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The Slow-Release Strategy in Suzuki–Miyaura Coupling

Alastair J. J. Lennox[a] and Guy C. Lloyd-Jones*[a]

Abstract: Despite great advances in metal-catalyzed cross-coupling reactions, their efficacy is often compromised by side reactions, reducing the yield, or requiring a large excess of one component. Suzuki–Miyaura cross-coupling is no exception, as the boronic acid functionality can be susceptible to a range of undesired processes. A number of methods have been developed to mitigate these side reactions, and herein we focus on the "slow-release" strategy. These conditions involve deployment of a "masking" reagent that protects the vulnerable boronic acid functionality from degradation, particularly protodeboronation, whilst simultaneously facilitating controlled liberation of the active reagent into the catalytic milieu. Under suitably tailored conditions, this dual-action approach ensures that the concentration of the free boronic acid is minimized, thus attenuating its degradation but still facilitating transmetallation of the organoboron species with the key organopalladium intermediate.

Keywords: boron · C–C coupling · palladium · slow-release · Suzuki–Miyaura coupling

1. Introduction

Transition metal-catalyzed cross-coupling reactions have developed to the point where they are now a mainstay in modern synthesis; a status that is reflected in the award of the 2010 Nobel Prize in Chemistry to Heck, Negishi, and Suzuki. Nonetheless, in many cases side reactions remain a major limitation in terms of the overall efficiency of the process. This is especially true in traditional Suzuki–Miyaura cross-coupling, where the boronic acid functionality can be susceptible to a range of undesired processes, including protodeboronation, oxidative homocoupling, and oxidative insertion.

Although a number of strategies have been developed to mitigate these side reactions, this review focuses on one strategy in particular, namely "slow release". This method can be highly effective and involves deployment of a "masking" reagent that serves as a stable reservoir for the vulnerable boronic acid. Two masking systems are covered in detail: the "MIDA" system developed by Burke, and the potassium trifluoroborate system developed by Molander. For each, we highlight the principal applications, as well as key benefits and any significant limitations.

2. Suzuki–Miyaura Coupling

2.1. Boronic Acids as Cross-Coupling Reagents

Boronic acids, $R–B(OH)_2$, play a key role as nucleophilic coupling partners in a wide range of metal-catalyzed reactions, including various rhodium-[1], copper-,[2] and gold-mediated[3] systems. However it is for their application in the palladium-catalyzed Suzuki–Miyaura coupling[4] reaction (Figure 1) that they have become best known. Compared to many other Pd-catalyzed reactions, Suzuki–Miyaura coupling proceeds under mild conditions, is exceptionally functional group tolerant, and is relatively cheap and facile to conduct. As such, it is a catalyzed reaction that is almost peerless in terms of the extent of its application in the industrial and academic research labo-

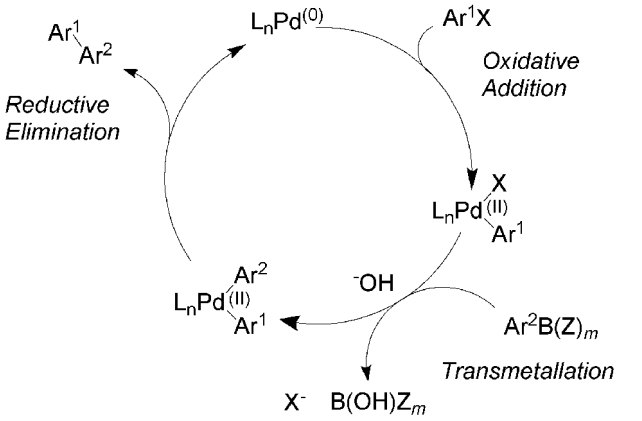

Figure 1. A generic mechanism for the Suzuki–Miyaura cross-coupling, showing the three key stages of catalytic turnover.

[a] A. J. J. Lennox, G. C. Lloyd-Jones
School of Chemistry,
University of Bristol
Cantock's Close
Bristol, BS8 1TS, UK
phone: +44 (0)177 928 8165
e-mail: guy.lloyd-jones@bristol.ac.uk

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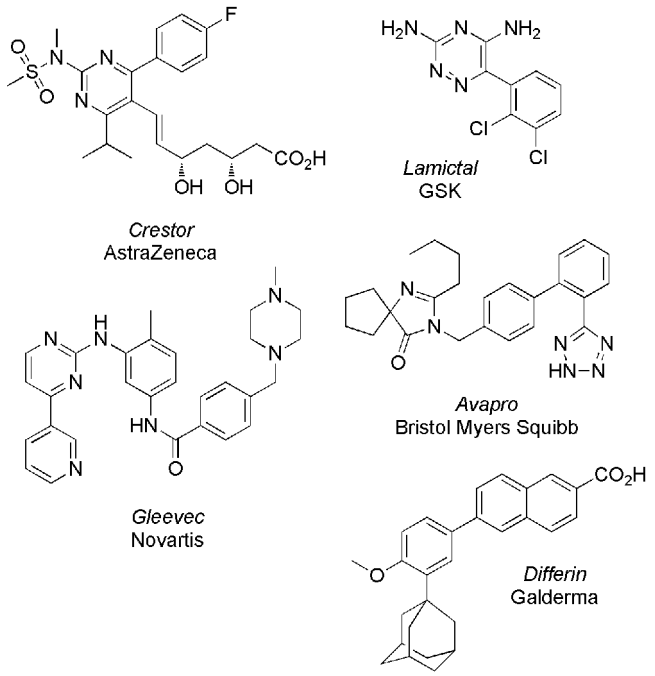

Figure 2. A selection of major pharmaceutical products that contain the ubiquitous biaryl moiety.

ratory. Indeed, it has become the "gold standard" for biaryl construction and is, in part, responsible for the ubiquity of this moiety in modern medicinal chemistry,[5] as exemplified in Figure 2.

