Palladium(II)-Catalyzed Intramolecular Aminobromination and Aminochlorination of Olefins

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The first intramolecular aminobromination and aminochlorination of olefins catalyzed by palladium(II) is reported. These reactions use a stoichiometric amount of copper(II) halide salt to aid in halogen transfer and catalyst oxidation. The yields are generally high and the degree of regioselectivity (endo vs exo cyclization) varies with substrate structure. Control experiments were performed to determine the requirements for a catalytic reaction. Solvent, temperature, and the nature of the copper halide salt all effect the course of the reaction.

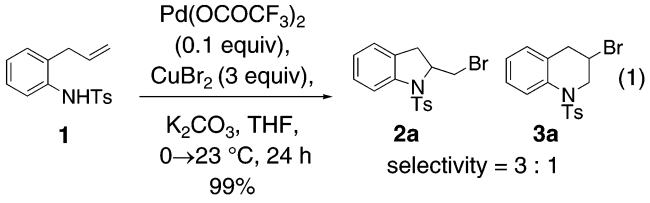
Introduction

Nitrogen heterocycles are common components of biologically active compounds and have demonstrated broad utility as components of organocatalysts as well as transition metal catalysts.[1−4] Vicinally halogenated nitrogen heterocycles offer potential both as mechanism-based medicinal agents[5] and as versatile synthetic intermediates.[6] Although a number of methods to form vicinal haloamines from olefins exist,[7−11] no method for reagent or catalyst based asymmetric induction has yet been reported. The extensive track record of asymmetric catalytic reactions performed by group 10 transition metals and the rich history of palladium(II)-catalyzed heterocycle synthesis indicate there is potential, using this strategy, for development of a catalytic asymmetric aminohalogenation reaction.[12] The first step toward such a goal is the development of a vicinal aminohalogenation method that involves the transition metal in the enantioselectivity-determining step. Herein is reported our progress toward this goal.

Our approach to this problem involves the use of Wacker-type reaction conditions, wherein a catalytic amount of expensive group 10 transition metal is used in conjunction with stoichiometric amounts of inexpensive copper(II) halide salts.[1] Henry and co-workers have recently reported that $CuBr_2$ and $CuCl_2$ can facilitate the palladium(II)-catalyzed enantioselective intermolecular dibromination and chlorohydration of olefins.[13−15] In these reactions, halogen transfer occurs more rapidly than β-hydride elimination, a common terminating event in Pd^{II}-catalyzed reactions.[1,16−18]

Results and Discussion

We were pleased to find that treatment of *N*-tosyl-*ortho*-allylaniline **1** with 10 mol % $Pd(OCOCF_3)_2$ and $CuBr_2$ (3 equiv) in THF (0 → 23 °C) for 24 h and in the presence of K_2CO_3 afforded a 3:1 mixture of aminobromides **2a** and **3a** in 99% combined yield. This reaction can be performed under either an Ar(g) or air atmosphere in dry THF (eq 1).



This reaction gives similar results when $CuCl_2$ is used as the oxidant (4 equiv), although the yield is higher in CH_3CN than in THF (eq 2). That Cu^{II} is a necessary ingredient in the halogen transfer event is illustrated by the fact that neither stoichiometric $PdBr_2$ nor stoichiometric $PdBr_2$ and LiBr (5 equiv) are effective at providing the aminohalogenated products (eq 3). It

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Scheme 1. Proposed Aminohalogenation Mechanism

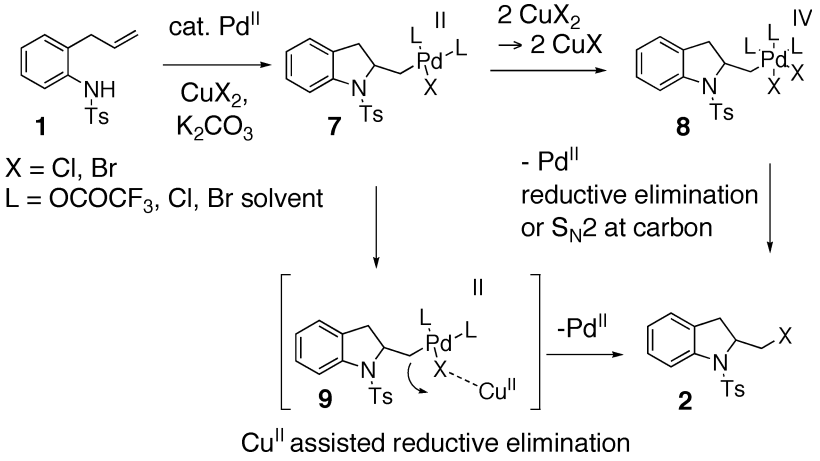
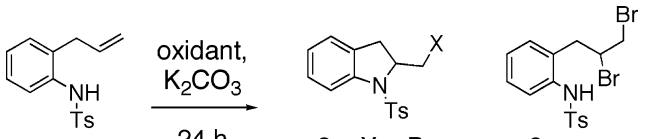


