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Titel der Diplomarbeit / Title of the Diploma Thesis

CONSTRUCTION OF TERTIARY CENTERS THROUGH CARBENOID MEDIATED HOMOLOGATION OF CARBONYL ELECTROPHILES

Verfasst von/ submitted by

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Foreword

During the course of my practical diploma thesis for a degree in pharmacy at the University of Vienna, I was part of a research group within the Chemistry department from March 2019 onwards. This step, in which Professor Vittorio Pace was instrumental, gave me the exciting opportunity of continuing my journey through the multifaceted world of carbon chemistry. As early as in the 6th form at school, organic chemistry had stimulated my young inquiring mind and hence also my passion for its key element, carbon. The distinctiveness and significance of its chemical structure, and the diversity thereby manifested, could be seen as limitless. My fascination with and desire to discover this diversity was to have its starting point in a pharmacy degree, which was the tailor-made option for me. From here, I set out on the trail of a complex element, and was excited to discover its ubiquitous nature, compound by compound. This began with things in our everyday life, covered the depths of life in cells, including their components, and concluded with medication. The carbon atom shows that the organic world which we inhabit is characterised by continuous change. These changes are, in their nature and depth, determined by the distinctiveness of the C atom. A virtually infinite field opens up to us in which, through research and observation, we can draw conclusions about fundamental mechanisms and modes of functioning of the C atom. Or, with the aid of experiments, generate different compounds and investigate their effects. My aim during my degree was to learn how to conduct and apply this experimental research at academic level, specifically at the level of current pharmaceutical practice.

Rising to this difficult and demanding challenge is not possible without the help, knowledge and expertise of other people – people who are pursuing the same goal in a team, and hence become colleagues and over time friends as well. Special people, such as those in the team led by Professor Pace, above all my lovely mentor Margerita Miele. She supported and instructed me as a teacher and friend during my practical diploma thesis, which meant I was able to complete my task step by step. I was therefore also pleased and honoured to be able to make a contribution to her work and, thanks to the knowledge sharing supported by her direction and guidance, to develop my skills in carbon chemistry research in the pharmaceutical context. Even if there is still a lot to research and discover, I have acquired, in this team, the ultimate tools of a good practical scientist, which is why I am commencing my theoretical thesis with this mention.

I would also like to take this opportunity to express some words of thanks and recognition to other important people who have accompanied me on my journey. At the end I look back and see the countless chains of people and coincidences which helped me to arrive at the destination I was working towards. Many interesting, instructive and formative people who appeared in a university context in the form of professors, tutors, assistants or fellow students, deserve my thanks, as do my father Ruhollah, my mother Shafiga, my brother Rostam Asra and my husband Arwin Abdullah. They have always known who I am and what abilities are there deep inside me. They therefore gave me the confidence in myself and the strength to progress through all the highs and lows of the degree course. Finally I would like to mention that without the caring assurance and motivating words of my best friend Judith Müller, as well as those of my fellow students and companions Nici, Magi, Maja and Azra, the period of my life which is coming to a close with this thesis would not have been the same wonderful, biggest ever adventure. I would like to extend my most sincere and heartfelt thanks to them.

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1. Abstract

For the purpose of investigating and constructing tertiary centres, I was able to carry out my work using the method comprising homologation with the aid of carbenoids, and make a contribution to the working group. Thus I succeeded in independently synthesising twelve compounds in the course of my diploma thesis and in assessing these both qualitatively and quantitatively. (See Chapter 5)

The application is concerned with the use of a carbanion which, under the given reaction conditions is capable, thanks to its reactivity, of generating additional and more diverse compounds. Hence this thesis describes a simple and effective synthesis of different chemical compounds with tertiary centres which otherwise stand out significantly for their functionalities, structures and substituents, and are difficult to produce.

Zur Untersuchung und Konstruktion von tertiären Zentren, konnte ich meine praktische Arbeit durch die Methode der Homologation von Carbenoiden realisieren und einen Beitrag zur Arbeitsgruppe leisten. So gelang es mir, eigenständig zwölf Verbindungen im Zuge meiner Diplomarbeit zu synthesieren und diese sowohl qualitativ als auch quantitativ zu erfassen. (siehe Kapitel 5)

Dabei beschäftigt sich die Anwendung mit dem Einsatz eines Carbanions, der unter gegebenen Reaktionsbedingungen durch seine Reaktivität fähig ist weitere und diversere Verbindungen zu erzeugen. Diese Arbeit beschreibt somit eine einfache und effektive Synthese von verschiedenen chemischen Verbindungen mit tertiären Zentren, die sonst durch ihre Funktionalitäten, Strukturen und Substituenten stark gekennzeichnet und so schwer zu erzeugen sind.

2. Introduction

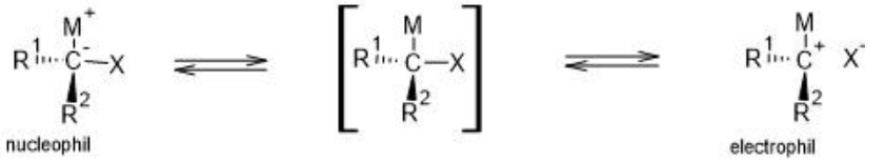
The Synthesis for a selective “one-carbon homologation” in the case of alkyl halides; these are substances which, in the field of organic chemistry, are particularly hard to determine. Hence this thesis is concerned with the sequential integration of a carbenoid with a hybrid in a carbonyl compound which offers an excellent and practical possibility for obtaining sp3-type halomethyl-alkyl derivatives.

The strategy of the working group led by Prof. Pace consisted of obtaining – through the use of carbonyl compounds as a starting material – a large quantity of synthesis product, which simultaneously displayed controlled chemoselectivity. This approach proved to be not only very flexible, but also useful, since it was not only confined to carbenoids. For example, different carbon-like structures could be used as nucleophiles and react further under the given conditions. Additionally, this method may play an important part when it comes to a wider application in organic synthesis, or, as in the context of our work, help to skip some synthesis process steps and design the process more efficiently.

The presence of a halogen and its important function within a carbon backbone influences the physiochemical conditions so strongly that the entire reaction profile is also determined thereby.[1]

This has already been thoroughly investigated in the past, according to the methods used in solid synthesis, on a variety of systems (radicalic, nucleophilic, electrophilic) and applied while developing a variety of homologation strategies.[2]

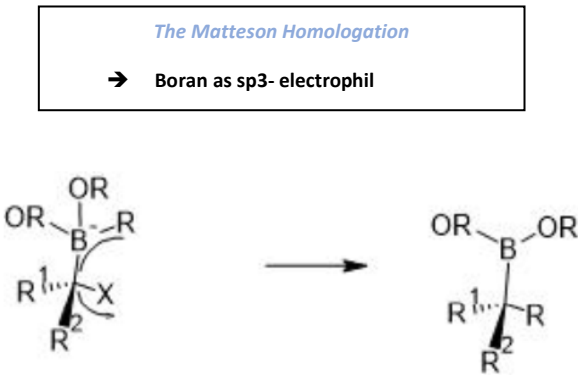
The introduction of a metallated α-halogenated carbon species $\boldsymbol{MCR^1R^2X}$ (= carbenoid reagents), characterised by its respective metallic character and which can either generate a nucleophilic or electrophilic environment, proved to be a useful tool *(Scheme 1).* By this means, a precise graduation can be produced during implementation of the synthons, according to the functionality requirements (e.g. with halogen complexes).[3]



Scheme 1: *Schematic of metall-behavoir*

In addition, with the aid of this method it was possible to conveniently bypass disadvantages such as polyhalogenation which were known from previous conceptual trials. The event amounts to the initial integration of the $\boldsymbol{MCR^1R^2Hal}$- moiety, which later turned out to offer suitable yields, for the construction of additional diverse and more complex molecule structures with a tertiary centre.

The distinctiveness of the above-mentioned method lies in releasing the desired end product through only a single synthetic mechanism which requires no further transformation. This is in contrast to the versatile Matteson homologation with an sp3-hybridised borane electrophile *(Scheme 2)*, with which a subsequent adaptation with the Aggarwal method is necessary to obtain monitoring with line concepts.[4]

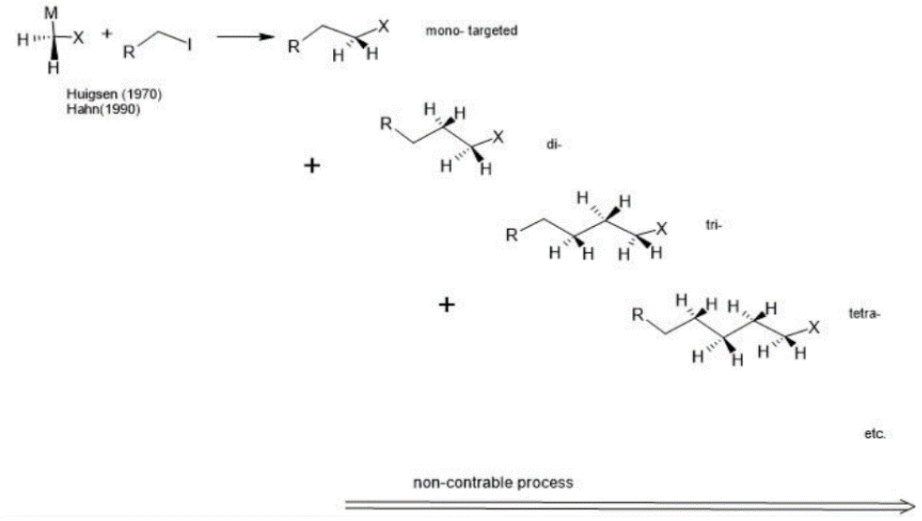


Scheme 2: *Matteson Homologation*

It is well known that, in the homologation of carbon-based platforms, only those are suitable which are restricted to an sp2-type system. The aim of this thesis is to demonstrate that the homologation of carbon-type derivatives is also possible in a single stage, which furthermore can also result in sophisticated molecular architectures, e.g.: (quaternary aldehydes [5] and aziridine [6]). Among these, olefins can also be used as accessible substrates, which can be converted into cyclopropanes through C1 insertion.[7]

Endeavours in the homologation of primary sp3 platforms usually result in multi-insertion phenomena (up to four successive homologations) *(Scheme 3)* with an inefficient synthesis value, as already observed in the seminal work by Hugisen [8] and later also by Hahn [9].

MCH_2X- Homologation of *carbon sp3-electrophile*
→Polyhalogenation – Problem

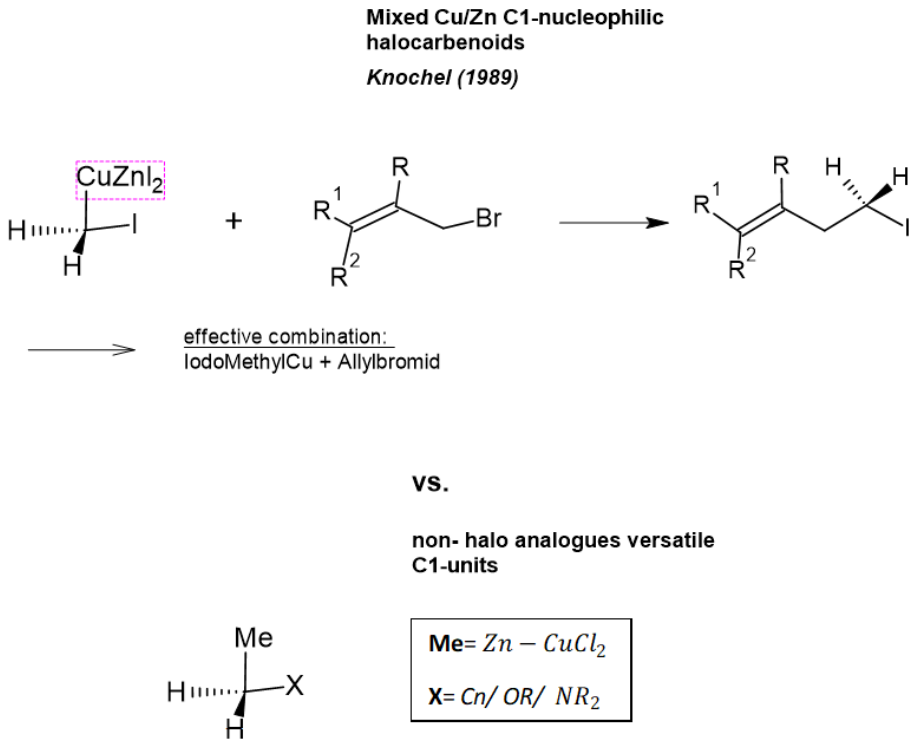


Scheme 3: Polyhalogenation-Problem

It was possible to rectify the problem with polymethylene homologation through the use of *Knochel's Mixture of Cu/Zn-mono-idocarbenoids*, which attracted attention in specialist circles as far back as 1989 [10]. The result of this application is that selective control of the process can be achieved through a single C1-halogenated unit.

This is because especially where precise gradation of synthetic reactions is desired, the accessibility in relation to chemical spatiality is particularly significant. However, this is mostly present in a scaled-down form, often as a result of the specific structural properties of the reaction partner.

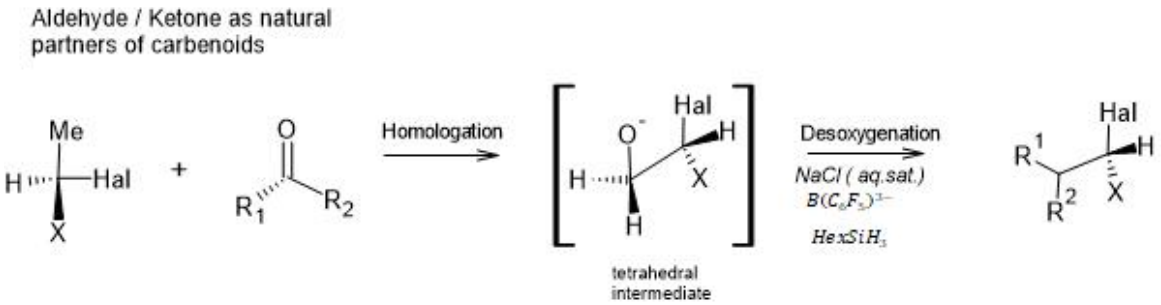
This is where we see a key approach of the method used. This is in contrast to the widespread applications with diverse halomethyl zinc carbenoids, which have already been thoroughly developed and applied, for example through the work of Marek [11] or the various non-halomethyl-Cu/Zn mixtures of Knochel [10] *(Scheme 4).*



Scheme 4: Halomethyl-zinc-carbenoids versus non-halo analogues

Thus representative of this method is the conversion through the introduction of the carbenoid on a carbon-sp2 type, with subsequent deoxygenation [12] of the intermediate, carbinol, which thus constitutes a general and modular synthesis for alkyl halides. At the same time, it is justifiable with this method that the starting materials do not necessarily have to be dependent on the specific configuration.

