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Palladium-Catalyzed C8-H Acylation of 1-Naphthylamines with Acyl Chlorides

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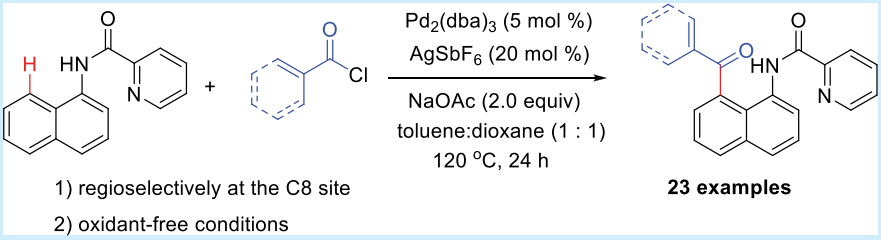
Supporting Information



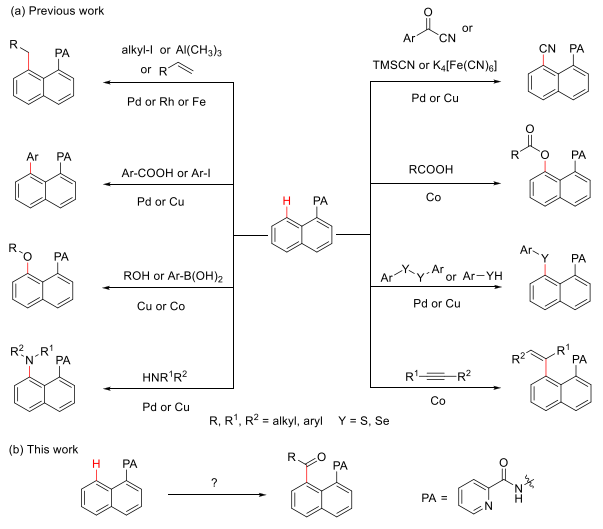
ABSTRACT: A facile and efficient protocol for palladium-catalyzed regioselective C8-H acylation of 1-naphthylamine derivatives with acyl chlorides has been developed. The reaction exhibits broad functional group tolerance, and both aromatic and α,β-unsaturated acyl chlorides can be effectively coupled with 1-naphthylamines. Moreover, the picolinamide moiety as a bidentate directing likely plays a key role in this regioselective transformation.

The carbonyl moiety is a ubiquitous structural scaffold found in natural products, functional materials, and pharmaceuticals.[1] Moreover, aryl ketones have also exhibited considerable practical value in industrial application. Therefore, the development of an effective aromatic arylation protocol has attracted a great deal of attention from synthetic chemists.

In the past decades, transition-metal-catalyzed direct C−H bond acylation under the assistance of a directing group has emerged as a reliable and valuable tool for the synthesis of various ketone compounds.[2] Compared with the traditional Friedel−Crafts acylation reaction, there are some obvious advantages of this approach, such as broad functional group tolerance, excellent regioselectivity, and high atom economy.[3]

Specifically, since Daugulis developed picolinamide (PA) as a bidentate directing group in 2005,[4] the direct C8-H functionalization on the naphthalene skeleton of 1-naphthylamines has been successfully achieved, and various catalytic versions have been developed within recent years, such as alkylation,[5] arylation,[6] etherification,[7] amination,[8] esterification,[9] cyanation,[10] chalcogenation,[11] and alkenylation[12] (Scheme 1a). For example, in 2016, our group reported a facile and efficient palladium-catalyzed C8-H amination of 1-naphthylamines employing simple secondary aliphatic amines as the amination reagents.[8c] Subsequently, an efficient protocol for the direct C8−H etherification with arylboronic acids was described by the group of Punniyamurthy.[7b] Recently, Chatani's group demonstrated rhodium(I)-catalyzed C8-H bond alkylation with various alkenes including some inactivated alkenes.[5c] However, reports for the direct C8-H acylation of 1-naphthylamines remain rare up to now.

