Speciation control during Suzuki-Miyaura cross-coupling of haloaryl and haloalkenyl MIDA boronic esters

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Abstract: Boronic acid solution speciation can be controlled during the Suzuki-Miyaura cross-coupling of haloaryl MIDA boronic esters to enable the formal homologation of boronic acid derivatives. The reaction is contingent upon control of the basic biphase and is thermodynamically driven: temperature control provides highly chemoselective access to either BMIDA adducts at room temperature or BPin products at elevated temperature. Control experiments and solubility analyses have provided some insight into the mechanistic operation of the formal homologation process.

Introduction

The development of protected boronic acids has been pivotal to the growth of iterative Suzuki-Miyaura cross-coupling processes.[1,2] In particular, the boronic esters (*N*-coordinated boronates) derived from *N*-methyliminodiacetic acid (BMIDA)[2a,b,d,3-5] and the aminoboranes derived from 1,8-diaminonaphthalene (BDAN)[2c,d,6,7] are readily installed and removable protecting groups that render iterative Suzuki-Miyaura cross-coupling relatively facile: following a first cross-coupling event, protecting group hydrolysis under basic (BMIDA) or acidic (BDAN) conditions liberates the reactive parent boronic acid, primed for further cross-coupling (Figure 1a).

Similar to the majority of methods for the preparation of reactive boron species, these chemistries proceed via stoichiometric and step-wise manipulation of a single reactive boron species,[8] such as a boronic acid. Conversion of a protected boronic acid to an alternative reactive boron species, such as a boronic acid pinacol ester (BPin) typically proceeds via the same synthetic pathway; conversion of BMIDA to BPin requires hydrolysis and subsequent esterification (Figure 1b).[4a,d] We recently demonstrated that it is possible to convert a BMIDA ester to a BPin ester during the Suzuki-Miyaura cross-coupling of a haloaryl BMIDA with an aryl BPin.[9] This is achieved via pinacol recycling via control of multiboron solution speciation leading to a formal sp^2 BPin homologation (Figure 1c).

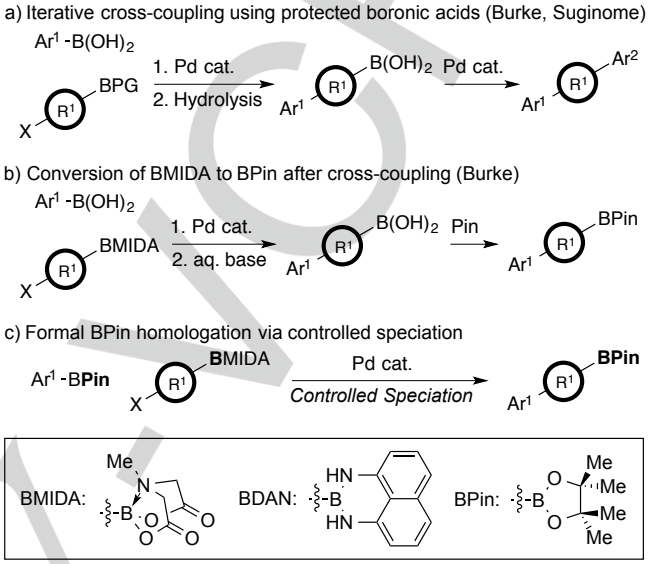

Figure 1. (a) Iterative cross-coupling using protected boronic acids, (b) cross-coupling of BMIDA followed by conversion to BPin; (c) formal BPin homologation by controlled speciation. DAN, 1,8-diaminonaphthalene; MIDA, *N*-methyliminodiacetic acid; Pin, pinacol/pinacolato.

Here we provide the full details of this study demonstrating (i) the dependence of the reaction on pH as well as the physical properties of the base, (ii) that the chemoselectivity of boron speciation can be thermodynamically controlled to provide selective access to either BMIDA or BPin products, and (iii) that the general concept of speciation control is transferrable across boronic acids, BPin esters, and catechol esters. We also provide an analysis of the parameters resulting in effective speciation control for this transformation and insight into the issues surrounding anomalous reactions.

Results and Discussion

Boronic acids and esters are known to exhibit complex and dynamic solution speciation equilibria.[10] Chemoselective control of boronic acid solution speciation comprising a mixture of boron species may therefore be expected to be difficult based on the requirement to simultaneously manipulate interlinked equilibria. Accordingly, the preparation of synthetically useful boron species, such as boronic acids and esters, is typically performed by manipulation of single boron component to avoid possible difficulties arising from these equilibria, potentially leading to mixtures of products.[10,11] However, exerting control over the equilibria associated with multiboron systems may provide useful and more efficient methods for the preparation of valuable boron reagents without resorting to the possibly more laborious

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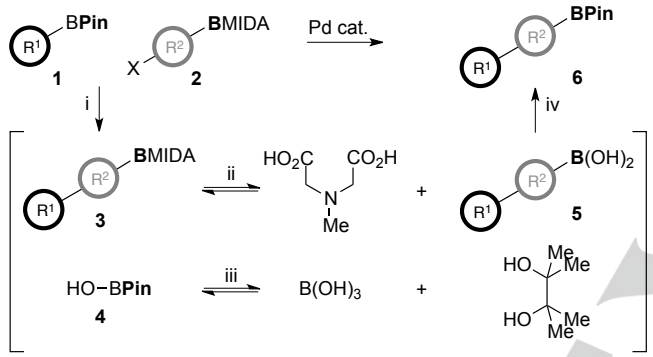
single molecule manipulations that are common throughout this preparative area.

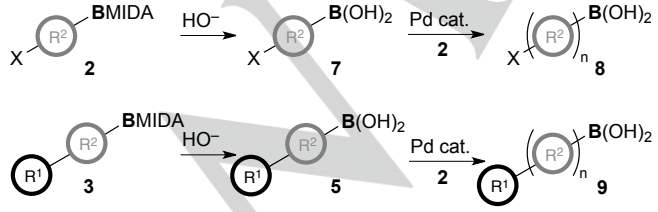
We sought to explore this idea in the context of Suzuki-Miyaura cross-coupling using two different boronic esters, specifically BPin esters (**1**) and haloaryl BMIDA esters (**2**) with the goal of ascertaining whether the boron speciation may be controlled during the reaction to produce a new BPin ester and thereby establishing a formal homologation process that would offer increased step efficiency over conventional approaches.[9]

The overall reaction was envisaged to take place via four elementary steps (Scheme 1): (i) C-C bond formation resulting from conventional Suzuki-Miyaura cross-coupling to generate an intermediate product BMIDA **3**; (ii) hydrolysis of **3** to the parent boronic acid **5**; (iii) hydrolysis of the Suzuki-Miyaura byproduct HO-BPin **4** to liberate pinacol; and (iv) esterification of **5** with the in situ generated pinacol to deliver the desired, formally homologated, product **6**.



Scheme 1. Proposed formal homologation of aryl BPin via controlled boron speciation during Suzuki-Miyaura cross-coupling of haloaryl BMIDA esters.

Each of the elementary steps are theoretically straightforward and are supported by studies from other research groups: cross-coupling of aryl BPin **1** with haloaryl BMIDA **2** to deliver the BMIDA **3** is typically a high yielding process.[4f] The subsequent hydrolysis of **3** to the latent boronic acid **5** is readily achieved with either NaOH or K_3PO_4.[4e,5d,g,q] Hydrolysis of boric acid esters, such as **4**, is similarly facile under aqueous basic conditions.[12] The final esterification of **5** with pinacol is also typically a high yielding and rapid process under a variety of conditions ranging from acidic to basic.[12,13] Based on this, steps (ii)-(iv) could all tentatively be controlled using an appropriate aqueous basic medium.



Scheme 2. Oligomerization of haloaryl BMIDA species during Suzuki-Miyaura cross-coupling due to premature in situ hydrolysis.

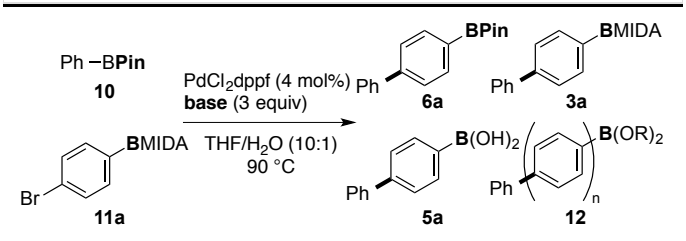
However, aqueous base is incompatible with the first reaction event due to the base lability of BMIDA esters.[4e,5d,g,q] Cross-coupling of BMIDA-containing compounds is typically performed under anhydrous conditions to avoid hydrolysis. In the envisioned process in Scheme 1, premature hydrolysis of **2** or **3** would lead to **5** and/or **7**, which may undergo uncontrolled oligomerization to **8** and/or **9** (Scheme 2).

In addition, the reaction would need to be staged appropriately to avoid cross-coupling conflict due to the similarities in reactivity profiles of starting material **1**, intermediate boronic acid **5**, and product **6** towards cross-coupling.

Design Plan. To reconcile the requirement for anhydrous conditions during cross-coupling and the aqueous basic conditions that would facilitate control over the subsequent reaction events, we sought to establish an internal water reservoir. This would be achieved by exploiting the physical properties of the inorganic bases typically associated with Suzuki-Miyaura cross-coupling.[14] Many of these bases are hygroscopic, and generate stable hydrates. In contrast to the majority of Suzuki-Miyaura reactions, which employ relatively large quantities of H_2O (commonly 4:1-7:1),[1e] addition of a controlled quantity of H_2O to a suitably hygroscopic inorganic base was proposed to sequester H_2O and safeguard BMIDA integrity during cross-coupling while simultaneously providing sufficient H_2O and base within the reaction mixture to facilitate the downstream hydrolytic and esterification events.

