Stereoselective allylboration of imines and indoles under mild conditions. An in situ E/Z isomerization of imines by allylboroxines†

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Direct allylboration of various acyclic and cyclic aldimine, ketimine and indole substrates was performed using allylboronic acids. The reaction proceeds with very high anti-stereoselectivity for both E and Z imines. The allylboroxines formed by dehydration of allylboronic acids have a dual effect: promoting E/Z isomerization of aldmines and triggering the allylation by efficient electron withdrawal from the imine substrate.

Results and discussion

It is well documented that the reaction of aldehydes and allylboronates proceeds with anti-selectivity in a self-catalyzed process. However, the low reactivity of the imines with allylboronates makes it difficult to gain insight into the mechanism of the stereo-selection. Most of the described allylboration methods require external catalysts as the imines have to be activated and/or generated in situ, which complicates the studies of the stereochemistry of self-catalyzed allylboration. Previously, we have published a convenient method for palladium-catalyzed synthesis of allylboronic acids from allyl alcohols and diboronic acids. Allylboronic acids proved to be much more reactive with carbonyl compounds than other allylboronates, such as allyl-Bpin derivatives. We have now found that allylboronic acids readily react with imines under dry conditions without any external Lewis acid or other additives (eqn (2)). The dry conditions were ensured by adding molecular sieves (MS) (4 Å). Without the addition of a drying agent we observed hydrolysis of the imine substrate to an aldehyde. In fact the tendency of imines to hydrolyse, such as 1a in the presence of allylboronic acids 2 (and absence of molecular sieves), was greater than in the pure form (i.e. without 2).
Interestingly, both the \( E \) and \( Z \) imines gave the same anti-selectivity, which is similar to aldehydes\(^5\) and ketones.\(^6\) Acyclic aroyl and heteroaryl amines (1a-c) with \( E \) geometry react readily with cinnamyl and octenyl boronic acids 2a and 2b in the presence of molecular sieves at room temperature in a couple of hours (Table 1, entries 1–7). The reactions of imines 1a, 1b, 1d and 1e gave single stereoisomers (3a, 3b, 3d and 3e) with anti-selectivity. The assignment of the stereochemistry for 3a and 3d is based on X-ray diffraction. Imine 1d underwent desilylation during the reaction and thus it gave the homoallyl amine product 3d (entry 4). Benzyl imine 1c also reacted with very high stereo-selectivity but in this case two diastereomers were formed in a 91 : 9 ratio. The reaction of geranyltronic acid 2e with imine 1d was surprisingly fast (only one hour) and resulted in 3h (entry 8) with adjacent quaternary and tertiary stereocenters, with a diastereomeric ratio (dr) of 95 : 5.

Cyclic imine\(^7\) 1f has a \( Z \) geometry, yet the stereochemistry of the sole product 3i also has anti-stereoselectivity (entry 9), which was confirmed by X-ray diffraction. Thus 1a with a stable \( E \)-geometry\(^8\) and its closely related analog 1f with \( Z \)-geometry gave the same product, the anti-stereoisomer (cf. entries 1 and 9) at room temperature in DCM/1 h without an external catalyst. Moreover, the stereochemistry of the allylboration (using 2a) of 1a and its aldehyde analog (benzaldehyde) are identical.\(^9\) Most of the ketimines, such as the methyl analogs of 1a and 1b resisted allylboration under the applied uncatalyzed conditions. However, ketimine 1g reacted with excellent stereoselectivity but much slower (in 24 h) than the aldimines. This indicates that allylboronic acids are able to react with ketimines as well but the reaction is sensitive to steric factors. Thus bulkier ketimines than 1g could be useful substrates for asymmetric allylboration. For example, chiral Lewis acids\(^10\) or chiral auxiliaries\(^10\) on the ketamine can be employed to increase the reactivity of the reactants. Glyoxylate imine 1h also reacted readily with allylboronic acids, opening a new synthetic route\(^11\) for allylboronate based stereoselective synthesis of amino acid derivatives. In previous studies\(^8\) we have shown that allylboronic acids react readily with ketones. Compound 1i has both keto and aldime functionalities (entry 12) but only the imine functionality was transformed when 2a was added. The high chemoselectivity indicates that aldimes react faster with allylboronic acids than ketones. Cyclic ketimine 1g was the only aliphatic imine that we could employ, as acyclic aliphatic imines underwent rapid hydrolysis even in the presence of molecular sieves. Our efforts to remove minute trace amounts of water proved to be fruitless.

