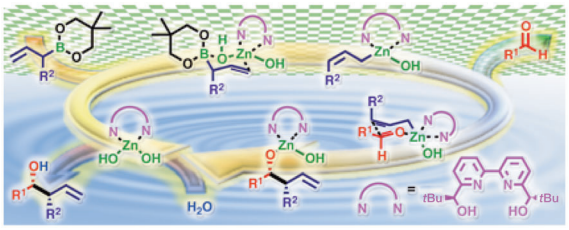
FULL PAPER



Still waters run deep: The $Zn(OH)_2$-catalyzed allylation of aldehydes with allylboronates in aqueous media exclusively afford the α-addition products. This reaction was also applied to alkylallylation, chloroallylation, and alkoxyallylation reactions. The role of water is discussed.

Allylation

Shū Kobayashi, Toshimitsu Endo, Takumi Yoshino, Uwe Schneider, Masaharu Ueno* ____ ▮▮▮▮–▮▮▮▮

Allylation Reactions of Aldehydes with Allylboronates in Aqueous Media: Unique Reactivity and Selectivity that are Only Observed in the Presence of Water

DOI: 10.1002/asia.201300440

Allylation Reactions of Aldehydes with Allylboronates in Aqueous Media: Unique Reactivity and Selectivity that are Only Observed in the Presence of Water

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Abstract: $Zn(OH)_2$-catalyzed allylation reactions of aldehydes with allylboronates in aqueous media have been developed. In contrast to conventional allylboration reactions of aldehydes in organic solvents, the α-addition products were obtained exclusively. A catalytic cycle in which the allylzinc species was generated through a B-to-Zn exchange process is proposed and kinetic studies were performed. The key intermediate, an allylzinc species, was detected by HRMS (ESI) analysis and by online continuous MS (ESI) analysis. This analysis revealed that, in aqueous media, the allylzinc species competitively reacted with the aldehydes and water. An investigation of the reactivity and selectivity of the allylzinc species by using several typical allylboronates (**6a**–**6d**) clarified several important roles of water in this allylation reaction. The allylation reactions of aldehydes with allylboronic acid 2,2-dimethyl-1,3-propanediol esters proceeded smoothly in the presence of catalytic amounts of $Zn(OH)_2$ and achiral ligand **4d** in aqueous media to afford the corresponding *syn*-adducts in high yields with high diastereoselectivities. In all cases, the α-addition products were obtained and a wide substrate scope was tolerated. Furthermore, this reaction was applied to asymmetric catalysis by using chiral ligand **9**. Based on the X-ray structure of the Zn-**9** complex, several nonsymmetrical chiral ligands were also found to be effective. This reaction was further applied to catalytic asymmetric alkylallylation, chloroallylation, and alkoxyallylation processes and the synthetic utility of these reactions has been demonstrated.

Keywords: aldehydes · allylation · C–C bond formation · water chemistry · zinc

Introduction

In modern organic chemistry, organic reactions are generally conducted in organic solvents. The use of water as a reaction medium is very rare, even though water is safe, environmentally benign, and inexpensive compared with organic solvents. Today's environmental consciousness befits the consideration of water as a solvent by both industrial and academic chemists.[1] However, there are two major obstacles to be surmounted for performing organic reactions in water: First, many reactive substrates, reagents, and catalysts are decomposed or deactivated by water (stability issue) and second, most organic substances are insoluble in water (solubility issue). On the other hand, unique reactivities and selectivities that are not observed in organic solvents have been reported in aqueous media.[2]

The allylation of aldehydes to provide homoallylic alcohols is one of the most-important carbon–carbon bond-forming reactions in organic synthesis.[3] To date, several allyl-metal/metalloid reagents have been developed for this transformation; of these reagents, allylboron reagents have been established as being among the most useful[4] because they are less toxic and more reactive than other allyl-metal/metalloid reagents, such as allylsilanes[4b,5] and allyltins.[6] The first allylboration of aldehydes was reported by Mikhailov and Bubnov in 1964 by using triallylborane.[7] Two years later, Favre, Gaudemar, and co-workers reported the allylation of aldehydes by using allylboronic ester.[8] Many fundamental studies were carried out by Hoffmann and co-workers, who reported regio- and diastereoselective crotylation reactions of both (*E*)- and (*Z*)-crotylboronates[9] and the regioselective allylation of α-substituted allylboronates.[10] The reactions proceeded without catalysts on the basis of a Lewis acidic boron atom through Zimmerman's six-membered transition states to exclusively afford γ-addition products.[11] Asymmetric allylation reactions that employ chiral allylboron reagents with auxiliaries have been reported by the groups of Hoffmann,[12] Roush,[13] Corey,[14] Reetz,[15] Masamune,[16] Brown,[17] and Soderquist.[18] Although high diastereo- and enantioselectivities were attained, stoichiometric amounts of the chiral sources were needed, even though some chiral sources could be recovered. More re-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201300440.

cently, Lewis acid catalyzed allylboration reactions were independently reported by Hall and co-workers[19,20] and by Miyaura and co-workers.[21] These allylation reactions were accelerated by catalytic amounts of external Lewis acids. Chiral Lewis acid catalyzed allylation reactions of aldehydes with allylboronates have also been developed to achieve asymmetric synthesis by using catalytic amounts of chiral sources. Jain and Antilla reported chiral-phosphoric-acid-catalyzed highly enantioselective allylboration reactions.[22]

One of the most characteristic features of the allylboration reaction is that the γ-addition step proceeds through Zimmerman's six-membered transition states to afford high stereoselectivity. To the best of our knowledge, there have been no reports of α-selective allylboration reactions with aldehydes, except for one example of the rearrangement of the γ-addition products.[23] The use of chiral Lewis or Brønsted acids in asymmetric synthesis is promising because only catalytic amounts of chiral sources can provide large amounts of optically active compounds.[24] On the other hand, thus far, most of the catalytic asymmetric reactions have been performed at low temperatures (mostly at −78 °C), because the allylboration reactions of aldehydes proceed spontaneously without catalysts.[25] Moreover, whereas the use of these reactions resulted in high yields with high diastereo- and enantioselectivities, they were performed under anhydrous conditions in many cases, because most chiral catalysts are easily decomposed in the presence of water. Furthermore, to the best of our knowledge, only the crotylation (α-methylallylation) reaction has been reported among the catalytic asymmetric α-alkylallylboration reactions of aldehydes.[26]

In 2008, we reported the ZnF_2-catalyzed asymmetric allylation reactions of acylhydrazones with allylboronates in aqueous media:[27] The acylhydrazones reacted with α-substituted allylboronates in the presence of catalytic amounts of ZnF_2 and a chiral diamine ligand to exclusively afford α-addition products. This report is a very rare example of the reaction of allylboronates with electrophiles to afford α-addition products.[23] Moreover, it was found that the use of water (aqueous media) was essential for this reaction, because no reaction occurred in anhydrous organic solvents. We became very interested in these unique reactivities and selectivities in aqueous media and we decided to investigate more-general reactions of aldehydes with allylboronates.[28,29]

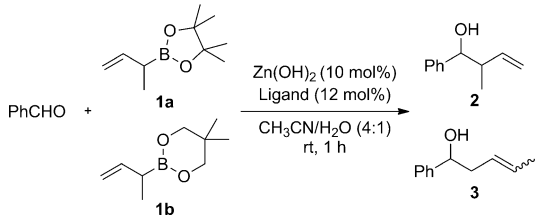
Herein, we report a full, detailed account of our efforts to develop a Zn-catalyzed aldehyde allylation reaction in an aqueous environment. We focus on the mechanistic aspects and an elucidation of the details of this process, with an emphasis on the conceptual and mechanistic details rather than the practical utility of the reaction.

