Cross-Coupling

DOI: 10.1002/anie.200900465

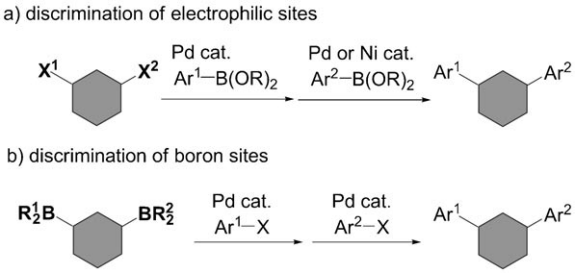
Devising Boron Reagents for Orthogonal Functionalization through Suzuki–Miyaura Cross-Coupling**

Mamoru Tobisu and Naoto Chatani**

boron · cross-coupling · Suzuki–Miyaura reaction

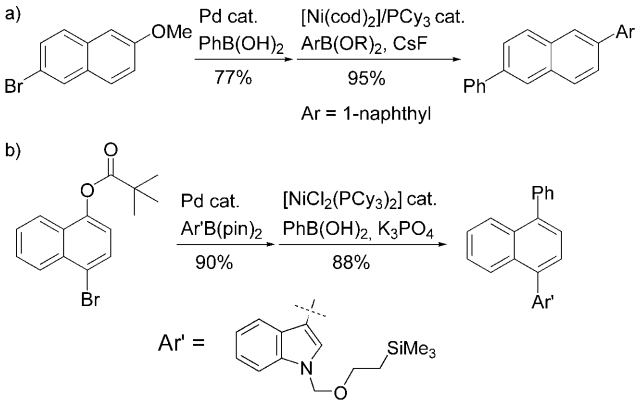
In 1979, Suzuki and Miyaura introduced organoboron reagents into the realm of cross-coupling chemistry by demonstrating a palladium-catalyzed reaction of 1-alkenylboranes with aryl and alkynyl halides.[1] Since its discovery, this reaction, which is now referred to as the Suzuki–Miyaura reaction, has seen significant advancement and has become one of the most powerful carbon–carbon bond forming methods in organic synthesis.[2] After exhaustive effort in the pursuit of active catalyst systems in the last decade, synthetic chemists have recently turned their attention to the application of this reaction to the synthesis of more complicated molecule: by using successive Suzuki–Miyaura coupling reactions with substrates containing two or more possible reactive sites. The key to obtaining the desired cross-coupling products in a selective manner by assembling such multifunctionalized compounds is to establish a strategy to discriminate the possible reaction sites. More specifically, chemists must modulate the reactivity of either the electrophilic sites (Scheme 1 a) or the boron reagents (Scheme 1 b) to realize orthogonal functionalization through consecutive Suzuki–Miyaura cross-coupling. Herein, we will provide an overview of this topic, with particular emphasis on the discrimination of boron reagents.

The simplest approach to orthogonal cross-coupling is to exploit the different reactivities of electrophilic coupling partners (Scheme 1 a). The difference in reactivity between aryl (pseudo)halides (I > Br ≫ Cl) has been successfully applied to the selective monofunctionalization of substrates bearing more than one (pseudo)halide.[3] Recent studies by our research group have revealed that aryl methyl ethers can be coupled with boronic esters under nickel catalysis.[4] This finding has provided us with an additional opportunity for orthogonal functionalization based on the strategy shown in Scheme 1 a, since aryl methyl ethers are completely inert toward boron reagents under standard palladium-catalyzed conditions (Scheme 2 a). Subsequently, the research groups of Shi and Garg independently reported a nickel-catalyzed Suzuki–Miyaura coupling reaction utilizing aryl pivalates, thereby further expanding the diversity of the electrophilic coupling partners for use in orthogonal cross-coupling (Scheme 2 b).[5]



Scheme 1. Strategies for orthogonal molecular functionalization through Suzuki–Miyaura cross-coupling reactions. Ar = aromatic group

In contrast, modulating the reactivity of boron reagents represents an alternative approach to orthogonal cross-coupling (Scheme 1 b). The critical issue to be addressed is the identification of a boron reagent that does not participate in a cross-coupling event under standard conditions but that can eventually serve as a nucleophile under differing con-



Scheme 2. Orthogonal Suzuki–Miyaura coupling reactions using aryl methyl ethers (a) and aryl pivalates (b). cod = cycloocta-1,5-diene, Cy = cyclohexyl, pin = pinacol.

