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Highly Enantioselective Allylation of Aldehydes Catalyzed by Indium(III)–PYBOX Complex

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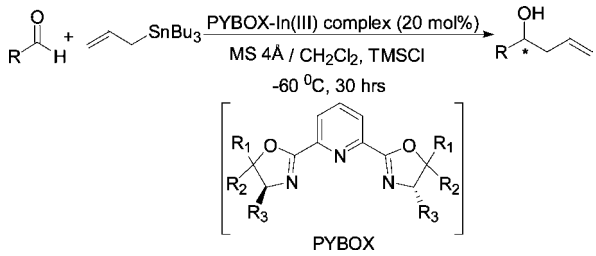
ABSTRACT



A chiral indium(III)–PYBOX complex prepared from indium triflate and chiral PYBOX has been discovered to effect high enantioselectivities in the addition of allyltributyl stannane to aldehydes. The allylation of a variety of aromatic, α,β-unsaturated, and aliphatic aldehydes resulted in good yields and high enantioselectivities (up to 94% ee).

The synthesis of enantiomerically enriched homoallylic alcohols is an important goal in organic synthesis. This is because homoallylic alcohols are versatile intermediates that can be converted to a wide variety of synthetically useful compounds.[1] Therefore, there has been intense research activity in this area in recent years, [2] leading to the development of a large and diverse array of chiral catalysts, especially chiral Lewis acid catalyzed addition of the allyl transfer reagents to carbonyl functionality. Most of them consist of chiral ligands attached to metals such as Zn, Ti, B, Cr, and Rh. However, enantioselective allylation using chiral indium(III) catalyst has been relatively unexplored, although indium(III) complexes have gained widespread application as efficient Lewis acid catalysts for various synthetic transformations.[3] In this paper, we describe a procedure for the synthesis of chiral homoallylic alcohols by the reaction of aldehydes with allyltributylstannane catalyzed by novel chiral In(OTf)$_3$−PYBOX[4] complexes (eq 1).

Our initial studies began with allyltributylstannane and benzaldehyde in the catalytic amount of chiral In(III)−PYBOX complex. The chiral complex was prepared by reacting In(OTf)$_3$ (0.2 equiv) and (*S*)-*i*-PrPYBOX (**1**) (0.22

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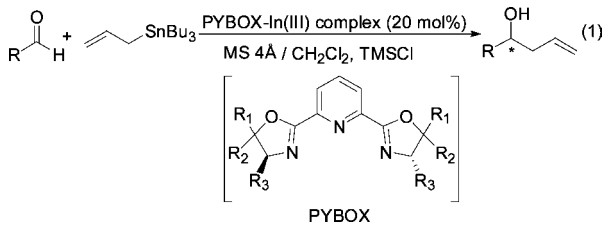
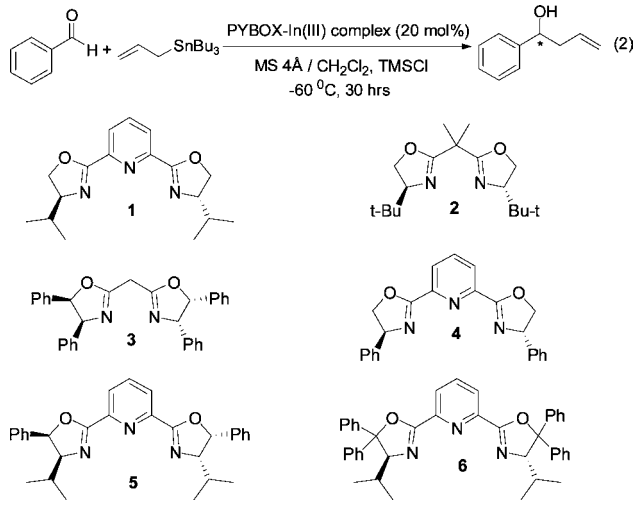


equiv) in solvent at room temperature in the presence of MS 4Å. After 2 h of stirring, allyltributylstannane (1.2 equiv) was added followed by benzaldehyde (1 equiv) with TMSCl (1.2 equiv). The homoallylic alcohol was then obtained by aqueous workup and column chromatography. The results are summarized in Table 1.

Table 1. Evaluation of Various Chiral Indium(III) Complexes for the Asymmetric Allylation Reaction[a]



entry	chiral ligand	indium salt	yield (%)[b]	ee (%)[c]
1	**1**	$In(OTf)_3$	80	85
2	**1**	$In(OTf)_3$	81	22[d]
3	**1**	$InBr_3$	12	31
4	**1**	$InCl_3$	84	40
5	**2**	$In(OTf)_3$	0	0
6	**3**	$In(OTf)_3$	0	0
7	**4**	$In(OTf)_3$	96	52
8	**5**	$In(OTf)_3$	84	63
9	**6**	$In(OTf)_3$	81	92

[a] All reactions were carried out with benzaldehyde (1 equiv), TMSCl (1.2 equiv), and allyltributylstannane (1.2 equiv) using indium salt (0.2 equiv) and chiral ligands (0.22 equiv) in the presence of activated MS 4Å in anhydrous CH_2Cl_2. The reaction mixture was kept for 30 h at −60 °C. [b] Isolated yield. [c] Ee determined by HPLC. [d] Without TMSCl.

