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Palladium-Catalyzed Regioselective C8−H Amination of 1-Naphthylamine Derivatives with Aliphatic Amines

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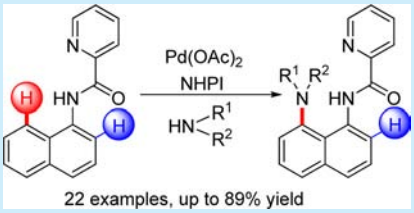
Supporting Information

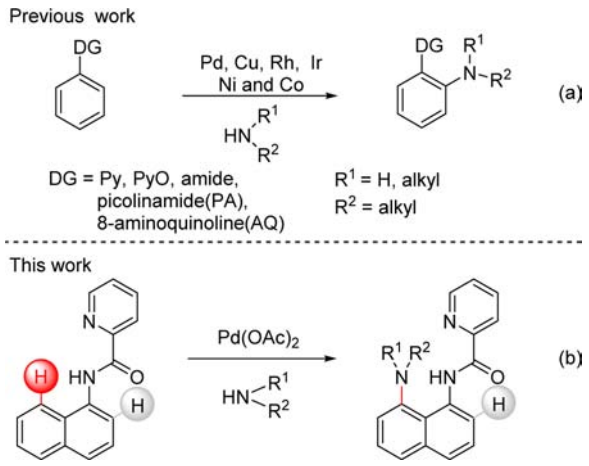
ABSTRACT: A simple and facile protocol for palladium-catalyzed picolinamide-directed C8−H amination of 1-naphthylamine derivatives with simple secondary aliphatic amines was developed, thereby providing a new route to 1,8-naphthalenediamine derivatives. It is noteworthy that the picolinamide moiety as a bidentate directing group may play a key role in this regioselective transformation.



During recent years, with the emergence of a large number of studies on transition-metal-catalyzed C−H bond activation,[1] C−H bond functionalization has also become an appealing and convenient tool to construct C(sp^2)−N bonds.[2] In general, the transition-metal-catalyzed intermolecular direct transformation from C−H bonds to C−N bonds via a cross-dehydrogenative coupling (CDC) process has been demonstrated with or without the help of a directing group.[3,4]

Specifically, the ligand-directed intermolecular C−N bond-forming reaction has received more and more attention because of its excellent regioselectivity, which takes place at the *ortho* position of the directing group (Scheme 1a).[4] In 2006, Yu's group introduced a Cu-catalyzed intermolecular nonacidic *ortho*-C−H bond amination of 2-phenylpyridine using $TsNH_2$ as a nitrogen anion source.[4a] In the same year, Che and Yu also reported an *O*-methyl oxime-directed intermolecular C−H amination, employing various amides such as carbamates, acetamides, and sulfonamides as the amination reagents.[4b] Since then, great progress has been achieved by the groups of Daugulis,[4c] Su,[4d] Chang,[4f] Zhang,[4g] and Song,[4h] who independently developed Cu-, Rh-, Ir-, Ni-, and Co-catalyzed amination protocols using different monodentate or bidentate chelating auxiliaries, respectively. In particular, Daugulis realized a removable bidentate auxiliary-directed nonacid *ortho*-C−H bond amination of 8-aminoquinoline benzamides with primary and secondary aliphatic amines.[4c]

Scheme 1. Ligand-Directed Regioselective C−H Amination



The research interest in our group is focused on regioselective C−H functionalization, especially that taking place at an unusual C−H site. We recently demonstrated a C5−H sulfonylation of 8-aminoquinoline amides with sulfonyl chlorides.[5] Since Daugulis and co-workers developed the picolinamide (PA) moiety as a directing group in 2005, the conversion of C−H bonds to C−C bonds[6a] and C−N bonds[6b] has been indicated with the help of this type of directing group. Chen's group also described a Cu-catalyzed, PA-directed *ortho* amination of *N*-naphthylamides in 2014.[4e] Inspired by these previous works, we envisioned achieving a direct C8−H bond amination version for *N*-naphthylamides with amines assisted by a picolinamide bidentate auxiliary (Scheme 1b).

Initially, the amination of *N*-(naphthalen-1-yl)picolinamide (**1a**) with morpholine (**2a**) was selected as a model reaction for optimization of the reaction parameters, and the results are displayed in Table 1. After a screening of the palladium species, $Pd(OAc)_2$ showed the highest catalytic activity (see the Supporting Information (SI)). Subsequently, after various

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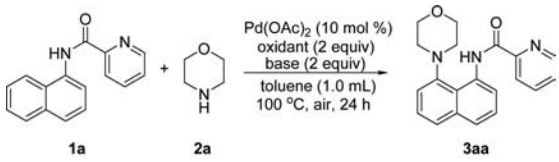
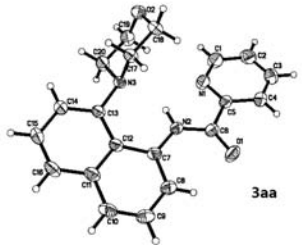
Table 1. Optimization of the Reaction Conditions[a]





