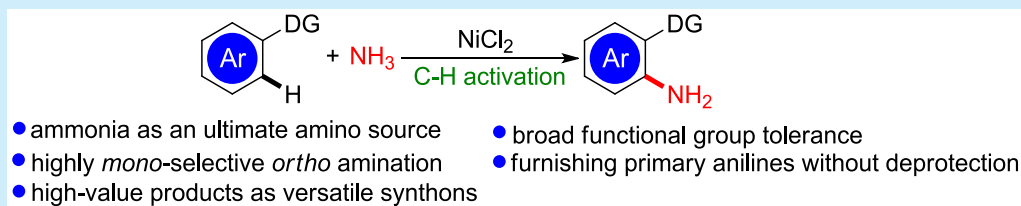# Ammonia as Ultimate Amino Source in Synthesis of Primary Amines via Nickel-Promoted C−H Bond Amination

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S *Supporting Information*

- ammonia as an ultimate amino source
- highly *mono*-selective *ortho* amination
- high-value products as versatile synthons
- broad functional group tolerance
- furnishing primary anilines without deprotection

ABSTRACT: The direct use of ammonia in transition-metal promoted C−H bond amination for the synthesis of primary amines is considered to be one of the major challenges in synthetic organic chemistry. Herein, we report that such transformation can be successfully achieved via nickel-promoted amination of inert arene C−H bonds with ammonia gas assisted by an 8-amino-quinoline directing group.

The synthesis of aromatic primary amines is very important because they are not only widely present in pharmaceutical agents, agrochemicals as well as functional materials[1−4] but also can be readily converted into other functionalities such as halides, OH, SH, CN, CF_3, etc., via diazonium salts as intermediates.[5−9] Therefore, development of efficient strategies toward this highly valuable building block is one of the central research topics in organic synthesis. Among the various known methods for the synthesis of aromatic primary amines, a two-step protocol involving nitration of arenes followed by reduction is typically the method of choice.[10] However, this classical method tends to suffer from issues such as generating large amount of waste acid as well as selectivity problems. Alternatively, transition-metal-catalyzed C−N couplings such as Ullmann−Goldberg-type condensation,[11−15] Buchwald−Hartwig-type amination,[16−21] and Chan−Lam-type coupling[22−24] can also provide efficient access to various primary anilines even though aryl halides (pseudohalides) or aryl boronic acids are required as starting materials.

In contrast, the direct conversion of aromatic C−H bonds to C−NH_2 is clearly advantageous because C−H bonds are ubiquitous, and no prefunctionalization is required. Toward this end, efficient approaches to primary anilines through direct C−H bond amination have been successfully achieved using electrochemical catalysis,[25] photoredox catalysis[26,27] as well as novel electrophilic amination reagents.[28] In addition, chelation-assisted transition-metal-catalyzed direct C−H functionalizations[29,30] have opened new avenues for the regioselective synthesis of aromatic primary amines, and chemists have devised several systems for regioselective C−H primary amination. For example in 2016, Hirano and Uchiyama group developed a copper-catalyzed or mediated amination protocol in which $BnONH_2$ was utilized as the aminating agent, and deprotonative

