Lanthanide-mediated C-F Bond Activation

Method Development and Mechanistic Investigations

Mario Janjetovic

UNIVERSITY OF GOTHENBURG

Department of Chemistry and Molecular Biology
University of Gothenburg
2016

DOCTORAL THESIS

Submitted for partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Chemistry

© Mario Janjetovic
ISBN: 978-91-628-9900-4 (Print)
ISBN: 978-91-628-9901-1 (PDF)
http://hdl.handle.net/2077/44873

Department of Chemistry and Molecular Biology
University of Gothenburg
SE-412 96 Göteborg
Sweden

Printed by Ineko AB
Kållered, 2016

To my family

Abstract

The use of transition-metals and main-group Lewis acids has proven to be an outstanding source for activation and subsequent functionalization of fluorinated compounds. However, the first is mainly limited to C(sp^2)–F bonds which partially are activated by an adjacent heteroatom, and the latter is limited to simple C(sp^3)–F bonds due to particularly strong Lewis acid character.

The main focus of this thesis has been directed towards development of mild and chemoselective lanthanide mediated C–F bond activation of simple and functionalized alkyl fluorides from a synthetic point of view.

The first part of the thesis covers a solvent dependent reductive HDF of alkyl fluorides by employing $Sm(HMDS)_2$ as a single-electron transfer reagent. The Sm(II)-reagent, assisted by microwave heating, is capable of reductive cleavage of primary, secondary, and tertiary alkyl fluorides to the corresponding hydrocarbons in excellent yields

The second part of the thesis describes the utilization of $YbI_3(THF)_3$ as a superior Lewis acid for the selective iodination of primary, secondary, and tertiary alkyl fluorides in presence of various common functional groups. The mechanism of the reaction was distinctively studied by the means of substrate reactivity, stereochemical analysis, and initial rate measurements. The reaction was further elaborated into a catalytic process in the presence of TMSI as a stoichiometric fluoride-trapping agent. ^1H and ^{19}F NMR spectroscopy demonstrated a two-step catalytic cycle where TMSI regenerates the active $YbI_3(THF)_3$.

The third and final part of the thesis involves the development of a facile and efficient protocol of direct amination of alkyl fluorides employing $La[N(SiMe_3)_2]_3$. The method was shown to tolerate various secondary nucleophilic amines as well as functionalized alkyl fluorides. A concerted transition state was proposed for the reaction based on ^1H NMR spectroscopy, initial rate measurements, KIE, and steric effects. It was also found that $La[N(SiMe_3)_2]_3$ promoted instantaneous and subsequent substitution of β-amino fluorides. ^1H NMR spectroscopy revealed that the reaction appears to proceed via an aziridinium ion. Consequently, the reactive intermediate was prone to undergo ring-opening by various nucleophiles, yielding the corresponding β-substituted amines in high to excellent yields.

Keywords: C–F bond activation, fluorine chemistry, lanthanides, single-electron transfer reagent, Lewis acid, chemoselectivity, synthetic method, catalysis

List of publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals. **I**. & **IV**. Reproduced by permission of The Royal Society of Chemistry. **II**. & **III**. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission. **V**. Copyright American Chemical Society. Reprinted with permission.

I. **Solvent dependent reductive defluorination of aliphatic C-F bonds employing $Sm(HMDS)_2$**
Mario Janjetovic, Annika M. Träff, Tobias Ankner, Jenny Wettergren and Göran Hilmersson, *Chem. Commun.* **2013**, 49, 1826-1828.

II. **Selective C-F Bond Activation: Substitution of Unactivated Alkyl Fluorides using YbI_3**
Annika M. Träff, Mario Janjetovic, Linda Ta and Göran Hilmersson, *Angew. Chem. Int. Ed.* **2013**, 52, 12073-12076.

III. **Mild and Selective Activation and Substitution of Strong Aliphatic C-F Bonds**
Mario Janjetovic, Annika M. Träff and Göran Hilmersson, *Chem. Eur. J.* **2015**, 21, 3772-3777.

IV. **C-F bond substitution *via* aziridinium ion intermediates**
Annika M. Träff, Mario Janjetovic and Göran Hilmersson, *Chem. Commun.* **2015**, 51, 13260-13263.

V. **Catalytic Iodination of the Aliphatic C-F Bond by $YbI_3(THF)_3$; Mechanistic Insight and Synthetic Utility**
Mario Janjetovic, Andreas Ekebergh, Annika M. Träff and Göran Hilmersson, *Org. Lett.* **2016**, 18, 2804-2807.

Abbreviations

BDE	Bond dissociation energy
Bn	Benzyl
Ce	Cerium
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
cod	Cyclooctadiene
DG	Directing group
DMPU	*N,N'*-dimethylpropyleneurea
DMF	Dimethylformamide
Dy	Dysprosium
EtOAc	Ethyl acetate
Et_2O	Diethylether
EtOH	Ethanol
Et_3SiH	Triethylsilane
GC/MS	Gas chromatography/Mass spectrometry
GC	Gas chromatography
gem	Geminal
HDF	Hydrodefluorination
HMDS	Hexamethyldisilazane
i-Pr	Isopropyl
KHMDS	Potassium bis(trimethylsilyl)amide
KI	Potassium iodide
KIE	Kinetic isotope effect
LA	Lewis acid

La	Lanthanum
Ln	Lanthanide
MeCN	Acetonitrile
MW	Microwave
PA	Pro analysis
PEt_3	Triethylphosphine
Ph	Phenyl
Sm	Samarium
THF	Tetrahydrofuran
TMSF	Fluorotrimethylsilane
TMSI	Iodotrimethylsilane
TPPA	Tripyrrolidiniophosphortriamide
Yb	Ytterbium

Contents

1. Introduction and background

1.1. The C–F bond

The carbon-fluorine bond is a unique functionality due to the high electronegativity of fluorine. As such, being the element with the highest electronegativity (4.0), the fluorine atom has the greatest capacity to attract electron density.[1] Accordingly, the C–F bond is highly polarized, leading to a bond with less covalent and more electrostatic (ionic) character. As a result of such physical properties, the C–F bond is the strongest single bond that can be formed between carbon and another element. The explicit strength of the bond can be ascribed to the significant electrostatic attraction between the two partial charges of $F^{\delta-}$ and $C^{\delta+}$. Also, the outer shell electrons of the compact fluorine atom contribute to the unusual bond strength of the C–F bond. Thus, the two partial charges are stabilized to a greater extent when the valence electrons are closer to the nucleus (comparing fluorine (2p) to chlorine (3p)).[2] As a result, the C–F bond length is about 1.35 Å, and is shorter than any other carbon-halogen bond (Table 1). In addition, the C–F bond has the highest bond dissociation energy (BDE) when comparing other common covalent bonds (Table 1).

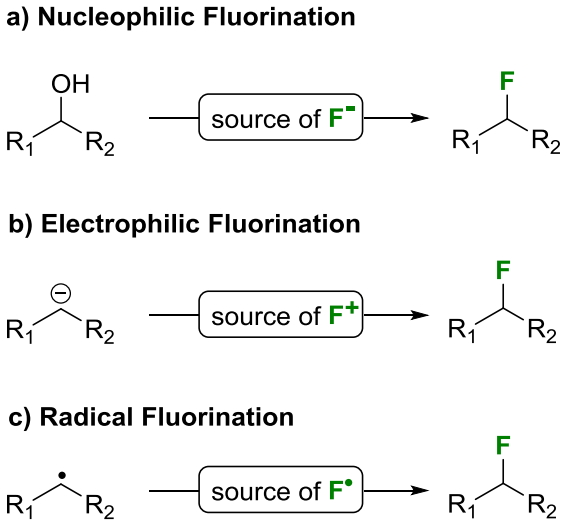
Table 1. Average bond lengths and bond dissociation energies of common C–X bonds.

Bond	Bond lengths (Å)	BDE (kcal mol^{-1})
C–F	1.35	105.4
C–Cl	1.78	78.5
C–Br	1.93	68.6
C–I	2.14	51.2
C–H	1.09	98.8
C–O	1.43	84.0
C–C	1.54	83.1
C–N	1.47	69.7

1.2. Fluorine incorporation

The characteristic features of the C–F bond and its ability to influence chemical and physical properties of organic molecules is what makes fluorine a hot and desired atom in modern pharmaceutical and agrochemical chemistry.[3,4,5,6] Today, there is an estimate that as many as 30-40% of agrochemicals and 20% of pharmaceuticals on the market contain fluorine.[7] A fluorination process, in particularly replacing hydrogen or oxygen with fluorine, is a well-established strategy to increase pharmaceuticals effectiveness, biological degradation, and bioabsorption.[8,9] These demands of fluorinated bioactive compounds have led to the development of numerous fluorinating protocols available nowadays,

ranging from nucleophilic or electrophilic substitution, to more recent protocols of radical fluorination (Scheme 1).[10,11]

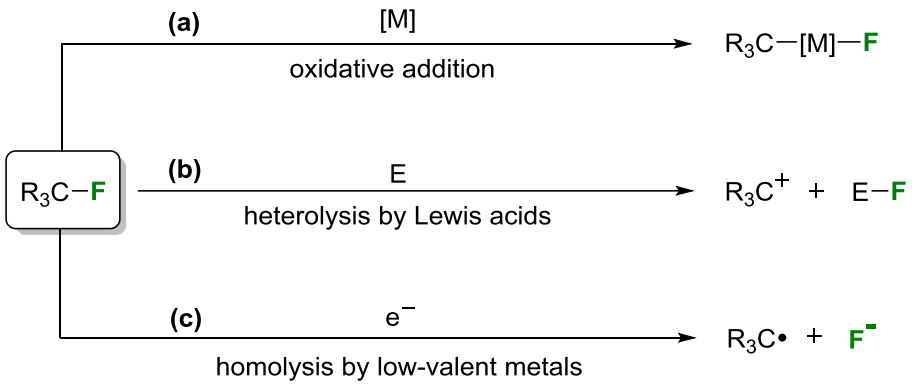


Scheme 1. Approaches for C–F Bond Formation.

In contrast to the C–F bond formation, the C–F activation and subsequent cleavage is a much less explored concept.[12] However, C–F bond activation has emerged as an interesting methodology due to the increase of fluorinated compounds. Not only would vital and novel methods to selectively activate and transform the C–F bond benefit the synthetic community, but it is also important from an environmental perspective since fluorinated compounds are extensively used, extremely long-lived, and potentially toxic.

1.3. C–F bond activation

Protocols for selective functionalization of the strong C–F bond into new carbon–element bonds would establish new methodology towards e.g. novel partially fluorinated building blocks as well as versatile non-fluorinated compounds.[12] However, since the BDE of a C–F bond is higher than the corresponding carbon–heteroatom bond, the cleavage requires thermodynamic compensation by the formation of an even stronger and more favorable element–fluorine bond, e.g. Si–F, B–F, Al–F and transition-metal–fluorine bond. Among the methods that exist for C–F bond activation (Scheme 2), significant work has already been done using transition-metals (Scheme 2**a**).[13,14,15] However, alternative protocols which have emerged as promising approaches for activation of C–F bonds are: 1) single-electron reductive processes (Scheme 2**c**)[16,17] and 2) heterolytic fluoride abstraction utilizing main-group or lanthanide Lewis acids (Scheme 2**b**).[18]

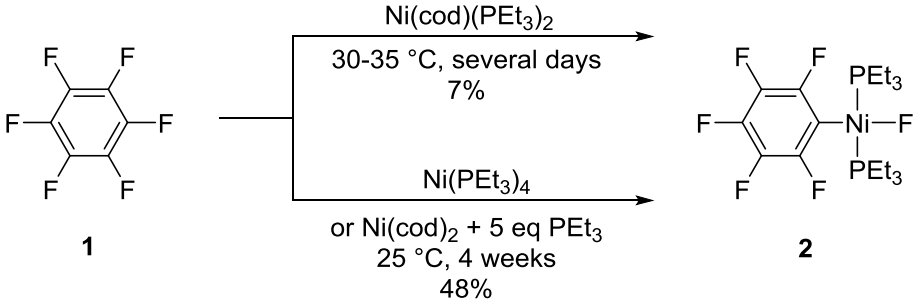


Scheme 2. General strategies for C–F bond activation ([M] = transition-metal complexes, E = main-group or lanthanide Lewis acids).

1.3.1. Transition-metal mediated C–F bond activation

Transition-metal mediated C–F bond activation has been extensively studied.[19,20,21,22] However, the substrate scope is mainly limited to the more activated C(sp^2)–F bond of aromatic (such as fluorinated heteroaromatics and polyfluorobenzenes) and vinylic fluorocarbons, where only few exceptions exist.[23,24,25] The mechanistic pathway of the transition-metal mediated C–F bond activation typically involves an oxidative addition to an electron rich metal center, or a less common homolytic cleavage induced by a single-electron transfer process (Scheme 2**a** and **c**).[26] Mainly electron-rich transition-metals such as Ni, Pd, Pt and Rh have been employed in the characteristic C–F bond activation.

Early examples reported in the literature make use of stoichiometric amounts of Ni(0) complexes for activation of C(sp^2)–F bonds. In 1977, Fahey and Mahan observed the oxidative addition of hexafluorobenzene (**1**) to Ni(cod)(PEt_3)$_2$ (Scheme 3).[27] However, the reaction yielded only 7% of the pentafluorophenyl fluoronickel(II) complex (**2**) after several days, and characterization of the complex was limited to elemental analysis and IR spectroscopy.

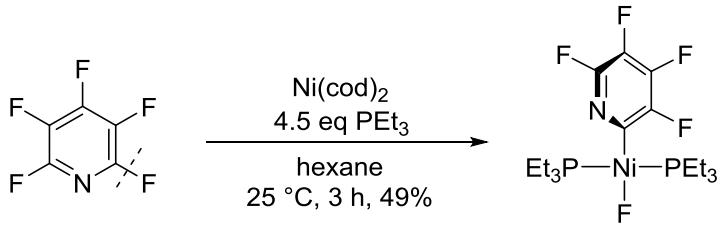


Scheme 3. Early examples of stoichiometric usage of Ni(0) complexes in activation of C(sp^2)-F bonds via oxidative addition.

Further validation and characterization of the resulting oxidative addition to Ni(0) complex was determined by Perutz et al.[28,29] Although the reaction proceeded slowly, the

pentafluorophenyl fluoronickel(II) complex (**2**) was isolated in 48% yield and the structure was confirmed by X-ray crystallography (Scheme 3).

Moreover, the group of Perutz also established selective C-F bond activation of fluorinated heteroaromatic compounds. They showed that the reaction of pentafluropyridine (**3**) with Ni(0) complexes underwent oxidative addition much more rapidly than that of hexafluorobenzene (Scheme 4).[30,31]



3 **4**

Scheme 4. Selective activation of pentafluoropyridine using stoichiometric amount of Ni(0).

Since then, numerous reactions towards selective activation of polyfluorinated heteroaromatic systems and polyfluorinated benzene derivatives utilizing metal complexes based on Ni(0),[32,33,34,35,36,37] Pd(0),[38,39,40,41] Pt(0),[42] and Rh(I)[43,44,45,46] centers has been developed. Significant studies have been conducted on polyfluoropyridine substrates, where regioselective C–F bond substitution at the 2- or 4-position are often found in the literature. The selectivity is most often dependent on the nature of the transition-metal complex, where Ni(0)-complexes has a preference for the 2-postion,[21,33.47] while Pd(0), Pt(0), and Rh(I) has mainly a preference for the 4-position (Figure 1).[38,42,48,49,50,51] The latter two transition metals presumably undergo C–F bond activation via aromatic nucleophilic substitution to afford a metal–carbon complex, and not via oxidative addition as in the case with Ni(0) and Pd(0).

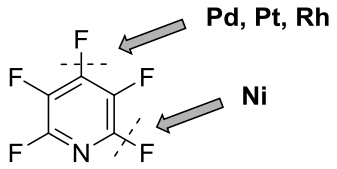
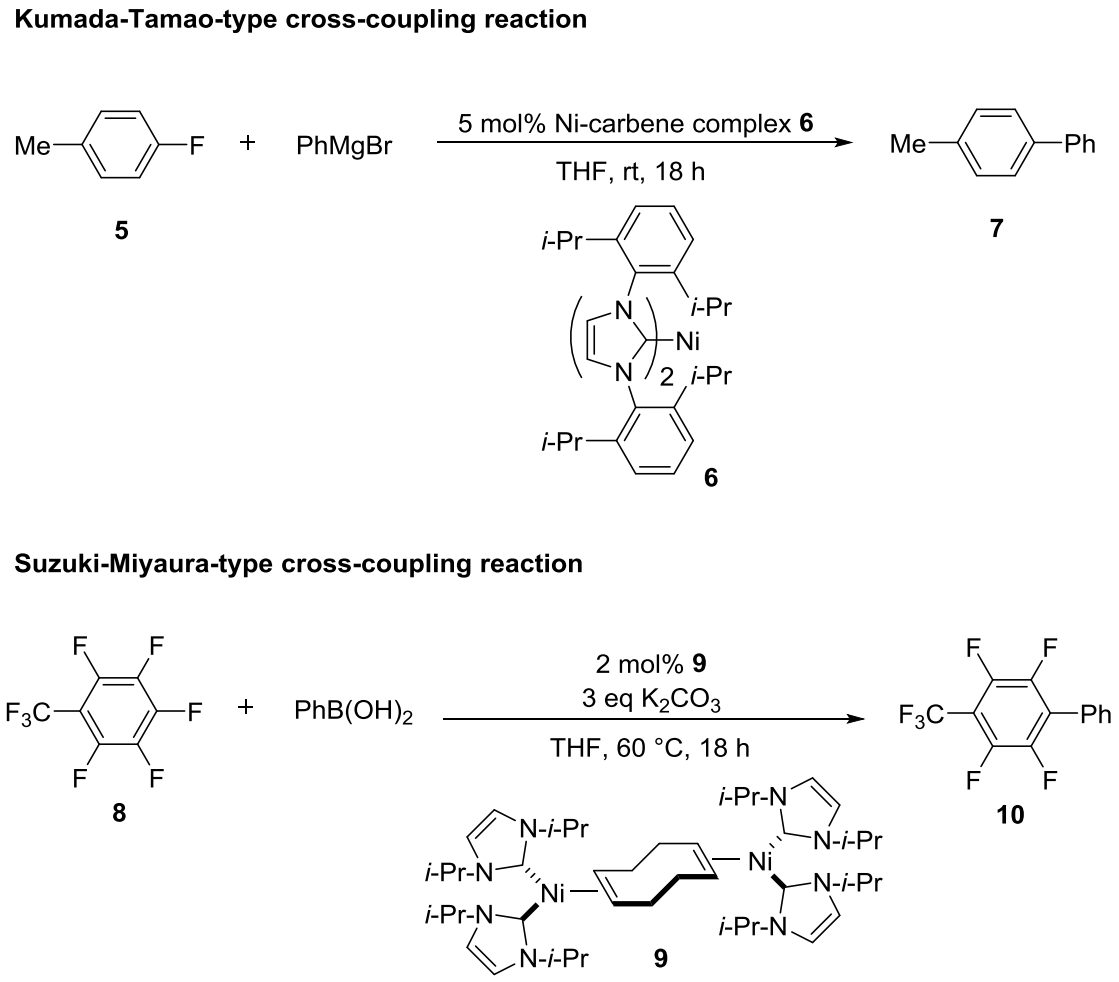


Figure 1. Transition-metal dependent *ortho*- or *para*-C(sp^2)–F bond activation of pentafluoropyridine.

The reactions presented in scheme 3 and 4 employs stoichiometric amount of metal and hold promising results for selective C–F bond activation and functionalization. However, more recent work describes several examples of catalytic transformations of C–F bonds of fluorinated benzene derivatives mainly via cross-coupling reactions. Herman et al. reported on a successful catalytic Kumada-Tamao-type cross coupling by C–F bond activation using an *in situ* generated Ni-carbene complex (**6**) and an aryl Grignard compound (Scheme 5).[52] The reaction is assumed to proceed via an oxidative

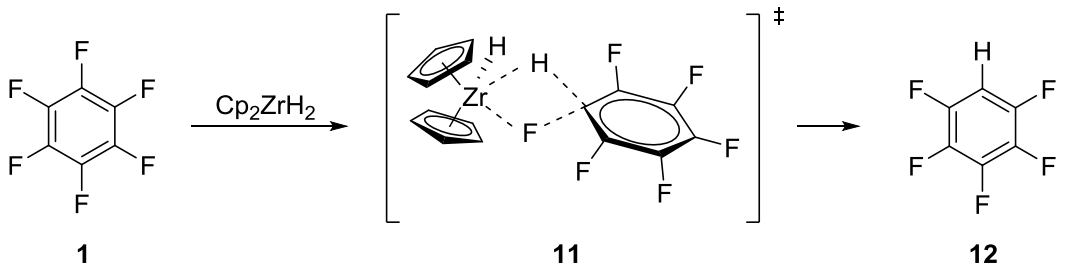
addition/transmetalation/reductive elimination sequence. The first Ni-catalyzed Suzuki–Miyaura cross-coupling involving C–F bond activation was reported by Radius et al.[53] In presence of a carbene stabilized Ni complex (**9**), they were able to cross-couple polyfluorinated benzene derivatives with phenylboronic acid (Scheme 5). Since then, several examples of C–F bond activation and cross-coupling reactions using Ni(0)[54,55,56,57,58,59,60] and Pd(0)[61,62,63] complexes with electron donating-ligands in combination of electron-deficient aryl fluorides have been developed. Also, utilization of both early and late transition-metal complexes have been used for C–F bond activation of aromatic fluorides.[12,14]



Scheme 5. Kumada-Tamao cross-coupling reaction of a monofluorobenzene with an aryl Grignard reagent and a Suzuki-Miyaura cross-coupling reaction of a perfluoroarene with an aryl boronate employing Ni as catalyst.

