EXPLORING MECHANISTIC PATHWAY OF C-F BOND ACTIVATION TO C-C BOND FORMATION WITH GRIGNARD REAGENTS BY FIRST PRINCIPLES SIMULATIONS

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By

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Declaration

I hereby declare that the matter embodied in this report is the result of investigation carried out by me in the Department of Chemistry, Indian Institute of Technology Hyderabad under the supervision of Dr. Bhabani Shankar Mallik

In keeping with general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

20/4/2015

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Certificate - I

The undersigned have examined the thesis entitled ‘**Exploring mechanistic pathway of C-F bond activation to C-C bond formation with Grignard reagents by first principle simulations**’ by **Dhwani Kansal** is approved for the degree of Master of Science from IIT Hyderabad.

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Dedicated to

My Parents

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ABSTRACT

Nucleophilic substitution reaction to form C-C bond from C-X bond with assistance of transition metal catalyst is one of the novel synthetic method for synthesis in organic chemistry. Recently, chemists have developed new synthetic methods for the formation of C-C bond from C-F bond with Grignard reagents without transition metal catalyst. Organofluorine compounds are of great importance and this proves to be a highly efficient method for the carrying out C-F activation to give C-C coupled product. The aim of this thesis is to predict the plausible mechanism for the pathway in going from C-F to C-C bond with nucleophilic Grignard reagents and to predict the transition state which is the highest point in the potential energy surface in going from reactant to product along the reaction coordinate. Here we present a computational study for the mechanistic pathway and the prediction of transition states for the reactions involving alkyl and aryl fluoride with aryl Grignard reagents. We have carried out ab-initio (HF/3-21G*) and density functional theory (DFT) calculations with hybrid functional B3LYP using 6-311+G (2d,p) basis set to study the reaction mechanism. Activation of both sp^3 C-F bond and sp^2C-F bond was investigated and it was observed that due to comparatively shorter bond length of aryl C-F bond the reaction requires some activating/directing groups in the latter case. The effect of halide and the mechanism with dimer of Grignard reagent was also examined.

It was observed that the reaction goes via transition state in which the alkyl group becomes planar and magnesium is tetrahedrally coordinated. In case of sp^3 C-F bond activation a cyclic four membered transition state is formed whereas in case of sp^2C-F bond activation with directing groups a six membered transition state is formed.

Chapter 1

1 Introduction and Motivation

1.1 Introduction

Fluorine was named *le fluor* by the French scientist *Ampere* in 1812 after its natural resource fluorspar. Fluorine with atomic number 9 is a second row element of Group 17, lightest and most electronegative element among all other halogens. It exists in nature as fluorides in fluorite ($CaF_{2)}$, Cryolite ($Na_3[AlF_6]$, and Phosphorite ($Ca_5[F,Cl][PO_4]_3$[1]. In 1886,Moissan[2] successfully achieved the isolation of fluorine by electrolyzing a melt mixture of potassium hydrogen difluoride and hydrogen fluoride at -23°C and received the Noble Prize in 1906 for this discovery. It was in 20th century when fluorine chemistry evolved as an emerging field with the development of synthetic methods for Organofluorine compounds. Dumas and Peligot[3] prepared the first organofluorine compound CH_3F, from dimethylsulfate and potassium fluoride. Aromatic compounds containing C-F bond were first prepared by the conversion of aromatic amines to diazonium salts with subsequent reaction with hydrofluoric acid (HF). Also, discovery of Teflon [Poly(tetrafluoroethylene)], which is a highly heat and chemical resistant polymer, revolutionized the whole chemical industry.

1.2 Importance of Carbon-Fluorine bond

Fluorine is the most electronegative atom in the periodic table. It is less polarizable[4], and hence it is a relatively poor hydrogen bond acceptor. As a consequence, C-F bond is the most polar bond owing to the electronegativity difference between carbon (2.5) and fluorine (4.0) and hence has a high dipole moment. Linus Pauling was the first, who said that C-F bond is the most polar bond in organic chemistry from his evaluation of electronegativity differences[5]. C-F bond has significant ionic character and hence is the strongest bond in organic chemistry with bond dissociation energy of 116 $kcalmol^{-1}$.

Table 1: Data for different physical properties of elements

Element	Ionization Potential	Electron Affinity $[kcalmol^{-1}]$	CH_3-X [A°]	Electronegativity (Pauling)	R[A°]	Bond Energy CH_3-X $[kcalmol^{-1}]$
H	313.6	17.7	1.09	2.1	1.20	99
F	401.8	79.5	1.39	4.0	1.35	116
Cl	299.0	83.3	1.77	3.0	1.80	81
Br	272.2	72.6	1.93	2.8	1.95	68
O(OH)	310.4	33.7	1.43	3.5	1.40	86

The data in Table 1 clearly indicates that as the Pauling electronegativity of the halogen atom increases, the bond dissociation energy decreases which is also in agreement with the increased polarity and hence increase in bond strength. This table also shows that after fluorine, hydrogen has the high bond dissociation energy and therefore carbon-hydrogen bond sometimes mimics the properties of C-F bond.Bond orbital energies of C(2p) is -10.7 eV and F(2p) is -18.6 eV indicates that it is a polar covalent bond with some ionic and covalent character and the bond can be cleaved heterolytically[6]. These compounds can react with polar compounds to give the substituted product. The molecular orbital electronic structure of C-F bond has an empty low lying LUMO $\sigma^*_{C\text{-}F}$ because of which it interacts with an unshared pair of electrons. The orbital of unshared pair of electrons (lone pair) overlaps with the antibonding orbital of C-F bond and have the antiperiplanar conformation. The overlap integrals S for the formation of bonds of first row elements N, O, F are parallel to the overlap integral for the formation of a C-C bond.

1.3 Grignard reagents and Schlenk Equilibrium

Grignard reagent was discovered in 19th century by French organic chemist Victor Grignard and received the Noble prize in 1912 for the same, which he shared with Paul Sabatier. Grignard reagent is the most widely used reagent in synthetic chemistry and is used for the formation of C-C bond. These can be prepared by the reaction of alkyl or aryl fluoride with elemental magnesium in a coordinating solvent such as Et_2O or THF.In THF or Et_2O,an equilibrium mixture best represents Grignard reagents as shown in Scheme 1.

$$(RMgX)_2 \rightleftharpoons 2RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons R_2Mg.MgX_2$$

Scheme 1: Schlenk Equilibrium

The Schlenk equilibrium[7] is the best representation of the Grignard reagents in solution, though direction of the equilibrium depends on the concentration as well as coordinating ability of the solvent, steric hindrance due to solvent molecules, and the temperature. The value of equilibrium constant in different solvents is given in Table 2[7].

Table 2: Equilibrium constant values for various Grignard reagents in Et_2O and THF solvent

Reagent	**Solvent**	**K_{eq}**
CH_3MgBr	Et_2O	~320
CH_3MgBr	THF	3.5
C_2H_5MgBr	Et_2O	482
C_2H_5MgBr	THF	5.09
C_2H_5MgCl	THF	5.52

Several dimeric structures of Grignard reagents are also present in solution; two of them are shown in the Figure 1. In Et_2O, X=F, Cl, Br, I and in THF X=F

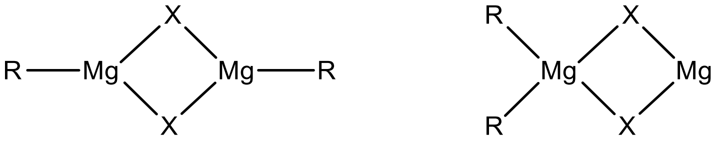


Figure 1: Dimeric species of Grignard reagent

It has been reported[8] that the order of stabilization on interaction with solvent molecules decreases in the order as MgX_2>RMgX> R_2Mg, with groups as Ph> Me > Et and halogen X as Cl> Br. All alkyl and aryl magnesium chlorides are reported to be monomeric in THF over a wide range of concentration (0.1-3.5 M), in contrast to this all alkyl and aryl magnesium chlorides are dimeric in Et_2O. This difference in coordinating abilities is a consequence of the Lewis basicity of the solvent molecule. Thus more basic the solvent, more it will coordinate to the metal centre, and hence lesser will be the dimerisation. Since THF is a stronger base it forms more stable acid base complex with the magnesium atom, which is electrophilic in nature. However, since THF is less sterically hindered than diethyl and therefore more number of solvent molecules can be coordinated to the metal as compared to latter.

1.4 Organofluorine compounds and its Importance

Under a broad definition, organofluorine compounds can be defined as the organic compounds containing C-F bond. These are rare in nature but play important roles in fields of science and technology. This small atom with great benefits is important in fields such as pharmaceuticals[9], pesticides[10], fluoro liquid crystal[11]. The C-F bond mimics the biological activity of C-O or C-H bond, due to small difference in their biological and chemical properties, and therefore, enzymes do not differentiate C-F bond from C-H/C-O bonds. Hence, monofluoro aromatic compounds are similar to corresponding nonfluorinated aromatic compounds. This property of C-F bond finds many applications in drug industry. For example, drug SCH 48461[12], used for lowering cholesterol, is metabolically unstable due to enzymatic hydroxylation and oxidative degradation reactions of aryl rings. In contrast, the analogous drug ezetimibe, with fluorine substituent on aryl rings has shown improved pharmacokinetics, and has shown improved activity than former due to the prevention of metabolic oxidation of the aryl ring by enzymes. Some of the other drugs are Ciprofloxacin (antibacterial agent), Linezolid, which shows increased efficacy and potency in vivo. Substitution of labile C-H bond with relatively stronger C-F bond also gives metabolic stability to the drug. Fluorinated drugs are lipophilic in nature, and thus the effective concentration of the drug is more at the enzyme/receptor active sites. The relatively lipophilic molecules have higher binding efficiency to the less polar binding sites of enzymes, thus relatively lower dose of the drug is required for optimal efficacy[13]. Hence organofluorine compounds find numerous applications due to above-mentioned properties of fluorinated compounds.

Reactions of Fluorinated compounds are difficult due to high bond strength of C-F bond as mentioned earlier**,** and these bonds are thermally, chemically and photochemically stable. Therefore, coupling reactions of these compounds with various nucleophilic reagents to the corresponding substituted product is very difficult and challenging[14]. Now, since C-F bond is a polar bond with partial negative charge on fluorine atom and partial positive charge on carbon atom, therefore, one can easily think of its reaction with some nucleophilic alkyl reagents for the formation of C-C bond. Few of the classical methods for the activation of C-F bond may be coupling with functionalized organometallic starting material such as Grignard reagent (RMgX), organoboron reagents ($RB(OH)_2$) , organolithium (RLi) or organozinc (R_2Zn) which renders the alkyl part nucleophilic due to Umplong nature of these compounds.Another way of carrying out this C-C bond conversion is to use mixed halides compounds like fluorinated aryl chlorides or bromides where the reaction takes place by nucleophilic substitution of Cl or Br atom, but since such mixed halides are expensive they cannot be used. S_NAr[15] is also another method for such conversion in which aryl C-F bond can be activated by nitro group or any other electron withdrawing group present on the aryl ring which stabilizes the negative charge due to incoming nucleophile and leads to substitution of fluorine atom with nucleophile. Transition metals are also very useful for the purpose. Some of the well known transition metal catalyzed reactions like Heck[16](Palladium), Kumada[17](Nickel/Palladium),Sonogashira[18](Palladium), Suzuki[19](organoboron reagent, Palladium) and Negishi[20](organozinc reagent, Nickel) were used for the synthesis of organofluorine compounds. But these methods have many challenges likerequirement of a complex system as well as harsh conditions, and contamination of metals. Therefore,economic and useful methods at industrial purpose were developed and were in high demand to avoid the drawbacks of earlier methods. Lithium reagents were used without transition metal catalyst in 1960's, but due to its high reactivity these reagents showed less selectivity and di- and tri- substituted products were also obtained. Also, the handling of lithated reagents is very difficult. Since then researchers have focused on finding new catalytic ways for the transformation of C-F to C-C bond. Earlier, the simple yet powerful way of using Grignard reagents as the nucleophilic reagents for the substitution reactions without transition metal catalyst has not got much attention. But researchers have now developed the method which is popular now a day is to use some activating as well as directing groups which are mostly nitrogen containing compounds for the transformation of polyfluorinated aryl C-F to C-C bond. The alkyl C-F bond can also be cleaved without the need of any activating group as they are much weaker than aryl C-F bonds.

