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$InCl_3$-Catalyzed Three-Component Asymmetric Mannich-Type Reaction in Methanol

Teck-Peng Loh* and Shui-Ling Chen

Department of Chemistry, National University of Singapore,
3 Science Drive 3, Singapore 117543

chmlohtp@nus.edu.sg

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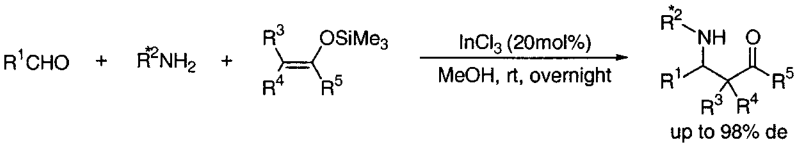
ABSTRACT

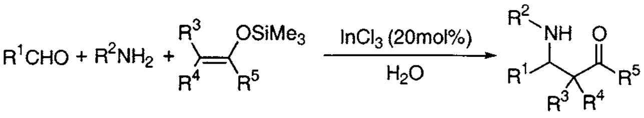


A one-pot $InCl_3$-catalyzed Mannich-type reaction was carried out in methanol. High diastereoselectivities and high yields were obtained. In addition, after the reaction was completed, $InCl_3$ can be recycled and reused without a drop of activity and selectivity.

The Mannich reaction is one of the most important fundamental reactions in organic chemistry because it affords synthetically and biologically important β-amino carbonyl compounds.[1,2] Therefore, it has found wide applications in the syntheses of numerous pharmaceuticals and natural products.

Most recently, our group has reported a novel three-component coupling $InCl_3$-catalyzed Mannich-type reaction in water (Scheme 1).[3,4] It has been found that the Mannich-type reaction involving aldehydes, amines, and silyl enol ethers/ketene silyl acetals proceeds smoothly in water under the catalysis of $InCl_3$ to afford the β-amino carbonyl compounds in high yields. However, this method was limited to the addition of nonenolizable aldehydes and aromatic amines. Furthermore, efforts to develop an enantioselective Mannich-type reaction in water by using a chiral amine were unsuccessful. In this paper, we present a new approach to overcome these limitations by using MeOH as solvent.

Scheme 1. Three-component Mannich-Type Reaction with $InCl_3$ in Water



Recently, Vilaivan and co-workers have reported an indium-mediated Barbier-type allylation of unactivated aldimines with allyl bromides in alcoholic solvents.[5] The ability of this reaction to work with a wide variety of substrates has encouraged us to investigate the asymmetric Mannich-type reaction in methanol using $InCl_3$.

First, we screened various chiral amines such as (*R*)-phenylethylamine, (*R*)-1-naphthylethylamine, (*R*)-2-naph-

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(1) For comprehensive reviews: (a) Risch, N.; Arend, M.; Westermann, B. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044 and references therein. (b) Tramontini, M.; Angiolini, L. In *Mannich Bases, Chemistry and Uses*; CRC: Boca Raton, FL, 1994, and references therein. (c) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 1, p 355 and references therein.

(2) (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blacky Academic and Professional: London, UK, 1998. (b) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (c) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640−5641. (d) Akiyama, T.; Onuma, Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1157−1158. (e) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209−217.

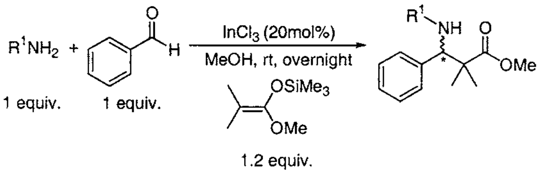
(3) Loh, T. P.; Wei, L. L. *Tetrahedron Lett.* **1998**, *39*, 323−326.

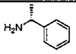
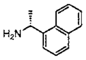
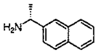
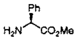
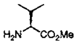
(4) Loh, T. P.; Liung, S. B. K. W.; Tan, K. L.; Wei, L. L. *Tetrahedron* **2000**, *37*, 3227−3237.

(5) Vilaivan, T.; Winotapan, C.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2001**, *42*, 9073−9076.