Batey and co-workers\(^12\) have recently shown that indoles react with allyl-BF\(_3\)K derivatives in the presence of BF\(_3\) \textit{via in situ} formation of allyl-BF\(_3\) species. We have found that allylboronic acids react readily with indoles 4a-c without any additives (Table 2). The allylation proceeded with very high stereo-selectivity, affording a single product. The reaction was complete in a couple of hours using 2a or 2b. Geranyltronic acid 2c reacted with 4a with high selectivity creating adjacent quaternary and tertiary stereocenters (3q) in 24 hours (entry 5). Methyl indole derivative 4c was also reacted at 60 °C with 2a to selectively give 3r with adjacent quaternary and tertiary stereocenters (entry 6). The longer reaction times and higher temperatures (entries 3 and 6) required for completion of these two latter processes indicate that the reaction is slower in the presence of bulky groups.

The most intriguing mechanistic aspect of the above allylboration of \( E \) and \( Z \) imines is the very fast anti-selective allylation. Since the stereochemistry is the same for the allylboration of aldehydes and ketones, we hypothesized that the reaction with imines also takes place according to the \( Z \)-T model\(^13\) \textit{via a chair-type TS}. However, according to this model a \( Z \)-geometry is required for the imines (such as in 1f) to predict anti-selectivity \textit{via a chair TS} (cf. eqn (1)). Thus, the acyclic \( E \)-aldimines 1a-d and 1h-i should undergo rapid isomerization to the corresponding \( Z \)-form prior to the allylboration. The thermal isomerization of aldimes has a high activation energy.\(^14\) For example, according to the \( ^1 \)H NMR spectrum 1a exists as a stable E isomer in CDCl\(_3\) even at elevated temperatures (50 °C). Application of organoboronic acids as organocatalysts has attracted great interest in the synthetic community\(^15\). Moreover, Piers and co-workers\(^16\) have shown that boron-based Lewis acids, such as \( \text{B} (\text{C}_6\text{H}_5)_3\), are able to catalyze the isomerization of aldimes. Accordingly, we assumed that allylboronic acid or its boroxine may catalyze the isomerization of \( E \)- to \( Z \)-aldimes prior to the allylboration process. We have observed several indications of possible interactions of allylboronates and imines prior to the allylation. As mentioned above, the hydrolysis of aldimes to aldehydes is much faster in the presence, rather than in the absence, of allylboronic acids. Without the use of molecular sieves we observed partial hydrolysis of imines 1a-d and 1h-i leading to the formation of homoallyl alcohols by the allylboration of the hydrolyzed products. The application of molecular sieves solved this problem but also gave rise to the dehydrolysis of allylboronic acids. This leads to the formation of allyl boroxines, such as 2a\(_b\) from 2a, which are detectable by \( ^1 \)H NMR.\(^17\) Since allylboronic acid 2a allylates \( Z \)-aldimes (such as 1f) rapidly, we studied the \( E \)/\( Z \) isomerization of 1a in the presence of aryl boroxine 5 (Fig. 1), which is obviously not able to allylate imines. Boroxine 5 was prepared from the corresponding aryloboronic acid by stirring with molecular sieves. Before the isomerization experiment the molecular sieves were removed by filtration in a glove box. It was found that 1a rapidly isomerized to 6 in the presence of boroxine 5. The process was monitored by \( ^1 \)H NMR, indicating the formation of a 1 : 1 mixture of 1a and 6. In 6 the phenyl and \( N \)-methyl groups are in the \( Z \)-geometry, which was ensured by detection of the dNOE effect between the \( N \)-methyl and \textit{ortho}-phenyl protons (Fig. 1). In 1a a dNOE effect was observed between the \( N \)-methyl group and the imine C–H, which shows that in isolated 1a the phenyl and \( N \)-methyl groups are in the \( E \)-geometry.
Table 1  Selective allylboration of imines

