

<https://doi.org/10.22643/JRMP.2018.4.1.16>

## Recent advance on the borylation of carbon-oxygen bonds in aromatic compounds

Seungwon Jeon,<sup>1,2</sup> and Eunsung Lee<sup>1,2,3\*</sup>

<sup>1</sup>Division of RI convergence research, Korea Institute of Radiological and Medical Sciences (KIRAMS),

<sup>2</sup>Radiological and Medico-Oncological Sciences major, University of Science and Technology, and

<sup>3</sup>Department of Bio-convergence Engineering, Korea University, Seoul, Korea

### ABSTRACT

Organoboron compounds and their derivatives are synthetically versatile building blocks because they are readily available, stable, and highly useful for potential organic transformations. Arylboronic esters are of particular interest due to their well-established synthetic methods: transition metal catalyzed borylations of aryl halides. However, the use of aryl halides as an electrophile has one serious disadvantage: formation of toxic halogenated byproducts. A promising alternative substrate to aryl halides would be phenol derivatives such as aryl ethers, esters, carbamates and sulfonates. The phenol derivatives involve several advantages: their abundance, relatively low toxicity and versatile synthetic application. However, utilization of the aryl methyl ether, which is one of the simplest phenol derivatives, remains as a challenge, as C–OMe bond activation requires high activation energy and methoxides are not good leaving groups. Nevertheless, there have been a significant recent progress on ipso-borylation of aryl methyl ether including Martin's nickel catalysis. Here, we review the current advance on the borylation of carbon-oxygen bonds of unactivated C–OMe bond in aromatic compounds.

**Key Word:** Organoboron, Borylations, Methoxides, Catalysis

Organoboron compounds and their derivatives are crucial building blocks for synthetic organic transformation such as Suzuki-Miyaura coupling reaction. In addition, organoboron compounds are readily available and useful for a potential variety of organic transformations (1). Traditionally, organoboron compounds have been synthesized by the reaction of organometallic nucleophiles, such as Grignard or organolithium reagents with boron electrophiles (2). However, these reagents are highly reactive and sensitive under aerobic condition. They are often corrosive and flammable. Due to their explosive characteristics, functional group tolerance is the

main limitation of these reactions (Figure 1).

To solve the limitations, transition metal catalyzed methods have been developed for the benign preparation of organoboron compounds: transition metal catalyzed C–H

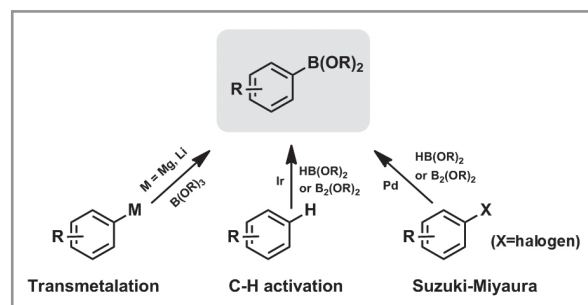


Figure 1. Typical methods for synthesis of organoboron compounds

Received: June 04, 2018 / Revised: June 25, 2018 / Accepted: June 28, 2018

**Corresponding Author :** Eunsung Lee, Tel: +82-54-279-2111, Fax: +82-54-279-8129, E-mail: eslee@postech.ac.kr

Copyright©2018 The Korean Society of Radiopharmaceuticals and Molecular Probes

bond and aryl halide borylation reaction. The first example is transition metal catalyzed C–H bond borylation reaction developed by various groups (3). A significant research has been progressed to the development of the catalyst that borylates C–H bonds in arenes with high yields and high selectivity. Transition metal catalyzed C–H bond borylation is an important method for the construction of complex organic molecules in pharmaceuticals, agrochemicals, and advanced materials with the good atom economy. For example, iridium (4), rhodium (5), and platinum (6) based catalysts have been studied for the catalysis of C–H bond borylation reaction.