Scheme 1. Direct C8-H Functionalization of 1-Naphthylamines



The recent research interest in our group mainly focuses on the C-H functionalization of aromatic skeletons at an unusual site, especially the C4 or C5 position of 8-aminoquinoline

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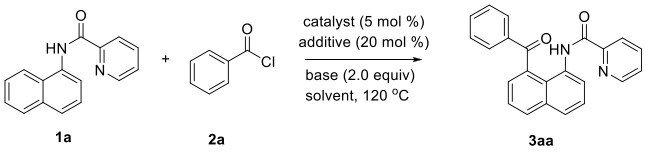
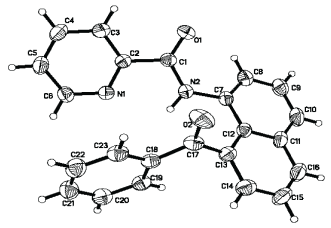
derivatives[13] and the C4[14] or C8[8c] site of 1-naphthylamides derivatives. Inspired by the above-mentioned previous report and our own work, we envisioned developing a simple and efficient reaction pattern for regioselective C8-H bond acylation of 1-naphthylamine derivatives under the assistance of the picolinamide (PA) moiety (Scheme 1b).

The acylation of *N*-(naphthalen-1-yl)picolinamide **1a** with benzoyl chloride **2a** was first conducted in 1,2-dichloroethane (DCE) in the presence of NaOAc under the catalysis of $Pd(OAc)_2$ at 120 °C, and gratifyingly, the desired product **3aa** was obtained in 29% yield (Table 1, entry 1). Further

Table 1. Optimization of the Reaction Conditions[a,b]





3aa

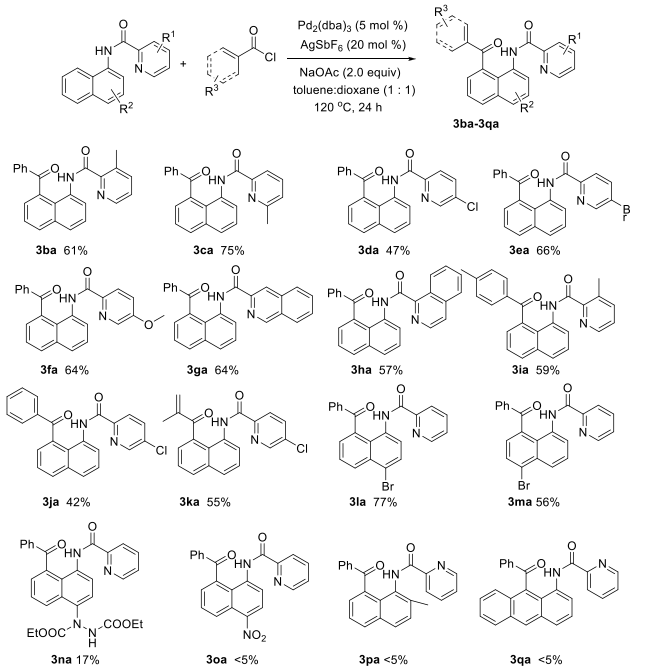
entry	catalyst	base	additive	yield[b] (%)
1[c]	$Pd(OAc)_2$	NaOAc		29
2	$Pd(OAc)_2$	NaOAc		49
3	$PdCl_2$	NaOAc		33
4	$Pd(PPh_3)_4$	NaOAc		41
5	$Pd_2(dba)_3$	NaOAc		57
6	$Pd_2(dba)_3$	$NaHCO_3$		42
7	$Pd_2(dba)_3$	Na_2CO_3		38
8	$Pd_2(dba)_3$	$KHCO_3$		25
9	$Pd_2(dba)_3$	K_3PO4		49
10	$Pd_2(dba)_3$	NaOAc	PPh_3	52
11	$Pd_2(dba)_3$	NaOAc	Xphos	57
12	$Pd_2(dba)_3$	NaOAc	Johnphos	60
13	**$Pd_2(dba)_3$**	**NaOAc**	**$AgSbF_6$**	**75**
14	$Pd_2(dba)_3$	NaOAc	$AgNTf_2$	61
15	$Pd_2(dba)_3$	NaOAc	AgI	68
16	$Pd_2(dba)_3$			nr
17		NaOAc		nr

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (5 mol %), additive (20 mol %), and base (0.2 mmol) in the mixture of toluene and 1,4-dioxane (1:1) (1.5 mL) at 120 °C under air for 24 h. [b]Isolated yield based on **1a**. [c]DCE (1 mL).

screening results of various solvents disclosed that a mixture of toluene and 1,4-dioxane (1:1) as the solvent was the optimal choice (see the Supporting Information). Subsequently, different palladium catalysts were examined, and $Pd_2(dba)_3$ showed the best catalytic activity in this reaction, affording the product **3aa** in 57% yield (Table 1, entry 5 vs entries 2−4). Unfortunately, other organic and inorganic bases did not provide better results (Table 1, entries 6−9, and the Supporting Information). Finally, a series of additives were screened, and the addition of $AgSbF_6$ could result in the product in a higher yield of 75% (Table 1, entries 10−15). Control experiments indicated that palladium catalyst and base were proven to be essential to this reaction (Table 1, entries 16 and 17). The molecular structure of **3aa** was unambiguously confirmed by single-crystal X-ray diffraction study.