Results and Discussion

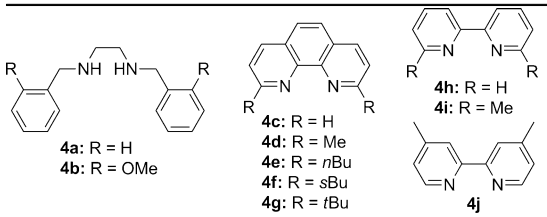
Initial Study of α-Selective Addition Reactions

In the ZnF_2-catalyzed asymmetric allylation of acylhydrazones with allylboronates, $Zn(OH)_2$ was assumed to be the "real" catalyst after an investigation of the catalytic cycle. $Zn(OH)_2$ is an inexpensive and ubiquitous compound that is very stable in water. Given these features, $Zn(OH)_2$ appeared to be a suitable catalyst in aqueous media and, hence, we examined the reaction of α-methyl-substituted allylboronate **1a** with benzaldehyde in the presence of 10 mol% $Zn(OH)_2$ in CH_3CN/H_2O (4:1).[28] The reaction proceeded at room temperature to afford a mixture of α-addition product **2** and γ-addition product **3** (**2**/**3** = 45:55) in 86% yield (Table 1, entry 1). The reaction of another allylboronate (**1b**) with benzaldehyde also proceeded smoothly under the same reaction conditions to afford α-addition product **2** with higher selectivity (**2**/**3** = 95:5) in 94% yield (Table 1, entry 2). Furthermore, we found a remarkable effect of the ligand on the α selectivity and diastereoselectivity of compound **2**: Both the α selectivity and *syn* selectivity of compound **2** increased significantly by using ligands **4a**, **4b**, **4d**, **4e**, **4f**, and **4i** with $Zn(OH)_2$ (Table 1, entries 3, 4, 6, 7, 8, and 11).[30] Only α-addition product **2** was obtained in excellent yield when allylboronate **1b** and ligand **4d** were used (Table 1, entry 13). Notably, the α-addition of allylboronate, which was previously observed in reactions with acyl-

Table 1. Reactions of α-methyl-substituted allylboronates **1a** and **1b**.



Entry	B	L	Yield [%]	**2**/**3**	*syn*/*anti* (**2**)
1	**1a**	–	86	45:55	2:1
2	**1b**	–	94	95:5	1:1
3	**1a**	**4a**	81	81:19	24:1
4	**1a**	**4b**	81	82:18	24:1
5	**1a**	**4c**	84	33:67	4:1
6	**1a**	**4d**	82	99:1	13:1
7	**1a**	**4e**	83	96:4	16:1
8	**1a**	**4f**	82	93:7	49:1
9	**1a**	**4g**	94	48:52	2:1
10	**1a**	**4h**	64	25:75	3:1
11	**1a**	**4i**	76	99:1	19:1
12	**1a**	**4j**	62	15:85	3:1
13	**1b**	**4d**	97	>99:<1	9:1



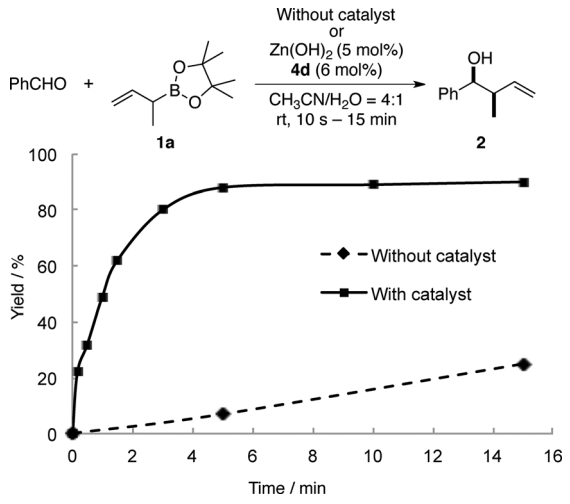


Figure 1. Allylation reaction of benzaldehyde with allylboronate **1a**.[a] [a] γ-Addition product **3** was obtained without a catalyst.

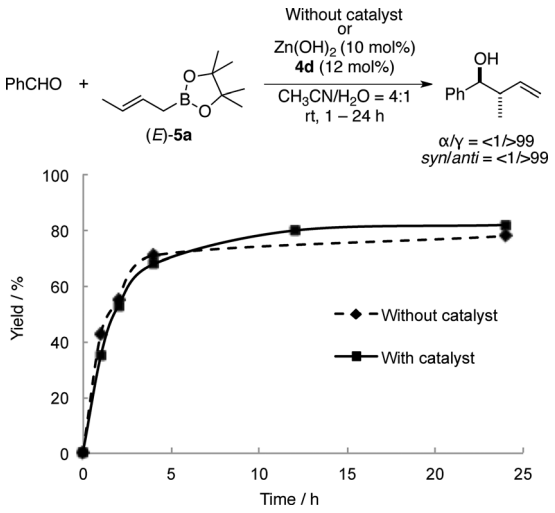


Figure 2. Allylation reaction of benzaldehyde with crotylboronate (*E*)-**5a**.

hydrazones, was also observed in a reaction with an aldehyde. Next, we carefully examined the reaction rate and found that remarkable catalyst acceleration occurred in this reaction (Figure 1). In the absence of any catalyst, γ-addition product **3** was obtained from benzaldehyde and allylboronate **1a** through a cyclic transition state because of the Lewis acidity of the boron atom in compound **1a**. On the other hand, in the presence of $Zn(OH)_2$ and ligand **4d**, the reactivity of the allylation reaction increased dramatically and the reaction was complete within 5 min.

Next, we examined the reactions of (*E*)- and (*Z*)-crotylboronates ((*E*)-**5a** and (*Z*)-**5a**) with benzaldehyde. We found that, as distinct from the allylation reactions of compound **1a**, the reactions proceeded very slowly and γ-addition product **2** was obtained exclusively. We carefully followed these reactions and found that no catalyst acceleration by $Zn(OH)_2$/**4d** occurred, that is, similar reaction profiles were observed in the presence and absence of $Zn(OH)_2$/**4d** (Figure 2 and Figure 3). Moreover, stereospecific reactions proceeded in these cases; *syn*- and *anti*-adducts of compound **2** were obtained from crotylboronates (*Z*)-**5a** and (*E*)-**5a**, respectively.

We further examined the reaction of simple allylboronate **6a** with benzaldehyde and found that the reaction proceeded faster in the presence of $Zn(OH)_2$/**4d** than without a catalyst (Figure 4).

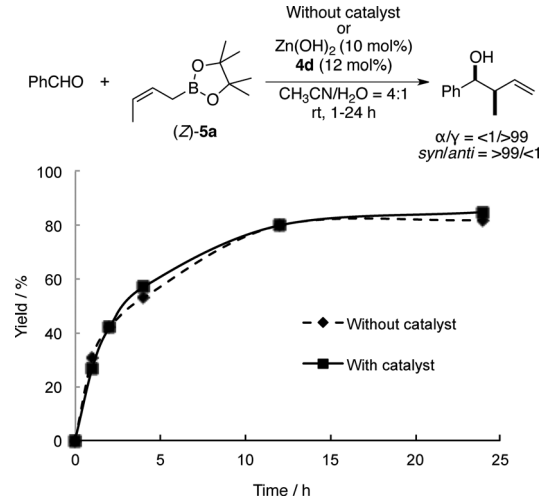


Figure 3. Allylation reaction of benzaldehyde with crotylboronate (*Z*)-**5a**.

