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Catalytic enantioselective allylation of aldehydes via a moisture-tolerant chiral BINOL–In(III) complex

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Abstract—A moisture-tolerant chiral indium complex has been developed to effect good enantioselectivities in the addition of allyltributylstannanes to aldehydes. The allylation of a variety of aromatic, α,β-unsaturated and aliphatic aldehydes resulted in both moderate to good yields and high enantioselectivities (up to 86% ee).

The asymmetric allylation of the carbonyl functionality to furnish homoallylic alcohols has acquired a major role in organic synthesis due to the flexibility of the products which are versatile building blocks for the construction of many natural products and pharmaceuticals.[1] For this reason, there has been an intense research focus in this area in recent years, leading to the development of a large and diverse array of chiral catalysts, especially for the chiral Lewis acid-catalyzed addition of an allyl transfer reagent to a carbonyl functionality.[2]

Despite the fact that various kinds of Lewis acid promoted reactions have been developed, these reactions must be carried out under strictly anhydrous conditions. The presence of even a small amount of water can stop the progress of the reaction because most Lewis acids react immediately with water. This leads to the decomposition or deactivation of the catalyst.[3]

The ability to perform enantioselective catalytic allylation in aqueous media[4] has attracted considerable interest among today's synthetic community.

Furthermore, the extension of catalytic enantioselective transformations to aqueous media poses additional challenges in catalyst-tolerance towards water.

Previous work from our laboratory, has demonstrated that (*S*)-BINOL–In(III) complexes can function as effective chiral Lewis acid catalysts for the enantioselective allylation of aldehydes[5] and ketones[6] and enantioselective Diels–Alder reactions.[7] The chiral indium(III) catalyst was prepared simply by mixing (*S*)-BINOL with $InCl_3$ in CH_2Cl_2 at room temperature for 2 h. In this paper, we report the enantioselective addition of allyltributylstannanes to aldehydes catalyzed by the water-tolerant chiral In(III) complex prepared from (*S*)-BINOL and $InCl_3$.

To evaluate the (*S*)-BINOL–$InCl_3$ catalyst for the enantioselective allylation of aldehydes in aqueous media, the reaction of benzaldehyde and allyltributylstannane in the presence of 3.7 equiv of water (relative to $InCl_3$) was carried out. In this experiment, the reaction was executed by adding water to a stirred solution of the pre-formed catalyst prior to the addition of the aldehyde and allyltributylstannane. The homoallylic alcohol was obtained in 40% yield and 80% ee. In contrast, a racemic product was obtained in <10% yield when water was added prior to the formation of the active catalytic indium species. This result demonstrated that the chiral catalyst was able to maintain its reactivity in the presence of a small amount of water.

A study was initiated to explore the optimum water-tolerance limit of the chiral catalyst for the allylation reaction. The results are shown in Table 1. Investigations into the water-tolerance limit of the chiral indium complex revealed that the addition of 37 equiv of water (relative to

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Keywords: Moisture-tolerant; Catalytic; Chiral indium complex; Enantioselective allylation.

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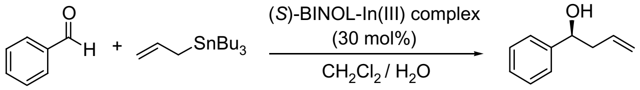
Table 1. Evaluation of the optimal water-tolerance limit for the asymmetric allylation reaction[a]



Entry	H_2O (equiv relative to $InCl_3$)	Yield[b] (%)	ee[c] (%)
1	3.7	40	80
2	7.4	53	83
3	11.1	43	78
4	18.5	41	77
5	22.2	40	74
6	37.0	23	50
7	7.4[d]	30	74

[a] Unless otherwise specified, the reaction was carried out with allyltributylstannane (1.0 mmol) and aldehyde (0.5 mmol) in the presence of the chiral indium(III) catalyst prepared from (*S*)-BINOL (33 mol%) and $InCl_3$ (30 mol%). The reaction mixture was kept for 20 h at rt.

[b] Isolated yield.

[c] Refer to Supplementary data for enantiomeric excess determination.

[d] $InBr_3$ was used as the indium reagent for catalyst formation.

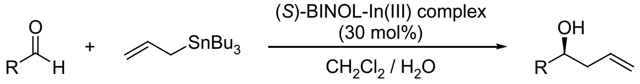
$InCl_3$) to the pre-formed catalyst in this series gave the lowest yield and enantioselectivity (Table 1, entry 6). The optimum water-tolerance limit was achieved at 7.4 equiv of water relative to the pre-formed catalyst, which afforded the homoallylic alcohol in 53% yield and 83% ee (Table 1, entry 2). Although an attempt was made to increase the chemical yield by using $InBr_3$ for catalyst formation due to its higher Lewis acidity, the product was isolated in a lower yield and enantioselectivity (Table 1, entry 7). It is noteworthy that the chiral ligand, (*S*)-BINOL can be easily recovered by silica gel chromatography in an almost quantitative yield (93%).