Accordingly, we began by interrogating a benchmark Suzuki-Miyaura cross-coupling reaction between phenylboronic acid pinacol ester (BPin) **10** and 4-bromophenyl BMIDA **11a** using a common Pd catalyst ($PdCl_2dppf$) in THF using two typical inorganic bases, K_3PO_4 and Cs_2CO_3, in conjunction with a comparatively restricted quantity of H_2O (10:1) vs. typical Suzuki-Miyaura reactions (Table 1).

Table 1. Initial reactions with K_3PO_4 and Cs_2CO_3 using 10:1 THF:H_2O.



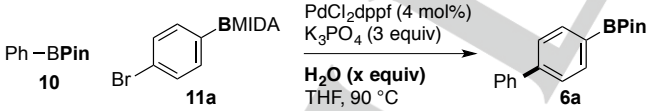
Entry	Base	Temp. (°C)	**6a:3a:5a:12** (%)[a]
1	K_3PO_4	50	57:13:7:0
2	Cs_2CO_3	50	52:6:7:0
3	K_3PO_4	90	30:0:0:70
4	Cs_2CO_3	90	27:0:0:73

[a] Determined by HPLC analysis.

Reactions at 50 °C and 90 °C were highly positive for both bases employed. At the more moderate 50 °C (entries 1 and 2), good conversion to product was observed (approx. 50%) with some of the intermediate boron species also detected – BMIDA **3a** was observed in 6-13% with the parent boronic acid **5a** seen at 7% in both cases. Pleasingly, no oligomerization was observed but conversion was incomplete at approximately 70%. Increasing the temperature of the reaction to 90 °C (entries 3 and 4) provided complete conversion of starting material, a relatively low conversion (approx. 30%) to the desired product **6a**, with the mass balance consisting of undefined oligomeric material (**12**).[15]

We believed the large degree of oligomerization was due to a more rapid hydrolysis of the BMIDA starting material **11a** and/or intermediate **3a** at this higher temperature: BMIDA compounds are readily hydrolyzed in the presence of aqueous base and this can proceed rapidly with strong bases (e.g., with NaOH) or more slowly with weaker bases (e.g., with K_3PO_4).[4e,5d,g,q] Burke employed K_3PO_4-mediated slow hydrolysis of BMIDA as a method to facilitate the cross-coupling of notoriously sensitive boronic acids via slow-release protocol.[5h,o] For the reaction in Table 1, while the conversion to product was greater at 50 °C, overall conversion was greater at 90 °C. Based on this we elected to pursue optimization at 90 °C as we believed that an appropriately balanced basic biphase[1d,1e] would mitigate premature BMIDA hydrolysis and thereby eliminate the oligomerization issue.

Systematic H_2O Evaluation. We first evaluated the quantity of H_2O added to the reaction using K_3PO_4 as the base. In terms of hygroscopicity, K_3PO_4 is known to form a stable tetrahydrate[14] and so was expected to support a specific quantity of H_2O. However, the availability of this 'captured' H_2O was unknown. In addition, based on the envisioned solution processes taking place (Scheme 1), as the reaction progresses, boric acid will accumulate and may condense to release additional H_2O.[14] This may be promoted by a desiccant, such as K_3PO_4. Therefore, the exact quantity of H_2O available within the reaction at any stage was uncertain. As such, we undertook a comprehensive H_2O evaluation (Scheme 3 and Chart 1).



Scheme 3. Evaluation of H_2O and the effect on conversion to **6a**.

As expected, the conversion to **6a** was highly dependent on the level of H_2O added to the system. The response surface in Chart 1 displayed three main regions in which the reaction could be predicted to deliver specific outputs. (1) Using 0 equivalents of H_2O. Cross-coupling was found to be very inefficient with only modest levels of product observed (<60%) and extended reaction times failing to provide any increase. No oligomerization was detected and the mass balance was principally unreacted starting material.

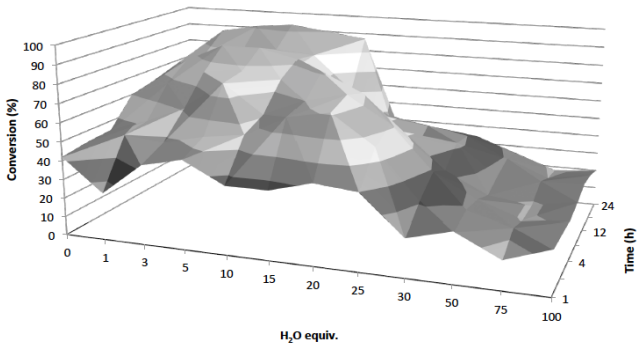


Chart 1. Experimental response surface: conversion to **6a** vs. H_2O equivalents/time for the formal homologation. Determined by HPLC analysis.

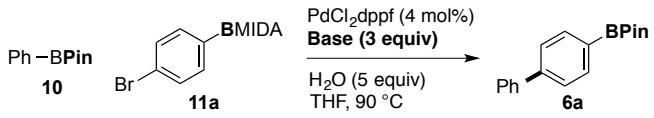
(2) Using 1-15 equivalents of H_2O. When the reaction was allowed to take place over 24 h, excellent levels of conversion to **6a** could be obtained (up to 92% at 5 equivalents H_2O) with no oligomerization and complete consumption of starting material. Shorter reaction times resulted in lower conversions to **6a** with variable levels of intermediate boron species **3a** and **5a** detected. (3) Using 15-25 equiv H_2O. Conversion to products, intermediates or byproducts was unpredictable and variable depending on the reaction time – shorter times appeared to enable good levels of conversion to **6a**, with oligomerization increasing markedly as the reaction time increased, potentially indicating that cross-coupling of **11a** was inefficient allowing further reaction of **11a** with **6a** or **3a**. (4) Using >25 equiv H_2O. Poor, but consistent levels of conversion to **6a** (approx. 20-30%) were observed throughout with the mass balance composed of oligomeric material, indicating poor control of the rate of BMIDA hydrolysis.

Based on this evaluation, we selected 5 equivalents of H_2O to move forward. This was chosen since it provided excellent levels of conversion as well as providing a tolerance for any additional H_2O arising from a less stringent reaction set up.

Base Evaluation. With a functional knowledge of H_2O influence, we next evaluated the role of the base. Different bases were predicted to exhibit broadly different impacts on the reaction. Amatore and Jutand have demonstrated the triple role of HO^- in the Suzuki-Miyaura reaction, affecting oxopalladium formation, boron solution equilibria, as well as reductive elimination.[16] These authors also demonstrated that different metal cations also affect Suzuki-Miyaura cross-coupling.[17] For the reaction under development, in addition to the expected effects detailed by Amatore and Jutand, variation of physical properties was expected to have a profound impact.

A first survey of potassium bases immediately revealed the importance of $pK_a^{\dagger}$ (Table 2 and Chart 2). Using KTFA (entry 1), no cross-coupling took place and starting materials were returned. As the pK_a increased through KOAc, K_2CO_3, and K_3PO_4 (entries 2-4), cross-coupling efficiency immediately improved and speciation control was also possible, with conversion reaching an optimum in the presence of K_3PO_4.

Table 2. Potassium base survey.



Entry	Base	pK_a[a]	**6a** (%)[b]
1	KTFA	0	0
2	KOAc	6	37
3	K_2CO_3	10	51
4	K_3PO_4	12	92
5	KOH	16	22
6	KO*t*-Bu	18	23
7	KH_2PO_4	2	0
8	K_2HPO_4	7	0

[a] Approximate values.[18] [b] Determined by HPLC analysis.

Starting material consumption was incomplete for KOAc and K_2CO_3. Interestingly, for entries 2-4, **3a** or **5a** were not detected – all Suzuki-Miyaura product was converted to the BPin adduct **6a**. Therefore, under specific conditions, the overall reaction efficiency becomes entirely dependent on cross-coupling efficiency. Use of KOH and KO*t*-Bu delivered incomplete conversion of starting materials, poor conversion to product (approx. 20%), and extensive oligomerization, presumably due to rapid hydrolysis of BMIDA (entries 5 and 6). The relationship between pK_a and conversion to **6a** is clearly demonstrated by entries 1-6.

However, the relationship between base and reaction efficiency is not so straightforward as bases of similar pK_a were found to provide starkly different results. KH_2PO_4 (entry 7) of similar pK_a to KTFA, also provides no conversion. In contrast, K_2HPO_4 (entry 8) provides no conversion while this has similar pK_a to KOAc, which provides 37% of **6a**. Consequently, the reaction is not solely dependent upon pK_a (or the resultant solution pH) although this is clearly highly important.

This was compounded when the effect of the metal countercation was evaluated. Tribasic phosphate appeared to be optimum for the reaction but the effect of variation of the associated metal ion – alkali metals or alkaline earths – was surprising (Table 3).

The pK_a and solution pH ranges of these phosphate salts are approximately equivalent. Accordingly, the widely different reaction response must be due to other factors. As noted above, Amatore and Jutand have shown that the countercation can impact upon cross-coupling efficiency via influencing transmetallation.[17] H_2O plays an important role in the transport of metal ions from the aqueous phase to the organic phase.[19] Accordingly, the quantity of H_2O present in the system may directly affect the availability of metal ions in the organic phase. This could contribute to the results observed in Table 3.

