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A one-pot tandem chemoselective allylation/cross-coupling via temperature control of a multi-nucleophile/electrophile system

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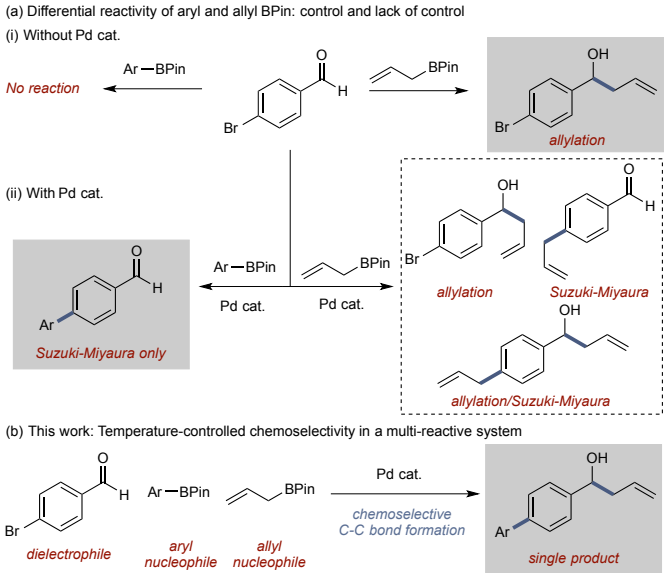
A chemoselective tandem reaction of a multi-reactive, two electrophile + two nucleophile, system is reported. An allylation/cross-coupling process of a haloaryl aldehyde, an aryl BPin, and an allyl BPin can be controlled using a temperature gradient to overcome natural reactivity profiles and allow two sequential chemoselective C-C bond formations without intervention. This process offers efficient access to an array of functionalised products including pharmaceutical and natural product scaffolds.

Organoboron compounds represent one of the most broadly useful classes of reagent, finding value across diverse areas of chemistry.[1] This popularity arises from their inherent reactivity towards a range of electrophilic partners, in a series of catalysed and non-catalysed reaction manifolds, while remaining easy to handle and readily available. Additionally, several classes of organoboron compounds are multi-functional, *i.e.*, capable of different reactivity modes depending on the prevailing reaction conditions. For example, allyl BPin is a competent nucleophile[1,2] (*e.g.*, with carbonyl electrophiles) and undergoes cross-coupling at the terminal carbon,[1,3] while also undergoing Suzuki-Miyaura (SM) cross-coupling at the boron-bearing carbon.[1,4,5]

Accordingly, in the reaction of allyl BPin with a dinucleophile, such as a haloaryl aldehyde, in the presence of a Pd catalyst, several products can be obtained based on the competency of this nucleophile towards both 1,2-addition and cross-coupling (Scheme 1a (i) and (ii)). On the contrary, aryl BPin reagents display no natural reactivity towards 1,2-addition (Scheme 1a (i)) but are similarly competent within SM cross-coupling.[1,5] The reaction of an aryl BPin with the same haloaryl aldehyde in the presence of a Pd catalyst will afford the cross-coupling product only (Scheme 1a (ii)).

Selective control of organoboron reactivity modes is an increasingly important challenge due to the emergence of methods that allow access to multi-organoboron system or products.[6,7] These novel systems have significant potential to enable novel tandem and multicomponent reactions, which will allow both more streamlined and efficient chemical synthesis and access to novel chemical space. However, the power of multi-organoboron systems can only be realised with appropriate control of reactivity.



Scheme 1. Chemoselective control of aryl and allyl BPin reagents: orthogonal reactivity, selective C-C bond formation, and product mixtures.

We have shown that aryl organoborons ($ArB(OH)_2$ and ArBPin) undergo chemoselective SM cross-coupling based on kinetic discrimination at transmetalation.[8] Based on these initial results using organoboron reagents with the same reactivity profile (*i.e.*, aryl organoborons), we questioned whether chemoselectivity could be exerted over increasingly complex systems with different modes of reactivity to develop tandem reactions. Here we describe a simple method to control a multi-reactive, two electrophile + two organoboron nucleophile system, allowing the development of a chemoselective allylation/SM reaction to generate functionalised homoallylic alcohols (Scheme 1b) and demonstrate the utility of this approach in the preparation of scaffolds of interest to pharmaceutical and natural product synthesis.

