## Nickel-Catalyzed Kumada Coupling of Boc-Activated Aromatic Amines via Nondirected Selective Aryl C-N Bond Cleavage

Zheng-Bing Zhang,<sup>†</sup> Chong-Lei Ji,<sup>‡</sup> Ce Yang,<sup>†</sup> Jie Chen,<sup>†</sup> Xin Hong,<sup>\*,‡</sup> and Ji-Bao Xia<sup>\*,†</sup>

<sup>†</sup>State Key Laboratory for Oxo Synthesis and Selective Oxidation. Suzhou Research Institute of LICP. Lanzhou Institute of Chemical Physics (LICP), University of Chinese Academy of Sciences, Chinese Academy of Sciences, Lanzhou 730000, China <sup>‡</sup>Department of Chemistry, Zhejiang University, Hangzhou 310027, China

Supporting Information

ABSTRACT: A nickel-catalyzed Kumada coupling of aniline derivatives was developed by selective cleavage of aryl C-N bonds under mild reaction conditions. Without preinstallation of an ortho directing group on anilines, the cross-coupling reactions of Boc-protected aromatic amines with aryl Grignard reagents afforded unsymmetric biaryls. Mechanistic studies by DFT calculations revealed that the nickel-mediated C-N bond cleavage is the rate-limiting step.

nilines are ubiquitous core structures of industrially  $oldsymbol{\Lambda}$  important and commercially valuable molecules such as dyes, agricultural chemicals, active pharmaceutical ingredients (APIs), and functional materials.<sup>1</sup> Numerous efficient methods have been developed for the synthesis of structurally diverse anilines via aryl C-N bond formation.<sup>2</sup> Considering the ubiquitous role of anilines, it is very useful to construct new chemical bonds by selective aryl C-N bond cleavage. This approach allows anilines as valuable synthetic building blocks as well as late-stage functionalization of molecules containing aniline subunits.<sup>3</sup> However, the C-N bonds of anilines are usually chemically inert due to the  $p-\pi$  conjugation, which is the leading cause for their well-known stability in multistep synthesis.<sup>4</sup> Therefore, there still remain key challenges regarding the selective cleavage of aryl C-N bond of aromatic amines.

Conventionally, activation of aryl C-N bonds into the corresponding highly reactive cationic diazonium salts and ammonium salts are widely utilized to facilitate the desired C-N bond cleavage for various C-C bond-forming reactions.<sup>5</sup> However, there have been only a handful of catalytic reactions of breaking aryl C-N bonds in electronically neutral molecules since the first report of stoichiometric metal-mediated C-N bond cleavage of anilines two decades ago.<sup>6</sup> As of now, successful progress on aryl C-N bond cleavage of aniline derivatives has been achieved for the Suzuki-Miyaura coupling,<sup>7</sup> deamination,<sup>8</sup> alkylation,<sup>9</sup> borylation, and reduction reactions<sup>10</sup> by Kakiuchi, Snieckus, Tobisu, Chatani, and Shi. All of these works required either an ortho-directing group on the substrate or high temperature to achieve the desired aryl C-N bond cleavage. In 2017, Zeng et al. reported a mild Crcatalyzed Kumada coupling of aromatic amines via aryl C-N bond cleavage, which also limited to aromatic amine substrates with an *ortho*-directing group (Scheme 1a).<sup>11</sup>



### Scheme 1. Transition-Metal-Catalyzed Cross-Coupling Reaction To Form C-C Bond via Selective C-N Bond Cleavage

a). Cr-catalyzed Kumada Coupling of Aromatic Amines with ortho-Directing Group



On the other hand, since the original report of Garg, Zou, and Szostak,<sup>12</sup> transition-metal-catalyzed cross-coupling reaction by cleavage of C(O)-N bonds of amides has been

Received: January 19, 2019

intensively studied.<sup>13</sup> All of these reports focused on activating the C(O)-N bond to obtain various ketones by coupling of amides with organometallic reagents (Scheme 1b, route I).<sup>14</sup> Inspired by the above reports, we envisioned that metalmediated oxidative addition of the aryl C-N bond could be achieved selectively by tuning the substituents on the nitrogen of aromatic amines, such as introducing an electron-withdrawing group to weaken the aryl C-N bond. If the newly formed aryl metal species undergoes transmetalation with organometallic reagents and subsequent reductive elimination smoothly, C-C bond-forming products would be obtained successfully. Herein, we report the first nickel-catalyzed Kumada coupling of aromatic amine derivatives by selective cleavage of aryl C-N bonds under mild reaction conditions without preinstallation of a directing group in electronically neutral molecules (Scheme 1b, route II). The key to this success was enhancement of the reactivity of aromatic amines via Boc activation. This transformation is expected to lead to further applications in the field of aryl C–N bond cleavage by non-precious-metal catalysis.

