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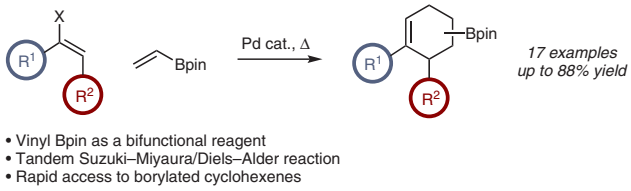
A Cascade Suzuki–Miyaura/Diels–Alder Protocol: Exploring the Bifunctional Utility of Vinyl Bpin

David L. Cain[a]
Calum McLaughlin[b]
John J. Molloy[b]
Cameron Carpenter-Warren[a]
Niall A. Anderson[c]
Allan J. B. Watson*[a]

[a] EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, KY16 9ST, UK
aw260@st-andrews.ac.uk
[b] WestCHEM, Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK
[c] GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road Stevenage, Hertfordshire, SG1 2NY, UK



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Abstract Cascade reactions are an important strategy in reaction design, allowing streamlining of chemical synthesis. Here we report a cascade Suzuki–Miyaura/Diels–Alder reaction, employing vinyl Bpin as a bifunctional reagent in two distinct roles: as an organoboron nucleophile for cross-coupling and as a Diels–Alder dienophile. Merging these two reactions enables a rapid and operationally simple synthesis of functionalized carbocycles in good yield. The effect of the organoboron subtype on Diels–Alder regioselectivity was investigated and postsynthetic modifications were carried out on a model substrate. The potential for a complementary Heck/Diels–Alder process was also assessed.

Key words Bpin, cascade, cross-coupling, Diels–Alder, Suzuki–Miyaura

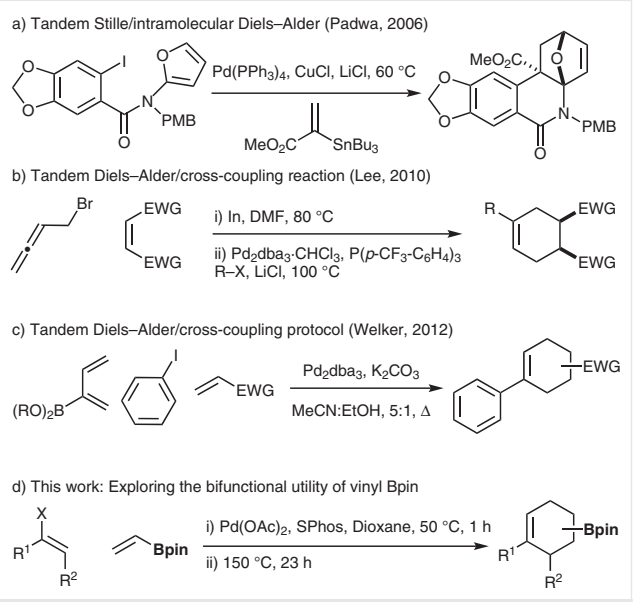
Cascade methodologies are recognized as an enabling approach to chemical synthesis.[1–4] The modularity with which complex molecules can be created from embedding downstream reactivity into small precursors is an appealing strategy for synthetic chemists, allowing the use of highly reactive, nonisolable intermediates, reducing step count, and leading to overall improvements in chemical efficiency.

The Diels–Alder (DA) reaction is one of the most widely explored reactions within cascade sequences.[1–4] This popularity stems from variety of methods to prepare dienes, in combination with the ability to effectively generate stereochemically enriched six-membered rings with relative ease. The diene component of the DA reaction can often be challenging to handle since particular dienes are prone to rapid decomposition or polymerization upon isolation.[5] As a result, considerable research has been focused on the generation and *in situ* applications of specific dienes.[6–15]

