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Mechanism of *N*-Fluorobenzenesulfonimide Promoted Diamination and Carboamination Reactions: Divergent Reactivity of a Pd(IV) Species

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Abstract: The mechanism of the Pd-catalyzed diamination and carboamination of alkenes promoted by *N*-fluorobenzenesulfonimide (NFBS) was investigated. Stereochemical labeling experiments established that the diamination reaction proceeds via overall *syn* addition of the two nitrogen groups, whereas carboamination is the result of an *anti* addition of arene and nitrogen to the alkene. The intermediate Pd-alkyl complex arising from aminopalladation was observed, and an X-ray crystal structure of its 2,2′-bipyridine (bipy) complex was obtained, revealing strong chelation of the amide protecting group to palladium. Aminopalladation was shown to be an *anti*-selective process in both the presence and the absence of added ligands, proceeding via external attack of the nitrogen on a Pd-coordinated alkene. The intermediate Pd-alkyl complex was converted to diamination product upon exposure to NFBS with inversion of configuration via oxidative addition followed by dissociation of the benzenesulfonimide anion and S_N2 displacement of the Pd−C bond. Conversely, arylation of the Pd-alkyl complex proceeds via retention of stereochemistry, consistent with C−H activation of the arene at the Pd(IV) center. A small intermolecular isotope effect ($k_H/k_D = 1.1$) and a large intramolecular isotope effect ($k_H/k_D = 4$) were measured for this process, indicating that C−H activation occurs via a poorly selective product-determining coordination of the arene followed by a highly selective C−H activation. Competition between arenes reveals an unusual reactivity order of toluene > benzene > bromobenzene > anisole.

Introduction

Oxidative aminations of alkenes such as oxyaminations, diaminations, and carboaminations are of special importance in synthetic chemistry. These reactions allow for the transformation of the ubiquitous carbon−carbon double bond into motifs with a range of important applications. Over the past several decades, numerous oxidative aminations of alkenes have been developed using a range of metal catalysts and stoichiometric reagents.[1]

Vicinal diaminations of alkenes have been accomplished using stoichiometric quantities of palladium,[2] mercury,[3] selenium,[4] osmium,[5] cobalt,[6] and copper.[7] Recently, a number of catalytic diaminations have been reported. Muñiz and Booker-Milburn and Lloyd-Jones have each reported palladium-catalyzed diaminations of alkenes using ureas and sulfamides in conjunction with an external oxidant.[8,9] Shi has developed several metal-catalyzed diamination reactions that use strained three-membered ring hydrazines as nitrogen sources.[10]

Development of an efficient method for addition of a nitrogen and carbon across an alkene is another important reaction, in part because of its rarity. Wolfe has shown that aryl bromides can be used to form C−C bonds via a Pd-catalyzed carboamination of aminoalkenes.[11] Chemler has reported a doubly intramolecular Cu-catalyzed bicyclization of arylsulfonamidoalkenes and arylamidoalkenes to give products resulting from carboamination and aminooxygenation of the olefin.[12] Booker-

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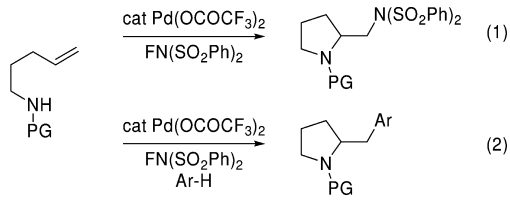

Figure 1. Palladium-catalyzed diamination and carboamination with NFBS.

Milburn and Lloyd-Jones have reported a closely related Pd-catalyzed carboamination of dienes using arylureas.[13]

We recently disclosed a series of remarkable palladium-catalyzed oxidative aminations using *N*-fluorobenzenesulfonimide (NFBS) as an oxidant and/or an electrophilic source of nitrogen (Figure 1). This set of reactions displayed a drastic solvent effect. In non-nucleophilic solvents, such as CH_2Cl_2 and EtOAc, diamination of the alkene took place by incorporation of benzenesulfonimide from the NFBS reagent.[14] In the presence of aromatic solvents, the reaction course was diverted to the formation of carboamination products via incorporation of 1 equiv of the arene (eq 2).[15] The change in reactivity observed with the same key reagents is remarkable. We sought to understand the mechanisms of diamination and carboamination in order to expand the already impressive scope of this Pd/NFBS system. The results of our mechanistic investigation are presented herein.

