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C−F and C−H Bond Activation of Fluorobenzenes and Fluoropyridines at Transition Metal Centers: How Fluorine Tips the Scales

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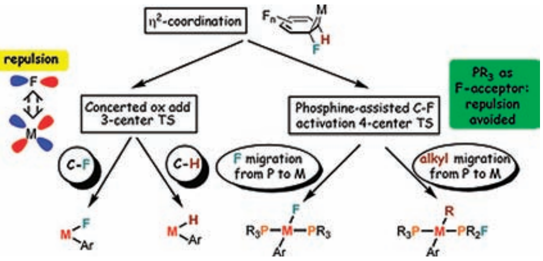

In this Account, we describe the transition metal-mediated cleavage of C−F and C−H bonds in fluoroaromatic and fluoroheteroaromatic molecules.

The simplest reactions of perfluoroarenes result in C−F oxidative addition, but C−H activation competes with C−F activation for partially fluorinated molecules. We first consider the reactivity of the fluoroaromatics toward nickel and platinum complexes, but extend to rhenium and rhodium where they give special insight. Sections on spectroscopy and molecular structure are followed by discussions of energetics and mechanism that incorporate experimental and computational results. We highlight special characteristics of the metal−fluorine bond and the influence of the fluorine substituents on energetics and mechanism.

Fluoroaromatics reacting at an ML_2 center initially yield η^2-arene complexes, followed usually by oxidative addition to generate $MF(Ar^F)(L)_2$ or $MH(Ar^F)(L)_2$ (M is Ni, Pd, or Pt; L is trialkylphosphine). The outcome of competition between C−F and C−H bond activation is strongly metal dependent and regioselective. When C−H bonds of fluoroaromatics are activated, there is a preference for the remaining C−F bonds to lie ortho to the metal.

An unusual feature of metal−fluorine bonds is their response to replacement of nickel by platinum. The Pt−F bonds are weaker than their nickel counterparts; the opposite is true for M−H bonds. Metal−fluorine bonds are sufficiently polar to form $M{-}F\cdots H{-}X$ hydrogen bonds and $M{-}F\cdots I{-}C_6F_5$ halogen bonds.

In the competition between C−F and C−H activation, the thermodynamic product is always the metal fluoride, but marked differences emerge between metals in the energetics of C−H activation. In metal−fluoroaryl bonds, ortho-fluorine substituents generally control regioselectivity and make C−H activation more energetically favorable. The role of fluorine substituents in directing C−H activation is traced to their effect on bond energies. Correlations between M−C and H−C bond energies demonstrate that M−C bond energies increase far more on ortho-fluorine substitution than do H−C bonds.

Conventional oxidative addition reactions involve a three-center triangular transition state between the carbon, metal, and X, where X is hydrogen or fluorine, but M(d)−F(2p) repulsion raises the activation energies when X is fluorine. Platinum complexes exhibit an alternative set of reactions involving rearrangement of the phosphine and the fluoroaromatics to a metal(alkyl)(fluorophosphine), $M(R)(Ar^F)(PR_3)(PR_2F)$. In these phosphine-assisted C−F activation reactions, the phosphine is no spectator but rather is intimately involved as a fluorine acceptor. Addition of the C−F bond across the M−PR_3 bond leads to a metallophosphorane four-center transition state; subsequent transfer of the R group to the metal generates the fluorophosphine product. We find evidence that a phosphine-assisted pathway may even be significant in some apparently simple oxidative addition reactions.

While transition metal catalysis has revolutionized hydrocarbon chemistry, its impact on fluorocarbon chemistry has been more limited. Recent developments have changed the outlook as catalytic reactions involving C−F or C−H bond activation of fluorocarbons have emerged. The principles established here have several implications for catalysis, including the regioselectivity of C−H activation and the unfavorable energetics of C−F reductive elimination. Palladium-catalyzed C−H arylation is analyzed to illustrate how ortho-fluorine substituents influence thermodynamics, kinetics, and regioselectivity.

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1. Introduction

Polyfluorinated aromatic and heteroaromatic molecules are activated toward nucleophilic attack and deactivated toward electrophilic attack. As this Account will demonstrate, their strong C−H and C−F bonds create opportunities and challenges for reaction at transition metal centers.[1,2] For example, C−F activation proves to be an excellent route to metal fluoride complexes allowing us to probe the special properties of metal−fluorine bonds. They include the ability to form discrete species in solution involving hydrogen and halogen bonds.[3] Our study of the regioselectivity of the C−H bond activation reactions demonstrates very general aspects of the effect of fluorine substituents on the strength of metal−aryl bonds. Another special feature derives from the ability of coordinated phosphines to act as fluorine acceptors, opening up new pathways for C−F activation.[4]

Stoichiometric reaction of fluoroaromatics at transition metals that cleave C−F bonds fall into four distinct types (Scheme 1, note that no particular mechanisms are implied).[5] In addition, processes that cleave C−H bonds are competitive in partially fluorinated systems, of which the most important are oxidative addition and base-assisted reactions (Scheme 1).[6] The fluorine substituents act as directors of the C−H activation process and are by no means just spectators. The ensuing competition between C−F and C−H cleavage leads to questions of energetics and mechanism that can be approached by a combination of experimental and theoretical methods.

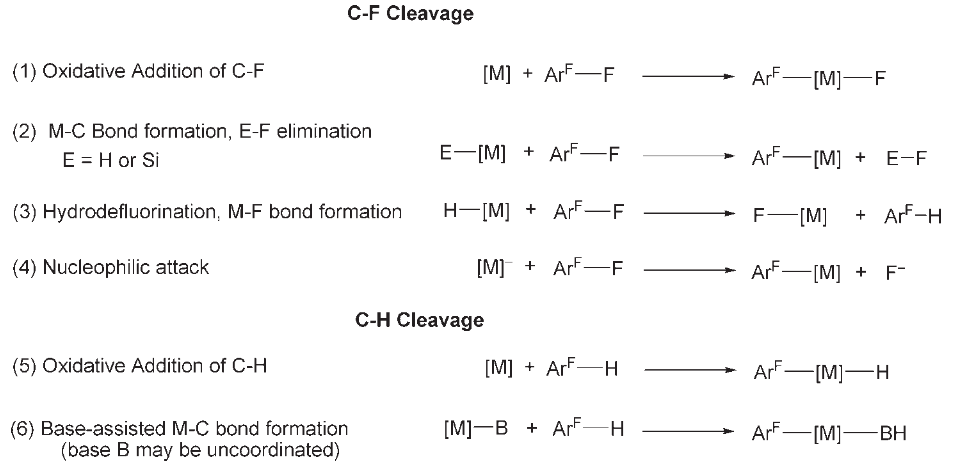
The wide variety of pharmaceuticals and materials that contain fluoroaromatics[7,8] invites the idea that transition-metal-mediated manipulation of fluorinated molecules may be synthetically useful, yet much remains to be done before it becomes a reality. There has been substantial progress in catalytic C−H bond activation of partially fluorinated aromatics. In these reactions, C−H bond activation is followed by C−C coupling to aryl halides[9] or to alkynes.[10] There are also opportunities for catalytic synthesis via C−F activation. Although more challenging than C−H activation, several new examples have been discovered recently.[11]

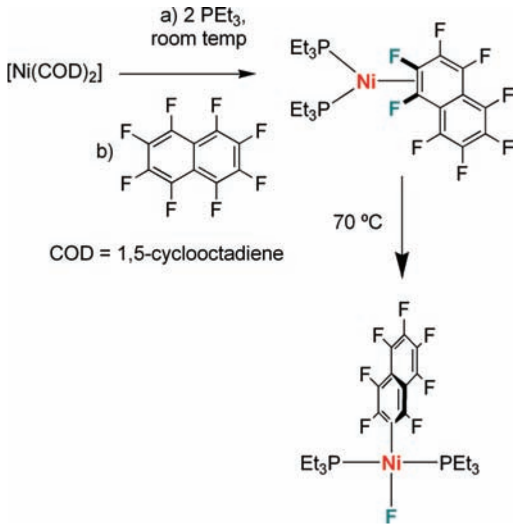
In this Account, we bring together our studies of C−F and C−H oxidative addition of fluoroaromatics and fluoroheteroaromatics, including experimental and computational investigations. We extend into other classes of reactivity that are closely related: of particular interest is phosphine-assisted C−F activation. Section 2 surveys reactivity, concentrating on group 10 metals since most C−F oxidative addition reactions involve these metals. In section 3, we consider group 7 and 9 examples that provide essential insight. Section 4 focuses on molecular structure and spectroscopy including unusual aspects of the M−F bond. In section 5, an analysis of the energetics of C−F and C−H activation paves the way for a review of reaction mechanisms (section 6). We consider the effects of fluorine substitution on catalytic C−H activation in section 7, before providing an outlook and summarizing some current developments in section 8.

