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Competition between sp^3-C–N vs sp^3-C–F Reductive Elimination from Pd^{IV} Complexes

Mónica H. Pérez-Temprano, Joy M. Racowski, Jeff W. Kampf, and Melanie S. Sanford*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

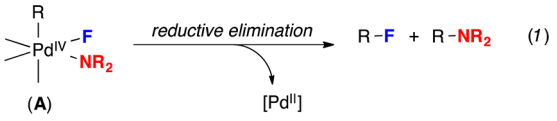
Supporting Information

ABSTRACT: This communication describes the design of a model system that allows direct investigation of competing sp^3-C–N and sp^3-C–F bond-forming reductive elimination from a Pd^{IV} fluoro sulfonamide complex. The reductive elimination selectivity varies dramatically as a function of reaction additives. A mechanism is proposed that provides a rationale for these effects.

Palladium-catalyzed reactions for constructing sp^3-carbon–heteroatom bonds have the potential to facilitate the synthesis of valuable classes of organic molecules.[1] In particular, sp^3-carbon–nitrogen bonds are ubiquitous in pharmaceuticals, agrochemicals, and commodity chemicals.[2] Despite the great importance of alkyl amines, it remains challenging to form sp^3-C–N linkages via palladium catalysis.[3] Indeed, there are only a handful of examples of well-characterized sp^3-C–N bond-forming reductive elimination from any transition metal complex.[4−6]

Yu and co-workers recently pioneered a high valent Pd-catalyzed strategy for C–N bond formation.[7] This approach involves the use of electrophilic fluorinating reagents[8] as bystanding oxidants in conjunction with nitrogen nucleophiles to promote C–N coupling reactions.[9] The earliest reports in this area focused on arene C–H amination (i.e., sp^2-C–N coupling).[10] However, subsequent efforts by Michael,[11] Muñiz,[12] Liu,[13] and others[14] have adopted similar approaches to generate sp^3-C–N bonds during alkene and alkane amination reactions.

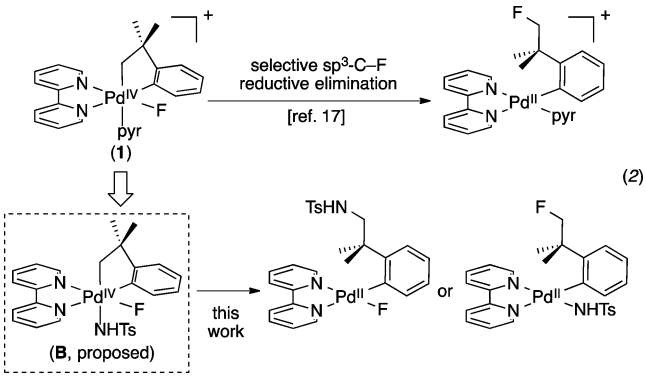
The latter transformations are proposed to proceed via Pd^{IV} alkyl amino fluoride intermediates of general structure **A** (eq 1).



(1)

These species can potentially undergo competing C–N and C–F[15,16] bond-forming reductive elimination to yield alkyl amines or alkyl fluorides. During catalysis, good to excellent selectivity is typically observed for sp^3-C–N coupling. However, a detailed understanding of the mechanism of reductive elimination and the factors governing this selectivity remains elusive.

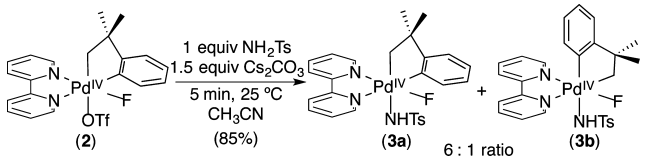
We sought to design a model system that would allow direct interrogation of competing sp^3-C–N and sp^3-C–F bond-forming reductive elimination from a well-defined Pd^{IV} complex. We recently reported that Pd^{IV} complex **1** undergoes sp^3-C–F reductive elimination upon heating to 80 °C (eq 2).[17] We hypothesized that replacing the pyridine (pyr) ligand with



TsNH would produce Pd^{IV} complex **B**, which should enable investigation of competing C–F and C–N coupling. Herein we report the synthesis and reactivity of **B**. We demonstrate that selective sp^3-C–F and sp^3-C–N bond formation can be achieved, depending on the reaction conditions. These studies represent the first example of sp^3-C–N bond-forming reductive elimination from an isolated Pd^{IV} complex.

