ACS Catalysis

Perspective

pubs.acs.org/acscatalysis

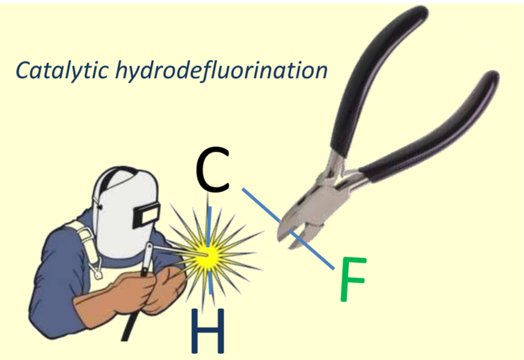
Catalytic Hydrodefluorination with Late Transition Metal Complexes

Michael K. Whittlesey*,† and Eduardo Peris*,‡

†Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, U.K.

‡Departamento de Química Inorgánica y Orgánica, Universitat Jaume I, Avda. Sos Baynat s/n, 12071 Castellón, Spain

ABSTRACT: This perspective article focuses its attention on the most recent advances in hydrodefluorination processes catalyzed by late transition metal complexes, a field that has been a matter of increasing interest during the past decade. The evolution of catalytic hydrodefluorination is treated by giving precise information on the nature of the catalysts, reductants and fluoroorganic substrates that have been used until now. An overview of the mechanistic studies that have been performed so far is also given.



KEYWORDS: *hydrodefluorination, catalysis, transition metal complexes, fluorinated compounds, C−F activation*

1. INTRODUCTION

The importance of organofluorine compounds in all aspects of the chemical industry is striking, but the fact that as many as 30−40% of agrochemicals and 25% of pharmaceuticals on the market are estimated to contain fluorine, including three of the top five drugs sold in 2013,[1] helps to explain why the demand for fluorinated molecules continues to grow at a tremendous speed. Because the properties of organic molecules, including stability, lipophilicity, and bioavailability, can be dramatically altered by the introduction of one or a small number of fluorine substituents,[2] a range of diverse synthetic strategies have been developed for the introduction of fluorine into biologically relevant molecules. This has been treated extensively in several books[3] and reviews,[4] and the area is currently considered as "a hot topic",[4f,5] although the interest in the field has been ongoing for over 35 years.[6] The reverse reaction, the selective cleavage and functionalization of a C−F bond, can also be considered as a pathway to the synthesis of fluoroorganic molecules,[7] for example, by transforming polyfluorinated species into partially fluorinated analogues. As simple perfluorinated substrates are readily available on an industrial scale, their use as synthons for the formation of lower fluorine-containing products is a highly attractive proposition. The study of processes allowing the substitution of fluorine by other functional groups represents not only an intellectual challenge but may also provide knowledge to more effectively approach the reverse reaction, the fluorination of organic molecules.

Fluorocarbons are highly resistant to aerobic degradation, and their atmospheric lifetimes can exceed 2000 years (see Table 1).[8] Fluoroalkenes are global-warming gases, and chloro-fluorocarbons (CFCs) have both global warming and ozone-depletion potential.[9] Some of the interest in the chemistry of fluoroorganic molecules has been boosted by the need to convert CFCs to hydrogenated derivatives with lower ozone-depletion potential.[8a]

Table 1. Atmospheric Lifetimes of Some Fluorocarbons[8b]

compound	atmospheric lifetime (years)
CF_4	$>5.0 \times 10^4$
C_2F_6	$>1.0 \times 10^4$
C_4F_{10}	$>2.6 \times 10^3$
C_5F_{12}	4.1×10^3
C_6F_{14}	3.1×10^3
CF_3Cl	1.7×10^3
CF_3CF_2Cl	300
SF_6	3.2×10^3

When fluorine binds to carbon, it forms the strongest single bond to a heteroatom that carbon can form. In addition to the thermodynamic stability of fluorocarbons, kinetic issues also explain the inertness of C−F bonds, thus making C−F bonds among the most unreactive functionalities in chemistry.[10] This situation, which is generally true for aliphatic C−F bonds, may be questionable for some aromatic C−F bonds, whose activation may imply noncatalyzed aromatic nucleophilic substitutions (S_NAr), for which the reactivity of aryl halides decreases in the order fluoride > chloride > bromide > iodide.[7a,8a,11] For this type of reaction, addition and subsequent elimination are involved, and the addition is the rate-determining step. This means that the small size and the electron-withdrawing character of the fluorine activates the addition step in fluoroarenes, and this step is more activated when more fluorides are present in the arene. As a

Received: June 23, 2014
Revised: August 6, 2014
Published: August 7, 2014

dx.doi.org/10.1021/cs500887p | ACS Catal. 2014, 4, 3152−3159

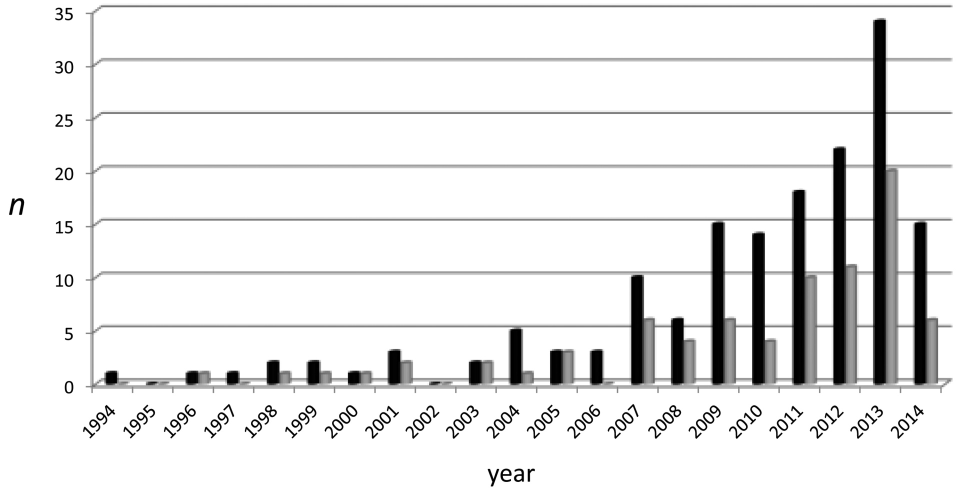


Figure 1. Number of publications (n) dealing with HDF, 1994-June 2014 (source Web of Science). Black bars refer to all HDF reactions. Gray bars refer to catalyzed HDF processes.