The other example is transition metal catalyzed borylation reactions of aryl halide (7). Among these transition metal catalyzed reactions, Suzuki-Miyaura borylation reaction is one of the most important method using organic halides as the cross-coupling partner. However, there are certain disadvantages in the usage of organic halides: the formation of halogenated byproduct. Thus, many research groups have been attempted to alter the organic halide to other cross-coupling partners.

On the other hand, the phenol derivatives are one of the most attractive alternatives (Figure 2). The advantages of phenol derivatives are the absence of halogenated byproduct waste, greater availability, cost efficiency as compared to organic halides, and the possibility for the development of new synthetic pathway even in the presence of halide atoms. Aryl sulfonates, esters, and carbamates has been studied for C–O bond cleavage

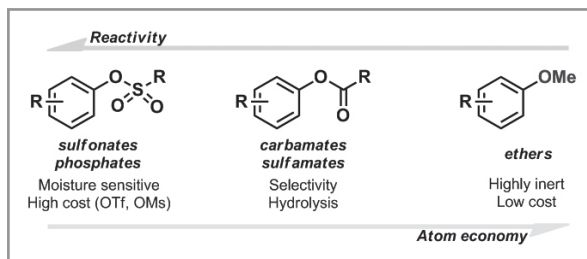
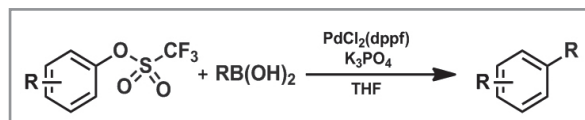
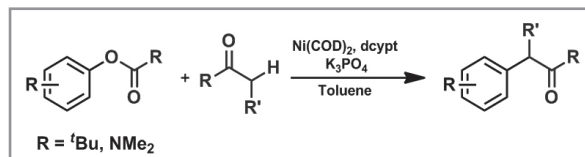


Figure 2. Features of C–O bond electrophiles



Scheme 1. Suzuki reaction with aryl sulfonates and Organoboron compounds



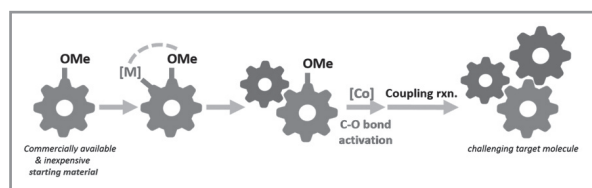
Scheme 2. Suzuki reaction with aryl sulfonates and organoboron compounds

reactions.

Aryl sulfonates are one of the most widely studied substrates in cross-coupling reactions (8). Aryl sulfonates have low activation energy in C–O bond cleavage. However, triflates are base sensitive so that the basic condition to be required to activate corresponding coupling boronic acid partners may not be compatible with aryl triflate. In 1993, Miyaura and Suzuki reported the Suzuki reaction with aryl sulfonates and organoboron compounds utilizing palladium catalysts. They used a weak base like  $K_3PO_4$  in polar solvents such as THF (Scheme 1) (8).

Aryl ester and aryl carbamate derivatives have been also studied for C–O bond cleavage reactions. Interestingly, according to many reports, aryl esters or carbamates are more active with nickel catalysts than with palladium catalysts, although the aryl sulfonates have been studied utilizing palladium catalysts in cross-coupling reactions (9). In 2014, the Itami group reported the first nickel catalyzed  $\alpha$ -arylation of ketones with aryl ester and aryl carbamate. In this reaction, air-stable 3, 4-bis(dicyclohexylphosphino)thio-phenol (dcypt) was used as the ligand. The intermediate of oxidative addition process was also isolated (Scheme 2) (9).

