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Selective Formation of Adjacent Stereocenters by Allylboration of Ketones under Mild Neutral Conditions

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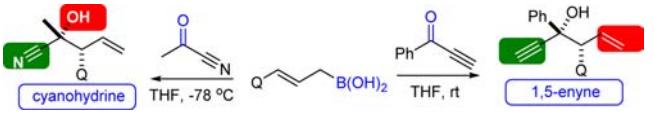
ABSTRACT



Allylboronic acids readily react with a broad variety of ketones, affording homoallylic alcohols with adjacent quaternary and tertiary stereocenters. The reaction proceeds with very high anti stereoselectivity even if the substituents of the keto group have a similar size. α-Keto acids react with syn stereoselectivity probably due to the formation of acyl boronate intermediates. The allylation reactions proceed without added acids/bases under mild conditions. Because of this, many functionalities are tolerated even with in situ generated allylboronic acids.

The selective creation of adjacent quaternary and tertiary stereocenters is a major challenge in organic synthesis. These transformations can be achieved by allylation of ketones by properly functionalized allyl-metal reagents.[1] A successful method has a number of important requirements: (i) the reagents need to be sufficiently reactive to allylate ketones; (ii) the allyl metal species have to be configurationally stable; and (iii) a high level of predictable stereodifferentiation is required in the TS of the allylation. Because of these reactivity (i) vs selectivity (ii and iii) requirements, relatively few allyl-metal reagents are suitable for stereo- and regioselective allylation of a wide variety of ketones. In recent years efficient methods have appeared based on organoboron,[2] indium,[1d,3] titanocene,[4] zinc,[5] aluminum,[6] and tin[7] reagents. The high reactivity of the allyl-metal reagents creates some problems in the functional group tolerance of the substrates or in the products. For example, In[8] and Zn[5] are incompatible with nitro or cyano groups; Zn, Mg, and Li reagents create basic conditions.[5b,c,9] Another problem is that in many cases the allyl-metal reagents cannot be isolated because of low thermal stability or other stability issues. Thus, the in situ generation of the allyl-metal species (such as In, Ti, Zn, and Al species) may impose limitations to the reaction conditions of the allylation reactions, such as, for example, the reaction temperature, solvent, or application of various additives. We have recently shown[2a] that allylboronic acids react with ketones without any additives, such as Lewis

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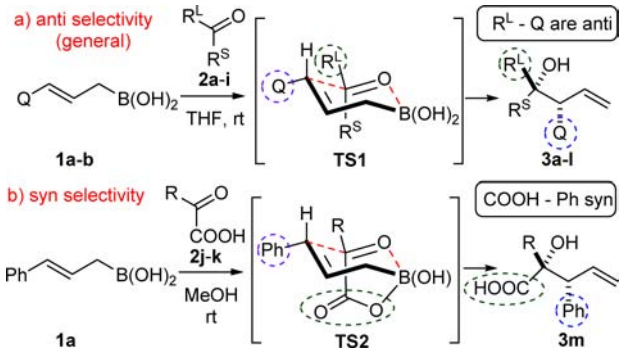
acids or bases. This is a remarkable property, as most of the commonly used allylboronates, such as allyl-Bpin and allyl-BF_3K, are inefficient for allylation of ketones in the absence of Lewis acids or other activators.[2c−e,g] Allylboronates have two particularly important attractive features for allylation of carbonyl compounds. These compounds do not undergo facile metallotropic rearrangements, such as allylzinc,[5a,10] allyltitanocene,[4a] allylalumiunium,[9] or allyl alkylborane species (e.g., allyl-9-BBN).[11] Thus, the regio- and stereochemical integrity of the allyboronate reagents can be maintained even at elevated temperatures.[1b,c,9,11a] Moreover, the reactants form tight six-membered ring TSs, which allow a very high level of stereodifferentiation.[9,12] In this study, we disclose our results on the application of allylboronic acids (**1**) for allylation of a wide variety of ketones **2**. We have focused mainly on applications, in which the allylboration of ketones may complement the scope of the previously described In, Ti, Zn, Al, and Sn species based methods. An obvious advantage of the allylboronic acid based processes is that these allylating reagents can be generated from allyl alcohols and diboronic acid[13] in a Pd-catalyzed process.[2a,b]

