Topics in Organometallic Chemistry 52

Thomas Braun
Russell P. Hughes *Editors*

# Organometallic Fluorine Chemistry

Springer

# 52
# Topics in Organometallic Chemistry

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Thomas Braun • Russell P. Hughes
Editors

# Organometallic Fluorine Chemistry

With contributions by

M.G. Campbell · B. Chen · A.J. Hoover · E.G. Hope · J.-Y. Hu · N.A. LaBerge · J.A. Love · S. Ogoshi · M. Ohashi · T. Ritter · R. Simayi · A.M. Stuart · D.A. Vicic · J.-L. Zhang

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# Preface

Despite its long history as an active area of research, fluorine chemistry is currently undergoing a surge of activity, particularly in the development of new and selective methods for fluorinating organic molecules and for engaging the strong C–F bond in chemistry of its own. Molecules containing carbon-fluorine bonds play significant positive and sometimes deleterious roles in the lives of human beings. Half of the top 10 drugs sold contain C–F bonds, as do about 20% of all pharmaceuticals, and 30−40% of agrochemicals. As a result, the importance of the introduction of strategically placed C–F, C–$CF_3$, and C–$CF_2H$ bonds in pharmaceutical, medicinal, and bioorganic chemistry has led to the development of new methodology for their selective generation. Methods for late-stage introduction of fluorine in synthesis have also burgeoned, due to the need for rapid introduction of short-lifetime $^{18}F$ into Positron Emission Tomography markers. Fluorinated materials, such as Teflon and other tailored fluoropolymers, continue to have a positive impact on the quality of human life, and their physical properties and chemical inertness are often a boost to technological advances.

Positive societal roles of fluorocarbons are sometimes offset by deleterious environmental effects. Accumulated atmospheric chlorofluorocarbons, now banned under the Montréal Protocol, contribute to ozone depletion and global warming. Hydrofluorocarbons, important in applications such as refrigerants, aerosols, foaming agents, inhalation anesthetics, and semiconductor cleaning solvents, are more environmentally benign. However, many saturated perfluorocarbons and their derivatives, used as cleaning agents and solvents for chemical separations and catalysis, have significant global warming potential, and environmental lifetimes of thousands of years because there is no environmental mechanism for their degradation.

Fluorine forms the strongest single bond to carbon, and the selective introduction or chemical manipulation of C–F bonds is a serious challenge to the imaginative chemist. Many of the methods for introduction of fluorine atoms and fluoroalkyl substituents into organic scaffolds involve organometallic reactions and catalysis.This volume presents reviews of recent advances from expert practitioners in the field.

We begin with an extensive review from Campbell, Hoover, and Ritter on stoichiometric and catalytic methods for the introduction of fluorine into organic molecules, with reference to late stage fluorination methods. Second comes a comprehensive review by the LaBerge and Love on the selective introduction and manipulation of C–F bonds in aromatic systems using transition metal reagents.

Reviews on C–F bond formation are followed by the discussion by Chen and Vicic on catalytic C–C bond formation methods for the introduction of $–CF_2H$ and $=CF_2$ groups using transition metal complexes.

A replacement of a C–F bond by a C–H bond in fluorinated molecules to access new building blocks is the focus of the review of Hu and Zhang on catalytic hydro defluorination methods.

This is complemented by a discussion of catalytic transformations, mainly by C–F bond activation, of fluorinated olefins by Ohashi and Ogoshi.

Finally an update on the remarkable application of the physical properties of long fluorous chains in organometallic compounds is provided by Hope, Simayi and Stuart.

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# Contents

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# Transition Metal-Mediated and Metal-Catalyzed Carbon–Fluorine Bond Formation

**Michael G. Campbell, Andrew J. Hoover, and Tobias Ritter**

**Abstract** The development of new C–F bond forming reactions from organotransition metal complexes has played a key role in advancing the field of fluorination chemistry and has allowed for improved access to fluorinated organic molecules of interest in medicine, materials, and agrochemicals. In this review, we describe the development of transition metal-mediated and metal-catalyzed fluorination methods over the past decade. Special attention is paid to the variety of organometallic mechanisms by which C–F bond formation can occur and the strengths and limitations of different approaches.

**Keywords** Catalysis · C–H functionalization · Fluorine · Transition metals

## Contents



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# 1 Introduction

The fundamental organometallic transformation of C–F reductive elimination from a transition metal center was only established in 2008 [1, 2], despite years of concentrated effort [3]; however, in the following decade, the rapid growth of organotransition metal fluorine chemistry has enabled the synthesis of fluorinated organic molecules that were previously challenging to access [4–7]. Further work has shown that synthetically useful C–F bond forming reactions can be achieved through diverse organometallic mechanisms, including C–F reductive elimination, electrophilic metal–F bond cleavage, and a variety of single-electron pathways. Here we review the development of transition metal-mediated and metal-catalyzed C–F bond formation, with a focus on the strengths and drawbacks of different mechanistic approaches. Additionally, the application of transition metal-mediated fluorination methods to $^{18}$F-radiofluorination for positron emission tomography (PET) is discussed.

# 2 C($sp^3$)–F Bond Formation

## *2.1 Nucleophilic Fluorination Reactions*

The synthesis of C($sp^3$)–F bonds from nucleophilic fluoride and alkyl electrophiles can be challenging due to the fluoride ion's weak nucleophilicity when coordinated to hydrogen bond donors and the tendency of fluoride to induce undesirable elimination reactions due to its basicity [8–11]. However, most C–F bond forming reactions are thermodynamically favorable [12], and therefore transition metal mediators or catalysts can potentially be used to selectively render kinetically difficult nucleophilic fluorination reactions more feasible. Additionally, as discussed in the following section, the formation of a metal–fluorine bond, as well as metal-mediated formation of reactive electrophiles, can result in surprisingly enhanced nucleophilic reactivity of fluoride.

### 2.1.1 Allylic Fluoride Synthesis

The synthesis of allylic C–F bonds from nucleophilic fluoride by transition metal-catalyzed allylic substitution remained undeveloped by the end of the twentieth century, despite robust allylation of carbon-, nitrogen-, and oxygen-based nucleophiles [13–15]. Catalysis development for allylic fluorination has been motivated by low regio- and stereochemical control in established allylic fluorination methods, such as the deoxyfluorination of allylic alcohols with DAST [16]. An intrinsic challenge in allylic fluorination chemistry is the reactivity of the desired allylic fluoride. Togni illustrated the difficulty of this transformation in reporting

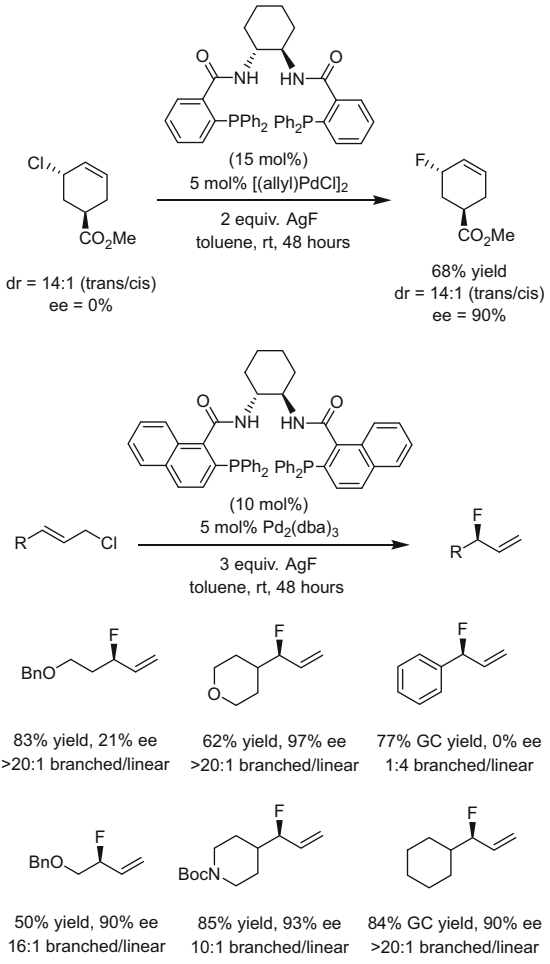



**Fig. 1** Palladium-catalyzed synthesis of allylic fluorides from allylic chlorides

that cationic allylpalladium complexes failed to yield allylic fluorides upon treatment with several fluoride sources [17].

Palladium-catalyzed allylic substitution chemistry was extended to the fluoride nucleophile by Doyle, who in 2010 reported the palladium-catalyzed enantioselective fluorination of cyclic allylic chlorides with silver fluoride (Fig. 1, top) [18]. In contrast to Togni's work on cationic allylpalladium complexes, Doyle showed that a neutral, phosphine-bound allylpalladium chloride reacts with silver fluoride to yield an allylic fluoride. Fluorination proceeded with inversion of configuration (from the allylpalladium) and retention of relative configuration (from allylic chlorides). While fluoride belongs to the "hard" class of nucleophiles, the stereochemical course of this allylic fluorination is the same as for most "soft" nucleophiles in nucleophilic substitution reactions involving allylpalladium intermediates [19, 20]. The intermediacy of a palladium(II)–fluoride nucleophile (*vide*

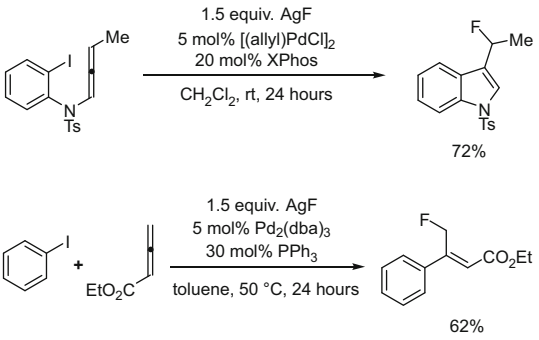



**Fig. 2** Carbofluorination of allenes catalyzed by palladium

*infra*) may explain this reactivity. Doyle showed that an allylic chloride underwent selective fluorination in the presence of an allylic carbonate and suggested that formation of insoluble silver(I) chloride increased the thermodynamic favorability of the reaction. Under reaction conditions with a palladium catalyst and chiral bisphosphine ligand originally developed by Trost for enantioselective allylic substitution [21], the highest enantioselectivities (85–96% ee) were observed with cyclic six-membered ring substrates; seven- and five-membered ring substrates, as well as acyclic substrates, were fluorinated with lower enantioselectivity.

Doyle later reported palladium-catalyzed asymmetric synthesis of acyclic, branched allylic fluorides (Fig. 1, bottom). High enantioselectivities (90–97% ee) were observed when the allyl group was bound to a cyclic alkyl or alkoxymethyl group [22]. Doyle also reported a palladium-catalyzed carbofluorination of allenes that yields allylic fluorides, in both intra- and intermolecular fashions, again with AgF as the source of nucleophilic fluoride (Fig. 2) [23].

Shortly after Doyle's initial report of palladium-catalyzed allylic fluorination, Gouverneur reported a palladium-catalyzed synthesis of linear allylic fluorides from allylic carbonates (Fig. 3) [24]. Gouverneur had previously reported that allylic fluorides are less reactive than allylic carbonates (but more reactive than allylic acetates) as electrophiles for palladium-catalyzed substitution with dimethylmalonate [25]. The para-nitrophenylcarbonate leaving group was superior to phenylcarbonate and methylcarbonate. In contrast to the use of AgF by Doyle for fluorination of allylic chlorides, Gouverneur reported that TBAF-(*t*-BuOH)$_4$ reacted to give high yields of allylic fluorides. Terminal allylic carbonates were fluorinated in higher yield and with greater regioselectivity than 1,3-disubstituted allylic carbonates, and elimination of the carbonate occurred readily when alpha C–H bonds were present. This method was applied to synthesize [$^{18}$F]cinnamyl fluoride from [$^{18}$F]TBAF and is the first reported instance of palladium-mediated C–$^{18}$F bond formation.

Nguyen subsequently reported an allylic fluoride synthesis from allylic trichloroacetimidates catalyzed by iridium, using $Et_3N(HF)_3$ as the source of fluoride (Fig. 4) [26]. Fluorination of terminal allylic electrophiles occurred regioselectively to give branched allylic fluorides in high yield. The reported substrate scope for terminal allylic electrophiles bound to a methylene group is similar to that of

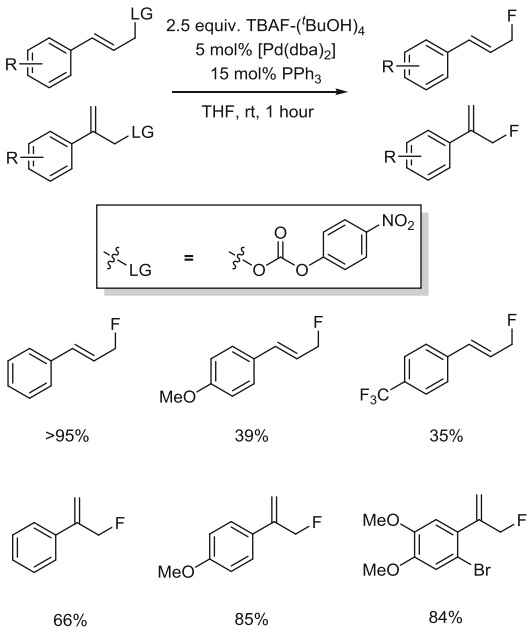



**Fig. 3** Synthesis of allylic fluorides from allylic carbonates catalyzed by palladium

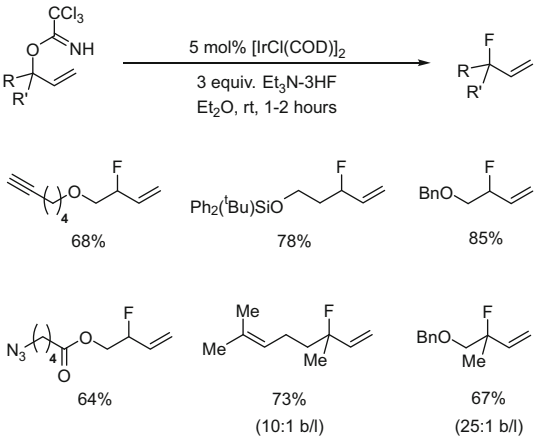



**Fig. 4** Synthesis of allylic fluorides from allylic trichloroacetimidates catalyzed by iridium

Doyle's allylic fluorination. The reaction times are short, and this practical advantage was highlighted with the synthesis of an [$^{18}$F]allylic fluoride in 38% radiochemical yield from [$^{18}$F]Kryptofix-KF in 10 min. Subsequently, Lautens reported enantioselective allylic fluorination of oxabicyclic alkenes with $Et_3N(HF)_3$ catalyzed by rhodium and a chiral bisphosphine [27]. Nguyen later reported that a rhodium(I) catalyst efficiently catalyzes hydrofluorination of vinylepoxides with $Et_3N(HF)_3$ to yield allylic fluorohydrins [28].

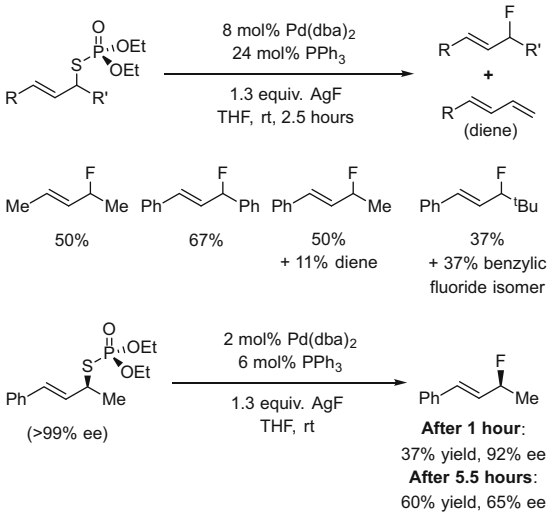



**Fig. 5** Synthesis of allylic fluorides from allylic phosphorothioates catalyzed by palladium

Wu reported the fluorination of allylic phosphorothioate esters, with a focus on 1,3-disubstituted allylic electrophiles (Fig. 5) [29]. By optimization of the palladium source and ligand combination, competitive elimination of the electrophile was minimized. Erosion of enantiomeric enrichment occurs when this method is used with an enantioenriched starting material, which is also the case with Nguyen's fluorination of allylic trichloroacetimidates.

Doyle reported a mechanism study of palladium-catalyzed fluorination of allylic chlorides [30]. Of key importance were the structure of the reactive electrophile and the identity of the reactive fluoride species. A palladium(II) fluoride was found to be a competent source of fluoride in place of silver fluoride and generated allylic fluoride with identical regioselectivity. Computational data were more consistent with an allylpalladium(II) fluoride as the reactive fluoride nucleophile than with a silver fluoride. To support a cationic allyl intermediate, Doyle showed that a neutral allylpalladium complex with chelating anionic ligand was unreactive and that an allylic trifluoroacetate was competent for allylic fluorination, whereas an allylic acetate was not. Although reaction heterogeneity precluded detailed kinetic studies, the authors proposed that the simplest model to explain the experimental and computational data was the mechanism shown in Fig. 6, where the C–F bond forming step involves attack of a palladium(II) fluoride on a cationic allyl intermediate. The enhanced nucleophilicity and attenuated basicity of fluoride when bound to palladium(II), as described by this study, may find valuable application in the development of new reactions involving fluoride as nucleophile.

A distinct approach to allylic fluoride synthesis was reported by Davies in 2013 [31]. Alkenyl diazoacetates were found to undergo vinylogous hydrofluorination upon treatment with $Et_3N(HF)_3$ under silver catalysis (Fig. 7). This reaction is high-yielding and regioselective for the synthesis of diverse 1,3-disubstituted allylic fluorides, and for this substrate class is superior to other allylic fluoride syntheses

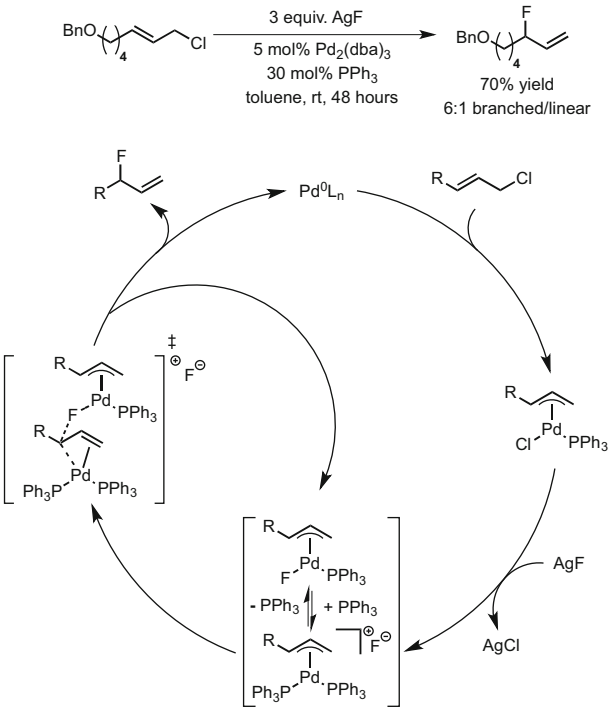



**Fig. 6** Mechanism of palladium-catalyzed substitution of allylic chlorides with fluoride

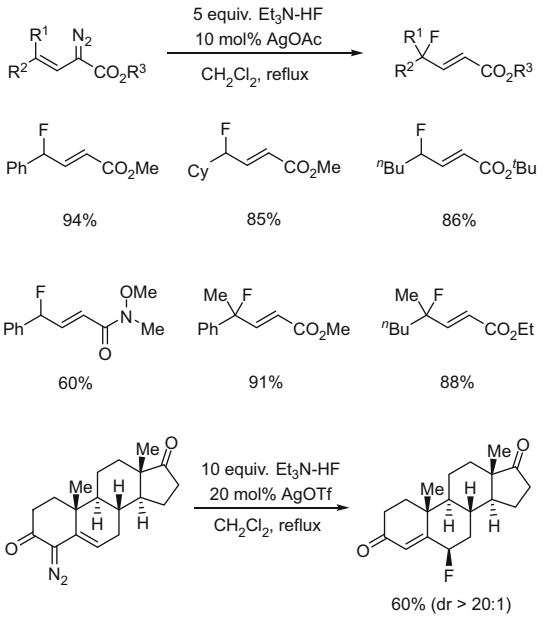



**Fig. 7** Hydrofluorination of alpha-diazocarbonylalkenes catalyzed by silver

from allylic electrophiles. However, the requirement of a carbonyl group alpha to the diazo function limits the product scope to allylic fluorides of alpha-beta unsaturated carbonyl compounds.

### 2.1.2 Hydrofluorination of Epoxides and Aziridines

Transition metal-catalyzed epoxide fluorination has been pursued with the goal of inducing asymmetry using chiral metal complexes. Early reports of metal-mediated asymmetric epoxide hydrofluorination emerged in the early twenty-first century from Haufe [32, 33], who reported that a chiral chromium(III) salen complex, pioneered by Jacobsen for catalytic enantioselective nucleophilic ring-opening reactions of epoxides [34], also mediates asymmetric ring opening of epoxides by nucleophilic fluoride.

Subsequently, Doyle reported the first transition metal-catalyzed asymmetric epoxide hydrofluorination that proceeds with high turnover and enantioselectivity [35]. Symmetric and terminal epoxides underwent asymmetric fluorination under catalysis by a cobalt salen complex with added chiral ligand **2**. HF was generated in situ from the reaction of benzoyl fluoride with hexafluoroisopropanol (HFIP) (Fig. 8). The cobalt salen complex was also competent for hydrofluorination of acylaziridines in the presence of a titanium co-catalyst (Fig. 9) [36]. Doyle then

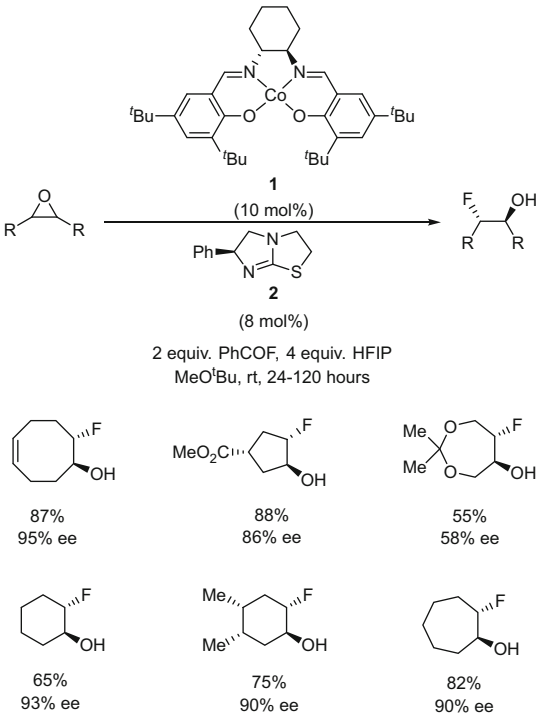



**Fig. 8** Enantioselective hydrofluorination of cyclic epoxides catalyzed by cobalt

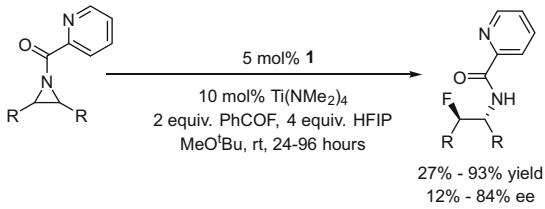



**Fig. 9** Hydrofluorination of aziridines catalyzed by cobalt

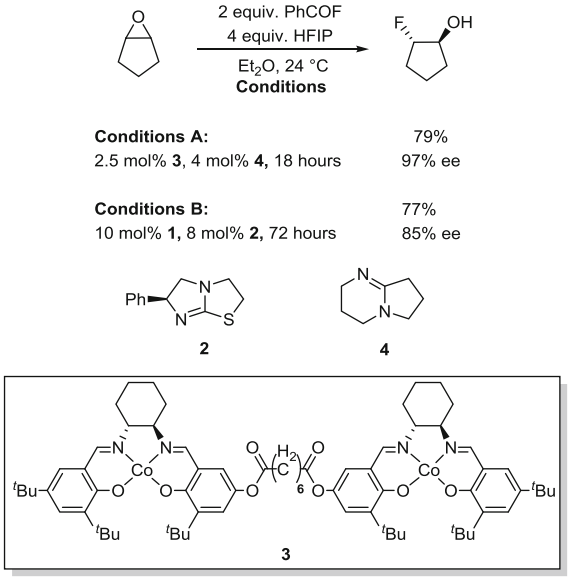



**Fig. 10** A dimeric cobalt catalyst for asymmetric hydrofluorination of epoxides

reported rate enhancement with a dimeric cobalt catalyst **3** (Fig. 10) and a detailed study that supports a mechanism in which both the epoxide and fluoride are activated by cobalt(III) salen complexes (Fig. 11) [37].

Based upon the reactivity described above, Doyle, Kung, and coworkers reported the improved syntheses of several biologically relevant [$^{18}$F]fluorohydrins, using an [$^{18}$F]fluoride-derived dinuclear cobalt complex **5** as a reagent that delivers [$^{18}$F]fluoride selectively to one enantiomer of racemic terminal epoxides (Fig. 12) [38].

### 2.1.3 Nucleophilic Substitution of Alkyl Halides and Pseudohalides

Nucleophilic substitution of alkyl bromides and triflates with fluoride is challenging, due to fluoride's attenuated nucleophilicity and tendency to react as a Brønsted base [8–11]. Weng reported an ionic copper(I) bifluoride reagent that efficiently induces formal $S_N2$ displacement of primary and secondary alkyl bromides with fluoride (Fig. 13) [39]. Protic functional groups including alcohols and an amide

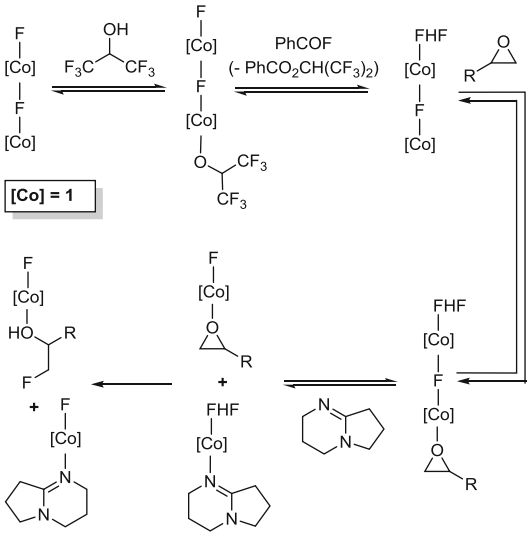



**Fig. 11** Mechanism of cobalt-catalyzed epoxide hydrofluorination

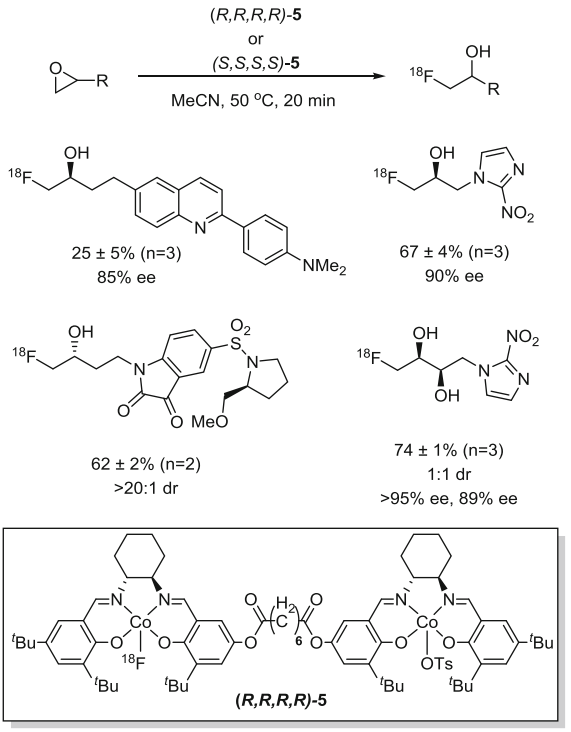



**Fig. 12** Enantioselective hydrofluorination of epoxides with [$^{18}$F]fluoride mediated by cobalt

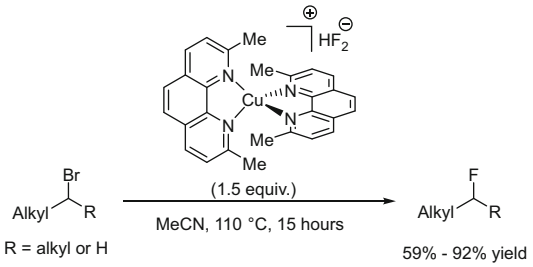



**Fig. 13** Fluorination of primary and secondary alkyl bromides with a copper bifluoride reagent

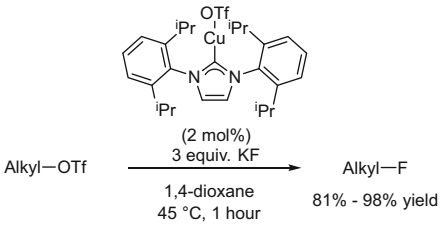



**Fig. 14** Fluorination of alkyl triflates catalyzed by copper

were tolerated. The reaction was not affected by radical scavengers and proceeded with inversion of configuration.

Lalic reported fluorination of primary alkyl triflates catalyzed by a copper(I) *N*-heterocyclic carbene complex (Fig. 14) [40]. The reaction proceeds with low catalyst loading (2 mol%) and with inversion of configuration. Negligible fluorination occurs in the absence of copper catalyst under the same reaction conditions.

## *2.2 Electrophilic Fluorination Reactions*

Formation of C($sp^3$)–F bonds occurs through reaction of organic molecules with $F_2$, the simplest electrophilic fluorination reagent, but typically results in the formation of multiple products without synthetically useful selectivity. Less reactive, more easily handled fluorination reagents derived from $F_2$ such as Selectfluor and *N*-fluorobenzenesulfonimide (NFBS) have been employed for catalytic fluorination of functional groups including C($sp^3$)–H bonds, C($sp^3$)–$CO_2H$ bonds, and alkenes. Additionally, several examples of electrophilic fluorination of C($sp^3$)-metal bonds have been reported.

### 2.2.1 Reactions Proposed to Proceed via Two-Electron Pathways

Electrophilic fluorination reagents can drive the formation of high oxidation state metal complexes. Although a number of high oxidation state alkylmetal fluorides were reported in the twentieth century [41, 42], they apparently were not reactive toward C($sp^3$)–F reductive elimination. Sanford reported early examples of

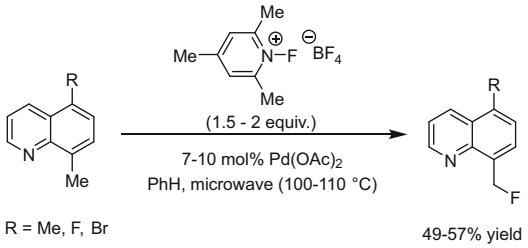



**Fig. 15** Electrophilic fluorination of benzylic C–H bonds catalyzed by palladium

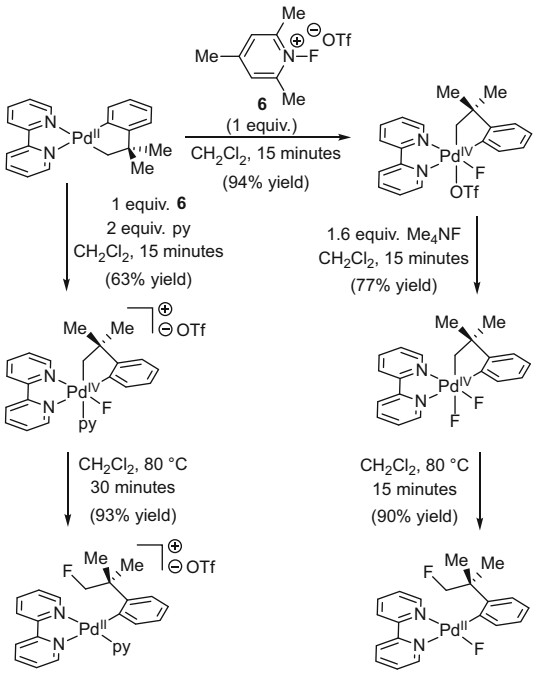



**Fig. 16** Reductive elimination of C($sp^3$)–F bonds from palladium(IV)

metal-catalyzed C($sp^3$)–H electrophilic fluorination reactivity (Fig. 15) [43]. However, C($sp^3$)–F bond formation was limited to benzylic methyl groups adjacent to a nitrogen directing group. Sanford later reported similar reactivity using silver fluoride and an iodine(III) oxidant (*vide infra*, Sect. 2.3).

In 2012, Sanford reported the synthesis of two isolable alkylpalladium (IV) fluoride complexes that undergo C($sp^3$)–F reductive elimination at 80°C (Fig. 16) [44]. Interestingly, although in this case Pd(IV) is bound to both an $sp^3$-carbon and an $sp^2$-carbon, no competitive C($sp^2$)–F bond formation is observed. A kinetic inverse order in pyridine supports a mechanism of reductive elimination from a five-coordinate palladium(IV) complex, and computations support a concerted C–F reductive elimination. The DFT-determined enthalpic barriers for reductive elimination indicate that C($sp^3$)–F reductive elimination is at least 5.8 kcal/mol more favorable than C($sp^2$)–F reductive elimination.

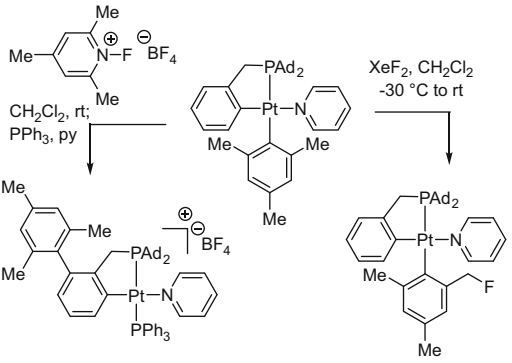



**Fig. 17** Platinum-mediated electrophilic fluorination of a benzylic C–H bond

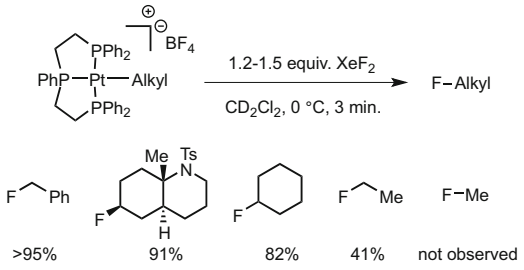



**Fig. 18** Electrophilic fluorination of platinum (II) alkyl complexes of various steric bulk

In studies initially intended to probe aryl C–C and C–F bond formation from high-valent platinum, Vigalok observed C–H fluorination of an adjacent benzylic methyl group upon reaction of a platinum(II)-aryl complex with $XeF_2$ (Fig. 17) [45]. Treatment of the same platinum precursor with an *N*-fluoropyridinium salt resulted instead in C–C bond formation. The authors propose a mechanism of oxidation to Pt(IV) with $XeF_2$, C–H metalation at Pt(IV) and C($sp^3$)–F reductive elimination that is favored due to steric congestion.

Gagné reported a study on the relevance of steric congestion for facile C($sp^3$)–F reductive elimination [46]. A series of alkylplatinum(II) complexes was described that have $\beta$-Pt C–H bonds, yet are stable toward $\beta$-hydride elimination at room temperature. Upon treatment with electrophilic fluorination reagents such as $XeF_2$ and NFBS, rapid C($sp^3$)–F bond formation occurs (Fig. 18). Fluorination is most efficient for bulky alkyl groups such as cyclohexyl. As a side reaction upon oxidation, $\beta$-hydride elimination occurs. The amount of $\beta$-hydride elimination product observed is inversely related to the steric congestion of the alkyl group bound to platinum. The high yield of fluorination of a platinum(II) benzyl complex compared to fluorination of substrates that have $\beta$-hydrogens is likely attributable to the absence of a competitive $\beta$-hydride elimination pathway. While observation of high-valent Pt intermediates was not reported in the case of the cyclohexyl and other hindered complexes, an ethyl-Pt(IV)–F intermediate was observable by NMR at −20°C. The methyl-Pt complex does not form a C–F bond; instead, reaction with $XeF_2$ affords NMR-observable methyl-Pt(IV)–F complexes. The fluorination

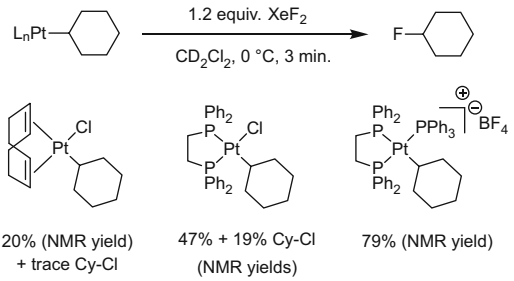



**Fig. 19** Electrophilic fluorination of a series of Pt (II) cyclohexyl complexes with increasingly bulky ligand sets

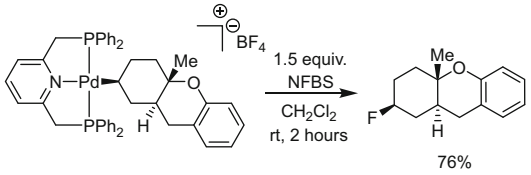



**Fig. 20** Electrophilic fluorination of a sterically congested Pd(II) alkyl complex

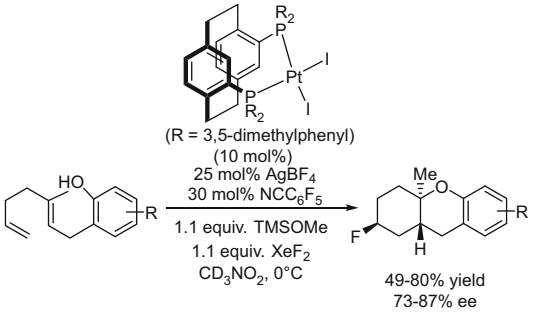
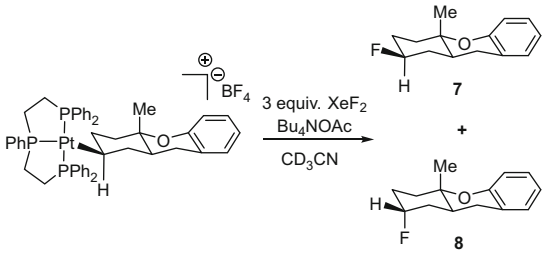



**Fig. 21** Asymmetric fluoroalkoxylative cascade cyclization of phenolic polyenes catalyzed by platinum

occurs with retention of configuration, and the authors propose a concerted C($sp^3$)–F reductive elimination from Pt(IV) based on the above evidence.

In line with the above study, Gagné varied the ligands on platinum(II) while keeping the alkyl group (cyclohexyl) fixed. Consistent with the previously observed trend, increased steric bulk on the Pt(II) alkyl complex resulted in higher fluorination yield (Fig. 19). Interestingly, although C–Cl bond formation was observed for the chloroplatinum complexes, C–F bond formation occurred in higher yield. Gagné also showed that this reactivity is not limited to platinum complexes: a sterically congested palladium(II)-alkyl complex also underwent electrophilic fluorination with retention of configuration to yield an alkyl fluoride in 76% yield (Fig. 20). The fluorination of sterically congested Pt(II) alkyls was exploited as part of a catalytic enantioselective cascade cyclization reaction (Fig. 21) [47].

In a 2014 report, Gagné disclosed a surprising switch in diastereoselectivity of Pt (II)-alkyl fluorination in the presence of acetate ion (Fig. 22) [48]. While in the absence of acetate the Pt–C($sp^3$) fluorination occurs with retention of configuration, inversion of configuration is observed in the presence of acetate. With enough




| Equiv. $Bu_4NOAc$ | (NMR Yields, %) 7 | 8 |
|---|---|---|
| 1 | 41 | 50 |
| 5 | 5 | 58 |
| 10 | 3 | 39 |

**Fig. 22** Addition of acetate ion changes the diastereoselectivity of Pt-C ($sp^3$) fluorination

acetate (5 or 10 equiv.), invertive fluorination is favored over retentive fluorination more than tenfold, although overall fluorination yield decreases. To explain the diastereoselectivity, the authors propose that after oxidation to Pt(IV), coordination of acetate inhibits formation of a pentacoordinate Pt(IV)-F that would undergo concerted C–F reductive elimination with retention of configuration. With concerted C–F reductive elimination thus retarded, fluoride ion may attack the carbon ligand bound to Pt(IV) to afford alkyl fluoride with inversion of configuration.

While most studies of electrophilic fluorination of metal-alkyl bonds have focused on group 10 metal complexes, Toste has reported examples of C($sp^3$)–F bond formation by electrophilic fluorination of gold(I) alkyl complexes (Fig. 23) [49]. Gold(III) intermediates were observable by NMR in several cases. Interesting parallels exist with the reactivity of platinum(II) alkyls reported by Gagné [46]: a sterically congested Au-menthyl complex underwent C–F bond formation in higher yield than the less bulky alkylgold complexes, and with retention of configuration; $\beta$-hydride elimination was a significant side reaction for many substrates; and the gold(I) methyl complex did not afford Me–F product. Among Toste's wide substrate survey, several of the alkyl fragments underwent rearrangements characteristic of carbocations. For example, a methyl [1, 2]-rearrangement was dominant in the fluorination of a gold(I) neopentyl complex. Reaction of alkylgold(III) difluoride was found to have a kinetic inverse order in added fluoride, which supports the authors' proposed mechanism of fluoride dissociation followed by concerted C–F reductive elimination from tricoordinate cationic gold(III). Similar carbocation rearrangements did not occur for electrophilic iodination of some of the same gold(I) complexes. DFT calculations that indicate a greater cationic character at gold in the Au(III)-F fragment as compared to the Au(III)-I fragment explain the greater propensity for carbocation-like rearrangements from the gold(III) fluorides.

An application of palladium-catalyzed electrophilic fluorination was reported by Liu and coworkers in 2010 [50]. Imidofluorination of styrenes with NFBS occurred regioselectively (Fig. 24). A mechanism of insertion of the styrene double bond to a Pd–F bond was proposed on the basis of observation of side product **9** from styrene aminofluorination. Initial Pd–F bond insertion to styrene and $\beta$-hydride elimination

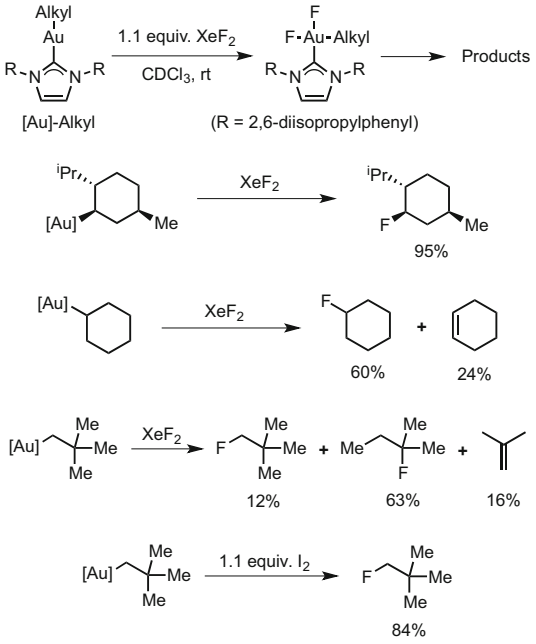



**Fig. 23** Electrophilic fluorination of gold(I) alkyl complexes

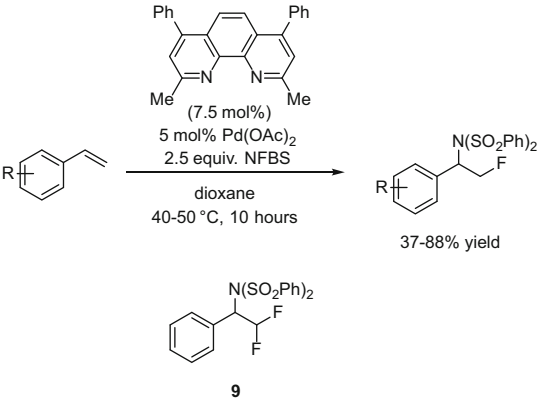



**Fig. 24** Intermolecular imidofluorination of styrenes catalyzed by palladium

would generate 2-fluorostyrene, which could then undergo imidofluorination to form **9**.

In 2014, Toste reported an asymmetric intermolecular arylfluorination of styrenes (Fig. 25) [51]. Amide directing groups enable the observed regioselective benzylic fluorination, and on the basis of the assumption that palladium forms a six-membered metallacycle with the amide, a mechanism is proposed in which the styrene undergoes insertion into a Pd–C bond, with subsequent benzylic C($sp^3$)–F reductive elimination from a high-valent Pd intermediate generated by oxidation with Selectfluor.

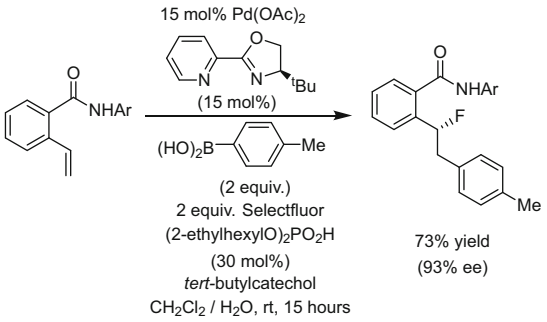



**Fig. 25** Amide-directed enantioselective fluoroarylation of styrenes catalyzed by palladium

### 2.2.2 Reactions Proposed to Proceed via One-Electron Pathways

Fluorination of C–H Bonds

Transition metal complexes exhibiting facile one-electron redox reactivity have since 2012 become prevalent in the literature of radical C($sp^3$)–F bond formation.

Lectka reported a copper-catalyzed method for the fluorination of C–H bonds with Selectfluor (Fig. 26) [52]. While fluorination occurred only once per substrate molecule, complex mixtures of C–H fluorination isomers were observed for substrates with multiple, nonidentical methylene groups. Lectka subsequently reported a simplified protocol, which employs a modified ligand and omits the borate salt, *N*-hydroxyphthalimide, and potassium iodide (Fig. 27) [53]. A detailed mechanistic study of this new system led to the proposal that the copper(I) complex acts as an initiator of a radical chain reaction. Triethylborane in the presence of oxygen (a combination known to form ethyl radicals [54]) was also a competent initiator for C–H fluorination. Rearrangement of a radical clock substrate was consistent with the formation of radical intermediates.

A series of computational analyses were reported to explain why monofluorination is observed rather than germinal difluorination in the Lectka system. The authors indicate that in the transition state for C–H cleavage, there is an increase in positive charge focused on the abstracted hydrogen atom, which is rendered unfavorable when an electronegative fluorine atom is adjacently bound. Therefore C–H cleavage is faster from $R_2CH_2$ groups than from $R_2CHF$ groups.

Britton and coworkers later reported the application of the oxotungstate **10** as a photocatalyst for the fluorination of C–H bonds with NFBS (Fig. 28) [55]. The reaction was designed on the basis of the documented ability of **10** to abstract hydrogen atoms from saturated organic fragments upon irradiation with light [56]. The authors propose that alkyl radicals thus generated abstract F atom from NFBS to generate fluorinated product. In line with C–H bond strengths and typical reactivity for metal-oxo-mediated C–H abstraction, fluorination occurred at C–H bonds distal to inductive electron-withdrawing groups and at more substituted carbons. Chen and coworkers reported C–H fluorination with Selectfluor catalyzed by vanadium(III) oxide, with similar selectivity trends (Fig. 29) [57].

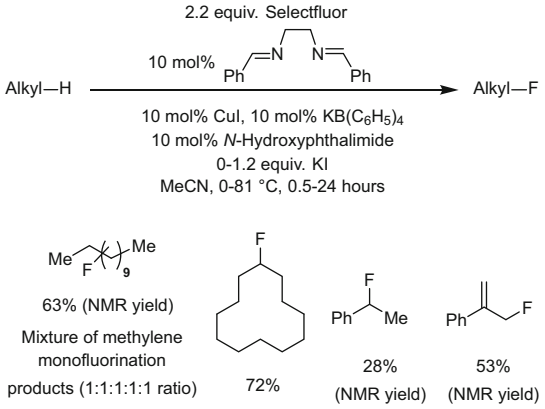



**Fig. 26** Copper-catalyzed radical C–H fluorination

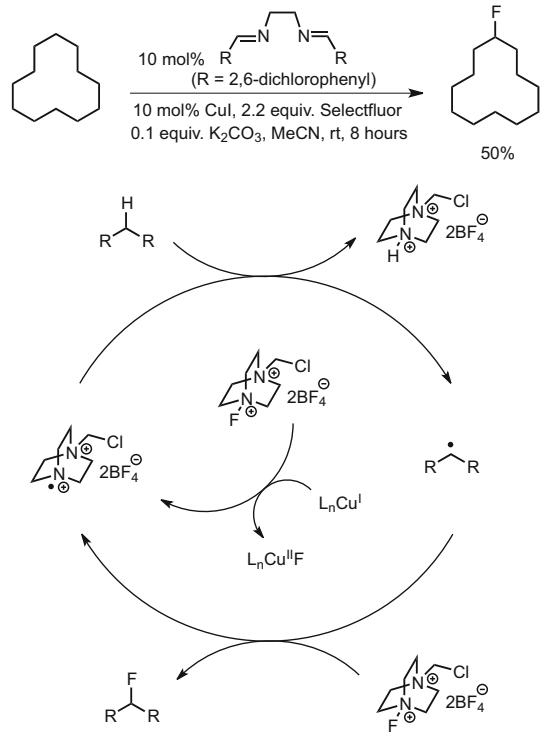



**Fig. 27** Mechanism of radical fluorination of alkyl C–H bonds mediated by copper

Lectka applied substoichiometric amounts of an iron(II) complex to enable a simple and selective benzylic C–H bond fluorination protocol, with Selectfluor in acetonitrile at room temperature (Fig. 30) [58, 59].

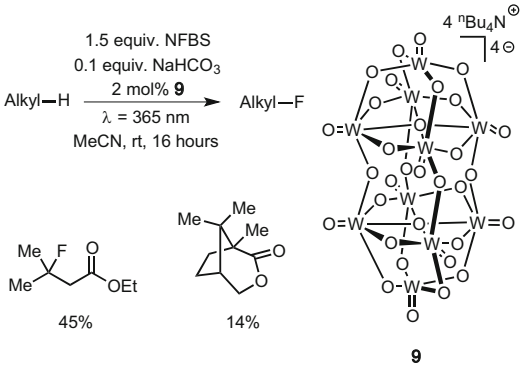



**Fig. 28** Photolytic alkyl C–H fluorination catalyzed by an oxotungstate

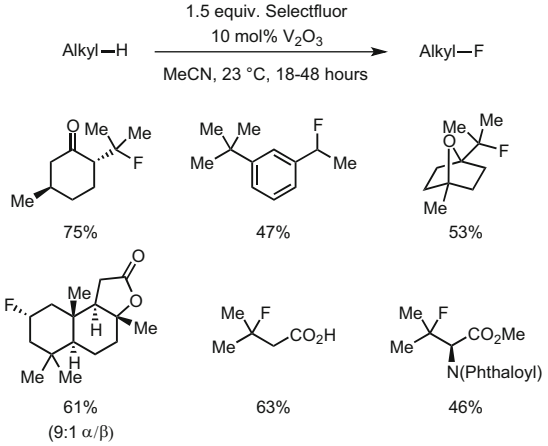



**Fig. 29** Fluorination of alkyl C–H bonds catalyzed by vanadium(III) oxide

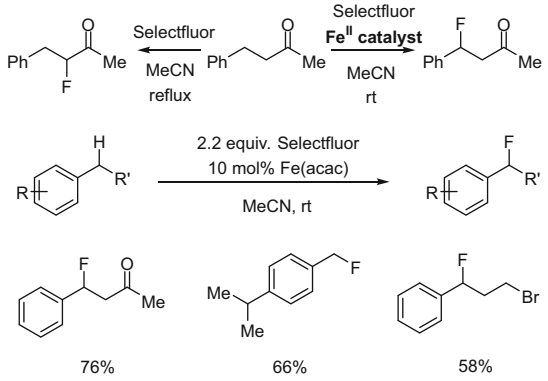



**Fig. 30** Fluorination of benzylic C–H bonds catalyzed by iron

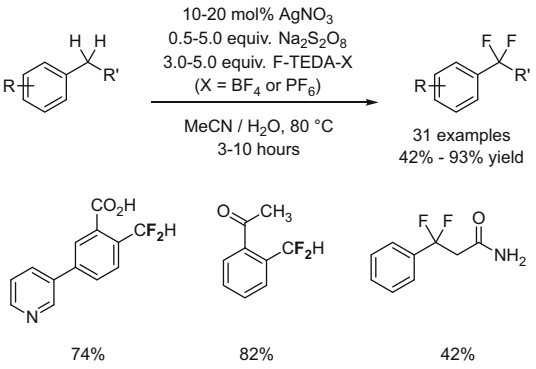



**Fig. 31** Selective difluorination of benzylic methylene groups catalyzed by silver

In 2014, Tang and coworkers reported a silver(I)-catalyzed difluorination of benzylic methylene groups (Fig. 31) [60]. The reaction is inhibited by BHT, TEMPO, and $O_2$, which supports the intermediacy of benzylic radicals. Based upon the precedented oxidation of Ag(I) to Ag(II) in the presence of sodium peroxydisulfate, the authors propose benzylic C–H abstraction by Ag(II), and F atom abstraction from Selectfluor by the benzylic radical thus generated.

## Decarboxylative Fluorination

A strategy for highly selective C($sp^3$)–F bond formation was reported by Li and coworkers in 2012, who applied alkylcarboxylic acids as precursors to alkylfluorides by reaction with Selectfluor in the presence of $AgNO_3$ as catalyst (Fig. 32) [61]. Faster fluorination was observed for more highly substituted carboxylic acids, while benzoic acids were not reactive. The authors propose a mechanism in which Ag(I) is oxidized by Selectfluor, and a high-valent silver complex induces oxidative decarboxylation to generate an alkyl radical. Indeed, a radical trap experiment supported the formation of alkyl radical intermediates. On the basis of inefficient fluorination reactivity of Selectfluor with an independently generated alkyl radical in the absence of silver catalyst, in addition to other mechanistic experiments, the authors propose that the alkyl radical intermediates are fluorinated by a high-valent silver fluoride.

A visible light photoredox approach to catalysis of decarboxylative fluorination was reported by Paquin and coworkers in 2014 (Fig. 33) [62]. The authors show that a ruthenium bipyridine catalyst is oxidized by Selectfluor after absorption of light. They propose that an oxidant in the reaction mixture induces oxidative decarboxylation of carboxylate anion and that the resulting aryloxymethyl radical abstracts F atom from Selectfluor. Aryloxyacetic acid substrates underwent decarboxylative fluorination in high yield (56–92%).

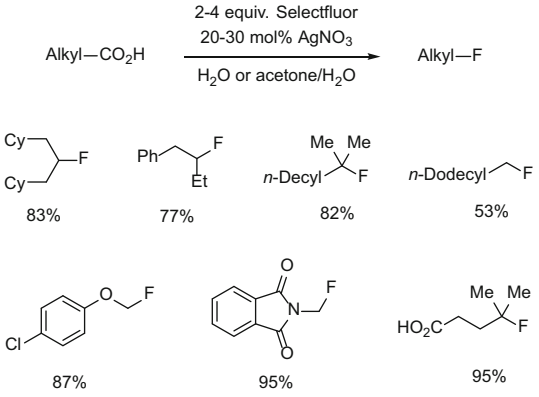



**Fig. 32** Fluorination of carboxylic acids with Selectfluor catalyzed by silver

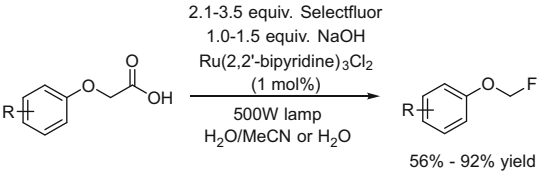



**Fig. 33** Photoredox decarboxylative fluorination of carboxylic acids catalyzed by ruthenium

## Fluorofunctionalization of Alkenes

Alkenes are useful handles for electrophilic fluorination, as a variety of nucleophilic functional groups may be installed adjacent to and concomitantly with C($sp^3$)–F bonds. Additionally, given the rich chemistry of radical addition to alkenes, and well-documented reactivity of alkyl radicals with electrophilic fluorination reagents like Selectfluor, a recent surge in the fruitful combination of these chemistries as described below is expected to continue.

In 2012, Boger reported the iron-mediated hydrofluorination of alkenes with sodium borohydride and Selectfluor (Fig. 34) [63]. Impressively, alkene substrates undergo hydrofluorination faster than the Selectfluor reagent is destroyed by sodium borohydride. Mono-, di-, and trisubstituted alkenes were shown to undergo efficient hydrofluorination with exclusive Markovnikov selectivity. Despite the use of the strongly oxidizing Selectfluor reagent, an unprotected amine was tolerated, as was an electron-rich hydroxyanisole derivative. Deuterofluorination of an achiral cyclic substrate (with $NaBD_4$) was not stereospecific and afforded equal amounts of *syn* and *anti* product, consistent with a radical mechanism (Fig. 35).

In a subsequent report from Shigehisa, Hiroya, and coworkers, Markovnikov hydrofluorination of alkenes was accomplished using a cobalt catalyst bearing a salen-type ligand, with an *N*-fluoropyridinium salt as fluorine source, and a disiloxane as hydrogen source (Fig. 36) [64].

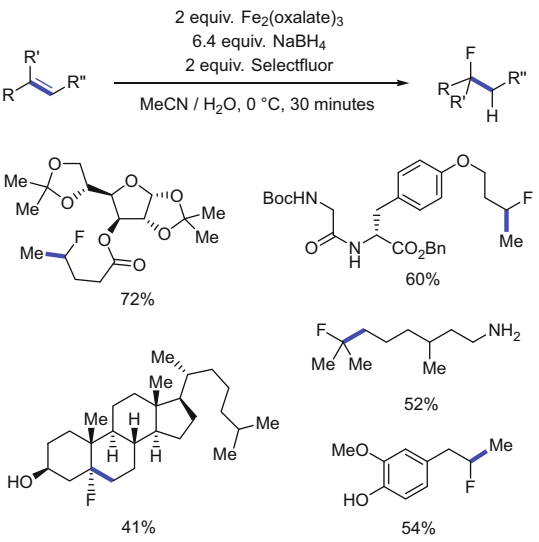



**Fig. 34** Markovnikov hydrofluorination of alkenes mediated by iron

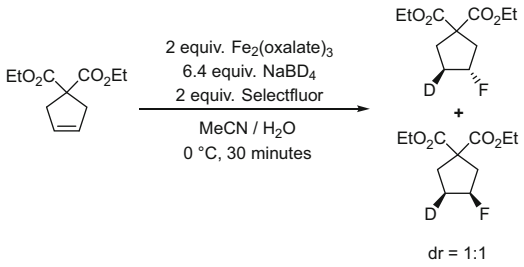



**Fig. 35** Radical intermediates in iron-mediated alkene hydrofluorination are implicated by a mechanistic experiment

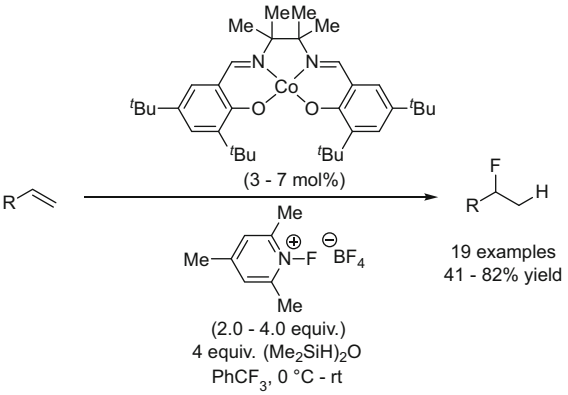



**Fig. 36** Hydrofluorination of alkenes catalyzed by cobalt

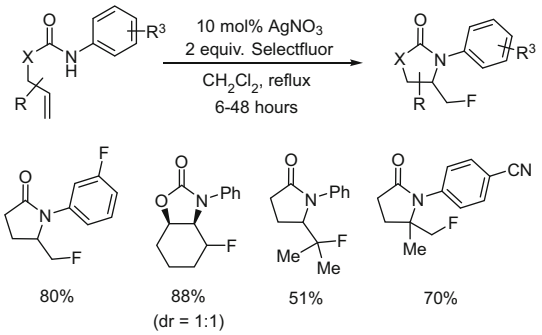



**Fig. 37** Aminofluorination of alkenes catalyzed by silver

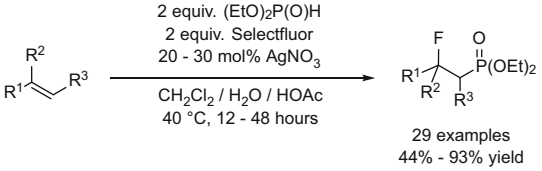



**Fig. 38** Phosphonofluorination of alkenes catalyzed by silver

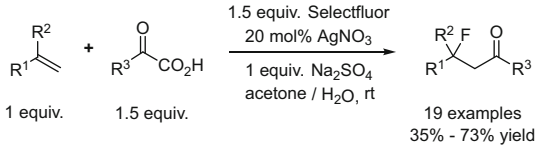



**Fig. 39** Acylfluorination of alkenes catalyzed by silver

Based on reactivity initially honed for decarboxylative fluorination (Fig. 32) [61], Li and coworkers developed a robust aminofluorination of alkenes catalyzed by silver (Fig. 37) [65]. A radical clock substrate underwent rearrangement, which supports the intermediacy of an alkyl radical. The authors propose a mechanism similar to what they proposed for decarboxylative fluorination: reaction of silver (I) with Selectfluor to generate a silver(III) complex that oxidatively generates an *N*-centered radical, which undergoes cyclization with the alkene to generate an alkyl radical that is trapped by Selectfluor. Li further leveraged this strategy to effect the intermolecular phosphonofluorination of alkenes (Fig. 38) [66].

Duan and colleagues reported a combination of reactivity described above (Fig. 39) [67] and proposed that silver acts as a catalyst for oxidative decarboxylation to afford a radical that undergoes reaction with an alkene. The radical generated by addition to the alkene would then undergo C($sp^3$)–F bond formation by reaction with Selectfluor.

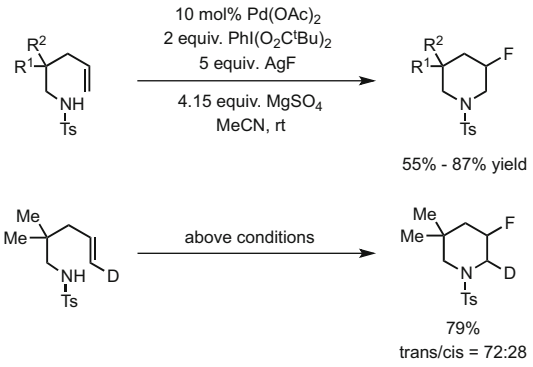



**Fig. 40** Oxidative aminofluorination of alkenes catalyzed by palladium

## *2.3 Oxidative Fluorination with Fluoride*

Fluorine is the most oxidizing element, and as a result the majority of other electrophilic fluorinating reagents are ultimately derived from fluorine gas [68]. Therefore, it is conceptually challenging to design an electrophilic fluorination reaction that utilizes fluoride anion and a separate oxidant. Despite the challenge, several groups have reported oxidative fluorination reactions using fluoride.

An early example of oxidative fluorination with fluoride was reported by Liu and coworkers in 2009 [69]. Treatment of *N*-tosylamino alkenes with an iodine(III) oxidant in the presence of AgF and a palladium catalyst afforded cyclization products arising from formal electrophilic fluorination of the alkene (Fig. 40). In contrast, conventional electrophilic fluorination reagents such as Selectfluor, an *N*-fluoropyridinium salt and NFBS did not promote the reaction. Cyclization of a deuterium-labeled substrate revealed a surprising stereochemical outcome consistent with simultaneous operation of competing retentive and invertive $C(sp^3)$–F bond formation processes (assuming that aminopalladation occurs stereospecifically). This outcome is similar to that of the Gagné study on the effect of carboxylate ions on $C(sp^3)$–F reductive elimination from Pt(IV) (Fig. 22) [48]. In this case, pivalate anions are present, and their coordination to a putative Pd(IV) intermediate may impede concerted $C(sp^3)$–F reductive elimination, resulting in competitive invertive $S_N2$ $C(sp^3)$–F bond formation.

Sanford and coworkers reported a modified protocol for directed benzylic C–H fluorination that utilizes AgF and an iodine(III) oxidant (Fig. 41) [70]. The modified protocol with AgF as fluoride source proceeded at 60°C, as opposed to the 100–110°C microwave irradiation required for efficient fluorination with an electrophilic fluorination reagent (see Sect. 2.2.1, Fig. 15).

In a 2014 study, Xu and coworkers reported another example of oxidative fluorination of an alkene with fluoride (Fig. 42) [71]. The combination of an iron (II) precatalyst with a bidentate nitrogenous ligand efficiently promoted intramolecular cyclization of the substrates with concomitant $C(sp^3)$–F bond formation,

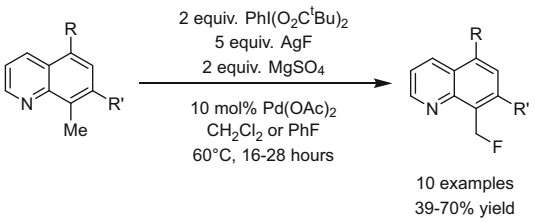



**Fig. 41** Oxidative fluorination of benzylic C–H bonds catalyzed by palladium

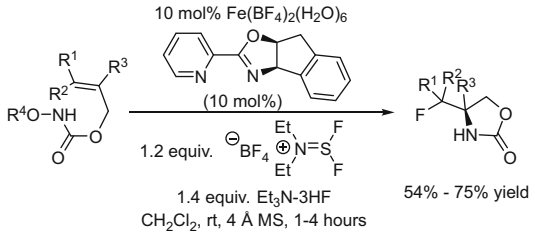



**Fig. 42** Oxidative aminofluorination of alkenes catalyzed by iron

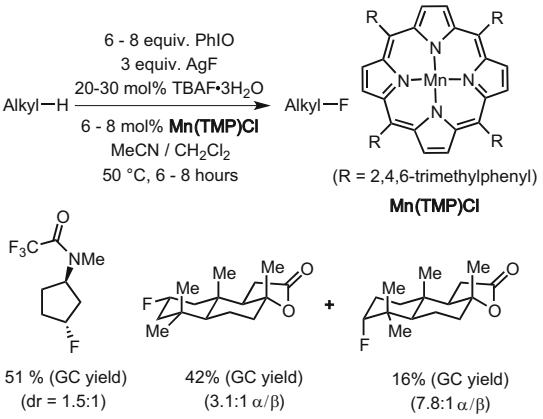



**Fig. 43** Oxidative fluorination alkyl C–H bonds catalyzed by manganese

which is proposed to occur by a mechanism involving transfer of an F atom from high-valent iron to an alkyl radical.

In 2012, Groves and coworkers reported the first fluorination of C($sp^3$)–H bonds with a nucleophilic fluoride source under oxidative conditions, with catalysis by a manganese porphyrin complex (Fig. 43) [72]. The selectivity of C–H fluorination is influenced by subtle electronic effects and favors fluorination distal to electron-withdrawing groups. The synthesis from AgF of Mn(TMP)$F_2$, a reagent that can serve as a formal source of fluorine radical for the fluorination of an alkyl radical, was also reported. A catalytic cycle was proposed in which a Mn(V) oxo abstracts hydrogen atom from a C–H bond that approaches from a suitable trajectory influenced by the steric environment of the porphyrin ligand and the

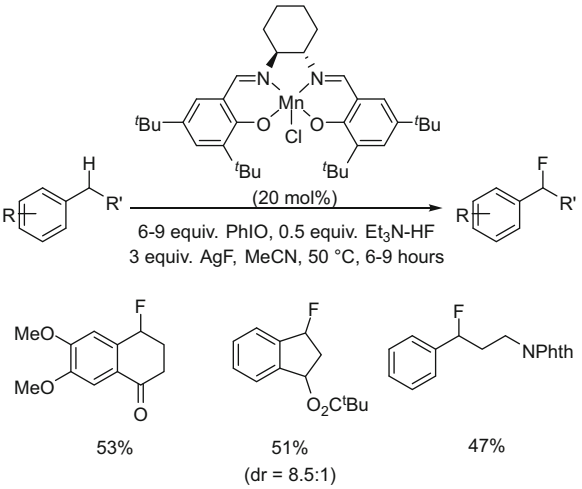



**Fig. 44** Oxidative fluorination of benzylic C–H bonds catalyzed by manganese

stereoelectronic nature of the oxo ligand. Metathesis of the anionic ligands at Mn with fluoride from AgF would generate a Mn(F) species that, in line with the reactivity observed for $Mn(TMP)F_2$, could capture an alkyl radical (generated by C–H cleavage). A radical clock experiment with norcarane indicated the formation of an alkyl radical intermediate.

Similar to C–H fluorination with electrophilic fluorinating reagents and one-electron redox mediators (see Sect. "Fluorination of C–H Bonds"), selectivity in the Groves system can be limited due to fluorination at multiple methylene sites in cases where electronic and steric differentiation is not sufficient. Also, favorable selectivity is observed for benzylic C–H fluorination. Groves reported that selective monofluorination of benzylic methylene C–H bonds is observed in the presence of other methylene groups, when they are adjacent to inductively withdrawing substituents (Fig. 44) [73]. A manganese complex with salen-type ligand was a competent precatalyst in place of the previously reported Mn(TMP)Cl complex.

In 2014, the Groves and Hooker groups reported the application of manganese-mediated benzylic C–H fluorination chemistry to labeling with [$^{18}$F]fluoride (Fig. 45) [74]. High radiochemical yields of C–H fluorination were described, for complex molecules with diverse functional groups, in fast reaction times (10 min). An elegant approach to separation of water from [$^{18}$F]fluoride was reported, based on previous work by Doyle, Kung, and coworkers who showed that [$^{18}$F]fluoride immobilized on an ion exchange cartridge can be captured and eluted by reaction with a cobalt(III) tosylate reagent in methanol solvent [37]. Likewise, Groves and coworkers employed a manganese(III) tosylate reagent, as a solution in acetone, to capture and elute [$^{18}$F]fluoride from the ion exchange cartridge, thereby avoiding time-intensive azeotropic drying procedures typically required for chemistry with [$^{18}$F]fluoride.

