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A site-selective and stereospecific cascade Suzuki–Miyaura annulation of alkyl 1,2-bisboronic esters and 2,2′-dihalo 1,1′-biaryls†

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A cascade Suzuki–Miyaura cross-coupling giving rise to 9,10-dihydro-phenanthrenes has been developed. Using biaryls with unsymmetrical substitution-pattern full site-selectivity was observed. Furthermore, this cross-coupling of an alkyl 1,2-bisboronic pinacol ester proceeds through the challenging coupling of a secondary boronate with complete stereoretention.

The Suzuki–Miyaura cross-coupling has found broad use in the synthesis of drugs, agrochemicals, fine chemicals, and polymers.[1–3] In combination with cascade annulations, in which multiple bonds are formed in a single reaction vessel, it offers the possibility to rapidly build up molecular complexity, limit chemical waste, and improve step-economy.[4]

Selected examples of cascade Suzuki–Miyaura cross-coupling reactions with alkenyl 1,2-bisboronic pinacol esters have been previously reported for the synthesis of polycyclic aromatic hydrocarbons (PAH) by Shimizu and Hiyama (Fig. 1).[5,6] In addition, Wang has reported a cascade annulation with alkyl 1,1-bisboronic pinacol esters in the synthesis of 9*H*-fluorenes.[7]

Alkyl 1,2-bisboronic pinacol esters can be readily accessed in racemic and stereoselective fashion using transition metal-catalyzed and organocatalytic approaches.[8–17] The Morken group has reported a Suzuki–Miyaura cross-coupling of the alkyl 1,2-bisboronic pinacol esters in which either the primary or secondary position can be selectively functionalized (Fig. 1).[18,19] However, despite their facile synthesis and intriguing site-selective reactivity, these reagents have not yet been evaluated in cascade annulation reactions.

Given the straightforward access and site-selective reactivity of the stable alkyl 1,2-bisboronic pinacol esters, we questioned

whether these reagents could be successfully employed in site-selective annulation reactions. We reasoned that the direct, modular synthesis of tricyclic 9,10-dihydrophenanthrenes, could be achieved using a tailored annulation reaction that takes advantage of these reagents. Key to the development of this reaction would be the high site-selectivity of both cross-coupling events (Fig. 1) that would, crucially, take advantage of the matching reaction rates between the two different nucleophilic (1° *vs.* 2° C–Bpin) and electrophilic (C–Br *vs.* C–Cl) sites present on the two reagents.

Herein we report the development of a Pd-catalyzed site-selective and stereospecific cascade annulation of alkyl 1,2-bisboronic pinacol esters and 2-bromo-2′-chloro biaryls.

We entered our studies by identifying a suitable model alkyl 1,2-bisboronic pinacol ester (Scheme 1). Initial exploration focused on the use of symmetrical 2,2′-dibromobiphenyl 2b, as this would simplify reaction monitoring and allow rapid identification of promising conditions for this highly challenging annulation reaction. Using previously reported reaction conditions,[19]
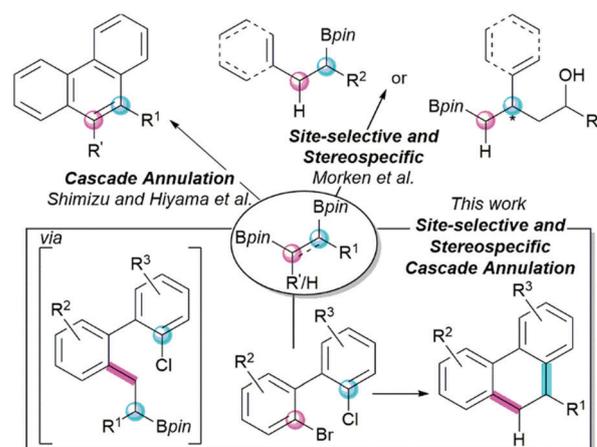
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Fig. 1 Reaction design of a cascade Suzuki–Miyaura cross-coupling based on alkyl 1,2-bisboronic pinacol esters.
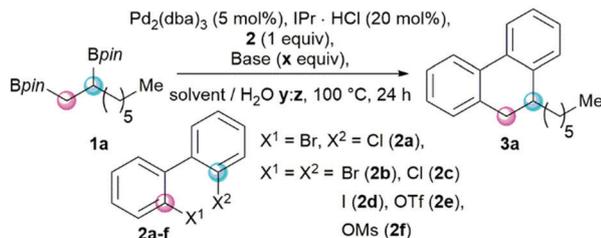
Scheme 1 Optimization of the annulation reaction using alkyl 1,2-bisboronic pinacol ester **1a** and biaryls **2** to yield 9,10-dihydrophenanthrene **3a**.