We began our studies by investigating metal-catalyzed cross coupling of commercially available 2-naphthylamine **1a** or *N*-phenyl-2-naphthylamine **1b** with excess PhB(OH)<sub>2</sub> or PhMgBr under various conditions, but no desired biaryl product **2** was observed (Table 1, entries 1 and 2). We were glad to find that a trace amount of **2** was obtained when coupling  $N_iN$ -diphenyl-2-naphthylamine **1c** and PhMgBr catalyzed by electron-rich NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> at room temperature (entry 3). In light of no improved yield by increasing the reaction temperature (entry 4), we further investigated the substituent

# Table 1. Development of the Ni-Catalyzed Kumada Coupling of Anilines by Selective Cleavage of Aryl C–N Bonds<sup>a</sup>



<sup>*a*</sup>All reactions were run with 0.2 mmol of 1 in 2 mL of toluene unless otherwise noted. <sup>*b*</sup>The yield was determined by GC with *n*-dodecane as an internal standard. <sup>*c*</sup>With 3.1 equiv of PhMgBr. <sup>*d*</sup>With 2.1 equiv of PhMgBr. <sup>*e*</sup>At 120 °C. <sup>*f*</sup>Isolated yield in parentheses. <sup>*s*</sup>With 10 mol % of NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>. <sup>*h*</sup>With 2.5 mol % of NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>. <sup>*i*</sup>With 1 mol % of NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>. <sup>*i*</sup>At 60 °C, 37% yield of *N*-Boc deprotection product 1b was obtained. <sup>*k*</sup>Without catalyst.

effect of amine. No reaction occurred with N-methyl-Nphenyl-2-naphthylamine 1d (entry 5), potentially because the aromatic C-N single bond possesses partial double bond character due to conjugation. We reasoned that this  $p-\pi$ conjugation could be weakened by adding an electronwithdrawing group on the nitrogen of aromatic amines, such as carbonyl groups, because there are strong resonance effects between the vicinal nitrogen with a lone-pair electron and the vacant  $\pi^*$  orbital of carbonyl.<sup>15</sup> We then replaced one phenyl substituent of 1c with various carbonyl substituents. The yield of 2 improved with some of them, such as acetyl (1e), methoxycarbonyl (1f), and N,N-dimethylaminocarbonyl (1g) (entries 6-8). To our delight, excellent results were achieved when N-Boc-protected N-phenyl-2-naphthylamine (1i) was used as the substrate (91% yield, entry 10). Good yield was also obtained with N-Boc-protected N-methyl-2-naphthylamine (1j), albeit with higher catalyst loading (entry 12). However, no reaction occurred with cyclic carbamate and amides derived from 2-naphthylamine (entries 15-17). We want to emphasize that the cleavage of C(O)-N bonds of carbamates, amides, and urea was not observed in the above reactions (entries 6–17). Notably, lower catalyst loadings (2.5 or 1 mol %) still delivered good yields of product 2 (entries 18-19). In order to accelerate the reaction rate, we increased the temperature to 60 °C. However, a large amount of N-Boc deprotection product was obtained (entry 20). A control experiment revealed the importance of the catalyst, and no reaction occurred in the absence of the Ni catalyst (entry 21).

With the optimized reaction conditions in hand, we evaluated the scope of the Ni-catalyzed Kumada coupling of N-Boc-activated aromatic amines (Figure 1). First, gram-scale reaction of 1i with PhMgBr delivered biaryl 2 in 86% yield, with only a slight loss in the isolated yield compared to the milligram-scale reaction. Next, aromatic Grignard reagents containing alkyl, alkoxy, or fluoride substituents at the para-, meta-, or ortho-position of benzene ring coupled with aryl C-N bond smoothly, affording the biaryl products 3-10 in moderate to good yields (55-91%). No product (11) was observed when alkylmagnesium bromide was employed. In addition, a variety of functional groups could be tolerated on the 2-naphthylamine derivatives, such as alkyl, functionalized alkyl, siloxy, amino, silyl, and phenyl groups at different positions, leading to the corresponding biaryls 12-20 in good yields. Remarkably, the Ni-catalyzed C-N cleavage is highly selective, and the cleavage of C-N bonds of N,N-dialkyl aryl amines was not observed (16 and 19). Selective C–N cleavage was achieved with these two substrates containing five or six different C-N bonds. Moreover, aryl C-N bonds of N-Boc protected 1-naphthylamine, 2-anthracenamine, and 9-henanthreneamine derivatives can be converted to the biaryls 21-23 successfully.

