

Late Transition Metal-Mediated Formation of Carbon–Halogen Bonds

Arkadi Vigalok and Ariela W. Kaspí

Abstract This chapter reviews the synthesis of nonactivated aromatic halides assisted by late transition metal complexes. Although some of these reactions have been known for over half-a-century, there was a tremendous progress in the stoichiometric and catalytic applications of late transition metals in halogenation of aromatic compounds. Both nucleophilic and electrophilic halogenation pathways have been explored, resulting in practical methods for making aryl-halides. The chapter provides a metal-by-metal discussion of the above reactions, including the possible mechanisms of the metal-promoted formation of C–Halogen bonds.

Keywords Aryl halides · Catalysis · Halide exchange · Reductive elimination · Transition metals

Contents

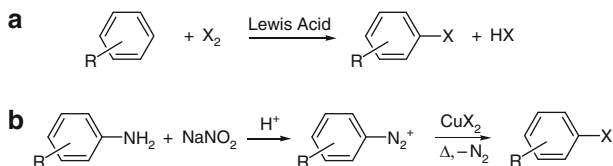
1	Introduction	20
2	Carbon–Halogen Bond Formation with Group 11 Metals	21
2.1	Copper	21
2.2	Silver	23
3	Carbon–Halogen Bond Formation with Group 10 Metals	24
3.1	Nickel	24
3.2	Palladium	25
3.3	Platinum	31
4	Carbon–Halogen Bond Formation with Group 9 Metals	34
4.1	Rhodium	34
5	Carbon–Halogen Bond Formation with Group 8 Metals	35
5.1	Ruthenium	35
6	Conclusions	36
	References	37

Abbreviations

Ac	acetyl
Ar	aryl
<i>t</i> -Bu	<i>tert</i> -butyl
cat	catalyst
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppe	bis(diphenylphosphino)ethane
equiv	equivalent(s)
Et	ethyl
h	hour(s)
L	liter(s)
Me	methyl
mol	mole(s)
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
Nu	nucleophile
Ph	phenyl
<i>i</i> -Pr	isopropyl
py	pyridine
rt	room temperature
TBAF	tetrabutylammonium fluoride
Tf	trifluoromethanesulfonyl (triflyl)
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl, 4-toluenesulfonyl

1 Introduction

Organic halides represent a very important class of organic compounds, both on their own and due to the well-developed processes toward functionalization of carbon–halogen bonds in the synthesis of valuable chemicals [1]. Many of the organic halides, in particular fluorides and iodides, have also found applications in medicine and agriculture [2–5]. Such a prominence resulted in the development of numerous synthetic approaches for preparation of organic halides, some of these approaches becoming cornerstones of organic chemistry [6, 7]. For a long time, late transition metals were not considered particularly useful for the preparation of organic halides. Furthermore, they have grown to be very prominent in *breaking* carbon–halogen bonds to make way for a variety of functional groups at the carbon atom.



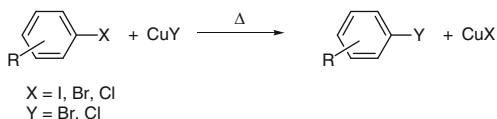
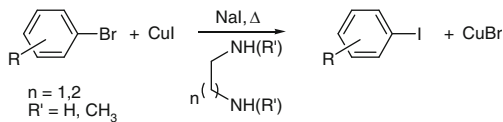
Scheme 1 Electrophilic halogenation and diazotization methods in synthesis of nonactivated aromatic halides

Yet, although a great deal of organic halides can (and should!) be prepared without utilizing transition metals, it is clear that there are cases when standard organic methods cannot produce the desired compounds and metal complexes have to come to the rescue. A particularly important class of organic compounds where typical synthetic approaches fail to deliver is the nonactivated aromatic halides, e.g., halides that have no electron-withdrawing groups in the *ortho*- or *para*-positions. Such halides are too unreactive to be involved in a halide exchange reaction under the nucleophilic aromatic substitution conditions [8] and are typically prepared via the direct electrophilic halogenation of the aromatic C–H bonds (Scheme 1a) [9] or diazotization of the corresponding anilines (Scheme 1b) [10]. Both approaches require rather harsh conditions which are often incompatible with a large variety of functional groups. In addition, the selectivity of electrophilic halogenation is predetermined by the directing properties of the substituents already present in the aromatic ring, while the laborious access to most synthetic anilines significantly limits the scope of the diazotization method. Finally, both classical methods often *do utilize* late transition metals, albeit not well-defined complexes, either as Lewis acids (iron salts) for electrophilic halogenation or source of the halide (copper salts) for the diazotization. In this chapter, we will focus on both stoichiometric and catalytic halogenation reactions of aromatic compounds that involve the participation of a late transition metal center.

2 Carbon–Halogen Bond Formation with Group 11 Metals

2.1 Copper

Copper salts have been used for nearly 100 years to introduce various nucleophiles into the aromatic ring. The first mentioning of copper-mediated halogenation reaction appeared over 50 years ago. Hardy and Fortenbaugh [11], and later Bacon and Hill [12] showed that heating haloaromatic compounds with a Cu(I) halide in pyridine or picoline results in the selective halogen exchange reaction (Scheme 2). Benzene derivatives as well as halogenated naphthalenes or anthraquinones were used as substrates. The direction of the reaction followed the bond strength of the carbon–halogen bond: iodide could be replaced by bromide or

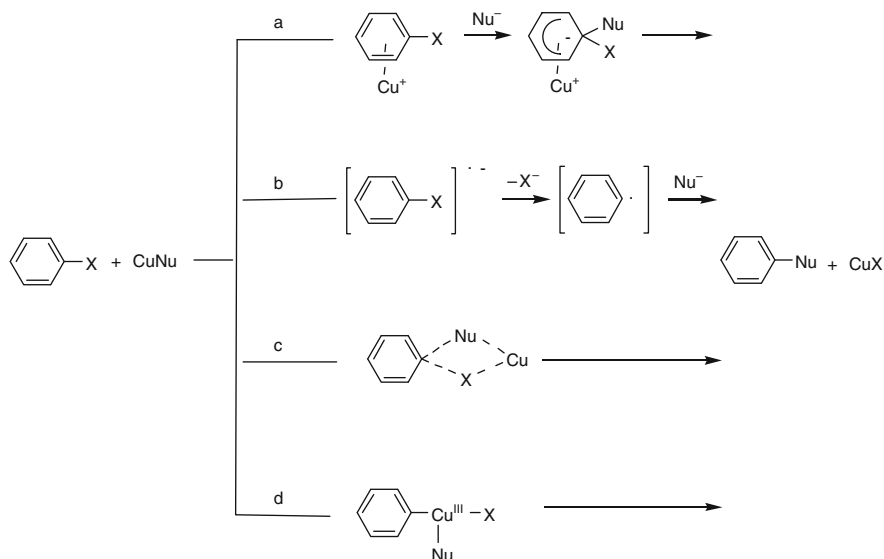
Scheme 2 Copper(I)-assisted halide exchange reactions**Scheme 3** Reversed halide exchange catalyzed by copper (I)/diamine mixture

