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Metal-Mediated Formation of Carbon–Halogen Bonds

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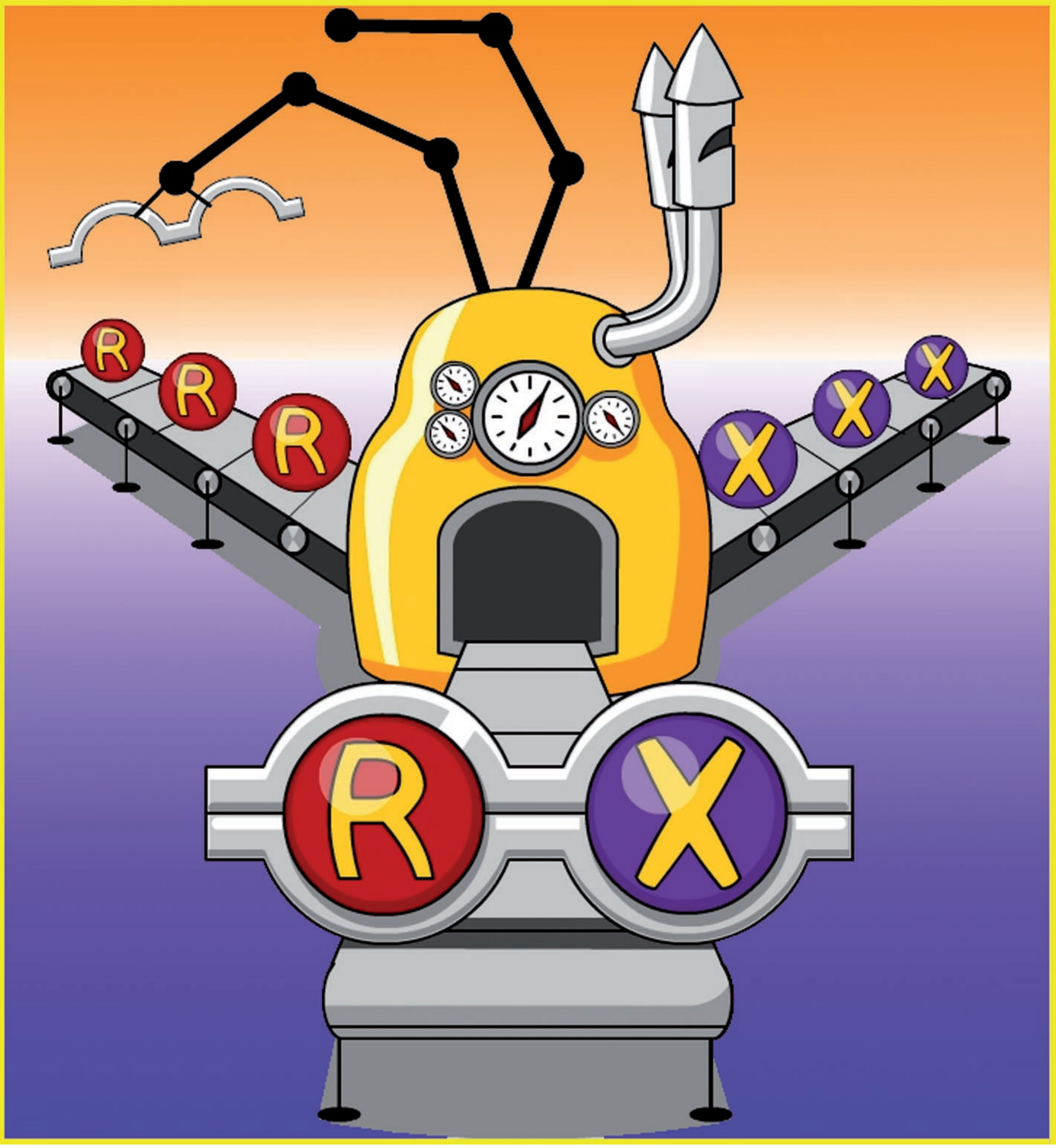
Dedicated to Professor David Milstein on the occasion of his 60th birthday



Abstract: Organic halides represent basic starting materials for numerous metal-catalyzed organic transformations. Generally, the carbon–halogen is broken in the first step, that is, an oxidative addition reaction, of the catalytic cycle. On the other hand, very little is known about the reverse reaction, carbon–halogen reductive elimination from a transition-metal center. In this Concept article, we describe the examples of C(sp^3)−halide and C(sp^2)−halide reductive-elimination reactions which demonstrate that this type of reactivity can be quite common in organometallic chemistry. Although the thermodynamic driving force for the formation of carbon–halogen bonds is relatively small, the kinetic barrier for these reactions can also be low. Thus, C−halide reductive elimination can compete favorably with the more established organic transformations, such as C−C reductive elimination.