Control reactions demonstrated that mixtures of products result when allylBPin (**1**) and 4-bromobenzaldehyde (**2**) are exposed to typical SM reaction conditions.[9] Mixtures of allylation and SM cross-coupling were observed (**3a-c**, Scheme 2).

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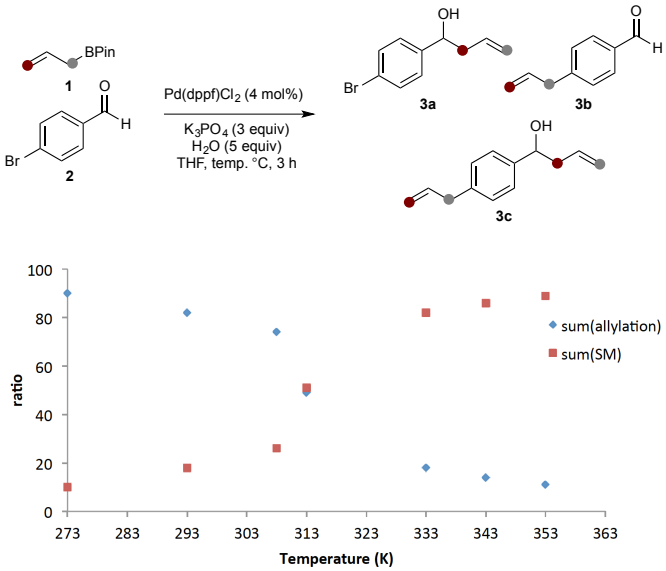
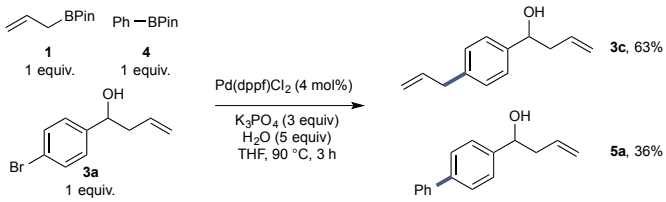


Scheme 2. Temperature study of Σ(allylation) vs. Σ(SM). Determined by ^{1}H NMR using internal standard (see ESI).

Sutherland reported an elegant one-pot allylation–Heck sequence for the preparation of carbocycles using stepwise addition of reagents to avoid selectivity issues.[10] We sought to establish control over this system that would avoid the need for intervention/sequential addition. We found that correlating product distribution as a function of Σ(allylation) vs. Σ(SM) bond formation with temperature revealed that allylation decreases with increasing temperature while the opposite trend was observed for the SM process. Accordingly, this provides a simple method for controlling the reactivity profile of **1** with **2** in the presence of a Pd catalyst – at low temperature allylation dominates.

Additional control experiments revealed that allyl BPin outcompetes aryl BPin in transmetalation. For example, the reaction of an equistoichiometric mixture of allyl BPin **1** and aryl BPin **4** with the aryl bromide **3a** led to approx 2:1 ratio of allylated:arylated products **3c** and **5a**, respectively (Scheme 3). **5a** is only observed due to the sensitivity of **1** to degradation at elevated temperatures, *i.e.*, **4** only undergoes reaction after all of **1** is consumed.

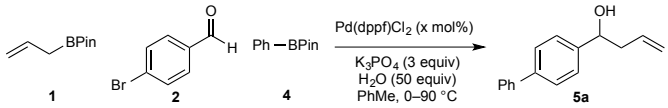


Scheme 3. Organoboron chemoselectvity of three-component Suzuki-Miyaura cross-coupling of aryl bromide **5** using aryl (**4**) and allyl (**1**) BPin nucleophiles. Isolated yields.