2. Reactivity of Fluoroaromatics at Group 10 Complexes

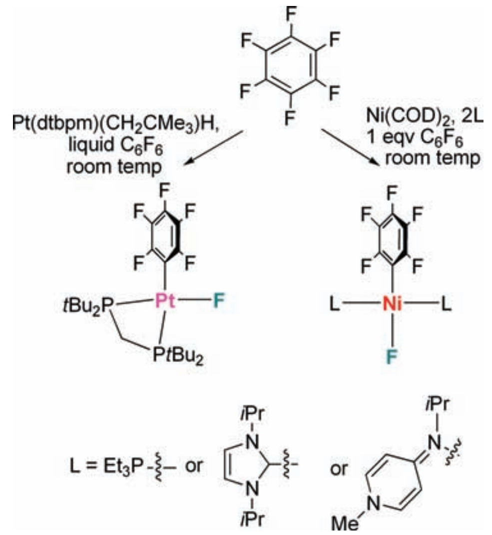
Coordination of Fluoroarenes. Ni^0 complexes frequently undergo C−F oxidative addition with perfluoroarenes (see below). The first stage of C−F oxidative addition is η^2-coordination of the fluoroarene, as is established for the reaction of octafluoronaphthalene with $Ni(PEt_3)_2$ (Scheme 2).[12] Conversion of the $Ni(\eta^2\text{-}C_{10}F_8)$ complex to the oxidative addition product can be observed, but not with clean

SCHEME 1. C−F and C−H Cleavage Reactions of Fluoroaromatics at Transition Metal Centers





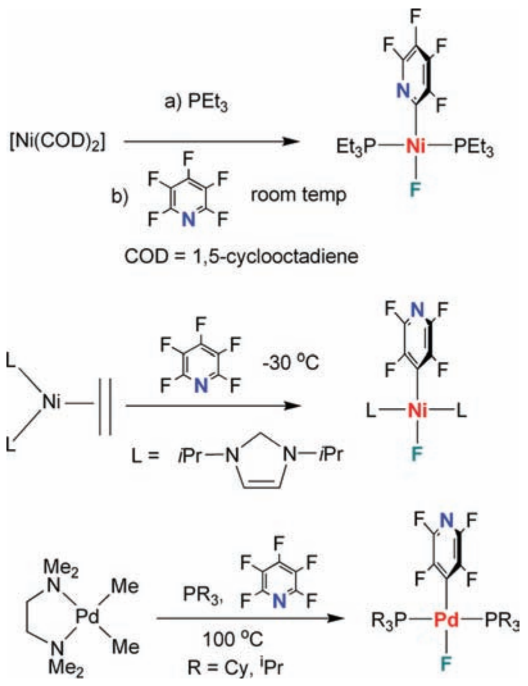
SCHEME 2. Reactivity of Ni^0 with Octafluoronaphthalene[12]



SCHEME 3. Reactivity[14,18–20] of Ni^0 and a Masked Pt^0 Precursor toward C_6F_6

kinetics. Recently, Johnson et al. have isolated complexes containing C_6F_5R (R = H, F) bridging two $Ni(PEt_3)_2$ moieties,[13] but they only detected the corresponding mononuclear complexes $Ni(PEt_3)_2(\eta^2\text{-}C_6F_5R)$ in solution. The equilibrium mixture of dinuclear and mononuclear adducts converts to *trans*-$[NiF(Ar^F)(PEt_3)_2]$. Analogous reactions have been observed with a carbene ligand in place of triethylphosphine.[14] Dynamic rearrangements of the $Ni(\eta^2\text{-arene})$ complexes are characteristic but will not be covered here.[12,13] Although local minima corresponding to $Pt^0(\eta^2\text{-fluoroarene})$ complexes have been located computationally,[15,16] only $Pt(\eta^2\text{-}C_6(CF_3)_6)$ complexes have been observed.[17]

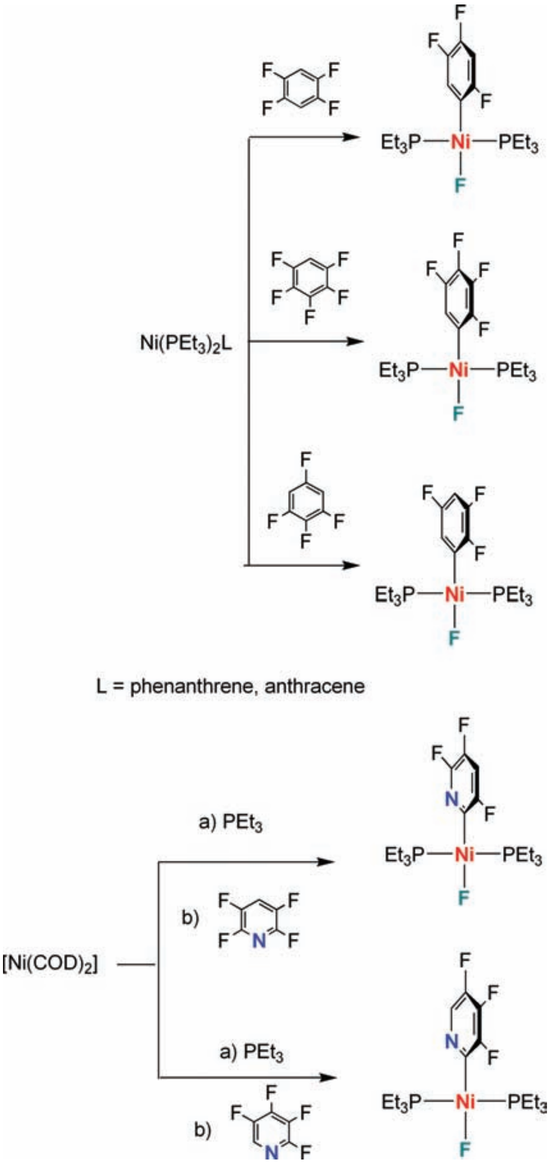
C–F and C–H Oxidative Addition. Following our early work with Ni^0, it is now established that Ni^0 complexes with phosphine, carbene, and even some nitrogen ligands undergo C–F oxidative addition with hexafluorobenzene in hydrocarbon solvents to yield *trans*-$[NiF(C_6F_5)(L)_2]$ (Scheme 3).[14,18,19] The reaction of $Pd(PCy_3)_2$ with hexafluorobenzene follows an analogous oxidative addition pathway,[4c] but the only oxidative addition reaction of hexafluorobenzene at platinum involves a sterically constrained phosphine in liquid hexafluorobenzene.[20] The corresponding reactions of pentafluoropyridine generally occur more readily, but subtle differences between the metals emerge. Oxidative addition is characteristic of nickel and palladium phosphines but there are differences in regioselectivity and temperature requirements (Scheme 4).[14,18,21] Of particular importance is the preference for activation of the C–F bond ortho to nitrogen for $Ni(PR_3)_2$ but para to nitrogen at palladium. Platinum analogues do not undergo oxidative addition with pentafluoropyridine.



SCHEME 4. Reactivity[14,18,21] of Pentafluoropyridine with Ni^0 and Pd^0 Complexes

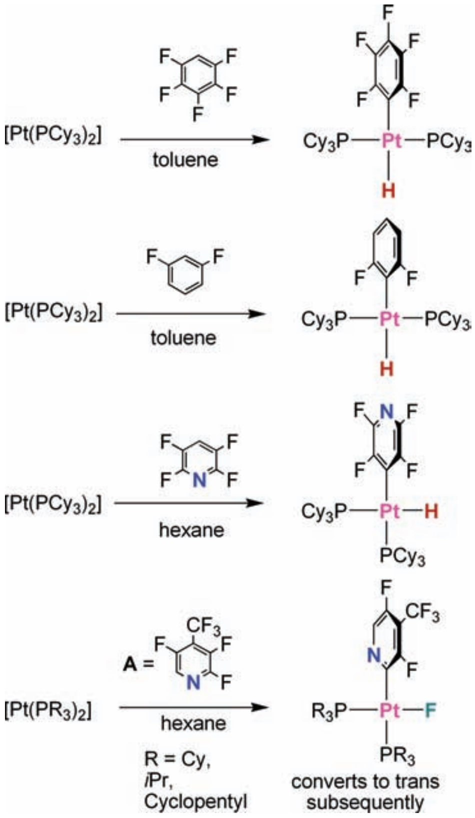
The introduction of C–H bonds into the substrate often slows the reactions and generates competition between C–F and C–H oxidative addition. The balance between these pathways is crucial to subsequent applications. For substrates C_6HF_5, 1,2,4,5-$C_6H_2F_4$, and 1,3,4,5-$C_6H_2F_4$, Johnson has shown that the C–H activated species are formed reversibly as kinetic products of reaction at $Ni(PEt_3)_2$, while C–F oxidative addition leads to the thermodynamic products (Scheme 5).[13,22] For the pyridines 2,3,4,5-tetrafluoropyridine and 2,3,5,6-tetrafluoropyridine, only the C–F

SCHEME 5. Principal Products of C−F Oxidative Addition of Partially Fluorinated Benzenes and Pyridines at Ni^0 (Secondary Reactions Omitted)[13,18,22,23]

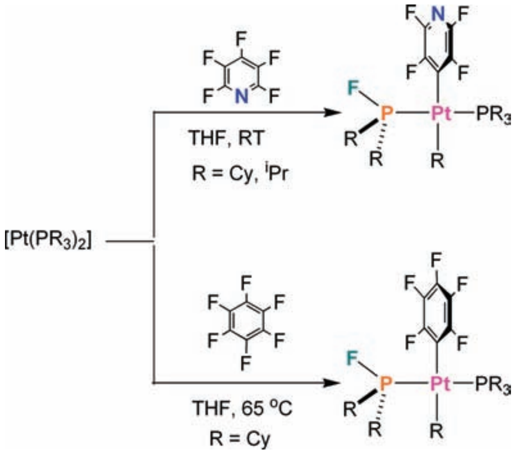


oxidative addition product has been found (Scheme 5).[18,23] The behavior of Pt^0 is intriguing: while pentafluorobenzene, 1,3-difluorobenzene,[24] and 2,3,5,6-tetrafluoropyridine[21] yield products of oxidative addition of C−H bonds only, the CF_3-substituted pyridine **A** gives aromatic C−F bond oxidative addition exclusively (Scheme 6).[16] These reactions give little hint of regioselectivity in C−H oxidative addition other than the reaction of $Pt(PCy_3)_2$ with 1,3-$C_6H_4F_2$, which gives exclusively the isomer with Pt ortho to both fluorines.[24]

