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Stereocontrol in Synthesis of Homoallylic Amines. Syn Selective Direct Allylation of Hydrazones with Allylboronic Acids

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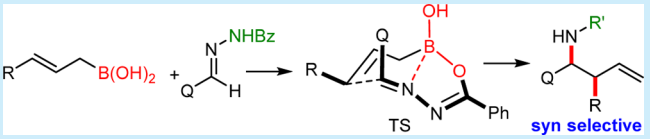
Supporting Information

ABSTRACT: Allylboronic acids directly react with acyl hydrazones, affording homoallylic amine derivatives. The reaction proceeds with very high syn selectivity, which is the opposite of the stereochemistry observed for allylboration of imines. The reaction can be carried out with both aromatic and aliphatic acyl hydrazones. Based on our studies the excellent syn stereochemistry can be explained by chelation control of the acyl hydrazone and the $B(OH)_2$ moiety.



Allylboration is a very important synthetic method,[1] which attracted considerable interest recently because of its high selectivity in allylation of carbonyl compounds[2] and imines.[1a,3] Allylboration is particularly suitable for creation of adjacent tertiary and quaternary stereocenters in one step with very high selectivity. The main application area has been the synthesis of homoallyl alcohols by allylation of carbonyl compounds.[2] In particular, substituted allylboronates, such as allyl-Bpin derivatives, react with very high stereoselectivity with aldehydes. Allylboration of aldehydes usually proceeds with higher selectivity than the alternative allylation reactions with allylsilanes and allylstannanes.[1] The allylboration does not require external additives,[1a] as the activation of the carbonyl group occurs by the boron atom via a Zimmerman−Traxler TS.[4] Therefore, this process is also called "self-activated".

Recently, interest has been focused toward the allylboration of imines.[1a,3] Imines are considered to be less reactive than carbonyl compounds because the carbon atom in an imine is less electrophilic than in a carbonyl group.[1a,5] A further complication arises from the geometry of the imine group, which can influence the reactivity and selectivity of the allylboration. Therefore, application of allylboronic esters, in particular the easily accessible allyl-Bpin compounds, is limited. The "self-activated" reactions of allylboronic esters are very unusual, and they often occur with special imine substrates, which are generated in situ prior to the allylation.[3i,j,6] Thus, the allylboration of stable imines usually requires catalysts and especially activated imine components.[3d−f,7] Many of these catalytic processes are developed to spectacular asymmetric allylation reactions.

In a couple of previous publications we have shown that ketones and imines can be efficiently allylated by allylboronic acids.[8] This reaction does not require any additives (i.e., "self-activated") and the allylation proceeds with a very high level of anti selectivity (Figure 1c) under mild neutral conditions.[8a] We have shown that the allylation of imines proceeds with *E* to *Z* isomerization of the imine, which is catalyzed by the allylboronic acid or allylboroxine substrate.[8a] Thus, the process

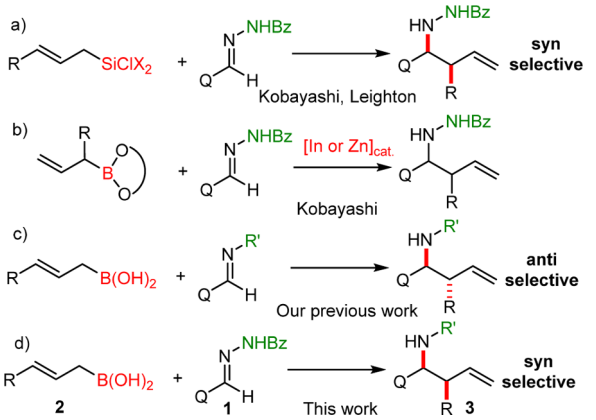


Figure 1. Stereoselective synthesis of homoallylamines.

is suitable for only the anti selective synthesis of homoallylamines.

Therefore, we decided to develop a complementary process for the synthesis of homoallylic amines with syn selectivity. We turned our attention toward the allylation of *N*-benzoylhydrazones, since these reagents are known for syn selective allylations using allyl chlorosilane derivatives (Figure 1a)[9,10] and related useful reactions affording organo-hydrazines.[11]

Kobayashi and co-workers[12] have shown that allylboronic esters do not react directly with *N*-benzoylhydrazones but in the presence of In and Zn catalysts. These processes are supposed to proceed via boron to indium or zinc transmetallation of the substrate, which also involves allylic rearrangement under the allylation process. We hypothesized that acylhydrazones do not undergo *E* to *Z* isomerization prior to the reaction, as do imines (Figure 1c). In addition, we supposed that formation of the syn stereoisomer (Figure 1d)

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might be favored by chelation control, which is exerted by the acylhydrazone group with the $B(OH)_2$ leaving group (see below). We have previously observed[8b] a similar chelation control for the allylation of pyruvic acid derivatives.

