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Reductive Elimination

Bystanding F^+ Oxidants Enable Selective Reductive Elimination from High-Valent Metal Centers in Catalysis**

*Keary M. Engle, Tian-Sheng Mei, Xisheng Wang, and Jin-Quan Yu**

bystanding oxidants · C–H functionalization ·
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reductive elimination

Reductive elimination from partially or completely oxidized metal centers is a vital step in a myriad of carbon–carbon and carbon–heteroatom bond-forming reactions. One strategy for promoting otherwise challenging reductive elimination reactions is to oxidize the metal center using a two-electron oxidant (that is, from $M^{(n)}$ to $M^{(n+2)}$). However, many of the commonly used oxidants for this type of transformation contain oxygen, nitrogen, or halogen moieties that are subsequently capable of participating in reductive elimination, thus leading to a mixture of products. In this Minireview, we examine the use of bystanding F^+ oxidants for addressing this widespread problem in organometallic chemistry and describe recent applications in Pd^{II}/Pd^{IV} and Au^{I}/Au^{III} catalysis. We then briefly discuss a rare example in which one-electron oxidants have been shown to promote selective reductive elimination in palladium(II)-catalyzed C–H functionalization, which we view as a promising future direction in the field.

1. Introduction

Reductive elimination from transition metal centers is the final step in the catalytic cycles of a variety of carbon–carbon (C–C) and carbon–heteroatom (C–Y) bond-forming reactions. Prominent among transformations of this type are those that proceed via a Pd^0/Pd^{II} catalytic cycle. In this case, reductive elimination from the square-planar $[L_2Pd^{II}R^1Y]$ or $[L_2Pd^{II}R^1R^2]$ (R^1, R^2 = alkyl or aryl) intermediates generally forges a new C–C or C–Y bond.[1,2] However, this elementary step is now often taken for granted, following the advent of powerful new classes of phosphine and *N*-heterocyclic carbene (NHC) ligands, which have been developed during the past few decades to accelerate these reactions.[3] The electron-rich character of these ligands helps facilitate oxidative addition, whilst their steric bulk promotes reductive elimination.

By contrast, in the intimately related field of Pd^{II}-catalyzed carbon–hydrogen (C–H) bond functionalization,[4] choreographing the steps in a given catalytic cycle can be more problematic, as the aforementioned phosphine and NHC ligands are normally incompatible with the Pd^{II}-mediated C–H cleavage step. Thus, to induce reductive elimination from the putative $[Pd^{II}R^1Y]$ or $[Pd^{II}R^1R^2]$ intermediates following C–H cleavage and nucleophile coordina-

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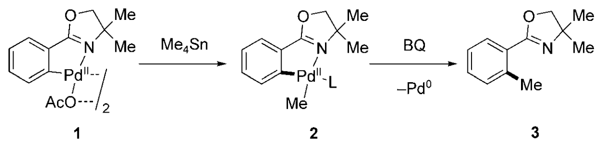
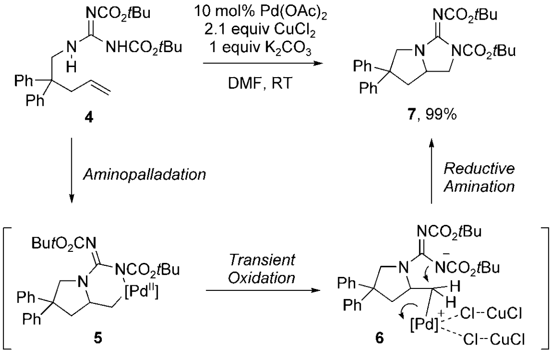
tion, several old tactics have been exploited. For instance, π-acceptor ligands, such as CO[5] and 1,4-benzoquinone (BQ),[6] are known to promote reductive elimination; as such, they have been found to play crucial roles in several C–H functionalization reactions. For instance, during the course of our group's work to develop the first Pd^{II}-catalyzed C–H activation/C–C cross-coupling reaction with organometallic reagents, BQ was found to be crucial for the C–C reductive elimination step from **2** to **3** (Scheme 1).[6d] Furthermore, in a Pd^{II}-catalyzed intramolecular olefin diamination reaction of guanidine **4**, $CuCl_2$ was elegantly used to induce reductive C–N bond formation from putative intermediate **5** (Scheme 2).[7] This step is proposed to proceed by transient oxidation[8] of Pd^{II} by $CuCl_2$, such that Pd^{II}, rather than Pd^0, serves as a leaving group.[9] Subsequently, $CuCl_2$ was also found to be effective in Pd^{II}-catalyzed C–H amination.[10] In this latter case, one mechanistic possibility is that $CuCl_2$ coordinates with the cyclopalladated intermediate and transiently oxidizes Pd^{II} to trigger reductive amination. Alternatively, Pd^{III} or Pd^{IV} intermediates could also be involved.

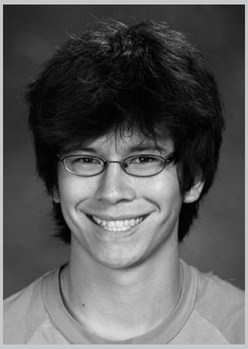


Scheme 1. BQ-promoted reductive elimination from a Pd^{II} intermediate in a Pd^{II}-catalyzed C–H activation/C–C cross-coupling reaction (Yu et al., **2006**).[6d] BQ = 1,4-benzoquinone.



Scheme 2. $CuCl_2$-promoted reductive amination in a Pd^{II}-catalyzed olefin diamination reaction (Muñiz et al., **2008**).[7] DMF = *N*,*N*-dimethylformamide.

The past decade has witnessed a renaissance in Pd^{IV} chemistry,[11–13] and among the transformations in this research area, C–H functionalization reactions that proceed by Pd^{II}/Pd^{IV} catalysis have received special attention.[13] Through recent investigations of C–H functionalization reactions, a number of new oxidants have been identified that are capable of inducing reductive elimination by oxidizing Pd^{II} to higher-energy Pd^{III}[14–16] or Pd^{IV} species. However, in the case of octahedral Pd^{IV} intermediates (**8**; Scheme 3), all three ligands *cis* to the aryl or alkyl fragment could, in principle, participate in reductive elimination. A lack of selectivity in this step would lead to a mixture of products **9**–**11**; therefore, controlling this process is a fundamental challenge for achieving selective catalysis.



Keary Mark Engle received his BSc from the University of Michigan for work on self-assembled monolayers under the supervision of Prof. Adam Matzger. As a Fulbright Scholar he carried out research in 2007–2008 with Prof. Manfred Reetz at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany). After a short research stay with Prof. Jan Bäckvall at Stockholm University (Sweden) he moved to the Scripps Research Institute under the supervision of Prof. Jin-Quan Yu as an NSF and NDSEG Predoctoral Fellow.

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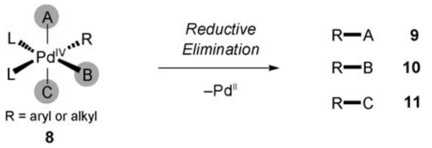


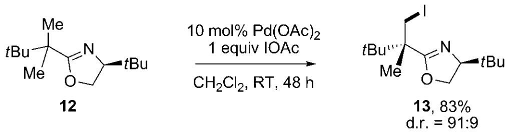
Scheme 3. Possible outcomes of reductive elimination from an octahedral Pd^{IV} intermediate.