SCHEME 6. Principal Reaction Products[16,21,24] of Partially Fluorinated Benzenes and Pyridines at Pt^0

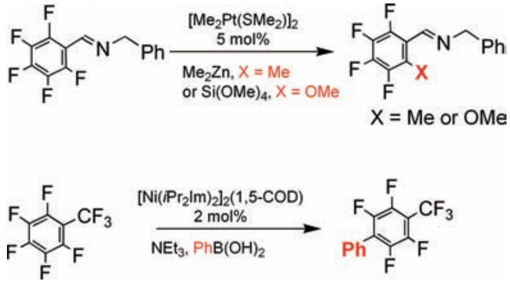


SCHEME 7. Reactions of Pentafluoropyridine[21] and Hexafluorobenzene[4] at Pt^0

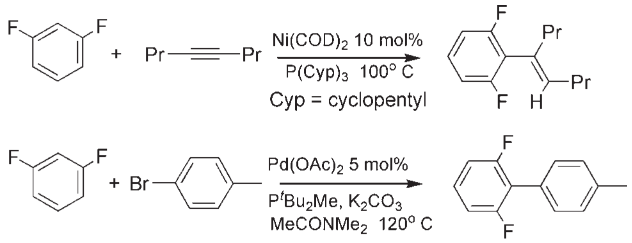


Reactions of Pt^0 with Perfluorinated Substrates. The reactions of $Pt(PR_3)_2$ with pentafluoropyridine were a total surprise to us. Instead of oxidative addition, the NMR spectra and crystal structure revealed that formation of a platinum-4-tetrafluoropyridyl bond was accompanied by a rearrangement in which a fluorine and an alkyl group had exchanged places (Scheme 7).[21] The resulting formation of P−F and metal−alkyl bonds was similar to Grushin's observations on the rearrangement of $Rh(PPh_3)_3F$, which were published as we were finalizing our manuscript.[4b] Grushin subsequently showed that

SCHEME 8. Catalytic C−F Activation Reactions[25,26]



SCHEME 9. Catalytic C−H Activation Reactions of Polyfluorinated Aromatics[9,10]



hexafluorobenzene reacts with $Pt(PCy_3)_2$ similarly to pentafluoropyridine but at a higher temperature.[4c] These discoveries left open the question of whether C−F oxidative addition occurs in an intermediate stage, see below.

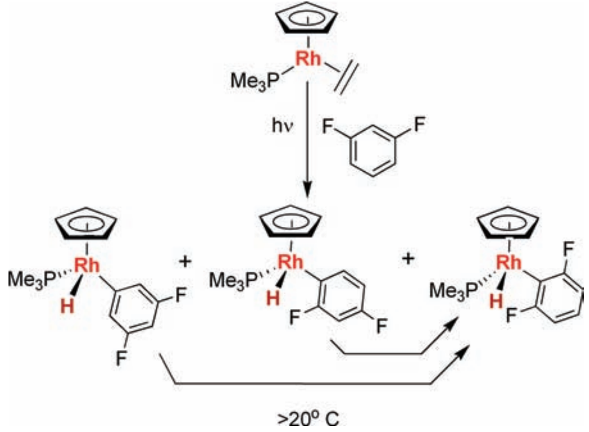
Catalytic Reactions of Fluoroaromatics. Although cross-coupling with group 10 metals is ubiquitous, only catalytic C−H or C−F bond activation of fluoroaromatics is directly relevant to this Account. Recent examples of cross-coupling involving C−F bond cleavage with polyfluorinated substrates are shown in Scheme 8;[25,26] for reviews, see refs 5 and 11. There have also been important advances in catalytic hydrodefluorination catalyzed by ruthenium complexes.[27]

The most remarkable progress has been made in C−C coupling reactions involving C−H cleavage of partially fluorinated aromatics. Fagnou's reactions involve coupling to aryl halides with a palladium catalyst,[9] a phosphine, and a base, while Nakao's reactions couple the aromatic to an alkyne with $Ni(COD)_2$ and a bulky phosphine.[10] Both reactions show selectivity for the product with two fluorine substituents ortho to the newly formed C−C bond (Scheme 9). These reactions raise questions regarding the origin of the regioselectivity and the preference for C−H bond activation (see section 7).

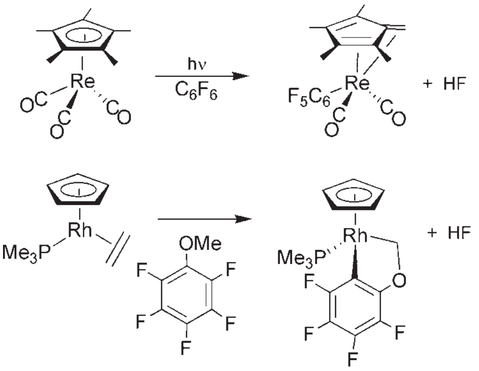
3. Related Reactivity at $(C_5R_5)Re(CO)_2$ and $(C_5R_5)Rh(PMe_3)$

C−H Bond Activation. The reactions of the group 10 metals give some indications about regioselectivity of C−H oxidative addition, but more decisive results were obtained in a collaborative study of group 9 metals between Perutz and Jones in the early 1990s.[28] Photolysis of $CpRh(PMe_3)(C_2H_4)$ with partially fluorinated benzenes yields exclusively products of C−H oxidative addition, $CpRh(Ar^F)(H)(PMe_3)$. The photochemical step is dissociation of ethylene leading to transient $[CpRh(PMe_3)]$, which reacts thermally with the fluorobenzene derivative. Reaction at low temperature with 1,3-difluorobenzene generates all possible product isomers. On warming, the isomers with zero or one fluorine ortho to the Rh−C bond isomerize to the product with two ortho fluorines (Scheme 10).[28] Similarly, the reaction of 1,2-$C_6H_4F_2$ leads to two products, and a thermodynamic preference emerges for the isomer with one ortho fluorine over that with no ortho fluorine substituents. Ortho selectivity is also found for other fluorinated benzenes and for thermal reactions of Cp* analogues; its origins are discussed in Section 5.

SCHEME 10. Preference[28] for ortho Fluorine at $[CpRh(PMe_3)]$



SCHEME 11. C−F Bond Activation with HF Elimination[31,32]



The photolysis of $Cp^*Re(CO)_2(N_2)$ in 1,3-$C_6H_4F_2$ provided a similar test of regioselectivity, but this time the only product detected was the rhenium(difluorophenyl)(hydride) with two ortho fluorine substituents.[29] Very recently, Jones

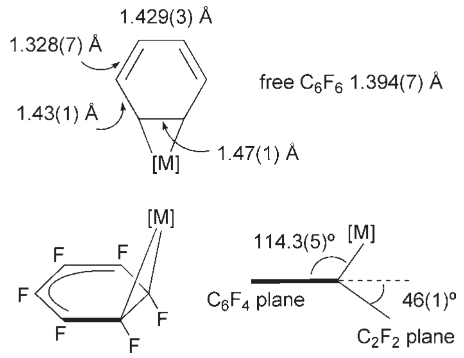


FIGURE 1. X-ray structural features of [M](η^2-C_6F_6) complexes: mean of data from three half-sandwich complexes, M = Re, Rh, and Ir. Figures in brackets represent range of values measured, except for free C_6F_6 where it is the esd. Copyright 1997 Royal Society of Chemistry, ref 33.

has investigated the photochemical reactions of Tp′Rh($CNCH_2CMe_3$)(carbodiimide) (Tp′ = tris(dimethylpyrazolyl)borate) with fluorinated benzenes. A full range of isomers is formed by C−H bond activation, but thermal isomerization demonstrates a clear energetic preference for ortho fluorine substituents.[30]

Combined C−H and C−F Activation. Rhenium and rhodium complexes reveal a class of reaction absent from group 10: C−F activation with HF elimination. While CpRe(CO)$_3$ reacts with hexafluorobenzene to give CpRe(CO)$_2$(η^2-C_6F_6), the Cp* analogue activates a methyl C−H bond to eliminate HF forming (η^6-$C_5Me_4CH_2$)Re(C_6F_5)(CO)$_2$.[31] The HF released causes conspicuous etching of the glass. In a related reaction of CpRh(PMe$_3$)(C_2H_4), it is the methoxy group of the substrate C_6F_5OMe that provides the C−H bond (Scheme 11).[32] It is not known whether these reactions are initiated by C−F or C−H oxidative addition.