Cross-coupling reactions are effective methods for the preparation of dienes for *in situ* DA reactions.[13–15] For example, Padwa reported a cascade Stille/intramolecular DA to form complex tetracyclic fused ring systems (Scheme 1, a).[16] Lee employed a cascade DA/cross-coupling protocol, generating an organoindium reagent *in situ*, to enable a subsequent Pd-catalyzed cross-coupling (Scheme 1, b).[17] Welker reported a three-component tandem Suzuki–Miyaura/DA cascade involving an initial cycloaddition between a borylated diene and electron-deficient dienophile followed by a subsequent cross-coupling with an aryl iodide (Scheme 1, c).[18] In all previously reported methods the DA is performed with a highly activated, electron-deficient dienophile. We recently disclosed a tandem cross-coupling/DA reaction, to generate molecular complexity.[19] Again, these reactions required highly activated dienophiles to promote reactivity.

Here we explore the utility of vinyl Bpin as both cross-coupling nucleophile and dienophile for the cascade synthesis of borylated carbocycles (Scheme 1, d). While vinyl Bpin is a competent cross-coupling nucleophile, its utility as a dienophile is underdeveloped.[19,20] However, a cross-coupling/DA cascade utilizing vinyl Bpin as both nucleophile and dienophile would construct borylated cyclohexenes, capable of an array of further transformations.

We initiated the optimization study (Table 1) using triflate **1a** with excess vinyl BPin. Employing conditions previously established in our group,[21–25] the Suzuki–Miyaura event proceeded rapidly and quantitatively, delivering Dane's diene (**2a**) as an intermediate.[26,27] We believed thermal promotion would enable cyclization, and a temperature screen indicated that a minimum of 150 °C (Table 1, entries 1–4) was necessary to drive the DA reaction to completion; 5 equivalents of vinyl BPin were required to overcome organoboron degradation and offset a competing homo DA consuming diene intermediate **2a** (Table 1, entries 6–8). A time study indicated that the reaction was complete in 6 h (Table 1, entries 9 and 10). Given the electron-rich,



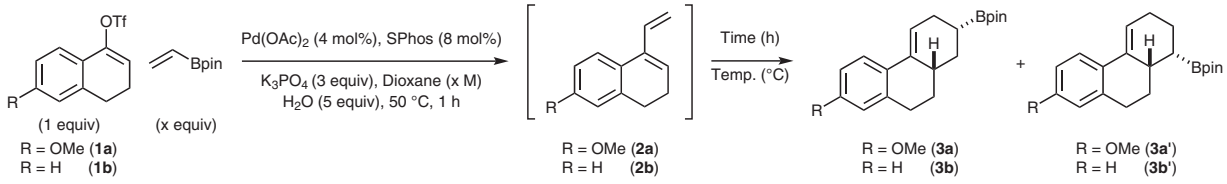
Scheme 1 Cross-coupling/DA in cascade methodologies; DMF = *N*,*N*-dimethylformamide; EWG = electron-withdrawing group; pin = pinacolato; PMB = *para*-methoxybenzyl.

reactive nature of the intermediate diene **2a**, we were concerned that these reaction conditions would not be broadly transferrable. A control experiment using des-methoxy triflate **1b**, via diene **2b**, indicated that longer reactions times would potentially be necessary for less electron-rich substrates (Table 1, entries 11 and 12).

The scope of the reaction was subsequently investigated (Scheme 2). All substrates were isolated as the corresponding alcohol to aid characterization and separation of the regioisomers generated from the cycloaddition. The tetralone-derived scaffolds (**4a–g**) displayed good yields in all examples, with both electron-donating (**4a**,**4d**,**e**) and electron-withdrawing groups (**4f**) tolerated, in addition to a chromane example (**4g**). The position and nature of the substituent on the aromatic ring had little effect on the regioselectivity of the cycloaddition, with a moderate (ca. 3:1) ratio of regioisomers observed throughout. However, a single diastereomer was produced, which following X-ray crystallographic analysis confirmed an *endo* DA adduct (*vide infra*).