10.1021/ol0265968 CCC: $22.00

Table 1. Diastereoselective Mannich-Type Reaction of Chiral Amines, Benzaldehyde, and 1-Methoxy-2-methyl-1-trimethylsilyloxypropene



Entry	Amine	Yield (%)[a]	Diastereomeric ratio[b] (*R*:*S*)[c]
1		94	26:84
2		89	25:75
3		88	25:75
4		71	64:36
5		80	99:1

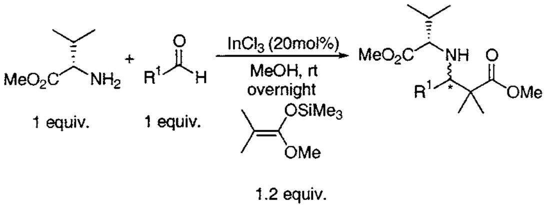
[a] Isolated yield. [b] The diastereomeric ratio was determined by ^{1}H and ^{13}C NMR. [c] .Absolute configuration assigned by analogy.[8]

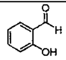
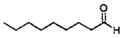
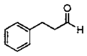
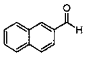
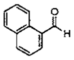
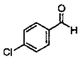
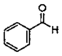
thylethylamine, L-phenylglycine methyl ester, and L-valine methyl ester to test the reaction as well as the diastereoselectivity. Table 1 summarizes the results obtained with various chiral amines, benzaldehyde, the commercially available 1-methoxy-2-methyl-1-trimethylsilyloxypropene,[6] and 20 mol % of $InCl_3$.[7]

In all cases, the desired β-amino esters were obtained in excellent yields. The highest diastereomeric excess was obtained when L-valine methyl ester was used as a chiral source (entry 5) while L-phenylglycine gave low selectivity (entry 4). Therefore, L-valine methyl ester was used as a chiral amine in subsequent reactions with various aldehydes. The results are shown in Table 2.

As shown in Table 2, these reactions proceeded smoothly in MeOH to afford the desired products in good yields with moderate to excellent diastereoselectivities. Furthermore, this protocol works with both aromatic and aliphatic aldehydes. Most importantly, these reactions work with enolizable aldehydes (entry 2 and 3), although the yields and selectivities were moderate. Entry 1 showed that these reactions could also work with an aldehyde having a hydroxyl functional group, however, with lower selectivity. As a result, no protection of the hydroxy group is required. This low selectivity may be attributed to the competing chelation between the hydroxyl group and the ester functionality of the chiral auxiliary.

Table 2. Diastereoselective Mannich-Type Reaction with L-Valine Methyl Ester as the Chiral Auxiliary



Entry	Aldehyde	Yield (%)[a]	Diastereomeric ratio[b] (*R*:*S*)[c]
1		40	77:23
2		60	82:18
3		51	86:14
4		79	93:7
5		56	95:5
6		57	99:1
7		80	99:1

[a] Isolated yield. [b] The diastereomeric ratio was determined by ^{1}H and ^{13}C NMR. [c] Absolute configuration assigned by analogy.[8]

The excellent diastereoselectivities observed may then be explained by using the transition state model as shown in Figure 1. In this model, $InCl_3$, nitrogen, and the carbonyl group of the ester are chelated together to form a rigid bidentate conformation. The bulky isopropyl group of the L-valine methyl ester selectively shields the *Re* face, thus leaving the *Si* face available for attack, thereby rendering the nucleophillic addition process a highly diastereoselective one. As a result, the (*R*,*S*)-diastereomer is the major product in all cases.

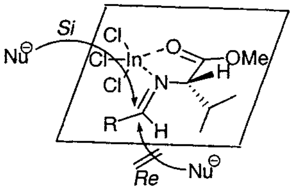


Figure 1. Transition state model of the highly diastereoselective Mannich-type reaction.

A ^{1}H NMR study has been carried out to investigate the progress of the reaction with and without $InCl_3$ in CD_3OD (Figure 2). It was found that, with $InCl_3$, the reaction was completed in 40 min after addition of the 1-methoxy-2-

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(6) The reaction was carried out with other nucleophiles, for example, (1-ethoxyvinyloxy)trimethylsilane gave the Mannich product in moderate yields, but the silylenol ether did not give any desired product.