chloride, but not vice versa. Similarly, bromide could be replaced by the chloride-ion while the reverse reaction did not occur. Considering that aryl iodides are usually more valuable products than bromides or chlorides, this reaction had received little attention in the following 20 years when modified protocols leading to reverse selectivity, i.e., aryl iodides from bromides or chlorides have been reported [13, 14]. Use of polar aprotic solvents or solid-supported Cu precursors provided aryl iodides from the corresponding bromides in high yields. The use of aryl chlorides instead of bromides resulted in significantly reduced reactivity. By using the isotopically labeled Na*I as a source of iodide, the copper-catalyzed reverse halide exchange was also successfully applied to the synthesis of ¹³¹I-enriched peptides in aqueous solutions [15]. In 2002, Klapars and Buchwald reported a catalytic method for converting aryl bromides into the iodides in quantitative yields and under relatively mild reaction conditions [16]. The key modification of this reaction was the addition of a bidentate secondary diamine ligand (Scheme 3). Lower yields were obtained when aryl chlorides were used as substrates. The reaction was later applied for in situ generation of iodoarenes for consequent catalytic transformations [17].

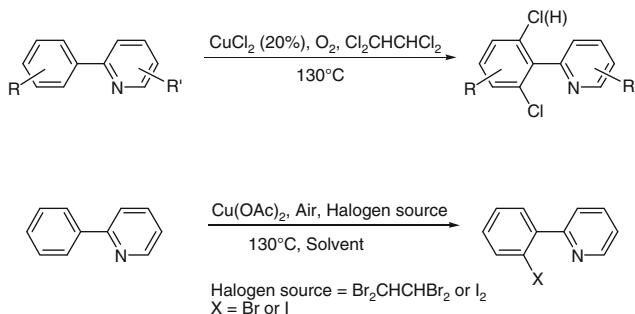
Finally, there was a recent report on the copper-mediated fluorination of nonactivated aryl chlorides using a heterogeneous copper aluminum fluoride system. The reactions were performed at very high temperatures and resulted in low-to-moderate yields of the fluoroaromatic products [18].

Mechanistic interpretations of the copper-catalyzed aromatic nucleophilic substitution reactions remain unsettled even after half-a-century of debate [19, 20]. Possible pathways involve an S_NAr reaction mediated by copper complexation to the pi-system (Scheme 4a), an electron transfer reaction followed by halide dissociation (Scheme 4b), four-centered σ-bond metathesis reaction (Scheme 4c) and Cu(I) oxidative addition to the Ar-X bond, followed by the nucleophile exchange and reductive elimination in the resulting Cu(III) system (Scheme 4d). There is presently a considerable body of experimental and theoretical data for and against each of the proposed mechanisms [21]. While the mechanistic studies were mostly related to the formation of C–C, C–O and C–N bonds, it is likely that the copper-catalyzed halogen exchange reactions follow a similar trend.

Although most of the copper-catalyzed halogenation involves the Ullmann-type halide exchange, Yu and coworkers recently reported an elegant aromatic



Scheme 4 Proposed mechanistic pathways for the copper-assisted halide exchange reactions in nonactivated aryl halides

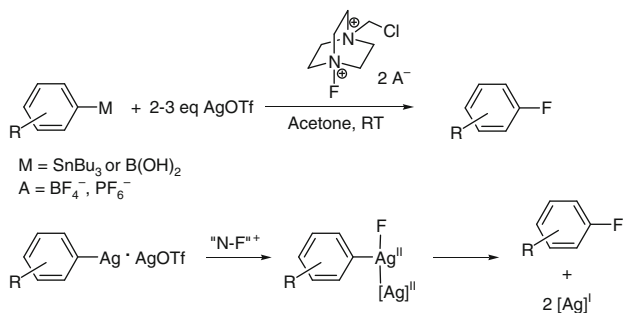


Scheme 5 Directing group-assisted copper-catalyzed electrophilic halogenation of aromatic C–H bonds

halogenation that proceeds via the ligand-directed C–H activation [22]. A variety of 2-arylpyridine derivatives could be selectively halogenated in good to excellent yields with dioxygen serving as an oxidant (Scheme 5).

2.2 Silver

Very recently, the Ritter group presented two examples of the silver-mediated fluorination of aryl stannanes and aryl boronic acids (Scheme 6) [23, 24]. Good yields were reported in both cases. The authors proposed the transmetallation



Scheme 6 Electrophilic fluorination of metal-aromatic compounds assisted by silver

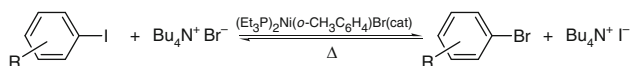
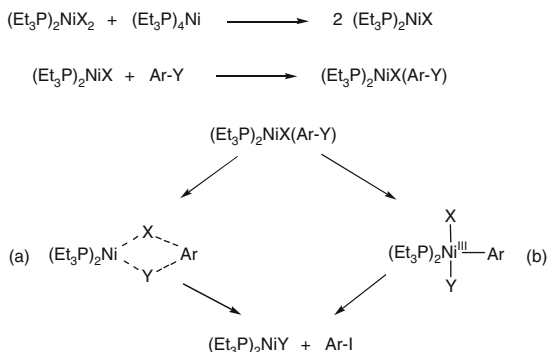
reaction leading to an Aryl-Ag(I) intermediate as the first step, followed by the one-electron two-metal oxidative addition–reductive elimination sequence. This mechanism can account for the necessary use of an excess of the silver salt (2–3 equiv.).

3 Carbon–Halogen Bond Formation with Group 10 Metals

3.1 Nickel

The preparation of chlorobenzene from bromobenzene catalyzed by a Ni(II) salt was reported by Cramer and Coulson in 1975 [25]. The reaction proceeded under harsh conditions (DMF, reflux or EtOH, 210°C), however, only small amounts of the Ni catalysts were sufficient to achieve good yields of the desired product. Use of stoichiometric amounts of the Ni(II) salt provided much better yields and allowed for the formation of the inverse halide exchange products, in addition to the normal ones. Employing microwave irradiation often facilitated the halide exchange [26].

