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Authors: Hong-Liang Li and Yoichiro Kuninobu

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COMMUNICATION

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Palladium-catalyzed Secondary C(sp^3)-H Arylation of 2-Alkylpyridines

Hong-Liang Li,*,† Yoichiro Kuninobu*,‡,§

† Institute for Molecular Design and Synthesis, School of Pharmaceutical Science and Technology, Tianjin University, 92Weijin Road, Nankai District, Tianjin 300072, China, E-mail: lhl522508@126.com

‡ Institute for Materials Chemistry and Engineering, Kyushu University, 6-1 Kasugakoen, Kasuga-shi, Fukuoka 816-8580, Japan, E-mail: kuninobu@cm.kyushu-u.ac.jp

§ Department of Molecular and Material Sciences, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, 6-1 Kasugakoen, Kasuga-shi, Fukuoka 816-8580, Japan

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Abstract. A pyridyl group-assisted palladium-catalyzed secondary C(sp^3)-H arylation protocol was developed. A substituent at the 3-position of the pyridyl group is proved to be important for promoting C-H arylation and controlling the regioselectivity. Aryl iodides can be used as coupling partners. The reaction proceeded in good to excellent yields with good functional group tolerance, even on the gram-scale. The preliminary asymmetric reaction was investigated using an L-proline derivative as a chiral ligand.

Keywords: C(sp^3)-H Arylation; Secondary C-H Activation; 2-Alkylpyridine; Aryl Iodide; Palladium

2-Phenethylpyridine moieties are very important skeletons that are commonly found in pharmaceuticals, agricultural chemicals, and natural products (Figure 1).[1] Many pharmaceuticals containing the 2-phenethylpyridine motif have been applied in many fields, such as clinical treatments. However, traditional methods of synthesizing this motif usually require complicated routes.[2]

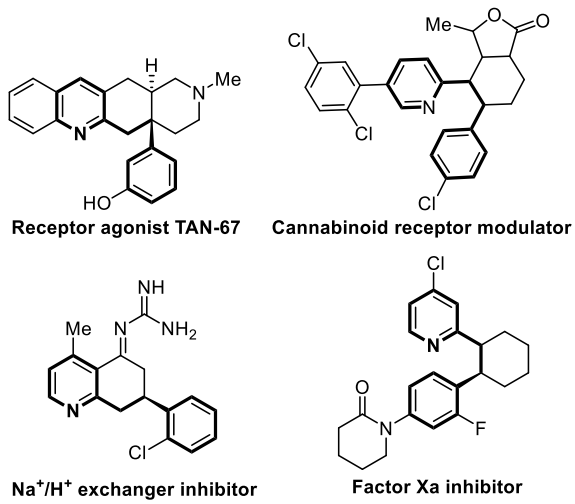

Figure 1. Bioactive compounds containing a 2-phenethylpyridine moiety.

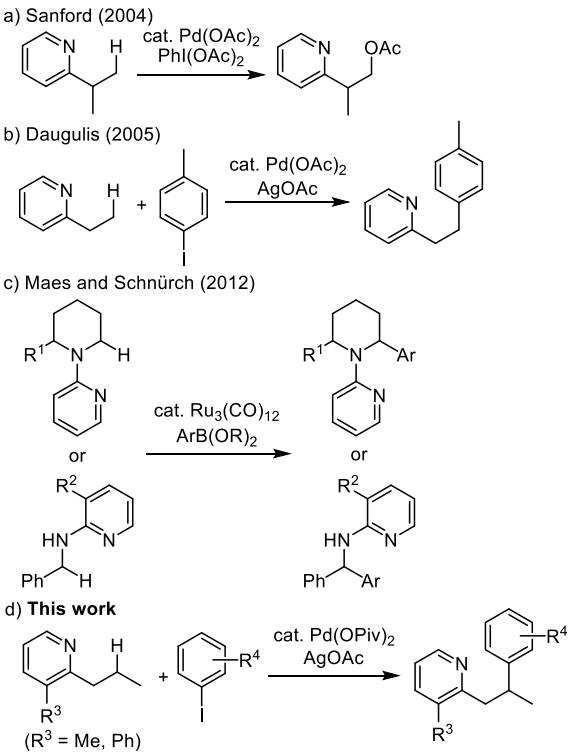

Figure 2. Examples of C(sp^3)-H transformations using pyridine directing group.