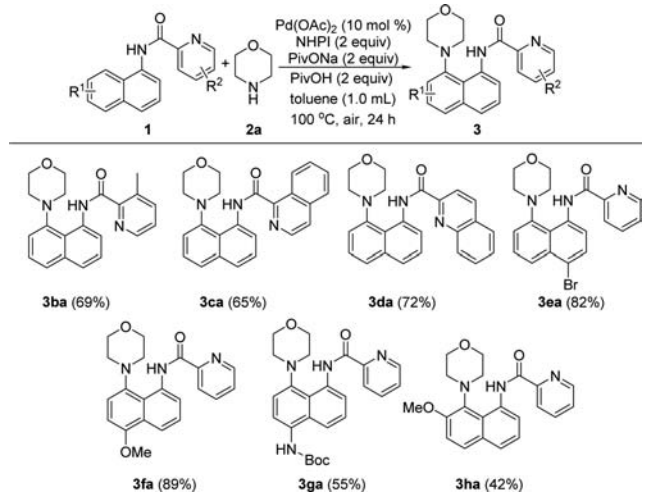
entry	oxidant	base	additive	yield (%)[c]
1	Ag_2CO_3	K_2CO_3	–	17
2	AgOAc	K_2CO_3	–	13
3	Ag_2SO_4	K_2CO_3	–	23
4	$AgNO_3$	K_2CO_3	–	19
5	TBHP	K_2CO_3	–	N.R.
6	$PhI(OAc)_2$	K_2CO_3	–	<5
7	$K_2S_2O_8$	K_2CO_3	–	N.R.
8	BQ	K_2CO_3	–	N.R.
9	NMO	K_2CO_3	–	<5
10	NHPI	K_2CO_3	–	26
11	NHPI	Cs_2CO_3	–	32
12	NHPI	K_3PO_4	–	38
13	NHPI	PivONa	–	45
14	NHPI	–	–	<5
15[d]	NHPI	PivONa	PivOH	68
16[e]	**NHPI**	**PivONa**	**PivOH**	**88**
17[f]	NHPI	PivONa	PivOH	72
18[g]	NHPI	PivONa	PivOH	70

[a]Reaction conditions: substrate **1a** (0.1 mmol), **2a** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), and base (2.0 equiv) in toluene (1.0 mL) at 120 °C in air for 24 h. Abbreviations: TBHP = *tert*-butyl hydroperoxide, BQ = *p*-benzoquinone, NHPI = *N*-hydroxyphthalimide, NMO = 4-methylmorpholine *N*-oxide, PivONa = sodium pivalate hydrate, PivOH = pivalic acid. [c]Isolated yields. [d]PivOH (1.0 equiv). [e]PivOH (2.0 equiv). [f]PivOH (2.0 equiv) at 90 °C. [g]$Pd(OAc)_2$ (5 mol %) and PivOH (2.0 equiv).

oxidants were examined, *N*-hydroxyphthalimide (NHPI) exhibited the highest efficiency, albeit in a lower yield of 26% (Table 1, entry 10 vs entries 1–9). Next, among the bases checked (e.g., K_2CO_3, PivONa, Cs_2CO_3, and K_3PO_4), PivONa gave the best result, generating the desired product in 45% yield (Table 1, entry 13 vs entries 11 and 12 and the SI). It should be noted that the reaction did not occur at all in the absence of the base (Table 1, entry 14). In order to further improve the conversion, several common additives were screened (see the SI). To our surprise, employing PivOH as an additive enhanced the catalytic efficiency, resulting in a higher yield of 68% (Table 1, entry 15), while other additives did not show any effect on the reaction (see the SI). When the loading of PivOH was increased from 1 to 2 equiv, the target product was obtained in a higher yield of 88% (Table 1, entry 16). With a decrease of the oil bath temperature from 100 to 90 °C, the yield of **3aa** was decreased to 72% (Table 1, entry 17). Finally, when the palladium catalyst loading was reduced to 5 mol %, the target product was obtained in a slightly lower yield of 70% (Table 1, entry 18). The molecular structure of **3aa** was unambiguously confirmed by a single-crystal X-ray diffraction study.

After the optimized reaction conditions had been established, the scope of *N*-(naphthalen-1-yl)picolinamide derivatives **1** was examined, and the results are summarized in Scheme 2. First,

Scheme 2. Substrate Scope of *N*-(Naphthalen-1-yl)picolinamide Derivatives



the PA directing group bearing different substituents could result in the products in moderate yields, and the substituents did not show remarkable influence (**3ba**–**3da**). The electronic effect at C4 of the 1-naphthylamine was not obvious in this amination, and the desired products were obtained in good yield (**3ea**). However, for the C5-substituted 1-naphthylamine, an electron-donating group was more conducive to the reaction than an electron-withdrawing group, affording the target product **3fa** in a good yield of 89% (compared with 55% for **3ga**). In the case of the C7 site of the 1-naphthylamine, steric effects would dominate the reaction process (**3ha**). A methoxy group at C7 of the substrate led to a decreased yield of 42%, and we suspect that the substituent at the C7 site may impede the cyclometalation step of the substrate at the C8–H bond (**3ha**).

