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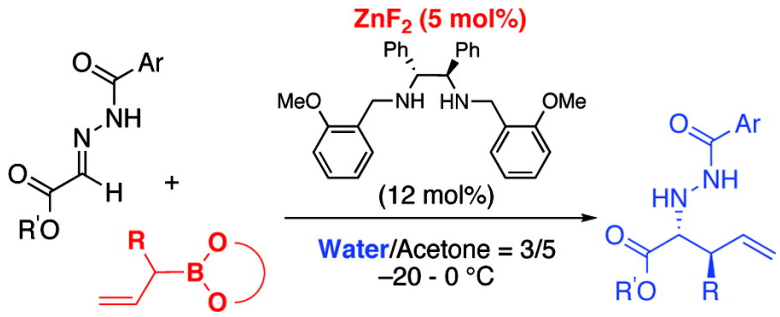

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Zn-Catalyzed Asymmetric Allylation for the Synthesis of Optically Active Allylglycine Derivatives. Regio- and Stereoselective Formal α-Addition of Allylboronates to Hydrazono Esters

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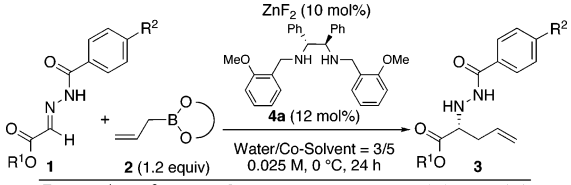
Enantioselective addition to iminoester and equivalents provides an efficient route to optically active α-amino acids.[1] While catalytic asymmetric Mannich-type reactions of iminoester derivatives have been reported,[2] less progress has been made for the corresponding allylations.[3] We now report catalytic asymmetric allylation of hydrazono esters with allylboronates; the remarkable regio- and stereoselective formal α-addition of allylboronates is also described.

Recently we reported catalytic asymmetric allylation of hydrazono esters with allyltrimethoxysilane.[3h] While the reactions proceeded smoothly in aqueous media (water/THF = 1/9) in the presence of ZnF_2-chiral diamine to afford the corresponding allylated products in high yields with good selectivities, they suffered from the requirement to employ an excess (3 equiv) of allyltrimethoxysilane, a relatively low reactivity, and a narrow substrate scope. To address these issues we decided to investigate allylboronates as allylating agents instead of allyltrimethoxysilane.

It was found that the desired reactions proceeded well when hydrazono ester **1a**[4] was treated with allylboronic acid pinacol ester (**2a**) in the presence of catalytic amounts of ZnF_2[5] and chiral diamine **4a** in water/organic solvent mixtures, affording the allylated products in high yields with good enantioselectivities (Table 1). It is noted that the reactions proceeded faster than those using allyltrimethoxysilane and that high yields were obtained using a slight excess of the allylating agent (1.2 equiv). Among organic co-solvents tested, acetone gave the best results (Table 1, entries 1−5). Interestingly, the reaction did not proceed at all in the absence of water (entry 1). Moreover, other allylboronates **2b** and **2c** gave the same levels of yield and enantioselectivity (entries 12, 13). After optimization of the reaction conditions, the desired allylated product **3h** was obtained quantitatively with 90% ee from hydrazono ester **1h** and allylboronate **2a** in water/acetone (3/5) at 0 °C in the presence of 5 mol% of ZnF_2 and 12 mol% of chiral diamine **4a** (entry 14).

