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Iterative reactions of transient boronic acids enable sequential C-C bond formation

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The ability to form multiple carbon-carbon bonds in a controlled sequence and thus rapidly build molecular complexity in an iterative fashion is an important goal in modern chemical synthesis. In recent times, transition metal-catalysed coupling reactions have dominated in the development of C-C bond forming processes. A desire to reduce the reliance on precious metals and a need to obtain products with very low levels of metal impurities has brought a renewed focus on metal-free coupling processes. Here, we report the *in situ* preparation of reactive allylic and benzylic boronic acids, obtained by reacting flow-generated diazo compounds with boronic acids, and their application in controlled iterative C-C bond forming reactions is described. Thus far we have shown the formation of up to three C-C bonds in a sequence including the final trapping of a reactive boronic acid species with an aldehyde to generate a range of new chemical structures.

Introduction

The generation of C-C bonds is at the heart of synthetic organic chemistry.¹ The ability to form multiple C-C bonds using iterative or one-pot methods allows a rapid increase in molecular complexity.²⁻⁵ While many such sequences are known, there is still room to exploit new reactivity patterns and different chemical combinations derived from reactive intermediates.⁶ In recent times, transition metal chemistry has dominated C-C bond cross-coupling strategies.⁷⁻¹³ This powerful approach has been central to the planning and execution of modern synthesis programs both in academia and industry. Nevertheless, the desire of industry to reduce its reliance on the use of precious metals in coupling reactions and the need for very low metal levels in active pharmaceutical ingredients has increased interest in metal-free coupling processes considerably.¹⁴

Boronic esters¹⁵ and acids¹⁶ are considered to be important coupling partners as they are versatile intermediates for the preparation of a wide variety of molecules. For example, Barluenga¹⁷ and others¹⁸⁻²⁰ recently demonstrated the powerful application of a reductive metal-free cross-coupling between tosylhydrazones and boronic acids. The reaction likely proceeds *via* a carbene-like species which on combination with a boronic acid initiates a sequence of reactions that terminates in the formation of a coupling product. However, high temperatures are necessary to affect these coupling processes so that any further exploitation of potentially useful intermediates in the reaction has not been possible so far.

From our own mechanistic studies based on the use of flow-generated diazo compounds,²¹ in the *metal-free* cross-coupling with aryl boronic acids at room temperature, we obtained strong evidence that highly reactive benzyl boronic acids are generated as intermediates. We were able to intercept these intermediates with an oxidant to give alcohols as opposed to the standard sp^2 - sp^3 coupled product generated after protodeboronation (**Figure 1a**).

This interesting result suggests that we might be able to exploit these highly transient benzyl boronic acid intermediates for further synthetic transformations. Due to the broad utility of boronic acids as starting materials in a number of key transformations, this approach could open up opportunities for new iterative C-C bond forming events which complement other elegant approaches.^{2,3, 22-26}

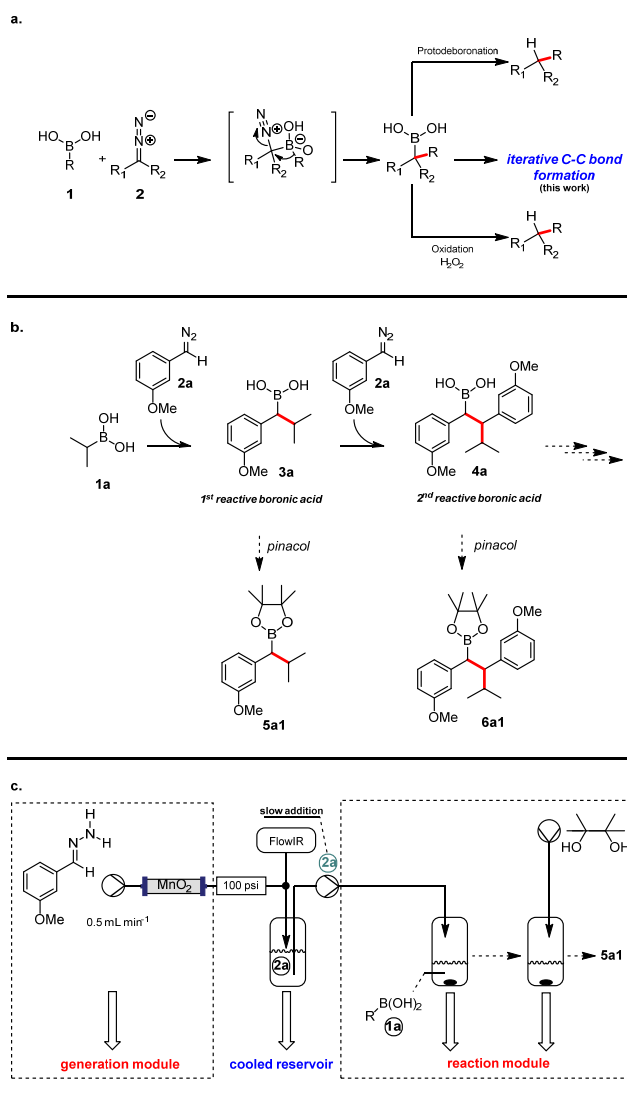


Figure 1 | Prior work on boronic acids-diazo coupling and development of an iterative reaction strategy. a) Proposed mechanism for the combination of diazo species and boronic acids, followed by either protodeboronation and oxidation (previous work), or exploration of new reactivity of transient boronic acid species; b) mechanistic description for the sequential generation of the single addition product **3a** and the double addition and generation of the corresponding products **5a1** and **6a1** via subsequent trapping with pinacol; c) setup for the generation, storage and reaction of the diazo species with boronic acids under full machine assistance (description of the setup can be found within the Supporting Information).