After determination of the optimum water-tolerance limit with retention of catalyst reactivity, we extended the catalytic enantioselective addition of allyltributylstannane to a selection of aldehydes. The results are shown in Table 2.

Substitution of benzaldehyde with a 4-chloro group resulted in comparable enantioselectivity and a higher yield, with the allylation product formed in 65% yield and 80% ee (Table 2, entry 2). A marginal electronic influence was also observed with 4-methylbenzaldehyde which afforded the product with 51% yield and 81% ee (entry 3). In addition, the allylation of 2-naphthaldehyde and 1-naphthaldehyde gave the corresponding homoallylic alcohols in 78% and 72% ee, respectively (entries 4 and 5).

The allylation of a representative conjugated enone gave exclusively the 1,2-allylation product in high yield and good enantioselectivity (entry 6). Interestingly, while *trans*-3-phenyl-2-butenal underwent allylation with 85% ee, the saturated derivative reacted to give the homoallylic alcohol with 80% ee and a lower yield (entry 7). Moreover, the allylation of nonanal also gave the product in good yield but moderate ee (entry 8).

Table 2. Enantioselective allylation of various aldehydes catalyzed by the chiral (*S*)-BINOL–In(III) complex[a]



1 2 3

Entry	R	3	Yield[b] (%)	ee[c] (%)
1	Ph	**3a**	53	83
2	4-ClC_6H_4	**3b**	65	80
3	4-MeC_6H_4	**3c**	51	81
4	2-Naphthyl	**3d**	47	78
5	1-Naphthyl	**3e**	51	72
6	PhCHCH	**3f**	76	85
7	$PhCH_2CH_2$	**3g**	57	80
8	*n*-C_8H_{17}	**3h**	75	78
9	$BnO(CH_2)_2$	**3i**	46	86
10	$BnO(CH_2)_3$	**3j**	42	86

[a] Unless otherwise specified, the reaction was carried out with allyltributylstannane (1.0 mmol) and aldehyde (0.5 mmol) in the presence of the chiral indium(III) catalyst prepared from (*S*)-BINOL (33 mol%) and $InCl_3$ (30 mol%). The reaction mixture was kept for 20 h at rt.

[b] Isolated yield.

[c] Refer to Supplementary data for enantiomeric excess determination.

The functionalized 3-benzyloxypropionaldehyde and 4-benzyloxybutyroaldehyde both underwent the allylation reaction to afford homoallylic alcohols with 86% ee and yields of 46% and 42%, respectively (entries 9 and 10).

In conclusion, we have demonstrated an enantioselective addition of the allylic moiety to aldehydes using a catalytic amount of a water-tolerant (*S*)-BINOL–In(III) complex.[8] The main features of this reaction are as follows: (1) the procedure can furnish a wide variety of homoallylic alcohols in moderate to good yields with good levels of enantioselectivities in the presence of water; (2) the allylation can be performed exclusively by using commercially available chemicals. The design of new BINOL-based ligands for stronger complexation with indium in order to function in fully aqueous media is currently in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.07.064.

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8. Representative procedure for asymmetric allylation of aldehydes: preparation of (*S*)-1-phenylbut-3-en-1-ol. To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (33 mg, 0.15 mmol, 0.30 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL × 2) prior to the addition of 1.5 mL of dichloromethane. (*S*)-BINOL (47 mg, 0.17 mmol, 0.33 equiv) was added to the mixture which was stirred under nitrogen at room temperature for 2 h. Allyltributylstannane (0.093 mL, 0.3 mmol, 0.60 equiv) was added to the resulting mixture and stirred for 10 min followed by addition of H_2O (0.02 mL, 1.11 mmol, 2.2 equiv) to afford a white suspension. The pre-formed catalyst was further treated with allyltributylstannane (0.22 mL, 0.7 mmol, 1.4 equiv) and stirred for 10 min followed by addition of benzaldehyde (0.05 mL, 0.5 mmol, 1.0 equiv). The reaction mixture was stirred for 20 h at room temperature and then quenched with 5 mL saturated sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic extracts washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residual crude product was purified via silica gel chromatography to afford the homoallylic alcohol as a colourless oil (53%); $[\alpha]_D$ −44.6 (*c* 2.50, CH_2Cl_2). The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (hexane–*i*-propanol, 99:1, 1.0 mL/min: $t_1 = 9.72$ min for the *R* enantiomer, $t_2 = 12.78$ min for the *S* enantiomer). It has been established that the *R* enantiomer elutes first.[5,9]
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