$InCl_3$-Promoted Allylation of Aldehydes in Ionic Liquid: Scope and Enantioselectivity Studies

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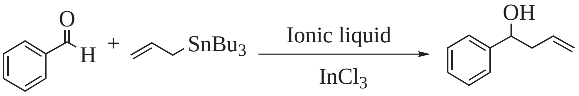
Abstract: Indium trichloride was successfully applied to allylation reaction of aldehydes using allytributyltin in ionic liquids. This accelerated catalytic system afforded the allylated products of various aldehydes in moderate to high yields. Preliminary studies on the enantioselectivity of this type of reaction have resulted in low to moderate enantioselectivities.

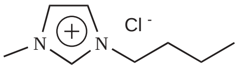
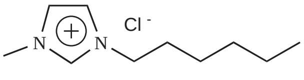
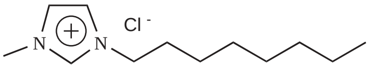
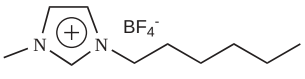
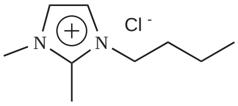
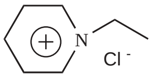
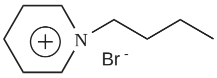
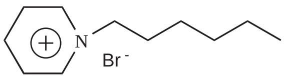
Key words: indium trichloride, allylation, aldehydes, catalyst, ionic liquid

Allylation reactions of various carbonyl compounds are valuable C–C bond formation methods for the preparation of synthetically useful homoallylic alcohols.[1] Although Lewis acids or Bronsted acids catalyzed allylation reactions in aqueous media with allytributyltin have been reported,[2–4] more active and efficient catalytic systems are still highly sought-after. Due to the increase in concerns about environmental effects which therefore requires the development of new synthetic manipulation that can minimize the use of hazardous chemicals. In order to achieve this goal, many strategies have been devised and investigated, especially by replacing the traditional organic solvents with other non-toxic solvents such as water or supercritical carbon dioxide. Recently, much attention has been focused on the use ionic liquids. Ionic liquids are considered to be excellent alternatives to traditional organic solvents, due to their favorable properties, such as non-flammability, no measurable vapor pressure, low toxicity, reusability, low cost, high thermal stability and experimental simplicity. As a result, ionic liquids are considered as promising alternative solvents for organic reactions.[5–9] Herein, we report that $InCl_3$-promoted allylation reactions of aldehydes with allytributyltin in ionic liquid to afford the corresponding allylated adducts in moderate to high yields.

First, we tested the allylation reaction of benzaldehyde (1 equiv) of allytributyltin (1.2 equiv) in hexylmethylimidazolium chloride ($[hmin^+][Cl^-]$) in the presence of $InCl_3$ or silver nitrate (0.5–2 equiv). Although silver nitrate was found to be not effective in catalyzing the formation of the allylation product, $InCl_3$ could promote the allylation reaction very effectively (Table 1, entry 2).

Table 1 $InCl_3$-Catalyzed Allylation of Benzaldehyde in Various Ionic Liquids



Entry	Ionic liquid	Temp (°C)	Time (h)	Yield (%)
1	 $[bmin^+] [Cl^-]$	40	16	70
2	 $[hmin^+] [Cl^-]$	25	16	80
3	 $[omin^+][Cl^-]$	25	14	82
4	 $[hmin^+] [BF_4^-]$	25	12	75
5	 $[bmmin^+] [Cl^-]$	55	16	68
6	 $[epy^+] [Cl^-]$	60	16	66
7	 $[bpy^+] [Br^-]$	45	14	60
8	 $[hpy^+] [Br^-]$	40	14	62

[a] Isolated yield.

Next using $InCl_3$, we investigated the effects of ionic liquids by carrying out the reaction in a series of ionic liquids. The results are summarized in Table 1. It can be

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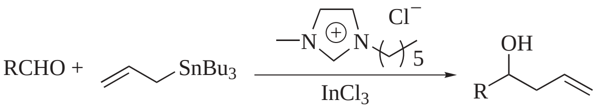
seen that all these ionic liquids gave the desired allylation product with moderate to good yields (60–82% yields), among which [hmin$^+$][Cl$^-$] and [omin$^+$][Cl$^-$] gave the best results (80% and 82% yields respectively).