In general, the strategy can be deemed to consist of the following: through the use of sp2-type systems, the naked sp3-C leaving group is revealed, which, according to the desired sequence, delivers the motif in a targeted manner *(Scheme 5).*



Hal= Cl/ Br/ I/ F/ CHI_2

X= CHF_2/CF_3/ SiPh/ SiMe_3/H/ Me/ Ph

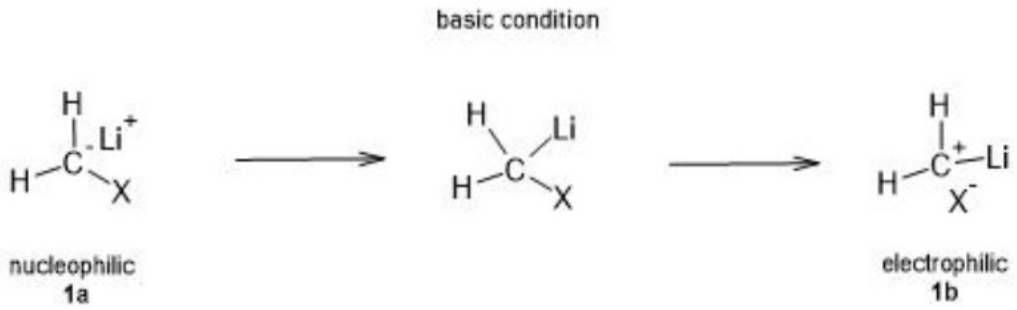
Scheme 5: *Principe of Homologation*

This approach seems not only to have high flexibility; in addition, good robustness can be expected, which in organic chemistry is also of great importance. Ultimately, it was only possible through the consideration of the operation of both reaction partners: the electrophilic carbonyl and the nucleophilic carbenoids, to achieve an initial solution for the rationalisation of homologous (n+1) halogenoalkyls with a tertiary centre.

2.1. Carbenoids

Lithium carbenoids is the term for organometallic compounds which, alongside the lithium atom, also have at least one electronegative atom (e.g. substituted halogen), which together are known as carbenoids.[13] According to Closs & Moss, indicative in the selection of the term “carbenoid”, is the intrinsic definition of the species that they should be understood as those which exhibit a reactive qualitative analogue. This is in contrast to the carbenes, whose ability does not consist of the necessary and bivalent character which singles out this species.[14]

The property of this chemistry is ultimately its intrinsic amphiphilia, between the nucleophilic / electrophilic behaviour.[15] Under experimental conditions it was possible to prove selectively that, in general, the character of this group, at low temperatures behaves in a more nucleophilic way **1a**, whilst at high temperatures electrophilic **1b** behaviour can be observed.



Scheme 6: *Resonance-structure of carbenoids*

The change in its basic state, as depicted above, can be rationalised in its resonance structure, which through the extreme ionisation of the carbon bond, in principle leads to carbanionic or -cationic species *(Scheme 6).* With the aid of the spectroscopic observations, it was possible to research and determine this zwitterion-like behaviour; for example, a high proportion of s-orbital is manifested in C-Li bonds, while carbohalogens have a strongly p-character.[16]

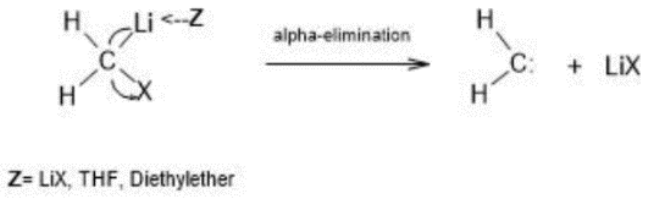
The capability and distinctiveness of the monohalomethyl-lithium reagent had already attracted attention in specialist circles and reinforced this, not least since its introduction as a nucleophilic agent in the case of Köbrich in the late 1960s.[17] It proved to be an excellent tool which could alternatively be used in the preparation of homologative series. In this case, parallel toxic processes, for example the diazomethane-based procedure [18] or that of sulphur ylides (e.g. Corey-Chaykovski type chemistry [19]), were easier to avoid. Significantly, it can also be established that the fluoromethyl-lithium species are, in their chemical form, too unstable and hence their application in organic processes can be viewed as heavily limited.[20]

The crucial, key factors in the chemical reactivity of lithium carbenoids can be summarised as follows:

When treating a dihalomethane-lithium with an alkyl-lithium base, the Li carbanion is formed immediately. In order to ensure the complete formation of the carbenoid and at the same time minimise the rival attack by the organomethyl-lithium on the electrophilic substrate, which results as a consequence of the high speed of exchange of the halogen-lithium [21], it is advisable to use a slight excess (0.2-0.4 eq.) of dihalomethyl versus the R-lithium***(Scheme 7a)*** [22] .

(Scheme 7a)

The marked thermal instability requires negative temperatures (-78°C) for the successful implementation of a homologation. Because of the easy decomposition via the α- elimination which they undergo, the reactions are mostly electrophilic in nature.[23] This kind of side reaction involves the simultaneous leaving of a proton and a functional group (e.g. a halogen) starting from an atom. Thus, in the presence of a strong base, first the proton is cleaved off (e.g. on a carbon atom), whereby, firstly, a negative carbanion remains. With further cleaving-off of the functional group, the ultimate carbene is produced (nucleophilic). In order, therefore, to increase the stability of this species, the Li-X salts are mixed in the presence of Lewis bases (THF or diethyl ether). Thus through their coordination to the lithium atom of the carbenoid, the internal lithium-X interactions are interrupted which otherwise result in a α-elimination and hence the systematic decomposition of the carbenoid to the carbene ***(Scheme 7b)*** [12]



(Scheme 7b)

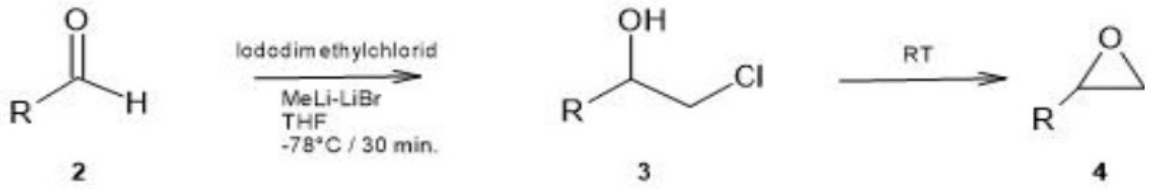
Scheme 7: *Formation and degration of lithium carbenoids*

The effective thermal stability of $LiCH_2Cl$ has already long been a topic of intense debate in the literature, where it has simply not been possible to reach agreement. Most successful in this, however, was Köbrich, whose efforts concentrated on determining a suitable temperature. In his investigations he particularly considered the three unstable monohalocarbenoids (with the exception of $LiCH_2F$), owing to their decompensation at temperatures above -110° C. [17] Subsequently this behaviour was also confirmed by Villieras in the 1980s.[24]

Ultimately, the answer to the question of what is the correct temperature still applies today, as the publications from the late 1980s [21] and 1990er [25] confirmed the stability at -78°C. Thus, during the

work at these non-prohibitive temperatures, the effectiveness of the reactions involved within such species could be understood as no longer impaired.

Thanks to their intrinsic electrophilicity, the carbonyl-type compounds homologate extensively with lithium carbenoids. The addition of $LiCH_2X$ on an aldehyde or a ketone **2** under mildly acidic treatment at -78° results in a high yield of the corresponding halohydrin **3**. Furthermore, the reaction, on reaching room temperature (RT), exhibits intramolecular nucleophilic displacement before the protonation step which involves a direct formation of epoxids **4** *(Scheme 8)*.



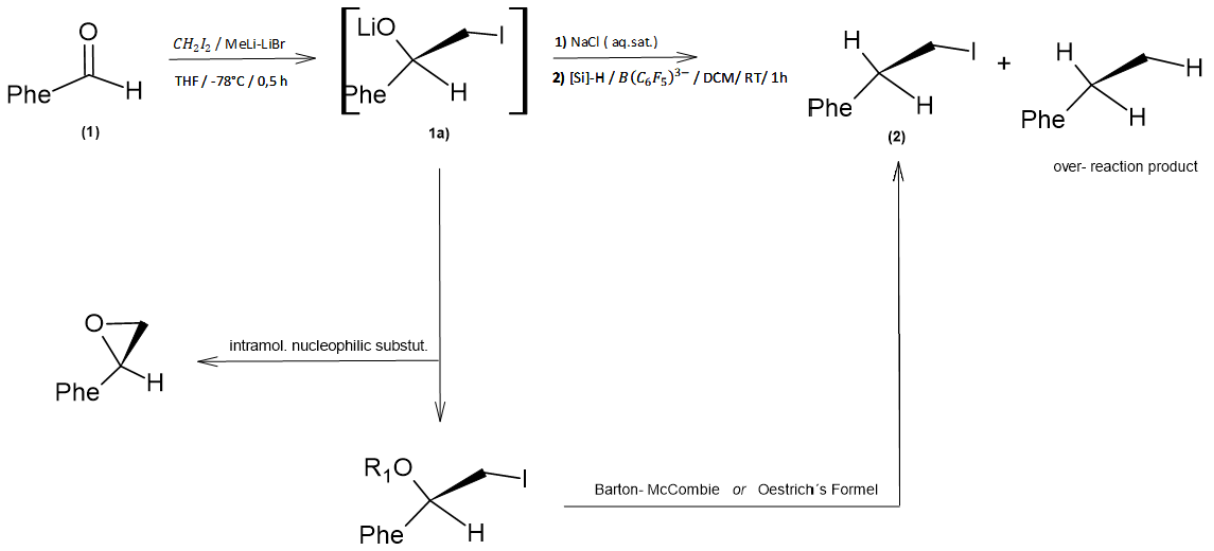
Scheme 8: *Reactivity of lithium carbenoids with carbonyl-typ-derivates*

2.2. Synthesis of the Halomethylalkanes

The working group chose, as its starting material substrate, benzaldehyde **(1)** *(Scheme 9)* for the homologative deoxygenation with $LiCH_2I$, in order to gain insight within the two separate moments during the process. In principle, the introduction of an iodine-containing structure must be regarded critically, because firstly the hazard of intrinsic nucleophilic displacement would be triggered, identified by the obtaining of expoids [5] (homologative side reduction). Secondly, these undergo, owing to the overreaction, a conversion to $C-H-$ compounds (deoxygenation side reduction).[25]

The optimum homologation step, using a quantitative procedure, can be achieved in 30 minutes at -78°C with a THF consumption of 1.4 equivalent to $LiCH_2I$. The process can be captured and assessed analytically with the aid of an H^1-NMR detector and GC-MS analyser. By using this, not only can the yield of the tetrahedric intermediate be derived, it also becomes possible to carry out monitoring at the intermediate stages of the reaction steps **(1a)**. If the reaction mixture is placed for a longer time at room temperature or, through higher temperatures up to -50°C, then significant epoxids can be expected. (see Capter 5)

Direct treatment under Barton-McCombie conditions [26] results in a low yield of iodoalkenes **(2)** after a longer time and high temperatures.



Scheme 9: *Model reaction*

For the next synthesis step, the reduction to alcohols, [27] we made use of the versatile and convenient Oestrich´s formula, which after its conversion into tosylates followed by a catalysed $B(C_6F_5)^{3-}$ - deoxygenation [28] in the presence of Et_3SiH, delivers a yield of up to 46 % (*entry 2)*. In further refining steps, the confinement of the homologative reaction product with water, formally iodohydrin was obtained, which was suitable for direct deoxygenation. This was previously separated from the organic phase through repeated washing steps. Thus the reduction delivered a moderate yield of 52%, however the assumption had to be checked regarding whether the presence of THF (used for homologation) represents a quantitative interference factor, because this continued to exist in the mixture and in a dilution with DCM. It is possible that the interference existed during the C-O cleaving process before (*entry 3)*, which in practice, in turn, displayed a low product yield.

In fact, the dehydroxylation step proved to be beneficial, as it featured the prior and complete removal of the THF from the raw reaction product (washing of the raw homologation product with sat. NaCl (aq.)). Thus an increase in the quantitative yield of 66% *(entry 4)* was established and the assumption, through the result, no longer be regarded as purely hypothetical.

Less sterically hindered silanes such as: Ph_2SiH_2/ Et_2SH_2/ $HexSiH_3$ likewise proved to be effective and highly recommended. Because here, too, excellent selectivity could be observed as no side effects were established in the course of the reaction. Hence suitable basic structures can be used which are subject to a targeted alteration of their substituents and simultaneously generate new structures (*entry 5-8).*

In addition, in the course of the work with the exchange of $B(C_6F_5)^{3-}$ - for another Lewis base, such as$\mathrm{In}\,Cl_3$ [29], negative side effects could be observed during the procedure *(entry 9)*.

entry	$LiCH_2I$ *(eq.) / time (h)*	*Desoxygenation reduct/ solvent*	*Lewis acid*	*Yield of* **(2)** in %
1 [b]	*1,4/ 0,5*	*BMC*	$B(C_6F_5)_3$	*11*
2 [c]	*1,4/ 0,5*	*Oestreich*	$B(C_6F_5)_3$	*46*
3 [d]	*1,4/ 0,5*	Et_3SiH */ DCM*	$B(C_6F_5)_3$	*52*
4[e]	*1,4/ 0,5*	Et_3SiH */ DCM*	$B(C_6F_5)_3$	*66*
5	*1,4/ 0,5*	Ph_2SiH_2 */DCM*	$B(C_6F_5)_3$	*68*
6	*1,4/ 0,5*	Et_2SiH_2 */DCM*	$B(C_6F_5)_3$	*77*
7	*1,4/ 0,5*	$PhSiH_3$*/ DCM*	$B(C_6F_5)_3$	*84*
8	*1,4/ 0,5*	$hexSiH_3$*/ DCM*	$B(C_6F_5)_3$	*89*
9	*1,4/ 0,5*	$hexSiH_3$*/ DCM*	$InCl_3$	*60*

[a] after the Homologation /desoxygenation sequence: isolated yield

[b] Barton- McCombie (R^1= PhCS, Bu_3SnH , AIBN, toluene, reflux)

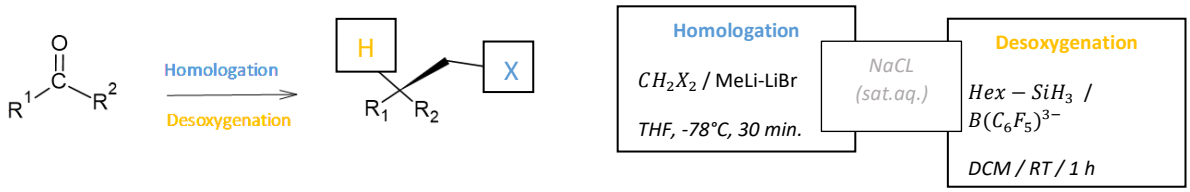
[c] Oestreich (R^1= Ts, Et_3SiH, $B(C_6F_5)_3$, DCM)

[d] Quenching with H_2O, add of DCM and separating of the two phases

[e] sat. NaCl (aq.) and DCM added prior to phase separation. Unless otherwise $B(C_6F_5)_3$ *(0,1 equiv.)* was used.

