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Nickel-Catalyzed Reductive and Borylative Cleavage of Aromatic Carbon–Nitrogen Bonds in N-Aryl Amides and Carbamates

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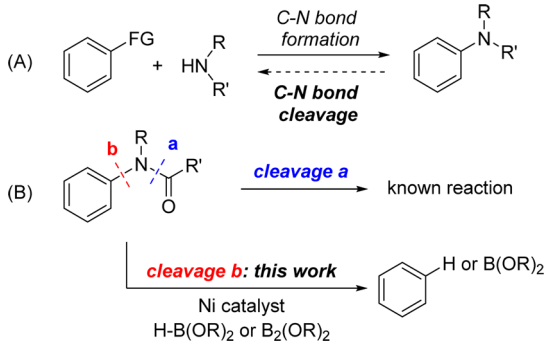
Supporting Information

ABSTRACT: The nickel-catalyzed reaction of N-aryl amides with hydroborane or diboron reagents resulted in the formation of the corresponding reduction or borylation products, respectively. Mechanistic studies revealed that these reactions proceeded via the activation of the C(aryl)–N bonds of simple, electronically neutral substrates and did not require the presence of an ortho directing group.

Over the course of the past decade, there has been substantial progress in the development of metal-catalyzed C(aryl)–N bond forming reactions for the construction of aryl amine derivatives (Scheme 1A, forward).[1]

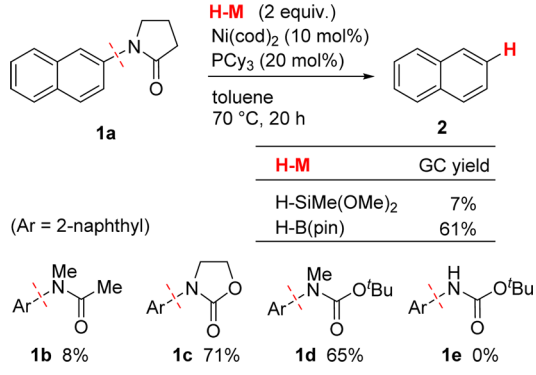
Scheme 1. Cleavage of Aromatic Carbon–Nitrogen Bonds



In contrast, research toward the reverse process involving the catalytic cleavage of C(aryl)–N bonds has been scarce (Scheme 1A, reverse).[2] The cleavage of the C(aryl)–N bonds of aniline derivatives has traditionally been accomplished using highly reactive cationic intermediates such as diazonium[3] and ammonium[4] salts, wherein the C(aryl)–N bond cleavage process is facilitated by the elimination of electronically neutral molecules, i.e., dinitrogen and an amine, respectively.[5] Kakiuchi et al. reported the development of a notable ruthenium-catalyzed C(aryl)–N bond activation reaction for electronically neutral aniline derivatives, but the process was limited to substrates bearing an ortho directing group.[6] Herein, we report the first catalytic C(aryl)–N bond cleavage reactions of electronically neutral and structurally simple aryl amine derivatives via the nickel-catalyzed reduction and borylation of N-aryl amides. These reactions therefore enable a new mode of bond disconnection for amide derivatives (Scheme 1A, cleavage b) and represent a valuable addition to the normal C(acyl)–N cleavage methods (Scheme 1A, cleavage a).

We initiated our study by examining the reaction of amide **1a** with a variety of different coupling partners in the presence of a wide range of transition metal catalysts. The results of these preliminary screening experiments revealed that the use of $HSiMe(OMe)_2$ in conjunction with a $Ni(cod)_2/PCy_3$ catalyst allowed for the successful conversion of **1a** to naphthalene (**2**) via the reductive cleavage of the C(aryl)–N bond,[7] although the yield for this transformation was very low at 7% (Scheme 2). Unfortunately, further changes to the catalyst, ligand,

Scheme 2. Nickel-Catalyzed Reductive Cleavage of C(aryl)–N Bonds: The Effect of the Reductant and Different N-Substituents[a]



[a]Reaction conditions: **1** (0.50 mmol), reductant (1.0 mmol), $Ni(cod)_2$ (0.050 mmol), and PCy_3 (0.10 mmol) in toluene (1.5 mL) at 70 °C for 20 h. Yields were determined by GC analysis versus a calibrated internal standard because of the volatility of the product.

substituents on the silicon, solvent, and reaction temperature did not result in any discernible improvement (details in Supporting Information (SI)). However, the use of HB(pin) as a reductant led to an increase in the yield of **2** to 61%. Several other reducing agents were also screened against the reaction, including $BH_3{\cdot}Me_2S$, KBH_4, and DIBALH, but these reagents led exclusively to the formation of 1-(naphthalen-2-yl)-pyrrolidine via the reduction of the carbonyl group, with no

