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

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Abstract

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 (i.e., 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, leading to a mixture of products. This minireview examines an emerging solution to this widespread problem in organometallic chemistry, the use of bystander F⁺ oxidants, and describes 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 Pd(II)-catalyzed C–H functionalization, which we view as a promising future directing in the field.

Keywords

bystander oxidants; reductive elimination; C–H functionalization; Pd catalysis; Au catalysis

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. Here, reductive elimination from the square-planar [L₂Pd(II)R¹Y] or [L₂Pd(II)R¹R²] (R¹, R² = 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, while 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)R¹Y] or [Pd(II)R¹R²] intermediates following C–H cleavage and nucleophile coordination, several old tactics have been exploited. For instance, π-acceptor ligands, such as CO^[5] and 1,4-benzoquinone (BQ),^[6] are well known to promote reductive elimination; as

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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] Additionally, in a Pd(II)-catalyzed intramolecular olefin diamination reaction of guanidine **4**, CuCl₂ was elegantly used to induce reductive C–N bond formation from putative intermediate **5** (Scheme 2).^[7] This step is proposed to proceed via transient oxidation^[8] of Pd(II) by CuCl₂, such that Pd(II), rather than Pd(0), serves as a leaving group.^[9] Subsequently, CuCl₂ was also found to be effective in Pd(II)-catalyzed C–H amination.^[10] In this latter case, one mechanistic possibility is that CuCl₂ 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.

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 *via* 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, which 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**; hence, controlling this process is a fundamental challenge for achieving selective catalysis.

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. (In this manuscript, we use “bystanding oxidant” 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 *in situ* a nucleophilic [Pd(II)–R] species that is capable of reacting with electrophilic X⁺ reagents (e.g., Cl₂, CuCl₂, NCS, NBS, NIS, IOAc, and PhICl₂). 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]

In contrast to other C–H halogenation reactions, fluorination has proven to be more problematic for two main reasons. Firstly, 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. Secondly, 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 hence 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)–R¹] species with an F⁺ reagent in a Pd(II)/Pd(IV) catalytic process. Seminal work by Vigalok in 2003 established that [L₂Pd(II)Me₂] complexes could engage in oxidation chemistry with XeF₂, 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 C–H activation—in the presence of F⁺ reagent **15**, which introduces a chelating pyridine ligand into the reaction medium. Subsequently our group focused on developing a synthetically versatile *ortho*-C–H fluorination method with benzyltriflamides (**17**) (Scheme 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 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** due 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 during the past few years (Schemes 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 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 **26** to **27** transformation 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, it was later found that exposing **29** to excess XeF₂ 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 *via* 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. Hence, C–H fluorination using nucleophilic F⁻ sources *via* Pd(II)/Pd(0) catalysis will 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, our research laboratory has long been interested in utilizing Pd(II)/Pd(IV) catalysis to construct heterocycles through direct cyclization of amino and hydroxyl 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 protocol 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]

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 coworkers disclosed a seminal example of Pd(II)-catalyzed C–H amination *via* a presumed Pd(II)/Pd(0) catalytic cycle (**39** to **40**, Scheme 11).^[30] In this 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 coworkers using Pd(II)/Pd(IV) catalysis at room temperature with PhI(OAc)₂ as the oxidant.^[32]

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 bystander 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, to our delight, we were able to carry out the desired intramolecular C–H amination reaction with phenethyltriflamides (**41**) in the presence of F⁺ oxidant **18**, 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 bears 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).

To our delight, we were also able to exploit *N*-fluorobenzenesulfonimide (NFSI, **44**) as a bystanding F⁺ oxidant for an unprecedented intramolecular C–H etherification reaction *via* 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 protocol, a diverse array of phenethyl alcohols could be cyclized to form the corresponding substituted dihydrobenzofurans (**45**) in a single step.^[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 [L₂Pd(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 (*e.g.*, OAc[−]) in solution to regenerate the active catalyst, prior to C–H activation. Alternatively, the [L₂Pd(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 [L₂Pd(II)FX] or [L₂Pd(II)F₂], respectively. If formed during catalysis, the [L₂Pd(II)F₂] 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 is unknown.

In addition to 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 [L₂Pd(II)F₂] and [L₂Pt(II)F₂] complexes, Vigalok and coworkers found that treatment of Pd(dipp)Me₂ complex **46** (dipp = di(*i*-propylphosphino)propane) with XeF₂ at −30 °C in DCM led to C–C reductive elimination of C₂H₆ (**49**) along with concomitant formation of Pd(dipp)F₂ complex **48** (Scheme 15).^[27] One possible mechanism would proceed *via* oxidation by XeF₂ to generate a Pd(IV) complex—**47** is an example of a possible structure—which undergoes facile C–C reductive elimination.

