

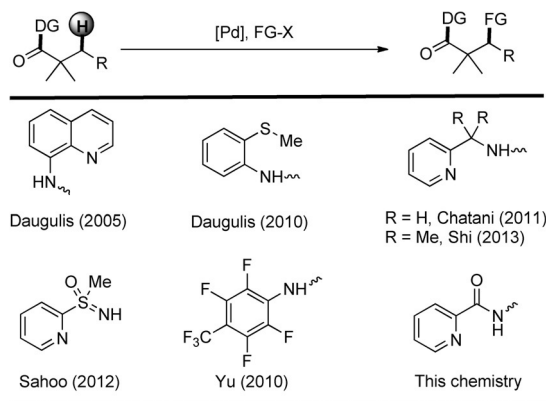
Readily Removable Directing Group Assisted Chemo- and Regioselective C(sp³)–H Activation by Palladium Catalysis

Yun-Fei Zhang, Hong-Wei Zhao, Hui Wang, Jiang-Bo Wei, and Zhang-Jie Shi*

Dedicated to Professor Xuelong Hou on the occasion of his 60th birthday

Abstract: Currently used directing groups for selective aliphatic β -functionalization of carbonyl compounds show excellent reactivity and selectivity with an amide as a linker. Described herein is 2-picolinamide, used for the first time with commercially available 2-picolinamide/2-picolinic acid as precursors, to direct C–H arylation/alkenylation by palladium catalysis. The directing group is essential for promoting the sequential primary and secondary C(sp³)–H arylation with different aryl iodides in one substrate. The directing group was easily removed under simple reaction conditions at room temperature.

Transition-metal-catalyzed direct C–H functionalization has attracted much interest in the past decades.^[1] Compared to C(sp²)–H functionalization,^[2] C(sp³)–H activation faces many more challenges and the progress is far behind.^[3] To conquer the challenges of both efficiency and selectivity in C(sp³)–H activation, the use of directing groups (DGs) has proven to be the most powerful, common, and practical strategy.^[4] Because of the importance of carboxylic acid derivatives, site-specific activation of their C–H bonds is highly appealing.^[5] To approach the β -functionalization of carboxylic acid derivatives, well-established directing groups have been developed since the first example was demonstrated by Daugulis and co-workers in 2005 (Scheme 1).^[6] Of the reported directing groups, bidentate ones showed much better performance.^[7] Another beautiful example was reported by Yu and co-workers on the use of 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline as a successful monodentate directing group.^[8] Undoubtedly, current directing groups have an excellent ability to promote the reactivity and selectivity. However, the stable amides linkers are difficult to remove, and some of them are relatively expensive and require several steps to prepare. Therefore, the development



Scheme 1. Directing groups for β -functionalization of carboxylic acid derivatives by palladium catalysis. FG = functional group.

of new directing groups, which are commercially available and readily removable under mild reaction conditions, is highly desirable.

To solve this problem, one can modify the directing groups to facilitate their removal. Chen and co-workers^[9a] and others made significant contributions to successfully modifying the 8-aminoquinyl scaffold.^[9] Shi and co-workers developed the PIP group,^[10] which is now commercially available, based on the previous reports by Chatani and co-workers.^[11] However, the structural complexity requires tedious synthetic procedures and thus increases of cost. Our goal is to develop commercially available and easily removable directing groups to facilitate site-selective aliphatic C–H activation. Therefore, we turned our attention to the much more labile imide linker between the directing group and the substrate.

We considered 2-picolinamide since it is commercially available and inexpensive. Potentially, it can serve as a DG because it contains coordinating N atoms. However, some challenges exist: 1) the high acidity of NH of imides, compared to those of amides, might intrinsically affect the reactivity; 2) the high reactivity of the imide seems beneficial for its removal while the stability of such a labile imide linker is unpredictable under the relatively harsh reaction conditions required for C–H functionalization in the presence of base or acid; 3) last but not the least, the introduction of such a DG by the formation of the imide might not be as easy as the corresponding amide.

To explore the possibility based on our design, we first developed an efficient protocol to prepare the substrate by formation of the imide. Indeed, it was an easy and reliable

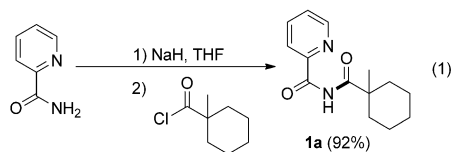
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protocol through a one-pot sequence involving the deprotonation of picolinamide and acylation with acyl chloride [Eq. (1); THF = tetrahydrofuran].



