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Catalytic Use of Zinc Amide for Transmetalation with Allylboronates: General and Efficient Catalytic Allylation of Carbonyl Compounds, Imines, and Hydrazones

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Abstract: The efficient catalytic allylation of ketones, imines, and hydrazones with allylboronates using a catalytic amount of zinc amide is reported. In this reaction, the boron-to-zinc exchange process occurred smoothly to afford the corresponding allylzinc amides, and the desired allylation reactions proceeded in high efficiency (~0.1 mol%). A mechanistic study revealed that transmetalation was a rate-determining step in the catalytic cycle, and also that the amide ligand on the zinc center played a key role in preparing reactive allylzinc species. Catalytic asymmetric allylations were also investigated, and high enantioselectivities were obtained using chiral diamine ligands.

Keywords: allylation; catalysts; metal amides; transmetalation; zinc

Introduction

The development of an efficient and operationally facile catalytic methodology for C–C bond formation is an important issue in organic chemistry.[1] The allylation of carbonyl compounds,[2] imines, and hydrazones[3] provides homoallylic alcohol and amine derivatives, which are very useful building blocks for further transformations. In particular, when an electrophilic partner is a ketone or a ketimine derivative, a crowded carbon center bearing a required functional group can be created.[4] Typical protocols for allylation of ketones involve the use of allylmetal reagents prepared *in situ* under Barbier-type conditions[5] from allyl halides and stoichiometric amounts of metals.

Recently, a significant advance has been made in catalytic allylation using allylboronates.[6] It is notable that the use of less toxic allylboronates is environmentally friendly compared with the use of toxic allylstannanes.[7] Allylation of carbonyl compounds, imines, and hydrazones with allylboronates has been disclosed in the presence of Cu-,[8] In-,[9] Ir-,[10] Ni-,[11] and Zn[12]-based catalysts, and Brønsted acids;[13] however, in most of those cases, relatively high catalyst loadings were required. Zinc catalysts have low toxicity, are inexpensive, and markedly tolerant toward various functional groups.[14]

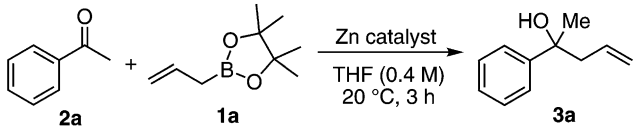
Our group has recently reported zinc hydroxide-catalyzed asymmetric allylation of aldehydes and hydrazono esters with allylboronates.[12a,c,d] In this reaction, zinc nucleophiles were formed through transmetalation from boron to zinc. We envisaged that zinc species with stronger conjugate Lewis bases, such as $Zn(HMDS)_2$,[15] might have advantages in promoting turnover of zinc species in a catalytic process.[16,17] Herein, we report a general catalytic allylation of carbonyl compounds, imines, and hydrazones in the presence of catalytic amounts of $Zn(HMDS)_2$.

Results and Discussion

Development of Zinc Amide-Catalyzed Allylation Reactions

The evaluation of various zinc catalysts for the allylation of acetophenone (**2a**) with pinacol allylboronate (**1a**) is summarized in Table 1. While zinc Lewis acids such as zinc chloride, bromide, fluoride, acetate, and even triflate provided poor conversions for the model system in the presence of 10 mol% catalyst (entries 2–6), zinc *tert*-butoxide (1.0 mol%) was also unsatisfactory, affording poor conversion (entry 7, 10% conversion). Zn catalysts prepared from diethylzinc and alcohols were also tested, and moderate conversions

Table 1. Examination of the zinc-catalyzed allylation of acetophenone **2a** with allylboronate **1a**.[a]



Entry	Catalyst[b]	Conv. [%][b]
1	none	0
2	$ZnCl_2$ (10 mol%)	2
3	$ZnBr_2$ (10 mol%)	4
4	ZnF_2 (10 mol%)	2
5	$Zn(OAc)_2$ (10 mol%)	0
6	$Zn(OTf)_2$ (10 mol%)	0
7[c]	$Zn(O\text{-}t\text{-}Bu)_2$ (1 mol%)	10
8[d]	$ZnEt(O\text{-}t\text{-}Bu)$[e] (1 mol%)	48
9[d]	ZnEt(OEt)[f] (1 mol%)	56
10	$Zn(HMDS)_2$ (1 mol%)	97

[a] The reaction of **2a** (0.40 mmol) with **1a** (0.44 mmol) was performed in 0.4 M THF at 20 °C for 3 h in the presence of a zinc catalyst, unless otherwise noted. The results shown in entries 1–7 and 10 have been reported in our communication.[16]

[b] Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

[c] The reaction of **2a** (1.60 mmol) with **1a** (1.76 mmol) was performed in 0.8 M THF at 20 °C for 3 h in the presence of $Zn(O\text{-}t\text{-}Bu)_2$ prepared *in situ* from 1 mol% of $ZnCl_2$ and 2 mol% of KO-*t*-Bu.

[d] **2a** (0.80 mmol) and **1a** (0.88 mmol) were used.

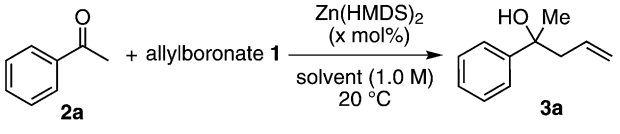
[e] ZnEt(O-*t*-Bu) was prepared from $ZnEt_2$ and an excess amount of *t*-BuOH in THF, and used after concentration and drying.

[f] ZnEt(OEt) was prepared from $ZnEt_2$ and an excess amount of EtOH in THF, and used after concentration and drying.

were observed (entries 8 and 9).[12b] To our delight, $Zn(HMDS)_2$ was found to be much more reactive, providing 97% conversion within 3 h with 1 mol% catalyst loading (entry 8). Compared with reported examples of allylation with allylboronates, this reaction is operationally facile, and no additional proton source is required to achieve high reactivity.

Based on this finding, we conducted further optimization with pinacol allylboronate **1a** (Table 2). Initial experiments were focused on solvent evaluation with 2.5 mol% $Zn(HMDS)_2$. During the optimization, we found that THF, diethyl ether, and pentane allowed this transformation to achieve full conversion (entries 1–6). In the subsequent screening, allylboronic acid 2,2-dimethyl-1,3-propanediol ester (**1b**) emerged with better activity than pinacol allylboronate (**1a**), although allylboronate **1a** has been used as a general allylating reagent for a long time in synthetic organic chemistry. We then tested the reactions of **1a** and **1b** with **2a** in the presence of 1.0 mol% $Zn(HMDS)_2$ in the optimized solvents (entries 7–9), and in all these

Table 2. Survey of allylboronates and solvents for the zinc amide-catalyzed allylation of acetophenone **2a**.[a]



Entry	Solvent	Cat. (x)	1a Time [h]	1a NMR Yield [%][b]	1b Time [h]	1b NMR Yield [%][b]
1	THF	2.5	3	>99	–	–
2	Et_2O	2.5	3	>99	–	–
3	DCM	2.5	3	80	–	–
4	CH_3CN	2.5	3	57	–	–
5	pentane	2.5	3	>99	–	–
6	toluene	2.5	3	82	–	–
7	THF	1.0	1	35	1	>99
8	Et_2O	1.0	1	28	1	93
9	pentane	1.0	1	67	1	>99
10	pentane	0.1	6	25	16	73
11	pentane	0.1	24	29	36	>99 (96[d])
12	pentane	0.1	48	30	–	–
13[c]	pentane	0.1	60	43	–	–

[a] In entries 1–9, the reaction of **2a** (0.40 mmol) with **1** (0.44 mmol) was performed at 20 °C in 0.4 M solvent in the presence of $Zn(HMDS)_2$. In entries 10–13, the reaction of **2a** (3.0 mmol) with **1** (3.3 mmol) was performed at 20 °C in 1.0 M solvent in the presence of $Zn(HMDS)_2$ unless otherwise noted. The results shown in entries 7–13 have been reported in our communication.[16]

[b] Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

[c] The reaction was run at 0 °C.

