Strategies Towards Chemoselective Suzuki-Miyaura Cross-Coupling

James W. B. Fyfe and Allan J. B. Watson*

WestCHEM, Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL (UK)

E-mail: allan.watson.100@strath.ac.uk

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Abstract: Chemoselective Suzuki-Miyaura cross-coupling has emerged as a powerful method for the rapid preparation of sp^2 - and sp^3 -hybridized carbon frameworks based on control of the oxidative addition or transmetallation events. The field of chemoselective transmetallation has recently seen considerable development with several different strategies emerging including protected boronic acids, neighboring group activation, and chemoselective speciation. Herein, these state-of-the-art approaches towards chemoselective Suzuki-Miyaura cross-coupling are highlighted.

Key words: Boron, catalysis, chemoselectivity, cross-coupling, palladium

The Suzuki-Miyaura (SM) reaction is one of the most widely used methods for catalytic C-C bond formation.¹ The popularity of this reaction in both academia and industry stems from not only the generally mild reaction conditions and excellent functional group tolerance, but also from the non-toxic nature, relative stability, and broad availability of organoboron coupling partners.

Since its initial discovery in 1979² significant advances have been made within SM cross-coupling, appreciably improving overall reaction efficiency along with the potential scope of coupling partners.³ Much of this has centered around the development of new catalysts and ligands to facilitate cross-coupling of less reactive substrates, such as aryl chlorides.⁴ Perhaps more importantly, there has also been a concerted effort to develop new SM-compatible boron reagents, each displaying potentially very useful benefits contingent on the cross-coupling scenario. In particular, such advances include reagents that facilitate the coupling of notoriously unstable boronic acids as well as protecting group strategies that effectively render boronic acids compatible with common organic synthetic manipulations and providing a method for streamlined iterative cross-coupling processes.⁵ This latter development represents one of the more recent approaches within the area of chemoselective SM cross-coupling.

Chemoselective cross-coupling is a valuable method for the preparation of molecules that retain a useful functional handle, which may be further used in a subsequent cross-coupling (or other) process. From the mechanistic perspective, chemoselective SM cross-coupling may be achieved either via control within the elementary oxidative addition or transmetallation events.

Chemoselective SM cross-coupling via control of oxidative addition. Chemoselective oxidative addition follows the generally accepted order of

reactivity of (pseudo)halides for Pd-catalyzed cross-couplings, in which $I > Br \geq OTf > Cl$.^{3a} A comprehensive demonstration of chemoselective oxidative addition within the SM context was provided by Fu who exploited this fundamental rate difference to enable chemoselective SM cross-coupling of a single boronic acid with a dihaloarene, for example 1-iodo-4-chlorobenzene (Scheme 1a).⁶ Of particular note was the ability to alter the chemoselectivity of oxidative addition with certain (pseudo)halides, simply by changing the catalyst system, which allowed aryl chlorides to be selectively coupled in the presence of the nominally more reactive aryl triflate (Scheme 1b).

While levels of chemoselectivity are generally high based on rate differentials of oxidative addition of two different carbon-halogen bonds, intriguingly, Sherburn has also shown that chemoselective control is possible in the SM cross-coupling of dibromo- and diiodoarenes leading to selective single or double cross-coupling, respectively (Scheme 1c).⁷

Scheme 1 Chemoselective SM cross-coupling via control of oxidative addition.

Chemoselective SM cross-coupling via control of transmetallation. More recently, the potentially more challenging chemoselective transmetallation has been demonstrated via two main strategies. A broadly useful approach has been established through the use of protected boronic acids. Here, one boronic acid is rendered inert to transmetallation thereby allowing the chemoselective cross-coupling of a second, more reactive, boron species. Following the cross-coupling

event, deprotection reveals the parent boronic acid that can then be further manipulated. Based on the simplicity and accessibility of the approach, a small range of protected boronic acids have been developed, with the boronic esters derived from *N*-methyliminodiacetic acid (BMIDA, also known as *N*-coordinated boronates) and the boronamides derived from 1,8-diaminonaphthalene (DAN) the most widely developed and employed (Figure 1).

Figure 1 BMIDA and BDAN: widely used protected boronic acid derivatives.

Development and use of BMIDA reagents.

Originally reported by Mancilla,⁸ and extensively developed by Burke,⁹ BMIDA esters have been applied most notably within iterative synthesis. Donation of the *N* lone pair into the vacant boron *p*-orbital renders boron sp^3 -hybridized and inert to a wide range of common organic transformations such as oxidation/reduction, olefination, Evans aldol, and halogenation.¹⁰ Importantly, BMIDA are inert to transmetalation and can therefore be readily taken through SM cross-coupling with the only prerequisite that the reaction must be anhydrous to avoid premature hydrolysis of the base-labile BMIDA.