Table 3. Tribasic phosphate countercation survey.

Entry	Base	**6a** (%)[a]
1	Li_3PO_4	0
2	Na_3PO_4	0
3	K_3PO_4	92
4	Cs_3PO_4	0
5	$Mg_3(PO_4)_2$	0
6	$Ca_3(PO_4)_2$	0

[a] Determined by HPLC analysis.

For the reaction under development, however, the physical properties of the base appear to be one of the principal contributors to reaction efficiency. Selected physical constants for the evaluated bases are provided in Table 4.

From this available data, two principal relationships can be established:

(1) The relationship between pK_a/pH and conversion. From the results in Table 2 and Chart 2 as well as previous studies of BMIDA cross-coupling and boronic ester esterification processes, the reaction is evidently dependent on pH control. An optimum is clearly reached with K_3PO_4 with an approximate pK_a and pH range of 12.7 and 10-14, respectively. However, evaluation of different metal phosphates, which exhibit approximately similar pK_a and pH shows that K_3PO_4 is exclusively effective while the other phosphates result in no conversion to the desired product – indeed, no cross-coupling at all under the same reaction conditions.

Solvation effects driven by the electrostatic parameter result in aqueous solutions of metal ions varying markedly in their pH, from 11.2–14 for the ions employed in Table 4.[14] The more acidic cations, such as Mg^{2+} or Ca^{2+}, may therefore result

Table 4. Selected physical constants for the bases used in Tables 2 and 3.

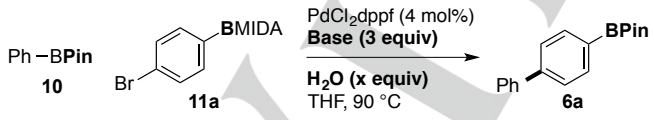
Entry	Base	pK_a[a]	Approx. pH of aqueous metal ion[b]	Solubility at RT (g/100 mL H_2O)[b]	**6a** (%)[c]
1	Li_3PO_4	12.7	13.6	0.027	0
2	Na_3PO_4	12.7	13.9	14.25	6
3	K_3PO_4	12.7	14.0	106	92
4	Cs_3PO_4	12.7	---	---	6
5	Cs_2CO_3	10.3	---	261	48
6	$Mg_3(PO_4)_2$	12.7	11.2	0.0009[d]	0
7	$Ca_3(PO_4)_2$	12.7	12.7	0.00012	0

8	KTFA	-0.25	14.0	---	0
9	KOAc	4.8	14.0	269	37
10	K_2CO_3	10.3	14.0	111	51
11	KOH	14.2	14.0	121	22
12	KO*t*-Bu	17.0	14.0	---	23
13	KH_2PO_4	2.1	14.0	25	0
14	K_2HPO_4	7.2	14.0	168	0

[a] Approximate values.[18]. [b] Approximate values.[14]. [c] Determined by HPLC analysis using an internal standard. [d] Value for the pentahydrate.

in a buffering effect and thereby negatively modulate pH, however, this is likely to be minor in contrast to the pH contribution of the anion and does not account for the complete absence of reactivity seen. For example, KOAc delivers a considerably lower solution pH than $Mg_3(PO_4)_2$, however, KOAc does deliver some observable cross-coupling and speciation control while this is completely absent for $Mg_3(PO_4)_2$ (entry 6 vs. entry 9). Accordingly, other properties of the bases must be considered in conjunction with pH to explain these observations. (2) The relationship between solubility of the base and conversion. Information on the hygroscopicity of the bases in Table 4 is generally only qualitative: these are typically designated as either hygroscopic or deliquescent with little quantitative information available. Some salts have specific hydrate states, such as K_3PO_4 and $Mg_3(PO_4)_2$ existing as the stable tetrahydrate and octahydrate, respectively.[14] In terms of the saturated aqueous solutions, relative humidity (%RH) as well as the more appropriate relative saturation (%RS) values have not been documented for all of these bases. Indeed, only KOAc, K_2CO_3, and KOH have %RH available – 23.1%, 43.2%, 9.3% (at 20 °C), respectively.[20] Accordingly, establishing a relationship between reaction efficiency and hygroscopicity was not possible. However, solubility data was informative. Specifically, as the aqueous solubility of the base increases, conversion also increases. For example, when comparing the alkali metal and alkaline earth phosphates, moving from Ca^{2+} to Mg^{2+} to Li^+ to Na^+ to K^+, both solubility and conversion increase (entries 1-3, 6, and 7). Unfortunately, no solubility data was available for Cs_3PO_4. If solubility is removed as a factor then pH drives the reaction efficiency. For example, K_2CO_3 and Cs_2CO_3 both exhibit good solubility (>1 g/mL) and equivalent pH and deliver very similar levels of conversion (approx. 50%). KOAc again demonstrates good solubility but with a lower pH, conversion decreases (entry 9).At the low quantity of H_2O used in this system (5 equiv), low base solubility appears to be a key issue. We considered the possibility that this may be rectified if the quantity of H_2O was increased. Indeed, analysis of the reactions of the alkali metal phosphates at 22 equiv H_2O (10:1 THF:H_2O) and 50 equiv H_2O shows that bases of lower solubility can begin to deliver some improved conversion in certain cases (Table 5). For example, Li_3PO_4 starts to show some C-C bond formation as well as speciation control at 50 equiv H_2O (Table 5, entry 2) and Na_3PO_4 improves from 6% (Table 4, entry 2) to 20% conversion to **6a** when increasing the H_2O quantity 10-fold (Table 5, entry 4). Conversely, control is rapidly lost in the reactions with K_3PO_4 using excesses of H_2O (Table 5, entries 5 and 6 vs. Table 4, entry 3), leading to extensive uncontrolled oligomerization, while H_2O loading had little effect on reactions using Cs_3PO_4 (entries 7 and 8).

Table 5. Increasing the quantity of H_2O with alkali metal phosphate bases.



Entry	Base	H_2O equiv	**6a** (%)[a]
1	Li_3PO_4	22 equiv	0
2	Li_3PO_4	50 equiv	8
3	Na_3PO_4	22 equiv	16
4	Na_3PO_4	50 equiv	20
5	K_3PO_4	22 equiv	30
6	K_3PO_4	50 equiv	26
7	Cs_3PO_4	22 equiv	8
8	Cs_3PO_4	50 equiv	6

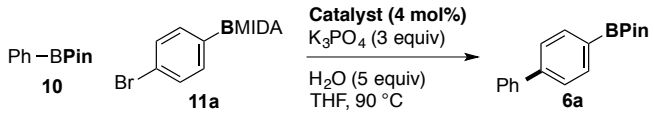
[a] Determined by HPLC analysis using an internal standard.

Overall, pH and solubility of the base are the primary factors responsible for control over the formal homologation reaction. When solubility is good, appropriate pH modulation then ensures effective control of the speciation events, with K_3PO_4 providing an ideal balance of both of these properties that allows efficient C-C bond formation and hydrolysis/esterification. There may be a 'threshold solubility' for a specific base pK_a in order to ensure reaction efficiency; however, this could not be established from the available data.

Catalyst and Electrophile Evaluation. Following optimization of H_2O and base, we subsequently performed a thorough analysis of reaction performance in relation to the catalyst and electrophile. From the preceding optimization phase, we were aware that, under specific conditions, the overall reaction efficiency became dependent upon the cross-coupling efficiency, i.e., that speciation events could be readily controlled and all available initial cross-coupling product **3a** could be smoothly funneled to **6a**. To ensure a robust C-C bond formation, we analyzed a range of catalyst systems under the emerging optimum base/H_2O conditions (Table 6).From these results, it was clear that use of Pd(II) precatalysts was preferred over Pd(0) (for example, entry 4 vs. entry 5). In addition, the reaction clearly requires a phosphine ligand in order to be synthetically useful and, in the majority of cases, $Pd(OAc)_2$ was superior to $PdCl_2$. In the absence of a ligand (entries 1-3), very poor cross-

coupling was observed. However, not all phosphine ligands were effective in promoting C-C bond formation under the conditions employed. For simple ligands, the reaction performance was generally greater when the catalyst was preformed – addition of separate Pd(II) source and ligand was often less effective than use of the same preformed catalyst. For example, addition of PPh_3 to $PdCl_2$ delivered approximately the same conversion to **6a** as the preformed $PdCl_2(PPh_3)_2$ (entry 5 vs. entry 7) whereas, addition of dppf to $PdCl_2$ was significantly less effective than use of the preformed $PdCl_2$dppf (entry 6 vs. entry 15). Use of more active catalyst systems such as the biaryl monophosphines developed by Buchwald,[21] gave good results but were less effective for bromophenyl BMIDA substrate **11a** than the simpler $PdCl_2$dppf (entry 6 vs. entries 21-28).

Table 6. Catalyst evaluation for the reaction of **10** and **11**.

