Asymmetric Catalysis

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Chiral Zinc-Catalyzed Asymmetric α-Alkylallylation and α-Chloroallylation of Aldehydes**

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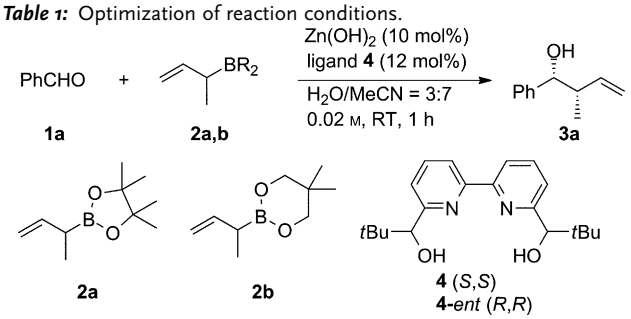
Asymmetric catalysis is now recognized as one of the most efficient methods for the preparation of optically active compounds.[1] Although many catalytic asymmetric reactions have been developed, most reactions are carried out under strictly anhydrous and oxygen-free conditions, because most chiral catalysts and reagents decompose in the presence of even small amounts of water or oxygen. Furthermore, many reactions are conducted at low temperature, such as −78 °C, to obtain high selectivities. It is energy efficient and thus preferable to perform reactions at 0 °C to ambient temperature.

Asymmetric allylation of aldehydes provides optically active homoallylic alcohols, which are useful intermediates for the synthesis of natural products, biologically important compounds, and so forth.[2] When substituted allylating reagents are used, it is possible to control the absolute configuration of two successive stereogenic centers during one carbon–carbon bond formation. For catalytic asymmetric allylation of aldehydes (using substoichiometric amounts of chiral sources) allylstannanes[3] and allylsilanes[4] have often been used as allylating reagents.[5] However, allylstannanes are toxic and allylsilanes are less reactive and sometimes have narrow substrate scope. More recently, allylboron reagents have received attention as reactive and less toxic allylating reagents in asymmetric catalysis.[6,7a–d] However, although allylboron reagents have been successfully used for allylation of less reactive ketones,[6j–l] because of their high reactivity the reactions with aldehydes proceeded instantaneously without catalysts,[7c] and therefore catalytic asymmetric reactions of aldehydes with allylboron reagents have been carried out at low temperature (mostly at −78 °C). Moreover, examples of catalytic asymmetric α-alkylallylation and α-chloroallylation of aldehydes with allylboron reagents to construct two successive stereogenic centers are very rare, and to our knowledge only catalytic asymmetric α-methylallylation (crotylation) using crotylboronates has been reported.[5b,e–i,6f,7]

Recently, we found that allylation reactions of allylboronates with aldehydes proceed smoothly in the presence of catalytic amounts of $Zn(OH)_2$ and 2,9-dimethyl-1,10-phenanthroline (dmp) in aqueous media.[8] When α-substituted allylboronates such as **2a** were employed, the α-addition products were obtained exclusively with *syn* selectivities.

As an extension of this work, we have investigated a catalytic asymmetric variant of this reaction. After the investigation of various chiral ligands and allylboronates, it was found that the combination of $Zn(OH)_2$ and the chiral bipyridine ligand **4**[9] with allylboronic acid 2,2-dimethyl-1,3-propanediol ester (**2b**) gave the best results. A certain amount of γ-adduct was obtained with the allylboronic acid pinacol ester (**2a**), whereas in the reaction with **2b** the desired α-addition product was obtained exclusively with excellent *syn* selectivity and good enantioselectivity (Table 1).

Table 1: Optimization of reaction conditions.



Entry	Allylboronate	Yield [%][a]	α/γ[b]	*syn*/*anti*[b]	e.r. (*syn*)[c]
1	**2a**	75	52/48	19/1	83/17
2	**2b**	96	94/6	10/1	81/19
3[d]	**2b**	92	89/11	16/1	86/14
4[e]	**2b**	92	>99/<1	10/1	85.5/14.5
5[e,f]	**2b**	85	>99/<1	10/1	86.5/13.5[g]

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC on a chiral stationary phase. [d] 0 °C. [e] 0 °C. **1a** was added over one hour. [f] **4**-*ent* was used. [g] The enantiomer of **3a** is the major product.