Alastair Lennox is a graduate of Manchester University (2008, M. Chem.) where he conducted a final year research project with Dr. Ian Watt after spending a year studying at UCLA. He is currently working towards his Ph.D. under the supervision of Prof. Guy Lloyd-Jones at Bristol University. His interests lie in the elucidation of organometallic reaction mechanisms.

Guy Lloyd-Jones is a graduate of Huddersfield Polytechnic (1989, B.Sc.) and Oxford University (1992, D. Phil. under J. M. Brown FRS). In 1993 he was awarded a Royal Society postdoctoral fellowship to work with A. Pfaltz (Basel) and he joined the School of Chemistry at Bristol in 1996. He is interested in the stereochemical, structural, and kinetic aspects of transition metal catalysis, and he is a Royal Society Wolfson Research Merit Award Holder (2008–2013).

This widespread utility, ease of application, and the relatively benign nature of the boron and halide co-products, has meant that, compared to many of its contemporaries that have been superseded by superior processes or less toxic reagents,[6] the Suzuki–Miyaura coupling[4] has stood the test of time. Indeed, rather than languish since its discovery, quite the opposite has occurred, with a series of substantial evolutions and improvements having been made over the last two decades. These have ranged from expansion of the substrate scope to include unactivated aryl chlorides[7] and sterically demanding substrates,[8] to lowering of the catalyst loadings[9] and reduction in the temperatures required for efficient catalytic turnover.[10]

However, as with any reaction of substantial scope, there remain problematic substrates and significant side reactions. Common side reactions include the protodeboronation, oxidation, homocoupling, and dehydration of the boron reagent; catalyst decomposition; and protodehalogenation of the organo halide. In this review we focus specifically on the degradation pathways of the boron reagent and, in particular, how slow-release of the boronic acid from a protected form can aid in mitigation of these undesired processes.

2.2. Boronic Acid Degradation Pathways

2.2.1. Oxidation

There are two primary undesired oxidative processes in Suzuki–Miyaura coupling, Figure 3. The first involves the generation of hydroperoxides in ethereal solvents, via their prior photo- or metal-catalyzed aerobic oxidation. This process can be surprisingly rapid in solvents that have been freed of radical inhibitor, for example, THF after distillation from sodium-benzophenone ketyl. Under the aqueous basic conditions that prevail in the classic Suzuki–Miyaura coupling reaction, ether hydroperoxides will readily oxidize[11] R–$B(OH)_2$ to R–$OB(OH)_2$, and thus liberate ROH via hydrolysis. This side reaction can be avoided by meticulous anaerobic manipulation, or more easily by addition of a quenching reagent to reduce

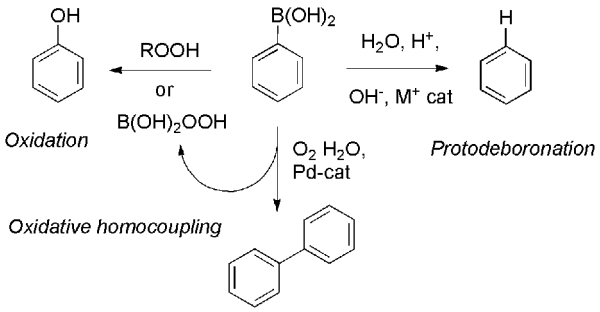

Figure 3. Three common side reactions of arylboronic acids under Suzuki–Miyaura cross-coupling conditions.

any hydroperoxides present in the solvent, prior to the coupling.

The second process also arises from aerobic oxidation but involves O_2-mediated homocoupling ($2 \times R–B(OH)_2 \rightarrow R–R$). The co-product from this is nominally peroxyboric acid, which oxidizes a third equivalent of $R–B(OH)_2$ to R–OH. The overall process differs from the hydroperoxide pathway in that it is palladium-catalyzed and runs in competition with the desired Suzuki–Miyaura coupling. Thus, whilst meticulous anaerobic manipulation will mitigate it, it cannot be stopped by prior reductive quenching of the medium. The mechanism of the oxidative homocoupling process has been elucidated by Amatore and Jutand et al., and a palladium–peroxo species, formed from $(L)_nPd(^0)$ and O_2, identified as a key intermediate.[12]

2.2.2. Protodeboronation

As noted above, the oxidative processes can often be avoided through practical modifications to the reaction procedure. This then leaves the major problem in using boronic acids in Suzuki–Miyaura coupling being the propensity of many of them to undergo protodeboronation; that is, the loss of the boron from the organic fragment in exchange for a proton. Despite this being a prevalent, sometimes even dominant, side reaction in coupling, rather little work has been conducted on the mechanism. For the protodeboronation of aryl boronic acids, the key mechanistic aspects were elucidated by Kuivila[13–15] in the early 1960 s, long before the ascendancy of the Suzuki–Miyaura coupling. Kuivila conducted detailed kinetic measurements on the aqueous protodeboronation of substituted aromatics. This work included linear free energy correlations, as well as the study of H/D isotope effects. He also tested the effect of various metal ions (Cd, Cu, Pb, Ag, Zn, Co, Mg, Ni, Pd, Pt, Fe, Au, Mn, Al, Cr), and reported detailed kinetic data for cadmium(II)-catalyzed hydrolysis, which was effective above pH 3. Through these studies he was able to identify four distinct pathways (**I**-**IV**), as illustrated in Figures 4 and 5, where it can be seen that the non-catalyzed hydrolytic pathway (**I**) undergoes specific and general acid catalysis (**II**),[13] specific base catalysis (**III**),[14] and Cd^{II}-catalysis (**IV**).[15]

