

論文の内容の要旨

Catalytic Asymmetric Carbonyl Allylation and Allylic Amination in Aqueous Media

(水溶媒中でのカルボニル化合物の触媒的不斉アリル化反応及びアリル位アミノ化反応)

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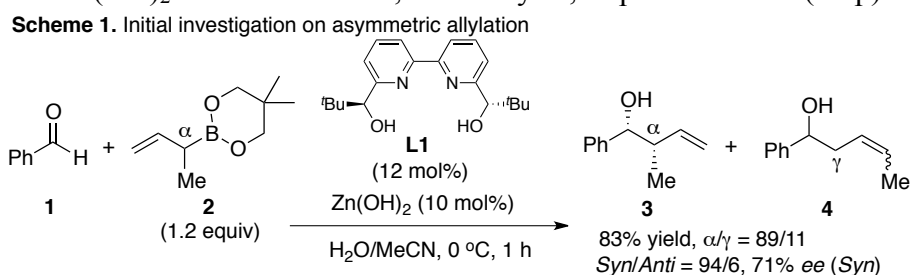
Introduction

Although water is cheap, safe, and environmentally friendly compared to organic solvents, most organic reactions have been conducted in organic solvents. On the other hand, unique reactivity and selectivity are sometimes observed in aqueous solvents. In this content, our laboratory has investigated organic reactions in aqueous media, and among them, I have focused on the use of metal hydroxides as catalysts in water (aqueous media) and aqueous ammonia as a nitrogen source in organic synthesis. In this work, I developed two kinds of catalytic asymmetric reactions in aqueous solvents.

Zinc Hydroxide ($\text{Zn}(\text{OH})_2$)-Catalyzed Asymmetric α -Selective Allylation of Aldehydes in Aqueous Media

Catalytic asymmetric allylation of aldehydes provides optically active homoallylic alcohols, which are useful intermediates for the synthesis of natural products and biologically important compounds. When allylboronates are used as reagents for allylation of aldehydes, most reactions are conducted under anhydrous conditions because most chiral reagents/catalysts are easily decomposed in the presence of even a small amount of water. In addition, most asymmetric reactions are carried out at low temperature (mostly at $-78\text{ }^\circ\text{C}$) because allylboration of aldehydes proceeds spontaneously without catalyst. On the other hand, it is well known that allylboration of aldehydes proceeds through a cyclic six-membered transition state to afford γ -addition products. γ -Addition products are also obtained in the catalytic asymmetric allylboration of aldehydes.

On the other hand, I have already developed α -selective allylation of aldehydes with α -substituted allylboronates catalyzed by 5 mol% of $\text{Zn}(\text{OH})_2$ and 6 mol% of 2,9-dimethyl-1,10-phenanthroline (dmp) in aqueous media.¹⁾ I also applied this catalytic system to asymmetric variant by using a chiral ligand. The reaction of benzaldehyde (**1**) with α -methylallylboronate (**2**) in the



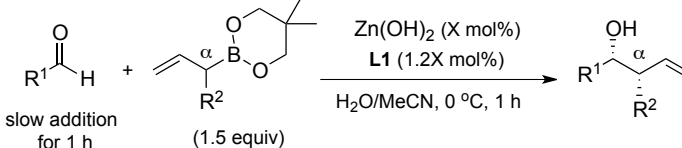
presence of 10 mol% of Zn(OH)₂ and 12 mol% of chiral bipyridine ligand (**L1**) at 0 °C afforded the α-addition product (**3**) in 83% yield with high *syn*-selectivity (*syn/anti* = 94/6) and 71% *ee* (*syn*-isomer) along with γ-addition product (**4**) (Scheme 1).

During my Ph.D. studies, I firstly examined the addition modes of the reagents to suppress the formation of the γ-adduct. As a result, when benzaldehyde was slowly added over 1 h, only α-adduct was obtained in 92% yield with keeping high *syn*-selectivity (*syn/anti* = 91/9) and good enantioselectivity (71% *ee*). Substrate generality was then surveyed under the optimized conditions (Table 1). The reactions proceeded

smoothly using 2–10 mol% of the catalyst, and in all cases exclusive α-selectivity was observed. When aliphatic aldehydes were employed, the desired products were obtained with high enantioselectivities, although diastereoselectivities were little decreased (entries 2-4). Not only α-methylallylation but also other α-alkylallylations proceeded smoothly, and moderate to excellent *syn*-selectivities and high to excellent enantioselectivities were obtained (entries 5-7). Moreover, α-benzyloxyallylation also proceeded well, and high diastereo- and enantioselectivities were attained using both aromatic and aliphatic aldehydes (entries 8-9). This catalytic system was also applicable to asymmetric α-chloroallylation. Aromatic as well as aliphatic aldehydes bearing some functional groups worked efficiently to afford the desired products in high to excellent yields with high to excellent diastereo- and enantioselectivities (entries 10-14). The reaction also proceeded smoothly in the presence of 2 mol% of the catalyst (entry 13). Some of the products were directly used for the synthesis of natural products, such as disparlure (entry 13) and spirastrellolide A (entry 14).