Although boron compounds have been known and used extensively for decades, benzylic and allylic boronic acids are unstable and are not readily accessible using typical chemistries.^{27,28} These species are usually isolated as their more stable ester derivatives.²⁹ Here, we report the controlled *in situ* generation of reactive allylic and benzyl boronic acids and their application in iterative C-C bond forming reactions leading to a range of new structures (**Figure 1a**).

Results and discussion

Interception of transient boronic acids with pinacol

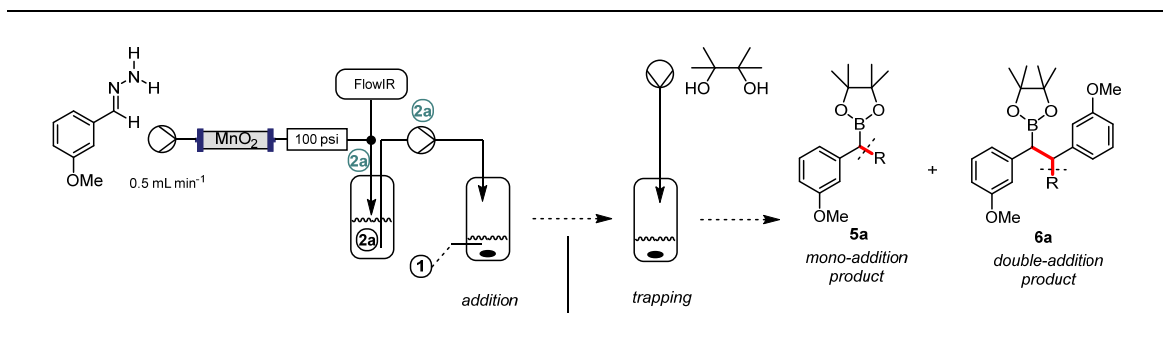
Using our previously established flow chemistry protocol for the generation of diazo compounds as a starting point, we first studied the formation of different transient boronic acids. Owing to their inherent instability, we chose to isolate them as their more stable pinacol ester derivatives to demonstrate reaction efficiency. Initial experiments began with the use of (3-methoxyphenyl)diazomethane (**2a**) as a model substrate, generated on demand under flow conditions, which was combined with isopropyl boronic acid **1a**, followed by addition of pinacol (**Figure 1b**). In this early experiment, we obtained the corresponding boronic ester **5a1** in modest yield (35%). Additionally, we were able to isolate a further product **6a1** (along with some other minor by-products) derived from the addition of a second equivalent of the diazo molecule to the *in situ* generated benzyl boronic acid (**Figure 1b**).










This interesting result gave us encouragement that by exploiting these reactivity profiles we might be able to develop a new iterative coupling protocol where different flow-generated diazo compounds add to a boronic acid in a controlled sequential fashion. To achieve this we first needed to control the formation of the first boronic acid intermediate (**3a**), in order to determine the reaction scope under an optimised set of conditions.

Initial optimisation studies showed that slow addition of the diazo compound to a solution of the boronic acid was needed to achieve selectivity towards compound **5a1** (**Figure 1b**). Whilst at a standard rate of addition (i.e., 0.5 mL min⁻¹ on a 5.0 mL scale) we obtained a 35% yield of **5a1** with approximately 18% of **6a1**, by reducing the rate of addition of the diazo compound **2a** we were able to increase both the yield and the selectivity of the reaction. This encouraging observation suggests that the starting boronic acid **1a** is more reactive than the secondary benzyl boronic acid **3a** formed from the first addition (**Figure 1b**), but that slow addition is required to avoid a local excess concentration of diazo compound **2a** leading to double adduct **4a**.

To ensure materials were prepared and used safely (due to the well-known hazardous nature of diazo compounds), we devised a reactor set-up that produced these compounds continuously in a cryogenic and contained system (**Figure 1c**). The solution containing diazo compound was briefly collected in a suitable cryogenic (double jacketed) buffering reservoir prior to being dispensed *via* various pumps to the quenching and reaction vessels. At no point are these diluted reaction streams concentrated or exposed throughout the synthesis. The diazo solution, after its formation, is immediately reacted with the substrate. Under these conditions there is never a build-up of concentrated diazo compound and this therefore minimises any potential hazard.

We examined the role of trace water in the reaction and found that drying the solutions of both the diazo compound and the boronic acid with molecular sieves prior to reaction improved the yield of **5a1**. Thus, under the optimised conditions, a dry solution of diazo **2a** (5 mL) was slowly dispensed (41 μ L min⁻¹) into a flask containing a solution of the boronic acid **1a** (1.2 equiv) and the reaction mixture was stirred at room temperature for 30 min under inert atmosphere. A solution of pinacol was then added to this mixture, stirred overnight (ensuring complete reaction) and passed through a plug of SiO₂. Purification by flash chromatography gave **5a1** in an 87% yield. Using these conditions, it was then possible to study the effect of changing the boronic acid coupling partner upon reaction with the model diazo compound **2a** (**Table 1**). Although, a low degree of selectivity was observed for small primary boronic acids (e.g. methyl boronic acid, **Table 1**, entry 5) with a 1:1.5 ratio in favour of the double addition product **6a** (**5a5** was obtained in 21% yield), the other partners all gave good yields of the mono-addition product **5a** (41-87%, **Table 1**).