Furthermore, transition-metal mediated HDF of C(sp^2)–F bonds has been a research interest for almost half a century.[13] It is a promising approach to access either partially fluorinated or non-fluorinated compounds from readily available polyfluorinated chemicals. Employing stoichiometric amount of zirconium complexes, especially zirconocene hydrido complexes, permitted HDF of several polyfluorinated aryl and vinyl

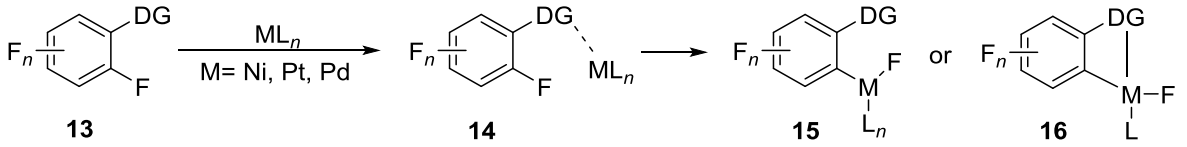
fluoride compounds. Mechanistically a four-centered *σ*-bond metathesis (**11**) is suggested in the HDF of hexafluorobenzene (**1**) (Scheme 6).[26,64]



Scheme 6. Zirconium-based HDF of hexafluorobenzene via a proposed *σ*-bond methathesis.

Some more recent studies on HDF reactions embraces catalytic amount of transition metal hydride complexes in the presence of silanes as hydride sources.[38,40,41,44,46,65,66] Usually the silane regenerates the active metal hydride specie by ligand exchange to form the stronger Si–F bond.

Another interesting approach for selective C–F bond activation of fluoroaromatics is the assistance of a directing group adjacent to the fluorine. Such a directing group enables significant functionalization of polyfluorinated aryl substrates where the C–F bond activation usually occurs at the *ortho*-position (Scheme 7).[14,67] Common directing groups in these cases are imines, pyridines, nitro, keto and hydroxyl groups.



Scheme 7. General transition-metal mediated *ortho*-C(sp^2)–F bond activation assisted by an adjacent directing group.

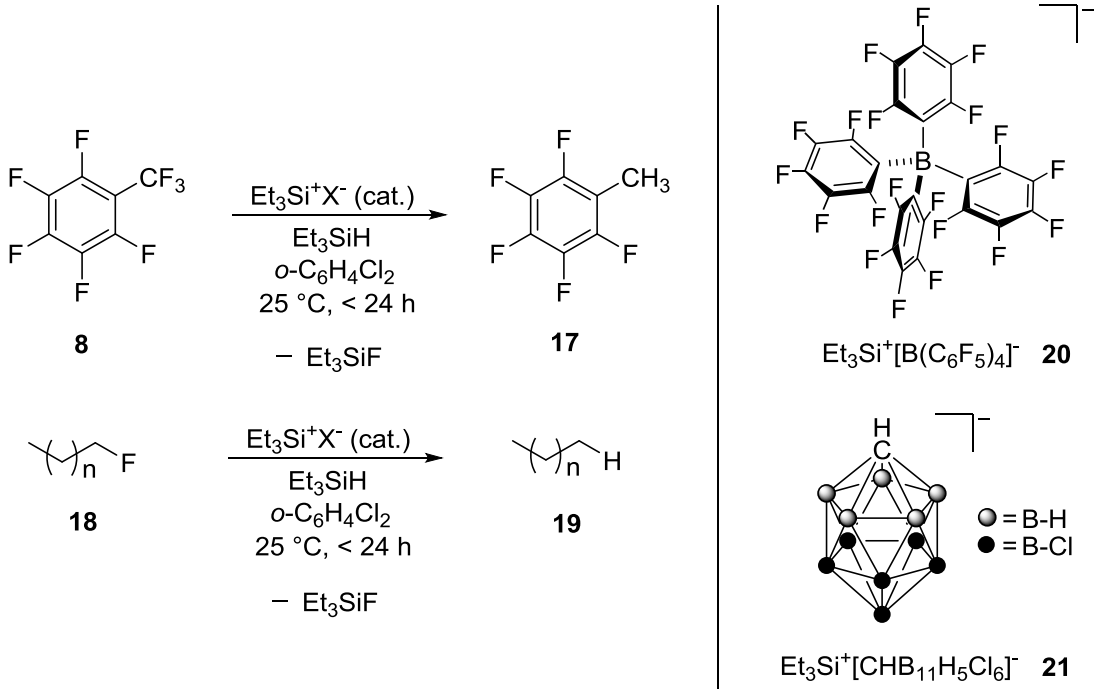
Many of the transformations presented in Scheme 5 and 7 involve a transformation of a C–F bond into a C–C bond. The cross-coupling reactions are mostly mediated by catalytic processes involving transition-metals such as Ni, Pd, and Pt. The transformations generally proceed via an oxidative addition, where typically fluorinated heterocycles and polyfluorinated aromatic compounds with directing groups are easier to activate. However, transition-metal mediated C–F bond activation is mostly limited to aromatic C–F bonds, where the activation of alkyl fluorides is practically non-existent.

1.3.2. Main-group Lewis acid mediated C-F bond activation

Over the past decade, much attention has been drawn towards Lewis acid mediated C–F bond activation utilizing main-group elements. This type of approach has emerged as a promising tool for selective C–F bond activation of simple monofluorinated and

polyfluorinated alkyl groups. The C–F bond cleavage typically proceeds via a heterolytic abstraction of the fluoride by a strong Lewis acid (Scheme 2**b**).[18] Several examples of main-group Lewis acid mediated C–F bond activation found in the literature employ silicon electrophiles, especially silylium ions (R_3Si^+) that combines both strong Lewis acidity and fluoride affinity.

Ozerov et al. has made substantial contribution to the development of catalytic HDF of C(sp^3)–F bonds in presence of silylium ions.[68,69,70] The active silylium ion catalyst $R_3Si^+X^-$ (X^- being weakly coordinating anions such as carboranes and tetraarylborates) is prepared *in situ* via addition of catalytic amount of Ph_3C–$[B(C_6F_5)_4]$ or Ph_3C–$[CHB_{11}H_5Cl_6]$ to stoichiometric amount Et_3SiH, forming $Et_3Si^+[B(C_6F_5)_4]^-$ (**20**) or $Et_3Si^+[CHB_{11}H_5Cl_6]^-$ (**21**) as "free" reactive silylium ions. Polyfluorinated and monofluorinated alkyl groups were cleaved to their corresponding hydrocarbons by employing the silylium–carborane catalyst $Et_3Si^+[CHB_{11}H_5Cl_6]^-$, (Scheme 8).

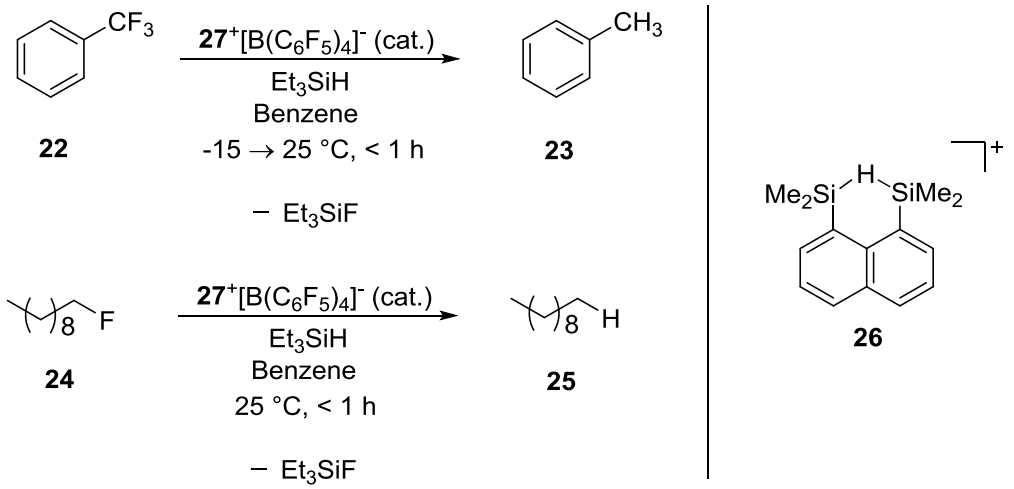


Scheme 8. Catalytic HDF of C–F bonds employing a borane stabilized silylium ion.

The conventional approach for catalytic HDF of aliphatic C–F bonds proceeds via fluoride abstraction by the silylium ion. The resulting intermediate carbenium ion undergoes hydride transfer by a stoichiometric hydride source such as R_3SiH, forming the corresponding hydrocarbon product. The overall process is thermodynamically favorable, as Si–F bonds are stronger than C–F bonds and C–H bonds are stronger than Si–H bonds.

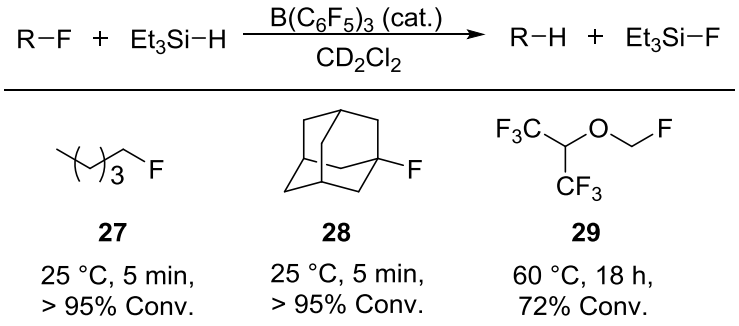
In a similar fashion, Müller et al. reported on catalytic HDF of C(sp^3)–F bonds using a hydride-bridged disilyl cation (**26**) as a "free" silylium ion stabilized by $[B(C_6F_5)_4]^-$.[71] In presence of stoichiometric Et_3SiH, full conversion of trifluoromethyl benzene (**22**) and 1-

fluorodecane (**24**) into their corresponding defluorinated hydrocarbons was obtained (Scheme 9).



Scheme 9. Catalytic HDF of C–F bonds employing a borane stabilized hydride-bridged disilyl cation.

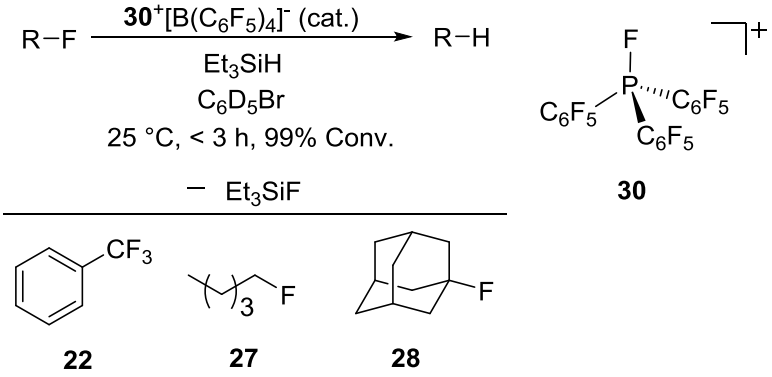
Alternative approach for catalytic HDF relies on the activation of the fluorophilic silicon electrophile by another Lewis acid. Some recent examples from Stephan and coworkers show on F–H exchange between alkyl fluorides and Et_3SiH in the presence of $B(C_6F_5)_3$ as the Lewis acid catalyst.[72] The electron-deficient borane is believed to coordinate and activate the Si–H bond forming a LA--H–SiR_3 specie which is sufficiently potent to abstract a fluoride.[73,74,75] The resulting Lewis acid-stabilized hydride is transferred to the carbenium ion. Consequently, various monofluorinated aliphatic fluorides can undergo HDF (Scheme 10).



Scheme 10. Borane-catalyzed HDF of alkyl fluorides in presence of Et_3SiH.

Functional groups incorporated in the fluoroalkanes may potentially inhibit the reaction due to interaction between the heteroatom and the strong Lewis acid. However, the $B(C_6F_5)_3/Et_3SiH$ reagent activates the primary fluoride in presence of a ether functionality in fluoroalkane **29**. The reagent system is also selective towards the mono fluoride over the trifluoro-groups. This is believed to be due to a reduced Lewis acidity of the B--H–SiR_3 specie compared to the exceptionally strong silylium ions.

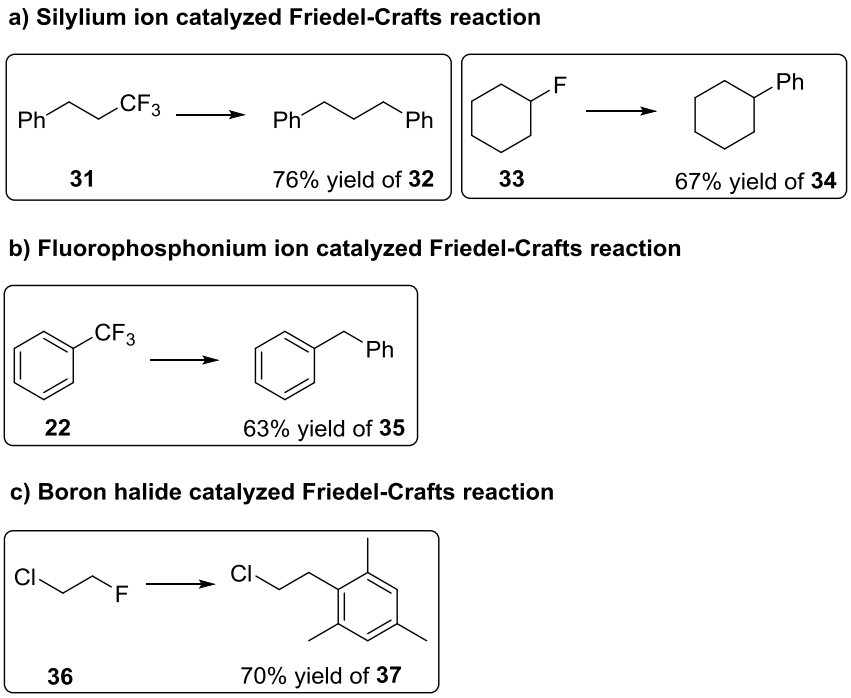
In analogy to the HDF reactions using silylium ions, organofluorophosphonium ions, stabilized by borane anions, afford highly Lewis acidic phosphonium centers with strong fluorophilic character.[76,77]



Scheme 11. Phosphonium-catalyzed HDF of C–F bonds in presence of Et_3SiH.

These organofluorophosphonium cations are shown to activate and react with fluoroalkanes to produce difluorophosphoranes. In the presence of a stoichiometric trialkylsilane, the organofluorophosphonium cation was shown to catalyze HDF of fluoroalkanes such as α,α,α-trifluorotoluene (**22**), 1-fluoropentane (**27**), and 1-fluoroadamantane (**28**) (Scheme 11).

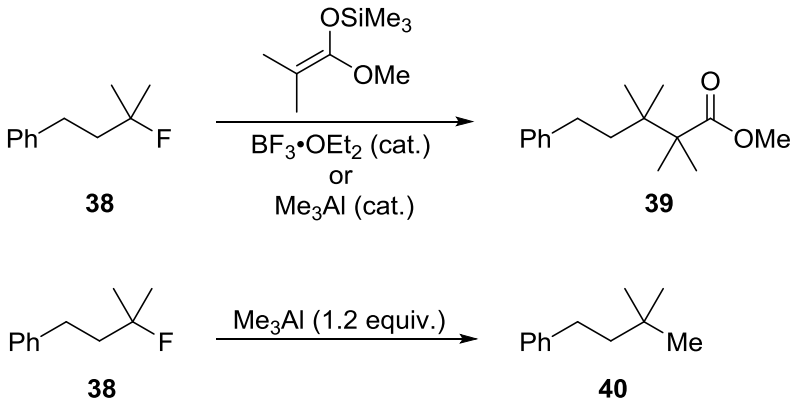
Parallel to the HDF of C(sp^3)–F, Ozerov,[69] Müller[78] and Stephan et al.[79] developed a Friedel–Crafts-type alkylation of primary and secondary alkyl fluorides and trifluoro-derivatives. When the following alkyl fluorides **31**, **33**, and **22** were treated with silylium or organofluorophosphonium ions in the presence of Et_3SiH, with benzene as solvent, a new C(sp^3)–C(sp^2) bond was formed (Scheme 12**a** and **b**).



Scheme 12. Examples on Friedel-Crafts benzene alkylation of C–F bonds catalyzed by either silylium ion, phosphonium ion, or borane.

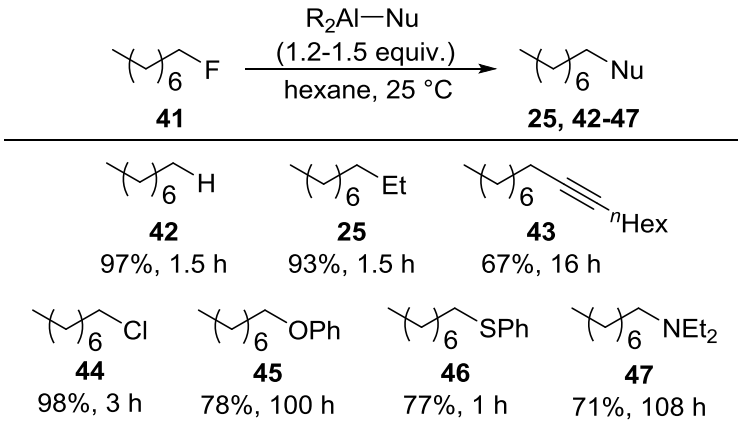
The results confirm presence of a carbenium ion which reacts with the aromatic solvent via electrophilic aromatic substitution. As early as half a century ago Olah et al. reported on BF_3- and BBr_3-catalyzed Friedel–Crafts-type alkylation of arenes via selective C(sp^3)–F bond activation (Scheme 12**c**).[80] Further on, stoichiometric amount of boron-, aluminium-, and magnesium-halide Lewis acids, such as BBr_3,[81,82] $AlCl_3$,[83,84] and MgI_2,[85] have also shown to promote halogen-exchange reactions of a variety of fluoroalkanes to the corresponding halides.

On the basis of strong Al–F and B–F interactions, tertiary alkyl fluorides are shown to readily undergo an alkylation reaction with silicon enolates in the presence of catalytic amount of $BF_3{\cdot}OEt_2$ or $AlMe_3$ (Scheme 13).[86,87] The Lewis acid is believed to cleave the C(sp^3)–F bond, generating a carbenium ion which undergos a nucleophilic attack of the silicon enolate. This affords the alkylated product and simultaneously regenerates the Lewis acid catalyst by formation of a Si–F bond.



Scheme 13. $BF_3 \cdot OEt_2$ or Me_3Al assisted alkylation of a tertiary alkyl fluoride.

Interestingly, when using only trimethylaluminium ($AlMe_3$) as a stoichiometric reagent, tertiary alkyl fluorides (**38**) underwent alkylation by a direct transfer of the methyl group. The group of Terao and Kambe further developed the use of stoichiometric amount of triorganoaluminium reagents in C(sp^3)–F bond activation and substitution.[88] Various R_2Al–X Lewis acids were shown to convert C(sp^3)–F to C(sp^3)–X bonds (X= Cl, C, H, O, S, N) via a S_N2-type mechanism (Scheme 14).



Scheme 14. Several examples on triorganoaluminium mediated functionalization of 1-fluorooctane.

As a compliment to transition-metal mediated activation of C(sp^2)–F bonds, reactions mediated by main-group Lewis acids has proven to be outstanding for activation and functionalization of unactivated C(sp^3)–F bonds. The recent progress in C–F bond activation enabled by Lewis acids have shown to be a promising toolbox to convert alkyl fluorides to potentially valuable and versatile non-fluorinated substrates. Despite the existing strategies involving Lewis acid mediated C–F bond activation, the development of mild Lewis acids and their application in chemoselective activation of aliphatic fluorides still remains a challenge.

1.3.3. Lanthanides and their application in C-F bond activation

The lanthanide series consist of 15 elements ranging from lanthanum to lutetium. They are most often called f-block elements since the valence electrons occupy the f orbitals. The common electronic structure for most of the lanthanides is $[Xe]4f^n6s^2$ or $[Xe]4f^{n-1}5d^16s^2$, where the 4f and 5d sub-shells have very similar energy levels.[89] All lanthanides preferentially exist in the +3 oxidation state, although particularly stable $4f^n$ configurations exist for the +2 oxidation state (e.g. for samarium). The loss of the three outermost electrons, namely one from the $5d^1$ sub-shell or the $4f^n$, and the $6s^2$, results in enhanced thermodynamic stability in which the Ln(III) adopts a closed-shell Xe-like electronic configuration.[90] Since Ln(II) species readily gives up an outer-shell electron to access the more thermodynamically stable Ln(III) form, a powerful and synthetically useful single-electron transfer reagent is accessible.

Consequently, LnX_2 (X= I, Br) has been established and recognized as a one-electron transfer reagent which has been exploited in functional group reductions.[90] The reactivity of Ln(II)-salts can be altered by exchanging ligands or by addition of proton donors and co-solvents. Lanthanide complexes are strongly electropositive and thus hard Lewis acids. As a consequence, they tend to form strong bonds with π-donor ligands such as OR, NR_2, and especially F.[91] As such, owing to the high affinity toward fluorides, lanthanides with their features are attractive candidates for C–F bond activation and could act as a complement to main-group Lewis acid mediated activation of alkyl fluorides. The fluorophilic character of lanthanides has not been widely exploited, little is known and only few reports exist. For example, the group of Deacon and co-workers have reported on divalent organolanthanide mediated *ortho*-C(sp^2)–F cleavage directed by a carboxyl- or a diaminate-group via radical abstraction (Figure 2).[92,93,94]

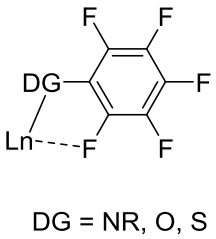


Figure 2. A general representation of common directing group assisted Ln--F interactions reported in literature.