It is a challenge to cleave the C–N bond of Boc-protected simple aromatic amines under the standard conditions (see Table S3). After extensive screening of the catalyst, we found the Ni-NHC catalysts could promote C–N bond cleavage of *p*-CF<sub>3</sub>-aniline much more efficiently (for details, see Table S4). The moderate to good yields of cross-coupling product **25** was obtained in the C–N bond cleavage of **24a** and **24b** when using (IMes)<sub>2</sub>NiI (**Cat. I**) as catalyst (Scheme 2, eq 1). Promising yield of **26** was also obtained by using (IMes)Ni-(cinnamyl)Cl (**Cat. II**) as catalyst when pivaloyl-activated diphenylamine **27** was used (Scheme 2, eq 2). The improved efficiency may be contributed to the better  $\sigma$ -donor property of



**Figure 1.** Scope of Ni-catalyzed nondirected Kumada coupling of *N*-boc-protected aromatic amines. (a) All reactions were conducted with 0.2 mmol of 1 and isolated yield was provided unless otherwise noted. (b) Gram-scale reaction with 1i (4 mmol, 1.28 g). (c) With NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (10 mol %). (d) With 2.1 equiv of PhMgBr. (e) At 60 °C.

Scheme 2. Ni-Catalyzed Nondirected Kumada Coupling of Aryl C–N Bonds<sup>*a*</sup>



<sup>*a*</sup>Reactions were run with 0.1 mmol of **24** or **27** in 1.0 mL of toluene, and isolated yield was provided unless otherwise noted. <sup>*b*</sup>The yield was determined by GC with *n*-dodecane as an internal standard.

NHC ligand comparing to phosphine ligand, which facilitated the desired aryl C–N bond oxidative addition.<sup>16b</sup>

Control experiments were then conducted to understand the current reactions. Coupling of **1i** with *p*-tolylmagnesium

bromide afforded biaryl 3 as the dominant product, indicating that the cleavage of naphthyl C–N bond is much faster than phenyl C–N bond (Scheme 3, eq 1). The competitive

#### Scheme 3. Control Experiments and Mechanistic Studies



<sup>*a*</sup>The yield was determined by GC with *n*-dodecane as an internal standard.

reactions were conducted by cleavage of naphthyl C–Br, C– N, and C–O bonds,<sup>16,17</sup> and the coupling of the C–Br bond with Grignard reagents is the dominant reaction (see the Supporting Information). Furthermore, biaryl 2 was obtained in 96% yield when using the arylnickel complex 28 as the catalyst (Scheme 3, eq 2). However, direct coupling of 28 with PhMgBr afforded 2 in only 35% yield (see the SI). These results indicated that 28 could be reduced to the active catalyst but not an on-cycle intermediate in the Ni-catalyzed Kumada coupling of the aryl C–N bond.

We next explored the reaction mechanism through DFT calculations<sup>18</sup> (Figure 2). The computed free energy profile of the Ni/PCy<sub>3</sub>-catalyzed Kumada coupling of 1i is shown in Figure 2a. The reaction proceeds via the classic cross-coupling mechanism. Amine 1i first undergoes the Ni-mediated C-N bond cleavage through the oxidative addition transition state TS30, leading to the arylnickel intermediate 31. Subsequent transmetalation with the Grignard reagent 32 is facile, generating intermediate 35. From 35, the dissociation of complex 36 leads to the LNi(naphthyl)(phenyl) intermediate 37, and the C-C reductive elimination via TS38 produces the observed biaryl product. The computations suggested that the resting state of the catalytic cycle is the separate  $Ni(PCy_3)_2$ complex and amine substrate, and the C-N bond cleavage is the rate-determining step with an overall barrier of 25.6 kcal/ mol. The computed overall barrier agrees well with the mild experimental conditions (Table 1).<sup>1</sup>

To understand the effective naphthyl C–N bond cleavage of substrate 1i, we also studied the phenyl C–N bond cleavage of 1i and the naphthyl C–N bond cleavage of 1d (Figure 2b). The naphthyl C–N bond cleavage of 1i is significantly more favorable than the other C–N bond cleavages, which is consistent with the observed reactivities and chemoselectivities (Table 1).<sup>20</sup> Scheme 4 includes the analysis of the controlling factors for the Ni-mediated C–N bond cleavage. For the competing C–N bond cleavages of 1i, both of the controlling factors for the Ni-mediated C–N bond oxidative addition transition states (TS30 vs TS39) favor the naphthyl C–N bond cleavage (Scheme 4a). This is because the d(nickel)– $\pi^*$ -

с



Figure 2. (a) DFT-computed free energy profile of the Ni/PCy<sub>3</sub>-catalyzed Kumada coupling of 1i. (b) Overall C–N bond cleavage barriers of 1i and 1d compared with the separate Ni(PCy<sub>3</sub>)<sub>2</sub> catalyst and amine substrate; free energy barriers are given in parentheses.