In 1973, Kumada[21]reported the first example of catalytic C−C cross-coupling of fluorobenzene with Grignard reagents by nickel catalysts.In 1978, Meyers [22]reported the first directing group-promoted coupling reactions between Grignard reagent and fluorobenzene bearing an oxazoline moiety as activating group in the ortho-position to the C−F bond.In 1999, Cahiez et al.described the cross-coupling reaction of Grignard reagents with an aryl fluoride bearing imino group in the ortho-position in the presence of $MnCl_2$ (10 mol %). They also indicated that in the absence of $MnCl_2$ the yield of coupling product decreased.Manabe et al.[23]developed the first examples of ortho-selective cross-coupling of fluorobenzene derivatives bearing electron-donating groups (OH, CH_2OH, and NH_2) with Grignard reagents in the presence of Pd-based catalysts.In 2009, Matsubara[24] showed reactions between Grignard Reagents and non functionalized/ unactivatedfluoroalkanes without metal catalyst. The reaction was specific to PhMgCl and proceeded via activation of an alkyl C-F bond. When MeMgCl or $MgCl_2$ were used then only halogen exchange reactions were reported due to Lewis acidity and high affinity of magnesium for fluorine atoms. Mechanism showed that both concerted and electron transfer (free radical) pathways were possible[1]. Recently, many research groups have been working actively on this theme of C-F activation with the help of Grignard reagents. Cao[25] developed a cross coupling of Grignard reagent and polyfluoroarenes using pyridine as a directing group in ortho position. Pyridine acted as a coordinating ligand and activated ortho C-F bond in preference to C-H bond in absence of metal catalyst. Though pyridine acts as a weak electron-withdrawing group in S_NAr reaction it acted as a strong coordinating ligand and is responsible for the activation of C-F bond. They also discussed that pyridinyl nitrogen and fluorine atom should be at a suitable distance for the complete transformation and the reaction proceeded via a six-member transition state. In the same year, Jin[26] reported the Sonogashira type reaction of aryl fluorides and terminal acetylenes with sodium, calcium hydroxide and sodium methoxide and isolated high yields of substituted C-C triple bonds. Li[27] reported a simple method for to the preparation of alkylated or arylatedpolyfluoro pyridine compounds at room temperature except for hexafluorobenzene which is at 60°C. According to their study, an increase in temperature does not necessarily lead to expected products, due to formation of homo-coupled byproducts of Grignard reagents in the reaction.Lu[28] developed the regioselectivenucleophilic substitution of polyfluoroarenes with Grignard reagents to get fluorinated benzaldehyde without transition metal catalyst activated by an imine group in the ortho position of C-F bond.The reaction becomes competitive when the group attached to nitrogen was changed to an electron-withdrawing group, which increased the nucleophilicity of the imine carbon, and hence addition reaction takes place instead of substitution of fluorine atom. However, this competition was overcome by substituting isopropyl groups (which was bulkier) at ortho position of benzene attached to nitrogen.

In this thesis, we present a computational study for the mechanistic pathway and the prediction of transition states for the reactions involving alkyl fluoride with both alkyl and aryl Grignard reagents. We will also discuss the routes for the activation of C-F bond and why it is a challenge to activate such bonds with classical methods. After this we will proceed to importance of Grignard reagents in synthetic methodology and the reaction of Grignard reagents with compounds containing C-F bond for the formation of C-C bond without transition metal catalyst.

Chapter 2

2 Computational Methodology

The electronic wave function for monatomic molecules is relatively simple and can be calculated easily but the problem comes with the electronic wave function of polyatomic molecule, which depends on bond distance, bond angles, and dihedral angles. The equilibrium bond distances, bond angles and dihedral angles are then found as the values that give the minimum electronic energy including nuclear repulsion. There are four main approaches for doing this (a)Semiempirical methods (b) *Ab initio* methods (c) DFT method and (d) molecular mechanics method. Semiempirical methods use a simpler Hamiltonian than the correct molecular Hamiltonian and use parameters whose values can be adjusted to fit experimental data or the results of ab initio calculations. In contrast, Ab initio (Latin for "from the beginning") method or the first principle calculations uses the correct Hamiltonian and does not use experimental data other than the values of physical constants.

2.1 Hatree-Fock Method

Hatree-Fock (HF) method is the basis for the use of atomic and molecular orbitals in many-electron systems. The Hatree SCF (Self Consistent Field) method approximates the atomic wave function as a product of one spatial orbitals and finds the best possible forms for the orbitals by an interactive calculation in which electron is assumed to move in the field produced by the nucleus and a hypothetical charge cloud due to other electrons.

To increase the accuracy of the method the wave function is taken as an antisymmetrized product of one electron spin-orbitals and the best possible forms for the spatial orbitals is found in the spin orbitals. Hatree-Fock calculations are done by expanding each orbital as a linear combination of basis functions and iteratively solving the Hatree-Fock equations. The Slater type orbitals are used as basis functions for HF method.The difference between exact nonrelativistic energy and the Hatree-Fock energy is the correlation energy of the atom or molecule. Since ab initio SCF MO calculation uses the approximation of taking Ψ as an antisymmetrized product of one electron spin orbitals and uses a finite and hence incomplete basis set, therefore there is need of some accurate and more realistic methods. Hence DFT is used to fill the gap made by not including correlation in HF methods.

2.2 Density Functional Theory (DFT)

Density Functional Theory has become an important method for quantum mechanical simulations for the past 30 years but only recently it has been used by the chemists for simulation of energy surfaces in molecules.

$$\Psi H = E\Psi$$

The Hamiltonian operator in the above equation involve on the coordinates of one or two electrons only. In order to know the total energy it is not necessary to know the 3N dimensional wave function. Here, the DFT comes into play. The DFT method does not calculate the molecular wave function but calculates the molecular electron probability density ρ and calculates the molecular orbital energy fromρ.In 1964 Hohenberg and Kohn proved two theorems. The first theorem states that:

The electron density determines the external potential (to within an additive constant)

The electron density uniquely determines the Hamiltonian operator in the equation above. Thus Hamiltonian can be calculated from the density by the integration all over the space.The second theorem states that:

For any positive definite trial density, ρ_t, *such that* $\int \rho_t(\mathbf{r})d\mathbf{r} = N$ *then* $E[\rho_t] \geq E_0$

The proof of this theorem is straightforward. From the first theorem we know that the trial density determines a unique trial Hamiltonian a wave function Ψ_t;

$$E[\rho_t] = \langle \Psi_t | H | \Psi_t \rangle \geq E_0,$$

follows from the variational theorem of Schrodinger equation.

In the 1964 paper of Hohenberg and Kohn, it was proved that the total electron density ρ completely and exactly determines all the (ground-state) properties of an *N*-electron system. Thus, ρ can be used as the fundamental "variable" in electronic structure theory.

$$V_{ext} \rightarrow \Psi_0 \rightarrow \rho \text{ or } V_{ext} \rightarrow \rho$$

For molecules with a nondegenerate ground state, the ground state molecular energy, wave function and all other molecular electronic properties can be uniquely determined by the ground state electron probability density $\rho_0(x, y, z)$, a function of only three variables, i.e. $E_0 = E_0[\rho_0]$. For calculations, which require energy calculations at the surface DFT offers a practical and an accurate alternative.

2.2.1 Methods and Basis sets

Any exchange functional can be combined with any correlation functional. B3LYP denotes a density functional calculation done with the Becke[29] 1998 exchange functional and the Lee-Yang-Parr[30] correlation functional. The basis set we have used here 6-311+G (2d, p) and 3-21G*. 6-311+G (2d, p) basis set is single zeta for the core atomic orbitals, triple zeta for valence atomic orbitals. The plus sign indicates diffuse functions on all atoms, the letters in parentheses indicate the two sets of five d-type Gaussian polarization functions are added to each non-hydrogen and one set of three p-type Gaussians. 3-21G* is a double zeta for valence atomic orbitals with one five d-type Gaussian polarization function. For second row elements 3-21G and 3-21G* are same. All the computational calculations are performed using Gaussian09[31] software. First principles methods have been applied for the optimization of different structures. Gauss View package was used drawing the preliminary structure and viewing the optimized structures.

We have used a lower level HF/3-21G* method for the optimization and B3LYP/6-311+G (2d, p) for the single point energy calculations of the optimized structures to lower the cost of calculations. We tried two ways for the optimization of the structures: (a) optimization with B3LYP/6-311+G (2d, p) and (b) optimization with HF/3-21G* and then single point energy calculation with B3LYP/6-311+G (2d, p)[29,30] and it was observed that both the results are very close within the error of approximations followed for the methods. Therefore, we decided to proceed via the second way, which saves time and also does not compromise with the accuracy of the results. Moreover, QST2[32] (without initial guess of transition state) calculations were used for the prediction of the most probable transition state from the most probable structures of reactants and products. Relaxed PES Scan has also been performed for the scanning of the bonds which undergo change while going from reactants to products for the confirmation of the transition state. All bond distances are in Å and energies have been calculated in kcalmol^{-1}.

2.3 Transition state

To know the regioselectivity of the reaction one need to know about the course of the reaction i.e. how the reaction is proceeding, the bonds which are broken and formed, and this is determined by the potential energy function for nuclear motion U. The geometry of a nonlinear molecule with N nuclei is defined by 3N-6 independent nuclear coordinates q_1, q_2,……..,q_{3N-6} and its electronic energy U is a function of these coordinates. Here U is a function of only one variable i.e .internuclear distance R and the function U gives the potential energy surface. When U is calculated at a particular fixed arrangement of the nuclei then it is called a single point (SP) calculation Once U is determined, the path of minimum potential energy on U which connects the reactants and products is examined and this is the most favorable path for the course of the reaction. The point of maximum potential energy U on the minimum energy path is called the Transition state. Transition state is a saddle point on potential energy surface. This is called saddle because it is a maximum point on the minimum-energy path. The structures obtained at this point, the so called transition state are not stable and cannot be isolated, therefore certain physical properties such as entropy, free energy and vibrational frequencies are used to confirm it. At a local minimum on the PES (Potential Energy Surface), all the vibrational frequencies are real numbers whereas since transition state is a first order saddle point it can have only single imaginary frequency. Other higher order saddle points have two or more imaginary vibrational frequencies and cannot be called as transition state[33].Reactants, Products and intermediates correspond to local minima. A reaction intermediate lies at a minimum in U for all nuclear displacements. To find a first-order saddle point (transition structure) a maximum needed to be discovered in one and only one direction and minima in all other directions. Quasi-Newton methods are efficient for minimizations but for finding transition structure they have smaller radius of convergence. The linear synchronous transit algorithm (LST) searches for a maximum along a linear path between reactants and products (in distant matrix space), though this method is useful but it gives the structure with more than one negative eigen values. Therefore an improved method is used which is quasi synchronous transit (QST) method is used. It searches for a maximum along a parabola connecting the reactants and products, and for a minimum in all the directions perpendicular to the parabola. QST2 requires two molecule specifications, for the reactant and product as its input while QST3 requires three molecule specifications, the reactant, the product and an initial structure for the transition state in that order. The order of the atoms in the atoms must be identical within all molecule specifications.

The main objective of our study is to predict the most probable mechanism and to find out the transition state for the reaction of organofluorine compounds with Grignard reagents to form the C-C bond. This type of nucleophilic substitution reaction with weak Lewis acidic Grignard reagents without metal catalyst is difficult due to high bond strength of C-F bond. In order to carry out this research we have used computational methods to understand the mechanism, HF (HatreeFock) and DFT (Density Functional Methods) have been used for the optimization of the structures and QST2 (Quasi Synchronous Transit) for the prediction of transition state.

Chapter 3

3 Activation of Aliphatic C-F bond with Grignard reagent

In this chapter we will discuss the activation of C-F bond of saturated carbons i.e. sp^3hybridized without the assistance of transition metals. We will also give emphasis how the reaction proceeds and what all bond parameters changes while undergoing the transformation from reactants to products.

