JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Subscriber access provided by UB + Fachbibliothek Chemie | (FU-Bibliothekssystem)

Communication

Deoxygenation of Ethers to Form Carbon-Carbon Bonds via Nickel Catalysis

Zhi-Chao Cao, and Zhang-Jie Shi

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 26 Apr 2017

Downloaded from http://pubs.acs.org on April 26, 2017

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

ACS Publications

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Deoxygenation of Ethers to Form Carbon-Carbon Bonds *via* Nickel Catalysis

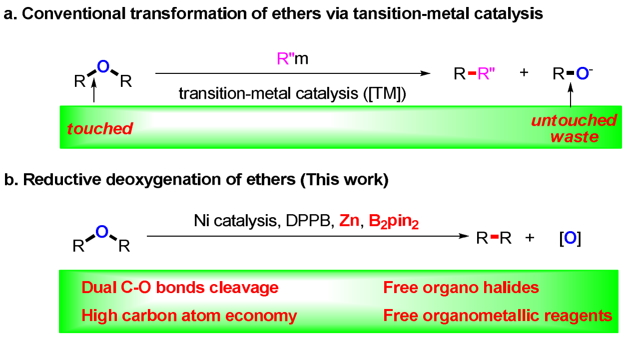
Zhi-Chao Cao,[a] Zhang-Jie Shi*[a,b]

[a] College of Chemistry and Molecular Engineering, Peking University, Beijing 100871 and [b] Department of Chemistry, Fudan University, Shanghai 200433, and State Key Laboratory of Organometallic Chemistry, Chinese Academy of Science, Shanghai 200032, China

Supporting Information Placeholder

ABSTRACT: In this article a successful protocol was developed to construct carbon-carbon bonds by the extrusion of O-atom of ethers *via* nickel catalysis in the presence of reductants. This methodology featured as a high economic route to construct sp^3-sp^3 C-C bonds through dual C-O activation of ethers with good functional group tolerance.

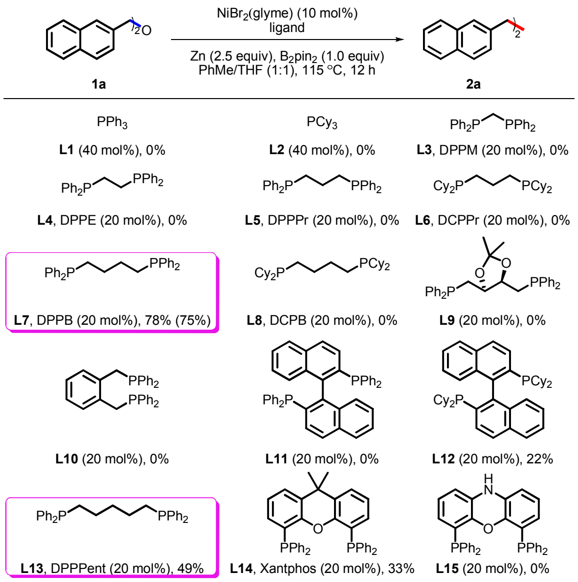
Ethers used as partners in cross-couplings exhibited a myriad of advantages due to their easy availability, stability, and non-toxicity. Recently, efforts to explore the potential utility of ethers, especially aryl ethers[1] and benzyl ethers[2], in cross couplings *via* transition-metal catalysis, have been made. However, in developed cross couplings with ethers, only one part of ether was used and the rest part was discarded with the second C-O bond untouched, to some extent showing the undesirable carbon atom economy (**Scheme 1a**).[3] To solve this problem, our recent focuses were set out to develop new protocols to apply both parts of ethers into organic synthesis through activation of both C-O bonds in one reaction. From this point of view, the deoxygenation of ethers to construct C-C bonds is an ideal choice, which was fundamentally important to investigate the activation of both etheric C-O bonds at different stages under the same conditions (**Scheme 1b**).



