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

Raful Alam,a Arindam Das,a Genping Huang,a Lars Eriksson,b Fahmi Himoa and Kálmán J. Szabó*a

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 allyboroxines 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.

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 imines3 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.4 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.14–5 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 stereochernistry of self-catalyzed allylboration.14–b Previously, we have published a convenient method for palladium-catalyzed synthesis of allylboronic acids6 from allyl alcohols and diboronic acids.7 Allylboronic acids proved to be much more reactive with carbonyl compounds than other allylboronates,8 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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**Introduction**

Reaction of allylboronates with imines is an attractive approach for selective synthesis of functionalized homoallyl amines, which are useful synthetic intermediates in pharmaceautical 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,c Another important issue concerns the stereochemistry of the allylboration. Imines may have E or Z geometry and the isomerization complicates the stereochernical 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,e

![Mechanistic Model](image)

**Mechanistic Model**

\[ \text{E-borate} \rightarrow \text{Zimmerman-Traxler (Z–T) model} \rightarrow \text{syn selectivity} \]

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** Citations and References **

Interestingly, both the $E$ and $Z$ imines gave the same anti-selec-
tivity, which is similar to aldehydes$^5$ and ketones.$^9$ Acyclic
aryl and heteroaryl imines (1a–c) with $E$ geometry react readily
with cinnamyl and octenyl boronics 2a and b in the pres-
ence 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
ratio of 91 : 9. The reaction of geranylboric 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 diastereomic ratio (dr) of 95 : 5.

Cyclic imine$^{10,11}$ 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 $E$-geo-
metry$^{12}$ 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 aldimes. This indicates that
allylboric 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$^{13,14}$ or chiral auxilia-
ries$^{15}$ on the ketimine can be employed to increase the reactivity of
the reactants. Glyoxylate imine 1h also reacted readily with
allylboric acids, opening a new synthetic route$^{16,17}$ for allyl
boronate based stereoselective synthesis of amino acid deriva-
tives. In previous studies$^8$ we have shown that allylboric acids
react readily with ketones. Compound 1i has both keto and
aldime functionalities (entry 12) but only the imine func-
tionality was transformed when 2a was added. The high che-
moselectivity indicates that aldimes react faster with
allylboric 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.

Baty and co-workers$^{18}$ have recently shown that indoles
react with allyl-BF$_3$K derivatives in the presence of BF$_3$ via in situ
formation of allyl-BF$_3$ species. We have found that allylboric
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. Geranylboric
acid 2c reacted with 4a with high selectivity creating adjacent
quaternary and tertiary stereocenters (3g) 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 stereo-
centers (entry 6). The longer reaction times and higher