Catalytic Cycle and Reaction Mechanism

In our initial studies, α-addition products were obtained from the reactions of an aldehyde with α-substituted allylboronates catalyzed by $Zn(OH)_2$/**4d** in aqueous media. To the best of our knowledge, this reaction a very rare example of an α addition with an aldehyde during the relatively long history of allylboration,[23] which made us interested in the reaction mechanism. Based on the obtained results, we proposed a catalytic cycle and reaction pathway for the

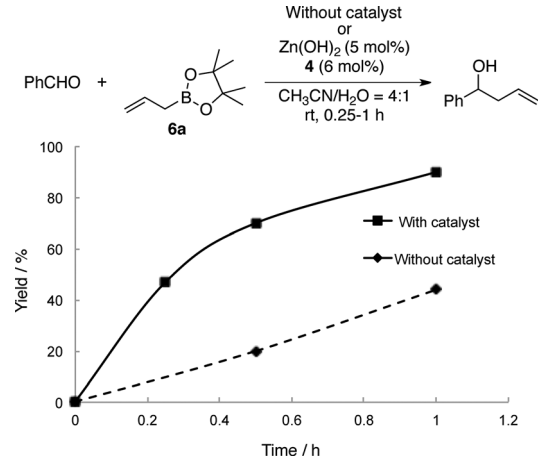


Figure 4. Allylation reaction of benzaldehyde with allylboronate **6a**.

$Zn(OH)_2$-catalyzed allylation reactions of aldehydes with α-methyl-substituted allylboronates in aqueous media (Figure 5): Initially, allylboronate **1a**, which is coordinated by a H_2O molecule, may attack $Zn(OH)_2$ to induce a B-to-Zn exchange process. This exchange may proceed in a γ-addition fashion via a six-membered transition state to form (*Z*)-crotylzincate, which may react with an aldehyde in a γ-addition fashion via another six-membered transition state to predominantly produce a *syn*-Zn amide, followed by protonation with H_2O to give homoallylic alcohol, along with the regeneration of $Zn(OH)_2$. Consequently, two γ-addition steps could give α-addition product **2**.

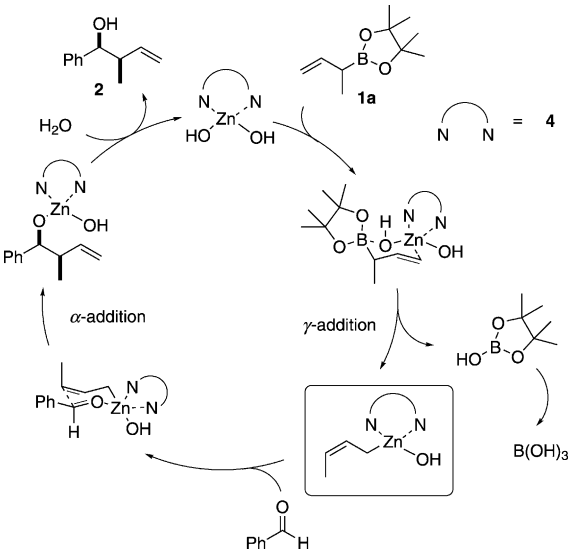


Figure 5. Proposed catalytic cycle.

The key step in this catalytic cycle is the exchange process from B to Zn to generate the crotylzincate species. Next, we attempted to detect the crotylzincate species. When $Zn(OH)_2$, compound **1a**, and compound **4d** were combined in CH_3CN/H_2O (4:1), the major signals of the crotylzincate species were detected by electrospray-ionization high-resolution mass spectrometry (HRMS (ESI), Figure 6a). The isotope pattern was identical to the calculated pattern (Figure 6b).[31] We also found that this crotylzincate species gradually decomposed in the aqueous media (reacted with H_2O). This decomposition (hydrolysis) was monitored by online continuous MS (ESI) analysis (Figure 6c), which was performed without stirring for technical reasons. Independently, we monitored the reaction between $Zn(OH)_2$, compound **1a**, and compound **4d** with stirring (Figure 6d–g). We found that the signals of the crotylzincate species were even detected after 1.5 min and that the signals disappeared after 30 min. Furthermore, another control experiment was conducted by changing the order of addition in the allylation reaction (Table 2). Namely, allylboronate **1a** and $Zn(OH)_2$/**4d** were combined for appropriate periods and then benzaldehyde was added. The yield of allylation product **2a** was dependent on the mixing time of compound **1a**

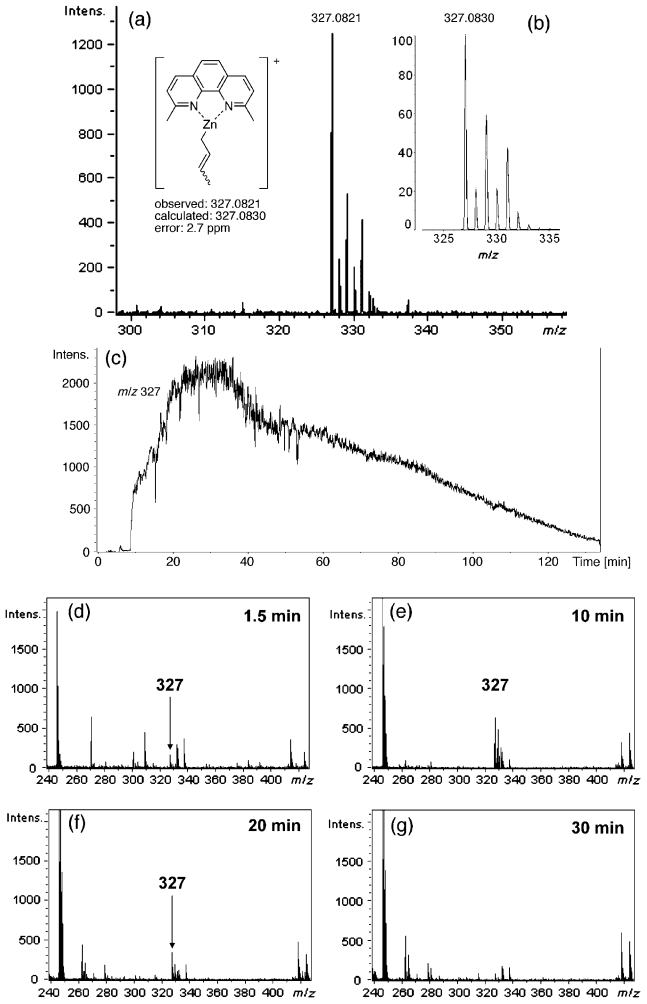
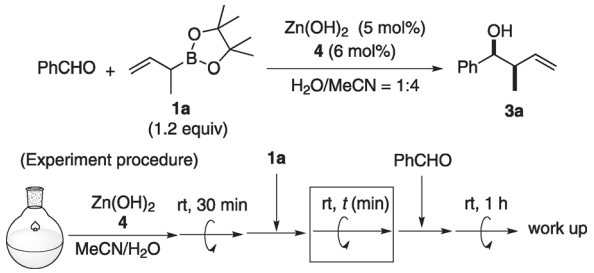


Figure 6. Detection of the crotylzincate species by MS (ESI) analysis: a) Experimental and b) calculated HRMS data. c) Online monitoring of the crotylzincate species by MS (ESI) analysis (without stirring). d–g) MS (ESI) data for $Zn(OH)_2$, compound **1a**, and compound **4d** in CH_3CN/H_2O with stirring for 1.5, 10, 20, and 30 min, respectively.