We have now found that cinnamylboronic acid **2a** reacts with *N*-benzoylhydrazone **1a** in DMSO at room temperature to give **3a** with excellent regio- and stereoselectivity (Table 1, entry 1). The X-ray structure determination of **3a** showed that the relative configuration of the amino and phenyl groups is syn. Thus, the allylation proceeds with syn selectivity. The reaction of **2a** with the imine analog of **1a** gives[8a] the homoallylamine product with opposite relative stereoselectivity in an anti selective reaction. Aromatic and heteroaromatic hydrazones **1b–e** also reacted with very high regio- and stereoselectivity, giving only a single diastereomeric product (entries 2–5). The selectivity and reactivity with aliphatic allylboronic acid **2b** is as high as with cinnamylboronic acid **2a**, when aromatic hydrazone **1a** was used (entry 6).

As we have reported, the reaction of aliphatic imines with allylboronic acids is problematic.[8a] As allylboronic acids catalyze the hydrolysis of aliphatic imines, their allylation had a very limited synthetic scoop. As alkyl hydrazones are more stable for hydrolysis than the imine analogs, allylation of these substrates could easily be realized for a broad range of substrates (**1f–l**). Thus, isopropyl hydrazone **1f** could easily be allylated with **2a**, affording syn product **3g** (entry 7). The stereochemistry of **3g** was also determined by X-ray diffraction. When sp^2 (entry 8) or sp (entry 9) hybridized carbons are attached to the hydrazone group, the reactions were still fast and very selective.

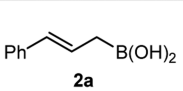
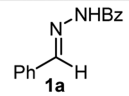
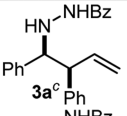
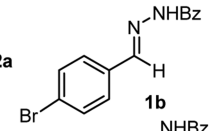
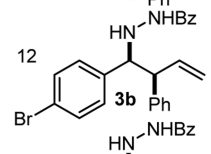
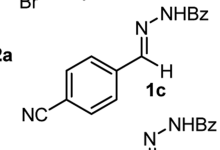
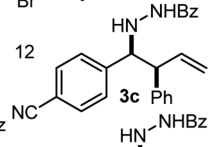
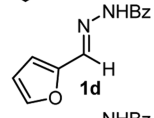
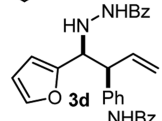
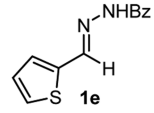
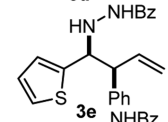
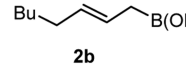
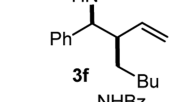
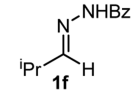
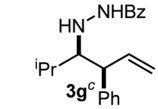
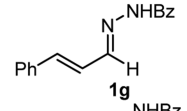
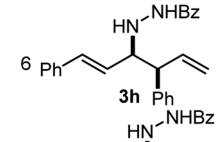
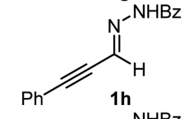
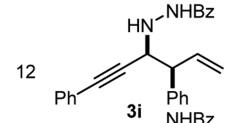
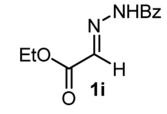
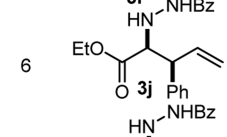
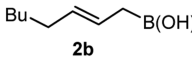
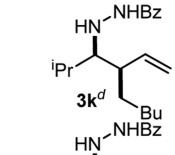
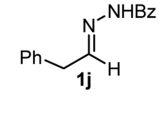
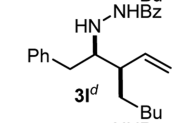
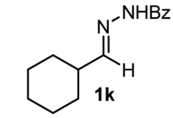
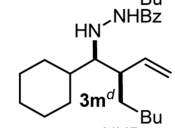
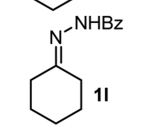
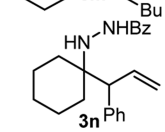
Ethyl glyoxalate derivative **1i** was also reacted with high syn selectivity with **2a** to give α-amino acid derivative **3j**. Conversely, the imine analog of **1i** reacted with clean anti selectivity.[8a] The reaction of aliphatic allylboronic acids with aliphatic imine derivatives is particularly challenging. These reactions could also be easily performed (entries 11–13), but the stereoselectivity was slightly lower. While most of the other reactions (entries 1–10) gave only a single stereoisomer, the reaction of aliphatic boronic acid **1b** with aliphatic hydrazones afforded a mixture of diastereomers in a ratio of 4:1 (entries 11–13). Keto-hydrazones have a more limited synthetic scope than hydrazones derived from aldehydes. Yet, cyclohexanone based hydrazone **1l** undergoes allylation with **2a** affording **3n**. We believe that more sterically demanding keto hydrazones (which do not react in the self-activated process) can be excellent substrates for asymmetric allylation by allylboronic acids (**2**). In these reactions the unreactive hydrazones can probably be activated by chiral additives.[3a]

