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Polycyclic Azetidines and Pyrrolidines via Palladium-Catalyzed Intramolecular Amination of Unactivated C(sp3)−H Bonds

Jie Zhao,[†,‡] Xiao-Jing Zhao,[†,‡] Pei Cao,[†] Ji-Kai Liu,[*,§] and Bin Wu[*,†,§]

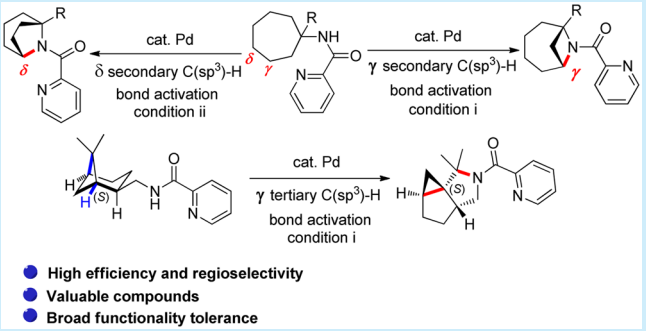
[†]State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China

[‡]University of Chinese Academy of Sciences, Beijing 100049, China

[§]School of Pharmaceutical Sciences, South-Central University for Nationalities, Wuhan 430074, China

Supporting Information

ABSTRACT: A novel strategy to construct complex polycyclic nitrogen-containing heterocycles from aliphatic amines via picolinamide-assisted palladium-catalyzed C−H bond activation reaction was reported. The reaction exhibits broad substrate scope for the synthesis of various azabicyclic scaffolds, including azetidines and tropane-class alkaloids. Application of this method to naturally occurring (−)-*cis*-myrtanylamine, an unprecedented type of carbon−carbon bond activation, in which the electron-pair involved initiates an intramolecular "S_N2-like" displacement of a cyclopalladium-fragment from a tertiary center, is described.



Because of their abundant structural diversity and broad spectrum of biological activities ranging from enzyme inhibition to antibiotic, antiviral, antitumor, and neurochemical properties, alkaloids are of great general interest, particularly to synthetic organic chemists and medicinal chemists.[1] Most structures of alkaloids contain nitrogen heterocycles, which are believed to be responsible for the biological activities.[2] The most popular approach that Nature uses in creating C−N bonds in the biosynthesis of various alkaloids is the use of the Mannich reaction, followed by stereoselective enzyme-catalyzed reactions.[3] Synthetic organic chemists have developed several multistep protocols to form the key C−N bonds in the core structures of alkaloids, including Mannich reaction, radical amination, pericyclic reaction, hydroamination of alkenes, as well as various rearrangements to install skeletal C−N bonds.[4] Unfortunately, most of these methods are based on the transformations of other functional groups, resulting in an increase in the number of synthetic steps and a decrease in the efficiency of the overall scheme.

Transition-metal-catalyzed C−H amination has become an attractive method for the formation of C−N bonds.[5] An intramolecular C−H bond amination reaction via Rh-catalyzed nitrene insertion[6] has been developed by the Breslow[7] and Du Bois[8] groups, and this reaction was further applied to the synthesis of complex natural products. Recently, the iron-catalyzed azidation of tertiary C−H bonds with a hypervalent iodine azide reagent, which has been predicted to occur via a radical mechanism, has been established by the Hartwig group.[9] An intriguing example of the β-methyl C−H bond activation of aliphatic amines via palladium catalysis affording strained aziridine compounds and β-lactams was reported by Gaunt and co-workers.[10] Palladium- or copper-catalyzed aliphatic C−H activation/intramolecular C−N bond formation to prepare β-lactams and γ-lactams has been achieved by several groups.[11] Although three examples on Pd-catalyzed C(sp^3)−H bond activation to construct C−N bonds with the PicolinAmide (PA) or 1,2,3-triazole as a directing group have been reported, these methods are limited by a narrow substrate scope and only afford the very simple azetidine or pyrrolidine compounds.[12] Herein, we report a new strategy to construct such molecules from aliphatic amines via picolinamide-assisted Pd-catalyzed C−H activation reaction followed by intramolecular cyclization. Reaction conditions have been discovered to form either 4- or 5-membered azacycles from various cyclic and acyclic amines, some carrying other diverse functional groups. The starting amines include naturally derived enantiopure substrates, further illustrating the utility of these reactions for late-stage functionalization in more complex settings. While applying this method to naturally occurring (−)-*cis*-myrtanylamine, we also uncovered an unprecedented type of C−C bond activation, in which the electron-pair involved initiates an intramolecular "S_N2-like" displacement of a Pd-fragment from a tertiary center.