Scheme 1. Stereoselectivity in Allylboration of Ketones (R^L = large, R^S = small substituent)



Thus, allyl halogenide or allyl sulfide species precursors used to generate In, Ti, Zn, Al, and Sn species are not required. Allylboronic acids are highly oxygen sensitive species but can be isolated by precipitation from the reaction mixture and can be stored under inert conditions.[2a]

Previously we have shown[2a] that acetophenone reacts with high selectivity with cinnamyl and 3-alkyl substituted allylboronic acids **1a**−**b** in dry THF at rt. We have now found that α-haloacetophenones **2a**−**c** react with **1a**−**b** under similar conditions with excellent regio- and stereoselectivity (Table 1, entries 1−4). The reactions proceeded with clean anti stereoselectivity (Scheme 1a) probably via a six-membered ring TS, in which the aryl group (R^L) is equatorial and the halomethyl (R^S) group is axial.[9,12] The stereochemistry of the reaction was confirmed by the X-ray structure determination of **3c**. We detected only a single anti stereoisomer in the crude reaction mixture of the processes with **1a** as an allyl source (entries 1−3); however with **1b**, a small amount of the syn diastereomer (dr 97:3) was also formed (entry 4). The reaction tolerated amide and cyanide functionalities, and the bromo- and chlorohydrine products could be isolated. Knochel et al.[5c] published an excellent method for the transformation of α-bromo ketones with cinnamyl zinc derivatives. However, under the basic conditions of this reaction the bromohydrine products underwent spontaneous cyclization to give epoxides.[5c]

We have also studied other base sensitive allylation reactions. Alkynyl ketone **2d** was reacted with **1a** and **1b** (entries 5−6). Similarly to the α-halo ketone reactions (entries 1−4), when **2d** was reacted with cinnamyl boronic acid **1a** (entry 5) a single regio- and stereoisomer was observed in the crude reaction mixture, while for alkyl derivative **1b** (entry 6) a small amount of the other diastereomer was also formed. Because of the mild, neutral reaction conditions the alkyne functionality in the products (**3e**−**f**) remained unchanged. Thus the reaction can be employed for the synthesis of stereodefined 1,5-enynes. Most of the previously described methods for the allylmetalation of ketones are probably inefficient for the synthesis of enynes, such as **3e**−**f**, as the basic conditions and/or the reactive low-valent metal species may be incompatible with the terminal alkyne functionality of **2d** (or of the products). Brown et al.[14] reported a single reaction of the parent allyl-$B(Ipc)_2$ with 3-butyn-2-one to obtain a 1,5-enyne derivative. However, as far as we know, the presented reactions (entries 5−6) are the first examples for the one-step synthesis of stereodefined 1,5-enynes with adjacent quaternary and tertiary stereocenters (e.g., **3e**−**f**).

Considering the high stability of products **3e**−**f** under the mild, neutral conditions of the allylboration, we wished to study the allylmetalation of acyl cyanide **2e**, which is isoelectronic with **2d** (entry 7). To our delight, **2e** reacted with high selectivity/reactivity with **1a** and **1b** providing cyanohydrines **3g**−**h**. Cyanohydrines, such as **3g**−**h**, are sensitive species, which easily undergo reversible decomposition even under mild basic conditions. Therefore, synthesis of stereodefined species (e.g., **3g**−**h**), in which the cyano group is attached to the quaternary center, is challenging. For example, the indium-mediated allylation of **2e** gives the corresponding ketones[15] probably because of HCN elimination. We wanted to study the degree of stereodifferentiation in the allylation of ketones and therefore performed reactions with acetyl cyanide **2f** (entry 9). In this substrate the two groups on the ketone (Me and CN) are similar in size. Surprisingly, the allylation reaction