With the starting material in hand, we set out to screen the reaction conditions for the desired C–H arylation with **1a** as a model substrate and **PhI** (**2a**; Table 1). At the beginning, Pd(OAc)₂ was used as a catalyst in DCE at 120 °C in the presence of AgOAc (2.0 equiv) as a base. The product **3aa** was obtained but the yield was very low after 3 hours (less than 10% by ¹H NMR analysis). As predicted, the rest of **1a** was decomposed (entry 1). However, this result encouraged us to search for other reaction conditions to promote the arylation because the observation of **3aa** indicated that the piconimide is a potential DG, albeit with a much lower pK_a value. Considering the solubility and stability of imides, the solvent effect should be very important. Polar solvents, such as *t*AmOH and THF, severely accelerated the decomposition of **1a** (entries 2 and 3). The nonpolar solvents were beneficial for stabilizing both the starting material and

Table 1: Palladium-catalyzed Direct C(sp³)–H arylation of **1a** with **2a** under different reaction conditions.^[a]

Entry	Catalyst	Ag ⁺ salt	Solvent	Yield [%] ^[b]
1	Pd(OAc) ₂	AgOAc	DCE	< 10
2	Pd(OAc) ₂	AgOAc	<i>t</i> AmOH	decomposed
3	Pd(OAc) ₂	AgOAc	THF	decomposed
4	Pd(OAc) ₂	AgOAc	<i>c</i> -hexane	30
5	Pd(OAc) ₂	AgOAc	toluene	40
6	Pd(OAc) ₂	AgOAc	chlorobenzene	42
7	Pd(OAc) ₂	AgOAc	<i>t</i> -butylbenzene	60
8	Pd(OAc) ₂	Ag ₂ CO ₃	<i>t</i> -butylbenzene	52
9	Pd(OAc) ₂	AgBF ₄	<i>t</i> -butylbenzene	n.r.
10	Pd(OAc) ₂	Ag ₃ PO ₄	<i>t</i> -butylbenzene	83
11	Pd(OTFA) ₂	Ag ₃ PO ₄	<i>t</i> -butylbenzene	87 (83)
12	Pd(OTFA) ₂	Ag ₃ PO ₄	<i>t</i> -butylbenzene	86 (83) ^[c]
13	Pd(OTFA) ₂	Ag ₃ PO ₄	<i>t</i> -butylbenzene	30 ^[c,d]
14	Pd(OTFA) ₂	Ag ₃ PO ₄	<i>t</i> -butylbenzene	84 (82) ^[c,e]
15	Pd(OTFA) ₂	Ag ₃ PO ₄	<i>t</i> -butylbenzene	85 (82) ^[c,e,f]
16	Pd(OTFA) ₂	Ag ₃ PO ₄	<i>t</i> -butylbenzene	50% ^[c,e,g]
17	–	Ag ₃ PO ₄	<i>t</i> -butylbenzene	n.r.

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (10 mol %), Ag salt (0.2 mmol) in 1.0 mL of solvent at 120 °C for 12 h in a 50 mL sealed tube if without further note. [b] ¹H NMR yields using benzo[d][1,3]dioxole as an internal standard. Yield of isolated product shown within parentheses. [c] 0.9 equiv Ag₃PO₄. [d] 80 °C. [e] 100 °C. [f] 3 h. [g] 1 h. TFA = trifluoroacetic acid.

product. For example, cyclohexane gave a better result (entry 4) and with toluene **3aa** was observed in 40% yield (entry 5). Other aromatic solvents were tested, and chlorobenzene and *tert*-butylbenzene gave **3aa** in 42 and 60% yield, respectively (entries 6 and 7). Silver salts were crucial. Other silver salts were tested, such as Ag₂CO₃ and AgBF₄, but better results were not obtained (entries 8 and 9). Fortunately, Ag₃PO₄ gave much better results and the yield (¹H NMR) was improved to 83% (entry 10). When Pd(OTFA)₂ was used instead of Pd(OAc)₂ as the catalyst, **3aa** was isolated in 83% (entry 11). The amount of Ag₃PO₄ could be reduced to 0.9 equivalents and the efficacy was not obviously affected (entry 12). Further reaction optimization indicated that this arylation took place at 100 °C for 3 hours to deliver the product in 82% yield (entries 13–16). A control experiment confirmed an essential role of the palladium catalyst (entry 17).

