## Nickel-Catalyzed Amination of Aryl Chlorides with Amides

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A lthough amides are prevalent in natural products, pharmaceuticals, and functional polymers,<sup>1-3</sup> they are generally considered inert due to the enhanced stability of the amide C–N bond caused by resonance effects.<sup>4</sup> Various efforts have been devoted to activate and cleave the amide C–N bond for further transformations, including transamidation, esterification, Suzuki–Miyaura, Negishi cross-coupling, and Heck reactions (Scheme 1a).<sup>5</sup> Among them, nickel salts and N-





heterocyclic carbene (NHC) ligands constitute one of the most efficient catalytic combinations for these purposes.<sup>5</sup> However, to fulfill these conversions, the active imide-type amides with bulky and electron-rich substituents are usually required.<sup>4a,5,6</sup> Consequently, the bulky amine fractions are usually generated as waste byproducts.<sup>7</sup> A means to activate general amides and utilize the amine moieties is thus highly desirable.

As one of the most common nucleophiles,<sup>5,8,9</sup> amines could react with aryl halides in the presence of transition-metal catalysts, named the Buchwald–Hartwig amination reaction, yielding a broad scope of aromatic amines.<sup>10,11</sup> However,

amines are often light-sensitive, easily oxidative, and hard to store and handle (e.g., gaseous dimethylamine).<sup>12</sup> On the contrary, amides are more stable and operable, which make them robust surrogates of amines (Scheme 1b). To the best of our knowledge, there is only one example of the NHC-Pdcatalyzed amination of aryl chlorides with amides, reported by Shao and coworkers, which gave moderate to excellent yields.<sup>13</sup> The largely underdeveloped amination of amides encouraged us to explore more efficient protocols, especially with earthabundant metal catalysts.

In recent years, we have successfully developed the NHCmetal-catalyzed amination of (hetero)aryl chlorides and their tosylates, mesylates, and other inactive analogues with diverse amines at low catalyst loadings (0.5 to 2 mol %).<sup>14</sup> We would like to further investigate their applicability with various amides as amino sources, conceiving decarbonylation as a suitable strategy<sup>15</sup> for cleaving the C–N bond of formamides or even general amides. It has to be noted that for amides with alkyl chains, their  $\alpha$ -arylation, giving alkylamides or ketones as byproducts, may also occur, which makes this transformation challenging (Scheme 1b).<sup>13</sup> Delightedly, herein we demonstrate the first example of the nickel-catalyzed amination of aryl chlorides with amides under mild reaction conditions with high selectivity and good to excellent yields (Scheme 1b). Not only formamides but also inactive alkyl/aryl amides are suitable amino sources for this challenging reaction, and no possible  $\alpha$ arylation products<sup>16</sup> or ketones were generated.

Initially, DMF 2a, the simplest formamide, was selected as an amine source for the amination of chlorobenzene 1a. In light of the good performance of nickel precursors and NHC

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ligands in the previous works,  ${}^{5b,14b,17}$  Ni(COD)<sub>2</sub> and acenaphthoimidazolium chloride (APr·HCl salt, a NHC precursor) were applied for the optimization of the reaction conditions (Supporting Information, Table S1). In the presence of 5 mol % Ni(COD)<sub>2</sub> and the NHC precursor, the best result was achieved with KO<sup>t</sup>Bu (4.0 equiv) in toluene at 35 °C for 24 h (57%, Table 1, entry 1). Inferior results were



"Reaction was carried out with aryl chloride **1a** (2.0 mmol), amide **2a** (5.0 mmol), Ni(COD)<sub>2</sub> (x mol %), salt (NHC precursor, x mol %), KO'Bu (8.0 mmol), and H<sub>2</sub>O (y equiv) in toluene (4.0 mL) under a N<sub>2</sub> atmosphere at 35 °C for 24 h. <sup>b</sup>Yield was determined by GC-MS using *n*-tridecane as an internal standard.

found with other tested strong bases (6-48%, Table S1, entries 1-3). The weak bases, including K<sub>3</sub>PO<sub>4</sub>, KOAc, and  $K_2CO_3$ , failed to produce the amination product 3 (Table S1, entries 5-7). Remarkably, additional water showed an obvious influence on the amination process. When 0.2 equiv of H<sub>2</sub>O was added, a slightly increased yield was observed (65%, Table 1, entry 2). An excellent yield was attained when 0.5 equiv of H<sub>2</sub>O was added (91%, Table 1, entry 3), which could be further increased to a quantitative yield when 1.0 equiv of  $H_2O$ was applied (Table 1, entry 4). Pleasingly, even with 1 mol % nickel catalyst, a quantitative yield was still achieved under the otherwise identical reaction conditions (Table 1, entry 5). Further decreasing the catalyst loading to 0.5 mol % gave only a 37% yield (Table 1, entry 6). Other viable NHC precursors utilized in the known C-N cleavage reactions<sup>5</sup> were also involved, which all resulted in diminished yields (0-70%)Table 1, entries 7-10).