Recently, the development of direct C-H transformations has provided a unique solution for this problem. As is well known,direct C(sp^2)-H transformations have been rapidly developed over the past few decades.[3] Direct C(sp^3)-H transformations catalyzed by a transition metal have also been reported.[4] In 2004, Sanford achieved the first example of palladium(II)-catalyzed C(sp^3)-H acetoxylation using an oxime or pyridine moiety as a directing group (Figure 2a).[5] Subsequently, Daugulis and co-workers reported the palladium(II)-catalyzed arylation of 2-ethylpyridine (Figure 2b).[6] Maes and Mihovilovic independently reported pyridyl group-assisted arylation of the C(sp^3)-H bond adjacent to a heteroatom or in the

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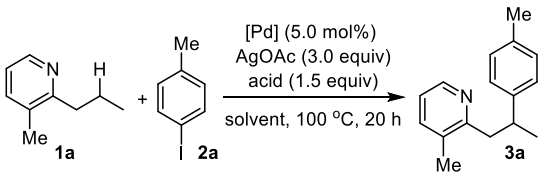
benzylic position (Figure 2c).[7,8] However, many reactions proceed at the terminal and/or activated C(sp^3)-H bond. Pyridyl group-assisted secondary C(sp^3)-H activation is still rare. The poor reactivity of the secondary C(sp^3)-H compared to activated and terminal C(sp^3)-H bonds is attributed to the higher bond energy and steric hindrance of the former.[9] In addition, pyridyl groups are strongly chelating directing groups that generally form thermodynamically stable cyclometalated intermediates that are less reactive in the subsequent functionalization steps.[10]

Herein, we report pyridyl group-assisted secondary C(sp^3)-H arylation process catalyzed by Pd(II). It was envisioned that an acid additive could decrease the coordination ability of the nitrogen atom of the pyridyl group and therefore enhance the reactivity of the cyclometalated intermediates in the arylation step.[11]

The reaction of 3-methyl-2-propylpyridine (**1a**) with 4-methyliodobenzene (**2a**) in the presence of $Pd(OAc)_2$ (5.0 mol%) and acetic acid (1.5 equiv) as an additive resulted in 25% yield of the arylated product **3a** (Table 1, entry 1). The yield of **3a** increased slightly when trifluoroacetic acid was used (Table 1, entry 2). Other acid additives, however, did not give better results (Table 1, entries 3 and 4). Several palladium(II) salts were further investigated (Table 1, entries 5-7), where the yield of **3a** improved dramatically with the use of $Pd(OPiv)_2$ as a catalyst (Table 1, entry 6). Several solvents were also screened along with neat conditions (Table 1, entries 8-11). Hexafluoroisopropanol (HFIP) was the best solvent (Table 1, entry 6). In order to further increase the yield of **3a**, we also screened the amount of catalyst and acid additive. The reaction conditions in entry 6 gave the best result (see the Supporting Information for details).

Table 1. Optimization of reaction conditions.[a]



entry	[Pd]	acid	solvent	yield/%[b]
1	$Pd(OAc)_2$	AcOH	HFIP	25
2	$Pd(OAc)_2$	CF_3COOH	HFIP	30
3	$Pd(OAc)_2$	Piv(OH)	HFIP	17
4	$Pd(OAc)_2$	PhCOOH	HFIP	--
5	$Pd(TFA)_2$	CF_3COOH	HFIP	<10
6	$Pd(OPiv)_2$	CF_3COOH	HFIP	70
7	$PdCl_2$	CF_3COOH	HFIP	<10
8	$Pd(OPiv)_2$	CF_3COOH	*t*-AmylOH	--
9	$Pd(Piv)_2$	CF_3COOH	1,4-dioxane	54
10	$Pd(OPiv)_2$	CF_3COOH	*p*-xylene	43
11	$Pd(OPiv)_2$	CF_3COOH	neat	66