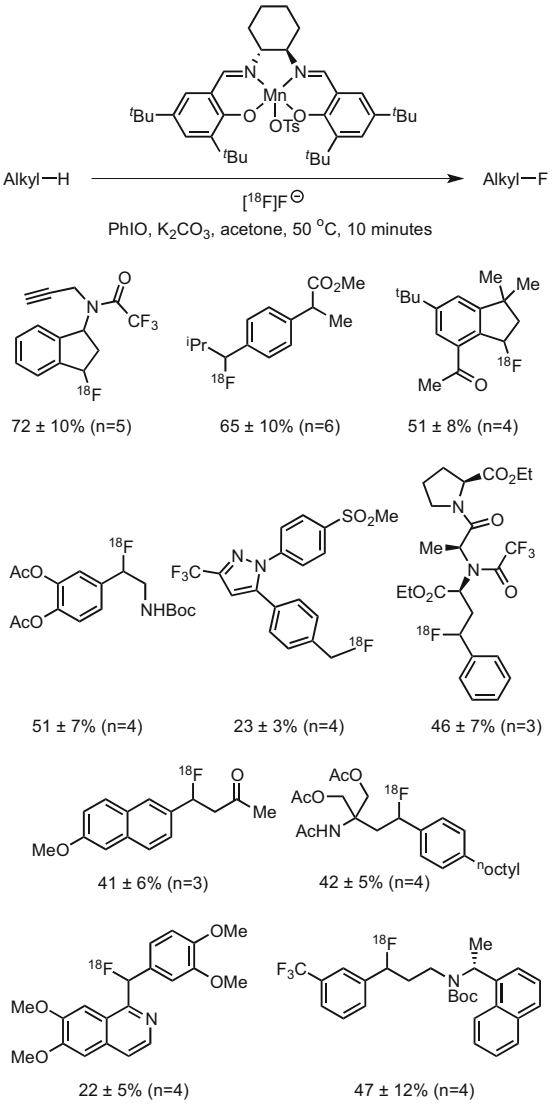



**Fig. 45** Fluorination of benzylic C–H bonds with [$^{18}$F]fluoride mediated by manganese

In a mechanistic study on the electrophilic fluorination reactivity of a palladium (IV) fluoride complex **11** derived from nucleophilic fluoride, Ritter and coworkers reported electrophilic fluorination reactions including the fluorination of silyl enol ethers, enamines, and an allylic/benzylic C–H bond with **11** as electrophilic fluorination reagent (Fig. 46) [75].

In 2013, Doyle reported an oxidative fluorination of allylic C–H bonds. Through the leverage of an approach developed by the group of White [68, 76, 77], allylic C–H bonds were activated under catalysis by palladium(II) (Fig. 47) [78]. Benzoquinone was used as oxidant in the presence of a chromium(III) complex known to enhance this

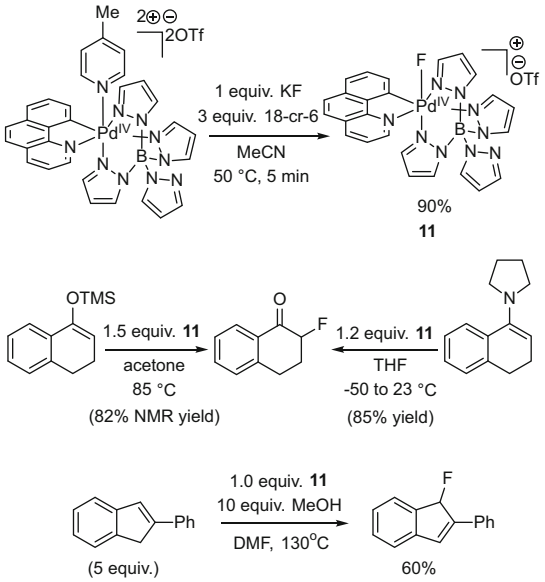



**Fig. 46** Synthesis of alkyl fluorides by oxidative fluorination with a fluoride-derived palladium (IV) fluoride

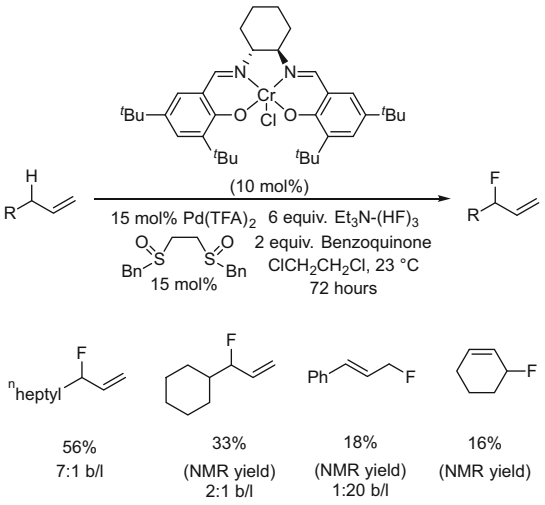



**Fig. 47** Oxidative fluorination of allylic C–H bonds catalyzed by palladium and chromium

oxidant's reactivity in oxidative allylic functionalization reactions. Doyle found that $Et_3N$-$(HF)_3$ was an effective source of nucleophilic fluoride and accomplished the synthesis of a number of allylic fluorides in moderate yield and regioselectivity.

# 3 C($sp^2$)–F Bond Formation

## *3.1 Nucleophilic Arene Fluorination*

The synthesis of fluoroarenes on industrial scale is commonly performed using traditional nucleophilic arene fluorination reactions that were developed in the early twentieth century, such as the halogen exchange ("Halex") process [79–81]. Halex reactions are only effective for electron-poor aryl halides, however, and typically require the use of forcing conditions (>200°C) and anhydrous fluoride salts. These limitations restrict the substrate scope to relatively simple arenes; additionally, the use of anhydrous fluoride salts can result in problematic side reactions due to the strong basicity of anhydrous fluoride [79, 80, 82]. The harsh conditions required for Halex-type fluorination reactions represent a significant kinetic barrier to C–F bond formation [83], but the nucleophilic fluorination of aryl halides is a thermodynamically favorable process [12]. Therefore, nucleophilic arene fluorination can conceptually be addressed by catalysis, and the search for suitable transition metal catalysts has been an area of highly active research in recent years. Metal-catalyzed nucleophilic arene fluorination can proceed through a mechanism analogous to a typical C–X cross-coupling reaction [3, 84–87], and a general catalysis cycle is shown in Fig. 48.

In large part due to the success of palladium-catalyzed arene cross-coupling reactions between carbon and a wide variety of other atoms – in particular B [88, 89], C [84, 90], N [91–94], and O [95, 96] – Pd-mediated and Pd-catalyzed arene fluorination has been targeted as a promising approach. Early work in this field was primarily led by Grushin, who began exploring the synthesis and reactivity of the first mononuclear arylpalladium (II) fluoride complexes (Fig. 49) [97–99]. It was quickly discovered, however, that such complexes did not undergo the desired C–F reductive elimination under any conditions investigated [3, 100]. Rather it was found that the phosphine ligands took part in competing side reactions such as P–F

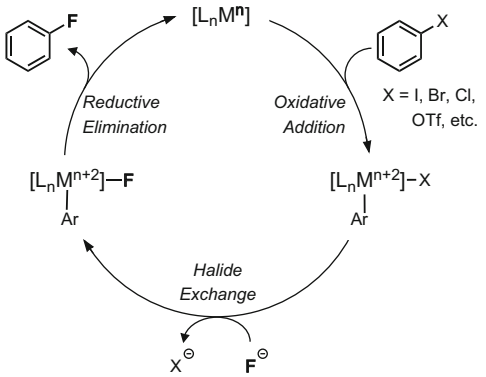



**Fig. 48** General catalysis cycle for transition metal-catalyzed nucleophilic arene fluorination

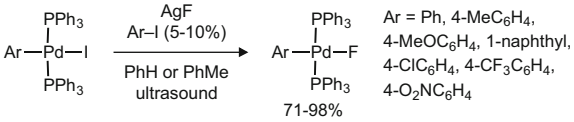



**Fig. 49** Synthesis of the first molecular arylpalladium(II) fluoride complexes, which do not undergo C–F reductive elimination

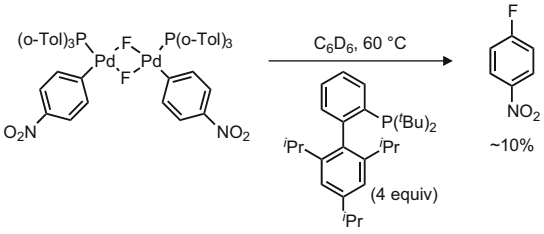



**Fig. 50** The first reported aryl C–F bond formation from an arylpalladium(II) fluoride complex

bond formation, giving $Ph_3PF_2$ among other side products. Early attempts at synthesis and C–F bond formation from phosphine-free arylpalladium(II) fluoride complexes were also reported to be unsuccessful [3, 82]. The possibility of C–F reductive elimination was also investigated from Rh(I) fluoride complexes, and the synthesis of $(Ph_3P)_3RhF$, the fluoro-analogue of Wilkinson's catalyst, was reported [101]. However, as for the early arylpalladium(II) fluoride complexes, $(Ph_3P)_3RhF$ was observed to undergo competitive side reactions involving P–F bond formation, via metallophosphorane intermediates [102].

A promising early result, reported by Yandulov, demonstrated C–F bond formation from an arylpalladium(II) fluoride dimer in the presence of the bulky monodentate phosphine ligand *t*Bu-XPhos (Fig. 50) [103]. Use of the *t*Bu-XPhos ligand is intended to promote C–F reductive elimination from a mononuclear, three-coordinate, "T"-shaped palladium complex [103]. However, a C–F reductive elimination mechanism for aryl fluoride formation was not rigorously established, and a $S_NAr$ pathway is also feasible [104].

A breakthrough in nucleophilic arene fluorination was reported by the Buchwald group in 2009, in which the Pd-catalyzed nucleophilic fluorination of aryl triflates was accomplished using the *t*Bu-BrettPhos ligand (Fig. 51) [105, 106]. The fluorination of aryl triflates displays a broad substrate scope and tolerates nucleophilic functional groups not often tolerated in electrophilic fluorination reactions because of competing side reactions (*vide infra*). Reduction of the aryl triflate substrates to form C–H (rather than C–F) bonds was sometimes observed as an undesired minor side reaction; separation of fluoroarenes from reduced arene side products is typically challenging using standard chromatographic methods [107]. Protic functional groups are not tolerated due to the strongly basic anhydrous fluoride used.

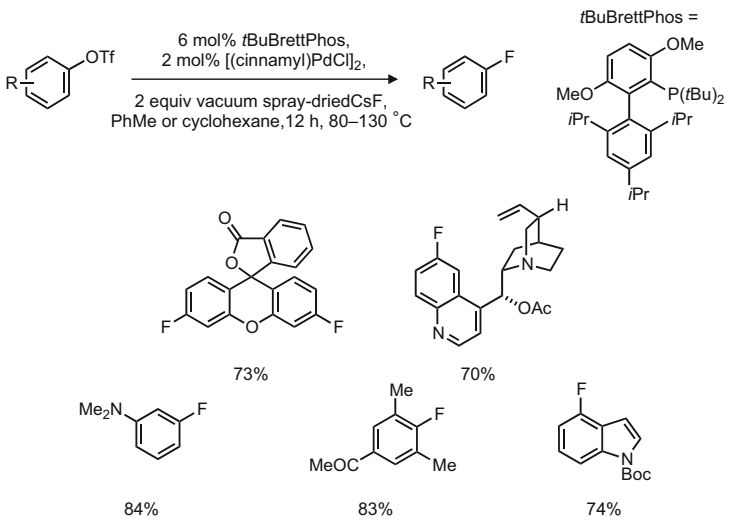



**Fig. 51** The first reported Pd-catalyzed nucleophilic arene fluorination, using aryl triflates

Furthermore, the strongly basic reaction conditions result in the formation of a mixture of aryl fluoride constitutional isomers for some substrates, potentially via aryne intermediates [82]. In many cases, however, the formation of constitutional isomer side products could be controlled through changing the reaction solvent from toluene to cyclohexane.

In the course of mechanistic investigations of Pd-catalyzed (pseudo)halide fluorination, it was observed that the active palladium catalyst in the fluorination reaction contained a ligand that was modified from the originally used *t*Bu-BrettPhos ligand [108]. A side reaction was discovered in which C–H arylation of *t*Bu-BrettPhos by the aryl halide substrate occurred, and the product of this reaction was a competent fluorination catalyst. Reactivity studies showed that the arylpalladium(II) fluoride complex featuring the arylated phosphine ligand underwent C–F reductive elimination under conditions relevant to catalysis, which was not true for the analogous complex featuring the unmodified *t*Bu-BrettPhos ligand (Fig. 52).

Subsequently, the Buchwald group has reported the development of an improved Pd catalyst system that allows for efficient nucleophilic fluorination of (hetero)aryl bromides (Fig. 53) [109, 110]. The new Pd(0) pre-catalyst features a monodentate triarylphosphine ligand, derived from arylation of adamantyl–BrettPhos, and 1,5-cyclooctadiene (COD) as a stabilizing "dummy" ligand. The improved reaction conditions provide better suppression of reduced arene side products, which make isolation of the aryl fluoride products easier. However, formation of aryl fluoride constitutional isomers is still observed for some substrates, such as 3-bromopyridine.

Along with palladium, copper-based catalysts have shown the most promise in recent years as catalysts for nucleophilic arene fluorination. The viability of an oxidative addition/reductive elimination sequence for fluorination of aryl halides

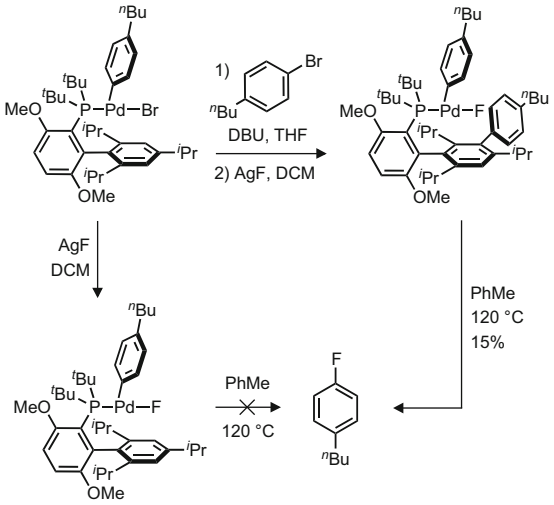



**Fig. 52** Evidence for in situ ligand modification during Pd-catalyzed fluorination of aryl (pseudo) halides

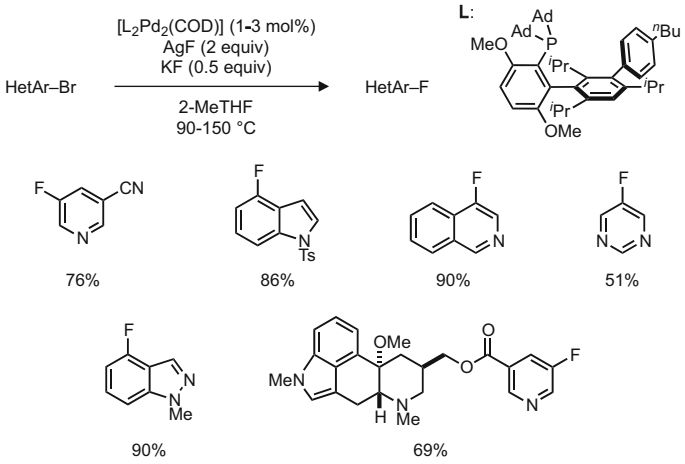



**Fig. 53** Pd-catalyzed nucleophilic fluorination of heterocyclic aryl bromides

via a Cu(I)/Cu(III) cycle was established by the Ribas group, using a designed macrocyclic substrate that allowed for isolation of key Cu(III) intermediates (Fig. 54) [111]. Halide exchange took place at an arylcopper(III) halide complex, followed by C–F reductive elimination from Cu(III).

A more general copper-mediated fluorination of aryl iodides was reported by Hartwig, using 3 equiv. of a Cu(I) complex and AgF (Fig. 55) [112]. The reaction is effective for electron-rich and electron-poor arenes as well as sterically hindered

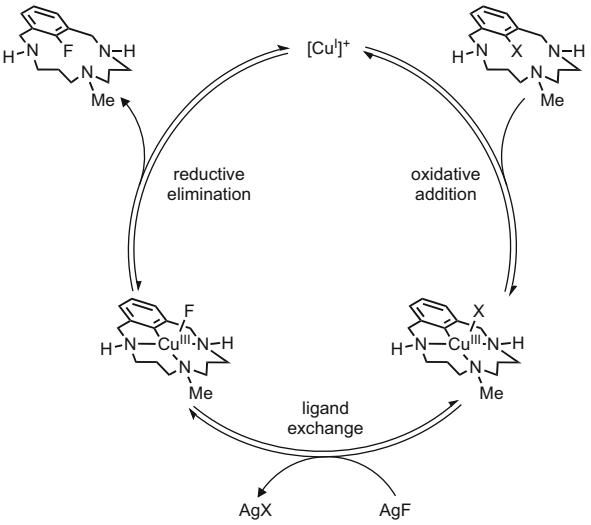



**Fig. 54** A Cu(I)/Cu(III) cycle for nucleophilic arene fluorination via halide exchange

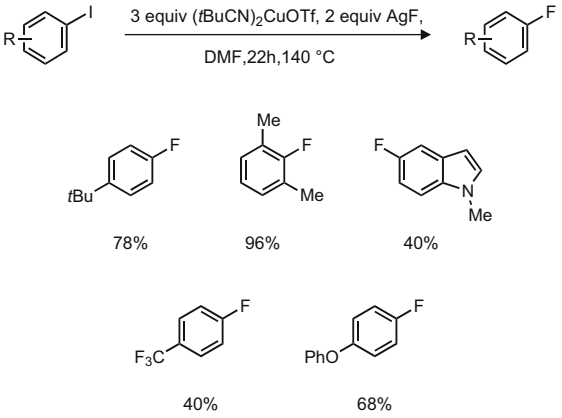



**Fig. 55** Cu-mediated fluorination of aryl iodides with AgF

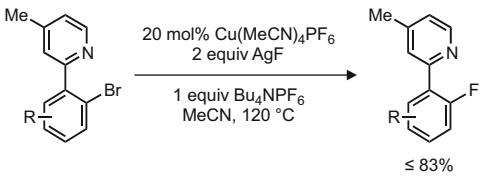



**Fig. 56** Cu-catalyzed fluorination of 2-pyridyl aryl bromides

substrates, but the formation of hydrodehalogenated side products renders purification of the aryl fluoride products challenging. Substoichiometric amounts of Cu (I) can be used for aryl bromide fluorination with AgF, but coordinating directing groups such as pyridine are required (Fig. 56) [113].

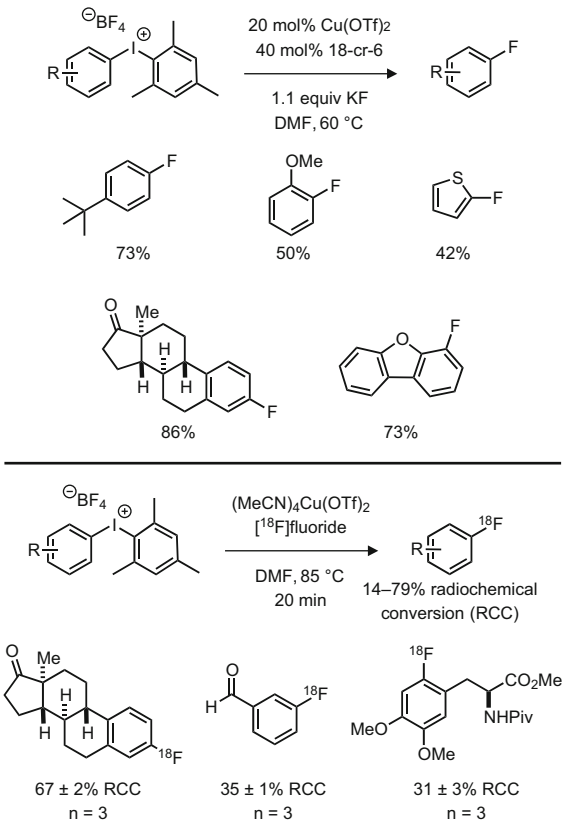



**Fig. 57** Cu-catalyzed nucleophilic fluorination of unsymmetrical diaryliodonium salts (*top*), and translation to arene radiofluorination with [$^{18}$F] fluoride (*bottom*)

Copper catalysis has also been used for a $S_NAr$-type nucleophilic fluorination of diaryliodonium salts. Nucleophilic fluorination of diaryliodonium salts has been known since the early 1980s [114]; however, the necessity of a symmetric diaryliodonium salt (to prevent formation of a mixture of different aryl fluorides) presented a synthetic challenge when targeting functionalized aryl fluorides. In 2013 Sanford reported a Cu-catalyzed fluorination of unsymmetrical diaryliodonium salts at 60 °C using KF (Fig. 57, top) [115]. It was found that fluorination of the less sterically hindered arene was preferred, allowing for use of a bulky mesityl group as an "innocent" aryl group on iodine(III). Based on DFT calculations, a Cu(I)/Cu(III) cycle was proposed for catalysis. Sanford and Scott subsequently demonstrated that this method was applicable to selective arene radiofluorination with [$^{18}$F]fluoride, allowing access to protected versions of the PET tracers 4-[$^{18}$F]fluorophenylalanine and 6-[$^{18}$F]fluoro-L-DOPA (Fig. 57, bottom) [116]. A remaining drawback is the need for preparation of the diaryliodonium substrates, as compared to more readily available aryl halides and pseudohalides.

## 3.2 *Electrophilic Arene Fluorination*

A complimentary approach toward arene fluorination is to use aryl nucleophiles and an electrophilic fluorinating reagent. Potential benefits of electrophilic fluorination are that problematic side reactions caused by the strong basicity of nucleophilic fluoride may be avoided, and substrates bearing protic functional groups may be tolerated. Drawbacks include the use of aryl–metal substrates that are less readily available than aryl (pseudo)halides, the potential for side reactions between electrophilic fluorinating reagents and nucleophilic functional groups such as amines, and the high cost and poor atom economy of most electrophilic fluorinating reagents.

While direct electrophilic fluorination of a variety of aryl nucleophiles has been reported—including aryl boron [117, 118], germanium [119], lead [120–122], mercury [123–126], silicon [127–132], and tin [119, 120, 123, 133–138] reagents—the substrate scope is typically limited and unselective fluorination is often observed. The use of a transition metal catalyst or mediator can enable more selective arene fluorination, using milder conditions and less reactive electrophilic fluorinating reagents such as Selectfluor (F-TEDA-$BF_4$) [83, 139], *N*-fluorobenzenesulfonimide (NFBS) [12, 140–144], and *N*-fluoropyridinium salts [3, 84–87, 145–150]. Additionally, transition metal-mediated or metal-catalyzed electrophilic arene fluorination can occur through a range of mechanisms, including one- and two-electron pathways. This mechanistic diversity has been useful in the development of modern fluorination reactions.

### 3.2.1 Reactions Proposed to Proceed via Two-Electron Pathways

As for nucleophilic arene fluorination, electrophilic arene fluorination can be addressed via a transition metal cross-coupling approach, and a general catalysis cycle is shown in Fig. 58. We note, however, that transmetallation of the arene

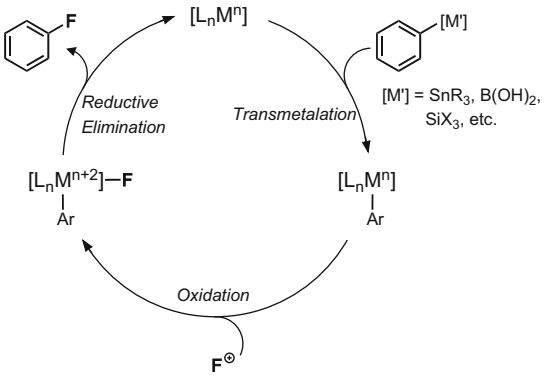



**Fig. 58** General catalysis cycle for metal-catalyzed electrophilic arene fluorination

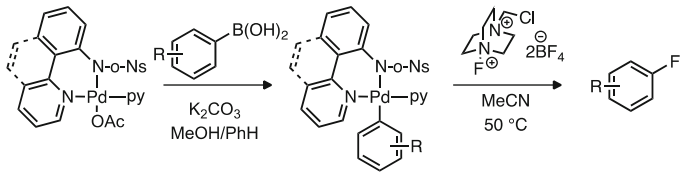



**Fig. 59** Pd-mediated fluorination of arylboronic acids

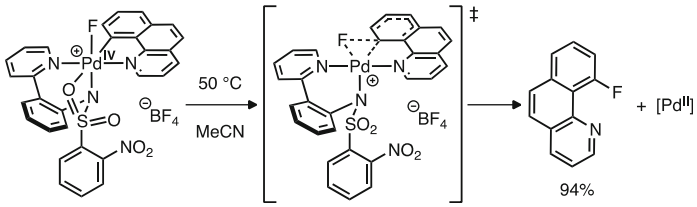



**Fig. 60** The first reported concerted C–F reductive elimination, from a Pd(IV) fluoride complex

substrate to the transition metal catalyst can potentially occur at either a low- or high-valent metal center (before or after the oxidation step), and examples of both have been reported.

The use of palladium as a mediator or catalyst for electrophilic fluorination has been widely explored; additionally, the viability of multiple mechanisms for electrophilic arene fluorination from palladium has been demonstrated (*vide infra*, Sect. 3.2.2). In 2008, the Ritter group reported a regioselective fluorination of arylboronic acids using Selectfluor and a stoichiometric palladium complex (Fig. 59) [88, 89, 151]. The two-step reaction sequence proceeded by transmetallation of the arene substrate from boron to palladium, followed by oxidation to afford the aryl fluoride product. Experimental and computational investigations supported a concerted C–F reductive elimination mechanism, in which dissociation of one oxygen atom of the tridentate pyridyl-sulfonamide ligand gives a five-coordinate Pd(IV) complex that readily undergoes C–F reductive elimination (Fig. 60) [1, 84, 90, 152]. While this work established the viability of arene fluorination via high-valent palladium complexes, stoichiometric amounts of palladium are needed. The incompatibility of reaction conditions for the transmetallation and fluorination steps prevented the application of this reactivity to a Pd-catalyzed fluorination reaction; however, the Pd-mediated reaction has successfully been applied to the synthesis of $^{18}$F-labeled arenes for radiotracer synthesis, in which Selectfluor is replaced by an [$^{18}$F]Pd(IV)–fluoride electrophilic fluorinating reagent derived from [$^{18}$F]fluoride (Fig. 61) [75, 153, 154].

The Sanford group has also reported the isolation and reactivity of an arylpalladium(IV) fluoride complex, synthesized by oxidation of an arylpalladium (II) fluoride complex with $XeF_2$ (Fig. 62) [3, 100, 155]. Interestingly, the Pd (IV) fluoride complex did not undergo C–F reductive elimination upon heating,

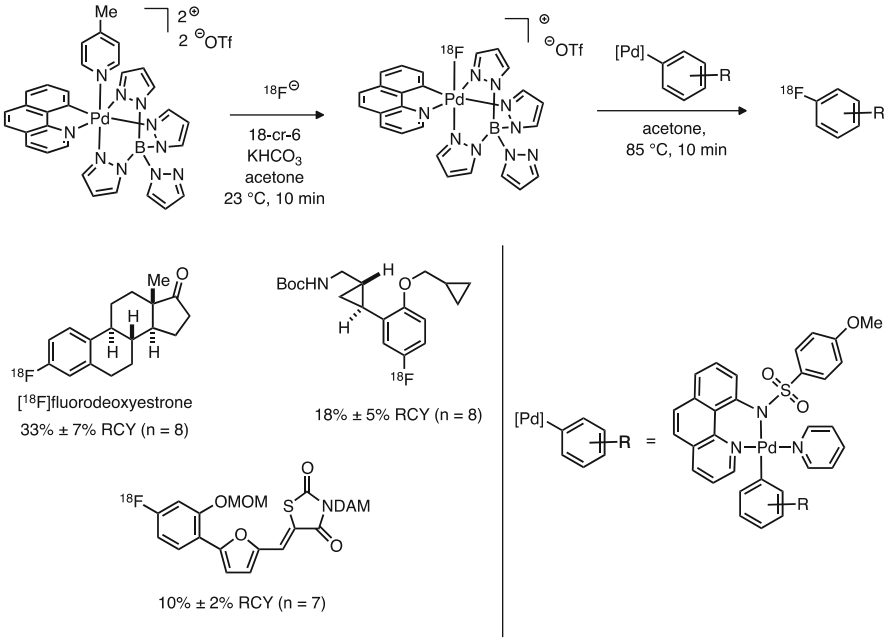



**Fig. 61** Palladium-mediated radiofluorination using a [$^{18}$F]Pd(IV)-fluoride electrophilic fluorinating reagent (*RCY* radiochemical yield)

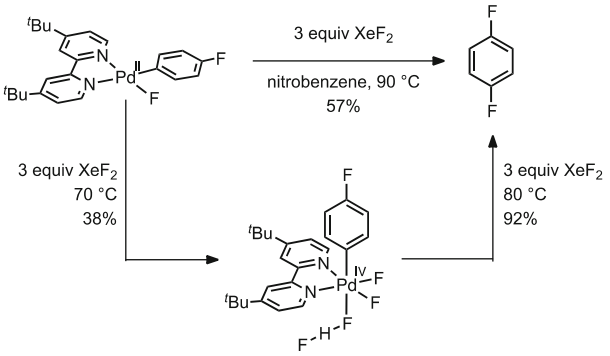



**Fig. 62** Oxidatively induced C–F bond formation from a Pd(IV) bifluoride complex

and the aryl fluoride product was only formed when the Pd(IV) complex was treated with an additional excess of $XeF_2$. Therefore the mechanism of C–F bond formation in this case is unclear, and both electrophilic C–Pd bond cleavage and C–F reductive elimination are feasible. The presence of multiple fluoride ligands may contribute to the stability of the Pd(IV) fluoride complex: similarly, the arylpalladium(IV) monofluoride complex shown in Fig. 60 was observed to be less thermally stable toward C–F reductive elimination than a related arylpalladium

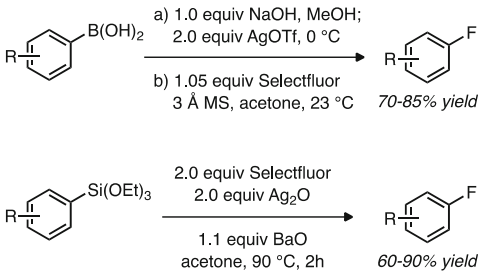



**Fig. 63** Ag-mediated fluorination of arylboronic acids and aryl silanes

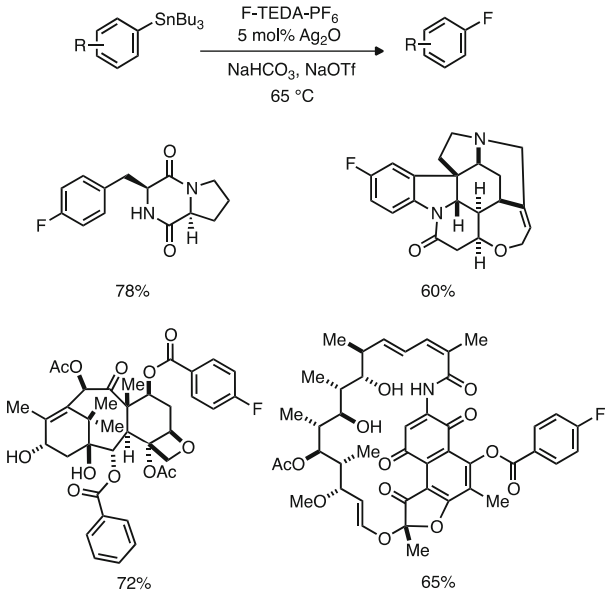



**Fig. 64** Ag-catalyzed fluorination of functionalized aryl stannanes

(IV) difluoride complex [1, 3, 82]. These observations may reflect the need for ligand dissociation to form a five-coordinate Pd(IV) complex prior to C–F reductive elimination, which is unfavorable for anionic fluoride ligands that form strong bonds to palladium.

Silver-mediated fluorination was first investigated by Tius, using $XeF_2$ [101, 138, 156, 157]. More recently, silver-mediated fluorination of arylboronic acids [102, 158], aryl silanes [103, 159], and aryl stannanes [104, 160] has been reported using Selectfluor (Fig. 63). Further development resulted in a silver-catalyzed fluorination of aryl stannanes, using F-TEDA-$PF_6$ (Fig. 64) [103, 161]. While the silver-catalyzed reaction requires the preparation and use of toxic aryl stannanes, this method displays the broadest substrate scope and functional group tolerance in

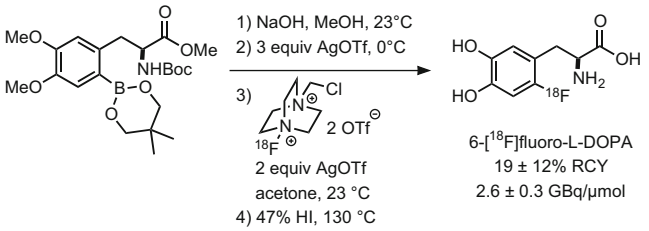



**Fig. 65** Ag-mediated synthesis of 6-[$^{18}$F]fluoro-L-DOPA using [$^{18}$F]Selectfluor bis(triflate)

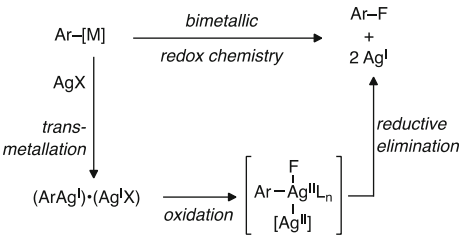



**Fig. 66** Proposed bimetallic mechanism for Ag-mediated and Ag-catalyzed electrophilic fluorination ([M]=$SnBu_3$, $B(OH)_2$, $Si(OEt)_3$)

the field so far, including nitrogenous heteroaryl nucleophiles; nucleophiles containing electron-rich, electron-poor, electrophilic, and protic functional groups; as well as complex natural product-derived substrates. Silver-mediated fluorination has also been used in radiofluorination for PET tracer synthesis: Gouverneur and coworkers have reported a synthesis of 6-[$^{18}$F]fluoro-L-DOPA via the silver-mediated electrophilic fluorination of the corresponding arylboronic ester, using [$^{18}$F]Selectfluor bis(triflate) (Fig. 65) [162, 163].

The silver-mediated and silver-catalyzed arene fluorination reactions are proposed to proceed via the intermediacy of high-valent, multinuclear arylsilver complexes (Fig. 66) [109, 110, 160, 161]. Fluorination of isolated mononuclear arylsilver complexes was found to proceed in lower yield than when an additional equivalent of AgOTf was added. Redox synergy of the multiple metal centers may help to lower the typically high kinetic barrier to C–F reductive elimination [111, 164, 165], allowing the fluorination of aryl stannanes and boronic acids with silver to occur at temperatures as low as 23°C.

In 2013, Hartwig and Sanford independently developed a copper-mediated electrophilic fluorination of arylboronic acid derivatives using an *N*-fluoropyridinium oxidant (Fig. 67, top), and Sanford also reported a related fluorination of aryl stannanes (Fig. 67, bottom) [112, 166, 167]. The copper-mediated fluorination reactions are effective for arenes bearing both electron-donating and electron-withdrawing substituents, as well as some heterocyclic substrates. However, superstoichiometric amounts of both transition metal and oxidant are required, and significant amounts of side products resulting from protodemetallation were

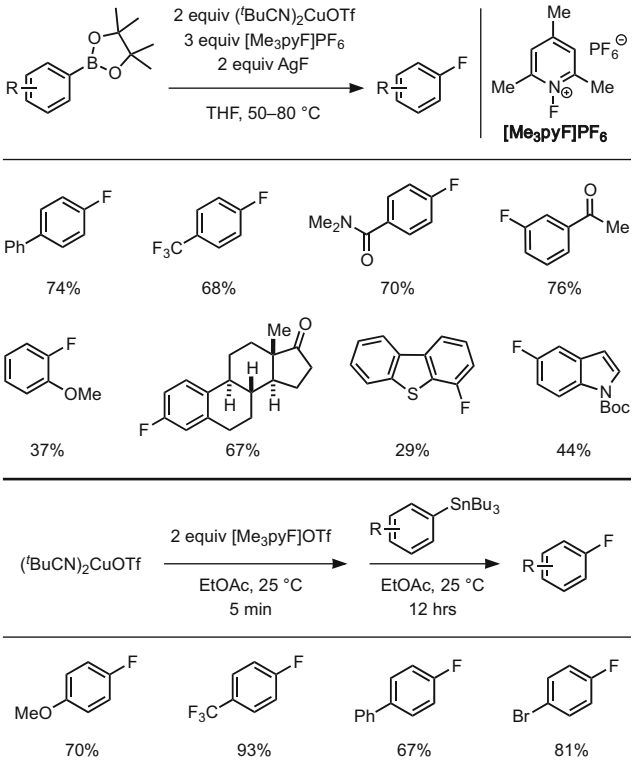



**Fig. 67** Cu-mediated fluorination of arylboronic acid derivatives and aryl stannes

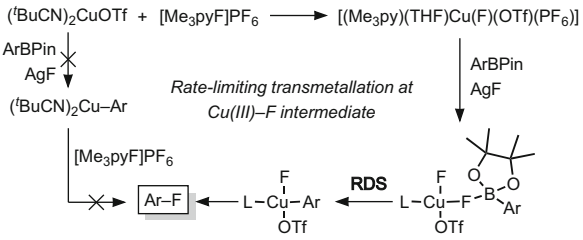



**Fig. 68** Proposed mechanism for Cu-mediated fluorination of arylboronic acid derivatives, involving arene transmetallation at Cu(III) (*RDS* rate-determining step)

observed. Isotopic labeling studies suggested that, in the case of arylboronic acid derivatives, protodemetallation is primarily caused by adventitious water [113, 166].

In the copper-mediated fluorination of pinacol boronic esters, mechanistic studies suggested that the reaction proceeds via oxidation of Cu(I) to a Cu(III) fluoride complex, followed by rate-limiting transmetallation of the arene from boron to Cu (III) (Fig. 68) [114, 166]. The putative Cu(III) fluoride complex was characterized

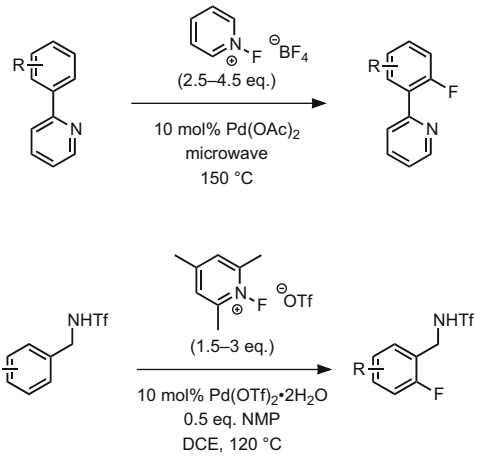



**Fig. 69** Pd-catalyzed C–H fluorination for arene substrates containing coordinating directing groups

by $^{19}$F NMR spectroscopy and was observed to undergo reaction with pinacol boronic esters only in the presence of AgF. Transmetallation was not observed to occur at Cu(I), and an independently prepared arylcopper(I) complex did not produce the aryl fluoride product upon reaction with the *N*-fluoropyridinium oxidant. The copper-mediated fluorination reaction is therefore distinct from the reported palladium- and silver-mediated electrophilic fluorination reactions, in that arene transmetallation occurs at the high-valent state of the metal mediator.

Currently, the development of functional group tolerant, direct conversion of arene C–H bonds to the corresponding C–F bonds with predictable regioselectivity is a frontier in the field of fluorination. Fluorination of arene C–H bonds with redox-active transition metal catalysts can potentially proceed via direct C–H metalation, followed by oxidation of the metal center with an electrophilic fluorinating reagent. Depending on the reaction conditions, oxidation can result in the formation of a monometallic high-valent intermediate [115, 168, 169] or a high-valent multimetallic complex [117, 118, 165, 170].

In 2006, the Sanford group reported that arene substrates bearing coordinating directing groups, such as 2-phenylpyridine, can undergo Pd-catalyzed C–H fluorination using an *N*-fluoropyridinium reagent (Fig. 69, top) [43, 119]. The Yu group subsequently reported a C–H fluorination of *N*-benzyltriflamide derivatives (Fig. 69, bottom) [120–122, 171]. These Pd-catalyzed fluorination reactions were the first examples of transition-metal-catalyzed aromatic fluorination. Double fluorination through two subsequent *ortho* fluorinations is a problematic side reaction for the reactions shown in Fig. 69: this problem can be addressed by using the weakly coordinating anionic *ortho*-directing group *N*-perfluorotolylamide, which allows for rapid displacement of the monofluorinated product by the substrate, thus affording high selectivity for monofluorination [123–126, 172]. A handful of related Pd-catalyzed electrophilic C–H fluorination reactions have since been reported, for arene substrates with a variety of coordinating directing groups [173–175]. While direct C–H fluorination is desirable, the necessity of coordinating

groups currently limits the scope of the substrates that can be fluorinated; a general selective C–H fluorination of arenes that do not bear coordinating directing groups has not yet been reported.

### 3.2.2 Reactions Proposed to Proceed via One-Electron Pathways

The C–H fluorination of pyridines and diazines with $AgF_2$ was reported by the Hartwig group (Fig. 70) [119, 120, 123, 133–138, 176]. The reaction proceeds at room temperature in 1 h and affords 2-fluoropyridines with high selectivity. Electron-donating and electron-withdrawing groups are tolerated, along with carbonyl-containing functional groups and base-sensitive functional groups such as alkyl tosylates; unprotected alcohols and amines are not tolerated. A mechanism analogous to amination of pyridines with $NaNH_2$ (the Chichibabin reaction) was proposed, in which nitrogen coordination of the pyridine substrate to $AgF_2$ is followed by F• transfer and subsequent H-atom abstraction by a second equivalent of $AgF_2$ to afford the 2-fluoropyridine product and 2 equiv. of AgF. The silver-mediated reaction was used to prepare a variety of fluorinated derivatives of medicinally relevant compounds, including fluoro-pioglitazone and a fluorinated Prilosec (omeprazole) precursor. While product isolation and purification is often a challenge for arene C–H fluorination reactions (due to similar polarities of the arene starting materials and fluoroarene products), the 2-fluoropyridine products differ sufficiently in basicity from the pyridine starting materials that product isolation is readily accomplished by standard silica gel chromatography.

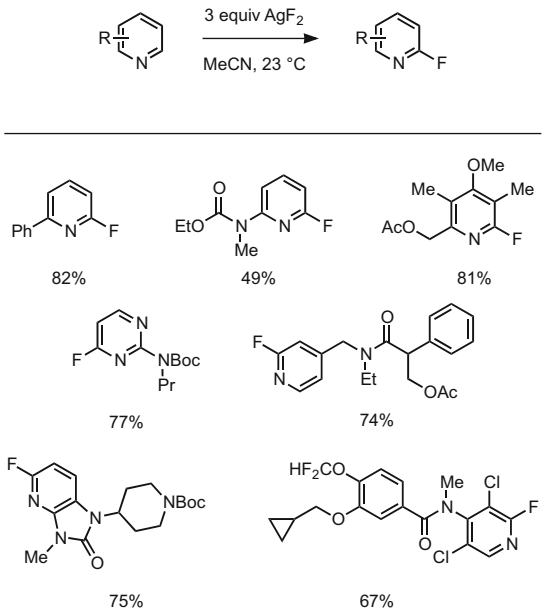



**Fig. 70** Synthesis of 2-fluoropyridines using $AgF_2$, via a radical C–H fluorination mechanism

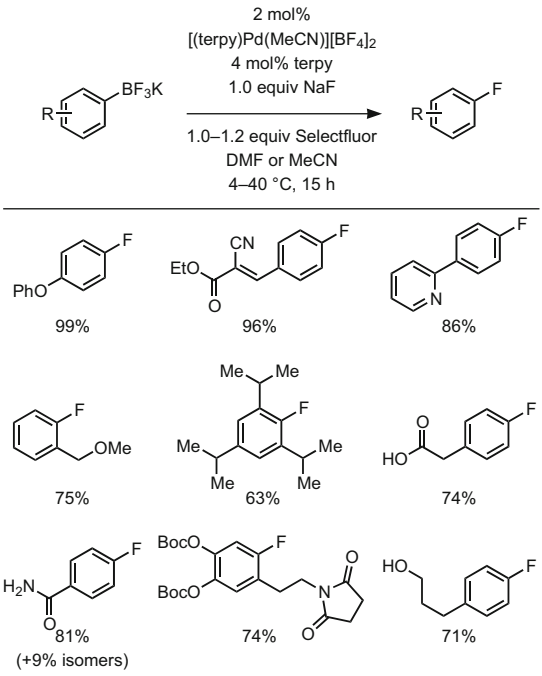



**Fig. 71** Pd-catalyzed fluorination of aryl trifluoroborates

A Pd-catalyzed fluorination of arylboronic acid derivatives was reported by the Ritter group in 2013 [177]. The Pd-catalyzed fluorination reaction proceeds in an open flask at 4–40°C using Selectfluor and a terpyridyl Pd(II) catalyst (Fig. 71). Aryl trifluoroborates featuring both electron-donating and electron-withdrawing groups are fluorinated, as well as very sterically hindered substrates, and protic functional groups such as alcohols, carboxylic acids, and primary amides are tolerated. Some substrates with electron-withdrawing substituents were found to give constitutional isomers and difluorinated products along with the expected aryl fluoride product (typically $\leq$10%), and the Pd-catalyzed reaction is ineffective for fluorination of heterocycles. Modified conditions were also reported for fluorination of pinacol boronic esters, arylboronic acids, and MIDA boronates.

As described above (Sect. 3.2.1), a key challenge for metal-catalyzed fluorination of arylboronic acid derivatives is the slow transmetallation of the arene from boron to the transition metal catalyst under conditions that are suitable for fluorination [151]. For the Pd-catalyzed fluorination of arylboronic acid derivatives, mechanistic studies indicate a catalysis cycle that does not involve transmetallation to form an arylpalladium intermediate. Instead, the data suggest a SET mechanism involving a Pd(III) intermediate and C–F bond formation via F• transfer from a partially reduced Selectfluor radical cation (Fig. 72). The putative Pd(III) intermediate (**12**) was synthesized under conditions relevant to catalysis and was characterized spectroscopically and by X-ray crystallography. The palladium-catalyzed

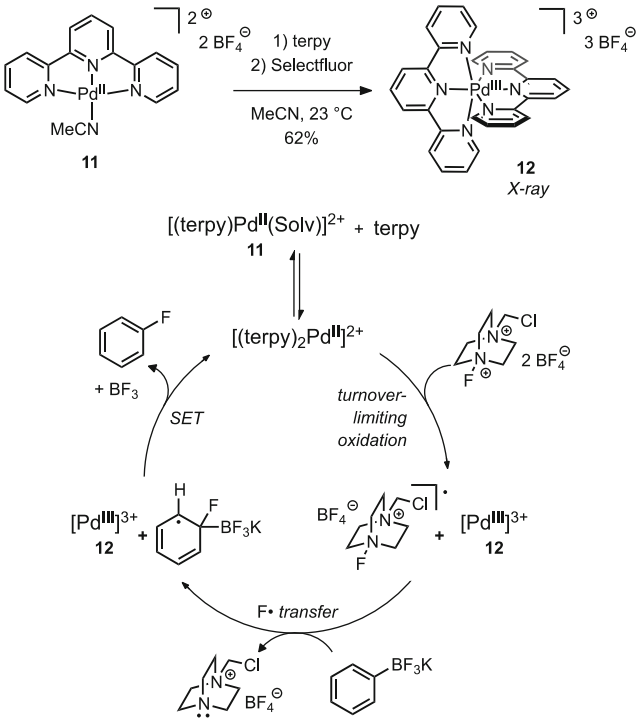



**Fig. 72** Proposed SET mechanism for Pd-catalyzed fluorination of arylboronic acid derivatives

fluorination reaction is unusual in that it seems to proceed without the formation of organopalladium intermediates, yet provides high levels of selectivity.

## *3.3 Oxidative Arene Fluorination with Fluoride*

As described above (Sect. 2.3), fluorine is the most electronegative and oxidizing element, and therefore the development of electrophilic arene fluorination reactions that utilize fluoride anion and a separate oxidant is challenging; however, the prospect of merging the benefits of electrophilic fluorination with the use of inexpensive and readily available fluoride salts is highly attractive. Most oxidative C–H fluorination reactions reported to date are effective only for alkane substrates (Sect. 2.3); however, work from the Daugulis group demonstrated that Cu catalysis can be used for oxidative C–H fluorination of benzoic acid derivatives, using a coordinating directing group derived from 8-aminoquinoline (Fig. 73) [178]. A combination of AgF as the fluoride source and NMO as the stoichiometric oxidant were used, resulting in mono- or difluorination of the arene substrates.

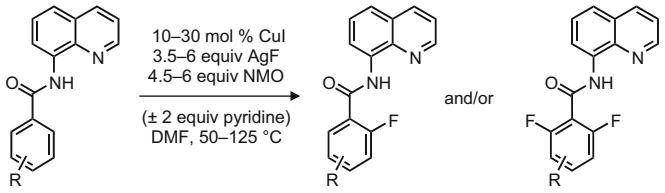



**Fig. 73** Cu-catalyzed N-directed oxidative fluorination of arene C–H bonds with AgF and NMO

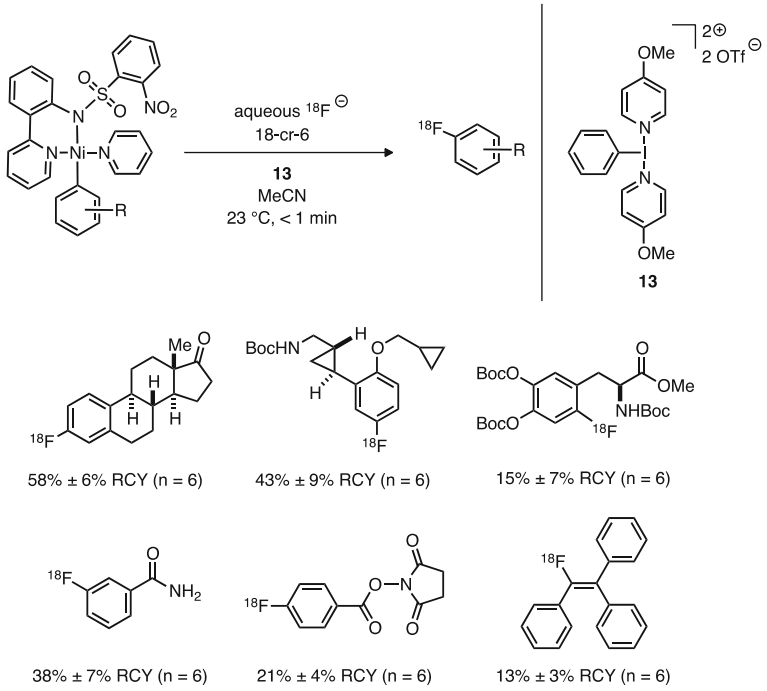



**Fig. 74** Ni-mediated oxidative arene radiofluorination with aqueous [$^{18}$F]fluoride

The oxidative fluorination of pre-functionalized aryl metal complexes has been developed by several groups and has especially been successful for radiofluorination with [$^{18}$F]fluoride. In 2012, the Ritter group reported that arylnickel(II) complexes could be used for the regioselective synthesis of aryl fluorides, with a combination of a fluoride source such at TBAT and hypervalent iodine oxidant **13** [179]. The nickel-mediated oxidative fluorination reaction enabled a one-step radiofluorination of arylnickel(II) complexes (synthesized by oxidative addition of an aryl halide to a Ni(0) precursor) using aqueous [$^{18}$F] fluoride and oxidant **13** (Fig. 74). The oxidative fluorination reaction proceeds in less than one minute for a variety of arylnickel(II) complexes: due to the 110 min half-life of $^{18}$F, the shortest possible preparation time is desirable [180]. The

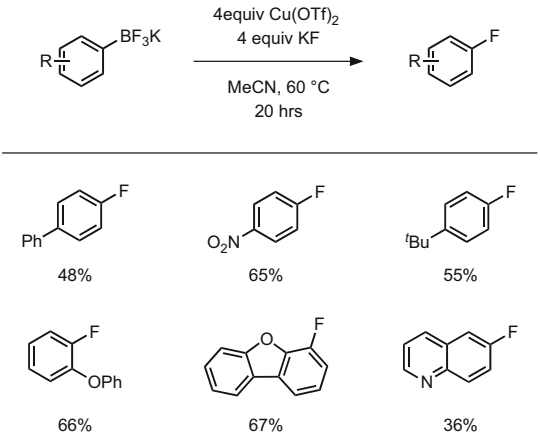



**Fig. 75** Cu-mediated oxidative fluorination of aryl trifluoroborates

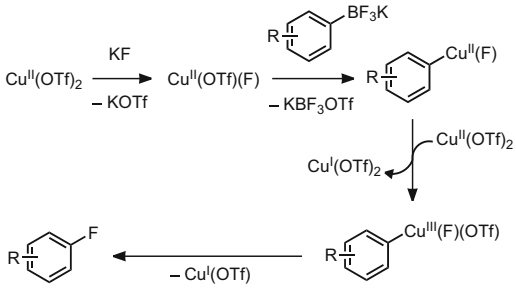



**Fig. 76** Proposed mechanism for Cu-mediated oxidative arene fluorination

stability of the nickel–aryl complexes could potentially allow for their eventual use in a synthesis of PET tracers [181]; however, oxidant **13** displays limited stability, and replacement of **13** with a suitable, stable oxidant would be a useful advance.

The Sanford group has described that their previously reported copper-mediated electrophilic fluorination of aryl trifluoroborates (*vide surpra*, Fig. 67) can be performed using KF and an excess of $Cu(OTf)_2$ (4 equiv.) in place of a *N*-fluorinated oxidant (Fig. 75) [182]. In this reaction, copper is hypothesized to play dual roles: as a redox-active mediator of C–F bond formation and as a stoichiometric oxidant. Transmetallation is proposed to occur at a Cu(II) fluoride complex, followed by oxidation by a second equivalent of $Cu(OTf)_2$ to afford an arylcopper(III) fluoride (as well as a Cu(I) by-product) and finally C–F reductive elimination from Cu(III) (Fig. 76).

In 2014, Gouverneur and coworkers reported that copper-mediated oxidative fluorination of arylboronic acid derivatives could be used for radiofluorination of (hetero)arylboronic esters with [$^{18}$F]fluoride [183]. Electron-rich, electron-poor, and sterically hindered arenes are effectively fluorinated in 20 min, and radiochemical yields up to $83 \pm 2\%$ were reported (Fig. 77). The utility of the copper-mediated method was exhibited through efficient synthesis of known radiotracers,

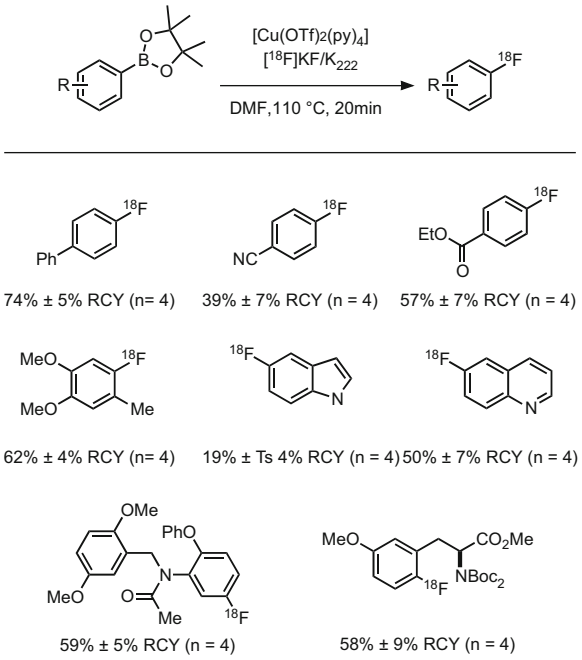



**Fig. 77** Cu-mediated oxidative radiofluorination of (hetero)arylboronic esters

including [$^{18}$F]DAA1106 and 6-[$^{18}$F]fluoro-*m*-D,L-tyrosine in 59 ± 5% and 58 ± 9% RCY, respectively (Fig. 77, bottom). Production of 6-[$^{18}$F]fluoro-L-DOPA from the corresponding arylboronic ester on a clinical dose scale was also demonstrated.

## *3.4 Alkenyl Fluoride Synthesis*

Alkenyl fluorides have utility as monomers for free-radical polymerization to form fluorinated polymers (e.g., Teflon) [184, 185], and as peptide mimics due to the similarity in size and dipole moment between amide bonds and fluoroalkene groups [186–190]. While fluoroalkene synthesis is often accomplished using Wittig-type reactions [191–195], several examples have been reported using gold catalysis and alkyne substrates. Gold-catalyzed hydrofluorination of alkynes was first demonstrated by the Sadighi group, using TREAT•HF (Fig. 78, top) [196]. Miller and coworkers subsequently reported a related transformation, in which directing groups such as carbamates can be used to provide >50:1 regioselectivity (Fig. 78, bottom) [197].

An electrophilic fluorination approach was used by the Gouverneur group to synthesize cyclic α-fluoro vinylogous esters, via gold-catalyzed fluorocyclization of propargyl ketones (Fig. 79) [198]. The major by-product in these reactions is

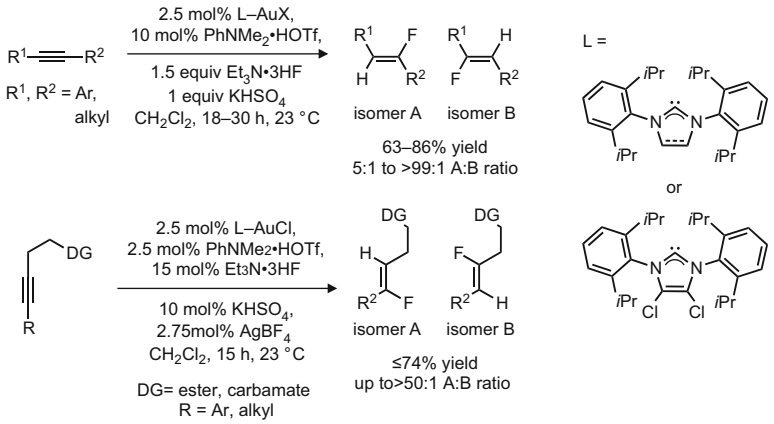



**Fig. 78** Au-catalyzed hydrofluorination of alkynes (*DG* directing group)

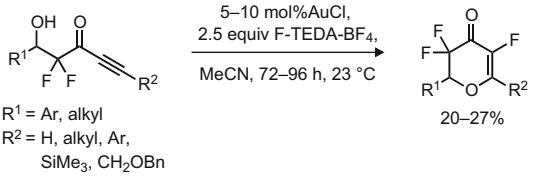



**Fig. 79** Au-catalyzed fluorocyclization of propargyl ketones

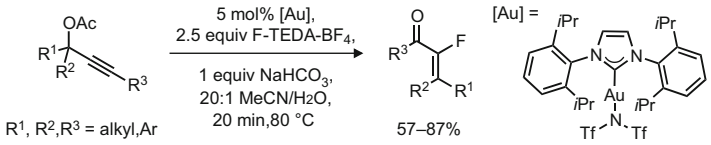



**Fig. 80** Au-catalyzed 1,3-acyloxy rearrangement of propargyl acetates for the synthesis of α-fluoroenones

typically the result of protodemetallation. Electrophilic fluorination can also be used to intercept the intermediates of gold-catalyzed rearrangements of propargyl acetates, affording α-fluoroenones (Fig. 80) [199]. This rearrangement/fluorination reaction was only reported to be successful for alkyl- or phenyl-functionalized propargyl acetates.

Palladium-catalyzed electrophilic C–H fluorination has also been demonstrated for the synthesis of alkenyl fluorides directed by *O*-methyl oxime ethers (Fig. 81) [175]. A mixed $Pd(OAc)_2/MNO_3$ (M=K or Ag) catalyst system was used along with the electrophilic fluorinating reagent NFBS, providing access to both cyclic and acyclic alkenyl fluorides. The authors proposed that in situ generation of a

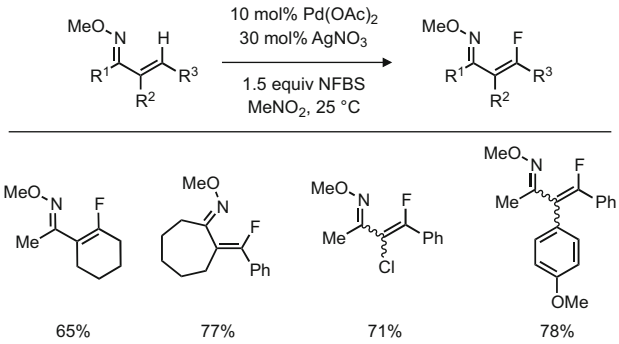



**Fig. 81** Pd-catalyzed fluorination of olefinic C–H bonds, directed by oxime esters

cationic $[Pd(NO_3)]^+$ complex is important for C–H palladation and that fluorination occurs from a high-valent Pd(IV) fluoride complex.

## 4 Outlook

The development of transition metal-mediated and metal-catalyzed C–F bond forming reactions over the past decade has played a major role in expanding the synthetic chemist's toolbox for accessing fluorinated organic molecules. Of particular importance has been the diversity of mechanisms through which C–F bond formation can occur, which provides a powerful breadth of approaches toward fluorination. There is significant room for advancement, however, and the field of organometallic fluorine chemistry is rapidly expanding. In particular, there is still a lack of transition metal-catalyzed fluorination reactions with broad utility. Nucleophilic fluorination reactions benefit from the use of readily available substrates and inexpensive fluoride salts, but the basicity of the fluoride anion under commonly used anhydrous reaction conditions can lead to problematic side reactions; the formation of transition metal–fluoride complexes can in some cases be used to tame the reactivity of nucleophilic fluoride. Electrophilic fluorination reactions have proved the most successful to date for highly functionalized substrates, but most common electrophilic fluorinating reagents are expensive and have poor atom economy. Despite these limitations, metal-mediated and metal-catalyzed C–F bond formation has already begun to impact areas such as drug discovery and PET tracer synthesis. Future work will need to address the development of C–F bond forming reactions that are more amenable to large-scale applications, with a focus on inexpensive, readily available reagents and catalysts.

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# Activation and Formation of Aromatic C–F Bonds

**Nicole A. LaBerge and Jennifer A. Love**

**Abstract** The presence of aryl C–F bonds in pharmaceuticals and agrochemicals is increasing rapidly. Incorporation of a fluorine substituent into biologically relevant molecules yields many benefits such as decreased metabolism, solubility, hydrophobicity and decreased negative side effects. Since there are no known examples of naturally occurring aryl fluorides all must be accessed through chemical synthesis. The formation and activation of aryl C–F bonds is a challenging endeavor, nevertheless several strategies are possible. Recent developments towards the synthesis of fluoroaromatics, as well as routes to selectively remove fluorine from polyfluoroaromatics are surveyed.

**Keywords** Catalysis · C–F activation · C–F bond formation · Cross-coupling · Transition metals

## Contents



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## Abbreviations

| | |
|---|---|
| Acac | Acetylacetonate |
| ACN | Acetonitrile |
| AdBrettPhos | [3,6-Dimethoxy-2′,4′,6′-tris(1-methylethyl)[1,1′-biphenyl]-2-yl]bis (tricyclo[3.3.1.1]dec-1-yl)-phosphine |
| Ar | Aryl |
| BrettPhos | 2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl |
| Bu | Butyl |
| C2 | Carbon 2 |
| cat. | Catalyst |
| C–F | Carbon–fluorine |
| cod | 1,5-Biscyclooctadiene |
| Cp | Cyclopentadienyl |
| $CuF_2$ | Cu(II)fluoride |
| Cy | Cyclohexyl |
| °C | Degrees Celsius |
| DCE | Dichloroethane |
| DCM | Dichloromethane |
| DFT | Density functional theory |
| DMAP | Dimethylaminopyridine |
| DMF | Dimethylformaldehyde |
| Dmpe | Dimethylphosphinoethane |
| DMSO | Dimethyl sulfoxide |
| DPEPhos | Bis[(2-diphenylphosphino)phenyl]methane |
| DPPB | Diphenylphosphinobutane |
| Ebthi | Ethylenebis(tetrahydro)indenyl |

| | |
|---|---|
| eq | Equation |
| equiv. | Equivalent |
| Et | Ethyl |
| *fac* | Facial |
| h | Hours |
| HEH | 2-Ethylhexyl hydrogen (2-ethylhexyl)phosphonate |
| $^{i}$Bu | Isobutyl |
| KF | Potassium fluoride |
| Me | Methyl |
| MeOH | Methanol |
| MW | Microwave |
| NHC | *N*-Heterocyclic carbene |
| NMP | *N*-Methyl-2-pyrrolidone |
| OAc | Acetate |
| PET | Positron emission tomography |
| Ph | Phenyl |
| Pr | Isopropyl |
| rt | Room temperature |
| TBAF | Anhydrous tetrabutylammoniumfluoride |
| $^{t}$Bu | Tertiary butyl |
| TEA | Triethylamine |
| TEAF | Tetraethylammonium fluoride |
| THF | Tetrahydrofuran |
| TON | Turnover number |
| Triphos | (Bis(diphenyl)phosphinoehtyl)phenyl phosphine |
| $XeF_2$ | Xenon difluoride |

## 1 Introduction

Carbon–fluorine bonds are present in up to 20 % of new pharmaceuticals and up to 50 % of new agrochemicals. Select examples include diflusinal, ciprofloxacin, and Lipitor (Fig. 1) [1]. Because fluorine has a similar a van der Waals radius to that of oxygen, as well as high electronegativity, the use of a fluorine substituent may simultaneously alter a compound's steric and electronic properties [2]. Thus, incorporation of C–F bonds into biologically active compounds yields many biological benefits such as decreased metabolism, solubility, hydrophobicity, and decreased negative side effects. C–F bonds are additionally present in contrast agents used in positron emission tomography (PET) [3].

At present, no naturally occurring aryl fluorides have been documented, and therefore, such molecules must be obtained by chemical synthesis [1]. This chapter will survey the recent developments toward the synthesis of fluoroaromatics, both by methods that incorporate a fluorine substituent into a functionalized aromatic

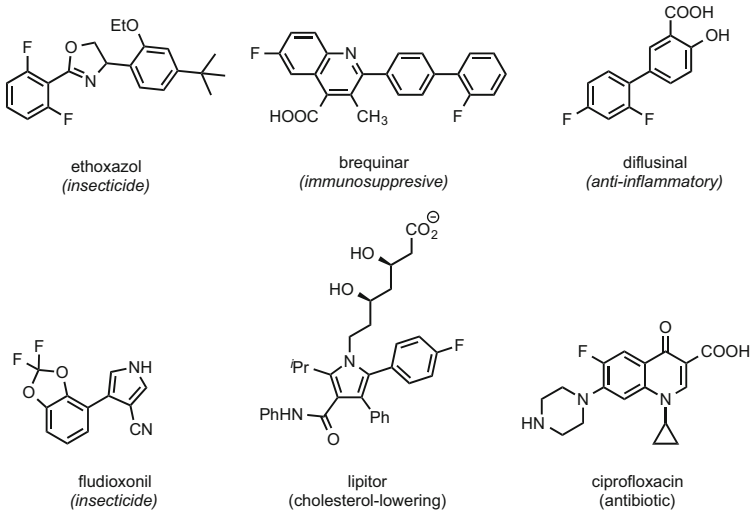



**Fig. 1** Select drugs and agrochemicals containing aryl C–F bonds

and methods that selectively remove a fluorine substituent from a polyfluorinated aromatic, and subsequently introduce more complexity.

## 2 Aryl C–F Bond Formation

The synthesis of carbon–fluorine bonds is a challenging endeavor. For instance, several reports of cross-coupling reactions for the formation of C–X (X = O, S, C) bonds have been accounted; however, methods for formation of C–F bonds are far less common [4]. The difficulty associated with C–F bond synthesis may be due to electronic features of the carbon substituent, as well as fluorine's potential reactivity with other functionality [5].

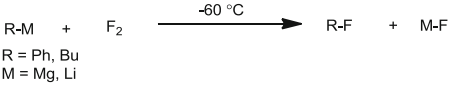
Traditional carbon–fluorine bond synthesis methodologies include direct fluorination [6], nucleophilic substitution of electron-poor bromine or chlorine arenes using KF [7], and transforming aryl iodides to their aryl fluorine counterparts using $CuF_2$ as the F-source [8]. These methods generally require harsh conditions and are usually not compatible with diverse functional groups, which limit the scope of fluorinated molecules that can be produced [9]. As the number of examples of fluorinated pharmaceuticals and agrochemicals expands, the demand to find more feasible user-friendly methods has grown. Fortunately, in recent years, new synthetic methodologies have been developed to overcome the limitations of traditional methods. New methods of carbon–fluorine bond formation include electrophilic and nucleophilic fluorination along with pyrolysis of tetrafluoroborates.

# 3 Electrophilic Fluorination

In the past decade, reports of introducing fluorine into organic molecules via electrophilic fluorinating sources have increased. This is attributable to the straightforward and clean way by which these reagents are able to introduce fluorine into organic molecules [10]. A number of groups have reported novel reactivity using commercially available fluorinating reagents (Fig. 2).

## *3.1 Organomagnesium and Organolithium Reagents*

Reports of electrophilic fluorination began in the early 1990s when Lagow et al. reported the fluorination of organomagnesium and organolithium reagents using fluorine gas (Eq. 1) [11]. Organolithium reagents were more reactive than organomagnesium reagents resulting in higher yields. Aliphatic reagents were also more reactive in the transformation.