Schelter and co-workers have shown on polarization of the *ortho*-C(sp^2)–F in bis(pentafluorophenyl) amine when attached to the diamagnetic La(III) and the paramagnetic Ce(III) cations by using ^{19}F NMR spectroscopy.[95] In an early example $Yb(fod)_3$ was used as a paramagnetic shift reagent for alkyl fluorides to assess Yb--F interaction by NMR spectroscopy.[96] A concentration dependent ^1H NMR shift was observed for *n*-propyl fluoride upon addition of $Yb(fod)_3$, implying that the alkyl fluoride is polarized in the presence of a Yb(III) cation.

Initial studies of the fluorophilic attribute of divalent and trivalent lanthanides holds promise for further development within Ln--F interaction. The affinity towards fluoride is remarkable, however, synthetic valuable methods for lanthanide mediated C–F bond activation is still lacking. The search for effective Ln(II)/(III) ions which enables simultaneous polarization and functionalization of fluorocarbons would lead to a novel and supplementary strategy within the C–F bond activation field.

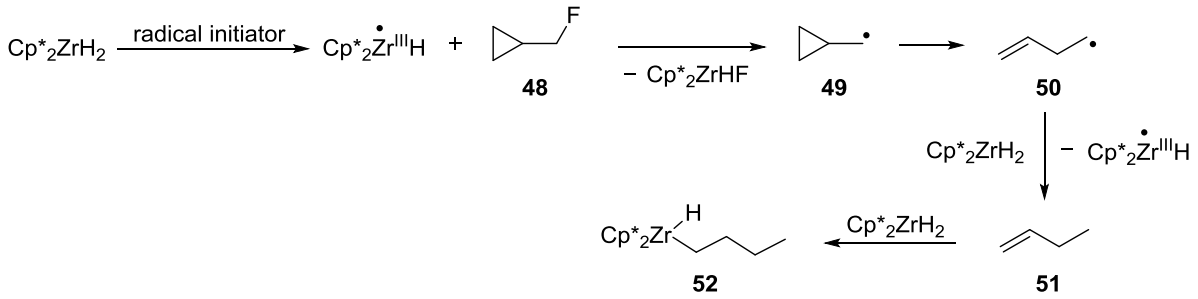
2. Objectives of this thesis

The aim of this thesis has been to extend and determine the possibilities of lanthanide mediated chemoselective C(sp^3)–F bond activation, and to introduce the fluoride as a chemically inert protecting group which can be selectively cleaved under mild conditions using new methodology.

First the focus was on finding and evaluating an appropriate Ln(II) specie which is capable of radical abstraction of simple unactivated alkyl fluorides. Secondly, Ln(III) species with labile nucleophilic ligands were examined. Such complexes should polarize the C(sp^3)–F bond upon coordination, and thus enable subsequent nucleophilic substitution into versatile non-fluorinated compounds. To achieve this, a variety of Ln(III) cations with alternating Lewis acidity and ionic radius were investigated in presence of different functionalized alkyl fluorides. Finally, results obtained from ^{1}H and ^{19}F NMR spectroscopy, initial rate studies, and stereochemical analysis, provided novel mechanistic insight towards the development of C–F bond activation accompanied by f-block elements.

3. Reductive defluorination (Paper I)

The chemically inert organofluoro compounds are persistent towards degradation, making them toxic and hazardous from an environmental perspective.[12] Development of efficient and selective chemical strategies for their transformation into more ecofriendly compounds is thus of vital importance. As described in section 1.3.2, Lewis acid mediated HDF of unactivated alkyl fluorides is a well-established approach in this sense. In contrary, radical promoted C-F bond cleavage of these compounds are scarce and only few efficient protocols exist. The group of Jones has made noteworthy contribution to the area of reductive defluorination reactions via radical abstraction (Scheme 2**c**). Jones et al. reported on transition-metal based cleavage of C(sp^3)–F bonds employing a $Cp^*_2ZrH_2$ complex.[26] A conclusive experiment were $Cp^*_2ZrH_2$ was mixed with cyclopropylcarbinyl fluoride (**48**) gave evidence of a radical pathway (Scheme 15).



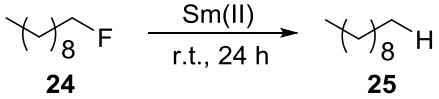
Scheme 15. Proposed radical mechanism for the zirconium mediated C–F bond cleavage of cyclopropylcarbinyl fluoride.

The intermediate cyclopropylcarbinyl radical (**49**) ring opens to give a butenyl radical (**50**), which converts to butene (**51**) that inserts into the Zr–H bond. Parallel to the lanthanide mediated C–F bond activation presented in section 1.3.3., our group recently developed a facile protocol using $SmI_2/H_2O/Et_3N$ for selective α-defluorination of polyfluorinated esters and amides.[97] Intrigued by the SmI_2 reagent and its applicability in carbon-halogen bond cleavage,[98] further expansion and usage of this reagent was elaborated to include defluorination of simple unactivated alipthatic fluorides.

3.1. Screening of Sm(II)-reagents

To be able to determine the optimal conditions for Sm(II)-induced reductive defluorination of unactivated alkyl fluorides, 1-fluorodecane (**24**) was chosen as a model substrate. 1-Fluorodecane was initially subjected to $SmI_2/H_2O/Et_3N$ at ambient temperature for 24 h, but the corresponding decane (**25**) was not obtained as determined by GC (Table 2, entry 1).

Table 2. Screening of various suitable Sm(II) species in the reductive HDF of 1-fluorodecane.[a]



24 **25**

Entry	Sm(II)-source	Solvent	Yield (%)[b]
1	$SmI_2/H_2O/Et_3N$	THF	no rxn
2	SmI_2/TPPA	THF	no rxn
3	SmI_2/DMPU	THF	no rxn
4	$Sm(HMDS)_2$	THF	26[c]
5	$Sm(HMDS)_2$	*n*-hexane	55[c]
6	$Sm(HMDS)_2$	THF	2
7	$NaSm^{II}(HMDS)_3$	*n*-hexane	30[c]
8	$NaSm^{II}(HMDS)_3$	THF	no rxn

[a] Reaction conditions: Sm(II)-source (1.0 mL, 0.1 M in solvent, 0.1 mmol), 1-fluorodecane (7.9 µL, 0.04 mmol). *n*-Dodecane (9.1 µL, 0.04 mmol) was added as an internal standard. The reaction was stirred for 24 h at r.t., after which a sample was collected and analyzed. [b] Measured by GC-FID. [c] Further conversion was observed after 24 h.

To further increase the reduction potential of the SmI_2 reagent, additives such as TPPA and DMPU were added. However, no reductive cleavage of 1-fluorodecane was observed (entries 2-3). Knowing that disilanes can coordinate and activate fluoroalkanes towards defluorination an interesting and relatively unexplored Sm(II)-source would be samarium bis(trimethylsilyl)amide ($Sm(HMDS)_2$). The reagent was first reported by Evans and co-workers, and is readily prepared from 2 equivalents of KHMDS and SmI_2.[99] KI precipitates and $Sm(HMDS)_2$ is obtained as a deep-purple solution. To our delight, when 1-fluorodecane was subjected to $Sm(HMDS)_2$ in THF, decane was obtained in 26% GC yield after 24 h (entry 4). As demonstrated by Evans et al., $Sm(HMDS)_2$ is soluble in *n*-hexane after prior removal of THF. In this case, additional KI precipitated, indicating that residual KI is soluble in THF. Interestingly, when adding 1-fluorodecane to $Sm(HMDS)_2$ in *n*-hexane an increase in conversion was attained, affording decane in 55% GC yield within 24 h (entry 5). The results illustrate a more reactive Sm(II)-specie when solvated in a non-coordinating and non-polar solvent such as *n*-hexane. Surprisingly, when subjecting 1-fluorodecane to the $Sm(HDMS)_2$, once again solvated in THF after prior removal of *n*-hexane, almost no conversion was observed (entry 6). This result indicates that residual KI solvated in THF affects the reactivity (comparing results in entry 4 and 6). An alternative approach to obtain KI-free $Sm(HDMS)_2$, reported by Evans et al., is achieved

by reducing $Sm(HMDS)_3$ in the presence of Na(s) in either *n*-hexane or THF, yielding tricoordinated divalent $NaSm^{II}(HMDS)_3$.[100,101] A reaction between 1-fluorodecane and $NaSm^{II}(HMDS)_3$ in *n*-hexane gave 30% decane (entry 7), whereas no reaction occurred when $NaSm^{II}(HMDS)_3$ solvated in THF was employed (entry 8). Consequently, KI in combination with solvent seems to have an effect on the reaction.

3.2. KI and THF effect

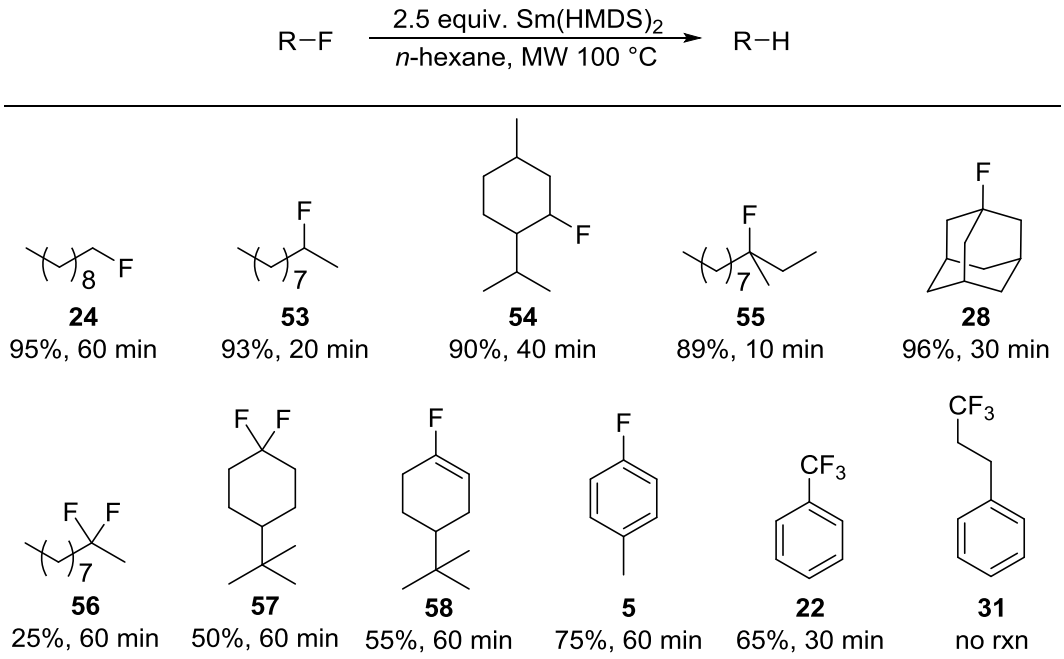
To establish the role of KI, and investigate how THF affects the reaction, two separate experiments were conducted.

Firstly, 4 different amounts of KI (0.3, 0.5, 1, 1.5 equiv.) were added to KI-free $Sm(HMDS)_2$ solvated in THF, followed by addition of 1-fluorodecane. With increasing amount of KI, the yield of decane increased up to 50% when the reaction was run at room temperature for 24 h. Adding more than 1.0 equiv. of KI to the $Sm(HMDS)_2$ did not enhance the reactivity. Interestingly, when observing the GC chromatogram of this experiment, a small peak belonging to 1-iododecane was detected. A hypothesis is that Sm(III) in combination with KI promotes a finkelstein-type reaction, where 1-fluorodecane is substituted forming 1-iododecane, which in turn is reductively cleaved. Reductive defluorination promoted by KI-contaminated $Sm(HMDS)_2$ (entry 4) may not be a clean $C(sp^3)$–F bond cleavage. This type of halogen exchange processes are further elaborated in the upcoming chapters.

Secondly, deliberative addition of THF (1, 6, 12, 24 equiv.) to $Sm(HMDS)_2$ solvated in *n*-hexane was conducted. 1-fluorodecane was added and the reaction was allowed to stir (at room temperature) for 24 h. The yield of decane steadily decreased upon increased concentration of THF. The reaction outcome indicates that presence of polar coordinating THF saturates the metal-sphere, thus inhibiting the crucial Sm--F interaction and activation.[102]

3.3. Substrate scope

$Sm(HMDS)_2$ solvated in *n*-hexane is the superior reagent for reductive defluorination of a $C(sp^3)$–F bond at room temperature (Table 2, entry 5). However the yield and the reaction time were not optimal in this case. In order to affect both of these parameters, a microwave-assisted method was developed. By heating the reaction to 100 °C in a microwave cavity for <60 min, primary, secondary and tertiary alkyl fluorides were reduced to their corresponding hydrocarbons in good to excellent yields (Scheme 16).



Scheme 16. Microwave assisted $Sm(HMDS)_2$ reductive HDF of various alkyl fluorides.

Also, a selectivity test between a primary, secondary, and a tertiary alkyl fluoride was performed. **24**, **53** and **28** were added in the same pot and subjected to the reaction conditions depicted in Scheme 16. The reactivity order showed a pattern of 3°>2°>1°, suggesting a radical mechanism since tertiary alkyl radicals are more stable and prone to undergo faster reduction to the corresponding anion. Furthermore, *gem*-difluoro substrates (**56** and **57**) were reduced to their corresponding alkene products. Low to moderate conversion of the starting material was reported. The reaction was believed to proceed either via a vinyl fluoride or via a carbene intermediate. The vinyl fluoride route was proven accessible, since **58** was reductively cleaved to the corresponding alkene in moderate yield. An aromatic C–F bond (**5**) was also possible to reduce yielding toluene in good yield. The possibility to fully reduce a CF_3-group was examined. The benzylic fluorides in **22** were fully reduced to toluene at room temperature. However, the alkyl CF_3 group in **31** did not react at all.

Since $Sm(HMDS)_2$ contains silyl groups, we speculated that these could somehow be involved in facilitating the activation of C–F bonds.[103] If such an interaction is present, a ^1H NMR experiment would reveal a shift of the protons in *a*-position to fluorine (R-C$\underline{H}_2$-F), or a shift of the fluorine signal in ^{19}F NMR. Titration of HMDS into a NMR tube containing 1-fluordecane was conducted. ^1H and ^{19}F NMR was recorded, however, no chemical shift changes were observed.

3.4. Conclusion

$C(sp^3)$–F and $C(sp^2)$–F bonds undergoes microwave assisted reductive HDF upon treatment with $Sm(HMDS)_2$ in *n*-hexane. The reactivity of the Sm(II) reagent is

dependent on the solvent and on the presence of residual KI (which is formed upon preparation of the reagent). KI-free $Sm(HMDS)_2$, solvated in THF, displays no reactivity in the HDF process, whereas KI contaminated $Sm(HMDS)_2$ in THF gives the corresponding hydrocarbon in reasonable yields at room temperature. This is probably due to a finklestein-type promoted reaction which affords the alkyl iodide, which in turn is reductively cleaved. However, $Sm(HMDS)_2$ solvated in *n*-hexane is the optimal reagent in which the HDF proceeds via direct cleavage of the C–F bond.

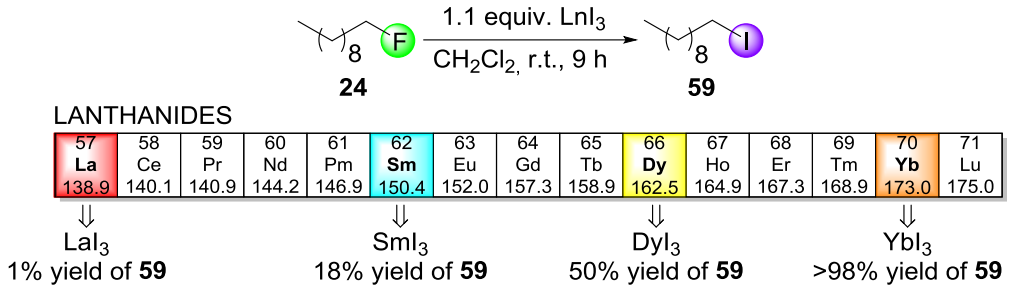
4. Lanthanide promoted iodination of the aliphatic C-F bond (Paper II and V)

There is no doubt that the C–F bond, due to its chemical features, is considered as an extremely useful moiety in the development of modern biological and material compounds. As a result, numerous fluorinating protocols have been developed in an attempt to access fluorinated materials from simple and advanced molecules.[10,11] The accessibility of fluorine within organic compounds now allows for exploration of simple and straightforward protocols to activate C–F bonds. As such, an intellectual appealing task would be to introduce the C–F bond as one of the most inert protecting groups within organic chemistry. However, to do so, methods to chemoselective transform the C–F bond into practical compounds needs to be established.

The intriguing findings of 1-iododecane as a byproduct during the Sm(II) induced reductive defluorination led to further investigation whether such a transformation (F/I) could be developed in a more controlled manner. It has been shown that Ln(III) cations effectively can polarize C–F bonds in different substrates upon coordination (see section 1.3.3). Therefore, it was speculated that LnI_3 Lewis acids, with labile iodides, could provide the opportunity for C–F bond activation with a subsequent nucleophilic substitution. The overall iodination process in this case is thermodynamically favorable, since the Ln–F bond is stronger than the C–F bond, and the formation of the new C–I bond is stronger than the Ln–I bond.[104] This strategy would potentially give access to highly reactive iodinated products from inert C–F bonds, which in theory can subsequently be converted to any other functionality.

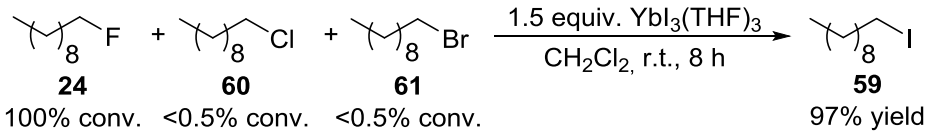
4.1. LnI_3 screening (Paper II)

The screening started off by allowing 1-fluorodecane (**24**) to react with $SmI_3(THF)_3$ in THF. After 24 h at room temperature, 1-iododecane (**59**) was only obtained in 10% GC yield. Since THF is a polar coordinating solvent and $SmI_3(THF)_3$ in THF displays poor solubility, the solvent was changed to CH_2Cl_2. The alkyl fluoride was added to the completely dissolved Sm(III)-salt, and after 24 h 1-iododecane was obtained in 50% yield. This was a promising result which showed that Sm(III) indeed polarizes the C–F bond enabling nucleophilic substitution. A stronger Lewis acid should possess an enhanced affinity towards fluoride. Since the Lewis acidity increases throughout the lanthanide series,[89] a screening of various LnI_3 salts was conducted (Scheme 17).



Scheme 17. Investigating the Lewis acidity of different $LnI_3(THF)_x$ complexes and their effect on the substitution of 1-fluorodecane.

1-fluorodecane was subjected to $LaI_3(THF)_4$, $SmI_3(THF)_3$, $DyI_3(THF)_3$, and $YbI_3(THF)_3$ using CH_2Cl_2 as solvent. The latter was proven to be a superior Lewis acid providing the iodinated product in >98% GC yield after 9 h. The reaction conditions were further elaborated by analyzing the results using various solvents (Et_2O, DMF, acetone, EtOH, MeCN, $CHCl_3$, toluene, *n*-hexane). Chloroform was the only solvent which afforded comparable results regarding the substitution reaction. Furthermore, traces of H_2O were proven to be destructive, thus preventing the C–F bond activation to occur, most likely due to hydrolysis of the $YbI_3(THF)_3$ reagent. However, the reaction was compatible with PA quality solvent, and could be performed open to the atmosphere. As a compliment, $YbBr_3(THF)_3$ was synthesized and tested under present reaction conditions in hope to allow bromination of alkyl fluorides. However, almost no F/Br exchange was observed, implying that the Yb–Br bond is more thermodynamically favorable. One could speculate that 1/3 equiv. of $YbI_3(THF)_3$ would be sufficient in promoting full conversion of 1-fluorodecane into 1-iododecane, thus generating $YbF_3(THF)_3$. However, only ~30% of 1-iododecane was obtained when employing 1/3 equiv. of the $YbI_3(THF)_3$ reagent. This implies that only one iodide is transferred. Thus, $YbI_2F(THF)_3$ exhibit much lower activity. $YbI_3(THF)_3$ was also added to a mixture of 1-fluoro-, 1-chloro-, and 1-bromo-decane (1:1:1) . Gratefully, the Ln(III)-reagent proved to be chemo-selective towards the C(sp3)–F bond while essentially no reaction was observed for C–Cl (**60**) and C–Br (**61**) bonds according to GC (Scheme 18).



