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Pd-Catalyzed Intramolecular Aminoalkylation of Unactivated Alkenes: Access to Diverse *N*-Heterocycles

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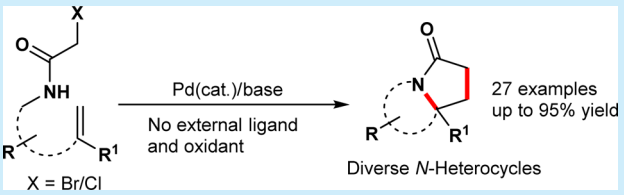
Supporting Information

ABSTRACT: A highly efficient palladium-catalyzed intramolecular aminoalkylation of unactivated alkenes in the absence of an external ligand and oxidant is described. New C−N and C(sp^3)−C(sp^3) bonds are formed simultaneously. This general transformation allows for construction of diverse *N*-heterocycles. Mechanistic studies show that the process may involve a four-membered Pd(alkyl)amido intermediate.



The Pd-catalyzed C−N bond formation via aminopalladation of alkene has emerged as a powerful tool to access diversely functionalized *N*-heterocycles.[1] The development of cascade reactions involving the formation of other bonds besides the C−N bond in one single operation is particularly appealing. Palladium-catalyzed carboamination (simultaneous formation of C−N and C−C bonds from an olefin) represents an effective strategy for the introduction of vicinal substituents onto a carbon−carbon double bond.[2] Despite impressive progress achieved in aminocarbonylation,[3] aminoarylation,[4] aminovinylation,[5] and aminoalkynylation,[6] the aminoalkylation of unactivated alkenes remains very rare.[7] Meanwhile, either an expensive and/or sensitive ligand or an excess amount of external oxidant is required in those reported transformations. Therefore, the development of an efficient Pd-catalyzed aminoalkylation of unactivated alkenes under mild conditions with a simple operation is a great challenge and highly desirable.

Nitrogen-containing heterocycles are commonly found in a diverse array of natural products and biologically active molecules.[8] Among them, pyrroloindole, pyrroloquinoline, pyrrolizidine, and indolizidine are important scaffolds due to their prevalence in pharmacologically active natural compounds (Figure 1).[9] Hence, the development of general protocols for the synthesis of these skeletons is of great interest. Recently, our group developed effective methods for accessing pyrroloindoline derivatives via Pd-catalyzed aminovinylation of unactivated alkenes (Scheme 1a).[5c−f] On the basis of our continued interest

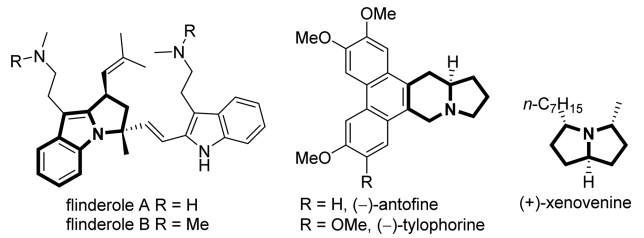
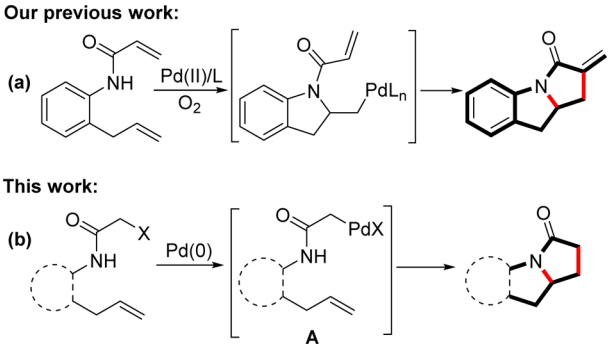


Figure 1. Representative N-containing heterocycles in natural products.

Scheme 1. Palladium-Catalyzed Intramolecular Aminovinylation and Aminoalkylation



in Pd-catalyzed carboamination, we envisioned that by replacing the unsaturated amide with an α-halo acetamide, we might realize an intramolecular aminoalkylation. It is expected that an initial oxidative addition of the C−X bond with Pd(0) would afford intermediate **A**,[10] which might undergo subsequent intramolecular aminopalladation[11] and the final reductive elimination to generate the target product (Scheme 1b). Herein, we report our efforts in achieving such an intramolecular aminoalkylation of unactivated alkenes under palladium catalysis without the requirement of an expensive and/or sensitive ligand or external oxidant, allowing for the expedient construction of a wide array of biologically important N-containing scaffolds.