Table 2. Control experiments by changing the addition order of the allylation reaction.



Entry	*t* [min]	Yield [%]	α/γ	*syn*/*anti*
1	0	85[a]	99:1	12:1
2	5	75[a]	99:1	10:1
3	15	51[b]	99:1	8:1
4	30	16[b]	99:1	4:1
5	45	7[b]	99:1	2:1
6	60	0[b]	–	–

[a] Yield of isolated product. [b] Yield calculated from the crude NMR spectrum.

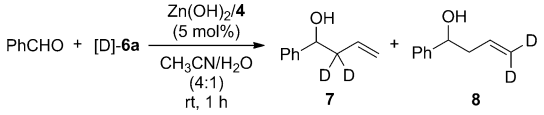
and $Zn(OH)_2$/**4d**. After the B-to-Zn exchange, the as-formed crotylzincate species competitively reacted with an aldehyde and H_2O.

Then, we conducted kinetic investigations on the allylation reaction of 3-phenylpropanal with allylboronate **1a**. With benzaldehyde at room temperature, the reaction was too fast to follow by NMR spectroscopy; thus, we used 3-phenylpropanal instead of benzaldehyde. First-order dependence on allylboronate **1a** and zero-order dependence on the aldehyde were observed, which indicated that the rate-determining step was the formation of the allylzincate through the B-to-Zn exchange reaction.[32]

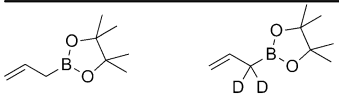
By assuming the catalytic cycle and the reaction pathway shown in Figure 5, several experimental results can be explained: Whereas α-methyl-substituted allylboronate **1a** smoothly reacted to afford the α-addition product, the reactions of crotylboronates (*E*)-**5a** and (*Z*)-**5a** proceeded slowly to give the γ-addition product. The B-to-Zn exchange proceeded smoothly in the former case and it was assumed to be inhibited in the latter case because of steric hindrance at the γ position of the crotylboronates. Uncatalyzed reactions were assumed to proceed through Zimmerman's six-membered transition states to stereospecifically afford *syn*-adduct **2** from compound (*Z*)-**5a** and *anti*-adduct **2** from compound (*Z*)-**5a**.

In the reactions of simple (nonsubstituted) allylboronates, the catalyzed reaction was found to proceed much faster than the uncatalyzed reaction in the reaction profiles shown in Figure 4. We further examined this reaction by using deuterated allylboronate [D]-**6a** (Table 3). We found that γ-addition product **8** was exclusively obtained in 44% yield with-

Table 3. Deuterium-scrambling experiments.

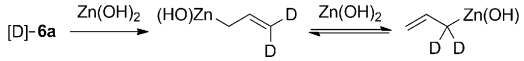


Entry	Catalyst	Yield [%]	**7**/**8**
1	without catalyst	44	<1:>99
2	$Zn(OH)_2$+**4d**	89	50:50



out a catalyst, whereas a mixture of α-addition product **7** and γ-addition product **8** (**7**/**8**=50:50) was obtained in 89% yield in the presence of $Zn(OH)_2$/**4d**.

We assumed that isomerization occurred in deuterated allylzincate, which was formed from allylboronates and $Zn(OH)_2$/**4d** through γ addition (Scheme 1). A similar isomerization is anticipated for (*Z*)-crotylzincate to form (*E*)-crotylzincate (Figure 5), which may explain the time-dependence of the *syn*/anti ratio of the products shown in Table 2.

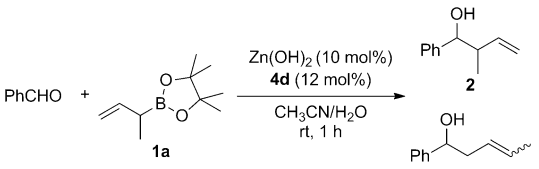


Scheme 1. Isomerization of deuterated allylzincate.

Role of H_2O: Organic Solvents versus Aqueous Solvents

Unique reactivities and selectivities were observed in the Zn-catalyzed allylation reactions of several allylboronates in aqueous media. We assumed that H_2O played a key role in the reactivities and selectivities because such reactivities and selectivities were not observed in organic solvents; thus, the effect of the amount of H_2O was examined next (Table 4): In the absence or presence of a small amount of H_2O

Table 4. Effect of the amount of H_2O.



Entry	Solvent	H_2O[a] [equiv]	Yield [%]	**2**/**3**	*syn*/*anti* (**2**)
1	CH_3CN	–	61	3:97	2:1
2	CH_3CN	10	66	2:98	2:1
3	CH_3CN	100	74	80:20	19:1
4	CH_3CN/H_2O (9:1)	–	77	99:1	16:1
5	CH_3CN/H_2O (4:1)	–	82	99:1	13:1
6	CH_3CN/H_2O (1:1)	–	74	93:7	12:1
7	CH_3CN/H_2O (1:4)	–	74	65:35	6:1
8	CH_3CN/H_2O (1:9)	–	74	37:63	5:1
9	H_2O	–	70	23:77	3:1

[a] Equivalents to benzaldehyde.

(10 equiv to the amount of benzaldehyde), γ-addition product **3** was obtained (Table 4, entries 1 and 2); however, when the amount of water was increased, α-addition product **2** was obtained selectively (Table 4, entries 3–7). Moreover, when the amount of H_2O was increased further, γ-addition product **3** was dominantly produced (Table 4, entries 8 and 9).

To further elucidate the role of H_2O in the allylation reactions, we examined the reactivities of allylboronates **6a**–**6d** in organic solvents and aqueous media in the presence and absence of $Zn(OH)_2$ (Figure 7). In CD_2Cl_2, we found that compound **6c** showed the highest reactivity, followed by **6a** and **6b**, which were much less reactive; compound **6d** showed the lowest reactivity (Figure 7a). This order of reactivity was almost consistent with that reported by Brown et al.[17j] Similar reactivity differences were observed in CD_3CN: Compound **6c** gave the highest reactivity, whilst compounds **6a**, **6b**, and **6d** showed much-lower reactivities (Figure 7b). In contrast, very different reactivities were observed in aqueous medium (CD_3CN/D_2O=4:1, Figure 7c): Compound **6a** gave the highest reactivity, whilst the other

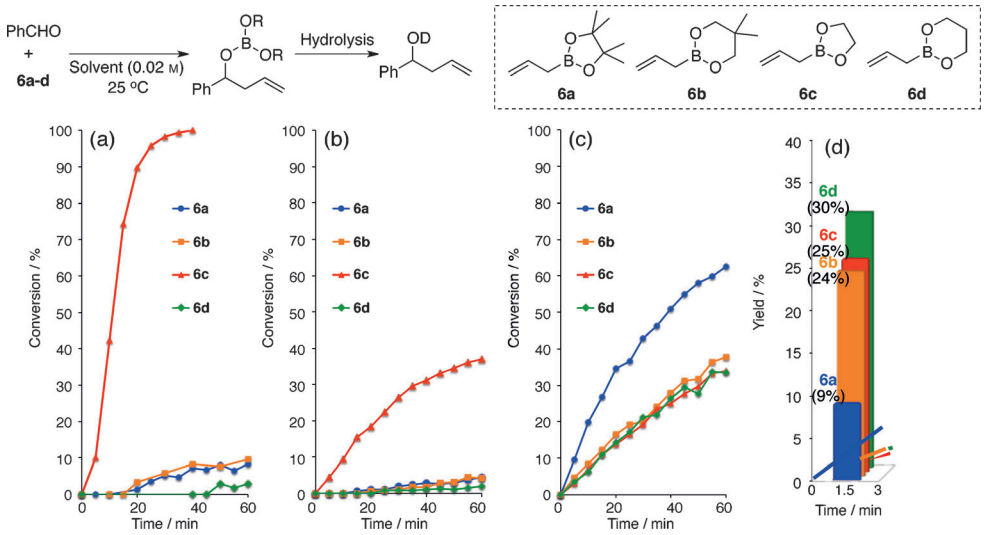


Figure 7. Allylation reactions of benzaldehyde with compounds **6a–6d** in a) CD_2Cl_2, b) CD_3CN, c) CD_3CN/D_2O (4:1), and d) in the presence of $Zn(OH)_2$/**4d** in CH_3CN/H_2O (4:1).