Scheme 4. Controlling Factors for Selected C–N Bond Cleavages



(arene) interaction is stronger with extended  $\pi$  system.<sup>21</sup> Comparing the naphthyl C–N bond cleavages of **1i** and **1d**, we found that the Boc protecting group promotes the C–N bond cleavage by weakening the intrinsic bond strength. The substituents of nitrogen can affect the C–N bond cleavage barrier by changing either the nickel–nitrogen interaction or the intrinsic strength of C–N bond. With the Boc substituent, the coordination ability of amino group to Ni(II) is actually

lower based on the heterolytic bond dissociation energy (HBDE) of Ni–N bond (43 vs. 44, Scheme 4b), which is contradictory to the trend of C–N bond cleavage barrier. Therefore, the Boc group facilitates the C–N bond cleavage by weakening the intrinsic bond strength. This is indeed reflected by the HBDE of the corresponding C–N bonds. The HBDE of the C(naphthyl)–N bond of 1i is 208.7 kcal/mol, while that of 1d is 228.9 kcal/mol (Scheme 4c).<sup>22</sup>

In summary, we have developed the first nickel-catalyzed Kumada coupling of *N*-Boc-protected aromatic amines by cleavage of aryl C–N bonds. Selective conversion of aryl C–N bonds into C–C bonds was realized under mild reaction conditions in the absence of an *ortho* directing group on the aniline substrates. The mechanistic studies by DFT calculations have revealed that the insertion of nickel complex into aryl C–N bonds is the rate-limiting step, and the Boc activation is important for the C–N bond cleavage via weakening of the intrinsic bond strength. The investigations of other cross-coupling reactions for the construction of C–C bonds with more challenging aryl C–N bonds are ongoing in our laboratory.

### ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b00242.

Experimental procedures and characterization data (PDF)

### AUTHOR INFORMATION

### Corresponding Authors

\*E-mail: hxchem@zju.edu.cn.

\*E-mail: jibaoxia@licp.cas.cn.

### ORCID ©

Xin Hong: 0000-0003-4717-2814 Ji-Bao Xia: 0000-0002-2262-5488

#### Notes

The authors declare no competing financial interest.

### ACKNOWLEDGMENTS

We acknowledge financial support from NNSFC (J.-B. X., 21772208; J.C., 21702212; X.H., 21702182), NSFC of Jiangsu Province (J.-B.X., BK20161260), the Hundred-Talented Program of the Chinese Academy of Sciences (J.-B.X.), LICP (J.-B.X), the Chinese "Thousand Youth Talents Plan" (X.H.), "Fundamental Research Funds for the Central Universities" (X.H.), and Zhejiang University (X.H.). Calculations were performed on the high-performance computing system at the Department of Chemistry, Zhejiang University.

### REFERENCES

(1) The Chemistry of Anilines, Parts 1-2; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 2007.