To test the hypothesis outlined in Scheme 1b, compound **1.1a** was initially chosen as the model substrate to screen the reaction conditions (Table 1). When 1.0 equiv of Na_2CO_3 was employed, the desired product was obtained only in moderate yield, along with a significant amount of olefin isomerization byproduct[12] (entry 1). Increasing the amount of Na_2CO_3 to 3.0 equiv remarkably improved the yield to 70% (entry 2). A further increase in the amount of Na_2CO_3 to 5.0 equiv, however, led to a

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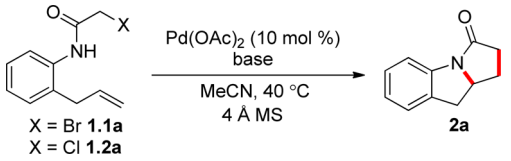
Table 1. Optimization of Reaction Conditions[a]



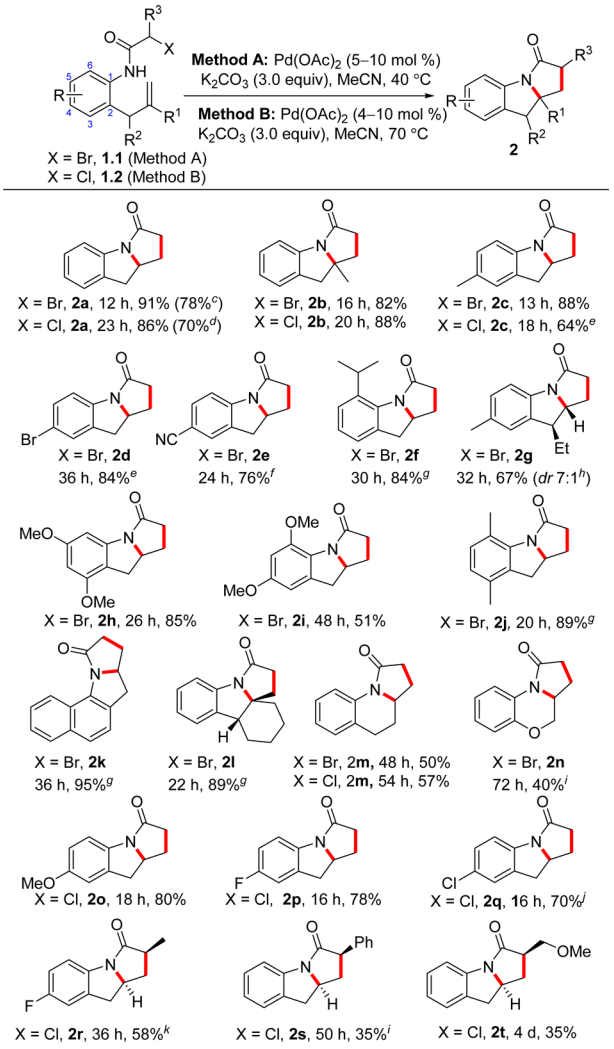
entry	substrate	base (equiv)	t (h)	yield (%)[b]
1	**1.1a**	Na_2CO_3 (1.0)	16	45
2	**1.1a**	Na_2CO_3 (3.0)	16	70
3	**1.1a**	Na_2CO_3 (5.0)	10	53
4	**1.1a**	K_2CO_3 (3.0)	10	86
5	**1.1a**	Cs_2CO_3 (3.0)	6	50
6[c]	**1.1a**	**K_2CO_3 (3.0)**	**12**	**91**
7[d]	**1.1a**	**Na_2CO_3 (1.0)**	**12**	**90**
8[c,e]	**1.1a**	K_2CO_3 (3.0)	34	82
9[c,e,f]	**1.2a**	K_2CO_3 (3.0)	23	86
10[c,f,g]	**1.2a**	K_2CO_3 (3.0)	48	69
11[c,f,h]	**1.2a**	K_2CO_3 (3.0)	15	86

