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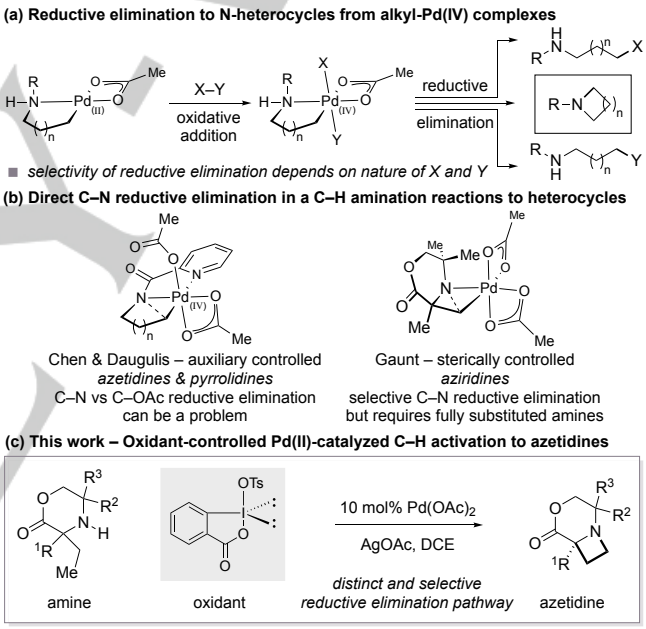
Selective Reductive Elimination at Alkyl Pd(IV) via Dissociative Ligand Ionization Enables Catalytic C(sp^3)–H Amination to Azetidines

Manuel Nappi,[+] Chuan He,[+] William G. Whitehurst, Ben G. N. Chappell and Matthew J. Gaunt*

Abstract: A Pd(II)-catalyzed γ-C–H amination of cyclic alkyl amines to highly substituted azetidines is reported. The use of a benziodoxole tosylate oxidant in combination with AgOAc was found to be crucial for controlling a selective reductive elimination pathway to the azetidines. The process is tolerant of a range of functional groups, including structural features derived from chiral α-amino alcohols, and leads to the diastereoselective formation of enantiopure azetidines.

The development of new methods for the synthesis of aliphatic N-heterocycles based on metal-catalyzed C–H activation has stimulated intense research effort.[1] Among these processes, intramolecular C–H amination using Pd(II) catalysts represents an attractive way to access saturated N-heterocycles from free(NH) amines. Key to the success of such a strategy would be the oxidation of an amine-ligated Pd(II) palladacycle to an alkyl-Pd(IV) species,[2] from which C–N reductive elimination would form the cyclic amine. Despite its apparent simplicity, the successful realization of this tactic is hindered by two factors. Firstly, oxidation of the amine-ligated palladacyle results in a Pd(IV) species displaying a number of different anionic ligands, meaning that the selectivity of reductive elimination can be difficult to control, leading to multiple products (Scheme 1a).[3] Secondly, Pd(II)-catalyzed C–H activation on free(NH) alkyl amines can be hampered by substrate degradation connected to the use of the strong oxidants required to affect the transition between Pd(II)/(IV) intermediates.[4] While a number of elegant solutions have emerged for C(sp^2)–H amination,[5] examples of Pd(II)-catalyzed C–H amination to aliphatic N-heterocycles are rare. In 2012, Daugulis and Chen independently reported that Pd(II)-catalyzed intramolecular C(sp^3)–H amination to 5- and 4-membered N-heterocycles could be affected by a hypervalent iodine oxidant (Scheme 1b).[1,6] However, the amine substrate required protection with a picolinamide auxiliary and, in some cases, the reaction led to product mixtures arising from non-selective reductive elimination. In 2014, our laboratory reported a Pd(II)-catalyzed C–H amination to aziridines, also using an I(III) oxidant.[7] In this case, the reaction could not accommodate amine substrates containing C–H bonds at the α-position to the amine. Consequently, the development of catalytic processes to form aliphatic cyclic amine products from aminoalkyl-Pd(IV) species remains a challenge.