Linear free energy correlations for protodeboronation in the upper pH range, indicate an increased electron demand in the aromatic ring on approach to the transition state, which is consistent with rate-limiting C–B cleavage (k_2) in an equilibrium-generated boronate (K_1, pathway **III**). Intriguingly, the opposed electronic influence of aromatic substituents on the two steps (K_1 and k_2), results in faster overall protodeboronation when any of the aromatic protons in $PhB(OH)_2$ is replaced with any other substituent. Substitution at the *ortho*-position results in the most profound effects (3–80-fold rate accelerations), due to steric decompression, possibly assisted by hydrogen-bonding when the substituent has a lone pair available. That pathway **III** proceeds via direct protonolysis in the second step (k_2), rather than via a Wheland intermediate, is suggested by the "regular" Hammett rho value ($\rho = -2.3$)[14] extracted for k_2, as compared to the "Brown–Okamoto" values required for correlation under

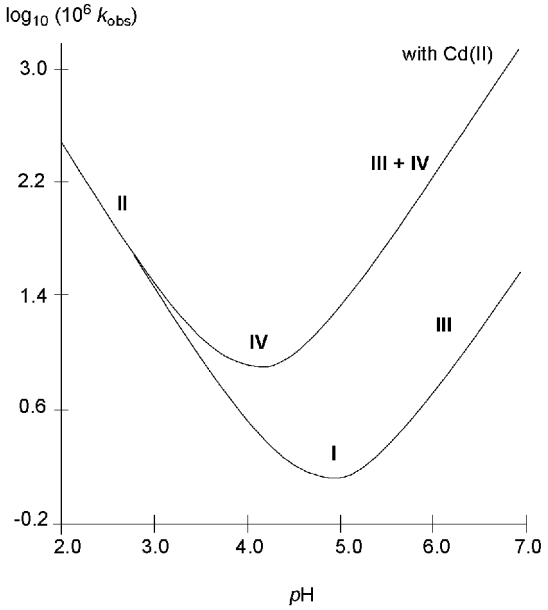

Figure 4. Schematic pH rate profiles for protodeboronation of 2,6-dimethoxyphenylboronic acid under aqueous malonate buffer conditions, in the presence and absence of Cd^{II}, 0.1 M.

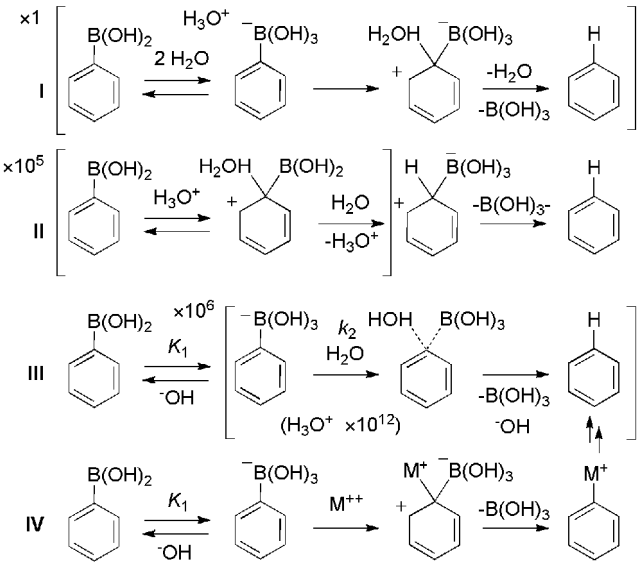

Figure 5. General pathways (**I**–**IV**) for protodeboronation of Ar–$B(OH)_2$ species under aqueous conditions. The relative rates are for when Ar = 2,6-dimethoxyphenyl, under aqueous malonate buffer conditions at 90 °C and relate only to the steps enclosed in square parentheses.

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acidic conditions ($\rho^+ = -5.0$, pathway **II**)[13a] or under Cd-catalysis ($\rho^+ = -1.2$, pathway **IV**).[15]

Whether the metallodeboronation–protodemetallation mechanism (**IV**) proposed by Kuivila for Cd-(II) catalysis is also operative with the other metal ions found to be active catalysts (Cu > Pb > Ag ⩾ Cd > Zn > Co > Mg > Ni) is not evident from his studies. Of note, however, is that of the d^8-metal (II) salts tested, only nickel effected any catalysis, albeit inefficient, whilst palladium was rapidly reduced, and platinum had no effect on the rate. From this it might be concluded that protodeboronation in Suzuki–Miyaura coupling does not involve metallodeboronation pathway (**IV**). However it should be borne in mind that i) Kuivila's kinetic studies were conducted at significantly lower pH than that employed under conventional coupling conditions, and ii) the possibility of metal ion contaminants acting as efficient catalysts for process **IV** should not be ignored. With regard to the latter, Kuivila found, for example, that traces of Cu^I halide, generated by in situ reduction of Cu^{II}, to be highly efficient protodeboronation catalysts. We also note that rather efficient Rh-catalyzed protodeboronation of arylboronic acids [1b,16d] always necessitates their use in excess during Rh-catalyzed conjugate addition to enones.[16]

2.3. Strategies for Mitigation of Protodeboronation

Boronic acids that are highly succeptible to protodeboronation under Suzuki–Miyaura coupling conditions are predominantly those bearing a heteroaryl, vinyl, cyclopropyl, or polyfluoroaryl substituent. Electron-rich heterobiaryls and species bearing a 2-pyridinyl unit are common structural motifs in biologically active molecules, and thus of specific interest in medicinal chemistry. It is understandable, then, why much effort has gone into the development of conditions for Suzuki–Miyaura coupling of boronic acids bearing these moieties. Their substantial rates of protodeboronation under the reaction conditions can often result in a large excess of the boronic acid being required.

Protodeboronation under classic Suzuki–Miyaura coupling conditions most likely occurs via specific base catalysis of a solvolytic reaction, and thus should follow pseudo first order kinetics,[12–14] provided that the pH, rather than the base concentration, stays approximately constant. When this linear two-step sequence is coupled with the cyclic multistep cross-coupling sequence, which has the possibility of kinetic saturation and variable resting states, the partitioning between coupling and protodeboronation is more complex and more manipulable than appears on first inspection. These features have allowed more elegant strategies to be developed to combat protodeboronation. Most effective are those based on catalyst acceleration (**A**), reagent activation (**B**), and reagent masking (**C**), as outlined in Figure 6. The use of masked reagent also features in the highly efficient "slow-release" strategy (**D**) on which this review focuses.

