UNIVERSITÀ DEGLI STUDI
DI MESSINA

NUCLEOPHILIC α-SUBSTITUTED ORGANOMETALLIC REAGENTS IN HOMOLOGATION CHEMISTRY:

SYNTHETIC APPLICATIONS AND BIOLOGICAL PERSPECTIVES

Ph.D. Thesis of

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ABSTRACT

The homologation chemistry pertains the possibility of obtaining from an organic substrate with n carbon atoms, the corresponding homologue with n + 1 carbon atoms and, among the most useful methods to obtain such derivatives, organometallic chemistry occupies a prominent role. The aim of this PhD thesis is to provide a detailed overview of the new methodologies developed for the homologation of organic substrates using organometallic reagents such as lithium halocarbenoids and potassium halocarbanion, mainly implicated in the synthesis of halodrins, primary alkyl halides, fluoromethylketones and difluoromethyl ketones. Because of the great importance of fluoroketones associated to the Medicinal Chemistry, the synthesis of difluoromethylketones has been applied to the design and development of peptide difluoromethylketones as new reversible/irreversible cysteine protease inhibitors.

AIM OF THE WORK

In the modern area of organic synthesis, *homologation chemistry* is strengthening itself as a very valuable approach for the development of new biologically active molecules. *Homologation chemistry* pertains the possibility of obtaining from an organic substrate with *n* carbon atoms, the corresponding superior homologue with *n* + 1 carbon atoms and, among the most useful methods to obtain such derivatives, organometallic chemistry occupies a prominent role. Among the countless compounds that can be accessed through these methodologies, fluorinated derivatives represent nowadays an inexhaustible source of pharmaceutical active molecules, thanks to the multiple properties that the fluorine can impart to organic compounds. The introduction of fluorine atoms into organic substrates can influence both the reactivity and the physical properties of the obtained derivatives. Fluorine can determine a noteworthy impact on lipophilicity, acid base properties and metabolic stability of substrates endowed with biological activity. Furthermore, being a bioisoster of the hydrogen, it can radically change the electronic properties and the mechanism of action of drugs. Thus, the development of solid, easy and rapid methodologies to obtain fluorinated compounds are becoming more and more a topic of relevance in drug discovery.

The aim of this PhD Thesis was to develop new synthetic strategies for obtaining pharmaceutically interesting compounds, specifically fluorine-containing derivatives. The use of nucleophilic organometallic reagents was a fundamental requirement for the development of such synthetic methodologies. Besides, the employment of suitable electrophilic partners allowed the modulation of the reactivity profile of the nucleophilic species under evaluation and the outcome of the process. A detailed report of the new methodologies developed by our research team will be presented and discussed. It essentially deals with the homologation of organic substrates by means of organometallic reagents such as lithium halocarbenoids and silylated halocarbanion, mainly implicated in the synthesis of halodrins, primary alkyl halides, fluoromethyl ketones and difluoromethyl ketones. A special focus will be devoted on α,α-difluoromethyl ketones, substrates of great pharmaceutical interest, since they can potentially act as reversible inhibitors of serine and cysteine proteases. The solidity of our synthetic methodologies emerged with the development of the first direct and chemoselective synthesis of a peptide-based α,α-difluoromethyl ketone, namely Z-Leu-Homophe-CHF_2. This fluorinated pseudopeptide showed to possess cytoprotective activity in the micromolar range towards lung fibroblasts MRC5 infected with hCoV-229E, one of four pathogenic human coronaviruses responsible for severe respiratory distress. Moreover, docking studies indicated that the antiviral activity might originate from the reversible-type inhibition of the Coronavirus Main Proteases (M^{pro}), a key enzyme responsible for the replication of the coronaviruses.

The Thesis is structured in two fundamental chapters.

1. The **Introduction** section describes the general features of the *homologation chemistry* with nucleophilic α-substituted organometallic reagents. A *focus* on **carbenoids**, highly reactive

species similar to carbenes, is presented, with the relative electrophilic partners employed in this type of reactions.

2. The **Result and Discussion** section contains the most important results obtained during my PhD, concerning the homologation of electrophiles with nucleophilic α-substituted organometallic reagents. It is sub-divided into three paragraphs. The first two paragraphs will exhaustively explain two new straightforward methodologies to homologate carbonyls and Weinreb amides to **primary alkyl halides** and **α,α-difluoromethyl ketone**, respectively. The last paragraph will describe biological application of the first **pseudopeptidic α,α-difluoromethyl ketone**, that demonstrated cytoprotective activity towards cells infected with a human coronavirus.

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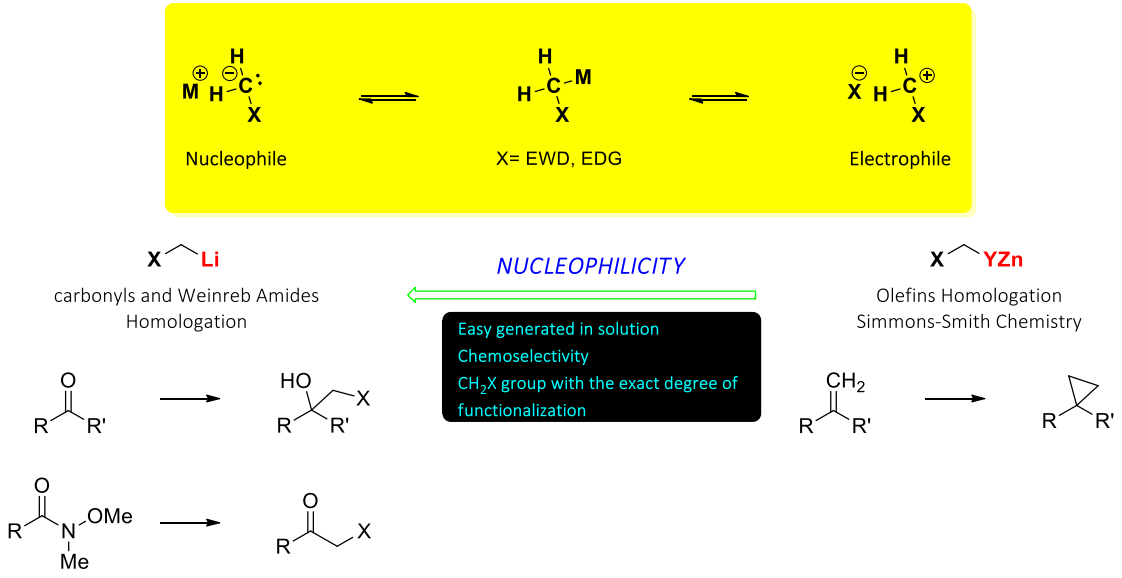
1. INTRODUCTION

1.1. CARBENOIDS IN HOMOLOGATION CHEMISTRY

Homologation chemistry the introduction of *C1 units* into organic structures and represents nowadays one of the most important strategies employed in organic synthesis and drug design.[1, 2] In the majority of cases, the concept behind the homologation is based on the elongation of a specific chemical fragment by adding a *formal unit C1* (*i.e.* CH_2 or CH units).[3] The importance of synthesizing higher homologues is a well known approach in Medicinal Chemistry, decamethonium and hexamethonium and their binding to the nicotinic receptor can be taken as an example.[4] The first consistent method used for homologative transformations was the diazomethane-mediated Arndt-Eistert reaction,[5-10] and many other reactions were developed thereafter such as Corey-Chaykovsky sulfur ylides transformation [11, 12] and the metal carbenoids chemistry.[13] Carbenoids are chemical entities whose reactivity, similarly to that of carbenes, possess ambiphilic characteristics, *i.e.* their ability to behave as nucleophiles or electrophiles, depending on the reaction conditions (Scheme **1**).[13-18] Two factors mainly influence the *equilibrium* switch between electrophilic and nucleophilic behavior of the carbenoids:

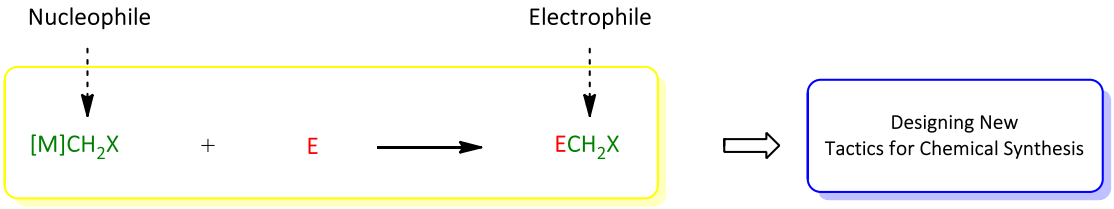
- Temperature
- Nature of metal



Scheme 1. Ambiphilic nature of carbenoids. Scheme modified from reference.[1]

The nature of the metal is the most important factor. It has been widely demonstrated that highly electropositive metals, such as lithium,[18] have a marked nucleophilic tendency unlike less electropositive ones, such as zinc.[19] The special behavior of the carbenoid is due to the presence of both the metal and the electron-withdrawing group (EWG; *halogen* for example). This is also reflected in the delicate stability of the carbenoids associated to the internal coordination between the metal and the halogen, a phenomenon that often results in an α-elimination with the release of metal halide and free carbene.[13, 20, 21] Since carbenoids possess many factors limiting their use, it is

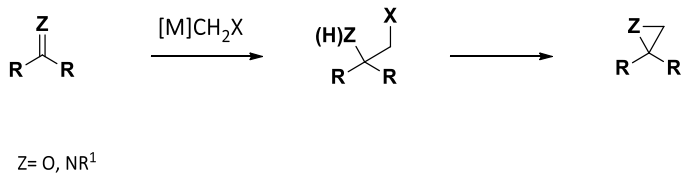
appropriate to find reaction conditions that increase their stability.[22, 23] Numerous studies, such as those conducted by Villieiras and Barluenga,[24, 25] have been able to demonstrate the ability of ethereal solvents to stabilize carbenoids by breaking the undesired coordination phenomenon, that leads to α-elimination. Magnus postulated the possibility of stabilizing the carbenoids by introducing silicon-based groups, which unfortunately needs to be removed.[26] In our research group we developed a direct method to transfer the CHF_2 carbanion stabilized by the presence of the TMS, without the need of removal reactions.[27, 28] A general use of carbenoids in chemical synthesis can be seen in Scheme **2**.



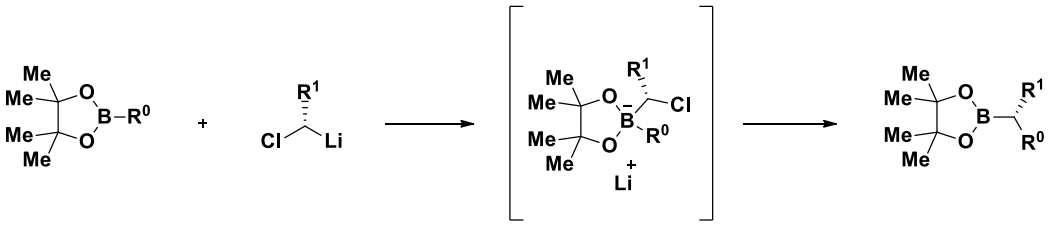
Scheme 2. Use of carbenoids in chemical synthesis. Scheme modified from reference [1].

1.2. HALOGENATED LITHIUM CARBENOIDS

Halogenated lithium carbenoids provide an excellent method for introducing a nucleophilic CH_2 unit, which by reacting with an electrophile becomes itself an electrophile for subsequent functionalization. The most well-known applications of these methodologies are represented by epoxidation reactions,[24,29, 30] aziridination of carbonyls or imines (Scheme **3**),[31-35] or the homologation of boronic esters proposed by Matteson (Scheme **4**).[36, 37] In the case of epoxides and aziridines, after the addition of the carbenoid, the three-membered ring is formed as a result of the attack by the intermediate alkoxide or amide to $[M]CH_2X$ with consequent expulsion of the halogen. In particular, this strategy for aziridine synthesis has been improved by our research team in the development of the first chemoselective synthesis of trifluoromethyl aziridine.[35]

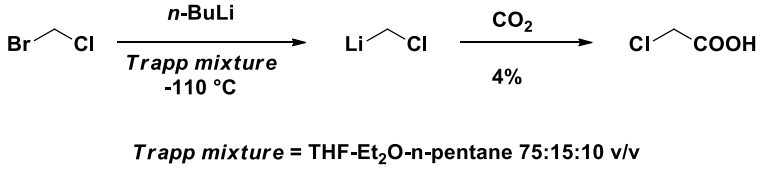


Scheme 3. (Aza)Carbonyl epoxidation and aziridination *via* carbenoids. Scheme modified from reference [1].



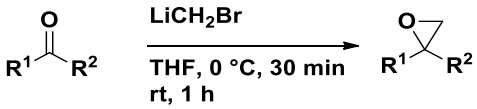
Scheme 4. Matteson Homologation. Scheme modified from reference [1].

Despite the extreme lability of lithium carbenoids, their stability can be increased by lowering the running temperature (-78 °C) and carrying out the reaction under Barbier conditions.[22, 23] In fact, it has been observed that the formation of the carbenoid is anyway faster than the attack of the alkyl lithium on the electrophile. Moreover, by carrying out the reaction in the presence of LiBr, the formation of this by-product is enormously reduced.[38] The importance of using Barbier conditions was first highlighted by Köbrich. During his studies, chloromethyllithium ($LiCH_2Cl$) was first generated from *n*-buthyllithium and bromochloromethane at -110 °C. Very low yield in the carboxylation of $LiCH_2Cl$ were observed when the reaction was conducted under non-Barbier conditions (Scheme **5**). [39, 40]



Scheme 5. Trapping of $LiCH_2Cl$ with carboxylic acids under non-Barbier conditions.

An efficient conversion of carbonyls into epoxides without any decomposition of the intermediate carbenoid was observed by Cainelli switching to Barbier-type conditions.[41] The reaction was conducted at -78 °C, and methallic lithium was able to generate the carbenoid more efficiently than alkyllithium reagents (Scheme **6**).[12, 41, 42]

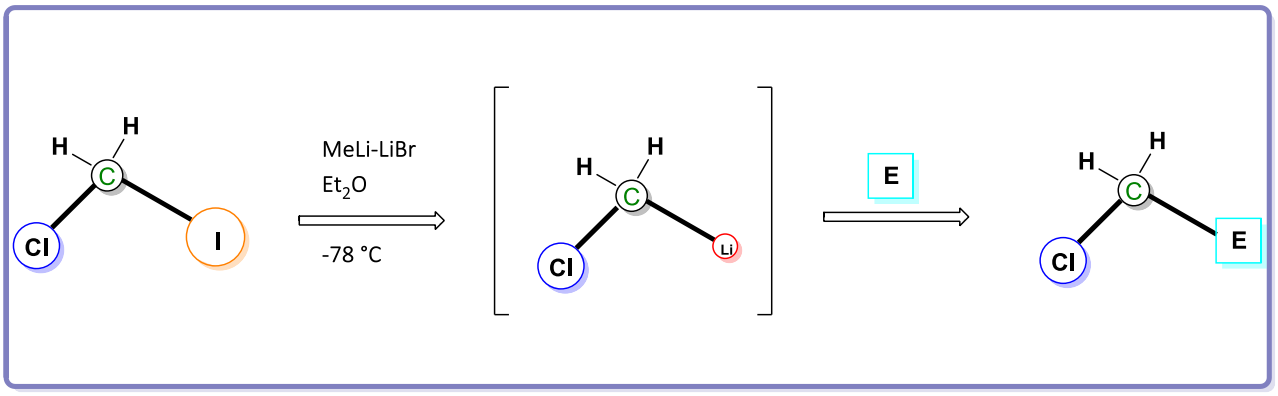


Scheme 6. Cainelli's bromomethyllithium-mediated epoxidation.

Villieras *et al*. suggested the use of lithium salts and Lewis base-type solvents to prevent α-elimination.[43] The running temperature -78 °C was set by Matteson and Barluenga as the optimum for generating and maintaining the stability of the carbenoids. [38, 44, 45] Only for carbonyl epoxidation the use of $LiCH_2I$ at 0 °C was reported by Cancellón.[29]

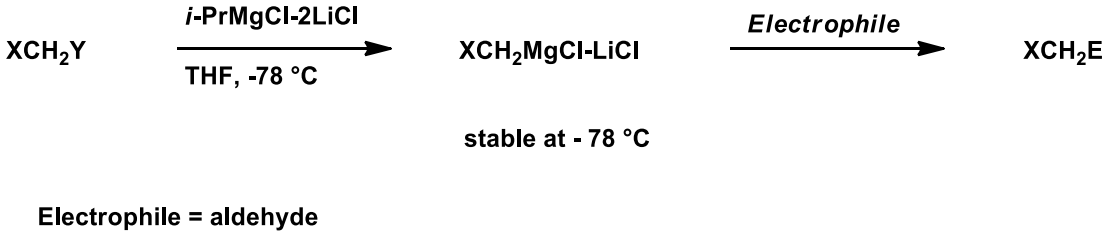
1.3. PREPARATION OF CARBENOIDS

The most used and simplest method for the generation of $LiCH_2Cl$ is represented by metal-halogen exchange (Scheme **7**).[22] In particular, the exchange between halogen and metal occurs faster for heavier halogens, and this makes the general XCH_2I the elective reagent type for this purpose, although the cheaper XCH_2Br is also widely used especially in industry.[46, 47] In regard to the choice of the organolithium, both methyllithium (MeLi) and *n*-buthyllithium (*n*-BuLi) perfectly carry out their task.[25] Nowadays, the use of a MeLi-LiBr complex in Et_2O is one of the most commercially available reagent to accomplish the generation of chloromethyllithium ($LiCH_2Cl$) starting from chloroiodomethane (ICH_2Cl).[48-50] The reaction is carried out by mixing a stoichiometric amount (1:1) of the dihalomethane and the organolithium derivative. Moreover, the latter must be added dropwise to the reaction mixture so that the carbenoid reacts immediately after its formation.[23] The slowly addition of the organolithium derivative to the reaction prevents the formation of substantial amount of by-products that can be formed due to degradation of the starting material and depend on the nature of the electrophile employed.[22]



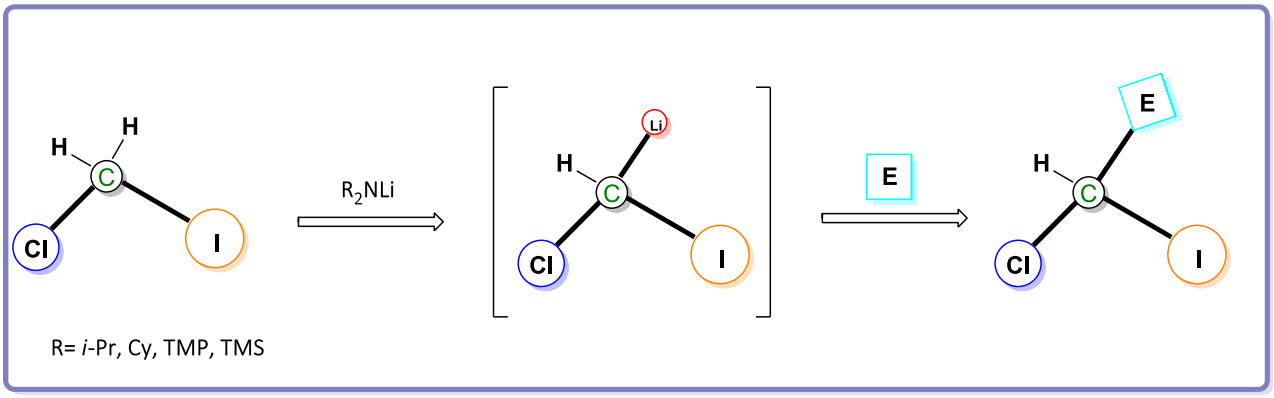
Scheme 7. Lithium-halogen exchange process in the generation of carbenoids.

If the exchanged metal is Mg, it is also possible to obtain magnesium carbenoids. In the presence of ICH_2Cl and a source of magnesium such as *i*-PrMgCl, the carbenoid XCH_2MgCl-LiCl is formed; it is stable at -78 °C and it is used mainly for homologating aldehydes.[51, 52] However, the magnesium carbenoids obtained in this way do not react with weak electrophiles such as Weinreb amides.[48]



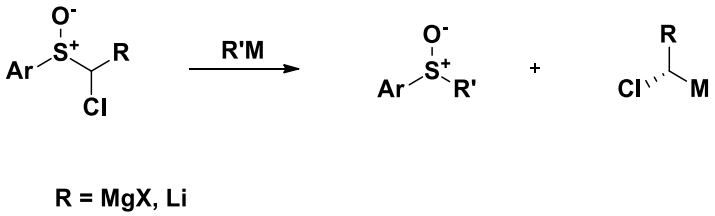
Scheme 8. Magnesium carbenoids. Scheme modified from reference.[22]

On the other hand, for the transfer of *di-halo units* it is possible to employ a lithium base such as LDA or LTMP to facilitate the removal of the acidic proton from the alkyl group and the formation of the carbenoid (Scheme **9**).[53]



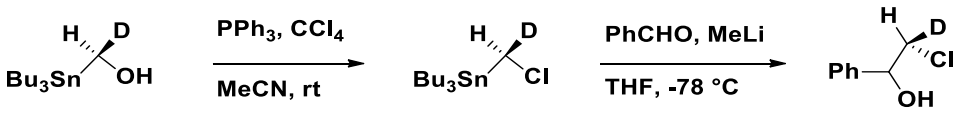
Scheme 9. Deprotonation mechanism for generating *di-halo* species.

α-Halo sulfoxide [54-57] can be used to generate lithium and magnesium carbenoids as reported by Hoffmann and Blakemore.[58, 59]



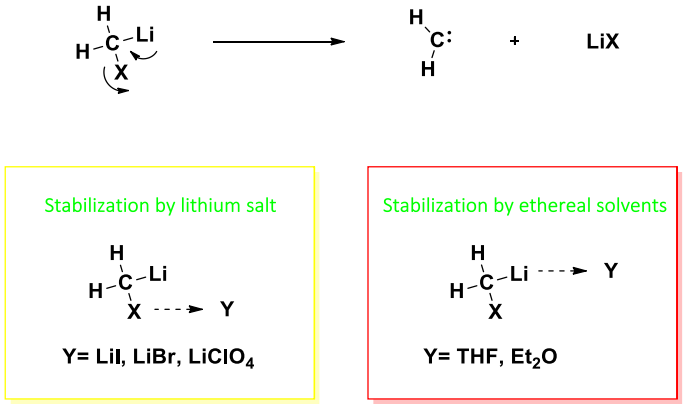
Scheme 10. Generation of carbenoids through metal-sulfinyl exchange. Scheme modified from reference [1].

Obtaining chiral carbenoids has always been a major goal in the modern homologation chemistry. Hammerschmidt *et al.* were the pioneers in this field as they developed a methodology to obtain a chiral $LiCH_2Cl$ *via* metal-tin exchange. The exchange between tin and lithium occurs by reacting chloromethylstannane with MeLi under Appel conditions (PPh_3/CCl_4); then the chiral carbenoid was generated and it reacted with aldehyde compounds to give homologation.[60] Starting from the homochiral tributylstannyl[D_1]-methanol, the corresponding chlorine compound was formed and then its subsequent reaction with MeLi produced the desired $LiCH_2Cl$ at -78 °C; after 30 min the electrophile was added and the reaction conditions maintained to afford products wherein the chiral features were kept intact (Scheme **11**).[22] The use of MeLi instead of *n*-BuLi was preferred because of the lower formation of undesired impurities.



Scheme 11. Generation of carbenoids through metal-tin exchange. Scheme modified from reference [22].

To increase the stability of the lithium carbenoids, the addition of the Lewis acid LiBr turned out to be remarkably advantageous. Furthermore, the addition into the reaction mixture of LiBr decreased the α-elimination process, the most important phenomenon that reduces the stability of the carbenoids (Scheme **12**).[43] It has been observed that this effect can be minimized by the use of ethereal solvents such as THF and ethyl ether. Conversely, the process is stimulated by the use excessively polar solvents, such as HMPA, which has been seen to increase the rate of degradation of such species (Scheme **12**).[22, 43]

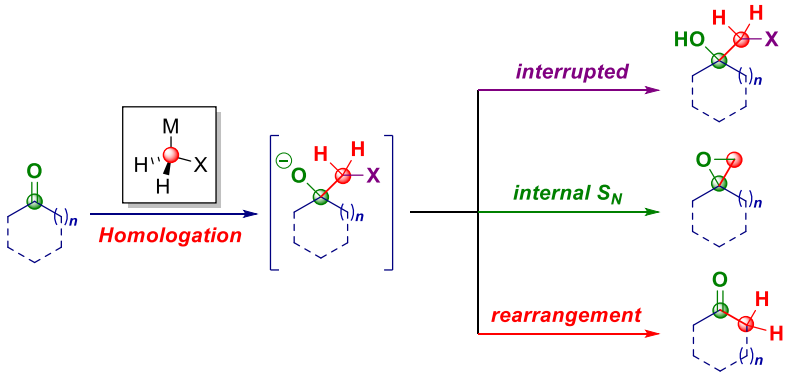


Scheme 12. α-Elimination mechanism and stabilizing factors.

1.4. OVERVIEW OF DESIGNED HOMOLOGATION REACTIONS WITH CARBENOIDS

Pace's group has been using halogenated metal carbenoids (metalated α-halomethyl reagents, M-CH_2-X) since many years to carry out homologation reactions.[1, 61, 62] A classical nucleophilic homologative process of a carbonyl derivative consists in two fundamental steps: 1) addition of the nucleophilic species to the electrophile, resulting in a tetrahedral intermediate; 2) the rearrangement of the intermediate with the expulsion of the leaving group. In our research group, different mechanisms have been proposed for the formation of new *C-C* bonds by means of halomethyllithium reagents.[1] As a whole, three main different homologation pathways can be summarized (Scheme **13**):

- The *interrupted* homologation (the resulting product still contains the original halogen available for further functionalizations).[63]
- The *ring-closure* through intermolecular nucleophilic rearrangement (*e.g.* Corey-Chaykovsky mode).[62]
- The *pure* homologation (the halogen is replaced during an internal molecular rearrangement, often leading to ring-enlargement operations).

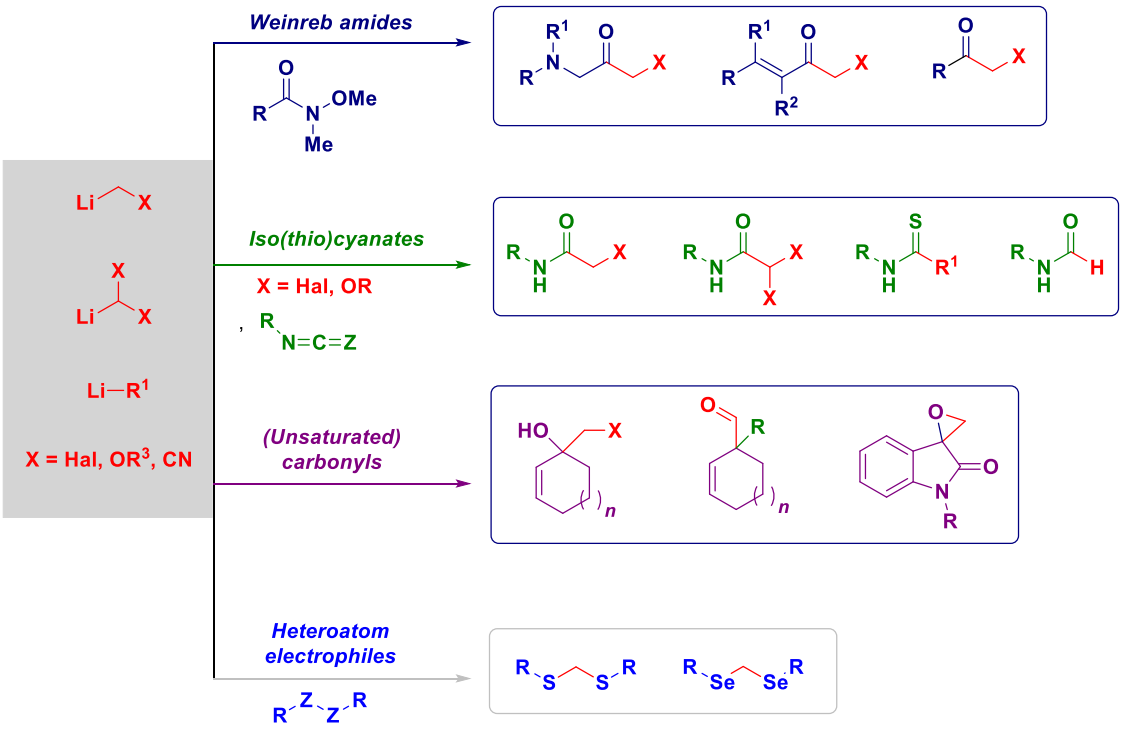


Scheme 13. Conceptually description of the three main homologation pathways of carbonyl with MCH_2X reagents.

Interrupted homologations are the most investigated reactions by Pace's group. A substantial part of our work was devoted to the synthesis of α-substituted methyl ketones. In this context, the use of Weinreb amides turned out to be the best choice to perform these reactions. [27, 64-71]

Once the metallation conditions were set, it was possible to acylate the electrophiles with a series of M-CH_2-X (Scheme **14**). No amok addition reactions neither chemoselectivity losses were observed. Moreover, the isolation of the tetrahedral intermediate confirmed the formation of a hemiaminal.[72] Weinreb amides react much more efficiently with α-substituted lithium carbenoids rather than magnesium ones.[73] The iso(thio)cyanates are highly reactive towards organometallic compounds to provide α-substituted *N*-methyl(thio)amides. [53, 74-78] This synthetic methodology has also been extended to the formation of formamides and thioformamides using hydrides as nucleophiles. [79-81] α,β-Unsaturated carbonyls give rise to halohydrins, epoxides and more complex

structures such as biologically relevant spiro-epoxyoxindoles;[82-84] furthermore, ketones can give rise to quaternary aldehydes after Meinwald rearrangement.[85] The high nucleophilicity of lithium carbenoids compared to other reagents (*e.g.* sulfur ylides, diazomethane), has allowed to homologate diselenides and disulfides in the corresponding diseleno- and dithio-acetals in high yields.[86]

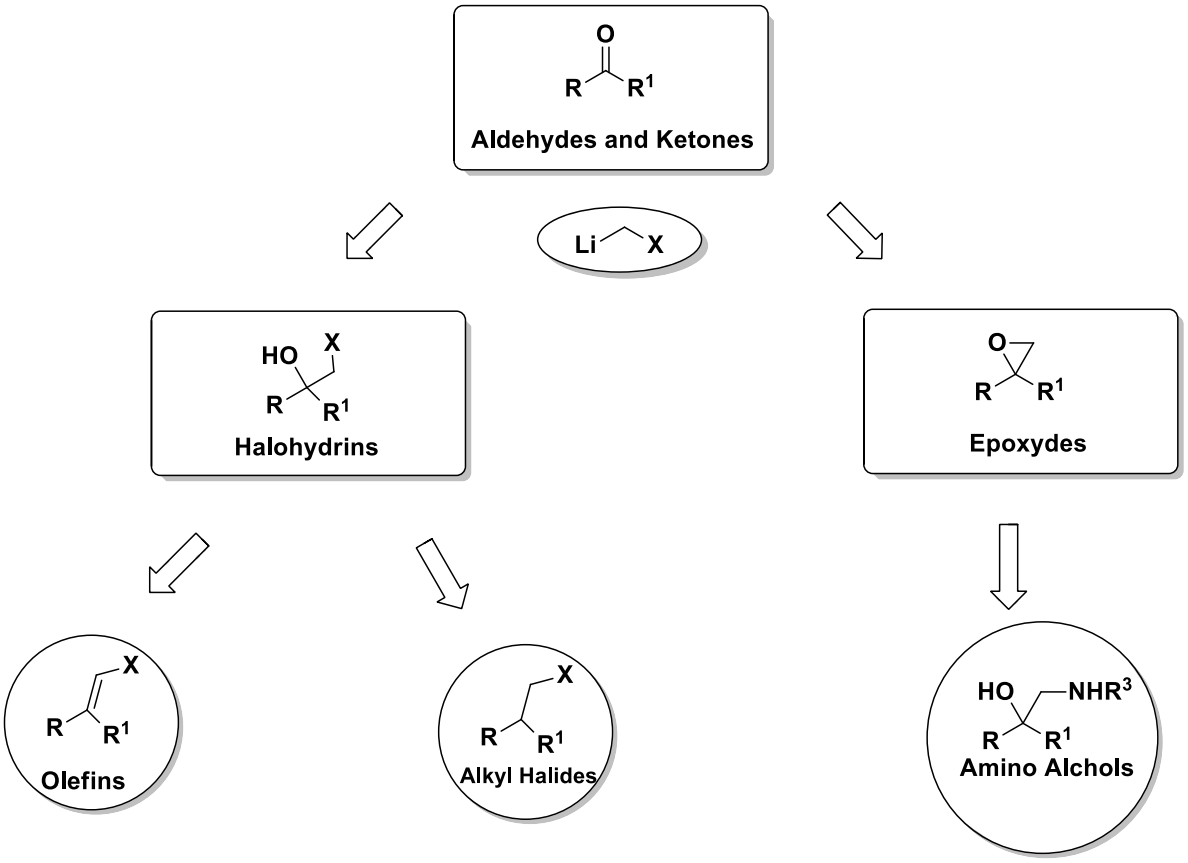


Scheme 14. Homologation strategies with various electrophiles.

1.5. ELECTROPHILIC PARTNERS

1.5.1. ALDEHYDES AND KETONES

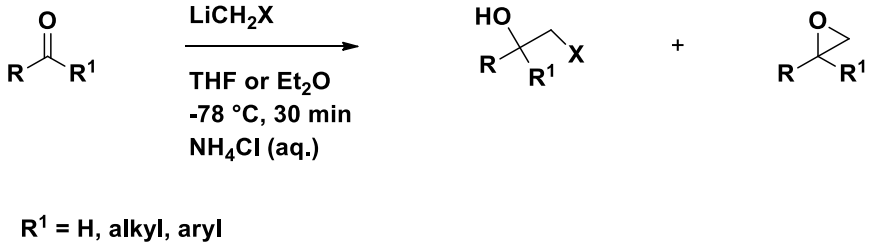
As documented in several literature works, carbonyls were among the first electrophilic partners employed in homologation reactions with lithium halogenated carbenoids.[29, 30, 38, 63, 87-90] Aldehydes and ketones are particularly reactive with respect to other functional groups (*e.g*. boronic esters), and through a simple homologation step it is possible to convert carbonyls into *n*+1 halohydrins and epoxides. The synthetic utility of halohydrins relies in their ability of being easily transformed into olefins by dehydration, and to be transformed into halogen alkanes through a double homologation/reduction process (See Results and Discussion); epoxides, on the other hand, can be the subject of a wide range of functionalization reactions due to their high reactivity (Scheme **15**).[29, 91]



Scheme 15. Synthetic homologation pathways related to aldehydes and ketones.

The generic procedure for obtaining both halohydrins and epoxides first involves the generation of the carbenoid and then the addition of a dialomethane in presence of an organolithium reagent such as MeLi and *n*-BuLi (Scheme **16**). The carbenoid thus generated possesses sufficiently nucleophilicity to attack the carbonyl of the starting material and provide the product over 30 min. The reaction occurs under Barbier conditions, *i.e.* the electrophile is present in the reaction mixture

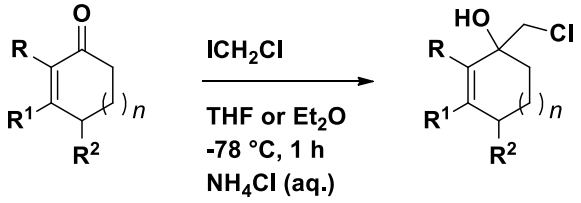
during the generation of the carbenoid; the generative event of the carbenoid and its subsequent addition to the electrophile are kinetically faster than the direct attack of the organolithium to the carbonyl compound, so that to obtain, after work up in acidic conditions, an almost total conversion of the starting material. The required temperature (-78 °C) is the same as seen hereinabove in the other homologation reactions and totally anhydrous conditions are also required to ensure an increase in the hemilife of the carbenoid in the reaction mixture.



Scheme 16. General synthesis of halohydrins and epoxides from carbonyls.

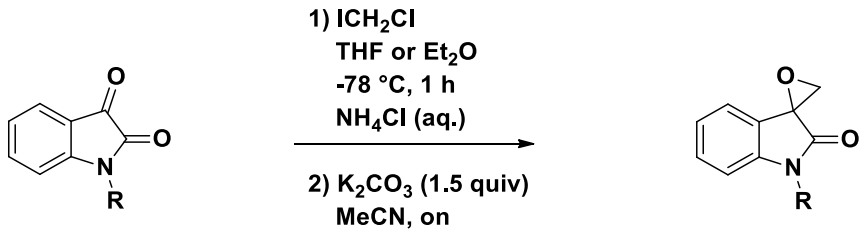
MeLi-LiBr in ethereal solution is the best choice among the organometallic reactants, in particular thanks to the presence of lithium salt which reduces the formation of by-products coming from the direct addition of the organolithium to the electrophile. Ethereal solvents (THF and Et_2O) provide the best results in terms of transformation rate and must be compulsorily anhydrous. It is possible to modulate the progress of the reaction to favor one of the two products; specifically, if the temperature is kept constant (-78 °C), the epoxidation pathway is avoided and it is mainly detected the formation of alohydrin; on the other hand, if the reaction is allowed to rise naturally after the initial cooling, the lithium alkoxide intermediate elicits an intermolecular nucleophilic substitution with the formation of the epoxide as a primary product. To further promote the formation of the epoxide, it is possible to employ a dihalide containing iodine, for example diiodomethane, which may acts as a better leaving group and favors the displacement process.

Exceptional results were obtained using α,β-unsaturated cyclic ketones (Scheme **17**). After reacting with $LiCH_2Cl$ they provided quaternary allylic halohydrins.[63] Their strong ability to provide high yields and excellent chemoselectivity is also confirmed by the use of more complex cyclic ketones as substrates. Furthermore, the process is carried out exclusively through a 1,2-addition mechanism, unlike other types of nucleophilic additions observed for similar carbenoids.[92, 93] The presence of lithium bromide, in this case, stabilizes the carbenoid and, at the same time, increases the electrophilicity of the carbonyl carbon.[94] Only in some cases, *e.g.* chromone derivatives, it has been detected a noteworthy mesomeric effect in which the 1,4-addition is favored over the 1,2.



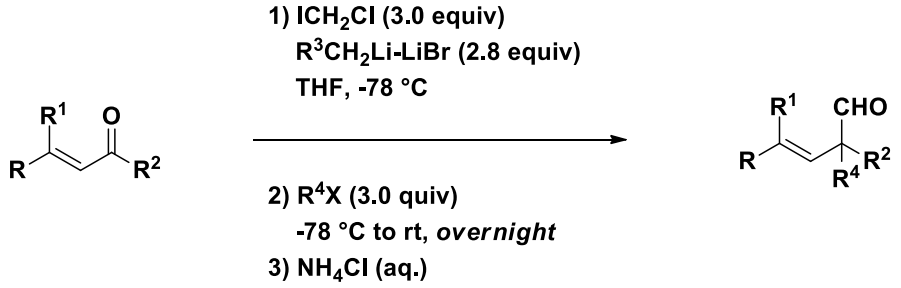
Scheme 17. Chemoselective addition of $LiCH_2Cl$ to cyclic enones.

Among the carbonyl derivatives, isatins represent a class of extremely reactive molecules due to the presence of the electron-withdrawing lactam nucleus.[82, 95] The C3 of the isatins may undergo nucleophilic addition by the halocarbenoid and, if other reactive functionalities are present within the structure, it acts as a privileged point of attack (Scheme **18**).[83] In fact, also in the presence of Weinreb amides, esters, nitriles, alkenes or alkynes moieties, the organolithium reagent retains a marked preference for the electrophilic C3 of isatin. Even a lactam -NH group does not alter the chemoselectivity of the process, underlining the peculiar reaction profile of the isatins. This is an absolute feature of this special class of compounds, since the difficulty in homologating Weinreb amides or esters in chemical frameworks bearing amide or amine NH has long been well-documented.[69, 96-98] Thanks to the strategy proposed by Pace, it is therefore possible to prepare spiroepoxyoxindoles from isatins in an extremely simple and reproducible way.[83]



Scheme 18. Synthesis of spiro-epoxyioxindoles from isatins.

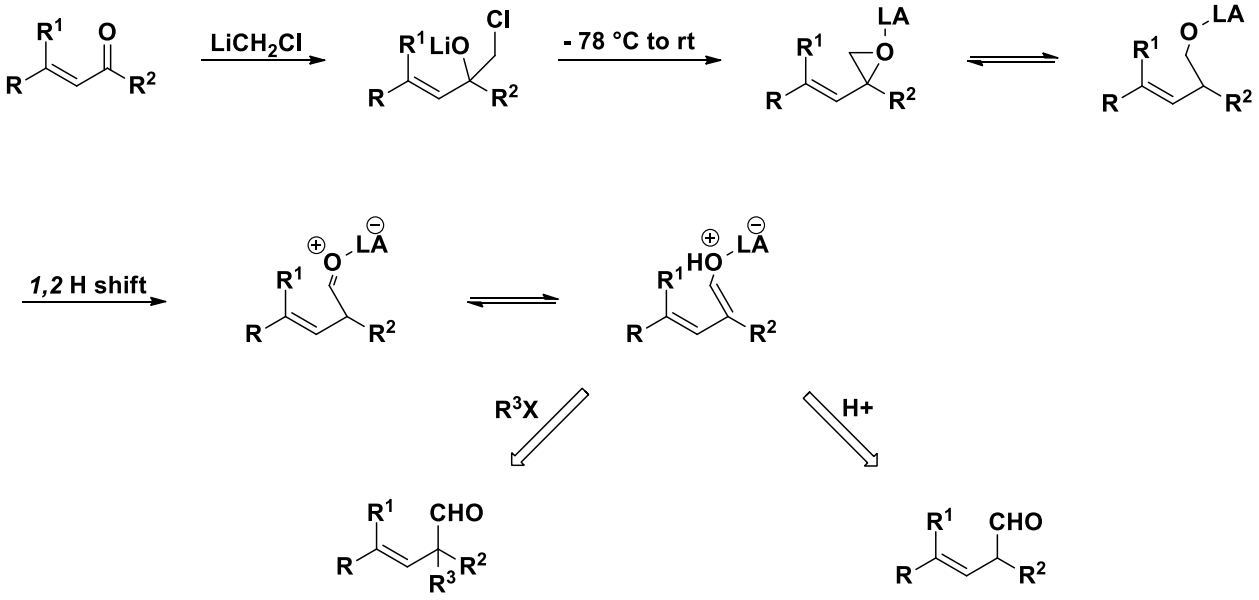
In an attempt to homologate α,β-unsaturated ketones into vinyl epoxides by ring closure of halohydrin alkoxy intermediates,[99] the formation of a α-substituted aldehyde was suprisingly observed (Scheme **19**).[85]



R, R^1 = akyl, aryl
R^2 = alkyl
R^3 = H, TMS
R^4 = benzyl, allyl
X = Br, I

Scheme 19. Quaternary and tertiary α-substituted homoallyl-type aldehydes.

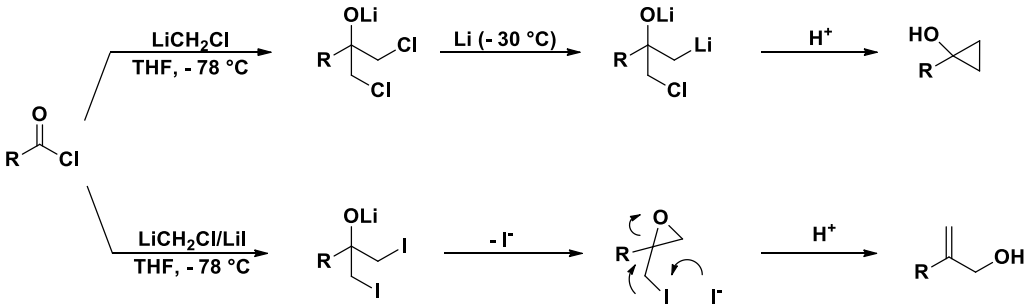
The peculiarity of this transformation derived from the presence, in the reaction mixture, of the electrophilic species MeI, which was added in α position to the newly formed aldehyde. The parameters that allow this process are considered the raising of the temperature from -78 °C to rt (in order to favor the first step of epoxidation) and the employment of LiBr as mild Lewis acid. The reaction mechanism, depicted in Scheme **20**, was demonstrated by the use of deuterated carbenoids.



Scheme 20. Reaction mechanism proposed for the transformation of α,β-unsaturated ketones into n+1 homoallyl-type aldehydes.

1.5.2. ACYL CHLORIDES

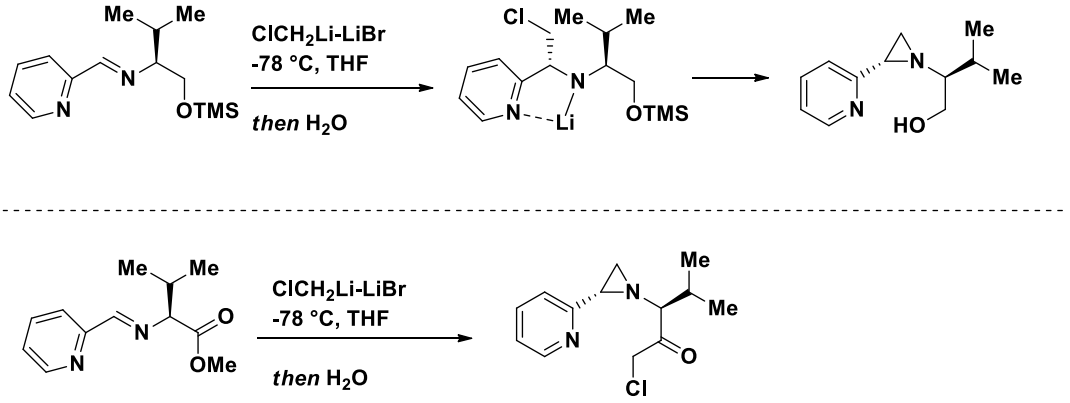
Barluenga *et al.* first described the synthesis of cyclopropanols from acyl chlorides and $LiCH_2Cl$ (Scheme **21**).[100, 101] The strong reactivity of the acyl chlorides causes an uncontrolled addition of the carbenoid; then, the resulting alkoxide intermediate, in the presence of Li, can cyclize to ~~a~~ cyclopropane. By using $LiCH_2I$ instead, it is possible to realize the conversion into allylic alcohol.



Scheme 21. Conversion of acyl chlorides into cyclopropanols and allylic alchools.

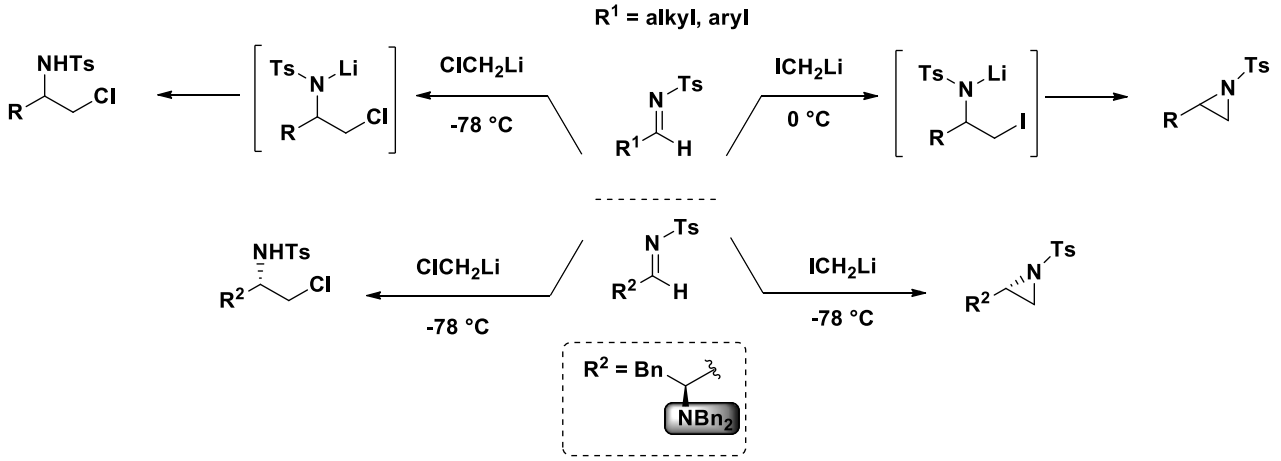
1.5.3. IMINES

Imines can be considered versatile electrophilic partners in organometallic chemistry. They react smoothly with halogenated carbenoids to give β-haloamines and aziridines.[102] Imines are also envisaged as fundamental *scaffolds* for the synthesis of amino acids, β-lactams and alkaloids[102-104], therefore, several methods for the conversion of imines into such biologically revelant derivatives have been proposed.[105] In 2006, Savoia and coworkers described the synthesis of diastereopure aziridines by using $LiCH_2Cl$ as homologation reactant and the spontaneous cyclization of the resulting β-haloamine intermediate (Scheme **22**).[105] The presence of pyridine proved to be an important requirement for this process as it is able to complex lithium and, at the same time, increase the nucleophilicity of the carbenoid. Unfortunately the reaction did not show significant chemoselectivity as the presence of an ester moiety produced an uncontrolled double addition.



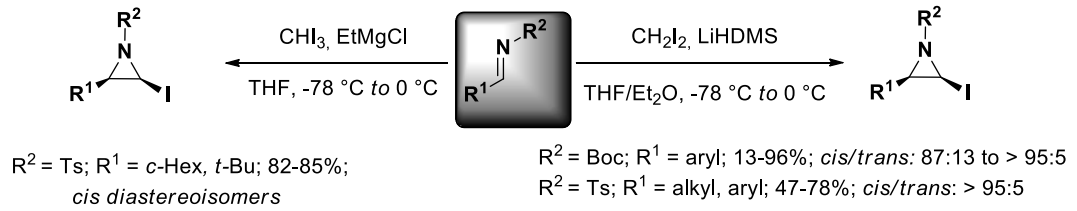
Scheme 22. Savoia's homologation of imines.

Concellon's research team proposed *N*-tosyl(Ts) imines as promising electrophiles for the homologation and cyclization to aziridines (Scheme **23**).[32, 105] In particular he observed that by using $LiCH_2I$, a greater tendency to the ring closure mechanism occurred with the consequent spontaneous formation of aziridines. Conversely, $LiCH_2Cl$ afforded mostly β-haloamines due to the low tendency of the chlorine to behave as a leaving group. Furthermore, the presence of the *N*,*N*-dibenzylamino group favored the maintenance of the stereochemical information during the process (9: 1 *dr*).