As expected, the stereoselectivity is dependent on the structure of the alkene. Thus, geranylboronic acid **2c** reacted with excellent syn selectivity with **1a** to give **3o** (Figure 2). On the other hand, the isomeric nerylboronic acid **2d** reacted with **1a** with clean anti selectivity, affording **3p**. Both epimeric products have an adjacent quaternary and tertiary carbon center.

The very high stereoselectivity of the allylation is a remarkable property of the hydrazones. It is particularly interesting that the corresponding imines react with opposite stereoselectivity. Probably all main structural elements of an acyl hydrazone functional group are important for the high level of syn stereoselectivity.

As mentioned above, **1a** reacted smoothly and with very high syn selectivity with **2a**, affording **3a** (entry 1). However, when under the same conditions **1a** was replaced with N-Me derivative **4**, we could not observe any reaction (Figure 3). Similarly, the presence of a carbonyl group is important for the

Table 1. Syn Selective Allylboration of Hydrazones[a]

entry	boronic acid	hydrazone	time (h)	product	yield[b]
1	 **2a**	 **1a**	6	 **3a**[c]	86
2	**2a**	 **1b**	12	 **3b**	85
3	**2a**	 **1c**	12	 **3c**	83
4	**2a**	 **1d**	6	 **3d**	61
5	**2a**	 **1e**	10	 **3e**	78
6	 **2b**	**1a**	15	 **3f**	86
7	**2a**	 **1f**	4	 **3g**[c]	76
8	**2a**	 **1g**	6	 **3h**	91
9	**2a**	 **1h**	12	 **3i**	89
10	**2a**	 **1i**	6	 **3j**	81
11	 **2b**	**1f**	15	 **3k**[d]	86
12	**2b**	 **1j**	12	 **3l**[d]	79
13	**2b**	 **1k**	12	 **3m**[d]	76
14	**2a**	 **1l**	10	 **3n**	78

[a]A mixture of **1** (0.20 mmol), **2** (0.30 mmol), and MS (4 Å) were stirred in DMSO (0.8 mL) at rt. [b]Isolated yield for a single diastereomer. [c]The structure determination is based on X-ray. [d]dr = 4:1.

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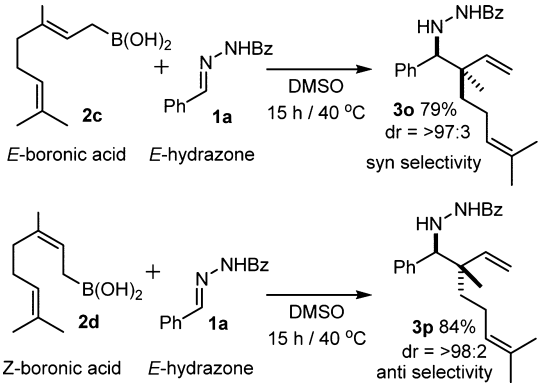

Figure 2. Dependence of the stereochemistry on the structure of alkene.

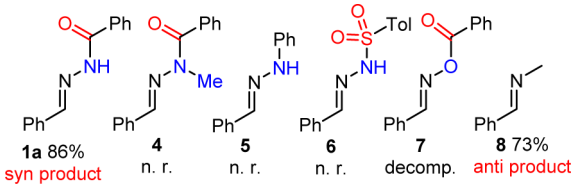

Figure 3. Hydrazone **1a** and its analogs in the allylation reactions.

successful allylation, as **5** did not react. The acyl hydrazone functional group cannot be replaced with a tosyl functional group (**6**) either. Under our standard conditions acyloxime derivative **7** underwent decomposition without any formation of the expected product. However, as reported previously[8a] **8** reacts readily with **2a** under basically the same conditions[13] as **1a**, but the reaction proceeds with opposite stereoselectivity, affording the epimer of **3a**.

