Indium-mediated Allylation of α-Imino Esters in Aqueous Media

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Indium-mediated allylation of carbonyl groups has attracted much attention due to the efficiency of achieving transformations in aqueous media. Since indium has gained great fame in chemical community for conducting allylation of C=O bonds, numerous examples have been reported to recent years.[1] Addition of the allylindium reagent to imines, however, has not enjoyed popularity even though allylation of C=N bond could be a natural extension of the allylation of carbonyl groups. Relative scarcity of reports on the addition of organometallic reagents to C=N bonds, in general, should be ascribed to the poor electrophilicity of the imines compared to the corresponding carbonyl groups. Therefore, it is often required to have organometallic reagents with higher reactivity or attaching the activating group to facilitate the addition. This is also the case for the allylation of C=N bond mediated by indium, especially in aqueous media due to the low electrophilicity of imines, ease of being hydrolyzed, and tendency to produce homocoupling products.[2] Indium-mediated allylations of C=N bonds in aprotic organic solvents, including THF[3] and DMF[4] has also been reported. Indium-mediated allylation of unactivated aldimines has been conducted in alcoholic solvent as an example of using protic solvents.[5] In this case allylation to C=N bonds in water was not successful and only produced the corresponding homoallylic alcohol via presumed indium salt-catalyzed hydrolysis of imines. Asymmetric allylation of aldimines in alcoholic solvents to synthesize optically active homoallylic amines has also appeared.[6]

Chan has first achieved the indium-mediated allylation of imines in aqueous media by employing sulfonimines instead of simple imines. The success of addition was ascribed to the enhanced electrophilicity due to the electron-withdrawing ability of the sulfonyl group.[7] Indium-mediated allylation of tosyl and aryl hydrazones and nitrones has been performed in DMF-H_2O system.[8] It is also noteworthy to mention that propargylation of imines and imine oxides in THF-H_2O has also been reported.[9]

Imines derived from glyoxylic acid derivatives have also been used as substrates for indium-mediated allylations. Glyoxylate oxime **1** (R' = H) or oxime ethers **1** (R' = alkyl) has been investigated as substrates for indium-mediated allylations of C=N bonds. Since C=N bonds in oxime glyoxylates (as well as α-imino esters **2**) are activated due to existence of COOR, facile addition of allylindium is anticipated. In fact, addition of allylzinc reagents, which exhibit similar behavior to allylindium reagents, to C=N bonds was reported by Hannesian.[10]

There have been a few reports on the indium-mediated allylation of glyoxylic oxime ethers in aqueous media. Asymmetric synthesis of α-amino acids by allylation of glyoxylic oxime ethers having Oppolzer's camphorsultam as a chiral auxiliary (**2'**) has been conducted.[11] Two other reports on allylation of glyoxylic oxime ethers in aqueous media have appeared.[12] Similar and still interesting allylation with palladium-indium iodide has been investigated with respect to regioselectivity and role of water added in enhancing diastereoselectivity.[13]

Despite these few reports, the allylation reactions mediated by indium on PMP (*p*-methoxyphenyl)-protected α-imino esters **3** have not been investigated. We have been interested in indium-mediated allylation of α-imino esters **3** especially in aqueous media. Here we wish to report our efforts on Barbier-type allylation of α-imino esters **3** mediated by indium in aqueous media.

We chose a PMP-protected α-imino ester **3a** (R = Et) as a substrate for indium-mediated allylation in organic and aqueous media. Results of the indium or zinc-mediated allylation of α-imino ethyl ester **3a** were summarized in Table 1.

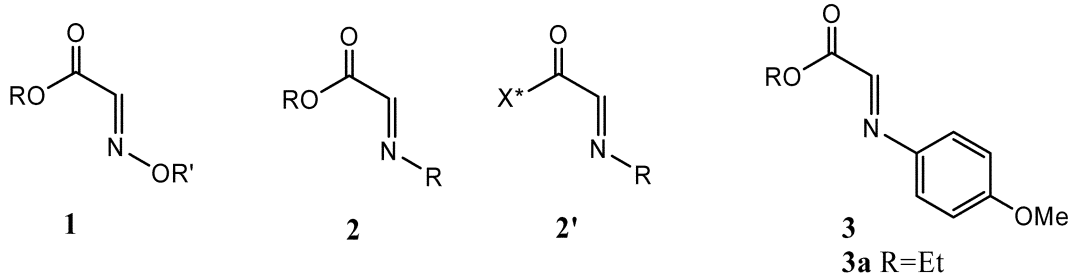
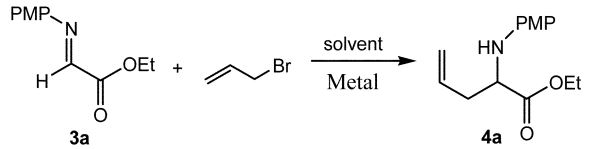