As shown in Scheme 1, the treatment of Pd^{IV} complex **2**[17] with 1 equiv of NH_2SO_2-*p*-tolyl (NH_2Ts) and 1.5 equiv of

Scheme 1. Synthesis of Complexes 3a and 3b



Cs_2CO_3 in CH_3CN at room temperature results in rapid substitution of triflate for NHTs to afford **3** in an 85% isolated yield. This complex is formed as a 6:1 mixture of inseparable isomers **3a** and **3b**. Each of these isomers was fully characterized by one- and two-dimensional ^1H, ^{13}C, and ^{19}F NMR spectroscopy (see Supporting Information (SI) for all spectra and a full discussion of structural assignments). In addition, an X-ray crystal structure of **3a** was obtained, and the ORTEP plot is shown in Figure 1.

Heating solutions of **3** for 30 min at 65 °C in CD_3CN results in competing sp^3-C–N, sp^3-C–F, and sp^3-C–sp^2-C bond-

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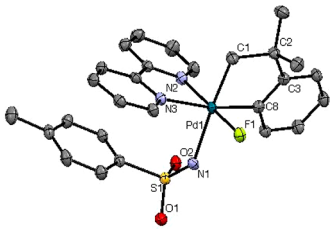
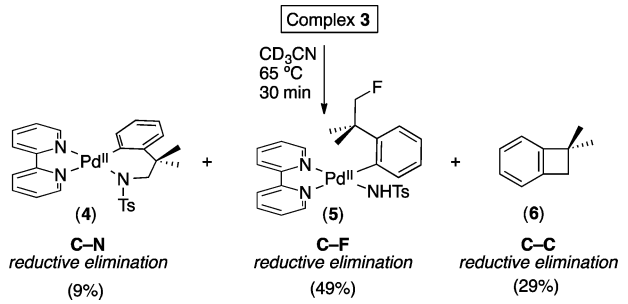


Figure 1. ORTEP plot of complex **3a**.

forming reductive elimination to form a mixture of products **4**, **5**, and **6**, respectively (Scheme 2). Importantly, no products

Scheme 2. Reductive Elimination from 3



derived from sp^2-carbon–heteroatom (C–X) bond-forming reductive elimination were observed. Selectivity for sp^3-C–X coupling over sp^2-C–X coupling is a hallmark of high valent Pd and Pt chemistry (and stands in contrast to the selectivity typically observed at other metal centers/oxidation states).[18] Products **4**, **5**, and **6** were fully characterized using one- and two-dimensional ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy (see SI for all spectra and a full discussion of structural assignments). Furthermore, X-ray crystal structures of **4** and **5** were obtained, and ORTEP plots for these Pd^{II} complexes are shown in Figure 2.

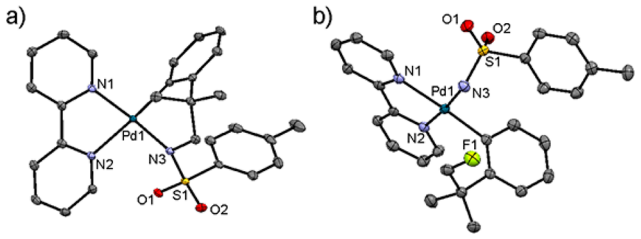
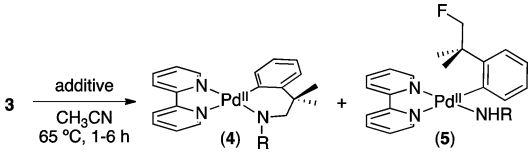


Figure 2. ORTEP plots of (a) **4** and (b) **5**.

As shown in Scheme 2, reductive elimination from **3** affords alkyl fluoride **5** as the major product in 49% yield. However, we hypothesized that the selectivity could be shifted to favor C–N reductive elimination product **4** by adding $TsNH^-$ to the reaction mixture. This hypothesis was predicated on a study of a related sp^3-C–N bond-forming reductive elimination from the Pt^{IV} complex *fac*-(dppbz)$Pt(CH_3)_3$(NHR). In this system, the addition of exogeneous RNH^- led to a dramatic increase in the yield of C–N coupled product CH_3NHR relative to that of C–C coupled product H_3C–CH_3.[4] Gratifyingly, an analogous effect is observed with complex **3**. Heating **3** in MeCN at 65 °C in the presence of 1 equiv of NMe_4NHTs leads to **4** as the sole detectable reductive elimination product (Table 1, entry 2). The yield of **4** is reasonably high (85%); however, free

