

Synthetic Methods

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Chemoselective Suzuki–Miyaura Cross-Coupling via Kinetic Transmetalation

James W. B. Fyfe, Neal J. Fazakerley, and Allan J. B. Watson*

Abstract: Chemoselective Suzuki–Miyaura cross-coupling generally requires a designed deactivation of one nucleophile towards transmetalation. Here we show that boronic acids can be chemoselectively reacted in the presence of ostensibly equivalently reactive boronic acid pinacol (BPin) esters by kinetic discrimination during transmetalation. Simultaneous electrophile control allows sequential chemoselective cross-couplings in a single operation in the absence of protecting groups.

Chemoselective Suzuki–Miyaura cross-coupling of multi-nucleophile systems has emerged as a powerful synthetic strategy for chemical synthesis.^[1,2] Chemoselectivity within systems containing two organoborons is typically achieved by a designed deactivation: 1) Highly effective p-orbital protecting group strategies developed by Burke (BMIDA)^[3] and Suginome (BDAN)^[4] render one organoboron unit unreactive towards transmetalation (Scheme 1 a);^[5,6] 2) a unique self-activation/protection mechanism developed by both Morken and Shibata allows chemoselectivity within geminal and vicinal diboron compounds (Scheme 1 b);^[7] and 3) Crudden has shown that benzyl BPin species are unreactive in the absence of specific additives, allowing selective aryl/benzyl

transmetalation (Scheme 1 c).^[8] Accordingly, current methods to achieve chemoselectivity rely upon employing one nucleophile that is unreactive towards transmetalation under the prevailing reaction conditions. In particular, selective discrimination of two arylboron nucleophiles is only achievable using a suitable protecting group strategy.^[9,10]

Here we report that the chemoselective cross-coupling of two seemingly equivalently reactive aryl organoboron compounds can be achieved by exploiting subtle differences in their respective rates of transmetalation (Scheme 1 d).

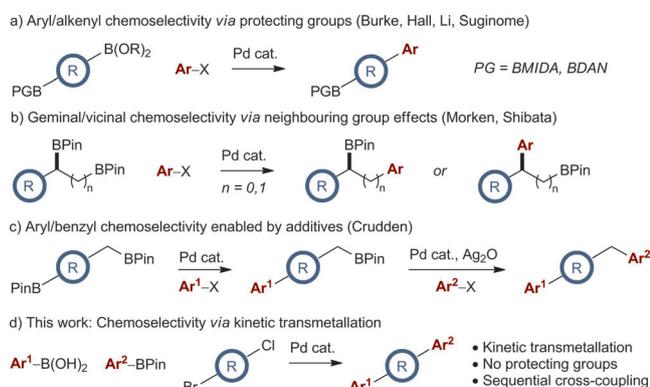
Elegant studies by Hartwig,^[11] Amatore and Jutand,^[12] Schmidt,^[13] and, recently, Denmark^[14] have demonstrated the role of oxopalladium transmetalation in the Suzuki–Miyaura reaction.^[15] As part of his seminal study, Hartwig reported that boronic acids were observed to transmetallate ca. 45 times faster than the equivalent BPin ester using stoichiometric quantities of a dimeric oxopalladium complex and in a non-competitive system.^[11] Based on these data we questioned whether chemoselective cross-coupling of a boronic acid over a BPin ester might be possible via kinetic discrimination during transmetalation in a catalytic system.

We initially independently assessed the relative rates of cross-coupling of boronic acid **1a** and the equivalent BPin **1b** with bromobenzene (**2**) under representative Suzuki–Miyaura reaction conditions (Scheme 2 a).

These initial results suggested comparable reactivity of **1a** and **1b**, with both nucleophiles rapidly consumed at the same initial rate and displaying a comparable reaction profile. However, under identical reaction conditions in a competitive system notable chemoselectivity was recorded (Scheme 2 b). Here, the cross-coupling of **4a** was found to significantly outcompete **1b**, with ca. 9:1 selectivity exhibited in this non-optimized system.

