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Catalytic asymmetric allylations of achiral and chiral aldehydes via BINOL–Zr complex

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Abstract—The complex generated from BINOL, $Zr(O^tBu)_4$, and 4 Å MS in toluene–pivalonitrile is very effective for catalytic asymmetric allylation of aldehydes using allyltributyltin. The reactions of achiral aldehyde under these conditions are completed within 3 h using 10–20 mol% of the complex at −20°C. The ees of homoallylic alcohols can be enhanced up to 98% via the tandem asymmetric allylation–Oppenauer oxidations. The scope and limitations of these conditions for β-alkoxy aldehydes were extensively examined.

The additions of the acetate unit to aldehydes play a significant role in the syntheses of most natural products of polyketide origin.[1] In a number of total syntheses of such molecules asymmetric allylations of aldehydes are often the start in constructing 1,3-polyol units, and the asymmetric allylation via chiral allyldialkylboranes[2] and allyldialkoxylboranes[3] has been widely utilized.[4] Since the stereochemical course is strongly controlled by a closed chair-like transition state, these methods have often suffered from lower selectivity when chiral aldehydes (mismatched substrates) were employed.[5] In order to overcome mismatched systems, it is especially important to induce the desired stereochemistry through an open-chained (acyclic) transition state. Although impressive advances have been achieved in Lewis acid and Lewis base-catalyzed enantioselective allylation of aromatic and reactive aldehydes,[6] few procedures can be applied to various types of aldehydes. Among the catalytic asymmetric allylation reactions developed so far, catalysts prepared from either BINOL/$Ti(O^iPr)_4$,[7] or BINOL/$TiCl_2(O^iPr)_2$[8] (BINOL = 1,1′-binaphtalen-2,2′-diol) using allyltributyltin are applicable to a certain type of chiral aldehydes. In many model studies described in the literature these reactions provide homoallylic alcohols in excellent enantiomeric excess (ee) but need to be further developed, because (1) in our hands, reported yields and ees were not reproducible,[9] (2) the catalysts require 20 mol% (with respect to BINOL), (3) the reactions require very long reaction times at controlled temperatures, (3) no generalization has been possible for catalytic symmetric allylation reactions of chiral aldehydes. We now wish to report a very efficient catalytic asymmetric allylation of aldehydes via BINOL and $Zr(O^tBu)_4$,[10] and its application to syntheses of 1,3-polyols.

In our studies on the structure elucidation of the BINOL-group IVB transition metals complexes by Fourier transform ion cyclotron resonance (FT-ICR) mass spectroscopy,[11] a 1:1 mixture of BINOL and $Ti(O^tPr)_4$ in CH_2Cl_2 in the presence of 4 Å molecular sieves (MS) formed a complex which contains four Ti atoms (calculated mass = 1819.0445). This complex,[12] however, exhibited very poor catalytic activity in the allylation of hydrocinnamaldehyde using allytributyltin (less than 5% conversion after 12 h at −20°C, the isolated product was 86% ee). On the other hand, the same reaction using 10 mol% of a 1:1 mixture of (*S*)-BINOL and $Zr(O^tBu)_4$ in toluene[13] at −20°C for 2.5 h afforded (*R*)-1-phenyl-hex-5-ene-3-ol in 75% yield with 88% ee. After extensive optimization of the reaction conditions using the BINOL-$Zr(O^tBu)_4$ complex, several critical findings emerged: (1) the reaction proceeded even at −78 to −60°C and was completed with 150 mol% of the catalyst, (2) the reactions at 0°C caused reduction of the aldehydes, (3) the addition of 4 Å MS was very important for minimizing the self-condensation of aldehydes, (4) the addition of 10% of pivalonitrile[14] to toluene was effective in increasing the ees (up to 93%), (5) in the presence of 4 Å MS and pivalonitrile addition of an excess of $Zr(O^tBu)_4$ did not result in a decrease of ees, (6) an excess (1.5–2.0 equiv.) of allyltributyltin was required to facilitate the catalytic

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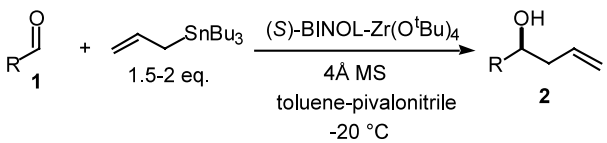
cycle, and (7) under these conditions the ees of products were not affected by the amount of catalyst used; the reactions with 10, 20, 100% of the catalyst gave the same values of ees. We have applied the optimized conditions to over 20 different aldehydes and the representative results are summarized in Table 1.[15]