Many research groups have had a long-standing interest in olefin difunctionalization technology *via* Pd(II)/Pd(IV) catalysis using bystanding^[36] and non-bystanding^[37–40] oxidants. As part of this effort, Michael and coworkers studied olefin diamination using a non-bystanding F⁺ oxidant, NFSI (**44**).^[40] During the course of this work, they discovered an unusual 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 treatment of **50** with NFSI (**44**) (2 equiv.) and Pd(O₂CCF₃)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 (MS) 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–CF₃ reductive elimination from Pd centers has proven to be challenging due to the strength and inertness of Pd–CF₃ bonds.^[19f,43,44] Indeed, reliable Pd-catalyzed protocols for Ar–CF₃ bond formation have largely remained elusive.^[43,45] In the area of C–H functionalization, our laboratory reported the first example of Pd(II)-catalyzed C–H trifluoromethylation (Scheme 17).^[45] Using this protocol, various heterocycle-containing substrates (**55**) could be coupled with electrophilic CF₃⁺ 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.). Because oxidation of Pd(II) to Pd(IV) by electrophilic CF₃⁺ reagents has not been demonstrated to date, the mechanism of the functionalization step remains unclear. Either a redox-neutral nucleophilic attack of the [Pd(II)–aryl] aryl species on the CF₃⁺ reagent or a Pd(II)/Pd(IV) oxidative addition/reductive elimination sequence could theoretically be at play, and neither can be ruled out at this time.

Given the challenges associated with C–CF₃ reductive elimination, using bystander F⁺ oxidants is potentially a viable approach. In an elegant mechanistic study, Sanford and coworkers demonstrated this concept, by taking advantage of an F⁺ reagent to promote an otherwise unfavorable C–CF₃ reductive elimination event from a Pd(IV) center (Scheme 18).^[44b] In this report, [Pd(II)–CF₃] intermediate **58** was treated with electrophilic N–F reagent **18**. Following oxidation, intermediate **59** was obtained, which, upon heating, was found to undergo C–CF₃ reductive elimination to form **60**. Notably, 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 due to a lack of selectivity in the reductive elimination step. The above examples illustrate how bystander 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 bystander 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 has remained a significant challenge,^[47] even though this mode of catalysis is isoelectronic to Pd(0)/Pd(II) redox 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]

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 coworkers 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**.

In 2009, Hashmi and coworkers 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 oxidative coupling product **73** (Entry 6). The operative mechanism in this case is likely one in which NFSI (**44**) serves as a bystander 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 bystander oxidants such as PhI(OAc)₂ and *t*BuO₂H.^[55–58]

Zhang and coworkers developed an important class of Au(I)-catalyzed reactions that take advantage of electrophilic N–F reagents as bystander oxidants to convert Au(I) to Au(III) and to induce selective C–O and C–C reductive elimination (Schemes 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)R¹(OR²)F] intermediate **78** undergoes selective C–O reductive elimination, rather than C–F reductive elimination.

The Zhang group then went on to demonstrate that Selectfluor (**66**) could further function as a bystander 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)R¹R²] intermediate **83**, which undergoes C–C reductive elimination to form arylated ketone **84**.

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.

Toste went on to show that the same type of transformation could be carried out using an *intermolecular* nucleophile in an elegant Au(I)-catalyzed three-component coupling reaction (Scheme 24).^[63] In addition to using 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 coworkers have shown that Selectfluor (**66**) can be used for direct intramolecular oxidative arylation of [Au(I)R] species **93** (Scheme 26).^[64] Under the current mechanistic proposal, the transformation is initiated by an oxyuration of **92** to form intermediate **93** with concomitant loss of isobutylene. Following oxidation, the resulting [Au(III)–vinyl] species **94** undergoes Friedel–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 and Sadighi described the first isolable [Au(I)–F] species by utilizing a highly stabilizing ancillary ligand, 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene (SIPr).^[66a] Mankad and Toste took advantage of this ligand, and found that oxidation of Au(I) complex **97** with XeF₂ led to formation of *cis*-(SIPr)Au(III)MeF₂ (**98**), which was observed to be in equilibrium with dimeric [(SIPr)Au(III)Me(μ-F)]₂[F]₂ species **99** via reversible fluoride dissociation (Scheme 27). By using a slightly perturbed ligand backbone, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr), the equilibrium could be shifted such that selective formation of monomeric *cis*-(IPr)Au(III)MeF₂ species **100** could be achieved (Scheme 28).^[66b] Treatment of **100**, which bears structural resemblance to the speculative [Au(III)RF] intermediates in the catalytic reactions above (*e.g.*, **82** in Scheme 22), with excess PhB(OH)₂ resulted in rapid formation of the coupling product, PhMe, in 45% yield (Scheme 28). Interestingly, attempts to react the analogous [Au(III)RI] species **101** (prepared *in situ*) with PhB(OH)₂ did not lead to formation of PhMe, suggesting that the presence of the 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.