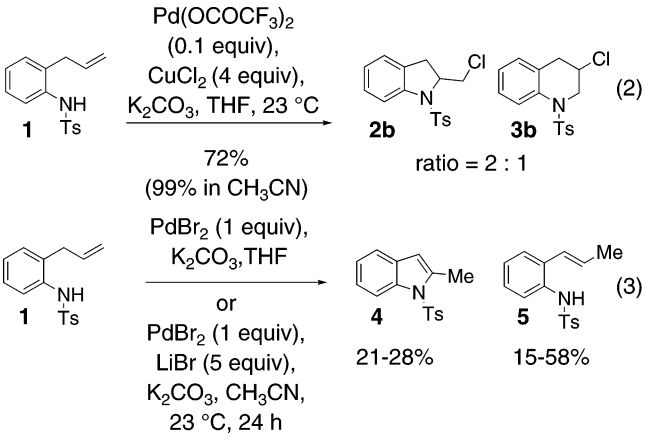
Table 1. Copper(II)-Promoted Background Reactions



oxidant (3 equiv)	solvent, temp	% yield **2**	% yield **6**
$CuBr_2$	THF, 23 °C	<5[a]	0
$CuBr_2$	THF, 70 °C	45	ca. 20[b]
$CuBr_2$	CH_3CN, 23 °C	54	22
$CuCl_2$	CH_3CN, 23 °C	no rxn[a]	0

[a] Little to no reaction was observed as determined by inspection of the crude ^1H NMR spectra. [b] Additionally, about 20% of the material was composed of compounds brominated at aromatic positions.

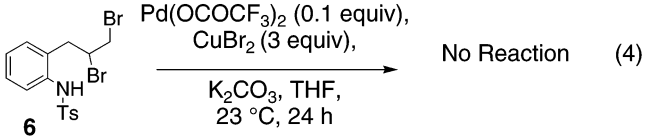
should also be noted that copper(I) bromide is also not effective in promoting aminobromination either alone or in conjunction with catalytic Pd^{II}.



Since we desire to render this reaction asymmetric using a chiral ligand on Pd^{II}, we checked for the presence of a background reaction. We found that solvent choice was key; at room temperature, background reaction was greatly minimized by use of THF vs CH_3CN (Table 1). Temperature is also key: treatment of *N*-tosyl-*ortho*-allylaniline **1** with $CuBr_2$ at 70 °C in THF resulted in the formation of a complex mixture of products which included 45% of the five-membered aminobromide **2a** and ca. 20% of dibromoamine **6**, along with approximately 20% of a product which appeared to result from bromination at an aromatic position. Notably, a change in product distribution is observed in the background reaction, compared to the Pd^{II}-catalyzed reaction: the five-membered aminobromide **2** and the dibromoamine **6** are now the predominant products of the reaction. No six-membered aminobromide **3** was detected in any of these reactions. The background reaction may occur through the formation of Br_2 ($2CuBr_2 \rightarrow 2CuBr + Br_2$).[19–21] An alternative mechanism, analogous to a $CuBr_2$-promoted olefin dibromination mechanism proposed by Fraser-Reid and Snyder, would involve Cu^{II} acting as an olefin activator, much like Pd^{II} would.[21]

The background reaction with $CuBr_2$ in CH_3CN was not inhibited upon addition of hydroquinone, indicating that this reaction likely occurs through an ionic mechanism (e.g., electrophilic addition of Br_2) rather than a radical mechanism.

The mechanism of formation of aminobromides **2** and **3** under Pd^{II} catalysis was also tested by subjection of dibromide **6** to the reaction conditions. Under the reaction conditions, no reaction occurred, indicating dibromoamine **6** is not an intermediate in the Pd^{II}-catalyzed reactions (eq 4).



Given this information, we can propose possible reaction pathways (Scheme 1). Aminopalladation of *N*-tosyl-*ortho*-allylaniline **1** gives the organometallic intermediate **7**. This intermediate may be converted to the alkylpalladium(IV) species **8**, which may decompose through either reductive elimination or S_N2 at carbon. Recent work by Canty and co-workers indicate that palladium(IV) species can be formed and then undergo subsequent S_N2 or reductive elimination reactions.[22–24]

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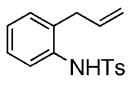
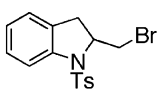
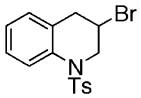
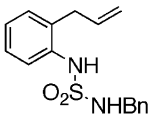
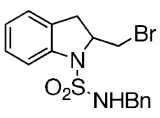
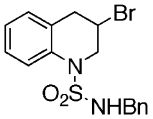
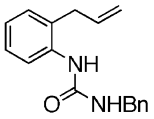
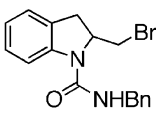
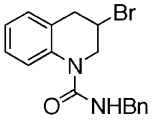
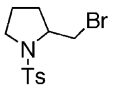
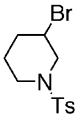
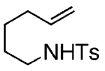
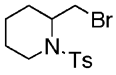
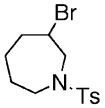
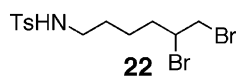
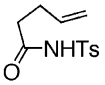
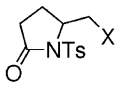
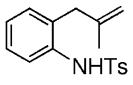
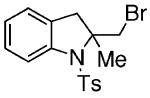
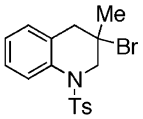
Table 2. Substrate Scope in the Pd^{II}-Catalyzed Intramolecular Aminobromination[a]

