Synthesis of Organic Halides via Palladium(0) Catalysis

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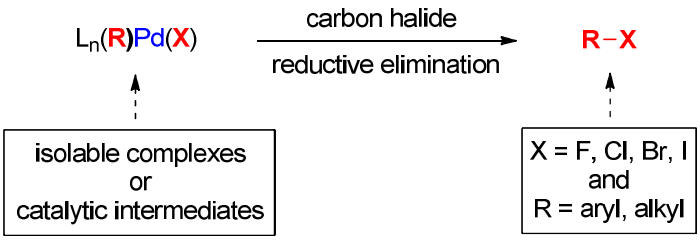

This review summarized the recent advances on the Pd(0)-catalyzed synthesis of organic halides, which involve the carbon halide reductive elimination as a key step in the catalytic cycle.

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Synthesis of Organic Halides via Palladium(0) Catalysis

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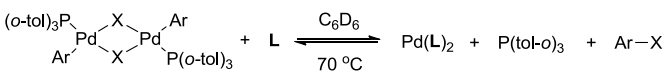
This Critical Review provides a brief overview of recent advances of palladium(0) catalysis toward synthesis of organic halides. It has been well established that very sterically hindered phosphine ligands are capable of promoting the reductive elimination of carbon halide from C-Pd(II)-X species (X = F, Cl, Br, I), which has been proven to be an elemental reaction more common than the previous assumption and has exhibited great potential for organic halides synthesis, including aryl fluorides.

Introduction

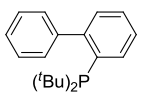
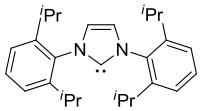
Organic halides represent one of the most widely-used starting materials in transition-metal catalysis. This is mainly due to their facile and viable oxidative addition to low valent metal center. In this context, numerous theoretical and experimental studies have been conducted to disclose the details of oxidative addition of organic halides to Pd(0)-complex, especially the ligand effects and the origins of different reactivities of organic halides on the formation of C-Pd(II)-X species.[1] Since the oxidative addition of organic halides to Pd(0)-center is usually thermodynamically favorable, the reverse process, the reductive elimination of C-Pd(II)-X, has been regarded as less likely to form organic halides. However, the principle of microscopic reversibility tells us that this type of reductive elimination still remains possible. This raises a fundamental question: how to realize this highly endothermic process.

Despite the apparent difficulty in the reductive elimination of C-Pd(II)-X, the recent developments have clearly demonstrated that this process can be a significantly more common reaction than the previous assumption and has exhibited some advantages toward organic halides synthesis. The purpose of this Critical Article is to provide a brief overview of these developments. Besides, this Article will also include some Pd(0)-catalyzed halide-atom-transfer cyclizations. The processes involving Pd(IV) complexes and other metals are not covered.[2]

The Stoichiometric Study on C-halide Reductive Elimination



1 [Ar = 2-Me-5-(^{t}Bu)C_6H_3]

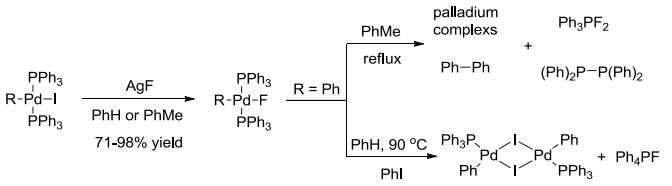
L	yield	L	yield
$P(^tBu)_3$	70% Ar-Cl 70% Ar-Br 39% Ar-I	$PFc(^tBu)_2$	0
$PCy(^tBu)_2$	10% Ar-Cl 15% Ar-Br		0
$P(1\text{-Ad})(^tBu)_2$	69% Ar-Cl 81% Ar-Br		0
Q-phos	52% Ar-Cl 42% Ar-Br		

Scheme 1: Reductive Elimination of Complex 1 and Ligand Effects

Although early examples of the carbon halide reductive elimination started to appear in the literature about 40 years ago,[3] the Pd(II)-involved variant was firstly observed from the isolable Pd(II)-complexes **1** by Roy and Hartwig in 2001 (Scheme 1).[4] The authors disclosed that only very sterically hindered phosphine ligands were able to promote the reductive elimination of **1**, leading to the formation of the corresponding

aryl halides. The details about ligand screening were summarized in Scheme 1. Furthermore, large excess of ligand was also found to be required and the highest yields were obtained when approximately 15 equiv of $P(^tBu)_3$ were used. Interestingly, the reactivity of the halide followed the trend I>Br>Cl, strongly indicating the importance of the kinetic factors in carbon halide reductive elimination.

These results clearly demonstrated that very sterically hindered phosphane ligands can alter the thermodynamics so severely that aryl halide reductive elimination is favored thermodynamically. We believed that sterically hindered phosphane ligands not only creates a crowded coordination environment in Pd(II) center to facilitate the aryl halide reductive elimination, but also makes the resulting Pd(0) species being crowded to slow down the reversed aryl halide oxidative addition.