Results and Discussion

Overall Stereochemistry of the Diamination and Carboamination Reactions. To obtain information about the mechanisms of the diamination and carboamination reactions, the overall stereoselectivity of both processes was investigated by taking advantage of stereospecifically deuterium-labeled substrate **(*E*)-1-*d*** (Figure 2). When substrate **(*E*)-1-*d*** was subjected to diamination conditions (10 mol % $Pd(OCOCF_3)_2$, NFBS), only one ^{1}H NMR resonance was absent in diamination product **2-*d***, indicating that a highly stereoselective reaction had taken place. To establish the stereochemistry, diamination product **2** was deprotected to give the free diamine and cyclized to give bicyclic thiourea product **3**. The *cis*/*trans* relationship between the

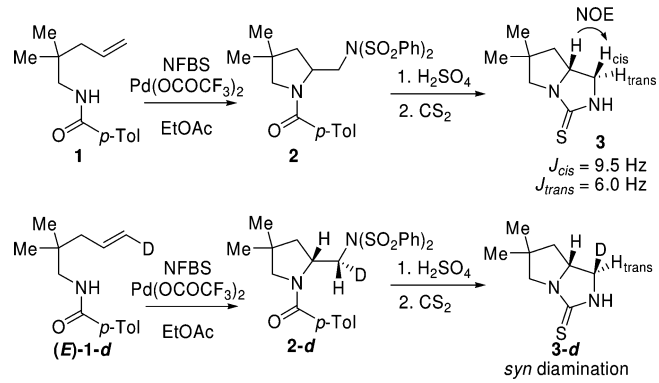

Figure 2. Assignment of diamination stereoselectivity via thiourea **3**.

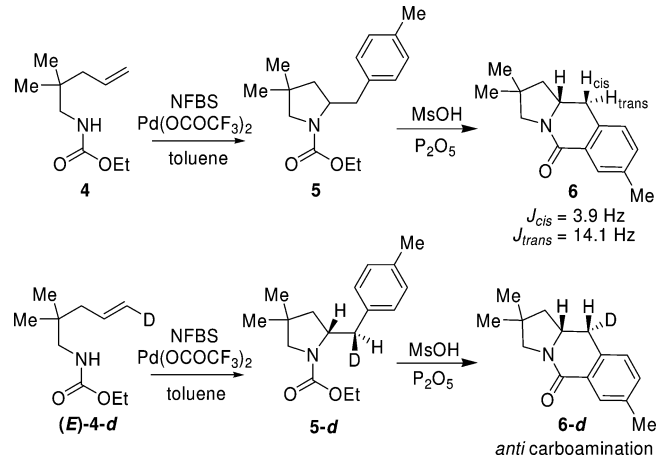

Figure 3. Assignment of carboamination stereoselectivity via cyclic amide **6**.

methylene and methine protons was determined by ^{1}H NMR and NOESY spectroscopy. The reaction sequence was repeated with deuterated substrate **2-*d***, and the resonance with the *cis* coupling constant of 9.5 Hz disappeared, indicating that diamination proceeded with overall *syn* selectivity.

The overall *syn* selectivity for this catalyst system is distinct from that observed in other catalytic diamination reactions. Muñiz has reported an intramolecular diamination of sulfonylureas that proceeds via overall *anti* selectivity.[8a] Chemler observed a nonstereospecific diamination in a Cu-catalyzed system, giving a 1:1 diastereomeric mixture of *syn* and *anti* products, presumably due to the intermediacy of radical species.[7]

Submitting substrate **(*E*)-4-*d*** to the carboamination reaction conditions also afforded a single stereoisomer of product **5-*d*** (Figure 3). To determine the overall stereoselectivity, carboamination product **5** was cyclized under Friedel−Crafts conditions to give tricyclic amide **6**. The reaction sequence was repeated with deuterated substrate **5-*d***, and the ^{1}H NMR resonance with $J = 14.1$ Hz was absent (*trans* diaxial), while the ^{1}H NMR resonance with $J = 3.9$ Hz was still present (*cis*), establishing that carboamination proceeds with overall *anti* selectivity. The overall *anti* selectivity for this catalyst system is also distinct from previous carboamination examples reported by Yorimitsu, Oshima,[16] and Wolfe,[11] in which overall *syn* selectivity is observed, and Chemler,[12b] which again proceeds with stereochemical scrambling. Furthermore, it is important to note that