Scheme 1, Design of reductive deoxygenation of ethers

Our strategy toward the deoxygenation was based on the reductive couplings, which have been developed as powerful methods to construct carbon-carbon bonds.[4] At current stage, the reductive coupling was used to carry out the transformation of organohalides. Recently, sporadic cases to elucidate the reductive coupling of ethers with organohalides were also reported.[5] To the best of our knowledge, there was no sufficient route of reductive coupling between two etheric C-O electrophiles presented, [5k] especially the proposed deoxygenation of acyclic ethers to date.[6] Compared to the developed reductive couplings, the deoxygenation of ethers faces the following predictable challenges: 1) the cleavage of both C-O bonds of ethers at different stages under the same conditions, especially the C-O bond in the formed alkoxide C-O bonds at the latter stage; 2) the proper O-acceptor to remove the oxygen atom from the ethers.

Table 1, Effects of ligands in deoxygenation reactions [a]



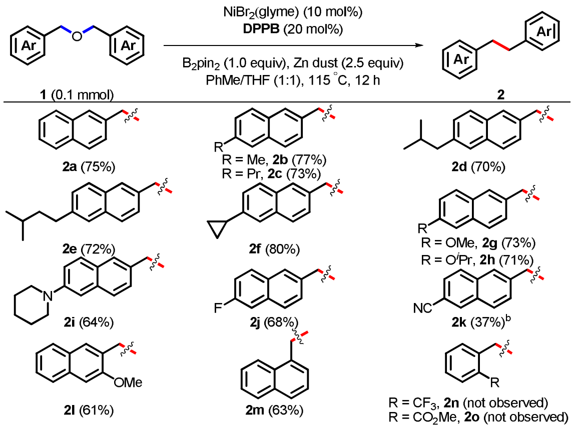
Reaction conditions: a cocktail containing substrate **1a** (0.1 mmol), catalyst NiBr$_2$(glyme) (0.01 mmol), ligand, zinc dust (0.25 mmol), B$_2$pin$_2$ (0.1 mmol) in PhMe/THF (1:1) was heated at 115 ^{o}C for 12 h. [a] NMR yields were reported based on **1a**, and benzo[*d*][1,3]dioxole was used as an internal standard; isolated yields of desired product was reported in parenthesis.

To interview our concept, we chose 2,2'-oxybis(methylene)dinaphthalene (**1a**) as the objective to investigate the designed deoxygenation. According to previous works in C-O activation and reductive coupling, Ni-catalysis was first considered in the presence of different ligand sets. As analyzed above, the proper reductant is required to provide the electrons to facilitate the reduction. The O-receptor was also demanded to remove the O-atom in the ethers. In previous reports, metal powder was usually used in "reductive coupling" as electron donor and halogen scavenger.[5] We also tested different metal powder. After systematical examination of different parameters, such as nickel catalysts, ligands, reductants, and solvents, to our delight, the desired product 1,2-dinaphthylethane **2a** was obtained in 17% NMR yield when 10 mol% $NiBr_2$(glyme) was used as the catalyst in the presence of DPPB as the ligand and zinc powder as an reductant (**Table S1 and S2**).

Considering the poor capability of zinc as an O-scavenger, B_2pin_2 (1.0 equiv) was used as the additive. To our satisfactory, the desired product (**2a**) was obtained in 75% isolated yield. Due to the Lewis acidity of B_2pin_2, it might be beneficial for reorganizing electron density of C-O bond of the ethers and also facilitating the 2nd oxidative addition by coordination. Other lewis acids, such as $AlCl_3$ and B_2nep_2, were tested but failed. This result indicated other effect of B_2pin_2 than a simple Lewis acid[7] (**Table S2**).

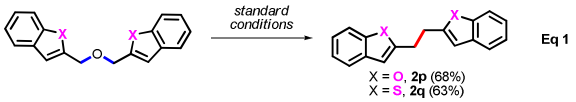
In the presence Zn and B_2pin_2, the effect of ligand was further systematically investigated (**Table 1**). Monodentate phosphine ligands, including PCy_3 (**L2**), which exhibited excellent reactivity to promote the C-O activation in nickel catalysis, were not effective. Various bidentate phosphine ligands with different bite angles were submitted to the catalytic transformation, and the results indicated that bidentate phosphine ligands with large bite angle promote the efficiency[8] (**L3-L7** and **L13**). For example, DPPB (**L7**) promoted the desired product **2a** formation in 78% NMR yield; only 49% NMR yield was obtained when DPPent (**L13**) was employed as the ligand. Furthermore, variants of DPPB and DPPent, such as more electron-efficient DCPB (**L8**), more rigid ligands (**L9-L12** and **L14-L15**) were tested. Unfortunately, none of them showed the better reactivity.