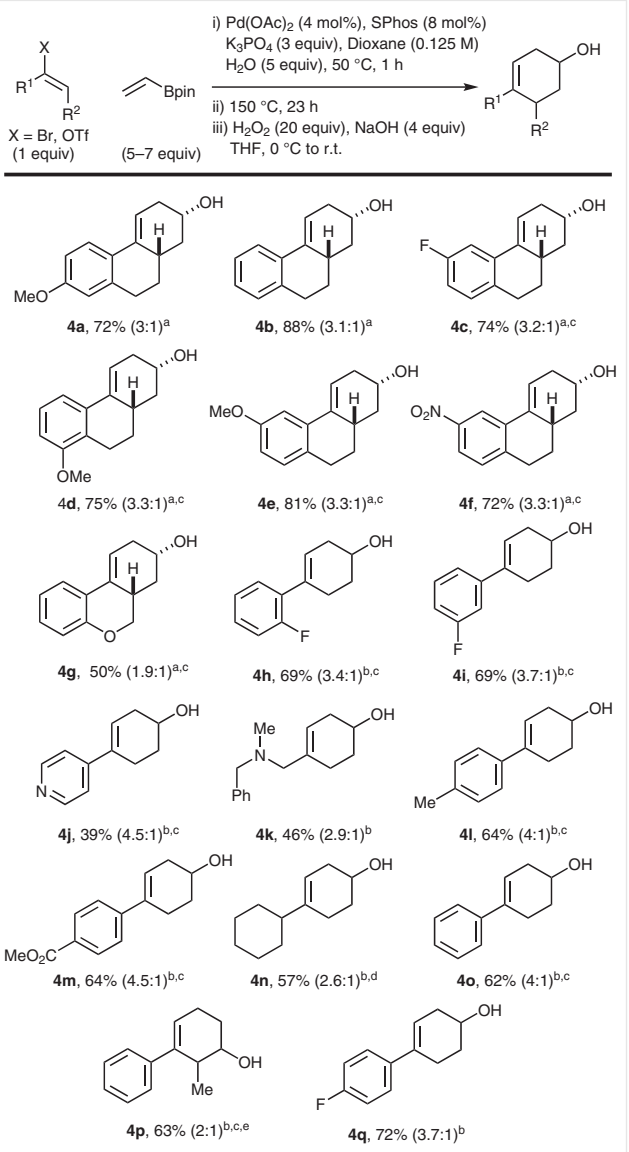
Use of styrenyl and alkenyl electrophiles (**4h–q**) allowed the formation of cyclohexenyl products (Scheme 2). Homo DA was found to be significantly more problematic in these cases. However, this could be circumvented using 7 equivalents of vinyl Bpin to deliver a range of products in good yield and with comparable levels of regiochemical control.

Table 1 Optimization of SM/DA Cascade Reaction



Entry	Time (h)	Temp (°C)	Vinyl Bpin (equiv)	Concentration (M)	Conv. (%)[a]	r.r.[b]
1	23	75	5	0.125	24	–[c]
2	23	100	5	0.125	33	–[c]
3	23	125	5	0.125	66	–[c]
4	23	150	5	0.125	98	3:1
5	23	150	5	0.25	85	3.1:1
6	23	150	2	0.125	62	3.1:1
7	23	150	3	0.125	84	3.2:1
8	23	150	4	0.125	93	3.2:1
9	4	150	5	0.125	88	3.1:1
10	6	150	5	0.125	99	3.5:1
11	6	150	5	0.125	88[d]	3.1:1
12	23	150	5	0.125	96[d]	3.1:1

[a] Conversion determined by ^{1}H NMR spectroscopy using an internal standard.
[b] r.r. = regioisomeric ratio of **3a**/**3a'** or **3b**/**3b'**. Determined by ^{1}H NMR spectroscopy after oxidation.
[c] Unable to be determined due to impurity profile.
[d] Reactions using **1b**.