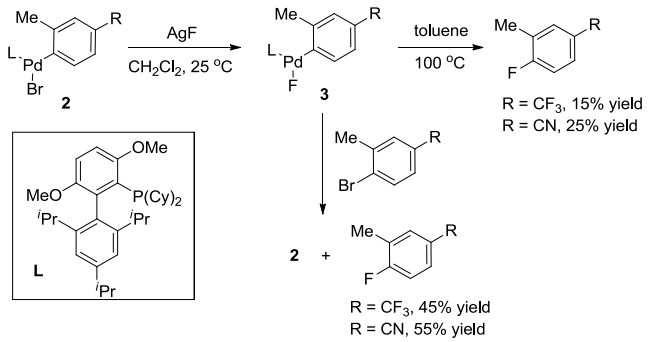
Scheme 2: Formation and Transformations of $(PPh_3)_2RPdF$

In contrast to the well-known heavier halide ligated complexes $(L)_nRPdX$ (X= Cl, Br, I), the fluoride-ligated analogues were rarely documented. The isolable and reliably characterized complex $(PPh_3)_2(Ph)PdF$ was firstly reported by Grushin and co-authors in 1997.[5] Treatment of $(PPh_3)_2(Ph)PdI$ with AgF readily forms $(PPh_3)_2(Ph)PdF$, which has been a standard method to synthesize this class of Pd(II)-F complexes (Scheme 2).

Although considerable efforts have been made by chemists, there are still few successful reports of the formation of ArF via the reductive elimination of $(PPh_3)_2(Ar)PdF$.[6] For example, the thermal decomposition of $(PPh_3)_2(Ph)PdF$ in refluxing toluene often resulted in the formation a P-F bond among other compounds such as Ph_3PF_2 and $[(Ph)_2P]_2$ instead of the desired reductive elimination product PhF. Even in the presence of additional PhI, $(PPh_3)_2(Ph)PdF$ was found to be converted into $[(PPh_3)PhPdI]_2$ dimer and Ph_4PF (Scheme 2). These results clearly demonstrate that to form an Ar-F bond via the carbon fluoride reductive elimination is extremely challenging.

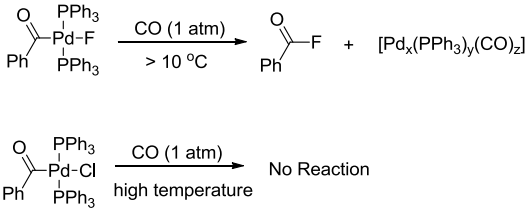
In 2007, Yandulov and Tran used the complex $[Pd(4\text{-}NO_2\text{-}C_6H_4)L(\mu\text{-}F)]_2$ [L = P(o-Tolyl)$_3$ or $P(^tBu)_3$)] to investigate the Ar-F reductive elimination.[7] Again, the thermal decomposition of these two complexes indeed formed somewhat complicated organic chemicals rather than the desired ArF, even in the case of bulky ligand $P(^tBu)_3$. However, treatment of $[Pd(4\text{-}NO_2\text{-}C_6H_4)(P^tBu_3)(\mu\text{-}F)]_2$ with bulkier ligand $P(2\text{-Trip-}C_6H_4)(^tBu)_2$ indeed led to the observation of ArF albeit in very low yield. Although the use of the strong activating nitro group might cast doubt on whether the resulted ArF arose from the aryl fluoride reductive elimination,[8] this finding may be on the right way towards this challenging task.

It is well-known that very sterically hindered phosphane ligands are capable of the formation of monomeric (L)RPdX with T-shaped geometry at palladium center, which has been proved to be essential for some Pd-catalyzed transformations.[9] Buchwald and co-workers recently disclosed that this capability of bulkier phosphine ligand is also crucial for this difficult aryl fluoride reductive elimination. Indeed, they found that monomeric complex **3** readily underwent reductive elimination to form ArF product upon heating in toluene (Scheme 3).[10] The yields in these reactions could be increased significantly if the thermolysis was conducted in the presence of additional aryl bromides. More importantly, in the latter cases, the oxidative-addition complexes **2** were detected as the only phosphorous-containing products, strongly suggesting that LPd(0) was formed along with the ArF product.



Scheme 3: the Reductive Elimination of Carbon Fluoride

Interestingly, $[(Ph_3P)_2(PhCO)PdF]$ complex, which was formed upon carbonylation of $[(Ph_3P)_2(Ph)PdF]$ with CO, rapidly underwent reductive elimination of benzoyl fluoride under CO atmosphere at room temperature (Scheme 4).[5] This observation may be attributed to the formation of σ-benzoyl-palladium bond which would create an electron-deficient metal center. In contrast, heavier halide analogues $[(Ph_3P)_2Pd(COPh)X]$ (X = I, Br, Cl) cannot undergo similar reductive elimination even at elevated temperatures (Scheme 4).[11]



Scheme 4: Reductive Elimination of $[(Ph_3P)_2Pd(COPh)X]$ (X = F or Cl)