Tsou and Kochi provided detailed mechanistic studies of the halogen exchange reaction in aryl- and vinyl halides catalyzed by Ni(II) complexes. Complexes of the formula $(\text{Et}_3\text{P})_2\text{Ni}(\text{Ar})\text{I}$ were found to be the active catalysts in this reaction (Scheme 7), although several Ni(II), Ni(I) or Ni(0) complexes could also be used instead [27]. Importantly, simple Ni(II) salts were inactive in catalysis and excess of the phosphine ligand was detrimental to the reaction. Both the direct and inverse halide exchange reaction required significant induction periods after which the reactions were complete within minutes in a number of solvents. Tsou and Kochi proposed the Ni(I) species $(\text{Et}_3\text{P})_2\text{Ni}^{\text{I}}\text{X}$ as the catalytically active one which can undergo the halide exchange reaction with Ar-Y either via the concerted σ -bond metathesis mechanism (Scheme 8a) or via oxidative addition–reductive elimination pathway (Scheme 8b). The authors suggested that the latter mechanism was less likely in their system since they found no cross-over products, common for the

**Scheme 7** Nickel-catalyzed halide exchange reaction**Scheme 8** Proposed mechanisms of the nickel-catalyzed halide exchange involving Ni(I) as the active catalytic species

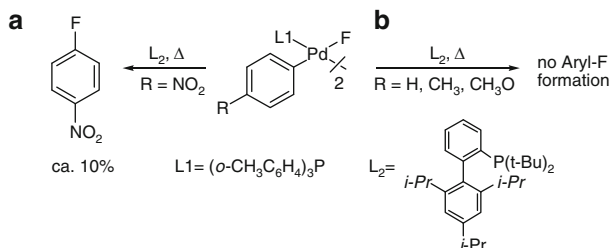
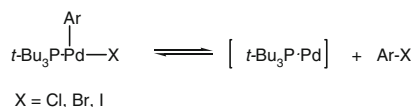
Ni(III) systems (Kochi), and the obtained p-value (~ 0.6) was small compared to what was observed in oxidative addition reactions to a Ni(0) center.

Ni(0) complexes were also employed in the halide exchange reactions in non-activated aryl halides. Both Ni powder and in-situ generated Ni(0) species (from Ni(II) and Zn dust) provided good yields of the exchange products, which included aryl iodides from the corresponding aryl bromides and chlorides [28–30]. In some cases, the reactions were accompanied by the formation of considerable amounts of C–C coupling products.

3.2 Palladium

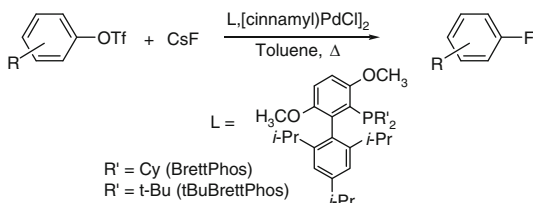
Pd(0) complexes have traditionally been employed in the variety of aromatic nucleophilic substitution reactions that utilize aryl halides or sulfonates as starting materials. In these reactions, an electron-rich metal center oxidatively adds to either C–Halide or C–OSO₂R bond in the first step. However, until recently, very little was known about the reverse reaction of carbon–halogen bond formation from Pd(II) species. Roy and Hartwig demonstrated that building up the bulk around the metal using a sterically hindered phosphine ligand can result in the formation of a three-coordinate (R₃P)Pd(Ar)X complex which is capable of the reductive elimination of the aryl halide molecule (Scheme 9) [31–33]. Although the elimination of aryl chlorides was the most thermodynamically favorable, the reactivity of the halide ligands followed the trend I > Br > Cl, indicating the importance of the kinetic factors in this reaction. The mechanistic studies suggested that the reductive Ar–X reductive elimination in a Pd(II) system takes place as the microscopic reverse of

Scheme 9 Directly observed aryl-halide reductive elimination from sterically hindered Pd(II) complexes



Scheme 10 C–F bond formation from Pd(II) complexes: **(a)** Proposed reductive elimination step in the synthesis of p-fluoronitrobenzene, **(b)** No fluoroaromatic compound was observed for aryl groups lacking the strong electron-withdrawing nitro substituent

Scheme 11 Nucleophilic fluorination of aromatic triflates catalyzed by Pd(0) phosphine complexes



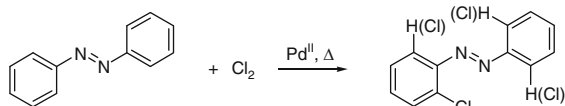
the Ar–X oxidative addition to the electron-rich Pd(0) complexes. No aryl fluoride reductive elimination was reported, however, it was recently proposed that the Ar–F reductive elimination results in the formation of small amounts of p-NO₂C₆H₄F in a Pd(II) system upon the addition of a sterically hindered Buchwald ligand (Scheme 10a) [34]. The presence of the strongly activating nitro group in the reported system and absence of any aryl fluoride formation with other aryl groups (Scheme 10b) raised questions about the mechanism by which the Ar–F bond was formed. It was proposed that the cationic Meisenheimer-type intermediate could be formed during the reaction course [35]. Until recently, the considerable effort invested in making C–F bonds gave limited results despite the significant thermodynamic gain expected from the formation of the very strong C–F bond [36]. To advance in this goal, one also had to overcome the side-reactions leading to the formation of strong P–F and H–F bonds, often observed in the reactions of organometallic fluorides. Nevertheless, Buchwald and coworkers recently reported the first example of catalytic fluorination of unactivated aryl triflates (Scheme 11) [37]. The major factor in making the key step of the catalytic cycle – Ar–F reductive elimination – work was the development of an extremely bulky BrettPhos ligand (Scheme 11). The three-coordinate (BrettPhos)Pd(Ar)F intermediate was isolated

and crystallographically characterized, and was shown to undergo the Ar-F reductive elimination upon heating in toluene.

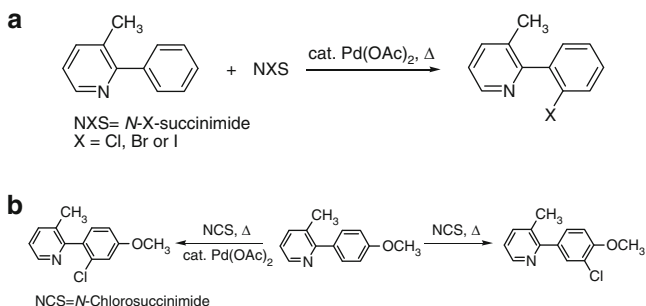
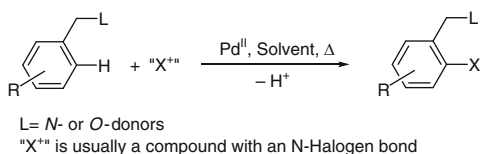
In addition to the formation of Ar-Halide bonds via the reductive elimination from Pd(II) complexes, there is much current interest in using palladium(II) complexes in combination with a source of an electrophilic halogen which usually results in Pd complexes in higher oxidation state (*vide infra*). Following the pioneering work of Fahey, who showed that Pd(II) complexes catalyze *ortho*-chlorination of azobenzene upon reaction with elemental chlorine (Scheme 12) [38, 39], several research groups developed synthetic methods for the *ortho*-directed halogenation of aromatic compounds using Pd(II) catalysts (Scheme 13).

