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Palladium-Catalyzed Remote C(sp^3)–H Arylation of 3-Pinanamine

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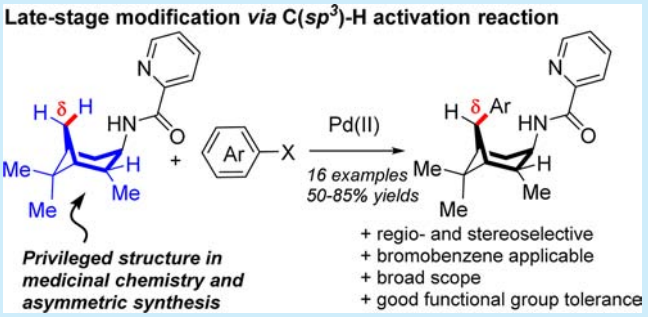
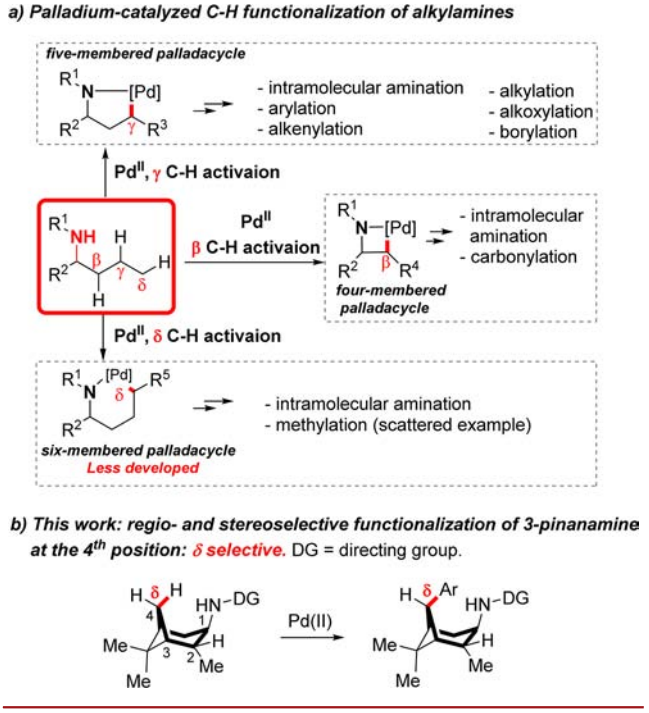
Supporting Information

ABSTRACT: 3-Pinanamine is a prevalent motif in medicinal chemistry and asymmetric synthesis. In line with the pursuit of novel 3-pinanamine based anti-influenza virus A agent, the direct functionalization of 3-pinanamine was achieved by using Pd-catalyzed C(sp^3)–H activation logic. Good substrate scope and functional group tolerance were observed. The reaction represents a rare example of a direct functionalization of an aliphatic amine at the remote δ position.



The past decade has witnessed great advances in transition-metal-catalyzed direct C–H functionalization reactions, allowing a facile assembly of C–C and C–heteroatom bonds.[1] In particular, the late-stage C–H functionalization of functional molecules, such as biologically active compounds and materials, in a divergent manner would greatly streamline their analogue synthesis.[2] Despite tremendous advances, current applications of the C–H functionalization reactions are generally focused on C(sp^2)–H activation processes. Although highly desirable, the selective functionalization of an unactivated C(sp^3)–H bond in a complex molecule is more challenging and thus far less developed.[3] Thanks to the intensive investigations by the groups of Yu,[4] Daugulis,[5] Sanford,[6] Baudoin,[7] Glorius,[8] Chen,[9] Shi,[10] and others,[11] Pd^{II}-catalyzed C(sp^3)–H activation reactions have met with greater success compared with other metals.[12] Amines are ubiquitous in functional molecules and building blocks in organic synthesis. Therefore, the direct and selective transformation of C–H bonds in amines is of great importance. Several examples targeting the functionalization of the C(sp^3)–H bond at different positions of alkylamines under the assistance of the native amine directing group have been recently developed. Nevertheless, most reactions proceed with the intermediacy of a kinetically favored five-membered palladacycle, thus enabling functionalization at the γ position (Scheme 1a).[13] Very recently, a remarkable intramolecular C–H amination and carbonylation reaction at the β position of amine through a four-membered palladacycle was also disclosed.[14] Unfortunately, the direct functionalization of the C(sp^3)–H bond at the remote δ position was less successful, with only one report of an intramolecular amination reaction[15] and scattered examples of methylation reactions[16] reported. Of note, current reactions are generally sensitive to steric hindrance, with a methyl C(sp^3)–H bond more favored than the methylene C(sp^3)–H bond. We envisioned that by taking advantage of the conformational characteristics of 3-pinanamine,[17] a highly valuable natural product derivative (vide infra), a regio- and stereoselective functionalization of the methylene C(sp^3)–H bond at the remote δ position would be possible (Scheme 1b).

