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Conversion of Carbon–Fluorine Bonds α to Transition Metal Centers to Carbon–Hydrogen, Carbon–Carbon, and Carbon–Heteroatom Bonds

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Pseudo-tetrahedral primary fluoroalkyl complexes of iridium provide a template on which to study the stereoselectivity of carbon–fluorine bond activation α to iridium by external protic acids. Coupled with migration of internal nucleophiles, this reaction leads to diastereoselective formation of new carbon–oxygen, carbon–sulfur, carbon–hydrogen, and carbon–carbon bonds. Stereochemical studies of the conformational properties of starting fluoroalkyl complexes and relative stereocenter configurations for diastereomeric products, together with kinetic studies of reactions in different solvents, allow a self-consistent mechanism for these reactions to be established.

Fluorocarbons

The chemistry of organic compounds containing carbon–fluorine bonds is well-documented, and a number of relatively recent comprehensive treatments of organofluorine chemistry are available for those desiring a detailed view of the field.[1–4] Additionally, a very readable and informative historical overview has appeared,[5] as have general perspectives on the key features that make the carbon–fluorine bond so unique.[6–7] The general topic of activation of carbon–fluorine bonds by transition metal complexes has also been the subject of extensive reviews.[8–11] A brief overview of this author's perception of the significance and utility of compounds containing carbon–fluorine bonds, as well as their selective activation at metal centers, is presented here.

Mankind benefits from organic fluorocarbon derivatives in chemistry, medicine, and technology. An estimated 30–40% of agrochemicals and 20% of pharmaceuticals, including half of the top ten pharmaceutical drugs sold, contain carbon–fluorine bonds.[12–13] Fluoropolymers play important roles in technology, including automotive hoses and gaskets, biomedical applications, reconstructive surgery, and fuel cell membranes.[14–19] Fluorine forms the strongest single bond to carbon,[20–21] and the polarity and inertness of the C–F bond is crucial to the chemical and materials performance of fluorocarbons.[1–4,6–7] The importance of strategically placed C–F and C–CF_3 bonds in pharmaceutical, medicinal, and bioorganic chemistry,[13,22–26] has led to development of new methodology for their selective generation.[27–30] But the darker aspects of fluorocarbons result from the very resistance to chemical change that gives them their utility. Environmentally persistent fluorocarbons, many of which impact long-term global environment quality, are of considerable concern. Chlorofluorocarbons (CFCs), engineered to be inert aerosols, refrigerants, cleaning solvents, and foaming agents, are among the chief culprits in disrupting the ozone balance; they are now banned

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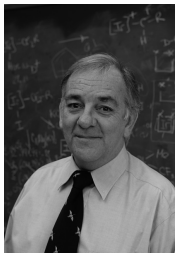


Born in Denbigh, Wales, Russ Hughes received his undergraduate education at the University of Manchester Institute of Science and Technology in England, and his Ph.D. at the University of Toronto, Canada, under the guidance of John Powell. After postdoctoral fellowships at the University of Bristol, England (with Michael Green) and McGill University, Montréal, Canada (with John Harrod), he joined the Chemistry Department at Dartmouth College, where he is now Frank R. Mori Professor of Chemistry. In 1990 he was awarded the degree of Doctor of Science by the University of Manchester (England). He has been a Fellow of the Alfred P. Sloan and the Alexander von Humboldt Foundations, a member of the Editorial Advisory Board of Organometallics and the Journal of Fluorine Chemistry. He is also a member of the Inorganic, Organic, and Fluorine Divisions of the American Chemical Society, and has served as Chairman of the Organometallic Subdivision of the American Chemical Society, on the Executive Committee of the Fluorine Division of the American Chemical Society, and as Chairman of the Organometallic Gordon Research Conference. In addition he is a Fellow of the Royal Society of Chemistry (UK) and a Chartered Chemist (UK). His academic interests include teaching courses in inorganic, freshman, organic, and organometallic chemistry, for which he is proud to have received the Dartmouth College Student Assembly's "Profiles in Excellence" Teaching Award. Research activities have focused on the synthesis and reactivity of fluorinated analogues of hydrocarbon organometallics, and transition-metal-promoted fluorocarbon chemistry, and he is co-author of approximately 175 research publications in organometallic chemistry. He will be the 2010 recipient of the American Chemical Society Award for Creative Work in Fluorine Chemistry.

under the Montréal Protocol.[31–33] However, they are still an item of illegal commerce in the USA; the cost of retrofitting automobile air conditioners to use replacement HFCs, the cost of HFCs themselves, and the cost of safe collection and disposal of residual CFCs, makes smuggling CFCs an economically viable activity.[34–35]

Replacements for CFCs are environmentally benign, although often more expensive, hydrofluorocarbons (HFCs), with zero ozone depleting potential,[36] some of which are nontoxic enough to be used as inhalation anesthetics.[37] Commercial routes to HFCs use chlorinated precursors, utilizing chemistry involving conversion of C–Cl to C–F bonds using HF, with HCl as a commercially useful chlorine-containing byproduct. Lewis acid catalysts are required, many of which are transition metal compounds or which have added transition metal co-catalysts.[36] The unique solvent properties of perfluorocarbons (PFCs), recognized long ago,[38–40] led to their use in synthesis, separations, and combinatorial chemistry.[41] PFCs are inert under ambient conditions, have high global warming potential, and atmospheric lifetimes of thousands of years, with adverse environmental impact if not recycled carefully.[31–33,36] Some fluorocarbon derivatives are detectable world-wide in the bloodstreams of humans, polar bears, dolphins, and pandas.[42] They have no known environmental or metabolic degradation pathways.

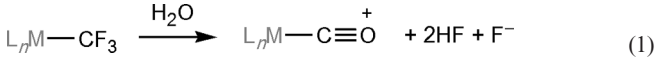
With both positive and negative properties in mind, our group and others[43–58] have approached the selective activation of C–F bonds using transition metal complexes. A different positive role for compounds containing C–F bonds has now evolved in bioorganic chemistry,[24–26] leading to significant recent interest in generating new methodology for synthesis of carbon stereocenters bearing a fluorine or fluoroalkyl group.[28–30,59–92] Targets of this research are anticipated either to have significant biological activity or to be useful as probes or mimics of their bioactive hydrocarbon analogues.[28,30,62,66] Synthetic approaches to fluorinated stereocenters involve addition of nucleophilic fluoride to a carbocation equivalent or electrophilic fluorination of a carbanion; that is, *making* a C–F bond. This is clearly a thermodynamically adventitious approach given that such reactions form the strongest known single bond to carbon.[21] While a complementary approach that results in net substitution of a C–F bond to form a new C–H or C–C bond would be very useful, the thermodynamics, and in some cases the kinetics, of breaking the C–F bond provide considerable impediment to its realization. Such chemistry would be doubly useful: providing a chemically useful transformation for functionalization of fluorocarbons and halofluorocarbons; and, *provided it can be accomplished with some control of selectivity*, complementing existing methodology for the preparation of fluorinated stereocenters.

Since bond dissociation energies (BDEs) of C–F bonds are higher than those of corresponding C–H bonds,[20] their replacement by C–H bonds requires thermodynamic compensation by formation of an even stronger bond to F in another reaction product; e.g. B–F, Si–F, or H–F bonds,[21,93] bonds between early transition metals or actinides and fluorine,[94] or ionic metal fluorides.[8,95–96] Aromatics can be readily activated by oxidative addition of the C–F bond via an η^2-arene intermediate[8,47,49–52,97–111] or by addition/elimination using metal nucleophiles.[8,51,112–113] Likewise, some fluorinated alkenes have yielded to C–F bond activation.[43,48,58] In contrast to aromatic or other unsaturated fluorocarbons containing π electrons, saturated PFCs have no strong binding site for interaction with a metal center. Radical pathways for the activation of these bonds by Zr and Hf hydrides have been successful,[114–115] as well as the recently reported conversion of aliphatic C–F bonds to C–H bonds using the R_3Si^+ cation as a catalyst and R_3SiH as the source of hydrogen atoms.[116–117] While the C–F bond is truly the strongest single bond to carbon, in part due to the polarity of the bond to electronegative fluorine, therein lies its Achilles' heel, as the electronegativity of fluorine also ensures that the C–F σ* antibonding orbitals are relatively low lying.[6–7,21] This feature allows for the reduction of fluorocarbons using strong reductants, and the exhaustive reduction of halofluorocarbons to carbon, the reductive equivalent of the oxidation of hydrocarbons to CO_2 and H_2O, has been studied as a way to dispose of environmentally harmful fluorocarbons.[95–96,118–119] Aliphatic C–F bond activation almost invariably involves strongly reducing conditions using metal complexes,[120–124] ammonia, alkali metals, or other metal salts,[95,125] with formation of strong bonds between early transition metals or actinide metals and fluorine,[94] or high-lattice-energy metal fluorides providing thermodynamic compensation for breaking the strong C–F bonds.[8,95–96] Tertiary C–F bonds are usually required, with their low-lying tertiary C–F σ* orbital thought to provide the initial Achilles' heel for reduction, although secondary C–F bonds can apparently also be reduced.[121] In some cases, especially when an aromatic organic compound can be formed, reduction stops at the aromatic fluorocarbon, providing a potentially useful method of producing a high-value organic molecule from a saturated precursor.[96] For example, in this manner perfluorodecalin is reduced to give perfluoronaphthalene.[121] The tertiary C–F bond apparently provides the initial site of reductive activation, but subsequent reduction at the resultant alkene function generates a reductive cascade on to the observed product. In contrast, the selective reductive activation of saturated fluorocarbons is rather rare;[126] in one case reduction was stopped at the fluoroalkene stage by chemical interception to give a stable enolate.[127]