However, Quesnel and Arndtsen very recently discovered that complex $[(P^tBu_3)(PhCO)PdCl]$ readily underwent reductive elimination upon treatment with CO, resulting in the nearly quantitative formation of benzoyl chloride, along with the phenyl iodide oxidative addition product $[(P^tBu_3)(PhCO)PdI]$ (Scheme 5).[12] The ability of $P(^tBu)_3$ to promote this transformation may arise from its size and donor ability, which both creates a coordination site on palladium for the π-acid CO

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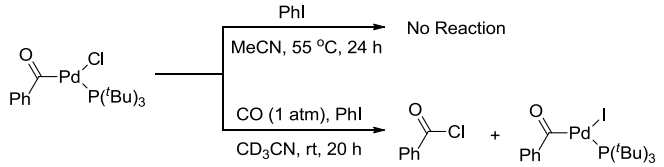
ligand. Accordingly, the associated CO ligand may result in an electron-deficient palladium center. Thus, the dual steric and electronic effects of $P(^tBu)_3$ and CO facilitate the reductive elimination of benzoyl chloride. Without CO atmosphere, no reaction was observed even at elevated temperature and in the presence of excess phenyl iodide to trap any resultant $(^tBu)_3PPd(0)$ species, suggesting that the reductive elimination of acid halide is neither kinetically viable nor thermodynamically favored.



Scheme 5: Reductive Elimanation of [(P^tBu_3)(PhCO)PdCl]

Palladium(0) Catalysis Involved Carbon Halide Reductive Elimination

The investigations based on the well-defined L_nRPdX (n =1, 2) complexes have shed light on the carbon halide reductive elimination. Most importantly, the above-mentioned researches have infrangibly established that very sterically hindered phosphane ligand is the key point for this thermodynamically disfavored process. These fundamental advances have paved the way for the emergence of some novel Pd(0)-catalyzed transformations involving the step of carbon halide reductive elimination in catalytic cycle, which provide an alternative for efficient synthesis of organic halides.

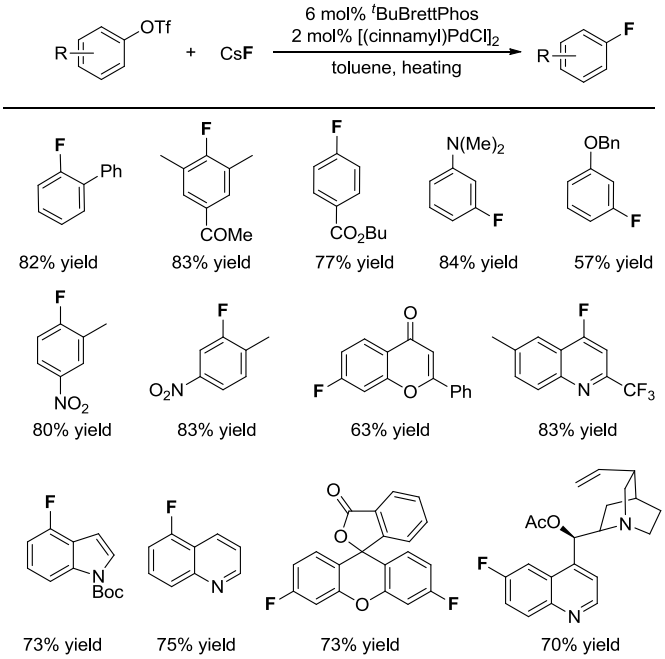


Figure 1: Pd(0)-Catalyzed Conversion of Aryl Triflates into the Corresponding Aryl Fluorides

Synthesis of aryl halides and acid chlorides

On the base of their observation of the reductive elimination of complex **3** to form ArF product, Buchwald and co-workers elegantly developed a Pd(0)-catalyzed process for direct conversion of aryl triflates into the corresponding aryl fluorides simply using CsF as fluoride source (Figure 1).[10] Ligand ^{t}BuBrettphos was proved to be most efficient for this transformation. The authors believed that the use of the sterically demanding, electron-rich biaryl monophosphine ^{t}BuBrettPhos not only promotes the event of reductive elimination because of its large size but also prevents the formation of dimeric $[LPdAr(F)]_2$ complexes. In consistence with the findings described in the section of stoichiometric version, both of these factors appear to be critical for reductive elimination of C-Pd(II)-X. As shown in Figure 1, this transformation features a wide range of substrate scope. Importantly, some heterocyclic substrates, including Flavones, indoles as well as quinolines, can be fluorinated. Fluorinated fluorescein and quinine can be synthesized using this system, demonstrating the potential of this method for the preparation of pharmaceutically relevant F-containing compounds.

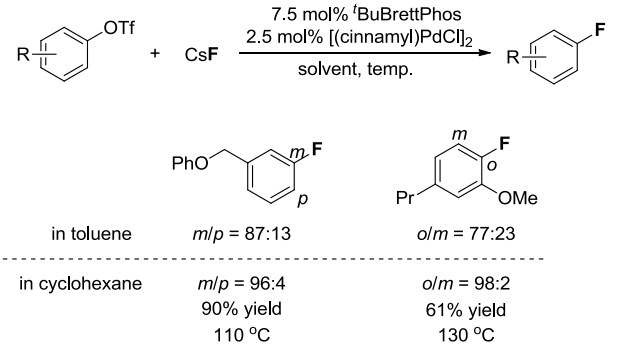


Figure 2: Solvent Effects on the Regioselectivity in Pd(0)-Catalyzed Fluorations

Interestingly, regioisomeric products were observed in a few cases. Although the authors did not provide a precise mechanism to explain the formation of regioisomers, they found that switching the reaction solvent from toluene to cyclohexane completely suppressed the formation of the undesired isomer. As can be seen in Figure 2, the use of cyclohexane afforded almost exclusively the desired product.