Scheme 1. Pd-Catalyzed Direct C(sp^3)–H Functionalization of Alkylamines



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Recently, one of our team discovered (1*R*,2*R*,3*R*,5*S*)-3-pinanamine **1**, derived from α-pinene, exhibiting as potent anti-influenza virus A activity as amantadine (Figure 1a).[18] The

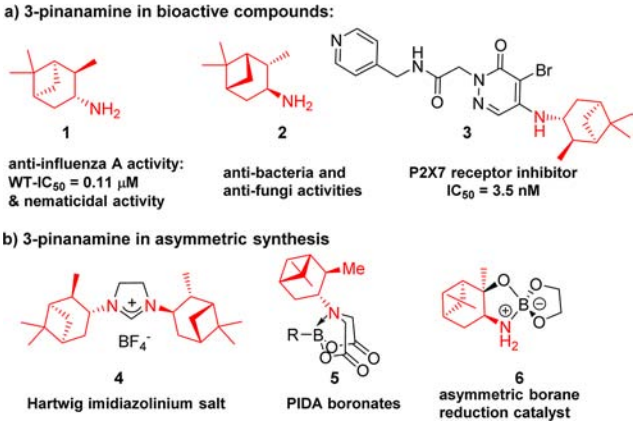
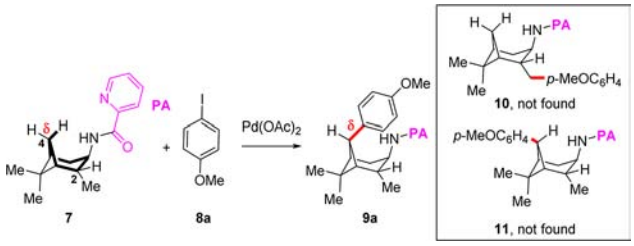


Figure 1. 3-Pinanamine and 3-pinanamine-containing molecules in bioactive compounds and asymmetric synthesis.

lead optimization on the amino group led to the discovery of several 3-pinanamine derivatives showing good activities against mutant influenza virus A.[19] Given the clear need for novel and efficient anti-influenza therapeutics, the development of methodology which allows for modification on the skeleton of 3-pinanamine is of great interest. Furthermore, preliminary structure−activity relationship (SAR) analysis indicates the introduction of bulky and hydrophobic functionality on the backbone could benefit the bioactivity. Moreover, compound **2**, the enantiomer of **1**, shows good antibacterial and antifungal activities.[20] Not surprisingly, 3-pinanamine-containing molecules display various bioactivities[21] as exemplified by compound **3**, an excellent P2X7 receptor inhibitor.[22] The importance of 3-pinanamine is also demonstrated by their occurrence in chiral auxiliaries for asymmetric synthesis, such as, the Hartwig imidiazolinium salt **4**,[23] the Burke PIDA boronates **5**,[24] and the asymmetric borane reduction catalyst **6** (Figure 1b).[25] According to our careful literature survey, no derivatives of 3-pinanamine at the δ position have ever been synthesized, and it seems that the C−H activation disconnection might be the easiest and only possible way for its derivatization. Herein, we disclose our realization of a Pd^{II}-catalyzed direct δ-C(sp^3)−H arylation of 3-pinanamine, driven by the strain-induced proximity of δ-C(sp^3)−H bond to the amino directing group.

To start, we chose 3-pinanamine **7** bearing a bidentate picolinamide (PA) directing group as the substrate (Table 1). The initial reaction of **7** (0.2 mmol) with 4-iodoanisole **8a** (0.3 mmol, 1.5 equiv) in the presence of $Pd(OAc)_2$ (10 mol %) as a catalyst and Ag_2CO_3 (0.2 mmol) as a base in decalin at 130 °C gave no arylation product (entry 1). A simple switch of solvent to toluene, however, delivered the arylation product **9a** in 76% yield (entry 2). Notably, the reaction took place exclusively at the δ-methylene C(sp^3)−H bond at the fourth position, with no arylation at the adjacent methyl C(sp^3)−H bond (**10**) observed even though a primary C(sp^3)−H bond is generally more reactive than a secondary C(sp^3)−H bond in Pd-catalyzed C−H activation reactions. We reasoned that the remarkable selectivity is derived from the strain-induced proximity of the δ methylene C(sp^3)−H bond to the PA directing group. For the same reason, stereoselective arylation at the methylene C(sp^3)−H bond pointing to the amino group was found. A screening of aromatic