In most cases the reactions were remarkably rapid; allylations of the achiral aldehydes were completed within 3 h and the isolated products exhibited 90–93% ees. Allylation of 3-benzyloxy-propionate afforded the desired homoallylic alcohol in greater than 80% yield with 93% ee (entry 7). In addition, the allylation of the alkynal gave rise to the propargyl alcohol with satisfactory ee (entry 8); asymmetric allylations that are controlled via a cyclic transition state usually result in poor asymmetric induction. Although modified BINOLs–$Zr(O^tBu)_4$ complexes have been applied to catalytic asymmetric Mannich-type reactions,[10b] Strecker-type reactions[10e] and aldol reactions[10f] with excellent enantioselectivities, unmodified BINOL–Zr complexes do not exhibit a useful level of asymmetric induction without the addition of complex additives.[6j,10c,16] However, we were able to attain a useful catalytic asymmetric allylstannylation of aldehydes via unmodified BINOL in combination with a solvent system such as toluene–pivalonitrile. Because (*S*)- and (*R*)-BINOLs are now available very cheaply[17] and because BINOLs can be recovered relatively easily from the reaction mixtures by chromatography, the catalytic asymmetric allylation reaction described here can be utilized for syntheses of relatively large amounts of optically active homoallyl alcohols; we have carried out allylation of the aldehydes on a 5–10 g scale (entries 3 and 5 in Table 1). Thus, these procedures are much more practical than others previously described.

We recognized that the ees of homoallylic alcohols could be enhanced by subsequent Oppenauer oxidations. Using the complex generated from a 1.2:1 mixture of $Zr(O^tBu)_4$ and BINOL a tandem catalytic asymmetric allylation–Oppenauer oxidation (AA–Oppenauer reaction) took place. The tandem AA–Oppenauer reactions were especially useful for relatively reactive aldehydes such as aromatic aldehydes and hydrocinnamaldehyde (Scheme 1 and Table 2).[18]

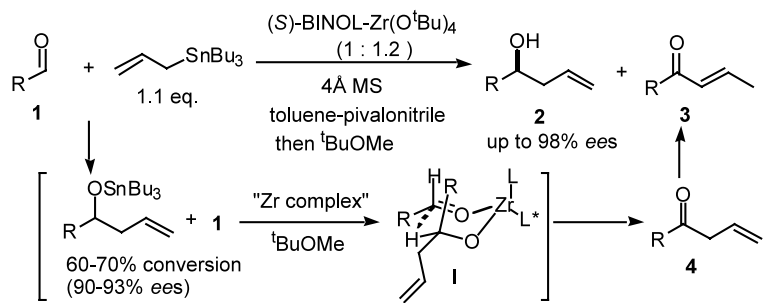
The catalytic allylation reactions using 1.1 equiv. of allytributyltin yielded the desired homoallyl alcohol in 60–70% yields. The intermediate, a homoallylic tin alkoxide, reacts with a chiral BINOL–Zr complex and the unreacted aldehyde **1** was utilized as a hydride

Table 1. Catalytic asymmetric allylation of achiral aldehydes via BINOL-$Zr(O^tBu)_4$



Entry	Aldehyde (R =)	Catalysts (mol%)	Time (h)	Yield (%)	ee (%)
1	Ph	10	1.5	90	85–90[a]
2	$PhCH_2CH_2$	10	2.5	85	93[a]
3	C_7H_{15}	10	2.5	86	93[b]
4	$TIPSOCH_2(CH_2)_3$	10	2	80–90	90–93[b]
5	$BnOCH_2(CH_2)_3$	10	2	80–90	90–93[b]
6	$TBSOCH_2CH_2$	10	2.5	75	92[b]
7	$BnOCH_2CH_2$	20[c]	2.5	88	93[b]
8	$CH_3(CH_2)_4CC$	10	1	89	90[b]
9	(*E*)-PhCH=CH	10	2.5	85	93[b]
10	$MeO_2C(CH_2)_4$	10	2	86	92[b]

[a] % ee determined by the HPLC analysis on a Chiralcel OD column.
[b] % ee determined by ^1H NMR spectroscopic analysis of its Mosher ester.
[c] Allylation reaction using 10 mol% of catalyst gave the product ranging from 70 to 75% yields.



Scheme 1. Tandem catalytic asymmetric allylation–Oppenauer oxidation.

Table 2.

