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Asymmetric Mannich-type reactions catalyzed by indium(III) complexes in ionic liquids

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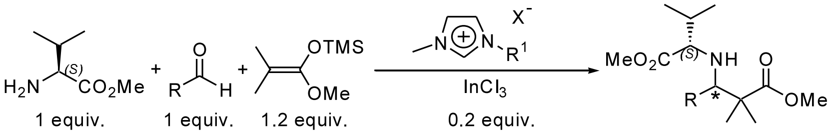
Abstract—In(III) complexes efficiently catalyse asymmetric Mannich-type reactions in ionic liquids with high diastereoselectivity and good yield. © 2003 Elsevier Science Ltd. All rights reserved.

The asymmetric synthesis of various functional molecules is one of the most important tasks in modern organic synthesis.[1] Therefore, it is important to develop efficient asymmetric C–C bond forming reactions. 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 the traditional organic solvents with other non-toxic solvents such as water or supercritical carbon dioxide. Recently, ionic liquids[2] 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. Over the past few years, these liquids have generated a significant amount of interest.[3] However, stereochemical features in these solvents have not been studied in detail. In this paper, we demonstrate an asymmetric Mannich-type reaction in ionic liquids (Scheme 1).

Recently, an In(III) complex-catalyzed, three-component Mannich-type reaction using aldehydes, amines and silyl enol ethers/ketene silyl acetals in water has been developed in this laboratory.[4] Although high yields were obtained, this protocol was mainly limited to non-enolizable aldehydes and aromatic amines. These limitations have hindered the development of an asymmetric version of this reaction. As a result, we directed our studies to investigate the reaction in ionic liquids. From our previous experience, the results obtained using L-valine methyl ester as a chiral auxiliary were excellent.[5] As a result, L-valine methyl ester was employed as a chiral auxiliary for the asymmetric version of the In(III) complex-catalyzed Mannich-type reaction.

Firstly, we investigated the effect of different ionic liquids on the asymmetric Mannich-type reaction using $InCl_3$. Four different ionic liquids were used in our investigation, i.e. butylmethylimidazolium tetrafluoroborate ([bmim][BF_4^-]), hexylmethylimidazolium



Scheme 1. $InCl_3$-catalyzed asymmetric Mannich-type reaction in ionic liquids.

Keywords: $InCl_3$; catalyst; asymmetric Mannich-type reaction; ionic liquids.

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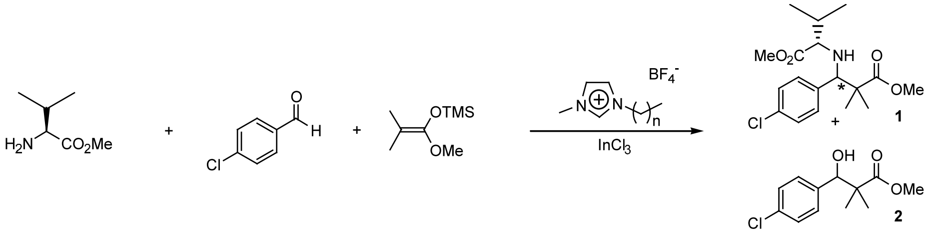
tetrafluoroborate ([hmim][BF_4^-]), octylmethylimidazolium tetrafluoroborate ([omim][BF_4^-]) and octylmethylimidazolium chloride ([omim][Cl^-]). The results are shown in Table 1.

It was found that this asymmetric Mannich-type reaction proceeded smoothly in all three [BF_4^- type ionic liquids but not in [omim][Cl^-]. Interestingly, the yields of the Mannich product **1** increased gradually when the cation carbon chain length of the ionic liquid used was reduced. Moreover, although the diastereoselectivities of the Mannich product **1** were consistently high, the ratios of the Mannich product to the aldol side product varied. The percentage of the Mannich product increased with shorter cation carbon chain lengths. This interesting result shows that we can progressively reduce the aldol side product by just altering the ionic liquid.

Next, a study was performed using [bmim][BF_4^-] with various aldehydes in the present of $InCl_3$. The yields and the diastereomeric ratios are shown in Table 2. In all cases, L-valine methyl ester was found to be a good chiral auxiliary for both aromatic and aliphatic aldehydes to afford the products in moderate to good yields with high diastereoselectivities. Contrary to the reaction carried out in water, even enolisable aldimines can be used in this system.

All efforts to recycle and reuse the ionic liquids in the same reaction failed to afford the desired Mannich product. However, addition of a further 0.2 equiv. of $InCl_3$ to recycled [hmin]BF_4^-, allowed the asymmetric Mannich-type reaction to proceed in 50% yield and 82% de with 4-chlorobenzaldehyde.

