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Nickel-Catalyzed Direct Amination of Arenes with Alkylamines

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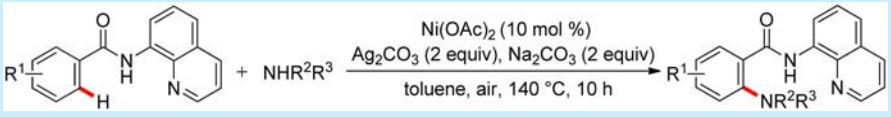
Supporting Information



ABSTRACT: The efficient nickel-catalyzed direct amination of arenes with simple alkylamines has been achieved with the assistance of a bidentate directing group through sp^2 C−H bond functionalization. Preliminary mechanistic investigations indicate that the reaction probably proceeds through a Ni^I/Ni^{III} catalytic pathway.

Arylamines are key building blocks that widely exist in natural products, pharmaceuticals, agrochemicals, and organic optoelectronic materials.[1] Consequently, research directed at discovering efficient and high-yielding methods for the preparation of arylamines has received much attention. Traditionally, the transition-metal-catalyzed cross-couplings, such as Ullmann−Goldberg, Buchwald−Hartwig, and Chan−Lam aminations, have been proven to be the practical methods for the synthesis of diverse arylamines.[2] However, the prefunctionalization of the substrates is inevitable in these transformations, which also gives rise to the formation of undesirable toxic waste.

Recently, transition-metal-catalyzed C−H amination has emerged as an alternative method for the synthesis of arylamine derivatives.[3] In particular, the direct cross-dehydrogenative coupling between arenes and simple amines represents an ideal and environmentally attractive strategy.[3,4] The pioneering work by Yu and Che groups discovered that the amidation of the *ortho* C−H bond of 2-phenylpyridine could be achieved by the copper[5a,b] or palladium[5c] catalysis. The Pd-catalyzed direct amination of arenes with alkylamines was developed by Yu and co-workers with the assistance of an amide directing group. In this transformation, benzoyl hydroxylamine was formed *in situ* as an aminating agent in the presence of benzoyl peroxide.[6] The copper-catalyzed amination of arenes with alkylamines was reported by Daugulis where an aminoquinoline directing group showed special effect on the amination.[7] Recently, the group of Chen and Carretero independently reported the Cu-catalyzed amination of anilines with alkylamines by the assistance of different directing groups.[8]

Nickel is a low-cost and readily available transition metal that is widely utilized as a catalyst in a huge number of organic transformations.[9] Very recently, the application of a nickel catalyst in the C−H activation was demonstrated by Chatani and others.[10] In light of these excellent achievements, we are intrigued by the example of nickel-catalyzed amination of arenes with alkylamines. We found that the direct amination of arenes with alkylamines could be successfully performed with the assistance of an 8-aminoquinolyl auxiliary[11] to give the corresponding arylamines in high yields. The transformation exhibited a broad substrate scope, and a variety of functional groups could be well tolerated.

We commenced our investigation with the substrate 8-aminoquinoline benzamide (**1a**) and morpholine (**2a**) in toluene using Ni salt as a catalyst. To our delight, the desired C−N bond coupling product was formed in 29% yield by using $Ni(acac)_2$ as the catalyst and Ag_2CO_3 as the oxidant (Table 1, entry 1). The screening of various commercially available nickel salts, such as $Ni(OTf)_2$, $Ni(OAc)_2$, $(Ph_3P)_2NiCl_2$, $NiCl_2$, and $NiBr_2$, revealed that $Ni(OAc)_2$ was the optimal catalyst and showed the highest reactivity, giving the product **3a** in 70% yield (entries 2−6). Other silver salts were also tested in the reaction, and the effects were inferior to that of Ag_2CO_3 (entries 7−10). A control experiment showed that $Ni(OAc)_2$ and Ag_2CO_3 were essential for the amination reaction (see Supporting Information). Some highly valent oxidants, such as $PhI(OAc)_2$ and $K_2S_2O_8$, could not give the desired product (entries 11−12). It was observed that the basic additives had a positive influence on the reaction and exhibited higher reactivity than acidic additives. Among different additives Na_2CO_3 turned out to be the most efficient in the formation of product **3a** (entries 13−16). The addition of Et_3N totally inhibited the reaction (entry 17). However, only a trace of the isolated product was obtained in the absence of base (entry 18). It was worth mentioning that the efficiency of the reaction was significantly improved when the reaction was carried out under an air atmosphere (entry 19). Replacing air atmosphere with O_2, the reaction conversion was slightly increased (entry 20). A temperature screening suggested that the transformation at 140 °C delivered the amination product in the highest isolated yield (entry 21). Other solvents, such as DCE, NMP, 1.4-dioxane, DMSO, and DMF, resulted in lower yields (see Supporting Information).

