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NHC-Nickel Catalyzed C−N Bond Cleavage of Mono-protected Anilines for C−C Cross-Coupling

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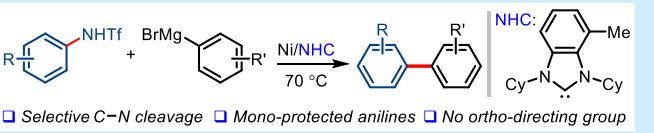
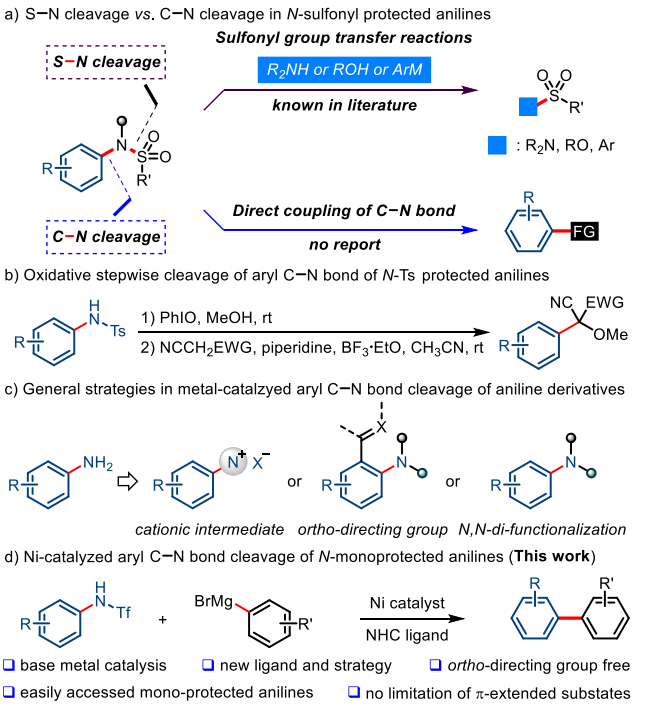
ABSTRACT: A Ni-catalyzed aryl C−N bond cleavage of mono-protected anilines, *N*-arylsulfonamides, has been developed. A new *N*-heterocyclic carbene derived from benzoimidazole shows high reactivity for the C−N cleavage/C−C cross-coupling reaction. The *ortho*-directing group is not required to break the C−N bond of sulfonyl-protected anilines, which are not limited to π-extended anilines. The mechanistic studies have revealed that a sulfamidomagnesium salt is the key coupling intermediate.



The sulfonamide is one of the ubiquitous functional groups in organic and medicinal chemistry.[1] As a robust and extensively utilized protecting group for amines, sulfonamide is a useful synthetic intermediate.[2] For instance, *N*-arylsulfonamides, easily accessed from anilines, have been used as sulfonyl group transfer reagents for protection of amines and alcohols (Scheme 1a).[3] Meanwhile, addition of Grignard or organic lithium reagents to sulfonamides produces sulfones by S−N bond cleavage.[4] Obviously, the S−N bond in sulfonamides is a much weaker chemical bond, which is more easily broken. In comparison, cleavage of the C−N bond in the *N*-arylsulfonamides is rare and challenging.[5] Remarkably, Fan and co-workers developed an interesting stepwise oxidative aromaticity destruction−reconstruction process for the cleavage of *N*-Ts anilines to form a C−C bond (Scheme 1b).[6] To the best of our knowledge, there is no precedent example for metal-mediated coupling of the C−N bond in *N*-arylsulfonamides to form a C−C or C−heteroatom bond.

Scheme 1. Selective Cleavage of S−N or C−N Bond in *N*-Arylsulfonamides



The formation of an aryl C−N bond is among the central topics in modern synthetic chemistry.[7] Inversely, The transformation of neutral aryl C−N bonds to other chemical bonds is rarely investigated because they are chemically inert.[8] Conventionally, the methods used to break aryl C−N bonds usually involve highly reactive cationic compounds, such as diazonium and ammonium salts (Scheme 1c).[9] Because of the strong coordinating ability of both aniline and its anionic amino species (R_2N^-), metal-mediated cleavage of the neutral aryl C−N bond is more difficult in the absence of a directing group on anilines.[10] In the past decade, a progressive *ortho*-directing group assisted strategy has been developed by Kakiuchi,[11] Snieckus,[12] Zeng,[13] Szostak,[14] and Wu et al.[15] for the metal-catalyzed cross-coupling of neutral aryl C−N bonds. As a limitation, additional manipulations are needed for prior installation of the *ortho*-directing group on the anilines and for its removal after the reactions. Impressively, Ni-catalyzed cross-coupling of the neutral aryl C−N bond in the absence of an *ortho*-directing group has been achieved by Chatani,[16] Shi,[17] and our group.[18] However, these reactions are restricted to π-