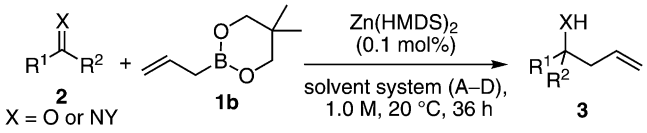
[d] Isolated yield.

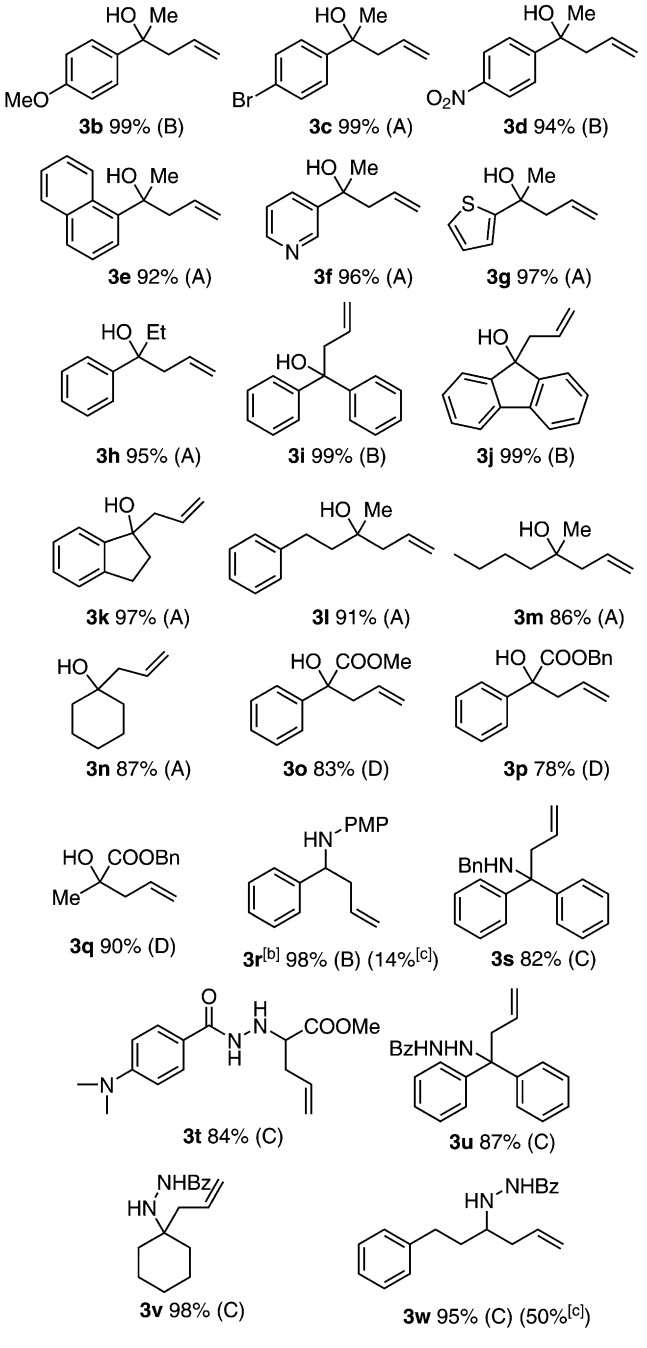
cases, **1b** showed higher yields. It was found that both pentane and THF were better solvents for this model system, and an apolar solvent, pentane, was found to be the most suitable solvent. It is noteworthy that, utilizing allylboronate **1b**, the reaction proceeded smoothly even using 0.1 mol% $Zn(HMDS)_2$, and that after 36 h at 20 °C, the homoallylic alcohol **3a** was obtained in complete conversion and 96% isolated yield. In contrast, the corresponding reaction with **1a** resulted in low conversion even when the reaction was conducted for a long time. The employment of allylboronate **1b** also has an economic advantage because it could be prepared from 2,2-dimethyl-1,3-propanediol, which is much cheaper than pinacol.[18]

Next, we investigated substrate generality of the allylation of ketones, imines, and hydrazones with allylboronate **1b** by using 0.1 mol% of $Zn(HMDS)_2$ (Table 3). Gratifyingly, the reaction proceeded with

good generality for a diverse array of functional groups including both aromatic and heteroaromatic ketones, providing the corresponding tertiary homoallylic alcohols in excellent yields. Moreover, aliphatic ketones were shown to react smoothly. Further, the methodology performed with excellent generality for aldimines and aldehyde-derived hydrazones, as well as for ketimines and ketone-derived hydrazones, which were all transformed into the corresponding homoallylic amines and hydrazides in high yields. Note that several functional groups such as methoxy, bromo, ester, pyridine, and nitro groups were compatible with this mild and operationally facile catalytic system.

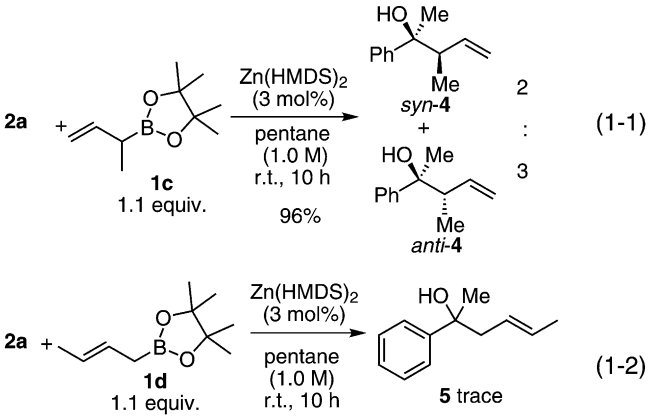
Table 3. Substrate scope for the zinc amide-catalyzed allylation of **2** with allylboronate **1b**.





Assumed Mechanism

We started the mechanistic studies by evaluating the reaction of acetophenone with a series of substituted allylboronates (Scheme 1). The allylation was found to proceed smoothly with α-methyl-substituted allylboronate (**1c**) to afford α-adducts in a 2:3 *syn*/anti ratio. On the other hand, with terminal methyl-substituted boronate (**1d**), this reaction was too sluggish to give any significant conversion. Both cases indicated that the boron-to-zinc exchange process was required to initiate the catalytic cycle, and that the exchange process occurred *via* a cyclic transition wherein the



Scheme 1. Allylation with a series of substituted allylboronates. These results have been reported in our communication.[16]

[a] The reaction of **2** (3.0 mmol) with **1b** (3.3 mmol) was performed in 1.0 M of the solvent system at 20 °C for 36 h in the presence of $Zn(HMDS)_2$ (0.1 mol%) unless otherwise noted. The yield was determined by isolation after column chromatography. Solvent conditions shown in parentheses. *Conditions A:* in pentane; *conditions B:* in pentane-THF (5:1); *conditions C:* in pentane-THF (3:2); *conditions D:* in THF. The results of product **3b**, **3e**, **3g–o**, **3r**, **3s**, **3u–w** have been reported in our communication.[16]

[b] PMP = *p*-methoxyphenyl.

[c] NMR yield of the reaction without using $Zn(HMDS)_2$.

