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# Catalytic enantioselective allylation of aldehydes via a chiral indium(III) complex in ionic liquids

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**Abstract**—The ionic liquid [hmim][$PF_6$] has been demonstrated as an efficient and environmentally-friendly reaction medium for the enantioselective allylation of aldehydes via a chiral indium(III) complex. The allylation of a variety of aromatic, α,β-unsaturated and aliphatic aldehydes resulted in moderate to good yields and enantioselectivities (upto 92% ee).


The asymmetric allylation of the carbonyl functionality to furnish optically active homoallylic alcohols has acquired a major role in organic synthesis due to the versatility of the products which are important building blocks for the synthesis of many natural products and pharmaceuticals.[1] To date, several catalysts have been devised for this purpose.[2] Recently, our group reported an efficient protocol for the asymmetric allylation of aldehydes using a catalytic amount of a chiral indium(III) complex[3] prepared from (*S*)-BINOL and $InCl_3$. This method has proven to be practical and convenient, furnishing a wide variety of homoallylic alcohols in good yields and excellent enantioselectivities. In this letter, we extended the utility of the asymmetric allylation of aldehydes catalyzed by the chiral In(III) complex through the use of the ionic liquid [hmim][$PF_6^-$] as an environmentally benign reaction medium.

Ionic liquids (IL) are a new class of solvents[4] which present interesting properties such as non-volatility, high stability and easy recyclability.

They have been found to be viable solvents for organic synthesis and have shown promising results in the investigations of many organic reactions, notably hydrogenations,[5] Diels–Alder reactions,[6] enantioselective allylation reactions,[7] enantioselective epoxidations of alkenes[8] and enantioselective ring-opening of epoxides.[9] Since these solvents are immiscible with many organic solvents, it is possible to perform the asymmetric allylation and to recover and recycle the ionic liquid layer containing the In catalyst after simple extraction of the product.

In our initial study, we investigated the asymmetric allylation of aldehydes in a series of ionic liquids using the following standardized protocol. The catalyst was prepared by mixing (*S*)-BINOL and $InCl_3$ in dichloromethane at room temperature. After 2 h of stirring, the ionic liquid was added to the pre-formed catalyst followed by removal of the organic solvent in vacuo. Subsequent addition of allytributylstannane and benzaldehyde afforded the corresponding homoallylic alcohol which was isolated by a simple extraction protocol. The results evaluating the merits of various ionic liquids are shown in Table 1.

Among the ionic liquids investigated, [hmim][$PF_6^-$] was shown to be the best solvent system which afforded the homoallylic alcohol in moderate yield and relatively good enantioselectivity whereas the [$Cl^-$]-type ionic liquids did not exhibit any enantioselectivity.

Having optimized the reaction parameters, we extended the catalytic enantioselective addition of allyltributylstannane to a wide variety of aldehydes using [hmim][$PF_6^-$] as the solvent system. The results are shown in Table 2.

*Keywords*: Ionic liquid; [hmim][$PF_6$]; Chiral indium complex; Enantioselective allylation.
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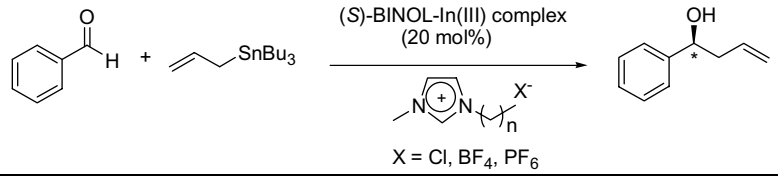
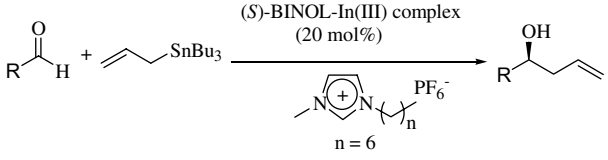
**Table 1.** Evaluation of various ionic liquids for asymmetric allylation[a]

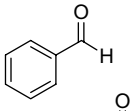
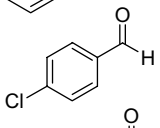
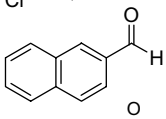
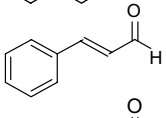
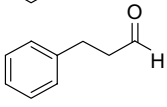
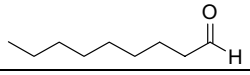



| Entry | Ionic liquid | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 | [bmim][$PF_6^-$], $n = 3$ | 35 | 64 |
| 2 | [hmim][$PF_6^-$], $n = 5$ | 62 | 70 |
| 3 | [bmim][$BF_4^-$], $n = 3$ | 26 | 11 |
| 4 | [hmim][$BF_4^-$], $n = 5$ | 28 | 20 |
| 5 | [hmim][$Cl^-$], $n = 5$ | 42 | 0 |
| 6 | [omim][$Cl^-$], $n = 7$ | 62 | 0 |

[a] Unless otherwise specified, the reaction was carried out with allyltributylstannane (1.0 mmol) and the aldehyde (0.5 mmol) in the presence of the chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%) and $InCl_3$ (20 mol%) in 1.0 mL of ionic liquid.
[b] Isolated yield.
[c] Please refer to Supplementary data for enantiomeric excess determination.