Table 1 | Trapping of the boronic acid intermediates with pinacol.

| entry ^a | R- | compound | 5a : 6a ratio | yield ^b |
|--------------------|---|------------|---------------|--------------------|
| 1 |  | 5a1 | 1 : 0.08 | 87% |
| 2 |  | 5a2 | 1 : 0.40 | 56% |
| 3 |  | 5a3 | 1 : 0.35 | 65% |
| 4 |  | 5a4 | 1 : 0.20 | 74% |
| 5 |  | 5a5 | 1 : 1.50 | 21% |
| 6 |  | 5a6 | 1 : 0.60 | 41% |
| 7 |  | 5a7 | 1 : 0.20 | 70% |
| 8 |  | 5a8 | 1 : 0.16 | 64% |
| 9 |  | 5a9 | - | 45% |

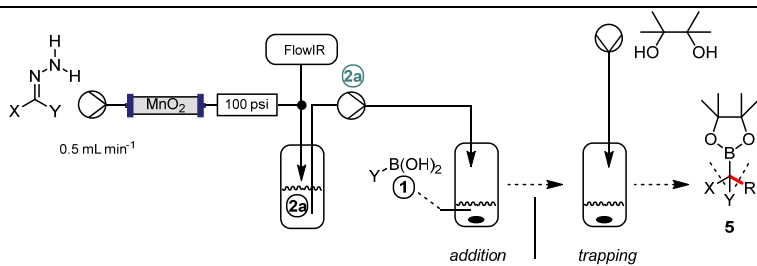
^aReaction conditions: 0.3 mmol of **2a** (41 $\mu\text{L min}^{-1}$), 1.5 equiv of **1**, CH_2Cl_2 , rt (30 min), then pinacol (overnight); ^byields refer to the isolated mono-addition product based on the diazo species. CAUTION: diazo compounds are unstable species hence they should be handled on small scale.

In all cases, we believe that the selectivity observed reflects the relative reactivity of the initial and first formed boronic acids (**Figure 1b**). In some cases, the intermediate boronic acid was observed to be particularly unstable and prone to protodeboronation. For example, in the case of the coupling between the diazo compound and aryl boronic acids, we observed rapid addition of the diazo species to the boronic acid partner but noted that some protodeboronation occurred even at room temperature. However, we found that the newly formed boronic acid intermediate could be successfully reacted with pinacol in reasonable yield (**Table 1**, compound **5a9**).

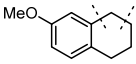

Motivated by this observation, we then investigated the scope of the diazo partner in more detail. Pleasingly, diazo compounds bearing electron-donating and electron-withdrawing groups on the arene gave good-to-excellent overall yields of the boronic pinacol esters, again confirming that the boronic acid intermediates were formed in high yields (**Table 2**). Electron donating substituents include alkoxy (**5c**, **5e**, **5r**) and aniline (**5b**) groups, whereas electron-withdrawing groups include ester (**5h**), halo (**5j**, **5q**), trifluoromethyl (**5l**) and nitro groups (**5n**). Notably, the system also tolerated heterocyclic substituents on the diazo compound including furan (**5f**), thiophene (**5g**) and pyridine (**5m**). Another distinctively useful aspect of this method is that allylic diazo compounds smoothly undergo coupling giving allylic boronic esters (**5o** and **5p**). In addition, ketone derivatives were

equally successful, resulting in high yields of the isolated tertiary pinacol ester products (**5q** and **5r**, 92% and 78% respectively).

Table 2 | Trapping the boronic acid intermediates with pinacol.



| entry | X | Y | R | compound | yield |
|-------|---|-----|---|-----------|-------|
| 1 | | -H | | 5b | 69% |
| 2 | | -H | | 5c | 84% |
| 3 | | -H | | 5d | 84% |
| 4 | | -H | | 5e | 90% |
| 5 | | -H | | 5f | 62% |
| 6 | | -H | | 5g | 61% |
| 7 | | -H | | 5h | 52% |
| 8 | | -H | | 5i | 94% |
| 9 | | -H | | 5j | 88% |
| 10 | | -H | | 5k | 86% |
| 11 | | -H | | 5l | 49% |
| 12 | | -H | | 5m | 68% |
| 13 | | -H | | 5n | 83% |
| 14 | | -H | | 5o | 78% |
| 15 | | -H | | 5p | 82% |
| 16 | | -Me | | 5q | 92% |

| | | | | |
|---|---|---|----|-----|
| 17 |  |  | 5r | 78% |
| <p><i>Reaction conditions:</i> 0.3 mmol of 2 ($41 \mu\text{L min}^{-1}$), 1.5 equiv of 1, CH_2Cl_2, rt (30 min), then pinacol (overnight); yields refer to the isolated mono-addition product and are based on the diazo species. <i>CAUTION:</i> diazo compounds are unstable species hence they should be handled on small scale.</p> | | | | |

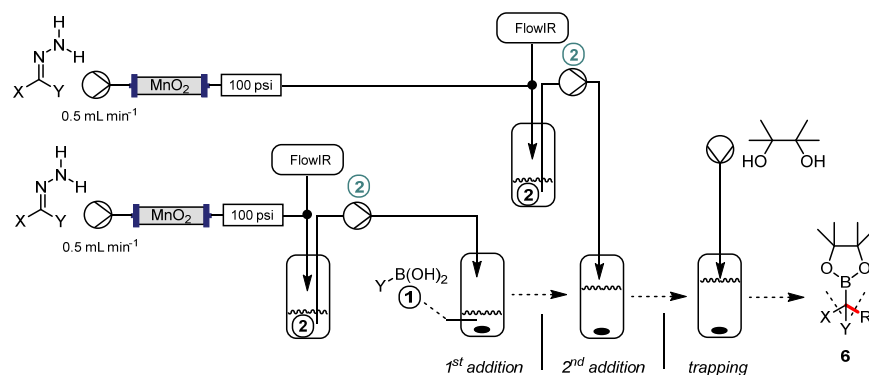
Sequential C-C bond formation

These studies clearly demonstrate the general utility of the method. With a good understanding of the optimal conditions for the generation of these boronate species, we then wished to utilise these species in new bond formation reactions to rapidly build molecular complexity and chemical diversity. We envisaged that the interception of each newly formed intermediate with a second diazo species (either the same one or different one) should be possible in a controlled manner. In doing so it would allow an iterative C-C bond formation and also provide access to a novel set of elaborated structures.

