A multicomponent approach for the preparation of homoallylic alcohols†‡

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Here we report the in situ generation of transient allylic boronic species, by reacting TMSCHN₂ and E-vinyl boronic acids, followed by subsequent trapping with aldehydes as electrophiles to yield homoallylic alcohols. This metal-free reaction was initially discovered by the use of a flow chemistry approach to generate a variety of homoallylic alcohols in a straightforward fashion and then transferred to a batch protocol.

Introduction

Homoallylic alcohols are valuable synthetic building blocks, in particular, for the construction of polyketide natural products.1–4 Whilst they can be accessed in a metal-free fashion by crotylation/allylation methods of Roush5–10 and Brown,11–19 the instability or availability of the appropriate allyl boronic coupling partner is an important limitation.20–22 Furthermore, installation of side chain groups other than methyl is not always straightforward using these methods. Other procedures are known but tend to lack generality.23–38 In a continuation of our work in the area (Fig. 1),39–44 we report here a new multi-component coupling to prepare homoallylic alcohols which was first discovered using flow chemistry methods and later transferred to a batch protocol, involving reactions of vinyl boronic acids with trimethylsilyl diazomethane (TMSCHN₂)46–49 to generate the allylic boronic species in situ which are then intercepted with aldehydes to form new C–C bonds.

Results and discussion

The reaction was initially optimised with available flow equipment using TMS-diazomethane 1 (TMSCHN₂), E-4-methylphenyl vinyl boronic acid 2a and 4-bromobenzaldehyde 3a as substrates (Scheme 1). Interestingly, early investigations showed the product to be a homoallylic alcohol (4a), which was obtained in good yield. We therefore initiated a rapid evaluation of the reaction parameters in order to obtain a robust system. The first attempt to define these reaction parameters employed a flow strategy whereby a solution containing the vinyl boronic acid 2a (0.04 M, in CH₂Cl₂ : THF, 4 : 1 v/v) and a solution of TMSCHN₂ 1 and aldehyde 3a (0.066 M and 0.033 M, respectively, in CH₂Cl₂) were combined at a T-piece and reacted in a 20 mL perfluoroalkoxy alkanes (PFA) reactor coil (t = 25 min). The
exiting stream of borylated intermediate was then quenched with MeOH (2 mL), in a batch-fed integrated fashion, to yield the final product 4a. Following this approach, we were able to rapidly identify suitable conditions, with compound 4a being generated (0.29 mmol scale, 91% yield) at 60 °C. The choice of solvent was crucial as solvent systems that are able to strongly coordinate with the boronic acid partner (e.g. neat THF) can favour the formation of by-products. We were soon able to identify that a mixture of CH2Cl2 and THF (4 : 1 v/v) was the optimal solvent system to carry out the reaction continuously without causing any undesirable rate or selectivity issues on the reaction.

With this protocol in place, we were able to rapidly access a range of homoallylic alcohols by using various vinyl boronic acids 2 and aldehydes 3 (Table 1).

Both electron withdrawing and electron-donating substituents on the vinyl boronic partner were associated with particularly good yields (including aryl and alkyl groups). Screening of both aromatic and aliphatic aldehyde traps successfully provided the products with good-to-excellent yields in all cases. In all the examples, high degree of diastereoselectivity was observed (confirmed by X-ray crystallography data, see ESI†).

It is worth mentioning that reacting Z-vinyl boronic acids under the standard conditions led to a complex mixture, suggesting that the molecular geometry of the boronic species is mechanistically relevant.

The robustness of the protocol was quickly assessed by performing a larger-scale reaction (10 mmol) which gave product 4b in a consistent yield of 73%.

In order to facilitate downstream processing and improve the practicality of the method, any residual aldehyde was scavenged using a polymer-supported tosylhydrazine resin.50,51

Wishing to broaden the practical aspect of this multicomponent metal-free reaction, we decided to transfer the method directly into a batch process (Scheme 2), having taken care to safely handle the TMSCHN2 reagent. The optimised batch protocol was developed at room temperature with reaction times being within the range from 2 h to 16 h for similar reaction scale (0.3 mmol). The scope of the reaction under batch conditions was expanded and demonstrated the generality of the method (Table 2).

The iterative importance of this methodology was then showcased in the generation of polyol backbone materials (Scheme 2). The iteration process consisted of a sequence of allylation processes. In between each allylation, the homoallylic alcohol intermediate underwent an alcohol protection
stage, followed by ozonolysis of the olefin to regenerate the aldehyde component for further reaction. The sequence was repeated four times to rapidly provide a complex derivative 8 (see ESI‡ for a detailed reaction description). Analysis of the 1H/13C hsoft acetide effort for the 2nd iteration product 6 confirms a twist-boat structure, indicating Felkin–Anh selectivity.52–55

In addition to this, we were able to selectively elaborate intermediate 7 into the corresponding tetrahydropyran derivative 9, showing the versatility of such a method for generation of rather underrepresented molecular entities.

From a mechanistic viewpoint, we speculate that the absence of the trimethylsilyl group in the product may be due to the instability of TMSCHN₂ in the presence of E-vinyl boronic acids.56–58 Efforts to elucidate the mechanism confirmed that the addition of a base (e.g. TEA) shuts down the reaction. Similarly, the treatment of the vinyl boronic acid solution with a drying reagent (e.g. molecular sieves) followed by addition of aldehyde and TMSCHN₂ afforded a very complex mixture and only traces of product. This suggests that the acidity of the vinyl boronic acid is important in respect to the desired reaction outcome.59

Another piece of information showed that when catechol borane 10 was employed as the vinyl boronic ester partner under the same reaction conditions, vinyl derivative 11 was obtained (19% yield) along with recovered starting material. Additionally, ¹H-NMR studies indicate that after addition of TMSCHN₂ to the boronic acid partner, the main intermediate in the reaction mixture is the corresponding allylic boronic acid, in which no silylated intermediate is observed.60 We therefore propose a mechanism where TMSCHN₂ is first protonated by the boronic acid; the boronate intermediate then reacts with the trimethylsilane group in order to generate a highly reactive diazomethane partner; this diazomethane reacts with the vinyl boronic acid to provide the corresponding allylic boronic acid (Scheme 3). This intermediate then reacts with the aldehyde electrophile to yield the final anti product after deborylation.
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Notes and references