Table 1. Reaction Optimization[a]



entry	**8a** (x equiv)	solvent	temp (°C)	base (1 equiv)	yield (%)
1	1.5	decalin	130	Ag_2CO_3	<5
2	1.5	toluene	130	Ag_2CO_3	76
3	1.5	mesitylene	130	Ag_2CO_3	65
4	1.5	*o*-DCB[b]	130	Ag_2CO_3	65
5	1.5	PhCN	130	Ag_2CO_3	33
6	1.5	$PhCF_3$	130	Ag_2CO_3	70
7	1.5	toluene	130	AgOAc[c]	9
8	1.5	toluene	130	K_2CO_3[c]	<5
9	1.5	toluene	130	NaOAc[c]	<5
10	1.5	toluene	130	$NaHCO_3$[c]	<5
11	1.5	toluene	100	Ag_2CO_3	10
12	**1.1**	**toluene**	**130**	**Ag_2CO_3**	**75**

[a]**7** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), solvent (2 mL), 24 h, isolated yields. [b]*o*-DCB = *ortho*-dichlorobenzene. [c]2.0 equiv of base were used.

solvents such as mesitylene, *o*-dichlorobenzene, PhCN, and $PhCF_3$ led to toluene being identified as the best (entries 3−6). The use of Ag_2CO_3 as the base was crucial for the reactivity. Other bases, including AgOAc, K_2CO_3, NaOAc, and $NaHCO_3$, gave a significantly lower yield or even no reaction (entries 7−10). Our attempt to decrease the temperature to 100 °C was unsuccessful as only a 10% yield was obtained (entry 11). Gratifyingly, only 1.1 equiv of 4-iodoanisole were needed to maintain a similar good yield (75%, entry 12).

We next explored the generality of this reaction under the optimized reaction conditions (Table 1, entry 12). A variety of aryl iodides with electron-donating or -withdrawing substituents were tested (Scheme 2). To our delight, many valuable functional groups such as methoxy (**9a** and **9e**), fluoro (**9f**), chloro (**9g** and **9h**), trifluoromethyl (**9i**), and nitro (**9j**) were well tolerated, giving the corresponding products in moderate-to-good yields (50%−85%). These functionalities are good handles for further derivatization of the products. *Ortho*-substituents did not hamper the reactivity (**9d**, 66%). We were pleased to find that not only aryl iodides but also aryl bromides were applicable in this transformation. For instance, the coupling of 1-bromo-4-ethoxybenzene gave a similar yield of 74% (**9k**) to 4-iodoanisole (75%) under identical reaction conditions. Interestingly, 4-bromofluorobenzene gave a higher yield of **9f** than 4-iodofluorobenzene (72% vs 52%).[26] It should be noted that bromobenzenes are less commonly applied in Pd^{II}-catalyzed C−H arylation reactions due to their lower reactivity toward oxidative addition. Difluoro-substituted bromobenzene also delivered the arylated products in 61% yield (**9l**). Due to the prevalence of heterocycles in medicinal chemistry, the coupling of heterocyclic halides was also studied. The reactions with 2- and 3-bromothiophene were successful, giving the corresponding products in moderate yields (**9m** and **9o**). The reaction of 3-bromo-4-chlorothiophene took place exclusively at the C−Br bond (**9n**). Disappointingly, nitrogen-containing heterocyclic halides such as 2-bromopyridine, 4-bromopyrimidine, 2-