Table 2, Reductive Deoxygenation of dibenzyl ethers [a]

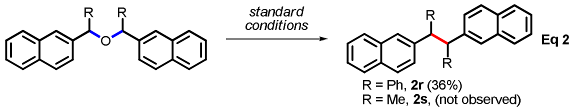


Reaction conditions: a cocktail contain substrate **1** (0.1 mmol), catalyst $NiBr_2$(glyme) (0.01 mmol), ligand, zinc dust (0.25 mmol), B_2pin_2 (0.1 mmol) in PhMe/THF (1:1) was heated at 115 °C for 12 h. [a] isolated yields were reported based on **1**; [b] NMR yield.

Subsequently, the optimal conditions were applied to the deoxygenation of various diarylmethyl ethers (**Table 2**). First of all, we tested the effect of substitutions on the naphthyl ring and found that, both electron-donating and electron-withdrawing substituents did not affect the efficiency (**2a-j**). The substrates bearing different alkyl groups converted to the corresponding targeted products in good to excellent yields. Moreover, cyclopropyl group (**1f**) survived well. The experiments to test the tolerance of sp^2 C-O and C-N bonds were conducted. Notably, various groups were tolerated, which provided another chance to diversify the products through nickel catalyzed cross couplings[2, 9] (**2g**, **2h** and **2l**). Substrate bearing cyano group also exhibited moderate reactivity under standard conditions (**2k**). At last, this deoxygenation also proceeded smoothly with the steric hindered *ortho*-substituent ethers (**2l** and **2m**), albeit in lower yields. Unfortunately, this catalytic system is unable to facilitate the reductive deoxygenation of simple dibenzyl ethers at this stage, even the ethers with electron withdrawing group (**2n**) or directing group (**2o**) at the *ortho*-position.

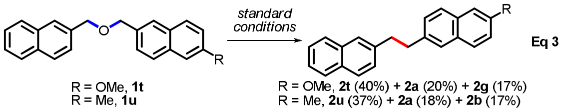


Eq 1



Eq 2

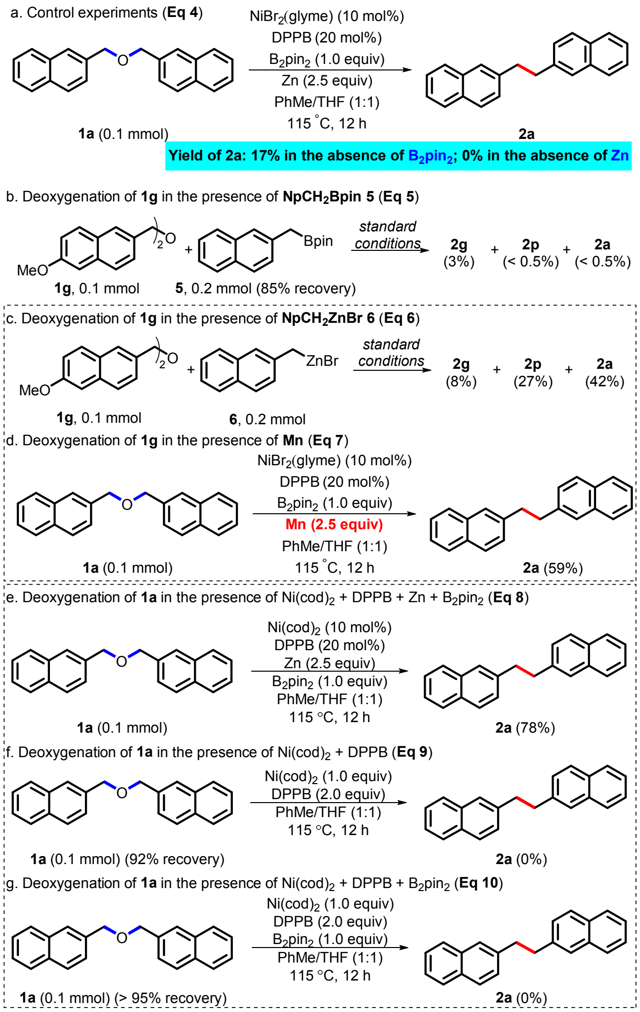
To further explore the potential applications, we conducted the reductive deoxygenation of substrates containing heterocycles. Both 2,2'-oxybis(methylene)dibenzofuran (**1p**) and 2,2'-oxybis(methylene)dibenzo[*b*]thiophene (**1q**) gave the desired products in good yields (**2p** and **2q**) (**Eq 1**). It is worth noting that product **2r** was obtained *via* the deoxygenation of highly steric hindered **1r** under the standard conditions in an acceptable yield (**Eq 2**). While, β-H elimination occurred in the presence of a methyl group at the α-position of ether and the desired product **2s** was not observed.