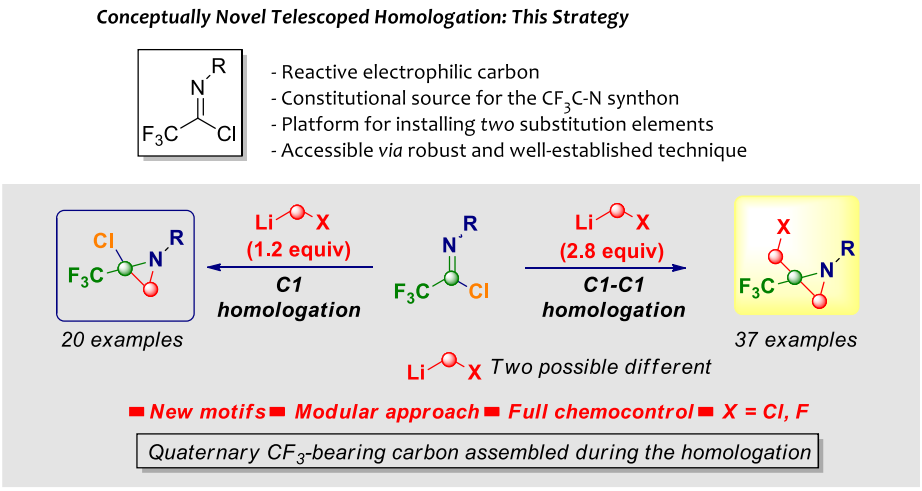
Scheme 23. Homologation pathways for *N*-Ts imines.

N-Boc and *N*-Ts imines react smoothly with diiodomethylithium ($LiCHI_2$) and diiodomethylmagnesium ($ClMgCHI_2$) to provide α-iodo aziridines, as evidenced by Bull (Scheme **24**).[106, 107] The reaction procedure showed a better yield profile by using magnesium carbenoids, and the stereochemistry of the process resulted in *cis*-selectivity.



Scheme 24. Synthesis of α-iodoaziridine proposed by Bull.

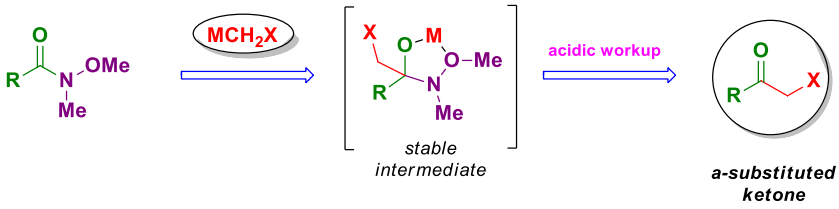
In 2019 Pace *et al.* carried out a novel and high-yielding mono/bis-homologation of trifluoroacetimidoyl chlorides into a new class of quaternary trifluoromethyl aziridines by means of $LiCH_2Cl$ and $LiCH_2F$ (Scheme **25**). By varying the stoichiometry of the process, it is possible to achieve one or two homologations, thus obtaining in a single route the formation of two different types of functionalized aziridines.[35]



Scheme 25. Homologation pathway of imines developed by Pace's group.

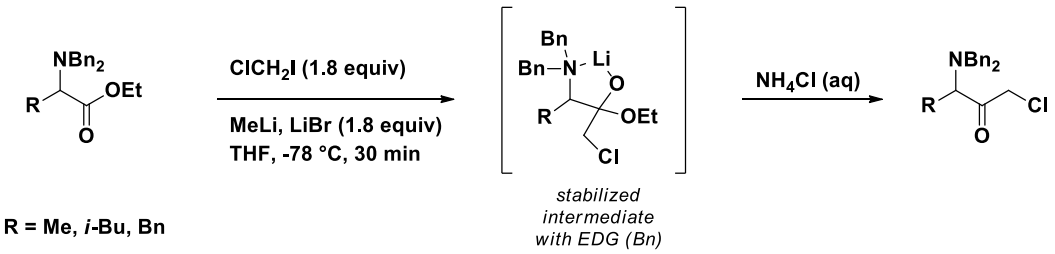
1.5.4. WEINREB AMIDES

In 1981 Steven M. Weinreb and Steven Nahm introduced the *N,O*-dimethyl-hydroxyl-amides as electrophilic functional group for the direct acylation of substituted α-methyl type carbanions and, from the on, Weinreb amides became fundamental substrates for the synthesis of α-substituted ketones.[108] Although there are numerous ways for the synthesis of ketones, the use of a direct *addition-elimination* mechanism involving the attack of methyl-type carbanions to an electrophilic substrate is the simplest procedure.[1, 22, 62, 109, 110] With the use of Weinreb amides it is possible to accomplish this task and obtain α-substituted ketones with the exact degree of substitution in a single homologation step (Scheme **26**).[1, 85, 111] α-Substituted ketones play a leading role in the synthetic panorama – because of the concomitant presence of two highly reactive moieties, the carbonyl and the adjacent α-carbon[112] - especially as regards their possible biological application in drug discovery. Therefore nowadays, finding new methodologies that allow their rapid and efficient synthesis is becoming prevalent.[8, 113-117] α-Substituted ketones bearing an EWG possess unique characteristics, especially if this consists in a fluorine (See Result and Discussion), because they may act as 1,2-dielectrophilic synthons. Moreover, these fragments are biologically relevant due to the possibility of the α-haloketones to behave as enzymatic inhibitors.[118, 119]

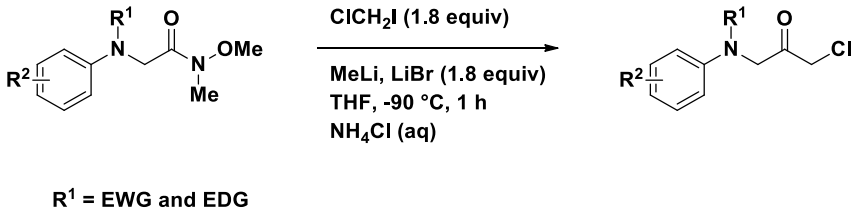


Scheme 26. Weinreb amides for the synthesis of α-substituted ketones. Scheme modified from reference [120].

The key factor of the use of Weinreb amides as acylating agents relies in the fact that, unlike other electrophilic carboxylic derivatives (esters or acyl chlorides), they are able to provide a controlled reaction, avoiding recurring additions of the nucleophile (Scheme **28**).[121-123] Overaddition *phenomena* are not observed for Weinreb amides due to the high stability of the tetrahedral intermediate (formed by the addition of carbanion to the amide) which also guarantees an excellent level of chemocontrol of the reaction. The stabilization of the tetrahedral intermediate derives from the presence of the -OMe group which coordinates the metal cation with the formation of a stable 5-term ring adduct. Moreover, the presence of the -OMe group increases the electrophilicity of the carbonyl making the Weinreb amide more susceptible to nucleophilic attack.[108, 124, 125] For these reasons the hemiaminal intermediate of the Weinreb amide turns out to be stabilized compared to that one which would have been obtained from the reaction of a metal carbanion with an ester moiety. The latter would provide a too unstable intermediate that does not evolve into a ketone moiety. Barluenga *et al.* showed how the homologation of amino esters with $LiCH_2Cl$ is doable thanks to the presence of stabilizing elements [*e.g.* the electron-donating group (EDG) – Bn] on the nitrogen atom, which increase electron density and allow the formation of a more stable intermediate (Scheme **27**). Indeed, this effect is not detected when an EWG stands on the nitrogen and this represents a strong limit of the reaction.[24] The high stability of the tetrahedral intermediate formed by the attack of $LiCH_2Cl$ to the Weinreb amide instead, allowed its isolation and characterization as reported by Pace *et al*.[126] The features of this process were the use of TMS-imidazole to trap the intermediate in the form of silyl ether and the use of neutral alumina (Brockmann grade 3, Alox-BG3) to allow its isolation and characterization. A similar protocol has been applied for hemiaminals derived from *N*-acyl pyrroles.[127]

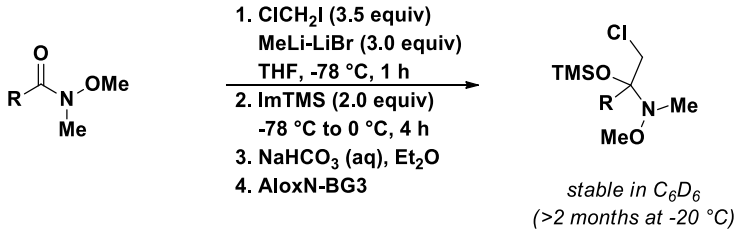


Scheme 27. Barluenga's α-amino esters homologation *via* halomethyllithium carbenoid. Scheme modified from reference [65].



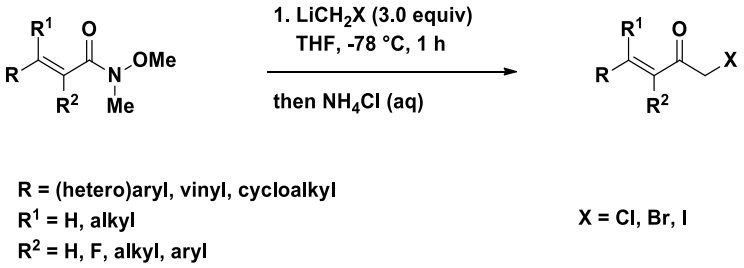
Scheme 28. Pace's Weinreb amides Homologation *via* halomethyllithium carbenoid. Scheme modified from reference [65].

The isolated tetrahedral intermediates formed by the addition of the carbenoid to the Weinreb amide is shown in Scheme **29**. Despite the controlled conditions used to preserve their chemical integrity, these species may undergo further modifications such as Feriga cross-coupling and the one-step formation of α,β-epoxyketone.[128, 129]



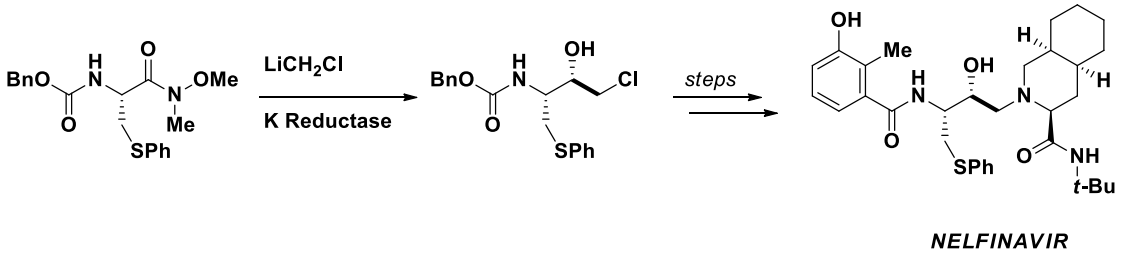
Scheme 29. Isolated tetrahedral intermediates generated from the reaction of Weinreb amides with $LiCH_2Cl$.

The remarkable chemoselectivity of the Weinreb amides has been demonstrated by employing α,β-unsaturated Weinreb amides in the reaction with $LiCH_2Cl$ in order to synthesize the corresponding α'-haloketones (Scheme **30**). The cinnamoyl framework is normally prone to undergo 1,2-addition reaction because the β-position of the olefinic double bond is activated. In this case instead, the cinnamoyl Weinreb amides reacted with carbenoids producing the corresponding ketones in high yields and avoiding this side phenomenon. This peculiar reactivity can be exploited for the synthesis of β-cycloalkyl or alkynyl derivatives which can be smoothly obtained.[48]



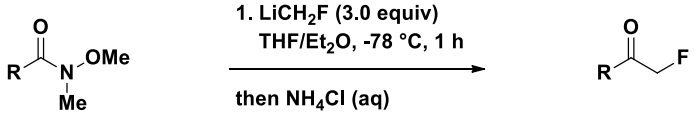
Scheme 30. α,β-Unsaturated α'-haloketones synthesis from Weinreb amides. Scheme modified from reference [65].

The feasibility of these synthetic strategies has been extended to the stereocontrolled preparation of a key fragment of the anti-HIV drug nelfinavir.[130] Scheme 31 shows the synthesis of nelfinavir by means of a Weinreb amide derivative as starting synthon, which was converted into the corresponding α-chloroketone. The biocatalytic reduction of the latter led to the *erythro* chlorhydrine derivative which afforded nelfinavir after subsequent steps.



Scheme 31. Application of halomethyllithium-mediated homologation of Weinreb amides for the synthesis of Nelfinavir. Scheme modified from reference [65].

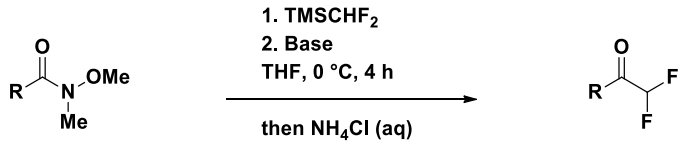
Among α-haloketones, the α-fluoro derivatives are the most interesting and synthetically challenging at the same time. In 2017 Pace and co-workers proposed the first method for the direct monofluoromethylation of Weinreb amides employing the highly instable carbenoid fluoromethyllithium ($LiCH_2F$) generated *in situ* from fluoroiodomethane and MeLi-LiBr for the synthesis of α-fluoromethyl ketones (Scheme **32**).[131] The commercially available fluoroiodomethane (bp 52 °C), properly activated under Barbier conditions, generates $LiCH_2F$ in the presence of MeLi-LiBr and, by using Weinreb amides as electrophiles, it is possible to obtain a wide range of α-fluoromethylketones in good yields.



Scheme 32. Using the highly unstable $LiCH_2F$ for the direct monofluoromethylation of Weinreb amides. Scheme modified from reference [65].

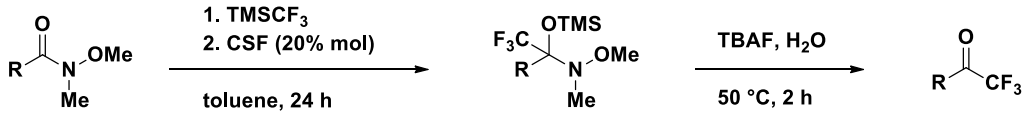
α,α-difluorinated ketones, on the other hand, are less explored compounds since their synthesis is difficult to achieve. Kuhakarn's group reported a multistep synthesis of α,α-difluoromethyl ketones from Weinreb amides using $PhSCF_2SiMe_3$, which allowed the addition of the fluorinated carbanion stabilized by the PhS group, which was eventually eliminated by a reductive cleavage.[132]

In view of the great importance of fluorinated ketones, our research group in 2019 introduced the first direct, high yielding and chemoselective synthesis of α,α-difluoromethyl ketones from Weinreb amides, using (difluoromethyl)trimethylsilane ($TMSCHF_2$; Scheme **33**).[27] This is a commercially available reagent (bp 65 °C) employed in difluoromethylation reactions and, when properly activated, it is able to release the CHF_2 carbanion responsible for the nucleophilic attack to the electrophilic partner. Although it is not a lithium carbenoid, it is noteworthy to underline the importance of the $TSMCHF_2$ activation conditions and the intrinsic stability of the potassium carbanion released in the reaction mixture at 0 °C which evades the need of electron-attracting groups to stabilize it and annoying cleavage methods that could decrease the reaction yield (See Results and Discussion).



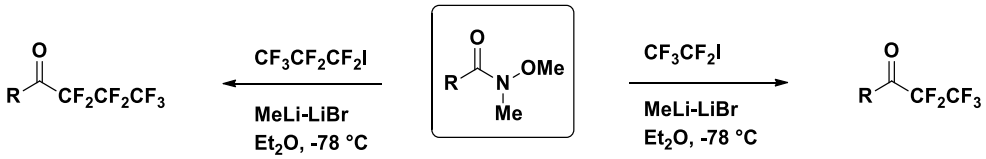
Scheme 33. First direct difluoromethylation strategy to access α,α-difluoromethyl ketones.

The introduction of the Ruppert-Prakash reagent ($TMSCF_3$) allowed the development of several methods for the trifluoromethylation of organic substrates. In particular, Leadbeater and co-workers used the CF_3-carbanion, generated with the aid of initiators (*e.g.* CsF) for the conversion of Weinreb amides to α-trifluoromethyl ketones (Scheme **34**).[133]



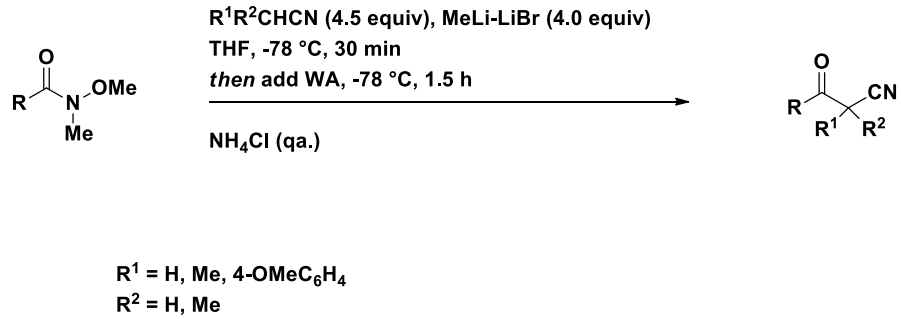
Scheme 34. Synthesis of α-trifluoromethyl ketones from Weinreb amides using the Ruppert-Prakash reagent. Scheme modified from reference [65].

Kokotos *et al.* described the addition of perfluoroalkyllithium carbanions to access polyfluoroketones of biological importance (Scheme **35**).[134-136]



Scheme 35. Synthesis of perfluoroalkyl ketones. Scheme modified from reference [65].

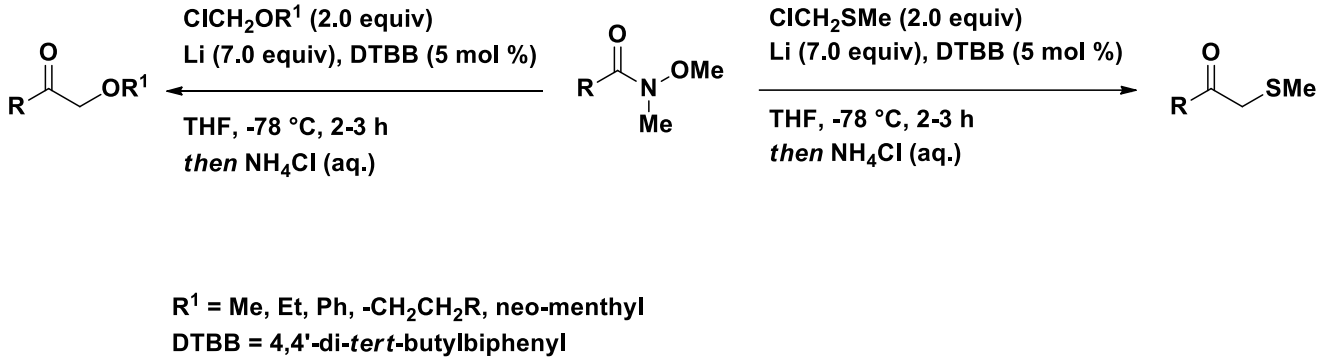
Pace's group reported a direct synthesis of β-oxonitriles (α-cyanoketones) from Weinreb amides, obtained from nitrile-containing carbanions.[137] The reaction starts with the formation of the carbanion (non-Barbier-type conditions); then, the addition of the electrophile promotes the synthesis of the desired products in high yields and with high chemoselectivity (Scheme **36**).



Scheme 36. Synthesis of α-cyanoketones from Weinreb amides. Scheme modified from reference [65].

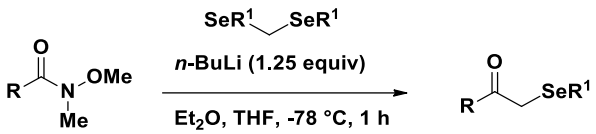
The first direct homologation of Weinreb amides into α-oxyketones via α-oxygenated methyllithium species ($LiCH_2OR$) was reported by Yus and co-workers.[138, 139] The reaction was carried out in the presence of metallic Li and a catalytic amount of DTBB (4,4'-di-*tert*-butylbiphenyl) and allowed the homologation of aromatic, aliphatic, heteroaromatic and α,β-unsaturated Weinreb amides with complete retention of the stereochemistry (Scheme **37**).

Yus and coworkers methodology was applied by Pace for the synthesis of β-oxo thiotethers (α-thioketones) employing the Weinreb amides as acylating partners. The carbenoid $LiCH_2SMe$, generated in the presence of metallic Li, was added quickly and with high rates to the electrophile in an excellent stereoselectivity regime (Scheme **38**).[67] Using thioanisole in Corey-Seebach conditions (*i.e.* presence of DABCO and *n*-BuLi) it was possible to obtain α-arylthiomethylketones both from aliphatic and aromatic Weinreb amides.[140]



Scheme 38. Synthesis of α-oxo and α-thioketones from Weinreb amides. Scheme modified from reference [65].

α-selenomethyl ketones can be efficiently prepared from diselenoacetals ($R^1SeCH_2SeR^1$). The latter, by Li/Se exchange in the presence of *n*-BuLi in Et_2O or THF, gave rise to the stable carbanion $LiCH_2Se$ responsible for the nucleophilic addition to the Weinreb amides in non-Barbier-type conditions. In this way, a wide series of α-selenomethyl ketones were synthesized for the first time in high yields and with marked chemoselectivity (Scheme **39**).

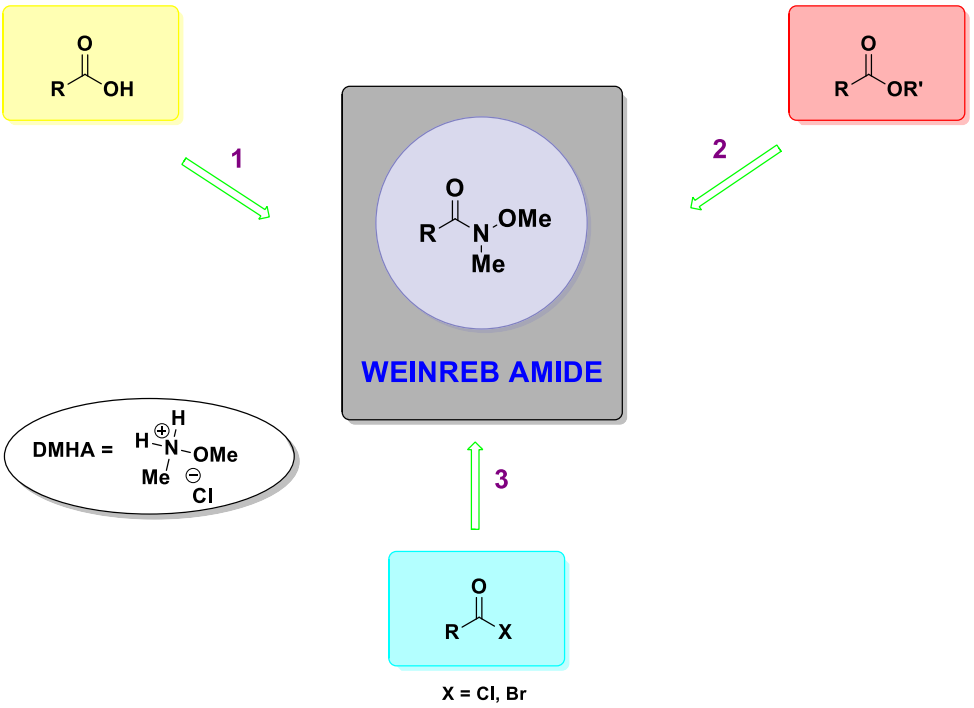


Scheme 39. Synthesis of α-selenomethyl ketones from Weinreb amides. Scheme modified from reference [65].

Weinreb amides represent excellent substrates for the synthesis of α-substituted ketones. Besides, their reactivity can be modulated by the presence of other highly electrophilic groups such as ketones, isatins[83, 84] and trifluoroacetimidoyl chlorides[35] in a competitive way. In particular, with respect to these functionalities, organometallic reagents leave intact the amide function, which in turn can be further functionalized.

Herein, I briefly summarize the most intuitive methods for the synthesis of Weinreb amides. They can be smoothly prepared from carboxylic derivatives *plus N,O*-dimethyl hydroxylamine:

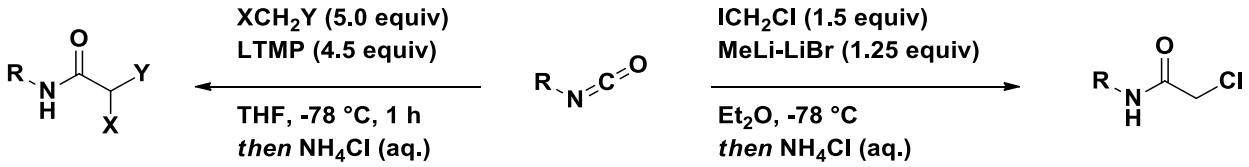
- From carboxylic acids it is possible to obtain a Weinreb amide after activation of the carboxylic group by conjugation with a good leaving group - CDI for example - in basic conditions.[124, 125]
- Esters can be converted in Weinreb amides *via* organoaluminium or Grignard reagents.[108, 141]
- Acyl chlorides represent the simplest and most immediate way to obtain the Weinreb amides in quantitative yields and without tedious chromatographic purifications.[142]



Scheme 40. Main routes of preparation of Weinreb amides. 1) CDI, DMHA; 2) AlR^1_3 or R^2MgX, DMHA, THF 0 °C; 3) K_2CO_3, DMHA, 2-MeTHF/H_2O, 0 °C to rt.

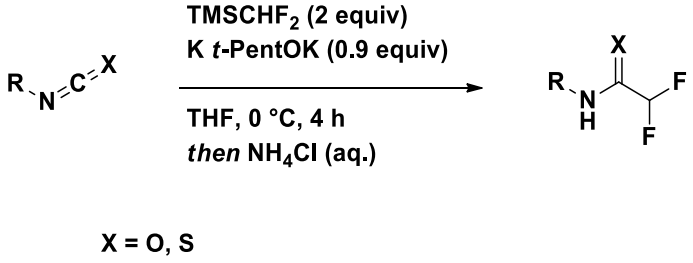
1.5.5. HETEROCUMULENES

The importance of the amide group originates from its almost ubiquitous presence in nature. Among the functional groups, amide plays a leading role as it is the most important bond between biological molecules (*e.g.* amino acids). Therefore, the development of easy methods for obtaining new amide bonds is still a topic of relevance of the synthetic organic chemistry.[143, 144] Originally, the titration of organometallic reagents such as RLi and RMgX was based on the reaction between them and iso(thio)cyanates;[145] during the process, the isothiocyanate is consumed with the production of iso(thio)amide. However, although this method has been known since 1920, only in 2014 Bode carried out the synthesis of sterically hindered amides starting from isocyanates and by using organometallic reagents.[76, 146-148] Nowadays, isothiocyanates are considered starting materials of utmost importance due to the high electrophilicity of carbon.[74] Our research group, therefore, decided to employ halogenated carbenoids as nucleophiles to homologate isocyanates and isothiocyanates into amides.[50] Moreover, by means of a deprotonation protocol which entails the use of a dihalide, it is possible to transfer halo units to obtain dihalo acetamides and dihalothioacetamides in high yields and with excellent chemoselectivity.[53] Also in this case, LTMP proved to be an excellent base for carrying out the process.



Scheme 41. Synthesis of α-haloacetamides from isocianates.

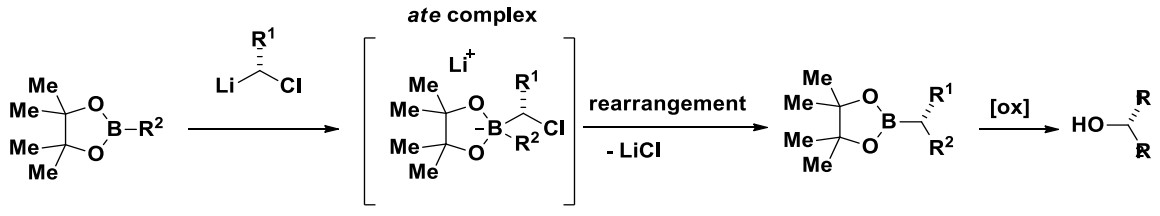
The sinthesis of α,α-difluoro(thio)acetamides, on the other hand, is achievable by using silicon based carbanions, generated starting from $TMSCHF_2$ in the presence of an alkoxide.[28] With this methodology (See Results and Discussion), we have set the first direct and chemoselective transfer of the formal unit CHF_2. By reacting iso(thio)cyanates under these conditions, it is therefore possible to obtain the corresponding difluoro(thio)acetamides in high yields and with excellent chemocontrol (Scheme **42**).



Scheme 42. First direct and chemoselective synthesis of α,α-difluoro(thio)acetamides.

1.5.6. BORON ELECTROPHILES

Donald S. Matteson was the first to report the homologation of boronic esters with halocarbenoids in 1980.[37, 149, 150] Lately, Blakemore explored the chemistry of the chiral carbenoids.[54, 59, 151] Using a diasteropure α-chloroalkyl sulfoxide, he applied the sulfoxide-lithium exchange to generate α-chloroalkyllithium (Scheme **43**).[57]

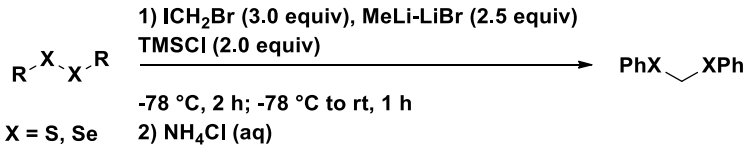


Scheme 43. Blakemore's homologation of boronic esters.

Furthermore, pinacol boronates are considered optimal starting material for achieving homologations reactions with full stereochemical integrity by employing enantioenriched lithium carbenoids.[57]

1.5.7. HETEROATOM ELECTROPHILES

Pace's group developed an efficient method to homologate disulfide[86] and diselenide with bromomethyllithium carbenoid, obtaining the insertion of a CH_2 group between two heteroatoms (Scheme **44**).

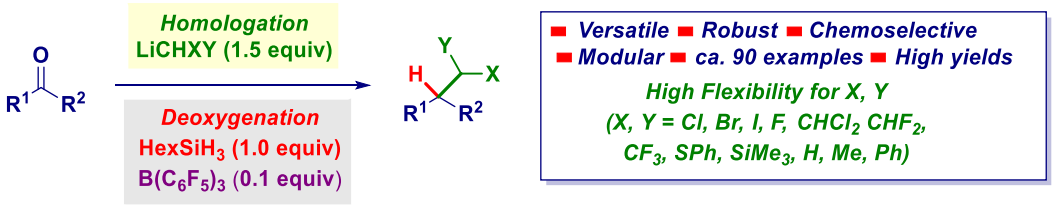


Scheme 44. Pace's heteroatoms homologation.

2. RESULTS AND DISCUSSION

2.1. HOMOLOGATION OF CARBONYLS INTO ALKYL HALIDES

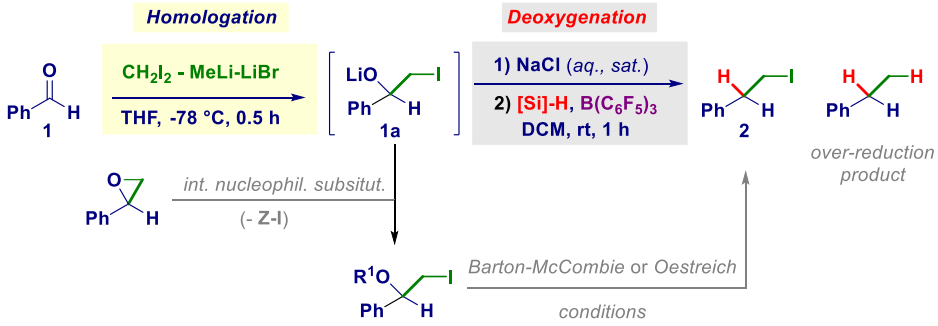
Herein we report a double step procedure for the chemoselective and high yield homologation of aldehydes and ketones in alkyl halides. The aim of our work was to optimize a homologation synthetic protocol of carbonyls through the employment of lithium halogenated carbenoids, and the subsequent deoxygenation of the intermediates to halo-alkanes. The strategy we carried out allowed the conversion of aldehydes and ketones into alkyl halides with high yields and under chemocontrol. Subsequently, the carbonyls were homologated using also other α-substituted organometallic nucleophilic species (Scheme **45**).[152]



Scheme 45. Versatile, robust, chemoselective, high yield and modular homologation of carbonyls into alkyl halides. Scheme modified from reference [152].

The basic principle on which our method has been developed involves the addition of an organometallic reagent (*i.e.* $LiCH_2X$) to carbonyls, with the formation of halohydrins. The oxygenated intermediate was immediately converted into halogenalkane employing a deoxygenation protocol based on a highly reactive silane. We chose benzaldehyde (**1**) as the model starting material for the homologation-deoxygenation with $LiCH_2I$ in order to explore the optimal conditions to operate in both stages of the process (Table **1**). First, the insertion of a iodo-containing motif would be difficult because, on one hand, it could undergo epoxidation due to an internal nucleophilic substitution (**5**) (**1b**, *homologation side reduction*), while on the other, it could be over-reduced to C-H (**1c**, *deoxygenation side reduction*).[85, 153] The first-stage of the homologation reaction was accomplished in quantitative yield within 0.5 h at -78 °C in THF using 1.4 equiv. of $LiCH_2I$ – as confirmed by ^{1}H-NMR and GCMS analysis - thus leading to the tetrahedral intermediate **1a**. By increasing the temperature (up to -50 °C) or leaving to react the mixture for more than 1 h, resulted in significant side epoxidation. The direct Barton-McCombie reaction gave iodoalkane **2** in low yield after long time and high temperature (*entry 1*).[154] We next applied the extremely easy and convenient Oestreich's formal reduction of alcohols[155] - *via* conversion into tosylates, followed by $B(C_6F_5)_3$-catalyzed deoxygenation[156-165] with Et_3SiH - to reach a good yield (46%; *entry 2*). Further improvement was obtained simply by quenching the homologation reaction crude with water, thus making a formal iodohydrin which straightforwardly deoxygenated after trivial separation of the organic phases. Although we got the final product in moderate yield (52%), we hypothesized that the residual THF

(best-choice solvent for the homologation step), after dilution with DCM, might have interfered with the deoxygenation mechanism (*entry 3*). Therefore, we went forward with the complete elimination of the residual THF, by washing the crude mixture with sat. NaCl, which led to an increase of the reaction yield (66%) (*entry 4*). Less hindered silanes such as Ph_2SiH_2, Et_2SiH_2, $PhSiH_3$ and *n*-$hexSiH_3$ were also effective, especially *n*-$hexSiH_3$ that we elected as ideal reagent (*entries 5-8*). The replacement of $B(C_6F_5)_3$ with a different Lewis acid such as $InCl_3$[166] had a negative effect on the reaction yield (*entry 9*) (Table **1**).



entry	$LiCH_2I$ (equiv) / time [h]	deoxygenation reductant / solvent	Lewis acid	yield of **2** (%)[a]
1[b]	1.4 /0.5	*BMC*	-	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*	*hexSiH₃/ DCM*	*B(C₆F₅)₃*	*89*
9	1.4 /0.5	$hexSiH_3$ / DCM	$InCl_3$	60

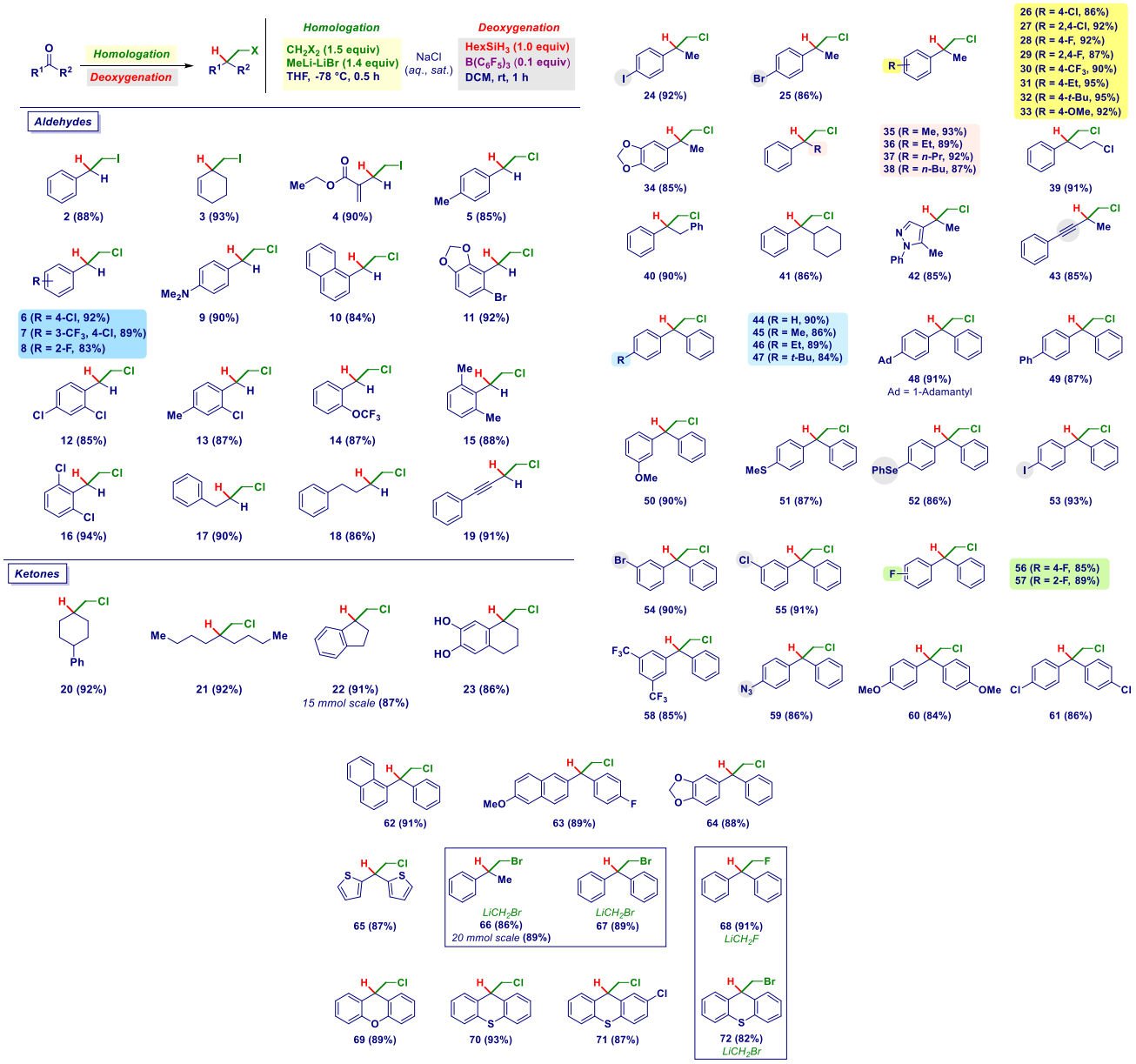
[a] Isolated yield after the homologation/deoxygenation sequence. [b] BMC = Barton-McCombie [R^1 = PhCS, Bu_3SnH, AIBN, toluene, reflux]. [c] Oestreich [R^1 = Ts, Et_3SiH, $B(C_6F_5)_3$, DCM]. [d] Upon quenching with H_2O, DCM was added and the two phases were separated. [e] Sat. NaCl and DCM were added prior to phases separation. Otherless stated, $B(C_6F_5)_3$ (0.1 equiv.) were used.

Table 1. Optimization of the reaction conditions. Table modified from reference [152].

Once the reaction conditions were optimized, we went through with the extent (Schemes **46, 47, 48**). The experimental protocol demonstrated a superb chemocontrol, as shown in the case of sensitive substrates such as a cyclic enone (**3**) and a α,β-unsaturated ester (**4**). By using an olefin as starting material, the reaction proceeded leaving the double bond unreacted; no overreduction of ester carbonyl moieties were observed as well. The procedure was highly versatile as inferred by switching the homologating agent with a different carbenoid. The chloromethylation-

deoxygenation methodology was particularly suitable for benzaldehyde derivatives bearing different functionalities such as alkyl (**5**), amino (**9**) and polyaromatic groups (**10**) *inter alia*. Surprisingly, the acetal moiety of the bromo-derivative (**11**) did not interfere both with homologation and reduction steps. The insertion of different halogens as substituents is tolerated (**6-8, 12-14**), as well as the increase of the sterical hindrance next to the carbonyl (*e.g*. 2,6-disubstituted systems, **15-16**). Aliphatic aldehydes showed a good reactivity under the reaction conditions furnishing ω-chloro phenylalkanes (**17-18**) in high yields. In addition, a propargylic aldehyde was converted smoothly into the homologated analogue (**19**) without altering the chemical integrity of the triple bond. Then, we applied the same protocol to ketones. Aliphatic ketones reacted well giving α-chloro tertiary centers both in the case of cyclic (**20**) and linear (**21**) starting substrates; likewise, indanone and tetralone derivatives (**22-23**) reacted very well; remarkably, the reaction scale up to 15 mmol was succesful (**22**, 87% yield). During the reduction step, concomitant *bis*-demethylation was observed, thus leading to the formation of the biologically relevant dihydroxyphenyl (catechol-like) scaffold **23**. Acetophenone-derivatives acted as excellent starting substrates, further remarking the high degree of chemocontrol associated to the reductive homologation. The presence of sensitive groups is entirely tolerated, as illustrated by the iodo (**24**), bromo (**25**), chloro (**26-27**), fluoro (**28-29**) or trifluoromethyl (**30**) halogenated derivatives. Decorated aromatic rings with ethyl (**31**), *tert*-butyl (**32**), methoxy (**33**) and acetal (**34**) groups did not alter the efficiency of the process. The progressive elongation of the aliphatic chain of the acetophenone scaffold (**35-38**) was not detrimental. The chemoselectivity of the homologation conditions were inferred by the specific nucleophilic attack-reduction on the carbonyl of ω-chloro-propiophenone without observing any collateral modification (*e.g.* side homologation) on the constitutive -CH_2Cl fragment (**39**). Similarly, the chloromethyl derivatives of 1,2-diphenylethane (**40**), cyclohexyl-toluene (**41**) and alkylpyrazole (**42**) were synthesized with high yields and with excellent selectivity. The propargyl group did not influence the course of the reaction, furnishing **43**. Diaryl ketones have been shown to be highly versatile substrates during the transformation, as indicated by a series of (mono) substituted alkyls (**44-47**), including benzophenone derivatives bearing adamantyl (**48**) and aryl (**49**) groups. The alkoxy (**50**), alkyl thio (**51**) and arylseleno (**52**) groups can be conveniently incorporated into the benzophenone nucleus, since any Se-Li exchange was observed during the formation of the carbenoid. As a further confirmation of the chemoselectivity, potentially exchangeable halogens such as iodine (**53**), bromine (**54**), chlorine (**55**) and fluorine (**56** and **57**), or their derivatives as CF_3 (**58**) did not suffer any collateral reactions during the entire process. It is interesting to observe that an azide substituent did not undergo concomitant reduction and therefore it appeared intact at the end of the transformation (**59**). Symmetrical (**60** and **61**) and asymmetrical (**62** and **63**) disubstituted benzophenones reacted with high yields on the basis of the electronic nature of the substituents, including cases of heteroaromatic systems such as benzofuran (**64**) and dithienyl (**65**). The versatility of the method was also demonstrated by modifying the nature of the nucleophilic carbenoids: when $LiCH_2Br$ [86] was employed, bromomethyl analogs (**66** and **67**) were obtained in high yields and also on a larger scale (20 mmol, **66**); using the highly unstable $LiCH_2F$[131] it was possible to perform an efficient synthesis of the derivative **68**. In particular, tricyclic ketones as the xanthenic (**69**) and thioxanthenic (**70-72**) ones reacted with

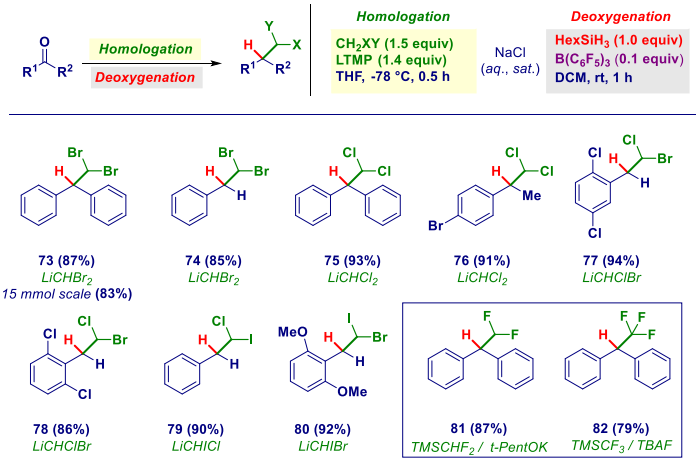
excellent results. From these extremely positive results, we decided to explore the scope of the reaction to the synthesis of dihalo derivatives, compounds that are still poorly investigated.[167-169]



Scheme 46. Scope of the reaction. Reactivity of $LiCH_2X$ towards aldehyde and ketones. Scheme modified from reference.[152]

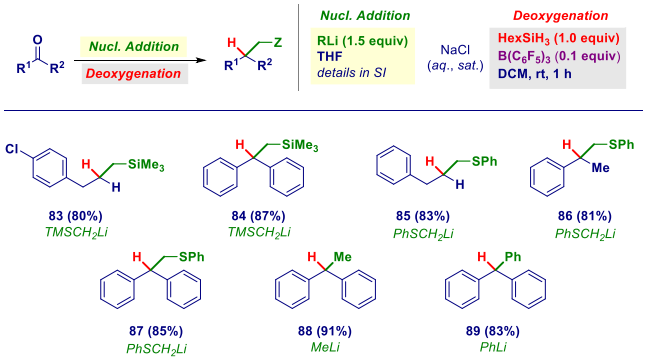
Benefitting from the inherent versatility of carbenoid precursors, the simple transition from a halogen-lithium exchange to a hydrogen-lithium exchange (*i.e.* deprotonation with LTMP) led to the formation of several dihalomethyl fragments (Scheme **47**) that rapidly reacted with aldehydes and ketones, thus giving, after deoxygenation, dibromo (**73** and **74**) and dichloro (**75** and **76**) derivatives. When a dialomethane (XCH_2Y), is treated with LTMP, it provides the corresponding carbenoids (LiCHXY).[53, 61, 72, 170, 171] Also in this case, the highly unstable species was able to react with aldehydes and ketones, in our conditions, with efficiency and good chemoselectivity. After deoxygenation, the chlorobromo (**77** and **78**), chloroiode (**79**) and bromoiode (**80**) derivatives were obtained at high yield and with high chemocontrol (Scheme **43**). As further proof of the applicability of the concept,

we have prepared the difluoromethyl (**81**) and trifluoromethyl (**82**) derivatives. The well known reluctance to the use of polyfluoromethyllium[172] was avoided using fluorinated silane precursors - $TMSCHF_2$[27] and $TMSCF_3$[173] - which, under adequate activation, provided the corresponding carbanions.



Scheme 47. Scope of the reaction. Synthesis of dihalo derivatives. Scheme modified from reference [152].

Our conceptually intuitive addition-deoxygenation sequence represents a formidable method of formation of new C-C bonds, as documented by the perfect extensibility to non-halogenated carbanions (Scheme **48**). Indeed, by adding an α-silyl methyl carbanion ($TMSCH_2Li$), the terminal silanes were produced starting from both an aldehyde (**83**) and a ketone (**84**), whereas the terminal thioethers were prepared through the reaction of carbonyls with a α-thio methyllium reagent (**85-87**). More generally, two non-functionalized organolithium reagents, *i.e.* MeLi and PhLi (selected as representatives of the model for the alkyl and aryl species), allowed us to obtain the corresponding trisubstituted methanes (**88** and **89**).



Scheme 48. Scope of the reaction. General nucleophilic addition/deoxygenation protocol with various carbanion-like reagents. Scheme modified from reference.[152]

In conclusion, it is possible to summarize the purpose of our work in the development of a two-step methods that allows the high-yield addition of two nucleophiles: a halogenated carbenoid (in the *homologation step*) and a hydride (in the *reductive step*). The overall operation therefore consists of two distinct events, the homologation, mediated by the reactivity of the carbenoids, and the deoxygenation mediated by the transfer of a hydride from a silane thanks to the $B(C_6F_5)_3$ catalysis. When the protocol is applied to various aldehydes and ketones as starting materials, a quite large series of halomethylalkyl derivatives can be obtained in high yields. The conditions established for both steps of the process are characterized by a very high chemocontrol, ensuring safe and reliable transformations in the presence of different sensitive functionalities such as halogens, olefins, alkynes, esters and so on. The solidity of the proposed logic, evaluated on *circa* 90 substrates presented, includes the addition not only of a wide range of mono- and halo-substituted methyl-type carbenoids, but also of fluorinated organolithium, silylates, mercapto and, more generally, simple alkyl and aryl Li reactants. In view of the great applicability of the proposed method, the concrete possibility of promoting the use of carbenoids and halogenated carbanions is increasingly emerging as a result of their high versatility in the panorama of the synthetic organic chemistry.