Overall, electrophilic F⁺ reagents (Selectfluor (**66**) in particular) represent a promising class of reagents for accessing Au(I)/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 Au(III) and F[–], the high degree of polarization in the 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 Pd(II)-Catalyzed C–H Activation

While the above examples in Sections 2 and 3 clearly demonstrate the power of bystander 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 laboratory's interest in developing practical 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 Pd(III) intermediate is unavoidable (even if it only occurs transiently) (**102**, Scheme 29). At this point, reductive

elimination could take place to generate a new C–C or C–Y bond with concomitant formation of Pd(I). 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 a Pd(IV) complex **104** from which reductive elimination could also take place (see Section 1).

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**) to indolines (**42**) using Pd(OAc)₂ (15 mol%) and Ce(SO₄)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.

In a recent mechanistic study, Mayer, Sanford, and coworkers investigated different reductive elimination pathways for pre-formed [L₂Pd(II)Me₂] species **105** (Scheme 31).^[6g] Using ferrocenium hexafluorophosphate (Cp₂Fe⁺PF₆[−]) (Cp = cyclopentadienyl) as an outer-sphere one-electron oxidant,^[68] reductive elimination of C₂H₆ (**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,11f,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 by organometallic reagents^[72,73] and facilitate C–C reductive elimination,^[74] possibly through a one-electron oxidation.^[6g]

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 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 Pd(II)/Pd(IV) and Au(I)/Au(III) catalysis, and to discuss illustrative examples of the novel transformations enabled by application of this concept. In the final section, we briefly discussed another emerging solution to the selective reductive elimination problem: the use of one-electron oxidants. While 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.

Acknowledgments

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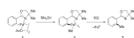
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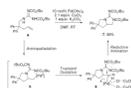
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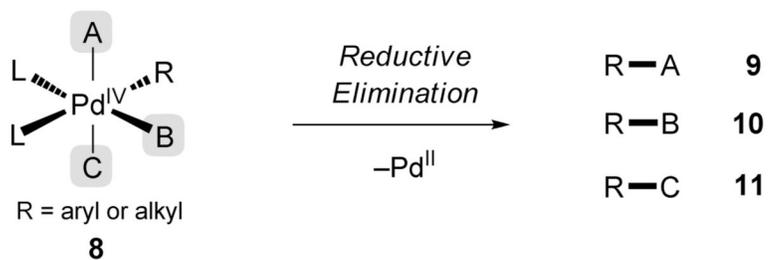
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**Scheme 1.**

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]

**Scheme 2.**

CuCl₂-promoted reductive amination in a Pd(II)-catalyzed olefin diamination reaction (Muñiz et al., **2008**).^[7] DMF = *N,N*-dimethylformamide.

**Scheme 3.**

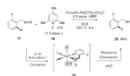
Possible outcomes of reductive elimination from an octahedral Pd(IV) intermediate.

**Scheme 4.**

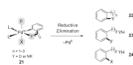
The first report of diastereoselective Pd(II)-catalyzed C(*sp*³)-H iodination *via* Pd(II)/Pd(IV) catalysis (Yu et al., **2005**).^[13b] DCM = dichloromethane. RT = room temperature.

