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

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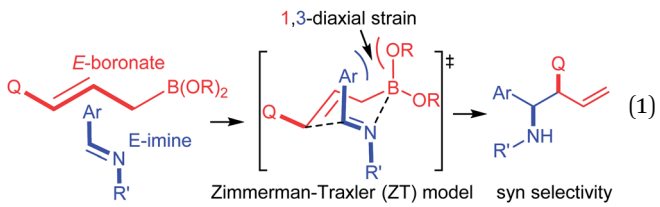
Direct allylboration of various acyclic and cyclic aldimine, ketimine and indole substrates was performed using allylboronic acids. The reaction proceeds with very high *anti*-stereoselectivity for both *E* and *Z* imines. The allylboroxines formed by dehydration of allylboronic acids have a dual effect: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

Introduction

Reaction of allylboronates with imines is an attractive approach for selective synthesis of functionalized homoallyl amines, which are useful synthetic intermediates in pharmaceutical chemistry and natural product synthesis.[1] According to the general view in the synthetic community the allylboration of imines is more difficult than that of carbonyl compounds, due to the lower electrophilicity of the carbon atom in the imine (C=N) compared to the carbonyl (C=O) group.[1a,b,2] Another important issue concerns the stereochemistry of the allylboration. Imines may have *E* or *Z* geometry and the isomerization complicates the stereochemical outcome of the process. When *E*-aldimines and (*E*)-3-substituted allylboronates react, *syn*-selectivity is expected on the basis of the Zimmerman–Traxler (Z–T) model (eqn (1)). Yet, in many cases (including also the present study) *anti*-selectivity has been observed, which is similar to cases involving carbonyl substrates.[2a,c]



(1)

The unexpected *anti*-selectivity was mainly explained by two mechanistic models: (i) either a boat TS (transition state)[2a,d] instead of a chair TS (eqn (1)) occurs during the course of the reaction or (ii) spontaneous *E/Z* isomerization of the imines[2c] takes place prior to the allylation. However, modeling studies for the allylboration of aldehydes have shown that the boat geometry is unlikely in these types of process.[3] Besides, the barrier for the thermal *E/Z* isomerization of aldimines is high; therefore it is unlikely to happen.[4]

Results and discussion

It is well documented that the reaction of aldehydes and allylboronates proceeds with *anti*-selectivity in a self-catalyzed process.[1a,5] 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.[1c–h] Previously, we have published a convenient method for palladium-catalyzed synthesis of allylboronic acids[6] from allyl alcohols and diboronic acids.[7] Allylboronic acids proved to be much more reactive with carbonyl compounds than other allylboronates,[6] 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**).

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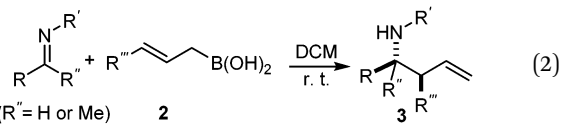
† Electronic supplementary information (ESI) available. CCDC 985818–985820. See DOI: 10.1039/c4sc00415a



1 (R″ = H or Me) 2 3 (2)

Interestingly, both the *E* and *Z* imines gave the same *anti*-selectivity, which is similar to aldehydes[5] and ketones.[6] Acyclic aryl and heteroaryl imines (**1a–e**) with *E* geometry react readily with cinnamyl and octenyl boronic acids **2a** and **b** 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.