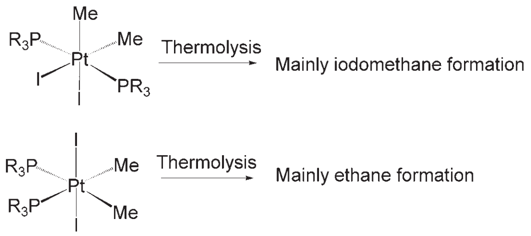
Keywords: carbon–halogen bonds · halides · organometallic chemistry · reductive elimination · transition metals

Introduction

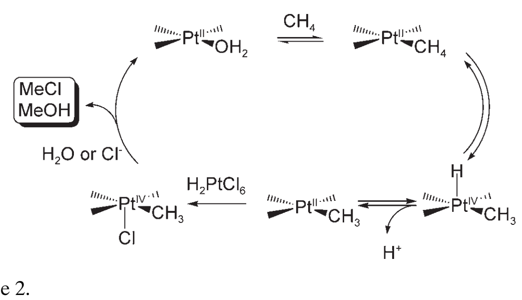
Halogenation of organic molecules is one of the most common methods towards their further functionalization.[1] Halides often serve as good leaving groups in a variety of organic transformations, with the carbon–halogen bond strength being relatively low.[2] With the dawn of organometallic chemistry, it was promptly recognized that metals readily insert into even relatively strong carbon–halogen bonds in a prototype of modern oxidative addition process.[3] Metal activation of carbon–halogen bonds has received an incredible amount of attention in the last few decades with the development of late-transition-metal-catalyzed organic transformations.[4,5] These reactions have became the keystone in a large number of very important organic reactions, as a starting point to the formation of new carbon–carbon, carbon–nitrogen, and carbon–oxygen bonds.[6–8] Since the oxidative addition of a carbon–halogen bond to an electron-rich late-transition-metal center is usually thermodynamically favorable, even for the strongest alkyl and aryl halides, much consideration was given to the development of metal complexes capable of rapid insertion into such bonds. At present, there are several catalytic systems in which the metal insertion into C−X bond is an extremely facile process.[9] In the background to this activity in the area of metal activation of carbon–halogen bonds, remarkably few examples of the reverse process—transition-metal-assisted formation of these bonds—have been reported. This process, the C−halide reductive elimination, can be a significantly more common reaction than is presently assumed and can play a prominent role in organometallic transformations. The purpose of this Concept article is to discuss the synthetic and mechanistic information relevant to carbon–halogen bond formation by means of the reductive elimination from a transition-metal center.[10]

C(sp^3)−Halide Reductive Elimination

Early examples of the C−halide reductive elimination started to appear in the literature about 40 years ago.[11] Ruddick and Shaw reported that the thermolysis of the isomeric Pt^{IV} complexes gave mixtures of products of C−C and C−I reductive-elimination reactions (Scheme 1). The products ratio appeared to be dependent on the complex geometry. However, it was not until the Shilov group discovered the homogeneous catalytic process for methane functionalization that the C−halide reductive elimination in solution received considerable attention.[12] It was reported that, in addition to methanol, substantial amounts of chloromethane could be obtained in the Shilov methane oxidation process catalyzed by platinum complexes (Scheme 2).[13] Careful mechanistic analysis of several catalytic steps by Bercaw and co-workers suggested that the formation of the carbon–chlorine bond takes place in parallel to the formation of methanol, often being the major reaction pathway.[14] Although it was difficult to distinguish between the intra- and intermolecular



Scheme 1.



Scheme 2.