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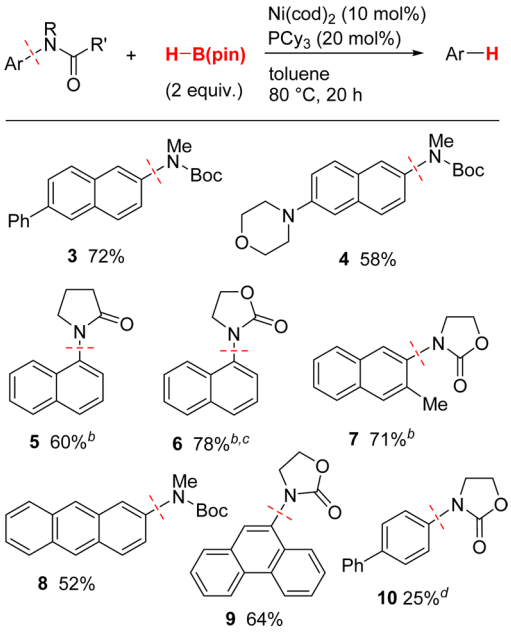
2 being detected. The nature of the C(aryl)−N bond structure had a profound effect on the outcome of the current C(aryl)−N bond cleavage reaction. For example, the acyclic amide **1b** did not react under the current conditions, whereas the cyclic and acyclic carbamates **1c** and **1d** successfully underwent the nickel-catalyzed reductive cleavage to give **2** in good yields. It is noteworthy that the current cleavage process could be readily applied to the Boc-protected aryl amine **1d**, which represents a common structural motif in synthetic chemistry, despite the substantial steric bulk of the Boc group. Furthermore, the presence of an unprotected N−H group on the carbamate, as in **1e**, was determined to be detrimental to the catalytic process.

As shown in Table 1, the current nickel-catalyzed reductive cleavage reaction could be successfully applied to a variety of

Table 1. Nickel-Catalyzed Reductive Cleavage of C(aryl)−N Bonds: Evaluation of the Substrate Scope[a]



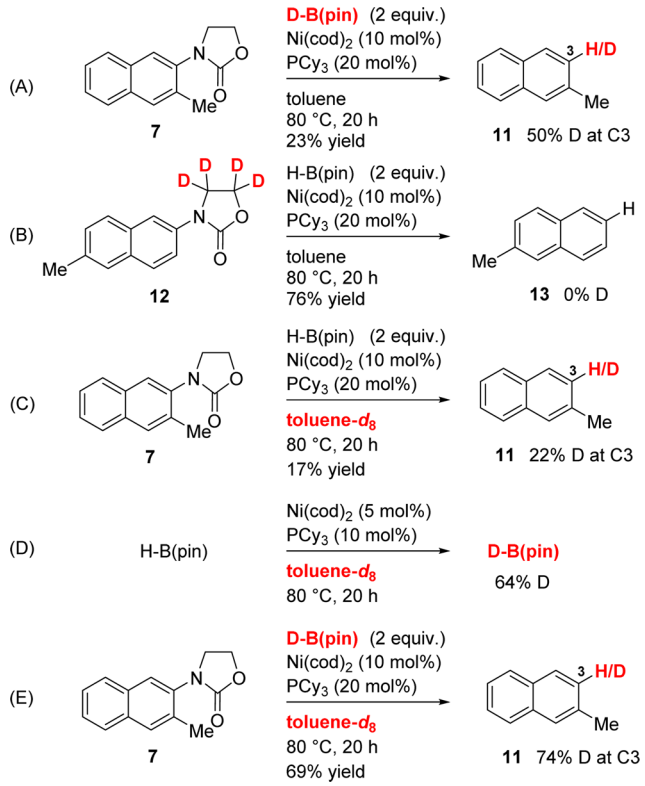
[a]Reaction conditions: Amide or carbamate (0.50 mmol), HB(pin) (1.0 mmol), $Ni(cod)_2$ (0.050 mmol), and PCy_3 (0.10 mmol) in toluene (1.5 mL) at 70 °C for 20 h. Isolated yield is shown unless otherwise noted. [b]GC yield because of the volatility of the product. [c]Reaction time of 48 h. [d]Reaction conducted at 120 °C using IMes instead of PCy_3. 71% of **10** was recovered.

different aromatic amides and carbamates. Under these conditions, the C−N bonds of amines remained intact, whereas those of amides and carbamates were substituted with hydrogen in a chemoselective manner (i.e., **4**).