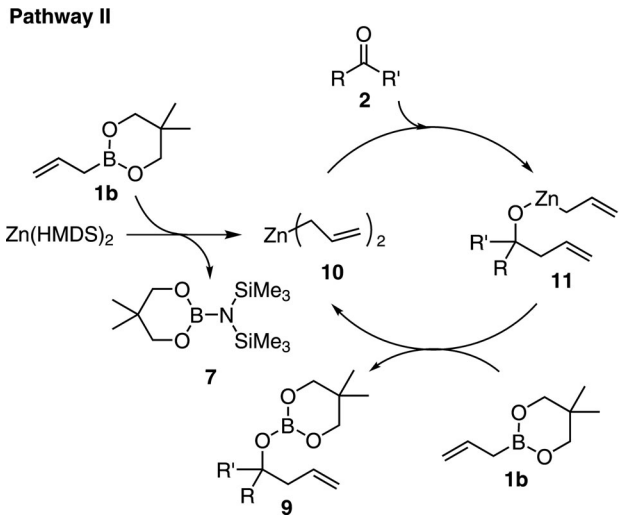
allyl group transferred from boron to zinc.[19] The steric effect around the allyl group would hinder the exchange rate.

In preliminary studies, we assumed the formation of a nucleophilic allylic zinc species for allylation of acetophenone. On the basis of previous studies and various experiments, the transmetalation would generate two allylic zinc species, allylic zinc amide and diallylic zinc, and both species can react with a ketone. Our next interest was to clarify how zinc amide was involved in the reaction. For the zinc amide-catalyzed allylation using allylboronate, we proposed four possible mechanistic pathways shown below.

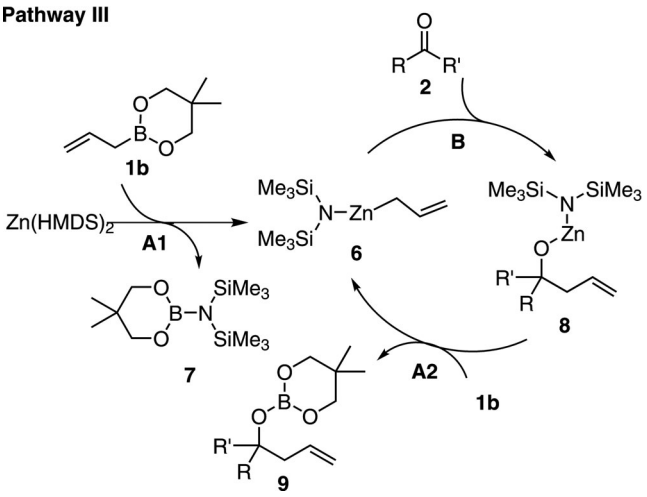
The first possible mechanism is a truly zinc amide-catalyzed mechanism involving an allylic zinc amide intermediate as shown in Scheme 2 (Pathway I). The transformation is initiated by a boron-to-zinc exchange reaction to generate nucleophilic allylzinc amide complex **6** and boron amide **7**. Next, this allylzinc amide complex **6** reacts with ketone **2** to provide zinc alkoxide (product) complex **8**. A subsequent transmetalation from boron amide **7** to zinc alkoxide (product) complex **8** regenerates $Zn(HMDS)_2$, and allylboronated product **9** is obtained.

An alternative mechanism is a zinc amide-initiated mechanism (Scheme 3, Pathway II). In this pathway, zinc amide is a precatalyst that reacts with allylboronate **1b** to afford diallylic zinc **7** as a viable reaction intermediate, accompanied by the generation of boron amide. The subsequent allylation provides allylic zinc alkoxide (product) complex **11**. The following exchange of this complex with allylboronate **1b** affords allylboronated product **9** along with regeneration of diallylic zinc **10** to complete the catalytic cycle.

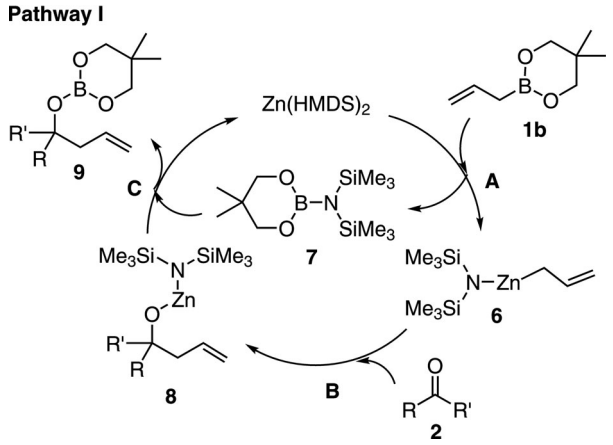
The third possible mechanism is a zinc amide-catalyzed mechanism with no regeneration of $Zn(HMDS)_2$ (Scheme 4, Pathway III). In this mechanism, allylzinc amide species **6** is formed after the first transmetalation and reacts with ketone **2** to form



Scheme 3. Possible catalytic pathway II.



Scheme 4. Possible catalytic pathway III.

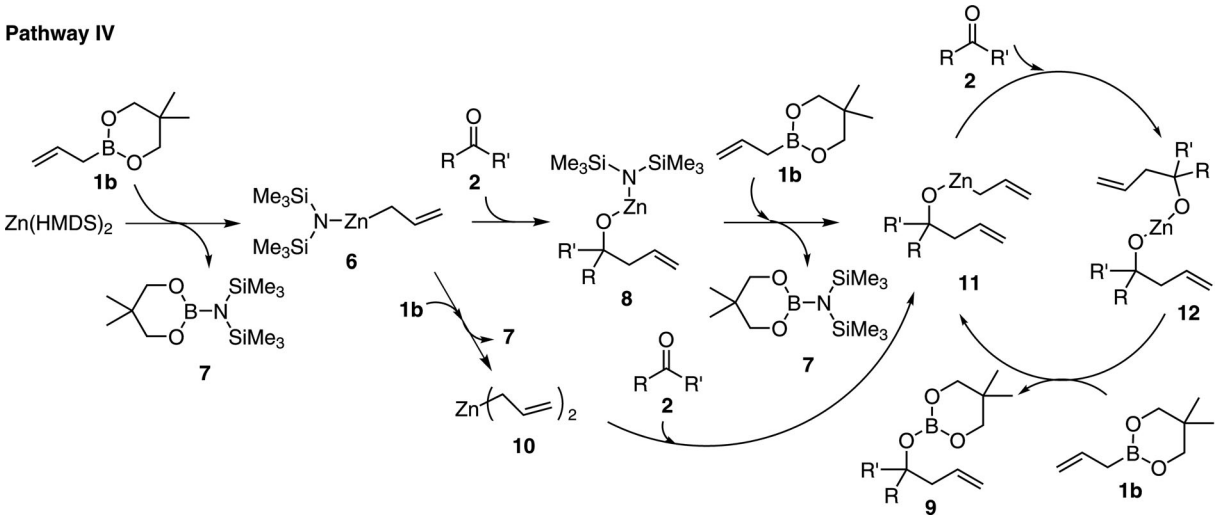


Scheme 2. Possible catalytic pathway I.

alkoxy(product)zinc amide complex **8**, which further reacts with allylboronate **1b** to regenerate allylzinc amide species **6** without formation of $Zn(HMDS)_2$.

Finally, the last possible mechanism is also a zinc amide-initiated mechanism. After an initiation step, allylzinc alkoxide (product) species **8** forms and works as a key catalytic species (Scheme 5, Pathway IV). In this mechanism, the key species **11** can be formed *via* alkoxy(product)zinc amide **8** or diallylzinc species **10**.

We performed mechanistic experiments to clarify which was the most plausible reaction mechanism.