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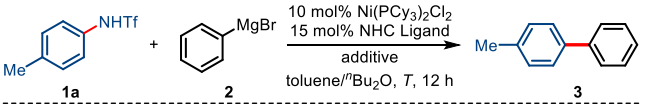
extended anilines with *N*,*N*-diprotection. To date, there is no report for coupling of the aryl C−N bond in simple NH-containing anilines in the absence of a directing group.

Direct aryl C−N bond cleavage of mono-protected anilines (ArNHR) is know to face several challenges. First, a formidable enthalpy barrier is encountered.[10] Second, because of the presence of a free amine (NH) group, mono-protected anilines are prone to amination under metal catalysis.[19] To solve these problems, we anticipated to introduce an electron-withdrawing protecting group onto the nitrogen of aniline. First, this type of protecting group would weaken the intrinsic bond strength of the aryl C−N bond. Second, due to the acidity of the NH being increased by the electron-withdrawing protecting group, the corresponding amido salt would be formed easily in the presence of a suitable deprotonation reagent. Then, the aryl C−N bond might be further activated by the formation of amido salt. In addition, the amido anion has a good σ-donor ability, which may bind to the metal catalyst to activate the aryl C−N bond. Thus, the selective cleavage of the aryl C−N bond of simple anilines in the absence of a directing group would be achieved. Based on this strategy, we report herein the first nondirected aryl C−N bond cleavage of mono-protected anilines under mild NHC−nickel catalysis (Scheme 1d).

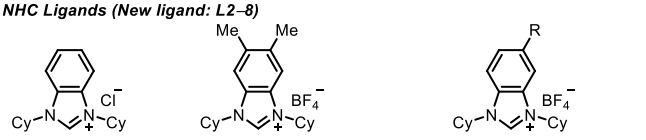
We started the research by investigating the aryl C−N bond cleavage of trifluoromethanesulfonyl (Tf) protected *p*-toluidine **1a** under nickel catalysis. With PhMgBr **2** as both a coupling and deprotonation reagent, a trace amount of desired biaryl product **3** was observed with $Ni(PCy_3)_2Cl_2$ as catalyst and toluene and THF as mixed solvent at 130 °C (Table 1, entry 1; for details, see Table S1 in Supporting Information). Different ligands were then tested, and **3** was obtained in 24% yield with *N*-heterocyclic carbene (NHC) precursor ICy·HCl (Table 1, entry 2). The yield of **3** was increased to 30% when switching the mixed solvent to toluene/^{n}Bu$_2$O (Table 1, entry 3). Further improvement was observed when the NHC precursor benzimidazolium salt (**L1**) was employed, which gave rise to the desired product **3** in 67% yield (Table 1, entry 4). Then, new NHC ligands **L2**−**8** were designed and synthesized by modification of the ligand **L1** with assembly of a methyl, *tert*-butyl, or phenyl group at its 4-, 5-, 6-, and/or 7-position to enhance the σ-donor ability of the ligand. After screening these new NHC ligands, we found that ligand **L7** with a methyl group at 4-position improved the yield of **3** to 78% (Table 1, entry 10). Subsequently, an attempt to lower the dosage of Grignard reagent to 3 equiv led to a significant decrease in the yield of product **3** (Table 1, entry 12). However, when 2 equiv of MeMgBr were used as an additive, product **3** was obtained in 65% yield with 3 equiv of PhMgBr (Table 1, entry 13). The yield was not improved by addition of a catalytic amount of organic base, such as DABCO (Table 1, entry 14). A further increase of the reaction scale and evaluation of the reaction temperature showed that the yield of **3** was improved to 86% with 0.2 mmol of **1a** at 70 °C (Table 1, entry 16). Finally, **3** was obtained in 82% yield with $Ni(cod)_2$ as the catalyst precursor, indicating that an active NHC-Ni(0) catalyst may exit in the catalytic cycle (Table 1, entry 17).