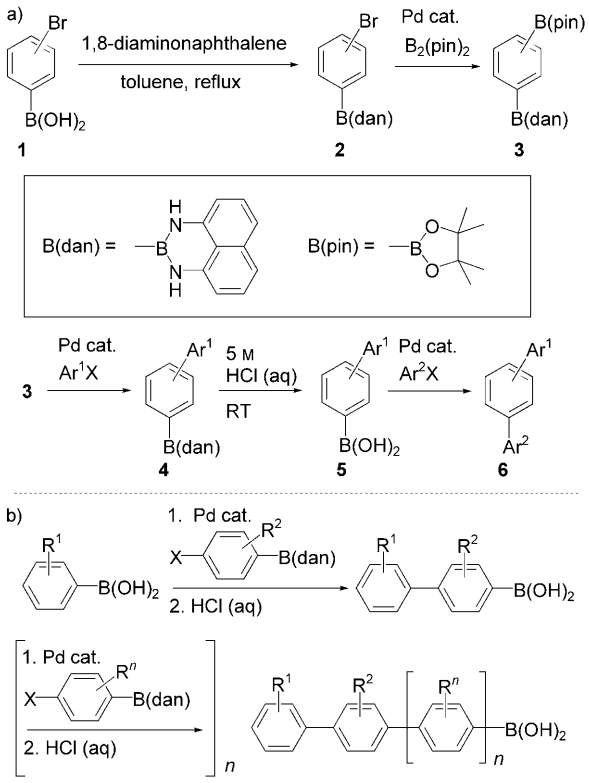
[*] Dr. M. Tobisu
Frontier Research Base for Global Young Researchers
Graduate School of Engineering, Osaka University
Suita, Osaka 565-0871 (Japan)
Fax: (+81) 6-6879-7396
E-mail: tobisu@chem.eng.osaka-u.ac.jp
Prof. Dr. N. Chatani
Department of Chemistry, Faculty of Engineering
Osaka University, Suita, Osaka 565-0871 (Japan)
Fax: (+81) 6-6879-7396
E-mail: chatani@chem.eng.osaka-u.ac.jp

[**] This work was carried out under the Program of Promotion of Environmental Improvement to Enhance Young Researchers' Independence, the Special Coordination Funds for Promoting Science and Technology, MEXT (Japan).

ditions. Suginome and co-workers proffered a general solution to this problem by establishing a boron masking strategy (Scheme 3a).[6] They developed a new protecting group, 1,8-diaminonaphthalene, which rendered the boronic acid moiety inactive to palladium-catalyzed cross-coupling by decreasing the Lewis acidity of the boron center through the π-electron donation of the nitrogen atoms. The masking procedure is accomplished simply by heating boronic acid and 1,8-diaminonaphthalene in refluxing toluene accompanied by the azeotropic removal of water (**1**→**2**). The robust nature of this diamine-based protecting group allows access to differentially protected diboronic acids **3** through the palladium-catalyzed borylation of aryl bromide **2**. After the first cross-coupling of **3**, the masking group in **4** can be removed in the presence of aqueous acid to form boronic acids **5**, which are amenable to the subsequent Suzuki–Miyaura coupling reaction. The utility of this strategy is highlighted by its application to the synthesis of oligoarenes by iterative cross-coupling using haloarene boronic acids (Scheme 3b). Notably, limitless iteration is theoretically possible with this strategy, and enables the synthesis of oligoarenes with a large molecular weight and with a well-defined structure.