**Scheme 5.**

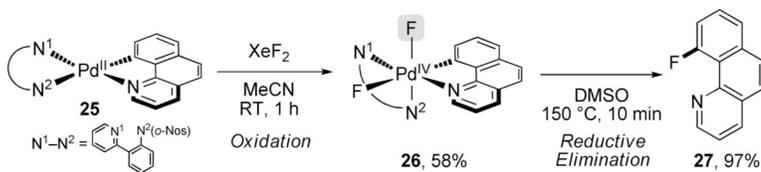
The first report of Pd(II)-catalyzed C–H fluorination *via* Pd(II)/Pd(IV) catalysis (Sanford et al., **2006**).^[28a]

**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.

**Scheme 7.**

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

**Scheme 8.**

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

**Scheme 9.**

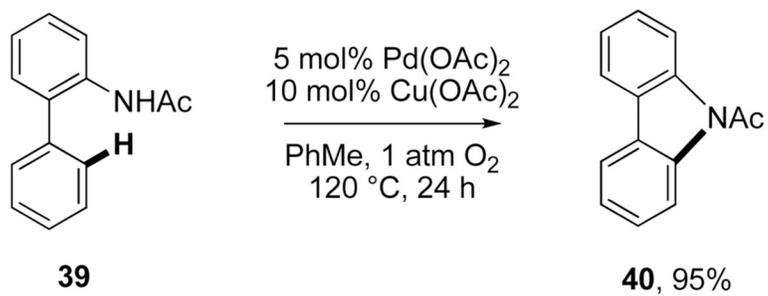
C–F reductive elimination from a Pd(IV) complex (Ball and Sanford, 2009).^[18c] *t*Bu-bpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine.



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

**Scheme 11.**

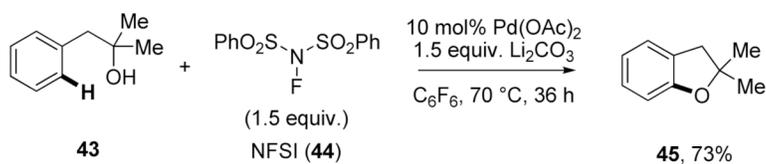
Challenges in selective C–Y reductive elimination from Pd(IV) intermediates. “Ox¹–Ox²” represents a generic oxidant.



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



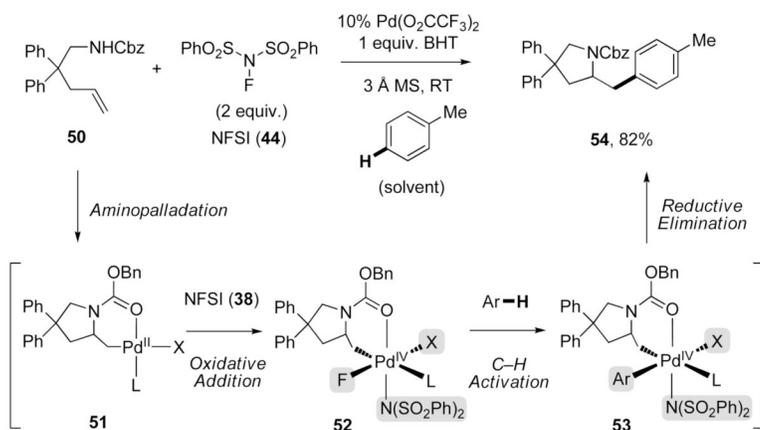
Scheme 13.
Pd(II)-catalyzed intramolecular C–H amination using a bystanding F⁺ oxidant (Yu et al.,
2009).^[16]



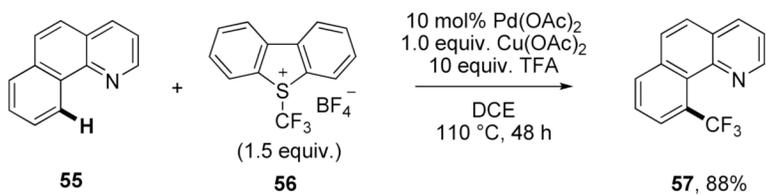
Scheme 14. Pd(II)-catalyzed intramolecular C–H etherification using a bystander F⁺ oxidant (Yu et al., 2010).^[34]

**Scheme 15.**

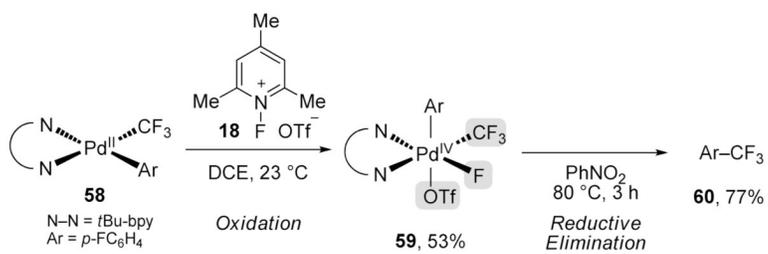
Selective C–C reductive elimination induced by XeF₂ (Vigalok et al., **2003**).^[27]