A computational study was carried out on the plausible predicted mechanism for the reaction between Grignard reagent and the unactivated sp^3alkyl fluorinated compounds, to highlight the mechanistic pathway and to predict the transition state. The analysis is done on gas phase reaction and the reactivity of PhMgCl versus CH_3MgC.It was observed that alkyl C-F bonds can react with Grignard reagent without the need of activating group and this reactivity is attributed to the comparatively longer bond length of sp^3C-F bond (1.43Å) as compared to sp^2C-F bond (1.35Å) and therefore activation of unactivated alkyl C-F bond with weak Lewis acidic magnesium reagents has been successfully achieved in the absence of the transition metal catalyst[34].

3.1 Choice of alkyl group

In the start of our calculations, first we made a decision on selection of alkyl fluoride. So, we optimized the molecules containing C-F bond in primary, secondary, tertiary alkyl groups. We observed that tertiary carbon was most stabilized one among the three types of carbon and the same trend was observed in corresponding product also where the C-C coupled product with secondary carbon was stabilized by -78.7 $kcalmol^{-1}$ below the product with the primary carbon and the C-C coupled product with tertiary carbon was further stabilized by -39.3 $kcalmol^{-1}$ below the secondary carbon. This made us conclude that the reaction with tertiary carbon is most favorable and hence we proceeded with the C-F bond in tertiary carbon as our reactive carbon site. First alkyl group substitution on primary carbon makes it highly stabilized but further alkyl substitution on secondary carbon shows exactly half the stabilization. This also indicates that the reaction will be going through carbocationic nature and not carbonanionic nature of the reactive carbon which follows from the established stability of the carbocation i.e. 3°>2°>1° and carbanion stability as 1°>2°>3°. Thus, to explore the reaction further and to know the pathway of the reaction, we have carried out computational optimizations in our further work.

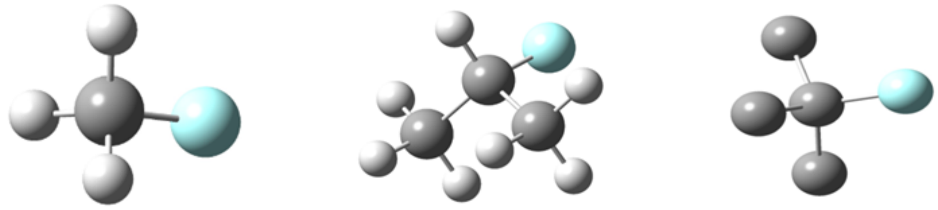


Figure 2: sp^3 hybridized carbons (a) primary (b) secondary (c) tertiary

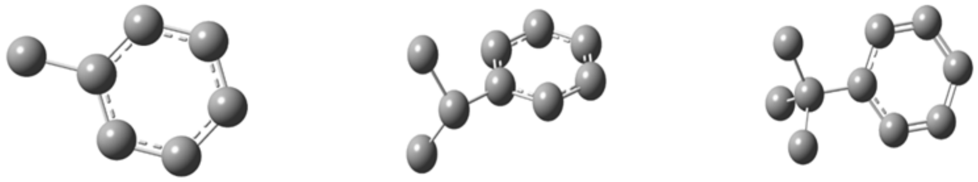


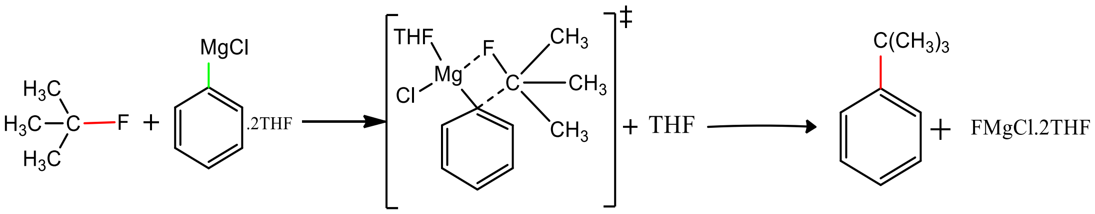
Figure 3: C-C coupled products with (a) primary carbon (b) secondary carbon (c) tertiary carbon(Hydrogen atoms are not shown for clarity)

3.2 Reaction of sp^3C-F with PhMgCl

We have studied three most probable mechanistic pathways for the reaction of sp^3C-F bond containing compounds with Grignard reagents:**(a)**Mono-solvated magnesium in the transition state **(b)**Magnesium is di-solvated in the transition state **(c)** the transition state with dimerization of Grignard reagent. These choices are based on the coordination ability of MG with solvent molecules and the existence of dimer of Grignard reagent as well as its participation in reaction mechanism.

3.2.1 Pathway 1: Mono-solvated Mg

When tertiary alkyl fluoride reacted with phenyl magnesium chloride then C-C coupled product i.e. substituted phenyl ring was formed. It was found that the reaction goes via an intermediate to give the desired product. The intermediate and product are stabilized by -42.04 and -45.8 kcal/mol as compared to energies of isolated reactants.



Scheme 2: Mechanism for reaction of sp^3 C-F bond with PhMgCl with Mg being mono-solvated in the transition state

The C-F and Ph-Mg bond lengths were 1.43 and 2.14 Å, respectively in the reactants. The proposed mechanism indicated that the intermediate was stabilized by -42.04 kcalmol^{-1} of energy below the reactants. This encouraged us to predict the actual transition state while going from reactants to intermediate. First, we performed QST2 calculations to get the transition state for the reaction. This produced a structure with energy of +32.6 kcalmol^{-1} above the reactants with an increment in C-F bond distance from 1.43 to 2.89 Å and in Ph-Mg from 2.14 to 2.16 Å. C-Ph bond distance was 4.16 Å and a new Mg-F bond formed with a bond distance of 1.80 Å. This clearly indicates that due to the high affinity of magnesium for fluorine the C-F distance increases and formation of Mg-F bond takes place. The single imaginary frequency confirmed it being a transition state.

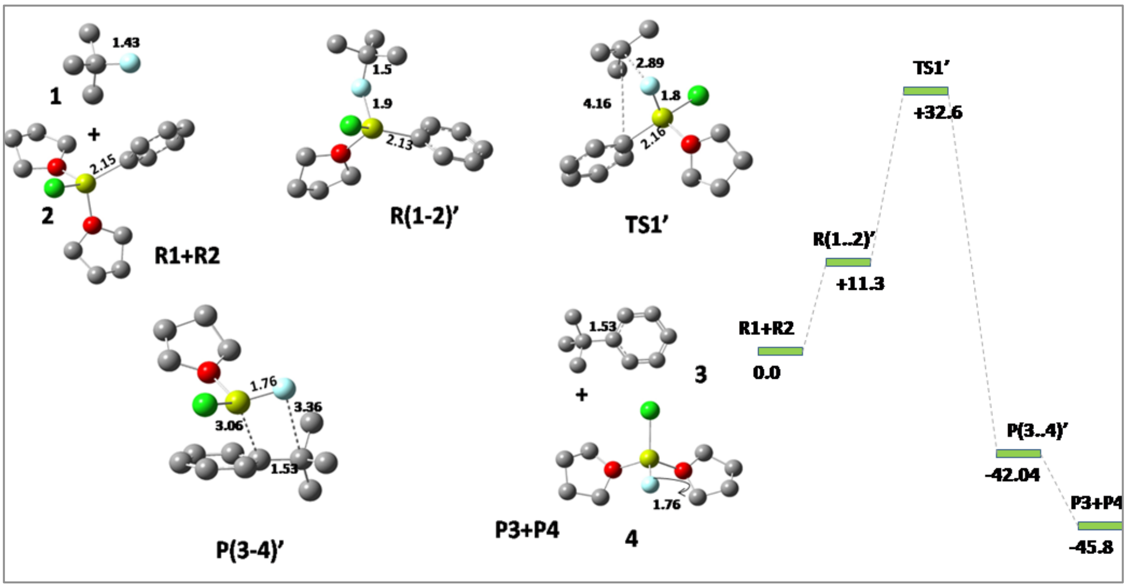
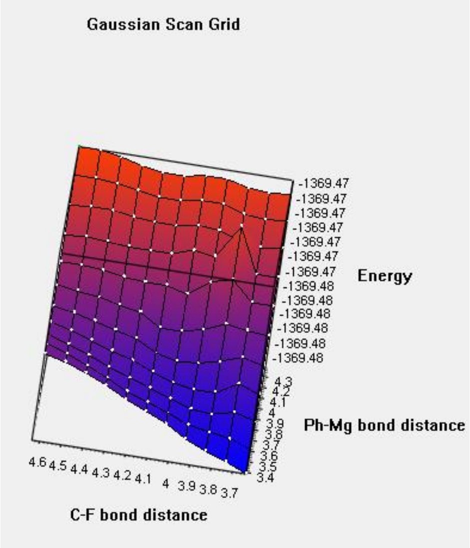


Figure 4: Optimized structures and energy profile diagram for scheme 2. Hydrogen atoms are removed for better visualization.

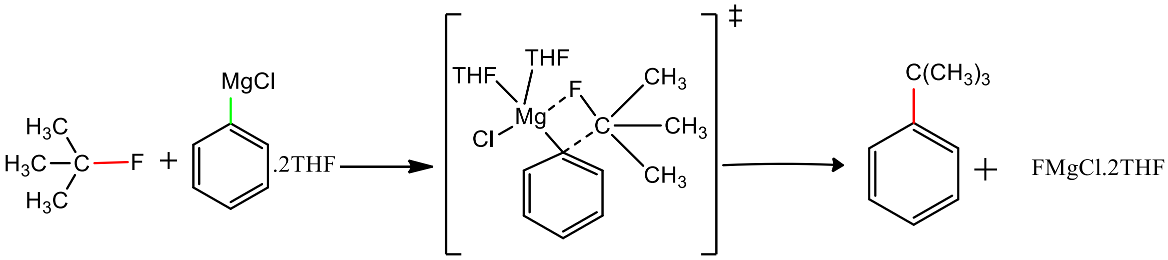
To know the complete reaction path, i.e. how the reaction goes from intermediate to the product, we again performed the relaxed PES scan. The C-F and Ph-Mg bond distances were scanned from 3.36 and 3.06 Å at intervals of 0.1 Å; the scanned potential energy surface revealed the highest energy structure having the same energy as intermediate i.e. -42.04 kcal/mol and C-F and Ph-Mg distances of 4.53 and 4.38 Å ,Ph-C and Mg-F bond length being the same as 1.53 Å and 1.76 Å, respectively. Hence, it implies that while going from intermediate to product there will be no energy maxima, and the only extra stabilization of the product is due to the coordination with THF solvent molecule.



So, we finally arrived at a transition state for the reaction which is at + 32.6 kcal/mol with C-F, Ph-Mg, C-Ph and Mg-F bond distances of 2.89, 2.16, 4.16 and 1.80 Å, respectively above the reactants.The above reaction follows stepwise mechanism with overall reaction being exothermic and the reaction proceeds via a transition state for which an activation barrier needs to be overcome. Because of more reactivity of tertiary alkyl fluoride as compared to primary alkyl fluoride we have taken tertiary alkyl fluoride for our calculations with phenyl magnesium chloride as Grignard reagent. In the reaction pathway the alkyl fluoride first undergo rehybridisation and then pyramidal inversion to form the substituted product. In the reactant the alkyl fluoride is sp^3 hybridized and magnesium in Grignard reagent is tetrahedrally coordinated, but while going from reactant to the transition state sp^3 carbon becomes planar and is now sp^2 hybridized with C-F bond distance changing from 1.43 to 2.89Å. This planarity of alkyl group motivated us to explore it further and possibility of it being a carbocation. We calculated separately the overall charge on this moiety and it was observed that the charge was not exactly equal to +1 and hence it is not a carbocation. In fact this planar alkyl moiety plays an important role in the mechanism and is very essential for the reaction to go forward. When this carbon is planar then the phenyl ring attacks and again the rehybridisation takes place which leads to the product formation.The Mg in transition state remains tetrahedrally coordinated where one of the solvent molecules has been replaced by fluorine due to high affinity of magnesium for fluorine.

3.2.2 Pathway 2: Disolvated Mg

Till now, we have discussed the mechanism with one solvent molecule explicitly attached to Mg in transition state but to examine whether 2 solvent molecules can be simultaneously attached to Mg, we explored the mechanism and predicted the transition state where Mg atom remains five coordinated. This type of five coordinated Mg is possible in the transition state as THF is not a bulky solvent like diethyl ether (Et_2O) and hence prevents the steric hindrance at Mg. The reaction barrier calculated through this pathway is ~3 $kcalmol^{-1}$ lower than the mechanism with 4 coordinated Mg in the Transition state. This extra stability and hence lower activation barrier for the reaction is due to the extra solvent molecule and Lewis acidity of magnesium atom. The overall reaction remains exothermic with – 45.8 $kcalmol^{-1}$release of energy.