(1)

The pioneer of directed *ortho*-metalation, Snieckus and colleagues, described the introduction of fluorine into aryls using *N*-fluorobenzenesulfonimide (NFSI) and *N*-fluoro-*o*-benzenedisulfonimide (NFOBS) (Eq. 2) [12]. The use of directing groups including amides, oxazolines, and anisoles provided access to a variety of fluorinated aromatics.

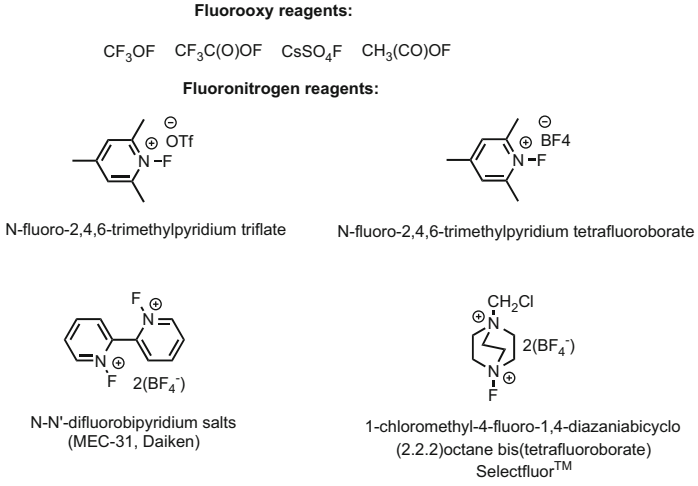
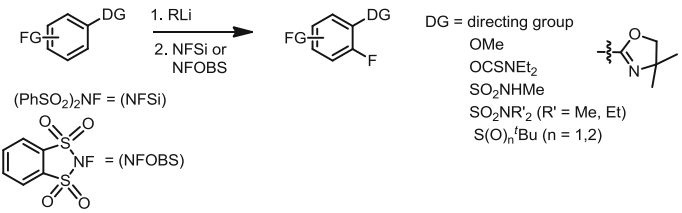


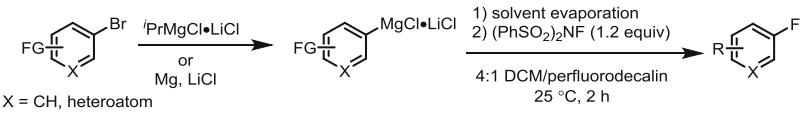

**Fig. 2** Electrophilic fluorinating reagents



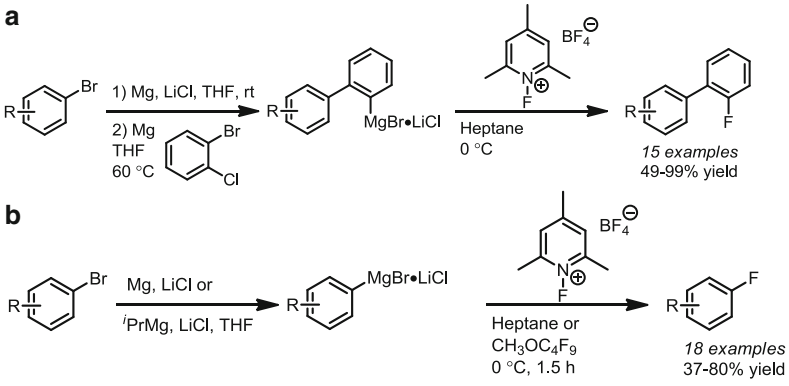

(2)

Knochel and coworkers showed that electrophilic fluorination of aryl and heteroaryl Mg reagents could be mediated by *N*-fluorobenzenesulfonimide (NFSI). This method is amenable to the fluorination of several heteroaromatics including pyridines, thiophenes, pyrroles, and isoquinolines as well as sterically hindered benzenes (Scheme 1) [13].

Beller and coworkers have also made important contributions in this area [14, 15]. In 2010, they reported a novel domino Grignard-coupling–fluorination sequence. A strategy not previously reported, this methodology provides access to 2-(hetero)aryl-fluoroarenes (Scheme 2a) [14]. Not long after, a related reaction involving nucleophilic fluorination of ArMgX-LiCl with F-TMP-$BF_4$ was described. The scope of this reaction included sterically hindered and electron-rich and electron-poor Grignard reagents (Scheme 2b) [15]. A variety of aryl fluorides can be obtained from readily available aryl bromides under user-friendly conditions.




**Scheme 1** Electrophilic fluorination of aryl and heteroaryl Mg reagents

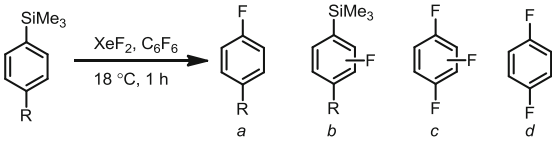



**Scheme 2** (**a**) Domino Grignard fluorination of aryl bromides with F-TMP-$BF_4$. (**b**) Fluorination of aryl bromides with F-TMP-$BF_4$

## 3.2 Organosilicon Reagents

Another route to accessing fluoroaromatics is fluorodesilylation. This process involves replacement of a silyl group by a fluorine atom. The method typically incurs a number of drawbacks such as the requirement of harsh F-containing oxidants including $XeF_2$ and $F_2$. Fluorodesilylation of aryltrimethylsilanes was achieved using $XeF_2$ in 1993 by the group of Ramsden. Yields of this reaction were dependent on aryl ring substituents and were also limited by by-product formation (Table 1, entries b–d) [16]. Moody et al. illustrated that fluorophenyltrimethylsilanes could undergo fluorodesilylation in the presence of $F_2$ (Table 2) [17]. The trimethylsilyl group undergoes a 1,2-migration to afford various fluorinated products. Unfortunately, the reaction is non-regioselective, and in some cases, polyfluorinated products were produced (Table 2, entries f–h).

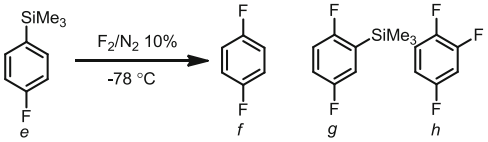
**Table 1** Effect of substituents on fluorodesilylation with $XeF_2$




| R | a[a] (%) | b[a] (%) | c[a] (%) | d[a] (%) |
|---|---|---|---|---|
| $^t$Bu | 86 | 8 | 6 | – |
| Cl | 82 | 12 | 6 | – |
| OMe | 61 | 39 | 0 | – |
| H | 65 | 0 | 0 | 35 |

[a]Numbers represent percent product conversion determined by GCMS

**Table 2** Elemental fluorination of 4-fluorophenyltrimethylsilane

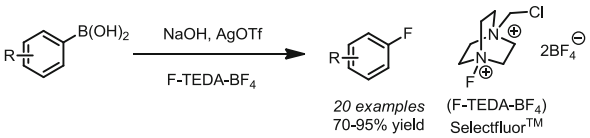



| Fluorination conditions | e[a] (%) | f[a] (%) | g[a] (%) | h[a] (%) |
|---|---|---|---|---|
| $CFCl_3$/MeOH (10 %) | 31 | 12 | 2 | 3 |
| $CFCl_3/CH_2Cl_2$/MeOH (10 %), 1 equiv. $BF_3$ MeOH | 43 | 12 | 5 | 6 |
| $CFCl_3$/MeOH (10 %), $BF_3$ $2CH_3COOH$ | 50 | 15 | 4 | 5 |

[a]Numbers represent percent product conversion determined by $^{19}$F NMR spectroscopy and GC

### 3.3 Organoboron Reagents

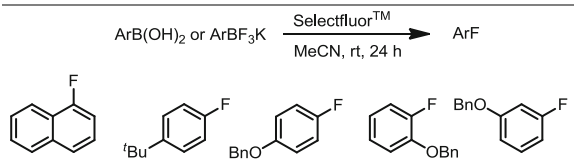
Electrophilic fluorination of boronic esters and acids was initiated by Petasis, Prakash, and Olah in the late 1990s [18]. They discovered alkenyl boronic acids and trifluoroborates could be electrophilically fluorinated using fluoro-(1-chloromethyl 1,4-diazoniabicyclo[2.2.2]octane tetrafluoroborate) (F-TEDA-$BF_4$) (commercially referred to as Selectfluor™) giving fluorine-containing alkenes, amides, and alcohols. More recently in 2009, Ritter and coworkers demonstrated fluorination of boronic acids with Selectfluor™ using silver triflate (AgOTf) [19]. This transformation was tolerant of protic, electrophilic, nucleophilic, as well as heterocyclic boronic acids (Eq. 3). Although stoichiometric in silver, this method employs cheap materials and can be carried out on a multigram scale, potentially relevant to industrial processes.

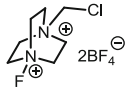



(3)

In a metal-free approach, Lemaire and colleagues illustrated electrophilic fluorination of boronic acids and boronate salts using Selectfluor™ [20]. Notably, boronic acids gave higher yields over boronate salts (Table 3; entries 1a–2a, 1b–2b). Substrates having increased electron density were also more reactive toward electrophilic substitution over the competing protodeboronation pathway. This observation was confirmed by screening a series of benzyloxyphenylboronic acids (Table 3, substrates c–e) where the *para*-substituted benzyloxyphenylboronic acid gave the highest yield followed by *ortho*- and *meta*-substituted substrates.

**Table 3** Electrophilic fluorination of boronic acids and boronate salts with Selectfluor™




Selectfluor™

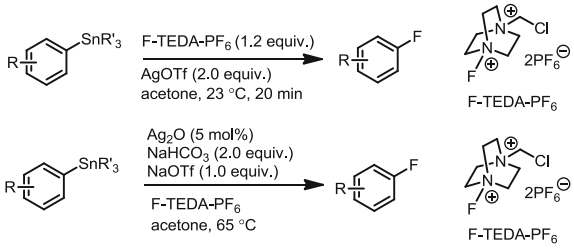
| | a (%) | b (%) | c (%) | d (%) | e (%) |
|---|---|---|---|---|---|
| **1** $ArB(OH)_2$ | 90[a] | 75[a] | 100[a] | 67[a] | 0[a] |
| **2** $ArBF_3K$ | 79[a] | 53[a] | | | |

[a]Percentage denotes GC conversion

### 3.4 Organotin Reagents

In 2009, Ritter and coworkers reported silver-mediated fluorination of aryl stannanes. In just 20 min at 25 °C, aryl stannanes (prepared from triflation) underwent fluorination with F-TEDA-$PF_6$ (Eq. 4) [21]. A variety of aromatics and heteroaromatics were tolerated in the reaction; some substrates, however, proved challenging to purify as they incurred protostannylation.

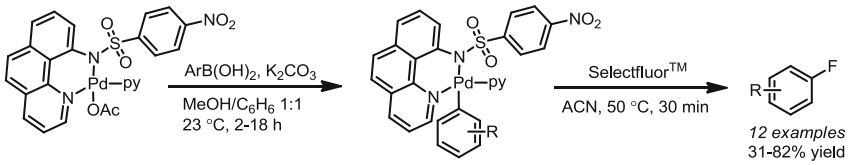
In a follow-up report, Ritter et al. also described late-stage fluorination of aryl stannanes catalyzed by Ag (Eq. 5) [22]. Using fluoro-(1-chloromethyl 1,4-diazoniabicyclo[2.2.2]octane hexafluorophosphate) (F-TEDA-$PF_6$) as the source of fluorine, a number of biologically active molecules such as carbohydrates, peptides, polyketides, and alkaloids were fluorinated. Basic functional groups however were not tolerated; it is suspected they may undergo a side reaction with F-TEDA-$PF_6$ ultimately quenching the reaction. Markedly, this method was the first example of a carbon–heteroatom bond formation reaction catalyzed by silver.



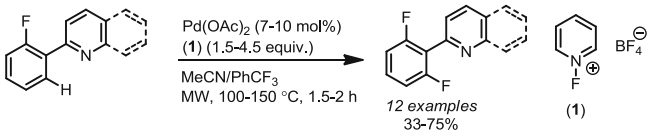

(4, 5)

### 3.5 Electrophilic Fluorination with Transition Metals

Electrophilic fluorination using transition metals is a relatively new strategy emerging in the literature within the last 10 years. In 2006, Sanford et al. described the Pd-catalyzed synthesis of aromatic C–F bonds. Substrates bearing quinoline or pyridine moieties directed fluorination of *ortho*-C–H bonds (Eq. 6) [23]. Under microwave conditions and using *N*-fluoropyridinium tetrafluoroborate (**1**) as the fluorine source, the desired products were achieved in modest yields. Mechanistic investigations indicated the reaction to proceed through a Pd(II)/Pd(IV) cycle [24]. A palladium(IV) species was also detected by Vigalok et al. who showed $XeF_2$ was capable of inducing reductive elimination of a palladium(IV) species to generate related difluoropalladium(II) complexes [25]. The palladium (IV) aryl iodide species also reacted with 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate generating 1,4-difluorobenzene and 4-fluoroiodobenzene.




**Scheme 3** Pd-mediated fluorination of boronic acids

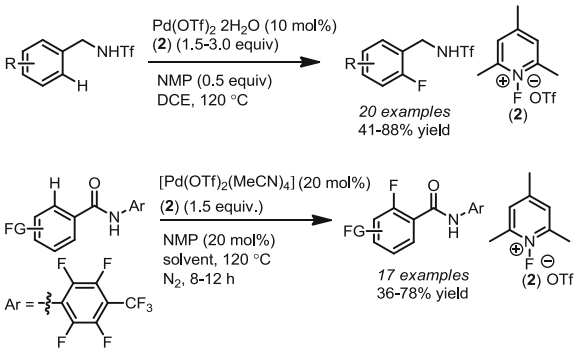



(6)

The Ritter group has also made important contributions to this area. In 2008, they reported aryl palladium complexes that were able to mediate the fluorination of aryl boronic acids using Selectfluor™ (Scheme 3) [26]. This method is highly regioselective even without a directing group and does not involve harsh reaction conditions. The use of organoboronic acid reagents is also an attractive feature as they are suitable transmetalation partners, readily available, and present in positron emission tomography (PET) tracers, which has a potential for use in medical imaging, particularly as this method offers potential for late-stage fluorination. Synthesis of related palladium complexes supported by pyridyl-sulfonamide ligands suggests that the reaction proceeds through palladium(IV) fluoride complexes [27].

More recently, Yu and colleagues described the selective *ortho*-fluorination of aryls having triflamides as directing groups. In the presence of $Pd(OTf)_2 \cdot 2H_2O$ and NMP, aryl-containing triflamides of varying electronic nature were fluorinated at the *ortho*-position in good to excellent yields (Eq. 7) [28]. The triflamide functionality prevents coordination of *N*-2,4,6-trimethylpyridinium triflate (**2**) to Pd. Based on similar reactions with palladium, it is likely the reaction proceeds through a Pd (IV) intermediate.

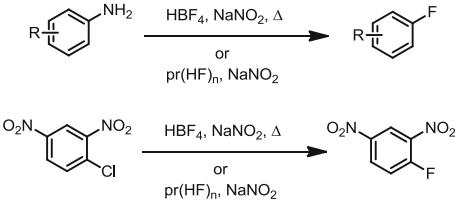
Selective *ortho*-fluorination of benzoic acids was also achieved with a large class of benzoic acid derivatives using removable *N*-arylamide auxiliaries (Eq. 8) [29]. Catalyzed by Pd(II) salts, these reactions use commercially available benzoic acids providing mono- and difluorinated products. Substrates having electron-donating groups required shorter reaction times, whereas electron-deficient substrates required longer reaction times.




(7, 8)

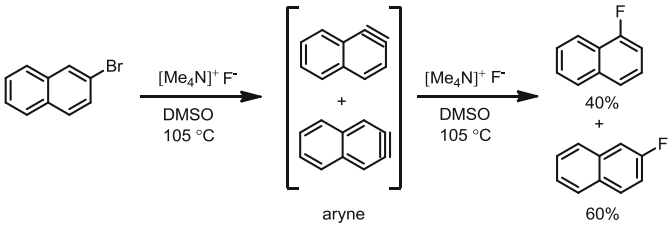
## 4 Nucleophilic Fluorination

The very first account of nucleophilic fluorination was the Balz–Schiemann reaction developed by Balz and Schiemann in 1927 [30]. This reaction proceeds through a diazonium species that is highly dangerous making for less than ideal reaction conditions (Eq. 9). Following this was the development of the Halex process that required successive heating and large amounts of KF limiting its applicability to late-stage fluorination methods (Eq. 10) [31].




(9, 10)

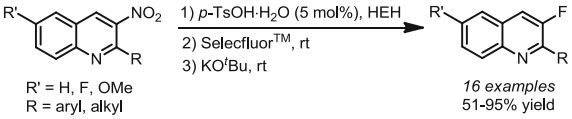
Fortunately, within the last decade, there have been a number of alternate nucleophilic fluorination pathways developed alleviating the requirement of such harsh reaction conditions. Working to improve the industrial Halex process, DiMagno and colleagues discovered that Halex and fluorodenitration reactions were possible at room temperature using anhydrous tetrabutylammoniumfluoride ($TBAF_{anh}$) as the fluorine source (Eq. 11) [32]. The reaction was tolerant of arenes and heteroarenes of differing electronic and steric nature. The reaction proceeded more rapidly when electron-withdrawing substituents were present on the ring. In 2008, Marshall et al. communicated the fluorination of nonactivated haloarenes using tetramethylammonium fluoride, generating a mixture of regioisomers (Scheme 4) [33]. This reaction is believed to proceed through an in situ generated aryne.




**Scheme 4** Recent developments in nucleophilic fluorination


(11)

Substitution of a nitro group by fluorine was recently described by Zhou et al. (Eq. 12) [34]. 3-Nitroquinolines possessing electron-donating and electron-withdrawing groups underwent substitution using commercially available Selectfluor™ at room temperature to afford fluorinated heteroaromatics. As the degree of saturation increased at the C2 position of quinoline, the product yields decreased. The reaction is believed to proceed through a one-pot triple-relay transformation process involving dearomatization, electrophilic fluorination, and finally rearomatization.



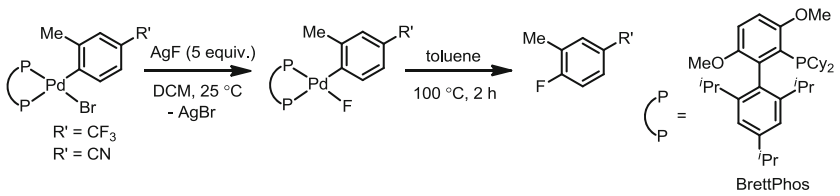

(12)

## *4.1 Nucleophilic Fluorination with Transition Metals*

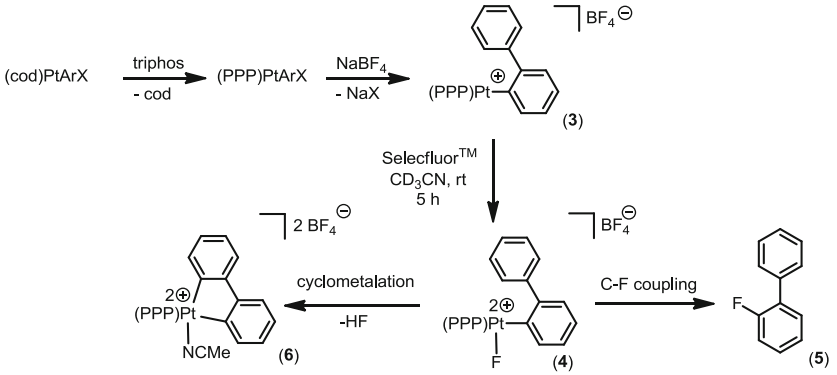
### 4.1.1 Group 10: Palladium and Platinum

Buchwald and colleagues first reported Pd-catalyzed nucleophilic fluorination in 2009. A Pd(II) complex possessing a monodentate phosphine ligand catalyzed nucleophilic fluorination of aryl bromides and triflates with fluoride salts (Scheme 5) [9]. The Pd complex was isolated and characterized and found to undergo reductive elimination to generate the corresponding aryl fluorides. A follow-up mechanistic study indicated reductive elimination was unsuccessful when an electron-rich aryl group was present [35]. This reaction was also applied to a microflow packed-bed reactor which constituted the first report of aryl C–F bond forming reaction under flow conditions [36].

Since their initial report in 2009, the Buchwald group has further optimized and expanded the scope of the palladium reaction to include a diverse selection of aryl bromides and iodides as well as heteroaryl bromides (Eqs. 13 and 14) [37]. The method was also amenable to the fluorination of the vascular drug, nicergoline (Sermion), suggesting the applicability of the methodology to late-stage

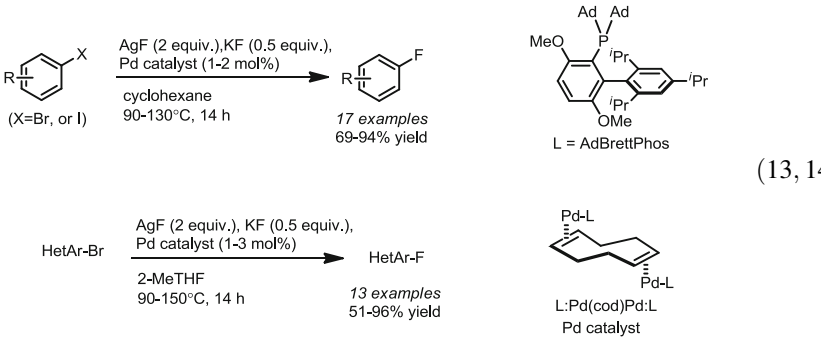



**Scheme 5** Formation and reductive elimination of [L-PdArF] species




**Scheme 6** Fluorination of Pt–aryl complexes

fluorination. Although this method accommodates a variety of substrates, the elaborate preparation of AdBrettPhos remains a limitation.



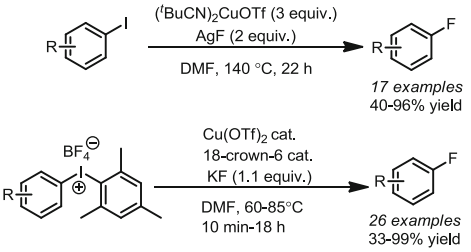

Platinum complexes have also been reported to facilitate nucleophilic fluorination. The first example of a Pt center involved in aryl-F coupling was provided by Gagné and coworkers in 2012 [38]. Beginning with ($\eta^4$-cod)PtAr(X) (cod = cycloocta-1,5-diene, X = Cl, I), ligand exchange occurs between cod and triphos (bis(diphenylphosphinoethyl)phenylphosphine) followed by salt metathesis with $NaBF_4$ to generate the cationic complex of (cod)Pt–*aryl*$^+$ (**3**) (Scheme 6). Subsequent treatment of (**3**) with Selectfluor™ generated the

corresponding Pt(IV)-F species (**4**). Further heating also gave the C–F-coupled (**5**) product as well as the cyclometalation product (**6**).

### 4.1.2 Group 11: Copper

Copper has also been shown to mediate and catalyze nucleophilic fluorination reactions. In 2012, Hartwig et al. described fluorination of aryl iodides mediated by a copper triflate complex (Eq. 15) [39]. The reaction proceeds through a cationic copper species that undergoes transmetalation with silver fluoride. Product isolation proved to be difficult as arene protonation was competitive with desired fluorination. A labeling study determined the proton was ligand derived.

Copper-catalyzed nucleophilic fluorination has also been established by Sanford and colleagues (Eq. 16) [40]. In the presence of copper triflate, 18-crown-6, and potassium fluoride, diaryliodonium salts underwent fluorination at the more substituted arene. The reaction accommodates electron-rich aryl rings that are typically difficult to fluorinate by nucleophilic processes. The procedure may be applicable to PET imaging for the installation of $^{19}F$ resulting because of the rapid reaction times.

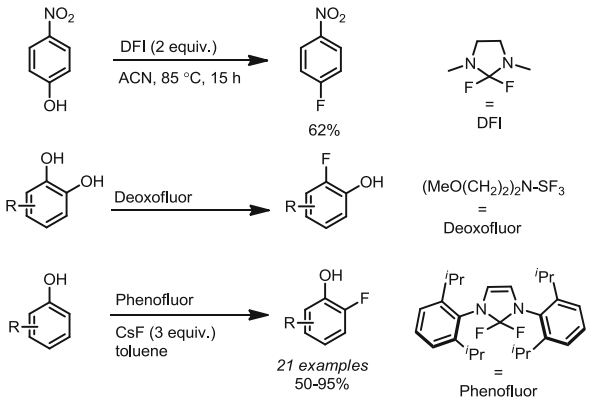



(15, 16)

## 5 Alternative Methods

### *5.1 Nucleophilic Deoxyfluorination*

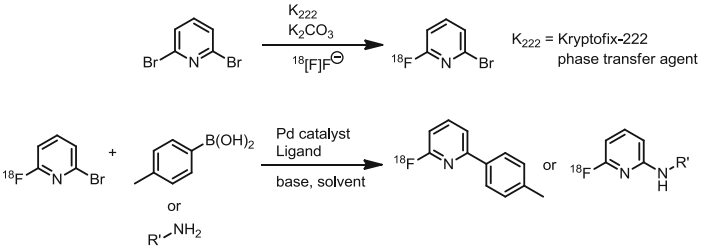
Replacement of hydroxy groups with fluorine has also been reported as a viable strategy for the synthesis of aryl fluorides. The first account of such a method was reported in 2002 by Nagata et al. Nitro-substituted phenols underwent deoxyfluorination with *N*,*N*′dimethyl-2,2-difluoroimidazoline (DFI) generating fluorinated products (Eq. 17) [41]. Akai et al. also reported an example of nucleophilic deoxyfluorination with catechols (Eq. 18) [42]. Through umpolung reactivity, one hydroxy group of the catechol is fluorinated, affording a variety of fluorinated phenol isomers. Lastly, the Ritter group described deoxyfluorination of phenols using PhenoFluor (Eq. 19) [43].




(17, 18, 19)

## 5.2 Phase Transfer Catalysis

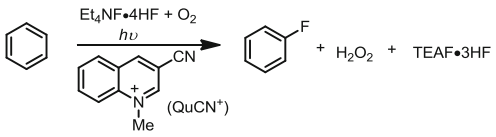
Other innovative methods including phase transfer catalysis show great promise in fluorination reactions, particularly those related to the installation of $^{18}F$ for PET imaging reagents. The phase transfer reagent, Kryptofix 222, was recently reported to aid in the installation of $^{18}F$ on heteroaryl bromides (Eq. 20) [44]. Once $^{18}F$ was in place, the bromo-heteroaryl subsequently underwent Suzuki–Miyaura cross-coupling with organoboronic acids. The same bromo-heteroaryls were also coupled to amines in a Buchwald–Hartwig reaction catalyzed by palladium (Eq. 21). This method overcomes the harsh reaction conditions typically required of nucleophilic $^{18}F$ fluorination of aromatic ring systems.




(20, 21)

## 5.3 Photocatalytic Fluorination

The use of light to catalyze aryl–fluorine bond formation had not been reported until a short time ago. Photocatalytic monofluorination of benzene was accomplished via a photoinduced electron transfer process using oxygen as the oxidant (Eq. 22) [45]. Although the method suffered a limited substrate scope and low yields, the account lays the ground work for future photocatalytic fluorination reactions.




(22)

## 6 Aryl C–F Activation

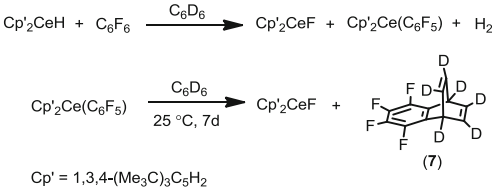
The activation of aryl C–F bonds is a long-standing challenge, owing to the strength of the C–F bond [46–48]. Such a process is also relevant to the development of methods to synthesize functionalized aryl fluorides. The activation of C–F bonds is the microscopic reverse of C–F bond formation. From a mechanistic perspective, anything discovered about activation necessarily yields information about bond formation.

Selective activation and functionalization of polyfluoroaromatics can provide a clever strategy for the synthesis of functionalized fluoroaromatics. Traditional methods of accessing aryl–fluorine bonds have a number of drawbacks including the need for specialized equipment and the production of toxic by-products [4]. Fortunately, new methods of C–F activation using transition metals such as nickel and platinum have been developed to overcome such limitations [5]. This section will discuss important advances made toward the activation of aryl C–F bonds with transition metals.

## 7 Early Transition Metals

### *7.1 Group 3, Lanthanides and Actinides*

Collaborative efforts of Anderson, Eisenstein, Maron, and colleagues provided an example of hexafluorobenzene and pentafluorobenzene hydrogen–fluorine exchange using a monomeric $Cp'_2CeH$ species ($Cp' = 1,3,4\text{-}(Me_3C)_3C_5H_2$) (Eq. 23) [49]. Over a period of days, $Cp'_2CeF$ was generated in addition to $Cp'_2Ce(C_6F_5)$ and $H_2$. Tetrafluorobenzene was also produced and confirmed by a trapping reaction with $C_6D_6$ to give (**7**) via a [4 + 2] cycloaddition (Eq. 24). Density functional theory (DFT) studies indicated hydrogen–fluorine coordination was a key step in the reaction as well as a $\eta^1$-F-$C_6F_5$ interaction with Ce–H.




(23, 24)

Overall, there are only a few examples of lanthanide complexes that are known to facilitate C–F bond activation. A report by Wang and coworkers demonstrated

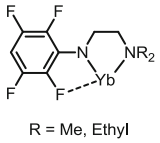
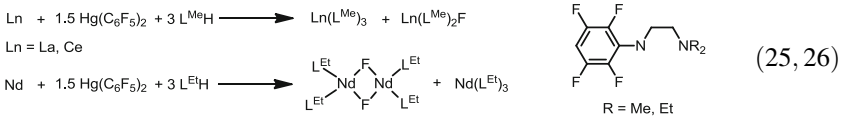



**Fig. 3** Yb interaction with *N*,*N*-dialkyl-*N*′2,3,5,6-tetrafluorophenylethane-1,2-diaminate ligand

intramolecular fluoro coordination of ytterbium to *N*,*N*-dialkyl-*N*′-2,3,5,6-tetrafluorophenylethane-1,2-diaminate ligands (Fig. 3) [50]. The ytterbium species undergoes intramolecular C–F activation to form fluoride-bridged clusters by a single electron transfer process or $F^-$ anion benzyne formation.

Other lanthanides including lanthanum (La), cerium (Ce), and neodymium (Nd) were also found to coordinate aryl C–F bonds, as reported by Deacon et al. in 2012. Homoleptic complexes of La, Ce, and Nd were accessed through a redox-transmetalation/protonolysis reaction (Eqs. 25 and 26) [51]. Additionally, trimeric heteroleptic fluorides were accessed through C–F activation, however, in low yields. Relative to ytterbium, the extent of C–F activation was not as great. Presently, these are the only examples of homoleptic rare-earth metal complexes.



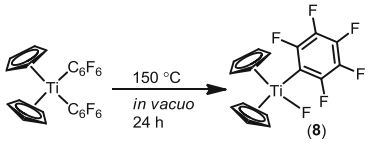

(25, 26)

## 7.2 Group 4

### 7.2.1 Titanium

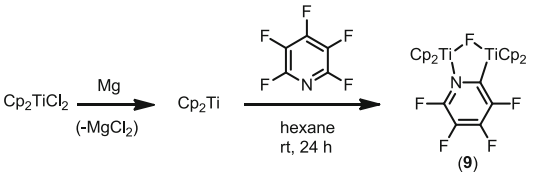
Stoichiometric Examples

C–F activation with titanium was first reported by Stone and colleagues in 1963 [52]. The titanium starting material $Cp_2Ti(C_6F_6)_2$; $Cp = C_6H_5$ was found to undergo pyrolysis leading to intramolecular fluorine migration generating (**8**) (Eq. 27). The reaction proceeded under vacuum at 150 °C over 24 h.

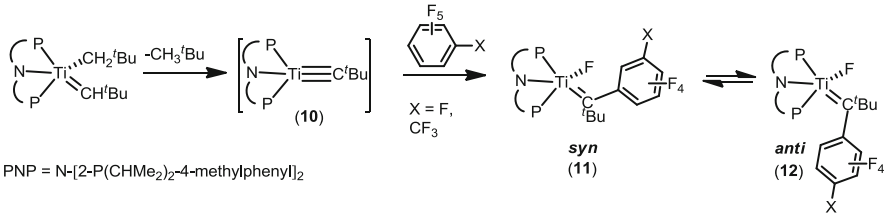



(27)

In recent times, titanium has been found to be reactive toward pentafluoropyridines. Saak et al. determined the highly reactive species $Cp_2Ti$ is effective in activating the 2-position of pentafluoropyridine to afford an unsaturated titanium metallacycle (**9**) (Scheme 7) [53]. Activation at the 2-position of pentafluoropyridine may be attributed to a three-centered oxidative addition step.



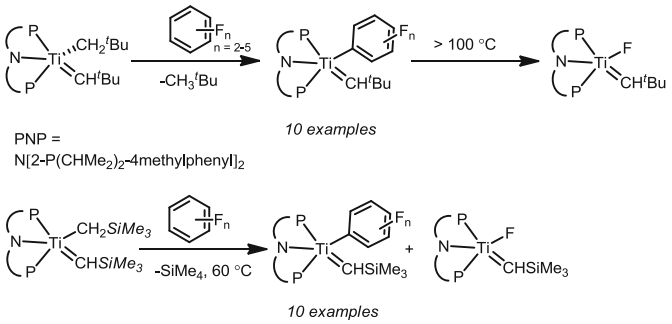

**Scheme 7** C–F activation of pentafluoropyridine with $Cp_2Ti$




**Scheme 8** Intermolecular C–F activation with a titanium alkylidyne

The Mindiola group has reported interesting reactivity of titanium alkylidynes with fluoroaromatics. In 2007, the group demonstrated intermolecular activation of C–F bonds by a Ti≡C$^t$Bu fragment [54]. Over a period of 48 h at 50 °C, the transient titanium alkylidyne species (**10**) is reacted with hexafluorobenzene to give a pentafluorophenyl-substituted alkylidene (PNP)Ti=C[$^t$Bu($C_6F_5$)](F) (Scheme 8).$^{13}$C NMR spectroscopic data indicated two alkylidene isomers present in the solution corresponding to *syn*- (**11**) and *anti*-isomers (**12**). The resulting isomers are able to interconvert through the flexible PNP ligand. DFT studies indicated the *syn*-isomer was lower in energy. A follow-up mechanistic study suggested C–F activation proceeds across the titanium triple bond [55].

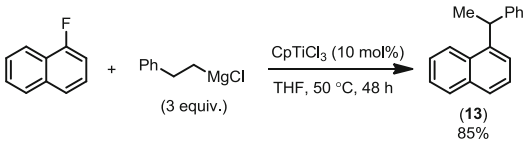
Using the same transient titanium alkylidyne (PNP)Ti≡C$^t$Bu, in addition to a silyl-substituted alkylidyne (PNP)Ti≡$CSiMe_3$, the Mindiola group also described the dehydrofluorination of hydrofluorocarbons [56]. These alkylidynes were found to undergo intramolecular C–F activation, dehydrofluorinating various aryl fluorine compounds. A selection of titanium alkylidene fluoride complexes was accessed via β-fluoride elimination of PNPTi=CH$^t$Bu(*o*-$FC_6H_4$) (Eq. 28). Substrates having electron-donating groups adjacent to the C–F bond that is cleaved by titanium proceeded at a faster rate. Similar titanium fluorides were accessed with the alkylidene derivative (PNP)Ti=$CHSiMe_3$ that activated the same series of aryl fluorides (Eq. 29).




(28, 29)

Catalytic Examples

Presently Ti-catalyzed C–F activation is rare. Described by Takahashi and colleagues in 2006, $CpTiCl_3$ was found to catalyze the cross-coupling of 1-fluoronaphthalene and 2-phenylmagnesium chloride leading to (**13**) (Eq. 30) in 85 % yield accompanied by rearrangement of the phenethyl group [57].




(30)

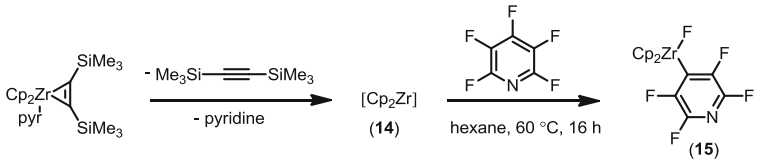
In 2013, Reissig et al. described an example of catalytic hydrodefluorination with a $[Cp_2TiF_2]$ diphenyl silane system for access to amino pyridine derivatives [58]. This titanium system was based on a related system for catalytic hydrodefluorination of alkenes [59].

### 7.2.2 Zirconium

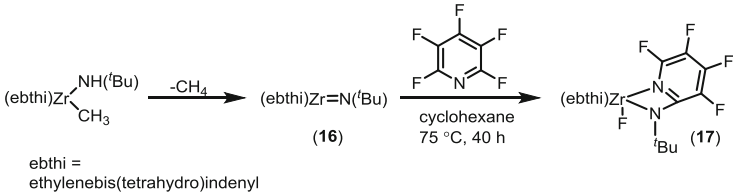
Stoichiometric Examples

Aryl C–F activation involving zirconium is less common. Cyclopentadienyl ligands are support ligands of zirconium species able to cleave aryl C–F bonds. Jones and colleagues described such an example in 1999 using zirconium hydride dimer complex to activation of hexafluorobenzene and pentafluorobenzene [60].

More recently, Rosenthal has made important contributions related to the use of early transition metals for C–F activation. In 2005, his group found that $Cp_2Zr$ precursors are effective for the activation of pentafluoropyridine [61]. The zirconocene complex (**14**) reacts with pentafluoropyridine at the 4-position to generate $Cp_2Zr(4\text{-}C_5NF_4)F$ (**15**) (Scheme 9). This result is different from its titanium analogue $Cp_2Ti(\eta^2\text{-}Me_3\text{-}SiC_2SiMe_3)$ that activates pentafluoropyridine in the 2-position. A possible rationale for preference of the 4-position invokes a bimolecular reaction involving pre-coordination of pentafluoropyridine followed




**Scheme 9** C–F activation of pentafluoropyridine with $Cp_2Zr$




**Scheme 10** 1,2-addition of a C–F bond at an imidozirconocene

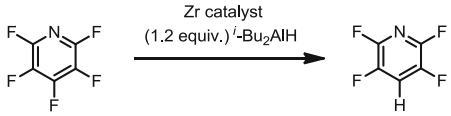
by the attack of another zirconocene molecule at the 4-position. Pre-coordination of the pyridine nitrogen to titanium is not possible due to its smaller size. Another possible rationale is that the titanium path proceeds through a concerted oxidative addition via a three-centered transition state.

In 2004, Bergman et al. reported activation of an aryl C–F bond across an imidozirconocene species [62]. Complex (**16**) reacts with pentafluoropyridine to generate (**17**) that was characterized by X-ray crystallography (Scheme 10). DFT calculations suggested the reaction is driven by formation of the [Zr]–F bond. This work is related to that of Mindiola, as these are the only examples of aryl C–F bond activation across a multiple bond.

## Catalytic Examples

Continuing their fruitful pursuits in early transition metal reactivity, the Rosenthal group has also reported elegant examples of catalytic C–F activation with zirconium. In 2007, they reported room temperature hydrodefluorination of pentafluoropyridine by zirconocene fluoro complexes and di(isobutyl)aluminum hydride (Scheme 11) [63]. Of the four zirconium complexes screened, *rac*-(ebthi)$ZrF_2$ (ebthi = $Cp'_2$) gave the highest turnover number (TON) of 57. Formation of the Al–F bond is thought to be the reaction's driving force.

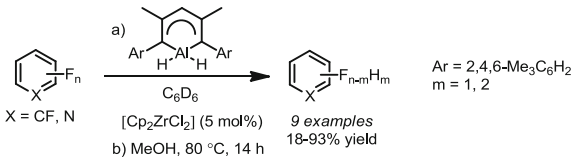
In 2012, zirconocene dichloride was shown to catalyze hydrodefluorination of *C* ($sp^2$)–F bonds using aluminum hydrides as reductants (Eq. 31) [64]. The yields and substrate scope were significantly increased when four-coordinate diketiminate-stabilized aluminum hydrides were used as reductants.




| Zr catalyst | Yield[a] | TON |
|---|---|---|
| *rac*-(ebthi)$ZrF_2$ | 26 | 57 |
| $Cp_2ZrF_2$ | 37 | 18 |
| [*rac*-(ebthi)ZrH(μ-H)]$_2$ | 33 | 67 |
| [$Cp_2$ZrH(μ-H)]$_2$ | 17 | 18 |

[a] isolated yield

**Scheme 11** Zr-catalyzed catalytic hydrodefluorination of pentafluoropyridine




(31)

## 7.3 Other Early Transition Metal Examples

### 7.3.1 Hafnium

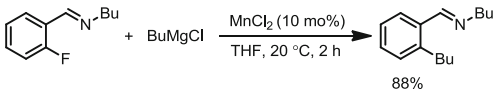
The only hafnium fluorine complex was reported by Schrock et al. in 2003 [65]. They synthesized a seven-coordinate [Hf]–F complex supported by pyridyldiamine ligands. The complex was characterized by X-ray crystallography and was found to have a [Hf]–F bond length of 1.989 Å.

# 8 Late Transition Metals

## 8.1 Group 7

### 8.1.1 Manganese

Cahiez reported the only example of a group 7 metal for the activation of aryl C–F bonds. In the presence of $MnCl_2$, activated aryl halides and ethers underwent cross-coupling with organomagnesium reagents (Eq. 32) [66]. In the absence of Mn, aromatic nucleophilic substitution proceeded affording the desired product, albeit in small amounts.




(32)

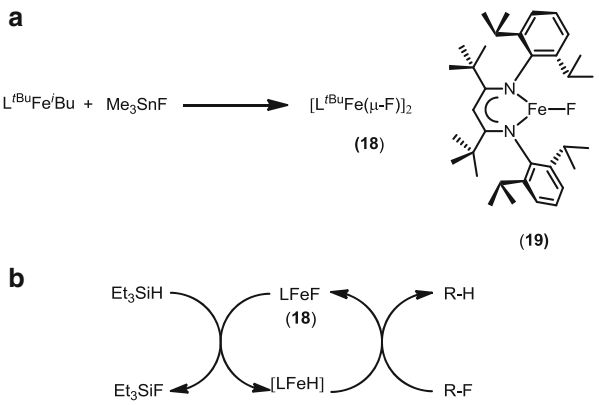
## 8.2 Group 8

### 8.2.1 Iron

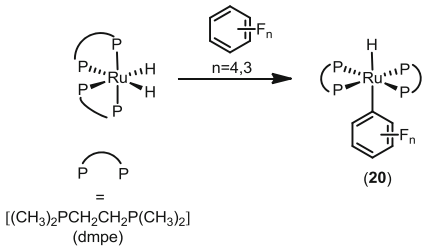
In 2005, Holland et al. reported the first example of iron fluoride complexes supported by diketiminate ligands [67]. Complexes (**18**) and (**19**) were accessed when an iron alkyl precursor was reacted with $SnMe_3F$. Confirmed by X-ray crystallography, the three-coordinate Fe species features a Fe–F bond length of 1.8079 Å (Scheme 12a). The dimer has a Fe–F bond length of 1.9557 and 1.9774 Å. The iron fluoride complex (**19**) was applied in catalysis where it was found to defluorinate hexafluorobenzene providing pentafluorobenzene (Scheme 12b). This process occurs via F–H exchange with $Et_3Si$–H and (**19**), which then reacts with hexafluorobenzene. Notably, complex **19** is the only known example of a trimeric fluoride complex of a transition metal.

### 8.2.2 Ruthenium

The Whittlesey group has been instrumental in pioneering stoichiometric and catalytic aryl C–F activation reactivity with ruthenium. In 1996, they reported activation of hexafluorobenzene using $[Ru(dmpe)H_2]$; dmpe = $(CH_3)_2PCH_2CH_2P(CH_3)_2$ at −78 °C to generate the pentafluorophenyl hydride complex, *trans*-$[Ru(dmpe)_2(C_6F_5)H]$ (**20**) (Eq. 33) [68]. The reaction also proceeded with 1,2,3,4-tetrafluorobenzene and 1,2,3-trifluorobenzene yielding C–F activation products only. Interestingly 1,3,5-trifluorobenzene or 1,2-difluorobenzene did not undergo C–F activation or C–H activation. The reaction is thought to proceed by a caged radical pair facilitating an electron transfer process [69].

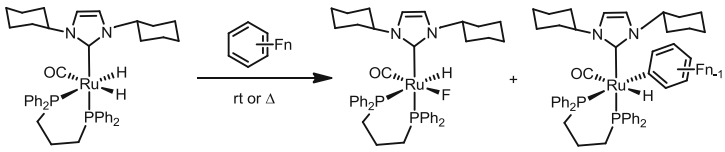



**Scheme 12** (**a**) Synthesis and catalytic reactivity of iron fluoride complexes. (**b**) Catalytic reactivity of iron fluoride complexes




(33)

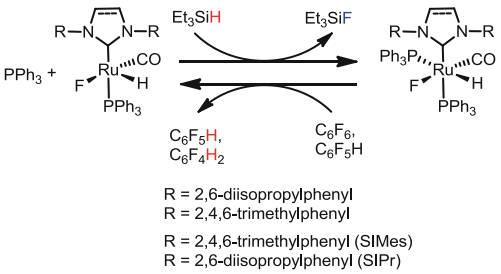
Whittlesey et al. found ruthenium *N*-heterocyclic carbene (NHC) complexes are able to activate C–F bonds of hexafluorobenzene, 1,2,3,4,5-pentafluoro-6-(trifluoromethyl)-benzene, and pentafluoropyridine (Eq. 34) [70]. Notably, only *N*-heterocyclic carbenes bearing alkyl groups were effective in C–F activation—NHCs bearing aryl groups, for example, were not active in C–F activation.




(34)

Related complexes having arene groups on the NHC were later found to be catalytically competent for the hydrodefluorination of aromatic fluorocarbons with alkyl silanes (Scheme 13) [71]. This reaction proceeded with high regioselectivity for 1,2-partially fluorinated products. This result is of particular relevance as examples of catalytic dehydrofluorination with rhodium and iron both generate 1,4-partially fluorinated products. A rationale for this result may be attributed to the preference of C–H activation over C–F activation followed by F/H exchange with silane.

Relative to C–F activation using ruthenium catalysts supported by NHC ligands, work of C–F activation with ruthenium catalysts supported by phosphorus ligands is less common. Even so Kakiuchi et al. illustrated $RuH_2(CO)(PPh_3)_3$ can effectively catalyze C–F activation of fluorinated aromatic ketones in the presence of CsF and trimethylvinylsilane [72].




**Scheme 13** Ruthenium-catalyzed hydrodefluorination of aryl fluorocarbons with triethylsilane

## 8.3 Group 9

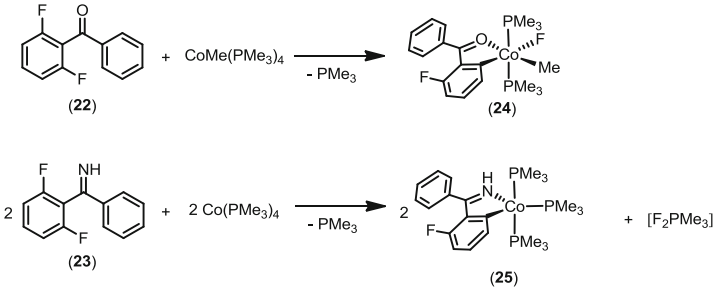
### 8.3.1 Cobalt

The first example of C–F-catalyzed cross-coupling with cobalt was reported by Knochel et al. in 2006 [73]. Aryl fluorides or tosylates were coupled with aryl copper reagents using 7.5 mol% of $Co(acac)_2$, 1 equivalent of $Bu_4NI$ and *p*-fluorostyrene. The reaction proceeded at room temperature in only 15 min affording a diverse selection of biaryls possessing various functional groups.

In 2009, Radius and Harms reported a cobalt-aryne (**21**) accessed through the C–F activation of perfluorinated toluene (Eq. 35) [77]. Detection of difluoromethylphosphorane supports a synergic mechanism involving the cobalt(0) center and a trimethylphosphine ligand.


(35)

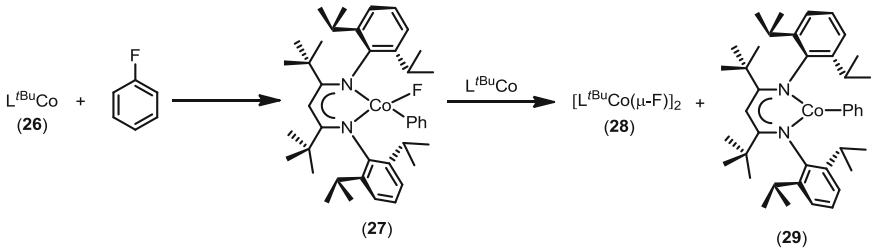
In 2010, a series of metallacycles accessed by C–F activation with cobalt was reported by Li and colleagues. The compounds (2,6-difluorophenyl)phenylmethanone (**22**) and 2,6-difluorobenzophenone (**23**) were reacted with $CoMe(PMe_3)_4$ and $Co(PMe_3)_2$ to form the respective metallacycles (**24**) and (**25**) (Eqs. 36 and 37) [74]. The C=N and C=O functionalities are believed to aid the C–F activation event by bringing the Co center and C–F bond closer together.




(36, 37)

More recently Li et al. described aryl C–F bond activation with $Co(PMe_3)_4$ on substrates without directing groups. In 2013 stoichiometric reactivity of $Co(PMe_3)_4$ with various polyfluorinated arenes was presented [75]. Depending on the substrate, aryl C–F and C–H bonds could be selectively activated. Not long after, in a follow-up report, $Co(PMe_3)_4$ was reported to catalyze hydrodefluorination of perfluoroarenes with sodium formate as a reducing agent [76, 78].

Holland and colleagues demonstrated C–F activation of fluorobenzene using a cobalt diketiminate-supported complex (**26**) to give a Co–F species (**27**)




**Scheme 14** Synthesis of cobalt fluoride complexes

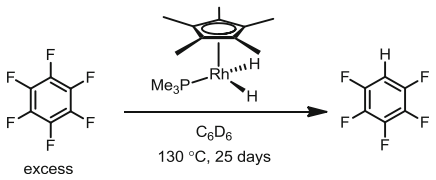
(Scheme 14) [79]. Upon reaction with another equivalent of L$^t$BuCo, a bridged fluoro complex (**28**) is obtained along with a Co–Ph species (**29**). A variety of other fluorinated arenes are tolerated in the reaction. Kinetic studies indicated the reaction to be first order in cobalt and fluorobenzene.

### 8.3.2 Rhodium

Stoichiometric Examples

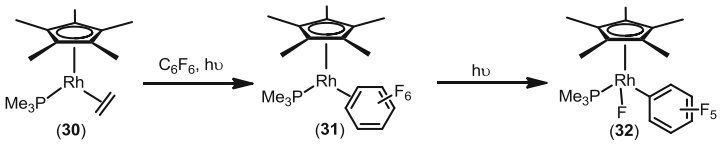
Stoichiometric reactions of rhodium with C–F bonds were first reported in 1991, when Perutz and coworkers described the reaction of hexafluorobenzene with Cp*Rh($PMe_3$)($C_2H_4$); Cp* = $C_5Me_5$ (**30**) (Scheme 15) [80]. Photolysis of Cp*Rh($PMe_3$)($C_2H_4$) in the presence of $C_6F_6$ gave rise to an $\eta^2$–$C_6F_6$ complex (**31**) which underwent subsequent C–F activation to yield (**32**). When Cp*Rh($PMe_3$)($C_2H_4$) was heated, the reaction did not proceed indicating the energetic barrier for C–F bond cleavage, and reorganization can only be overcome photochemically.

A report by Jones and colleagues described the reactivity of a related rhodium hydride complex. Cp*Rh($PMe_3$)$H_2$ was able to cleave C–F bonds of various fluoroaromatics 130 °C (Eq. 38) [81]. The rate of C–F bond activation increased with a greater number of fluorine atoms on the aromatic ring.

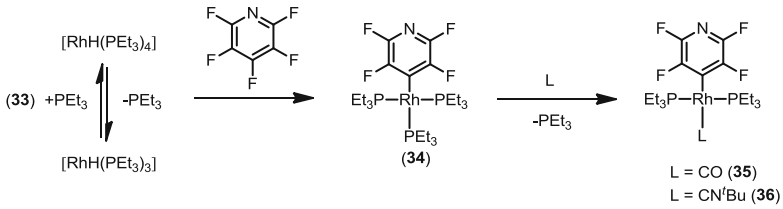



(38)

The fluoro analogue of Wilkinson's catalyst, RhF($PPh_3$)$_3$, was described by Grushin in 2004 [82]. The fluorine surrogate was achieved by reaction of [($Ph_3P$)$_2$Rh(μ-OH)]$_2$ with $Et_3N$·3HF to yield the dimer [($PPh_3P$)$_4$Rh(μ-F)$_2$]. Subsequent treatment of the dimer with $PPh_3$ gave the orange/yellow solid. Solid-state data indicated a Rh–F bond length of 2.070 Å and Rh–P bond length *trans* to fluorine of




**Scheme 15** Photolytic formation of Rh–F complex

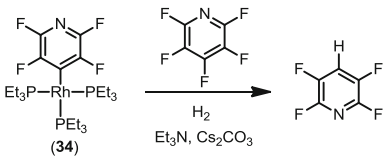



**Scheme 16** C–F activation of pentafluoropyridine with rhodium triethylphosphine complexes

2.193 Å. Reactivity screening indicated the complex to be unreactive toward chloroarenes.

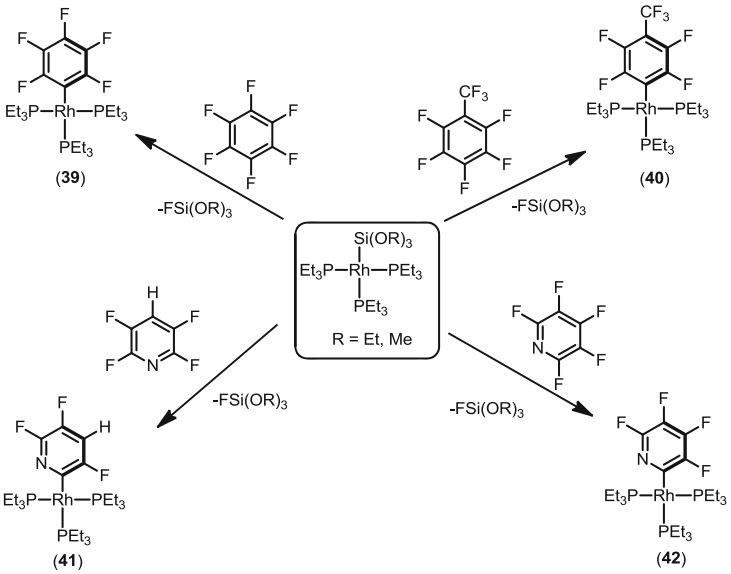
The rhodium triethylphosphine complex (**33**) was found effective in activating the 4-position of pentafluoropyridine to generate the tertrafluoro pyridyl complex (**34**) having a square planar geometry (Scheme 16) [83]. Treatment of (**34**) with CO or $CN^tBu$ produced (**35**) and (**36**). Further reaction of (**34**) with $CH_3I$ and heating led to reductive elimination generating acylated and methylated tetrasubstituted pyridines.

Complex (**34**) was also found to facilitate the hydrodefluorination of pentafluoropyridine (Eq. 39) [84]. The use of $H_2$ in the presence of TEA and $Cs_2CO_3$ with (**34**) yielded the hydrodefluorinated product over a period of days.

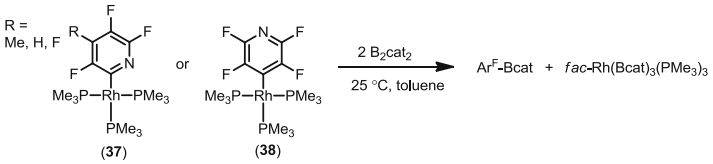



(39)

Also employing alkyl phosphine-supported Rh complexes, Perutz and colleagues found $[Rh(SiPh_3)(PMe_3)_3]$ to activate C–F bonds of pentafluoropyridine at the 2- and 4-position (Eq. 40) [85]. Subsequent treatment of (**37**) and (**38**) with bis-catecholatodiboron yields *fac*-$Rh(Bcat)_3(PMe_3)_3$ and pyridyl boronic esters.




**Scheme 17** C–F activation of fluoroaromatics mediated by rhodium silyl complexes



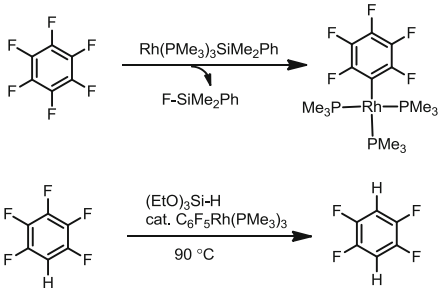

(40)

Recently Braun and coworkers reported experimental and computational results of related rhodium(I) silyl phosphine complexes [86]. Rhodium silyl complexes having different R groups, $RhSi(OR)_3(PEt_3)_3$; R = Me, Et, were found to activate hexafluorobenzene and perfluorotoluene giving (**39**) and (**40**) (Scheme 17). The fluorinated heterocycles, 1,2,4,5-tetrafluoropyridine and pentafluoropyridine, also underwent C–F activation at the 2-position affording (**41**) and (**42**). DFT calculations suggested C–F activation is assisted by the silyl group showing preference for activation in the 2-position. This route was shown to be more accessible than a C–F oxidative addition/Si–F reductive elimination pathway.

## Catalytic Examples

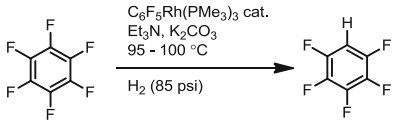
The first catalytic example of C–F activation using rhodium was reported by Milstein and coworkers in 1994. Rhodium silyl complexes accessed via reaction of $Rh(PMe_3)_3SiMe_2Ph$ and hexafluorobenzene (Eq. 41) were found to catalytically transform $C_6F_5H$ into 1,4-$C_6F_4H_2$ in a regioselective manner with $(EtO)_3SiH$ as a

hydride source (Eq. 42) [87]. The silyl ligand is thought to facilitate aromatic C–F cleavage by electron transfer from the electron-rich Rh complex.



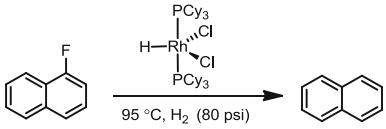

(41, 42)

Later, Milstein demonstrated hydrodefluorination of hexafluorobenzene could be achieved using $C_6F_5Rh(PMe_3)_3$ and hydrogen gas instead of hydrosilanes as the reductant. The reaction occurred with TEA and potassium carbonate $K_2CO_3$ with TONs up to 114 (Eq. 43) [88].




(43)

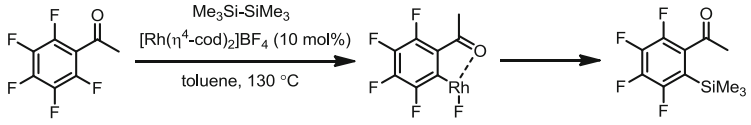
Hydrodefluorination by rhodium has also been achieved with unreactive fluorobenzenes under mild reaction conditions. In the presence of $H_2$, the rhodium phosphine complex $(Cy_3P)_2Rh(H)Cl_2$ hydrogenated 1-fluoronaphthalene homogenously as confirmed by Hg tests (Eq. 44) [89].




(44)

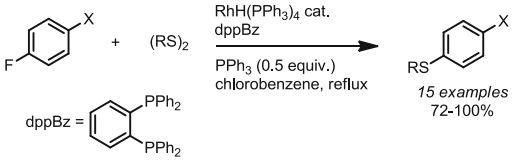
A cationic species was found to catalyze an exchange reaction between disilanes and fluorobenzenes. In the presence of $[Rh(cod)_2]BF_4$, fluoroacetophenones and (fluorophenyl)oxazolines exchange fluorine atoms with TMS groups to generate *o*-(trimethylsilyl)acetophenones (Scheme 18) [90]. The carbonyl and oxazoline functionality plays a role in initial coordination of Rh to F to facilitate Si–F exchange.

In 2008, Yamaguchi et al. described the formation of aryl thiols from aryl fluorides using a $RhH(PPh_3)_4$ and dppBz (1,2-Bis(diphenylphosphino)benzene)



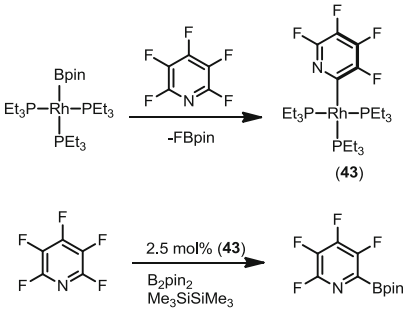

**Scheme 18** Rhodium-catalyzed fluorine exchange with disilanes

catalyst system (Eq. 45) [91]. The reaction tolerates a range of functionalities including halides, ketones, nitro, and cyano groups. The mechanism is not understood at present; however, the authors suggest two possibilities. The first involves oxidative addition, while the second encompasses nucleophilic aromatic substitution of the aryl fluoride with a rhodium thiolate species.




(45)

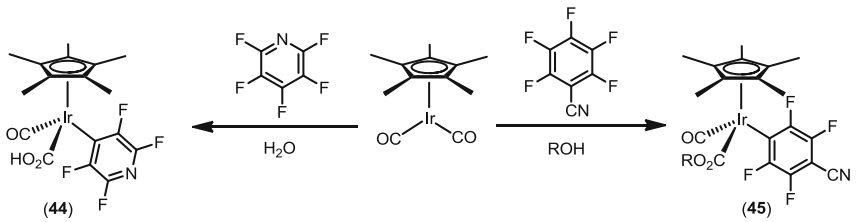
Braun et al. reported a 16-electron rhodium(I)–boryl complex to C–F activation of pentafluoropyridine at the 2-position to give (**43**) (Eq. 46) [92]. DFT studies indicated that the observed regioselectivity originated through a boryl-assisted pathway. In this manner, boron acts as a Lewis acid assisting in the transfer of fluorine via a four-centered transition state. The nitrogen lone pair plays a key role in stabilizing the Rh center. The rhodium(I)–boryl complex was found to successfully catalyze borylation of pentafluoropyridine at the 2-position (Eq. 47). This reaction is relevant as the functionalization of pyridines at the 2-position is nontrivial.



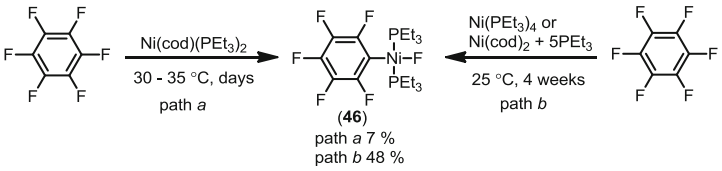

(46, 47)

### 8.3.3 Iridium

Unlike rhodium, examples of aryl C–F activation with iridium are uncommon. Chan and Leong described C–F activation of pentafluoropyridine and pentafluorobenzonitrile with $Cp^*Ir(CO)_2$. Upon C–F activation, the generated complexes reacted with water to generate the iridacarboxylic acids (**44**) and (**45**) (Scheme 19) [93]. The reaction is thought to proceed by nucleophilic aromatic substitution, followed by attack of ROH on the carbonyl ligand.




**Scheme 19** Reaction of pentafluoropyridine and pentafluorobenzonitrile with $Cp^*Ir(CO)_2$




**Scheme 20** Oxidative addition of hexafluorobenzene to nickel

## *8.4 Group 10*

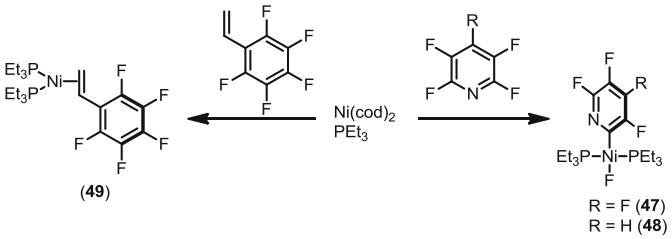
### 8.4.1 Nickel

Stoichiometric Examples

The first example of C–F oxidative addition at a transition metal center was using nickel in 1977 reported by Mahan et al. Over a period of days, hexafluorobenzene underwent oxidative addition across $Ni(cod)(PEt_3)_2$ to generate the pentafluorophenylnickel(II) complex (**46**) in 7 % yield (Scheme 20, path *a*) [94]. Unfortunately the complex was only characterized by infrared spectroscopy and elemental analysis due to the small amount isolated. Since this report, however, a crystal structure has been obtained by Perutz et al. (Scheme 20, path *b*) [95]. The oxidative addition process occurred via an alternate synthetic route involving $Ni(PEt_3)_4$ or $Ni(cod)_2$ and $PEt_3$ giving (**46**) in 48 % yield.

Mechanistic work by Johnson and colleagues suggests $Ni(PEt_3)_4$ may activate aryl C–F bonds through radical intermediates. Experiments with a $Ni(PEt_3)_2$ synthon and $C_6F_5H$ resulted in *ortho*- and *meta*-C–F activation suggesting a radical mechanism may be operating [96]. Reactivity of $Ni(PEt_3)_4$ with other aryl fluorides has also been investigated. Johnson and colleagues have also considered reactivity of $Ni(PEt_3)_4$ with other aryl fluorides including tetrafluorobenzenes [97]. Results from these experiments revealed unexpected aryl C–F activation products, further suggesting radical mechanism may be present.

At the same time, Perutz described analogous reactivity with pentafluoropyridine and 2,3,5,6-tetrafluoropyridine which underwent oxidative addition at Ni (0) (Scheme 21) [95]. Activation predominantly occurred at the 2-position of the



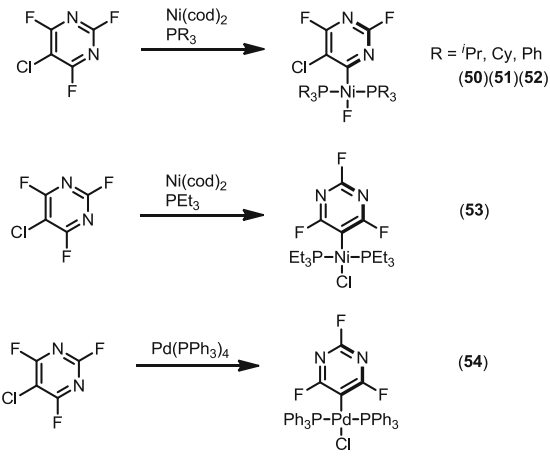

**Scheme 21** Nickel-mediated C–F activation of fluoroarenes

pyridyl ring resulting in the Ni–F complexes (**47**) and (**48**) with the aryl ring perpendicular to the plane of nickel. It is noteworthy that pentafluoropyridine and 2,3,5,6-tetrafluoropyridine usually undergo nucleophilic substitution in the 4-position. DFT studies indicate regioselectivity is attributable to a phosphine-assisted pathway. This involves initial transfer of fluorine to phosphine before migrating to nickel [95]. The pyridine nitrogen helps to stabilize the metallophosphorane species by coordinating in a 1,2-diyl coordination mode. Reaction of Ni $(cod)_2$ and $PEt_3$ with 2,3,4,6-pentafluorostyrene resulted in an alkene coordination product (**49**) [98].

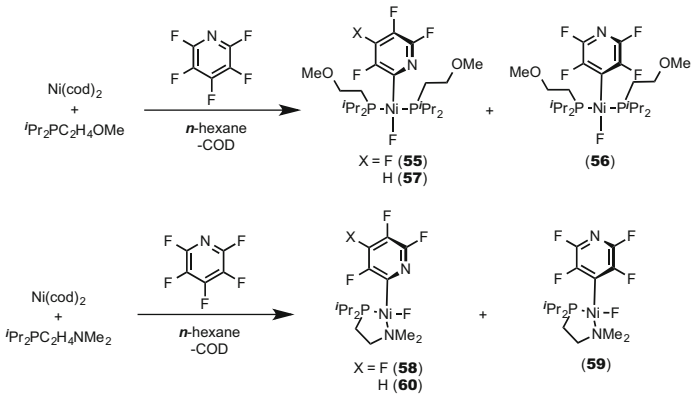
An experimental and computational study on the mechanism of $Ni(PEt_3)_2$ with *N*-heterocyclic fluorinated aryls by Johnson et al. indicated unusual selectivity in the C–F activation of pentafluoropyridine and tetrafluoropyridine resulting in a mixture of 2 and 4 activation products [99]. An EPR (electron paramagnetic resonance) spectrum of an isolated intermediate indicated the presence of a radical intermediate suggesting a concerted oxidative addition or phosphine-assisted pathway may not be operative in these examples. Further evidence however is warranted for a greater understanding of such a possible radical route.

Other *N*-heterocyclic fluorinated aryls have also been considered for C–F activation. Braun et al. reported an example of selective C–X; X = Cl, F activation in 5-chloro-2,4,6-trifluoropyrimidine with $Ni(cod)_2$. Depending on the choice of ligand, the C–Cl or C–F bond was selectively activated (Scheme 22) [100]. Pre-coordination of the nitrogen atom to the nickel center is believed to be crucial for the C–X activation to proceed. The difference in regiospecificity is postulated to be a result of steric factors. In a subsequent report, the Braun group also described the formation of a related $P^iPr_3$ complex $NiF(4\text{-}C_4N_2ClF_2)(P^iPr_3)_3$ (**50**). When the same reaction was carried out with $Pd(PPh_3)_4$, insertion into the C–Cl bond resulted yielding *trans*-$[PdCl(5\text{-}C_4N_2F_3)(PPh_3)_3]$ (**52**) [101].

Braun et al. have also described C–F activation of *N*-heterocyclic fluorinated aryls with the phosphine ligands $^iPr_2PCH_2CH_2OMe$ and $^iPr_2PCH_2CH_2NMe_2$ in the presence of $Ni(cod)_2$ [102]. Pentafluoropyridine underwent C–F activation in the 2- and 4-positions generating (**55**) and (**56**) (Eq. 48). 2,3,5,6-Tetrafluoropyridine was also C–F activated in the presence of each phosphine ligand to give (**57**) and (**60**) (Eq. 49). Complexes (**55**), (**56**), (**58**), and (**59**) were later determined to show catalytic reactivity with various aryl-substituted boronic acids affording new polyfluorinated building blocks.