Eq 3

Beside symmetric ethers, asymmetric ether **1t** was submitted to this catalytic system and the product **2t** was obtained as the major product in 40% yield, while by-products **2a** and **2g** were observed in lower yields. The similar phenomenon was also observed in the deoxygenation of **1u**. This result indicated that this reaction occur in an intermolecular manner (**Eq 3**).

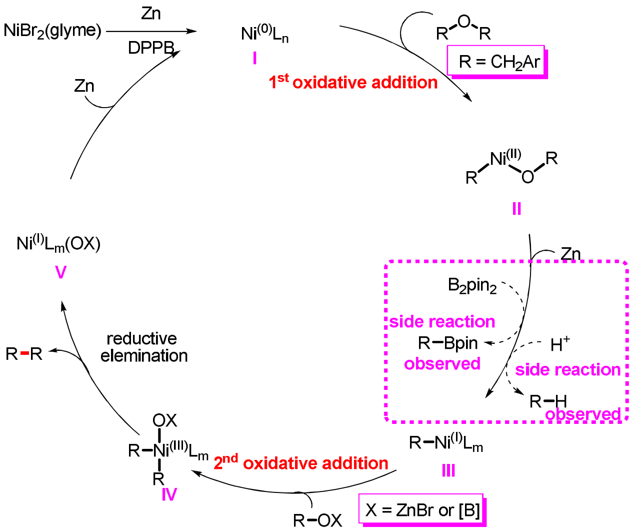
During the deoxygenation, a small amount of 2-napththylmethyl boronate was observed by GC-MS. In fact, the borylation of benzyl ethers were reported during we conducted these studies.[2k, 10] To gain insight into the mechanism, we carefully reviewed the reaction system and conducted the additional experiments (**Scheme 2**). As mentioned above, in the absence of B_2pin_2, the desired product **2a** was indeed observed albeit in a low yield (17% NMR yield) (**Eq. 4**). This result clearly demonstrated the catalytic pathway could proceed in the absence of any B-based intermediates. To further understand the roles of the possible benzylboronate in the catalytic cycle, prepared aryl methyl boronate (2.0 equiv) was added in this deoxygenation (**Eq 5**).[11] To our surprise, the additional naphthylmethyl boronate **5** was recovered in more than 80% yield (the rest part was protonated to methylarene). The cross coupling product between **1g** and **5** was detected in trace amount by both the crude ^1H NMR spectra and GC-MS. This result ruled out the participation of benzylboronate as a key intermediate in the catalytic cycle. It is important to note that, the additional benzylboronate suppressed this transformation and the yields of desired products were severely decreased.



Scheme 2, Mechanism studies

To unveil the role of benzyl zinc reagent in catalytic cycle, we conducted the deoxygenation reaction of **1g** in the presence of prepared benzylzinc **6** (**Eq 6**), the desired product **2g** was formed in only 8% yield. In this catalytic system, a coupling product between **1g** and **6** was observed in 27%. Furthermore, Mn was used to instead of Zn as the reductant to promote the deoxygenation of **1a**, and the target product was prepared in 59% yield (**Eq 7**). Combining with the capturing experiments, we ruled out the role of benzyl zinc reagent as an intermediate in catalytic cycle (**see SI for details**).