Scheme 3: Plausible predicted mechanism for sp^3 C-F bond with Grignard reagent where Mg is disolvated in the transition state

The reaction proceeds via a four membered cyclic transition state where Mg-Ph bond length is 2.15Å, C-Ph is 2.89Å, C-F is 3.42Å, and Mg-F is 1.82Å. It was observed that while going from reactant to product the Mg-Ph bond distance increases from 2.15 to 2.30Å and C-F distance from 1.43 to 3.418Å, simultaneously the C-Ph bond and Mg-F bond starts forming. The high activation energy i.e. 29.4 $kcalmol^{-1}$ is due to pyramidal inversion and rehybridisation of the reacting alkyl group carbon during C-C bond formation. The alkyl group becomes planar so that now the phenyl group from the Grignard reagent can attack from the opposite side and C-C bond formation can take place. After that the usual reaction path was followed.

As it can be seen that when Mg is 4 coordinated **(Scheme 2)**C-Ph bond distance is 4.16Å which is quiet high for an interaction to be made , whereas when Mg is 5 coordinated (**Scheme 3**) this C-Ph bond distance decreases comparatively and is now 2.89Å which is more realistic for a bond to be formed. Hence, it can be concluded that second mechanism is the actual mechanism while undergoing the reaction.

The reaction goes directly to the product from the transition state and no intermediate is involved.

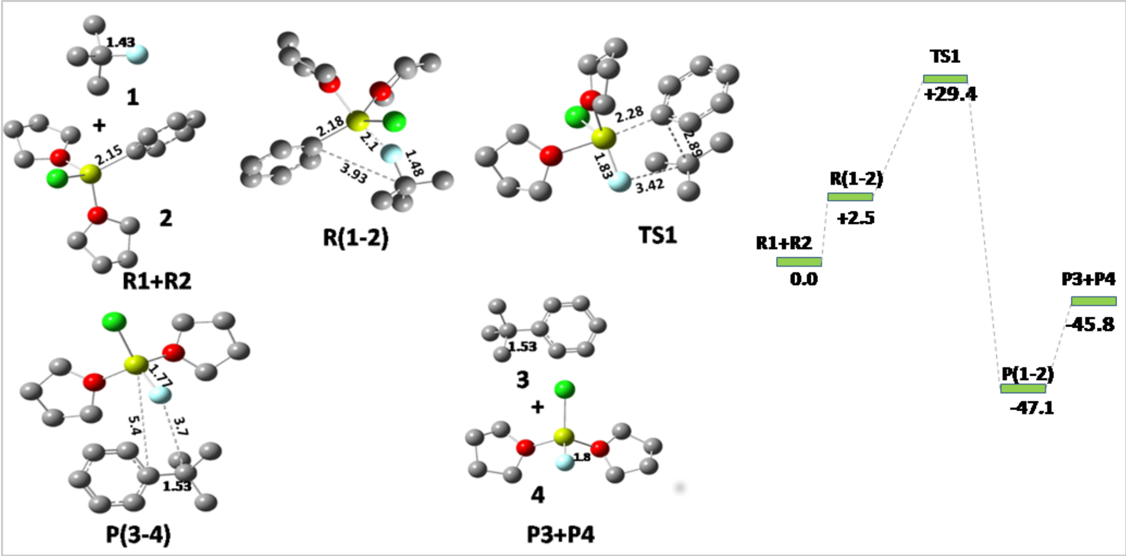
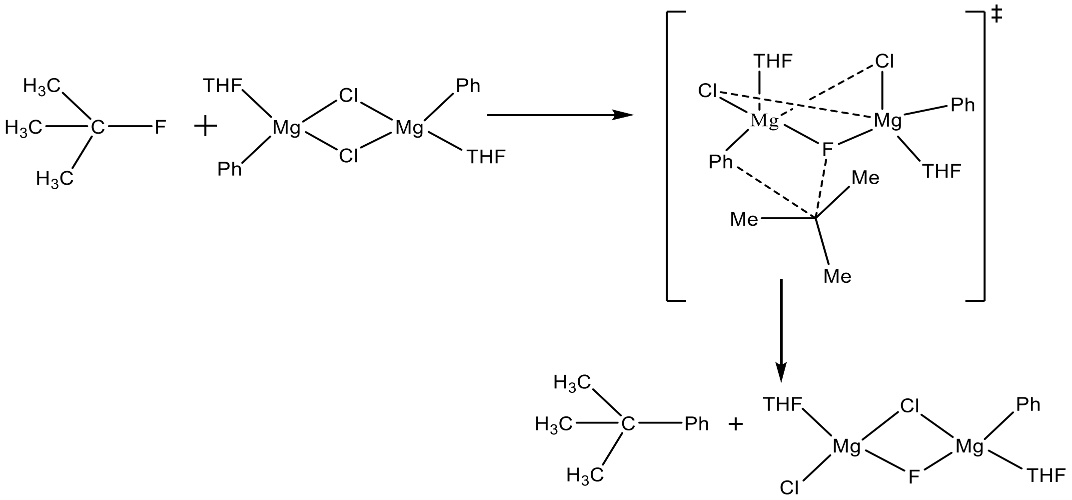


Figure 5: Optimized structures and energy profile diagram for scheme 3

3.2.3 Pathway3: Dimerization of Grignard reagent

According to Schlenk equilibrium Grignard reagent can exist in dimeric form also. So, here we predicted the mechanism via the dimeric pathway where the Grignard reagent is in the dimer form (PhMgCl)$_2$.(THF)$_2$ which then reacts with the sp^3C-F bond. The reaction barrier is now only + 16.9 kcalmol^{-1} which is very low as compared to the monomeric pathway. Hence, the most favorable pathway for the C-C bond coupling reaction is via the dimerization of Grignard reagent. Firstly, the Grignard reagent gets dimerized according to Scheme 4.



Scheme 4: Plausible mechanism for C-F activation with dimer of Grignard reagent

The two chlorine atoms forms the bridge between two Mg atoms, each Mg atom remains 4 coordinated which is the most stable coordination number of magnesium in Grignard reagent. Now, alkyl C-F bond approaches the Grignard reagent and where two main interactions take place; one is between Mg-F and another is between C-Ph and a transition state starts forming. In the transition state fluorine acts as the bridging atom between two Mg atoms with Mg-F bond distance of 1.87Å, each Mg atom remains tetrahedrally coordinated. It was observed that the reaction proceeds via the linear dimeric pathway instead of traditionally followed cyclic dimer pathway via a 4 membered cyclic transition state, with reactive alkyl group being planar. The various bond distances are Mg-Ph (2.15Å), Mg-F (1.87Å), C-F (3.8Å), and Ph-C (4.09Å).

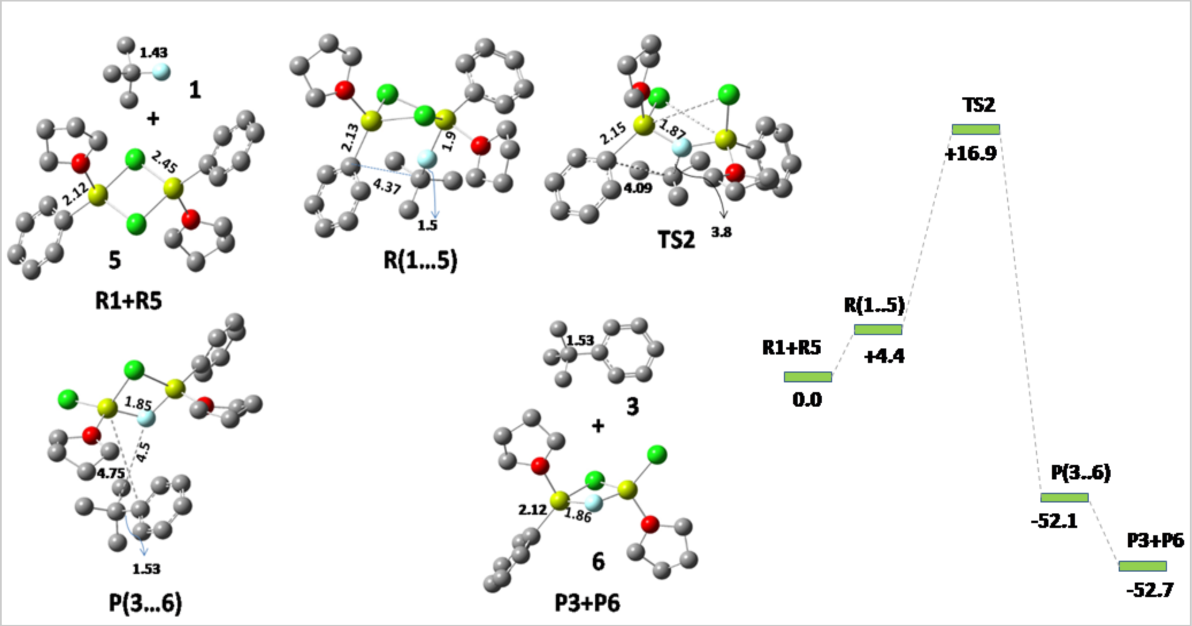


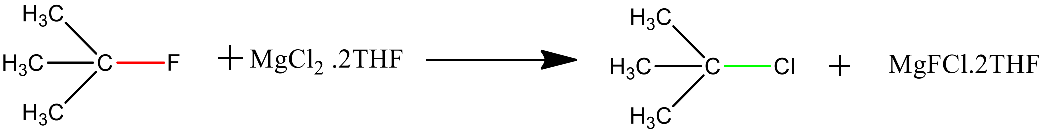
Figure 6: Optimized structures and Energy profile diagram for scheme 4

3.3 *Reaction of sp^3C-Cl with PhMgCl*

3.3.1 Monomer mechanism

To further explore the scope of the reaction we changed the Grignard reagent to Methyl Magnesium chloride (MeMgCl).According to Schlenk equilibrium when MeMgCl is used, then the reaction is more towards the right side of the equilibrium **(Scheme 1)** and hence instead of monomeric MeMgCl, $MgCl_2$is present in larger amount and therefore it was observed that only the halogen exchange and no C-C bond formation reaction takes place in the first step. This is mainly due to the predominantly existing $MgCl_2$ species in the reaction and due to higher affinity of magnesium for fluorine than for chlorine, fluorine being more electronegative.

The first step remains exothermic and if further PhMgCl is added then the same reaction path is followed as for fluorine above and the reaction is more exothermic due to low bond energy of C-Cl bond.



Scheme 5: Reaction of organofluorine compound with $CH_3MgCl/MgCl_2$and subsequent reaction with PhMgCl

Here also we have explored the transition state for the reaction but with the monomer mechanism where the Mg is attached to two solvent molecules in the transition state. The mechanism is quiet similar with the fluorine atom. The reaction proceeds via a four membered transition state with bond distances as Mg-Ph 2.23Å, Mg-Cl 2.49Å, C-Ph 3.43Å, and C-Cl 4.14Å. The activation energy for the reaction is +23.48 kcalmol^{-1} above the reactants. This a exchange reaction where to make C-C bond Mg-Ph bond is exchanged with Mg-X, where X is the halogen atom, in our case it is chlorine. To undergo this exchange Mg-Ph bond length increases and simultaneously C-Ph bond starts forming and the carbon at the reaction site becomes planar to facilitate the attack. Since it is easy to break the C-Cl bond as compared to the C-F bond due to comparatively longer bond length in the former therefore it was observed that the reaction barrier is also comparatively smaller in C-Cl transformation to C-C bond formation as compared to C-F bond transformations. A close inspection of the transition state revealed that since the tertiary carbon has the carbocationic character in the transition state, it sits on the top of the pyramidal like structure from where it has interactions with the electron rich atoms which are Ph ring, two chlorine atoms. The sp^3 carbon and Ph ring are lie almost perpendicular to each other at a distance of 3.43 Å. These are the required conditions for the reaction to go forward. After this step the reaction proceeds smoothly with the complete separation of the two products gives the final release of energy.