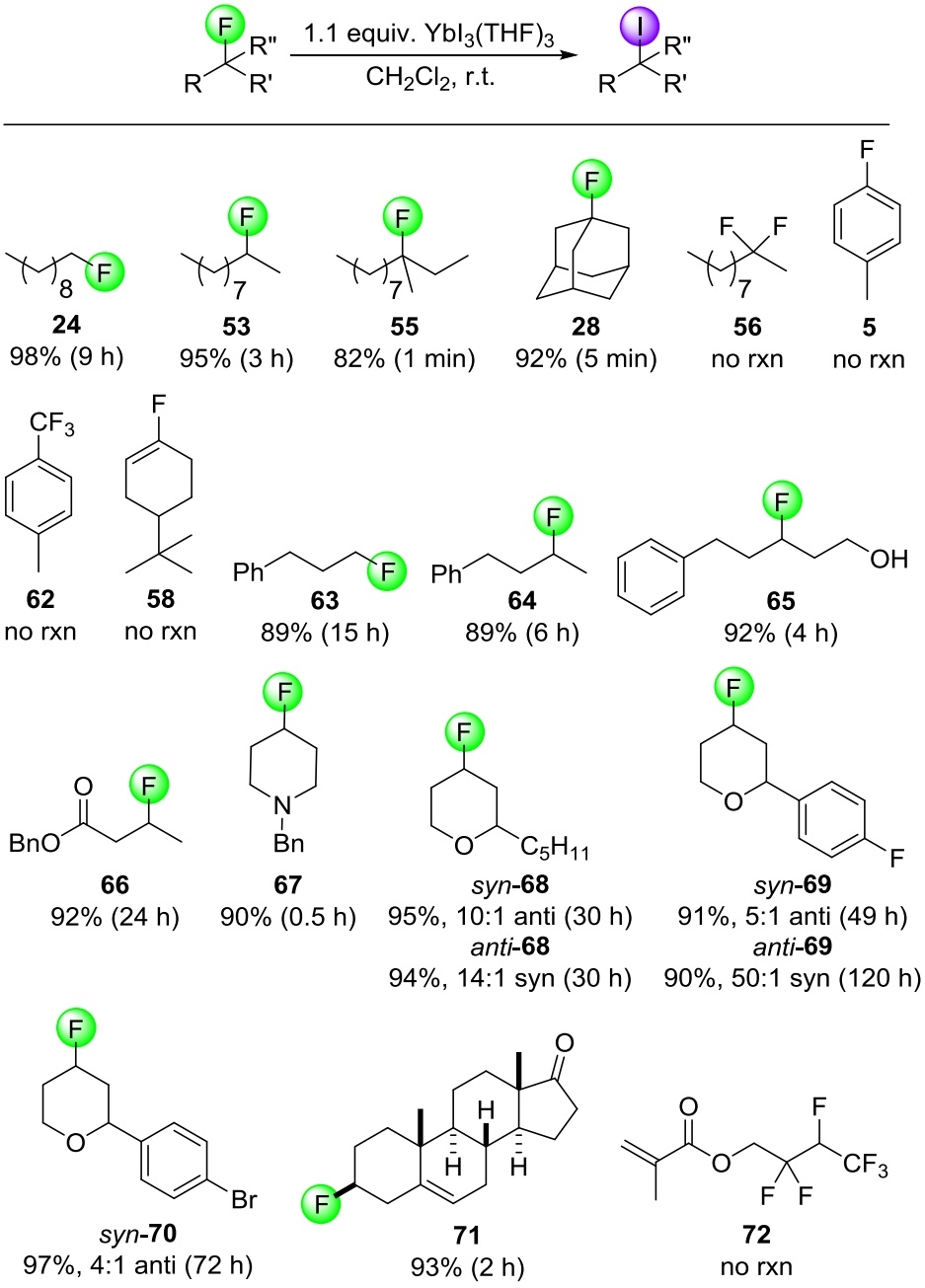
Scheme 18. A chemoselective study of $YbI_3(THF)_3$ towards different aliphatic carbon-halogen bonds.

4.1.1. Substrate scope

The $YbI_3(THF)_3$ mediated C–F bond activation was extended and applied to various alkyl fluoride substrates. Since C–F bond activation through fluoride abstraction typically requires an exceptionally strong Lewis acid, heteroatoms such as oxygen and nitrogen

often prevent the reaction, due to their own interaction with the Lewis acid forming a Lewis pair.[18] To explore the methodology and the chemoselectivity, various substrates, each containing a common functional group, were added to the reaction between 1-fluorodecane and $YbI_3(THF)_3$ and studied by GC. Functionalities such as ketone, alcohol, cyanide, trialkylamine, and ether were all compatible with the present reaction conditions and full conversion of 1-fluorodecane was achieved after several hours. A primary amine, amide, and a carboxylic acid reduced the rate of the reaction but not the yield, possibly due to chelation and interaction with the Yb(III) reagent. It should be mentioned that the following substrates were also recovered in quantitative yield following the reaction. A thiol was however not suitable under present reaction conditions, due to oxidative formation of disulfide.[105]

The compatibility of the reaction was further explored by subjecting various functionalized alkyl fluorides under the reaction conditions depicted in Scheme 19. Simple secondary $C(sp^3)$–F bonds (**53** and **64**) underwent substitution under 6 h, affording the iodinated products in excellent yields. In addition, simple tertiary aliphatic fluorides (**55** and **28**) underwent iodination in the matter of minutes. Both were isolated in good to excellent yields, however, **55** afforded some by-products due to elimination. *Gem*-difluoro and trifluoro-substrates (**56** and **62**) did not give any substitution, neither did $C(sp^2)$–F bonds such as in **5** and **58**. This is probably due to the lower reactivity of $YbI_3(THF)_3$ compared to e.g. silylium ions as Lewis acids (*vide supra*). In turn, it is most likely this reduced Lewis acidity that enables the conversion of more functionalized alkyl fluorides. Therefore compounds containing functionalities such as alcohol (**65**), ester (**66**), amine (**67**), ether (**68**-**70**), and ketone (**71**) were all compatible with the reaction conditions providing clean and selective activation of the $C(sp^3)$–F bond. Thus, the corresponding iodinated products were all isolated in excellent yields. The polyfluorinated substrate **72** did not react, possibly due to interaction of Yb(III) with two or several fluorides, thus weakening the activation of the preferred C–F bond of the monofluorinated carbon.



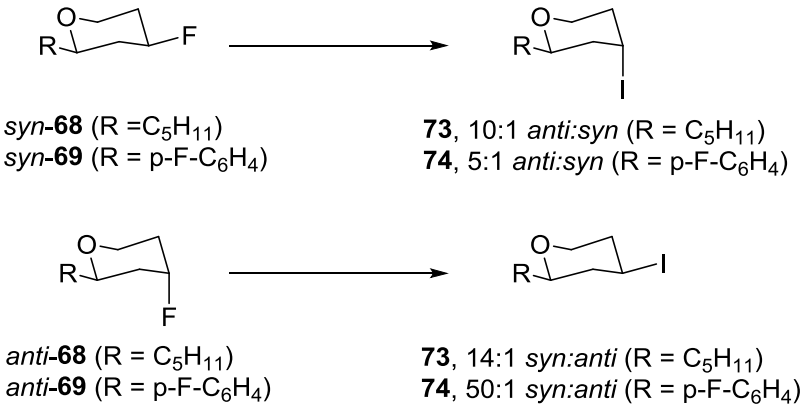
Scheme 19. $YbI_3(THF)_3$ mediated iodination of various functionalized alkyl fluorides.

4.1.2. Mechanistic proposal

Some mechanistic insights could be extracted from the reactivity pattern and the stereochemical outcome of the substrates depicted in Scheme 19. Firstly, a competition experiment was performed, where a comparison in reactivity order between a primary (**24**), secondary (**53**), and tertiary (**28**) alkyl fluoride was studied. All three substrates were combined in one flask and subjected to $YbI_3(THF)_3$ under present reaction conditions. The following order of reactivity was revealed, 3°>2°>1°, indicative of an S_N1 mechanism. However, the formation of a carbocation at a bridgehead substrate (**28**) is most likely to be unfavorable.[106] In addition, no rearrangement of the primary alkyl

fluoride was observed. As such, an internal nucleophilic substitution in which an S_Ni-type mechanism operates could describe the reaction behavior for these substrates. By using the initial rate method the rate orders for all involved components in the reaction could be determined. A rate order of 1.0 with respect to [1-fluorodecane] was obtained. In contrast, the rate order for [$YbI_3(THF)_3$] was determined to be 1.5, implying that the mechanism for the reaction is more complex.

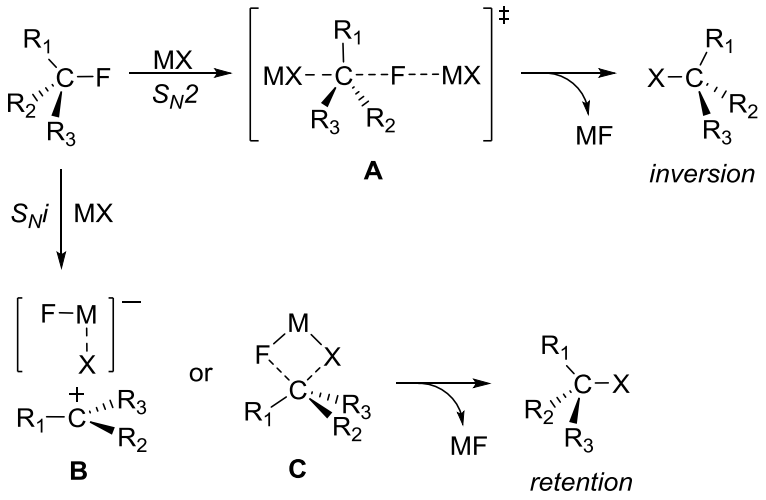
Further insight into the mechanism was gained by analyzing the isomeric distribution of the product, employing diastereomerically pure fluorinated tetrahydropyran derivatives **68** and **69** as substrates. When subjected to $YbI_3(THF)_3$ in CH_2Cl_2, *syn*-**68** and *syn*-**69** afforded the corresponding iodinated tetrahydropyran in a 10:1 *anti*/*syn* ratio (**73**) and 5:1 *anti*/*syn* ratio (**74**), respectively (Scheme 20).



Scheme 20. Stereochemical analysis of diastereomerically pure fluorinated tetrahydropyran derivatives.

When starting from the corresponding *anti*-**68** and *anti*-**69**, a 14:1 *syn*/*anti* (**73**) and 50:1 *syn*/*anti* (**74**) was obtained respectively (Scheme 20). Thus, the reaction displays a high degree of stereoselectivity with a clear evidence for inversion at the stereogenic center, indicating that an S_N2-type mechanism is present.[88]

All results taken together, a mechanistic understanding could be brought forward. It is clearly evident that the mechanistic pathway is dependent on the substrate. Two reaction pathways were postulated, one being an S_Ni type mechanism proceeding via either an intimate ion-pair or a concerted nucleophilic substitution intermediate, both resulting in retention of configuration (Scheme 21**B** and **C**). This pathway is consistent with the reactivity of **28**. The second pathway is suggested to proceed via an S_N2-type mechanism. This is believed to occur via an transition state involving a nucleophilic attack of an iodide simultaneously as the Yb(III) activates the fluoride towards substitution, probably by a dual interchange of two equivalents of $YbI_3(THF)_3$ (Scheme 21**A**). This results in inversion as observed in the reactivity of *syn*- and *anti*-fluorinated tetrahydropyranes. These mechanistic suggestions also explains the rate order of 1.5 for $YbI_3(THF)_3$.



Scheme 21. Mechanistic proposal for the C–F bond activation mediated by $YbI_3(THF)_3$. MX= $YbI_3(THF)_3$. MF= $YbI_2F(THF)_3$.

4.2. Making it catalytic (Paper V)

Reactions performed in stoichiometric amount can potentially be considered for development of a catalytic cycle. There is always a need for progress and expansion of reliable catalytic methods across the fields of chemistry. Turning a reaction into a catalytic process is considered to be both environmentally friendly and cost effective. Under ideal conditions, the catalyst is not consumed and should be able to recover from the reaction.[107]

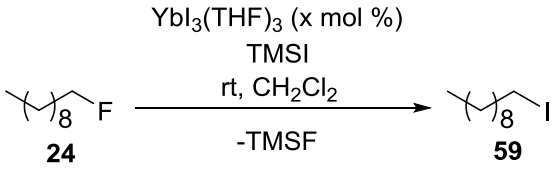
Catalytic main-group Lewis acid assisted C–F bond activation has been established and is accessible due to the potency and high fluoride affinity of the Lewis acids such as Si, B, and Al (see section 1.3.2). Addition of a stoichiometric fluoride trapping agent has paved the way for regeneration of the active Lewis acid, and thus resulted in noteworthy reports on catalytic C–F bond activation methods.[18,108] It was speculated that addition of TMSI to $YbI_3(THF)_3$ would provide a catalytic process of the C–F bond substitution reaction. The TMSI would act as a stoichiometric fluoride trapping agent, thus regenerating the active $YbI_3(THF)_3$ from the inactive $YbI_2F(THF)_3$ while simultaneously forming TMSF.

4.2.1. Tuning of the reactivity

As a first step, TMSI was added to 1/3 equiv. of $YbI_3(THF)_3$ in the presence of 1-fluorodecane, in CH_2Cl_2. As mentioned previously in section 4.1, 1/3 equiv. of $YbI_3(THF)_3$ alone gave only ~30% yield, whereas in the presence of TMSI the reaction reached full conversion affording 1-iododecane in 96% GC yield within 8 h. Thus, TMSI has an influence on the reaction in this case. The actual effect of TMSI can be questioned if it is to reactivate $YbI_2F(THF)_3$ or if it plays another role in the reaction. Already in 1981 Olah et al. reported on the iodination of fluoroalkanes using only TMSI.[109] They observed that for primary alkyl fluorides the F/I substitution was sluggish, affording incomplete

reactions even after heating and extended reaction times. In addition, rearrangement of the iodinated products was reported. A blank sample was therefore made, where $YbI_3(THF)_3$ was excluded, and only TMSI with 1-fluorodecane was stirred at room temperature. Analysis made by GC showed almost no conversion after 13 h (Table 3, entry 1).

Table 3. Optimization of the $YbI_3(THF)_3$ catalyzed C–F bond substitution of 1-fluorodecane in the presence of TMSI.[a]



24 **59**

Entry	$YbI_3(THF)_3$ (mol %)	TMSI (equiv.)	t (h)	Yield (%)[b]
1	0	3	13	2
2	1	3	13	21
3	5	3	13	60
4	10	3	13	95
5	10	1.5	13	77
6	10	6	8	95

[a] Reaction conditions: 1-fluorodecane (0.04 mmol), CH_2Cl_2 (0.4 mL). Dodecane was used as internal standard. [b] Analyzed by GC-FID.

The reaction conditions were further elaborated by varying the catalyst loading of $YbI_3(THF)_3$ (entries 2-4). Satisfactory results were obtained when 10 mol % of $YbI_3(THF)_3$ and 3 equiv. of TMSI were used, affording 1-iododecane in 95% GC yield within 13 h (entry 4). Using less TMSI gave lower yield (entry 5), while 6 equiv. TMSI gave a shorter reaction time (entry 6). To avoid unnecessary consumption of TMSI, optimal reaction conditions were found to be 10 mol % loading of $YbI_3(THF)_3$ and 3 equiv. of TMSI.

^1H and ^{19}F NMR experiments were conducted in order to validate details regarding the effect of TMSI, the reaction was slightly modified. 1-Fluoroadamantane was chosen as a model substrate and the equivalents were kept in stoichiometric quantity to each other in order to directly follow the path of the fluorine by ^1H- and ^{19}F-NMR spectroscopy (Figure 3**A** and 4**A**). ^1H and ^{19}F NMR spectra acquired directly after adding 1 equiv. of

$YbI_3(THF)_3$ to 1 equiv. of 1-fluoroadamantane in CD_2Cl_2 showed full conversion of starting material yielding 1-iodoadamantane (no ^{19}F signal present) and most likely forming the paramagnetic "$YbI_2F(THF)_3$" *in situ* (Figure 3**B** and 4**B**). Based on previous results (see section 4.1), it is know that "$YbI_2F(THF)_3$" is inactive and cannot participate in C-F bond substitution. Thus, if TMSI was added at this point, an interchange between Yb–F and Si–I would be observable due to the formation of Si–F.[110] Indeed, when adding 1 equiv. of TMSI, a new set of signals appeared instantaneously corresponding to TMSF, as determined by ^1H and ^{19}F NMR spectroscopy (Figure 3**C** and 4**C**).

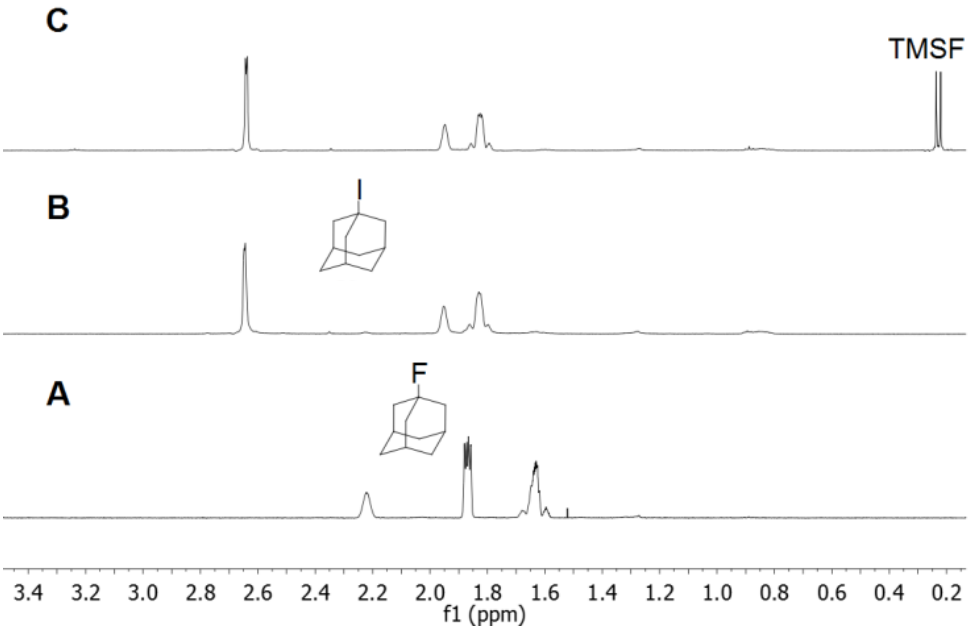


Figure 3. ^1H NMR spectra of **A**: 1-fluoroadamantane in CD_2Cl_2. **B**: Instantaneous and quantitative conversion of 1-fluoroadamantane to 1-iodoadamantane upon addition of $YbI_3(THF)_3$ to **A**. **C**: Further addition of TMSI reveal instantaneous formation of TMSF.

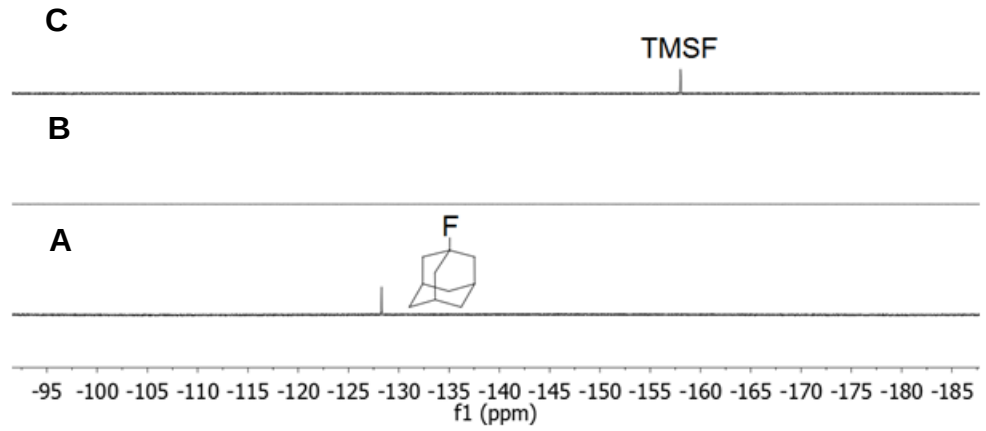


Figure 4. ^{19}F NMR spectra of **A**: 1-fluoroadamantane in CD_2Cl_2. **B**: No fluorine signal observable due to instantaneous and quantitative conversion of 1-fluoroadamantane to 1-iodoadamantane upon addition of $YbI_3(THF)_3$ to **A**. **C**: Further addition of TMSI reveal instantaneous formation of TMSF.

These findings confirm that TMSF, formed upon addition of TMSI, appear from subtraction of fluorine from the "$YbI_2F(THF)_3$" complex. Thus, there is strong evidence supporting that TMSI acts as a trapping agent with subsequent regeneration of $YbI_3(THF)_3$ as a result. Again, with full conversion of TMSI to TMSF, the only iodination source present is $YbI_3(THF)_3$. So when adding 1-fluoroadamantane once again, full conversion of starting material to 1-iodoadamantane occurred.

Upon analysis of the $YbI_3(THF)_3$/TMSI mediated substitution of 1-fluorodecane, a small peak was identified. Analysis with GC/MS gave a mass corresponding to $C_7H_{17}IOSi$, probably arising from TMSI promoted ring-opening of the THF ligands on $YbI_3(THF)_3$. This hypothesis was established by ^1H NMR spectroscopy. In order to subtract information from NMR spectroscopy, the paramagnetic $YbI_3(THF)_3$ was exchanged to the diamagnetic $LaI_3(THF)_4$ (Figure 5**A**).