Activation of Carbon–Fluorine Bonds α to Transition Metal Centers

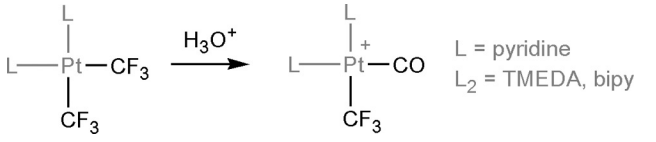
Stable transition metal organometallic compounds containing fluoroalkyl ligands have been known since the halcyon days of organotransition metal chemistry,[128–132] and an early report indicated that their C–F bonds were reactive towards acids (and bases).[133] Not surprisingly, the first

complexes of transition metals with tetrafluoroethylene ligands were prepared by chemists at DuPont,[134–135] and it was quickly realized that the structure of the M(η^2-C_2F_4) fragment resembled that of a saturated metallacyclopropane, with extensive rehybridization of the C–F bonds to acquire more p character.[135–136] Tucked away in one of these early reports, with no experimental details given, was the observation that the coordinated C_2F_4 ligand in Rh(acac)(C_2H_4)(C_2F_4) reacted upon dissolution in acetic acid with hydrolysis of the C–F bonds to give CO; this reaction appeared to be catalytic and several mol of C_2F_4 could be converted to CO.[135] The synthesis of early examples of M–CF_3 complexes also resulted in observations that the CF_3 group could be hydrolyzed to give CO, with formation of HF providing the thermodynamic driving force for breaking the strong C–F bond, as shown in Equation (1). Addition of external protic or Lewis acids accelerated this chemistry.



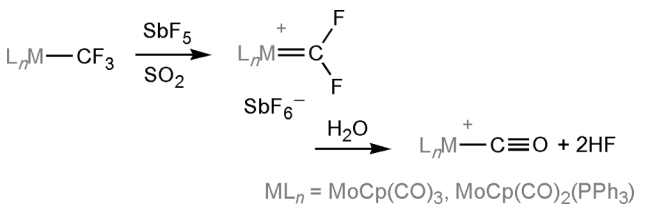
(1)

A curious example involving bis(CF_3) complexes is shown in Equation (2), in which only one CF_3 group reacts to give CO;[137] apparently formation of a cationic complex by hydrolysis of one CF_3 ligand results in deactivation of the second CF_3 group.



(2)

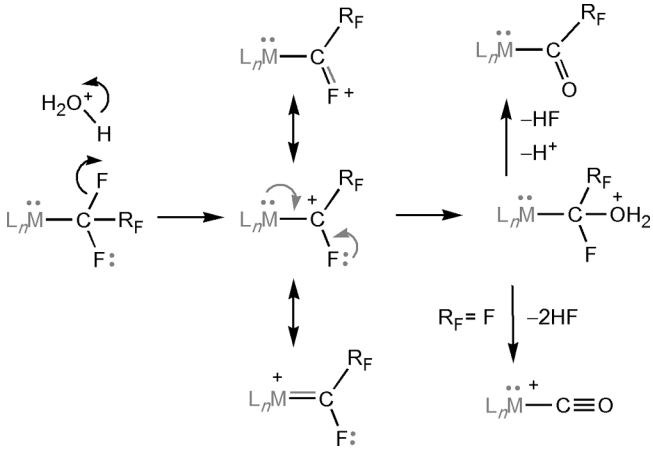
Abstraction of fluoride from M–CF_3 groups to give cationic [M=CF_2]$^+$ compounds was also discovered, along with the realization that these cations were extremely sensitive to attack by water to give HF and a cationic CO complex [Equation (3)].[138] In the examples shown in Equation (3), the cationic CF_2 complexes could only be observed in solution by NMR spectroscopy, but similar reactions afforded isolable analogues, [MoCp*$(CO)_3(CF_2)]^+CF_3SO_3^-$[139] and [FeCp(CO)$(PPh_3)(CF_2)]^+BF_4^-$,[140] which were crystallographically characterized, but which were also extremely reactive towards reaction with water to give cationic CO complexes. BF_3[138–145] and protic acids[137,146–148] have been shown to act as fluoride acceptors, leading to similar hydrolysis reactions.



(3)

Subsequently, reactions of M–CF_3 compounds with Lewis acids such as BX_3 (X = Cl, Br, H) led to conversion to M–CX_3 compounds; analogous reaction of longer chain M–CF_2R_F compounds illustrated that this reactivity was limited to the α-fluorine atoms only.[141–143] More recently, reversible migrations of fluorine in a M–CF_3 group to the metal center have been reported.[149–151]

A reasonable mechanism for these reactions is shown in Scheme 1, in which a protic acid (or Lewis acid) abstracts fluoride ion to give a carbocation intermediate, in which resonance stabilization is afforded by π donation from F and from M. Nucleophilic attack by water, followed by elimination of HF, affords the cationic CO complex, or if only one F is directly attached, a metal acyl product, as shown. An analogous process involving the metallacyclopropane formed by C_2F_4 coordination to Rh[135] can be put forth to explain the formation of CO (vide supra). Likewise, when BX_3 is the fluoride acceptor, X^- acts as the nucleophile to generate C–X bonds.[141–143]



Scheme 1. Hydrolysis of C–F bonds α to a transition metal.

This mechanism proposes a role for the transition metal in stabilizing the *product* formed by initial loss of an α-fluoride. Alternatively α-CF bonds could be weakened in the *ground state* of the fluoroalkyl complex by interactions of low-lying C–F σ* orbitals with metal d electrons (equivalent to heteroatom lone pairs) or in a reaction transition state with developing positive charge at the α-carbon. Descriptions of this effect often depend upon the carbocentric or metallocentric mindset of the authors; most organic chemists prefer to describe it as negative hyperconjugation,[152–153] while inorganic chemists categorize the same phenomenon as backbonding from metal d into C–F σ* orbitals.[154–158] A spectacular example of such a ground-state effect occurs in the structure of the CF_3O^- anion, in which backbonding, or negative hyperconjugation, from O lone pairs to C–F σ* orbitals results in a structure with a virtual C=O double bond and extremely long C–F bonds (Figure 1A).[159] There is no reason why a transition metal heteroatom should not have the same capabilities based on orbital symmetry requirements (Figure 1C), but clearly the energy match between M(*n*d) and C–F(σ*) will not be as

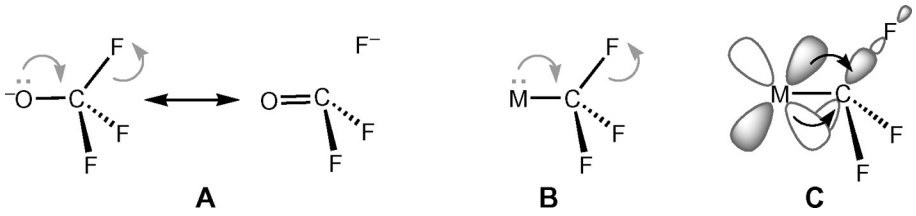


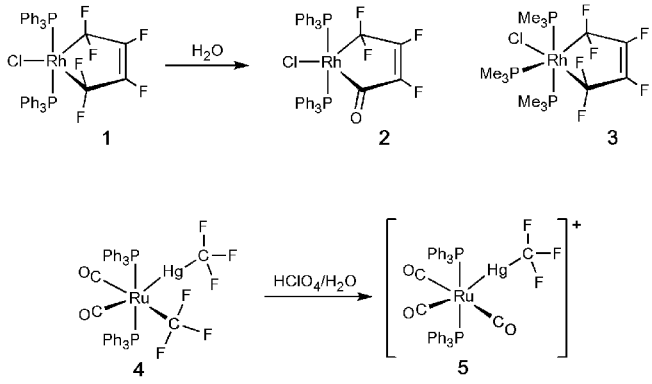
Figure 1. (A) two resonance structures for the CF_3O^- anion; the C=O structure is a dominant contributor to the resonance hybrid.[159] (B) An analogous depiction of a metal heteroatom. (C) M(d)→C–F(σ*) overlap; an MO depiction of the same phenomenon.

good as that with an oxygen atom lone pair. Nevertheless, the proposition that C–F bonds α to metals could be weakened by backbonding from filled M(d) orbitals to low-lying C–F(σ*) orbitals has been put forth,[154–155] and subsequently rejected,[156] at least as an explanation for lower C–F stretching frequencies in transition metal CF_3 compounds.