three boronates showed almost-similar and lower reactivities. Next, we conducted the reactions in the presence of 10 mol% $Zn(OH)_2$/**4d** in CH_3CN/H_2O (4:1). Because the reaction system was heterogeneous and the reaction rates were very fast, it was difficult to follow the reactions by NMR spectroscopy. Therefore, we quenched the reactions after 1.5 min and compared the yields directly (Figure 7d, average of three experiments). Notably, in all cases, the reaction rates increased significantly in the presence of $Zn(OH)_2$/**4d**. Moreover, the order of reactivity changed to: **6d** > **6b** ≈ **6c** ≫ **6a**. It was interesting that compound **6a** was the most reactive in aqueous media without a catalyst but was the least reactive in the same solvent in the presence of $Zn(OH)_2$/**4d**. The reactivity order is summarized in Scheme 2.

In CD_2Cl_2: **6c** >> **6a**, **6b** > **6d**
In CD_3CN: **6c** >> **6a**, **6b**, **6d**
In CD_3CN/D_2O (4/1): **6a** > **6b**, **6c**, **6d**
$Zn(OH)_2$/**4d** in CD_3CN/D_2O (4/1): **6d** > **6b**, **6c** >> **6a**

Scheme 2. Order of reactivity of compounds **6a–6d** in various solvent systems.

In organic solvents, the allylation reactions proceed through Zimmerman's six-membered transition states to afford γ-addition products and the reactivity is mainly dependent on the Lewis acidity of the boron atom of the allylboronates. The ^{11}B NMR chemical shifts of allylboronates **6a–6d** are shown in Table 5, which indicate that the five-membered allylboronates (**6a** and **6c**) are more Lewis acidic than the six-membered allylboronates (**6b** and **6d**) in CD_2Cl_2 and CD_3CN. Thus, the highest reactivity of compound **6c** in both CD_2Cl_2 and CD_3CN corresponds well with its ^{11}B NMR chemical shift and the lower reactivity of compound **6a** than compound **6c** could be explained by the

Table 5. ^{11}B NMR chemical shifts [ppm] in compounds **6a–6d**.

Solvent	6a	6b	6c	6d
CD_2Cl_2	32.8	29.1	33.5	29.5
CD_3CN	33.6	29.9	34.2	30.2
CD_3CN/D_2O 4:1	33.3	29.8	31.8	28.7

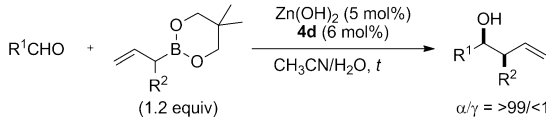
steric hindrance of the four methyl groups on compound **6a**. On the other hand, similar transition states are assumed in uncatalyzed reactions in aqueous media. The ^{11}B NMR spectrum in CD_3CN/H_2O suggests that compound **6a** is the most Lewis acidic, which corresponds to the highest reactivity of compound **6a** in CD_3CN/H_2O. In aqueous media, H_2O coordinates to the B atom to decrease its Lewis acidity. Owing to steric reasons, the coordination of H_2O to allylboronate **6a** is more difficult than that to compound **6c** and, hence, compound **6a** retains its high Lewis acidity, even in aqueous media. On the other hand, in the $Zn(OH)_2$/**4d**-catalyzed reactions in aqueous media, the rate-determining step is the B-to-Zn exchange process to generate the allylzincate species. In this step, H_2O coordinates to the B atom of the allylboronates to form borates to accelerate the exchange process. Although H_2O also coordinates to Zn, the exchange-rate constant of the inner-sphere H_2O ligand is much faster for Zn than for B.[33] This result means that Zn can retain its Lewis acidity in the presence of H_2O, in contrast to B. Under these conditions, we assume that the borate formation is slower for compound **6a** than for allylboronates **6b–6d**, which may be why compound **6a** shows the lowest reactivity. Because of the steric hindrance of the two methyl groups in compound **6b**, it shows lower reactivity than compound **6d**; however, it is noted that compound **6b** is much more reactive than compound **6a** under these conditions. Because compound **6d**, with its six-membered ring, is more sterically unstable after the coordination of H_2O than compound **6c**, with its five-membered ring, compound **6d** is con-

sidered to be more reactive than compound **6c**. Thus, some key roles of H_2O in the allylation reaction are revealed. It is further noted that H_2O also plays a key role in the protonation of Zn amides to give the products, along with the regeneration of $Zn(OH)_2$ (Figure 5).[34]

Substrate Scope (Achiral Reactions)

Several aldehydes and allylboronates were examined in the presence of $Zn(OH)_2$ (5 mol%) and compound **4d** (6 mol%) in aqueous media (Table 6). We selected allylboronic acid 2,2-dimethyl-1,3-propanediol esters rather than pinacol allylboronates because the catalyzed reactions were faster than the uncatalyzed reactions with allylboronic acid 2,2-dimethyl-1,3-propanediol esters and because 2,2-dimethyl-1,3-propanediol was less expensive than pinacol.[35] Benzaldehyde derivatives that contained electron-donating and electron-withdrawing groups smoothly reacted with allylboronate **1b** to afford the desired adducts in high yields with high *syn*-selectivities (Table 6, entries 1–7). Another aromatic aldehyde and heteroaromatic aldehydes also worked well under these conditions (Table 6, entries 8–11). In the reaction of cinnamaldehyde with compound **1b**, high yields and moderate diastereoselectivities were obtained (Table 6, entry 12). 3-Phenylpropionaldehyde also reacted with compound **1b** to give an allylated product in high yield, but with low diastereoselectivity (Table 6, entry 13). Other allylboronates reacted smoothly to afford the desired compounds in high yields with good diastereoselectivities (Table 6, entries 14–16). Notably, in all cases, only the α-addition products were obtained exclusively.

Table 6. Substrate scope.



Entry	R^1	R^2	Conditions[a]	t [h]	Yield [%]	*syn*/*anti*
1	Ph	Me (**1b**)	A	2	88	19:1
2	4-Me-C_6H_4	Me	B	1	86	13:1
3	4-OMe-C_6H_4	Me	A	2	81	24:1
4	4-Br-C_6H_4	Me	B	1	quant.[b]	12:1
5	4-NO_2-C_6H_4	Me	B	4	94	12:1
6	2-MeO-C_6H_4	Me	B	3	94	16:1
7	3-MeO-C_6H_4	Me	A	4	94	19:1
8	1-naphthyl	Me	B	3	96	99:1
9	4-pyridinyl	Me	B	1	83	9:1
10	2-thienyl	Me	A	12	91	13:1
11	5-Me-2-furyl	Me	A	4	81	5:1
12	(*E*)-PhCH=CH	Me	A	4	92	3:1
13	$PhCH_2CH_2$	Me	B	2	94	1:1
14	Ph	Et	B	3	96	6:1
15	Ph	*n*Bu	B	2	81	6:1
16	Ph	*i*Bu	B	1	90	6:1

[a] Conditions A: CH_3CN/H_2O = 12:1 (0.02 M), −20 °C; conditions B: CH_3CN/H_2O = 4:1 (0.025 M), −10 °C. [b] quant. = quantitative yield.