Broadly speaking, devising strategies to suppress undesired reductive elimination events from high-valent metal species is crucial for enabling selective C–C and C–Y bond formation in a wide range of different catalytic processes. In this Minireview, we describe how bystanding F^+ oxidants can be applied to control selective reductive elimination in Pd^{II}/Pd^{IV} catalysis and in Au^{I}/Au^{III} catalysis. (We use "bystanding oxidant" herein to refer to a reagent that participates in electron transfer to increase the oxidation state of a transition metal species but is not incorporated into the final product during subsequent reductive elimination.)[17] The effectiveness of F^+ oxidants stems from the reluctance of metal species to undergo carbon–fluorine (C–F) reductive elimination,[18,19] which renders other high-energy reductive elimination pathways more tenable. In addition to examining examples from the literature, we discuss potential limitations of this strategy. We conclude by highlighting recent studies in which non-coordinative one-electron oxidants are similarly used to induce selective reductive elimination from high-valent metal centers, a complementary strategy that holds great promise for widespread application in catalysis.

Throughout the text, our emphasis is on catalytic transformations. Thus, we discuss stoichiometric transition metal complexes only to showcase the mechanistic features of particular organometallic reactions and to illustrate their potential relevance to individual steps in catalysis. On this note, we would like to caution readers to interpret this information in the appropriate context. Most isolable high-valent organometallic complexes are stabilized using strongly coordinating ancillary pyridine, phosphine, or NHC ligands and are often studied under conditions that are not necessarily compatible with all of the steps in a would-be catalytic cycle. In these cases, due diligence should be taken in extending the insights gleaned from mechanistic investigations of stoichiometric complexes to catalytic reactions, especially in cases where the substrates in question are known to exhibit comparatively weaker interactions with the metal during catalysis.[20]

2. Bystanding F^+ Oxidants in Pd^{II}/Pd^{IV} Catalysis

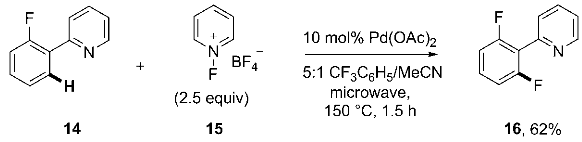
The prospect of devising catalytic processes to convert C–H bonds into carbon-halogen (C–X) bonds in a controlled and position-selective fashion has captivated organic and organometallic chemists for several decades. In the context of metal-mediated reactions, one method that has gained traction is using Pd^{II}-mediated C–H cleavage to generate a nucleophilic [Pd^{II}–R] species in situ that is capable of reacting with electrophilic X^+ reagents (for example, Cl_2, $CuCl_2$, NCS, NBS, NIS, IOAc, and $PhICl_2$). Oxidation to Pd^{IV} and subsequent C–X reductive elimination with concomitant regeneration of Pd^{II} then closes the catalytic cycle. Early studies showed the viability of this approach,[11a–c,13a] setting the stage for several more recent Pd^{II}-catalyzed C–H halogenation reactions reported by our group[13b,21] and others,[13a,22] including an asymmetric version using a removable chiral auxiliary developed in our laboratory (Scheme 4).[13b,23]



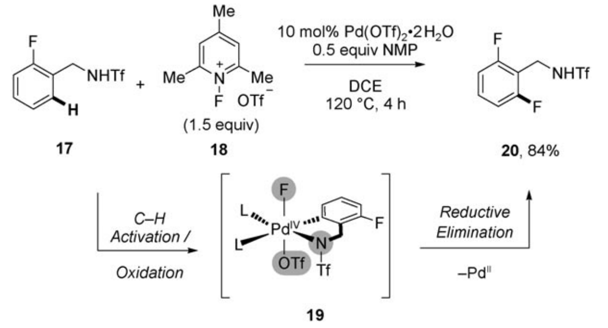
Scheme 4. The first report of diastereoselective Pd^{II}-catalyzed C(sp^3)–H iodination by Pd^{II}/Pd^{IV} catalysis (Yu et al., **2005**).[13b]

In contrast to other C–H halogenation reactions, fluorination has proven to be more problematic for two main reasons. First, electrophilic F^+ reagents[24] often contain chelating groups that can act as strong σ-donor ligands with Pd^{II}, thereby hampering the C–H cleavage step. Second, C–F reductive elimination is known to be less facile than other types of C–X reductive elimination.[18,19] This is presumably because fluorine is highly electronegative and thus forms a highly polarized bond with the metal center and because fluoride anions possess exceptionally low polarizability (and thus low nucleophilicity). Both of these factors are known to attenuate the rate of concerted reductive elimination reactions.[2]

Electrophilic F^+ sources have long been known to react with a wide range of organometallic reagents to form C–F bonds.[25,26] An attractive alternative approach is to exploit Pd^{II}-mediated C–H activation and react the resulting [Pd^{II}–R^1] species with an F^+ reagent in a Pd^{II}/Pd^{IV} catalytic process. Seminal work by Vigalok in 2003 established that [$L_2Pd^{II}Me_2$] complexes could engage in oxidation chemistry with XeF_2, a powerful F^+ electrophile (see below for a complete discussion).[27] In 2006, pioneering efforts by Sanford and coworkers then led to the development of the first Pd^{II}-catalyzed C–H fluorination reaction (Scheme 5).[28a] In Sanford's reaction, the use of substrate **14** containing a strongly coordinating pyridine directing group was crucial for facilitating Pd^{II} binding (and hence cyclometalation) in the presence of F^+ reagent **15**, which introduces a chelating pyridine ligand into the reaction medium. Our group then focused on developing a synthetically versatile *ortho*-C–H fluorination method with benzyltriflamides (**17**; Sche-



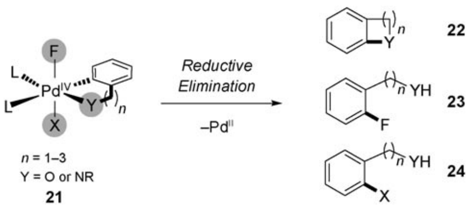
Scheme 5. The first report of Pd^{II}-catalyzed C–H fluorination by Pd^{II}/Pd^{IV} catalysis (Sanford et al., **2006**).[28a]



Scheme 6. Selective C–F reductive elimination using catalytic Pd(OTf)$_2$ with benzyltriflamide substrates (Yu et al., **2009**).[28b] DCE = 1,2-dichloroethane, NMP = *N*-methyl-2-pyrrolidone.

me 6).[28b] Our approach hinged upon the use of substrate **17**, containing a triflamide (Tf = trifluoromethanesulfonyl) directing group.[21c,29] We hypothesize that the nitrogen atom of this group coordinates to Pd as an X-type ligand. Thus, by design, the substrate can bind Pd^{II} without being in direct competition with the strongly chelating L-type pyridine ligand contained in F^+ reagent **18**.