Here, we detail a Pd(II)-catalyzed intramolecular C–H amination process in which a distinct oxidation system exerts control over competitive reductive elimination pathways leading to the formation of azetidines (Scheme 1c). The C–H amination converts a class of synthetically versatile alkyl amines into highly substituted, functionally complex and stereochemically defined azetidines, which could be useful as novel building blocks.[8]



Scheme 1. Pd-catalyzed C–H amination to N-heterocycles.

Recently, we described a Pd(II)-catalyzed process for β-C–H amination on hindered alkyl amines to form aziridines, which proceeded by direct intramolecular C–N reductive elimination from an aminoalkyl Pd(IV) intermediate.[7] We speculated that reaction of a related homologated amine **1a** should undergo γ-C–H amination to form the corresponding azetidine **2a** (Scheme 2). We were surprised to find, however, that reaction of amine **1a** produced only the γ-C–H acetoxylation product **3a**, with no sign of azetidine **2a**, when treated under identical conditions to the aziridine forming process.[7a] Notably, Chen et al observed competitive C–H acetoxylation as an (often significant) by-product in their related azetidine-forming reaction.[6b] Drawing analogy with our mechanistic work on aziridine formation,[7b] we assumed aminoalkyl-Pd(IV) species **int-I** (from oxidation of palladacycle **4**, Scheme 3) would precede C–O reductive elimination and provide

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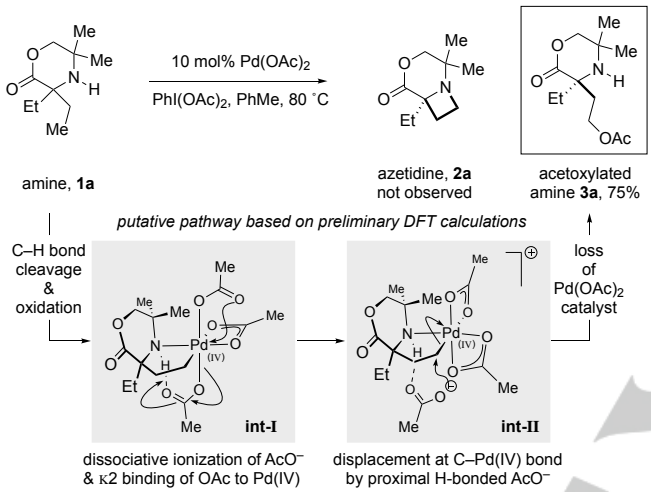
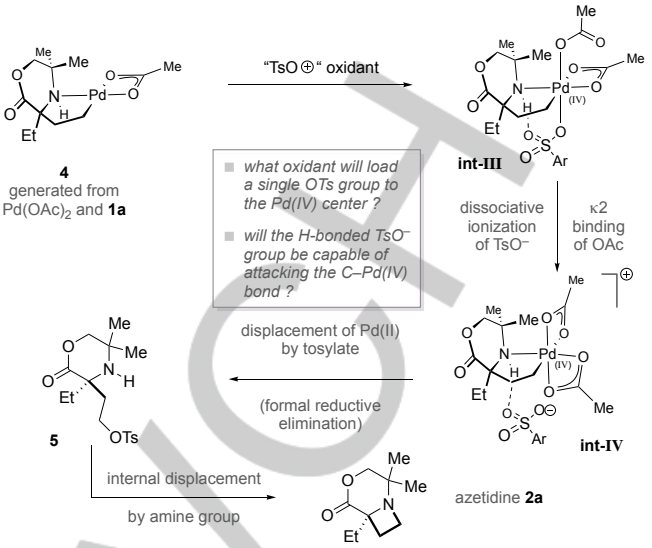
a starting point for computational studies. We were cognizant of the important effect imparted by the adjacent carbonyl motif; while its precise role remains uncertain, we believe that it modulates the reactivity of the NH group and affects both the steps leading to C–H activation as well as modulating the pathways leading to reductive elimination. Although a number of catalytic C(sp^3)–H acetoxylation methods have been reported via alkyl-Pd(IV) intermediates, the salient features of the crucial C(sp^3)–O reductive elimination step have proved difficult to elucidate.[9] Towards the formation of **3a**, computational interrogation of the fate of **int-I** surprisingly showed that the lowest energy pathway did not involve direct C–O reductive elimination.