| Entry | Boronic acid | Imine | Time (h) | Product | Yield | Yield |
|-------|--------------|-------|----------|---------|-------|-------|
| 1     | 2a           | 1a    | 1        | 3a      | 73    |       |
| 2     | 2a           | 1b    | 3        | 3b      | 84    |       |
| 3     | 2a           | 1c    | 1        | 3c      |       | 72    |
| 4     | 2a           |       | 1        | 3d      | 78    |       |
| 5     | 2a           |        | 3        | 3e      | 92    |       |
| 6     | 2b           | 1d    | 1        | 3f      | 80    |       |
| 7     | 2b           | 1a    | 3        |         | 74    |       |
| 8     | 2c           | 1d    | 1        | 3h      | 66    |       |
| 9     | 2a           | 1f    | 1        | 3i      | 93    |       |
| 10    | 2a           | 1g    | 24       | 3j      |       | 65    |
| 11    | 2a           | 1h    | 3        | 3k      | 72    |       |
| 12    | 2a           | 1i    | 1        | 3l      | 71    |       |

*a* Unless otherwise specified 2 (0.28 mmol) and the MS (4 Å) were stirred in DCM (0.6 mL) then 1 (0.20 mmol) was added. The mixture was stirred at rt for the indicated times and isolated as a single diastereomer. *b* Isolated yield. *c* dr = 91 : 9. *d* dr > 95 : 5. *e* Boronic acid solution in CDCl₃ (0.3 M) was used. *f* The structure determination is based on X-ray. Ar = p-bromophenyl. PMP = p-methoxyphenyl.
Although, the reaction mixture (Fig. 1) contained 100% boroxine \( \text{5} \) based on the \(^1\text{H}-\text{NMR} \) spectrum, we also considered the possibility that traces of water could generate arylboronic acid by the hydrolysis of \( \text{5} \). Hall and co-workers\(^\text{14}\) reported that molecular sieves may act as reservoirs of water and, thus traces of active boronic acid may be available by the hydrolysis of boroxine. When small amounts of water were added to boroxine solution \( \text{5} \), the appearance of the \(^1\text{H}-\text{NMR} \) signal of the corresponding boronic acid was observed. Under these conditions we did not observe any \( E/Z \) isomerization of \( \text{1a} \). Thus, we conclude that boroxine under dry conditions is required for the efficient isomerization of \( E \)-imines (such as \( \text{1a} \)) to \( Z \)-imines.

We employed molecular sieves (4 Å) to remove residual water completely from the reaction mixture. However, molecular sieves may act as (weak) acid catalysts in certain processes.\(^\text{16}\) To check this possibility we performed the allylation of \( \text{1a} \) with \( \text{2a} \) under standard conditions (entry 1) in the presence of NaHCO\(_3\) to buffer the acidity of the employed molecular sieves. We did not observe any effect by NaHCO\(_3\) on the outcome of the reaction, and thus we conclude that molecular sieves do not act as acid catalysts for the presented allylation process.

The \( Z \) relationship of the \( N \)-methyl and phenyl groups in \( \text{6} \) may satisfactorily explain the \textit{anti}-selectivity of the allylboration via a chair TS in line with the \( Z \)-T model. To prove this assumption we performed a computational DFT study using the B3LYP functional\(^\text{17}\) (for computational details see ESI†). The results show (Fig. 2) that the formation of imine–boroxine complex \( \text{7a} \) from \( \text{1a} \) and allyl boroxine \( \text{2ab} \) is an exergonic process (by \(-4.1 \text{ kcal mol}^{-1}\)). This assumes that facile \( E/Z \) isomerization of the imine takes place, as established above for \( \text{1a} \) (Fig. 1). It is interesting to note that \( \text{7a} \), in which the \( N \)-methyl and phenyl groups are in a \( Z \)-geometry (like in \( \text{6} \)), is more stable by 6.2 kcal mol\(^{-1}\) than \( \text{7b} \), which has an \( E \)-geometry.