Asymmetric Reactions

Thus, we have developed a new reaction to create C–C bonds, in which the relative stereochemistry could be controlled. Next, we intended to control the absolute configurations of the newly created stereogenic centers, which is regarded as the "ultimate goal" in developing a new reaction; in other words, the reaction would provide a new route to optically active compounds. Among the several methods that are used to obtain optically active compounds, we focused on asymmetric catalysis because, by using this method, large amounts of optically active compounds can be obtained by using small amounts of chiral sources.[36]

Based on the catalytic cycle shown in Figure 5, we decided to search for appropriate chiral ligands for allylzincates that worked well in aqueous media. Asymmetric catalysis in aqueous media is extremely difficult because most chiral catalysts are not stable in the presence of even a small amount of H_2O. After the discovery of water-compatible Lewis acids,[37] we searched for appropriate chiral ligands for these Lewis acids to develop chiral Lewis acid catalysis in aqueous media and we found chiral crown ethers to be appropriate ligands for our purpose.[38] Furthermore, we showed that the combination of the $Sc(OTf)_3$/chiral bipyridine ligand **9**, whose structure is a "half-crown ether", worked well for asymmetric hydroxymethylation reactions in aqueous media.[39,40]

Against this background, we examined compound **9**[41] as a chiral ligand for allylzincate species. In the presence of $Zn(OH)_2$ (10 mol%) and compound **9** (12 mol%), allylboronate **1b** reacted with benzaldehyde in CH_3CN/H_2O (7:3) at 0 °C to exclusively afford the desired α-addition product with high *syn*-selectivity (*syn*/*anti* = 10:1) and the enantiomeric ratio (e.r.) of the *syn* adduct was 86.5:13.5; no γ-addition product was obtained. To further improve the enantioselectivity, we examined the X-ray crystallographic structure of the Zn-**9** complex.[40b] For comparison, Figure 8 also shows the X-ray crystallographic structure of Sc-**9**,[39f,i] which is a typical Lewis acid and works well in aqueous media.

In the Sc-**9** complex, the two nitrogen atoms and two oxygen atoms of compound **9** are bound to the Sc^{III} center in a tetradentate manner and the complex adopts a pentagonal-bipyramidal structure. On the other hand, the Zn-**9** complex adopts a square-pyramidal structure, in which two nitrogen atoms and only one of the oxygen atoms of compound **9** are attached to the Zn^{II} center in a tridentate manner. Based on these structures, we assumed that the tetrahedral ligands were not absolutely necessary. Then, we designed several bipyridine ligands, including tridentate ligands, and tested them in the asymmetric allylation reaction of benzaldehyde with compound **1b** in aqueous media (Table 7).

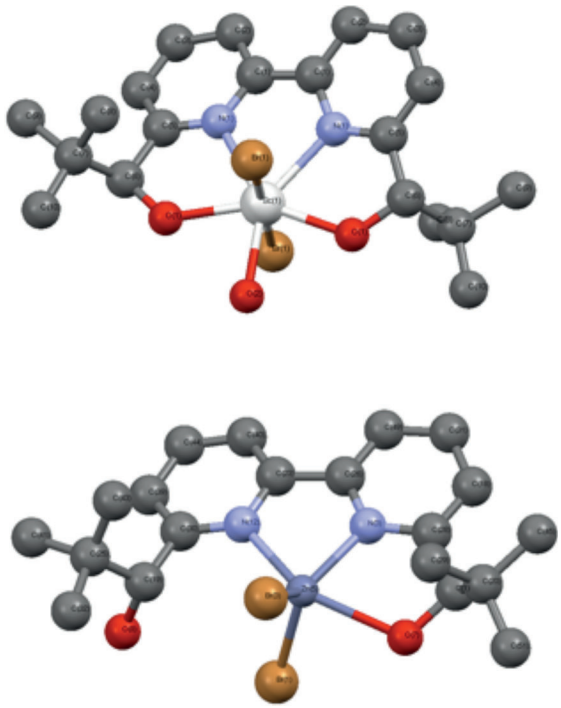
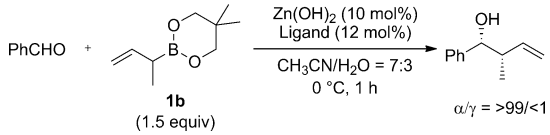


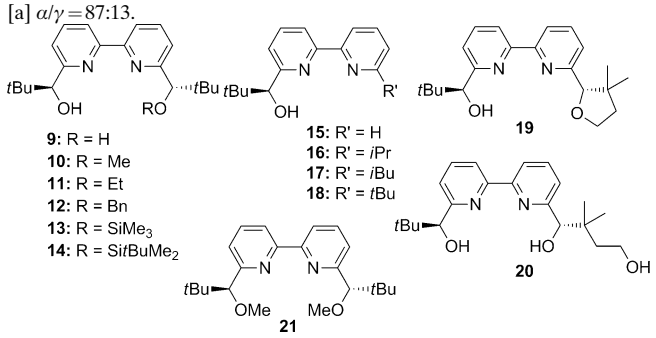
Figure 8. X-ray structure of the $[ScBr_2{\cdot}H_2O{\cdot}\mathbf{9}]^+$ moiety in the X-ray structures of $[ScBr_2{\cdot}H_2O{\cdot}\mathbf{9}]{\cdot}Br{\cdot}H_2O$ (top) and $[ZnBr_2{\cdot}\mathbf{9}]$ (bottom); hydrogen atoms are omitted for clarity. CCDC 253182 (top) and CCDC 827315 (bottom) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 7. Effect of chiral ligands.



Entry	Ligand	Yield [%]	*syn*/*anti*	e.r. (*syn*)
1	**9**	85	10:1	86.5:13.5
2	**10**	56	10:1	82:18
3	**11**	84	12:1	82.5:17.5
4	**12**	79	8:1	78.5:21.5
5	**13**	93	4:1	60.5:39.5
6	**14**	90	4:1	56:44
7	**15**	86[a]	24:1	68:32
8	**16**	89	16:1	80.5:19.5
9	**17**	87	4:1	79:21
10	**18**	88	4:1	50:50
11	**19**	91	9:1	82.5:17.5
12	**20**	96	3:1	84.5:15.5
13	**21**	93	1:1.2	50.5:49.5

[a] $\alpha/\gamma = 87:13$.

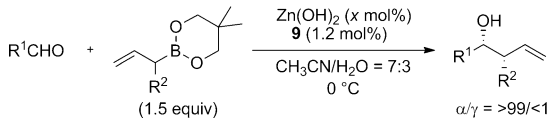


Interestingly, some nonsymmetrical ligands showed good enantioselectivity: In the asymmetric reactions with the Sc-**9** complex as a catalyst, no selectivity was obtained with compound **10** as a ligand.[40c] However, when compound **10** was used as a ligand for the allylation reaction, the desired product was obtained in high diastereoselectivity and good enantioselectivity (Table 6, entry 2). Ligands **10**–**12**, which contained smaller ethers, gave higher enantioselectivities than those that contained bulky ethers, such as ligands **13** and **14** (Table 6, entries 3–6). Moreover, even some 2-alkyl-substituted bipyridine ligands (**16** and **17**) showed promising selectivities (Table 6, entries 8 and 9). Ligand **18** might be too bulky to coordinate to the Zn center in a bidentate fashion (Table 6, entry 10). Whereas other ligands (**19** and **20**) also showed good enantioselectivities (Table 6, entries 11 and 12), ligand **21**, which did not contain an alcohol moiety, gave no enantioselectivity (Table 6, entry 13).