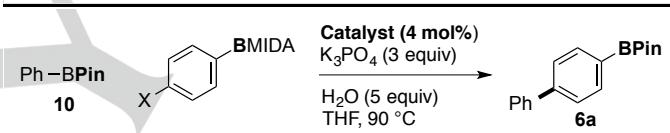


Entry	Catalyst	Ligand[a]	**6a** (%)[b]
1	$PdCl_2$	---	0
2	$Pd(OAc)_2$	---	5
3	$Pd_2(dba)_3$	---	7
4	$Pd(PPh_3)_4$	---	36
5	$PdCl_2(PPh_3)_2$	---	63
6	$PdCl_2$dppf	---	92
7	$PdCl_2$	PPh_3	56
8	$Pd(OAc)_2$	PPh_3	70
9	$PdCl_2$	P*t*-Bu_3	41
10	$Pd(OAc)_2$	P*t*-Bu_3	55
11	$PdCl_2$	dppe	4
12	$Pd(OAc)_2$	dppe	0
13	$PdCl_2$	dppp	0
14	$Pd(OAc)_2$	dppp	55
15	$PdCl_2$	dppf	1
16	$Pd(OAc)_2$	dppf	24
17	$PdCl_2$	BINAP	13
18	$Pd(OAc)_2$	BINAP	67
19	$PdCl_2$	XantPhos	0
20	$Pd(OAc)_2$	XantPhos	10
21	$PdCl_2$	SPhos	14
22	$Pd(OAc)_2$	SPhos	77
23	$PdCl_2$	XPhos	20
24	$Pd(OAc)_2$	XPhos	67
25	$PdCl_2$	CyJohnPhos	4
26	$Pd(OAc)_2$	CyJohnPhos	72
27	$PdCl_2$	DavePhos	23
28	$Pd(OAc)_2$	DavePhos	71

[a] Added independently. [b] Determined by HPLC analysis.

To ensure synthetic scope, an analysis of halide and pseudohalide derivatives of **11a** was conducted with the most successful catalyst ($PdCl_2$dppf) as well as a more activated $Pd(OAc)_2$/monophosphine-based catalyst system (Table 7). With the exception of the less reactive chlorophenyl BMIDA substrate (entries 7-9), $PdCl_2$dppf provided superior levels of conversion, with bromophenyl BMIDA being optimum. Pleasingly, excellent conversion could be achieved with chlorophenyl BMIDA using $Pd(OAc)_2$/SPhos (entry 9).

Table 7. Variation of the electrophile.



Entry	Catalyst	Ligand	X	**6a** (%)[a]
1	$PdCl_2$dppf	---	I	60
2	$Pd(OAc)_2$	SPhos	I	34
3	$PdCl_2$dppf	---	Br	90
4	$Pd(OAc)_2$	SPhos	Br	77
5	$PdCl_2$dppf	---	OTf	61
6	$Pd(OAc)_2$	SPhos	OTf	48
7	$PdCl_2$dppf	---	Cl	0
8	$Pd(OAc)_2$	CyJohnPhos	Cl	68
9	$Pd(OAc)_2$	SPhos	Cl	82

[a] Determined by HPLC analysis.

Substrate Scope.

The scope of the optimized reaction conditions was explored through the synthesis of a range of substrates (Figure 2).[9]

A broad range of common and synthetically useful functionality was tolerated including amides (**6b**), esters (**6e**, **6n**), ethers (**6h**), and nitriles (**6g**), encompassing both electron-rich and electron-poor BPin starting materials. Pleasingly, the reaction also tolerated heterocyclic moieties, such as pyrazoles, furans, pyrans, and thiophenes (**6d**, **6i**, **6k**, **6m**). All three

substitution patterns on the haloaryl MIDA were compatible, although *ortho*-substitution was more effective with less sterically demanding BPins. For these reaction conditions, fluoro-substituted BMIDA esters were found to be amenable but other functionalization of the BMIDA component was less successful. This could be overcome by the use of a more active catalyst system (*vide infra*).

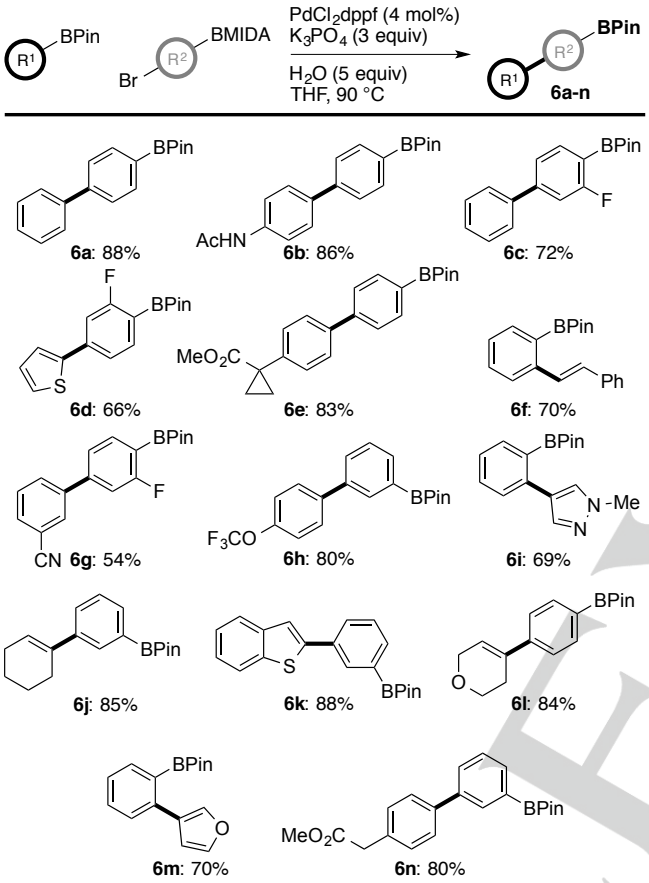


Figure 2. Formal homologation of Ar-BPin using haloaryl BMIDA esters. Yields of isolated products.

The homologation process was also found to be immediately transferable to haloalkenyl BMIDA reagents (Figure 3).[9] This enabled the preparation of a set of elaborated alkenes that included both aryl (**13c**, **13e**, **13g**) and heteroaryl (**13a**, **13b**, **13d**, **13f**) substituents. While 1,2-disubstituted haloalkenyl BMIDA components were broadly successful, the use of 1,1 disubstituted olefins led to isomerization providing mixtures of 1,1- and 1,2-disubstituted olefinic BPin products (**13g**).[5h] Unfortunately, dienyl BPin products could not be prepared using this protocol (**13h**).

To further broaden the scope of the reaction, a set of functionalized haloaryl BMIDAs was employed (Figure 4).[9] For these substrates the standard catalyst system ($PdCl_2$dppf) was not sufficiently reactive to promote efficient C-C bond formation. However, use of a more reactive catalyst system ($Pd(OAc)_2$/SPhos) easily circumvented this reactivity issue, allowing these less reactive electrophiles to be effectively cross-coupled as well as preserving the speciation control. This enabled the use of haloaryl BMIDA esters with CF_3 (**6o**, **6q**) and OMe (**6r**) functionality as well heterocyclic BMIDA esters (**6p**). Certain functionality, however, in particular *o*-OMe (**6s**, **6t**) and *o*-CO_2Me (**6u**, **6v**), were not tolerated (*vide infra*).

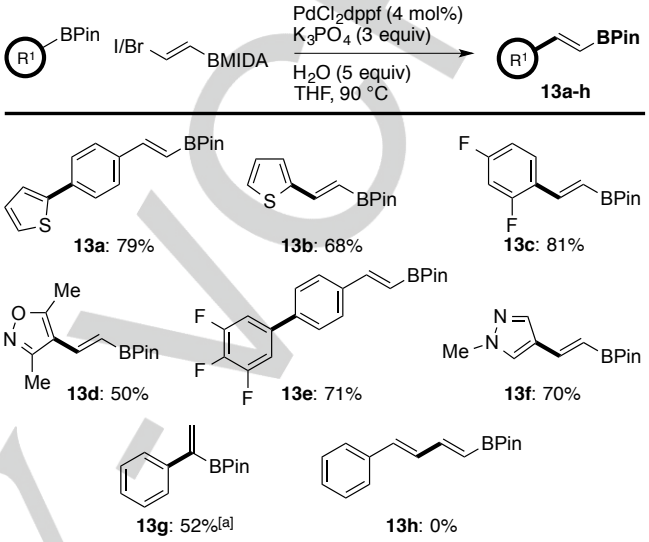


Figure 3. Using alkenyl BMIDA boronic esters. Yields of isolated products. [a] As a mixture of olefin regioisomers and stereoisomers.