Accordingly, while exhibiting similar reactivity in isolation, chemoselectivity can be leveraged in a competitive system by kinetic discrimination of the nucleophiles by the catalytically generated Pd^{II}-intermediate. Since transmetalation occurs after the rate-determining step (RDS),^[16] the overall rate is unaffected by transmetalation in the isolated reactions (Scheme 2 a) but a rate difference exists and therefore chemoselectivity can still be leveraged between nucleophiles post-RDS (Scheme 2 b).^[17] However, this is contingent on ensuring inhibition of pinacol equilibration (Scheme 3).^[18,19]

Competitive coupling of the in situ generated BPin-derived boronic acid erodes selectivity and thus must be controlled in order to exploit any natural kinetic advantage (see below). Fortunately, however, diol transfer can be controlled by the basic media typically used for Suzuki–Miyaura reactions,^[18,20] allowing optimization of this nascent

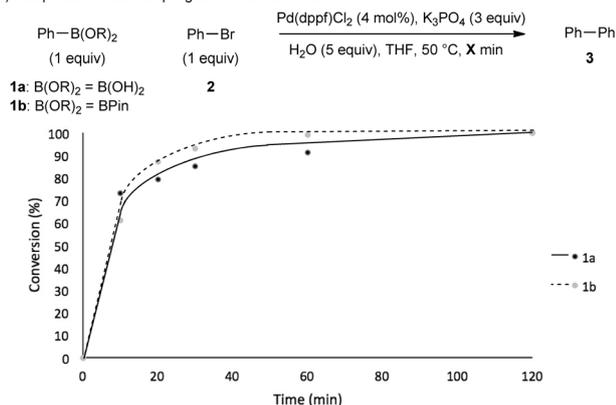
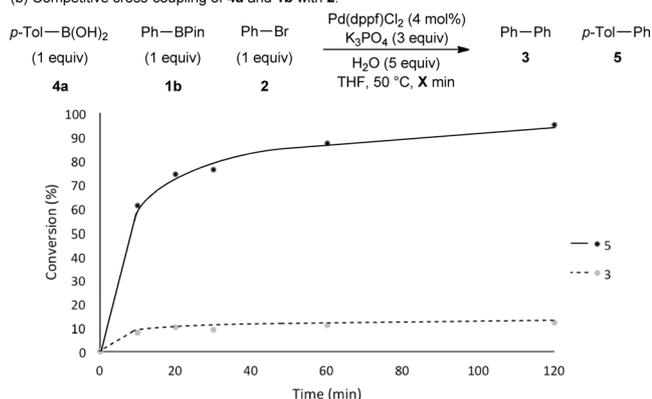
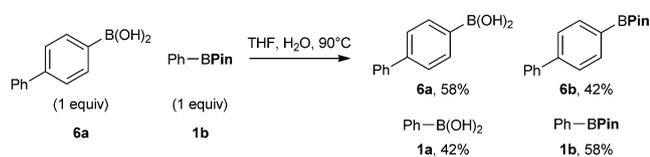


Scheme 1. Nucleophile-selective Suzuki–Miyaura reactions.

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(a) Independent cross-coupling of **1a** and **1b** with **2**.(b) Competitive cross-coupling of **4a** and **1b** with **2**.**Scheme 2.** Independent and competitive cross-couplings of boronic acid (**1a/4a**) vs. BPin (**1b**) with aryl bromide **2**. Determined by HPLC analysis.**Scheme 3.** Equilibration in a boronic acid/BPin system.

system (Table 1; see the Supporting Information for full details of the investigation of all variables).

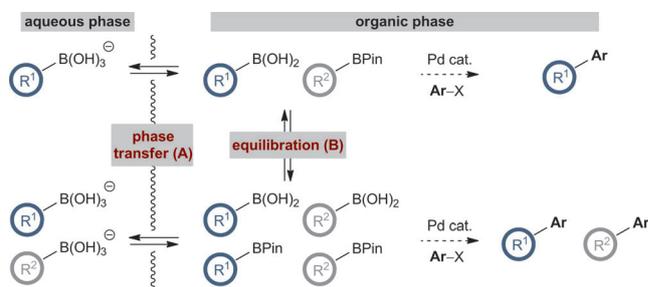
Table 1: Chemoselective cross-coupling of B(OH)_2 vs. BPin. Optimization.