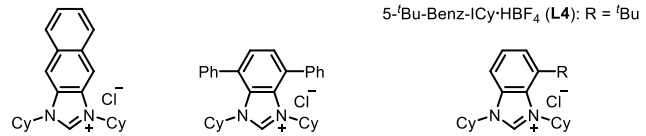
Then, we investigated different protecting groups on the nitrogen of 4-methylaniline in this Ni-catalyzed nondirected C−N cleavage/C−C cross-coupling reaction (Scheme 2). It comes as no surprise that no reaction occurred with *N*-methyl aniline **1b**. A lower yield was observed with *N*-pivaloyl or *N*-pivalate protected 4-methylaniline as substrate (**1c** and **1d**). However, no reaction occurred with aniline bearing a *N*-methanesulfonyl or *N*- benzenesulfonyl group on the nitrogen (**1e** and **1f**). When we used the *N*-Me-*N*-Tf-aniline **1g** as substrate, **3** was obtained in 35%yield. These results suggest

Table 1. Reaction Development[a]



NHC Ligands (New ligand: L2–8)

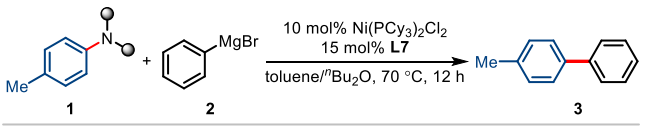


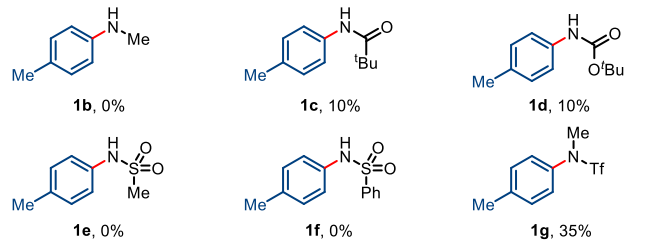


Entry	Ligand	Additive (x equiv)	T (°C)	Yield[b] (%)
1[c]	–	–	130	trace
2[c]	ICy·HCl	–	130	24
3	ICy·HCl	–	130	30
4	**L1**	–	130	67
5	**L2**	–	130	57
6	**L3**	–	130	6
7	**L4**	–	130	17
8	**L5**	–	130	6
9	**L6**	–	130	16
10	**L7**	–	130	78
11	**L8**	–	130	68
12[d]	**L7**	–	130	8
13[d]	**L7**	MeMgBr (2)	130	65
14[d]	**L7**	MeMgBr (2), DABCO (0.25)	130	66
15[e]	**L7**	–	130	84
16[e]	**L7**	–	**70**	**86**
17[e,f]	**L7**	–	70	82

[a]All reactions were carried out with **1a** (0.1 mmol) and **2** (0.5 mmol) if otherwise noted. [b]Determined by GC with *n*-dodecane as an internal standard. [c]With toluene/THF (1 mL/1 mL) as solvent. [d]With **2** (0.3 mmol). [e]With **1** (0.2 mmol), **2** (1.0 mmol). [f]With $Ni(cod)_2$ (10 mol %) as catalyst.

Scheme 2. *N*-Substituent Effect on the Anilines[a]





[a]Conditions: **1** (0.2 mmol), **2** (1.0 mmol), $Ni(PCy_3)_2Cl_2$ (10 mol %), **L7** (15 mol %), toluene/^{n}Bu$_2$O (1 mL/1 mL), 70 °C, 12 h, and the yield was determined by GC with *n*-dodecane as an internal standard.