The substrate scope of the asymmetric allylation reactions is shown in Table 8. We examined the reactions of aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes with α-alkyl-substituted allylboronates in the presence of $Zn(OH)_2$ (3–10 mol%) and ligand **9** (3.6–12 mol%) in aqueous media. In all cases, the reactions proceeded well and the α-addition products were predominantly obtained. As a general tendency of the selectivities, aromatic, heteroaromatic, and α,β-unsaturated aldehydes gave high diastereoselectivities and good enantioselectivities, whereas aliphatic aldehydes showed good diastereoselectivities and high enantioselectivities.

This asymmetric reaction was also applicable to several synthetically useful procedures. α-Chloroallylboronate **22** smoothly reacted with various aldehydes to afford chloroallylated products in high yields with high diastereo- and enantioselectivities (Table 9). In all cases, no γ-addition products were obtained. The products, 2-chloro-homoallylic alcohols, could be converted into optically active epoxides and other compounds, which could act as versatile chiral building blocks. As a demonstration of the utility of this procedure, we performed the reaction of 3-*tert*-butyldimethylsiloxy-propionaldehyde with compound **22** in the presence of $Zn(OH)_2$/**9**. The reaction proceeded smoothly at 0 °C in aqueous media to afford chloroallylated product **23** in high yield and high stereoselectivity. Adduct **23** is an intermediate in the synthesis of spirastrellolide A (Scheme 3).[42,43] Another example is the synthesis of an intermediate of disparlure (Scheme 4).[44,45] The reaction of dodecanal with compound **22** in the presence of 2 mol% $Zn(OH)_2$ and 2.4 mol% ligand **9** proceeded smoothly to afford the corresponding chloroallylated adduct **24**, which is the intermediate, in high yield with high diastereo- and enantioselectivities. In these cases, previous methods utilized stoichiometric amounts of chiral sources and the reactions were conducted at −95 °C under strictly anhydrous conditions. Notably, this method can be performed by using a catalytic amount of a chiral ligand and the reactions proceed under mild conditions in aqueous media. Furthermore, chiral aldehyde **25** was successfully employed in this asymmetric allylation re-

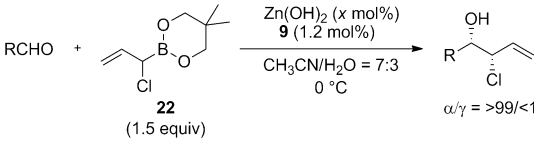
Table 8. Substrate scope of the asymmetric allylation reaction.



Entry	R^1	R^2	Loading[a] [mol%]	Yield [%]	Syn/ Anti	e.r. (*syn*)
1	Ph	Me	10	85	10:1	86.5:13.5
2	4-Me-C_6H_4	Me	10	84	12:1	83:17
3	4-Me-C_6H_4	Me	5	79	19:1	87:13
4	4-MeO-C_6H_4	Me	10	78	13:1	88:12
5	2-MeO-C_6H_4	Me	10	94	32:1	85.5:14.5
6	3-MeO-C_6H_4	Me	10	59[d]	16:1	85.5:14.5
7	2-thienyl	Me	10	92	16:1	92.5:7.5
8	5-Me-2-furyl	Me	10	67	16:1	95:5
9	(*E*)-PhCH=CH	Me	10	89	6:1	88:12
10	$PhCH_2CH_2$	Me	10	94	6:1	94:6
11	$PhCH_2CH_2$	Me	5	94	5:1	92.5:7.5
12	$CH_3(CH_2)_8$	Me	3	94	7:1	91:9
13	*c*-C_6H_{11}	Me	3	80	5:1	98.5:1.5
14[b]	$PhCH_2CH_2$	Et	5	96	3:1	95.5:4.5
15[b]	$PhCH_2CH_2$	*i*Bu	5	95	3:1	95.5:4.5
16[b]	$PhCH_2CH_2$	*n*Bu	5	97	3:1	95:5
17[c]	Ph	Et	10	95[e]	6:1	90:10
18[c]	Ph	*i*Bu	10	83	3.5:1	91:9

[a] Conditions A: $CH_3CN/H_2O = 12:1$ (0.02 M), −20 °C; Conditions B: $CH_3CN/H_2O = 4:1$ (0.025 M), −10 °C. [b] Slow addition of the aldehyde over 3 h. [c] Slow addition of the aldehyde over 2 h. [d] $\alpha/\gamma = 95:5$. [e] $\alpha/\gamma = 93:7$.

Table 9. Asymmetric chloroallylation reactions.



Entry	R	X	Yield [%]	*syn*/*anti*	e.r. (*syn*)
1	Ph	10	93	99:1	94:6
2	Ph	5	92	24:1	94:6
3	4-MeC_6H_4	10	94	99:1	93.5:6.5
4	4-MeC_6H_4	3	91	24:1	93.5:6.5
5	3-$MeOC_6H_4$	10	97	99:1	93.5:6.5
6	3-$MeOC_6H_4$	7.5	99	19:1	95.5:4.5
7	4-BrC_6H_4	10	quant.	32:1	92:8
8	4-BrC_6H_4	7.5	quant.	19:1	92.5:7.5
9	1-naphthyl	10	quant.	19:1	93:7
10	1-naphthyl	5	94	13:1	92.5:7.5
11	(*E*)-PhCH=CH	10	97	19:1	97:3
12	$C_5H_{11}C{\equiv}C$	10	99	16:1	91.5:8.5
13	$PhCH_2CH_2$	10	85	19:1	98.5:1.5
14	$PhCH_2CH_2$	3	92	13:1	97.5:2.5
15[a]	$PhCH_2CH_2$	3	87	13:1	97:3[b]
16	$(CH_3)_2CHCH_2$	10	64	49:1	99:1
17	*c*-C_6H_{11}	7.5	66	19:1	99:1

[a] Compound *ent*-**9** was used as a ligand. [b] The major isomer was the opposite enantiomer of the product in entries 13 and 14.

action. In the presence of $Zn(OH)_2$/**9**, the reaction of compound **25** with α-chloroallylboronate **22** proceeded smoothly to afford the desired adduct (**26**) in excellent yield with excellent diastereo- and enantioselectivities. The product (**26**) is an intermediate in the synthesis of Botryolide B (Scheme 5).[46]

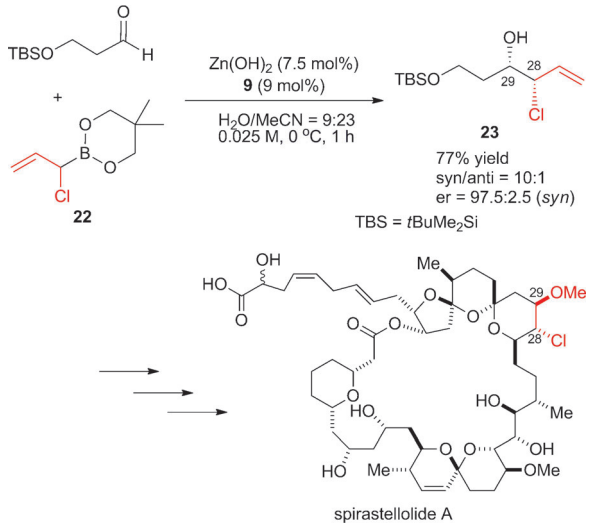
The reaction of 2-methylpropionaldehyde (isobutyraldehyde) with compound **1b** in the presence of $Zn(OH)_2$/**9** also proceeded smoothly to afford the corresponding adduct (**27**),[47] which is an intermediate in the syntheses of RK-397[48] and Mycoticin,[49] in good yield with high diastereo- and enantioselectivities (Scheme 6). The enantiomer of compound **27** is also an intermediate in the synthesis of (−)-Madumicin II (Scheme 6).[50]