(2) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. Rational Development of Practical Catalysts for Aromatic Carbon-Nitrogen Bond Formation. Acc. Chem. Res. 1998, 31, 805-818. (b) Hartwig, J. F. Carbon-Heteroatom Bond-Forming Reductive Eliminations of Amines, Ethers, and Sulfides. Acc. Chem. Res. 1998, 31, 852-860. (c) Ma, D.; Cai, Q. Copper/Amino Acid Catalyzed Cross-Couplings of Aryl and Vinyl Halides with Nucleophiles. Acc. Chem. Res. 2008, 41, 1450-1460. (d) Jiao, J.; Murakami, K.; Itami, K. Catalytic Methods for Aromatic C-H Amination: An Ideal Strategy for Nitrogen-Based Functional Molecules. ACS Catal. 2016, 6, 610-633. (e) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. Photoinduced Ullmann C-N Coupling: Demonstrating the Viability of a Radical Pathway. Science 2012, 338, 647. (f) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. Site-Selective Arene C-H Amination via Photoredox Catalysis. Science 2015, 349, 1326. (g) Paudyal, M. P.; Adebesin, A. M.; Burt, S. R.; Ess, D. H.; Ma, Z.; Kürti, L.; Falck, J. R. Dirhodium-Catalyzed C-H Arene Amination using Hydroxylamines. Science 2016, 353, 1144. (h) Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; DiRocco, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W. C. Aryl Amination Using Ligand-Free Ni(II) Salts and Photoredox Catalysis. Science 2016, 353, 279. (i) Gao, H.; Zhou, Z.; Kwon, D.-H.; Coombs, J.; Jones, S.; Behnke, N. E.; Ess, D. H.; Kürti, L. Rapid Heteroatom Transfer to Arylmetals Utilizing Multifunctional Reagent Scaffolds. Nat. Chem. 2016, 9, 681. (3) (a) Ouyang, K.; Hao, W.; Zhang, W.-X.; Xi, Z. Transition-Metal-Catalyzed Cleavage of C-N Single Bonds. Chem. Rev. 2015, 115, 12045-12090. (b) Wang, Q.; Su, Y.; Li, L.; Huang, H. Transition-Metal Catalysed C-N Bond Activation. Chem. Soc. Rev. 2016, 45, 1257-1272. (c) Desnoyer, A. N.; Love, J. A. Recent Advances in Well-Defined, Late Transition Metal Complexes That Make and/or Break C-N, C-O and C-S Bonds. Chem. Soc. Rev. 2017, 46, 197-238

(4) Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of Organic Molecules. Acc. Chem. Res. 2003, 36, 255-263.

(5) (a) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. Diazonium Salts as Substrates in Palladium-Catalyzed Cross-Coupling Reactions. *Chem. Rev.* 2006, 106, 4622–4643. (b) Li, G.; Chen, Y.; Xia, J. Progress on Transition-Metal-Catalyzed Cross-coupling Reactions of Ammonium Salts via C–N Bond Cleavage. *Youji Huaxue* 2018, 38, 1949–1962. (c) Wenkert, E.; Han, A.-L.; Jenny, C.-J. Nickel-induced conversion of carbon-nitrogen into carbon-carbon bonds. One-step transformations of aryl, quaternary ammonium salts into alkylarenes and biaryls. *J. Chem. Soc., Chem. Commun.* 1988, 975–976. (d) Blakey, S. B.; MacMillan, D. W. C. The First Suzuki Cross-Couplings of Aryltrimethylammonium Salts. *J. Am. Chem. Soc.* 2003, 125, 6046–6047. (e) Reeves, J. T.; Fandrick, D. R.; Tan, Z.;

Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. Room Temperature Palladium-Catalyzed Cross Coupling of Aryltrimethylammonium Triflates with Aryl Grignard Reagents. *Org. Lett.* **2010**, *12*, 4388– 4391. (f) Xie, L.-G.; Wang, Z.-X. Nickel-Catalyzed Cross-Coupling of Aryltrimethylammonium Iodides with Organozinc Reagents. *Angew. Chem., Int. Ed.* **2011**, *50*, 4901–4904. (g) Wang, D.-Y.; Kawahata, M.; Yang, Z.-K.; Miyamoto, K.; Komagawa, S.; Yamaguchi, K.; Wang, C.; Uchiyama, M. Stille coupling via C–N bond cleavage. *Nat. Commun.* **2016**, *7*, 12937–12945.

(6) (a) Bonanno, J. B.; Henry, T. P.; Neithamer, D. R.; Wolczanski, P. T.; Lobkovsky, E. B. Arylamine C–N Bond Oxidative Addition to  $(silox)_3$ Ta  $(silox = {}^{t}Bu_3SiO)$ . J. Am. Chem. Soc. **1996**, 118, 5132–5133. (b) Man, W.-L.; Xie, J.; Pan, Y.; Lam, W. W. Y.; Kwong, H.-K.; Ip, K.-W.; Yiu, S.-M.; Lau, K.-C.; Lau, T.-C. C–N Bond Cleavage of Anilines by a (Salen)ruthenium(VI) Nitrido Complex. J. Am. Chem. Soc. **2013**, 135, 5533–5536.