Sterically demanding substrates bearing a C−N bond at the 1-position of the naphthalene, such as **5** and **6**, as well as those containing an ortho substituent, such as **7**, underwent the reductive cleavage reaction to give the corresponding reduction products. Several other fused aromatic systems, including anthracene **8** and phenanthrene **9**, also proceeded smoothly under the optimized condition to give the corresponding reduction products, whereas benzene derivatives, such as **10**, were found to be much less reactive. The trend in reactivity observed in the current transformation is similar to that reported previously for the nickel-catalyzed cleavage of inert C−O bonds.[8]

We next conducted a series of labeling experiments to develop a deeper understanding of the reaction mechanism in terms of the origin of the hydrogen atom incorporated in the final product.[9] The use of DB(pin) afforded the reduction product **11** with only 50% deuterium incorporation at the 3-position. This result suggested that the hydrogen atom in the reduction product was not derived exclusively from hydroborane and that some other source of hydrogen must be present in the system (Scheme 3A). The deuterium labeling of

Scheme 3. Labeling Studies



the methylene groups of the oxazolidinone ring in compound **12** followed by reduction under the standard conditions delivered the anticipated reduction product, but with no deuterium incorporation (Scheme 3B). In contrast, 22% deuterium incorporated was observed at the 3-position when deuterium labeled toluene was used as the reaction solvent (Scheme 3C), which indicated that a H/D exchange reaction was occurring between the HB(pin) and the toluene solvent. This possibility was confirmed to be true by a simple experiment, where the exposure of HB(pin) to the nickel-catalyzed conditions in toluene-d_8 led to the formation of DB(pin) (Scheme 3D).[10] When the reaction was run with DB(pin) in toluene-d_8, deuterium incorporation at the 3-position of the product increased to 74% (Scheme 3E). The hydrogen incorporation (26%) in this experiment was attributed to a decrease in the deuterium content of the DB(pin) reductant resulting from the H/D exchange reaction of the C−H bonds in the naphthalene rings of the products and the starting carbamates with the deuterium of the DB(pin).[11] Although the rapidity of the hydrogen exchange reactions between DB(pin) and the aromatic C−H bonds may have complicated the outcome of the labeling studies, the

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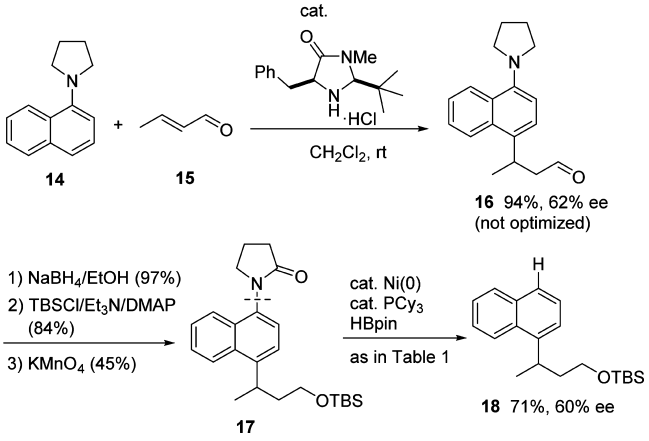
experimental observations collectively indicate that the C−N bonds were substituted by the hydride derived from HB(pin).

The potential utility of this C−N bond cleavage reaction is demonstrated in Scheme 4. Thus, the 1,4-addition of **14** to enal **15** using MacMillan's amine catalyst afforded **16**, where the pyrrolidine group was essential both in terms of the reactivity and regiochemical outcome of the reaction.[12] Subsequent removal of the pyrrolidine group was enabled by the α-oxidation of the pyrrolidine followed by the cleavage of the resulting amide **17** using our newly developed nickel-catalyzed C−N bond cleavage, which gave the corresponding reduced product **18** in good yield. This C−N bond cleavage process was accomplished without having any discernible impact on the stereochemical integrity of the benzylic stereocenter. In this way, the amino groups on an aromatic ring can now be used as a removable activating and directing group in electrophilic aromatic substitutions.

