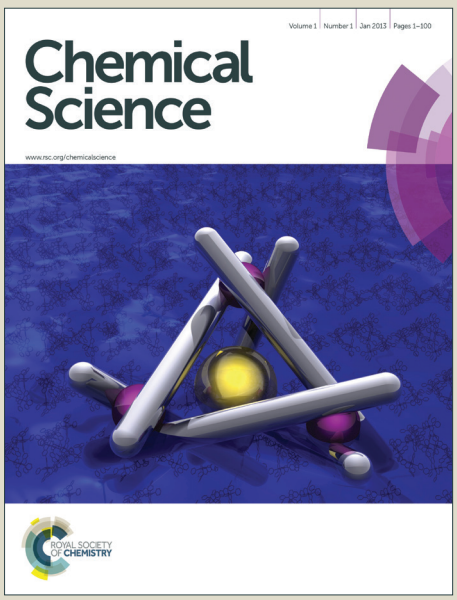
Chemical Science

Accepted Manuscript



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ARTICLE

Stereoselective Allylboration of Imines and Indoles under Mild Conditions. In Situ E/Z Isomerization of Imines by Allylboroxines

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

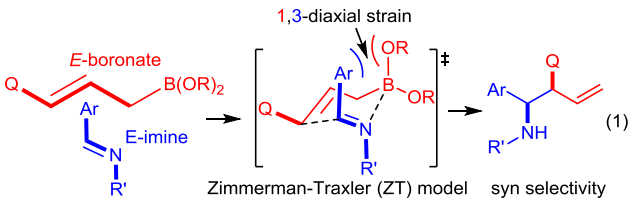
www.rsc.org/

Rauful Alam,[a] Arindam Das,[a] Genping Huang,[a] Lars Eriksson,[b] Fahmi Himo,[a] and Kálmán J. Szabó *[a]

Direct allylboration of various acyclic, 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: E/Z isomerization of aldimines and triggering the allylation by efficient electron withdrawing from the imine substrate.

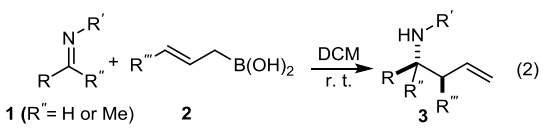
Introduction

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 the carbonyl compounds, due to the lower electrophilicity of the carbon atom in the imine (C=N) compared to the carbonyl (C=O) groups.[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 (ZT) model (eq. 1). Yet, in many cases (including also the present study) anti selectivity has been observed, similarly to the carbonyl substrates. [2a,c]



The unexpected anti-selectivity was mainly explained by two mechanistic models: i) either a boat TS[2a,d] instead of a chair TS (eq. 1) occurs in 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 allylboration of aldehydes have shown that the boat geometry is unlikely in these type of process.[3] Besides, the barrier for the thermal E/Z isomerization of aldimines is high; therefore it is unlikely to happen.[4]

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 difficult to gain insight into the mechanism of the stereo-selection. Most of the described allylboration methods require external catalysts, the imines have to be activated and/or generated in situ, which complicates the studies of the stereochemistry of the 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 (eq. 2). The dry conditions were ensured by adding molecular sieves (4Å). Without addition of drying agent we observed hydrolysis of the imine substrate to aldehyde. In fact the tendency for hydrolysis of imines, such as **1a** in the presence of allylboronic acids **2** (and absence of molecular sieves) was larger than in pure form (i.e. without **2**).



Interestingly, both E and Z imines gave the same anti-selectivity, similarly 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-b** in the presence of molecular sieves at

room temperature in a couple of hours (Table 1, entries 1-7). The reaction of imines **1a-b, 1d** and **1e** gave a single stereoisomer (**3a-b**, **3d** and **3e**) with anti-selectivity.

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 MS (4 Å) were stirred in DCM (0.6 mL) then **1** (0.20 mmol) was added. The mixture was stirred at r.t. for indicated times and isolated as 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.

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 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 of 95:5.

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 (0.4ml). [b] Isolated yield as single diastereomer. [c] Reaction scale up to 0.5mmol of indole. [d] Reaction performed at 60°C.

