Enantioselective allylation of aldehydes catalyzed by chiral indium(III) complexes immobilized in ionic liquids†

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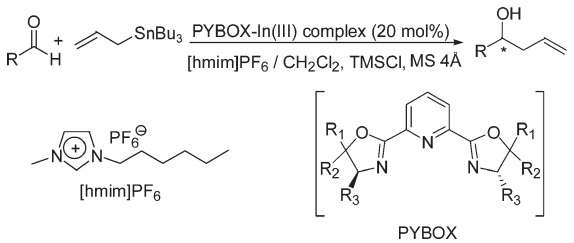
In the presence of chiral catalytic complexes prepared from $In(OTf)_3$ and chiral PYBOX ligands, allytributylstannane reacted with aldehydes in ionic liquids to afford the corresponding homoallylic alcohols in high enantioselectivities (86–94% ee) and good yields (68–89%); the chiral catalysts immobilized in ionic liquids could be reused with comparable enantioselectivities and yields.

The asymmetric allylation reaction is one of the most efficient asymmetric C–C bond forming reactions.[1] This is because enantiomerically enriched homoallylic alcohols are important intermediates in organic synthesis, which can be converted to a wide variety of synthetically useful compounds.[2] Therefore, there has been intense research activity in this area in recent years, leading to the development of a large and diverse array of chiral catalysts, especially concerning chiral Lewis acid-catalyzed addition of allyl transfer reagents to carbonyl functionalities.[3]

Furthermore, there are increasing concerns about environmental effects, which require synthetic manipulation that minimize the use of hazardous chemicals. Aiming to achieve this goal, many strategies have been devised and investigated, especially by replacing traditional organic solvents with other non-toxic solvents such as water or supercritical carbon dioxide. Recently, ionic liquids have attracted extensive interest as excellent alternatives to organic solvents, due to their favourable properties, such as non-flammability, no measurable vapour pressure, low toxicity, reusability, low cost and high thermal stability. In addition to the polar properties of ionic liquids, they are non-coordinating, which avoids any undesired solvent binding in pre-transition states, and hence offer great advantages for asymmetric synthesis. As a result, ionic liquids are considered as promising alternative solvents for organic reactions.[4] Over the past few years, these liquids have generated a significant amount of interest. It was reported that the allylation reaction of aldehydes with allytributystannane in ionic liquids could afford the corresponding allylated adducts smoothly.[5]

In this paper, we report asymmetric allylation reactions in ionic liquids, which proceeded smoothly in the presence of chiral In(III) complexes (Scheme 1).

Recently, a chiral In(III) complex-catalyzed asymmetric allylation reaction of aldehydes with allytributystannane in dichloromethane had been developed in our laboratory.[6] Although high enantioselectivities and good yields were obtained, it is rather inconvenient to reuse the chiral catalyst. As a result, we directed our studies to investigate the allylation reaction in ionic liquids, and the recyclability of the catalytic system, which is important from the industrial point of view, especially when expensive catalysts are used.



Scheme 1 In(III) complex-catalyzed asymmetric allylation in ionic liquids.

From our previous experience, the results obtained using In(III) complexes prepared from $In(OTf)_3$ and chiral PYBOX ligands as catalysts were excellent. The best results were obtained when the reactions were carried out at −60 °C. As a result, the asymmetric allylation reactions were performed as described below.

Our initial studies began with allyltributylstannane and benzaldehyde in the presence of a catalytic amount of a chiral In(III)–PYBOX complex. The chiral complex was prepared by reacting $In(OTf)_3$ (0.2 equiv.) and chiral PYBOX (**2**) (0.22 equiv.) in ionic liquid at room temperature in the presence of powdered activated 4Å molecular sieves. After stirring for 2 h, allyltributylstannane (1.2 equiv.) was added followed by benzaldehyde (1 equiv.) with TMSCl (1.2 equiv.). The homoallylic alcohol was then obtained by aqueous work-up and column chromatography after stirring at −60 °C for 30 h.

The initial study was performed using $[hmim]PF_6$ at −60 °C. Unfortunately, the reaction mixture was sticky, and the product was obtained in low yield (10%) and low enantioselectivity (17% ee). This is most probably due to the poor solubility of $[hmim]PF_6$ at −60 °C. To circumvent this problem, the reaction was carried out in the presence of $[hmim]PF_6$–CH_2Cl_2. To our delight, the product was obtained in good yield (72%) with high enantioselectivity (88% ee). Other solvent systems, such as $[bmim]PF_6$–CH_2Cl_2, $[omim]PF_6$–CH_2Cl_2, $[bmim]BF_4$–CH_2Cl_2, $[hmim]BF_4$–CH_2Cl_2, $[omim]BF_4$–CH_2Cl_2, [bmim]Cl–CH_2Cl_2, [hmim]Cl–CH_2Cl_2 and [omim]Cl–CH_2Cl_2 were also screened. The products were obtained in lower yields and enantioselectivities.