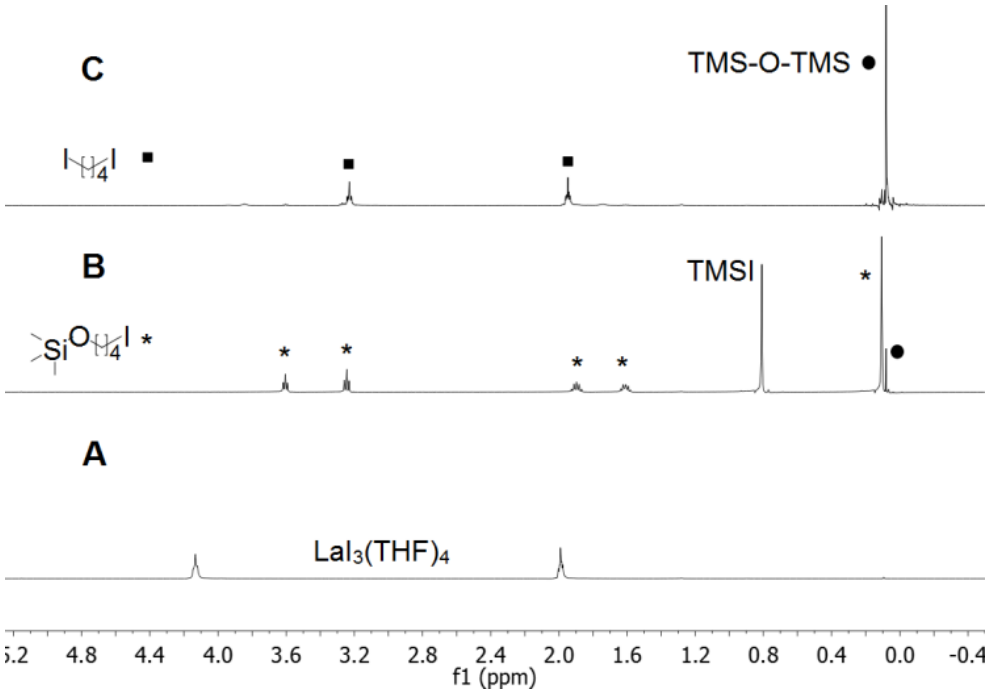
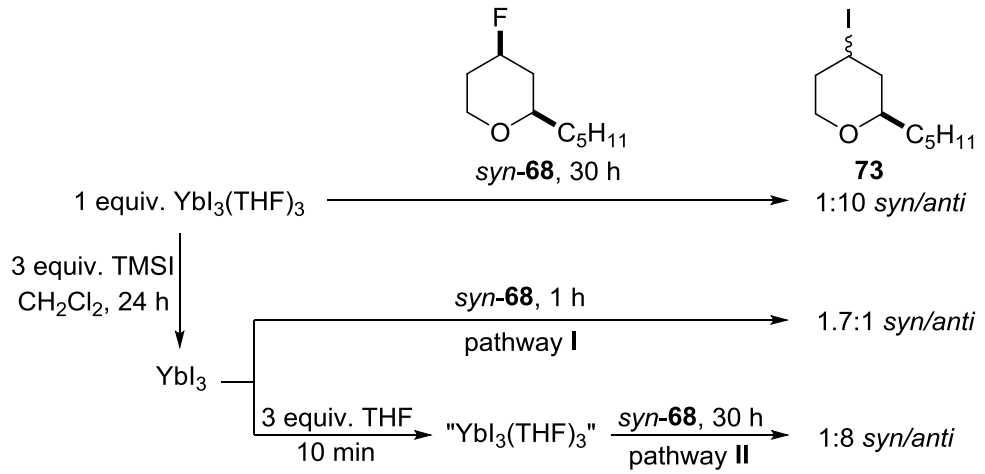


Figure 5. ^1H NMR spectra of **A**: THF signals from $LaI_3(THF)_4$ in CD_2Cl_2. **B**: Spectra obtained 5 min after addition of TMSI showing quantitative ring-opening of THF to yield (4-iodobutoxy)trimethylsilane. **C**: After additional 18 h only 1,4-diiodobutane and hexamethyldisiloxane is detected.

Careful analysis of the ^1H NMR spectra acquired after mixing 8 equiv. of TMSI and 1 equiv. of $LaI_3(THF)_4$ in CD_2Cl_2 showed a new set of signals corresponding to (4-iodobutoxy)trimethylsilane (Figure 5**B**). Thus, Ln(III) acts as a Lewis acid catalyst in the THF ring-opening reaction with TMSI. Upon allowing the NMR tube to stand overnight, (4-iodobutoxy)trimethylsilane was further substituted to 1,4-diiodobutane and hexamethyldisiloxane (Figure 5**C**). In conclusion, the results strongly suggest that a THF free catalytic LaI_3 complex is formed *in situ* over time.[111,112,113]

4.2.2. Stereochemical analysis

The desolvation of $YbI_3(THF)_3$, promoted by TMSI, could potentially afford a different reactive specie. To get insight to the mechanism of the reaction, the *syn*-fluorinated tetrahydropyran derivative **68** was again chosen as a model substrate. When subjected to $YbI_3(THF)_3$ alone, a 1:10 ratio of *syn*/*anti* was obtained for the iodinated tetrahydropyran derivative, indicative of a S_N2-type mechanism (see section 4.3). In contrary, when adding *syn*-**68** to YbI_3, afforded by premixing 1 equiv. $YbI_3(THF)_3$ and 3 equiv. TMSI for 24 h, a striking difference in selectivity was observed. The *syn*-configuration was now slightly favored (1.7:1 *syn*/*anti*), indicative of a S_N1-type mechanism when THF free YbI_3 specie was applied (Scheme 22, pathway **I**). Furthermore, to conclude how the THF ligands affect the reactivity, deliberative addition of THF to YbI_3 was performed, thus enabling regeneration of "$YbI_3(THF)_3$". Addition of *syn*-**68** to the reaction mixture, followed by stereochemical analysis, revealed that the selectivity was nearly reverted to the original ratio (Scheme 22, pathway **II**, 1:8 *syn*/*anti* ratio).



Scheme 22. Study of the stereochemical outcome of the substitution of *syn*-**68** employing $YbI_3(THF)_3$ or YbI_3.

As the active catalytic specie, affected by the premix time between $YbI_3(THF)_3$ and TMSI, has a profound effect on the stereoselectivity, a screening of various premix times was implemented in order to establish the stability of the catalytic specie. *Syn*-**68** was added to eight separate tubes with premix times ranging from 1 min to 180 min. Each reaction was quenched and the product ratio was analyzed after 30 s. Various initial *syn*/*anti* ratios were obtained (Figure 6). Shorter premix times resulted in a larger variation of the initial stereochemical ratio, whereas the ratio seemed to level out at 180 min premix time, possibly due to the formation of a catalyst with a distinct reactivity.

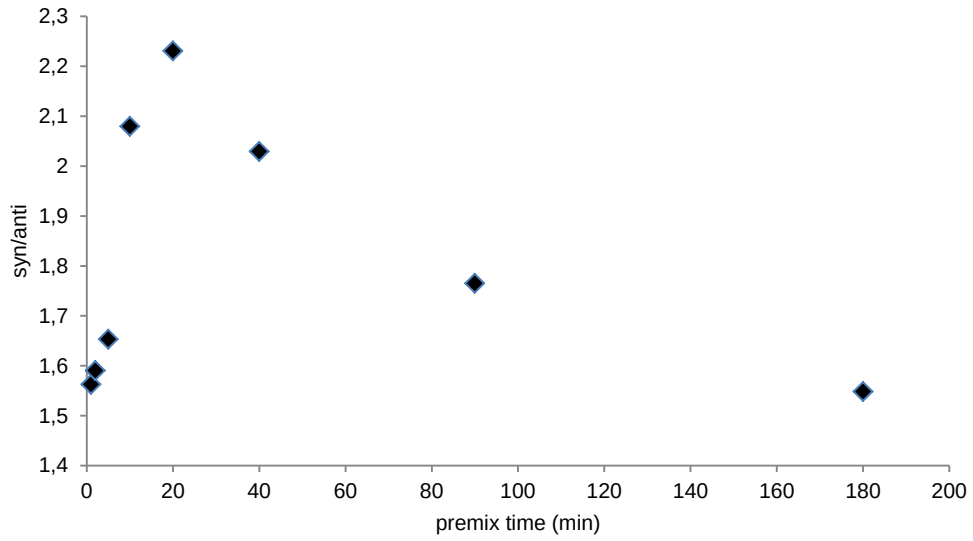
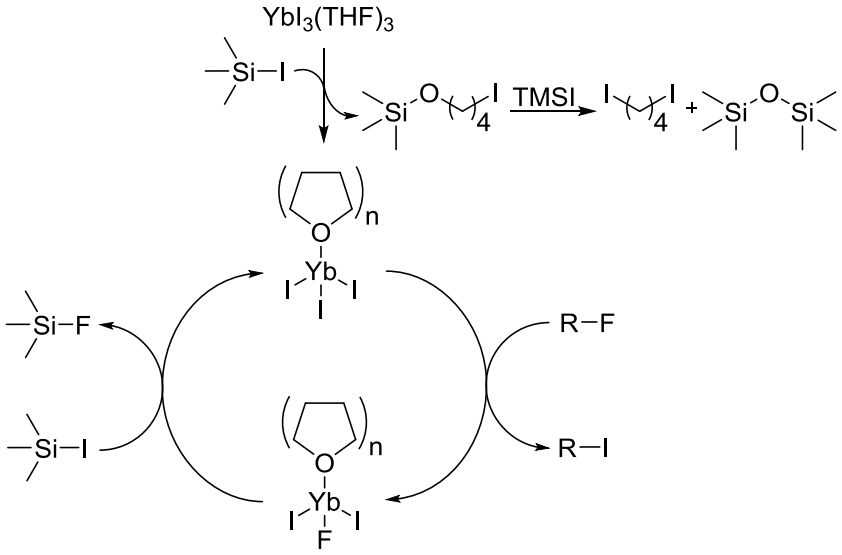


Figure 6. Analysis of initial *syn*/*anti* ratios from the stereochemical outcome of *syn*-**68** when subjected to various premixed solutions of $YbI_3(THF)_3$ and TMSI.

In addition, to further confirm the results obtained above, *syn*-**68** was subjected to $YbI_3(THF)_3$-TMSI with a premix time of 180 min and followed over the course of the reaction. A constant *syn*/*anti* ratio (1.6:1) was obtained for the reaction. Thus, different reactive catalytic species are generated in an early stage of the reaction as a result of ring opening of THF. However, a premix time of 180 min is sufficient to generate a THF free catalytic complex with a well-defined reactivity.

4.2.3. Catalytic cycle

The following catalytic cycle was proposed (Scheme 23) considering all results presented in section 4.2.1. and 4.2.2.

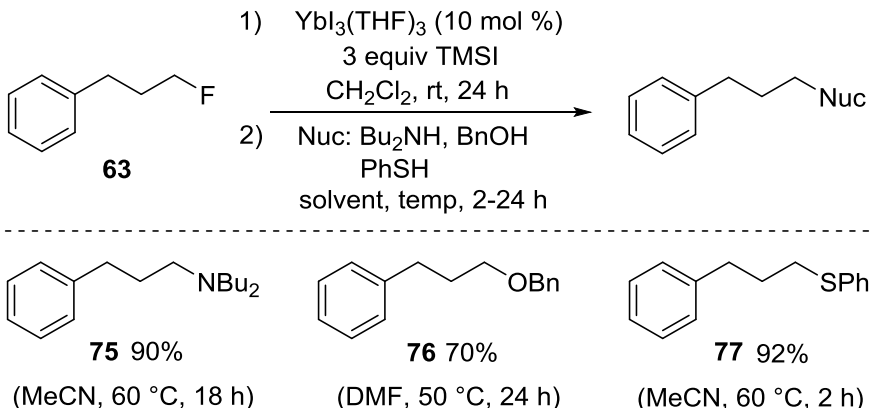


Scheme 23. Proposed catalytic cycle for the $YbI_3(THF)_n$ catalyzed C–F bond substitution in presence of TMSI. n= 0-3 THF ligands.

The initial step of the cycle involves the TMSI assisted ring-opening of the THF ligands on the $YbI_3(THF)_3$ reagent. This step is clearly supported by NMR studies conducted between $LaI_3(THF)_4$ and TMSI (Figure 5). Simultaneously as the desolvation proceeds, the F/I substitution between an alkyl fluoride and $YbI_3(THF)_n$ occurs, forming the alkyl iodide as product and most likely the inactive "$YbI_2F(THF)_n$" *in situ*. The "$YbI_2F(THF)_n$" is in turn regenerated to the active $YbI_3(THF)_n$ in the presence of TMSI. This step has been verified by formation of TMSF using ^1H and ^{19}F NMR spectroscopy (Figure 3 and 4). The desolvation process was further supported by studying the stereochemical outcome of *syn*-**68** as depicted in Scheme 22 and Figure 6. Thus, the *syn*/*anti* ratio varied over time as a result of the following ring-opening of THF.

4.2.4. Application

Since labile iodinated products are formed from chemically inert fluorides, a one-pot two-step reaction was designed to show the applicability of the system. 3-Iodopropyl benzene was formed *in situ* via $YbI_3(THF)_3$-TMSI mediated substitution of 3-fluoropropyl benzene (**63**). Subsequent addition of different nucleophiles to the reactive iodo-intermediate afforded the corresponding products in high to excellent yields (Scheme 24).



Scheme 24. Design of a one-pot two-step substitution reaction of 3-fluoropropyl benzene to different substituted propyl benzene derivatives using $YbI_3(THF)_3$ and TMSI as a key step.

4.3. Conclusion

In conclusion, it has been shown that $YbI_3(THF)_3$ mediates mild and very fast selective iodination of unactivated C(sp^3)–F bonds. The method is exceptionally selective towards alkyl fluorides in presence of other carbon-halogen bonds. The reagent is compatible with a large range of common functional groups due to the unique properties of the lanthanide salt. The substitution is proposed to proceed via an S_N2 mechanism with a competing S_Ni pathway, the ratio being dependent on the substrate. In addition, a $YbI_3(THF)_3$ catalyzed C–F bond activation protocol has been developed. It has been shown that upon addition of stoichiometric amount of TMSI the active $YbI_3(THF)_3$ reagent can be regenerated. The $YbI_3(THF)_3$ mediated selective iodination of the exceptionally strong C–F bond is expected to initiate novel routes in synthetic organic chemistry, as it paves the way for the use of fluorine as a small, sterically unhindered protecting group that can easily be removed. Also, this strategy may open up new applications and methodologies to be explored within C–F bond activation employing lanthanide(III) reagents. In addition, the concept of selectively manipulating the strong aliphatic C-F bond can be envisioned to be useful as a late stage activation of that specific carbon by transforming it into a reactive C-I bond.

5. Direct amination of aliphatic fluorides (Paper III and IV)

The efficiency of $YbI_3(THF)_3$ mediated iodination of alkyl fluorides presented in chapter 4 shows an extraordinary potential of lanthanide mediated C–F bond activation. However, from a synthetic point of view, it would be of high interest to transform the C–F bond directly into other functionalities.[114,115] Thus, allowing for synthesis of complex molecules starting from simple and readily available fluorinated building blocks.

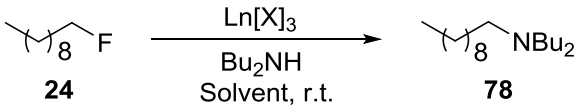
As described in section 1.3.2., main-group Lewis acid activation of $C(sp^3)$–F bonds has paved the way for more complex transformation of alkyl fluorides. In contrast to transition-metal mediated C–F bond activation, in which C–H and C–C bond formation is dominant, main-group Lewis acid C–F bond activation benefit from the generation of a reactive carbenium ion which can be trapped by various nucleophiles. However, main-group elements suffer from being highly Lewis acidic, thus restricting the usage of functionalized alkyl fluorides. Therefore, trivalent lanthanide with various labile nucleophilic ligands can serve as potential Lewis acids for mild and selective $C(sp^3)$–F bond activation.

5.1. Reaction optimization (Paper III)

It was postulated that a $C(sp^3)$–F bond could undergo nucleophilic displacement by an amine in presence of a lanthanide Lewis acid. If so, a new protocol of C–N bond formation would enable synthesis of valuable amines directly from inert alkyl fluorides. As such, the possibility to use e.g. dibutylamine as an external nucleophile in presence of stoichiometric amount of $YbI_3(THF)_3$ to substitute 1-fluorodecane was examined. Full conversion of 1-fluorodecane was obtained, however only 33% yield of product was achieved within 24 h (Table 4, entry 14). The rest was converted to 1-iododecane. The formation of the 3°-amine is possibly a one-pot two-step reaction as illustrated in Scheme 24. In pursuing the optimal conditions for amination of aliphatic fluorides, different Ln(III)-source with appropriate ligands were considered. During the screening of $Ln[X_3]$-salts it was found that stoichiometric amount of the homoleptic $La[N(SiMe_3)_2]_3$ reagent was superior in promoting this reaction, yielding full conversion after only 1 h in CH_2Cl_2 (Table 4, entry 1). Full conversion was even reached when running the reaction in weakly or non-coordinating solvents such as toluene, Et_2O, and *n*-hexane for 1 h (entries 2-4). Due to its many TMS groups the complex was fully soluble even in the non-polar solvent *n*-hexane. It was further found that low or no reactivity was achieved in coordinating solvents such as THF, MeCN, EtOAc, and EtOH, probably due to competing interaction of the solvent with the metal (entries 5-8). By decreasing the concentration the reaction rate decreased (entry 9). The reaction was compatible with PA solvents, and even stoichiometric amount of H_2O could be added, although this affected the reaction rate negatively. When utilizing $Sm[N(SiMe_3)_2]_3$ in CH_2Cl_2 (entry 10), the substitution reaction took twice as long compared to $La[N(SiMe_3)_2]_3$ (entry 1). This decrease in reactivity could

be explained by the size of the Ln^{3+} ionic radius, where the larger radius (La > Sm) has a wider metal coordination sphere.[116,117] Thus, implying that C–F bond activation assisted by Ln(III) species is not only govern by the Lewis acidity of the metal, but also by the size of the cation, and by the sterics of the ligand. The lanthanide salts, $Yb(Br)_3$, $Yb(OTf)_3$, and $La(OTf)_3$ did not facilitate the reaction at all (entries 11-13). Suitable reaction conditions were found to be 1.1 equiv. of $La[N(SiMe_3)_2]_3$ and 3 equiv. of amine in CH_2Cl_2. Since hexamethyldisilazane acts only as a ligand and not as a nucleophile (*vide infra*), it is considered a direct amination of the alkyl fluoride and not a one-pot two-step reaction.

Table 4. Optimization of the $Ln[X]_3$ mediated amination of 1-fluorodecane in the presence of dibutylamine.[a]



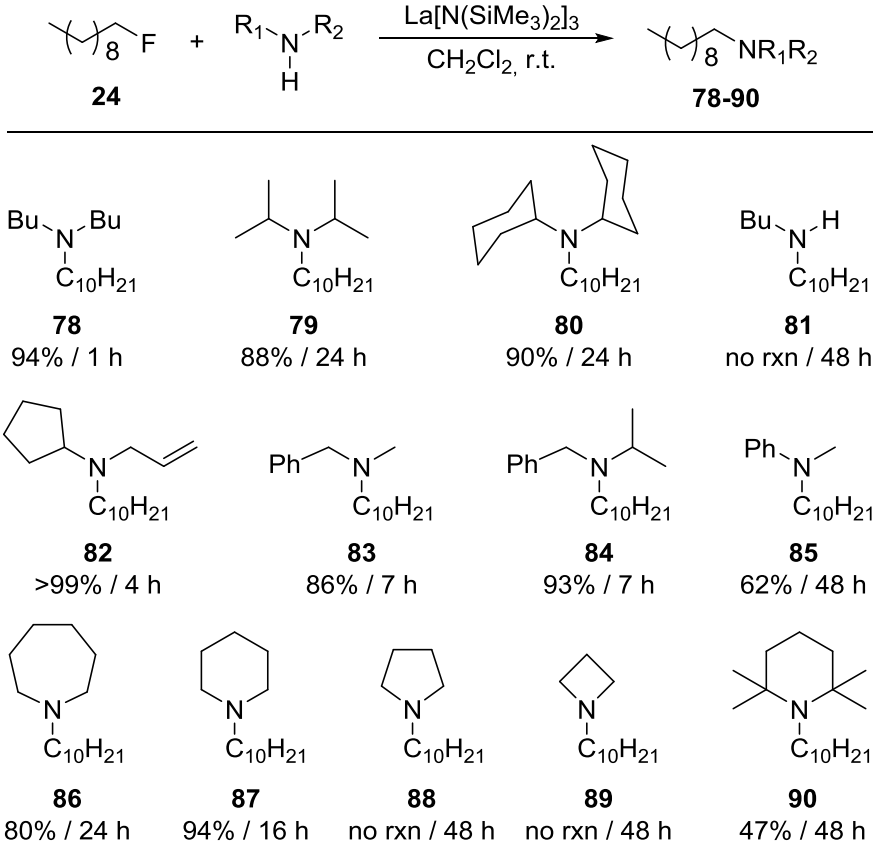
24 **78**

Entry	$Ln[X]_3$	Solvent	c (M)	t (h)	Conv. of **24** (%)[b]
1	$La[N(SiMe_3)_2]_3$	CH_2Cl_2	0.18	1	>99
2	$La[N(SiMe_3)_2]_3$	Toluene	0.18	1	97
3	$La[N(SiMe_3)_2]_3$	Et_2O	0.18	1	>99
4	$La[N(SiMe_3)_2]_3$	*n*-hexane	0.18	1	98
5	$La[N(SiMe_3)_2]_3$	THF	0.18	1	48
6	$La[N(SiMe_3)_2]_3$	MeCN	0.18	1	8
7	$La[N(SiMe_3)_2]_3$	EtOAc	0.18	1	no rxn[d]
8	$La[N(SiMe_3)_2]_3$	EtOH	0.18	1	no rxn[d]
9	$La[N(SiMe_3)_2]_3$	CH_2Cl_2	0.044[c]	1	49
10	$Sm[N(SiMe_3)_2]_3$	CH_2Cl_2	0.18	2	>99
11	$Yb[Br]_3$	CH_2Cl_2	0.18	4	no rxn[d]
12	$Yb[OTf]_3$	CH_2Cl_2	0.18	1	no rxn[d]
13	$La[OTf]_3$	CH_2Cl_2	0.18	1	no rxn[d]
14	$YbI_3(THF)_3$	CH_2Cl_2	0.022[e]	24	33[f]

[a] Reaction conditions: $Ln[X]_3$ (0.044 mmol), 1-fluorodecane (0.040 mmol), dibutylamine (0.12 mmol), solvent (0.25 mL). *n*-Dodecane (0.040 mmol) was used as internal standard. [b] Analyzed by GC-FID. [c] CH_2Cl_2 (1 mL). [d] No change in conversion was observed with prolonged reaction time (24 h). [e] $YbI_3(THF)_3$ (0.044 mmol), CH_2Cl_2 (2 mL). [f] yield of *N,N*-dibutyl-decyl amine.