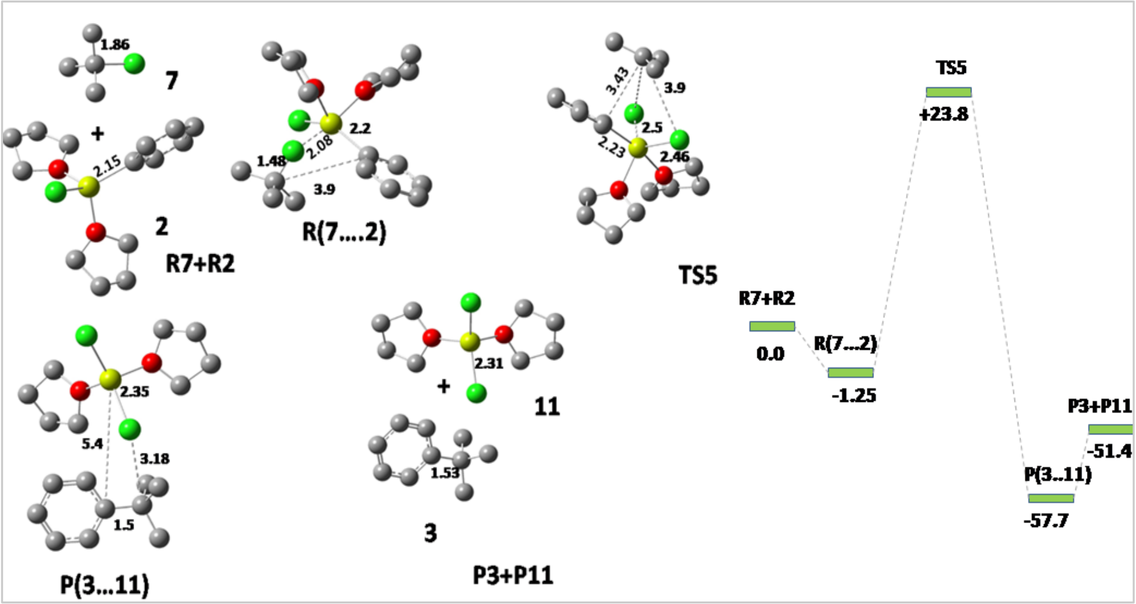
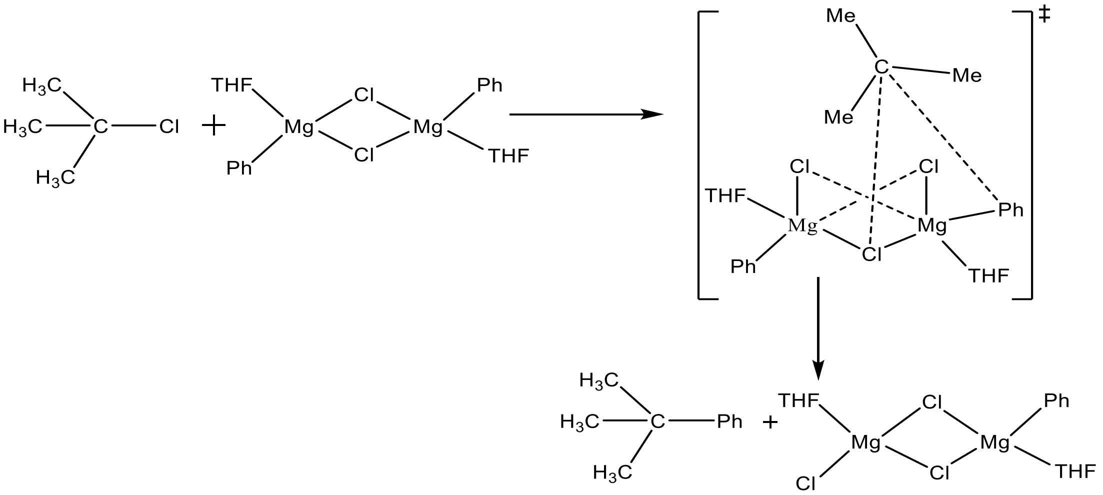


Figure 7: Optimized structures with energy profile diagram for C-Cl bond activation with PhMgCl for scheme 5

3.3.2 Dimer Mechanism

The reaction with the dimerised Grignard reagent was explored to know whether C-Cl bond also favors the transformation to C-C bond via dimeric pathway the way C-F bond preferred or not. The reaction proceeds with an energy barrier of +25.1 kcalmol^{-1} and the separated products are stabilized by -47.06 kcalmol^{-1} energy. In the transition state structure the two magnesium atoms were found to be tetrahedrally coordinated with Cl atom acting as bridging atom between two magnesium atoms. The sp^3 alkyl moiety was found to be planar and lies above the other atoms.



Scheme 6: Plausible mechanism for the activation of C-Cl bond with dimer of PhMgCl

The high bond distances i.e. C-Ph=4.15Å and C-Cl=6.02Å implies that the four membered transition state has not formed here. This can be predicted due to low bond strength of C-Cl bond because of which chlorine atom readily gets transferred to electropositive magnesium atom. Hence it can be concluded that the C-C bond formation from C-Cl bond proceeds via the monomer mechanism instead of dimer mechanism.

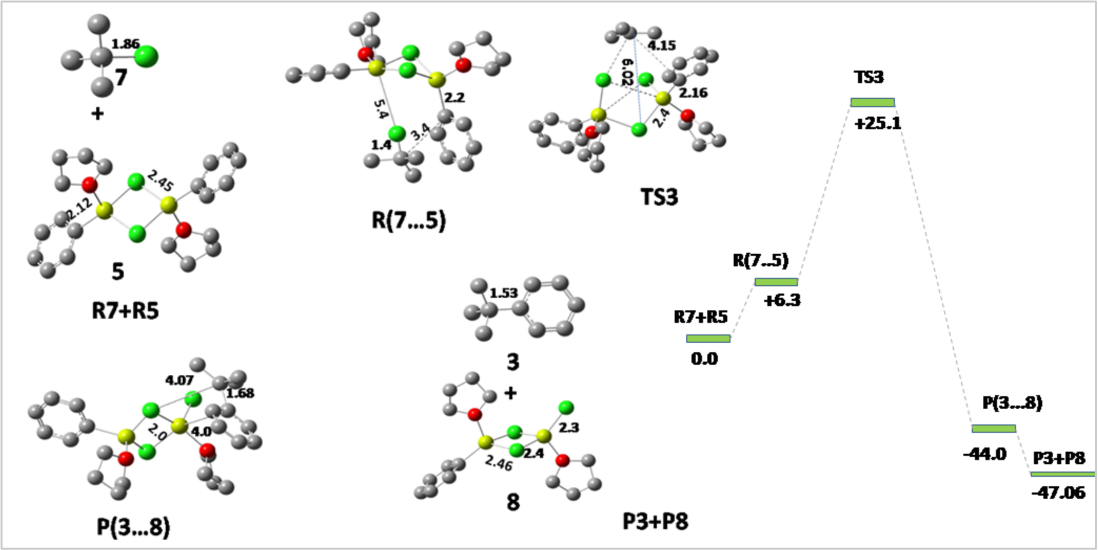
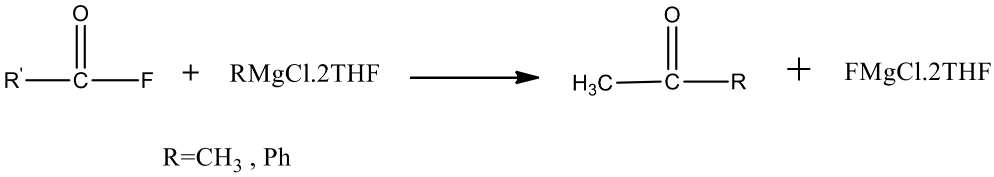


Figure 8: Optimized structures and energy profile diagram for scheme 6

3.4 Reaction of acetyl fluoride with PhMgCl

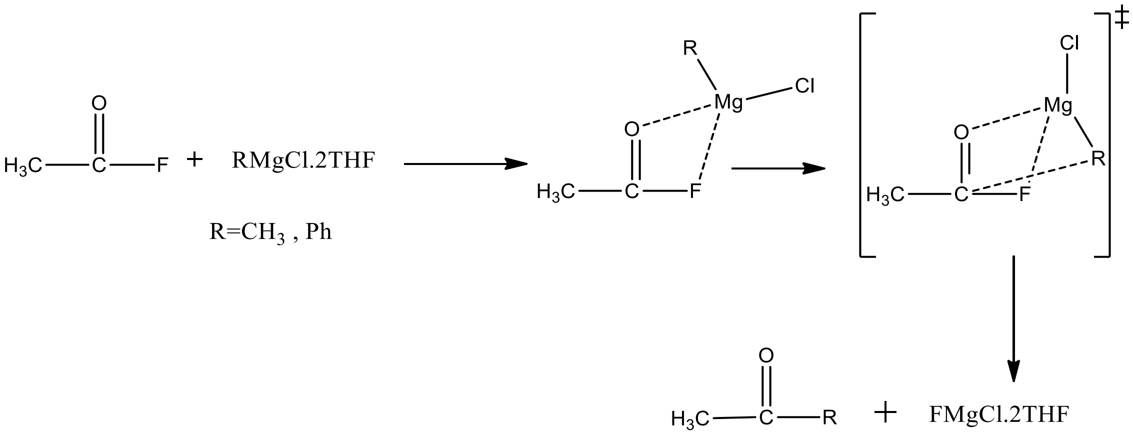
3.4.1 Monomer mechanism

After exploring the reaction mechanism for sp^3C-F bond with Grignard reagent we were enthusiastic to know how the reaction proceeds with the alkyl sp^2C-F bond, with directing group. So, we have tried to explore the mechanism and also predicted the feasibility of the reaction with PhMgCl and CH_3MgCl Grignard reagent. For simplicity we have taken $R'=CH_3$**(Scheme 6)**.This type of activation is difficult because of increased partial positive charge on the carbonyl carbon which leads to a stronger bond strength of C-F bond (1.38Å). There has been a computational study where acetyl group acts as an activating/directing group in activating C-O bond by Grignard reagent[35]. To know how the C-F bond behaves when it is directly attached to the carbonyl carbon we carried out the theoretical calculations and have predicted the transition state in the mechanism.



Scheme 7: Reaction of acetyl fluoride with Grignard reagent

The reaction mechanism pathway for the gas phase reaction between acetyl fluoride and PhMgCl/CH_3MgCl to give ketone as product is studied. Firstly, a reaction pathway was predicted (**Scheme 7**) and then the optimizations and energy calculations were performed by the same methods and basis set as mentioned above. The product was stabilized by -56.47kcal/mol of energy with PhMgCl as well as with CH_3MgCl, indicating that the reaction is equally probable with both PhMgCl and CH_3MgCl.



Scheme 8: Plausible predicted mechanismfor the reaction in scheme 7

To confirm the transition state we carried out QST2 calculation and we got exactly the same transition state as predicted in the mechanism with one imaginary frequency, with Mg-O bond length of 3.06, Mg-F of 1.87, Mg-R of 2.14 Å, this clearly indicates that as Mg comes in an environment of more electronegative element it starts coordinating to fluorine and simultaneously the R-Mg bond weakens to facilitate the formation of C-C bond. A 4 membered transition state is formed with magnesium simultaneously coordinating to fluorine and oxygen atom. Similar pathway was followed by MeMgCl.