This trend is reversed compared to the free imines, \( \text{1a} \) vs. \( \text{1ac} \). From \( \text{7a} \), the allylboration proceeds via chair TS \( \text{8a} \) with a low activation barrier (14.9 kcal mol\(^{-1}\)) affording \( \text{9a} \) with \textit{anti}-selectivity. This is in agreement with the \( Z \)-T model. The chair-shape of TS structure \( \text{8a} \) and the TS geometry for the allylboration of aldehydes\(^\text{4} \) are very similar, which is in line with the identical stereochemistry observed for the two processes. Allylation of the other imine–allyl boroxine complex (\( \text{7b} \)) or \( \text{1a} \), in

### Table 2: Reaction of indoles with allyboronic acids\(^a\)

| Entry | Boronic acid | Indole | Time (h) | Product | Yield\(^b\) |
|-------|-------------|--------|---------|---------|------------|
| 1     | 2a          | 4a     | 3       | ![Product 3m](image) | 90         |
| 2     | 2a          | 4b     | 1       | ![Product 3n](image) | 96/97\(^c\) |
| 3     | 2b          | 4a     | 3       | ![Product 3o](image) | 95         |
| 4     | 2b          | 4b     | 1       | ![Product 3p](image) | 85         |
| 5     | 2c          | 4a     | 24      | ![Product 3q](image) | 74         |
| 6\(^d\) | 2a          |        | 12      | ![Product 3r](image) | 75         |

\(^a\) Unless otherwise stated, allylboronic acid \( \text{2a-c} (0.15 \text{ mmol}) \) was reacted with indoles \( \text{4a-c (0.1 mmol)} \) at rt in DCM (0.4 mL).\(^b\) Isolated yield as a single diastereomer.\(^c\) Reaction scale up to 0.5 mmol of indole.\(^d\) Reaction performed at 60 °C.

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**Fig. 1** \( E/Z \) isomerization of \( \text{1a} \) in the presence of aryl boroxine (\( \text{Ar} = 4\)-fluorophenyl). The major \(^1\text{H} \) dNOE is indicated for the two observed isomeric forms.
which the N-methyl and phenyl are in an E geometry, requires 5.4 kcal mol\(^{-1}\) higher activation barriers to give the syn product 9b. The high barrier is apparently because of the axial position of the phenyl group in 8b, which is sterically unfavorable in line with the Z–T model (see eqn (1)). We have also calculated the activation barriers via boat TSs\(^{8a,b}\) (8c and 8d). However, formation of the anti-product 9a via boat TS 8d involves a much higher barrier than via chair TS 8a (by 7.8 kcal mol\(^{-1}\)). The high energy of the boat forms 8c and 8d compared to the chair forms 8a and 8b is not surprising, as the unfavorable eclipsing strains and 1,4-diaxial strain in the boat form are well known by analysis of the conformational energy surface of cyclohexane.\(^{18}\)

Due to the relatively short B–C (2 Å) and B–N (1.5 Å) distances, the steric strains in TS structures 8a–d (Fig. 4) and the corresponding stationary points in the potential energy surface of the “ideal” cyclohexane structure are surprisingly similar. In fact, one of the main reasons for the remarkably high stereoselectivity of the allylboration of carbonyls and imines is due to the short B–C, B–O/B–N, and C–C distances in the TSs.

Due to this geometry feature the bulky substituents are brought into close proximity, which allows very efficient stereodifferentiation. A good example is the strong 1,3-diaxial strain between the axial phenyl and the boroxine groups in 8b (Fig. 4), which leads to the less favorable formation of the syn product 9b over the anti product 9a (Fig. 2).

Fig. 2 Reaction profile for the allylboration of 1a in the presence of allylboroxine 2ab. The \(\Delta G\) values are given in kcal mol\(^{-1}\).