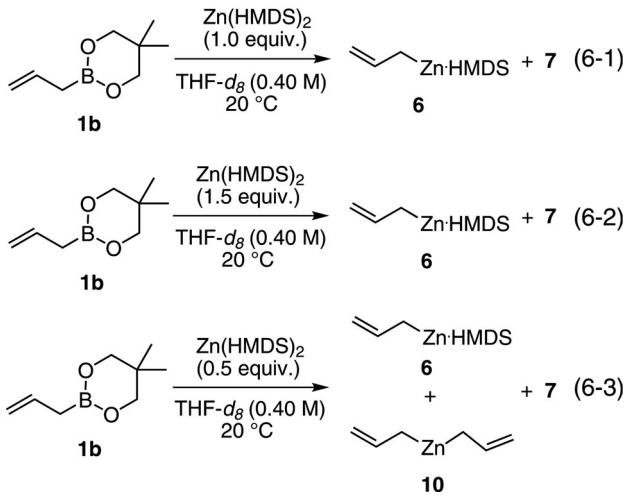
Scheme 5. Possible catalytic pathway IV.

Mechanistic Study

NMR Experiments on Allylzinc Species

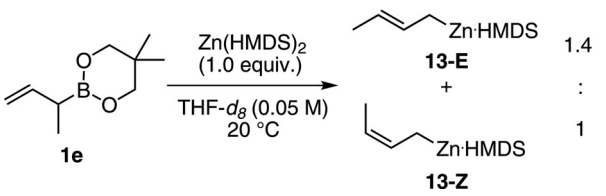
Transmetalation of Allyl- and α-Methylallylboronates with a Stoichiometric Amount of Zinc Amide

To verify the boron-to-zinc transmetalation hypothesis directly, we monitored a stoichiometric reaction of allyboronate **1b** with $Zn(HMDS)_2$ by ^1H, ^{13}C, and ^{11}B NMR analyses at 20 °C (Scheme 6). When allylboronate **1b** was treated with $Zn(HMDS)_2$ (1.00 equiv.) in THF-d_8 at 0.40 M at 20 °C, we could clearly observe the boron–zinc exchange [Scheme 6, Eq. (6-1)]. In this process, a series of signals belonging to allylboronate **1b** gradually faded. Analysis by the continuous variation method was consistent with a 1:1 stoichiometry of the exchange. The newly emerged signals were assigned to those of allylic zinc species **6**. The ^{11}B NMR experiment clearly showed a new single signal ($\delta = 20.9$ ppm), which appeared in the spectrum upfield of the signal of allylboronate ($\delta = 28.1$ ppm) and was assigned to the boron amide **7**. After 30 min, the exchange achieved 54 % boronate conversion, and after 1 h, complete consumption of allylboronate **1b** provided the allylic zinc species in 98 % NMR yield. We assigned the major zinc species to allylic zinc amide **6** based on its ^1H NMR analysis. The ^1H NMR signals of the major zinc species were substantially consistent with the observed ^1H NMR signals obtained in the reaction of allylboronate **1b** with excess $Zn(HMDS)_2$ (1.50 equiv.) [Eq. (6-2)]. The typical and sharply contoured signals that appeared in both cases corresponded to those of allylic zinc amide **6**, which was considerably more prevalent than diallylic zinc species **10**. The ^1H NMR spectrum of diallylic zinc species **10** in our system was very obscure (see the Supporting Information). Moreover, this gradual exchange process and the generation of allylic zinc amide **6** were also observed in the ^{13}C NMR spectra.



Scheme 6. NMR experiments for transmetalation of boron to zinc.

On the other hand, we performed NMR studies by using allylboronate **1b** combined with 0.5 equiv. of $Zn(HMDS)_2$. This condition seemed to be more likely to resemble the actual catalytic status [Eq. (6-3)]. It was assumed that an excess amount of allylboronate **1b** would contribute to the second allyl group transfer to the zinc center. Nevertheless, it was found that the first exchange of the allyl group with one amide group of $Zn(HMDS)_2$ could take precedence over the second exchange of another allyl group with the remaining amide group. Indeed, the transmetalation proceeded smoothly with nearly 50% boronate conversion in 30 min to yield the allylzinc amide **6**, which was shown by ^1H NMR analysis. Importantly, we



Scheme 7. Transmetalation of **1e** to zinc.

found that the second transmetalation was obtuse and afforded diallylic zinc **10** in 73% boron conversion after 1 h. Moreover, the complete consumption of allylboronate **1b** was protracted, and even after 48 h, a small amount of allylboronate **1b** remained.

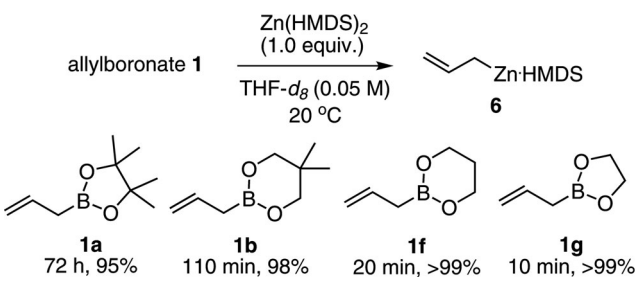
At this stage, we confirmed the boron-to-zinc transmetalation as an initial step in the catalytic cycle. With the aim of confirming the origin of diastereoselectivity (*syn*/*anti* = 2/3) by using α-methyl-substituted allylboronate, we investigated the exchange of α-methyl-substituted allylboronate **1e** with 1 equivalent of $Zn(HMDS)_2$ in THF-d_8 (0.05 M) at 20 °C. Under these conditions, a smooth boron-to-zinc exchange was observed, achieving complete conversion to afford crotyl zinc species **13** with *Z*/*E* = 1/1.4 selectivity after 2 h (Scheme 7). This result might explain the diastereoselectivity (*syn*/*anti* = 2/3), if kinetically generated Z and *E* crotyl zinc amide species **13** reacted with a ketone stereospecifically.

Transmetalation of a Series of Allylboronates with a Stoichiometric Amount of Zinc Amide

To shed light on the substituent effect on allylboronates and also to seek out the origin of the different reactivities of allylboronates **1a** and **1b**, we investigated the transmetalation of zinc amide with one equivalent of each of a series of allylboronates by NMR analysis (Scheme 8).

As shown in Scheme 8, the addition of allylboronates (**1a**, **1b**, **1f**, **1g**) to a solution of $Zn(HMDS)_2$ (1.00 equiv.) in dry THF-d_8 (0.05 M) all provided allylic zinc amide at 20 °C. Under these typical conditions, the exchange of $Zn(HMDS)_2$ with allylboronate **1b** provided the allylic zinc species **6** in a short time (110 min, 98% boronate conversion). In contrast, the exchange of zinc amide with pinacolyl allylboronate **1a** was very slow (72 h, 95% conversion). Based on the previous experiments, even if pinacolyl allylboronate **1a** was treated with $Zn(HMDS)_2$ (1.00 equiv.) in a concentrated THF-d_8 solution (0.40 M) at 20 °C, the allylic zinc species was formed with 66% boronate conversion after 5 h, and a longer time (16 h) was required to achieve full conversion. Based on these results, we assumed that less-hindered non-substituted cyclic allylboronates might facilitate boron-to-zinc transmetalation more rapidly. As we anticipated, the exchanges with allylboronates **1f** and **1g** proceeded strikingly promptly, providing access to the corresponding allylic zinc species in full conversion quite quickly (**1f**, 20 min; **1g**, 10 min). Based on these reaction outcomes, we attributed the significantly different exchange rates of allylboronates (**1a**, **1b**, **1f**, **1g**) with $Zn(HMDS)_2$ to a tendency for increased steric demands of the boron sites, which suppressed the exchange of boron to zinc in a cyclic transition structure.