[a]Reaction conditions: substrate (0.2 mmol), $Pd(OAc)_2$ (10 mol %), and 4 Å MS (1 g/mmol substrate) in MeCN (2.0 mL) at 40 °C. [b]Yield of the isolated product. [c]Without 4 Å MS. [d]10 mol % $PdCl_2$ and 0.63 equiv of Ag_2O were employed instead. [e]5 mol % $Pd(OAc)_2$. [f]Reaction temperature was 70 °C. [g]2.5 mol % $Pd(OAc)_2$. [h]5 mol % $Pd_2(dba)_3$ in place of $Pd(OAc)_2$.

diminished yield of the desired product (53%), favoring the formation of the alkene isomerization product (entry 3). Gratifyingly, the use of K_2CO_3 further enhanced the yield to 86% (entry 4). In contrast, a much stronger base, Cs_2CO_3, has given rise to the formation of a dimer as the major side product (see the Supporting Information (SI) for details) (entry 5). Thus, the reaction efficiency seems to be greatly dependent on the nature of the base employed, and the moderately basic K_2CO_3 proved to be the best. The optimal yield (91%) was obtained when the reaction was performed without the addition of 4 Å molecular sieves (MS) (entry 6). An alternative catalyst system composed of $PdCl_2$ and Ag_2O, which presumably acts as an efficient scavenger for the generated bromide anion, was also developed at the same time to afford the desired product in 90% yield (entry 7). Given the relative high expense of a silver salt, we preferred the silver-free conditions whenever comparable efficiency was observed for these two conditions (entries 6 and 7). Reducing the catalyst loading from 10 to 5 mol % caused a slightly decreased efficiency after an extended reaction time (entry 8). Notably, the presumably less reactive substrate **1.2a** was also suitable for the cyclization, producing **2a** in 86% isolated yield at an elevated temperature (entry 9). In this case, a catalyst loading as low as 2.5 mol % was sufficient to deliver a moderate yield of **2a** (entry 10). Replacing $Pd(OAc)_2$ with $Pd_2(dba)_3$ gave a comparable yield of **2a** (entry 11), which implies that a Pd(0)/(II) catalytic cycle is likely involved in this transformation.

With the optimized conditions in hand, we next investigated the scope of this reaction for the synthesis of pyrroloindolines from aromatic α-halo acetamides (Scheme 2). A variety of substrates, tethered by monocyclic aromatic rings with either electron-donating (Me, ^{i}Pr and OMe) or electron-withdrawing substituents (Br and CN) or a bicyclic naphthalene ring (**1.1k**), were all effectively converted into the desired products, whereas a relatively low yield was observed with 4,6-dimethoxy-substituted substrate **1.1i**. Notably, the reaction yield was good (78%) when performed on gram scale with an 8 mol % catalyst loading. Of particular note is the tolerance of aryl bromide, which enables

Scheme 2. Substrate Scope of Aromatic α-Halo Acetamides[a,b]



[a]Reactions were run on 0.2 mmol scale; method A was employed for α-bromo substrates, and method B was employed for α-chloro substrates. [b]Yield of the isolated product. [c]Reaction was run on 9.0 mmol scale with 8 mol % $Pd(OAc)_2$. [d]Reaction was run on 2.0 mmol scale with $Pd(OAc)_2$ (4 mol %). [e]$Pd(OAc)_2$ (5 mol %). [f]$PdCl_2$ (10 mol %) and Ag_2O (0.63 equiv) were used instead. [g]$PdCl_2$ (10 mol %) and Ag_2O (0.63 equiv) were used instead. [h]Ratio was determined by ^{1}H NMR analysis, and the major diastereomer is depicted. [i]$PdCl_2$ (10 mol %). [j]$Pd(OAc)_2$ (6.5 mol %). [k]16% OAc-substitution product was detected by crude ^{1}H NMR.