**Scheme 16.**

Pd(II)-catalyzed olefin carboamidation using a bystander F⁺ oxidant for selective reductive elimination from a Pd(IV) intermediate (Michael et al., **2009**).^[41,42]

**Scheme 17.**

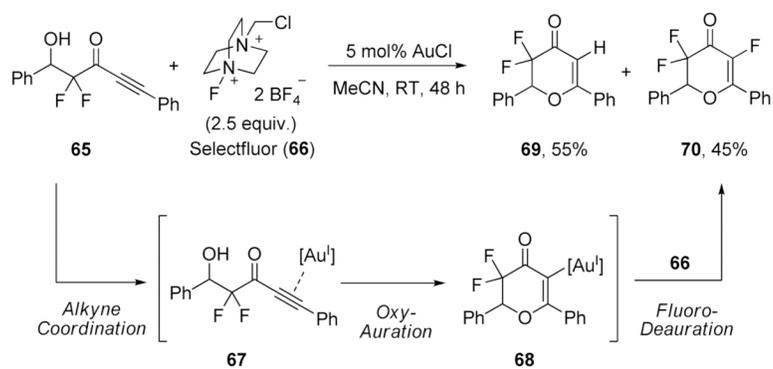
The first example of Pd(II)-catalyzed C–H trifluoromethylation (Yu et al., **2010**).^[45] TFA = trifluoroacetic acid.

**Scheme 18.**

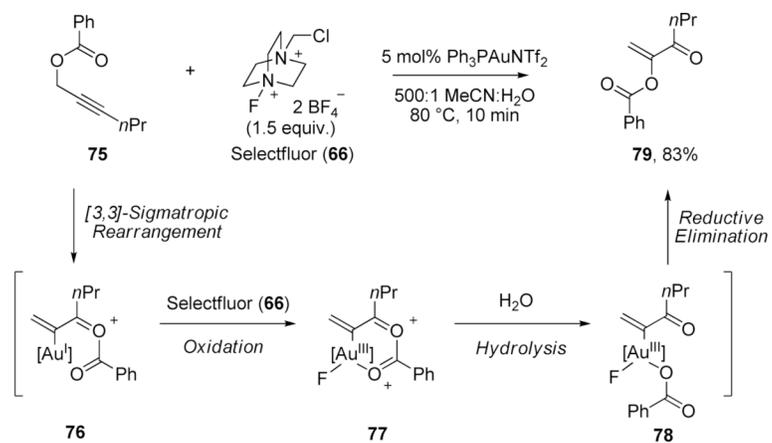
Selective C–CF₃ reductive elimination from a Pd(IV) complex induced by a bystander electrophilic N–F reagent (Sanford et al., **2010**).^[44b]



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

**Scheme 20.**

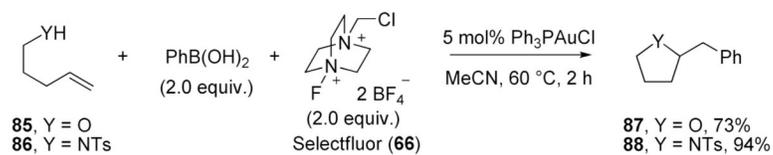
Electrophilic fluorination of a [Au(I)-vinyl] intermediate in an Au(I)-catalyzed cyclization reaction (Gouverneur et al., **2008**).^[52a]



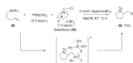
Scheme 21. Selectfluor (**66**) as a bystander oxidant in C–O bond-forming Au(I)/Au(III) catalysis (Zhang et al., 2009).^[59]



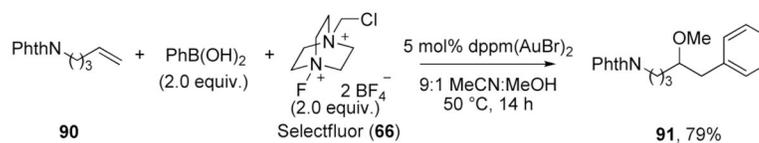
Scheme 22.
Selectfluor (**62**) as a bystanding oxidant in C–C bond-forming Au(I)/Au(III) catalysis
(Zhang et al., **2009**).^[60]

