Aldehyde allylation with allylboronates providing α-addition products†

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$Zn(OH)_2$-catalyzed allylation reactions of allylboronates with aldehydes proceeded smoothly in aqueous media; when α-substituted allylboronates were employed, the α-addition products were obtained exclusively, and *syn*-adducts were formed selectively in most cases; the use of $Zn(OH)_2$ with dmp (ligand) in aqueous media is the key to these reactions.

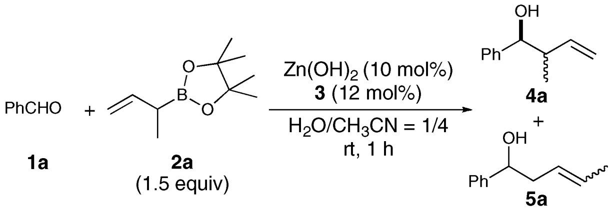
Allylation is one of the most important and widely-used carbon–carbon bond-forming reactions in organic chemistry. While several allylating reagents have been extensively studied, allylsilanes,[1] allylstannanes[2] and allylborons[3–6] are among the most popular species especially from a synthetic utility viewpoint. As for the reactions with aldehydes, allylsilanes and allylstannanes often react in the presence of Lewis acids *via* acyclic transition states affording predominantly *syn*-products.[1,2] Allylborons are more reactive than allylsilanes and allylstannanes. They react with aldehydes spontaneously *in the absence of a catalyst via* cyclic transition states due to the Lewis acidity of boron, to give *syn*- and *anti*-products depending on the geometry of starting allylborons.[3–5] Lewis acid-catalyzed reactions of allylboronates with aldehydes have also been reported.[6] While boron reagents have been established as one of the most reactive and non-toxic reagents, *γ-addition products have been obtained in almost all cases in the reactions with aldehydes*.[7] We report here that α-addition products are obtained exclusively by the reactions of allylboronates with aldehydes in the presence of a catalytic amount of zinc hydroxide [$Zn(OH)_2$] with a ligand in aqueous media.

In an earlier report,[8] we detailed that allylboronates reacted with hydrazono esters in aqueous media in the presence of zinc fluoride–chiral diamine complex to afford allylglycine derivatives in high yields with high enantioselectivities. In that work, α-addition products were obtained using α-substituted allylboronates. We envisioned that the system might be expanded to very rare, α-selective aldehyde allylation, although the difference in reactivity between hydrazono esters and aldehydes with allylboronates was critical; namely, hydrazono esters do not react with allylboronates without catalysts, while aldehydes react with allylboronates spontaneously without catalysts as mentioned above.

First, pinacol allylboronate was treated with benzaldehyde in the presence of 10 mol% of $Zn(OH)_2$ in H_2O–CH_3CN (1/4). The reaction proceeded smoothly to afford the desired homoallylic alcohol in high yield. However, since it was difficult to distinguish catalyzed- and non-catalyzed reactions at this stage, we then examined the reaction of α-methyl-substituted allylboronate **2a** with benzaldehyde (Table 1). When the reaction was carried out *in the absence of $Zn(OH)_2$*, γ-addition product **5a** was obtained selectively (entry 1, non-catalyzed reaction), while a mixture of α-adduct **4a** and γ-adduct **5a** (α/γ = 45/55) was produced in the presence of $Zn(OH)_2$ (entry 2). It was noted that the very rare α-addition product was formed in the presence of $Zn(OH)_2$, although the selectivities (both α/γ and diastereoselectivity of **4a**) were not high. We further examined various parameters and finally uncovered interesting ligand effects. When $Zn(OH)_2$ was combined with diamine **3a**, the *syn*/*anti* ratio of **4a** was improved albeit with moderate α/γ selectivity (entry 3). The α/γ selectivity was improved significantly in the presence of $Zn(OH)_2$ with 2,9-dimethyl-1,10-phenanthroline (**3c**, dmp), and the *syn*/*anti* ratio was also high (entry 5). Furthermore, when the reaction was conducted in dry CH_3CN, γ-adduct **5a** was obtained exclusively (entry 6). Thus, it was revealed that the use of water is essential for the α-selectivity.[9]