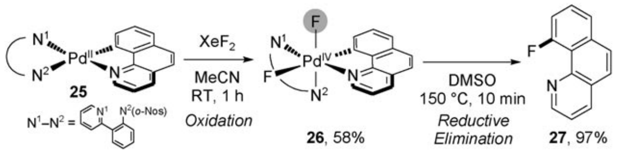
During the course of our work on C–H fluorination, we faced the aforementioned reductive elimination problem depicted in Scheme 3, as three possible pathways could theoretically proceed from the putative octahedral Pd^{IV} complex **21** (Scheme 7). Accordingly, we observed that



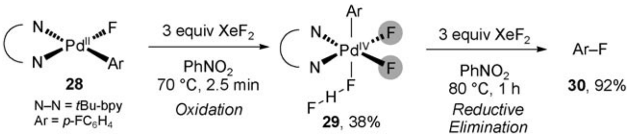
Scheme 7. Possible outcomes of reductive elimination from an octahedral Pd^{IV} intermediate in our studies of Pd^{II}-catalyzed C–H fluorination.[28b]

achieving selective C–F reductive elimination to form **23** was challenging when other nucleophilic anions (X) were present in the reaction solution. Various anions could compete favorably with fluoride in reductive elimination to generate **24** owing to the polarization of the Pd^{IV}–F bond and the comparatively low nucleophilicity of F^-. Gratifyingly, we eventually found that the use of Pd(OTf)$_2$ allowed for selective C–F reductive elimination. In this case, the poor nucleophilicity of the OTf^- anion plays a crucial role in facilitating the desired C–F reductive elimination pathway from **21**.

Detailed mechanistic studies on C–F reductive elimination from Pd complexes have also been reported in the past few years (Scheme 8 and 9).[18,19] These investigations have focused on characterizing Pd^{III} and Pd^{IV} intermediates in an effort to understand the factors that influence selectivity and reactivity in C–F reductive elimination. Notably, in 2008, Furuya and Ritter studied fluorination of **25**, a palladacycle with an ancillary stabilizing pyridyl sulphonamide ligand.[18b] They found that treatment with F^+ oxidants led to formation



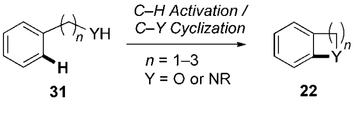
Scheme 8. C–F reductive elimination from a Pd^{IV} complex (Furuya and Ritter, **2008**).[18b] *o*-Nos = 2-nitrobenzenesulfonyl, DMSO = dimethylsulfoxide.



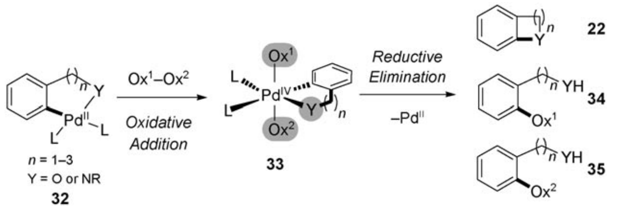
Scheme 9. C–F reductive elimination from a Pd^{IV} complex (Ball and Sanford, **2009**).[18c] *t*Bu-bpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

of a characterizable Pd^{IV} complex, **26**, which underwent C–F reductive elimination upon thermolysis. In 2009, Ball and Sanford examined C–F reductive elimination from **28**, the first example of a well characterized mono-σ-aryl Pd^{IV} complex in which the aryl unit is not stabilized by a neighboring chelating group.[18c] Intriguingly, attempts to heat **29** to induce C–F reductive elimination (analogous to the transformation of **26** to **27** in Scheme 8) led to formation of the corresponding biaryl homocoupling product. This finding suggests that C–F reductive elimination is slow relative to σ-aryl exchange. Nevertheless, they ultimately found that exposing **29** to excess XeF$_2$ led to the desired C–F reductive elimination to give **30** in good yield. At this stage, the mechanistic rationale of this finding remains unclear.

Though C–H fluorination using F^+ electrophiles by Pd^{II}/Pd^{IV} catalysis has proven to be an intriguing research area, the practicality of this approach is limited by the high cost of F^+ reagents. Thus, C–H fluorination using nucleophilic F^- sources by Pd^{II}/Pd^0 catalysis will most likely be more widely used in the long run. Nevertheless, our research efforts using electrophilic F^+ reagents ultimately guided us in other fruitful directions. In particular, we have long been interested in utilizing Pd^{II}/Pd^{IV} catalysis to construct heterocycles through direct cyclization of amino and hydroxy groups onto C–H bonds (**31** to **22**; Scheme 10).[16,21c] However, our early efforts in this direction were plagued by problems with selective reductive elimination from the putative high-valent Pd^{IV} intermediates (**33**; Scheme 11). For instance, our initial attempts to develop a Pd^{II}-catalyzed intramolecular C–H amination procedure for phenethyltriflamides (**30**) led to mixtures of the corresponding amination (**37**), acetoxylation (**38a**), and halogenation (**38b** and **38c**) products.[16,21c,29] Indeed, this problem persisted even as we examined a wide range of oxidants, a small sampling of which are shown in Table 1.[16]

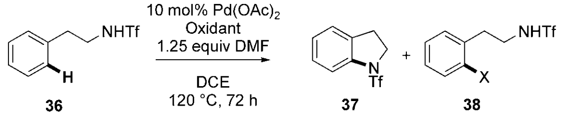


Scheme 10. Heterocycle formation by C–H activation/C–Y cyclization.



Scheme 11. Challenges in selective C–Y reductive elimination from Pd^{IV} intermediates. "Ox^1–Ox^2" represents a generic oxidant.

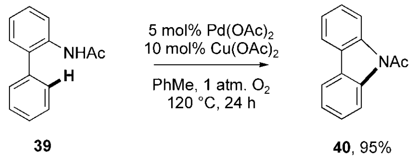
Table 1: Attempts to utilize common oxidants for selective C–N reductive elimination (Yu et al., **2009**).[16]



Entry	Oxidant[a]	% Yield (**37**)[b]	% Yield (**38**)[b]	X
1	PhI(OAc)$_2$	15	45	OAc (**38a**)
2	AcOO*t*Bu	13	50	OAc (**38a**)
3	NCS	0	20	Cl (**38b**)
4	NIS	0	35	I (**38c**)
5	IOAc[c]	0	40	I (**38c**)

[a] NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide. [b] The yield was determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. [c] Generated in situ from PhI(OAc)$_2$ and I_2.