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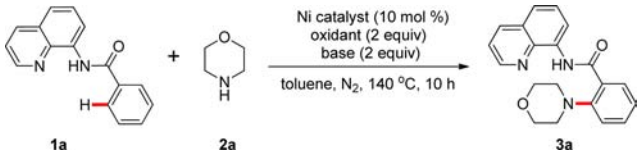
Table 1. Optimization of the Reaction Conditions[a]

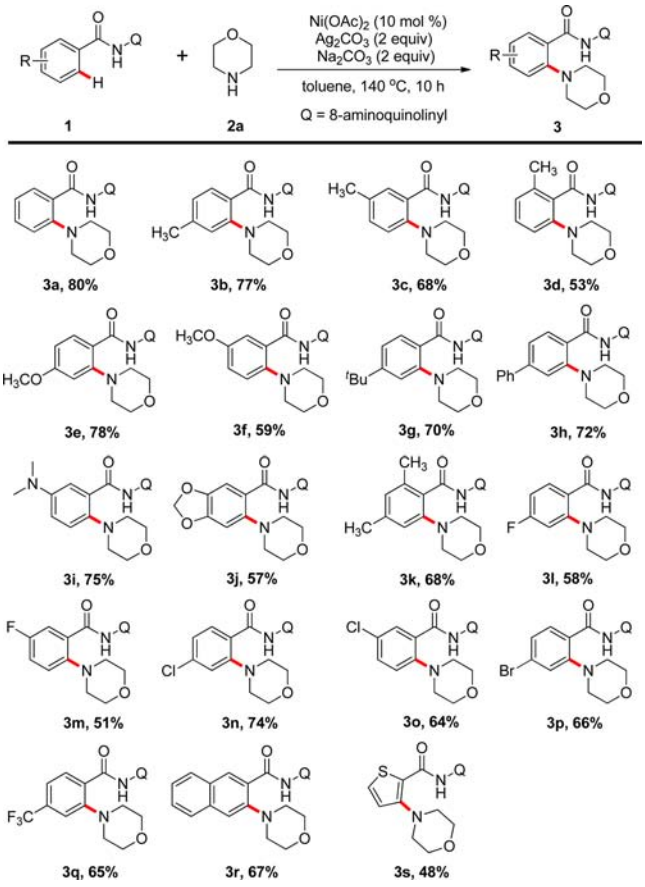


entry	catalyst	oxidant	additive	yield[b] (%)
1	$Ni(acac)_2$	Ag_2CO_3	Na_2CO_3	29
2	$Ni(OTf)_2$	Ag_2CO_3	Na_2CO_3	26
3	$Ni(OAc)_2$	Ag_2CO_3	Na_2CO_3	70
4	$(Ph_3P)_2NiCl_2$	Ag_2CO_3	Na_2CO_3	15
5	$NiCl_2$	Ag_2CO_3	Na_2CO_3	10
6	$NiBr_2$	Ag_2CO_3	Na_2CO_3	8
7	$Ni(OAc)_2$	Ag_2O	Na_2CO_3	38
8	$Ni(OAc)_2$	AgOAc	Na_2CO_3	46
9	$Ni(OAc)_2$	$AgNO_3$	Na_2CO_3	0
10	$Ni(OAc)_2$	AgOTf	Na_2CO_3	trace
11	$Ni(OAc)_2$	$PhI(OAc)_2$	Na_2CO_3	0
12	$Ni(OAc)_2$	$K_2S_2O_8$	Na_2CO_3	0
13	$Ni(OAc)_2$	Ag_2CO_3	PivOH	0
14	$Ni(OAc)_2$	Ag_2CO_3	K_2CO_3	62
15	$Ni(OAc)_2$	Ag_2CO_3	K_2HPO_4	63
16	$Ni(OAc)_2$	Ag_2CO_3	NaOAc	66
17	$Ni(OAc)_2$	Ag_2CO_3	Et_3N	trace
18	$Ni(OAc)_2$	Ag_2CO_3	–	trace
19	**$Ni(OAc)_2$**	**Ag_2CO_3**	**Na_2CO_3**	**80**[c]
20	$Ni(OAc)_2$	Ag_2CO_3	Na_2CO_3	82[d]
21[c]	$Ni(OAc)_2$	Ag_2CO_3	Na_2CO_3	62,[e] 66,[f] 78[g]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Ni catalyst (0.02 mmol), oxidant (2 equiv), base (2 equiv), toluene (0.2 M), 140 °C, N_2, 10 h. [b]Isolated yield. [c]Under air. [d]Under O_2 atmosphere. [e]120 °C. [f]130 °C. [g]150 °C.

