Rearrangements Hot Paper

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Chelation-Driven Rearrangement of Primary Alkyl Aminopalladation Products to Stable Trisubstituted Alkyl–Palladium Complexes**

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Abstract: *The formation of highly substituted carbon centers using catalysis has been a widely sought after goal, but complexes of highly substituted carbon atoms with transition metals are rare, and the factors that affect the relative stability of complexes with differentially substituted carbon atoms are poorly understood. In this study, a set of equilibrating alkyl–palladium complexes were subtly tuned to form either a primary or trisubstituted alkyl complex as the more thermodynamically favored state, depending on either the substrate or reaction conditions. An X-ray crystal structure of the trisubstituted alkyl–palladium complex is presented and compared with the corresponding primary alkyl complex. The mechanism for rearrangement and the factors that drive the change in stability are discussed.*

Alkyl–metal complexes are key intermediates in a wide variety of important organic reactions.[1] Among the more challenging goals of organic synthesis is the formation of highly substituted carbon centers, and metal-catalyzed reactions have the potential to be powerful tools in the realization of this goal.[2] However, such reactions are still quite challenging because of the scarcity of highly substituted alkyl–metal complexes. Understanding the factors that control the structure and stability of alkyl–metal intermediates is critical to expanding the scope of these metal-catalyzed processes.

The relative stability of primary, secondary, and tertiary alkyl–metal complexes is generally expected to follow the trend for organolithium compounds,[3] in which the highly polarized C–Li bond results in a large negative-charge density at the carbon atom. Increasing the substitution of the carbon atom with electron-donating alkyl groups increases the negative charge at the carbon center, and thus destabilizes tertiary alkyllithium compounds relative to primary alkyllithium compounds. This model works well for many alkyl–metal complexes, but the analysis is more complicated for transition metals such as palladium. Information on the relative stability of alkyl–palladium complexes is sparse, contradictory, and without clear general trends.

Two experimental studies of the relative stability of alkyl–palladium complexes have been reported. Reger et al.[4] studied Pd complexes bearing dithiocarbamate ligands, in which the small size of the ligands presumably minimizes any steric effects on stability. In this study, the stability of the alkyl complexes followed the traditional order: primary > secondary ≫ tertiary. However, alkyl groups bearing electron-withdrawing groups, such as CF_3 or CN, overrode this preference to put those groups next to the Pd–C bond. More recently, Brookhart and co-workers[5] studied the isomerization of alkyl–palladium complexes with a diimine ligand. Here, the relative stability of the alkyl complexes was highly dependent on the structure of the fourth ligand. When no ligand or acetonitrile was bound in *cis* position to the alkyl ligand,[6] the secondary alkyl complex was more stable, but when bulkier ligands were present, the primary alkyl complex was favored. In a computational study, Harvey[7] calculated the energies of both sets of complexes and explained this data with a trade-off between electronic and steric factors. While steric factors favor complexes with less-substituted carbon atoms, electronic factors will favor complexes with more-substituted carbon atoms, if the M–C bond is nonpolar.

Most structurally characterized trisubstituted alkyl–palladium complexes[8] are stabilized by strong electron-withdrawing groups, such as CN or CO_2R,[9] are η^1-allyl or benzyl complexes,[10] or are cyclopropyl complexes.[11] Only a few examples of nonstabilized trisubstituted alkyl–palladium complexes have been reported.[12] Furthermore,systems that allow the formation and control over the interconversion of two differentially substituted alkyl–metal complexes are even more rare. Here we describe a finely balanced system in which the rearrangement between a primary alkyl complex and a trisubstituted alkyl complex can be controlled by the choice of substrate and the reaction conditions.

We have developed several oxidative difunctionalization reactions of alkenes that proceed through the common alkyl–palladium intermediate **2**, which was isolated and structurally characterized after the addition of a 2,2′-bipyridyl (bipy) ligand (Scheme 1).[13] In the course of these studies, we noticed that complex **2** changed to a new complex upon standing.

The ^{1}H NMR spectrum of this new complex lacked a resonance corresponding to the methine proton in α position to the nitrogen atom and featured a new singlet at 1.5 ppm. We assigned this complex as the product of palladium migrating to the carbon atom in α position to the nitrogen atom (**4**). Unfortunately, this rearrangement did not progress beyond a 1:2 ratio of **2** and **4**, so we were unable to isolate and characterize complex **4**.