the octyl-1,2-bisboronic pinacol ester **1a** only gave trace amounts of the cyclized product, further highlighting the challenges in developing such a process. A sequence of experiments allowed us to find a promising Pd$_2$(dba)$_3$/IPr HCl (1 : 4) catalytic system in THF which gave 35% of 9-hexyl-9,10-dihydrophenanthrene **3a** in the presence of KOH (Scheme 1 and Table 1, entry 1). We next explored the reactivity of other electrophilic coupling partners in the cyclization reaction. 2,2′-Dichlorobiphenyl **2c** gave a cleaner reaction and a similar amount of annulated product compared to the dibromide **2b** (entry 1 and 2). In contrast, the diiodide **2d** gave a diminished product yield (entry 3). 2,2′-Biphenol derived ditriflate **2e** and dimesylate **2f** were unreactive and starting materials were recovered (entry 4 and 5). Combining these preliminary observations, we envisioned that optimizing conditions for 2-bromo-2′-chloro biphenyl **2a** may set the stage for the subsequent development of a fully site-selective annulation process.[20,21]

Excitingly, using 2-bromo-2′-chloro biphenyl **2a**, the yield increased to 48% (entry 6). Further optimization showed that the use of barium hydroxide as a base under more dilute reaction conditions was crucial to increase the yield of the double Suzuki–Miyaura to 76% (entry 12). The availability of hydroxides plays a pivotal role in the efficiency of the Suzuki–Miyaura cross-coupling as discussed by Amatore and Jutand,[22] as well as Hartwig.[23] Based on these studies, we postulate that changing the counterion of the hydroxide-source may increase the activity of the Pd-catalyst during transmetalation due to a weaker binding affinity of the barium-compared to the potassium-counterion.[24,25] Furthermore, barium hydroxide

might release hydroxide ions more gradually as compared to potassium hydroxide due to its lower solubility.[26]

Having optimized the reaction conditions, we next investigated whether we could verify the central hypothesis of this work, namely that the two unsymmetrically substituted reagents can undergo a site-selective cross-coupling reaction.

In an attempt to observe a single regioisomer, we used unsymmetrically substituted biaryls and performed an annulation with alkyl 1,2-bisboronic pinacol esters (Scheme 2). Excitingly, introduction of a Me- or F-substituent on the biaryl substrate indeed led to a single regioisomer (**3b–3i**). Additionally, an electron-poor mono CF$_3$-substituted biaryl and an electron-rich methoxy-substituted biaryl also gave the corresponding products with high regioselectivity (**3j, 3k**). We rationalize this selectivity with the different reaction rates of the reactive centers in both bifunctional reagents (1° vs. 2° C–Bpin, C–Br vs. C–Cl). Initially, a C–C bond between the primary C–Bpin and Ar–Br is formed, followed by the intramolecular cyclization between the secondary C–Bpin and Ar–Cl.

Biaryls with a symmetric substitution pattern (**3l, 3m**) were also well tolerated. An attempt to cyclize 2,2′-dibromo-1,1′-binaphtalene did not afford any annulated product. The ability to rotate freely around the biaryl bond might therefore be crucial to the efficiency of the second coupling step. Furthermore, an extension to heterocyclic biaryls proved unsuccessful.

Turning our focus to the alkyl 1,2-bisboronic pinacol ester scope, sterically more encumbered substituents showed good compatibility with the annulation reaction (**3n–s**). A dinucleophile containing a primary chloride (**3s**) and a eugenol-derivative (**3t**) were efficiently converted to the annulated product. Unfortunately, nitrile, ester or ketone functionalities were not tolerated. Similarly, double secondary, ethane- or methane-derived dinucleophiles did not yield cyclized products. Finally, the model reaction could be scaled up to a 5 mmol scale yielding 57% (0.76 g) of the annulated product **3a**.