Scheme 2. Rationalization of C–H acetoxylation.

Instead, we found that **3a** could be formed via a two-step reaction at the Pd(IV) center; dissociative ionization of an axial acetate from Pd(IV) in **int-I** and simultaneous κ2 binding of the axial acetate forms an octahedral complex **int-II**. Notably, the dissociated acetate remains hydrogen bonded to the ligated amino group in **int-II**, which aids the displacement of the high valent metal group, installing the acetoxy motif at the γ-position. This pathway draws an important parallel with the elegant work of Sanford et al, who recently reported C–O reductive elimination from stoichiometric alkyl Pd(IV) complexes based on a dissociative ionization mechanism.[9e,f] In light of these preliminary computational studies, we re-evaluated our design hypothesis for azetidine formation (Scheme 3).



Scheme 3. Proposed C–H Amination to Azetidines.

We proposed that replacing one of the acetate ligands on the aminoalkyl-Pd(IV) species with a OTs group (**int-III**) would promote dissociative ionization of the better leaving group. Accompanied by the anchimeric κ2 binding of the trans (axial) acetate, the dissociation of the OTs from the aminoalkyl-Pd(IV) center generates the octahedral Pd(IV) intermediate **int-IV**, in which the H-bonded tosylate is primed for displacement at the electrophilic C–Pd(IV) bond to form the γ-amino tosylate **5**.[9e-f,10] Cyclization of the amine to displace the γ-tosylate completes the formal C–N reductive elimination process to azetidine **2a**.

Guided by this mechanistic blueprint, we first considered an oxidant capable of transferring the single tosylate group required to form crucial aminoalkyl-Pd(IV) species **int-III**. We began by testing conditions related to the C–H acetoxylation process (Scheme 2), wherein TsOH was added in expectation that the desired pathway could be triggered by the substitution of acetate on a Pd(IV) intermediate with a TsO ligand (Table 1, entry 1); unfortunately, none of the desired azetidine was observed. Similarly, the use of NFSI in combination with TsOH, conditions reported independently by Dong[10] as part of C(sp^3)–H oxysulfonylation processes, also failed to give the azetidine **2a**. Our first success was realized through the use of Koser's reagent, a tosylate-containing hypervalent iodine oxidant (entry 2).[11] We were pleased to observe the formation of azetidine **2a**, albeit in 6% yield. We were surprised to find that addition of AgOAc increased the yield of **2a** to 27% with only trace acetoxylation observed (entry 3). With this in mind and based on Rao's use of benziodoxoles in Pd(II)-reactions,[12] reaction of **1a** with a tosylate derivative of these reagents (**6**), retaining AgOAc, increased the yield of **2a** to 52% (entry 4). Further improvements were made by increasing the amount of AgOAc and **6** (entry 5). Reaction without AgOAc gave trace amounts of **2a** and there was no reaction in the absence of $Pd(OAc)_2$ (entries 6,7). These results point to an important role for both the oxidant **6** and AgOAc. The use of **6** suggests oxidative transfer of the tosylate to form aminoalkyl-

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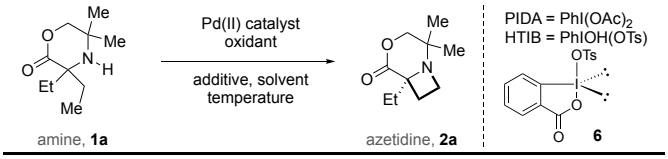
Pd(IV) species, **int-III**. Interestingly, use of AgOTs precludes any reaction (entry 8).

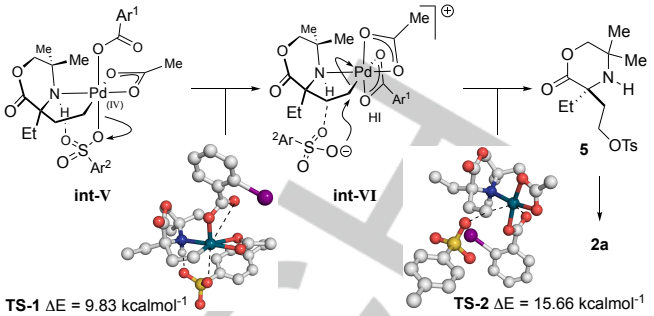
Table 1. Optimization of reaction conditions.