However, at low temperature SM cross-coupling can be inhibited: Denmark and Hartwig have shown that transmetalation proceeds at low temperature[11,12] but oxidative addition generally requires thermal promotion.[13] Accordingly we hypothesised that we may be able to use a simple temperature gradient to control a multi-reactive system containing **1**, **2**, and **4**. Allylation of **1** and **2** then subsequent SM cross-coupling of **4** with the allylation product (**5**) will allow two distinct chemoselective C-C bond formations, based on two different reactivity profiles, and deliver **5a**.

Optimisation of the tandem system was performed using allyl BPin (**1**), 4-bromobenzaldehyde (**2**), and phenyl BPin (**4**) as the model substrates, with Pd(dppf)Cl_2 as catalyst, and K_3PO_4 based on our previous work with SM cross-coupling (Table 1).[9] The reaction was first carried out employing THF as solvent; however, the process was highly variable with little consistency under these conditions due to unexpected variability of the allylation event in THF (see ESI).

Table 1. Reaction optimisation.[a]



Entry	Pd(dppf)Cl_2 (mol%)	Allyl BPin (equiv.)	PhBPin (equiv.)	Yield **5a** (%)[b]
1	4	1.2	1.3	58
2	3	1.2	1.3	67
3	2	1.2	1.3	70
4	1	1.2	1.3	76
5	0.5	1.2	1.3	77
6	0.5	1.25	1.3	87
7	0.5	1.25	1.4	89
8	0.5	1.25	1.3	69[c]

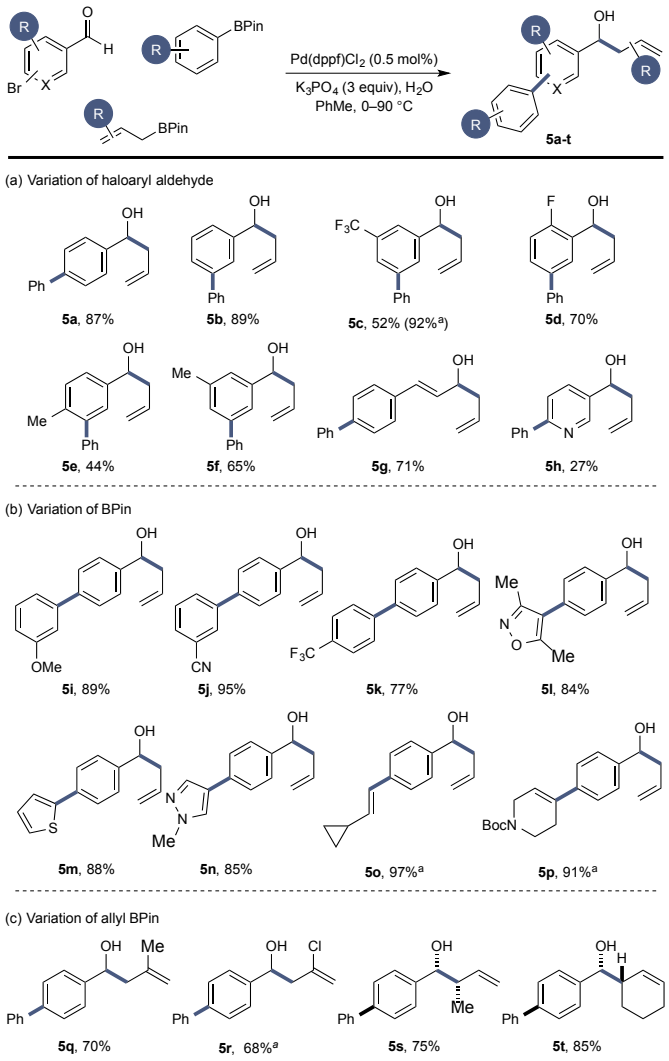
[a] Reaction conditions: **1** (1 equiv.), Pd(dppf)Cl_2 (x mol%), allyl BPin (x equiv.), PhBPin (x equiv.), K_3PO_4 (3 equiv.), H_2O (50 equiv.), PhMe (0.25 M), 0–90 °C, 25 h, unless stated otherwise; [b] Isolated yield. [c] Using rt-90 °C.