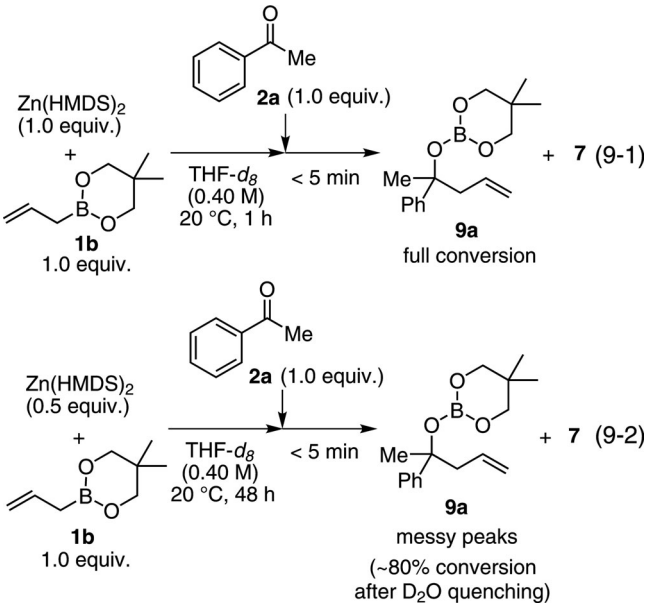
These results clearly indicated that $Zn(HMDS)_2$ reacted with allylboronates to afford allylzinc amide species preferentially at the initial stage of the transmetalation even in the presence of an excess amount of allylboronate.



Scheme 8. Effect of allylboronate structures.

Allylation of Acetophenone with Stoichiometric Amounts of Allylzinc Amide and Diallylzinc

Based on the above results, which give direct evidence of the boron-to-zinc transmetalation, we moved our attention to allylation (Scheme 9). Upon addition

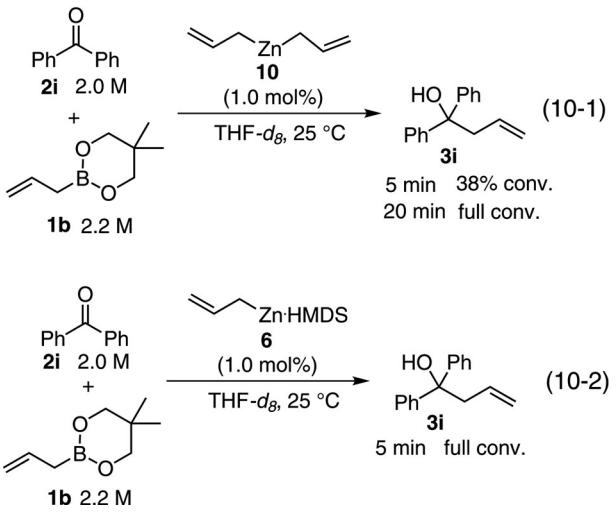


Scheme 9. Reactivities of allylzinc amide and diallylzinc.

of one equivalent of acetophenone to the resultant allylic zinc amide system (generated from the combination of allylboronate **1b** with one equivalent of $Zn(HMDS)_2$ in 0.40 M THF-d_8 at 20 °C, 1 h), the ^{1}H NMR spectrum showed that the C–C bond formation proceeded immediately with full conversion [Scheme 9, Eq. (9-1)]. Furthermore, when acetophenone, allylboronate **1b**, and $Zn(HMDS)_2$ (1:1:1, in THF-d_8 at 0.40 M, 20 °C) were mixed, the ^{11}B NMR spectrum clearly supported the formation of allylboronated product **9a** ($\delta = 16.5$ ppm) and boron amide ($\delta = 20.9$ ppm). On the other hand, the subsequent allylation of acetophenone (1.00 equiv.) with diallylic zinc (generated from the combination of allylboronate **1b** with 0.5 equiv. $Zn(HMDS)_2$ in 0.40 M THF-d_8 at 20 °C, 48 h) led to an untidy ^{1}H NMR spectrum. After quenching the reaction with D_2O, the desired homoallylic alcohol was obtained in nearly 80% conversion [Eq. (9-2)].

Allylation of Benzophenone with Catalytic Amounts of Allylic Zinc Amide and Diallylic Zinc Species

Next, we attempted to clarify a critical catalytic intermediate in our catalytic system: allylic zinc amide or diallylic zinc species. From another point of view, we expected to show the significant effect of the amide group on the high activity of zinc amide towards allylation compared with other zinc sources (Scheme 10). We therefore prepared allylic zinc amide and diallylic zinc as catalysts, and conducted the allylation. It was found that, in these two different systems, a significant reactivity difference was observed in relative rates for the subsequent allylation of benzophenone. In the presence of a catalytic amount of diallylic zinc (1.00 mol%), the allylation proceeded with 38% conversion in 5 min and full conversion in 20 min [Scheme 10, Eq. (10-1)]. In contrast, allylic zinc amide (1.00 mol%) catalyzed this reaction to obtain full conversion within 5 min [Eq. (10-2)].



Scheme 10. Catalytic reactivities of allylzinc amide and diallylzinc.

To summarize the NMR transmetalation experiments, the transfer of the allyl group from allylboronates to allylic zinc amides was fast, and the allylation in the presence of catalytic amounts of allylic zinc amide identified the indispensable role of one amide group on the zinc center for achieving high reactivity in our system. These mechanistic experiments were consistent with the formation of a nucleophilic allylic zinc amide complex as a key catalytic intermediate in the favored pathways I or III rather than pathways II or IV.

Kinetic Studies of the Allylation Reactions Using $Zn(HMDS)_2$

In the possible pathways I and III, we perceived that the allylation might not be a rate-determining step on the basis of the results shown in Table 2 and the above NMR experiments. To confirm our hypothesis, we next conducted a kinetic study to investigate the effect of substrates and zinc amide on the rate of the

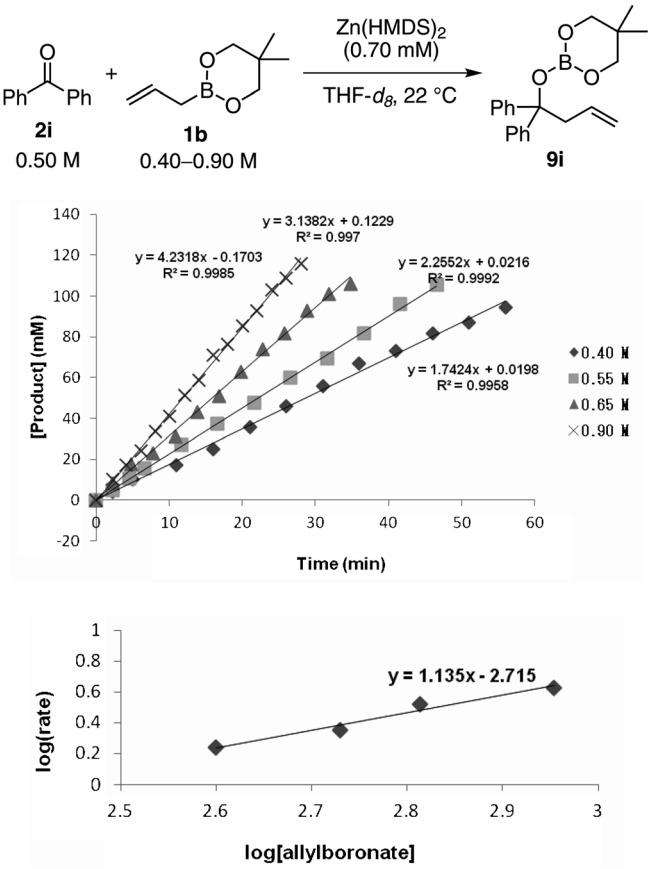


Figure 1. Effect of concentration of allylboronate **1b**.

allylation reaction. To determine the kinetic order of allylboronate **1b** and a ketone, we measured the rate of the reaction with various concentrations of allylboronate **1b** and benzophenone (Figure 1). We were able to observe a first-order dependence of the allylation rate on the allylboronate concentration. The observed rate of the product formation remained constant until 30% conversion.

