A new approach to the anticancer drug Velcade was developed by performing asymmetric borylation of an imine anchored with a chiral \(N\)-phosphinyl auxiliary. Throughout the 7-step synthesis, especially in the imine’s synthesis and in the asymmetric borylation reactions, operations and work-up were conducted in simple and easy ways without any column chromatographic purification, which defines the GAP (group-assisted purification) chemistry concept. It was found that the optically pure isomer (dr > 99:1) can be readily obtained by washing the crude mixture of the asymmetric borylation reaction with hexane; the chiral \(N\)-phosphinyl auxiliary can be easily recovered after deprotection is finished. Several other \(N\)-phosphinylimines were also investigated for the asymmetric borylation reaction. The absolute configuration of the borylation product was confirmed by single crystal X-ray diffraction analysis.

**Introduction**

The synthesis of chiral \(\alpha\)-aminoboronic acids and their derivatives has attracted much attention in the organic and medicinal chemistry communities because of their importance for drug discovery and biological research [1-8]. In the past several years, asymmetric catalysis and auxiliary-directed asymmetric synthesis has been conducted for assembling adjacent chiral centers of boronic acids [9-13], but only a few methods for generating chiral \(\alpha\)-aminoboronic acids have been reported so far [14-20]. Among the resulting products from the above methods, \((R)-(1\text{-amino-3-methylbutyl})boronic\ acid\ served\ as\ the\ key\ mechanism-based\ pharmacophore\ in\ the\ anticancer\ drug\ Velcade,\ which\ was\ the\ first\ FDA\ approved\ proteasome
inhibitor, and has been in clinical use for the treatment of multiple myeloma and mantle cell lymphoma [21]. This product is usually synthesized in three representative processes: (1) to use (1S,2S,3R,5S)-(+)-2,3-pinanediol as the chiral auxiliary for the addition reaction followed by chlorination and amination [14,15]; (2) to perform copper-catalyzed borylation of the imine anchored with chiral auxiliaries [16,17]; (3) to conduct asymmetric catalytic hydrogenation as the key step to control the chiral center of the boronic acid [18]. As anticipated, the above known syntheses required traditional purification methods using column chromatography or recrystallization (Scheme 1).

Recently, our group has established a concept called GAP (group-assisted purification) chemistry for greener synthesis [22-25]. This concept describes a process where special functional groups are attached onto reaction substrates, facilitating purification of crude products by avoiding traditional purification methods such as chromatography or recrystallization. The pure products, often pure stereoisomers, can be easily obtained by washing the crude products with common solvents or co-solvents [22-25]. Our GAP concept was attributed to the study of a series of new compounds containing achiral/chiral N-phosphonyl and chiral N-phosphinylimines, and the reactions of these compounds.

Scheme 1: Previous work for (R)-[1-amino-3-methylbutyl]boronic acid synthesis.
The requirements of GAP chemistry are shown by the fact that the functional groups of the reactants should generate products of adequate solubility. The GAP products should be soluble in some solvents such as THF and DCM for further reactions. However, they should have poor solubility in other solvents such as petroleum ether, hexanes, and their co-solvents with EtOAc. The GAP requirements should include adequate chemical reactivity of GAP compounds towards many reactants and species. If GAP groups are chiral, they should control asymmetric additions efficiently. Our GAP functional groups have also showed the flexibility for structural modifications in order to control the solubility of products and also to control the chemical tolerance towards various reactions under different conditions. Moreover, the GAP auxiliaries have been proven to be easily deprotected under several conditions for re-use.

Herein, we report the synthesis of the anticancer drug Velcade and its derivatives of chiral α-aminoboronic esters via GAP chemistry. Simple operations are needed during purification without the need for column chromatography; GAP washing can lead to a single isomeric product, which was deprotected with quantitative recovery of the phosphinic acid as shown in Scheme 2.

### Results and Discussion

We started our synthesis with (2S,5S)-1-amino-2,5-diphenylphospholane 1-oxide (1), which was synthesized according to the literature and our previous work in 7 steps from (1E,3E)-1,4-diphenylbuta-1,3-diene with an overall high yield (27% for 7 steps) [25,26]. With the optically pure amide 1 in hand, we screened the condensation conditions to generate the imine 2a. Titanates, such as Ti(OiPr)₄ and Ti(OEt)₄, resulted in the complete conversion of the aliphatic aldehyde in two days, but the hemiaminal was obtained as the main product [27], which can slowly decompose to release the desired imine 2a. Anhydrous CuSO₄, which was used as a mild condensation reagent by Ellman’s group, was found to be not suitable for this condensation reaction. This lack of suitability can probably be attributed to the strong coordination tendency of the imine to a copper ionic center. TiCl₄ was proven to be an efficient reagent and lead to complete condensation within 2 hours to give 90% conversion to imine according to crude ³¹P NMR. We also found that when the crude imine product was purified by column chromatography, isomerization of 2a to enamino was observed; this observation became more obvious when the solvents used for chromatography contained a higher water content. Eventually, MgSO₄ or CaSO₄ was chosen as the dehy-

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**Scheme 2**: Synthesis of (R)-4 and Velcade.
B<sub>2</sub>Pi<sub>2</sub> and ICuO<sub>t-Bu</sub> were utilized as the electrophilic addition reagent and catalyst, respectively, for the borylation reaction as previously reported [16,28]. Unlike the previous system, in which benzene was employed as the solvent, we used the much less toxic solvent toluene to successfully replace benzene. We achieved full conversion with 2 equiv of B<sub>2</sub>Pi<sub>2</sub> in the presence of 20 mol % of ICuO<sub>t-Bu</sub> catalyst after 3 days to afford a dr value of 7.7:1 as revealed by crude <sup>31</sup>P NMR analysis. After simple work-up and washing with hexanes, the dr value was improved to a single isomer (Scheme 2) in 56% yield for two steps. The absolute configuration of product 3a was unambiguously determined by X-ray analysis [29] to be in the (S,S,R)-configuration (Figure 1). As shown in Figure 1, H-bonds exist between the molecules, which would further help the formation of the solid.

