

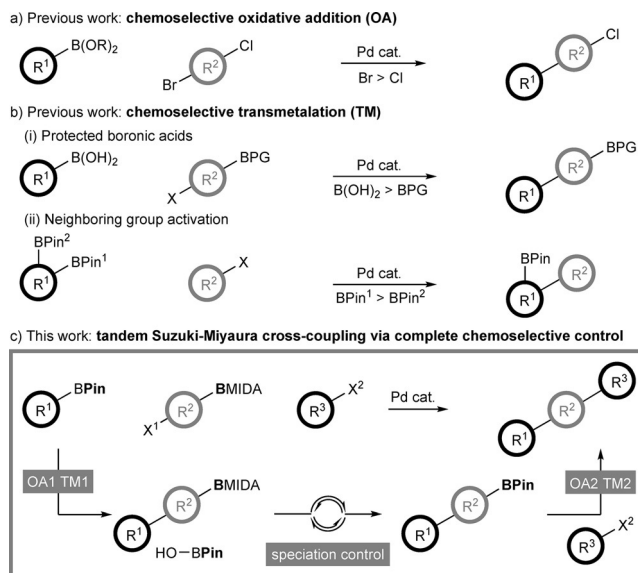
Tandem Chemoselective Suzuki–Miyaura Cross-Coupling Enabled by Nucleophile Speciation Control**

Ciaran P. Seath, James W. B. Fyfe, John J. Molloy, and Allan J. B. Watson*

Abstract: Control of boronic acid speciation is presented as a strategy to achieve nucleophile chemoselectivity in the Suzuki–Miyaura reaction. Combined with simultaneous control of oxidative addition and transmetalation, this enables chemoselective formation of two C–C bonds in a single operation, providing a method for the rapid preparation of highly functionalized carbogenic frameworks.

The Suzuki–Miyaura reaction is the primary method for Pd-catalyzed cross-coupling, accounting for over 40% of C–C bond constructions in the pharmaceutical industry alone.^[1,2] Chemoselective control of this reaction is currently limited to single mechanistic events, focusing on either the electrophile or nucleophile independently.^[3] Electrophile selectivity has been thoroughly demonstrated by exploiting the well-defined principles of oxidative addition ($I > Br > Cl$, etc.; Scheme 1a)^[4,5] while nucleophile selectivity has been achieved through the use of inert (protected) boronic acid derivatives (Scheme 1b(i))^[6] or a geminal/vicinal diboron self-activation mechanism (Scheme 1b(ii)).^[7] Despite these advances, general nucleophile chemoselectivity remains elusive. Reactions are therefore limited to only one selective C–C bond forming event,^[8] with sequential chemoselective cross-coupling achieved only through separate reactions.^[3,6a,9] Establishing simultaneous electrophile and nucleophile selectivity to allow successive C–C bond-forming events in a single reaction remains unsolved.

Recently, we demonstrated that boron speciation can be controlled during Suzuki–Miyaura cross-coupling to enable chemoselective and quantitative ligand exchange in situ.^[10] Here we report that boron speciation, oxidative addition, and transmetalation can be simultaneously controlled to enable two chemoselective Suzuki–Miyaura C–C bond formations in a single catalytic process (Scheme 1c). This provides a simple yet powerful solution to achieving nucleophile chemoselectivity and enables the rapid and efficient synthesis of high-value products.



Scheme 1. Approaches to chemoselective Suzuki–Miyaura cross-coupling. Cat = catalyst, MIDA = *N*-methyliminodiacetic acid, OA = oxidative addition, PG = protecting group, Pin = pinacolato, TM = transmetalation.

Tandem chemoselective Suzuki–Miyaura cross-coupling was initially explored using the benchmark reaction of phenyl BPin **1**, 4-bromophenyl BMIDA **2**, and aryl chloride **3** (Table 1). The reaction design plan required three distinct chemoselective events to cooperate simultaneously. 1) Cross-coupling of **1** and **2** to produce the expected biaryl BMIDA intermediate **4**,^[6r,10] based upon selective oxidative addition of **2** vs. **3** and transmetalation of **1** vs. **2**; 2) formation of BPin **6** from the BMIDA intermediate and **5** via control of speciation;^[10] and 3) cross-coupling of **6** with **3** to deliver **7a**. Control of these events represented a significant challenge. Chemoselective oxidative addition can be capricious and reaction/catalyst dependent^[4a,5]—premature reaction of **1** and **3** would deliver **8**. Hydrolysis of **2** must be controlled to avoid premature transmetalation of the latent boronic acid and uncontrolled oligomerization, leading to **9**.^[10,11] However, this must be levied against the requirement of aqueous base to facilitate effective cross-coupling^[12] and ensure effective speciation manipulation.^[10]