Furthermore, this reaction can also be applied to the synthesis of optically active diols. The reactions of benzyloxyallylboronate **28** with aldehydes smoothly proceeded in an exclusive α-addition fashion to afford the corresponding 2-benzyloxyhomoallylic alcohols in high yields with high diastereo- and enantioselectivities (Scheme 7). It is noteworthy that the products are useful chiral synthons.[51]

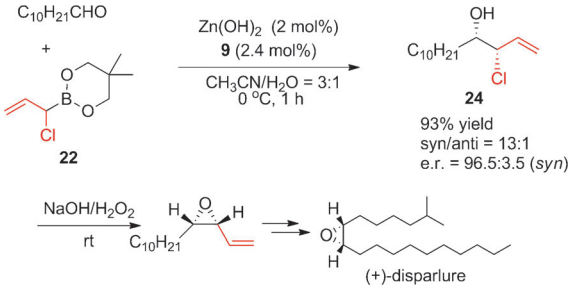
The assumed transition states of these catalytic asymmetric allylation reactions are shown in Scheme 8. We assumed a cyclic transition state of the chiral allylzinc species with an aldehyde, in which the aldehyde is activated by Zn. One face of the allylzincate is shielded by the chiral ligand (**9**) and the aldehyde reacts with the *Si* face of the allylzinc species.

Conclusions

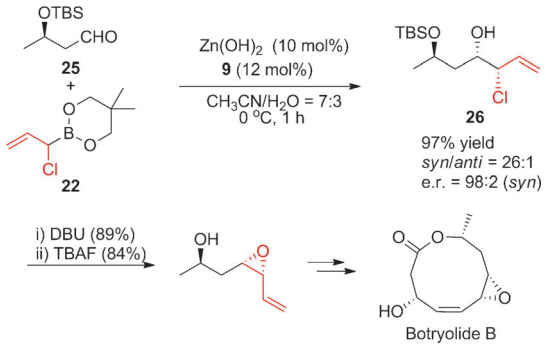
In summary, we have developed $Zn(OH)_2$-catalyzed allylation reactions of aldehydes with allylboronates in aqueous media. In contrast to conventional allylboration reactions of aldehydes in organic solvents, the α-addition products were exclusively obtained. A catalytic cycle in which the allylzinc species was generated through a B-to-Zn exchange process was proposed and kinetic studies were also performed. The key intermediate, an allylzinc species, was detected by HRMS (ESI) analysis and by online continuous MS (ESI) analysis. In aqueous media, the allylzinc species competitively reacted with aldehydes and H_2O. Several important roles of H_2O in this allylation reaction were also clarified by a comparison of the reactivity and selectivity of the allylzinc species that were generated from several typical allylboronates (**6a**–**6d**). The allylation reactions of aldehydes with allylboronic acid 2,2-dimethyl-1,3-propanediol esters proceeded smoothly in the presence of catalytic amounts of $Zn(OH)_2$ and achiral ligand **4d** in aqueous media to afford the corresponding *syn* adducts in high yields with high diastereoselectivities. In all cases, the α-addition products were obtained and a wide substrate scope was tolerated. Furthermore, this reaction was applied to asymmetric catalysis by using chiral ligand **9**. Based on the X-ray structure of the



Scheme 3. Synthesis of spirastrellolide A.



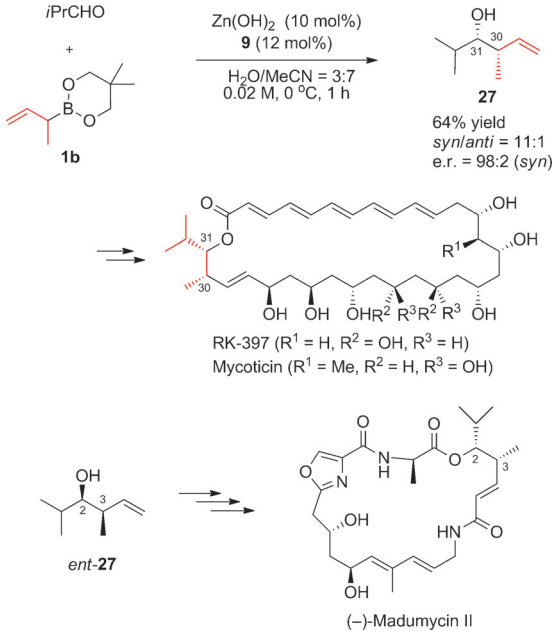
Scheme 4. Synthesis of (+)-disparlure.



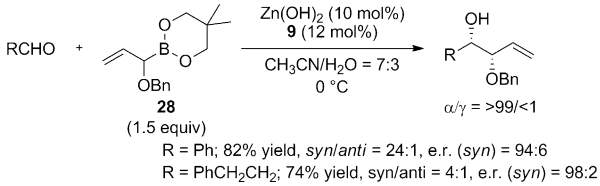
Scheme 5. Synthesis of Botryolide B. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBAF = tetra-*n*-butylammonium fluoride.

Zn-**9** complex, several nonsymmetrical chiral ligands were also found to be effective. This reaction was further applied to catalytic asymmetric alkylallylation, chloroallylation, and alkoxyallylation processes and the synthetic utility of these reactions was demonstrated. Through this work, the following important roles of H_2O were clarified: 1) as a polar solvent that can form hydrogen-bonding interactions to promote the reactions; 2) as a ligand and solvent to create active zinc–hydroxide species; 3) as a ligand on the B and Zn atoms to control their Lewis acidity; 4) as a Lewis base to promote B-to-Zn exchange; 5) as a ligand on the chiral Zn atom to control its Lewis acidity and asymmetric environment; 6) as a Brønsted acid to form the product from the zinc–alkoxide; and 7) as a Brønsted base to regenerate $Zn(OH)_2$.

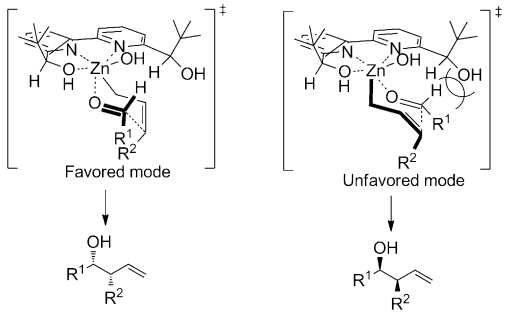
Further investigations to develop other new reactions and new systems in aqueous media are now underway.[52]



Scheme 6. Synthesis of RK-397, Mycoticin, and (−)-Madumycin II.



Scheme 7. Asymmetric alkoxyallylation reactions.



Scheme 8. Assumed transition states.

Acknowledgements

This work was supported by a Grant-in-Aid for Science Research from the Global COE Program of the Japan Society for the Promotion of Science (JSPS), the University of Tokyo, MEXT (Japan), the Japan Science and Technology Agency (JST), and NEDO. We also thank Dr. Miyuki Yamaguchi (University of Tokyo) for her assistance with the MS (ESI) analysis.

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Received: March 30, 2013
Published online: ■■ ▮▮, 0000