(7) (a) Ueno, S.; Chatani, N.; Kakiuchi, F. Ruthenium-Catalyzed Carbon–Carbon Bond Formation via the Cleavage of an Unreactive Aryl Carbon–Nitrogen Bond in Aniline Derivatives with Organoboronates. *J. Am. Chem. Soc.* **2007**, *129*, 6098–6099. (b) Koreeda, T.; Kochi, T.; Kakiuchi, F. Cleavage of C–N Bonds in Aniline Derivatives on a Ruthenium Center and Its Relevance to Catalytic C–C Bond Formation. *J. Am. Chem. Soc.* **2009**, *131*, 7238–7239. (c) Zhao, Y.; Snieckus, V. Beyond Directed Ortho Metalation: Ruthenium Catalyzed Amide-Directed C<sub>Ar</sub>–N Activation/C–C Coupling Reaction of Anthranilamides with Organoboronates. *Org. Lett.* **2014**, *16*, 3200–3203. (d) Cao, Z.-C.; Xie, S.-J.; Fang, H.; Shi, Z.-J. Ni-Catalyzed Cross-Coupling of Dimethyl Aryl Amines with Arylboronic Esters under Reductive Conditions. *J. Am. Chem. Soc.* **2018**, *140*, 13575–13579.

(8) (a) Koreeda, T.; Kochi, T.; Kakiuchi, F. Ruthenium-Catalyzed Reductive Deamination and Tandem Alkylation of Aniline Derivatives. *J. Organomet. Chem.* **2013**, 741–742, 148–152. (b) Koreeda, T.; Kochi, T.; Kakiuchi, F. Substituent Effects on Stoichiometric and Catalytic Cleavage of Carbon–Nitrogen Bonds in Aniline Derivatives by Ruthenium–Phosphine Complexes. *Organometallics* **2013**, *32*, 682–690.

(9) Kondo, H.; Akiba, N.; Kochi, T.; Kakiuchi, F. Ruthenium-Catalyzed Monoalkenylation of Aromatic Ketones by Cleavage of Carbon–Heteroatom Bonds with Unconventional Chemoselectivity. *Angew. Chem., Int. Ed.* **2015**, *54*, 9293–9297.

(10) (a) Tobisu, M.; Nakamura, K.; Chatani, N. Nickel-Catalyzed Reductive and Borylative Cleavage of Aromatic Carbon-Nitrogen Bonds in N-Aryl Amides and Carbamates. J. Am. Chem. Soc. 2014, 136, 5587-5590. (b) Cao, Z.-C.; Li, X.-L.; Luo, Q.-Y.; Fang, H.; Shi, Z.-J. Direct Borylation of Tertiary Anilines via C-N Bond Activation Org. Org. Lett. 2018, 20, 1995-1998.

(11) Cong, X.; Fan, F.; Ma, P.; Luo, M.; Chen, H.; Zeng, X. Low-Valent, High-Spin Chromium-Catalyzed Cleavage of Aromatic Carbon–Nitrogen Bonds at Room Temperature: A Combined Experimental and Theoretical Study. J. Am. Chem. Soc. 2017, 139, 15182–15190.

(12) (a) Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. Conversion of Amides to Esters by the Nickel-Catalysed Activation of Amide C–N Bonds. *Nature* **2015**, *524*, 79–83. (b) Li, X.; Zou, G. Acylative Suzuki Coupling of Amides: Acyl-nitrogen Activation via Synergy of Independently Modifiable Activating Groups. *Chem. Commun.* **2015**, *51*, 5089–5092. (c) Meng, G.; Szostak, M. Sterically Controlled Pd-Catalyzed Chemoselective Ketone Synthesis via N–C Cleavage in Twisted Amides. *Org. Lett.* **2015**, *17*, 4364–4367. (d) Meng, G.; Szostak, M. General Olefin Synthesis by the Palladium-Catalyzed Heck Reaction of Amides: Sterically Controlled Chemoselective N $\Box$ C Activation. *Angew. Chem., Int. Ed.* **2015**, *54*, 14518–14522.

(13) For reveiws, see: (a) Liu, C.; Szostak, M. Twisted Amides: From Obscurity to Broadly Useful Transition-Metal-Catalyzed Reactions by N-C Amide Bond Activation. *Chem. - Eur. J.* 2017, 23, 7157-7173. (b) Gao, Y.; Ji, C.-L.; Hong, X. Ni-Mediated C-N Activation of Amides and Derived Catalytic Transformations. *Sci.* 