At the time of our work, there was precedent for C–N reductive elimination in Pd^{II}-catalyzed C–H functionalization reactions, though examples were limited in number.[10,30–33] Interestingly, in 2005 Buchwald and co-workers disclosed a seminal example of Pd^{II}-catalyzed C–H amination by a presumed Pd^{II}/Pd^0 catalytic cycle (**39** to **40**, Scheme 12).[30]

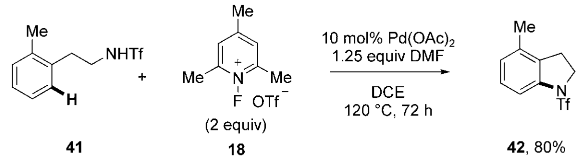


Scheme 12. Pd^{II}-catalyzed C–H amination (Buchwald et al., **2005**).[30]

In that report, C–N reductive elimination from Pd^{II} could be achieved in the absence of external ligands, generating substituted carbazole products (**40**) in good yields. The same transformation was later achieved by Gaunt and co-workers using Pd^{II}/Pd^{IV} catalysis at room temperature with PhI(OAc)$_2$ as the oxidant.[33]

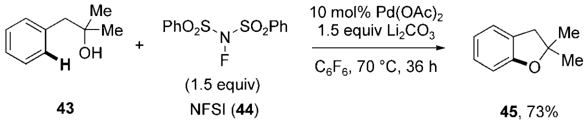
In the context of our work,[16] the disappointing data in Table 1 motivated us to consider alternative oxidation systems. In particular, we reflected on the insights gleaned from the recent developments in C–H fluorination chemistry and wondered whether we might be able to utilize an F$^+$ oxidant and take advantage of the slow C–F reductive elimination from Pd^{IV}. We hypothesized that F$^+$ reagents could serve as effective bystanding oxidants that would be capable of both oxidizing Pd^{II} to Pd^{IV} and promoting the desired (yet otherwise unfavorable) C–Y reductive elimination from the high-valent metal species, provided that our intramolecular heteroatom (Y) was appropriately nucleophilic (Scheme 11).

Indeed, we were able to carry out the desired intramolecular C–H amination reaction with phenethyltriflamides (**41**) in the presence of F$^+$ oxidant **18**, thus enabling a highly expedient route to functionalized indolines (**42**; Scheme 13).[16] Given the similarity of the reaction conditions to those used in the C–H fluorination reaction described in Scheme 8, it is worth mentioning that in this case C–N reductive elimination is energetically favorable because it forms a five-membered ring, whereas C–N reductive elimination event from **19** is not observed because it would form a strained four-membered ring (Scheme 6).



Scheme 13. Pd^{II}-catalyzed intramolecular C–H amination using a bystanding F$^+$ oxidant (Yu et al., **2009**).[16]

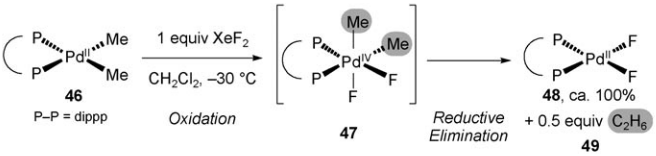
We were also able to exploit *N*-fluorobenzenesulfonimide (NFSI, **44**) as a bystanding F$^+$ oxidant for an unprecedented intramolecular C–H etherification reaction by Pd^{II}/Pd^{IV} catalysis (Scheme 14). We later found that PhI(OAc)$_2$ (1.5 equiv) offered better conversions under reduced catalyst loadings, and using this procedure, a diverse array of phenethyl alcohols could be cyclized to form the corresponding substituted dihydrobenzofurans (**45**) in a single step.[34]



Scheme 14. Pd^{II}-catalyzed intramolecular C–H etherification using a bystanding F$^+$ oxidant (Yu et al., **2010**).[34]

As part of the catalytic cycles for the two reactions discussed above, following selective C–Y reductive elimination from the putative Pd^{IV} complex, a [L$_2$Pd^{II}FX] species is formed. At this stage, several possible pathways exist. In one scenario, the F$^-$ anion would be displaced by an X$^-$ anion (for example, OAc$^-$) in solution to regenerate the active catalyst, prior to C–H activation. Alternatively, the [L$_2$Pd^{II}FX] complex could perform C–H activation directly, with either the F$^-$ anion or the X$^-$ anion serving as the internal base; oxidation by the F$^+$ bystanding oxidant and C–Y reductive elimination would then lead to [L$_2$Pd^{II}FX] or [L$_2$Pd^{II}F$_2$], respectively. If formed during catalysis, the [L$_2$Pd^{II}F$_2$] species could also theoretically engage in C–H activation or be converted into a catalytically active complex through anion exchange. At the present time, the operative mechanism in unknown.

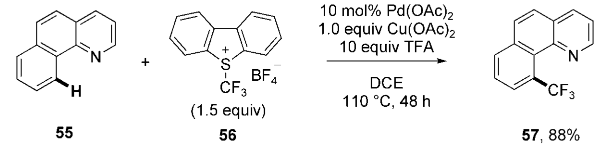
Along with C–Y reductive elimination in Pd^{II}/Pd^{IV} catalysis, bystanding F^+ oxidants have been shown to be effective in C–C reductive elimination.[27,35] In 2003, in a manuscript describing the synthesis of $[L_2Pd^{II}F_2]$ and $[L_2Pt^{II}F_2]$ complexes, Vigalok and co-workers found that treatment of $[Pd(dippp)Me_2]$ complex **46** (dippp = diisopropylphosphino)propane) with XeF_2 at −30 °C in dichloromethane led to C–C reductive elimination of C_2H_6 (**49**) along with concomitant formation of $[Pd(dippp)F_2]$ complex **48** (Scheme 15).[27] One possible mechanism would proceed via oxidation by XeF_2 to generate a Pd^{IV} complex (**47** is an example of a possible structure), which undergoes facile C–C reductive elimination.



Scheme 15. Selective C–C reductive elimination induced by XeF_2 (Vigalok et al., **2003**).[27]

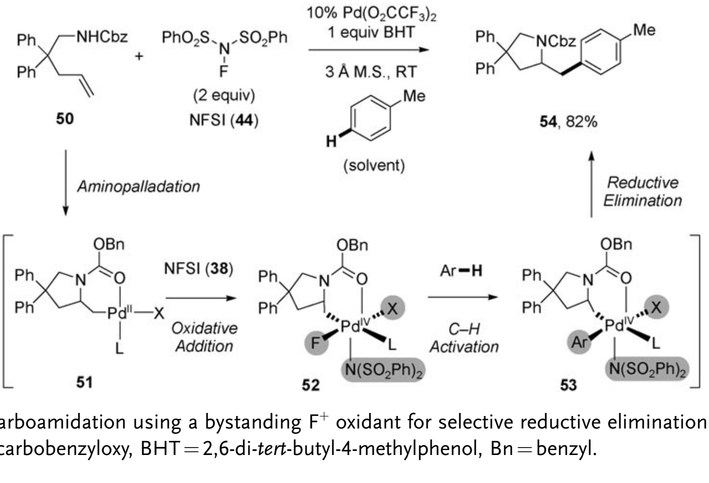
Many research groups have had a long-standing interest in olefin difunctionalization technology by Pd^{II}/Pd^{IV} catalysis using bystanding[36] and non-bystanding[37–40] oxidants. As part of this effort, Michael and co-workers studied olefin diamination using a non-bystanding F^+ oxidant, NFSI (**44**).[40] During the course of this work, they discovered an usual oxidative carboamidation when aromatic solvents were used, in which a solvent molecule was functionalized by a Pd-mediated C–H activation event (Scheme 16).[41,42] Specifically, they found that that treatment of **50** with NFSI (**44**) (2 equiv) and $Pd(O_2CCF_3)_2$ (10 mol %) in toluene in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT, a radical scavenger) and 3 Å molecular sieves (M.S.) effected intramolecular aminopalladation across the tethered olefin, followed by C–H alkylation of the arene solvent. Based on extensive mechanistic studies, the operative mechanism appears to proceed via an unusual Pd^{IV}-mediated C–H activation event, as depicted in Scheme 16. In this pathway, the F^+ reagent presumably triggers oxidation of intermediate **51** to Pd^{IV} species **52**. At this stage, C–F and C–N reductive elimination are sufficiently sluggish, such that a sequence of arene coordination, C–H activation, and C–C reductive elimination is the predominant pathway, giving carboamidated product **54** in good yield and excellent *para*-selectivity.