[a]**2a** (1.5 equiv).[b]Yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

With the optimized conditions in hand, we investigated the substrate scope of pyridine derivatives **1** and aryl iodides **2** (Table 2). 2-Propylpyridine, with no substituent at the 3-position, did not give the desired arylation product. Jun and Mihovilovic reported that a substituent at the 3-position of the pyridine directing group is crucial for promoting C-H arylation and controlling the regioselectivity.[12] They speculated that the substituent at the 3-position of the pyridine directing group could shorten the distance between the nitrogen atom of the pyridyl group and the β-position of the alkyl chain. To our delight, arylated product **3b** was obtained in 82% yield in the reaction of a substrate bearing a phenyl group at the 3-position with 4-iodobiphenyl. Several aryl iodides having a substituent at the *para*- or *meta*-positions were also investigated. The corresponding arylated products **3c**-**3i** were produced in 58-69% yield without loss of the functional groups (electron-donating or -withdrawing groups).[13,14] Biaryl iodides showed higher reactivity than monoaryl iodides and provided the corresponding arylated products **3j**-**3w** in 70-90% yield. The reaction also proceeded smoothly using 3-methyl-2-butylpyridine and 3-methyl-2-hexylpyridine to give arylated products **3x** and **3y** in 80% and 72% yields, respectively. The desired products were afforded with good functional group tolerance using substrates with an electron-donating or electron-withdrawing group. However, the desired arylated products were not obtained using 2-(*sec*-butyl)-3-methylpyridine and 2-isopentyl-3-methylpyridine, and *ortho*-substituted aryl iodides, probably due to the steric hindrance.

Table 2. Substrate scope of 2-alkylpyridines and aryl iodides[a]

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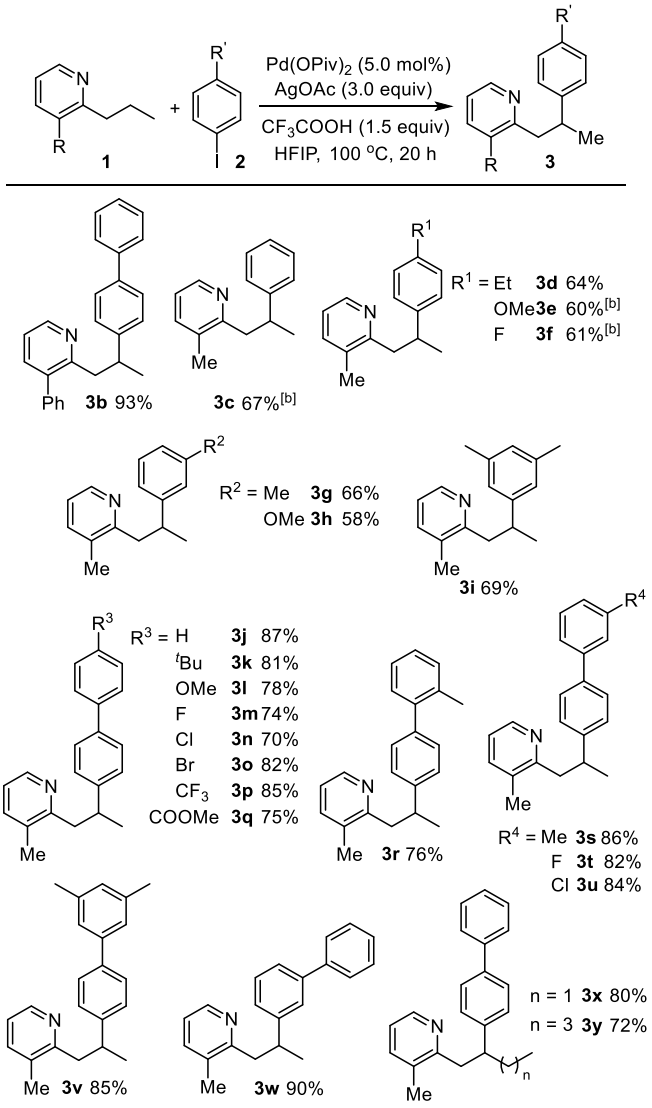
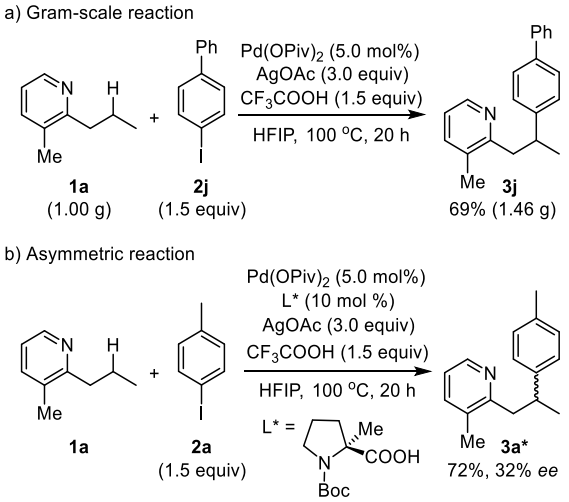