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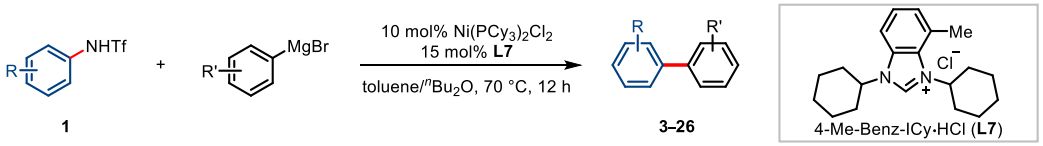
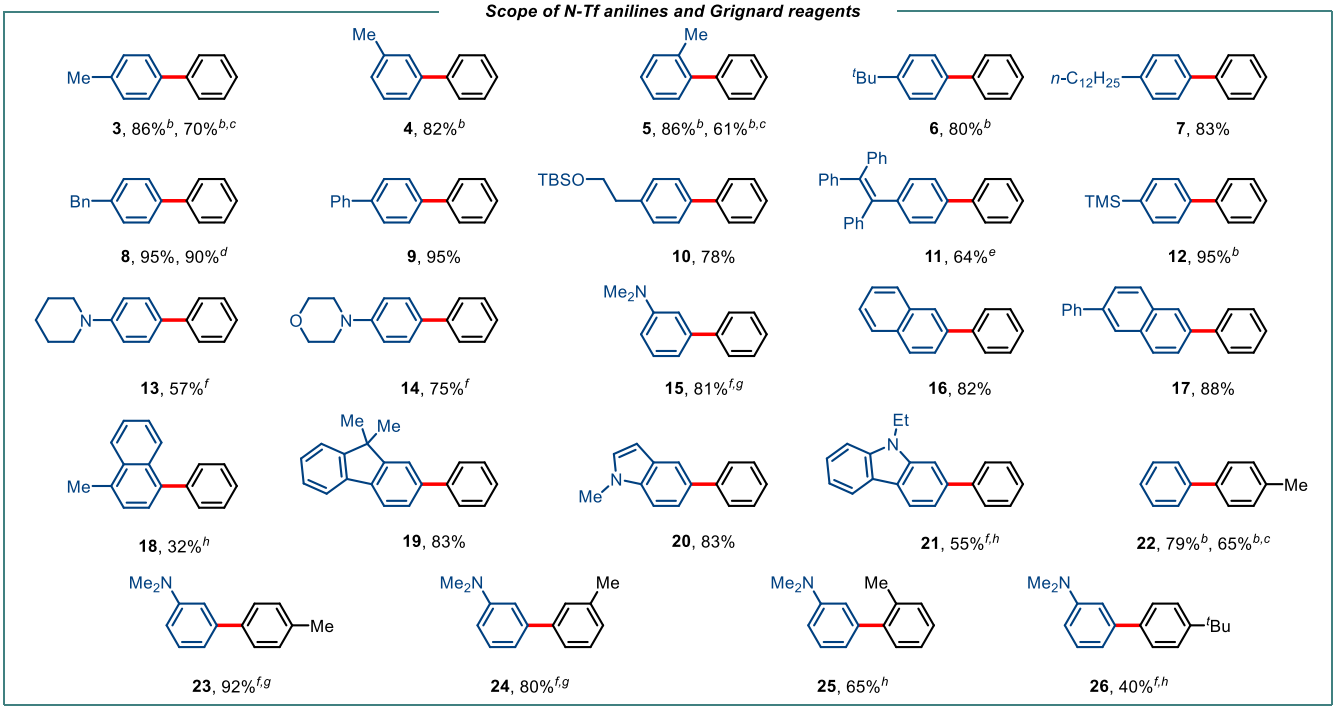
Scheme 3. Reaction Scope[a]





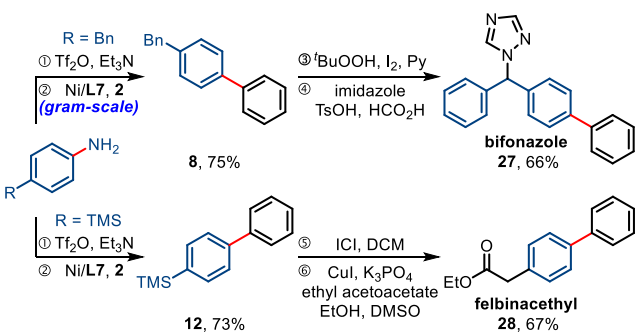
[a]All reactions were run with **1** (0.2 mmol) and ArMgBr (1.0 mmol) in toluene/^{n}Bu$_2$O (1 mL/1 mL), isolated yield. [b]Determined by GC with *n*-dodecane as an internal standard. [c]With **1** (0.2 mmol), ArMgBr (0.6 mmol), MeMgBr (0.6 mmol). [d]Gram scale. [e]24 h. [f]36 h. [g]90 °C. [h]130 °C.

that the *N*-trifluoromethylsulfonyl (*N*-Tf) group as a strong electron-withdrawing group may feature an activation group to weaken the aryl C−N bond strength and enhance the acidity of NH to form an amido salt intermediate.