In 2013, the Pd(0)-catalyzed fluorination of aryl triflates was significantly improved by the same group.[13] Buchwald and coworkers found that complex $(AdBrettPhos\text{-}Pd)_2(COD)$ is an efficient precatalyst for the fluorination of electron-rich substrates, as well as heterocycle-containing aryl triflates, providing the corresponding aryl fluorides in synthetically useful yields and contaminated only with easily separated side products (Figure 3). Although the precise structure of $(AdBrettPhos\text{-}Pd)_2(COD)$ has not been well established, the authors believed that this precatalyst could provide the active catalytic species without generation of reactive byproducts, such as "Cl^-", dba, carbazole, or HF, that accompany the

activation of other Pd sources and represents a significant improvement for this reaction.

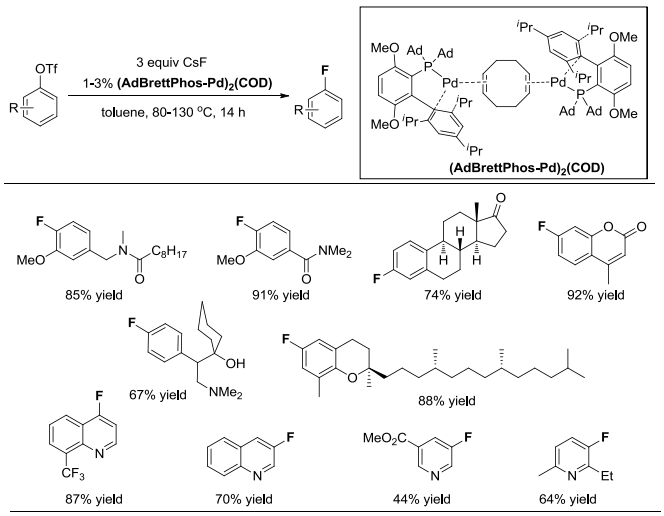
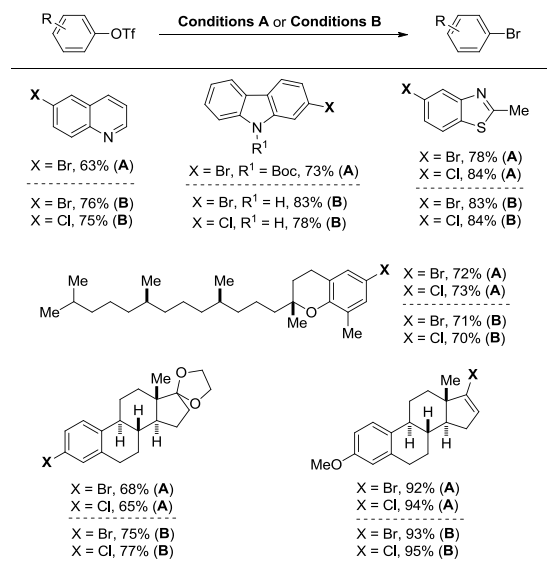


Figure 3: An Improved Catalyst System for the Pd(0)-Catalyzed Fluorination

Later on, Buchwald and co-workers successfully expanded these reaction conditions for conversion of aryl and vinyl triflates to bromides and chlorides.[14] As highlighted in Figure 4 (conditions **A**), a wide range of organic bromides and chlorides can be synthesized with the use of KBr or KCl as the halide source. PEG 3400 as the phase transfer catalyst was required to increase the solubility of KX (X = Br, Cl) while the combination of butanone and $(^{i}Bu)_3Al$ was believed to generate the dialkylaluminum alkoxide *in situ* to suppress the formation of undesired by-products (Figure 3).

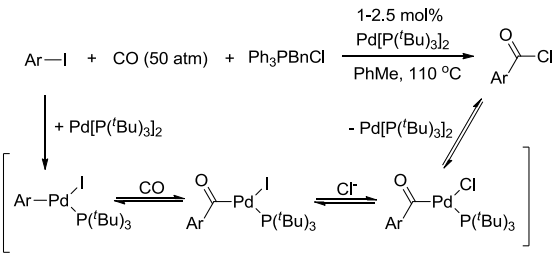


Conditions A: 1.5-2.5 mol% $Pd_2(dba)_3$, 3.75-6.25 mol% ^{t}BuBrettPhos,1.5 equiv K**X**, PEG3400, 1.5 equiv 2-butanone, 1.5 equiv $^{t}Bu_3Al$, toluene,100°C.
Conditions B: 1.5 mol% $Pd_2(dba)_3$, 4.5 mol% ^{t}BuBrettPhos, 2 equiv K**X**, 0.5 equiv KF, dioxane, 130 °C.