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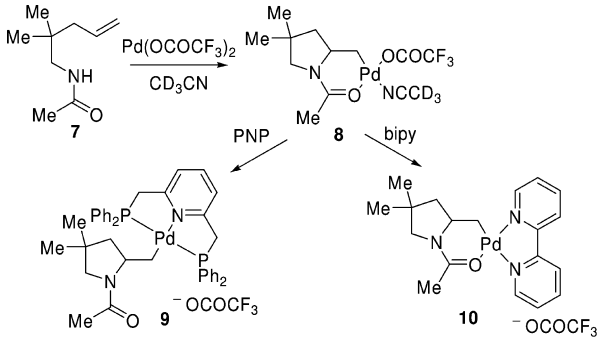

Figure 4. Observation and isolation of intermediate Pd-alkyl complexes.

the carboamination and diamination reactions promoted by NFBS proceed with opposite stereoselectivities.

Alkene Aminopalladation. Since the diamination and carboamination products observed in the presence of NFBS and catalytic Pd(II) differ only in the identity of the exocyclic group, our initial hypothesis was that these products arose from divergent reactions of a common intermediate. The most likely candidate for such an intermediate is the Pd-alkyl complex arising from aminopalladation of the alkene. Similar Pd complexes have often been invoked as intermediates in alkene amination reactions, and a few have been reported to be observable, albeit without full characterization.[8a,17] To confirm the intermediacy of a Pd-alkyl complex and to determine the stereochemical outcomes of both the aminopalladation and Pd−C bond functionalization steps, the reaction between the aminoalkene and the Pd complex in the absence of NFBS was investigated.

Aminoalkene substrate **7** was treated with $Pd(OCOCF_3)_2$ in CD_3CN and monitored by ^1H NMR spectroscopy. After 15 min, complete consumption of the starting alkene was observed, replaced by new ^1H NMR resonances corresponding to a Pd-alkyl complex tentatively identified as **8** (Figure 4). As expected, this putative Pd-alkyl complex was unstable, decaying over the course of several hours at room temperature. However, treatment of the putative Pd-alkyl complex with various ligands (pyridine, 2,2′-bipyridine (bipy), bis(diphenylphosphinomethyl)pyridine (PNP)) prevented this decay and gave Pd-alkyl complexes (**9**, **10**) that were bench-stable for a minimum of several weeks at room temperature. A closely related Pd-alkyl complex bearing a tridentate PNP ligand but with a tetrafluoroborate counterion (**9-BF$_4$**) has been previously isolated and characterized as an intermediate in a catalytic hydroamination reaction.[18] The ^1H NMR spectrum of the species formed by trapping Pd-alkyl complex **8** with free PNP ligand was identical to that previously formed from the dicationic (PNP)Pd complex **11** and the aminoalkene substrate in the presence of base.

To further confirm its structure, crystals of the Pd-alkyl complex with 2,2′-bipyridine (**10**) were obtained from Et_2O/MeCN, and an X-ray crystal structure was solved (Figure 5). The structure reveals tight chelation of the oxygen of the acetamide protecting group, which is possibly responsible for the abnormal stability of this complex with respect to β-hydride elimination. Interestingly, both trifluoroacetates of the original

