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Selectivity of C-H activation and competition between C-H and C-F bond activation at fluorocarbons

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ABSTRACT

Partially fluorinated alkanes, arenes and alkenes can be transformed by a variety of transition metal and lanthanide systems. Although the C-H bond is weaker than the C-F bond regardless of the hybridization of the carbon, the reaction of the C-F bond at the metal is usually more exothermic than the corresponding reaction of the C-H bonds. Both bonds are activated by the metal systems, but the preference for activating these bonds depends on the nature of the hydrocarbon and of the metal system, so that the reaction can be directed exclusively toward C-H or C-F bonds or yield a mixture of products. Additionally, the presence of fluorine differentiates between C-H bonds at different positions resulting in regioselective C-H bond activation; paradoxically, the strongest C-H bond reacts preferentially. The purpose of this review is to describe the field of reaction of partially fluorinated substrates with transition metal atoms, ions and molecular complexes. The controlling physical properties (thermodynamics and kinetics) are described first, followed by a description of stoichiometric reactions, with the competition between the C-H and C-F activations as focus. A few representative catalytic systems are discussed. The review also highlights the benefit of combining experimental and theoretical studies.

CONTENTS

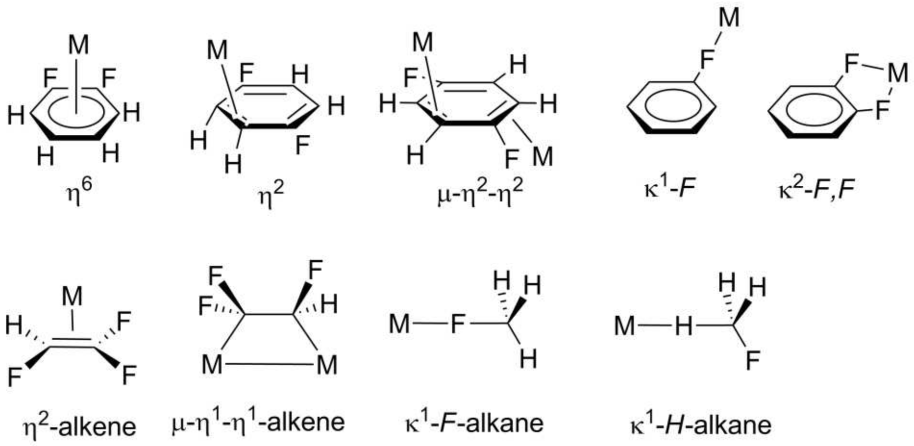
1. INTRODUCTION

The importance of hydrofluorocarbons is well documented in pharmaceuticals, agrochemicals, materials, refrigeration and air conditioning. A large proportion of new drugs and agrochemicals include fluorine substituents at sp^3 or sp^2 carbons in order to modify the acidity, the lipophilicity, the conformations and, especially, the metabolism of the drugs.[1-4] The favorable radiochemical properties of ^{18}F make it a crucial isotope for positron emission tomography, leading to a requirement for radiopharmaceuticals that include a fluorine substituent.[1,5] Fluorinated materials are employed for their hydrophobic properties, their chemical inertness and physical properties such as elasticity.[6-8] The introduction of long fluorinated chains or “fluorous pony-tails” can produce phase behavior that is particularly favorable for catalysis, solvent extraction and chemical synthesis.[9-13] Saturated hydrofluorocarbons have also found important applications as refrigerants, and propellants, but several of them will now be phased out following the Kigali agreement of 2016 for reduction of greenhouse gases, leading to disposal issues.

The chemical properties and reaction patterns of polyfluorinated compounds are different from those of the corresponding hydrocarbons. Hydrofluorocarbons present a particularly challenging problem for bond activation, because reaction may occur at the C-H bonds or the C-F bonds or even at both types of bond. The presence of C-F bonds in a hydrofluorocarbon alters the strength of C-H bonds with respect to the corresponding hydrocarbon with the consequence that the energetics and kinetics of C-H bond activation are modulated by the introduction of fluorine substituents. These effects, which depend on the number and location of fluorine substituents, lead to changes in chemoselectivity and regioselectivity of bond activation that vary with the metal and ligand centers and have an impact on both stoichiometric and catalytic reactions. In this review, our principal goal is to put across current understanding of the C-H bond activation of hydrofluorocarbons at transition metal and lanthanide centers, indicating the circumstances that affect the balance between C-F activation and C-H activation, as derived from experimental and computational studies. To set the scene, we have selected for the introduction some key features of the interactions of hydrofluorocarbons with transition metal or lanthanide fragments.

Partially fluorinated arenes and alkenes can coordinate to transition metals without bond breaking. Such coordination of arenes can occur via π-bonding to the carbon skeleton in η^2, η^4 or η^6 modes or via C-F σ-coordination through the fluorine lone pairs;[14,15] all of these possibilities except η^4-arenes have yielded examples of characterized products (Scheme 1). Examples of fluorine-substituted hydrocarbons (excluding perfluorocarbons) binding as in Scheme 1 may be found in the references indicated: (η^2-fluoroarene) and (μ-η^2-η^2-fluoroarene),[16,17] (η^6-fluoroarene),[18,19] (κ^2-*F,F*-fluoroarene),[20] (κ^1-*F*-fluoroarene),[20,21] η^2-fluoroalkene and bridging μ-fluoroalkene.[22] Partially fluorinated alkanes have been demonstrated to coordinate to tungsten pentacarbonyl by time-resolved IR spectroscopy[23] and to metal ions in the gas-phase by mass spectrometry.[24] In both cases, their geometries have been characterized computationally.[25-27]

Scheme 1. Coordination of hydrofluoroarenes and hydrofluoroalkenes without bond breaking



When a hydrofluorocarbon reacts by bond breaking there is a possibility of either C-H or C-F bond cleavage. There is a tendency for early metals (especially d^0 metals) to yield C-F bond activation products, while metals with occupied d shells ($d^6 – d^{10}$) are more variable. Among the reactions of fluoroarenes, there are examples of chemoselective C-F or C-H bond cleavage, as well as situations where both are observed. Preference for C-F activation via F-coordination dominates in the reaction with atomic ions but considerable more diversity is observed with molecular transition metal complexes in solution. For example, the photochemical reactions of Cp*Rh(PMe_3)(C_2H_4) or Tp'Rh(CNneopentyl)(carbodiimide) (Tp' = hydrotris(3,5-dimethylpyrazolyl)borate) with partially fluorinated benzenes give C-H activation exclusively.[28,29] The reactions of nickel complexes containing N-heterocyclic carbene ligands with partially fluorinated benzenes give C-F activation exclusively.[30] The kinetic products of reactions of Ni(PEt_3)$_2$L (L = phenanthrene, anthracene, isobutene) with partially fluorinated benzenes follow the C-H activation route, while the thermodynamic products involve C-F activation.[17] Catalytic reactions of fluorinated benzenes can also lead to reaction either at the C-H or C-F bond. Catalytic hydrofluoroarylation[31] and direct arylation[32] provide examples for the former and are defined in a scheme in Section 5. Catalytic C-F activation is illustrated by hydrodefluorination and cross-coupling.[33,34] The reactions of fluoroalkanes demonstrate similar issues of chemoselectivity. For these reasons, chemoselectivity is one of the principal topics of the review.

In addition to chemoselectivity, the C-H activation of arenes raises questions of regioselectivity. We distinguish intermolecular activation (Section 4.2.2) and intramolecular cyclometalation (Section 4.2.3) of arenes. We describe reactions as intermolecular when the reactant is a simple fluorinated benzene or pyridine, regardless of whether there is an intermediate with coordinated arene. The term intramolecular cyclometalation is used when the reactant contains an anchoring group which is coordinated in the product. In numerous examples of intermolecular activation of fluorinated arenes, strong selectivity for the C-H bonds ortho to fluorine substituents has been observed.[35] This selectivity can have a kinetic or a thermodynamic origin. When we turn to cyclometalation by intramolecular C-H activation, it is possible to steer the selectivity to positions ortho or para to fluorine substituents by subtle alteration of the metal-ligand system.[36,37]

Several factors influence the selectivity. A coordination complex resulting from coordination of the substrate to the metal fragment, shown in Scheme 1, may be an intermediate on the way to the C-H activation product but this is not a requirement. The relative stability of the coordination complexes shown in Scheme 1 and any C-H activation products vary with the metal and its ligands. It is of particular importance that fluorine substitution modifies the C-H bond strength of hydrocarbons and, to an even greater extent, the bond strength of the M-C bonds in their C-H activation products, leading to profound effects on selectivity.[38,29]

Among stoichiometric reactions, we highlight several recent advances: the discovery of selective 1,2-C-H addition reactions of fluorinated benzenes at alkylidyne titanium complexes;[39] the observation of reaction intermediates and the development of a kinetic model in the C-F and C-H activation reactions of $Ni(PEt_3)_2(\eta^2$-phenanthrene) with tetrafluoropyridine;[40] the rearrangement of the hydride complex *trans*-$[NiH(C_6F_4(CF_3))(i Pr_2Im)_2]$ via the η^2-arene complex to two fluoride complexes;[41] the experimental demonstration that M-C(aryl) bonds increase in strength far faster than H-C(aryl) bonds as the number of ortho fluorine substituents increases, as predicted by computation.[29,38] The reactivity of CH_3F towards atoms and ions has been studied particularly thoroughly in the gas phase.[24] Among reactions of aliphatic hydrofluorocarbons in solution, we draw attention to the reactions of CH_3F and CHF_3 at iridium pincer complexes[42] and the discovery of niobium complexes that are selective for activation of benzylic CF_3 groups, even in the presence of C-H bonds.[43]

Carbon-fluorine bond activation has been the subject of numerous recent reviews,[33-34,44-61] but competing C-H bond activation receives little attention in most of these publications. Two reviews pay particular attention to partially fluorinated substrates and C-H activation, one on nickel chemistry[62] and the other on organometallic chemistry particularly with fluorobenzene and difluorobenzene.[15] There are a few more personal reviews that treat C-H activation of fluoroarenes specifically[63,35] or address organofluorine chemistry at an individual metal.[64]

We start this review with thermodynamic considerations, considering the energetics of free hydrofluorocarbons and then the energetics of C-H bond activation at a metal. We follow these general sections, with a survey of stoichiometric reactions divided up into reactions at atoms or ions and reactions in solution, dividing the latter into reactions with aliphatics, aromatics and alkenes. In section 5, we move to catalytic activation. We do not survey the full range of catalytic reactions but review a few examples where the fluorine plays a major role. Finally, we tease out the major general mechanistic principles in the concluding section 6.

2. ENERGETICS OF FREE HYDROFLUOROCARBONS

The knowledge of energetics of bond breaking is essential for determining the feasibility of a reaction. Unfortunately, the experimental determination of bond energies or bond enthalpies is a demanding task, which cannot be achieved for all molecules. Nevertheless, homolytic bond dissociation enthalpies in which the molecule is dissociated into two radicals have been measured in the gas phase for numerous systems and the compilation in Comprehensive Handbook of Chemical Bond Energies by Luo gives the most accurate values.[65] Table 1 reports selected values for C-H and C-F bond dissociation enthalpies in kJ/mol for molecules relevant to the present review.

Table 1 Experimental bond dissociation enthalpy (kJ/mol) in gas phase

	Experimental		Calculated	
molecule	X = H[a]	X = F[a]	X = H	X = F
X-CH_3	439.3 ± 0.4	460.2 ± 8.4	439[b]	462.9[b]
X-CH_2F	423.8 ± 4.2	496.2 ± 8.8	424[b]	501.7[b]
X-CHF_2	431.8 ± 4.2	533.9 ± 5.9	426.8[b]	534.7[b]
X-CF_3	446.4 ±4.2	546.8 ± 2.1	448.4[b]	547.4[b]
X-C_6H_5	472.2 ± 2.2	525.5 ± 8.4	489.8[c]	539.9[e]
X-C_6F_5	487.4[d]	485 ± 22	514.7[c]	519.4[e]

[a] Ref 65

[b] high level computational protocol[66]

[c] DFT(B3PW91) calculations[38]

[d] no reported error range

[e] DFT(BP86) calculations from ΔH_{298} data[67]

The bond dissociation enthalpy is smaller for C-H than C-F in all molecules except the pentafluorobenzene derivatives. However, in this latter case, the absence of an error bar for X = H and the large uncertainty for X = F prevents any definitive conclusion. Replacing one and even two hydrogen atoms by fluorine in methane results in weaker C-H bonds in H-CH_2F and H-CHF_2 than in methane but the C-H bond in H-CF_3 is stronger than in methane. While substituents can influence the stability of the substrate and the molecular radical that is formed on homolysis, it is currently thought that the influence is larger in the radicals. Consequently, the relative C-H bond energies were interpreted in terms of stabilization of the radical by the F calculated with several DFT and wave function-based computational methods.[68] The situation is different for the C-F bond energy since it increases in a monotonic manner upon substitution of H by F as shown in Table 1.[66]

The C-H bond in benzene is stronger than in methane and likewise the C-F bond is stronger in monofluorobenzene than in monofluoromethane; this is associated with the carbon hybridization with bonds to sp^2 carbon stronger than to sp^3 carbon. Another irregularity occurs in C_6F_5X: the C-H bond in H-C_6F_5 is stronger than that in benzene but the C-F bond in F-C_6F_5 is weaker than that in F-C_6H_5, perhaps due to the electronic repulsion between the fluorine atoms. However, as mentioned above the large or unknown uncertainty in the experimental values make these trends somewhat unreliable. High level calculations reproduce these experimental values with great accuracy, especially for the methane derivatives that have been studied with a particularly high level computational protocol which has been optimized to reproduce 261 bond dissociation enthalpy values.[68]

The trends in C-H and C-F bond energies of benzene derivatives have also been studied computationally and show very spectacularly that C-F bonds weaken while C-H bonds strengthen with the number of ortho-fluorine substituents.[67] In Figure 1 the C-F bond dissociation energies are defined relative to the para C-F bond in C_6F_5H and the C-H bonds are shown relative to C-H bond energy for the same molecule. The figure shows that the C-F bond energy decreases by 7.5 kJ/mol for each *o*-fluorine substituent while the C-H bond energy increases by 10.5 kJ/mol for each *o*-fluorine substituent. The meta and para fluorines have a much smaller influence in both cases. The C-H bond energies show a marked clustering into three groups according to the number of *o*-F substituents, but the clustering is less conspicuous for the C-F bond energies. The consequence of these trends is that hydrodefluorination and C-F bond activation become more favorable as the number of *o*-F substituents increases.

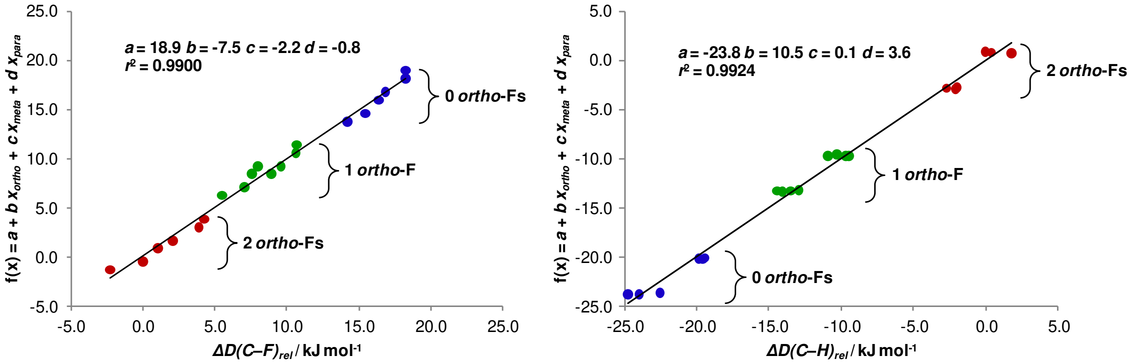


Figure 1. Plots of the best fit to the trends in DFT(BP86) calculated C-F (left) and C-H (right) bond dissociation energies for $C_6F_{6-n}H_n$ (n = 0-5). $\Delta D(C\text{-}F)_{rel}$ and $\Delta D(C\text{-}H)_{rel}$ are defined relative to those of C_6F_5H (see text). Reproduced with permission from ref 67. Copyright 2013 Royal Society of Chemistry

Experimental determination of acidity of the C-H bond in fluorinated benzenes is rather limited. Values of the enthalpy of deprotonation of benzene determined in the gas phase by mass spectrometry range from 1663 to 1671 kJ/mol.[69] A single F substituent decreases the energy of deprotonation of benzene in the gas phase by 56 kJ/mol and a CF_3 substituent decreases it by 57 kJ/mol.[70] Studies in solution based on proton exchange between a cesium ion pair and a substrate were used to determine pK_a's . In cyclohexylamine the pK_a's of benzene, 1,2-difluorobenzene, 1,2,3,4-tetrafluorobenzene, and pentafluorobenzene were determined as 43.0, 34.98, 31.52 and 23.81, respectively, at 34°C.[71] In THF, the pK_a's of several hydrofluorobenzenes (but not pentafluorobenzene) could be determined at 25 °C with an accuracy of 0.2 pK_a units (values in red in Figure 2). The effect of fluorine in decreasing the pK_a was shown to be additive with contributions depending on its position. Thus, F decreases the pK_a of benzene by 5.2, 3 and 1.4 units for ortho, meta and para positions, respectively, leading to an estimate of the pK_a of benzene as 44.8 by extrapolation.[72] Computational studies (B3LYP with large basis set and polarization on all atoms) including the cesium ion pair reproduced the data fairly well after careful calibration (values in black in Figure 2). However, the calculated and experimental pK_a's differ significantly for 1,2,3,4-tetrafluorobenzene, which is calculated to be less acidic than 1,3,5-trifluorobenzene in contrast to experimental values. This illustrates the difficulties in computing quantitative data on this topic. The same computational protocol shows the pK_a in DMSO to vary by less than 2 units compared to the value in THF.[73] A related computational study was carried out for a full set of hydrofluorobenzenes in DMSO but the values cannot be compared to the experimental values because the cesium ion pair is not included in the protocol.[74]

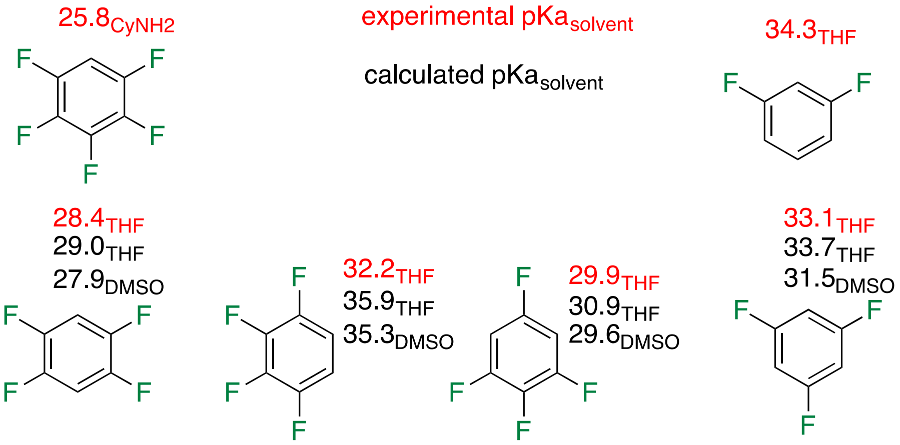


Figure 2. pK_a values of fluorinated benzenes. Experimental (red) for cyclohexylamine $CyNH_2$ solvent,[71] and THF solvent[72] and calculated (black).[73]

Hammett σ-constants, which are also useful to describe the influence of fluorine,[75] have been calculated from the core-electron binding energy of the carbon atom with PW86-PW91 functionals.[76-77] The contribution of the acidity to the activation of the C-H bond at metal centers will be discussed in Section 3.2.[38,78-80]

Heterolytic cleavage of fluorinated species into either R^+ and H^- or R^+ and F^- has been considered by computational studies. Insight into this question was obtained with DFT(M05-2X in the gas phase and in solution) calculations of the affinity for hydride (HA) and fluoride (FA) for a set of carbon-and silicon-based cations in gas phase and chlorobenzene solution.[81] HA and FA are defined in equations 1 and 2.

$$R_3X\text{-}F \rightarrow R_3X^+ + F^- \quad \Delta H = FA \qquad (1)$$

$$R_3X\text{-}H \rightarrow R_3X^+ + H^- \quad \Delta H = HA \qquad (2)$$

The calculations show that there are linear relationships between FA and HA for carbocations and Si-cations with slopes that are not far from unity (Figure 3). However, deviations from the correlation line are more frequent for the carbocations than for the silylium cations. The hydride affinity is higher for carbocations than for related silylium systems by an average value of 60 kJ/mol. However, the fluoride affinity is higher for X_3Si^+ than for carbocations with similar substituents but the fluoride affinities of perfluorocarbocations far outstrip those of the X_3Si^+ cations. The difference between HA and FA ($\Delta_{H\text{-}F}$) is small for the silylium cations but varies widely in the range of 140-240 kJ/mol (33-57 kcal/mol) in favor of the hydride for the carbocations.

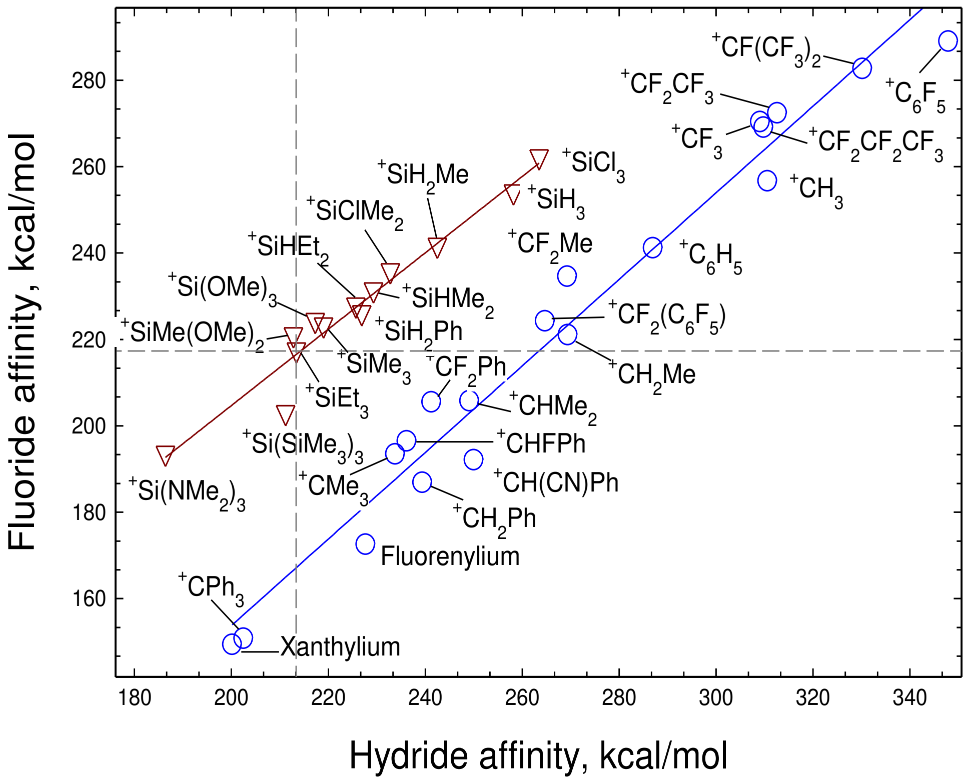


Figure 3. Calculated hydride and fluoride affinities (kcal/mol) of a series of carbenium and silylium cations in the gas phase. Species above the horizontal dashed line have FA greater than FA(Et_3Si^+), and species to the right of the vertical dashed line have HA greater than HA(Et_3Si^+). Reproduced with permission from ref 81. Copyright 2011 Wiley.

For reference, we mention here the positions of nucleophilic attack in typical nucleophilic substitution reactions of partially fluorinated benzenes and fluorinated pyridines. Pentafluorobenzene typically undergoes substitution at the position para to H; the positions of substitution of less fluorinated benzenes are summarized elsewhere.[62] The rate of substitution is fastest for pentafluorobenzene and decreases very rapidly for less fluorinated benzenes.

3. ENERGETICS OF C-H AND C-F ACTIVATION AT METAL CENTERS

Bond enthalpies determine the thermodynamic feasibility of a chemical transformation in the gas phase, together with entropy. In the case of organic molecules, considerable information has been accumulated,[82,83,65] but this is not the case for systems where a transition metal is present. Determination of absolute values of metal-ligand bond enthalpies is very difficult and some simplifications are often necessary.[84-86]

There are three important aspects to the thermochemistry of hydrofluorocarbons that are needed for a general understanding of the thermodynamics of hydrofluorocarbon activation. One is the nature and magnitude of the interaction of the whole hydrofluorocarbon with the transition metal complex (Section 3.1), the second concerns the energetics of C-H oxidative addition, including the interaction of hydrofluorocarbyl fragment with the metal fragment after bond activation (Section 3.2) and the third concerns the corresponding energetics of C-F oxidative addition (Section 3.3).

3.1. Energetics of coordination

Quantitative information on the binding energy of fluoroalkanes is limited. No fluoroalkane complex has been isolated and structurally characterized, but spectroscopic information and computational studies indicate that fluoroalkanes interact with the metal center via F rather than via C-H. We present the limited data in section **4.2.1.2.** More data has been accumulated for the fluoroarene family – see also the recent review by Pike et al..[15] The binding affinity of fluoroarenes with Cr^+ ions, probed by radiative association kinetics in the gas-phase using Fourier transform ion cyclotron resonance mass spectrometry and DFT(B3LYP) calculations, showed that increasing fluorination decreases the binding affinity.[87] For all 1,2-difluoro substituted arenes, coordination through the F atoms is preferred over that via the π-bond but the decrease in binding energy with the number of fluorine substituents applies to the two coordination modes. With metal-ligand complexes, coordination via the fluorine atoms rather than via the π-arene bond has been reported in several cases. Thus, fluorobenzene and 1,2-difluorobenzene lead to isolable complexes coordinated via either one or two fluorines, respectively with d^0 Cp$_2$Ti^{IV},[21] d^0 Cp$_2$Sc$^+$ and d^1 Cp$_2$Ti$^+$ (but no coordination is observed with d^2 Cp$_2$V$^+$).[20] DFT(BP86) calculations confirmed the preference for F coordination in these systems and the decrease of binding energy from d^0 to d^1 and to d^2. With other metal complexes, coordination to the *C,C*-π-bonds (η^2- or η^6-modes) has been observed. Fluoroarenes tend thus to coordinate via F to metal complexes with empty d shells due to the absence of back-donation needed for C-C π-coordination. The same coordination may be obtained for d^n with $n \leq 2$, but π-complexes dominate with higher d occupancy.

A quantitative evaluation of binding energies of several fluorobenzenes to d^8 [Rh(*i*Bu$_2$PCH$_2$CH$_2$P*i*Bu$_2$)]$^+$ has been derived from a combination of electrospray ionization mass spectrometry (ESI-MS) and collision induced dissociation (CID) techniques. Increasing the number of fluorine substituents on the benzene decreases the stability of the η^6-arene complex as shown by the study of the equilibrium (Figure 4).[18]

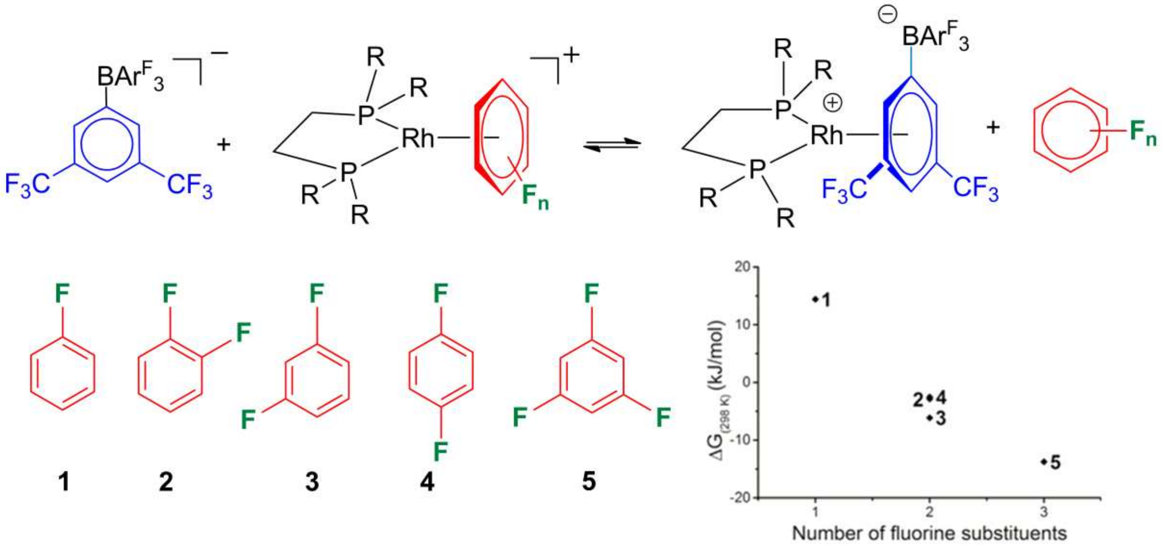


Figure 4. Plot of ∆G(298K) versus degree of fluorine substitution for the equilibrium shown above. Adapted with permission from ref 18. Copyright 2015 Elsevier.

The binding energy to a given fluorobenzene, as calculated in a d^6 cyclopentadienyl rhenium complex with DFT(B3LYP) method, decreases from η^2-HC=CH bond to η^2-HC=CF, and to η^2-FC=CF (discussed in more detail in section 4.2.2.3).[16,88] The preference for coordinating the least fluorinated double bond of fluoroarenes is not general. $Ni(PEt_3)_2$ forms an η^2-complex with C_6F_5H which could be detected by NMR spectroscopy, but was fluxional even at the lowest temperatures measured. DFT(B3LYP) calculations indicate that the energy of coordination to the C(3)F=C(4)F double bond (numbering starting at C1(H)) is almost equal to that of coordination to the C1(H)=C2(F), but the product of coordination to the C2(F)=C3(F) lies significantly higher in energy. Calculations of the ^{19}F NMR chemical shifts and comparison with the experiment values support the proposed coordination preferences.[17] A corresponding study was carried out for 1,2,3,4-tetrafluorobenzene and 1,2,3,5-tetrafluorobenzene in which NMR spectroscopy and DFT(B3LYP) calculations were combined to characterize the various species.[89] Coordination by a single and two $Ni(PEt_3)_2$ moieties are observed by NMR spectroscopy and the various isomers of these complexes are indicated to be in equilibria, as also supported by calculations. In the case of the monocoordinated complex, coordination to C(H)=C(F) is preferred for 1,2,3,5-tetrafluorobenzene and to C(F)=C(F) for 1,2,3,4-tetrafluorobenzene. These Ni complexes are discussed in more detail in section 4.2.2.5.

A related computational study was carried out for d^{10} $Ni(H_2PCH_2CH_2PH_2)$. In this case, the two arenes C_6H_6 and C_6F_6 form η^2-complexes with the metal fragment and C_6F_6 binds more strongly than C_6H_6 (by around 20 kJ/mol).[90] Replacing Ni by Pt decreases the stability of the η^2-C_6H_6 complex toward dissociation by 32 kJ/mol and decreases that of the η^2-C_6F_6 complex by 36 kJ/mol. There is a contrast in the effect of fluorination on the binding energy in the

$[Rh(iBu_2PCH_2CH_2PiBu_2)]^+$ system compared with $M(H_2PCH_2CH_2PH_2)$ (M = Ni, Pt). Considering the evidence that neutral centers such as $CpM(PMe_3)$ (M= Rh, Ir) form isolable, sublimable η^2-C_6F_6 complexes but not η^2-C_6H_6 complexes,[91] this switch may be charge controlled.

3.2 Energetics and regioselectivity of C-H oxidative addition

The energetics of an oxidative addition of a C-H bond describe the changes associated with the loss of the C-H bond and the formation of the metal-C and metal-H bond. As mentioned above, determination of the absolute energies of the bonds involving the metal is exceptionally difficult.[84,86] In addition, the chemist is mostly interested in the energetics of the overall transformation.

Computational studies were carried out by Landis *et al.* to explore whether the concept of intrinsic bond energies could be defined for transition elements.[92] For this purpose, the first bond dissociation enthalpies for neutral and cationic complexes of the type H_nM-R (R = H, CH_3, C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2F, C_2H, C_2H_3, NH_2, OH, F and BH_2) were calculated for all transition elements with DFT(B3LYP) and CCSD(T) calculations and compared with related ion beam mass spectrometry data. This study showed great variations in bond energies across the Periodic Table and indicated that it was not possible to determine intrinsic bond energies in the case of transition metal complexes, since the ligands and their coordination modes influence the values too much.

It has been shown that it is possible to employ kinetic and equilibrium methods to determine the free energies for a series of related reactions. If it is assumed that entropic factors are constant within the series, bond enthalpies for M-X bonds may be estimated relative to a standard. For instance, Bryndza *et al.* were among the first to note that relative M-X bond enthalpies correlate with H-X bond enthalpies, where X was a carbon- or heteroatom-based group.[93] Several related studies were published.[94,95] Large numbers of studies focused on the relationship between M-C and H-C bond enthalpies. Wick and Jones established that there was a linear correlation between the M-C and H-C bond enthalpies with a slope slightly larger than unity in the case of a Rh complex[96] and a similar result was found for Ti complexes.[97,98] DFT(B3PW91) calculations reproduced the experimental slopes of these correlations within 4% of the experimental values.