Entry	H_2O [equiv]	Solvent	Conv. 3:5 [%] ^[a]
1	5	THF	6:76
2	5	1,4-Dioxane	0:100
3	20	1,4-Dioxane	12:80
4	50	1,4-Dioxane	28:68
5	100	1,4-Dioxane	30:58

[a] Determined by HPLC analysis. See the Supporting Information.^[21]

Temperature was important for reaction efficiency, with 70 °C optimum over a 1 h timeframe.^[21] As predicted, the choice of reaction medium was crucial to both efficiency and selectivity.^[21] Of the inorganic bases known to be effective in limiting boron speciation processes,^[18,19] K_3PO_4 was most effective.^[21] A solvent survey found 1,4-dioxane offered improved selectivity vs. THF (entry 1 vs. entry 2).^[21] Lastly, there was a notable correlation between conversion/selectivity and the quantity of H_2O added to the system (entries 2–5). Limiting the quantity of H_2O to 5 equiv (entry 2) provided a robust and highly selective system, while selectivity rapidly decreased as H_2O increased (entries 3–5). Importantly, in order to rule out any effects of the *p*-Me substituent, the corresponding experiment using Ph-B(OH)_2 and *p*-tol-BPin was conducted, affording comparable results (95:5 **3:5**).^[21]

Excesses of H_2O negatively impacted selectivity in this system due to competing processes arising from the formation of a visibly biphasic system at > 20 equiv H_2O .^[20] 1) Equilibration increased as H_2O increased, thereby reducing selectivity due to the formation of a competing boronic acid from the BPin component (see Scheme 3). 2) Introduction of a bulk basic aqueous phase promotes phase transfer of boronic acid from the organic phase to the aqueous as its cognate boronate.^[19] Assuming a largely organic phase bound Pd catalyst,^[15,20] this lowers the concentration of boronic acid available for transmetalation in the organic phase, instead requiring a contra-thermodynamic transfer of boronic acid boronate from the aqueous phase to the organic,^[15,20] and thereby negatively impacting both reaction efficiency and selectivity. Spectroscopic investigations supported these hypotheses, the key solution events are shown in Scheme 4.

**Scheme 4.** Key events affecting chemoselectivity: phase transfer (A) and equilibration (B).

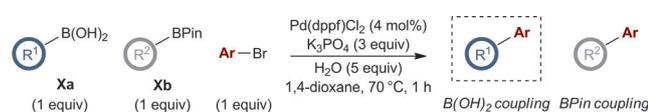
Under reaction-like conditions (i.e., in the absence of Pd catalyst and aryl halide) using restricted quantities of H_2O (98/2 1,4-dioxane/ H_2O), the formation of a bulk aqueous phase is prevented and, consequently, phase transfer of boronic acid to the aqueous (A, Scheme 4) is restricted. In contrast, in a highly biphasic medium (50/50 1,4-dioxane/ H_2O), boronic acid phase transfer was observed to begin immediately (< 5 min). The BPin species were not observed to undergo phase transfer, consistent with previous studies.^[19,21]

In addition, under optimum (low H_2O) conditions, diol equilibration (B, Scheme 4) was inhibited, maintaining ca. 95% integrity of the initial system (16.4:1 B(OH)_2 :BPin after

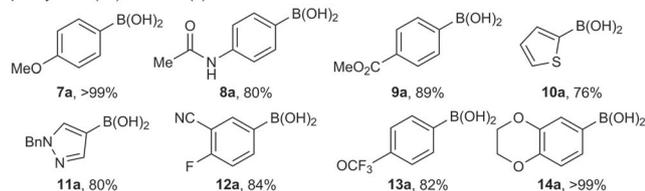
10 min). However, under biphasic conditions, equilibration was much more significant (2:1 B(OH)₂:BPin within 10 min).

Chemoselective transmetalation of boronic acid over BPin takes place with high fidelity. The principal determinant for chemoselectivity is therefore the generation of a mixture of boronic acids as a result of diol equilibration. In the optimized system (low H₂O), diol equilibration takes place more slowly. As the boronic acid is consumed by cross-coupling, equilibration is further suppressed, i.e., chemoselectivity is assisted by Le Chatelier's principle.