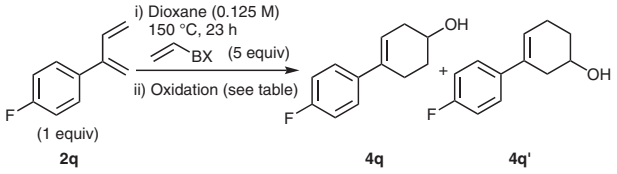


Scheme 2 Substrate scope of the cascade reaction. Major regioisomer displayed. Isolated yields of regioisomeric products. Numbers in brackets are the r.r. [a] Using 5 equiv vinyl Bpin. [b] Using 7 equiv vinyl Bpin. [c][n = 2]. [d][n = 3]. [e] d.r. of both regioisomers = 2:1.

Lastly, use of β-methyl styrene resulted in the formation of the product **4p** in moderate yield. Interestingly, a change in regioselectivity was observed with this substrate, now favoring what was the minor regioisomer for all previous examples.

Based on the moderate regioselectivity observed throughout as well as the reversal of regioselectivity in example **4p**, we were interested to assess what, if any, impact the nature of the organoboron substituent had on the regioselectivity of the cycloaddition (Table 2).

Table 2 Diels–Alder Regioselectivity: Variation of Vinyl Boron Species



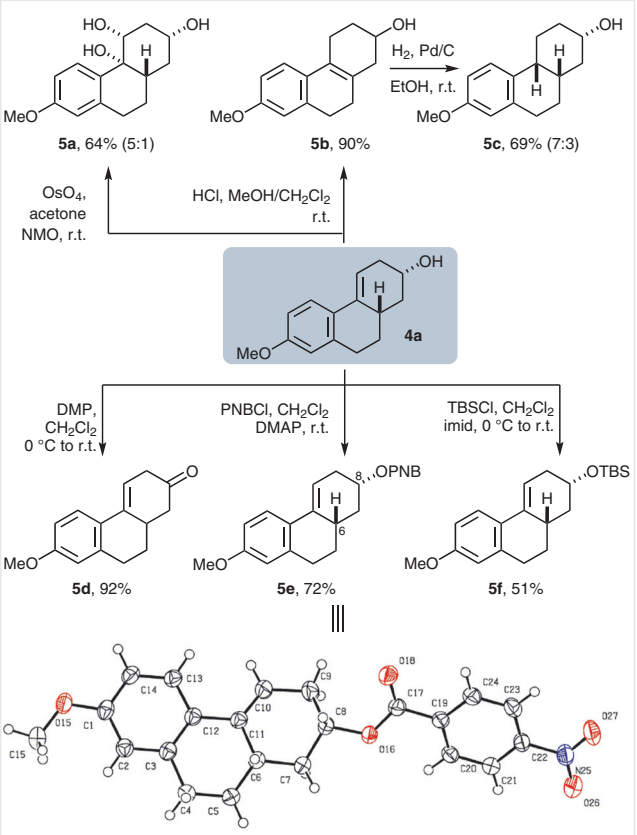
Entry	Vinyl boron species (BX)	Ratio (**4q**/**4q'**)[a]
1	Bpin	3.7:1[b]
2	BF_3K	3.5:1[c]
3	Bdan	3.5:1[d]
4	BMIDA	2.8:1[e]
5	boroxine	3.6:1[b]

[a] Determined after oxidation to the corresponding alcohol.
[b] Oxidation conditions: H_2O_2 (20 equiv), 2 M NaOH (4 equiv), THF, 0 °C to r.t., 1 h.
[c] Oxidation conditions: Oxone® (1.1 equiv), acetone/H_2O (1:1), r.t., 2 h.
[d] (i) 2 M HCl (6 equiv), THF, r.t., 23 h; (ii) H_2O_2 (20 equiv), 2 M NaOH (4 equiv), THF, 0 °C to r.t., 1 h.
[e] (i) K_3PO_4 (3 equiv), H_2O (5 equiv), CPME, 80 °C, 10 min; (ii) Oxone® (2.5 equiv), CPME/H_2O (4:1), 70 °C, 1 h; dan = 1,8-diaminonaphthalenate; MIDA = *N*-methyliminodiacetate; pin = pinacolato.