Other examples of chiral zinc-catalyzed asymmetric α-alkylallylation and α-chloroallylation are shown in Table 2. The reactions proceeded smoothly using 2–10 mol% of the catalyst, and in all cases exclusive α-selectivity was observed at 0 °C in aqueous media. A gram-scale preparation is also possible. Not only α-methylallylation (crotylation) but also other α-alkylallylations proceeded smoothly, and moderate to excellent *syn* selectivities and high to excellent enantioselectivities were obtained (Table 2, entries 1–7). Moreover, α-benzyloxyallylation also proceeded well under the conditions, and high yields and diastereo- and enantioselectivities were attained using both aromatic and aliphatic aldehydes

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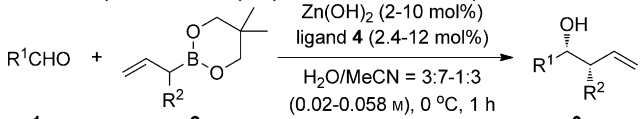
Table 2: Asymmetric α-alkylallylation and α-chloroallylation.[a]



Entry	R^1	R^2	Loading (mol%)	Yield [%][b]	*syn*/*anti*[c]	e.r. (*syn*)[d]
1	$PhCH_2CH_2$	Me	10	94	6/1	94/6
2	$PhCH_2CH_2$	Me	5	94	5/1	92.5/7.5
3	$CH_3(CH_2)_8$	Me	3	94	7/1	91/9
4	*c*-C_6H_{11}	Me	3	80	5/1	98.5/1.5
5[e]	$PhCH_2CH_2$	Et	5	96	3/1	95.5/4.5
6[e]	$PhCH_2CH_2$	*i*Bu	5	95	3/1	95.5/4.5
7[e]	$PhCH_2CH_2$	*n*Bu	5	97	3/1	95/5
8	Ph	OBn	10	82	24/1	94/6
9	$PhCH_2CH_2$	OBn	10	74	4/1	98/2
10	Ph	Cl	10	93	99/1	94/6
11	Ph	Cl	5	92	24/1	94/6
12	4-MeC_6H_4	Cl	3	91	24/1	93.5/6.5
13	3-$MeOC_6H_4$	Cl	7.5	99	19/1	95.5/4.5
14	4-BrC_6H_4	Cl	7.5	quant.	19/1	92.5/7.5
15	1-naphthyl	Cl	10	quant.	19/1	93/7
16	1-naphthyl	Cl	5	94	13/1	92.5/7.5
17	$PhCH_2CH_2$	Cl	10	85	19/1	98.5/1.5
18	$PhCH_2CH_2$	Cl	3	92	13/1	97.5/2.5
19[f]	$PhCH_2CH_2$	Cl	3	87	13/1	97/3[g]
20	$CH_3(CH_2)_{10}$	Cl	10	93	32/1	99/1
21	$CH_3(CH_2)_{10}$	Cl	3	93	13/1	96.5/3.5
22	$CH_3(CH_2)_{10}$	Cl	2	92	13/1	96.5/3.5
23	$(CH_3)_2CHCH_2$	Cl	10	64	49/1	99/1
24	TBSO-CH_2CH_2	Cl	10	73	7/1	96/4

[a] Compound **1** was slowly added over one hour unless otherwise noted. The α/γ ratio was determined by ^{1}H NMR spectroscopy and found to be >99/<1 in all cases. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a stationary phase. [e] **1** was added over three hours. [f] **4**-*ent* was used. [g] The enantiomer of **3** is the major product.

(Table 2, entries 8 and 9). This Zn catalysis was also applicable to asymmetric α-chloroallylation (Table 2, entries 10–24). Optically active α-chlorohomoallylic alcohols (**3**; R^2 = Cl) are useful intermediates for the synthesis of natural products and other compounds (see below). 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. Because both enantiomers of ligand **4** are readily available, both enantiomers of the products can be easily obtained according to this protocol (Table 2, entry 19, see also Table 1, entry 5). The reaction also proceeded smoothly in the presence of 2 mol% of the catalyst (Table 2, entry 22). It is noteworthy that some of the products were directly used for the synthesis of natural products, such as disparlure[10] (Table 2, entries 20–22) and spirastrellolide A[11] (Table 2, entry 24).