Initial evaluation of a catalyst system based on our previous work failed to deliver the desired triaryl product **7a**; the reaction produced only the formal homologation adduct **6** with aryl chloride **3** returned, indicating problematic oxidative addition with this less reactive electrophile (entry 1). Moving to a more activated catalyst system (Pd(OAc)₂, SPhos;^[13,14] entry 2) provided low conversion to **7a** with the

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Table 1: Reaction development.

Entry	Catalyst ^[a]	K ₃ PO ₄ [equiv]	H ₂ O [equiv]	7a:6:8 [%] ^[b]
1	[PdCl ₂ (dppf)] ^[c]	3	5	0:100:0
2	Pd(OAc) ₂ , SPhos	3	5	17:42:4
3	Pd(OAc) ₂ , SPhos	3	10	35:23:11
4	Pd(OAc) ₂ , SPhos	3	20	53:4:25
5	Pd(OAc) ₂ , SPhos	4	20	88:0:0
6	Pd(OAc) ₂ , SPhos	4	30	41:0:24
7	Pd(OAc) ₂ , SPhos	4	40	25:13:0
8	Pd(OAc) ₂ , SPhos	5	20	80:0:11

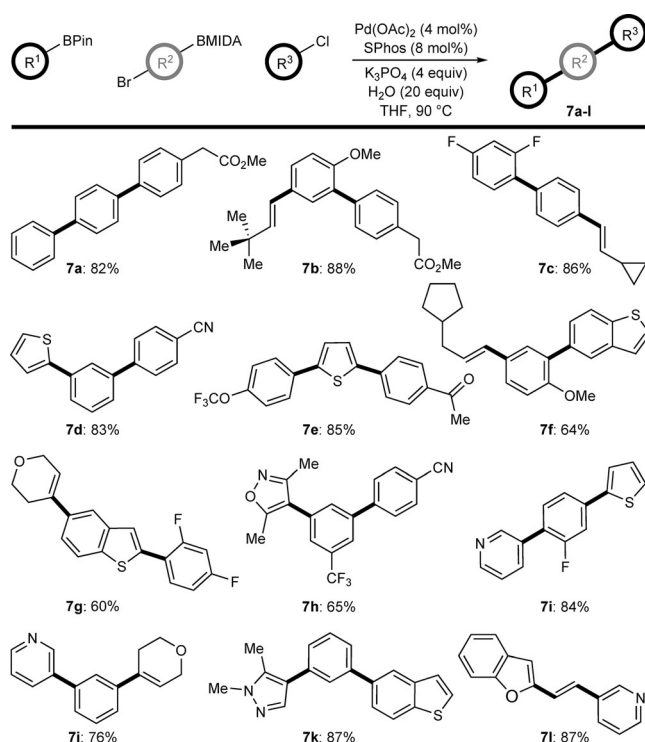
[a] 4 mol % Pd, 8 mol % ligand. [b] Determined by HPLC analysis.

[c] 4 mol %.

mass balance consisting mainly of **6** as well as **8**, the product of reaction of **1** + **3**, indicating a lack of electrophile chemoselectivity. Lowering the reaction temperature to avoid premature engagement of **3** led to lower overall conversion (see Supporting Information (SI)). A systematic evaluation of the stoichiometric relationship between K₃PO₄ (a range of bases were evaluated, see SI) and H₂O revealed that cross-coupling efficiency could be directly influenced by the medium without resorting to specific tailoring of the catalyst.^[5] Increasing the quantity of H₂O increased the overall conversion (i.e., improved engagement of **3**) but also led to extensive oligomerization due to poor speciation control (entries 3 and 4). This could be mitigated by increasing the quantity of K₃PO₄,^[10] which provided excellent levels of conversion to **7a** (entry 5). Further increases in H₂O led to oligomerization giving increased **9** (entries 6 and 7), which could again be tempered by increasing the quantity of K₃PO₄ (entry 8). Accordingly, these results further demonstrate that in addition to speciation control, cross-coupling efficiency can also be directly influenced by relatively minor adjustments to the composition of the reaction medium.^[1c] A survey of various catalyst systems with the optimum biphasic composition did not provide any further improvement in the chemical yield (see SI).