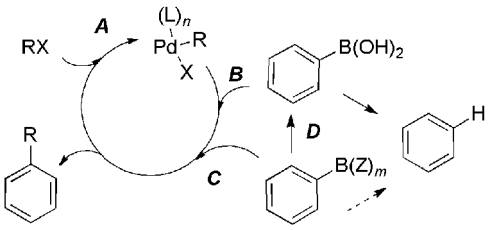

Figure 6. The four general strategies (**A**–**D**) for mitigation of protodeboronation in Suzuki–Miyaura cross-coupling.

2.3.1. Catalyst Acceleration (A)

Higher activity catalyst systems, predominantly achieved by ligand tuning, can increase both the rate constant for transmetallation and—by shifting the resting state from oxidative addition to transmetallation—the concentration of the transmetallating complex, leading to improved efficiency. Some examples in which ligand tuning allows successful cross-coupling of "troublesome" boronic acids, such as those based on heteroaromatics,[17] are outlined below. Buchwald and co-workers have developed highly active mono-coordinated dialkylbiaryl phosphine ligands, which prove to be very effective[18] for increasing the rates of transmetallation and reductive elimination in the catalytic cycle, thereby reducing the competition by protodeboronation. Buchwald has also developed very practical pre-catalysts bearing these ligands; the catalyst can be readily activated, under conditions that are mild enough for protodeboronation to be slow.[19] Fu has successfully cross-coupled heteroaryl boronic acids by utilizing the electron rich and bulky PCy_3 ligand. The system is able to generate the products of coupling with aryl and heteroaryl halides in very high yields.[20] Phosphine chloride and oxide ligands have also offered another viable alternative.[21]

2.3.2. Boron Reagent Activation (B)

The second strategy is to use additives that make the boronic acid undergo transmetallation more efficiently. This could be envisaged as proceeding via an assisted transmetallation, or more effectively as proceeding via generation of a discrete reagent. Stoichiometric amounts of silver oxide have been shown to be highly effective in assisting polyfluorophenyl[22,23] and *n*-alkyl[24] couplings. In an attempt to deduce the nature of the enhancing effect,[23c] oxidative addition intermediates were isolated and reacted stoichiometrically with the silver oxide and boronic acid, in a toluene–water biphase. It is proposed that silver oxide effects a replacement of the iodo ligand with a hydroxide group, thus priming the complex towards the transmetallation reaction with boronic acid. In a similar

vein, copper salts have been added to increase the rate of transmetallation.[25] In these cases, it is proposed that the boronic acid initially reacts with the copper salt, which then delivers a heteroaryl–copper reagent to palladium more efficiently than the boronic acid, thereby reducing protodeboronation.

2.3.3. Boron Reagent Masking (C)

In general, due to the two extra steps required, the use of protecting groups is in decline in organic synthesis. Nonetheless, the third strategy presented herein involves protection or stabilization of the vulnerable boronic acid functionality, and is a process that is proving very useful in the development of Suzuki–Miyaura coupling reactions. Boronic acids most likely undergo protodeboronation via mechanism **III** (Figure 5), in which the Lewis acidic boron center readily complexes a water molecule or a hydroxide ion, and the trihydroxyborate undergoes C–B protolysis. By switching from hydroxyl ligands to more electron-donating ligands, so as to attenuate the Lewis acidity at the boron center (reducing K_1), or by addition of a Lewis base ligand to form a more inert anionic tetrahedral "ate" complex (reduce k_2), the boron center can be efficiently stabilized under the Suzuki–Miyaura coupling conditions.

We shall use the term "masking" for this effect, as distinct from "protection" since the latter implies that a "deprotection" step is a pre-requisite part of the overall process. However, we note that although many of the masked boronic acid methods reported in the literature do not require a formal deprotection step, for example, Figure 7, the exact nature of the active transmetalating species is not always clear. Examples of this include pinacol esters,[21,25,26] which, unlike their boronic acid counterparts, are monomeric in nature and can often be purified easily before cross-coupling. Miyaura[27] has demonstrated that cyclic triolborates are proficient reagents for Suzuki–Miyaura coupling. They are easily prepared from the corresponding triol and boronic acid: water is removed azeotropically, followed by treatment with KOH and subsequent precipitation of the salt. Buchwald[28] has reported an elegant method for the cross-coupling of a masked 2-pyridyl boronic acid moiety, via preparation of the lithium triisopropyl 2-pyridylborate using standard lithium halogen exchange and workup with triisopropyl borate. Under optimized conditions, this reagent proved to be an efficient partner for coupling. A third example of this type involves reaction of the boronic acid with an excess of *N*-phenylethanolamine[29] or simply diethanolamine.[31] This protecting group has also been used as part of a solid support, which can aid in the derivatization of the boronic acid substituent before release of the acid from the support.[30]

A number of alternative strategies exist for stabilizing the boron center whereby a formal deprotection is necessary, most often because they are more robust protecting groups. Suginome[32] has demonstrated that 1,8-diaminonaphthalene (dan) can completely mask the boronic acid towards Suzuki–Miyaura coupling. A simple acidic deprotection liberates the boronic acid ready for coupling. Simple diol protecting groups have also been shown to be effective in this regard.[33]

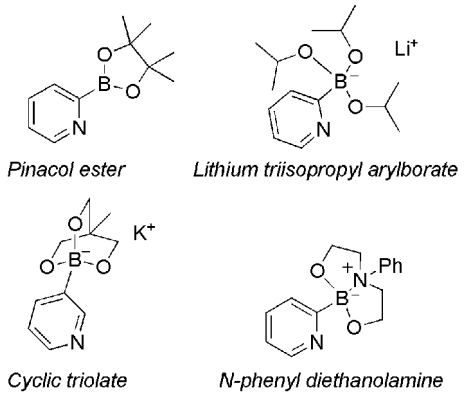

Figure 7. Examples of masked pyridyl boronic acid reagents.