The mechanism of this catalytic process has not yet been completely elucidated; however, because α-addition products were obtained exclusively, we assumed the double γ-addition mechanism operated.[8] A key species is assumed to be γ-substituted allylzinc with chiral ligand **4**,[12] which can react smoothly with aldehydes in a γ-addition fashion. A kinetic investigation revealed a first-order dependence on the concentration of allylboronate and a zero-order dependence on the concentration of electrophile.[13] Our analysis leads us to conclude that transmetalation from B to Zn is the rate-determining step in this reaction. Another characteristic feature of this catalytic process is that the reactions proceeded smoothly in aqueous media, where water plays a key role to facilitate release and regeneration of the catalyst from the products.

We also conducted an X-ray crystal-structure analysis. Single crystals that were suitable for X-ray analysis were obtained from a $ZnBr_2$-**4** complex (Figure 1).[14] The complex

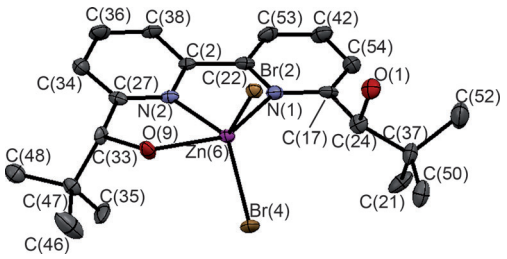
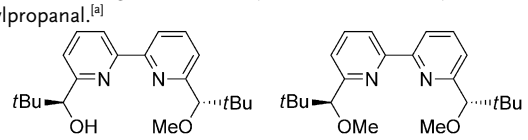


Figure 1. X-ray structure of $ZnBr_2$-**4**-*ent* complex.

adopts a square-pyramidal structure, in which the two pyridine nitrogen atoms and one of the two hydroxy groups of **4** coordinate to Zn^{2+}. It is interesting that one of the two hydroxy groups of **4** does not coordinate to Zn^{2+} in this structure.[15,16] It is likely that the two Br groups dissociate in aqueous media, and it may be possible that the square-pyramidal structure converts to the trigonal-pyramidal structure in solution.[17] In any case, if one of the Br atoms is replaced by an allyl group by transmetalation from B to Zn in a γ-addition fashion, one face of the allylzinc moiety could be shielded by the fixed *tert*-butyl group (left in Figure 1). This transition state model is consistent with the absolute configuration of the products obtained. We also evaluated chiral ligands **5** and **6** in the reaction of 3-phenylpropanal with α-chloroallylboronate (**2**, R^2 = Cl) under the standard conditions (Table 3). Very interestingly, in both cases the reactions proceeded smoothly exclusively in an α-addition fashion, but almost no selectivity was observed using **6**, whereas the same high diastereo- and enantioselectivities as obtained using ligand **4** were obtained using **5**. Furthermore, these results contrast strikingly with our previous results in an asymmetric ring-opening reaction of a *meso*-epoxide with aniline, where almost no diastereo- or enantioselectivity was obtained using either **5** or **6**.[18]

In summary, we have developed chiral zinc-catalyzed asymmetric α-alkylallylation and α-chloroallylation of aldehydes. Various homoallylic alcohols bearing two neighboring stereogenic centers were synthesized in high yields with high diastereo- and enantioselectivities. The reactions proceeded at 0 °C in an α-addition fashion exclusively with high stereoselectivities in aqueous solution.[19] It is noteworthy from a practical point of view that a low temperature such as −78 °C and anhydrous conditions are not necessary. More-

Table 3: Effect of ligands **4**–**6** in asymmetric α-chloroallylation of 3-phenylpropanal.[a]



5 **6**

Entry	Ligand	Yield [%][c]	*syn*/*anti*[d]	e.r. (*syn*)[e]
1[b]	**4**	85	19/1	98.5/1.5
2	**5**	91	32/1	97.5/2.5
3	**6**	93	1/1.2	50.5/49.5

[a] The reaction conditions are shown in Table 2 ($Zn(OH)_2$ 10 mol%, ligand 12 mol%). The α/γ ratio was determined by ^{1}H NMR spectroscopy and found to be $>99/<1$ in all cases. [b] The same as Table 2, entry 17. [c] Yield of isolated product. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by HPLC on a stationary phase.

over, $Zn(OH)_2$ used in this reaction as a catalyst is a common compound, and the combined use with less toxic boron reagents makes the whole process environmentally benign. Furthermore, α-addition is a rare case of asymmetric allylation with allylboron reagents.[8,20] It is noted that optically active boron reagents **2**[21] are not needed, and that racemic **2** and a catalytic amount of a chiral source efficiently gave optically active homoallylic alcohols with neighboring stereogenic centers.

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[14] CCDC 827315 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from

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