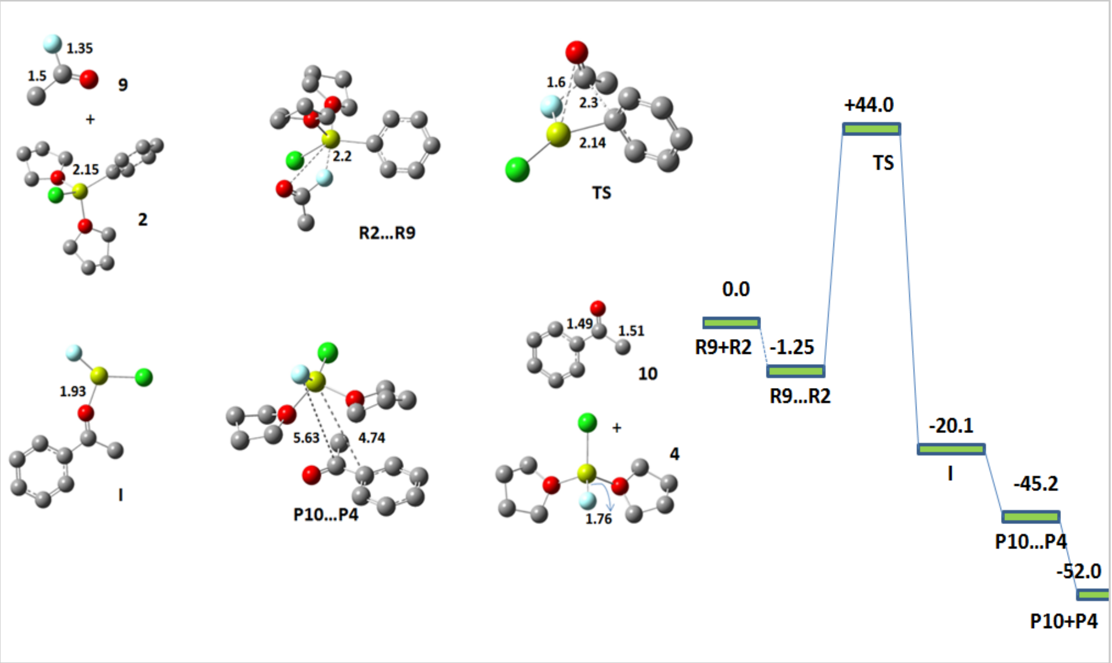
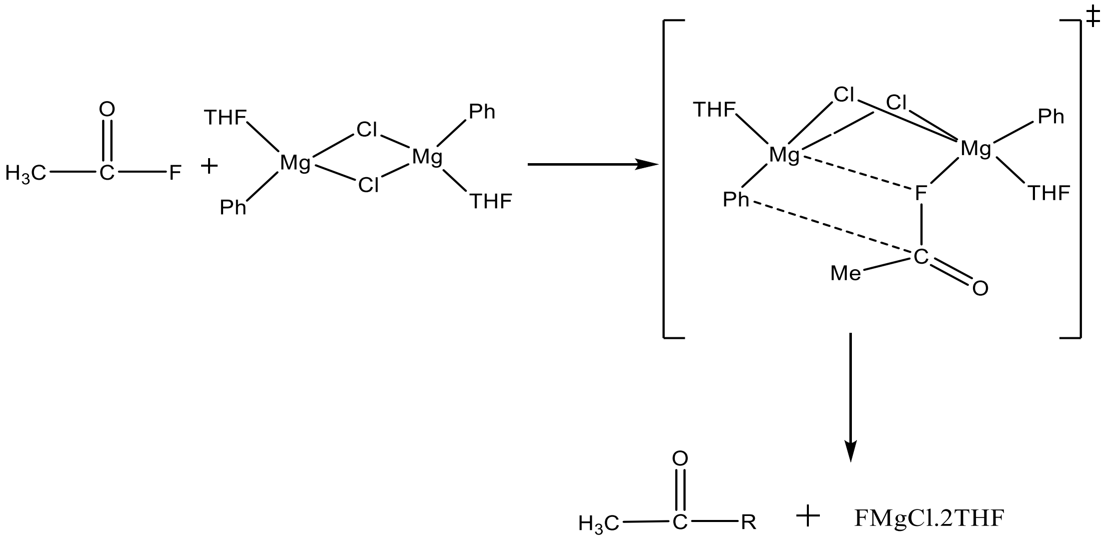


Figure 9: Optimized structures and energy profile diagram for scheme 8 where R=Ph

3.4.2 Dimer mechanism

In the dimer pathway the reaction barrier was found to be +11.3 kcalmol^{-1} and reaction stabilizing energy of -57.7 kcalmol^{-1}. A cyclic four membered transition state was observed with C-Ph bond distance of 3.73Å, Mg-F of 3.14Å, Mg-Ph of 2.14Å and C-F of 1.46Å. In the transition state structure the two bonds C-Ph and Mg-F bond starts forming. Since sp^{2}C-F is a strong bond the fluorine atom does not act as the bridging atom in the T.S. instead it remains bonded to carbonyl carbon.

To confirm the transition state we carried out QST2 calculation and we got exactly the same transition state as predicted in the mechanism with one imaginary frequency. A very low reaction barrier of +11.3 kcalmol^{-1} was observed in this case, which is due to stabilization of acylium ion due to +R effect of oxygen atom. In the first step of the mechanism reactants **R9** and **R5** remain as separated reactants , then as they start coming close they make an interaction with Mg-F bond distance of 2.0Å, C-F of 1.44Å, Mg-Ph of 2.13Å and C-Ph of 4.06Å as shown in structure **R(9…5)** (**Figure 4).** In the next step they form a nice four membered transition state where C-Ph bond distance further decreases to 3.7Å and C-F distance increases to 1.9Å. The reaction barrier is due to inability of carbonyl carbon of acetyl fluoride to undergo rehybridisation from sp^2 to sp by transfer of fluorine atom. Then nucleophilic attack of the phenyl group from Grignard reagent takes place onto the carbonyl carbon to form the C-Ph bond.



Scheme 9: Plausible mechanism for C-F activation in acetyl fluoride with Grignard reagent

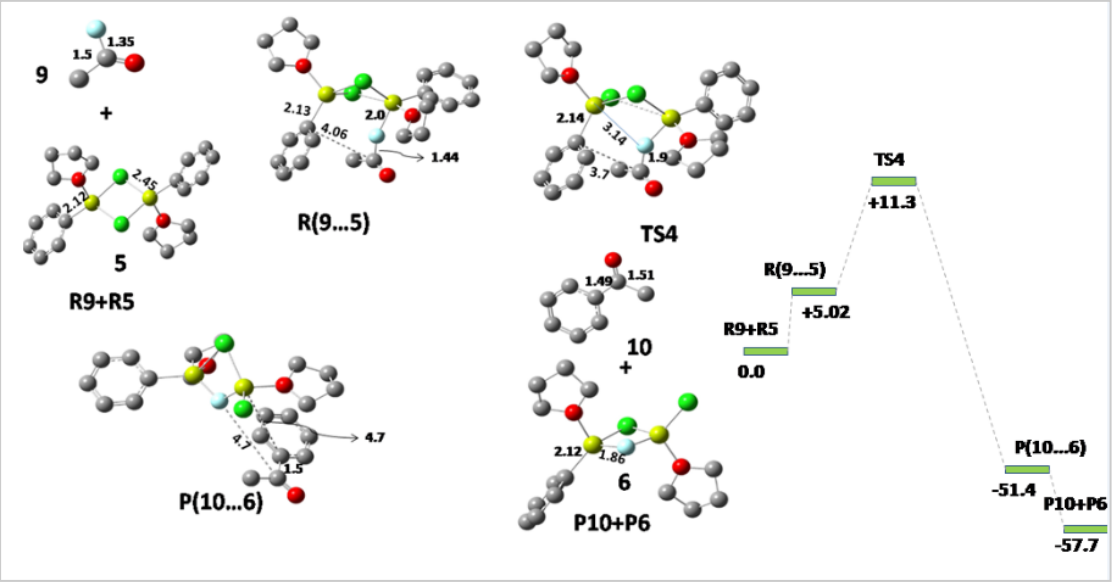


Figure 11: Optimized structures and energy level diagram for scheme 9

Chapter 4

4 Activation of aromatic C-F bond with Grignard reagent in presence of directing group

In this chapter we will look how a C-F bond can be activated for the coupling reaction with Grignard reagent to give C-C coupled product. We will also understand why a sp^2 carbon cannot be activated without the assistance of a directing group, so what groups can act as directing group in these types of reactions. The two systems that we will study here are C-F bond activation on pyridine ring, pyrimidine ring and in which pyridine acts as an ortho directing group for the activation of C-F bond. These reactions are found to be highly regioselective.

4.1 Discussion

Here we carried out the computational study to understand and explore the mechanism of aryl C-F bond activation with Grignard reagents in the presence of directing groups to form the C-C bond. Since aryl C-F bonds are stronger than alkyl C-F bonds, the former cannot be activated without the activating/directing groups. The activation of these groups is challenging due to short bond length and higher bond strength, still this coupling has been successfully carried out with Grignard reagents (RMgX) with good yields[25]. These types of compounds mimic the reactivity of Nucleophilic aromatic substitution (S_NAr) reactions and show nucleophilic substitution reactions where the nucleophile comes from the Grignard reagent and attacks at the electrophilic site in the ring which is the C-F bond in the presence of some electron withdrawing groups which acts as directing as well as activating groups.

4.2 Activation of sp^2 C-F bond – Pyridine as ortho directing group

The analysis is done on gas phase reaction with PhMgCl as Grignard reagent and pyridine in ortho position to C-F reactive site as directing group without transition metal catalyst.The transition state is the highest energy state in the reaction pathway while going from reactants to products in the energy profile diagram and is also the most unstable state which is therefore it cannot be isolated experimentally and hence we need some computational calculations to find it.

4.2.1 Analysis of results

A plausible mechanism was predicted first and then the various optimizations and energy calculations were performed on it to obtain the energy profile diagram and the plausible transition state. In the first step the two reactants are well separated, where the two rings in **fig.** i.e. pyridine and fluorine containing benzene ring are antiplanar to each other, but it was observed that as soon as Grignard reagent approaches the reactant the interaction between electrophilic magnesium and electron rich nitrogen takes place due to which the antiplanarity is lost and the two rings becomes planar, with magnesium simultaneously coordinating to both electron rich fluorine and nitrogen atom(from pyridine). The reaction barrier is of about 12.5 kcalmol^{-1} above the reactants and is due to the loss of antiplanarity of the rings due to coordination of electronegative nitrogen of pyridine with electron deficient magnesium atom and the presence of single imaginary frequency confirms this structure as the transition state. A planar 6 membered ring is formed in the transition state and Mg atom is 5 coordinated with various bond distances as Mg-F of 2.04 Å, Mg-N of 2.27 Å, C-F of 1.37 Å, Mg-Ph of 2.17 Å, C-Ph of 4.04 Å. Magnesium is coordinated to one THF molecule to satisfy the 5 coordination number of magnesium, and it first coordinates to more electronegative fluorine atom and then to nitrogen atom which is also predictable from Mg-F and Mg-N bond distances. As first step is exothermic the transition state resembles the reactants according to Hammond's postulate.

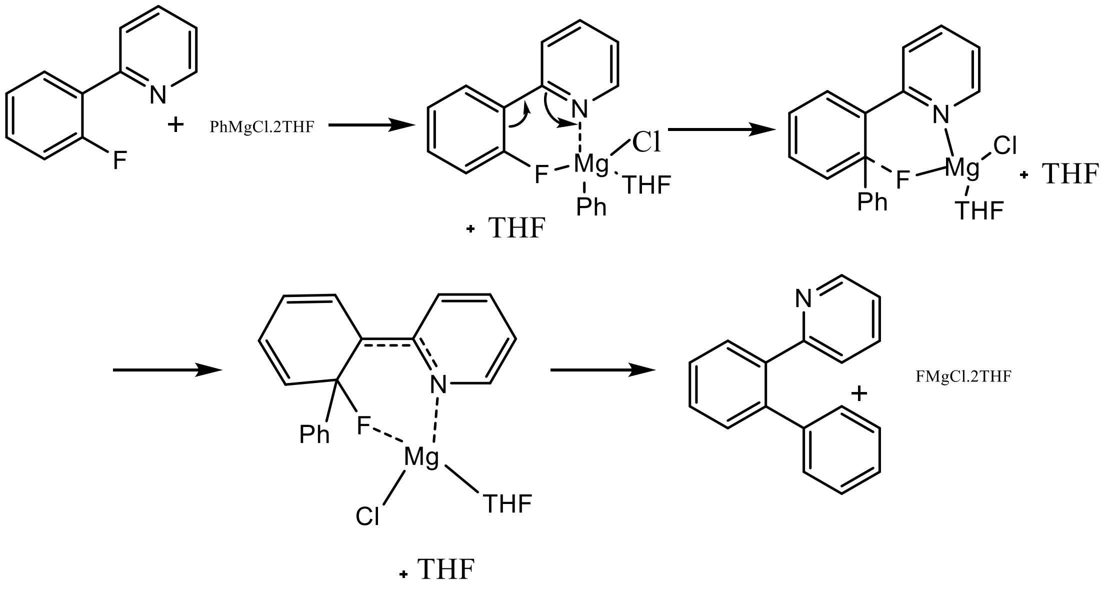
In the second steps the nucleophilic attack of phenyl ring from Grignard reagent to the reactive site i.e. C-F bond takes place and stabilization energy of -56.4 kcalmol^{-1} is released to produce the intermediate **I**. Here Mg-N and Mg-F bond distances are 2.10Å and 1.73Å, which indicates that now magnesium, has coordinated to both nitrogen and fluorine strongly. All three rings are antiplanar to each other **.**The extra stabilization is predicted due to chelation where 3 rings are formed, two of them being six membered and one four membered. The four membered ring contains Mg, F, C and C (of phenyl ring) atoms. This ring is the actual reaction site where a simultaneous bond lengthening of Mg-Ph and C-F and bond formation between C-Ph and Mg-F occurs.

