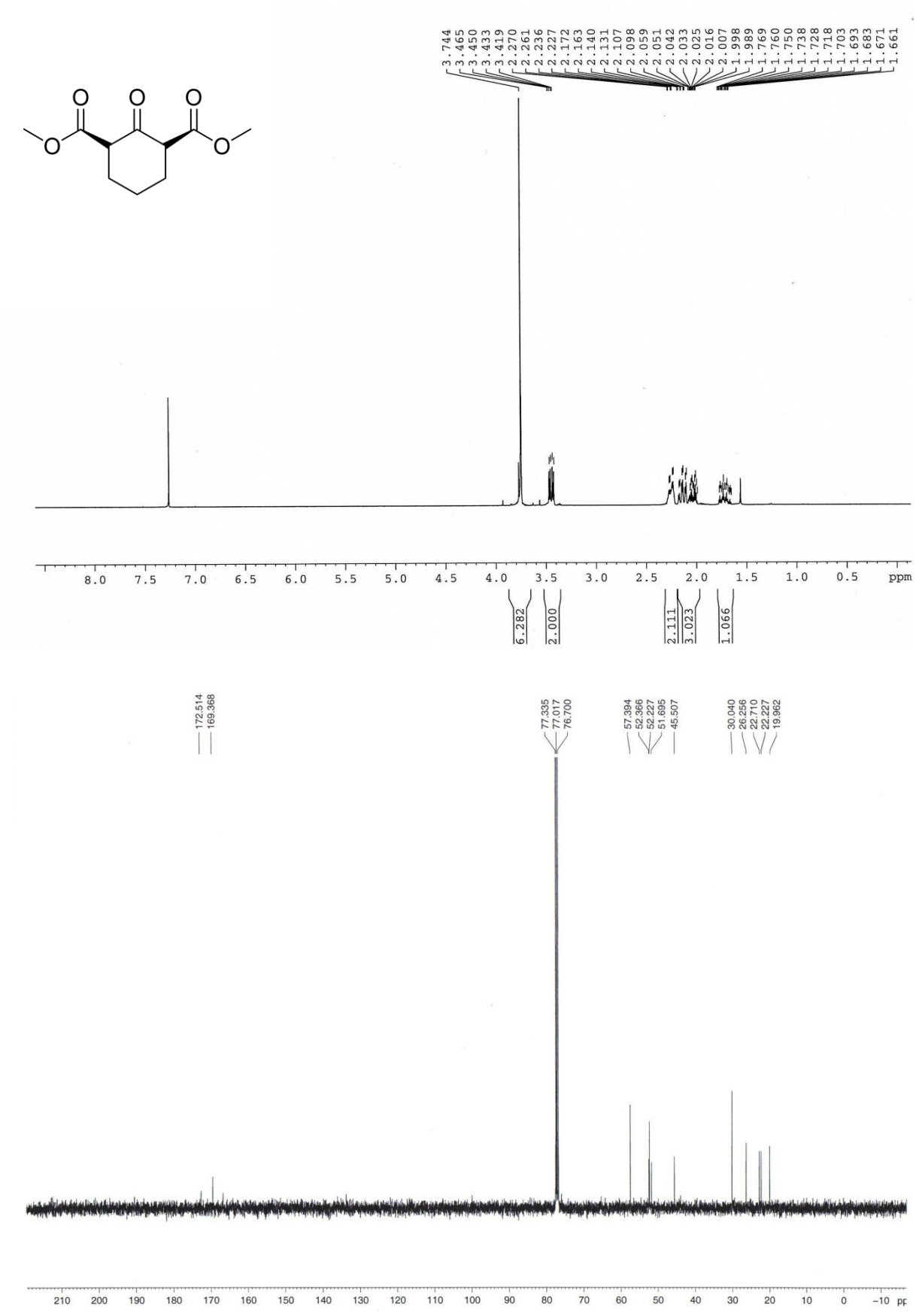


2.5. Ketal hydrolysis

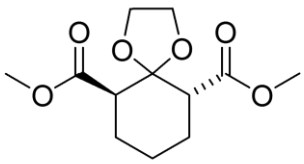


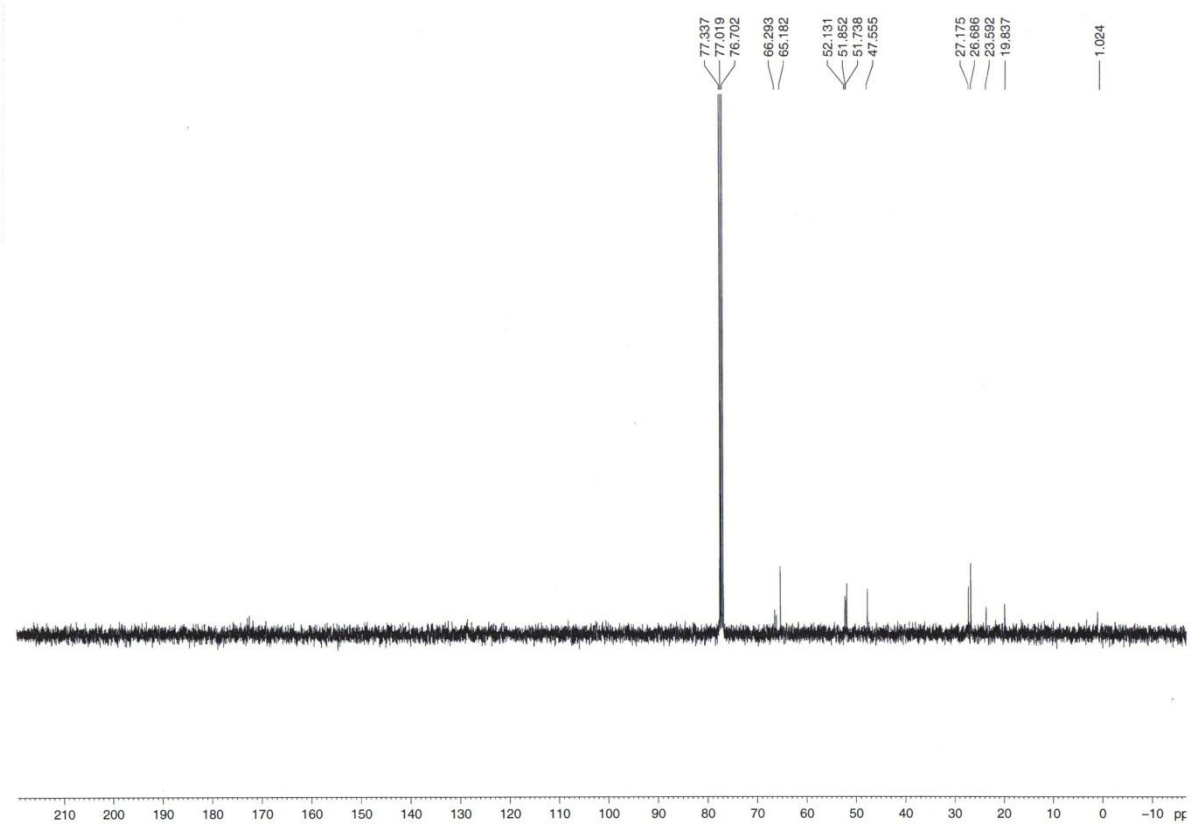
NMR Spectra

Dimethyl-2-oxocyclohexan-1,3-dicarboxylate (2)