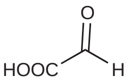
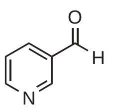
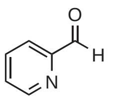
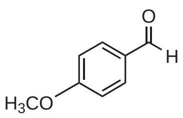
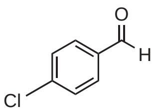
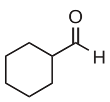
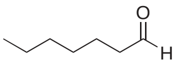
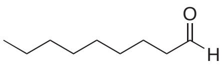
Next, we directed our studies to investigate the allylation reaction with various aldehydes in the present of InCl$_3$ in hexylmethylimidazolium chloride ([hmin$^+$][Cl$^-$]). The results are shown in Table 2. In all cases, InCl$_3$ has been shown to be efficient promoter for both aromatic and aliphatic aldehydes to afford the products in moderate to high yields (Table 2).

Effort to recycle and reuse the ionic liquid was also attempted. The recycle process was investigated starting with fresh hexylmethylimidazolium chloride ([hmin$^+$][Cl$^-$]) and 4-chlorobenzaldehyde in the presence of InCl$_3$ (Table 3). After the reaction was complete, the ionic liquid was recycled and reused in the second cycle (2nd cycle) directly. Unfortunately, no desired allylated product was obtained. This is consistent to the previously proposed mechanism that proposed the transmetallation of tin with InCl$_3$. Therefore, addition of a further 1 equivalent of InCl$_3$ to the recycled ionic liquid on every cycle, allowed the allylation reaction to proceed in good yields.

Table 2 InCl$_3$-Catalyzed Allylation Reaction with Various Aldehydes using [hmin$^+$][Cl$^-$]

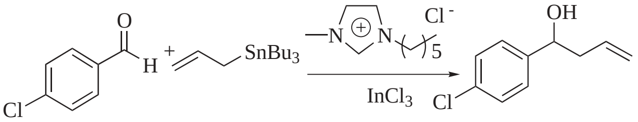


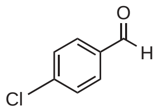
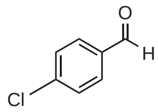
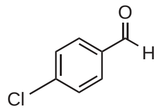
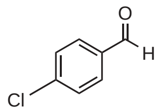
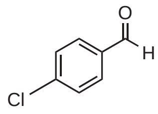
1a–i **2a–i**

Entry	Aldehyde	Product	Time (h)	Yield (%)[a]
1		**2a**	8	93
2		**2b**	14	88
3		**2c**	14	86
4		**2e**	16	78
5		**2f**	16	82
6		**2g**	18	76
7		**2h**	20	72
8		**2i**	20	73

[a] Isolated yield of allylated product. All of the products were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy.

Table 3 Recycling Study on the Allylation Reaction in [hmin$^+$][Cl$^-$]



Entry	Aldehyde	Product	Isolated yield (%)
1st cycle		**2f**	86
2nd cycle		**2f**	0
3rd cycle		**2f**	80
4th cycle		**2f**	76
5th cycle		**2f**	66

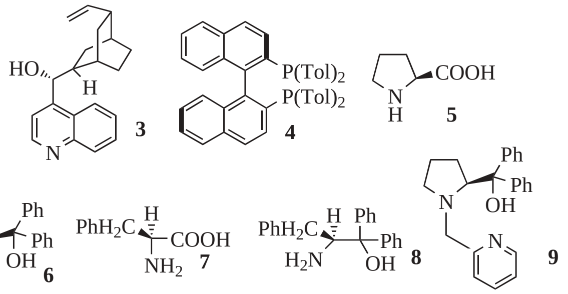
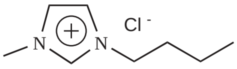
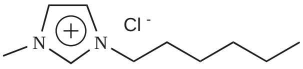
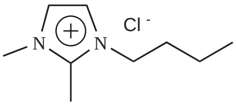
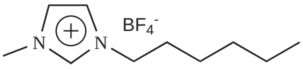
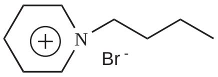
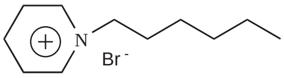