2.2. HOMOLOGATION OF WEINREB AMIDES WITH A CHF_2-CARBENE EQUIVALENT

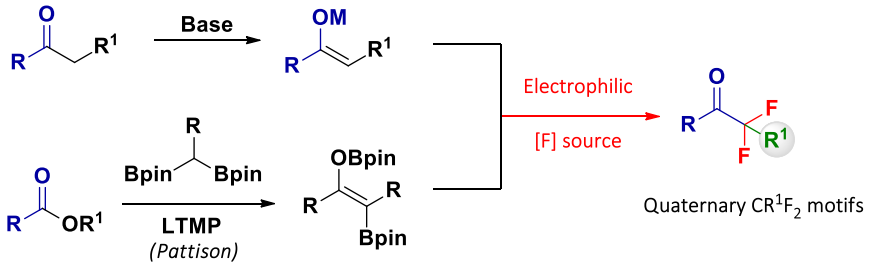
The introduction of the CHF_2 unit in organic substrates can deeply modify the chemical-physical properties of the newly obtained molecules.[174-186] In particular, among the many compounds that exhibit the -CHF_2 group, α,α-difluoromethyl ketones possess unique properties: the concomitant presence of the carbonyl group and the near difluoromethyl group makes these ketones H bond acceptors and donors at the same time.[187] The -CHF_2 in difluoromethyl ketones exhibits a weakly acidity since the α substitution with halogens decreases the pKa of the α-CH.[188] This leads to the possibility of this chemical environment to act as an isoster of important functional groups in Medicinal Chemistry such as the -OH, -SH group, hydroxamic acid and amide.[189]

In addition, the proximity of the difluoromethyl group significantly increases the electrophilicity of carbonyl carbon which becomes more susceptible to nucleophilic attack.[190, 191] This effect is believed to be associated with a decrease in the energy of the LUMO orbital of the carbonyl group and by increasing the substitution in α with fluorine atoms, this decrease intensifies;[192] the presence of fluorine also decreases the stability of the corresponding enolate.[193]

Unfortunately, the importance of difluoromethyl ketones clashes with a lack of rapid and efficient methods for their synthesis.[194-197] We can conceptually divide the strategies used for the synthesis of difluoromethylketones into two groups:

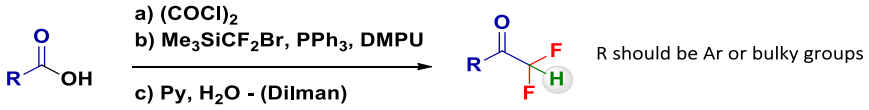
1. "Progressive introduction of fluorine through C−F bond formation operations" (Scheme **49**)
2. "Transfer of the difluorinated building block onto a proper acceptor, thus formally constituting a C−C bond formation event" (Scheme **50**)

In **Scheme 49** is reported the fluorination of ketone equivalents, wich involves the use of *enolate-like* materials and fluorine electrophilic sources (DAST, Selectfluor). This group of fluorination reactions occurs under electrophilic regime, *i.e.* the halogen atom is transferred from the electrophilic source to the acceptor (alkyne, activated enolate etc.). Unfortunately, this type of reactions does not show regioselectivity, it is also highly dependent on the structure of the nucleophile and on its reactivity. A step forward in the synthesis of difluoroketones has been made by Pattison and coworkers with homologative ester difluorination coupling with lithiated bis(boron) species, although with this technique it is possible to synthesize exclusively *quaternary* difluoromethyl ketones (completely α substituted) (Scheme **49**).[120, 198]



Scheme 49. Electrophilic fluorination of ketone equivalents. Scheme modified from reference [27].

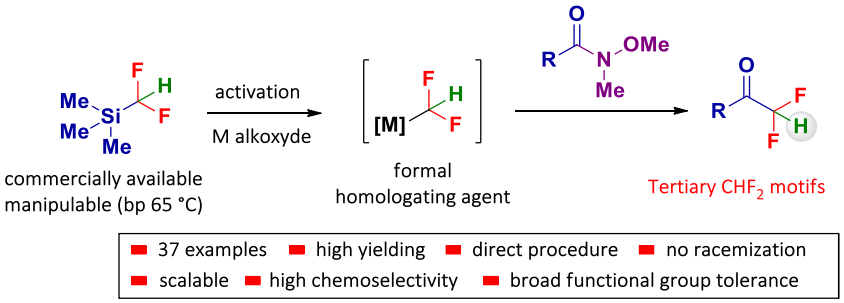
The second group of methodologies is represented by the direct transfer of the -CHF_2 unit, from a pro-nucleophilic donor to an electrophilic acceptor, realizing effectively a homologation reaction (Scheme **50**).[199]



Scheme 50. -CHF_2 formal transfer strategies. Scheme modified from reference [27].

-CHF_2 carbanion is unstable, therefore, for its efficient transfer and insertion onto electrophilic substrates, the presence of stabilizing elements, functional electron attracting groups, which can decrease their electronic density and increase their stability, is essential.[200-206] However, the use of these methods, such as the one reported by Kuhakarn,[207] provides for a multistep synthesis - with inevitable decreases in the reaction yield - and often the removal of these stabilizing elements results in compromising other sensitive functional groups within the molecule. Dilman first published a one-step protocol for the difluoromethylation of carboxylic acids, wich employ $TMSCF_2Br$ as a donor of the -CHF_2 unit, *via* the addition of difluorinated phosphorus ylide to acyl chlorides (Scheme **50**); unfortunately, this method does not allow to obtain difluoromethyl ketones, unless the starting material contains a bulky functional group (*e.g.* adamantane) because the reaction proceeds too quickly with a further difluoromethylation with the obtainment of a double adduct.[208] In 2011, difluoromethyl trimethylsilane ($TMSCHF_2$) was first used by Hu and coworkers for the difluoromethylation reactions.[186, 209] This reactant, in a similar way to trifluoromethyl trimethylsilane ($TMSCF_3$),[173, 210] used since years for trifluoromethylation reactions, requires stronger activation conditions[209] as the C-Si bond is stronger than its analog.

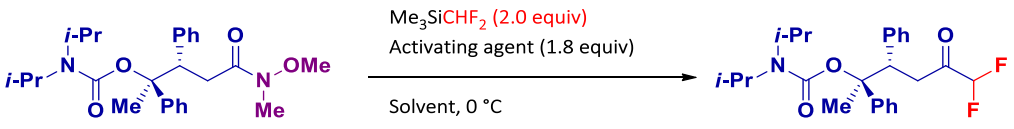
In our research team we used difluoromethyl trimethylsilane for difluoromethylative homologation of iso(thio)cyanates to difluoro(thio)amides.[28]



Scheme 51. First direct and chemoselective difluoromethylation of Weinreb amides. Scheme modified from reference.[27]

Behind the development of our work, we hypothesized that for a simple and intuitive synthesis of tertiary difluoromethylketones we could have used the difluoromethyl trimethylsilane as a donor of -CHF_2 moiety and Weinreb Amides as electrophilic substrates for carrying out the reaction.[65, 211-213] Weinreb Amides are highly competitive electrophilic substrates against carbanions and methyl type carbenoids.[214-217] In our research group, we used these substrates as electrophiles for the transfer of the highly reactive $LiCH_2F$ unit, thus realizing the first direct synthesis of monofluoromethyl ketones.[218]

Concerning the reaction optimization, we choose the Weinreb amide **90**,[219] which simultaneously bears two chiral centers, as starting material because we wanted to demonstrate the complete retention of stereochemical information during the process. At this point, we screened reaction conditions to find the best combination of solvent and activating agent, capable of freeing the CHF_2 carbanion and allowing its subsequent addition to the electrophile. TBAT and alkaline fluorides in DMF did not give adequate results (*entry 1-3*); moreover, the use of an amide solvent such as DMF can give rise to *self*-fluorination phenomena, as we can observe from crude ^{1}H NMR analysis. By switching the solvent, and using THF (*entry 4*), no reactivity is observed. By using potassium *t*-butoxide as the activating agent, it was possible to obtain an improvement in the yields of the reaction. However, there was observed substantial epimerization phenomena (*entry 5-6*). Finally, the use of a commercial solution of the more sterically indered potassium *t*-pentoxide (*i.e*. amylate, 0.9 M in cyclohexane) led to an increase in reaction yield of up to 91% and complete retention of stereochemical information (*entry 7*). THF gave the best results, in comparison with diethyl ether and toluene even after longer reaction times (*entry 8-9*); further, reducing the stoichiometry of the base, we can observe a dramatic decrease in the yield, and the same result is obtained by increasing the temperature of the reaction, probably due to a reduction in the stability of the carbanion. Finally, an important point to underline is the need to use Barbier type conditions: the electrophile and the pronucleophilic agent are present at the same time in the reaction mixture when the base is added, and the speed of formation of the carbanion and the its subsequent addition to the electrophile, are kinetically faster than the direct attachment of the base to the electrophile; in fact, the use of non-Barbier type conditions has led to a net decrease in the reaction yield.



90 91

entry	solvent	base	reaction time (h)	yield (%)	er
1	DMF	TBAT	8	Traces	-
2	DMF	KF/18-crown-6	8	27	95:5
3	DMF	CsF	8	15	96:4
4	THF	KF/18-crown-6	4	Traces	96:4
5	THF	Solid *t*-BuOK	4	63	96:4
6	THF	*t*-BuOK	4	75	96:4
7	**THF**	***t*-PentOK**	**4**	**91**	**99:1**
8	Et_2O	*t*-PentOK	8	52	97:3
9	Toluene	*t*-BuOK	8	75	98:2

[a] Otherwise stated reactions were run at 0 °C with *t*-PentOK 1 M solution in cyclohexane under Barbier-type conditions. [b] *t*-BuOK solid. [c] *t*-BuOK 1.0 M in THF. [d] Me_3SiCHF_2 (1.5 equiv) and *t*-PentOK (1.4 equiv) were used. [e] Reaction run at rt (23 °C). [f] Non-Barbier-type conditions (e.g., CHF_2-transfer agent generated from Me_3SiCHF_2 (2.0 equiv) and *t*-PentOK (1.8 equiv)) and then Weinreb amide **1** was added.

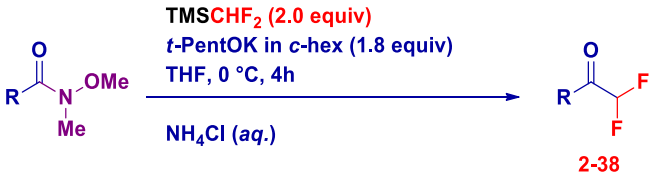
Table 2. Model Reaction: Optimization.[a]

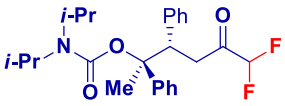
Scheme **52** describes the scope of the reaction:

- Cinnamoylic Weinreb amides are converted into the corresponding ketones (compounds **92-97**), in high yields, without affecting the double bond. In particular, substitutions on the cinnamoyl olefin function are perfectly tolerated, both in the presence of a Me group (compound **96**) and a F atom (compound **95**).
- Triple bonds do not influence the reactivity towards Weinreb amide position (compound **98**).
- Compounds **99-118** represent ideal examples of aromatic Weinreb amides for which the reaction proceeds quickly and with excellent yields. Electron-withdrawing and electron-donor substituents on the aromatic ring are tolered in any case, and even bulky groups in ortho do not influence the outcome of the reaction. Compound **101**, containing the terminal olefin, does not undergo any variation at level of the double bond during the process and it has been chosen to carry out *scale-up* tests (15 mmol) with lucky results. It is possible to substitute the aromatic ring with the complete set of halogens without affecting the

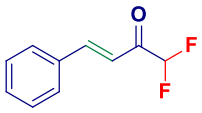
outcome of the reaction. The most important challenge has been overtaken by introducing electrophilic substituents (-CN, -$COCH_3$, -$COOCH_3$, etc.) in the aromatic ring that could compete with Weinreb amide: the reaction proved to proceed with a strong selectivity towards the Weinreb amide moiety without affecting the electrophile group.

- Using a starting material containing two Weinreb amide functions in *para* position, it was possible, by modulating equivalents and reaction temperature, to selectively accomplish the addition of -CHF_2 only to one out of the two reactive sites (compound **119**), leaving the other intact. In fact, by using mild reaction conditions (half equiv. of pronucleophile and -20 °C) it is possible to obtain the mono-addition derivative. On the other hand, if we increase the nucleophilic equivalents up to 3.0, a double addition product is obtained in excellent yields (compound **120**).

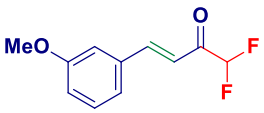




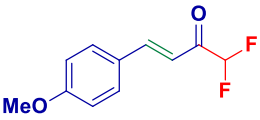
91 (93%, 99:1 *er*)



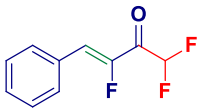
92 (92%)



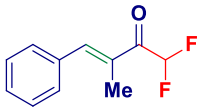
93 (91%)



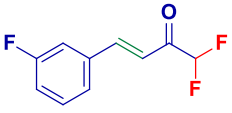
94 (91%)



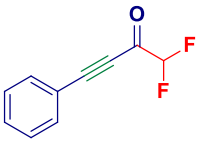
95 (94%)



96 (93%)



97 (93%)



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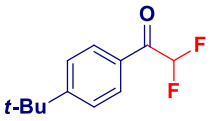

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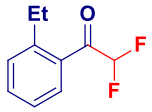

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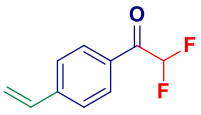
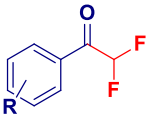
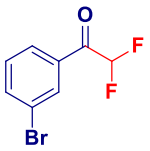


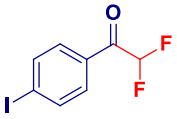
101 (94%)
15 mmol scale (90%)



102 (R= 2-Cl, 94%)
103 (R= 3-Cl, 92%)
104 (R= 4-Cl, 95%)



105 (91%)



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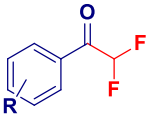

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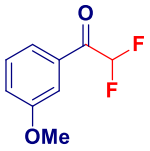
108 (R= 3-F, 89%)
109 (R= 4-F, 90%)



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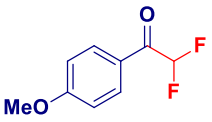

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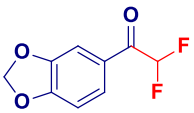

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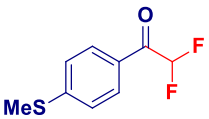
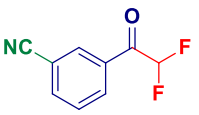
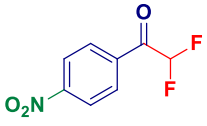


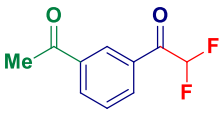
113 (94%)



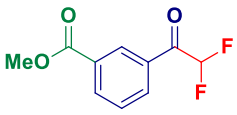
114 (73%)



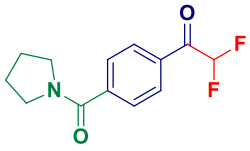
115 (90%)



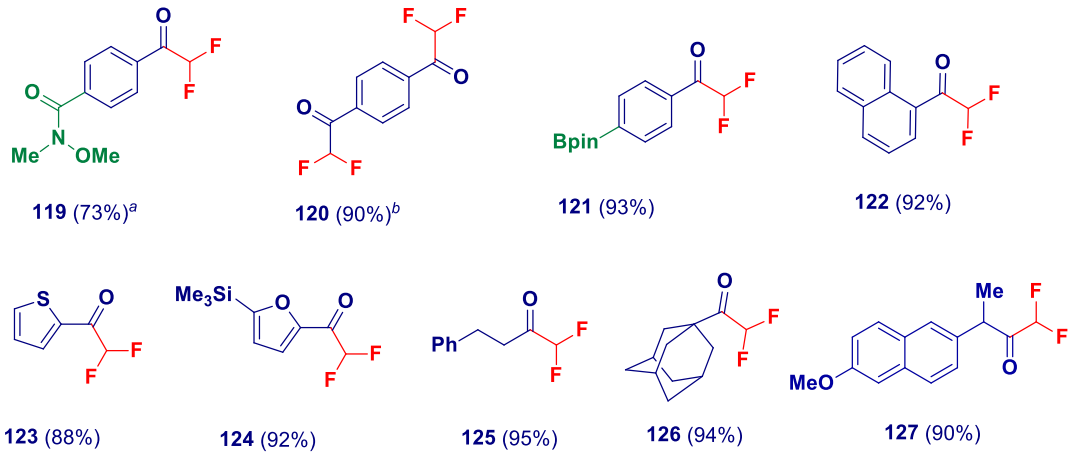
116 (95%)



117 (93%)



118 (77%)



[a] Reaction run with 1.0 equiv of nucleophile at -20 °C. [b] Reaction run with 3.0 equiv of nucleophile at 0 °C

Scheme 52. Scope of the reaction. Scheme modified from reference.[27]

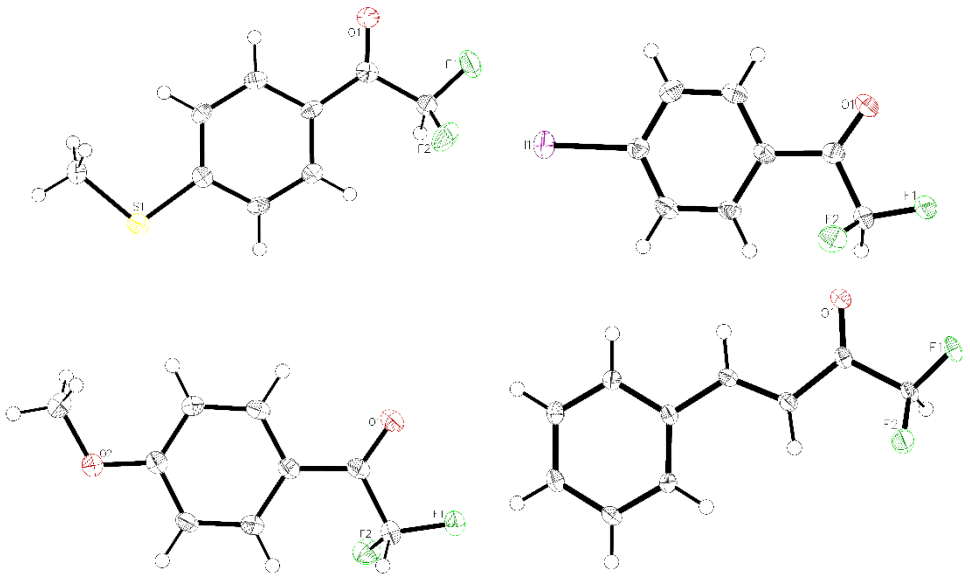


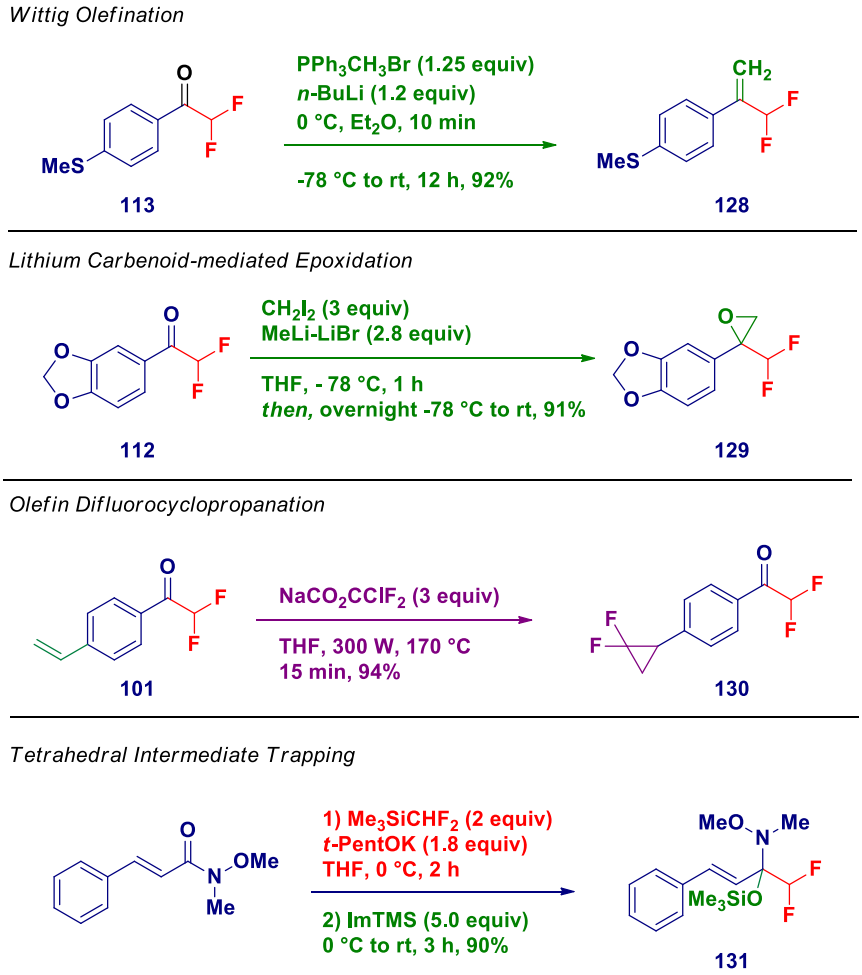
Figure 1. X-rays of compounds **113**, **106**, **111** and **125**.

Scheme **53** shows the applications of the reactions carried out on the synthesized compounds.

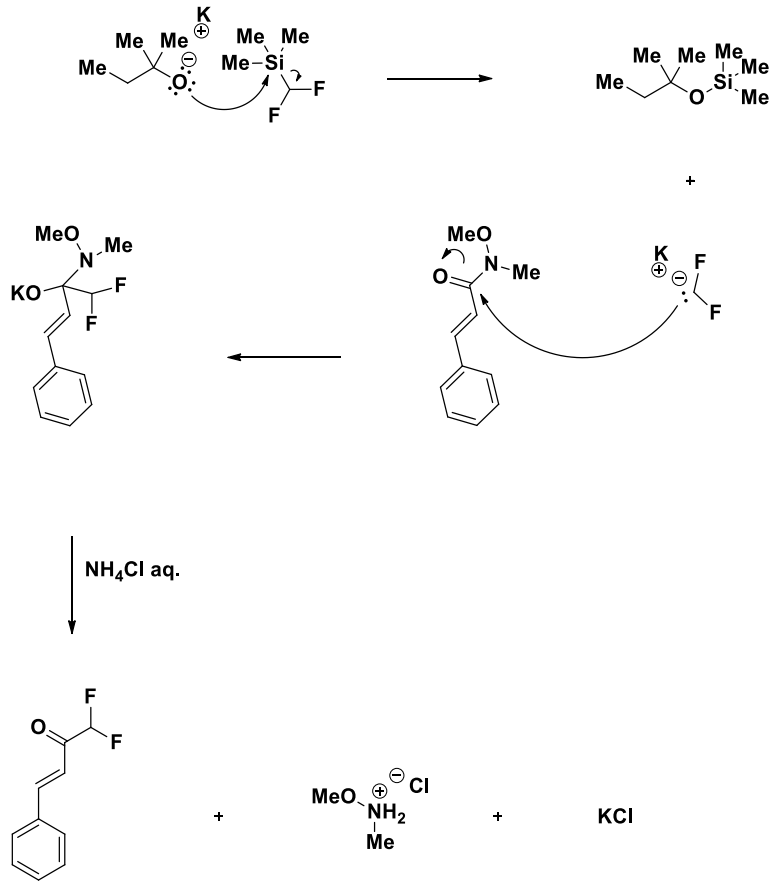
- A classic Wittig olefination led to the conversion of the carbonyl of compound **13** into an olefin (compound **128**).
- The rare α-difluoromethyl epoxyde[220, 221] **129** was synthesized in a single step procedure thanks to the addition of $LiCH_2Cl$ and subsequent cyclization.[170, 222]
- A simple microwave-assisted reaction led to the conversion of compound **101** into a not known difluorocyclopropane derivative **130** containing high density of fluorine atoms.[223]

Finally, in order to demonstrate that the reaction proceeds according to an *addition-elimination* mechanism, we isolated the tetraetric intermediate obtained by the addition of the CHF_2 carbanion, trapping it with TMS-imidazole in a procedure reported by our group (compound **131**).[224] Indeed, it is important to underline how such tetrahedral adducts could be relevant from a pharmacological point of view.[196]

Synthetic versatility of α,α-difluoromethylketones.



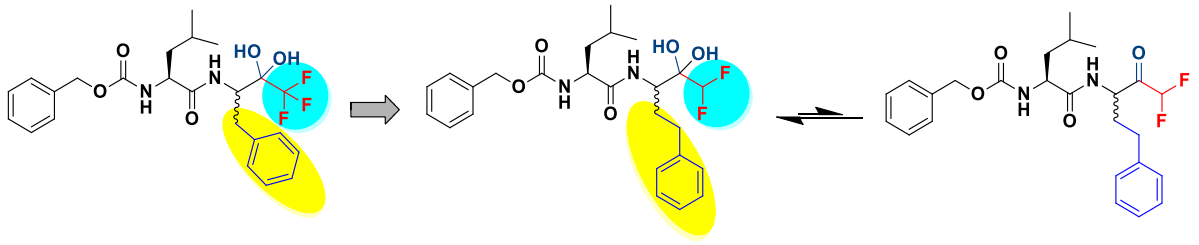
Scheme 53. Applications. Scheme modified from reference.[27]



Scheme 54. Proposed reaction mechanism.

2.3. SYNTHESIS AND BIOLOGICAL EVALUATION OF A PEPTIDE-BASED α,α-DIFLUOROMETHYL KETONE WITH ACTIVITY AGAINST CORONAVIRUSES

The final chapter of my doctoral thesis pertains the application of the homologation chemistry to the synthesis of a pseudodipeptide with biological activity against the human coronavirus hCoV-229E. Coronaviruses are a family of RNA viruses that cause respiratory diseases, from the common cold to severe pneumonia. Throughout history, three major epidemics that have plagued humanity have been caused by coronaviruses, namely SARS (2003, caused by SARS-CoV), MERS (2012, caused by MERS-CoV) and COVID-19 (2019-2020, caused by SARS-CoV-2).[225] The recurrence of such epidemics reflects the high urgency in finding new antiviral molecules that can fight coronaviruses. Peptide-based α-fluorinated ketones have long been considered as valuable compound in drug discovery as selective enzyme inhibitors and activity-based probes.[226] To date, a considerable number of α,α-difluoromethyl ketones (DFMKs) have been proposed mostly as protease inhibitors.[227-231] Besides, a considerable number of biologically active peptidic ketones bearing the *C*-terminal -$COCF_3$ moiety as electrophilic warhead have been developed.[226, 232] In details, the dipeptidyl TFMK **132** (drawn in its predominant hydrated form; Figure **2**) has shown activity against SARS-CoV M^{pro}, the main proteases involved in the maturation of viral proteins which are fundamental for coronaviruses replication.[233] However, compound **132** and its derivatives were no further investigated. Considering the urgency of the topic and the interest of our current research in the development of antiviral drugs,[234-236] we decided to synthesize the pseudopeptide Z-Leu-Homophe-CHF_2 (**133**) by making structural changes to the lead compound **132**, taken as a reference. The terminal -$COCF_3$ electrophilic group was replaced with -$COCHF_2$ and the Phe residue at P_1 was replaced by its superior homolog Homophe (Figure **2**).



132, Z-Leu-Phe-CF_3
SARS-CoV M^{pro} inhibitor
IC_{50} = 10 μM

133, Z-Leu-Homophe-CHF_2 (hydrated)

134, Z-Leu-Homophe-CHF_2 (ketone)

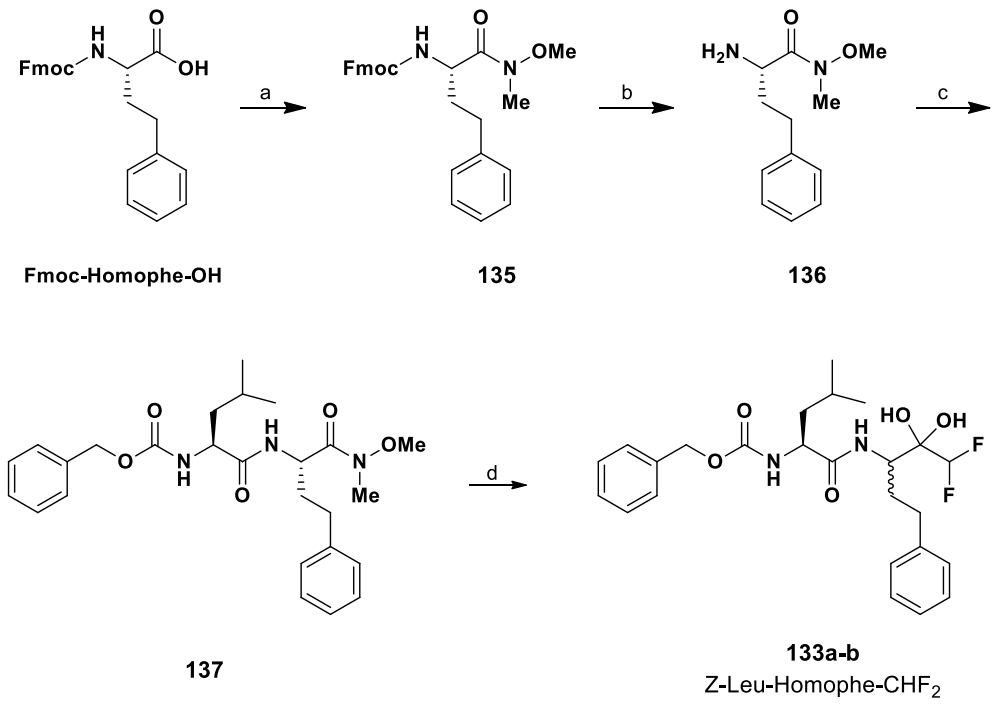
Figure 2. Lead compound TFMK **132** and Z-Leu-Homophe-CHF_2 in its hydrated form **133** and ketone form **134**.

2.3.1. CHEMISTRY

In our work, the preparation of **133** is configured as a direct application of the chemistry developed by our research group to a peptide-based structure. The direct introduction of the -CHF_2 group was discussed hereinabove and the same methodology was used to obtain the pseudopeptide derivative **133**. We strongly believe that the chemistry of methyl-type α-fluorinated carbanions can be of great importance in the development of new molecules with high biological potential.

The chemoselective synthesis of the dipeptidyl α,α-difluoromethyl ketone **133a-b** (Scheme **55**) consists in a four-step synthetic procedure starting from the commercially available Fmoc-Homophe-OH, which was converted into the corresponding Weinreb amide **135**. Then, the Fmoc group was cleaved off by piperidine treatment and the resulting amine **136** underwent a classical EDCI/HOBt coupling reaction to afford **137** in 65% yield. Finally, **137** was converted into **133a-b** via halocarbene transfer reaction with $TMSCHF_2$ in basic conditions.[27]

The reaction proved to be chemoselective, leaving unreacted the other functional groups but Weinreb amide and providing the designed α,α-difluoroketones in good yield (87%) as a mixture of two diastereomers (**133a-b**). An interesting feature concerning compounds **133a-b** is that these difluoromethyl ketones were isolated in their hydrated form, in agreement with what is reported in the literature for other (poly)α-fluoroketones.[237-240] The acidity of the amide groups of the peptide backbone did not interfere with the progress of the reaction; the deprotonation of the -CONH moieties was restored by an acidic work-up.



Scheme 55. Synthesis of Z-Leu-Homophe-CHF_2 (**133**). Reagents and conditions: a) CDI, DMHA, dry CPME, 0 °C to rt, on. b) Piperidine, dry DMF, 24 h, rt. c) Z-Leu-OH, EDCI, HOBt, dry DMF 0 °C to rt, on. d) $TMSCHF_2$, *t*-PentOK, dry THF, 0 °C, 4 h.

NMR spectroscopic data unequivocally indicated the presence of the hydrated form of compound **133** as a mixture of two diastereomers in the ratio 3:1. ^{1}H NMR spectrum of **133a-b** in methanol-d_4 exhibited the characteristic signal associated with the -CHF2 group (5.69 ppm major isomer; 5.73 minor isomer, $^{2}J_{H,F}$ = 54.4 Hz) (Figure **S1** in Experimental Section). As expected, under the experimental conditions, the compound underwent a partial racemization at the α position of the -$COCHF_2$ moiety. Furthermore, ^{13}C NMR spectrum did not show any carbonyl signal when performed in methanol-d_4; a peak at 96.8 ppm corresponding to the quaternary carbon of the hydrated ketone form was observed instead (Figure **S2** in Experimental Section). In markedly non-polar solvents such as benzene-d_6, the equilibrium was slightly shifted toward the ketone form **134a-b** as detected by the appearance of a carbonyl signal at 197.3 ppm in ^{13}C NMR spectrum (Figure **S3** in Experimental Section). HRMS spectrum displays the peak ascribed to the hydrated form as sodiated species at 501.2176 *m/z* $[M+Na]^+$ and the peak ascribed to the ketone form as sodiated species at 483.2065 *m/z* $[M+Na]^+$ (Figure **S4** in Experimental Section). These experimental data suggest that the equilibrium hydrated form/carbonyl form is affected by the medium.

2.3.2. BIOLOGICAL EVALUATION

The ability of Z-Leu-Homophe-CHF_2 to inhibit the replication of hCoV-229E, one of the four endemic human coronaviruses and a common cause of upper respiratory tract infections,[241] was investigated by a CPE-based assay in normal human lung fibroblasts. To this end, MRC5 cells were infected at low multiplicity of infection (MOI) to allow for multicycle replication and at an extended endpoint measurement (72 h post-infection, p.i.), and a cell viability assay was used as a surrogate of CPE to measure inhibition of hCoV-229E replication. As shown in Figure **3**, a significant concentration-dependent inhibition of the replication of hCoV-229 was observed in MRC5 cells treated with **133**. The EC_{50} and EC_{90} were 12.9 µM and 38.6 µM, respectively. Then, **133** cytotoxicity was evaluated in different types of uninfected cells, such as the lung fibroblasts MRC5 and HELFs, and the lung epithelial cells A549 (Figure **S5** in Experimental Section). The Cytotoxic Concentrations (CC_{50}) were 170 µM, 307 µM, and 174 µM for A549, HELFs, and MRC5 cells, respectively, thus indicating that the antiviral activity of **133** against hCoV-229E was not due to cytotoxicity of the target cells themselves.

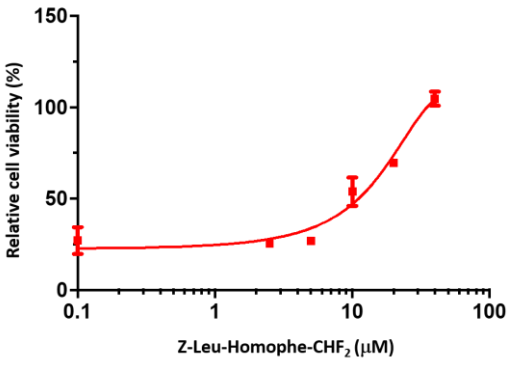


Figure 3. Antiviral activity of **133** against hCoV-229E. MRC5 cell monolayers were infected with hCoV-229E (100 PFU/well) and treated with increasing concentrations (0-40 µM) of Z-Leu-Homophe-CHF_2 during virus adsorption and throughout the experiment. At 72 h p.i., cell viability was measured using the CellTiter-Glo luminescent assay. The data shown represent means ± SD (error bars) of three independent experiments performed in triplicate.

2.3.3. COMPUTATIONAL

The 2.37 Å crystal structure resolution (PDB ID: 1P9U) of hCoV-229E M^{pro} [242] shows that the molecule is mainly made up of three domains (Figure **4a**). Domains I and II (residues 8 to 99 and 100 to 183, respectively) are six-stranded antiparallel β-barrels and resemble chymotrypsin and picornavirus 3C proteinases structure. The substrate-binding site is in a gap between these two domains. A long loop (residues 184 to 199) connects domain II to the C-terminal domain (domain III, residues 200 to 300). This latter domain, a globular cluster of five helices, has been implicated in the catalytic activity of M^{pro}.[243] hCoV Mpro forms a dimer (the contact interface is mainly located between the domain II of monomer A and the *N*-terminal residues of monomer B, is ~1300 Å 2) with the two molecules oriented perpendicular to each other. In the M^{pro} dimer, the *N*-terminal amino acid residues are compressed between domains II and III of the parent monomer and domain II of the other monomer, where they create a series of very specific interactions, made to bind this segment with high affinity after autocleavage. This mechanism would allow the catalytic site to bind to other cleavage sites in the polyprotein. Cys144 and His41, in the active site of hCoV-229E Mpro, form a catalytic dyad inside the S1' pocket.[242]

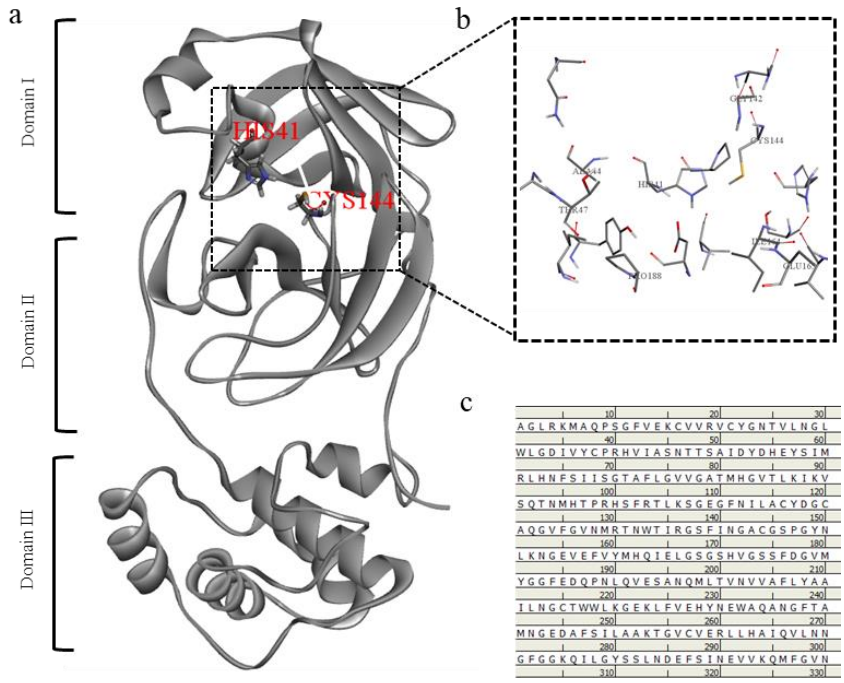


Figure 4. a) Cartoon representation of one protomer of the hCoV-229E M^{pro} (PDB ID: 1P9S). b) Amino acid residues of the catalytic site are indicated as stick. c) The amino acid sequences of M^{pro}.

Molecular modeling studies were conducted to identify and evaluate the receptor/ligand recognition's key molecular interactions. Molecular docking was performed using the crystal structure of hCoV-229E M^{pro} (PDB ID: 1P9U). The poses presenting the difluoro carbonyl group in the vicinity of the His41/Cys144 catalytic dyad were selected for further stability studies. All three selected poses show a different orientation of the phenethyl group and the isobutyl group (Figure **5a**) within the binding site. In fact, in pose 1 the phenethyl group is inserted inside the S2 sub-pocket, while in pose 2 the phenethyl is arranged in the region overlying the S1' pocket and the isobutyl group occupies the S2 sub-pocket. Pose 3 reverses the positions of the two groups with respect to pose 1. In fact, the phenethyl group is incorporated inside the S1 sub-pocket and the isobutyl group inside the S2 pocket. The only difference between pose 2 and pose 3 lies in the position of the phenethyl group.

To verify the reliability of the docking results, Molecular Dynamic (MD) simulations were performed, based on the results of the molecular docking. The first three Z-Leu-Homophe-CHF_2 docking poses were evaluated in complex with hCoV-229E M^{pro} for 5 ns of MD Simulation. To explore the dynamic stability of both systems and to ensure the rationality of the sampling method, progression of the root mean square deviations (RMSD) from the starting structure are analyzed (Figure **5b**). The superposition of coordinates of each complex structure in a trajectory onto the initial structure allowed us to analyze the RMSD of ligand and protein in complex. The RMSD graph of the ligand (Figure **5c**) indicates that the conformations of the complex in pose 1 reach equilibrium around 1.5 ns, while in pose 2 and pose 3 after 0.05 ns and 0.15 ns, respectively. Laying 2 provided a lower RMSD than the starting structure (2.11 Å), and the conformations oscillate on average around 1.3 Å. The protein structure in complex with the ligand in pose 2 also shows a more stable RMSD during MD Simulation, reaching equilibrium after 1.5 ns.

Consequently, we focused on pose 2 for further study. Indeed, it has been previously shown that the S2 sub-pocket in the human coronavirus hCoV-229E M^{pro} due to the limited size of the S2 pocket, the benzyl group (in the studied inhibitors) cannot enter deeply into this site, also due to the low plasticity of the pocket.[244] This could explain the better stability of the protein complex in pose 2.

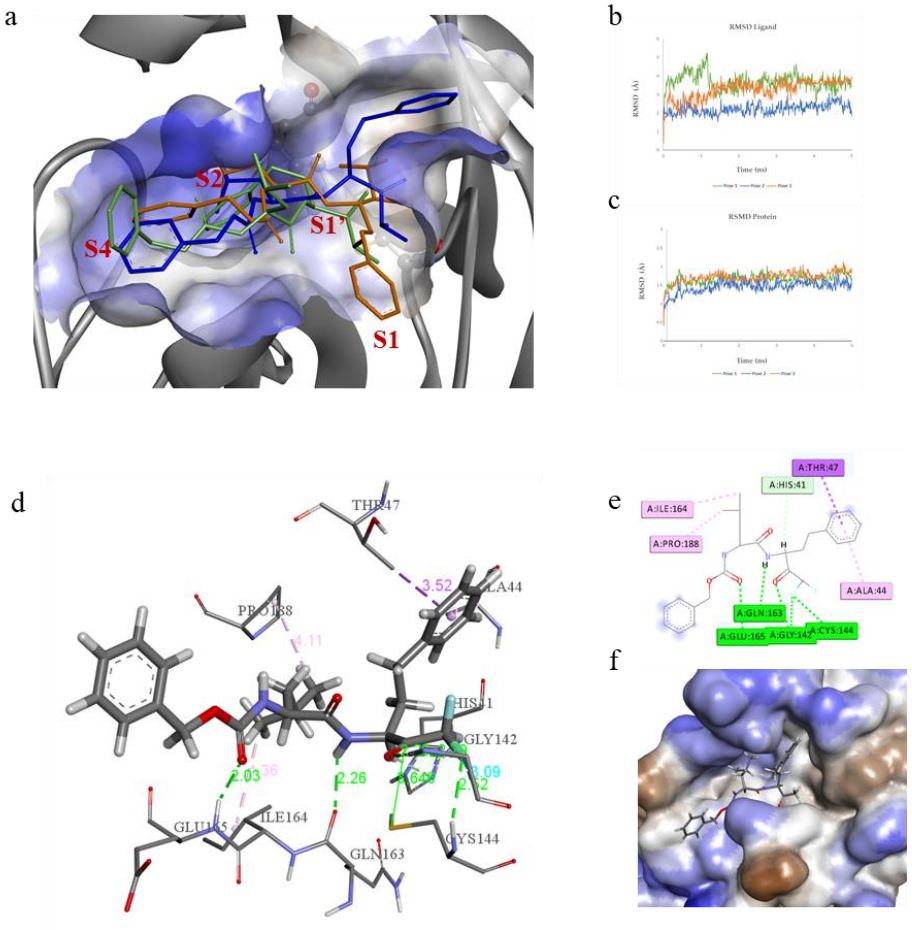


Figure 5. a) Results from molecular docking and their overlap in the hCoV-229E M^{pro} binding site: pose1 (green), pose2 (blue), and pose3 (orange). The binding site of hCoV-229E M^{pro} is represented as a hydrophobic surface (hydrophobic: brown, hydrophilic: blue, neutral: white). b), c) Time evolution of RMSD of backbone atoms of Mpro relative to their respective minimized structure and heavy atoms of poses. d) Detailed interactions of pose2 of Z-Leu-Homophe-CHF_2 inside the hCoV-229E M^{pro} binding site. Hydrogen bonds are represented as green dashed lines and hydrophobic interactions with pink dashed lines. e) 2D Interaction inside the binding pocket of the protein. f) Hydrophobic surface of hCoV-229E M^{pro} in complex with Z-Leu-Homophe-CHF_2.

Pose 2 at the binding site of hCoV-229E M^{pro} establishes H bonds with Gln163 and Glu165 at 2.03 Å and 2.36 Å, respectively. The isobutyl group is stabilized by hydrophobic interactions with Ile164 and Pro168 within the S2 pocket, while the phenethyl portion by the π-CH bond with Thr47 and π-alkyl with Ala44. The difluoromethyl ketone group is located at 3.46 Å from Cys144, stabilized by the H bond with Gln163 at 2.25 A. The H bonds between the fluorine atom and Gly142 and Cys144 at 2.59 Å and 2.52 Å could contribute together with Gln163 a stabilize the transition state during the nucleophilic attack on the carbonyl group.

A 100 ns MD Simulation was performed to analyze in greater detail any changes in the protein-ligand complex. The protein structure and the ligand reached equilibrium after 30 ns and a very similar average RMSD, 2.1 Å, and 2.3 Å for ligand and protein, respectively (Figure **S6** in Experimental

Section). The flexibility of the different residues of hCoV-229E M^{pro}, by calculating the root mean square oscillations (RMSFs) of Cα atoms, was analyzed. A relatively higher RMSF value is obtained around residue 50 (domain I), while more excellent stability occurs in domain II.

Furthermore, to understand the effect of Z-Leu-Homophe-CHF_2 binding on the internal dynamics of hCoV-229E M^{pro}, the dynamic cross-correlation matrix (DCCM) was calculated by using the coordinates of Cα atoms from the trajectories. Domain I (residues 8-99) display correlated motions while domain II (residues 100-183) shows highly anti-correlated movements. However, domain III (residues 201-300) has a lower strength of anti-correlation motions relative to the domain I. Further, it is evident from (Figure **S6** in Experimental Section) that the inhibitor binding increases the strength of anti-correlated motions in the region of domain II, which indicates the residual motion of domain III. Overall, the binding of Z-Leu-Homophe-CHF_2 with M^{pro} creates a stable environment near the binding cavity.

Given the high similarity between hCoV-229E M^{pro} and SARS-CoV-2 M^{pro} we decided to investigate the in silico affinity between Z-Leu-Homophe-CHF_2 with SARS-CoV-2 M^{pro}. However, there are many common features shared between the two types of proteases, particularly their almost absolute requirement for Gln in the S1 position of the substrate and space for only small amino-acid residues as a common target for the design of broad-spectrum antiviral compounds. The fact that there is no known human protease with a specificity for Gln at the substrate's cleavage site increases the attractiveness of this viral target, as there is hope that the inhibitors to be developed will not show toxicity versus the host cell.

Table 1. Calculated binding energies (kcal/mol) and K_i (μM) for the binding sites of hCoV-229E M^{pro} and SARS-CoV-2 M^{pro} receptors for Z-Leu-Homophe-CHF_2.

Enzyme	Calcd. Δ*G*	Calcd. K_i (μM)
hCoV-229E M^{pro}	−7.0	7.3
SARS-CoV-2 M^{pro}	−7.3	4.4

The high similarity of the binding site (Figure **6c**) between the two enzymes produced comparable results in energy of binding and docking pose. Indeed, the free energy of binding (Table **1**) showed a slightly lower value for SARS-CoV-2 M^{pro} (ΔG = −7.3 kcal/mol) than for hCoV-229E M^{pro} (ΔG = −7.0 kcal/mol).

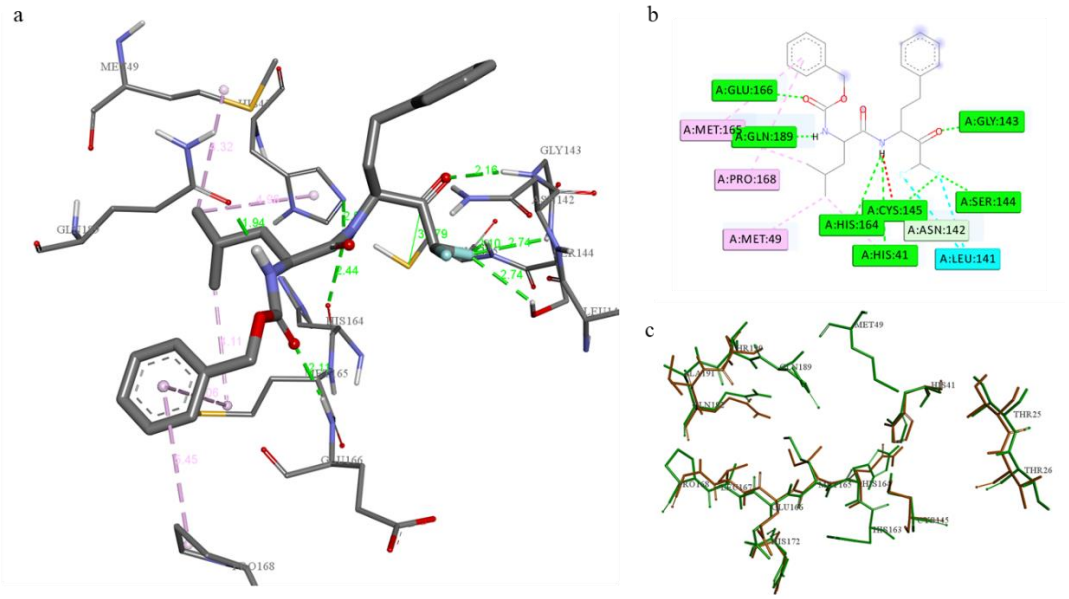


Figure 6. a) Detailed interactions of pose2 of Z-Leu-Homophe-CHF_2 inside the SARS-CoV-2 M^{pro} binding site. b) 2D Interaction inside the binding pocket of the protein. c) Alignment of amino acids of the binding site of hCoV-229E M^{pro} (green) and SARS-CoV-2 M^{pro} (orange).

By visualizing in detail, the pose of Z-Leu-Homophe-CHF_2 inside the pocket of SARS-CoV-2 M^{pro} we can see that the difluoromethyl ketone is located at a distance of 3.38 A from Cys145, optimal for a nucleophilic attack on the carbonyl group. The oxygen atom of the aldehyde group also plays a crucial role in stabilizing the inhibitor's conformations by forming a 2.16 Å hydrogen bond with the backbone of residue Cys143 at the S1' site. Furthermore, the amide bonds on the Z-Leu-Homophe-CHF_2 chain form hydrogen bonds with the main chains of Cys145 (3.44 Å), Glu 166 (2.11 Å), and Gln 189 (1.94 Å), respectively. The isobutyl moiety of Z-Leu-Homophe-CHF_2 in S2 inserts deeply into the S2 site, stacking with the imidazole ring of His 41. The side chains of Met49, Met165, Asp187, and Pro168, also surround the isobutyl group producing extensive hydrophobic interactions. Furthermore, the difluoromethyl ketone moiety is further stabilized by the halogen interaction with Leu141 at 3.68 Å and the H-halogen bonds with Ser144 and Cys145 at 2.74 Å.

A detailed analysis of the trajectories developed by MD Simulation highlights the good stability of the protein-ligand complex. Z-Leu-Homophe-CHF_2 reaches equilibrium after 20 ns, while the protein structure seems to reach a slight flexion at 65 ns, remaining, however, at low RMSD levels. The DCCM plots (Figure **S7** in Experimental Section) of the Z-Leu-Homophe-CHF_2-SARS-CoV-2 M^{pro} complex shows a correlation region in the binding site domain and anti-correlation zones in domain II and domain III, confirming the analysis of RMSFs (Figure **S7** in Experimental Section) showing fluctuations between the residues 40–70 (domain II) and 210-240 (domain III).