Table 1. Investigation of an asymmetric Mannich-type reaction using various ionic liquids

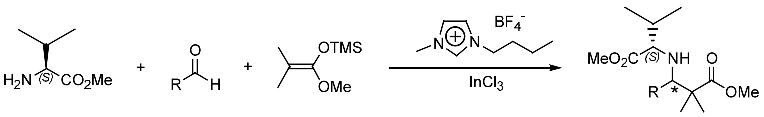


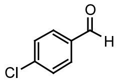
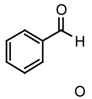
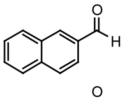
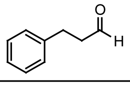
Ionic liquid	Yield[a]	Diastereomeric ratio[b] (R:S)	**1**:**2**
[omim][BF_4^-], $n=7$	50%	92:8	73:27
[hmim][BF_4^-], $n=5$	65%	93:7	93:7
[bmim][BF_4^-], $n=3$	71%	93:7	95:5
[omim][Cl^-], $n=7$	No desired product		

[a] Isolated yield of Mannich product **1**.

[b] The diastereomeric ratio of **1** was determined using ^1H and ^{13}C NMR spectroscopy.

Table 2. $InCl_3$-catalyzed asymmetric Mannich-type reaction with various aldehydes using [bmim][BF_4^-]



Entry	Aldehyde	Yield[a]	Diastereomeric ratio[b] (R:S)
1		71%	93:7
2		86%	91:9
3		74%	90:10
4		50%	93:7

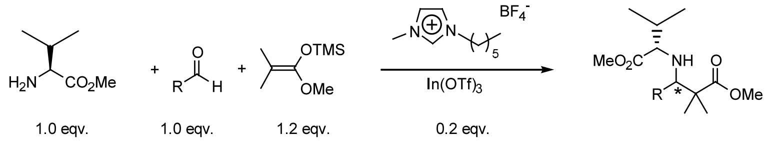
a. Isolated yield of Mannich product. b. The diastereomeric ratio was determined using ^1H and ^{13}C NMR spectroscopy.

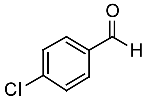
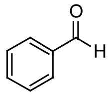
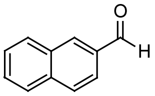
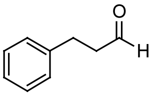
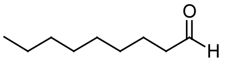
$In(OTf)_3$ can be recycled and reused and it was envisaged that this In(III) complex could be employed in the three-component asymmetric Mannich-type reaction with various aldehydes. The results are shown in Table 3. To our delight, $In(OTf)_3$ also performed very well as a catalyst in this reaction.

The recycle process was investigated (Table 4) starting with fresh $[hmim]BF_4^-$ and 4-chlorobenzaldehyde. After the reaction was complete (monitored by TLC), the ionic liquid and $In(OTf)_3$ were recycled and reused in the second cycle with the same aldehyde. The yield and selectivity were comparable to that of fresh ionic liquid and catalyst. However, the third cycle using benzaldehyde resulted in a decrease in yield to only 13% and the selectivity was found to be only 76% de.

In summary, we have developed a highly asymmetric Mannich-type reaction catalyzed by $InCl_3$ or $In(OTf)_3$ using ionic liquids. In general, the reactions proceeded smoothly at room temperature, and gave high diastereoselectivities and yields. Efforts to develop an asymmetric catalyst for this reaction in ionic liquids are currently in progress.

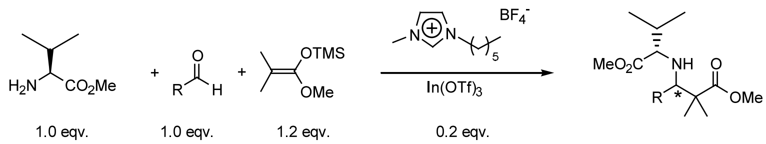
Table 3. $In(OTf)_3$-catalyzed asymmetric Mannich-type reaction with various aldehydes using $[hmim][BF_4^-]$

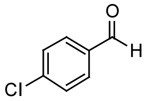
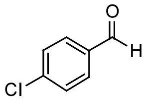
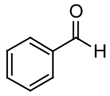


Entry	Aldehyde	Yield[a]	Diastereomeric ratio[b] (*R*:*S*)
1		65%	93:7
2		51%	91:9
3		61%	89:11
4		50%	80:20
5		53%	82:18

a. Isolated yield of Mannich product. b. The diastereomeric ratio was determined using ^1H and ^{13}C NMR spectroscopy.

Table 4. Recycling investigation on the asymmetric Mannich-type reaction in $[hmim][BF_4^-]$ using $In(OTf)_3$



Entry[a]	Aldehyde	Yield[b]	Diastereomeric ratio[c] (*R*:*S*)
1st cycle		65%	93:7
2nd cycle		65%	92:8
3rd cycle		13%	88:12

a. For each entry, <5% of aldol product was observed. b. Isolated yield of Mannich product. c. The diastereomeric was determined using ^1H and ^{13}C NMR spectroscopy.

Acknowledgements

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