The substrate scope was further investigated and the representative data with different aryl iodides are shown in Table 2. The results demonstrate the broad substrate scope

Table 2: Palladium-catalyzed direct arylation of **1a** with different aryl iodides (**2**).^[a]

Aryl Iodide (2)	Yield [%]
R = H, 2a	82%
R = 4-Me, 2b	84%
R = 3-Me, 2c	84%
R = 2-Me, 2d	0%
R = 4- <i>t</i> Bu, 2e	67%
R = 3,5-dimethyl, 2f	82%
R = 4-OMe, 2g	40%
R = 4-OPiv, 2h	66%
R = 4-F, 2i	70% + (14%) ^[b]
R = 4-Cl, 2j	73% + (12%) ^[b]
R = 4-Br, 2k	63%
R = 4-acetyl, 2l	75% + (11%) ^[b]
2m (COOMe)	76% + (10%) ^[b]
2n (CF ₃)	71% + (13%) ^[b]
2o (Ts)	65%
2p (Ac)	53% + (9%) ^[b]

[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.20 mmol), Pd(OTFA)₂ (10 mol %), Ag₃PO₄ (0.090 mmol) in 1.0 mL of TBB (*tert*-butylbenzene) at 100 °C for 3 h and open to air. All the yields reported are those for the isolated products. [b] Diarylated products were isolated.

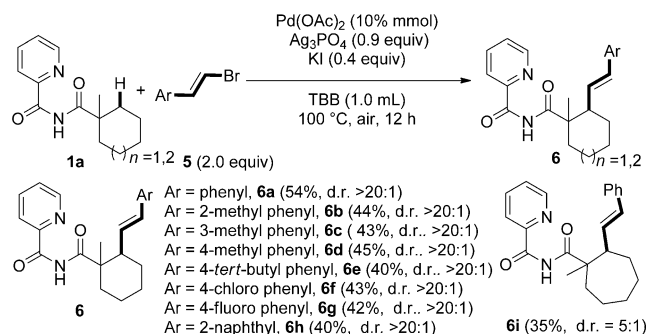
with **1a** as a partner, and the corresponding arylated products (**3**) were obtained in good to excellent yields. Both electron-rich (**2b,c**, **2e–h**) and electron-deficient (**2i–n**) aryl iodides performed well. Aryl iodides bearing various functional groups, such as alkyl (**2b–f**), acetyl (**2l**), ester (**2m**), trifluoromethyl (**2n**) etc., proceeded smoothly. Steric effects were critical, and *o*-tolyl iodide (**2d**) failed to react. Methoxy (**2g**), halo (**2i–2k**), and pivaloyl (**2h**) groups survived, thus providing the potential for orthogonal functionalization through well-established cross-couplings.^[12] Heteroaryl iodides, for example, *N*-tosyl-5-iodo-1*H*-indole (**2o**), also gave the arylated product in good yield. Notably, aryl iodides, bearing strong electron-withdrawing substituents on the phenyl ring (**2i**, **2j**, **2l–n**) reacted well at the primary C–H bonds, but a second C–H activation, at the secondary carbon atom of the

cyclohexyl ring, did occur, probably because of their better oxidative ability toward in situ generated palladium(II) species. Both mono- and diarylated products were isolable by flash chromatography. It is worth noting that transition-metal-catalyzed C(sp³)-H arylation with much less reactive aryl bromides still remain challenging. However, in our present system, a good yield was obtained by using 4'-bromoacetophenone (**2p**).