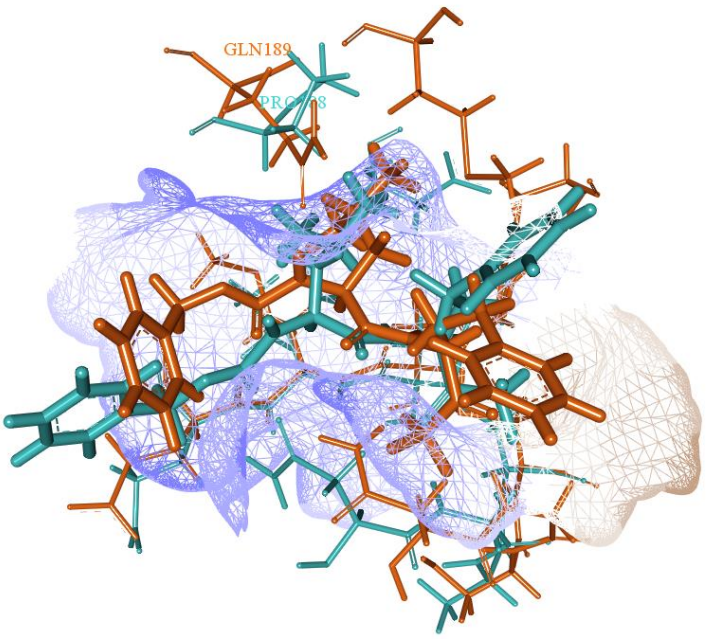


Figure 7. Alignment of the binding site amino acids of hCoV-229E M^{pro} (marine green) and SARS-CoV-2 M^{pro} (orange) in complex with Z-Leu-Homophe-CHF_2 represented as a hydrophobic surface (hydrophobic: brown, hydrophilic: blue, neutral: white).

Despite the small size of the isobutyl substituent, this is possible because the S2 pocket of SARS-CoV-2 M^{pro} is flexible enough to contract and enclose small substituents. This plasticity is expressed in a conformational change of residue Gln189, both in the main and side chains. As a consequence of these changes, the side-chain oxygen of Gln189 can accept a 1.94 Å hydrogen bond from the main-chain NH residue in the Z-Leu-Homophe-CHF_2 complex (Figure **7**). However, the affinity of Z-Leu-Homophe-CHF_2 for the S2 pocket of hCoV-229E M_{pro} is good because of an almost ideal match of size and not requiring conformational changes, which this enzyme would not be able to undergo because of the replacement of the flexible Gln189 by the more rigid proline.[244] The more remarkable plasticity of the S2 pocket can accommodate the isobutyl substituent deeper. Thus, both effects could increase the stability, hence the affinity, of Z-Leu-Homophe-CHF_2 against SARS-CoV-2 M^{pro}.

3. CONCLUSIONS

To sum up, my PhD thesis represents a valid planning approach wherein the Synthetic Organic Chemistry matches the applicability requirements of the Medicinal Chemistry. The aim of my work was to find and carry out novel and straightforward synthetic methods to construct fluorinated functionalities in order to employ them as electrophilic warheads of organic substrates with the perspective of obtaining pharmacologically active compounds. The discovery of innovative synthetic methodologies can accelerate the development of new drugs and can have great academic and industrial relevance. Organometallic chemistry is often considered to be of poor applicability and with my work, I wanted to emphasize how nucleophilic organometallic reagents, such as carbenoids, can provide an exceptional tool for the development of biologically active derivatives, as evidenced by the discovery of the dipeptidyl derivative Z-Leu-Homophe-CHF_2 which turned out to be able to exert a notable cytoprotective effect towards cells infected with one of the viruses of the *Coronaviridae* family, *i.e.* hCoV-229E, with a very low cytotoxic profile on healthy cells. Moreover, docking and molecular dynamics studies performed on Z-Leu-Homophe-CHF_2 indicated that this compound may bind to the cysteinic main protease (M^{pro}) of the coronaviruses, including SARS-CoV-2 M^{pro}, making it a candidate as lead structure for future drug design on this topic. Finally, the great versatility of these synthetic methodologies is highlighted even more by the possibility of introducing fluorinated syntons into organic molecules, providing the substrates with unique characteristics deriving from the presence of fluorine.

4. EXPERIMENTAL SECTION

4.1. MATERIALS AND METHODS

4.1.1. CHEMISTRY

Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Brüker maXis 4G instrument (ESI-TOF, HRMS). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 297 K on a Brüker Avance III 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 40 MHz for ^{15}N, 376 MHz for ^{19}F) equipped with a directly detecting broadband observe (BBFO) probe, with a Brüker Avance III 500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C) using a Prodigy cryoprobe, and with a Brüker DRX 200 spectrometer (200 MHz for ^{1}H, 50 MHz for ^{13}C) with a $^{1}H/^{13}C$ dual probe.
The centre of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$), δ 7.16 ppm (^{1}H in C_6D_6), δ 77.00 ppm (^{13}C in $CDCl_3$) and δ 128.06 ppm (^{13}C in C_6D_6), 4.87 ppm (^{1}H in CD_3OD) and 49.00 ppm (^{13}C in CD3OD). Absolute referencing via *Ξ* ratio was used for the ^{19}F 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 pre-coated with silica gel 60 F_{254} (Macherey-Nagel, Merk); the spots were visualised under UV light (λ = 254 nm).

4.1.2 BIOLOGICAL ASSAYS

4.1.2.1. Cells and viruses

Low-passage human embryonic lung fibroblasts (HELFs) were prepared and grown as monolayers in MEM supplemented with 10% FBS (Euroclone), 1 mM sodium pyruvate, 2 mM glutamine, 100 U ml^{-1} penicillin and 100 µg/ml streptomycin sulphate. MRC5 (ATCC® CCL-171™) lung fibroblasts were purchased from the American Type Culture Collection (ATCC) and cultured in Eagle's Minimum Essential Medium (MEM; EuroClone) supplemented with 10% fetal bovine serum (FBS, Euroclone), 2 mM glutamine, 1 mM sodium pyruvate, 100 U/ml penicillin, and 100 µg/ml streptomycin sulfate (P/S, both from Euroclone). Lung epithelial A549 (ATCC® CCL-185™) cells were purchased from ATCC and cultured in cultured in Dulbecco's Modified Eagle Medium (DMEM; EuroClone) supplemented with 10% fetal bovine serum (FBS, Euroclone), 2 mM glutamine, 1 mM sodium pyruvate, 100 U/ml penicillin, and 100 µg/ml streptomycin sulfate (P/S, both from Euroclone). The human coronavirus 229E (ATCC® VR-740™) was purchased from the ATCC and propagated and titrated on MRC5 cells.

4.1.2.2. Cytotoxicity assay

HELFs, MRC5, or A549 cells were seeded in a 96-well plates (18000 cells/well) and after 24 h the cells were exposed to increasing concentrations of Z-Leu-Homophe-CHF_2 (**133**) or vehicle (DMSO), as control. After 72 h of incubation, the number of viable cells was determined using the CellTiter-Glo Luminescent assay (Promega) according to the specifications of the manufacturer.

4.1.2.3. Antiviral assay

To evaluate the antiviral activity of different concentrations of Z-Leu-Homophe-CHF_2, MRC5 cells seeded in 48-well plates (30000 cells/well) and then treated with different concentrations of the compound during infection with hCoV-229E at 100 PFU/well. Following virus adsorption (2 h at 37 °C), viral *inocula* were removed, and cells were maintained in medium containing the corresponding compounds, and 2% FBS. Cells treated with vehicle (DMSO) and cells infected and treated with vehicle were used as mock infection control for normalization and infection control, respectively. After 72 h p.i., cell viability was measured using CellTiter-Glo assay as a surrogate measurement of the viral cytopathic effect (CPE). The mean values for Z-Leu-Homophe-CHF_2 were normalized to the mean values for the mock-infected control cells (DMSO-treated), and the concentration that produced a 50% of reduction cell viability (EC_{50}) was determined by GraphPad Prism software, version 7.

4.1.3. COMPUTATIONAL

4.1.3.1. Molecular docking

Flexible ligand docking experiments, successfully used in our previous work[234, 245-250], were performed employing AutoDock 4.2.6 software implemented in YASARA (v. 20.10.4, YASARA Biosciences GmbH, Vienna, Austria)[251, 252] using the three-dimensional crystal structure of hCoV-229E M^{pro} (PDB ID: 1P9S), the three-dimensional crystal structure of SARS-CoV-2 M^{pro} in complex with an inhibitor N3 PRD_002214 (PDB ID: 6LU7), both obtained from the Protein Data Bank (PDB, http://www.rcsb.org/pdb), and the Lamarckian genetic algorithm (LGA). The covalent bond between the Cys145 residue and the crystallized ligand has been eliminated. His41 and Cys145 residues were protonated and optimized using YASARA software. The maps were generated by the program AutoGrid (4.2.6) with a spacing of 0.375 Å and dimensions that encompass all atoms extending 5 Å from the surface of the structure of the crystallized ligands. All the parameters were inserted at their default settings, as previously reported. In the docking tab, the macromolecule and ligand are selected, and GA parameters set as ga_runs = 100, ga_pop_size = 150, ga_num_evals = 25000000, ga_num_generations = 27000, ga_elitism = 1, ga_mutation_rate = 0.02, ga_crossover_rate = 0.8, ga_crossover_mode = two points, ga_cauchy_alpha = 0.0, ga_cauchy_beta = 1.0, number of generations for picking worst individual = 10. Since no water molecules are directly involved in complex stabilization, they were not considered in the docking process. All protein amino acid residues were kept rigid, whereas all single bonds of ligands were treated as fully flexible.

4.1.3.2. Molecular optimization

The semiempirical calculations were performed using the parameterized model number 6 Hamiltonian as implemented in MOPAC package (J.J.P. Stewart, MOPAC2016, (2017)) (MOPAC2016 v. 18.151, Stewart Computational Chemistry, Colorado Springs, Colorado, USA).

4.1.3.3. Molecular dynamics simulations

The MD simulations of the M^{pro}/ligand complexes were performed with the YASARA Structure package (19.11.5). A periodic simulation cell with boundaries extending 8 Å from the surface of the complex was employed. The box was filled with water, with a maximum sum of all bumps water of 1.0 Å, and a density of 0.997 g/mL with explicit solvent. YASARA's pK_a utility was used to assign pK_a values at pH $7.4^{253253253251245}$, and system charges were neutralized with NaCl (0.9% by mass). Water molecules were deleted to readjust the solvent density to 0.997 g/mL. The final system dimensions were approximately 80 × 80 × 80 $Å^3$. The ligand force field parameters were generated with the AutoSMILES utility, employs semiempirical AM1 geometry optimization. Moreover, the assignment of charges, by the assignment of the AM1BCC atom and bond types with refinement using the RESP charges, and finally, the assignments of general AMBER force field atom types. Optimization of the hydrogen bonds network of the various enzyme-ligand complexes was obtained using the method established by Hooft *et al.*. This model allowed us to address ambiguities arising from multiple side-chain conformations and protonation states that are not well resolved in the electron density. A short MD simulation was run on the solvent only. The entire system was then energy minimized using first a steepest descent minimization to remove conformational stress, followed by a simulated annealing minimization until convergence (<0.01 kcal/mol Å). The MD simulation was then initiated, using the NVT ensemble at 298 K, and integration time steps for intramolecular and intermolecular forces every 1.25 fs and 2.5 fs, respectively. Finally, short 5 ns MD simulations were conducted for the assessment of the correct pose and a final MD simulation of 100 ns was performed. The conformations of each system were recorded every 100 ps.

4.2. GENERAL PROCEDURES

4.2.1. GENERAL PROCEDURE **1**

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 Et_2O (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 mixture was extracted with dichloromethane (3 x 3 mL) and the organic phase dried over anhydrous Na_2SO_4. 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.*) NH_4Cl (3 mL) and extracted with dichloromethane (3 mL). The organic layer was washed with saturated (*aq.*) NaCl

(5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (bath: rt) to give the crude compound eventually purified as indicated below.

4.2.2. GENERAL PROCEDURE **2**

Preparation of LTMP. Freshly distilled 2,2,6,6-tetramethylpiperidine (TMP) was added to THF (3 mL) and the resulting mixture was cooled at 0 °C. Then, MeLi-LiBr (2.2 M solution in Et_2O) was added dropwise over 10 min. The so obtained solution was transferred *via* cannula to the solution indicated below.

Homologation / Deoxygenation sequence. To a solution of carbonyl compound (aldehyde or ketone, 1 equiv) in dry THF (3 mL) cooled at -78 °C, the dihalomethane carbenoid precursor was added (1.5 equiv) under Argon atmosphere. After 10 min, the above prepared LTMP solution (1.4 equiv) was added *via* syringe pump (0.20 mL/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 mixture was extracted with dichloromethane (3 x 3 mL) and the organic phase dried over anhydrous Na_2SO_4. 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.*) NH_4Cl (3 mL) and extracted with dichloromethane (3 mL). The organic layer was washed with saturated (*aq.*) NaCl (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (bath: rt) to give the crude compound eventually purified as indicated below.

4.2.3. GENERAL PROCEDURE **3**

To a solution of carbonyl compound (1 equiv) in dry THF (3 mL) cooled at 0 °C, difluoromethyltrimethylsilane (1.5 equiv) was added under Argon atmosphere. Then, potassium *tert*-pentoxide 0.9 M in toluene (1.4 equiv) was added *via* syringe pump (0.20 mL/min) at 0 °C during a period of 15 min. The reaction mixture was further stirred to reach rt within 4 h. Subsequently, a saturated (*aq.*) NaCl was added to the mixture and the cooling bath was removed; the mixture was extracted with dichloromethane (3 x 3 mL) and the organic phase dried over anhydrous Na_2SO_4. 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.*) NH_4Cl (3 mL) and extracted with dichloromethane (3 mL). The organic layer was washed with saturated (*aq.*) NaCl (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (bath: rt) to give the crude compound eventually purified as indicated below.

4.2.4. GENERAL PROCEDURE **4**

To a solution of carbonyl compound (1 equiv) in dry THF (3 mL) cooled at 0 °C, trifluoromethyltrimethylsilane (1.5 equiv) was added under Argon atmosphere. Then, tetrabutylammonium fluoride (TBAF) solution 1.0 M in THF (1.4 equiv) was added *via* syringe pump (0.20 mL/min) at 0 °C during a period of 15 min. The reaction mixture was further stirred to reach rt within 6 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 Na_2SO_4. 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.*) NH_4Cl (3 mL) and extracted with dichloromethane (3 mL). The organic layer was washed with saturated (*aq.*) NaCl (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (bath: rt) to give the crude compound eventually purified as indicated below.

4.2.5. GENERAL PROCEDURE **5**

To a solution of carbonyl compound (1 equiv) in dry THF (3 mL) cooled at -50 °C, the competent organolithium reagent (1.5 equiv) was added under Argon atmosphere *via* syringe pump (0.20 mL/min). The reaction mixture was further stirred to reach 0 °C within 2 h. Subsequently, a saturated (*aq.*) NaCl was added to the mixture and the cooling bath was removed; the mixture was extracted with dichloromethane (3 x 3 mL) and the organic phase dried over anhydrous Na_2SO_4. 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.*) NH_4Cl (3 mL) and extracted with dichloromethane (3 mL). The organic layer was washed with saturated (*aq.*) NaCl (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (bath: rt) to give the crude compound eventually purified as indicated below.

4.2.6. GENERAL PROCEDURE **6**

Preparation of $LiCH_2SPh$. To a solution of thioanisole (1.5 equiv) in dry THF (3 mL) cooled at 0 °C, under Argon atmosphere, 1,4-diazabicyclo[2.2.2]octane (DABCO, 1.5 equiv) was added. Then, *n*-butyllitium 2.5 M in *n*-hexane (1.4 equiv) was added dropwise for 1.5 h, before transferring *via* cannula to the solution indicated below containing the carbonyl compound.

Addition to the carbonyl compound / deoxygenation sequence. To a solution of carbonyl compound (1 equiv) in dry THF (3 mL) cooled at 0 °C, the THF solution of $LiCH_2SPh$ prepared above (1.5 equiv) was added under Argon atmosphere was added *via* syringe pump (0.20 mL/min). The reaction mixture was further stirred for further 3 h at this same temperature. Subsequently, a saturated (*aq.*) NaCl was added to the mixture and the cooling bath was removed; the mixture was

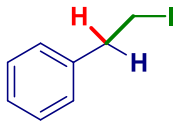
extracted with dichloromethane (3 x 3 mL) and the organic phase dried over anhydrous Na_2SO_4. The filtered solution was flushed under argon and tris(pentafluorophenyl)borane (0.1 equiv) was incorporated to it at room temperature. After 2 min, hexylsilane (1 equiv) was added in one pot and, the reaction was stirred for 1 h. Finally, the mixture was quenched with saturated (*aq.*) NH_4Cl (3 mL) and extracted with dichloromethane (3 mL). The organic layer was washed with saturated (*aq.*) NaCl (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (bath: rt) to give the crude compound eventually purified as indicated below.

4.2.7. GENERAL PROCEDURE **7**

To a solution of Weinreb amide (1 equiv) in dry THF (5 mL) cooled at 0 °C was added (difluoromethyl)trimethylsilane (2 equiv) under Argon atmosphere. Then potassium *tert*-pentoxide 0.9 M (1.8 equiv) was added dropwise with good stirring at 0 °C during a period of 15 min. The reaction mixture was further stirred to reach rt within 4 h. After complete conversion of the starting material, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (3 mL) and extracted with Et_2O (3 × 5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure (bath: rt). The crude was purified *via* column chromatography on silica gel to afford the corresponding pure compound.

4.3. CHARACTERIZATION DATA

(2-Iodoethyl)benzene (2)



By following the **General procedure 1**, 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).

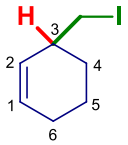
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.28 (m, 1H, Ph H-4), 7.20 (m, 2H, Ph H-2,6), 3.56 (m, 2H, CH_2I), 3.19 (m, 2H, CH_2).

^{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).

HRMS (ESI), *m/z*: calcd. for $C_8H_9INa^+$: 254.9641 $[M+Na]^+$; found: 254.9643.

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

3-(Iodomethyl)cyclohexene (3)



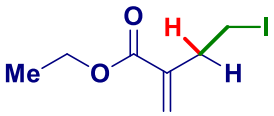
By following the **General procedure 1**, starting from cyclohex-2-enone (200 mg, 2.08 mmol, 1 equiv) in dry THF (3 mL), diiodomethane (0.3 mL, 3.12 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.32 mL, 2.9 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (107 mg, 0.2 mmol, 0.1 equiv) and hexylsilane (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.

Ethyl 4-Iodo-2-methylidenebutanoate (4)



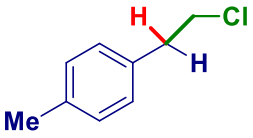
By following the **General procedure 1**, starting from ethyl 2-formylacrylate (200 mg, 1.56 mmol, 1 equiv) in dry THF (3 mL), diiodomethane (0.2 mL, 2.34 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (80 mg, 0.2 mmol, 0.1 equiv) and 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 v/v 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$$CH_3$), 3.32 (t, *J* = 7.2 Hz, 2H, $CH_2C\underline{H}_2I$), 2.86 (dt, J_t = 7.2 Hz, J_d = 1.2 Hz, 2H, C$\underline{H}_2$$CH_2I$), 1.31 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2 (C=O), 138.8 ($\underline{C}$=CH_2), 127.2 (C=$\underline{C}$$H_2$), 60.9 (O$\underline{C}$$H_2CH_3$), 36.4 ($\underline{C}$$H_2CH_2I$), 14.2 ($OCH_2\underline{C}H_3$), 3.9 ($CH_2\underline{C}H_2I$).

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

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



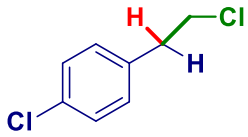
By following the **General procedure 1**, starting from 4-methylbenzaldehyde (200 mg, 1.66 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.2 mL, 2.49 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (85 mg, 0.17 mmol, 0.1 equiv) 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-Chloro-4-(2-chloroethyl)benzene (6)



By following the **General procedure 1**, 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).

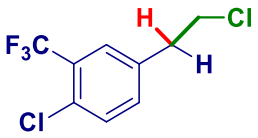
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29 (m, 2H, Ph H-2,6), 7.16 (m, 2H, Ph H-3,5), 3.69 (t, 2H, $^3J_{H,H}$ = 7.2 Hz, CH_2Cl), 3.04 (t, 2H, $^3J_{H,H}$ = 7.2 Hz, Ph-CH_2).

^{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).

HRMS (ESI), *m/z*: calcd. for $C_8H_8Cl_2Na^+$: 196.9895 $[M+Na]^+$; found: 196.9897.

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

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



By following the **General procedure 1**, 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).

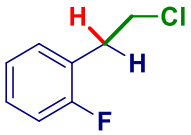
^{13}C NMR (125 MHz, C_6D_6) δ: 137.4 (Ph C-4), 133.4 (Ph C-5), 131.6 (Ph C-6), 130.8 (Ph C-1), 128.5 (q, $^2J_{C,F}$ = 31.2 Hz, Ph C-2), 127.9 (Ph C-3), 123.6 (q, $^1J_{C,F}$ = 273.0 Hz, CF_3), 43.9 (CH_2Cl), 37.8 (Ph-CH_2).

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

HRMS (ESI), *m/z*: calcd. for $C_9H_7Cl_2F_3Na^+$: 264.9769 $[M+Na]^+$; found: 264.9771.

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

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



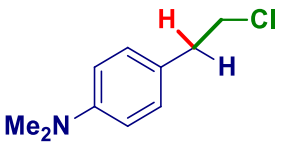
By following the **General procedure 1**, starting from 2-fluorobenzaldehyde (200 mg, 1.61 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.18 mL, 2.42 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.03 mL, 2.25 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (82 mg, 0.2 mmol, 0.1 equiv) 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.

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



By following the **General procedure 1**, 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 v/v as eluent).

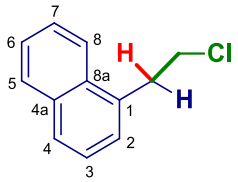
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10 (m, 2H, Ph H-3,5), 6.74 (m, 2H, Ph H-2,6), 3.66 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, CH_2Cl), 2.98 (t, 2H, $^3J_{H,H}$ = 7.5 Hz, Ph-CH_2), 2.94 (s, 6H, N-CH_3).

^{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 $C_{10}H_{14}ClNNa^+$: 206.0707 $[M+Na]^+$; found: 206.0709.

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

1-(2-Chloroethyl)naphthalene (10)



By following the **General procedure 1**, 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).

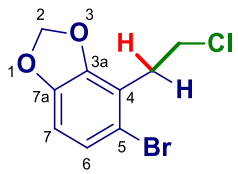
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (m, 1H, Naph H-8), 7.92 (m, 1H, Naph H-5), 7.82 (m, 1H, Naph H-4), 7.59 (m, H, Naph H-7), 7.54 (m, 1H, Naph H-6), 7.47 (m, 1H, Naph H-3), 7.42 (m, 1H, Naph H-2), 3.87 (t, 2H, $^3J_{H,H}$ = 7.8 Hz, CH_2Cl), 3.59 (t, 2H, $^3J_{H,H}$ = 7.8 Hz, Naph-CH_2).

^{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).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_{11}Cl\,Na^+$: 213.0441 $[M+Na]^+$; found: 213.0440.

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

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



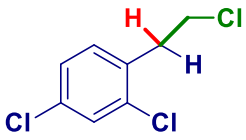
By following the **General procedure 1**, starting from 5-bromobenzo[*d*][1,3]dioxole-4-carbaldehyde (200 mg, 0.87 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.3 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.55 mL, 1.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (45 mg, 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.

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



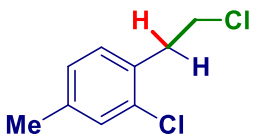
By following the **General procedure 1**, starting from 2,4-dichlorobenzaldehyde (200 mg, 0.89 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.3 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.57 mL, 1.3 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (46 mg, 0.09 mmol, 0.1 equiv) 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.

2-Chloro-1-(2-chloroethyl)-4-methylbenzene (13)



By following the **General procedure 1**, starting from 2-chloro-4-methylbenzaldehyde (200 mg, 1.29 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.14 mL, 1.9 mmol, 1.5 equiv), MeLi-LiBr 2.2

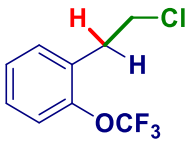
M solution in Et_2O (0.82 mL, 1.8 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (66 mg, 0.13 mmol, 0.1 equiv) and hexylsilane (0.21 mL, 1.29 mmol, 1 equiv), **compound 13** was obtained in 87% yield (212 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.20 (d, 1H, $^4J_{H,H}$ = 2.1 Hz, Ph H-3), 7.15 (d, 1H, $^3J_{H,H}$ = 7.7 Hz, Ph H-6), 7.03 (dd, 1H, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 2.1 Hz, Ph H-5), 3.73 (t, 2H, $^3J_{H,H}$ = 7.4 Hz, CH_2Cl), 3.16 (t, 2H, $^3J_{H,H}$ = 7.4 Hz, Ph-CH_2), 2.32 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.6 (Ph C-4), 133.7 (Ph C-2), 132.4 (Ph C-1), 131.1 (Ph C-6), 130.1 (Ph C-3), 127.6 (Ph C-5), 43.3 (CH_2Cl), 36.5 (Ph-CH_2), 20.8 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_{10}Cl_2Na^+$: 211.0052 [M+Na]$^+$; found: 211.0055.

1-(2-Chloroethyl)-2-(trifluoromethoxy)benzene (14)



By following the **General procedure 1**, starting from 2-(trifluoromethoxy)benzaldehyde (200 mg, 1.05 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.12 mL, 1.6 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.67 mL, 1.5 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (54 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.17 mL, 1.05 mmol, 1 equiv), **compound 14** was obtained in 87% yield (205 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

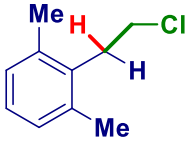
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (m, 1H, Ph H-6), 7.30 (m, 1H, Ph H-4), 7.26 (m, 2H, Ph H-3,5), 3.72 (t, $^3J_{H,H}$ = 7.3 Hz, 2H, CH_2Cl), 3.15 (m, $^3J_{H,H}$ = 7.3 Hz, 2H, Ph-CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.7(q, $^3J_{H,F}$ = 1.5 Hz, Ph C-2), 131.5 (Ph C-6), 130.3 (Ph C-1), 128.5 (Ph C-4), 126.8 (1C, Ph C-5), 120.5 (q, $^4J_{H,F}$ = 1.5 Hz, 1C, Ph C-3), 120.5 (q, $^1J_{H,F}$ = 257.5 Hz, CF_3), 43.3 (CH_2Cl), 33.4 (Ph-CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ: -57.0 (s, CF_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_8ClF_3NaO^+$: 247.0108 [M+Na]$^+$; found:247.0110.

2-(2-Chloroethyl)-1,3-dimethylbenzene (15)



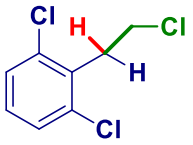
By following the **General procedure 1**, starting from 1,3-dimethylbenzaldehyde (200 mg, 1.49 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.16 mL, 2.24 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.1 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (76 mg, 0.15 mmol, 0.1 equiv) and hexylsilane (0.24 mL, 1.49 mmol, 1 equiv), **compound 15** was obtained in 88% yield (221 mg) as colorless oil without any further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.05 (m, 1H, Ph H-5), 7.03 (m, 2H, Ph H-4,6), 3.56 (m, 2H, CH_2Cl), 3.14 (m, 2H, Ph-CH_2), 2.36 (s, 6H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.7 (Ph C-1,3), 134.6 (Ph C-2), 128.4 (Ph C-4,6), 126.8 (Ph C-5), 42.2 (CH_2Cl), 33.4 (Ph-CH_2), 19.8 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{13}ClNa^+$: 191.0598 $[M+Na]^+$; found: 191.0596.

1,3-Dichloro-2-(2-chloroethyl)benzene (16)



By following the **General procedure 1**, starting from 2,6-dichlorobenzaldehyde (200 mg, 1.14 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.17 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.7 mL, 1.6 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (58 mg, 0.11 mmol, 0.1 equiv) and hexylsilane (0.18 mL, 1.14 mmol, 1 equiv), **compound 16** was obtained in 94% yield (224 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

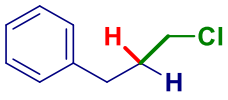
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 (d, 2H, $^3J_{H,H}$ = 8.1 Hz, Ph H-4,6), 7.14 (m, 1H, Ph H-5), 3.69 (m, 2H, CH_2Cl), 3.43 (m, 2H, Ph-CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.8 (Ph C-1,3), 133.8 (Ph C-2), 128.7 (Ph C-5), 128.3 (Ph C-4,6), 41.1 (CH_2Cl), 34.4 (Ph-CH_2).

HRMS (ESI), *m/z*: calcd. for $C_8H_7Cl_3Na^+$: 230.9506 $[M+Na]^+$; found: 230.9508.

GCMS, *m/z*: calcd. for $C_8H_7Cl_3^{\,+}$: 207.9613 $[M^\bullet]^+$; found: 208.0.

(3-Chloropropyl)benzene (17)



By following the **General procedure 1**, starting from 2-phenylacetaldehyde (200 mg, 1.66 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.18 mL, 2.49 mmol, 1.5 equiv), MeLi-LiBr 2.2 M

solution in Et_2O (1.1 mL, 2.3 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (85 mg, 0.17 mmol, 0.1 equiv) and hexylsilane (0.27 mL, 1.66 mmol, 1 equiv), **compound 17** was obtained in 90% yield (231 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

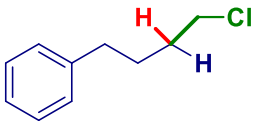
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.24 (m, 3H, Ph H-2,4,6), 3.56 (t, 2H, $^3J_{H,H}$ = 6.5 Hz, CH_2Cl), 2.81 (t, 2H, $^3J_{H,H}$ = 7.6 Hz, Ph-CH_2), 2.13 (m, 2H, CH_2-CH_2-CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.7 (Ph C-1), 128.5 (Ph C-2,3,5,6), 126.1 (Ph C-4), 44.2 (CH_2Cl), 34.0 (CH_2-CH_2-CH_2), 32.7 (Ph-CH_2).

HRMS (ESI), *m/z*: calcd. for $C_9H_{11}ClNa^+$: 177.0441 $[M+Na]^+$; found: 177.0443.

GCMS, *m/z*: calcd. for $C_9H_{11}Cl^+$: 154.0549 $[M^\bullet]^+$; found: 154.0.

(4-Chlorobutyl)benzene (18)



By following the **General procedure 1**, starting from 3-phenylpropanal (200 mg, 1.49 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.16 mL, 2.24 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.95 mL, 2.1 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (76 mg, 0.15 mmol, 0.1 equiv) and hexylsilane (0.24 mL, 1.49 mmol, 1 equiv), **compound 18** was obtained in 86% yield (216 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

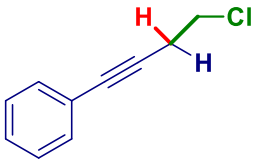
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 (m, 2H, Ph H-3,5), 7.21 (m, 1H, Ph H-4), 7.20 (m, 2H, Ph H-2,6), 3.56 (m, 2H, CH_2Cl), 2.66 (t, 2H, $^3J_{H,H}$ = 7.2 Hz, Ph-CH_2), 1.82 (m, 2H, H-3), 1.80 (m, 2H, H-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.8 (Ph C-1), 128.3 (Ph C-2,3,5,6), 125.9 (Ph C-4), 44.9 (CH_2Cl), 35.1 (Ph-CH_2), 32.0 (C-3), 28.5 (C-2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{13}ClNa^+$: 191.0598 $[M+Na]^+$; found: 191.0599.

GCMS, *m/z*: calcd. for $C_{10}H_{13}Cl^+$: 168.0706 $[M^\bullet]^+$; found: 168.0.

(4-Chloro-1-butyn-1-yl)benzene (19)



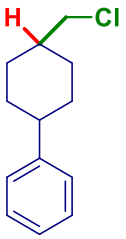
By following the **General procedure 1**, starting from 3-phenylpropionaldehyde (200 mg, 1.53 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.17 mL, 2.3 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.95 mL, 2,1 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (78 mg, 0.15 mmol, 0.1 equiv) and hexylsilane (0.25 mL, 1.53 mmol, 1 equiv), **compound 19** was obtained in 91% yield (230 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, C_6D_6) δ: 7.44 (m, 2H, Ph H-2,6), 6.97 (m, 3H, Ph H-3,4,5), 3.08 (t, 2H, $^3J_{H,H}$ = 7.0 Hz, CH_2Cl), 2.34 (t, 2H, $^3J_{H,H}$ = 7.0 Hz, H-3).

^{13}C NMR (125 MHz, C_6D_6) δ: 132.0 (Ph C-2,6), 128.6 (Ph C-3,5), Ph C-4 not found, 124.0 (Ph C-1), 86.4 (C-2), 83.0 (C-1), 42.2 (CH_2Cl), 23.8 (C-3).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_9ClNa^+$: 187.0285 $[M+Na]^+$; found: 187.0288.

[4-(Chloromethyl)cyclohexyl]benzene (20)



By following the **General procedure 1**, starting from 4-phenylcyclohexanone (200 mg, 1.15 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.13 mL, 1.7 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.73 mL, 1.6 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (59 mg, 0.12 mmol, 0.1 equiv) and hexylsilane (0.19 mL, 1.15 mmol, 1 equiv), **compound 20** was obtained in 92% yield (221 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

ISOMER 1 (major isomer)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (m, 2H, Ph H-3,5), 7.24 (m, 2H, Ph H-2,6), 7.21 (m, 1H, Ph H-4), 3.47 (d, 2H, $^3J_{H,H}$ = 6.3 Hz, CH_2Cl), 2.51 (m, 1H, Cyclo H-1), 2.02 (m, 2H, H-3), 2.02 and 1.23 (m, 4H, Cyclo H-3,5), 1.99 and 1.52 (m, 4H, Cyclo H-2,6), 1.75 (m, 1H, Cyclo H-4).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.1 (Ph C-1), 128.4 (Ph C-3,5), 126.8 (Ph C-2,6), 126.0 (Ph C-4), 50.9 (CH_2Cl), 44.1 (Cyclo C-1), 39.9 (Cyclo C-4), 33.6 (Cyclo C-2,6), 30.9 (Cyclo C-3,5).

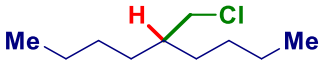
ISOMER 2 (minor isomer)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (m, 2H, Ph H-3,5), 7.24 (m, 2H, Ph H-2,6), 7.21 (m, 1H, Ph H-4), 3.65 (d, 2H, $^3J_{H,H}$ = 7.8 Hz, CH_2Cl), 2.65 (m, 1H, Cyclo H-1), 2.09 (m, 1H, Cyclo H-4), 1.87 and 1.74 (m, 4H, Cyclo H-3,5), 1.74 (m, 4H, Cyclo H-2,6).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.6 (Ph C-1), 128.4 (Ph C-3,5), 126.9 (Ph C-2,6), 125.9 (Ph C-4), 47.3 (CH_2Cl), 43.1 (Cyclo C-1), 36.1 (Cyclo C-4), 28.7 (Cyclo C-2,6), 27.9 (Cyclo C-3,5).

HRMS (ESI), *m/z*: calcd. for $C_{13}H_{17}ClNa^+$: 231.0911 $[M+Na]^+$; found: 231.0914.

5-(Chloromethyl)nonane (21)



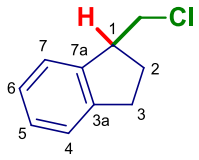
By following the **General procedure 1**, starting from nonan-5-one (200 mg, 1.41 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.15 mL, 2.1 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.91 mL, 2.0 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (72 mg, 0.14 mmol, 0.1 equiv) and hexylsilane (0.23 mL, 1.41 mmol, 1 equiv), **compound 21** was obtained in 92% yield (229 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.53 (d, 2H, $^3J_{H,H}$= 5.0 Hz, CH_2Cl), 1.65 (m, 1H, CH), 1.36 (m, 4H, H-4,6), 1.30 (m, 4H, H-2,8), 1.28 (m, 4H, H-3,7), 0.90 (t, 6H, $^3J_{H,H}$= 7.1 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.9 (CH_2Cl), 39.9 (CH), 31.3 (C-4,6), 28.8 (C-3,7), 22.9 (C-2,8), 14.0 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{21}ClNa^+$: 199.1224 $[M+Na]^+$; found: 199.1226.

1-(Chloromethyl)indane (22)



By following the **General procedure 1**, starting from 2,3-dihydro-1*H*-inden-1-one (200 mg, 1.51 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.17 mL, 2.3 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.96 mL, 2.1 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (77 mg, 0.15 mmol, 0.1 equiv) and hexylsilane (0.24 mL, 1.51 mmol, 1 equiv), **compound 22** was obtained in 91%yield (229 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

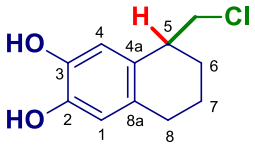
Scaling-up of the reaction (15 mmol) - By following the **General procedure 1**, employing 2,3-dihydro-1*H*-inden-1-one (1982 mg, 15.0 mmol, 1 equiv) in dry THF (30 mL), chloroiodomethane (1.66 mL, 22.5 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (9.6 mL, 21.0 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (770 mg, 1.5 mmol, 0.1 equiv) and hexylsilane (2.4 mL, 15.0 mmol, 1 equiv), **compound 22** was obtained in 87% yield (2459 mg) as as colorless oil after column chromatography on silica gel (*n*-hexane as eluent). *Spectroscopic and spectrometric data match with those reported for the 1.51 mmol scale reaction.*

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31 (m, 1H, Ind H-7), 7.27 (m, 1H, Ind H-4), 7.23 (m, 1H, Ind H-5), 7.22 (m, 1H, Ind H-6), 3.87 (dd, 1H, $^2J_{H,H}$ = 10.4 Hz, $^3J_{H,H}$ = 4.7 Hz, CH_2Cl), 3.62 (dd, 1H, $^2J_{H,H}$ = 10.4 Hz, $^3J_{H,H}$ = 8.2 Hz, CH_2Cl), 3.57 (m, 1H, Ind H-1), 3.01 (m, 1H, Ind H-3), 2.92 (m, 1H, Ind H-3), 2.39 (m, 1H, Ind H-2), 2.02 (m, 1H, Ind H-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.4 (Ind C-3a), 143.3 (Ind C-7a), 127.3 (Ind C-5), 126.3 (Ind C-6), 124.8 (Ind C-4), 124.0 (Ind C-), 48.2 (CH_2Cl), 47.4 (Ind C-1), 30.9 (Ind C-3), 30.0 (Ind C-2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{11}ClNa^+$: 189.0441 $[M+Na]^+$; found: 189.0439.

5-(Chloromethyl)-5,6,7,8-tetrahydro-2,3-naphthalenediol (23)



By following the **General procedure 1**, starting from 6,7-dihydroxy-3,4-dihydro-2*H*-naphthalen-1-one (200 mg, 1.12 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.12 mL, 1.7 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.71 mL, 1.6 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (57 mg, 0.11 mmol, 0.1 equiv), and hexylsilane (0.18 mL, 1.12 mmol, 1 equiv), **compound 23** was obtained in 86% yield (205 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 as eluent).

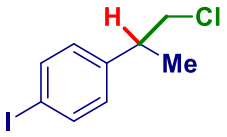
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.69 (s, 1H, Naph H-4), 6.59 (s, 1H, Naph H-1), 5.24 (bs, 2H, OH), 3.71 (A-part of an AB system, $^2J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 4.1 Hz, 1H, CH_2Cl), 3.58 (B-part of an AB system, $^2J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 9.9 Hz, 1H, CH_2Cl), 3.00 (m, 1H, Naph H-5), 2.68 – 2.60 (m, 2H, Naph H-8), 2.03 and 1.84 (m, 2H, Naph H-6), 1.79 – 1.67 (m, 2H, Naph H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.2 (Naph C-3), 141.5 (Naph C-2), 130.5 (Naph C-8a), 129.0 (Naph C-4a), 115.6 (Naph C-1), 115.5 (Naph C-4), 49.1 (CH_2Cl), 39.7 (Naph C-5), 28.9 (Naph C-8), 25.3 (Naph C-6), 19.0 (Naph C-7).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{13}ClNaO_2^+$: 235.0496 $[M+Na]^+$; found: 235.0498.

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{14}Cl^-$: 211.0531 $[M+H]^-$; found: 211.0530.

1-(1-Chloro-2-propanyl)-4-iodobenzene (24)



By following the **General procedure 1**, starting from 1-(4-iodophenyl)ethanone (200 mg, 0.81 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.2 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.5 mL, 1.1 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (42 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.13 mL, 0.81 mmol, 1 equiv), **compound 24** was obtained in 92% yield (209 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

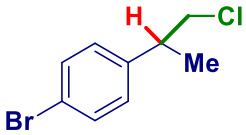
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (m, 2H, Ph H-3,5), 6.98 (m, 2H, Ph H-2,6), 3.64 (dd, 1H, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 6.5 Hz, H-1a), 3.57 (dd, 1H, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.3 Hz, H-1b), 3.05 (m, 1H, CH), 1.36 (d, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.9 (Ph C-1), 137.6 (Ph C-3,5), 129.3 (Ph C-2,6), 92.2 (Ph C-4), 50.3 (CH_2Cl), 41.8 (CH), 18.9 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_{10}ClINa^+$: 302.9408 $[M+Na]^+$; found: 302.9406.

GCMS, *m/z*: calcd. for $C_9H_{10}ClI^+$: 279.9516 $[M^\bullet]^+$; found: 280.0.

1-Bromo-4-(1-chloro-2-propanyl)benzene (25)



By following the **General procedure 1**, starting from 1-(4-bromophenyl)ethanone (200 mg, 1.0 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.11 mL, 1.5 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.64 mL, 1.4 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (51 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.0 mmol, 1 equi), **compound 25** was obtained in 89% yield (208 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

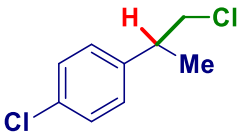
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 (m, 2H, Ph H-2,6), 7.11 (m, 2H, Ph H-3,5), 3.64 (dd, 1H, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 6.5 Hz, CH_2), 3.58 (dd, 1H, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.2 Hz, CH_2), 3.07 (m, 1H, CH), 1.37 (d, 3H, $^3J_{H,H}$ = 7.0Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.2 (Ph C-4), 131.6 (Ph C-2,6), 128.9 (Ph C-3,5), 120.7 (Ph C-1), 50.4 (CH_2Cl), 41.7 (CH), 18.9 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_{10}BrClNa^+$: 254.9547 $[M+Na]^+$; found: 254.9549.

GCMS, *m/z*: calcd. for $C_9H_{10}BrCl^+$: 231.9654 $[M^\bullet]^+$; found: 232.0.

1-Chloro-4-(1-chloropropan-2-yl)benzene (26)



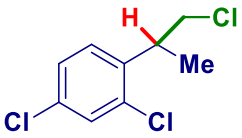
By following the **General procedure 1**, starting from 1-(4-chlorophenyl)ethanone (200 mg, 1.3 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.14 mL, 2.0 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.82 mL, 1.8 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (67 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.21 mL, 1.3 mmol, 1 equiv), **compound 26** was obtained in 86% yield (211 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 (m, 2H, Ph H-2,6), 7.16 (m, 2H, Ph H-3,5), 3.64 (dd, 1H, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 6.4 Hz, CH_2), 3.58 (dd, 1H, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.3 Hz, CH_2), 3.09 (m, 1H, CH), 1.37 (d, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.7 (Ph C-4), 132.6 (Ph C-1), 128.7 (Ph C-2,6), 128.6 (Ph C-3,5), 50.5 (CH_2Cl), 41.7 (CH), 19.0 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_{10}Cl_2Na^+$: 211.0052 $[M+Na]^+$; found: 211.0055.

2,4-Dichloro-1-(1-chloropropan-2-yl)benzene (27)



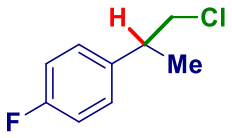
By following the **General procedure 1**, starting from 1-(2,4-dichlorophenyl)ethanone (200 mg, 1.06 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.6 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.68 mL, 1.5 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (54 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.17 mL, 1.06 mmol, 1 equiv), **compound 27** was obtained in 92% yield (218 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (d, 1H, $^4J_{H,H}$ = 2.1 Hz, Ph H-3), 7.25 (dd, 1H, $^3J_{H,H}$ = 8.4 Hz, $^4J_{H,H}$ = 2.1 Hz, Ph H-5), 7.21 (d, 1H, $^3J_{H,H}$ = 8.4 Hz, Ph H-6), 3.72 (dd, 1H, $^2J_{H,H}$ = 10.1 Hz, $^3J_{H,H}$ = 5.2 Hz, CH_2), 3.65 (m, 1H, CH), 3.60 (dd, 1H, $^2J_{H,H}$ = 10.1 Hz, $^3J_{H,H}$ = 6.7 Hz, CH_2), 1.38 (d, 3H, $^3J_{H,H}$ = 6.7 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.8 (Ph C-1), 134.5 (Ph C-2), 133.1 (Ph C-4), 129.5 (Ph C-3), 128.6 (Ph C-6), 127.3 (Ph C-5), 49.0 (CH_2Cl), 37.4 (CH), 17.8 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_9Cl_3Na^+$: 244.9662 $[M+Na]^+$; found: 244.9664.

1-(1-Chloro-2-propanyl)-4-fluorobenzene (28)



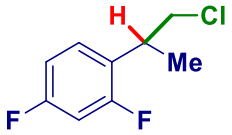
By following the **General procedure 1**, starting from 1-(4-fluorophenyl)ethanone (200 mg, 1.5 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.16 mL, 2.3 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.1 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (102 mg, 0.2 mmol, 0.1 equiv) and hexylsilane (0.24 mL, 1.5 mmol, 1 equiv), **compound 28** was obtained in 92% yield (238 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, C_6D_6) δ: 6.75 (m, 2H, Ph H-3,5), 6.63 (m, 2H, Ph H-2,6), 3.17 (dd, 1H, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 6.2 Hz, CH_2), 3.07 (dd, 1H, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.7 Hz, CH_2), 2.62 (m, 1H, CH), 1.00 (d, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_3).

^{13}C NMR (125 MHz, C_6D_6) δ: 162.2 (d, $^1J_{C,F}$ = 244.1 Hz, Ph C-4), 139.2 (d, $^4J_{C,F}$ = 2.8 Hz, Ph C-1), 128.9 (d, $^3J_{C,F}$ = 8.1 Hz, Ph C-2,6), 115.5 (d, $^2J_{C,F}$ = 21.6 Hz, Ph C-3,5), 50.6 (CH_2Cl), 41.6 (CH), 18.9 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_{10}ClFNa^+$: 195.0347 $[M+Na]^+$; found: 195.0345.

1-(1-Chloro-2-propanyl)-2,4-difluorobenzene (29)



By following the **General procedure 1**, starting from 1-(2,4-difluorophenyl)ethanone (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 (0.8 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 29** was obtained in 87% yield (212 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

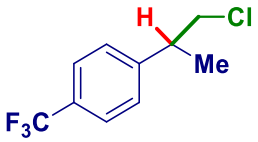
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.20 (m, 1H, Ph H-6), 6.85 (m, 1H, Ph H-5), 6.80 (m, 1H, Ph H-3), 3.71 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 6.3 Hz, CH_2), 3.63 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.0 Hz, CH_2), 3.41 (m, 1H, CH), 1.39 (d, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.9 (dd, $^1J_{C,F}$ = 248.0 Hz, $^3J_{C,F}$ = 12.8 Hz, Ph C-4), 160.7 (dd, $^1J_{C,F}$ = 248.6 Hz, $^3J_{C,F}$ = 11.6 Hz, Ph C-2), 129.2 (dd, $^3J_{C,F}$ = 9.9 Hz, $^3J_{C,F}$ = 6.5 Hz, Ph C-6), 125.8 (dd, $^2J_{C,F}$ = 15.0 Hz, $^4J_{C,F}$ = 3.6 Hz, Ph C-1), 111.2 (dd, $^2J_{C,F}$ = 20.7 Hz, $^4J_{C,F}$ = 3.6 Hz, Ph C-5), 104.0 (dd, $^2J_{C,F}$ = 26.6 Hz, $^2J_{C,F}$ = 25.2 Hz, Ph C-3), 49.2 (CH_2Cl), 35.3 (CH), 17.8 (CH_3).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -112.4 (1F, F-4), -114.3 (m, 1F, F-2).

HRMS (ESI), *m/z*: calcd. for $C_9H_9ClF_2Na^+$: 213.0253 $[M+Na]^+$; found: 213.0256.

1-(1-Chloro-2-propanyl)-4-(trifluoromethyl)benzene (30)



By following the **General procedure 1**, starting from 1-(4-(trifluoromethyl)phenyl)ethanone (200 mg, 0.83 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 (0.5 mL, 1.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (43 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.13 mL, 0.83 mmol, 1 equiv), **compound 30** was obtained in 90% yield (166 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

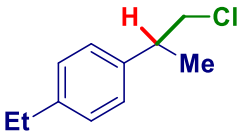
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.59 (m, 2H, Ph H-3,5), 7.35 (m, 2H, Ph H-2,6), 3.68 (dd, 1H, $^2J_{H,H}$ = 10.9 Hz, $^3J_{H,H}$ = 6.7 Hz, CH_2), 3.63 (dd, 1H, $^2J_{H,H}$ = 10.9 Hz, $^3J_{H,H}$ = 7.0 Hz, CH_2), 3.18 (m, 1H, CH), 1.41 (d, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.9 (Ph C-1), 129.3 (q, $^2J_{C,F}$ = 32.4 Hz, Ph C-4), 127.6 (Ph C-2,6), 125.5 (q, $^3J_{C,F}$ = 3.5 Hz, Ph C-3,5), 124.1 (q, $^1J_{C,F}$ = 271.9 Hz, CF_3), 50.1 (CH_2Cl), 42.1 (CH), 19.0 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.5 (3F, CF_3).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{10}ClF_3Na^+$: 245.0315 $[M+Na]^+$; found: 245.0317.