Figure 1 Chiral ligands **3**–**9**

In the meanwhile, we investigated the asymmetric allylation reaction in ionic liquids. First we initiated our study by using benzaldehyde and allytributyltin as substrates in [hmin$^+$][Cl$^-$]. During this study, the chiral ligands **3**–**9** (Figure 1) have been screened, among which (*S*)-2-(diphenylmethanol)-1-(2-pyridylmethyl) pyrrolidine **9** gave the best result (Table 5, entry 4). Next, using ligand **9**, a series of ionic liquids were also examined. The results are summarized in Table 4. It can be seen that all ionic liquids gave the desired allylation products of 4-chlorobenzaldehyde with low to moderate ee (16–48%), and the reaction carried out in [hmin$^+$][Cl$^-$] gave the best result. Meanwhile we found that changing to organic solvents led to lower selectivities (26% ee in CH$_2$Cl$_2$, 16% ee in THF).

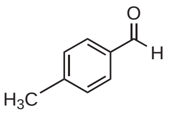
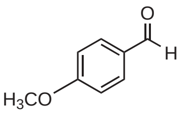
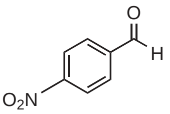
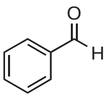
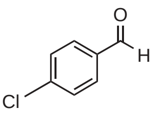
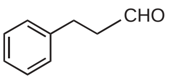
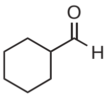
With these results, other aldehydes were also examined in [hmin$^+$][Cl$^-$] using chiral ligand **9** as chiral promoter (Table 5). In all cases, good chemical yields were obtained. The aromatic aldehydes furnished the products in moderate selectivities (Table 5, entries 1–5) while the aliphatic aldehydes gave a low value (Table 5, entries 6–8).

Table 4 Enantioselective Allylation of 4-Chlorobenzaldehyde in Various Ionic Liquids using **9**[11,]

Entry	Ionic liquid	Temp (°C)	Yield (%)[a]	ee (%)[b]
1		35	86	39
2		25	88	48
3		65	84	16
4		25	78	26
5		40	82	21
6		35	80	38

[a] Isolated yield.
[b] The %ee was determined by HPLC analysis of the ester from *O*-Methyl-(*S*)-Mandelic acid.

Table 5 Enantioselective Allylation of Aldehyde Catalyzed by Ligand **9** in [hmin$^+$][Cl$^-$]

Entry	Aldehyde	Yield (%)[a]	ee (%)[b]
1		88	42 (*R*)
2		85	39 (*R*)
3		89	56 (*R*)
4		88	46 (*R*)
5		88	48 (*R*)
6		81	10 (*S*)
7		79	12 (*R*)
8		76	8 (*R*)

[a] Isolated yield.
[b] The %ee was determined by ^{1}H NMR analysis of the ester from *O*-Methyl-(*S*)-Mandelic acid.
[c] The absolute configuration was determined by comparison to literature values of optical rotations.[10]

In conclusion, we have explored the InCl$_3$-catalyzed allylation system and studied the enantioselective allylation in ionic liquids for the first time. Although the ee’s are only low to moderate, these results showed that we could study the enantioselective allylation in ionic liquids. Further work to increase the enantioselectivity by designing new chiral ligands and other modification of the allylation system are in progress.

Acknowledgment

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(8) Chen, S. L.; Ji, S. J.; Loh, T. P. *Tetrahedron Lett.* **2003**, *44*, 2405.
(9) Dupont, J.; Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667.
(10) Kobayashi, S.; Aoyama, N.; Manabe, K. *Chirality* **2003**, *15*, 124; and references cited therein.
(11) **Typical Experimental Procedure**: To a 25 mL round-bottom flask containing an egg-shaped stirring bar were added [hmin$^+$][Cl$^-$] (0.5mL) and InCl$_3$ (53 mg, 0.24 mmol). After stirring at 25 °C for 15 min, benzaldehyde (21.2mg, 0.2mmol) was added followed by allytributyltin (81.9 mg, 0.24 mmol). The reaction mixture was stirred at 25 °C for 16 h. Then the mixture was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine, dried over anhyd Na$_2$SO$_4$, concentrated under vacuum, and purified by silica gel column chromatography to afford 80% of the product as a colorless oil.