The Sanford group developed a method for an electrophilic halogenation of a variety of aromatic substrates containing a nitrogen-based ligand that directs the halogenation reaction to the *ortho*-position. *N*-halosuccinimides were found to be the best reagents for the selective introduction of Cl, Br and I-substituents to the aromatic ring (Scheme 14a) [40, 41]. Interestingly, in many cases, the ligand-directed method is complementary to the metal-free halogenation of the same

Scheme 12 Catalytic chlorination of azobenzene via the proposed Pd(II)/Pd(IV) catalytic cycle. The first directing group-assisted electrophilic halogenation reaction

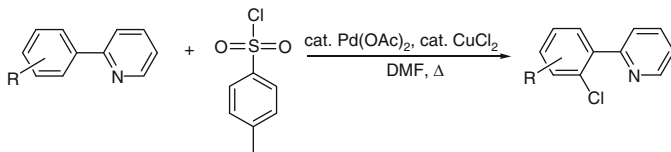
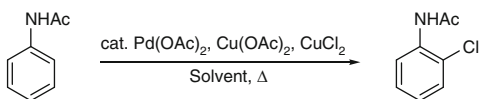


Scheme 13 General approaches to the electrophilic halogenation of aromatic C–H bonds using a Pd(II) catalyst

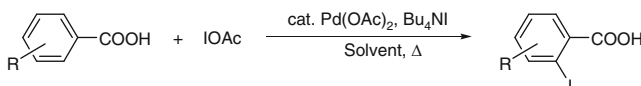


Scheme 14 Pyridyl group assisted halogenation: (a) General *ortho*-halogenation catalyzed by Pd(II). (b) Complementary Pd-catalyzed *ortho*-chlorination and electrophilic chlorination with NCS

Scheme 15 Pd(II)-catalyzed copper-promoted *ortho*-chlorination of acetanilide



Scheme 16 Pd(II)-catalyzed *ortho*-chlorination of 2-arylpyridines with arylsulfonyl chloride. The reaction requires copper(II) to give the chlorination product



Scheme 17 Pd(II)-catalyzed selective monoiodination of benzoic acids in the presence of a tertiary ammonium salt

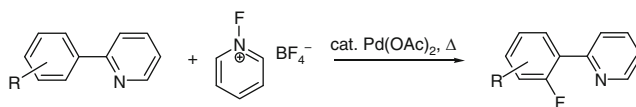
substrates under the identical reaction conditions which generally introduces the halogen atom to the most electron-rich position in the aromatic ring (Scheme 14b) [42].

More recently, the Shi group reported an *ortho*-halogenation of acetylanilide with copper(II) as oxidant (Scheme 15) [43]. Cu(II) salt was also found to be crucial to the formation of chloroarenes in the Pd(II)-catalyzed reaction of 2-phenylpyridine derivatives with arylsulfonyl chlorides. Only sulfonylation was observed when no copper was present in the system (Scheme 16) [44].

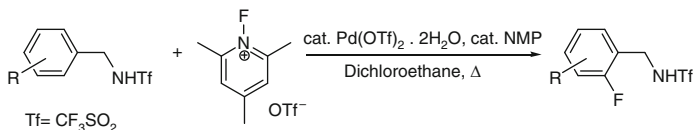
Very recently, Pd-catalyzed halogenation of various *N*-heterocyclic compounds was achieved under the electrochemical conditions with aqueous HX (X = Cl or Br) as the halogen source [45]. The reactions proceed without supporting electrolyte making the overall process more attractive from the environmental point of view.

Kodama et al. [46] and later Mei et al. [47] reported a selective *ortho*-halogenation of arylcarboxylic acids using the Pd(OAc)₂ precatalyst. Although both mono and dihalogenation products were usually obtained, especially in the iodination reaction, it was found that the presence of tertiary ammonium salts significantly improves the reaction selectivity mainly producing the monohalogenated product (Scheme 17) [47]. The bulky ammonium cation likely facilitates the displacement of the monohalogenated product from the metal coordination sphere, minimizing the competing formation of the dihalogenated side product.

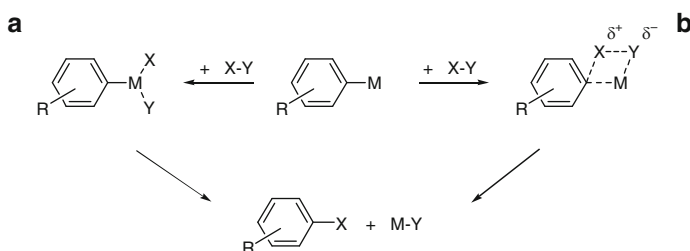
Considering that organofluorine compounds feature prominently in the pharmaceutical and agrochemical industries due to their important biological activities [2, 48], there were significant efforts to extend the above methods to making fluoroaromatic compounds. Sanford et al. reported a Pd-catalyzed C–H activation/*ortho*-fluorination of several 2-phenylpyridine derivatives with various N–F donors of “an electrophilic” fluorine (Scheme 18) [49]. Under the same conditions,



Scheme 18 Catalytic *ortho*-fluorination of 2-arylpyridines catalyzed by Pd(II)



Scheme 19 Pd(II)-catalyzed *ortho*-fluorination of triflamide-protected benzylamines. The triflamide group can later be converted to variety of synthetically important functional group



Scheme 20 Proposed mechanistic pathways of reaction of an organometallic compound with an electrophilic halogen source: (a) Oxidative addition–reductive elimination pathway. (b) Electrophilic Metal–Carbon bond cleavage

it was also possible to fluorinate the methyl group in 8-methylquinoline, thus making the method applicable to the synthesis of both C(sp²)- and C(sp³)-fluorinated products.

In a recent modification, Yu et al. described a Pd-catalyzed C–H activation/*ortho*-fluorination of triflamide-protected benzylamines with *N*-fluoro-2,4,6-collidininium cation (Scheme 19) [50]. The authors found that to achieve high yields it was crucial to use small amounts of NMP as a promoter. As the triflamide group can be easily converted to many other functional groups, such as aldehydes or azides, the reported method allows for an efficient synthesis of various *ortho*-fluorinated aromatic products.

The use of highly reactive electrophilic halogenation reagents can lead to the Pd(II) oxidation to give Pd(IV) complexes which can undergo the C–X reductive elimination reaction. Although this mechanism is often indistinguishable from the S_E2/metathesis mechanism [51], where no change in the metal oxidation state takes place (Scheme 20a, b), there is substantial evidence that the oxidative addition–reductive elimination path is viable in the Pd(II)-mediated halogenation of aromatic compounds [52, 53].