After this step, the reaction again goes via a constrained state and this structure is the second transition state in the reaction mechanism. The barrier is of 8.78 kcalmol^{-1} above the reactants. In the structure the C-C bond length of the bond connecting pyridine ring and phenyl ring is 1.44Å which is comparatively shorter than the reactants i.e.1.48Å and hence it can be deduced that now the two rings are not in resonance and there is partial double bond character in the bond. Moreover, the reactive carbon is now sp^3 hybridized having four substituents as shown in the **fig.**A perfect six membered (open book form) ring is formed in the transition state. Here, also the transition state resembles the reactants due to exothermic reaction which is in accordance with the Hammond's postulate.

Now, the reaction has to go from a high energy state to some stable state, which is our second intermediate denoted by **I2**in the **fig.**Here the stabilization of -62.75kcalmol^{-1} is predicted due to the bond formation of Mg-F and bond breaking of C-F bond. The energy released during bond formation overcomes the energy required during bond breaking and this is due to higher affinity of Mg for fluorine. The pyridine ring rotates in the opposite direction which is an important requisite for the stabilization of the products.

The activation and subsequent substitution of these kind of strong C-F bonds can only be done in the presence of activating groups which serves two main functions here (a) due to electron withdrawing nature of pyridine ring it creates more of positive charge on the ortho C-F bond which polarizes the C-F bond and hence facilitates the attack of nucleophile from Grignard reagent which is also polar and hence reacts easily, (b) It coordinates to electropositive magnesium atom , making the attack of nucleophile on the reactive site easy.

The overall process for the formation of C-C bond by breaking C-F bond is exothermic.



Scheme 10: Plausible predicted mechanism for the activation of C-F bond with PhMgCl in presence of ortho directing group

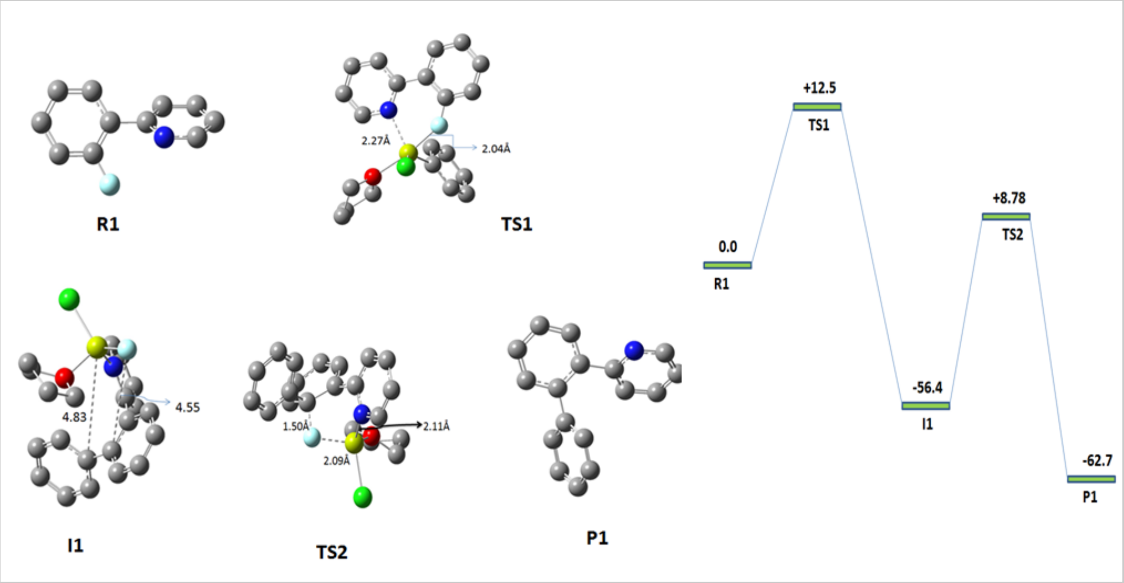
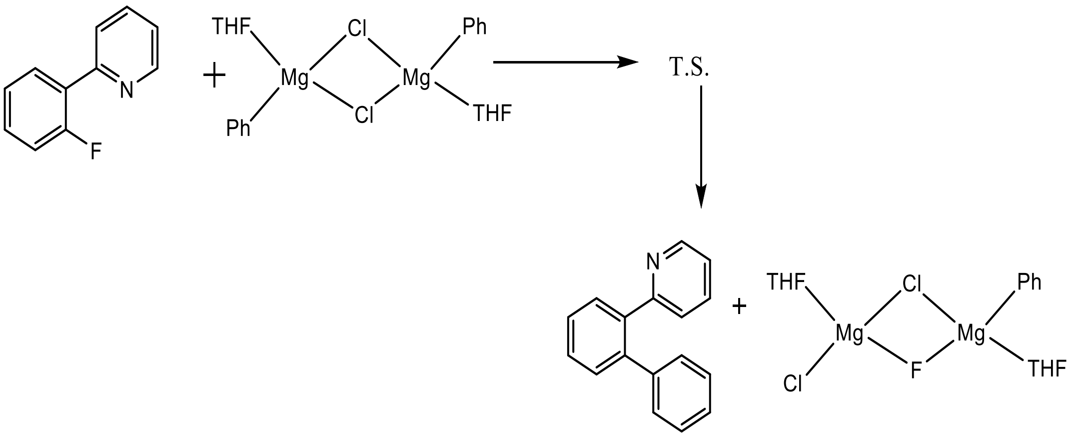


Figure 10: Optimized structures and energy profile diagram for the scheme 10

4.2.2 Dimer mechanism

The reaction energy via the dimerisation pathway of the Grignard reagent was -62.75kcalmol^{-1}.



Scheme 11: Plausible mechanism for the C-F activation in presence of directing group with dimerised Grignard reagent

The reaction is exothermic when the Grignard reagent gets dimerised in the reaction. The dimerisation of the Grignard reagent is a consequence of electron deficient nature of magnesium atom. Since, magnesium atom is electron deficient i.e. it has an incomplete octet, so to fulfill its electron deficiency it has two options either it can coordinate with the sigma coordinating solvents or it can dimerised itself with halogen atom acting as bridging atom. The former case we have already explored and here we have calculated the stabilization energy for the second pathway. This stabilization can be of due to chelation in the structures.

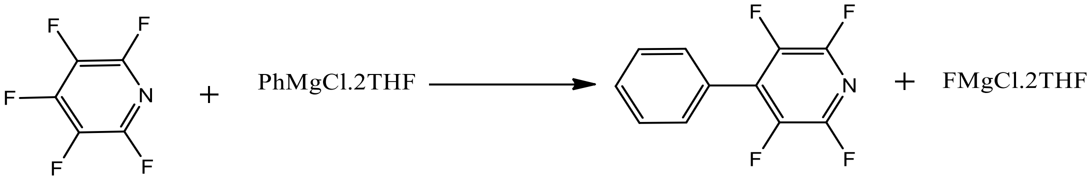
4.3 Activation of C-F bond on pyridine ring

Now, in the second part we tried to know how the C-F bond activates when it is itself present on the pyridine ring. The experimental work has been done on this and it has been observed that the reaction can occur without the assistance of transition metal catalyst and under normal reaction conditions. In our attempt, we have carried out QST2 calculations to get the transition state and the energy barrier which a reactant has to cross in order to get converted to the products.

The regioselectivity of the reaction has also been explored i.e. Ortho vs. Meta vs. Para substituted product and the transition states involved. In the study we found that, the reaction between pentafluoro substituted pyridine with Phenyl magnesium chloride proceeded exothermally with the -70 kcalmol^{-1} release of energy to give phenyl substituted pyridine as the final product. From our previous knowledge it can be assumed that the substitution can take place either at ortho or Para position which are most probable sites for the nucleophilic substitution reactions of pyridine and is due to less availability of electron density at these positions in resonance. So, we first tried the reaction with para substitution since it is experimentally reported also and then explored the mechanism of C-F to C-C bond conversion.

4.3.1 Para Product

In the para substitution of the fluorine atom with phenyl ring the reaction goes via an energy barrier of +18.82 kcalmol^{-1} above the reactants.



Scheme 12: Reaction of C-F activation on pyridine ring with PhMgCl

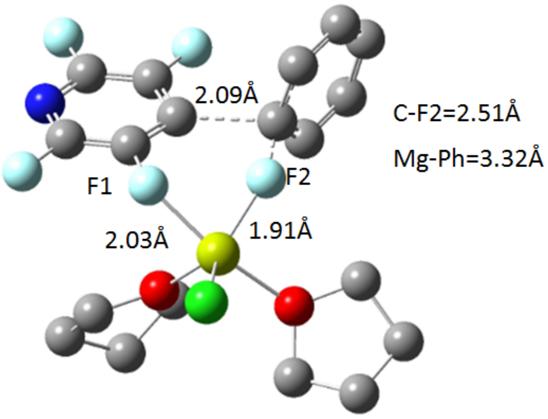


Figure 11: Transition state structure from QST2 calculation for C-F activationon pyridine ring

A close inspection of the transition state reveals that it is not a 4 membered transition state as it was observed for all other systems discussed in this work rather it is an unusual 6-membered transition state.

In the transition state a number of interesting things were observed, we will discuss them one by one. Firstly, it was observed that the pyridine ring in the mechanism here plays a role only via electronic effects. In the para substitution of the fluorine atom on the atom ring more and more of the positive charge is to be created so that the charge separation in the C-F bond increases creating more of partial positive charge on the carbon atom and more of partial negative charge on the fluorine atom. This is easily done by nitrogen atom of the pyridine ring. As we all know that pyridine ring is a more electron withdrawing group where the nitrogen atom withdraws the ring electron density toward itself, now since this resonance creates more partial positive charge on the ortho and para positions which further facilitates the nucleophilic attack at these positions. The orientation of the pyridine ring in the structure clearly indicates that it enjoys no coordination with magnesium atom. Secondly, magnesium atom enjoys coordination with two fluorine atoms one is para fluorine atom (Mg-F2=1.91Å) whose substitution it facilitates and other is one of the meta fluorine atom where it enjoys only an interaction with it and this is evident from the relatively longer Mg-F1 bond distance of 2.03Å. Thirdly, Mg-Ph bond distance of 3.32Å shows that there should be some interaction between magnesium atom and phenyl ring but when we looked at the line of alignment joining the two atoms it was observed that though the distance is small but due to presence of fluorine atom in between them inhibits any form of interaction.

With these observations we can conclude that the transititon state is a six membered transition state here and nucleophilic attack by Ph occurs almost perpendicularly to the carbon reactive site. Mg is 5 coordinated; the driving force for the forward reaction is the high affinity of magnesium for fluorine atom. The activation barrier is found to be +18.82 kcalmol^{-1} above the reactants. The overall reaction is exothermic with -69.25 kcalmol^{-1} release of energy. The transition state resembles the reactant in accordance with Hammond's postulate.