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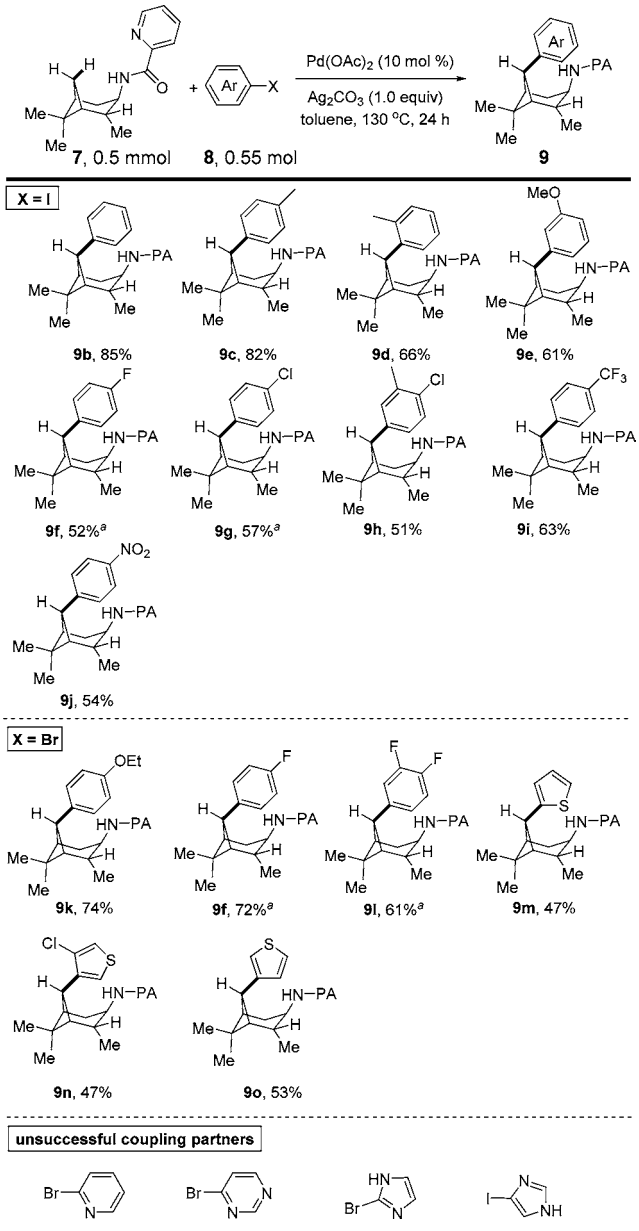
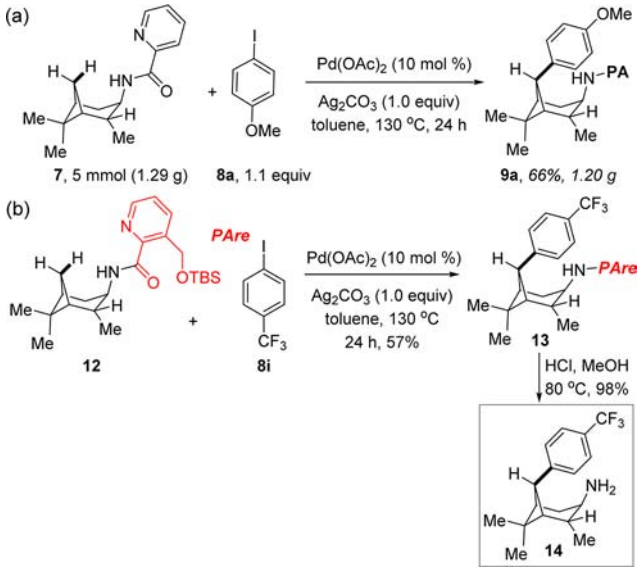
Scheme 2. Pd-Catalyzed C(sp^3)−H Arylation of 3-Pinanamine



[a]At 140 °C.

Scheme 3. Gram-Scale Synthesis and Removal of the Directing Group



bromoimidazole, and 4-iodoimidazole shut down the reactivity completely, probably due to the deleterious coordination of the nitrogen atoms to the Pd catalyst.

A 5 mmol scale reaction was performed to give 1.20 g of arylation product in 66% yield, demonstrating that the reaction is practical (Scheme 3a). Moreover, another directing group PAre was installed on 3-pinanamine following a protocol reported by Chen.[13c] Gratifyingly, the new substrate **12** underwent direct C(sp^3)−H arylation without difficulty to give **13** in 57% yield. Importantly, the subsequent removal of PAre was easily achieved under acidic reaction conditions, giving free amine **14** in almost quantitative yield (Scheme 3b). The arylated free amines obtained using this protocol are presently being evaluated against influenza virus A in our laboratories and will be reported in due course.

In summary, in line with our pursuit of a novel anti-influenza virus A agent, we have developed a novel Pd-catalyzed C(sp^3)−H bond activation reaction for the regio- and stereoselective functionalization of 3-pinanamine. This reaction represents a rare example of a direct functionalization of an aliphatic amine at a remote δ position. A variety of aromatic iodides and bromides bearing different functionalities were well tolerated in this process and gave arylated products in moderate-to-good yield. The reaction is practical, and the PAre directing group enables the facile synthesis of free amine derivatives. Due to the prevalence of 3-pinanamine as a motif in medicinal chemistry and asymmetric synthesis, we anticipate this methodology will find other applications.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(26) Starting material **7** was recovered in 6% and 34% yields from the reactions of 4-bromo- and 4-iodofluorobenzene, respectively.