We commenced our study with the PA-protected aliphatic amine **1a** as a test substrate.[13] To our delight, 21% yield of azabicyclo[3.1.1] nitrogen-containing heterocycle (±)-**2a** was obtained in the initial attempt (Table 1, entry 1). After an extensive scouting of reaction conditions including the solvent, base, stabilizing additives, and temperature, the optimized

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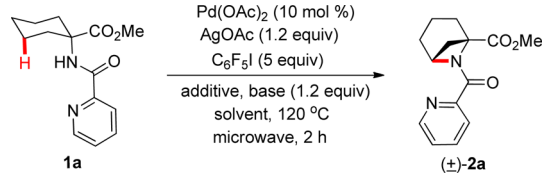
Table 1. Optimization of Reaction Conditions



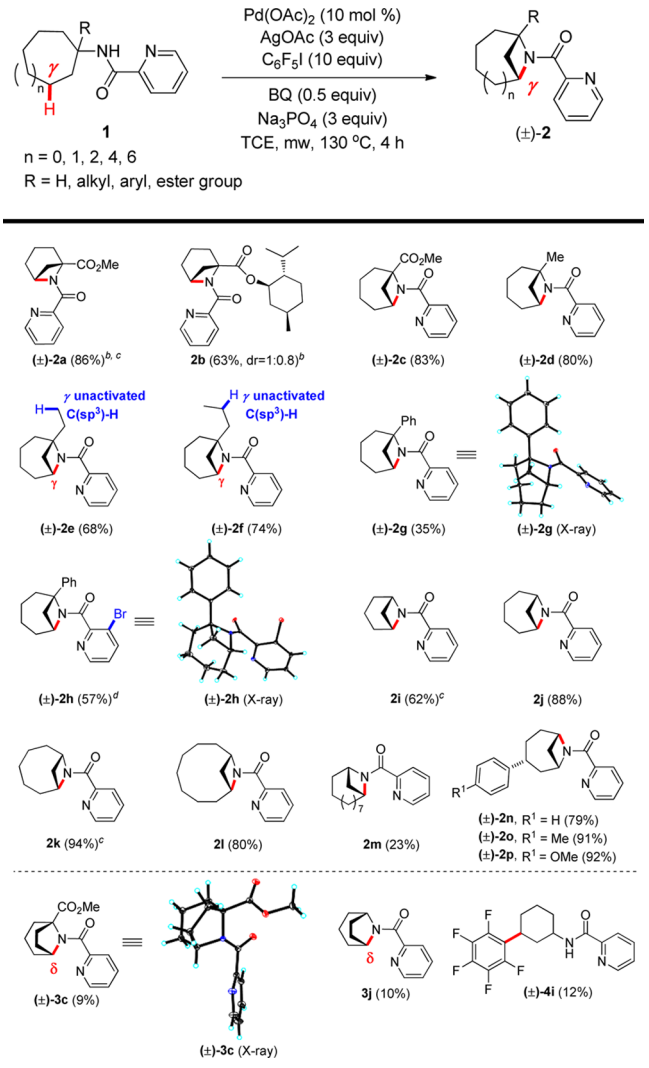
entry	solvent	base	additive (equiv)	yield[a] (%)
1	DCE			21
2	dioxane			19[b]
3	*m*-xylene			30[b,c]
4	DCE	NaOAc		49
5	DCE	Na_2CO_3		39
6	DCE	Na_3PO_4		58
7	DCE	K_3PO_4		41
8	DCE		BQ (0.1)	23
9	DCE		BQ (0.3)	34
10	DCE		BQ (0.5)	44
11	DCE		BQ (0.7)	29
12	DCE	Na_3PO_4	BQ (0.5)	62
13	DCE	Na_3PO_4	BQ (0.5)	69[d]
14	DCE	Na_3PO_4	BQ (0.5)	86[b,d,e]