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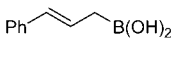
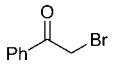
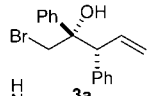
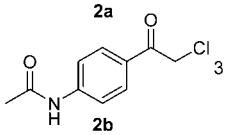
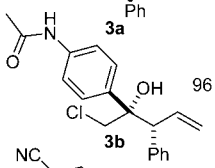
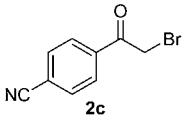
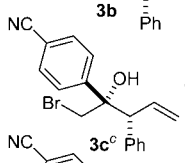
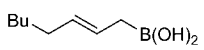
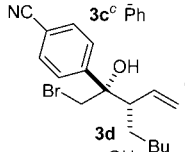
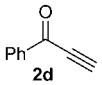
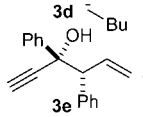
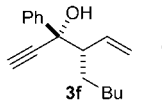
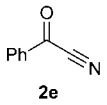
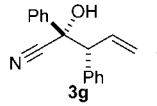
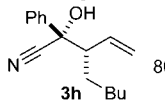
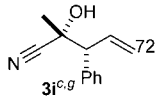
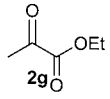
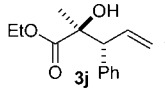
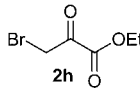
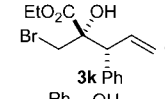
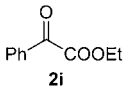
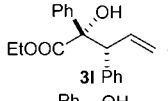
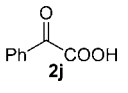
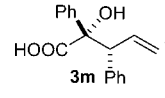
Table 1. Reaction of Allylboronic Acids with Ketones[a]

entry	boronic acid	ketone	time (h)	product	yield (%)[b]
1	 **1a**	 **2a**	8	 **3a**	97
2	**1a**	 **2b**	3	 **3b**	96
3	**1a**	 **2c**	3	 **3c**[c]	83
4	 **1b**	**2c**	1	 **3d**	92[d]
5	**1a**	 **2d**	3	 **3e**	85
6	**1b**	**2d**	3	 **3f**	93[d]
7	**1a**[e]	 **2e**	>1	 **3g**	86
8	**1b**	**2e**	1	 **3h**	80[d]
9	**1a**	 **2f**	1[f]	 **3i**[c,g]	72
10	**1a**	 **2g**	3	 **3j**	70
11	**1a**	 **2h**	3	 **3k**	88
12	**1a**	 **2i**	18	 **3l**	87
13	**1a**[e]	 **2j**	0.5[h]	 **3m**	72

[a] Compound **1** (0.39 mmol) and **2** (0.30 mmol) were stirred in THF (0.6 mL) at rt. Unless indicated the products are single diastereomer. [b] Isolated yield. [c] Based on X-ray. [d] dr = 97:3. [e] 0.36 mmol of **1a** was used. [f] The reaction is performed at −78 °C to rt. [g] dr = 9:1. [h] Solvent MeOH (0.6 mL).

proceeded with high selectivity (dr 9:1) providing **3i** as the major diastereomer. The structure of **3i** was confirmed by X-ray diffraction (via its ester derivative). The structure of **3i** reveals that in the transition state (Scheme 1a, **TS1**) the CN group is axial (R^S) and the methyl group is equatorial (R^L). The stereochemical integrity of the cyanohydrine structure was maintained under the mild and neutral reaction conditions applied. Elimination of HCN was not observed either. We have found only a single literature example[16] for the preparation of a homoallyl cyanohydrine. In the reported process,[16] the parent allyl-$SiMe_3$ was reacted with acyl cyanide **2f** in the presence of $TiCl_4$. However, the synthesis of stereodefined quaternary cynohydrines (such as **3g**−**i**) by allylation of acyl cyanides (such as **2e**−**f**) was not reported before.