This concept was first validated by generating complex structures using repeated additions of the same diazo compounds and eventually trapping the final product as its pinacol ester. We found that the sequential coupling of both electron-rich and electron-poor diazo compounds could be successfully achieved with good isolated yields (**Table 3**). The applicability of allylic derivatives was demonstrated by the fact that the geraniol diazo compound afforded a good yield of the double addition product **6d**. Given these results, the next step was to elaborate the process by trapping an intermediate boronic acid species with a different diazo compound. This is illustrated by the preparation of **6g**, which demonstrated that two different diazo compounds could be utilised in sequence, affording the final product as a pinacol ester. A final protodeboronation could also be used to complete the sequence, providing products **6h-o**. For this specific class of compounds, where the presence of electron-withdrawing aromatic rings in the diazo partners reduces the reactivity of the system, the optimised conditions necessitated a slight excess of the second diazo compound (i.e. (3-pyridyl)-diazomethane and [4-(methoxycarbonyl)phenyl]-diazomethane). The use of equimolar quantities of these species led to lower conversion to the desired product. These compounds, which are readily prepared by this controlled sequential addition process, display novel molecular architectures that would be difficult to access using conventional chemistries other than by much longer sequences.

In this work we focused on the bond forming processes and no attempt was made to separate or determine diastereomeric ratios. Nevertheless, in one single example (**6a**) we demonstrated that the major diastereomer is *syn* configured with respect to the two aromatic rings (see SI). The rationalisation of this observation will be examined in due course.

Table 3 | Sequential interception of transient boronic intermediates.



| entry | X | Y | R | compound | yield |
|-------|---|---|---|-----------|-------|
| 1 | | | | 6a | 69% |
| 2 | | | | 6b | 58% |
| 3 | | | | 6c | 73% |
| 4 | | | | 6d | 90% |
| 5 | | | | 6e | 62% |
| 6 | | | | 6f | 70% |
| 7 | | | | 6g | 51% |
| 8 | | | | 6h | 41% |
| 9 | | | | 6i | 40% |
| 10 | | | | 6j | 48% |
| 11 | | | | 6k | 32% |
| 12 | | | | 6l | 66% |
| 13 | | | | 6m | 35% |
| 14 | | | | 6n | 45% |
| 15 | | | | 5o | 51% |

Reaction conditions: 0.3 mmol of **2** (41 $\mu\text{L min}^{-1}$), 1.5 equiv of **1**, CH₂Cl₂, rt (30 min), then pinacol (overnight); yields refer to the isolated mono-addition product and are based on the diazo species. **CAUTION:** diazo compounds are unstable species hence they should be handled on small scale.

Having established the controlled addition of different diazo compounds in a sequential mode, we now wished to determine whether the approach could be extended with a third step. Under the previously optimised conditions, we could access structures **9a-d**, each corresponding to the addition of three diazo compounds (**Figure 2**). In particular, the ability to construct a compound derived from three different diazo species, as in compound **9d**, demonstrates the versatility of the method and presents opportunities which we believe have a very wide ranging of applications.