Absolute bond enthalpies were reproduced within 6% for the H-C bonds and relative bond enthalpies for M-C bonds were reproduced within 30 kJ/mol for Rh and within 19 kJ/mol for Ti.[99] This study indicated that computations can be used as a substitute for experiments when data cannot be obtained and several studies indeed followed.

DFT(B3PW91) calculations were used to determine the energetics of C-H oxidative addition of benzene and fluorinated benzenes Ar^F-H ($Ar^F = C_6F_nH_{5-n}$, n = 1-5) at a variety of metal fragments that differ by the metal (early to late), the coordination mode and nature of the ligands and the formal oxidation state.[100,38] These metal fragments were selected as they are models of experimental systems that can undergo oxidative addition with C-H bonds. The calculations correlated the H-C and M-C bond dissociation energies for all possible C-H bonds in the substrates. The calculations indicated that fluorine substituents have a major influence on the energetics of C-H oxidative addition to the metal fragments, and that the determining factor is the number of fluorines ortho to the activated C-H bond. The M-C bond energy is much more sensitive than the H-C bond; thus the M-C bond energy increases by 25-30 kJ/mol while the H-C bond increases by only 10-12 kJ/mol for each ortho fluorine (Figure 5, correlations shown for $RhCp(PH_3)$). The minor role of the meta and para fluorines is illustrated by the grouping in three sets on the correlation with 0, 1 or 2 ortho fluorines. It is thus possible to write the relative bond dissociation energy ΔD(M-C) as a linear function of the number n of fluorine substituents at the ortho, meta and para positions, where $b \gg a$ or c (equation 3).

$$\Delta D(\text{M-C}) = a + b n_{ortho} + c(n_{meta} + n_{para}) \text{ kJ/mol} \qquad \textbf{(3)}$$

The nature of the metal and its substituents has a relatively small influence as shown by the slope $\mathscr{R}^{\text{M-C/H-C}}$ of the correlation which ranges from 1.93 to 3.05. The values of the slope are as follows: $ZrCp_2$: 3.05, $TaCp_2H$: 2.52, $TaCp_2Cl$: 2.08, WCp_2: 2.34, $ReCp(CO)_2$: 2.25, $ReCp(CO)(PH_3)$: 2.43, $ReCp(PH_3)_2$: 2.62, $RhCp(PH_3)$: 2.62, $RhCp(CO)$: 1.98, $TaCp(PH_3)$: 2.39, $IrCp(CO)$: 1.93, $Ni(PH_2CH_2CH_2PH_2)$: 2.80 and $Pt(PH_2CH_2CH_2PH_2)$: 2.80.

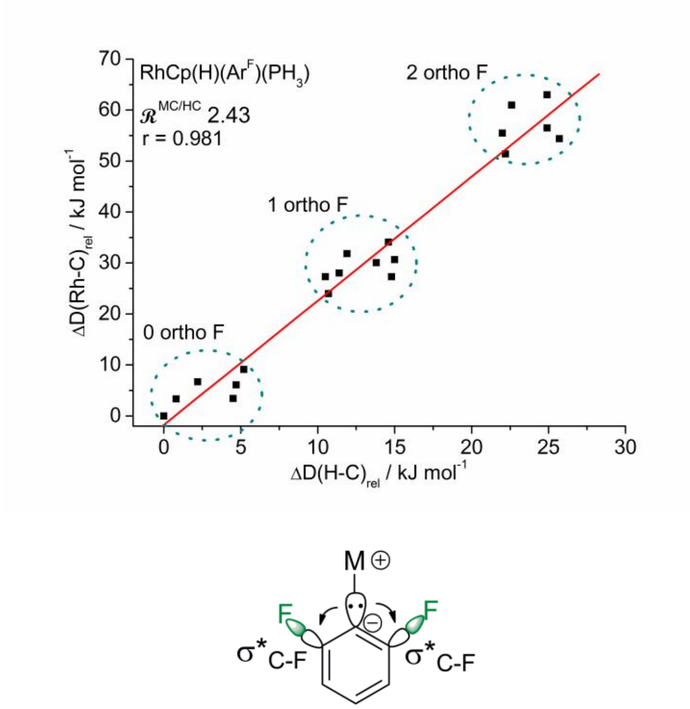


Figure 5. Above: Correlation between the Rh-C bond dissociation energy of RhCp(H)(Ar^F)(PH$_3$) and the H-C bond dissociation energies of fluorobenzenes. Below: schematic representation of the stabilization of the zwitterionic form of the M-C bond by ortho fluorine. Reproduced from ref 38. Copyright 2009 American Chemical Society

The origin of the ortho-fluorine effect revealed by these correlations is not fully understood[92] but the larger ionic character of the M-C bond relative to the H-C bond is likely to be an important factor. This ionic character results in a negative charge at the ipso carbon of the M-aryl bond, which is stabilized by fluorine substituents especially at the ortho position where hyperconjugation is effective as shown by the lengthening of the C-F bonds (see schematic representation of the lone pair on the carbanion to the C-F σ* orbitals in Figure 5). This stabilization adds to the electron-withdrawal effect, which influences all carbons and decreases from ortho to para carbons. These computations offered an interpretation of the selectivity of the C-H activation ortho to the C-F bond for which there are many manifestations. One of the best illustrations is the reaction of 1,3-difluorobenzene with CpRh(PMe$_3$) where all possible isomers are formed initially at low temperature by activation of the various C-H bonds. On warming, all isomers with zero or one fluorine ortho to the Rh-C bond isomerize to a unique product in which the Rh-C bond lies ortho to two fluorine substituents as shown in Figure 6.[28,35]

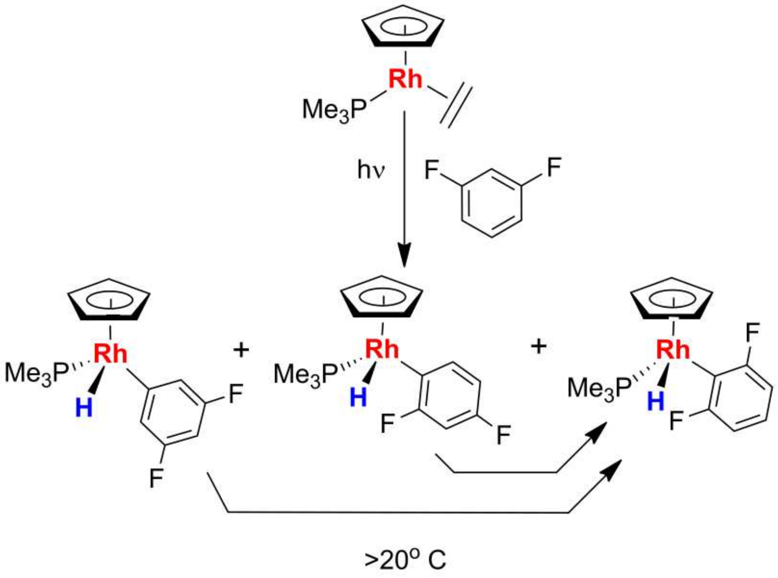


Figure 6. Preference for ortho fluorine at [CpRh(PMe_3)]. Adapted from ref 35. Copyright 2011 American Chemical Society

Furthermore, the quantitative aspect of the correlation, in terms of the value of the slope, was tested on Tp'RhH(Ar^F)($CNCH_2CMe_3$), where the experimental value of the correlation slope $\mathscr{R}^{M\text{-}C/H\text{-}C}$ of 2.14 could be advantageously compared to the calculated value of 1.96.[29] Similar results were obtained with other metal fragments.[101] These studies highlight the large impact of a fluorine substituent on the C-H bond dissociation energy.

The impact of the M-C bond energy of the product on the transition state for the C-H bond activation was also discussed. Since the C-H, M-H and M-C bonds are partially cleaved or made at the transition state, the energy relationship described between reactants and products may also apply to the transition state and therefore to the kinetics. This concept was first considered in the C-H activation reactions of fluorobenzenes at [CpRe($(CO)_2$)]. In this reaction, the C-H oxidative addition yields *cis*-[CpRe($(CO)_2$)(H)(Ar^F)] which transforms into the more stable *trans*-

[$CpReH(Ar^F)(CO)_2$]. The activation energies and the relative energies of the cis and trans products are separated into groups with 0,1 and 2 ortho fluorines (Figure 7).[88] Selectivity of C-H bond activation was also observed in the arylation reactions of fluorinated arenes where only an M-C bond is made since the H atom does not transfer to the metal (Section 5). Two factors were put forward, the acidity of the activated C-H bond[79,32] and the energy of the M-C bond being made.[78] These two factors run in parallel since the most acidic C-H bond and the strongest M-C bond being formed both lie ortho to fluorine. At this stage, it is not easy to separate the two factors.

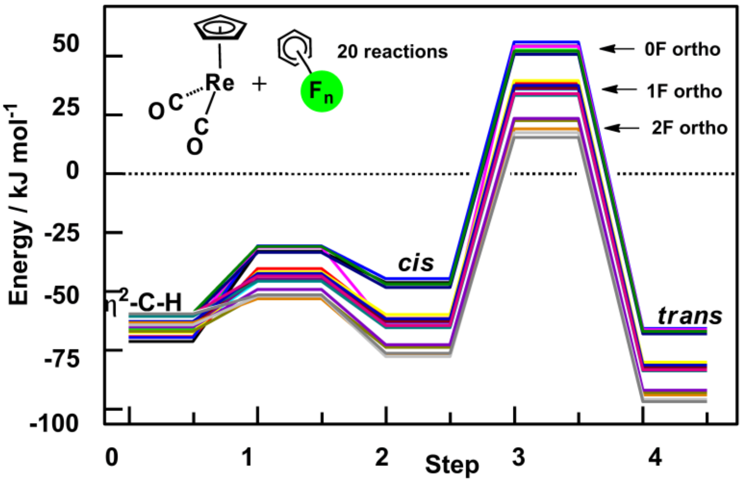


Figure 7. DFT(B3PW91) calculated electronic energies (kJ/mol) of steps on the pathway for reaction of all possible fluorobenzenes $C_6F_nH_{6-n}$ (n = 0-5) starting from $CpRe(CO)_2(\eta^2$-*C-H*-$Ar^FH)$ to t*rans*-$CpReH(Ar^F)(CO)_2$. Each line represents the pathway for one of the 20 possible complexes. The energy zero is taken as the isolated reactants. Note that the activation energies follow the energies of the products in falling into groups with 0, 1 or 2 F_{ortho}. Adapted with permission from ref 88. Copyright 2003 Royal Society of Chemistry.

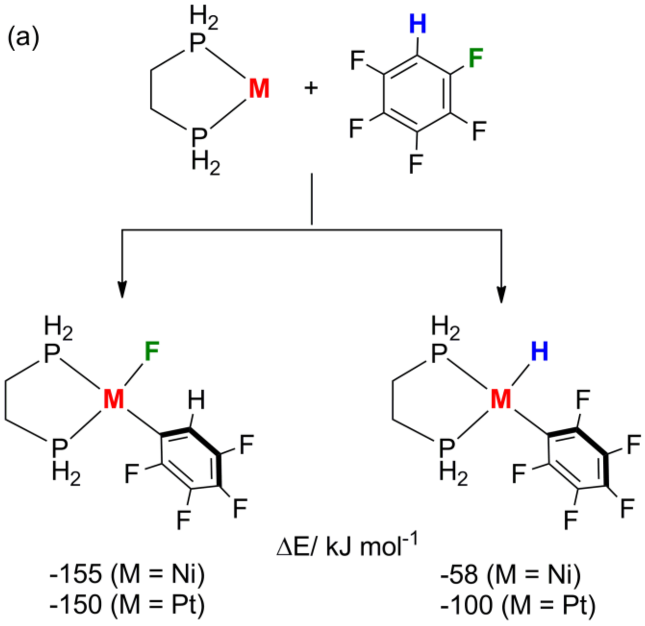
In rare cases, in particular when the product of C-H addition is in equilibrium with another compound, it was possible to obtain experimental values of the thermodynamics of the C-H addition step. $Ni(PEt_3)_2(\eta^2-C_6F_5H)$ is in equilibrium with the C-H oxidative addition product $Ni(PEt_3)_2(H)(C_6F_5)$ and the analysis of the NMR data gave a $\Delta G^0_{(303K)}$ of 3.3 ± 0.4 kJ/mol in pentane. DFT (B3LYP) calculations give a slight exoergicity of 8 kJ/mol in the gas phase. This disagreement between experiment and calculations is within the recognized limit of accuracy especially when solvent effects are not included in the calculations.[17] An equilibrium between the C-H oxidative addition product and the Ni-coordinated fluorobenzene complexes was also shown to occur in the reaction of 1,2,4,5- and 1,2,3,5-tetrafluorobenzenes with $Ni(PEt_3)_2$. In this case the formation of Ni-H complex is also marginally endoergic relative to the coordinated Ni^0 adduct.[89] More details on these reactions will be given in Section 4.2.3.3 on nickel.

3.3 Energetics and regioselectivity of C-F oxidative addition

Twenty years ago, the authors of this review, on describing some of the failures to activate the C-F bond by molecular transition metal complexes, wrote "*It is tempting to postulate that these failures to effect C-F activation can be explained by it being thermodynamically unfavorable and to point to the observation that C-F bonds are about 120 kJ/mol stronger than the C-H bonds. (…) However, the validity of this argument is questionable since metal fluorine bond energies are unknown.*"[102] From the experimental side, the situation remains unchanged but computationally determined values are now considered as more reliable.[103] This section will thus be based essentially on this approach.

Early computations (B3LYP) of the C-F oxidative addition of CH_3F to 3-coordinate $M(X)(PH_3)_2$, M = Rh, Ir, X = H, CH_3, Cl), considered as models of relevant transition metal complexes, showed that the reaction was exothermic.[104] This result was extended in a DFT(B3LYP) study of the oxidative addition of 1,4-difluorobenzene with $CpRh(PH_3)$ and $Os(PH_3)_2(CO)$, as illustrated by the greater stability of the isomer with the M-F bond.[102] The determination of the transition state for bond activation in the case of $CpRh(PH_3)$ gave an energy barrier for C-H bond activation about 100 kJ/mol lower than for C-F bond activation. DFT and limited CASSCF calculations of the α-X (X = H, F) isomerization from $RuCl(CH_2X)(PH_3)_2$ to $RuCl(X)(CH_2)(PH_3)_2$ showed that the product of α-X migration is thermodynamically favorable for both X (especially at the CASSCF level). The reaction has a significantly higher barrier for X = F, which was attributed in part to the repulsion between the occupied metal d orbitals and the F lone pairs at the transition state.[105]

Moreover, computational studies showed show how much the metal matters in determining the relative thermodynamics of C-H vs. C-F activation. The oxidative addition of d^{10} $M(PH_2\text{-}CH_2CH_2\text{-}PH_2)$ (M = Ni, Pt) to pentafluorobenzene starts with η^2-coordination of the arene to the metal and proceeds via C-H or C-F bond activation to yield a square planar d^8 M^{II} complex. The results from the DFT (B3LYP) calculations show that C-F oxidative addition is more favorable than C-H oxidative addition by ca. 100 kJ/mol for M = Ni and by ca. 50 kJ/mol for M = Pt (Figure 8).[90] If one includes the fact that the oxidative addition barriers are lower for Ni than Pt, the consequence of these features are that both C-H and C-F bond activation can be observed with Ni but that C-F bond activation would not be observed with Pt. The repulsion between the occupied d orbitals of the metal and the lone pairs of fluorine has been proposed as an interpretation of these results. Even if bonds are longer with Pt, the more diffuse character of this metal in comparison to Ni leads to larger repulsion with the neighboring fluorine lone pairs.



(b) In general:
Weaker η^2-coordination to Pt than Ni
C-F oxidative addition strongly exothermic
C-H oxidative adition: Pt more exothermic than Ni
Bond strength
D(**Pt**-**F**) < D(**Ni**-**F**)   D(**Pt**-**H**) > D(**Ni**-**H**)

Figure 8. (a) Thermodynamics of reaction of M(dhpe) with pentafluorobenzene with calculated ΔE C-H and C-F activation at M(dhpe) (dhpe = $H_2PCH_2CH_2PH_2$, M = Ni, Pt) , (b) general differences between nickel and platinum (adapted for (a) from ref 35 and (b) from ref 90). Copyright American Chemical Society, 2011 and 2004, respectively

The corollary of exothermic C-F oxidative addition of aromatic C-F bonds is that reductive elimination is endothermic. However, we now know that this is not always the case. It has been shown that reductive elimination of Ar-F is possible from higher oxidation state palladium, Pd^{IV}(Ar)F.[106,107] Similarly, there is strong evidence that reductive elimination of C-F is possible from Cu^{III} complexes by reaction of a macrocycle including an Ar-X (X = Cl or Br) bond with Cu^{I} and AgF. In this process, Cu^{I} reacts with the macrocycle undergoing oxidative addition to form a Cu^{III}-Cl complex that is converted to Cu^{III}-F before reductive elimination occurs to form an Ar-F bond.[108] DFT(B3LYP) calculations indicate that the reductive elimination step is exothermic by 17 kJ/mol. In a simpler reaction, aromatic boronate esters have been fluorinated using an electrophilic fluorinating agent in the presence of Cu^{I} and AgF, implicating reductive elimination from Cu^{III}F(Ar)(OTf)(NC*t*Bu).[109] Further related reactions have been described using $Cu^{II}(OTf)_2$ reagents and KF.[110] It has also been reported that C-F reductive elimination is possible from 3-coordinate T-shaped Pd^{II}F(Ar)L where L is a phosphine that blocks the fourth site on square-planar Pd (though there may be an agostic interaction at the fourth position).[111,112]

The regioselectivity of C-F oxidative addition has also been highlighted in several studies. Pentafluorobenzene typically undergoes C-F activation at the position para to H, just as in nucleophilic substitution reactions of functionalized pentafluorobenzenes,[44] but there are notable exceptions such as its reaction with $Ni(PEt_3)_2(\eta^2$-anthracene).[17] The C-F activation of 2,3,5,6-tetrafluoropyridine has also been studied extensively, revealing several reactions which are selective for the 2-position.[44] Since C-F oxidative addition is exoergic and irreversible, the selectivity can be assumed to be kinetic in origin.

4. SURVEY OF STOICHIOMETRIC REACTIONS WITH HYDROFLUOROCARBONS

4.1 Reactions of Metal Atoms and Ions.

The reactions between neutral or charged atoms and fluorinated aliphatic or aromatic molecules in the gas phase or in matrices have been studied by a combination of spectroscopic techniques and calculations (various DFT methods and high level correlated wave function methods). These reactions should inform of the intrinsic reactivity pattern of a naked element (neutral or charged depending on the techniques) towards activation of bonds in representative molecules in the absence of any interaction with other chemical systems such as the solvent. However, the solvent and the coordinated ligands have a major influence so that the pattern of C-H/C-F selectivity established in the gas phase for bare atoms and ions does not transfer fully to metal complexes in solution. On the same lines, computations show that that it is not possible to obtain intrinsic M-X bond energies because of the large influence of the other groups and ligands coordinated to the metal as described in section 3.2.[92]

4.1.1. Neutral metal atoms. Ablation of metal surfaces by a focused laser beam produces atoms that react with simple molecules under further excitation. The resulting products have been studied mostly by combining IR spectroscopy in low temperature matrices with DFT(B3LYP) calculations. (Note that there are differences in nomenclature between the solution and gas-phase literature. Where solution chemists would use *oxidative addition*, gas-phase chemists use *insertion*. Similarly, *complex formation* or *coordination* or *adduct*, as used by inorganic chemists, is replaced by *clustering* in the physical chemistry literature.) A large number of studies with early transition metals showed that activation of the C-F bond is systematically preferred. In the reactions of CH_3F with Ti, Zr, and Hf ,[113-115] the metal inserts into the C-F bond to yield $(CH_3)MF$ and there is no trace of insertion into the C-H bond. However, the C-H bond can be cleaved after the formation of $(CH_3)MF$. Thus a reversible photochemical reaction is observed in which $(CH_3)TiF$ forms $CH_2{=}TiHF$ by H α-migration. The Zr analogue, $CH_2{=}ZrHF$, which is trapped in argon matrix in singlet and triplet states behaves similarly. In the reaction with Hf, $CH_2{=}HfHF$ in its singlet state was the only product detected.[116] It was thus suggested that the reaction follows the same pathway as for Ti and

Zr and that undetected CH_3-Hf-F yielded the observed methylene complex via α-H migration. The reaction of the same group 4 metal atoms with CH_2F_2 and CHF_3 yielded $CHF{=}MF_2$ and HC-MF_3 in a triplet state for M = Zr and Hf.[117] CASSCF-MRMP2 calculations were carried out to determine the mechanism of formation of $(CH_3)MF$ in the case of M = Zr.[118]

With later metals of the Periodic Table, C-H and C-F activation are in competition. For instance the reaction of atomic Pt with CH_3F gives C-H and C-F insertion products to yield $(CH_2F)Pt(H)$ and $(CH_3)PtF$.[119] Analysis of the relative intensities of vibrational modes suggests that four times as much $(CH_3)PtF$ is formed as $(CH_2F)PtH$ and that migration of one of the CH_3 hydrogens to the metal is associated with the reverse migration of F yielding more $(CH_2F)PtH$. This latter complex is calculated to be 40 kJ/mol more stable than $(CH_3)PtF$. Analysis of bond energies suggests that Pt-H and Pt-F bond energies are similar and that the greater stability of $(CH_2F)PtH$ is due to the larger C-F strength. DFT(B3LYP) and single point CCSD(T) computations show that the coordination of CH_3F to (^{3}D and ^{1}S) Pt is marginally stabilizing and that insertion of Pt into the C-F is energetically facile and exoergic.[120] Migration of H from the methyl group to Pt has a very low energy barrier and the subsequent reverse F migration from the metal to the ligand has an accessible transition state and is energetically favorable.

4.1.2. Cationic metal ions. The reaction of cationic species with aliphatic (usually CH_3F) and fluorinated aromatic hydrocarbons has been studied by mass spectrometry. The group of Schwarz used Fourier transform ion cyclotron resonance[121] for the study of selected lanthanide ions with a variety of fluorinated molecules. The Bohme group used Inductively Coupled Plasma/Selected Ion Flow Tube (ICP/SIFT) tandem mass spectrometry to study the reaction of CH_3F with the entire set of lanthanide ions (except Pm^+).[122] The same group also studied the reaction of CH_3F with 46 ions including early to late transition metals and main group ions.[24]

4.1.2.1. Lanthanide ions. With lanthanide cations (Ln^+) the predominant primary reactive channel is the activation of the C-F bond and the formation of $M\text{-}F^+$. The efficiency of the reaction, studied with CH_3F as the substrate, was shown to depend significantly on the nature of the lanthanide (Figure 9).[122] The influence of the substrate was studied with a selection of lanthanide ions. Selective activation of the C-F bonds was observed for fluoromethane, 1,1-difluoroethane, hexafluorobenzene, and fluorobenzene. However, trifluoromethane and perfluorinated alkanes compounds such as tetrafluoromethane, hexafluoroethane do not react with any of the lanthanide ions.[123] Thus, C-F bond activation predominates for sp^3 as well as sp^2 carbon but the efficiency of the reaction depends on the metal as shown in Figure 9 in the case of a study with CH_3F. Two mechanisms, insertion-elimination and the harpoon mechanism were proposed but are unlikely to be distinguishable on the basis of rate measurements. They can differ by the correlations that can be established with some properties of the metal ions (Scheme 2).[122]

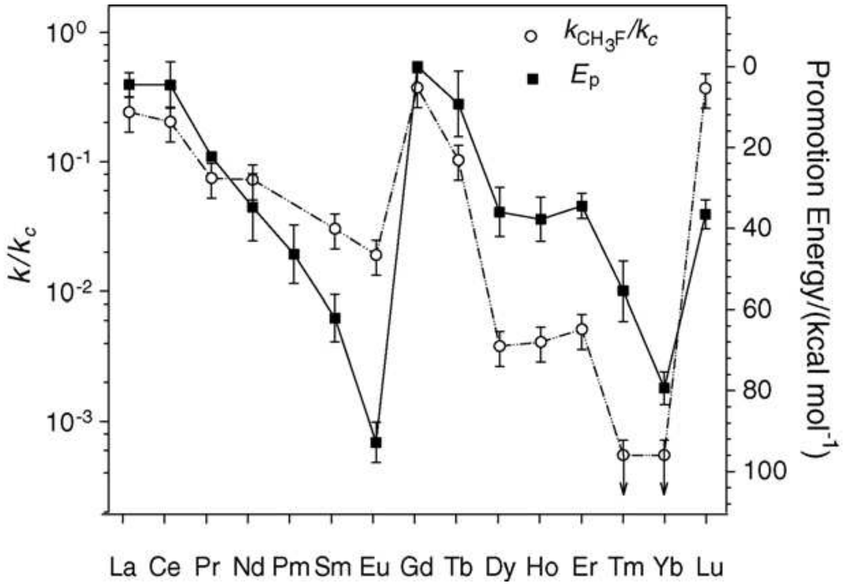
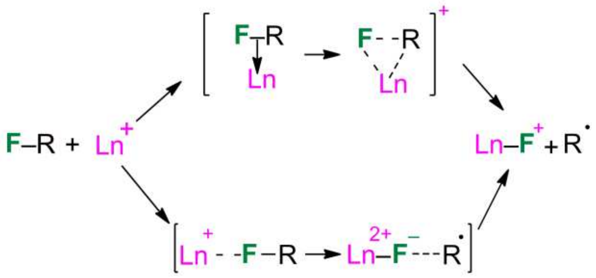


Figure 9. Reaction efficiency (open circles and left ordinate axis) and the promotion energy of Ln^+ to the $5d^16s^1$ electron configuration (filled squares and right ordinate axis in kcal/mol). Reproduced with permission from ref 122. Copyright 2005 Elsevier.

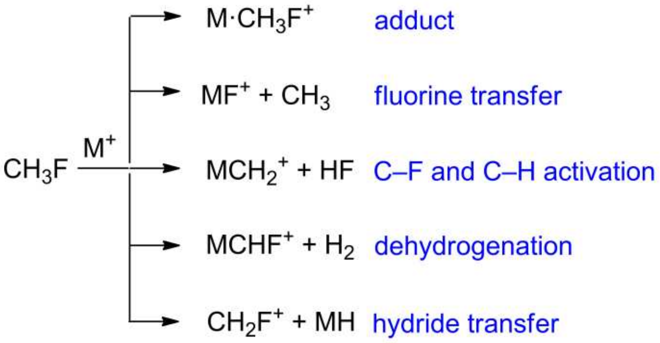
Scheme 2. Proposed mechanisms for the reaction of a lanthanide ion with a hydrofluorocarbyl (top) insertion-elimination, (bottom) harpoon mechanism



A key aspect of the harpoon mechanism is that it requires an electron transfer from the lanthanide Ln^+ to F-R through the encounter complex $[Ln\dots F\text{-}R]^+$. A consequence is that the efficiency of the reaction should depend on the second ionization energy (I_2) of the metal atom. ACPF and CCSD(T) calculations using a calcium ion as model for the lanthanide and CH_3F as the substrate confirmed that the harpoon mechanism applied in this case.[124] The presence of a correlation between the efficiency of the reaction and I_2 was shown in the initial study where only a limited number of lanthanide ions were used.[123] However, inclusion of all lanthanide ions showed that this correlation was not valid and a better correlation was obtained with the promotion energy to the first $5d^16s^1$ electron configuration of the ion (Figure 9).[122] It was concluded that the insertion-elimination mechanism should not be ignored. As will be mentioned in Section 4.1, the energy barrier of the harpoon mechanism may not entirely account for the global rate so that the lack of relationship between the rate and I_2 may have a variety of origins.[125] DFT(B3LYP) computational studies of the reaction of La^+ and Lu^+ with CH_3F confirmed that the two mechanisms proposed in Scheme 2 are in competition.[126,127] A study including the lanthanide ions from Ce^+ to Yb^+ showed that the harpoon and insertion mechanisms are feasible for all ions.[128] As proposed by Bohme *et al.*, it is possible that different substrates can prefer different mechanisms. A computational study of the reaction of CH_3F and C_6H_5F with Ce^+ and Ho^+ rationalized the higher rate of reaction observed for the fluoroarene by showing that a stabilizing interaction between the arene π system and the metal lowers the transition for the harpoon mechanism.[129] Furthermore, the activation of the carbon-halogen bond is specific to fluorine since no reaction was observed in the case of C_6H_5Cl. This lack of reactivity was attributed to the absence of an encounter complex between C_6H_5Cl and Ln^+.[130]

4.1.2.2. Non-lanthanide atomic ions. The systematic study of the reaction of CH_3F with 46 atomic ions, the fourth-period atomic cations from K^+ to Se^+, the fifth period atomic cations from Rb^+ to Te^+ (excluding Tc^+) and the sixth period atomic cations for Cs^+ to Bi^+, gives a broad perspective on the activation of naked atomic ions.[24] Five reactive channels were observed in varying amounts with different atomic ions (Scheme 3).

Scheme 3. The five primary reactive channels describing the reactions between a non-lanthanide atomic ion and CH_3F (Adapted from Ref 24; Copyright 2006 American Chemical Society)



Primary reaction channels were observed corresponding to F transfer, CH_3F addition, HF and H_2 eliminations; hydride transfer was obtained only with the excited state of some ions. Early transition metal ions are more reactive than late metal ions and further display a preference for F abstraction. Coordination of CH_3F is preferred from Mn^+ to Ga^+, Ru^+ to Te^+, and Hg^+ to Bi^+ as well as Re^+. Elimination of HF is the major channel for As^+ while dehydrogenation dominates the reactions of W^+, Os^+, Ir^+, and Pt^+. Thus, the sixth period atomic cations have the striking feature that they favor the dehydrogenation channel as a primary reaction. The hydride transfer occurs only in small quantities in the primary reaction. In a number of cases, multiple reactions occur yielding several F transfers and CH_3F additions as well as other reactions such as hydride transfer. The overall reactivity for the primary channels (excluding the minor competing channels associated with excited states of the ions) is schematically represented by the periodic graphic in Figure 10.

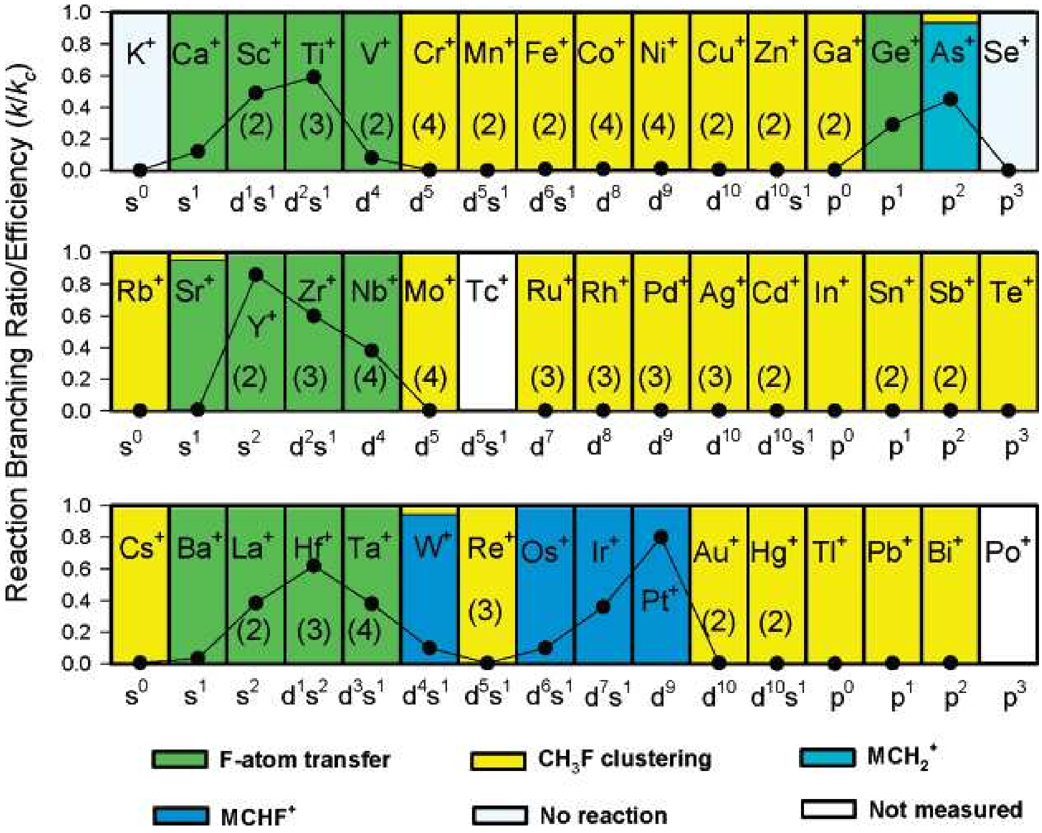


Figure 10. Periodic variations observed in the efficiencies, *k/k*$_c$ (represented as solid circles), for reactions of atomic cations with methyl fluoride, where *k* represents the measured reaction rate coefficient, and *k*$_c$ is the calculated collision rate coefficient. Also indicated are the observed reaction channels and the electron configurations of the atomic cations. Note that the term *clustering* in the physical chemistry literature is equivalent to *complex formation* or *coordination* as used by inorganic chemists. The numbers in parentheses indicate the number of sequential reactions of the same type. Trace amounts (≤ 12%) of MCH_2^+ that were observed in the reactions of Os^+, Ir^+, Pt^+, and Au^+ have not been included since these may be formed from excited M^+. Reproduced from ref 24. Copyright 2006 American Chemical Society.