A variety of aliphatic the carboxylic acid derivatives were examined. The structure of carboxylic acids had intrinsic effects on the reactivity. As shown in Table 3, a tertiary α -carbon atom was important for this transformation. In the absence of a C-H bond, acyclic aliphatic imides reacted very smoothly. The monomethyl substrates were arylated in good to excellent yields (**4a-g**). It was very important to note that, the arylation only took place at the primary carbon center, thus leaving secondary and activated benzyl C-H, and even sp²-hybridized aryl C-H bonds untouched. Similar to previous reports with the amide linker, imides bearing two methyl groups at the α -position also performed well, and mono- and diarylated products at both methyl groups were obtained (**4h, 4i, 4l**). Similar to **1a**, cyclic substrates showed good reactivity (**4j,k**). In previous reported systems, isobutyramide, 2-methylbutanamide, 2-phenylpropionylamide,

propionylamide, and the cyclic substrate bearing an α -C-H bond were problematic substrates.^[4e] However, in our reaction, all of them (**4l-o**) reacted. This chemistry showcases the potential of developing new directing groups.

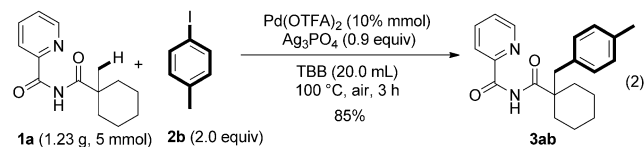
With the successful access to the direct arylation of C(sp³)-H bonds, we started exploring C(sp³)-H alkenylation.^[13] Although alkenyl bromides were commercially available and inexpensive, they had never been used as an alkenylating reagent in C(sp³)-H alkenylation. For the first time we tested (2-bromovinyl)benzene (**5a**) as an alkenylating reagent, and to our delight, the desired product **6a** was obtained in 54% yield, upon isolation, with very good distereoselectivity (Scheme 2). It is important to note that



Scheme 2. Palladium-catalyzed direct alkenylation with alkenyl bromides.

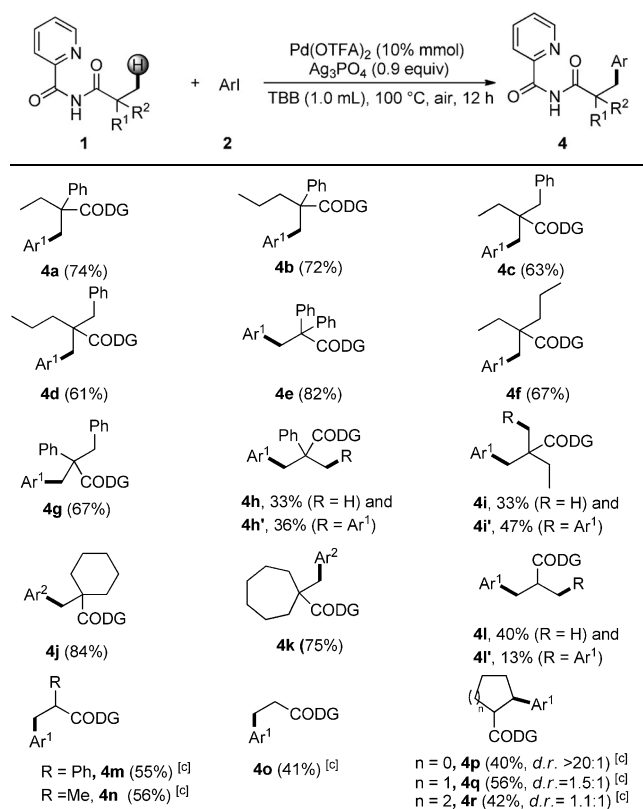
this unexpected alkenylation took place at the secondary C-H bond on the backbone instead of at the primary carbon center, which was completely different from previous reports.^[13] Different alkenyl bromides were tested and both electron-rich (**6b-e**) and electron-deficient (**6f,g**) alkenyl bromides gave acceptable yields. Alkyl (**6b-e**), halo (**6f,g**), and naphthyl (**6h**) groups were suitable substrates. The C-H bond of a seven-membered ring was alkenylated but in a lower yield and with lower distereoselectivity (**6i**).

To further explore the potential application of this arylation, the reaction of **1a** and **2b** was scaled up to 5.0 mmol in a 50 mL one-necked flask, open to the air, and the same efficiency was maintained [Eq. (2)].