In contrast to other C–C bond forming events, $C-CF_3$ reductive elimination from Pd centers has proven to be challenging owing to the strength and inertness of $Pd-CF_3$ bonds.[19f,43,44] Indeed, reliable Pd-catalyzed procedures for $Ar-CF_3$ bond formation have largely remained elusive.[43,45] In the area of C–H functionalization, we reported the first example of Pd^{II}-catalyzed C–H trifluoromethylation (Scheme 17).[45] Using this method, various heterocycle-containing substrates (**55**) could be coupled with electrophilic CF_3^+ reagent **56**[46] in the presence of $Pd(OAc)_2$ (10 mol %) and two crucial additives: $Cu(OAc)_2$ (1.0 equiv) and TFA (10 equiv). One plausible mechanism for this reaction involves oxidation of Pd^{II} to Pd^{IV} by the CF_3^+ reagent, followed by reductive elimination to forge the new $C-CF_3$ bond. Recent mechanistic data support this potential pathway.[44c]

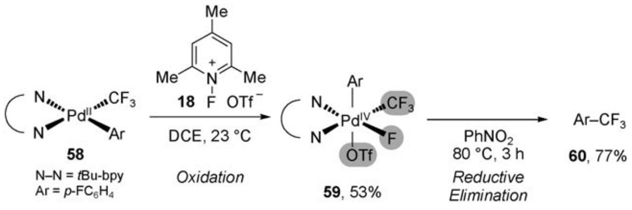


Scheme 17. The first example of Pd^{II}-catalyzed C–H trifluoromethylation (Yu et al., **2010**).[45] TFA = trifluoroacetic acid.

Given the challenges associated with $C-CF_3$ reductive elimination, using bystanding F^+ oxidants is potentially a viable approach. In an elegant mechanistic study, Sanford and co-workers demonstrated this concept, by taking advantage of an F^+ reagent to promote an otherwise unfavorable $C-CF_3$ reductive elimination event from a Pd^{IV} center (Scheme 18).[44b] In that report, $[Pd^{II}-CF_3]$ intermediate **58** was treated with electrophilic N–F reagent **18**. Following oxidation, intermediate **59** was obtained, which, upon heating, underwent $C-CF_3$ reductive elimination to form **60**. Notably,



Scheme 16. Pd^{II}-catalyzed olefin carboamidation using a bystanding F^+ oxidant for selective reductive elimination from a Pd^{IV} intermediate (Michael et al., **2009**).[41,42] CBz = carbobenzyloxy, BHT = 2,6-di-*tert*-butyl-4-methylphenol, Bn = benzyl.



Scheme 18. Selective C–CF$_3$ reductive elimination from a Pd^{IV} complex induced by a bystanding electrophilic N–F oxidant (Sanford et al., **2010**).[44b]

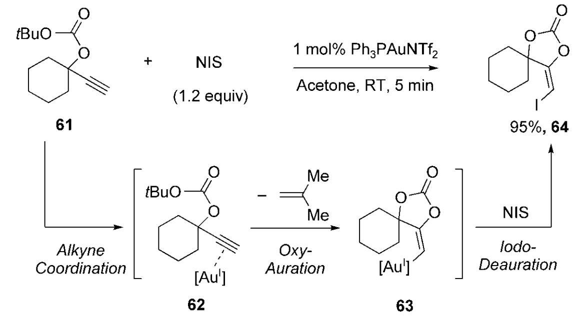
other common oxidants, such as PhI(OAc)$_2$, NCS, and NBS, gave less than 5% of **60**. In these cases, C–X and C–O reductive elimination predominated.

Given the versatility of Pd^{II} intermediates in different catalytic processes, developing strategies to enable otherwise unfavorable reductive elimination events is of paramount importance. Treating Pd^{II} species with a strong oxidant, with the aim of inducing reductive elimination from the resulting high-energy Pd^{III} or Pd^{IV} intermediates, is an attractive approach. However, its efficacy has been limited owing to a lack of selectivity in the reductive elimination step. The above examples illustrate how bystanding F$^+$ oxidants can engage in electron transfer with Pd^{II} species and facilitate C–N, C–O, and C–C reductive elimination.

3. Bystanding F$^+$ Oxidants in Au^I/Au^{III} Catalysis

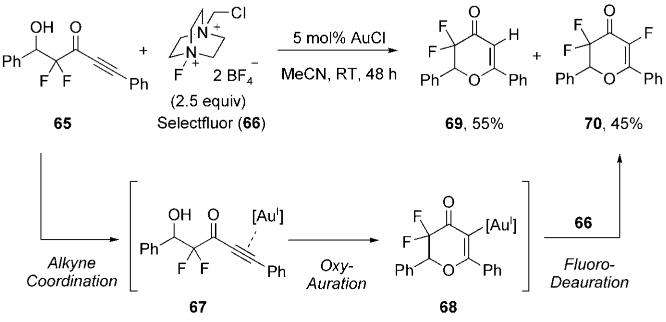
In parallel, F$^+$ reagents have also recently found great utility as bystanding oxidants in the field of homogeneous gold catalysis. During the past decade, Au^I and Au^{III} have been extensively used as soft carbophilic π Lewis acids for activation of alkynes, allenes, and alkenes for attack from a range of different nucleophiles.[47] However, given the high redox potential of Au^I, the development of general reactions based on Au^I/Au^{III} redox couple has remained a significant challenge,[47] even though this mode of catalysis is isoelectronic to Pd^0/Pd^{II} redox couple and is thus of practical interest from a reactivity standpoint. Indeed, Au-catalyzed variants of traditional cross-coupling reactions (generally catalyzed by Pd^0 or Ni^0 catalysts) have been actively investigated by several research groups.[48–50]

Alongside this work, it has been found that treatment of the putative [Au–vinyl] intermediates generated in Au-catalyzed reactions with halonium sources (e.g., NBS and NIS) can be an effective means of forming C–X bonds,[51,52a] presumably through a redox-neutral electrophilic functionalization mechanism (Scheme 19). For example, in 2006 Buzas and Gagosz disclosed a single example of iododeauration in an Au^I-catalyzed cyclization reaction. They found that treatment of **61** with catalytic Au^I in the presence of NIS led to formation of vinyl iodide **64** in good yield (Scheme 19).[51a]



Scheme 19. Electrophilic iodination of a [Au^I–vinyl] intermediate in a Au^I-catalyzed cyclization reaction (Buzas and Gagosz, **2006**).[51a]

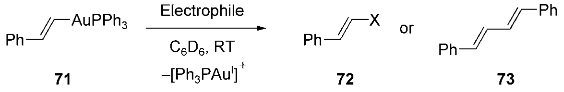
More recently, it has also been found that F$^+$ electrophiles can effect C–F bond formation in a similar manner.[52] Drawing on similar alkyne activation/cyclization/electrophilic functionalization sequence, in 2008, Gouverneur and co-workers found that exposure of **65** to a mixture of AuCl (5 mol%) and Selectfluor (**66**) (2.5 equiv) gave **70** in moderate yield (Scheme 20).[52a] In this reaction, the major byproduct was **69**, resulting from protodeauration of intermediate **68**.