2.4. Slow-Release (D)

There are two specific examples of masked boronic acid systems, namely the *N*-methyliminodiacetic acid (MIDA) boronates and the potassium organotrifluoroborates, which stand out from the rest in terms of their broad applicability and increasing general use in Suzuki–Miyaura coupling reactions. Indeed their popularity has progressed to the point where many examples of both classes of these reagents are commercially available (Figure 8).

Both reagents are extremely resistant to the classic degradation pathways, and to Suzuki–Miyaura coupling. However, under the appropriate conditions, they release the reactive boronic acid, or partly masked reagent, which can then participate in transmetallation and facilitate catalytic turnover. The clever feature of their mode of action is that the reaction conditions can be adjusted to control the rate at which reagent release occurs. This then allows the active reagent to be liberated at a rate at which it can be efficiently trapped via transmetallation, and thus onto the productive cross-coupling cycle. This ensures that the reactive species stays in low concentration and minimizes the opportunity for competitive protodeboronation or oxidative homocoupling. These are not the only applications of "slow-release" strategy in metal-

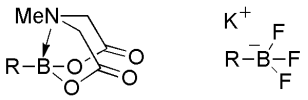

Figure 8. MIDA boronates and organotrifluoroborates.

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catalyzed cross-couplings. For example, Nakamura[34] found that during iron-catalyzed cross-couplings, slow-addition of the Grignard reagent was beneficial. This concept was then extended by Jacobi Von Wangelin[35] to an in situ procedure where the rate of formation of Grignard reagent is slow, keeping the concentration low, which then reduces the generation of homo-coupled product and substantially increases the cross-coupled yield. More recently, Lipshutz has developed a similar method for zinc-mediated Negishi couplings in water.[36]

2.4.1. MIDA Boronates

The seminal work by Burke and co-workers[37] revolutionized the concept of boron reagent masking by developing an easy synthesis of *N*-methyliminodiacetic acid (MIDA) boronates, and then demonstrating their facile in situ hydrolysis and subsequent cross-coupling capabilities. The MIDA reagents provide excellent yields for many substrates and the methodology has been used in a number of natural product syntheses.[38] The only drawback to their use is that the MIDA ligand is fairly expensive; however economies of scale with increasing demand, and recent advances in the synthesis of MIDA in one step from commodity chemicals,[39] will soon negate this issue.

For simple boronic acid substrates, refluxing under Dean–Stark conditions is enough to evict the water released upon condensation with the MIDA ligand. For the more challenging unstable 2-heterocyclic boronic acids, lithium halogen exchange from the corresponding heteroaryl halide, followed by treatment with triisopropyl borate and subsequent quench with MIDA, gives good to excellent yields on the gram scale.[39] All of the MIDA boronates reported thus far by Burke, including the troublesome 2-heterocyclic surrogates, are indefinitely stable to air and moisture and can be stored without precaution "on the bench top".

The MIDA boronates have shown promise in iterative synthesis,[40] a technique which many propose to be a keystone in the future of automated synthesis.[41] The concept is that small bifunctional building blocks, with all necessary functionalization pre-installed, are coupled together using one reaction, followed by deprotection. This should ensure that each reagent is cheap and readily available, and it will increase the diversity of molecules that one can reach automatically. Whilst iterative synthesis[40] requires considerable development before it becomes a standard technique, the library of building blocks is steadily increasing, and the vinyl[42] and ethynyl[43] MIDA boronates, prepared as shown in Figure 9, are useful linking blocks.

Unlike boronic acids, MIDA boronates are inert enough to withstand a number of standard organic reaction conditions, even including harsh acidic Jones oxidation,[44] and can thus be carried through many synthetic sequences. The enhanced stability is due to the boron-

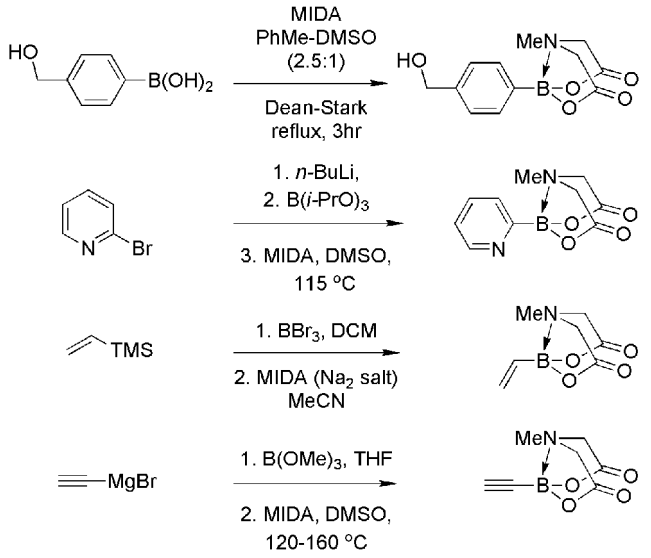


Figure 9. Routes to MIDA boronates.

complexation by the Me–*N*-ligand, changing the B hybridization from sp^2 to sp^3. Once complexed in this manner, the MIDA conformation is rigid, certainly at the ^{1}H NMR time-scale (Figure 10), and inert to Suzuki–Miyaura coupling.[44] This stands in stark contrast to the analogous *N*-methyldiethanolamine complex, which undergoes NMR-detectable conformational flipping that, under the right conditions, leaves it exposed to Suzuki–Miyaura coupling and other processes.