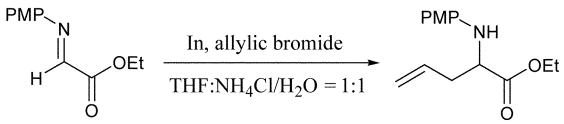
Table 1. Indium or zinc-mediated allylation of PMP (*p*-methoxyphenyl)-protected α-imino ethyl ester[a]

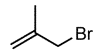
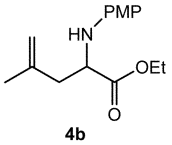
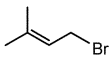
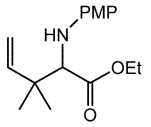
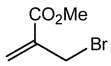
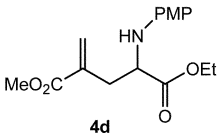
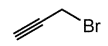
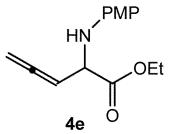


Entry	Solvent[b]	Metal	Time (h)	Isolated Yield (%)
1	THF	In	3	81
2	THF:H_2O (1:1)	In	18	59
3	THF:NH_4Cl/H_2O (1:1)	In	5	88
4	DMF	In	3	82
5	DMF:H_2O (1:1)	In	5	68
6	DMF:NH_4Cl/H_2O (1:1)	In	5	67
7	EtOH	In	3	46
8	H_2O	In or Zn	24	NR
9	EtOH:NH_4Cl/H_2O (1:1)	In	5	36
10	THF	Zn	3	83
11	THF:H_2O (1:1)	Zn	5	62
12	THF:NH_4Cl/H_2O (1:1)	Zn	4	88
13	DMF	Zn	3	80
14	DMF:H_2O (1:1)	Zn	5	66
15	DMF:NH_4Cl/H_2O (1:1)	Zn	3	69
16	EtOH	Zn	3	45
17	EtOH:NH_4Cl/H_2O (1:1)	Zn	5	37

[a]The following molar ratios were used: **3a** (1.0 equiv), allyl bromide (2.0 equiv), metal (In or Zn) (1.2 equiv), and AcOH (6.0 equiv). [b]NH_4Cl/H_2O means that saturated aqueous ammonium chloride was used.

Table 2. Indium-mediated allylation of PMP (*p*-methoxyphenyl)-protected α-imino ethyl ester with various allyl bromides[a]



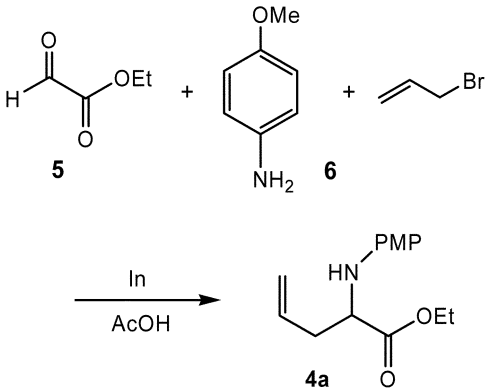
Entry	Allylic Bromide	Product	Time (h)	Isolated Yield (%)
1		 **4b**	5	83
2		 **4c**	5	80
3		 **4d**	5	79
4		 **4e**	5	82

[a]The following molar ratios were used: **3a** (1.0 equiv), allyl bromide (2.0 equiv), metal (In) (1.2 equiv), and AcOH (6.0 equiv). THF and saturated aqueous ammonium chloride was used as a solvent system.