With the optimized reaction conditions in hand, the applicability of 1-naphthylamine derivatives in this acylation was examined, and the results are summarized in Scheme 2.

Scheme 2. Scope of 1-(Naphthalenyl)picolinamides



Generally, the reaction showed broad functional group scope and could tolerate diverse electron-donating and -withdrawing substituents in the pyridine ring or the naphthalene moiety, generating the corresponding products in moderate to good yields (**3ba**−**3na**). The electronic effect at the C4 site of the naphthalene ring would dominate the reaction process (**3la** vs **3oa**). For example, the substrate bearing a weak electron-withdrawing group such as a bromine atom resulted in the product (**3la**) in a high yield of 77%; when there was a strong electron-withdrawing group (NO_2) at the C4 site, the reactivity was switched off and little product (**3oa**) was observed. Unfortunately, the products **3pa** and **3qa** cannot be obtained due to the strong steric hindrance of a methyl group at the C2 site and a hydrogen atom at the C8 site, respectively.

Subsequently, the scope of acyl chlorides were examined under the standard reaction conditions. As showed in Scheme 3, generally, substrates bearing electron-donating groups resulted in the target products in slightly higher yields (63%−75%) than those (39−61%) of substrates containing electron-withdrawing groups (**3aa**−**3ac** vs **3ad**−**3ai**). Notably, *α,β*-unsaturated acyl chloride could also provide the product **3aj** in a moderate yield 64%. However, this reaction could not be applicable to aliphatic acyl and 2-naphthoyl chlorides (3**ak** and 3**al**).

Several control experiments were conducted in order to gain insight into the mechanism (Scheme 4). Initially, the designed substrates (**4a**, **5a**, **6a**, **7a**) bearing N- or N,O-chelating groups were performed under the standard reaction conditions, and

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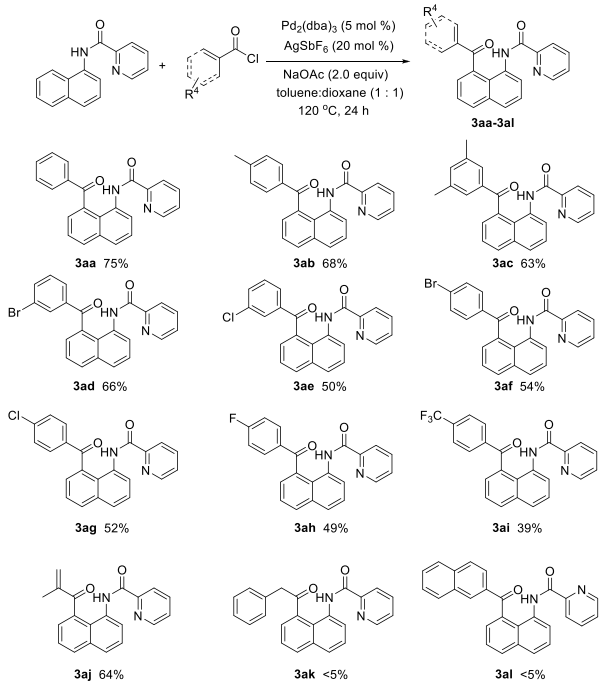
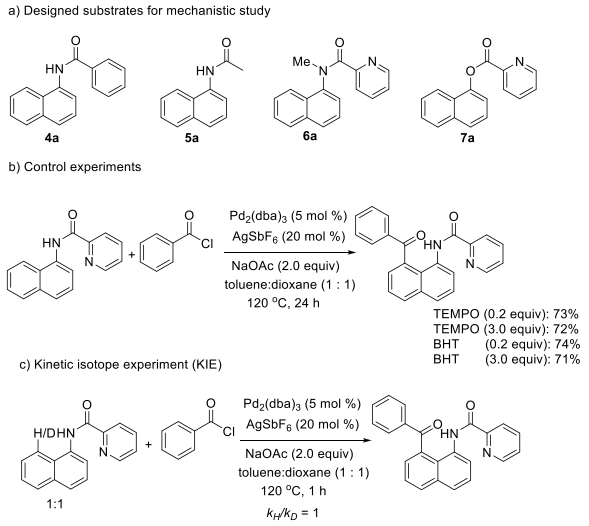
Scheme 3. Scope of Various Acyl Chlorides