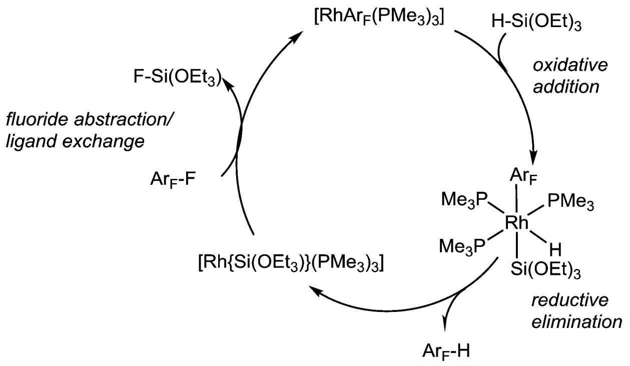
consequence, the activation of the C−F bond in fluorobenzene is a tremendous challenge, whereas hexafluorobenzene can react at room temperature with nucleophiles in the absence of catalysts, despite the fact that both molecules display a similar C−F bond strength (ca. 126 kcal/mol).[12] For aliphatic halides, the nucleophilic addition occurs via an S_N2 reaction, and therefore the bond breaking between the carbon and the halide plays a decisive role (in this case, aliphatic iodides are the fastest to react).[7a,8a] Some organometallic complexes have demonstrated that fluorocarbons can act as reactive molecules,[13] although C−F activation can often produce stable metal-fluoride complexes, which often hamper catalytic turnovers.[7b,14] The most straightforward C−F bond transformation is hydrodefluorination (HDF) which, despite its apparent simplicity, shows a surprising mechanistic diversity.[7,14b,15] The reaction formally involves the activation of a carbon−fluorine bond followed by the introduction of hydrogen to form the final hydrodefluorinated molecule. While C−F bond formation has been a very active research field during the past decade, interest in hydrodefluorination has only flourished in the last 5−6 years, as shown by Figure 1, which illustrates the number of papers dealing with the HDF process.

In this perspective, we do not intend to provide a comprehensive overview of HDF; for this, we recommend two recent reviews on the topic.[7] Instead, we will focus our attention on the most recent advances in HDF processes catalyzed by late transition metal complexes, from the perspective of the metal catalysts, reductants, and fluoroorganic substrates that have been used so far. Other hydrodefluorination processes catalyzed by silylium[10,16] and phosphonium ions,[17] other main group elements,[18] or by early transition metal complexes[19] will not be discussed. An overview of the experimental and theoretical studies relating to the mechanisms governing the process will also be given.

2. CATALYTIC HYDRODEFLUORINATION BY LATE TRANSITION METAL COMPLEXES

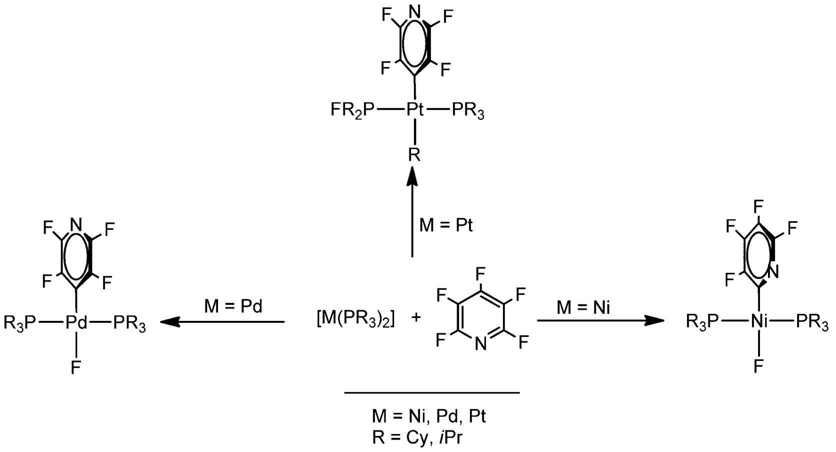
2.1. Selected Early Examples. The first example of a catalytic hydrodefluorination reaction was reported by Swarts in 1920, who developed Pt and Ni alloys for the hydrodefluorination of monofluorinated arenes using hydrogen gas.[20] However, this method suffers from the inconveniences derived from the need for high temperatures and pressures. The field remained silent until 1994, when Milstein and Aizenberg showed that $[Rh(SiMe_2Ph)(PMe_3)_3]$ easily cleaves a C−F bond of C_6F_6 to produce $[Rh(C_6F_5)(PMe_3)_3]$, which reacts further with $(EtO)_3Si{-}H$ to yield C_6F_5H. The second step of the reaction is believed to proceed as a consequence of the oxidative addition of the silane to the metal, followed by reductive elimination of the hydrodefluorinated product. The reaction also works for C_6F_5H, which yields $C_6F_4H_2$.[21] The high affinity of fluoride to form Si−F bonds was used by the authors to remove and replace the silyl ligand at the resulting Rh(I)-silyl complex by the fluorinated aryl (Ar_F), thus closing the well-accepted catalytic cycle (Scheme 1). The overall reaction is energetically favorable, because C−H bonds are stronger than Si−H bonds, whereas Si−F bonds are stronger than C−F bonds. This work is regarded as the first example of a homogeneous system for catalytic HDF.

Scheme 1. Catalytic Cycle for the First Reported Late Metal Catalyzed Hydrodefluorination of Fluoroarenes



2.2. Cobalt, Rhodium, and Iridium. In 1999, Grushin used the rhodium complex $[Rh(H)Cl_2(PCy_3)_2]$ for the homogeneously catalyzed hydrodefluorination of 1-fluoronaphthalene under a pressure of H_2, although the conversions were rather low (40%). The catalyst was also active for the HDF of fluorobenzenes (which are known to be less reactive than fluoronaphthalenes), although, in this case, the process appeared to involve heterogeneous catalysis, as suggested by the mercury-drop test.[11] In the same year, Angelici tethered two rhodium(I) complexes to Pd-SiO_2 and showed that the solid material

Scheme 2. Different Reactivities Shown by $[M(PR_3)_2]$ (M = Ni, Pd, Pt) with C_5F_5N



promoted the hydrogenolysis of fluorobenzene and 1,2-difluorobenzene in the presence of H_2. The synergistic action of both rhodium and palladium facilitated not only the substitution of fluorine by hydrogen but also the reduction of the arene to cyclohexene, although the reaction was not fully selective and always gave mixtures with fluorocyclohexane. A maximum conversion of 89% to cyclohexane was obtained for the reduction of fluorobenzene.[22] This work constitutes an interesting development in catalytic HDF as it suggests for the first time that the synergistic action of two metals may produce some benefits in the HDF process. It also describes a heterogenized catalyst, which can be easily separated from the reaction mixtures, facilitating the purification of the reaction products. In subsequent work, the same authors described the hydrodefluorination of fluorobenzene with H_2 by a SiO_2-supported rhodium metal catalyst and observed that polar protic solvents favored hydrodefluorination to benzene and subsequent hydrogenation to cyclohexane, whereas nonpolar aprotic solvents favored hydrogenation to fluorocyclohexane.[23] More recently, it was demonstrated that a Rh/Al_2O_3-based heterogeneous catalyst is capable of fully defluorinating and hydrogenating polyfluorinated benzenes in water, under mild reaction conditions (room temperature, 1 atm H_2).[24] The observed fluorinated intermediates indicate that adjacent fluorine substituents are removed preferentially.