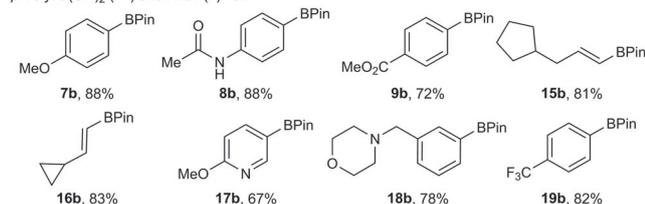
With optimized conditions for selective cross-coupling in a model system, we sought to evaluate the generality of the procedure by varying the structure of the boronic acid, BPin, and bromide coupling partners in an equimolar system (Scheme 5). High selectivity was observed in all cases with cross-coupling favoring the boronic acid, leaving the BPin unreacted. Importantly, selectivity was unaffected by steric (e.g., *ortho*-substituted compounds) or electronic composition. Crossover experiments demonstrated that selectivity was not influenced by specific combinations of boronic acid and BPin partners—chemoselectivity was independent of the functionality of the boron coupling partner (e.g. **7a–9a** vs. **7b–9b**). Importantly, the mass balance was generally returned starting material, with some protodeboronation observed in specific cases.^[22] Reactions were halted at 1 h and the yields represent the efficiency of the boronic acid coupling over this time frame; however, increasing the reaction time did not negatively affect chemoselectivity.



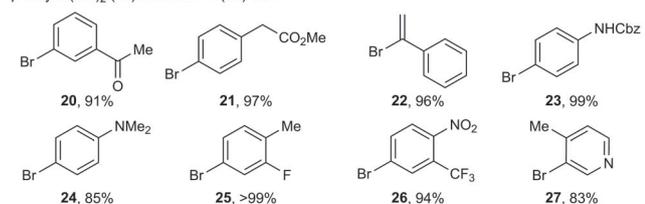
p-Tolyl BPin (**4b**) and PhBr (**2**) vs.:



p-Tolyl B(OH)₂ (**4a**) and PhBr (**2**) vs.:



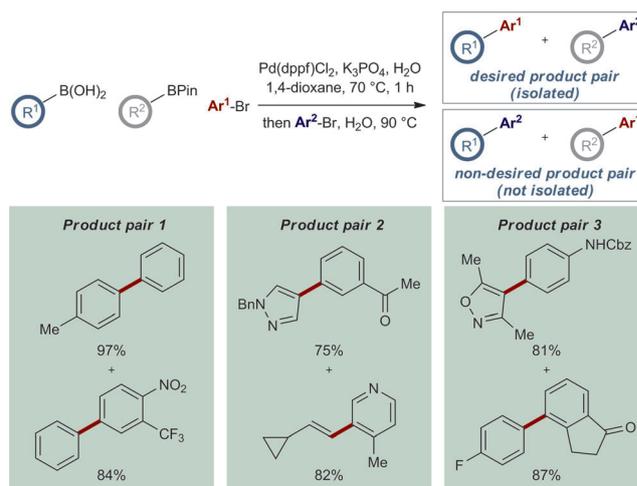
p-Tolyl B(OH)₂ (**4a**) and PhBPin (**1b**) vs.:



Scheme 5. Chemoselective cross-coupling of B(OH)₂ vs. BPin. Isolated yields of the desired B(OH)₂ coupled product.

Electron-rich boronic acids delivered greater efficiency over those comparatively electron-poor, in agreement with previous studies.^[1a,10]

Having demonstrated the generality of our protocol, we sought to explore the utility of this process, specifically through subsequent use of the unreacted BPin component. Our first goal was to determine the integrity of the Pd catalyst following the initial coupling. Simply adding a second aryl bromide to the reaction mixture after the initial coupling was complete allowed coupling of the unreacted aryl BPin to produce pairs of selectively cross-coupled products in one pot without the need for intermediate isolation or renewal of the catalyst (Scheme 6). Reaction efficiency was generally > 80%