With the optimal reaction conditions in hand, the scope of aryl chlorides was then investigated. As shown in Scheme 2, this protocol well tolerated diverse aryl chlorides with electrondonating, electron-withdrawing, sterically hindered, and heterocyclic groups. The relative position of substituents in the aromatic moieties affected the efficiency of the coupling process; only a 16% yield was observed with *o*-chlorotoluene (4a). In contrast, moderate to excellent yields were obtained with *m*- and *p*-isomers (4b,c, 71–90%). For electron-deficient, heterocyclic, and even bulky aryl chlorides, up to 98% yields

#### Scheme 2. Scope of Aryl Chlorides<sup>a</sup>



<sup>*a*</sup>Reaction was carried out with aryl chloride **1** (2.0 mmol), amide **2a** (5.0 mmol), Ni(COD)<sub>2</sub> (1 mol %), APr·HCl (1 mol %), KO<sup>*t*</sup>Bu (8.0 mmol), and H<sub>2</sub>O (2.0 mmol) in toluene (4.0 mL) under a N<sub>2</sub> atmosphere at 35 °C for 24 h. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>Yield was determined by GC-MS using *n*-tridecane as an internal standard. <sup>*d*</sup>With 2 mol % Ni(COD)<sub>2</sub> and APr·HCl for 36 h. <sup>*e*</sup>10 mmol scale. <sup>*f*</sup>After 36 h. <sup>*g*</sup>At 60 °C.

could be achieved (6-26). Remarkably, the gram-scale synthesis of 7a (10 mmol) was carried out, and an excellent yield (92%) was also obtained, which demonstrated the scalability of our protocol. In some cases, a high catalyst loading, extended reaction time, or elevated reaction temperature had to be applied to achieve satisfactory outcomes. For instance, moderate yields (60%) were obtained with pchloroanisol (**5b**) and 4-chloro-4'-methoxy-1,1'-biphenyl (14c) at 2 mol % catalyst for 36 h, indicating that the electron-donating group may be slightly unfavorable for the coupling process. Similarly, when 2-chloropyridine and 3chloropyridine were used, a slightly higher temperature (60 °C) helped to accomplish the transformation to deliver the desired products 19 and 20 in 65 and 85% yield, respectively. In the case of the very sterically hindered 9-chloroanthracene or the heterocyclic chlorophenyl-furan, -thiophene, and -pyridine, moderate to excellent yields (59-92%, 13, 22a,b, and 23) could be attained after 36 h.

Subsequently, a variety of amides were explored. As shown in Scheme 3, compared with DMF, formamides with longer alkyl substituents (R' or R'') on the nitrogen atom showed slightly negative impacts on the amination efficiency. Moderate to excellent (50–90%) yields were attained whenever acyclic

#### Scheme 3. Scope of Amides<sup>a</sup>



<sup>*a*</sup>Reaction was carried out with aryl chloride 1 (1.5 mmol), amide 2 (1.0 mmol), Ni(COD)<sub>2</sub> (1 mol %), APr·HCl (1 mol %), KO<sup>t</sup>Bu (4.0 mmol), and H<sub>2</sub>O (1.0 mmol) in toluene (2.0 mL) under a N<sub>2</sub> atmosphere at 35 °C for 24 h. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>At 60 °C. <sup>*d*</sup>With 2 mol % Ni(COD)<sub>2</sub> and APr·HCl at 100 °C for 36 h. <sup>*e*</sup>After 36 h. <sup>*f*</sup>After 10 h. <sup>*g*</sup>With 2 mol % Ni(COD)<sub>2</sub> and APr·HCl at 120 °C for 36 h.

or cyclic formamides were involved (27-39). When benzyl or phenyl substitutes (R') were attached to the nitrogen atom of amides instead of alkyl chains, similar outcomes were observed (74 to 75%, 29-31). When other more challenging *N*-alkyl/ aryl formamides (R' or R'' = H) were investigated, moderate yields (58-76%, 40-43) could be achieved by doubling the catalyst loading (2 mol %), elevating the reaction temperature (120 °C), and extending the reaction time (36 h).