3. Work project

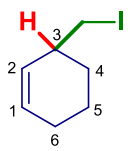
After the reaction conditions were given, the extent of the sequential process was investigated *(Scheme 10)*.



Scheme 10: *Homologation / Desoxygenation*

3.1. Aldehyde

The chemical control proved outstanding, as was shown by the illustrated cases, such as the sensitive substrates of cyclic enones **(3)** and unsaturated α-β esters **(4)**: no overreaction of the olefins and ester carbonyl compounds.



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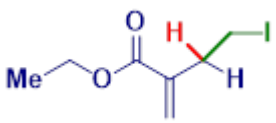
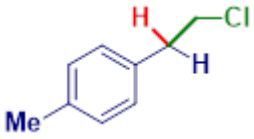


(4) 85%

The protocol turned out to be highly flexible and could therefore be understood as a manual for further use of different carbenoid homologation reactants. The method of chloromethylation-deoxygenation also proved particularly effective in the case of derivatives such as benzaldehyde derivatives, which especially stand out for their numerous functionalities and electronic behaviour; these included alkyl **(5)**, amino **(9)** and polyaromatic compounds **(10)** (see Fig.)



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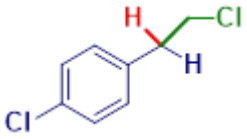

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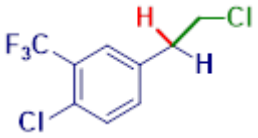

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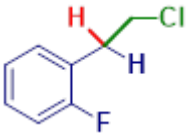

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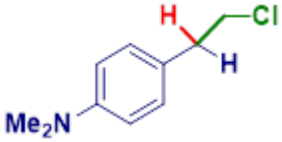

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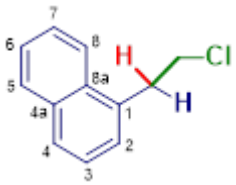

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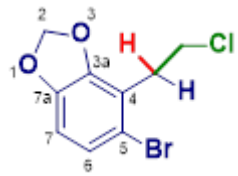
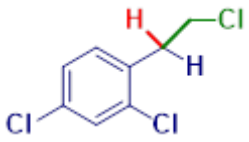
In addition, it can be noted that acetal-containing bromine derivatives **(11**) interfered neither through sterical hindrances, proximity of the carbonyl group, nor in the reduction steps (e.g. di-substituted systems **(12)**).

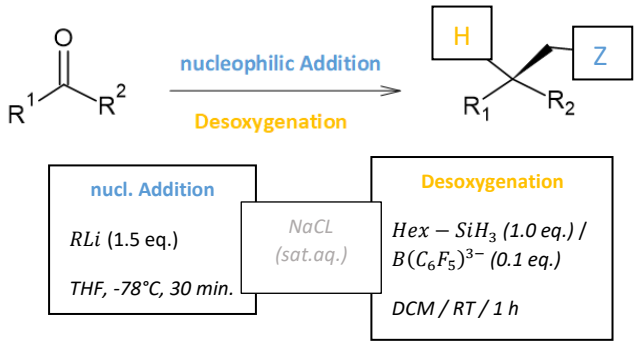


(11) 90%



(12) 90%

The conceptual, intuitive carbonyl-nucleophile addition- deoxygenation constitutes an excellent tool for the construction of C-C bonds *(Scheme 11)*. At the same time, the perfect theoretical option in relation to non-halogenated could be documented.



Scheme 11: *General nucleophilic Addition/ Desoxygenation*

4. Conclusion

In summary, it can be established with this thesis that through the high-yielding addition of two nucleophiles, a halocarbenoid and a hybrid to basic carbonyl structures such as aldehydes or ketones, the potential and the diversity in synthesis which were already documented [36] could be increased further.

The entire process consists of 2 different mechanisms, specifically homologation and silane-mediated deoxygenation under $B(C_6F_5)_2$ catalysis. This access, and the compounds thereby released, result in a wealth of additional and different halomethyl-alkyl derivatives.

In both phases of the sequence, the conditions could be shown to be established, which stood out through the high chemical control. The transformation was deemed secure and reliable, in particular also in the presence of sensitive functionalities or systems, such as halogens, olefins, alkynes, esters and many more. The robustness of the stated structures contained approx. 90 compounds which were able to be detected and assessed. Furthermore, in addition to the extensive creation of mono-/dihalomethylene carbenoids, also fluorinated, silylated mercapto compounds were obtained. As a result, in the research associated with this thesis it can be established that this method constitutes a general, simple and optimum method for the production of tertiary alkyl- & aryl organolithium.

5. Eperimental Section

5.1. Material & Methods

Melting Points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS). 1H, 13C and 19 F NMR spectra were recorded at 297 K on a Bruker Avance III 400 spectrometer (400 MHz for 1H, 100 MHz for 13C, 40 MHz for 15N, 376 MHz for 19F) equipped with a directly detecting broadband observe (BBFO) probe, with a Bruker Avance III 500 spectrometer (500 MHz for 1H, 125 MHz for 13C) using a Prodigy cryoprobe, and with a Bruker DRX 200 spectrometer (200 MHz for 1H, 50 MHz for 13C) with a 1H/13C dual probe.

The centre of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (1H in CDCl3), δ 7.16 ppm (1H in C6D6), δ 77.00 ppm (13C in CDCl3) and δ 128.06 ppm (13C in C6D6). Absolute referencing via Ξ ratio was usd for the 19F NMR spectra. Spin-spin coupling constants (J) are given in Hz.

In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, HSQC-TOCSY, COSY and NOESY experiments.

All the reactions were carried out under inert atmosphere of argon. THF was distilled over Na/benzophenone. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fluorochem and TCI Europe. Solutions were evaporated under reduced pressure with a rotary evaporator.

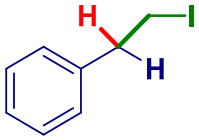
TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Merchery-Nagel, Merk); the spots were visualised under UV light (λ = 254 nm).

5.2. General Procedures

To a solution of carbonyl compound (aldehyde or ketone, 1 equiv) in dry THF (3 mL) cooled at -78 °C, the dihalomethane carbenoids precursor was added (1.5 equiv) under Argon atmosphere. After 10 min, MeLi-LiBr 2.2 M solution in Et2O (1.4 equiv) was added via syringe pump (0.20 mL/min) during a period of 15 min and, then the stirring was continued for additional 0.5 h. Subsequently, a saturated (aq.) NaCl was added to the mixture and the cooling bath was removed; the organic phase was extracted with dichloromethane (3 x 3 mL) and, dried over anhydrous Na2SO4. The filtered solution was flushed under argon and tris(pentafluorophenyl)borane (0.1 equiv) was incorporated to it at room temperature. After 2 min, hexylsilane (1 equiv) was added in one pot and, the reaction was stirred for 1 h. Finally, the mixture was quenched with saturated (aq.) NH4Cl (3 mL) and extracted with dichloromethane (3 mL). The organic layer was washed with saturated (aq.) NaCl (5 mL), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure (bath: rt) to give the crude compound eventually purified as indicated below.

5.3. Spectral & Characterization Data

(2-Iodoethyl)-benzene (2)

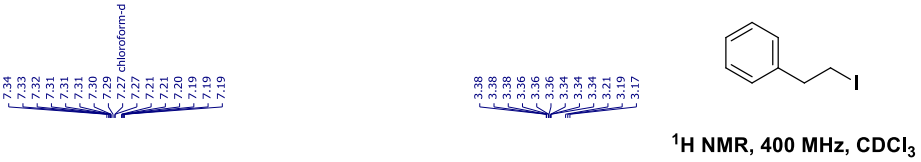


By following the **General procedure**, starting from benzaldehyde (200 mg, 1.88 mmol, 1 equiv) in dry THF (3 mL), diiodomethane (0.23 mL, 2.8 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.2 mL, 2.6 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (96 mg, 0.2 mmol, 0.1 equiv) and hexylsilane (0.3 mL, 1.88 mmol, 1 equiv), **compound 2** was obtained in 88% yield (384 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

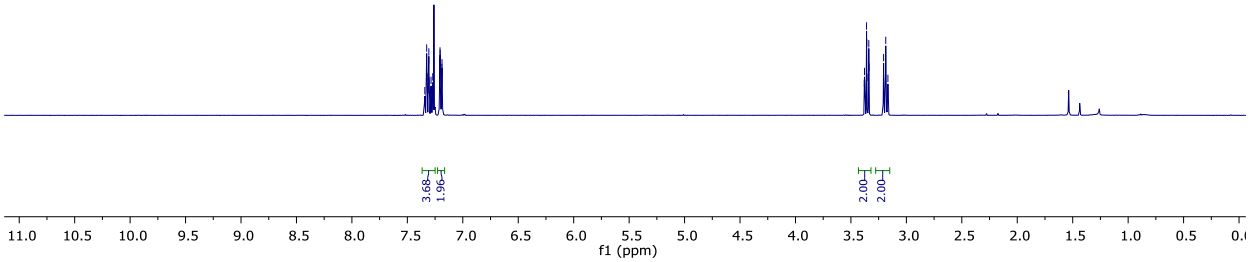
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.28 (m, 1H, Ph H-4), 7.20 (m, 2H, Ph H-2,6), 3.56 (m, 2H, CH_2I), 3.19 (m, 2H, CH_2).

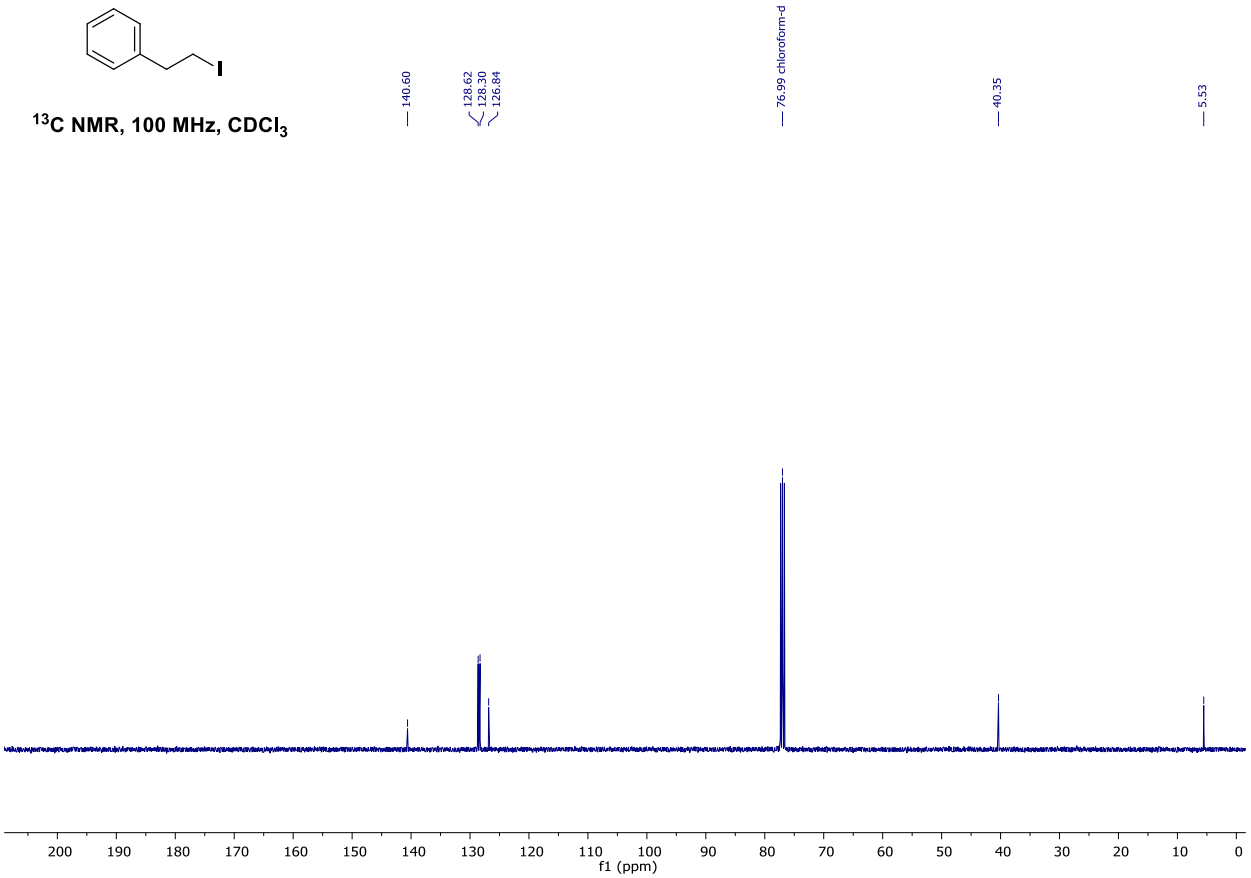
^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.6 (Ph C-1), 128.6 (Ph C-3,5), 128.3 (Ph C-2,6), 126.9 (Ph C-4), 40.4 (CH_2), 5.5 (CH_2I).

GCMS (ESI), *m/z*: calcd. for $C_8H_9I^+$: 231.9749 $[M^\bullet]^+$; found: 232.0.