[a] **2** (1.5 equiv).[b] $Pd(OPiv)_2$ (5.0 mol %), CF_3COOH (1.5 equiv), HFIP, 120 °C, 30 h.

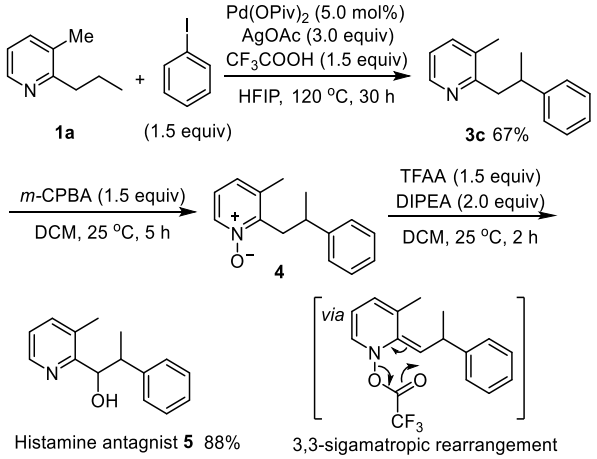
The secondary C(sp^3)-H arylation reaction proceeded in good yield, even on the gram-scale (Scheme 1a). Treatment of 1.00 g of 3-methyl-2-propylpyridine (**2a**) with biaryl iodide **2j** in the presence of a $Pd(OPiv)_2$ (5.0 mol%) catalyst, AgOAc (1.5 equiv), and CF_3COOH (1.5 equiv) gave 1.46 g of arylated product **3j** in 69% yield.

We also investigated asymmetric secondary C(sp^3)-H arylation (Scheme 1b).[15] After screening a series of chiral ligands, the preliminary result was obtained using *N*-Boc-2-methyl-L-proline as a chiral ligand. To the best of our knowledge, this is the first example of pyridine-directed enantioselective secondary C(sp^3)-H arylation. Efforts to improve the enantioselectivity are underway in our laboratory.



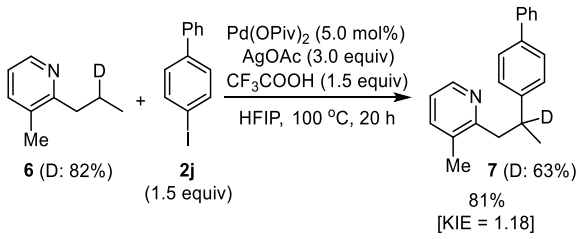
Scheme 1. Gram-scale and asymmetric reactions.