Next the following six chiral PYBOX ligands (**1–6**) were screened in $[hmim]PF_6$–CH_2Cl_2. The results are summarized in Table 1.

† Electronic supplementary information (ESI) available: Spectroscopic and analytical data for all compounds and description of a representative procedure. See http://www.rsc.org/suppdata/cc/b5/b500086f/

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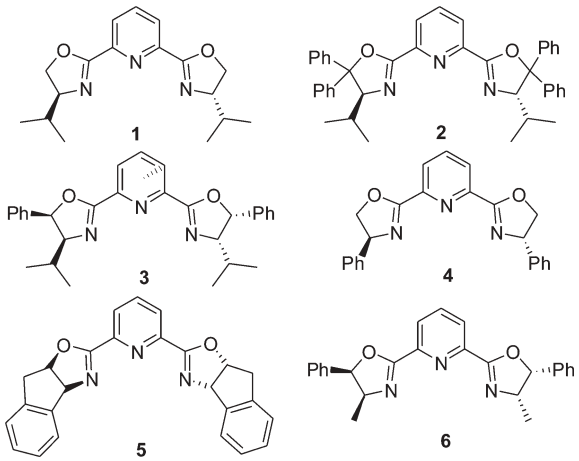


From this screening, it was found that the asymmetric allylation reaction proceeded smoothly in [hmim]PF_6–CH_2Cl_2 at −60 °C in the presence of chiral In(III) complexes. Of the complexes surveyed, the tetraphenyl substituted (*S*)-i-PrPYBOX (**2**) derived complex provided superior levels of asymmetric induction, affording the homoallylic alcohol in 88% ee (Table 1, entry 2).

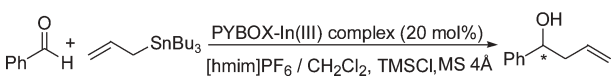
Having optimized the reaction conditions, we extended the catalytic enantioselective allylation to a wide variety of aldehydes in the presence of the tetraphenyl substituted (*S*)-*i*-PrPYBOX (**2**). The results obtained are shown in Table 2.

In all cases, the homoallylic alcohols were obtained in good yields and high enantioselectivities (up to 94% 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.

With the success of the above reactions, we continued our investigation by exploring the recyclability of the catalytic system. The recycling process was studied starting with benzaldehyde and 2-naphthaldehyde as starting materials. After the reaction was completed, CH_2Cl_2 was removed *in vacuo*. The resulting mixture was extracted with dry hexane to give [hmim]PF_6 containing the chiral In(III) complex. The chiral catalytic system could be used four times with comparable enantioselectivity and yield (Table 3).

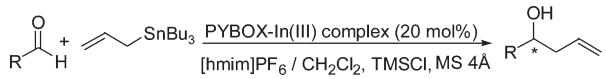
In summary, chiral In(III) complex-catalyzed allylation reactions have been successfully carried out in ionic liquids to give enantiomerically enriched homoallylic alcohols in good yields and excellent enantiomeric excess. Further study regarding the recycling of the catalytic system has revealed that the chiral In(III) complex in ionic liquid could be reused with good yields and ee values.

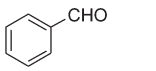
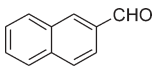
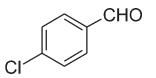
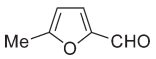
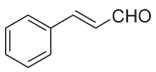
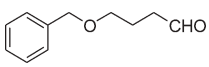
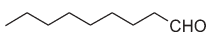
Table 1 Evaluation of various chiral indium(III) complexes for the asymmetric allylation of benzaldehyde



Entry	Chiral ligand	Yield (%)	Ee (%)
1	**1**	81	70
2	**2**	72	88
3	**3**	78	55
4	**4**	76	49
5	**5**	85	74
6	**6**	75	16

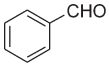
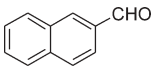
Table 2 In$(OTf)_3$–PYBOX (**2**) catalyzed allylation of aldehydes[a]



Entry	R	Yield[b] (%)	Ee[c] (%)
1		72	88
2		88	91
3		68	94
4		81	92
5		89	91
6		82	92
7		71	86

[a] All the 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 chiral PYBOX (**2**) (0.22 equiv.) in the presence of activated 4Å MS in [hmim]PF_6–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 ^{1}H NMR spectrum of the corresponding MTPA ester.

Table 3 Recycling study of asymmetric allylation of aldehyde

Entry	Aldehyde	Cycle no.	Yield (%)	Ee (%)
1		1	74	89
2		2	76	87
3		3	81	84
4		4	78	78
5		1	88	92
6		2	86	89
7		3	87	87
8		4	84	80

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