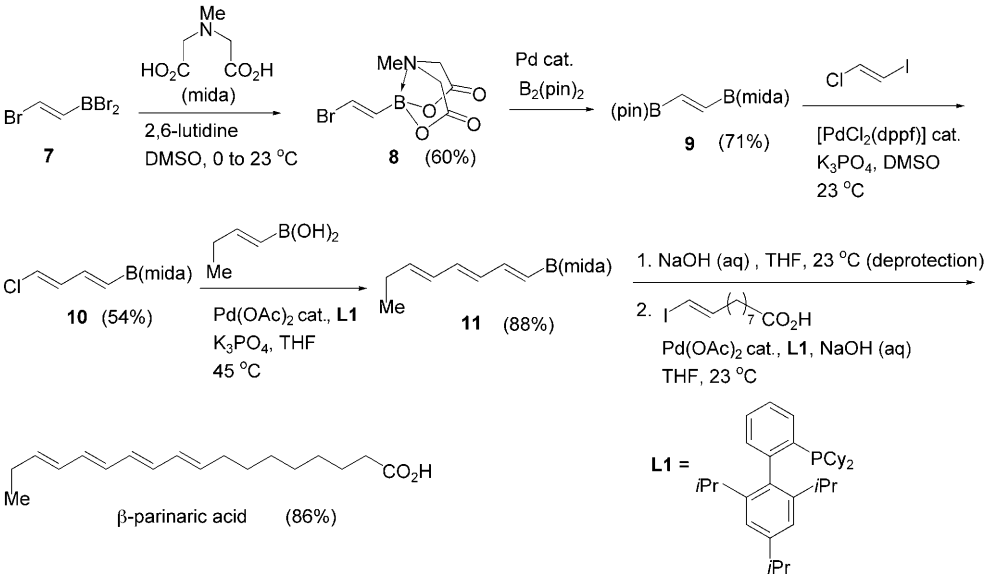
Meanwhile, Burke and co-workers reported another type of masking group for boronic acid based on the use of the trivalent ligand, *N*-methyliminodiacetic acid (mida).[7] The complexation of mida involves the rehybridization of the boron center from sp^2 to sp^3 (as in **8** in Scheme 4), which reduces the Lewis acidity of the boron center and attenuates the reactivity toward transmetalation under Suzuki–Miyaura reaction conditions. This tetrahedral adduct can be cleaved under mild aqueous basic conditions, such as 1M aqueous NaOH, which allows the use of this masking group—and is complementary to a Suginome's diamine-based group. In spite of the base-sensitive nature of the protecting group, it is possible to perform a Suzuki–Miyaura coupling reaction that allows the remaining mida-protected boron reagents to remain intact by employing anhydrous conditions (**9**→**11** in Scheme 4). The power of this masking group is demonstrated in the synthesis of polyene natural products through iterative Suzuki–Miyaura coupling (Scheme 4). The use of a mida protecting group not only directs the cross-coupling in a desired manner, it also permits the avoidance of acidic conditions, which is essential to the synthesis of acid-sensitive polyene compounds.

Although the boron masking/unmasking protocol offers a reliable method for orthogonal functionalization of the compounds



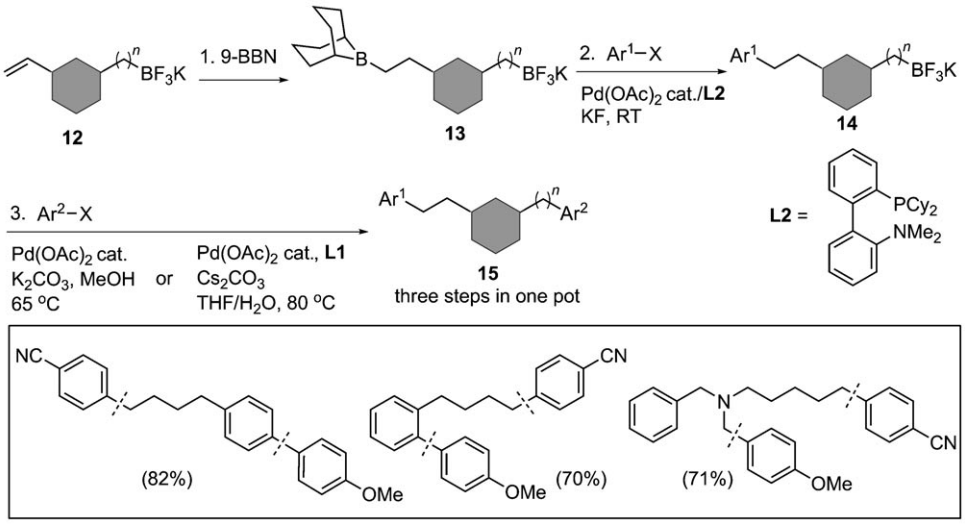
Scheme 3. Suginome's boron masking strategy (a) and its application to iterative cross-coupling (b).

bearing two nucleophilic coupling sites, it would be more practical if the unmasking stage could be skipped. Molander and Sandrock recently achieved this goal by exploiting the unique reactivities of trialkylboranes and organotrifluoroborates ($R-BF_3K$).[8] It has long been known that trialkylboranes serve as nucleophilic coupling partners in Suzuki–



Scheme 4. Burke's trivalent protecting group for boronic acids and its application to the synthesis of polyene natural products. DMSO = dimethyl sulfoxide, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, THF = tetrahydrofuran.