Scheme 21 Xenon difluoride-induced aryl-iodide reductive elimination from Pd complexes. The reaction is very general with regard to the aryl group involved

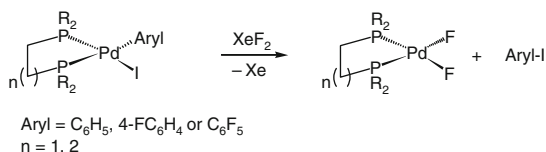
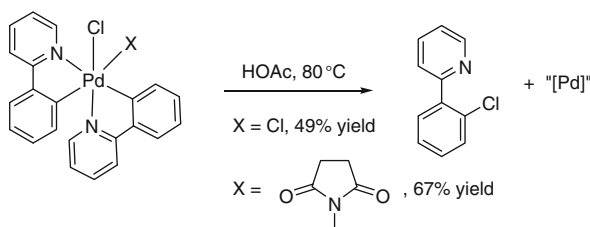
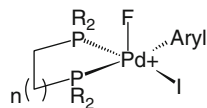


Fig. 1 Proposed cationic Pd(IV) intermediate in the reductive elimination of Aryl-I and Aryl-F in the reaction between the Pd(II) aryl iodo complexes and *N*-fluoro-2,4,6-collidinium cation

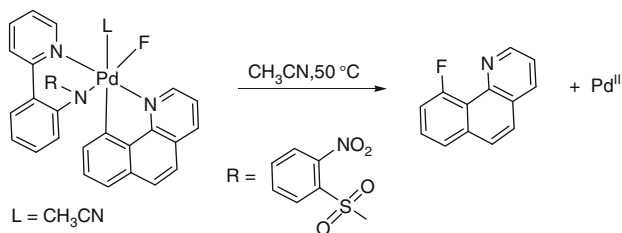


Scheme 22 Directly observed formation of an aryl-chloride bond from an isolated Pd(IV) complex

We recently reported an unexpectedly facile reductive elimination of aryl-iodides that takes place upon the reaction of Pd(II) aryl iodo complexes (P~P)Pd (Ar)I with XeF₂ (Scheme 21) [54]. The reaction was very general in terms of the aryl ligand involved; even the pentafluorophenyl group readily eliminated from the metal coordination sphere to quantitatively give iodopentafluorobenzene and (P~P) PdF₂. Interestingly, the reaction with *N*-fluoro-2,4,6-collidinium cation resulted in the mixture of Ar-I and Ar-F as organic products indicating the possibility of a single cationic Pd(IV) intermediate for both reductive elimination products (Fig. 1).

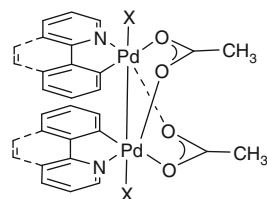
Whitfield and Sanford isolated di and monochloro Pd(IV) complexes of 2-phenylpyridine which upon heating in acetic acid gave substantial amounts of the chloroarene (Scheme 22) [55], although the fate of the transition metal remained unclear. More recently, Furuya and Ritter presented the first example of a reductive elimination of aryl fluoride from an isolated Pd(IV) center (Scheme 23) [56].

Although the C–X reductive elimination from Pd(IV) complexes has been established, it was recently suggested that Pd(III) dimers can also participate in the reductive elimination (Fig. 2) [57, 58]. Such, and relevant Pt(III) dimers, have been isolated and structurally characterized [59–63], however, it is not yet clear whether the mechanistic interpretation of the C–X elimination from these species should be treated differently from the established elimination from M(IV). As one

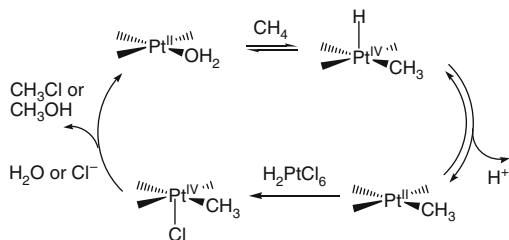


Scheme 23 Aryl-fluoride reductive elimination from an isolated Pd(IV) fluoro complex

Fig. 2 Isolated Pd(III) dimer was shown to reductively eliminate aryl-chloride. This and similar complexes were proposed to participate in the catalytic C–X bond formation catalyzed by Pd(OAc)₂



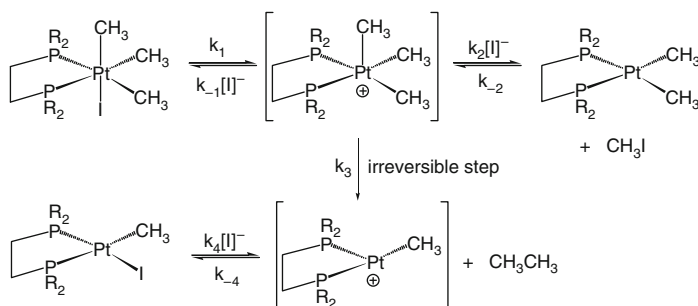
Scheme 24 Proposed catalytic cycle for the Shilov methane oxidation process. Under typical reaction conditions, chloromethane is formed parallel to methanol



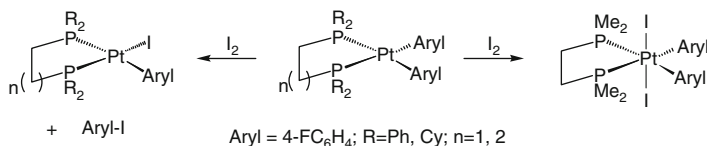
of the metal centers does not participate in the reductive elimination step, it can be viewed as a spectator ligand. It is also possible that the Pd(IV)–Pd(II) disproportionation takes place prior to the elimination step.

3.3 Platinum

CH₃–Halide bond formation is a side reaction in the Shilov methane oxidation process (Scheme 24) [64]. Mechanistic analysis of several catalytic steps by Bercaw and coworkers showed that the formation of the carbon–chlorine bond takes place in parallel to the formation of methanol, often being the major reaction pathway [65]. The reaction most likely involves a nucleophilic attack of the chloride-anion at the coordinated methyl group of the Pt(IV) intermediate [66]. Thus, the overall mechanism is closely related to the organic S_N2-type reaction. Further support for such a mechanism operating in Pt(IV) systems came from the Goldberg group which reported the competitive CH₃–I and CH₃–CH₃ reductive elimination reactions in platinum phosphine complexes (Scheme 25) [67, 68].