Brown reported that allylboration proceeds more slowly in THF *vs.* PhMe or CH_2Cl_2 ($t_{1/2(THF)}$ = 180 min, $t_{1/2(PhMe)}$ = 90 min $t_{1/2(CH_2Cl_2)}$ = 40 min).[14] Based on the faster rate of transmetalation of **1** *vs.* **4** (Scheme 3), complete consumption of **1** is necessary to avoid product mixtures. Changing solvent to PhMe significantly improved the consistency of the allylation event and after heating to promote SM cross-coupling, product **5a** was obtained in yield of 58% yield (Table 1, entry 1).

A negative correlation of Pd catalyst loading *vs.* reaction performance was noted and reduction of Pd catalyst led to improvement of the yield from 58% to 77% (entries 1 to 5). An adjustment to the allyl BPin stoichiometry provided an elevation of the yield to 87% (entry 6) while only minor increases were obtained by increasing PhBPin loading (entry 7). Finally, a significant loss of efficiency was noticed when the reaction was performed at rt (*ca.* 18 °C), which was in agreement observations from the temperature study (Scheme 2).

With an optimised system in hand, the general performance of the chemoselective sequential process was examined (Scheme 4). Variation of the haloaryl aldehyde was readily

accommodated, delivering the expected homoallyl alcohols in moderate to excellent yields (Scheme 4a). Both *para*- and *meta*-substitution was possible, with *ortho*-substitution incompatible due to the competing, and more favourable, intramolecular Heck process as previously described by Sutherland.[10] Interestingly, despite accelerating both allylation and oxidative addition, electron-withdrawing groups led to a reduced yield; however, this could be remedied by increasing the stoichiometry of the BPin component.



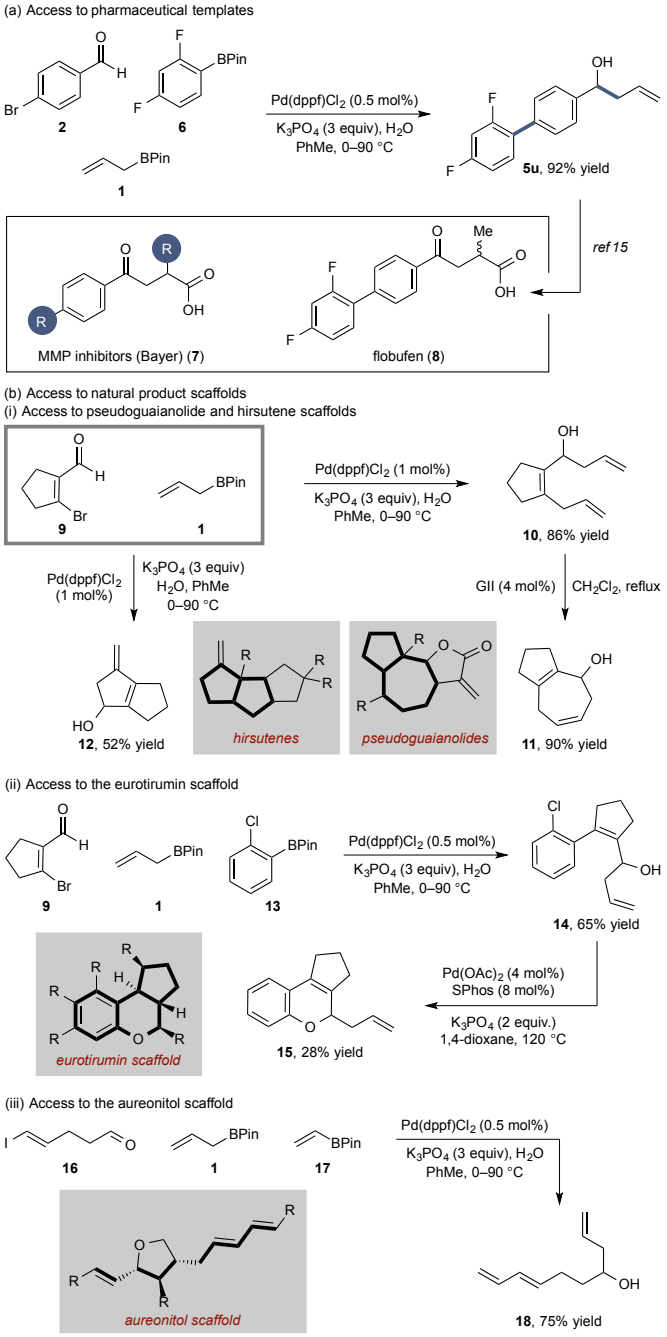
Scheme 4. Scope of the chemoselective one-pot allylation/cross-coupling process. Isolated yields. [a] PhBPin (2 equiv.) was employed.