Conversion of Carbon–Fluorine Bonds to Carbon–Oxygen and Carbon–Sulfur Bonds

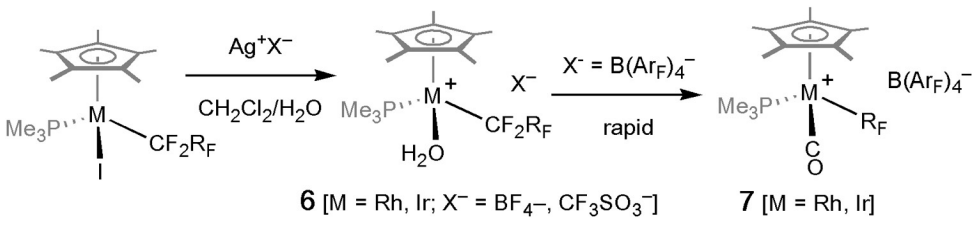
We chose to study fluoroalkyl metal systems as models for fluorocarbon activation. Building on early reports from pioneers in the field,[128,131,160–161] we have published accounts of synthetic routes to such compounds from readily available fluoroalkyl iodides, along with detailed structural characterization of the products.[142–152] Our current long-term objectives are to develop methodology for the catalytic conversion of C–F bonds to C–H and C–C bonds and to design and develop catalytic systems that will accomplish metathesis reactions of perfluorinated alkenes. Key to these goals is the ability to use transition metal centers as tunable templates upon which to construct fluorinated ligands by chemical transformations α to transition metals. This Microreview summarizes our efforts to understand the mechanism and scope of the stoichiometric chemical transformations of such C–F bonds by means of experimental synthetic and mechanistic work.

We were encouraged along this path by the initial observation that the five-coordinate metallacyclic complex **1** formed by reaction of $Rh(PPh_3)_3Cl$ with hexafluorobutadiene under anhydrous conditions underwent an exceptionally facile reaction with adventitious water on glass surfaces to give **2**, the structure of which had earlier been assigned incorrectly.[162] This observation was reminiscent of the reaction shown in Equation (2) in that only one CF_2 group was hydrolyzed. The analogous coordinatively saturated compound **3** was unreactive to water, suggesting that coordination of water to **1** was responsible for enhanced reactivity. Moreover, the X-ray structure of metallacycle **3** afforded the opportunity to obtain intramolecular C–F bond length information for a CF_2 group *trans* to π-donor Cl and π-acceptor PMe_3. We expected that backbonding from Rh d orbitals to the C–F α* orbitals would differ significantly *trans* to ligands of quite different π properties and were surprised to find that the α C–F bond lengths were identical within experimental error, as were the F–C–F angles, although the Rh–C bond *trans* to P was significantly longer than that *trans* to Cl, as expected from the *trans* influences of the ligands. So there appears to be no ground-state difference in the C–F bond lengths or angles, at least as manifested by crystallographic distances. Crystallographic parameters have previously been interpreted in terms of weaker C–F bonds α to transition metals; a noteworthy example is compound **4**. The CF bonds α to Ru [1.38(1) Å] are reported to be longer than those α to Hg [1.29(1) Å], an observation interpreted as involving a relative weakening of the C–F bonds α to Ru and consistent with the fact that only the Ru–CF_3 group underwent hydrolysis under acidic conditions, leaving the Hg–CF_3 group untouched.[146] However, DFT calculations on **4** indicate that the C–F bond lengths are not significantly different α to Ru [1.38Å] or Hg [1.37Å],[163] and it may be worthwhile to redetermine these bond lengths crystallographically.



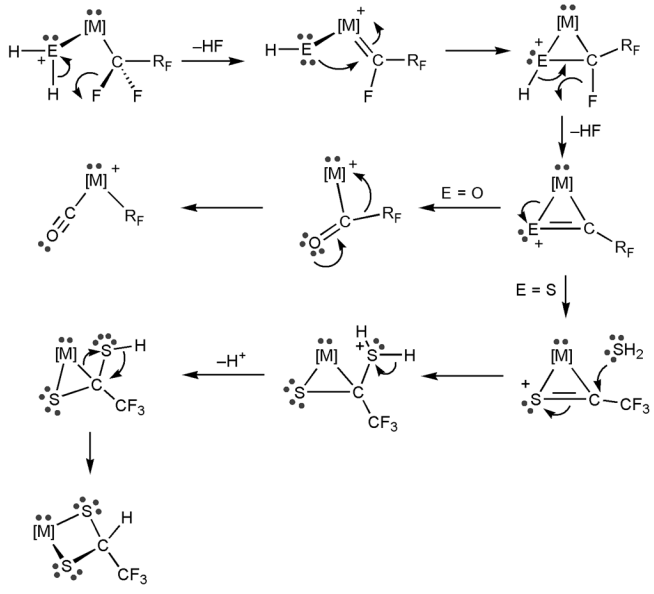
The idea that coordination of water adjacent to a fluoroalkyl ligand could result in activation of α-C–F bonds towards hydrolysis led us to attempt the rational synthesis of compounds containing this structural motif. Several rhodium(III) and iridium(III) compounds of general structure **6** were prepared as shown in Equation (4).[164–165] These compounds could be isolated, and in many cases crystallographically characterized, provided that the counterion [X^- = BF_4^- or $CF_3SO_3^-$] was capable of hydrogen-bonding to the coordinated water molecule.[165] However, when the counterion was replaced by $B[Ar_F]_4^-$, which is not an H-bonding anion, immediate hydrolysis of the α-CF_2 group was observed for primary fluoroalkyl ligands, with formation of the cationic carbonyl derivatives **7**.[164]

The mechanism shown in Scheme 2 was proposed to explain these observations:[164] when the bound water is not H-bonded to the anion it becomes acidic enough to pro-



(4)

tonate an α-C–F bond, eliminating HF, the metal lone pair (of d electrons) participating in stabilizing the resultant carbocation; intramolecular nucleophilic attack by O on the stabilized carbocation makes the O–C bond and allows elimination of a second molecule of HF to give a metal acyl; rearrangement of the acyl with migration of R_F into the vacant coordination site affords the observed product. Notably, secondary perfluoroalkyl ligands were unreactive,[164–165] while attempts to make CF_3 analogues of **6** resulted in almost instant transformation to CO and HF, illustrating a significant reactivity difference between CF_3, primary, and secondary fluoroalkyl ligands.

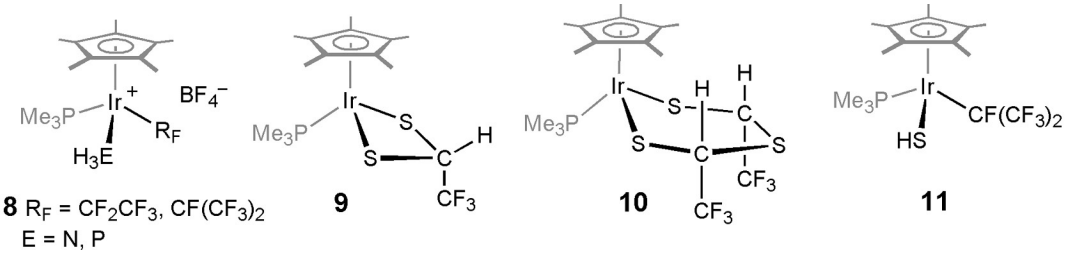


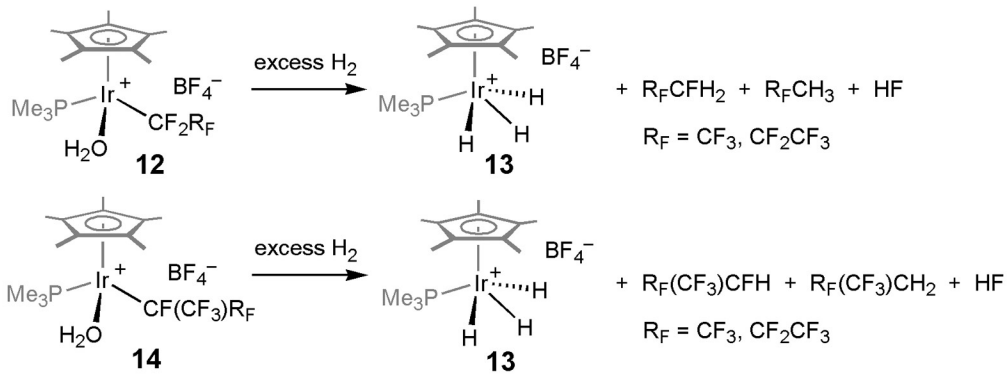
Scheme 2. Intramolecular conversion of C–F bonds to C–O and C–S bonds. [M] = Rh/Ir(η^5-C_5Me_5)(PMe_3), E = O; [M] = Ir(η^5-C_5Me_5)(PMe_3), E = S.