Besides diverse formamides, the protocol was also suitable for other general amides with alkyl or (hetero)aryl substitutents. For instance, when  $R^2 = Me$  or Et, good isolated yields were obtained for the selective amination reactions (71%, 7a), and no possible  $\alpha$ -arylation products<sup>16</sup> were detected, even in the presence of excess base. In the case of aryl amides, besides phenyl (71–81%, 7a, 29, and 35), other heterocyclic substitutes (N, O, S) were all well tolerated, and moderate to good yields could also be achieved (55–71%, 27, 33, and 37) by slightly increasing the catalyst loading to 2 mol % at 100 °C for 36 h. Furthermore, this methodology was readily applicable for double-amination reactions with diamides to produce diamines in good to excellent yields (44 and 45, 76–94%).

Several control experiments were carried out to gain insight into the reaction mechanism. First, an excess amount of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was used as a radical inhibitor in the amination of p-CF<sub>3</sub>-chlorobenzene **1b** with amide **2k** under the otherwise identical standard reaction conditions (Scheme 4a and Scheme S1). As expected, the desired amine 36 was still obtained in 80% yield, clearly

# Scheme 4. Control Experiments and the Proposed Mechanism



indicating that no radical intermediate was involved. Second, the role of the Ni catalyst in the transformation was explored (Scheme 4b and Scheme S2). In the absence of Ni(COD)<sub>2</sub> and under standard reaction conditions, formamide **2b** was quantitatively converted to the corresponding amine **46** with the release of carbon monoxide (CO) gas, as confirmed by gas chromatography (GC) (Figure S9). The decarbonylation process was further supported by the detection and isolation of R<sup>2</sup>H byproducts (thiophene or thianaphthene) upon using amides **2u** and **2v** as substrates. Therefore, the Ni-catalyzed amination protocol we developed underwent decarbonylation pathway,<sup>18</sup> which was different from the previous Pd-catalyzed amination of aryl chlorides with amides.<sup>13</sup>

Furthermore, in consideration that  $H_2O$  could hydrolyze KO<sup>t</sup>Bu, a mixture containing 1.0 equiv of KOH, 1.0 equiv of <sup>t</sup>BuOH, and 3.0 equiv of KO<sup>t</sup>Bu was applied under the otherwise identical standard conditions, which gave a quantitative yield of amine 3. A similar outcome was also attained with 1.0 equiv of <sup>t</sup>BuOH and 3.0 equiv of KO<sup>t</sup>Bu, whereas only a 42% yield was found with 3.0 equiv of KO<sup>t</sup>Bu and 1.0 equiv of KOH. Therefore, the generated <sup>t</sup>BuOH was crucial for the transformation. This was further confirmed by the control experiments with 0.2, 0.5, and 2.0 equiv of <sup>t</sup>BuOH under the otherwise identical standard reaction conditions, which all gave inferior yields (48–63%, Figure S3). These results indicated that the small amount of <sup>t</sup>BuOH (tolue-

ne/<sup>t</sup>BuOH 22/1) was vital to achieve high yields, which could be ascribed to the formation of a possible conjugated acid–base pair (<sup>t</sup>BuO···H···O<sup>t</sup>Bu), consistent with our recent publication.<sup>19</sup>

On the basis of these control experiments and combined with previous reports,<sup>18</sup> a plausible mechanism is proposed in Scheme 4d. Initially, after the coordination of the NHC ligand derived from APr·HCl with Ni(0), the generated active catalytic species **A** was readily reacted with aryl chlorides to form intermediate **B** via oxidative addition. The intermediate **B** could be immediately trapped by amines generated from the corresponding amides under strong basic conditions, leading to the formation of intermediate **C**. After reductive elimination, product amines were produced along with the regeneration of active species **A** to complete the catalytic cycle.

In summary, an unprecedented Ni-catalyzed amination of aryl chlorides with inactive amides as amino sources under mild reaction conditions has been developed. Moderate to excellent yields were obtained for both coupling partners with electron-rich, electron-poor, and sterically hindered substituents with low catalyst loading. The selectivity for the amination was relatively good, and no possible carbonyl products were generated. The plausible mechanism was proposed based on several control experiments in which a strong base was responsible for the cleavage of the amide's C–N bond under ambient reaction conditions. This protocol complements the routine nickel-catalyzed cross-coupling transformations of amides, potentially providing a new approach to achieve aromatic amines from amides and aryl chlorides with earthabundant metal catalysts.

## ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03836.

Experimental procedures and <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra of compounds (PDF)

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#### Notes

The authors declare no competing financial interest.

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