4. Structural and Spectroscopic Studies of M(η^2-C_6F_6) and M−F Bonds

This section highlights general features of the molecular structures of the products of reaction of fluoroaromatics with transition metals that are essential for understanding energetics and mechanism. We begin with complexes containing the M(η^2-C_6F_6) unit. The metal lies above the plane of the C_6 ring, while the C−F bonds attached to the coordinated carbons are bent below the plane. The bond lengths follow an ene-diene pattern (Figure 1).[33]

For complexes containing a metal−fluorine bond, there are two straightforward experimental probes: X-ray diffraction and NMR spectroscopy. The X-ray structures reveal that all nickel complexes of the type *trans*-[NiF(Ar^F)L$_2$] adopt square planar structures with typical Ni−F distances in the range 1.84−1.86 Å.[14,18,19] The only example with cis phosphines, NiF(C_5NF_4)($Cy_2PCH_2CH_2PCy_2$), has a similar Ni−F distance (Figure 2, upper),[34] while the Pt−F bond lengths of the complexes in Scheme 6 are 2.03−2.04 Å.[16] An important structural issue is the large change in M−F bond lengths from Ni to Pt (Δr(Pt/Ni)), which we first predicted computationally.[15] Experimental values for Δr(Pt/Ni) are 0.188 Å for cis and 0.180 Å for trans complexes, much greater than is observed typically for M−H or M−C bonds.

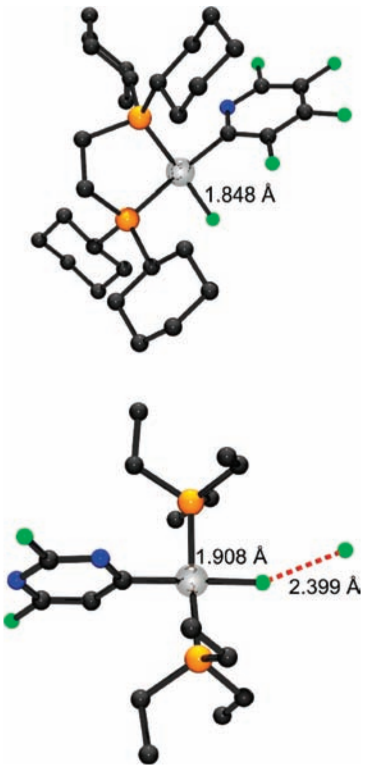


FIGURE 2. X-ray structures: upper panel, fluoride complex [NiF(C_5NF_4)($Cy_2PCH_2CH_2PCy_2$)];[34] lower panel, bifluoride complex *trans*-[Ni(FHF)($C_4N_2F_2$)(PEt$_3$)$_2$]; hydrogens atoms omitted, nickel metallic gray, fluorine green, nitrogen blue, and phosphorus orange.[36]

The two inequivalent M−P distances for complexes with cis phosphines demonstrate that the trans influence of fluoride is much weaker than that of fluoroaryl, Δr(M−P) = 0.0624(8) Å for Ni and 0.163(1) Å for Pt examples.[16,34] The extreme difference in trans influence between 2-py^F (2-py^F = 2-C_5NHF_2-(CF_3), see Scheme 6) and F ligands in *cis*-[PtF(2-py^F)(P*i*Pr$_3$)$_2$] is also indicated by the NMR coupling constants, J_{PtP} of 4010 Hz for P trans to F and 1852 Hz for P trans to 2-py^F.[16]

The difference in electronegativity between metal and fluorine should lead to very polar M−F bonds, capable of forming secondary bonds to hydrogen bond donors. We first observed such effects in solution by NMR spectroscopy when we synthesized "bifluoride" complexes by reaction of metal dihydride complexes with the HF source $Et_3N\cdot3HF$. Thus

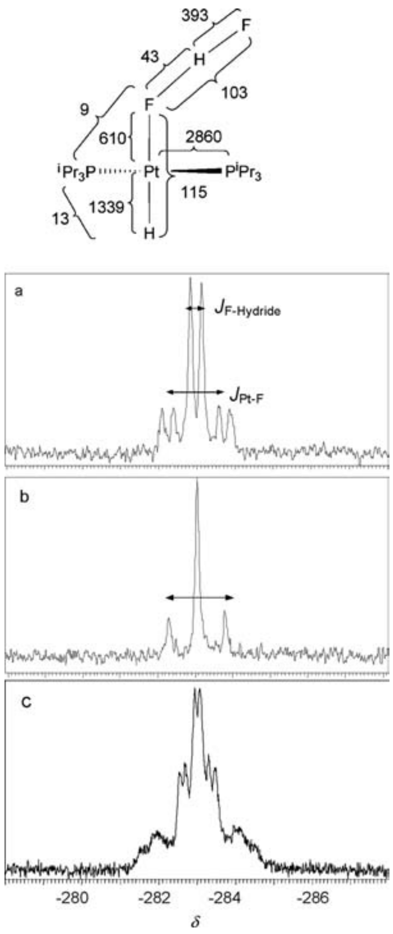


FIGURE 3. Top, NMR coupling network in *trans*-[Pt(H)(FHF)(P*i*PR$_3$)$_2$], (*J*/Hz). Bottom, ^{19}F NMR spectra in deuterated-THF in Pt—*F* region (a) at room temperature showing J_{Pt-F} and $J_{F\text{-}Hydride}$, (b) with ^{1}H decoupling of the hydride at room temperature, removing $J_{F\text{-}Hydride}$, and (c) without decoupling at 193 K showing additional couplings to HF.[35]

trans-[PtH$_2$(PR$_3$)$_2$] (R = Cy, *i*Pr) reacts with Et$_3$N·3HF to form *trans*-[Pt(H)(FHF)(PR$_3$)$_2$].[35] The complexes undergo rapid dynamic rearrangements at room temperature, but low-temperature NMR measurements reveal a complete coupling network involving Pt, phosphine, hydride, and the FHF ligand. Unusually, spin—spin coupling occurs across the hydrogen bond (Figure 3).

Metal fluoride complexes can also act as sources of bifluoride complexes through reaction with Et$_3$N·3HF, as shown by the reaction of the Ni(pyrimidyl) derivative. The resulting bifluoride complex, *trans*-[Ni(FHF)(C$_4$N$_2$F$_2$)(PEt$_3$)$_2$] exhibits a relatively long Ni—F bond (1.908(3) Å; Figure 2, lower panel) and a fluoride resonance shifted downfield from δ −362 to −333 in the ^{19}F NMR spectrum.[36]

In a collaboration with Brammer, we took advantage of these large changes in the chemical shift to measure the strengths of hydrogen bonds and halogen bonds to metal fluoride complexes. We chose indole as a hydrogen bond donor that could act as neither a nitrogen ligand nor a hydrogen bond acceptor. Halogen bonds are formed between a Lewis base and an electropositive halogen that acts as a Lewis acid.[37] Here the electronegative group is the fluoride of *trans*-[NiF(2-C$_5$NF$_4$)(PEt$_3$)$_2$] and the electropositive halogen is the iodine of I—C$_6$F$_5$. Our measurements showed a downfield shift in the fluoride resonance, while changes in all other resonances were negligible.[3] The ^{19}F NMR chemical shift was temperature and concentration dependent consistent with fast exchange between bound and free indole (or IC$_6$F$_5$) (Figure 4), allowing determination of the thermodynamics of binding (the first measurements of halogen bond strength in solution). The halogen bond strength is somewhat weaker in toluene than the hydrogen bond strength. In heptane, where π-stacking with IC$_6$F$_5$ is impossible, the halogen bond strengthens (ΔH°_1, kJ mol^{-1}: indole in toluene −23.4(2); IC$_6$F$_5$ in toluene −16(1); IC$_6$F$_5$ in heptane −26(1)).[3] Halogen bond strengths increase down the group Ni, Pd, and Pt in a series of very closely related complexes.[38] The formation of strong secondary bonds is consistent with very polar M—F bonds and an increase in polarity down group 10, although other factors may also be influential.

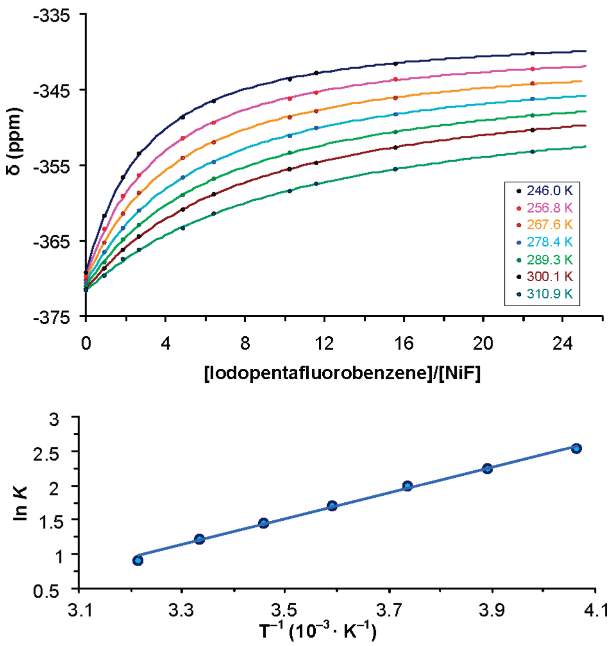
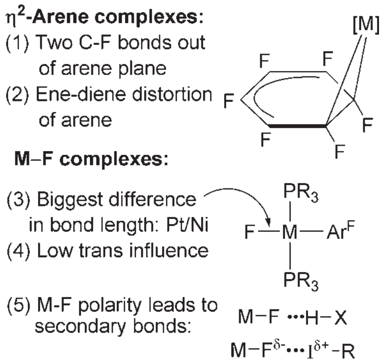


FIGURE 4. (a) Titration curves showing observed δ_{NiF} versus concentration ratio [iodopentafluorobenzene]/[NiF(2-C$_5$NF$_4$)(PEt$_3$)$_2$] in toluene-d_8 from 246 to 311 K; (b) Van't Hoff plot.[3]

The conclusions from this section are summarized in Scheme 12.