cupration with a strong base such as $(TMP)_2Cu(CN)Li_2$ is used to generate the aryl-metal species in situ.[31] In 2017, Bolm showed that dibenzothiophene sulfoximine could be used as a NH_3 surrogate to participate in Cu-catalyzed C−H bond amination for the synthesis of primary anilines.[32] In 2018, our group reported an efficient synthesis of primary anilines via Ni-promoted C−H bond amination employing NaN_3 as a nitrogen source.[33] More recently, Yu and Dai disclosed an elegant route to primary anilines via copper-mediated C−H bond amination with oxime esters.[34]
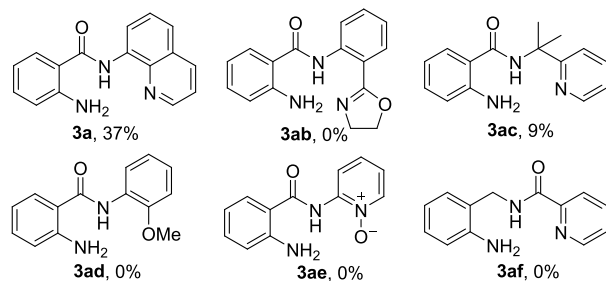
However, the direct use of ammonia, the ultimate amino source, in transition-metal-catalyzed C−H bond amination assisted by directing groups for the preparation of primary amines is still scarce and considered to be one of the "Holy Grails" in synthetic organic chemistry.[35] It is believed that the difficulty of developing such a reaction may be due to (a) the basic ammonia may coordinate strongly to the transition-metal center to form metal-amine complexes, which may be inactive toward C−H activation; (b) fundamentally, ammonia is a reductant capable of reducing the high valent organometallic intermediate, which is responsible for the critical C−H activation step, thus quenching the reaction; (c) the reaction may be faced with selectivity issues such as overamination because the resultant primary amine product may be more reactive than the parent ammonia. Hence, secondary or even tertiary amine products can be formed as well. In this Letter, we wish to report that transition-metal-mediated C−H bond amination for the direct synthesis of primary amines using the ultimate amino source, i.e., ammonia gas as the amination reagent, could be successfully achieved through nickel-mediated C−H activation/amination sequence.

The reaction is not only highly efficient but also exhibits excellent regio- and monoselectivities in forming various primary aniline products, which can be easily converted into anthranilic acids, a critical scaffold in perfumes, agrochemicals, and medicinal chemistry.[36,37] It should be noted that very recently, Chang and co-workers also reported an elegant Cu-promoted *ortho*-amination of benzamides using aqueous ammonia as the amine source.[38]

In order to achieve the regioselective activation of specific C–H bonds, chemists have developed a series of bidentate auxiliary groups,[39−41] which can guide the desired C–H bond activation via chelation assistance. In addition to the well-studied noble metal catalysts such as Pd, Rh, Ru, and Ir complexes, there is a growing interest for the use of first row transition-metals in C–H bond activations[42] as well because they are typically inexpensive and earth-abundant. We believe that the combination of bidentate directing groups with the use of stoichiometric amount of first row transition-metal salt may hold the key for overcoming the problems faced with ammonia participated C–H bond amination. Guided by this working principle, we have decided to use benzamide as our model substrate because this system is well studied and a variety of bidentate auxiliary groups have been reported on this system. As a result, various directing group bearing benzamides have been synthesized accordingly and treated with ammonia in the presence of more than stoichiometric amount of metal promoters including Co, Cu, Fe, and Ni salts (Figure 1). To our delight, we found that when

(1) Screening of bidentate directing groups[a]:

3a, 37%   **3ab**, 0%   **3ac**, 9%

3ad, 0%   **3ae**, 0%   **3af**, 0%

(2) Screening of transition metal promoters[a] :

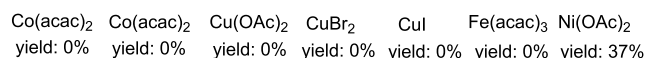| Co(acac)$_2$ | Co(acac)$_2$ | Cu(OAc)$_2$ | CuBr$_2$ | CuI | Fe(acac)$_3$ | Ni(OAc)$_2$ |
| yield: 0% | yield: 0% | yield: 0% | yield: 0% | yield: 0% | yield: 0% | yield: 37% |

Figure 1. Screening of bidentate directing groups and transition-metal promoters. [a]Reaction conditions: amide **1a** (0.15 mmol), metal salt (0.3 mmol), K$_2$CO$_3$ (0.3 mmol), DMSO (5.0 mL), reaction run in a sealed tube at 140 °C under NH$_3$ (1 atm, closed) for 2 h.

benzamides bearing 8-aminoquinoline[43] and PIP-amine directing groups[44,45] were treated with 2 equiv of Ni(OAc)$_2$ and 2 equiv of K$_2$CO$_3$ in DMSO at 140 °C under NH$_3$ (gas) in a sealed tube, the desired aminated product **3a** and **3ac** could be isolated in 37% and 9% yield, respectively, while other directing groups and metal promoters all failed to give any desired amination products (Figure 1). Consequently, we focused our attention on substrate **1a** and carried out further optimization of the reaction conditions using Ni salt as the promoter (Table 1).