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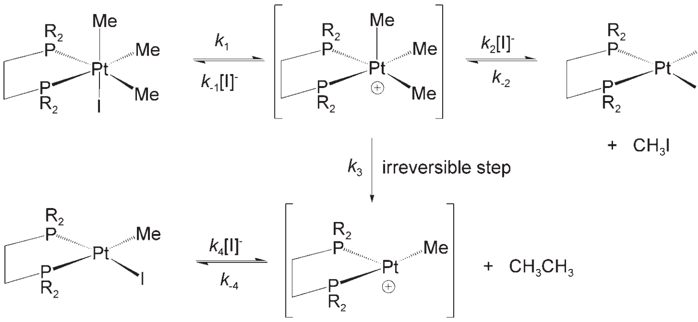
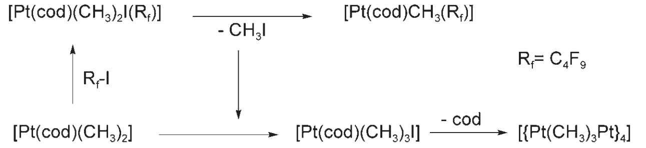
bond-forming step, the reaction most likely involves a nucleophilic attack of the chloride-anion at the coordinated methyl group of the Pt^{IV} intermediate.[15] Thus, the overall mechanism is closely related to the organic S_N2-type reaction. Convincing evidence for such a mechanism operating in Pt^{IV} systems came from the work of Goldberg and co-workers, who studied the competitive CH_3–I and CH_3–CH_3 reductive-elimination reactions in platinum–phosphane complexes (Scheme 3).[16] The Goldberg group demonstrated that the reductive elimination of iodomethane is kinetically preferred over the much more common C–C reductive elimination. Since the resulting Pt^{II} complex readily reacts with free CH_3–I to regenerate the starting material, the overall reaction eventually results in the products of the ethane reductive elimination. It was also shown that the addition of free iodide decreases the concentration of the cationic Pt^{IV} intermediate and significantly slows down the C–C reductive-elimination reaction. In addition to the thorough analysis of the rare C–I reductive elimination from an *isolated* metal complex in solution, this work by the Goldberg group demonstrated that such elimination can successfully compete with the more thermodynamically favorable C–C reductive elimination. An important factor in the successful observation of the C–I reductive elimination, in the presence of two methyl groups at the metal center, is the difference of the reaction mechanisms for the competing reductive-elimination reactions.



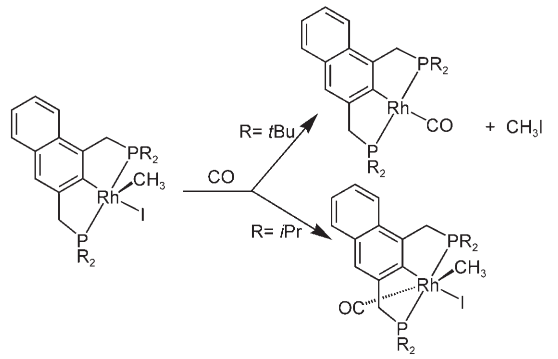
Scheme 3.

Hughes and co-workers reported another Pt^{IV} system in which the C–I reductive elimination readily occurs by the assumed S_N2-type mechanism.[17] The resulting iodomethane was rapidly consumed by a Pt^{II} complex present in the system, making the overall reaction irreversible (Scheme 4).

Milstein and Frecht very recently showed that the reductive elimination of CH_3–I can take place in a Rh^{III} pincer-type complexes. The elimination reaction is apparently driven by the steric bulk at the metal center, since no such reaction was observed in a structurally similar, but less sterically encumbered, system (Scheme 5).[18] The Milstein system represents the first direct observation of the $C(sp^3)$–X reductive elimination in metal complexes other than Group 10. Although the electronic configuration of the Rh^{III} complex is analogous to that of the previously described Pt^{IV} system, the mechanistic studies of the reductive-elimination reaction suggested that the S_N2-type mechanism is not operative under the reaction conditions. Instead, concerted elimination of both atoms from the metal coordination sphere was proposed.



Scheme 4.



Scheme 5.