A benchmark study of the level of theory required to evaluate the activation energy was carried out for the reaction of Pd with CH_3F where only C-F activation occurs.[131] A total of 26 functionals were compared using CCSD(T) and the relativistic effect represented at the highest level (all electrons, 4-component Dirac-Coulomb approach) as the reference. This study shows that numerous functionals performed well and highlighted the need for a very rich basis set on the metal including *f* and *g* functions. The concerted oxidative addition is shown to be preferred to the S_N2 reaction. Overall, all calculations cited in the following paragraph used appropriate methods.

As shown above, the C-H bond can be activated in the reaction of non-lanthanide ions with CH_3F. Several experimental and computational studies have been carried out to search for the factors that control the selectivity. Reactions of $Au^+(^1S)$ and $Au^+(^3D)$ with CH_3F were carried out in a drift cell in He at room and low temperatures in order to show the influence of the electronic state of the ion on the outcome of the reaction.[24,132] Ground state $Au^+(^1S)$ has two reaction channels, one where a coordination adduct $[Au(CH_3F)]^+$ is formed and one where HF is eliminated and $AuCH_2^+$ is formed. Excited state $Au^+(^3D)$ also eliminates HF presumably via formation of $^3AuCH_2^+$. It initiates a second reaction sequence with CH_3F^+ yielding ultimately CH_2F^+. DFT(B3LYP) exploration and CCSD(T) single point calculations contributed to understand the influence of Au^+ electronic state on the nature of the reaction.[27] $Au^+(^1S)$ and CH_3F form adducts via either F or one of the C-H bonds, the latter being less stable by about 50 kJ/mol. These two adducts lead to HF elimination in a multi-step process. The reaction with the lowest energy barrier corresponds to the C-H activation, which starts at the C-H coordinated Au^+ adduct. With $Au^+(^3D)$, only the C-H adduct is found to be stable and this adduct leads to C-H activation ultimately yielding H_2 and $AuCHF^+$.

The DFT(B3LYP) computational studies of the reactions of Ir^+ with CH_3F highlighted the diversity of elementary steps that can occur. Although the adduct between CH_3F and Ir^+ is bound by way of the fluorine atom, the activation of the C-H bond is calculated to occur with lower energy transition states than that for C-F activation. The outcome of these activations is either the elimination of H_2 or of HF, the former having lower energy barriers and being more exothermic than the latter by 15 kJ/mol. For elimination of HF, the initial activation is that of the C-H bond. Reaction pathways have been identified for various spin states of the metal.[133]

High level CASSCF-MRMP2 calculations were carried out for the reaction of Ru^+ with CH_3F.[134] No favorable channels for the insertion of the cation into the C-H bond could be detected but stable products resulting from the oxidative addition of Ru^+ to the C-F bond activation were obtained for all electronic states of Ru^+ studied. The formation of RuF^+ and CH_3 was found to be endothermic so that CH_3RuF^+ is the preferred product. Related calculations with neutral Ru showed that the insertion of the metal into the C-H bond is only possible for excited states of the metal while ground state of Ru yields the oxidative addition product, CH_3RuF.[135]

One remarkable result of the comprehensive exploration of metal-ion reactions with CH_3F by Bohme *et al.* was that formation of H_2 was obtained with metals of the sixth period. This was addressed computationally by Kim *et al.* with a combination of DFT(PBE0), CASSCF and DKH2 methods to consider the scalar relativistic effect. They showed that inclusion of the spin-orbit coupling (SOC) in the potential energy surface leads to a negligible energy barrier (< 8 kJ/mol) for the insertion of Os^+ into the C-H bond, while the energy barrier remains for insertion into the C-F bond. A full study of the reaction pathway established that indeed the elimination of H_2 is the favored product.[136] Not all heavy metals will be associated with large SOC and facilitate the C-H bond activation. Thus, Re^+ has a small SOC due to its electron configuration $5d^26s$ (^7S state) and consequently coordination to CH_3F is preferred (Figure 10). The results obtained for the effects of SOC on atomic metal ions are not transferable to coordinated metal complexes. Calculations show that the SOC depends significantly on the ligand coordination and oxidation state of the metal. SOC increases as the singlet-triplet gap decreases, the latter gap being smaller for less coordinated metal complexes. Thus, SOC is smaller at the transition state for oxidative addition to ligated metal complexes of Pt^0 and Ir^I, and the C-H activation barriers increase with SOC as shown by calculations at the CASSCF and CASPT2 levels.[137]

A computational study also tried to simulate the rate of reactions of metal ions with CH_3F in order to get more insight on the controlling factors.[125] The study focused on C-F activation at Sc^+, Ti^+, V^+ and Zn^+ where F abstraction is observed for the three first ions and coordination of CH_3F for the last (Figure 10). Combining DFT (mPW1K functional and QZVPP basis set) electronic calculations and a RRKM approach gave a preference for the harpoon mechanism. It showed that it was not possible to neglect the exothermic coordination between M^+ and CH_3F and the endothermic separation between the final product $M\text{-}F^+$ and CH_3 in order to describe the global rate of reaction. It was concluded that this was one of the reasons that the correlation between the rate of reaction and the second ionization energy of the metal fails. Finally, the lack of reaction with Zn^+ was shown to be due to the low affinity of Zn^+ for fluoride anion.

Dehydrohalogenation was observed by mass spectrometry in the reaction of Sc^+, Ti^+, V^+, Fe^+, Co^+, and Ni^+ with 1-fluoronaphthalene. An unusual loss of C_2H_2 was obtained with Sc^+.[138]

4.2 Reactions in Solution

4.2.1 Reactions with Aliphatic Hydrofluorocarbons. Overall the number of studies of the reaction of fluoroalkanes or CF_3 groups with transition metal complexes in solution is modest.

4.2.1.1 Lanthanides and metals of groups 3 to 5. The monomeric metallocene cerium hydride Cp'_2CeH (Cp' = 1,2,4-tri-*t*-butylcyclopentadienyl) reacts instantaneously with CH_3F, but more slowly with CH_2F_2 to give Cp'_2CeF and CH_4 in each case.[139] The reaction is thus formally a net H for F exchange. The cerium hydride complex reacts very slowly with CHF_3 to give Cp'_2CeF, H_2 and 1,2,4- and 1,3,5-tri-*t*-butylbenzene and does not react at all with CF_4. In the case of the reactions of CH_3F and CH_2F_2, the formation of intermediates Cp'_2CeCH_2F and Cp'_2CeCHF_2 was inferred from the non-metal products which derive from the trapping of CH_2 and CHF, respectively, by the solvent. Thus, the formation of Cp'_2CeF is initiated by selective C-H bond activation of the fluoroalkanes. DFT(B3PW91) calculations indicated that a σ-bond metathesis reaction between Ce-H and Ce-F bonds via a 4-membered transition state has high energy barriers for all fluoromethane substrates (Figure 11). A two-step reaction was shown to be preferred: deprotonation of CH_3F by the hydride yields H_2 and an intermediate containing a $Ce(\eta^2\text{-}CH_2\text{-}F)$ moiety. This intermediate has a carbenoid CH_2 group that inserts into H_2 to form CH_4 and the cerium fluoride complex in the rate determining step. The corresponding transition state lies at higher energy for CH_2F_2 and no transition state could be located for CHF_3 (Figure 11). This mechanism accounts for the trapping of carbenes. It is also supported by the isolation and characterization of a related carbenoid intermediate Cp'_2CeCH_2OR.[140]

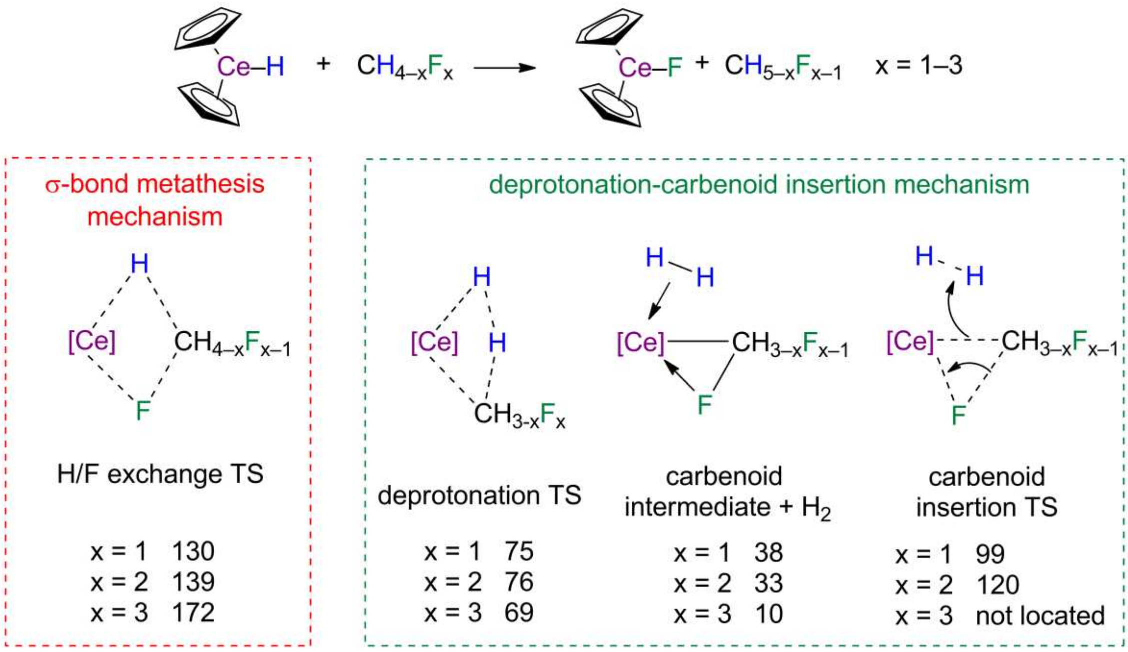


Figure 11. Mechanisms explored by DFT calculations (free energies in kJ/mol) for the reaction of fluoroalkanes with bis(cyclopentadienyl)cerium hydride since Cp' was modeled by C_5H_5. The zero of free energy corresponds to Cp_2CeH + substrate. Information taken from ref 139.

The reaction of Cp'_2CeCH_2Ph with CH_3F yields the metathetical exchange products Cp'_2CeF and CH_3CH_2Ph.[141] Labeling studies show that the methyl group of CH_3F is transferred intact, excluding a mechanism involving activation of the C-H bond of CH_3F. DFT(B3PW91) computations excluded the traditional σ-bond metathesis mechanism via a 4-center transition state. They suggested a transition state (Figure 12**)** in which the benzyl group interacts with the metal only by way of the arene group. This liberates the methylene group from the interaction with the metal with a consequent increase in its nucleophilicity. CH_3F interacts with the cerium center via F, which activates the methyl group towards a nucleophilic substitution. Thus, concerted formation of the C-C bond, cleavage of the C-F bond and formation of the Ce-F bond becomes possible.

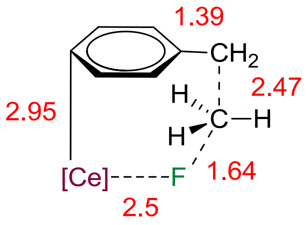
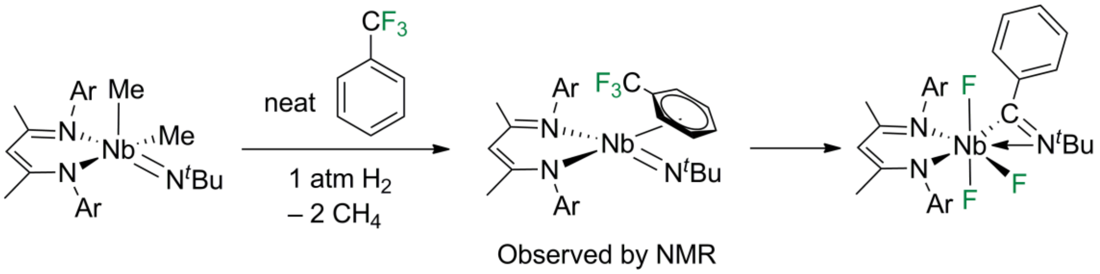


Figure 12. Schematic representation of the transition state for the reaction of Cp'_2CeCH_2Ph with CH_3F to form Cp'_2CeF and CH_3CH_2F. Adapted from ref 141**.** Copyright 2010 Royal Society of Chemistry

$Cp^*_2ZrH_2$ ($Cp^* = \eta^5$-C_5Me_5) reacts with primary, secondary and tertiary monofluorinated aliphatic hydrocarbons to give Cp^*_2ZrHF and/or $Cp^*_2ZrF_2$ and alkane quantitatively through a radical chain mechanism. The rate decreases in the order primary to tertiary and is also greatly reduced by the presence of CF_2H and CF_3 groups on the hydrocarbon.[142,143] The behavior of $Cp^*_2HfH_2$ resembles that of $Cp^*_2ZrH_2$ but with reduced reactivity.[144] The alkylidyne titanium complex (PNP)Ti≡C^{t}Bu (PNP^- = N[2-P($CHMe_2)_2$-4-methylphenyl]$_2$) generated by elimination of neopentane from the alkylidene precursor dehydrofluorinates 1-fluorohexane and fluorocyclohexane.[39] The terminal olefin product is identified spectroscopically in the case of 1-fluorohexane. More information on the reactions of this titanium complex is presented in Section 4.2.2.2.

All three C-F bonds in CF_3-substituted arenes are activated by a niobium imido complex as shown in Scheme 4.[43] NMR spectroscopy revealed the intermediacy of an Nb^{III} arene with C-F bonds that were still intact. DFT(B3LYP) calculations show a strongly exergonic pathway avoiding a concerted oxidative addition step and with no significant energy barrier to product. The calculations suggest a two-step reaction initiated by an F abstraction with Nb bonded to the aryl and not to the CF_2-Ph moiety. A 1,3 shift generates the Nb-CF_2-Ph bond. The two subsequent C-F activations appear to occur stepwise. Attempts to extend this chemistry to non-aromatic CF_3 groups led to intramolecular reactivity of the Nb complex. This activation of an sp^3-C-F bond is thus specific to the presence of an arene group.

Scheme 4. Selective activation of the CF_3 group (Adapted from ref 43; Copyright 2013 American Chemical Society)



4.2.1.2 Metals of group 6 and groups 9-11. While complexes of various metal fragments with hydrocarbons have been studied extensively, few studies concerned the coordination of fluorinated hydrocarbons. Fluoroalkanes have the potential to bind weakly to a metal complex with an empty coordination site through a C-H bond or through a lone pair on F, as was explored with photogenerated $[W(CO)_5]$.[23] This study gave gas-phase equilibrium constants between this metal carbonyl complex and CH_3F and C_2H_5F. Fluoromethane is more strongly bonded (around 48 kJ/mol) to W than methane (< 20 kJ/mol). Increasing the number of fluorines decreases the binding energy: the binding energy of CH_2F_2 is estimated to be ca. 20 kJ/mol and CHF_3 is found not to coordinate to the metal. Fluoroethane forms a complex bound by around 50 kJ/mol whereas CH_3CF_3 does not bind. The nature of the atoms of the substrates involved in the interaction with the metal could not be determined and the authors presumed that the interaction was via a C-H bond.[145] An ab-initio computational study of complexes of CH_3F, CH_2F_2 and CHF_3 with $W(CO)_5$ showed that the fluoroalkanes are bonded via the fluorine rather than by C-H and reproduced the decrease of bond dissociation energy with the increasing number of fluorines with BDE values of 58, 43 and 30 kJ/mol, respectively (at the MP2-BSSE corrected level) in good agreement with the experimental values.[25] At the same time, time-resolved spectroscopy confirmed that 1-fluorohexane binds to F in preference to C-H in $(1\text{-}C_6H_{13}F)W(CO)_5$.[23]

Fluoroalkanes such as CH_3F, CH_2F_2 and CH_3CF_3 undergo C-H oxidative addition exclusively in the reaction with the unsaturated Tp'Rh(CNneopentyl) complex to yield Tp’Rh(CNneopentyl)(R)(H).[146] The kinetic selectivity was established to be $CH_3F > CH_3CF_3 >$

CH_2F_2, all of them being slower than CH_4. This was attributed to the steric effect of the fluorine atoms on the carbon of the activated C-H bond. This study of the kinetics and thermodynamics of oxidative addition of R-H revealed that the presence of fluorine atoms on the alkyl group R increases the Rh-R bond dissociation energy (see section 3.2). Due to the preference for activating a primary C-H bond, the reaction of 1-fluoropentane occurs selectively at the carbon that is more remote from the fluorine atom.[147]

The reactions of the Ir^I pincer complex (^{tBu4}PCP)Ir(NBE) (NBE = norbornene) with CH_3F and with benzyl fluoride give products that derive formally from the insertion of the metal into the C-F bond, but proceed via an initial C-H bond activation (Figure 13**).**[42] The corresponding reaction with CHF_3 yields the C-H oxidative addition product, followed by HF elimination to form the difluorocarbene complex. The hypothesis of initial C-H activation proposed for CH_3F, is supported by the intermediates characterized in the reaction of CHF_3. In addition, DFT(M06) calculations show that the reaction pathway initiated by the C-H bond activation is a multi-step process, in which the highest transition state at 69 kJ/mol is associated with the α-fluorine migration. In contrast, the transition state for oxidative addition of the C-F bond is ca. 130 kJ/mol. This mechanism accounts for the formation of an alkene via C-H bond activation followed by β-fluorine elimination in the reaction with ethyl and isopropyl fluoride. The mechanism proposed by Goldman in which the C-H activation is the initial step for the C-F activation is closely related to that proposed for the cerium complex with CH_3F in Section 4.2.1.1.[139] In related chemistry of a rhodium complex,[148] (^{iPr4}PNP*)Rh(TBE) (TBE = *t*-butyl ethylene, ^{iPr4}PNP* = $i\text{Pr}_2\text{PC}_6\text{H}_3\text{Me-N-C}_6\text{H}_3\text{MeP}i\text{Pr}_2$) was reacted with CHF_3 and C_2HF_5 at 80° give $Rh{=}CF_2$ and $Rh{=}CF(CF_3)$, respectively. No intermediate is observed in this reaction with CHF_3, which may indicate that dissociation of TBE is the rate-limiting step. Presumably, the reactions occur with a similar mechanism to those of the Ir complex.

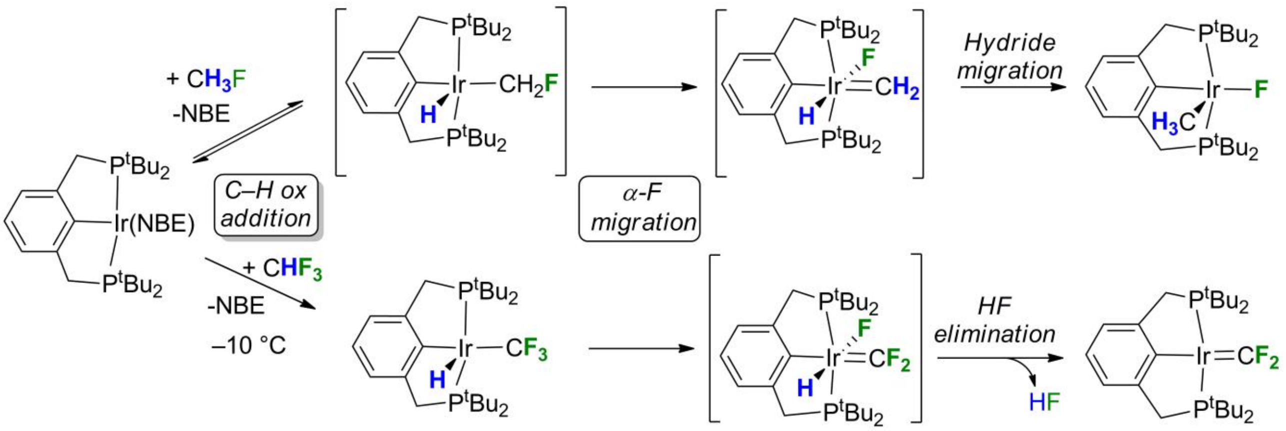
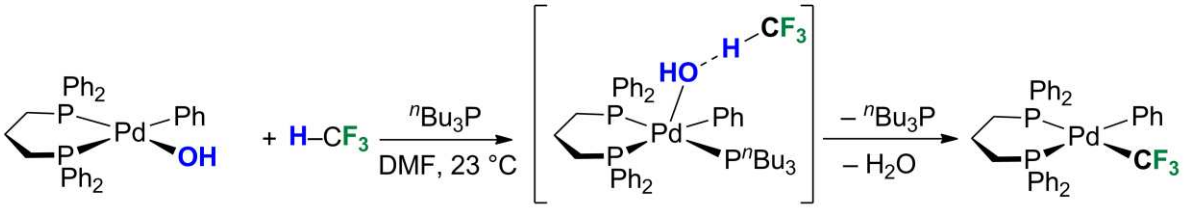


Figure 13. Proposed mechanism for oxidative addition of CH_3-F (above) and CHF_3 (below) to (^{tBu4}PCP)Ir. Adapted with permission from ref 42. Copyright 2011 American Association for the Advancement of Science.

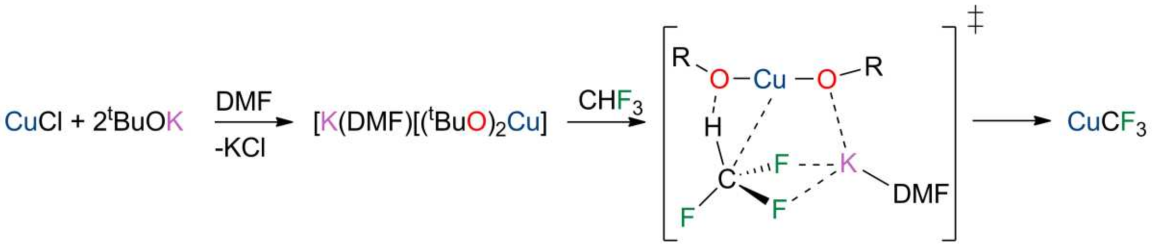
The C-H bond is also activated selectively in the reaction of the Pd^{II} hydroxy complex shown in Scheme 5.[149] In this case, a phosphine ($^nBu_3P$) serves as a Lewis base promoter for the deprotonation of CHF_3 by the OH group. DFT(M06L) computations suggest that the phosphine activates the OH group by coordinating to the metal. The computed free activation barrier of ca. 90 kJ/mol is compatible with the observed rate.

Scheme 5. Activation of the C-H bond of CHF_3 by a Pd^{II} complex (Adapted from Ref [149] Copyright 2013; American Chemical Society)



Fluoroform CHF_3 was activated exclusively via C-H bond cleavage when treated with CuCl and MOR (M = K, Na, 2 equiv) (equation 4).[150] The reaction involves the formation of alkoxycuprates $Cu(OR)_2^-$ yielding $CuCF_3$ at room temperature and 1 bar. It was shown that neither

CF_3^- nor CF_2 mediate the Cu-CF_3 bond formation but that the counter ion plays a critical role since cryptands inhibit the reaction. A DFT(B97D) study of the reaction mechanism shows that the transition state is maintained at low energy by a network of non-covalent interactions which also contribute to increase the acidity of the C-H bond of fluoroform through the K…F interactions (equation 4).[151]



(4)

4.2.2 Intermolecular Reactions with Aromatic Hydrofluorocarbons

4.2.2.1. Lanthanides. The reaction of Cp'_2CeH with partially and fully fluorinated benzene was studied in C_6D_6.[152] The reaction with C_6F_6 yields Cp'_2CeF, H_2 and tetrafluorobenzyne which was trapped by C_6D_6. An intermediate $Cp'_2Ce(C_6F_5)$ was isolated and its X-ray structure reveals a C_6F_5 group κ^2-bonded to the metal via a Ce-C bond and a donor-acceptor F→Ce interaction. The reaction of C_6F_5H with Cp'_2CeH yields Cp'_2CeF, H_2, and tetra- and trifluorobenzyne. One of the intermediates was identified as $Cp'_2Ce(2,3,5,6\text{-}C_6F_4H)$, the other intermediate being dinuclear $Cp'_2Ce(2,3,5,6\text{-}C_6F_4)CeCp'_2$ns. Direct H/F exchange (Figure 14) was disregarded on the basis of DFT(B3PW91) calculations as no transition state could be located. Instead, a rather unusual mechanism was proposed involving coordination of the fluorobenzene ring via one of the fluorines and activation of an α-C-F bond by the hydride. At the transition state, the activated HF moiety is H-bonded to Ce while it is F-bonded in the product. It was noted that the cerium-bonded hydrogen was only weakly negatively charged and that most of the negative charge was located on the aryl ring at this transition state. This favors the simultaneous formation of the Ce-C and H-F bonds; subsequent release of HF leads to the observed intermediate $Cp'_2Ce(\kappa^2\text{-}C_6F_5)$. Activation of the C-F bond in this intermediate yields C_6F_4. Alternatively, protonation of the Ce-C bond by HF yields

Cp'_2CeF and C_6F_5H that itself reacts to yield H_2 (observed) and C_6F_4 and C_6F_3H (C-F activation). Pentafluorobenzene reacts with the Ce-H through coordination of the F ortho to the C-H-bond, activation of the C-H bond by way of proton transfer to the cerium hydride and formation of H_2. In these reactions the C-H activation is associated with a lower energy barrier than the C-F activation but the final distribution of products is not determined by the relative energy barriers of these two events.

In a subsequent study, various partially fluorinated benzenes were reacted with Cp'_2CeH.[153] The regiochemical principle that emerges from this study is that when a choice of isomers is available, the observed product has fluorine atoms ortho to the Ce-C bond, whether this achieved by C-H or by C-F activation. This preference is in agreement with the analysis of the metal-carbon bond dissociation energies presented in section 3. The elementary reactions that comprise the net reaction are consistent with the postulate that the stereochemistry of the product is determined by the change in free energy of the net reaction rather than the activation energy of the elementary reactions which are proposed to have comparable values for C-H and C-F. In particular, this is illustrated by the irreversible rearrangement in the solid state of $Cp'_2Ce(2,3,4,5\text{-}C_6HF_4)$ where the Ce-C bond lies ortho to a single fluorine to $Cp'_2Ce(2,3,4,6\text{-}C_6HF_4)$ in which the Ce-C bond lies ortho to two fluorines.

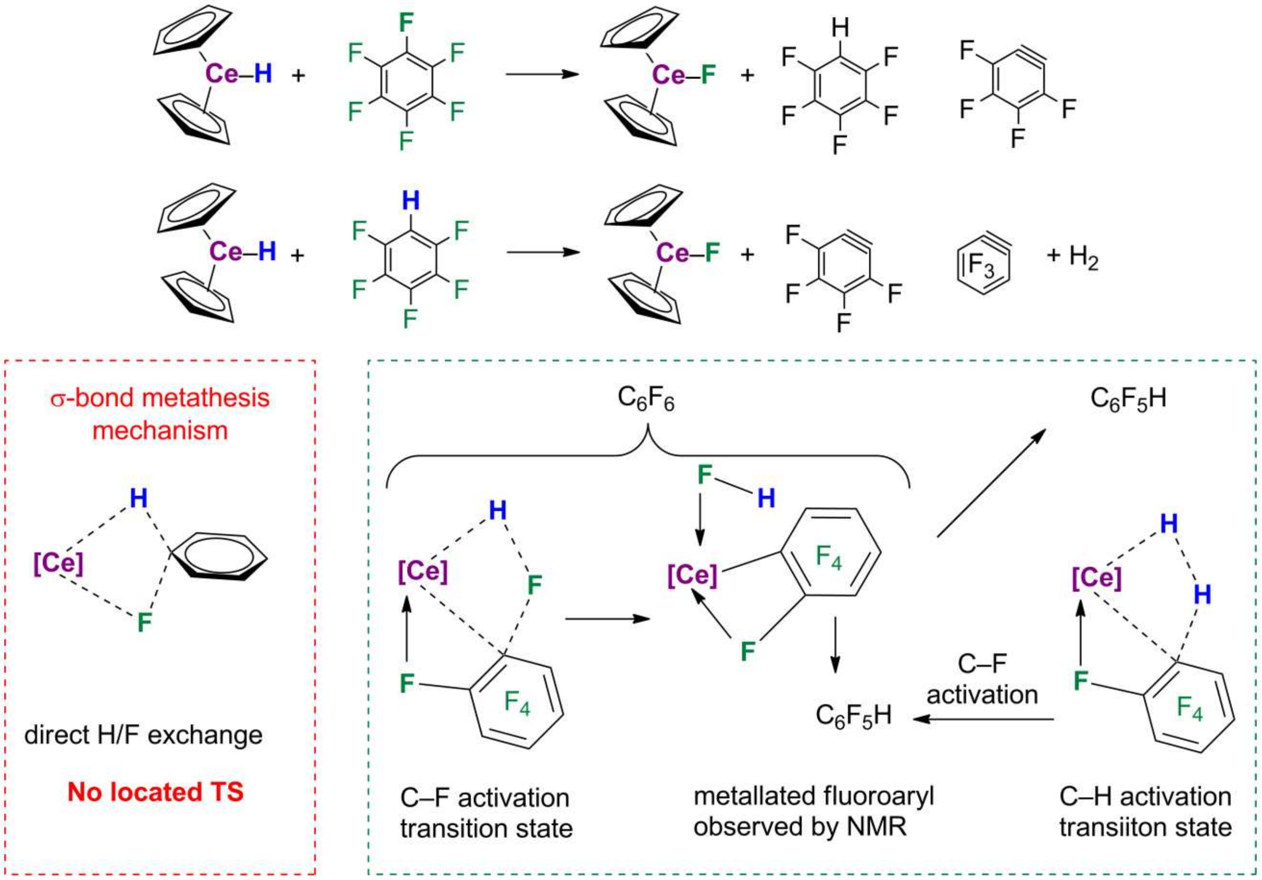


Figure 14. Above: reactions of C_6F_6 and C_6F_5H with Cp'_2CeH. Below: mechanisms and transition states. Adapted from ref 152. Copyright 2005 American Chemical Society

4.2.2.2. Early transition metals of groups 3 to 6. The C-F activation reactions of group 4 elements have been reviewed.[56] Of particular interest is the formation of isolable complexes of κ[1]-*F*-fluorobenzene and κ[2]-*F,F*-1,2-difluorobenzene with Cp^*_2M cations: $[Cp^*_2Sc(\kappa^1\text{-}F\text{-}FC_6H_5)_2]^+$, $[Cp^*_2Ti(\kappa^1\text{-}F\text{-}FC_6H_5)]^+$, $[Cp^*_2Sc(\kappa^2\text{-}F,F\text{-}1,2\text{-}F_2C_6H_4)]^+$, $[Cp^*_2Ti(\kappa^2\text{-}F,F\text{-}1,2\text{-}F_2C_6H_4)]^+$.[20] A related fluorobenzene complex of Ti^{IV} $[(nacnac)Ti{=}NAr(\kappa^1\text{-}F\text{-}FC_6H_5)]^+$ has also been described.[21]

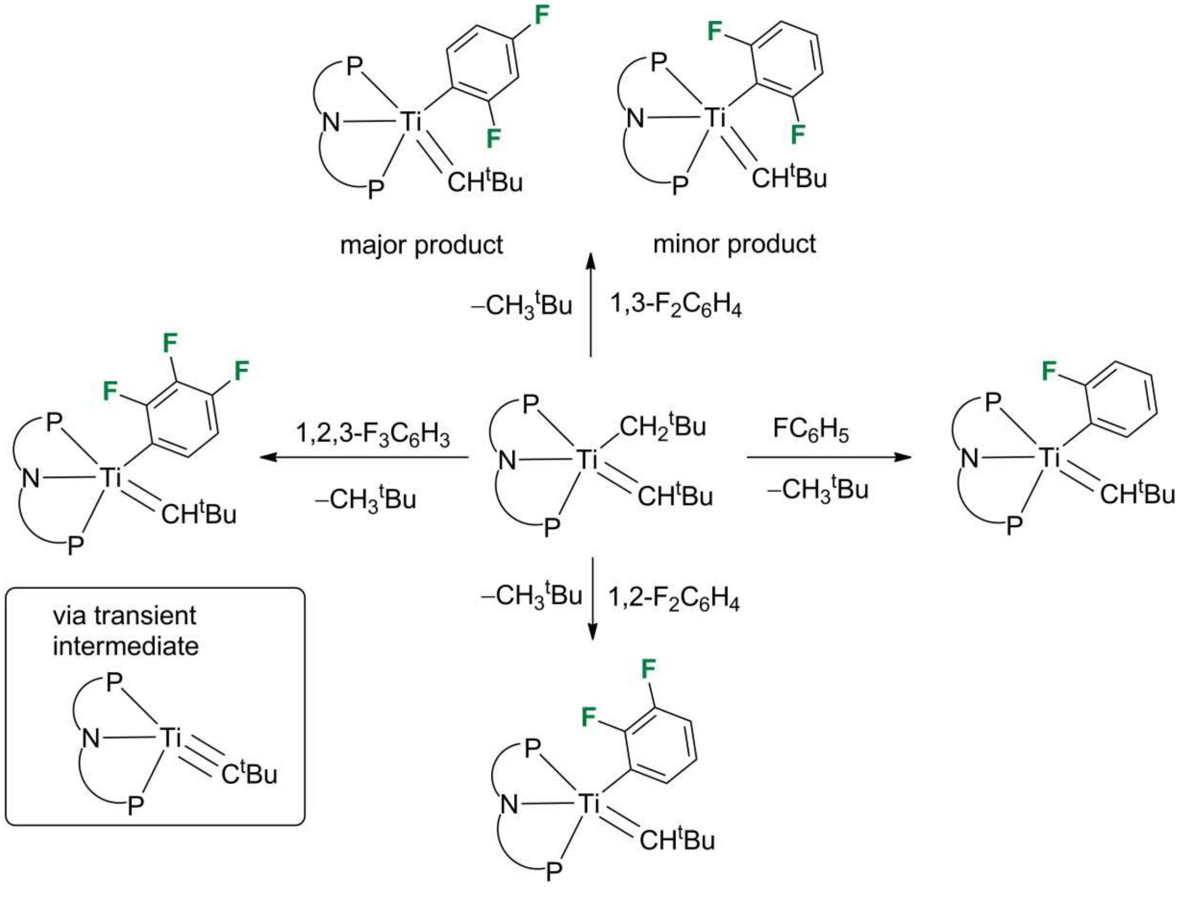
A base stabilized ketiminato scandium complex with a terminal imido ligand forms a reactive intermediate after loss of the coordinated Lewis base.[154] This intermediate reacts with partially fluorinated benzenes to form scandium anilido fluoride complexes indicating that both C-H and C-F bonds have been activated. The reaction rates depends on the substrate: fluorobenzene < 1,4-difluorobenzene ≈ 1,3,5 trifluorobenzene < pentafluorobenzene. A computational study (B3PW91) of the reaction pathway, calculated for C_6H_5F shows initial coordination of the hydrofluoroarene to Sc via F followed by proton transfer and Sc-aryl bond formation. C-F activation, which is associated with the highest transition state of the reaction, occurs via β-F migration as in the cerium complex described above.