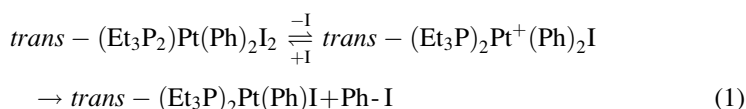


Scheme 25 Proposed mechanism of the kinetically controlled methyl iodide reductive elimination from Pt(IV). Due to the reversibility of the reductive elimination step, the thermodynamic products of $\text{CH}_3\text{-CH}_3$ coupling are eventually formed as the major species



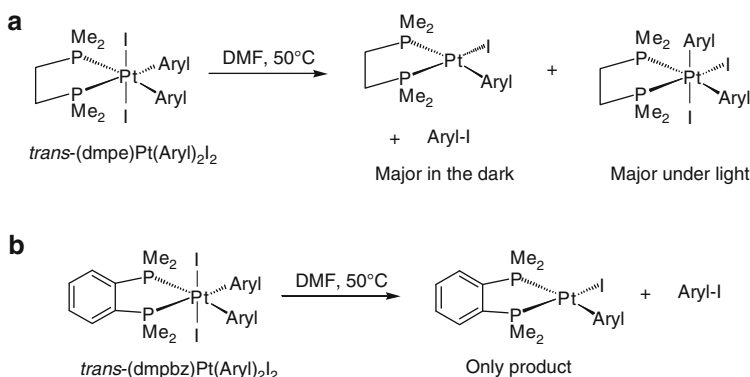
Scheme 26 Reactivity of Pt(II) diaryl complexes bearing chelating diphosphine ligands toward I_2

Goldberg et al. demonstrated that the reductive elimination of iodomethane is kinetically preferred over the much more common C–C reductive elimination in solution. As the resulting Pt(II) complex readily reacts with free $\text{CH}_3\text{-I}$ to regenerate the starting material, the overall reaction eventually results in the products of the ethane reductive elimination.



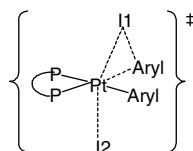
The first example of Aryl-Halide reductive elimination from a Pt complex was reported by Ettorre in 1969 [69]. Following the reaction progress by UV-vis spectroscopy provided evidence for the iodide dissociation taking place prior to the reductive elimination step (1).

Our group recently showed that addition of I_2 to chelated Pt(II) diaryl complexes resulted in the formation of free iodoarene and Pt(II) aryl iodo complexes, with the exception of the small dmpe ligand system, where stable oxidative addition Pt(IV) complex $\text{trans}-(\text{dmpe})\text{Pt}(\text{Ar})_2\text{I}_2$ was isolated (Scheme 26) [70]. Heating this complex in polar solvents gave the mixture of products: the thermodynamically stable *cis*-isomer and Ar-I reductive elimination products (Scheme 27a) [71]. The isomerization reaction was light-assisted with the light triggering the diphosphine chelate



Scheme 27 Competitive aryl-iodide reductive elimination/isomerization reactions involving Pt(IV) diaryl diido complexes: (a) The competition is light-dependent with dmpe as the ligand. (b) No isomerization takes place in the rigid dmpbz system suggesting that the diphosphine chelating opening is important for the isomerization reaction

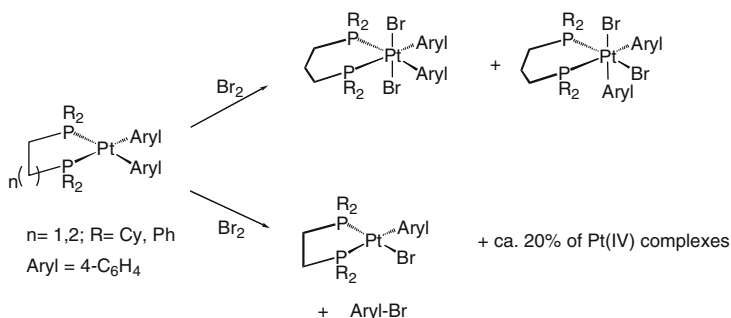
Fig. 3 Proposed transition state for the aryl-iodide reductive elimination from Pt(IV) complexes



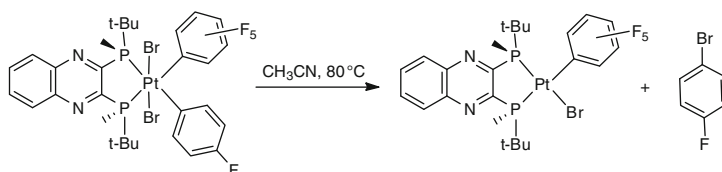
ring-opening. In the absence of light, the iodoarene reductive elimination reaction was the major one. Using a more rigid ligand dmpbz further hindered the ring-opening pathway leaving Ar-I reductive elimination the only observable reaction in DMF (Scheme 27b). The reaction proceeds via the concerted mechanism which was also confirmed by DFT calculations. There is a considerable cleavage of a Pt–I bond in the ion pair-like transition state (Fig. 3) [71]. Interestingly, the more stable *cis*-isomer of (dmpe)Pt(Ar)₂I₂, gave only C–C reductive elimination products upon prolonged heating at high temperatures.

We also reported that addition of Br₂ to chelated Pt(II) diaryl complexes gave product distribution dependent on the diphosphine bite angle. Use of larger chelates, dcpp or dppp, gave mainly Pt(IV) oxidative addition products, while smaller dppe or dcpe ligand systems gave mainly products of Ar–Br elimination, with very little of Pt(IV) products formed (Scheme 28) [70]. Heating these compounds at higher temperatures gave more of the Ar–Br, providing evidence for the first directly observed bromoarene reductive elimination from platinum.

More recently, we designed the system which can undergo selective Ar–Br elimination even when there is a possibility of C–C coupling. Using the quinoxaline-based ligand (Scheme 29) we were able to prepare a stable *trans* dibromo complex (P~P)Pt(4-C₆H₄F)(C₆F₅)Br₂ which undergoes C–Br elimination upon heating in CH₃CN at 70°C [72]. No C–C coupling was observed under these conditions.