Variation of the aryl BPin component was straightforward, accommodating variation of steric and electronic parameters, with generally excellent yields of the desired products recorded (Scheme 4b).

Lastly, a range of substituted allyl BPins were successful, allowing access to alternatively functionalised products on the allyl unit in addition to crotyl and cyclohexenyl allylboron reagents delivering the expected products as single diastereomers (Scheme 4c).

Reactions to probe the application of this tandem approach with imine electrophiles were unsuccessful due to the requirement of increased temperatures (compromising organoboron chemoselectivity) or Lewis acids (affecting the Pd catalysis).

Finally, to demonstrate the utility of this one-pot tandem C-C bond formation, we sought to generate valuable scaffolds of relevance to both pharmaceutical and natural product synthesis (Scheme 5).



Scheme 5. Access to pharmaceutical and natural product templates using the chemoselective one-pot allylation/cross-coupling process.

Chemoselective reaction of 1 and 2 with difluorophenyl BPin **6** leads to biaryl adduct **5u** in 92% yield (Scheme 5a). **5u** is an intermediate in the synthesis of the antinflammatory agent flobufen (**8**).[15] In addition, the biaryl scaffold of products **5a-u**

form the principal architecture of a class of matrix metalloprotease (MMP) inhibitors developed by Bayer (**7**),[16] providing a rapid method for generation of libraries of this chemotype.

Control of the reaction between two equivalents of **1** and the bromocyclopentenal **9** allows preparation of triene **10** (Scheme 5b (i)). Ring-closing metathesis of **10**, delivers 5,7-fused carbocycle **11** that represents the core of the pseudoguaianolide natural products.[17] Alternatively, using an equistoichiometric mixture of **1** and **9** gives access to the 5,5-carbocycle **12**, forming part of the hirstuene scaffold,[18] *via* intramolecular Heck in an analogous fashion to the Sutherland procedure.[10] Reaction of **1** with bromoenal **9** and aryl BPin **13** delivers the diene **14** in good yield (Scheme 5b (ii)). This reaction also tests the chemoselectivity of oxidative addition between the bromoenal **9** and the chloroarene **13**. Subsequent intramolecular Buchwald-Hartwig etherification forges the eurotrimin scaffold **15**.[19] Lastly, using all acyclic substrates **1**, **16**, and **17** delivers the linear triene product **18** in good yield and provides access to the aureonitol scaffold (Scheme 5b (iii)).[20]

In summary, a simple temperature gradient allows control of chemoselective tandem reaction of a multi-reactive, two electrophile + two nucleophile, system. Temperature and product profiling revealed that the reactivity mode of allyl BPin reagents could be controlled to allow 1,2-addition to a haloaryl aldehyde selectively in the presence of a Pd catalyst. This allowed the inclusion of an aryl BPin reagent and the development of a one-pot sequential allylation/cross-coupling process to deliver a series of functionalised aryl/allyl products. The application of this process to pharmaceutical and natural product synthesis was also demonstrated. We anticipate that the knowledge generated with respect to control of organoboron reagents will facilitate the development of tandem or cascade synthesis processes using multi-organoboron systems.

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