Figure 4: Selected Examples of the Pd(0)-Catalyzed Conversion of Aryl Triflates into the Corresponding Aryl Halides

To address the issue of the complexity of the reaction conditions, the authors developed more general and practical conditions only with the use of KF as the additive, which greatly improved the reaction efficiency (Figure 3, conditions **B**).[15] Although, in these cases, the involved aryl halide reductive elimination is a endoergic step, the overall reaction proceeds downhill.

Very recently, Arndtsen and co-workers developed the first example of the Pd(0)-catalyzed synthesis of acid chlorides from aryl iodides and CO (Scheme 6).[12]



Scheme 6: Palladium-Catalyzed Carbonylation Approach to Acid Chloride Synthesis

For these reaction conditions, the following issue should be emphasized: *i)* high reaction temperature. Due to much higher reactivity of product (acid chloride) than starting material (aryl iodide), the oxidative addition of acid chloride to Pd(0) was presumed to slow down the reaction. Thus, high reaction temperature was required to overcome this kinetic product inhibition, resulting in a clean catalytic route to generate benzoyl chloride from phenyl iodide and CO. *ii)* high CO pressure. Moderate pressure is viable and elevated CO pressure allows the isolation of these acid chloride products via simple filtration of the insoluble halide salts and precipitation of the palladium catalyst. These two issues are very different from those in the case of stoichiometric experiments relevant to isolated complex [($P^{t}Bu_3$)(PhCO)PdCl].

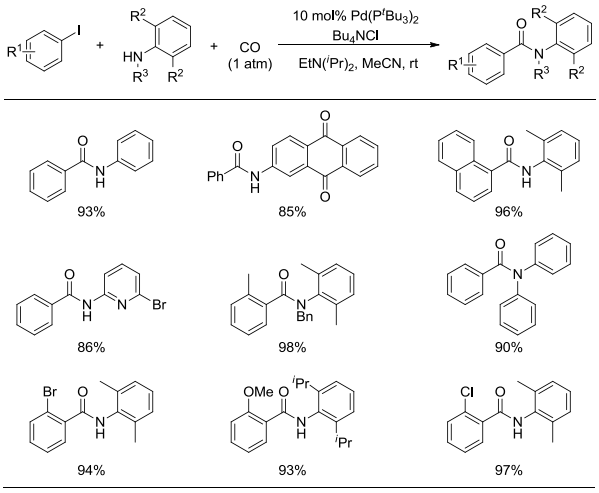


Figure 5: Ambient Temperature and Pressure Palladium-Catalyzed Aminocarbonylationsa

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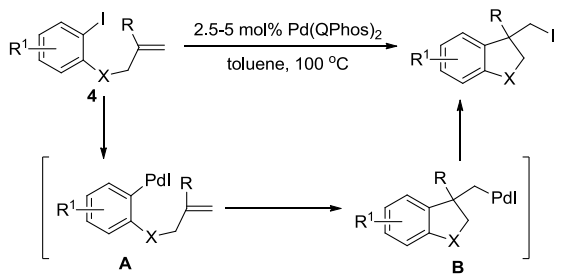
When the resulting acid chloride was trapped by amine, the so-called aminocarbonylation of aryl iodide was smoothly realized at room temperature under CO atmosphere. As illustrated in Figure 5, a wide range of aryl iodides and amines are suitable substrates under these reaction conditions, even including nitrogen-containing heterocycles which are too poor nucleophilicity and coordinating ability to participate in palladium-catalyzed carbonylations.

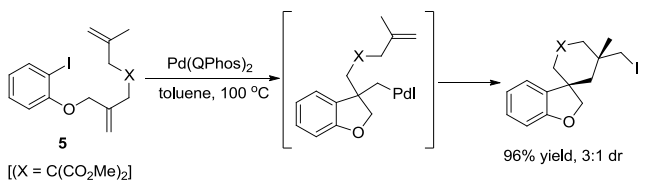
Synthesis of alkyl iodides

In sharp contrast to the isolable and well-characterized L_n(aryl)PdX complex, the L_n(alkyl)Pd(II)X complexes are less documented. The L_n(alkyl)PdX complex is believed to be highly reactive owing to the absence of stabilizing electronic interaction with metal *d*-orbitals.[16] The fast and thermodynamically favored β-hydride elimination is a predominant process for the (alkyl)PdX specie. Therefore, in the researches toward synthesis of alkyl halides via reductive elimination of alkyl halide, the utmost attention should be paid to form a L_n(alkyl)PdX specie without β-hydride in alkyl group.