Recently, the use of simple and commercially available aryl methyl ethers has been studied to alter the other phenol derivatives such as aryl esters, carbamates, and sulfonates. Aryl methyl ethers are the simplest phenol derivative



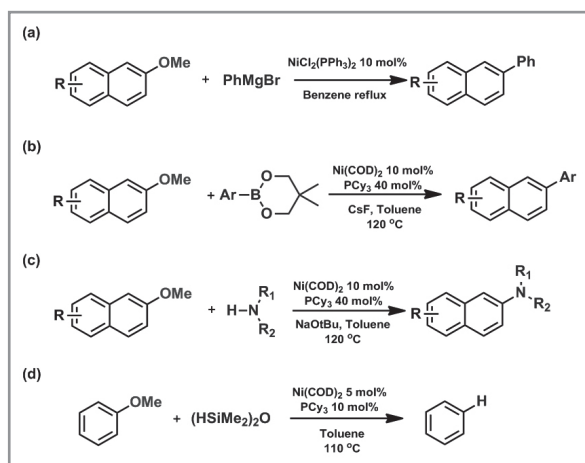
**Figure 3.** Site selectivity of the methoxy group and its synthetic application

and the reactions to utilize them are much eco-friendly. Because they generate much fewer byproducts than the other phenol derivatives does. In addition, aryl methyl ethers are commercially available and inexpensive. More importantly, orthogonal cross-coupling reaction could be possibly developed with transition metal catalysts that are inert toward C–OMe bond (10).

Moreover, the presence of methoxy group could give excellent site-selectivity for the substrate molecules. Ortho, meta or para position could be activated selectively in the presence of methoxy group by ortho-metalation, electrophilic aromatic substitution or C–H bond activation (11).

This is the most important feature for application in potential orthogonal syntheses. As shown in Figure 3, the complex target molecule can be synthesized by the 2-step strategy: methoxy directed activation followed by C–OMe functionalization. However, the activation barrier for breaking C–OMe bond is much higher than one for breaking C–O bond of other phenol derivatives. The methoxy group hardly acts as a leaving group. Therefore, the methoxy group is tolerated under the condition of most of aryl sulfonates, ester and carbamate cleavage reactions (12).

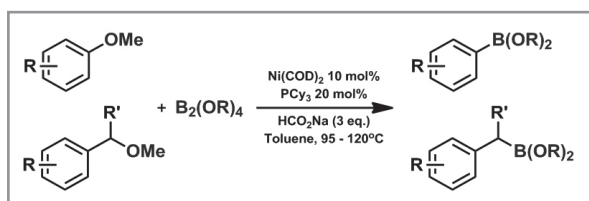
The first study of C–OMe bond activation was focused on C–C bond coupling reaction (13). For the reasons mentioned above, C–OMe bond activation reaction were limited to the cross-coupling reaction using highly reactive, moisture sensitive organometallic reagents such as Grignard reagents.



**Scheme 3.** Recently developed C–OMe bond activation reactions

In 1979, Wenkert reported the Kumada–Tamao–Corriu-type cross-coupling reaction based on C–OMe bond activation with low-valent nickel catalyst (Scheme 3(a)) (13). The following research was reported in 2007 by the Chatani group. They demonstrated the Suzuki–Miyaura type cross-coupling reaction with organoboron compounds as less reactive nucleophiles under nickel catalyst (Scheme 3(b)) (13). Unlike the Wenkert’s reaction, this reaction is tolerant with the various functional groups including ketones and esters. In addition, in 2009, the Chatani group reported nickel catalyzed C–N bond formation reaction with simple amine that could be applied in the pharmaceutical fields (13). Very recently, the Martin group reported a unique reactivity of nickel catalyst. They demonstrated the reductive cleavage of C–OMe bond in a good yield utilizing tetramethyldisiloxane (TMDSO) as a reducing agent (13). The methoxy group is a good directing group for selectivity. However, the selective cleavage of the methoxy group is still a challenge to be achieved. This method allows aryl methyl ethers to be used as removable directing groups.