Having established that coordination of a small molecule like water could make it sufficiently acidic to protonate an adjacent α-C–F bond led us to contemplate whether other otherwise weak protic acids might behave in a similar fashion. To this end, the NH_3 and PH_3 complexes **8** were prepared, but proved unreactive in any C–F activation reactions. However, attempts to isolate an analogous H_2S complex did lead to C–F activation, coupled with formation of carbon–sulfur bonds, to give **9** and **10**.[166] Formation of **9** is rationalized in Scheme 2 by a pathway that follows that proposed for the water reaction; divergence occurs by nucleophilic attack of more H_2S on the cationic thioacyl intermediate. Formation of trithiacyclohexane product **10** is more difficult to explain and clearly requires participation of two iridium centers to produce the observed compound containing two CF_3 groups. Once again a complex containing a secondary perfluoroisopropyl ligand did not afford any C–F bond activation under these conditions, yielding instead sulfhydryl complex **11**.[166]

Conversion of Carbon–Fluorine Bonds to Carbon–Hydrogen and Carbon–Carbon Bonds

Given the lack of reactivity of NH_3 and PH_3 ligands, we were astonished to find that exposure of cationic complexes **12** to H_2 gas in solution, or even in the solid state, produced the known trihydride **13**[167] and liberated a mixture of hydrofluorocarbons R_FCFH_2 and R_FCH_3, as shown in Scheme 3. No R_FCF_2H was produced, and spiking the reaction with this HFC resulted in no consumption, indicating that it was not formed initially and then back reacted to give the observed organic products.[168] Careful monitoring of the reaction system by NMR spectroscopy allowed observation of HF in the product mixture, illustrating that elimination of the HFC from the metal center was preceded

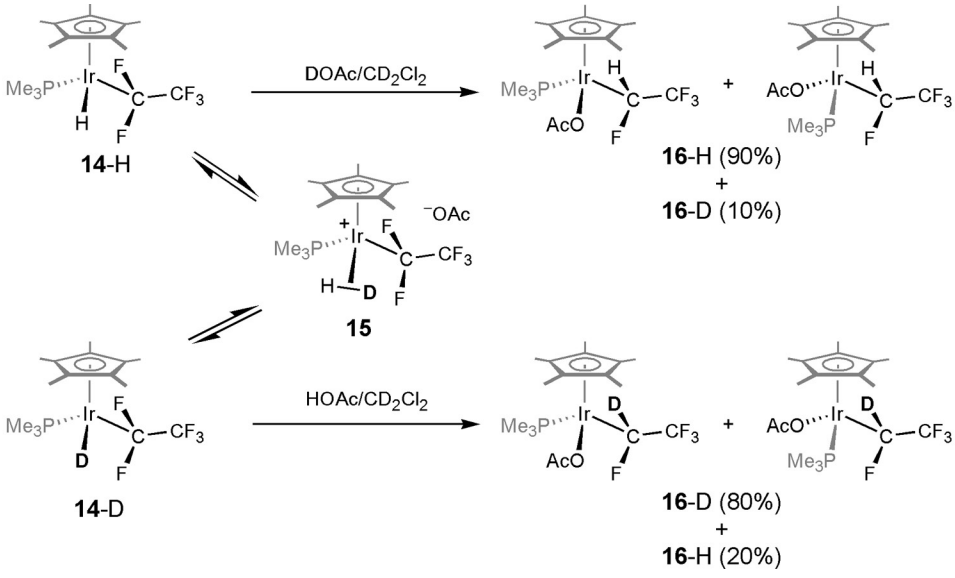




by hydrogenolysis of one or both α-CF bonds. Secondary perfluoroalkyl complexes **14** were much slower to react and showed some metal dependence; Rh[CF(CF_3)(R_F)] (R_F = CF_3, C_2F_5) gave mostly CHF(CF_3)(R_F) with traces of CH_2(CF_3)(R_F), while Ir[CF(CF_3)(R_F)] afforded mostly CH_2(CF_3)(R_F) with traces of CHF(CF_3)(R_F).[169]

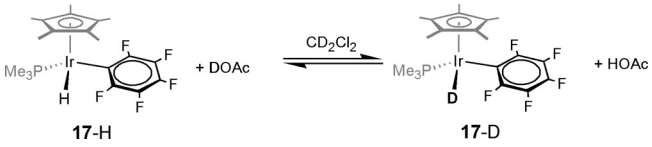
Displacement of water ligands by H_2 was well-established for other d^6 metal complexes,[170] and it seemed probable that a metal–dihydrogen complex was involved in this chemistry. We were fortunate enough to have serendipitously discovered a simple route to fluoroalkyl(H/D) complexes **14**-H(D);[171] clearly reaction of **14**-H with D^+ or reaction of **14**-D with H^+ should afford the identical H/D complex **15**. However, while no such intermediate could be observed directly, and C–F activation coupled with C–H bond formation was observed, unequivocal evidence for an H/D complex was obtained.

Specifically, treatment of the isotopically pure hydride complex **14**-H[171] with CH_3CO_2D in CD_2Cl_2 afforded a 90% yield of a 2:1 mixture of the two diastereomers of **16**-H contaminated with 10% of the same diastereomeric mixture of **16**-D.[172] Treatment of isotopically pure **14**-D with CH_3CO_2H yielded 80% of a 2:1 mixture of diastereomers **16**-D contaminated with 20% of **16**-H. These observations are clearly inconsistent with protonation of the α-CF bond occurring directly from a common η^2-H/D intermediate **15** in which complete scrambling of H and D should be facile, and from which an identical ratio of **16**-H and **16**-D is expected. We concluded that there were two competing processes; a fast exogenous protonation (or deuteriation) at an α-fluorine with intramolecular H (or D) migration to give the principal product, with some competitive scrambling of H^+ and D^+ (and thereby **14**-H and **14**-D) via intermediate **15**. Observation that only a small amount of label scrambling occurred indicated that the dominant process was the former; this is not the case for HCl, as discussed below. For each product isotopologue, the diastereoselectivity was about 2:1, the (R_{Ir},R_C)($S_{Ir}$$S_C$) diastereomer predominating.[172] Thus, external H^+ (or D^+) appears to be responsible for protonation of the α-C–F bond, D (or H) originally present on the metal migrating to form the new C–D (or C–H) bond. The isotopic impurity present in each reaction is consistent with some equilibration, presumably via η^2-H/D intermediate **15**, but this is clearly significantly slower than the rate of protonation at F. The differential amount of isotopic impurity in each reaction is consistent with the



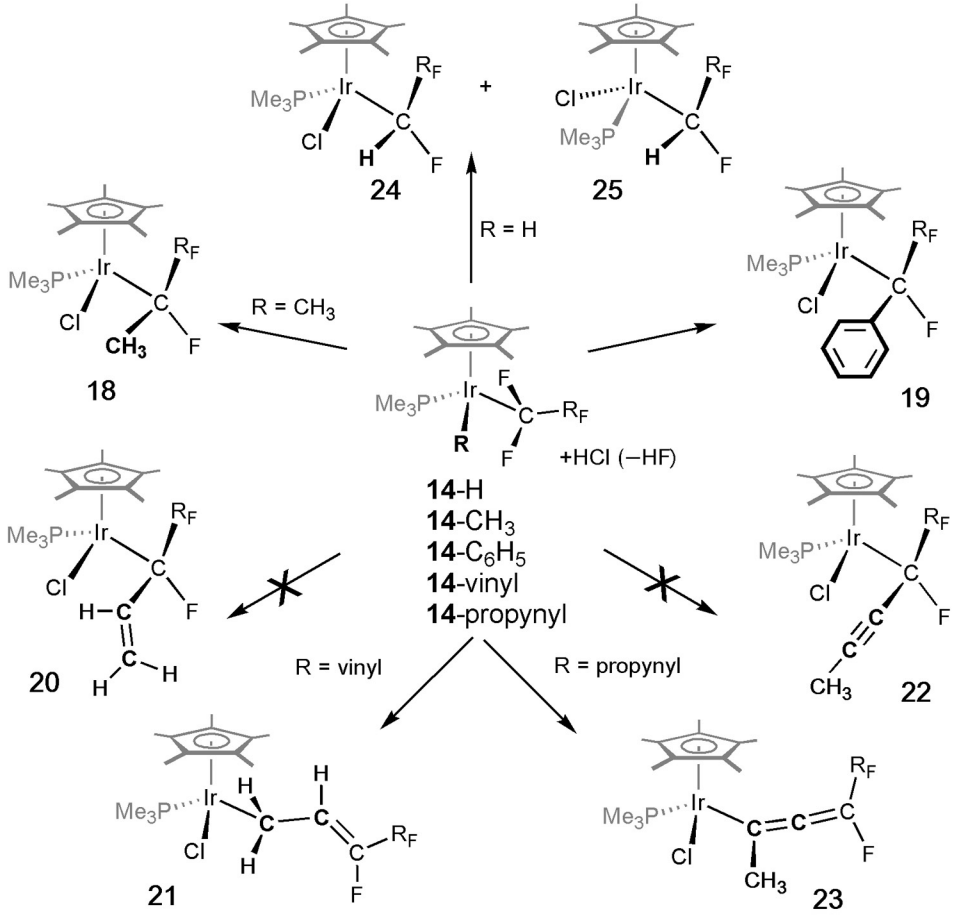
Scheme 3. Reactions of C–F bonds with HOAc and DOAc.

expected equilibrium isotope effect[173–174] favoring **14**-H (with an Ir–H bond) and CH_3CO_2D, over **14**-D (with an Ir–D bond) and CH_3CO_2H, consequently the rate of isotopic leakage from **14**-D to **14**-H should exceed the reverse rate, as observed. Second-order rate constants for the overall reaction measured at –30 °C were all approximately 1×10^{-3} L mol^{-1} sec^{-1}. In agreement with the observation that H/D scrambling via **15** is slower than protonation of the α-CF bond, the second-order rate constant for H/D exchange to equilibrate pentafluorophenyl complexes **17**-H and **17**-D[175] (in which no competitive CF bond activation occurs) is 6.5 ($\pm$0.2) $\times 10^{-5}$ at 25 °C, the expected equilibrium isotope effect reflected by K_{eq} = 2.6 ($\pm$0.2). We also noted that secondary perfluoroalkyl analogues were unreactive under these conditions.