First, the effects of solvent and temperature were surveyed. The allylation reaction carried out at room temperature in CH_2Cl_2 afforded the product in 59% ee (only 12% ee without TMSCl). The use of other solvents led to lower selectivities (42% ee in toluene, 54% ee in EtCN, 55% ee in 1:1 CH_2Cl_2/toluene).

Next, the reaction was performed in CH_2Cl_2 at different temperatures. The best result was obtained (80% yield, 85% ee; Table 1, entry 1) when the reaction was carried out at at −60 °C (78% ee at −10 °C, 84% ee at −40 °C, 81% ee at −78 °C).

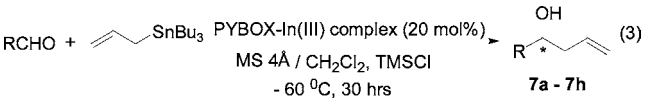
We also screened other indium salts using identical conditions and found that the products were obtained in lower yields and enantioselectivities (Table 1, entries 3 and 4).

After optimizing these allylation reaction conditions, several other chiral ligands were synthesized and screened with $In(OTf)_3$, among which tetraphenyl-substituted (*S*)-*i*-PrPYBOX (**6**) gave the best result (81% yield, 92% ee; Table 1, entry 9).

Through this screening process, the following points could be established: (1) The use of tridentate bis(oxazolinyl)-pyridine (PYBOX) (entries 1−4, 7−9, Table 1) gave the homoallylic alcohols in good yields with high enantioselectivities. (2) The yields and enantioselectivities of homoallylic alcohols depends on the indium salt (Br < Cl ≪ OTf) (Table 1, entries 1, 3, 4). (3) As a "promoter", it was found that TMSCl was more superior than TESCl, TBSCl, and TIPSCl. (4) Of these complexes surveyed, the tetraphenyl-substituted (*S*)-*i*-PrPYBOX (**6**)-derived complex provided superior levels of asymmetric induction, affording the homoallylic alcohol in 92% ee (Table 1, entry 9).

Having optimized the reaction conditions, we extended the catalytic enantioselective allylation to a wide variety of aldehydes in the presence of the tetraphenyl-substituted (*S*)-*i*-PrPYBOX (**6**). The results obtained are shown in Table 2.

Table 2. $In(OTf)_3$−Pybox (**6**)-Catalyzed Allylation of Aldehyde[a]



entry	R	yield (%)[b]	ee (%)[c]
1	Ph	81[d]	92
2	Ph	85[e]	91
3	2-naphthyl	86	94
4	4-ClC_6H_4	61	90
5	5-Me-furyl	80	94
6	$PhCH_2CH_2$	81	84
7	PhCH=CH	91	86
8	$BnO(CH_2)_3$	78	91
9	*n*-C_8H_{17}	68	85

[a] All reactions were carried out with aldehyde (1 equiv), TMSCl (1.2 equiv), and allyltributylstannane (1.2 equiv) using $In(OTf)_3$ (0.2 equiv) and (*S*)-*i*PrPYBOX (**6**) (0.22 equiv) in the presence of activated MS 4Å in anhydrous CH_2Cl_2. The reaction mixture was kept for 30 h at −60 °C. [b] Isolated yield. [c] ee determined by HPLC or 500 MHz ^1H NMR of the corresponding MTPA ester. For further details see Supporting Information. [d] 88% of chiral ligand was recovered. [e] Recovered (*S*)-*i*-Pr PYBOX (**6**) was used for the reaction.

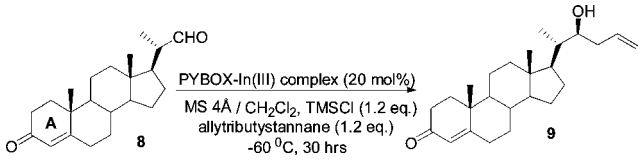
As shown in Table 2, all of the aldehydes, including aromatic aldehydes, α,β-unsaturated, and aliphatic aldehydes, furnished the products in high enantioselectivities (84−94% ee) and good yields. Furthermore, (*S*)-*i*-PrPYBOX (**6**) could be easily recovered in 88% yield without racemization and

could be reused to afford the product in equal yield and enantioselectivity (Table 2, entry 2). This makes the cost of the chiral catalyst irrelevant.

It is noteworthy that the chiral steroidal aldehyde **8** was allylated to give **9** with high enantioselectivity (22*S*:22*R* = 96:4) (Scheme 1). Furthermore, the reaction was highly chemoselective, reacting only with the aldehyde functionality. No reaction was observed with the enone functionality in the A ring. Interestingly, the use of (*R*)-*i*-PrPYBOX (**6**) afforded the 22*S*-product as a single isomer (22*S*:22*R* = 100:0).

In conclusion, we have developed a highly catalytic enantioselective allylation of aldehydes to give enantiomerically enriched homoallylic alcohols in good yields and excellent enantiomeric excess in the presence of a catalytic amount of $In(OTf)_3$−PYBOX complexes. Further work on redesigning high affinity chiral PYBOX applicable to the allylation reaction as well as for other organic transformations is in progress.

Scheme 1. Application to the Steroid Side-Chain Synthesis



(*S*)-*i*-PrPYBOX **6** : 46% yield (22*S*:22*R* = 96:4)
(*R*)-*i*-PrPYBOX **6** : 62% yield (22*S*:22*R* = 100:0)

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Supporting Information Available: Experimental details, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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