As expected the allylation reactions underwent efficiently in organic solvents such as THF and DMF with both metals (entries 1, 4, 10, and 13) at room temperature. However, allylation in ethanol only proceeded in low yield either with In or Zn (entries 7 and 16). More importantly, we have tested the reaction in aqueous media. Addition of water to organic solvents resulted in reduction of yields (entries 2, 5, 11, and 14). Fortunately, employing saturated aqueous ammonium chloride restored the yields up to the level of using organic solvents such as THF and DMF only. The equal ratio of organic solvents and aqueous saturated NH_4Cl solution (1 : 1 (*v*/*v*)) offered optimum yields. Among organic solvents tested, THF provided the best yield of the allylations when aqueous saturated NH_4Cl solution was added (entry 3). Addition of lesser amount of water or further addition of water led to lowering of yields. Use of water only as a solvent prohibited the reaction (entry 8) to provide the allylated product.

Since allylation to the PMP-protected α-imino ester **3a** was most efficiently achieved with indium in THF : NH_4Cl/H_2O (1 : 1). Several allylic bromides and propargyl bromide were tested for addition under this condition (Table 2). With 3-methyl-2-butenyl bromide allylation took place at γ-position. No α-allylation was observed (entries 2). Even with propargyl bromide allenylation only occurred (entry 4). All reactions in Table 2 was achieved in good yield and completed in less than 3 h.

The allylation was further simplified by starting with α-ketoesters. Instead of using α-imino ester **3a**, α-ketoester **5** was directly used a starting substrate without preparing PMP-protected α-imino ester **3a** as shown in the following equation.

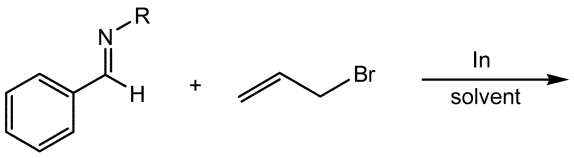


We have tested the one-pot reaction in THF (Table 3). Thus, α-ketoester **5** and *p*-methoxyaniline **6** was dissolved and stirred for 15 min before allyl bromide and indium were added (Method A). The resulting mixture was stirred until the reaction was completed. Three hours were enough to

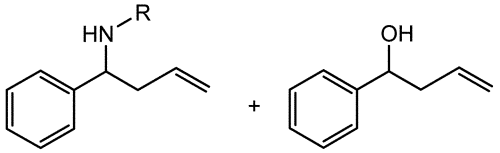
provide the allylated product **4a** in good yield in THF (entry 1). Switching to an aqueous solvent system (*i.e.*, THF : NH_4Cl/H_2O (1 : 1)) resulted in allylation also in good yield (85%) (entry 2). Furthermore, it was also possible to perform the reaction by mixing all of the reagents (**5**, **6**, and allyl bromide as well as indium in the presence of acetic acid) in solvents at the same time (Method B). In THF this one-pot reaction provided the product in good yield (87%) (entry 3). This one-pot allylation was, however, not efficient in THF : NH_4Cl/H_2O (1 : 1) and only to give in 45% yield (entry 4). One-pot allylations were similarly achieved in good yields with other allylic bromides (Table 3, entries 5-7).

Employing the PMP (*p*-methoxybenzyl) group as the protecting group of imine functionality provided a unique opportunity to proceed the allylation in good yield. Thus, reactions of *N*-benzylidenebenzylamine (**7a**) with the allylindium reagent generated by addition of allyl bromide and indium undergo efficiently to give **8a** when anhydrous THF is used as a solvent. The reaction in water, however, only gave the corresponding homoallyl alcohol **9** (not **8a**) in good yield presumably due to the allylation of the aldehyde derived from the hydrolysis of the imine **7a**.[5] We tested the allylation of **7a** in THF : NH_4Cl/H_2O (1 : 1) (the same condition as we selected for the efficient allylation of the PMP (*p*-methoxyphenyl) protected *α*-imino ester **3a**, see Table 1 and 2) and confirmed that the homoallylic alcohol **9** was formed in good yield (90%).

However, the PMP-protected aldimine **7b** was reacted with allyl bromide in the presence of indium to provide the corresponding allylated product **8b** in good yield both in THF and the aqueous system (THF : NH_4Cl-H_2O (1 : 1)). This result has confirmed that the PMP group can act to stabilize the aldimines by withdrawing electrons from the nitrogen atom and exert a favorable effect to facilitate the allylation and prevent hydrolysis possibly catalyzed by the indium salts in aqueous media.