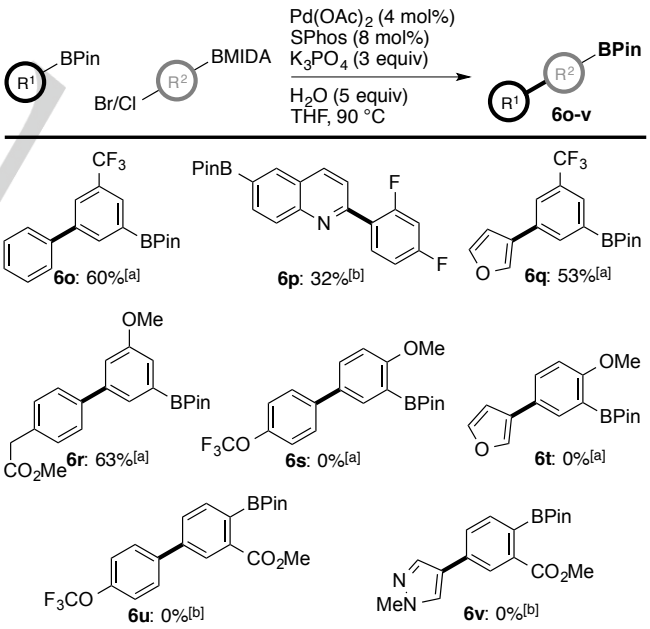
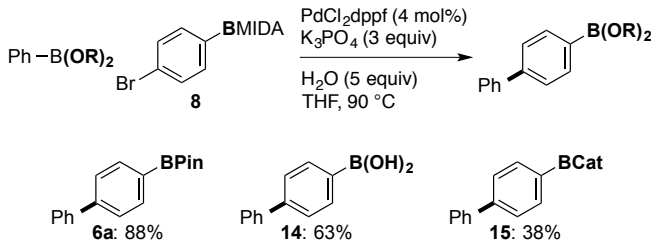


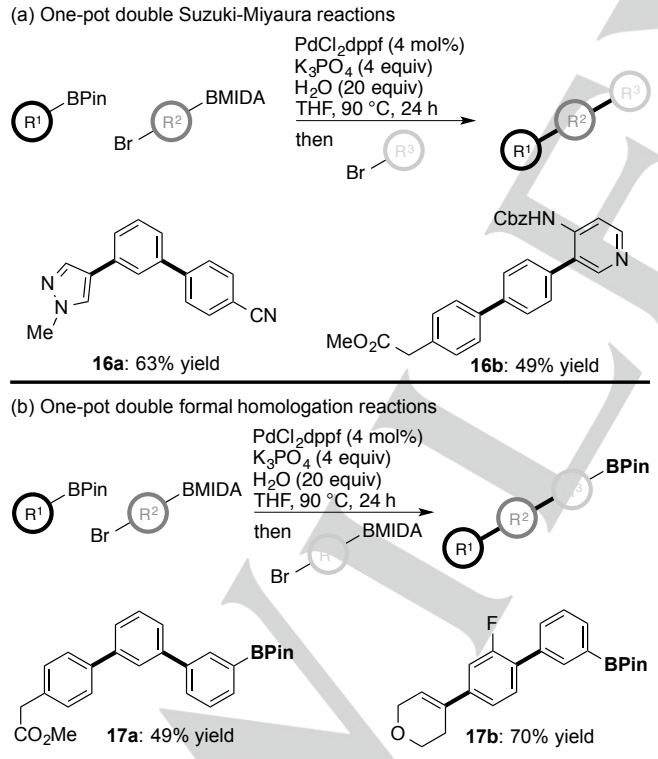
Figure 4. Homologation employing chloroaryl BMIDA and specific substituted aryl BMIDA components. Yields of isolated products. [a] Using bromoaryl BMIDA. [b] Using chloroaryl BMIDA.

The generality of the overall reaction with regards to speciation control was also assessed using three different boron

species (Scheme 4). As shown above, the model BPin system is readily controlled under the optimized conditions to enable the formal BPin homologation process: 88% isolated yield of **6a**. Changing the starting boron species to both boronic acids and boronic acid catechol esters (BCat) was found to be relatively well accommodated using these conditions to provide access to the expected formally homologated adducts **14** and **15**, respectively, without any further optimization. It should be noted that the low conversion to **15** was due to the stability of the catechol ester, which was found to readily hydrolyze to the boronic acid. These processes demonstrate the promising generality of speciation control to facilitate access to higher homologues of boron species in a one-pot operation.



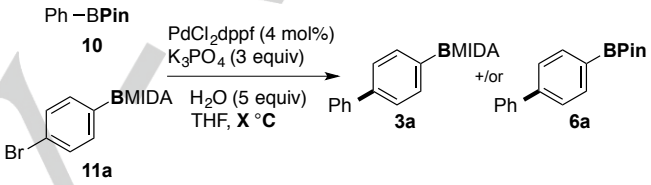
Scheme 4. Generality of speciation control using different boron species. Cat, catecholate.



Scheme 5. One-pot double Suzuki-Miyaura and double formal homologation reactions. Yields of isolated products.

To probe whether the Pd catalyst remained active, after completion of the formal BPin homologation, a second aryl bromide was added to the reaction mixture (Scheme 5a).[9] Pleasingly, the catalyst was found to be sufficiently active to enable a second Suzuki-Miyaura cross-coupling to take place between the newly formed BPin species and the added aryl bromide. This provided a method for one-pot double Suzuki-Miyaura cross-coupling proceeding in good yield for products **16a** and **16b**. Moreover, if a second equivalent of bromoaryl BMIDA was added, the formal homologation reaction could be extended further (Scheme 5b).[9] Pinacol turnover could be conducted once again in this one-pot reaction now enabling a method for controlled oligomerization of BPin species, again in good yield for products **17a** and **17b**.

Speciation Control via Temperature Regulation. During the course of the optimization process, the effect of temperature on both the cross-coupling and speciation turnover was investigated. While 90 °C was found to be efficient at enabling conversion to product **6a**, lower temperatures gave much lower conversion (Scheme 6, Chart 2).



Scheme 6. Evaluation of reaction temperature during Suzuki-Miyaura cross-coupling of Ar-BPin and haloaryl BMIDA. See Chart 3, below.

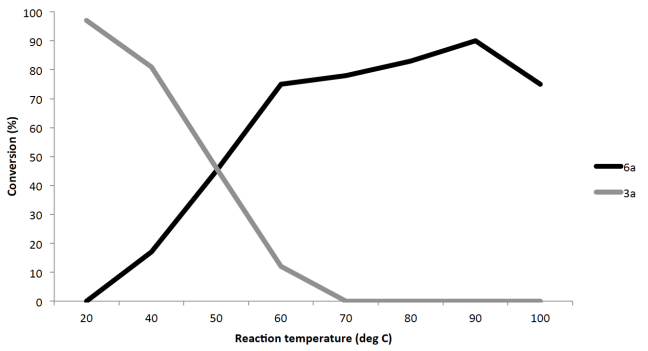
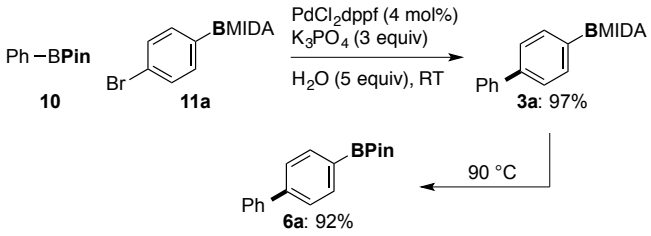


Chart 2. Temperature dependent control of speciation during Suzuki-Miyaura cross-coupling of Ar-BPin and haloaryl BMIDA. Determined by HPLC analysis.

However, it was noted that although conversion to **6a** was decreased at lower temperature, the mass balance of the reaction was the product of the initial cross-coupling, specifically the biphenyl BMIDA species **3a**. Indeed, at room temperature, **3a** was found to be the sole product of the reaction. This demonstrated that, in the absence of a thermal driving force, the availability of aqueous base was sufficiently retarded under the developed conditions to ensure the integrity of BMIDA ester **3a**. Upon heating, **3a** is hydrolyzed to boronic acid **13**, allowing conversion to **6a**. Unlike BMIDA esters, BPin esters are not easily hydrolyzed under the prevailing hydrolytic conditions.[22]

Accordingly, **6a** is thermodynamically more stable under the basic reaction conditions.

This was readily demonstrated in a control reaction where carrying out the optimized reaction at room temperature led to 97% of **3a** which, upon heating to 90 °C, was smoothly converted to **6a** (Scheme 7).



Scheme 7. Temperature control of speciation. Determined by HPLC analysis.

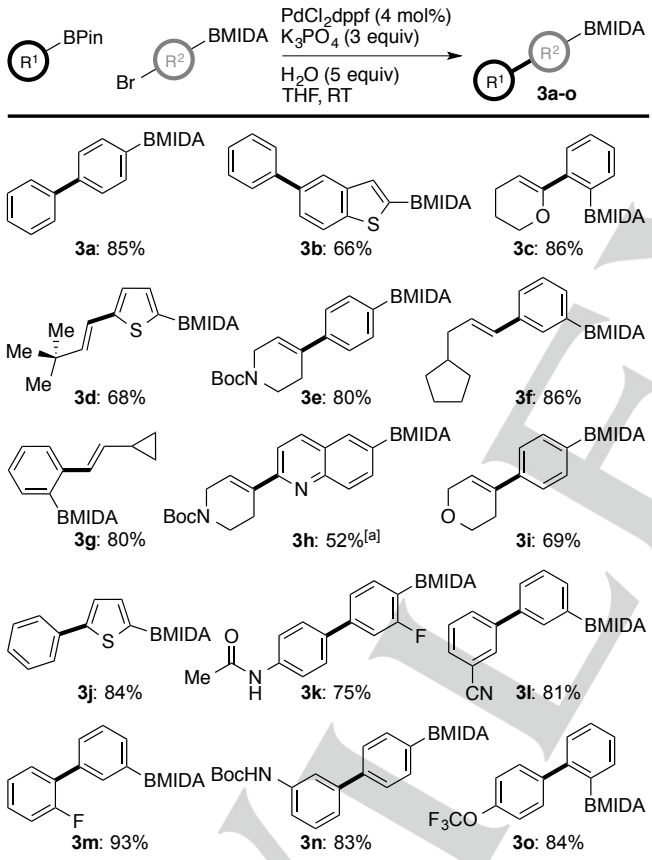


Figure 5. Room temperature cross-coupling of haloaryl BMIDA in the presence of aqueous base. Yields of isolated products.