Tests revealed that a better yield as high as 51% could be obtained with NiCl$_2$ when Ni(OAc)$_2$ was substituted with other Ni salts such as Ni(OTf)$_2$, NiCl$_2$, and NiBr$_2$ (Table 1, entries 1–4). In contrast, changing the base from K$_2$CO$_3$ to NaHCO$_3$, KOH, or ^{t}BuOK all led to sharp drop in product yields (Table 1, entries 5–7). Additionally, switching the solvent from DMSO to

Table 1. Optimization of the Reaction Conditions[a]

entry	Ni salt	base	solvent	additive	yield (%)[b]
1	Ni(OAc)$_2$	K$_2$CO$_3$	DMSO	-	37
2	Ni(OTf)$_2$	K$_2$CO$_3$	DMSO	-	22
3	NiCl$_2$	K$_2$CO$_3$	DMSO	-	51
4	NiBr$_2$	K$_2$CO$_3$	DMSO	-	46
5	NiCl$_2$	NaHCO$_3$	DMSO	-	16
6	NiCl$_2$	KOH	DMSO	-	32
7	NiCl$_2$	^{t}BuOK	DMSO	-	28
8	NiCl$_2$	K$_2$CO$_3$	NMP	-	40
9	NiCl$_2$	K$_2$CO$_3$	MeCN	-	25
10	NiCl$_2$	K$_2$CO$_3$	toluene	-	<10
11	NiCl$_2$	K$_2$CO$_3$	DMSO	TBAI	41
12	NiCl$_2$	K$_2$CO$_3$	DMSO	TBAB	45
13	NiCl$_2$	K$_2$CO$_3$	DMSO	TBAA	63
14[c]	NiCl$_2$	K$_2$CO$_3$	DMSO	TBAA	68
15[d]	NiCl$_2$	K$_2$CO$_3$	DMSO	TBAA	38
16[e]	NiCl$_2$	K$_2$CO$_3$	DMSO	TBAA	<10
17[f]	NiCl$_2$	K$_2$CO$_3$	DMSO	TBAA	<10
18[g]	NiCl$_2$	K$_2$CO$_3$	DMSO	TBAA	48
19[g]	**NiCl$_2$**	**K$_2$CO$_3$**	**NMP**	**TBAA**	**66**
20[h]	NiCl$_2$	K$_2$CO$_3$	NMP	TBAA	47
21[i]	NiCl$_2$	K$_2$CO$_3$	NMP	TBAA	18