The MIDA group can be cleaved from boron by mild aqueous base, thus liberating a reactive Suzuki–Miyaura coupling partner.[45] Keeping the concentration of the free boronic acid low is vital for the unstable, 2-heterocyclic vinyl and cyclopropyl species, and by careful manipula-

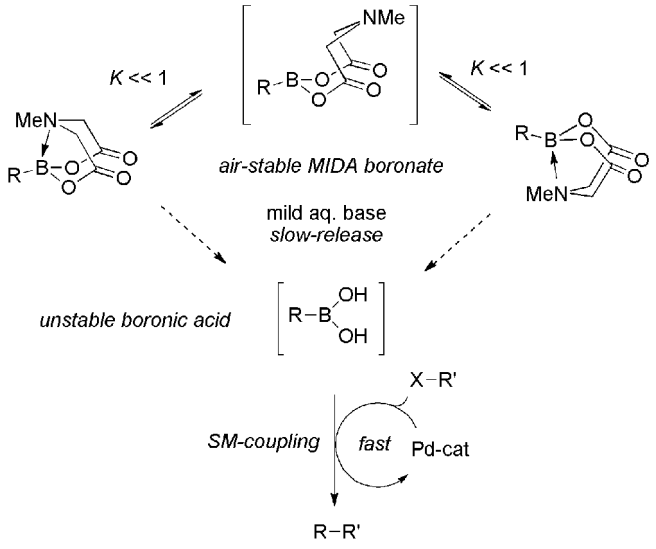


Figure 10. Slow-release and rapid capture of a generic unstable boronic acid from a stable MIDA boronate.

tion of base, temperature, and solvent, Burke has been able to simultaneously slow down hydrolysis and increase the rate of catalytic turnover relative to protodeboronation.

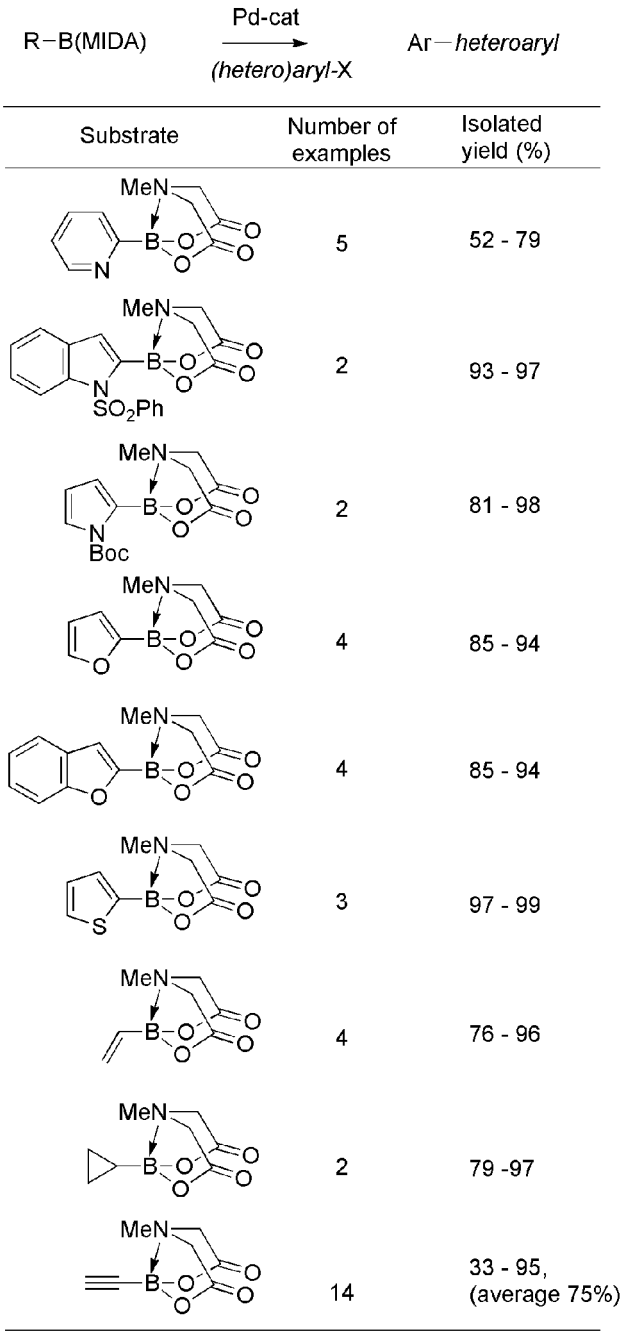
Control experiments showed that under fast-release conditions, the reagent behaved in an analogous way to the unprotected boronic acid, and thus there is no benefit inherent to having the MIDA ligand present.[45] In other words, it is the slow-release that is pivotal, as is supported by comparable yields being obtained when freshly prepared unstable boronic acid was added slowly via a syringe-pump. Indeed, the slow-release mechanism is so efficient, that unlike many other reagents,[25] only one equivalent of the MIDA boronate is required, even with boronic acids that are highly succeptible to degradation. The range of substrates that Burke has successfully coupled, including various 2-heterocyclic cores, vinyl and cyclopropyl systems, and difficult aryl chlorides, makes MIDA boronates the reagents of choice. Some examples are presented in Figure 11.

2.4.2. Potassium Organotrifluoroborates

It was initially recognized by Genet[46] that potassium aryltrifluoroborates can participate in Suzuki–Miyaura coupling; but it is Molander[47] who has extensively developed their use in this reaction. Potassium organotrifluoroborates are easily synthesized from their parent boronic acids by treatment with KHF_2 in methanol at room temperature.[48] It is a rapid reaction which precipitates the desired organotrifluoroborate, thus easing isolation. Extraction into hot acetone or acetonitrile and filtration removes the KF side-product, and upon cooling the product conveniently crystallizes out. Unfortunately, the KHF_2 reagent is very corrosive to glassware, which necessitates the use of PTFE or plastic vessels. However, once isolated, the potassium organotrifluoroborates are air- and moisture-stable, and most are free-flowing powders, making handling and storage facile.