Scheme 28 Chelate ring size-controlled oxidative addition – C–Br bond formation in bromination of Pt(II) diaryl complexes with Br₂



Scheme 29 Directly observed aryl-bromide formation from an isolated Pt(IV) complex

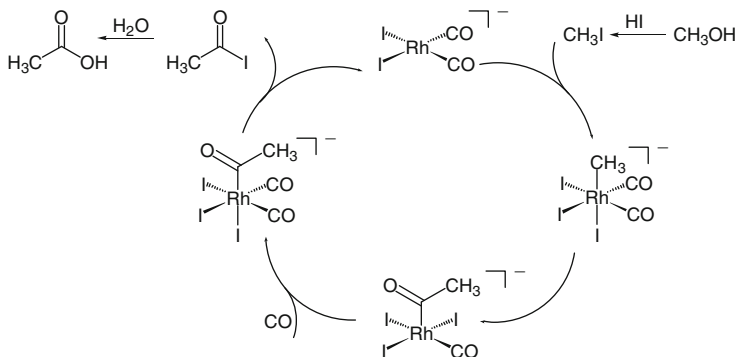
4 Carbon–Halogen Bond Formation with Group 9 Metals

4.1 Rhodium

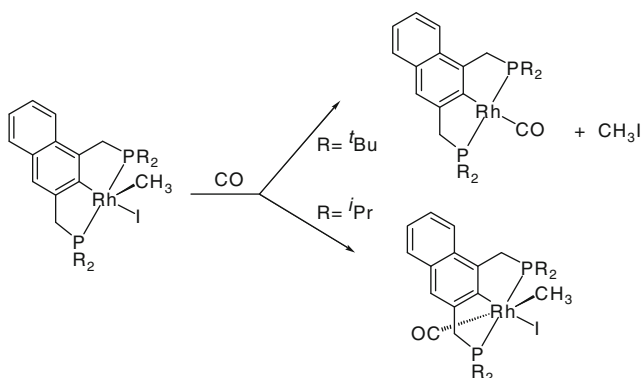
The proposed reductive elimination of acetyl iodide from the Rh(III) coordination sphere is an important step in the Monsanto methanol carbonylation process (2) [73]. In the proposed catalytic cycle (Scheme 30), the oxidative addition of iodo-methane, formed from HI and methanol, is followed by the carbonyl insertion into the Rh–Me bond. The reductive elimination of acetyl iodide followed by its rapid hydrolysis furnishes the acetic acid and regenerates free HI.



Recently, Milstein and coworkers reported an interesting CH₃–I reductive elimination chemistry from Rh(III) complexes (Scheme 31) [74]. The reactions, driven by steric bulk of the pincer ligands, represent the first example of the directly observed reductive elimination from metal complexes other than group 10. It was proposed that the reactions proceed via a concerted three-centered transition state rather than the S_N2-type back attack of the halide at the methyl group, as was proposed for the isoelectronic Pt(IV) complexes. To the best of our knowledge, no



Scheme 30 Proposed catalytic cycle for methanol carbonylation to acetic acid (Monsanto process). Acyl-iodide reductive elimination from a Rh(III) center is the key step toward the product formation



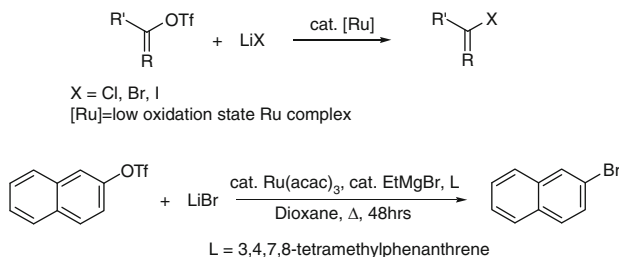
Scheme 31 Reductive elimination of methyl-iodide controlled by the steric bulk around the metal in Rh(III) complexes

confirmed examples of an aryl-halide bond formation assisted by group 9 metals have been reported.

5 Carbon–Halogen Bond Formation with Group 8 Metals

5.1 Ruthenium

There is a single recent report on the Ru-assisted formation of $\text{C}(\text{sp}^2)\text{--Halide}$ bonds in vinylic substrates. Shirakawa et al. very recently reported that low valent Ru complexes are good catalysts for the triflate-for-halide exchange reaction for a great variety of alkenyl triflates (Scheme 32) [75]. The reaction was also successfully



Scheme 32 Ruthenium catalyzed nucleophilic halogenation of selected vinyl- and aryl-triflates

applied to the synthesis of 2-bromonaphthalene albeit under harsher conditions, although no exchange was observed with p-tolyl triflate as substrate.

6 Conclusions

The last several years saw a dramatic increase in interest in the metal-mediated formation of carbon–halogen bonds. Late transition metal complexes, which until recently were only considered as useful in breaking such bonds, are now recognized as playing an important role in making C–Halogen bonds, particularly the most challenging aryl-halide bonds. Naturally, nucleophilic substitution reactions received most of the attention; however, there were significant advances in the utilization of the electrophilic halogenation reagents in the synthesis of nonactivated aromatic halides. At present, the latter method still suffers from the necessity to use a directing group which significantly reduces its scope. Still, there were many instances when such a necessity was turned into a blessing. Both, the nucleophilic and electrophilic halogenation methods are likely to advance rapidly in the near future.

As expected from their relevance to the pharmaceutical and agrochemical industries, nonactivated aryl-fluorides received most of the attention, although other newly discovered aryl-halide bond forming reactions prepared the ground for the successful accomplishments in synthesis of fluoroaromatic compounds. In the middle of 2008, we published a Concept article [76] which concluded with: “Perhaps the most synthetically challenging, although also most rewarding, problem involving the C–Halide reductive elimination is the formation of carbon–fluorine bonds. . . Considering the recent awakening of the interest in the metal-assisted C–X bond formation, we are likely to see more of the interesting work in this area in the near future.” Within a year, two papers describing the formation of Aryl-F bonds from Pd(IV) and Pd(II) complexes appeared in the literature [37, 56]. Considering the timescale of a book publishing process, it is very likely that any prophecy regarding the near future now, in the middle of 2009, will become an accomplished fact by the time this Volume appears on the shelf. At present,

selective catalytic transformations using low cost late transition metals (Cu, Ni) leading to nonactivated aryl fluorides seems to be the next big challenge to address.