Having identified conditions to achieve the selective aryl C−N bond cleavage, we evaluated the Ni-catalyzed C−C coupling of *N*-Tf-anilines with Grignard reagents (Scheme 3). First, we test the reactivity of different anilines with a methyl substituent at the *para-*, *meta-*, or *ortho*-position, affording the biaryl products **3**−**5** in good yields (82−86%). Next, the cross-coupling of aniline substrates bearing an alkyl substituent, such as *tert*-butyl, *n*-dodecyl, and benzyl, at the *para*-position was conducted, and the desired biaryl products **6**−**8** were obtained in 80−95% yields. In addition, a variety of functionalities were tolerated on the aniline, such as phenyl, functionalized alkyl, alkenyl, and silyl groups, leading to the corresponding biaryls **9**−**12** in moderate to excellent yields (64−95%). Remarkably, selective cleavage of the aryl C−N bond of *N*-Tf-anilines was achieved affording the corresponding products **13**−**15** in 57−81% yield, with the *N*,*N*-dialkyl group on the benzene ring untouched. The cross-coupling of the C−N bond in π-extended 2-naphthylamine also occurred smoothly delivering **16**−**17** in good yields. Moreover, the cleavage of the *N*-containing heteroaryl C−N bond, such as 5-indolamine and 2-carbazolamine, took place selectively leading to the corresponding products **20** and **21** in 83% and 55% yield. Furthermore, the coupling of aromatic Grignard reagents containing alkyl substituents at the *para-*, *meta-*, or *ortho*-position of benzene ring with aryl C−N bonds occurred smoothly, giving the biaryl products **22**−**26** in moderate to good yields (40−92%). Unfortunately, no reaction occurred when alkenyl or alkyl Grignard reagents were used in this Ni-catalyzed nondirected C−N cleavage/C−C cross-coupling reaction.

Biaryls are ubiquitous core structures in drug molecules, such as antifungal bifonazole (**27**) and antiphlogistic analgesic felbinacethyl (**28**). Gram-scale synthesis of biaryl **8** was achieved in 75% total yield in two steps through mono-protection of 4-benzylaniline with Tf_2O and our Ni-catalyzed cross-coupling of *N*-Tf-aniline with PhMgBr via C−N bond cleavage (Scheme 4). Subsequently, benzylic oxidation of **8** to ketone followed by Eschweiler−Clarke reductive alkylation of imidazole delivered **27** in 66% yield. Similarly, the biaryl **12** was

Scheme 4. Synthetic Applications



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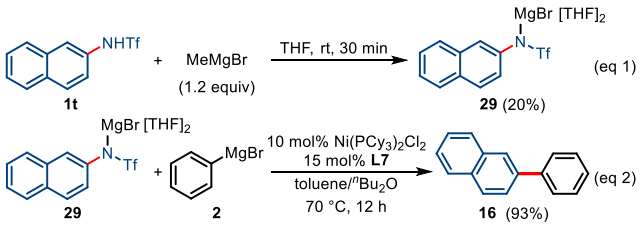
obtained in 73% yield over two steps via mono-protection of 4-(trimethylsilyl)aniline followed by Ni-catalyzed cross-coupling via C−N bond cleavage. Then, desilylative iodination of **12** led to the corresponding aryl iodide, which was subjected to the Cu-catalyzed α-arylation of ethyl acetoacetate generating **28** in 67% yield after deaceylation.