Like the MIDA masking group, trifluoroborates are robust materials capable of withstanding a number of standard organic reaction conditions.[49] In solution, the trifluoroborate moiety is stable under anhydrous conditions, but when subjected to aqueous or protic media they hydrolyze, via equilibrium involving mixed hydroxy or alkoxy fluoroborate intermediates, to form the corresponding boronic acid/ester.[50,51] These then are the species that are able to participate in the Suzuki–Miyaura coupling reaction.

We have recently reported a mechanistic investigation[51] into the chemistry of aryltrifluoroborates, aimed at elucidating why they are a viable solution to many lower-yielding boronic acid Suzuki–Miyaura coupling reactions. A combined ^{19}F NMR/^{2}H-labelling/computational approach revealed *p*-F–C_6H_4–BF_3K to undergo slow release to the corresponding boronic acid under the reported cross-coupling conditions (aq. THF, Cs_2CO_3). The hydrolysis process was found to be rather capricious, with the glassware surface playing a key role, and we surmised that the extensive optimization of reaction conditions reported in the literature for the various classes of aryltrifluoroborate substrate is therefore probably due to a rather narrow window for balance of hydrolysis against transmetallation rate. The potential for involvement of



Substrate	Number of examples	Isolated yield (%)
	5	52 - 79
	2	93 - 97
	2	81 - 98
	4	85 - 94
	4	85 - 94
	3	97 - 99
	4	76 - 96
	2	79 -97
	14	33 - 95, (average 75%)

Figure 11. Heteroaryl Suzuki–Miyaura cross-coupling with MIDA boronates under slow-release conditions.

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the reaction vessel surface[51] in the kinetics of the hydrolysis, and thus the rate of slow release, makes the process rather unpredictable.

Molander has taken advantage of the stability of trifluoroborates under anhydrous conditions, to conduct elaborate orthogonal and iterative one-pot chemistry.[52] Unlike in the dan, MIDA, and *N*-phenylethanolamine examples, the deprotection to reveal the boronic acid occurs in situ with a simple solvent switch. For example, anhydrous cross-coupling occurs with the 9-BBN moiety after simple hydroboration of an alkene. A subsequent switch to an aqueous or protic environment initiates hydrolysis of the trifluoroborate functionality, and the liberated boronic acid, or intermediate, then undergoes the second, and thus iterative,[40] coupling (Figure 12).

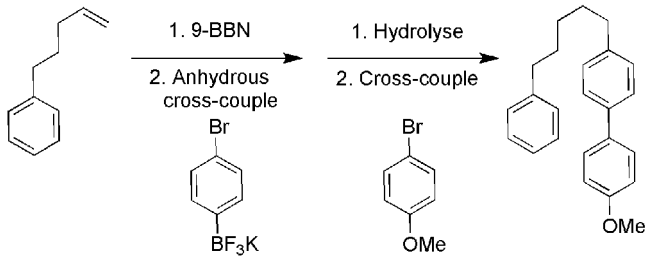

Figure 12. Iterative synthesis exploiting the orthogonal reactivity of R-9-BBN/R-BF_3K in Suzuki–Miyaura cross-coupling.

Molander has developed an extensive collection of difficult cyclopropyl and cyclobutyl boronate couplings.[53] There are also many examples of heteroaryl couplings, Figure 13, although there are no examples of coupling of the 2-pyridylboronate species,[54] which, because of the high propensity for protodeboronation, has become the benchmark unstable coupling substrate.

As discussed in section 2.2.1, another pathway for boronic acid degradation is oxidative homo-coupling.[12,51] This unwanted palladium-catalyzed side reaction can significantly reduce yields when there is ingress of air, or incomplete solvent or reactor degassing has occurred. The slow-release aryltrifluoroborate system is found to facilitate a substantial reduction in the extent of oxidative homocoupling, as compared to direct use of the corresponding boronic acid. Reactions run with deliberately low concentrations of the boronic acid were also shown to display this beneficial effect.[51] A low concentration of the active transmetallating reagent will affect the resting state of the palladium in the two competing catalytic cycles, Figure 14.

If the O_2 addition to palladium (0) species (***i***) is reversible and oxidative addition of the aryl halide is not, and the supply-rate for the aryl boronic acid is limited via slow-release, then the resting state of the catalyst can be the oxidative addition product (***ii***). Now transmetallation

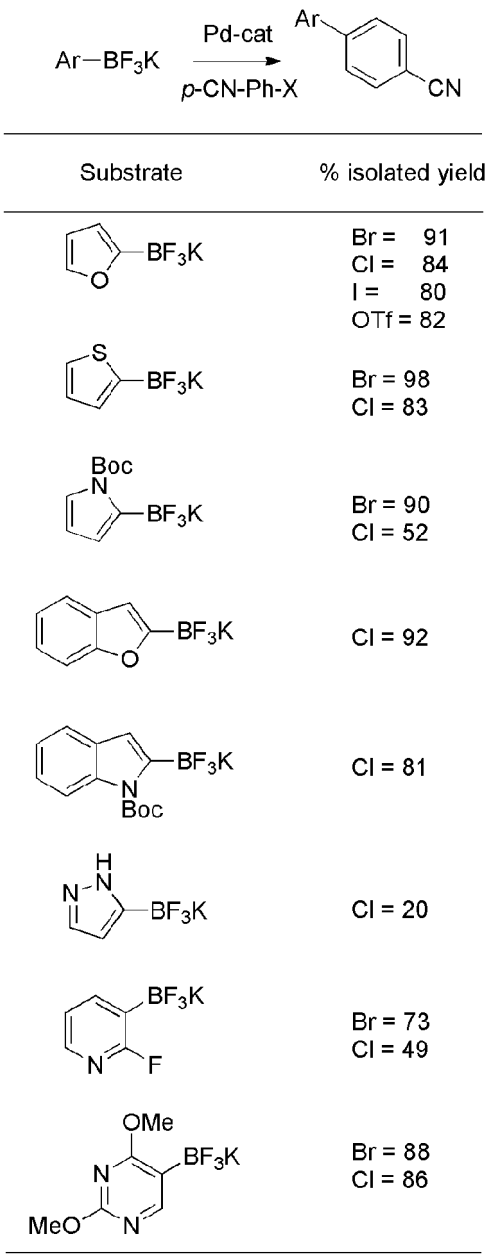

Figure 13. Suzuki–Miyaura cross-coupling with potassium heteroaryl trifluoroborates.