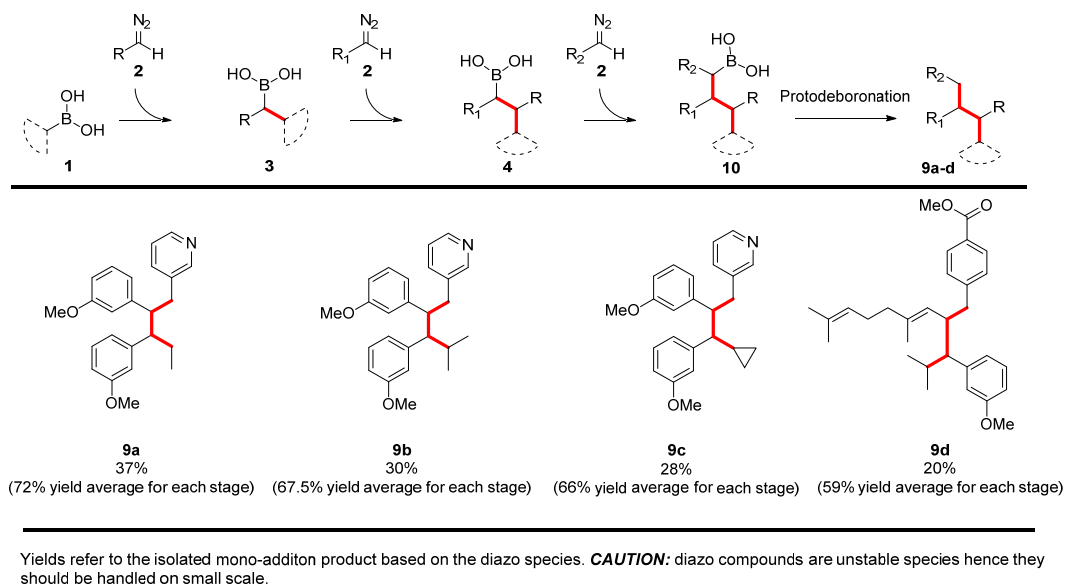


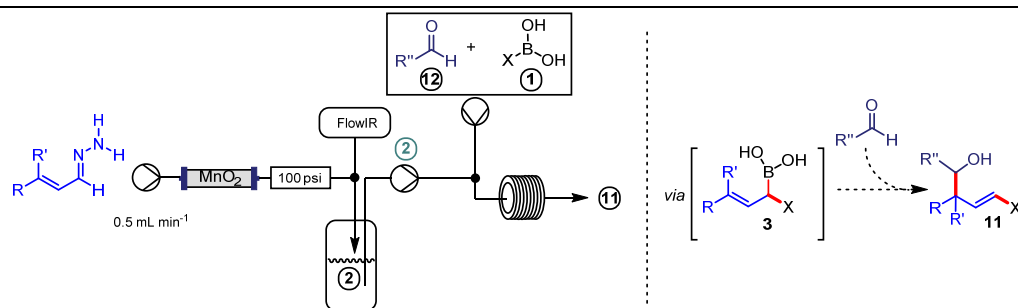
Figure 2 | Iterative strategy for the sequential addition of three diazo species.

Interception of transient allylic boronic acids with aldehydes and extended C-C bond formation strategy

We further demonstrated that it was possible to incorporate other methodologies into the sequence by generating an intermediate allylic boronic acid and performing allylations of carbonyl electrophiles.³⁰ As noted in **Table 1**, allylic boronic acid intermediates could be easily generated from simple commercially available boronic acids and allylic diazo compounds. These allylic boronic acid intermediates showed high reactivity in allylation reactions with different aldehydes. We were delighted to find that we could both generate the allyl boronic acids and utilise them in subsequent allylation reactions all in one pot. The diazo species could be directly added to a solution of boronic acid and aldehyde, giving a very selective addition (no trace of double diazo addition was detected) to the boronic acid which was then followed by subsequent quench with the aldehyde. A first set of experiments (**Table 4**) using 1-diazo-3,7-dimethylocta-2,6-diene (**2o**) as model substrate, generated structures **11a-g** in a very straightforward manner with very high yields and a broad substrate scope (77%-98%). Moreover, by using different α,β -unsaturated diazo compounds we were able to generate an unusual level of diversity (**Table 4**). At this stage no attempt was made to separate

diastereoisomers although we note that high diastereoselectivity (anti) is achieved in these allylation reactions, as expected from mechanistic considerations.

Table 4 | Cascade interception of allylic boronic acids intermediates with aldehydes.



| entry | R | R' | R'' | X | compound | yield |
|-------|---|----|-----|---|------------|-------|
| 1 | | | | | 11a | 83% |
| 2 | | | | | 11b | 83% |
| 3 | | | | | 11c | 77% |
| 4 | | | | | 11d | 97% |
| 5 | | | | | 11e | 90% |
| 6 | | | | | 11f | 88% |
| 7 | | | | | 11g | 98% |
| 8 | | | | | 11h | 90% |
| 9 | | | | | 11i | 27% |
| 10 | | -H | | | 11j | 48% |
| 11 | | | | | 11k | 41% |
| 12 | | | | | 11l | 64% |
| 13 | | | | | 11m | 61% |
| 14 | | -H | | | 11n | 36% |
| 15 | | | | | 11o | 35% |

Reaction conditions: 0.2 mmol of **2**, 1 equiv of **1**, 1.2 equiv of **12**; yields refer to the isolated mono-addition product and are based on the diazo species. **CAUTION:** diazo compounds are unstable species hence they should be handled on small scale.

Finally, to briefly demonstrate the utility of this method we showed that, in one single operation, we could prepare **11p** (60% yield) as a valid precursor to the natural product *Bakuchiol* (**Figure 3**).³¹ In contrast the known route to this compound utilises a multi-step sequence of reactions.

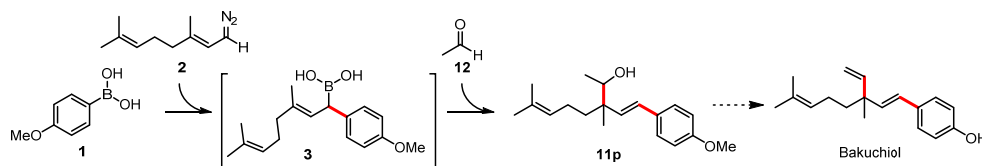


Figure 3 | Synthesis of *Bakuchiol* precursor (**11p**) using this new method.

The versatility of the approach was broadened further when we investigated a combination of our procedures. Therefore, by reacting a boronic acid **1** with a diazo compound **2** we obtained boronic acid **3**. This was then captured by another allylic diazo compound **2** resulting in the formation of allylic boronic acid **3'**; this in turn was quenched by an aldehyde to terminate the sequence. Following this new cascade we were able to prepare the alcohols **13a-c** as an illustration of what might be possible using this new iterative bond forming concept (**Figure 4**).

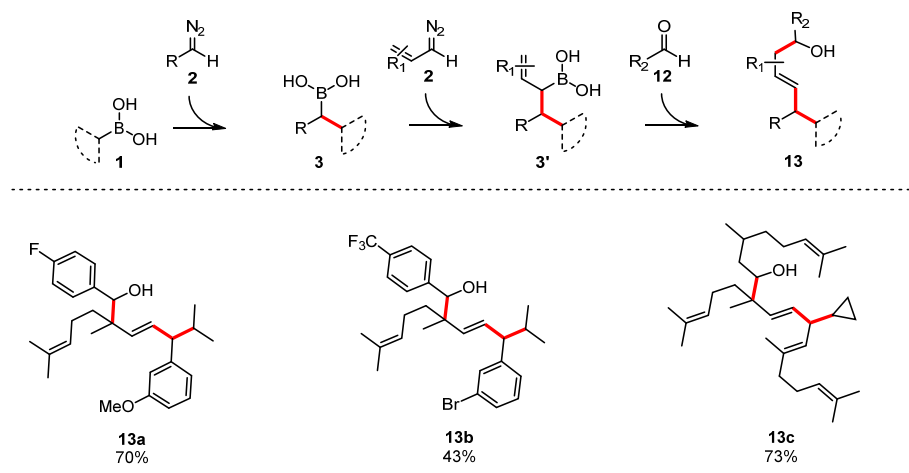


Figure 4 | Sequential interception of boronic acid species and final reaction with aldehydes.