Despite many advantages of organoboron compounds and aryl methyl ethers, direct conversion of C–OMe bond to C–B bond had little explored. In 2015, the Martin



**Scheme 4.** C-OMe bond borylation developed by the Martin group

group reported C(sp<sub>2</sub>) and C(sp<sub>3</sub>)-OMe bond borylation reaction under Ni(COD)<sub>2</sub>/PCy<sub>3</sub> catalytic system using 5,5,5',5'-tetramethyl-2,2'-bi-1,3,2-dioxaborinane (B2nep2) or bis(4,4,5,5,-tetramethyl-1,3,2-dioxaborolane) (B2pin2) as boron sources (Scheme 4). Commercially available reagents were used in these reactions. However, the requirement of high temperature (95 - 120°C) could be a limitation for the temperature sensitive substrates (14). Therefore, the research theme of the borylation of C-OMe bond will be directed to find more benign catalysis conditions.

In summary, we reviewed the functionalization of the phenol derivatives, which are one of promising alternative substrates for the cross-coupling reactions and borylation reactions because of their abundance, low toxicity and synthetic application. The presented reactions can be operated under benign reaction condition and in the practical reaction process. Overall, the method that developed by the Martin group provides the borylation methods of both C(sp<sub>3</sub>)-OMe and C(sp<sub>2</sub>)-OMe bonds. The presented mild and practical nickel-catalyzed borylation of various substrates will enable a new reaction strategy in synthetic chemistry.

## Acknowledgments

This work was supported by the Institute for Basic Science (IBS) [IBS-R007-D1]. The work is initially taken in part from M.S. dissertation of Seungwon Jeon

at POSTECH, Department of Chemistry. There is no related work by us on this subject previously submitted for publication, in press, or made publicly available otherwise. The manuscript is being submitted exclusively to the *Journal of radiopharmaceuticals and molecular probes*.

## References

- (a) Miyaura N, Suzuki A. Stereoselective synthesis of arylated (E)-alkenes by the reaction of alk-1-enylboranes with aryl halides in the presence of palladium catalyst. *J Chem Soc, Chem Commun* 1979;19:866-867. (b) Miyaura N, Suzuki A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem Rev* 1995;95:2457-2483. (c) Suzuki A. Organoborates in new synthetic reactions. *Acc Chem Res* 1982;15:178-184.
- (a) Brown HC, Cole TE. Organoboranes. 31. A simple preparation of boronic esters from organolithium reagents and selected trialkoxyboranes. *Organometallics* 1983;2:1316-1319. (b) Lappert MF. Organic compounds of boron. *Chem Rev* 1956;56:959-1064. (c) Letsinger RL, Skoog IH. The preparation and some properties of 2-methyl-1-propene-1-boronic acid. *J Org Chem* 1953;18:895-897. (d) Yamamura M, Moritani I, Murahashi SI. The reaction of  $\sigma$ -vinylpalladium complexes with alkyllithiums. Stereospecific syntheses of olefins from vinyl halides and alkyllithiums. *J Organomet Chem* 1975;91:C39-C42.
- Mkhalid IAI, Barnard JH, Marder TB, Murphy JM, Hartwig JF. C-H activation for the construction of C-B bonds. *Chem Rev* 2010;110:890-931.
- (a) Cho JY, Tse MK, Holmes D, Maleczka RE, Smith MR. Remarkably selective iridium catalysts