C(sp^2)–Halide Reductive Elimination

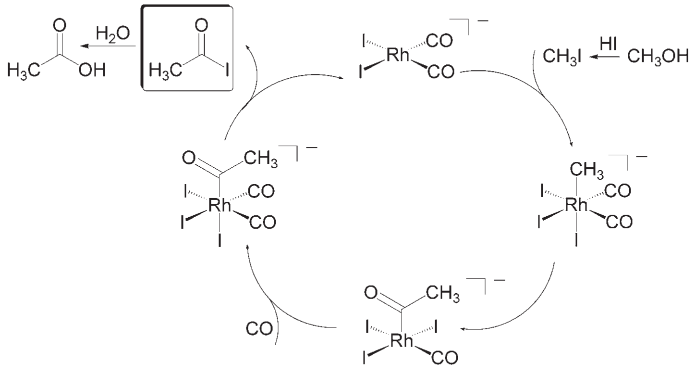
The first example of such reductive elimination from an isolated metal complex was reported in 1969 by Ettorre, who showed that heating in methanol the Pt^{IV} complex bearing phenyl and iodo ligands gave free iodobenzene and a Pt^{II} phenyl iodo complex.[19] The reaction progress was followed by UV/Vis spectroscopy and the conclusion was that the iodide dissociation from the platinum coordination sphere is required prior to the Ar–I reductive-elimination step [Eq. (1)].[20]

$$\textit{trans}\text{-}[Pt(Et_3P)_2I_2(Ph)_2] \underset{-I^-}{\overset{+I^-}{\rightleftharpoons}} \textit{trans}\text{-}[Pt(Et_3P)_2I(Ph)_2]^+ \rightarrow \textit{trans}\text{-}[Pt(Et_3P)_2I(Ph)] + PhI \qquad (1)$$

Perhaps the most prominent example of the importance of the $C(sp^2)$–halide reductive elimination in organometallic chemistry comes from the mechanistic studies of the Monsanto methanol carbonylation process [Eq. (2)].[21]

$$CH_3OH + CO \xrightarrow{\text{Rh cat.}} CH_3COOH \qquad (2)$$

It was reported that the catalytic cycle is greatly influenced by the presence of free iodide in the reaction mixture.[22,23] Further analysis revealed that, in the product forming step, acyl iodide reductive elimination from a Rh^{III} center takes place, followed by the rapid acyl iodide hydrolysis to carboxylic acid (Scheme 6).[24] The hydrolysis step



Scheme 6.

renders the reductive elimination of the highly reactive acyl–iodide bond irreversible. Just as in the case of the Ar–I reductive elimination, the carbon atom is sp^2-hybridized. This hybridization allows the reductive-elimination mechanism to proceed via the concerted, three-coordinate transition state. Although not observed directly, the reductive elimination of an acyl–hloride was proposed in the Rh^{III} system.[25]

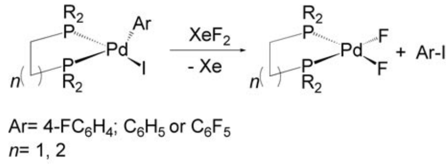
Electron-rich Pd^0–phosphane complexes are the most commonly used catalysts for a variety of aromatic nucleophilic substitution reactions involving aryl halides. Thus, it was an especially important finding by the Hartwig group that, under the appropriate conditions, aryl halide reductive elimination from Pd^{II}–phosphane complexes can be observed. To accomplish this otherwise thermodynamically unfavorable reaction, the authors used very sterically hindered phosphane ligands that squeezed the aryl and halide groups from the metal coordination sphere. The initially dimeric Pd^{II}–aryl-halide complexes were treated with tBu_3P or similarly bulky phosphanes to give the three-coordinate monomeric compounds which underwent facile reductive-elimination reactions under mild conditions [Eq. (3)].[26]