In conclusion, we have developed a new approach for delivering iterative C-C bond formation sequences using transiently generated boronic acids. These intermediates were generated by a combination of diazo compounds (generated in flow) with boronic acids at room temperature. This method opens many opportunities for multiple C-C bond forming strategies by creating alternatives to conventional synthetic routes.

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Authors contributions

C.B., D.N.T. and S.V.L. conceived the project; C.B., A.H. and S.V.L. designed the experiments; C.B., F.F., A.H., M.S. and D.N.T. performed the experiments; D.M.A. analysed the data and prepared the supporting information; D.C.B. provided crucial information for the development of the project; C.B., A.H. and S.V.L. wrote the paper.

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Methods

Given the complexity of the reactions setup and of the chemical variations we refer the reader to the Supporting Information section for detailed material.

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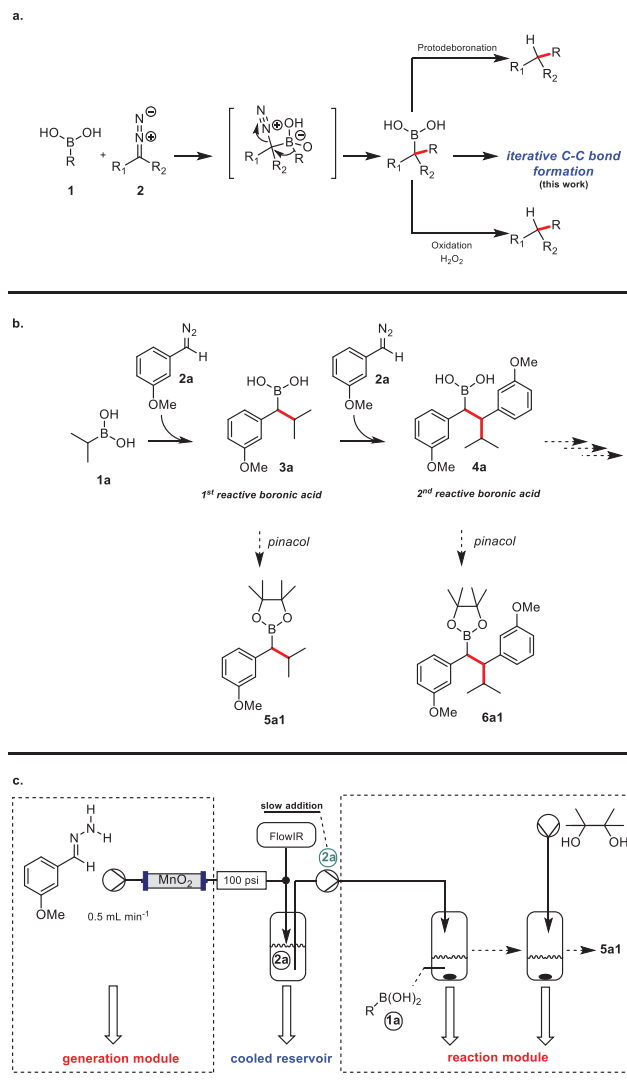
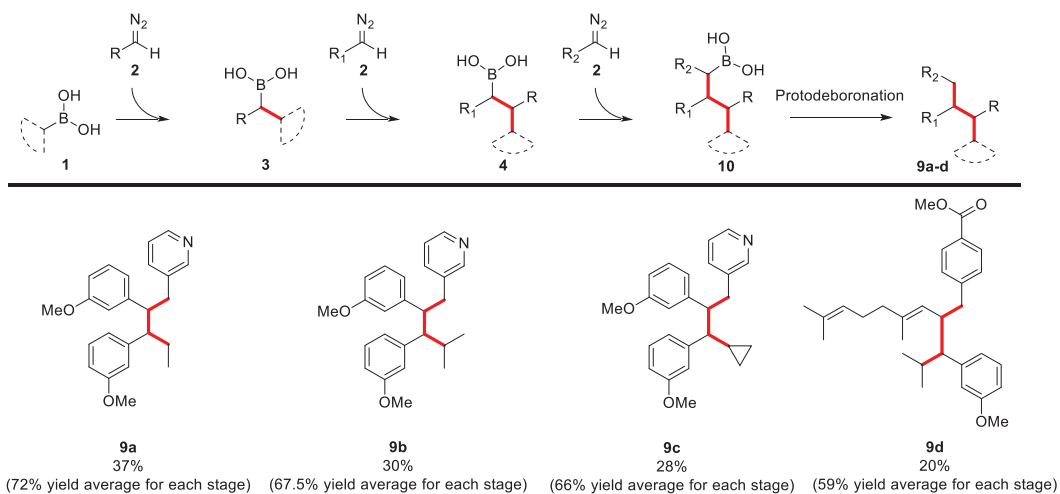


Figure 1 | Prior work on boronic acids-diazo coupling and development of an iterative reaction strategy. a) Proposed mechanism for the combination of diazo species and boronic acids, followed by either protodeboronation and oxidation (previous work), or exploration of new reactivity of transient boronic acid species; b) mechanistic description for the sequential generation of the single addition product **3a** and the double addition and generation of the corresponding products **5a1** and **6a1** via subsequent trapping with pinacol; c) setup for the generation, storage and reaction of the diazo species with boronic acids under full machine assistance (description of the setup can be found within the Supporting Information).