Some homogeneous rhodium catalysts are known. Thus, $[RhCl(PPh_3)_3]$ proved to effectively hydrodefluorinate fluorinated alkenes with $HSiEt_3$ as the reductant at temperatures as low as 35 °C.[25] $[RhH(PEt_3)_3]$ is also capable of hydrodefluorinating pentafluoropyridine in the presence of H_2 and NEt_3, achieving up to 12 turnovers after 2 days at room temperature.[26] The catalytic reaction was developed after confirming the ability of $[RhH(PEt_3)_3]$ to generate the C−F activation product $[Rh(4\text{-}C_5F_4N)(PEt_3)_3]$ upon reaction with pentafluoropyridine.[27] In a more recent example, the dimetallic complex $[Rh(\mu\text{-H})(dippp)]_2$ (dippe = $i\text{Pr}_2\text{P}(\text{CH}_2)_3\text{P}i\text{Pr}_2$) and was used for the HDF of aromatic fluorocarbons (pentafluoropyridine, hexa- and pentafluorobenzene, and 2,3,5,6-tetrafluoropyridine) using $HSiEt_3$ as the hydrogen source, with up to 19 turnovers after 48 h at 50 °C. The different selectivities found for the reactions carried out with the dimetallic complex $[Rh(\mu\text{-H})(dippp)]_2$ and the monometallic compound $[Rh(H)(\eta^2\text{-HSiEt}_3)(dippp)]$ suggest that two different C−F activation mechanisms may be taking place. The authors propose that [Rh(H)(dippp)] might be an important species in the catalytic cycle and that $[Rh(H)(\eta^2\text{-HSiEt}_3)(dippp)]$ serves as an intermediate for its formation.[28]

Cobalt complexes have been rarely used in the HDF of fluoroarenes. In 2013, $[Co(PMe_3)_4]$ was used for the monohydrodefluorination of octafluorotoluene, hexafluorobenzene, pentafluorobenzene, and perfluorobiphenyl using sodium formate as the hydrogen source.[29]

Despite the well-known activity of iridium complexes in catalytic processes involving C−H activation, their use in C−F bond activation has received only limited attention.[30] The iridium complex tris[2-phenylpyridinato-C,N]iridium(III), $[Ir(ppy)_3]$, has very recently been used to bring about the first photocatalytic HDF of a series of fluoroarenes. The initial idea for using this complex was its inability to form M—F bonds, which in turn avoids the need to use strong fluorophillic reductants, such as aluminum hydrides or hydrosilanes. In this case, an amine is used as reductant, and mono, di- and tri-HDF can be performed in variety of arenes, thus giving access to a number of polyfluoroaromatic rings.[31]

2.3. Nickel, Palladium, and Platinum. An interesting improvement in the catalytic hydrodefluorination of fluoronaphthalene and activated fluorobenzenes was brought about by using a series of Ni(II)-NHC complexes (NHC = N-heterocyclic carbene). In the presence of Et_2CHONa, the reduction of fluoronaphthalene and 4-fluoroanisole gave the corresponding hydrodefluorinated products in very high yields, under relatively mild reaction conditions (3h, 100 °C). However, the catalyst failed to effectively hydrodefluorinate nonactivated fluorobenzenes, such as 4-fluorotoluene (toluene was produced in only 30% yield).[32] The work outlines for the first time the possible use of transfer hydrogenation in HDF reactions as an alternative to the more widely extended use of hydrosilanes, or H_2 at elevated pressure. More recently, platinum on carbon was used to efficiently hydrodefluorinate a series of fluoroarenes in the presence of $i\text{PrOH}/H_2O/Na_2CO_3$. Acetone is produced, thus confirming the suitability of the transfer hydrogenation strategy to facilitate the reduction of C−F bonds.[33]

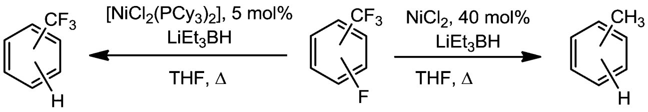
In 2004 Perutz, Braun, and co-workers compared the reactivity of $[M(PR_3)_2]$ complexes (M = Ni, Pd, Pt; R = Cy, *i*Pr) in the activation of fluoropyridines. Although the work does not specifically lead to examples of catalytic hydrodefluorination, it established the basis to explain the different reactivities shown by Group 10 metal complexes. Due to the Pd−F bond being stronger than the related Pt−F bond, the reactivity of $[Pt(PR_3)_2]$ and $[Pd(PR_3)_2]$ with pentafluoropyridine yields different metal species.[34] While the palladium complexes oxidatively add C_5F_5N to yield Pd(II)-F complexes ($[PdF(4\text{-}C_5NF_4)(PR_3)_2]$), the platinum precursors yield $[Pt(4\text{-}C_5NF_4)(R)(PR_3)(PFR_2)]$, resulting from a combination of C−F and P−C bond activation steps (Scheme 2). Under similar conditions, $[Ni(PR_3)_2]$ forms $[NiF(2\text{-}C_5NF_4)(PR_3)_2]$, thus displaying a different regioselectivity to that shown by palladium. This observation was later rationalized by DFT calculations, which suggested that the preferred activation at the 2-position by $[Ni(PR_3)_2]$ involves a phosphine-assisted pathway, in which the fluoride is initially passed from carbon (in C_5F_5N) to phosphorus to form a metallophosphorane intermediate, before it migrates to the metal center. This intermediate can only be formed when the attack occurs at the C−F bond adjacent to the nitrogen center, so that the lone pair of the nitrogen can coordinate to the metal.[35] However, the activation of 1,2,4,5-tetrafluorobenzene with a $Ni(PR_3)_2$ synthon reveals that all possible C−F activation products can be obtained, yielding the corresponding Ni(II) oxidative addition products, but also unwanted byproducts that result from C−H activation.[36] This suggests that the use of nickel for catalytic C−F activation processes may require the right choice of ancillary ligands in order to give the desired chemoselectivity for C−F over C−H bonds. With regard to the role of ancillary ligands facilitating the regioselective activation of C−F bonds, in a very interesting piece of work, it is proposed that the sulfide bridging ligands at $[Pt_2(\mu\text{-}S)_2(dppp)_2]$ trigger the C−F activation of 1,3-difluoro-2-propanol through an S_N2 mechanism, where the O−H···F hydrogen bond established between the alcohol group at the substrate may assist the departure of a/the fluoride anion.[37]