Miyaura coupling reactions, which enables the introduction of a sp^3 carbon into electrophiles, even under anhydrous conditions.[9] On the other hand, organotrifluoroborates, which represent relatively new but increasingly useful boron reagents,[10] require aqueous or protic conditions to generate the intermediates that are capable of promoting transmetalation. In other words, organotrifluoroborates could be tolerated during the course of catalytic cross-coupling when conducted under anhydrous conditions. It has been established that the tetracoordinate nature of the boron center, which is fortified by strong carbon–fluorine bonds, renders the carbon–boron bond in organotrifluoroborates unaffected by various functional group manipulations involving bases, nucleophiles, oxidants, and others.[10] However, under Suzuki–Miyaura reaction conditions the stability of this tetrahedral boron species has remained elusive. Molander and Sandrock have determined that the use of $Pd(OAc)_2$/DavePhos (**L2**) as the catalyst and KF as a base is a suitable system for the cross-coupling of trialkylboranes without affecting the trifluoroborate moiety. For example, the catalytic cross-coupling of dibora-substituted substrate **13**, which is generated in situ through the hydroboration of alkene-containing organotrifluoroborates **12**, proceeds selectively at the trialkylborane site to afford **14** under the aforementioned reaction conditions (Scheme 5). The elaborated organotrifluoroborates **14** can be directly used for subsequent cross-coupling under protic or aqueous conditions. From a practical point of view, it is important to note that these three reaction sequences (hydroboration and two cross-coupling reactions) can be conducted by a one-pot procedure. The authors extended this protocol to the selective cross-coupling of trialkylboranes with aryl halides bearing trifluoroborates, which can be further elaborated in a one-pot sequence. The trialkylborane component is rather limited in scope since its preparation depends on hydroboration. Nevertheless, the applicability of sp^3-carbon nucleophiles is a feature that is distinguished from other cross-coupling methods. Recognizing that cross-couplings of trialkylboranes have been utilized as critical carbon–carbon bond formation reactions in the total syntheses of a wide array of natural products,[9] Molander's protocol has significantly increased the value of the Suzuki–Miyaura coupling reaction and promises even further utilization in future synthetic endeavors.



Scheme 5. Molander's one-pot hydroboration and orthogonal Suzuki–Miyaura coupling protocol.

In addition to sophisticated catalyst systems developed in the last decade, synthetic organic chemists have acquired several strategies for assembling complex molecules through consecutive Suzuki–Miyaura coupling reactions. One of the key elements of the strategy is to modulate the reactivity of the boron moiety by changing the electron density and/or the hybridization state through the introduction of well-designed ligands. Now that the establishment of the reactivity modulation of organoboron compounds has been demonstrated in consecutive Suzuki–Miyaura coupling reactions, these concepts should find numerous opportunities for application, including in tandem catalysis and in asymmetric synthesis.[11] Also, these studies will stimulate research on the reactivity control of other organometallic reagents by designing a tailor-made ligand.[12] These protocols should provide powerful tools for the synthesis of natural products and high molecular weight π-conjugated oligomers with well-defined structures, and, thus, will contribute to advances in related fields of science.

Published online: March 23, 2009

[1] a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437; b) N. Miyaura, A. Suzuki, *J. Chem. Soc. Chem. Commun.* **1979**, 866.

[2] Selected reviews: N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11; A. Suzuki, H. C. Brown, *Organic Synthesis via Boranes, Vol. 3*, Aldrich, Milwaukee, **2003**; N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; F.-X. Felpin, T. Ayad, S. Mitra, *Eur. J. Org. Chem.* **2006**, 2679.

[3] For a leading reference, see: A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.

[4] M. Tobisu, T. Shimasaki, N. Chatani, *Angew. Chem.* **2008**, *120*, 4944; *Angew. Chem. Int. Ed.* **2008**, *47*, 4866.

[5] a) K. W. Quasdorf, X. Tian, N. K. Garg, *J. Am. Chem. Soc.* **2008**, *130*, 14422; b) B.-T. Guan, Y. Wang, B.-J. Li, D.-G. Yu, Z.-J. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 14468.

[6] a) H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758; b) H. Noguchi, T. Shioda, C.-M. Chou, M. Suginome, *Org. Lett.* **2008**, *10*, 377; c) N. Iwadate, M. Suginome, *J. Organomet. Chem.*, DOI: 10.1016/j.jorgchem.2008.11.068.

[7] a) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716; b) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 14084; c) S. J. Lee, K. C. Gray, J. S. Paek, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 466.

[8] G. A. Molander, D. L. Sandrock, *J. Am. Chem. Soc.* **2008**, *130*, 15792.
[9] For a review, see: S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.
[10] For reviews, see: a) S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2003**, 4313; b) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275.
[11] For an excellent example of the regulation of the stereochemical outcome of the reaction through the nature of boron reagents, see: J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778.
[12] Y. Nakao, J. Chen, M. Tanaka, T. Hiyama, *J. Am. Chem. Soc.* **2007**, *129*, 11694.