5.1.1. Scope of the reaction

Expanding the scope of the nucleophiles showed that a variety of secondary amines were compatible with the reaction conditions, and the corresponding tertiary amines were isolated in high to excellent yields (Scheme 25).

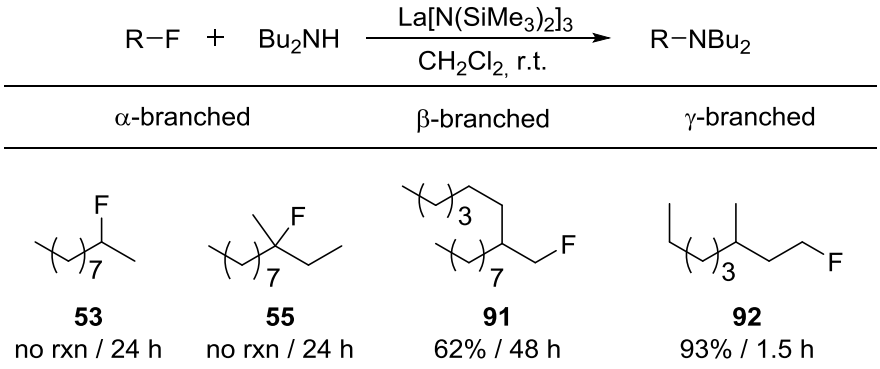


Scheme 25. $La[N(SiMe_3)_2]_3$ promoted substitution of 1-fluorodecane with various secondary nucleophilic amines.

The model reaction between 1-fluorodecane and *N,N*-dibutylamine was completed within 1 h and *N,N*-dibutyl-decyl amine (**78**) was isolated in 94% yield. Several other secondary amines, ranging from simple to more sterically demanding, were all well-suited for the substitution reaction (**79**-**85**). However, with increasing steric hindrance of the secondary amine the reaction progressed slower. This was also further confirmed when testing various cyclic amines (**86**-**90**). Piperidine yielded N-decylpiperidine in 94% isolated yield within 16 h (**87**), while hexamethyleneimine reached 80% conversion first within 24 h (**86**). The sterically hindered tetramethylpiperidine gave 47% conversion in the substitution reaction of 1-fluorodecane within 48 h (**90**). No reaction occurred with the primary butyl amine, or with the smaller cyclic amines pyrrolidine and azetidine. The corresponding products (**81**), (**88**), and (**89**) were never observed in this case. An immediate precipitation was also observed upon addition of butyl amine, pyrrolidine, and azetidine. This is believed to be due to instantaneous protonolysis of the amine and

$La[N(SiMe_3)_2]_3$, leading to an unproductive pathway (section 5.1.2.). Since $HN(SiMe_3)_2$ is released during the course of the reaction it is particularly important that it does not act as a nucleophile, since this would lead to a mixture of products. Fortunately, hexamethyldisilazane did not react with the alkyl fluorine under these conditions, and the corresponding tertiary amine was never detected.

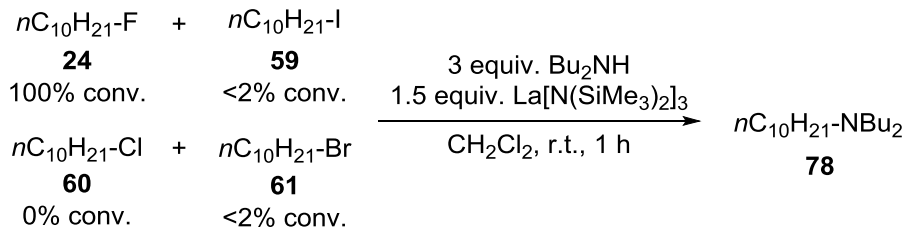
The scope of the substitution reaction was further investigated by testing if various branched alkyl fluorides are prone to undergo amination under present reaction conditions (Scheme 26).



Scheme 26. Studying the reactivity of different branched alkyl fluorides in the $La[N(SiMe_3)_2]_3$ assisted amination.

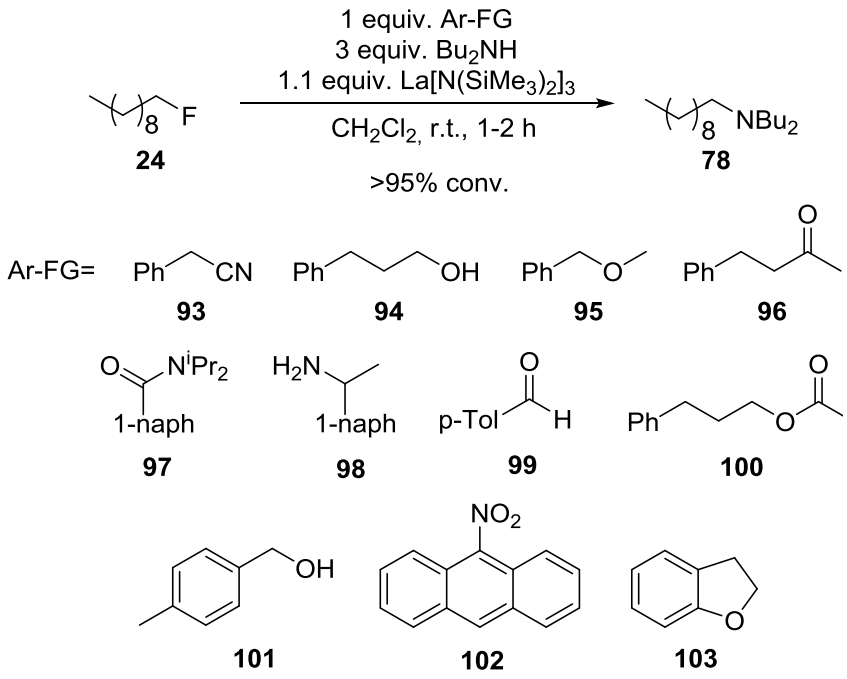
Unfortunately, no reaction occurred with the α-branched secondary (**53**) and tertiary (**55**) alkyl fluorides. As a direct outcome, the S_N1-type mechanism could be rejected in this case. A β-branched alkyl fluoride (**91**) underwent substitution, however, after 48 h only 62% conversion was observed. Meanwhile, full conversion after 1.5 h was observed for a γ-branched alkyl fluoride (**92**), and the corresponding tertiary amine was isolated in 93% yield. Consequently, increasing the steric hindrance of the organofluorine resulted in a decrease of the reaction rate. In analogy, the same reactivity pattern was observed when using sterically demanding amine nucleophiles (*vide supra*). Thus, the transition state of the nucleophilic substitution seems to be govern by steric effects.

The substitution reaction promoted by $La[N(SiMe_3)_2]_3$, displayed excellent selectivity towards alkyl fluorides in the presence of other alkyl halides (Cl, Br, I). Within 1 h full conversion of 1-fluorodecane was reached, leaving 1-chlorodecane completely untouched while 1-2% conversion of 1-bromodecane and 1-iododecane occurred (Scheme 27). Within 4 h the alkyl halides had started reacting slowly with 1% conversion of 1-chlorodecane and 5% conversion of 1-bromodecane and 1-iododecane respectively. Similar results were obtained running the reaction in *n*-hexane or toluene.



Scheme 27. A chemoselective study of the La[N(SiMe$_3$)$_2$]$_3$ assisted amination of different aliphatic carbon-halogen bonds.

A facile way to study the compatibility of the reaction is to separately add various substrates containing a common functional group to the reaction mixture. The addition of a substrate containing nitril (**93**), alcohol (**94** and **101**), ether (**95** and **103**), ketone (**96**), nitro (**102**), or amide (**97**) functionality did not affect the reaction and full conversion of 1-fluorodecane into *N,N*-dibutyl-1-decylamine was achieved within less than 2 h (Scheme 28). Thus, the reaction displays a high degree of chemoselectivity in this case.

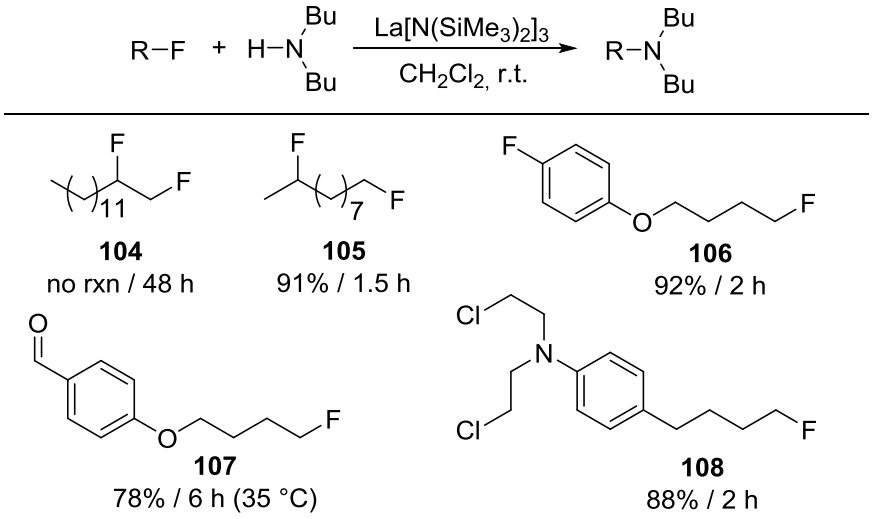


Scheme 28. A chemoselective study of the La[N(SiMe$_3$)$_2$]$_3$ assisted amination of 1-fluorodecane upon separate addition of various substrates containing common functional groups.

The same was true for primary amines (**98**), where only substitution with the secondary amine was observed. However, a slight decrease in reaction time was observed, most likely due to competing protonolysis of the primary amine and La[N(SiMe$_3$)$_2$]$_3$, thus affording an inactive La(III) reagent. Recent reports by others have demonstrated the reactivity of esters and aldehydes with amines in the presence of lanthanum(III) salts. Exposing 3-phenyl-1-propyl acetate (**100**) to the reaction conditions gave full hydrolysis of the ester into alcohol and acetylated amine within 30 minutes.[118] Parallel to this C-F

substitution still occurred at a slightly lower rate than previously. On the other hand, addition of *p*-tolylaldehyde (**99**) did not interfere with the substitution reaction, and only traces of *N,N*-dibutyl-*p*-tolyl-amide was observed.[116]

The scope was further expanded to involve functionalized alkyl fluorides. Secondary fluorine in vicinal position to primary fluorine (**104**) repressed the reactivity, and no substitution occurred (Scheme 29). The lack of reactivity is probably due to chelation of the La(III) to the two fluorines, and as a consequence the activation of the primary C–F bond is weakened. When the two fluorines were situated further apart (**105**), selective substitution of the primary fluoride occurred, affording the corresponding tertiary amine in 91% yield.



Scheme 29. The $La[N(SiMe_3)_2]_3$ mediated amination of functionalized alkyl fluorides.

The substitution was proven to be selective towards $C(sp^3)$–F bonds over $C(sp^2)$–F bonds (**106**) under present reaction conditions. Moreover, an aldehyde containing alkyl fluoride (**107**) underwent selective activation of the C–F bond. However, the temperature needed to be slightly increased, which promoted amide formation as reported in the literature.[116] Still, the tertiary amine product could be isolated in 78% yield. Once again exclusive selectivity towards the C–F bond over the C–Cl bond was demonstrated when subjecting the fluorinated chloroambucil (**108**) to $La[N(SiMe_3)_2]_3$ in presence of dibutylamine. The chlorines in β-position to the amine did not undergo any substitution.

5.1.2. Mechanistic investigations

Some carefully designed experiments were conducted in order to propose an operating mechanism for the reaction. As a first step, rate orders were determined using the initial rate method for the substitution of 1-fluorodecane. From the initial rate data the substitution reaction was found to be overall third order, i.e. first order in $La[N(SiMe_3)_2]_3$, alkyl fluoride, and amine (HNR^1R^2) respectively, and zero order in $HN(SiMe_3)_2$. In

addition, the kinetic isotope effect (KIE) was measured exchanging Bu_2NH with Bu_2ND. Both were independently measured to avoid isotopic scrambling. The KIE effect was determined to be relatively small (k_{Bu_2NH}/k_{Bu_2ND}= 1.03±0.09). This effect indicates that the expected nucleophilic attack involved in the TS is not a simple S_N2 mechanism. If this would be the case, an inverse KIE should be observed (k_H/k_D ~ 0.5-0.9).[119]

According to Seo and Marks, who developed an amidation protocol for esters using $La[N(SiMe_3)_2]_3$ in presence of amines, the homoleptic $La[N(SiMe_3)_2]_3$ undergoes instantaneous protonolysis with secondary amines to afford "$La[N(SiMe_3)_2]_x[NR^1R^2]_y$" and free hexamethyldisilazane in C_6D_6.[116] Accordingly, it was believed that such a specie was responsible for the C–F bond activation in this specific case. However, careful analysis after mixing 1 equiv. of $La[N(SiMe_3)_2]_3$ with 3 equiv. of Bu_2NH in CD_2Cl_2, a slightly broaden quartet was observable at δ 2.57 (J = 7.0 Hz), corresponding to the -C<u>H</u>$_2$-NH-C<u>H</u>$_2$- fragment (Figure 7**A**).

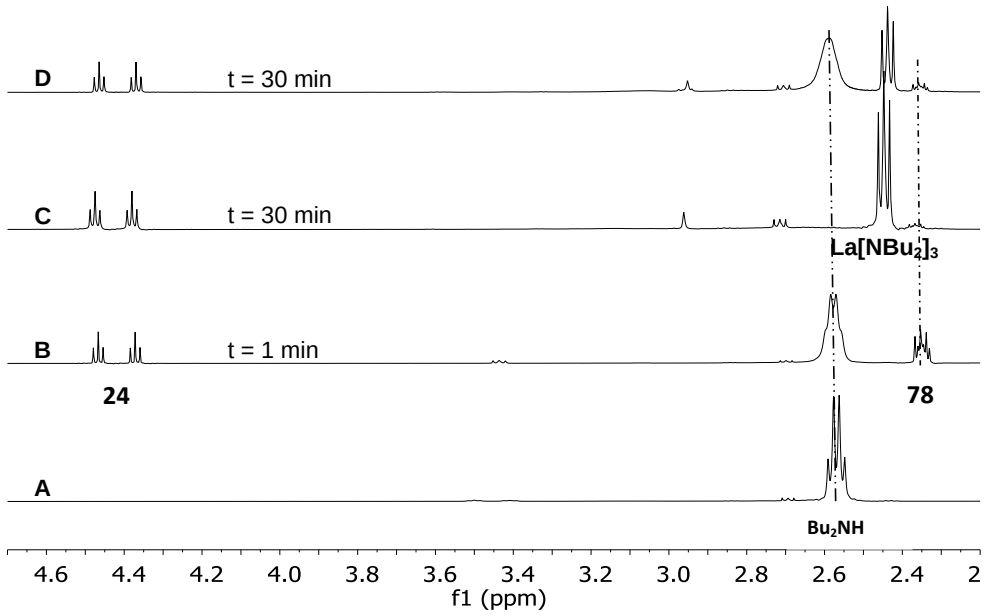
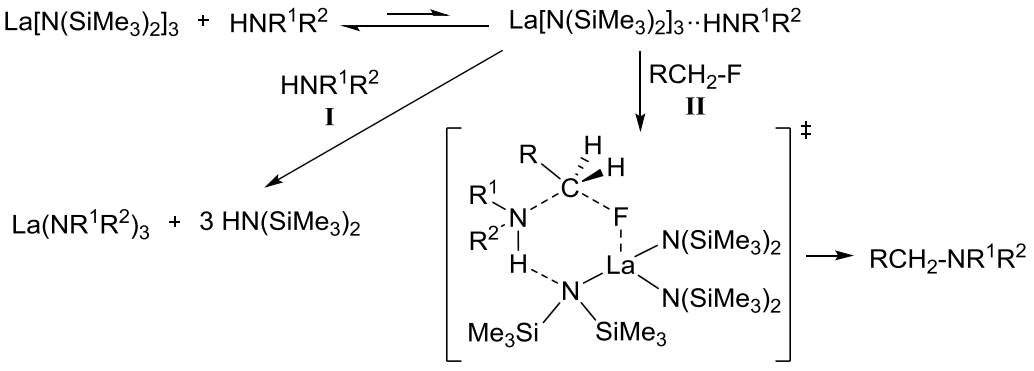


Figure 7. ^{1}H NMR monitoring of the F to N substitution reaction mediated by the lanthanum amides $La[N(SiMe_3)_2]_3$ and $La[NBu_2)_3$. **A**: Spectra recorded immediately upon addition of Bu_2NH to $La[N(SiMe_3)_2]_3$ in CD_2Cl_2 (showing the -C<u>H</u>$_2$-NH-C<u>H</u>$_2$- fragment of the amine). **B**: Addition of 1-fluorodecane to A revealed a fast substitution reaction into *N*,*N*-dibutyldecan-1-amine after only 1 min (showing only the important fragments). **C**: When **A** was allowed to equilibrate for 24 h $La[NBu_2]_3$ was obtained. Addition of 1-flurodecane showed almost no substitution after 30 min. **D**: Prior addition of Bu_2NH to $La[NBu_2]_3$ followed by 1-flurodecane showed no enchantment on the substitution reaction after 30 min.

The shift is nearly identical to that of free Bu_2NH. However, free Bu_2NH displays a triplet in CD_2Cl_2, so the quartet which arises from mixing $La[N(SiMe_3)_2]_3$ and Bu_2NH in CD_2Cl_2 is believed to appear due to scalar coupling to the acidic -NH- proton. This occurrence is only observed for solutions containing $La[N(SiMe_3)_2]_3$. However, the broadening of this peak indicates the presence of a dynamic process, suggested to be the Bu_2NH exchange

between its free and its La[N(SiMe$_3$)$_2$]$_3$--HNBu$_2$ coordinated form. The shifts are almost independent of the La/amine ratio and since the shifts of the quartet and the triplet are nearly identical, the equilibrium is mainly driven towards the free amine. In addition, the ^{1}H NMR revealed only a very weak signal from the methyl groups of released HN(SiMe$_3$)$_2$, altogether showing that protonolysis is not instantaneous with Bu$_2$NH in CD$_2$Cl$_2$. When dibutylamine and La[N(SiMe$_3$)$_2$]$_3$ were allowed to equilibrate for 24 h, a new signal appeared at δ 2.43 (a triplet, J = 7.0 Hz) (Figure 7**C**) in addition to that of HN(SiMe$_3$)$_2$ at δ 0.07. Clearly, this slow transformation, observed in CD$_2$Cl$_2$, corresponds to the protonolysis reported by Seo and Marks, which yields La(NBu$_2$)$_3$.[116] No re-formation of La[N(SiMe$_3$)$_2$]$_3$ was observed, even upon addition of large excess of HN(SiMe$_3$)$_2$ to this mixture, demonstrating that the protonolysis is apparently irreversible. Furthermore, the F to N substitution reaction was followed by ^{1}H NMR and recorded after 1 min when adding 3 equiv. of dibutylamine to a sample containing 1-fluorodecane (1 equiv.) and La[N(SiMe$_3$)$_2$]$_3$ (1 equiv.) (Figure 7**B**). The broad quartet at δ 2.57 was found to decrease over time, simultaneously with the appearance of a new peak at 2.35, assigned to a fragment of the product *N*,*N*-dibutyldecan-1-amine (**78**). However, when utilizing La(NBu$_2$)$_3$ formed *in situ*, the F to N substitution was much slower, and almost no conversion occurred within 30 min (Figure 7**C**). Slow substitution was also observed upon further addition of dibutylamine (3 equiv.) to La(NBu$_2$)$_3$ (Figure 7**D**). The ^{1}H NMR spectra of this mixture similarly displays a broad signal at δ 2.58 from dibutylamine. ^{1}H NMR experiment conducted with diisopropylamine gave matching results. In addition, since the La[N(SiMe$_3$)$_2$]$_3$ is diamagnetic, we speculated that the La--F interaction could be observed by NMR spectroscopy. If such an interaction was present, a ^{1}H NMR experiment would reveal a shift of the protons in α-position to fluorine (R-C<u>H</u>$_2$-F) or fluorine shift in ^{19}F NMR. Titration of 1-fluorodecane into a NMR tube containing La[N(SiMe$_3$)$_2$]$_3$ was conducted. ^{1}H and ^{19}F NMR were recorded, however, the shift was independent of the La:F ratio (5:1-15), implying no or only a very weak La--F interaction.

All results taken together support the mechanistic proposal depicted in Scheme 30.

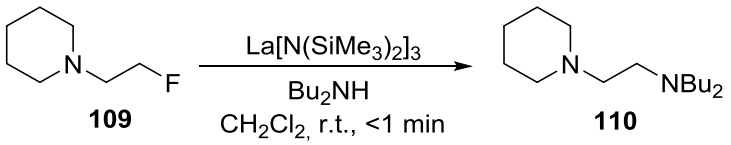


Scheme 30. Proposed mechanism for the La[N(SiMe$_3$)$_2$]$_3$ mediated amination of an alkyl fluoride.