Yields refer to the isolated mono-addition product based on the diazo species. **CAUTION:** diazo compounds are unstable species hence they should be handled on small scale.

Figure 2 | Iterative strategy for the sequential addition of three diazo species.

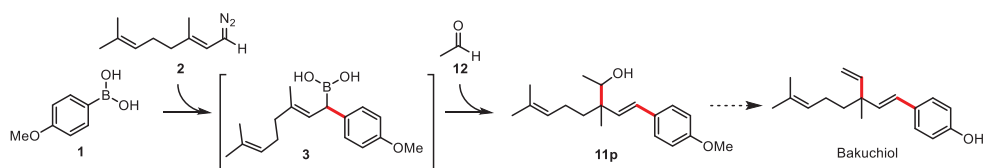


Figure 3 | Synthesis of *Bakuchiol* precursor (11p) using this new method.

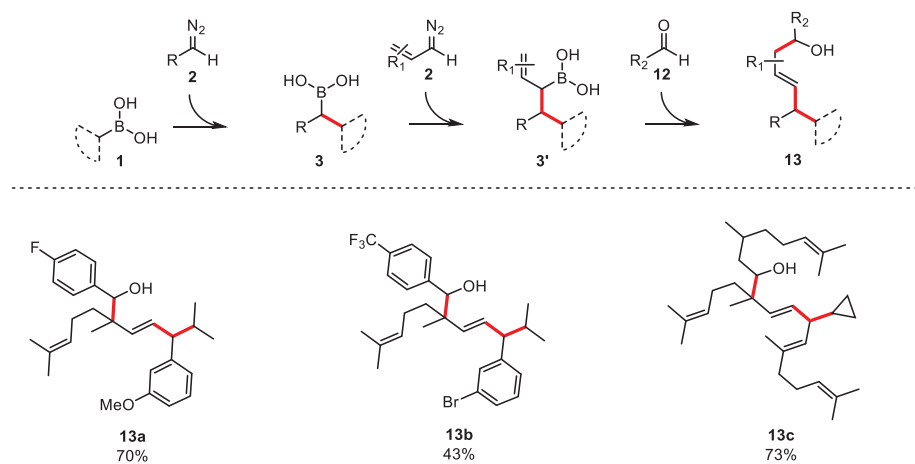
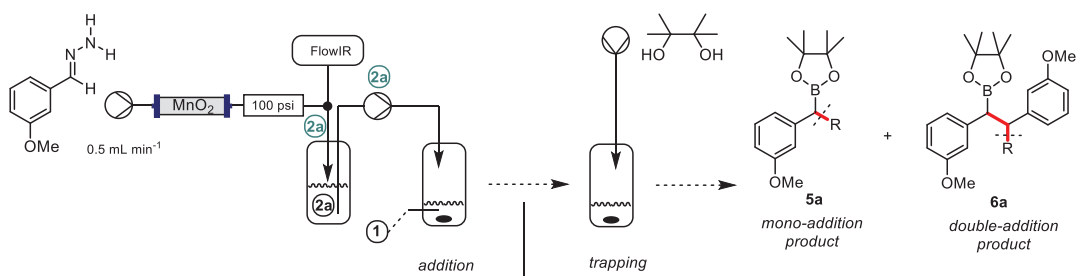


Figure 4 | Sequential interception of boronic acid species and final reaction with aldehydes.

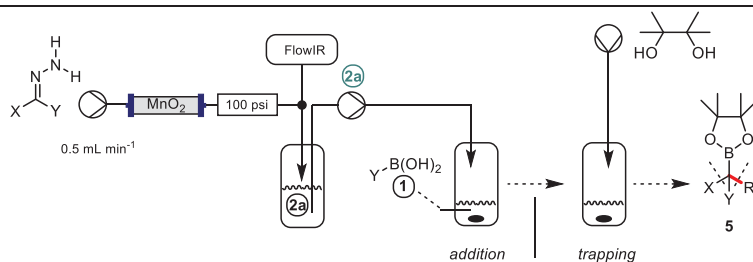
Table 1 | Trapping of the boronic acid intermediates with pinacol.



| entry ^a | R- | compound | 5a : 6a ratio | yield ^b |
|--------------------|----|------------|---------------|--------------------|
| 1 | | 5a1 | 1 : 0.08 | 87% |
| 2 | | 5a2 | 1 : 0.40 | 56% |
| 3 | | 5a3 | 1 : 0.35 | 65% |
| 4 | | 5a4 | 1 : 0.20 | 74% |
| 5 | | 5a5 | 1 : 1.50 | 21% |
| 6 | | 5a6 | 1 : 0.60 | 41% |
| 7 | | 5a7 | 1 : 0.20 | 70% |
| 8 | | 5a8 | 1 : 0.16 | 64% |
| 9 | | 5a9 | - | 45% |

^aReaction conditions: 0.3 mmol of **2a** ($41 \mu\text{L min}^{-1}$), 1.5 equiv of 1, CH_2Cl_2 , rt (30 min), then pinacol (overnight); ^byields refer to the isolated mono-addition product based on the diazo species. **CAUTION:** diazo compounds are unstable species hence they should be handled on small scale.

Table 2 | Trapping the boronic acid intermediates with pinacol.