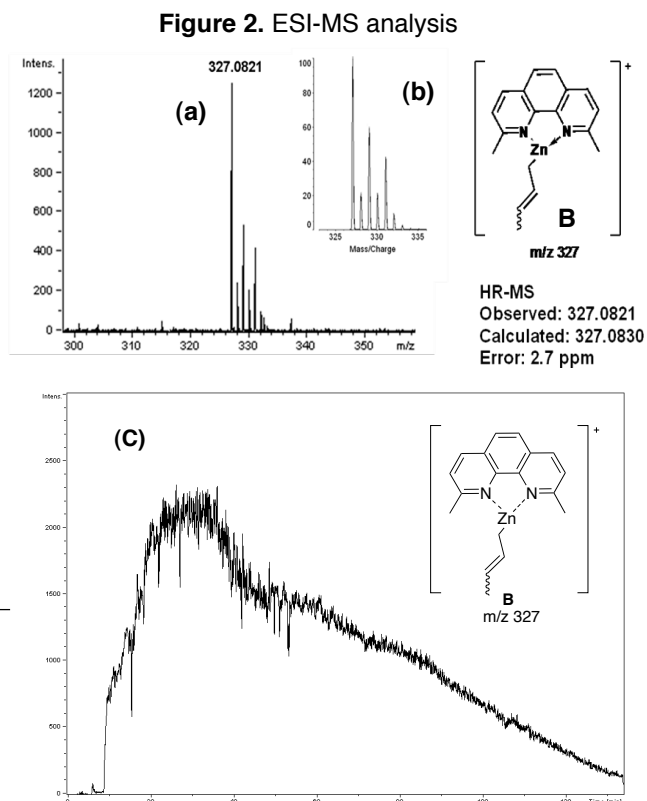
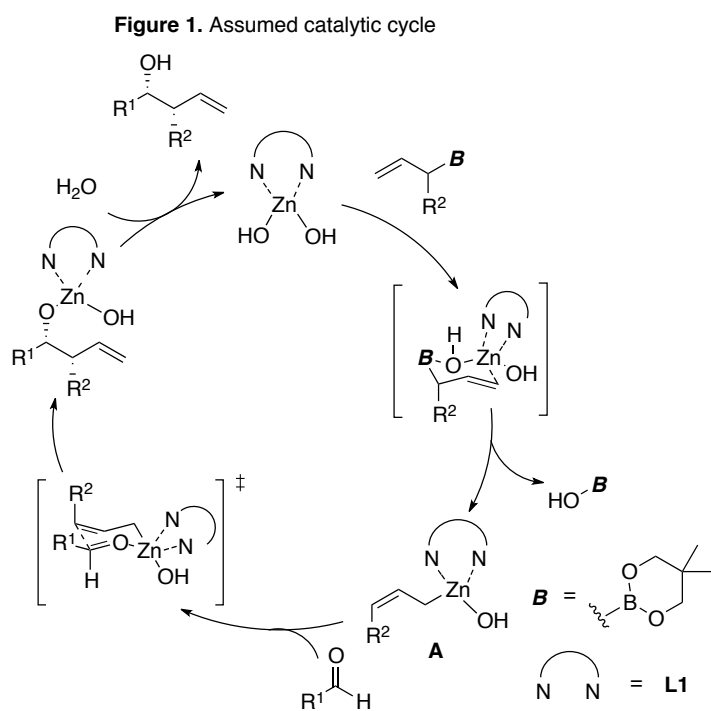
As for the mechanism of this catalytic process, because α-addition products were obtained exclusively, I assumed the double γ-addition mechanism (Figure 1). The catalytic cycle is initiated by boron-to-zinc transmetalation to form the γ-substituted allylzinc **A**, which can react smoothly with aldehydes via a γ-addition fashion. In order to examine more detail of the reaction mechanism, I initially tried to detect the allylzinc **A** directly. When Zn(OH)₂, dmp and α-methylallylboronate were combined in H₂O/MeCN (1/4), the major signals of the crotylzincate **B** were detected by ESI-MS analysis (Figure 2(a)). The isotope pattern was identical with the calculated one (Figure 2(b)). It was found that this crotylzincate **B** was not stable and gradually decomposed in aqueous media. This decomposition was successfully monitored by online ESI-MS analysis (Figure 2(c)).