SCHEME 12. Principal Features of Molecular Structures of M(η^2-arene) and Metal Fluoride Complexes



5. Energetics of Reaction Products

Quantitative measures of the energetics of coordination of fluoroaromatics and of C−F or C−H bond activation depend on computational studies. All calculations were carried out with DFT methods with appropriate modeling of the experimental systems. In this section, we will address the questions of energetics concerning coordination of a fluoroaromatic, C−F oxidative addition, competition between C−F and C−H oxidative addition, the influence of fluorine substitution on the M−Ar^F bond strength, and differences between Ni and Pt. Although absolute values of energies vary with the methods, relative values should be accurate.

η^2-Coordination of Fluorinated Benzenes. Fluorine has two opposing effects on η^2-coordination of partially fluorinated benzenes. It lowers the LUMO of the arene making the fluorinated arene a better electron acceptor; on the other hand, the through-space M···F interaction destabilizes the complex because of repulsion between occupied metal orbitals and electron density around fluorine. The outcome, according to calculations on CpRe(CO)$_2$ complexes, is that binding energies for a given fluorinated benzene $C_6H_{6-n}F_n$ follow the order η^2-CH=CH > η^2-CH=CF > η^2-CF=CF yielding selectivity in the site of coordination. No systematic variation could be discerned, however, between the binding energies of different fluorinated benzenes at CpRe(CO)$_2$.[39]

Comparison of the η^2-coordination of either benzene or hexafluorobenzene to M(dhpe) (dhpe = $H_2PCH_2CH_2PH_2$, M = Ni, Pt) showed that binding energies follow the order Pt(C_6H_6) < Pt(C_6F_6) < Ni(C_6H_6) < Ni(C_6F_6) with a striking difference of ca. 34 kJ mol^{-1} between nickel and platinum analogues (Figure 5).[15] For these metals, there is a clear preference for binding C_6F_6 compared with C_6H_6.

C−F Oxidative Addition. We find that C−F oxidative addition is strongly exothermic for Ni(dhpe), both with respect to Ni(dhpe) + C_6F_6 (−187 kJ mol^{-1}) and with respect to Ni(dhpe)(η^2-C_6F_6) (Figure 5).[15] The analogous reaction of Pt(dhpe) + C_6F_6 is almost as exothermic (−170 kJ mol^{-1}). Studies with monodentate phosphines and with pentafluoropyridine have reinforced the evidence that C−F oxidative addition is extremely favorable thermodynamically for both metals.[15,16,40] A corollary is that C−F reductive elimination from square planar nickel and platinum is very unfavorable. However, the question of why C−F oxidative addition is frequent at nickel but rare at platinum is left unresolved by these energetic arguments. A resolution to this issue is found through other approaches shown below.

A comparison of C−F oxidative addition of C_6F_6 with C−H oxidative addition of C_6H_6 reveals striking differences (Figure 5). For Ni(dhpe), C−H oxidative addition is thermoneutral, whereas η^2-coordination is exothermic (complexes such as Ni(PEt$_3$)$_2$(phenanthrene) are well established).[13] In contrast, PtH(Ph)(dhpe) and Pt(dhpe)(η^2-C_6H_6) are both formed exothermically and should be close to equilibrium. In reactions with a partially fluorinated benzene, there is intramolecular competition between C−H and C−F bond activation. Since the strengths of the H−C and H−M bonds change with fluorine substitution, we cannot simply take the calculated values for benzene and hexafluorobenzene. The example of C_6F_5H shows that all the oxidative addition reactions are energetically favorable, but C−F activation is strongly preferred (Scheme 13). Further analysis shows that the Pt−H bond is stronger than Ni−H, but Pt−F is weaker than Ni−F, leading to relatively long Pt−F bonds (section 4). The most likely explanation of this change is increased repulsion between the fluorine lone pairs and the diffuse 5d orbitals in platinum.[15]

Energetics of Carbon−Hydrogen Oxidative Addition, Variation with Fluorine Substitution. We have seen above that C−H oxidative addition of benzene at Ni^0 is much less favorable than η^2-coordination, although this balance may be altered by fluorine substitution. Indeed, we have found that fluorine substituents direct C−H activation. The idea that M−R bond energies track with H−R bond energies led to the development of experimental bond energy correlations. Jones established that the slope of these correlations is slightly bigger than unity, meaning that M−R bond energies in the series R = benzyl, cycloalkyl, alkyl, and aryl grow faster than their H−C counterparts.[41] This result led us to examine the trends in bond energies for oxidative addition of fluorinated benzenes to metal−ligand fragments using a purely

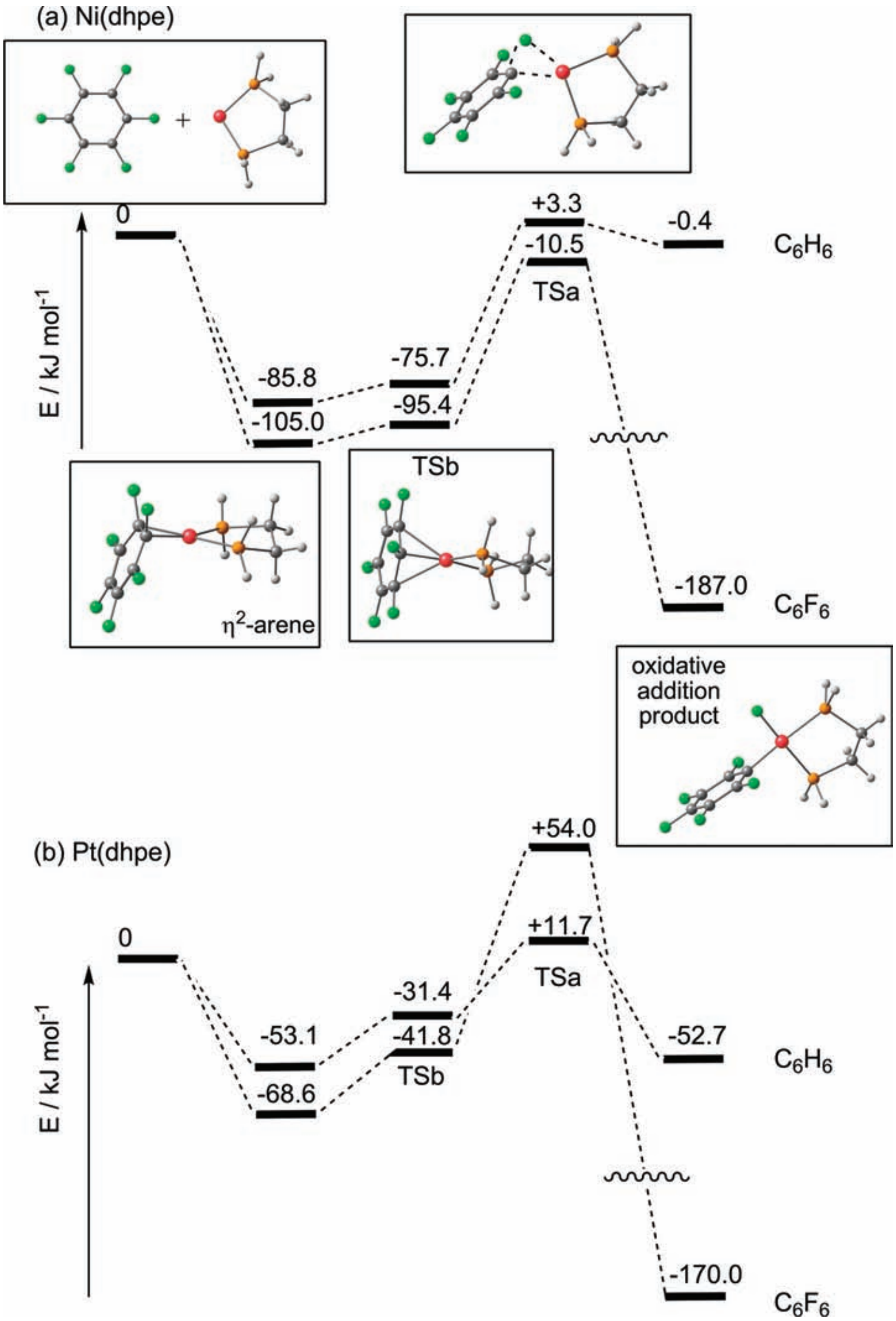
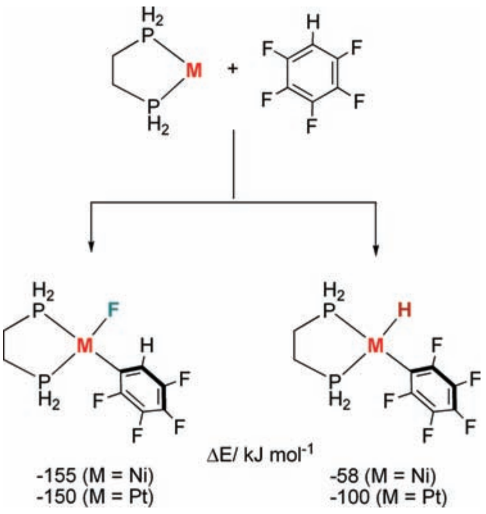