Entry	Catalyst	Oxidant (equiv.)	Additive (equiv.)	T °C	Solvent	2a (%)[a]
1	$Pd(OAc)_2$	PIDA (2)	TsOH (2)	80	PhMe	0
2	$Pd(OAc)_2$	HTIB (2)	–	80	PhMe	6
3	$Pd(OAc)_2$	HTIB (2)	AgOAc (2)	80	PhMe	27
4	$Pd(OAc)_2$	**6** (2)	AgOAc (2)	80	PhMe	52
5	$Pd(OAc)_2$	**6** (3)	AgOAc (3)	60	DCE	81
6	$Pd(OAc)_2$	**6** (3)	–	60	DCE	trace
7	–	**6** (3)	AgOAc (3)	60	DCE	–
8	$Pd(OAc)_2$	**6** (3)	AgOTs (3)	60	DCE	–

[a] Yields by ^{1}HNMR using Ph_3CH or $(Cl_2CH)_2$ as internal standard.

Although the precise role of the AgOAc is unclear, it could be responsible for converting any non-acetate Pd(II) species, formed at the end of the cycle, back to the essential $Pd(OAc)_2$ catalyst.[13] We validated our hypothesis through computation (Scheme 4). Probing the fate of aminoalkyl-Pd(IV) species **int-V** (formed from **4** and **6**) revealed a low energy pathway involving the dissociative ionization of tosylate (TS_{diss}=9.83 kcalmol^{-1}), via **TS-1**, assisted by the concerted κ2 binding of the 2-iodobenzoate ligand to form **int-VI.** The tosylate then attacks the γ-carbon atom (in **int-VI**, via **TS-2**), displacing the nucleofugal Pd(IV) species (TS_{displ}=15.66 kcalmol^{-1}) to form the C–OTs bond in **5**.[10] Following decomplexation of Pd(II), displacement of tosylate with the amine forms azetidine **2a**.[14,15] With the optimal conditions, we examined the scope of the γ-C–H amination.



Scheme 4. Computational validation of C–H amination.

Table 2 shows that a range of fully substituted morpholinones displaying an α-ethyl group alongside functionalized α'-sidechains undergo efficient C–H amination to azetidines **2a-h**; sidechain groups compatible with the reaction comprised hydroxymethyl derivatives (**2c,d**), fluoromethyl (**2e**), protected amines (**2f**), esters (**2g**) and arenes (**2h**). In addition, an amine containing a spiro-cyclohexane motif provided the corresponding azetidine **2i** in 83% yield. The C–H amination of a cyclic amide derivative lead to the piperazinone **2j** in moderate yield.

Typically, the C(sp^3)–H functionalization of unprotected alkyl amines via classical cyclopalladation/Pd(IV) pathways is often restricted to molecules displaying fully substituted carbon atoms around the free(NH) motif. This is, partly, because deleterious oxidation reactions at the α-position to the amine are initiated by the requisite oxidant, leading to decomposition. On the basis that the benziodoxole **6** is less oxidizing than its acyclic counterparts,[16] we reasoned that amine substrates with fewer substituents might be compatible with the modified reagent. This feature would be attractive for two reasons: chiral amino alcohols could be used to assemble the morpholinones; and a chiral center adjacent to the NH motif would introduce a previously unexplored diastereoselectivity question to the C–H activation step. Accordingly, a range of enantioenriched substrates were prepared starting from different amino alcohols. At 80 °C, the C–H amination delivered the azetidines in useful yields and excellent diastereoselectivity (**2k-x**).

