Indium Trichloride-Catalyzed Conjugate Addition of Amines to α,β-Ethylenic Compounds in Water

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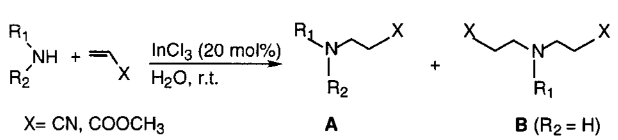
Abstract: Catalytic amount of indium (III) trichloride efficiently catalyzed Michael reaction between amines and α,β-ethylenic compounds in water and under mild conditions. Indium trichloride can be recovered and reused without decrease in yield.

One of the most straightforward routes for the synthesis of β-amino derivatives such as β-aminoesters[1] is *via* the Lewis acid-mediated addition of amines to α,β-ethylenic compounds. However, only simple primary nonbulky amines can react with simple unsubstituted acrylic compounds without special activation[2,3] such as high temperature,[4] high pressure,[5] the use of appropriate catalysts,[6] as well as with various such combinations.[7] In order to develop new catalysts to promote this reaction under mild reaction conditions, we examined a novel and useful catalyst namely indium (III) trichloride.

Organic reactions in water or aqueous media have recently attracted great interest.[8,9] Recently, we have reported indium trichloride as an excellent catalyst in the Mukaiyama aldol reactions,[10-12] Diels-Alder reactions,[13] aldol-type Mannich reaction[14] and Michael reaction[15] neat or in water under mild conditions. As indium trichloride has these unique properties compared to other Lewis acids which include stability and recoverability from water, we are interested to apply it to other carbon-carbon bond formation reactions in water. In this paper, we showed that indium trichloride can promote the conjugate addition of α,β-ethylenic substrates such as acrylate, crotonate and acrylnitrile with primary and secondary amines in water (**Scheme 1**).

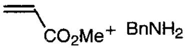
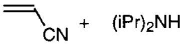
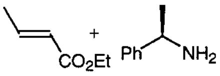
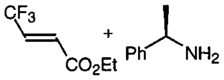


Scheme 1

A typical experimental procedure is as follows: An α,β-ethylenic substrate (1 mmol) and $InCl_3$ (20 mol%) were stirred in distilled water (5 mL) at room temperature for 10 minutes. Amine (1.2 equiv.) was then added in small portions. The resulting mixture was stirred for 6-40 hours at room temperature. Usual workup afforded the β-amino products. The results are summarized in Tables 1, 2 and 3.

Indium trichloride was first tested for its effectiveness as a Lewis acid in the reaction of methyl acrylate and benzylamine in water (Table 1, entries 1 and 2). Competitive experiments were carried out with and without $InCl_3$ in water. The reaction of methyl acrylate with benzylamine in the presence of $InCl_3$ was completed in 6 h giving a mixture of mono and disubstituted products (70 %). However, the control reaction without any catalyst gave much lower yields (20 %) confirming the effectiveness of $InCl_3$ as catalyst for the addition of amine to α,β-unsaturated ester. Similarly, when the reaction of acrylnitrile with diisopropyl amine was carried out in the presence of $InCl_3$ (Table 1, entries 3 and 4), the monosubstituted product was obtained as the sole product in much higher yield as compared to the reaction without $InCl_3$. $InCl_3$ can also be recovered and reused. The yields of the 2nd and 3rd runs were comparable to the first run (Table 1, entry 3). Finally, the $InCl_3$-catalyzed addition of (*R*)-methyl benzylamine to *trans*-ethyl crotonate and *trans*-ethyl 4,4,4-trifluorocrotonate afforded the corresponding products in higher yield than the control reactions without $InCl_3$ separately (Table 1, entries 5 to 8). These results confirmed the efficiency of $InCl_3$ as a catalyst for the conjugate addition of amines to α,β-ethylenic compounds and show that recovered $InCl_3$ can be reused without decrease in yield.

Table 1. Effect of $InCl_3$

Entry	Reactions	Conditions	Yields[a]
1		$InCl_3$ (20 mol%), H_2O, r.t., 6 h	70 (33:67)[b]
2	"	H_2O, r.t., 6 h	20 (35:65)[b]
3		$InCl_3$ (20 mol%), H_2O, r.t., 16 h	82, 85, 81[c]
4	"	H_2O, r.t., 16 h	62[d]
5		$InCl_3$ (20 mol%), H_2O, r.t., 23 h	45 (14 %de)
6	"	H_2O, r.t., 23 h	40 (15 %de)
7		$InCl_3$ (20 mol%), H_2O, r.t., 3 d	70 (7 de%)
8	"	H_2O, r.t., 3 d	51 (8 de%)

[a] Isolated yields. [b] the ratio of **A/B**. [c] Yields of 1st, 2nd and 3rd runs separately. [d] 69% at 50 °C [7]