Scheme 20. Electrophilic fluorination of a [Au^I–vinyl] intermediate in a Au^I-catalyzed cyclization reaction (Gouverneur et al., **2008**).[52a]

In 2009, Hashmi and co-workers carried out a direct investigation of the reactivity of [Au^I–vinyl] complex **71**, prepared using stoichiometric organometallic techniques, with various commonly used electrophilic reagents (Table 2).[53] In entries 1–4, the use of electrophilic X$^+$ reagents, NCS, NBS, NIS, and Barluenga's reagent (**74**),[54] led to formation of halogenated products **72a–c** in good yields. Selectfluor (**66**), on the other hand, was found to be unreactive, possibly because of low solubility (entry 5). Intriguingly, NFSI (**44**) led to the exclusive formation of

Table 2: Reactions of a [Au^I–vinyl] complex with common halonium sources (Hashmi et al., **2009**).[53]

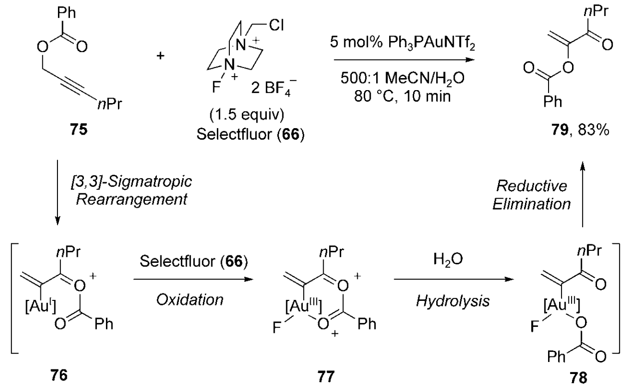


Entry	Electrophile[a]	X	% Yield (72)	% Yield (73)
1	NCS	Cl (**72a**)	95	0
2	NBS	Br (**72b**)	95	0
3	NIS	I (**72c**)	96	0
4	Py$_2$I$^+$BF$_4^-$ (**74**)	I (**72c**)	88	0
5	Selectfluor (**66**)	F (**72d**)	0	0
6	NFSI (**44**)	F (**72d**)	0	96

[a] Py = pyridine.

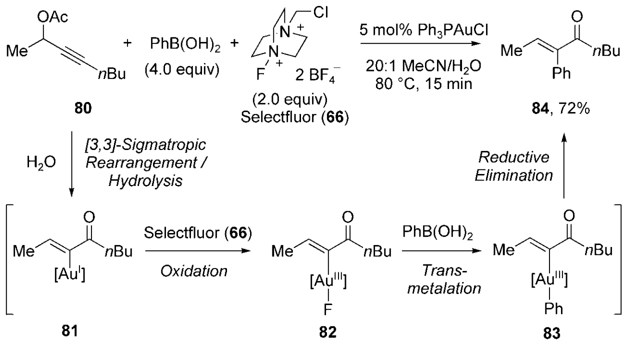
oxidative coupling product **73** (entry 6). The operative mechanism in this case is most likely one in which NFSI (**44**) serves as a bystanding F^+ oxidant, adding to **71** to generate an Au^{III} species. Following transmetalation and C–C reductive elimination, **73** can be obtained. Indeed, a variety of transformations based on Au^I/Au^{III} catalysis have previously been reported using other powerful bystanding oxidants such as $PhI(OAc)_2$ and *t*BuOOH.[55–58]

Zhang and co-workers developed an important class of Au^I-catalyzed reactions that take advantage of electrophilic N–F reagents as bystanding oxidants to convert Au^I into Au^{III} and to induce selective C–O and C–C reductive elimination (Scheme 21 and 22).[59,60] The Zhang group's first report concerned an intramolecular C–O bond-forming reaction in which Selectfluor (**66**) facilitated Au^I/Au^{III} catalysis (Scheme 21).[59] In the proposed mechanism, following a Au^I-mediated propargylic ester [3,3]-sigmatropic rearrangement/isomerization sequence, Au^I intermediate **76** is oxidized in the presence of Selectfluor (**66**). After double hydrolysis, $[Au^{III}R^1(OR^2)F]$ intermediate **78** undergoes selective C–O reductive elimination, rather than C–F reductive elimination.

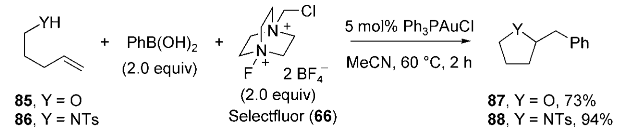


Scheme 21. Selectfluor (**66**) as a bystanding oxidant in C–O bond-forming Au^I/Au^{III} catalysis (Zhang et al., **2009**).[59]

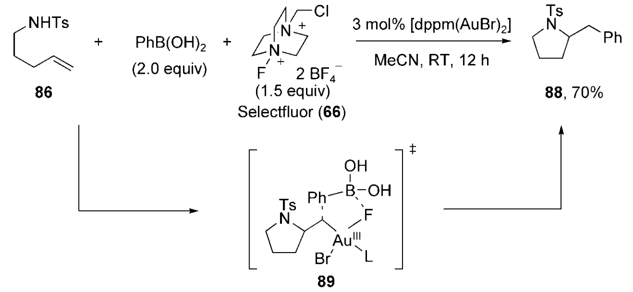
The Zhang group then went on to demonstrate that Selectfluor (**66**) could further function as a bystanding oxidant to generate analogous $[Au^{III}RF]$ species **82** which either could undergo facile homocoupling in the absence of other reactants or could be effectively cross-coupled with aryl boronic acids (Scheme 22).[60] In the Zhang group's speculative catalytic cycle for the cross-coupling reaction, transmetalation of the aryl boronic acid with **82** leads to putative $[Au^{III}R^1R^2]$ intermediate **83**, which undergoes C–C reductive elimination to form arylated ketone **84**.



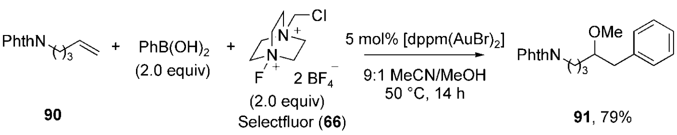
Scheme 22. Selectfluor (**66**) as a bystanding oxidant in C–C bond-forming Au^I/Au^{III} catalysis (Zhang et al., **2009**).[60]



Scheme 23. Selectfluor (**66**) as a bystanding oxidant in olefin oxyarylation and aminoarylation by Au^I/Au^{III} catalysis (Zhang et al., **2010**).[61] Ts = *p*-toluenesulfonyl.