The most intriguing mechanistic aspect of the above allyl-
boration of $E$ and $Z$ imines is the very fast anti-selective ally-
laction. 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$^{19}$ 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
saldehyde imines 1a–d and 1b–i should undergo rapid isomerization
to the corresponding $Z$-form prior to the allylboration. The
thermal isomerization of aldimes has a high activation energy.$^{19}$ For example, according to the $^1$H NMR spectrum 1a
exists as a stable $E$ isomer in CDCl$_3$ even at elevated tempera-
tures (50 °C). Application of organoboronic acids as organo-
catalysts has attracted great interest in the synthetic
community.$^{20}$ Moreover, Piers and co-workers$^{21}$ have shown that
boron-based Lewis acids, such as B(C$_6$F$_5$)$_3$, are able to
catalyze the isomerization of aldimes. Accordingly, we
assumed that allylboric 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 ally-
lation. As mentioned above, the hydrolysis of aldimes to
aldehydes is much faster in the presence, rather than in the
absence, of allylboric acids. Without the use of molecular
sieves we observed partial hydrolysis of imines 1a–d and 1b–i
leading to the formation of homoallyl alcohols by the allyl-
boration of the hydrolyzed products. The application of molecular
sieves solved this problem but also gave rise to the dehydro-
ization of allylboric acids. This leads to the formation of allyl
boroxines, such as 2a$_b$, from 2a, which are detectable by $^1$H
NMR.$^{22}$ Since allylboric acid 2a allylates $Z$-aldimes (such as 1f)
rapidly, we studied the $E$/$Z$ isomerization of 1a in the presence of
d-arm bora-oxine 5 (Fig. 1), which is obviously not able to allylate
imines. Boroxine 5 was prepared from the corresponding
dialylboronic 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 iso-
merized 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>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acid</th>
<th>Imine</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield $^b$</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>$^2$a</td>
<td>$^1$a</td>
<td>1</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$^2$a</td>
<td>$^1$b</td>
<td>3</td>
<td>84$^d$</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$^2$a</td>
<td>$^1$c</td>
<td>1</td>
<td>72$^c$</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>$^2$a</td>
<td>$^1$d</td>
<td>1</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$^2$a</td>
<td>$^1$e</td>
<td>3</td>
<td>92</td>
<td></td>
</tr>
<tr>
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<td>$^2$b</td>
<td>$^1$d</td>
<td>1</td>
<td>80$^f$</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>$^2$b</td>
<td>$^1$a</td>
<td>3</td>
<td>74$^d$</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>$^2$c</td>
<td>$^1$d</td>
<td>1</td>
<td>66$^{d,e}$</td>
<td></td>
</tr>
<tr>
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<td>$^2$a</td>
<td>$^1$f</td>
<td>1</td>
<td>93</td>
<td></td>
</tr>
<tr>
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<td>$^2$a</td>
<td>$^1$g</td>
<td>24</td>
<td>65</td>
<td></td>
</tr>
<tr>
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<td>$^2$a</td>
<td>$^1$h</td>
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<tr>
<td>12</td>
<td>$^2$a</td>
<td>$^1$i</td>
<td>1</td>
<td>71$^e$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ 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.
Although, the reaction mixture (Fig. 1) contained 100% boroxine \( \text{Ar} = 4\)-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\(^{14}\) 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 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 \textit{anti}-selectivity of the allylboration \textit{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 2ab 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. 1ac. From 7a, the allylboration proceeds \textit{via} chair TS 8a with a low activation barrier (14.9 kcal mol\(^{-1}\)) affording 9a with \textit{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\(^4\) are very similar, which is in line with the identical stereochemistry observed for the two processes. Allylation of the other imine–allyl boroxine complex (7b) or 1a, in

### Table 2: Reaction of indoles with allylboronic acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acid</th>
<th>Indole</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>4a</td>
<td>3</td>
<td>3m</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>3n</td>
<td>1</td>
<td>96/97</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>4a</td>
<td>3</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>4b</td>
<td>1</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2c</td>
<td>4a</td>
<td>24</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>6(^d)</td>
<td>2a</td>
<td>4c</td>
<td>12</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 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.
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 $8c$ 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 stereo-differentiation. 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 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, followed by a fast isomerization to Z-imine before the formation of the product.

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

Fig. 3 Allylboration of 1a with cinnamyl boronic acid 2a. The $\Delta G$ values are given in kcal mol$^{-1}$.

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 (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 boronic acid and allyl chlorosilane based cinnamylation reactions is substantially lower (by 5.7 kcal mol⁻¹) than the corresponding activation barrier involving allylboronic acid 2a.

The higher efficiency of 2a 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) lone-pair to the empty B(p) orbital of boron in boroxine 2a than in allylboronic acid 2a. This leads to a much higher electrophilicity (Lewis acidity) of the boron B(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 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 aldimes 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 have reported E/Z isomerization of 2-aminophenol derived imines during cyanamination of imines with cinnamyl chlorosilanes (Ci-silane analog of 2a). The proposed isomerization is based on the chelation of the hydroxyl unit of 2-aminophenol imine with the siyl group of cinnamyl chlorosilane. An interesting analogy between the allylboron 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 allylboron 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 allylboric 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. 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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Notes and references