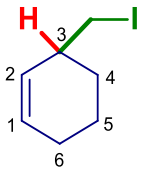
^{1}H NMR, 400 MHz, $CDCl_3$





^{13}C NMR, 100 MHz, $CDCl_3$

3-(Iodomethyl) - cyclohexene (3)

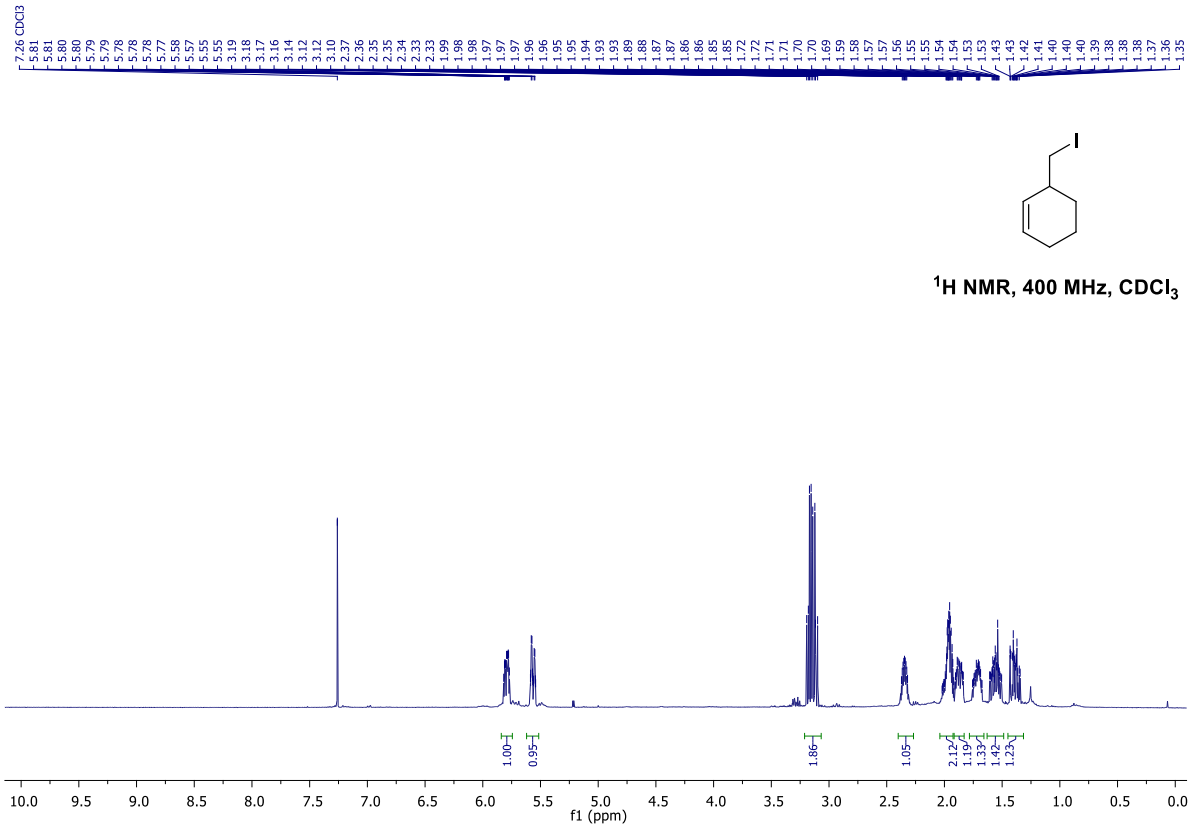


By following the **General procedure**, starting from cyclohex-2-enone (200 mg, 2.08 mmol, 1 equiv) in dry THF (3 mL), diiodomethane (0.3 mL, 3.12 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.32 mL, 2.9 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (107 mg, 0.2 mmol, 0.1 equiv) and hexylsilane (0.3 mL, 2.08 mmol, 1 equiv), **compound 3** was obtained in 88% yield (407 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

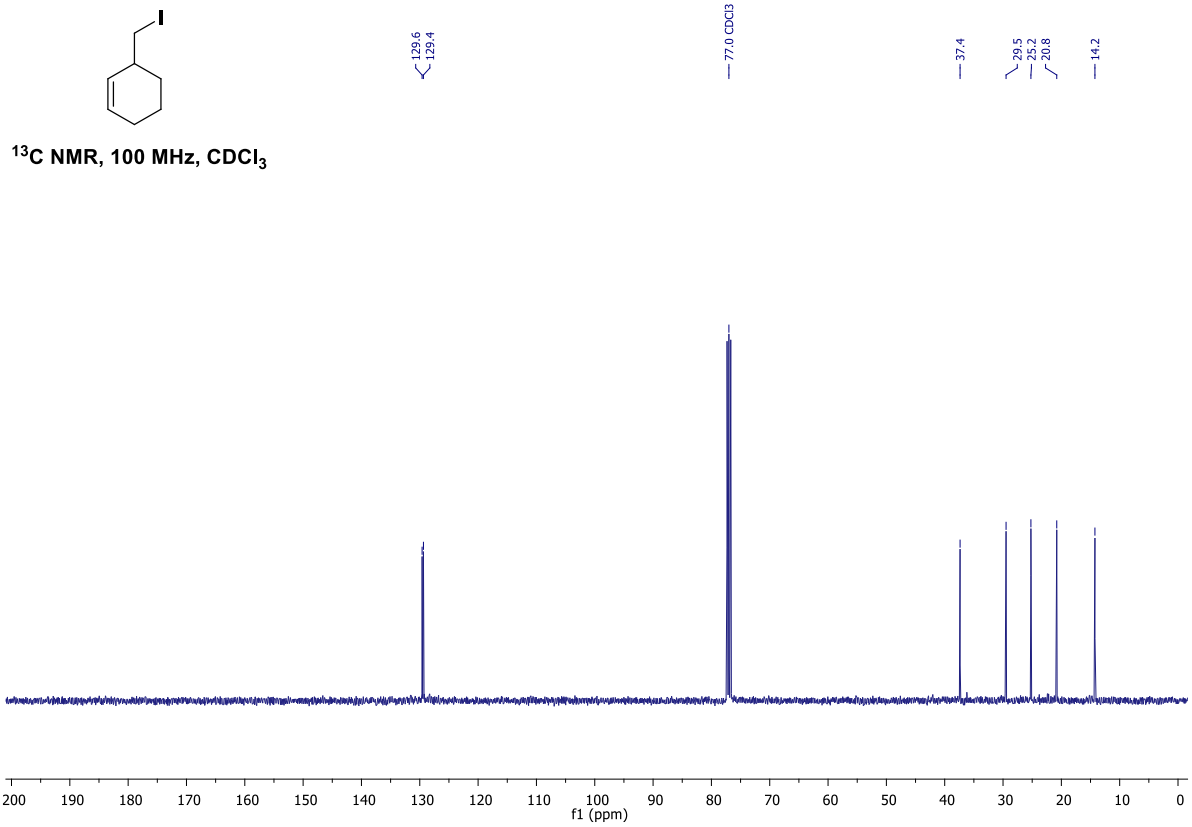
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.79 (m, 1H, Cyclohexene H-1), 5.56 (m, 1H, Cyclohexene H-2), 3.17 (dd, *J* = 9.6, 5.8 Hz, 1H, CH_2I), 3.12 (dd, *J* = 9.6, 7.3 Hz, 1H, CH_2I), 2.35 (m, 1H, Cyclohexene H-3), 1.96 (m, 2H, Cyclohexene H-6), 1.87 (m, 1H, Cyclohexene H-4), 1.71 (m, 1H, Cyclohexene H-5), 1.56 (m, 1H, Cyclohexene H-5), 1.39 (m, 1H, Cyclohexene H-4).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 129.6 (Cyclohexene C-2), 129.4 (Cyclohexene C-1), 37.4 (Cyclohexene C-3), 29.5 (Cyclohexene C-4), 25.2 (Cyclohexene C-6), 20.8 (Cyclohexene C-5), 14.3 (CH_2I).

HRMS (ESI), *m/z*: calcd. for $C_7H_{12}I^+$: 222.9978 $[M+H]^+$; found 222.9976.

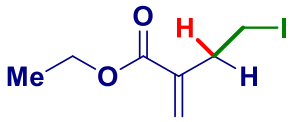


^{1}H NMR, 400 MHz, $CDCl_3$



^{13}C NMR, 100 MHz, $CDCl_3$

Ethyl 4-Iodo-2-methylidenebutanoate (4)

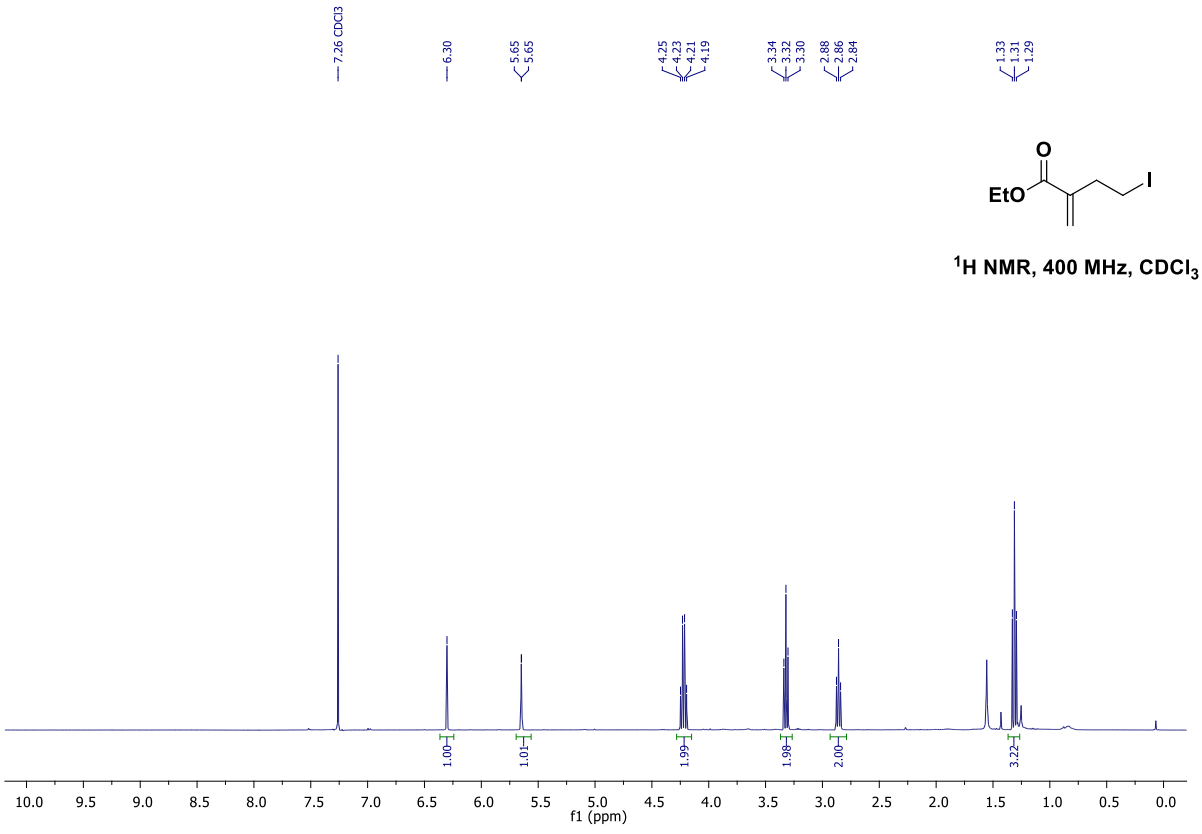


By following the **General procedure**, starting from ethyl 2-formylacrylate (200 mg, 1.56 mmol, 1 equiv) in dry THF (3 mL), diiodomethane (0.2 mL, 2.34 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (80 mg, 0.2 mmol, 0.1 equiv) and hexylsilane (0.3 mL, 1.56 mmol, 1 equiv), **compound 4** was obtained in 85% yield (337 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 95:5 as eluent).

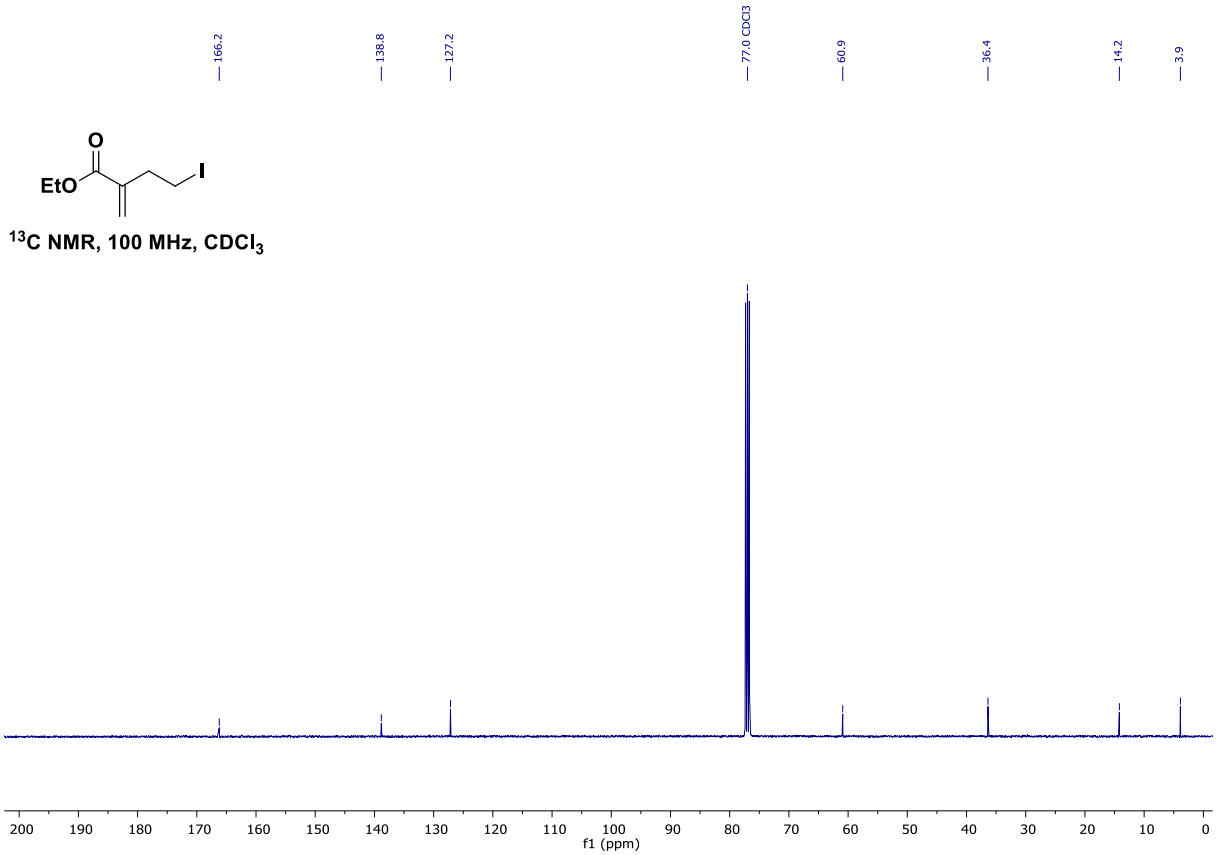
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.30 (d, *J* = 1.2 Hz, 1H, C=CH_2, *cis* to ester group), 5.65 (q, *J* = 1.2 Hz, 1H, C=CH_2, *trans* to ester group), 4.22 (q, *J* = 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 3.32 (t, *J* = 7.2 Hz, 2H, CH$_2$C$\underline{H}_2$I), 2.86 (dt, J_t = 7.2 Hz, J_d = 1.2 Hz, 2H, C$\underline{H}_2$CH$_2$I), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2 (C=O), 138.8 (C=CH$_2$), 127.2 (C=$\underline{C}$H$_2$), 60.9 (O$\underline{C}$H$_2$CH$_3$), 36.4 ($\underline{C}$H$_2$CH$_2$I), 14.2 (OCH$_2\underline{C}$H$_3$), 3.9 (CH$_2\underline{C}$H$_2$I).

HRMS (ESI), *m/z*: calcd. for $C_7H_{12}IO_2^+$: 254.9876 [M+H]$^+$; found 254.9878.