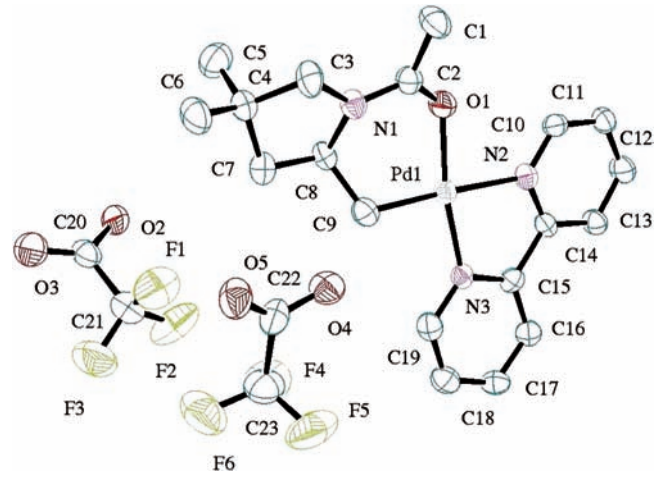

Figure 5. Crystal structure of bipy-Pd-alkyl $[(CF_3CO_2)_2H]$ complex **10**. Bond distances (Å): Pd−O = 2.024, Pd−C = 2.010, Pd−N2 = 2.102, Pd−N3 = 2.026.

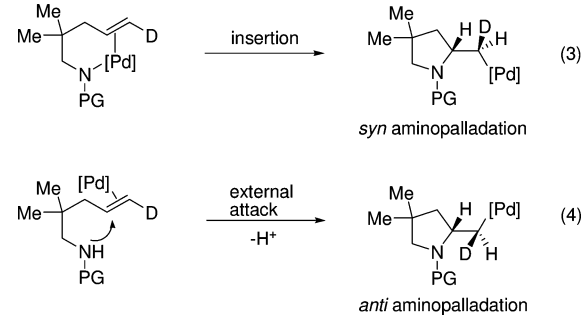

Figure 6. *Syn* versus *anti* aminopalladation.

Pd salt were found in the crystal structure as a complex counterion between trifluoroacetate and trifluoroacetic acid.

With stable Pd-alkyl complexes in hand, it was possible to determine the stereochemistry of the initial aminopalladation step. Initial palladation can proceed either through insertion of a coordinated alkene into a Pd−N bond to form the product of *syn* aminopalladation or via external nucleophilic attack of the nitrogen on a Pd-coordinated alkene, giving the *anti* aminopalladation product (Figure 6). Examples of both *syn* and *anti* heteropalladation have been established as viable possibilities in alkene functionalization reactions. In a number of early studies by Stille, Bäckvall, and Kurosawa, *anti* oxypalladation was reported.[19] It was later observed by Henry and Thompson that oxypalladation selectivity could be controlled through the concentration of Cl^- present (*syn* oxypalladation at low concentrations and *anti* oxypalladation at higher concentrations).[20,21] A number of recent reports including those by Muñiz,[8a,22] Stahl,[23] Sanford,[24] and Wolfe[11b−d] report initial *syn* aminopal-

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(21) This result was later supported by Hayashi and co-workers, who observed *anti*-palladation in the presence of chloride and *syn*-palladation in the absence of chloride. Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036–3037.

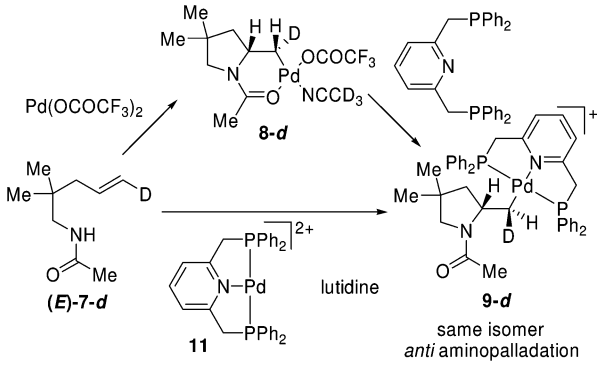

Figure 7. Formation of deuterated palladium-PNP-alkyl complex **9-*d*** in the presence and absence of tridentate ligand.

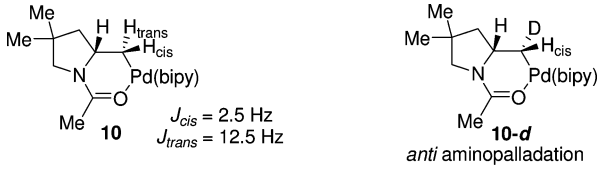

Figure 8. Stereochemistry of aminopalladation as determined from bipy-Pd-alkyl complex **10**.

ladation in oxidative aminations of alkenes. Stahl has also conducted a systematic study of *syn* versus *anti* aminopalladation and has concluded that *syn* addition is usually preferred.[25]