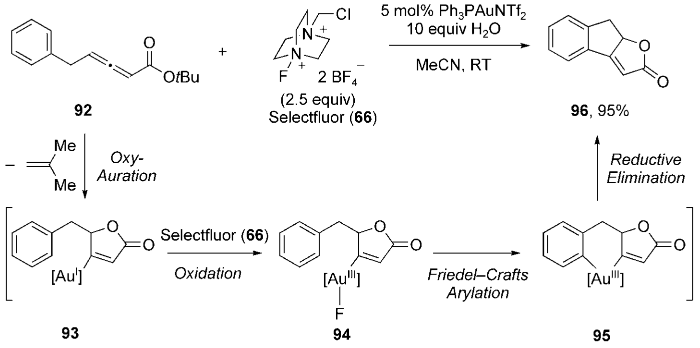
Scheme 24. Selectfluor (**66**) as a bystanding oxidant in olefin aminoarylation by Au^I/Au^{III} catalysis (Toste et al., **2010**).[62] dppm = 1,1-bis(diphenylphosphino)methane.



Scheme 25. A three-component coupling reaction by Au^I/Au^{III} catalysis using Selectfluor (**66**) (Toste et al., **2010**).[63] Phth = phthaloyl.

Several additional reports utilizing Selectfluor (**66**) to mediate the coupling of $[Au^I–R]$ species with aryl boronic acids along a Au^I/Au^{III} manifold have also recently been reported (Schemes 23–25).[61–63] Zhang[61] and Toste[62] independently described olefin difunctionalization reactions in which a Au^I catalyst is first oxidized by Selectfluor to generate a more electrophilic Au^{III} complex, which activates an olefin for intramolecular attack by tethered nucleophile. The resulting $[Au^{III}–alkyl]$ species reacts with arylboronic acids to give oxyarylated (**87**) and aminoarylated (**88**) products.

Interestingly, based on mechanistic studies and computational evidence,[62] Toste has proposed a bimolecular reductive elimination mechanism proceeding via five-membered cyclic transition state **89** (Scheme 24).[62,63] In this model, the B–F interaction plays a crucial role in facilitating reductive elimination. Acting as a hard Lewis base, the fluoride group activates the boronic acid, increasing its nucleophilicity. At the same time, electron density is drawn off the Au^{III} center rendering it more electrophilic.

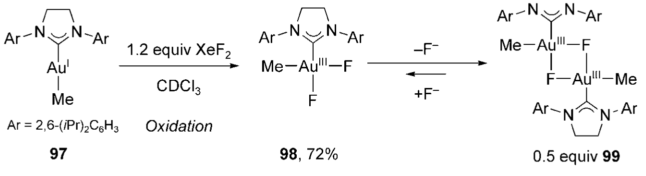


Scheme 26. Intramolecular oxidative arylation of a $[\mathrm{Au^I}$–vinyl] intermediate by $\mathrm{Au^I/Au^{III}}$ catalysis using Selectfluor (**66**) as a bystanding oxidant (Gouverneur et al., **2010**).[64]

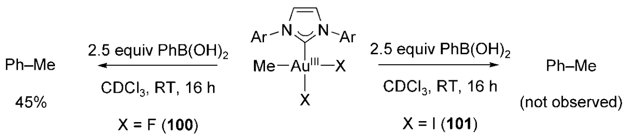
Toste went on to show that the same type of transformation could be carried out using an intermolecular nucleophile in an elegant $\mathrm{Au^I}$-catalyzed three-component coupling reaction (Scheme 25).[63] In addition to a range of different alcohol nucleophiles, water was also found to be effective. Using this method, acyclic oxyarylated products (**91**) could be obtained in good yields.

In a final example, Gouverneur and co-workers have shown that Selectfluor (**66**) can be used for direct intramolecular oxidative arylation of $[\mathrm{Au^IR}]$ species **93** (Scheme 26).[64] Under the current mechanistic proposal, the transformation is initiated by an oxyauration of **92** to form intermediate **93** with concomitant loss of isobutylene. Following oxidation, the resulting $[\mathrm{Au^{III}}$–vinyl] species **94** undergoes Fridel–Crafts arylation, followed by reductive elimination to generate **96**.

Recently, Mankad and Toste explored the reactivity of stoichiometric Au complexes in an effort to gain insights into individual steps in the speculative catalytic cycles of the reactions described above.[65] In 2005, Gray, Sadighi and co-workers described the first isolable $[\mathrm{Au^I{-}F}]$ species by utilizing a highly stabilizing ancillary ligand, 1,3-bis(2,6-disiopropylphenyl)imidazolin-2-ylidene (SIPr).[66a] Mankad and Toste took advantage of this ligand, and found that oxidation of $\mathrm{Au^I}$ complex **97** with XeF_2 led to formation of *cis*-$[(\mathrm{SIPr})\mathrm{Au^{III}MeF_2}]$ (**98**), which was observed to be in equilibrium with dimeric species $[\{(\mathrm{SIPr})\mathrm{Au^{III}Me}(\mu\text{-F})\}_2]$ (**99**) by reversible fluoride dissociation (Scheme 27). By using a slightly perturbed ligand backbone, 1,3-bis(2,6-disiopropylphenyl)imidazol-2-ylidene (IPr), the equilibrium could be shifted such that selective formation of monomeric species *cis*-$[(\mathrm{IPr})\mathrm{Au^{III}MeF_2}]$ (**100**) could be achieved (Scheme 28).[66b] Treatment of **100**, which bears structural resemblance to the speculative $[\mathrm{Au^{III}RF}]$ intermediates in the catalytic reactions above (for example, **82** in Scheme 22), with excess $PhB(OH)_2$ resulted in rapid formation of the coupling product, toluene, in 45 % yield (Scheme 28). Interestingly, attempts to react the analogous $[\mathrm{Au^{III}RI}]$ species **101** (prepared in situ) with $PhB(OH)_2$ did not lead to formation of toluene, suggesting that the presence of the $\mathrm{Au^{III}{-}F}$ bond is crucial for cross-coupling reactivity. Further mechanistic studies were consistent with the bimolecular reductive elimination pathway depicted in Scheme 24.



Scheme 27. Oxidation of $\mathrm{Au^I}$ complex **97** with an F^+ reagent (Mankad and Toste, **2010**).[65]



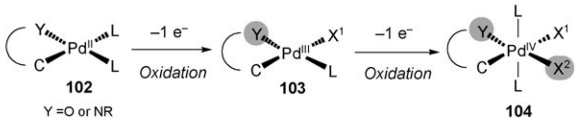
Scheme 28. Reactivity of complexes **100** and **101** with $PhB(OH)_2$ (Mankad and Toste, **2010**).[65]

Overall, electrophilic F^+ reagents (Selectfluor (**66**) in particular) are a promising class of reagents for accessing $\mathrm{Au^I}$/$\mathrm{Au^{III}}$ redox chemistry in homogenous Au catalysis. Using this strategy, both C–C and C–O reductive elimination have already been demonstrated. The key factors that enable F^+ reagents to function in this context are the oxidative strength of these compounds, the soft/hard mismatch between $\mathrm{Au^{III}}$ and F^-, the high degree of polarization in the $\mathrm{Au^{III}{-}F}$ bond, and the slow rate of C–F reductive elimination.[66a] As the mechanistic underpinning of these transformations become clearer, new opportunities for expedient bond construction using Au redox catalysis will continue to emerge.