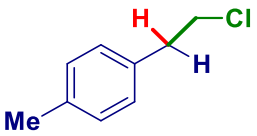


^{1}H NMR, 400 MHz, $CDCl_3$



^{13}C NMR, 100 MHz, $CDCl_3$

1-(2-Chloroethyl)-4-methylbenzene (5)

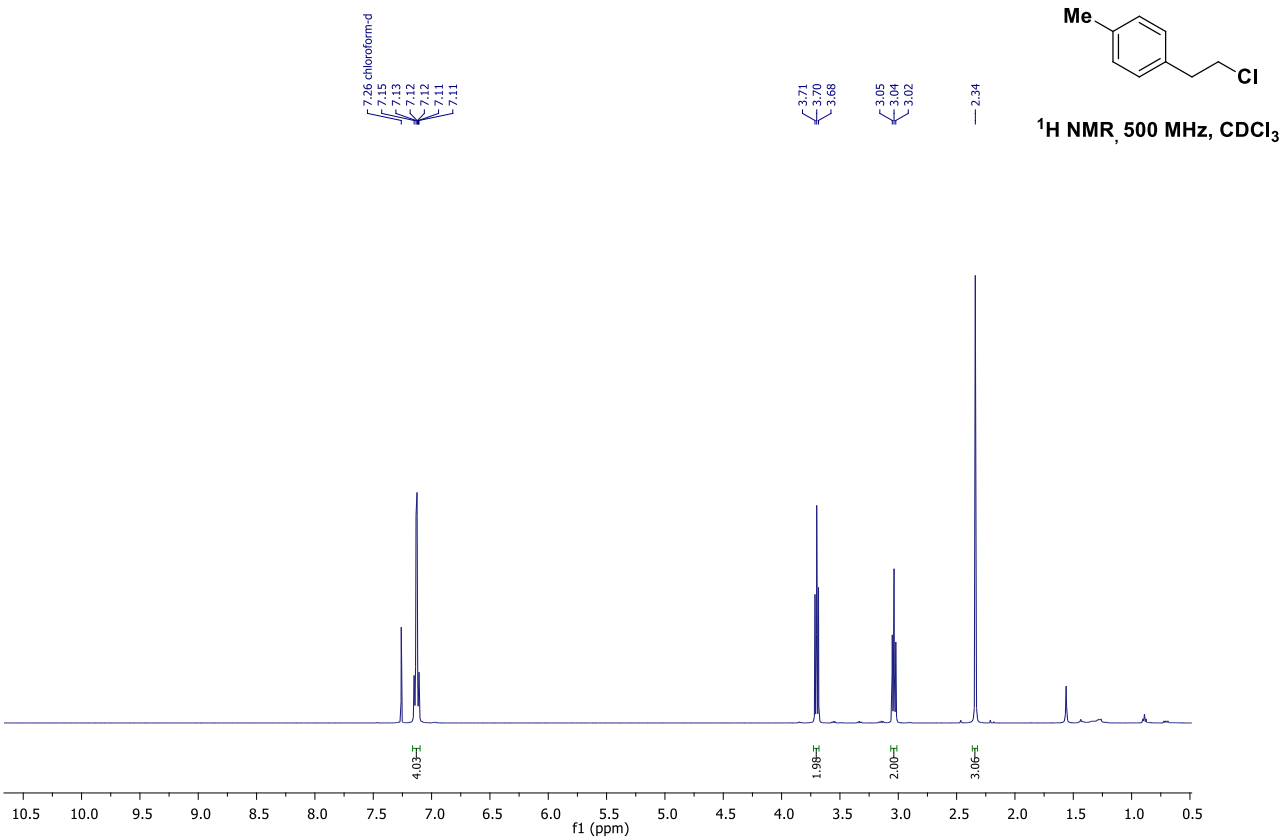


By following the **General procedure**, starting from 4-methylbenzaldehyde (200 mg, 1.66 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.2 mL, 2.49 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (85 mg, 0.17 mmol, 0.1 equiv) and hexylsilane (0.3 mL, 1.66 mmol, 1 equiv), **compound 5** was obtained in 85 % yield (218 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

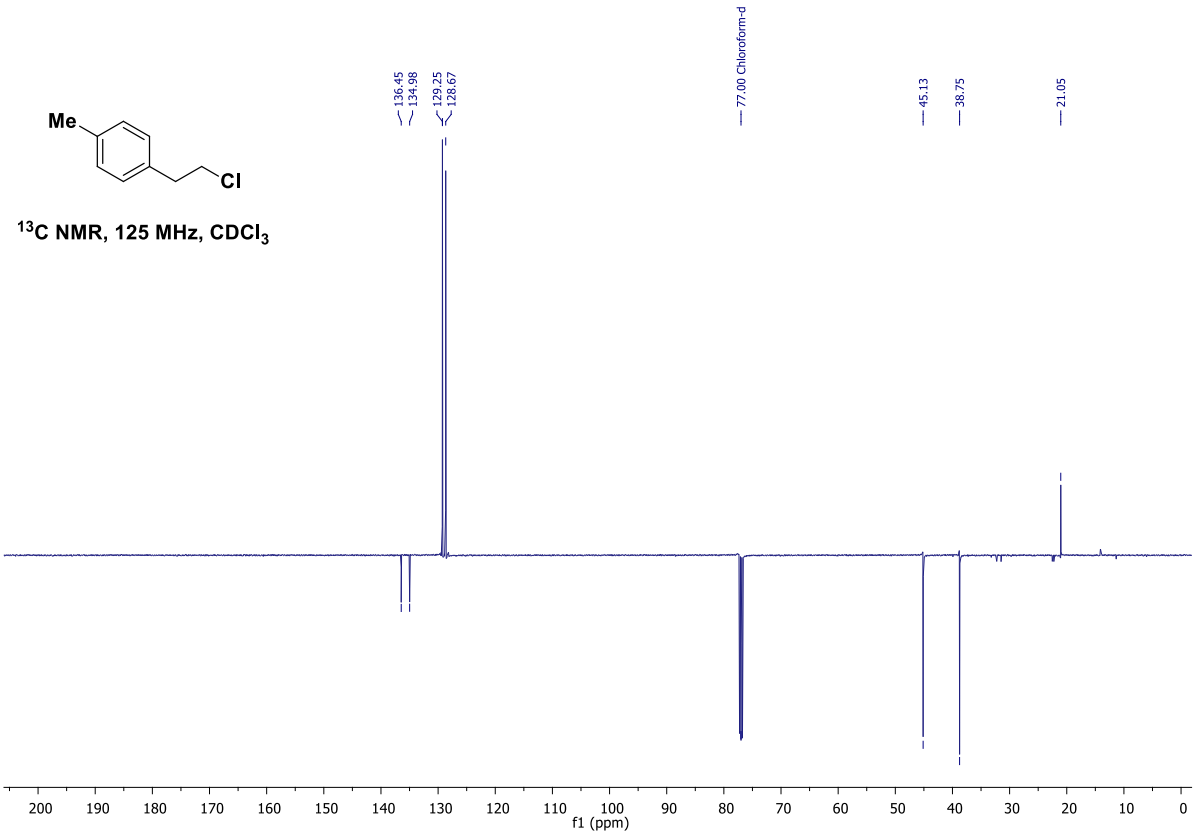
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.14 (m, 2H, Ph H-3,5), 7.12 (m, 2H, Ph H-2,6), 3.70 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, CH_2Cl), 3.04 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, Ph-CH_2), 2.34 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.5 (Ph C-4), 135.0 (Ph C-1), 129.3 (Ph C-3,5), 128.7 (Ph C-2,6), 45.2 (CH_2Cl), 38.8 (Ph-CH_2), 21.0 (s, 3H, CH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_{11}ClNa^+$: 177.0441 $[M+Na]^+$; found: 177.0444.

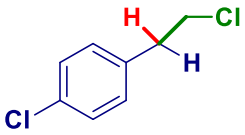


^{1}H NMR, 500 MHz, $CDCl_3$



^{13}C NMR, 125 MHz, $CDCl_3$

1-Chloro-4-(2-chloroethyl)-benzene (6)

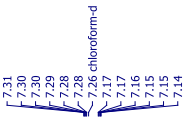


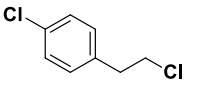
By following the **General procedure**, starting from 4-chlorobenzaldehyde (200 mg, 1.42 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.16 mL, 2.13 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.9 mL, 1.99 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (73 mg, 0.14 mmol, 0.1 equiv) and hexylsilane (0.23 mL, 1.41 mmol, 1 equiv), **compound 6** was obtained in 92% yield (229 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29 (m, 2H, Ph H-2,6), 7.16 (m, 2H, Ph H-3,5), 3.69 (t, 2H, $^3J_{H,H}$ = 7.2 Hz, CH_2Cl), 3.04 (t, 2H, $^3J_{H,H}$ = 7.2 Hz, Ph-CH_2).

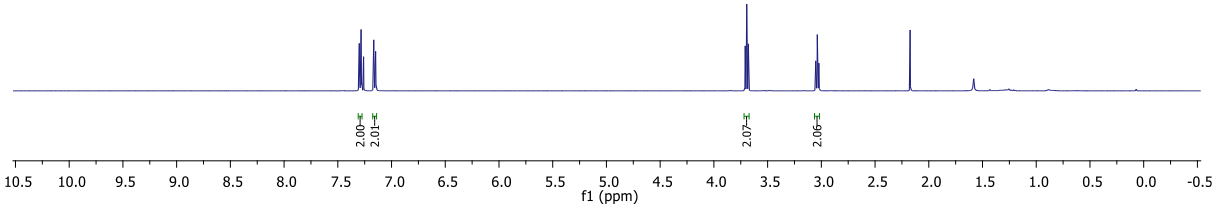
^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.5 (Ph C-4), 132.7 (Ph C-1), 130.2 (Ph C-3,5), 128.7 (Ph C-2,6), 44.7 (CH_2Cl), 38.3 (Ph-CH_2).

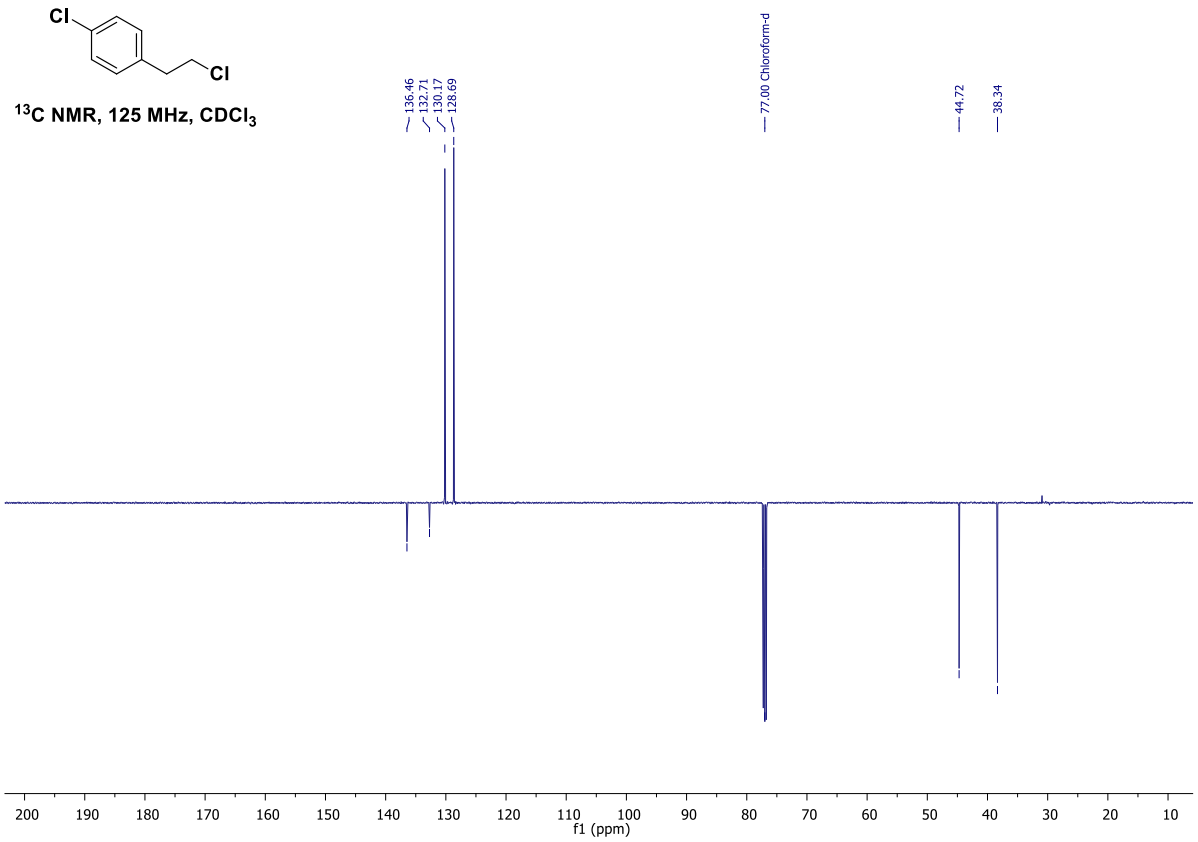
GCMS, *m/z*: calcd. for $C_8H_8Cl_2^+$: 174.0003 $[M^\bullet]^+$; found: 174.0.