To determine the stereoselectivity of the initial palladation step, the (PNP)Pd-alkyl complex was formed from deuterated alkene **(*E*)-7-*d*** under two distinct sets of conditions (Figure 7). First, **9-*d*** can be formed by treatment of the dicationic (PNP)Pd complex **11** with alkene **(*E*)-7-*d*** in the presence of mild base. It is unlikely that *syn* aminopalladation can occur in the presence of the tridentate ligand due to the lack of an additional coordination site, so this experiment is expected to yield only the *anti* aminopalladation product. Alternately, the same Pd-alkyl complex can be formed by aminopalladation with $Pd(OCOCF_3)_2$ without added ligand, followed by trapping with the tridentate ligand. Both reactions afforded the same stereoisomer of the deuterium labeled Pd-alkyl complex. Therefore, it appears that *anti* aminopalladation is predominant with this substrate in both the presence and absence of added ligand. ^{1}H NMR coupling constants are also consistent with *anti* aminopalladation.

Further confirmation of the stereochemistry of aminopalladation comes from the X-ray crystal structure of bipy-Pd-alkyl complex **10**. When the deuterated Pd-alkyl complex **8-*d*** was trapped with bipy to form **10-*d***, the ^{1}H NMR resonance with the large vicinal coupling constant of 12.5 Hz was absent (Figure 8). On the basis of the half-chair conformation adopted by **10** in the crystal structure, this result is consistent with *anti* aminopalladation.

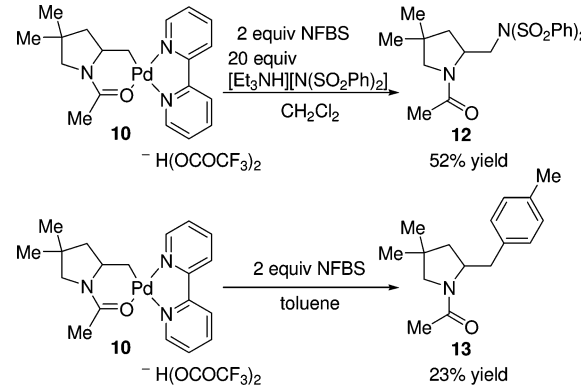

Figure 9. Reaction of Pd-alkyl complex **10** with NFBS.

The preference for *anti* aminopalladation in this system, in contrast to the general preference for *syn* aminopalladation observed by others, is likely due to two factors. First, the reaction conditions here are relatively acidic, which has already been shown to promote *anti* aminopalladation reactions.[20,21] Second, many of the reports of *syn* aminopalladation involve addition of relatively acidic N−H bonds to alkenes (phthalimides and sulfonamides), which can be more easily deprotonated to form the Pd-amide necessary for *syn* addition. The amides and carbamates in this study are more difficult to deprotonate and more nucleophilic as neutral species, so the external attack mechanism (*anti* addition) is favored.

Pd-Alkyl Complex Functionalization. Having established that the overall stereochemical outcome is *syn* for the diamination reaction and *anti* for the carboamination reaction, and since the stereochemistry of the aminopalladation step is *anti*, the stereochemistry of the Pd-alkyl functionalization steps in each reaction can be deduced. Specifically, diamination must occur with inversion of stereochemistry at the Pd−C bond, whereas carboamination must occur with retention of stereochemistry. To confirm the intermediacy of Pd-alkyl complex **10** in the diamination reaction, the isolated bipy-Pd-alkyl complex **10** was dissolved in CH_2Cl_2, and $[Et_3NH][N(SO_2Ph)_2]$ and NFBS were added. Conversion to diamination product **12** was observed in 52% yield (Figure 9). In situ generation of **10-*d*** followed by treatment with $[Et_3NH][N(SO_2Ph)_2]$ and NFBS afforded deuterated diamination product **12-*d*** with the same relative stereochemistry as was observed in the catalytic reaction (Figure 2).[26]

The inversion of stereochemistry in the amination of the Pd-alkyl complex can be explained by the mechanism depicted in Figure 10. Oxidative addition of the N−F bond to the Pd(II)-alkyl complex generates Pd(IV) species **B**. Dissociation of a benzenesulfonimide anion and S_N2 displacement of the Pd(IV)-alkyl would regenerate Pd(II) and explain the overall inversion of stereochemistry in this step. A similar dissociative mechanism has been shown to predominate in the functionalization of Pt(IV)-alkyl complexes.[27]