Intrigued by the high efficiency and selectivity of the transformation, we monitored the model reaction more closely. The chlorinated reaction intermediate **4** could be isolated when stopping the reaction after three hours (Scheme 3A). In contrast, the corresponding brominated intermediate was not observable. NMR studies showed that compound **4** exists as a mixture of two atropoisomers that are interconvertible at elevated temperature (see ESI,† for details). Using the intermediate **4** as a starting material in our reaction, the annulated product was observed in high yield (Scheme 3A). Interestingly, using potassium hydroxide as a base gave a comparable conversion (77%, see ESI†) to the cyclized product in this single-step, intramolecular coupling reaction. The intramolecular nature of the coupling between the secondary boronic pinacol ester and the aryl chloride may be key to facilitate the challenging secondary cross-coupling. To substantiate this hypothesis, an intermolecular control reaction was performed. As expected, both reactions using the corresponding homobenzylic boronic pinacol ester and either bromobenzene or chlorobenzene did not yield any of the cross-coupled product (see ESI,† for details). Usually, the Pd-catalyzed Suzuki–Miyaura cross-coupling of aliphatic,

Table 1 Optimization of reaction conditions[a]

Entry	Base (x equiv.)	2a–f X^1, X^2	Solvent/H$_2$O (y : z)	3a^b [%]
1	KOH (3)	Br, Br	THF (10 : 1)	35
2	KOH (3)	Cl, Cl	THF (10 : 1)	33
3	KOH (3)	I, I	THF (10 : 1)	6
4	KOH (3)	OTf, OTf	THF (10 : 1)	4
5	KOH (3)	OMs, OMs	THF (10 : 1)	0
6	KOH (3)	Br, Cl	THF (10 : 1)	48
7	Ba(OH)$_2$ (2)	Br, Cl	THF (1 : 1)	70
8	Ba(OH)$_2$ (2)	Br, Cl	Dioxane (1 : 1)	31
9	Ba(OH)$_2$ (2)	Br, Cl	H$_2$O	53
10^c	**Ba(OH)$_2$ (2)**	**Br, Cl**	**THF (4 : 1)**	**76**
11^c	—	Br, Cl	THF (4 : 1)	0
12^{cd}	Ba(OH)$_2$ (2)	Br, Cl	THF (4 : 1)	0