Subsequently, the scope of amines was also explored under the standard reaction conditions. As summarized in Scheme 3, a wide range of six-membered cyclic secondary amines containing various functional groups were well-tolerated under the optimized conditions, and the desired products were obtained in mostly moderate to good yields (**3ab**–**3ag**). However, in the case that the secondary amine possessed an unprotected hydroxyl group, the reaction conversion dropped sharply, and an even lower yield of 20% was observed (**3ah**).

To demonstrate potential applications, transformation of the products was also investigated. For example, the PA directing group could be easily removed by simple base hydrolysis, affording the corresponding 2-morpholinonaphthylamine **4a** in 74% yield (Scheme 4).

To gain insight into the reaction mechanism, control experiments were carried out (Scheme 5). For example, performing the reaction under a nitrogen or oxygen atmosphere instead of air resulted in product **3aa** in similar yields, indicating that oxygen might have no effect on this amination; the addition of a radical quencher, 2,2,6,6-

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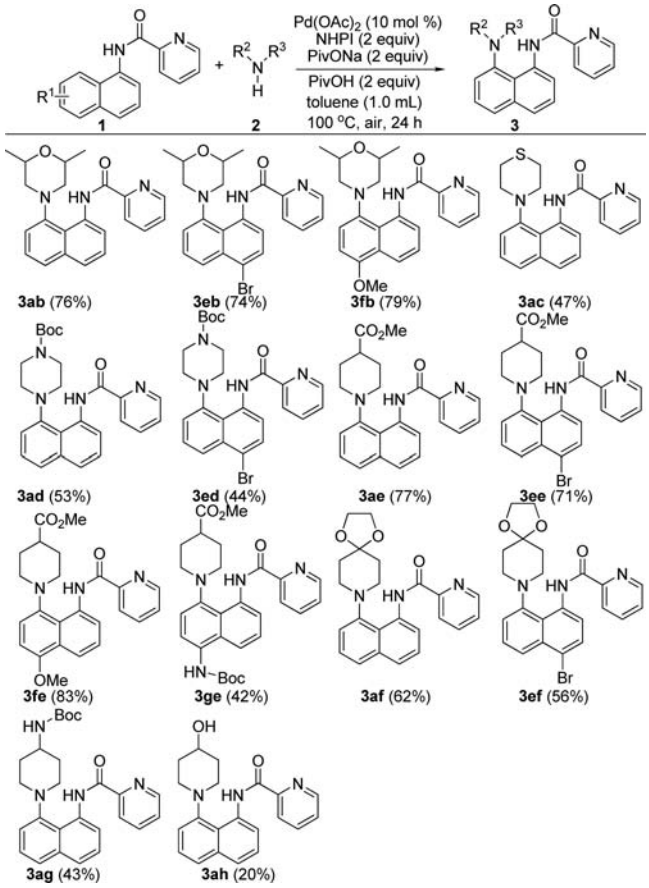
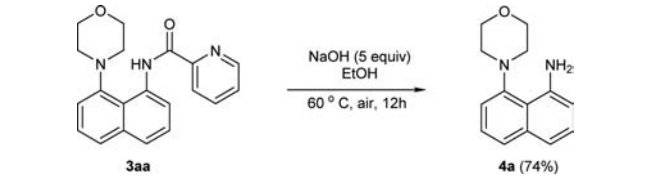
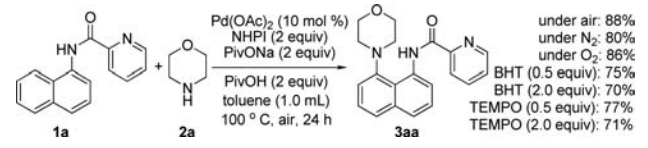
Scheme 3. Substrate Scope of Secondary Aliphatic Amines



Scheme 4. Removal of the Directing Group



Scheme 5. Control Experiments



tetramethylpiperidin-1-oxyl (TEMPO) or 2,6-diisopropyl-4-methylphenol (BHT), had no obvious effect on the reaction, suggesting that the reaction might not involve a radical process. A previous report pointed out that NHPI served as oxidant in the reaction via the cleavage of the N−O bond[7] and would be transformed to *o*-phthalimide or *o*-phthalic anhydride as a reductive product. In this reaction, *o*-phthalic anhydride was successfully detected by HRMS (see the SI). In addition, when the picolinamide bidentate system was changed into the benzamide or picolinate monodentate system, the reaction could not be carried out (see the SI), indicating that the coordination of the picolinamide bidentate system to the Pd species should play an important role in the successful reaction.

In conclusion, we have developed a palladium-catalyzed direct amination of 1-naphthylamine derivatives with aliphatic amines, providing a facile and convenient route to C8-aminated 1-naphthylamides. This reaction features regioselective amination at C8 of the naphthylamine moiety and a broad substrate scope for inactive secondary aliphatic amines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02243.

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

Crystallographic data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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