Cyclic imine[1h] **1f** has a Z geometry, yet the stereochemistry of the sole product **3i** has also 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, the anti-stereoisomer (c.f. entries 1 and 9) at room temperature in DCM/1h without external catalyst. Moreover, the stereochemistry of allylboration (using **2a**) of **1a** and its aldehyde analog (benzaldehyde) is identical.[8] Most of the ketimines, such as the methyl analogs of **1a-b**, resisted allylboronation under the applied uncatalyzed conditions. However, ketimine **1g** reacted with excellent stereoselectivity but much slower (in 24h) than the aldimines. This indicates that allylboronic acids are able to react with ketimines as well but the reaction is sensitive to the steric factors. Thus more bulky ketimines than **1g** could be useful substrates for asymmetric allylation. For example, chiral Lewis acids[1c,d,9] or chiral auxilaries[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 stereo selectivity 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 give selectively **3r** with adjacent quaternary and tertiary stereocenters (entry 6). The longer reaction time and the higher temperature (entries 5-6) 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 as for allylboration of aldehydes and ketones, we hypothesized that the reaction with imines also takes place according to the ZT 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 (c.f. eq. 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 a large 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 for 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 than in the absence of allylboronic acids. Without use of molecular sieves we observed a partial hydrolysis of imines **1a-d** and **1h-i** leading to formation of homoallyl alcohols by the allylboration of the hydrolyzed products. Application of molecular sieves solved this problem but also gave rise to dehydration of allylboronic acids. This leads to formation of allyl boroxines, such as $\mathbf{2a_b}$ from **2a**, which are detectable by ^{1}H NMR.[6a] Since allylboronic acid **2a** allylates rapidly Z-aldimines (such as **1f**), we studied the E/Z isomerization of **1a** in the presence of aryl boroxine **5** (Figure 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 Z-geometry, which was ensured by detection of the dNOE effect between the N-methyl and ortho-phenyl protons (Figure 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 E geometry.

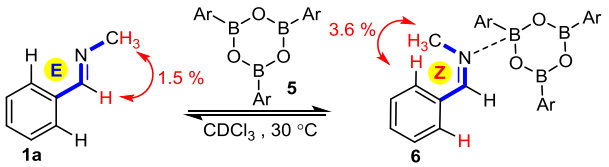


Figure 1. E/Z isomerization of 1a in the presence of aryl boroxine (Ar = 4-fluorophenyl). The major 1H dNOE is indicated for the two observed isomeric forms.

Although, the reaction mixture (Figure 1) contained 100% boroxine **5** based on the ^{1}H-NMR spectrum, we considered also the possibility that traces of water could generate arylboronic acid by hydrolysis of **5**. Hall and co-workers[14d] reported that molecular sieves may act as a reservoir of water and, thus traces of active boronic acid may be available by hydrolysis of boroxine. When small amounts of water were added to the boroxine solution **5** appearance of the ^{1}H-NMR shift of the corresponding boronic acid was observed. Under these conditions we could 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 (4Å) 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 the $NaHCO_3$ on the outcome of the reaction, and, thus we conclude that molecular sieves do not act as acid catalyst 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 ZT model. To prove this assumption we performed a computational DFT study using the B3LYP functional[17] (for computational details see SI). The results show (Figure 2) that 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** (Figure 1). It is interesting to note that **7a**, in which the N-methyl and phenyl groups are in Z-geometry (like in **6**), is more stable by 6.2 kcal mol^{-1} than **7b**, which has an E-geometry.

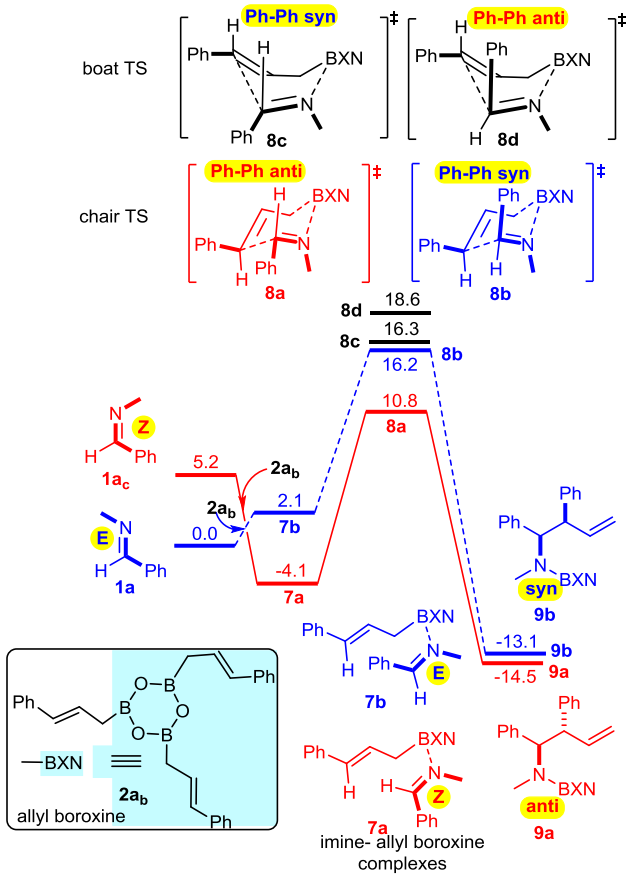


Figure 2. Reaction profile for the allylboration of **1a** in the presence of allylboroxine $\mathbf{2a_b}$ The ΔG values are given in kcal mol^{-1}.