Table 2. $InCl_3$ Catalyzed Conjugate Addition of Amines to Methyl Acrylate

Entry	R_1	R_2	Time	Yields(%) [a]
1	4-Cl-Ph	H	18 h	6
2	Ph	H	18 h	45
3	4-CH_3O-Ph	H	18 h	65
4	CH_3	CH_3	18 h	85
5	EtO_2CCH_2	H	18 h	65 (82:18)[b]
6	$PhCH_2$	H	6 h	70 (33:67)[b]
7	$Ph(CH_3)CH$	H	18 h	44 (75:25)[b]

[a] Isolated yields. [b] The ratio of **A/B**

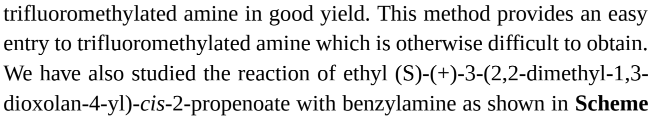
Table 3. $InCl_3$ Catalyzed Conjugate Addition of Amines to Acrylnitrile

Entry	R_1	R_2	Time	Yields(%) [a]
1	4-Cl-Ph	H	40 h	7
2	Ph	H	40 h	33
3	4-CH_3O-Ph	H	40 h	54
4	CH_3	CH_3	16 h	92
5	iPr	iPr	16 h	82, 85, 81[c]
6	EtO_2CCH_2	H	20 h	61
7	$PhCH_2$	H	16 h	98 (98:2)[d]
8	$Ph(CH_3)CH$	H	20 h	72 (93:7)[d]

[a] Isolated yields. [b] 69 % at 50 °C [7]. [c] the yields of 1st, 2nd and 3rd runs separately. [d] The ratio of **A/B**

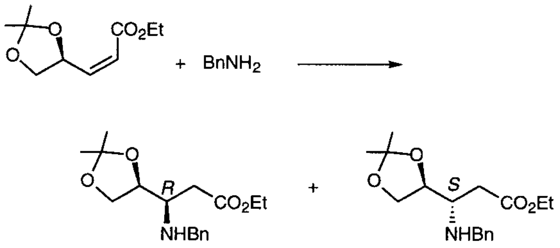
After confirming the efficiency of indium trichloride, a wide variety of primary and secondary amines were reacted with acrylate and acrylnitrile in water. The results are summarized in Tables 2 and 3. The following characteristic features of these reactions are noted: (1) In all cases indium trichloride catalyzed the addition of various amines with acrylate and acrylnitrile in water gave the corresponding β-amino esters in moderate to high yields. (2) $InCl_3$ can catalyze both alkyl and aromatic amines addition reactions. For the reactions of simple alkyl amines such as dimethylamine, the yields are high. (3) Reactivities of nonbulky amines relate to their basicity (Tables 2 and 3, entries 1, 2 and 3). Generally, higher basicity results in higher yields. (4) The additional alkylation reaction is difficult to control (Table 2, entries 5, 6 and 7; Table 3, entries 7 and 8). This further alkylation cannot be avoided either by changing the addition sequence or the changing of the ratios of reactants. (5) $InCl_3$ can be recovered and reused after the completion of reactions without any decrease in yields (Table 1, entries 3). The experimental procedure is very simple: after being extracted with ethyl acetate three times, the aqueous layer was separated and reused directly for the second run.

Preliminary studies using chiral amine ((*R*)-methyl benzylamine) with *trans*-ethyl crotonate resulted in poor diastereoselectivity as shown below (**Scheme 2**). The isomers resulting from *trans*-ethyl crotonate can be easily separated by silica gel chromatography. Interestingly, indium trichloride can also catalyze the addition of (*R*)-methyl benzylamine to *trans*-ethyl 4,4,4-trifluorocrotonate to afford the corresponding chiral trifluoromethylated amine in good yield. This method provides an easy entry to trifluoromethylated amine which is otherwise difficult to obtain. We have also studied the reaction of ethyl (S)-(+)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-*cis*-2-propenoate with benzylamine as shown in **Scheme 3**. Efforts to increase the diastereomeric selectivity using other chiral amines are ongoing.



Y = CH_3 Yield 45% (14% d.e.) [16]
Y = CF_3 Yield 70% (7% d.e.) [17]

Scheme 2



Condition 1. H_2O, r.t., 21 h;
80% conversion; 63% isolated yield; (3*R*):(3*S*) = 80:20[18,19];

Condition 2. $InCl_3$(20% mol), H_2O, r.t., 21 h;
100% conversion; 78% isolated yield; (3*R*):(3*S*) = 80:20[18].

Scheme 3

In conclusion, $InCl_3$ is an efficient catalyst for Michael conjugate addition of amines to α,β-unsaturated ethylenic compounds in water under mild reaction conditions.

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References and Notes:

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(19) The ratio of *cis/trans* of recovered ethyl (S)-(+)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenoate is 5/95 respectively as compared to the pure *cis* starting material.