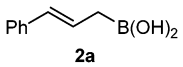
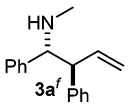
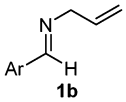
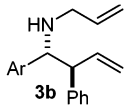
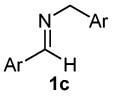
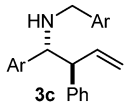
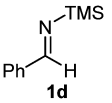
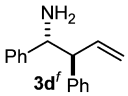
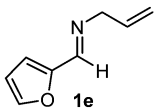
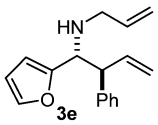
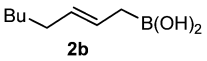
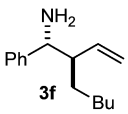
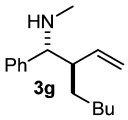
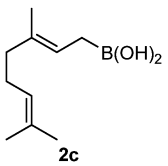
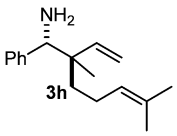
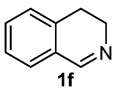
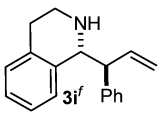
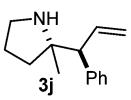
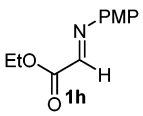
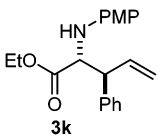
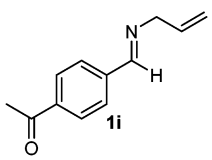
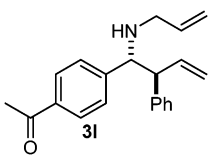
The assignment of the stereochemistry for **3a** and **3d** is based on X-ray diffraction. Imine **1d** underwent desilylation during the reaction and thus it gave the homoallyl amine product **3d** (entry 4). Benzyl imine **1c** also reacted with very high stereoselectivity but in this case two diastereomers were formed in a 91 : 9 ratio. The reaction of geranylboronic acid **2c** 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[1h] **1f** has a *Z* geometry, yet the stereochemistry of the sole product **3i** also has *anti*-geometry (entry 9), which was confirmed by X-ray diffraction. Thus **1a** with a stable *E*-geometry[4b] 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.[8] 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 allylation. For example, chiral Lewis acids[1c,d,9] or chiral auxiliaries[10] on the ketimine can be employed to increase the reactivity of the reactants. Glyoxylate imine **1h** also reacted readily with allylboronic acids, opening a new synthetic route[8,11] for allyl boronate based stereoselective synthesis of amino acid derivatives. In previous studies[6] we have shown that allylboronic acids react readily with ketones. Compound **1i** has both keto and aldimine functionalities (entry 12) but only the imine functionality was transformed when **2a** was added. The high chemoselectivity indicates that aldimines 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_3K derivatives in the presence of BF_3 *via in situ* formation of allyl-BF_2 species. We have found that allylboronic acids react readily with indoles **4a–c** without any additives (Table 2). The allylation proceeded with very high stereoselectivity, affording a single product. The reaction was complete in a couple of hours using **2a** or **2b**. Geranylboronic 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 5 and 6) required for completion of these two latter processes indicate that the reaction is slower in the presence of bulky groups.

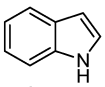
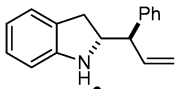
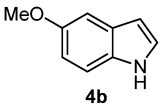
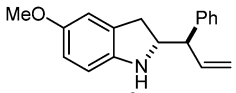
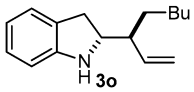
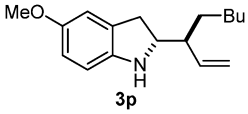
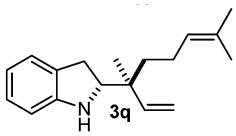
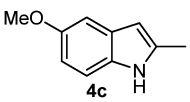
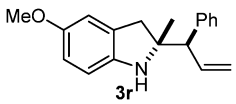
The most intriguing mechanistic aspect of the above allylboration of *E* and *Z* imines is the very fast *anti*-selective allylation. Since the stereochemistry is the same for the allylboration of aldehydes and ketones, we hypothesized that the reaction with imines also takes place according to the Z–T model[13] *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 *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 aldimines has a high activation energy.[4b] 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.[14] Moreover, Piers and co-workers[15] have shown that boron-based Lewis acids, such as $B(C_6F_5)_3$ are able to catalyze the isomerization of aldimines. Accordingly, we assumed that allylboronic acid or its boroxine may catalyze the isomerization of *E*- to *Z*-aldimines 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 aldimines 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 dehydration of allylboronic acids. This leads to the formation of allyl boroxines, such as $\mathbf{2a_b}$ from **2a**, which are detectable by ^{1}H NMR.[6a] Since allylboronic acid **2a** allylates *Z*-aldimines (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 arylboronic 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 *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[a]

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

[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 $CDCl_3$ (0.3 M) was used. [f] The structure determination is based on X-ray. Ar = *p*-bromophenyl. PMP = *p*-methoxyphenyl.

Table 2 Reaction of indoles with allylboronic acids[a]

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

[a] Unless otherwise stated, allylboronic acid **2a–c** (0.15 mmol) was reacted with indoles **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.