To hydrolyze the resulting aminoboronic ester, the known method [16] was followed first by treating the ester with one equivalent of HCl in co-solvents of methanol and dioxane. A mixture of products was generated indicating a poor yield according to the crude <sup>31</sup>P and <sup>1</sup>H NMR analysis. Another co-solvent system consisting of H<sub>2</sub>O and MeOH (2:1) was examined. It was found that treatment of the aminoboronic ester with 1.5 equiv of HCl for 16 hours resulted in complete deprotection; work-up consisted of extraction with DCM followed by concentration to give product 4 as a white solid in 92% yield. Pure phosphinic acid 5 was recovered by simple filtration in quantitative yield. The final product, Velcade 6, was synthesized according to the literature procedure [16] in 83% yield after 4 steps (Scheme 2). <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of the product were proven to be identical to the literature data.
Scheme 3: Synthesis of phosphinylimines and their borylation products.

Table 1: Results of borylation reactions.

| Entry | Imines | R       | Products | dr (crude)\(^b\) | dr (GAP)\(^b\) | Yield\(^c\) |
|-------|--------|---------|----------|------------------|----------------|-------------|
| 1     | 2b     | iPr     | 3b       | 75:25            | >99:1          | 26%         |
| 2     | 2c     | cyclohexyl | 3c       | 78:22            | 99:1           | 40%         |
| 3     | 2d     | PhCH\(_2\)CH\(_2\) | 3d       | 84:16            | 98:2           | 45%         |
| 4     | 2e     | Ph      | 3e       | 97:3             | –              | 51%         |
| 5     | 2f     | 4-MeOPh | 3f       | >99:1            | –              | 44%         |

\(^a\)Reaction conditions: 0.74 mmol scale, [substrate] = 1.8 M, 2.0 equiv B\(_2\)Pin\(_2\), 20 mol % ICyCuOt-Bu, toluene (4 mL), room temperature, 3 days.

\(^b\)Determined by \(^{31}\)P NMR analysis.

\(^c\)Calculated from the starting amide 1, isolated yields with GAP washing (for 3e and 3f, GAP washing was not conducted).

excellent diastereoselectivities, dr = 97:3 and >99:1, respectively, were achieved according to the \(^{31}\)P NMR analysis of crude products. Pure products 3e and 3f were obtained via flash column chromatography since GAP washing led to some decomposition in these two cases.

Conclusion

We have successfully demonstrated that \(N\)-phosphinylimines can undergo electrophilic borylation reactions, and that this reaction can be applied in the synthesis of the anticancer drug Velcade. The \(N\)-phosphinyl auxiliary displayed good to excellent asymmetric induction and great stability in the catalytic borylation and deprotection reactions. GAP washing is found to enhance the diastereopurity of the borylation products in most cases. The absolute configuration of the borylation product in Velcade’s synthesis has been confirmed by single crystal X-ray diffraction analysis.

Experimental

Standard operations for catalytic borylation and GAP: A 10 mL Schlenk tube was charged with crude imine 2, B\(_2\)Pin\(_2\) (375 mg, 2 equiv), catalyst ICyCuOt-Bu (54 mg, 20 mol %) and 4 Å molecular sieves (~500 mg). The mixture was protected with argon atmosphere, followed by toluene (4 mL) addition via syringe. The reaction mixture was stirred vigorously for 3 days, and the resulting slurry was filtered through Celite and washed with EtOAc 5 times. The filtrate was then concentrated and checked by \(^{31}\)P NMR to determine the % conversion and the crude dr value. GAP operations: 1) **Method A**: The filtrate was re-dissolved in EtOAc and washed with 1 N HCl, water, and brine successively, then dried over anhydrous Na\(_2\)SO\(_4\). The crude product was obtained after filtration and concentration, followed by addition of 5 mL of hexanes to triturate the crude product. After 30 minutes, the solvent was decanted and another 5 mL hexanes were added. The resulting slurry was then filtered and the solid was washed with another 2 mL hexanes. The solid product was collected and dried in vacuo. The yield was calculated and the dr value and purity were checked by \(^{31}\)P NMR and \(^{1}\)H NMR. 2) **Method B**: The filtrate was re-dissolved in EtOAc/ hexanes (20 mL, v/v = 1:1), and then filtered through Celite. The filtrate was concentrated and triturated with hexanes (5 mL). After 30 minutes, the solvent was decanted and another
5 mL hexanes was added. The resulting slurry was then filtered and the solid was washed with another 2 mL hexanes. The solid product was collected and dried in vacuo. The yield was calculated from the starting amide I. The dr value and purity were checked by $^{31}$P NMR and $^{1}H$ NMR.

Supporting Information

Supporting Information File 1

Experimental details, characterization data of all products, and copies of NMR spectra.

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