$$L-\overset{Ar}{Pd}-X \rightleftharpoons [L-Pd] + Ar-X \qquad (3)$$

L= Bulky phosphine ($^tBu_3P$)
X= Cl, Br, I

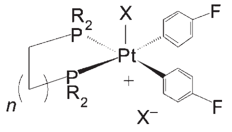
Although the elimination of aryl chlorides was the most thermodynamically favorable, the reactivity of the halide ligands followed the trend I > Br > Cl, indicating the importance of the kinetic factors in this reaction. The mechanistic studies suggested that the reductive Ar–X reductive elimination in a Pd^{II} system takes place as the microscopic reverse of the Ar–X oxidative addition to the electron-rich Pd^0 complexes. In the continuation of this approach, it was recently proposed that the Ar–F reductive elimination results in the formation of small amounts of $p\text{-}NO_2C_6H_4F$ in a Pd^{II} system.[27] However, the necessity to use the strongly activating nitro group suggests that alternative pathways, such as involving the cationic Meisenheimer-type intermediates, may be operative.[28] Thus far, 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.[29] To advance in this goal, one also has 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.

A different approach to Ar–I reductive elimination in Pd complexes was recently demonstrated in our group. The reaction between Pd^{II}–aryl-iodo complexes with one equivalent of XeF_2 cleanly gave the corresponding Pd^{II}–difluoro complexes and iodoarenes (Scheme 7).[30] A less strong fluorinating reagent, p-tolyliododifluoride did not react under these conditions, while use of N-fluoropyridinium tetrafluo roborate gave mixtures of iodo- and fluoroarenes. Simple oxidation of the starting Pd^{II} complexes with $Fc^+BF_4^-$ (Fc = Ferrocene) did not result in the iodoarene formation; however, other oxidants, such as CAN (CAN = cerium ammonium nitrate) also gave significant amounts of Ar–I. The reaction with XeF_2 was also very general in terms of the aryl ligand involved; even the pentafluorophenyl group readily eliminated from the metal coordination sphere to quantitatively give iodopentafluorobenzene.

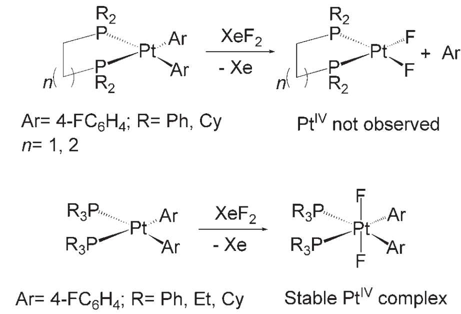


Scheme 7.

While studying the oxidative addition chemistry of Pt^{II}–aryl complexes with XeF_2, we surprisingly found that the isoelectronic and isostructural complexes bearing different types of phosphane ligands show markedly different reactivity patterns. The cis-chelating phosphane ligands imparted the C–C reductive-elimination chemistry, whereas the monodentate phosphanes supported the formation of stable Pt^{IV} oxidative addition products (Scheme 8).[31] Since the Pt^{IV}–difluoro complexes with bidentate phosphane ligands are reasonably stable,[32] this reactivity difference suggested that the reductive elimination takes place prior to their formation. We hypothesized that the cationic intermediate **A**, formed in the S_N2-type mechanism,[33] can be responsible for the reductive-elimination step. We decided to expand these studies to include halogen molecules that are known to react with square-planar d^8 metals by means of the S_N2-type mechanism. Interestingly, addition of

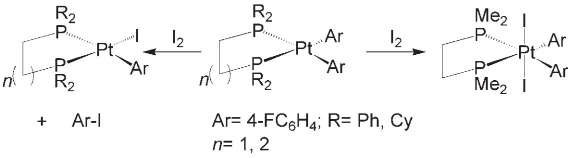


A

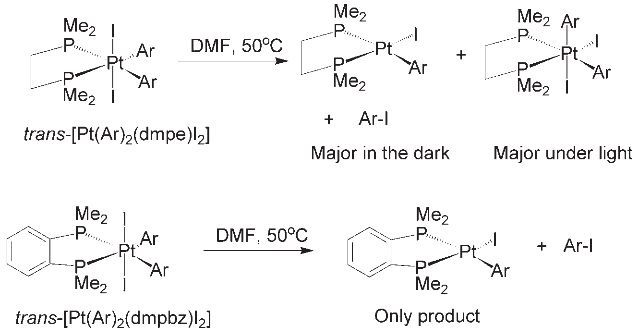


Scheme 8.