[a]Reaction conditions: amide **1a** (0.15 mmol), Ni salt (0.3 mmol), base (0.3 mmol), additive (0.3 mmol), solvent (5.0 mL), reaction run in a sealed tube at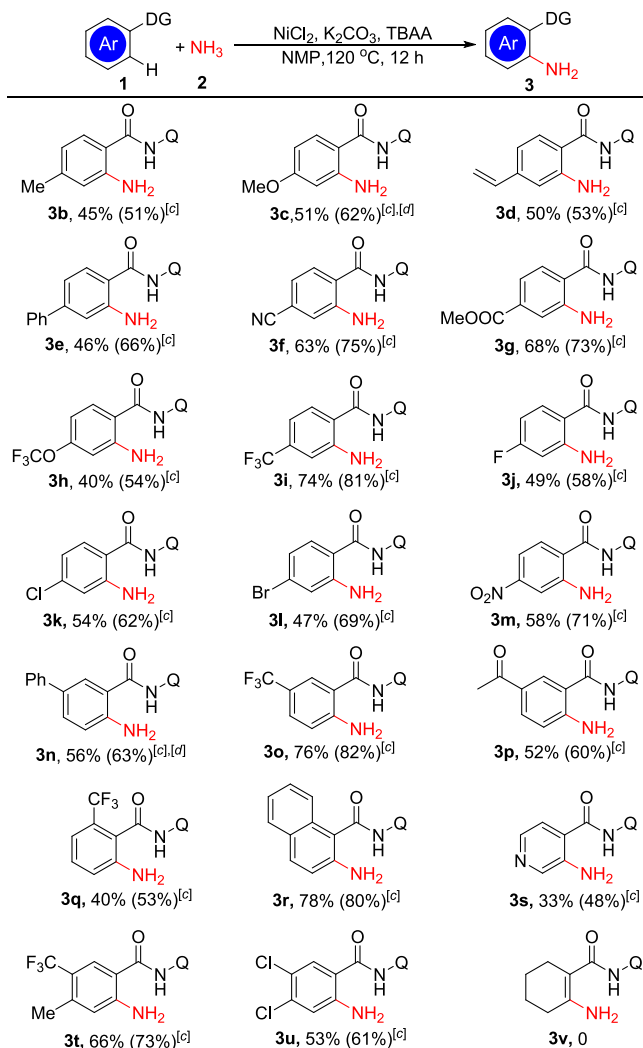 140 °C under NH$_3$ (1 atm, closed) for 2 h. [b]Isolated yield. [c]Add 0.3 mmol of AgTFA as additive. [d]NiCl$_2$ (0.15 mmol, 1.0 equiv) is used. [e]NiCl$_2$ (0.015 mmol) and under O$_2$. [f]Ni salt (0.015 mmol), AgTFA (0.3 mmol). [g]Reaction run at 120 °C for 12 h. [h]Reaction run at 110 °C for 24 h. [i]Using aqueous ammonia (10 equiv) instead of gaseous ammonia.

other solvents such as NMP, CH$_3$CN, or toluene did not benefit the reaction either (Table 1, entries 8−10). Finally, it was discovered that addition of tetrabutylammonium acetate (TBAA) and AgTFA as additives was able to elevate the yield of product **3a** to 68% (Table 1, entries 13−14). Tests also revealed that use of less amount of NiCl$_2$ led to incomplete reaction (Table 1, entry 15). Since the use of more than a stoichiometric amount of silver salt makes our protocol less attractive, we attempted to substitute the silver salt with other oxidants. However, attempts to carry out the reaction in the presence of 10 mol % of NiCl$_2$ using O$_2$ or Ag salt as the oxidant all failed (Table 1, entry 16−17, please see SI for more unsatisfactory examples with other oxidants and ligands). Luckily for us, we found that running the reaction in NMP with TBAA as additive was able to provide us product **3a** in comparable yield (Table 1, entry 19), and the reaction can be carried out at 120 °C even though the reaction took much longer to finish (Please refer to the SI for further optimization details). Further drop of the reaction temperature led to even more sluggish reaction (Table 1, entry 20). As a result, we decided to set the reaction conditions in entry 19 as our standard conditions. It should be noted that much lower yield of **3a** was obtained when NH$_3$ (gas) was replaced with aqueous NH$_3$ solution. In addition, product **3a** was not formed in the absence of the metal promoter, showing that the metal promoter is essential for the reaction to proceed. It should be

mentioned that the reaction only provided the *ortho*-aminated product **3a** and that diamination product was not observed.

With the optimized conditions in hand, the scope of the aromatic amides was studied, and the results are shown in Scheme 1. From the scheme, we can see various aromatic amides

Scheme 1. Substrate Scope of Aromatic Amides of 1[a,b]

*a*Reaction condition A: amide **1** (0.15 mmol), NiCl$_2$ (0.3 mmol), K$_2$CO$_3$ (0.3 mmol), TBAA (0.3 mmol), NMP (5.0 mL), reaction run in a sealed tube at 120 °C under NH$_3$ (1 atm, closed) for 12 h. *b*Isolated yield. *c*Reaction condition B: amide **1** (0.15 mmol), NiCl$_2$ (0.3 mmol), K$_2$CO$_3$ (0.3 mmol), TBAA (0.3 mmol), AgTFA (0.3 mmol), DMSO (5.0 mL), reaction run in a sealed tube at 140 °C under NH$_3$ (1 atm, closed) for 2 h. *d*Twelve hours.

with diverse functional groups can react satisfactorily under the standard reaction conditions to give the desired mono-*ortho*-aminated benzamides in 33−78% yields. It should be mentioned that, even though most substrates performed well under the silver-free conditions (Condition A), we do see some substrates performed much better with the silver additive (Condition B).