FIGURE 5. Potential energies (E, kJ mol^{-1}) of oxidative addition to (a) Ni(dhpe) (upper pathway C_6H_6, lower pathway C_6F_6) and (b) Pt(dhpe) (upper pathway C_6H_6, lower pathway C_6F_6). Molecular structures are drawn for C_6F_6 pathway on Ni, but are also applicable to Pt. For comment about the linked transition states, see ref 15.

computational approach. We validated our method by calculating the correlations that had already been established by experiment.[42] We discovered that fluorine substitution had a major effect on the energetics of C–H oxidative addition to $CpRe(CO)_2$ and that the principal determinant of the bond energy is the number of ortho-fluorine substituents.[29,39] Thus the M–C bond energy increases by 25–30 kJ mol^{-1} with each fluorine substituent, while the H–C bond energy grows only 10–12 kJ mol^{-1}. The meta and para fluorine substituents have only minor effects. These changes can be expressed quantitatively in two ways, (a) as a bond energy correlation, with slope

SCHEME 13. Competition between C−H and C−F Activation at M(dhpe)[15]



$\mathscr{R}^{\mathrm{M-C/H-C}} = 2.25$ for $CpRe(CO)_2$, or (b) as an equation relating the bond energies to the number of substituents,[43]

$$\Delta D(\mathrm{M-C}) = a + b n_{\mathrm{ortho}} + c(n_{\mathrm{meta}} + n_{\mathrm{para}}) \quad \mathrm{kJ\ mol^{-1}} \tag{1}$$

where n_{ortho}, n_{meta}, and n_{para} are the numbers of ortho, meta and para fluorines, and *a*, *b*, and *c* are coefficients. For $CpRe(CO)_2$, the values of *b* and *c* are 24.1(2) and 2.0(2) kJ mol^{-1} and *a* is negligible, clearly indicating the dominance of ortho substitution. These results allowed us to rationalize known reactions with fluorinated benzenes and predict that equilibria that place fluorine substituents in ortho positions as in eqs 2 and 3, should be favorable. Moreover, the same principles apply to a wide variety of metal−ligand fragments. Notably, the thermodynamic preference for ortho-fluorine substituents illustrated in Scheme 10 could now be understood via calculations on $MH(Ar^F)(dhpe)$ (M = Ni, Pt) (Figure 6).[43] Similarly, the formation of nickel hydride complexes by oxidative addition of polyfluorinated benzenes (section 2) is now explained.[7] The climax of this investigation came when Jones et al. tested our predictions on $Tp'RhH(Ar^F)(CNCH_2CMe_3)$ and found an experimental slope $\mathscr{R}^{\mathrm{M-C/H-C}}$ of 2.14 in agreement with a calculated slope of 1.96.[30] The extreme sensitivity of the $M-Ar^F$ bond energies to ortho fluorine substituents is not fully explained, but one of the main factors is the ionicity of the $M-Ar^F$ bond. Whatever its origin, the fact that M−C bond energies are far more sensitive to substituents than their H−C counterparts means that we can stabilize C−H oxidative addition products with ortho fluorine substituents.

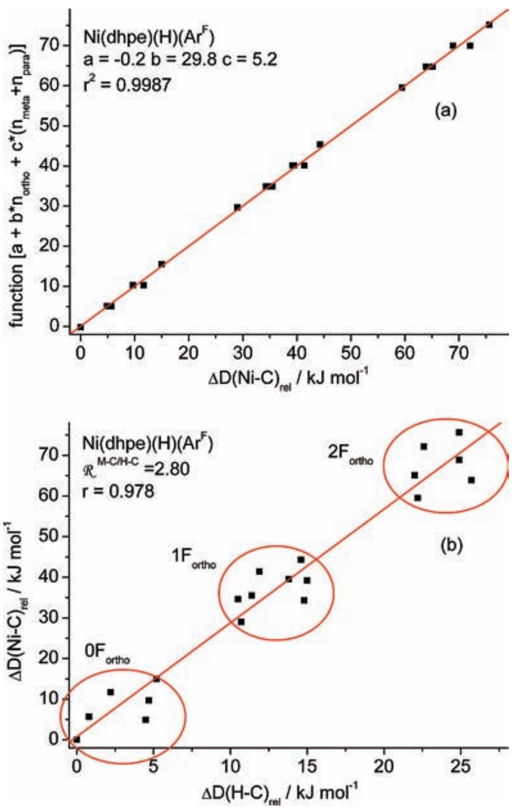
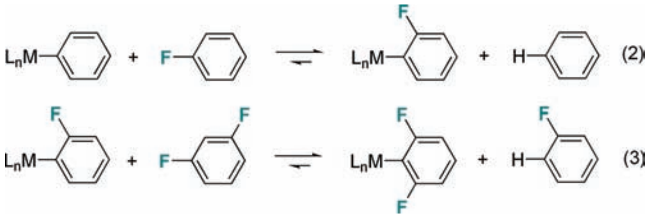


FIGURE 6. (a) Regression analysis for Ni−C bond energies for $NiH(Ar^F)(dhpe)$ and (b) correlation between calculated Ni−C bond energy and H−C bond energy. Derived values, $b = 29.8(3)$ kJ mol^{-1}, slope $\mathscr{R}^{\mathrm{Ni-C/H-C}} = 2.80$.[43]

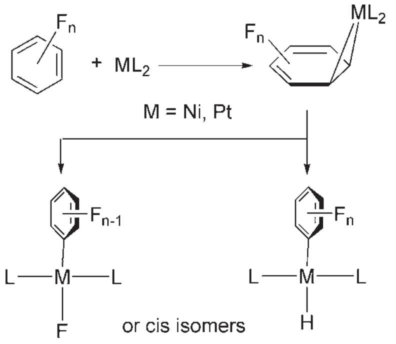


The main findings concerning energetics are summarized in Scheme 14.

6. Mechanisms of Oxidative Addition

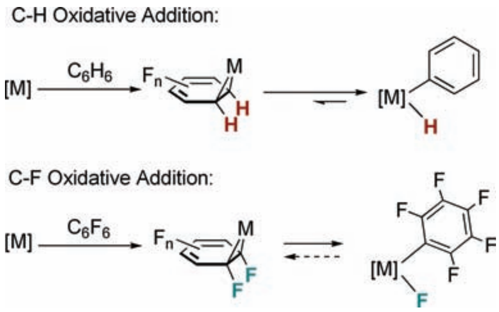
C−H and C−F Oxidative Addition. The mechanism of C−H oxidative addition of benzene is usually thought to involve precoordination of benzene followed by concerted oxidative cleavage of the C−H bond (Scheme 15). The conversion of the η^2-benzene adduct to the phenyl hydride

SCHEME 14. Principal Features of Energetics of C—F or C—H Oxidative Addition

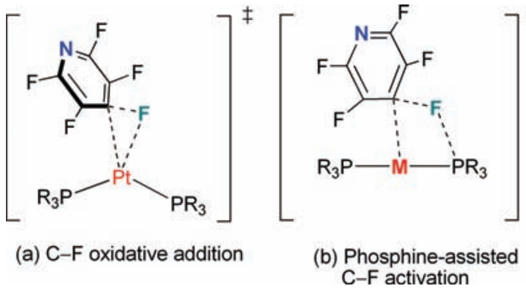


(1) Weaker η^2-coordination to Pt than Ni
(2) C-F oxidative addition strongly exothermic
(3) C-H oxidative addition: Pt more exothermic than Ni
(4) Bond strength: D(Pt-F) < D(Ni-F) but D(Pt-H) > D(Ni-H)
(5) Bond strength: D(M-Ar^F) increases on ortho-fluorine substitution (effect on catalysis in section 7)

SCHEME 15. Mechanisms of Oxidative Addition



SCHEME 16. Transition State Structures from Calculations on Reactions of Pt$(PR_3)_2$ with Pentafluoropyridine



(a) C–F oxidative addition

(b) Phosphine-assisted C–F activation

complex was first followed by laser flash photolysis for CpRh(PMe_3), and the barrier was measured as 48 ± 4 kJ mol^{-1}.[44] Since then, experimental evidence has been obtained for Pt(η^2-arene) intermediates in C—H oxidative addition.[45−47]

There are strong indications that the same type of mechanism applies to oxidative addition of C—F bonds at Ni^0. The η^2-fluoroarene intermediates may be isolated, and the conversion to MF(Ar^F) may be followed directly (section 2).[12−14] However, the lack of clean kinetics hints that there may be some mechanistic complications. Computational studies of the reaction pathways support the mechanisms of Scheme 15 (Figure 5) for reaction of M(dhpe) (M = Ni, Pt) with C_6H_6 and C_6F_6. Each reaction has a three-center triangular transition state between the carbon, metal, and X, where X is hydrogen or fluorine (Scheme 16a), but there are marked differences between Ni and Pt.[15] The η^2-C_6H_6 and η^2-C_6F_6 intermediates are more stable for Ni than for Pt (see Figure 5). The barrier to C—H oxidative cleavage is higher for Ni than for Pt, and oxidative cleavage of C—H bonds becomes more exothermic with ortho fluorine substituents. For C—F oxidative cleavage, the barrier is lower for Ni than for Pt and the reaction is more exothermic. Thus we can understand the outcome of competition between C—F and C—H oxidative addition.[15] For Ni, C—F activation is dominant, though kinetic C—H activation products can be seen. For platinum, C—H oxidative addition is dominant and leads to the kinetic product. Only in a few examples can C—F oxidative addition be observed at platinum.