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.1 mmol), Pd$_2$(dba)$_3$ (0.005 mmol), IPr HCl (0.02 mmol), base (0.2–0.3 mmol), THF/H$_2$O (0.1 mol L^{-1}), 100 °C, 24 h. [b] GC yield using n-tetradecane as internal standard. [c] THF/H$_2$O (0.04 mol L^{-1}). [d] Without Pd$_2$(dba)$_3$ and IPr HCl.
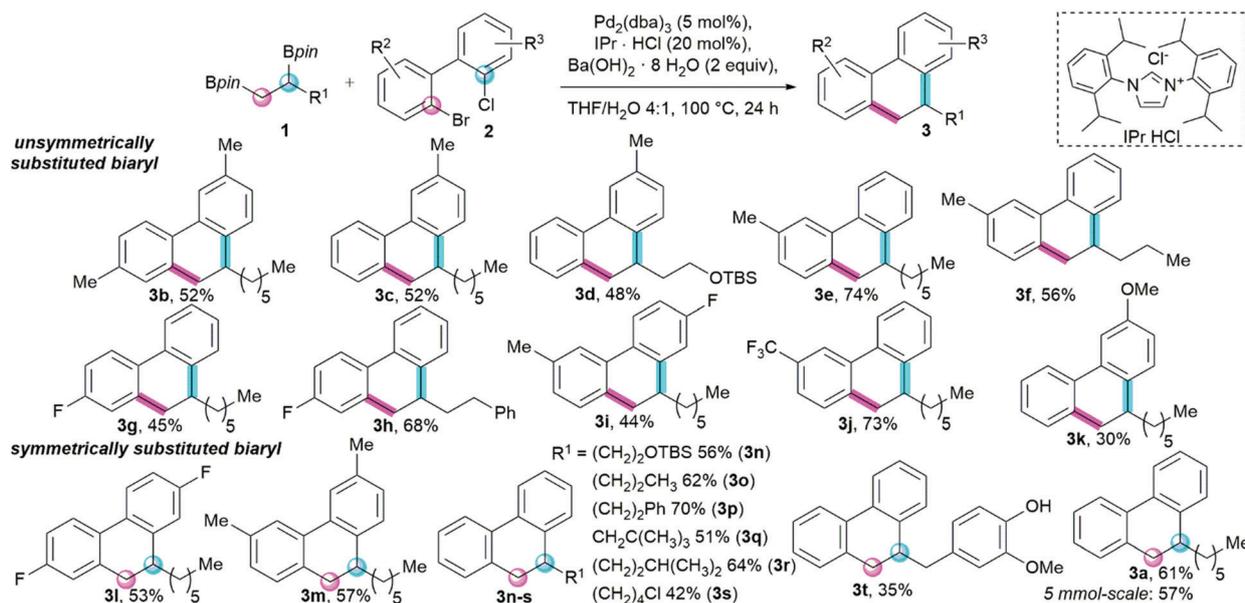
Scheme 2 Scope of the double Suzuki–Miyaura cross coupling of alkyl 1,2-bisboronic pinacol esters **1** with 2-bromo-2′-chloro biaryls **2** to afford 9,10-dihydrophenanthrenes **3**. Yields are for isolated products. See ESI,† for further information.
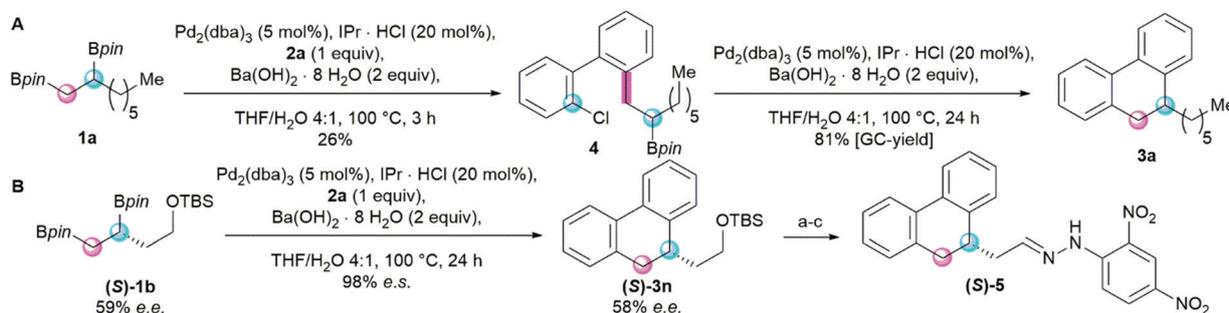
Scheme 3 Mechanistic studies of the Suzuki–Miyaura annulation reaction. (A) Isolation of the key reaction intermediate **4** and a mono-coupling to the annulated 9,10-dihydrophenanthrene **3a**. (B) Cascade cross-coupling of the enantioenriched alkyl 1,2-bisboronic pinacol ester **(S)-1b** and the derivatization to crystallize **(S)-5** (CCDC #2054485†): (a) TBAF (2 equiv.), THF, r.t., 3 h, (b) DMP (1.25 equiv.), DCM, 0 °C to r.t., 1.5 h, (c) DNP (1.2 equiv.), HCl (35% in H$_2$O, 2 equiv.), MeOH, r.t., 24.

chiral coupling reagents is stereospecific.[27] Thus, using the Pt(dba)$_3$/TADDOL-protocol developed by Morken *et al.* for the enantioselective diborylation of terminal alkenes, we synthesized an enantioenriched dinucleophile **(S)-1b** and performed the annulation reaction (Scheme 3B).[9] The product was obtained with complete enantiospecificity.[28] Derivatization and crystallization of the major enantiomer after preparative HPLC revealed the absolute configuration of enantiomer **(S)-3n**, showing that the configuration is retained during the annulation reaction. This result is in accordance with literature precedent showing that stereoretentive transmetalation is the predominant pathway in this type of cross-coupling reactions.[27]

In summary, we have reported a site-selective double Suzuki–Miyaura cross-coupling using non-symmetric bifunctional reagents. This reaction allows for easy access to twenty different 9,10-dihydrophenanthrenes, a biologically-relevant scaffold.[29] The high stereospecificity of our annulation reaction shows that it offers a direct access to enantiomerically enriched 9,10-dihydrophenanthrenes. We have shown that a notoriously challenging cross-coupling of a secondary pinacol boronic ester and the aryl chloride is enabled by the proximity of the reactive sites which plays a key role to the success of this annulation. Thus, this cascade reaction also suggests a new avenue to facilitate the otherwise challenging cross-coupling of secondary aliphatic boron nucleophiles.[30]

Conflicts of interest

There are no conflicts to declare.

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