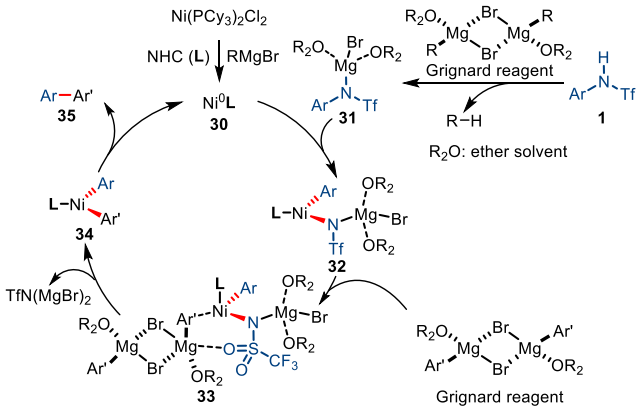
Control experiments have been conducted to understand the reaction mechanism. Based on our previous computational studies on cross-coupling of the aryl C−N bond with a Grignard reagent[18] and the conditions used for the current reaction, this reaction should take place via a Ni(0)/Ni(II) catalytic pathway. We attempted to verify the starting reactant in the catalytic cycle. The NH-containing sulfonamide could be deprotonated easily to form a sulfamidomagnesium salt in the presence of Grignard reagent. To capture the sulfamidomagnesium salt intermediate, deprotonation of *N*-Tf-2-naphthalenamine (**1t**) was performed with MeMgBr in THF. As expected, the corresponding sulfamidomagnesium salt **29** was isolated with two coordinated THF molecules (monomer or dimer), which was confirmed by ^{1}H NMR (eq 1). Then, the cross-



coupling of **29** with PhMgBr afforded **16** in 93% isolated yield (eq 2). These results indicate that the monomeric sulfamidomagnesium salt is a key intermediate in this aryl C−N bond cross-coupling reaction.

Based on the mechanistic studies, a possible catalytic pathway is proposed as shown in Scheme 5. In the presence of an NHC

Scheme 5. Proposed Catalytic Pathway



ligand and Grignard reagent, the nickel catalyst precursor $Ni(PCy_3)_2Cl_2$ is first reduced to NHC coordinated Ni(0) species **30**. Meanwhile, deprotonation of *N*-Tf-aniline **1** with the Grignard reagent generates sulfamidomagnesium salt **31**. The following oxidative addition of the aryl C−N bond with **30** leads to arylnickel intermediate **32**, which may be facilitated by coordination of nickel catalyst with the magnesium or the ether solvent on the sulfamidomagnesium salt **31**.[20] Subsequent transmetalation with the aryl Grignard reagent generates diarylnickel **34**, which may be through a six-membered transition state **33**. Finally, the C−C bond reductive elimination produces the desired biaryl product **35** and regenerates the NHC-Ni catalyst **30**.

In summary, we have developed the first nickel-catalyzed C−C cross-coupling reaction by aryl C−N bond cleavage of *N*-Tf-anilines with a new NHC ligand (4-Me-Benz-ICy). The *ortho*-directing group is not needed on the aniline substrates. And the aniline substrates are not limited to π-extended aryl amines. The *N*-trifluoromethylsulfonyl (*N*-Tf) group features as an activation group to weaken the aryl C−N bond strength and enhance the acidity of NH to form the amido salt intermediate. Mechanistic studies have revealed that the in situ generated sulfamidomagnesium salt is the key coupling intermediate. We have disclosed a new strategy for the direct cleavage of the neutral aryl C−N bond to synthesize useful biaryl compounds. Further studies based on this strategy are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03660.

Experimental procedures, characterization data for new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Mitchell, M. S. *Biological Interaction of Sulfur Compounds*; CRC Press: Boca Raton, FL, 1996. (b) Shigeru, O.; Tadashi, O. *Organic Sulfur Chemistry: Biochemical Aspects*; CRC Press: Boca Raton, FL, 1992.

(2) Larock, R. C. *Comprehensive Organic Transformations. A Guide to Functional Group Preparations*; Wiley: New York, 1999.

https://dx.doi.org/10.1021/acs.orglett.0c03660
Org. Lett. XXXX, XXX, XXX−XXX

(3) (a) Bengtson, A.; Hallberg, A.; Larhed, M. Fast Synthesis of Aryl Triflates with Controlled Microwave Heating. *Org. Lett.* **2002**, *4*, 1231−1233. (b) Wentworth, A. D.; Wentworth, P.; Mansoor, U. F.; Janda, K. D. A Soluble Polymer-Supported Triflating Reagent: A High-Throughput Synthetic Approach to Aryl and Enol Triflates. *Org. Lett.* **2000**, *2*, 477−480. (c) Satake, A.; Ishii, H.; Shimizu, I.; Inoue, Y.; Hasegawa, H.; Yamamoto, A. Palladium-Catalyzed Ring-Opening Reactions of 1-Acetyl-4-vinyl-2-azetidinones and 1-Sulfonyl-2-vinylazetidines. Role of Intramolecular Participation of Amide Anion. *Tetrahedron* **1995**, *51*, 5331−5340.