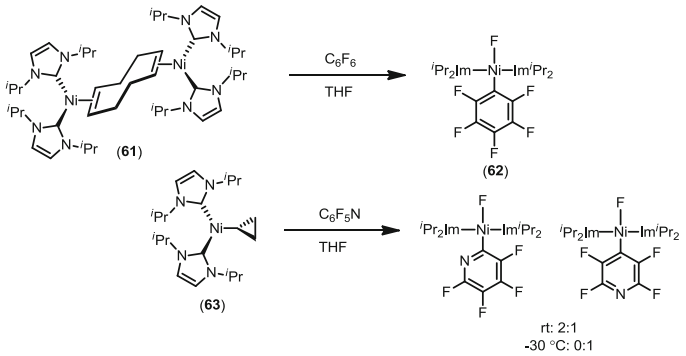



**Scheme 22** Reactivity of 5-chloro-2,4,6-trifluoropyrimidine with Ni and Pd



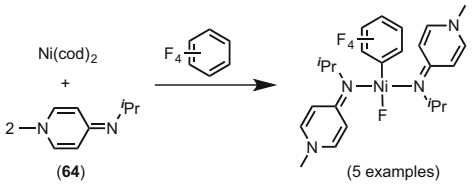

(48, 49)

In addition to phosphine ligands, NHCs have also been used as support ligands in aryl C–F activation with nickel. In 2005, Radius and colleagues reported the nickel NHC complex $[Ni_2(^iPr_2Im)_4(cod)]$; (**61**) was effective in activating hexafluorobenzene to afford *trans*-$[Ni(^iPr_2Im)_2(F)(C_6F_5)]$ (**62**) in a distorted square planar orientation (Eq. 50) [103]. Relative to phosphine ligands, C–F activation with nickel NHC complexes proceeds much faster. Based on DFT calculations, this observation is attributed to the charge separation of the highly nucleophilic $Ni(^iPr)_2$ and the C–F bond. Complex (**59**) has also been found reactive toward other fluorinated aryls including octafluorotoluene and perfluorotoluene [98]. A related complex (**63**) was found to activate the 2- and 4-position of pentafluoropyridine depending on the temperature (Eq. 51) [104].




(50, 51)

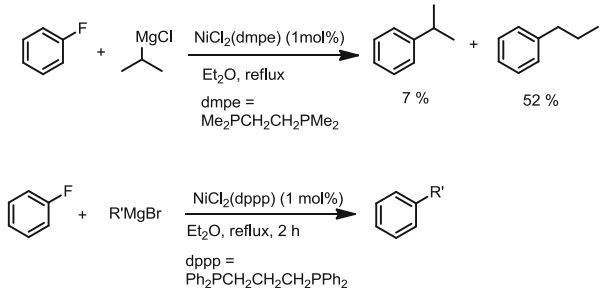
In 2009, Johnson and Doster reported a nitrogen donor ligand (**64**) similar to an NHC was able to facilitate C–F activation of tetrasubstituted fluorobenzenes (Eq. 52) [105]. The 4-isopropylaminopyridine derivative's strong σ-donor properties were shown to facilitate oxidative addition of C–F bonds to nickel. This example further highlights an alternative ligand set to the commonly employed NHCs in activation of inert bonds such as C–F.




(52)

Catalytic Examples

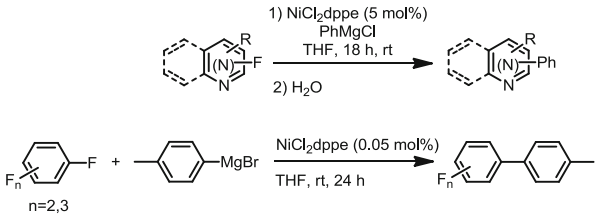
Catalytic C–F activation with nickel was first reported in the early 1970s by the Japanese group of Kumada [106]. They determined Ni(II) salts were able to cross-couple fluorobenzene to isopropyl magnesium chloride under refluxing conditions in diethyl ether to generate new carbon–carbon bonds with isomerization of the secondary alkyl Grignard reagent (Eq. 53). Since this report, a number of groups have expanded the scope of this reaction to include alkyl, aryl, and alkenyl Grignard reagents (Eq. 54) [107].




(53, 54)

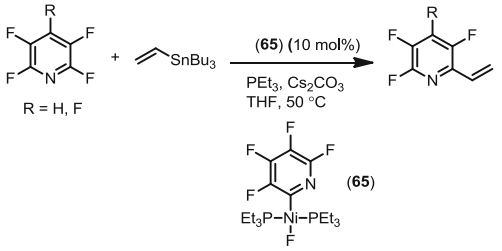
Commercially available bidentate phosphine ligands in combination with Ni $(cod)_2$ have also been found successful in coupling fluoroaromatics and Grignard

reagents [108]. A variety of fluoroazines and fluorodiazines are tolerated in the transformation (Eq. 55). Tomao et al. also reported nickel-catalyzed cross-coupling reactions of fluoroaromatics with Grignard reagents using bidentate phosphine ligands (Eq. 56) [109].



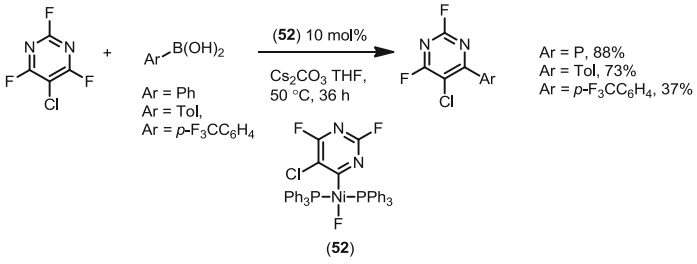

(55, 56)

Within the last decade, incorporation of nickel phosphine complexes into various C–F coupling reactions has increased significantly. Perutz and Braun reported the first cross-coupling reaction of a polyfluorinated molecule with nickel in 2001 [110]. Nickel phosphine complex (**65**) was used for the cross-coupling of pentafluoropyridine and 2,3,5,6-tetrafluoropyridine with vinyltin reagents to generate polyfluorinated aryls (Eq. 57).




(57)

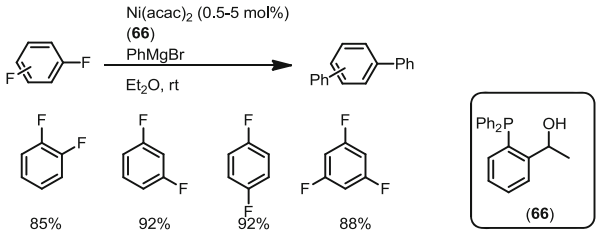
Following stoichiometric studies of nickel and 5-chloro-2,4,6-trifluoropyrimidine, complex (**52**) was found to be effective in catalyzing the Suzuki–Miyaura cross-coupling of 5-chloro-2,4,6-trifluoropyrimidine to boronic acids (Eq. 58) [101]. In the presence of $Cs_2CO_3$ and THF at 50 °C $TolB(OH)_2$; (Tol = Toluene), $PhB(OH)_2$ and $p\text{-}CF_3C_6H_4B(OH)_2$ were coupled to 5-chloro-2,4,6-trifluoropyrimidine to generate new $C(sp^2)$–$C(sp^2)$ bonds.




(58)

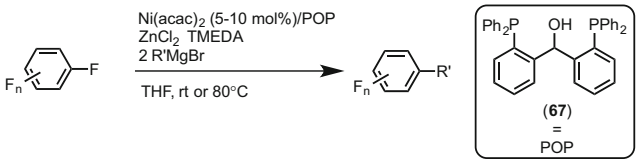
The Nakamura group reported a push-pull strategy for nickel-catalyzed cross-coupling reactions of aryl fluorides with Grignard reagents. Through careful ligand

design, they discovered a hydroxyphosphine ligand could cross-couple typically unreactive fluoroarenes with Grignard reagents. The catalyst system was so effective that all aryl C–F bonds were transformed into aryl–aryl bonds (Eq. 59) [111]. The necessity of the OH group in the ligand (**66**) was established as the anisole analogue did not generate the desired products. DFT and kinetic isotope experiments indicated the reaction proceeds through a nickel–magnesium bimetallic catalytic species that reduces Ni(II) to Ni(0) upon deprotonation of the PO ligand.



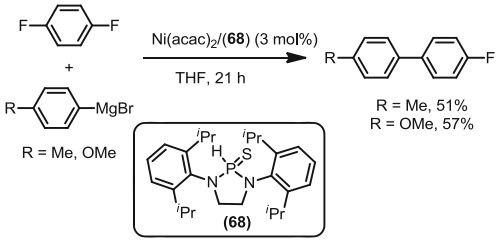

(59)

Since their report using the hydroxyphosphine ligand (**66**), the Nakamura group has illustrated a related ligand bearing two phosphines to be effective in nickel-catalyzed monosubstitution of aryl fluorides with organozinc reagents (Eq. 60) [112]. The alkoxydiphosphine ligand (**67**) is believed to act in a similar manner as (**67**), stabilizing the Ni(0) complex, accelerating product expulsion, and preventing multisubstitution from occurring on substrates bearing more than one carbon–fluorine bond. Computational results indicated that the alkoxy and phosphine functionalities on the ligand act independently in enabling Lewis acid and nickel catalyst cooperation [113].




(60)

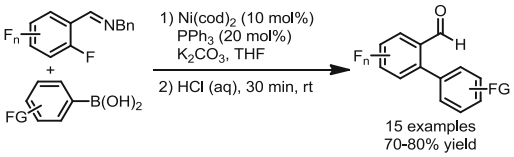
Nonactivated fluoroaromatics have also been cross-coupled to Grignard reagents using a diaminophosphine sulfide ligand (**68**)/Ni(acac)$_2$ catalyst system (Eq. 61) [114]. The reaction proceeded at ambient temperatures and produced monosubstituted products exclusively.




(61)

The Love group recently reported an example of Suzuki–Miyaura cross-coupling of aryl fluorides and boronic acids to generate polyfluorinated aromatics

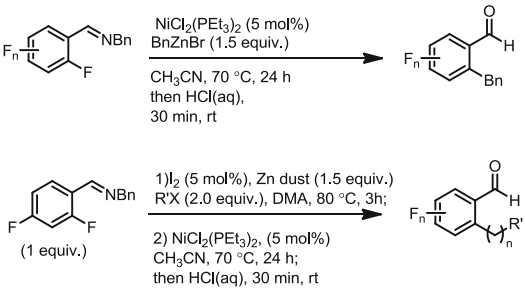
(Eq. 62) [115]. The reaction proceeds under mild reaction conditions and is tolerant to a range of boronic acids of varying electronic nature. Although the reaction does require an imine directing group, it is readily hydrolyzed during workup procedures to afford an aldehyde, providing a site for further synthetic manipulation.




(62)

Around the same time the above reaction was described, Chatani and coworkers communicated two methods of nickel-catalyzed Suzuki–Miyaura cross-coupling reactions using fluoride cocatalysts and ($sp^2$) hybridized N-containing directing groups [116]. Although a variety of functional groups and substituents were tolerated in the reactions, products were limited to having one remaining fluorine atom or none at all.

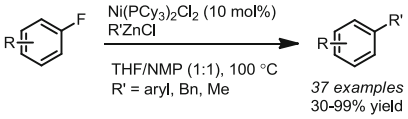
The Love group has also recently described an example of nickel-catalyzed Negishi cross-coupling of aryl fluorides with organozinc reagents to afford new C ($sp^2$)–C($sp^3$) bonds [117]. Employing a bench-stable $NiCl_2(PEt_3)_2$ salt, a variety of polysubstituted fluoroaromatics may be accessed using either alkyl zinc halide reagents including those having β-hydrogen or diorganozinc reagents (Eq. 63). In addition, this system can catalyze the Negishi reaction of organozinc reagents made in situ (Eq. 64). This is an attractive feature as many organozinc reagents are not readily available from commercial suppliers.




(63, 64)

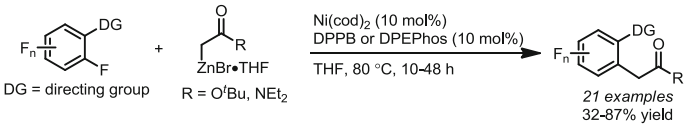
It is also possible to install methyl groups of polyfluoroimines using $ZnMe_2$. The nickel-catalyzed transformation was illustrated, and Li and coworkers further highlighted the utility of imine directing groups in C–F activation [118].

Negishi cross-coupling of aryl fluorides is not limited to aryl fluorides having a directing group. Wang and Zhu revealed $Ni(PCy_3)_2Cl_2$ is able to catalyze cross-coupling of aryl, methyl, and benzyl zinc chlorides to aryl fluorides not having directing groups in the presence of a THF/NMP solvent mixture at 100 °C affording a variety of substituted polyfluorinated arenes (Eq. 65) [119].



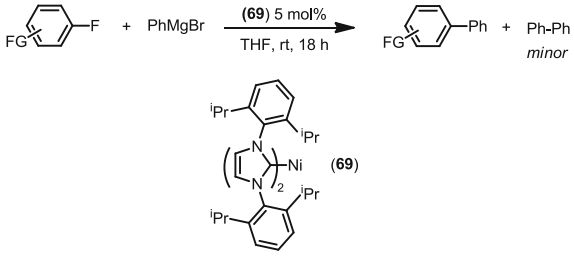

(65)

Zinc enolates have been reported to cross-couple to polyfluoroarenes possessing directing groups such as pyridines, oxazolines, and quinoxalines in the presence of nickel catalysts. Lu and colleagues reported the first example of nickel-catalyzed α-arylation of polyfluoroarenes providing a route to alpha-aryl carboxylic acids and alpha-aryl amides (Eq. 66) [120]. The transformation requires the use of bidentate phosphine ligands and tolerates amines, amides, ethers, and esters.



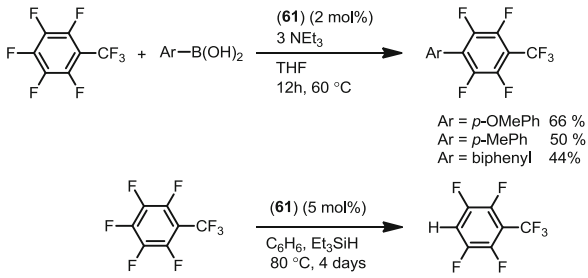

(66)

Nickel NHC complexes have been found catalytically active toward fluoroaromatics as well. The group of Herrmann determined that the nickel NHC complex (**69**) could catalyze the reaction between aryl fluorides and Grignard reagents to create biaryls (Eq. 67) [121]. A small amount of homocoupled Grignard reagent was also detected. The catalytically active species is thought to be a Ni (0) species coordinated by a sole NHC ligand.



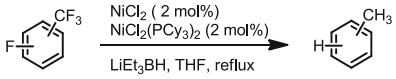

(67)

The previously mentioned nickel NHC complex, [Ni($^{I}$Pr)$_4$(cod)] (**61**), was found to catalyze Suzuki–Miyaura cross-coupling of fluoroaromatics (Eq. 68) [122]. Notably, cross-coupling only took place at the *para*-position, while the *ortho*- and *meta*-positions were untouched in the transformation. A short time ago, complex (**61**) was also found to catalyze hydrodefluorination of fluoroaromatics with hydrosilanes as the hydride source (Eq. 69) [123].




(68, 69)

Nickel has also been found to catalyze hydrodefluorination of polyfluorinated arenes. In 2012, Cao et al. illustrated a cocatalyst system composed of nickel(II) chloride, and bis(tricyclohexylphosphine)nickel(II)chloride was able to hydrodefluorinate various aryl fluorides in the presence of superhydride (Eq. 70) [124]. The hydrodefluorination of heterocycle-polyfluoroarenes has also been reported by Zhang et al. in 2013. Using $NiCl_2 \cdot 6H_2O$ and triethylsilane as a hydride source, *ortho*-selective hydrodefluorination was achieved [125].



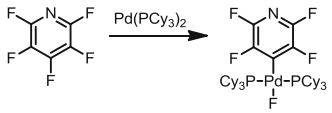

(70)

The scope of nickel-catalyzed hydrodefluorination has recently been expanded to a variety of other fluoroaromatics using a bridging hydride nickel dippe complex under thermal conditions [126]. Hydrodefluorination products of fluoroaromatics were also obtained when only phosphine ligands were added to the reaction solution. Thus, it is possible that hydrodefluorination may proceed in the absence of a metal or silane source. Mechanistic details are vague at present although they remain an ongoing area of research.

### 8.4.2 Palladium

Stoichiometric Examples

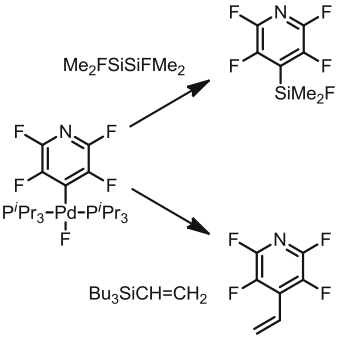
Extending their work to other group 10 metals, Perutz and Braun have also considered the reactivity of palladium and platinum toward C–F bonds. In 2004, $Pd(PCy_3)_2$ was found to selectively activate pentafluoropyridine at the 4-position (Eq. 71) [95]. Follow-up experimental and theoretical studies determined the reaction to proceed through a phosphine-assisted pathway whereby the phosphine ligand accepts a fluorine atom followed by the transfer of the alkyl group from phosphine to palladium. It should be noted that concerted oxidative addition may also be operational [127, 128].



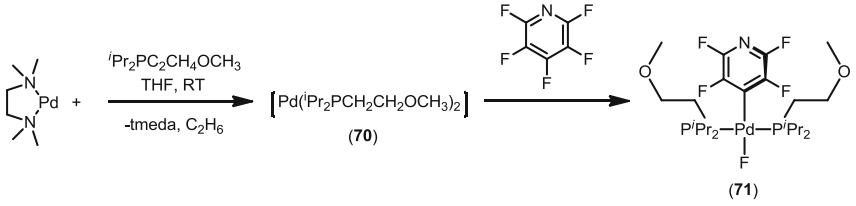

(71)

A related Pd complex having $P^iPr_3$ ligands, namely, $Pd(^iPr_3)_2$, was found to react with $Me_2FSi–SiFMe_2$ and $Bu_3SnCH=CH_2$ to form the corresponding silyl and vinyl products (Scheme 23) [129].

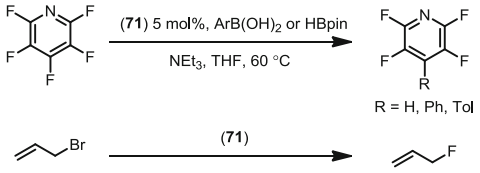
In 2014, Braun et al. described the reactivity of a Pd complex bearing OMe ligands toward C–F activation. The palladium complex (**70**) having extended alkyl chains on phosphorus ligands was found to activate pentafluoropyridine exclusively at the 4-position giving (**71**) (Scheme 24) [130]. The OMe group on the ligand is thought to accelerate the reaction in some way; however, the exact role is not currently understood. The mechanism is believed to operate through a phosphine-assisted, concerted oxidative addition, or nucleophilic attack pathway at the fluorinated pyridine. Complex (**71**) was also able to catalytically cross-couple pentafluoropyridine with boronic acids. Moreover, complex (**71**) was able to hydrodefluorinate pentafluoropyridine with HBin (Eq. 72) and react with electrophilic compounds including 3-bromopropene for C($sp^3$)–F bond formation (Eq. 73).




**Scheme 23** Reactivity of a Pd–F complex




**Scheme 24** Synthesis and reactivity of *trans*-[Pd(F)(4-$C_5NF_4$)($^iPr_2PCH_2CH_2OCH_3$)$_2$]




(72, 73)

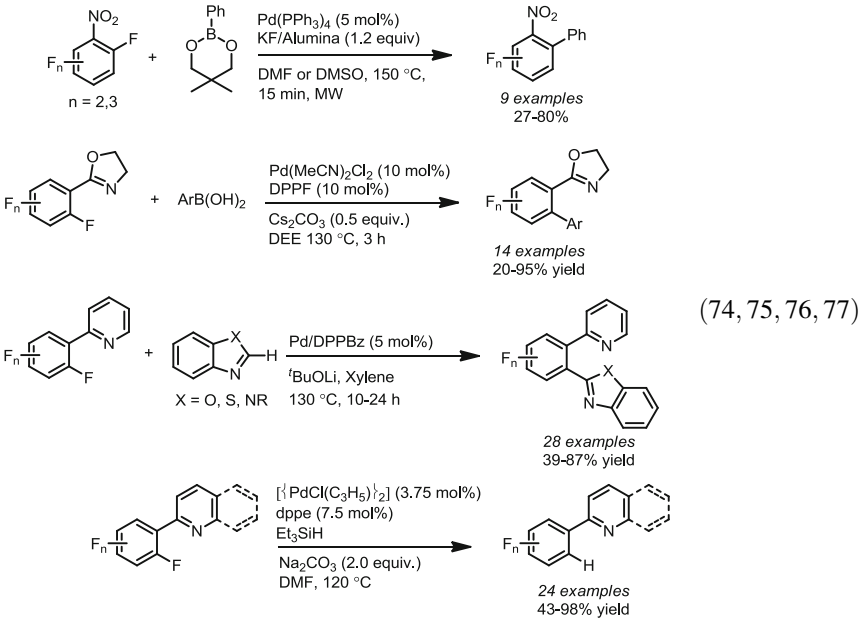
Catalytic Examples

Relative to the number of stoichiometric C–F activation examples with palladium, the number of catalytic examples is much greater and has been increasing rapidly. Although there are many examples of palladium-catalyzed cross-coupling reactions with aryl fluorides, this section will focus on examples from the last 5 years.

Palladium-catalyzed regioselective C–F activation has been achieved using a number of different directing groups. In 2010, the group of Cargill reported a regioselective cross-coupling reaction of polyfluorinated nitrobenzene and boronic esters to afford fluorinated nitrobenzene derivatives (Eq. 74) [131]. C–F activation occurred exclusively at the *ortho*-position suggesting the nitro group directs the palladium catalyst toward the C–F bond. A number of substrates differing in fluorine substitution were tolerated in the reaction under microwave and thermal conditions.

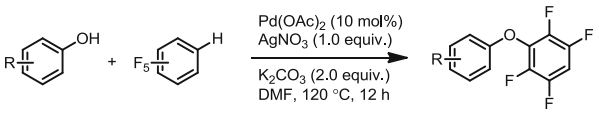
Selective *ortho*-C–F activation was reported using an oxazoline directing group in the presence of a $Pd(MeCN)_2Cl_2$ and DPPF (1-1′-Bis(diphenylphosphino)ferrocene) (Eq. 75) [132]. The transformation was tolerant to a large selection of functional groups including cyano, ester, ketones, aldehydes, and trifluoromethyl groups.

The use of a pyridyl directing group has also been found effective in Pd-catalyzed *ortho*-C–F activation. The pyridine directing group has been used in C–F/C–H cross-coupling as well as hydrodefluorination of fluoroaromatics with $Et_3SiH$ (Eqs. 76 and 77) [133, 134].



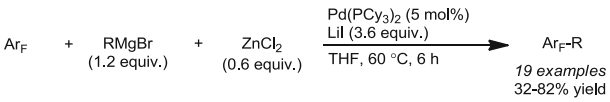

(74, 75, 76, 77)

So far all catalytic examples thus far involving palladium have required the use of a directing group. It should be noted palladium is able to catalyze C–F activation on substrates not possessing such groups. One such example was reported by Weng et al. in 2013, where polyfluorinated aryl ethers were obtained using $Pd(OAc)_2$ upon reaction of phenols with aryl fluorides (Eq. 78) [135]. The reaction proceeded with high chemo- and regioselectivity under ligand-free conditions.




(78)

Palladium has also been found to cross-couple perfluoroarenes to diaryl zinc compounds with the additive LiI (Eq. 79) [136]. A three-coordinate monophosphine-ligated species $[Pd(CF_5)I(PCy_3)]$ was identified as being a key intermediate in the transformation. The additive LiI is believed to play a role in accelerating the oxidative addition step. LiI also facilitates the formation of a reactive zincate species involved in the transmetalation step. A number of polyfluoroarenes were tolerated in the reaction including octafluorotoluene, pentafluoropyridine, and perfluoronaphthalene.

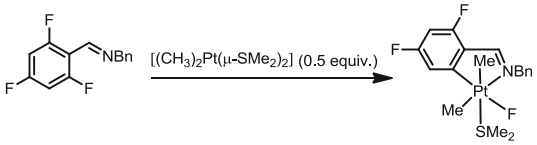


(79)

### 8.4.3 Platinum

Stoichiometric Examples

The first account of stoichiometric C–F activation with platinum was reported by Crespo and Martinez in the early 1990s. They discovered that the platinum dimer $[(CH_3)_2Pt(\mu\text{-}SMe_2)]_2$ was able to activate a series of aryl imines. C–F activation occurred exclusively in the *ortho*-position even when weaker C–Cl and C–Br bonds were present on the aryl ring (Eq. 80) [137]. Thorough mechanistic studies indicated the reaction proceeds via an oxidative addition process [138, 139]. Notably reductive elimination of ethane was not observed, a typical side reaction of these Pt (IV) species.

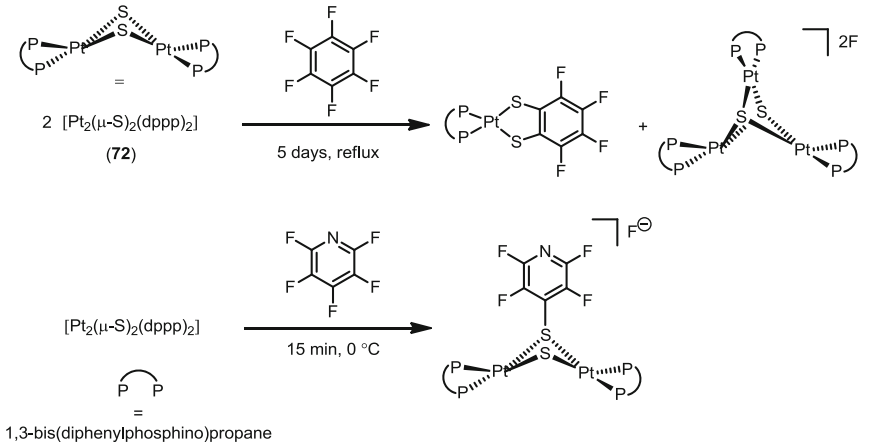


(80)

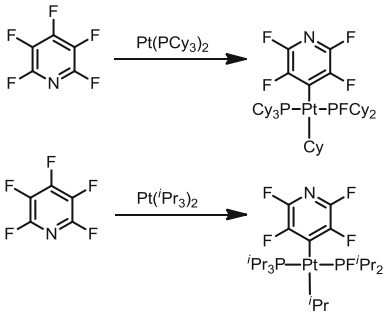
Much more recently, Nova and colleagues described another platinum dimer, namely, $[Pt_2(\mu\text{-}S)_2(dppp)_2]$ (**72**), to activate C–F bonds of hexafluorobenzene and pentafluoropyridine (Scheme 25) [140]. The reaction with hexafluorobenzene required refluxing for 5 days, whereas the reaction with pentafluoropyridine took place in just 15 min at 0 °C. The reactivity rate difference is attributable to the initial C–F activation energetic barrier. The first C–F activation barrier of pentafluoropyridine is 85.9 kJ mol$^{-1}$ much lower than hexafluorobenzene at 131.7 kJ mol$^{-1}$. Mechanistic investigations determined the reaction to proceed via a nucleophilic aromatic substitution pathway where the sulfido bridging ligand replaces the fluoride anion.

Platinum phosphine complexes are also able to activate pentafluoropyridine. Analogous to palladium, C–F activation of pentafluoropyridine occurs only at the 4-position (Scheme 26) [95, 128]. C–F activation is believed to occur via alkyl transfer to platinum.

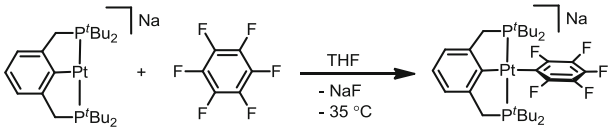
Not long ago, Milstein and coworkers described reactivity of an electron-rich Pt pincer complex with hexafluorobenzene to form a Pt(II)–F complex (Eq. 81) [141]. The reaction proceeded in just 2 h at −35 °C in THF. It is likely the operative mechanism involves an electron transfer process where Pt(0) becomes Pt(I) via transfer of an electron to hexafluorobenzene to form the radical anion $[C_6F_6]^-$. A fluoride is then lost from $[C_6F_6]^-$ to give $[C_6F_5]^-$ that then couples to Pt(I).




**Scheme 25** C–F activation of fluoroaromatics with $[Pt_2(\mu\text{-}S)_2(dppp)_2]$




**Scheme 26** Stoichiometric Pt C–F activation of pentafluoropyridine

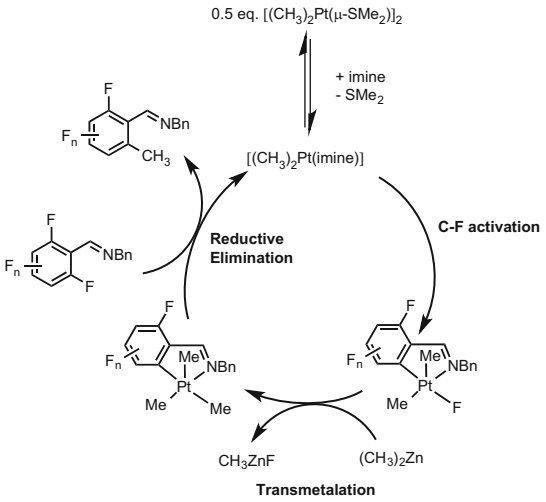



(81)

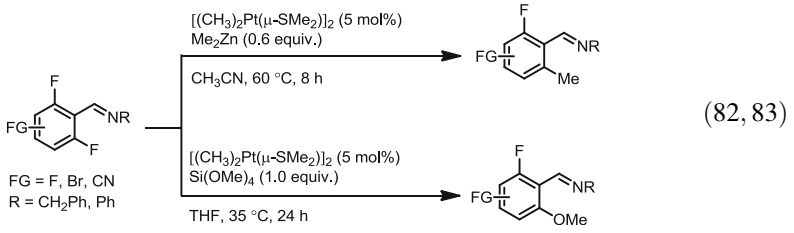
## Catalytic Examples

The Love group was the first to report examples of platinum-catalyzed methylation and methoxylation of fluorinated aryl imines in the late 2000s (Eqs. 82 and 83) [142, 143]. Having Crespo and Martinez's stoichiometric Pt C–F activation studies [137] for inspiration, the Love group determined the Pt(II) dimer $[(CH_3)_2Pt(\mu\text{-}SMe_2)]_2$ was an effective catalytic precursor for the cross-coupling reaction of polyfluorinated aryl imines and dialkyl zinc reagents. These methods offer high selectivity for the *ortho*-position and are tolerant to a number of functional groups. Additionally, directing groups other than imines are accommodated including oxazolines and imidazoles [144]. It should be noted that the imine scope is limited

**Scheme 27** Possible Pt(II)-catalyzed methylation mechanism




to substitution at both the ortho-positions, due to preferential *ortho*-C–H activation by Pt. Furthermore, there must be at least three electron-withdrawing groups present on the imine aryl ring in order for the reaction to proceed.



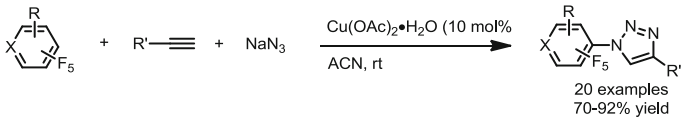

(82, 83)

Mechanistic studies indicate the reaction to proceed through a classical two-electron coupling pathway beginning with oxidative addition, transmetalation, and reductive elimination (Scheme 27) [145, 146].

## 8.5 Group 11

### 8.5.1 Copper

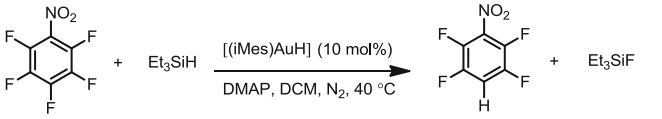
Until very recently, an example of C–F activation employing copper had not been described. Although not directly involved in aryl C–F activation, $Cu(OAc)_2$ $H_2O$ was found to play a role in accessing 1-polyfluoroaryl-1,2,3 triazoles (Eq. 84) [147]. Fluorine-containing triazoles were obtained in a three-component one-pot reaction involving aryl fluorides, sodium azide, and a variety of terminal alkynes. Sodium azide C–F activates the fluorinated arene that is coupled to the alkyne facilitated by copper. The reaction is similar to that of the extensively studied copper cycloaddition reactions between azides and alkynes to access triazoles; thus, it further expands possible triazoles that may be accessed.




(84)

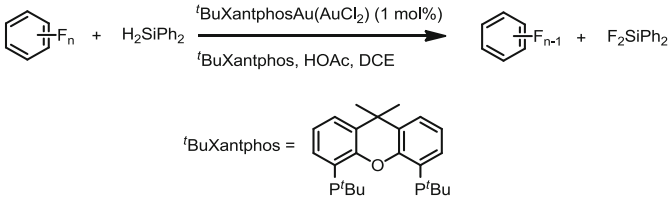
### 8.5.2 Gold

Examples of C–F activation with gold are rare. Zhang and colleagues described the first example of π–π-assisted hydrofluorination of fluoroaromatics using a gold hydride complex (Eq. 85) [148]. This work constitutes a new pathway for intermolecular C–F activation that occurs via a π–π-assisted route. Pentafluoronitrobenzene (PFNM) was strategically chosen to lower the π* orbital of the arene rendering the C–F group more susceptible to cleavage. UV–Vis spectra illustrated a new band at 413 nm indicating an interaction between PFNM and DMAP, although the exact interaction has not yet been characterized.




(85)

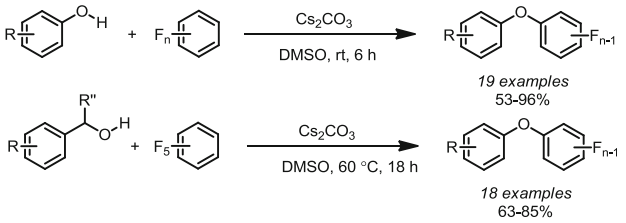
Following this report, Zhang and coworkers reported the very first example of gold-catalyzed C–F activation of polyfluorinated arenes (Eq. 86) [149]. Hydrodefluorination of varying fluoroaromatics occurs with a xantphos/gold-supported complex. A wide variety of functional groups were tolerated in the reaction including ketones, esters, amides, carboxylates, alkenyl, and alkynyl groups. Computational studies indicated C–F bond oxidative addition across gold is an important step for the reaction.




(86)

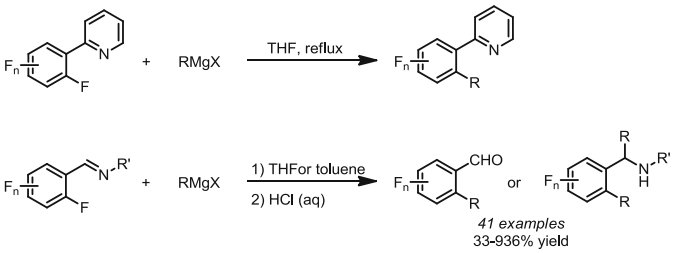
## 8.6 Transition Metal-Free Processes

Selective C–F activation may also be achieved without the use of transition metals. Although there are few examples to date, methods not requiring transition metal catalysts represent an attractive route to accessing polyfluorinated building blocks. In 2013 Zhang and coworkers described selective C–F activation of polyfluoroarenes with subsequent coupling to phenols and benzyl alcohols to access to unsymmetrical polyfluoroaryl ethers (Eqs. 87 and 88) [150]. A variety of electron-rich and electron-poor phenols were coupled to aryl fluorides in the presence of DMSO and $Cs_2CO_3$.




(87, 88)

Polyfluoroarenes have also been reported to couple to aryl and alkyl Grignard reagents in the absence of a metal catalyst. The first report involved the use of pyridine directing groups (Eq. 89) [151]. A possible mechanism for reaction involves coordination of the Grignard reagent to the lone pair of electrons on nitrogen of the pyridine that leads to a six-membered transition state similar to that of a Meisenheimer complex. Polyfluoroimines were also reported to undergo selective alkylation and arylation with Grignard reagents in the absence of a metal catalyst (Eq. 90) [152]. This transformation however was plagued by the competing nucleophilic addition of the Grignard to the imine. Nevertheless, the method still generated the desired C–F activation product in good to excellent yields.

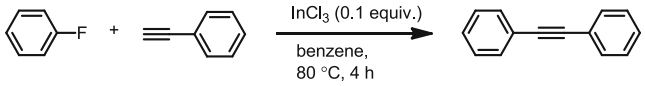



(89, 90)

As can be seen from the above examples, much remains to be investigated and discovered in the area of metal-free C–F activation transformations.

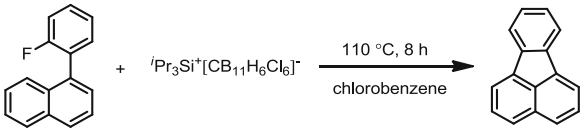
## 9 Main Group Elements

To date there has been much less work reported on C–F activation using main group elements. In 2005 a novel Sonogashira coupling reaction of monofluorinated arenes and phenylacetylene catalyzed by $InCl_3$ was reported (Eq. 91) [153]. This method is of particular relevance as access to C($sp^2$)–C($sp$) bonds by activation of aryl C–F bonds is uncommon.



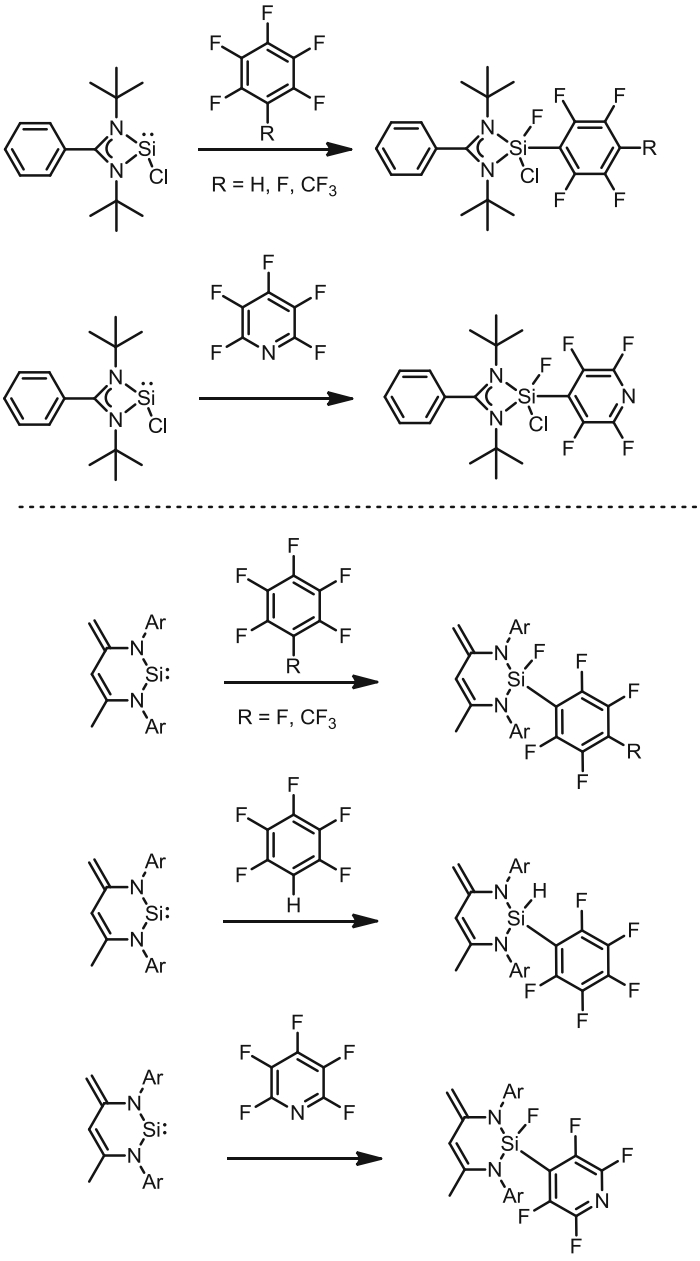

(91)

The Siegel group reported a clever intramolecular Friedel–Crafts reaction of monofluorinated arenes catalyzed by silylcations and carboranes (Eq. 92) [154]. The reaction is driven by Si–F bond formation.




(92)

Silylenes have also been found reactive toward cleaving aromatic C–F bonds. In an innovative report, Roesky and coworkers described a series of reactions involving two- and three-coordinate silylenes with fluoroaromatics including hexafluorobenzene, pentafluorobenzene, octafluorotoluene, and pentafluoropyridine (Eqs. 93–97) [155]. Interestingly, in the case of the two-coordinate silylene, chemo-selective C–H activation took place when reacted with pentafluorobenzene to afford the corresponding silicon hydride (Eq. 96). The insertion of silylenes into the inert C–F bonds showcases dual reactivity mode inherent to the silylene synthon bearing a singlet electronic ground state.




(93, 94, 95, 96, 97)

## 10 Summary and Outlook

This chapter has provided an overview of the synthesis and reactivity of aryl C–F bonds. The increased number of pharmaceuticals, agrochemicals, and materials possessing aryl C–F bonds has warranted further development of reactions accessing this ever-important motif. A number of strategies now exist for the generation of functionalized fluoroaromatics, including C–F bond formation and the selective functionalization of polyfluoroarenes. However, a number of methods still suffer from poor selectivity and limited substrate scope. Further mechanistic studies are required to better understand these drawbacks and address these issues. Nevertheless, these reports lay the ground work for future discoveries in the field maintaining this important topic for years to come.

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# Transition-Metal-Catalyzed Difluoromethylation, Difluoromethylenation, and Polydifluoromethylenation Reactions

**Bo Chen and David A. Vicic**

**Abstract** One way to introduce fluorine into a molecule is through fluoroalkylation reactions. Transition-metal catalysts play an increasing role in selectively incorporating fluoroalkyl groups into organic molecules, especially during the late stages of a synthesis. In this review, we highlight the development of methodologies to incorporate the [$CF_2H$], [$CF_2R$], and [$(CF_2)_n$] functionalities into organic substrates by transition-metal complexes. Also discussed are the structural changes that can arise when repeating arrays of [$CF_2$] or [$CH_2CF_2$] units are introduced into a single molecule through polydifluoromethylenation reactions.

**Keywords** Copper • Difluoromethylation • Difluoromethylenation • Fluoroalkylation • Polydifluoromethylenation

## Contents



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## Abbreviations

| | |
|---|---|
| bpy | 2,2′-Bipyridyl |
| Bu | Butyl |
| cat | Catalyst |
| d | Day(s) |
| DBU | 1,8-Diazabicyclo [5.4.0]undec-7-ene |
| DCE | 1,2-Dichloroethane |
| DME | 1,2-Dimethoxyethane |
| DMF | Dimethylformamide |
| DMPU | 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone |
| DMSO | Dimethyl sulfoxide |
| equiv. | Equivalent(s) |
| Et | Ethyl |
| h | Hour(s) |
| i-Pr | Isopropyl |
| M | Metal |
| Me | Methyl |
| MeCN | Acetonitrile |
| min | Minute(s) |
| mol | Mole(s) |
| NMP | *N*-Methyl-2-pyrrolidone |
| Ph | Phenyl |
| rt | Room temperature |
| tbpy | 4,4′-Di-tert-butyl-2,2′-dipyridyl |
| *t*-Bu | *tert*-butyl |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TMEDA | *N*,*N*-*N*′,*N*′-Tetramethylethylenediamine |
| TMS | Trimethylsilyl |
| Xantphos | 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene |

## 1 Introduction

Until World War II, there was no commercial production of elemental fluorine, and thus studies on fluorinated molecules and materials were limited. Once it was discovered that $UF_6$ exhibits a high vapor pressure and could be used to purify isotopically enriched uranium, production of, followed by reserves of, fluorine grew [1]. Scientists were able to tap into these reserves and develop the field of organofluorine chemistry. Organofluorine chemists have been able to parse out the properties and reactivities of various fluorine-containing functional groups, and the development of new methods to incorporate such groups into organic substrates has received considerable attention. The fluoroalkyl family represents one class of

fluorinated functional groups that has grown in significance in recent years. Metal-catalyzed methods to incorporate fluoroalkyl groups into organic substrates can represent an atom economical synthetic approach, but the stabilizing properties of fluoroalkyl groups makes fluoroalkylations difficult because fluoroalkyl ligands can also render a metal catalyst more stable and less reactive [2]. The growth in attention devoted to developing new fluoroalkylation methods can be reflected by the large number of reviews regarding advances in metal-catalyzed trifluoromethylation reactions that have recently appeared in the literature [3–23]. Far fewer accounts describing the roles that transition metals play in the development of difluoromethylation [5, 8, 13, 24–30], difluoromethylenation, and especially polydifluoromethylenation reactions have appeared, so this document attempts to serve as a review of the state of the art in those fields.

Many features contribute to the value of the fluoroalkyl-containing functional group. Ligands [31–33] and counterions [34] that allow metals to operate under oxidative conditions often feature fluoroalkyl substituents due to the chemical inertness of the [$CF_3$] and [$CF_2$] functional groups. Fluoroalkyl moieties can also serve as isosteres of important organic functional groups. The difluoromethyl group has been described as a lipophilic isostere of the carbinol, thiol, hydroxamic acid, and amide groups that is capable of hydrogen bonding [35, 36] while the difluoromethylene group has been described as an isostere of an oxygen atom functionality [37]. Under such a model, a *gem*-difluorovinyl moiety was reported to act as an isostere for aldehydes and ketones [37]. Such features, together with the fact that the strength of the carbon-fluorine bonds can moderate the metabolism of fluorinated compounds, make the [$CF_2$] and [$CF_2H$] important functional groups for drug design and agricultural applications. Indeed, the breadth of applications of these functional groups in the medicinal chemistry field is highlighted by some select drugs shown in Fig. 1.

## 2 Syntheses of Transition-Metal-Difluoromethyl Complexes

The first reports of a transition-metal-difluoromethyl complex were provided by Calderazzo and co-workers in 1967, who prepared [$(CO)_4Mn(CF_2H)$] through the thermal decarbonylation of [$(CO)_4Mn(COCF_2H)$] [39, 40]. $^{55}$Mn NMR data from their group (Table 1) revealed a direct correlation between the degree of fluorination of the Mn-bound methyl ligand with the $^{55}$Mn chemical shift from a reference sample. Since Calderazzo and co-workers' initial synthesis of a metal-difluoromethyl complex, the difluoromethyl ligand has exhibited rich coordination chemistry with transition metals, and select examples of well-defined complexes are shown in Fig. 2. Eisenberg and co-workers were the first to publish structurally characterized transition-metal-difluoromethyl complexes in 1973, namely, ([$IrCl(OCOCF_2Cl)CF_2H)(CO)(PPh_3)_2$] and [$IrCl_2(CF_2H)(CO)(PPh_3)_2$]) [41].

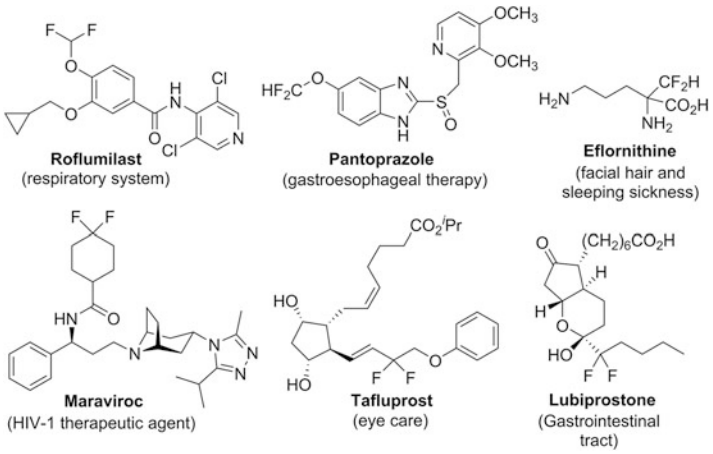



**Fig. 1** Select drugs containing the difluoromethyl and difluoromethylene group [28, 38]

**Table 1** $^{55}$Mn NMR chemical shifts of [XMn$(CO)_5$] derivatives (ppm from aqueous [$KMnO_4$]) [39]

| Compound | $\delta$ |
|---|---|
| $H_3C$-Mn$(CO)_5$ | 2,265 |
| $H_2FC$-Mn$(CO)_5$ | 2,130 |
| $HF_2C$-Mn$(CO)_5$ | 1,970 |
| $F_3C$-Mn$(CO)_5$ | 1,850 |

The difluoromethyl groups in Eisenberg's iridium complexes were generated by a metal promoted decomposition of the [$CF_2ClCO_2$] anion.

The ability of transition metals to coordinate difluoromethyl groups has sparked substantial interest in learning how to involve such [M-$CF_2H$] species in catalytic cycles affording net transfer of [$CF_2H$] to organic substrates. Historically, structurally simple difluoromethylated organic species can be prepared without the use of transition metals. Reagents such as $FSO_2CF_2CO_2TMS$, $CF_2N_2$, and $HCF_2SO_2R$ are known to generate difluorocarbene in neutral or basic conditions for insertion into O–H, N–H, C=C, C=O, and C≡C bonds, forming difluoromethylated ethers, amines, cyclopropanes, alkenes, and cyclopropenes [42]. These and other reagents for classical organic transformations [13, 27, 28, 35, 43, 44] toward the difluoromethyl and *gem*-difluoromethylene functional groups will not be reviewed here. Rather, our attention will be placed solely on more sophisticated *metal-mediated* transformations involving the [$CF_2H$] or [$CF_2R$] functional groups. Such attention requires first a basic understanding of how to form a [metal-$CF_2H$] complex. Typical synthetic routes to the metal-difluoromethyl functional group are outlined in Scheme 1. Transition metals are known to activate the C–H bond in difluoromethane (Scheme 1, Eq. a) [45] or the C–X bond in a species like difluoroiodomethane (Scheme 1, Eq. b) [46] to produce metal-difluoromethyl complexes. As mentioned above, decarbonylation of a [M-$COCF_2H$)] complex may also lead to well-defined [M-$CF_2H$] species (Scheme 1, Eq. c) [41]. Transition-metal carbenes may also be used as [M-$CF_2H$] precursors, and the [M=$CF_2$]

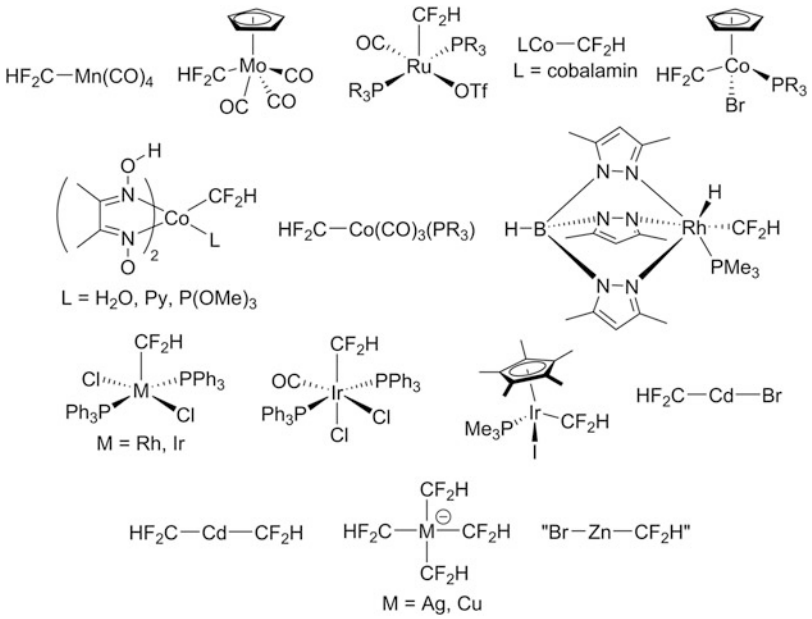


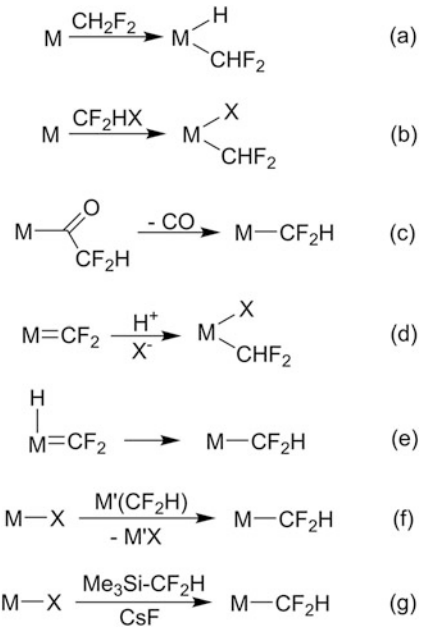

**Fig. 2** Selected known transition-metal-difluoromethyl complexes

functionality may react as a formal electrophile (Scheme 1, Eq. e) [47] or as a formal nucleophile (Scheme 1, Eq. f) [48]. Finally, transition metals may react with transmetalating reagents such as $[Cd(CF_2H)_2]$ [49], $[Bu_3Sn(CF_2H)]$ [50] (Scheme 1, Eq. f), or the combination of $[Me_3Si–CF_2H]$ plus an initiator (Scheme 1, Eq. g) [51].

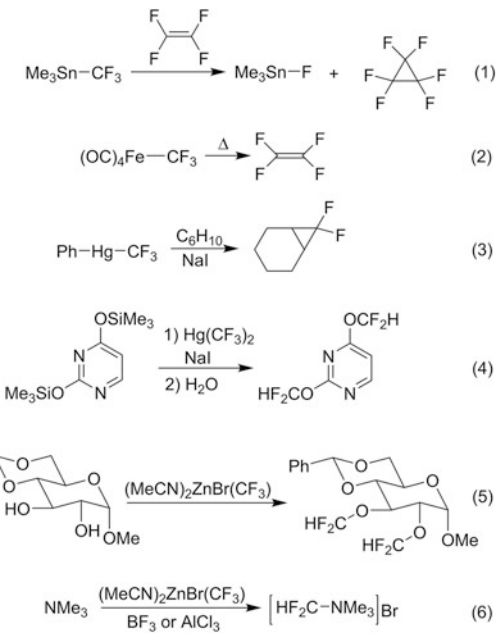
## *2.1 Metal-Catalyzed Methods for Difluoromethylation and Difluoromethylenation*

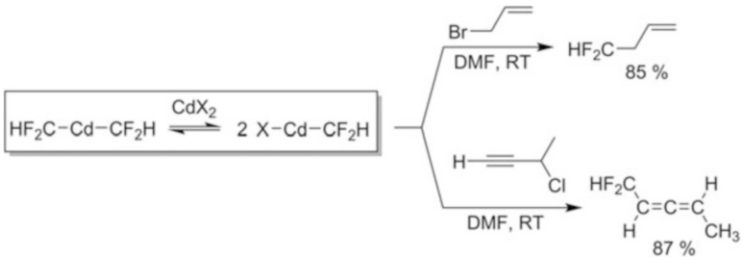
By the 1960s, it was well established that trifluoromethyl-substituted main group metals such as tin could be used as a difluorocarbene source for additions to olefins (Eq. 1) [52]. In 1961 Stone and co-workers provided evidence that similar decomposition reactions could occur for transition metals. They noted that the thermal decomposition of $[(CO)_4Fe(CF_3)]$ led to the production of tetrafluoroethylene, presumably by way of difluorocarbene generation (Eq. 2). Seyferth and co-workers in 1969 were the first to show that mercury trifluoromethyl complexes could be used to generate difluorocarbene under mild conditions in the presence of sodium iodide and could subsequently trap the difluorocarbene with acceptor molecules such as cyclohexene (Eq. 3). They suggested the reactions proceeded through nucleophilic displacement of a $[CF_3]$ anion by iodide, followed by decomposition of the $[CF_3]$ anion to the difluorocarbene [53]. Such mercury salts could be employed to form difluoromethylated products, and in 1985, Pein and Cech demonstrated that $[Hg(CF_3)_2]$ in the presence of sodium iodide could be used to introduce a $CF_2H$

**Scheme 1** Typical methods used to prepare transition-metal-difluoromethyl complexes

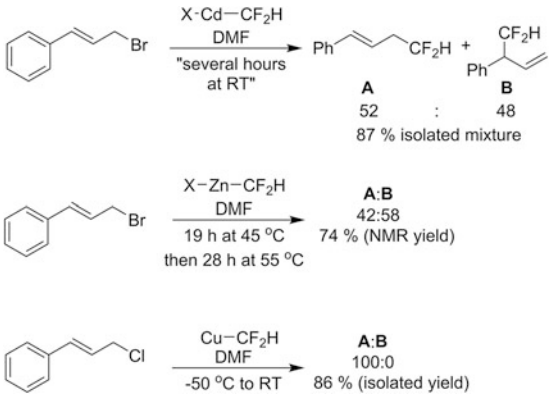



functionality into a more complex organic substrate (Eq. 4) [54, 55]. In a similar vein, less toxic zinc reagents can be used as formal difluorocarbene sources to perform difluoromethylations as described in Eqs 5 and 6 [56, 57].






**Scheme 2** Reactivity of difluoromethyl cadmium reagents toward organic halides [58, 59]

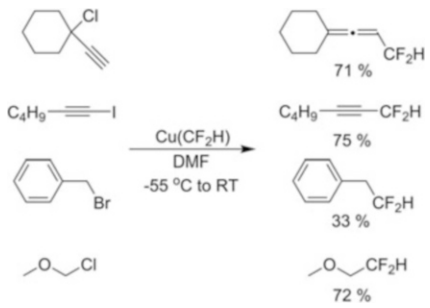



**Scheme 3** Reactivity of cadmium, zinc, and copper difluoromethyl complexes with cinnamyl halides

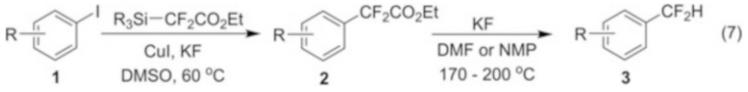
Subsequently, it was shown that metal-bound difluoromethyl complexes could be used to directly transfer the [$CF_2H$] functionality to organic substrates. Burton found that difluoromethyl complexes of cadmium could be prepared by reaction of cadmium metal with [$CF_2HX$], where X = Br or I [58]. When prepared as such, the cadmium reagent exists as a 25:75 mixture of [$(CF_2H)_2Cd$] and [$(CF_2H)CdX$] in DMF solution. Notably, this equilibrium mixture of cadmium salts reacted with allylic and propargylic halides to form the difluoromethylated products as described in Scheme 2.

Burton later went on to prepare a zinc difluoromethyl reagent by similarly reacting zinc metal with [$CF_2HX$] [46]. The zinc reagent that formed was thermally stable, but reacted with allylic halides much slower than the analogous cadmium derivative (Scheme 3). A difluoromethyl copper reagent could be prepared by reacting [$XCd(CF_2H)$] with copper halides, but unlike the cadmium and zinc reagents, the copper species was thermally unstable and decomposed rapidly at temperatures above −30°C [46]. Nevertheless, the copper species reacted with allylic halides at −50°C with regiospecificities that were superior to both cadmium and zinc (Scheme 3). Other organic difluoromethylation reactions that are possible with [$Cu(CF_2H)$] as prepared by Burton are outlined in Scheme 4.

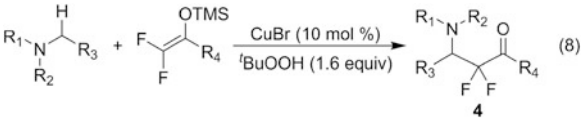
**Scheme 4** Reactions of the $[Cu(CF_2H)]$ reagent prepared from CuX with $[XCd(CF_2H)]$




Because of the reported lack of stability of the $[Cu(CF_2H)]$ reagents prepared via Burton's procedure, Amii and co-workers in 2011 developed a new reaction sequence to directly couple difluoroacetates to organic halides [60]. The reaction sequence is believed to involve the generation of a relatively stable $[Cu(CF_2CO_2Et)]$ species that is capable of performing coupling reactions with aryl iodides to afford **2** (Eq. 7) at temperatures of 60°C. Then, under forcing conditions, the resulting difluoroester can be first hydrolyzed then decarboxylated to form product **3** (Eq. 7) in yields ranging from 59 to 89%. The drawback of this method is the high temperatures needed for decarboxylation of the difluoroester.

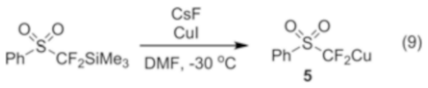



Two years prior to Amii's report on copper difluoroacetates, Qing and co-workers published a CuBr-catalyzed oxidative difluoromethylenation of tertiary amines with difluoroenol ethers to afford β-amine-α,α-difluoroketones (Eq. 8). The reaction presumably proceeds through coupling of iminium ions generated in situ with the difluoroenol silyl ethers, which are synthetic equivalents of α,α-difluoroacylsilanes and can be easily transformed to α,α-difluorocarbonyl compounds such as aldehydes, carboxylic acids, amides, and other derivatives [61]. No attempt was made to convert **4** into $[CF_2H]$ derivatives.




In 2011, Hu and co-workers explored the use of a different fluoroalkyl copper species to perform difluoromethylenation reactions [62]. They observed that reaction of $PhSO_2CF_2TMS$ with CsF in the presence of CuI at −30°C generated a $[PhSO_2CF_2Cu]$ species (**5**) that showed two forms in DMF solution (Eq. 9). This

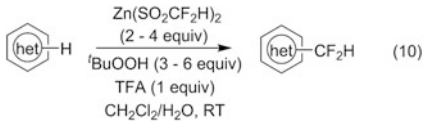
species, similar to [$CuCF_2H$], exhibited thermal instability and decomposed completely after stirring at room temperature for 2 h.



(9)

Nevertheless, similar to Burton's [$Cu(CF_2H)$] chemistry [46], reactions of **5** with propargyl and alkynyl halides could be run at low temperature to afford (phenylsulfonyl)difluoromethylation products (Scheme 5). Notably, for **6**, when R = phenyl, this product could be reduced to Ph-CC-$CF_2H$ by magnesium metal in the presence of a catalytic amount of $HgCl_2$ in 75% yield.

In 2012, Baran and co-workers published the synthesis of [$Zn(SO_2CF_2H)_2$], a reagent that could be used in the direct difluoromethylation of aromatic heterocycles (Eq. 10) [63, 64]. A notable feature of the zinc reagent is that it can be isolated as a free-flowing solid with an extended shelf life and is now commercially available from Aldrich. Reactions involving this zinc reagent with heterocycles proceeded in moderate yields and required the use of $^t$BuOOH co-reagent. The [$CF_2H$] radical that is produced under these conditions was reported to be nucleophilic in character. In selectivity studies, radical trifluoromethylation of dihydroquinine (**8**) occurred at the most electron rich position of the arene rings, while difluoromethylation with [$Zn(SO_2CF_2H)_2$] occurred at the electron poor site next to the heteroatom (Eq. 11). Baran's [$Zn(SO_2CF_2H)_2$] reagent was later used in an iron-catalyzed decarboxylative difluoromethylation procedure developed by Liu and co-workers to functionalize cinnamic acids into $CF_2H$-containing products in yields up to 68% (Eq. 12) [65].



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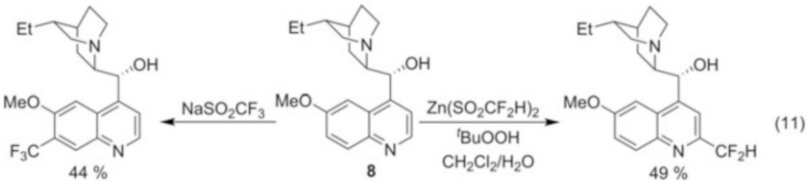

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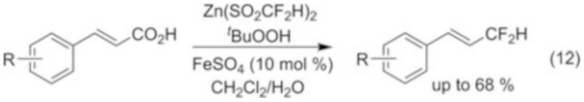
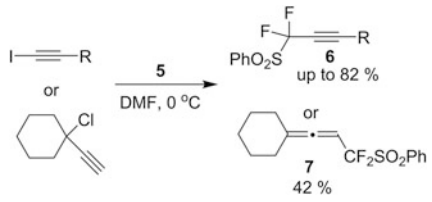
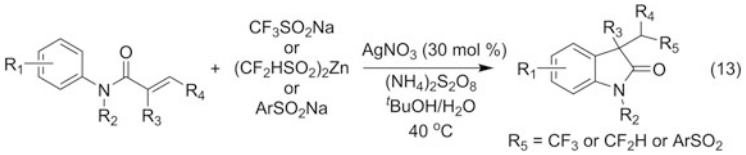


(12)

**Scheme 5** Difluoromethylenation reactions with [$PhSO_2CF_2Cu$]




Baran's reagent and Langlois' reagent have also been used in combination with silver salts to prepare difluoromethyl and difluoromethylene substituted oxindoles as described in Eq. 13 [66]. The reactions proceed by addition of the in situ generated difluoromethyl radical to an alkenyl fragment followed by subsequent cyclization with the aromatic ring.

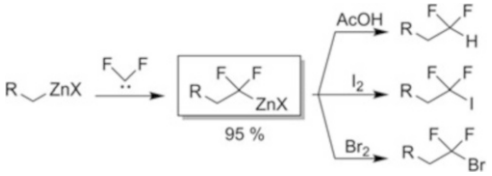


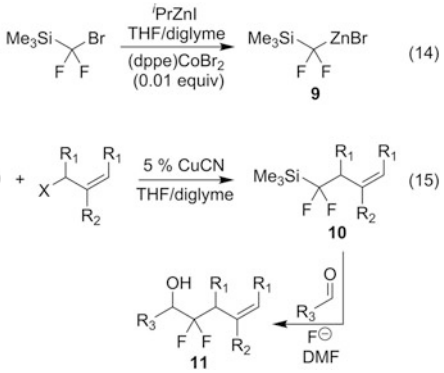

(13)

The enhanced stability of fluoroalkyl zinc reagents, together with the relatively low toxicity of zinc, bodes well for its future use and development of fluoroalkylation reactions. Dilman and co-workers have shown that difluoromethylenated compounds can also be prepared by reacting benzyl and alkyl zinc halides with difluorocarbene as described in Scheme 6 [67]. The strategy exploits the fact that difluorocarbene is intrinsically electrophilic and is capable of reacting with nucleophiles like alkyl zinc reagents. The chemistry is versatile in the sense that once the difluorinated organozinc reagents have been synthesized from the organozinc of choice, they can react with electrophiles of choice to form organic products containing the [$CF_2$] fragment (Scheme 6). For benzylzinc halides, the yields are high and the reaction tolerates halogen, cyano, ester, and boryl groups on the aromatic ring [67]. The yields with aliphatic organozinc reagents were more variable.

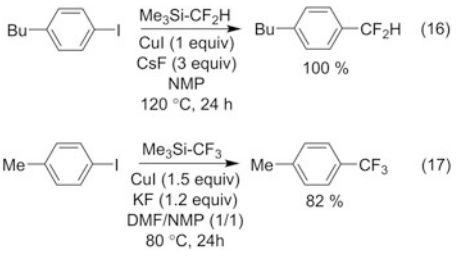
Dilman also found that a new difluorinated reagent [$Me_3SiCF_2ZnBr$] (**9**) can be coupled with two different carbon-based electrophiles in a stepwise manner, showing reactivity that could be described as a difluoromethylene bis-carbanion equivalent [68]. The reagent **9** is prepared by a cobalt-catalyzed halogen/zinc exchange reaction [69, 70] as described in Eq. 14. An example of the utility of reagent **9** is the allylation reaction described in Eq. 15. The intermediate allylic silanes (**10**) were obtained in yields from 68 to 88%, and the conditions employed (0–20°C for 17 h) were operationally simple. The allyl silanes were then employed as nucleophilic reagents for aldehyde additions to afford the *gem*-difluorinated alcohols **11** in excellent yields.

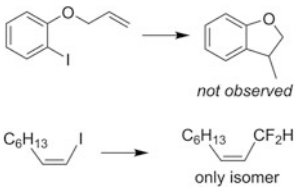
**Scheme 6** Difluoromethylenated products through insertion of difluorocarbene into zinc-carbon bonds




Fluoroalkyl-derivatized silanes have also shown great versatility in fluoroalkylation reactions [71], and in 2012, the first copper-mediated difluoromethylation reactions employing [$Me_3Si$-$CF_2H$] were reported. Hartwig and co-workers were able to design reaction conditions employing [$Me_3Si$-$CF_2H$] that allow copper-mediated difluoromethylations to proceed at higher temperatures (Eq. 16) than any previously reported [51]. The difluoromethyl source was [$Me_3Si$-$CF_2H$], which could be prepared on a multigram scale by the reduction of [$Me_3Si$-$CF_3$] with sodium borohydride. The reaction conditions were amenable for the conversion of a wide range of aryl and vinyl iodides, and electron neutral, electron rich, and sterically hindered aryl iodides reacted in high yields [51]. It is noteworthy to compare the conditions for difluoromethylations reported by Hartwig (Eq. 16) with the conditions similarly used to trifluoromethylate aryl iodides with the [$Me_3Si$-$CF_3$] reagent (Eq. 17) [72]. The difluoromethylations proceeded at temperatures 40°C higher than the trifluoromethylations, indicating that a stable yet more reactive difluoromethyl source for reactions with copper still remains a desirable synthetic target.