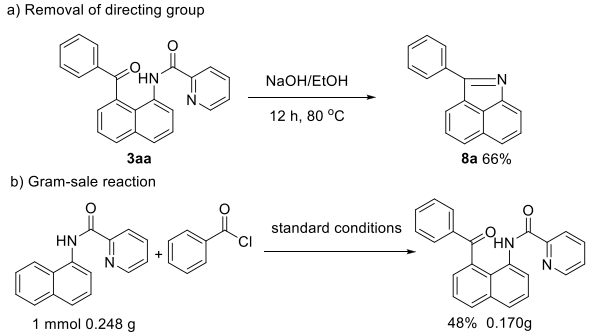
Scheme 4. Mechanistic Studies



no products were observed, indicating that the N,N-bidentate directing group should be essential in this transformation. The addition of radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) did not inhibit this reaction, and therefore, this reaction maybe not involve a radical process. Furthermore, the experiment for calculating the kinetic isotope effect (KIE) was carried out (see the Supporting Information), and the corresponding KIE value (k_H/k_D = 1) may imply that the C−H bond cleavage of the arene ring should be not involved in the rate-limiting step, and therefore, oxidative addition of benzoyl chloride (**2a**) to the Pd(II) center may be the rate-determining step.

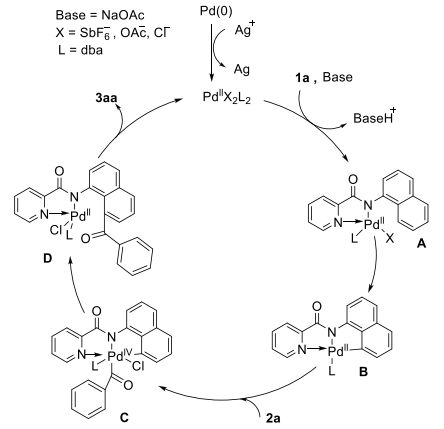
Furthermore, to demonstrate the synthetic utility of this protocol, the removal of the directing group and a gram-sale reaction were investigated. After acylated product **3aa** was heated in EtOH for 12 h in the presence of the NaOH, the compound **8a** was obtained in 66% yield (Scheme 5a). A gram-scale reaction of C8-H acylation was performed under the standard conditions, affording the product (**3aa**) in a yield of 48% (Scheme 5b).

Scheme 5. Synthetic Applications



On the basis of the above-mentioned results and previous reports,[8c,11a] a plausible mechanism is illustrated in Scheme 6.

Scheme 6. Proposed Reaction Mechanism



Initially, $Pd_2(dba)_3$ would be oxidized into Pd(II) species by $AgSbF_6$, and the coordination of amide **1a** with Pd(II) species affords an intermediate **A** in the presence of base. Subsequently, the cleavage of the *ortho* C−H bond smoothly proceeds, generating a five-membered cyclopalladated(II) intermediate **B**. Oxidative addition of a C−Cl bond of the chlorocarbonyl group to the intermediate **B** results in a Pd(IV) intermediate **C**, the reductive elimination of which takes place to afford an intermediate **D**. Ligand dissociation of the intermediate **D** finally occurs to furnish the product **3aa** and regenerate the active Pd(II) species to fulfill the catalytic cycle.

In summary, we have developed an efficient protocol for palladium-catalyzed regioselective C8-H bond acylation of 1-naphthylamine derivatives with abundant and commercially available acyl chlorides, thereby providing a feasible access to benzo[*cd*]indoles. In this reaction, oxidant is not essential. Moreover, the reaction exhibits broad functional group tolerance, and both aromatic and α,β-unsaturated can be effectively coupled with 1-naphthylamines.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00283.

Experimental details, characterization, and NMR spectra of all products (PDF)

Accession Codes

CCDC 1884982 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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