Synthesis and application of aminoboronic acids as bifunctional catalysts
Clean, green and asymmetric!

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ABSTRACT
The development of Lewis acid-Lewis base bifunctional catalysts in asymmetric catalysis has been inspired by the idea of emulating natural catalysts, such as enzymes. Recent interest has been shown in the design, synthesis and application of aminoboronic acids as bifunctional catalysts, though this was based on the early work by Lestinger who proved the bifunctional concept using aminoboronic acids. The aim of this article is to briefly summarise the synthesis of aromatic, ferrocene and nonaromatic aminoboronic acids and outline their recent applications, particularly in direct amide formation and aldol reactions.

INTRODUCTION
Despite extensive research in the area of boric and boronic acids, bifunctional aminoboronic acids are relatively undeveloped. Their use in catalytic reactions is based on the cooperative relationship between the Lewis acidic boronic acid and the nucleophilic or basic amino group (Figure 1).

SYNTHESIS OF AMINOBORONIC ACIDS
The most used method for the synthesis of aminoboronic acids is via lithium-halogen exchange or directed lithiation. One of the first attempts to prepare quinoline boronic acids was made by Lestinger et al. who reacted lithiated quinoline with tributyl borate [1]. A series of aromatic aminoboronic acids were synthesised, however, one of the major drawbacks was the formation of boroxines which exist in equilibrium with the boronic acid [4]. Over the last decade a variety of aminoboronic acids have been formed, including ferrocene (5-7) and proline-based (8, 9) bifunctional catalysts (Figure 2). In the first case, directed ortho-metalation using (-)-sparteine followed by the addition of B(OMe) 3 was the key step for the synthesis of ferrocene-based aminoboronic acids [5]. A similar procedure was used for the synthesis of proline-based...
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formation (13). The most attractive feature of this process is the fact that it is clean and green with the only by-product to be water if the solvent is recycled.

The report of the successful use of bifunctional aminoboronic acids as catalysts for the direct amide formation reaction, was followed by the development of ferrocene-based bifunctional catalysts, such as 8, in order to achieve enantioselective amide formation via kinetic resolution (Scheme 3) (7). Low asymmetric induction was observed using several substrate combinations, leading to the conclusion that the reaction involved the benzimidazole function hydrogen bonding to the incoming ammonium salt to react with a diacylboronate intermediate.

APPLICATION OF AMINOBORONIC ACIDS

Following the development of routes for the synthesis of various aminoboronic acids, a number of catalytic applications have been examined. One such example published by Whiting et al. in 2006 involved comparative kinetic studies using boric acid, boronic acids 2 and 3 and the aminoboronic acid 4 for the direct formation of amides (Scheme 2) (12). All the reactions were carried both in refluxing tolulene or fluorobenzene. The most important observation was that the bifunctional catalyst 4 showed higher reactivity with less reactive substrate combinations (Table 1). In addition, applying ionization electrospray spectrometric techniques, it was proposed that diacyloxyboronate species were the most likely to be involved in the amide formation process. Moreover, it was observed that the addition of an electron-withdrawing group, such as a trifluoromethyl, to catalyst 4 increased the rate of the amide formation (13).

The second major development of bifunctional aminoboronic acids in catalysis was the application in aldol reactions. Whiting et al. first introduced the ability of the “ate”-complex of benzimidazolylphenylboronic acid 12 to catalyze direct aldol reactions in water (Scheme 4) and importantly, involving the aminoboronic acids. The methodology relies on the reaction of α-chloro boronate esters with N-protected pyrrolidine through a (-)-sparteine-mediated lithiation step (10). A more extended review on the synthesis of aminoboronic acid catalysts has been recently reported (11).

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Demonstration of a boron-enolate-mediated aldol reaction was followed by the use of proline-based aminoboronic acids involving enamine formation with a proximal Lewis acid group [9]. As a result, homoboroproline 17 and its ester derivatives were used from the catalytic reactions of p-nitrobenzaldehyde with acetone (Scheme 5). Due to the fact that the catalyst could not be isolated in its neutral form, it was produced in situ by neutralization of its salt using triethylamine. It was proposed that catalyst 17 activated the aldehyde by the boronic acid function since boroproline 18 was a poor catalyst compared to 17 (Table 3). Moreover, the in situ esterification of the boronic acid with chiral and achiral diols increased the Lewis acidity of the boronate providing the aldol adducts in high asymmetric induction. It is worth mentioning that when the reaction was carried out in the absence of molecular sieves, the e.e. decreased but higher conversion was observed. This was explained by the importance of the iminium ion intermediate hydrolysis which leads to faster catalyst regeneration. Although the use aminoboronic acids as catalysts is relatively under explored, it is clear from the early results summarized in this report there is considerable scope for the development of novel processes. The first examples of kinetic resolution in direct amide formation, catalytic boron enolate formation in water and the compatibility of enamine-mediated aldol reaction and Lewis acid assistance suggest that there are many more developments likely in the future.

REFERENCES AND NOTES