entry	substrate	products	% yield,[b] selectivity[c]
1	 **1**	 **2**  **3**	99, **2** : **3** = 3 : 1
2	 **10**	 **11**  **12**	91, **11** : **12** = 1.6 : 1
3	 **13**	 **14**  **15**	92, **14** : **15** = 4.4 : 1
4	 **16**	 **17**  **18**	72, **17** : **18** = 1 : 1.7
5	 **19**	 **20**  **21**  **22**	59,[d] **20** : **21** : **22** = 2.3 : 1.7 : 1
6	 **23**	 **24a**, X = Br **24b**, X = Cl	94
7			50[e]
8	 **25**	 **26**  **27**	66, **26** : **27** = 4.2 : 1

[a] Conditions: A solution of substrate, K_2CO_3 (2 equiv), and $CuBr_2$ (3 equiv) in THF (0.1 M w/r to substrate) at 0 °C was treated with $Pd(OCOCF_3)_2$ (0.1 equiv). The solution was allowed to warm to 23 °C slowly. After 24 h, the mixture was filtered through SiO_2 with Et_2O and the products were purified by flash chromatography on SiO_2. [b] Yields refer to sum of the isolated products. [c] Ratio of the crude product mixture by ^1H NMR analysis. [d] Reaction was run for 48 h. [e] $CuCl_2$ (5 equiv) in CH_3CN was used instead of $CuBr_2$ in THF.

An alternative mechanism that does not involve a higher oxidation state of palladium is shown in the conversion of **7** to **2** via **9**. In this mechanism, which is analogous to that proposed by Henry in his olefin dibromination and chlorohydration reactions,[13,15] copper(II) acts to assist in ligand transfer while also retaining palladium in its +2 oxidation state. These mechanisms cannot be differentiated without further studies.

The scope of the Pd^{II}-catalyzed aminobromination reaction was explored using the reaction conditions found optimal for background reaction minimization (Table 2).

The nitrogen substituent greatly affects the reactivity and the product distribution. Sulfonamides, sulfamides, and ureas underwent the aminobromination reaction smoothly, and the products were stable (Table 2, entries 1−3). Of the aniline-derived substrates, the urea gave the most regioselective reaction (4.4:1 in favor of the exo-cyclized product **14**). *N*-Benzoyl-*ortho*-allylaniline is poorly reactive under these conditions (predominately starting material is observed), while the *N*-benzylated-*ortho*-allylaniline reacts rapidly, but the derived aminobromide products rapidly decompose, presumably due to aziridinium ion formation. The more entropically

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challenged aliphatic substrates were less reactive, and in the case of substrate **19**, olefin dibromination became competitive (Table 2, entries 4 and 5).

We hypothesized that the regioselectivity of the reaction might be influenced by the presence of an endocyclic carbonyl. The bond angles of the carbonyl may lend curvature to the substrate, thus increasing the rate of cyclization. Additionally, the bond angles of an internal carbonyl may favor formation of a five-membered ring over a six-membered ring. In the event, cyclization of tosylamide **23** gave the five-membered ring **24a** as the sole product in 94% yield (Table 2, entry 6).

It should be noted that $PdBr_2$, which is ca. one-third the price of $Pd(OCOCF_3)_2$, can also be used in this reaction: aminobromination of **1** catalyzed by $PdBr_2$ in the presence of 3 equiv of $CuBr_2$ in THF occurred in 83% yield, giving a 3:1 mixture of aminobromides **2a** and **3a**.

Conclusion

In conclusion, we have identified conditions for a palladium(II)-catalyzed intramolecular aminohalogenation of olefins. The yields are generally high and the degree of regioselectivity is dependent on the structure of the substrate. Future work includes changing the ligands on Pd^{II} with the hope that a catalytic enantioselective intramolecular aminohalogenation protocol may be developed. Work toward this objective in currently in progress and will be reported in due course.

Acknowledgment. We thank Dr. Alice Bergman for mass spectral analysis and the NSF for providing funds for the mass spectrometers (CHE0091977). We thank Dr. Robert Bogadi for obtaining the X-ray crystal structure of **2a** and Oksana O. Gerlits for obtaining the X-ray crystal structure of **26**. The University at Buffalo is gratefully acknowledged for support of this work (start-up funds for S.R.C.).

Supporting Information Available: Full experimental details and characterization of all new compounds, including ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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