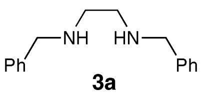
Several aldehydes were then treated with α-substituted allylboronates in the presence of 5 mol% of $Zn(OH)_2$–**3c** in H_2O–CH_3CN (1/4) (Table 2). It is noted that in all cases only α-adducts **4** were obtained in high yields. To the best of our

Table 1 Effect of $Zn(OH)_2$, ligands and water

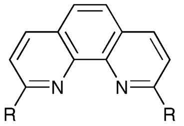


Entry	Ligand (3)	Yield (%)	4a/5a	*Syn*/*anti* (4a)
1[a]	—	77	5/95	—
2	—	86	45/55	70/30
3	**3a**	81	81/19	96/4
4	**3b**	84	33/67	78/22
5	**3c**	82	>98/<2	93/7
6[b]	**3c**	61	<2/>98	—

[a] In the absence of $Zn(OH)_2$. [b] In dry CH_3CN.



3a



3b: R=H
3c: R=Me (dmp)

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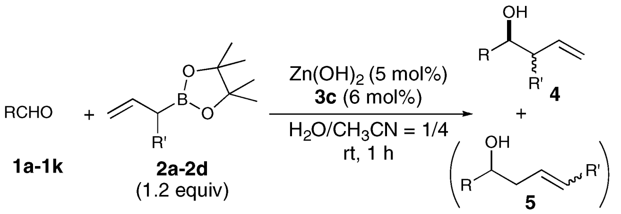
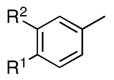
Table 2 $Zn(OH)_2$–**3c**-catalyzed allylation reactions in aqueous media



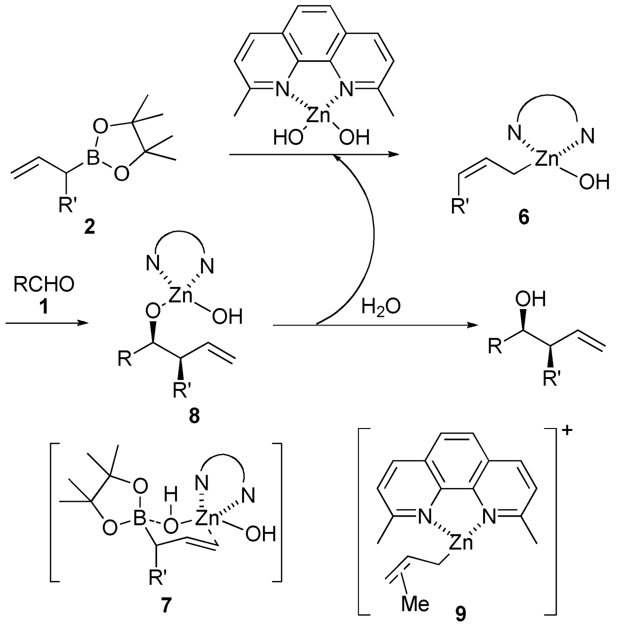
Entry	R (aldehyde)	2 (R′)	Yield (%)	4/5	*Syn*/*anti* (4)
1	 **1a**: R^1 = H, R^2 = H	**2a** (Me)	83	$>98/<2$	94/6
2	**1b**: R^1 = CH_3, R^2 = H	**2a**	85	$>98/<2$	93/7
3	**1c**: R^1 = OCH_3, R^2 = H	**2a**	82	$>98/<2$	93/7
4	**1d**: R^1 = NO_2, R^2 = H	**2a**	91	$>98/<2$	96/4
5	**1e**: R^1 = Br, R^2 = H	**2a**	92	$>98/<2$	94/6
6	**1f**: R^1 = H, R^2 = OCH_3	**2a**	92	$>98/<2$	91/9
7	1-Naphthaldehyde (**1g**)	**2a**	91	$>98/<2$	97/3
8	4-Pyridinecarboxaldehyde (**1h**)	**2a**	85	$>98/<2$	93/7
9	2-Thienylcarboxaldehyde (**1i**)	**2a**	84	$>98/<2$	86/14
10	5-Methyl-2-furaldehyde (**1j**)	**2a**	85	$>98/<2$	77/23
11	3-Phenylpropionaldehyde (**1k**)	**2a**	84	$>98/<2$	50/50
12	**1a**	**2b** (Et)	89	$>98/<2$	89/11
13	**1a**	**2c** (Bu)	81	$>98/<2$	88/12
14	**1a**	**2d** (*i*-Bu)	85	$>98/<2$	90/10