Under the aqueous basic conditions used for the initial Suzuki–Miyaura cross-coupling of the tandem process the vinyl BPin could conceivably exist as its boronate derivative,[28] which exhibits significantly different electronic properties to the parent neutral boronic ester. Since altering the electronics of the dienophile may have a direct influence on the regioselectivity of the cycloaddition, we assessed several different organoboron species (Bpin, BMIDA, boroxine, BF_3K, Bdan) to determine any influence on regioselectivity (Table 2). However, no noticeable trends were observed, with all reactions producing a similar regioisomeric ratio. The cycloaddition requires significant thermal promotion and it is possible that these observations could be explained by the high temperatures required for reactivity overriding any potentially subtler electronically induced kinetic effects.

In order to demonstrate potential synthetic application of this method, we carried out postsynthetic modifications of a benchmark substrate (**4a**; major regioisomer). Dihydroxylation, alkene migration, hydrogenation, oxidation, acylation, and alcohol protection were all shown to be feasible, giving compounds **5a–f** and illustrating the potential of diversification capabilities (Scheme 3). Compound **5e** was characterized by X-ray diffraction, confirming relative stereochemistry and providing evidence that the cycloaddition proceeds via the *endo* transition state.

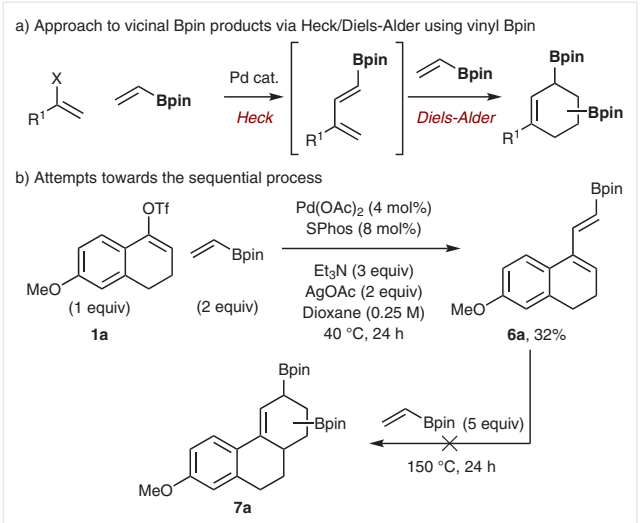
Lastly, we explored the feasibility of performing a Heck/DA cascade reaction using vinyl Bpin (Scheme 4, a), given the recent successful methodology implementing a variety of dienophiles,[19] as this would provide expedient



Scheme 3 Illustrative synthetic modifications of **4a**; DMAP = 4-dimethylaminopyridine; DMP = Dess–Martin periodinane; imid = imidazole; NMO = *N*-methylmorphonline *N*-oxide; PNB = *para*-nitrobenzoyl chloride; TBS = *tert*-butyldimethylsilyl.

access to vicinyl Bpin systems. Initial efforts in performing the reaction in a one-pot process proved unsuccessful; as a result, a stepwise approach was adopted for proof of concept. The Bpin diene intermediate **6a** was successfully isolated, albeit in low yield (Scheme 4b): this reaction delivered complex mixtures of products, likely *via* homo-Diels–Alder as well as protodeboronation. Despite our best efforts, and our acquired knowledge on this DA reaction, we were unable to obtain the DA adduct **7a** upon exposing the diene **6a** to excess vinyl Bpin at elevated temperatures. The reaction yielded a complex mixture of unknown products, this could be due to the noted poor stability/high reactivity of intermediate **6a** and exacerbated by the requirement for high temperatures.