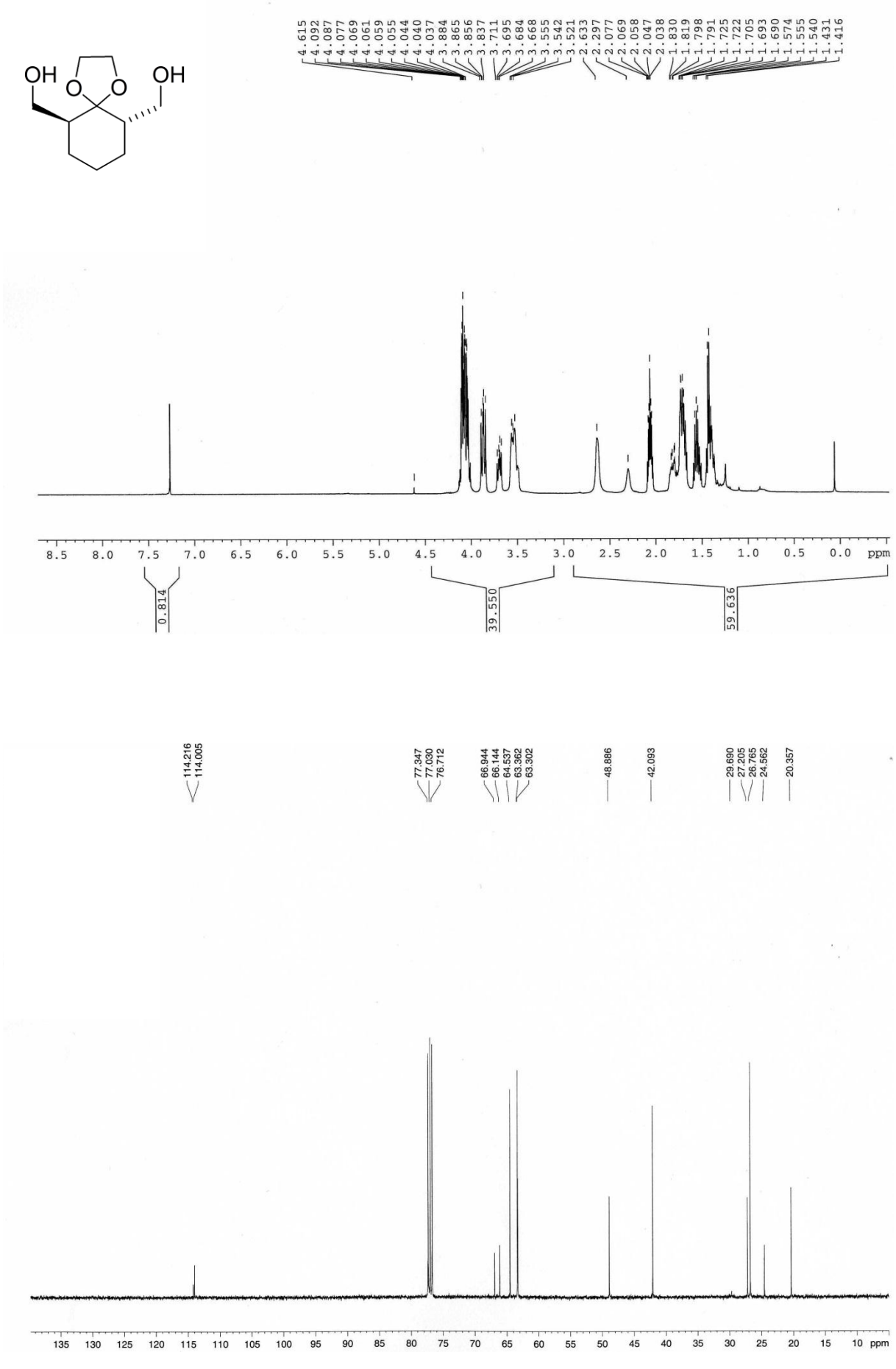


Dimethyl -1,4-dioxosparo[4,5]decane-6,10-dicarboxylate (5)

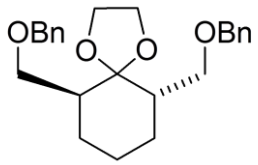


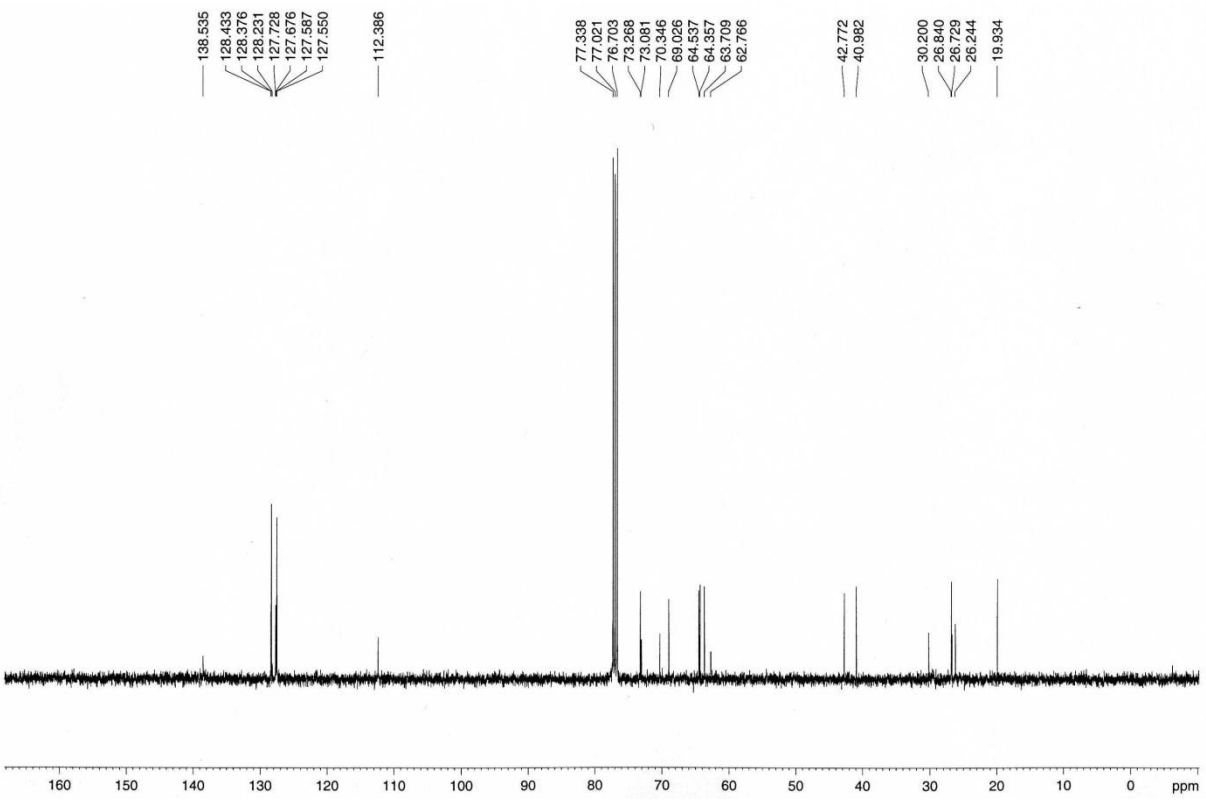


1,4-dioxosparo[4,5]decane-6,10-dihydroxymethyl (6)



1,4-dioxosparo[4,5]decane-6,10-dibenzyloxymethyl (7)





2,6-bis((benzyloxy)methyl) cyclohexanone (8)