4. One-Electron Oxidants: Applications in $\mathrm{Pd^{II}}$-Catalyzed C–H Activation

Whilst the above examples in Sections 2 and 3 clearly demonstrate the power of bystanding F^+ oxidants in catalysis, one unfortunate aspect of these reagents is that they are generally expensive, a drawback that hampers widespread application, particularly on larger scales. As part of our interest in developing practical $\mathrm{Pd^{II}}$-catalyzed C–H functionalization reactions,[4i] we have explored alternative approaches to address the selective reductive elimination problem. A promising strategy in this respect is the use of one-electron oxidants.

One-electron oxidants have two principal advantages over two-electron oxidants, such as F^+ reagents. Firstly, they are inherently "bystanding" in the sense that no additional nucleophile is introduced to the metal centers during oxidation (provided that the solvent medium does not contain strongly coordinating counteranions). Secondly, following treatment of a [Pd^{II}–R] species with a one-electron oxidant, formation of a Pd^{III} intermediate is unavoidable, even if it only occurs transiently (**103**; Scheme 29). At this point, reductive elimination could take place to generate a new C–C or C–Y bond with concomitant formation of a Pd^I species. It is known that Pd^{III} adopts either a monomeric square planar[67] or dimeric octahedral[15a] geometry. Thus, in the case of square planar complexes, the number of possibilities for reductive elimination is reduced, as only the two groups *cis* to the carbon atom could theoretically participate. Alternatively, the Pd^{III} intermediate can be further oxidized by loss of one electron to form a Pd^{IV} complex **104** from which reductive elimination could also take place (see Section 1).



Scheme 29. Depiction of one-electron oxidation events that can take place with a [Pd^{II}-R] intermediate.

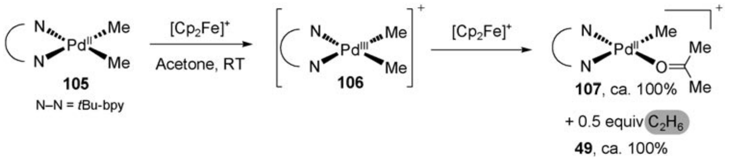
In 2009, our group achieved success in using Ce^{IV} as a one-electron oxidant for C–N reductive elimination (Scheme 30).[16] At this point it remains unclear whether C–N reductive elimination occurs from a Pd^{III} or Pd^{IV} species (Scheme 29). Using Ce^{IV}, we were able to develop an efficient route to convert phenethyltriflamides **41** into indolines **42** using $Pd(OAc)_2$ (15 mol%) and $Ce(SO_4)_2$ (3 equiv) in the presence of DMF (6 equiv) in DCE. Importantly, using this oxidant we were able to suppress competitive reductive elimination pathways, such as C–H acetoxylation.

Scheme 30. Ce^{IV} as a one-electron oxidant for selective C–N reductive elimination in an intramolecular Pd^{II}-catalyzed C–H amination reaction (Yu et al., **2009**).[16]

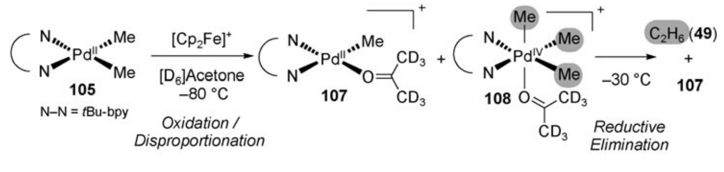
In a recent mechanistic study, Mayer, Sanford and co-workers investigated different reductive elimination pathways for pre-formed [$L_2Pd^{II}Me_2$] species **105** (Scheme 31).[6g] Using ferrocenium hexafluorophosphate ($Cp_2Fe^+PF_6^-$; Cp = cyclopentadienyl) as an outer-sphere one-electron oxidant,[68] reductive elimination of C_2H_6 (**49**) and formation of Pd^{II} complex **107** were observed. Based on detailed analysis of mechanistic data, a sequence of one-electron oxidation/disproportionation/reductive elimination was proposed (Scheme 32). Intermediates **107** and **108** could be directly observed by ^1H NMR and could also be trapped and isolated following treatment with NaI.

Generally speaking, the most common one-electron oxidants used in Pd^{II}-catalyzed C–H functionalization reactions are Ag^I salts, which are known to play a variety of different roles in catalysis, such as reoxidizing Pd^0[6e,69] and/or scavenging halide anions.[11e,f,13c,70] Our group has had success in using Ag^I salts in a series of C–H activation/C–C cross-coupling reactions,[71] where they serve to promote transmetalation of organometallic reagents[72,73] and facilitate C–C reductive elimination,[74] possibly through a one-electron oxidation.[6g,32c]

Further investigations focused on the development of practical and inexpensive one-electron oxidants hold the potential to enable novel Pd^{II}-catalyzed C–H functionalization reactions that hinge upon selective C–C and C–Y reductive elimination events. One-electron oxidants are advantageous because they are "bystanding" by nature (in that they do not necessitate the coordination of a counteranion to the metal center) and because they offer the potential for reductive elimination from non-traditional high-valent oxidation states. We envision this strategy as



Scheme 31. C–C reductive elimination promoted by Cp_2Fe^+, a one-electron oxidant (Mayer and Sanford et al., **2009**).[6g]



Scheme 32. Proposed mechanism for C–C reductive elimination (Mayer and Sanford et al., **2009**)[6g]

being relevant and applicable to other oxidative transition metal-catalyzed reactions. In the future, many of the oxidants that we discuss above could ultimately be replaced by electrochemical processes, which could play a pivotal role in accomplishing one-electron oxidation in an environmentally friendly and atom-economical fashion.[75]

5. Conclusion

Achieving selective reductive elimination from high-valent metal species is a challenging goal with implications throughout the broad field of chemical catalysis. In this Minireview, we sought to highlight recent advances using F$^+$ reagents as bystanding oxidants in $\mathrm{Pd^{II}}$/$\mathrm{Pd^{IV}}$ and $\mathrm{Au^{I}}$/$\mathrm{Au^{III}}$ catalysis and to discuss illustrative examples of the novel transformations enabled by application of this concept. In Section 4, we briefly discussed another emerging solution to the selective reductive elimination problem: the use of one-electron oxidants. Although F$^+$ reagents have proven to be the most generally applicable to challenging oxidation/reductive elimination sequences, in the long run, one-electron oxidants (including those based on electrochemical technology) are likely to be the most practical. Taken together, these strategies constitute an exciting new frontier in enabling new methods of C–C and C–Y bond construction in organometallic chemistry.

6. Addendum (January 7, 2011)

Recently, two examples of olefin oxyarylation by $\mathrm{Au^{I}}$/$\mathrm{Au^{III}}$ catalysis using arylsilanes as the coupling partner and Selectfluor as the bystanding oxidant have been reported.[76] Furthermore, a related cascade cyclization/oxidative alkynylation has been developed.[77]

Received: August 17, 2010

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[1] A. Gillie, J. K. Stille, *J. Am. Chem. Soc.* **1980**, *102*, 4933–4941.

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