In summary, we have developed a cascade Suzuki–Miyaura/Diels–Alder protocol enabling expedient access to borylated carbogenic frameworks, exploiting the unique reactivity of vinyl Bpin as both cross-coupling partner and dienophile.[29] The process tolerates a variety of functional groups, producing cycloadducts in moderate to good yields and with moderate regioselectivity. The effect of the organoboron substituent on the Diels–Alder regioselectivity



Scheme 4 a) Proposed one-pot cascade Heck/DA reaction; b) stepwise approach to elucidating feasibility of reaction.

was assessed and found to have little impact on the outcome of the process, suggesting the thermal activation required erodes any potential stereoelectronically induced regioselectivity. In addition, a set of derivatization reactions was carried out to demonstrate synthetic versatility of these building blocks as intermediates. Finally, the possibility of a cascade Heck/Diels–Alder reaction was investigated through a stepwise approach, however, the reaction could not be driven to the desired product.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611228.

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(29) **General Experimental Procedure for the Tandem Suzuki–Miyaura/Diels–Alder Reaction**
$Pd(OAc)_2$(4 mol%), SPhos (8 mol%), vinyl (pseudo)halide (1 equiv), vinyl Bpin (5–7 equiv), and K_3PO_4(3 equiv) were weighed into an oven-dried microwave vial. The reaction vessel was then capped and purged with N_2 before the addition of 1,4-dioxane (0.125 M) and H_2O (5 equiv). The reaction mixture was heated at 50 °C with stirring. After 1 h the temperature was increased to 150 °C, and the reaction mixture was stirred for 23 h. The reaction mixture was allowed to cool to room temperature, vented, and de-capped. The reaction mixture was diluted with EtOAc (20 mL) and passed through a layer of Celite, eluting with EtOAc. The filtrate was concentrated under reduced pressure. THF (0.25 M) was added to the crude residue, and the solution was cooled to 0 °C before the addition of H_2O_2 (30% w/v, 20 equiv) and 2 M NaOH (4 equiv) sequentially. After 5 min the reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The mixture was quenched with $Na_2S_2O_3$ at 0 °C until effervescence ceases and diluted with sat. aq. NH_4Cl. The organics were extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography to afford the desired products.
Compound 4a
Prepared according to General Procedure using 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (77.0 mg, 0.25 mmol, 1 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), vinyl Bpin (192 mg, 1.25 mmol, 5 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (2 mL, 0.125 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv), then aqueous H_2O_2 (30% w/v, 500 µL, 5 mmol, 20 equiv), 2 M NaOH (500 µL, 1 mmol, 4 equiv), and THF (1 mL). After the reaction was complete, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in PE 40–60°) to afford the desired mixture of products as a yellow oil (41.3 mg, 72%, 3:1 r.r.). The major regioisomer was separated by column chromatography (ca. 95% purity).
Data for the Major Regioisomer
IR (film): ν_{max} = 3364 (br), 2914, 2847, 2830, 1605, 1493, 1456, 1279, 1253, 1231, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 8.8, 6.0 Hz, 1 H), 6.71 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.60 (d, *J* = 2.6 Hz, 1 H), 6.07–6.02 (m, 1 H), 4.04–3.95 (m, 1 H), 3.79 (s, 3 H), 2.95–2.75 (m, 2 H), 2.61–2.54 (m, 1 H), 2.52–2.39 (m, 1 H), 2.23–2.10 (m, 2 H), 2.02–1.94 (m, 1 H), 1.54–1.49 (m, 1 H), 1.46–1.36 (m, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.7, 138.0, 135.7, 127.1, 125.1, 115.5, 113.4, 112.9, 67.7, 55.4, 40.7, 36.7, 36.1, 31.2, 30.5. HRMS: *m/z* calcd for $[M + H]^+$ ($C_{15}H_{19}O_2$): 231.1380; found: 231.1378.