As previously mentioned, in the presence of pentafluoropyridine, $[Pd(P\textit{i}Pr_3)_2]$ affords the oxidative addition product $[PdF(4\text{-}C_5F_4N)(P\textit{i}Pr_3)_2]$. This compound can be transformed into the corresponding hydride complex $[PdH(4\text{-}C_5F_4N)(P\textit{i}Pr_3)_2]$ upon treatment with HBpin (HBpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, pinacolborane). Subsequent reductive elimination affords 2,3,5,6-tetrafluoropyridine. By employing 10 mol % of $[PdH(4\text{-}C_5F_4N)(P\textit{i}Pr_3)_2]$, pentafluoropyridine could be catalytically hydrodefluorinated in the presence of HBpin to give 44% of 2,3,5,6-tetrafluoropyridine.[38]

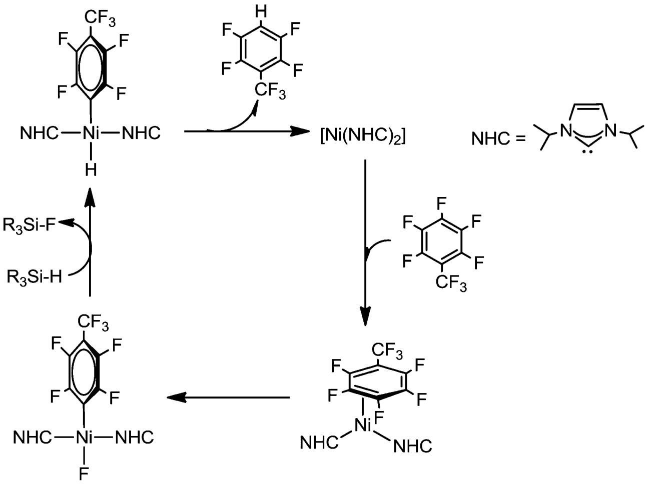
In a more recent example, $[NiCl_2]$ and $[NiCl_2(PCy_3)_2]$ were shown to catalyze the HDF of a series of fluoroarenes and trifluorotoluenes with LiR_3EH (E = B, Al). $[NiCl_2(PCy_3)_2]$ was found to be effective for the HDF of fluoroarenes in the presence of lithium tri-*t*-butoxyaluminum hydride,[39] whereas in the case of trifluorotoluenes, only $[NiCl_2]$ was active, although a high catalyst loading of 40 mol % was needed in order to achieve full HDF of the CF_3 group (Scheme 3).[40] However, addition of $[NiCl_2(PCy_3)_2]$ (2 mol %) as a cocatalyst greatly improves the catalytic activity of $[NiCl_2]$ allowing conversion with only 2 mol %.[41]

The Ni-NHC complex $[Ni_2(\textit{i}Pr_2Im)_4(COD)]$ ($\textit{i}Pr_2Im$ = 1,3-di-isopropyl-imidazolylidene) was demonstrated to be an active catalyst for the HDF of polyfluorinated arenes using hydrosilanes as the reductant. For example, the reaction of hexafluorobenzene with triphenylsilane in the presence of 5 mol % of the Ni(0) catalyst affords 1,2,4,5-tetrafluorobenzene after 2 days at 60 °C. Mechanistic studies pointed to the involvement of the mononuclear fragment $[Ni(\textit{i}Pr_2Im)_2]$ in C−F activation of the fluoroarene, H/F exchange of the resulting nickel fluoride, and lastly reductive elimination from the polyfluoroaryl nickel hydride complex (Scheme 4).[42] The formation of an η^2-C=C complex between a fluoroarene and Ni(0) phosphine fragment [Ni(dippe)] (dippe = $\textit{i}Pr_2P(CH_2)_2P\textit{i}Pr_2$) and further oxidative addition of the metal into the C−F bond was experimentally demonstrated in very recent work.[43] Surprisingly, the same article shows that the HDF process may be promoted in the absence of a metal catalyst or silane, suggesting that HDF reactions may involve just phosphine-mediation.[43]

Scheme 3. Hydrodefluorination of Fluorotoluenes by $NiCl_2$ and $[NiCl_2(PCy_3)_2]$



Scheme 4. Proposed Catalytic Cycle for the HDF of Perfluorotoluene with a $[Ni(NHC)_2]$ Complex

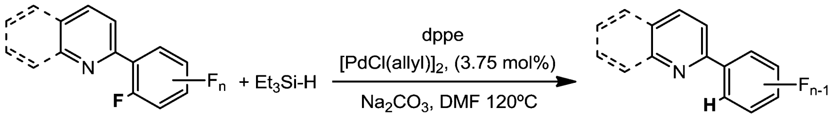


A very recent example of a palladium-catalyzed HDF of polyfluoroarenes was developed by Zhang and co-workers, who described an efficient method for the preparation of partially fluorinated aromatic compounds involving a chelation-assisted, ortho-selective C−F activation of N-heterocyclic-substituted polyfluoroarenes with Et_3SiH (Scheme 5).[44]

2.4. Iron and Ruthenium. Holland and co-workers were the first to describe the catalytic HDF of fluorocarbons using inexpensive iron(II) β-diketiminate fluoride complexes. The hydrodefluorination of perfluorinated aromatic compounds with R_3SiH yielded the singly hydrodefluorinated products in up to five turnovers. It is proposed that the reaction of the hydrosilane with the iron fluoride generates an active Fe−hydride complex, which kinetic studies suggest is the rate-determining step of the reaction.[45] Fluorinated alkenes were also hydrodefluorinated, with up to 10 turnovers in the case of hexafluoropropene.