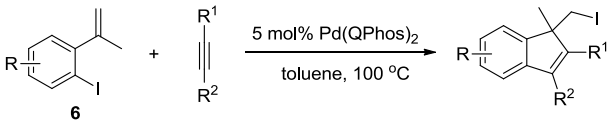
Scheme 7: Palladium-Catalyzed Intramolecular Carboiodination of Alkene-tethered Aryl iodides

In 2011, Newman and Lautens employed $Pd(Qphos)_2$ as the catalyst to realize carboiodination of alkenes **4**.[17] As drawn in Scheme 7, insertion of alkene into the Ar-Pd(II) bond of intermediate **A**, which was readily generated via oxidative addition between Pd(0) and aryl iodide, was cleverly designed to form (alkyl)-Pd(II)-I intermediate **B** in which the β-hydride was blocked by R group. The authors found that only bulky ligands such as Qphos, $P(t\text{-}Bu)_3$ as well as $PhP(t\text{-}Bu)_2$ were able to promote the reductive elimination of intermediate **B**, giving alkyl iodide in good conversion, while less bulky ligands PCy_3 and $P(o\text{-}tol)_3$ were totally inert. Again, these results clearly demonstrate the importance of very sterically hindered phosphane ligand for the reductive elimination of C-Pd(II)-X.



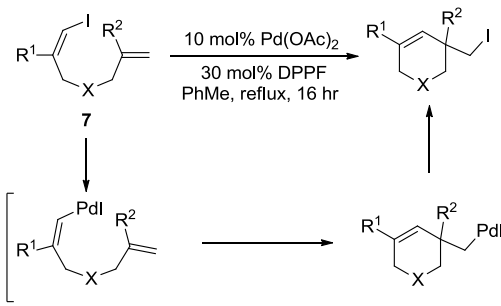
Scheme 8: Domino Synthesis of Polycyclic Alkyl Iodide

Then, Lautens and co-workers developed a novel "zipper"-type transformation of polyunsaturated aryl iodides **5**, under the same conditions (Scheme 8), in which the reductive elimination of carbon iodide was firstly used as an efficient terminating step in a domino process.[18]



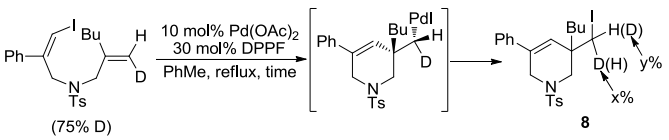
Scheme 9: Pd(0)-Catalyzed Conjunctive Carboiodination to Indene Synthesis

Again, Lautens and co-workers used the reductive elimination of carbon iodide as the terminating step to realize the domino reaction of 2-iodo-a-methyl styrene **6** with alkyne (Scheme 9).[19] This methodology allows access to polysubstituted indenes through the formation of two new carbon–carbon bonds and one new carbon–iodine bond.



Scheme 10: Pd(0)-Catalyzed Carboiodination of Alkene-tethered Vinyl iodides

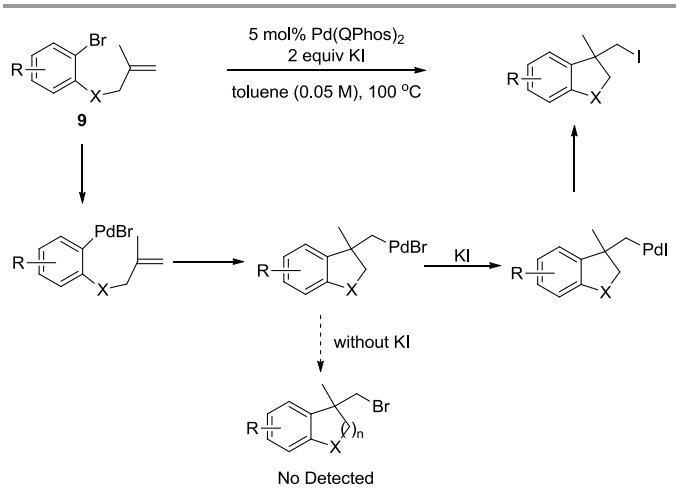
Almost at the same time, Tong and co-workers developed a similar Pd(0)-catalyzed carboiodination process with the use of vinyl iodides **7** (Scheme 10).[20] Not like the very sterically hindered phosphane ligand for the above-mentioned reductive elimination event, DPPF was found to be most efficient for this transformation although its high loading (30 mol%) was required.



entry	time	substrate recovery	product	isolated yield
1	2 hr	33%	**8a** (x = 75, y = 0)	60%
2	6 hr	20%	**8b** (x = 73, y = 2)	64%
3	10 hr	5%	**8c** (x = 71, y = 4)	75%
4	16 hr	0%	**8d** (x = 58, y = 17)	79%
5	24 hr	0%	**8e** (x = 40, y = 35)	72%

Scheme 11: Time-dependent Deuterium Scrambling

Furthermore, no observation of deuterium scrambling in product **8a** strongly supported that the reductive elimination of (alkyl)-Pd(II)-X is a stereospecific process (Scheme 11). Interestingly, the deuterium scrambling was found to be strongly time-dependent, implying that the combination of $Pd(OAc)_2$ and DPPF might be able to initiate a radical process.