(4) (a) Mustafa, A.; Asker, W.; Hishmat, O. H.; Shalaby, A. F. A.; Kamel, M. Action of Grignard Reagents. VI. (a) Cleavage by Organomagnesium and Lithium Compounds and by Lithium Aluminum Hydride; (b) Action of Phenyllithum on Phenanthraquinone and Benzil Monoximes. *J. Am. Chem. Soc.* **1954**, *76*, 5447. (b) Eisch, J. J.; Qian, Y.; Chiu, C. S. Intermediacy of *o*-Sulfonylium Arenide Ylides in the Reactions of Arenesulfonyl Derivatives with Strong Bases: Insight into the Puzzling Rearrangement of *N*-Arylarenesulfonamides into 2-Aminodiaryl Sulfones. *J. Org. Chem.* **1996**, *61*, 1392−1398.

(5) (a) Frank, S.; Guziec, J.; Wei, D. Convenient Halodeamination and Hydrodeamination of Primary Amines. *J. Org. Chem.* **1992**, *57*, 3772−3776. (b) Wang, Y.; Guziec, F. S. A Convenient Reductive Deamination (Hydrodeamination) of Aromatic Amines. *J. Org. Chem.* **2001**, *66*, 8293−8296.

(6) (a) Wang, S. E.; Wang, L.; He, Q.; Fan, R. Destruction and Construction: Application of Dearomatization Strategy in Aromatic Carbon-Nitrogen Bond Functionalization. *Angew. Chem., Int. Ed.* **2015**, *54*, 13655−13658. (b) Han, D.; He, Q.; Fan, R. Formal Group Insertion into Aryl C−N Bonds through An Aromaticity Destruction-Reconstruction Process. *Nat. Commun.* **2018**, *9*, 3423−3429.

(7) (a) Kürti, L.; Czakó, B. VII. Named Organic Reactions in Alphabetical Order. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: London, 2005 (b) Ley, S. V.; Thomas, A. W. Modern Synthetic Methods for Copper-Mediated C(aryl)−O, C(aryl)−N, and C(aryl)−S Bond Formation. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−49. (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) Kruger, K.; Tillack, A.; Beller, M. Recent Innovative Strategies for the Synthesis of Amines: from C−N Bond Formation to C−N Bond Activation. *ChemSusChem* **2009**, *2*, 715−717. (e) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C−N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564−12649. (f) Korch, K. M.; Watson, D. A. Cross-Coupling of Heteroatomic Electrophiles. *Chem. Rev.* **2019**, *119*, 8192−8228.

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

(9) For reviews: (a) Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. Diazonium Salts as Substrates in Palladium-Catalyzed Cross-Coupling Reactions. *Chem. Rev.* **2006**, *106*, 4622−4643. (b) Ouyang, K.; Hao, W.; Zhang, W. X.; Xi, Z. Transition-Metal-Catalyzed Cleavage of C−N Single Bonds. *Chem. Rev.* **2015**, *115*, 12045−12090. (c) Wang, Q.; Su, Y.; Li, L.; Huang, H. Transition-Metal-Catalysed C−N bond Activation. *Chem. Soc. Rev.* **2016**, *45*, 1257−1272. (d) Li, G.; Chen, Y.; Xia, J. Progress on Transition-Metal-Catalyzed Cross-Coupling Reactions of Ammonium Salts via C−N Bond Cleavage. *Chin. J. Org. Chem.* **2018**, *38*, 1949−1962. (e) Wang, Z.-X.; Yang, B. Chemical Transformations of Quaternary Ammonium Salts via C−N Bond Cleavage. *Org. Biomol. Chem.* **2020**, *18*, 1057−1072. Selected examples: (f) Wenkert, E.; Han, A.-L.; Jenny, C.-J. Nickel-Induced Conversion of Carbon−Nitrogen into Carbon−Carbon Bonds. Onestep Transformations of Aryl, Quaternary Ammonium Salts into Alkylarenes and Biaryls. *J. Chem. Soc., Chem. Commun.* **1988**, 975−976. (g) Blakey, S. B.; MacMillan, D. W. C. The First Suzuki Cross−Couplings of Aryltrimethylammonium Salts. *J. Am. Chem. Soc.* **2003**, *125*, 6046−6047. (h) Xie, L.-G.; Wang, Z.-X. Nickel-Catalyzed Cross-Coupling of Aryltrimethylammonium Iodides with Organozinc Reagents. *Angew. Chem., Int. Ed.* **2011**, *50*, 4901−4904. (i) 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. (j) Zhou, Y.; Wang, Y.; Song, Z.; Nakano, T.; Song, Q. Cu-Catalyzed C−N Bond Cleavage of 3-Aminoindazoles for the C−H Arylation of Enamines. *Org. Chem. Front.* **2020**, *7*, 25−29.