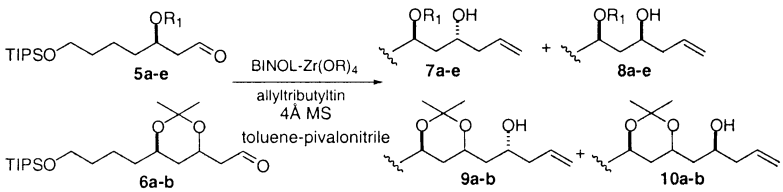
Entry	Aldehyde (R=)	Catalysts (mol%)	Time (h)	Yield (%)	ee[a] (%)
1	Ph	10	24	50	98
2	4-BrPh	10	24	45	98
3	(*E*)-PhCH=CH	10	24	58	96
4	$PhCH_2CH_2$	10	24	50	97

[a] % ee determined by the HPLC analysis on a Chiralcel OD column.

acceptor to produce ketone **4** via transition model **I**. Undesired homoallyl tinalkoxides were oxidized faster than desired tinalkoxides. The terminal double bond of **4** was isomerized during work-up to afford enone **3**. For the Oppenauer oxidation with the BINOL–Zr complex use of ^{t}BuOMe was most effective among the solvents investigated.[19]

Although asymmetric allylations via acyclic transition states might be useful for chiral aldehydes, few such applications were found in the literature.[20] The major drawback in these reactions of aldehydes possessing a β-chiral center using reported methods is that the reactions require an extremely long reaction time (6 days at −20°C). In addition, the diastereoselectivities of allylated products seem to be influenced significantly by the protecting groups used. On the basis of data provided by FT-ICR mass spectroscopy, the rather large catalyst (calculated mass = 1775.2592) generated from BINOL-Zr(O^{t}Bu)$_4$ in toluene–pivalonitrile might interact with the functional groups at the β-position. To investigate how the BINOL–Zr catalyst ignores the β-chiral center of aldehydes, we first synthesized a variety of β-hydroxy aldehydes possessing different protecting groups. These aldehydes were used for the asymmetric allylations using both (*S*)- and (*R*)-BINOLs. As summarized in Table 3, the allylation reactions using BINOL–Zr complex were significantly influenced by protecting groups at the β-position. The reaction of **5a** (R_1 = Me) proceeded in favor of the *anti*-product regardless of the chirality of BINOL (entries 1 and 2). The TBS protected substrate **5e** did not afford a useful level of asymmetric induction (entries 9 and 10). Allylation reactions of the Bn and MPM protected substrates, **5c** and **5d**, using (*R*)-BINOL as a chiral source afforded *anti*:*syn* selectivity of 4.2:1 and 4.0:1, respectively. However, reactions using (*S*)-BINOL gave poor selectivity of *anti*:*syn* = 1:1.2 and 1:1.4, respectively (entries 5–8). The MOM protecting group for the β-hydroxyl turned out to be superior to others in the BINOL–Zr-catalyzed allylation reactions (entries 3 and 4). *syn*-3,5-Isopropylidene ketal aldehyde **6a** was a good substrate for synthesizing both 4,6-*syn*- and 4,6-*anti*-1,3-diol systems using the (*S*)- and (*R*)-BINOL–Zr complexes. Although in the allylation of *anti*-3,5-isopropylidene ketal aldehyde **6b**, the *anti*-induction using (*S*)-BINOL showed a reasonable selectivity of 5:1, the *syn*-induction using (*R*)-BINOL resulted in poor diastereoselectivity (entries 13 and 14).[21]

Table 3. Asymmetric allylation of chiral aldehydes via BINOL-Zr(O^{t}Bu)$_4$[a]



Entry	Aldehyde	BINOL	Selectivity (*anti*:*syn*)[b]	Yield (%)
1	R_1 = Me (**5a**)	*S*	**7a**:**8a** = 2.3:1	90
2	R_1 = Me (**5a**)	*R*	**7a**:**8a** = 8.5:1	90
3	R_1 = MOM (**5b**)	*S*	**7b**:**8b** = 1:8.0	90
4	R_1 = MOM (**5b**)	*R*	**7b**:**8b** = 8.5:1	85
5	R_1 = Bn (**5c**)	*S*	**7c**:**8c** = 1:1.2	80
6	R_1 = Bn (**5c**)	*R*	**7c**:**8c** = 4.2:1	78
7	R_1 = MPM (**5d**)	*S*	**7d**:**8d** = 1:1.4	88
8	R_1 = MPM (**5d**)	*R*	**7d**:**8d** = 4.0:1	89
9	R_1 = TBS (**5e**)	*S*	**7e**:**8e** = 1:1.5	85
10	R_1 = TBS (**5e**)	*R*	**7e**:**8e** = 1.5:1	85
11	3,5-*syn* (**6a**)	*S*	**9a**:**10a** = 1:6	90
12	3,5-*syn* (**6a**)	*R*	**9a**:**10a** = 10:1	90
13	3,5-*anti* (**6b**)	*S*	**9b**:**10b** = 1:5.0	87
14	3,5-*anti* (**6b**)	*R*	**9b**:**10b** = 1.5:1	85

