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Model Complexes for the Palladium-Catalyzed Transannular C–H Functionalization of Alicyclic Amines

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Abstract

This report describes the synthesis of model complexes for key intermediates in the Pd-catalyzed transannular C(sp³)–H arylation of alicyclic amines. These complexes react stoichiometrically with phenyl iodide to afford C–H arylation products. Furthermore, they participate in H/D exchange with *d*₁₀-*tert*-butanol at temperatures as low as 40 °C. Overall, these studies provide insights into the factors controlling transannular C(sp³)–H activation in these systems.

INTRODUCTION

Alicyclic amines appear in a wide variety of biologically active molecules.¹ As such, there is great interest in developing synthetic methods for the late-stage functionalization of these structural motifs.² In 2016, our group reported the transannular C–H arylation of piperidines and other alicyclic amine cores (Scheme 1).^{3a} Notably, this transformation enables highly selective functionalization of the C–H₄ bond in lieu of the more activated C–H bonds at the 2-position.⁴ In our original report,^{3a} we proposed that this selectivity derives from bidentate coordination of the amine nitrogen and the tethered amide⁵ of the substrate (**I**) at Pd^{II} to form an intermediate of general structure **II** (Scheme 1, step i).^{3a} Subsequent isomerization to the boat conformer then positions the C–H₄ bond proximal to the Pd^{II} center for C(sp³)–H activation to form **III** (step ii), followed by functionalization with ArI and subsequent ligand exchange to release the product (step iii).

The proposed transannular C(sp³)–H activation (step ii) is unusual in that it forms a strained bicyclo[2.2.1]palladacycle (**III**). Very few examples of this type of structure have been

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isolated and characterized from C–H activation reactions.⁶ Indeed, recent DFT calculations suggest that complex **III** is approximately 20 kcal/mol uphill from **II**,⁷ indicating that this transannular C(sp³)–H activation is highly thermodynamically unfavorable. This stands in contrast to other C(sp³)–H cyclopalladation reactions, which often produce isolable 5-membered palladacycles under mild conditions.^{8,9}

We sought to interrogate the C–H activation step of the proposed catalytic cycle by isolating and studying key intermediates along this pathway. Herein we demonstrate that amines of general structure **I** bind to Pd in a bidentate fashion to form isolable intermediates in which the C–H₄ bond is in close proximity to both the Pd center and the carboxylate ligand. We further show that these complexes react stoichiometrically with aryl iodides to afford C–H arylation products. Finally, we demonstrate that they participate in H/D exchange with *d*₁₀-*tert*-butanol at temperatures as low as 40 °C. Overall these studies are consistent with the mechanism proposed in Scheme 1 and provide new insights into the transannular C(sp³)–H activation step of this catalytic cycle.

RESULTS AND DISCUSSION

We initially focused on synthesizing the putative catalytic intermediate **II**. Two different alicyclic amine cores [3-azabicyclo[3.1.0]hexane (**A**) and 2,3,4,5-tetrahydro-1H-1,5-methano-3-benzazepine (**B**)] were selected for these studies based on their effectiveness as substrates for catalytic C–H arylation.^{3a} The reactions of **A** and **B** with various Pd^{II} sources yielded complex mixtures that could not be definitively isolated or characterized (Scheme 2). We hypothesized that the palladium product(s) might be stabilized by the addition of a monodentate pyridine ligand to generate the pyridine adduct **1**.

The reaction of **A** with Pd(OAc)₂, CsOPiv, and pyridine in *tert*-amyl alcohol at 60 °C for 24 h afforded **1-A** in 58% isolated yield (eq. 1). ¹H NMR spectroscopic analysis of **1-A** in CDCl₃ at room temperature shows the presence of two isomers (**1-A**¹ and **1-A**²) in an approximately 1:1 ratio. Yellow crystals of **1-A**¹ and **1-A**² were obtained in the same unit cell by vapor diffusion of hexanes into a dichloromethane solution at 25 °C. The solid state structure shows that **1-A**¹ and **1-A**² are square planar Pd^{II} complexes in which **A** is bound through the amine and amide nitrogen atoms (Figure 1). The key difference between these complexes is the orientation of the cyclopropane ring relative to the Pd^{II} center. In **1-A**², this ring points away from Pd, while in **1-A**¹ the ring is oriented towards the Pd center and pivalate ligand. Notably, isomer **1-A**¹ is the conformation from which transannular C–H activation is expected to take place. The reactive C(sp³)–H (H1) is 3.411 Å from the C=O of the pivalate ligand and 4.421 Å from the Pd center in **1-A**¹ (Table 1). Both of these distances are significantly shorter than those in complex **1-A**² (5.293 and 5.173 Å, respectively).

(1)

An analogous complex was formed in 66% isolated yield from the reaction of **B** with $\text{Pd}(\text{OAc})_2$, CsOPiv , and pyridine in *tert*-amyl alcohol at 60 °C for 24 h (eq. 2). Both ¹H NMR spectroscopy and X-ray crystallography show that **1-B** is a singlex isomer, with the transannular C–H bond (H1) pointing toward the Pd center and pivalate ligand (Figure 1). In this case the O2–H1 and Pd–H1 distances are even shorter, at 2.711 Å and 3.694 Å, respectively (Table 1).