Activation of C-H and C-F bonds has also been observed with metallocene derivatives. Although $Cp_2Ti\{\eta^2\text{-}C_2(SiMe_3)_2\}$ reacts with pyridine to form C-H activation products, the corresponding reaction with 2-fluoropyridine yields a dinuclear titanium fluoride.[155] In contrast, zirconium analogues, $Cp_2Zr\{\eta^2\text{-}C_2(SiMe_3)_2\}(THF)$ react with tetrafluoropyridines to form mononuclear products of C-H bond activation, $Cp_2Zr\{C_2(SiMe_3)_2H\}(C_5NF_4)$.[156]

$Cp^*_2ZrH_2$ reacts with fluorobenzene (1 equiv) under hydrogen to form $Cp^*_2Zr(H)F$, benzene and $Cp^*_2Zr(C_6H_5)F$ in a 1:1:0.75 ratio. An intermediate formed by loss of H_2 is identified as the C-H activation product, $Cp^*_2Zr(2\text{-}C_6FH_4)H$; this reaction is shown to be reversible. On heating in the absence of H_2, this complex isomerizes to $Cp^*_2Zr(C_6H_5)F$; arguments are presented to support isomerization via the *o*-benzyne complex $Cp^*_2Zr(H)(F)(C_6H_4)$. The formation of $Cp^*_2Zr(H)F$ and benzene is postulated to occur by direct nucleophilic attack by hydride on the aromatic ring (S_NAr2) and fluoride abstraction by zirconium. The reaction with 1-fluoronaphthalene is faster and the hydride intermediate is not observed.[142] The hafnium analogue $Cp^*_2HfH_2$ reacts with 2-fluoropyridine and 3-fluoropyridine to form C-F activation products, $Cp^*_2Hf(H)F$ and $Cp^*_2HfF_2$.[144]

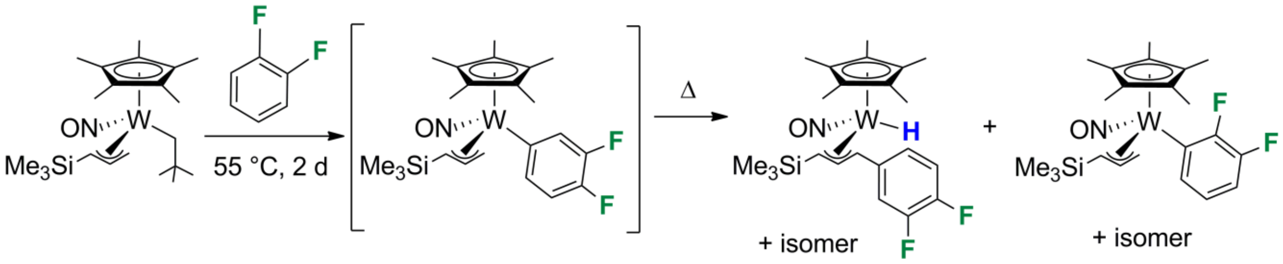
The alkylidyne titanium complex $(PNP)Ti{\equiv}C^tBu$ ($PNP^- = N[2\text{-}P(CHMe_2)_2\text{-}4\text{-methylphenyl}]_2$) generated by elimination of neopentane from the alkylidene precursor reacts with a series of partially fluorinated benzenes to form products by 1,2-C-H addition, (PNP)Ti(alkylidene)(fluorophenyl).[39] Initial elimination of neopentane generates a titanium alkylidyne complex (still with a d^0 configuration) that undergoes the 1,2-C-H addition. The reactions are selective for C-H bonds ortho to fluorine, though the major product from 1,3-difluorobenzene has Ti ortho to a single fluorine (Scheme 6). All of these products react on heating to form the titanium fluoride (PNP)Ti(alkylidene)F and organic products derived from the resulting benzyne. The C-H activation reaction with fluorobenzene was first order in [Ti]. Competition reactions between benzene and fluorobenzene show no significant preference for one substrate and both reactions have negligible kinetic isotope effects. The ortho-selectivity may result from activation of a random C-H bond, followed by ring-walking to the preferred position. The C-F activation reaction has a free energy of activation that is estimated to be ca. 20 kJ/mol higher than that for C-H activation at 298 K. DFT(B3LYP) calculations suggest that C-H activation proceeds via a κ-*F*-fluorobenzene adduct. In contrast, reactions of the same alkylidyne complex with 2-fluoropyridine or 2,4-difluoropyridine form titanium fluoride complexes by cycloaddition with no sign of C-H activation. Exploration of the hypothetical C-H activation pathway shows that C-H activation has a higher barrier and yields a less thermodynamically stable product than C-F activation.[157]

Scheme 6. 1,2-C-H addition reactions of titanium alkylidyne complex with fluorinated benzenes (Adapted from Ref 39; Copyright 2009 American Chemical Society)



The reactions of niobium imido complexes (β-diketiminate)Nb(=N^{t}Bu)(η^6-C_6H_6) with partially fluorinated benzenes Ar-F yield C-F activation products (β-diketiminate)Nb(=N^{t}Bu)(Ar)F.[158] Similarly, TpW(NO)(PMe_3)(η^2-C_6H_6) reacts with fluorobenzene to form TpW(NO)(PMe_3)(Ph)F with no sign of a C-H activation product or of TpW(NO)(PMe_3)(η^2-C_6H_5F).[159] In contrast, the reactions of Cp*W(NO)($CH_2{}^tBu$)(η^3-$CH_2CHCHSiMe_3$) with fluorobenzenes Ar^F-H yield only C-H activation products Cp*W(NO)(Ar^F)(η^3-$CH_2CHCHSiMe_3$) (Ar^F = C_6F_5, 1,4-$C_6F_2H_3$) releasing neopentane. The reaction with 1,2-$C_6F_2H_4$ yields a mixture of Cp*W(NO)($C_6F_2H_3$)(η^3-$CH_2CHCHSiMe_3$) with the tungsten ortho to a C-F bond and Cp*W(NO)(H){η^3-CH($C_6F_2H_3$)$CHCHSiMe_3$} in which the $C_6F_2H_3$ substituent lies meta to the C-F bond (Scheme 7). The latter product is formed preferentially.[160]

Scheme 7. Reactivity of Legzdins' tungsten complex toward 1,2-difluorobenzene (Adapted from Ref 160 Copyright 2012; American Chemical Society)

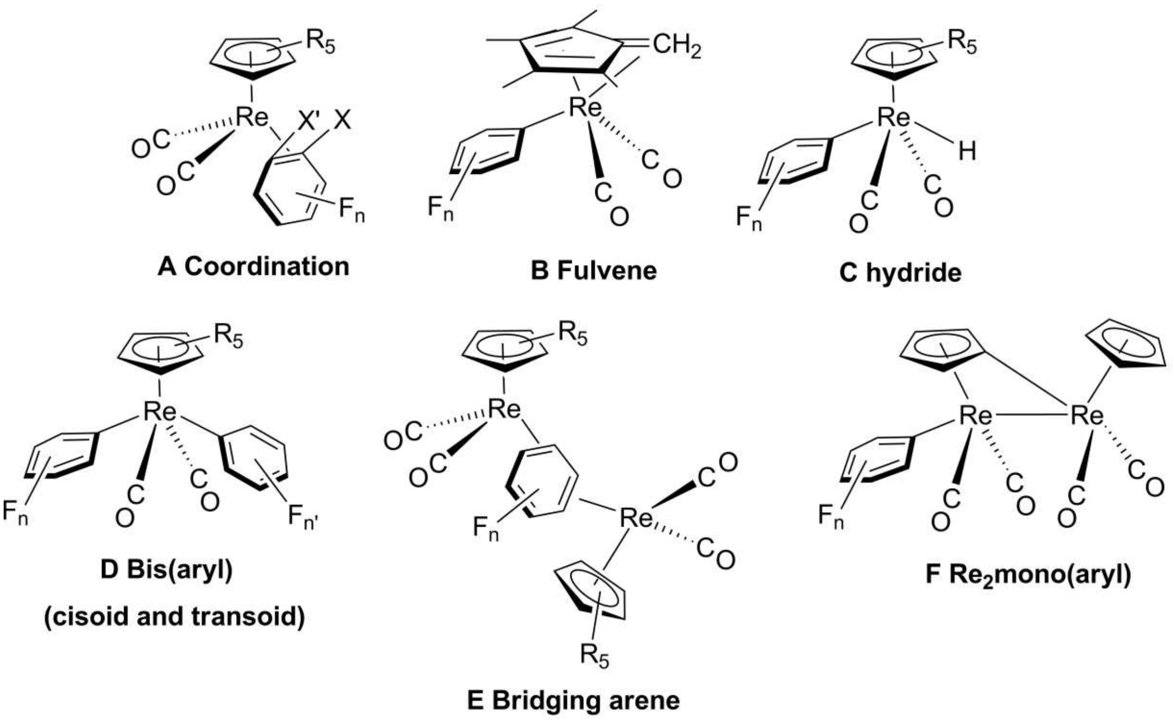


To summarize the reactivity of group 3-6 complexes toward fluorinated aromatics as far as it is known, many of the reactions result in C-F activation but C-H activation may also occur on making quite small changes to the ligand set. The most striking C-H bond activation reactions are the 1,2-addition reactions of (PNP)Ti≡C^{t}Bu and the reactions of Cp*W(NO)($CH_2{}^tBu$)(η^3-$CH_2CHCHSiMe_3$) that occur irreversibly by elimination of neopentane.

4.2.2.3. Groups 7 and 8. The 18-electron complexes CpRe$(CO)_3$, Cp*Re$(CO)_3$, and their dinitrogen analogues (η^5-C_5R_5)Re$(CO)_2(N_2)$ are reactive towards partially fluorinated benzenes under photochemical conditions (the N_2 complexes exhibit higher quantum yields). The reactions generate three types of product **A**-**C** containing Re and fluoroaryl (or fluoroarene) groups in a 1: 1

ratio that vary systematically with the Re precursor and the fluoroarene. Additional products of types **D**-**F** are formed with different ratios of Re : fluoroaryl (Scheme 8).[16,161-163] Product types **A** and **E** require η^2-coordination of the fluoroarene and offer choices between CH=CH, CH=CF and CF=CF coordination in the cases of partially fluorinated arenes. Product type **B** requires a η^5-C_5Me_5 precursor and involves C-F bond activation of the fluoroarene and abstraction of a hydrogen from a methyl group to form $(\eta^6\text{-}C_5Me_4CH_2)Re(CO)_2(C_6F_5)$ and HF, with the formation of HF giving the reaction a strong thermodynamic driving force. Product type **C** effects C-H activation of the fluoroarene. The dramatic changes in the product distribution are shown in Table 2 and originate in substantial part from the extra strength of metal-aryl bonds with ortho-fluorine substituents as discussed in Section 3.

Scheme 8. Product types from photo-reactions of fluorinated arenes with $CpRe(CO)_2$ and $Cp^*Re(CO)_2$ precursors



A Coordination

B Fulvene

C hydride

D Bis(aryl)
(cisoid and transoid)

E Bridging arene

F Re₂mono(aryl)

Table 2. Product distribution of $CpRe(CO)_2$ and $Cp^*Re(CO)_2$ toward fluoroarenes (1:1 products only)

Fluoroarene	Product type Cp	Product type Cp*	Reference
C_6F_6	**A**	**B**	161,162
C_6F_5H	**C**	**B** and **C**	163
1,2,4,5-$C_6F_4H_2$	**C**	**B** and **C**	163
1,3-$C_6F_2H_4$	**-**	**C**[a]	100
1,4-$C_6F_2H_4$	**A** and **C**	**A** and **C**	16
C_6H_6	-	**A**	164

[a] Only $Cp^*Re(2,6\text{-}C_6F_2H_3)H(CO)_2$ product

We first consider products of type **A**-**C** and highlight the contrast between the reactivity of Cp and Cp* precursors toward hexafluorobenzene. Whereas irradiation of $CpRe(CO)_3$ yields the (η^2-arene) complex of type **A**, the corresponding reaction with the Cp* analogue results in a product of type **B**.[161,162] When one or two hydrogens are introduced into the substrate as C_6F_5H or 1,2,4,5-$C_6F_4H_2$, the Cp complex gives a C-H activation product of type **C** while the Cp* analogues gives a mixture of types **B** and **C**.[163] The reactions with 1,4-$C_6H_4F_2$ yield products of type **A** and **C** with both Cp and Cp* precursors.[16] Independent synthesis of the hydride $Cp^*ReH(2,5\text{-}C_6F_2H_3)(CO)_2$ at low temperature shows that it converts to $Cp^*Re(\eta^2\text{-}1,4\text{-}C_6F_2H_4)(CO)_2$ on warming, demonstrating that the η^2-arene complex is the thermodynamic product and the hydride is the kinetic product. The difluorobenzene in $Cp^*Re(\eta^2\text{-}1,4\text{-}C_6F_2H_4)(CO)_2$ is coordinated by the CH=CH bond only. DFT(B3LYP) calculations show a preference for CH=CH coordination over CH=CF coordination of around 18 kJ/mol. EXSY measurements show that this complex undergoes an intramolecular [1,4] metallotropic shift to form the degenerate isomer coordinated by the alternative CH=CH bond. The calculations have shown that this is, in reality, a multi-step process involving three [1,2]-shifts. Thermal decomposition of Cp*Re(η^2-1,4-$C_6F_2H_4$)$(CO)_2$ leads to a dinuclear product of type **E** that exhibits both CH=CH and CH=CF coordination. Following the predictions of DFT calculations that complexes with two fluorines ortho to the C-F bond would be strongly stabilized, it was shown that the product of reaction of Cp*Re$(CO)_2(N_2)$ with 1,3-$C_6F_2H_4$ is exclusively of type **C** and C-H activation only occurs at the position with two ortho fluorine substituents.[100] Benzene itself forms η^2-arene products of type **A** and **E**.[164] The origin of the secondary products of type **D** and **F** are discussed in reference [163].

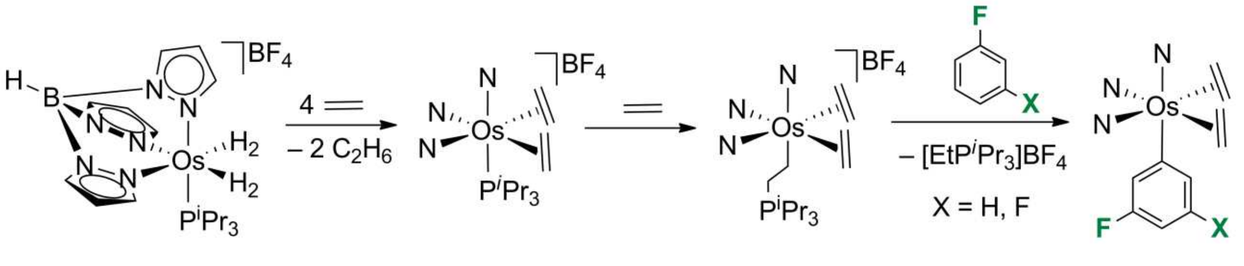
The mechanism of the C-H activation reaction to form products of type **C** has been probed by DFT(B3PW91) calculations.[88,100] The Re(η^2-arene) complex is converted to a σ-C-H complex before oxidative addition occurs to yield a cis product that then isomerizes to the final trans-isomer. The rate-determining step is not the oxidative addition, but the cis-trans isomerization. When comparing the complete set of fluorinated benzenes, it is found that the barriers vary systematically with the number of ortho F substituents, as do the energies of the final products (Figure 7). Thus the selectivity described above is kinetically determined, but the kinetics mirror the thermodynamics (see Section 3).

The dihydride complex *cis*-Ru$(H)_2(dmpe)_2$ reacts readily with fluorinated benzenes to give C-F activated products, *trans*-RuH(Ar^F)$(dmpe)_2$. The reaction with C_6F_6 or C_6F_5H proceeds rapidly at –78 °C, but the reaction with less fluorinated substrates is much slower. The reaction with 1,2,3-$C_6F_3H_3$ requires days at room temperature.[165] Pentafluorobenzene undergoes attack at the position para to H as usual, 1,2,3,4-trifluorobenzene and 1,2,3 trifluorobenzene are both attacked at the 2-position. These reactions also generate *trans*-RuH(FHF)$(dmpe)_2$ unless excess NEt_3 is added.[166] The mechanism of these reactions has yet to be established conclusively.

The 16-electron osmium complex OsH(Ph)(CO)(P*t*$Bu_2Me)_2$ reacts with 1,3-$C_6F_2H_4$ to give benzene and the C-H activation product with two ortho fluorines OsH(2,6-$C_6F_2H_3$)(CO)(P*t*$Bu_2Me)_2$.[167] There is no evidence for any other isomer either after short reaction times or on heating. Both DFT(B3LYP) calculations and the experimental evidence indicate that this is the thermodynamic isomer and that the reaction is exoergic. Reaction with 1,4-$C_6F_2H_4$ and C_6FH_5 also give C-H activation products, in each case with two rotamers. The monofluoro complex exhibits ortho selectivity. Slow rotation is also characteristic of the product from C_6F_5H. These reactions are slowed down by a factor of 20 with 1 equiv added phosphine and the rate depends also on the type of arene. There is no exchange of incoming and outgoing hydride. The mechanism is proposed to involve initial coordination of arene followed by subsequent loss of phosphine. Only at that stage is benzene eliminated so phosphine can re-coordinate, but the full details of this mechanism remain elusive. Although these reactions yield the thermodynamic product of C-H activation, it should be emphasized that the overall thermodynamic product would yield the fluoride. Thus, the choice of C-H vs C-F activation is kinetically controlled. In the absence of C-H bonds as in hexafluorobenzene, there is no reaction.[102]

Reaction of an osmium bis(dihydrogen) complex with ethylene in fluorobenzene results ultimately in C-H bond activation of the fluorobenzene at the position meta to fluorine Os(3-C_6FH_4). The reaction proceeds via two isolated bis(ethylene) complexes: the first has a conventional ligand arrangement while the second contains a triisopropylphosphoniumethyl ligand. Elimination of the phosphonium salt precedes the reaction with fluorobenzene which is postulated to occur by a σ-bond metathesis mechanism. Reaction with 1,3-difluorobenzene gives the corresponding Os(3,5-$C_6F_2H_3$) complex (Scheme 9).[168]

Scheme 9. Reactivity of osmium dihydrogen complexes (note abbreviation of Tp ligand), (Adapted from ref 168; Copyright 2011 American Chemical Society)

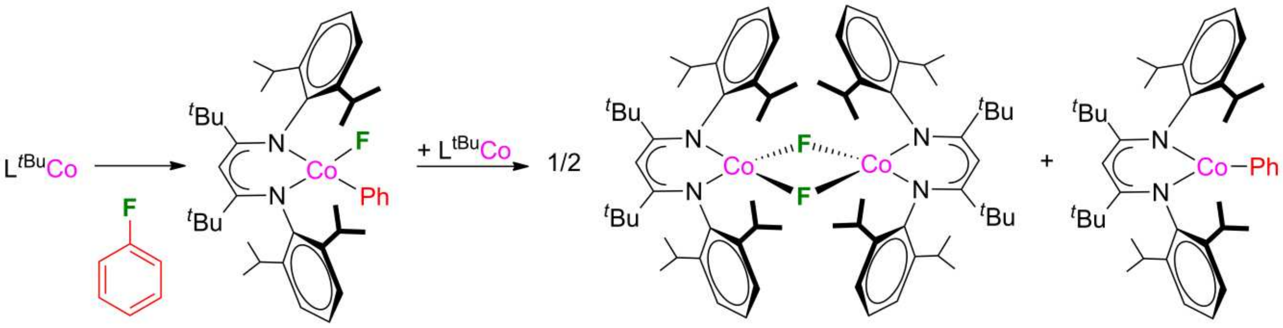


4.2.2.4. Group 9. The examples of intermolecular aromatic C-H activation of fluoroaromatics at rhodium and iridium provide the most decisive examples of the energetic principles described in

Section 3.2, but C-H activation at cobalt has not been recorded. While intermolecular C-F activation is well documented for cobalt, the intermolecular C-F oxidative addition reactions of rhodium and iridium complexes are rare. There are some exceptional reactions of rhodium leading to C-F activation with fluorinated pyridines and some reactions of a rhodium anion involving nucleophilic attack on the fluoroarene. The dominance of C-H oxidative addition at Rh and Ir is very different from the intramolecular cyclometalation reactions of the same elements to be described in Section 4.2.3.

A paramagnetic η^6-coordinated fluoroarene (3,5-*i*Pr$_2$-Ar*)Co(η^6-C$_6$H$_5$F) is formed by reduction of a dimeric Co^{II} precursor in the presence of fluorobenzene (3,5-*i*Pr$_2$-Ar* is a terphenyl).[169] The reaction of a masked two-coordinate (*t*Bu$_2$L)Co^{I} complex with fluorinated benzenes results in C-F activation exclusively to yield (*t*Bu$_2$L)CoAr and dinuclear [(*t*Bu$_2$L)Co(μ-F)]$_2$. The reaction follows simple second order kinetics. Comparisons of different difluorobenzenes showed that the reaction is speeded up by a meta-F, slowed down by an ortho-F and unaffected by a para-F. The authors conclude that rate-determining C-F oxidative addition is followed by disproportionation (Scheme 10).[170,171] A DFT (B97D) investigation of the reaction used a model with methyl groups in place of *t*Bu and diisopropylphenyl, before moving to a QM/MM approach for the full ligand. Two initial pathways are considered, a radical pathway via Co^{II} and an oxidative addition pathway leading directly to Co^{III}. Their relative energies are strongly affected by the choice of model, indicating the danger of simplified models. According to the QM/MM method, the barriers for the two pathways are almost identical, but only the oxidative addition pathway is exoergic. The Co^{III}-F bond energy is calculated to be D(Co^{III}-F) = 395 with L^{Me} and 352 kJ/mol with the QM/MM approach.[172]

Scheme 10. Reactivity of Co^{I} complex (Adapted from ref 170; Copyright 2011 American Chemical Society)



The reactions of $Co(PMe_3)_4$ with perfluorinated aromatics yield C-F activation products, but reaction with pentafluorobenzene in the presence of CO generates $CoH(C_6F_5)(PMe_3)_2(CO)_2$.[173] This reaction forms the basis of a catalytic hydrodefluorination study.[174] In a related reaction with 2,3,5,6-tetrafluorobenzene, but without the CO as trap, the products are Co(2,3,5,6-C_6F_4H)$(PMe_3)_3$ together with the difluorophosphorane F_2PMe_3 and trifluorobenzene. When CO was added as a trap, a Co(I) complex Co(2,3,5,6-C_6F_4H)$(PMe_3)_2(CO)_2$ is formed in place of the expected Co^{II} hydride.[175]

The energetics of coordination of fluorobenzenes to cationic rhodium complexes were discussed in Section 3.1.[18] The C-H selective oxidative addition of fluorobenzenes on photochemical reaction of $(\eta^5\text{-}C_5H_5)Rh(PMe_3)(C_2H_4)$ or thermal reaction of $(\eta^5\text{-}C_5Me_5)Rh(PMe_3)(Ph)H$ and the associated energetic preference for ortho-F was highlighted in section 3.2 and Figure 6.[28,35,100] These reactions were key to the development of bond energy correlations. The C-H selectivity extends to reaction of $(\eta^5\text{-}C_5R_5)Rh(PMe_3)(C_2H_4)$ with 2,3,5,6-tetrafluoropyridine.[176] The mechanism of the reactions has also been examined by DFT(B3LYP) calculations and the strong preference for C-H activation over C-F activation has been traced to the difference in geometries of the transition states. The TS for C-F activation shows much less making of the Rh-C bond than that for C-H activation.[102]

The thermal reaction of $Cp^*Rh(H)_2(PMe_3)$ with pentafluorobenzene follows a different course, resulting in C-F bond activation to yield Cp*Rh(H)(2,3,5,6-C_6F_4H)(PMe_3). The corresponding reactions with perfluoroarenes are catalyzed by the fluoride product and evidence is presented that these reactions proceed via deprotonation to yield [Cp*RhH(PMe$_3$)]$^-$ followed by nucleophilic attack on the fluorinated arene at the position para to H.[177]

Photochemical reaction of Tp′Rh(CNneopentyl)(η^2-Ph-N=C=N-neopentyl) or Tp'Rh(H)$_2$(PR$_3$) (Tp' = tris(3,5-dimethylpyrazolyl)borate, PR$_3$ = PMe$_3$ or PMe$_2$Ph) with fluorinated benzenes is also C-H selective yielding Tp′Rh(Ar^F)(H)(CNneopentyl) and Tp′Rh(Ar^F)(H)(PR$_3$), respectively. The isomer mix from the PMe$_2$Ph complex and the thermal conversion to ortho-fluorinated isomers is illustrated in Figure 15. The relative Rh-C bond energies and their significance were discussed in Section 3.2.[29,101] Unlike many related complexes, hexafluorobenzene is unreactive toward Tp′Rh(Ar^F)(H)(PMe$_3$) under photochemical conditions and can even be used as an inert solvent. Pentafluoropyridine does undergo C-F oxidative addition, however, and 2,3,5,6-tetrafluoropyridine forms a mixture of C-H activation (80%) and C-F activation (20%) products.[178]

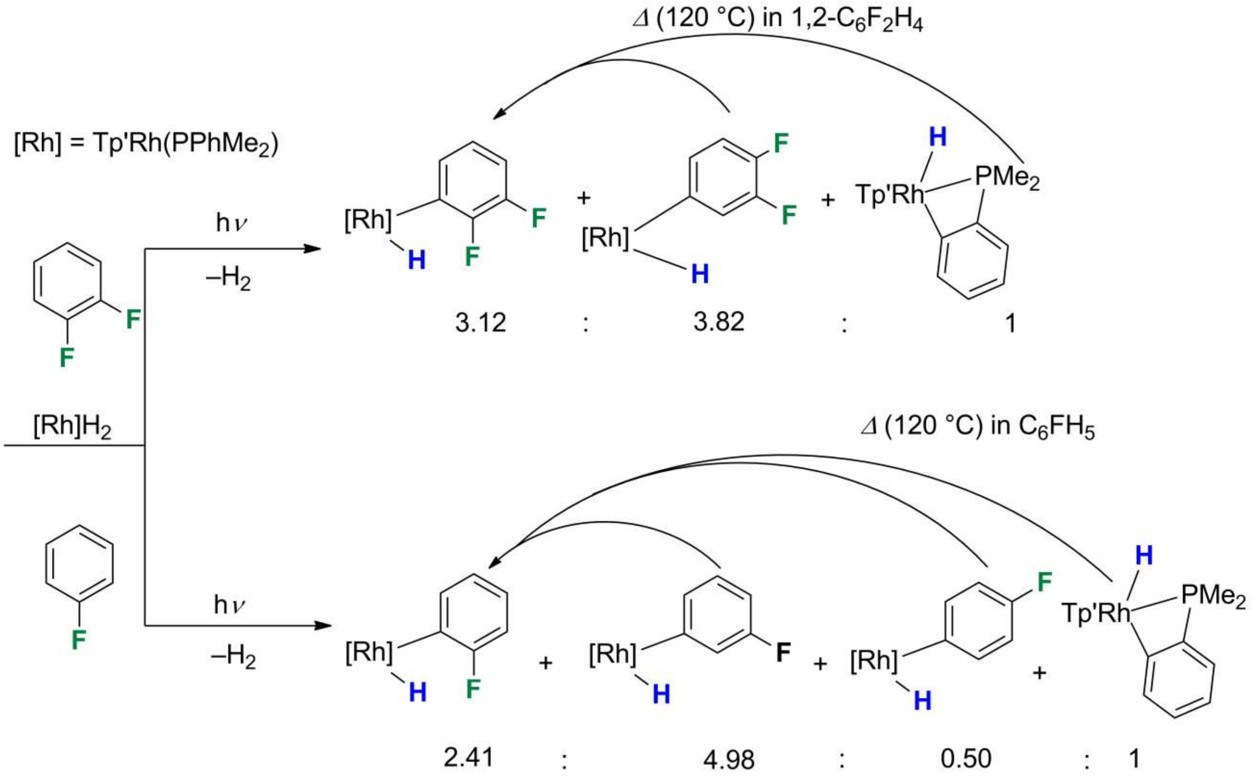
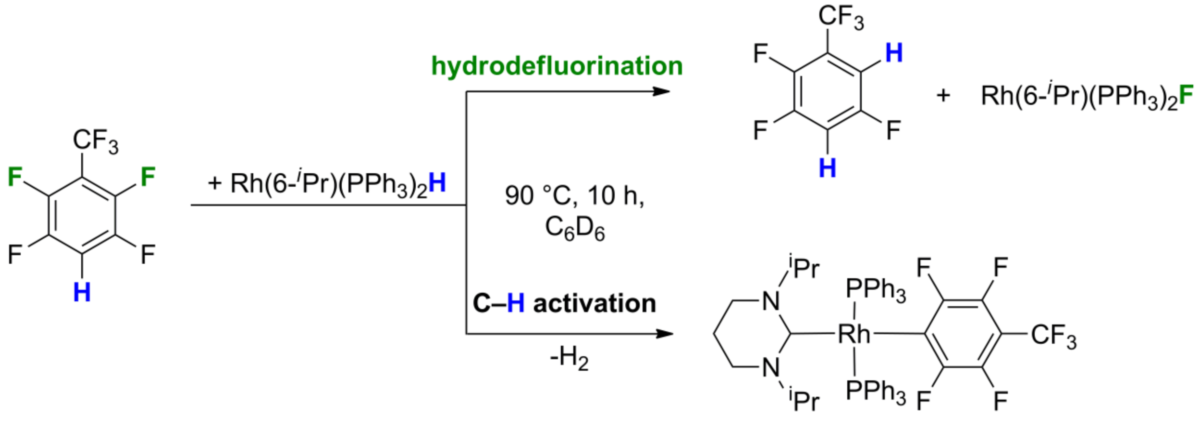


Figure 15. Photochemical reactions of Tp'Rh(H)$_2$(PPhMe$_2$) with fluorinated benzenes and thermal conversion of products to most stable isomers showing product distribution. Adapted with permission from ref 101. Copyright 2010 Royal Society of Chemistry.