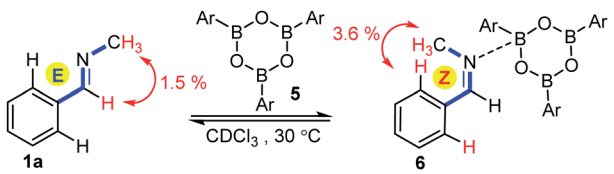


Fig. 1 *E*/*Z* isomerization of **1a** in the presence of aryl boroxine (Ar = 4-fluorophenyl). The major ^{1}H dNOE is indicated for the two observed isomeric forms.

Although, the reaction mixture (Fig. 1) contained 100% boroxine **5** based on the ^{1}H-NMR spectrum, we also considered the possibility that traces of water could generate arylboronic acid by the hydrolysis of **5**. Hall and co-workers[14d] 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 **5**, the appearance of the ^{1}H-NMR shift of the corresponding boronic acid was observed. Under these conditions we did not observe any *E*/*Z* isomerization of **1a**. Thus, we conclude that boroxine under dry conditions is required for the efficient isomerization of *E*-imines (such as **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.[16] To check this possibility we performed the allylation of **1a** with **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 **6** may satisfactorily explain the *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[17] (for computational details see ESI†). The results show (Fig. 2) that the formation of imine–boroxine complex **7a** from **1a** and allyl boroxine $\mathbf{2a_b}$ is an exergonic process (by −4.1 kcal mol^{-1}). This assumes that facile *E*/*Z* isomerization of the imine takes place, as established above for **1a** (Fig. 1). It is interesting to note that **7a**, in which the *N*-methyl and phenyl groups are in a *Z*-geometry (like in **6**), is more stable by 6.2 kcal mol^{-1} than **7b**, which has an *E*-geometry.

This trend is reversed compared to the free imines, **1a** *vs.* $\mathbf{1a_c}$. From **7a**, the allylboration proceeds *via* chair TS **8a** with a low activation barrier (14.9 kcal mol^{-1}) affording **9a** with *anti*-selectivity. This is in agreement with the Z–T model. The chair-shape of TS structure **8a** and the TS geometry for the allylboration of aldehydes[3] are very similar, which is in line with the identical stereochemistry observed for the two processes. Allylation of the other imine–allyl boroxine complex (**7b**) or **1a**, in

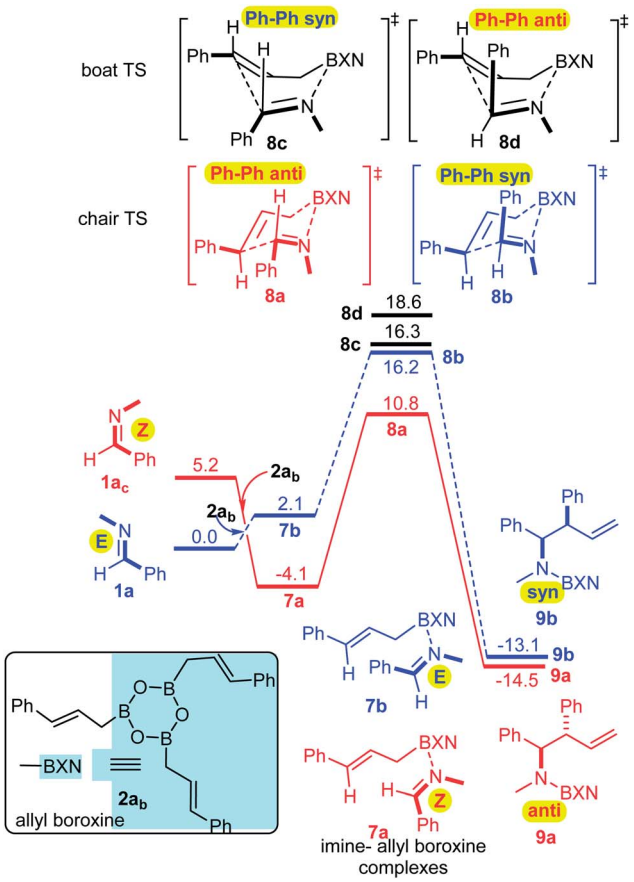


Fig. 2 Reaction profile for the allylboration of **1a** in the presence of allylboroxine $\mathbf{2a_b}$. The ΔG values are given in kcal mol^{-1}.