**Scheme 23.**

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

**Scheme 24.**

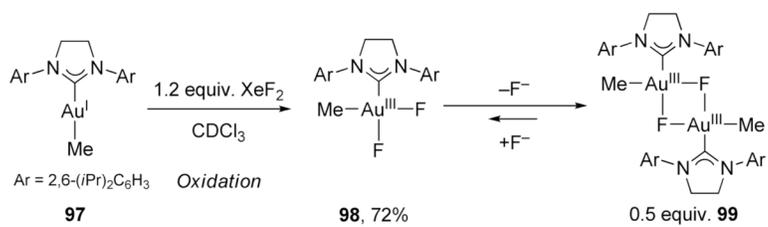
Selectfluor (**66**) as a bystander oxidant in olefin aminoarylation *via* Au(I)/Au(III) catalysis (Toste et al., **2010**).^[62] dppm = 1,1'-bis(diphenylphosphino)methane.

**Scheme 25.**

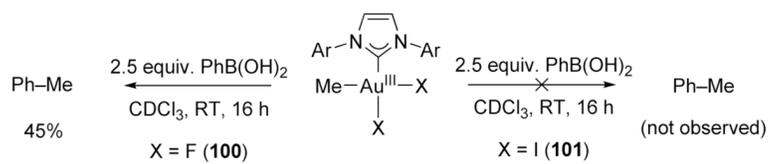
A three component coupling reaction *via* Au(I)/Au(III) catalysis using Selectfluor (**66**) (Toste et al., **2010**).^[63] Phth = phthaloyl.

**Scheme 26.**

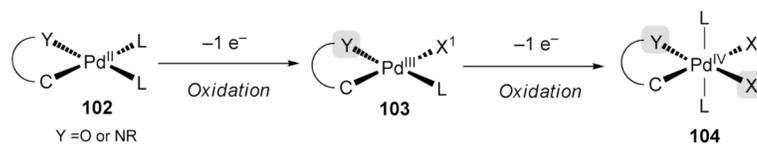
Intramolecular oxidative arylation of a [Au(I)-vinyl] intermediate *via* Au(I)/Au(III) catalysis using Selectfluor (**66**) as a bystanding oxidant (Gouverneur et al., **2010**).^[64]

**Scheme 27.**

Oxidation of Au(I) complex **97** with an F⁺ reagent (Mankad and Toste, 2010).^[65]



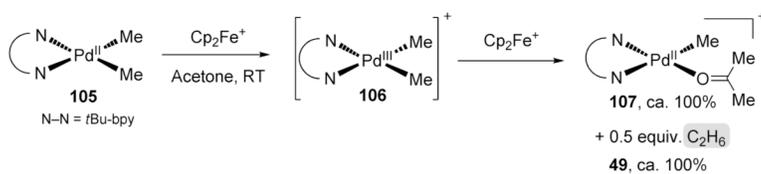
Scheme 28.
Reactivity of **98** and **100** complexes with PhB(OH)₂ (Mankad and Toste, **2010**).^[65]

**Scheme 29.**

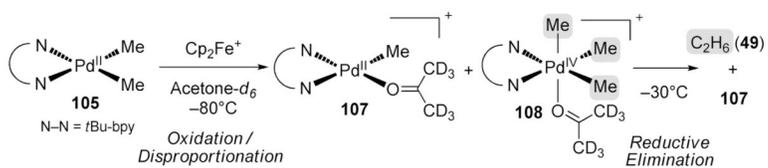
Depiction of one-electron oxidation events that can take place with a $[Pd(II)-R]$ intermediate.

**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]

**Scheme 31.**

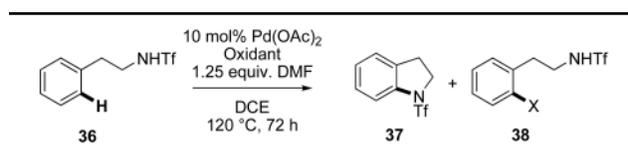
C–C reductive elimination promoted by Cp_2Fe^+ , a one-electron oxidant (Mayer and Sanford et al., 2009).^[6g]

**Scheme 32.**

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

Table 1

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



Entry	Oxidant	% Yield (37) ^[a]	% Yield (38) ^[a]	X =
1	PhI(OAc) ₂	15	45	OAc (38a)
2	AcOOtBu	13	50	OAc (38a)
3	NCS	0	20	Cl (38b)
4	NIS	0	35	I (38c)
5	IOAc ^[b]	0	40	I (38c)

NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide.

^[a]The yield was determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as an internal standard.

^[b]Generated *in situ* from PhI(OAc)₂ and I₂.

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

Entry	Electrophile	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

Py = pyridine