As illustrated in Scheme 1, this protocol was compatible with a wide range of functional groups such as alkyl (**3b**), alkoxy (**3c** and **3h**), vinyl (**3d**), fluoro (**3j**), chloro (**3k**), bromo (**3l**), ester (**3g**), acyl (**3p**), aryl (**3e** and **3n**), trifluoromethyl (**3i**, **3o**, and **3q**), and cyano groups (**3f**). It is worthwhile to mention that even the reaction of a nitro-substituted benzamide proceeded unevent-

fully to give **3m** in good yield, showing that electron density on the benzene ring of the benzamide may not be an important factor for this reaction. We can also see that substrates bearing electron-withdrawing groups tend to give the aminated products in higher yields than those bearing electron-donating groups. In addition, the tolerance of halogen substituents on the benzamides is also important because this shows that C−H activation process should be faster than the classical nucleophilic aromatic substitution pathway or Ni-catalyzed cross coupling between the halides and ammonia. Furthermore, these halogens can provide handles for later transformations such as transition-metal catalyzed cross couplings (**3j**, **3k**, **3l**, and **3u**). Gratifyingly, an isonicotinic acid derived amide, which is a heteroaromatic substrate, was smoothly converted to the corresponding aminated product **3s** in yield as high as 48%. However, we failed to obtain the desired product **3v** when an amide derived from 1-cyclohexene-1-carboxylic acid was subjected to our standard reaction conditions.

Since pyridine and pyrazole have also been shown to be potent directing groups for transition-metal-catalyzed or promoted C−H bond activations, we tested substrate **1w** and **1x** to see whether selective C−H bond activations can be achieved in the presence of these heterocycles. We were pleased to find that the desired *ortho*-aminations took place smoothly and that products **3w** and **3x** can be selectively formed in 51% and 59% yield, respectively, highlighting the synthetic power of our protocol (Scheme 2).

Scheme 2. Overcoming Positional Selectivity
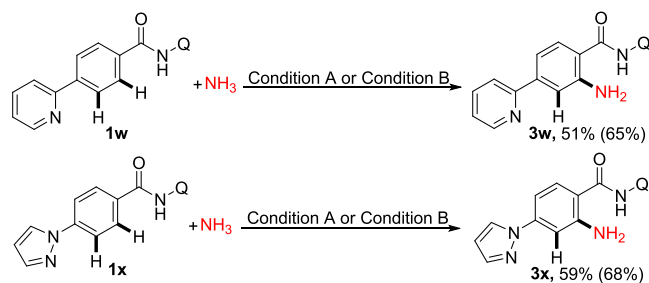
As reported before,[33] the 8-aminoquinoline directing group can be easily removed through alcohol hydrolysis followed by careful pH adjustment and the corresponding anthranilic acids can be isolated in excellent yields.

Some preliminary experiments were carried out to elucidate the reaction mechanism. When radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 1,1-diphenylethylene (DPE) were added into the reaction mixture, the reaction proceeded normally (Scheme 3a). These results indicated that the reaction may not go through radical processes. A competitive experiment showed that substrate **1i** bearing a trifluoromethyl group can give higher yield of the aminated product than **1c**, suggesting that electron withdrawing substituents may be favored in the reaction than electron donating groups (Scheme 3b). We next conducted several experiments to measure the kinetic isotopic effect. The value of the inter-molecular kinetic isotopic effect (KIE) was determined to be 2.3 in a competition reaction run with a mixture of **1a** and **1a-*d*$_5$**, whereas the parallel reaction provided a KIE value of 2.6 (Scheme 3c). These large KIE values indicated that the C−H activation step may be involved in the rate determining step.