[a]Isolated yield. [b]The reaction temperature was 130 °C. [c]The reaction was conducted in sealed tube. [d]AgOAc (3 equiv) was used. [e]The reaction time was 4 h.

conditions were determined as a combination of $Pd(OAc)_2$ (10 mol %), AgOAc (1.2 equiv), C_6F_5I (5 equiv), Na_3PO_4 (1.2 equiv), and benzoquinone (BQ) (0.5 equiv) in $ClCH_2CH_2Cl$ (DCE) at 130 °C in a microwave for 2 h, affording the desired product (±)-**2a** in 86% yield (Table 1, entry 14). Control experiments were conducted to show that $Pd(OAc)_2$, AgOAc, and C_6F_5I were all essential for the reaction to occur.

After optimizing reaction conditions, we explored the substrate scope for this palladium-catalyzed intramolecular C(sp^3)–H amination reaction. In general, PA-protected aliphatic amine substrates (**1a–p**) with various ring scaffolds proceeded to afford the corresponding polycyclic nitrogen-containing heterocyclic compounds (**2a–p**) in good to excellent yields (Scheme 1). Cycloalkylamino acid substrates **1a** and **1c** underwent the palladium-catalyzed intramolecular C(sp^3)–H amination reaction at the γ position of the cyclohexane and cycloheptane rings to yield the unnatural azabicyclo[3.1.1] and [4.1.1] α-amino acid derivatives (±)-**2a** and (±)-**2c**, respectively, in high yields. These products contain a quaternary carbon center and have potential utility for the synthesis of uncommon amino acids, and, peptides derived from them. Under this protocol, L-menthyl ester **1b** gave the corresponding product **2b** in 63% yield with a low diastereoselectivity (dr = 1:0.8), which indicates that the reaction center is likely far away from the chiral centers of the menthyl group. PA-protected cycloheptylamines **1d–f**, bearing an alkyl-substituted quaternary carbon center, reacted to afford the azabicyclo[4.1.1] scaffolds (±)-**2d–f** in good yields. Notably, this reaction preferred to activate the secondary C(sp^3)–H bonds on the ring over the primary or secondary C(sp^3)–H bonds on the acyclic side chain (e.g., (±)-**2e–f**). The phenyl-substituted substrate **1g** gave a synthetically useful yield of product (±)-**2g** along with 51% of recovered starting material, whereas the 2-bromopicolinamide-protected substrate **1h**, also bearing a phenyl-substituted quaternary carbon center, led to the product (±)-**2h** in 57% yield, which provided a

Scheme 1. Substrate Scope of Aliphatic Amines Bearing Various Ring-Sized Alkyl Groups[a]



[a]Isolated yield. [b]C_6F_5I (5 equiv) and Na_3PO_4 (1.2 equiv) was used. [c]DCE was used as solvent. [d]The reaction temperature was 140 °C.

handle for further modification on the *ortho* position of the pyridine group. Substrates **1i–l**, bearing various ring scaffolds including six-, seven-, eight-, and 10-membered rings, underwent the palladium-catalyzed C(sp^3)–H amination reaction to afford the corresponding meso-products **2i–l** in high yields, whereas the cyclododecylamine substrate **1m** gave a modest yield of *meso*-**2m**. Interestingly, during the studies of substrates **1c** and **1j**, the intramolecular palladium-catalyzed C(sp^3)–H amination reaction at the δ position of cycloheptyl amines afforded the azabicyclo[3.2.1] products (±)-**3c** and *meso*-**3j** in 9% and 10% yield, respectively, which are core structures for tropane alkaloids. In the case of substrate **1i**, the coupling product (±)-**4i** was formed in 12% yield. Another set of substrates, **1n–p**, underwent the C(sp^3)–H amination reaction via palladium catalysis to form the products (±)-**2n–p** in excellent yields.