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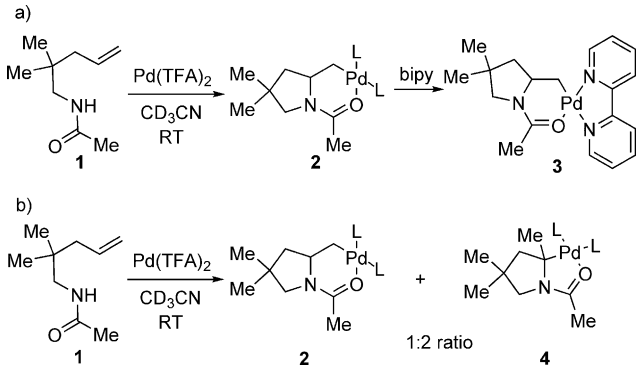
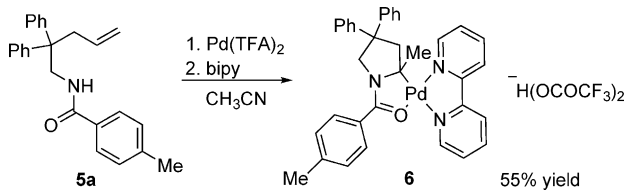


Scheme 1. Formation of Pd–alkyl intermediates.



Scheme 2. Formation and isolation of palladium complex **6**.

When toluamide **5a** was used, complete rearrangement to the analogous alkyl–palladium complex was observed (Scheme 2). After trapping this complex with bipy, complex **6** was isolated and an X-ray crystal structure was obtained (Figure 1). The structure of **6** shows the C–Pd bond to be nearly coplanar with both C–N bonds, thus ruling out any stereoelectronic contribution from an η^2-iminium-type complex. A comparison of the structural data of complex **6** with those of original complex **3** revealed a few notable differences. The Pd–C bond distance in complex **6** (more highly substituted C atom) is 0.03 Å longer than in complex **3** (primary C atom). Also, there is a slight distortion of the C_{sp3}–N bond lengths for the amide in the rearranged complex. In complex **3**, both C–N bonds are 1.49 Å long, whereas in complex **6**, the C–N bond of the C atom bound to Pd is elongated to 1.52 Å, and the other C–N bond contracts to 1.46 Å. As the Pd–C bond in **6** is longer and therefore presumably weaker than in **3**, and the 5–5 fused ring system appears to be more strained than the 6–5 fused ring system in **3**, it is not clear why the rearrangement to complex **6** proceeds.

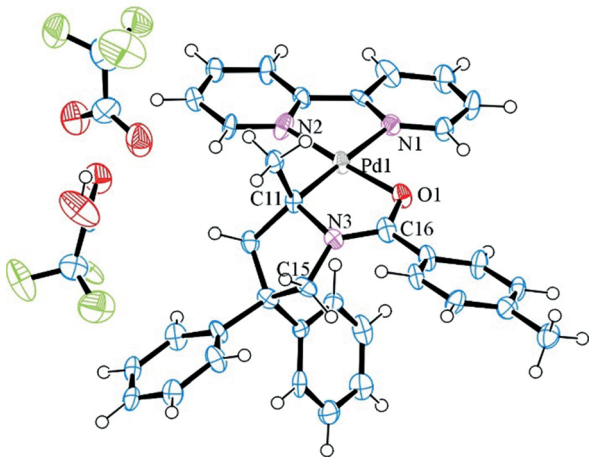
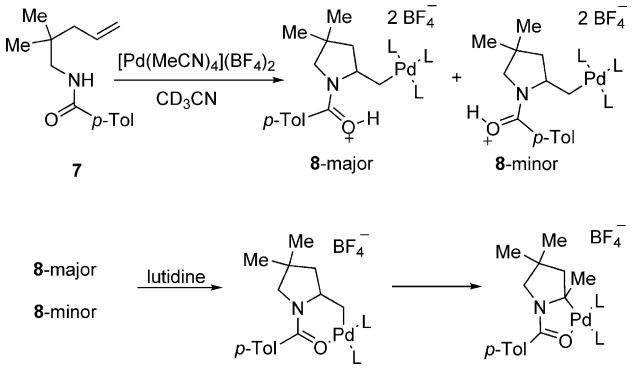