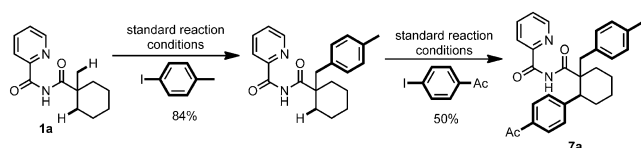


We then explored the sequential aliphatic C-H functionalization of both primary and secondary C-H bonds in the same molecule (Scheme 3). With the use of **2b** as the first arylating reagent, **1a** was successfully and selectively arylated at the primary C-H bond of the methyl group in an excellent yield. After the transformation finished, another arylating reagent, **2l**, was submitted with an additional palladium

Table 3: Palladium-catalyzed direct arylation of different imides (**1**) with **2**.^[a,b]



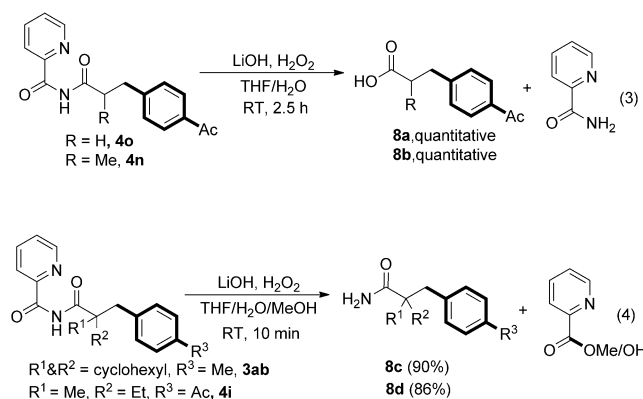
[a] Reaction conditions: **1** (0.10 mmol), **2** (0.20 mmol), Pd(OTFA)₂ (10 mol%), Ag₃PO₄ (0.090 mmol) in 1.0 mL of *tert*-butylbenzene at 100 °C for 12 h and open to air. All the yields reported are those for the isolated products. [b] Ar¹ = 4-acetylphenyl, Ar² = 4-methylphenyl. [c] At 130 °C.



Scheme 3. Sequential double C–H arylation.

catalyst and silver salt. Thus the second arylation took place solely at the methylene group on the cyclohexyl ring with high chemo- and regioselectivity, and the formed, more active benzyl C–H was untouched. This sequential double C–H arylation showed good efficiency and ideal selectivity, thus providing a new protocol to produce the complex molecules through sequential C–H activation with the same directing group.

To further test the ability to remove this directing group, we chose different types of arylated product, including **4o**, **4n**, **3ab**, and **4i** to explore the reaction conditions. To our delight, all these products were hydrolyzed under mild reaction conditions in a short time (please refer to the Supporting Information). For **4o** and **4n**, the carboxylic acid and 2-picolinamide were obtained in quantitative yields, thus showing the great recovery of the directing group [Eq. (3)]. However, both **3ab** and **4i** gave the picolic acid/ester and the corresponding amide as products with very high efficiency [Eq. (4)].^[6]



To gain insight into the mechanism, deuterium-labeling experiments were carried out. The kinetic isotope studies indicated that the C–H cleavage was reversible (see page S11 in the Supporting Information). According to a previous report^[4e] and our observations, a catalytic cycle has been proposed (see page S11 in the Supporting Information).

In conclusion, we have discovered the commercially available and inexpensive 2-picolinamide to be a novel directing group for palladium-catalyzed C(sp³)–H arylations with an imide as a linker. A wide range of aryl halides and carboxylic acid derivatives were successfully applied. Additionally, alkenylation was carried out for the first time with alkenyl bromide. With this unique directing group, the programmed arylations of both primary and secondary C–H bonds were carried out. The directing group can be removed

at room temperature. Studies on the application of 2-picolinamide as a directing group in other transformations and a clear understanding of mechanism are underway.

Experimental Section

General procedure for gram-scale reaction: Pd(OTFA)₂ (166.2 mg, 0.5 mmol), Ag₃PO₄ (1.8836 g, 4.5 mmol), imide (**1a**, 1.2315 g, 5.0 mmol), and aryl halide (**2b**, 4.3606 g, 10 mmol) were added to a 50 mL one-neck round-bottom flask open to the air. Then the solvent (TBB, 20.0 mL) was added. The mixture was stirred at 100°C in oil bath for 3 h. After the reaction was complete, the system was cooled to room temperature and purified directly (without removal of TBB) by flash chromatography on silica gel with petroleum ether/EtOAc (10:1→3:1) to give the product. **3ab** was obtained as a colorless liquid in 85% yield (1.4288 g).

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