BMIDA can be rapidly hydrolyzed using aq. NaOH¹⁰ or more slowly hydrolyzed with aq. K_3PO_4 .¹¹ This slow hydrolysis has provided a method for overcoming shortfalls in SM cross-coupling of unstable boronic acids, such as protodeboronation-prone heterocyclic derivatives, via slow-release of the parent boronic acid, which is rapidly cross-coupled.¹² Burke has also capitalized upon this in the context of polyene natural product synthesis where olefinic boronic acids can also display a tendency to protodeboronate.¹³ Use of a slow-release BMIDA process limits the boronic acid's exposure and thus the potential for protodeboronation. This strategy has enabled the concise and flexible synthesis of a wide range of polyene natural products from a small number of halovinyl BMIDA building blocks and is a potent example of the utility of protected boronic acids to enable chemoselective transmetalation in the context of complex molecule synthesis (Scheme 2).¹⁴

Development and use of BDAN reagents. The BDAN reagents first described by Suginome¹⁵ are broadly similar to BMIDA esters in that boron is stabilized by the lone pairs of the adjacent nitrogen atoms, again precluding transmetalation. However, unlike their BMIDA counterparts, boron remains sp^2 -hybridized and BDAN are acid labile. Accordingly, BDAN are more compatible with the aqueous basic

conditions commonly employed within Suzuki-Miyaura cross-coupling.¹⁶

Scheme 2 Polyene synthesis using iterative cross-coupling with BMIDA building blocks.

Suginome has demonstrated the utility of BDAN to facilitate the preparation and chemoselective cross-coupling of diboron compounds.¹⁶ Miyaura borylation of haloarylBDAN compounds affords differentially protected phenyldiboron acid derivatives (Scheme 3a). The BPin moiety can then be selectively coupled under basic SM conditions while leaving the BDAN intact. Similar to BMIDA, subsequent hydrolysis then reveals the parent boronic acid, which can be further functionalized. Interestingly, the steric bulk of BDAN can be exploited to enable regioselective formation of differentially protected olefinic diboron species (Scheme 3b).¹⁷ Diboration across a terminal alkyne using an unsymmetrical diboron reagent affords an intermediate that can then undergo chemoselective SM cross-coupling at its more hindered position.

Scheme 3 Chemoselective cross-coupling using BDAN.

Use of vicinal and geminal diboron species in chemoselective cross-coupling. In 2011, Hall and co-workers capitalized upon the unique features of BDAN reagents to demonstrate asymmetric hydroboration of alkenyl BDAN compounds leading to geminal diboron BPin/BDAN derivatives (Scheme

4).¹⁸ The BPin moiety could then be chemoselectively cross-coupled with complete inversion of stereochemistry (via the BF_3K derivative).

Scheme 4 Chemoselective cross-coupling of geminal diboron species with orthogonal reactivity.

Protected boronic acids therefore provide a highly accessible method for chemoselective transmetallation. However, in the context of synthetic efficiency, the use of protecting groups is typically disfavored.¹⁹ More recently a strategy for the chemoselective cross-coupling of sp^3 -hybridized diboron species, of apparent equivalent reactivity, has been developed. Specifically, vicinal or geminal di-BPin compounds have been shown to undergo chemoselective mono-cross-coupling.²⁰

Shibata first demonstrated the chemoselective cross-coupling of geminal BPins in 2010 (Scheme 5a).²¹ More recently, Morken has expanded upon the Shibata process and has shown that this chemoselective process can also be rendered enantioselective by use of a suitable chiral ligand to discriminate between the enantiotopic geminal BPins (Scheme 5b).²²

Scheme 5 Chemoselective cross-coupling of geminal diboron species of equivalent reactivity.

Morken has shown that chemo- and stereoselective SM cross-coupling of vicinal BPins can also be achieved (Scheme 6).²³ Enantioselective diboration of alkenes under Pt-catalysis generates enantioenriched vicinal di-BPin compounds that undergo chemo- and stereoselective SM cross-coupling.

Scheme 6 Chemoselective cross-coupling of vicinal diboron species of similar reactivity.

The introduction of a chiral BPin using either the geminal or vicinal di-BPin strategies allows rapid access to a diverse range of enantioenriched organic compounds in a small number of synthetic steps from readily available starting materials. This further emphasizes the increased step efficiency that can be provided by progressing beyond from protecting group strategies: chemoselective transmetallation in this way provides reactive boronic acid derivatives directly without the need for deprotection events.