further access to more complex compounds by well-established cross-coupling reactions, thus rendering this cyclization methodology more attractive. Besides, both 2,2-disubstituted alkene substrate **1.1b** and substrate **1.1g** bearing an ethyl substituent at the benzylic position reacted smoothly to give the expected products in 82% and 67% yields, respectively. In addition, complex tetracyclic product **2l** was obtained as a single diastereomer from substrate **1l** possessing an exocyclic alkene moiety in 89% yield. More significantly, the present catalytic system could be applied to the construction of indolizidine derivative **2m** and tricyclic heterocycle **2n**, albeit with lower efficiency. In fact, only a few successful methods have been reported for the synthesis of six-membered nitrogen heterocycles via aminocyclization reactions.[13]

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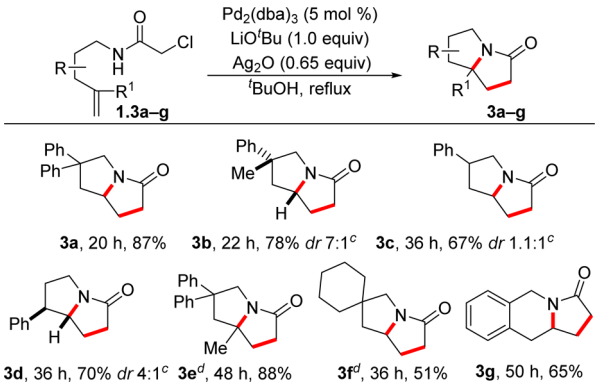
In addition, less reactive α-chloro-substituted substrates are amenable for this cyclization (Scheme 2). Substrates **1.2a−c** and **1.2m** provided roughly comparable yields of the same products with those from corresponding α-bromo-substituted substrates. Substituents, such as OMe, F, and Cl, para to the amide moiety were all well tolerated. In some cases, ester side products resulting from reaction of the nucleophilic acetate ligand with alkyl chloride were detected. In contrast to the unreactive secondary α-bromo acetamide substrate,[14] the analogous secondary α-chloro ones successfully cyclized to give corresponding products as single diastereomers.[15] Compared to α-phenyl and α-methoxymethyl substituted products **2s** and **2t**, a better yield was obtained for α-methyl substituted product **2r**, which might be attributed to less steric hindrance of the methyl group. It is also interesting to note that no β-H elimination side products were detected from substrates **1.2r** and **1.2t** given the facile nature of such a common competitive pathway in palladium-catalyzed transformations.

Evaluation of the substrate scope was then focused on the synthesis of more challenging pyrrolizidine derivatives. However, the catalytic system described above was not productive. After rescreening a variety of reaction parameters (base, solvent, temperature, additive, etc.), the modified conditions were established as follows: $Pd_2(dba)_3$ (5 mol %), LiO^{t}Bu (1.0 equiv), and Ag_2O (0.65 equiv) in ^{t}BuOH (0.1 M) under reflux (Scheme 3). Gem-disubstituted substrates either with the same

Scheme 3. Substrate Scope of Aliphatic Chloro-acetamides[a,b]

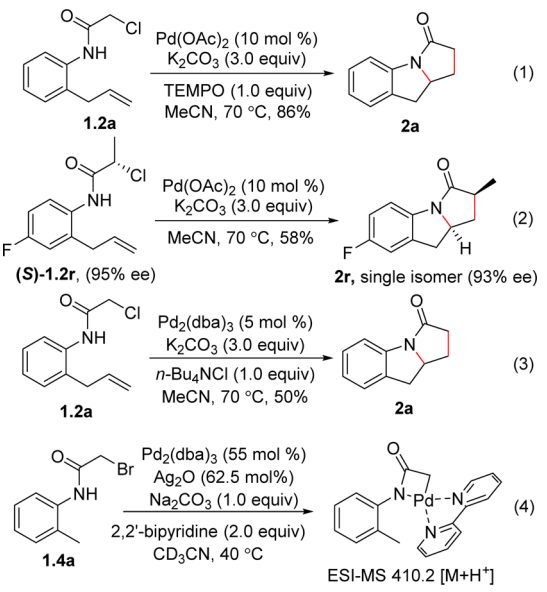


[a]Reaction conditions: substrate **1.3** (0.3 mmol), $Pd_2(dba)_3$ (5 mol %), Ag_2O (0.65 equiv), and LiO^{t}Bu (0.3 mmol) in ^{t}BuOH (3.0 mL) under reflux temperature. [b]Yield of the isolated product. [c]Ratio determined by crude ^{1}H NMR analysis. [d]$Pd(cod)_2Cl_2$ (10 mol %) was used.