1-(1-Chloro-2-propanyl)-4-ethylbenzene (31)



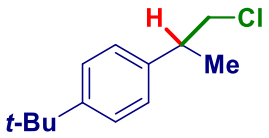
By following the **General procedure 1**, starting from 1-(4-ethylphenyl)ethanone (200 mg, 1.35 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.15 mL, 2.03 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.9 mL, 1.9 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (69 mg, 0.14 mmol, 0.1 equiv) and hexylsilane (0.22 mL, 1.35 mmol, 1 equiv), **compound 31** was obtained in 95 % yield (234 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.16 (m, 2H, Ph H-3,5), 7.15 (m, 2H, Ph H-2,6), 3.68 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz $^3J_{H,H}$ = 6.0 Hz, CH_2Cl), 3.57 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.0 Hz, CH_2Cl), 3.08 (m, 1H, CH), 2.64 (q, $^3J_{H,H}$ = 7.7 Hz, Ph-CH_2), 1.39 (d, 3H, $^3J_{H,H}$ = 6.9 Hz, CHC$\underline{H}_3$), 1.27 (t, 3H, $^3J_{H,H}$ = 7.7 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.9 (Ph C-4), 140.6 (Ph C-1), 128.0 (Ph C-3,5), 127.1 (Ph C-2,6), 51.0 (CH_2Cl), 41.9 (CH), 28.4 (Ph-CH_2), 18.9 (CH$\underline{C}H_3$), 15.5 ($CH_2\underline{C}H_3$).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{15}ClNa^+$: 205.0755 $[M+Na]^+$; found: 205.0756.

1-(1-chloro-2-propanyl)-4-(2-methyl-2-propanyl)benzene (32)



By following the **General procedure 1**, starting from 1-[4-(*tert*-butyl)phenyl]ethanone (200 mg, 1.14 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.13 mL, 1.7 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.73 mL, 1.6 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (58 mg, 0.12 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.14 mmol, 1 equiv), **compound 32** was obtained in 95 % yield (228 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

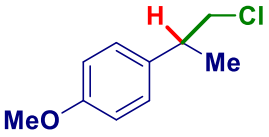
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (m, 2H, Ph H-3,5), 7.16 (m, 2H, Ph H-2,6), 3.69 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 5.8 Hz,CH_2), 3.56 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.2 Hz, CH_2), 3.08 (m, 1H, CH), 1.39 (d, 3H, $^3J_{H,H}$ = 7.0 Hz, $CHC\underline{H}_3$), 1.32 (s, 9H, $C\text{-}C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 149.7 (Ph C-4), 140.2 (Ph C-1), 126.8 (Ph C-2,6), 125.4 (Ph C-3,5), 51.0 (CH_2Cl), 41.8 (CH), 34.4 [$\underline{C}(CH_3)_3$], 31.3 [$C(\underline{C}H_3)_3$], 18.8 ($CH\underline{C}H_3$).

HRMS (ESI), *m/z*: calcd. for $C_{13}H_{19}ClNa^+$: 233.1068 $[M+Na]^+$; found: 233.1069.

GCMS, *m/z*: calcd. for $C_{13}H_{19}Cl^+$: 210.1175 $[M^\bullet]^+$; found: 210.1.

1-(1-Chloro-2-propanyl)-4-methoxybenzene (33)



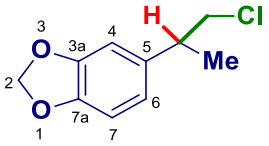
By following the **General procedure 1**, starting from 1-(4-methoxyphenyl)ethanone (200 mg, 1.33 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.15 mL, 2.0 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.9 mL, 1.9 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (68 mg, 0.13 mmol, 0.1 equiv) and hexylsilane (0.22 mL, 1.33 mmol, 1 equiv), **compound 33** was obtained in 92 % yield (226 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.15 (m, 2H, Ph H-2,6), 6.87 (m, 2H, Ph H-3,5), 3.80 (s, 3H, OCH_3), 3.65 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 6.1 Hz, CH_2), 3.55 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.9 Hz, CH_2), 3.06 (m, 1H, CH), 1.38 (d, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.5 (Ph C-4), 135.4 (Ph C-1), 128.1 (Ph C-2,6), 113.9 (Ph C-3,5), 55.2 (OCH_3), 51.1 (CH_2Cl), 41.4 (CH), 19.0 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{13}ClNaO^+$: 207.0547 $[M+Na]^+$; found: 207.0550.

5-(1-Chloro-2-propanyl)-1,3-benzodioxole (34)



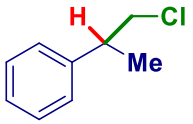
By following the **General procedure 1**, starting from 1-(1,3-benzodioxol-5-yl)ethanone (200 mg, 1.22 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.13 mL, 1.8 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.78 mL, 1.7 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (63 mg, 0.12 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.22 mmol, 1 equiv), **compound 34** was obtained in 85 % yield (206 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dicloromethane 9:1 v/v as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.76 (d, 1H, $^3J_{H,H}$ = 8.0 Hz, Benz H-7), 6.71 (d, 1H, $^4J_{H,H}$ = 1.8 Hz, Benz H-4), 6.68 (dd, 1H, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 1.8 Hz, Benz H-6), 5.94 (s, 2H, -OCH_2O-), 3.63 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 6.3 Hz, CH_2), 3.54 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.7 Hz, CH_2), 3.02 (m, 1H, CH), 1.35 (d, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.7 (Benz C-3a), 146.4 (Benz C-7a), 137.2 (Benz C-5), 120.3 (Benz C-6), 108.3 (Benz C-7), 107.4 (Benz C-4), 101.0 (O-CH_2-O), 50.9 (CH_2Cl), 42.0 (CH), 19.1 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{11}ClNaO_2^+$: 221.0340 $[M+Na]^+$; found: 221.0344.

(1-Chloropropan-2-yl)benzene (35)



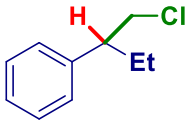
By following the **General procedure 1**, starting from acetophenone (200 mg, 1.66 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.18 mL, 2.5 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.1 mL, 2.3 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (85 mg, 0.17 mmol, 0.1 equiv) and hexylsilane (0.27 mL, 1.66 mmol, 1 equiv), **compound 35** was obtained in 93 % yield (238 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 9:1 v/v as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (m, 2H, Ph H-3,5), 7.26 (m, 1H, Ph H-4), 7.24 (m, 2H, Ph H-2,6), 3.70 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 6.1 Hz, CH_2), 3.60 (dd, 1H, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.9 Hz, CH_2), 3.11 (m, 1H, CH), 1.41 (d, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.3 (Ph C-1), 128.6 (Ph C-3,5), 127.2 (Ph C-2,6), 126.9 (Ph C-4), 50.8 (CH_2Cl), 42.3 (CH), 19.0 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_{11}ClNa^+$: 177.0441 $[M+Na]^+$; found: 177.0443.

(1-Chloro-2-butanyl)benzene (36)



By following the **General procedure 1**, starting from propiophenone (200 mg, 1.49 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.16 mL, 2.2 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.1 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (76 mg, 0.15 mmol, 0.1 equiv) and hexylsilane (0.24 mL, 1.49 mmol, 1 equiv), **compound 36** was obtained in 89 % yield (224 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

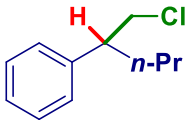
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.25 (m, Ph H-4), 7.19 (m, 2H, Ph H-2,6), 3.69 (d, 2H, $^{3}J_{H,H}$ = 6.9 Hz, CH_2Cl), 2.82 (m, 1H, CH), 1.96 (m, 1H, $C\underline{H}_2CH_3$), 1.64 (m, 1H, $C\underline{H}_2CH_3$), 0.83 (t, 3H, $^{3}J_{H,H}$ = 7.4 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.9 (Ph C-1), 128.5 (Ph C-3,5), 127.8 (Ph C-2,6), 126.9 (Ph C-4), 49.9 (CH), 49.5 (CH_2Cl), 26.1 ($\underline{C}H_2CH_3$), 11.8 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{13}ClNa^+$: 191.0598 $[M+Na]^+$; found: 191.0596.

GCMS, *m/z*: calcd. for $C_{10}H_{13}Cl^+$: 168.0706 $[M^\bullet]^+$; found: 168.1.

(1-Chloro-2-pentanyl)benzene (37)



By following the **general procedure 1**, starting from 1-phenylbutan-1-one (200 mg, 1.35 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.15 mL, 2.0 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.9 mL, 1.9 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (69 mg, 0.14 mmol, 0.1 equiv) and hexylsilane (0.22 mL, 1.35 mmol, 1 equiv), **compound 37** was obtained in 92 % yield (227 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

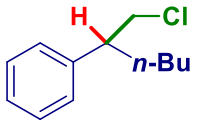
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.25 (m, Ph H-4), 7.19 (m, 2H, Ph H-2,6), 3.67 (d, 2H, $^{3}J_{H,H}$ = 6.9 Hz, CH_2Cl), 2.91 (m, 1H, CH), 1.86 (m, 1H, H-3a), 1.61 (m, 1H, H-3b), 1.21 (m, 2H, H-4), 0.88 (t, 3H, $^{3}J_{H,H}$ = 7.3 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.1 (Ph C-1), 128.5 (Ph C-3,5), 127.8 (Ph C-2,6), 126.9 (Ph C-4), 49.7 (CH_2Cl), 48.0 (CH), 35.4 (C-3), 20.4 (C-4), 14.0 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{15}ClNa^{+}$: 205.0755 $[M+Na]^{+}$; found: 205.0757.

GCMS, *m/z*: calcd. for $C_{11}H_{15}Cl^{+}$: 182.0862 $[M^{\bullet}]^{+}$; found: 182.1.

(1-Chloro-2-hexanyl)benzene (38)



By following the **General procedure 1**, starting from 1-phenylbutan-1-one (200 mg, 1.23 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.14 mL, 1.85 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.8 mL, 1.7 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (63 mg, 0.12 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.23 mmol, 1 equiv), **compound 38** was obtained in 87% yield (196 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

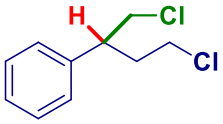
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.25 (m, Ph H-4), 7.19 (m, 2H, Ph H-2,6), 3.67 (d, 2H, $^{3}J_{H,H}$ = 6.9 Hz, H-1), 2.89 (m, 1H, CH), 1.90 (m, 1H, H-3a), 1.62 (m, 1H, H-3b), 1.16 (m, 2H, H-4), 1.27 (m, 2H, H-5), 0.84 (t, 3H, $^{3}J_{H,H}$ = 7.2 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.2 (Ph C-1), 128.5 (Ph C-3,5), 127.8 (Ph C-2,6), 126.9 (Ph C-4), 49.8 (CH_2Cl), 48.2 (CH), 32.9 (C-3), 29.4 (C-4), 22.6 (C-5), 13.9 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_{17}ClNa^{+}$: 219.0911 $[M+Na]^{+}$; found: 219.0913.

GCMS, *m/z*: calcd. for $C_{12}H_{17}Cl^{+}$: 196.1019 $[M^{\bullet}]^{+}$; found: 196.1.

(1,4-Dichloro-2-butanyl)benzene (39)



By following the **General procedure 1**, starting from 4-chloro-1-phenylbutan-1-one (200 mg, 1.19 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.13 mL, 1.8 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.8 mL, 1.7 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (61 mg, 0.12 mmol,

0.1 equiv) and hexylsilane (0.2 mL, 1.19 mmol, 1 equiv), **compound 39** was obtained in 91 % yield (219 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 95:5 /v as eluent).

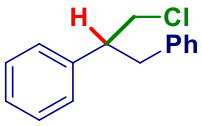
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (m, 2H, Ph H-3,5), 7.29 (m, 1H, Ph H-4), 7.22 (m, Ph, H-2,6), 3.73 (dd, 1H, $^{2}J_{H,H}$ = 10.9 Hz, $^{3}J_{H,H}$ = 6.4 Hz, H-1a), 3.69 (dd, 1H, $^{2}J_{H,H}$ = 10.9 Hz, $^{3}J_{H,H}$ = 7.3 Hz, H-1b), 3.49 (m, 1H, H-4a), 3.28 (m, 1H, H-4b), 3.23 (m, 1H, CH), 2.40 (m, 1H, H-3a), 2.09 (m, 1H, H-3b).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.1 (Ph C-1), 128.9 (Ph C-3,5), 127.8 (Ph C-2,6), 127.5 (Ph C-4), 48.9 (C-1), 45.1 (CH), 42.5 (C-4), 35.7 (C-3).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{12}Cl_2Na^+$: 225.0208 $[M+Na]^+$; found: 225.0210.

GCMS, *m/z*: calcd. for $C_{10}H_{12}Cl_2^+$: 202.0316 $[M^\bullet]^+$; found: 202.0.

1,1'-(3-Chloro-1,2-propanediyl)dibenzene (40)



By following the **General procedure 1**, starting from 1,2-diphenylethanone (200 mg, 1.02 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.11 mL, 1.5 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.7 mL, 1.4 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (52 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.02 mmol, 1 equiv), **compound 40** was obtained in 90 % yield (212 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 v/v as eluent).

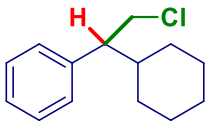
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (m, 2H, Ph H-3,5), 7.26 (m, 1H, Ph H-4), 7.24 (m, 2H, Bn H-3,5), 7.19 (m, 1H, Bn H-4), 7.18 (m, 2H, Ph H-2,6), 7.09 (m, 2H, Bn H-2,6), 3.73 (m, 2H, CH_2Cl), 3.25 (m, 1H, CH), 3.20 (m, 1H, CH_2Ph), 2.98 (dd, 1H, $^{2}J_{H,H}$ = 13.1 Hz, $^{3}J_{H,H}$ = 7.0 Hz, CH_2Ph).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.4 (Ph C-1), 139.1 (Bn C-1), 129.1 (Bn C-2,6), 128.4 (Ph C-3,5), 128.3 (Bn C-3,5), 127.8 (Ph C-2,6), 127.0 (Ph C-4), 126.2 (Bn C-4), 49.6 (CH), 48.5 (CH_2Cl), 39.5 (CH_2Ph).

HRMS (ESI), *m/z*: calcd. for $C_{15}H_{15}ClNa^+$: 253.0755 $[M+Na]^+$; found: 253.0757.

GCMS, *m/z*: calcd. for $C_{15}H_{15}Cl^+$: 230.0862 $[M^\bullet]^+$; found: 230.1.

(2-Chloro-1-cyclohexylethyl)benzene (41)



By following the **General procedure 1**, starting from cyclohexyl(phenyl)methanone (200 mg, 1.06 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.12 mL, 1.6 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.7 mL, 1.5 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (54 mg, 0.11 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.06 mmol, 1 equiv), **compound 41** was obtained in 86% yield (203 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

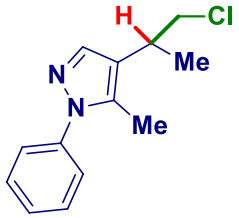
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32(m, 2H, Ph H-3,5), 7.26 (m, 1H, Ph H-4), 7.17 (m, 2H, Ph H-2,6), 3.90 (m, 1H, CH_2Cl) 3.80 (m, 1H, CH_2Cl), 2.73 (m, 1H, Ph-CH), 1.74 (m, 1H, Cyclo H-1), 1.89-0.70 (m, 10H, Cyclo H-2,3,4,5,6).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.3 (Ph C-1), 128.5 (Ph C-2,6), 128.1 (Ph C-3,5), 126.7 (Ph C-4), 53.9 (Ph-CH), 47.5 (CH_2Cl), 40.5 (Cyclo C-1), 31.2, 30.5, 26.3 (Cyclo C-2,3,4,5,6).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{19}ClNa^+$: 245.1068 $[M+Na]^+$; found:245.1066.

GCMS, *m/z*: calcd. for $C_{14}H_{19}Cl^+$: 222.1175 $[M^\bullet]^+$; found: 222.1.

4-(1-Chloro-2-propanyl)-5-methyl-1-phenyl-1*H*-pyrazole (42)



By following the **General procedure 1**, starting from 1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)ethan-1-one (200 mg, 0.72 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.07 mL, 1.1 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.5 mL, 1.0 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (37 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.12 mL, 0.72 mmol, 1 equiv), **compound 42** was obtained in 85 % yield (203 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/ethyl acetate 7:3 v/v as eluent).

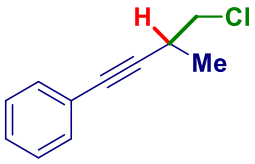
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 (s, 1H, Pyr H-3), 7.47 (m, 2H, Ph H-3,5), 7.43 (m, 2H, Ph H-2,6), 7.38 (m, 1H, Ph H-4), 3.64 (A-part of AB system, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 5.9 Hz, 1H, CH_2), 3.56 (B-part of AB system, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 7.8 Hz, 1H, CH_2), 3.05 (m, 1H, CH), 2.28 (s, 3H, Pyr-CH_3), 1.41 (d, 3H, $^3J_{H,H}$ = 7.0 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.9 (Ph C-1), 137.8 (Pyr C-3), 135.5 (Pyr C-5), 129.0 (Ph C-3,5), 127.6 (Ph C-4), 125.0 (Ph C-2,6), 121.8 (Pyr C-4), 50.7 (CH_2Cl), 32.7 (CH), 18.9 (CH_3), 10.9 (Pyr-$\underline{C}H_3$).

HRMS (ESI), *m/z*: calcd. for $C_{13}H_{15}ClN_2Na^+$: 257.0816 $[M+Na]^+$; found: 257.0818.

HRMS (ESI), *m/z*: calcd. for $C_{13}H_{16}ClN_2^+$: 235.0997 $[M+H]^+$; found: 235.0995.

(4-Chloro-3-methyl-1-butyn-1-yl)benzene (43)



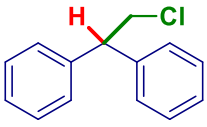
By following the **General procedure 1**, starting from (200 mg, 1.39 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.14 mL, 2.1 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.9 mL, 2.0 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (71 mg, 0.14 mmol, 0.1 equiv) and hexylsilane (0.23 mL, 1.39 mmol, 1 equiv), **compound 43** was obtained in 95 % yield (236 mg) as colorless oil after column chromatography on silica gel (cyclohexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (m, 2H, Ph H-2,6), 7.29 (m, 3H, Ph H-3,4,5), 3.70 (dd, 1H, $^{2}J_{H,H}$ = 10.6 Hz, $^{3}J_{H,H}$ = 5.6 Hz, CH_2), 3.54 (dd, 1H, $^{2}J_{H,H}$ = 10.6 Hz, $^{3}J_{H,H}$ = 7.5 Hz, CH_2), 3.03 (m, 1H, CH), 1.39 (d, 3H, $^{3}J_{H,H}$ = 6.9 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 131.7 (Ph C-2,6), 128.2 (Ph C-3,5), 128.0 (Ph C-4), 123.1 (Ph C-1), 90.3 (C-2), 82.3 (C-1), 48.7 (CH_2Cl), 29.6 (CH), 18.6 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{11}ClNa^+$: 201.0441 $[M+Na]^+$; found: 201.0443.

1,1'-(2-Chloro-1,1-ethanediyl)dibenzene (44)



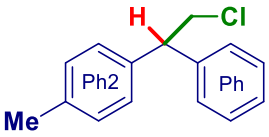
By following the **General procedure 1**, starting from benzophenone (200 mg, 1.1 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.12 mL, 1.7 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.7 mL, 1.5 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (56 mg, 0.11 mmol, 0.1 equiv) and hexylsilane (0.18 mL, 1.1 mmol, 1 equiv), **compound 44** was obtained in 90% yield (214 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/chloroform 1:1 v/v as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (m, 4H, Ph H-3,5), 7.27 (m, 4H, Ph H-2,6), 7.26 (m, 2H, Ph H-4), 4.36 (t, 1H, $^{3}J_{H,H}$ = 7.8 Hz, CH), 4.09 (d, 2H, $^{3}J_{H,H}$= 7.8 Hz, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.2 (Ph C-1), 128.6 (Ph C-3,5) 128.0 (Ph C-2,6), 127.0 (Ph C-4), 53.6 (CH), 47.2 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{13}ClNa^+$: 239.0598 $[M+Na]^+$; found: 239.0595.

1-(2-Chloro-1-phenylethyl)-4-methylbenzene (45)



By following the **General procedure 1**, starting from phenyl(*p*-tolyl)methanone (200 mg, 1.02 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.11 mL, 1.5 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.65 mL, 1.4 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (52 mg, 0.11 mmol, 0.1 equiv) and hexylsilane (0.17 mL, 1.02 mmol, 1 equiv), **compound 45** was obtained in 86% yield (201 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 v/v as eluent).

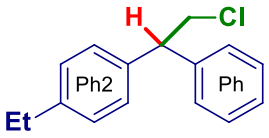
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (m, 2H, Ph H-3,5), 7.24 (m, 2H, Ph H-2,6), 7.23 (m, 1H, Ph H-4), 7.14 ('s', 4H, Ph2 H-2,3,5,6), 4.30 (t, 1H, $^3J_{H,H}$= 7.8 Hz, CH), 4.05 (d, 2H, $^3J_{H,H}$= 7.8 Hz, CH_2Cl), 2.32 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.5 (Ph C-1), 138.3 (Ph2 C-1), 136.7 (Ph2 C-4), 129.4 (Ph2 C-3,5), 128.6 (Ph C-3,5), 128.0 (Ph C-2,6), 127.9 (Ph2 C-2,6), 126.9 (Ph C-4), 53.2 (CH), 47.3 (CH_2Cl), 21.0 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{15}H_{15}ClNa^+$: 253.0755 $[M+Na]^+$; found: 253.0757.

GCMS, *m/z*: calcd. for $C_{15}H_{15}Cl^+$: 230.0862 $[M^\bullet]^+$; found: 230.1.

1-(2-Chloro-1-phenylethyl)-4-ethylbenzene (46)



By following the **General procedure 1**, starting from (4-ethylphenyl)(phenyl)methanone (200 mg, 0.95 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.4 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.6 mL, 1.3 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (49 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.15 mL, 0.95 mmol, 1 equiv), **compound 46** was obtained in 89% yield (207 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

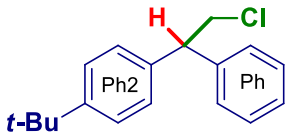
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (m, 2H, Ph H-3,5), 7.28 (m, 2H, Ph H-2,6), 7.26 (m, 1H, Ph H-4), 7.18 (m, 4H, Ph2 H-2,3,5,6), 4.34 (t, 1H, $^{3}J_{H,H}$= 7.8 Hz, CH), 4.08 (d, 2H, $^{3}J_{H,H}$= 7.8 Hz, CH_2Cl), 2.65 (q, 2H, $^{3}J_{H,H}$= 7.6 Hz, Ph2-$C\underline{H}_2$), 1.24 (t, 3H, $^{3}J_{H,H}$= 7.6 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.9 (Ph2 C-4), 141.4 (Ph C-1), 138.5 (Ph2 C-1), 128.6 (Ph C-3,5), 128.1 (Ph2 C-3,5), 128.0 (Ph C-2,6), 127.9 (Ph2 C-2,6), 126.9 (Ph C-4), 53.3 (CH), 47.3 (CH_2Cl), 28.4 (Ph2-$\underline{C}H_2$), 15.4 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{16}H_{17}ClNa^{+}$: 267.0911 $[M+Na]^{+}$; found: 267.0913.

GCMS, *m/z*: calcd. for $C_{16}H_{17}Cl^{+}$: 244.1019 $[M^{\bullet}]^{+}$; found: 244.1.

1-(2-chloro-1-phenylethyl)-4-(2-methyl-2-propanyl)benzene (47)



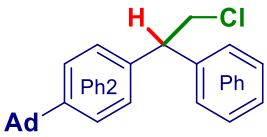
By following the **General procedure 1**, starting from (4-(tert-butyl)phenyl)(phenyl)methanone (200 mg, 0.56 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 0,9 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.4 mL, 0.8 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (29 mg, 0.06 mmol, 0.1 equiv) and hexylsilane (0.1 mL, 0.56 mmol, 1 equiv), **compound 47** was obtained in 84% yield (184 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, 4H, Ph2 H-3,5, Ph H-2,6), 7.28 (m, 2H, Ph H-3,5), 7.26 (m, 2H, Ph H-2,6), 7.24 (m, 1H, Ph H-4), 7.17 (m, 2H, Ph2 H-3,5), 4.26 (t, 1H, $^{3}J_{H,H}$= 7.8 Hz, CH), 4.01 (d, 2H, $^{3}J_{H,H}$= 7.8 Hz, CH_2), 1.24 (s, 9H, CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 149.8 (Ph2 C-1), 141.4 (Ph C-1), 138.2 (Ph2 C-4), 128.6 (Ph C-3,5), 128.0 (Ph C-2,6), 127.5 (Ph2 C-3,5), 126.9 (Ph C-4), 125.6 (Ph2 C-2,6), 53.2 (CH), 47.3 (CH_2Cl), 34.4 [$\underline{C}(CH_3)_3$], 31.3 [$C(\underline{C}H_3)_3$].

HRMS (ESI), *m/z*: calcd. for $C_{18}H_{21}ClNa^{+}$: 295.1224 $[M+Na]^{+}$; found: 295.1226.

1-[4-(2-Chloro-1-phenylethyl)phenyl]adamantane (48)



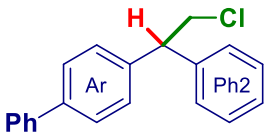
By following the **General procedure 1**, starting from (4-(adamantan-1-yl)phenyl)(phenyl)methanone (200 mg, 0.63 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.0 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.4 mL, 0.9 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (32 mg, 0.06 mmol, 0.1 equiv) and hexylsilane (0.10 mL, 0.63 mmol, 1 equiv), **compound 48** was obtained in 91 % yield (201 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 98:2 v/v as eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.30 (m, 2H, Ph2 H-2,6), 7.27 (m, 2H, Ph H-2,6), 7.24 (m, 1H, Ph H-4), 7.18 (m, 1H, Ph2 H-3,5), 4.31 (t, $^3J_{H,H}$ = 7.8 Hz, 1H, CH), 4.07 (d, $^3J_{H,H}$ = 7.8 Hz, 2H, CH_2Cl), 2.08 -1.82 (15H, Ad).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.1 (Ph2 C-1), 141.4 (Ph C-1), 138.3 (Ph2 C-4), 128.6 (Ph C-3,5), 128.1 (Ph C-2,6), 127.6 (Ph2 C-3,5), 126.9 (Ph C-4), 125.1 (Ph2 C-2,6), 53.3 (CH), 47.4 (CH_2Cl), 43.1 (Ad C-2,8,9), 36.8 (Ad C-4,6,10), 35.9 (Ad C-1), 28.9 (Ad C-3,5,7).

HRMS (ESI), *m/z*: calcd. for $C_{24}H_{27}ClNa^+$: 373.1694 $[M+Na]^+$; found: 373.1696.
GCMS, *m/z*: calcd. for $C_{24}H_{27}Cl^+$: 350.1801 $[M^\bullet]^+$; found: 350.2.

4-(2-Chloro-1-phenylethyl)biphenyl (49)



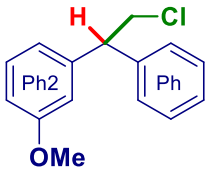
By following the **General procedure 1**, starting from [1,1'-biphenyl]-4-yl(phenyl)methanone (200 mg, 0.77 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.2 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.5 mL, 1.1 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (39 mg, 0.08 mmol, 0.1 equiv) and hexylsilane (0.13 mL, 0.77 mmol, 1 equiv), **compound 49** was obtained in 87% yield (196 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.57 (m, 2H, Ph H-2,6), 7.56 (m, 2H, Ar H-2,6), 7.43 (m, 2H, Ph H-3,5), 7.35 (m, 2H, Ph2 H-3,5), 7.34 (m, 1H, Ph H-4), 7.33 (m, 2H, Ar H-3,5), 7.29 (m, 2H, Ph2 H-2,6), 7.27 (m, 1H, Ph2 H-4), 4.40 (t, 1H, $^3J_{H,H}$= 7.8 Hz, CH), 4.11 (d, 2H, $^3J_{H,H}$= 7.8 Hz, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.2 (Ph2 C-1), 140.6 (Ph C-1), 140.3 (Ar C-4), 139.9 (Ar C-1), 128.7 (Ph C-3,5, Ph2 C-3,5), 128.4 (Ar C-3,5), 128.0 (Ph2 C-2,6), 127.4 (Ar C-2,6), 127.3 (Ph C-4), 127.1 (Ph2 C-4), 127.0 (Ph C-2,6), 53.3 (CH), 47.1 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{20}H_{17}ClNa^+$: 315.0911 $[M+Na]^+$; found: 315.0914.

1-(2-Chloro-1-phenylethyl)-3-methoxybenzene (50)



By following the **General procedure 1**, starting from 1-(3-methoxyphenyl)ethanone (200 mg, 0.94 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.4 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in THF (0.6 mL, 1.4 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (48 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.15 mL, 0.94 mmol, 1 equiv), **compound 50** was obtained in 90 % yield (156 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

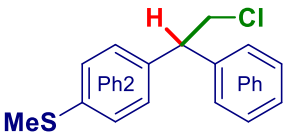
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.26 (m, 2H, Ph H-2,6), 7.25 (m, 2H, Ph H-4, Ph2 H-5), 6.85 (m, 1H, Ph2 H-6), 6.79 (s, 1H, Ph2 H-2), 6.78 (m, 1H, Ph2 H-4), 4.31 (t, 1H, $^{3}J_{H,H}$ = 7.8 Hz, CH), 4.06 (d, 2H, $^{3}J_{H,H}$ = 7.8 Hz, CH_2Cl), 3.78 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.7 (Ph2 C-3), 142.8 (Ph2 C-1), 141.1 (Ph C-1), 129.6 (Ph2 C-5), 128.7 (Ph C-3,5), 128.0 (Ph C-2,6), 127.1 (Ph C-4), 120.3 (Ph2 C-6), 114.3 (Ph2 C-2), 111.9 (Ph2 C-4), 55.2 (OCH_3), 53.6 (CH), 47.1 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{15}H_{15}ClNaO^{+}$: 269.0704 $[M+Na]^{+}$; found: 269.0702.

GCMS, *m/z*: calcd. for $C_{15}H_{15}ClO^{+}$: 246.0811 $[M^{\bullet}]^{+}$; found: 246.1.

1-(2-Chloro-1-phenylethyl)-4-(methylsulfanyl)benzene (51)



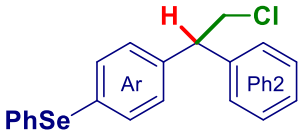
By following the **General procedure 1**, starting from (4-(methylthio)phenyl)(phenyl)methanone (200 mg, 0.88 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.3 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.6 mL, 1.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (45 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.14 mL, 0.63 mmol, 1 equiv), **compound 51** was obtained in 87 % yield (201 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 98:2 v/v as eluent).

^{1}H NMR (400 MHz, C_6D_6) δ: 7.08 (m, 2H, Ph H-3,5), 7.02 (m, 2H, Ph2 H-3,5), 7.01 (m, 1H, Ph H-4), 6.96 (m, 2H, Ph H-2,6), 6.83 (m, 2H, Ph2 H-2,6), 4.04 (t, $^{3}J_{H,H}$ = 7.7 Hz, 1H, CH), 3.67 (m, 2H, CH_2Cl), 1.96 (s, 3H, SCH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 141.8 (Ph C-1), 138.5 (Ph2 C-1), 137.7 (Ph2 C-4), 128.9 (Ph2 C-2,6), 128.8 (Ph C-3,5), 128.4 (Ph C-2,6), 127.1 (Ph2 C-3,5), 53.2 (CH), 47.1 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{15}H_{15}ClNaS^+$: 285.0475 $[M+Na]^+$; found: 285.0477.
GCMS, *m/z*: calcd. for $C_{15}H_{15}ClS^{+}$: 262.0583 $[M^{\bullet}]^+$; found: 262.1.

1-(2-Chloro-1-phenylethyl)-4-(phenylselanyl)benzene (52)



By following the **General procedure 1**, starting from phenyl(4-(phenylselanyl)phenyl)methanone (200 mg, 0.59 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.7 mL, 0.9 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.4 mL, 0.8 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (31 mg, 0.06 mmol, 0.1 equiv) and hexylsilane (0.1 mL, 0.59 mmol, 1 equiv), **compound 52** was obtained in 86 % yield (189 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 v/v as eluent).

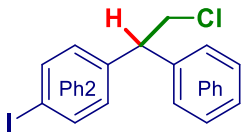
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48 (m, 2H, Ph H-2,6), 7.39 (m, 2H, Ar H-3,5), 7.33 (m, 2H, Ph2 H-3,5), 7.28 (m, 3H, Ph H-3,4,5), 7.25 (m, 1H, Ph2 H-4), 7.23 (m, 2H, Ph2 H-2,6), 7.15 (m, 2H, Ar H-2,6), 4.30 (t, 1H, $^3J_{H,H}$ = 7.8 Hz, CH), 4.04 (d, 2H, $^3J_{H,H}$ = 7.8 Hz, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.9 (Ph2 C-1), 140.4 (Ar C-1), 133.3 (Ph C-2,6), 132.8 (Ar C-3,5), 130.6 (Ph C-1), 129.4 (Ph C-3,5), 129.0 (Ar C-2,6), 128.7 (Ph2 C-3,5), 128.0 (Ph2 C-2,6), 127.5 (Ph C-4), 127.2 (Ph2 C-4), 53.2 (CH), 47.0 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{20}H_{17}ClNaSe^+$: 395.0076 $[M+Na]^+$; found: 395.0078.

GCMS, *m/z*: calcd. for $C_{20}H_{17}ClSe^{+}$: 372.0184 $[M^{\bullet}]^+$; found: 372.1.

1-(2-Chloro-1-phenylethyl)-4-iodobenzene (53)



By following the **General procedure 1**, starting from (4-iodophenyl)(phenyl)methanone (200 mg, 0.65 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.07 mL, 1.0 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.4 mL, 0.9 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (33

mg, 0.07 mmol, 0.1 equiv) and hexylsilane (0.10 mL, 0.65 mmol, 1 equiv), **compound 53** was obtained in 93 % yield (207 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 v/v as eluent).

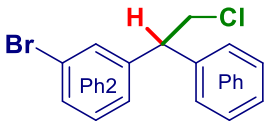
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.66 (m, 2H, Ph2 H-3,5), 7.34 (m, 2H, Ph H-3,5), 7.26 (m, 1H, Ph H-4), 7.22 (m, 2H, Ph H-2,6), 7.02 (m, 2H, Ph2 H-2,6), 4.31 (t, 1H, $^3J_{H,H}$ = 7.8 Hz, CH), 4.04 (m, 2H, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.9 (Ph C-1), 140.7 (Ph2 C-1), 137.7 (Ph2 C-3,5), 130.1 (Ph2 C-2,6), 128.8 (Ph C-3,5), 127.9 (Ph C-2,6), 127.2 (Ph C-4), 92.5 (Ph2 C-4), 53.1 (CH), 46.7 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{12}ClINa^+$: 364.9564 $[M+Na]^+$; found: 364.9566.

GCMS, *m/z*: calcd. for $C_{14}H_{12}ClI^+$: 341.9672 $[M^\bullet]^+$; found: 342.0.

1-Bromo-3-(2-chloro-1-phenylethyl)benzene (54)



By following the **General procedure 1**, starting from (3-bromophenyl)(phenyl)methanone (200 mg, 0.77 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.08 mL, 1.2 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.5 mL, 1.1 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (39 mg, 0.08 mmol, 0.1 equiv) and hexylsilane (0.13 mL, 0.77 mmol, 1 equiv), **compound 54** was obtained in 90 % yield (205 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 v/v as eluent).

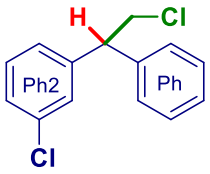
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (m, 1H, Ph2 H-2), 7.40 (m, 1H, Ph2 H-6), 7.35 (m, 2H, Ph H-3,5), 7.28 (m, 1H, Ph H-4), 7.24 (m, 2H, Ph H-2,6), 7.21 (m, 2H, Ph2 H-4,5), 4.32 (t, 1H, $^3J_{H,H}$ = 7.8 Hz, CH), 4.05 (d, 2H, $^3J_{H,H}$ = 7.8 Hz, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.5 (Ph2 C-3), 140.5 (Ph C-1), 131.1 (Ph2 C-2), 130.2 (Ph2 C-5,6), 128.8 (Ph C-3,5), 127.9 (Ph C-2,6), 127.3 (Ph C-4), 126.7 (Ph2 C-4), 122.7 (Ph2 C-1), 53.2 (CH), 46.7 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{12}BrClNa^+$: 316.9703 $[M+Na]^+$; found: 316.9705.

GCMS, *m/z*: calcd. for $C_{14}H_{12}BrCl^+$: 293.9811 $[M^\bullet]^+$; found: 294.0.

1-Chloro-3-(2-chloro-1-phenylethyl)benzene (55)



By following the **General procedure 1**, starting from (3-chlorophenyl)(phenyl)methanone (200 mg, 0.92 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.10 mL, 1.4 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.6 mL, 1.3 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (47 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.15 mL, 0.92 mmol, 1 equiv), **compound 55** was obtained in 91 % yield (210 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 v/v as eluent).

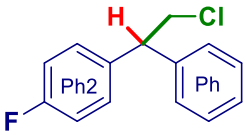
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (m, 2H, Ph H-3,5), 7.26 (m, 2H; Ph H-4, Ph2 H-4), 7.25 (m, 1H, Ph2 H-5), 7.23 (m, 1H, Ph2 H-2), 7.22 (m, 2H, Ph H-2,6), 7.15 (m, 1H, Ph2 H-4), 4.31 (t, 1H, $^3J_{H,H}$ = 7.7 Hz, CH), 4.04 (d, 2H, $^3J_{H,H}$ = 7.7 Hz, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.2 (Ph2 C-3), 140.6 (Ph C-1), 134,5 (Ph2 C-1), 128.9 (Ph2 C-5), 128.8 (Ph C-3,5), 128.2 (Ph2 C-2), 127.9 (Ph C-2,6), 127.3 (Ph C-4), 126.2 (Ph2 C-4), 53.3 (CH), 46.8 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{12}Cl_2Na^+$: 273.0208 $[M+Na]^+$; found: 273.0209.

GCMS, *m/z*: calcd. for $C_{14}H_{12}Cl_2^+$: 250.0316 $[M^\bullet]^+$; found: 250.0.

1-(2-Chloro-1-phenylethyl)-4-fluorobenzene (56)



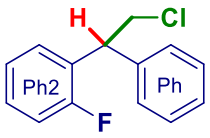
By following the **General procedure 1**, starting from (4-fluorophenyl)(phenyl)methanone (200 mg, 1.00 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.11 mL, 1.5 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.64 mL, 1.4 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (51 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.16 mL, 1.00 mmol, 1 equiv), **compound 56** was obtained in 85 % yield (199 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 95:5 v/v as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (m, 2H, Ph H-3,5), 7.27 (m, 1H, Ph H-4), 7.24 (m, 4H, Ph H-2,6, Ph2 H-2,6), 7.03 (m, 2H, Ph2 H-3,5), 4.35 (m, 1H, CH), 4.06 (m, 2H, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.7 (d, $^1J_{C,F}$ = 245.8 Hz, Ph2 C-4), 141.1 (Ph C-1), 136.9 (d, $^4J_{C,F}$ = 3.5 Hz, Ph2 C-1), 129.5 (d, $^3J_{C,F}$ = 8.1 Hz, Ph2 C-2,6), 128.7 (Ph C-3,5), 127.8 (Ph C-2,6), 127.1 (Ph C-4), 115.5 (d, $^2J_{C,F}$ = 21.8 Hz, Ph2 C-3,5), 52.8 (CH), 47.1 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{12}ClFNa^+$: 257.0504 $[M+Na]^+$; found: 257.0506.

1-(2-Chloro-1-phenylethyl)-2-fluorobenzene (57)



By following the **General procedure 1**, starting from (2-fluorophenyl)(phenyl)methanone (200 mg, 1.00 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.11 mL, 1.5 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.6 mL, 1.4 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (51 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.16 mL, 1.00 mmol, 1 equiv), **compound 57** was obtained in 89 % yield (208 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/ethyl acetate 9:1 v/v as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.28 (m, 2H, Ph H-2,6),7.26 (m, 1H, Ph H-4), 7.25 (m, 1H, Ph2 H-6), 7.24 (m, 1H, Ph2 H-4), 7.13 (m, 1H, Ph2 H-5), 7.05 (m, 1H, Ph2 H-3), 4.66 (t, 1H, $^3J_{H,H}$ = 7.9 Hz, CH), 4.12 (dd, 1H, $^2J_{H,H}$ = 11.1 Hz, $^3J_{H,H}$ = 8.1 Hz, CH_2Cl), 4.06 (dd, 1H, $^2J_{H,H}$ = 11.1 Hz, $^3J_{H,H}$ = 7.6 Hz, CH_2Cl).

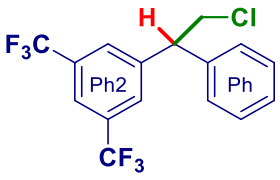
^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.8 (d, $^1J_{C,F}$ = 246.4 Hz, Ph2 C-2), 140.1 (Ph C-1), 128.8 (d, $^4J_{C,F}$ = 3.6 Hz, Ph2 C-6), 128.7 (Ph C-3,5, Ph2 C-4), 128.2 (d, $^2J_{C,F}$ = 14.5 Hz, Ph2 C-1), 128.0 (Ph C-2,6), 127.2 (Ph C-4), 124.2 (d, $^4J_{C,F}$ = 3.4 Hz, Ph2 C-5), 115.8 (d, $^2J_{C,F}$ = 22.9 Hz, Ph2 C-3), 46.9 (d, $^3J_{C,F}$ = 2.3 Hz, CH), 46.0 (d, $^4J_{C,F}$ = 1.5 Hz, CH_2Cl).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -117.1 ppm.

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{12}ClFNa^+$: 257.0504 $[M+Na]^+$; found: 257.0502.

GCMS, *m/z*: calcd. for $C_{14}H_{12}ClF^+$: 234.0612 $[M^\bullet]^+$; found: 234.1.

1-(2-Chloro-1-phenylethyl)-3,5-bis(trifluoromethyl)benzene (58)



By following the **General procedure 1**, starting from (3,5-bis(trifluoromethyl)phenyl)(phenyl)methanone (200 mg, 0.63 mmol, 1 equiv) in dry THF (3 mL),

chloroiodomethane (0.1 mL, 0.9 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.40 mL, 0.9 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (32 mg, 0.06 mmol, 0.1 equiv) and hexylsilane (0.10 mL, 0.63 mmol, 1 equiv), **compound 58** was obtained in 85 % yield (189 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 99:1 v/v as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.78 (s, 1H, Ph2 H-4), 7.71 (s, 2H, Ph2 H-2,6), 7.37 (m, 2H, Ph H-3,5), 7.30 (m, 1H, Ph H-4), 7.20 (m, 2H, Ph H-2,6), 4.47 (t, $^3J_{H,H}$ = 7.7 Hz, 1H, CH), 4.09 (d, $^3J_{H,H}$ = 7.7 Hz, 2H, CH_2Cl).

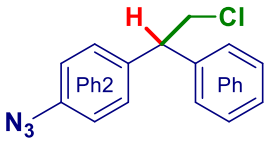
^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.6 (Ph2 C-1), 139.6 (Ph C-1), 129.2 (Ph C-3,5), 128.4 (Ph2 C-2,6), 127.9 (Ph C-4), 127.8 (Ph C-2,6), 121.2 (Ph2 C-4), 53.1 (CH), 46.3 (CH_2Cl), Ph2 C-3,5 not found.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.8 (CF_3).

HRMS (ESI), *m/z*: calcd. for $C_{16}H_{11}ClF_6Na^+$: 375.0346 $[M+Na]^+$; found: 375.0348.

GCMS, *m/z*: calcd. for $C_{16}H_{11}ClF_6^+$: 352.0453 $[M^\bullet]^+$; found: 352.1.

1-Azido-4-(2-chloro-1-phenylethyl)benzene (59)

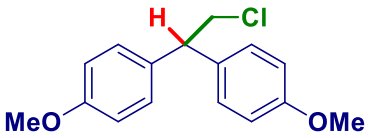


By following the **General procedure 1**, starting from (4-azidophenyl)(phenyl)methanone (200 mg, 0.89 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.34 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.6 mL, 1.3 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (46 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.15 mL, 0.89 mmol, 1 equiv), **compound 59** was obtained in 86% yield (189 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 9:1 v/v as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.25 (m, 1H, Ph H-4), 7.24 (m, 2H, Ph2 H-3,5), 7.21 (m, 2H, Ph H-2,6), 6.99 (m, 2H, Ph2 H-2,6), 4.32 (m, 1H, CH), 4.08-4.00 (m, 2H, CH_2Cl).
^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.0 (Ph C-1), 138.8 (Ph2 C-1), 138.0 (Ph2 C-4), 129.5 (Ph2 C-3,5), 128.8 (Ph C-3,5), 127.9 (Ph C-2,6), 127.2 (Ph C-4), 119.3 (Ph2 C-2,6), 52.9 (CH), 47.0 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{12}ClN_3Na^+$: 280.0612 $[M+Na]^+$; found: 280.0614.

1,1'-(2-Chloroethane-1,1-diyl)bis(4-methoxybenzene) (60)



By following the **General procedure 1**, starting from bis(4-methoxyphenyl)methanone (200 mg, 0.83 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 (0.5 mL, 1.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (43 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.13 mL, 0.77 mmol, 1 equiv), **compound 60** was obtained in 84 % yield (192 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/ethyl acetate 8:2 v/v as eluent).

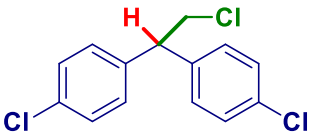
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.15 (m, 4H, Ph H-2,6), 6.86 (m, 4H, Ph H-3,5), 4.25 (t, 1H, $^3J_{H,H}$= 7.8 Hz, CH), 4.01 (d, 2H, $^3J_{H,H}$= 7.8 Hz, CH_2Cl), 3.79 (s, 6H, OCH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.4 (Ph C-4), 133.7 (Ph C-1), 128.9 (Ph C-2,6), 114.0 (Ph C-3,5), 55.2 (OCH_3), 51.9 (CH), 47.6 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{16}H_{17}ClNaO_2^+$: 299.0809 $[M+Na]^+$; found: 299.0810.

GCMS, *m/z*: calcd. for $C_{16}H_{17}ClO_2^+$: 276.0917 $[M^\bullet]^+$; found: 276.1.

1,1'-(2-Chloro-1,1-ethanediyl)bis(4-chlorobenzene) (61)



By following the **General procedure 1**, starting from (4-chlorophenyl)(phenyl)methanone (200 mg, 0.80 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.2 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.5 mL, 1.1 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (41 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.13 mL, 0.80 mmol, 1 equiv), **compound 61** was obtained in 86 % yield (173 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 8:2 v/v as eluent).

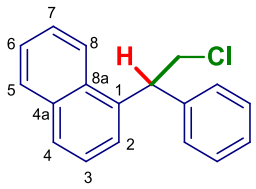
^{1}H NMR (500 MHz, C_6D_6) δ: 7.03 (m, 4H, Ph H-3,5), 6.66 (m, 4H, Ph H-2,6), 3.83 (t, 1H, $^3J_{H,H}$ = 7.8 Hz, CH), 3.51 (d, 2H, $^3J_{H,H}$ = 7.8 Hz, CH_2Cl).

^{13}C NMR (125 MHz, C_6D_6) δ: 139.6 (Ph C-1), 133.3 (Ph C-4), 129.6 (Ph C-2,6), 129.1 (Ph C-3,5), 52.3 (CH), 46.6 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{11}Cl_3Na^+$: 306.9819 $[M+Na]^+$; found: 306.9821.

GCMS, *m/z*: calcd. for $C_{14}H_{11}Cl_3^+$: 283.9926 $[M^\bullet]^+$; found: 284.0.

1-(2-Chloro-1-phenylethyl)naphthalene (62)



By following the **General procedure 1**, starting from naphthalen-1-yl(phenyl)methanone (200 mg, 0.86 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 (0.6 mL, 1.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (44 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.13 mL, 0.77 mmol, 1 equiv), **compound 62** was obtained in 91 % yield (208 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 v/v as eluent).

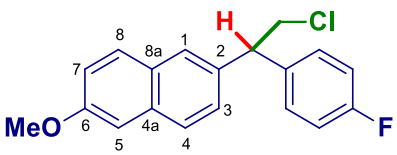
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.11 (d, 1H, , $^3J_{H,H}$= 8.0 Hz, Naph H-8), 7.90 (d, 1H, , $^3J_{H,H}$= 7.9 Hz, Naph H-5), 7.84 (d, 1H, $^3J_{H,H}$= 8.0 Hz, Naph H-4), 7.53 (m, 1H, Naph H-3), 7.52 (m, 1H, Naph H-7), 7.51 (m, 1H, Naph H-6), 7.47 (d, 1H, $^3J_{H,H}$= 7.2 Hz, Naph H-2), 7.35 (m, 4H, Ph H-2,3,5,6), 7.28 (m, 1H, Ph H-4), 5.21 (m, 1H, CH), 4.26 (m, 1H, CH_2Cl), 4.20 (m, 1H, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.1 (Ph C-1), 136.4 (Naph C-1), 134.1 (Naph C-4a), 131.6 (Naph C-8a), 128.9 (Naph C-5), 128.6 (Ph C-3,5), 128.3 (Ph C-2,6), 127.8 (Naph C-4), 127.1 (Ph C-4), 126.4 (Naph C-7), 125.6 (Naph C-6), 125.2 (Naph C-3), 124.6 (Naph C-2), 123.2 (Naph C-8), 49.0 (CH), 47.0 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{18}H_{15}ClNa^+$: 289.0755 $[M+Na]^+$; found: 289.0756.

GCMS, *m/z*: calcd. for $C_{18}H_{15}Cl^+$: 266.0862 $[M^\bullet]^+$; found: 266.1.