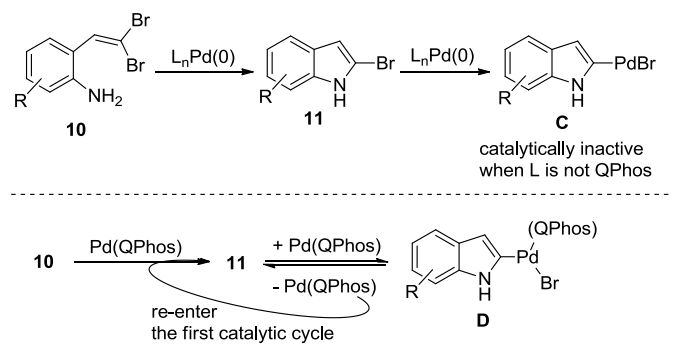


Scheme 12: Palladium-Catalyzed Halogen-Exchange Carboiodination

Later, Lautens and co-workers successfully realized the Pd(0)-catalyzed carboiodination of aryl bromides **9** with the help of 2 equiv of KI in dilute toluene solvent (Scheme 12).[18] Without the additive KI, no synthetically useful quantities of carbobromination product was detected, strongly implying that alkyl halide reductive elimination may be less efficient with bromides than it is with iodides.

Houk and co-workers employed DFT study to investigate the mechanism of Lautens's carboidodinations.[21] Their calculated data disclosed that the dissociative mechanism is favored for the step of alkyl halide reductive elimination. Thus, the origins of different reactivities of halides may arise from the different bond dissociation energies of the Pd-X bond. Indeed, the calculated bond dissociation energies of the Pd-I, Pd-Br and Pd-Cl are 72.8 kcal/mol, 81.1 kcal/mol, 91.9 kcal/mol, respectively, indicating that C-Br and C-Cl reductive eliminations are required to overcome higher activation-energy barriers. Their calculation also showed that the alkene insertion step is exergonic by 10 kcal/mol, which strongly compensates the energy of alkyl iodide reductive elimination and serves as an important driving force in this catalytic cycle.

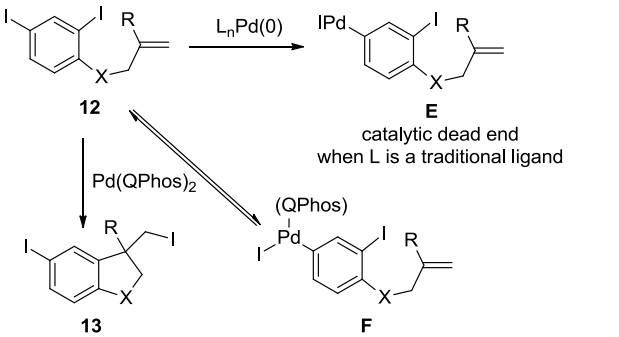
Harnessing the reductive elimination of carbon halide



Scheme 13: the Importance of the C-Br Reductive Elimination in Palladium-Catalyzed Synthesis of 2-Bromoindoles

During their study on the Pd(0)-catalyzed transformation of gem-dibromoolefins **10**, Lautens and co-workers observed that a boronic acid was necessary for conversion of the starting material (Scheme 13).[22]

The intermediacy of **11** should be formed after the first catalytic cycle relevant to the C-N band formation. However, this product was never observed directly in the reaction and the starting material was recovered in the absence of boronic acid. These results forced the authors to suggest that the active Pd(0) catalyst was undergoing irreversible oxidative addition after the first turnover, leading to catalytically inactive Pd(II) species **C**, thus shutting down the whole of catalytic cycle. Fortunately, $P(^tBu)_3$ was found to be efficient to promote the aryl bromide reductive elimination of intermediate **D**, therefore releasing the catalyst to re-enter the first catalytic cycle (Scheme 13). [23] This unique mechanism allows for the efficient C-N bond formation to form novel 2-bromoindoles **11** from gem-dibromoolefins **10**. These findings clearly demonstrate the importance of harnessing the carbon halide reductive elimination in some palladium(0) catalysis.



Scheme 14: the Importance of the C-I Reductive Elimination in Palladium-Catalyzed Transformation of Polyhalogenated Substrates

The power of this concept was further highlighted by the Pd(0)-catalyzed transformation of polyhalogenated substrates **12** (Scheme 14).[24] In the case of di-iodinated substrate **12**, one can anticipate that the 4-iodo group would react before the more hindered 2-iodo group, which might generate intermediate **E**. As is the case for the reaction of compound **10**, intermediate **E** could lead to catalytic dead end without additional reaction partner such as alkenes or nucleophiles. Through the carbon iodide reductive elimination of intermediate **F** enforced by QPhos ligand, di-iodinated substrate **12** was readily converted into the desired product **13**. The concept of harnessing the reductive elimination of carbon halide provides a general and attractive solution for commonly encountered problems associated with polyhalogenated substrates.