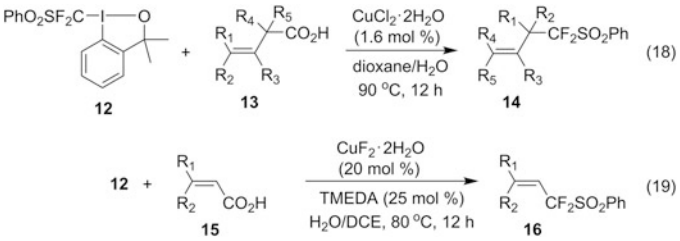


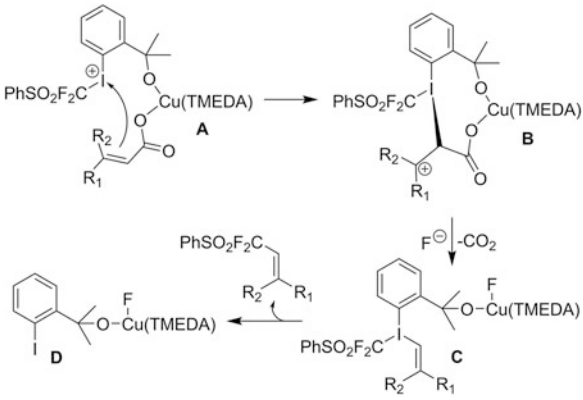



**Scheme 7** Support for non-radical processes in the copper-mediated difluoromethylation of aryl and vinyl iodides with [$Me_3Si$–$CF_2H$] [51]

When mixtures of [CuI], [CsF], and [$Me_3Si$-$CF_2H$] were heated in the absence of any organo-iodide, $^{19}F$ NMR evidence for the formation of $[Cu(CF_2H)_2]^-$ was observed [51]. The authors suggest that $[Cu(CF_2H)_2]^-$ acts as a stable reservoir for the active and neutral $[Cu(CF_2H)]$ species. It has recently been reported that perfluoroalkyl cuprates similar to $[Cu(CF_2H)_2]^-$ do not react as fast as the neutral copper perfluoroalkyl species [73]. The authors speculate that the low concentration of $[Cu(CF_2H)]$ should decrease the rate of bimolecular decomposition, relative to reaction with haloarene [51]. Further experiments to probe the mechanism were performed with radical traps (Scheme 7). No radical cyclizations were observed with [1-(allyloxy)-2-iodobenzene], which rules out the intermediacy of aryl radicals. Moreover, the difluoromethylation of *Z*-1-iodo-1-octene proceeded with complete retention of olefin geometry, which rules out the intermediacy of vinyl radicals.

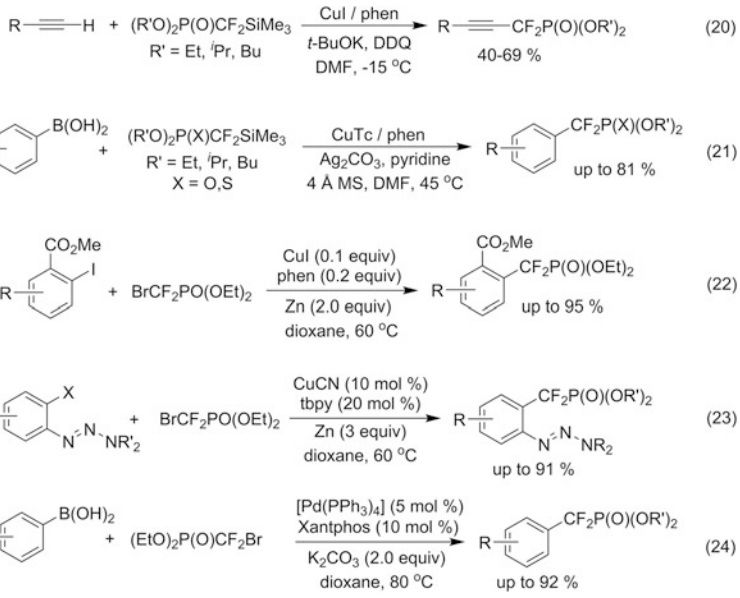
Hypervalent iodine reagents have also been tested for effectiveness in copper-mediated difluoromethylation reactions. High yielding protocols for the synthesis of $C_{vinyl}$-$CF_2R$ ($R \neq F$) bonds were discovered by Hu and co-workers in 2012 [74, 75]. They observed that the [iodine(III)-$CF_2SO_2Ph$] reagent **12** could be used in combination with copper(II) salts for the regiospecific incorporation of allyic difluoromethyl groups by a copper catalyzed decarboxylation of β,γ-unsaturated carboxylic acids (Eq. 18). Functionalizations using this method occurred at the γ-position of **13** only. Gratifyingly, the products **14** can be further transformed into [R-$CF_2H$] derivatives by reductive desulfonylation with Mg/HOAc/NaOAc in DMF solution at room temperature [74]. The same [iodine(III)-$CF_2SO_2Ph$] reagent could be used to difluoromethylate α,β-unsaturated carboxylic acids as described in Eq. 19 [75]. The proposed mechanism of the decarboxylative functionalization is outlined in Scheme 8. It is believed that intermediate **A** is generated in the course of the reaction, which then undergoes an intramolecular transformation to species **B** which then decarboxylates and liberates product through a reductive elimination at iodine.





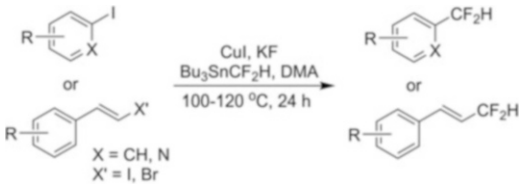

**Scheme 8** Key steps in the proposed mechanism of the decarboxylative fluoroalkylation of α,β-unsaturated carboxylic acids [75]

Another *gem*-difluorinated functional group which has received much attention is the difluorophosphonate group [76–83]. Organodifluoromethylphosphonates are an important class of compounds because of their significant bioactivities as protein tyrosine phosphate (PTP) inhibitors [77]. Burton and co-workers prepared the first transition-metal difluorophosphonate in 1981 by the reaction of $[(EtO)_2P(O)CF_2Br]$ with cadmium metal to produce the stable $[(EtO)_2P(O)CF_2CdBr]$ [81]. They showed that $[(EtO)_2P(O)CF_2CdBr]$ reacted with a variety of electrophiles (e.g., with allyl bromide to afford allyl difluorophosphonate) to form new organic difluorophosphonates. Selected recent advances in this area are shown in Eqs 20–24. In 2012, Qing and co-workers showed that terminal alkynes react with $[(RO)_2P(O)CF_2SiMe_3]$ through a copper-mediated oxidative cross-coupling reaction to afford α,α-difluoropropargylphosphonates in moderate to good yields with excellent functional group compatibility (Eq. 20) [76]. Their group subsequently extended their oxidative coupling method to include aryl boronic acids (Eq. 21) [78]. Also in 2012, Zhang and co-workers demonstrated an operationally simple protocol whereby copper difluorophosphonates can be generated in situ and then reacted with iodobenzoates to afford aryldifluorophosphonates in excellent yields (Eq. 22) [83]. Their group extended this method to include iodo- and bromo-triazenes coupling partners (Eq. 23) [77]. Within the triazene family, aryl bromides could be coupled with copper difluorophosphonates for the first time in yields up to 69%. Zhang and co-workers also developed a palladium-catalyzed method to prepare aryldifluoromethylated phosphonates from aryl boronic acids and $[(EtO)_2P(O)CF_2Br]$ (Eq. 24) [79]. The palladium method also worked for coupling aryl boronic acids with $[EtCO_2CF_2Br]$ and $[R_2NCOCF_2Br]$ and was compatible with late-stage functionalization of scaffolds present in bioactive molecules [79].



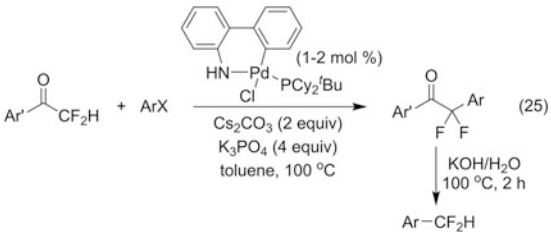

Prakash and co-workers developed a copper protocol using [*n*-$Bu_3SnCF_2H$] to difluoromethylate aryl, heteroaryl, and vinyl halides (Scheme 9). One of their motivations for using a tin reagent was that the Hartwig procedure for difluoromethylation, which uses [$Me_3Si$-$CF_2H$] as the difluoromethyl source (Eq. 16), is not compatible with aldehydes and ketones owing to competitive nucleophilic addition reactions [50]. Indeed, reactions with iodo-substituted benzaldehydes and acetophenones afforded excellent yields of difluoromethylated products [50]. [*n*-$Bu_3SnCF_2H$] is benchtop stable and can be stored in air for weeks to months without any apparent decomposition. The use of tin reagents for the formation of vinyl difluoromethylated complexes also outperformed Baran's reagent in decarboxylative protocols [65].

Other metals besides copper have shown promise in fluoroalkylation chemistry. A recent breakthrough in difluoromethylenation chemistry was the ability to perform palladium-catalyzed α-arylations with α,α-difluoroketones. In 2014, Hartwig and co-workers found that a palladacycle precatalyst that releases [$Pd(PCy_2{}^tBu)$] as the active component was able to couple α,α-difluoroacetophenone derivatives with aryl bromides and aryl chlorides to generate α-aryl-α,α-difluoroketones in excellent yields (Eq. 25) [84]. The formation of product presumably arises from reductive elimination at a [$Pd(Ar)(CF_2COAr')$] center, which is noteworthy because reductive eliminations of perfluoroalkyl groups at palladium have previously been limited to complexes of bulky ligands or with large bite angles [84]. The ability to incorporate a carbonyl atom next to the difluoromethylene group is synthetically attractive, due to the wide range of transformations that could be performed in subsequent derivatizations. In the course of these studies, the authors also found that the C–C bond adjacent to the carbonyl group in the α-aryl-α,α-difluoroketones




**Scheme 9** Copper-mediated difluoromethylation of heteroaryl iodides and β-styryl halides with tributyl (difluoromethyl)stannane

could be readily cleaved to form difluoromethylarenes (Eq. 25) [84]. The pathway to the difluoromethylarenes could be done in a stepwise fashion as shown in Eq. 25 or in a single pot procedure.




Two unconventional methods to prepare difluoromethyl and difluoromethylenated arenes using the combination of silver and Selectfluor were recently reported. In 2013, Gouverneur and co-workers found that silver could promote the decarboxylative fluorination outlined in Eq. 26 in yields up to 91% [85]. Importantly, the authors demonstrated that if $^{18}$F-labeled Selectfluor was used, the successful radiosynthesis of difluoromethyl arenes could be performed for the first time. The radiochemical yield of [*para*-Ph-$C_6F_4$-$CF_2H$] using this method was $8.6 \pm 2.6\%$ [85]. Tang and co-workers found that the combination of silver salts with Selectfluor was able to mediate a quite different transformation, namely, the fluorination of benzylic C–H bonds (Eq. 27) [86]. The procedure tolerates a variety of functional groups, and gram-scale syntheses of functionalized difluoromethyl and difluoromethylenated arenes could be realized. This procedure is interesting because no C–C bond coupling is required to generate fluoroalkylated products from nonfluorinated substrates.

## 3 Polydifluoromethylenation

There are interesting considerations for the preparation and use of molecules containing repeating difluoromethylene groups. It is well known that molecules containing $CF_2$ groups exhibit geometric parameters that are dissimilar to their nonfluorinated congeners [26, 87]. O'Hagan and co-workers analyzed crystallographically determined molecular structures bearing the $CH_2CF_2CH_2$ motif and found that the average C–$CF_2$–C angle was 118° and the average F–C–F angle was 104° [26]. These angles are significantly wider and narrower than those counterparts found in $CH_2CH_2CH_2$ motifs. Less appreciated, however, is the fact that structural differences become more complex when there are repeating arrays of $CF_2$ or $CH_2CF_2$ units in a single molecule. Consider the structural differences between *n*-hexane (**A**) and *n*-perfluorohexane (**E**, Fig. 3). Density functional theory (DFT) calculations predict (Figs. 3 and 4) that in the gas phase, the interior $CH_2CH_2CH_2$ and $CF_2CF_2CF_2$ angles are nearly identical, at 113.7° and 113.9°, respectively. The calculated bond angle of 113.9° in **E** matches well with the experimentally determined bond angles of 113.8(1)° and 113.9(1)° for the two innermost difluoromethylenes in perfluorohexane [88].

Figure 3 also shows that when there are repeating arrays of $CH_2CF_2CH_2$ motifs like in all-*trans* 1,1,1,3,3,5,5-heptafluorohexane (**$C_1$**), the interior $CH_2CF_2CH_2$ bond angle may actually be less than that calculated for *n*-hexane. The angle for this motif, however, is highly dependent on the chain structure, and when the *trans*-gauche or "zigzag" conformation (**$C_2$**) is accessed, the calculated $CH_2CF_2CH_2$ bond angles become larger than the corresponding angles in *n*-hexane (Fig. 3). The only two known examples of molecules containing repeating arrays of $CH_2CF_2$ moieties that were characterized by single crystal X-ray diffraction exhibit the *trans*-gauche configurations (Fig. 5) [89].

Despite the similarity of C–C–C bond angles in *n*-hexane versus *n*-perfluorohexane, the interior C–C–C–C dihedral angles vary significantly (calculated difference of 17.6° between **A** and **E**). Repeating $CF_2$ groups are known to impart a significant twist along the carbon chain into a helix with dihedral angles reported near 17° [90]. The variation in twisting for the nonfluorinated versus fluorinated structures is graphically illustrated for **A**, **$C_1$**, **$C_2$**, and **E** in Fig. 4 as well as for the phenyl capped species **B** and **F** (Figs. 6 and 7). Such twisting is clearly exhibited in the experimentally determined crystal structure for 4,4″-(perfluorohexane-1,6-diyl)di-1,1′-biphenyl (Fig. 7) [91]. Figure 6 illustrates how both the changes in C–C–C and dihedral angles in fluorinated versus nonfluorinated hexyl derivatives influence the distance between the C1 and C6 termini. The general observed trend is that for all-*trans* geometries, fluorination has the effect of increasing the C1–C6 distance largely in part due to the changes in dihedral angles of the hexyl carbon chain. Once the *trans*-gauche conformation has been obtained for derivatives bearing repeating $CF_2CH_2$ linkages (**$C_2$** and **$D_2$**, Figure 6), the distance between termini drastically shortens. Such geometric

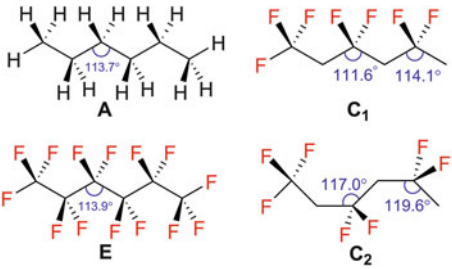



**Fig. 3** Calculated (6-31++G(d,p)) bond angles in fluorinated hexane derivatives

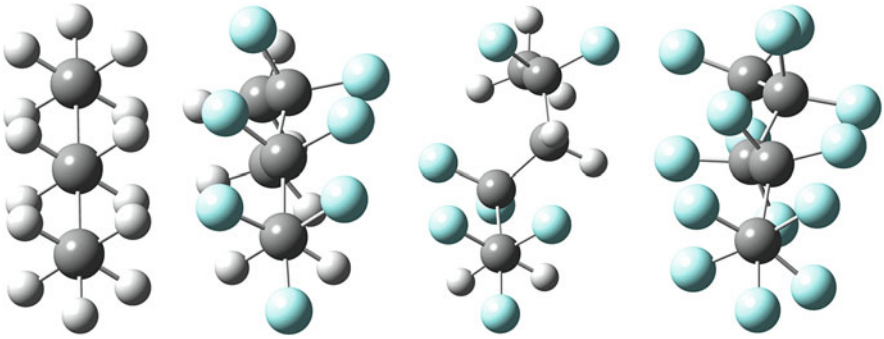


**Fig. 4** Optimized geometries of, from left to right, **A**, $\mathbf{C_1}$, $\mathbf{C_2}$, and **E** from Fig. 3 projected down the C1–C2 bond axis

considerations play an important practical role in the applications and ferroelectric properties of molecules like poly(vinylidene fluoride) [92].

Having multiple repeating difluoromethylene groups in an organic molecule can also largely affect its hydrophobicity. Here, it is important to understand the difference between the lipophilic character of a molecule from the hydrophobic character. In simple aromatic molecules, addition of fluorine or fluorinated groups tends to increase the lipophilicity of the molecule [93]. For aliphatic molecules or molecules containing large perfluoroalkyl chains, fluorination can actually induce a decrease in lipophilicity while enhancing the hydrophobic character [94]. This leads to the phenomenon where highly fluorinated compounds may form a third phase from water and organic solvents. Bégué and Bonnet-Delphon note that the confusion about hydrophobicity and lipophilicity comes from the way we measure lipophilicity, by taking the logarithm of the partition coefficient between 1-octanol and water (log *P*) [94]. They note that it is often considered that the higher the log *P* value, the more lipophilic a compound is perceived to be. However, it must be kept in mind that the log *P* value is only a measure of relative solubility. Bégué and Bonnet-Delphon go on to state that "considering that the solubility of a fluorinated substance decreases more in water than in octanol, this measurement leads one to think that fluorinated compounds are more 'lipophilic'. Actually, this represents the

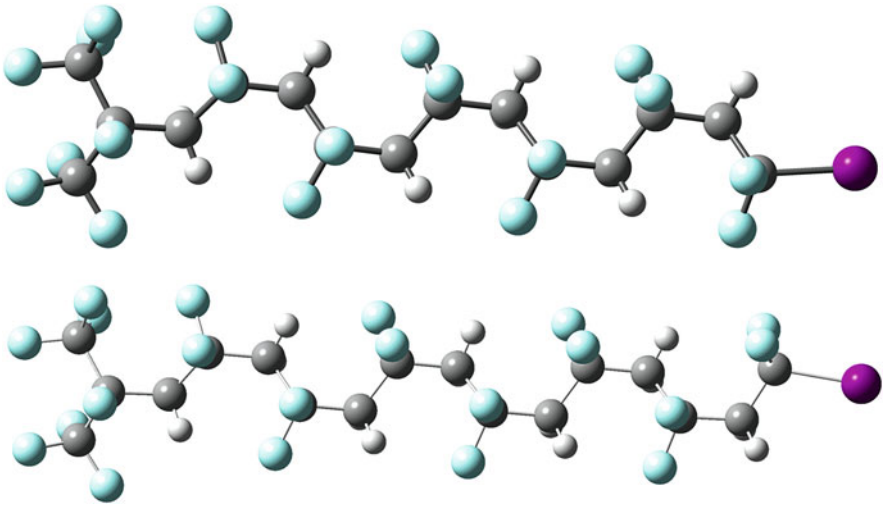


**Fig. 5** Experimentally obtained X-ray crystal structures of $(CF_3)_2CF\text{-}(CH_2CF_2)_6\text{-}I$ (top) and $(CF_3)_2CF\text{-}(CH_2CF_2)_7\text{-}I$ (bottom), demonstrating the zigzag geometry in the solid state [89]

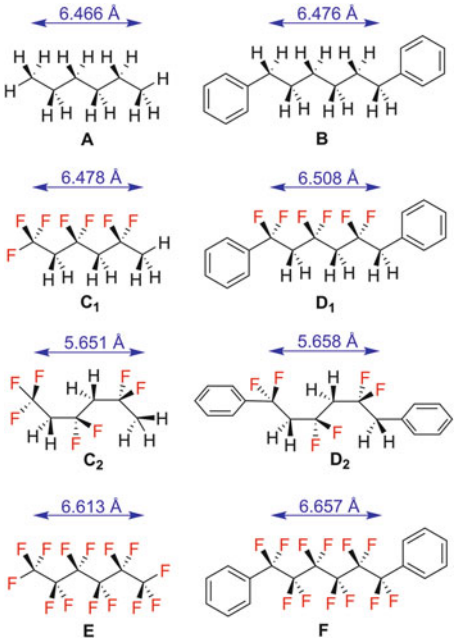



**Fig. 6** Calculated (6-31++G(d,p)) bond distances of the terminal carbon atoms of the fluorocarbon chain in hexyl and dodecafluorohexyl linkages for selected conformations

relative lack of affinity of fluorinated compounds for both phases." For these reasons and the complicated dependence of log *P* values on the reference solvent [94], observed log P values are often difficult to interpret. Therefore, caution should be taken when referring to a polydifluoromethylenated molecule as more lipophilic

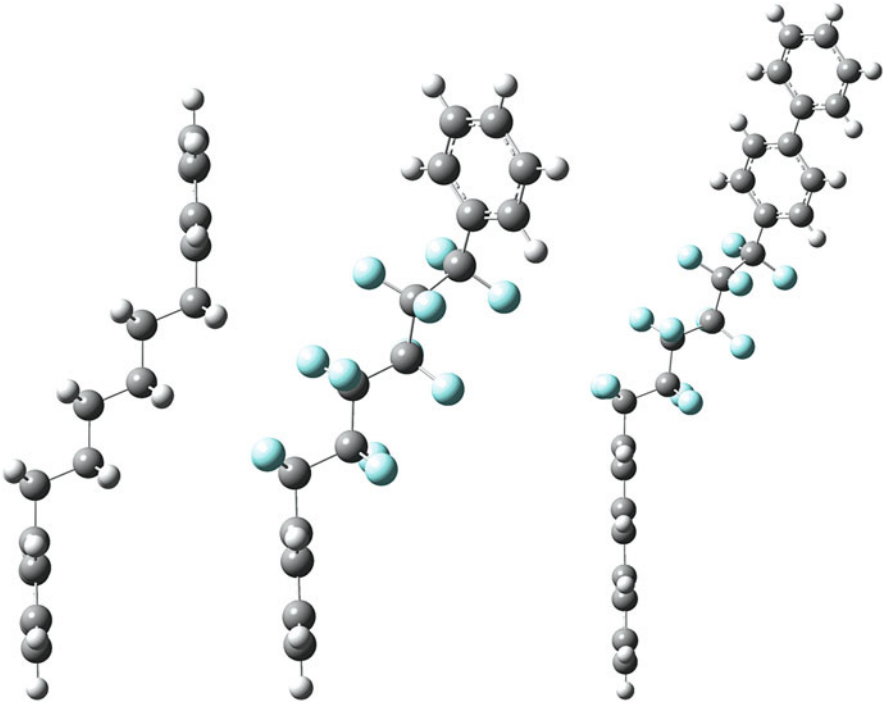


**Fig. 7** Optimized geometries of **B** (*left*) and **F** (*middle*), with the plane of the lower aryl ring set perpendicular to the page. Note the twisting of the upper aryl ring caused by changes in the dihedral angles in the perfluoroalkyl linker. Shown to the right is the experimentally determined structure of 4,4″-(perfluorohexane-1,6-diyl)di-1,1′-biphenyl [91]

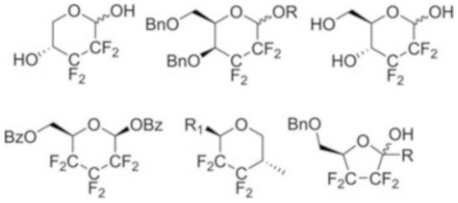
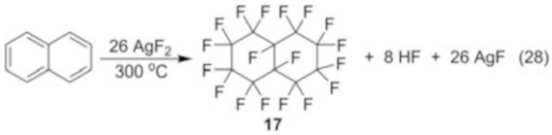



**Fig. 8** Examples of sugar molecules containing repeating difluoromethylene groups

than its unsubstituted derivative. The hydrophobic nature of fluorocarbons, however, remains less controversial [95]. One important field that exploits the "polar hydrophobicity" [96] of repeating difluoromethylene groups is the pharmaceutical field. For instance, heavily fluorinated sugars, like those shown in Fig. 8, have been targeted as probes for protein-carbohydrate interactions and as carbohydrate-based therapeutics [96–102]. Incorporating repeating difluoromethylene groups into organic molecules through metal-mediated processes is quite challenging, however, and is discussed below.

### 3.1 Transition-Metal-Mediated Polydifluoromethylenation

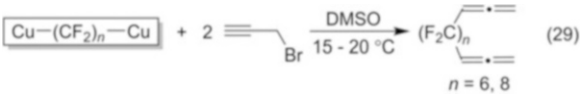
Early syntheses of molecules containing polydifluoromethylene linkages were often performed under forcing conditions in the gas phase. In 1947, McBee and Bechtol reported that fused ring fluorocarbons such as perfluoronaphthalane (**17**) could be prepared by reaction of silver difluoride with naphthalene at temperatures up to 300°C [103]. The resulting products were *perfluorinated*, limiting the application of the procedure to prepare molecules with other functionalities.



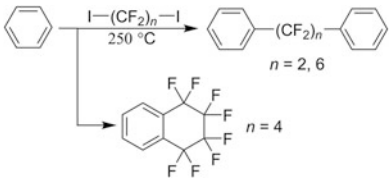

**17**

*Partially* difluoromethylenated molecules could also be prepared under metal-free conditions, given the appropriate fluoroalkylated reagents. In 1967, Knunyants and co-workers showed that the thermolysis of α,ω-diiodoperfluoroalkanes in the presence of benzene led either to diarylated products or to fluoroalkyl-containing ring formation, depending on the size of the diiodoperfluoroalkane (Scheme 10) [104]. Such methodology was later exploited by Boltalina to form $C_4F_8$-annulated corannulene derivatives [105]. These radical and metal-free processes require temperatures above 250°C, at which point the reactions take place in the gas phase.

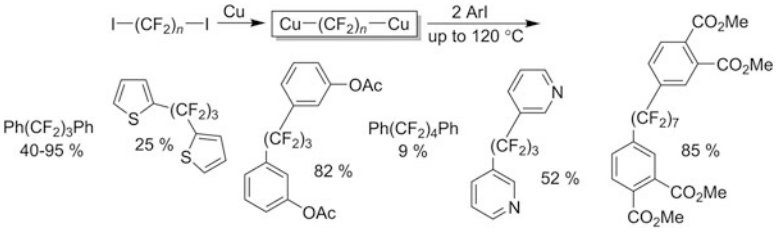
In 1969, McLoughlin and Thrower reported that α,ω-diiodoperfluoroalkanes could be doubly cuprated to form a [Cu-$(CF_2)_n$-Cu] species which react with aryl iodides at temperatures much lower than the metal-free systems described above (Scheme 11) [106]. With iodobenzene as the substrate, [$Ph(CF_2)_3Ph$] could be formed in 40–95% yield, depending on the choice of solvent. The milder reaction conditions were amenable to functionalized aromatics and heterocycles, producing products in moderate to good yields (Scheme 11). However, superstoichiometric amounts of copper (up to 13 equivalents) were required [106]. Such dicopper perfluoroalkyl reagents, prepared using copper powder, were later used to prepare fluorinated allenes as described in Eq. 29 [107]. However, the diallene products were formed in only 27–32% yield.




Chen and co-workers developed a stepwise protocol to cyclize α,ω-difunctionalized perfluoroalkanes onto aromatic rings [108–110]. The procedure first involves coupling [$I(CF_2)_nCl$] with aryl iodides in the presence of copper metal to form an [Ar-$(CF_2)Cl$] such as **18** (Eq. 30). Then, the aryl perfluoroalkyl chloride was activated using a sulfinatodehalogenation system, inducing a radical cyclization to afford **19**. The protocol is compatible with functionalized aromatics

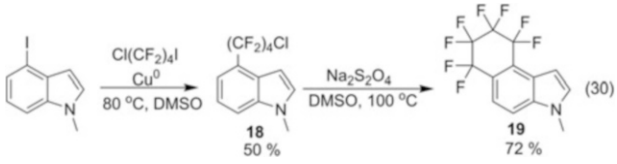



**Scheme 10** Reaction of diiodoperfluoroalkanes with benzene under metal-free conditions

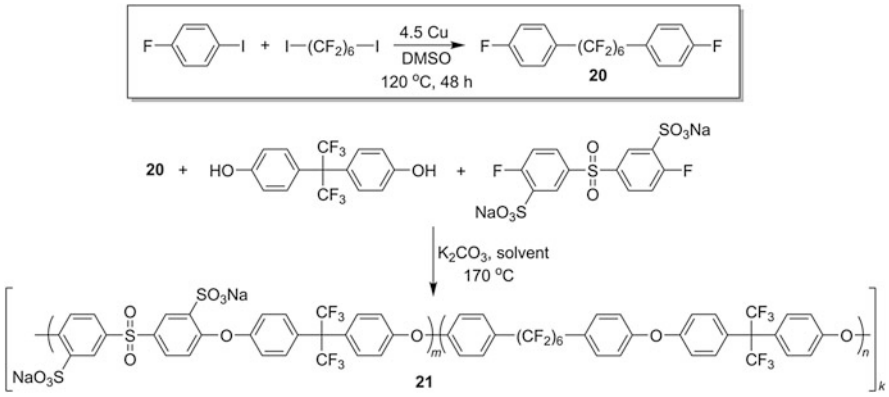



**Scheme 11** Routes to fluoroalkyl-substituted aromatics using copper metal

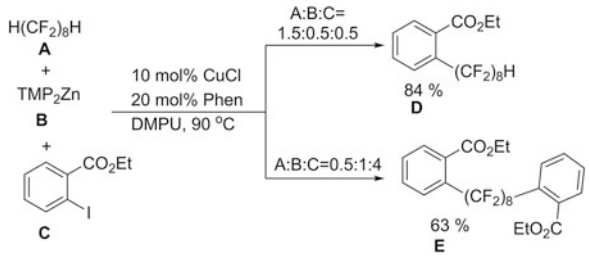
and even porphyrins [109] and was ultimately performed under purely metal-free and radical conditions since the two-step process involving copper leads to somewhat low overall yields based on starting organic iodide.




One application of the copper-mediated polydifluoromethylenation chemistry is the design of new fuel cell membranes. It has been reported that when sulfonated poly(arylene ether sulfone) (SPAES) ionomer membranes possess a high degree of sulfonation, in particular above 50%, they tend to deliver relatively high methanol permeability and water uptake which results in the low selectivity (a ratio of proton conductivity to methanol permeability) and poor cell performance [111]. To combat these problems, the effect of polydifluoromethylenation on the membrane properties and membrane-electrode assembly performance for direct methanol fuel cell applications was investigated comprehensively and compared with the non-difluoromethylenated derivative as well as with Nafion membranes. The synthesis of the new SPAES involved as a key step the copper catalyzed coupling of [I-$(CF_2)_6$-I] with 4-fluoro-iodobenzene to afford **20** (Scheme 12). 1,6-Bis (4-fluororphenyl)-perfluorohexane and 2,2-bis(4-hydroxyphenyl) hexafluoropropane were designed to replace diphenyl sulfone and bisphenol groups, respectively. The resulting copolymer membrane (**21**) presented higher selectivity than Nafion®117 as well as pristine SPAES membranes [111].



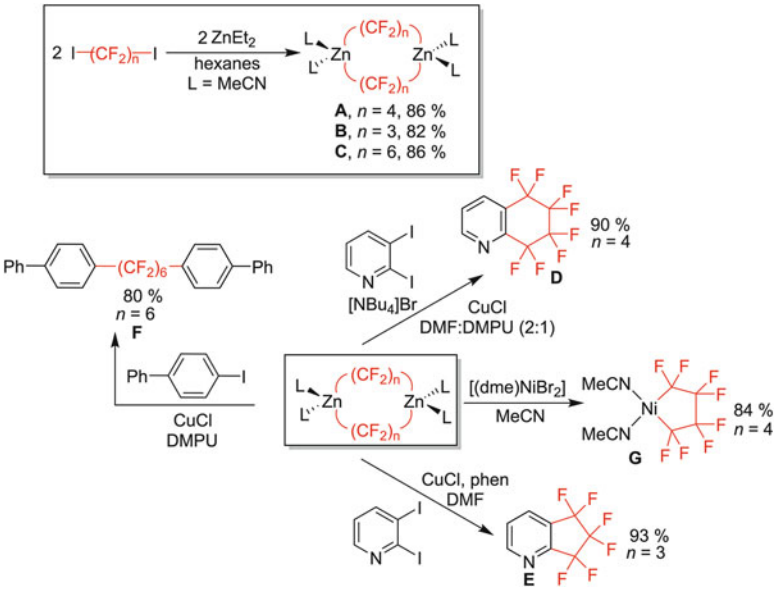

**Scheme 12** Synthesis of partially fluorinated copolymers for fuel cell applications




**Scheme 13** Polydifluoromethylenation catalytic in copper

A method to incorporate polydifluoromethylene linkages that was catalytic in copper was developed in 2011. Daugulis and co-workers demonstrated that zinc bis-2,2,6,6-tetramethylpiperidide [($TMP_2Zn$)] could be used to generate perfluoroalkyl zinc reagents directly from α-*H*- and α,ω-*H*-perfluoroalkanes (Scheme 13) [112]. The resulting bis(perfluoroalkyl)zinc reagents were then used in situ for a copper-catalyzed perfluoroalkylation reaction (Scheme 13). DMPU solvent was key for high yields. When [H-$(CF_2)_8$-H] was used as the perfluoroalkane, reaction with ethyl 2-iodobenzoate afforded either monosubstituted product **D** or dimeric product **E**, depending on the ratio of reagents used. The work was significant not only because the method was catalytic in copper but also because α-*H*-perfluoroalkanes could be used in the coupling reactions, instead of the commonly employed and expensive $R_f$-$SiMe_3$ reagents. Only one example of polydifluoromethylenation using α,ω-*H*-perfluoroalkanes was tested in this work, however (Scheme 13).

In 2013, Vicic and co-workers developed synthetic routes to perfluoroalkyl dizinc reagents by reacting α,ω-diiodoperfluoroalkanes with diethylzinc (Scheme 14) [91]. Complexes **A** and **B** were structurally characterized to confirm




**Scheme 14** Synthesis and utility of perfluoroalkyl dizinc reagents

the dimeric nature of those derivatives. The $n = 3$ and $n = 6$ derivatives **B** and **C** display enhanced stabilities relative to the $n = 4$ derivative **A**, which is prone to decompose to form [H-$(CF_2)_4$-H]. Nevertheless, **A** could be used in combination with CuCl and [$NBu_4$]Br to afford novel perfluoroalkyl-containing ring systems like octafluoroquinoline (**D**) from diiodoarenes in good yields. Interestingly, routes to hexafluorocyclopentapyridine (**E**) did not require the use of [$NBu_4$]Br to afford high yields of product. It was determined that formation of the unusual bis-cuprate species $[Cu_2(C_4F_8)_2]^{2-}$ was competitive with perfluoroalkylation of organic diiodides in the case of reagent **A**. It should be mentioned that the large-scale synthesis of [$Me_3Si(CF_2)_4SiMe_3$] (**22**) has recently been reported [113]. Importantly, it was shown that **22** could not be used as a perfluoroalkyalting agent under standard conditions. Such results reinforce the utility of the dizinc reagent **A** for transferring the $C_4F_8$ fragment. For the dizinc reagent bearing six difluoromethylene groups (**C**), reactions with diiodoarenes did not afford ring structures, but instead led to dimeric compounds like **F** in good yields.

The dizinc reagent **A** also reacts with nickel dihalides to form perfluoroalkylmetallacyclopentanes such as **G**. Monomer/dimer preferences are likely due to the fact that zinc(II) complexes prefer tetrahedral geometries while nickel (II) complexes prefer square planar ones, and the angles to accommodate such geometries with a perfluoroalkyl chain are more optimal in one or the other form. Bickelhaupt and co-workers suggested that metal electronegativities also play a role in monomer/dimer preferences in similar reactions [114] and that the geometric forms are also governed by Bent's rule [115, 116]. The ability to form

perfluoroalkyl metallacycles like **G** was significant, because all previous synthetic routes to perfluoroalkyl-metallacyclopentanes involved the oxidative coupling of tetrafluoroethylene (TFE) [91]. TFE has become increasingly unavailable to acquire in a small laboratory setting because of the explosion hazards associated with its use [91]. It is expected that the new dizinc reagents will be useful for laboratories that want to explore the chemistry of perfluoroalkyl metallacycles and are less equipped to handle or generate perfluorinated gases.

**Summary, Conclusions, and Outlook**

Fluoroalkylation reactions are becoming increasingly important in the chemical, biological, and materials fields. While the methodology for *perfluoro*alkylations has matured significantly in the past decade, relatively fewer studies have focused on the historically less common difluoromethylation, difluoromethylenation, and polydifluoromethylenation reactions. The design of new reagents such as [$PhSO_2CF_2Cu$], [$Me_3Si\text{-}CF_2H$], [$Zn(SO_2CF_2H)_2$], [$n\text{-}Bu_3SnCF_2H$], [$HCF_2Cu$], and [$L_2Zn((CF_2)_n)_2ZnL_2$] is further enabling new methods development in these areas. The ability to tailor the amount of fluorine in *small molecules* continues to be important for drug design, biological probes and imaging, and ligands for transition-metal catalysts operating under oxidative conditions. Tailoring the amount of difluoromethylene linkages in *large molecules* will also allow for better control of the unique optical, electronic, processing, environmental stability, and surface properties of new materials [117].

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# Hydrodefluorination Reactions Catalyzed by Transition-Metal Complexes

**Ji-Yun Hu and Jun-Long Zhang**

**Abstract** Activation of the C–F bond by transition-metal catalysts not only advances fundamental understanding of the formation and reactivity of organometallic fluoride complexes but also provides a potential approach to partially fluorinated organic compounds from readily available perfluorinated bulk chemicals. Hydrodefluorination (HDF) is regarded as a simple but important reaction among various C–F functionalizations, which features a mechanistic diversity as model reactions for C–F bond activations. Following Lentz and Braun's review (Angew Chem Int Ed 52, 3328–3348, 2013), we review transition-metal-mediated HDF reactions according to periodic table from group 3–12 metals.

**Keywords** Catalysis · C–F activation · Hydrodefluorination · Transition metals

## Contents



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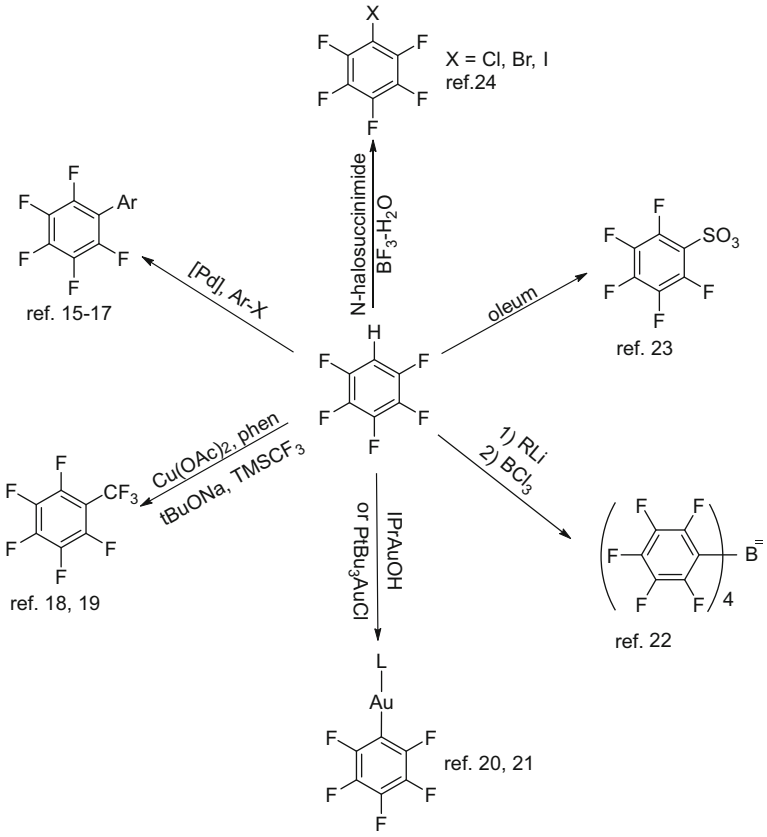
## 1 Introduction

Fluorine chemistry attracts increasing attention for the importance of fluorine-containing pharmaceuticals, imaging agents, agrochemicals, polymers, optoelectronics, and high-performance materials [1–5]. For the small size ($r = 1.47$ Å) and the high electronegativity ($\chi = 4$) of the fluorine atom, fluorine substitution of a certain compound results in remarkable changes in its physical properties, chemical reactivity, and physiological activity with subtle changes of steric parameters [1, 6, 7]. Toward this goal, in past several decades, many methodologies have been developed, including electrophilic or nucleophilic fluorination, electrochemical fluorination, and radical fluorination [8–12], which paved the way to perfluorinated bulk chemicals and the fluorine-containing building blocks. However, further development of a defined partial fluorination was still challengeable for the selectivity of the known fluorination methods and the functional-group tolerance during the harsh fluorination reaction condition. As transition-metal-mediated selective fluorination is currently ongoing, carbon–fluorine bond activation or transformation concerning the availability of suitable fluorine-containing synthons becomes an alternative to circumvent this roadblock. On the other hand, C–F bond activation is the reverse reaction for C–F bond formation. The insights of M–F, M–C bond formation in C–F bond activation would facilitate the design of effective catalytic fluorination system. From an environmentally concerned point of view, the strong and unreactive C–F bond renders fluorinated compounds highly resistant to oxidative degradation, and the extremely long-lived species such as chlorofluorocarbons (CFCs) are potentially related to global warming and ozone depletion [13, 14]. Thus, conversion of CFCs into disposable solid products or hydrogenated derivatives is another impetus to explore new approaches for C–F bond activation. Taking these facts into account, investigation of carbon–fluorine bond activation or transformation is equally important to fluorination in organofluorine chemistry.

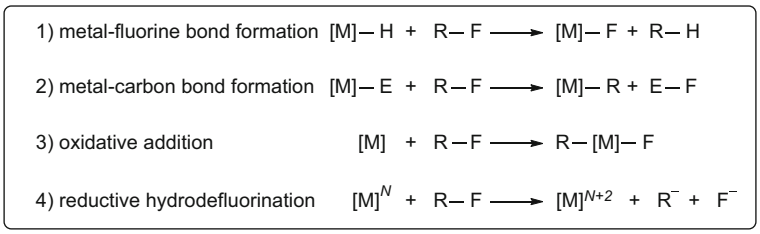
Despite the promising prospects, C–F bond activation is still a challenging task and leads to great efforts in organic chemistry. Firstly, C–F bond is the strongest single bond between a carbon atom and any element ($105 \pm 10$ kcal·mol$^{-1}$), which results from the small size and the high electronegativity of fluorine atom. Secondly, fluorine substituents are weak Lewis bases and fluoride is a poor leaving group. Thus, the strategies for C–F bond activation mainly aim to handle the high thermodynamic stability and kinetic inertness of C–F bonds. Choosing thermodynamically favorable fluorophilic reagents as "fluorine sink" which forms stronger X–F (X = H, P, Si, B or metal) bonds than C–F bond is the preliminary consideration. To resolve the kinetic problem, transition-metal complexes have been widely pursued, which facilitates to break C–F bond and consequently form M–F and/or M–C bonds to lower activation barriers. Among various C–F bond activations, HDF is the simplest C–F bond transformation, which bridges the fundamental understanding of the reactivity of M–F, C–F, and M–H bonds and catalytic C–F activation process. Although HDF products have less been applied as synthetic intermediates at current stage, the proton at perfluoroaryl group could be activated




**Scheme 1** Pentafluorobenzene as a versatile synthon

by palladium [15–17], copper [18, 19], gold [20, 21], lithiates [22], or (Lewis) acid [23, 24], which is potentially useful in synthetic chemistry (Scheme 1). More importantly, an overwhelming number of past and current fluorine-containing natural products or pharmaceutical products have been discovered, which might bring about a renaissance of HDF reactions [25].

Several excellent reviews covering C–F activations including hydrodefluorination (HDF) had been published in recent years [26–34]. In 2013, Braun and Lentz reviewed metal-mediated HDF reactions and summarized the fundamental aspects such as thermodynamics, hydrogen source, selectivity, and reaction profiles [31]. In their excellent and comprehensive review, special emphasis is placed on discussing the underlying mechanistic patterns, including metal fluoride complex formation, metal–carbon bond formation, and their impact on scope and selectivity (Scheme 2) [31]. More recently, Whittlesey and Peris reviewed the late transition-metal-catalyzed HDF reactions [33]. These reviews suggest the importance of the critical metal intermediates such as metal hydride, metal fluoride, and oxidative addition product, which provide important clues for




**Scheme 2** Reaction profiles for C–F bond cleavage ([M] = transition-metal complex fragment, E = fluorophilic ligand) proposed by Lentz and Braun [31]

our understanding of the underlying rules that govern these HDF reactions. In the context, we use the metal–fluorine bond formation as an example to further elucidate the roles of metal in HDF reactions.

## 2 General Consideration of Metal–Fluorine Bond Formation in HDF

For thermodynamic considerations, M–F bonding directly indicates the affinity of metal to fluorine and represents the basic ability of "capturing fluorine" from C–F bonds for a certain metal. Thus, metal fluorides deserve special attention regarding the fate of fluorine. Caulton and coworkers has discussed the influence of σ-stabilized unsaturation and filled/filled repulsions in organometallic fluorides [35]. They also pointed filled/filled interactions will be at a maximum for the short distances which are characteristic of M–F bonds in organometallic halide chemistry. In the review of Murphy, Murugavel, and Roesky in 1997, they summarized the compounds containing carbon–metal–fluorine fragments of *d*-block metals and related reactions [36]. However, the research of organometallic fluorido derivatives is limited, compared to metal complexes with heavier halides. Herein the thermodynamic data for the M–F bonds is chosen from "Comprehensive Handbook of Chemical Bond Energies" [37]. We summarize the bond disassociation energies of M–F bonds and group the metals according to periodic table (Fig. 1). BDE of C–F bond ($105 \pm 10$ kcal·mol$^{-1}$) is set as the criterion (blue region). For a particular metal, the BDE located in the up-region of the criterion indicates the M–F bond is thermodynamically favorable for breaking a C–F bond. With or below the BDE criterion region, M–F bond is weak and thermodynamic compensation is necessary by the formation of other bonds such as metal–carbon bond. As shown in Fig. 1, the BDE decrease from group 3 to 12 (left to right) in each row except vanadium, which could be interpreted by Caulton's hypothesis for the electron-deficient metal has high affinity to electronegative fluorine [35]. Similar trends are found for row 4 and 5 metals, although some BDE of M–F bonds are not available. For the same group, BDE of M–F bonds have no systematic trend for early transition metals, whereas the decrease from row 3 to 5 is observed for late

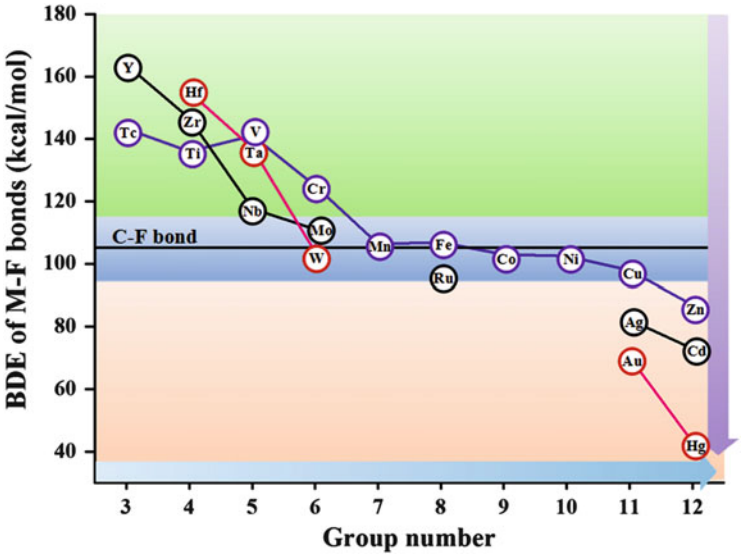



**Fig. 1** Periodic trend of BDE of M–F bonds (*x* axial represents the group of metals and *y* axial is the BDE of M–F bonds from Luo's handbook)

transition metals. This clearly indicates the trend that early transition metals form more stable M–F bonds than late transition metals, which is important to understand and decipher the reaction mechanisms.

Since the relative bond strength of M–F bond is roughly followed by the periodic trend, the relationship between the ability of M–F bond formation and C–F bond activation can be used roughly to understand metal activating mechanism. In HDF reactions, for early transition metals (group 3–5), the high affinity to a fluorido ligand is a thermodynamic favor to C–F bond cleavage, whereas the catalytic process is hampered by the challenging reconversion of stable fluorido complexes into the corresponding hydrido complexes. Starting from metal hydrides, the nucleophilic hydrido ligand could attack the most electrophilic site in the fluorocarbons, similar to typical nucleophilic displacement reactions. In some cases, aluminum hydride, silane, and hydrogen have been employed as regenerating hydride sources to complete the catalytic cycles and achieve reaction turnovers. For late transition metals (group 8–11), M–F bond energies are much lower than those of early metals. The formation of M–F bond energetically disfavors over M–C bond formation. For the electronegativity and polarity of fluorine atom, electron-rich metal can form σ-bonds to fluorinated carbon atoms, which are often more stable than σ-bonds to analogous hydrocarbon moieties. To induce C–F bond cleavage, concomitant formation of a strong E–F bond (E = H, P, Si, B, or metal) and M–C bond has to provide the thermodynamic driving force. In a subsequent step, hydrogen transfer from an external hydrogen source to the carbon atom cleaves the metal–carbon bond and releases the HDF product. For group 12 metals, the BDE of M–F bonds are the lowest among the transition metals as shown in

Fig. 1. In this case, the formation of a metal–carbon or a metal–fluorine bond is not necessarily involved. Alternatively, electron transfer from electron-rich metal centers to the low-lying LUMO of fluorocarbon gives a radical anion, which is prone to fluoride expelling. The resulting radical would be quenched by hydrogen-atom transfer or undergo further reduction followed by protonation to yield the final HDF product. Thus, this also indicated that the sole consideration of the property of M–F bond in HDF reactions is not enough. It is not surprising that there are many factors that may influence HDF reactions, such as substrate type, redox properties of the metal, M–H bond strength, and so on. The mechanisms for metal-catalyzed HDF reactions are complicated, and metals play diverse roles in HDF through different mechanistic processes. In the present review, we will review HDF reaction mediated by group 3–12 metals, following the periodic trends of transition metals.

## 3 Transition-Metal-Catalyzed HDF Reactions

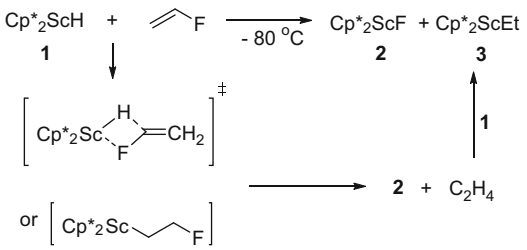
1. Groups 3–4

   As shown in Fig. 1, early transition metals form much stronger bonds with fluorine than carbon does, especially for group 3 and 4 metals. Consequently, C–F bond cleavage through metal fluorine bond formation (Scheme 2, type 1) is typically observed for group 3 and 4 metal hydride complexes. Also arising from the high BDE of M–F bonds is the requirement of sufficiently fluorophilic hydrogen source reagents to cleave M–F bond to regenerate active M–H intermediate, thus completing a possible catalytic cycle. In this section, lanthanide and actinide were discussed for the similar M–F bonding.

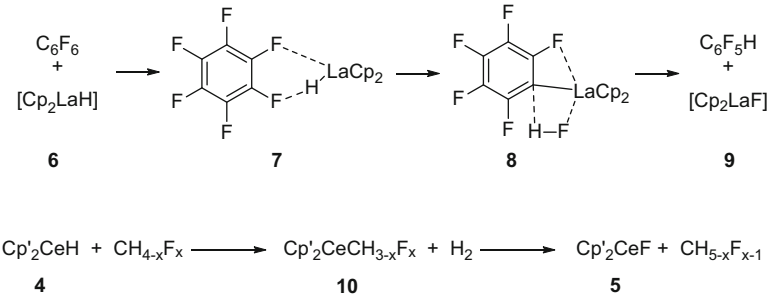
   (a) H/F Exchange Reactions

   In Burger's PhD thesis, he described the fast reaction of permethylscandocene hydride [$Cp^*_2ScH$] (**1**) with fluoroethene at −80 °C, giving an equimolar mixture of [$Cp^*_2ScF$] (**2**) and [$Cp^*_2ScEt$] (**3**, Scheme 3) [38]. The detailed mechanism for the C–F bond cleavage via two-step olefin insertion/β-fluoride elimination or one-step H/F metathesis remains unclear.

   Andersen et al. showed that monomeric metallocerium hydrido complex [$Cp'_2CeH$] (**4**, Cp′ = 1,2,4-($tBu_3$)$C_5H_2$) underwent H/F exchange reactions with perfluorobenzenes [39] and fluoromethanes $CH_{4-x}F_x$ ($x = 1$–3) [40]. **4** reacts with $C_6F_6$ in $C_6D_6$ to give cerium fluorido complex [$Cp'_2CeF$] (**5**), $H_2$ and tetrafluorobenzyne, which is trapped as a Diels–Alder adduct. DFT calculations on [$Cp_2LaH$] (**6**) reveal that H/F exchange reaction between $C_6F_6$ and the cerium hydride is the key step of the reaction (Scheme 4). H/F exchange process starts with the fluorine lone pair coordination to the metal center. And consequent metathesis occurs between M–H and the *ortho*-C–F bond to yield an aryl complex **8** with a coordinated




**Scheme 3** Stoichiometric reactions between permethylscandocene hydrido complex and fluoroethene (Cp* = $\eta^5$-$C_5Me_5$)

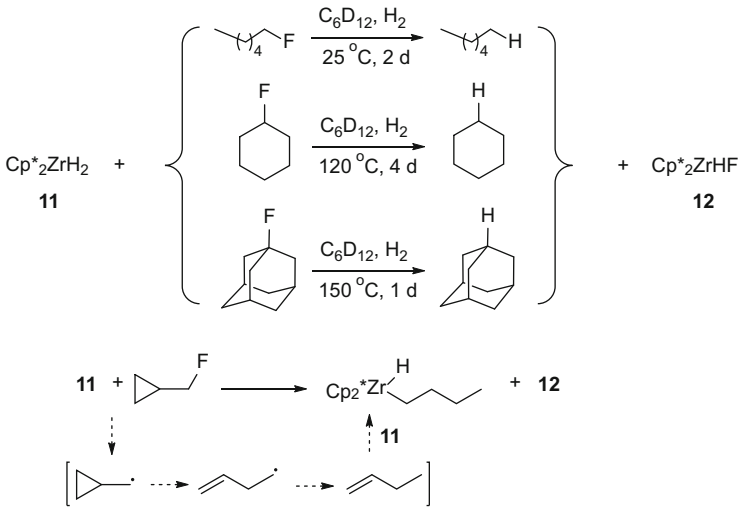



**Scheme 4** Calculated reaction profiles of cerium hydride with (*top*) hexafluorobenzene; (*bottom*) hydrofluoromethanes (Cp′ = 1,2,4-($tBu_3$)$C_5H_2$)

hydrofluoride. Subsequent intramolecular hydrolysis by HF gives $C_6F_5H$ and the fluorido complex **9**. Note that the fluorine atom is hooked to the electropositive metal center throughout the exchange process.

The reaction of cerium hydride **4** with hydrofluoromethanes was found to occur in a rate order of $CH_3F > CH_2F_2 > CHF_3$. Methane was the HDF product for $CH_3F$ and $CH_2F_2$, while $H_2$ and 1,2,4- and 1,3,5-tri-*tert*-butylbenzene for $CHF_3$. No reaction was observed with $CF_4$ [40]. DFT calculations showed C–H activation pathway was the lowest energy barrier reaction profile, forming cerium alkyl intermediate $Cp_2CeCH_{3-x}F_x$ (**10**) and $H_2$ (Scheme 4). The next rate-determining step via a transition state involving synchronous C–F bond cleavage, Ce–F bond formation, and carbene fragment trapping with $H_2$ gives cerium fluoride **5** and hydrodefluorinated fluoromethane. The different products for the reaction of $CHF_3$ are thus a result of the $CF_2$ carbene trapping by Cp ring, rather than by $H_2$. The raised barrier of the rate-determining step with the increasing number of fluorines accounts for the observed reactivity.

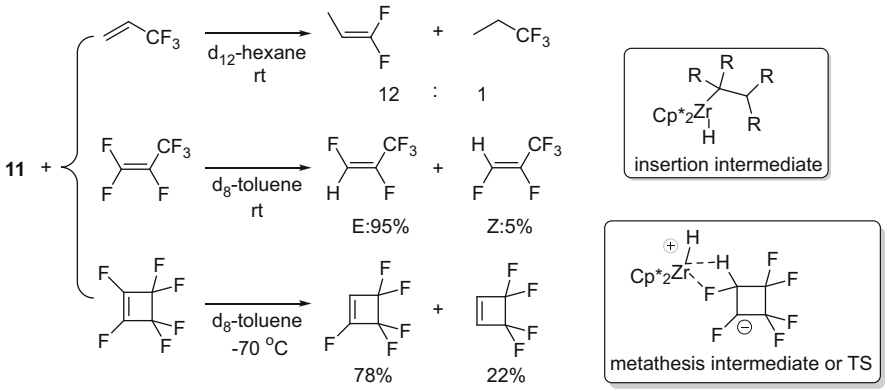
Jones et al. performed a careful study of stoichiometric H/F exchange reactions of group 4 metallocene hydrides with various fluorinated substrates [41], including alkanes [42], alkenes [41, 43–45], and arenes [42, 46, 47]. And diverse mechanisms operate regarding the different types of substrates [48].




**Scheme 5** Stoichiometric reactions between zirconocene hydride and fluoroalkanes via radical mechanism (Cp* = $\eta^5$-$C_5Me_5$)

Aliphatic C–F bonds reacted with [Cp*$_2$ZrH$_2$] (**11**, Cp* = $\eta^5$-$C_5Me_5$) in a rate order of $1° > 2° > 3°$ and **11** was converted to [Cp*$_2$ZrHF] (**12**, Scheme 5) [42, 48]. An atmosphere of $H_2$ is necessary to prevent **11** from dihydrogen loss and dimerization. The reaction rate was affected obviously by radical initiators and inhibitors, indicating a radical mechanism, which was supported by the reaction of **11** with cyclopropylcarbinyl fluoride. The generation of [Cp*$_2$Zr(n-Bu)H] is best explained by butane radical insertion of the Zr–H bond through a radical rearrangement process. Abstracting a fluorine atom from the fluorocarbon by a Zr(III) radical intermediate was proposed as the rate-determining step, in which the steric hindrance of **11** would make less-hindered C–F bond more reactive.

Compared to the relative sluggish reactivity toward fluoroalkanes, the reaction of [Cp*$_2$ZrH$_2$] (**11**) with fluoroalkenes proceeds much faster under mild conditions [43–45]. Two competing reaction mechanisms, namely, olefin insertion/β-fluoride elimination and H/F metathesis, were carefully examined. By choosing different substrates, these pathways can be distinguished (Scheme 6). For acyclic alkenes, both vinylic and allylic C–F bonds were shown to be hydrodefluorinated via two-step insertion/elimination pathway. In the case of non-perfluorinated alkenes such as 3,3,3-trifluoropropene, insertion products of both internal and terminal regioisomers were observed by NMR spectroscopy at low temperature. And the terminal insertion isomer gave 3,3,3-trifluoropropane as non-HDF product upon reductive elimination [45]. Perfluoropropene was selectively defluorinated to *E*-1,2,3,3,3-pentafluoropropene [44]. Though

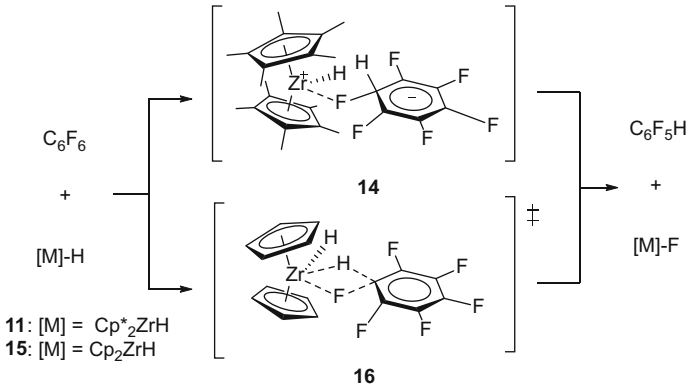



**Scheme 6** Stoichiometric reactions between zirconocene hydride and fluoroalkenes via olefin insertion/β-fluoride elimination or metathesis mechanism

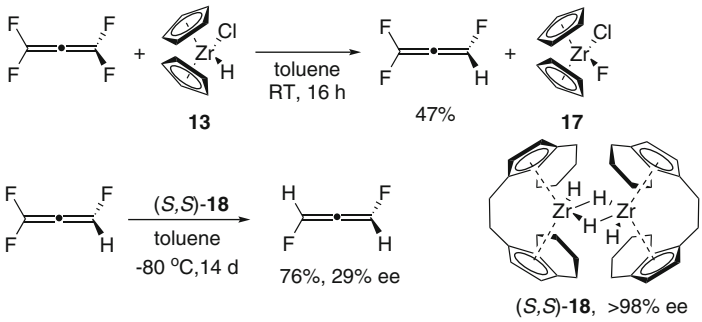
no insertion intermediates were observed even at low temperature, DFT calculations revealed that F/H metathesis reaction was energetically disfavored than the insertion/elimination pathway, which is similar to the reaction of Schwartz's reagent [$Cp_2ZrHCl$] (**13**) with fluoroethene shown by Caulton et al. [49]. Terminal defluorination was the outcome of the strong electrophilicity of the terminal carbon, which prefers nucleophilic attacking by hydrido ligand. However, the reason for *E*-stereochemistry was not resolved in the simplified calculation model using the replacement of Cp to Cp* ligand. For cyclic perfluorinated olefins, like perfluorocyclobutene, selective HDF of the vinylic positions occurred first and was proposed through an σ-bond metathesis mechanism according to DFT calculations (Scheme 6) [43]. After both vinylic fluorines were replaced, further HDF of allylic positions proceeded by insertion/elimination sequence, as the same reaction pattern shown by 3,3,3-trifluoropropene.

HDF of perfluorinated aromatic compounds by [$Cp^*_2ZrH_2$] (**11**) was also examined. The mechanism was assumed to be $S_NAr$ mechanism via a Meisenheimer-type intermediate (**14**, Scheme 7, top) [42, 47]. Similar reactivity was found for a zirconium hydride dimer [$Cp_2ZrH_2]_2$ (**15**). However, a concerted σ-bond metathesis mechanism via a four-centered transition state **16** between the disassociated zirconocene monomer and $C_6F_6$ was suggested (Scheme 7, down), considering the small hindrance of Cp than Cp* ligand [46].

In a recent study, Lentz et al. presented that Schwartz's reagent **13** was able to hydrogenate allene C–F bond with the formation of the corresponding fluorido complex [$Cp_2ZrClF$] (**17**) [50]. Impressively, when a chiral Brintzinger-type *ansa*-zirconocene hydrido complex [(ebthi)$ZrH_2$] (**18**, ebthi = 1,2-ethylene-bis(tetrahydroindenyl)) was used, optically active 1,3-difluoroallene can be obtained from trifluoroallene. This is the first example of an asymmetric C–F bond activation (Scheme 8).




**Scheme 7** Different HDF mechanisms arising from steric factors: metathesis (*top*) versus $S_NAr$ (*bottom*)

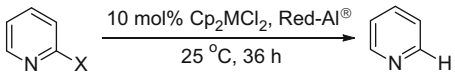



**Scheme 8** HDF of allene C–F bond and asymmetric C–F bond activation

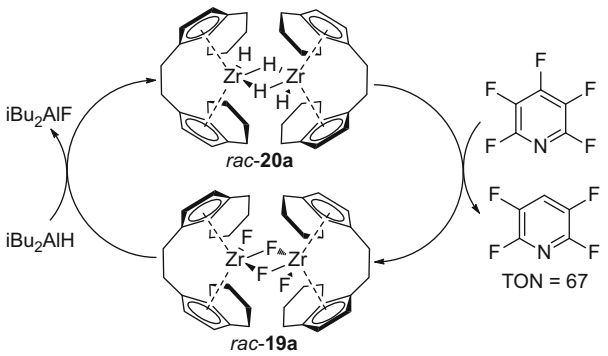
The hafnium analogue $Cp^*_2HfH_2$ has a similar reactivity pattern to **11** but is less reactive [51]. Although less mechanistic studies had been undertaken with hafnium, similar mechanisms as in the zirconium situation are likely the case.

Catalytic transformations using group 4 metallocene dihalide pre-catalysts including difluoride ones were achieved in the presence of aluminum hydrides or hydrosilanes. Until now, only HDF of $sp^2$ C–F bonds have been realized. Hwang group used Red-Al® ($NaAlH_2(OC_2H_4OCH_3)_2$) for dehalogenation of monohalopyridines including 2-fluoropyridine in the presence of group 4 metallocene catalysts (Scheme 9) [52]. The catalytic activity decreases in the order of Ti > Zr > Hf. However, this system was ineffective toward other fluorinated substrates such as fluorobenzene and perfluorodecalin and no mechanism studies were presented.

Rosenthal et al. reported the catalytic HDF of pentafluoropyridine by zirconocene difluorido complexes [$Cp'_2ZrF_2$] (Cp′ = ebthi, **19a**; = Cp, **19b**) using diisobutylaluminum hydride ($iBu_2AlH$) as hydrogen source at room




**Scheme 9** Group 4 metallocene-catalyzed dehalogenation of monohalopyridines (X = F, Cl, Br; M = Ti, Zr, Hf)

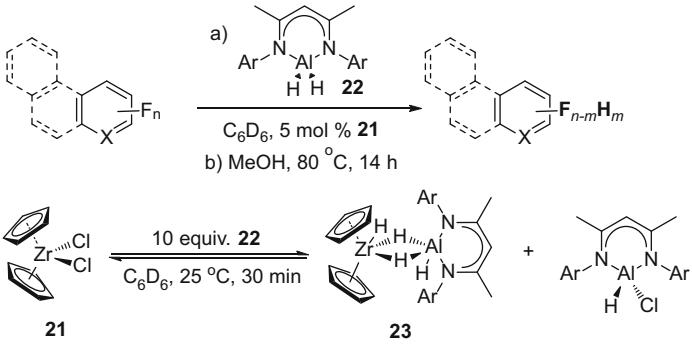



**Scheme 10** Zirconocene hydride-catalyzed HDF of pentafluoropyridine in the presence of aluminum hydride

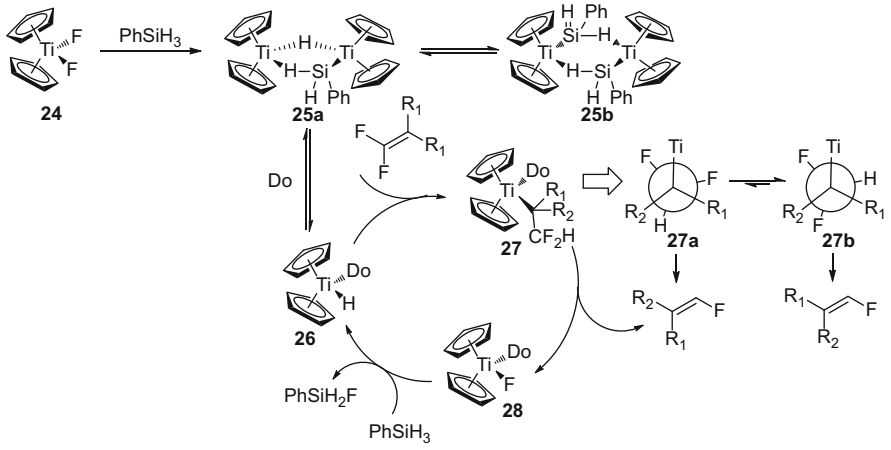
temperature (Scheme 10) [53]. The zirconocene hydride dimer [rac-(ebthi)$ZrH(\mu\text{-}H)]_2$ (20a) and $[Cp_2ZrH(\mu\text{-}H)]_2$ (20b), formed in the reaction of **19** with $i$Bu$_2$AlH, served as the active species. And a maximum TON of 67 could be achieved applying **20a** as the catalyst. The ligands were critical to the catalytic performance, where higher TONs were obtained with the ebthi-ligand than the Cp-ligands. And $[Cp^*_2ZrF_2]$ cannot be converted to the corresponding active hydrido complex when treated with $i$Bu$_2$AlH.

A broader fluoroarene scope was achieved by combining catalytic $[Cp_2ZrCl_2]$ (**21**) with diketiminate ligand (BDI)-stabilized aluminum dihydride (**22**) (Scheme 11) [54]. [(BDI)AlHF], $[(BDI)AlF_2]$, and [(BDI)$Al(Ar^F)X$] (X = H or F) complexes were observed as reaction by-products or intermediates. A fast ligand transfer process between the catalyst and **22** was proposed and supported by NMR studies. Although a heterobimetallic complex 2**3** had been observed as a catalyst resting state, its role in the catalysis was yet unclear.

Lentz et al. reported that titanocene fluorido complex $[Cp_2TiF_2]$ (**24**) could be applied as a catalyst precursor in HDF of fluoroalkenes in the presence of silane [55, 56]. A maximum TON of 125 and a high TOF of 1,500 $h^{-1}$ were achieved [55]. Substrate-dependent E/Z selectivity was observed. A detailed mechanistic study indicated a titanium(III) hydrido complex **26**, produced in the reaction of **24** with silane, was the active species. After HDF reaction with fluorocarbons, titanium(III) fluoride **28** is generated, thus closing the catalytic cycle (Scheme 12) [56]. Following an alkene insertion/β-fluoride elimination mechanism, the observed substrate-dependent E/Z selectivity could be explained regarding the conformational aspects of the insertion intermediate **27**. S*yn* β-fluoride elimination makes



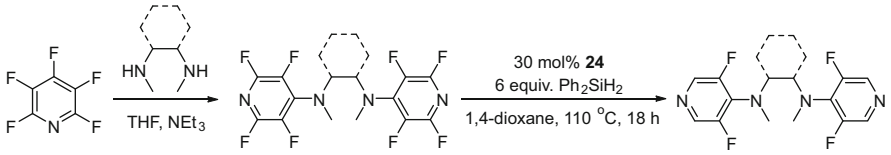

**Scheme 11** Zirconocene-catalyzed HDF of fluoroarenes in the presence of aluminum hydride (Ar = 2,4,6-$Me_3C_6H_2$; X = CF, N)



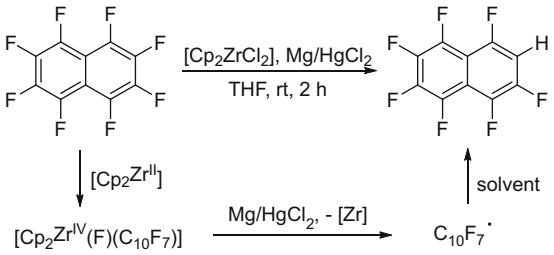

**Scheme 12** Mechanism of titanium-catalyzed HDF of fluoroalkenes in the presence of silane (Do = donor solvent)

an eclipsed conformation of either $R_1$ or $R_2$ with a vicinal fluorine substituent. The sizes of $R_1$ and $R_2$ determine the preferred rotamer and thus the configuration. In the case of hexafluorocyclobutene substrate, σ-bond metathesis became the preferred reaction pathway, as only a minor allylic HDF product is produced which would be expected in an insertion/elimination pathway.