A secondary amine (HNR^1R^2), or a primary, which is prone to undergo protonolysis with $La[N(SiMe_3)_2]_3$ affords the corresponding $La(NR^1R^2)_3$ complex over time (Figure 7). The faster the protonolysis is, the slower the substitution proceeds, thus, affording an unproductive pathway **I** incapable of C–F bond activation (Scheme 30). In contrast, slow protonolysis affords a pre-complexed specie between (HNR_1R_2) and $La[N(SiMe_3)_2]_3$, which upon addition of an alkyl fluoride is believed to form a concerted transition state (pathway **II**). This is supported by initial rate data which revealed that all three components are present in the rate determining step. The reaction being concentration and steric-dependent is also consistent with a concerted transition state (Scheme 25 and 26). If a more classical S_N2-type mechanism would be operating, an inverse KIE effect would have been observed.

5.2. Instantaneous C-F bond activation of β-amino fluorides (Paper IV)

It is well established that good leaving groups in β-position to amines readily undergo intramolecular substitution to form aziridinium ions.[120,121,122] In contrast to other β-haloamines, β-fluoroamines have been shown to be almost inert towards this type of transformations.[123] During the progress and development of the $La[N(SiMe_3)_2]_3/Bu_2NH$ promoted substitution of primary alkyl fluorides, fascinating reactivity was observed when subjecting a β-amino fluoride (**109**) to the present reaction conditions (Scheme 31).



Scheme 31. Instantaneous F/N substitution of an β-fluoro amine when employing $La[N(SiMe_3)_2]_3$ as a Lewis acid.

As determined by GC/MS, an immediate substitution to the diamine product (**110**) was observed, possibly indicating a neighboring group participation of the 3°-amine which in combination with the fluorophilic La(III) lowers the activation barrier for C(sp^3)–F bond substitution. This substitution is closely related to the direct amination presented in section 5.1., however the reactivity is unique and the mechanism is believed to procced via an aziridinium ion. As such, the concept was further elaborated and expanded.

5.2.1. Aziridinium ion formation

To confirm the formation of the aziridinium ion, a ^1H NMR experiment was performed where *N*-benzyl-*N*-methyl-2-fluoroethylamine (**112**) was added to the diamagnetic $La[N(SiMe_3)_2]_3$ in CD_2Cl_2 (Figure 8**A**).

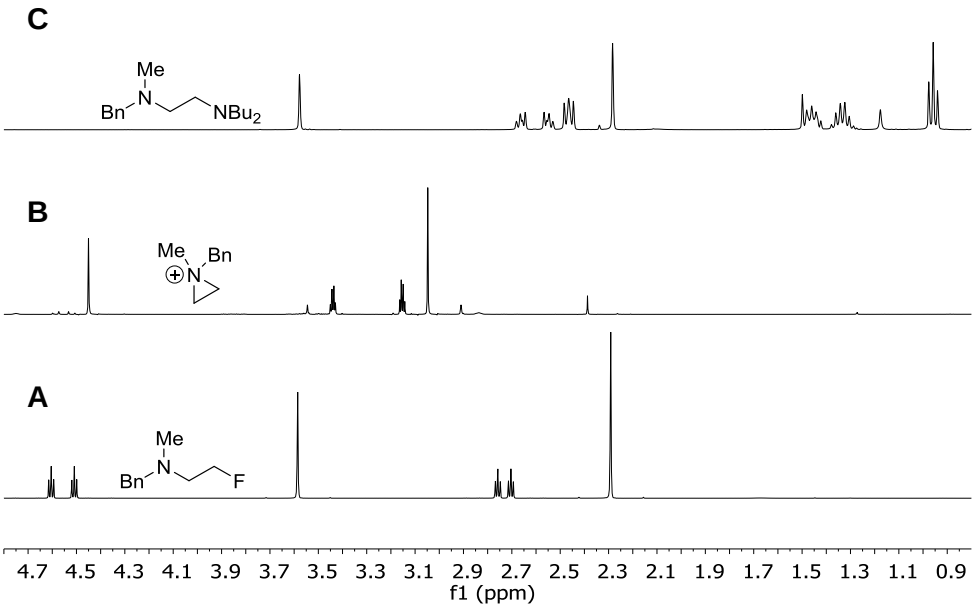


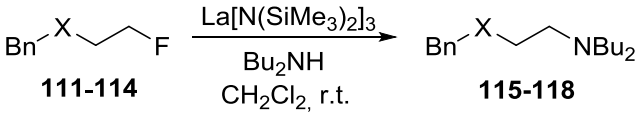
Figure 8. A ^{1}H NMR overview of the β-amino fluoride substitution mediated by La[N(SiMe$_3$)$_2$]$_3$ in CD_2Cl_2. **A**: *N*-benzyl-*N*-methyl-2-fluoroethylamine. **B**: Aziridinium ion intermediate formed by mixing *N*-benzyl-*N*-methyl-2-fluoroethylamine with La[N(SiMe$_3$)$_2$]$_3$ (1:1). **C**: Formation of *N*1-benzyl-*N*2,*N*2-dibutyl-*N*1-methylethane-1,2-diamine upon ring-opening of the aziridinium ion with Bu_2NH.

Direct measurements of the sample revealed a larger downfield shift of approximately 0.9 ppm for the Ph–C<u>H</u>$_2$–N– and 0.8 ppm for the –N–C<u>H</u>$_3$ protons, simultaneously with an upfield shift of 1.1 ppm for the –C<u>H</u>$_2$–F protons, clearly indicating an instantaneous C–F bond cleavage and subsequent formation of the aziridinium ion (Figure 8**B**).[124,125] Furthermore, the charged intermediate underwent immediate ring-opening upon addition of Bu_2NH, affording the β-substituted amine product (**116**) after work-up (Figure 8**C**).

5.2.2. Neighboring group effect

A screening of various neighboring groups in β-position to fluorine was performed to test whether the reactivity is affected by the type of heteroatom. Since carbon is not assisting in the substitution of fluoride, this substrate was used as a reference (**111**) (Table 5, entry 1). A reaction time of 60 min was necessary to reach full conversion and the corresponding diamine product (**115**) was isolated in 93% yield. Replacing the carbon for nitrogen (**112**) or sulphur (**113**) gave a remarkable increase in the reaction rate, clearly showing a neighboring group effect (entries 2-3). Changing to oxygen (**114**) did not give any significant enhancement, the reaction still required 60 min to reach completion. An amide was also investigated as a neighboring group participant, however the substrate degraded under present reaction conditions.

Table 5. The effect of different β-fluoro heteroatom assisted C–F bond substitution.[a]



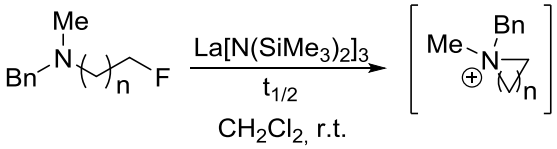
111-114 **115-118**

entry	X	t (min)	Yield (%)[b]
1	CH_2 (**111**)	60	93 (**115**)
2	NMe (**112**)[c]	1	93 (**116**)
3	S (**113**)[d]	1	87 (**117**)
4	O (**114**)[d]	60	89 (**118**)

[a] Reaction conditions: $La[N(SiMe_3)_2]_3$ (0.176 mmol), CH_2Cl_2 (1.0 mL), Bu_2NH (0.176 mmol), substrate (1.0 M in CH_2Cl_2, 0.160 mmol). [b] isolated yields are reported. [c] 95% conversion within 10 s measured by GC. [d] Bu_2NH (0.48 mmol).

Furthermore, the distance between the neighboring group and the fluorine was also increased to test how the reactivity was affected. As such, a relative rate study of the ring formation of each charged intermediate was estimated based on their respective half-life-times ($t_{½}$) (Table 6).

Table 6. Studying the effect of the ring formation by varying the distance between the chelating nitrogen and the fluoride.[a]



entry	n	$t_{½}$ (s)[b]
1	1 (**112**)	~4
2	2 (**119**)	~30
3	3 (**120**)	<<1
4	4 (**121**)	~1
5	5 (**122**)	240

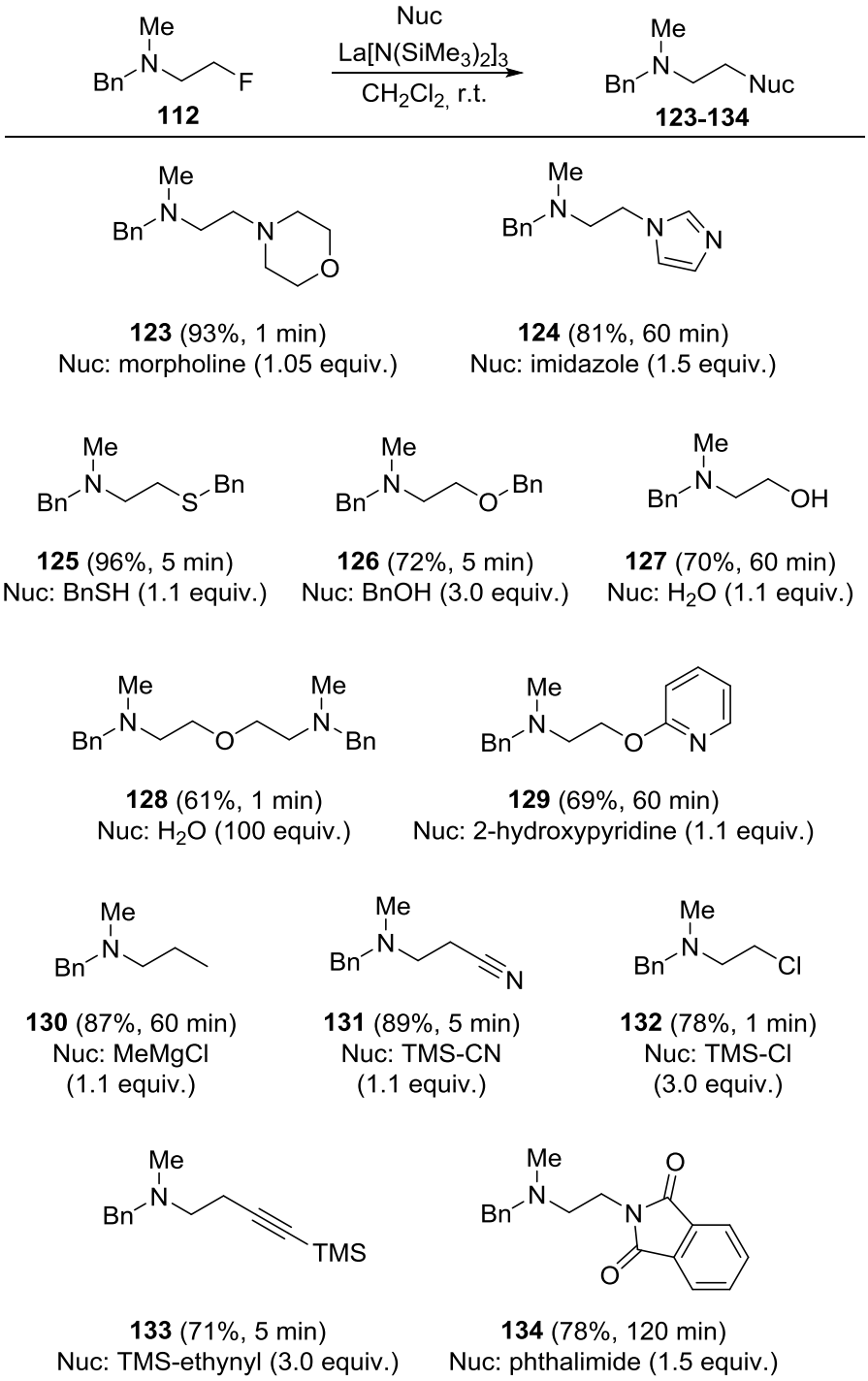
[a] Reaction conditions: $La[N(SiMe_3)_2]_3$ (0.044 mmol), CH_2Cl_2 (0.25 mL), substrate (1.0 M in CH_2Cl_2, 0.040 mmol). *n*-Dodecane (0.040 mmol) was added to the reaction as internal standard. [b] Analyzed by GC.

For the β-amino fluoride (**112**) and the formation of the aziridinium ion, a $t_{½}$ of 4 s was observed (Table 6, entry 1). With the fluorine in γ-position (**119**), a $t_{½}$ of approximately 30 s was observed for the formation of the corresponding azetidinium ion (entry 2).[124] The

5- and 6-exo-tet ring formations were extremely fast, with $t_{½}$ <<1 s and $t_{½}$ ~1 s respectively (entries 3-4), while the 7-exo-tet ring formation was observed at a lower rate (entry 5). 5-, 6-, and 7-membered rings form stable quaternary amines. Neither of the charged intermediates showed any reactivity towards the nucleophilic amine even with prolonged reaction time (24 h).

5.2.3. Expanding the usage of nucleophiles

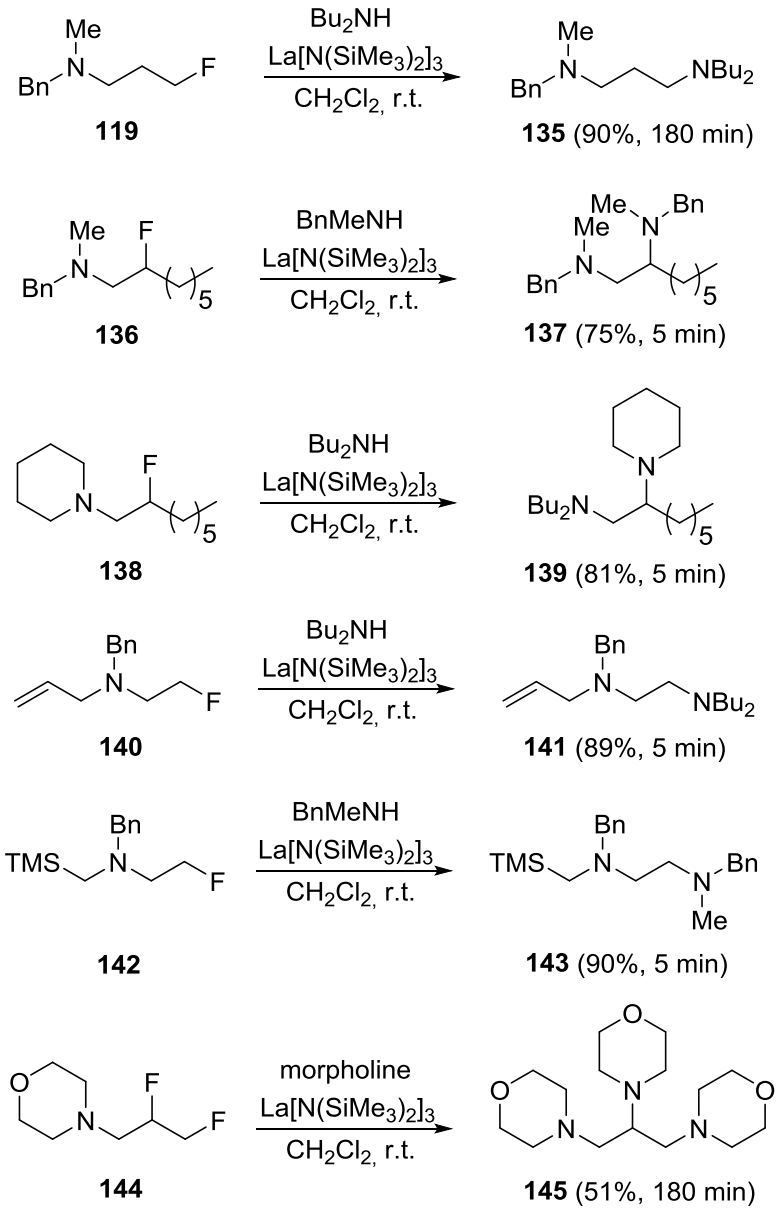
It should be noted that aziridinium ions can be obtained via two main pathways, i.e. through *N*-functionalization of neutral non-activated aziridines or trough intramolecular nucleophilic substitution of the 3°-amines bearing a leaving group at the β-position.[120,122] Since the activated aziridinium ions are formed *in situ*, an interesting aspect would be to add different nucleophiles which allows for subsequent ring-opening to afford various β-substituted amines (Scheme 32). Complementary to dibutylamine as a nucleophilic source, the heterocyclic morpholine underwent clean ring-opening of the aziridnium ion within 1 min affording the corresponding diamine (**123**) in 93% yield. Even the heteroaromatic imidazole, gave facile ring-opening and **124** was obtained in 81% yield. The nucleophilic amide phthalimide was incorporated, affording **134** in 78% isolated yield. Thiol and alcohol as nucleophiles gave the corresponding thioether (**125**) and ether (**126**) in high to excellent yields within 5 min. In a similar fashion 2-hydroxypyridine, which potentially can react in both its tautomeric forms, only yielded the ether product (**129**). With water as nucleophile either the β-hydroxy amine (**127**) or the tridentate ether ligand (**128**) was obtained in high to moderate yields, with the outcome being dependent on the amount of water added as well as the reaction time.



Scheme 32. Ring-opening of *in situ* generated aziridinium ions by various nucleophiles.

With the benefits of forming a reactive aziridinium ion *in situ*, it was even possible to achieve C-C bond formation upon addition of MeMgCl, TMS-CN, or ethynyltrimethylsilane, all isolated in high yields (**130**, **131**, and **133**). Noteworthy, in the case of **133** the TMS group is not cleaved of. A halogen exchange was possible by utilizing TMS-Cl as nucleophile, and the corresponding β-chloro amine (**132**) was obtained within 1 min in high yield. **132** was subjected to the same conditions as **112** (Table 5, entry 2),

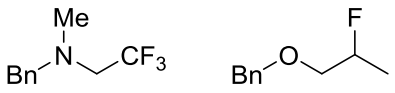
and only 10% conversion into product was observed within 1 min, showing a higher affinity of the $La[N(SiMe_3)_2]_3$ reagent towards fluoride under these conditions.
The synthetic versatility was further elaborated by examining other β-amino alkyl fluorides. As described in the literature, the azetidinium ion is less prone to undergo ring-opening then the corresponding aziridinium ion.[124] As such, the nucleophilic substitution of γ-fluoro amine **119** was a bit slower and full conversion into **135** was achieved after 180 min (Scheme 33).



Scheme 33. $La[N(SiMe_3)_2]_3$ mediated C–F bond substitution of various neighboring group assisted alkyl fluorides.

Notably, assistance from amines in β-position to a secondary alkyl fluoride (**136** and **138**) allowed for fluorine to easily be cleaved within 5 minutes. The corresponding diamines were isolated in high yield (**137** and **139**). Since secondary alkyl fluorides in β-position to

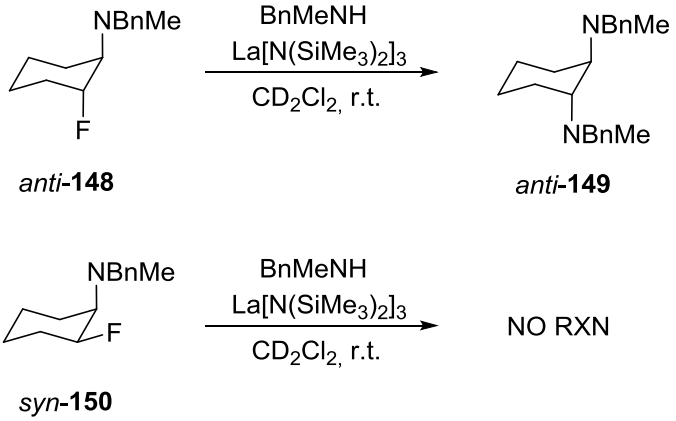
an amine can generate non-symmetric aziridinium ions, different isomeric products can be obtained in the nucleophilic ring opening as a consequence. In the examples displayed herein, **139** was obtained in high regioselectivity. Thus, the substitution predominantly occurs on the unsubstituted carbon of the corresponding aziridinium ion intermediate, being consistent with that reported in the literature.[120,124] Furthermore, even vicinal fluorides (**144** yielding **145**) were substituted with the assistance of a neighboring group. Of the two possible charged intermediates, the substitution preferably proceeds via formation of two aziridinium ions. Allylbenzylamine (**140**) and *N*-[(trimethylsilyl)methyl]benzylamine (**142**), which both are capable of rearrangement, yielded the corresponding diamines (**141** and **143** respectively) within 5 min, indicating an extremely fast and selective activation and substitution of the β-alkyl fluoride. Compound **146**, with a trifluoromethyl group in the α-position, was unreactive under present reaction conditions, resulting from a shorter and stronger C-F bond as more fluorines are added to the carbon (Figure 9). Neither did substitution of the secondary fluoride in **147** occur, once again showing the lack of neighboring group assistance from the oxygen (Figure 9).



146 **147**

Figure 9. Non-reactive β-heteroatom fluorides in the La[N(SiMe$_3$)$_2$]$_3$ mediated C–F bond substitution.

Literature reports propose that the intramolecular nucleophilic substitution of amines bearing a leaving group at the β-position with a subsequent ring-opening of the corresponding aziridinium ion proceeds via two S_N2 reactions. [120,122,123] Accordingly, double inversion of *anti*-**148** afforded *anti*-**149**, while *syn*-**150** did not react at all (Scheme 34).



Scheme 34. Stereochemical analysis of the La[N(SiMe$_3$)$_2$]$_3$ mediated aziridinium ion formation and subsequent ring-opening.