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 1,2-bis(dimethylphosphino)ethane (dmpe) ligand system, in which stable oxidative addition Pt^{IV} complex *trans*-$[Pt(Ar)_2(dmpe)I_2]$ was isolated (Scheme 9).[34] Heating this complex in polar solvents resulted in the mixture of products: the thermodynamically stable *cis* isomer and Ar–I reductive-elimination products (Scheme 10).[35] The isomerization reaction was light-assisted with the light triggering the diphosphane chelate ring-opening. In the absence of light, the iodoarene reductive-elimination reaction was the major one. By using a more rigid ligand 1,2-bis(dimethylphosphino)benzene (dmpbz) further hindered the ring-opening pathway leaving Ar–I reductive elimination the only observable reaction in dimethyl formamide (Scheme 10). The kinetic analysis suggested a late transition state for the reductive-elimination step ($\Delta H^{\#}\approx 29\ \mathrm{kcal\,mol^{-1}}$, $\Delta S^{\#}\approx 16\ \mathrm{kcal\,mol^{-1}}$), with the reaction proceeding via the concerted mechanism. This mechanism was further confirmed by DFT calculations, performed by Andrei Vedernikov (University of Maryland), which showed considerable cleavage of a Pt–I bond in the ion-pair-like transition state (Figure 1).[35]



Scheme 9.



Scheme 10.

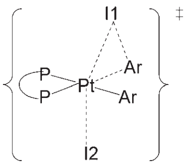
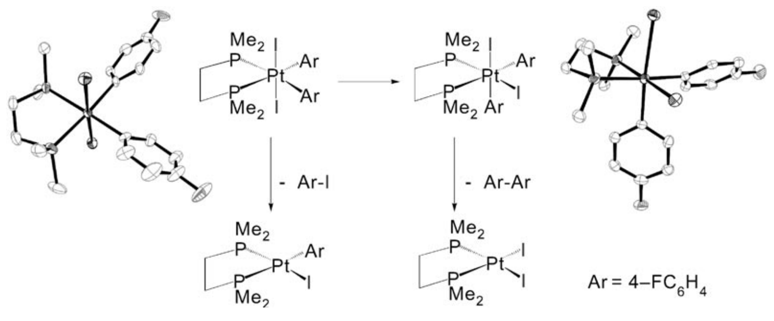


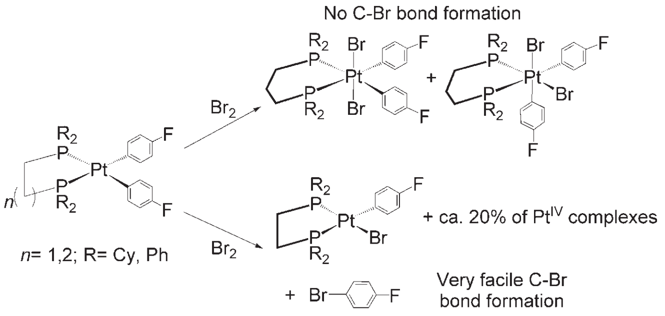
Figure 1. Ion-pair-like transition state.

Interestingly, the more stable *cis* isomer of $[Pt(Ar)_2(dmpe)I_2]$ gave only C–C reductive-elimination products upon prolonged heating at high temperatures. This geometry-dependent reactivity is summarized in Scheme 11. Addition of Br_2 to chelated Pt^{II}–diaryl complexes gave product distribution dependent on the diphosphane bite angle. Use of larger chelates, dichlorophenylphosphane (dcpp) or 1,3-bis(diphenylphosphino)propane (dppp), gave mainly Pt^{IV} oxidative addition products, while smaller 1,3-bis(diphenylphosphino)ethane (dppe) or 1,2-bis(dicyclohexylphosphino)ethane (dcpe) ligand systems gave mainly products of Ar–Br elimination, with very little of Pt^{IV} products formed (Scheme 12).[34] Heating these compounds at higher temperatures gave more of the Ar–Br, providing evidence for the first directly observed bromoarene reductive elimination from platinum.