(7) 5 and 10 mol % of $InCl_3$ were used in the investigation respectively and both gave equally good results.

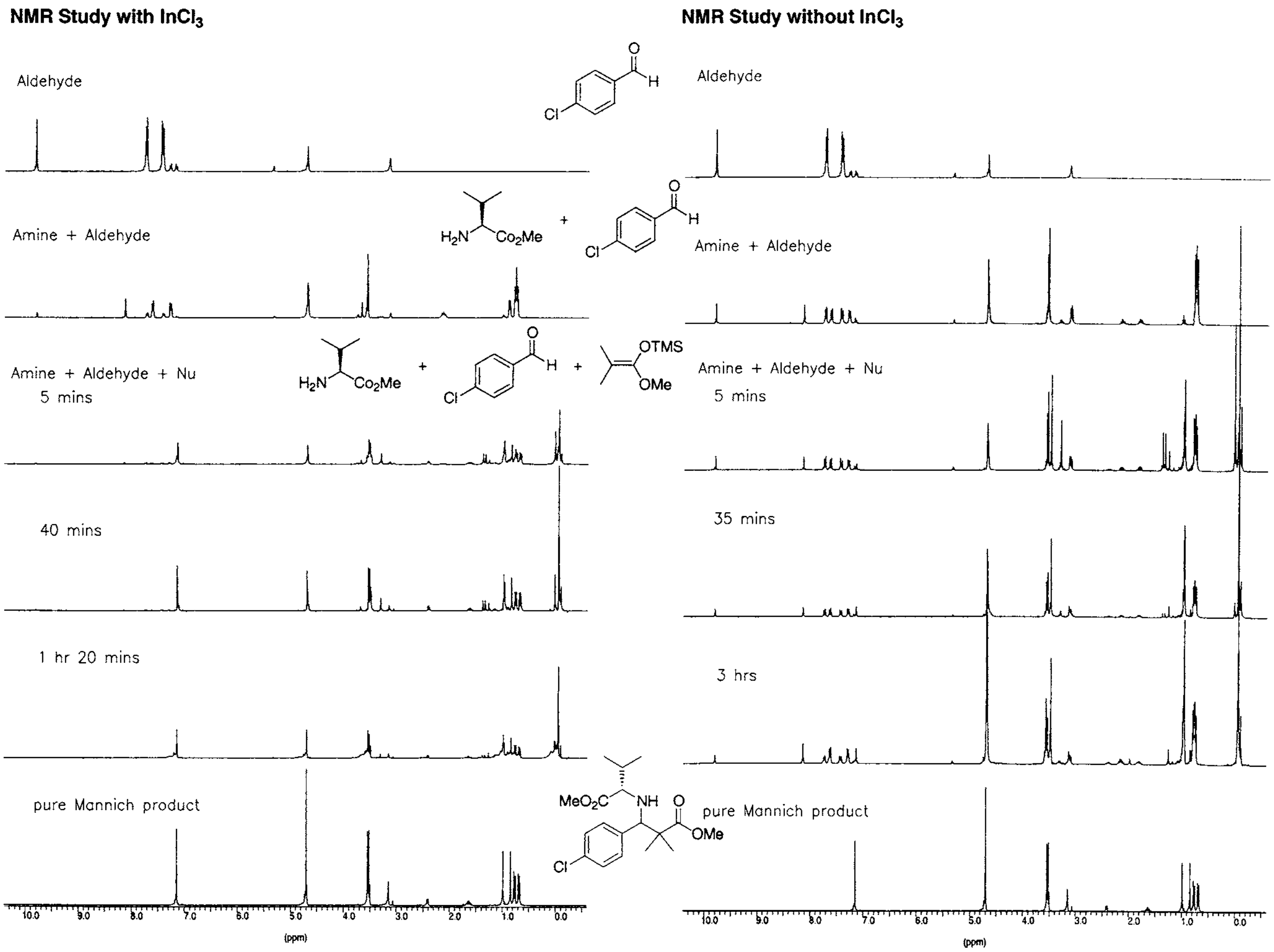


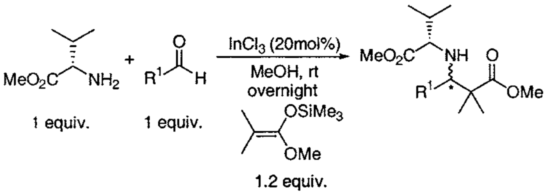
Figure 2. ^{1}H NMR study of the effect of $InCl_3$ in the Mannich-type reaction with CD_3OD.

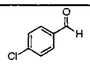
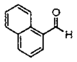
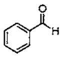
methyl-1-trimethylsilyloxypropene. However, without $InCl_3$, even though a small amount of the imine was formed, there was no reaction between the imine and 1-methoxy-2-methyl-1-trimethylsilyloxypropene. All these evidences showed not only that $InCl_3$ is a driving force for imine formation but also that it plays a very essential role in the nucleophilic attack of the imine.

Since $InCl_3$ plays an important role in our methodology, we then turned our attention to recycling and reusing the catalyst.[9] To demonstrate the efficiency of the recovered $InCl_3$, the three-component Mannich-type reaction of various aldehydes, L-valine methyl ester, and 1-methoxy-2-methyl-1-trimethylsilyloxypropene in MeOH was carried out with recycled $InCl_3$. The results are shown in Table 3. It was found that by using recycled $InCl_3$, the selectivities and yields are as good as with fresh $InCl_3$.

An attempt was made on removing the chiral auxiliary. It was found that the ester group on the chiral auxiliary could be selectively reduced with $NaBH_4$ in THF/MeOH (Scheme 2). This suggests that the chiral auxiliary can be further removed by oxidative chiral auxiliary cleavage with H_5IO_6.[10]

Table 3. Asymmetric Mannich-Type Reaction with Recycled $InCl_3$