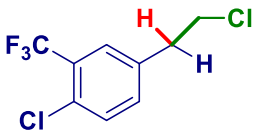


^{1}H NMR, 500 MHz, $CDCl_3$





1-Chloro-4-(2-chloroethyl) -2-(trifluoromethyl) -benzene (7)



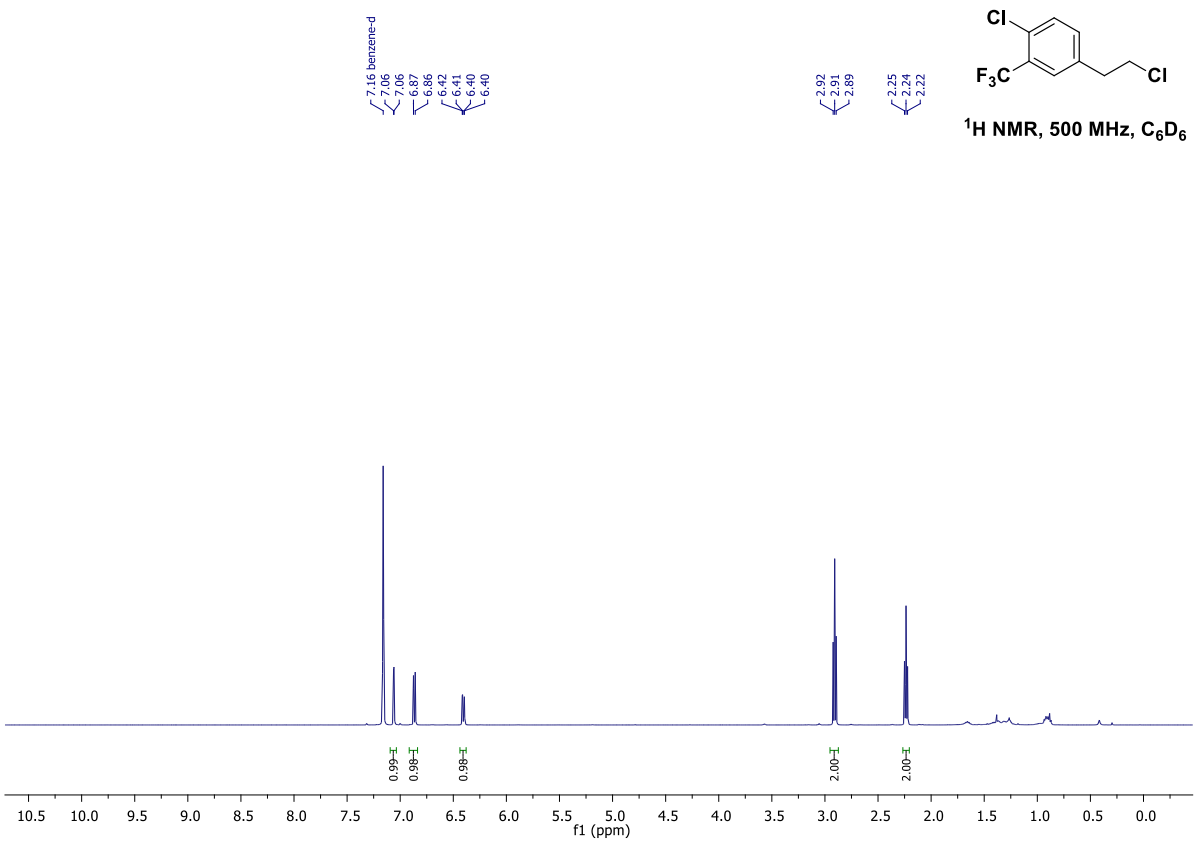
By following the **General procedure**, starting from 4-chloro-3-(trifluoromethyl)benzaldehyde (200 mg, 0.96 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.11 mL, 1.44 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.61 mL, 1.34 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (49 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.16 mL, 0.96 mmol, 1 equiv), compound **7** was obtained in 89% yield (208 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, C_6D_6) δ: 7.06 (d, 1H, $^4J_{H,H}$ = 2.0 Hz, Ph H-3), 6.86 (d, 1H, $^3J_{H,H}$ = 8.2 Hz, Ph H-6), 6.40 (dd, 1H, $^3J_{H,H}$ = 8.2 Hz, $^4J_{H,H}$ = 2.0 Hz, Ph H-5), 2.91 (t, 2H, $^3J_{H,H}$ = 7.1 Hz, CH_2Cl), 2.24 (t, 2H, $^3J_{H,H}$ = 7.1 Hz, Ph-CH_2).

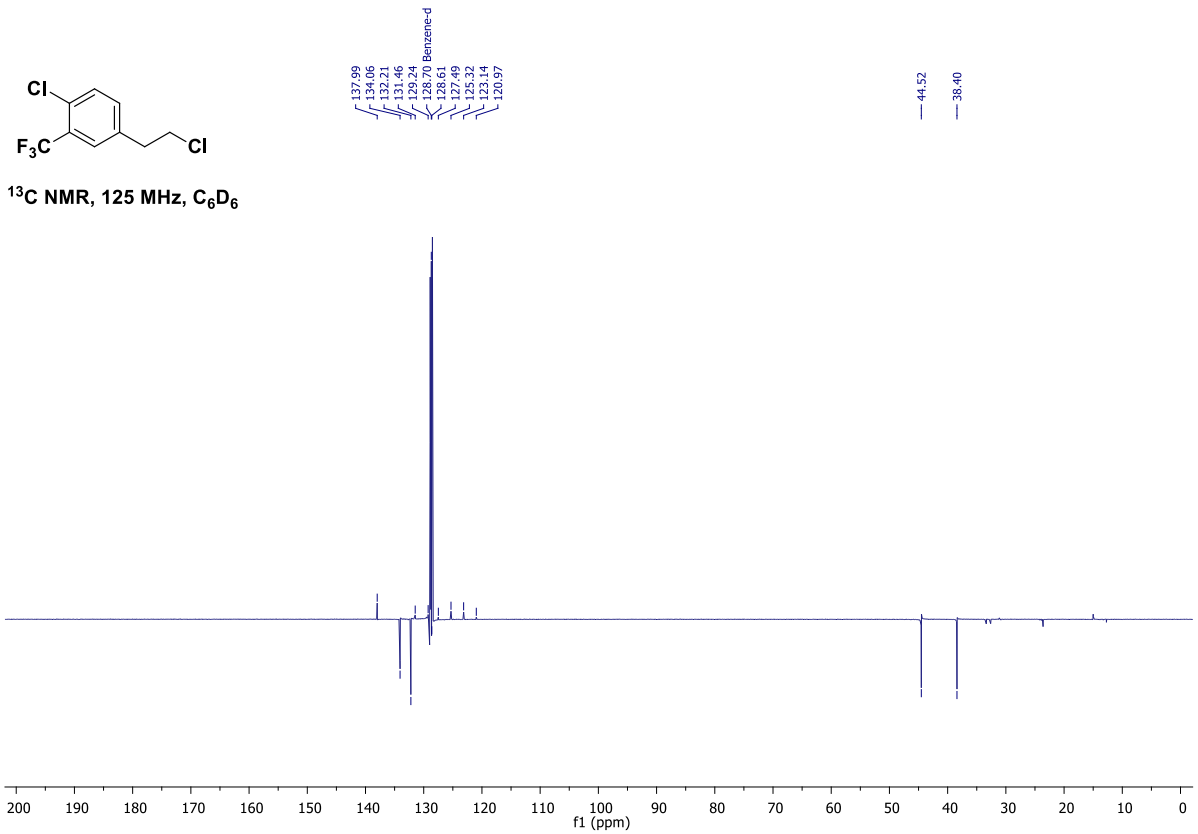
^{13}C NMR (125 MHz, C_6D_6) δ: 137.4 (Ph C-4), 133.4 (Ph C-5), 131.6 (Ph C-6), 130.8 (Ph C-1), 128.5 (q, $^2J_{C,F}$ = 31.2 Hz, Ph C-2), 127.9 (Ph C-3), 123.6 (q, $^1J_{C,F}$ = 273.0 Hz, CF_3), 43.9 (CH_2Cl), 37.8 (Ph-CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.7 (CF_3).

GCMS, *m/z*: calcd. for $C_9H_7Cl_2F_3^+$: 241.9877 [M•]$^+$; found: 241.9.

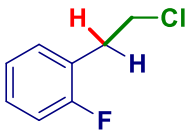


^{1}H NMR, 500 MHz, C_6D_6



^{13}C NMR, 125 MHz, C_6D_6

1-(2-Chloroethyl)-2-fluorobenzene (8)

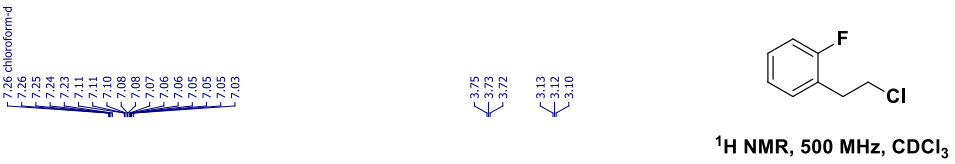


By following the **General procedure**, starting from 2-fluorobenzaldehyde (200 mg, 1.61 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.18 mL, 2.42 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.03 mL, 2.25 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (82 mg, 0.2 mmol, 0.1 equiv) and hexylsilane (0.23 mL, 1.61 mmol, 1 equiv), **compound 8** was obtained in 83% yield (211 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

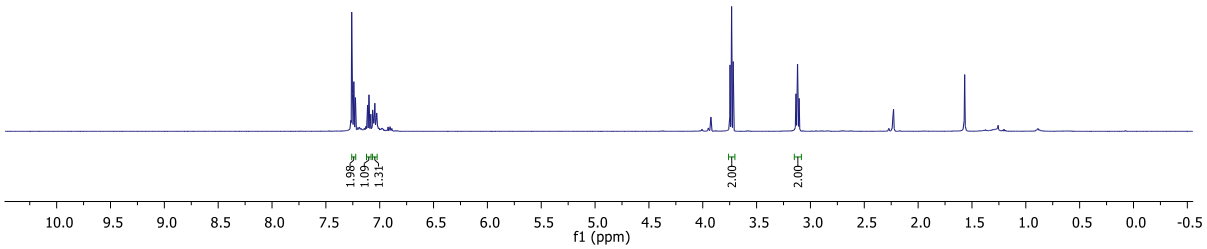
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (m, 1H, Ph H-4), 7.23 (m, 1H, Ph H-6), 7.10 (m, 1H, Ph H-5), 7.04 (m, 1H, Ph H-3), 3.73 (t, 2H, $^3J_{H,H}$ = 7.3 Hz, CH_2Cl), 3.12 (t, 2H, $^3J_{H,H}$ = 7.3 Hz, Ph-CH_2).

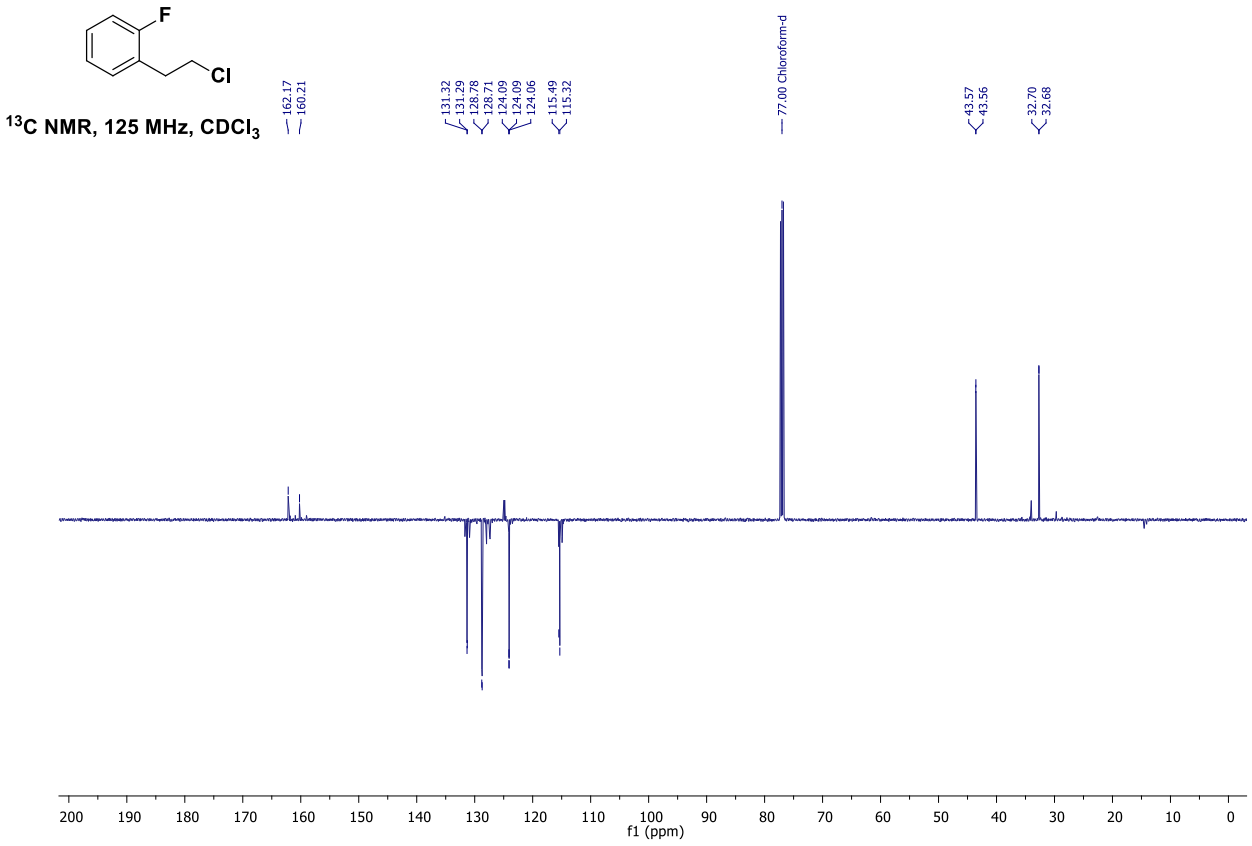
^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.2 (d, $^1J_{C,F}$ = 245.3 Hz, Ph C-2), 131.3 (d, $^3J_{C,F}$ = 4.6 Hz, Ph C-6), 128.7 (d, $^3J_{C,F}$ = 8.1 Hz Ph C-4), 124.9 (d, $^2J_{C,F}$ = 15.1 Hz, Ph C-1), 124.1 (d, $^4J_{C,F}$ = 3.5 Hz, Ph C-5), 115.4 (d, $^2J_{C,F}$ = 22.0 Hz, Ph C-3), 43.6 (CH_2Cl), 32.7 (Ph-CH_2).

HRMS (ESI), *m/z*: calcd. for $C_8H_8ClFNa^+$: 181.0191 [M+Na]$^+$; found: 181.0194.