Furthermore, the kinetic study indicated that the addition of increasing equivalents of benzophenone resulted in no significant change in the observed rate of the reaction. The plot clearly showed a zero-order dependence of the rate on the ketone (Figure 2).

On the other hand, the catalyst curve represented a first-order dependence of the rate on the increasing concentration of zinc amide (Figure 3). In view of this accessible catalytic process, wherein no obvious induction period and side reactions were observed, we were able to determine the effect of ketone, allylboronate, and the catalyst concentrations on the rate from the initial stage. The first orders for allylboronate and zinc amide were consistent with a mechanism involving transmetalation of boron to zinc to generate allylic zinc amide at the outset (Step A in Pathway I or Step A1 or A2 in Pathway III). The zero order for the ketone suggested that allylation (Step B in Pathways I and III) was not the rate-determining step.

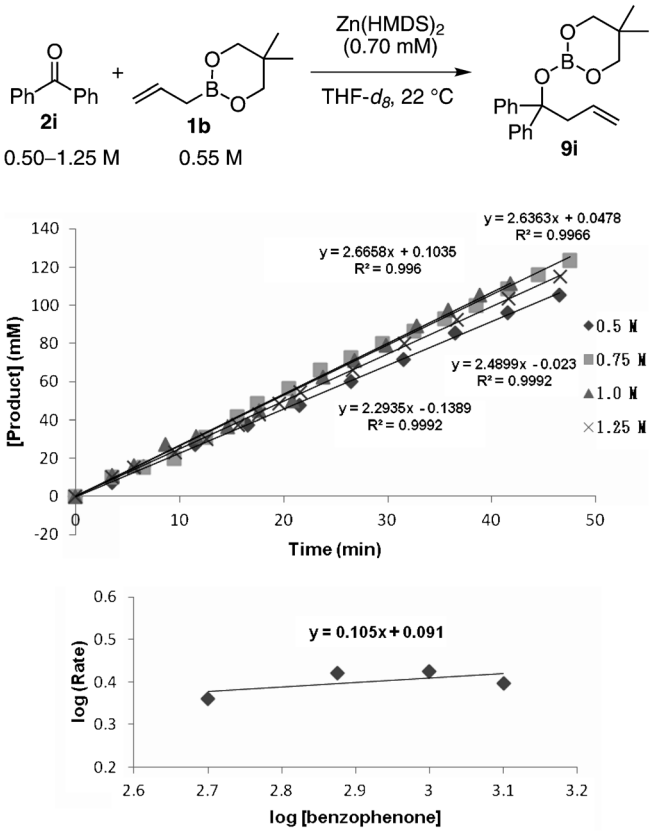


Figure 2. Effect of concentration of benzophenone (**2h**).

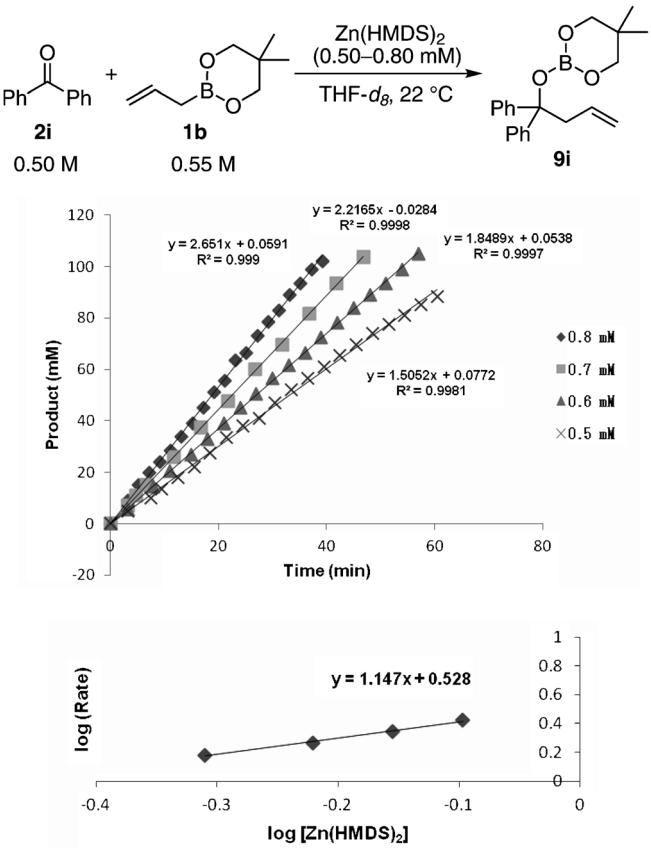


Figure 3. Effect of concentration of $Zn(HMDS)_2$.

Next, we prepared boron amide independently to clarify its effect on the catalytic turnover. In the ^{11}B NMR spectrum, the signal of the prepared boron amide was consistent with that observed during transmetalation. This signal confirmed our catalytic cycle and showed that the formation of boron amide was involved as an intermediate.

With this compound in hand, we conducted a kinetic study to investigate the effect of boron amide on the rate of the reaction (Figure 4). Compared with our general system, additional boron amide accelerated the reaction rates. Whereas, with various concentrations of additional catalytic amounts of boron amide [0.80 to 2.0 equiv. with respect to $Zn(HMDS)_2$], given the lack of an observable induction period, the reaction rates were essentially constant until 30% conversion because of the zero-order kinetics of boron amide. We considered that the existence of boron amide might play a role as Lewis acid to accelerate the reaction rate, but it was clear that transboronation (Step C in Pathway I) was not a rate-determining step.

In addition, we found that the introduction of a large amount of boron amide (0.10 and 0.20 equiv. with respect to benzophenone) resulted in a 60% decrease in the observed initial rate of the reaction. This

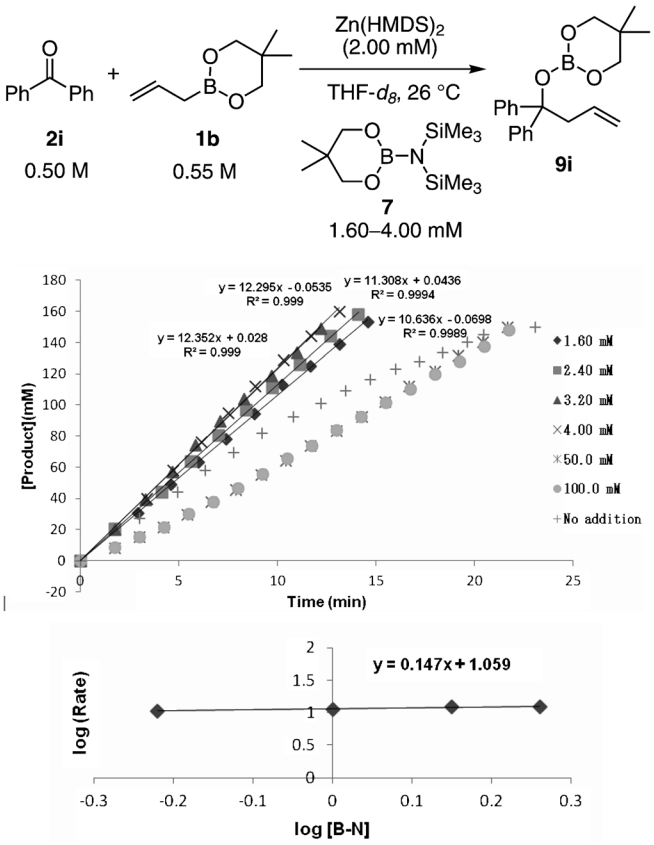


Figure 4. Effect of concentration of boron amide **7**.