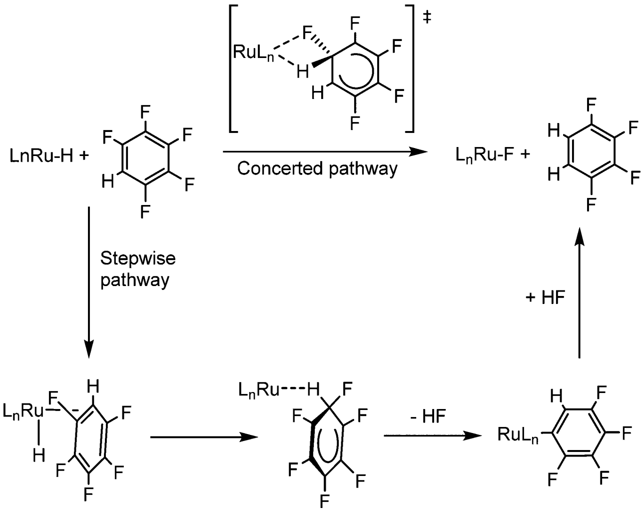
The activity of ruthenium complexes in catalytic HDF was first reported in 2009. The N-aryl substituted N-heterocyclic carbene complexes $[RuH_2(NHC)(CO)(PPh_3)_2]$ were able to facilitate the hydrodefluorination of hexafluorobenzene, pentafluorobenzene, and pentafluoropyridine with a series of alkylsilanes. The turnovers were as high as 200, for the case of the HDF of pentafluorobenzene, and the reaction was shown to be highly selective for the 2-position of pentafluorobenzene and pentafluoropyridine, affording 1,2-substituted partially fluorinated products.[46] This reactivity pattern contrasts with the 1,4-products formed in the Rh- and Fe-catalyzed reactions reported by Milstein[47] and Holland,[45] respectively. Although the authors

Scheme 5. Selective Chelation-Assisted Ortho-Hydrodefluorination of Pyridine-Substituted Polyfluoroarenes



first proposed that the reaction mechanism involved the formation of a fluorinated benzyne intermediate, subsequent DFT calculations revealed that the formation of such an intermediate was 200 kJ mol^{-1} above the reactants, effectively ruling it out as a viable species.[48] The calculations showed instead that after the initial loss of phosphine, nucleophilic attack on the fluorinated benzene (i.e., C_6F_5H) can occur by the two pathways shown in Scheme 6. In both processes, the key feature is the nucleophilic attack of the Ru hydride ligand on the fluoroarene. The overall HDF may then occur either through a stepwise or concerted pathway, as shown in Scheme 6. By this mechanism, a modest barrier of 84.1 kJ mol^{-1} is computed for the formation of 1,2,3,4-$C_6F_4H_2$ from C_6F_5H, consistent with the unusual ortho-selectivity observed experimentally. The NHC ligand plays an important role in both promoting the HDF reaction and determining the regioselectivity of the process.[12] Computed C−F bond dissociation energies (BDEs) for $C_6F_{6-n}H_n$ substrates show an increase with larger *n*, and the energies are sensitive to the number of ortho-F groups present.[12] The combination of this with the opposite trend in the C−H BDEs suggests that the thermodynamics of HDF become less favorable with increased *n*. The two mechanisms were also found to have complementary regioselectivities. For the concerted pathway, the reaction is directed to the sites with two ortho-F substituents, as these have the weakest C−F bonds. In contrast, the reaction along the stepwise pathway is directed to sites with only one ortho-F substituent.[12]

Scheme 6. Two Possible Reaction Pathways for the Ru-Catalyzed Hydrodefluorination of C_6F_5H



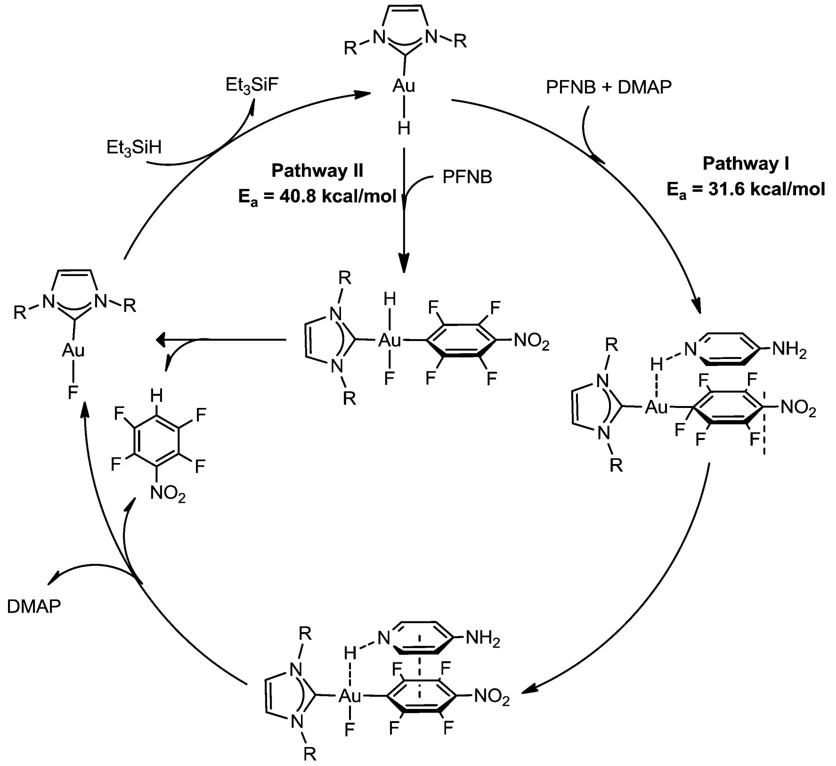
HDF of *p*-$C_6H_4F(CO_2H)$ in a basic aqueous medium by the Ru(III) precursor Ru(IPI)Cl_3 (IPI = 2,6-imidazoylpyridine) becomes more efficient as the concentration of base (KOH) increases. This provides support for a mechanism that involves reversible deprotonation of the protic IPI ligand.[49]