We then investigated the reactions using substituted allylboronates. When (*E*)-crotylboronate **2d** was treated with hydrazono ester **1a** under the optimal conditions, the reaction proceeded diastereoselectively (*syn*/*anti* = 96/4) but very slowly in low yield (19% after 110 h at 0 °C), and the enantiomeric excess of the major diastereomer was also low (7% ee). Similarly, (*Z*)-crotylboronate **2e** reacted with **1a** to afford the crotylated product diastereoselectively (*syn*/*anti* = 1/99), but again the yield and the enantioselectivity of the major product were very low (25% yield, 14% ee). These results were unexpected since high reactivity was observed in the reactions using unsubstituted allylboronates **2a**−**c**. We next studied the reactions of α-substituted allylboronates (Table 2). When α-methyl-substituted allylboronate **2f**[6] was reacted with hydrazono ester **1h** under the optimal conditions, the reaction proceeded faster, and unexpected crotylated product **3i** was isolated in high yield; remarkably, no γ-addition product was obtained. Only an *anti*-adduct was produced in high enantiomeric excess. The reaction proceeded at −20 °C to afford the crotylated product quantitatively with perfect *anti*-selectivity and 88% ee (entry 1). We tested other α-substituted allylboronates (entries 2−5), and in all cases only formal α-addition products were obtained. In addition, *anti*-adducts were obtained exclusively in high yields with high enantioselectivities in all cases. These results are especially remarkable because stereoselective reactions of various allylating agents with carbonyl and related compounds have been well investigated, and to the best of our knowledge no *catalytic* regio- and stereoselective formal α-addition reactions have been reported to date.[7,8]

Table 1. Zn-Catalyzed Asymmetric Allylation of Hydrazono Esters **1** with Allylboronates **2a**−**c**

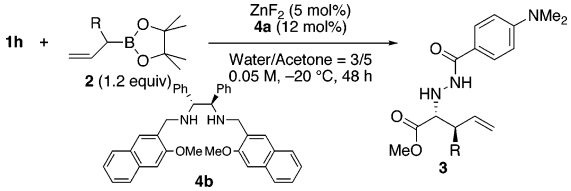


Entry	R^1	R^2	1	2[a]	Co-Solvent	3	Yield (%)	Ee (%)
1	Et	H	**1a**	**2a**	Acetone	**3a**	Quant (0)[b]	79
2	Et	H	**1a**	**2a**	DME	**3a**	Quant	72
3	Et	H	**1a**	**2a**	THF	**3a**	Quant	68
4	Et	H	**1a**	**2a**	DMSO	**3a**	71	71
5	Et	H	**1a**	**2a**	MeCN	**3a**	76	62
6	Bn	H	**1b**	**2a**	Acetone	**3b**	Quant	74
7	Me	H	**1c**	**2a**	Acetone	**3c**	84	82
8	Et	NO_2	**1d**	**2a**	Acetone	**3d**	79	77
9	Et	OMe	**1e**	**2a**	Acetone	**3e**	82	82
10	Et	OH	**1f**	**2a**	Acetone	**3f**	80	86
11	Et	NMe_2	**1g**	**2a**	Acetone	**3g**	98	86
12	Et	NMe_2	**1g**	**2b**	Acetone	**3g**	95	86
13	Et	NMe_2	**1g**	**2c**	Acetone	**3g**	95	87
14[c]	Me	NMe_2	**1h**	**2a**	Acetone	**3h**	Quant	90

[a] Allylating agents: **2a:** $R^3 = R^4 = H$; **2d:** $R^3 = H$, $R^4 = Me$; **2e:** $R^3 = Me$, $R^4 = H$; **2b:** n = 1; **2c:** n = 2.

[b] In the absence of water. [c] ZnF_2 (5 mol%), **4a** (12 mol%), 0.05 M, 36 h.

Table 2. Zn-Catalyzed Asymmetric Allylation of Hydrazono Ester **1h** with α-Substituted Allylboronates **2**



Entry	R	3	Yield (%)	α/γ	*syn*/*anti*	Ee (%)
1	Me (**2f**)	**3i**	Quant	>99/<1	<1/>99	88
2	Et	**3j**	98	>99/<1	<1/>99	87
3	Bu	**3k**	88	>99/<1	<1/>99	87
4	*i*-Amyl	**3l**	76	>99/<1	<1/>99	87
5[a]	OBn	**3m**	65	>99/<1	<1/>99	82

[a] **4b** was used instead of **4a**.