Treatment of bipy-Pd-alkyl complex **10** with NFBS in toluene results in conversion to the carboamination product **13**, albeit in low yield (Figure 9). Poor solubility of complex **10** in toluene may be responsible for the reduced efficiency of the stoichiometric carboamination. Since our proposed mechanism of carboamination requires an open coordination site (see below),

(22) Muñiz' mechanistic study[8a] has recently been called into question. On the basis of calculations, Lin and co-workers suggest that the reaction actually goes through an anti aminopalladation followed by reductive elimination rather than the *syn* aminopalladation/nucleophilic attack reported by Muñiz Yu, H.; Fu, Y.; Guo, Q.; Lin, Z. *Organometallics* **2009**, *28*, 4507–4512.

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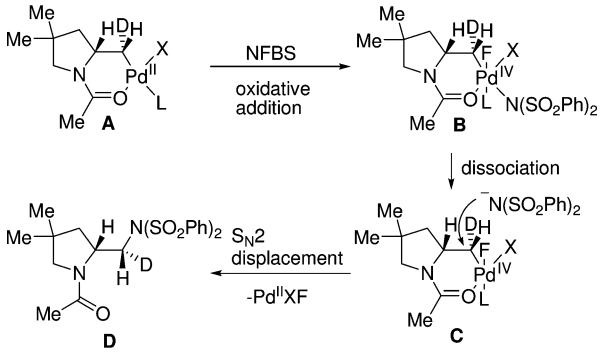
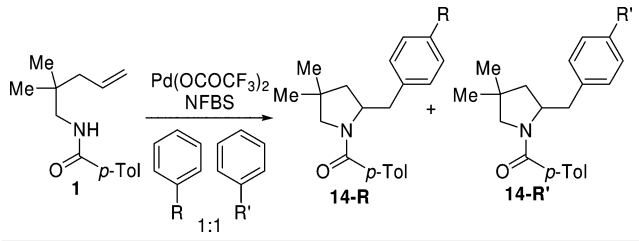


Figure 10. Proposed mechanism for Pd−C bond amination.

Table 1. Arene Competition Experiments[a]



R/R′	H	Me	Br	OMe
H	1	1.1	0.6	0.4
Me	0.9	1	0.5	0.5
Br	1.8	2.1	1	0.7
OMe	2.4	2.1	1.4	1

[a] Number represents ratio of top row to left column incorporation, i.e., anisole product is 0.4 times as prevalent as benzene product. Determined by ^{1}H NMR spectroscopy.

the blocking of these sites by the bipy ligand may also be responsible for the low yield of this stoichiometric reaction.

To indirectly probe the arene activation step, carboamination reactions were run with various mixtures of arenes, and the relative extent of incorporation of the two arenes was determined (Table 1). Interestingly, while a methyl substituent offered a slight enhancement in reactivity, both halide and methoxy groups made the arene less likely to be incorporated. Furthermore, these substituent effects are approximately multiplicative and rather small, never approaching an order of magnitude. To ensure that the polarity of the solvent mixture did not affect selectivity, carboamination of substrate **1** was run in varying ratios of anisole/toluene. Little variation in the relative rate of anisole incorporation relative to toluene incorporation was observed (see Supporting Information). It should also be noted that all monosubstituted arenes that participate in this reaction give exclusively *para* substitution on the aromatic ring.[15]

Substrate **1** was subjected to carboamination conditions in a 1:1 mixture of toluene and toluene-d_8 to determine the intermolecular isotope effect. A small normal isotope effect was observed ($k_H/k_D = 1.1$, Figure 11). No scrambling of deuterium between toluene and toluene-d_8 was observed in either the product. In contrast, when substrate **1** was treated with 1,3,5-trideuterobenzene, a large primary isotope effect ($k_H/k_D = 4$) was observed. A similar large difference between inter- and intramolecular isotope effects has been observed by Mayer in an arene C−H activation by a Re═O complex.[28]