The 4-coordinate NHC complex trans-[RhH(6-*i*Pr)$(PPh_3)_2$] is an active catalyst for hydrodefluorination of 2,3,4,5-$C_6F_4H(CF_3)$, but a competing C-H activation of the substrate yields catalytically inactive product (Scheme 11).[179]

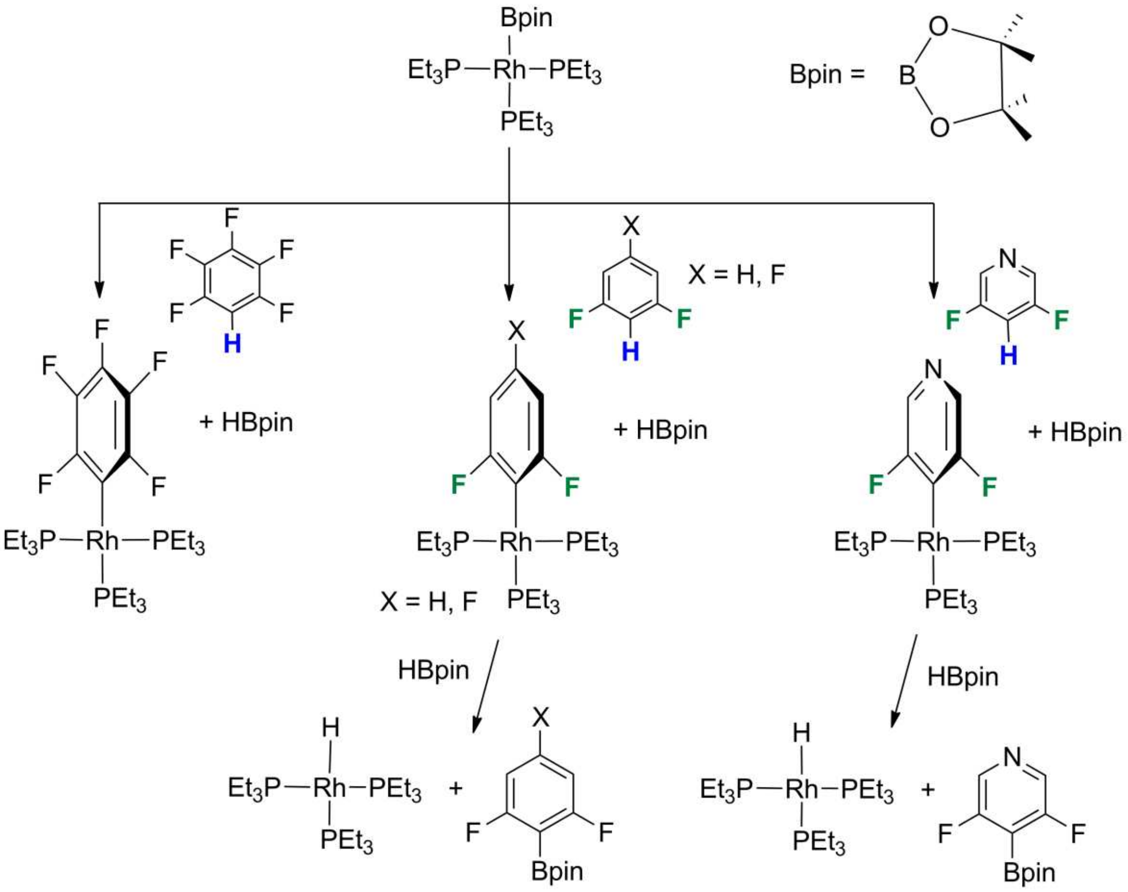
Scheme 11. Reactivity of rhodium NHC complexes (Adapted from Ref 179; Copyright 2014 American Chemical Society)



In an important study, it was shown that $Rh(SiMe_2Ph)(PMe_3)_3$ reacts with pentafluorobenzene by C-H activation to form $Rh(C_6F_5)(PMe_3)_3$ together with the hydrodefluorination product 1,2,4,5-tetrafluorobenzene.[180] The related reaction of $Rh(SiPh_3)(PMe_3)_3$ with 2,3,5,6-tetrafluoropyridine exhibited both C-H and C-F bond activation yielding a mixture of Rh(4-C_5NF_4)$(PMe_3)_3$ and Rh(2-C_5NF_3H)$(PMe_3)_3$ in which C-F activation had occurred at the position ortho to N.[181] The reactivity of square planar Rh(Bpin)$(PEt_3)_3$, Rh{Si(OEt)$_3$}$(PEt_3)_3$ and $Rh(GePh_3)(PEt_3)_3$ toward fluorinated pyridines has been explored extensively. The reactions of the boryl complex with partially fluorinated benzenes, 3,5-difluoropyridine, and 2,3,5,6-tetrafluoropyridine are C-H selective (Scheme 12).[182],[183] The ortho-selectivity of 1,3-difluorobenzene and 3,5-difluoropyridine is in perfect accord with the bond energy considerations. Reaction with perfluorinated aromatics and pentafluoropyridine yield C-F activation products. A boryl-assisted mechanism has been postulated for the reaction with pentafluoropyridine and may also apply to other perfluorinated substrates. These reactions have been developed for the catalytic borylation of partially fluorinated benzenes. The authors show that

$Rh(H)(PEt_3)_3$ also activates the C-H bonds of fluorinated benzenes and pyridines.[182-184] The germyl complex reacts with pentafluorobenzene and 2,3,5,6-tetrafluoropyridine by C-H activation.[185] In a related but photochemical reaction, $Rh\{Si(OEt)_3\}(CO)(dippe)$ reacts to form Rh(4-C_5NF_4)(CO)(dippe) (dippe = *i*$Pr_2PCH_2CH_2P$*i*Pr_2).[186]

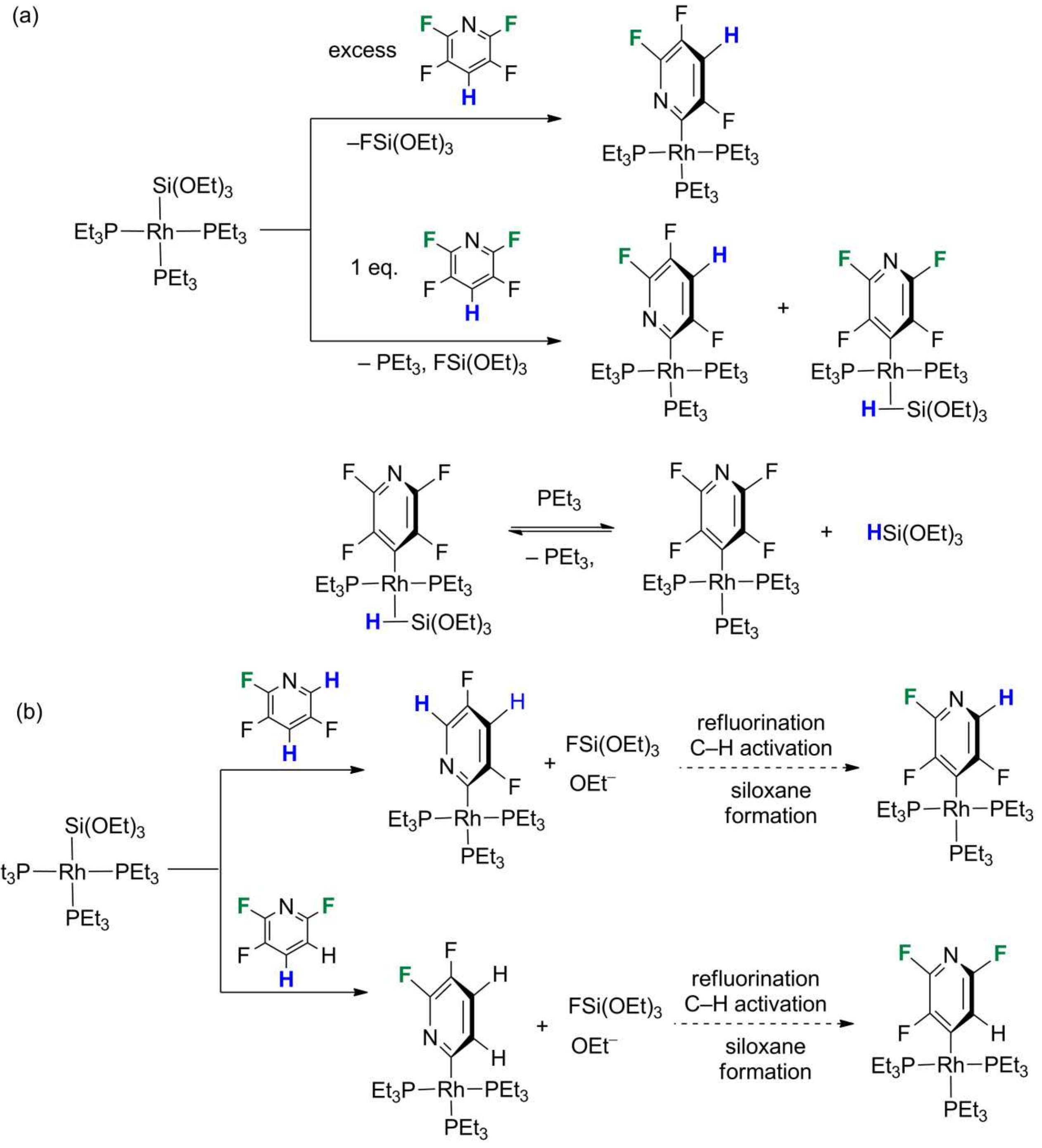
Scheme 12. Reactivity of square planar rhodium boryl complex (Adapted from Ref 183; Copyright 2015 American Chemical Society)



The behavior of the silyl complex $Rh\{Si(OEt)_3\}(PEt_3)_3$ toward 2,3,5,6-tetrafluoropyridine is rather different, yielding a C-F activation product Rh(3,5,6-C_5NHF_3)$(PEt_3)_3$ and ca. 10% of an unusual C-H activation product containing an η^2-silane ligand when 1 equiv of substrate is added. The η^2-silane complex is at equilibrium with Rh(2,3,5,6-C_5NF_4)$(PEt_3)_3$ as formed in the reaction of the boryl complex (Scheme 13a). In an unusual process, the by-product $FSi(OEt)_3$ fluorinates the initial C-F activation product in the presence of ethoxide to convert it to Rh(2,3,5,6-C_5NF_4)$(PEt_3)_3$.

Similar reactions are observed by C-F activation of trifluoropyridines and subsequent fluorination (Scheme 13b).[187]

Scheme 13. (a) Reactivity of Rh{Si(OEt)$_3$}(PEt$_3$)$_3$ towards 2,3,5,6-tetrafluoropyridine. (b) C–F activation of trifluoropyridines by Rh{Si(OEt)$_3$}(PEt$_3$)$_3$ and consecutive fluorination reactions (Adapted with permission from Ref 187; Copyright 2015 Royal Society of Chemistry)



Activation of C-H bonds has been studied at the iridium pentahydride complex *trans*-$[IrH_5(P\textit{i}Pr_3)_2]$. Photochemical reaction with partially fluorinated aromatics or heteroaromatics results in $Ir(Ar^F)(H)_2(H_2)(P\textit{i}Pr_3)_2$, while thermal reaction using neohexene as a hydrogen acceptor results in a mixture of the same complex and $Ir(Ar^F)(H)_2(P\textit{i}Pr_3)_2$. Notably, typical ortho selectivity is observed with 1,3-difluorobenzene yielding C-H activation at the 2-position with two ortho fluorines.[188]

As with $[IrH_5(P\textit{i}Pr_3)_2]$, C-H bond activation products are formed exclusively when $[Ir(IBioxMe_4)_3]^+$ reacts with fluoroarenes ($IBioxMe_4$ is a conformationally rigid, bioxazoline-derived N-heterocyclic carbene ligand). The reaction with 1,2-difluorobenzene generates the isomer with the metal at the ortho position. Detailed mechanistic studies show that this is the thermodynamic product and indeed the reaction intermediate $[IrH(C_6F_2H_2)(IBioxMe_4)_2]^+$ that precedes this product is a mixture of isomers. The product $[IrH(2,3\text{-}C_6F_2H_2)(IBioxMe_4)_3]^+$ undergoes exchange with other fluoroarenes allowing both kinetics and energetics to be established (Figure 16). If the intermediate $[IrH(C_6F_2H_2)(IBioxMe_4)_2]^+$ is trapped with bipyridine, a mixture of regioisomers is formed. This is a key experiment in establishing that the energetic models described in Section 3 apply to iridium NHC complexes.[189]

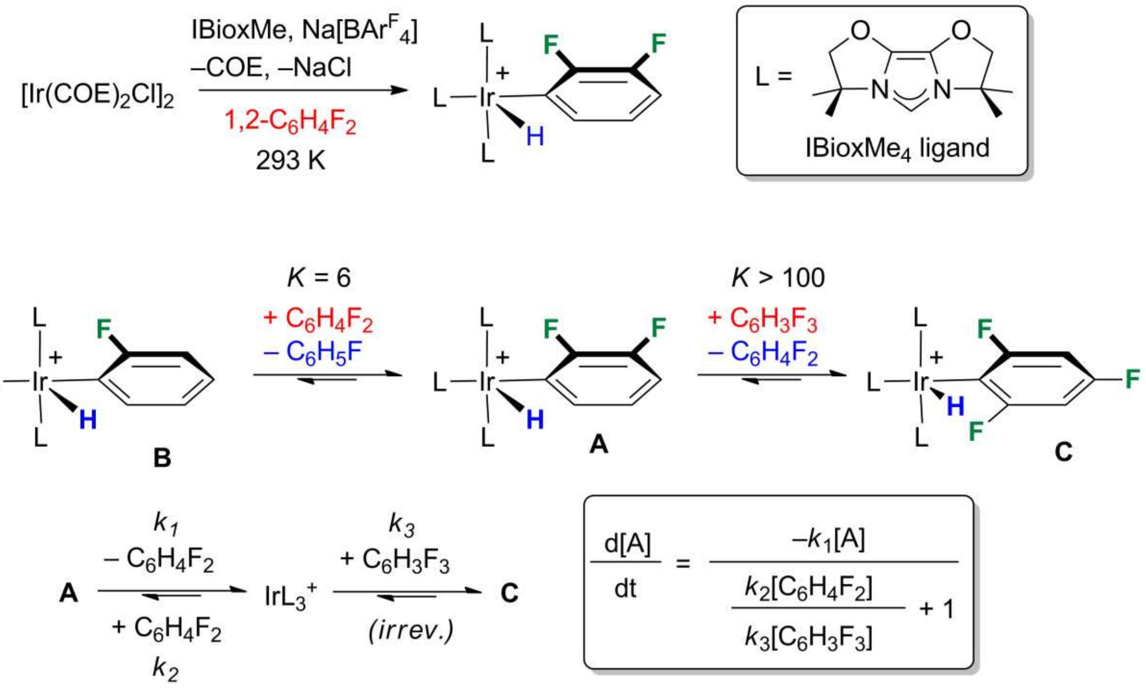
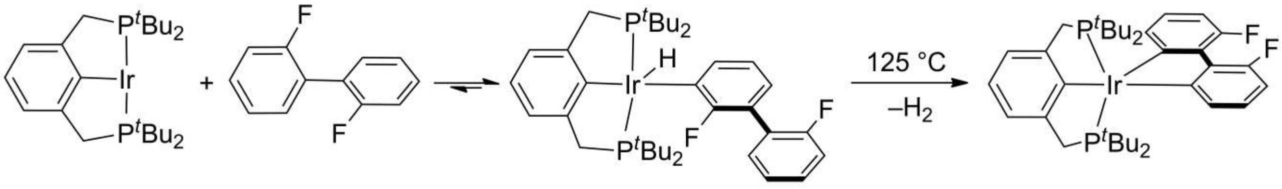


Figure 16. C-H activation of 1,2-$C_6F_2H_4$ at iridium complex of sterically constrained N-heterocyclic carbene and exchange reactions with fluorobenzenes. Adapted with permission from ref 189. Copyright 2015 Royal Society of Chemistry.

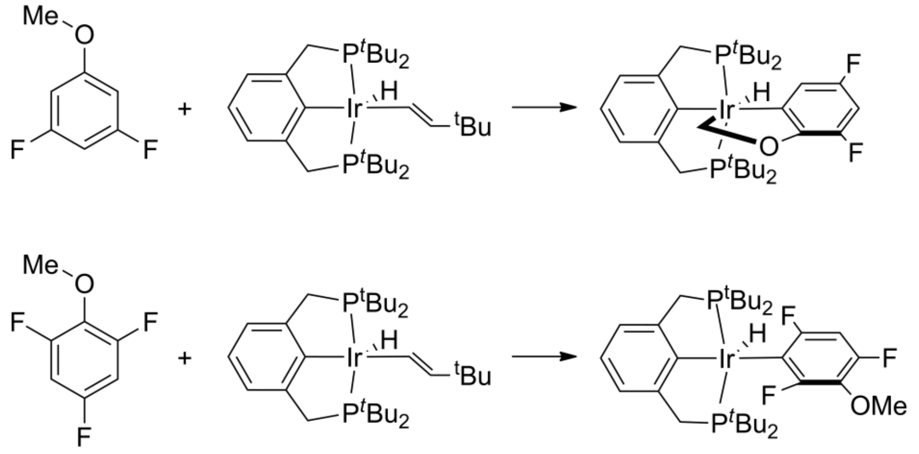
As part of a study of C-H activation of phenanthrene and biphenyl, the reaction of (^{tBu4}PCP)IrH_2 with norbornene (as hydrogen acceptor) and 2,2'-difluorobiphenyl was investigated. This substrate was chosen because the planar conformers lie well above the twisted conformer at ca. 20 and 43 kJ/mol for the anti and syn conformers, respectively. The initial product resulted from C-H activation at one of the ortho positions and the cyclometalated product was formed only after prolonged heating at 125 °C (Scheme 14). The latter requires a change in the position of C-H activation and a second activation step. In contrast, biphenyl reacts to form the analogous product at ambient temperature.[190]

Scheme 14. Reactivity of iridium pincer complex toward fluorobiphenyl (Adapted from Ref 190; Copyright 2016 American Chemical Society)



The reaction of (^{tBu4}PCP)IrH(alkenyl) with 3,5-bis(trifluoromethyl)anisole results in O-CH_3 activation as the principal product together with a cyclometalated product resulting from activation of an aromatic and an aliphatic C-H bond. When the corresponding reactions are performed with fluorine substituted anisoles, only O-CH_3 activation is observed if the ortho positions of the anisole are fluorinated, indicating a lack of C-F activation. If one or more ortho sites are available, the cyclometalation products are formed exclusively. The corresponding reaction with 2,4,6-trifluoroanisole simply yields a C-H activation product without cyclometalation. Once again, we see ortho-selectivity (Scheme 15).[191]

Scheme 15. Reactivity of fluorinated anisoles toward iridium pincer complexes (Adapted from Ref 191; Copyright 2013 American Chemical Society)



The PCP-pincer complex (^{tBu4}PCP)IrCO undergoes photo-dissociation of CO and C-H bond activation with exclusive ortho selectivity for fluorobenzene and 1,2-difluorobenzene. The C-H activation product is trapped by re-coordination of CO yielding (^{tBu4}PCP)IrH(Ar^F)(CO) which is formed in a photostationary state. DFT(BP86) and TDDFT calculations indicated that other isomers lie considerably higher in energy. The authors postulate that the increased selectivity compared to the PNP system arises because of the strong trans influence of the carbon ligand and the reversibility of the photochemical reaction. However, low-temperature experiments to establish whether equilibration occurs at the 16- or 18-electron stage were not recorded. The ortho-selectivity is contrasted to the weak selectivity with PNP ligands (see below).[192]

The reaction of [(^{tBu4}PNP)Ir(coe)]$^+$ (coe = cyclooctene) with benzene yields a C-H oxidative addition product. The related reaction with fluorobenzene at 50 °C yields [(^{tBu4}PNP)Ir(H)(C_6H_4F)]$^+$ with a mixture of ortho, meta and para isomers. Prolonged heating gives a mixture of ortho and para isomers in a ratio of 1.8:1 at 60 °C and 2.3:1 at 70 °C. The reactions with chlorobenzene and bromobenzene give analogous C-H activation products initially with significantly more of the ortho-isomer, but show complete preference for the ortho isomer on heating. These ortho-isomers exhibit a donor-acceptor bond from the halogen to the metal; there is no C-halogen activation. DFT(ONIOM/mPW1k) calculations show that the reaction with benzene progresses through η^2-

arene and η^2-C-H intermediates. The calculations trace the kinetic and thermodynamic preference for ortho-Cl in the reaction with chlorobenzene to coordination of Cl by the metal. However, corresponding calculations for the fluorobenzene reaction are not mentioned.[193] A related reaction of $({}^{iPr4}\mathrm{PNP}^*)_2\mathrm{IrH}_2$ (${}^{iPr4}\mathrm{PNP}^* = i\mathrm{Pr}_2\mathrm{PC}_6\mathrm{H}_3\mathrm{Me\text{-}N\text{-}C}_6\mathrm{H}_3\mathrm{MeP}i\mathrm{Pr}_2$) with neat fluorobenzene yields a mixture of isomers/rotamers at room temperature that simplifies on heating to yield ^{19}F NMR spectra consistent with two rotamers of the ortho product, although assignments are not provided.[194]

Porphyrins present different opportunities for C-H and C-F bond activation. The iridium porphyrin $\mathrm{Ir(ttp)(SiEt_3)}$, where ttp = tetratolylporphyrin, reacts with 1,4-$\mathrm{C_6F_2H_4}$ in the presence of KOH at 200 °C to yield $\mathrm{Ir(ttp)(Ar^F)}$ generating the C-F activation product followed by the C-H activation product. The authors show that C-F activation proceeds via formation of $[\mathrm{Ir(ttp)}]^-$ and nucleophilic substitution generating fluoride. The subsequent C-H activation is postulated to involve a radical pathway. These reactions show a preference for fluorine meta to the metal unlike many reactions described previously. DFT(B3LYP with single point D3 correction) calculations indicate that the meta isomer is the most thermally stable. A crystal structure of the ortho-isomer reveals strong steric hindrance between the fluorine and the porphyrin ring accounting for the unusual selectivity.[195]

4.2.2.5 Group 10. The group 10 metals exemplify some of the differences between the first, second, and third row transition metals. Nickel provides more examples of C-F bond activation than any other metal, with Ni(η^2-arene) complexes and nickel hydrides formed as kinetic products. For palladium, there are almost no examples of stoichiometric C-H or C-F bond activation of fluorinated arenes unless silver salts are also present. This observation is particularly puzzling considering the dominance of palladium in catalytic reactions of these compounds. Platinum complexes typically yield C-H activation products although studies are scarce.

The reactivity of $\mathrm{Ni^0}$ complexes toward partially fluorinated benzenes and pyridines has been investigated extensively. Numerous reactions have been studied using as the precursors $\mathrm{Ni(COD)_2}$ (COD = 1,4-cyclo-octadiene) with 2 equiv of ligand L where L = $\mathrm{PR_3}$, N-heterocyclic carbene, or zwitterionic amide. Recently, better defined precursors have been used such as $Ni(PR_3)_2(\eta^2$-phenanthrene), $Ni(PR_3)_2(\eta^2$-anthracene) (R = Et, *i*Pr) and $Ni(PEt_3)_2(\eta^2\text{-}CH_2{=}CMe_2)$,[63] $[Ni(PCy_3)_2]_2(\mu\text{-}N_2)$,[31] $[Ni_2(iPr_2Im)_4(COD)]$ (iPr_2Im = 1,3-diisopropylimidazole-2-ylidene),[196] $[Ni(dippe)(\mu\text{-}H)]_2$,[197] and $Ni(PEt_3)_4$[17] enabling the study of the reactivity of Ni^0 complexes in a more satisfactory way. Reviews of some aspects of these studies are available.[63,35,54,62]

A clear demonstration of the formation of $Ni(\eta^2\text{-}C_6F_5H)$ complexes is provided by the reaction of $Ni(PEt_3)_2(\eta^2$-anthracene) with pentafluorobenzene yielding isolable dinuclear complex $[Ni(PEt_3)_2]_2(\mu\text{-}\eta^2,\eta^2\text{-}C_6F_5H)$. The dynamic rearrangements of $[Ni(PEt_3)_2]_2(\mu\text{-}\eta^2,\eta^2\text{-}C_6F_5H)$ studied by variable temperature ^{19}F NMR spectroscopy are consistent with a series of 1,3-shifts of one $Ni(PEt_3)_2$ at a time but not consistent with 1,2-shifts. On addition of C_6F_5H (less than 1 equiv) to solutions of the dinuclear complex, the mononuclear $Ni(PEt_3)_2(\eta^2\text{-}C_6F_5H)$ is formed at equilibrium together with the C-H oxidative addition product *trans*-$[NiH(C_6F_5)(PEt_3)_2]$. These solutions ultimately convert to the C-F oxidative addition product *trans*-$[NiF(2,3,4,5\text{-}C_6F_4H)(PEt_3)_2]$, but the kinetics are not sufficiently clear to establish the mechanism in full (Figure 17). Unusually, the nickel in the C-F oxidative addition product is not bound ortho to two fluorines but only to one. These studies are supported by DFT(B3LYP) calculations.[17]

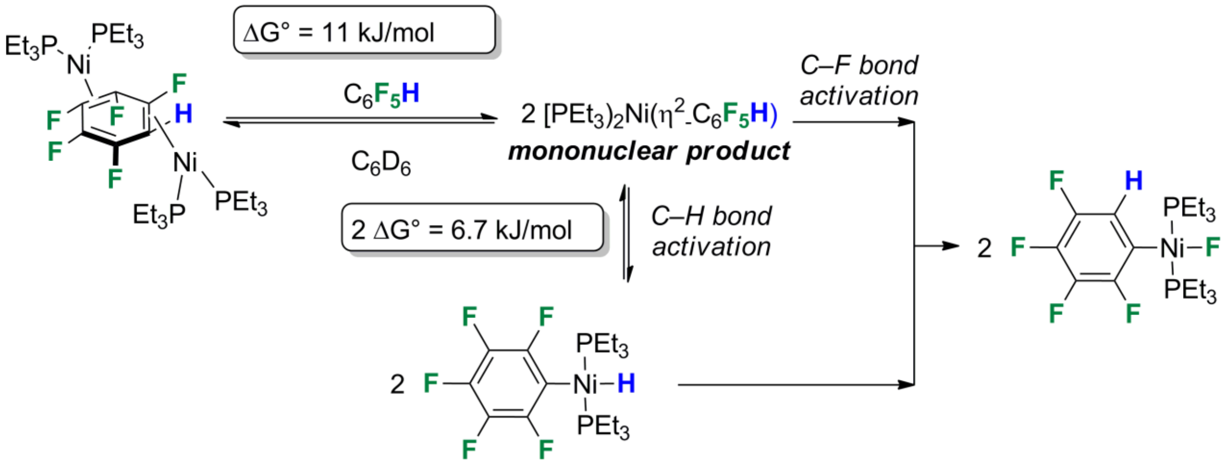
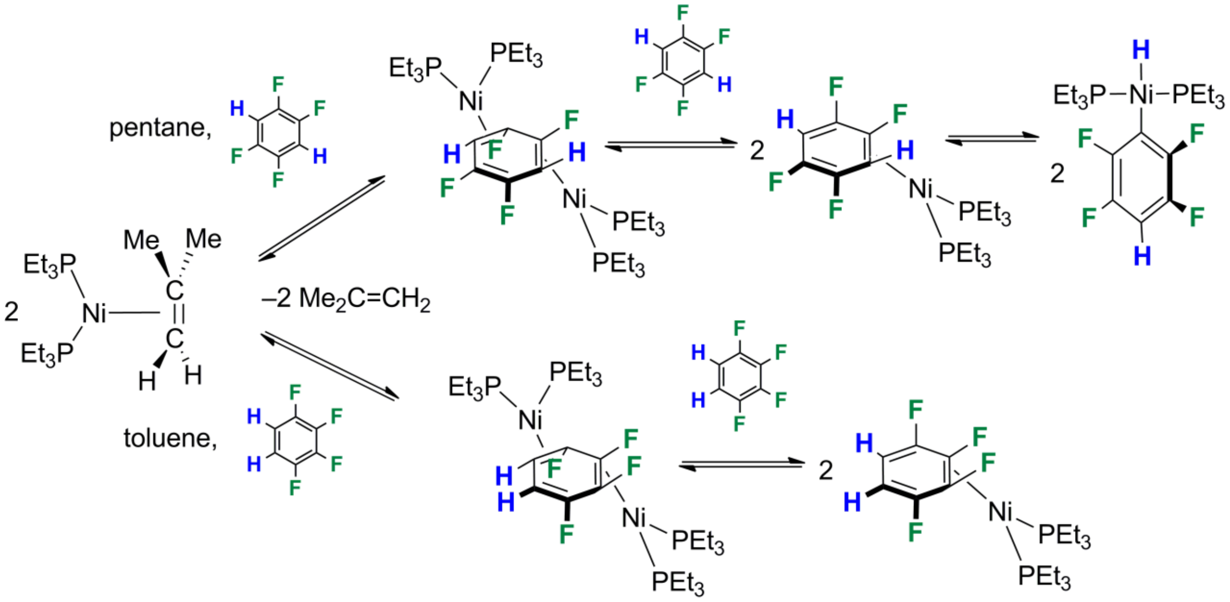


Figure 17. Interconversion of $[Ni(PEt_3)_2]_2(\mu\text{-}\eta^2,\eta^2\text{-}C_6F_5H)$, the hydride *trans*-$[NiH(C_6F_5)(PEt_3)_2]$ and the fluoride *trans*-$[NiF(C_6F_4H)(PEt_3)_2]$. Adapted with permission from ref 17. Copyright 2009 American Chemical Society.