Accordingly, it became possible to chemoselectively control the outcome of the haloarylBMIDA cross-coupling reaction reaction in terms of two possible boron species, BMIDA **3a** or BPin **6a**, entirely through temperature control. The ability to control the product of this reaction by simply altering the temperature opened up a potentially useful synthetic possibility. Due to their rapid hydrolysis with aqueous base, cross-coupling of haloaryl BMIDA esters is normally carried out under strictly anhydrous conditions, often employing elevated temperatures or alternate promoters such as F^- to ensure synthetic efficiency.[4e] However, overly harsh thermal promotion can limit the potential scope of these processes due to conflicting decomposition pathways of sensitive substrates, including promoting protodeboronation of the boron-derived coupling partners.[23] The ability to carry out cross-couplings of haloaryl BMIDA species at ambient temperature in the presence of aqueous base may therefore be desirable. With no further optimization required, we then sought to demonstrate the utility of this reaction by generating a small library of functionalized BMIDA products (Figure 5).

Once again a range of common functionality was compatible with the developed process. In addition, this protocol readily accommodated temperature-sensitive functional groups such as heterocyclic BMIDA (**3b**, **3d**, **3h**, **3j**) and protecting groups (**3e**, **3h**, **3n**), which were found to protodeboronate or hydrolyze, respectively, at more elevated temperatures.

It is worthwhile noting that this procedure had the added benefit of requiring very little purification – no chromatography was necessary with products isolated following a single aqueous wash and precipitation of the product using Et_2O. If reactions do not proceed to completion, separation of two different BMIDAs, either via crystallization or chromatography, is exceptionally difficult. Beyond the examples given in Figure 5, many similar cross-couplings do proceed effectively to deliver the product in good yield but in approx. 90% purity. Alkenyl BPin were also readily employed, with the synthesis of a set of vinyl MIDAs including aryl (**18a**, **18b**, **18d**), heterocyclic (**18c**, **18e**), and dienyl (**18f**) functionality (Figure 6).

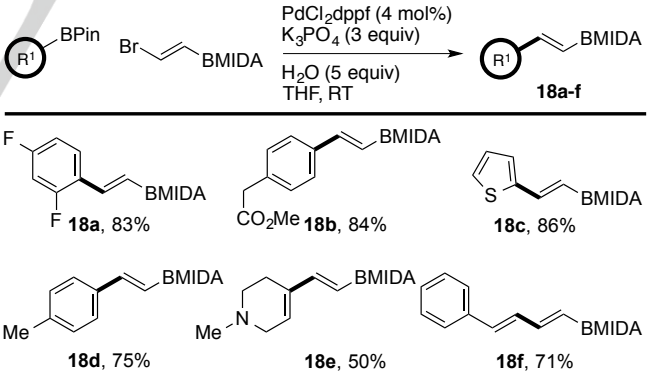
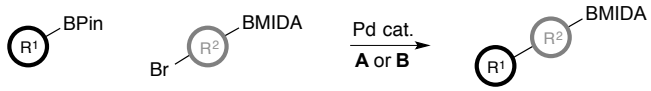


Figure 6. Room temperature cross-coupling of haloalkenyl BMIDA in the presence of aqueous base. Yields of isolated products.

From the utility perspective, the developed method compares favorably with existing methods. A comparison of reaction performance with the developed room temperature protocol vs. previously described methods[4b] using five representative substrates (aryl, heteroaryl, alkenyl and with variation of regiochemistry) is provided in Table 8.

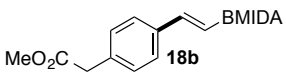
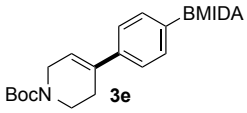
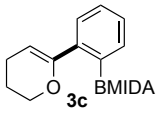
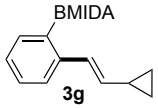
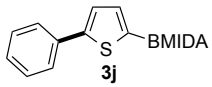
Table 8. Comparison of similar procedures for retaining the BMIDA functionality during Suzuki-Miyaura cross-coupling.



Reactions conditions

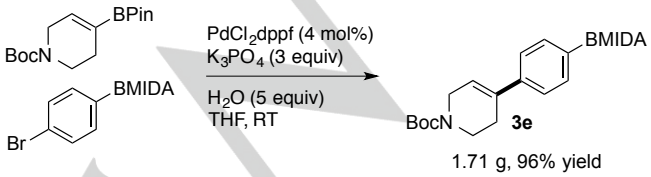
A: $PdCl_2dppf$ (4 mol%), K_3PO_4 (3 equiv), H_2O (5 equiv), THF, RT

B: $PdCl_2dppf$ (5 mol%), K_3PO_4 (6 equiv), DMSO, 45 °C

Entry	Product	Procedure	Yield (%)[a]
1	 **18b**	A B[4b]	84 64
2	 **3e**	A B[4b]	80 87
3	 **3c**	A B[4b]	86 ---[b]
4	 **3g**	A B[4b]	80 ---[c]
5	 **3j**	A B[4b]	84 39[d]

[a] Yields of isolated products. [b] No coupling observed, BMIDA starting material returned. Pyranyl BPin observed to rapidly decompose at the temperature associated with conditions B. [c] No coupling observed, BMIDA starting material returned. [d] Reaction did not proceed to completion.

The mild room temperature protocol provided consistently useful yields of the desired BMIDA products (conditions A). In some cases, the previously described protocol (conditions B) was comparable (entries 1 and 2). In other cases, conditions B provided low yields of the desired product (entry 5) or no product at all (entries 3 and 4). Lack of product using the conventional protocol could be attributed mainly to the stability of either the starting materials (**3c**, **3j**) or product (**3j**) for which protodeboronation was a significant issue, even at the very moderately elevated reaction temperature.



Scheme 8. Room temperature cross-coupling of haloalkenyl BMIDA in the presence of aqueous base on gram scale. Yield of isolated product.

Lastly, the room temperature procedure was also found to be readily scalable and the product can be straightforwardly isolated without resorting to chromatography (Scheme 8).

Rationalization of Anomalous Observations. 1. Efficiency of Cross-coupling: Regioisomer Disparity. During the course of substrate application for the room temperature BMIDA cross-coupling studies above, we observed a reactivity difference with the regioisomers of bromophenyl BMIDA (**11a**, **11b**, and **11c**, Figure 7). Specifically, in several cases we observed the efficiency of the cross-coupling of the *meta*-isomer **11b** to be noticeably lower than that of **11a** and **11c**, and that this was independent of the BPin coupling partner.

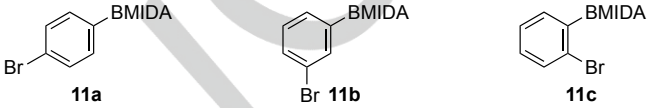


Figure 7. Regioisomeric bromophenyl BMIDA.

Following NMR analysis, Burke noted that the BMIDA motif is neither a strongly electron-donating nor electron-withdrawing functional group.[4b] Based on this preceding analysis, the disparity in the efficiency of cross-coupling of **11a-c** analogues was unlikely to be electronic in nature, i.e., that the dissimilarity was unlikely to be driven by large variation in the rates of oxidative addition of the regioisomeric bromides.[24] Analysis of the ^{13}C NMR spectra of **11a-c** as an indication of relative electronic disposition of the bromide-bearing carbon, revealed that the *para*- and *meta*-isomers, **11a** and **11b**, were very similar but that the *ortho*-isomer **11c** was the electronic outlier based on the large downfield shift of this signal (124.4 ppm for **11a**, 123.3 ppm for **11b**, and 128.7 ppm for **11c**).

Based on this NMR analysis, it may be predicted that, amongst these regioisomers, **11c** would have been most likely to exhibit a different reactivity profile. Similarly, the crystal structure data of **11a**, **11b**, and **11c** suggests that **11c** would potentially experience the largest issue with reactivity due to the proximity of the bulky BMIDA while **11a** and **11b** would be relatively much more accessible (Figure 8).

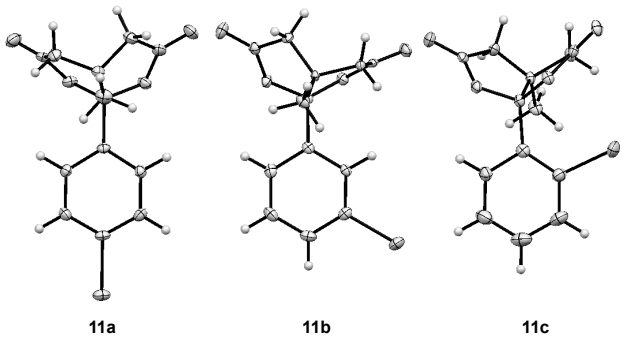


Figure 8. Selected poses of the crystal structures of **11a**, **11b**, and **11c**. For full details, see the Supporting Information.

