Catalytic asymmetric allylation of aldehydes *via* a chiral indium(III) complex†

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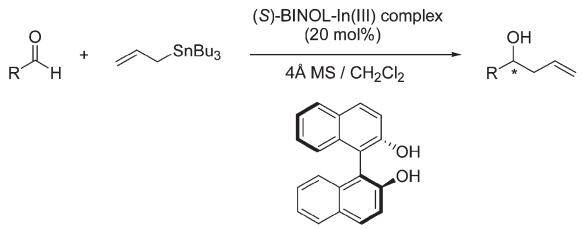
A chiral indium complex has been discovered to effect high enantioselectivities in the addition of allyltributyl stannanes to aldehydes. The allylation of a variety of aromatic, α,β-unsaturated and aliphatic aldehydes resulted in good yields and high enantioselectivities (90–96% ee).

In recent years, indium(III) complexes have gained widespread application as efficient Lewis acid catalysts for various important organic synthetic transformations.[1] The ability of some of these complexes to catalyze organic transformations in aqueous media is especially noteworthy.[2] Accordingly, much effort has been directed towards the development of an efficient chiral indium complex for asymmetric transformations[3] which continues to pose a challenge to synthetic chemists.

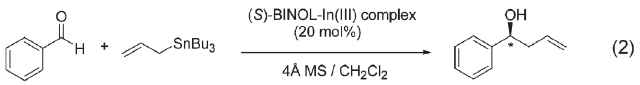
The asymmetric allylation of carbonyl functionality to furnish homoallylic alcohols has acquired a major role due to the versatility of the products, which are important building blocks for the synthesis of many natural products and pharmaceuticals.[4] In this paper, we report our work towards the development of a chiral indium complex for catalytic asymmetric allylation.[5] To the best of our knowledge, catalytic asymmetric allylation of carbonyl functionality using a chiral indium(III) catalyst has never been reported. Herein, we report the first asymmetric addition of allyltributyl stannane to aldehydes and ketones based on the use of a catalytic amount of chiral (*S*)-BINOL-In(III) complex (eqn. (1)).



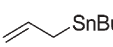
(1)

In our initial study, we subjected benzaldehyde to a series of experiments to evaluate the merits of various indium reagents (eqn. (2)). The various (*S*)-BINOL-indium complexes were prepared by reacting the indium salts and (*S*)-BINOL at room temperature in the presence of activated 4Å MS. After stirring for 2 h, allyltributyl stannane (1 equiv.) was added followed by benzaldehyde (1 equiv.). The results obtained are shown in Table 1. Among them, the reaction catalyzed by the (*S*)-BINOL-$InCl_3$ complex exhibited the best conversion and enantiomeric excess

Table 1 Evaluation of various indium reagents for the asymmetric allylation reaction[a]



(2)

Entry	Indium reagent	Solvent		Yield (%)[b]	ee (%)[c]
1	InF_3	CH_2Cl_2	1.0	0	—
2	$In(OiPr)_3$[d]	CH_2Cl_2	1.0	36	0
3	$InBr_3$	CH_2Cl_2	1.0	38	73
4	$InCl_3$	CH_2Cl_2	1.0	52	78
5	$InCl_3$	CH_2Cl_2	2.0	76	92
6	$InCl_3$[e]	CH_2Cl_2	2.0	36	83
7	$InCl_3$[f]	CH_2Cl_2	2.0	12	73
8	$InCl_3$	$CHCl_3$	2.0	52	90

[a] Unless otherwise specified, the reaction was carried out with allyltributyl stannane (0.5 mmol) and aldehyde (0.5 mmol) in the presence of chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%) and $InCl_3$ (20 mol%) in the presence of 15 mg powdered activated 4Å molecular sieves in 2.5 mL of CH_2Cl_2. The reaction mixture was kept for 4 h at −78 °C and then 16 h at r.t. [b] Isolated yield. [c] Please refer to supporting information for enantiomeric excess determination. [d] The catalyst preparation involved refluxing for 1 h prior to the addition of allyltributyl stannane and aldehyde. [e] The reaction was carried out using 50 mg of 4Å molecular sieves. [f] The reaction was carried out with 10 mol% catalyst loading.

(entry 5). The reaction carried out using 2 equivalents of allyltributyl stannane afforded the homoallylic alcohol in 76% isolated yield with 92% ee. It is important to note that the reaction carried out with more 4Å MS resulted in the formation of the product in lower yield and enantiomeric excess (entry 6). Moreover, the reaction carried out in chloroform was found to afford the product in good yield with similar enantioselectivities (entry 8). It is noteworthy that the chiral ligand, (*S*)-BINOL can be easily recovered by silica gel chromatography in almost quantitative yield (98%), making the amount of the chiral (*S*)-BINOL used in this reaction irrelevant and the allylation process cost effective.

After determination of the optimized reaction parameters, we extended the catalytic enantioselective addition of allyltributyl stannane to a wide variety of aldehydes (eqn. (3)). The results obtained are shown in Table 2.