Table 1. Influence of Additives on Reductive Elimination from 3[a]



entry	additive	yield **4** (%)	yield **5** (%)	yield **6** (%)
1	none	9	49	29
2	1 equiv of NMe_4NHTs	85	<1	<1
3	1 equiv of NMe_4NHTs + 2 equiv of bpy	98	<1	<1

[a]Yields of **4**–**6** determined by ^{1}H NMR spectroscopic analysis relative to 4-fluoroanisole as a standard.

bipyridine (bpy) is also formed in ~10% yield. We propose that the free bpy is derived from decomposition of product **4** via ligand substitution of bpy with $TsNH^-$. Consistent with this proposal, subjecting an isolated sample of **4** to 3 equiv of NMe_4NHTs at room temperature for 1 h in CD_3CN results in the formation of a 61% yield of free bpy.

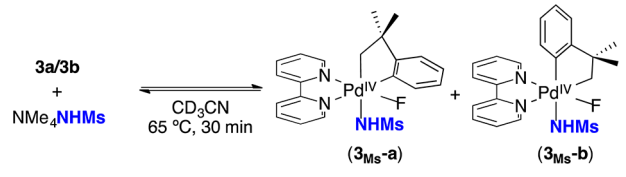
This undesired ligand exchange can be suppressed by adding 2 equiv of bpy along with 1 equiv of NMe_4NHTs to reductive elimination reactions of **3**. Under these conditions, **4** is formed in nearly quantitative yield (98%, Table 1, entry 3). Furthermore, the rate of reductive elimination from **3** is essentially identical in the presence and absence of 2 equiv of bpy (see Figure S1). This supports the proposal that the bpy additive does not influence the primary reductive elimination process, but merely limits product decomposition.

With conditions in hand to achieve selective and high yielding C–N bond-forming reductive elimination from **3**, we next conducted studies to probe the reaction mechanism. In the presence of ≥1 equiv of NMe_4NHTs, the reaction exhibits clean kinetics with a first-order dependence on [**3**] and zero-order dependence on [NMe_4NHTs]. This rules out a pathway involving a direct S_N2 reaction between $TsNH^-$ and **3**, since this should show first-order kinetics in both **3** and the nucleophile.

We next probed the lability of the $TsNH^-$ ligand of **3** under the reductive elimination reaction conditions. EXSY NMR studies of a mixture of 1 equiv of **3** and 1 equiv of NBu_4NHTs show that exchange between free and bound NHTs is slow at 25 °C on the NMR time scale. However, the treatment of **3** with 1 equiv of NMe_4NHMs (Ms = $MeSO_2$) for 30 min at 65 °C in CD_3CN results in rapid substitution of TsNH for MsNH to form an equilibrium mixture of **3** and $\mathbf{3_{Ms}}$ (Scheme 3).[19] These latter results show that sulfonamide exchange is significantly faster than reductive elimination from **3**.

Scheme 4 shows a mechanism for reductive elimination from **3a** that is consistent with all of the data presented above.[20] Step *i* of this process involves pre-equilibrium dissociation of RNH^-

Scheme 3. Substitution of the Sulfonamide Ligand



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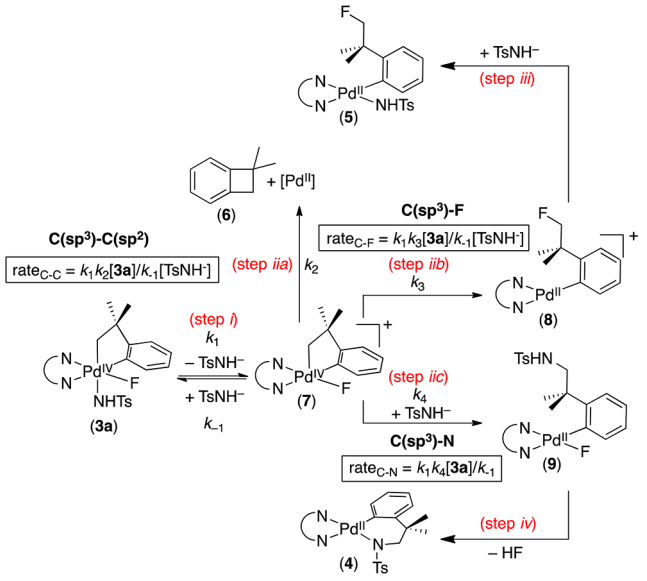
Scheme 4. Proposed Mechanism for sp^3-C–N and sp^3-C–F Reductive Elimination from 3-a



to afford five-coordinate cationic intermediate **7**. Importantly, analogous five-coordinate intermediates are involved in the vast majority of reductive elimination reactions from octahedral Pd^{IV} and Pt^{IV} complexes.[1c,21] Furthermore, the results in Scheme 3 demonstrate the feasibility of step *i* under the reductive elimination reaction conditions.