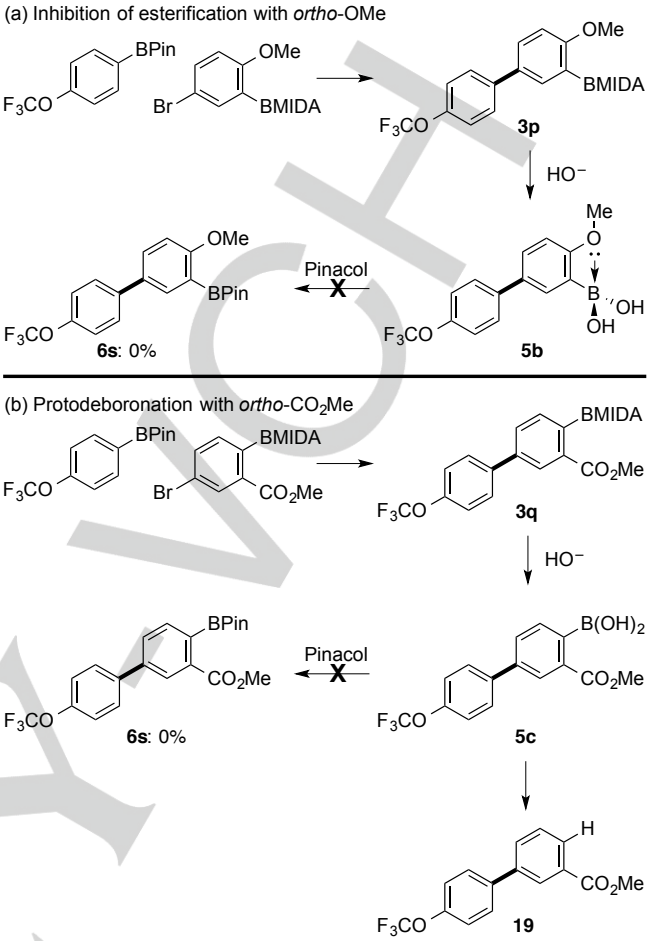
Interestingly, the C-C-B bond angle for **11a** and **11b** was ~122° but ~128° for **11c**, highlighting the nature of the steric environment of the C-Br bond in **11c**.

Based on these overall stereoelectronic considerations, **11c** would seem to have the greatest likelihood of diminished reactivity. However, **11b** was the consistent outlier, with **11a** and **11c** remaining comparable throughout, providing the steric demands of **11c** were met. Accordingly, we considered physical properties as the source of this anomaly. Empirical observations recorded during experimental set up suggested **11b** was less soluble in the reaction mixture than **11a** or **11c**. BMIDA substrates exhibit low solubility in many organic solvents – a property that enables their facile purification.[5o] While many BMIDA-based reactions are performed in solvents such as DMF presumably to aid solubility of these compounds, other solvents have been used, such as 1,4-dioxane, THF, and PhMe.[4d,f,5n]

To gauge whether solubility may be a factor, we analyzed the solubility of **11a**, **11b**, and **11c** in THF at room temperature, and obtained the following values: **11a**, 56 mg/mL, **11b**, 19 mg/mL, **11c**, 27 mg/mL. **11b** was found to be markedly less soluble than **11a** and **11c**. We believe that this lower solubility may contribute to the observed discrepancy in reaction efficiency when using **11b**.

2. Efficiency of Speciation Control with *ortho*-Substituted BMIDA. The cross-coupling of substituted haloaryl BMIDA (**6c**, **6d**, **6g**, Figure 2 and **6o-v** Figure 4) were typically reasonably effective, providing yields of BPin products in the region of 50-70%. However, we noticed a particular disparity when certain *ortho*-substituted BMIDA components were used. Specifically, when a methoxy or methyl ester substituent was located *ortho* to the BMIDA group, we observed little to no conversion to the desired BPin product (Figure 4, **6s**-**6v**). In both cases the initial cross-coupling and hydrolysis to the boronic acid were sufficiently effective; however, the turnover of pinacol in order to form the desired BPin ester was found to be problematic. For MeO-substituted products, **6s** and **6t**, the reaction tended to produce only the biphenyl boronic acid intermediate **5b** even after extended periods of time, suggesting a sluggish esterification process (Scheme 9a). The reasons for this are unclear; although we suspect this could be due to an intramolecular O-B Lewis pair interaction (as shown in **5b**).[25] Such an interaction may inhibit the esterification process. However, NMR analysis did not confirm any deviation of the ^{11}B signal for this species. Regioisomeric MeO-substitution did not present this issue (for example, **6r**, Figure 4).

Conversion to BPin was similarly poor for the *ortho*-ester substituted products **6u** and **6v**. For these reactions, we observed a large quantity of the protodeboronated biphenyl product **19** (Scheme 9b). We believe this is due to the proximity of the electron-withdrawing ester functionality, which leads to accelerated rates of protodeboronation.[23b] It should also be noted that *ortho*-F was tolerated and did not provide any issues with either the esterification process or protodeboronation (see **6c**, **6d**, **6g**, Figure 2).

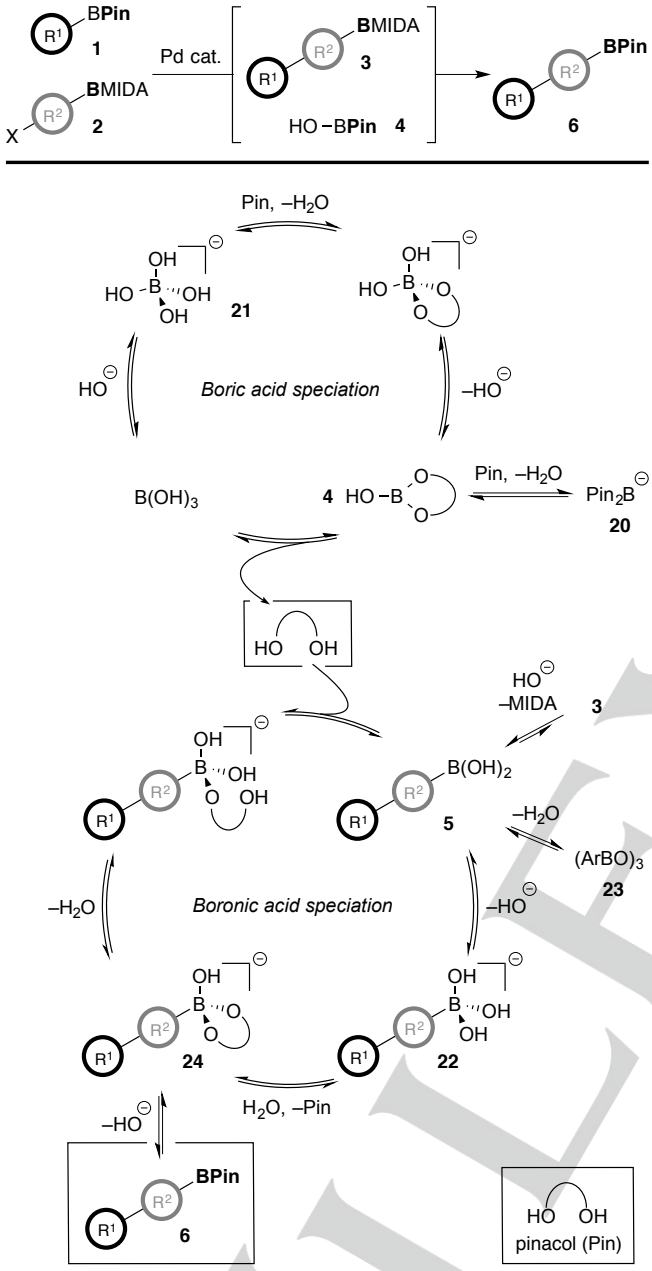


Scheme 9. Inhibition of esterification (a) and protodeboronation (b) when using *ortho*-substituted bromophenyl BMIDA reagents.

Manipulation of Boron Speciation Equilibria – Control Reactions. We believe the formal homologation reaction relies upon the simultaneous control of a series of boron speciation equilibria (Scheme 10). Cross-coupling of BPin **1** with conjunctive BMIDA **2** provides the expected adduct **3**.[4f] A frequently overlooked and generally discarded by-product of this process is the boric acid ester **4**. Both of these intermediate boron species, **3** and **4**, can then participate in independent equilibria that can be modulated via pH control.[12,13]

Liberation of pinacol requires hydrolysis of **4** and control over 2:1 complex (**20**) formation.[12] Hydrolysis of **4** under aqueous basic conditions delivers $B(OH)_3$ (and the boronate derivative **21**), both of which will be sequestered to the basic phase.[12,26] Hydrolysis of **3** under basic conditions liberates the corresponding boronic acid **5**,[4e,5d,g,q] which can establish a series of equilibria including formation of the boronate **22** and boroxine **23**.[27] Esterification of boronic acids (**5**) and the corresponding boronate derivatives (**22**) with 1,2-diols is accelerated at high pH, with the former being the kinetically more competent species.[13] Following esterification, the newly

generated BPin **6** will exist as the thermodynamically favored boronate **24**, with **6** isolated upon completion of the reaction.



Scheme 10. Main solution speciation equilibria associated with the formal homologation process.

The staging of the reaction is crucial. The initial cross-coupling of **1** and **2** to produce **3** must be complete before hydrolysis of **3** takes place. If **3** hydrolyzes prematurely to boronic acid **5** before consumption of **2**, competing cross-coupling may take place. Similarly, cross-coupling of **1** and **2** must be complete before generation of product **6** in order to avoid competing cross-coupling with **2** (see Scheme 2). Analysis of these events using independent reactions demonstrated that, under the optimized reaction conditions, cross-coupling is rapid and is complete in <1 h whereas hydrolysis of BMIDA intermediate **3** requires approximately 4 h. Accordingly, oligomerization can be robustly avoided with this hydrolysis latency period. For the benchmark reaction, production of the desired BPin product **6a** vs. presence/consumption of the intermediate BMIDA **3a** could be followed by HPLC (Chart 3).