(2)

We next explored the reactivity of **1-A/B** towards C–H activation and functionalization with PhI (Scheme 1, steps *ii* and *iii*). A key question for these studies is whether **1** is a viable model system for catalytic intermediate **II**, or whether the pyridine impedes C–H activation and/or functionalization. To test this, each complex was treated with PhI under catalytically relevant conditions (3 equiv of CsOPiv , 3 equiv of PhI in *tert*-amyl alcohol at 100 °C for 18 h).^{3b} The reactions were then quenched with hydrazine (to cleave the ligands and precipitate palladium black) and analyzed by GC to quantify the C–H arylation products. As shown in eq. 3, the reactions of **1-A** and **1-B** afforded C–H arylation products **2-A** and **2-B** in 98% and 72% yield, respectively, confirming that these model complexes are competent for the C–H activation/arylation sequence.¹⁰

(3)

As discussed above, DFT calculations suggest that transannular C(sp³)–H activation at **II** to form σ -alkyl complex **III** is thermodynamically unfavorable.⁷ Consistent with these calculations, attempts to observe or isolate analogues of **III** under a variety of conditions (with and without added base) were unsuccessful. Thus, we turned to hydrogen/deuterium (H/D) exchange¹¹ as a method to interrogate C–H activation at **1-A/B**. H/D exchange studies were carried out using the solvent *d*₁₀-*tert*-butanol (C₄D₉OD) as the source of deuterium. **1-A** and **1-B** were initially heated at 100 °C for 18 h in C₄D₉OD in the presence of 3 equiv of CsOPiv. The reactions were then quenched with hydrazine and analyzed by GCMS as well as ¹H and ²H NMR spectroscopy. Both **1-A** and **1-B** reacted under these conditions to form mono-deuterated amine products with 65% and 81% D incorporation, respectively (Table 2, entries 1 and 7).¹² NMR analysis shows that the deuterium is site- and stereoselectively incorporated at the transannular site on the amine core to form **A-d** and **B-d**.¹² These results demonstrate that this C–H activation reaction is reversible and that it occurs in the absence of the aryl iodide oxidant.

We next probed the role of CsOPiv in this H/D exchange process. C–H activation at Pd^{II}–carboxylate complexes is believed to proceed via a concerted-metalation-deprotonation (CMD) pathway, in which the carboxylate ligand acts as an intramolecular base (**TS-I** in Figure 2).^{6,13} As such, we hypothesized that the added CsOPiv should not be required for H/D exchange. Indeed, nearly identical yields of **A-d** and **B-d** were obtained in the absence of CsOPiv (entries 2 and 8).

The CMD transition state **TS-I** requires an open coordination site for interaction between the C–H bond and the Pd center. Thus, this pathway is expected to require pyridine dissociation from **1-A/B** prior to C–H activation. Consistent with this proposal, the addition of 2 equiv of pyridine-*d*₅ resulted in a significant decrease in the % deuterium incorporation for both amines (compare entries 2 and 8 to entries 3 and 9).

Finally, we investigated the temperature required for C–H activation in these systems. Remarkably, H/D exchange was observed after 18 h at temperatures as low as 60 °C for **1-A** (entry 5) and 40 °C for **1-B** (entry 12). These results suggest that C–H functionalization reactions of **A** and **B** (which were previously conducted at temperatures >100 °C)³ can potentially be optimized to proceed under much milder conditions.¹⁰ In addition, the observation that **1-B** is more reactive than **1-A** is consistent with the observation that this complex is formed as a single isomer with the transannular C–H bond in close proximity to the Pd center and the reactive carboxylate oxygen.

In summary, this report describes the design, synthesis, and characterization of Pd^{II} complexes that serve as models for catalytic intermediates in the Pd-catalyzed transannular C(sp³)–H arylation of alicyclic amines. While the C–H activation intermediates appear to be thermodynamically uphill, the C–H cleavage step can be directly interrogated via H/D exchange. These studies show that transannular C(sp³)–H activation occurs with high site-selectivity at temperatures as low as 40 °C, suggesting that C–H activation is likely occurring reversibly during catalysis. Furthermore, the results are consistent with C–H cleavage occurring via a CMD mechanism at the Pd^{II} oxidation state. Overall, we anticipate that these

investigations will inform the development of new, mild catalytic methods for the late-stage functionalization of alicyclic amine substrates.

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Figure 1.
X-ray crystal structures of **1-A¹**, **1-A²** and **1-B**

Figure 2.
Proposed transition state for C–H activation via CMD mechanism

Scheme 1.

Proposed mechanism for the transannular C-H arylation of alicyclic amines

Scheme 2.

Attempted synthesis of **II** and hypothesis for stabilization of this intermediate with pyridine

Table 1.Comparison of bond distances for complexes **1-A¹**, **1-A²**, and **1-B**

	Pd–N1	Pd–N2	Pd–N3	Pd–O1	Pd–H1	O2–H1
2-A¹	2.037 Å	2.060 Å	2.007 Å	2.033 Å	4.421 Å	3.411 Å
2-A²	2.023 Å	2.058 Å	2.003 Å	2.023 Å	5.173 Å	5.293 Å
2-B	2.031 Å	2.094 Å	2.002 Å	2.039 Å	3.694 Å	2.711 Å

Table 2.H/D Exchange at Complexes **1-A** and **1-B**

entry	complex	temp	additive	% deuteration
1	1-A	100 °C	3 equiv CsOPiv	65%
2	1-A	100 °C	none	58%
3	1-A	100 °C	2 equiv pyridine- <i>d</i> ₅	31%
4	1-A	80 °C	none	40%
5	1-A	60 °C	none	16%
6	1-A	40 °C	none	2%
7	1-B	100 °C	3 equiv CsOPiv	81%
8	1-B	100 °C	none	80%
9	1-B	100 °C	2 equiv pyridine- <i>d</i> ₅	64%
10	1-B	80 °C	none	78%
11	1-B	60 °C	none	74%
12	1-B	40 °C	none	18%