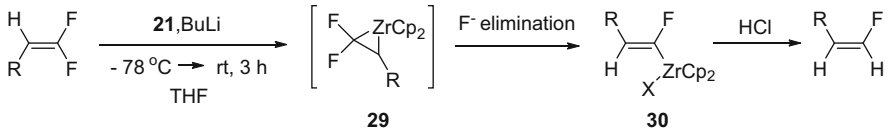
Later, this catalytic system proved its synthetic utility in the preparation of aminopyridine derivatives, combining traditional nucleophilic aromatic substitution. The orthogonal regioselectivity of nucleophilic substitution and HDF process gave expected 4-aminopyridine derivatives in good yields (Scheme 13).




**Scheme 13** Selective HDF as a key step for the synthesis of aminopyridine derivatives




**Scheme 14** Zirconocene-mediated HDF of octafluoronaphthalene




**Scheme 15** Zirconocene-mediated HDF of fluoroalkenes (R = $Et_2NCO_2$, PhO, p-$MeOC_6H_4O$, p-$Me_2NC_6H_4O$; X = F, Cl, 1-fluoroethenyl)

(b) Oxidative Addition

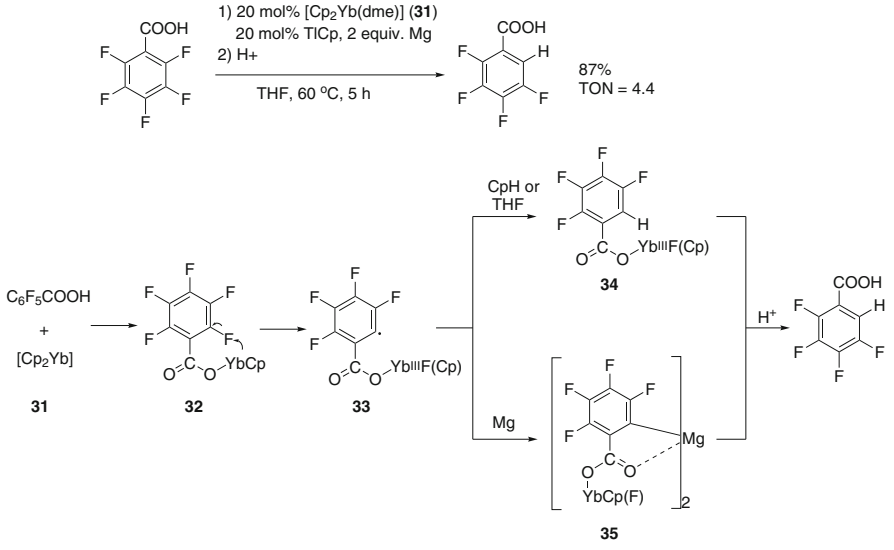
Group 4 complex-mediated HDF reactions involving oxidative addition process are also possible. In the first example of selective HDF of aromatic C–F bonds by [$Cp_2ZrCl_2$] (**21**), critical C–F bond activation step was suggested to occur via oxidative addition to low-valent zirconocene fragment [$Cp_2Zr^{II}$] generated in the reductive reaction conditions (Scheme 14). Subsequent electron transfer from the external reductant induces metal–carbon bond breaking and liberates an aryl radical, which abstracts hydrogen atom from solvent to yield HDF product.

[$Cp_2ZrCl_2$] (**21**)-mediated HDF of fluoroalkenes had also been reported by Ichikawa and Minami et al. [57]. At low temperature, the reaction of difluorovinylethers with in situ generated [$Cp_2Zr^{II}$] gives the zircoacyclopropane intermediate **29**, which is postulated to eliminate β-fluoride to give *E*-1-fluorovinyl zirconocene **30** stereoselectively (Scheme 15). Upon protonation, *E*-1-fluorovinylether is released. In addition, **30** can be coupled with aryl iodides in the presence of palladium catalyst and zinc iodide.

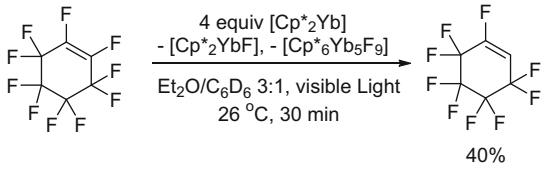
(c) Reductive HDF and radical involving process

On the other hand, lanthanide compounds are readily engaged in electron transfer process in their low oxidation states, capable of promoting reductive HDF reactions. Deacon et al. reported that pentafluorobenzoic acid reacted with $YbI_2$ or $[Yb(C_6F_5)_2]$ to yield, after hydrolysis, 2,3,4,5-tetrafluorobenzoic acid [58]. Using $[Cp_2Yb(dme)]$ (**31**, dme = 1,2-dimethoxyethane), catalytic *ortho*-selective HDF of pentafluoro- and 2,5-difluorobenzoic acid was achieved with a TON of 4.4 in the presence of activated magnesium and additional Cp source (Scheme 16) [59]. The observed selectivity was explained by the formation of Yb (II) pentafluorobenzoate complex **32**, which undergoes intramolecular electron transfer to an *ortho*-fluorine and then fluoride abstraction. The resulting Yb(III) aryl radical **33** can abstract an hydrogen atom from CpH or solvent, giving the corresponding Yb(III) aryl complex **34**. Alternatively, **33** can be further reduced to a highly carbanionic complex **35**. Upon hydrolysis, **34** and **35** liberates the HDF product 2,3,4,5-tetrafluorobenzoic acid.

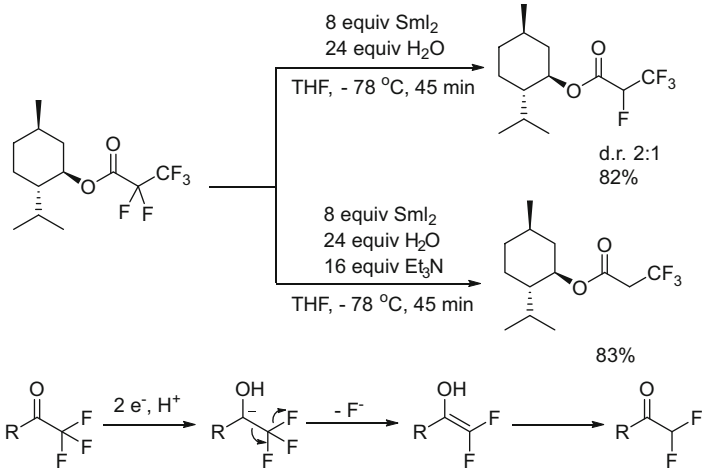
Lanthanide metallocenes $[Cp^*_2M{\cdot}L]$ (M = Yb, Eu, Sm; L = diethyl ether, THF) and $[Cp'_2Yb{\cdot}THF]$ ($Cp' = \eta^5$-$C_5H_4Me$) were able to HDF $sp^2$ C–F bond of perfluorocyclohexene to give 2,3,3,4,4,5,5,6,6-nonafluorocyclohexene and multiple fluorine abstraction products 3,3,4,4,5,5,6,6-octafluorocyclohexene, perfluorobenzene and pentafluorobenzene also formed in these reactions (Scheme 17) [60]. The organometallic products consisted of trivalent fluoride species $Cp^*_2MF$, $Cp^*MF_2$, and clusters. Light was found to enhance both the reaction rate and the product yield,




**Scheme 16** Ytterbium-catalyzed *ortho*-selective HDF of pentafluorobenzoic acid (dme = 1,2-dimethoxyethane)




**Scheme 17** Light-promoted HDF of fluoroalkenes by rare-earth metallocenes

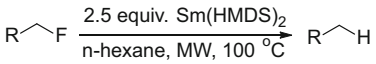



**Scheme 18** Samarium-mediated selective HDF of pentafluoropropanoate derivatives

consistent with a SET process. An increased fluorine abstraction reactivity was also observed experimentally with increasingly negative reduction potential of the three studied complexes in the order of Sm > Yb > Eu.

Otaka et al. have reported on reductive defluorination of γ-difluoro-α,β-unsaturated esters using $SmI_2$ via successive two-electron transfer process [61]. Later, Hilmerson demonstrated that selective HDF of polyfluorinated esters and amides can be achieved using $SmI_2/Et_3N/H_2O$ system [62]. Removing one or two fluorines from the α-position of amide or ester group can be controlled by adjusting the amount of $NEt_3$. It is worth noting that a menthol-derived pentafluoropropionylester could be hydrodefluorinated stereoselectively, although with low diastereoselectivity (2:1) (Scheme 18). Mechanistically, electron transfer to the carbonyl, followed by protonation and a second SET process, gives a carbanion. Subsequent elimination of the fluoride anion yields an enolate which rearranges to the HDF product.

HDF of simple fluoroalkanes was accomplished by $Sm(HMDS)_2$ in *n*-hexane under microwave conditions (Scheme 19) [63]. Primary, secondary, and tertiary alkyl fluorides were suitable substrates with an increased reactivity order. *Gem*-difluoro substrates were converted to the

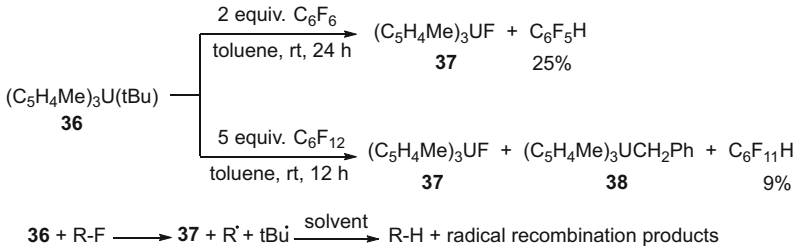



**Scheme 19** Samarium-mediated reductive HDF of alkylfluorides

corresponding alkenes. Besides, both *p*-fluorotoluene and benzyl trifluoride were reduced to toluene. The reactivity decreases in THF compared to that in *n*-hexane, indicating samarium weakens the C–F bond through an inner-sphere interaction [64].

HDF of hexafluorobenzene and perfluorocyclohexane via radical process by U(IV) metallocene complex had been reported by Bergman et al. [65]. The reaction of $[(C_5H_4Me)_3U(^tBu)]$ (**36**) with 2 equiv. $C_6F_6$ yielded $C_6F_5H$ and a quantitative uranium fluorido complex $[(C_5H_4Me)_3UF]$ (**37**) (Scheme 20). Similar reaction was found with saturated perfluorocyclohexane, and another uranium complex $[(C_5H_4Me)_3UCH_2Ph]$ (**38**) was generated, an indication of radical involvement. Deuterium labeling revealed that solvent was the hydrogen source. Based on the results of radical trapping experiments and the existence of radical recombination products in the reaction, radical mechanism was suggested for both reactions.

In summary, group 3 (Sc) and 4 metals including lanthanide and actinide metals have been used as catalysts in HDF reaction. These reactions could be classified into two types: H/F exchange reactions and electron transfer reaction. For the former, the valence of metals may not change during the reaction process, but most of the reactions are stoichiometric for the difficulty to regenerate the active M–H intermediate. To overcome this problem, using strong hydrogen donor such as aluminum hydride or "fluorine sink" such as silane could be an effective approach to achieve high turnover numbers. For the practical application, $Ti^{3+}$ or $Ti^{4+}$ could be prospective catalysts in the early transition metals in HDF reaction because of the easy handle of silane as hydrogen donor. On the other hand, electron transfer mechanism either in radical involving process (lanthanide) or oxidative addition (Zr) was observed. However, strong reductants are used to reduce high-valent metals to their active low-valent states. Thus,




**Scheme 20** HDF by uranium complex via radical process

appropriate ligand design is very important to lower redox potentials for these metals, which might render these catalysts more practical.

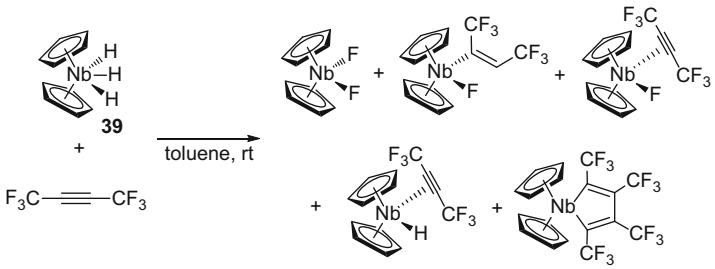
2. Groups 5–7

Examples of C–F bond activation for group 5 metals are rather limited, although the corresponding M–F bond strength is comparable with that of group 4 metals. Recently, significant progress has been made on Ar–$CF_3$ group reduction with low-valent niobium species [66–68]. The first transition-metal-activated C–F bonds at room temperature were based on a tungsten (0) carbonyl complex [$W(CO)_3(EtCN)_3$], which reacts with a fluorinated aromatic ligand through an intramolecular chelate-assisted oxidative addition manner [69]. Similar chemistry was found on molybdenum(0). Activation of aromatic C–F bonds has also been observed by molybdenum, tungsten, and rhenium cyclopentadienyl complexes and low-valent manganese [26, 70]. Despite of these early findings, the C–F bond activation potential of groups 6 and 7 has not progressed too much in the past 20 years.

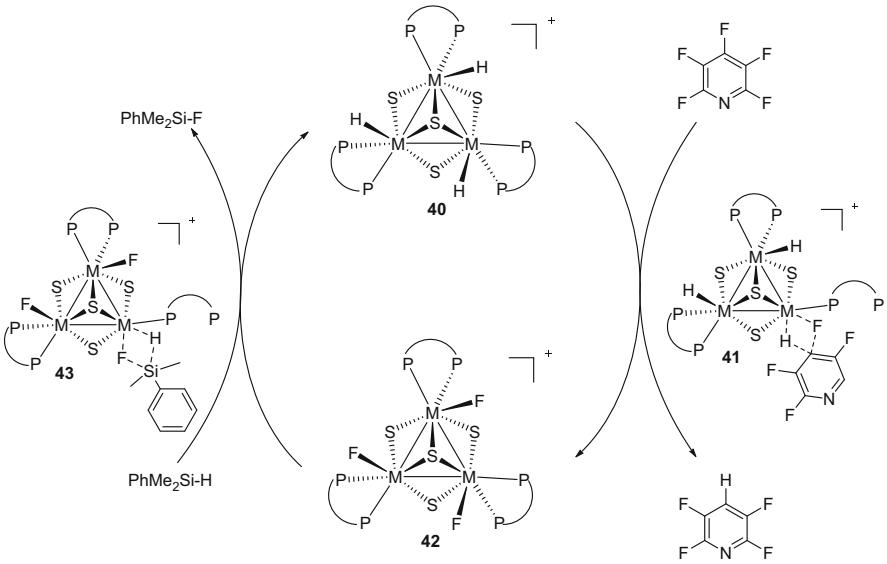
(a) H/F exchange

Unlike its early counterparts like $Cp^*_2ZrH_2$, F/H exchange reaction was not observed for niobium(V) hydrido complex [$Cp_2NbH_3$] (**39**) with hexafluoro-2-butyne. Instead, a mixture of reduced niobium (IV) complexes was produced (Scheme 21) [71, 72]. The mechanism for this reaction remains unclear.

Only one example probing catalytic HDF reactivity could be found in literature by group 6 triangular cluster hydrides [$M_3S_4H_3(dmpe)_3$]X (**40**, M = Mo, W; dmpe = 1,2-(bis)dimethylphosphinoethane; X = $PF_6^-$, $SO_3CF_3^-$) [73]. A maximum TON of 90 was achieved by the tungsten complex in the model reaction of HDF of pentafluoropyridine. C–F bond activation exclusively occurs at *para*-position in the presence of arylsilanes under microwave radiation conditions. DFT calculation suggests a coordinately unsaturated intermediate **41** by partial decoordination of the diphosphine ligand, which reacts with pentafluoropyridine through σ-bond metathesis (Scheme 22). Regeneration of the catalyst requires another σ-bond metathesis between the formed metal fluorido complex **42**




**Scheme 21** Reaction of niobium hydride with hexafluoro-2-butyne



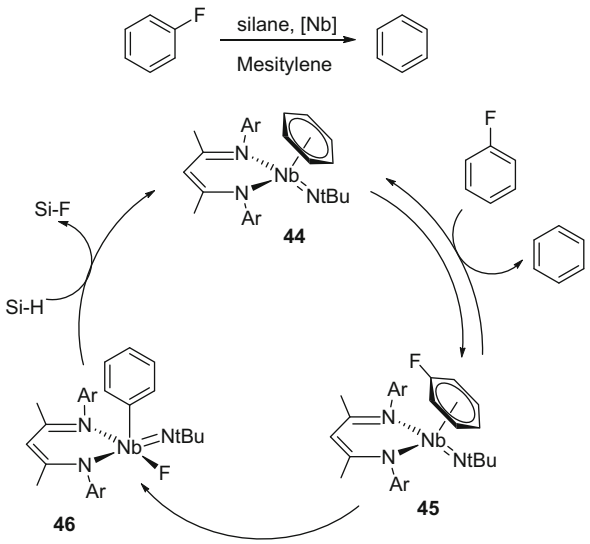

**Scheme 22** Catalytic cycle of HDF of pentafluoropyridine by group 6 triangular cluster hydrides (counterions omitted for clarity; P,P = 1,2-(bis)dimethylphosphinoethane)

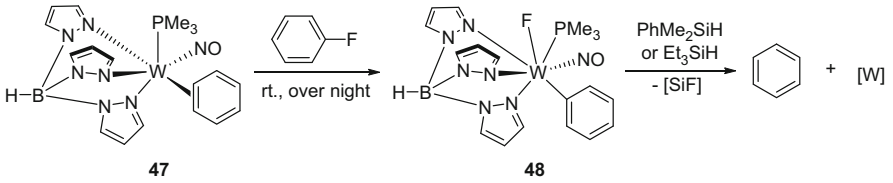
and silane, involving a similar unsaturated intermediate **43**. Computational results also ascribe the slower conversion and higher yields of tungsten complexes compared to its molybdenum analogue to a higher energy demanding reaction profile and lower stability of fluorido complex **42**.

(b) Oxidative Addition

Very recently, Bergman and Arnold et al. reported a well-defined niobium (III) imido complex-catalyzed C–F bond activation for fluoroarenes (Scheme 23) [74]. The reaction of the diketiminate ligand-ligated niobium complex [(BDI)Nb(NtBu)($C_6H_6$)] (**44**, BDI = 2,6-diisopropylphenyl-β-diketiminate) with fluorinated benzenes gives niobium (V) aryl fluorides [(BDI)Nb(N$^t$Bu)(Ar)(F)]. Interestingly this reaction shows an unusual and nonlinear rate trend as a function of degree of fluorination: 1,2-$C_6H_4F_2$ > 1,3-$C_6H_4F_2$ > 1,4-$C_6F_2H_4$ > $C_6H_5F$ ≫ 1,2,4,6-$C_6H_2F_4$ > $C_6F_6$. However, selective C–Cl bond activation was observed for 1-chloro-3-fluorobenzene. NMR studies implicate that $\eta^6$-fluoroarene coordination to metal center prior to C–F bond activation takes place. Therefore, the lack of reactivity of highly fluorinated arenes might originate from their electron deficiency property, being unable to form the critical $\eta^6$-arene-bound complexes. DFT calculation suggests a bimolecular process involving arene-bridged inverted sandwich complex in C–F bond cleavage step, which lowers energy level than conventional concerted oxidation addition pathway. Treating C–F bond activation product with 5 equiv. of $nBuSiH_3$ in $C_6D_6$ yields HDF product and $C_6D_6$-bounded Nb complex

**Scheme 23** Catalytic cycle for niobium-catalyzed HDF of fluoroarene (Ar = 2,6-$C_6H_3Me_2$)




**Scheme 24** Tungsten complex-mediated HDF of fluorobenzene

[(BDI)Nb(NtBu)($C_6D_6$)]. A maximum TON of 19 in the presence of $nBuSiH_3$ was obtained by applying niobium(V) phenyl fluorido complex **46** as the catalyst.

Stoichiometric HDF reaction at a six-coordinate tungsten complex [TpW(NO)($PMe_3$)($\eta^2$-$C_6H_6$)] (**47**, Tp = trispyrazolylborate) via C–F bond oxidative addition has been reported by Harman et al. [75]. Complex **47** reacted with fluorobenzene at room temperature to cleanly give C–F bond insertion product [TpW(NO)($PMe_3$)(F)($C_6H_5$)] (**48**) in 78 % yield (Scheme 24). No C–H bond activation products were observed. When subjected to triethyl- or phenyldimethylsilane, **48** yielded free benzene, the corresponding silyl fluoride, and unknown paramagnetic metal fragments. Decomposition of the complex under the reaction conditions precludes its catalytic application. DFT calculations suggest C–F bond activation starts from a fluorine-bound σ-complex intermediate with a modest 3 kcal/mol barrier. However, when extent of fluorination on benzene increases, either C–H bond insertion or $\eta^2$-coordination becomes dominant.

(c) Others

Akiyama et al. discovered that $NbCl_5$ was capable of hydrogenation aromatic [76, 77] and benzylic fluorides [67, 77] with lithium aluminum hydride $LiAlH_4$. The reaction is likely to be catalyzed by Nb(0) species, as $NbCl_5$ can be reduced to metallic niobium by $LiAlH_4$. Although aromatic C–Br and C–Cl bonds were reduced prior to the C–F bond, an unusual preference for benzylic fluoride was observed when both aromatic and benzylic fluoride substituents existed. For $sp^2$ fluorine substituents, a $S_NAr$-like nucleophilic substitution mechanism with low-valent niobium hydride species was suggested. Based on the deuterium incorporation experiments, a niobium fluorocarbenoid species **49** was proposed in reduction Ar-$CF_3$ groups (Scheme 25) [76]. The competing C–H bond activation process accompanied provides a good chance to perform intramolecular C–C coupling [66, 78].

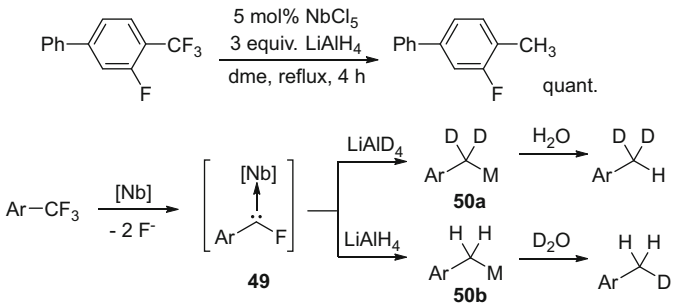
In summary, group 5–7 metals catalyzed HDF reaction mainly dependent on the low-valent metal intermediates; however, exploring a suitable hydrogen donor or reductant is critical for HDF catalysis. Similar to group 3–4 metals, to improve the efficiency or turnover number is an important issue for further development of these metal catalysts.

3. Groups 8–10

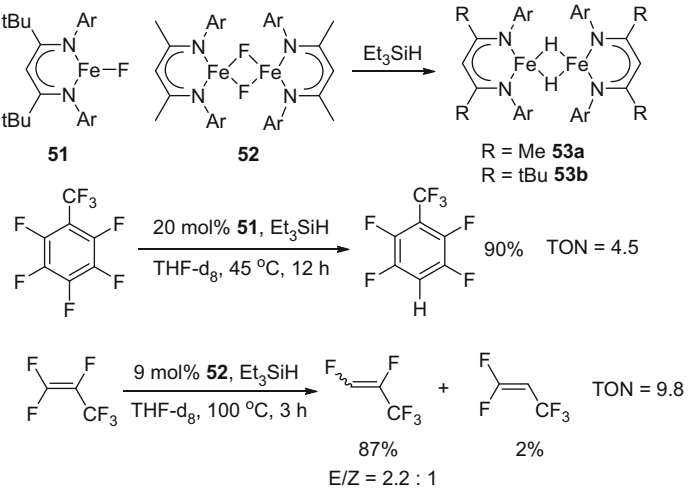
Although weakened M–F bonds are not favored to directly cleave C–F bond, the electron-rich property of late transition metals is advantageous for oxidative insertion of metal to C–F bond. This resembles to C–H bond activation process. Thus, benefited from the tremendous progress of metal activating C–H bond, group 8–10 metals are the most studied catalysts in HDF reactions.

(a) Iron

Low-coordinate iron(II) fluorido complexes have been used in catalytic HDF perfluoroarenes and fluoroalkenes in the presence of triethylsilane by Holland and coworkers (Scheme 26) [79]. The preferable catalyst for fluoroarenes and fluoroalkenes is **51** and **52,** respectively, both of which react with triethylsilane to give the dimeric hydrido complexes (**53**).




**Scheme 25** HDF of benzylic C–F bond involving a niobium fluorocarbenoid species (M = Li, $AlX_2$; dme = 1,2-dimethoxyethane)

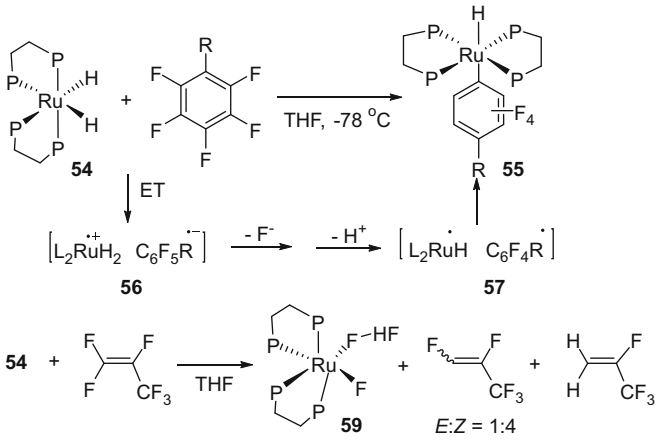



**Scheme 26** Iron fluoride complex-catalyzed HDF of $sp^2$ C–F bond (Ar = 2,6-di(isopropyl) phenyl)

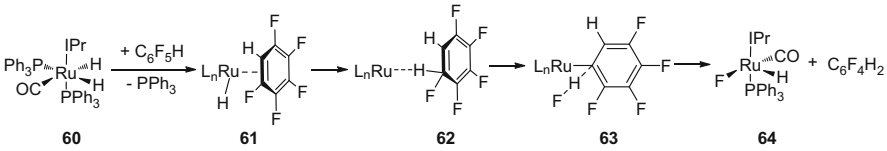
Nevertheless, no reactivity between **53a** and $C_6F_6$ and $C_6F_5CF_3$ was observed in the absence of silane, ruling out the hydrido complexes as the active intermediate. The catalytic perfluoroarene HDF reactions proceed with good selectivity at *para*-position of perfluoroarenes with electron-withdrawing substituents. Substrate electronic properties, solvent polarity, and silane are found to influence the reactions greatly. Kinetic studies suggested hydride generation was the rate-limiting step and outer sphere electron transfer pathways were unlikely. However, the catalyst's instability in the reaction conditions hampered further mechanistic elucidation. For alkene substrates, a higher reaction temperature was needed and decreased selectivity was observed, in contrast to group 4 metallocene hydrides [44]. Observation of an iron (II) alkyl complex by NMR spectroscopy strongly supported an insertion–elimination mechanism. Hence, the minor C2 C–F bond activation product might be a result of less steric congestion between **52** and the terminal carbon. In spite of the high catalyst loadings and low catalyst robustness, the chemical inertness toward C–H bond and low price of iron metal make iron complex still promising efficient and industrial potential HDF catalysts.

(b) Ruthenium

The group of Whittlesey described that a ruthenium phosphine hydrido complex [*cis*-Ru(dmpe)$_2$(H)$_2$] (**54**) reacted with several fluorinated benzenes to give ruthenium aryl complexes (**55**) and to lose HF as thermodynamic sink under mild conditions (Scheme 27) [80]. C–H bond activation was not observed in the case of partially fluorinated arenes. Electron transfer from electron-rich metal complex to the electron-poor fluoroarenes




**Scheme 27** Different reaction outcomes of ruthenium phosphine hydrido complex with fluoroarenes and fluoroalkene




**Scheme 28** Ruthenium dihydrido complex-catalyzed *ortho*-selective HDF of pentafluorobenzene (IPr = *N*,*N*′-1,3-bis(isopropyl)imidazolin-2-ylidene)

to give a solvent-caged radical pair (**56**) was proposed to initiate C–F bond activation, similar to a previous proposal on [*trans*-Pt(H)$_2$(PCy$_3$)$_2$] (**58**) by Clark et al. [81]. The resulting aromatic radical anion is liable to expel a fluoride ion, yielding an aryl radical. Radical recombination in the solvent cage with the deprotonated ruthenium gives the final ruthenium aryl complex. Or alternatively, if the aryl radical abstracts hydrogen from the metal radical cation, HDF product can be produced, like in the case of [*trans*-Pt(H)$_2$(PCy$_3$)$_2$].

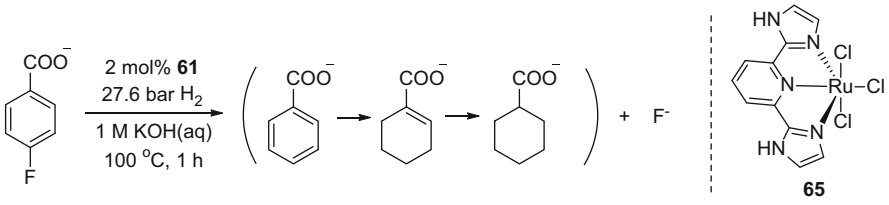
Nevertheless, F/H exchange reaction is still feasible on [*cis*-Ru(dmpe)$_2$(H)$_2$] (**54**) when perfluoroalkenes present as substrates [82]. Stoichiometric reaction between **54** and hexafluoropropene yields bifluoride fluoride complex [*cis*-Ru(dmpe)$_2$F(FHF)] (**59**) and *Z*-, *E*-CF$_3$CF = CFH and CF$_3$CF = CH$_2$ in a ratio of 4:1:3 (Scheme 27).

The same group then showed that ruthenium(II) dihydrido complex [(PPh$_3$)$_2$(IPr)Ru(CO)H$_2$] (IPr = *N*,*N*′-1,3-bis(isopropyl)imidazolin-2-ylidene, **60**) with mixed NHC, phosphine, and carbonyl ligands reacted with 10 equiv. C$_6$F$_5$H to yield the corresponding hydrido fluorido complex **64** losing one molecule PPh$_3$ and 1 equiv. 1,2-C$_6$F$_4$H$_2$, presenting an unusual *ortho*-regioselectivity (Scheme 28) [83]. When treated with

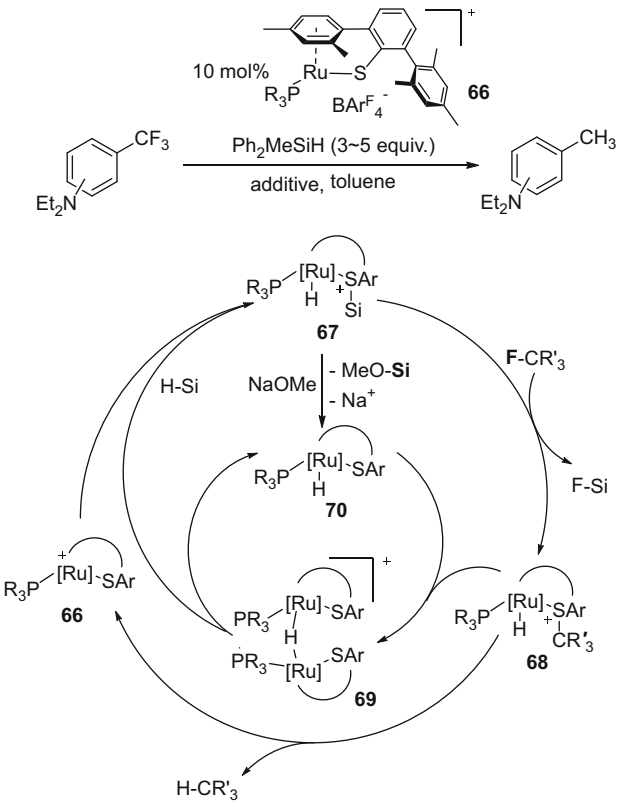
$Et_3SiH$, **64** was reconverted to the dihydrido compound, furnishing a complete catalytic cycle. A turnover number of up to 200 and a turnover frequency of up to 0.86 $h^{-1}$ could be achieved in HDF of $C_6F_5H$ with $Et_3SiH$. More detail mechanism elucidation was carried out with the help of DFT calculations [84, 85]. A stepwise mechanism was suggested as follows: (1) initial $PPh_3$ dissociation and $C_6F_5H$ coordination gives $\eta^2$-arene complex **61**, (2) intramolecular nucleophilic attack of the *cis* hydride ligand at the *ortho*-carbon takes place via a Meisenheimer intermediate **62**, (3) and elimination of one HF from **62** produces a Ru-σ-aryl complex **63**, which is protonated by HF to afford the HDF product and ruthenium fluorido complex **64**. Note that, in the critical C–F bond cleavage step, it is a Ru–C bond rather than a Ru–F bond that forms. The observed *ortho*-selectivity originates from F···HC (NHC aryl) interactions which maximized along the lower energy stepwise pathway when an *ortho*-H substituent is present. New ruthenium HDF catalysts using chelating phosphine ligands like Xantphos (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) were demonstrated to be unsuccessful and leaded to intramolecular C–H bond activation of the NHC ligand [86, 87]. A possible reason for this observation is the difficulty of chelated phosphine dissociation to form the arene coordinated intermediate.

Hashiguchi et al. reported a ruthenium complex (**65**) ligated by a noninnocent protic ligand 2,6-imidizoylpyridine to catalyze HDF of 4-fluorobenzoic acid in alkaline aqueous media with $H_2$ (Scheme 29) [88]. It was postulated that reversible deprotonation of the protic ligand yielded a coordinatively unsaturated, powerful π-donor metal center, which interacted more readily with the anti-bonding orbital of the C–F bond. Higher conversion was observed upon increasing the concentration of potassium hydroxide. Prolonged reaction time leaded to increased yields of aromatic hydrogenation product. In addition, $RuCl_3{\cdot}3H_2O$ was demonstrated to be an active catalyst in a heterogeneous manner, capable of HDF of fluoroarenes at room temperature. C–F bond oxidative addition at in situ generated Ru(II) or F/H metathesis between ruthenium hydrido complex [RuH] and substrate was proposed as a possible mechanism.

Merging transition-metal catalysis with main-group catalysis in HDF $CF_3$-substituted anilines with silane was introduced by Oestreich




**Scheme 29** Ruthenium-catalyzed HDF of 4-fluorobenzoic acid in aqueous potassium hydroxide media




**Scheme 30** Dichotomy C–F bond activation mechanism at ruthenium complex: electron-donating vs. electron-withdrawing phosphine ligands (counterions omitted for clarity; $PR_3 = PEt_3$, $PMe_3$, $PPh_2Me$, $PPh_3$, $P(4\text{-}FC_6H_4)_3$; $Ar^F = 3,5\text{-}(CF_3)_2C_6H_3$)

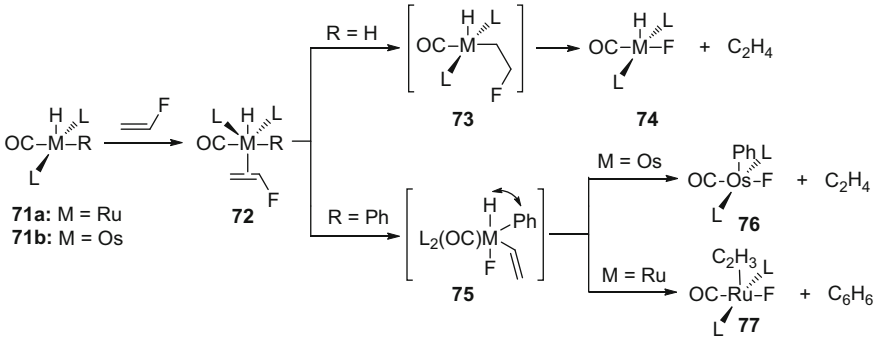
et al. with a tethered ruthenium thiolate complexes (**66**) (Scheme 30) [89]. The active species that cleaves C–F bond is believed to be the sulfur-stabilized silylium moiety of intermediate **67**, which has a Ru–H bond in the organometallic part. Upon abstracting the fluorine atom from the substrate, intermediate **68** containing a thioether-stabilized carbenium is formed, with the Ru–H part being intact. Intramolecular hydride transfer from metal center to the carbenium releases the HDF product and regenerates the catalyst. Electronic properties of the phosphine ligand were found to play a critical role on the hydride transfer process. For electron-rich ligands such as $PEt_3$, the electron-donating property makes intermediate **68** a good hydride donor and facilitates the hydride transfer. This is consistent with the experiment result that electron-rich phosphine ligand promotes catalytic performance. However, electron-poor ligands such as $PPh_2Me$, $PPh_3$, and $P(4\text{-}FC_6H_4)_3$ impede the 16e Ru complex's formation, rendering their complexes catalytically inactive. Nevertheless, the authors found that

with the assistance of another ruthenium hydrido complex **70**, the hydride transfer step became feasible through the formation of a hydride-bridged ruthenium dimer complex **69**, which can react with silane to give intermediate **67**. The ruthenium complex **70** can be achieved via removing the silicone electrophile from intermediate **67**. Thus, these catalysts recovered the activity, when combined NaOMe (stoichiometric based on Ru) as a silicon scavenger was used.

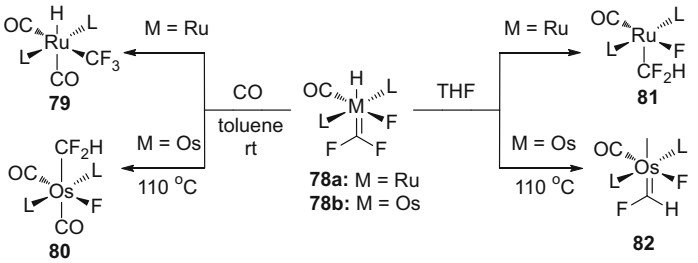
(c) Osmium

Intermolecular C–F bond activation of related ruthenium and osmium hydrido complexes (**71**) was shown to be dependent on both the metal center and the coordinated R group by Caulton et al. (Scheme 31) [90]. When R=H, both complexes react with fluoroethene to give ethene by the insertion–elimination pathway, via $\eta^2$-vinylfluoride intermediate (**72**). When R=Ph, ethene and benzene are released as organic product for osmium and ruthenium, respectively. The different reaction products were interpreted by C–F bond oxidative addition pathway regarding the metals' redox properties. The Os(IV) intermediate **75b** is stable enough to permit H isomerization *cis* to the vinyl group, making reductive elimination of $C_2H_4$ possible. While ruthenium is difficult to achieve Ru(IV) state and rapid reductive elimination of H with $C_6H_5$ occurs when π-acidic fluoroethene coordinates to the metal center. Thus, it is a kinetically controlled process for ruthenium.

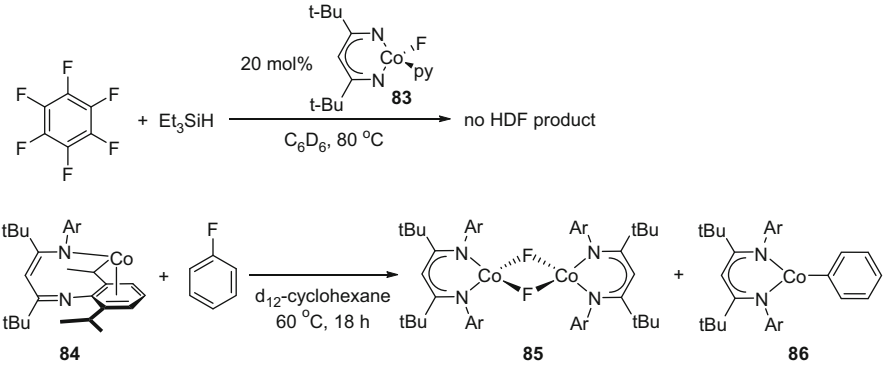
The influence of the redox changes at a 4d versus a 5d metal on intramolecular HDF is manifested by related ruthenium and osmium difluorocarbene complexes [91]. In toluene and CO atmosphere, ruthenium difluorocarbene complex **78a** is converted to hexacoordinated trifluoromethyl complex **79** via fluoride migration, whereas osmium analogue **78b** undergoes hydride migration to produce difluoromethyl complex **83** (Scheme 32). When THF was used as a weaker ligand, hydride migration occurs at complex **78a** to yield the 16e difluoromethyl complex **81**, while F/H exchange takes place at osmium complex **78b** to produce a coordinatively saturated monofluorocarbene complex **82**. DFT calculation ascribed this different reactivity to the preference for a higher oxidation state of osmium.




**Scheme 31** HDF of fluoroethene by ruthenium and osmium hydrido complex (L = $P^tBu_2Me$)




**Scheme 32** Intramolecular HDF at group 8 complexes (L = P$^t$Bu$_2$Me)

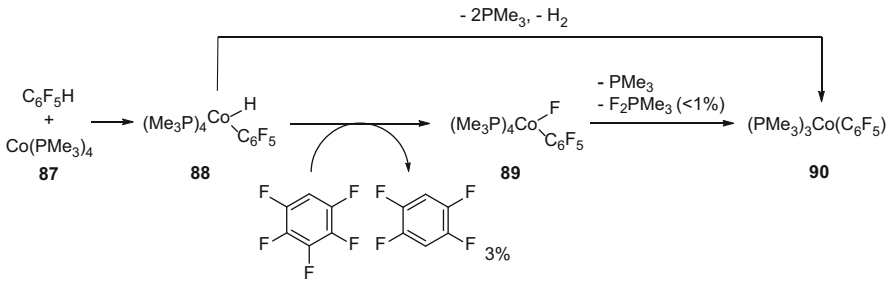



**Scheme 33** *Top*: catalytic HDF inactivity of a low coordinated cobalt fluorido complex; *bottom*: aromatic C–F activation at two-coordinated cobalt(I) complex (Ar = 2,6-(*i*Pr)$_2$C$_6$H$_3$)

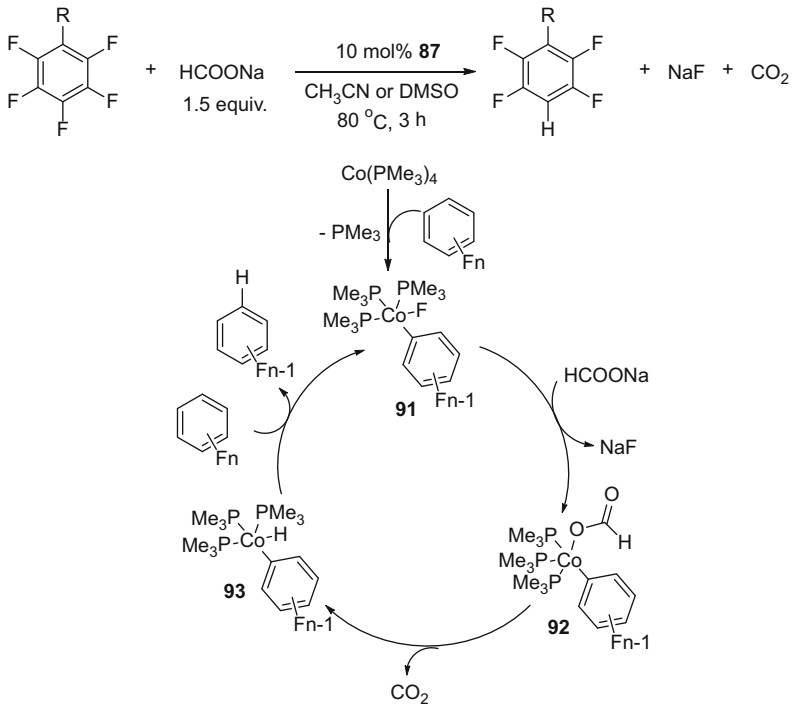
(d) Co

Holland and coworkers tried to extend their low coordinated complexes in catalytic HDF reactions to cobalt complexes [92]. However, cobalt fluorido complex **83** displayed poor HDF reactivity toward $C_6F_6$ and $C_5F_5N$ in the presence of $Et_3SiH$ (Scheme 33). Two factors were supposed to explain the inferior reactivity of Co complexes than the Fe analogues: (1) the instability of cobalt hydride, which releases $H_2$ through reductive elimination, and (2) the presence of a fourth coordinated ligand on cobalt. Later, they succeeded in synthesizing a masked two-coordinate cobalt (I) complex (**84**), which was capable of activation of aromatic C–F bonds (Scheme 33); however, the HDF activity has not been reported yet [93, 94].

Phosphine supported cobalt(0) complexes were shown to be able to activate aromatic C–F bonds in the absence/presence of directing groups such as ketone [95, 96] and azine [97]. Competitive C–H bond activation was frequently observed for partially fluorinated benzenes [95, 98]. Li et al. reported that [Co(PMe$_3$)$_4$] (**87**) reacted with $C_6F_5H$ to give selective C–H bond activation product [(PMe$_3$)$_3$CoC$_6$F$_5$] (**90**), along with minor 1,4-$C_6F_4H_2$ by-products (Scheme 34). Similar findings were found in the reaction of **87** with 1,4-$C_6F_4H_2$ [99]. The possible reaction pathway was




**Scheme 34** Proposed mechanism of reaction of pentafluorobenzene with $Co(PMe_3)_4$




**Scheme 35** Cobalt-catalyzed HDF of perfluoroarenes and proposed mechanism (R = $CF_3$, F, H, $C_6F_5$)

proposed that a hydrido cobalt(II) intermediate (**88**) is formed in situ via C–H bond oxidative addition and then exchanges its hydrido ligand with $C_6F_5H$ [95].

The potential catalytic HDF ability of $[Co(PMe_3)_4]$ was later realized using sodium formate as the reducing agent (Scheme 35). Among the studied aryl fluorides, more electron-deficient substrates showed higher reactivity. Selective HDF at *para*-positions was observed and a maximum TON about 9 was achieved. In situ IR spectra suggested the existence of a

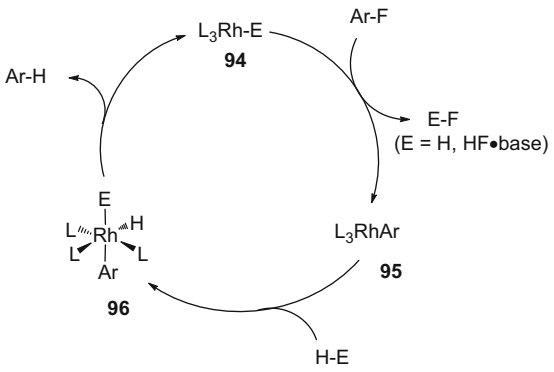
carboxyl and a hydride coordinated cobalt(II) intermediates. Based on these results, a mechanism involving the key cobalt hydrido intermediate **93** was proposed. C–F bond activation at Co(0) yields Co(II) fluoride intermediate **91**, which changes its fluoride ligand with formate to give the formate coordinated intermediate **92**. Subsequent decarboxylation step produces the key cobalt hydrido intermediate **93** and following H/F exchange process with C–F bond yields HDF product.

(e) Rh

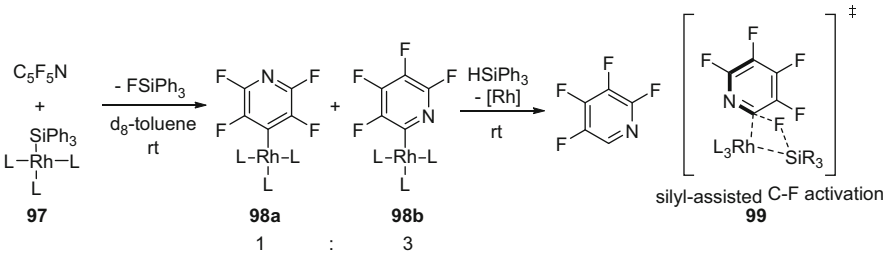
The first example of rhodium-catalyzed HDF of hexafluorobenzene was reported by Milstein group [100, 101]. The strong affinity between silicon and fluorine promotes the reaction of Rh silyl complex (**94**) with hexafluorobenzene to yield fluoroaryl complex **95**. Adding hydrosilane to **95** affords Si–H bond oxidative addition product **96**, which liberates $C_6F_5H$ and regenerates the Rh silyl complex **94** by C–H bond reductive elimination (Scheme 36) [100]. This reactivity leads to the development of catalytic HDF of $C_6F_6$ and $C_6F_5H$, with up to 38 and 33 TONs, respectively. For $C_6F_5H$, 1,2,4,5-$C_6F_4H_2$ was obtained, rendering a chemo- and regioselective HDF.

Hydrido ligand itself can act as a fluorine acceptor as well. When a base is present to trap the released HF, rhodium hydrido complex is capable of breaking C–F bond. Thereby, economical $H_2$ can replace silane as the hydrogen source, providing a more efficient catalytic system (TON up to 114) (Scheme 36) [101]. The C–F bond activation step was suggested to be operated through an electron transfer mechanism, based on the experiment results that less fluorinated substrates with lower electron affinity showed less reactivity. Catalytic HDF heterocyclic compound pentafluoropyridine is also accessible in a similar reaction pathway with exclusive *para*-selectivity, albeit less efficient (TON = 12, TOF = 0.25 $h^{-1}$) [102].

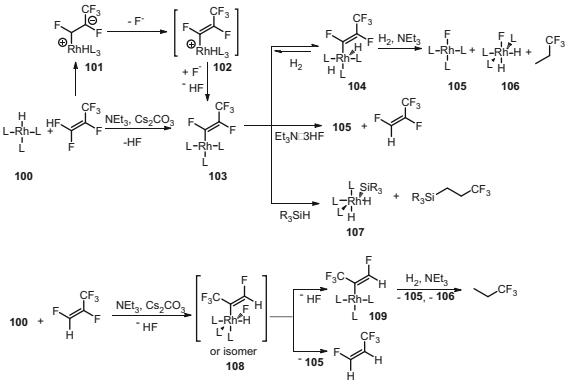
The reactivity of rhodium silyl complex with pentafluoropyridine was further studied by Perutz et al. Unlike its hydrido analogue, a preference for 2-position C–F bond activation via N coordination effect was observed for complex [$(PMe_3)_3RhSiPh_3$] (**97**) [103]. Only 2-position product can be




**Scheme 36** Catalytic HDF of fluoroarenes by rhodium complex with fluorophilic ligand (L = $PMe_3$, $PEt_3$; E = $Si(OEt_3)$, $SiMe_2Ph$, $SiPh_3$, H)




**Scheme 37** Silyl-assisted *ortho*-selective C–F bond activation of pentafluoropyridine at rhodium silyl complex (L = $PMe_3$; R = $C_6H_5$)




**Scheme 38** Substrate-dependent reaction mechanism at rhodium hydrido complex: nucleophilic attack (*up*) vs. oxidative addition (*down*) (L = $PEt_3$; R = Ph and OMe)

converted to the corresponding HDF product when treated with triphenylsilane, along with unidentified Rh complex (Scheme 37). Combined experiment and computational studies on a related Rh silyl complex [$(PEt_3)_3RhSiR_3$] (R = OMe, OEt) by Braun et al. revealed a silyl-assisted C–F activation mechanism, which is more accessible than a C–F oxidative addition/Si–F reductive elimination pathway [104]. The preference for activation at the 2-position in the silyl-assisted process is a result of extra stabilization through an Rh···N interaction in the transition state **99** (Scheme 37).

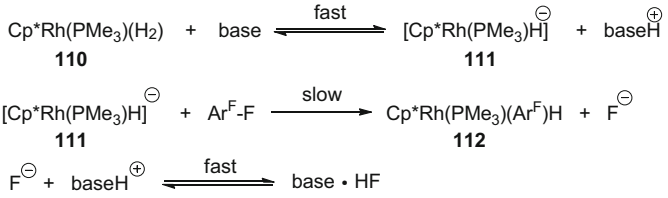
The rhodium hydrido complex has a broad fluorocarbon scope, serving as an active fluoroalkene HDF reagent too (Scheme 38). A substrate-dependent reaction pathway has been disclosed [105, 106]. In the presence of base, [$(PEt_3)_3RhH$] (**100**) reacts fast with hexafluoropropene to afford a rhodium propenyl complex **103** regioselectively [105]. A Meisenheimer intermediate **101**, generated by nucleophilic attack of the rhodium center at the fluorinated molecule, was postulated to interpret the reactivity [106]. Upon fluoride loss and deprotonation via intermediate **102**, the

propenyl complex **103** forms. Treatment of **103** with $H_2$ results in the formation of an unstable dihydrido complex **104**, which gives two Rh fluorido complexes $[(PEt_3)_3RhF]$ (**105**) and $[(PEt_3)_3Rh(H_2)F]$ (**106**) and $CH_3CH_2CF_3$, probably via a repeated HDF and subsequent hydrogenation processes (Scheme 37) [105]. Hydrogenation by $Et_3N{\cdot}3HF$ can release the mono-HDF product (*E*)-1,2,3,3,3-pentafluoropropene. However, hydrosilane is not a proper hydrogen source, which results in the formation of 3,3,3-trifluoropropylsilane as a C–F bond functionalization product and rhodium dihydrido silyl complex **107** [106].

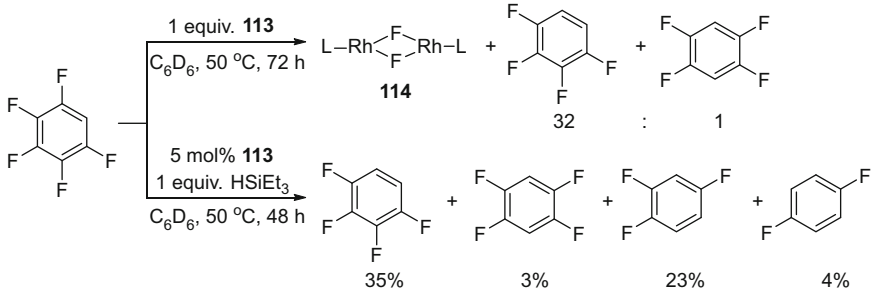
When (*E*)-1,2,3,3,3-pentafluoropropene was chosen as a substrate, about equimolar propenyl complex **109**, rhodium fluorido complex **105,** and (*Z*)-1,3,3,3-tetrafluoropropene produced from the reaction (Scheme 38) [106]. The weaker C–H bond remained intact, providing good chemoselectivity. C–F bond oxidative addition mechanism was suggested in this case, considering the regioselectivity and the products composition. From the addition intermediate **108**, F–H and C–H bond reductive eliminations give a reasonable explanation for all the three observed products. **109** exhibits similar reactivity as its perfluoro analogue **103** when treated with $H_2$.

Aromatic C–F bond nucleophilic substitution was postulated by Jones et al. at a half-sandwich Rh(III) dihydrido complex $[Cp^*Rh(PMe_3)H_2]$ (**110**) [107]. The reaction of **110** with several perfluoroarenes such as $C_6F_6$, $C_6F_5H$, and perfluoronaphthalene gives metal aryl complexes $[Cp^*Rh(PMe_3)(Ar^F)H]$ (**112**). Subsequent thermolysis of the aryl complex liberates the HDF product. The reaction rates are accelerated in the presence of a base. Thus, breaking the C–F bond was believed to go through nucleophilic aromatic substitution by a metal anion **111**, generated from the reaction of **110** with an external base (Scheme 39). However, only TON of 1.4 was obtained in the presence of $H_2$.

Braun et al. reported stoichiometric and catalytic HDF reactivity toward fluoroaromatics of a binuclear rhodium hydrido complex $[Rh(\mu\text{-}H)(dippp)]_2$ (dippp = $i$Pr$_2$P(CH$_2$)$_3$P$i$Pr$_2$) (**113**) [108]. The reaction of **113** with pentafluorobenzene shows an unusual *ortho*-selectivity and gives a corresponding binuclear fluorido complex $[Rh(\mu\text{-}F)(dippp)]_2$ (**114**) (Scheme 40). Catalytic HDF of $C_6F_5H$ using **113** as pre-catalyst and $HSiEt_3$ as hydrogen source results in preferential *para*-selectivity and




**Scheme 39** HDF of fluoroarenes by nucleophilic attack of metal anion



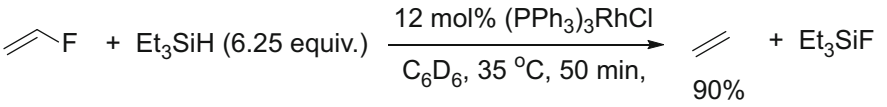

**Scheme 40** Diverse regioselectivity in stoichiometric and catalytic HDF at a binuclear rhodium hydrido complex

multiple HDF products, suggesting a different mechanism from that of stoichiometric reaction. The fluorido complex reacts with excess $HSiEt_3$ to give a fluxional $\eta^2$-silane hydrido complex [Rh(H)($\eta^2$-$HSiEt_3$)(dippp)] (**115**) which cannot be isolated and loses silane under vacuum to give **113**. This species was assumed as an intermediate in the catalytic cycle, which may release the weak coordinated silane to form a mononuclear rhodium hydrido complex [Rh(H)(dippp)] (**116**), serving as the active species for catalytic C–F bond activation.

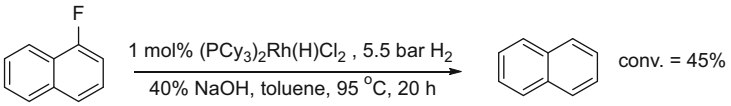
McNeill et al. reported a catalytic dehalogenation of fluorinated and chlorinated ethylenes by $[(PPh_3)_3RhCl]$ in the presence of $Et_3SiH$ at 35 °C (Scheme 41) [109]. Kinetic studies revealed an intramolecular preference for Cl over F removal, an intermolecular preference for F- over Cl-containing alkenes, and a strong preference for $sp^2$ over $sp^3$ carbon–halogen bonds. No mechanism details were presented for the C–F bond activation.

Grushin et al. reported an Rh-catalyzed HDF of non-activated monofluoroarenes with $H_2$ under basic conditions (Scheme 42) [110]. However, the exact structure of active Rh hydrido complex is unclear, making the mechanism elusive. When residual air is present, this reaction becomes heterogeneously catalyzed.

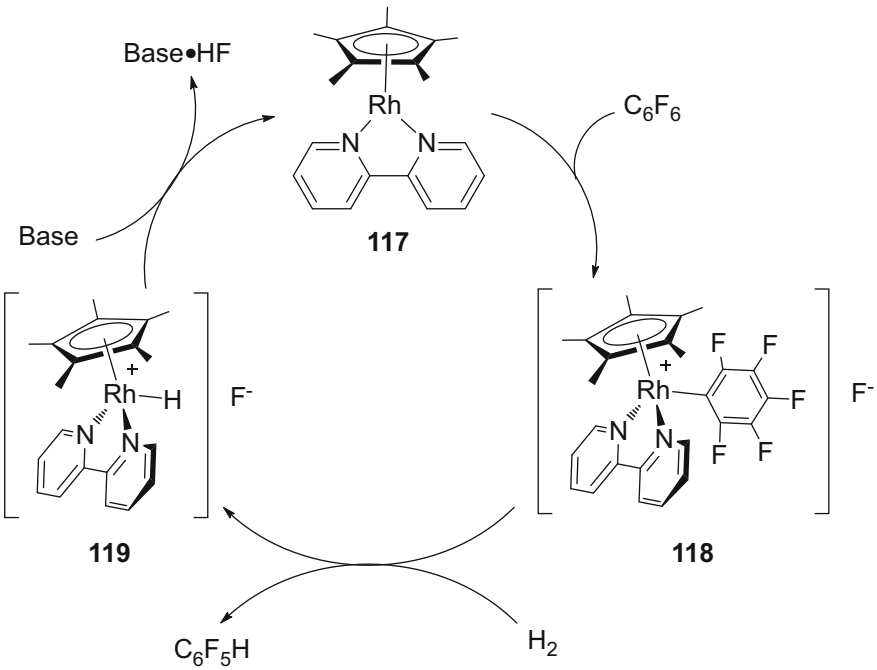
The group of Ogo developed a new efficient Rh(I) catalyst for HDF perfluoroarenes under mild conditions [111]. Up to 380 TONs for $C_6F_6$ were achieved by [Cp*Rh(bpy)] (**117**) with 0.8 MPa of $H_2$ at room temperature. They successfully isolated the C–F bond cleavage product $[Cp^*Rh(bpy)(C_6F_5)^+]F^-$ (**118**), which reacted undoubtedly with $H_2$ in the presence of $Et_2NH$ to give [Cp*Rh(bpy)] and $C_6F_5H$. Based on these




**Scheme 41** Rhodium-catalyzed HDF of fluoroethene



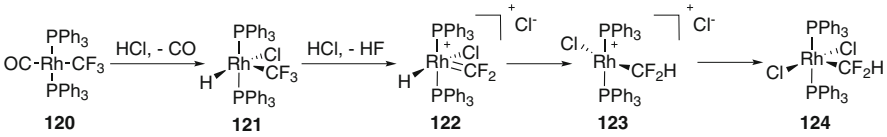

**Scheme 42** HDF of fluoronaphthalene by rhodium catalyst



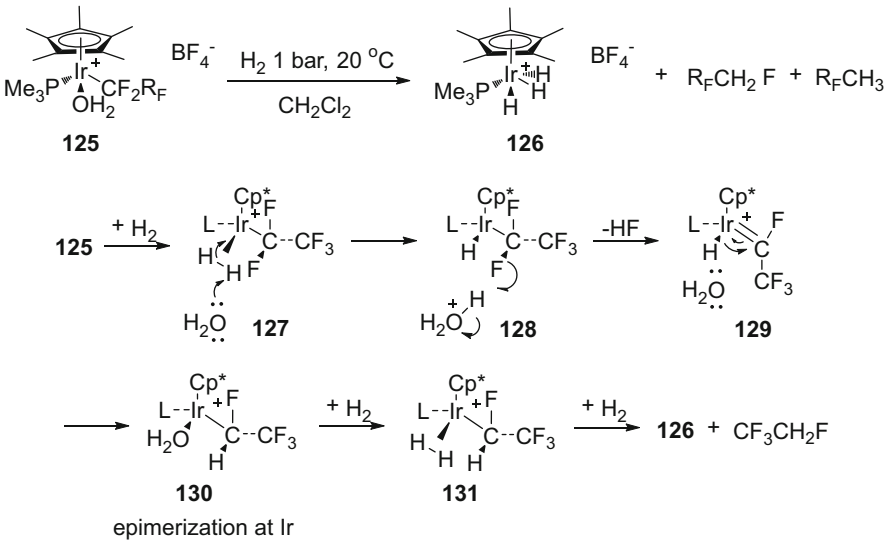

**Scheme 43** Proposed mechanism for rhodium-catalyzed HDF of fluoroarenes

observations and the fact that **117** didn't react with $H_2$, a plausible catalytic cycle was suggested, involving a step of deprotonation of a possible hydrido intermediate **119** to regenerate the catalyst (Scheme 43). As for the C–F bond cleavage step, whether it occurs via nucleophilic aromatic substitution, electron transfer process, or oxidative addition pathway cannot be simply determined at the current stage.

Weakening of C–F bond of fluoroalkyl group in the coordination sphere of transition metals has been known for long time. For example, the C–F bonds α to the metal center feature increased bond lengths and reduced infrared stretching frequencies compared to the aliphatic compounds [26]. This makes them more susceptible to electronic attack and α-fluorine elimination. An intramolecular HDF of a rhodium trifluoromethyl complex (**120**) was reported by Roper et al. [112]. When treated with HCl, **120** is converted to rhodium(III) hydrido complex **121**, which eliminates fluoride to give difluorocarbene hydrido complex **122**.




**Scheme 44** Intramolecular HDF of a rhodium trifluoromethyl complex




**Scheme 45** HDF of fluoroalkyl ligand at iridium complexes (counterion omitted for clarity; $L = PMe_3$; $R_F = CF_3$, $C_2F_5$)

Hydride transfers intramolecularly at **122,** and then chloride trapping gives the HDF product difluoromethyl complex **124** (Scheme 44).

(f) Ir

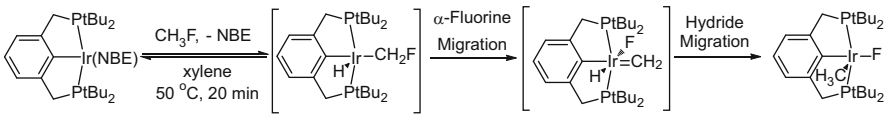
Hughes et al. took a detailed investigation at hydrogenation of the α-$CF_n$ group of iridium fluoroalkyl complexes under $H_2$ atmosphere (**125**), from which hydrofluorocarbons were liberated [113]. Monohydrogenated species had not been detected and were also ruled out as intermediate product [114]. Inspection of the reaction of iridium hydrido complex [Cp*Ir($PMe_3$)($CF_2CF_3$)H] with acetic acid via deuterium incorporation revealed that hydrogenation occurred through an intramolecular hydrogen migration from iridium to the α-carbon rather than protonation by exogenous proton (Scheme 45). These results suggested a mechanism involving heterolytic $H_2$ activation at iridium center to generate a proton and an iridium hydrido intermediate **128**. Following exogenous protonation at fluorine and intramolecular H migration through iridium carbene intermediate **129** yields the monohydrogenated intermediate **130**. Repeated aforementioned process finally releases the hydrodefluorinated fluoroalkanes [115]. The low

isotopic impurity implies a slow equilibration process between Ir-H and Ir-D presumably via a Ir($\eta^2$-HD) intermediate. The observed diastereoselectivity during hydride transfer was accredited to iridium cation intermediate **130** which can undergo epimerization at the metal center [116].

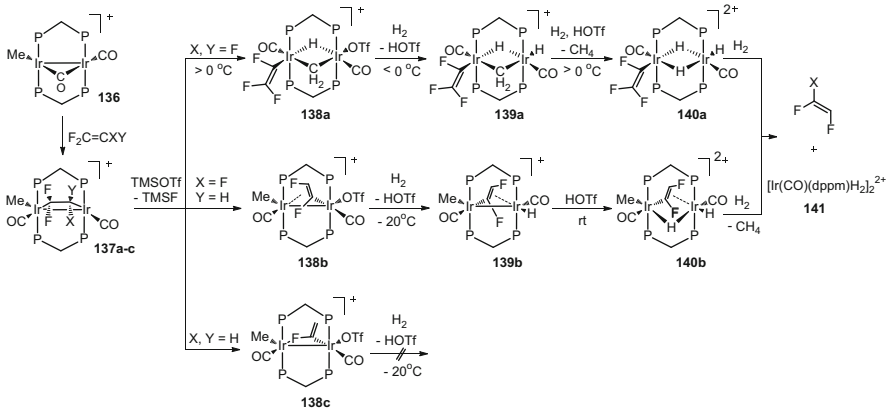
Fluoroalkyl transition-metal complexes readily undergoing α-fluorine elimination provide new insights for intermolecular C–F bond activation. Krogh-Jespersen and Goldman et al. reported a formal C($sp^3$)–F bond oxidative addition at a iridium pincer complex **132** [117]. Mechanism studies suggested initial oxidative addition of a C($sp^3$)–H bond triggers α-fluoride elimination to give the carbene complex **134**. Subsequent intramolecular hydride migration affords the fluorido complex **135** (Scheme 46). Alkyl fluorides with β-hydrogen atoms also reacted with **132**, but alkenes were the main products as a result of β-fluorine elimination. This may inspire new HDF protocol for those inter C–F bonds via circuitous strategy.

Metal–metal cooperativity had been exploited for C–F bond activation by Cowie et al. using the binuclear iridium complex $[Ir_2(Me)(CO)_2dppm_2][OTf]$ (**136**, dppm = $(PPh_2)_2CH_2$). 1,1-difluoroethylene, trifluoroethylene, and tetrafluoroethylene react with binuclear iridium complex to yield the corresponding fluoroalkene-bridged complexes **137a–c** [118], of which fluorine could be abstracted by Lewis acids like TMS-OTf (TMS = $Me_3Si$; OTf = $CF_3SO_3$) (Scheme 47) [119–121]. The vinyl moiety of the resulting fluorovinyl complexes **138a–c** adopts different coordination modes. Except for **138c**, **138a** and **138b** exhibit reactivity with $H_2$ to afford iridium hydrido complexes **139a** and **139b,** respectively. And further hydrogenation finally gives the HDF product [121].

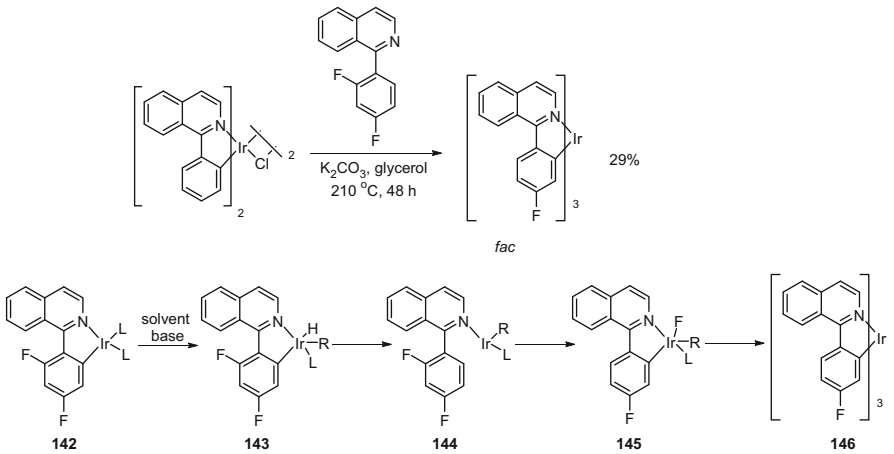
Regioselective HDF of the fluorinated ligand of phosphorescent Ir(III) complexes during its preparation, either as free ligand or ligated ligand, were reported by several groups [122–125]. It was found that only *ortho*-fluorine of the fluorinated phenyl moiety can be removed. The *para*-fluorine was unaffected whether the *ortho* position was fluorine or hydrogen atom [124]. A possible mechanism involving formation of an iridium hydrido intermediate **143** via hydrogen transfer from solvent, followed by reductive elimination and iridium insertion into the C–F bond was suggested (Scheme 48) [125]. These results might provide a smart chance of developing iridium-catalyzed regioselective HDF.