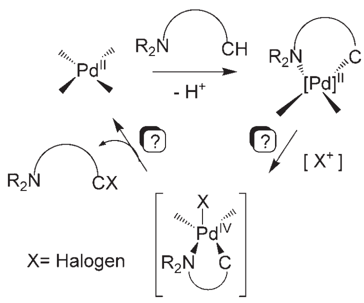
The described examples of the direct C–halide reductive elimination in M^{IV} complexes may provide support for such reactions taking place in the palladium-catalyzed halogenation of C–H bonds. First reported by Fahey,[36] and significantly improved by Sanford et al.,[37] the catalytic halogenation of sp^2- and sp^3-carbon atoms in the presence of a directing ligand group utilizes an electrophilic halogenation reagent (X_2 or "N–X" compounds) and a Pd^{II} catalyst. The proposed catalytic cycle involves the participation of Pd^{II} and Pd^{IV} species (Scheme 13). Although the reductive-elimination step was not observed under the catalytic conditions, several examples of C–halide reductive elimination from unstable Pd^{IV} complexes were reported in other systems.[38,39] These results and the ease with which such reaction takes place in Pt^{IV} systems suggest that the proposed reductive



Scheme 11.



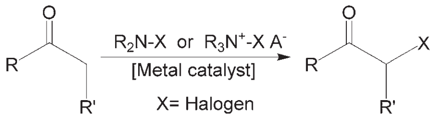
Scheme 12.



Scheme 13.

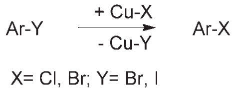
elimination as the product-forming step in the catalytic cycle can be feasible.[40]

Although this Concept article describes the formation of carbon–halogen bonds by means of the reductive-elimination pathway, it is worth noting that there are other mechanisms by which a halide can be introduced into an organic molecule, for example, through a metal-assisted pathway. Halogenation of a C–H bond in the α-position to a carbonyl group by using a metal catalyst is a known reaction (Scheme 14). The metal center acts as a Lewis acid, activating the α-position to an attack by an electrophilic halogenation reagent. The stereoselective version of this reaction is of interest to synthetic organic chemistry, since it allows for the introduction of a good leaving group in the α-position to the carbonyl.[41]



Scheme 14.

The copper-assisted nucleophilic aromatic substitution reaction (the Ullmann reaction) has been known for almost a century.[42] Although O-, N- or C-based nucleophiles have generally been employed, halogen exchange reaction using Cu^I derivatives was also demonstrated. The original reports of such a reaction describe the halogen exchange trend that follows the thermodynamic stability of the C–X bond; that is, the iodo substituent could be replaced by Cl or Br, but not the other way around (Scheme 15).[43] With the development of general understandings of the principles of organometallic and coordination chemistry it became possible to affect the reactivity of the metal by using the appropriate organic ligands. Recently, the reaction was revisited with a variety of nitrogen chelating ligands applied in the copper-catalyzed *trans*-halogenation of aryl halides.[44] Use of these ligands allowed the reversal of the reactivity pattern of the copper reagent making it possible to replace Br and even Cl substituents by iodide in non-activated aromatic compounds. The reaction can also be used in making transient iodoarenes for further catalytic transformations without their isolation.[45]



Scheme 15.

Conclusion

While metal complexes are routinely utilized in cleavage of carbon–halogen bonds, there is significant evidence that the reverse reaction of C–halide reductive elimination can be quite common and synthetically important. Such reactions have been observed with the alkyl, acyl, and aryl groups, and it was shown that they can successfully compete with the more thermodynamically favorable C–C reductive elimination. Transient C–X bonds can also be formed during a metal-catalyzed process and must be considered in elucidation of the reaction mechanisms. Additionally, making carbon–halogen bonds with an aid of a transition-metal complex might provide an access to organic halides that cannot be prepared without the metal. Perhaps the most synthetically challenging, although also most rewarding, problem involving the C–halide reductive elimination is the formation of carbon–fluorine bonds. While only marginal in their natural abundance, organofluorine compounds play a very prominent role in the pharmaceutical and agrochemical industries due to important biological activities shown by many organic fluorides.[46] 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.

Acknowledgement

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[10] In this Concept article, we will try to discuss only the unequivocally confirmed C–X reductive-elimination reactions. Some examples of C–X bond-forming reactions, not necessarily involving the reductive-elimination step, will be described in the end.

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