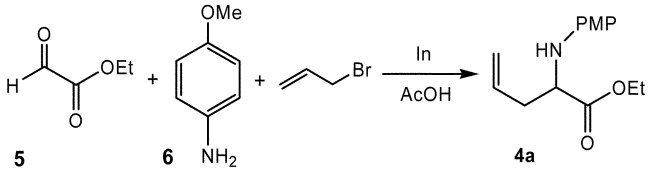
7a R = -CH_2Ph
7b R = -C_6H_4-OMe(PMP)



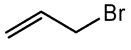
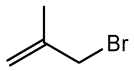
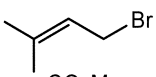
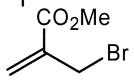
8a R = -CH_2Ph
8b R = -C_6H_4-OMe(PMP)

9

Table 3. One-pot allylation starting with ethyl glyoxylate **5**



5 **6** **4a**

Entry	Allylic Bromide	Method[a]	Solvent	Time (h)	Isolated Yield (%)
1		A	THF	3	91
2		A	THF:NH_4Cl/H_2O = 1:1	5	85
3		B	THF	3	87
4		B	THF:NH_4Cl/H_2O = 1:1	5	45
5		A	THF:NH_4Cl/H_2O = 1:1	5	77
6		A	THF:NH_4Cl/H_2O = 1:1	5	80
7		A	THF:NH_4Cl/H_2O = 1:1	5	78

[a]Method A: *α*-Ketoester **5** and *p*-methoxyaniline **6** was dissolved and stirred for 15 min before allyl bromide and indium were added. Method B: *α*-Ketoester **5**, *p*-methoxyaniline **6**, and allyl bromide was dissolved at the same time.

Experimental Section

All materials and solvents were purchased from either Sigma-Aldrich or Tokyo Chemical Industries Co. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300. The chemical shifts are reported in ppm on δ scale downfield from TMS, and signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak.

Ethyl 2-(*N*-(4-methoxy)phenyl)amino-4-pentenoate (4a). To a mixture of ethyl 2-(4-methoxyphenylimino)acetate (30 mg, 0.14 mmol) and indium powder (20 mg, 0.17 mmol) in THF (1.5 mL) and saturated aqueous ammonium chloride (1.5 mL) was added acetic acid (50 μL, 0.86 mmol) at room temperature. While stirring the mixture allyl bromide (25 μL, 0.29 mmol) was added slowly. The mixture was stirred for 3 h at room temperature. The mixture was extracted with ether (3 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography (Hexane : Ethyl acetate = 5 : 1) provided the desired product as a transparent yellow liquid (32 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ6.77 (d, 2H, J = 8.8 Hz, 2 x ArH in *p*-methoxyphenyl), 6.60 (d, 2H, J = 8.8 Hz, 2 x ArH in *p*-methoxyphenyl), 5.80 (dddd, 1H, J = 7.2, 7.2, 10, 17 Hz, CH_2-C*H*=CH_2), 5.16 (bd, 1H, J = 17 Hz, one of CH_2-CH=CH_2), 5.15 (bd, 1H, J = 10 Hz, one of CH_2-CH=CH_2), 4.18 (q, 2H, J = 7.1 Hz, -OCH_2-CH_3), 4.05 (t, 1H, J = 6.1 Hz, -CH_2(NH)C*H*-C=O), 3.91 (bs, 1H, -NH), 3.74 (s, 3H, -$C_6H_4OCH_3$), 2.45-2.65 (m, 2H, =CH-CH_2-CH(NH)), 1.24 (t, 3H, J = 7.1 Hz, -OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ173.6, 152.7, 140.7, 132.9, 118.8, 115.2, 114.8, 61.0, 57.2, 55.7, 37.2, 14.2.

One-pot allylation: Typical procedure. Ethyl glyoxylate (polymeric form, 47% in toluene, 32 mg, 0.15 mmol) and *p*-

anisidine (18 mg, 0.15 mmol) were dissolved in THF (2 mL) and stirred for 15 min at room temperature. To the resulting solution was added indium powder (20 mg, 0.18 mmol) and allyl bromide (25 μL, 0.29 mmol). THF (1 mL) and saturated aqueous ammonium chloride (3 mL) and acetic acid (51 μL, 0.88 mmol) were added successively to the reaction mixture. The mixture was stirred for 5 h at room temperature until the reaction was completed. The mixture was extracted with ether (3 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography (hexane : ethyl acetate = 5 : 1) provided the desired product as a transparent yellow liquid (31 mg, 85%).