A feature of all the studies of C—F oxidative addition, first noted for reaction of difluorobenzene with CpRh(PMe_3),[48] is the evidence for repulsive interactions between fluorine lone pairs and the occupied d-orbitals, usually leading to higher barriers for C—F than for C—H cleavage.[15,16,40] The transition state (TS) structures show limited elongation of the C—F bond and formation of the M—F bond. Comparison of the TS structures for Ni and Pt shows that the C—F bond is more elongated for Pt than for Ni ($\Delta r = 0.21$ vs 0.13 Å), while the Pt—C and Pt—F bonds are formed to a lesser extent.[15] Interaction of occupied metal orbitals with the F lone pairs is repulsive, while interaction with the C—F σ^* leads to C—F bond breaking and formation of the M—C and M—F bonds. The higher barrier for C—F activation at platinum suggests that increased Pt(5d)—F(2p) repulsions dominate.

In section 2, we highlighted the rearrangement reaction of Pt$(PR_3)_2$ with pentafluoropyridine to form *trans*-[Pt(R)(4-C_5NF_4)$(PR_3)(PR_2F)$] (Scheme 7).[21] Our initial ideas of C—F oxidative addition followed by rearrangement were eliminated by calculations of the energetics, since the alkyl product is less stable than the isomeric fluoride. A full analysis by DFT showed, to our amazement, that this complex reaction occurred in a single step with no intermediates. This process, *phosphine-assisted C—F bond activation*, is initiated by nucleophilic attack by the Pt center on pentafluoropyridine resulting in addition of the C—F bond across the Pt—P bond in a four-center transition state (Scheme 16b). The

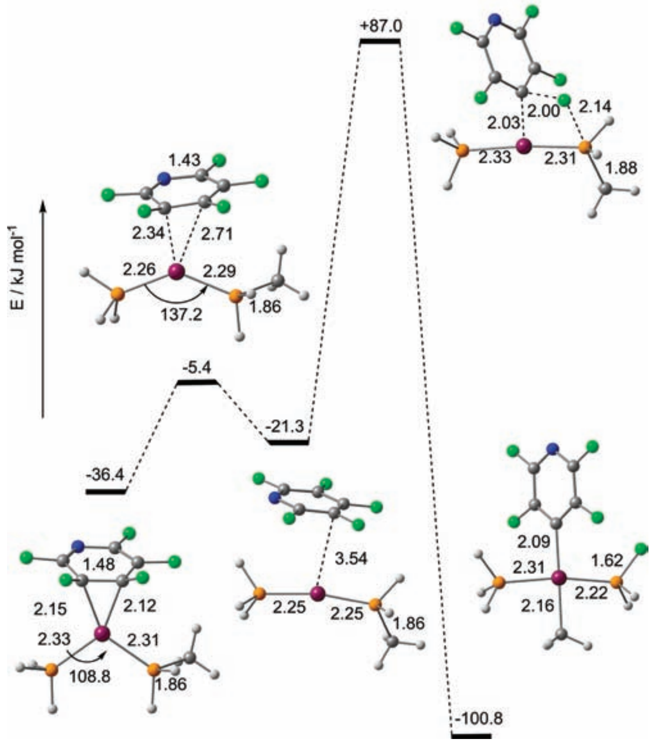
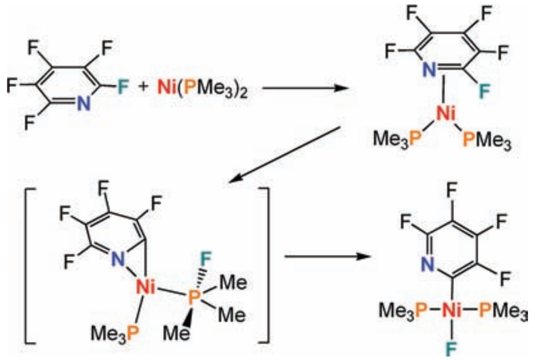


FIGURE 7. Calculated potential energy profile (E, kJ mol^{-1})[16] for phosphine-assisted C−F activation of pentafluoropyridine at $Pt(PH_3)(PH_2Me)$ acting as model for $Pt(PCy_3)_2$.

resulting TS may be described as a metallophosphorane; the R group migrates to the metal after the TS.[16] Once more, Pt(5d)−F(2p) repulsions force the fluorine away from the metal to the phosphorus, which acts as the F-acceptor. This mechanism (Figure 7) is reminiscent of that for the reaction of C_6F_6 with $IrMe(PEt_3)_3$.[49,50]

One of the most challenging mechanistic problems proved to be the selectivity for C−F oxidative addition at the 2-position of pentafluoropyridine with $Ni(PEt_3)_2$. After rejection of several ideas that did not stand up to scrutiny by DFT calculations, it was phosphine-assisted C−F activation that gave us the clue. A metallophosphorane transition state similar to that in Scheme 16b could evolve by transferring either alkyl or fluorine from phosphorus to the metal. A full analysis showed that pentafluoropyridine reacts via a metallophosphorane TS to form a Ni(η^2-C,N-tetrafluoropyridine) intermediate (Scheme 17).[40] The nitrogen and carbon are coordinated in a geometry reminiscent of a κ^2-pyridyne that imposes the selectivity. Transfer of fluorine to nickel completes the reaction with selectivity for the 2-position. This mechanism proves competitive with conventional C−F oxidative addition at the 4-position. The differences between nickel and platinum (compare Scheme 16b) arise from the greater role of N-coordination for nickel and the

SCHEME 17. Reaction Mechanism[40] for Phosphine-Assisted C−F Activation of Pentafluoropyridine at $Ni(PR_3)_2$



decomposition of this intermediate through alkyl transfer (Pt) or fluoride transfer (Ni) to the metal.[40]

A summary of the mechanistic choices is shown in Figure 8.

7. Energetic Impact of Fluorine Substituents on Catalysis: Direct Arylation

Because we had shown that M−C bond energies grow markedly with ortho-fluorine substitution, we postulated that steps in catalytic reactions involving C−H cleavage and M−C bond formation should be facilitated by ortho-fluorines.[42] In contrast, steps involving M−C cleavage and C−C bond formation should be raised in energy. The overall impact should depend on the identity of the rate-determining step and on whether the kinetics follow the energetics (Hammett Principle). We tested this hypothesis on Fagnou's C−H arylation reactions at palladium that couple an arene to a haloarene and work well for fluorine-substituted aromatics.[9] Fagnou has developed a mechanism termed concerted metallation−deprotonation (CMD) that involves assistance by coordinated base in the C−H cleavage step. The C−C bond forming step is a conventional reductive elimination (Figure 9). The CMD nomenclature is equivalent to ambiphilic metal ligand activation (AMLA), introduced to account for intramolecular base-assisted C−H activation.[51]

We analyzed the cycle computationally via a set of model reactions (Scheme 18). The CMD transition state illustrates the role of the intramolecular base (Figure 10 upper). We find that the CMD step is indeed strongly affected by fluorine substitution such that the energies of the TS for the formation of the bis(aryl)palladium intermediate **3** follow the pattern 2Fo < 1Fo < 0Fo with barriers ranging from 61 to 107 kJ mol^{-1} (Figure 10 lower, 2Fo indicates two ortho fluorine substituents). Similar differences are found in the

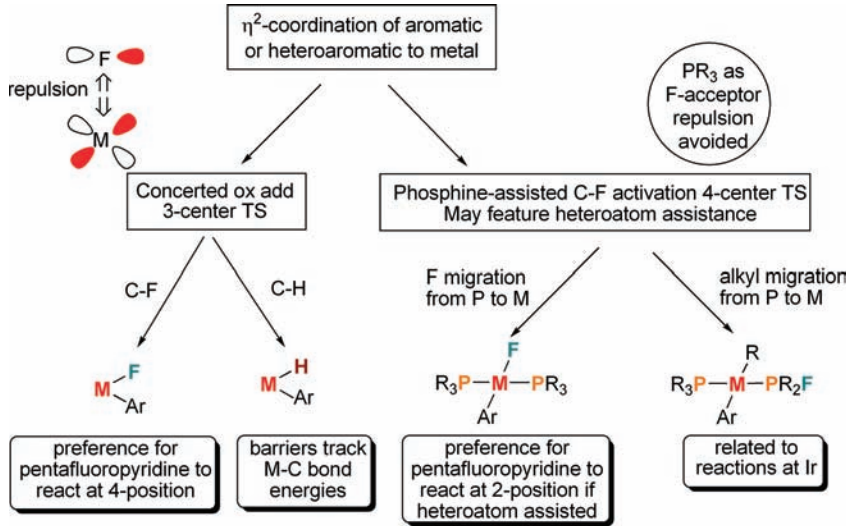


FIGURE 8. Principal mechanistic choices in activation of fluoroaromatics.