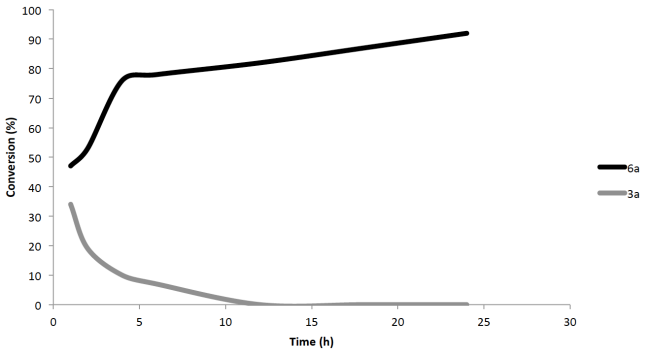
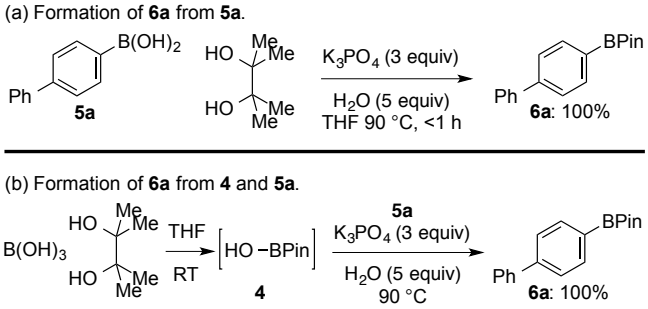


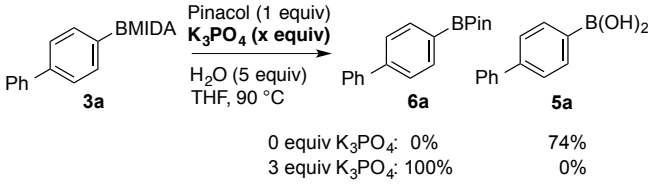
Chart 3. Production of **6a** and presence/consumption of **3a**. Determined by HPLC analysis.

Throughout, no boronic acid **5a** was detected, in agreement with previous observations that the esterification process is rapid and the efficiency of the reaction, under the optimized conditions, is directly linked to the efficiency of cross-coupling. Indeed, independent treatment of **5a** with pinacol under the reaction conditions delivers quantitative formation of **6a** in <1 h (Scheme 11a). Similarly, **5a** is quantitatively converted to **6a** under representative reaction conditions from the byproduct from the initial Suzuki-Miyaura cross-coupling **4** (Scheme 11b).



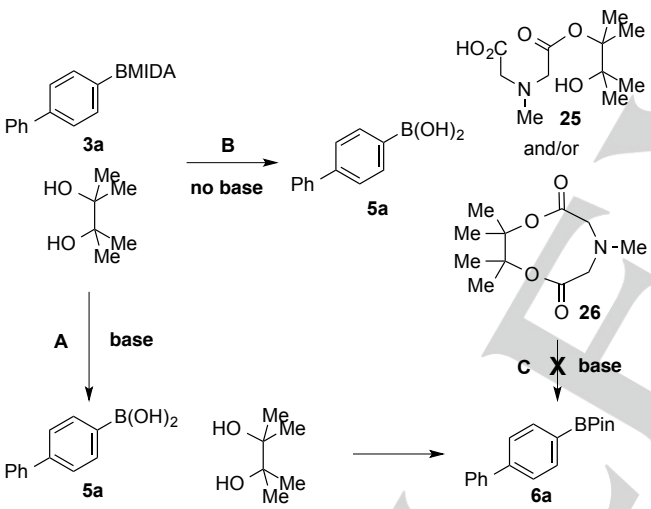
Scheme 11. Conversion of **5a** to **6a** under representative reaction conditions. Determined by HPLC analysis.

To ensure no other possible esterification pathways, we conducted a series of control experiments. Treatment of **3a** with pinacol under the reaction conditions either in the presence or absence of base was informative (Scheme 12).



Scheme 12. Esterification of **3a** using pinacol to deliver **6a** in the presence and absence of base. Determined by HPLC analysis.

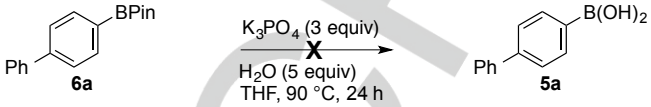
In the absence of base, **3a** is converted to the boronic acid derivative **5a** only. However, when base is included, **3a** is converted smoothly to the BPin adduct **6a**. These results support a mechanism in which, when base is present, the hydrolysis of BMIDA **3a** to boronic acid **5a** is followed by subsequent esterification (Scheme 13, pathway A). In the absence of base, pinacol engages BMIDA to induce hydrolysis to the boronic acid **5a**. In doing so, a pinacol-MIDA ester (**25** or **26**) is generated, disabling boronic acid esterification (Scheme 13, pathway B).



Scheme 13. Reaction of **3a** with pinacol in the presence and absence of base.

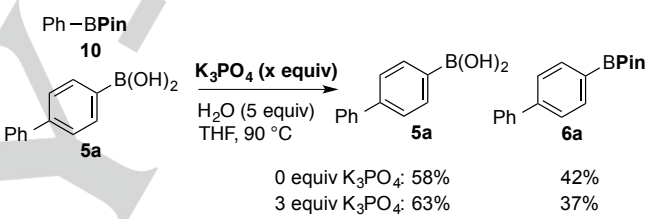
It may be reasoned that **6a** could ultimately be generated following formation of **25**/**26**, subsequent hydrolysis to liberate pinacol, followed by the expected esterification of **5a** (Scheme 13, pathway B+C). However, after completion of the base-free reaction (Scheme 12), addition of K_3PO_4 did not induce formation of **6a**, lending further support to the basic hydrolysis/esterification sequence of events.

The formation of boronic esters from boronic acids and diols has been extensively researched and the requirements for effective esterification have been thoroughly established.[12,13] Under basic conditions, formation of **6a** from **5a** and pinacol is rapid. Accordingly, as might be expected based on the generally high efficiency of the reaction (Figure 2), the reverse process is unfavorable. The BPin product **6a** is rapidly converted to the boronate derivative **24**, which is the thermodynamic end point for the boronic acid species in the reaction mixture. Direct hydrolysis of BPin, under basic conditions, is exceedingly difficult. Indeed, exposure of **6a** to the reaction conditions, even for prolonged reaction times, failed to deliver any of the derivative biaryl boronic acid **5a** (Scheme 14).



Scheme 14. Attempted hydrolysis of **6a** to **5a** under the reaction conditions.

Hydrolysis of BPin is more readily achieved by exploiting speciation equilibria with the addition of a second boron species, such as a polymeric phenyl boronic acid, relying upon equilibrium distortion to completely drive pinacol transfer.[22a,b] In this regard, treatment of PhBPin **10** with boronic acid **5a** leads to equilibration to deliver mixtures of **5a** and **6a** (Scheme 15).



Scheme 15. Equilibration of **5a** and **10**. Determined by HPLC analysis.

This observation supports the proposed sequence of events, in particular a rapid Suzuki-Miyaura cross-coupling that is complete before hydrolysis of **3a**. If **3a** were hydrolyzed before consumption of **10**, equilibration of **5a** and **6a** would lead to problems with oligomerization from residual **11a** present in the reaction mixture due to the higher cross-coupling reactivity of the boronic acid **5a** than the BPin starting material **10**.

All of the above observations support the following sequence of events for the formal homologation reaction: (1) a rapid Suzuki-Miyaura cross-coupling; (2) a comparatively slow BMIDA hydrolysis; and (3) a rapid esterification of the liberated boronic acid. The reaction is also highly dependent upon (1) the nature of the base, which must possess good solubility and guarantee a suitable pH to enable speciation control and (2) the thermodynamic stability of the BPin product.

Conclusions

In summary, the fundamental physical properties of inorganic bases enable the formation of an in situ desiccant that controls the availability of aqueous base during Suzuki-Miyaura cross-coupling of haloaryl and haloalkenyl BMIDA esters. This internal aqueous base control mechanism enables the cross-coupling to be readily conducted with speciation control possible

by temperature modulation to enable the production of BPin adducts or BMIDA adducts. The requirements for effective speciation control have been investigated and the sequence of events supported by a series of independent transformations.

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Keywords: boron • chemoselectivity • cross-coupling • palladium • speciation

† Throughout, pK_a refers to the pK_a of the conjugate acid.

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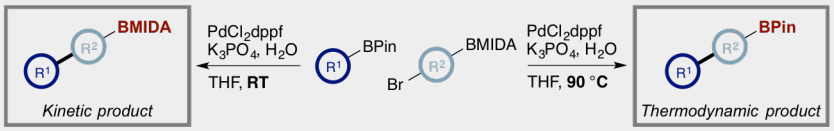

Boronic acid solution speciation can be controlled during the Suzuki-Miyaura cross-coupling of haloaryl MIDA boronic esters to enable chemoselective access to either BMIDA or BPin products. The reaction is contingent upon control of the basic biphase and product distribution can be controlled by temperature regulation. Control experiments and analysis of the physical properties of inorganic bases have provided insight into the mechanistic operation of the formal homologation process.

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Speciation control during Suzuki-Miyaura cross-coupling of haloaryl and haloalkenyl MIDA boronic esters