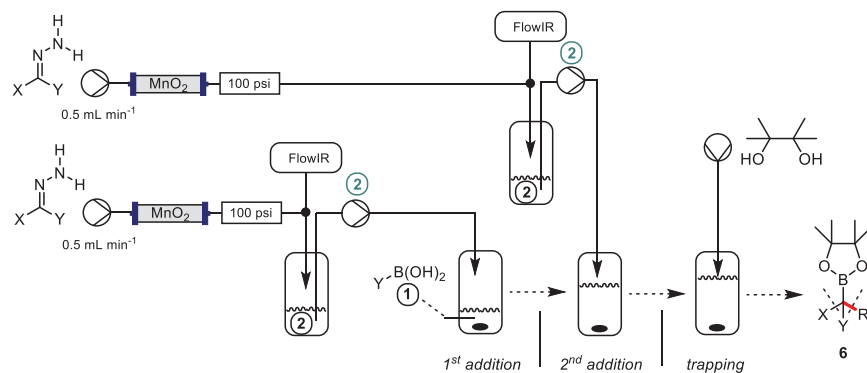


| entry | X | Y | R | compound | yield |
|-------|---|-----|---|-----------|-------|
| 1 | | -H | | 5b | 69% |
| 2 | | -H | | 5c | 84% |
| 3 | | -H | | 5d | 84% |
| 4 | | -H | | 5e | 90% |
| 5 | | -H | | 5f | 62% |
| 6 | | -H | | 5g | 61% |
| 7 | | -H | | 5h | 52% |
| 8 | | -H | | 5i | 94% |
| 9 | | -H | | 5j | 88% |
| 10 | | -H | | 5k | 86% |
| 11 | | -H | | 5l | 49% |
| 12 | | -H | | 5m | 68% |
| 13 | | -H | | 5n | 83% |
| 14 | | -H | | 5o | 78% |
| 15 | | -H | | 5p | 82% |
| 16 | | -Me | | 5q | 92% |
| 17 | | | | 5r | 78% |

Reaction conditions: 0.3 mmol of **2** (41 $\mu\text{L min}^{-1}$), 1.5 equiv of **1**, CH_2Cl_2 , rt (30 min), then pinacol (overnight); yields refer to the isolated mono-addition product and are based on the diazo species. **CAUTION:** diazo compounds are unstable species hence they should be

handled on small scale.

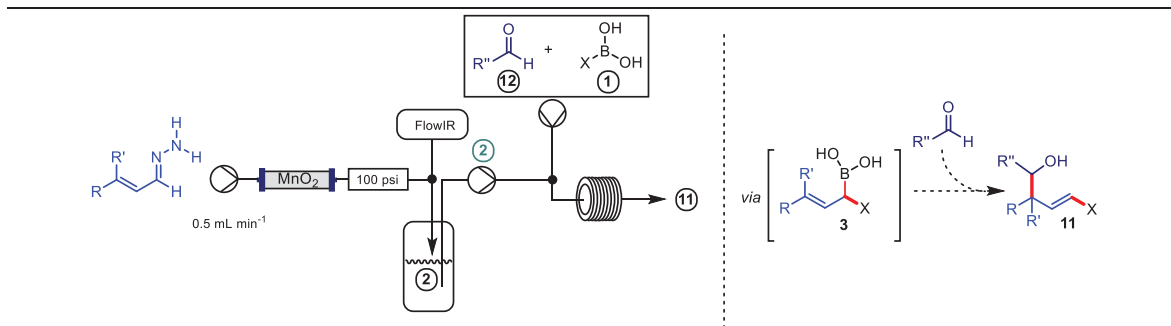
Table 3 | Sequential interception of transient boronic intermediates.



| entry | X | Y | R | compound | yield |
|-------|---|---|---|-----------|-------|
| 1 | | | | 6a | 69% |
| 2 | | | | 6b | 58% |
| 3 | | | | 6c | 73% |
| 4 | | | | 6d | 90% |
| 5 | | | | 6e | 62% |
| 6 | | | | 6f | 70% |
| 7 | | | | 6g | 51% |
| 8 | | | | 6h | 41% |
| 9 | | | | 6i | 40% |
| 10 | | | | 6j | 48% |
| 11 | | | | 6k | 32% |
| 12 | | | | 6l | 66% |
| 13 | | | | 6m | 35% |
| 14 | | | | 6n | 45% |
| 15 | | | | 5o | 51% |

Reaction conditions: 0.3 mmol of **2** ($41 \mu\text{L min}^{-1}$), 1.5 equiv of **1**, CH_2Cl_2 , rt (30 min), then pinacol (overnight); yields refer to the isolated mono-addition product and are based on the diazo species. CAUTION: diazo compounds are unstable species hence they should be handled on small scale.

Table 4 | Cascade interception of allylic boronic acids intermediates with aldehydes.



| entry | R | R' | R'' | X | compound | yield |
|-------|---|----|-----|---|------------|-------|
| 1 | | | | | 11a | 83% |
| 2 | | | | | 11b | 83% |
| 3 | | | | | 11c | 77% |
| 4 | | | | | 11d | 97% |
| 5 | | | | | 11e | 90% |
| 6 | | | | | 11f | 88% |
| 7 | | | | | 11g | 98% |
| 8 | | | | | 11h | 90% |
| 9 | | | | | 11i | 27% |
| 10 | | -H | | | 11j | 48% |
| 11 | | | | | 11k | 41% |
| 12 | | | | | 11l | 64% |
| 13 | | | | | 11m | 61% |
| 14 | | -H | | | 11n | 36% |
| 15 | | | | | 11o | 35% |

Reaction conditions: 0.2 mmol of **2**, 1 equiv of **1**, 1.2 equiv of **12**; yields refer to the isolated mono-addition product and are based on the diazo species. **CAUTION:** diazo compounds are unstable species hence they should be handled on small scale.