In all cases, the homoallylic alcohols were obtained in good yields and high enantioselectivities (up to 96% ee) not only with aromatic aldehydes but also with α,β-unsaturated and aliphatic aldehydes. In the reaction with α,β-unsaturated aldehydes, the 1,2-addition reaction proceeded exclusively. The absolute configuration of the homoallylic alcohols was determined by comparison of the sign of the optical rotation and HPLC results with the

† Electronic supplementary information (ESI) available: spectroscopic and analytical data for all compounds and the representative procedure. See http://www.rsc.org/suppdata/cc/b4/b412736f/

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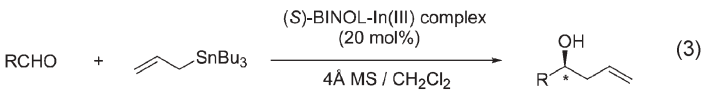
Table 2 Enantioselective allylations of various aldehydes catalyzed by chiral (*S*)-BINOL–In(III) complex[a]



(3)

Entry	RCHO	Yield (%)[b]	ee (%)[c]
1	(*E*)-PhCHCH	72	96
2	Ph	76	92
3	$PhCH_2CH_2$	64	90
4	2-naphthyl	55	90
5	n-C_8H_{17}	72	94
6	*c*-C_6H_{11}	53	94
7	$BnO(CH_2)_3$	70	94

[a] Unless otherwise specified, the reaction was carried out with allyltributyl stannane(1.0 mmol) and aldehyde (0.5 mmol) in the presence of chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%) and $InCl_3$ (20 mol%) in the presence of 15 mg powdered activated 4Å molecular sieves in 1.5 mL of CH_2Cl_2. The reaction mixture was kept for 4 h at −78 °C and then 16 h at r.t. [b] Isolated yield. [c] Please refer to supporting information for enantiomeric excess determination.

literature value.[6] The *si* face of the aldehyde is attacked when the (*S*)-catalyst is used, in agreement with the constant preference shown by BINOL-based catalysts.[5]

It is of mechanistic interest to note that the chiral indium complex can function as a catalyst even though indium trichloride has been known to undergo transmetallation reaction with allylic stannanes. As such, we decided to conduct ^{1}H NMR studies to gain insight to the active species of the catalyst and understand the origin of the high enantioselectivities. (1) The addition of equimolar of allyltributyl stannane to the mixture of (*S*)-BINOL–$InCl_3$ indicates the formation of a quantitative set of new allylic signal on the NMR spectrum together with tributyl stannane chloride; nevertheless, the allylindium derivative thus formed did not afford any detectable amounts of products upon addition of an equimolar amount of benzaldehyde after 24 h. This study shows that an allyl transfer from indium to aldehyde can be excluded as the actual reaction pathway. (2) The addition of 1.0 mmol of allyltributyl stannanes to a 0.1 mmol mixture of of (*S*)-BINOL–$InCl_3$ indicates the formation of the new allylic signal with excess allyltributyl stannanes. The intensity ratio of this new allylic signal relative to the allyltributyl stannanes was 10:90. Subsequent addition of 0.5 mmol benzaldehyde afforded the product in 52% yield with 90% ee after 12 h. This study shows that 10% of allyltributyl stannanes underwent transmetallation reaction with $InCl_3$ and the excess allyltributyl stannane act as the allylating reagent for the subsequent reaction. On the basis of the above observations, we postulated that $InCl_3$ underwent transmetallation with allyltributyl stannane to form a new allylic species which forms a chiral indium complex with BINOL. A (*S*)-BINOL–In–allyl complex probably acts as the chiral Lewis acid for the asymmetric allylation reaction but further mechanistic investigations are in course.

A study with the BINOL ligand of different optical purity exhibited no non-linear in correlating the enantiopurity of allylation product **2** (R = Ph) with the ee of (*S*)-BINOL. The results obtained are shown in Chart 1. This study also suggested that the BINOL–In(III) complex most probably exists as a monomeric species in solution and even if aggregates are present, they have no catalytic effect.

Next, we proceeded to extend the catalytic protocol to aqueous media. The reaction was carried out by adding water

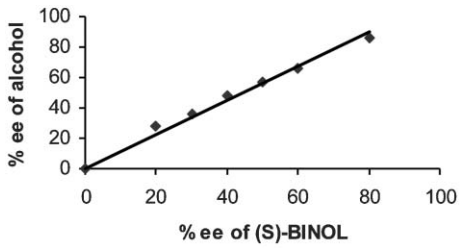


Chart 1 Non-linear effect in asymmetric allylation catalyzed by non racemic (*S*)-BINOL.

either before or after the formation of the chiral active indium complex prior to the addition of aldehydes. The reaction carried out with the addition of water after the formation of the active catalytic indium species resulted in the formation of the homoallylic alcohols in 42% yield with 80% ee. On the contrary, a racemic product was obtained in <10% yield when water was added prior to the formation of the active catalytic indium species. These results suggested that the addition of 4Å MS is important for high asymmetric induction and provide insights to designing better chiral ligand for stronger complexation with the indium salts.

In conclusion, we have demonstrated the first highly enantioselective addition of allylic moiety to aldehydes using a catalytic amount of the (*S*)-BINOL–In(III) complex. The main features of this reaction are as follows: (1) the procedure is operationally simple and can furnish a wide variety of homoallylic alcohols in good yields with high levels of enantioselectivities; (2) the allylation can be performed exclusively by using commercially available chemicals; (3) the chiral ligand can be recovered in high yield thus, making this method attractive for scale-up preparation of homoallylic alcohols with high enantioselectivities. Continuing investigations in this laboratory will attempt to elucidate the identity of the BINOL–In(III) species and further expand the scope of the process.

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