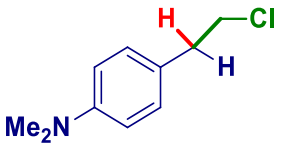


^{1}H NMR, 500 MHz, $CDCl_3$





4-(2-Chloroethyl)-*N*, *N*-dimethylaniline (9)

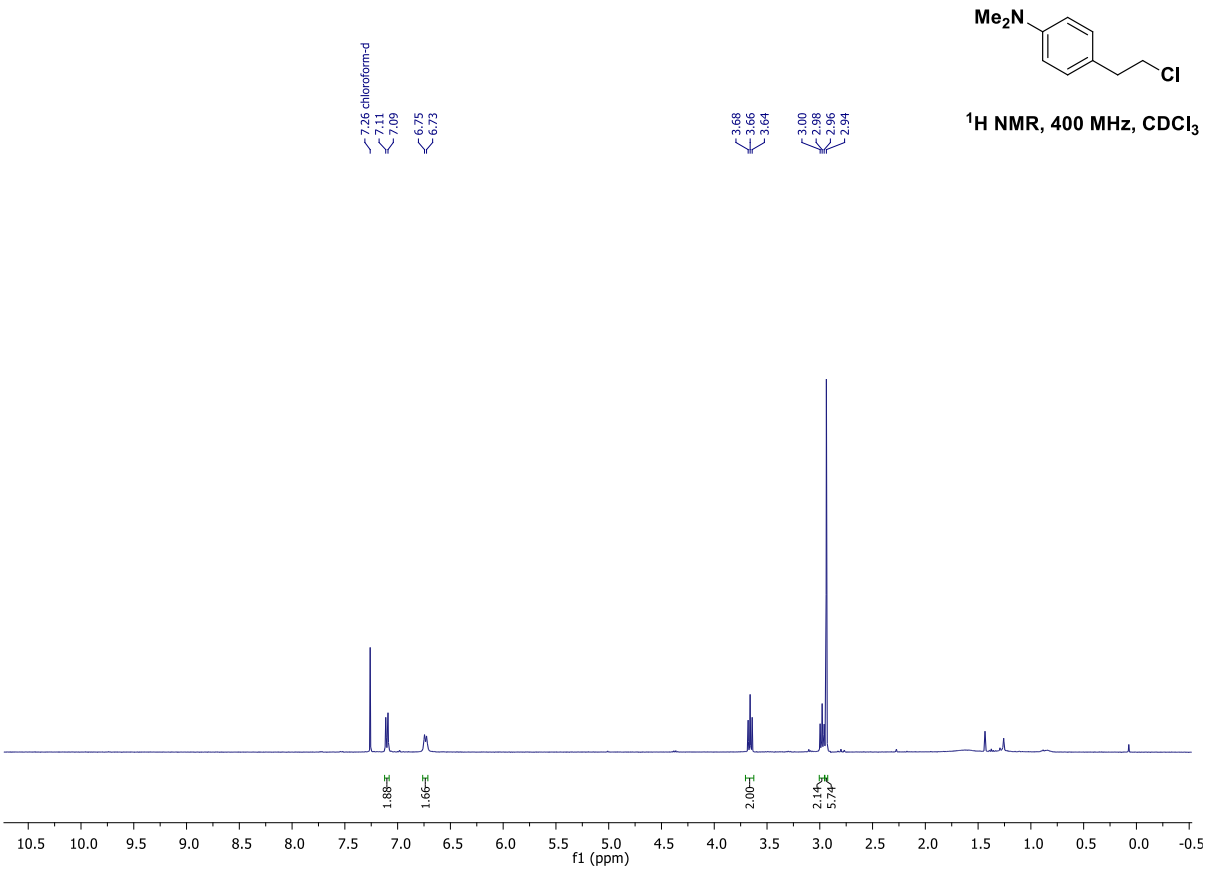


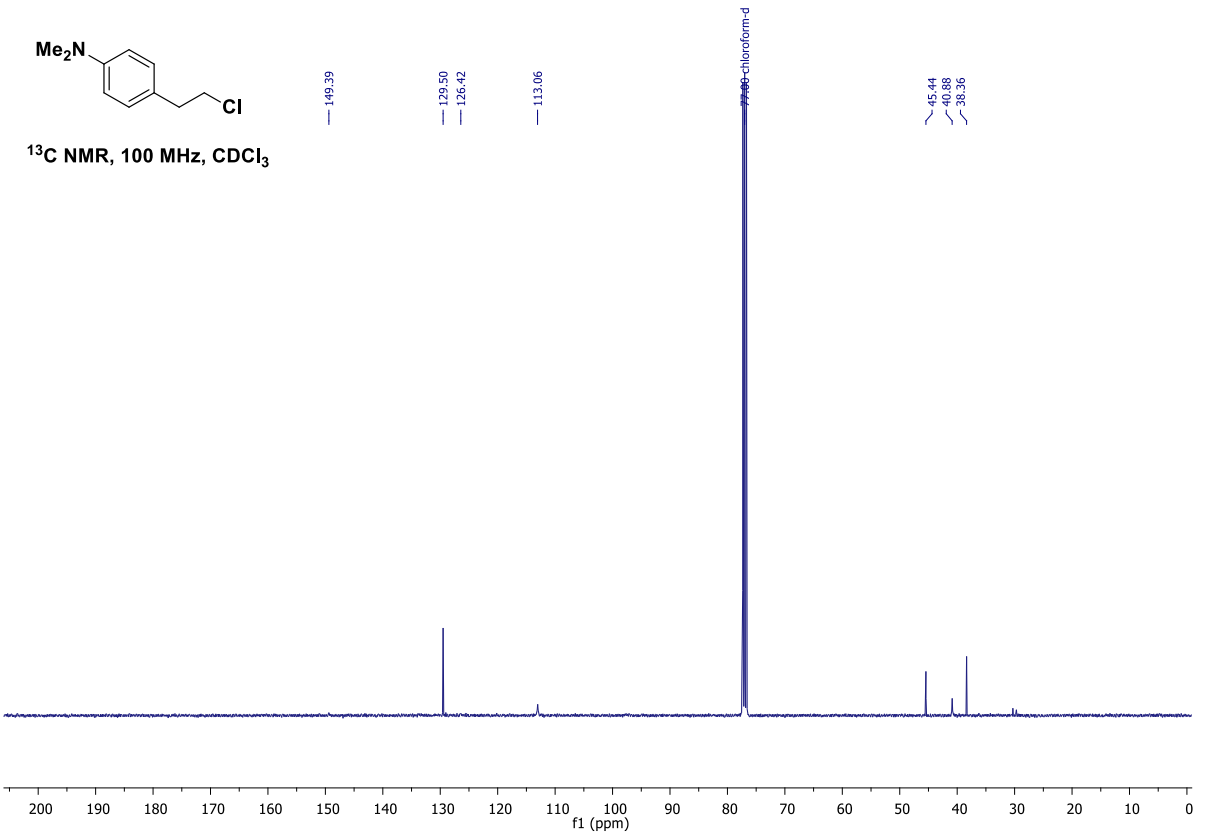
By following the **General procedure**, starting from 4-(dimethylamino)benzaldehyde (200 mg, 1.34 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.15 mL, 2.01 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.85 mL, 1.9 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (69 mg, 0.13 mmol, 0.1 equiv) and hexylsilane (0.13 mL, 1.34 mmol, 1 equiv), **compound 9** was obtained in 90% yield (222 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 9:1 as eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10 (m, 2H, Ph H-3,5), 6.74 (m, 2H, Ph H-2,6), 3.66 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, CH_2Cl), 2.98 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, Ph-CH_2), 2.94 (s, 6H, N-CH_3).

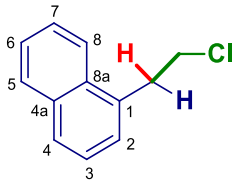
^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.4 (bs, Ph C-1), 129.5 (Ph C-3,5), 126.4 (Ph C-4), 113.0 (bs, Ph C-2,6), 45.4 (CH_2Cl), 40.9 (N-CH_3), 38.4 (Ph-CH_2)

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{15}ClN^+$: 184.0888 $[M+H]^+$; found: 184.0892.


Me2N
Cl
1H NMR, 400 MHz, CDCl3
7.26 chloroform-d
7.11
7.09
6.75
6.73
3.68
3.66
3.64
3.00
2.98
2.96
2.94
1.88
1.66
2.00
2.14
5.74
f1 (ppm)


Me2N
Cl
13C NMR, 100 MHz, CDCl3
149.39
129.50
126.42
113.06
77.00-chloroform-d
45.44
40.88
38.36
f1 (ppm)

1-(2-Chloroethyl)-naphthalene (10)

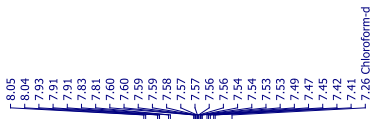


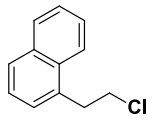
By following the **General procedure**, starting from 1-naphthaldehyde (200 mg, 1.28 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.14 mL, 1.9 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.82 mL, 1.8 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (66 mg, 0.13 mmol, 0.1 equiv) and hexylsilane (0.21 mL, 1.28 mmol, 1 equiv), **compound 10** was obtained in 84% yield (205 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (m, 1H, Naph H-8), 7.92 (m, 1H, Naph H-5), 7.82 (m, 1H, Naph H-4), 7.59 (m, H, Naph H-7), 7.54 (m, 1H, Naph H-6), 7.47 (m, 1H, Naph H-3), 7.42 (m, 1H, Naph H-2), 3.87 (t, 2H, $^3J_{H,H}$ = 7.8 Hz, CH_2Cl), 3.59 (t, 2H, $^3J_{H,H}$ = 7.8 Hz, Naph-CH_2).

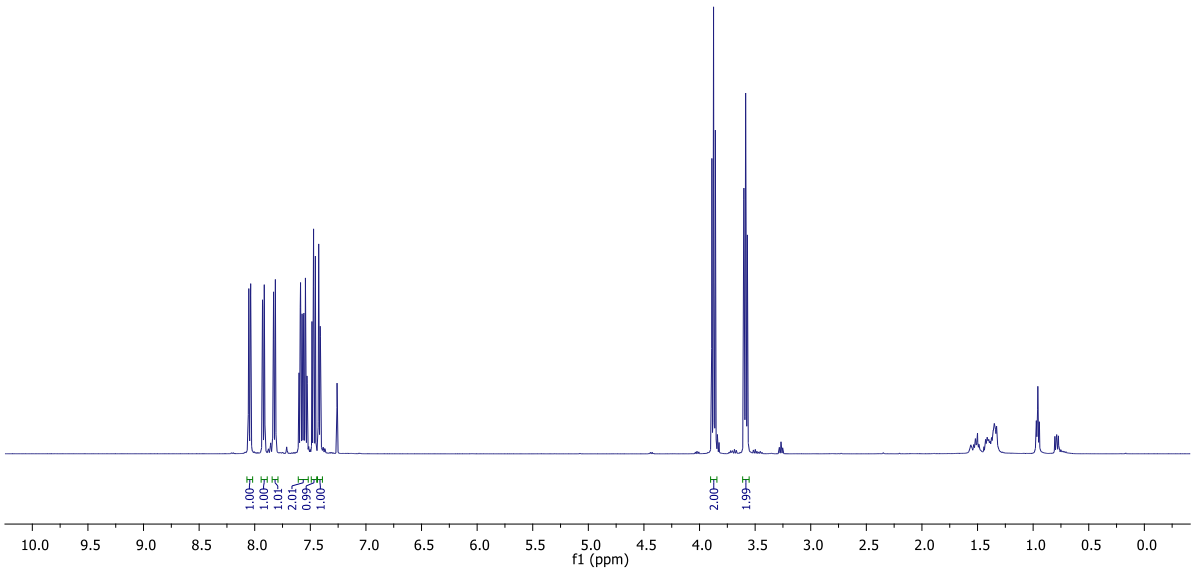
^{13}C NMR (125 MHz, $CDCl_3$) δ: 133.9 (Naph C-4a), 133.8 (Naph C-8a), 131.6 (Naph C-1), 128.9 (Naph C-5), 127.7 (Naph C-4), 127.1 (Naph C-2), 126.3 (Naph C-7), 125.7 (Naph C-6), 125.4 (Naph C-3), 123.1 (Naph C-8), 44.1 (CH_2Cl), 36.4 (Naph-CH_2).

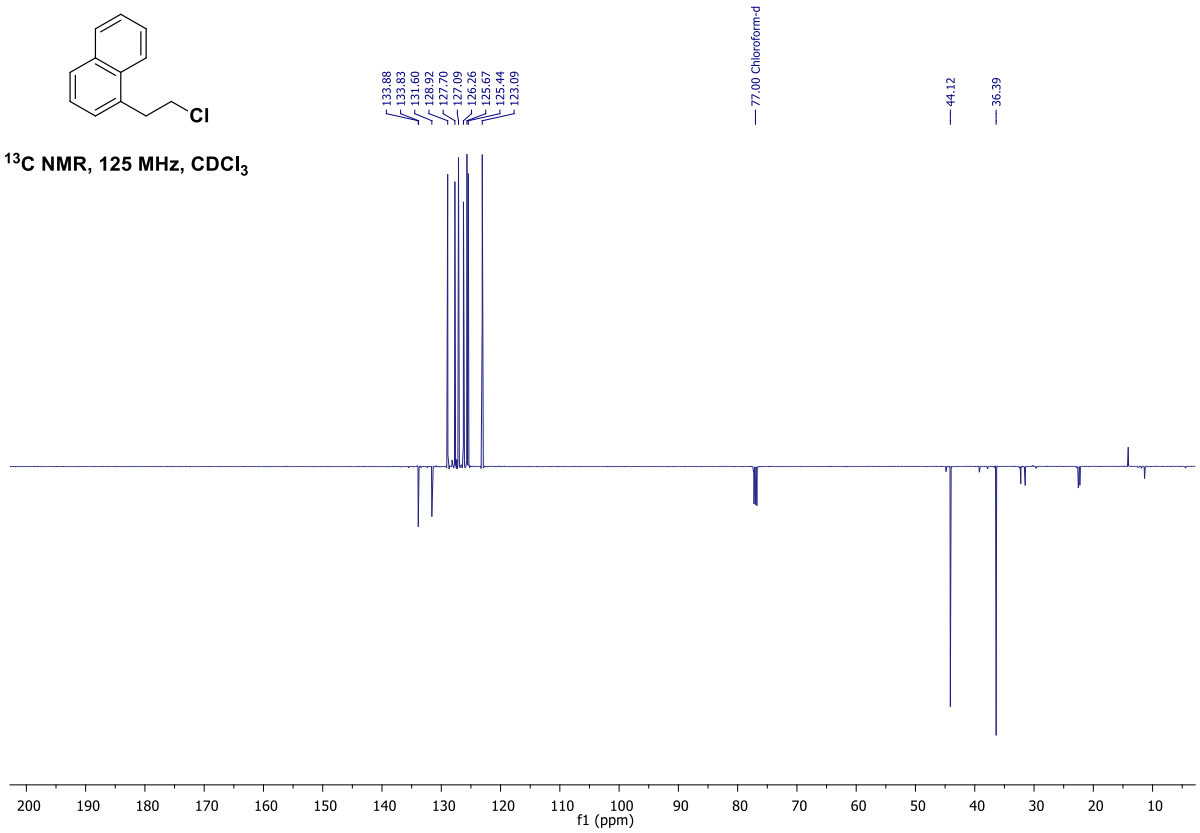
GCMS, *m/z*: calcd. for $C_{12}H_{11}Cl^+$: 190.0549 $[M^\bullet]^+$; found: 190.1.