5.3. Conclusion

In summary, a facile and novel protocol for direct aliphatic C-F to C-N substitution utilizing $La[N(SiMe_3)_2]_3$ in presence of various nucleophilic amines has been developed. The substitution shows excellent selectivity towards the primary alkyl fluorides compared to other aliphatic carbon-halogen bonds, and various functionalized primary fluorinated compounds are compatible with the reaction conditions. A concerted transition state is proposed based on steric effects, initial rate studies, KIE, and ^{1}H NMR spectroscopy. In addition, the F to N substitution senses a competing protonolysis pathway between the amine and the $La[N(SiMe_3)_2]_3$. Thus, the faster the protonolysis is the slower the substitution proceeds. The utilization of $La[N(SiMe_3)_2]_3$ was further extended into substrates containing a nitrogen as a chelating groups in β-position to fluoride. The β-amino fluorides underwent mild and instantaneous substitution into various functionalized amines. The transformation relies on the formation of an aziridinium ion which is subsequently ring-opened by a nucleophile. ^{1}H NMR spectroscopy confirmed double inversion of a cyclic diastereomerically pure β-amino fluoride, leading to retention of configuration.

6. Concluding remarks and future outlook

This thesis describes the development of facile and mild C–F bond activation procedures with the use of lanthanides. This novel methodology revolves around a stoichiometric protocol which was also turned into a catalytic process. The different lanthanides possess exclusive selectivity towards functionalized alkyl fluorides. Carefully designed experiments have been evaluated to obtain new mechanistic insights regarding the C–F bond substitution. It has been shown that the reaction pattern clearly depends on the lanthanide(III) cation and its surroundings. Most importantly, the methodology developed and presented in this thesis allows for introduction of fluorine as an inert protecting group, which now easily can be cleaved and transformed into versatile non fluorinated compounds using the described protocols.

To continue the progression of lanthanide mediated C–F bond activation and subsequent functionalization the following aspects should be considered:

- Elaborate and introduce new labile nucleophilic ligands on the Ln(III) cations to further expand the synthetic utility.

- Improve and expand the catalytic process regarding Ln(III) promoted C–F bond activation by testing different fluoride-trapping agents.

- An interesting, and potentially promising approach, would be the use of chiral ligands in combination with labile nucleophilic ligands to introduce asymmetric functionalization of fluorinated compounds.

- An appealing task, which is in progress, is the use of $Sm(HMDS)_2$ in n-hexane as a radical induced protocol for development of fluorinating reactions.

7. Acknowledgment

Härmed vill jag passa på att tacka alla de personer som under åren bidragit och hjälpt till med diverse sakfrågor som resulterat i utformningen av denna avhandling.

Hilmersson gruppen:

Professor Göran Hilmersson — Finns inga ord som kan beskriva min tacksamhet. Tack för att du antog mig. Tack för alla råd och tips under vägens gång. Tack för den frihet jag fick och all givande handledning som lett till att vi står här idag. Jag har verkligen utvecklats som kemist och person hos dig. Vårt samarbete har varit utmärkt och bättre boss får man leta efter.

Annika Träff — Vilken medarbetare. Tack för att du funnits där under min tid som doktorand. Tack för all hanledning, för alla diskussioner, för att du styrt upp forskningen, för vårt fina samarbete, för att du orkat med min organiserade kaos. Du har allt man kan önska hos en vän och kollega. Vi har haft det riktigt kul, och även om forskningen inte alltid varit på vår sida, så har vi ägt projekten och inte projekten oss.

Tobias Ankner — Du var till stor hjälp i början av min tid som doktorand. Även om vi inte jobbade länge tillsammans så hjälpte du till i alla lägen och visade mig allt inom gruppen. Dina tankar och råd kring Sm(II) kemin var oerhört värdefulla och till stor del bidragande till att utforma reductive defluorination projektet.

Andreas Ekebergh — Tack för fint samarbete inom det katalytiska projektet. Vi fixade det till slut. Det var många fler spännande resultat som dök upp under tiden, det var synd att du var tvungen att lämna för Stanford.

Linda Ta, *Martin Ratsch*, *Yang Wang* och *Irma Vreto* — Mina hårt arbetande examensarbetare. Tack för ert jobb. Det har varit riktigt kul att jobba med er.

Våning 8:

Alberte Veiga — Tack för din fina vänskap. För alla trevliga lunchraster och diskussioner från allt mellan livsfrågor till kemi. Du har varit en riktigt vän och jag är tacksam för att ha lärt känna dig.

Alavi Karim — Tack för allt min vän. Alla våra roliga och konstiga diskussioner har underlättat vardagen. Det har varit ett nöje att dela kontor med dig.

Per-Ola Norrby och *Carl-Johan Wallentin* — Tack för alla era diskussioner och smarta kommentarer kring manuskript och forskning.

Alla trevliga människor på våning 8 — Tack för att ni bidragit till en fin atmosfär och tack för all hjälp jag har fått och att ni har hållit igång allt från instrument till fester.

Familj:

Jag vill tacka min ”lilla familj” och mina föräldrar. Tack för ert stöd och tålamod, utan er hade det varit svårt att motivera sig genom alla hinder som har dykt upp under vägen.

8. References

(1) D. O'Hagan, *Chem. Soc. Rev.*, **2008**, *37*, 308.

(2) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications,* Wiley-VCH, Weinheim, **2004**.

(3) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.*, **2016**, *116*, 422.

(4) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.*, **2014**, *114*, 2432.

(5) K. L. Kirk, *J. Fluorine Chem.*, **2006**, *127*, 1013.

(6) P. Jeschke, *ChemBioChem*, **2004**, *5*, 570.

(7) M. A. Thayer, *Chem. Eng. News*, **2006**, *84*, 15.

(8) K. Müller, C. Faeh, F. Diederich, *Science*, **2007**, *317*, 1881.

(9) A. Harsanyi, G. Sandford, *Green Chem.*, **2015**, *17*, 2081.

(10) P. A. Champagne, J. Desroches, J-D. Hamel, M. Vandamme, J-F. Paquin, *Chem. Rev.*, **2015**, *115*, 9073.

(11) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.*, **2013**, *52*, 8214.

(12) H. Amii, K. Uneyama, *Chem. Rev.*, **2009**, *109*, 2119.

(13) M. F. Kuehnel, D. Lentz, T. Braun, *Angew. Chem. Int. Ed.*, **2013**, *52*, 3328.

(14) T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, *Chem. Rev.*, **2015**, *115*, 931.

(15) M. K. Whittlesey, E. Peris, *ACS Catal.*, **2014**, *4*, 3152.

(16) V.D. Shteingarts, *J. Fluorine Chem.*, **2007**, *128*, 797.

(17) K. Uneyama, H. Amii, *J. Fluorine Chem.*, **2002**, *114*, 127.

(18) T. Stahl, H. F. T. Klare, M. Oestreich, *ACS Catal.*, **2013**, *3*, 1578.

(19) R. P. Hughes, *Eur. J. Inorg. Chem.*, **2009**, 4591.

(20) H. Torrens, *Coord. Chem. Rev.*, **2005**, *249*, 1957.

(21) T. Braun, R. N. Perutz, *Chem. Commun.*, **2002**, 2749.

(22) T. G. Richmond, *Angew. Chem. Int. Ed.*, **2000**, *39*, 3241.

(23) J. Terao, Y. Naitoh, H. Kuniyasu, N. Kambe, *Chem. Commun.*, **2007**, 825.

(24) J. Choi, D. Y. Wang, S. Kundu, Y. Choliy, T. J. Emge, K. Krogh-Jespersen, A. S. Goldman, *Science*, **2011**, *332*, 1545.

(25) Z. Mo, Q, Zhang, L. Deng, *Organometallics*, **2012**, *31*, 6518.

(26) W. D. Jones, *Dalton Trans.*, **2003**, 3991.

(27) D. R. Fahey, J. E. Mahan, *J. Am. Chem. Soc.*, **1977**, *99*, 2501.

(28) M. Reinhold, J. E. McGrady, R. N. Perutz, *J. Am. Chem. Soc.*, **2004**, *126*, 5268.

(29) R. Bosque, E. Clot, S. Fantacci, F. Maseras, O. Eisenstein, R. N. Perutz, K. B. Renkema, K. G. Caulton, *J. Am. Chem. Soc.*, **1998**, *120*, 12634.

(30) L. Cronin, C. L. Higgitt, R. Karch, R. N. Perutz, *Organometallics*, **1997**, *16*, 4920.

(31) S Burling, P. I. P. Elliot, N. A. Jasim, R. J. Lindup, J. McKenna, R. N. Perutz, S. J. Archibald, A. C. Whitwood, *Dalton Trans.*, **2005**, 3686.

(32) T. Braun, S. P. Foxon, R. N. Perutz, P. H. Walton, *Angew. Chem. Int. Ed.*, **1999**, *38*, 3326.

(33) J. A. Hatnean, S. A. Johnson, *Organometallics*, **2012**, *31*, 1361.

(34) D. Breyer, J. Berger, T. Braun, S. Mebs, *J. Fluorine Chem.*, **2012**, *143*, 263.

(35) T. Braun, S. Parsons, R. N. Perutz, M. Voith, *Organometallics*, **1999**, *18*, 1710.

(36) M. I. Sladek, T. Braun, B. Neumann, H. G. Stammler, *J. Chem. Soc. Dalton Trans.*, **2002**, 297.

(37) A. Steffen, M. I. Sladek, T. Braun, B. Neumann, H. G. Stammler, *Organometallics*, **2005**, *24*, 4057.

(38) N. A. Jasim, R. N. Perutz, A. C. Whitwood, T. Braun, J. Izundu, B. Neumann, S. Rothfeld, H. G. Stammler, *Organometallics*, **2004**, *23*, 6140.

(39) H. Weissman, L. J. W. Shimon, D. Milstein, *Organometallics*, **2004**, *23*, 3931.

(40) T. Braun, J. Izundu, A. Steffen, B. Neumann, H. G. Stammler, *Dalton Trans.*, **2006**, 5118.

(41) D. Breyer, T. Braun, P. Kläring, *Organometallics*, **2012**, *31*, 1417.

(42) A. Nova, S. Erhardt, N. A. Jasim, R. N. Perutz, S. A. Macgregor, J. E. McGrady, A. C. Whitwood, *J. Am. Chem. Soc.*, **2008**, *130*, 15499.

(43) T. Yoshida, D. L. Thorn, T. Okano, S. Otsuka, J. A. Ibers, *J. Am. Chem. Soc.*, **1980**, *102*, 6451.

(44) D. Noveski, T. Braun, B. Neumann, A. Stammler, H. G. Stammler, *Dalton Trans.*, **2004**, 4106.

(45) T. Braun, R. N. Perutz, M. I. Sladek, *Chem. Commun.*, **2001**, 2254.

(46) R. J. Lindup, T. B. Marder, R. N. Perutz, A. C. Whitwood, *Chem. Commun.*, **2007**, 3664.

(47) A. Nova, M. Reinhold, R. N. Perutz, S. A. Macgregor, J. E. McGrady, *Organometallics*, **2010**, *29*, 1824.

(48) B. L. Edelbach, W. D. Jones, *J. Am. Chem. Soc.*, **1997**, *119*, 7734.

(49) M. Aizenberg, D. Milstein, *Science*, **1994**, *265*, 359.

(50) M. Aizenberg, D. Milstein, *J. Am. Chem. Soc.*, **1995**, *117*, 8674.

(51) M. K. Whittlesey, R. N. Perutz, M. H. Moore, *Chem. Commun.*, **1996**, 787.

(52) V. P. W. Böhm, C. W. K. Gstöttmayr, T. Weskamp, W. A. Herrmann, *Angew. Chem. Int. Ed.*, **2001**, *40*, 3387.

(53) T. Schaub, M. Backes, U. Radius, *J. Am. Chem. Soc.*, **2006**, *128*, 15964.

(54) N. Yoshikai, H. Mashima, E. Nakamura, *J. Am. Chem. Soc.*, **2005**, *127*, 17978.

(55) L. Ackermann, R. Born, J. H. Spatz, D. Meyer, *Angew. Chem. Int. Ed.*, **2005**, *44*, 7216.

(56) L. Ackermann, C. Wechsler, A. R. Kapdi, A. Althammer, *Synlett*, **2010**, 294.

(57) Z. Jin, Y.-J. Li, Y.-Q. Ma, L.-L. Qiu, J.-X. Fang, *Chem. Eur. J.*, **2012**, *18*, 446.

(58) M. Tobisu, T. Xu, T. Shimasaki, N. Chatani, *J. Am. Chem. Soc.*, **2011**, *133*, 19505.

(59) J. Zhou, M. W. Kuntze-Fechner, R. Bertermann, U. S. D. Paul, J. H. J. Berthel, A. Friedrich, Z. Du, T. B. Marder, U. Radius, *J. Am. Chem. Soc.*, **2016**, *138*, 5250.

(60) M. Ohashi, H. Saijo, M. Shibata, S. Ogoshi, *Eur. J. Org. Chem.*, **2013**, 443.

(61) J. W. Dankwardt, *J. Organomet. Chem.*, **2005**, *690*, 932.

(62) T. Saeki, Y. Takashima, K. Tamao, *Synlett*, **2005**, 1771.

(63) M. Ohashi, R. Doi, S. Ogoshi, *Chem. Eur. J.*, **2014**, *20*, 2040.

(64) B. L. Edelbach, A. K. Fazlur Rahman, R. J. Lachicotte, W. D. Jones, *Organometallics*, **1999**, *18*, 3170.

(65) P. Fischer, K. Götz, A. Eichhorn, U. Radius, *Organometallics*, **2012**, *31*, 1374.

(66) J.-H. Zhan, H. Lv, Y. Yu, J.-L. Zhang, *Adv. Synth. Catal.*, **2012**, *354*, 1529.

(67) Z. Chen, C.-Y. He, Z. Yin, L. Chen, Y. He, X. Zhang, Angew. *Chem. Int. Ed.*, **2013**, *52*, 5813.

(68) V. J. Scott, R. Celenligil-Cetin, O. V. Ozerov, *J. Am. Chem. Soc.*, **2005**, *127*, 2852.

(69) C. Douvris, O. V. Ozerov, *Science*, **2008**, *321*, 1188.

(70) C. Douvris, C. M. Nagaraja, C.-H. Chen, B. M. Foxman, O. V. Ozerov, *J. Am. Chem. Soc.*, **2010**, *132*, 4946.

(71) R. Panisch, M. Bolte, T. Müller, *J. Am. Chem. Soc.*, **2006**, *128*, 9676.

(72) C. B. Caputo, D. W. Stephan, *Organometallics*, **2012**, *31*, 27.

(73) T. Robert, M. Oestreich, *Angew. Chem. Int. Ed.*, **2013**, *52*, 5216.

(74) S. Render, M. Oestreich, *Angew. Chem. Int. Ed.*, **2008**, *47*, 5997.

(75) J. Yang, P. S. White, C. K. Schauer, M. Brookhart, *Angew. Chem. Int. Ed.*, **2008**, *47*, 4141.

(76) C. B. Caputo, L. J. Hounjet, R. Dobrovetsky, D. W. Stephan, *Science*, **2013**, *341*, 1374.

(77) L. J. Hounjet, C. B. Caputo, D. W. Stephan, *Dalton Trans.*, **2013**, *42*, 2629.

(78) N. Lühmann, R. Panisch, T. Müller, *Appl. Organomet. Chem.*, **2010**, *24*, 533.

(79) J. Zhu, M. Pérez, C. B. Caputo, D. W. Stephan, *Angew. Chem. Int. Ed.*, **2016**, *55*, 1417.

(80) G. A. Olah, S. Kuhn, J. A. Olah, *J. Chem. Soc.*, **1957**, 2174.

(81) G. Theodoridis, *Tetrahedron Lett.*, **1998**, *39*, 9365.

(82) G. K. S. Prakash, J. Hu, J. Simon, D. R. Bellew, G. A. Olah, *J. Fluorine Chem.*, **2004**, *125*, 595.

(83) J. Riera, J. Castañer, J. Carilla, A. Robert, *Tetrahedron Lett.*, **1989**, *30*, 3825.

(84) J. Carilla, Ll. Fajarí, R. García, L. Juliá, C. Marcos, J. Riera, C. R. Whitaker, J. Rius, C. Alemán, *J. Org. Chem.*, **1995**, *60*, 2721.

(85) S. A. Begum, J. Terao, N. Kambe, *Chem. Lett.*, **2007**, *36*, 196.

(86) T. Ooi, D. Uraguchi, N. Kagoshima, K. Maruoka, *Tetrahedron Lett.*, **1997**, *38*, 5679.

(87) K. Hirano, K. Fujita, H. Yorimitsu, H. Shinokubo, K. Oshima, *Tetrahedron Lett.*, **2004**, *45*, 2555.

(88) J. Terao, S. A. Begum, Y. Shinohara, M. Tomita, Y. Naitoh, N. Kambe, *Chem. Commun.*, **2007**, 855.

(89) S. Kobayashi, *Lanthanides: Chemistry and Use in Organic Synthesis*, Springer, Verlag Berlin Heidelberg, **1999**.

(90) D. J. Procter, R. A. Flowers II, T. Skrydstrup, *Organic Synthesis Using Samarium Diiodide; A Practical Guide*, The Royal Society of Chemistry, Cambridge, **2010**.

(91) R. H. Crabtree, *The organometallic chemistry of the transition metals*. 4th Ed. Wiley, New York, **2005**.

(92) G. B. Deacon, P. I. MacKinnon, *Tetrahedron Lett.*, **1984**, *25*, 783.

(93) G. B. Deacon, C. M. Forsyth, *Organometallics*, **2003**, *22*, 1349.

(94) G. B. Deacon, C. M. Forsyth, P. C. Junk, J. Wang, *Chem. Eur. J.*, **2009**, *15*, 3082.

(95) H. Yin, A. J. Lewis, U. J. Williams, P. J. Caroll, E. J. Schelter, *Chem. Sci.*, **2013**, *4*, 798.

(96) J. San Filippo, R. G. Nuzzo, L. J. Romano, *J. Am. Chem. Soc.*, **1975**, *97*, 2546.

(97) J. Wettergren, T. Ankner, G. Hilmersson, *Chem. Commun.*, **2010**, *46*, 7596.

(98) M. Szostak, M. Spain, D. J. Procter, *J. Org. Chem.*, **2014**, *79*, 2522.

(99) W. J. Evans, D. K. Drummond, H. Zhang, J. L. Atwood, *Inorg. Chem.*, **1988**, *27*, 575.

(100) W. J. Evans, M. A. Johnston, R. D. Clark, R. Anwander, J. W. Ziller, *Polyhedron*, **2001**, *20*, 2483.

(101) W. J. Evans, D. S. Lee, D. B. Rego, J. M. Perotti, S. A. Kozimor, E. K. Moore, J. W. Ziller, *J. Am. Chem. Soc.*, **2004**, *126*, 14574.

(102) T. V. Chciuk, G. Hilmersson, R. A. Flowers II, *J. Org. Chem.*, **2014**, *79*, 9441.

(103) D. Guijarro, P. Martínez, M. Yus, *Tetrahedron*, **2003**, *59*, 1237.

(104) Y. R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, FL, **2007**.

(105) D. Witt, *Synthesis*, **2008**, 2491.

(106) M. B. Smith, J. March, *March´s Advanced Organic Chemistry: Reactions, Mechanism, and Structure*, 6th Ed., Wiley, Hoboken, **2007**.

(107) P. Atkins, J. De Paula, *Atkins Physical Chemistry*, 7th Ed., Oxford University Press, New York, **2000**.

(108) Y. Mizukami, Z. Song, T. Takahashi, *Org. Lett.*, **2015**, *17*, 5942.

(109) G. A. Olah, S. C. Narang, L. D. Field, *J. Org. Chem.*, **1981**, *46*, 3727.

(110) U. J. Williams, P. J. Carroll, E. J. Schelter, *Inorg. Chem.*, **2014**, *53*, 6338.

(111) C. J. Schaverien, H. Van Der Heijden, A. G. Orpen, *Polyhedron*, **1989**, *8*, 1850.

(112) H. Van Der Heijden, C. J. Schaverien, A. G. Orpen, *Organometallics*, **1989**, *8*, 255.

(113) G. A. Olah, S. C. Narang, *Tetrahedron*, **1982**, *38*, 2225.

(114) Q. Shen, Y.-G. Huang, C. Liu, J.-C. Xiao, Q.-Y. Chen, Y. Guo, *J. Fluorine Chem.*, **2015**, *179*, 14.

(115) T. A. Unzner, T. Magauer, *Tetrahedron Lett.*, **2015**, *56*, 877.

(116) S. Seo, T. J. Marks, *Org. Lett.*, **2008**, *10*, 317.

(117) H. Yin, A. V. Zabula, E. J. Schelter, *Dalton Trans.*, **2016**, *45*, 6313.

(118) H. Morimoto, R. Fujiwara, Y. Shimizu, K. Morisaki, T. Ohshima, *Org. Lett.*, **2014**, *16*, 2018.

(119) I. Lee, *Chem. Soc. Rev.*, **1995**, *24*, 223.

(120) S. Stankovic, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. V. Speybroeck, N. D. Kimpe, H.-J. Ha, *Chem. Soc. Rev.*, **2012**, *41*, 643.

(121) H.-S. Chong, Y. Chen, *Org. Lett.*, **2013**, *15*, 5912.

(122) T.-X. Métro, B. Duthion, D. G. Pardo, J. Cossy, *Chem. Soc. Rev.*, **2010**, *39*, 89.

(123) H.-S. Chong, X. Sun, Y. Chen, M. Wang, *Tetrahedron Lett.*, **2015**, *56*, 946.

(124) N. D. Rycke, O. David, F. Couty, *Org. Lett.*, **2011**, *13*, 1836.

(125) P. Sulmon, N. D. Kimpe, N. Schamp, *Tetrahedron*, **1988**, *44*, 3653.