References

1. Patai S, Rappoport Z (eds) (1995) *Chemistry of halides, pseudo-halides and azides*. Wiley, Chichester
2. Park BK, Kittenringham NR, O'Neill PM (2001) *Annual Rev Pharmacol Toxicol* 41:443
3. Cai L, Lu S, Pike VW (2008) *Eur J Org Chem* 2853
4. Brill AB, Stabin M, Bouville A, Ron E (2006) *Rad Res* 166:128
5. Jeschke P (2004) *ChemBioChem* 5:570
6. Stanforth SP (2005) In: Katritzky AR, Taylor RJK (eds) *Comprehensive organic functional group transformations II*, vol 2. Elsevier, Oxford, p 561
7. Christie SDR (1999) *Organic halides (Series)*. *J Chem Soc Perkin Trans* 1:737
8. March J (1992) *Advanced organic chemistry*, 4th edn. Wiley, NY, p 641
9. Ratnasamy P, Singh AP (2008) In: Ertl G (ed) *Handbook of heterogeneous catalysis*, 2nd edn, vol 7. Wiley-VCH, Weinheim, p 3564
10. Gribble GW (2007) In: Li JJ, Corey EJ (eds) *Name reactions for functional group transformations*. Wiley, NY, p 552
11. Hardy WB, Fortenbaugh RB (1958) *J Am Chem Soc* 80:1716
12. Bacon RGR, Hill HAO (1964) *J Chem Soc* 1097
13. Suzuki H, Kondo A, Inouye M, Ogawa T (1986) *Synthesis* 121
14. Suzuki H, Kondo A, Ogawa T (1985) *Chem Lett* 411
15. Ceusters M, Tourwe D, Callaerts J, Mertens J, Peter A (1995) *J Org Chem* 60:8324
16. Klapars A, Buchwald SL (2002) *J Am Chem Soc* 124:14844
17. Zanon J, Klapars A, Buchwald SL (2003) *J Am Chem Soc* 125:2890
18. Janmanchi KM, Dolbier WR (2008) *Org Proc Res Develop* 12:349
19. Lindley J (1984) *Tetrahedron* 40:1433
20. Beletskaya IP, Cheprakov AV (2004) *Coord Chem Rev* 248:2337
21. Monnier F, Taillefer M (2009) *Angew Chem Int Ed* 48:2
22. Chen X, Hao X-S, Goodhue CE, Yu J-Q (2006) *J Am Chem Soc* 128:6790
23. Furuya T, Strom AE, Ritter T (2009) *J Am Chem Soc* 131:1662
24. Furuya T, Ritter T (2009) *Org Lett* 11:2860
25. Cramer R, Coulson DR (1975) *J Org Chem* 40:2267
26. Arvela RK, Leadbeater NE (2003) *Synlett* 1145
27. Tsou TT, Kochi JK (1980) *J Org Chem* 45:1930
28. Takagi K, Hayama N, Okamoto T (1978) *Chem Lett* 191
29. Takagi K, Hayama N, Inokawa S (1980) *Bull Chem Soc Jpn* 53:3691
30. Yang SH, Li CS, Cheng CH (1987) *J Org Chem* 52:691
31. Roy AH, Hartwig JF (2001) *J Am Chem Soc* 123:1232
32. Roy AH, Hartwig JF (2003) *J Am Chem Soc* 125:13944
33. Roy AH, Hartwig JF (2004) *Organometallics* 23:1533
34. Yandulov DV, Tran NT (2007) *J Am Chem Soc* 129:1342
35. Grushin VV, Marshall DJ (2007) *Organometallics* 25:4997
36. Grushin VV (2010) *Acc Chem Res* 43:160
37. Watson DA, Su M, Teverovskiy G, Zhang Y, García-Fortanet J, Kinzel T, Buchwald SL (2009) *Science* 325:1661
38. Fahey DR (1970) *J Chem Soc D Chem Commun* 417
39. Fahey DR (1971) *J Organomet Chem* 27:283
40. Kalyani D, Dick AR, Anani WQ, Sanford MS (2006) *Org Lett* 8:2523

41. Kalyani D, Dick AR, Anani WQ, Sanford MS (2006) *Tetrahedron* 62:11483
42. Dipannita K, Sanford MS (2007) *Top Organomet Chem* 24:85
43. Wan X, Ma Z, Li B, Zhang K, Cao S, Zhang S, Shi Z (2006) *J Am Chem Soc* 128:7416
44. Zhao X, Dimitrijevic E, Dong VM (2009) *J Am Chem Soc* 131:3466
45. Kakiuchi F, Kochi T, Mutsutani H, Kobayashi N, Urano S, Sato M, Nishiyama S, Tanabe T (2009) *J Am Chem Soc* 131:11310
46. Kodama H, Katsuhira T, Nishida T, Hino T, Tsubata K (2003) US Patent 0181759
47. Mei T-S, Giri R, Maugel N, Yu J-Q (2008) *Angew Chem Int Ed* 47:5215
48. Hiyama T (2000) *Organofluorine compounds: chemistry and applications*. Springer, Berlin
49. Hull KL, Anani WQ, Sanford MS (2006) *J Am Chem Soc* 128:7134
50. Wang X, Mei T-S, Yu J-Q (2009) *J Am Chem Soc* 131:7520
51. Romeo R, D'Amico G (2006) *Organometallics* 25:3435
52. Alsters PL, Engel PF, Hogerheide MP, Copijn M, Spek AL, van Koten G (1993) *Organometallics* 12:1831
53. van Belzen R, Elsevier CJ, Dedieu A, Veldman N, Spek AL (2003) *Organometallics* 22:722
54. Kaspi AW, Yahav-Levi A, Goldberg I, Vigalok A (2008) *Inorg Chem* 47:5
55. Whiefield SR, Sanford MS (2007) *J Am Chem Soc* 129:15142
56. Furuya T, Ritter T (2008) *J Am Chem Soc* 130:10060
57. Powers DC, Ritter T (2009) *Nat Chem* 1:302
58. Deprez NR, Sanford MS (2009) *J Am Chem Soc* 131:11234
59. Cotton FA, Gu J, Murillo CA, Timmons DJ (1998) *J Am Chem Soc* 120:13280
60. Cotton FA, Koshevoy IO, Lahuerta P, Murillo CA, Sanaú M, Ubeda MA, Zhao Q (2006) *J Am Chem Soc* 128:13674
61. Baxter LAM, Heath GA, Raptis RG, Willis AC (1992) *J Am Chem Soc* 114:6944
62. Dick AR, Kampf JW, Sanford MS (2005) *Organometallics* 24:482
63. Canty AJ, Gardiner MG, Jones RC, Rodemann T, Sharma M (2009) *J Am Chem Soc* 131:7236
64. Shilov AE, Shul'pin GB (1997) *Chem Rev* 97:2879
65. Luinstra GA, Wang L, Stahl SS, Labinger JA, Bercaw JE (1995) *J Organomet Chem* 504:75
66. Zamashchikov VV, Rudakov ES, Mitchenko SA, Pekhtereva TM (1985) *Koord Khim* 11:69
67. Goldberg KI, Yan J, Winter EL (1994) *J Am Chem Soc* 116:1573
68. Goldberg KI, Yan J, Breitung EM (1995) *J Am Chem Soc* 117:6889
69. Ettore R (1969) *Inorg Nucl Chem Lett* 5:45
70. Yahav-Levi A, Goldberg I, Vigalok A (2006) *J Am Chem Soc* 128:8710
71. Yahav-Levi A, Goldberg I, Vigalok A, Vedernikov AN (2008) *J Am Chem Soc* 130:724
72. Yahav-Levi A, Goldberg I, Vigalok A, Vedernikov AN (2010) *Chem Commun*, Accepted for Publication
73. Dekleva TW, Forster D (1986) *Adv Catal* 34:81
74. Frech CM, Milstein D (2006) *J Am Chem Soc* 128:12434
75. Shirakawa E, Imazaki Y, Hayashi T (2009) *Chem Commun* 5088
76. Vigalok A (2008) *Chem Eur J* 14:5102