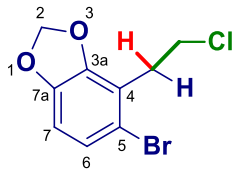


^{1}H NMR, 500 MHz, $CDCl_3$





5-Bromo-4-(2-chloroethyl) -1,3-benzodioxole (11)

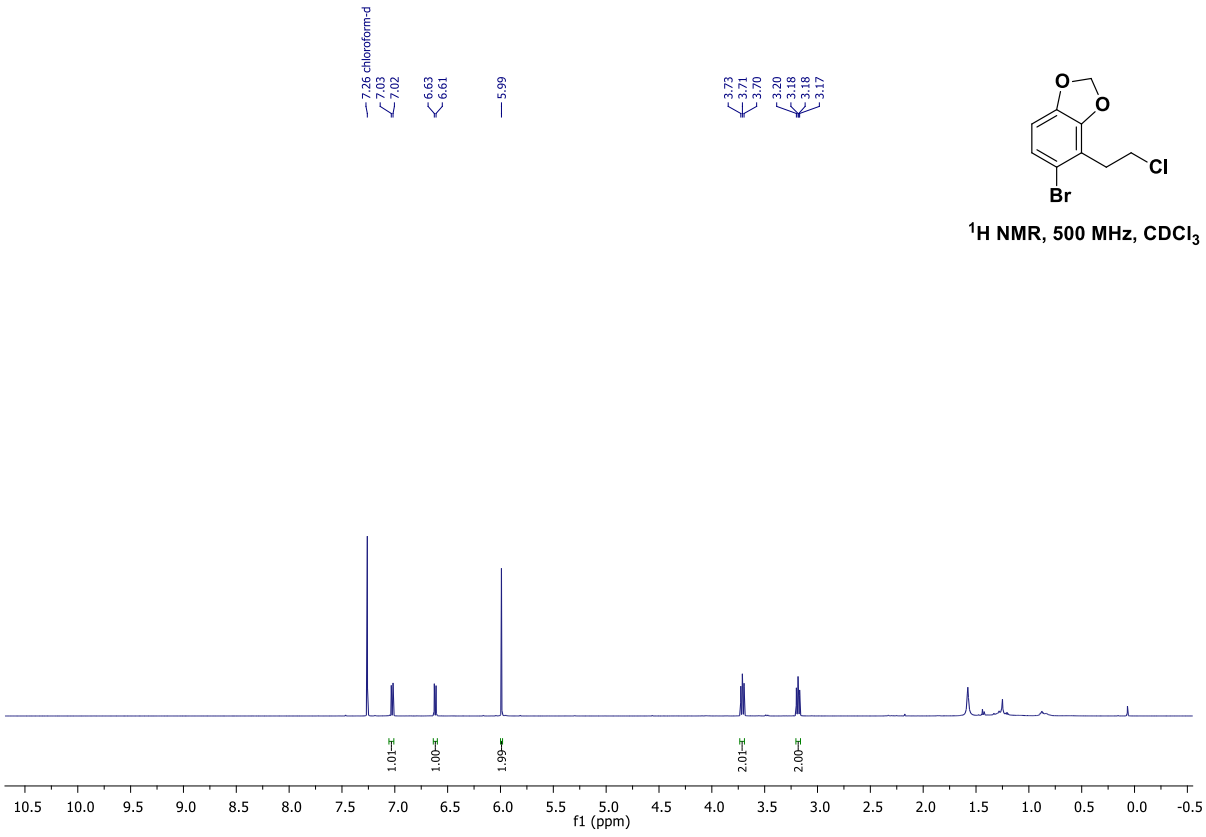


By following the **General procedure**, starting from 5-bromobenzo[*d*][1,3]dioxole-4-carbaldehyde (200 mg, 0.87 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.3 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.55 mL, 1.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (45 mg, 0.09 mmol, 0.1 equiv) and hexylsilane (0.14 mL, 0.87 mmol, 1 equiv), **compound 11** was obtained in 92% yield (211 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

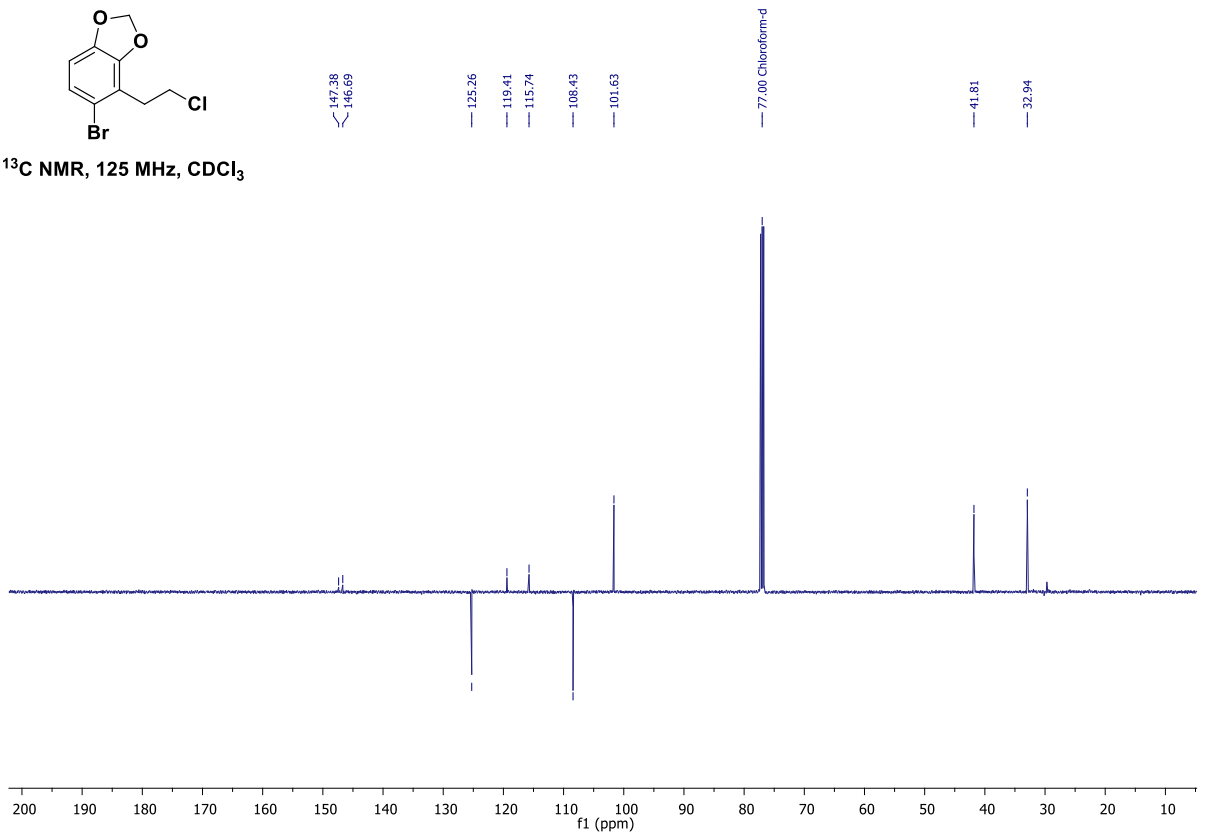
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.02 (d, 1H, $^3J_{H,H}$ = 8.3 Hz, Benz H-6), 6.62 (d, 1H, $^3J_{H,H}$ = 8.3 Hz, Benz H-7), 5.99 (s, 2H, Benz H-2), 3.71 (m, 2H, CH_2Cl), 3.18 (m, 2H, Ph-CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.4 (Benz C-3a), 146.7 (Benz C-7a), 125.3 (Benz C-6), 119.4 (Benz C-4), 115.7 (Benz C-5), 108.4 (Benz C-7), 101.6 (Benz C-2), 41.8 (CH_2Cl), 32.9 (Benz-CH_2).

HRMS (ESI), *m/z*: calcd. for $C_9H_8BrClNaO_2^+$: 284.9288 $[M+Na]^+$; found: 284.9285.

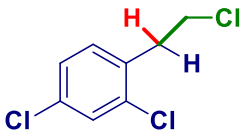


^{1}H NMR, 500 MHz, $CDCl_3$



^{13}C NMR, 125 MHz, $CDCl_3$

2,4-Dichloro-1-(2-chloroethyl)-benzene (12)

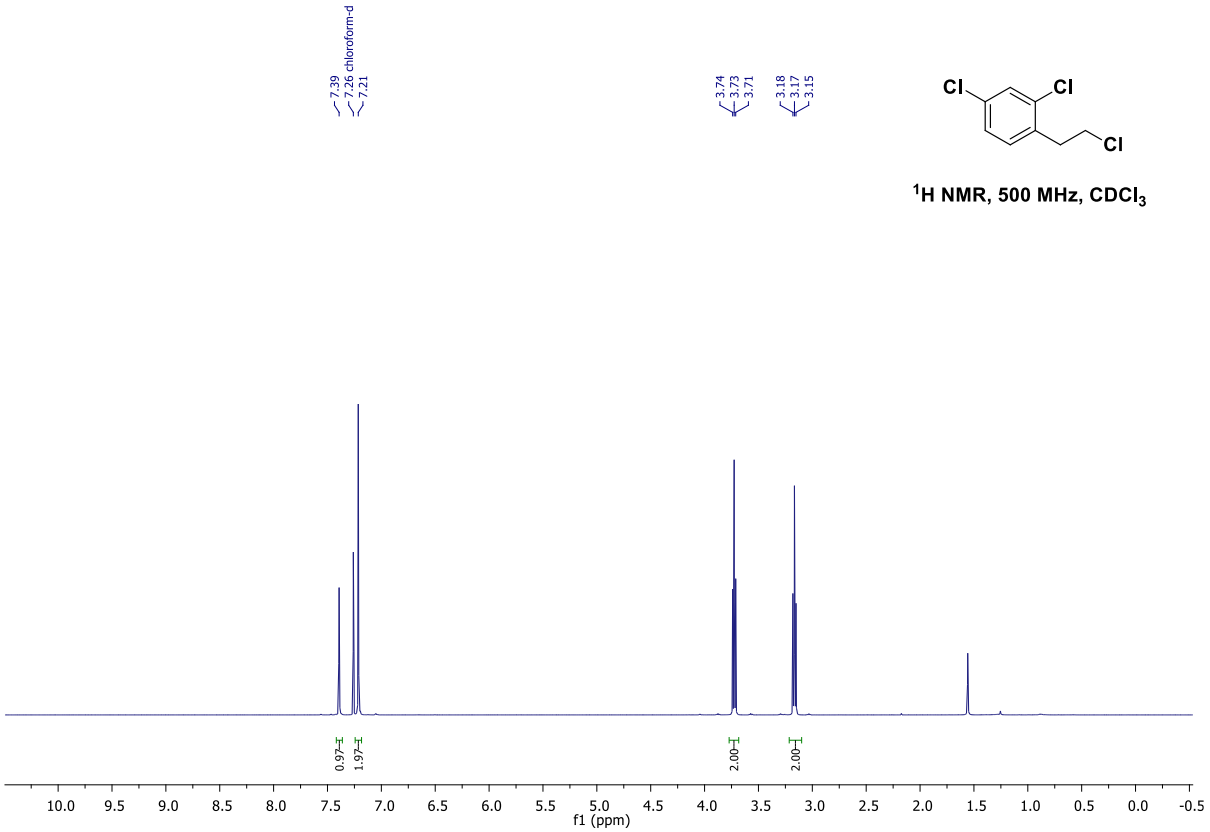


By following the **General procedure**, starting from 2,4-dichlorobenzaldehyde (200 mg, 0.89 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.3 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.57 mL, 1.3 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (46 mg, 0.09 mmol, 0.1 equiv) and hexylsilane (0.14 mL, 0.89 mmol, 1 equiv), **compound 12** was obtained in 85% yield (158 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

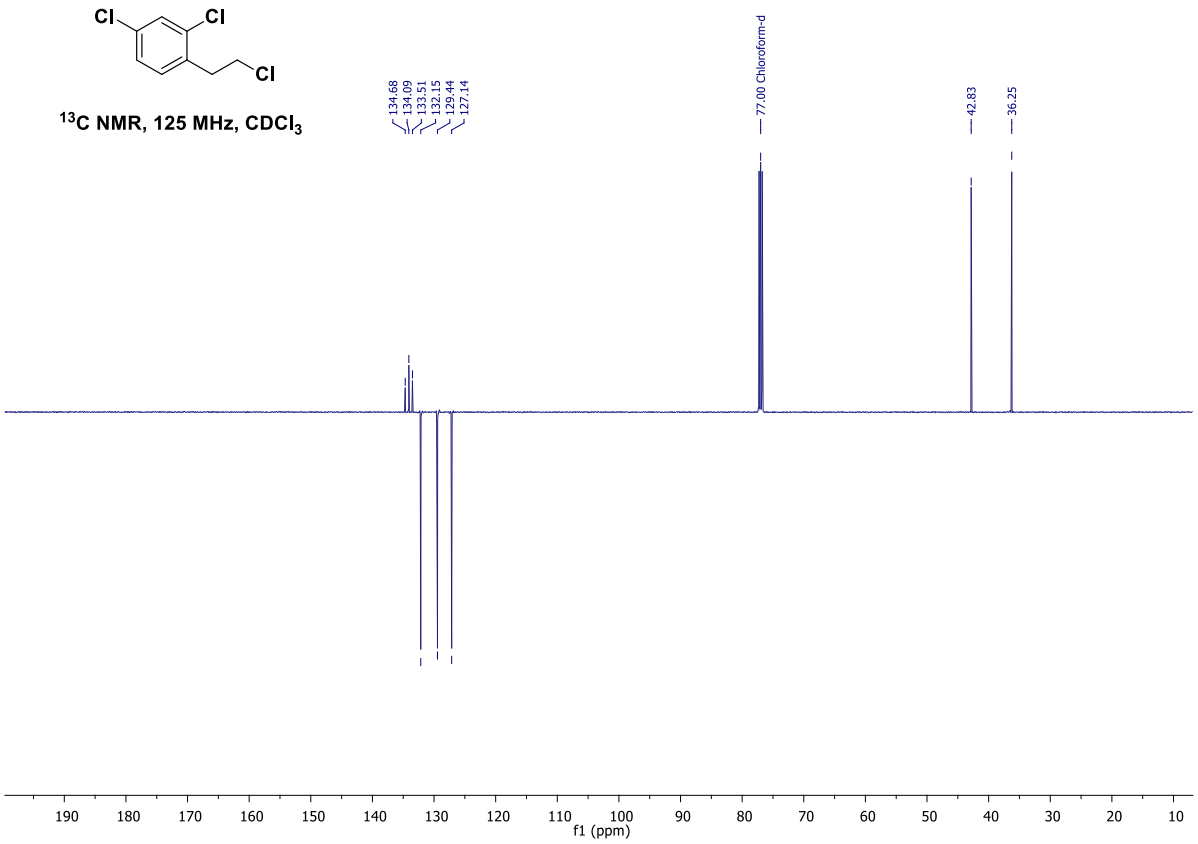
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39 (m, 1H, Ph H-3), 7.21 (m, 2H, Ph H-5,6), 3.73 (t, 2H, $^3J_{H,H}$ = 7.2 Hz, CH_2Cl), 3.17 (t, 2H, $^3J_{H,H}$ = 7.2 Hz Ph-CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 134.7 (Ph C-2), 134.1 (Ph C-1), 133.5 (Ph C-4), 132.2 (Ph C-6), 129.4 (Ph C-6), 127.1 (Ph C-5), 42.8 (CH_2Cl), 36.3 (Ph-CH_2).

HRMS (ESI), *m/z*: calcd. for $C_8H_7Cl_3Na^+$: 230.9506 $[M+Na]^+$; found: 230.9509.



^{1}H NMR, 500 MHz, $CDCl_3$


Cl
Cl
Cl
^{13}C NMR, 125 MHz, $CDCl_3$
134.68
134.09
133.51
132.15
129.44
127.14
77.00 Chloroform-d
42.83
36.25
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

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7. List of Schemes