With the optimized conditions in hand, the scope of carboxamide substrates was examined by the employment of a variety of 8-aminoquinoline benzamides (Scheme 1). To our delight, the substrates with electron-withdrawing (**3b**−**3k**) or electron-donating substituents (**3l**−**3q**) on the aryl ring were successfully compatible with the reaction, showing the excellent functional group compatibility. The desired aminated products were afforded in moderate to good yields. Notably, the good regioselectivity was observed and the monoaminated product was solely obtained in the reaction, without the formation of a diaminated product. The reactivity of *para*- and *meta*-substituted carboxamides (**3b**−**3c**) was similar to the *ortho*-substituted ones (**3d, k**), indicating steric hindrance played little influence on this transformation. It should be noted that the reaction proceeded exclusively at the less hindered *ortho* position for the *meta*-substituted carboxamides. The reaction showed good tolerance toward halogenated substituents, including F, Cl, and Br, to give the corresponding aminated products in acceptable yields (**3l**−**p**, 51−74%). This satisfactory result provided possible access to further derivatization of the obtained products. The substrate bearing the strong electron-withdrawing trifluoromethyl group could also be involved in the reaction to afford **3q** in 65% isolated yield. Gratifyingly, 2-naphthalenecarboxamide was applicable under the standard conditions as well and produced the desired product (**3r**) in reasonable yield. More importantly, a heteroaromatic substrate such as thiophene-carboxamide could also participate smoothly in the reaction to furnish the corresponding product **3s** in moderate yield.

Scheme 1. Substrate Scope of Carboxamides[a,b]



[a]Yield of isolated product. [b]Reaction conditions: benzamides **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(OAc)_2$ (0.02 mmol), Ag_2CO_3 (0.4 mmol), Na_2CO_3 (0.4 mmol), Toluene (2.0 mL), 140 °C, air, 10 h.

As shown in Scheme 2, we subsequently investigated the scope of different secondary amines. We were delighted to find that various functional groups were well tolerated under the standard reaction conditions. A wide range of 6-membered cyclic secondary amines, such as 4-methylpiperidine, ethyl isonipecotate, the ethylene ketal of 4-ketopiperidine, Boc-protected 4-aminopiperidine, Boc-protected piperazine, and 2,6-dimethylmorpholine, could all afford the corresponding aminated products in good yields (**4a**−**4e**, **4j**−**4l**). In addition, some simple secondary amines, such as methylbenzylamine, dibutylamine, and *N*-methylpropan-1-amine, were smoothly introduced to deliver the desired products (**4f**−**4i**). Unfortunately, primary amines, such as aniline and propan-1-amine, were inactive under the reaction conditions. In addition, the *N*-methylaniline also failed to participate in this amination reaction.

The 8-aminoquinolyl directing group could be readily removed under simple conditions. As shown in Scheme 3, the product **3a** was treated with NaOH in ethanol for 72 h to afford the corresponding 2-morpholinobenzoic acid in high yield.

To gain further insights into the reaction mechanism, an intermolecular deuterium-labeling experiment was carried out (Scheme 4). The kinetic isotope effect (KIE) values of 4.3 and 4.9 were observed from the competitive and parallel reactions of **1a** and **1a**-d_5 respectively. The above results indicated that

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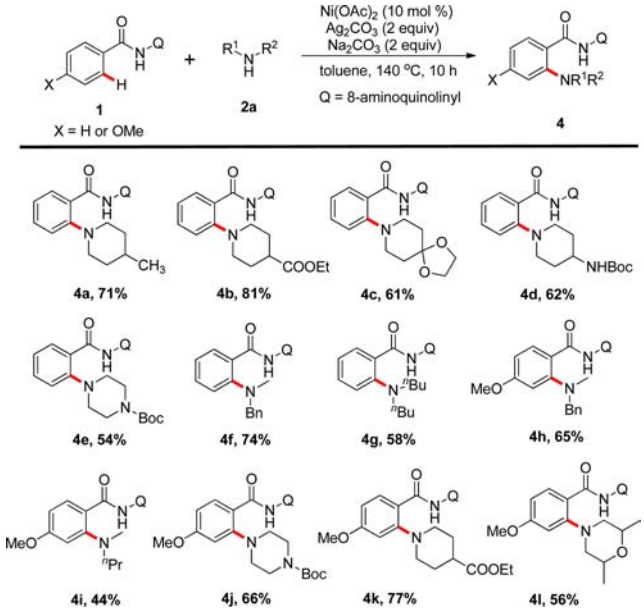
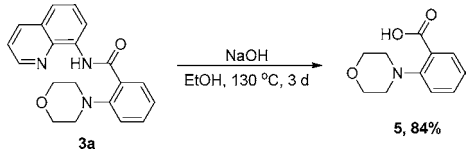
Scheme 2. Substrate Scope of Secondary Amines[a,b]