When $Ni(PEt_3)_4$ is reacted with pentafluorobenzene, the same $Ni(\eta^2-C_6F_5H)$ complexes and the same hydride were formed as with the anthracene precursor. However, the C-F activation products were very different with four products present, of which the largest proportion was formed by C-F activation at the para-position, indicating a change in reaction mechanism.[17]

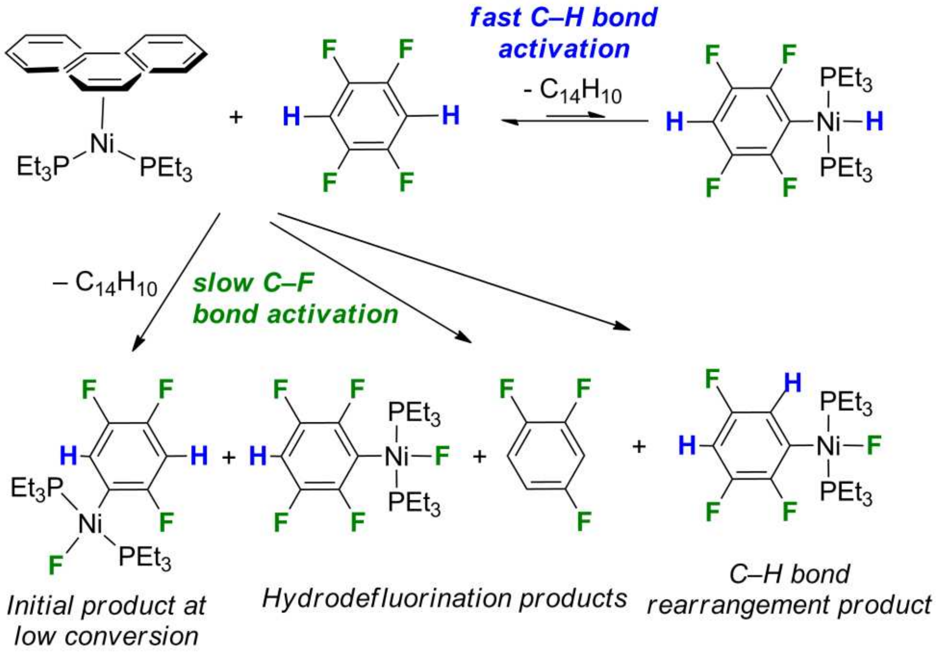
The need for highly controlled reaction conditions is emphasized by the reaction of $Ni(PEt_3)_2(\eta^2-CH_2=CMe_2)$ with 1,2,4,5-$C_6F_4H_2$ yielding the isolable dinuclear complex $[Ni(PEt_3)_2]_2(\mu-\eta^2,\eta^2-C_6F_4H_2)$ which can be reacted with excess C_6F_4H to form observable mononuclear arene complex in solution. This complex and the dinuclear adduct are at equilibrium with the hydride *trans*-$[NiH(C_6F_4H)(PEt_3)_2]$ (Scheme 16). The mononuclear arene complex undergoes rapid dynamic rearrangements in solution at room temperature by 1,2-shifts. DFT calculations were used successfully to assign the chemical shifts of the ^{19}F NMR spectra and to predict the relative stability of the different coordination positions of the fluorinated benzenes (see section 3). With 1,2,3,4-$C_6F_4H_2$, both the dinuclear and the mononuclear adducts undergo dynamic rearrangements, but unlike the 1,2,4,5-complex, no conversion to the C-H activation product is observed. Indeed, DFT(B3LYP) calculations predict that the corresponding hydride should be present at equilibrium in quantities that are too small to be observed by NMR spectroscopy. With 1,2,3,5-$C_6F_4H_2$, the reactions follow a similar pattern to the reaction with 1,2,4,5-$C_6F_4H_2$ but the hydride is observable. Notably, a dinuclear aryne complex and the C-F activation product are formed in small quantities. The ortho-fluorine effect helps to rationalize the formation of the hydrides from 1,2,4,5- and 1,2,3,5-difluorobenzene, but not from 1,2,3,4-difluorobenzene. In the first two cases, the hydride has two ortho fluorines, while in the last case, the hydride would only have one ortho fluorine.[89]

Scheme 16. Reactivity of Ni^0 complex toward fluorinated benzenes (Adapted from Ref 89; Copyright 2011 American Chemical Society)



The phenanthrene precursor Ni(PEt$_3$)$_2$(η^2-phenanthrene) has been used to generate nickel hydrides from 1,2,4,5-$C_6F_4H_2$ and monitor their conversion to C-F activation products at room temperature. The initial product, *trans*-[NiF(2,4,5-$C_6F_3H_2$)(PEt$_3$)$_2$], is formed by simple oxidative addition as expected, but more prolonged reaction yields two more fluoride complexes with the distribution dependent on conditions. They appear to be formed by a combination of transmetalation effecting H/F exchange and hydrodefluorination (Scheme 17).[198]

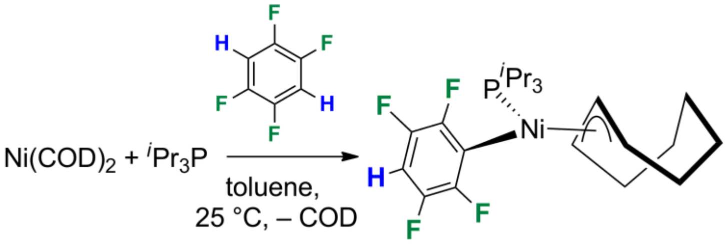
Scheme 17. Reactivity of Ni^0 complex toward tetrafluorobenzene (Adapted from Ref 198; Copyright 2008 American Chemical Society)



Activation of difluorobenzenes and trifluorobenzenes does not occur significantly with any of these sources of $Ni(PEt_3)_2$. However, it has recently been shown that they react with $Ni(PEt_3)_4$ in the presence of 1 equiv $AlMe_3$ to form the transmetalation product *trans*-$[NiMe(Ar^F)(PEt_3)_2]$ and $AlMe_2F$. This type of reaction occurs for di-, tri and tetra-fluorobenzenes, but with the tetrafluorobenzenes also gives the reductive elimination products, $C_6H_2F_3Me$. Intriguingly, replacement of $AlMe_3$ by $AlMe_3$.pyridine increases the selectivity of these reactions both between different regioisomers derived from the same trifluorobenzene and in competition reactions between different fluorobenzenes.[199]

Replacement of PEt_3 by $P\textit{i}Pr_3$ has a considerable effect on the outcome of these reactions. The anthracene precursor $Ni(P\textit{i}Pr_3)_2(\eta^2$-anthracene) reacts with pentafluorobenzene, 1,2,4,5-$C_6F_4H_2$, and 1,2,3,5-$C_6F_4H_2$ to give the hydrides *trans*-$[NiH(Ar^F)(P\textit{i}Pr_3)_2]$ with no direct sign of η^2-arene.[200] Initially, it was thought that the C-F activation complexes were formed in negligible amounts but later it was shown that they are formed on prolonged reaction. As with the reactions of the PEt_3 complex, the fluorines on the fluoroaryl ring had been rearranged or exchanged in some of the NiF products. The major C-F activation product from reaction with pentafluorobenzene has nickel in the more typical position para to the C-H bond so it lies ortho to two fluorines; this contrasts with the corresponding product with PEt_3 ligands. Most strikingly, the only fluoride formed from 1,2,4,5-$C_6F_4H_2$ is *trans*-[$NiF(C_6F_4H_2)(PiPr_3)_2$]. Importantly, the reaction of $Ni(COD)_2$ and 2 equiv $PiPr_3$ with fluorobenzenes gives different products in which the COD ligand inserts into the metal-hydride bond and rearranges into $Ni(Ar^F)(\eta^3\text{-}C_8H_{13})(PiPr_3)$ (Scheme 18). Moreover, the reaction of $Ni(PiPr_3)_2(\eta^2$-anthracene) with hexafluorobenzene gives an isolable Ni^I product $Ni(C_6F_5)(PiPr_3)_2$ as well as the expected Ni^{II} product, *trans*-[$NiF(C_6F_5)(PiPr_3)_2$].[200,201]

Scheme 18. Reactivity of $Ni(COD)_2$ and $PiPr_3$ toward tetrafluorobenzene (Adapted from Ref 200; Copyright 2010 American Chemical Society)

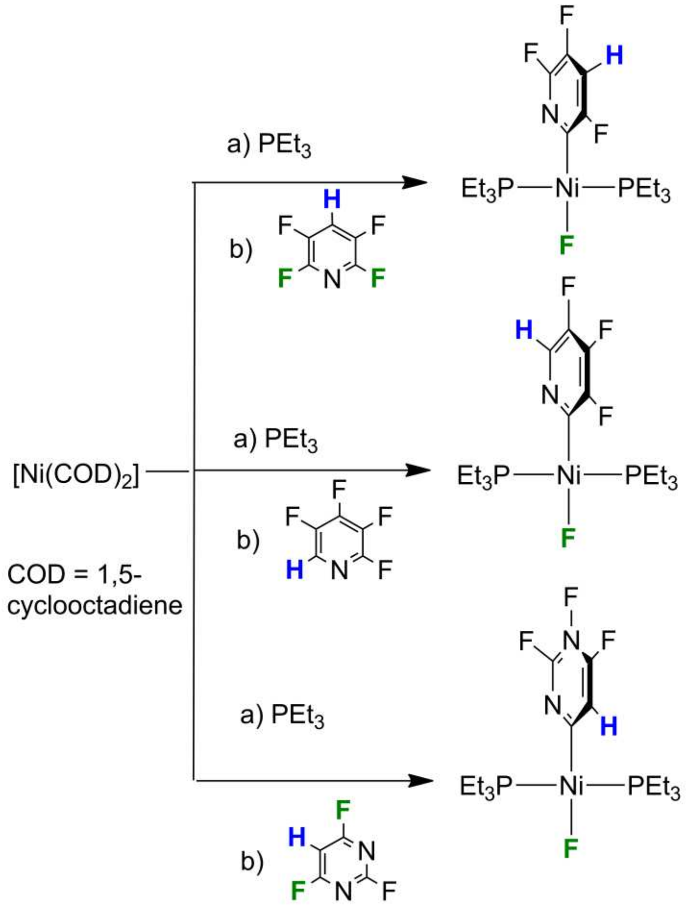


Pentafluorobenzene has also been reacted with $[Ni(PCy_3)_2](\mu\text{-}N_2)$ yielding a mixture of the expected C-H and C-F activation products *trans*-[$NiH(C_6F_5)(PCy_3)_2$] and *trans*-[$NiF(C_6F_4H)(PCy_3)_2$] in a 4:1 ratio. Similar results were obtained by heating $Ni(COD)_2$ with PCy_3 and pentafluorobenzene at 50 °C.[31] Another source of Ni^0 is $[Ni(dippe)(\mu\text{-}H)]_2$, which reacts with pentafluorobenzene to give $[Ni(dippe)]_2(\mu\text{-}\eta^2,\eta^2\text{-}C_6F_5H)$ with one Ni coordinated to a CH=CF bond and the other to a CF=CF bond. This complex converts on heating to the C-F oxidative addition product NiF(2,3,4,5-C_6F_4H)(dippe) where C-F activation has occurred ortho to the C-H bond as in the $Ni(PEt_3)_2$ reaction.[197]

The overall picture of these reactions of the $Ni(PR_3)_2$ complexes with fluorinated benzenes is that there is considerable sensitivity to the precursor, that cyclo-octadiene may become involved if it is present and that there is a potential role for Ni^I complexes. The product distribution is complicated by H/F exchange and hydrodefluorination. In the most controlled reactions, there is strong evidence for a pathway involving coordination of the fluoroarene followed by concerted C-F or C-H oxidative cleavage leading to NiF(Ar^F)(PR$_3$)$_2$ or NiH(Ar^F)(PR$_3$)$_2$, respectively, but other pathways may also occur. It is abundantly clear that C-F activation products are more stable energetically than C-H activation products and the latter may be at equilibrium with Ni(η^2-fluoroarene) products.

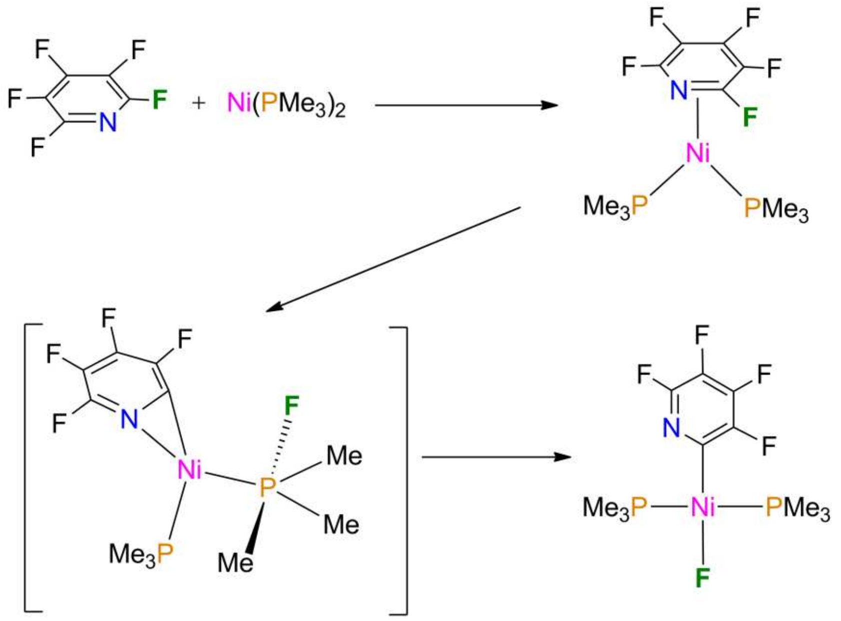
The reaction of Ni(COD)$_2$ with PEt$_3$ and 2,3,5,6-tetrafluoropyridine generates the C-F activated product metalated at the 2-position (ortho), *trans*-[NiF(3,5,6-C$_5$NF$_3$)(PEt$_3$)$_2$], with small quantities of the product metalated at the meta-position.[202] The reaction with 2,3,5,6-tetrafluoropyridine is 5.4 times slower than the corresponding reaction with pentafluoropyridine which also exhibits ortho selectivity.[203] With 2,3,4,5-tetrafluoropyridine, the ortho-C-F activated product is formed once again (Scheme 19).[204] Similarly, reaction with 2,4,6-trifluoropyrimidine results in C-F oxidative addition.[205] In the original reports, none of these reactions show any C-H activation, but it has since been shown that the C-H activation product from 2,3,5,6-tetrafluoropyridine can be observed at low temperature.[40] The ortho-F selectivity persists, even in the presence of NMe$_2$ or OMe substituents in the 4-position of the pyridine.[206]

Scheme 19. Reactivity of Ni(COD)$_2$ and PEt$_3$ toward fluorinated pyridines and pyrimidines (Adapted from Ref 54; Copyright 2002, Royal Society of Chemistry)



The ortho-selectivity of the reaction with pentafluoropyridine has been examined by DFT(BP86) calculations with PMe_3 as a model for PEt_3. The preferred mechanism involves initial transfer of F to P to yield a metallofluorophosphorane intermediate and then from P to Ni, termed the phosphine-assisted pathway (Scheme 20). Although this mechanism cannot be distinguished from alternative mechanisms on the grounds of the height of the barrier, it is the only one that explains the ortho-selectivity. The corresponding calculations for tetrafluoropyridines have not been performed, but it is reasonable to postulate the same mechanism.[207] A related phosphine-assisted mechanism has been postulated for other C-F activation reactions.[208]

Scheme 20. Phosphine-assisted mechanism of C-F activation (Adapted from Ref 207; Copyright 2010 American Chemical Society)



The related reactions of 2,3,5,6-tetrafluoropyridine were examined using Ni(PEt$_3$)$_2$(η^2-phenanthrene) as precursor and low temperature conditions, allowing observation of several intermediates, including the Ni(η^2-C$_5$NF$_4$H) adduct, the C-H activation product and the cis-C-F activation product (Scheme 21).[40] The observed isomer of Ni(η^2-C$_5$NF$_4$H)(PEt$_3$)$_2$ corresponds to that calculated to be lowest in energy by DFT(B3LYP) methods, but the complex undergoes dynamic rearrangements even at low temperature. The kinetics of these reactions were determined (Table 3) showing that the activation barriers for C-F oxidative addition and *cis-trans* isomerization are essentially equal and much lower than calculated for pentafluoropyridine. The intermediacy of the cis-C-F activation product is inconsistent with the phosphine-assisted mechanism that should generate the trans-C-F activation product directly. [40]

Scheme 21. Reaction mechanism for Ni^0 with tetrafluoropyridine (Adapted from Ref 40; Copyright 2012 American Chemical Society)

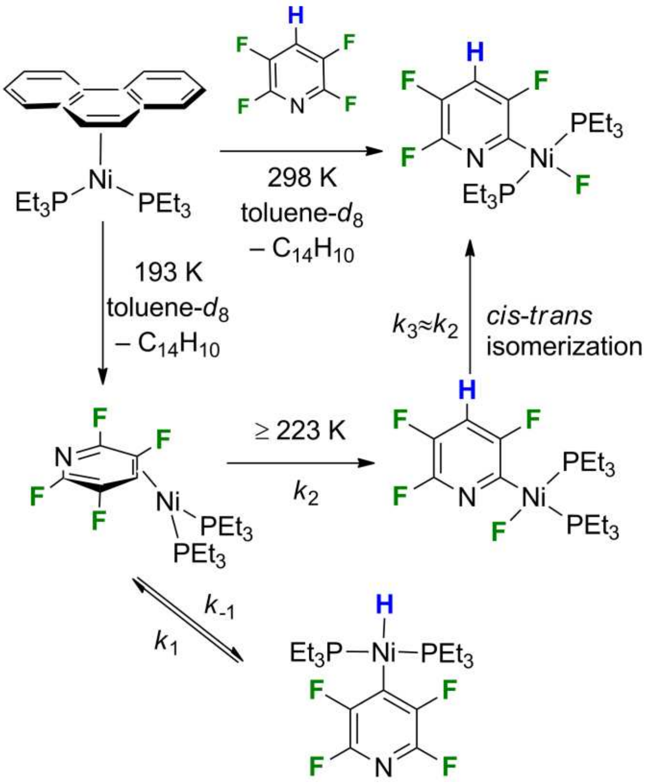


Table 3. Experimental activation parameters for reaction of tetrafluoropyridine at Ni(PEt$_3$)$_2$(η^2-phenanthrene)[40]

	C-F oxidative addition step	cis/trans isomerization step
$\Delta H^\ddagger$ (kJ/mol)	78.6	79.8
$\Delta S^\ddagger$ (J/K·mol)	22	27
$\Delta G_{298}^\ddagger$ (kJ/mol)	72.3	71.9

The preferred precursor for reactions with the N-heterocyclic carbene *i*Pr$_2$Im as the spectator ligand is [Ni(*i*Pr$_2$Im)$_2$](μ-η^2,η^2-COD).[30] This complex reacts with a wide variety of partially fluorinated benzenes to give C-F activation products, *trans*-[NiF(Ar^F)(*i*Pr$_2$Im)$_2$]. DFT(BP86) calculations indicate that η^2-arene complexes are formed as intermediates in C-F bond activation and hydrodefluorination. For example, the lowest energy isomer of Ni(*i*Pr$_2$Im)$_2$(η^2-1,2,4-C$_6$F$_3$H$_3$) is predicted to have the Ni coordinated η^2-CF=CH at the 2,3-position, consistent with the observed activation at the 2-position (Figure 18). The calculations provide an estimate that the overall C-F oxidative addition of hexafluorobenzene to the dinuclear complex is *exothermic* by 150 kJ/mol per Ni. For comparison, the oxidative addition of benzene is estimated to be *endothermic* by 74 kJ/mol.[30] These figures may be compared to the calculated ΔE for reaction of $Ni(H_2PCH_2CH_2PH_2)$ with C_6F_6 and C_6H_6 of -187 and -0.4 kJ/mol, respectively (see Section 3).[90]

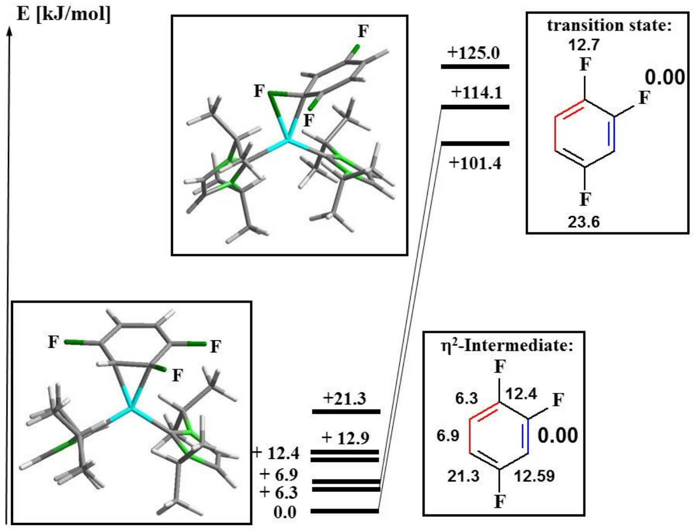
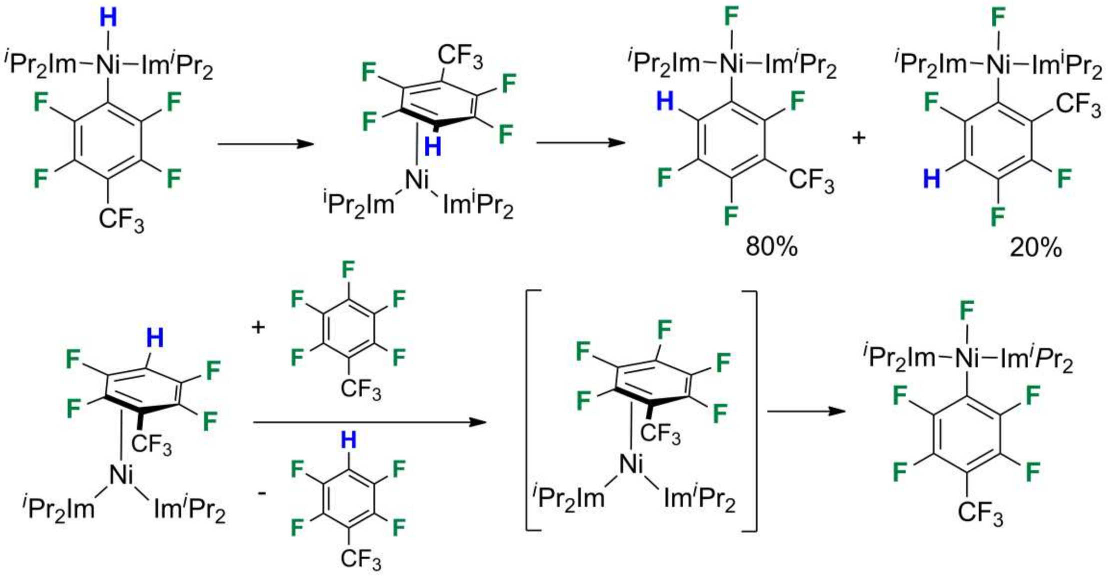


Figure 18. DFT(BP86) calculations of different isomers of Ni(*i*PrIm)$_2$(η^2-1,3,4-$C_6F_3H_3$) and barriers to C-F activation. Adapted from ref 30. Copyright 2008 American Chemical Society.

The first such complex to be detected as an intermediate was Ni(*i*Pr$_2$Im)$_2$(η^2-$C_6F_4H(CF_3)$). This complex could be isolated and is demonstrated to react with perfluorotoluene to give the C-F activation product of perfluorotoluene (Scheme 22). Without added substrate, it rearranges to a mixture of two isomeric fluorides in a ratio of 4:1 in favor of the ortho-isomer. Another significant aspect is the rearrangement of the corresponding hydride complex *trans*-[NiH($C_6F_4(CF_3)$)(*i*Pr$_2$Im)$_2$]. This hydride, which can be made independently by reaction with a silane, rearranges via the η^2-arene complex to these two fluoride complexes (Scheme 22). DFT(BP86) calculations show that the NiH to Ni(η^2-arene) conversion is exothermic by 28 kJ/mol and the conversion to the fluorides is exothermic by a further 88 kJ/mol. Intriguingly, the calculations assuming a concerted C-F activation mechanism (i.e. simultaneous formation of M-C and M-F bonds) predict the reverse of the observed preference for the two isomeric fluoride complexes. The authors suggest that this may be an indication that other pathways may occur.[41]

Scheme 22. Interconversion of hydride, fluoride and arene complexes at Ni carbene (Adapted from Ref 41; Copyright 2012 American Chemical Society)



Nickel complexes with zwitterionic amido ligands have also proved reactive toward hexafluorobenzene and partially fluorinated benzenes. Reaction of the methylazolium isopropylamide ligand yielded exclusively C-F oxidative addition products.[209]

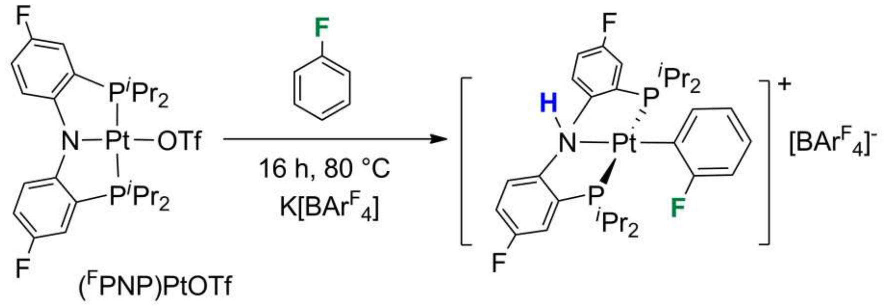
When it is considered that palladium is the commonest element for metal-mediated reactions of hydrofluoroarenes, it would be expected that there would be plenty of evidence of stoichiometric reaction between Pd complexes and hydrofluoroarenes; in reality, our search was barely successful. The best example is to be found in a recent study reported on the influence of silver salts on the reaction of $Pd(OAc)_2(dtbpy)$ (dtbpy = 4,4'-di-*t*-butyl-2,2'-bipyridine) with pentafluorobenzene. The reaction yields a mixture of $Pd(C_6F_5)(OR)(dtbpy)$ (R = Ac or C(O)*t*Bu) and $Pd(C_6F_5)_2(dtbpy)$. The reaction requires silver salts AgOC(O)*t*Bu, Ag_2CO_3, AgOAc or $AgOC(O)CF_3$, but the product distribution varies according to the salt. An intermediate was observed that was demonstrated to contain an Ag-(C_6F_5) bond. The authors propose that AgOC(O)*t*Bu and C_6F_5H react to generate this species which undergoes transmetalation at Pd. The intermediate is proposed on the basis of DFT (B3LYP plus large basis set single points) calculations to be a $Ag_2(C_6F_5)$ species with bridging carboxylate.[210]

Although the oxidative addition reaction of $Pd(PCy_3)_2$ with pentafluoropyridine yields *trans*-$[PdF(C_5F_4N)(PCy_3)_2]$, there have been no corresponding reports of reactions with partially fluorinated pyridines or benzenes, perhaps because the reaction with pentafluoropyridine needs considerably higher temperatures than the corresponding reactions of nickel or platinum complexes.[211]

One of the earliest demonstrations of C-H selectivity was the reaction of $Pt(PCy_3)_2$ with C_6F_5H, 1,3,5-$C_6F_3H_3$ and 1,3-$C_6F_2H_4$ yielding trans-$[PtH(Ar^F)(PCy_3)_2]$ by oxidative addition. Fluorobenzene and the other difluorobenzenes did not react. Although the authors did not identify the regio-isomer formed with 1,3-$C_6F_2H_4$, with current knowledge we can recognize from the ^{19}F NMR data that the Pt lies ortho to both fluorines.[212] Later investigation of the corresponding reaction with 2,3,5,6-tetrafluoropyridine also showed C-H oxidative addition,[211] but reaction with 2,3,5-trifluoro-4-(trifluoromethyl)pyridine resulted in C-F oxidative addition to yield *trans*-$[PtF\{2\text{-}C_5NHF_2(CF_3)\}(PCy_3)_2]$.[213] These oxidative addition reactions contrast with the behavior of $Pt^0(PR_3)_2$ toward pentafluoropyridine which results in transfer of fluorine to the phosphine and R to the metal yielding *trans*-$[Pt(R)(4\text{-}C_5NF_4)(PR_3)(PR_2F)]$ by a phosphine-assisted C-F bond activation.[211,213] The computational comparison of the energetics and kinetics of C-H and C-F bond activation at $Pt(H_2PCH_2CH_2PH_2)$ is discussed in Section 3.3.

The reaction of the pincer complex (^{F}PNP)PtOTf with benzene results in a 1,2-addition reaction at the C-H bond with transfer of hydrogen to the nitrogen atom of the pincer ligand. Fluorobenzene follows the same pattern with reaction at the ortho-C-H bond (Scheme 23).[214]

Scheme 23. Reactivity of platinum PNP pincer toward fluorobenzene (Adapted with permission from ref 214, Copyright 2013; Royal Society of Chemistry)

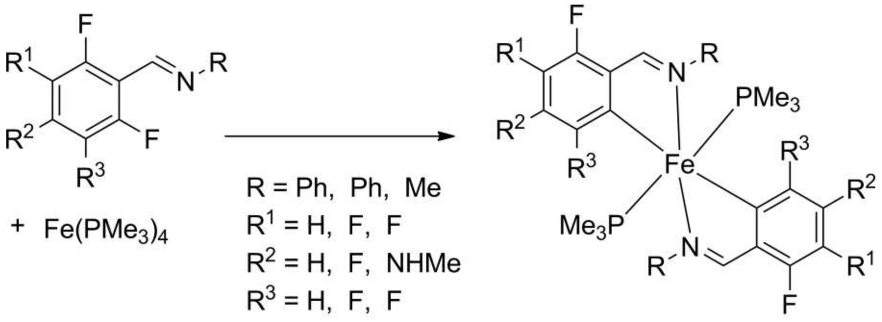


4.2.2.6 Group 11. We referred to the important demonstration of Cu-catalyzed fluorination in Section 3 and to the evidence for the role of Ag salts in Pd-mediated reactions in Section 4.2.2.5. The role of Ag will also appear in section 5 under catalysis. A study of hydrodefluorination of fluoroarenes by AuH(IPr) (IPr = N,N-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene) revealed that a charge-transfer complex was formed between AuH(IPr) and $C_6F_5(NO_2)$; however, the UV/vis measurements did not extend to partially fluorinated arenes.[215] The reaction of 2-(2,3,4,5-tetrafluorophenyl)pyridine (Htfppy) with AuCl(IDipp) (IDipp = bis(2,6-diisopropylphenyl)imidazole-2-ylidene) generates Au(tfppy)(IDipp) in which C-H activation has occurred at the fluorinated phenyl moiety leaving the pyridyl unit uncoordinated. An analogue can also be synthesized with a $P(tol)_3$ ligand in place of IDipp. The corresponding reaction of Cu(OH)(IDipp) with 2-(2,4-difluorophenyl)pyridine behaves similarly, resulting in a copper difluorophenylpyridine complex with two C-F bonds ortho to the Cu-C bond in another example of ortho selectivity. Further related reactions are covered under cyclometalation (section 4.2.3).[216]

4.2.3 Intramolecular Aromatic Cyclometalation. Direct C-H/C-F bond activation reactions at transition metals form key steps in many cyclometalation processes. The synthesis of a metallacycle involves the coordination of a transition metal to a donor atom, such as N, S or O, followed by an intramolecular C-X activation, where X could be H or F, which closes the 5- or 6-membered ring.[217,218] Achieving chemoselectivity in systems where both C-F and C-H activation are possible is one of the main challenges in cyclometalation reactions of fluorinated systems. The intermolecular activation of a C–F bond with first row transition metals is well established, in particular with Ni and Co, whereas with second and third row transition metals it is much less common due to the higher kinetic barrier, as has been shown in the preceding sections. This section of the review will cover examples of systems where competition exists between C-H and C-F activation in the formation of metallacycles, and will highlight the factors which play a role in determining the outcome. We show that C-F activation may accompany cyclometalation, even for 3rd-row transition metals.

4.2.3.1 Group 8. The degree of fluorination in a partially fluorinated substrate has been shown to have a large influence on the selectivity of cyclometalation at Fe^0.[219] The Fe^0 complex $Fe(PMe_3)_4$ reacts with ortho-fluorinated benzylimines giving Fe^{II} complexes via a double C-F activation reaction. The proposed mechanism involves the π-coordination of the imine to the Fe^0 followed by C-F activation *ortho* to the anchoring group to give the C-F activation product (Scheme 24).

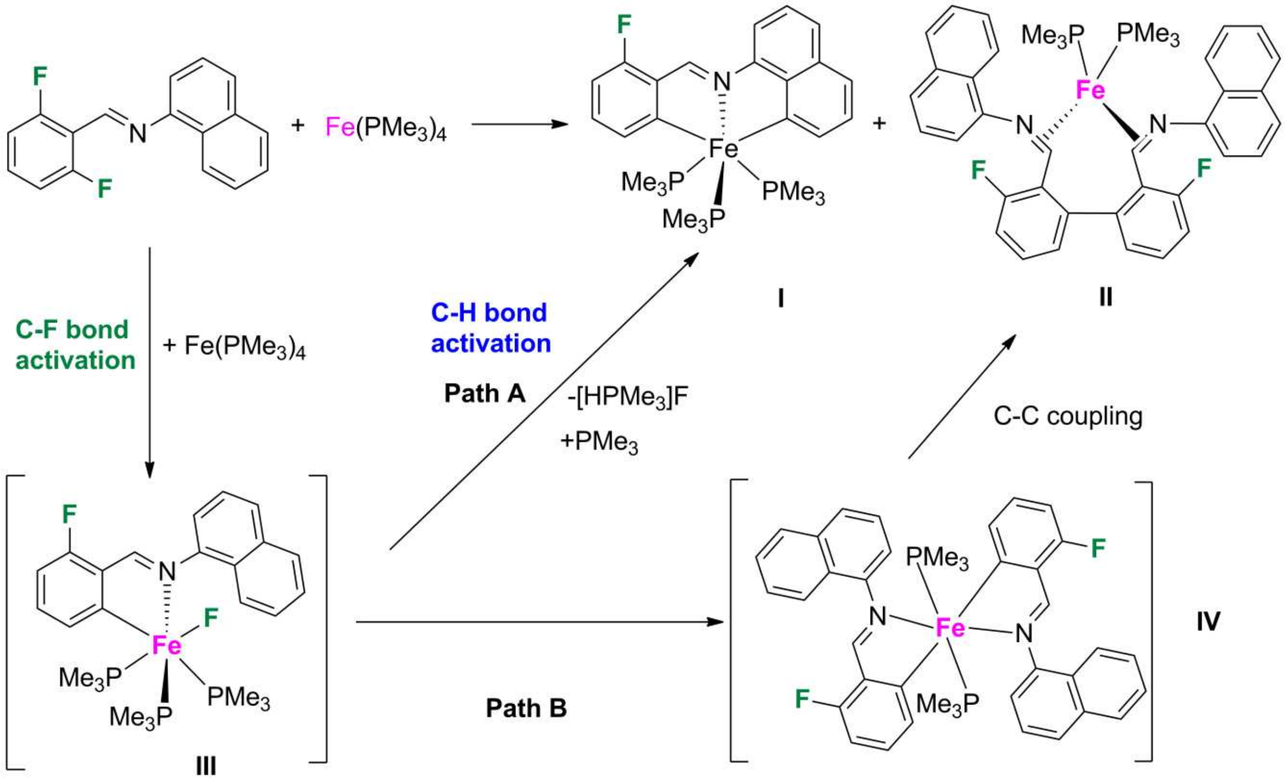
Scheme 24. Reactivity of $Fe(PMe_3)_4$ toward fluorinated imines (Adapted with permission from ref 219; Copyright 2011 Royal Society of Chemistry)



The synergic effect of the PMe_3 ligand and of the electron-rich Fe^0 favor the C-F activation, and the yield of the products increases with the number of fluorine atoms on the phenyl ring of the imine. The effect of the aryl groups of the imines on the activation reaction was also investigated, showing that it was not possible to observe the corresponding metallacycle obtained by C-F activation when using the difluorinated substrate including a naphthyl group. Instead, the reactions afforded a mixture of two metallacycles: **I** obtained via a combination of C-F and C-H activation, and **II,** the product of a double C-F activation (Scheme 25). The proposed mechanism involves the formation of intermediate **III** via C-F activation through oxidative addition to the Fe^0 complex.

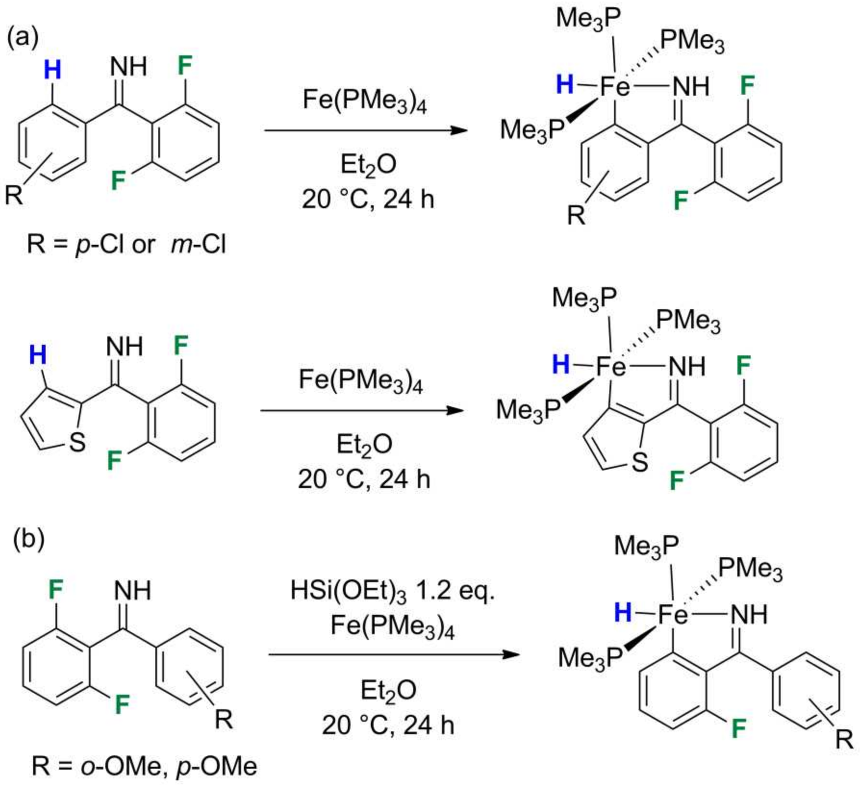
Complex **I** is then formed by subsequent C-H activation. Intermediate **III** can also undergo double C-F activation, as for the complexes in Scheme 24, to form complex **IV**, which undergoes C-C coupling via reductive elimination due to the bulkiness of the naphthyl groups (Scheme 25).