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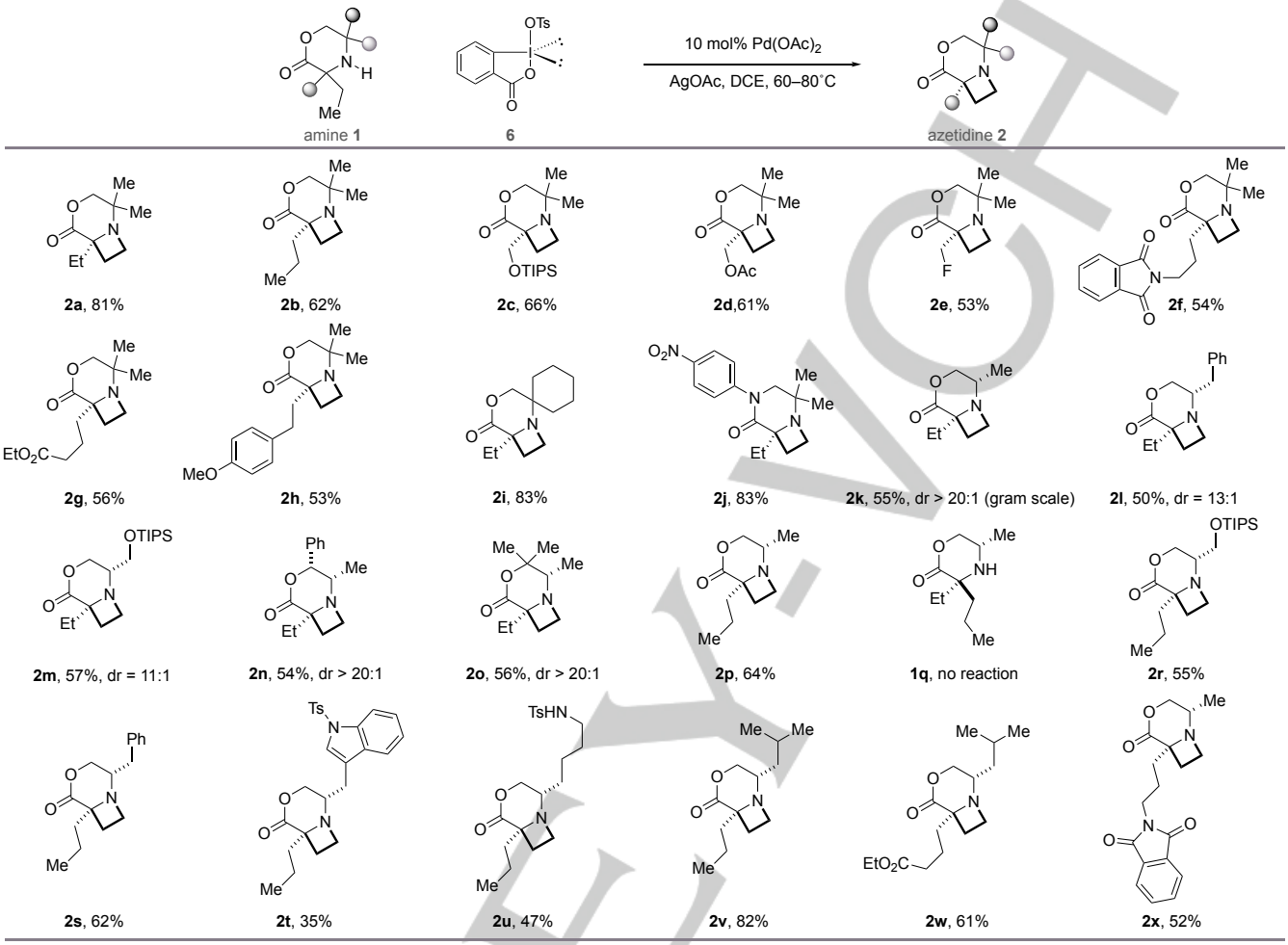
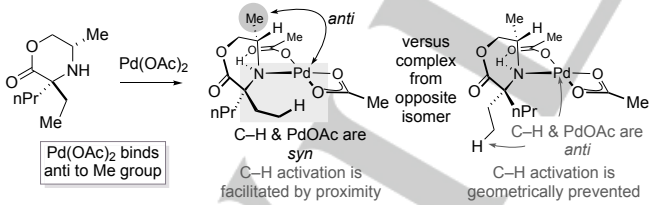
Table 1. Substrate ccope for C–H amination to azetidines[a]

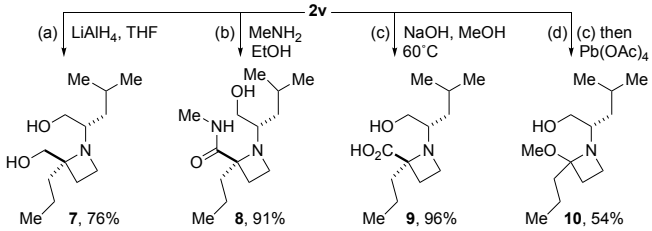


[a] Yields are of isolated products. See Supporting Information for details. [b] Stoichiometric reaction over 2 steps. TIPS = triisopropylsilyl, Ts = *p*-toluenesulfonyl.