**Scheme 46** Intramolecular HDF at iridium pincer complex (NBE = norbornene)



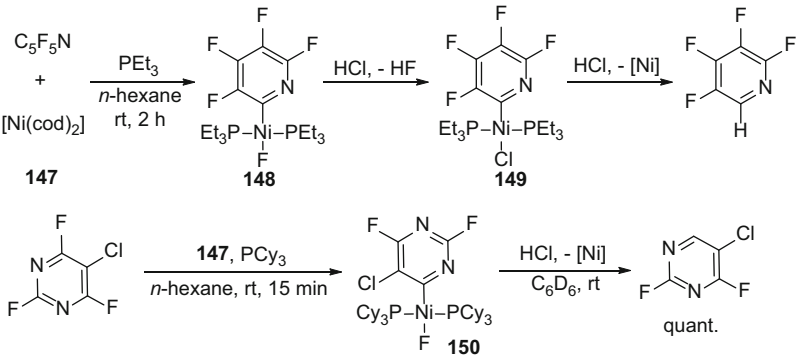
**Scheme 47** HDF of fluoroethenes at a dinuclear iridium complex (OTf counterions omitted for clarity; dppm = $Ph_2PCH_2PPh_2$; TMS = $Me_3Si$; OTf = $CF_3SO_3$; X = F, H)



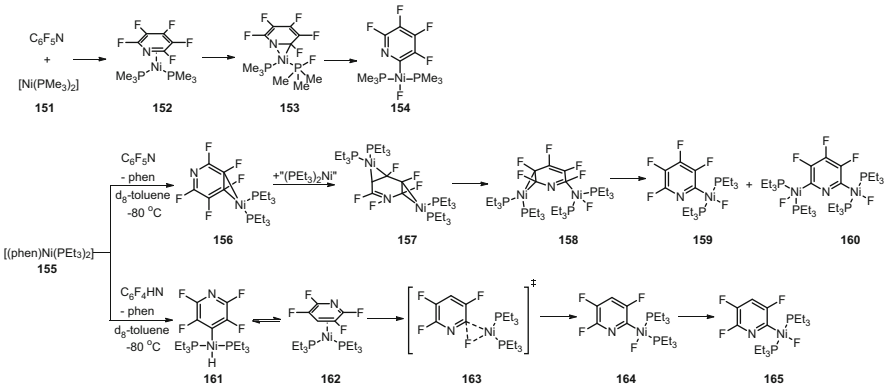
**Scheme 48** *Ortho*-selective HDF of fluorinated ligand at an iridium complex

(g) Ni

Perutz et al. confirmed Fahey and Mahan's early finding on slow oxidative addition of hexafluorobenzene to a nickel(0) complex in the presence of $PEt_3$ [126] and extended this reaction to other fluorinated arenes and heteroarenes [127]. In the presence of $PEt_3$, $[Ni(cod)_2]$ (**147**, cod = cyclooctadiene) selectively activates the 2-position C–F bond of pyridine derivatives even in the presence of a weaker C–H bond (Scheme 49). However, the C–Cl bond of 3,5-dichloro-2,4,6-trifluoropyridine was more active, yielding C–Cl bond oxidative addition product [127, 128]. With $PCy_3$ ligand, Braun et al. reported selective activation of C–F bond of 5-chloro-2,4,6-trifluoropyrimidine, without affecting the more




**Scheme 49** *Ortho*-selective HDF of fluorinated heterocycles at nickel complex




**Scheme 50** *Top*: DFT calculated phosphine-assisted pathway for *ortho*-selective C–F bond activation of pentafluoropyridine; *bottom*: experiment evidence for dinuclear species for the activation C–F bond of penta- and tetrafluoropyridine

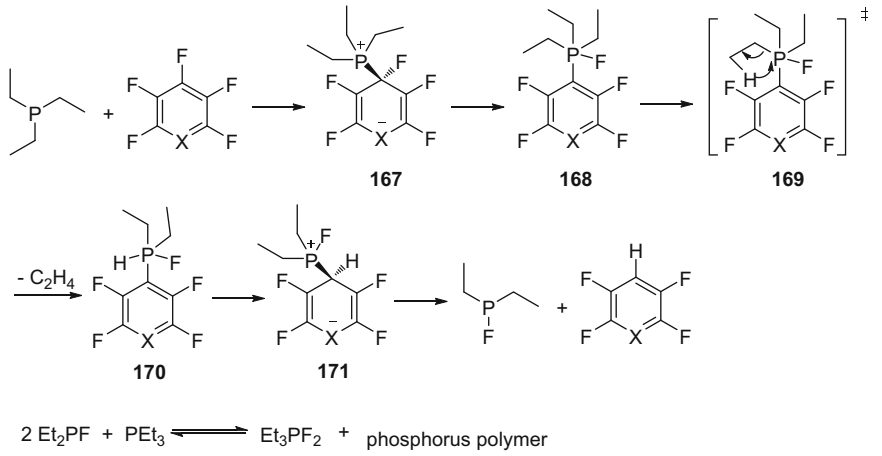
reactive C–Cl bond [129, 130], while in the case of 3-chloro-2,4,5,6-tetrafluoro pyridine, the selective activation of C–F bond was not obtained (Scheme 49). The obtained nickel fluorido complexes **148** and **150** liberate the HDF product upon hydrolysis.

However, the unusual selectivity of nickel complex has not been fully understood yet. DFT calculations at model complex $[Ni(PMe_3)_2]$ (**151**) attribute this selectivity to a phosphine-assisted reaction pathway (Scheme 50, top) [131]. In this pathway, when the reaction occurs at the 2-position, the pyridyl nitrogen coordination to nickel center lowers the activation barrier by stabilizing the key metallophosphorane intermediate **153**. At *para*-position, there is a lack of additional "chelating" effect. It should be noted that the computed reaction starts with a $\eta^2$-arene complex **152**.

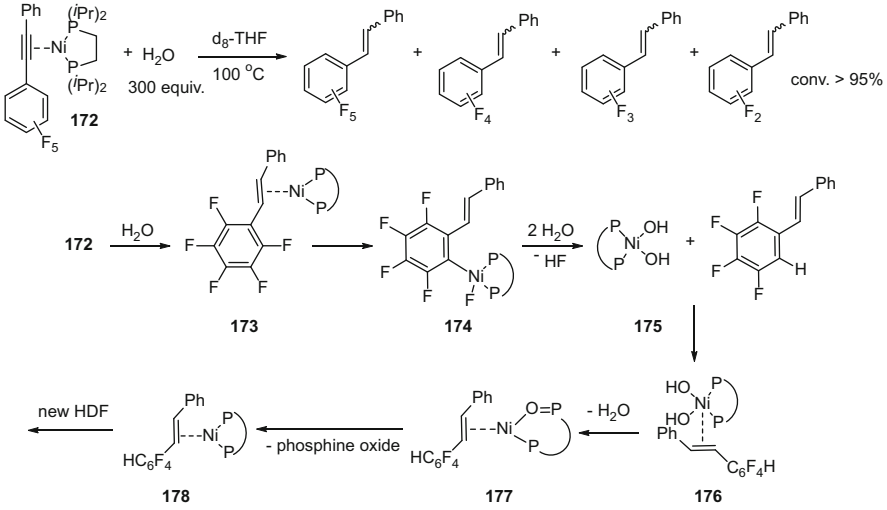
Johnson et al. opened up another possibility for the mechanism based on the reaction of [(phen)Ni($PEt_3$)$_2$] (**155**, phen = phenanthrene) with pentafluoropyridine [132]. Low-temperature NMR spectroscopy confirmed the formation of a fluxional arene adduct [($PEt_3$)$_2$Ni($\eta^2$-$C_5F_5N$)] (**156**), which converts to *ortho*-C–F bond activation product **159** upon warming along with minor double *ortho*-C–F bond activation product **160**. Dinuclear intermediates **157** and **158** are formed in this process (Scheme 50, bottom); however, their role in the transformation is not clear. Kinetic studies show the concerted or phosphine-assisted C–F bond activation from intermediate **156** or **157** is not the major mechanism. EPR spectroscopy displayed a typical signal of $d^9$ three-coordinate bis-phosphine Ni(I) complex in the reaction mixture, suggesting that the reactions may involve radicals. The unambiguous characterization of nickel(I) species including X-ray structure of [($i$Pr$_3$P)$_2$Ni($C_6F_5$)] produced in the reaction of [(phen)Ni(P$i$Pr$_3$)$_2$] with $C_6F_6$ is again suggestive of a radical pathway [133].

In the case of 2,3,5,6-tetrafluoropyridine, the $\eta^2$-arene complex **162** was also observed, equilibrating with the C–H bond oxidative addition product **161** (Scheme 50, bottom). The observation of [*cis*-($PEt_3$)$_2$NiF(3,5,6-$C_5F_3HN$)] intermediate **164** and low activation barrier derived from kinetic analysis disputes the phosphine-assisted pathway. Thus, a concerted C–F bond oxidative addition mechanism was proposed. Studies on HDF of hexa-, penta- [134], and tetra-fluorobenzenes [135, 136] showed the existence of mono- and dinuclear arene complexes, and the reversible C–H bond oxidative addition process was suggested.

In a very recent study, the role of the phosphine ligand in HDF process was revisited by García et al. [137]. They intended to apply a hydride-bridged dinuclear nickel complex [(dippe)Ni(μ-H)]$_2$(**166**, dippe = $i$Pr$_2$PCH$_2$CH$_2$P$i$Pr$_2$) as catalyst for HDF of fluoroarenes with silane. During the course of optimization of the reaction conditions, they found that ancillary ligand $PEt_3$ alone without metal and silane was capable of converting fluoroarenes to the corresponding HDF products with good selectivity. Isotope labeling experiments ruled out the solvent as hydrogen source, leaving $PEt_3$ as the only possibility. $PEt_3$ also served as fluoride acceptor, producing difluorophosphorane $Et_3PF_2$ as a major organophosphorous product containing fluorine. Based on these observations, nucleophilic attack C–F bond by phosphine via a Meisenheimer intermediate **167** was proposed (Scheme 51). Following fluoride migration and β-hydride elimination generates a phosphorane intermediate with a P–H bond (**170**). Subsequent hydride nucleophilic addition and then elimination of fluorophosphine $Et_2PF$ yield the hydrodefluorinated product. The observation of $Et_3PF_2$ rather than $Et_2PF$ might derive from further reactivity or exchange. Similar findings that free phosphine mediates HDF of pentafluoropyridine had been observed by Braun et al. using either nickel [128, 138] or palladium [139] phosphine complexes.




**Scheme 51** HDF of perfluoroarenes by phosphine (X = N, CF)



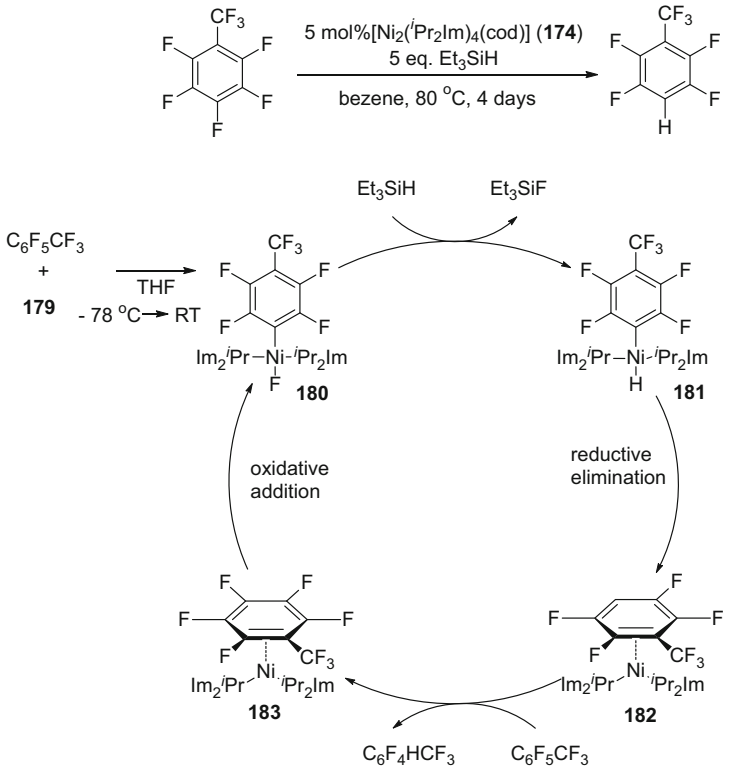

**Scheme 52** HDF of fluorinated aromatic alkyne ligand of nickel complex

Defluorination of ligands was observed at nickel(0) complexes with fluorinated alkyne ligands by García et al. (Scheme 52) [140]. The alkyne nickel complex **172** reacts with water to give a mixture of alkyne semihydrogenation product and isomeric mono- and di-HDF products in varied amounts according to the reaction conditions. Through coordination with the triple bond, alkyne is firstly hydrogenated to alkenes with $H_2O$ as hydrogen source. Formation of alkene helps to chelate Ni center and facilitates next step C–F bond activation. The formation of HF and phosphine monoxide as by-products hampers further reactivity beyond

stoichiometric reaction. Combination of triethylsilane as oxygen and fluorine scavenger makes a more efficient system with lowered selectivity.

Though phosphine ligands might be directly involved in the HDF reactions, several examples using NHC ancillary ligands unambiguously demonstrate the genuine Ni(0)-catalyzed HDF reactions.

Radius et al. reported that NHC ligand supported nickel complex $[Ni_2(^iPr_2Im)_4(cod)]$ (**179**, $^iPr_2Im$ = 1,3-bis(isopropyl)-imidazolin-2-ylidene; cod = cycloocta-1,5-diene) catalyzing HDF of hexafluorobenzene and perfluorotoluene (Scheme 53) [141]. The reactions were sensitive to the reaction conditions and the silane. Mechanistic investigation points to the pathway which involves initial coordination of perfluoroarene to the Ni (0) fragment and subsequent C–F bond oxidative addition [142]. The resulting aryl fluorido complex **180** changes fluoro ligand with hydride of silane to give the corresponding hydrido complex **181**, which reductively eliminates hydrodefluorinated arene as a coordinated molecule. Ligand substitution with another perfluoroarene molecule releases the HDF product (Scheme 53).

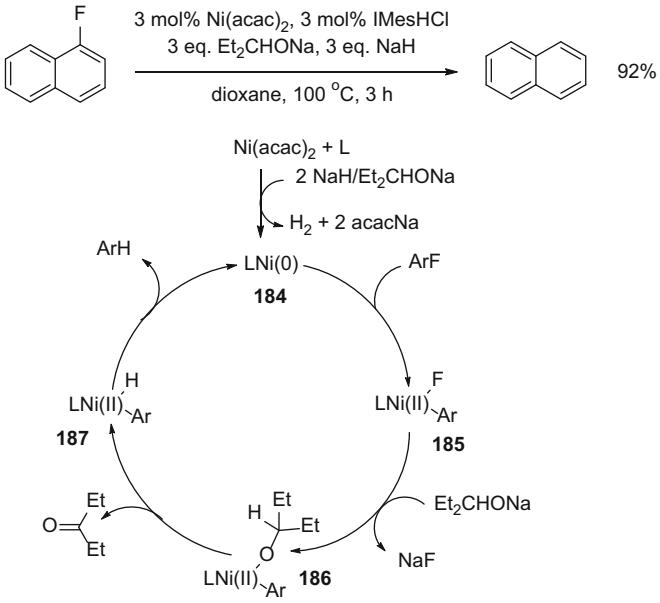



**Scheme 53** Nickel-catalyzed HDF of octafluorotoluene

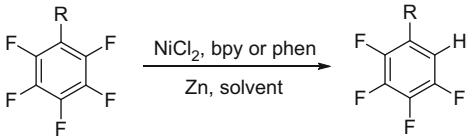
Fort et al. reported HDF of monofluoroarenes by Ni(0)/NHC combination with secondary alkoxide as hydrogen source [143]. Similar sequence of C–F bond insertion to the in situ formed Ni(0) complex and then C–H bond reductive elimination from nickel(II) is proposed to be the reaction pathway. The key Ni(II) hydrido intermediate **187** is believed to generate from fluorido complex **185** via ligand substitution by alkoxide and then intramolecular hydride transfer (Scheme 54).

Using zinc as terminal reductant, regioselective *ortho*-HDF of perfluorobenzenes of the type $C_6F_5R$ catalyzed by low-valent nickel complexes had been reported by Adonin et al. (Scheme 55) [144–148]. Solvent and the molar ratio of $NiCl_2$/ligand and substrate/zinc were found to influence the reaction outcome. Two possible pathways in respecting the in situ generated Ni(0) species were suggested. One involves C–F bond oxidative addition at the Ni(0) complex [148], and another includes a nickel hydrido complex acting as the reactive intermediate [144].

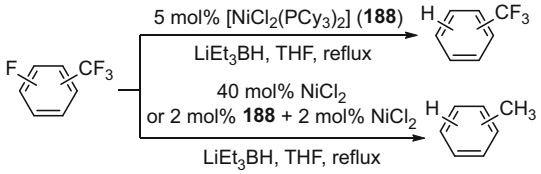
The combination of aluminum hydride or boron hydride reagents with Ni (II) salts proves to be an efficient catalytic HDF system for aromatic and benzylic C–F bond. $NiCl_2$ exhibited high reactivity in HDF of both $sp^2$- and $sp^3$-C–F bond in the presence of excess $LiEt_3BH$, albeit a high catalyst loading (40 mol%) is necessary (Scheme 56) [149]. Complete defluorination for perfluoroarenes such as hexafluorobenzene and octafluorotoluene is observed. With a phosphine-ligated Ni(II) source $[(PCy_3)_2NiCl_2]$ (**188**), lower loading (5 mol%) and chemoselectivity for




**Scheme 54** Nickel-catalyzed HDF of fluoronaphthalene (acac = acetylacetonate)




**Scheme 55** Nickel-catalyzed *ortho*-selective reductive HDF of pentafluorobenzene derivatives (R = F, COOH, $CONH_2$, $CO_2Et$, $NHCOCH_3$, $BF_3^-$; bpy = 2,2′-bipyridine; phen = 1,10-phenanthroline)



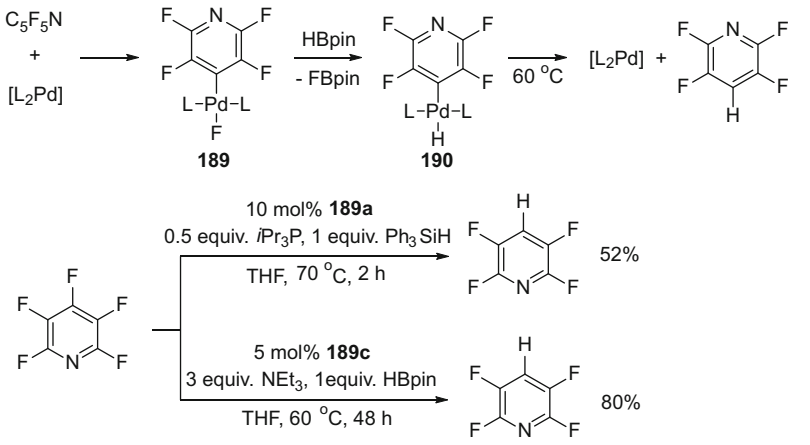

**Scheme 56** Nickel-catalyzed HDF of aromatic fluoride and benzylic fluoride

aromatic fluoride over benzylic fluoride are achieved. More powerful hydride source such as $LiAl(OtBu)_3H$ leads to the loss of chemoselectivity [150]. Combination of both the nickel(II) species gives a more efficient HDF system with lower loading to 2 mol% (Scheme 56) [151]. The main drawback of the protocol is poor functional-group tolerance for aldehyde and other halogen bonds (C–Cl, Br, I). Similar catalytic cycle involving Ni (0)/Ni(II) redox cycle (see Scheme 54) is also proposed.

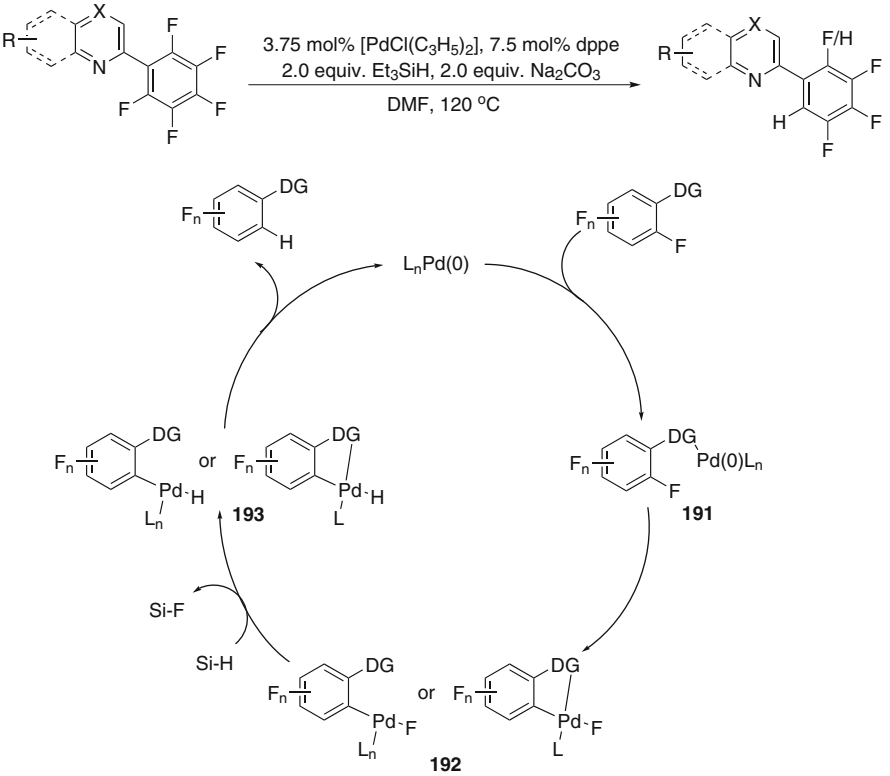
(h) Pd

Braun et al. reported the oxidative addition of *para* C–F bond of pentafluoropyridine at palladium(0) phosphine complexes [152, 153]. Catalytic HDF processes were developed [139, 154], as well as several cross-coupling reactions [139, 153]. The addition complexes *trans*-$[L_2Pd(F)(4\text{-}C_5NF_4)]$ (**189a–c**, L = P*i*Pr$_3$, $PCy_3$, $iPr_2PC_2H_4OCH_3$) reacted with HBpin (HBpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane) to give the corresponding hydrido compound **190a–c**. Reductive elimination occurred at elevated temperature to afford 2,3,5,6-tetrafluoropyridine and palladium (0) complex (Scheme 57). Catalytic transformation could be achieved in the presence of HBpin, although in low efficiency (Scheme 57) [153, 154]. Hydrosilane such as $Ph_3SiH$ proved to be a more effective hydrogen source.

Taking advantage of a directing group, Zhang et al. successfully developed an *ortho*-selective HDF of polyfluoroarenes with triethylsilane catalyzed by palladium (Scheme 58) [155]. The author reasoned that a directing group, specifically like N-containing heterocycle used in this work, would facilitate the oxidative addition of the C–F bond to Pd(0) through chelating effect. Di-hydrodefluorination by a sequential C–F bond activation was




**Scheme 57** Stoichiometric and catalytic HDF of pentafluoropyridine by palladium (L = P*i*Pr$_3$, PCy$_3$, *i*Pr$_2$PC$_2$H$_4$OCH$_3$; HBpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane)



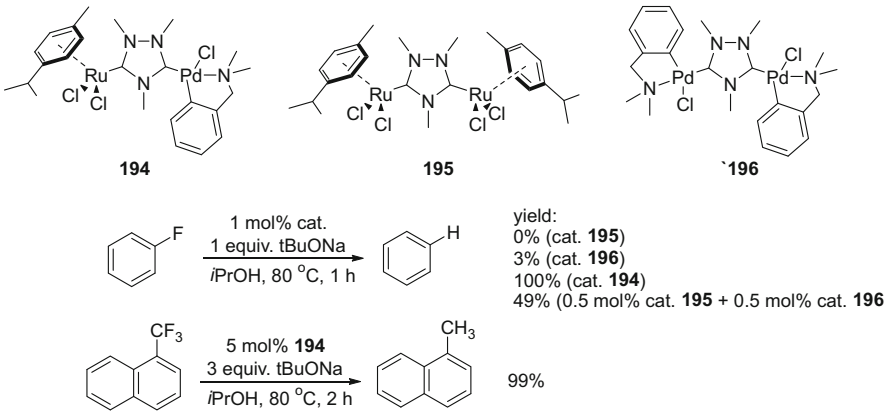

**Scheme 58** Palladium-catalyzed chelation-assisted *ortho*-selective HDF of polyfluoroarenes with silane (dppe = $Ph_2PCH_2CH_2PPh_2$)

also operable. Mechanism studies indicated C–F bond oxidative addition at Pd(0) species.

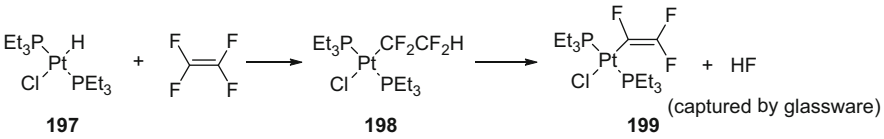
Mata et al. reported heterodimetallic ruthenium–palladium complex **194**-catalyzed HDF of low fluorinated arenes and trifluoromethylarenes by using isopropyl alcohol as hydrogen source (Scheme 59) [156]. Based on the triazolyldiylidene ligand, poor catalytic performance of a combination of the related homodimetallic complexes of ruthenium (**195**) and palladium (**196**) demonstrated an apparent synergistic action of the two metal centers of **194**. Up to 660 TONs were achieved. Electronic effects of the substituent had a small impact on the reactivity of HDF of fluoroarenes, whereas steric factors played an important role, with hindered substrates showing lower rate. C–Br, C–Cl, and C=O bonds were all reduced in the reaction conditions. When both $sp^2$ C–F and $sp^3$ C–F bond were present, reduction of the former occurred first. Kinetic studies suggested the rate-determining step being reduction process, rather than C–F bond activation step. It was proposed that palladium center facilitates the C–F activation, and the ruthenium moiety allows the reduction of the substrate via transfer hydrogenation from isopropanol/sodium *t*-butoxide.

(i) Pt

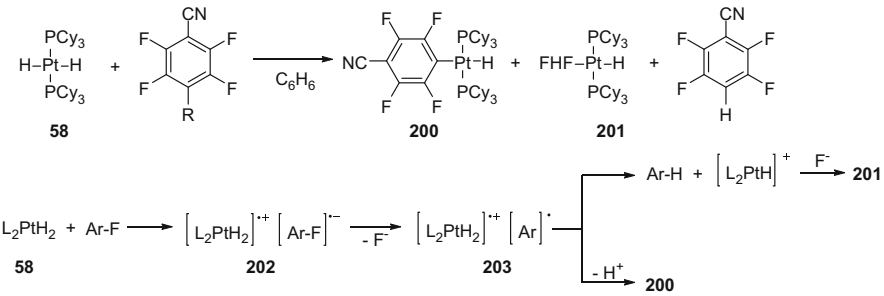
Platinum(II) complexes have been shown to engage in C–F bond oxidative addition process [157, 158], based on which catalytic cross-coupling reactions have been achieved [159, 160]. It is intriguing that HDF reactions remain undeveloped. F/H exchange was not observed in the reaction of platinum(II) hydrido complex *trans*-[$(Et_3P)_2PtHCl$] (**197**) with tetrafluoroethene [161–163]. The initial insertion complex **198** decomposes to perfluorovinyl platinum complex **199** as a result of elimination of HF (Scheme 60). The HDF productive process via β-fluoride elimination is not a feasible route which might be partially due to the weaker Pt–F bond than H–F bond.




**Scheme 59** Synergistic action on HDF of heterodimetallic complex in a single ligand frame




**Scheme 60** Reaction of platinum hydrido complex with tetrafluoroethene




**Scheme 61** Electron transfer-induced C–F bond activation at platinum hydrido complex

Another platinum dihydrido complex [*trans*-$Pt(H)_2(PCy_3)_2$] (**58**) was found to react with activated fluorobenzonitriles to give HDF product $C_6HF_3R(CN)$ and two organoplatinum compounds, *trans*-[$PtH(C_6F_3RCN)(PCy_3)_2$] (**200**) and *trans*-[PtH('F')$(PCy_3)_2$] (**201**, "F" means a probable form of coordinated $F(HF)^-$) (Scheme 61) [81]. Based on the dependence on the electron affinities of substrates, an electron transfer mechanism was proposed. Initial electron transfer from the electron-rich **58** to the electron-poor fluorobenzonitrile yields solvent-caged tight ion pair **202**, in which the aromatic radical anion easily propels a fluoride. The existence of the aryl radical was substantiated by radical trap experiment. The resulting aryl radical is quenched in two competing ways: abstracting a hydrido ligand from the platinum cation radical to yield HDF product and reaction with the mono-hydrido platinum radical to give platinum aryl complex (**200**).

In summary, group 8–10 metals exhibit high reactivity toward C–F bond and are the most studied metals in HDF, although their M–F bonding is weaker than those of the early transition metals. Dependent on the rich redox chemistry, these metal catalysts are favored to undergo oxidative addition to C–F bond, which is the predominant reaction pathway. Recently, Whittlesey and coworkers reviewed late transition-metal-catalyzed HDF reactions and highlighted the potential application [33]. However, for the similar oxidative addition process in HDF reaction, the competitive activation of C–H bond, when a molecule has both C–F and C–H bonds, is a challenge [164]. In this aspect, the electrophilic property of C–F bond might be considered to overcome this shortcoming. Breaking

C–F bond via nucleophilic attack of coordinated ligands, including a hydride and a N-, O-, or S-nucleophile, has been reviewed by Lledós and coworkers [29]. Thus, appropriate design of catalysts to perform nucleophilic substitution might be an alternative approach [30]. Fluorophilic ligand (E = H, B, Si, P)-assisted C–F bond cleavage through strong E–F bond formation is another strategy to provide thermodynamic driving force, circumventing unfavorable M–F bond formation process. In addition, electron transfer from electron-rich metal center to electron-poor fluorinated substrate is also feasible to induce C–F bond cleavage.

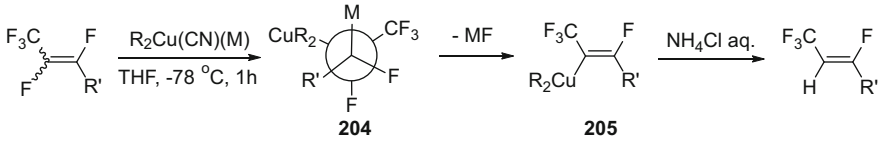
4. Groups 11–12

According to hard/soft acid–base theory, group 11 and 12 metals in low oxidative states would form the most labile and reactive M–F bonds with hard fluoride ion compared to their early analogues. We can also see the weak bonding from Fig. 1, whose BDE values lie much down to the mean value of C–F bonds. Organo-copper [165–168] and organo-gold [169, 170] fluoride complexes have recently been reported, of which the wise choice of supporting ligands plays a pivotal role. Catalytic HDF reactions involving the two groups' metals only limit to a handful of literatures.

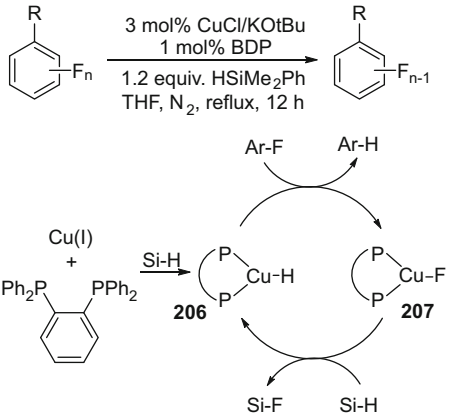
(a) Cu

Ishihara et al. reported an example of activation alkene C–F bond via metalation with organocuprate reagents [171, 172]. A sequence of nucleophilic *cis*-addition of organocuprate to pentafluoropropene derivatives and then *anti*-elimination of M–F was believed to stereoselectively generate the corresponding vinylcopper species **205** (Scheme 62). **205** can react with various electrophiles including $H_2O$ to give β-substituted fluoropropene derivatives.

Zhang and coworkers reported the first example of a copper-catalyzed HDF of fluoroarenes via copper hydride intermediate [173]. In the presence of $HSiMe_2Ph$, the combination of CuCl/KOtBu/BDP (BDP = 1,2-bis (diphenylphosphino)benzene) exhibited a high reactivity toward a broad scope of fluoroarenes with a preferred *para*-selectivity (Scheme 63). Functional groups such as nitro, ester, and alkynyl substituents remained intact, whereas acetyl and formyl substituents were partially or completely reduced. Lower conversions were obtained toward substrates with




**Scheme 62** HDF of functionalized pentafluoropropenes mediated by organocuprate (M = MgBr, ZnR′; R = $CO_2Bn$, $SO_2Tol$, SOTol)



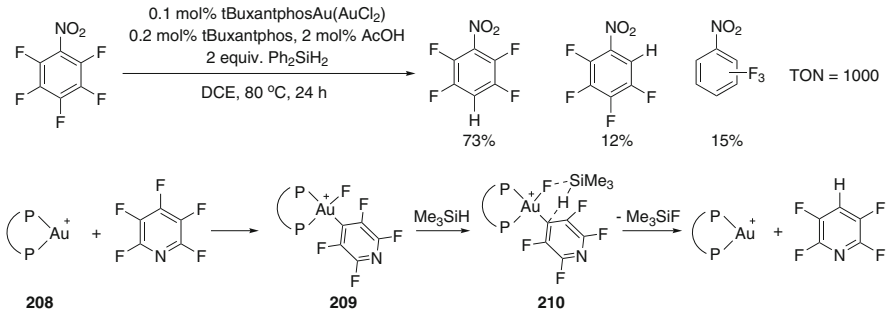

**Scheme 63** Copper-catalyzed HDF of fluoroarenes (BDP = 1,2-bis (diphenylphosphino) benzene)

electron-donating substituents. Even kinetically inert 4-fluoronitrobenzene can be hydrodefluorinated, despite of a decreased chemoselectivity. A copper hydride intermediate was observed by NMR spectroscopy which undoubtedly hydrodefluorinated pentafluoronitrobenzene (PFNB) to 1,2,4,5-tetrafluoronitrobenzene and itself turned into a copper fluoride species after reaction. Later the solid structure of BDP ligand-chelated copper hydride was shown to be trinuclear $[BDPCuH]_3$ with $\mu_2$ hydride in the plane of the three Cu atoms and the hydride signal appeared at 0.60 ppm in $C_6D_6$ [174], different from what they observed (δ 1.49 ppm in $C_6D_6$). DFT calculations on the model terminal hydrido complex [BDPCuH] suggested a concerted nucleophilic attack pathway with a low barrier of 8.33 kcal/mol.

(b) Au

Gold(I) complex-catalyzed HDFs of fluoroarenes were demonstrated by the same group [175, 176]. Tricoordinated gold(I) phosphine complexes supported by Xantphos-type ligands exhibit efficacy in the HDF of electron-deficient perfluoroarenes with silane as hydrogen source [175]. Up to 1000 TONs can be achieved when $^t$BuXantphos ($^t$BuXantphos = 4,5-bis(di-*tert*-butylphosphino)-9,9-dimethylxanthene) ligand was used (Scheme 64). This catalytic system shows exceptionally good functional group tolerance toward nitro, nitril, keto, carboxylate, amide, ester, alkynyl, alkenyl, and other halide groups. Mechanistic studies prove that dinuclear gold hydrido complex "$Au_2H$," produced from the reaction of catalyst precursor and silane, is not the active intermediate. Computational studies on the HDF of pentafluoropyridine suggest that C–F bond activation takes place through oxidative addition at the cationic $Au^I$center **208** via a three-centered transition state (Scheme 64). Catalyst recycling and HDF product formation occurs in one step via an unusual five-membered transition state **210** between **209** and silane.

Gold hydrides with NHC ancillary ligand fail to activate aromatic C–F bonds either [176]. No reactions between (IMes)AuH (**211**, IMes = *N*,

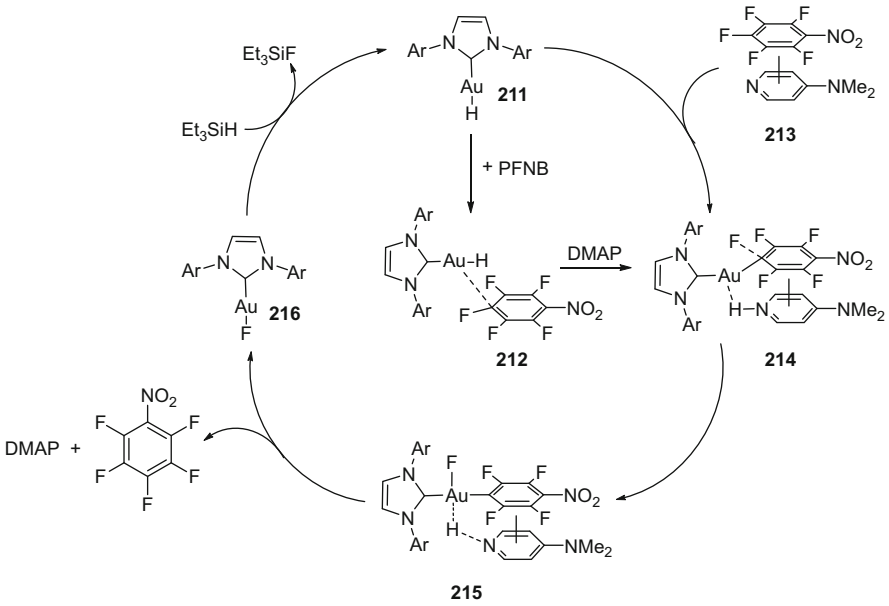



**Scheme 64** Gold-catalyzed HDF via C–F bond oxidative addition pathway (tBuXantphos = 4,5-bis(di-*tert*-butylphosphino)-9,9-dimethylxanthene; DCE = 1,2-dichloroethane)

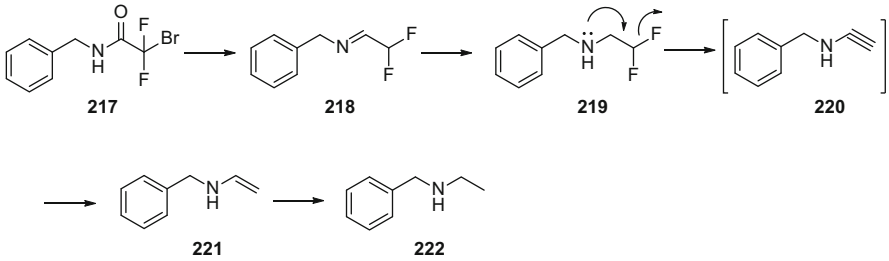
*N*′-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) and PFNB occurred, though π–π interaction between them was observed by NMR and UV-Vis spectroscopies. And in the presence of $Et_3SiH$, poor results with low substrate conversion (<20 %) were achieved in catalytic tests. DFT calculations ascribed the difficulty to a high activation barrier of 40.8 kcal/mol. Interestingly, when additive *p-N,N*-dimethylaminopyridine (DMAP) was introduced, the reactivity improved and a TON of 9 toward PFNB was obtained with good *para*-selectivity. Careful examination of the exact role of the DMAP disclosed a novel π–π interaction-assisted C–F bond activation (Scheme 65). Starting from the three-component "face-to-face" π–π stacking intermediate **214**, the energy barrier of rate-determining C–F bond oxidative addition step was 8.4 kcal/mol lower than that in the absence of DMAP.

(c) Zn

Zinc has been used as the terminal reductant coupled with a proton source for HDF purpose. As a catalyst for HDF, zinc is not well studied. Cao et al. reported the HDF of difluoromethylene derivatives with lithium aluminum hydride in the presence of 5 mol% $ZnCl_2$ [177]. Though the reaction also occurs without metal catalyst, a much longer reaction time is needed to achieve satisfactory yield [178]. Reductants such as amide, ester, and carboxyl cannot be tolerated. A heteroatom (such as N or O) in the β-position relative to $CF_2$ group could accelerate the HDF reaction. A mechanism was proposed that stepwise reduction of **217** to difluoro imine species **218** and then to amine species **219** occurs first (Scheme 66). The nitrogen atom in intermediate **219** assists C–F bond cleavage to produce an aminoalkyne intermediate **220**, whose triple bond is successively hydrogenated to yield the final product. All proposed intermediates except for **220** were detected by GC/MS. However, the role of zinc catalyst in the reactions hadn't been elucidated.




**Scheme 65** Gold-catalyzed π–π interaction-assisted HDF of fluoroarenes (DMAP = 4-dimethylaminopyridine, PFNB = pentafluoronitrobenzene, Ar = 2,4,6-trimethyl phenyl)




**Scheme 66** Proposed mechanism for HDF of difluoromethylene-containing derivatives in the presence of $LiAlH_4$

In summary, group 11–12 metals are underdeveloped for catalytic HDF reactions, and only recently has their importance been recognized. Nevertheless, economical copper and zinc metals deserve special attention for practical applications. Compared to other noble metals (Rh, Pd, Pt, etc.), the much lower price and the stronger relativistic effects provide gold another chance to take a share in C–F bond activation.

## 4 Conclusion

In summary, over the past decades numerous examples of transition-metal complex-mediated HDFs have been achieved. These successful examples provide helpful insights to understand the roles of M–F, M–C, and M–H bonds during catalytic processes, which would facilitate the transformations of C–F to C–X bonds beyond HDF. Based on M–F bond strength in Fig. 1, the mechanistic variability of HDF reactions offers several approaches to further optimize HDF reagents.

For early transition metals, although strong M–F bonds are thermodynamically favored to C–F bond activation, removing fluorido ligand to complete catalytic cycle is challenging. H/F exchange through nucleophilic displacement between C–F and M–H bonds requires the regeneration of metal hydrides using an external hydride reagent. Exploring such external hydrogen source is a tricky issue regarding the high BDE of M-F bonds. Thus, adjusting the metal center's Lewis acidity through ligand optimization or extending to group 4–5 metals with weaker M–F bond is critical to develop early transition-metal catalysts.

For late transition metals, the electron-rich metal centers have lower affinity to fluorido ligands but higher affinity to the carbon of C–F bonds, resulting in possible M–C bond formation and further facilitating C–F bond cleavage. Oxidative addition of carbon–fluorine bonds at late transition metals is the most studied pathway. With fluorido ligand transferring to a fluorophilic moiety such as a boryl, silyl, or hydrido ligand of hydrogen sources, M–C bond breaks along with the release of the HDF product. During the catalytic cycle, M–F bond might be formed and fluorido ligand can be removed through formation of strong X–F (X = B, Si, and H) bonds. However, the competing activation of C–H bond remains challengeable for partially fluorinated molecules. Generally, in the competition between C–F and C–H activation, the thermodynamic product is always the metal fluoride, 没太懂. Other than metal and ligand effects, weak interactions between metal fluoride intermediates and substrates, solvents, or ligands may be significant to modulate the overall energetics and selectivity of reactions. Thus, to design such framework depending on the use of secondary interactions through mimicking the enzyme active site is potentially useful to enhance the selectivity of C–F bond activation.

Other than M–F or M–C bond formation, HDF reactions can be achieved by the low-valent transition metals through single-electron transfer mechanism. Due to a low-lying LUMO of fluorinated molecules, low-valent transition metals may reduce fluorocarbon to generate a substrate radical anion. The resulting radical is quenched by hydrogen-atom transfer or further reduction followed by protonation. However, this approach always needs stoichiometric or excess amount of low-valent metals. This inspires the application of photocatalytic process in HDF reaction. Recently, Weaver and coworkers reported the HDF of perfluoroarenes through visible light photocatalysis, which demonstrated the potential of

combination of photocatalysis and C–F activation [179]. We expect that the present photocatalytic protocol expands the research field of radical reactions and stimulates development of novel methodology for HDF and further C–F bond activation.

Finally, it is worthy to note that transition-metal-catalyzed HDF or functionalization of unreactive C($sp^3$)–F bonds has been much less reported than C($sp^2$)–F bonds, despite of significant progress made in this field recently. In contrast, the application of main-group Lewis acids containing boron [180], aluminum [181, 182], or silylium ions [183–185] to activate C($sp^3$)–F bond had been well established, but good catalytic turnover numbers had not been achieved [32]. We envision that a combination of remarkable reactivity of main-group Lewis acids and transition-metal catalysis might hold promise for further developments of HDF or functionalization of unreactive C($sp^3$)–F bonds toward potentially greener and more sustainable processes. Furthermore, it can be seen that the chemist's synthetic toolbox has been significantly improved over the last few years. Therefore, it is possible to obtain new research results which would expand the scope of substrates and establish HDF as a synthetically useful tool.

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# Catalytic Transformations of Fluorinated Olefins

**Masato Ohashi and Sensuke Ogoshi**

**Abstract** Progress in the development of catalytic transformation reactions of fluorinated olefins is reviewed. Four different types of transition-metal-catalyzed transformations have been distinguished: (a) oligomerization, (b) hydrodefluorination, (c) C–X bond formation via C–F bond cleavage, and (d) C–C bond formation via C–F bond cleavage.

**Keywords** C–F bond activation · Fluorinated olefins · Homogeneous catalysis · Transition metals

## Contents



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# 1 Introduction

This chapter covers the development of catalytic transformation reactions that involve transition-metal-mediated C–F bond activation processes of fluorinated olefins. Such processes are rare by comparison with the number of catalytic systems that involve aromatic and aliphatic C–F bond activation. Stoichiometric C–F bond activation reactions leading to catalytic transformation systems have also been elucidated. For a more comprehensive description of stoichiometric C–F bond activation, the reader is directed to a list of the leading general reviews in this field [1–18]. The purpose of this chapter is to review the established or potential synthetic methodologies available via vinylic C($sp^2$)–F bond cleavage by transition metals.

# 2 Transition-Metal-Catalyzed Oligomerization of Fluorinated Olefins

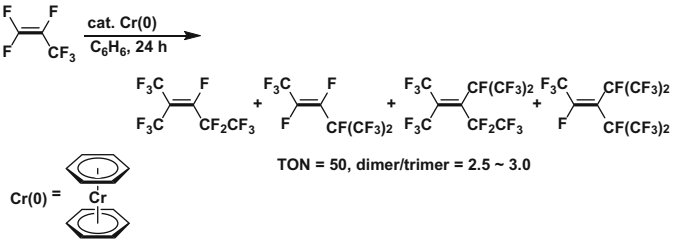
## *2.1 Chromium(0)-Catalyzed Oligomerization of Hexafluoropropylene*

To the best of our knowledge, the first catalytic transformation reaction in which a fluorinated olefin was employed as a substrate was the Cr(0)-catalyzed oligomerization of hexafluoropropylene, as reported by Huang et al. in 1981 [19, 20]. Hexafluoropropylene is oligomerized in the presence of $(\eta^6\text{-}C_6H_6)_2Cr$ to yield a mixture of the corresponding dimers and trimers (Scheme 1). In stark contrast to $(\eta^6\text{-}C_6H_6)_2Cr$, monovalent bisbenzenechromium(I), $[(\eta^6\text{-}C_6H_6)_2Cr]^+$,which can be generated in situ by air passing through a benzene solution of $(\eta^6\text{-}C_6H_6)_2Cr$ prior to exposure to hexafluoropropylene, will not, however, catalyze oligomerization. A fluoride plays an important role in a number of other reports concerning the oligomerization or isomerization of perfluoroalkenes [21], and it leads to the generation of a key perfluorocarbanion intermediate. However, when hexafluoropropylene was treated with a fluoride source, such as KF, $CrF_2$, or $Me_4NF$, instead of $(\eta^6\text{-}C_6H_6)_2Cr$ in benzene, no oligomerization occurred at all in each case.

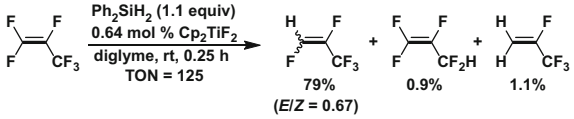
# 3 Transition-Metal-Catalyzed Hydrodefluorination of Fluorinated Olefins

## *3.1 Group 4 Metal Catalyst*

Lentz and coworkers have demonstrated that air-stable titanocene difluoride, $Cp_2TiF_2$, shows a high catalytic efficiency for the hydrodefluorination of hexafluoropropylene. Thus, in the presence of diphenylsilane and a catalytic amount of




**Scheme 1** Bis(benzene)chromium-catalyzed oligomerization of hexafluoropropylene



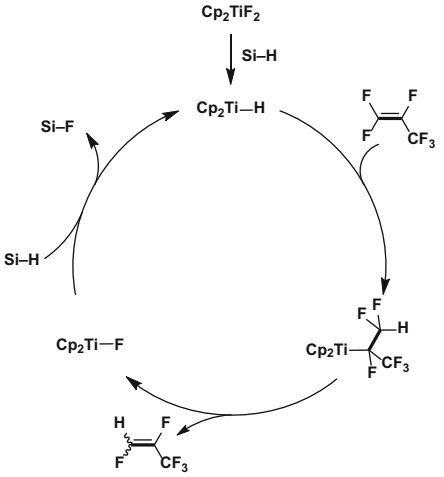

**Scheme 2** Titanium-catalyzed hydrodefluorination of hexafluoropropylene

$Cp_2TiF_2$, the hydrodefluorination of hexafluoropropylene takes place at room temperature very smoothly, resulting in the formation of an *E*/*Z* mixture of 1,2,3,3,3-pentafluoropropane (Scheme 2) [22, 23]. In this hydrodefluorination system, secondary silanes such as $Ph_2SiH_2$ act as the best hydride source, and cyclopentadienyl ligands with a low steric hindrance and a high electron density have shown better catalytic performance. This catalytic reaction can achieve a TOF as high as 1,500 $h^{-1}$ with a TON as high as 125. The application of 1,1,3,3,3-pentafluoropropene leads to 1,3,3,3-tetrafluoropropene (*E*/*Z* mixture) and 1,1,3,3-tetrafluoropropene. Other fluorinated olefins are also applicable to this hydrodefluorination process, while the performance of the catalytic hydrodefluorination of perfluoroallene is less robust. When employing hexafluoropropylene, 1,1,3,3,3-pentafluoropropene, or perfluorocyclobutene as a substrate, an undesired allylic hydrodefluorination can compete with vinylic hydrodefluorination, but the rate of the latter reaction is much faster.

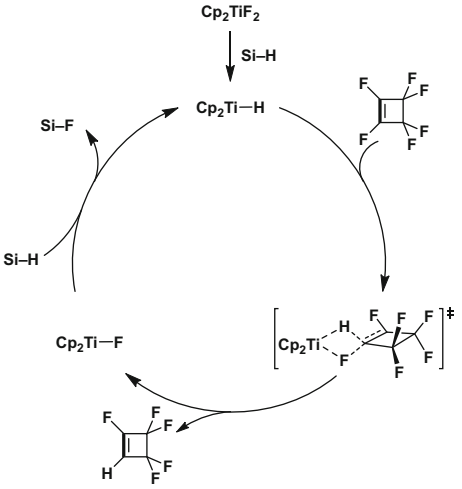
Mechanistic investigations have revealed that titanocene(III) monohydride is the active species that is generated in situ by the reaction of titanocene(IV) difluoride with hydrosilane (Scheme 3). The key hydrodefluorination step is assumed to be mainly an alkene insertion/$\beta$-fluoride elimination mechanism, whereas both the insertion/elimination mechanism and the $\sigma$-bond metathesis mechanism are assumed to be involved in the generation of perfluorocyclobutene (Scheme 4).

Although stoichiometric, the hydrodefluorination of a variety of vinylic fluorides has also been achieved by using zirconium and hafnium hydride species [24–27]. Their mechanistic studies have also been discussed in the literature; two different mechanisms, the insertion/elimination mechanism [25, 28] and the concerted $\sigma$-bond metathesis mechanism [24, 27], have been proposed. Replacing zirconium or hafnium with titanium enables catalytic hydrodefluorination, which

**Scheme 3** A plausible mechanism for titanium-catalyzed hydrodefluorination of hexafluoropropylene




**Scheme 4** A plausible mechanism for titanium-catalyzed hydrodefluorination of perfluorocyclobutene

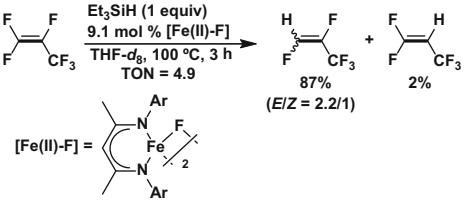



is rationalized by the presence of a Ti–F bond that is weaker than an M–F bond (M = Zr or Hf).

## *3.2 Group 8 Metal Catalyst*

### 3.2.1 Iron-Catalyzed Hydrodefluorination of Hexafluoropropylene

Holland et al. demonstrated how hexafluoropropylene undergoes hydrodefluorination in the presence of triethylsilane and a catalytic amount of an



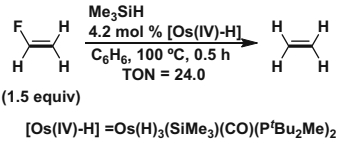

**Scheme 5** Iron-catalyzed hydrodefluorination of hexafluoropropylene

iron(II) fluoride species to yield a mixture of 1,1,3,3,3-pentafluoropropene (*E*/*Z* mixture) and 1,2,3,3,3-pentafluoropropene (Scheme 5) [29]. The turnover number in this reaction has reached 4.9. In addition, the use of 3,3,3-trifluoropropene ($CH_2$=$CHCF_3$) as a substrate gives 1,1-difluoropropene ($CF_2$=$CHCH_3$), albeit with a lower catalytic efficiency (100 °C, 4 days, TON = 1.2). Stoichiometric reactions as well as NMR observation of the catalytic reaction have indicated that an iron(II) hydride species, generated via the reaction of an iron(II) fluoride precatalyst with hydrosilane, is a key intermediate, and this hydrodefluorination reaction of fluoroolefins proceeds via a metal hydride insertion/$\beta$-fluoride elimination mechanism.

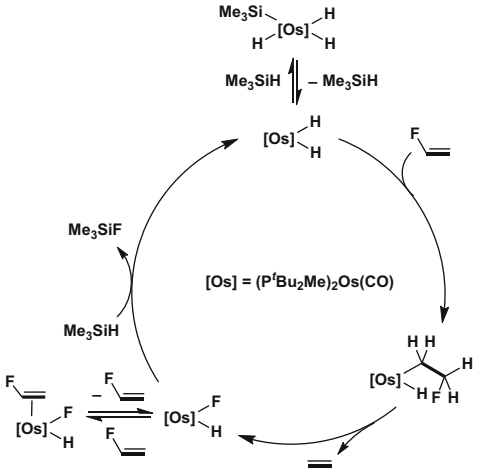
### 3.2.2 Osmium-Catalyzed Hydrodefluorination of Vinyl Fluoride and Vinylidene Fluoride

Caulton and his coworkers have demonstrated the osmium-catalyzed hydrodefluorination of vinyl fluoride in the presence of hydrosilane as a hydrogen source, yielding ethylene [30]. When $OsH_3(SiMe_3)(CO)(P^tBu_2Me_2)_2$ was treated with vinyl fluoride (36 equiv.) in the presence of trimethylsilane (24 equiv.) in $C_6D_6$ at 20 °C for 0.5 h, trimethylsilane was fully consumed, and the generation of ethylene as well as trimethylsilyl fluoride was detected by NMR analysis (Scheme 6). In this reaction mixture, the osmium complex was $OsHF(CO)(\eta^2\text{-}CH_2$=$CHF)(P^tBu_2Me_2)_2$. In this hydrodefluorination system, trimethylsilane was the best hydride source; the use of triphenylsilane instead of trimethylsilane retarded the reaction, and neither diphenylsilane nor phenylsilane was effective for the hydrodefluorination reaction. In addition, the use of vinylidene fluoride as a substrate gave a mixture of ethylene and vinyl fluoride, wherein ethylene was the major hydrodefluorinated product.

Some stoichiometric reactions have been conducted to gain deeper insight into the reaction mechanism. When $OsHF(CO)(P^tBu_2Me_2)_2$ was treated with an excess amount of trimethylsilane, the catalyst precursor, $OsH_3(SiMe_3)(CO)(P^tBu_2Me_2)_2$, was regenerated at 20 °C within 1 h, with a concomitant formation of trimethylsilyl fluoride. Reversible reductive elimination of trimethylsilane from the 18-electron osmium(IV) precatalyst $OsH_3(SiMe_3)(CO)(P^tBu_2Me_2)_2$ might generate an active osmium(II) dihydride species, $OsH_2(CO)(P^tBu_2Me_2)_2$, which reacts with fluoroolefins to yield the corresponding hydrodefluorination product as well as




**Scheme 6** Osmium-catalyzed hydrodefluorination of vinyl fluoride



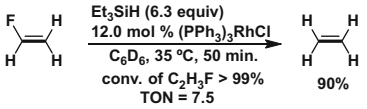

**Scheme 7** A plausible mechanism for osmium-catalyzed hydrodefluorination of vinyl fluoride

$OsHF(CO)(P^tBu_2Me_2)_2$ (Scheme 7). The key hydrodefluorination step is assumed to be an alkene insertion/$\beta$-fluoride elimination mechanism [31].

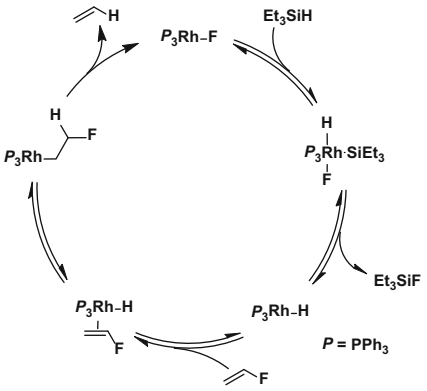
## *3.3 Group 9 Metal Catalyst*

Hydrodefluorination of vinyl fluoride has also been achieved by employing $(PPh_3)_3RhCl$ as a catalyst. Thus, treatment of vinyl fluoride (20 mM) with $Et_3SiH$ (125 mM) in the presence of a catalytic amount of $(PPh_3)_3RhCl$ (2.4 mM) in $C_6D_6$ at 35 °C results in the complete hydrodefluorination of vinyl fluoride within 50 min, leading to the generation of ethylene (90% yield; Scheme 8) [32, 33].

This hydrodefluorination reaction can be conducted starting with the corresponding fluoride, $(PPh_3)_3RhF$. This hydrodefluorination system can be applied to other haloalkenes, such as when ethylene is produced from vinyl chloride. In addition, both 1,1-chlorofluoroethylene and 1,2-chlorofluoroethylene participate in dehalogenation, and only vinyl fluoride is observed as an intermediate in both reactions. Kinetics studies have revealed that the rate of the pseudo first-order consumption of vinyl fluoride is six times faster than that of vinyl chloride and that



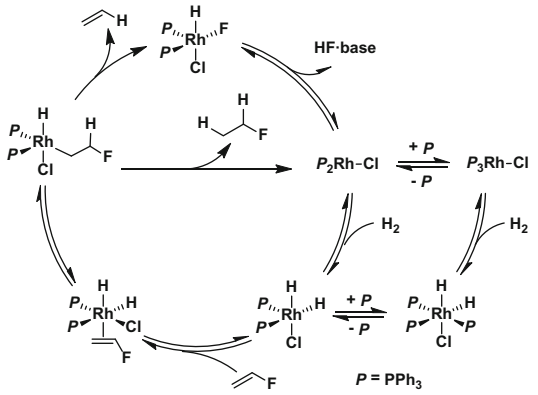

**Scheme 8** Rhodium-catalyzed hydrodefluorination of vinyl fluoride



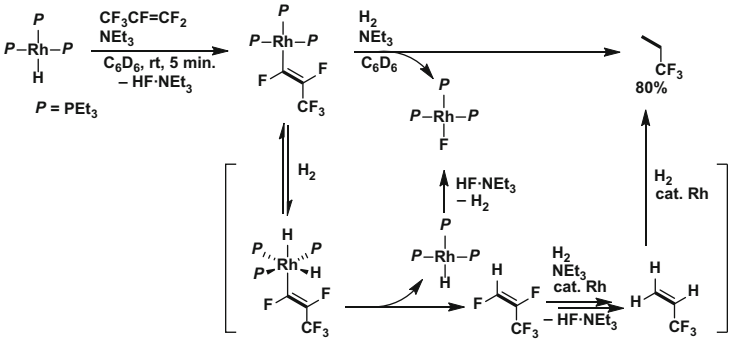

**Scheme 9** A plausible mechanism for rhodium-catalyzed hydrodefluorination of vinyl fluoride in the presence of hydrosilane

such an intermolecular kinetic preference for the C–F bond cleavage stands in sharp contrast to the intramolecular preferential C–Cl bond cleavage observed in chlorofluoroalkenes. These observations as well as some labeling experiments support a reaction mechanism involving a rhodium(I) hydride key intermediate (Scheme 9). Coordination of vinyl fluoride to the Rh(I)–H species followed by insertion into the Rh–H bond gives a rhodium(I) alkyl complex. The alkylrhodium intermediate would then undergo $\beta$-fluoride elimination to give ethylene and the rhodium(I) fluoride. Oxidative addition of $Et_3SiH$ to the rhodium(I) fluoride is followed by the reductive elimination of $Et_3SiF$ from a transient Rh(III) intermediate that then regenerates the Rh(I)–H species.

McNeill has also shown the Rh-catalyzed hydrodefluorination of vinyl fluoride using dihydrogen gas instead of hydrosilanes as the reducing agent. The major product in this reaction is the undesired hydrogenation product, fluoroethane, rather than the desired hydrodefluorinated product, ethylene. Such a difference in the major products between these catalytic reactions is caused by the fact that there are two different reaction mechanisms if $Et_3SiH$ or $H_2$ is used. When $H_2$ is employed as a hydrogen source, the likely key intermediate is a rhodium(III) dihydride species generated via the oxidative addition of $H_2$ to a rhodium(I) monohalide (Scheme 10). Phosphine dissociation might be involved before or after the oxidative addition step. Coordination of vinyl fluoride to the Rh(III)–H species followed by insertion into the Rh–H bond affords a rhodium(III) alkyl complex. Then, this alkylrhodium intermediate would undergo either $\beta$-fluoride elimination, giving ethylene and a rhodium(III) monohydride dihalide, or reductive elimination, yielding fluoroethane and a Rh(I)–Cl species. Andersson and coworkers have demonstrated that the Ir(I) species,



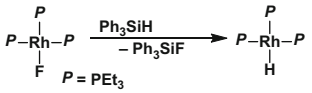

**Scheme 10** A plausible mechanism for rhodium-catalyzed hydrodefluorination of vinyl fluoride in the presence of dihydrogen



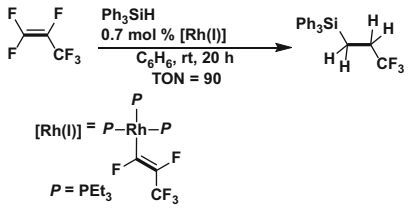

**Scheme 11** A plausible reaction mechanism for rhodium-mediated hydrodefluorination of hexafluoropropylene

which catalyze the asymmetric hydrogenation of monofluoroolefins, would also mediate an undesired defluorination reaction [34].

Although not catalytic, Braun has demonstrated the conversion of hexafluoropropylene into 1,1,1-trifluoropropene by using $H_2$ gas as a hydrogen source [35]. This reaction involves the formation of a *Z*-perfluoropropenyl Rh(I) intermediate by treating tris(triethylphosphine)rhodium(I) hydride with hexafluoropropylene in the presence of $NEt_3$ (Scheme 11). In this reaction step, hydrogen fluoride was concomitantly generated and trapped by a base. The *Z*-perfluoropropenyl rhodium complex undergoes a successive hydrodefluorination/hydrogenation under an $H_2$ atmosphere, which leads to the formation of 1,1,1-trifluoropropene (80% yield) and tris(triethylphosphine)rhodium(I) fluoride. This hydrodefluorination/hydrogenation step might involve the formation of a *Z*-perfluoropropenyl rhodium(III) dihydride intermediate generated by the oxidative addition of $H_2$, and then the reductive elimination of 1,2,3,3,3-(*E*)-pentafluoropropene results in the concomitant regeneration of the




**Scheme 12** Regeneration of $(PEt_3)_3RhH$ by treating $(PEt_3)_3RhF$ with triphenylsilane




**Scheme 13** Rhodium-catalyzed defluoronative hydrosilylation of hexafluoropropylene

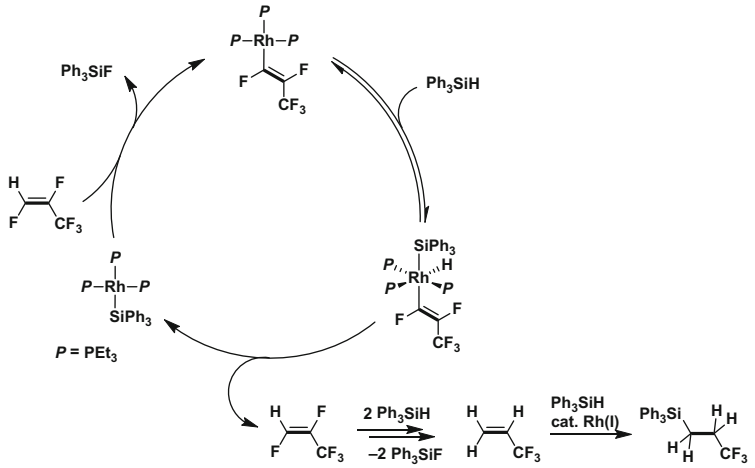
Rh(I) hydride. This monohydrodefluorinated product finally undergoes further hydrodefluorination to give 3,3,3-trifluoropropylene, which is catalytically hydrogenated into 1,1,1-trifluoropropene in the presence of the Rh(I) hydride species. The formation of the Rh(I) fluoride might be rationalized by the protonolysis of rhodium intermediates with $Et_3N$/HF generated in situ. Again, this hydrodefluorination reaction is stoichiometric rather than catalytic, but the Rh(I) fluoride regenerates into the Rh(I) hydride by treatment with triphenylsilane (Scheme 12) [36], and thus, these stoichiometric reactions formally achieve a cyclic system.

# 4 Transition-Metal-Catalyzed C–X Bond Formation Reactions via C–F Bond Activation of Fluorinated Olefins

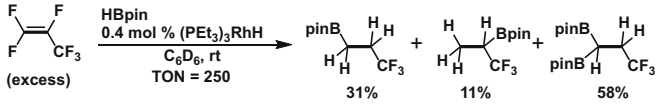
## *4.1 Group 9 Metal Catalyst*

By employing the same *Z*-perfluoropropenyl rhodium(I) species as a precatalyst, Braun has developed a novel functionalization reaction that does not lead to simple hydrodefluorination products. In the presence of triphenylsilane and a catalytic amount of ((*Z*)-perfluoropropenyl)$Rh(PEt_3)_3$, hexafluoropropylene is selectively transferred into 3,3,3-trifluoropropylsilane (Scheme 13) [37]. This catalytic reaction is very selective and only 3,3,3-trifluoropropylsilane is generated (TON = 90). Among the hydrosilanes used, triphenylsilane shows the best performance.

When dihydrogen is used, this transformation involves the oxidative addition of $Ph_3SiH$ to Rh(I) to yield a perfluoro propenylrhodium(III) silyl hydride species (Scheme 14). Then, the reductive elimination of 1,2,3,3,3-(*E*)-pentafluoropropene might lead to the generation of a key Rh(I) silyl intermediate, which reacts with hexafluoropropylene to regenerate the *Z*-perfluoropropenyl rhodium(I) species.




**Scheme 14** A plausible mechanism for rhodium-catalyzed defluoronative hydrosilylation of hexafluoropropylene in the presence of triphenylsilane




**Scheme 15** Rhodium-catalyzed defluoronative hydroborylation of hexafluoropropylene

Although the mechanism of the C–F bond cleavage steps has not been examined in detail, either the oxidative addition of a C–F bond to Rh(I) or the alkene insertion/$\beta$-fluoride elimination pathway might be involved. The resultant 1,2,3,3,3-(*E*)-pentafluoropropene undergoes a further hydrodefluorination reaction to form 3,3,3-trifluoropropene, which is finally converted into 3,3,3-trifluoropropylsilane via Rh(I)-catalyzed hydrosilylation. Another possible pathway might involve the reductive elimination of (*Z*)-(perfluoropropenyl)triphenylsilane from the perfluoro propenylrhodium(III) silyl hydride intermediate, yielding (*Z*)-(perfluoropropenyl) silane.

When HBpin (HBpin=4,4,5,5-tetramethyl-1,3,2-dioxaborolane) is employed in place of hydrosilanes, hexafluoropropene is catalytically converted into a mixture of fluoroalkyl dioxaborolanes (Scheme 15) [38]. The turnover number in this reaction reached as high as 250. Stoichiometric treatment of a rhodium(I) boryl complex, $(PEt_3)_3Rh(Bpin)$, with hexafluoropropylene results in the formation of a *Z*-perfluoropropenyl rhodium(I) species and its isomer, $(CF_2{=}C(CF_3))Rh(PEt_3)_3$, in a ratio of 2:7, which indicates that the Rh(I)-boryl complex might be a reaction intermediate in the catalytic transformation of hexafluoropropylene and HBpin into Bpin-derivatized trifluoropropanes [39].