Figure 1. Crystal structure of palladium complex **6**. Selected bond distances [Å]:[14] Pd–C: 2.041, Pd–O: 2.015, Pd–N(1): 2.123, Pd–N(2): 2.045, C11–N3: 1.52, C15–N3: 1.46

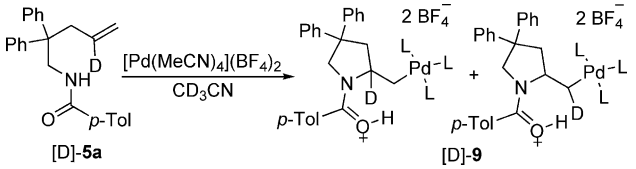
While screening palladium sources, we observed that the rearrangement did not occur when we used $[Pd(MeCN)_4](BF_4)_2$ instead of $Pd(TFA)_2$. In the absence of a base, the treatment of aminoalkene **7** with $[Pd(MeCN)_4](BF_4)_2$ afforded primary alkyl complex **8**, as a mixture of two rotamers (Scheme 3). Protonation of the amide oxygen atom prevents its chelation to Pd. Complex **8** was indefinitely stable to rearrangement until a Brønsted base was added, at which point the rearrangement proceeded.[15] From this observation we concluded that the coordination of the amide to Pd drives the rearrangement process.



Scheme 3. Chelation-dependent rearrangement.[16]

These new conditions enabled us to synthesize and characterize several other rearranged trisubstituted alkyl complexes in 70–85% yields. These alkyl–palladium complexes with a tetrafluoroborate counterion were bench stable. The X-ray crystal structure of a piperidinyl alkyl–palladium complex was also determined (see Supporting Information for details).

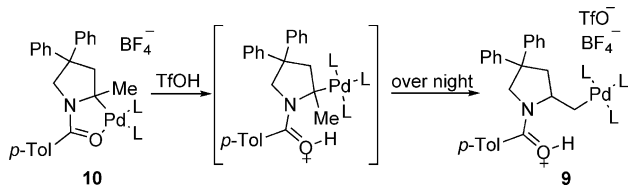
The exclusive formation of primary alkyl complex **8** in the absence of a base could be either thermodynamically or kinetically driven. In order to determine the driving force, we subjected deuterated substrate [D]-**5a** to the same conditions as above (Scheme 4). Immediate scrambling of the deuterium was observed by ^{1}H NMR spectroscopy, suggesting that the β-hydride elimination/reinsertion is rapid. Consequently, the formation of the primary alkyl complex must be under



Scheme 4. Reversibility indicated by deuterium scrambling.

thermodynamic control and this complex is thermodynamically more stable in the absence of amide chelation.

As deprotonation of the protonated amide carbonyl moiety is required to form the rearranged complex, we hypothesized that the addition of a Brønsted acid would halt and/or reverse the rearrangement. To test this hypothesis, TfOH was added to a sample of the completely rearranged trisubstituted alkyl–palladium complex **10** (Scheme 5). After

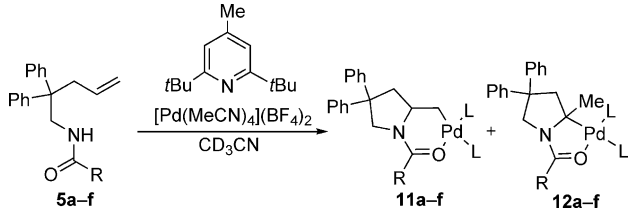


Scheme 5. Reversal of the rearrangement with Brønsted acid.

several minutes, the resonances in the ^{1}H NMR spectrum were broadened and shifted downfield, possibly reflecting protonation of the complex. After one day, protonated complex **10** had completely rearranged back to the protonated primary alkyl complex **9**. The reversibility of this reaction in the presence of an acid supports our hypothesis that the driving force for the rearrangement to the trisubstituted alkyl–palladium complex is the chelation of the amide carbonyl moiety.