(***ii*** → ***iii***) becomes the turn-over limiting step, reducing the concentration of (***i***), and in turn (***iv***), and thus the amount of homo-coupling (via ***v*** and ***vi***) that can occur. In fact, a simple slow addition of the aryl boronic acid via a syringe pump has been shown to circumvent the need for its prior transformation into the corresponding trifluoroborate, as it simulates the same slow-release process.[51]

Process chemists at GlaxoSmithKline have also demonstrated that semi-batch addition of a boronic acid is very

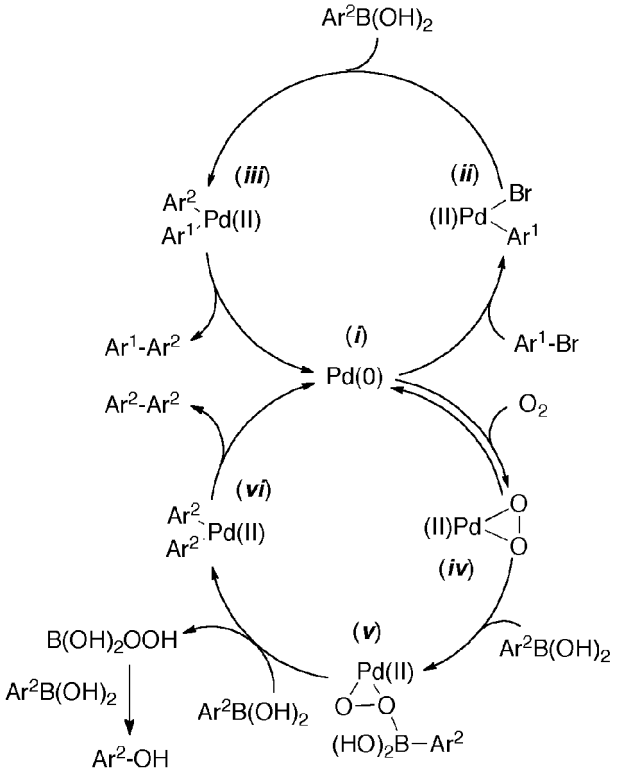

Figure 14. Competing cycles for Pd-catalyzed cross-coupling and oxidative homo-coupling of an aryl boronic acid.

efficient in reducing the level of a toxic polychlorobiphenyl (PCB) by-product.[55] Based on their kinetic data, they proposed that the slow addition caused an analogous shift in the resting state of the catalytic cycle.

2.4.3. Applications to Rh-Catalysis

Ellman[56] has demonstrated the importance of the slow-release strategy by comparing the MIDA boronate and trifluoroborate boronic acid surrogates in the rhodium-catalyzed addition to N-*tert*-butanesulfinyl aldimines, Figure 15.

In this example it has been shown that decomposition of the active alkenyl boronic acid is facile: addition to rhodium and subsequent protonation leads to the proto-deboronated product (analogous to mechanism **IV**). It was observed that excess of the boronic acid improved yields, but it was not as effective as the slow-release of the reagent from its protected form. Both the MIDA boronate and trifluoroborate are resistant to this degradation pathway. The former was superior to the latter under the conditions used, presumably due to the more effective slow-release conditions for MIDA boronates; but both performed better than the naked boronic acid.

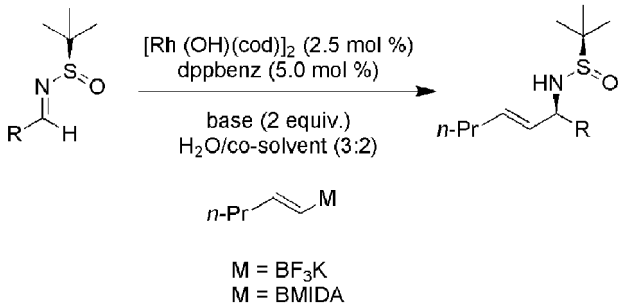

Figure 15. Slow-release in Rh-catalyzed imine addition.

3. Summary and Outlook

There are many examples reported in the literature where conditions have been developed to reduce the extent of side-product generation in the Suzuki–Miyaura coupling reaction. Most of these concern themselves with improving the activity of certain reagents, thereby favoring one reaction pathway over a less desired other. The art of masking group chemistry in metal-catalyzed cross-coupling concerns itself with the opposite: to make the reagent as unreactive under the desired reaction conditions as possible. It then relies on the slow-release of the reactive component to out-compete the side reactions. This has been shown to be a highly successful approach, as exemplified by the MIDA boronates developed by Burke, and the trifluoroborates developed by Molander. Using slow-release of the active component, they have been able to cross-couple some of the most troublesome substrates known. The alternative approach, to slowly add the boronic acid, will of course only suit those substrates that are stable enough to isolate. However it could serve as an easy and cheap method where substrates are unstable in solution or for processes where stringent degassing is difficult, or the MIDA boronate or trifluoroborate too expensive to prepare or purchase. The full potential of the slow-release technique is yet to be fully realised in catalysis, but it is hoped this article will stimulate the design of new reagents and application of the concept in other reactions.

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[6] Compare, for example, the very benign silicon-based reagents developed by Denmark a) S. E. Denmark, C. S. Regen, *Acc. Chem. Res.* **2008**, *41*, 1486–1499; with the rather toxic tin-based reagents of Stille b) D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.

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