**Table 2.** Enantioselective allylation of various aldehydes catalyzed by the chiral (*S*)-BINOL–In(III) complex in [hmim][$PF_6^-$][a]




| Entry | Aldehyde | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 |  | 62 | 70 |
| 2 |  | 42 | 72 |
| 3 |  | 46 | 78 |
| 4 |  | 60 | 92 |
| 5 |  | 40 | 74 |
| 6 |  | 72 | 26 |

[a] Unless otherwise specified, the reaction was carried out with allyltributylstannane (1.0 mmol) and the aldehyde (0.5 mmol) in the presence of the chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%) and $InCl_3$ (20 mol%) in 1.0 mL [hmim][$PF_6^-$].
[b] Isolated yield.
[c] Please refer to Supplementary data for enantiomeric excess determination.

The allylation of benzaldehyde and 4-chlorobenzaldehyde under the influence of the chiral indium catalyst furnished homoallylic alcohols with comparable enantioselectivites of 70% and 72%, respectively (Table 2, entries 1 and 2). In addition, 2-naphthylaldehyde also underwent the allylation reaction affording the product in 46% yield and 78% ee. Allylation of a representative conjugated enone gave exclusively 1,2-allylation in good yield and with high enantioselectivity (entry 4). Interestingly, while *trans*-4-phenyl-3-buten-2-one underwent allylation with 92% ee, the saturated derivative reacted to give the homoallylic alcohol with 74% ee (entry 5). However, the reaction of nonanal under the influence of the chiral catalyst gave the homoallylic alcohol in good yield but with low selectivity (entry 6).

The absolute configurations of the homoallylic alcohols were determined by comparison of the signs of their optical rotation and HPLC results with the literature values.[10] The *si*-face of the aldehyde is attacked when the (*S*)-catalyst is used, in agreement with the usual preference shown by BINOL-based catalysts.[2]

Next, we continued our study by exploring the recyclability of the chiral indium catalyst which is important from the viewpoint of cost-effectiveness. We carried out our study by using the reaction of benzaldehyde and allytributylstannane in [hmim][$PF_6^-$] as a model study. After the reaction was completed, the reaction mixture was extracted with ether (15 mL × 4) to give the ionic liquid residue. Use of this residue for subsequent addition of the aldehyde and allyltributylstannane resulted in no product formation even after 72 h. Investigations into this problem revealed the presence of the BINOL ligand in the ether extracts as observed in the $^1H$ NMR spectra. This suggests that the erosion of the catalytic activity was most likely due to catalyst hydration leading to deactivation of the chiral complex.

In conclusion, we have demonstrated an efficient catalytic enantioselective allylation of aldehydes using the ionic liquid [hmim][$PF_6^-$] as a solvent at room temperature.[11] The mild reaction and the simplicity of the reaction procedure should attract interest among organic chemists. The combinatorial synthesis of other ionic liquids for this asymmetric allylation reaction to increase conversion and enantioselectivity are 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.2005.05.014.

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11. Representative procedure for the 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 $InCl_3$ (22 mg, 0.1 mmol, 0.2 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 (31 mg, 0.11 mmol, 0.22 equiv) was added to the mixture which was stirred under nitrogen at room temperature for 2 h. Allyltributylstannane (0.093 mL, 0.3 mmol, 0.6 equiv) was added to the resulting mixture which was then stirred for 10 min. The solvent was removed in vacuo after the addition of 1.0 mL of [hmim][$PF_6^-$]. The pre-formed catalyst in ionic liquid was further treated with allyltributylstannane (0.22 mL, 0.7 mmol, 1.4 equiv) and stirred for 10 min followed by benzaldehyde (53 mg in 0.5 mL dichloromethane, 0.5 mmol, 1.0 equiv). The reaction mixture was stirred for 40 h at room temperature and then extracted with ether (5 × 10 mL). The combined organic extracts were 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. Colourless oil (62%). $[\alpha]_D$ −29.5 (*c* 1.57, $CH_2Cl_2$). 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.[10]