Scheme 25. Reactivity of Fe(PMe$_3$)$_4$ toward difluorinated imine (Adapted with permission from ref 219; Copyright 2011 Royal Society of Chemistry)



Structural features also influence the chemoselectivity in reactions of Fe^0 with fluorinated arylimines. When Fe(PMe$_3$)$_4$ was reacted with fluorinated arylimines with chlorophenyl or thiophene groups in diethyl ether, C-H activation was obtained selectively.[220] The anchoring arm of the imine system plays a role in the chemoselective formation of the product, and the coordination of the metal center to the nitrogen atom allows the activation to occur in the *ortho* position (Scheme 26a).

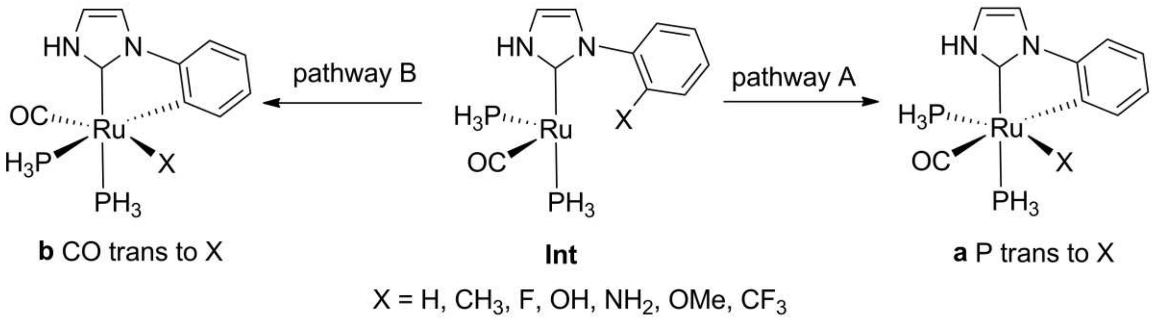
Scheme 26 Reactivity of $Fe(PMe_3)_4$ toward functionalized imines (Adapted with permission from ref 220; Copyright 2015 Wiley VCH)



When the same Fe complex is reacted with substrates containing methoxy substituents in the presence of $HSi(OEt)_3$, the only products formed are two hydride complexes arising by C-F activation and H/F exchange. The presence of EDGs on the non-fluorinated ring seems to be responsible for the selective process, while the presence of EWGs favored the C-H activation as shown in the system above (Scheme 26b).

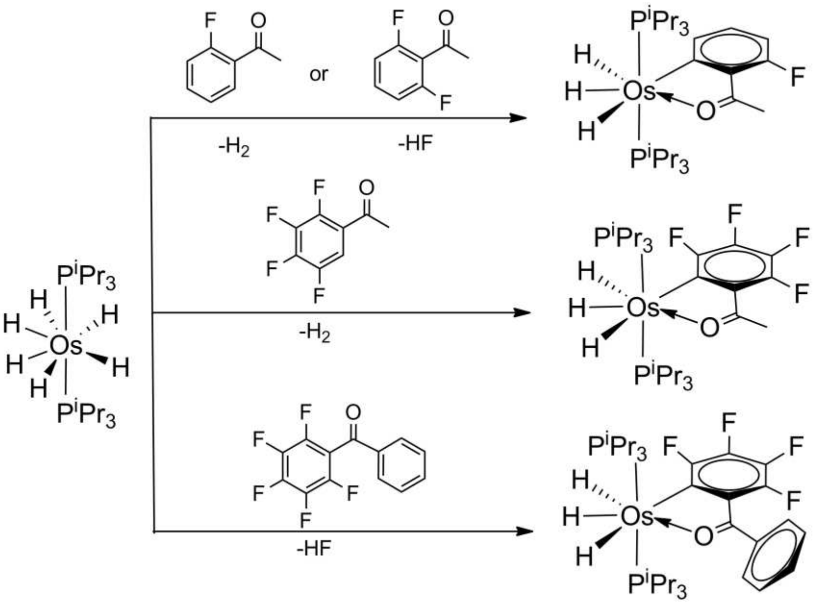
The metal-ligand coordination environment can also affect the electronic energy and energy barrier of the C-X (X = H, F) activation reaction, leading to different pathways depending on the X group and the spectator ligands, as shown in a DFT(BP86) study of cyclometalation of C-aryl substituted NHCs containing heteroatoms at the model system $Ru(NHC)(PH_3)_2(CO)$, (NHC = 1-(C_6H_4-2-X)imidazol-2-ylidene, X = H, F, CH_3, etc.) (Scheme 27).[221] The trends in ΔE and $\Delta E^{\ddagger}$ are correlated with the strength of the Ru-X bond formed. The C-H activation occurs preferentially following the pathway where the C-H bond is *trans* to the PH_3 ligand. This geometry enables formation of a strong agostic interaction between the Ru and the *ortho* C-H bond allowing it to undergo C-H activation without any energy barrier. In contrast, with X = F, there is an energy barrier of 38 kJ/mol and a long Ru···F distance at the transition state (3.07 Å), but the process is still thermodynamically favorable (ΔE = -161 kJ/mol). The two pathways (A and B) for the C-F activation differ in the orientation of the NHC ligand (Scheme 27). The product obtained from pathway B is more stable due to the greater 'push-pull' interactions along the F-Ru-CO axis, which relieves the Ru-F filled-filled dπ-pπ interaction.

Scheme 27. Models for the computational study of cyclometalation of Ru carbene complexes (Adapted from ref 221; Copyright 2008 American Chemical Society)



The chemoselectivity of C-H /C-F activation reactions can also be influenced by the structure of the final product. When the osmium complex $Os(H)_4(PiPr_3)_2$ was reacted with 2,3,4,5,6-pentafluorobenzophenone, a substrate with one perfluorinated benzene ring, C-F activation was favored over C-H (Scheme 28).[222] With 2-fluoroacetophenone, C-H activation is preferred, whereas with 2,6-difluoroacetophenone it is C-F activation that occurs. These two substrates therefore yield the same organometallic product. DFT(B3LYP) calculations were performed to understand the difference between this system and the reaction with 2-fluoroacetophenone. C-H activation occurred preferentially in the case of the monophenyl group due to kinetic factors, related to the preferred arrangement of the starting ketone, where the fluorine atom is *anti* with respect to the carbonyl group and thus out of reach of the metal. From a thermodynamic point of view, the C-F activation of the perfluorinated ketones is favored with respect to C-H activation due to the greater H-F bond energy compared to that of H-H in the products, which compensates for the higher energy required to break a C-F bond. Related studies have been reported on $Os(H)_4\{xant(P\textit{i}Pr_2)_2\}$ ($\{xant(P\textit{i}Pr_2)_2\}$ = 9,9-dimethyl-4,5-bis(diisopropylphosphino)xanthene). In this case, C-H activation is preferred both with 2-fluoroacetophenone and 2,6-difluorobenzophenone. An analogous reaction at a ruthenium complex also effects C-H activation.[223]

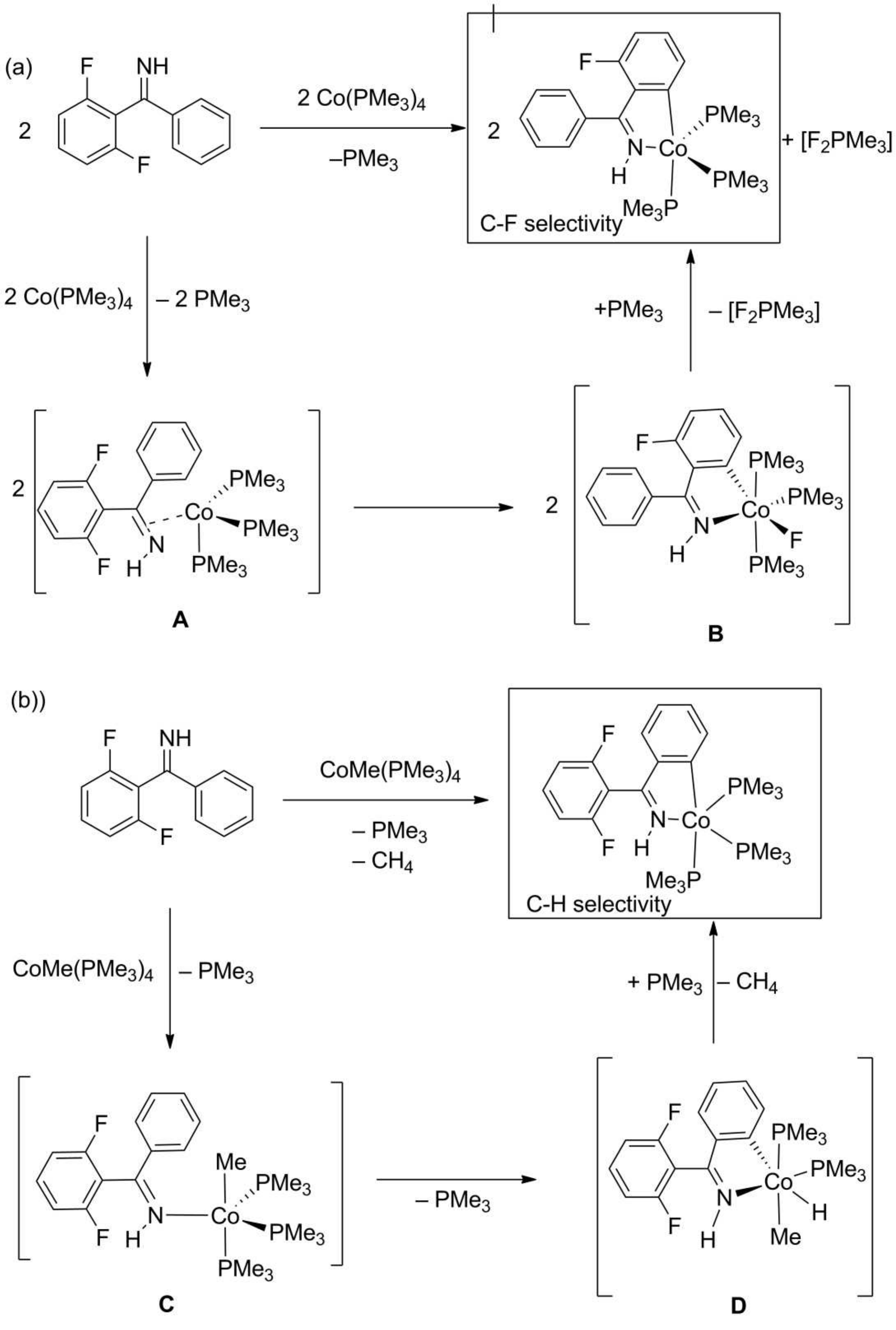
Scheme 28. Cyclometalation of ketones at osmium (Adapted from ref 222; Copyright 2001 American Chemical Society)



4.4.3.2. Group 9. The chemoselectivity at an electron rich cobalt center can also be changed depending on the substrates. When $CoMe(PMe_3)_4$ and $Co(PMe_3)_4$ were reacted with fluorinated phenylimines and fluorinated phenylketones, C-H and C-F bond activation could be obtained only with imines, with C=NH being a better anchoring group compared to C=O. When $Co(PMe_3)_4$ was reacted with 2,6-difluorobenzophenone imine, selective C-F activation was obtained (Scheme 29a).[224] The proposed mechanism suggests a π-coordination of the C=N bond to the cobalt center which allows the C-F bond ortho to the anchoring group to approach the metal (intermediate **A**).

Oxidative addition of the C-F bond at the Co^0 center forms intermediate **B** that undergoes reductive elimination to form product. When the same substrate (2,6-difluorobenzophenone imine) was reacted with Co^I complex CoMe(PMe$_3$)$_4$, only selective C-H activation occurred. The suggested mechanism involves the coordination of the imine in the first step (intermediate **C**) followed by cyclometalation via the activation of the C-H bond of the phenyl group ortho to the anchoring group, which leads to the formation of a Co^{III} intermediate (**D**) that undergoes reductive elimination to form the product (Scheme 29b).

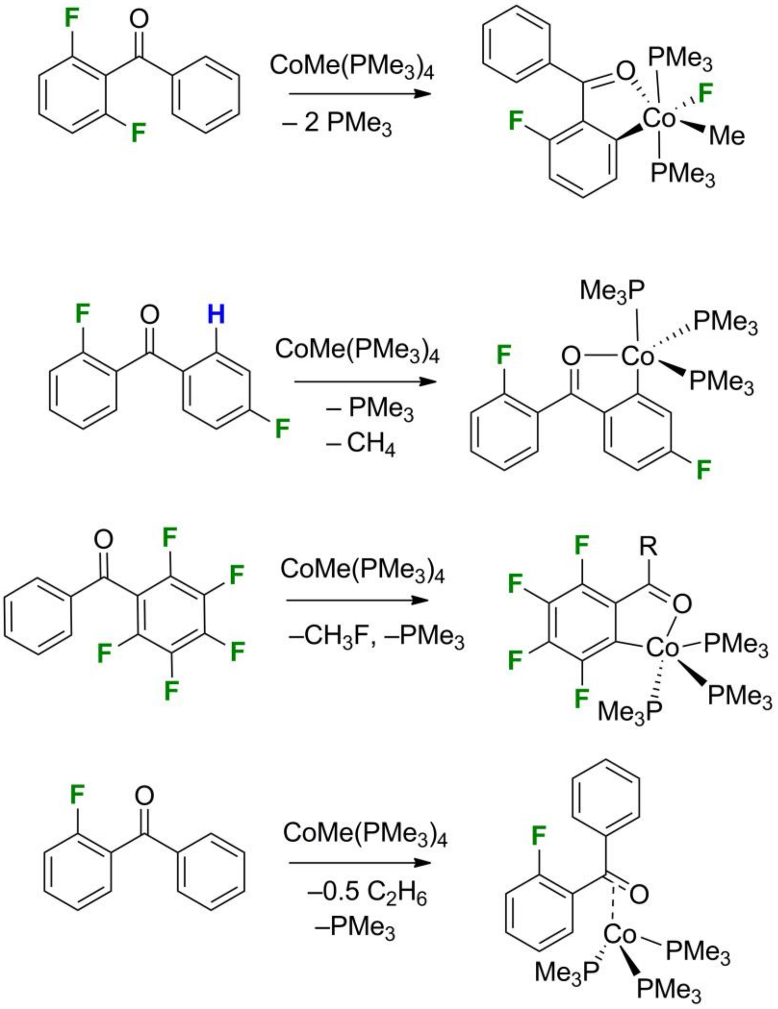
Scheme 29. Dependence of cyclometalation product on Co precursor (a) Co(PMe$_3$)$_4$, (b) CoMe(PMe$_3$)$_4$ (Adapted with permission from ref 224; Copyright 2010 Elsevier)



When 2,6-difluorobenzophenone was reacted with $CoMe(PMe_3)_4$, only the C-F activation product could be observed: the product corresponds to intermediate **B** in Scheme 29a. When the same Co complex was reacted with 2,4'-difluorobenzophenone, the C-H activation product was obtained in good yield due to the thermodynamically favored evolution of methane (Scheme 30).

The reaction of $CoMe(PMe_3)_4$ with a ketone containing two phenyl groups, of which one was perfluorinated, showed complete chemoselectivity for C-F activation.[225] The corresponding reaction with mono-fluorinated benzophenone yields a Co π-complex with intramolecular elimination of ethane (Scheme 30). The effect of the geometry of the product on the chemoselectivity of C-H/C-F activation reactions in partially fluorinated substrates has been investigated by DFT(B3LYP) calculations for cobalt complexes formed by cyclometalation of Co^{III} with fluorinated phenylimines.[226]

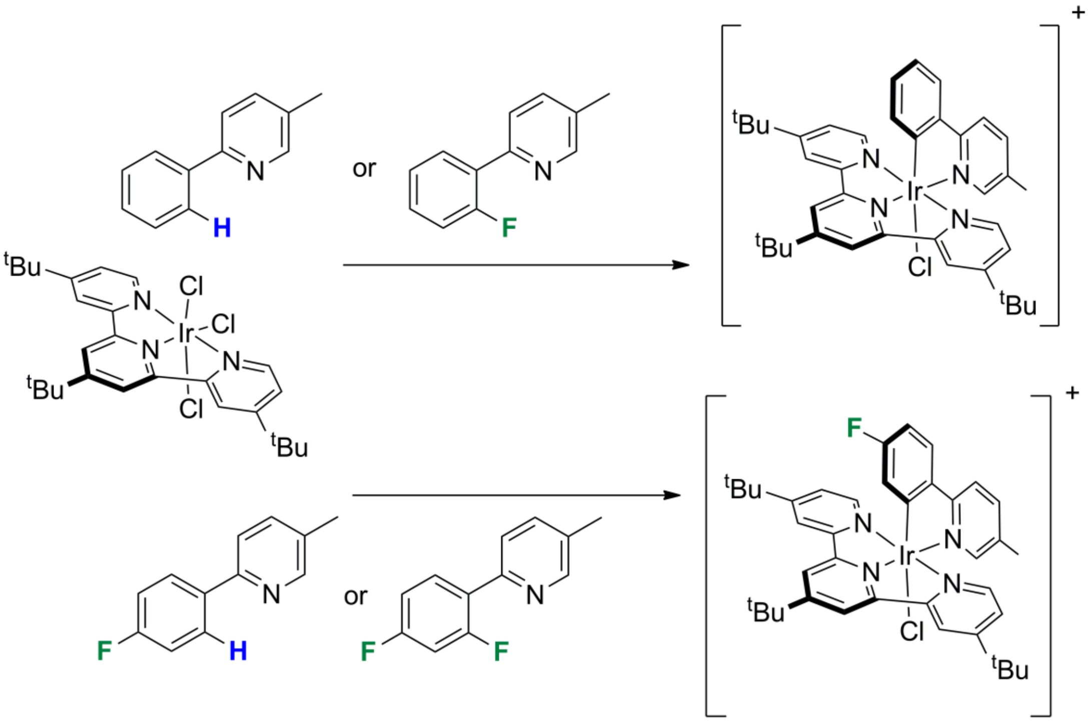
Scheme 30. Reactions of fluorinated benzophenones with $CoMe(PMe_3)_4$ (Adapted with permission from ref 225; Copyright 2008 Royal Society of Chemistry)



The cyclometalation of fluorinated biphenyls and fluorinated anisoles at iridium pincer complexes was discussed in Section 4.2.2.4.[190,191]

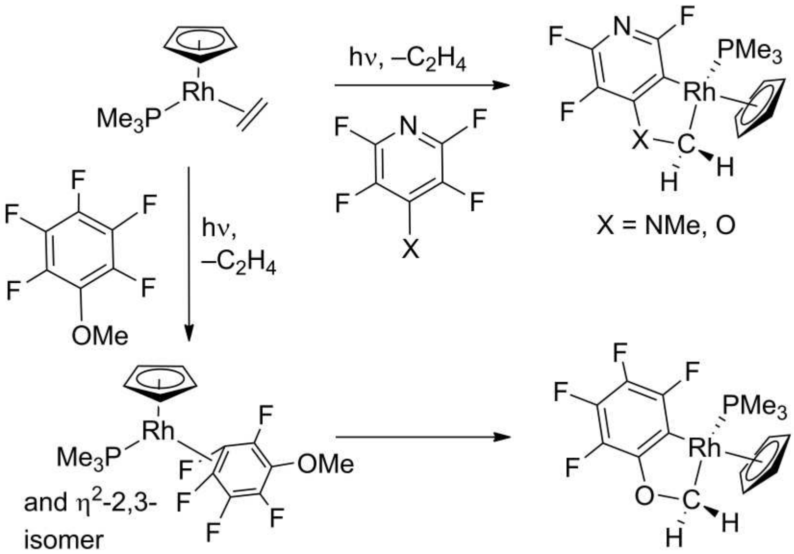
Kinetic and thermodynamic conditions have an impact on the chemoselectivity of the product in cyclometalation reactions at Ir^{III}. When $[Ir(^{tBu}tpy)Cl_3]$ (tpy = terpyridyl) reacts with fluorinated phenylpyridine substrates, only C-F activation is observed in preference to C-H. The chemoselectivity appears related to the formation of an Ir^{I} species during the cyclometalations generated at high temperature by oxidizing solvents. The Ir^{I} complex then undergoes oxidative addition to give the final Ir^{III} complex via C-F activation, favored thermodynamically over C-H activation. The final products are the same as those formed by C-H activation without the ortho fluorine in the substrate (Scheme 31).[227]

Scheme 31. Cyclometalation of fluorinated terpyridyls at Ir (Adapted from ref 227; Copyright 2016 American Chemical Society)



The influence of thermodynamic factors has also been observed to have an effect on the chemoselectivity at Rh. When $CpRh(PMe_3)(C_2H_4)$ is photolyzed, it loses ethylene, forming an unsaturated 16-electron complex, which is able to undergo different kinds of activation reactions (Section 4.2.2.2). If reacted with C_6F_5OMe, $C_5NF_4(4\text{-}OMe)$ or $C_5NF_4(4\text{-}NMe_2)$, cyclometalation products are obtained where the C-F activation occurs selectively at the position ortho to the OMe/NMe_2 group (Scheme 32). In the reaction with C_6F_5OMe, it is possible to observe the Rh(η^2-C_6F_5OMe) intermediate.[228,176] This cyclometalation requires C-H and C-F activation along with elimination of HF which can be considered the driving force of the reaction. This result is in agreement with what was observed by Jones *et al.*[229] but contrasts with the behavior of the same substrate with $Ni(COD)_2$, where C-F occurs in the ortho position to the nitrogen atom.[202] The Rh complex needs a primary carbon and a donor atom on the substrate to undergo cyclometalation. Different products were observed when the Rh complex was reacted with ethyl- and ethoxy-tetrafluoropyridine. Again, this behavior contrasts with that observed for Ni^0.[206]

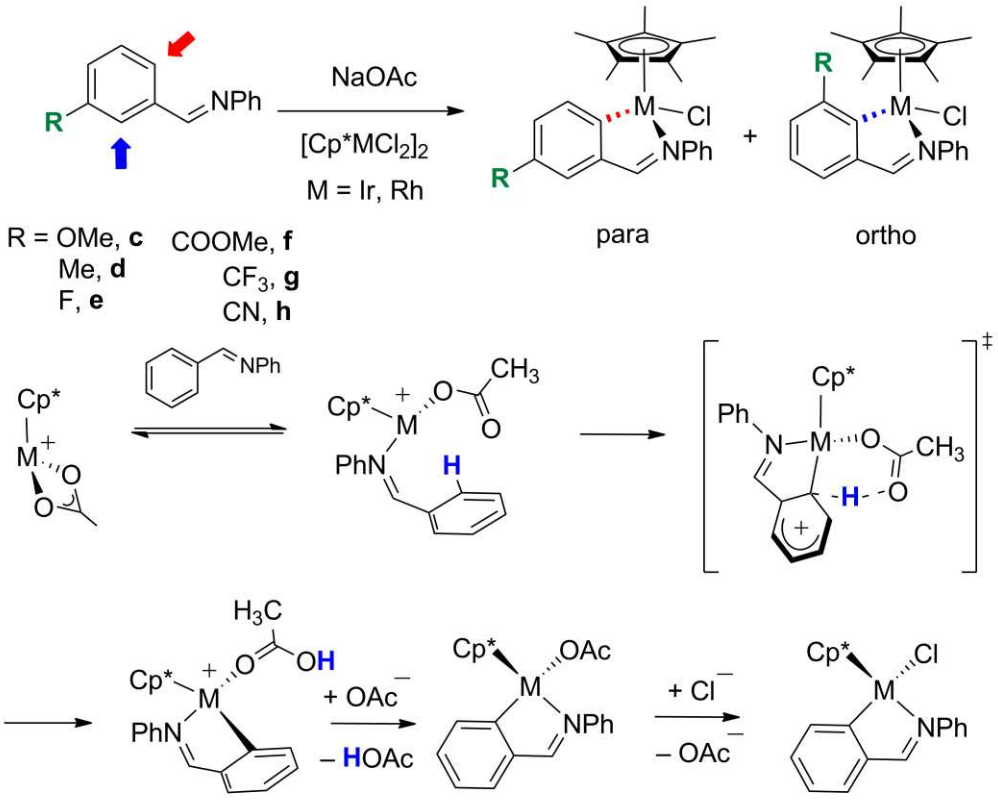
Scheme 32 Photo-induced cyclometalation at CpRh[228,176]



The ortho-fluorine effect has been observed in acetate-promoted reactions at iridium and rhodium of fluorinated phenylimines.[147] When $[Cp^*MCl_2]_2$ (M = Rh, Ir) complexes were reacted with phenylimines in the presence of NaOAc, only C-H activation was observed. The isomer (Scheme 33) obtained from C-H activation with F in the ortho position with respect to the metal is the favored product (*o:p* = 2.3:1 for Ir and 8.5:1 for Rh). All other phenylimines yield para-substituted products.

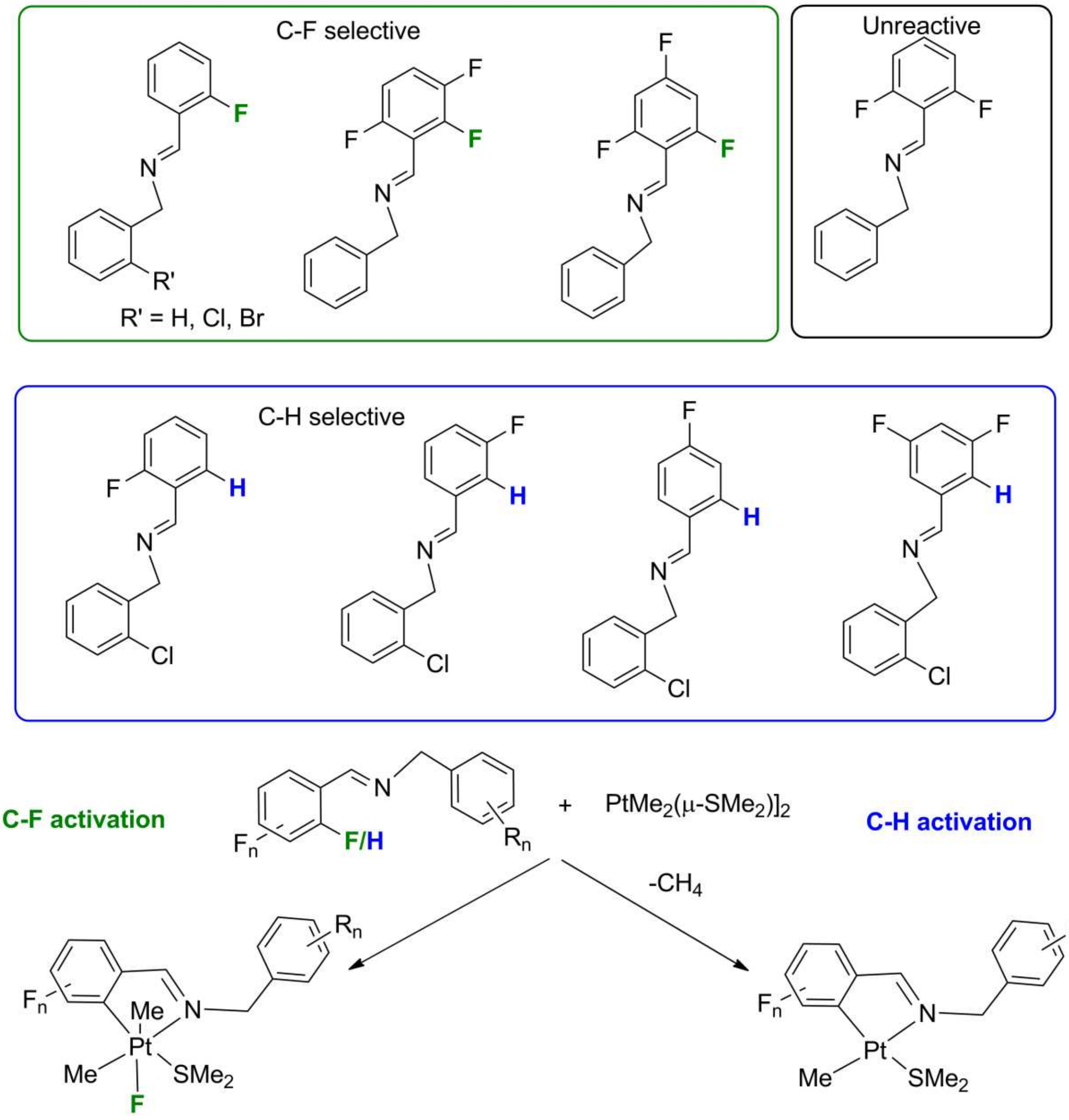
Kinetic studies show that the reactions proceed by electrophilic activation of the aromatic C-H bond. The imine attacks $[Cp^*M(OAc)]^+$ via N initially causing decoordination of the acetate carbonyl group. This carbonyl group receives the proton from the aromatic (Scheme 33). Iridium reacts more quickly than rhodium in this electrophilic aromatic substitution.