China: Chem. 2017, 60, 1413-1424. (c) Dander, J. E.; Garg, N. K. Breaking Amides using Nickel Catalysis. ACS Catal. 2017, 7, 1413-1423. (d) Meng, G.; Szostak, M. N-Acyl-Glutarimides: Privileged Scaffolds in Amide N-C Bond Cross-Coupling. Eur. J. Org. Chem. 2018, 2018, 2352-2365. (e) Shi, S.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)-NHC Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective N-C/O-C Cleavage. Acc. Chem. Res. 2018, 51, 2589-2599. Selected recent examples: (f) Hu, j.; Zhao, Y.; Liu, J.; Zhang, Y.; Shi, Z. Nickel-Catalyzed Decarbonvlative Borylation of Amides: Evidence for Acyl C-N Bond Activation. Angew. Chem., Int. Ed. 2016, 55, 8718-8722. (g) Medina, J. M.; Moreno, J.; Racine, S.; Du, S.; Garg, N. K. Mizoroki-Heck Cyclizations of Amide Derivatives for the Introduction of Quaternary Centers. Angew. Chem., Int. Ed. 2017, 56, 6567-6571. (h) Yue, H.; Guo, L.; Lee, S.-C.; Liu, X.; Rueping, M. Selective Reductive Removal of Ester and Amide Groups from Arenes and Heteroarenes through Nickel-Catalyzed C-O and C-N Bond Activation. Angew. Chem., Int. Ed. 2017, 56, 3972-3976. (i) Walker, J. A.; Vickerman, K. L.; Humke, J. N.; Stanley, L. M. Ni-Catalyzed Alkene Carboacylation via Amide C-N Bond Activation. J. Am. Chem. Soc. 2017, 139, 10228-10231. (j) Hu, J.; Wang, M.; Pu, X.; Shi, Z. Nickel-catalysed Cetrohydroamidocarbonylation of Aliphatic Amides to Olefins. Nat. Commun. 2017, 8, 14993. (k) Ji, C.-L.; Hong, X. Factors Controlling the Reactivity and Chemoselectivity of Resonance Destabilized Amides in Ni-Catalyzed Decarbonylative and Nondecarbonylative Suzuki-Miyaura Coupling. J. Am. Chem. Soc. 2017, 139, 15522-15529.

(14) (a) Liu, C.; Li, G.; Shi, S.; Meng, G.; Lalancette, R.; Szostak, R.; Szostak, M. Acyl and Decarbonylative Suzuki Coupling of N-Acetyl Amides: Electronic Tuning of Twisted, Acyclic Amides in Catalytic Carbon-Nitrogen Bond Cleavage. ACS Catal. 2018, 8, 9131-9139. (b) Lei, P.; Meng, G.; Shi, S.; Ling, Y.; An, J.; Szostak, R.; Szostak, M. Suzuki-Miyaura Cross-Coupling of Amides and Esters at Room Temperature: Correlation with Barriers to Rotation around C-N and C-O Bonds. Chem. Sci. 2017, 8, 6525-6530. (c) Lei, P.; Meng, G.; Szostak, M. General Method for the Suzuki-Miyaura Cross-Coupling of Amides Using Commercially Available, Air- and Moisture-Stable Palladium/NHC (NHC = N-Heterocyclic Carbene) Complexes. ACS Catal. 2017, 7, 1960-1965. (d) Weires, N. A.; Baker, E. L.; Garg, N. K. Nickel-catalysed Suzuki-Miyaura Coupling of Amides. Nat. Chem. 2016, 8, 75-79. (e) Liu, C.; Meng, G.; Liu, Y.; Liu, R.; Lalancette, R.; Szostak, R.; Szostak, M. N-Acylsaccharins: Stable Electrophilic Amide-Based Acyl Transfer Reagents in Pd-Catalyzed Suzuki-Miyaura Coupling via N-C Cleavage. Org. Lett. 2016, 18, 4194-4197. (f) Meng, G.; Shi, S.; Szostak, M. Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling of Amides via Site-Selective N-C Bond Cleavage by Cooperative Catalysis. ACS Catal. 2016, 6, 7335-7339. (g) Shi, S.; Szostak, M. Nickel-Catalyzed Diaryl Ketone Synthesis by N-C Cleavage: Direct Negishi Cross-Coupling of Primary Amides by Site-Selective N,N-Di-Boc Activation. Org. Lett. 2016, 18, 5872-5875. (h) Cui, M.; Chen, Z.; Liu, T.; Wang, H.; Zeng, Z. N-Acylsuccinimides: Efficient Acylative Coupling Reagents in Palladiumcatalyzed Suzuki Coupling via C-N cleavag. Tetrahedron Lett. 2017, 58, 3819-3822. (i) Huang, P.-Q.; Chen, H. Ni-Catalyzed Cross-Coupling Reactions of N-Acylpyrrole-type Amides with Organoboron Reagents. Chem. Commun. 2017, 53, 12584-12587. (j) Liu, C.; Liu, Y.; Liu, R.; Lalancette, R.; Szostak, R.; Szostak, M. Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling of N-Mesylamides by N-C Cleavage: Electronic Effect of the Mesyl Group. Org. Lett. 2017, 19, 1434-1437. (k) Boit, T. B.; Weires, N. A.; Kim, J.; Garg, N. K. Nickel-Catalyzed Suzuki-Miyaura Coupling of Aliphatic Amides. ACS Catal. 2018, 8, 1003-1008.