2.5. Copper and Gold. The reactivity of a series of [AuH(NHC)] complexes toward perfluoroarenes revealed a π−π interaction between the gold complex and incoming fluoroarene substrates. This interaction can be detected by NMR and UV−vis spectroscopies. However, subsequent HDF does not occur, basically due to the high activation barrier, which was calculated to be 40.8 kcal/mol. When the strongly electron-donating *p*-*N*,*N*-dimethylaminopyridine (DMAP) is introduced into the reaction mixture, the barrier is reduced to 31.6 kcal/mol. The formation of a π−π intermediate between the DMAP and pentafluoronitrobenzene (PFNB) facilitates the reaction to become catalytic. Scheme 7 shows the two reaction pathways, for the π−π-interaction assisted C−F bond activation (pathway I) and for the one in the absence of DMAP (pathway II).[50] This interesting work illustrates how synergistic effects may have important implications in the design of homogeneous catalyzed reactions by organometallic complexes. The same research group developed a series of tricoordinate gold(I) complexes supported by Xantphos ligands, which exhibited significant activity in the HDF of various types of perfluoroarenes. For example, a turnover number of 1000 was obtained for the HDF of pentafluoronitrobenzene with diphenylsilane using [(*t*BuXantphos)Au-(AuCl_2)] as the catalyst. DFT calculations suggested the key step in the catalytic cycle is the direct oxidative addition of a C−F bond to the gold(I) complex.[51]

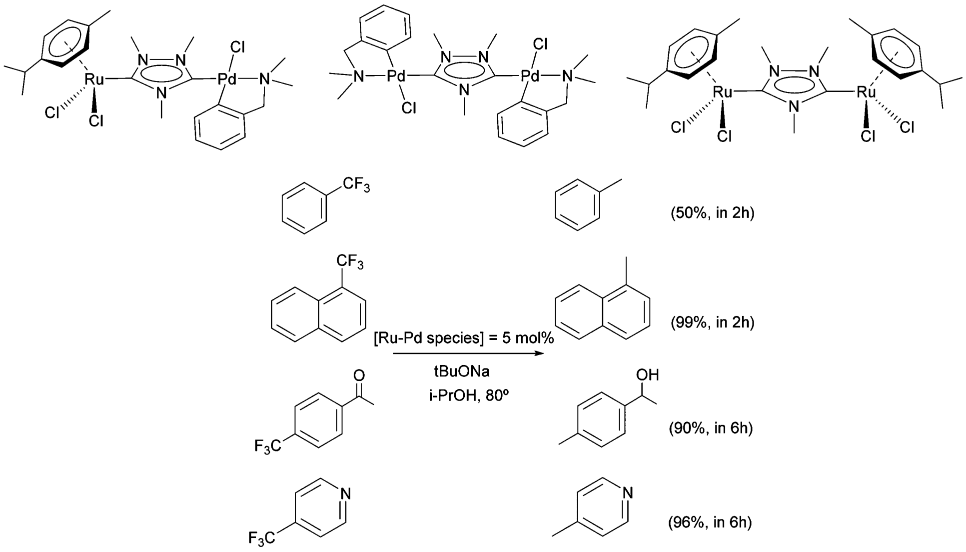
The only example of a copper-catalyzed HDF of fluoroarenes was reported in 2013 by Zhang and co-workers. CuCl in the presence of 1,2-bis(diphenylphosphino)benzene showed high reactivity and regioselectivity toward a broad scope of mono- and poly-fluoroarenes, using a silane as hydrogen source. In the reaction process, copper hydrides were observed. DFT calculations support a mechanism that involves the nucleophilic attack of the copper hydride on the C−F bond.[52]

2.6. Synergistic Action of Two Metals with a Single Frame Ligand. The heterodimetallic complex of Pd/Ru (Scheme 8) with a bridging triazole-diylidine ligand proved to be a very efficient catalyst for the hydrodefluorination of a wide variety of fluoroarenes, affording quantitative yields in very short reaction times, and under mild reaction conditions (*i*PrOH, 80 °C).[53] The observation that the combination of the two different metals is crucial for promoting the process is very interesting. A mixture of the two different homodimetallic complexes of palladium and ruthenium partially catalyzes the process, but the outcome clearly improves when the two different metal fragments are linked by the single-frame ligand. These results support the idea of catalytic cooperativity between the two vicinal metals in the heterometallic complex.[53] The complex is also very active in the hydrodefluorination of more inert aliphatic C−F bonds in a series of trifluoromethyl-toluenes (Scheme 8), thus showing that the Pd/Ru complex behaves as an effective two-component catalyst, capable of activating all types of C−F bonds (aliphatic and aromatic). To justify the activity of this catalyst, a synergistic action between the two metals is suggested, in which the C−F activation is performed by the palladium fragment while the introduction of the hydrogen is facilitated by the ruthenium center through a transfer hydrogenation pathway, in which *i*PrOH is oxidized to acetone.

Scheme 7. Two Reaction Pathways, for the $\pi-\pi$ Interaction-Assisted Gold-Catalyzed C−F Bond Activation (Pathway I) and for the One in the Absence of DMAP (Pathway II)



Scheme 8. (Top) Triazole-di-ylidene Complexes Used in the Study; (Bottom) Results for the Hydrodefluorination of Trifluorotoluenes Using the Pd/Ru Heterometallic Complex



3. OUTLOOK

Overall, remarkable progress has been achieved in the past decade in the transition-metal-catalyzed hydrodefluorination of fluoroorganic molecules. Most of the catalysts used in the process are Ni-, Pd-, Au-, Ru-, and Rh-based, but some other metals, such as Cu, Ir, and Co, are emerging as alternatives to these. With regard to the reductants used, the process is still dominated by the use of strong fluorophilic reagents, such as hydrosilanes and aluminum hydrides. However, interesting alternatives have been published, such as those derived from the use of alcohols and base, which facilitate the incorporation of hydrogen through a transfer hydrogenation pathway, or the recently described photocatalytic processes that allow the use of safe and inexpensive amines as hydrogen sources. From the substrate point of view, most of the articles published to date deal with HDF of aromatic C−F bonds, and among these, those referring to polyfluorinated arenes are the ones that have received most attention. The activation of sp^3 hybridized C−F bonds has been much less studied and would most certainly benefit from greater attention in the near future.

In the cases of both homogeneous and heterogeneous catalysts, most of the examples involve the action of a single metal. In this regard, some efforts have recently been made to explore the synergistic action provided by the combination of two metals, each playing a distinct role.

Significant strides have been made in the last five years in developing experimental and theoretical methods to elucidate the reaction mechanisms underpinning HDF, and major advances have been achieved in the field. With continued efforts, we expect to see additional developments in useful methods in this rapidly developing research area.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: eperis@uji.es.
*E-mail: M.K.Whittlesey@bath.ac.uk.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the financial support from the Ministerio de Economía y Competitividad of Spain (CTQ2011-24055/BQU).