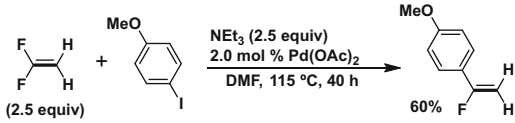
# 5 Transition-Metal-Catalyzed C–C Bond Formation Reactions via C–F Bond Activation of Perfluorinated Olefins

## *5.1 Group 10 Metal Catalyst*

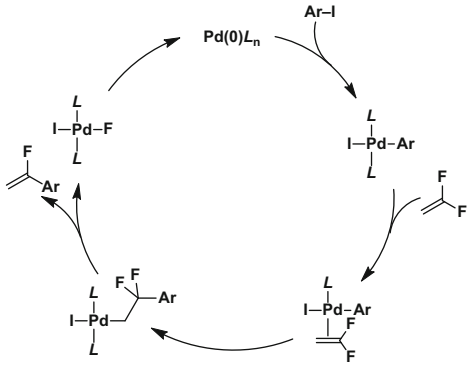
### 5.1.1 Palladium-Catalyzed C–C Bond Formation Reactions via an "Atypical" Mizoroki–Heck-Type Coupling Reaction

Although the Mizoroki–Heck reaction is one of the most widely used catalytic C–C bond formation reactions and is an established method for both the arylation and the alkenylation of olefins [40–49], vinylidene fluoride has shown an entirely different reactivity with other alkenes under the typical Mizoroki–Heck reaction conditions. Thus, treatment of vinylidene fluoride with 1-iodo-4-methoxybenzene in the presence of $NEt_3$ (2.5 equiv.) and a catalytic amount of $Pd(OAc)_2$ in DMF resulted in the formation of 4-methoxy-$\alpha$-fluorostyrene instead of the typical Mizoroki–Heck reaction product, 4-methoxy-$\beta$,$\beta$-difluorostyrene (Scheme 16) [50].

This C–C bond-forming reaction involves the oxidative addition of Ar-I to Pd(0), followed by carbopalladation to vinylidene fluoride to give an Ar-$CF_2CH_2$-Pd(II) intermediate, which is preferred rather than another carbopalladation product, Ar-$CH_2CF_2$-Pd(II), due to the charge-controlled reaction (Scheme 17). As a result, $\beta$-fluoride elimination then took place, exclusively affording 4-methoxy-$\alpha$-fluorostyrene. The resultant Pd(II) dihalide might be regenerated to Pd(0) by treatment with either solvent or excessive vinylidene fluoride in the presence of a base. It should be mentioned that the reaction of iodobenzene with vinyl fluoride




**Scheme 16** Palladium-catalyzed cross-coupling reaction of vinylidene fluoride with aryl iodide



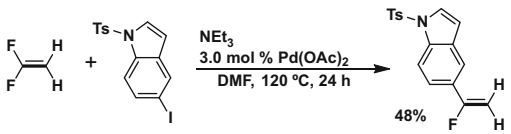

**Scheme 17** A plausible mechanism for palladium-catalyzed cross-coupling reaction of vinylidene fluoride with aryl iodide

gave a mixture of styrene and stilbene, indicating that $\beta$-fluoride elimination is preferred even though competing $\beta$-hydride elimination is possible.

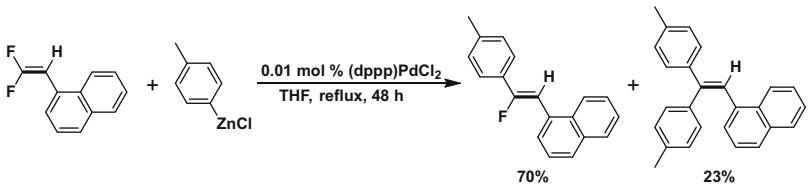
Martin et al. reported a related coupling reaction of vinylidene fluoride with *N*-tosyl-5-iodoindole (Scheme 18) [51, 52].

### 5.1.2 Palladium-Catalyzed Negishi-Type Cross-Coupling Reaction with *Gem*-Difluoroalkene

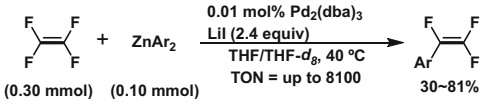
Saeki and Tamao have demonstrated that (dppp)$PdCl_2$ (dppp = 1,3-bis(diphenylphosphino)propane) is effective for the cross-coupling reaction of 1-(2,2-difluorovinyl)naphthalene with (*p*-tol)ZnCl, leading to the selective formation of (*Z*)-fluoroalkene as a major product (Scheme 19) [53]. In this reaction, the *trans*-fluorine atom to the 1-naphthyl group is selectively cleaved probably due to the steric hindrance of the naphthyl group. The bis-substituted product, 1-(2,2-di-*p*-tolylvinyl)naphthalene, was concomitantly generated as a minor product, and the corresponding (*E*)-fluoroalkene was not observed. Such *E*/*Z* selectivity is not to be observed in the reaction of the same *gem*-difluoroalkene with (*p*-tol)MgBr in the absence of any transition-metal catalysts, because this reaction might involve an addition–elimination mechanism [54–59] to yield a mixture of the *E*/*Z* regioisomers in 50% total yield (*E*/*Z* ratio = 4:1, 68% conversion after stirring for 48 h under THF reflux conditions). The reaction employing (dppp)$NiCl_2$ in place of (dppp)$PdCl_2$ as a catalyst in the presence of an excess amount of (*p*-tol)MgBr affords the bis-substituted product as a major product.



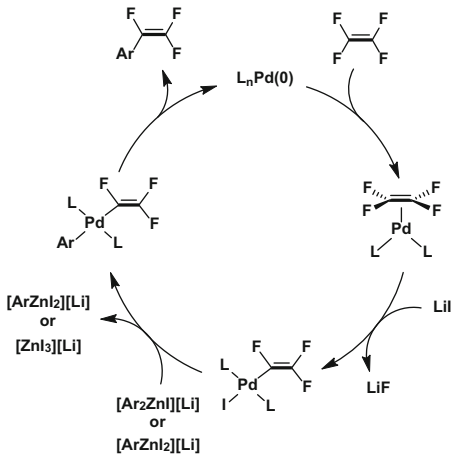

**Scheme 18** Palladium-catalyzed cross-coupling reaction of vinylidene fluoride with *N*-tosyl-5-iodoindole




**Scheme 19** Palladium-catalyzed cross-coupling reaction of 1-(2,2-difluorovinyl)naphthalene with (*p*-tolyl)zinc chloride




**Scheme 20** Palladium-catalyzed cross-coupling reaction of tetrafluoroethylene with diarylzinc

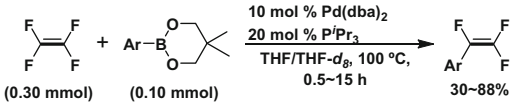



**Scheme 21** A plausible mechanism for palladium-catalyzed cross-coupling reaction of tetrafluoroethylene with diarylzinc

### 5.1.3 Palladium-Catalyzed Negishi-Type Cross-Coupling Reaction with Tetrafluoroethylene

Our group has achieved the first catalytic transformation of tetrafluoroethylene (TFE; $CF_2{=}CF_2$) [60], whereas C–F bond activation of TFE was accomplished in a few stoichiometric reactions [61–65]. In the presence of lithium iodide and a catalytic amount of $Pd_2(dba)_3$, the Negishi-type cross-coupling reaction of TFE with a variety of diarylzinc reagents proceeds in THF at 40 °C, yielding the corresponding $\alpha,\beta,\beta$-trifluorostyrene derivatives (Scheme 20). When diphenylzinc is employed as a coupling partner with TFE, the highest TON number can be observed (TON = 8,100).

This Pd-catalyzed monoaryl substitution reaction of TFE might involve the mechanism depicted in Scheme 21 wherein the coordination of a TFE molecule to Pd(0) occurs to generate an $\eta^2$-TFE species, and then oxidative addition of a C–F bond to Pd(0) is promoted by lithium iodide, generating a trifluorovinyl palladium (II) intermediate. Transmetalation with reactive zincates generated in situ, Li [ArZnXI], yields a transient aryl palladium intermediate, which undergoes reductive elimination to give an ($\alpha,\beta,\beta$-trifluoro)styrene together with regeneration of the Pd(0) species. Stoichiometric treatment of the isolable bis(triphenylphosphine)




**Scheme 22** Palladium-catalyzed cross-coupling reaction of tetrafluoroethylene with arylboronate

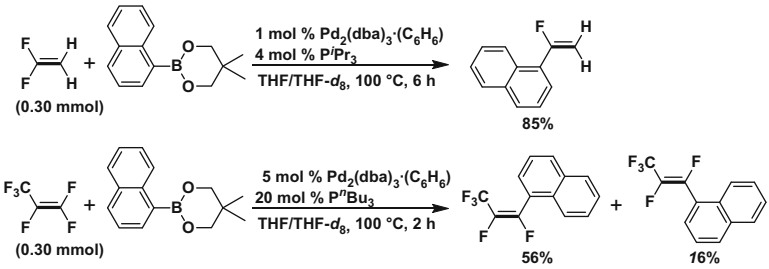
$\eta^2$-TFE complex, ($\eta^2$-TFE)Pd($PPh_3$)$_2$, with lithium iodide leads to a smooth formation of the corresponding trifluorovinyl palladium iodide, *trans*-($PPh_3$)$_2$Pd(I)($CF{=}CF_2$) [60, 66]. In addition, the resultant trifluorovinyl palladium iodide, which has been isolated and its molecular structure unambiguously confirmed by X-ray diffraction study, can be efficiently transferred into trifluorostyrene by treatment with diphenylzinc in the presence of lithium iodide and DBA (*trans*, *trans*-dibenzylideneacetone), whereas the reaction in the absence of lithium iodide was notably retarded. These results support the proposed reaction mechanism, and the key role of lithium iodide in this catalytic reaction is summarized as follows: (a) accelerating the cleavage of the C–F bond in TFE and (b) enhancing the reactivity of arylzinc reagents via the formation of zincates such as Li[ArZnXI].

### 5.1.4 Palladium-Catalyzed Base-Free Suzuki–Miyaura-Type Cross-Coupling Reaction with Tetrafluoroethylene

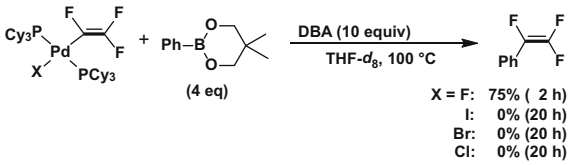
We have also demonstrated a novel Pd(0)-catalyzed cross-coupling reaction involving fluoroalkenes and organoboron reagents [67]. Thus, the reaction of TFE with 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane in the presence of a catalytic amount of $Pd(dba)_2$ and $P^iPr_3$ in THF at 100 °C leads to the formation of trifluorostyrene in 83% yield (Scheme 22). Among the tertiary phosphines employed, $PCy_3$ was found to be slightly less effective (66% yield, under the same reaction conditions), and $PPh_3$ shows no catalytic activity.

This catalytic reaction takes place even in the absence of bases, while the use of a base is generally indispensible for the Suzuki–Miyaura coupling reaction in order to enhance the reactivity of the organoboron reagents. In fact, most of the reported Suzuki–Miyaura-type cross-coupling reactions via C–F bond cleavage have been conducted in the presence of a base [68–79]. Although this reaction leaves much to be desired regarding the catalyst loading as well as the product yield, it is of great importance in preparing substituted trifluorostyrenes bearing nitro, aldehyde, ester, and cyano groups. These functional groups can easily react with Grignard reagents that are required for the in situ preparation of organozinc reagents, and therefore, these products are difficult to synthesize from a coupling reaction with organozinc reagents.

This base-free cross-coupling reaction with arylboronates can be successfully expanded to other fluorinated alkenes (Scheme 23); both vinylidene fluoride and hexafluoropropylene react with 5,5-dimethyl-2-($\alpha$-naphthyl)-1,3,2-dioxaborinane in the presence of a Pd(0) catalyst, leading to the corresponding cross-coupling




**Scheme 23** Palladium-catalyzed cross-coupling reaction of either vinylidene fluoride or hexafluoropropylene with 1-naphthylboronate



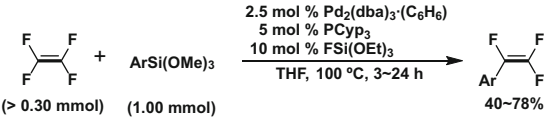

**Scheme 24** Reactivity of trifluorovinylpalladium(II) halides toward phenylboronate

products. It should be mentioned that a Pd(0) catalyst is ineffective for the base-free coupling reaction of fluoroarenes, while the Ni(0)/NHC complex [75, 80–82] shows catalytic activity.

Based on the results of a stoichiometric reaction of a series of trifluorovinylpalladium(II) halides with 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (Scheme 24), the key intermediacy of a trifluorovinylpalladium(II) fluoride species is indisputable in this catalytic reaction. Also, trialkylphosphines with strong $\sigma$-donor ability, such as $PCy_3$ and $P^iPr_3$, enable the oxidative addition of a C–F bond of TFE to Pd(0) without the use of additives in the generation of trifluorovinylpalladium(II) fluoride. These findings support a plausible reaction mechanism that involves the following steps: (a) the coordination of a TFE molecule to Pd(0); (b) oxidative addition of a C–F bond of TFE, generating a palladium(II) fluoride intermediate; (c) a transmetalation between the palladium fluoride and arylboronates, yielding a transient aryl trifluorovinylpalladium(II) intermediate; and (d) a reductive elimination to afford trifluorostyrenes along with regeneration of the Pd(0) species.

### 5.1.5 Palladium-Catalyzed Base-Free Hiyama-Type Cross-Coupling Reaction with Tetrafluoroethylene

Among the transition-metal-catalyzed C–C bond formation reactions, the Hiyama cross-coupling reaction of organic halides with organosilicon reagents has attracted a great deal of interest in recent years, because of the ease of preparation, stability,




**Scheme 25** Palladium-catalyzed cross-coupling reaction of tetrafluoroethylene with aryltrimethoxysilane

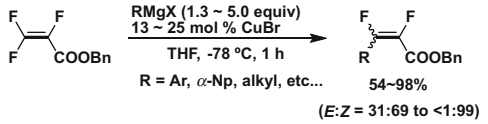
and environmentally benign nature of organosilicon reagents [83–87]. Our group recently developed a novel base-free Hiyama coupling reaction of TFE via its C–F bond activation (Scheme 25) [88]. This catalytic reaction is also based on the generation of the transition-metal fluoride intermediate that is considered to have high reactivity toward organosilicon reagents sufficient to promote transmetalation in the absence of any base. In this reaction, the concomitant generation of a small amount (~10%) of trifluoroethylene is observed, and it would be generated via methoxy group transfer, followed by $\beta$-hydride elimination and successive reductive elimination. Unlike the coupling reaction with organoboronates, the use of $PCyp_3$ ($Cyp = c\text{-}C_5H_{11}$) results in the best catalytic performance. In addition, fluorosilanes that are generated in situ as a by-product of the coupling reaction are found to accelerate the catalytic reaction, which makes a base-free mechanism unnecessary. The role of fluorosilanes might be the facilitation of the oxidative addition of a C–F bond of TFE to Pd(0). Again, similar to the reaction mechanism involving organoboronates, the trifluorovinylpalladium(II) fluoride intermediate plays an important role in this base-free Hiyama-type coupling reaction. It should be mentioned that the mechanism involving free fluoride anion has been ruled out because of the observation of the negative effect of the addition of TBAF on the coupling reaction.

## *5.2 Group 11 Metal Catalyst*

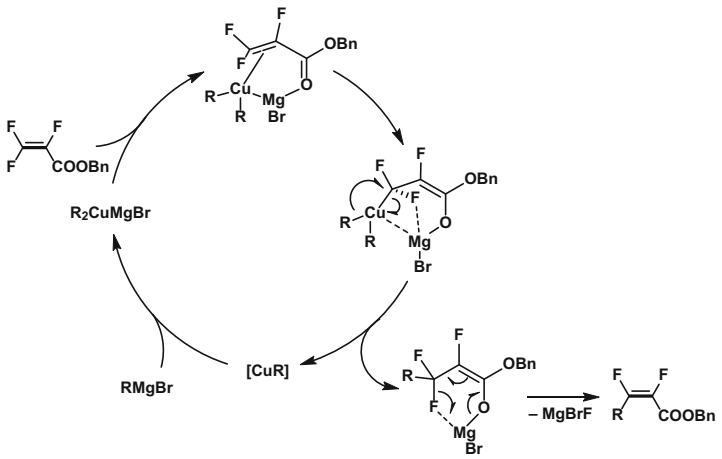
### 5.2.1 Copper-Catalyzed C–C Bond Formation Reactions via a Highly Stereoselective Addition–Elimination Reaction with Grignard Reagents

Ishihara and coworkers have reported that the reaction of benzyl 2,3,3-trifluoroacryrate with a variety of Grignard reagents in the presence of a catalytic amount of copper(I) bromide proceeds to give the corresponding $\alpha,\beta$-difluoroacrylates with high *Z*-selectivity (Scheme 26) [89, 90]. The reaction without copper (I) salt does not afford the desired coupling product.

This reaction mechanism might involve the following steps (Scheme 27): organocuprate reagents generated in situ react with 2,3,3-trifluoroacrylate to form a $\pi$-complex, in which copper and magnesium are simultaneously coordinated by the C=C double bond and the oxygen atom in the carbonyl group, respectively. This transient $\pi$-complex undergoes oxidative addition to give a copper(III)




**Scheme 26** Copper-catalyzed cross-coupling reaction of benzyl 2,3,3-trifluoroacryrate with Grignard reagents




**Scheme 27** A plausible mechanism for copper-catalyzed cross-coupling reaction of benzyl 2,3,3-trifluoroacryrate with Grignard reagents

intermediate, and 1,2-migration of the alkyl group results in the formation of a magnesium enolate as well as a neutral copper(I) species. The subsequent elimination of magnesium dihalide leads to (*Z*)-$\alpha$,$\beta$-difluoroacrylate, while the resultant copper(I) species reacts with Grignard reagents to regenerate the key organocuprate intermediate.

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# Fluorous Organometallic Chemistry

**Eric G. Hope, Rena Simayi, and Alison M. Stuart**

**Abstract** The synthesis, characterisation and application of organometallic complexes functionalised with fluorous substituents are reviewed.

**Keywords** Fluorous · Organometallic · Review

## Contents



## 1 Introduction

Organometallic chemistry has made a significant contribution to the developments in fluorous chemistry since its inception in 1994 [1], but this science has never been brought together or reviewed from an organometallic perspective previously. In this article, we attempt to draw together the various strands of fluorous organometallic

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chemistry and present an overview of its contribution to the evolution of fluorous separation methods.

Although originally envisioned by analogy to "aqueous" to embody a third, orthogonal liquid phase that is both lipophobic and hydrophobic, such as a perfluoroalkane or perfluoroether, the scope, meaning and application of the fluorous concept have evolved rapidly, such that it now encompasses solid-phase extraction [2], chromatographic separation [3], solid-supported catalysis [4–8], thermoregulated solubility [9, 10] and release-and-capture concepts [11]. In each of these areas, molecules of interest are adorned with one or more perfluoroalkyl segments in order to generate the desired physical and/or chemical property. These perfluoroalkyl segments are called "ponytails" or "labels" and have traditionally been at least six carbon atoms long (i.e. $C_6F_{13}$) in order to give a molecule the desired "fluorous" characteristics (solubility or separability). More recently, there has been interest in the development of alternative fluorophilic segments based upon smaller perfluorinated groups, e.g. $-OC(CF_3)_3$ [12–22], or perfluoropolyethers [23–29] that are designed to reduce the potential environmental impact of the degradation products of organic or organometallic species derivatised with long perfluoroalkyl groups [30–33], but their applications in organometallic systems have been restricted to just a couple of research articles.

In organometallic systems, it is possible to envisage the attachment of the perfluoroalkyl segment either directly within the metal-bound organic ligand, such as an alkyl, cyclopentadienyl or *N*-heterocyclic carbene (NHC), or as part of another donor ligand (phosphine, pyridine, carboxylate, etc.) in the metal coordination sphere. The synthesis, physical properties and applications of these two classes of fluorous organometallic complexes will be considered separately.

## 2 Organometallic Complexes with Ancillary Fluorous Ligands

Organometallic systems derivatised with perfluoroalkylated ancillary ligands, such as phosphines or carboxylates, have been absolutely fundamental in the development of the fluorous approach to catalysis, whether that catalysis is under classical fluorous biphase conditions, as part of release-and-capture methodologies or for recycling using solid-phase extraction. However, in many instances, the fluorous organometallic catalysts are only formed in situ, e.g. ene catalysts from fluorous rhodium carboxylates [34–36] or fluorous silver trispyrazolylborates [37], and hydrogenation catalysts from fluorous Wilkinson analogues [38–41]. Much of the chemistry in such systems has been very well reviewed elsewhere [42–45] and, since the focus of this article is on the synthesis and characterisation of fluorous

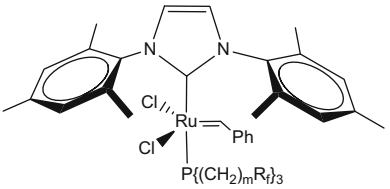
organometallic complexes, these non-isolated fluorous organometallic species will not be discussed further here.

The synthetic approaches to organometallic complexes with fluoroalkylated ligands mirror those applied throughout organometallic chemistry. Cleavage of chloride bridges in $[MCl(CO)_2]_2$ (M=Rh, Ir) or $[Cp^*MCl_2]_2$ (M=Rh, Ir; $Cp^*=\eta^5$-$C_5Me_5$) with a variety of classes of perfluoroalkylated monodentate phosphorus(III) ligands generates well characterised $[MCl(CO)L_2]$ [46–60] and $[Cp^*MCl_2L]$ [50, 52, 55–57, 61] that have been used to establish the impact of the fluorous substituents on the electronic, physical and structural properties of the metal complexes. A number of these systems have been the subject of single crystal X-ray analyses, which generally revealed that the ponytails had little influence on the structural features of the metal centres (bond lengths, bond angles) but dictated the packing of these species in the solid state. Oxidative addition reactions (of $H_2$, $O_2$, MeI, $C_8F_{17}C_2H_4I$) on the iridium Vaska's complex analogues {$P(C_2H_4C_6F_{13})_3$ and $PPh_n(C_6H_4$-4-$C_6F_{13})_{3-n}$ ($n=0$, 1, 2) ligands} generate the anticipated octahedral Ir(III) species, but in-depth studies suggest a different mechanism for the addition reactions to these fluorous-functionalised complexes compared to those with protio ligands [46, 47, 50]. The hydroformylation catalyst $[HRh(CO)\{P(C_2H_4C_6F_{13})_3\}_3]$ is formed quantitatively in the reaction of the phosphine with $[Rh(CO)_2(acac)]$ under Syngas in a closed system [62]. It has been fully identified in solution by spectroscopic studies, but not isolated. The analogous complex with the $P(C_6H_4$-4-$OCH_2C_7F_{15})_3$ ligand has also been detected in solution by high-pressure NMR spectroscopy [63]. Carbonyl displacement from tungsten hexacarbonyl with perfluoroalkylated phosphines affords $[W(CO)_5L]$ {L=$P(C_6H_4$-4-$C_2H_4C_8F_{17})_3$, $P(C_2H_4C_6F_{13})_3$}, the former of which has been structurally characterised [64]. Using the same ligands, this group has also prepared some acetate-bridged ruthenium dimers $[Ru(\mu\text{-}O_2CCH_3)(CO)L]_2$, again using an established organometallic approach, for which the trialkylphosphine complex was the subject of a structural characterisation [65]. The only examples of metal carbonyl clusters derivatised with fluorous ligands were reported in 2010 [66]. $[Os_3(CO)_{11}L]$ and $[Os_3(CO)_{10}L_2]$ {L=$P(C_2H_4C_6F_{13})_3$} were prepared in moderate yields by ligand displacement from the respective acetonitrile adducts. Reaction of the former with triphenylphosphine gave a mixture of $[Os_3(CO)_{10}L(PPh_3)]$ and $[Os_3(CO)_9L(PPh_3)_2]$, which are readily separated by chromatography; the latter has been structurally characterised. Alternatively, reaction of $H_2Os_3(CO)_{10}$ with either $P(C_2H_4C_6F_{13})_3$ or $P(C_6H_4$-4-$C_2H_4C_8F_{17})_3$ gave the hydrido-bridged complex $[(\mu\text{-}H)_2Os_3(CO)_9L]$ [66]. Displacement of tetramethylethylenediamine (tmeda) from [PdCl(Me)(tmeda)] with 2-[bis(4-{[2-(perfluorohexyl)ethyl]dimethylsilyl}phenyl)phosphine]pyridine gave the desired *trans*-square planar $[PdCl(Me)L_2]$ [67]. Similar displacement, this time of norbornadiene, using $P[C_6H_4$-4-$SiMe_2(C_2H_4C_6F_{13})]_3$ has been used to access the palladium(0) alkene adduct, [Pd(maleic anhydride)$L_2$] which is a relatively poor pre-catalyst for the methoxycarbonylation of styrene [68]. In an attempt to improve the solubility of [1, 2]-methanofullerene-substituted cyclometalated (C-N) platinum(II)-

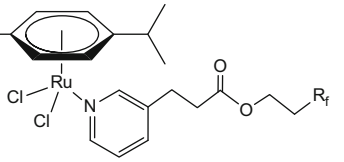
based macrostructures, van Koten et al. have displaced DMSO from platinum with $P[C_6H_4\text{-}4\text{-}SiMe_{3-n}(C_2H_4C_6F_{13})_n]_3$ ($n = 1, 2$) (L) to generate highly soluble [Pt(C-N)ClL] and [{Pt(C-N)L}$_2$(4,4′-bipy)] in which the fluorinated ligand has no electronic impact on the fullerene moieties [69].

In the area of bidentate ligands, coordination of a 2,2′-fluorous-tagged-bipyridine to $[Re(CH_3)O_3]$ generates a molecular olefin epoxidation catalyst [70]. Ligand-bridged dinuclear [{Cp*RhCl$_2$}(L-L)] and cationic mononuclear [Cp*RhCl(L-L)]$^+$ complexes are formed in the cleavage of $[Cp^*RhCl_2]_2$ with a perfluoroalkylated diphenylphosphinoethane ligand [71]. Displacement of one equivalent of cyclooctadiene (COD) from $[Rh(COD)_2](BF_4)$ or $[Rh(COD)_2](BPh_4)$ with perfluoroalkylsilyl dppe ligands generates [Rh(COD)(L-L)]$^+$ cations; [Rh(COD){$P(C_6H_4\text{-}4\text{-}SiMe_2C_2H_4C_6F_{13})_2CH_2CH_2P(C_6H_4\text{-}4\text{-}SiMe_2C_2H_4C_6F_{13})_2$}]$(BPh_4)$ has been structurally characterised [72]. Alternatively, displacement of acetylacetonate (acac) from [Rh(COD)(acac)] with fluorous bidentate phosphines, in the presence of fluorous tetraphenyl borate anions, generates highly fluorophilic [Rh(COD)(L-L)]$(BPh^{Rf}{}_4)$ recyclable hydrogenation catalysts [73]. Ligand displacement is also employed in the reaction of $[CpMX(PPh_3)_2]$ (M=Ru, X=Cl; M=Os, X=Br) with fluorous bidentate phosphines to generate [CpMX(L-L)] [74]. Displacement of COD from [MClMe(COD)] (M=Pd, Pt) or $[PtMe_2(COD)]$ with the $P(C_6H_4\text{-}4\text{-}C_6F_{13})_2CH_2CH_2CH_2P(C_6H_4\text{-}4\text{-}C_6F_{13})_2$ ligand affords the desired organometallic [MClMe(L-L)] (M=Pd, Pt) and $[PtMe_2(L\text{-}L)]$ in modest to good yields; [PtClMe(L-L)] has been structurally characterised [75].

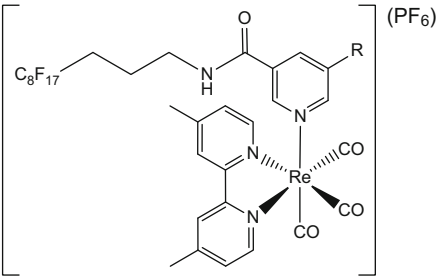
Recently, organometallic systems have been targeted where the fluorous ligand has been engineered for a specific purpose (Fig. 1). Displacement of pyridine from the Grubbs–Hoveyda catalyst with fluorous trialkyl phosphines (**1**) generates new ring-opening metathesis polymerisation catalysts that offer dramatic rate accelerations in a two-phase organic–fluorous system where "phase transfer activation" following phosphine dissociation is envisaged [76–78]. Cleavage of the chloride bridges in $[(p\text{-cymene})RuCl_2]_2$ with a perfluoroalkyl-tagged pyridine generates the anticipated mononuclear complexes (**2**) in high yield [79]. These compounds with fluorous tails show greater uptake by tumoral cells than analogues with long alkyl tails and are thermoresponsive, exerting considerable chemotoxicity on mild hyperthermia. Three luminescent rhenium(I) bipyridyl complexes [Re(CO)$_3$(4,4′-dimethylbipy)$L^{Rf}$]$(PF_6)$ (**3**) [80] and the closely related $[Re(CO_3)(phen^R)L^{Rf}](PF_6)$ ($phen^R$=phen/4,7-diphenylphen/3,4,7,8-tetramethylphen) (**4**) [81], prepared by displacement of acetonitrile from the parent organometallic complexes, have been investigated as trifunctional biological probes that have luminescent properties for detection and a reactive group for bioconjugation and exploit the perfluoroalkyl functionalisation for straightforward isolation using fluorous solid-phase extraction.



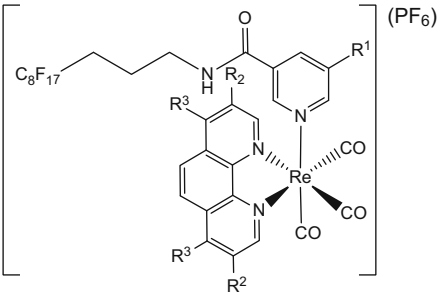

(**1a,** m = 2, $R_f = C_6F_{13}$);
(**1b,** m = 2, $R_f = C_8F_{17}$);
(**1c,** m = 2, $R_f = C_{10}F_{21}$);
(**1d,** m = 3, $R_f = C_8F_{17}$)




(**2a,** $R_f = C_6F_{13}$);
(**2b,** $R_f = C_8F_{17}$);
(**2c,** $R_f = C_{10}F_{21}$)




(**3a,** R = $NH_2$);
(**3b,** R = NCS);
(**3c,** R = NHC(S)NHEt)




(**4a,** $R^1 = NH_2$, $R^2 = R^3 = H$);
(**4b,** $R^1$ = NCS, $R^2 = R^3 = H$);
(**4c,** $R^1$ = NHC(S)NHEt, $R^2 = R^3 = H$);
(**4d,** $R^1 = NH_2$, $R^2 = R^3 = Me$);
(**4e,** $R^1$ = NCS, $R^2 = R^3 = Me$);
(**4f,** $R^1$= NHC(S)NHEt, $R^2 = R^3 = Me$);
(**4g,** $R^1 = NH_2$, $R^2$ = H, $R^3$ = Ph);
(**4h,** $R^1$ = NCS, $R^2$ = H, $R^3$ = Ph);
(**4i,** $R^1$= NHC(S)NHEt, $R^2$ = H, $R^3$ = Ph)

**Fig. 1** Designer organometallic complexes incorporating perfluoroalkyl-functionalised ligands

# 3 Organometallic Complexes with Fluorous Organic Ligands

## *3.1 Cyclopentadienyl Metal Complexes*

Given the ubiquity of the cyclopentadienyl (Cp) and related ligands in organometallic chemistry, it is not surprising that the first perfluoroalkyl-substituted Cp ligand ($Cp^{Rf}$) was reported relatively soon after Horváth and Rábai's seminal paper, and a number of both early and late transition metal-$Cp^{Rf}$ complexes have been reported. A number of groups found that the usual, direct route to functionalised cyclopentadienes (Fig. 2), the reaction of a metal cyclopentadienide with a

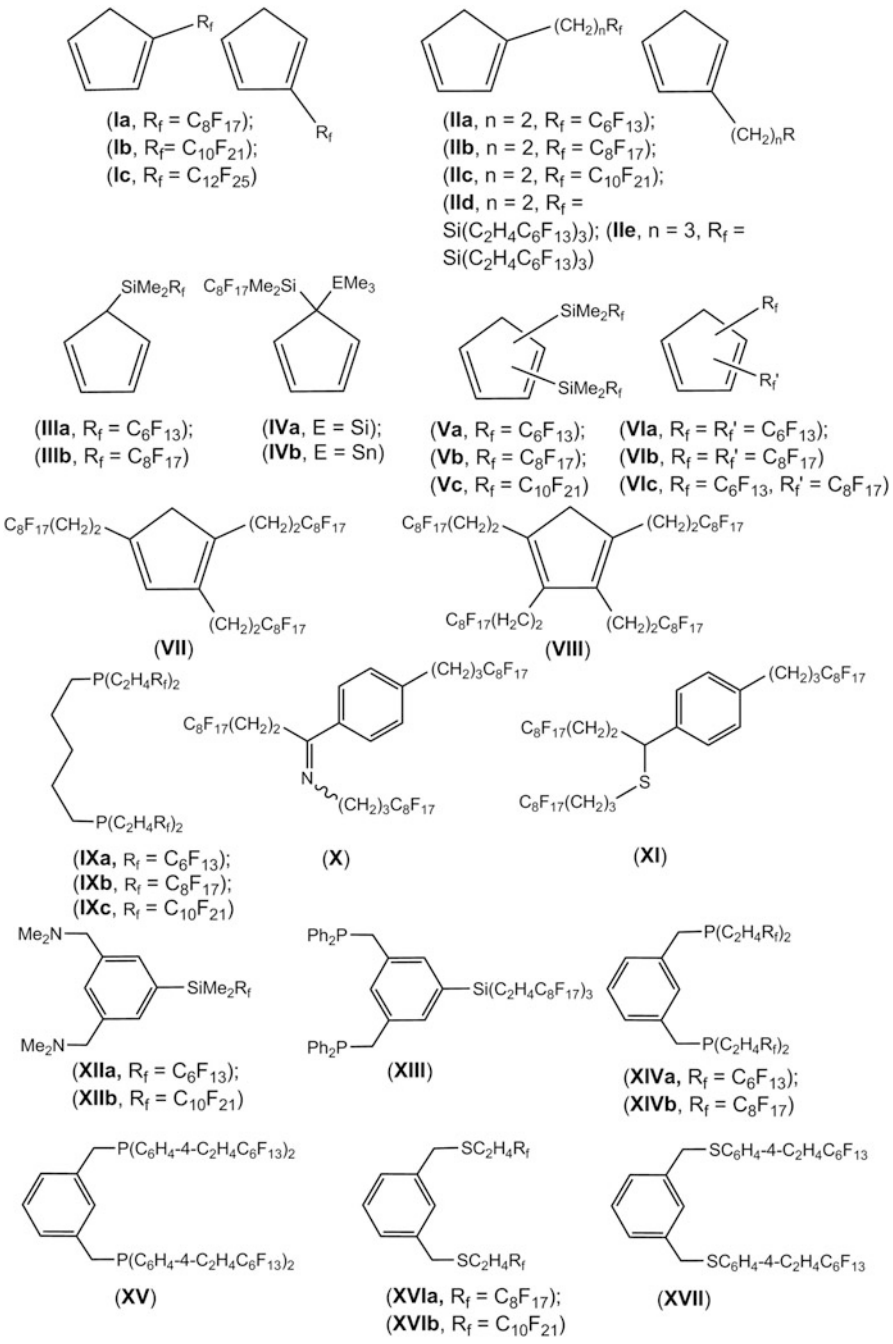



**Fig. 2** Perfluoroalkylated pre-ligands and ligands

perfluoroalkyl iodide, gave complicated mixtures of products with the desired perfluoroalkyl cyclopentadienes (**I**) produced in poor yields. In contrast, Hughes and Trujillo [82] adapted Månsson's methodology [83] through the reaction of nickelocene with the appropriate iodide in the presence of triphenylphosphine, to give a series of mixtures of the respective double bond isomers. The dienes with the fluorous ponytail directly attached demonstrated very different properties to those containing the short ethylene spacer unit. Whilst the latter were stable in solution for several days at room temperature and could be deprotonated with butyl lithium to give synthetically useful anions (vide infra), the former dimerise relatively quickly in solution and decomposed on attempted deprotonation. Low-temperature reactions of the more stable lithium cyclopentadienide of (**IIc**) with $[MBr(CO)_5]$ (M=Mn, Re) or of (**IIa**, **IIb**, **IIc**) with $FeCl_2{\cdot}2THF$ gave the first light fluorous cyclopentadienyl metal complexes with one or two fluorous substituents, respectively. Alternatively, the reaction of (**Ib**, **Ic** or **IIc**) with $[Co_2(CO)_8]$ in the presence of 1,3-cyclohexadiene gave the desired $Cp^{Rf}Co(CO)_2$ complexes (Fig. 3; **5a–c**) with and without the ethylene spacer group, although the latter could only be isolated in relatively low yield. As expected, although these light fluorous complexes are soluble in perfluorinated solvents, they are not preferentially soluble in the fluorous phase of a fluorous–organic biphasic system. Later, Horváth and Hughes extended this chemistry to the synthesis of $[Cp^{Rf}Rh(CO)_2]$ (**5d**) and $[Cp^{Rf}Rh(CO)\{P(C_2H_4C_6F_{13})_3\}]$ by the reaction of the $LiCp^{Rf}$ with $[Rh(CO)_2Cl]_2$ and, subsequently, ligand substitution [84]. Most recently [85], the iridium analogue, $[Cp^{Rf}Ir(CO)_2]$ (**5e**), has been used to study photolytic C–H activation and dehydrogenation processes of alkanes (methane, cyclopentane, cyclohexane) in $CF_3C_6F_{11}$. Here, the light fluorous complex–perfluorinated solvent combination engenders both enhancements in catalyst stability and unprecedented reactivity; for example, methane undergoes photolytic oxidative addition to generate $[Cp^{Rf}Ir(CO)(CH_3)(H)]$ under 1 bar pressure at room temperature.

There have been three reports on the synthesis of fluorous analogues of the ubiquitous Cp* ligand. Tetramethylcyclopenta-1,3-dienes with $C_6F_{13}$, $C_8F_{17}$ or $C_{10}F_{21}$ side chains on reaction with rhodium precursors yielded the anticipated $[Cp^{*Rf}Rh(CO)_2]$ (**6a**) and $[Cp^{*Rf}RhCl_2]_2$; exemplars of both have been structurally characterised [86, 87]. Cleavage of the chloride-bridged dimer with $PMe_3$ or a series of pyridines generated rhodium(III) piano-stool monomers with single $C_6F_{13}$ ponytails [88]. Reduction in the presence of ethylene or various dienes, on the other hand, affords rhodium(I) bisalkene complexes (**6b–e**) [87].

Elsewhere, silicon-based chemistry has been used in order to elaborate cyclopentadienyl ligands with fluorous ponytails. The light fluorous cyclopentadienes with a single fluorous ponytail (**III**, **IV**) were readily prepared by the reaction of $RfSiMe_2Cl$ with LiCp or $LiC_5H_4EMe_3$ (E = Si, Sn) [89, 90]. As expected, the monosubstituted species were obtained as mixtures of the 1-, 2- and 5-isomers, of which the 5-isomer was the major species, and the disubstituted species as highly complex mixtures, of which the 5,5-isomer was the major species. The pre-ligand (**Vb**) with two fluorous ponytails was prepared similarly, again as a mixture of isomers, following lithiation of the previously isolated (**IIIb**) and

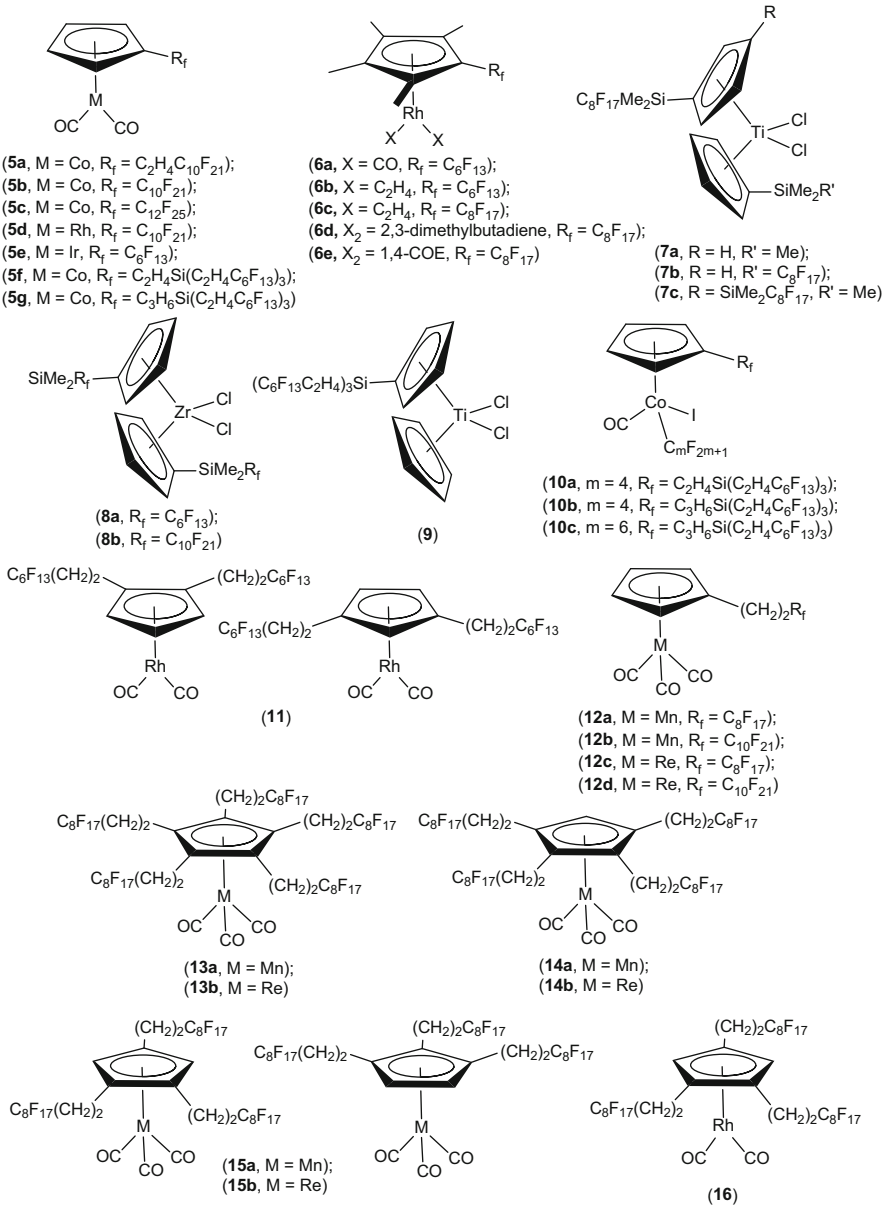



**Fig. 3** Perfluoroalkylated cyclopentadienyl metal complexes

reaction with a further equivalent of $RfSiMe_2Cl$ [89]. On the reaction of (**IVb**) with $TiCl_4$, loss of trimethyltin gave a good yield of the $[Cp^{Rf}TiCl_3]$ complex with a single ponytail. Alternatively, using well-established protocols from non-fluorous chemistry, $LiCp^{Rf}$ from (**IIIb** and **Vb**) on reaction with $Cp^{SiMe3}TiCl_3$ gave

asymmetric bis-cyclopentadienyltitaniumdichlorides (**7a**, **7c**) with one or two ponytails, respectively, whilst reaction of $LiCp^{Rf}$ with $TiCl_3$, followed by oxidation with $PbCl_2$, gave the highly-insoluble symmetrical bis-Cp complex with two ponytails (**7b**), which has been crystallographically characterised [89]. Extending these methodologies has been used to make $[Cp^{Rf2}TiCl_3]$ with two ponytails and the asymmetric $[Cp^{Rf}Cp^{Rf2}TiCl_2]$ with three ponytails [90]. In closely related chemistry, the symmetrical bis-Cp zirconium dichloride complex (**8a**) was prepared from the reaction of the cyclopentadienyl lithiate with $ZrCl_4$ and has been structurally characterised [91]. Van Koten has taken this zirconocene derivative further, demonstrating that the dichlorides can be converted into the dimethyl complexes in a stoichiometric reaction with MeLi. The dichloride has also been used, in the presence of methylaluminoxane (MAO), as an ethylene polymerisation catalyst, which interestingly appeared to be more robust than the standard catalyst leading to increased productivity over prolonged polymerisation times [91]. The related zirconocene dichloride (**8b**) with $C_{10}F_{21}$ substituents has also been reported [92].

Various attempts to increase the number of perfluoroalkyl substituents on the cyclopentadienyl ring have been made. $[Cp^{Rf}CpTiCl_2]$ (**9**) can be formed via a similar protocol to that described above using $BrSi(C_2H_4C_6F_{13})_3$ and LiCp, followed by lithiation and reaction with $CpTiCl_3$ [93]. Recently, cyclopentadienes with the same three-tailed silane unit, but separated from the ring by ethyl or propyl spacer units (**IId**, **IIe**), were prepared in three steps from the chloroalkyltrichlorosilanes as mixtures of the 1- and 2-isomers [94]. The subsequent reaction using the $[Co_2(CO)_8]$/1,3-cyclohexadiene approach gave the desired $[Cp^{Rf}Co(CO)_2]$ complexes (**5f**, **5g**) in good yields. Oxidative addition of medium and long perfluoroalkyl iodides to these cobalt(I) derivatives afforded cobalt(III) complexes (**10**) with both functionalised Cp rings and directly metal-bound fluoroalkyl ligands [94]. Reaction of $LiCp^{Rf}$ with 2-(perfluoroalkyl)ethyl triflates afforded inseparable mixtures of four isomers of cyclopentadienes with two fluorous ponytails (**VI**) [95]. Lithiation and reaction with $[Rh(CO)_2Cl]_2$ gave mixtures of the [1,2- and 1,3-$\{C_5H_3(C_2H_4C_6F_{13})_2\}Rh(CO)_2$] (**11**), whilst reaction with $FeCl_2{\cdot}2THF$ gave highly fluorophilic tetrasubstituted ferrocenes as mixtures of the bis-1,2, bis-1,3 and mixed 1,2/1,3 regioisomers [96]. Alternatively, the pre-ligands with two ponytails [**Va**, **Vc**] on lithiation and reaction with $ZrCl_4$ generate zirconocene dichloride complexes with four perfluoroalkyl substituents, for which the $C_6F_{13}$ complex has been structurally characterised [92].

An alternative approach to fluorous cyclopentadienes involves the reaction of preformed metal complexes. Acylation of ferrocene with perfluoroalkylated acyl chlorides with $C_2H_4$ spacers [97] or $C_{10}H_{20}$ spacers [98] in the presence of $AlCl_3$ generates, depending on stoichiometry, mono- or di-acylated ferrocenes. Reduction readily affords complexes with $(CH_2)_3C_6F_{13}$ or $(CH_2)_{11}C_6F_{13}$ ponytails respectively. $[(\eta^5\text{-}C_5H_4Br)M(CO)_3]$ (M = Mn, Re) undergoes a palladium-catalysed cross-coupling reaction with $IZn(CH_2)_2Rf$ to generate the associated $Cp^{Rf}M(CO)_3$ (**12**) with a single fluorous ponytail in high yields [99, 100]. This approach can be extended to multiply functionalised Cp metal complexes. $[(\eta^5\text{-}C_5Br_5)M(CO)_3]$, $[(\eta^5\text{-}C_5HBr_4)M(CO)_3]$ or $[(\eta^5\text{-}1,2,3\text{-}C_5H_2Br_3)M(CO)_3]$ (M = Mn, Re) reacts with

$IZn(CH_2)_2Rf$ to give fairly complex mixtures of products with varying fluorophilicities, which could be readily separated by chromatography on fluorous silica. The pentabromocyclopentadienyl starting materials gave the desired complexes with five perfluoroalkyl substituents (**13**) in poor yields (Mn = 2 %, Re = 15 %) alongside complexes with four perfluoroalkyl substituents (**14**) in which the fifth bromine had been replaced by a hydrogen atom (Mn = 45 %, Re = 30 % yields) and mixtures of the 1,2,4- and 1,2,3-trisubstituted derivatives (**15**) with two hydrogens (Mn = 7 %, Re = 7 %). The tetrasubstituted (**14**) and trisubstituted (**15**) derivatives were similarly isolated following reactions of the parent tetrabromo or tribromo complexes in 50–55 % yields. One of the standard routes for detaching Cp ligands from transition metals involves high-pressure mercury lamp photolysis of manganese tricarbonyl adducts, which has been applied in this study to liberate the parent cyclopentadienes with three and four perfluoroalkyl substituents (**VII**, **VIII**) in reasonable yields. The application of this route to generate other metal complexes of these polyderivatised ligands was amply demonstrated by the subsequent lithiation of 1,2,4-$C_5H_2(C_2H_4C_8F_{17})_3$ (**VII**) and reaction with $[Rh(CO)_2Cl]_2$ to give the desired $[Cp^{Rf}Rh(CO)_2]$ (**16**) [99, 100]. As expected, the fluorophilicities of these multiply functionalised complexes are very high with "no detectable amount of complex remaining in the toluene phase" of a $CF_3C_6F_{11}$/toluene two-phase system.

## 3.2 Other π-Ligands

In comparison to the studies on functionalised Cp ligands, complexes of other π-donor ligands have received scant attention (Fig. 4). Reaction of the unsymmetrical $F_{17}C_8(CH_2)_3C{\equiv}CSi(CH_3)_3$ alkyne with dicobalt octacarbonyl at low temperature gave the fluorous-functionalised $[Co_2(CO)_6\{\eta^2\text{-}\mu\text{-}F_{17}C_8(CH_2)_3CCSi(CH_3)_3\}]$ in good yield [101]. Fluorous benzenes with 1, 2 or 3 ponytails [102] and more recently with the shorter $-OC(CF_3)_3$ pigtail [103] have been synthesised. Reaction of the former with $Cr(CO)_6$ under standard conditions affords in moderate to good yields the unremarkable piano-stool $[(arene)Cr(CO)_3]$ complexes (e.g. **17**) with 1–3 fluorous substituents [101]; the equivalent reactivity of the latter to generate organometallic derivatives has not yet been reported. Alternatively, reaction of the symmetrical $F_{17}C_8(CH_2)_3C{\equiv}C(CH_2)_3C_8F_{17}$ or unsymmetrical $F_{17}C_8(CH_2)_3C{\equiv}CSi(CH_3)_3$ alkynes with $[CpCo(CO)_2]$ gave the well-established mixed sandwich $[CpCo\{\eta^4\text{-}C_4[(CH_2)_3C_8F_{17}]_2[SiMe_3]_2\}]$ as a mixture of *cis*- and *trans*-isomers with two ponytails for the latter and the quadruply ponytailed $[CpCo\{\eta^4\text{-}C_4[(CH_2)_3C_8F_{17}]_4\}]$ (**18**) for the former [101]. The intriguing possibility of combining this dimerisation complexation with the multiple functionalisation of the Cp ring described above to generate a mixed-π-sandwich complex with eight fluorous ponytails has not yet been pursued.

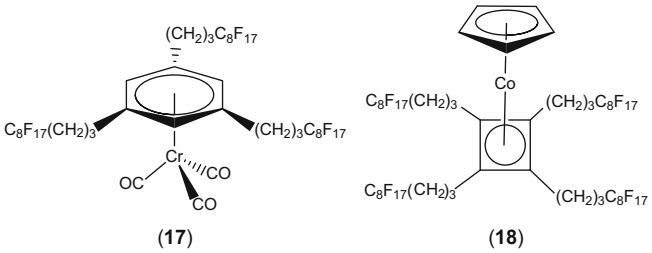



**Fig. 4** Perfluoroalkylated arene metal complexes

## *3.3 Alkyl and Aryl Metal Complexes*

The fluorous analogues of classical organometallic reagents (Grignards, organozincs, organocoppers, aryl lithiates, etc.) have been exploited widely throughout the development of fluorous synthetic chemistry, in most cases without isolation or even identification. In contrast, the number of formally isolated and characterised complexes containing a transition metal-$sp^3$ carbon bond in which the organometallic ligand incorporates a fluorous unit is extremely rare. As outlined above, one of the $Cp^{Rf}Co(CO)Rf$ complexes (**10c**) contains a directly bound $C_6F_{13}$ ponytail [86], whilst $[IrClI(C_2H_4C_8F_{17})(CO)\{P(C_2H_4C_6F_{13})_3\}_2]$ contains a ponytail with a spacer group [47, 49]; both complexes are formed by oxidative addition of the respective alkyl iodides to metal(I) precursors. The reactions of $C_nF_{2n+1}I$ with diethylzinc generate bis(perfluoroalkyl)zinc compounds, $Zn(C_nF_{2n+1})_2{\cdot}2solv$ (solv = MeCN, THF, DMSO), which have been comprehensively characterised in solution by multinuclear NMR [104, 105]. Reaction of 1,6-diiodododecafluorohexane with $ZnEt_2$ generates an unusual bisperfluoroalkyl-bridged dizinc species, $[(solv)_2Zn(\mu^2\text{-}C_6F_{12})Zn(solv)_2]$ (solv = MeCN, 1,3-dimethyl-3,4,5,6-tetrahydro-1(1*H*)-pyrimidinone); the latter has been used as a transfer reagent for the perfluoroalkyl chain to form perfluoro-bridged diaryls in the presence of CuCl [106]. Some experimental details for the isolation of the highly active Lewis acid scandium and ytterbium(III) tris(perfluoroalkylsulfonyl) methide catalysts have been reported [107–110]. The reaction of fluorous-1,5-diphosphinopentanes (**IX**) with $Pd(O_2CCF_3)_2$ in benzotrifluoride at elevated temperatures afforded a small series of palladium(II) PCP pincers complexes (Fig. 5; **19**) with four perfluoroalkyl substituents in modest yields [111]. Metathesis of (**19b**) gave the chloride complex, which has been crystallographically characterised, and further reaction with MeLi gave the palladium–methyl complex, which has limited stability. The striking exception to this situation arises outside the transition metal series where not only have a wide range of fluorous organotin reagents been widely employed as reagents in organic synthesis but also fluorous tin halides, fluorous tin hydrides and fluorous tin allyl complexes have also been prepared and isolated on large scales [2, 112–116], and even the tetraalkyltin complex, $[Sn(C_2H_4C_6F_{13})_4]$, has been described [117].

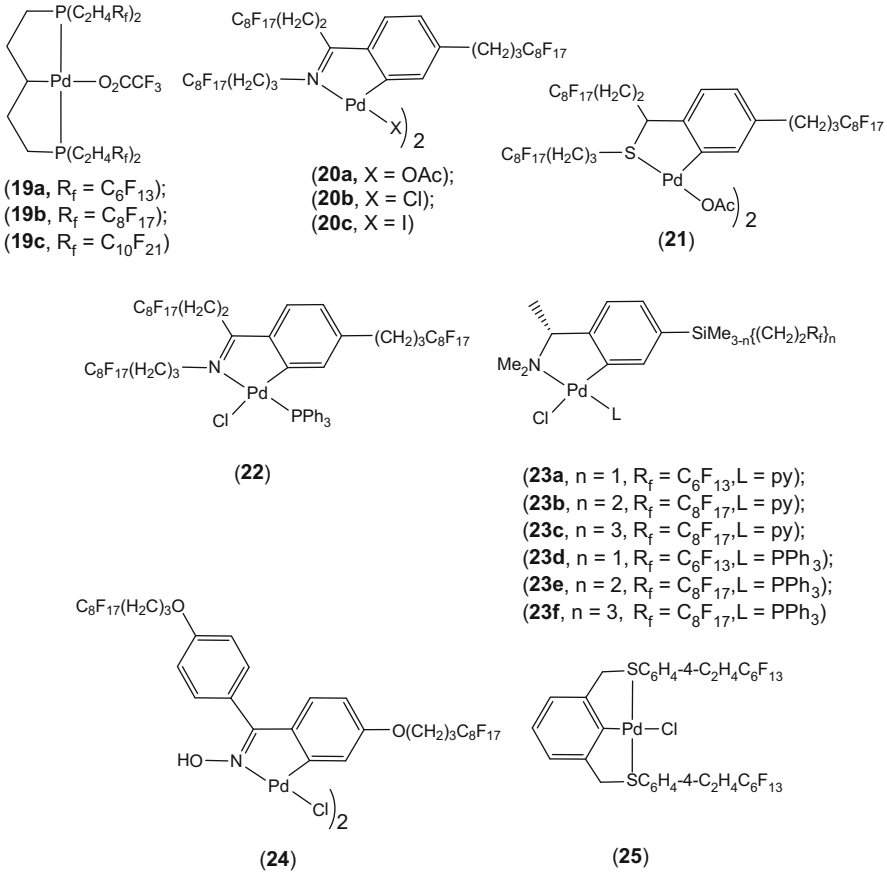


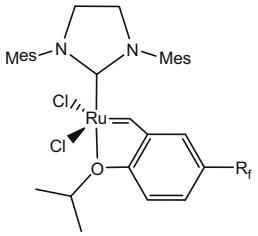

**Fig. 5** Perfluoroalkylated cyclometalated and pincer metal complexes

In a similar vein, there are no reports of unsupported fluorous $sp^2$ hybridised carbon–metal complexes; however, there are a variety of reports of such interactions when they form part of cyclometalated or pincer ligand systems. *Ortho*-C–H activation on the aryl rings in (**X** and **XI**) with palladium acetate readily afforded the cyclopalladated acetate-bridged dimers (**20a** and **21**) with six $C_8F_{17}$ ponytails [118, 119]. These complexes are thermomorphic in that they have little or no solubility in conventional organic solvents at room temperature but have significant solubility at elevated temperatures, but they act mainly as sources of soluble colloidal palladium nanoparticles, rather than as a discrete molecular catalyst, when applied in Heck or Suzuki reactions. The related halide (X = Cl, I)-bridged dimers (**20b**, **20c**) are formed readily for the imine palladacycle, and the bridge can be cleaved with triphenylphosphine to give (**22**). A similar C–H activation protocol with $Pd(OAc)_2$, this time in the presence of LiCl, affords the related chloride-bridged dimers of chiral NC ligands with two, four or six perfluoroalkyl groups

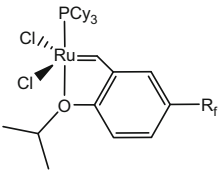
attached via the silyl linker [120]. Bridge cleavage with pyridine or $PPh_3$ generates a series of mononuclear complexes (**23**); the complex with one $C_6F_{13}$ unit and L=$PPh_3$ (**23d**) has been structurally characterised. In 2011, a series of luminescent iridium(III) biscyclometalated cations $[Ir(N\text{-}C)_2(N\text{-}N)](PF_6)$ with two $C_8F_{17}$ ponytails were reported, in which the fluorous substituents appeared to impact positively on the photophysical and biological properties [121]. The oxime-based palladacycle (**24**), formed in a slow reaction of the free oxime with $Li_2PdCl_4$ in acetone at reflux, has been shown to be a highly effective pre-catalyst for Suzuki–Miyaura, Sonagashira, Stille, Heck and Kumada reactions, either in aqueous solution or organic solvents, that could be recycled and reused up to five times [122, 123].

The first metal-pincer ligand complex was reported in 1998. Heteroatom-assisted lithiation of the perfluoroalkylsilyl pre-ligands (**XII**) followed by reaction with metal dichloride reagents gave the desired NCN-metal complexes with one ponytail in high yields; one of the nickel complexes was structurally characterised [124]. In a standard Kharasch addition reaction of $CCl_4$ to methyl methacrylate in dichloromethane, the nickel complexes exhibited almost identical activities to that of the analogous, underivatised pincer complex. Three groups have reported closely related PCP pincer metal complexes; firstly, van Koten et al. described the synthesis of the ruthenium(II) complex with three $C_8F_{17}$ ponytails attached via a silyl spacer to the arene unit in (**XIII**) [125]. Incorporating the fluorous ponytails using the phosphorus donors is an alternative approach: The trialkylphosphine PCP pre-ligands (**XIV**) react readily with $Pd(O_2CCF_3)_2$ or $[IrCl(COE)_2]_2$ (COE = cyclooctene) to generate square planar palladium(II) or trigonal bipyramidal iridium(III) complexes, each with four perfluoroalkyl groups; the Pd (II) complex with $C_8F_{17}$ groups has been structurally characterised [126]. The triarylphosphine PCP pre-ligand (**XV**) reacts with either $NiCl_2{\cdot}6H_2O$, $PdCl_2(MeCN)_2$ or $PtCl_2(COD)$ to generate the anticipated square planar complexes [127]. The palladium(II) complex performed reasonably as a catalyst for the Heck reaction under standard conditions and was recycled four times using a fluorous solid-phase extraction protocol. Analogous alkyl- and aryl-SCS pre-ligands (**XVI** and **XVII**) have also been reported [128, 129]. Coordination of the pre-ligands to palladium(II) is straightforward affording complexes with two fluorous ponytails, and the aryl-SCS-PdCl complex (**25**) has been structurally characterised. These complexes have all been evaluated as catalysts for the Heck reaction and, whilst the S-alkyl catalyst precursors are consumed during the reaction, the S-aryl catalyst could be recycled three times using a fluorous solid-phase extraction approach.

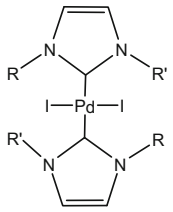
The final area where perfluoroalkyl groups have been incorporated into carbon-based ligands for coordination to a metal centre is in functionalised benzylidenes for the synthesis of Grubbs–Hoveyda-type catalysts (Fig. 6) and their applications in alkene metathesis. In the first of these, a fluorocarbon-soluble acrylate polymer bearing the key isopropoxystyrene unit for coordination was reacted with the Grubbs–Hoveyda catalyst in the presence of CuCl for styrene group exchange [130]. The air-stable catalyst (**26a**) was tested in a series of ring-closing metathesis (RCM) reactions, with a variety of di-, tri- and tetrasubstituted dienes, delivering



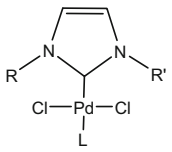

(**26a**, $R_f$ = fluorous polyacrylamide);
(**26b**, $R_f = C_6F_{13}$);
(**26c**, $R_f = C_2H_4C_8F_{17}$);
(**26d**, $R_f = Si(C_2H_4C_8F_{17})_3$



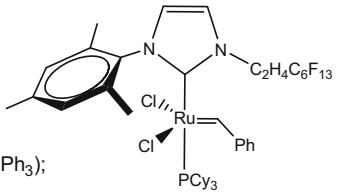

(**27a**, $R_f = C_6F_{13}$);
(**27b**, $R_f = C_2H_4C_8F_{17}$);
(**27c**, $R_f = C_3H_6C_8F_{17}$)



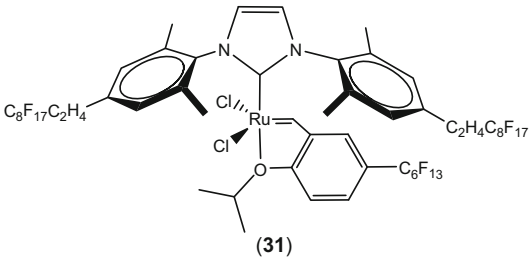

(**28a**, R = Me, R' = $C_2H_4C_6F_{13}$);
(**28b**, R = Me, R' = $C_2H_4C_{10}F_{21}$);
(**28c**, R = R' = $C_2H_4C_6F_{13}$);
(**28d**, R = R' = $C_2H_4C_8F_{17}$)




(**29a**, R = Me, R' = $C_2H_4C_{10}F_{21}$, L = $PPh_3$);
(**29b**, R = R' = $C_2H_4C_6F_{13}$, L = $PPh_3$);
(**29c**, R = R' = $C_2H_4C_6F_{13}$, L = 3-Cl-$C_5H_4N$)




(**30**)




(**31**)

**Fig. 6** Perfluoroalkylated benzylidene and *N*-heterocyclic carbene metal complexes

excellent conversions. The catalyst could be readily recovered following extraction with FC-72 and up to 20 catalyst recovery/reuse cycles were demonstrated. More conventional molecular first- and second-generation Grubbs–Hoveyda catalysts have been prepared (**26b–d**; **27a–c**) with a directly attached $C_6F_{13}$ ponytail [131], spacer $(CH_2)_{2/3}C_8F_{13}$ ponytail [132] and a silyl spacer with three $C_2H_4C_8F_{17}$ ponytails [133]. Each of these catalysts shows good activity in model RCM reactions, with recovery/reuse cycles (up to five times) either via a fluorous solid-phase extraction protocol or via noncovalent immobilisation on fluorous silica gel. Most recently, the functionalised benzylidene complexes (**26b**, **27a**) have been converted into their fluorocarboxylate salts to improve their fluorophilicities [134]. Whilst the two complexes with the linear $C_6F_{13}$ carboxylate ligands are modestly fluorophilic, those complexes with the perfluoropolyoxyalkanoate ligands are highly fluorophilic, in line with this group's observations on functionalised silver NHC complexes (vide infra). Whilst those complexes with linear

carboxylates showed reasonable activities in RCM reactions, those with branched carboxylate ligands were virtually inactive, suggesting that steric crowding at the ruthenium centre is an issue for these species.

## *3.4 NHC Metal Complexes*

The versatility and applications of *N*-heterocyclic carbene ligands in catalysis and beyond is now extremely well established. However, the number of reports of fluoroalkylated NHC ligands and their complexes is relatively small (Fig. 6). In 2000, rotationally equilibrated, 1:1 mixtures of the *trans-anti* and *trans-syn* isomers of the palladium(II) complexes (**28a**) with two ponytails were generated readily in the reaction of the parent imidazolium salt with $Pd(OAc)_2$, for which the *trans-anti* isomer has been structurally characterised [135]. Presumably, a similar isomeric mixture of *trans*-$[PdI_2(NHC)_2]$ (**28b**) with one $C_2H_4C_{10}F_{21}$ ponytail per NHC ligand (generated in situ but not isolated) and preformed, or generated in situ, *trans*-$[PdCl_2(NHC)(PPh_3)]$ (**29a**) with one $C_2H_4C_{10}F_{21}$ ponytail have each been used in Mizoroki–Heck arylations of α,β-unsaturated acids in a fluorous ether with similar activities and separation characteristics [136]. In closely related work, *trans*-$[PdCl_2(NHC)(PPh_3)]$ (**29b**) [137] and *trans*-$[PdCl_2(NHC)(3\text{-chloropyridine})]$ (**29c**) [138], both with two $C_2H_4C_6F_{13}$ ponytails, have been tested as catalysts for Suzuki cross-coupling reactions. Finally in palladium(II) chemistry, the more heavily perfluoroalkylated *trans*-$[PdI_2(NHC)_2]$ complexes with either four $C_2H_4C_6F_{13}$ (**28c**) [135] or four $C_2H_4C_8F_{17}$ (**28d**) [139] ponytails have been reported separately, the former being structurally characterised.

Elsewhere, the perfluoroalkylated analogue of the Grubbs-II catalyst with a single $C_2H_4C_6F_{13}$ ponytail on the carbene (**30**) has been prepared [140], ostensibly to enhance the solubility of such catalysts in $scCO_2$, but, to date, further work with this complex has not been published. Three perfluoroalkyl units have been attached to a Grubbs–Hoveyda-type catalyst via both the benzylidene and a symmetrically substituted NHC (**31**) [132]. This catalyst showed higher activity in the challenging RCM of a tetrasubstituted diene than the commercially available catalyst, but recycling of the catalyst has not been described. The reactions of perfluoroalkylated imidazolium salts with silver oxide in acetonitrile gave silver NHC complexes, formulated as $[Ag(NHC)_2][AgX_2]$ (X = I, OTf) on the basis of $APCI^+$ MS. The analogous complexes formed from imidazolium salts functionalised with perfluoropolyether ponytails exhibit enhanced fluorophilicities, which the authors ascribe to the enhanced flexibility of the perfluoropolyether over the conventional perfluoroalkyl ponytail [28].

## 4 Conclusions and Future Prospects

In the past 20 years, the synthetic challenges of incorporating long perfluoroalkyl ponytails into organometallic complexes have, for the most part, been overcome through the development and adaptation of existing methodologies. These have generated fluorous analogues of almost every class of organometallic complex that have, almost without fail, been thoroughly characterised analytically and spectroscopically, generating a large amount of new insight into fluorous systems. Studies on the single most extensively studied class of organometallic complex, the Vaska's analogues, have been used to establish the electronic influence of incorporating the fluorinated substituents, but, perhaps, the insight into the role of the fluorous solvent and/or substituents on the kinetics and mechanism of oxidative addition in these systems, mentioned in the work from two groups [47, 50], has been overlooked. Structurally, more than 20 single crystal structure determinations have been reported on fluorous organometallic complexes, and these reveal two significant facts: The perfluoroalkyl groups have little or no impact upon the key structural features in the first metal coordination sphere (M–L bond lengths, L–M–L′ bond angles), but they dominate the packing in the solid-state generating fluorous and non-fluorous domains throughout the extended structures. Another aspect that has received considerable attention is the relative partition coefficients of organometallic complexes within organic–fluorous two-phase systems. However, the realisation that the FBS system (as originally conceived) is untenable on an industrial scale, due to the cost of and environmental factors associated with perfluorocarbon solvents, has led to the development of light fluorous and thermomorphic approaches to separation diminishing the importance of relative partition coefficients.

Isolated organometallic compounds, as outlined above, or perfluoroalkylated organometallic catalysts generated in situ, have been evaluated in a diverse range of catalytic processes, with particular emphasis on oxidations, reductions and C–C bond-forming reactions. Generally, these fluorous organometallic systems have performed adequately, some better, some worse, in terms of catalytic activity or selectivity, than other systems reported in the academic literature. The recovery and reuse of the catalysts, combined with the amount of metal leaching to the product phase, have been determined for many systems, but to date none has performed sufficiently better than their non-fluorous counterparts to warrant their development beyond laboratory scale systems.

Where will fluorous organometallic chemistry go in the future?

Firstly, the concerns over the bioaccumulation of the degradation products from organic molecules with the archetypal fluorous ponytails, $C_6F_{13}$ or $C_8F_{17}$, are challenging the fluorous community to consider alternative strategies. A number of reports on two of these, the incorporation of perfluoro-*t*-butoxy or perfluoropolyethers, have appeared in the synthetic organic chemistry literature. The recent observation [28] of enhanced fluorophilicity of species functionalised with perfluoropolyether groups over those with perfluoroalkyl groups is a clear signpost of a

direction to be followed in organometallic chemistry. Secondly, insight is provided by the recent work on the engineering of organometallic systems in which the fluorous substituent imparts specific, even unique, biological properties to the organometallic complex [79–81], and this is undoubtedly an area that is going to grow in the next few years. We look forward to the continued evolution of research in fluorous organometallic chemistry.

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# Index