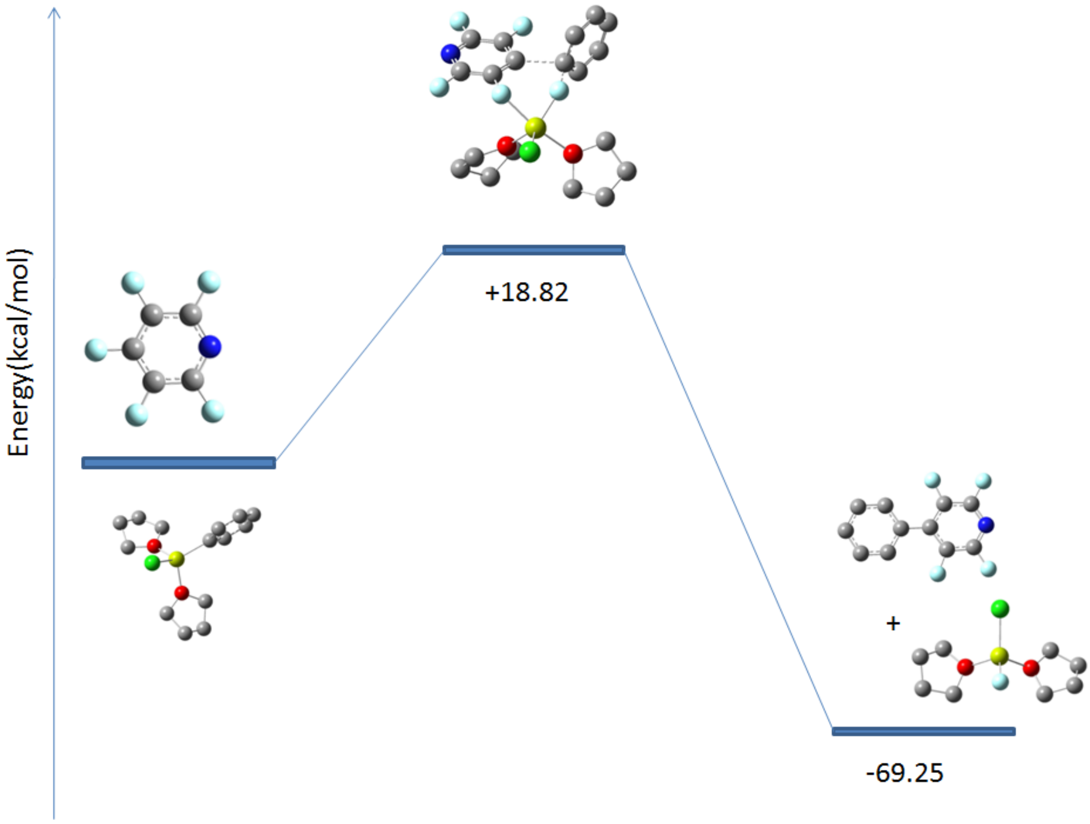
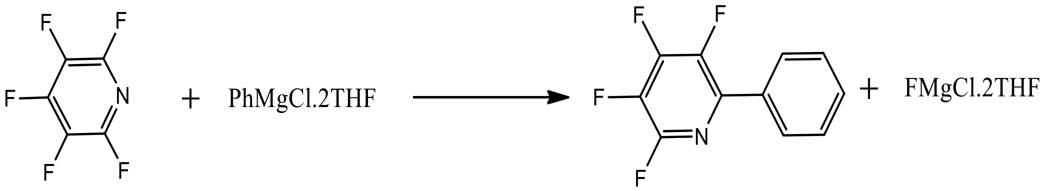


Figure 12: Energy profile diagram for para C-C coupled product from C-F bond on pyridine ring

4.3.2 Ortho product

The second possibility that we explored in our study is whether this type of coupling reactions can take place at ortho position the way they occurred at the para positions. Since this type of work has not been reported we carried out the optimizations and other related calculations in order to predict the feasibility of the reaction and the possible transition state. In this case the reaction barrier was found to be +43.9 kcalmol^{-1} above the reactants and the stabilization energy of the reaction was -69.02 kcalmol^{-1} .



Scheme 13: Reaction of polyfluorinated pyridine with PhMgCl to give ortho substituted C-C coupled product

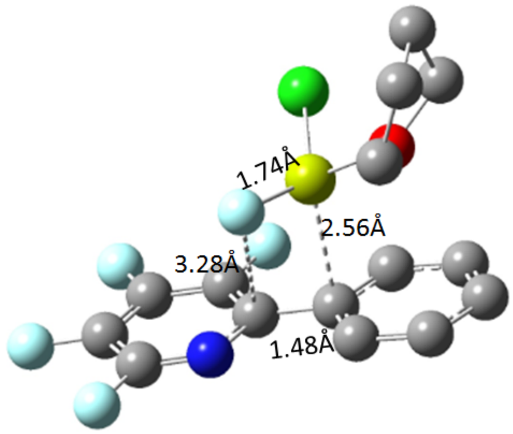


Figure 13: Transition state from QST2 calculation for C-C coupled product

In the reaction, a four membered transition state is formed where the four distances undergoing change while going from reactants to products are as: Mg-Ph=2.56Å, Mg-F=1.74Å, C-F=3.28Å, C-Ph=1.48Å. This transition state was at +43.9 kcalmol^{-1} energy above the reactants which is a high energy barrier as compared to the mechanism of para substituted product and hence it can be concluded that the reaction only para substituted product can be formed or para substituted product is the kinetic product and ortho substituted is the thermodynamic product. Mg remains 4 coordinated. Again there is no coordination of nitrogen atom with magnesium and the necessary conformation for the formation of the product an d the only effect seen is electronic effect.

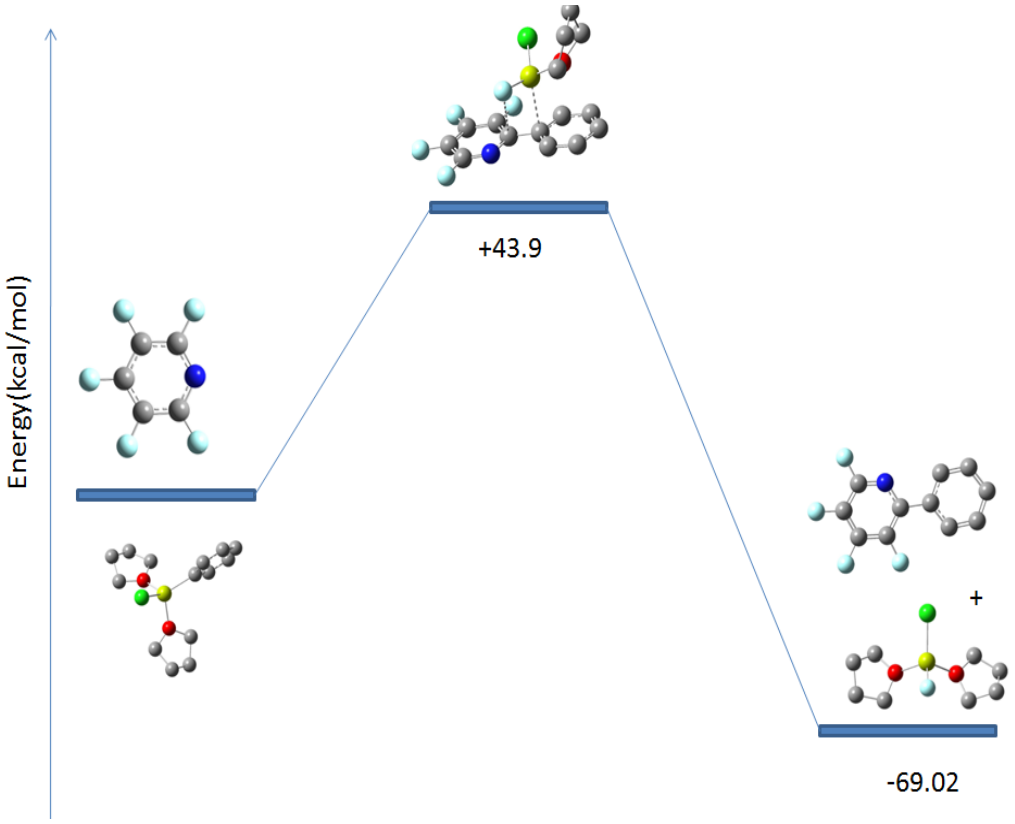


Figure 14: Energy profile diagram for ortho substituted C-C coupled product

4.3.3 Meta Product

Third and the last possibility that we have checked here is the reaction at meta carbon of the pyridine ring i.e. nucleophilic substitution of fluorine atom with phenyl ring and the formation of the product. It was observed that the reaction still remains exothermic with a release of -75.3 kcalmol^{-1} and it can be concluded that the among all the three possible products most probable is the meta substituted then para substituted and then the ortho substituted product.

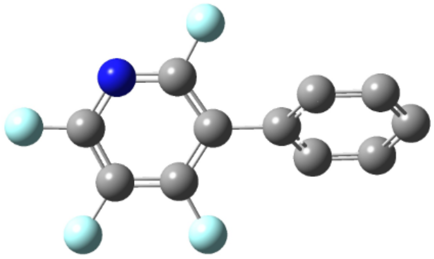
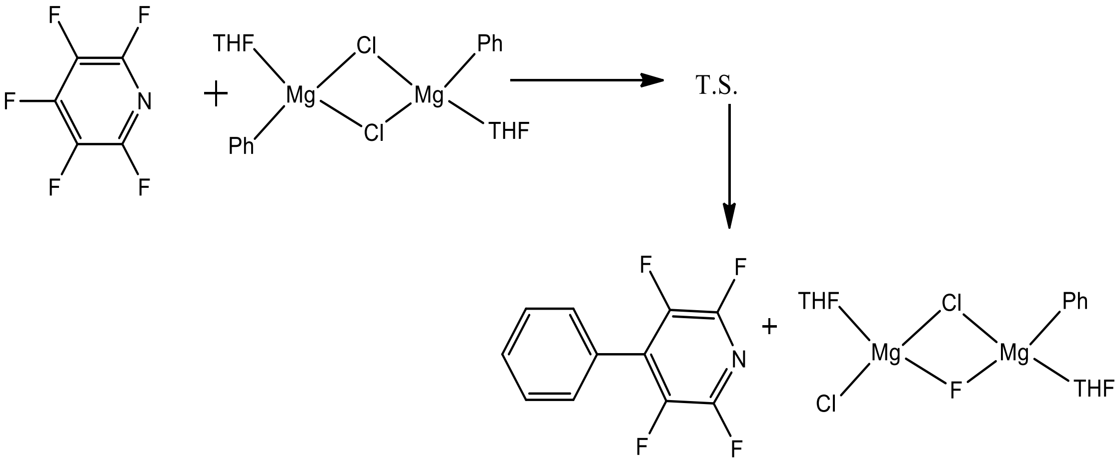


Figure 15: Product for the reaction of C-F activation to give meta substituted C-C coupled product

4.3.4 Dimer Mechanism

The energy for the reaction where the Grignard reagent is present as dimeric species is found to be -75.3 kcalmol^{-1}. This is high stabilization energy and just like all other systems this is also predicted to be more favorable pathway for the reaction to undergo the transformation from C-F to C-C bond.



Scheme 14: Plausible mechanism for the C-F activation on pyridine ring with dimerised Grignard reagent to give para substituted C-C coupled product

SUMMARY

We have carried out a computational study for the prediction of pathways of mechanism for the nucleophilic substitution reaction of organofluorine compounds with weakly acidic nucleophilic Grignard reagents. Since organofluorine compounds are extremely important in daily life, their reaction to form C-C coupled product is of great use. In the activation of sp^3 C-F bond, we found that among three predicted pathways dimer pathway was most favorable with final release of energy of -52.7 $kcalmol^{-1}$. The transition state for this was only +16.9 $kcalmol^{-1}$above the reactants with alkyl group being planar, magnesium as tetrahedrally coordinated and fluorine acting as bridging atom. In contrast, when fluorine was replaced by chlorine then monomer mechanism was favored. This can be explained by the lower affinity of magnesium for chlorine than for fluorine hence chlorine bridges are less stable than fluorine bridges. In case of alkyl sp^2C-F activation in acetyl fluoride the mechanism through dimerisation of Grignard reagent was found to be highly favorable with an activation barrier of only +11.3 $kcalmol^{-1}$.This is due to resonance stabilized acylium ions, which provides stability to the acetyl group in the transition state. In addition to this we compared the reactivity of aryl C-F bond with Grignard reagents. It was observed that in this case a directing group is required where a six membered transition state is formed with Mg being tetrahedrally coordinated. Pyridine acts as directing group assisting in the transformation with its both electronic and directing effects. On the contrary when the activation of C-F present on pyridine ring was studied then para product was found to be most stable one.

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