With the observation that exogenous protonation of an α-CF bond could be coupled with formation of a C–H bond by migration to the α-C of a hydride ligand already present in the coordination sphere, an obvious extension was to see if other ligands would participate in this kind of migration to form new C–C bonds. Fortunately, we were able to generate synthetic routes to **14**-CH_3,[176–177] **14**-C_6H_5,[176,178] **14**-vinyl,[179] and **14**-propynyl[180] (Scheme 4). Reactions using acetic acid were fast enough to require rather inconvenient low-temperature kinetic monitoring, and 2,6-lutidinium hydrochloride (LutHCl) and its deuteriated analogue (LutDCl) were chosen as easily metered sources of HCl and DCl, respectively. These reagents gave slower reaction rates than that with acetic acid, allowing more extensive kinetic studies to be carried out.

We were delighted to observe the chemistry shown in Scheme 4, in which CH_3 and C_6H_5 groups would migrate to give only a *single diastereomer of the products* **18** and **19**, respectively. The relative configurations of the Ir and C stereocenters in each of these compounds were defined crystallographically[176] and by using $^{19}F\{^1H\}$ HOESY[181] as (R_{Ir},R_C)(S_{Ir},S_C), which, as will be demonstrated later, is the product of kinetic control of stereochemistry at Ir and at C. No free methane formation was observed, and use of 2,6-lutidinium deuteriochloride (LutDCl) gave no D incorporation into the $CF(CH_3)C_2F_5$ group. The reaction using **14**-CD_3 with LutHCl likewise afforded only the CD_3 migration product, with no scrambling of H/D. This is consistent with external protonation occurring exclusively at the



Scheme 4. C–F bond activation by external HCl with loss of HF, coupled with migration of H and various organic groups.

α-CF bond *to the complete exclusion of protonation at the Ir–CH_3 bond* to give the kind of η-methane intermediate found in many other systems.[182–188] Extension of these studies to migration of a vinyl ligand afforded additional complexity in that the expected migration product **20** was not formed; instead the rearranged compound **21** was observed.[179] Likewise alkynyl migration did not yield the expected propargyl compound **22** but gave the allenyl isomer **23** *as a single kinetically controlled diastereomer*.[180] However, H-migration was the odd man out, giving a mixture of diastereomeric products **24** and **25**. As it is important for later discussions, it should be noted that, once isolated form the reaction mixture, the ratio of diastereomers **24**/**25** did not change in CD_2Cl_2 solution. However, observation of lower diastereoselectivity led to a much more detailed study of the kinetics and mechanism of H-migration, which is clearly of some significance in explaining the outcome of the HFC-producing reactions discussed above using H_2.

In order to understand any reaction stereoselectivity, the preferred conformational stereochemistry of reactants and relative configurations of product stereocenters had to be established. The ground-state conformational stereochemistries of the reactants and the products of all these reactions were identified in solution using $^{19}F\{^1H\}$ HOESY and $^1H\{^1H\}$ NOESY experiments.[181] Newman projections of the various staggered conformations, viewed down the C–Ir bond, are depicted in Figure 2. The Newman projections are drawn with an acute angle (ca. 90°) between the R and PMe_3 ligands, and a much more obtuse angle (ca. 135°) between each of these ligands and the centroid of the Cp* ligand. These angular relationships are always found in the crystallographic structure of these molecules and make steric issues between the R, R_F and PMe_3 ligands more important than those between any of these ligands and Cp*, even though Cp* is the ligand of largest cone angle.[189] Consequently, a position between the R and PMe_3 ligands (conformer C) is the least energetically favorable for the CF_3 (or other R_F) substituent attached to the α-carbon, and this group almost invariably occupies the region of space between PMe_3 and Cp* (conformer A rather than conformer B), perhaps because of the longer Ir–P bond compared to the Ir–R bond. The single exception to this rule involves the hydride complexes, in which the R_F group sits between Cp* and H (conformer B), presumably as a result of the small steric demand of the hydride ligand. Notably, while a single conformer is populated in solution, other conformations are not prohibitively high in energy, and conformational exchange is rapid on the NMR timescale. As illustrated in Figure 3, we have established that there is a low rotation barrier about the Ir–C bond ($\Delta H^{\ddagger} \approx 33 \pm 2$ kJ mol^{-1}), which interconverts the environments of F^1 and F^2 in $[IrCp^*(CF_2R_F)(PMe_3)_2]^+$ cations and in $IrCp^*(CF_2R_F)(acac)$.[190] Likewise, HOESY studies on the H and CH_3 migration products allow the conformations and relative stereochemistries of the Ir and C stereocenters to be established for the major (R_{Ir},R_C)(S_{Ir},S_C) and minor (R_{Ir},S_C)(S_{Ir},R_C) diastereomers, as shown in Figure 2.[181,191] It is noteworthy that of all the solution HOESY measurements we have made on these and related compounds the fluorinated ligand conformation is invariably that observed in the solid state using X-ray crystallography.

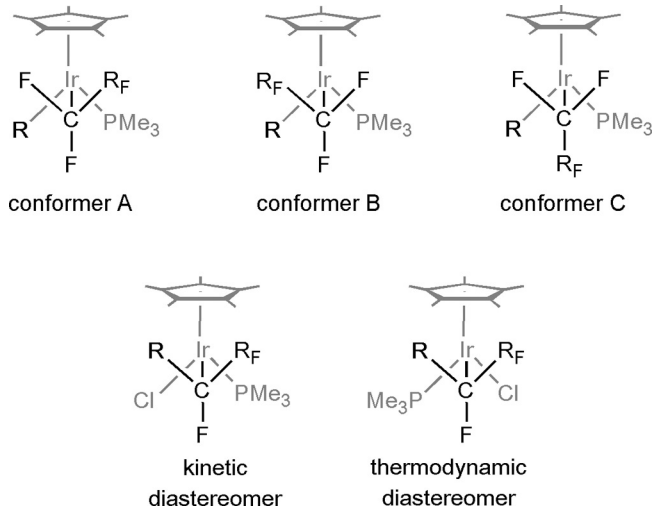


Figure 2. Staggered conformations (A, B, C) for the fluoroalkyl group in compounds **14** and relative diastereomer stereochemistries for migration products.

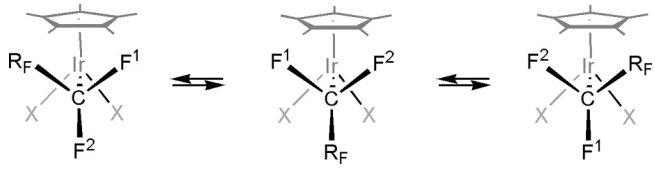
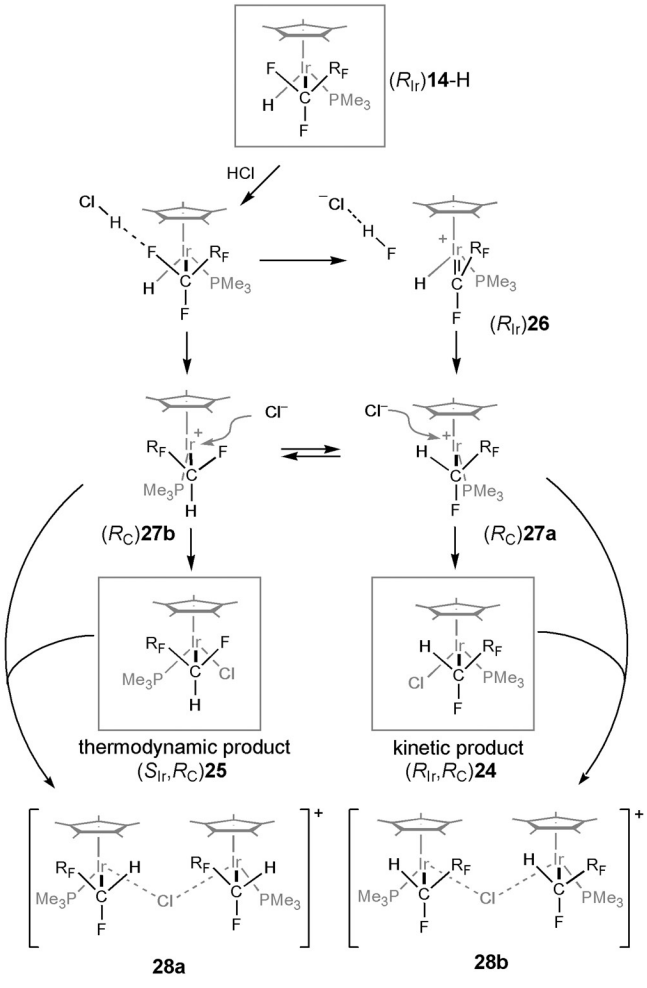


Figure 3. Facile conformer interchange for the primary fluoroalkyl ligands in cationic complexes [X = PMe_3] and neutral analogues [X = O (acac)].