We have also performed modeling studies for allylation with allylboronic acid 2a instead of its boroxine 2ab (Fig. 3). The corresponding reaction profiles show the same mechanistic features as the above processes with boroxine (Fig. 2). Thus, the lowest energy path involves isomerization of E-imine 1a to Z-imine via the formation of an imine–boronic acid complex.

Fig. 3 Allylboration of 1a with cinnamyl boronic acid 2a. The \(\Delta G\) values are given in kcal mol\(^{-1}\).
which eventually gives the anti-diastereomer. However, there are also notable differences between the reaction profiles for the allylation with boroxine 2a\(_h\) (Fig. 2) and boronic acid 2a (Fig. 3). Formation of the boroxine-imine complex 7a is exergonic, while formation of the boronic acid-imine complex 10a is endergonic. Furthermore, the activation barrier involving allyl boroxine 2a\(_h\) via the 1a → 7a → 8a → 9a path (Fig. 2) is substantially lower (by 5.7 kcal mol\(^{-1}\)) than the corresponding activation barrier involving allylboronic acid 2a.

The higher efficiency of 2a\(_h\) vs. 2a for the allylation of 1a can be explained by the higher B/O ratio in boroxine (1 : 1) than in allylboronic acid (1 : 2). Accordingly, less electron density is transferred from the oxygen O(p\(_{\text{n}}\)) lone-pair to the empty B(p\(_{\text{p}}\)) orbital of boron in boroxine 2a\(_h\) than in allylboronic acid 2a. This leads to a much higher electrophilicity (Lewis acidity) of the boron B(p\(_{\text{p}}\)) in boroxine than in allylboronic acid. The high electrophilicity of boron in boroxine is favorable for both the E/Z isomerization of the aldimes (such as 1a) and the allylation of the imine. A possible failure of direct allylation of imines, such as 1a-d, with allyl-Bpin and analogs may arise from the fact that the boron atom of the Bpin functionality is not sufficiently electrophilic for the E/Z isomerization of acyclic aldimines and/or triggering the allylation (by interacting with the N-lone-pair of the imine substrate).

To our knowledge, until now allylboration mediated E/Z isomerization of imines has not been suggested for the anti-selective allylation of imines. However, Leighton and co-workers\(^{19}\) have reported E/Z isomerization of 2-aminophenol derived imines during cinnamylation of imines with cinnamyl chlorosilanes (Cl-silane analog of 2a). The proposed isomerization is based on the chelation of the hydroxyl unit of 2-aminophenol imine with the silyl group of cinnamyl chlorosilane. An interesting analogy between the allylboration and allyl chlorosilane based cinnamylation reactions is that in both cases in situ E/Z isomerization of the imine may occur by the allylation reagent leading to excellent anti-selectivity.

**Conclusions**

We have demonstrated that allylboration acids may readily react with imines. The reaction proceeds under mild conditions with E-aldimine, cyclic aldime, ketimine and indole substrates with very high anti-stereoselectivity. The process is chemoselective, as aldimes can be allylated in the presence of a keto group. The experimental and DFT mechanistic studies show that boroxines (formed by dehydration of allylbonic acids) have a dual activating effect in this reaction: promoting E/Z isomerization of aldimes, and as efficient electron acceptors/ Lewis acids triggering the allylation process. Allylboration is a widely used methodology in natural product synthesis and in advanced organic chemistry.\(^{11-19,28}\) Based on the above results the scope of allylboration can be further extended for synthesis of complex stereoinduced amine structures. In addition, new insights into the stereochemistry of allylboration and into the validity of the Z-T model are helpful for the design of new selective transformations.

**Conflict of interest**

The authors declare no competing financial interests.

**Acknowledgements**

The authors thank the financial support of the Swedish Research Council (VR) and the Knut och Alice Wallenberg Foundation. The authors also thank Dr Carolina Fontana for helping with some of the NMR experiments. GH thanks the Carl Tryggers Foundation for a postdoctoral fellowship.

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