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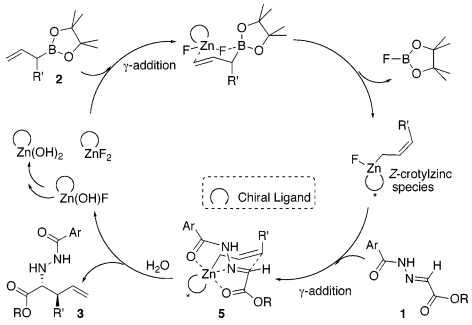
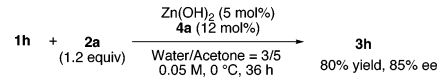
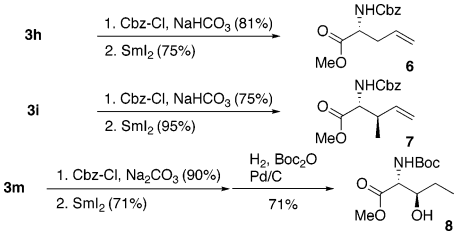
Scheme 1. Assumed Reaction Pathway and Catalytic Cycle



Scheme 2. $Zn(OH)_2$-Catalyzed Asymmetric Allylation in Aqueous Media



Scheme 3. Synthesis of Allylglycine Derivatives



At present we assume this unprecedented reaction pathway and catalytic cycle as shown in Scheme 1. In an initial stage, allylboronate **2** may react with ZnF_2 to form allylzincate. While this process was confirmed by NMR analysis using allylboronate **2a** and ZnF_2, similar experiments using α-methyl-substituted allylboronate **2f** and ZnF_2 have so far proved unsuccessful. We assume that **2f** may react with ZnF_2 via a six-membered chairlike transition state (γ-addition of **2f** toward ZnF_2) to afford *Z*-crotylzinc species, which may react with hydrazono ester **1** stereoselectively via γ-addition, giving the crotylated product with *anti*-selectivity.[9] Another interesting point regarding this proposed pathway and catalytic cycle is regarding the regeneration of ZnF_2 or other active Zn species. Since water is necessary in this reaction, hydrolysis of intermediate **5** may proceed smoothly to afford the product along with generation of Zn(OH)F. Since after the second turnover $Zn(OH)_2$ may be formed, we then conducted the reaction employing catalytic $Zn(OH)_2$ instead of ZnF_2 to test its efficacy as a catalyst and probe the mechanism. Interestingly, the allylation reaction of **1h** with **2a** proceeded using $Zn(OH)_2$ as a catalyst to afford the desired allylated product in 80% yield with 85% ee (Scheme 2). It should be noted that, to the best of our knowledge, this is the first example of a chiral metal hydroxide-catalyzed asymmetric reaction and that metal hydroxides are ideal catalysts for organic reactions in aqueous media.[10]

To demonstrate the utility of this asymmetric allylation and determine the relative and absolute configurations of the products, several transformations of the products were conducted. Allylated adduct **3h** was treated with Cbz-Cl, followed by SmI_2 to afford allylglycine derivative **6**;[11] similarly, **3i** was converted to **7**.[12] **3m** was also converted to the previously reported allylglycine derivative **8** bearing a hydroxy group in good yield (Scheme 3).[13]

In summary, we have developed Zn-catalyzed asymmetric allylation of hydrazono esters with allylboronates. Several characteristic features of these reactions have been revealed. (1) Catalytic asymmetric allylation of imine derivatives was attained in high yields and high stereoselectivities. (2) Formal α-addition occurred for α-substituted allylboronates exclusively, and excellent stereoselectivities were observed. This is the first example of *catalytic* regio- and stereoselective allylations with formal α-addition. (3) The reaction proceeded in aqueous media. The use of water is essential. (4) $Zn(OH)_2$ might be a catalyst in this asymmetric allylation. The catalytic activity of $Zn(OH)_2$ was confirmed, and this is also the first case of chiral metal hydroxide catalyzed asymmetric reactions. Further investigations to clarify the precise mechanism of the formal α-addition as well as catalytic cycle of Zn species and to use metal hydroxides in organic reactions in aqueous media are now in progress in our laboratories.

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Supporting Information Available: Procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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