Synthesis of Alkyl Halide via Pd(0)-Catalyzed Radical Process

As early as 1988, Mori and co-workers reported the $Pd(PPh_3)_4$-catalyzed halide-transfer cycloisomerization of alkene-tethered α-haloester **14** (Scheme 15).[25] Interestingly, no β-hydrogen

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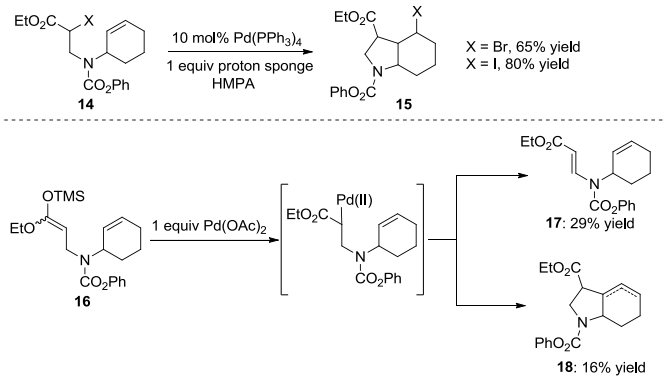
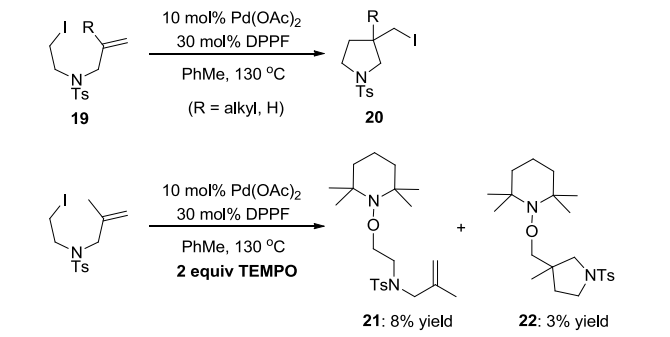
elimination products were observed, which might rule out the reaction pathway involving any σ-alkyl palladium(II) intermediates. In fact, the σ-alkyl palladium(II) species, which were produced by the viable reaction of compound **16** and $Pd(OAc)_2$, really led to two types of β-hydrogen elimination products **17** and **18** (Scheme 15). Thus, one can conclude that the Pd(0)-catalyzed conversion of **14** to **15** might be a free-radical chain reaction.



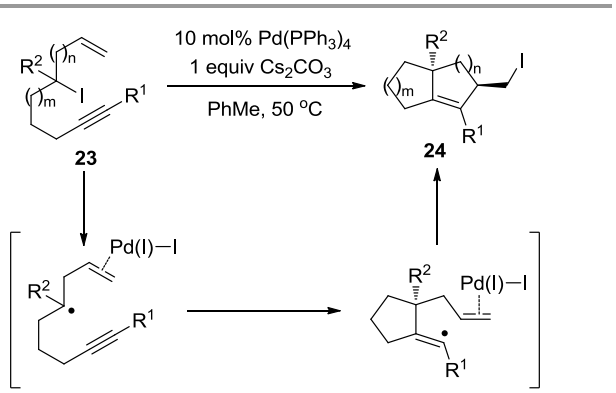
Scheme 15: Mori's Pd(0)-Catalyzed Halide-Transfer Cyclization

The Pd(0)-initiated free-radical type of halide-transfer reaction was further proved by Jiang and co-workers (Scheme 16).[26] They found that the combination of $Pd(OAc)_2$ and DPPF could efficiently promote the transformation of alkene-tethered alkyl iodide **19** into product **20**. The free-radical chain mechanism was solidly established on the base of the isolation of two TEMPO radical adducts **21** and **22** (Scheme 16).



Scheme 16: Pd(0)-Catalyzed Iodide-Transfer Cyclization

Very recently, Cook and Monks developed a $Pd(PPh_3)_4$-catalyzed zipper-type reaction of alkyl iodide **23**, leading to the isolation of the diquinane **24** bearing a primary iodide group (Scheme 17).[27] Their observations, such as ligand influence on stereoselectivity and compromised reactivity in the absence of the terminal olefin, strongly indicated the importance of the coordination between a putative Pd(I)I intermediate and the terminal olefin (Scheme 17). More importantly, the authors found that alkyl iodide **23** was quantitatively recovered under various conditions for some well-known radical atom-transfer cyclizations, clearly demonstrating the superiority of this Pd(0)-catalyzed transformation over traditional free radical methods.



Scheme 17: Palladium-Catalyzed Intramolecular Iodine-Transfer Reactions in the Presence of b-Hydrogen Atoms

Conclusions and Outlook

This Critical Review provides an overview of the recent advances related to the reductive elimination of C-Pd(II)-X. Very sterically hindered phosphane ligands have been proven to be essential for this thermodynamically disfavored process. While oxidative additions normally as the initial step in catalytic cycle are widely utilized in numerous Pd-catalyzed transformations, there is evidence that the reverse reaction of carbon halide reductive elimination can be significantly more common than the previous assumption and has exhibited some advantages for the synthesis of organic halides, especially the synthetically challenging organofluorine compounds. It is now clear that further attentions should be paid on the following issues: *i)* to develop the asymmetric version, *ii)* to uncover more precise mechanism of alkyl iodide reductive elimination, *iii)* to realize more challenging alkyl-Br and alkyl-Cl reductive elimination, *iv)* to develop novel Pd-catalyzed transformations with the use of reductive elimination of C-Pd(II)-X as the terminating step. It is our hope and expectation that these aims will be addressed in the future by chemists worldwide to result in more generally applicable synthetic methods.

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Notes and references

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