Ethyl pyruvate **2g** (which is a close analog of **2f**) could also be allylated in very high selectivity (entry 10). As expected, the keto group could be selectively functionalized in the presence of the ester group. The product was obtained as a single stereoisomer **3j** indicating that the ester group is probably equatorial (R^L) and the Me group is axial (R^S) in the transition state of the reaction (Scheme 1a, **TS1**). A similar selectivity was reported by Yamamoto et al.[17] for the allylation of **2g** by crotyl-9-BBN. Ethyl pyruvate derivatives **2h**−**i** also reacted with similarly high chemo-, regio-, and stereoselectivity as **2g**. Surprisingly, phenylglyoxylic acid **2j**, which is closely related to **2i**, reacted with poor stereoselectivity (dr 1:1) under our standard conditions in THF. After optimization, we found that the reaction is highly selective and very fast in MeOH (instead of THF). This was a surprising finding, as the allylation reactions with other substrates, in particularly with acetophenone[2a,b] and derivatives (**2a**−**d**), were strongly retarded or inhibited by traces of protic solvents, such as MeOH or water. Because of this,[2b] we could not use one-pot conditions for the generation of allylboronates for the allylation of ketones (see below). We reasoned that in MeOH the reaction proceeds with the formation of acylboronate type intermediates (Scheme 1b). Formation of the acylboronate increases the electrophilicity of the boron and firmly orientates the ketone in the transition state (Scheme 1b, **TS2**) of the allylation affording highly stereoselective allylation.

Allylboration of carbonyl compounds with in situ generated boronates is a useful and widely applied one-pot procedure.[2b,f,18] The Pd-catalyzed borylation to obtain allylboronic acids requires application of MeOH or water (Table 2).[2a] For example, **3m** could also be prepared via in situ generated **1a** using cinnamyl alcohol **4a** as an allyl source (Table 2, entry 1) without a significant drop in the yield. Pyruvic acid **2k** itself could also be allylated using in situ generated **1a** (entry 2). The stereoselectivity of the reaction indicated that the carboxyl group is axial and the methyl group (R) is equatorial in **TS2** of the reaction (Scheme 1b). Thus full stereocontrol can be achieved for the allylation of pyruvic acid and its derivatives. Ethyl pyruvate **2g** is allylated by **1a** with anti selectivity (Scheme 1a) to give **3j** (Table 1, entry 10), while allylation

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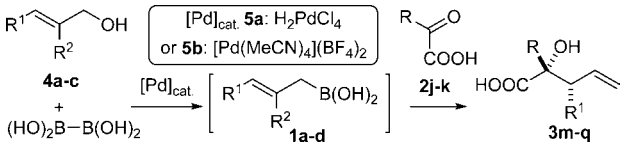
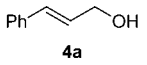
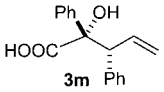
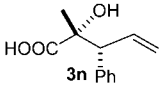
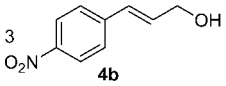
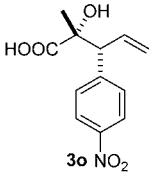
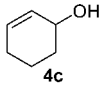
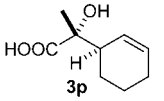
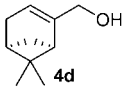
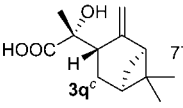
Table 2. One-Pot Borylation–Allylation Sequence Involving Allyl Alcohols and Ketoacids[a]



entry	allyl alcohol	conditions (step 1)	ketone	product	yield (%)[b]
1	 4a	**5a** (1 mol %) MeOH, 18 h	**2j**	 **3m**	60
2	**4a**	**5a** (1 mol %) MeOH, 18 h	**2k**	 **3n**	83
3	 **4b**	**5a** (5 mol %) MeOH/DMSO 0.5 h	**2k**	 **3o**	66
4	 **4c**	**5b** (5 mol %) DMSO/H_2O 3 h	**2k**	 **3p**	65
5	 **4d**	**5b** (5 mol %) DMSO/H_2O 1 h	**2k**	 **3q**[c]	77