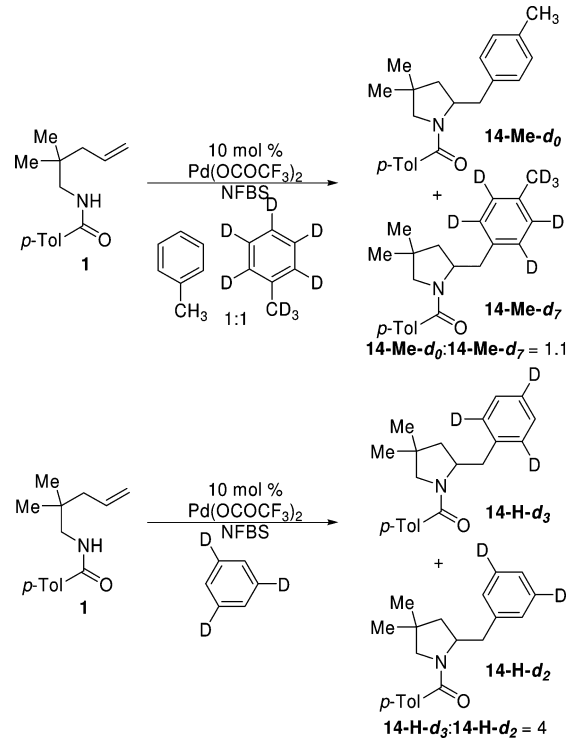


Figure 11. Inter- and intramolecular isotope effects.

A mechanism that explains the experimental data is illustrated in Figure 12. The Pd(II) alkyl complex is inert toward arenes in the absence of NFBS, so initial oxidative addition to form a Pd(IV) complex (**B**) must be the first step in functionalization of the Pd−C bond. Arene incorporation from the Pd-alkyl complex occurs with retention of stereochemistry, which is consistent with C−H bond activation at Pd(IV) followed by reductive elimination. Direct nucleophilic displacement of the Pd(IV)-C bond by the arene would result in inversion of configuration, so it can be ruled out.

A mechanism for C−H activation must explain the following key observations: (1) the high *para* selectivity, (2) the low intermolecular selectivity between arenes, (3) the low reactivity of anisole, (4) the high intramolecular isotope effect, and (5) the low intermolecular isotope effect. At first glance, many of these observations are unusual for aromatic activation. C−H activations of toluene at Pt(II), Pd(II), and Ir(III) are generally poorly regioselective, often giving statistical mixtures of *meta* and *para* isomers.[29] In this system, however, very high *para* selectivity is observed. This could be a result of the higher electrophilicity of the Pd(IV) center; C−H activations at Pt(IV)[30] and Rh(III)[31] give high *para* selectivity under kinetic conditions.[32]

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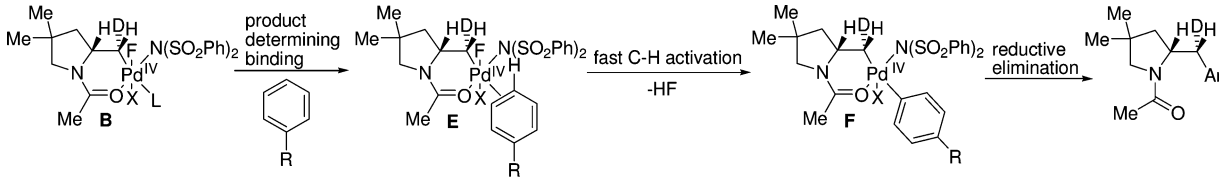

Figure 12. Mechanism for arene incorporation from Pd-alkyl complex.