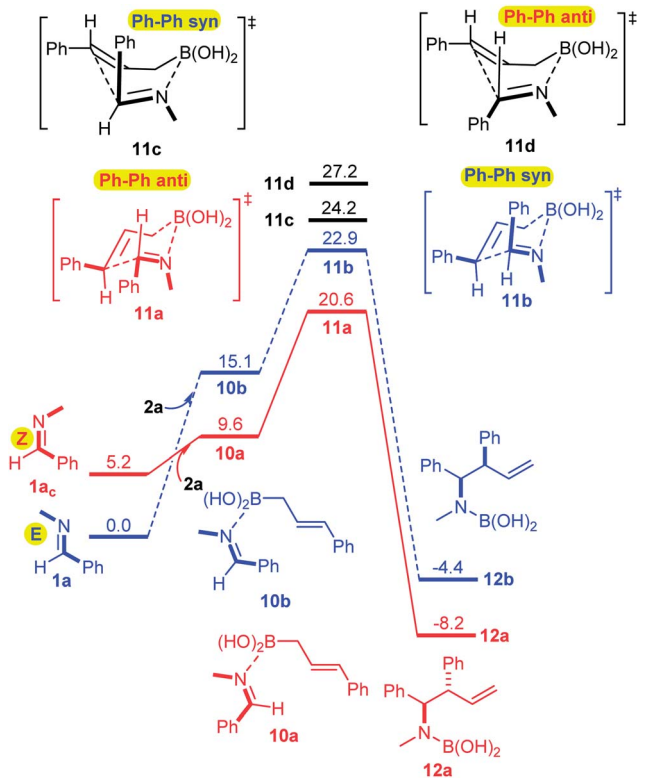


Fig. 3 Allylboration of **1a** with cinnamyl boronic acid **2a**. The ΔG values are given in kcal mol^{-1}.

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[2a,b] (**8c** and **8b**). 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).

We have also performed modeling studies for allylation with allylboronic acid **2a** instead of its boroxine $\mathbf{2a_b}$ (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,

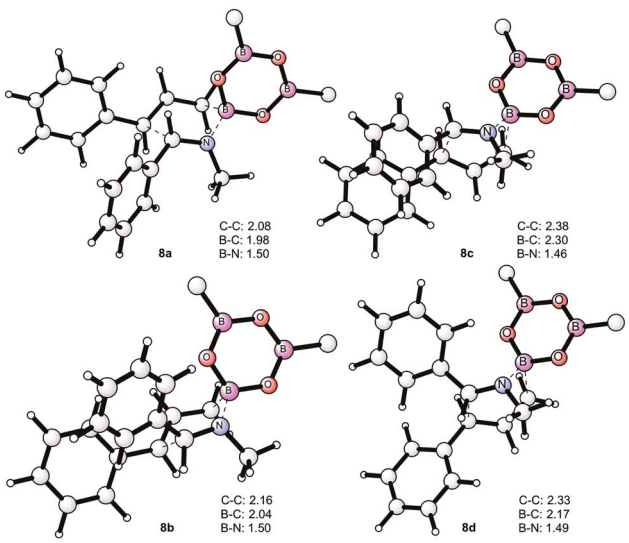


Fig. 4 Optimized geometries of the TS structures **8a–d**. Two of the allyl moieties of the boroxines have been removed for clarity. The distances are in Å.

which eventually gives the *anti*-diastereomer. However, there are also notable differences between the reaction profiles for the allylation with boroxine **2a$_b$** (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$_b$** *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$_b$** *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(n_π) lone-pair to the empty B(p_π) orbital of boron in boroxine **2a$_b$** than in allylboronic acid **2a**. This leads to a much higher electrophilicity (Lewis acidity) of the boron B(p_π) in boroxine than in allylboronic acid. The high electrophilicity of boron in boroxine is favorable for both the *E*/*Z* isomerization of the aldimines (such as **1a**) and the allylation of the imine. A possible failure of direct allylboration 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 allylboroxine 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 allylboronic acid 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 allylboronic acids may readily react with imines. The reaction proceeds under mild conditions with *E*-aldimine, cyclic aldimine, ketimine and indole substrates with very high *anti*-stereoselectivity. The process is chemoselective, as aldimines can be allylated in the presence of a keto group. The experimental and DFT mechanistic studies show that boroxines (formed by dehydration of allylboronic acids) have a dual activating effect in this reaction: promoting *E*/*Z* isomerization of aldimines, 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.[1c–h,20] Based on the above results the scope of allylboration can be further extended for synthesis of complex stereodefined 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.

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