Scheme 5. Stereoselective C–H Activation.

Interestingly, the highest diastereoselectivity was observed when using morpholinones based on alaninol (**2k**), in comparison to phenylalanine and serine-derived amines (**2l**-**m**). To probe the stereochemical features of the C–H activation step, we prepared isomeric substrates that displayed the reactive ethyl group both syn and anti to the stereogenic center. We found that only the anti-isomer produced the desired azetidine **2p**, with the syn-isomer returning starting material **1q**. A possible explanation involves binding $Pd(OAc)_2$ to the less sterically hindered face of the cyclic amine, placing the key C–H bond in a syn-orientation to the Pd(II) center (Scheme 5).



Scheme 6. Derivatization of Azetidines.

Further examples of the C–H amination demonstrated that substituents can be accommodated on either side of the amine

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linkage forming azetidines **2r-x** displaying functional groups useful for downstream synthetic modification. Azetidine **2x** was crystalline, enabling unambiguous confirmation of the absolute configuration of the product by X-ray diffraction.[17] Acyclic amines proved to be poor substrates, requiring stoichiometric amounts of $Pd(OAc)_2$ to afford **2y** in modest yield.[18]

Finally, we showed that the azetidine products serve as substrates for a selection of simple transformations to potentially useful products (Scheme 6). Reduction of the lactone of **2t** with $LiAlH_4$ generated diol **7**; aminolysis of the lactone gave amide **8** in very good yield; hydrolysis of the morpholinone delivered the corresponding hydroxy-acid **9.** We also found that oxidative decarboxylation of **9** delivered the 4-membered ring cyclic-hemiaminal **10** as a stable, single diastereomer.

In conclusion, we have developed a Pd(II)-catalyzed γ-C–H amination process in which cyclic secondary alkyl amines are converted into highly substituted azetidines. The use of a benziodoxole tosylate as oxidant, in combination with AgOAc, was crucial in delivering the azetidines. We propose that the C–H amination to azetidines is facilitated by a selective reductive elimination that involves dissociative ionization of a tosylate and anchimeric κ2 carboxylate binding to form an octahedral aminoalkyl-Pd(IV) complex. Nucleophillic attack of the tosylate at the carbon atom bearing the Pd(IV) group forms the C–OTs bond, which in turn is displaced by the proximal amino group to form the azetidine. The reaction displays a broad tolerance to functional groups, including structural features derived from chiral α-amino alcohols, which leads to a diastereoselective process forming enantiopure azetidines. We believe that the distinct reductive elimination pathway will be applicable to other C–H functionalization processes.

Acknowledgements

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Keywords: keyword 1 • keyword 2 • keyword 3 • keyword 4

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[14] Alternative mechanisms for direct C–O or C–N reductive elimination (to **3a** & **2a**, respectively) from **int-VI** were significantly higher in energy. See supporting information, figure S2, for details.

[15] Although we were unable to isolate tosylate **5**, support for the proposed pathway is demonstrated via the preparation of the corresponding chloride, by the same pathway, and observation of the formation of azetidine **2a**. See supporting information for details.

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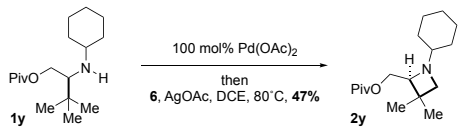
[17] **2x** was obtained as a single crystal, whose structure was confirmed by X-ray diffraction, see supporting information for details.

[18] Acyclic amine (**1y**) formed the corresponding azetidine (**2y**) in 47% yield over two steps using a stoichiometric amount of palladium.



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