It is important to note that the optimized reaction is effective with equal stoichiometries of **1**, **2**, and **3**, i.e., the chemoselectivity and yield are not statistically prejudiced through use of impractical and uneconomical stoichiometries of any component or by tailoring (e.g., electronic or steric bias) of the nucleophile.^[9] The reaction rates are harmonized such that BPin **1** reacts only with aryl bromide **2**, speciation control delivers BPin **6** at a rate that avoids oligomerization or competition with **1**,^[10b] and **6** reacts only with aryl chloride **3**.

With our optimum reaction conditions in hand, the scope of the tandem cross-coupling protocol was explored (Scheme 2). The general concept was also readily transferred

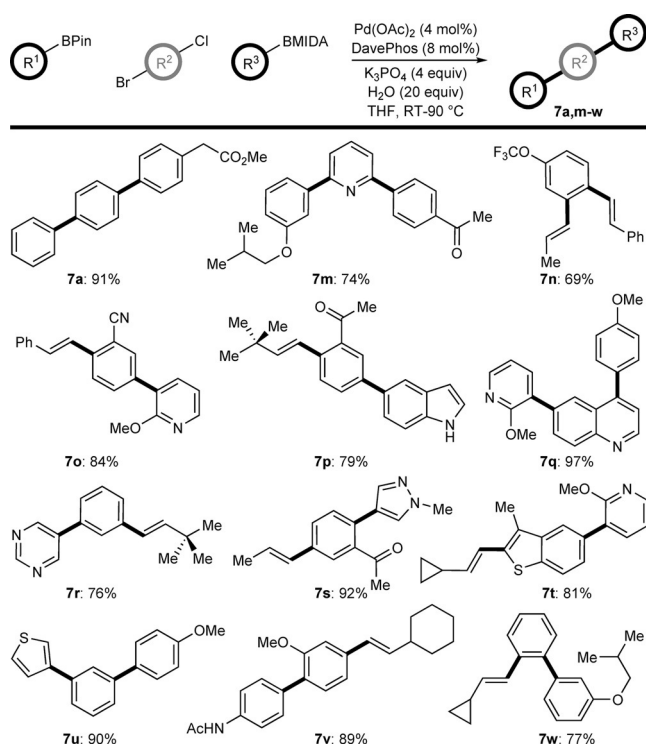


Scheme 2. Chemoselective tandem Suzuki–Miyaura cross-coupling using conjunctive haloaryl BMIDA components. Isolated yields of pure products.

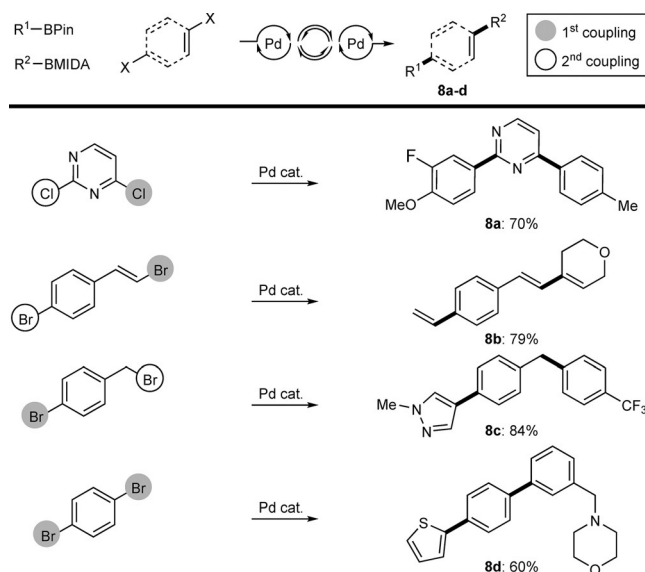
to a modified system using dihaloarenes as conjunctive bis-electrophiles in combination with two differentiated boronic acid-derived nucleophiles (Scheme 3). In this process, the slightly less active DavePhos^[14,15] ligand was found to be more suitable. The reaction efficiencies between the two complementary processes are comparable, for example, the preparation of **7a** is produced in 82% and 91% yield, respectively (Scheme 2 vs. Scheme 3). This synthetic flexibility provides an array of diverse product scaffolds in a single operation and enhances scope based on the wider selection of available reaction components.