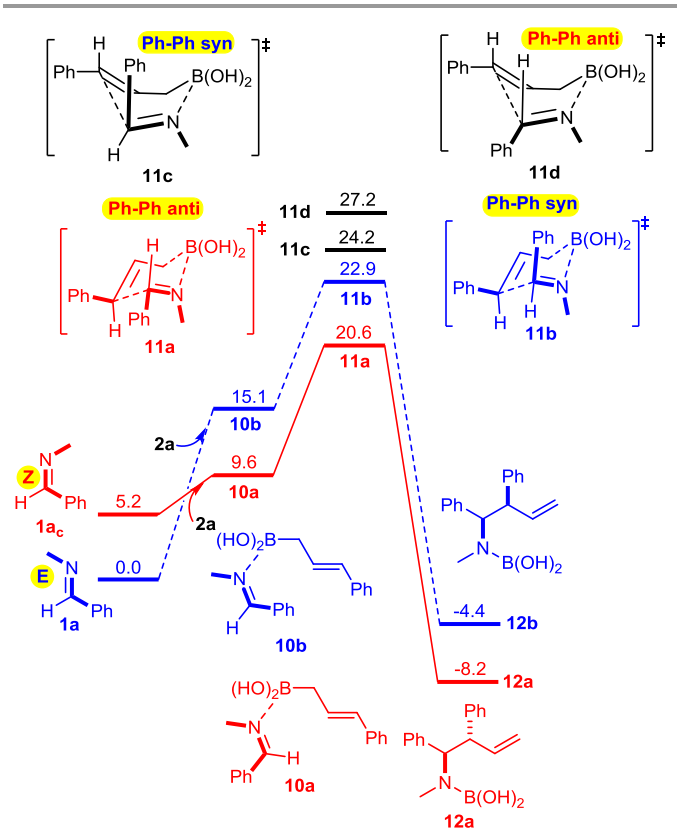


Figure 3. Allylboronation of allylboration of **1a** with cinnamyl boronic acid **2a**. The ΔG values are given in kcal mol^{-1}.

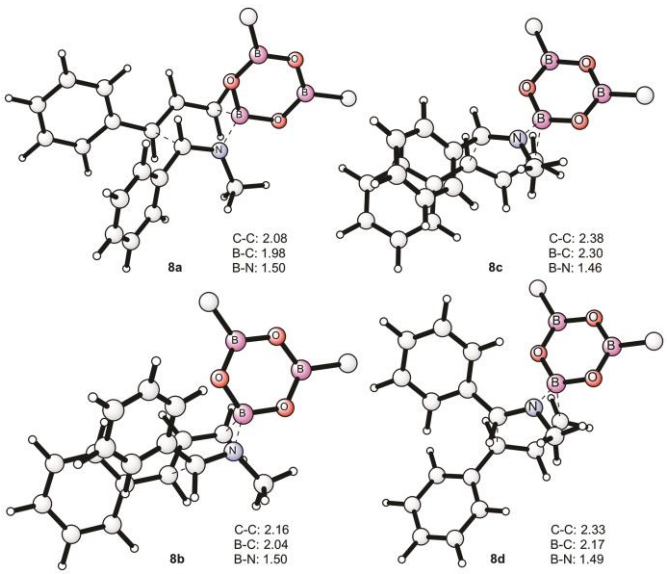


Figure 4. Optimized geometries of the TS structures **8a-d**. Two of the allyl moieties of the boroxines are removed for clarity. The distances are in Å.

This trend is thus 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 ZT model. The chair-shape of TS structure **8a** and the TS geometry of 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 which the N-methyl and phenyl are in 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 ZT model (see eq. 1). We have also calculated the activation barriers via boat TSs[2a,b] (**8c-d**). 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-d** compared to the chair forms **8a-b** is not surprising, as the unfavorable eclipsing strains and 1,4-diaxial strain in the boat form are well known by the 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** (Figure 4) and the corresponding stationary points in the PES of the "ideal" cyclohexane structure are surprisingly similar. In fact, one of the main reasons of the remarkably high stereoselectivity of the allylboration of carbonyls and imines is due to the short B-C, B-N and C-C distances in the TS.

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

We have also performed modeling studies for allylation with allylboronic acid **2a** instead of its boroxine **2a$_b$** (Figure 3). The corresponding reaction profiles show the same mechanistic features as the above processes with boroxine (Figure 2). Thus, the lowest energy path involves isomerization of E-imine **1a** to Z-imine via formation of an imine-boronic acid complex, which gives eventually the anti diastereomer. However, there are also notable differences between the reaction profile for the allylation with boroxine **2a$_b$** (Figure 2) and boronic acid **2a** (Figure 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 (Figure 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** in 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 allyl boronic 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 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 that in both cases in situ E/Z isomerization of the imine may occur by the allylation reagent leading to excellent anti selectivity.

Conclusions

In summary, 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: 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 ZT model are helpful for the design of new selective transformations.

Acknowledgements

The authors thank the financial support of the Swedish Research Council (VR) and the Knut och Alice Wallenbergs 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.

Notes and references

[a]Department of Organic Chemistry.
[b]Department of Inorganic and Structural Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden.

†The authors declare no competing financial interests..

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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