This intramolecular palladium-catalyzed C(sp^3)–H amination reaction could be applied to other types of aliphatic amine substrates to afford various other nitrogen-containing skeletal heterocycles (Scheme 2). Azabicyclo[4.2.0] products **6a–d** were obtained in good yields. Notably, in the case of substrate

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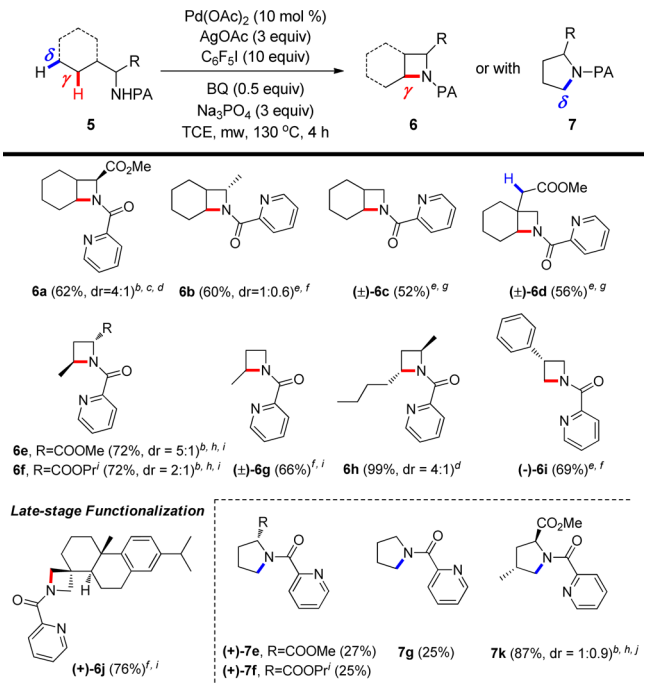
Scheme 2. Substrate Scope of Other Types of Aliphatic Amines[a]

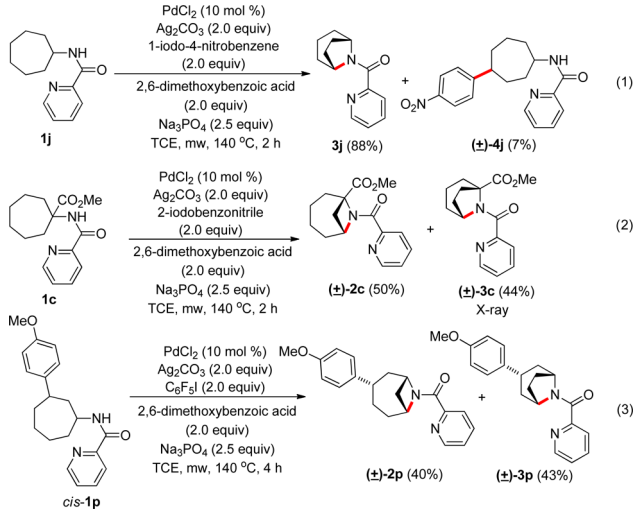


[a]Isolated yield. [b]C_6F_5I (5 equiv) was used. [c]Na_3PO_4 (1.2 equiv) was used. [d]DCE was used as solvent. [e]$Pd(OAc)_2$ (20 mol %) was used. [f]The reaction temperature was 170 °C. [g]The reaction temperature was 160 °C. [h]Na_3PO_4 (1.5 equiv) was used. [i]The reaction time was 2 h. [j]The reaction temperature was 150 °C.