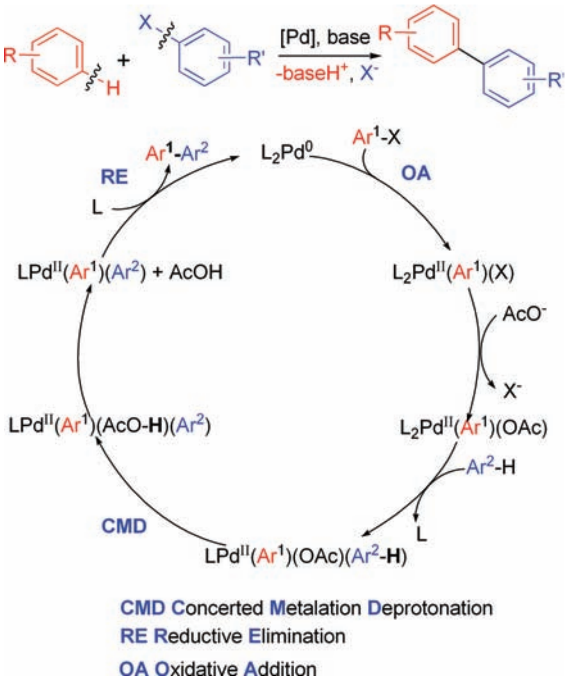
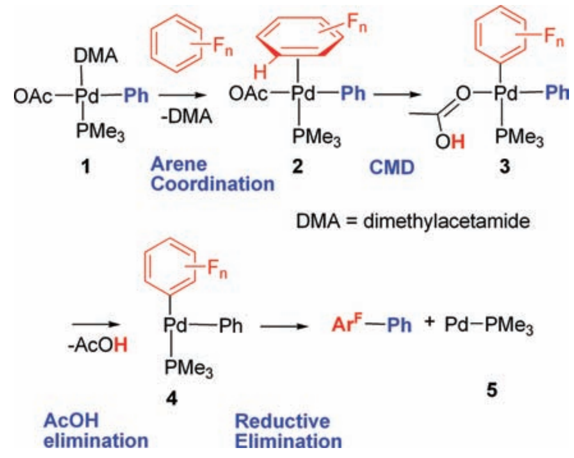


FIGURE 9. Top, general reaction for direct arylation (X = Br, I); bottom, catalytic cycle Base = OAc⁻. Copyright 2010 Royal Society of Chemistry, ref 52.

SCHEME 18. Model Reaction Sequence for Direct Arylation [a]



[a] Copyright 2010 Royal Society of Chemistry, ref 52.

energy of the intermediate **3**.[52] In contrast, the barrier to reductive elimination from intermediate **3** is raised by ortho fluorines bringing the energies of the transition states for different arenes back together. Our study shows that Pd–C bond energies show the typical increase on ortho-fluorine substitution. According to conventional wisdom, such reactions are facilitated by fluorine substituents because fluoroaromatics are more acidic. Our findings indicate a role both for increased C–H acidity and for increased Pd–C bond energies in the CMD step, while the changes in the C–C bond-forming step are dependent mainly on the Pd–C bond energies. The observed regioselectivity is associated with the lower barrier for CMD with ortho-fluorine substituents.

The balance between the CMD and RE steps is harder to determine computationally, because of the difficulty in evaluating entropy changes in solution. There is a significant entropy gain on release of acetic acid from **3**, which will result in the stabilization of **4**, **5**, and **TS4–5**. Although the nature of the rate-determining step cannot be determined securely by computation, calculations show that the CMD step is more sensitive to fluorine substitution than the reductive elimination step.[52]

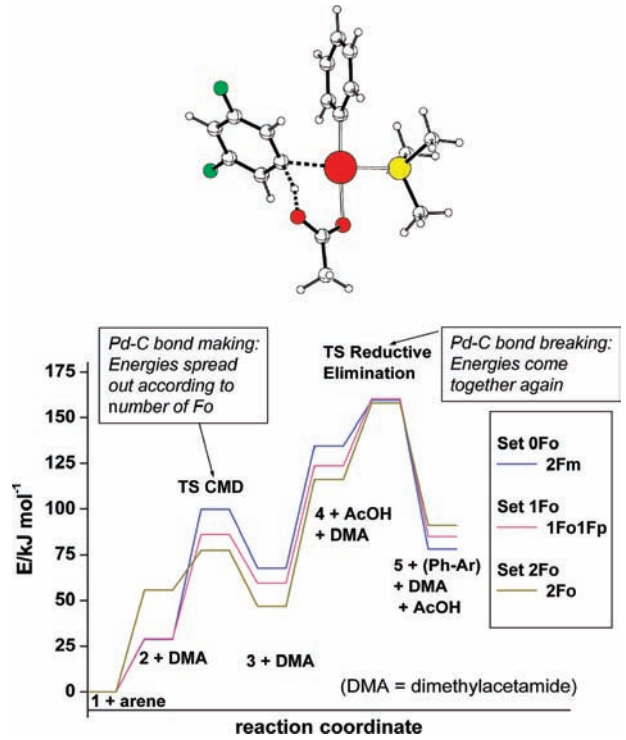


FIGURE 10. Top, transition state (TS) for CMD with 1,3-difluorobenzene, **2Fm**; bottom, calculated potential energy profiles for direct arylation following the pathway in Scheme 18 for three isomeric products with 1,3-$C_6H_4F_2$. Key indicates position of substituents in product.

8. Outlook

We have summarized the principal features of the molecular structures, energetics, and mechanisms in Scheme 12, Scheme 14, and Figure 8, respectively. In this final section, we consider very briefly some of the recent developments in the field and the outlook for applications.

C−F Activation Mechanisms. In section 6, we showed that C−F oxidative addition reactions can proceed via a phosphine-assisted mechanism as well as the typical concerted mechanism. This principle has already been extended to assistance by boron ligands[53] and may well be valid for other fluorine-accepting ligands. Such mechanisms have implications for the selection of different ancillary ligands and for regioselectivity. It has been applied to the regioselective synthesis of 2-boryl tetrafluoropyridine.

Balance between C−F and C−H Oxidative Addition. The C−F activation approach to catalysis concentrates on selective removal of fluorine and introduction of other substituents. Because polyfluorinated aromatics are readily available, it can be very attractive, but it is still hard to achieve in high yield.[11] The C−H activation approach can exploit the lower barriers that are observed with fluorine substituents (Scheme 9 and section 7). Comparison of Schemes 5 and 9 shows that catalytic C−H activation may occur in preference to C−F activation as a result of a change of ancillary ligands or substrates.[10] Recent work by Johnson has emphasized that C−H oxidative addition can occur at nickel with fluorinated benzenes and that the reactions are sensitive to precursors and ancillary ligands, but it is too early to make generalizations about ligand effects.[13,22,54] Moreover, catalytic C−H activation to form $Ar^F{-}SnBu_3$ with (vinyl)$SnBu_3$ has been discovered[55] in addition to the alkyne insertion illustrated in Scheme 9.[10] The principle of increased M−C bond strength with ortho fluorine substituents is now established as a general phenomenon. The stannylation reaction[55] illustrates its exploitation in a catalytic process where the rate-determining step probably involves M−C bond making (see section 7). Control of the balance between C−F and C−H oxidative addition is of decisive importance in catalytic applications.

How To Make C−F Reductive Elimination Go Downhill. We showed that C−F reductive elimination is energetically unfavorable for square planar nickel and platinum complexes, and this principle may extend to palladium analogues. Two approaches have demonstrated how to overcome this problem. Both Sanford and Ritter have shown that C−F reductive elimination is possible for Pd(IV) complexes,[56] while Buchwald has introduced fluorine into aromatics with the aid of a phosphine that restricts the Pd(II) catalyst to 3-coordination or lower.[57] Thus it is now possible to remove or to introduce fluorine catalytically.

Implications of Secondary Bonding. In section 4, we showed that metal fluorides are capable of forming secondary hydrogen and halogen bonds. Their effect in the overall energetics and selectivity of reactions may be significant. It is important to stress the need to look out for secondary interactions in crystal structures and to use low-temperature NMR spectroscopy to characterize metal fluoride complexes. It may also be possible to exploit these features in framework materials that depend on the use of secondary interactions. The formation of hydrogen bonds to a MgF_3^- moiety in an enzyme active site illustrates the potential for such interactions in complex structures.[58]

We would like to thank all our colleagues who have contributed to the work described here. We also acknowledge our funding bodies, especially EPSRC and CNRS.

BIOGRAPHICAL INFORMATION

Eric Clot has worked in the University of Montpellier since 1996. In 2007, he was promoted to Director of Research at the CNRS (French National Scientific Research Center). His main research interests lie in computational studies of transition-metal catalyzed reactions.

Odile Eisenstein is Director of Research at the CNRS. She uses computational methods to understand the structure and reactivity of metal d and f block systems. She received the Organometallic Chemistry Award of the ACS in 2009.

Naseralla Jasim has worked in the University of York since 1996 and investigated synthesis and reactivity of transition metal fluoride and bifluoride complexes and also C—F activation of aromatic molecules.

Stuart Macgregor holds a personal chair at Heriot-Watt University, Edinburgh. He uses computational chemistry to model the structure and reactivity of transition metal systems.

John McGrady is Professor of Computational Inorganic Chemistry at the University of Oxford. His interests focus on the electronic structure of inorganic systems. His collaboration with Robin Perutz began as a Lecturer at the University of York.

Robin Perutz has worked at the University of York since 1983 and has investigated transition-metal-mediated activation of fluoroaromatics since 1989. He was awarded the Franco-British prize of the French Chemical Society in 2009 and was elected to a Fellowship of the Royal Society in 2010.

FOOTNOTES

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