Entry[a]	Aldehyde	Yield (%)[b]	Diastereomeric ratio[c] (*R*:*S*)[d]
1		57	99:1
2		63	95:5
3		80	99:1

[a] Entry 2 and entry 3 are in order of sequence when the reaction was carried out with recycled $InCl_3$ from the previous reaction. [b] Isolated yield. [c] The diastereomeric ratio was determined by ^{1}H and ^{13}C NMR. [d] Absolute configuration assigned by analogy.[8]

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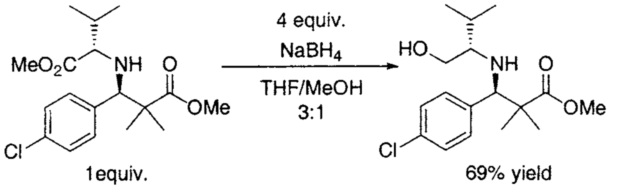
(8) Ojima, I.; Inaba, S. *Tetrahedron Lett.* **1980**, *21*, 2081−2084.

Scheme 2. Selective Reduction of One Ester Functionality from the Mannich Product with $NaBH_4$



In brief, we have reported a $InCl_3$-catalyzed asymmetric three-component Mannich-type reaction using methanol. This reaction works with both enolizable and nonenolizable aldehydes, as well as with aliphatic amines. This new method provides an easy entry into synthetically useful β-amino carbonyl compounds in protic solvent.

Acknowledgment. We would like to thank the National University of Singapore for providing the research grants and also the Chemical Process and Engineering Centre and Singapore Millennium Fund for providing the scholarship.

Supporting Information Available: General procedure of the three-component asymmetric Mannich reaction and ^1H and ^{13}C NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) First, the MeOH was removed azeotropically followed by the extraction of the organic compounds with ether/hexane (1:1, ×5). The remaining residue in the reaction flask was the recycled $InCl_3$, which would be ready for further reactions.

(10) Alvara, G.; Savoia, D. *Tetrahedron: Asymmetry* **1996**, *7*, 2083−2092.