5d, the reaction preferred to induce formation of a C−N bond at the γ position of the secondary C(sp^3)−H bond on the cyclohexyl ring over reacting at the more electron-deficient C(sp^3)−H bond at the α position of the carbonyl group on the side chain. For the simple acyclic aliphatic amine substrates **5e−g**, the reaction provided the azetidine products **6e−g** in approximately 70% yields and the pyrrolidine products **7e−g** in approximately 25% yields. In contrast, substrate **5h** only afforded the azetidine product **6h** in 99% yield with a diastereoselectivity of 4:1. Our protocol can also be applied to the late-stage functionalization. For example, for the natural chiral substrates (−)-**5i** and (+)-**5j** (structures in the Supporting Information), the chiral azetidine products (−)-**6i** and (+)-**6j** were obtained in 69% and 76% yields, respectively. Notably, a spiro-quaternary carbon center is present in the structure of (+)-**6j**. In the case of substrate **5k**, which bears a substituted-methyl group at the γ position, the chiral pyrrolidine product **7k**, an analogue of proline, was formed in 87% yield.

The formation of a small amount of product (±)-**3c** and its X-ray crystal structure (Scheme 1) provides evidence for the possibility of the Pd-catalyzed C(sp^3)−H amination reaction at the δ position of substrate **1j**. We subsequently conducted an extensive exploration of the reaction conditions, including optimizing the palladium and silver sources, aryl iodides, bases, other additives, and temperature, for the preparation of *meso*-**3j**, containing the core skeleton of tropane alkaloids (details in the SI). 2,6-Dimethoxybenzoic acid and aryl iodides were found to be the key elements that govern the distribution of products. Finally, a combination of $PdCl_2$ (10 mol %), Ag_2CO_3 (2.0 equiv), 1-iodo-4-nitrobenzene (2.0 equiv), and Na_3PO_4 (2.5 equiv) in $Cl_2CHCHCl_2$ (TCE) in a microwave reactor at 140 °C for 2 h led to the desired product **3j** in 88% yield along with a small amount of the cross-coupling product (±)-**4j** (Scheme 3, eq 1). For substrates **1c** and **1p**, the desired products (±)-**3c**

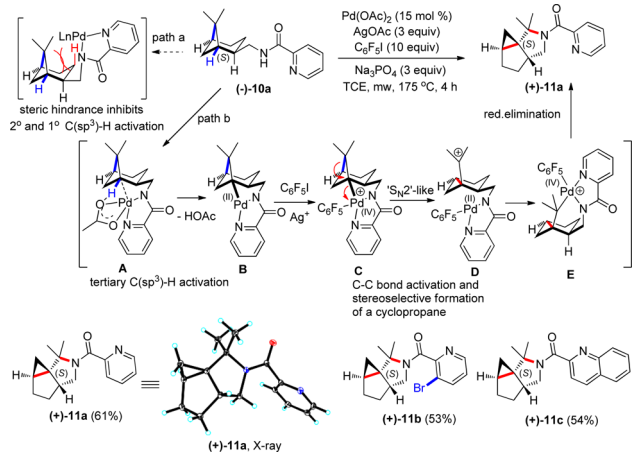
Scheme 3. Intramolecular Remote (γ or δ) C(sp^3)−H Bond Amination Reaction via Palladium Catalysis



and (±)-**3p** were optimized to obtain 44% and 43% yields, respectively, along with almost equal amounts of (±)-**2c** and (±)-**2p** (Scheme 3, eqs 2 and 3).