Table 1. Substrate scope of asymmetric allylation



Entry	R ¹	R ²	X	Yield (%)	α/γ	Syn/Anti	Ee (Syn)
1	Ph	Me	10	92	>99/<1	91/9	71
2	PhCH ₂ CH ₂	Me	5	94	>99/<1	82/18	85
3	CH ₃ (CH ₂) ₈	Me	3	94	>99/<1	88/12	82
4	<i>c</i> -C ₆ H ₁₁	Me	3	80	>99/<1	84/16	97
5 ^a	PhCH ₂ CH ₂	Et	5	96	>99/<1	74/26	91
6 ^a	PhCH ₂ CH ₂	^t Bu	5	95	>99/<1	72/28	91
7 ^a	PhCH ₂ CH ₂	ⁿ Bu	5	97	>99/<1	73/27	90
8	Ph	OBn	10	82	>99/<1	96/4	88
9	PhCH ₂ CH ₂	OBn	10	74	>99/<1	80/20	96
10	Ph	Cl	5	92	>99/<1	96/4	88
11	PhCH ₂ CH ₂	Cl	3	92	>99/<1	92/8	95
12	<i>c</i> -C ₆ H ₁₁	Cl	10	66	>99/<1	95/5	98
13	CH ₃ (CH ₂) ₁₀	Cl	2	93	>99/<1	93/7	93
14	TBSOCH ₂ CH ₂	Cl	7.5	77	>99/<1	91/9	95

^a Slow addition for 3 h



I then conducted kinetic investigation in the reaction of 3-phenylpropanal with α -methylallylboronate. As a result, a first-order dependence on the allylboronate and a zero-order dependence on the 3-phenylpropanal were observed, respectively. These observations conclude that transmetalation from B to Zn is the rate determining step in this reaction. I also evaluated chiral ligands **L2** and **L3** in the reaction of 3-phenylpropanal with α -chloroallylboronate under the standard conditions (Table 2). Interestingly, the reactions proceeded smoothly in the presence of **L2** and **L3** to provide α -addition products exclusively. However, while high diastereo- and enantioselectivities were observed using **L2**, almost no selectivity was observed in the case of **L3**. In addition, our group already obtained X-ray crystallographical data of the ZnBr_2 and **L1** complex, and it adopts a square-pyramidal structure, in which the two pyridine nitrogen atoms and one of the two hydroxy groups of **L1** coordinate to zinc. These data suggested that one face of the allylzinc moiety could be shielded by the fixed *tert*-butyl group.

Table 2. Effect of chiral ligands

Entry	R ¹	R ²	L	Yield (%)	α/γ	Syn/Anti	Ee (Syn)
1	H	H	L1	85	>99/<1	95/5	97
2	H	Me	L2	91	>99/<1	97/3	95
3	Me	Me	L3	93	>99/<1	45/55	1

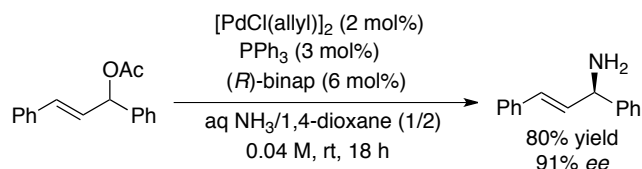
Palladium-Catalyzed Asymmetric Allylic Amination Using Aqueous Ammonia

To use aqueous ammonia as a N1 source in organic chemistry is one of the most attractive methods for the synthesis of primary amines. However, in the use of ammonia for metal-catalyzed processes, many kinds of transition metals are deactivated by ammonia to give stable amine complexes. Moreover, when a primary amine is formed, this product is more reactive than ammonia and causes overreactions to provide secondary amines. On the other hand, we have already developed the first palladium-catalyzed allylic amination using aqueous ammonia for the preparation of primary amines.²⁾ The reactions proceeded

smoothly in the presence of 10 mol% of Pd(PPh₃)₄ to afford the desired primary amines with high selectivities.

I found that when the reaction was conducted with 2 mol% of [PdCl(allyl)]₂ and 6 mol% of (*R*)-BINAP, enantioselective allylic amination proceeded smoothly (Scheme 2).

Scheme 2. Catalytic asymmetric allylic amination



Conclusion

Catalytic asymmetric synthesis using aqueous solvents was investigated. First, Zn(OH)₂-catalyzed α -selective asymmetric allylation of aldehydes with α -substituted allylboronates was achieved. Various aldehydes were converted to optically active homoallylic alcohols in the presence of catalytic amounts of Zn(OH)₂ and **L1** in aqueous media with exclusive α -selectivity. It is noted that this method does not require strictly anhydrous reaction conditions and low temperature. Second, palladium-catalyzed asymmetric allylic amination using aqueous ammonia has been accomplished. These reactions only proceed in aqueous media or the optimal selectivities are observed only in aqueous media. In both cases, water plays a key role for the reactivity and selectivity.

References

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- ²⁾ T. Nagano, S. Kobayashi, *J. Am. Chem. Soc.* **2009**, 131, 4200-4201.