We applied this reaction to the synthesis of histamine antagonist.[16] Treatment of **1a** with iodobenzene under the standard reaction conditions gave **3c** in 67% yield. Product **4** was obtained by oxidation using *m*-CPBA, then a successive [3,3]-sigamatropic rearrangement produced the histamine antaonist **5** in 88% yield. This method was not only enhanced the yield of **5** dramatically, but also provided an easy way to synthesize derivatives of **5** with different aryl group at the β-position.[17,18]



Scheme 2. Application for synthesizing Histamin Antagnist.

We investigated a kinetic isotope effect (KIE) experiment to confirm whether C-H activation step is the rate-determing step (scheme 3). When we performed a reaction of 3-methyl-2-(propyl-2-*d*)-pyridine (**6**) with 4 iodobiphenyl (**2j**), the arylated proudct **7** was obtained in 81% yield with 63% of deuterium. This result showed the KIE valuse was 1.18, which indicated that the C-H activation is not the rate-determing step.



Scheme 3. KIE experiment

The proposed reaction mechanism is as follows (Figure 3):[11d,19-21] (1) A nitrogen atom of the pyridine moiety of **1** coordinates to the palladium catalyst to form intermediate **A** and the palladium center approaches the β-position of the alkyl chain. In this step, the substituent at the 3-position of the pyridine directing group is very important for promoting the reaction and controllingthe regioselectivity; (2) formation of intermediate **B** proceeds by a concerted metalation deprotonation (CMD) mechanism; (3) oxidative addition of aryl iodide **2** to intermediate **B** furnishes intermediate **C**; and (4) reductive elimination of PdX_2 species by the participation of silver acetate yields arylated product **3**.

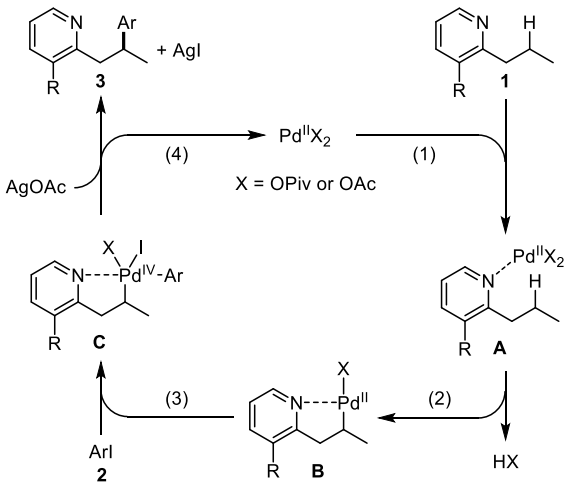


Figure 3. Proposed mechanism of secondary C(sp^3)-H arylation using pyridine directing group.

In summary, we successfully developed a pyridine-directing-group-assisted palladium-catalyzed secondary C(sp^3)-H arylation protocol. Although several examples of activated and/or terminal C(sp^3)-H bond transformations assisted by pyridine directing groups have recently been reported, examples of pyridine directing group-assisted unactivated C(sp^3)-bond arylation are still rare. The key to success was the introduction of a substituent at the 3-poistion of the pyridine directing group and utilizing trifluoroacetic acid as an additive to reduce the strong coordination ability of the pyridine moiety. Biaryl iodides can enhance the reactivity compared with monoaryl iodides. The desired arylation products were obtained in good to excellent yields, even on the gram-scale, without loss of the functional groups. Further, preliminary asymmetric C(sp^3)-H arylation was achieved.

Experimental Section

3-Methyl-2-propylpyridine (**1a**, 0.250 mmol), substituted iodobenzene (**2**, 0.375 mmol, 1.50 equiv), $Pd(OPiv)_2$ (3.86 mg, 0.0125 mmol, 5.0 mol%), CF_3COOH (42.8 mg, 0.375 mmol, 1.5 equiv), and HFIP (2.0 mL) were added into a 10 mL sealed tube. The mixture was stirred at 100 °C for 20 h. Then, the solvent was removed under vacuum, and the arylation products were separated by column chromatography on silica gel (hexane/ethyl acetate = 10:1).

Acknowledgements

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