Scheme 4. Synthetic Application

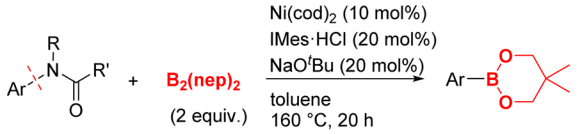


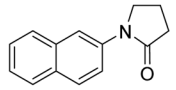
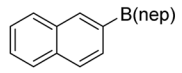
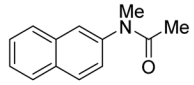
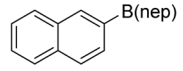
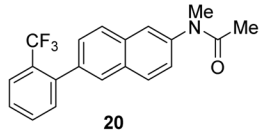
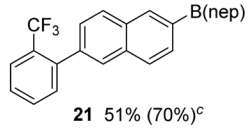
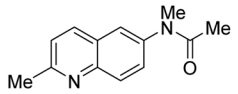
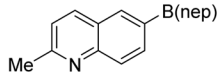
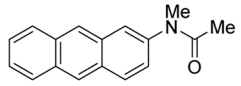
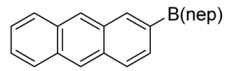
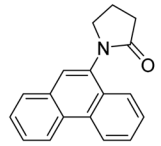
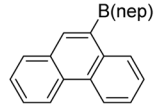
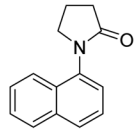
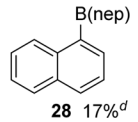
Importantly, we also found that the use of diboron reagents instead of hydroborane resulted in the formation of the borylated product via the cleavage of the C−N bond (Table 2). Following a brief period of optimization, IMes was determined to be the optimal ligand for this nickel-catalyzed borylation reaction (details in SI). This borylation process was found to be amenable to both acyclic and cyclic amides. In the case of acyclic amide **1b**, the deacylated material *N*-methyl-2-naphthylamine was also formed as a minor product. The application of the nickel-catalyzed reaction conditions to *N*-methyl-2-naphthylamine, however, did not provide **19**, which precluded its involvement as an intermediate in the catalytic borylation of **1b**. Fluoride **20** and quinoline **22** were compatible with the conditions and gave the corresponding borylated products in good yields. Once again, polyaromatic substrates, including naphthalenes, quinolines, anthracenes, and phenanthrenes were shown to exhibit significantly higher levels of reactivity toward the borylative cleavage of their C−N bonds under these conditions than the corresponding benzanilides.[13] Unlike the reductive cleavage reaction using HB(pin), the borylation reaction was found to be relatively sensitive to the steric environment of the substrate, as indicated by the decreased yield with 1-substituted amide **5**.

Although several experiments have been conducted with the aim of establishing the mechanism of this novel nickel-mediated C−N bond cleavage reaction, very little is known about the precise nature of the catalyst. To address this issue, we investigated the effect of adding mercury to the reaction. When the nickel-catalyzed reductive cleavage reaction was conducted with HB(pin) in the presence of an excess of mercury, the reaction was completely suppressed, whereas the addition of an excess of mercury to the borylation reaction involving diboron still proceeded, albeit to a lesser extent.[14] Interestingly, the reductive cleavage reaction with HB(pin) continued to proceed even after the reaction mixture was filtered following 5 h, and the filtrate subsequently reheated.[15] Although these data do not provide a definitive understanding as to whether the catalysis is homogeneous or heterogeneous,[16,17] it is likely that the reactions described in the current study were mediated by soluble or nanosized (~10 nm) nickel species,[18] rather than larger-sized nickel aggregates.

In summary, we have developed a nickel-catalyzed C(aryl)−N bond cleavage reaction for the cleavage of amides and

Table 2. Nickel-Catalyzed Borylation of C(aryl)−N Bonds[a]



substrate	product[b]
 **1a**	 **19** 55%
 **1b**	 **19** 72%
 **20**	 **21** 51% (70%)[c]
 **22**	 **23** 72%
 **24**	 **25** 72%
 **26**	 **27** 76%
 **5**	 **28** 17%[d]

[a]Reaction conditions: Amide (0.50 mmol), $B_2(nep)_2$ (1.0 mmol), $Ni(cod)_2$ (0.050 mmol), IMes·HCl (0.10 mmol), and NaO^{t}Bu (0.10 mmol) in toluene (1.5 mL) at 160 °C for 20 h. [b]Isolated yield. [c]NMR yield. [d]61% of **5** was recovered.

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carbamates in the absence of an ortho directing group. In the current transformation, the C−N bonds were converted into C−H and C−B bonds with hydroborane and diboron reagents, respectively. Although further studies will be required to develop a greater understanding of the scope and efficiency of the these reactions, this work clearly demonstrates that the current C(aryl)−N bond cleavage reaction represents a viable disconnection process capable of enabling a nonconventional synthetic strategy. The application of this strategy to other C−N bonds as well as computational studies aimed at revealing the mechanism of the reaction are currently being investigated in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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