To further elucidate the mechanism, other control experiments were performed (**Eq 8-10**). In the absence of the reductant Zn, the deoxygenation reaction was terminated despite in the presence of a stoichiometric amount of Ni(cod)$_2$. Obviously, zinc played an essential role to fulfill the whole catalytic cycle. On the other hand, this result also indicated that the product was unlikely furnished *via* the transmetallation of two Ni(II) species **II,** which was generated from the first oxidative addition. Meanwhile, the recovery of **1a** indicated that the oxidative addition of C-O bond to Ni(0) could not occur in the absence of Zn.[12] Moreover, this result also excluded the formation of Ni(IV) species in this catalytic reaction through double sequential oxidative addition of two types of C-O bonds from Ni(0) species (**See SI for details**). Otherwise, the coupling could take place in the presence of stoichiometric Ni(0) species and in the absence of any reductants.[13] Obviously, the reductant Zn was not only involved into the catalytic cycles at the initiate stage.



Scheme 3, Proposed mechanism of deoxygenation of ethers

On the basis of the current results and previous reports, a plausible mechanism was depicted in **Scheme 3**. First of all, the nickel(II) species **II** was formed *via* the first oxidative addition of ether toward Ni(0) species, which was reduced to the nickel(I) species **III** by zinc[14]. Subsequently, the second oxidative addition of another C-O bonds took place on the Ni(I) species to form the Ni(III) species. Indeed, the proper reductant was very important to reduce the formed Ni(II) species. Since the difficulty to form the carbon-centered radical *via* the homo session of etheric C-O bond[15], this oxidative addition probably took place through a concerted or SN$_2$ pathway, which should be different from the reported radical pathway.[5] Finally, the desired product released through sp^3-sp^3 carbon-carbon bond reductive elimination on nickel (III) central to regenerate Ni(I) species. Such a Ni(I) species was further reduced to Ni(0) by zinc to fulfill the catalytic cycle, thus showing the second role of the reductant. During this catalytic cycle, B$_2$pin$_2$ probably played a key role as a Lewis acid to promote the reactivity of the ethers and *in-situ* generated alkoxide as well as the oxygen scavenger although other possibilities could not be rooted out at this stage.[7]

In summary, we for the first time developed the method to synthesize 1,2-diarylethanes *via* direct deoxygenation of diarylmethyl ethers. Challenges in this transformation were conquered toward the extrusion of oxygen of ethers. This chemistry exhibited good atom- and step- economy and offered a complementary strategy in organic synthesis to produce C-based skeletons from O-linked molecules.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data of products PDF

AUTHOR INFORMATION

Corresponding Author

*E-mail: zshi@pku.edu.cn, zjshi@fudan.edu.cn

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Support of this work by the "973" Project from the MOST (2015CB856600 and 2013CB228102) and NSFC (Nos. 21332001 and 21431008) is gratefully acknowledged. Thanks Xiao-Lei Li and Pei-Ling Xu (both in Peking University) for the assistance of melting point measurement.

REFERENCES

(1) (a) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246; (b) Dankwardt, J. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 2428; (c) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706; (d) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4866; (e) Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett.* **2009**, *38*, 710; (f) Álvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352; (g) Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, *332*, 439; (h) Kelley, P.; Lin, S.; Edouard, G.; Day, M. W.; Agapie, T. *J. Am. Chem. Soc.* **2012**, *134*, 5480; (i) Cornella, J.; Gómez-Bengoa, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997; (j) Leiendecker, M.; Hsiao, C.-C.; Guo, L.; Alandini, N.; Rueping, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 12912; (k) Cong, X.; Tang, H.; Zeng, X. *J. Am. Chem. Soc.* **2015**, *137*, 14367; (l) Tobisu, M.; Takahira, T.; Ohtsuki, A.; Chatani, N. *Org. Lett.* **2015**, *17*, 680; (m) Zarate, C.; Manzano, R.; Martin, R. *J. Am. Chem. Soc.* **2015**, *137*, 6754; (n) Liu, X.; Hsiao, C.-C.; Kalvet, I.; Leiendecker, M.; Guo, L.; Schoenebeck, F.; Rueping, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6093; (o) Guo, L.; Liu, X.; Baumann, C.; Rueping, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 15415; (p) Tobisu, M.; Takahira, T.; Morioka, T.; Chatani, N. *J. Am. Chem. Soc.* **2016**, *138*, 6711.