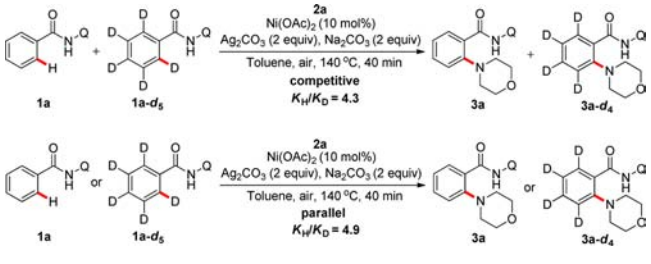


[a]Yield of isolated product. [b]Reaction conditions: benzamides **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(OAc)_2$ (0.02 mmol), Ag_2CO_3 (0.4 mmol), Na_2CO_3 (0.4 mmol), Toluene (2.0 mL), 140 °C, air, 10 h.

Scheme 3. Removal of the Directing Group



Scheme 4. Deuterium Labeling Experiments

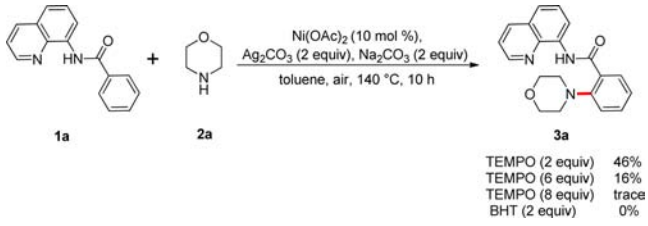


the C−H cleavage of benzamide might be involved in the rate-determining step.

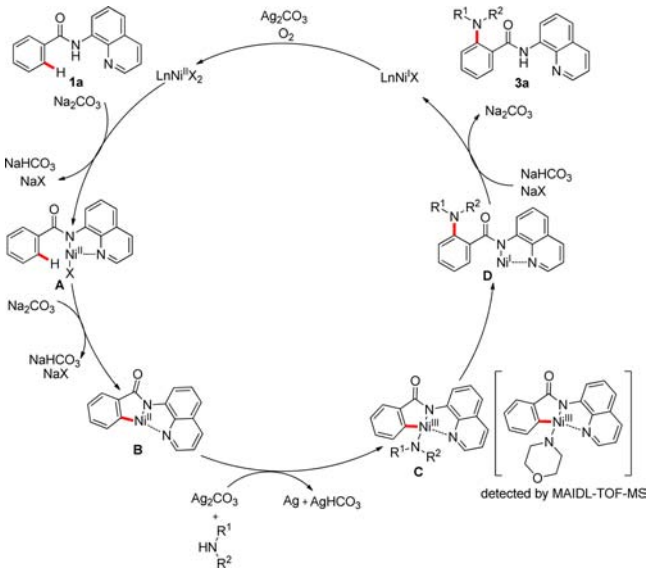
Furthermore, a radical trapping experiment was also conducted. It should be noted that the addition of a radical scavenger of TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl) resulted in the dramatic decrease of the reaction yield. Not surprisingly, the reaction was totally inhibited with the addition of 2 equiv of BHT (2,4-di-*tert*-butyl-4-methylphenol) (Scheme 5), and a radical coupling product between morpholine and BHT was isolated (see Supporting Information). These results implicated that a single electron transfer (SET) process might be involved in the reaction.

Based on the preliminary mechanistic investigations and some relevant publications,[12] it is speculated that the reaction might proceed through a Ni^I/Ni^{III} catalytic cycle and a plausible mechanism is proposed as shown in Scheme 6. The reaction process is initiated by coordination of amide **1a** to the Ni^{II}

Scheme 5. Radical Trapping Experiments



Scheme 6. Proposed Reaction Mechanism



species followed by a ligand exchange process to genetate nickel complex **A**. Cyclonickelation of this intermediate via C−H activation gives the Ni^{II} complex **B**, which is oxidized to the Ni^{III} species **C**. A single electron transfer process may be involved in this step.[5a,13] The analysis of MAIDL-TOF-MS provided the evidence for the possible formation of the intermediate **C**, which partially supported the proposed mechanism (see Supporting Information). The subsequent reductive elimination of the intermediate **C** followed by protonation delivers the final aminated product **3a** and liberates the Ni^I species. The oxidation of Ni^I species by Ag_2CO_3 and O_2 fulfils the catalytic cycle.

In summary, we have developed a new approach for the direct amination of unactivated arenes with simple alkylamines. For the first time, nickel was employed as an efficient catalyst for the amination of arenes with the assistance of a bidentate directing group. The transformation exhibited high efficiency and a broad substrate scope, and a variety of functional groups could be well tolerated. Further investigations to elucidate the reaction mechanism and extend the practical application of this methodology are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral and analytical data, copies of ^1H NMR and ^{13}C NMR spectra for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00990.

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Notes

The authors declare no competing financial interest.

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