Acetamide substrate **1** gave a mixture of primary and trisubstituted alkyl–palladium complexes, but substrates with the *p*-toluamide protecting group (**5a**, **7**) converted entirely to the trisubstituted alkyl–palladium complex. We hypothesized that the size of the protecting group was determining the propensity for rearrangement. To test this hypothesis, amides **5a–f** were allowed to form Pd complexes and rearrange, and the final ratio of complexes was determined (Table 1). The extent of rearrangement correlated well with the steric bulk of the protecting group. Small acyl groups, such as formamide (in **5b**), did not result in any rearranged complex, while large acyl groups, such as *p*-toluoyl (in **5a**) and pivaloyl (in **5f**),

Table 1: Effect of the acyl group on the rearrangement.



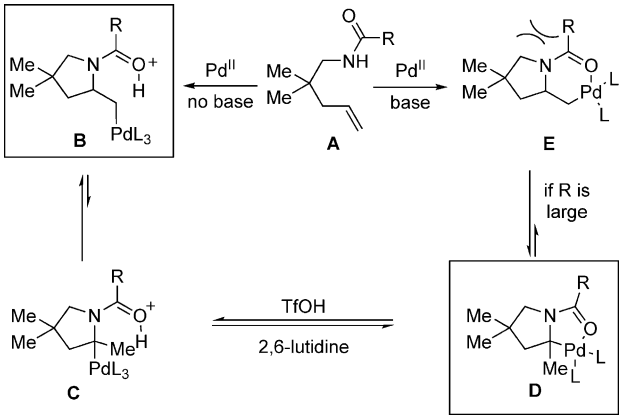
Entry	5	R	A value[17][a]	11:12[b]
1	**5b**	H	0	100:0
2	**5c**	Me	1.7	50:50
3	**5d**	Et	1.75	37:63
4	**5e**	*i*Pr	2.15	25:75
5	**5a**	*p*-Tol	3.0	0:100
6	**5f**	*t*Bu	>4.5	0:100

[a] kcal/mol. [b] Determined by ^{1}H NMR spectroscopy.

afforded complete rearrangement to the corresponding trisubstituted alkyl–palladium complex **12**.

In order to explain this correlation, we propose that larger protecting groups interact sterically with the α-methylene group of the pyrrolidine backbone. Contraction of the chelate size from a six-membered ring to a five-membered ring expands the distance between the α-methylene and the acyl group, relieving the steric strain. Indeed, X-ray structures of complexes **3** and **6** show that the distance between the α-carbon atom of the acyl group and the methylene carbon atom expands from 2.92 to 3.10 Å with the contraction of the chelate.

Combining all of the data, we propose the following mechanism for formation of the trisubstituted alkyl–palladium complex (Scheme 6). An initial aminopalladation of **A**



Scheme 6. Interconversion of isomeric complexes determined by chelation.

generates the expected primary alkyl complex **B**. Under all conditions, β-hydride elimination and reinsertion is rapid, allowing the complex to rearrange to the thermodynamically most stable structure. In the absence of base, the primary alkyl–palladium complex **B** is more stable than the trisubstituted alkyl–palladium complex **C**. In the presence of base, the amide chelates to Pd and the resulting steric hindrance between the acyl group and the ring destabilizes the chelated primary alkyl complex **E**. Rearrangement to the now more stable trisubstituted alkyl–palladium complex **D** relieves this strain. Protonation of complex **D** reverses the process, opening the chelate ring, relieving the steric strain, and reverting to primary alkyl complex **B**.

In conclusion, we have found a rare case where complexes of more highly substituted carbon centers are more stable than their isomeric complexes with less-substituted carbon centers. The fact that the relative thermodynamic stability of the primary and trisubstituted alkyl–palladium complexes can be inverted by relatively subtle structural changes implies that the difference in energy between these complexes must be quite small. These results point to the fact that highly substituted alkyl–palladium complexes can be accessed from more readily available primary alkyl complexes by minor manipulations of the overall structure. Understanding the subtle combination of steric and electronic factors observed in

this and other systems may help us expand the available possibilities in Pd-catalyzed organic transformations.

Keywords: alkyl complexes · chelation · palladium · rearrangement · tertiary carbon centers

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[14] The X-ray structure and data for complex **6** can be found in the Supporting Information. CCDC 1037741 (**6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[15] Any base that is strong enough to deprotonate the protonated amide was sufficient to induce chelation and rearrangement, including trifluoroacetate.
[16] The ligand L is most likely MeCN in all schemes.
[17] "A values" are a measure of the substituent size derived from conformational energies: E. L. Eliel, S. H. Wilen in *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**.

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