The kinetic rate law was established in three different solvents (CD_2Cl_2, [D_7]DMF, CD_3NO_2) to be $-d[\mathbf{14}\text{-H}]/dt = k[\mathbf{14}\text{-H}][LutH(D)Cl]^{1/2}$. The half-order dependence on the concentration of lutidinium salt indicates that *the active source of the exogenous proton is H(D)Cl*, generated by dissociation of LutH(D)Cl.[191] Because only small concentrations of HCl are available at any given point, overall reactions are slower than those with one full equivalent of acetic acid; measured in CD_2Cl_2, the overall values of $\Delta G^{\ddagger}_{(298K)}$ are 84 ± 4 kJ mol^{-1} for the reaction of **14**-H and LutHCl and 64 ± 2 kJ mol^{-1} for reaction of **14**-H with acetic acid;[172] in each case this is a significantly higher barrier than that for any conformational change in the starting materials. The slower C–F activation reaction using LutH(D)Cl also results in complete H/D scrambling before C–F activation occurs, so that the mixture of isotopologues obtained is identical, unlike the observations made in the acetic acid reaction.

All of our results are consistent with the mechanism shown in Scheme 5, illustrated for a single enantiomer of starting material (R_{Ir})**14**-H; a mirror image sequence exists for (S_{Ir})**14**-H. Selective protonation of F as shown yields cationic intermediate (R_{Ir})**26**, in which the α-carbocation formed by loss of fluoride is shown as stabilized by π do-

nation from Ir, that is, as a cationic perfluoroalkylidene complex. The departed fluoride is shown as a putative $[FHCl]^-$ anion. Subsequent migration of H produces the (*R*)- stereocenter at C in cation (R_C)**27a**. Irreversible trapping of (R_C)**27a** at the now cationic iridium center by chloride as shown gives the observed kinetic product diastereomer (R_{Ir},R_C)**24**. In competition with trapping by chloride, inversion at iridium may occur, with (R_C)**27a** equilibrating with (R_C)**27b**, which can then be trapped by chloride to give the thermodynamic product diastereomer (S_{Ir},R_C)**25**. Inversion at the metal in similar 16-electron cations is fast on the NMR timescale.[164] It is also possible that the iridium cation is essentially planar at the metal, in which case the equilibration involves only a low-barrier rotation of the CHF(R_F) ligand, as shown. So, the ratio of product diastereomers is determined by the relative rates of trapping by external chloride vs. configurational inversion at iridium, *provided there is an excess of chloride*. It should be noted that the abstraction of an α-C–F bond to give a cationic fluoroalkylidene species has been demonstrated previously.[138–143,147] Furthermore, migration of a metal-H to a CF_2 ligand in a cationic Ru complex has been demonstrated previously,[192] so the proposals illustrated in Scheme 5 are certainly not new.



Scheme 5. Mechanism for formation and interconversion of product diastereomers in C–F activation coupled with H-migration.

These proposals are also supported by the observations illustrated in Figure 4, in which plots of the time-dependent concentrations of reactants and products are plotted for different concentrations of available chloride, in the form of LutHCl. With an excess of LutHCl (2.0 equiv.), the ratio of products remains essentially constant over the course of the reaction; with 1.05 equiv., the ratio starts out similarly, but as the chloride ion concentration falls, the thermodynamic product takes over as the dominant product; with a deficiency of chloride (0.87 equiv.), a similar crossover occurs, followed by a dramatic event late in the reaction, *in which the kinetic product is consumed and converted into the thermodynamic product*. This process is catalyzed by residual cations **27a**/**27b** for which no chloride is available; they can form bridged cations **28a**/**28b** by reacting reversibly with previously formed product molecules and thereby catalyze a net inversion at iridium.[191]

Consistent with this idea, a 2:1 diastereomer mixture of **24**/**25** was treated with 0.1 equiv. $Cp^*Ir(PMe_3)(C_3F_7)(O_3SCF_3)$[176] in CD_2Cl_2; this complex, with its weakly bound triflate ligand, serves as a reasonable substitute for the cationic intermediate **27**. A rapid change in the diastereomer ratio of **24**/**25** from 2:1 to less than 1:10 was observed, which is consistent with our prediction.

Solvent dielectric and donor properties[193] play a key role; overall rates are faster in CD_3NO_2 and slower in [D_7]-DMF compared to those in CD_2Cl_2. The activation parameters are dominated by the magnitude and sign of the $\Delta S^{\ddagger}$ term. Strong donor solvent stabilization of the protic acid component of the starting materials slows the overall rate, while a high dielectric constant solvent accelerates the rate. Reactions are at least twice as fast in the higher dielectric constant solvent CD_3NO_2, consistent with polar intermediates, and significantly, the product diastereomer ratio is inverted relative to that observed in CD_2Cl_2 under similar conditions. This is consistent with the stabilization of polar intermediate **27** in nitromethane, allowing intramolecular inversion at iridium to occur more competitively with chloride trapping. In addition, a 3:2 mixture of kinetic/thermodynamic diastereomers **24**/**25** generated in CD_2Cl_2 was unchanged after one day, but upon dissolution in CD_3NO_2, the diastereomer ratio rapidly changed to 1:2 and eventually to an apparent equilibrium value of approximately 1:15. This is consistent with irreversible coordination of chloride and consequent configurational stability at iridium in CD_2Cl_2 but reversible dissociation of chloride in nitromethane, allowing thermodynamic control of the diastereomer ratio to prevail via inversion at iridium. In the better donor solvent [D_7]DMF, reactions were significantly slower than in CD_2Cl_2, probably due to solvation of the key HCl reagent in this donor solvent. Unlike reactions in CD_2Cl_2 or CD_3NO_2, diastereomer ratios of 2:1 were typically found to be invariant over the course of the reaction, indicating that in [D_7]DMF inversion at iridium may be slowed, perhaps by coordination of DMF.

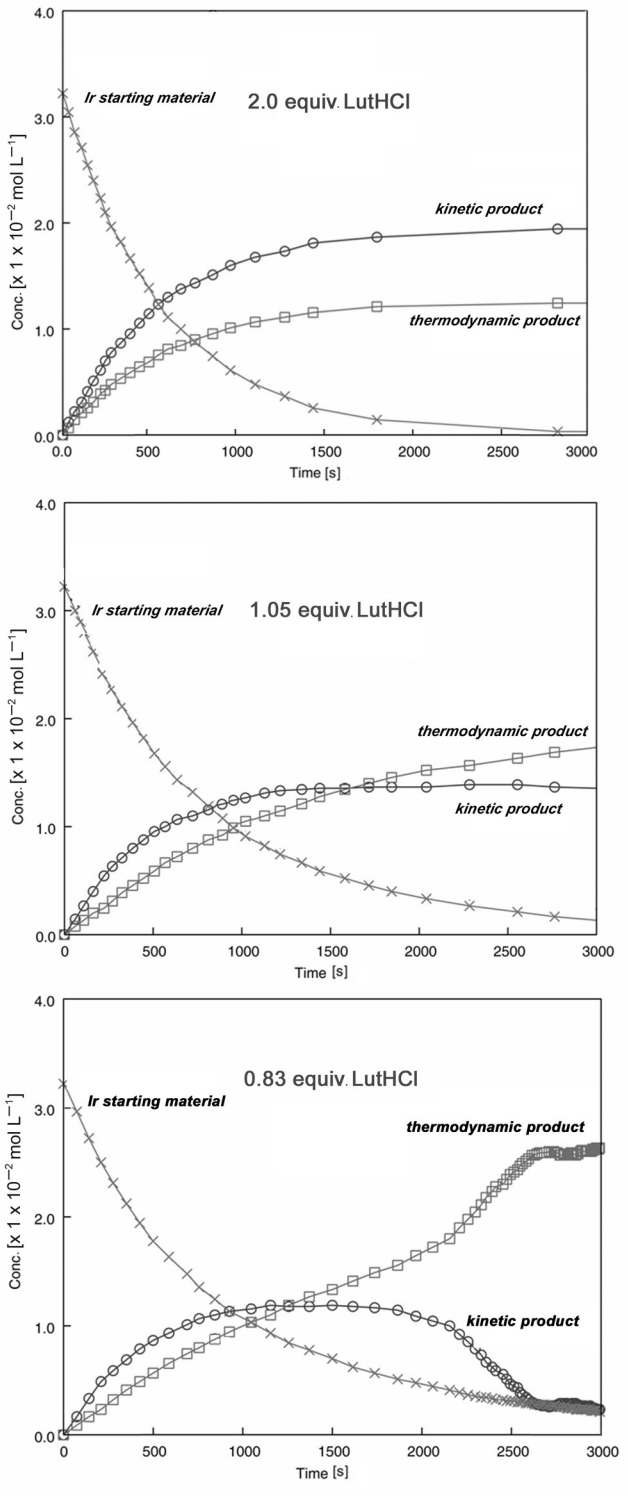


Figure 4. Plots of concentration vs. time for reactant and products in the conversion of **14**-H to a mixture of product diastereomers **24** (kinetic product) and **25** (thermodynamic product) in the presence of different concentrations of chloride (LutHCl).