[a] All reactions were carried out in the range of 0.1–0.2 mmol scale using 100 mol% of the BINOL–Zr(O^{t}Bu)$_4$ complex at −20°C for 3 h. Allylations with 20 mol% of the catalyst require 12 h to complete the reactions.
[b] Diastereoselectivity of the products was established by ^{1}H NMR.

The tendency in the diastereoselectivities observed in the allylation reactions of a series of chiral aldehydes using BINOL–$Zr(O^tBu)_4$ clearly indicates that it is difficult to attain high 1,3-*syn* selectivity except in the case of entries 3 and 11 in Table 3. Because of the higher oxophilicity of the BINOL–Zr complex the reaction rate was far greater than with the BINOL–Ti complexes.[9] This catalyst causes a significant interaction with the coordinative oxygen atoms at the β-position of aldehydes to increase the chelation controlled allylation products.[22]

In conclusion, an expeditious catalytic allylation of aldehydes with BINOL–$Zr(O^tBu)_4$ is reported. The reaction proceeds within a few hours at −20°C and the ees of the homoallylic alcohols are greater than 90%. The ees of the products can be enhanced via tandem catalytic asymmetric allylation–Oppenauer reactions. These tandem reactions are especially useful for reactive aldehydes. The asymmetric allylation with BINOL–$Zr(O^tBu)_4$ may be useful for a variety of protected chiral β-hydroxy aldehydes. However, the choice of protecting groups is crucial for inducing useful levels of diastereoselectivity.

Representative procedure for the synthesis of (R)-undec-1-en-4-ol (entry 3 in Table 1). $Zr(O^tBu)_4$ was purchased from either Aldrich or Strem and stored as a 0.55 M toluene solution. This was stored in a desiccator over KOH pellets. To a stirred mixture of (*S*)-BINOL (892 mg, 3.11 mmol), and 4 Å MS (1.5 g) in dry toluene (15 mL) and dry pivalonitrile (1.5 mL) was added $Zr(O^tBu)_4$ (5.6 mL, 3.11 mmol). The reaction mixture was stirred for 30–60 min at rt. At −50 to −78°C allyltributyltin (14.4 mL, 46.7 mmol) and octanal (4.9 mL, 31.1 mmol) were added. After 2 h at −20°C, saturated $NaHCO_3$ solution (20 mL) was added and the reaction mixture was stirred for an additional 30 min. An Et_2O/water partition was conducted;[23] the organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to afford the crude homoallyl alcohol. This was purified by silica gel chromatography (hexanes:EtOAc:CH_2Cl_2, 20:1:2 to 10:1:2) to afford (*R*)-1-heptybut-3-en-1-ol (4.65 g, 27.4 mmol, 88%), $[\alpha]^D$ +6.9° (*c* 1.0, $CHCl_3$ at 27°C).

Representative procedure for the synthesis of (R)-1-phenyl-5-hexen-3-ol (entry 4 in Table 2) via the tandem asymmetric allylation–Oppenauer oxidation. To a stirred mixture of (*S*)-BINOL (100 mg, 0.35 mmol), and 4 Å MS (200 mg) in dry toluene (1.8 mL) and dry pivalonitrile (0.18 mL) was added $Zr(O^tBu)_4$ (0.84 mL, 0.46 mmol). The reaction mixture was stirred for 30–60 min at rt. At −50 to −78°C allyltributyltin (1.19 mL, 3.84 mmol) and hydrocinnamaldehyde (0.46 mL, 3.5 mmol) were added. After 3 h at −20°C, dry ^{t}BuOMe (3 mL) was added and the reaction mixture was stirred at 0°C for 24 h. The crude mixture was purified by silica gel chromatography (hexanes:EtOAc:CH_2Cl_2, 20:1:2 to 10:1:2) to afford (*R*)-1-phenyl-5-hexen-3-ol (308 mg, 1.75 mmol, 50%).

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14. The addition of 30–40% of pivalonitrile in 0.2–0.3 M toluene solution of reaction mixtures resulted in slower conversion, but the ees of products were retained. The same reactions in other nitrile solvents resulted in lower conversion yields and ees (50% yield (80% ee) in acetonitrile, 50–60% yield (82% ee) in propionitrile).
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