2-[2-Chloro-1-(4-fluorophenyl)ethyl]-6-methoxynaphthalene (63)



By following the **General procedure 1**, starting from (4-fluorophenyl)(6-methoxynaphthalen-2-yl)methanone (200 mg, 0.71 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.1 mL, 1.1 mmol, 1.5 equiv) , MeLi-LiBr 2.2 M solution in Et_2O (0.5 mL, 1.0 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (36 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.12 mL, 0.71 mmol, 1 equiv), **compound 63** was obtained in 89 % yield (199 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 9:1 v/v as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 (d, 1H, $^3J_{H,H}$ = 8.9 Hz, Naph H-8), 7.70 (d, 1H, $^3J_{H,H}$ = 8.5 Hz, Naph H-4), 7.62 (d, 1H, $^3J_{H,H}$ = 1.1 Hz, Naph H-1), 7.27 (m, 1H, Naph H-3), 7.26 (m, 2H, Ph H-2,6), 7.16 (dd, 1H, $^3J_{H,H}$ = 8.9 Hz, $^4J_{H,H}$ = 2.6 Hz, Naph H-7), 7.11 (d, 1H, $^4J_{H,H}$ = 2.6 Hz, Naph H-5), 7.02 (m, 2H, Ph H-3,5), 4.46 (t, 1H, $^3J_{H,H}$ = 7.8 Hz, CH), 4.15 (dd, 1H, $^2J_{H,H}$ = 11.2 Hz, $^3J_{H,H}$ = 7.4 Hz, CH_2Cl), 4.10 (dd, 1H, $^2J_{H,H}$ = 11.2 Hz, $^3J_{H,H}$ = 8.1 Hz, CH_2Cl), 3.91 (s, 3H, OCH_3).

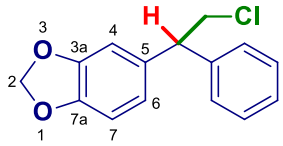
^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.7 (d, $^1J_{C,F}$ = 245.0 Hz, Ph C-4), 157.7 (Naph C-6), 137.1 (d, $^4J_{C,F}$ = 2.8 Hz, Ph C-1), 136.2 (Naph C-2), 133.6 (Naph C-4a), 129.7 (d, $^3J_{C,F}$ = 8.1 Hz, Ph C-2,6), 129.3 (Naph C-8), 128.8 (Naph C-8a), 127.4 (Naph C-4), 126.7 (Naph C-3), 126.2 (Naph C-1), 119.1 (Naph C-7), 115.5 (d, $^2J_{C,F}$ = 21.3 Hz, Ph C-3,5), 105.6 (Naph C-5), 55.3 (OCH_3), 52.7 (CH), 47.2 (CH_2Cl).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -115.6 (m).

HRMS (ESI), *m/z*: calcd. for $C_{19}H_{16}ClFNaO^+$: 337.0766 $[M+Na]^+$; found: 337.0768.

GCMS, *m/z*: calcd. for $C_{19}H_{16}ClFO^+$: 314.0874 $[M^\bullet]^+$; found: 314.1.

5-(2-Chloro-1-phenylethyl)-1,3-benzodioxole (64)



By following the **General procedure 1**, starting from benzo[d][1,3]dioxol-5-yl(phenyl)methanone (200 mg, 0.88 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 (0.6 mL, 1.2 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (45 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.14 mL, 0.88 mmol, 1 equiv), **compound 64** was obtained in 88 % yield (201 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 8:2 v/v as eluent).

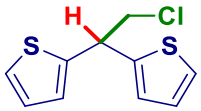
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (m, 2H, Ph H-3,5), 7.24 (m, 3H, Ph H-2,4,6), 6.76 (d, 1H, , $^3J_{H,H}$= 8.0 Hz, Ph H-7), 6.73 (dd, 1H, , $^3J_{H,H}$= 8.0 Hz, $^4J_{H,H}$= 1.8 Hz, Ph H-6), 6.70 (dd, 1H, $^4J_{H,H}$= 1.8 Hz, Ph H-4), 5.93 (AB system, 2H, $^2J_{H,H}$= 1.5 Hz, Ph H-2), 4.25 (t, 1H, $^3J_{H,H}$= 7.8 Hz, CH), 4.01 (m, 2H, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.9 (Ph C-3a), 146.5 (Ph C-7a), 141.3 (Ph C-1), 135.2 (Ph C-5), 128.7 (Ph C-3,5), 127.8 (Ph C-2,6), 127.1 (Ph C-4), 121.2 (Ph C-6), 108.4 (Ph C-4), 108.3 (Ph C-7), 101.1 (Ph C-2), 53.2 (CH), 47.2 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{15}H_{13}ClNaO_2^+$: 283.0496 $[M+Na]^+$; found: 283.0498.

GCMS, *m/z*: calcd. for $C_{15}H_{13}ClO_2^{\ +}$: 260.0604 $[M^\bullet]^+$; found: 260.1.

2,2'-(2-Chloro-1,1-ethanediyl)dithiophene (65)



By following the **General procedure 1**, starting from di(thiophen-2-yl)methanone (200 mg, 1.03 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.11 mL, 1.6 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.66 mL, 1.4 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (53 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.17 mL, 1.03 mmol, 1 equiv), **compound 65** was obtained in 87 % yield (205 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

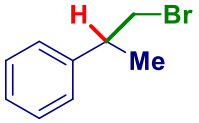
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.24 (dd, 1H, $^3J_{H,H}$ = 4.9 Hz, $^4J_{H,H}$ = 1.5 Hz, Th H-5), 6.99 (m, 1H, Th H-3), 6.98 (m, 1H, Th H-4), 4.83 (t, 1H, $^3J_{H,H}$ = 7.3 Hz, CH), 4.03 (d, 2H, $^3J_{H,H}$ = 7.3 Hz, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.1 (Th C-2), 126.8 (Th C-4), 125.4 (Th C-3), 124.7 (Th C-5), 49.0 (CH_2Cl), 44.5 (CH).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_9ClNaS_2^+$: 250.9726 $[M+Na]^+$; found: 250.9728.

GCMS, *m/z*: calcd. for $C_{10}H_9ClS_2^+$: 227.9834 $[M^\bullet]^+$; found: 228.0.

(1-Bromo-2-propanyl)benzene (66)



By following the **General procedure 1**, starting from acetophenone (200 mg, 1.66 mmol, 1 equiv) in dry THF (3 mL), bromoiodomethane (0.12 mL, 1.7 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.1 mL, 2.3 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (85 mg, 0.2 mmol, 0.1 equiv), and hexylsilane (0.3 mL, 1.66 mmol, 1 equiv), **compound 66** was obtained in 86% yield (280 mg)

as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 v/v as eluent).

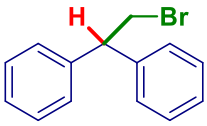
Scaling-up of the reaction (20 mmol) - By following the **General procedure 1**, starting from acetophenone (2403 mg, 20.0 mmol, 1 equiv) in dry THF (30 mL), bromoiodomethane (2.26 mL, 30.0 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (12.7 mL, 28.0 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (1024 mg, 2.0 mmol, 0.1 equiv), and hexylsilane (3.2 mL, 20.0 mmol, 1 equiv), **compound 66** was obtained in 89% yield (3543 mg) as as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 v/v as eluent). *Spectroscopic and spectrometric data match with those reported for the 1.66 mmol scale reaction.*

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (m, 2H, Ph H-3,5), 7.26 (m, 1H, Ph H-4), 7.22 (m, Ph, H-2,6), 3.59 (dd, 1H, $^2J_{H,H}$ = 9.9 Hz,$^3J_{H,H}$ = 6.0 Hz, CH_2Br), 3.49 (dd, 1H, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 8.1 Hz, CH_2Br), 3.14 (m, 1H, CH), 1.43 (d, 3H, $^3J_{H,H}$ = 6.9 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.7 (Ph C-1), 128.6 (Ph C-3,5), 127.03 (Ph C-2,6), 126.98 (Ph C-4), 42.2 (CH), 40.0 (CH_2Br), 20.0 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_{11}BrNa^+$: 220.9936 $[M+Na]^+$; found: 220.9933.

1,1'-(2-Bromo-1,1-ethanediyl)dibenzene (67)



By following the **General procedure 1**, starting from benzophenone (200 mg, 1.1 mmol, 1 equiv) in dry THF (3 mL), bromoiodomethane (0.12 mL, 1.7 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.7 mL, 1.5 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (56 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.1 mmol, 1 equiv), **compound 67** was obtained in 89% yield (256 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

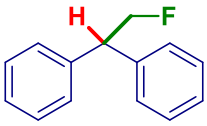
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (m, 4H, Ph H-3,5), 7.27 (m, 6H, Ph H-2,4,6), 4.41 (t, 1H, $^3J_{H,H}$ = 8.0 Hz, CH), 3.96 (d, 2H, $^3J_{H,H}$ = 8.0 Hz, CH_2Br).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.7 (Ph C-1), 128.7 (Ph C-3,5), 127.9 (Ph C-2,6), 127.0 (Ph C-4), 53.6 (CH), 35.5 (CH_2Br).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{13}BrNa^+$: 283.0093 $[M+Na]^+$; found: 283.0095.

GCMS, *m/z*: calcd. for $C_{14}H_{13}Br^+$: 260.0201 $[M^\bullet]^+$; found: 260.0.

1,1'-(2-Fluoro-1,1-ethanediyl)dibenzene (68)



By following the **General procedure 2**, starting from benzophenone (273 mg, 1.5 mmol, 1.5 equiv) in dry mixture of THF (3 mL), fluoroiodomethane (0.1 mL, 1.0 mmol, 1 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.0 mmol, 2 equiv), tris(pentafluorophenyl)borane (56 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.12 mL, 0.73 mmol, 1 equiv), **compound 68** in 91% yield (200 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 9:1 v/v as eluent).

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.34-7.21 (m, 10H, Ph H-2,3,4,5,6), 4.92 (dd, 2H, $^2J_{H,F}$ = 47.1 Hz, $^3J_{H,H}$ = 7.0 Hz, CH_2F), 4.40 (m, 1H, CH).

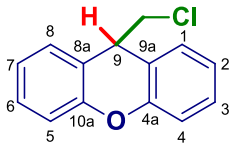
^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.3 (d, $^3J_{C,F}$ = 5.0 Hz, Ph C-1), 128.6 (Ph C-3,5), 128.3 (Ph C-2,6), 126.9 (Ph C-4), 85.3 (d, $^1J_{C,F}$ = 175.0 Hz, CH_2F), 51.3 (d, $^2J_{C,F}$ = 19.6 Hz, CH).

^{19}F NMR (376 MHz, $CDCl_3$) δ: -214.7 (dt, $^2J_{H,F}$ = 47.1 Hz, $^3J_{H,F}$ = 15.0 Hz).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{13}FNa^+$: 223.0894 $[M+Na]^+$; found: 223.0896.

GCMS, *m/z*: calcd. for $C_{14}H_{13}F^+$: 200.1001 $[M^\bullet]^+$; found: 200.1.

9-(Chloromethyl)-9*H*-xanthene (69)



By following the **General procedure 1**, starting from 9H-xanthen-9-one (200 mg, 1.02 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.11 mL, 1.53 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.65 mL, 1.42 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (52 mg, 0.10 mmol, 0.1 equiv) and hexylsilane (0.16 mL, 1.02 mmol, 1 equiv), **compound 69** was obtained in 89 % yield (209 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

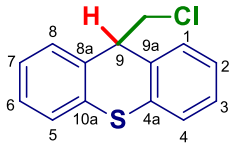
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (m, 2H, Ar H-1,8), 7.32 (m, 2H, Ar H-3,6), 7.16 (m, 2H, Ar H-4,5), 7.14 (m, 2H, Ar H-2,7), 4.29 (t, 1H, $^3J_{H,H}$ = 6.1 Hz, CH), 3.69 (d, 2H, $^3J_{H,H}$ = 6.1 Hz, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 152.2 (Ar C-4a,10a), 129.2 (Ar C-1,8), 128.6 (Ar C-3,6), 123.2 (Ar C-2,7), 121.7 (Ar C-8a,9a), 116.6 (Ar C-4,5), 51.1 (CH_2Cl), 41.5 (CH).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{11}ClNaO^+$: 253.0391 $[M+Na]^+$; found: 253.0393.

GCMS, *m/z*: calcd. for $C_{14}H_{11}ClO^+$: 230.0438 $[M^\bullet]^+$; found: 230.0.

9-(Chloromethyl)-9*H*-thioxanthene (70)



By following the **General procedure 1**, starting from 9H-thioxanthen-9-one (200 mg, 0.94 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.10 mL, 1.41 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.6 mL, 1.3 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (46 mg, 0.09 mmol, 0.1 equiv) and hexylsilane (0.15 mL, 0.94 mmol, 1 equiv), **compound 70** was obtained in 93 % yield (215 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

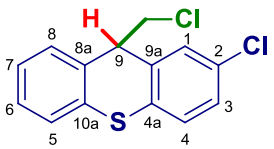
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43- 7.23 (m, 8H, Ar H-1,2,3,4,5,6,7,8), 4.31 (t, 1H, $^3J_{H,H}$ = 7.9 Hz, CH), 3.72 (d, 2H, $^3J_{H,H}$ = 7.9 Hz, CH_2Cl).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 134.4 (C_q), 132.2 (C_q), 130.2 (Ar CH), 127.5 (Ar CH), 126.9 (Ar CH), 126.6 (Ar CH), 51.6 (CH), 44.1 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{11}ClNaS^+$: 269.0162 $[M+Na]^+$; found: 269.0163.

GCMS, *m/z*: calcd. for $C_{14}H_{11}ClS^+$: 246.0270 $[M^\bullet]^+$; found: 246.0.

2-Chloro-9-(chloromethyl)-9*H*-thioxanthene (71)



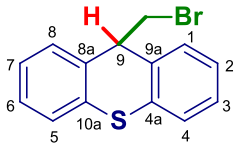
By following the **General procedure 1**, starting from 2-chloro-9H-thioxanthen-9-one (200 mg, 0.81 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.08 mL, 1.21 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.51 mL, 1.13 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (40 mg, 0.08 mmol, 0.1 equiv) and hexylsilane (0.13 mL, 0.81 mmol, 1 equiv), **compound 71** was obtained in 87 % yield (198 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (m, 1H, Ar H-5), 7.37 (m, 2H, Ar H-1,8), 7.34 (m, 1H, Ar H-4), 7.28 (2H, Ar H-6,7), 7.24 (dd, $^3J_{H,H}$ = 8.4 Hz, $^4J_{H,H}$ = 2.2 Hz, 1H, Ar H-3), 4.26 (t, $^3J_{H,H}$ = 7.9 Hz, 1H, Ar H-9), 3.72 (dd, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 8.0 Hz, 1H, CH_2Cl), 3.68 (dd, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.7 Hz, 1H, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.1 (Ar C-9a),133.8 (Ar C-8a), 132.2 (Ar C-2), 131.8 (Ar C-10a), 130.8 (Ar C-4a), 130.1 (Ar C-1), 130.0 (Ar C-8), 128.0 (Ar C-4), 127.7 (Ar C-6), 127.6 (Ar C-3), 127.0 (Ar C-5), 126.9 (Ar C-7), 51.4 (Ar C-9), 43.7 (CH_2Cl).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{10}Cl_2NaS^+$: 302.9772 $[M+Na]^+$; found: 302.9773.
GCMS, *m/z*: calcd. for $C_{14}H_{10}Cl_2S^{+}$: 279.9880 $[M^{\bullet}]^+$; found: 280.0.

9-(Bromomethyl)-9*H*-thioxanthene (72)



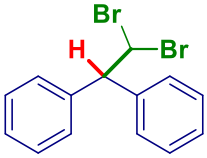
By following the **General procedure 1**, starting from 9H-thioxanthen-9-one (200 mg, 0.94 mmol, 1 equiv) in dry THF (3 mL), bromoiodomethane (0.11 mL, 1.41 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.6 mL, 1.3 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (48 mg, 0.1 mmol, 01 equiv) and hexylsilane (0.2 mL, 0.94 mmol, 1 equiv), **compound 72** was obtained in 82% yield (225 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (400 MHz, C_6D_6) δ: 7.19 (m, 2H, Ar H-4,5), 6.98 (m, 2H, Ar H-1,8), 6.94 (m, 2H, Ar H-2,7), 6.87 (m, 2H, Ar H-3,6), 4.05 (t, $^3J_{H,H}$ = 7,9 Hz, 1H, CH) , 3.38 (d, $^3J_{H,H}$ = 7.9 Hz, 2H, CH_2Br).

^{13}C NMR (100 MHz, C_6D_6) δ: 135.3 (Ar C-8a,9a), 132.6 (Ar C-4a,10a),130.4 (Ar C-1,8), 127.6 (Ar C-3,6), 127.2 (Ar C-4,5), 126.6 (Ar C-2,7), 51.7 (Ar C-9), 33.2 (CH_2Br).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{11}BrNaS^+$: 312.9657 $[M+Na]^+$; found: 312.9658.
GCMS, *m/z*: calcd. for $C_{14}H_{11}BrS^{+}$: 289.9765 $[M^{\bullet}]^+$; found: 289.9.

1,1'-(2,2-Dibromo-1,1-ethanediyl)dibenzene (73)



By following the **General procedure 2**, starting from benzophenone (200 mg, 1.09 mmol, 1 equiv) in dry THF (3 mL), dibromomethane (0.11 mL, 1.63 mmol, 1.5 equiv), TMP (0.26 mL, 1.53 mmol, 1.4 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.69 mL, 1.53 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (56 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.17 mL, 1.09 mmol, 1 equiv), **compound 73** was obtained in 87% yield (322 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 95:5 v/v as eluent).

Scaling-up of the reaction (15 mmol) - By following the **General procedure 2**, starting from benzophenone (2733 mg, 15.0 mmol, 1 equiv) in dry THF (30 mL), dibromomethane (1.6 mL, 22.5 mmol, 1.5 equiv), TMP (3.6 mL, 21.0 mmol, 1.4 equiv), MeLi-LiBr 2.2 M solution in Et_2O (9.5 mL, 21.0 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (768 mg, 1.5 mmol, 0.1 equiv) and hexylsilane (2.4 mL, 15.0 mmol, 1 equiv), **compound 74** was obtained in 83% yield (4207 mg) as as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 95:5 v/v as eluent). *Spectroscopic and spectrometric data match with those reported for the 1.09 mmol scale reaction.*

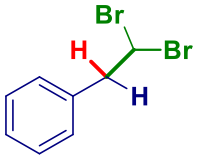
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (m, 4H, Ph H-3,5), 7.33 (m, 4H, Ph H-2,6), 7.27 (m, 2H, Ph H-4), 6.31 (d, 1H, $^3J_{H,H}$ = 9.7 Hz, $CHBr_2$), 4.69 (d, 1H, $^3J_{H,H}$ = 9.7 Hz, Ph-C<u>H</u>).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.8 (Ph C-1), 128.7 (Ph C-3,5) 127.9 (Ph C-2,6), 127.5 (Ph C-4), 63.7 (CH), 47.5 ($CHBr_2$).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{12}Br_2Na^+$: 360.9198 $[M+Na]^+$; found: 360.9196.

GCMS, *m/z*: calcd. for $C_{14}H_{12}Br_2S^+$: 337.9306 $[M^\bullet]^+$; found: 337.9.

(2,2-Dibromoethyl)benzene (74)



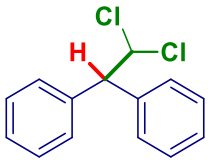
By following the **General procedure 2**, starting from benzaldehyde (200 mg, 1.88 mmol, 1 equiv) in dry THF (3 mL), dibromomethane (0.2 mL, 2.82 mmol, 1.5 equiv), TMP (0.44 mL, 2.63 mmol, 1.4 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.19 mL, 2.63 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (96 mg, 0.19 mmol, 0.1 equiv) and hexylsilane (0.3 mL, 1.88 mmol, 1 equiv), **compound 74** was obtained in 85% yield (422 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (m, 2H, Ph H-3,5), 7.35 (m, 1H, Ph H-4), 7.27 (m, 2H, Ph H-2,6), 5.77 (t, 1H, $^{3}J_{H,H}$ = 6.8 Hz, $CHBr_2$), 3.72 (d, $^{3}J_{H,H}$ = 6.8 Hz, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.7 (Ph C-1), 129.5 (Ph C-2,6), 128.6 (Ph C-3,5), 127.7 (Ph C-4), 51.4 (CH_2), 45.1 ($CHBr_2$).

HRMS (ESI), *m/z*: calcd. for $C_8H_8Br_2Na^+$: 284.8885 $[M+Na]^+$; found: 284.8883.

1,1'-(2,2-Dichloro-1,1-ethanediyl)dibenzene (75)



By following the **General procedure 2**, starting from benzophenone (200 mg, 1.09 mmol, 1 equiv) in dry THF (3 mL), dichloromethane (0.1 mL, 1.63 mmol, 1.5 equiv), TMP (0.26 mL, 1.53 mmol, 1.4 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.69 mL, 1.53 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (56 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.17 mL, 1.09 mmol, 1 equiv), **compound 75** was obtained in 93% yield (256 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 9:1 v/v as eluent).

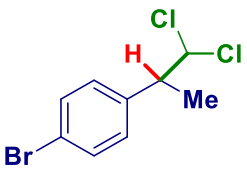
^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.34 (m, 4H, Ph H-2,6), 7.33 (m, 4H, Ph H-3,5), 7.26 (m, 2H, Ph H-4), 6.38 (d, 1H, $^{3}J_{H,H}$ = 8.7 Hz, $CHCl_2$), 4.56 (d, 1H, $^{3}J_{H,H}$ = 8.7 Hz, Ph-C<u>H</u>).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.8 (Ph C-1), 128.7 (Ph C-3,5) 128.3 (Ph C-2,6), 127.5 (Ph C-4), 74.6 ($CHCl_2$), 62.7 (Ph-<u>C</u>H).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{12}Cl_2Na^+$: 273.0208 $[M+Na]^+$; found: 273.0210.

GCMS, *m/z*: calcd. for $C_{14}H_{12}Cl_2S^+$: 250.0316 $[M^{\bullet}]^+$; found: 250.0.

1-Bromo-4-(1,1-dichloro-2-propanyl)benzene (76)



By following the **General procedure 2**, starting from 4'-bromoacetophenone (200 mg, 1.01 mmol, 1 equiv) in dry THF (3 mL), dichloromethane (0.1 mL, 1.51 mmol, 1.5 equiv), TMP (0.24 mL, 1.41 mmol, 1.4 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.64 mL, 1.41 mmol, 1.4 equiv),

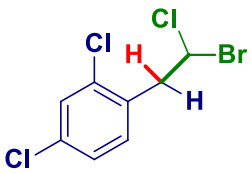
tris(pentafluorophenyl)borane (52 mg, 0.1 mmol, 0.1 equiv) and hexylsilane (0.16 mL, 1.01 mmol, 1 equiv), **compound 76** was obtained in 91% yield (245 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47 (m, 2H, Ph H-2,6), 7.17 (m, 2H, Ph H-3,5), 5.84 (d, 1H, $^{3}J_{H,H}$ = 4.9 Hz, $CHCl_2$), 3.41 (dq, 1H, q: $^{3}J_{H,H}$ = 7.0 Hz, d: $^{3}J_{H,H}$ = 4.9 Hz, CH), 1.52 (d, $^{3}J_{H,H}$ = 7.0 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.2 (Ph C-1), 131.6 (Ph C-2,6), 130.0 (Ph C-3,5), 121.7 (Ph C-1), 77.5 ($CHCl_2$), 49.6 (CH), 15.9 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_9BrCl_2Na^+$: 288.9157 [M+Na]$^+$; found: 288.9159.

1-(2-Bromo-2-chloroethyl)-2,4-dichlorobenzene (77)



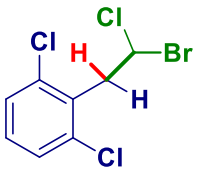
By following the **General procedure 2**, starting from 2,4-dichlorobenzaldehyde (200 mg, 1.14 mmol, 1 equiv) in dry THF (3 mL), bromochloromethane (0.14 mL, 1.71 mmol, 1.5 equiv), TMP (0.27 mL, 1.6 mmol, 1.4 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.72 mL, 1.6 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (58 mg, 0.11 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.14 mmol, 1 equiv), **compound 77** was obtained in 94% yield (303 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (d, 1H, , $^{4}J_{H,H}$= 1.9 Hz, Ph H-3), 7.27 (d, 1H, $^{3}J_{H,H}$= 8.2 Hz, Ph H-6), 7.24 (dd, 1H, $^{3}J_{H,H}$= 8.2 Hz, $^{4}J_{H,H}$= 1.9 Hz, Ph H-5), 5.95 (dd, 1H, $^{3}J_{H,H}$= 7.1 Hz, $^{3}J_{H,H}$= 6.6 Hz, CHClBr), 3.72 (dd, 1H, $^{2}J_{H,H}$= 14.4 Hz, $^{3}J_{H,H}$= 6.6 Hz, CH_2), 3.67 (dd, 1H, $^{2}J_{H,H}$= 14.4 Hz, $^{3}J_{H,H}$= 7.1 Hz, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 134.9 (Ph C-2), 134.6 (Ph C-4), 133.2 (Ph C-6), 132.4 (Ph C-1), 129.5 (Ph C-3), 127.3 (Ph C-5), 57.3 (CHClBr), 47.9 (CH_2).

HRMS (ESI), *m/z*: calcd. for $C_8H_6BrCl_3Na^+$: 308.8611 [M+Na]$^+$; found: 308.8614.

2-(2-Bromo-2-chloroethyl)-1,3-dichlorobenzene (78)



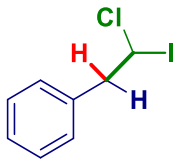
By following the **General procedure 2**, starting from 2,6-dichlorobenzaldehyde (200 mg, 1.14 mmol, 1 equiv) in dry THF (3 mL), bromochloromethane (0.14 mL, 1.71 mmol, 1.5 equiv), TMP (0.27 mL, 1.6 mmol, 1.4 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.72 mL, 1.6 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (58 mg, 0.11 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.14 mmol, 1 equiv), **compound 78** was obtained in 94% yield (303 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (d, 2H, Ph H-3,5), 7.20 (t, 1H, Ph H-4), 6.17 (t, 1H, CHClBr), 3.99 (dd, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.2 (Ph C-1), 132.5 (2C, Ph C-2,6), 129.5 (2C, Ph C-4), 128.6 (Ph C-3), 56.6 (CH_2), 45.0 (CHClBr).

HRMS (ESI), *m/z*: calcd. for $C_8H_6BrCl_3\ Na^+$: 308.8611 $[M+Na]^+$; found: 308.8614.

(2-Chloro-2-iodoethyl)benzene (79)



By following the **General procedure 2**, starting from benzaldehyde (200 mg, 1.88 mmol, 1 equiv) in dry THF (3 mL), chloroiodomethane (0.2 mL, 2.83 mmol, 1.5 equiv), TMP (0.44 mL, 2.63 mmol, 1.4 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.19 mL, 2.63 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (96 mg, 0.19 mmol, 0.1 equiv) and hexylsilane (0.3 mL, 1.88 mmol, 1 equiv), **compound 79** was obtained in 90% yield (453 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

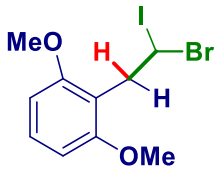
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (m, 3H, Ph H-3,4,5), 7.25 (m, 2H, Ph H-2,6), 5.81 (m, 1H, CHICl), 3.68 (dd, $^2J_{H,H}$ = 14.4 Hz, $^3J_{H,H}$ = 6.5 Hz, $^1J_{H,H}$ = 1H, CH_2) 3.58 (dd, $^2J_{H,H}$ = 14.4 Hz, $^3J_{H,H}$ = 7.2 Hz, 1H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.4 (1C, Ph C-1), 129.4 (Ph C-2,6), 128.6 (Ph C-3,5), 127.7 (Ph C-4), 52.7 (CH_2), 29.5 (CHClI).

HRMS (ESI), *m/z*: calcd. for $C_8H_8ClINa^+$: 288.9251 $[M+Na]^+$; found: 288.9253.

GCMS (ESI), *m/z*: calcd. for $C_8H_8ClI^+$: 265.9359 $[M^\bullet]^+$; found: 265.9.

2-(2-Bromo-2-iodoethyl)-1,3-dimethoxybenzene (80)



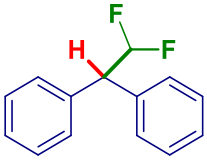
By following the **General procedure 2**, starting from 2,6-dimethoxybenzaldehyde (200 mg, 1.2 mmol, 1 equiv) in dry THF (3 mL), bromoiodomethane (0.13 mL, 1.8 mmol, 1.5 equiv), TMP (0.28 mL, 1.68 mmol, 1.4 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.76 mL, 1.68 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (61 mg, 0.12 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.2 mmol, 1 equiv), **compound 80** was obtained in 92% yield (409 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 9:1 v/v as eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (t, $^2J_{H,H}$ = 8.3 Hz, 1 H, Ph H-5), 6.54 (d, 2H, $^2J_{H,H}$ = 8.3 Hz, Ph H-4,6), 3.82 (s, 6H, OCH_3), 3.46 (m, 1H, CHBrI), 3.23 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4 (Ph C-1,3), 128.0 (Ph C-5), 115.3 (Ph C-2), 103.6 (Ph C-4,6), 55.6 (OCH_3), 31.3 (CHBrI), 27.1 (CH_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{12}BrINaO_2^+$: 392.8957 $[M+Na]^+$; found: 392.8958.

1,1'-(2,2-Difluoro-1,1-ethanediyl)dibenzene (81)



By following the **General procedure 3**, starting from benzophenone (200 mg, 1.09 mmol, 1 equiv) in dry THF (3 mL), difluoromethyltrimethylsilane (0.23 mL, 1.64 mmol, 1.5 equiv), potassium *tert*-pentoxide 0.9 M in toluene (1.7 mL, 1.53 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (56 mg, 0.11 mmol, 0.1 equiv) and hexylsilane (0.17 mL, 1.09 mmol, 1 equiv), **compound 81** was obtained in 87% yield (209 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

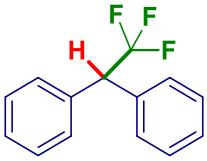
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (m, 4H, Ph H-3,5), 7.32 (m, 4H, Ph H-2,6), 7.29 (m, 2H, Ph H-4), 6.33 (dt, 1H, $^2J_{H,F}$ = 55.8 Hz, $^3J_{H,H}$ = 4.5 Hz, CH, CHF_2), 4.42 (dt, 1H, $^3J_{H,F}$ = 15.8 Hz, $^3J_{H,H}$ = 4.5 Hz, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.1 (t, $^3J_{H,F}$ = 3.7 Hz, Ph C-1), 129.0 (Ph C-2,6), 128.7 (Ph C-3,5), 127.5 (Ph C-4), 116.9 (t, $^1J_{C,F}$ = 244.4 Hz, CHF_2), 55.0 (t, $^2J_{C,F}$ = 20.8 Hz, CH).

^{19}F NMR (376 MHz, $CDCl_3$) δ: -118.1 (dd, $^2J_{H,F}$ = 55.8 Hz, $^3J_{H,F}$ = 15.8 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{12}F_2Na^+$: 241.0799 [M+Na]$^+$; found: 241.0797.

1,1'-(2,2,2-Trifluoro-1,1-ethanediyl)dibenzene (82)



By following the **General procedure 4**, starting from Benzophenone (140 mg, 0.77 mmol, 1 equiv) in dry THF (3 mL), trifluoromethyltrimethylsilane (0.17 mL, 1.16 mmol, 1.5 equiv), tetrabutylammonium fluoride (TBAF) solution 1.0 M in THF (1.1 mL, 1.09 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (39 mg, 0.08 mmol, 0.1 equiv), and hexylsilane (0.12 mL, 0.77 mmol, 1 equiv), **compound 82** was obtained in 79% yield (144 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/dichloromethane 1:1 v/v as eluent).

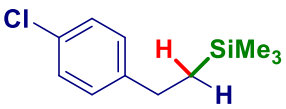
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (m, 4H, Ph H-2,6), 7.38 (m, 4H, Ph H-3,5), 7.36 (m, 2H, Ph H-4), 4.73 (q, $^3J_{H,F}$ = 10.0 Hz, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 135,4 (q, $^3J_{C,F}$ = 1.6 Hz, Ph C-1), 129.1 (q, $^4J_{C,F}$ = 1.2 Hz, Ph C-2,6), 128.7 (Ph C-3,5), 127,9 (Ph C-4), 126.2 (q, $^1J_{C,F}$ = 280.5 Hz, CF_3), 55.5 (q, $^2J_{C,F}$ = 27.5 Hz, CH).

^{19}F NMR (376 MHz, $CDCl_3$) δ: -65.8 (d, $^3J_{F,H}$ = 10.0 Hz, CF_3).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{11}F_3Na^+$: 259.0705 [M+Na]$^+$; found: 259.0703.

[2-(4-Chlorophenyl)ethyl](trimethyl)silane (83)



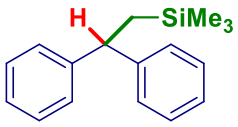
By following the **General procedure 5**, starting from 4-chlorobenzaldehyde (200 mg, 1.42 mmol, 1 equiv) in dry THF (3 mL), trimethylsilyl-methyllithium solution 0.7 M in pentane (3.0 mL, 2.13 mmol, 1.5 equiv), tris(pentafluorophenyl)borane (73 mg, 0.14 mmol, 0.1 equiv) and hexylsilane (0.23 mL, 1.4 mmol, 1 equiv), **compound 83** was obtained in 84% yield (250 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.23 (m, 2H, Ph H-3,5), 7.12 (m, 2H, Ph H-2,6), 2.59 (m, 2H, Ph-C$\underline{H_2}$), 0.84 (m, 2H, C$\underline{H_2}$Si), 0.01 (s, 9H, Me_3Si).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.7 (Ph C-1), 131.0 (Ph C-4), 129.1 (Ph C-2,6), 128.3 (Ph C-3,5), 29.5 (Ph-$\underline{C}H_2$), 18.6 ($\underline{C}H_2Si$), -1.8 (Me_3Si).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{17}ClNaSi^+$: 235.0680 $[M+Na]^+$; found: 235.0682.

(2,2-Diphenylethyl)trimethylsilane (84)



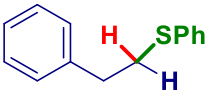
By following the **General procedure 5**, starting from benzophenone (200 mg, 1.09 mmol, 1 equiv) in dry THF (3 mL), trimethylsilyl-methyllithium solution 0.7 M in pentane (2.3 mL, 1.64 mmol, 1.5 equiv), tris(pentafluorophenyl)borane (56 mg, 0.11 mmol, 0.1 equiv) and hexylsilane (0.17 mL, 1.09 mmol, 1 equiv), **compound 84** was obtained in 87% yield (244 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, C_6D_6) δ: 7.19 (m, 4H, Ph H-2,6), 7.12 (m, 4H, Ph H-3,5), 7.01 (m, 2H, Ph H-4), 4.01 (t, 1H, $^3J_{H,H}$ = 8.1 Hz, CH), 1.29 (d, 2H, $^3J_{H,H}$ = 8.1 Hz, CH_2), -0.16 (s, 3H, CH_3).

^{13}C NMR (125 MHz, C_6D_6) δ: 147.5 (Ph C-1), 128.6 (Ph C-3,5), 128.0 (Ph C-2,6), 126.3 (Ph C-4), 47.7 (CH), 24.3 (CH_2), -1.1 ($SiCH_3$).

HRMS (ESI), *m/z*: calcd. for $C_{17}H_{22}NaSi^+$: 277.1383 $[M+Na]^+$; found: 277.1385.

[(2-Phenylethyl)sulfanyl]benzene (85)



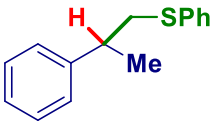
By following the **General procedure 6**, starting from benzaldehyde (150 mg, 1.41 mmol, 1 equiv) in dry THF (3 mL), thioanisole (0.25 mL, 2.16 mmol, 1.5 equiv), DABCO (242 mg, 2.16 mmol, 1.5 equiv), *n*-butyllitium 2.5 M in *n*-hexane (0.78 mL, 1.96 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (72 mg, 0.14 mmol, 0.1 equiv) and hexylsilane (0.23 mL, 1.41 mmol, 1 equiv), **compound 85** was obtained in 83% yield (250 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (m, 2H, SPh H-2,6), 7.31 (m, 2H, Ph H-3,5), 7.30 (m, 2H, SPh H-3,5), 7.23 (m, Ph H-4), 7.20 (m, 3H, SPh H-4, Ph H-2,6), 3.18 (m, 2H, $C\underline{H_2}S$), 2.93 (m, 2H, Ph-$C\underline{H_2}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.2 (Ph C-1), 136.3 (SPh C-1), 129.2 (2C, SPh C-2,6), 128.9 (2C, Ph C-3,5), 128.5 (4C, SPh C-3,5, Ph C-2,6), 126.4 (Ph C-4), 126.0 (SPh C-4), 35.6 (Ph-$\underline{C}H_2$), 35.1 (SCH_2).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{14}NaS^+$: 237.0708 $[M+Na]^+$; found: 237.0709.

[(2-Phenylpropyl)sulfanyl]benzene (86)



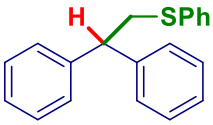
By following the **General procedure 6**, starting from acetophenone (150 mg, 1.25 mmol, 1 equiv) in dry THF (3 mL), thioanisole (0.22 mL, 1.88 mmol, 1.5 equiv), DABCO (210 mg, 1.88 mmol, 1.5 equiv), *n*-butyllitium 2.5 M in *n*-hexane (0.7 mL, 1.75 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (66 mg, 0.13 mmol, 0.1 equiv) and hexylsilane (0.2 mL, 1.25 mmol, 1 equiv), **compound 86** was obtained in 81% yield (231 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 95:5 v/v as eluent).

^{1}H NMR (500 MHz, C_6D_6) δ: 7.22 (m, 2H, SPh H-2,6), 7.13 (m, 2H, Ph H-3,5), 7.06 (m, 1H, Ph H-4), 7.01 (m, 2H, SPh H-3,5), 6.97 (m, 2H, Ph H-2,6), 6.92 (m, 1H, SPh H-4), 3.03 (dd, 1H, $^{2}J_{H,H}$= 12.0 Hz, $^{3}J_{H,H}$= 5.3 Hz, CH_2S), 2.83 (m, 1H, CH), 2.79 (dd, 1H, $^{2}J_{H,H}$= 12.0 Hz, , $^{3}J_{H,H}$= 8.4 Hz, CH_2S), 1.22 (d, 3H, $^{3}J_{H,H}$= 6.7 Hz, CH_3).

^{13}C NMR (125 MHz, C_6D_6) δ: 145.9 (Ph C-1), 137.7 (SPh C-1), 129.3 (SPh C-2,6), 129.2 (SPh C-3,5), 128.8 (Ph C-3,5), 127.3 (Ph C-2,6), 126.8 (Ph C-4), 125.9 (SPh C-4), 42.0 (CH_2S), 39.7 (CH), 21.1 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{15}H_{16}NaS^{+}$: 351.0865 $[M+Na]^{+}$; found: 351.0867.

1,1'-[2-(Phenylsulfanyl)-1,1- ethanediyl]dibenzene (87)



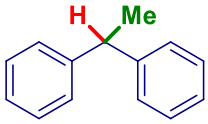
By following the **General procedure 6**, starting from benzophenone (150 mg, 0.8 mmol, 1 equiv) in dry THF (3 mL), thioanisole (0.14 mL, 1.2 mmol, 1.5 equiv), DABCO (134 mg, 1.2 mmol, 1.5 equiv), *n*-butyllitium 2.5 M in *n*-hexane (0.45 mL, 1.22 mmol, 1.4 equiv), tris(pentafluorophenyl)borane (41 mg, 0.08 mmol, 0.1 equiv) and hexylsilane (0.13 mL, 0.8 mmol, 1 equiv), **compound 87** was obtained in 85% yield (197 mg) as colorless oil after column chromatography on silica gel (*n*-hexane/diethyl ether 95:5 v/v as eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33(m, 6H, Ph H-3,5, SPh H-2,6), 7.30 (m, 2H, SPh H-3,5), 7.27 (m, 4H, Ph H-2,6), 7.24 (m, 2H, Ph H-4), 7.21 (m, 1H, SPh H-4), 4.24 (t, $^{3}J_{H,H}$ = 7.9 Hz, 1H, CH), 3.63 (d, $^{3}J_{H,H}$ = 7.9 Hz, 2H, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.0 (Ph C-1),136.5 (SPh C-1), 129.4 (SPh C-2,6), 128.9 (SPh C-3,5), 128.5 (Ph C-3,5), 127.9 (Ph C-2,6), 126.7 (Ph C-4), 126.0 (SPh C-4), 50.5 (CH), 39.6 (CH_2).

HRMS (ESI), *m/z*: calcd. for $C_{20}H_{18}NaS^{+}$: 313.1021 $[M+Na]^{+}$; found: 313.1023.

1,1'-(1,1-ethanediyl)dibenzene (88)



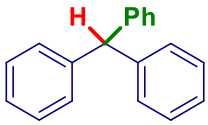
By following the **General procedure 5**, starting from benzophenone (200 mg, 1.09 mmol, 1 equiv) in dry THF (3 mL), MeLi solution 1.6 M in THF (1.02 mL, 1.64 mmol, 1.5 equiv) , tris(pentafluorophenyl)borane (55 mg, 0.11 mmol, 0.1 equiv) and hexylsilane (0.17 mL, 1.09 mmol, 1 equiv), **compound 88** was obtained in 91% yield (183 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (m, 4H, Ph H-3,5), 7.26 (m, 4H, Ph H-2,6), 7.22 (m, 2H, Ph H-4), 4.19 (q, 1H, $^{3}J_{H,H}$ = 7.3 Hz, CH), 1.68 (d, 3H, $^{3}J_{H,H}$ = 7.3 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 146.3 (Ph C-1), 128.3 (Ph C-3,5) 127.6 (Ph C-2,6), 126.0 (Ph C-4), 44.7 (CH), 21.8 (CH_3).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{14}Na^{+}$: 205.0988 $[M+Na]^{+}$; found: 205.0989.

Triphenylmethane (89)



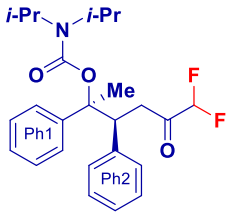
By following the **General procedure 5**, starting from benzophenone (200 mg, 1.09 mmol, 1 equiv) in dry THF (3 mL), phenyllithium solution 1.9 M in *n*-Bu_2O (0.79 mL, 1.64 mmol, 1.5 equiv), tris(pentafluorophenyl)borane (55 mg, 0.11 mmol, 0.1 equiv) and hexylsilane (0.17 mL, 1.09 mmol, 1 equiv), **compound 89** was obtained in 83% yield (222 mg) as colorless oil after column chromatography on silica gel (*n*-hexane as eluent).

^{1}H-NMR (400 MHz, CDCl3) δ: 7.31 (m, 6H, Ph H-3,5), 7.23 (m, 3H, Ph H-4), 7.15 (m, 6H, Ph H-2,6), 5.58 (s, 1H, CH).

^{13}C NMR (100 MHz, CDCl3) δ: 143.9 (Ph C-1), 129.4 (Ph C-2,6), 128.3 (Ph C-3,5), 126.3 (Ph C-4), 56.8 (CH).

HRMS (ESI), *m/z*: calcd for $C_{19}H_8^{+}$: 245.1325 $[M+H]^{+}$; found 245.1327.

(2*S*,3*R*)-6,6-difluoro-5-oxo-2,3-diphenyl-2-hexanyl diisopropylcarbamate (91)



By following the General Procedure **7**, starting from 5-[methoxy(methyl)amino]-5-oxo-2,3-diphenylpentan-2-yl diisopropylcarbamate (15 mg, 0.0344 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.02 mL, 0.1 mmol, 3 equiv), potassium *tert*-pentoxide 0.9 M (0.08 mL, 0.07 mmol, 2 equiv) and dry THF (2 mL), the desired 6,6-difluoro-5-oxo-2,3-diphenyl-2-hexanyl diisopropylcarbamate was obtained in 91% yield (13 mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 8:2).
The corresponding racemic sample (MaMi-349) has been prepared starting from racemic 5-(methoxy(methyl)amino)-5-oxo-2,3-diphenylpentan-2-yl diisopropylcarbamate and spectroscopic data match with those ones reported below.
$[\alpha]^{20}D$: -20.1 (c 0.5 $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6) δ: 7.16 (m, 1H, Ph1 H-2,6), 7.10 (m, 2H, Ph1, H-3,5), 7.02 (m, 1H, Ph1 H-4), 7.02 (m, 3H, Ph2 H3,4,5), 6.95 (m, 2H, Ph2 H-2,6), 4.78 (t, $^{2}J_{H,F}$ = 54.0 Hz, 1H, CHF_2), 4.09 (dd, 1H, $^{3}J_{H,H}$ = 9.8 Hz, $^{3}J_{H,H}$ = 4.5 Hz, H-3), 4.08 and 3.38 (br m, 2H, N-CH), 3.09 – 2.94 (m, 2H, CH_2), 1.91 (s, 3H, C-CH_3), 1.20 – 0.9 (br m, 6H, CH-CH_3).

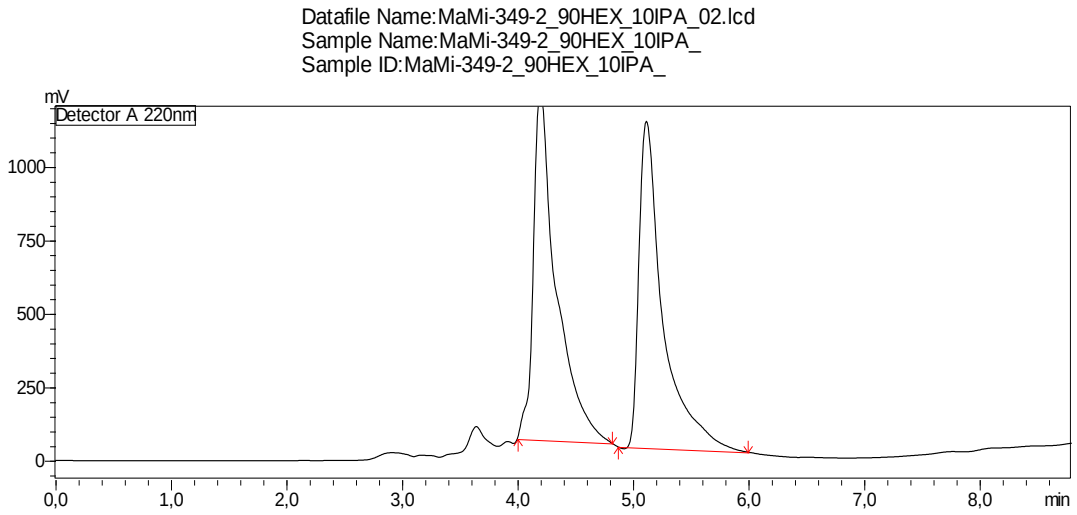
^{13}C NMR (100 MHz, C_6D_6) δ: 197.1 (t, $^{2}J_{C,F}$ = 25.8 Hz, C=O), 152.6 (N-C=O), 143.8 (Ph1 C-1), 139.5 (Ph2 C-1), 130.6 (Ph2 C-2,6), 128.0 (Ph1 C-3,5), 127.9 (Ph2 C-3,5), 127.4 (Ph2 C-4), 127.3 (Ph1 C-4), 126.4 (Ph1 C-2,4), 110.0 (t, $^{1}J_{C,F}$ = 252.6 Hz, CHF_2), 84.3 (C-2), 51.6 (C-3), 46.7 (br, CH-N), 45.6 (br, CH-N), 37.8 (C-4), 22.5 (CH_3), 20.8 -21.2 (br, 4C, -CH-CH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -127.1 (d, $^{2}J_{H,F}$ = 54.0 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{25}H_{31}F_2NO_3Na^+$: 454.2164 $[M+Na]^+$; found: 454.2162.

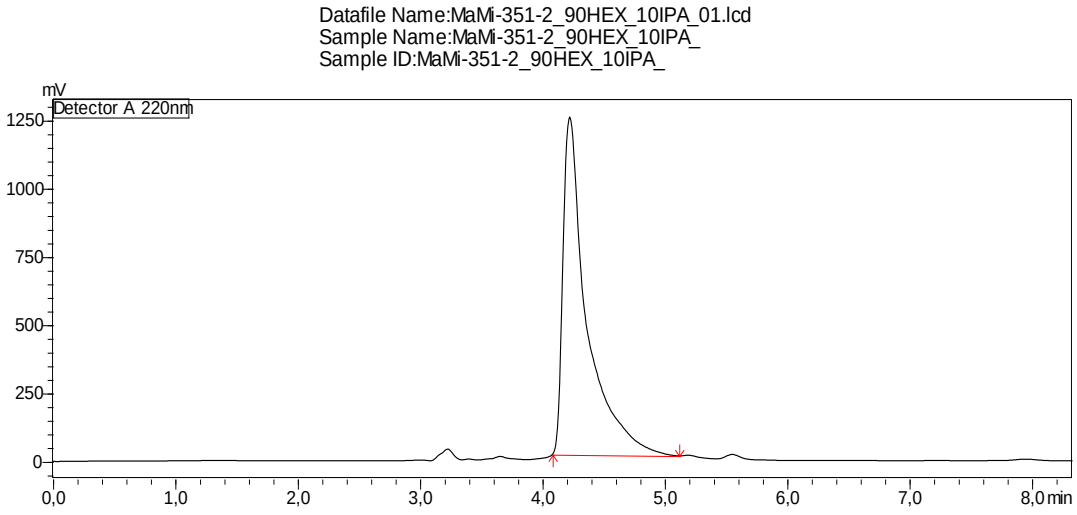
HPLC analysis: Chiralpak IA Column, λ 220 nm, eluent: n-hexane / i-propanol 9:1. Flow: 1 mL/min

Racemate:



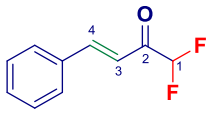
Peaks	Ret. Time	Area	Area%
1	4,200	16320433	50,562
2	5,118	15957427	49,438
Total		32277860	100,000

Enantioenriched:



Peaks	Ret. Time	Area	Area%
1	4,224	16687470	100,00
		16687470	100,00

(3*E*)-1,1-difluoro-4-phenyl-3-buten-2-one (92)



By following the General procedure **7**, starting from *N*-methoxy-*N*-methylcinnamamide (100 mg, 0.52 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.15 mL, 1.05 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.05 mL, 0.94 mmol, 1.8 equiv) and dry THF (5 mL), the desired (3*E*)-1,1-difluoro-4-phenyl-3-buten-2-one was obtained in 92% yield (87 mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 9:1 v/v as eluent).