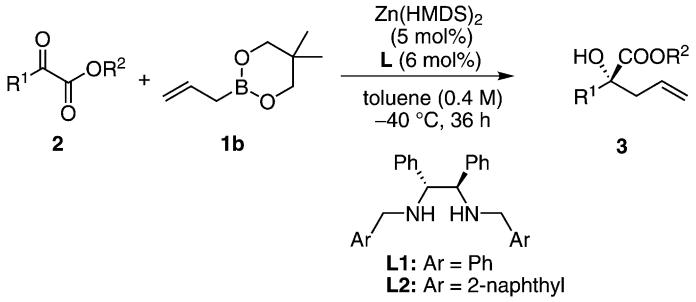
result presented one aspect of the equilibrium within transmetalation, wherein boron amide was formed as a product. This plot demonstrated competitive boron amide inhibition and supported the suggestion of relatively slow exchange between allylboronate and zinc amide (Step A in Pathway I or Step A1 or A2 in Pathway III) in contrast to allylation (Step B in Pathways I and III) and transboronation (Step C in Pathway I). Herein, we observed first-order kinetic dependences on allylboronate and zinc amide, and zero-order kinetics for ketone and boron amide. The rate law implied by these kinetic orders demonstrated a mechanism involving a turnover-limiting boron-to-zinc transmetalation (Step A in Pathway I or Step A1 or A2 in Pathway III). Therefore, the mechanistic proposal summarized in Scheme 2 or Scheme 4 did not fit the NMR experimental data and the kinetics studies. The last unclear point is whether the plausible catalytic pathway is Pathway I or Pathway III. However, it is difficult to evaluate the two pathways. Further mechanistic study is required to clarify this issue.

Catalytic Asymmetric Allylation Reactions Using a Chiral Zinc Amide

Next, we considered asymmetric reactions using a chiral zinc amide. While catalytic allylations of ketones using zinc catalysts have been intensively studied, there are few successful examples of asymmetric allylation using a chiral zinc species. In the initial screening, we investigated some combinations of chiral ligands and $Zn(HMDS)_2$, and found that chiral diamine ligand **L1** derived from 1,2-diphenylethylenediamine was promising, and high enantioselectivity was observed in the allylation reaction of α-keto ester **3o** with allylboronate **1b** after optimization of reaction conditions (Table 4, entry 1, 92% yield with 92% *ee*).[20] Those reaction conditions could also be employed in the reaction of **3q** with **1b**; however, lower enantioselectivity was obtained (entry 2). The reaction at lower temperature improved the enantioselectivity (entry 3). In the same reaction conditions, α-keto ester **3p** also reacted with **1b** in moderate enantioselectivity (entry 4). We then further examined the effect of arylmethyl structures of the ligand and found that a chiral diamine ligand **L2** bearing a 2-naphthylmethyl substituent was effective, and higher selectivities were obtained (entries 5–7). On the other hand, acetophenone (**1a**) was also employed in the asymmetric reaction; however, almost no enantioselectivity was observed. Those results indicated that the second chelation moiety of the substrate-to-zinc center was important to form an effective asymmetric environment around the ketone moiety.

The structure of the chiral zinc amide was then investigated. $Zn(HMDS)_2$ and **L2** were combined in toluene-d_8 and the mixture was heated at 75 °C, and ^1H and ^{13}C NMR analyses were conducted (see the Supporting Information). After heating for 1 h, three trimethylsilyl peaks and eight other aliphatic carbon peaks in ^{13}C NMR charts were observed, although the ^1H NMR chart was complicated. Further heating of the complex solution afforded relatively simple NMR charts, in which two major trimethylsilyl peaks and four other aliphatic carbons were observed in the ^{13}C NMR chart. The solution, after heating for 24 h, was then concentrated under vacuum, and ^1H and ^{13}C NMR analyses were conducted after dissolving in toluene-d_8. In the charts obtained, we observed the disappearance of one trimethylsilyl peak of the two major peaks in ^1H and ^{13}C NMR, which correspond to $HN(SiMe_3)_2$ (H-HMDS). These results indicate that one hydrogen of two NH parts of the ligand was deprotonated by $Zn(HMDS)_2$ after heating to form a chiral zinc amide (Scheme 11).

Table 4. Asymmetric allylation of α-keto ester **2o–q** with $Zn(HMDS)_2$ and chiral ligand.[a]

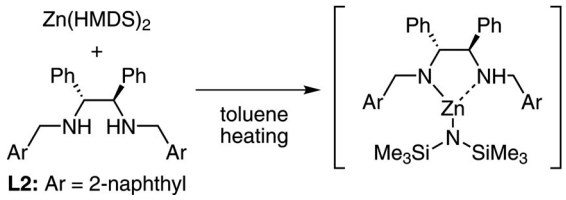


Entry	L	Conditions	R^1	R^2	3	Yield [%][b]	*ee* [%][c]
1	**L1**	–20 °C, 24 h	Ph	Me	**3o**	92	92
2	**L1**	–20 °C, 24 h	Me	Bn	**3q**	98	69
3	**L1**	–40 °C, 36 h	Me	Bn	**3q**	75	78
4	**L1**	–40 °C, 36 h	Ph	Bn	**3p**	81	76
5	**L2**	–40 °C, 36 h	Ph	Me	**3o**	86	97
6	**L2**	–40 °C, 36 h	Ph	Bn	**3p**	78	83
7	**L2**	–40 °C, 36 h	Me	Bn	**3q**	72	89

[a] The reaction was conducted using **2** (0.40 mmol) and **1b** (0.44 mmol) in toluene. The chiral zinc amide was prepared by mixing $Zn(HMDS)_2$ and the ligand and heating at 75 °C in toluene for 1 h. The result shown in entry 1 has been reported in our communication.[16]

[b] Isolated yield.

[c] Determined by chiral HPLC analysis.



Scheme 11. Preparation of chiral zinc amide complex.

Conclusions

In summary, we have developed a highly efficient zinc amide-catalyzed allylation of carbonyl compounds, imines, and hydrazones with a more reactive and more economical allylboronic acid 2,2-dimethyl-1,3-propanediol ester (**1b**). Mechanism studies elucidated that this transformation succeeds *via* a boron-to-zinc transmetalation, and this transmetalation successfully accesses a nucleophilic allylzinc amide species as a key catalytic intermediate and has been clearly observed by NMR spectroscopy analysis. This allylation presents broad substrate generality with high tolerance to various functional groups, and also proceeds well with α-methyl-substituted boronates to yield the α-addition product exclusively. It is noteworthy that, to the best of our knowledge, this report presents the first example of a synthesis method involving the use of a catalytic amount of zinc amide. Our mechanistic study revealed that the actual reactive allylating species was allylzinc amide, and that the rate-determining step of the allylation reaction was the formation of the allylzinc amide species. Asymmetric allylation using a chiral zinc amide was also achieved. Further application of the zinc amide for other carbon-carbon bond-forming reactions is now ongoing.