One particularly interesting application of this method is for the construction of more complex molecular scaffolds, such as derived from a bicyclo[3.1.1] amine, (−)-*cis*-myrtanyl amine **10a** (Scheme 4). In this substrate, derived from natural sources,

Scheme 4. Synthetic Application of Pd-Catalyzed Tertiary C(sp^3)−H Bond Activation



there are three types of C(sp^3)−H bonds, including primary, secondary, and tertiary C(sp^3)−H bonds at different positions in the same molecule. The intramolecular palladium-catalyzed C(sp^3)−H amination reaction with substrate **10a** proceeded successfully with high regioselectivity at the neighboring bridgehead tertiary C(sp^3)−H bond, located at the trans position of the alkylamino group. Mechanistically, this transformation can be envisioned to occur via a five-step sequence involving (i) auxiliary-directed insertion into the tertiary C(sp^3)−H bond to form a palladium(II) species (**10a**

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to **B**), (ii/iii) oxidation of Pd(II) to Pd(IV) by C_6F_5I and abstraction of iodine by the silver salt (to form **C**), (iv) a new type of C−C bond cleavage with the concomitant rearrangement of the skeleton to form a Pd(IV) intermediate **E**, and (v) reductive elimination leading to the chiral polycyclic alkaloid **11a** as a single enantiomer. The product **11a** and related products **11b** and **11c** were obtained in good yields. The structure of **11a** was further confirmed by single-crystal X-ray diffraction. Features of this reaction involve not only the highly site-selective activation favoring tertiary C(sp^3)−H bond over secondary or primary C(sp^3)−H bonds, but also an uncommon, stereoselective formation of a cyclopropane through four-membered bridged ring contraction.[14] This is a new type of C−C bond activation,[15,16] where the electron-pair from a C−C bond is involved in a new C−C bond-forming reaction that proceeds with the complete reversal of configuration at a tertiary stereogenic center. Further, a cationic metal "leaving group" is involved and the process results in the formation of an all carbon quaternary center. To the best of our knowledge, this is the first example of such a reaction, and the overall scheme represents the facial skeletal rearrangement of a terpenoid into a new scaffold of an alkaloid-like structure.

In conclusion, we have developed a strategy for using an intramolecular palladium-catalyzed amination of unactivated γ or δ C(sp^3)−H with readily available aliphatic straight-chain and cycloalkyl amine substrates to construct complex polycyclic nitrogen-containing heterocycles. The reaction exhibits high functional group tolerance and enables the synthesis of various azabicyclic scaffolds, including azabicyclo[*x*.1.1] (*x* = 3, 4, 5, 7, 9), [3.2.1], and [4.2.0] skeletons, simple azetidines, and azetidine with a chiral spiro-quaternary carbon center. This method is also suitable for late-stage functionalization of naturally derived amines for increasing the complexity of their basic skeletons. Among the [3.2.1]-heterobicyclic compounds that are accessible by this route are members of tropane class of alkaloids. In the case of a natural substrate, (−)-*cis*-myrtanylamine derivative (−)-**10**, a new type of C−C bond activation initiated by a highly site-selective palladium-catalyzed tertiary C(sp^3)−H bond activation is followed by stereoselective formation of a cyclopropane via a ring contraction that involves inversion of configuration at a quaternary center. The reaction seems to involve a cationic Pd(IV) species as a leaving group. We anticipate that this approach will be useful for the construction of more complex alkaloid-like structures with potential applications in medicinal chemistry and also in natural product synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02339.

Experimental details, spectral data, ^1H and ^{13}C NMR spectra, X-ray crystallographic data for compounds (±)-**2g**, (±)-**2h**, (±)-**3c**, (±)-**8**, and (+)-**11a**, and synthetic applications for the preparation of compounds **8** and **9** (PDF)

X-ray crystallographic data for compound (±)-**2g** (CIF)

X-ray crystallographic data for compound (±)-**2h** (CIF)

X-ray crystallographic data for compound (±)-**3c** (CIF)

X-ray crystallographic data for compound (±)-**8** (CIF)

X-ray crystallographic data for compound (±)-**11a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jkliu@mail.kib.ac.cn.

*E-mail:wubin@mail.kib.ac.cn.

ORCID

Bin Wu: 0000-0001-6048-4965

Notes

The authors declare no competing financial interest.

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