phenyl groups or a phenyl and a methyl one afforded the desired products **3a** and **3b** in 87% and 78% yield, respectively. Substrates bearing one phenyl substituent at either a homoallylic or an allylic position proceeded smoothly to produce cyclized products in good yields (**3c** and **3d**). Notably, for geminally disubstituted alkene **1.3e**, the use of $Pd(cod)_2Cl_2$ instead of $Pd_2(dba)_3$ gave a better yield of **3e**. The spiro-tricyclic product **3f** could be obtained from cyclohexylidene-substituted substrate **1.3f**, albeit with low effectiveness. Importantly, tetrahydroisoquinoline derivative **3g** with a newly generated 6/5 fused ring skeleton was also delivered in 65% yield. It is worthy to note that a O^{t}Bu-substituted byproduct resulting from nucleophilic substitution by LiO^{t}Bu was occasionally observed.

To gain more insight into the reaction mechanism, some control experiments were performed (Scheme 4). The addition of a stoichiometric amount of TEMPO did not affect the reaction efficiency, which indicates that a radical pathway for this

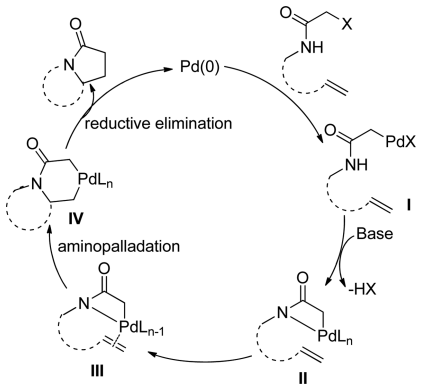
Scheme 4. Control Experiments



cyclization is not likely (eq 1; for details see Scheme S1).[16] The enantiopure substrate **1.2r** was converted to **2r** with an almost complete chirality transfer,[17] which further rules out the radical pathway (eq 2; for details see Figure S1). Furthermore, it provides an alternative method to prepare chiral pyrroloindole derivatives starting from readily available enantioenriched α-chloro acetamides. The presence of an additional chloride anion has a deleterious effect on the efficacy, which reveals that the dissociation of the Cl ligand from a putative intermediate complex may be of importance in the transformation (eq 3).[18] Although no pure intermediate was isolated, the ESI-MS analysis of the reaction mixture of substrate **1.4a** with a bipyridine ligand strongly supports the formation of a four-membered Pd(alkyl)-amido intermediate (eq 4).[19]

Based on the aforementioned observations, we propose a catalytic cycle for this intramolecular aminoalkylation reaction (Scheme 5). Pd(0), either from $Pd_2(dba)_3$ or *in situ* generated

Scheme 5. Plausible Mechanism



from $Pd(OAc)_2$, was first oxidized by α-halo acetamide to Pd(II) species **I**.[10] Subsequent amide deprotonation and coordination to the Pd(II) center produced four-membered palladacycle intermediate **II**.[19,20] The following alkene coordination afforded four-coordinated Pd intermediate **III**.[21] The conversion of **III** to the desired product presumably proceeded through sequential *syn*-aminopalladation[11] and reductive elimination.[22]

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In summary, we have developed an efficient intramolecular aminoalkylation reaction involving the simultaneous formation of C−N and C(sp^3)−C(sp^3) bonds. This reaction represents a rather rare example of Pd-catalyzed carboamination. It shows good functional group tolerance and provides a step-economical synthetic approach toward diverse *N*-heterocycles, such as pyrroloindole, pyrroloquinoline, pyrrolizidine, and indolizidine, from simple and readily available α-halo acetamides under mild conditions. The asymmetric variant of this transformation is ongoing. This intramolecular aminoalkylation may find broad application in the chemical synthesis of alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03295.

Experimental procedures, characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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