Experimental Section

General Information

NMR spectra were recorded on a JEOL ECX-400, a JEOL ECA-500, or a JEOL ECX-600 spectrometer. Chemical shifts were reported downfield from tetramethylsilane (TMS) or in the scale relative to the corresponding solvent used as an internal reference. IR spectra were measured using a JASCO FT/IR-4200 spectrometer. High resolution mass spectra (HR-MS) were recorded using a JEOL JMST100TD (DART) spectrometer. High-performance liquid chromatography was carried out using following apparatuses; Shimadzu LC-20AB (liquid chromatograph), Shimadzu SPD-M20A (photo diode array detector) and DGU-$20A_3$. Preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F from Wako Pure Chemical Industries, Ltd. Flash column chromatography was performed over silica gel 60 N from Kanto Chemical Co., Inc. All solvents used were commercially available dry solvents that were further dried and degassed appropriately under an argon atmosphere, and stored over activated molecular sieves in an argon box prior to use. Unless otherwise specified, all ketones, imines and hydrazones (purchased from commercial sources) used in this work were distilled under an argon atmosphere or recrystallized prior to use. Pinacol

allylboronate **1a**, allylboronate **1b**[21] and α-methylallylboronate **1c**[22] were prepared by reported methods; their analyses are in agreement with the reported data. Zinc bis[bis(trimethylsilyl)amide] ($Zn(HMDS)_2$)[17] was prepared according to a reported procedure, and stored in glove box at −30 °C. Chiral ligand **L**[23] was prepared according to a literature procedure. Zinc chloride was purchased from Wako Pure Chemical Industries, Ltd.; zinc bromide and zinc triflate were purchased from Tokyo Chemical Industry. Co., Ltd (TCI); zinc fluoride hydrate and zinc acetate were purchased from Aldrich Co. Inc. All the zinc sources were stored in glove box at −30 °C or room temperature, respectively. All reactions were carried out under an argon atmosphere in flame-dried glassware.

Typical Procedure for $Zn(HMDS)_2$-Catalyzed Allylation with Allylboronate 1b

To a dried septum-capped 10-mL flask with magnetic stirring bar under an argon atmosphere was added $Zn(HMDS)_2$ (1.2 mg, 0.0030 mmol, 0.10 mol%). After addition of dry solvent (pentane or THF or co-solvent of both, depending on substrates) (3.0 mL, 1.0 M), allylboronate **1b** (508 mg, 560 μL, 3.30 mmol) and the corresponding substrates **2a–w** (3.00 mmol) were added. The mixture was stirred under an argon atmosphere at 20 °C for 36 h. After dilution with ethyl acetate was added a saturated aqueous NH_4Cl and the phases were separated. The aqueous phase was then extracted with ethyl acetate (15 mL × 3) and the combined organic layers were dried on Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate = 15:1 to 2:1) to afford the corresponding homoallylic alcohols, amines and hydrazides **3a–w**. Physical data of **3a**, **3b**, **3e**, **3g–o**, **3r**, **3s**, **3u–w** were reported in our communication.[16]

Typical Procedure for Asymmetric Allylation of α-Keto Ester with Allylboronate 1b

To the chiral ligand **L** (0.024 mmol) in a dry flask was added $Zn(HMDS)_2$ (7.7 mg, 0.020 mmol) in dry toluene (0.5 mL) under an argon atmosphere, and the mixture was stirred at 75 °C for 1 h, the color of solution gradually changed to red. Then the solution was cooled to −40 °C. To the cooled solution was added allylboronate **1b** (68 mg, 75 μL, 0.44 mmol) and then α-keto ester **1o–q** (0.40 mmol) solution in dry toluene (0.5 mL) was added dropwise, the mixture was stirred at −40 °C for 36 h. The reaction was quenched with saturated aqueous NH_4Cl. The resultant mixture was extracted with ethyl acetate (10 mL × 3), and the combined organic layers were dried over anhydrous Na_2SO_4. The solvents were evaporated under vacuum, and the residue was purified by preparative TLC (hexane/AcOEt = 6/1) to give **3o–q**. The enantiomeric excess of the product was determined by HPLC analysis.

2-(4-Bromophenyl)pent-4-en-2-ol (3c):[24] Colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.44 (ddd, *J* = 9.2, 5.2, 2.9 Hz, 2H), 7.30 (ddd, *J* = 9.2, 5.2, 2.9 Hz, 2H), 5.62–5.56 (m, 1H), 5.11–5.07 (m, 2H), 2.62 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.47 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.32–2.30 (m, 1H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.6, 133.1, 131.0, 126.6, 120.4, 119.5, 73.3, 48.2, 29.5.

2-(4-Nitrophenyl)pent-4-en-2-ol (3d):[9a] Colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.20 (d, *J* = 8.9 Hz, 2H),7.63 (dd, *J* = 6.9, 2.0 Hz, 2H), 5.63–5.56 (m, 1H), 5.17–5.14 (m, 2H), 2.69 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.56 (dd, *J* = 13.7, 7.6 Hz, 1H), 2.15(br, 1H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 155.1, 146.8, 132.5, 125.9, 123.5, 120.5, 73.7, 48.3, 29.9.

2-(Pyridin-3-yl)pent-4-en-2-ol (3f):[10] Colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.63 (d, *J* = 4.6 Hz, 1H), 8.37 (t, *J* = 5.2 Hz, 1H), 7.84 (dd, *J* = 5.7, 4.0 Hz, 1H), 7.26 (d, *J* = 12.0, 6.9 Hz, 1H), 5.73–5.66 (m, 1H), 5.08–5.04 (m, 2H), 4.68 (brs, 1H), 2.62–2.53 (m, 2H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$,125 MHz): δ = 146.9, 146.4, 143.5, 133.1, 133.0, 122.8, 118.8, 72.0, 48.4, 29.0.

Benzyl 2-hydroxy-2-phenylpent-4-enoate (3p): Colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.60–7.59 (m, 2H), 7.34–7.24 (m, 8H), 5.80–5.73 (m, 1H), 5.21 (m, 1H), 5.13–5.07 (m, 3H), 3.78 (s, 1H),3.00 (dd, *J* = 13.7, 7.6 Hz, 1H), 2.79 (dd, *J* = 14.4, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 174.4, 141.1, 134.9, 132.1, 128.5, 128.5, 128.2, 128.1, 127.8, 125.5, 119.4, 78.0, 68.0, 43.9.IR (neat): ν = 3518, 3066, 3033, 2980, 2959, 2918, 1729, 1643, 1497, 1450, 1372, 1262, 1221, 1145, 921, 733, 696 cm^{-1}; HR-MS (DART): *m*/*z* = 265.1230, calcd. for $C_{18}H_{17}O_2^+$ $[M-OH]^+$: *m*/*z* = 265.1229; HPLC [conditions for **3p**: Chiralpak AS-H column, hexane/*i*.PrOH (91:9) 0.5 mL min^{-1}]: t_R = 16.0 min (minor), t_R = 21.5 min (major); $[\alpha]_D^{20}$: +5.1° (*c* 0.42, $CHCl_3$).

Benzyl 2-hydroxy-2-methylpent-4-enoate (3q):[25] Colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.36–7.35 (m, 5H), 5.75–5.71 (m, 1H), 5.19 (s, 2H), 5.09–5.04 (m, 2H), 3.20 (s, 1H), 2.53 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.42 (dd, *J* = 14.3, 6.9 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 176.3, 135.2, 132.1, 128.6, 128.5, 128.2, 119.2, 74.4, 67.4, 44.6, 25.4. HPLC [conditions for **3q**: Chiralpak AS-H column, hexane/*i*-PrOH (500:1) 0.6 mL min^{-1}]: t_R = 46.9 min (*S*), t_R = 53.1 min (*R*).

Methyl 2-{2-[4-(dimethylamino)benzoyl]hydrazinyl}-pent-4-enoate (3t):[12a] Pale yellow oil;^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.28 (s, 1H), 7.69–7.67 (m, 2H),6.63–6.62 (m, 2H), 5.91–5.83 (m, 1H), 5.20–5.12 (m, 2H), 4.70 (br, 1H),3.86–3.84 (m, 1H), 3.72 (s, 3H), 2.98 (s, 6H), 2.62 (dd, *J* = 14.3, 8.0 Hz, 1H), 2.49 (dd, *J* = 14.9, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 173.2, 167.4, 152.7, 133.2, 128.5, 119.1, 118.5, 111.0, 62.5, 51.9, 40.0, 35.3.

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