REFERENCES

(1) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432−2506.

(2) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308−319.

(3) (a) *Organofluorine Chemistry: Fluorinated Alkenes and Reactive Intermediates*; Chambers, R. D., Ed.; Springer-Verlag: Berlin, 1997. (b) *Organofluorine Chemistry: Techniques and Synthons*; Chambers, R. D., Ed.; Springer-Verlag: Berlin, 1997. (c) *Fluorine-Containing Synthons*; Soloshonok, V., Ed.; ACS Symposium Series 911; American Chemical Society: Washington, DC, 2005. (d) Kirsh, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004. (e) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, U.K., 2006. (f) *C-H and C-X Bond Functionalization, Transition Metal Mediation*; Ribas, X., Ed.; RSC Publishing: Cambridge, U.K., 2013.

(4) (a) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160−171. (b) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123−131. (c) Maggiarosa, N.; Tyrra, W.; Naumann, D.; Kirij, N. V.; Yagupolskii, Y. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2252−2253. (d) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666. (e) Burton, D. J.; Yang, Z. Y. *Tetrahedron* **1992**, *48*, 189−275. (f) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475−4521. (g) Luis Acena, J.; Simon-Fuentes, A.; Fustero, S. *Curr. Org. Chem.* **2010**, *14*, 928−949. (h) Farinola, G. M.; Cardone, A.; Babudri, F.; Martinelli, C.; Naso, F.; Bruno, G.; Losurdo, M. *Materials* **2010**, *3*, 3077−3091. (i) Cheng, Y.; Guo, A.-L.; Guo, D.-S. *Curr. Org. Chem.* **2010**, *14*, 977−999. (j) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (k) Mueller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886. (l) Hird, M. *Chem. Soc. Rev.* **2007**, *36*, 2070−2095. (m) Shteingarts, V. D. *J. Fluorine Chem.* **2007**, *128*, 797−805. (n) Perutz, R. N. *Science* **2008**, *321*, 1168−1169. (o) Reddy, V. P.; Vadapalli, A.; Sinn, E.; Hosmane, N. *J. Organomet. Chem.* **2013**, *747*, 43−50.

(5) (a) Takemoto, S.; Grushin, V. V. *J. Am. Chem. Soc.* **2013**, *135*, 16837−16840. (b) Lishchynskyi, A.; Novikov, M. A.; Martin, E.; Escudero-Adán, E. C.; Novák, P.; Grushin, V. V. *J. Org. Chem.* **2013**, *78*, 11126−11146. (c) Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2013**, *135*, 12584−12587. (d) Konovalov, A. I.; Benet-Buchholz, J.; Martin, E.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 11637−11641. (e) Novák, P.; Lishchynskyi, A.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 7767−7770. (f) Novák, P.; Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2012**, *134*, 16167−16170. (g) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901−20913.

(6) (a) Banks, R. E. *Organofluorine Chemicals and Their Industrial Applications*; Ellis Harwood: West Sussex, U.K., 1979;. (b) Campbell, M. G.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 474−480. (c) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264. (d) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470−477.

(7) (a) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119−2183. (b) Kuehnel, M. F.; Lentz, D.; Braun, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 3328−3348.

(8) (a) Burdeniuc, J.; Jedlicka, B.; Crabtree, R. H. *Chem. Ber./Recl.* **1997**, *130*, 145−154. (b) Ravishankara, A. R.; Turnipseed, A. A.; Jensen, N. R.; Barone, S.; Mills, M.; Howard, C. J.; Solomon, S. *Science* **1994**, *263*, 71−75.

(9) (a) Han, W. F.; Li, Y.; Tang, H. D.; Liu, H. Z. *J. Fluorine Chem.* **2012**, *140*, 7−16. (b) Shine, K. P.; Sturges, W. T. *Science* **2007**, *315*, 1804−1805. (c) Rowland, F. S.; Molina, M. J.; Chou, C. C. *Nature* **1975**, *258*, 775−776. (d) Rowland, F. S.; Molina, M. J. *Rev. Geophys.* **1975**, *13*, 1−35. (e) Molina, M. J.; Rowland, F. S. *Nature* **1974**, *249*, 810−812.

(10) (a) Douvris, C.; Ozerov, O. V. *Science* **2008**, *321*, 1188−1190. (b) Ahrens, M.; Scholz, G.; Braun, T.; Kemnitz, E. *Angew. Chem., Int. Ed.* **2013**, *52*, 5328−5332.

(11) Young, R. J., Jr.; Grushin, V. V. *Organometallics* **1999**, *18*, 294−296.

(12) Macgregor, S. A.; McKay, D.; Panetier, J. A.; Whittlesey, M. K. *Dalton Trans.* **2013**, *42*, 7386−7395.

(13) (a) Braun, T.; Perutz, R. N. *Chem. Commun.* **2002**, 2749−2757. (b) Richmond, T. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3241−3244. (c) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363−3384. (d) Murphy, E. F.; Murugavel, R.; Roesky, H. W. *Chem. Rev.* **1997**, *97*, 3425−3468. (e) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373−431.

(14) (a) Jones, W. D. *Dalton Trans.* **2003**, 3991−3995. (b) Nova, A.; Mas-Ballesté, R.; Lledós, A. *Organometallics* **2012**, *31*, 1245−1256.

(15) Meier, G.; Braun, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 1546−1548.

(16) (a) Douvris, C.; Nagaraja, C. M.; Chen, C. H.; Foxman, B. M.; Ozerov, O. V. *J. Am. Chem. Soc.* **2010**, *132*, 4946−4953. (b) Scott, V.; Çelenligil-Çetin, R.; Ozerov, O. V. *J. Am. Chem. Soc.* **2005**, *127*, 2852−2853.

(17) Caputo, C. B.; Hounjet, L. J.; Dobrovetsky, R.; Stephan, D. W. *Science* **2013**, *341*, 1374−1377.

(18) Stahl, T.; Klare, H. F. T.; Oestreich, M. *ACS Catal.* **2013**, *3*, 1578−1587.