Proceeding in the forward direction, intermediate **7** is proposed to participate in three competing reductive elimination reactions: (1) C–C bond-forming reductive elimination to release **6** (step *iia*); (2) C–F coupling to generate **8** (*step iib*);[22] and (3) C–N bond formation (likely by an S_N2 pathway[1,4–6]) to generate **9** (*step iic*). To complete the reaction sequence, coordination of RNH^- to **8** (step *iii*) would yield **5**, while loss of HF from **9** (step *iv*) would produce **4**.

The observed effect of exogenous NMe_4NHTs on the product distribution is consistent with the mechanism proposed in Scheme 4. The rates of C–C and C–F reductive elimination are expected to be inverse order in $[TsNH^-]$, while that of C–N coupling is zero order in $[TsNH^-]$. As a result, the addition of NMe_4NHTs should lead to an increase in selectivity for **4** over **5** and **6**, as observed.

The proposed mechanism suggests that the addition of acids should also impact reductive elimination selectivity. In particular, acids that can protonate $TsNH^-$ (pK_a of $TsNH_2$ = 16 in DMSO)[23] should remove this nucleophile from solution, thereby leading to less of product **4** and more of **5**/**6**. Indeed, the addition of 1 equiv of HF (pK_a = 16 in DMSO, added as 1 equiv of $NEt_3{\cdot}3HF$)[23] to reductive elimination reactions of **3** resulted in the formation of **5** and **6** as the major products (yields of **4**–**6** were <1%, 32%, and 68%, respectively, under these conditions). Similarly, <1% of the C–N reductive elimination product **4** was observed upon the addition of 1 equiv of HOTf (pK_a = 0.3 in DMSO; yields of **4**–**6** were <1%, <1%, and 95%, respectively, under these conditions).[24] This mechanism also leads us to predict that H_2O should not appreciably impact the product ratios, since its pK_a is too high to protonate $TsNH^-$ (pK_a of H_2O in DMSO = 32).[23] Indeed, a nearly identical product distribution was observed upon the addition of 10 equiv of H_2O to reductive elimination reactions of **3** (yields of **4**–**6** were 11%, 40%, and 29%, respectively, under these conditions).

In summary, this communication describes the design of a model complex for studying competing sp^3-C–F and sp^3-C–NHTs bond-forming reductive elimination from Pd^{IV}. These studies provide preliminary insights into the role of reaction additives on these processes. Ongoing studies are focused on obtaining additional mechanistic data on these transformations as well as applying the insights learned from these studies to catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and complete characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

mssanfor@umich.edu

Notes

The authors declare no competing financial interest.

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(19) At room temperature, only **3a** underwent fast exchange with MsNH to form $\mathbf{3}_{\mathbf{Ms}}$**-a**. See SI for full details.
(20) An alternative pathway that is consistent with all of the data would involve pre-equilibrium isomerization of **3a** to **3b** followed by direct C−N bond-forming reductive elimination from **3b**. This pathway is discussed in detail in the SI (p S15). We preliminarily believe that this mechanism is less likely because the vast majority of reductive elimination reactions from Pd^{IV} proceed via five-coordinate intermediates (see ref 21).
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(22) See ref 17 for a detailed discussion of the mechanism of C−F reductive elimination from **1**, which is believed to proceed through intermediate **7**.
(23) http://evans.harvard.edu/pdf/evans_pka_table.pdf. The pK_a for $TsNH_2$ is approximated based on that of $PhSO_2NH_2$.
(24) The impact of reaction additives on the relative ratio of C−F and C−C coupling products **5** and **6** is the subject of ongoing investigations. Preliminary results suggest that H-bonding between the additive and the fluoride ligand on Pd^{IV} may play a role in the selectivity.

■ NOTE ADDED AFTER ASAP PUBLICATION

The amounts of reagents used in Scheme 1, and a typographical error in the sentence describing the rates of reductive elimination in the third-from-last paragraph, were corrected after the ASAP version was published February 28, 2014. The revised version was re-posted on March 5, 2014.