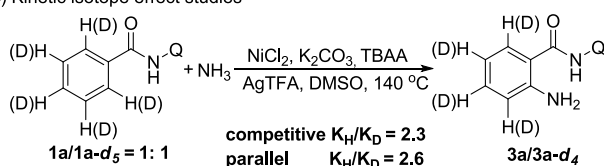## Scheme 3. Preliminary Mechanistic Studies

(a) Radical trapping experiments
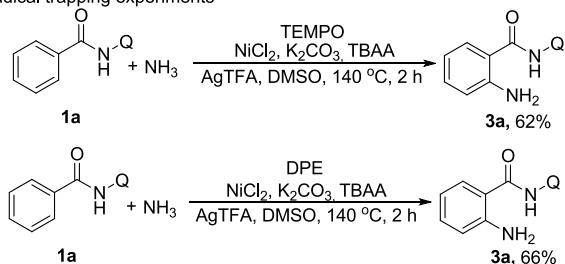
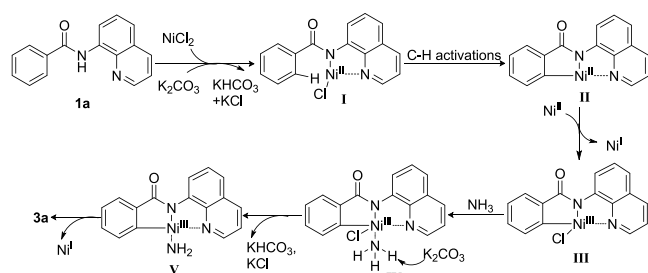(b) Competitive experiment between electron-deficient and electron-rich arenes
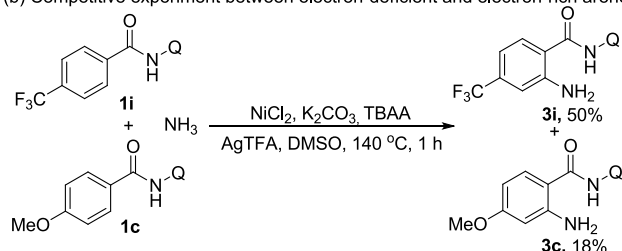
(c) Kinetic isotope effect studies

On the basis of the above results and literature precedents,[46−58] a plausible mechanism is proposed for this nickel-promoted amination reaction and depicted in Scheme 4. First,

Scheme 4. Plausible Reaction Mechanism

amide **1a** reacts with the Ni(II) salt to give the amide-coordinated intermediate **I** in the presence of base which undergoes cleavage of the *ortho*-C−H bond to give intermediate nickelacycle **II**. Next trivalent Ni(III) complex **III** is formed via Ni(II)-promoted oxidation of **II** possibly through disproportion.[46] After reacting with ammonia, intermediate **III** is transformed to complex **IV**, which subsequently is converted into intermediate **V** via abstraction of a hydrogen by the base. Finally, **V** will undergo reductive elimination and protonolysis to give the *ortho*-aminated product **3a**.

In summary, we have successfully developed a highly efficient and selective synthesis of primary amines via transition-metal promoted C−H amination with the ultimate amino source, ammonia gas. Key to success is the use of a stoichiometric amount of first row transition-metal salt NiCl$_2$ in conjunction with using 8-amino-quinoline as the directing group. By treating various benzamides with simple NiCl$_2$ in the presence of K$_2$CO$_3$ and TBAA under NH$_3$, a variety of substituted benzamides

bearing diverse functional groups could be efficiently *ortho*-aminated to give the corresponding aniline derivatives in yields ranging from 33 to 82%. Other notable features of the reaction include excellent regioselectivity and high monoselectivity. Preliminary results indicated that the reaction may go through a C−H activation process. Current efforts are underway to make this reaction a catalytic process, and the results will be reported in due course. We believe that our finding is significant and can inspire future development of transition-metal-catalyzed C−H aminations with ammonia.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01968.

Experimental procedure, characterization data, and NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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