As we have shown,[8a] imine **8** undergoes *E* to *Z* isomerization prior to the allylation, and it reacts with anti selectivity with **2a** (Figure 4).

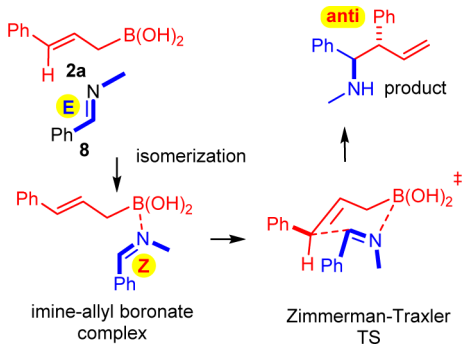

Figure 4. Anti selectivity in allylation of imines.

The *E* to *Z* isomerization of **8** was even catalyzed by arylboronic acid derivatives. Conversely, our studies indicate that under similar reaction conditions[13] **1a** did not undergo *E* to *Z* isomerization. Thus, **1a** reacts with allylboronic acid, such as **2a**, in a syn configuration (Figure 5). However, this would lead to unfavorable 1,3-diaxial repulsions involving the phenyl group of **1a** in the Zimmerman−Traxler TS **11** of the reaction. This thermodynamically unfavorable diaxial interaction can probably be compensated by chelation of the nitrogen and oxygen atoms of the hydrazone functional group to the $B(OH)_2$ group, such as in **9**. The chelation can be reinforced by

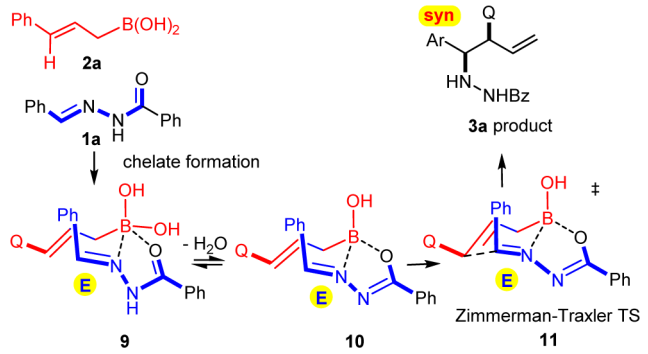

Figure 5. Syn selectivity in allylation of hydrazones.

water elimination to give **10**. The water elimination requires the presence of a proton on one of the nitrogen atoms of **1a**. When this hydrogen is replaced by a methyl group (**4**), the allylation reaction cannot be performed (Figure 3). Furthermore, the absence of the carbonyl group (as in **5**) also leads to an inactive substrate.

It is interesting to point out that the syn selectivity in the allylation of hydrazones by allylchlorosilanes was also explained by a similar chelation control process.[9,10] In addition, Leighton and Huber[14] demonstrated that allylchlorosilanes and imines may also react with anti selectivity due to the in situ *E* to *Z* isomerization of the imine. Apparently, there is a remarkable similarity between the reactivity and selectivity in the allylation with allylchlorosilanes and allylboronic acids. A possible advantage of the synthetic use of allylboronic acids is their high stability against hydrolysis and their simple synthesis[8c] by palladium- catalyzed borylation of allylic alcohols

In summary, we have shown that acylhydrazones react with high regio- and stereoselectivity with allylboronic acids in a self-activated process. The reaction proceeds with a high level of syn selectivity with *γ*-substituted *E*-allylboronic acids and with anti selectivity with *Z*-allylboronic acids. This is exactly the opposite of the stereoselectivity observed for the allylation of imines (cf., Figure 1c and d). Thus, using allylboronic acids (**2**), full control of the relative configuration can be achieved with minor changes of the reaction conditions. The reaction of *γ*-substituted *E*-allylboronic acids (e.g., **2a**−**c**) with *E*- or *Z*-imines (such as **8** and its cyclic analog) give an anti product. While the same *E*-allylboronic acids with *E*-acyl hydrazones analogs (such as **1a**−**e** and **i**) give the corresponding syn products. In several reactions (entry 14 and Figure 2) adjacent tertiary and quaternary stereocenters are created with excellent selectivity. The synthetic scope of the application of acylhydrazones is broader than the imines, as aliphatic acylhydrazones are more stable for hydrolysis than imines. Therefore, aliphatic acylhydrazones can also be easily allylborated with allylboronic acids. The high level of stereocontrol of the reaction of allylboronic acids with imines and acyl hydrazones broadens the synthetic routes to stereodefined homoallylic amines, which are important synthetic motifs in advanced organic synthesis.[3a,c−f,15]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization and crystallographic data (.cif files) are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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