(2) (a) Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268; (b) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389; (c) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2012**, *51*, 7790; (d) Tollefson, E. J.; Dawson, D. D.; Osborne, C. A.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 14951; (e) Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825;.

(3) (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2010**, *111*, 1346; (b) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486; (c) Li, B. J.; Yu, D. G.; Sun, C. L.; Shi, Z. J. *Chem. Eur. J.* **2011**, *17*, 1728; (d) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081; (e) Su, B.; Cao, Z.-C.; Shi, Z.-J. *Acc. Chem. Res.* **2015**, *48*, 886; (f) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717; (g) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. *Acc. Chem. Res.* **2015**, *48*, 2344.

(4) (a) Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 607; (b) Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920; (c) Qian, X.; Auffrant, A.; Felouat, A.; Gosmini, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10402; (d) Knappke, C. E. I.; Grupe, S.; Gartner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. *Chem. Eur. J.* **2014**, *20*, 6828; (e) Everson, D. A.; Weix, D. J. *J. Org. Chem.* **2014**, *79*, 4793; (f) Gu, J.; Wang, X.; Xue, W.; Gong, H. *Org. Chem. Front.* **2015**, *2*, 1411; (g) Weix, D. J. *Acc. Chem. Res.* **2015**, *48*, 1767; (h) Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480; (i) Wang, X.; Wang, S.; Xue, W.; Gong, H. *J. Am. Chem. Soc.* **2015**, *137*, 11562; (j) Ackerman, L. K. G.; Lovell, M. M.; Weix, D. J. *Nature* **2015**, *524*, 454; (k) Iranpoor, N.; Panahi, F. *Org. Lett.* **2015**, *17*, 214.

(5) (c) Tollefson, E. J.; Erickson, L. W.; Jarvo, E. R. *J. Am. Chem. Soc.* **2015**, *137*, 9760; for selected example on cross-electrophile-coupling on aryl ethers with aryl halides: Cao, Z.-C.; Luo, Q.-Y.; Shi, Z.-J. *Org. Lett.* **2016**, *18*, 5978.

(6) Nakamura, K.; Tobisu, M.; Chatani, N. *Org. Lett.* **2015**, *17*, 6142.

(7) Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H. *Chem. Sci.* **2013**, *4*, 4022.

(8) (a) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895; (b) Freixa, Z.; van Leeuwen, P. W. N. M. *Dalton Trans.* **2003**, 1890; (c) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.

(9) Tobisu, M.; Nakamura, K.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 5587.

(10) (a) Kinuta, H.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 1593; for case on Pd-catalyzed C-O bond borylation: (b) Cao, Z.-C.; Luo, F.-X.; Shi, W.-J.; Shi, Z.-J. *Org. Chem. Front.* **2015**, *2*, 1505; for case on Ni-catalyzed C-O bond borylation: ref. 2k.

(11) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433.

(12) The $ZnBr_2$ generated in the reduction of high valent nickel species could be acting as a Lewis acid, lowering down the barrier for oxidative addition.

(13) In this cases, if reductant is not essential, desired product can be observed and the yield equal to the loading of catalyst.

(14) (a) Dauth, A.; Love, J. A. *Dalton Transactions* **2012**, *41*, 7782; (b) Horvath, S.; Fernandez, L. E.; Appel, A. M.; Hammes-Schiffer, S. *Inorg. Chem.* **2013**, *52*, 3643.

(15) Diéguez, H. R.; López, A.; Domingo, V.; Arteaga, J. F.; Dobado, J. A.; Herrador, M. M.; Quílez del Moral, J. F.; Barrero, A. F. *J. Am. Chem. Soc.* **2010**, *132*, 254; and ref. 5a and 5b.

Insert Table of Contents artwork here