(10) Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC: 2002.

(11) (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) 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. (d) Koreeda, T.; Kochi, T.; Kakiuchi, F. Ruthenium-Catalyzed Reductive Deamination and Tandem Alkylation of Aniline Derivatives. *J. Organomet. Chem.* **2013**, *741*, 148−152.

(12) Zhao, Y.; Snieckus, V. Beyond Directed Ortho Metalation: Ruthenium-Catalyzed Amide-Directed C_{Ar}−N Activation/C−C Coupling Reaction of Anthranilamides with Organoboronates. *Org. Lett.* **2014**, *16*, 3200−3203.

(13) (a) 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. (b) Tang, J.; Fan, F.; Cong, X.; Zhao, L.; Luo, M.; Zeng, X. Reductive Cross-Coupling between Unactivated C(aryl)−N and C(aryl)−O Bonds by Chromium Catalysis Using a Bipyridyl Ligand. *J. Am. Chem. Soc.* **2020**, *142*, 12834−12840.

(14) Zhao, Q.; Zhang, J.; Szostak, M. Ruthenium(0)-Catalyzed Cross-Coupling of Anilines with Organoboranes by Selective Carbon−Nitrogen Cleavage. *ACS Catal.* **2019**, *9*, 8171−8177.

(15) (a) Xu, J.-X.; Zhao, F.; Yuan, Y.; Wu, X.-F. Ruthenium-Catalyzed Carbonylative Coupling of Anilines with Organoboranes by the Cleavage of Neutral Aryl C−N Bond. *Org. Lett.* **2020**, *22*, 2756−2760. (b) Xu, J.-X.; Zhao, F.; Franke, R.; Wu, X.-F. Ruthenium-Catalyzed Suzuki Coupling of Anilines with Alkenyl Borates via Selective Aryl C−N bond Cleavage. *Catal. Commun.* **2020**, *140*, 106009.

(16) 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.

(17) (a) 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. Lett.* **2018**, *20*, 1995−1998. (b) 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.

(18) Zhang, Z.-B.; Ji, C.-L.; Yang, C.; Chen, J.; Hong, X.; Xia, J.-B. Nickel-Catalyzed Kumada Coupling of Boc-Activated Aromatic Amines via Nondirected Selective Aryl C−N Bond Cleavage. *Org. Lett.* **2019**, *21*, 1226−1231.

(19) (a) Ilies, L.; Matsubara, T.; Nakamura, E. Nickel-Catalyzed Synthesis of Diarylamines via Oxidatively Induced C−N Bond Formation at Room Temperature. *Org. Lett.* **2012**, *14*, 5570−5573. (b) Nakamura, Y.; Ilies, L.; Nakamura, E. Iron-Catalyzed Oxidative Monoarylation of Primary Amines with Organozinc Reagents. *Org. Lett.* **2011**, *13*, 5998−6001. (c) Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.; Heydari, M.; Malmir, M. Buchwald-Hartwig Reaction: An Overview. *J. Organomet. Chem.* **2018**, *861*, 17−104.

(20) Ogawa, H.; Minami, H.; Ozaki, T.; Komagawa, S.; Wang, C.; Uchiyama, M. How and Why Does Ni(0) Promote Smooth Etheric C−O Bond Cleavage and C−C Bond Formation? A Theoretical Study. *Chem. - Eur. J.* **2015**, *21*, 13904−13908.

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