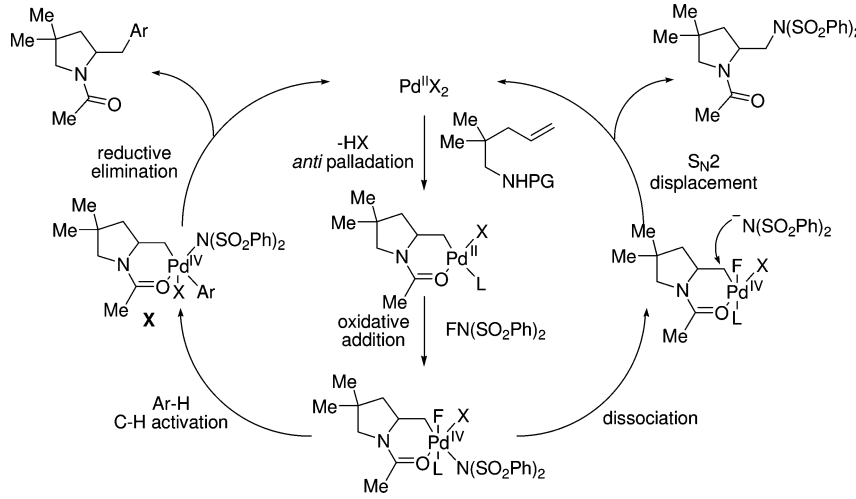

Figure 13. Proposed mechanistic cycle.

In electrophilic aromatic substitution mechanisms with either conventional electrophiles or electrophilic metal centers, the rate of reaction with anisole is usually much faster than that of toluene, which is faster than that of benzene.[29−31,33] However, in this system anisole was substantially *less* reactive than benzene, indicating that the methoxy group is operating exclusively as an inductively electron-withdrawing group in the product-determining step.

The differences between the intramolecular and intermolecular selectivities are striking. High levels of intramolecular selectivity are observed in both the deuterium isotope effect ($k_H/k_D = 4$) and the regioselectivity (exclusively *para* substitution). On the other hand, relatively low levels of intermolecular selectivity are observed in the isotope effect ($k_H/k_D = 1.1$) and arene competition ($k_{anis}/k_{benz} = 2.4$) experiments.

The observation of different inter- and intramolecular kinetic isotope effects requires that the C−H activation cannot be a one-step process, i.e,. it must take place in two separate steps with different selectivities. The intramolecular KIE is in the normal range for a C−H bond breaking step, but the intermolecular KIE is very small, implying that the step that determines the intermolecular selectivity occurs before the C−H bond breaking step. A plausible explanation is that binding of the arene to the highly electrophilic Pd(IV) center is the intermolecular selectivity-determining step, followed by subsequent rapid C−H activation and reductive elimination to form the product (Figure 10).[28,34] In this mechanism, the observed intermolecular arene incorporation selectivities do not reflect the actual C−H bond activation step and therefore tell us nothing about the nature of that C−H bond cleavage. They must instead reflect the relative propensity to bind to the Pd(IV) intermediate. Electron-rich arenes should bind more strongly to an electrophilic Pd(IV) species than electron-poor arenes, which would explain the observed reactivity order toluene > benzene > bromobenzene. The fact that anisole is the least reactive arene in competition experiments seems to imply that it binds especially poorly to Pd(IV), perhaps indicating that the inductively electron-withdrawing character of the methoxy group is the primary determinant of binding selectivity.

The only observations that allow any insight into the actual C−H bond breaking step are the intramolecular isotope effect and the high *para* regioselectivity. Both of these are consistent with either a σ-bond metathesis process or an electrophilic aromatic substitution mechanism with rate-limiting deprotonation. We favor the σ-bond metathesis mechanism based on the similarity of the isotope effects and regioselectivities to the C−H activation at a Re(IV)═O.[28]

Conclusion

In conclusion, we have described the mechanism of a Pd^{II}/Pd^{IV} reaction cycle in which NFBS is used as a versatile oxidant and/or electrophile in catalytic diamination and carboamination reactions. The unified catalytic cycle for both reactions is depicted in Figure 13. Initial activation of the substrate by the Pd catalyst occurs by an *anti* aminopalladation of the alkene to form a Pd-alkyl complex. Oxidative addition of NFBS to this species generates a reactive Pd(IV) species that is the branch

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point between diamination and carboamination processes. In the diamination reaction, dissociation of the benzenesulfonimide anion occurs, followed by S_N2 displacement of the Pd−C bond to form the second C−N bond and regenerate Pd(II). In the presence of arenes, C−H activation at Pd(IV) takes place to generate a Pd(IV)-aryl species that undergoes reductive elimination to form the carboamination product. This C−H activation occurs via product determining complexation to Pd(IV) followed by a highly regioselective C−H activation. The results of this study show a significant deviation from the mechanisms observed in similar oxidative difunctionalizations and will play a significant role in further development of Pd-catalyzed reactions using NFBS.

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Supporting Information Available: Reaction conditions and experimental data for the synthesis of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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