Further independent evidence as to the nature of cationic intermediate **26** has also been accrued. Clearly this cation is required to have the R_F group *cis*- to Cp*, as shown, in order to obtain the correct stereochemistry at carbon when the H-migration step occurs. Difluorocarbene complexes are not unprecedented,[146,192,194–196] and we have been able to devise a simple route to the neutral perfluoroalkylidene complexes **29**.[197] The preferred configurational stereochemistry at the Ir=C double bond does indeed place the R_F group (CF_3 or CF_2CF_3) *cis* to the Cp* ligand; once again this appears to be controlled by steric effects arising from the approximately 90° angle between the PMe_3 and alkylidene ligands, the bulky R_F group preferring the more open region of space adjacent to Cp*. The alkylidene prefers the *conformation* illustrated because of the orientation of the Ir 5d orbital required for π bonding. This is shown in Figure 5, and is analogous to other treatments of ligand positional and conformational preferences using the isolobal analogy.[198–199] The important consequence for the mechanism shown earlier in Scheme 5 is that in the conversion of **14** to **26** by HCl there is a leaving group requirement that only the fluorine shown as departing as fluoride can do so, in order that the developing p orbital on carbon can be stabilized by iridium. In turn, this requires intermediate **26** to have the structure shown, and thus for H-migration to afford the observed stereochemistry at carbon.

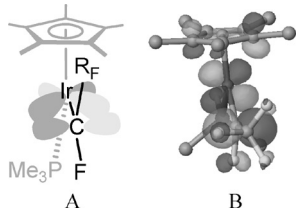
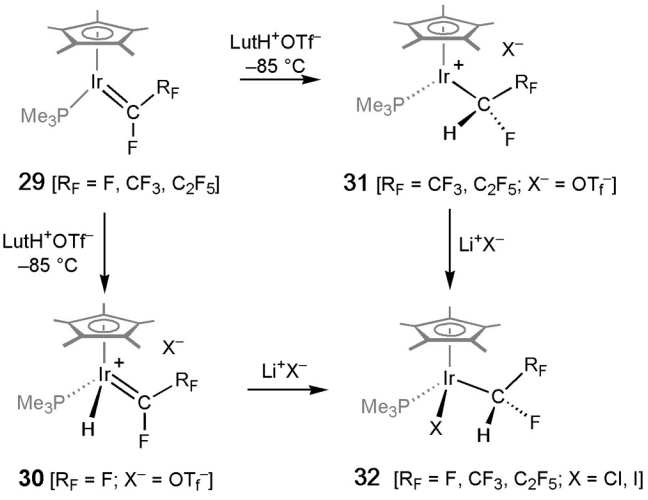


Figure 5. (A) Cartoon of the interaction of the alkylidene p orbital on carbon with the Ir 5d orbital that controls the conformation of the Ir=C double bond. (B) Kohn–Sham LUMO of **29** [R_F = CF_3] calculated by DFT and illustrating the π*-interaction of the C 2p and Ir 5d orbitals.[163]

As shown in Scheme 6, addition of a proton to **29** [R_F = F] at low temperatures gives cation **30**, which can be observed by low-temperature NMR spectroscopy and in which the proton is unambiguously bound to iridium; the weakly coordinating triflate counterion does not bind. Addition of a coordinating anion, in the form of chloride or iodide, leads to rapid H-migration to carbon and formation of **32** [R_F = F]. In contrast, the same reaction using **29** [R_F = CF_3] gives cation **31**, in which the proton is bound to carbon and which reacts with chloride or iodide to give **32** [R_F = CF_3].[197] It seems likely, therefore, that the kinetic site of protonation is at iridium to give a cation analogous to **26** (Scheme 5), but that the thermodynamics of H-migration differ according to the substituents on carbon.

With details of the α-C–F activation/H-migration reaction more clearly understood, and some reasons for the poor diastereoselectivity established, significant differences are apparent in the corresponding chemistry involving migration of groups other than H, as shown earlier in Scheme 4. First, there is no evidence for isotopic scrambling between the added HCl/DCl and the organic groups. For example, **14**-CH_3 yields only **18**-CH_3 on treatment with LutDCl, and **14**-CD_3 yields only **18**-CD_3 on treatment with

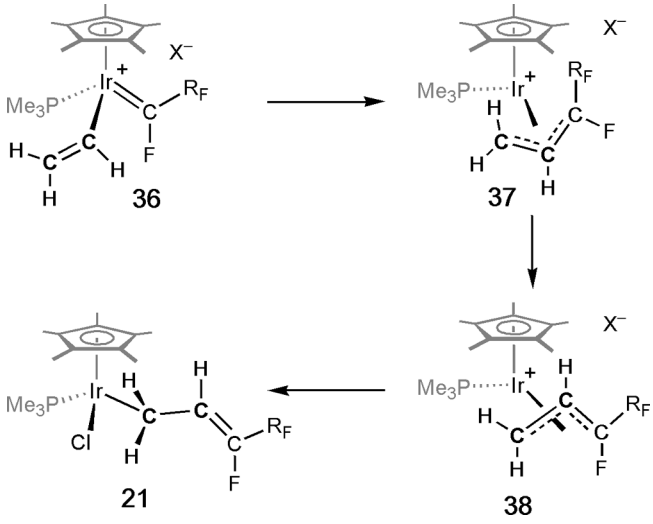


Scheme 6. Reactions of perfluoroalkylidene complexes with protic acids.

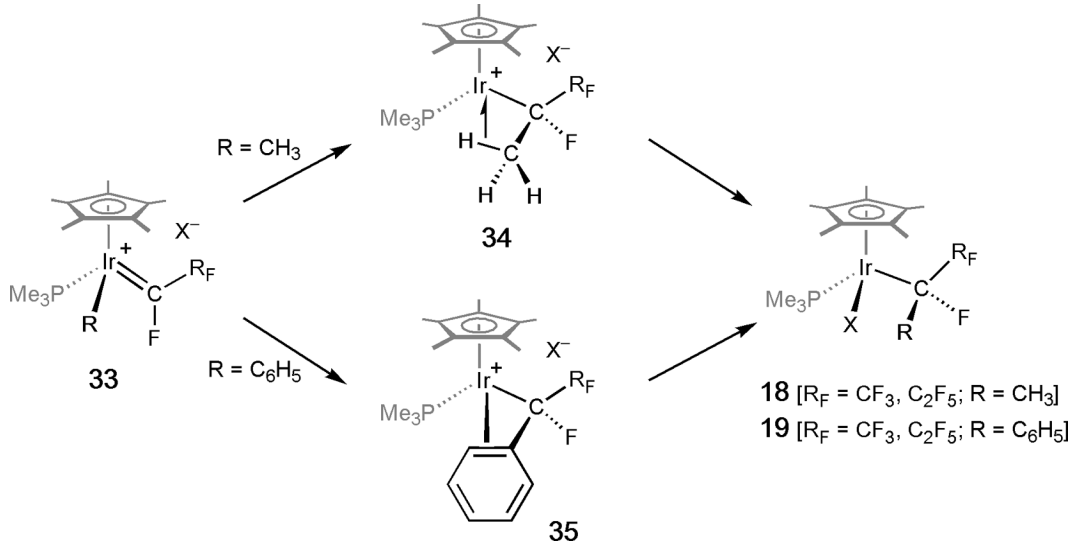
LutHCl; there is, therefore, no evidence for formation of a CH_4 complex, as established in other systems.[187,200–203] Second, these reactions are completely diastereoselective to give the $(R_{Ir},R_C)(S_{Ir},S_C)$ relative configurations; this is the diastereomer produced under kinetic control, shown by slow subsequent reactions to give other diastereomers or rearrangement products, as discussed below.

The α-C–F protonation reaction presumably occurs as shown in Scheme 5 for the H-migration case, with the same conformational requirements for the starting material and the alkylidene formed by loss of fluoride; this must afford intermediate **33** as shown in Scheme 7. Migration of CH_3 to form the new C–C bond can now occur to form **34**, in which the stereochemistry at iridium is preserved by formation of an agostic bond to a β-C–H; this intermediate is associated with other thermodynamically controlled chemistry to be discussed below but, provided trapping at iridium by chloride is fast and irreversible, **34** proceeds smoothly to form the observed kinetic product diastereomer **18**. Likewise, migration of phenyl affords an η^3-benzyl intermediate **35**, thereby preserving stereochemistry at the metal, and trapping with chloride yields **19**.