[a] Compounds **1a**–**d** were generated by addition of diboronic acid (0.36 mmol) to allyl alcohols **4** (0.30 mmol) in the presence of Pd-catalyst **5a**–**b**[2a] followed by addition of **2j**–**k** (0.24 mmol). [b] Isolated yield. [c] X-ray structure. dr = 98:2.

of pyruvic acid **2k** (using MeOH as solvent) proceeded with syn selectivity (Scheme 1b) to give the epimeric acid **3n** (Table 2, entry 2). Comparison of the NMR data of **3j** with those of the ethyl ester of **3n** confirmed that two different epimers are formed selectively from **2k** and its ethyl ester **2g**. Kabalka et al.[19] studied the allylation of **2k** with allyl-B(O^iPr)$_2$ in the presence of Et_3N. The fast allylation reaction suggested that the process took place via a bicyclic transition state similar to **TS2** in Scheme 1b. Interestingly, our reactions (entries 1–5) did not require the use of Et_3N (or other bases) to obtain the acyl boronate intermediates. This is probably due to the higher reactivity of allylboronic acids compared to allyl-B(O^iPr)$_2$ to form acyl boronates (**TS2**) from pyruvic acid and derivatives. The formation of chelating intermediates with pyruvic acid was also reported for allyl indium mediated reactions.[1d,3a] These reactions also proceed with syn selectivity, similarly to the process in Scheme 1b. Allylboronic acid formed from nitro cinnamyl alcohol **4b** is very reactive and thus cannot be isolated without substantial purification losses. However, in situ generation of the allylboronic acid followed by the reaction with **2k** gives the final product with excellent selectivity (entry 3) and the nitro group survives the reaction unchanged. The allylboronic acid derived from **4c** resists precipitation, as it dissolves readily in both organic solvents and in water.[2a] However, the reaction of in situ generated allylboronic acid from **4c** with **2k** furnishes the corresponding homoallylic alcohol **3p** with very high selectivity (entry 4). Finally, we wished to demonstrate that chirality transfer from myrtenol **4d** can be easily performed by the above-described one-pot sequence (entry 5). Thus rapid generation of the corresponding chiral allylboronic acid from **4d** followed by the addition of pyruvic acid **2k** provides **3q** with excellent stereoselectivity including adjacent quaternary and tertiary stereocenters. The structure of **3q** was confirmed by X-ray crystallography.

In summary, we have shown that the application of allylboronic acids complements the synthetic scope of the allylation of ketones based on organoboron, indium, titanocene, zinc, aluminum, and tin reagents. The usefulness of the application of allylboronic acids is based on their high reactivity, stereochemical integrity (even at elevated temperatures), and highly predictable stereoselectivity. An important factor is that allylboronic acids react with various ketones without Lewis acid or base additives under mild neutral conditions. The synthetic highlights are the preparation of base/acid/redox sensitive products, which have been formed with remarkably high stereoselectivity. The easy formation of acylboronates (such as **TS2**, Scheme 1b) creates opportunities for the synthesis of quaternary homoallylic alcohols with syn stereoselectivity, while the usual reactions proceed with anti selectivity (Scheme 1a). At least for α-keto acids the allylation process can be integrated with the generation of allyl boronates. The reaction proceeds with excellent stereoselectively, and thus it could be a valuable new tool in natural product synthesis via allylboration.[18e,20]

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Supporting Information Available. 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.

The authors declare no competing financial interest.

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