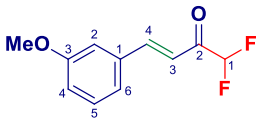
^{1}H NMR (400 MHz, C_6D_6) δ: 7.69 (d, $^{3}J_{H,H}$ = 16.1 Hz, 1H, H-4), 6.99 (m, 1H, Ph H-4), 6.98 (m, 2H, Ph H-2,6), 6.92 (m, 2H, Ph H-3,5), 6.76 (dt, $^{3}J_{H,H}$ = 16.1 Hz, $^{4}J_{H,F}$ = 1.3 Hz, 1H, H-3), 5.37 (t, $^{2}J_{H,F}$ = 54.1 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 187.2 (t, $^{2}J_{C,F}$ = 25.6 Hz, C=O), 147.6 (C-4), 134,1 (Ph C-1), 131.4 (Ph C-4), 129.1 (Ph C-2,6), 129.0 (Ph C-3,5), 118.1 (C-3), 111.0 (t, $^{1}J_{C,F}$ = 252.5 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -125.9 (d, $^{2}J_{H,F}$ = 54.1 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_8F_2ONa^+$: 205.0435 [M+Na]$^+$; found: 205.0434.

(3*E*)-1,1-difluoro-4-(3-methoxyphenyl)-3-buten-2-one (93)



By following the General procedure **7**, starting from (*E*)-*N*-methoxy-3-(3-methoxyphenyl)-*N*-methylacrylamide (50 mg, 0.23 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.06 mL, 0.45 mmol, 2 equiv) , potassium *tert*-pentoxide 0.9 M (0.45 mL, 0.41 mmol, 1.8 equiv) and in dry THF (5 mL), the desired (*E*)-1,1-difluoro-4-(3-methoxyphenyl)-3-buten-2-one was obtained in 91% yield (44 mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 97:3 v/v as eluent).

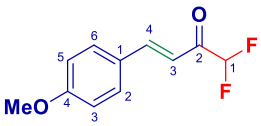
^{1}H NMR (400 MHz, C_6D_6) δ: 7.71 (d, $^{3}J_{H,H}$ = 16.1 Hz, 1H, H-4), 6.90 (m, 1H, Ph H-5), 6.81 (td, $^{3}J_{H,H}$= 16.1 Hz, $^{4}J_{H,F}$= 1.2 Hz, 1H, H-3), 6.76 (m, 1H, Ph H-2), 6.73 (m, 1H, Ph H-6), 6.70 (m, 1H, Ph H-4), 5.39 (t, $^{2}J_{H,F}$ = 54.1 Hz, 1H, CHF_2), 3.20 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 187.3 (t, $^{2}J_{C,F}$ = 25.6 Hz, C=O), 160.4 (Ph C-3), 147.7 (C-4), 135.5 (Ph C-1), 130.1 (Ph C-5), 121.6 (Ph C-6), 118.4 (C-3), 117.9 (Ph C-4), 113.9 (Ph C-2), 111.0 (t, $^{1}J_{C,F}$ = 252.4 Hz, CHF_2), 54.8 (OCH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -126.0 (dd, $^{2}J_{H,F}$ = 54.1 Hz, $^{4}J_{H,F}$ = 1.2 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{10}F_2O_2Na^+$: 235.0541 $[M+Na]^+$; found: 235.0544.

(3*E*)-1,1-difluoro-4-(4-methoxyphenyl)-3-buten-2-one (94)



By following the general procedure **7**, (*E*)-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methylacrylamide (100 mg, 0.452 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.12 mL, 0.9 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.9 mL, 0.8136 mmol, 1.8 equiv) and dry THF (5 mL), the desired (3*E*)-1,1-difluoro-4-(4-methoxyphenyl)-3-buten-2-one was obtained in 91% yield (87 mg) as transparent oil without any further purification.

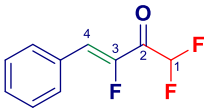
^{1}H NMR (400 MHz, C_6D_6) δ: 7.79 (d, $^3J_{H,H}$ = 16.0 Hz, 1H, H-4), 6.98 (m, 2H, Ph H-2,6), 6.79 (dt, $^3J_{H,H}$ = 16.0 Hz, $^4J_{H,F}$ = 1.3 Hz, 1H, H-3), 6.52 (m, 2H, Ph H-3,5), 5.43 (t, $^2J_{H,F}$ = 54.2 Hz, 1H, CHF_2), 3.16 (s, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 187.2 (t, $^2J_{C,F}$ = 25.4 Hz, C=O), 162.8 (Ph C-4), 147.5 (C-4), 131.1 (Ph C-2,6), 126.9 (Ph C-1), 115.7 (C-3), 114.6 (Ph C-3,5), 111.3 (t, $^1J_{C,F}$ = 252.7 Hz, CHF_2), 54.9 (CH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -125.7 (dd, $^2J_{H,F}$ = 54.2 Hz, $^4J_{H,F}$ = 1.3 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{10}F_2O_2Na^+$: 235.0541 $[M+Na]^+$; found: 235.0543.

1,1,3-trifluoro-4-phenyl-3-buten-2-one (95)



By following the general procedure **7**, 2-fluoro-*N*-methoxy-*N*-methyl-3-phenylacrylamide (100 mg, 0.48 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.13 mL, 0.96 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.96 mL, 0.86 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1,1,3-trifluoro-4-phenyl-3-buten-2-one was obtained in 94% yield (90 mg) as transparent oil without any further purification.

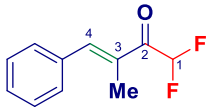
^{1}H NMR (400 MHz, C_6D_6) δ: 7.28 (m, 2H, Ph H-2,6), 6.98 (m, 3H, Ph H-3,4,5), 6.75 (d, $^3J_{H,F}$ = 36.9 Hz, 1H, H-4), 5.46 (dt, $^2J_{H,F}$ = 53.0 Hz, $^4J_{H,F}$ = 2.2 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 180.9 (dt, $^2J_{C,F}$ = 32.0 Hz, $^2J_{C,F}$ = 25.5 Hz, C=O), 151.3 (d, $^1J_{C,F}$ = 267.9 Hz, C-3), 131.4 (d, $^4J_{C,F}$ = 8.3 Hz, Ph C-2,6), 131.0 (d, $J_{C,F}$ = 2.9 Hz, Ph C-4), 130. 6 (d, $^3J_{C,F}$ = 4.1 Hz, Ph C-1), 129.1 (Ph C-3,5), 121.4 (m, C-4), 109.3 (t, $^1J_{C,F}$ = 251.2 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -129.1 (dt, $^3J_{H,F}$ = 36.9 Hz, $^4J_{F,F}$ = 7.8 Hz, =CH-F), -126.0 (dd, $^2J_{H,F}$ = 53.0 Hz, $^4J_{F,F}$ = 7.8 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_7F_3ONa^+$: 223.0341 [M+Na]$^+$; found: 223.0342.

1,1-difluoro-3-methyl-4-phenyl-3-buten-2-one (96)



By following the general procedure **7**, 2-fluoro-*N*-methoxy-*N*-methyl-3-phenylacrylamide (100 mg, 0.49 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.14 mL, 0.97 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.96 mL, 0.86 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1,1-difluoro-3-methyl-4-phenyl-3-buten-2-one was obtained in 93% yield (89 mg) as transparent oil without any further purification.

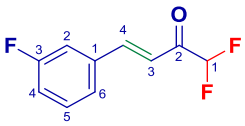
^{1}H NMR (400 MHz, C_6D_6) δ: 7.43 (q, $^4J_{H,H}$ = 1.3 Hz, 1H, H-4), 7.05 (m, 5H, Ph H-2,3,4,5,6), 5.77 (t, $^2J_{H,F}$ = 53.7 Hz, 1H, CHF_2), 1.85 (dt, $^5J_{H,F}$ = 0.7 Hz, $^4J_{H,H}$ = 1.3 Hz, CH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 188.7 (t, $^2J_{C,F}$ = 23.6 Hz, C=O), 143.8 (t, $^4J_{C,F}$ = 3.6 Hz, C-4), 135,2 (Ph C-1), 133.1 (t, $^3J_{C,F}$ = 1.0 Hz, C-3), 130.4 (Ph C-2,6), 129.5 (Ph C-4), 128.7 (Ph C-3,5), 110.8 (t, $^1J_{C,F}$ = 252.4 Hz, CHF_2), 12.9 (CH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -120.9 (d, $^2J_{H,F}$ = 53.7 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{10}F_2ONa^+$: 219.0592 [M+Na]$^+$; found: 219.0591.

(*E*)-1,1-difluoro-4-(3-fluorophenyl)-3-buten-2-one (97)



By following the general procedure **7**, (*E*)-3-(3-fluorophenyl)-*N*-methoxy-*N*-methylacrylamide (120 mg, 0.57 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.16 mL, 1.15 mmol, 2 equiv), potassium

tert-pentoxide 0.9 M (1.14 mL, 1.026 mmol, 1.8 equiv) and dry THF (5 mL), the desired (*E*)-1,1-difluoro-4-(3-fluorophenyl)-3-buten-2-one was obtained in 93% yield (106 mg) as transparent oil, after column chromatography on silica gel (hexane/ethyl acetate 9:1 v/v as eluent).

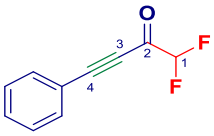
^{1}H NMR (400 MHz, C_6D_6) δ: 7.48 (d, $^{3}J_{H,H}$ = 16.0 Hz, 1H, H-4), 6.68 (m, 2H, Ph H-2 and Ph H-5), 6.67 (m, 1H, Ph H-4), 6.61 (m, 1H, Ph H-6), 6.60 (m, 1H, H-3), 5.35 (t, $^{2}J_{H,F}$ = 54.0 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 187.1 (t, $^{2}J_{C,F}$ = 25.8 Hz, C=O), 163.2 (d, $^{1}J_{C,F}$ = 247.0 Hz, Ph C-3), 146.0 (m, C-4), 136.2 (d, $^{3}J_{C,F}$ = 7.7 Hz, Ph C-1), 130.5 (d, $^{3}J_{C,F}$ = 8.1 Hz, Ph C-5), 125.0 (d, $^{4}J_{C,F}$ = 2.9 Hz, Ph C-6), 119.2 (C-3), 118.2 (d, $^{2}J_{C,F}$ = 21.4 Hz, Ph C-4), 115. 2 (d, $^{2}J_{C,F}$ = 21.9 Hz, Ph C-2), 110.9 (t, $^{1}J_{C,F}$ = 252.5 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -126.1 (d, $^{2}J_{H,F}$ = 54.0 Hz, CHF_2), -112.3 (m, Ph-F)

HRMS (ESI), *m/z*: calcd. for $C_{10}H_7F_3ONa^+$: 223.0341 [M+Na]$^+$; found: 223.0343.

1,1-difluoro-4-phenyl-3-butyn-2-one (98)



By following the general procedure **7**, *N*-methoxy-*N*-methyl-3-phenylpropiolamide (100 mg, 0.53 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.15 mL, 1.06 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.06 mL, 0.95 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1,1-difluoro-4-phenyl-3-butyn-2-one was obtained in 96% yield (91 mg) as transparent oil without any further purification.

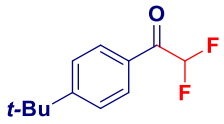
^{1}H NMR (400 MHz, C_6D_6) δ: 7.14 (m, 2H, Ph H-2,6), 6.89 (m, 1H, Ph H-4), 6.77 (m, 2H, Ph H-3,5), 5.12 (t, $^{2}J_{H,F}$ = 54.2 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 175.3 (t, $^{2}J_{C,F}$ = 29.8 Hz, C=O), 133.8 (Ph C-2,6), 131.7 (Ph C-4), 128.8 (Ph C-3,5), 118.9 (Ph C-1), 109.3 (t, $^{1}J_{C,F}$ = 252.4 Hz, CHF_2), 98.5 (C-4), 84.7 (C-3).

^{19}F NMR (376 MHz, C_6D_6) δ: -125.2 (d, $^{2}J_{H,F}$ = 54.2 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_6F_2ONa^+$: 181.0459 [M+Na]$^+$; found: 181.0457.

1-(4-*tert*-butylphenyl)-2,2-difluoroethanone (99)



By following the general procedure **7**, 4-(*tert*-butyl)-*N*-methoxy-*N*-methylbenzamide (100 mg, 0.45 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.12 mL, 0.9 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.9 mL, 0.81 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1-(4-tert-butylphenyl)-2,2-difluoroethanone was obtained in 96% yield (92 mg) as transparent oil without any further purification.

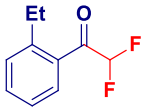
^{1}H NMR (400 MHz, C_6D_6) δ: 7.88 (m, 2H, Ph H-2,6), 7.08 (m, 2H, Ph H-3,5), 5.73 (t, $^{2}J_{H,F}$= 53.6 Hz, 1H, CHF_2), 1.05 (s, 9H, C-CH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 187.0 (t, $^{2}J_{C,F}$ = 25.0 Hz, C=O), 158.4 (Ph C-4), 129.8 (t, $^{4}J_{C,F}$ = 2.2 Hz, Ph C-2,6), 129.6 (t, $^{3}J_{C,F}$ = 1.7 Hz, Ph C-1), 126.1 (Ph C-3,5), 111.7 (t, $^{1}J_{C,F}$ = 253.1 Hz, CHF_2), 35.1 [*C*$(CH_3)_3$], 30.8 (CH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -121.8 (d, $^{2}J_{H,F}$ = 53.6 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_{14}F_2ONa^+$: 235.0905 $[M+Na]^+$; found: 235.0905.

1-(2-ethylphenyl)-2,2-difluoroethanone (100)



By following the general procedure **7**, 2-ethyl-*N*-methoxy-*N*-methylbenzamide (50 mg, 0.26 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.07 mL, 0.52 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.52 mL, 0.47 mmol, 1.8 equiv), and dry THF (5 mL), the desired 1-(2-ethylphenyl)-2,2-difluoroethanone was obtained in 95% yield (45 mg) as transparent oil without any further purification.

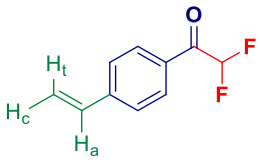
^{1}H NMR (400 MHz, C_6D_6) δ: 7.43 (m, 1H, Ph H-6), 7.01 (m, 1H, Ph H-4), 6.89 (m, 1H, Ph H-3), 6.82 (m, 1H, Ph H-5), 5.64 (t, $^{2}J_{H,F}$ = 53.7 Hz, 1H, CHF_2), 2.75 (q, $^{3}J_{H,H}$ = 7.5 Hz, 2H, CH_2), 1.10 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 190.1 (t, $^2J_{C,F}$ = 24.4 Hz, C=O), 147.2 (Ph C-2), 133.2 (Ph C-4), 131.6 (Ph C-1), 131.0 (Ph C-3), 130.0 (t, $^4J_{C,F}$ = 3.6 Hz, Ph C-6), 125.8 (Ph C-5), 110.8 (t, $^1J_{C,F}$ = 253.4 Hz, CHF_2), 27.4 (CH_2), 15.8 (CH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.1 (dd, $^2J_{H,F}$ = 53.7 Hz, $J_{H,F}$ = 1.7 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{10}F_2ONa^+$: 207.0592 [M+Na]$^+$; found: 207.0590.

2,2-difluoro-1-(4-vinylphenyl)ethanone (101)



By following the general procedure **7**, *N*-methoxy-*N*-methyl-4-vinylbenzamide (100 mg, 0.52 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.14 mL, 1.046 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.04 mL, 0.936 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-(4-vinylphenyl)ethanone was obtained in 94% yield (89 mg) as transparent oil without any further purification.

Scaling-up of the reaction (15 mmol) - By following the general procedure *N*-methoxy-*N*-methyl-4-vinylbenzamide (2885 mg, 15 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (4.04 mL, 30 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (30 mL, 27 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-(4-vinylphenyl)ethanone **12** was obtained in 90% yield (2459 mg) as a transparent oil without any further purification. *Spectroscopic and spectrometric data match with those reported for the 0.52 mmol scale reaction.*

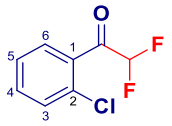
^{1}H NMR (400 MHz, C_6D_6) δ: 7.80 (m, 2H, Ph H-2,6), 6.98 (m, 2H, Ph H-3,5), 6.33 (dd, 1H, $^3J_{H,H}$ = 17.6 (trans), $^3J_{H,H}$ = 10.8 Hz (cis), 1H, H_a), 5.66 (t, $^2J_{H,F}$ = 53.5 Hz, 1H, CHF_2), 5.50 (d, 1H, $^3J_{H,H}$ = 17.6 Hz, H_t), 5.06 (d, 1H, $^3J_{H,H}$ = 10.8, 1H, H_c).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.7 ($^2J_{C,F}$ = 25.1 Hz, C=O), 143.6 (Ph C-4), 135.9 (=CH-Ar), 131.1 (t, $^3J_{C,F}$ = 1.7 Hz, Ph C-1), 130.1 (t, $^4J_{C,F}$ = 2.3 Hz, Ph C-2,6), 126.7 (Ph C-3,5), 117.5 (=CH_2), 111.5 (t, $^1J_{C,F}$ = 253.0 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.0 (d, $^2J_{H,F}$ = 53.6 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_8F_2ONa^+$: 205.0435 [M+Na]$^+$; found: 205.0433.

1-(2-chlorophenyl)-2,2-difluoroethanone (102)



By following the general procedure **7**, 2-chloro-*N*-methoxy-*N*-methylbenzamide (100 mg, 0.50 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.14 mL, 1.00 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.00 mL, 0.90 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1-(2-chlorophenyl)-2,2-difluoroethanone was obtained in 94% yield (89 mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 8:2 v/v as eluent).

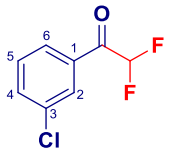
^{1}H NMR (400 MHz, C_6D_6) δ: 7.16 (m, 1H, Ph H-6), 6.87 (m, 1H, Ph H-3), 6.65 (m, 1H, Ph H-4), 6.60 (m, 1H, Ph H-5), 5.82 (t, $^{2}J_{H,F}$ = 53.5 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 189.8 (t, $^{2}J_{C,F}$ = 26.0 Hz, C=O), 133.6 (Ph C-1), 133.3 (Ph C-4), 132.7 (Ph C-2), 130.8 (Ph C-3), 130.5 (t, $^{4}J_{C,F}$ = 2.0 Hz, Ph C-6), 126.9 (Ph C-5), 111.0 (t, $^{1}J_{C,F}$ = 251.9 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -124.7 (d, $^{2}J_{H,F}$ = 53.5 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_8H_5ClF_2ONa^+$: 212.9889 $[M+Na]^+$; found: 212.9890.

1-(3-chlorophenyl)-2,2-difluoroethanone (103)



By following the general procedure **7**, 3-chloro-*N*-methoxy-*N*-methylbenzamide (100 mg, 0.50 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.14 mL, 1.0 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1 mL, 0.9 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1-(3-chlorophenyl)-2,2-difluoroethanone was obtained in 92% yield (87mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 9:1 v/v as eluent).

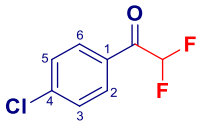
^{1}H NMR (400 MHz, C_6D_6) δ: 7.82 (m, 1H, Ph H-2), 7.47 (m, 1H, Ph H-6), 6.98 (m, 1H, Ph H-4), 6.58 (m, 1H, Ph H-5), 5.47 (t, $^{2}J_{H,F}$ = 53.2 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.0 (t, $^2J_{C,F}$ = 25.5 Hz, C=O), 135.3 (Ph C-3), 134.4 (Ph C-4), 133.3(t, $^4J_{C,F}$ = 1.6 Hz, Ph C-1), 130.2 (Ph C-5), 129.5 (t, $^4J_{C,F}$ = 2.1 Hz, Ph C-2), 127.5 (t, $^4J_{C,F}$ = 2.6 Hz, Ph C-6), 110.9 (t, $^1J_{C,F}$ = 252.8 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.5 (d, $^2J_{H,F}$ = 53.2 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_8H_5ClF_2ONa^+$: 212.9889 [M+Na]$^+$; found: 212.9887.

1-(4-chlorophenyl)-2,2-difluoroethanone (104)



By following the general procedure **7**, 4-chloro-*N*-methoxy-*N*-methylbenzamide (100 mg, 0.5 mmol, 1 equiv), (Difluoromethyl)Trimethylsilane (0.14 mL, 1 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1 mL, 0.9 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1-(4-chlorophenyl)-2,2-difluoroethanone was obtained in 95% yield (90 mg) as transparent oil without any further purification.

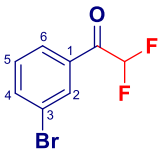
^{1}H NMR (400 MHz, C_6D_6) δ: 7.49 (m, 2H, Ph H-2,6), 6.84 (m, 2H, Ph H-3,5), 5.52 (t, $^2J_{H,F}$ = 53.4 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.1 (t, $^2J_{C,F}$ = 25.3 Hz, C=O), 141.2 (Ph C-4), 131.0 (t, $^4J_{C,F}$ = 2.3 Hz, Ph C-2,6), 130.1 (t, $^3J_{C,F}$ = 1.8 Hz, Ph C-1), 129.3 (Ph C-3,5), 111.2 (t, $^1J_{C,F}$ = 253.0 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.2 (d, $^2J_{H,F}$ = 53.4 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_8H_5ClF_2ONa^+$: 212.9889 [M+Na]$^+$; found: 212.9888.

1-(3-bromophenyl)-2,2-difluoroethanone (105)



By following the general procedure **7**, 3-bromo-*N*-methoxy-*N*-methylbenzamide (100 mg, 0.41 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.11 mL, 0.82 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.82 mL, 0.74 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1-(3-bromophenyl)-

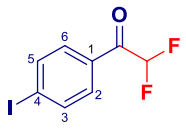
2,2-difluoroethanone was obtained in 91% yield (87 mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 9:1 v/v as eluent).
^{1}H NMR (400 MHz, C_6D_6) δ: 7.98 (m, 1H, Ph H-2), 7.50 (m, 1H, Ph H-6), 7.14 (m, 1H, Ph H-4), 6.52 (m, 1H, Ph H-5), 5.47 (t, $^{2}J_{H,F}$ = 53.2 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 185.9 (t, $^{2}J_{C,F}$ = 25.5 Hz, C=O), 137.4 (Ph C-4), 133.5 (t, $^{3}J_{C,F}$ = 1.6Hz, Ph C-1), 132.4 (t, $^{4}J_{C,F}$ = 2.1Hz, Ph C-2), 130.4 (Ph C-5), 127.9 (t, $^{4}J_{C,F}$ = 2.5Hz, Ph C-6), 123.3 (Ph C-3), 110.8 (t, $^{1}J_{C,F}$ = 252.8 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.6 (d, $^{2}J_{H,F}$ = 53.2 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_8H_5BrF_2ONa^+$: 256.9384 [M+Na]$^+$; found: 256.9380.

2,2-difluoro-1-(4-iodophenyl)ethanone (106)



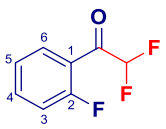
By following the general procedure **7**, 4-iodo-*N*-methoxy-*N*-methylbenzamide (100 mg, 0.34 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.1 mL, 0.69 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.61 mL, 0.61 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-(4-iodophenyl)ethanone was obtained in 93% yield (89 mg) as transparent oil without any further purification.
^{1}H NMR (400 MHz, C_6D_6) δ: 7.25 (s, 4H, Ph H-2,3,5,6), 5.50 (t, $^{2}J_{H,F}$ = 53.4 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.7 (t, $^{2}J_{C,F}$ = 25.4 Hz, C=O), 138.3 (Ph C-3,5), 130.9 (t, $^{3}J_{C,F}$ = 1.7 Hz, Ph C-1), 130.6 (t, $^{4}J_{C,F}$ = 2.3 Hz, Ph C-2,6), 111.1 (t, $^{1}J_{C,F}$ = 253.0 Hz, CHF_2), 103.3 (Ph C-4).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.3 (d, $^{2}J_{H,F}$ = 53.4 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_8H_5F_2IONa^+$: 304.9245 [M+Na]$^+$; found: 304.9243.

2,2-difluoro-1-(2-fluorophenyl)ethanone (107)



By following the general procedure **7**, 2-fluoro-*N*-methoxy-*N*-methylbenzamide (100 mg, 0.55 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.15 mL, 1.1 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.1 mL, 0.99 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-(2-fluorophenyl)ethanone was obtained in 90% yield (86 mg) as transparent oil without any further purification.

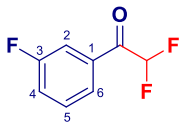
^{1}H NMR (400 MHz, C_6D_6) δ: 7.60 (m, 1H, Ph H-6), 6.75 (m, 1H, Ph H-4), 6.53 (m, 1H, Ph H-5), 6.48 (m, 1H, Ph H-3), 5.84 (dt, $^{5}J_{H,F}$ = 2.9 Hz, $^{2}J_{H,F}$ = 53.2 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 185.5 (dt, $^{3}J_{C,F}$= 3.6 Hz, $^{2}J_{C,F}$ = 25.6 Hz, C=O), 162.1 (d, $^{1}J_{C,F}$ = 256.3 Hz, Ph C-2), 136.1 (d, $^{3}J_{C,F}$ = 9.1 Hz, Ph C-4), 131.3 (m, Ph C-6), 124.8 (d, $^{4}J_{C,F}$ = 3.3 Hz, Ph C-5), 121.5 (d, $^{2}J_{C,F}$ = 13.6 Hz, Ph C-1), 116. 5 (d, $^{2}J_{C,F}$ = 22.9 Hz, Ph C-3), 110.0 (dt, $^{1}J_{C,F}$ = 249.1 Hz, $^{4}J_{C,F}$ = 7.9 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -127.8 (dd, $^{2}J_{H,F}$ = 53.2 Hz, $^{5}J_{F,F}$ = 12.8 Hz, CHF_2), -108.8 (m, Ph-F)

HRMS (ESI), *m/z*: calcd. for $C_8H_6F_3O^+$: 175.0365 $[M+H]^+$; found: 175.0362.

2,2-difluoro-1-(3-fluorophenyl)ethanone (108)



By following the general procedure **7**, 3-fluoro-*N*-methoxy-*N*-methylbenzamide (100 mg, 0.55 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.15 mL, 1.1 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.1 mL, 0.99 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-(3-fluorophenyl)ethanone was obtained in 89% yield (85 mg) as transparent oil without any further purification.

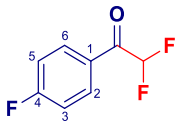
^{1}H NMR (400 MHz, C_6D_6) δ: 7.50 (m, 1H, Ph H-2), 7.42 (m, 1H, Ph H-6), 6.68 (m, 1H, Ph H-4), 6.66 (m, 1H, Ph H-5), 5.50 (t, $^{2}J_{H,F}$ = 53.3 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.1 (dt, $^{4}J_{C,F}$ = 2.3 Hz, $^{2}J_{C,F}$ = 25.4 Hz, C=O), 162.9 (d, $^{1}J_{C,F}$ = 248.6 Hz, Ph C-3), 133.7 (dt, $^{3}J_{C,F}$ = 6.7 Hz, $^{3}J_{C,F}$ = 1.6 Hz, Ph C-1), 130.7 (d, $^{3}J_{C,F}$ = 7.6 Hz, Ph C-5), 125.3 (q, $^{4}J_{C,F}$= 2.8 Hz, Ph C-6), 121.6 (d, $^{2}J_{C,F}$= 21.4 Hz, Ph C-4), 116. 2 (dt, $^{2}J_{C,F}$= 23.0 Hz, $^{4}J_{C,F}$= 2.1 Hz, Ph C-2), 111.0 (t, $^{1}J_{C,F}$= 252.8 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.4 (d, $^{2}J_{H,F}$ = 53.3 Hz, CHF_2), -110.8 (m, Ph-F)

HRMS (ESI), *m/z*: calcd. for $C_8H_5F_3ONa^+$: 197.0185 $[M+Na]^+$; found: 197.0188.

2,2-difluoro-1-(4-fluorophenyl)ethanone (109)



By following the general procedure **7**, 4-fluoro-*N*-methoxy-*N*-methylbenzamide (100 mg, 0.55 mmol, 1 equiv), (Difluoromethyl)Trimethylsilane (0.15 mL, 1.1 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.1 mL, 0.99 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-(4-fluorophenyl)ethanone was obtained in 90% yield (86 mg) as transparent oil without any further purification.

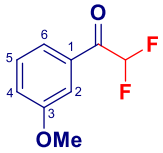
^{1}H NMR (400 MHz, C_6D_6) δ: 7.62 (m, 2H, Ph H-2,6), 6.50 (m, 2H, Ph H-3,5), 5.57 (t, $^{2}J_{H,F}$ = 53.4 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 185.7 (t, $^{2}J_{C,F}$ = 25.4 Hz, C=O), 166.6 (d, $^{1}J_{C,F}$ = 257.1 Hz, Ph C-4), 132.5 (dt, $^{3}J_{C,F}$ = 9.7 Hz, $^{4}J_{C,F}$ = 2.3 Hz, Ph C-2,6), 128.2 (m, Ph C-1), 116.1 (d, $^{2}J_{C,F}$ = 22.2 Hz, Ph C-3,5), 111.4 (t, $^{1}J_{C,F}$ = 253.1 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.0 (d, $^{2}J_{H,F}$ = 53.4 Hz, CHF_2), -102.1 (m, Ph-F).

HRMS (ESI), *m/z*: calcd. for $C_8H_5F_3ONa^+$: 197.0185 $[M+Na]^+$; found: 197.0186.

2,2-difluoro-1-(3-methoxyphenyl)ethanone (110)



By following the general procedure **7**, *N*,3-dimethoxy-*N*-methylbenzamide (100 mg, 0.54 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.15 mL, 1.08 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.08 mL, 0.97 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-(3-methoxyphenyl)ethan-1-one was obtained in 94% yield (94 mg) as transparent oil without any further purification.

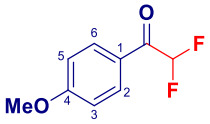
^{1}H NMR (400 MHz, C_6D_6) δ: 7.50 (m, 1H, Ph H-2), 7.43 (m, 1H, Ph H-6), 6.87 (m, 1H, Ph H-5), 6.81 (m, 1H, Ph H-4), 5.67 (t, $^{2}J_{H,F}$ = 53.5 Hz, 1H, CHF_2), 3.15 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 187.1 (t, $^{2}J_{C,F}$ = 24.9 Hz, C=O), 160.4 (Ph C-3), 133.3 (Ph C-1), 130.0 (Ph C-5), 122.4 (t, $^{4}J_{C,F}$ = 2.9 Hz, Ph C-6), 121.8 (Ph C-4), 113.3 (t, $^{4}J_{C,F}$ = 1.7 Hz, Ph C-6), 111.2 (t, $^{1}J_{C,F}$ = 252.7 Hz, CHF_2), 54.8 (OCH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.1 (d, $^{2}J_{H,F}$ = 53.5 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_9H_8F_2O_2Na^+$: 209.0385 [M+Na]$^+$; found: 209.0383.

2,2-difluoro-1-(4-methoxyphenyl)ethanone (111)



By following the general procedure **7**, *N*,4-dimethoxy-*N*-methylbenzamide (100 mg, 0.54 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.15 mL, 1.08 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.08 mL, 0.97 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-(4-methoxyphenyl)ethanone was obtained in 96% yield (96 mg) as transparent oil without any further purification.

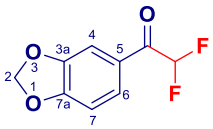
^{1}H NMR (400 MHz, C_6D_6) δ: 7.88 (m, 2H, Ph H-2,6), 6.48 (m, 2H, Ph H-3,5), 5.74 (t, $^{2}J_{H,F}$ = 53.7 Hz, 1H, CHF_2), 3.08 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 188.8 (t, $^{2}J_{C,F}$ = 24.9 Hz, C=O), 164.9 (Ph C-4), 132.2 (t, $^{4}J_{C,F}$ = 2.3 Hz, Ph C-2,6), 125.0 (t, $^{3}J_{C,F}$ = 1.8 Hz, Ph C-1), 114.4 (Ph C-3,5), 111.9 (t, $^{1}J_{C,F}$ = 253.2 Hz, CHF_2), 54.9 (OCH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -121.4 (d, $^{2}J_{H,F}$ = 53.7 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_9H_8F_2O_2Na^+$: 209.0385 [M+Na]$^+$; found: 209.0386.

1-(1,3-benzodioxol-5-yl)-2,2-difluoroethanone (112)



By following the general procedure **7**, *N*-methoxy-*N*-methylbenzo[d][1,3]dioxole-5-carboxamide (100 mg, 0.47 mmol, 1 equiv), (Difluoromethyl)Trimethylsilane (0.13 mL, 0.95 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.94 mL, 0.85 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1-(1,3-benzodioxol-5-yl)-2,2-difluoroethanone was obtained in 91% yield (85 mg) as transparent oil without any further purification.

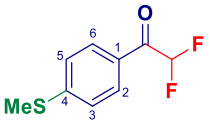
^{1}H NMR (400 MHz, C_6D_6) δ: 7.43 (m, 1H, H-4), 7.39 (m, 1H, H-6), 6.33 (d, $^{3}J_{H,H}$ = 8.2 Hz, 1H, H-7), 5.66 (t, $^{2}J_{H,F}$ = 53.6 Hz, 1H, CHF_2), 5.08 (s, 2H, H-2).

^{13}C NMR (100 MHz, C_6D_6) δ: 185.3 (t, $^{2}J_{C,F}$ = 24.9 Hz, C=O), 153.3 (C-7a), 148.7 (C-3a), 126.8 (t, $^{4}J_{C,F}$ = 3.1 Hz Ph C-6), 126.6 (t, $^{3}J_{C,F}$ = 1.8 Hz, C-5), 111.5 (t, $^{1}J_{C,F}$ = 253.1 Hz, CHF_2), 108.9 (t, $^{4}J_{C,F}$ = 1.8 Hz, C-4), 108.3 (C-7), 101.9 (C-2).

^{19}F NMR (376 MHz, C_6D_6) δ: -121.3 (d, $^{2}J_{H,F}$ = 53.6 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_9H_6F_2O_3Na^+$: 223.0177 $[M+Na]^+$; found: 223.0178.

2,2-difluoro-1-[4-(methylsulfanyl)phenyl)ethanone (113)



By following the general procedure **7**, *N*-methoxy-*N*-methyl-4-(methylthio)benzamide (100 mg, 0.47 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.13 mL, 0.94 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.94 mL, 0.846 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-[4-(methylsulfanyl)phenyl)ethanone was obtained in 94% yield (89 mg) as transparent oil without any further purification.

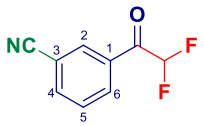
^{1}H NMR (400 MHz, C_6D_6) δ: 7.72 (m, 2H, Ph H-2,6), 6.76 (m, 2H, Ph H-3,5), 5.67 (t, $^{2}J_{H,F}$ = 53.6 Hz), 1.74 (s, 3H, SCH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.3 (t, $^{2}J_{C,F}$ = 25.4 Hz, C=O), 148.8 (Ph C-4), 130.0 (t, $^{4}J_{C,F}$ = 2.3 Hz, Ph C-2,6), 127.9 (Ph C-1), 125.1 (Ph C-3,5), 111.7 (t, $^{1}J_{C,F}$ = 253.2 Hz, CHF_2), 13.9 (S-CH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -121.7 (d, $^2J_{H,F}$ = 53.6 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_9H_8F_2OSNa^+$: 225.0156 [M+Na]$^+$; found: 225.0160.

3-(difluoroacetyl)benzonitrile (114)



By following the general procedure **7**, 3-cyano-*N*-methoxy-*N*-methylbenzamide (110 mg, 0.578 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.16 mL, 1.157 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.156 mL, 1.04 mmol, 1.8 equiv) and dry THF (5 mL), the desired 3-(difluoroacetyl) benzonitrile was obtained in 73% yield (76 mg) as transparent oil after column chromatography on reversed phase silica gel (acetonitrile/water 6:4 v/v as eluent).

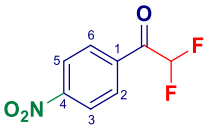
^{1}H NMR (400 MHz, C_6D_6) δ: 7.72 (m, 1H, Ph H-2), 7.52 (m, 1H, Ph H-4), 6.83 (m, 1H, Ph H-6), 6.46 (m, 1H, Ph H-5), 5.42 (t, $^2J_{H,F}$ = 53.1 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 185.5 (t, $^2J_{C,F}$ = 25.8 Hz, C=O), 137.0 (Ph C-6), 132.7 (t, $^4J_{C,F}$ = 2.2 Hz, Ph C-2), 132.5 (t, $^4J_{C,F}$ = 2.4 Hz, Ph C-4), 132.2 (t, $^3J_{C,F}$ = 1.6 Hz, Ph C-3), 129.4 (Ph C-5), 117.4 (C≡N), 113.9 (Ph C-1), 110.6 (t, $^1J_{C,F}$ = 252.7 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.8 (d, $^2J_{H,F}$ = 53.1 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_9H_5F_2NONa^+$: 204.0231 [M+Na]$^+$; found: 204.0232.

2,2-Difluoro-1-(4-nitrophenyl)ethanone (115)



By following the general procedure **7**, *N*-methoxy-*N*-methyl-4-nitrobenzamide (100 mg, 0.48 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.17 mL, 1.2 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.17 mL, 1.0 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-(4-nitrophenyl)ethanone was obtained in 90% yield (86 mg) as transparent oil after column chromatography on reversed phase silica gel (acetonitrile/water 6:4 v/v as eluent).

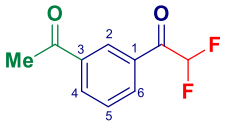
^{1}H NMR (400 MHz, C_6D_6) δ: 7.56 (m, 2H, Ph H-3,5), 7.43 (m, 2H, Ph H-2,6), 5.49 (t, $^2J_{H,F}$ = 53.1 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.1 (t, $^2J_{C,F}$ = 26.0 Hz, C=O), 151.0 (Ph C-4), 135.4 (t, $^3J_{C,F}$ = 1.7 Hz, Ph C-1), 130.3 (t, $^4J_{C,F}$ = 2.4 Hz, Ph C-2,6), 123.7 (Ph C-3,5), 110.8 (t, $^1J_{C,F}$ = 252.9 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.7 (d, $^2J_{H,F}$ = 53.1 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_8H_5F_2NO_3Na^+$: 224.0130 $[M+Na]^+$; found: 224.0133.

1-(3-acetylphenyl)-2,2-difluoroethanone (116)



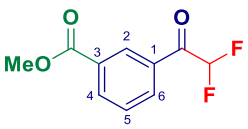
By following the general procedure **7**, 3-acetyl-*N*-methoxy-*N*-methylbenzamide (110 mg, 0.48 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.13 mL, 0.96 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.96 mL, 0.864 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1-(3-acetylphenyl)-2,2-difluoroethanone was obtained in 95% yield (90 mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 7:3 v/v as eluent).
^{1}H NMR (400 MHz, C_6D_6) δ: 8.39 (m, 1H, Ph H-2), 7.80 (m, 1H, Ph H-6), 7.75 (m, 1H, Ph H-4), 6.85 (m, 1H, Ph H-5), 5.62 (t, $^2J_{H,F}$ = 53.3 Hz, 1H, CHF_2), 1.98 (s, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 195.3 (CH_3-*C*=O), 186.8 (t, $^2J_{C,F}$ = 25.4 Hz, CHF_2-*C*=O), 137.9 (Ph C-3), 133.7 (Ph C-4), 133.2 (t, $^4J_{C,F}$ = 2.3 Hz, Ph C-6), 132.1 (t, $^3J_{C,F}$ = 1.5 Hz, Ph C-1), 129.3 (t, $^4J_{C,F}$ = 2.1 Hz, Ph C-2), 129.2 (Ph C-5), 111.1 (t, $^1J_{C,F}$ = 252.7 Hz, CHF_2), 25.9 (CH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.5 (d, $^2J_{H,F}$ = 53.3 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_8F_2O_2Na^+$: 221.0385 $[M+Na]^+$; found: 221.0382.

methyl 3-(2,2-difluoroacetyl)benzoate (117)



By following the general procedure **7**, methyl 3-(methoxy(methyl)carbamoyl)benzoate (100 mg, 0.4479 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.05 mL, 0.9 mmol, 0.75 equiv), potassium *tert*-pentoxide 0.9 M (0.25 mL, 0.2239 mmol, 0.5 equiv) and dry THF (5 mL), the desired methyl 3-

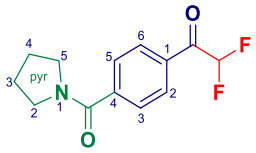
(2,2-difluoroacetyl)benzoate was obtained in 93% yield (89 mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 7:3 v/v as eluent).
^{1}H NMR (400 MHz, C_6D_6) δ: 8.70 (m, 1H, Ph H-2), 8.04 (m, 1H, Ph H-6), 7.81 (m, 1H, Ph H-4), 6.82 (m, 1H, Ph H-5), 5.55 (t, $^{2}J_{H,F}$ = 53.2 Hz, 1H, CHF_2), 3.41 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.6 (t, $^{2}J_{C,F}$ = 25.5 Hz, C=O), 165.4 (-OC=O), 135.3 (Ph C-6), 133.3 (t, $^{4}J_{C,F}$ = 2.1 Hz, Ph C-4), 132.1 (t, $^{3}J_{C,F}$ = 1.5 Hz, Ph C-3), 131.5 (Ph C-1), 130.7 (t, $^{4}J_{C,F}$ = 2.4 Hz, Ph C-2), 129.2 (Ph C-5), 111.0 (t, $^{1}J_{C,F}$ =252.7 Hz, CHF_2), 51.9 (OCH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.5 (d, $^{2}J_{H,F}$ = 53.2 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_8F_2O_3Na^+$: 237.0334 [M+Na]$^+$; found: 237.0330.

2,2-Difluoro-1-[4-(pyrrolidin-1-ylcarbonyl)phenyl]ethanone (118)



By following the general procedure **7**, *N*-methoxy-*N*-methyl-4-(pyrrolidine-1-carbonyl)benzamide (100 mg, 0.39 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.04 mL, 0.29 mmol, 0.75 equiv), potassium *tert*-pentoxide 0.9 M (0.22 mL, 0.19 mmol, 0.5 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-[4-pyrrolidin-1-ylcarbonyl)phenyl]ethanone was obtained in 77% yield (76 mg) as transparent oil after column chromatography on silica gel (ethyl acetate as eluent).

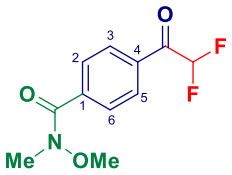
^{1}H NMR (400 MHz, C_6D_6) δ: 7.79 (m, 2H, Ph H-2,6), 7.30 (m, 2H, Ph H-3,5), 5.65 (t, $^{2}J_{H,F}$ = 53.4 Hz, 1H, CHF_2), 3.46 (t, $^{3}J_{H,H}$ = 7.0 Hz, 2H, pyr H-5), 2.64 (t, $^{3}J_{H,H}$ = 6.7 Hz, 2H, pyr H-2), 1.26 (m, 2H, pyr H-4), 1.12 (m, 2H, pyr H-3).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.8 (t, $^{2}J_{C,F}$ = 25.3 Hz, C=O), 167.3 (N-C=O), 143.6 (Ph C-4), 132.5 (t, $^{3}J_{C,F}$ = 1.6 Hz, Ph C-1), 129.6 (t, $^{4}J_{C,F}$ = 2.2 Hz, Ph C-2,6), 128.0 (Ph C-3,5), 111.2 (t, $^{1}J_{C,F}$ = 252.8 Hz, CHF_2), 48.8 (pyr C-2), 46.3 (pyr C-5), 26.3 (pyr C-3), 24.2 (pyr C-4).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.4 (d, $^{2}J_{H,F}$ = 53.4 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{13}H_{13}F_2NO_2Na^+$: 276.0807 [M+Na]$^+$; found: 276.0804.

4-(difluoroacetyl)-*N*-methoxy-*N*-methylbenzamide (119)



By following the general procedure **7**, N^1,N^4-dimethoxy-N^1,N^4-dimethylterephthalamide (100 mg, 0.4 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.04 mL, 0.30 mmol, 0.75 equiv), potassium *tert*-pentoxide 0.9 M (0.22 mL, 0.2 mmol, 0.5 equiv) and dry THF (5 mL), the desired 4-(difluoroacetyl)-*N*-methoxy-*N*-methylbenzamide was obtained in 73% yield (71 mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 7:3 v/v as eluent).

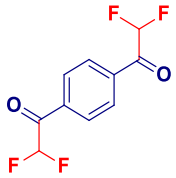
^{1}H NMR (400 MHz, C_6D_6) δ: 7.75 (m, 2H, Ph H-3,5), 7.52 (m, 2H, Ph H-2,6), 5.58 (t, $^2J_{H,F}$ = 53.3 Hz, 1H, CHF_2), 2.91 (s, 3H, NCH_3), 2.80 (br s, 3H, OCH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.8 (m, C=O), 168.5 (N-C=O), 140.7 (Ph C-1), 132.9 (Ph C-4), 129.3 (t, $^4J_{C,F}$ = 2.2 Hz, Ph C-3,5), 128.0 (Ph C-2,6), 111.1 (t, $^1J_{C,F}$ = 252.7 Hz, CHF_2), 60.5 (OCH_3), 32.7 (NCH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.5 (d, $^2J_{H,F}$ = 53.3 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{11}F_2NO_3Na^+$: 266.0599 [M+Na]$^+$; found: 266.0596.

1,1'-(1,4-phenylene)bis(2,2-difluoroethanone) (120)



By following the general procedure **7**, N^1,N^4-dimethoxy-N^1,N^4-dimethylterephthalamide (100 mg, 0.4 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.08 mL, 0.59 mmol, 2 equiv), potassium tert-pentoxide 0.9 M (0.44 mL, 0.396 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1,1'-(1,4-phenylene)bis(2,2-difluoroethanone) was obtained in 90% yield (84 mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 97:3 v/v as eluent).

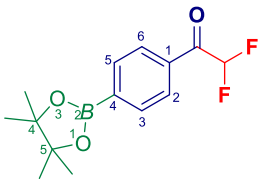
^{1}H NMR (400 MHz, C_6D_6) δ: 7.58 (s, 4H, Ph H-2,3,5,6), 5.51 (t, $^2J_{H,F}$ = 53.2 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 186.7 (t, $^2J_{C,F}$ = 25.9 Hz, C=O), 135.6 (t, $^3J_{C,F}$ = 1.7 Hz, Ph C-1,4), 129.7 (t, $^4J_{C,F}$ = 2.3 Hz, Ph C-2,3,5,6), 111.0 (t, $^1J_{C,F}$ = 253.0 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.6 (d, $^2J_{H,F}$ = 53.2 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_6F_4O_2Na^+$: 257.0196 [M+Na]$^+$; found: 257.0195.

2,2-Difluoro-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanone (121)



By following the general procedure **7**, *N*-methoxy-*N*-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (100 mg, 0.34 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.01 mL, 0.69 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.68 mL, 0.61 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanone was obtained in 93% yield (89 mg) as transparent oil after column chromatography on silica gel (hexane as eluent).

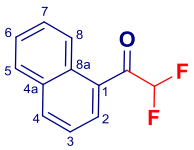
^{1}H NMR (400 MHz, C_6D_6) δ: 7.99 (m, 2H, Ph H-3,5), 7.84 (m, 2H, Ph H-2,6), 5.64 (t, $^2J_{H,F}$ = 53.3 Hz, 1H, CHF_2), 1.09 (s, 12H, CH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 187.4 (t, $^2J_{C,F}$ = 24.8 Hz, C=O), 135.5 (Ph C-3,5),134.1 (Ph C-1), 128.7 (Ph C-2,6), 110.8 (t, $^1J_{C,F}$ = 252.0 Hz, CHF_2), 84.4 (O-*C*$(CH_3)_2$), 24.9 (CH_3), Ph C-4 was not found.

^{19}F NMR (376 MHz, C_6D_6) δ: -123.1 (dt, $^2J_{H,F}$ = 53.3 Hz, $^5J_{H,F}$ = 1.0 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{17}BF_2O_3Na^+$: 305.1131 [M+Na]$^+$; found: 305.1129.

2,2-Difluoro-1-(naphthyl)ethanone (122)



By following the general procedure **7**, *N*-methoxy-*N*-methyl-1-naphthamide (110 mg, 0.51 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.14 mL, 1.022 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.02 mL, 0.92 mmol, 1.8 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-

(naphthyl)ethanone was obtained in 92% yield (96 mg) as transparent oil without any further purification.

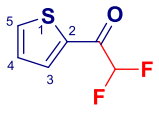
^{1}H NMR (400 MHz, C_6D_6) δ: 9.02 (m, 1H, naph H-8), 7.69 (m, 1H, naph H-2), 7.51 (m, 1H, naph H-4), 7.44 (m, 1H, naph H-5), 7.30 (m, 1H, naph H-7), 7.17 (m, 1H, naph H-6), 6.92 (m, 1H, naph H-3), 5.78 (t, $^{2}J_{H,F}$ = 53.8 Hz, 1H, CHF_2).

^{13}C NMR (100 MHz, C_6D_6) δ: 189.5 (t, $^{2}J_{C,F}$ = 24.1 Hz, C=O), 135.2 (naph C-4), 134.3 (naph C-4a), 131.5 (naph C-8a), 131.1 (t, $^{4}J_{C,F}$ = 4.0 Hz, naph C-2), 129.3 (naph C-7), 128.9 (naph C-5), 128.7 (m, naph C-1), 127.1 (naph C-6), 126.0 (naph C-8), 124.2 (naph C-3), 111.0 (t, $^{1}J_{C,F}$ = 253.8 Hz, CHF_2)

^{19}F NMR (376 MHz, C_6D_6) δ: -120.8 (dd, $^{2}J_{H,F}$ = 53.8 Hz, $J_{H,F}$ = 1.6 Hz, CHF_2),

HRMS (ESI), *m/z*: calcd. for $C_{12}H_8F_2ONa^+$: 229.0435 $[M+Na]^+$; found: 229.0436.

2,2-Difluoro-1-(2-thienyl)ethanone (123)



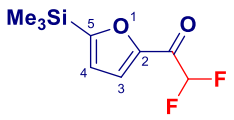
By following the general procedure **7**, *N*-methoxy-*N*-methylthiophene-2-carboxamide (100 mg, 0.58 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.32 mL, 2.32 mmol, 4 equiv), potassium *tert*-pentoxide 0.9 M (2.16 mL, 1.94 mmol, 3.6 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-(2-thienyl)ethanone was obtained in 88% yield (82 mg) as transparent oil after column chromatography on silica gel (hexane as eluent).