(15) Pauling, L. The Nature of the Chemical Bond. Application of Results Obtained from the Quantum Mechanics and from a Theory of Paramagnetic Susceptibility to The Structure of Molecules. *J. Am. Chem. Soc.* **1931**, *53*, 1367–1400.

(16) For reviews, see: (a) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. Exploration of New C-O Electrophiles in Cross-Coupling Reactions. *Acc. Chem. Res.* **2010**, *43*, 1486–1495. (b) Rosen, B. M.; Quasdorf, K. W.;

Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. Nickel-Catalyzed Cross-Couplings Involving Carbon-Oxygen Bonds. *Chem. Rev.* 2011, 111, 1346–1416. (c) Mesganaw, T.; Garg, N. K. Niand Fe-Catalyzed Cross-Coupling Reactions of Phenol Derivatives. *Org. Process Res. Dev.* 2013, 17, 29–39. (d) Su, B.; Cao, Z.-C.; Shi, Z.-J. Exploration of Earth-Abundant Transition Metals (Fe, Co, and Ni) as Catalysts in Unreactive Chemical Bond Activations. *Acc. Chem. Res.* 2015, 48, 886–896. (e) Tobisu, M.; Chatani, N. Cross-Couplings Using Aryl Ethers via C-O Bond Activation Enabled by Nickel Catalysts. *Acc. Chem. Res.* 2015, 48, 1717–1726.

(17) For selected examples, see: (a) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. Nickel-Induced Conversion of Carbon-Oxygen into Carbon-Carbon Bonds. One-step Transformations of Enol Ethers into Olefins and Aryl Ethers into Biaryls. J. Am. Chem. Soc. 1979, 101, 2246-2247. (b) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. Ruthenium-Catalyzed Functionalization of Aryl Carbon-Oxygen Bonds in Aromatic Ethers with Organoboron Compounds. J. Am. Chem. Soc. 2004, 126, 2706-2707. (c) Dankwardt, J. W. Nickel-Catalyzed Cross-Coupling of Aryl Grignard Reagents with Aromatic Alkyl Ethers: An Efficient Synthesis of Unsymmetrical Biaryls. Angew. Chem., Int. Ed. 2004, 43, 2428-2432. (d) Tobisu, M.; Shimasaki, T.; Chatani, N. Nickel-Catalyzed Cross-Coupling of Aryl Methyl Ethers with Aryl Boronic Esters. Angew. Chem., Int. Ed. 2008, 47, 4866-4869. (e) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. Biaryl Construction via Ni-Catalyzed C-O Activation of Phenolic Carboxylates. J. Am. Chem. Soc. 2008, 130, 14468-14470. (f) Quasdorf, K. W.; Tian, X.; Garg, N. K. Cross-Coupling Reactions of Aryl Pivalates with Boronic Acids. J. Am. Chem. Soc. 2008, 130, 14422-14423. (g) Yu, D. G.; Li, B. J.; Zheng, S. F.; Guan, B. T.; Wang, B. Q.; Shi, Z. J. Direct Application of Phenolic Salts to Nickel-Catalyzed Cross-Coupling Reactions with Aryl Grignard Reagents. Angew. Chem., Int. Ed. 2010, 49, 4566-4570.

(18) Full computational details and complete references of Gaussian and computational methods are included in the Supporting Information.

(19) The possibility of a Ni(I)/(III) redox cycle can not be ruled out for this reaction, particularly in the case of using NHC-Ni catalysts in Scheme 2. See: Zhang, K.; Conda-Sheridan, M.; Cooke, S. R.; Louie, J. N-Heterocyclic Carbene Bound Nickel(I) Complexes and Their Roles in Catalysis. *Organometallics* **2011**, *30*, 2546–2552.

(20) The detailed free energy changes of the three C–N bond cleavage pathways are included in the Supporting Information (Figure S1).

(21) Frenking, G.; Fröhlich, N. The Nature of the Bonding in Transition-Metal Compounds. *Chem. Rev.* **2000**, *100*, 717–774.

(22) The C–N bond dissociation of amine has significant heterolytic character. Detailed charge analysis is included in the Supporting Information (Figure S2).