A broad range of coupling partner was accommodated in both protocols, including useful functionality on the BPin, BMIDA, and aryl chloride components, such as ethers, esters, fluorides, nitriles, ketones, olefins, and heterocyclic residues. Notably, heteroaryl and alkenyl BMIDA, which must progress via the protodeboronation prone parent boronic acids,^[6c,16] were effectively incorporated. Yields were typically high and synthetically useful, especially when the number of individual processes is considered.

In a departure from exploiting the standard reactivity profiles of the electrophile (i.e., Br > Cl), we sought to further demonstrate the potential of tandem chemoselective Suzuki–Miyaura cross-coupling by utilizing specific reactivity gradients of dibromo or dichloro electrophiles (Scheme 4). For example, tandem C–C bond formation was possible using 2,4-dichloropyrimidine to deliver **8a** in 70% yield.^[17] The increased lability of alkenyl electrophiles vs. aryl electrophiles allows chemoselective cross-coupling of 1,β-dibromostyrene to provide **8b** in 79% yield.^[18] Similarly, sp²/sp³ electrophile

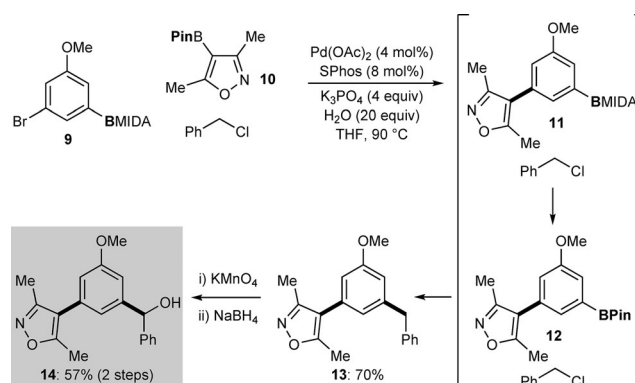


Scheme 3. Chemoselective tandem Suzuki-Miyaura cross-coupling using conjunctive dihalide components. Isolated yields of pure products. Ac = acetyl.



Scheme 4. Chemoselective tandem Suzuki-Miyaura cross-coupling using dibromo and dichloro electrophiles. Isolated yields of pure products.

selectivity can be achieved using 4-bromobenzyl bromide to provide **8c** in 84% yield. Lastly, more subtle effects can be exploited: Dihaloarenes have been shown to undergo either selective mono-arylation or exhaustive arylation under specific Suzuki-Miyaura conditions.^[8,19] Under our developed protocol, 1,4-dibromobenzene undergoes sequential chemoselective C–C bond formation to provide **8d** in 60% yield.



Scheme 5. Synthesis of BET bromodomain inhibitor **14** by tandem sp^2 – sp^2 / sp^2 – sp^3 Suzuki-Miyaura cross-coupling.

The synthetic applicability of our protocol was further exemplified in the rapid synthesis of the BET bromodomain inhibitor **14** (Scheme 5).^[20] Chemoselective sp^2 – sp^2 cross-coupling of conjunctive bromoaryl BMIDA **9** and dimethyl isoxazole BPin **10**, delivers intermediate BMIDA **11**, which is converted to the reactive BPin derivative **12** in situ via speciation control. This then engages benzyl chloride in an sp^2 – sp^3 C–C bond formation to provide the key core structure **13** in 70% yield. Oxidation and reduction delivers **14**.

In conclusion, we have shown that oxidative addition, boron speciation, and transmetalation can be chemoselectively and simultaneously controlled to enable tandem Suzuki-Miyaura C–C bond formation in a single operation. This method provides a simple solution to the nucleophile selectivity issue within Suzuki-Miyaura cross-coupling and demonstrates the power of chemoselective cross-coupling to access highly functionalized carbogenic frameworks.

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

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