^{1}H NMR (400 MHz, C_6D_6) δ: 7.47 (m, 1H, Th H-3), 6.84 (m, 1H, Th H-5), 6.43 (m, 1H, Th H-4), 5.54 (t, $^{2}J_{H,F}$ = 53.7 Hz, 1H, CHF_2).
^{13}C NMR (100 MHz, C_6D_6) δ: 180.8 (t, $^{2}J_{C,F}$ = 26.3 Hz, C=O), 138.2 (t, $^{3}J_{C,F}$ = 2.0 Hz, Th C-2), 136.2 (Th C-5), 135.2 (t, $^{4}J_{C,F}$ = 3.8 Hz, Th C-3), 128.6 (Th C-4), 111.1 (t, $^{1}J_{C,F}$ = 253.1 Hz, CHF_2).

^{19}F NMR (376 MHz, C_6D_6) δ: -121.9 (d, $^{2}J_{H,F}$ = 53.7 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_6H_4F_2OSNa^+$: 184.9838 $[M+Na]^+$; found: 185.9840.

2,2-Difluoro-1-[5-(trimethylsilyl)-2-furyl)ethanone (124)



By following the general procedure **7**, *N*-methoxy-*N*-methylfuran-2-carboxamide (144 mg, 0.92 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.26 mL, 1.856 mmol, 4 equiv), potassium *tert*-pentoxide 0.9 M (1.84 mL, 1.656 mmol, 3.6 equiv) and dry THF (5 mL), the desired 2,2-difluoro-1-[5-(trimethylsilyl)-2-furyl)ethanone was obtained in 92% yield (184 mg) as transparent oil after column chromatography on silica gel (hexane as eluent).

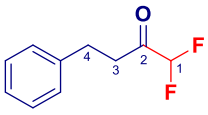
^{1}H NMR (400 MHz, C_6D_6) δ: 7.03 (m, 1H, fur H-3), 6.23 (m, 1H, fur H-4), 5.61 (t, $^{2}J_{H,F}$ = 53.6 Hz, 1H, CHF_2), 0.07 (s, 9H, $SiCH_3$).

^{13}C NMR (100 MHz, C_6D_6) δ: 175.7 (t, $^{2}J_{C,F}$ = 26.0 Hz, C=O), 169.3 (fur C-5), 152.3 (t, $^{3}J_{C,F}$ = 1.3 Hz, fur C-2), 121.67 (fur C-4), 121.65 (t, $^{4}J_{C,F}$ = 3.4 Hz, fur C-3), 110.5 (t, $^{1}J_{C,F}$ = 251.9 Hz, CHF_2), -2.2 ($SiCH_3$).

^{19}F NMR (376 MHz, C_6D_6) δ: -124.2 (d, $^{2}J_{H,F}$ = 53.6 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_9H_{12}F_2OSiNa^+$: 241.0467 [M+Na]$^+$; found: 241.0471.

1,1-Difluoro-4-phenylbutan-2-one (125)



By following the general procedure **7**, *N*-methoxy-*N*-methyl-3-phenylpropanamide (100 mg, 0.517 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.28 mL, 2.07 mmol, 4 equiv), potassium *tert*-pentoxide 0.9 M (2 mL, 1.86 mmol, 3.6 equiv) and dry THF (5 mL), the desired 1,1-difluoro-4-phenylbutan-2-one was obtained in 95% yield (90 mg) as transparent oil without any further purification.

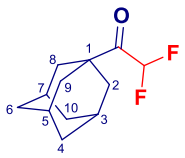
^{1}H NMR (400 MHz, C_6D_6) δ: 7.09 (m, 2H, Ph H-3,5), 7.02 (m, 1H, Ph H-4), 6.88 (m, 2H, Ph H-2,6), 4.94 (t, $^{2}J_{H,F}$ = 53.9 Hz, 1H, CHF_2), 2.60 (t, $^{3}J_{H,H}$ = 7.5 Hz, 2H, H-4), 2.37 (t, $^{3}J_{H,H}$ = 7.5 Hz, 2H, H-3).

^{13}C NMR (100 MHz, C_6D_6) δ: 198.1 (t, $^{2}J_{C,F}$ = 25.7 Hz, C=O), 140.3 (Ph C-1), 128.8 (Ph C-3,5), 128.6 (Ph C-2,6), 126.6 (Ph C-4), 110.1 (t, $^{1}J_{C,F}$ = 252.3 Hz, CHF_2), 37.7 (C-3), 28.4 (C-4).

^{19}F NMR (376 MHz, C_6D_6) δ: -127.1 (d, $^{2}J_{H,F}$ = 53.9 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{10}F_2ONa^+$: 207.0592 $[M+Na]^+$; found: 207.0588.

1-(adamantan-1-yl)-2,2-difluoroethanone (126)



By following the general procedure **7**, (3r,5r,7r)-N-methoxy-N-methyladamantane-1-carboxamide (100 mg, 0.45 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.12 mL, 0.89 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (0.9 mL, 0.81 mmol, 1.8 equiv) and dry THF (5 mL), the desired 1-(adamantan-1-yl)-2,2-difluoroethanone in 94% yield (90 mg) as transparent oil without any further purification.

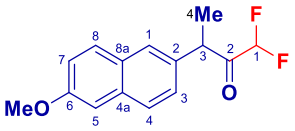
^{1}H NMR (400 MHz, C_6D_6) δ: 5.46 (t, $^{2}J_{H,F}$ = 53.3 Hz, 1H, CHF_2), 1.71 (m, 3H, H-3,5,7), 1.67 (m, 6H, H-2,8,9), 1.43 (m, 6H, H-4,6,10).

^{13}C NMR (100 MHz, C_6D_6) δ: 201.0 (t, $^{2}J_{C,F}$ = 21.5 Hz, C=O), 109.6 (t, $^{1}J_{C,F}$ = 252.6 Hz, CHF_2), 45.2 (C-1), 37.1 (C-2,8,9), 36.3 (C-4,6,10), 27.8 (C-3,5,7).

^{19}F NMR (376 MHz, C_6D_6) δ: -124.4 (d, $^{2}J_{H,F}$ = 53.3 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_{16}F_2ONa^+$: 237.1061 $[M+Na]^+$; found: 237.1062.

1,1-Difluoro-3-(6-methoxy-2-naphthyl)-2-butanone (127)



By following the general procedure **7**, *N*-methoxy-2-(6-methoxynaphthalen-2-yl)-*N*-methylpropanamide (170 mg, 0.622 mmol, 1 equiv), (Difluoromethyl)trimethylsilane (0.17 mL, 1.24 mmol, 2 equiv), potassium *tert*-pentoxide 0.9 M (1.2 mL, 1.1196 mmol, 1.8 equiv) and dry THF (5

mL), the desired 1,1-difluoro-3-(6-methoxy-2-naphthyl)-2-butanone was obtained in 90% yield (147 mg) as transparent oil after column chromatography on silica gel (hexane/ethyl acetate 8:2 v/v as eluent).

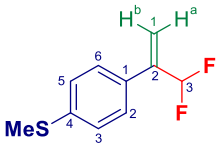
^{1}H NMR (400 MHz, C_6D_6) δ: 7.48 (d, $^{3}J_{H,H}$ = 8.2 Hz, 1H, naph H-4), 7.40 (d, $^{3}J_{H,H}$ = 9.0 Hz, 1H, naph H-8), 7.37 (d, $^{4}J_{H,H}$ = 1.8 Hz, 1H, naph H-1), 7.16 (dd, $^{3}J_{H,H}$ = 9.0 Hz, $^{4}J_{H,H}$ = 2.5 Hz, 1H, naph H-7), 7.10 (dd, $^{3}J_{H,H}$ = 8.5 Hz, $^{4}J_{H,H}$ = 1.8 Hz, 1H, naph H-3), 6.87 (d, $^{4}J_{H,H}$ = 2.5 Hz, 1H, naph H-5), 5.11 (t, $^{2}J_{H,F}$ = 53.6 Hz, 1H, CHF_2), 3.89 (dq, $^{3}J_{H,H}$ = 6.9 Hz, $^{4}J_{H,F}$ = 2.4 Hz, 1H, H-3), 3.36 (s, 3H, OCH_3), 1.30 (d, $^{3}J_{H,H}$ = 6.9 Hz, 3H, H-4).

^{13}C NMR (100 MHz, C_6D_6) δ: 198.8 (dd, $^{2}J_{C,F}$ = 24.9 Hz and 23.4 Hz, C=O), 158.6 (naph C-6), 134.6 (naph C-4a), 133.2 (naph C-2), 129.70 (naph C-8), 129.65 (naph C-8a). 128.1 (naph C-4), 127.5 (naph C-1), 126.4 (naph C-3), 119.8 (naph C-7), 109.7 (t, $^{1}J_{C,F}$ = 252.2 Hz, CHF_2), 105.9 (naph C-5), 54.8 (OCH_3), 47.4 (C-3), 17.6 (C-4).

^{19}F NMR (376 MHz, C_6D_6) δ: -128.3 (‚dd', B part of AB system, $^{2}J_{F,F}$ = 313.1 Hz, $^{2}J_{H,F}$ = 53.8 Hz, CHF_2), -125.7 (‚ddd', A part of AB system, $^{2}J_{F,F}$ = 313.1 Hz, $^{2}J_{H,F}$ = 53.2 Hz, $^{4}J_{H,F}$ = 2.4 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{15}H_{14}F_2O_2Na^+$: 287.0854 $[M+Na]^+$; found: 287.0850.

4-(3,3-difluoro-1-propen-2-yl)phenyl) methyl sulfide (128)



A suspension of methyl triphenylphosphonium bromide (11mg, 0.31 mmol, 1.25 equiv) in dry Et_2O (2ml) under Argon atmosphere was cooled at 0 °C. *n*-BuLi (0.3 mL, 1.2 equiv) was added dropwise and the resulting solution was stirred for 10 min at 0 °C. The reaction mixture was cooled at -78 °C then a solution of 2,2-difluoro-1-(4-(methylthio)phenyl)ethanone **113** (50 mg, 0.25 mmol, 1 equiv) in dry Et_2O (2 mL) was added dropwise over 30 min. The cooling bath was removed and the reaction was allowed warm to room temperature. The reaction was stirred at room temperature for 12 h. The reaction mixture was quenched with NH_4Cl (3 mL) and extracted with Et_2O (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum (bath rt) to remove the solvent.
The crude was purified via column chromatography on silica gel (hexane/diethyl ether 9:1 v/v as eluent) to afford the corresponding (4-(3,3-difluoroprop-1-en-2yl)phenyl)(methyl)sulphide in 92% yield (46 mg) as transparent oil.

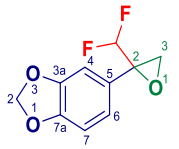
^{1}H NMR (400 MHz, C_6D_6) δ: 7.19 (m, 2H, Ph H-2,6), 6.99 (m, 2H, Ph H-3,5), 5.92 (t, $^{2}J_{H,F}$ = 55.2 Hz, 1H, CHF_2), 5.24 (t, $^{2}J_{H,H}$ and $^{4}J_{H,F}$ = 2.0 Hz), 1H, H^b), 5.16 (t, $^{2}J_{H,H}$ and $^{4}J_{H,F}$ = 2.2 Hz, 1H, H^a), 1.93 (s, 3H, SCH_3).

^{13}C NMR (100 MHz, C_6D_6) δ: 141.8 (t, $^{2}J_{C,F}$ = 20.1 Hz, C-2), 140.2 (Ph C-4), 131.3 (Ph C-1), 127.6 (Ph C-2,6), 126.5 (Ph C-3,5), 118.0 (t, $^{3}J_{C,F}$ = 9.5 Hz, C-2), 116.0 (t, $^{1}J_{C,F}$ = 239.4 Hz, CHF_2), 15.0 (SCH_3).

^{19}F NMR (376 MHz, C_6D_6) δ: -112.8 (dt, $^{2}J_{H,F}$ = 55.2 Hz, $^{4}J_{H,F}$ = 2.1 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{10}F_2SNa^+$: 223.0363 [M+Na]$^+$; found: 223.0361.

5-[2-(difluoromethyl)-2-oxiranyl)]-1,3-benzodioxole (129)



To a solution of 1-(1,3-benzodioxol-5-yl)-2,2-difluoroethanone **112** (60 mg, 0.31 mmol, 1 equiv) in dry THF (3 mL) cooled at -78 °C was added diiodomethane (75 □L, 0.93 mmol, 3 equiv) under Argon atmosphere. Then, MeLi-LiBr complex 1.5M in diethyl ether (0.58 mL, 0.89 mmol, 2.8 equiv) was added dropwise at -78 °C. The reaction mixture was stirred at that temperature for 1 h and then, it was left warming to room temperature overnight. The reaction mixture was quenched with water (3 mL) and extracted with Et_2O (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum (bath rt) to remove the solvent. The crude was purified via column chromatography on 2° grade alumina (hexane/diethyl ether 7:3 v/v as eluent) to afford the corresponding 5-[2-(difluoromethyl)-2-oxiranyl)]-1,3-benzodioxole in 91% yield (60 mg).

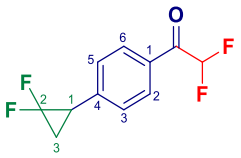
^{1}H NMR (400 MHz, C_6D_6) δ: 6.93 (d, $^{4}J_{H,H}$ = 1.7 Hz, 1H, H-4), 6.82 (dd, $J_{H,H}$ = 8.0 Hz, $^{4}J_{H,H}$ = 1.7 Hz, 1H, H-6), 6.53 (d, $J_{H,H}$ = 8.0 Hz, 1H, H-7), 5.23 (A-part of AB system, $^{2}J_{H,H}$ = 1.4 Hz, 1H, H-2), 5.22 (B-part of AB system, $^{2}J_{H,H}$ = 1.4 Hz, 1H, H-2), 5.18 (t, $^{2}J_{H,F}$ = 55.2 Hz, 1H, CHF_2), 2.48 (m, 1H, oxirane H-3), 2.25 (m, 1H, oxirane H-3).

^{13}C NMR (100 MHz, C_6D_6) δ: 148.6 (C-7a), 148.3 (C-3a), 126.6 (C-5), 121.6 (C-6), 116.0 (t, $^{1}J_{C,F}$ = 244.7 Hz, CHF_2), 108.5 (C-7), 108.3 (C-4), 101.2 (C-2), 58.2 (t, $^{2}J_{C,F}$ = 28.0 Hz, oxirane C-2), 50.7 (m, oxirane C-3).

^{19}F NMR (376 MHz, C_6D_6) δ: -122.6 (m, $^{2}J_{F,F}$ = 292.9 Hz, $^{2}J_{F,H}$ = 55.4 Hz, $^{4}J_{F,H}$ = 3.8 Hz, CHF_2), -121.2 (m, $^{2}J_{F,F}$ = 292.9 Hz, $^{2}J_{F,H}$ = 55.0 Hz, $^{4}J_{F,H}$ = 1.7 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_8F_2O_3Na^+$: 237.0334 $[M+Na]^+$; found: 237.0333.

1-(4-(2,2-difluorocyclopropyl)phenyl)-2,2-difluoroethanone (130)



Sodium chlorodifluoroacetate (188 mg, 1.24 mmol, 3 equiv) was completely dissolved in a THF (1.5 mL) solution of 2,2-difluoro-1-(4-vinylphenyl)ethanone **101** (75 mg, 0.41 mmol, 1 equiv) and exposed to MW irradiation (Method parameters were set at 300W, 170 °C, 00:05:00). The reaction mixture was diluted with water (3 mL) and extracted with Et_2O (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum (bath rt) to remove the solvent. The crude was purified via column chromatography on 4° grade alumina (hexane/diethyl ether 6:4 v/v as eluent) to afford the corresponding 1-(4-(2,2-difluorocyclopropyl)phenyl)-2,2-difluoroethanone in 94% yield (270 mg).

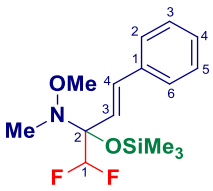
^{1}H NMR (400 MHz, C_6D_6) δ: 8.05 (m, 2H, Ph H-2,6), 7.37 (m, 2H, Ph H-3.5), 6.26 (t, $^2J_{H,F}$ = 53.5 Hz, 1H, CHF_2), 2.82 (m, 1H, cyclo H-1), 1.95 (m, 1H, cyclo H-3), 1.73 (m, 1H, cyclo H-3).

^{13}C NMR (100 MHz, C_6D_6) δ: 187.1 (t, $^2J_{C,F}$ = 25.4 Hz, C=O), 141.4 (m, Ph C-4), 130.3 (m, Ph C-1), 129.8 (Ph C-2,6), 128.4 (m, Ph C-3,5), 112.1 (dd, $^2J_{C,F}$ = 288.1 Hz, $^2J_{C,F}$ = 284.2 Hz, cyclo C-2), 111.3 (t, $^1J_{C,F}$ = 253.9 Hz, CHF_2), 27.4 (dd, $^2J_{C,F}$ = 12.2 Hz and 11.2 Hz, cyclo C-1), 17.8 (t, $^2J_{C,F}$ = 10.5 Hz, cyclo C-3).

^{19}F NMR (376 MHz, C_6D_6) δ: -142.0 (m, $^2J_{F,F}$ = 155.1 Hz, cyclo-F), -125.3 (m, $^2J_{F,F}$ = 155.1 Hz, cyclo-F), -121.8 (d, $^2J_{H,F}$ = 53.5 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_8F_4ONa^+$: 255.0403 $[M+Na]^+$; found: 255.0400.

(3*E*)-1,1-difluoro-*N*-methoxy-*N*-methyl-4-phenyl-2[(trimethylsilyl)oxy]-3-buten-2-amine (131)



To a solution of *N*-methoxy-*N*-methylcinnamamide (100 mg, 0.52 mmol, 1 equiv) in dry THF (5 mL) cooled at 0°C was added (Difluoromethyl)trimethylsilane (0.15 mL, 1.05 mmol, 2 equiv) under Argon atmosphere. Then potassium tert-pentoxide 0.9 M (1.05 mL, 0.94 mmol, 1.8 equiv) was added dropwise with good stirring at 0 °C during a period of 15 min. After 3 min, ***N*-trimethylsilylimidazole (0.38 mL, 2.6 mmol, 5.0 equiv) is added to the mixture and** the reaction was allowed to stir at 0 °C to reach the rt within 3 h. The reaction mixture was quenched with NH_4Cl (3 mL) and extracted with EtOAc (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum (bath rt) to remove the solvent. The reaction gives the desired (3*E*)-1,1-difluoro-*N*-methoxy-*N*-methyl-4-phenyl-2[(trimethylsilyl)oxy]-but-3-en-2-amine in 90% yield (147 mg) as transparent oil without any further purification.

^{1}H NMR (400 MHz, C_6D_6) δ: 7.22(m, 2H, Ph H-2,6), 7.08 (d, $^3J_{H,H}$ = 15.9 Hz, 1H, H-4), 7.04 (m, 2H, Ph H-3,5), 7.02 (m, 1H, Ph H-4), 6.29 (dd, $^3J_{H,H}$ = 15.9 Hz, $^4J_{H,F}$ = 1.9 Hz, 1H, H-3), 6.06 (dd, $^2J_{H,F}$ = 56.4 Hz and = 57.5 Hz, 1H, CHF_2), 3.30 (s, 3H, OCH_3), 2.44 (s, 3H, NCH_3), 0.29 (s, 9H, $Si(CH_3)_3$).

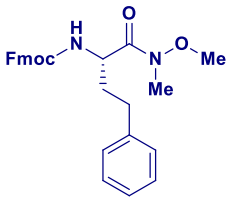
^{13}C NMR (100 MHz, C_6D_6) δ: 136.5 (Ph C-1), 135.5 (t, $^4J_{C,F}$ = 1.2 Hz, C-4), 128.9 (Ph C-3,5), 128.3 (Ph C-4), 127.3 (Ph C-2,6), 124.1 (t, $^4J_{C,F}$ = 0.9 Hz, C-3), 113.9 (dd, $^1J_{C,F}$ = 249.7 Hz and 244.2 Hz, CHF_2), 93.4 (dd, $^2J_{C,F}$ = 25.8 Hz and 21.5 Hz, C-2), 59.8 (OCH_3), 35.9 (NCH_3), 2.2 ($Si(CH_3)_3$).

^{19}F NMR (376 MHz, C_6D_6) δ: -133.4 (dd, $^2J_{F,F}$ = 282.3 Hz, $^2J_{H,F}$ = 57.5 Hz, CHF_2), -126.8 (dd, $^2J_{F,F}$ = 282.3 Hz, $^2J_{H,F}$ = 56.4 Hz, CHF_2).

^{15}N NMR (40 MHz, C_6D_6) δ: -214.9 (NCH_3).

HRMS (ESI), *m/z*: calcd. for $C_{15}H_{23}F_2NO_2SiNa^+$: 338.1358 $[M+Na]^+$; found: 338.1354.

Fmoc-D-Homophe Weinreb Amide - **((S)-(9H-fluoren-9-yl)methyl (1-(methoxy(methyl)amino)-1-oxo-4-phenylbutan-2-yl)carbamate) – (135)**



To a solution of Fmoc-D-Homophe-OH (1.0 g, 0.0025 mol, 1.0 equiv) in dry CPME (10 mL) was added 1,1'-carbonyldiimidazole (0.444 g, 0.0027 mol, 1.1 equiv) in one portion and the resulting mixture was allowed to stir for 1 h at rt. Then, *N,O*-dimethylhydroxylamine hydrochloride (DMHA, 0.270 g, 0.0027 mol, 1.1 equiv) was added to the mixture, turning the solution a cloudy white. The reaction mixture was stirred at rt overnight, then quenched with 3 mL of a saturated aq. solution of NH_4Cl and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers

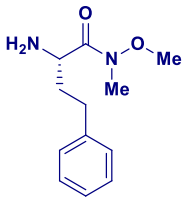
were washed with a saturated aq. solution of $NaHCO_3$ (3 × 10 mL) and brine (3 × 10 mL) then, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to afford the corresponding Fmoc-D-Homophe Weinreb Amide **135**, in 95 % yield (1.05 g), as a yellow oil without any further purification.

^{1}H NMR (200 MHz, CD_3OD) δ: 7.74 - 7.61 (m, 4H, Ar-H), 7.37 - 7.13 (m, 9H, Ar-H), 4.54 (m, 1H, α-CH), 4.32 (d, 2H, $^3J_{H,H}$ = 7.17 Hz, CH_2), 4.14 (t, 1H, $^3J_{H,H}$ = 6.62 Hz, Fmoc-CH), 3.51 (s, 3H, OCH_3), 3.09 (s, 3H, NCH_3), 2.78 – 2.50 (m, 2H, CH_2Ph), 1.98 – 1.87 (m, 2H, CH_2-CH Homophe).

^{13}C NMR (50 MHz, CD_3OD) δ: 174.8 (C=O Fmoc), 158.5 (C=O Homophe), 145.3 (Fmoc Ar-C), 145.0 (Fmoc Ar-C), 142.5 (Ph C-1), 129.6 (2C, Ph C-3,5), 129.4 (2C, Ph C-2,6), 128.7 (2C, Fmoc Ar-CH), 128.1 (2C, Fmoc Ar-CH), 127.0 (Ph C-4), 126.2 (Fmoc Ar-CH), 120.9 (Fmoc Ar-CH), 67.8 (CH_2 Fmoc), 61.8 (OCH$_3$), 51.9 (NCH$_3$), 48.3 (CH Fmoc), 34.0 (CH$_2$-CH Homophe), 32.9 (CH$_2$Ph).

HRMS (ESI), *m/z*: calcd. for $C_{27}H_{28}N_2O_4Na^+$: 467.1945 $[M+Na]^+$; found: 467.1941.

D-Homophe Weinreb Amide **- (S)-2-amino-*N*-methoxy-*N*-methyl-4-phenylbutanamide – (136)**



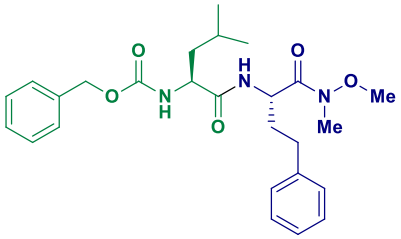
To a solution of **135** in dry DMF (10 mL), piperidine (20%) was added and the resulting mixture was left stirring at rt overnight. The reaction mixture was dried under reduced pressure and the crude product was purified *via* silica gel chromatography (DCM: MeOH 98:2) to afford compound **136** in 96% yield (0.504 g) as a yellow oil.

^{1}H NMR (200 MHz, CD_3OD) δ: 7.33 - 7.19 (m, 5H, Ph H-1,2,3,4,5,6), 3.81 (m, 1H, α-C*H* Homophe), 3.61 (s, 3H, OCH_3), 3.20 (s, 3H, NCH_3), 2.78 – 2.64 (m, 2H, CH_2Ph), 2.04 – 1.76 (m, 2H, CH_2-CH Homophe).

^{13}C NMR (50 MHz, CD_3OD) δ: 162.0 (C=O Homophe), 142.6 (Ph C-1), 129.6 (2C, Ph C-3,5), 129.4 (2C, Ph C-2,6), 127.0 (Ph C-4), 61.9 (OCH$_3$), 51.1 (NCH$_3$), 37.3 (CH$_2$-CH Homophe), 32.7 (CH$_2$Ph).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_{19}N_2O_2^+$: 223.1446 $[M+H]^+$; found: 223.1441.

Z-Leu-Homophe Weinreb amide - **Benzyl ((S)-1-(((S)-1-(methoxy(methyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate – (137)**



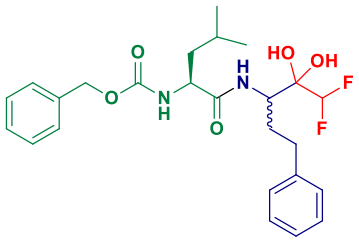
Compound **11** (176 mg, 0.792 mmol, 1.2 equiv) and Z-Leu-OH (175 mg, 0.66 mmol, 1 equiv) were dissolved in dry DMF (8 mL) and EDCI (152 mg, 0.792 mmol, 1.2 equiv) and HOBt (107 mg, 0.792 mmol, 1.2 equiv) were added to the mixture at rt. The reaction was left stirring under Argon atmosphere at rt overnight. The reaction mixture was then diluted with ethyl acetate and washed with saturated aq. solution of NH_4Cl (3 × 10 mL), saturated aq. solution of $NaHCO_3$ (3 × 10 mL) and brine (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **137** as a colorless liquid which readily crystallized in a white solid upon trituration with diethyl ether (65 % yield, 202 mg).

^{1}H NMR (400 MHz, CD_3OD) δ: 7.36 (m, 2H, Bn H-2,6), 7.31 (m, 2H, Bn, H-3,5), 7.27 (m, 1H, Bn H-4), 7.24 (m, 2H, Ph, H-3,5), 7.18 (m, 2H, Ph H-2,6), 7.16 (m, 1H, Ph H-4), 5.13 – 5.09 (m, AB System, $^2J_{A,B}$ = 12.3 Hz, 2H, CH_2O), 4.77 (m, 1H, α-C*H* Homophe), 4.26 (dd, $^3J_{H,H}$ = 9.1 Hz, $^3J_{H,H}$ = 5.9 Hz, 1H, α-C*H* Leu), 3.57 (s, 3H, OCH_3), 3.13 (s, 3H, NCH_3), 2.75 – 2.61 (m, 2H, CH_2Ph), 2.05 – 1.85 (m, 2H, CH_2-CH Homophe), 1.72 (m, 1H, C*H*-CH_3), 1.57 (m, 2H, CH_2-CH Leu), 0.94 (d, $^3J_{H,H}$ = 6.67 Hz, 3H, CH_3-CH), 0.91 (d, $^3J_{H,H}$ = 6.67 Hz, 3H, CH_3-CH).

^{13}C NMR (100 MHz, CD_3OD) δ: 175.5 (C=O Leu), 174.1 (C=O Homophe), 158.4 (C=O CBZ), 142.2 (Ph C-1), 138.2 (Bn C-1), 129.8 (2C, Ph C-2,6), 129.5 (2C, Bn, C-3,5), 129.4 (2C, Ph C-3,5), 129.0 (Bn C-4), 128.8 (2C, Bn C-2,6), 127.1 (Ph C-4), 67.6 (*C*H_2O), 61.9 (O*C*H_3), 54.7 (α-*C*H Leu), 50.2 (α-*C*H Homophe), 41.9 (*C*H_2-CH Leu), 34.1 (*C*H_2-CH Homophe), 32.8 (*C*H_2Ph), 32.4 (N*C*H_3), 25.8 (*C*H-CH_3), 23.5 (*C*H_3-CH), 22.0 (*C*H_3-CH).

HRMS (ESI), *m/z*: calcd. for $C_{26}H_{35}N_3O_5Na^+$: 492.2487 $[M+Na]^+$; found: 492.2469.

Z-Leu-Homophe-CHF_2 - **Benzyl ((2S)-1-((1,1-difluoro-2,2-dihydroxy-5-phenylpentan-3-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate - (133a-b)**



To a solution of compound **137** (120 mg, 0.255 mmol, 1 equiv) in dry THF (5 mL) cooled at 0 °C was added (difluoromethyl)trimethylsilane (0.18 mL, 1.275 mmol, 2 equiv) under Ar atmosphere. Then potassium *tert*-pentoxide 0.9 M (1.25 mL, 1.122 mmol, 4.4 equiv) was added dropwise with good stirring at 0 °C during a period of 15 min. The reaction mixture was further stirred to reach rt within 3 h. After complete conversion of the starting material, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (3 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified *via* column chromatography on silica gel (DCM: MeOH 98:2) to afford the corresponding compounds **133a-b** as diastereomeric mixture (3:1) in 87 % yield (106 mg).

The following ***^{1}H NMR*** *characterization is mainly relative to the major diasteroisomer-*

^{1}H NMR (400 MHz, CD_3OD) δ: 7.34 (m, 2H, Bn H-2,6), 7.31 (m, 2H, Bn), 7.27 (m, 1H, Bn), 7.24 (m, 2H, Ph), 7.16 (m, 2H, Ph H-2,6), 7.16 (m, 1H, Ph), 5.76/5.69 (td, $^2J_{H,F}$ = 54.4 Hz, $^3J_{H,H}$ = 12.2 Hz, 1H, C*H*F_2), 5.14 – 5.06 (m, 2H, C*H*$_2$O), 4.20 (m, 2H, α-C*H* Homophe, α-C*H* Leu), 2.65 – 2.47 (m, 2H, C*H*$_2$Ph), 2.06 – 1.75 (m, 2H, C*H*$_2$-CH Homophe), 1.74 (m, 1H, C*H*-CH_3), 1.57 (m, 2H, C*H*$_2$-CH Leu), 0.97 (d, $^3J_{H,H}$ = 6.7 Hz, 3H, C*H*$_3$-CH), 0.94 (d, $^3J_{H,H}$ = 6.7 Hz, 3H, C*H*$_3$-CH).

^{13}C NMR (100 MHz, CD_3OD) δ: 175.77/175.72 (C=O Leu), 158.6/158.5 (C=O CBZ), 143.2 (Ph C-1), 138.2 (Bn C-1), 129.6 (2C, Ph C-2,6), 129.4 (2C, Ph), 129.0 (Bn), 128.9 (2C, Bn) 128.9 (2C, Bn C-2,6), 126.89/126.83 (Ph C-4), 116.1 (t, $^1J_{C,F}$ = 247.0 Hz, *C*HF_2), 96.8 (HO-*C*-OH), 67.73/67.68 (*C*H_2O), 55.25/55.19 (α-*C*H Leu),53.45/53.14 (α-*C*H Homophe), 41.89/41.86 (*C*H_2-CH Leu), 33.42/33.20 (*C*H_2Ph), 31.93/31.56 (*C*H_2-CH Homophe), 25.85/25.83 (*C*H-CH_3), 23.33/23.31 (*C*H_3-CH), 22.05/21.99 (*C*H_3-CH).

^{19}F NMR (376 MHz, CD_3OD) δ: -136.4 (d, $^2J_{H,F}$ = 54.7 Hz, CHF_2).

HRMS (ESI), *m/z*: calcd. for hydrated ketone $C_{25}H_{32}F_2N_2O_5Na^+$: 501.2176 $[M+Na]^+$; found: 501.2171**;** *m/z*: calcd. for ketone $C_{25}H_{30}F_2N_2O_4Na^+$: 483.2065 $[M+Na]^+$; found: 483.2066.

4.4. OTHER SUPPLEMENTARY MATERIAL

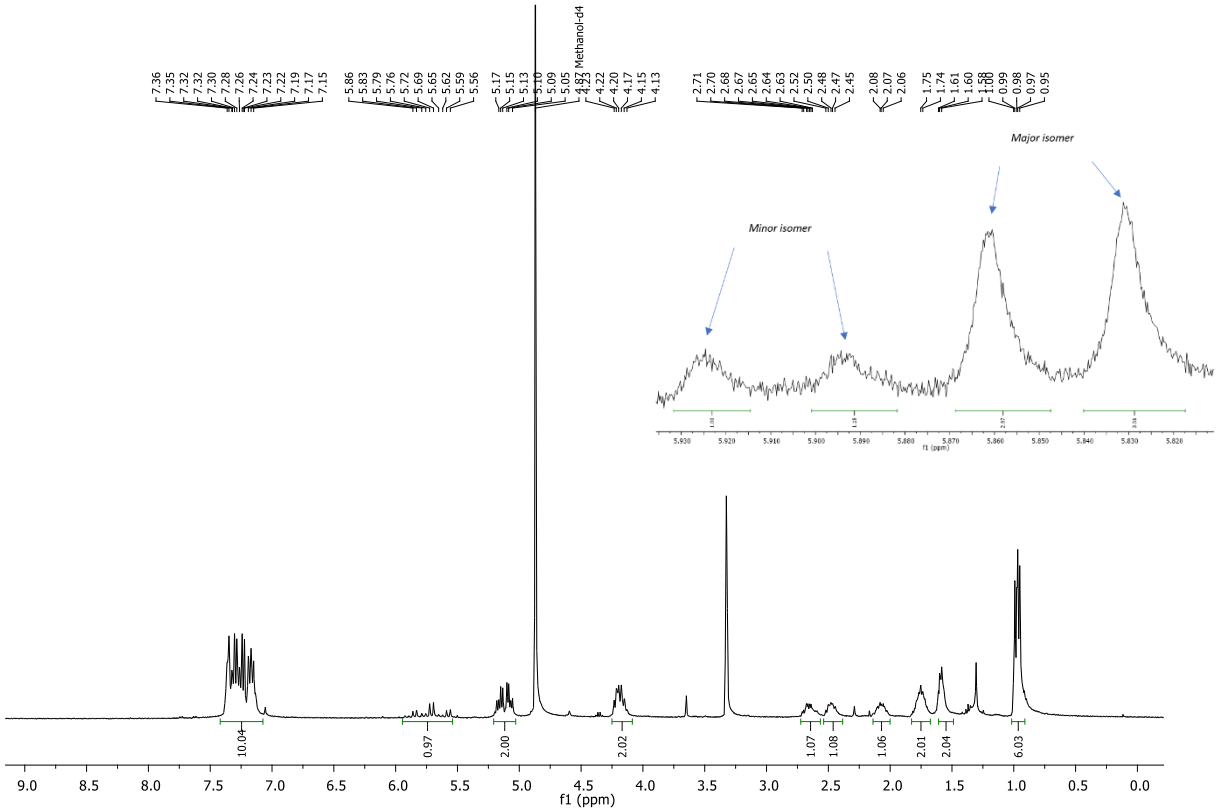


Figure S1. Copy of ^{1}H NMR spectrum of Z-Leu-Homophe-CHF_2 recorded in methanol-d_4.

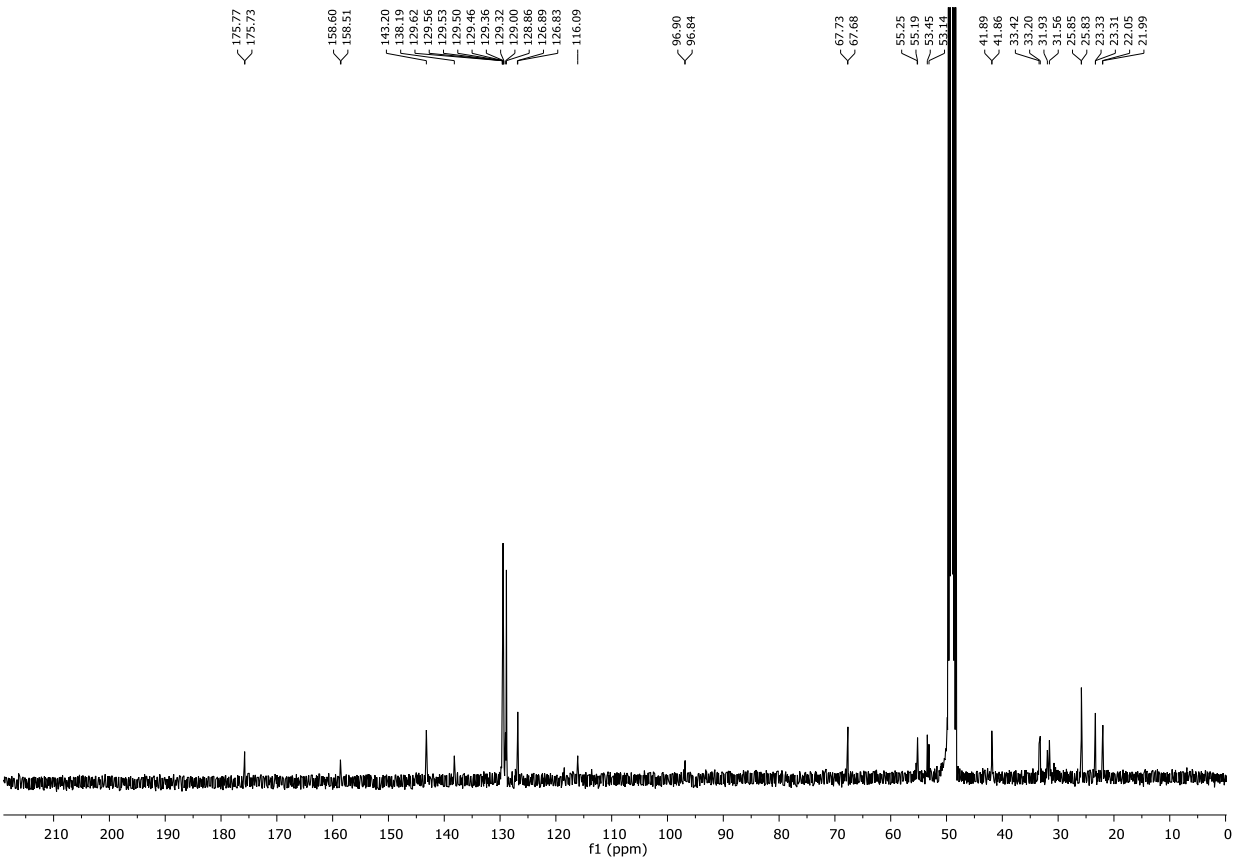


Figure S2. ^{13}C NMR spectrum of Z-Leu-Homophe-CHF_2 recorded in methanol-d_4.

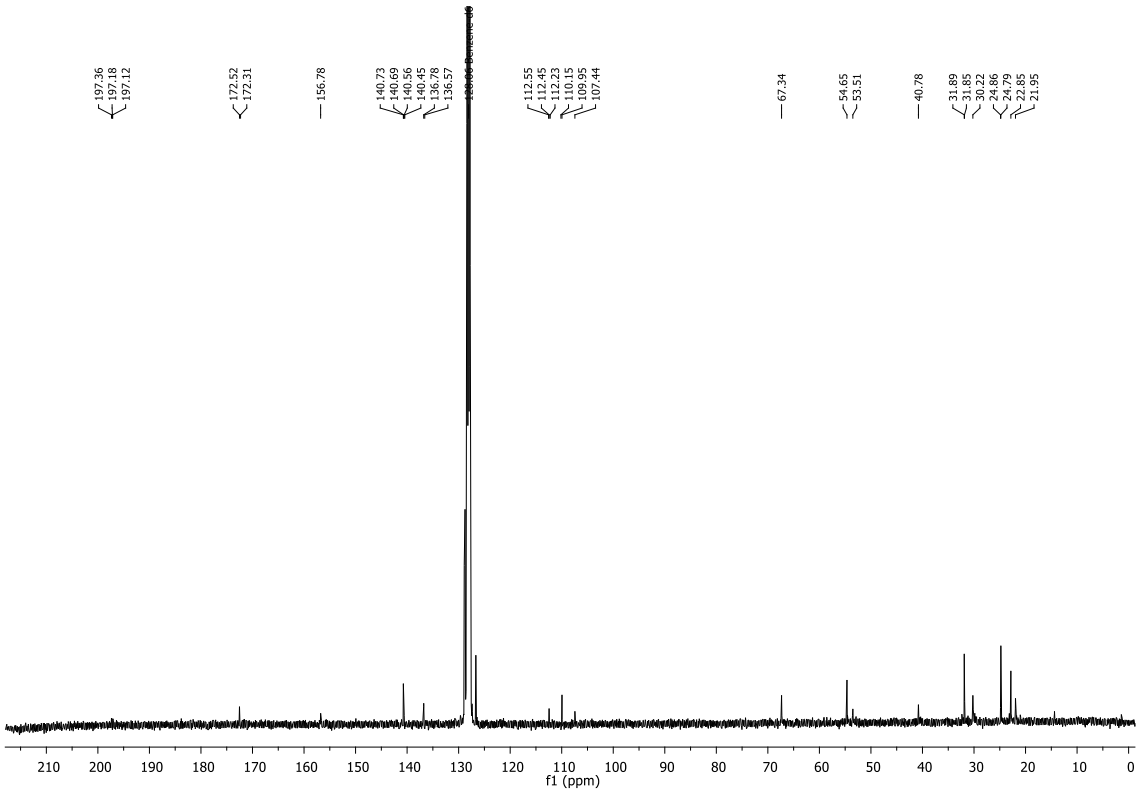
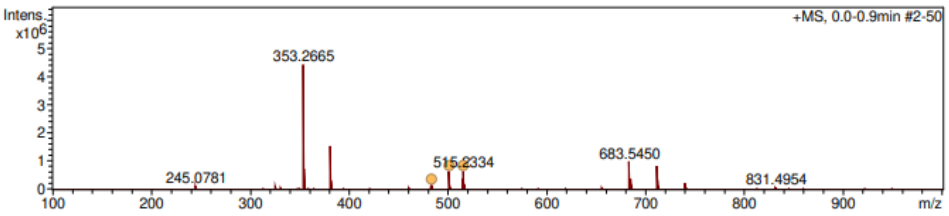


Figure S3. ^{13}C NMR spectrum of Z-Leu-Homophe-CHF_2 recorded in benzene-d_6.



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
483.2065	1	C33H27N2O2	483.2067	0.4	44.6	1	100.00	21.5	even	ok
	1	C25H30F2N2NaO4	483.2066	0.1	0.4	1	100.00	10.5	even	ok
501.2176	1	C30H30FN2O4	501.2184	1.6	33.6	1	100.00	16.5	even	ok
	2	C33H29N2O3	501.2173	-0.7	50.2	2	78.12	20.5	even	ok
	1	C25H32F2N2NaO5	501.2171	-0.9	6.5	1	100.00	9.5	even	ok
515.2334	1	C31H32FN2O4	515.2341	1.2	32.6	1	100.00	16.5	even	ok
	2	C34H31N2O3	515.2329	-1.0	49.2	2	67.72	20.5	even	ok
	1	C26H34F2N2NaO5	515.2328	-1.2	4.8	1	100.00	9.5	even	ok

Figure S4. HRMS spectrum of Z-Leu-Homophe-CHF_2.

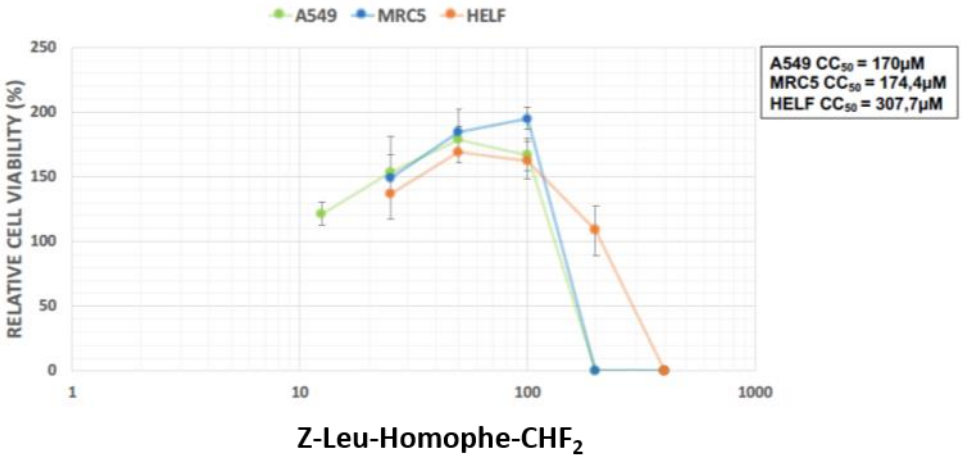


Figure S1. Effect of Z-Leu-Homophe-CHF_2 on cell viability**.** A549. HELF, and MRC5 cells were treated.

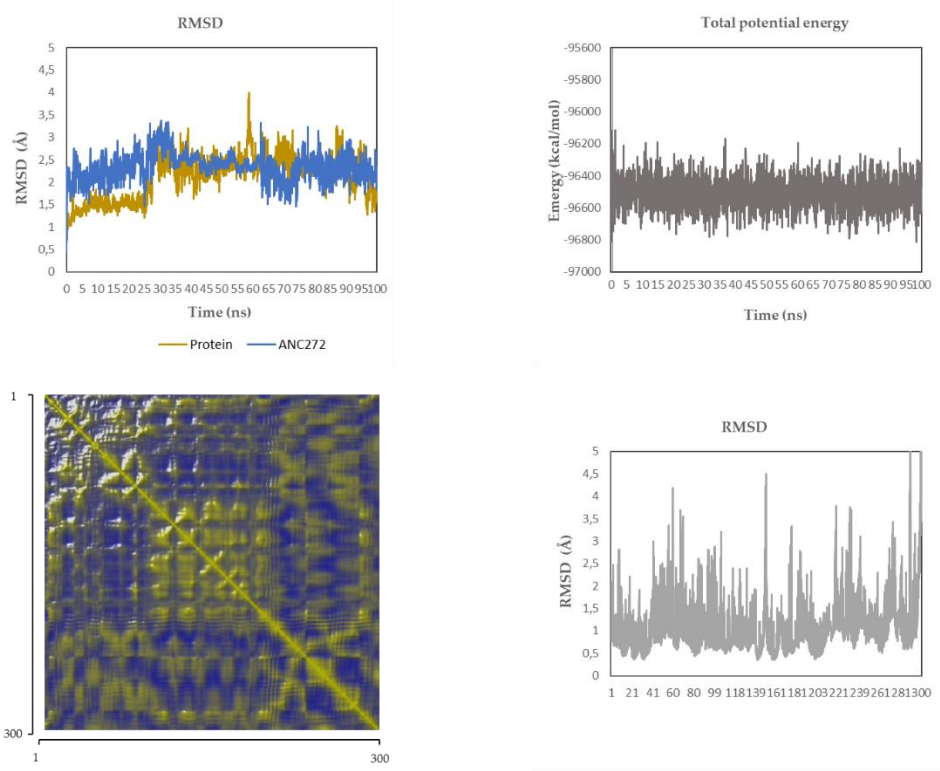


Figure S6. RMSDs of hCoV 229E M^{pro} and its complexes with Z-Leu-Homophe-CHF_2 (up-left) and Total potential energy (up-right). DCCM is visualized with colors ranging from blue (−1, fully anti-correlated) to yellow (+1, fully correlated). (down-left) Root Mean Square Fluctuation [vertical axis] for solute protein residue [horizontal axis] calculated from the average RMSF of the atoms.

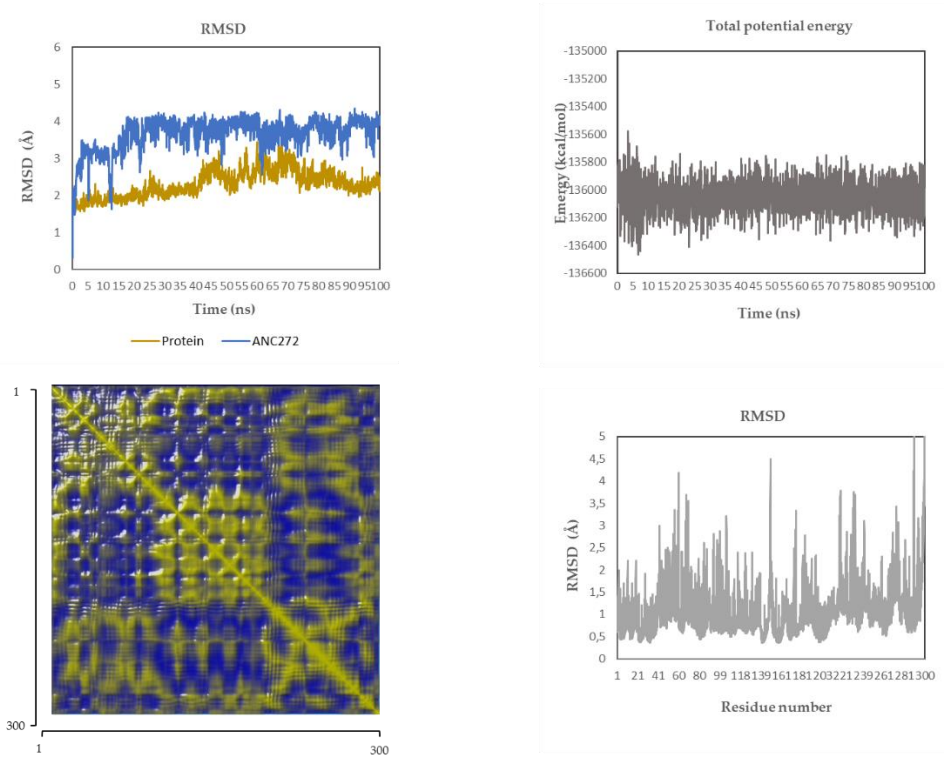


Figure S7. RMSDs of SARS-CoV-2 M^{pro} and its complexes with Z-Leu-Homophe-CHF_2 (up-left) and Total potential energy (up-right). DCCM is visualized with colors ranging from blue (−1, fully anti-correlated) to yellow (+1, fully correlated). (down-left) Root Mean Square Fluctuation [vertical axis] for solute protein residue [horizontal axis] calculated from the average RMSF of the atoms.

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