knowledge, during a relatively long history of allylboron chemistry, this is a very rare case where α-addition products are obtained exclusively from aldehydes.[7,10] As for the *syn*/*anti* selectivities of **4**, high *syn*-selectivities were obtained in the reactions of **2a** with aromatic aldehydes (entries 1–7). While the *syn*/*anti* selectivities decreased slightly for heteroaromatic aldehydes (entries 8–10), a mixture of *syn*- and *anti*-**4** was obtained from 3-phenylpropionaldehyde (entry 11).

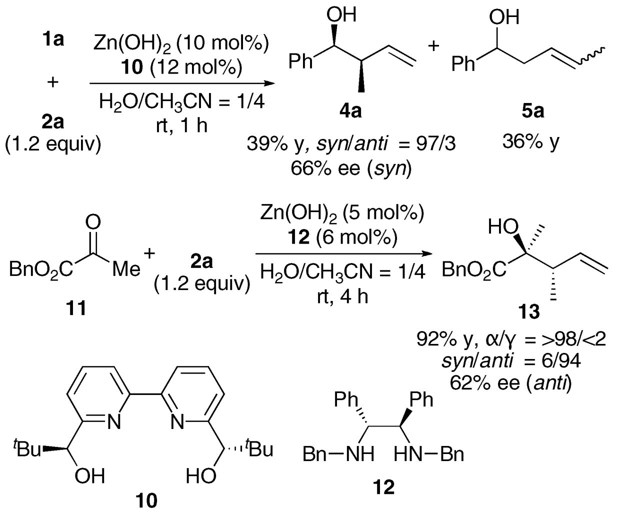
Regarding the α-substituted allylboronates, not only **2a** but ethyl- (**2b**), butyl- (**2c**), and *i*-butyl- (**2d**) substituted allylboronates reacted smoothly to afford α-adducts **4** exclusively in high yields with high *syn*-selectivities (entries 12–14).

On the mechanism of this α-selective allylation (Scheme 1), we assume that the key is conversion of allylboronates **2** into *Z*-allylzincate species **6** (*via* **7**, γ-addition), which could immediately react with aldehydes **1** to afford **8** (*via* γ-addition); thus, two γ-additions could result in providing α-addition products. Water could facilitate regeneration of the zinc catalyst from **8**. ESI-mass spectra of a mixture of $Zn(OH)_2$ with **3c** and **2a** (see Table 1) showed a signal that corresponded to **9**, although the position and geometry of the methyl group were unknown. According to the mechanism proposed, it should be noted that the Zn-catalyzed reactions proceed much faster than background (non-catalyzed) reactions.[11]

We then surveyed the possibility of asymmetric catalysis using $Zn(OH)_2$ and chiral ligands (Scheme 2). In the presence of $Zn(OH)_2$ (10 mol%) and chiral bipyridine ligand **10** (12 mol%),[12] benzaldehyde (**1a**) reacted with **2a** in



Scheme 1 Possible formation of allylzincate **6**.



Scheme 2 Preliminary results of asymmetric catalysis.

H_2O–CH_3CN (1/4) to afford the α-addition product **4a** in 39% yield with high *syn*-selectivity, and the enantiomeric excess of the *syn*-adduct was 66%. In this reaction, a certain amount of γ-adduct **5a** was also produced (36% yield). On the other hand, α-ketoester **11** reacted with **2a** smoothly in the presence of $Zn(OH)_2$ (5 mol%) and chiral diamine ligand **12** (6 mol%)[13] to afford the corresponding α-addition product **13**[14] in 92% yield. No γ-addition product was produced under these conditions. It is noteworthy that the *anti*-adduct was obtained in high diastereoselectivity with promising enantiomeric excess.

In summary, we have found very rare, α-selective allylation reactions of allylboronates with aldehydes. The use of $Zn(OH)_2$ with ligand **3c** as a catalyst in aqueous media is a key in these reactions. Preliminary results of asymmetric catalysis using chiral ligands have also been demonstrated. We are now investigating the role of the ligand and water toward full elucidation of the mechanism of these unique α-selective allylation reactions of allylboronates with aldehydes.

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