Morken has proposed that the chemoselectivity of these processes arises from the generation of an intramolecular Lewis acid-Lewis base interaction (Figure 2). For the vicinal di-BPin compounds, interaction between the proximal boron (**a**) and an oxygen from the pinacol of the terminal boron (**b**) renders the terminal BPin more Lewis acidic and increases its relative rate of transmetallation. The proximal BPin is simultaneously rendered less Lewis acidic and therefore less prone to transmetallation. This process can therefore also be considered as a neighboring group protection strategy. The same activation is operational for the geminal di-BPin compounds.

Figure 2 Neighboring group activation/protection of vicinal di-BPin compounds.

Controlling boron solution speciation. The use of protected boronic acids enables chemoselective SM cross-coupling to provide a protected sp^2 -hybridized boronic acid as the product while the neighboring group activation/protection strategy provides reactive sp^3 -hybridized BPin esters as the products. Recently, a strategy that provides direct access to reactive sp^2 -hybridized BPin products using protected boronic acids has been described via controlling boron speciation during SM cross-coupling (Figure 3).²⁴

Figure 3 Chemoselective boronic ester synthesis by controlled speciation.

SM cross-coupling of an aryl BPin with a conjunctive haloaryl BMIDA generates an intermediate biaryl BMIDA and, the by-product from the SM reaction, HO-BPin. Through appropriate control of the basic biphasic these species can be hydrolyzed and the resulting biaryl boronic acid and pinacol can be driven towards formation of the formally homologated product by modulation of the boron solution equilibria. Accordingly, under this protocol a protected boronic acid affords reactive boronic ester products with no need for deprotection events.

This methodology was found to be broadly applicable to the formation of sp^2 -hybridized BPin products in a general sense with both aryl and alkenyl products isolated in good yield (Figure 4).

Figure 4 Examples of the formal homologation of ArBPin via controlled solution speciation during SM cross-coupling.

Moreover, the authors demonstrated that the Pd catalyst remains active and, following completion of the formal homologation event, addition of an aryl bromide results in a second SM cross-coupling to provide triaryl compounds, such as **1**, in good yield in a one-pot process (Figure 5). Accordingly, iterative SM cross-coupling can be rendered more step-efficient. Similarly, addition of a second equivalent of haloaryl BMIDA results in a second formal

homologation to provide tricyclic BPin compounds, such as **2**, in good yield. Considering that pinacol must be transferred over at least three boron species (without consideration of equilibria exchange processes), this represents a very high level of reaction efficiency and provides a unique opportunity for establishing methods for controlled oligomerization of sp^2 -hybridized BPin species.

Figure 5 Examples of the one-pot iterative SM and controlled oligomerization opportunities afforded by controlling boron solution speciation during cross-coupling. X = Halogen, Y = H or BMIDA, Z = H or BPin.

Summary

Since its discovery in 1979, the Suzuki-Miyaura reaction has emerged as the leading method for catalytic sp^2 - sp^2 C-C bond formation. Recent advances in chemoselective control have provided a wealth of new opportunities for this cornerstone reaction. Chemoselectivity has arisen from both well-established rate differences in oxidative addition of different carbon-halogen bonds as well as surprising selectivities in the cross-coupling of dibromo- and diiodoarenes. Novel innovations in this field have now enabled chemoselectivity to be realized in the pivotal and unique transmetalation event: The use of protected boronic acids provides a general and readily accessible method for achieving chemoselectivity of one boron species over another; exploiting neighboring group activation/protection allows chemoselective transmetalation of geminal and vicinal boronic esters; and, finally, controlling the solution speciation during SM cross-coupling now allows reactive boronic esters to be prepared directly from protected species. All of these methods have served to broaden the applicability and reach of one of the most versatile and widely used C-C bond forming reactions and serve as a platform from which to launch a new era of Suzuki-Miyaura cross-coupling chemistry.

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Biographical sketches of the authors

Allan Watson is a native of Glasgow, Scotland. He completed his MSci at the University of Strathclyde in 2004 before undertaking PhD research with Prof. Billy Kerr, completing in 2008. This was followed by postdoctoral work with Prof. David MacMillan at Princeton, USA, and an industrial postdoctoral research position at GlaxoSmithKline. He returned to a Lecturer position at the University of Strathclyde in 2011. His research interests are synthetic methodology, boron chemistry, medicinal chemistry, and sustainable synthesis.

Jamie Fyfe was born in Glasgow, Scotland, UK, in 1990. He studied chemistry at the University of Strathclyde, working for a year at Syngenta, and completed a Masters in Chemistry in 2013. He began his PhD studies with Dr Allan Watson in 2013 where he is focused on the development of chemoselective Suzuki-Miyaura cross-coupling methods.

Photos of the authors

James Fyfe

Allan Watson

Graphical Abstract

Strategies Towards Chemoselective Suzuki-Miyaura Cross-Coupling