Scheme 33. Cyclometalation of phenylimine at Cp*Rh and Cp*Ir (Adapted from ref 147; Copyright 2009 American Chemical Society)



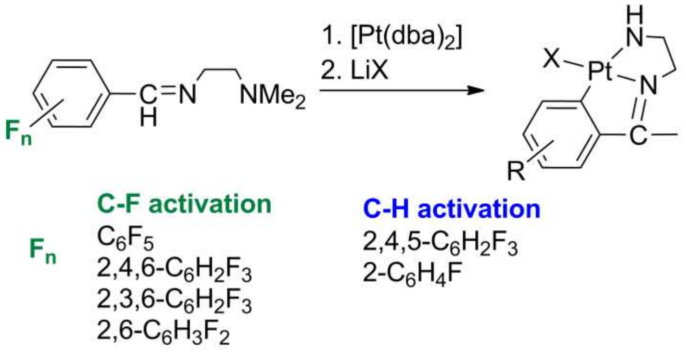
4.2.3.3 Group 10. Pt^0 and Pt^{II} complexes have been studied extensively to understand the factors involved in the different chemoselectivity toward intramolecular reactions with fluorinated substrates. Pt^{II} complexes are able to undergo oxidative addition with a range of different C–X bonds. When fluorinated imines react with a Pt^{II} complex, the cyclometalation reaction proceeds via the oxidative addition of a C-X bond, where X is H, F, Br or Cl. When $[Pt_2Me_4(\mu\text{-}SMe_2)_2]$ is reacted with fluorinated imines, not only is the reactivity of a C–F bond increased by a higher number of other fluorine substituents, but also by its proximity to another fluorine substituent.[230,47,231] Scheme 34 shows those substrates that react *via* C-F activation and those that react via C-H activation and one unreactive substrate. Although the nature of the activated bond and its position affect the activation parameters,[232,233] the reaction mechanism seems to be the same and consists of an oxidative addition at Pt^{II} to form a Pt^{IV} complex.[231] Of all the C-X bonds, the activation of the C-F bond seems to be the most difficult but it can nevertheless be achieved in preference to C-H bonds.[234,232,235] Full kinetic studies have been performed as a function of temperature and pressure leading to activation enthalpies, entropies and volumes providing the most detailed kinetic information that we have available for C-H and C-F bond activation for any reaction.[234] A comparison between the activation parameters for the oxidative addition of C-X bonds at Pt^{II} shows a remarkably low value for $\Delta H^{\ddagger}$ in the C-F bond activation compared to that for the weaker C-H or C-Cl bonds. These very low values are compensated by the more negative $\Delta S^{\ddagger}$ values for all the substrates, suggesting that a rearrangement to put the C-F bond in the correct orientation takes place before the activation. Thus, the measured C-F activation parameters for substrate C_6F_5-CH=NCH_2Ph are $\Delta H^{\ddagger}$ 30 kJ/mol and $\Delta S^{\ddagger}$ −198 J/K/mol, while the C-H activation parameters for 2-C_6FH_4-CH=$NCH_2C_6H_4Cl$ are $\Delta H^{\ddagger}$ 61 kJ/mol and $\Delta S^{\ddagger}$ −85 J/K/mol. These reactions have been developed for catalytic C-F activation.[51]

Scheme 34. Substrates for cyclometalation at Pt[47]



The degree of fluorination can influence the selectivity of cyclometalation as also observed for iron complexes.[219] When Pt^0 compound $Pt(dba)_2$ (dba= dibenzylidene acetone) is reacted with imine aryl groups having different degrees of fluorination, C-F activation is the dominant process with the exception of substrates bearing only one F ortho to the bond to be activated; the latter undergo C-H activation. When the Pt^0 complex was reacted with imines with a pendant NMe group, metallacycles were formed via C-H or C-F activation, followed by a ligand metathesis reaction with LiBr or LiCl. With the substrate containing a 2,3,6-$C_6F_3H_2$ substituent where two positions are available for C-F activation, only the one with a fluorine in the ortho position is activated, giving as a result a single isomer (Scheme 35).[236]

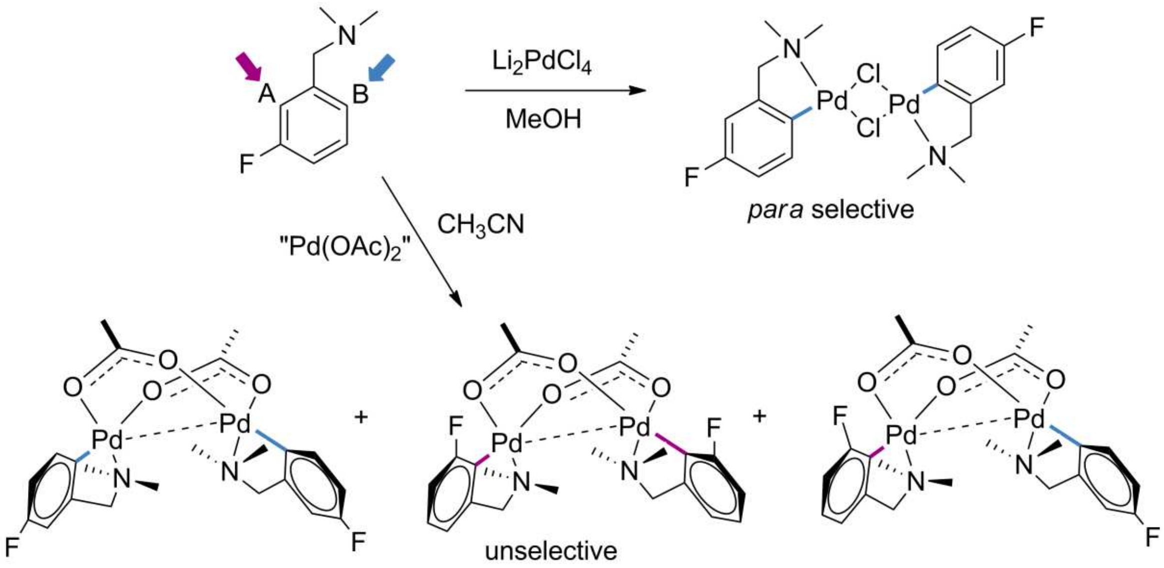
Scheme 35. Imine cyclometalation at Pt^0 (Adapted with permission from ref 236; Copyright 2004 Elsevier)



These results contrast with the activation of chlorinated and brominated imines at Pt^0 where the oxidative addition occurs at the less hindered C-Cl bond,[237] but also shows that the presence of a fluorine atom *ortho* to the bond to be activated can enhance its reactivity.[233,231,235]

By contrast, different regioselectivity was observed for the intramolecular C-H activation of fluorinated benzylamines at Pd^{II} according to the source of Pd.[36] When the substrate was reacted with Li_2PdCl_4 to form chloride-bridged palladacycles the activation was regioselective para to the transition metal (Scheme 36), behavior which differs from that observed for phenylimines at Rh and Ir.[37] When the substrates were reacted with palladium acetate, to form acetate-bridged palladacycles, a mixture of different isomers was obtained and no regioselectivity was observed. It is postulated that Li_2PdCl_4 reacts via an electrophilic substitution mechanism, while palladium acetate reacts by a concerted metalation deprotonation (CMD) mechanism. This behavior could be attributed primarily to the structure of the resulting palladacycles. Crystallographic analysis of the products shows that acetate-bridged palladacycles have flexible clam-shell structures, which can distort to avoid repulsion between a fluorine atom and the oxygen of the acetate bridge. In the case of the chloride palladacycles formed with Li_2PdCl_4, the structure is planar and the repulsion between the chlorine and the fluorine cannot be avoided.

Scheme 36. Cyclometalation reactions of Pd^{II} with fluorinated benzylamines (Adapted from ref 36; Copyright 2015 American Chemical Society)



The reaction of 2-(2,3,4,5-tetrafluorophenyl)pyridine (Htfppy) with Cu(OH)(IDipp) generates a copper difluorophenylpyridine complex with a bidentate phenyl pyridine ligand by C-H activation. An analogue can also be made a chelating diphosphine; these complexes have striking luminescence properties.[216]

4.2.4 Intermolecular Reactions with Fluorinated Alkenes. The number of studies on the C-H/C-F activation of partially fluorinated alkenes is modest although numerous papers concern fully fluorinated alkenes. A review on the topic including perfluorinated and partially fluorinated alkenes has been published by Ohashi and Ogoshi.[52]

4.2.4.1 Early transition metal complexes. Investigations of the reactivity of $Cp^*_2ZrH_2$ with various fluoroalkenes show that C-F activation is observed exclusively regardless of the position of fluorine, vinylic or allylic or a substituent on a saturated carbon chain. The reactions are always run under H_2 so that in general, the defluorinated alkene is not the final product and defluorinated alkanes are obtained. The substrate 3,3,3-trifluoropropene reacts with 4 equiv of $Cp^*_2ZrH_2$ to give propane and Cp^*_2ZrHF. Complete defluorination occurs within 10 min at room temperature. The intermediate fluorocarbon $CF_2{=}CH{-}CH_3$ was identified by GC/MS and ^{19}F NMR spectroscopy.

Propene was not observed as an intermediate as the reaction is run under H_2 pressure.[238] $Cp^*_2ZrH_2$ reacts with vinylic carbon−fluorine bonds of $CF_2{=}CH_2$ and 1,1-difluoromethylenecyclohexane ($CF_2{=}C_6H_{10}$) to afford Cp^*_2ZrHF and hydrodefluorinated products. Experimental evidence suggests that an insertion/β-fluoride elimination mechanism is occurring. The same precursor reacts with allylic C−F bonds of the olefins, $CH_2{=}CHCF_3$, $CH_2{=}CHCF_2CF_2CF_2CF_3$, and $CH_2{=}C(CF_3)_2$ to give preferentially Cp^*_2ZrHF and $CH_3{-}CH{=}CF_2$, $CH_3{-}CH{=}CF{-}CF_2CF_2CF_3$, and $CF_2{=}C(CF_3)(CH_3)$, respectively, by insertion/β-fluoride elimination. In the reactions of $Cp^*_2ZrH_2$ with $CH_2{=}CHCF_3$ and $CH_2{=}CHCF_2CF_2CF_2CF_3$, both primary and secondary alkylzirconium olefin insertion intermediates were observed in the ^1H and ^{19}F NMR spectra at low temperature.[239] This reaction can be explained by two mechanisms: olefin insertion into the Zr-H bond followed by fluorine elimination or H/F exchange in a 4-center metathesis type transition state as shown in Figure 19. The latter mechanism would be disfavored because it would build negative charge on the β-carbon during metathesis. Experimental evidence favors the mechanism via insertion/β-F elimination.[143] A similar preference for C-F activation is obtained in the reaction of $Cp^*_2HfH_2$ with various fluorinated arenes.[144]

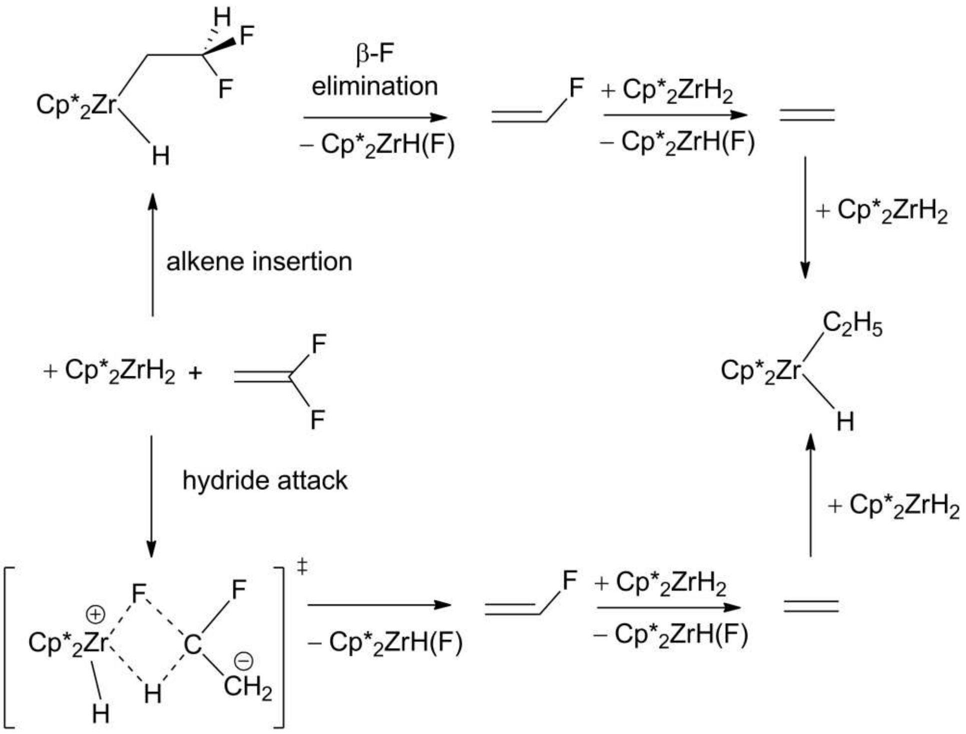


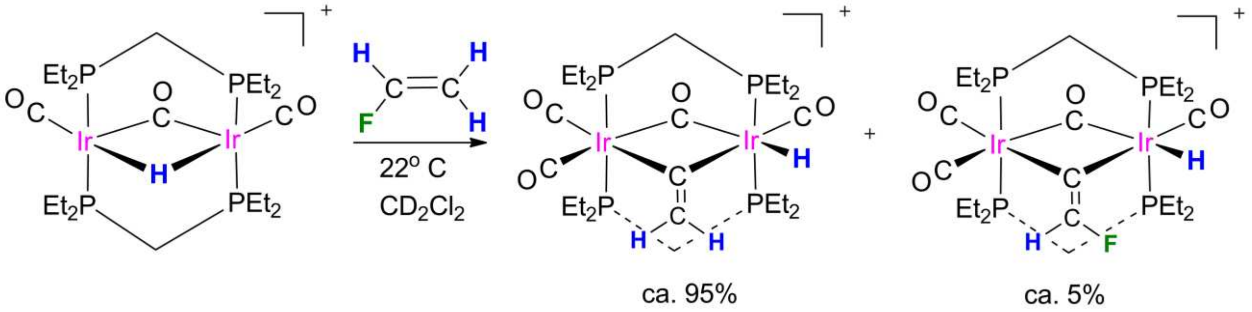
Figure 19. Mechanisms of reaction of fluoroalkene at Cp*$_2$ZrH$_2$. The olefin insertion, β-F elimination mechanism is preferred. Adapted with permission from ref 143. Copyright 2003 Royal Society of Chemistry.

A combined experimental and computational study of the reaction of vinyl fluoride with Cp$_2$ZrHCl gives clear evidence for the preference of the reaction initiated by the insertion of the alkene.[240] Vinyl fluoride reacts with Cp$_2$ZrHCl in benzene to give Cp$_2$ZrFCl and C_2H_4 as primary products but ethylene is not isolated and Cp$_2$Zr(C$_2$H$_5$)Cl is the observed secondary product. DFT(B3PW91) calculations show that the reaction is strongly exothermic. The σ-bond metathesis H/F exchange via a 4-center transition state is associated with activation energies between 80 and 110 kJ/mol, but calculations show that the pathway initiated by insertion of the alkene has lower energy barriers. The reaction occurs by preferential coordination of CH$_2$=CHF between the Zr-Cl and Zr-H bonds (inside pathway) followed by a Zr-H addition across the CH$_2$=CHF double bond in a regioselective manner that puts the F-substituted carbon at the β-position. The reaction gives the primary products by β-fluorine elimination.[240] The mechanism may also depend on the nature of the alkenes. Thus in the reaction of acyclic perfluorinated alkenes with Cp$_2$ZrH$_2$, DFT(BP86) calculations give a preference for the insertion mechanism,[241] while the hydride/fluoride exchange mechanism is preferred with perfluorinated cycloalkenes.[242]

4.2.4.2 Late transition metal complexes. While preferred C-F activation of fluoroalkenes is not surprising with early d^0 transition metal complexes, an experimental-computational study shows that similar selectivity can be observed with late transition metal complexes, but for different reasons.[243] The reaction of OsH$_3$ClL$_2$ (L = P*i*Pr$_3$) with vinyl fluoride in toluene at 20° C gives H_2 and a compound that is identified as an alkylidyne complex, OsH(Cl)(F)(≡CMe)L$_2$. The release of H_2 leads to another reaction that is competitive for vinyl fluoride in which ethylene and HF are produced by the reaction of CH$_2$=CHF with H_2 in presence of the osmium complex. The DFT(B3LYP) calculations on several possible pathways have identified an insertion reaction of the alkene, followed by α- or β-F migration in the monofluorinated alkyl intermediates as the elementary steps that could yield all observed products. However, all steps involving C-F activation are calculated to have high energy barriers so that unimolecular F-migration seems energetically unrealistic. These high-energy barriers are associated with repulsion between *d*-electrons and the fluorine lone pairs, as presented in section **3.3**. It was thus proposed that these fluorine migrations require Brønsted acid assistance and HF was assumed to have this role, leading to the idea that the reaction could be autocatalytic. This interpretation was consistent with the reaction of OsH_3ClL_2 with $CH_2=CF_2$ where HF is released and $OsH(Cl)(F)(\equiv CMe)L_2$ is the only observed osmium product and no ethylene, vinyl fluoride or ethyl fluoride are detected.[243] Other complexes showed similar preferences for C-F activation. Catalytic dehalogenation (F/Cl) of fluorinated/chlorinated ethylene by $(PPh_3)_3RhCl$ in the presence of Et_3SiH at 35 °C gives ethylene as the final product with the intermediate formation of monohalogenated (F/Cl) ethylene.[244]

Activation of both C-H and C-F bonds in partially fluorinated alkenes has been observed in the reaction of the diiridium complex $[Ir_2(CO)_3(\mu\text{-}H)\text{-}depm)_2]^+$ (depm = bis(diethylphosphino)methane, $\mu\text{-}Et_2PCH_2PEt_2$).[245] The reaction of the diiridium complex with vinyl fluoride at ambient temperature results in a product derived from C-H and C-F that dominates over the alternative where two C-H bonds have been activated (Scheme 37). This reaction, however, depends on the experimental conditions. In the presence of trimethylamine-N-oxide, only the double C-H activation product is observed while if water is added the C-F, C-H activation product is formed exclusively. 1,1-difluoroethylene also displays C-H and C-F bond activations but trifluoroethylene prefers coordination to the two iridium centers although C-H/C-F bond activation is observed upon warming. While water clearly has a role in the selectivity of these reactions, the precise nature of its action could not be detailed further but it was suggested that water assists several steps in this multistep reaction.

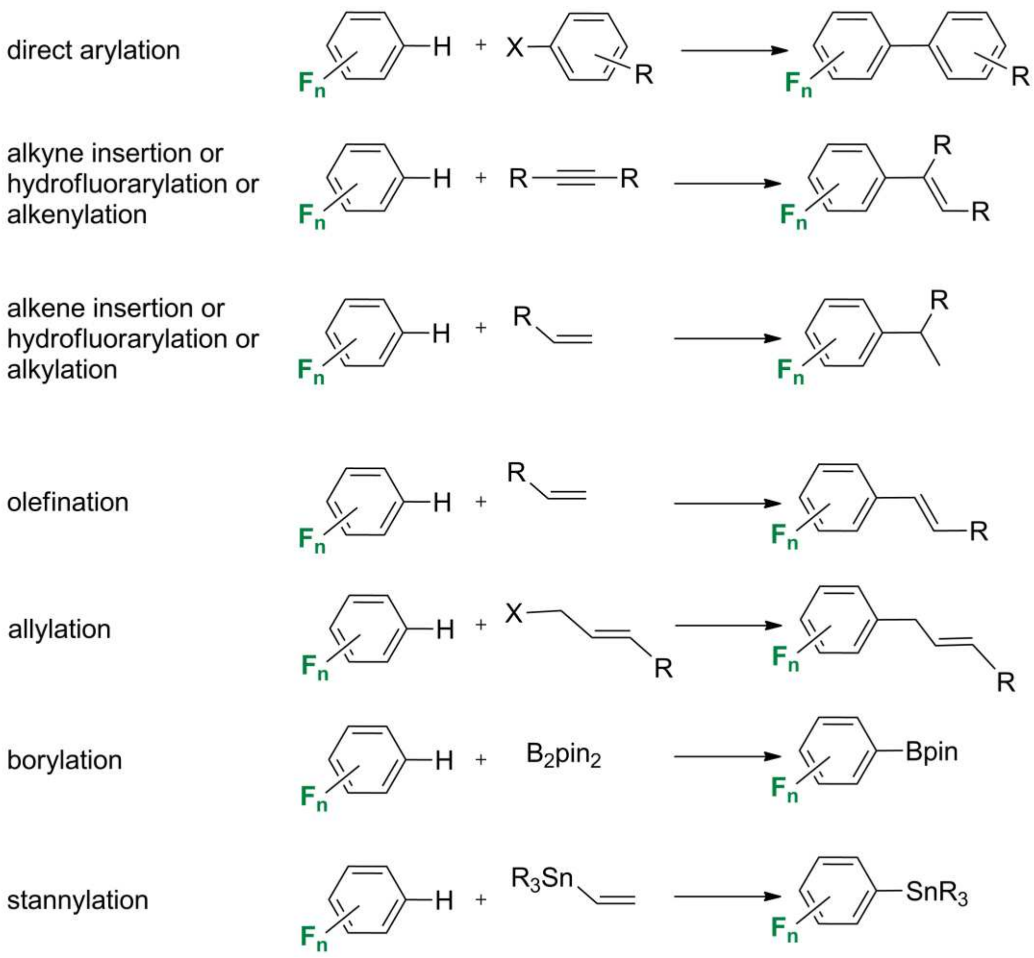
Scheme 37. Reaction of fluoroethylene at diiridium center (Adapted from ref 245; Copyright 2012 American Chemical Society)



5. EXAMPLES OF CATALYTIC REACTIONS INFLUENCED BY FLUORINE SUBSTITUENTS

The purpose of this short section is to point out examples of catalytic C-H activation or C-H functionalization reactions that are strongly influenced by the presence of fluorine substituents. A number of these reactions may exist for non-fluorinated substrates but fluorine makes these reactions more efficient. For C-F activation reactions, the reader is referred to the reviews mentioned in Section 1. The principal classes of catalytic reaction involving C-H activation are shown in Scheme 38; they are direct arylation,[32,79-80,246-255] alkyne insertion,[31,200,256-257] alkene insertion,[256] olefination,[258] allylation,[259] stannylation[260-261] and borylation[183,262] but it is important to note that they have been published under more than one name. The metals used for these reactions include Pd+Ag for direct arylation and olefination; Ru for direct arylation; Cu for allylation, arylation, and alkenylation; Ni for alkyne insertion, alkene insertion and stannylation; Pt or Rh for borylation. For each of these reactions, the considerations of the energetics of the fluoroarene substrate discussed in Section 3 will influence the energetics of catalysis. Moreover, the catalytic cycles postulated for these reactions invariably involve a metal fluoroaryl complex, the energy of which will be influenced by the number of ortho-fluorine substituents in the standard way. However, the hydrogen atom of the substrate does not necessarily form an intermediate M-H bond but may be removed by a base or be transferred to another ligand.

Scheme 38. Principal classes of catalytic C-H activation of fluoroarenes



Such catalytic reactions typically yield kinetic products, so the chemoselectivity (C-H vs C-F) and regioselectivity (ortho, meta, para) are determined by the rate-determining states that control the energy span. Full kinetic studies are limited in number, but we note the studies of stannylation[261] and direct arylation.[251] However, numerous computational studies have addressed the lack of experimental data, some of which are mentioned below.

The postulate that direct arylation occurs via a Concerted Metalation Deprotonation (CMD) mechanism, also known as Ambiphilic Metal-Ligand Activation (AMLA), in which the hydrogen atom of the substrate is transferred to a metal-coordinated carbonate or acetate has received strong support from theory (Figure 20).[32,79,263-265] The variation in the barriers to C-H functionalization with the fluoroarenes in Pd-catalyzed CMD reactions has been addressed directly through DFT(B3PW91) calculations.[78] It was shown that the energy barriers in the CMD and in the reductive elimination steps follow the sequence of the Pd–C bond energies according to the number of ortho fluorine substituents. The CMD barrier decreases with the number of ortho fluorines, while the barrier to reductive elimination increases: these effects influence the regioselectivity and the kinetics. The evidence points to a role both for the C-H acidity and the Pd-C bond energies though the role of the Pd-C bond energies has been questioned.[80,266]

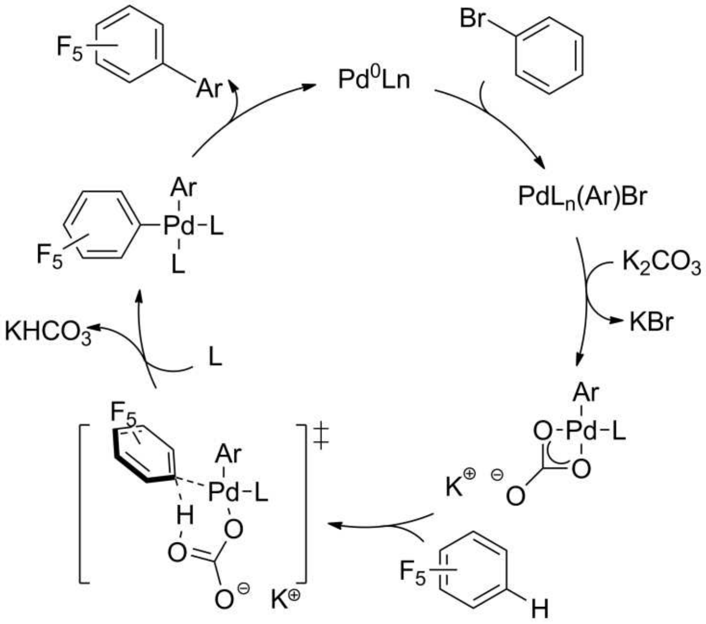
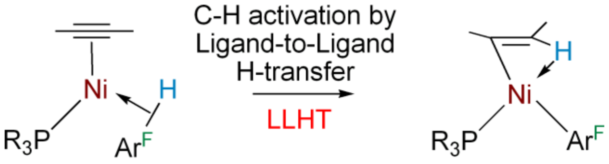


Figure 20. Typical catalytic cycle for palladium catalyzed direct arylation.

The role of silver salts in Pd-catalyzed C-H bond functionalization has been somewhat enigmatic. A recent study reported on the influence of silver salts on the reaction of $Pd(OAc)_2(dtbpy)$ (dtbpy = 4,4'-di-t-butyl-2,2'-bipyridine) with pentafluorobenzene (section 4.2.2.5).[210] A related paper concerns the Pd/Ag-mediated reaction (η^6-fluoroarene)$Cr(CO)_3$ with iodoarenes in the presence of excess triphenylphosphine leading to cross coupling of the fluoroarenes with the iodoarenes. Considerable kinetic evidence indicates that Ag(I) is responsible for the C-H activation step with the excess phosphine serving to solubilize the Ag salt as $Ag(O_2CR)(PPh_3)$.[251]

The mechanism of hydrofluoroarylation of alkynes at nickel has also been examined computationally,[267] revealing a ligand-to-ligand hydrogen transfer step (LLHT). Initial coordination of the fluoroarene via a σ-C-H bond is followed by LLHT to the alkyne yielding a nickel(aryl)(vinyl) complex (Scheme 39) which has to rearrange before undergoing reductive elimination of the arylalkene. Once more, there are strong correlations between the calculated barriers and the number of ortho-fluorine substituents. A related LLHT step has also been described for hydroarylation of alkenes at nickel using CF_3-substituted arenes.[268]

Scheme 39. Ligand-to-ligand hydrogen transfer (LLHT) in hydrofluoroarylation of alkynes at Ni (Adapted from ref 267; Copyright 2012 American Chemical Society)



6. GENERAL MECHANISTIC PRINCIPLES AND CONCLUSIONS

This review has illustrated the diversity of the activation of C-H and C-F bonds of partially fluorinated hydrocarbons by transition metal and lanthanide species. The thermodynamics in the reactants and products are superficially simple: the C-F bond is stronger than the C-H bond regardless of the hybridization of the carbon but the metal-F bond is stronger than the metal-H bond for any transition metal of the Periodic Table. Even for low oxidation state metals, the influence of the metal usually dominates so that there is no thermodynamic impediment to the cleavage of the C-F bond. However, the fact that the C-F bond is stronger than the C-H bond impacts on the kinetic factors and the situation can be complex so that the outcome C-H vs C-F activation depends on the exact nature of the metal complex as well as the substrate itself. For aromatics, C-F bond energies weaken systematically with the number of ortho-fluorine substituents, while C-H bonds strengthen. There are parallel systematic increases in M-C(aryl) bond strengths that are even more pronounced than those of the C-H bonds in the parent arenes. These changes have a major impact on the chemo- and regioselectivity of reaction. For a few late transition metals in high oxidation states, C-F reductive elimination has been observed, indicating that there can be exceptions to the generalization that C-F oxidative addition is favorable.

The review has mentioned extensive experimental-computational collaborations. It was, for instance, possible to obtain absolute or relative bond energies computationally, information which has been critical for studying molecules containing the strongest single bonds known for organic substrates. In addition, the number of experimental studies that could give direct information on mechanism by kinetics or isotope studies is limited. Thus, computation became an essential partner in this field and we have highlighted its role as well as pointing out where kinetic information is available.

We can summarize with some overall guiding factors. For reactions of bare atoms or ions in the gas phase or matrices, the repulsion between the fluorine lone pairs and the electrons on the metal results in very different behavior for the early metals on the one hand and late metals on the other hand. Coordination of the fluorinated substrate (extensively studied for fluoromethane) occurs through fluorine for these atoms and ions. Activation of the C-F bond by two pathways (harpoon and insertion-elimination) is observed mostly with early metal atoms/ions, while later metals exhibit complex formation (termed clustering) by way of F-coordination with less frequent bond breaking. Activation of the C-H bond is rare but has been observed with late heavy metals via various pathways.

With metal complexes in solution, lanthanide and early metals also exhibit significant differences from late metals. Coordination of fluorinated hydrocarbons has been observed mostly with arenes. It occurs through fluorine with early metals while coordination of the π-system is observed with late metals. In the case of η^2-coordination, the least fluorinated C=C bond is preferred although exceptions are known. These structural preferences have been suggested to arise from electron repulsion between the fluorine lone pairs and the electron density at the metal.

Overall, an increase in the number of fluorine substituents decreases the coordination energy although exceptions have been found.

The product of C-F activation dominates with lanthanides and early metals (mostly d^0 electron configuration). The mechanisms are diverse and do not exclude C-H activation as initial step. There are substantial differences in reaction pathways and reactivity for alkanes, arenes and alkenes. Radical reactions are inferred for alkanes but non-radical reactions are preferred for unsaturated substrates. Since these metals have no d electrons, non-redox pathways have to occur. The ligand (in particular hydride) thus plays a role by providing the source of electrons. The most direct pathway of H/F exchange is rarely preferred and pathways involving insertion followed by β-F elimination can occur for alkenes and S_NAr2 for arenes. A pathway for 1,2-C-H addition has been documented for titanium.

With metal centers with partially filled or full d shells, the situation becomes more complex. Reactions with fluorinated alkanes or aliphatic C-F are rarities, but significant progress has been made in reactions of groups 9-11 metals with partially fluorinated methanes. The intrinsic electron repulsion between the fluorine lone pairs and the d-electrons can be overcome by adding a Lewis acid or by adding a nucleophile leading to C-H cleavage. Activation of C-F bonds can be initiated by C-H bond breaking followed by fluorine migration. We do not encounter intermolecular bond activation of arenes for 1st row transition metals until we reach Co and Ni where we find the best examples of C-F bond activation. Recent studies document Ni(η^2-arene) complexes and C-H activation pathways to kinetic products while C-F activation leads to the thermodynamic product. However, with suitable choice of ligands only C-H activation is observed. Among the 2nd row metals, only rhodium complexes are well studied; here it is C-H bond activation that dominates, but C-F bond activation can compete occasionally. There are extensive studies of intermolecular C-H activation of arenes for 3rd row metals, W, Re, Os, Ir and Pt, whereas C-F bond activation is essentially absent. The mechanistic studies of aromatic activation point to oxidative addition pathways in the majority of cases, but ligand-assisted activation mechanisms have also been postulated (CMD and AMLA for C-H, and phosphine-assistance for C-F activation).

Studies of partially fluorinated benzenes were especially successful in demonstrating how fluorine substituents contribute to selectivity favoring the activation of the C-H bond ortho to the fluorine. In this review, we have encountered such ortho-selectivity again and again. It appears to be almost universal when the outcome of reaction is determined by energetics but is also encountered when under kinetic control. The origin of the effect lies in the fact that the C-H bond in the substrate is strengthened by the ortho F, but the M-C bond in the product is strengthened even more. The role of the metal dominates and this selectivity illustrates the important observation that strongest C-H bonds can be activated selectively. It was also noted that the C-H ortho to F is also the most acidic. The variation in the C-H bond energy in fluoroalkanes with the presence of fluorine is more complex.

Reactions with a ligand that can be anchored through N or O exhibit very different selectivity from intermolecular reactions. These intramolecular cyclometalation processes have been observed for metals of groups 8, 9, and 10 revealing competition between C-H and C-F bond activation for all three transition metal rows. Here, it is necessary to treat mechanism on a case-by-case basis, but we draw attention to the experimental evidence for electrophilic C-H activation of phenyl imines by rhodium acetate complexes and C-F oxidative addition of related substrates at platinum.

This review has also revealed important gaps in our knowledge. There is a lack of accurate quantitative experimental information concerning C-F and M-F bond strength which would have been of great value for validating computational methods. The presence of several lone pairs at F is expected to be associated with high correlation energies which challenge computation. There are numerous metals for which there is scant information about reaction with hydrofluorocarbons, especially among the first row transition metals and palladium. The reactions with hydrofluoroalkanes still stand out as very unusual compared to hydrofluorarenes. They are rare and when they occur, the mechanistic studies indicate that may be initiated by C-H activation; thus it should be possible to use designs for alkane activation to reveal more examples.

Finally, the review has once again demonstrated the unique characteristics of fluorine that derive from its ability to form strong bonds both to carbon and to metals. Moreover, the presence of fluorine not only enables metal-fluorine bond formation but can also favor C-H activation, thus modulating the outcome of reactions in fascinating ways.

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Notes

The authors declare no competing financial interests

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Robin Perutz is a professor of chemistry in the University of York, UK. After undergraduate studies in Cambridge he studied for his PhD, partly in Cambridge and partly in Newcastle-upon-Tyne under the supervision of J. J. Turner. After postdoctoral work in Mülheim, he took up positions in Edinburgh and Oxford before moving to York in 1983. He has investigated the chemistry of C-F bond activation and associated C-H bond activation and metal fluoride complexes since 1989. He is also very active in organometallic photochemistry. He has received awards from the Royal Society of Chemistry, the Italian Chemical Society and the French Chemical Society, and became a Fellow of the Royal Society, the UK's national academy, in 2010. He has been very active in the women in science agenda for almost 15 years. He served as President of Dalton Division of the Royal Society of Chemistry. In 2015, he was elected a Fellow of the American Association for the Advancement of Science.

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ABBREVIATIONS

AMLA	ambiphilic metal-ligand activation
BIOX	bioxazoline
CMD	concerted metalation deprotonation
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl

Cp'	1,2,4-tri-*t*-butylcyclopentadienyl
CASSCF	Complete active space SCF (multiconfigurational method)
CASPT2	multiconfigurational method with second order perturbation correction
CCSD(T)	Coupled Cluster method
DFT	density functional theory
DKH2	Douglas Kroll Hess second order
depm	bis(diethylphosphino)methane
dippe	$i\text{Pr}_2\text{PCH}_2\text{CH}_2\text{P}i\text{Pr}_2$
dppm	bis(diphenylphosphino)methane
EDG	electron donating group
EWG	electron withdrawing group
Htfppy	2-(2,3,4,5-tetrafluorophenyl)pyridine
IDipp	bis(2,6-diisopropylphenyl)imidazole-2-ylidene)
$i\text{Pr}_2\text{Im}$	1,3-diisopropylimidazole-2-ylidene
IPr	*N,N*-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene
LLHT	ligand-to-ligand hydrogen transfer
NBE	norbornene
NHC	N-heterocyclic carbene
RRKM theory	Rice-Ramsperger-Kassel-Marcus theory
SOC	spin-orbit coupling
tol	p-tolyl
Tp'	hydrotris(3,5-dimethylpyrazolyl)borate
ttp	tetratolylporphyrin

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