(19) (a) Yow, S. H.; Gates, S. J.; White, A. J. P.; Crimmin, M. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 12559−12563. (b) Beltrán, T. F.; Feliz, M.; Llusar, R.; Mata, J. A.; Safont, V. S. *Organometallics* **2011**, *30*, 290−297. (c) Kühnel, M. F.; Lentz, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 2933−2936. (d) Jäger-Fiedler, U.; Klahn, M.; Arndt, P.; Baumann, W.; Spannenberg, A.; Burlakov, V. V.; Rosenthal, U. *J. Mol. Catal. A: Chem.* **2007**, *261*, 184−189. (e) Fuchibe, K.; Ohshima, Y.; Mitomi, K.; Akiyama, T. *J. Fluorine Chem.* **2007**, *128*, 1158−1167. (f) Kraft, B. M.; Lachicotte, R. J.; Jones, W. D. *J. Am. Chem. Soc.* **2001**, *123*, 10973−10979.

(20) (a) Swarts, F. *Bull. Cl. Sci., Acad. R. Belg.* **1920**, 399−417. (b) Swarts, F. *Bull. Cl. Sci., Acad. R. Belg.* **1936**, *22*, 122−124.

(21) Aizenberg, M.; Milstein, D. *Science* **1994**, *265*, 359−361.

(22) Yang, H.; Gao, H. R.; Angelici, R. J. *Organometallics* **1999**, *18*, 2285−2287.

(23) Stanger, K. J.; Angelici, R. J. *J. Mol. Catal. A: Chem.* **2004**, *207*, 59−68.

(24) Baumgartner, R.; Stieger, G. K.; McNeill, K. *Environ. Sci. Technol.* **2013**, *47*, 6545−6553.

(25) Peterson, A. A.; McNeill, K. *Organometallics* **2006**, *25*, 4938−4940.

(26) Braun, T.; Noveski, D.; Ahijado, M.; Wehmeier, F. *Dalton Trans.* **2007**, 3820−3825.

(27) Noveski, D.; Braun, T.; Schulte, M.; Neumann, B.; Stammler, H. G. *Dalton Trans.* **2003**, 4075−4083.

(28) Zámostná, L.; Ahrens, M.; Braun, T. *J. Fluorine Chem.* **2013**, *155*, 132−142.

(29) Li, J.; Zheng, T.; Sun, H.; Li, X. *Dalton Trans.* **2013**, *42*, 13048−13053.

(30) (a) Slaney, M. E.; Anderson, D. J.; Ristic-Petrovic, D.; McDonald, R.; Cowie, M. *Chem.—Eur. J.* **2012**, *18*, 4723−4737. (b) Erhardt, S.;

Macgregor, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 15490−15498. (c) Anderson, D. J.; McDonald, R.; Cowie, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3741−3744. (d) Hughes, R. P.; Laritchev, R. B.; Zakharov, L. N.; Rheingold, A. L. *J. Am. Chem. Soc.* **2005**, *127*, 6325−6334. (e) Garratt, S. A.; Hughes, R. P.; Kovacik, I.; Ward, A. J.; Willemsen, S.; Zhang, D. H. *J. Am. Chem. Soc.* **2005**, *127*, 15585−15594. (f) Blum, O.; Frolow, F.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1991**, 258−259.

(31) Senaweera, S. M.; Singh, A.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 3002−3005.

(32) Kuhl, S.; Schneider, R.; Fort, Y. *Adv. Synth. Catal.* **2003**, *345*, 341−344.

(33) Sawama, Y.; Yabe, Y.; Shigetsura, M.; Yamada, T.; Nagata, S.; Fujiwara, Y.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Adv. Synth. Catal.* **2012**, *354*, 777−782.

(34) Jasim, N. A.; Perutz, R. N.; Whitwood, A. C.; Braun, T.; Izundu, J.; Neumann, B.; Rothfeld, S.; Stammler, H. G. *Organometallics* **2004**, *23*, 6140−6149.

(35) Nova, A.; Reinhold, M.; Perutz, R. N.; Macgregor, S. A.; McGrady, J. E. *Organometallics* **2010**, *29*, 1824−1831.

(36) Johnson, S. A.; Huff, C. W.; Mustafa, F.; Saliba, M. *J. Am. Chem. Soc.* **2008**, *130*, 17278−17280.

(37) Nova, A.; Mas-Ballesté, R.; Ujaque, G.; González-Duarte, P.; Lledós, A. *Chem. Commun.* **2008**, 3130−3132.

(38) Breyer, D.; Braun, T.; Penner, A. *Dalton Trans.* **2010**, *39*, 7513−7520.

(39) Xiao, J.; Wu, J. J.; Zhao, W. W.; Cao, S. *J. Fluorine Chem.* **2013**, *146*, 76−79.

(40) Wu, J. J.; Cao, S. *ChemCatChem* **2011**, *3*, 1582−1586.

(41) Zhao, W. W.; Wu, J. J.; Cao, S. *Adv. Synth. Catal.* **2012**, *354*, 574−578.

(42) Fischer, P.; Gotz, K.; Eichhorn, A.; Radius, U. *Organometallics* **2012**, *31*, 1374−1383.

(43) Arévalo, A.; Tlahuext-Aca, A.; Flores-Alamo, M.; García, J. J. *J. Am. Chem. Soc.* **2014**, *136*, 4634−4639.

(44) Chen, Z.; He, C.-Y.; Yin, Z.; Chen, L.; He, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 5813−5817.

(45) Vela, J.; Smith, J. M.; Yu, Y.; Ketterer, N. A.; Flaschenriem, C. J.; Lachicotte, R. J.; Holland, P. L. *J. Am. Chem. Soc.* **2005**, *127*, 7857−7870.

(46) Reade, S. P.; Mahon, M. F.; Whittlesey, M. K. *J. Am. Chem. Soc.* **2009**, *131*, 1847−1861.

(47) Aizenberg, M.; Milstein, D. *J. Am. Chem. Soc.* **1995**, *117*, 8674−8675.

(48) Panetier, J. A.; Macgregor, S. A.; Whittlesey, M. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2783−2786.

(49) Konnick, M. M.; Bischof, S. M.; Periana, R. A.; Hashiguchi, B. G. *Adv. Synth. Catal.* **2013**, *355*, 632−636.

(50) Lv, H. B.; Zhan, J. H.; Cai, Y. B.; Yu, Y.; Wang, B. W.; Zhang, J. L. *J. Am. Chem. Soc.* **2012**, *134*, 16216−16227.

(51) Zhan, J. H.; Lv, H. B.; Yu, Y.; Zhang, J. L. *Adv. Synth. Catal.* **2012**, *354*, 1529−1541.

(52) Lv, H. B.; Cai, Y. B.; Zhang, J. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 3203−3207.

(53) Sabater, S.; Mata, J. A.; Peris, E. *Nat. Commun.* **2013**, *4*, 2553.