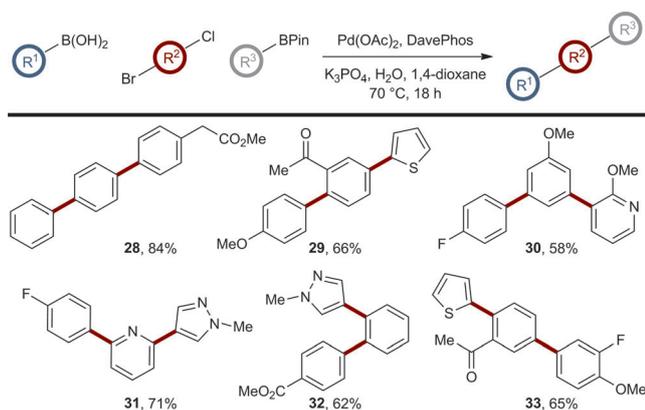


Scheme 6. One-pot sequential chemoselective coupling. Isolated yields.

per C–C bond formation, with the same efficiency trend displayed for electronic variation as noted for Scheme 5. The undesired coupling products were not observed. Residual aryl halide could be observed but unreacted organoboron compounds were not recovered, likely due to protodeboronation.^[22]

In order to fully probe the power of this methodology, we sought to combine chemoselective transmetalation of the organoboron nucleophile with chemoselective discrimination of the electrophile, i.e., chemoselective oxidative addition.^[18b,23] This would establish the first complete chemoselective control over two of the three key mechanistic processes of the Suzuki–Miyaura reaction. Using the reactivity gradient afforded by dihaloarenes, a one-pot sequential chemoselective Suzuki–Miyaura reaction was enabled without the requirement for any in situ modification of the reaction conditions (temperature change, sequential addition) or reactants (protecting group removal, boron species interconversion) (Scheme 7).

A change to the more active catalyst system of Pd(OAc)₂ and DavePhos was required in order to engage the less reactive aryl chloride, while a short screen of base and water equivalents revealed optimum conversion could be achieved using 4 equiv of K₃PO₄ with 15 equiv of H₂O. Under these



Scheme 7. Chemoselective tandem cross-coupling. Isolated yields.

conditions a range of aryl and heteroaryl boron species were tolerated, along with substituted and heteroaryl dihalides, affording the desired triaryl products in good to excellent yield. Catalyst efficiency was similar to that of the sequential coupling (Scheme 6) at ca. 80% per C–C bond formation. Importantly, similar to the observations for Scheme 5 and 6, reactions with lower efficiency were not due to poor chemoselective control. Instead, the efficiency of the process was limited by the second cross-coupling event (i.e., aryl chloride/BPin): the mass balance was mainly unreacted intermediate biaryl chloride. The unreacted BPin was typically not recovered, again, presumably due to protodeboronation.^[22] Use of olefinic organoboron compounds in this one-pot procedure led to mixtures of products. Investigations into the origin of this specific lack of chemoselectivity are ongoing.

In conclusion, chemoselective Suzuki–Miyaura cross-coupling of two seemingly equivalently reactive boron species has been achieved through exploitation of kinetic transmetalation. Selectivity for boronic acid cross-coupling is demonstrated regardless of the functionality present on the boron species. Diol equilibration and phase transfer of boronic acid must be inhibited to allow the natural kinetic advantage to be leveraged. These data allow the one-pot sequential cross-coupling of multi-nucleophile/electrophile systems and have immediate ramifications for general (i.e., non-competitive) Suzuki–Miyaura cross-coupling and other transition metal-mediated reactions of boronic acids that use basic biphasic reaction conditions: improvements in reaction profile (e.g., efficiency and side reactions such as protodeboronation) may be gleaned by adjusting the medium to avoid competing processes.

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Conflict of interest

The authors declare no conflict of interest.

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

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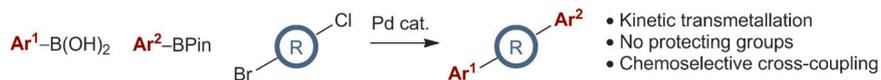


Synthetic Methods

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Chemoselective Suzuki–Miyaura Cross-Coupling via Kinetic Transmetalation



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