Scheme 8 illustrates the same features for vinyl migration.[179] An analogous intermediate **36** is formed by protonation of the α-C–F bond and loss of fluoride. When X^- is Cl^- only the final rearranged product **21** is observed, but use of $LutH^+B[Ar_F]_4^-$,[204] with an essentially noncoordinating anion, allows observation of various intermediates. At low temperatures the kinetically controlled species arising from vinyl migration is the *endo-anti* η^3-allyl isomer **37** in which the R_F group is *cis* to Cp*, thus providing further definition of the location of R_F in the preceding intermediate **36**. On warming this rearranges eventually to the *exo-syn* isomer **38**, and addition of a coordinating anion like chloride or iodide results in $\eta^3 \rightarrow \eta^1$ rearrangement of the allylic ligand to give **21**.

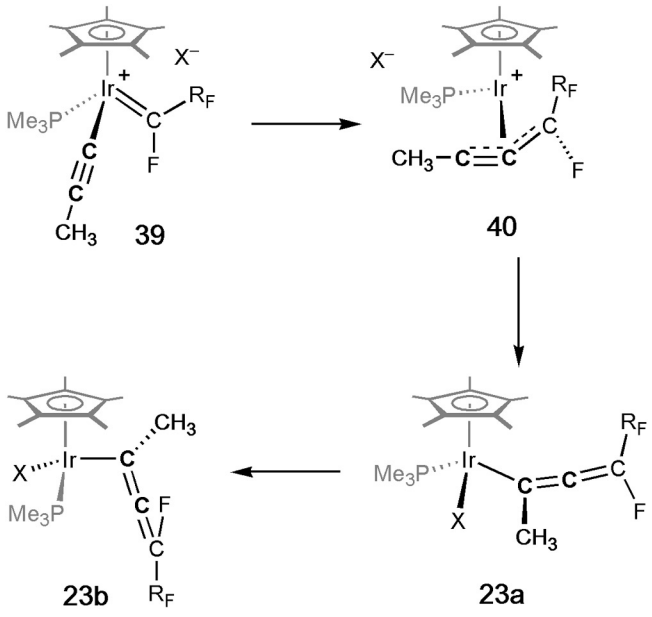


Scheme 8. η^3-Allylic intermediates in vinyl migration.



Scheme 7. C–H agostic and η^3-benzylic intermediates in H and phenyl migrations.

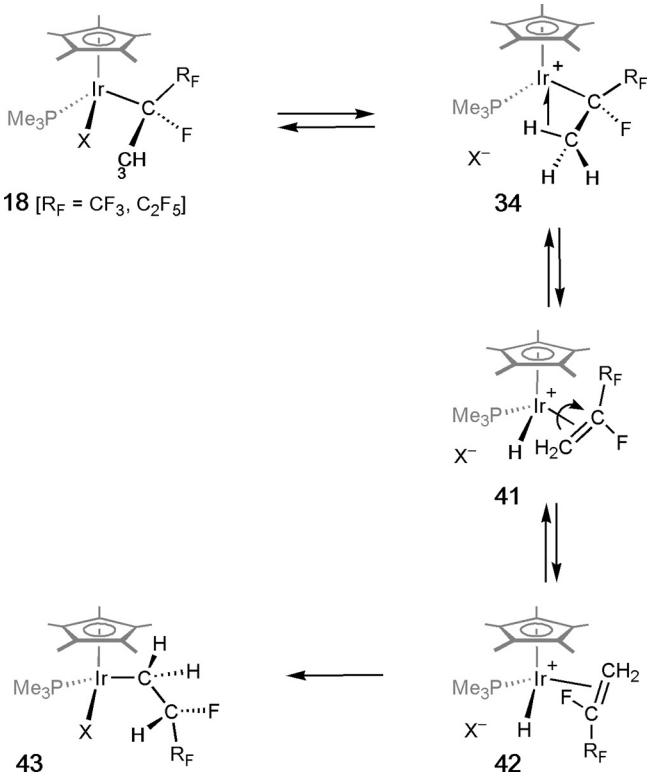
Analogously, Scheme 9 rationalizes the corresponding observation made in the propynyl migration.[180] Protonation and loss of fluoride affords cationic intermediate **39**; propynyl migration yields the η^3-allenyl(propargyl) species **40** with the stereochemistry shown; trapping at the metal by halide gives the kinetically controlled allenyl diastereomer **23a** having the (S_{Ir}M)(R_{Ir}P) relative configurations at iridium and at the helical allene;[205] and slow rearrangement by inversion at iridium gives the thermodynamically favored (R_{Ir}M)(S_{Ir}P) diastereomer **23b**. Attempts to observe intermediate **40** using $LutH^+B[Ar_F]_4^-$ were unsuccessful.[180]



Scheme 9. η^3-Allenyl(propargyl) intermediates in propynyl migration.

Finally, as mentioned earlier, the agostic methyl group in **34** is proposed as a key intermediate in the formation of methyl migration product **18** (Scheme 7). One would expect that such a species would have the option of undergoing β-hydride elimination if it is not trapped quickly. When the counterion is chloride or iodide, trapping of **34** is faster than β-H elimination and is irreversible in CD_2Cl_2.[176] However, when trifluoroacetate is the counterion trapping of **34** is still faster than elimination, and product **18** [X = $CF_3CO_2^-$] can be observed. But the more weakly coordinating trifluoroacetate coordinates reversibly, and product **18** is in equilibrium with intermediate **34** as shown in Scheme 10. A relatively slow β-H elimination occurs to give alkene intermediate **41** in which alkene rotation affords **42**; re-addition of Ir–H to the other end of the alkene yields two diastereomers of **42**, the product of ultimate thermodynamic control.[176]

Taken together, these experimental observations establish an internally consistent, common pathway involving stereoselective α-C–F bond activation to give a cationic alkylidene



Scheme 10. Isomerization following CH_3 migration [R_F = CF_3, C_2F_5; X = $CF_3CO_2^-$].

intermediate of defined stereochemistry, with stereoselective formation of new bonds to the α-carbon under kinetic control by migration of H, CH_3, C_6H_5, $CH{=}CH_2$, and $C{\equiv}C{-}CH_3$; loss of diastereoselectivity in the H-migration reaction presumably occurs because the resultant α-C–H does not effectively preserve the stereochemistry at iridium by forming an agostic interaction. These reactions seem to be ideal candidates for DFT studies, which are being carried out and which will be reported in due course.

A further concluding comment may be worthwhile concerning the difference in reactivity between different kinds of metal–perfluoroalkyl compounds towards α-C–F bond activation by this kind of protonation (or other electrophilic attack) mechanism; $M{-}CF_3 > M{-}CF_2R_F > M{-}CF(CF_3)_2$. The critical intermediate formed by loss of fluoride can stabilize the carbocation center by π donation from the transition metal center and from the substituents on carbon; for a given metal center, we expect the order of cation stability to be $M{-}CF_2^+ > M{-}CF(R_F)^+ > M{-}C(R_F)_2^+$; that is, the more π-donating F-substituents the better.[20–21] In axially symmetric complexes this will be the principal effect, but in the compounds described here there is also a conformational requirement, as summarized in Figure 6. For primary and secondary fluoroalkyl complexes of these types, we have established the solution-phase ground-state conformations to be as shown.[181] Only fluorine atoms in the shaded locations have the correct leaving group stereochemistry such that as fluoride is lost the resultant carbocation

can be stabilized by the metal (see Figure 5). Thus, a CF_3 ligand always has two fluorine atoms correctly oriented for departure *and* gives the best stabilized cation; a primary fluoroalkyl group always has one fluorine atom in the ejector seat, but gives a less stabilized cation; and a secondary fluoroalkyl group does not have a fluorine atom in the correct location to leave and so requires an additional rotational activation to do so and affords the least stable cation. The sensitivity to reaction with external electrophiles, and subsequently towards internal and external nucleophiles observed here and elsewhere, is explained. Using primary fluoroalkyl ligands has therefore provided the most convenient rates coupled with the maximum amount of stereochemical information about these reactions in which carbon–fluorine bonds are converted to carbon–carbon, carbon–hydrogen, and carbon–heteroatom bonds.

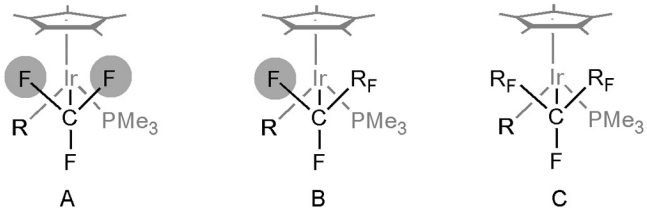


Figure 6. Ground-state solution conformations of CF_3, primary CF_2R_F, and secondary $CF(R_F)_2$ ligands in some iridium complexes. Fluorine atoms in the correct locations to act as fluoride leaving groups are shaded.

Now, if only we could make these reactions catalytic!

Acknowledgments

The U.S. National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, have been generous in supporting this research, which could not have been carried out without the able assistance of several skilled postdoctoral fellows, graduate students, and undergraduates, whose names appear in the literature citations from our group. The invaluable assistance of Professor Arnie Rheingold's group at the University of California at San Diego in determining many X-ray crystal structures is also gratefully acknowledged.

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