- for the elaboration of aromatic C-H bonds. *Science* 2002;295:305-308. (b) Larsen MA, Hartwig JF. Iridium-catalyzed C-H borylation of heteroarenes: scope, regioselectivity, application to late-stage functionalization, and mechanism. *J Am Chem Soc* 2014;136:4287-4299.
5. Cho JY, Iverson CN, Smith MR. Steric and chelate directing effects in aromatic borylation. *J Am Chem Soc* 2000;122:12868-12869.
6. (a) Labinger JA. Platinum-catalyzed C-H functionalization. *Chem Rev* 2017;117:8483-8496. (b) Furukawa T, Tobisu M, Chatani N. C-H borylation by platinum catalysis. *Bull Chem Soc Jpn* 2017;90:332-342.
7. (a) Norio M. Metal-catalyzed reactions of organoboronic acids and esters. *Bull Chem Soc Jpn* 2008;81:1535-1553. (b) Primas N, Bouillon A, Rault S. Recent progress in the synthesis of five-membered heterocycle boronic acids and esters. *Tetrahedron* 2010;66:8121-8136. (c) Pilarski LT, Szabó KJ. Palladium-catalyzed direct synthesis of organoboronic acids. *Angew Chem Int Ed* 2011;50:8230-8232.
8. (a) Ohe T, Miyaura N, Suzuki A. Palladium-catalyzed cross-coupling reaction of organoboron compounds with organic triflates. *J Org Chem* 1993;58:2201-2208. (b) Percec V, Bae JY, Hill DH. Aryl mesylates in metal catalyzed homocoupling and cross-coupling reactions. 2. Suzuki-type nickel-catalyzed cross-coupling of aryl arenesulfonates and aryl mesylates with arylboronic acids. *J Org Chem* 1995;60:1060-1065.
9. (a) Takise R, Muto K, Yamaguchi J, Itami K. Nickel-catalyzed  $\alpha$ -arylation of ketones with phenol derivatives. *Angew Chem Int Ed* 2014;53:6791-6794. (b) Muto K, Yamaguchi J, Itami K. Nickel-catalyzed C-H/C-O coupling of azoles with phenol derivatives. *J Am Chem Soc* 2012;134:169-172.
10. Mahatthananchai J, Dumas AM, Bode JW. Catalytic selective synthesis. *Angew Chem Int Ed* 2012;51:10954-10990.
11. (a) Sibi MP, Snieckus V. The directed ortho lithiation of O-aryl carbamates. An anionic equivalent of the Fries rearrangement. *J Org Chem* 1983;48:1935-1937. (b) Waltz KM, Muhoro CN, Hartwig JF. C-H activation and functionalization of unsaturated hydrocarbons by transition-metal boryl complexes. *Organometallics* 1999;18:3383-3393. (c) Pena MA, Pérez Sestelo J, Sarandeses LA. Palladium-catalyzed aryl-aryl cross-coupling reaction using ortho-substituted arylindium reagents. *J Org Chem* 2007;72:1271-1275. (d) Cornella J, Zarate C, Martin R. Metal-catalyzed activation of ethers via C-O bond cleavage: a new strategy for molecular diversity. *Chem Soc Rev* 2014;43:8081-8097. (e) Xue C, Luo Y, Teng H, Ma Y, Nishiura M, Hou Z. Ortho-selective C-H borylation of aromatic ethers with pinacol-borane by organo rare-earth catalysts. *ACS Catal* 2018;5017-5022.
12. Wilson DA, Wilson CJ, Moldoveanu C, Resmerita AM, Corcoran P, Hoang LM, Rosen BM, Percec V. Neopentylglycolborylation of aryl mesylates and tosylates catalyzed by Ni-based mixed-ligand systems activated with Zn. *J Am Chem Soc* 2010;132:1800-1801.
13. (a) Wenkert E, Michelotti EL, Swindell CS. 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) Álvarez-Bercedo P, Martin R. Ni-catalyzed reduction of inert C-O bonds: A new strategy for using aryl ethers as easily removable directing groups. *J Am Chem Soc* 2010;132:17352-17353. (c) Li BJ, Yu DG, Sun CL, Shi ZJ. Activation of "inert" alkenyl/aryl C-O bond and its application in cross-coupling reactions. *Chemistry* 2011;17:1728-

1759. (d) Rosen BM, Quasdorf KW, Wilson DA, Zhang N, Resmerita AM, Garg NK, Percec V. Nickel-catalyzed cross-couplings involving carbon-oxygen bonds. *Chem Rev* 2011;111:1346-1416. (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.
14. Zarate C, Manzano R, Martin R. Ipso-borylation of aryl ethers via Ni-catalyzed C–OMe cleavage. *J Am Chem Soc* 2015;137:6754-6757.