Compound **4b:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, 2H, J = 8.9 Hz, 2 x ArH in *p*-methoxyphenyl), 6.59 (d, 2H, J = 8.9 Hz, 2 x ArH in *p*-methoxyphenyl), 4.90 (bs, 1H, one of =CH_2), 4.83 (bs, 1H, one of =CH_2), 4.17 (q, 2H, J = 7.1 Hz, OCH_2CH$_3$), 4.08 (t, 2H, J = 7.1 Hz, -NHCH-C=O), 3.80 (bs, 1H, NH), 3.73 (s, 3H, -OCH$_3$), 2.55 (dd, 1H, J = 6.5, 13.8 Hz, one of =C-CH_2-C(NH)), 2.47 (dd, 1H, J = 8.0, 13.8 Hz, one of =C-CH_2-C(NH)), 1.78 (s, 3H, CH_3-C=), 1.23 (t, 3H, J = 7.1 Hz, -OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 152.7, 140.9, 140.8, 115.0, 114.8, 114.3, 61.0, 56.2, 55.7, 41.4, 21.9, 14.2.

Compound **4c:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, 2H, J = 8.9 Hz, 2 x ArH in *p*-methoxyphenyl), 6.60 (d, 2H, J = 8.9 Hz, 2 x ArH in *p*-methoxyphenyl), 5.95 (dd, 1H, J = 10.8, 17.3 Hz, CH$_2$-CH=CH$_2$), 5.15 (d, 1H, J = 10.8 Hz, one of CH$_2$-CH=CH_2), 5.12 (d, 1H, J = 17.3 Hz, one of CH$_2$-CH=CH_2), 4.14 (q, 2H, J = 7.1 Hz, -OCH_2-CH$_3$), 3.8-4.0 (m, 2H, NH and (NH)CH-C=O), 3.73 (s, 3H, -C$_6$H$_4$OCH_3), 1.23 (t, 3H, J = 7.1 Hz, -OCH$_2$CH_3), 1.20 (s, 3H, -C-CH_3), 1.14 (s, 3H, -C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 152.7, 143.5, 141.4, 115.3, 114.8, 114.0, 66.0, 60.6, 55.7, 40.6, 24.9, 23.7, 14.3.

Compound **4d:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, 2H, J = 8.9 Hz, 2 x ArH in *p*-methoxyphenyl), 6.60 (d, 2H, J = 8.9 Hz, 2 x ArH in *p*-methoxyphenyl), 6.25 (d, 1H, J = 1 Hz, one of =CH$_2$), 5.67 (d, 1H, J = 1 Hz, one of =CH_2), 4.23 (t, 1H, J = 6.8 Hz, NH-CH-C=O), 4.13 (q, 2H, J = 7.1 Hz, -OCH_2-CH$_3$), 3.97 (bs, 1H, NH), 3.77 (s, 3H, COOCH_3), 3.73 (s, 3H, -C$_6$H$_4$OCH_3), 2.88 (dd, 1H, J = 6.9, 13.6 Hz, one of =C-CH_2-CH(NH)), 2.70 (dd, 1H, J = 6.8, 13.6 Hz, one of =C-CH_2-CH(NH)), 1.22 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 167.2, 152.7, 140.5, 136.0, 128.3, 115.1, 114.8, 61.0, 57.0, 56.7, 52.1, 35.6, 14.2.

Compound **4e:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, 2H, J = 8.9 Hz, 2 x ArH in *p*-methoxyphenyl), 6.62 (d, 2H, J = 8.9 Hz, 2 x ArH in *p*-methoxyphenyl), 5.33 (q, 1H, J = 6.5 Hz, CH=C=CH$_2$), 4.91-4.96 (m, 2H), 4.54 (b, 1H, =C-CH(NH)), 4.22 (q, 2H, J = 7.1 Hz, -OCH_2-CH$_3$), 4.13-4.2 (b, 1H, NH), 3.74 (s, 3H, C$_6$H$_4$OCH_3), 1.28 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 171.8, 152.7, 140.0, 115.3, 114.8, 89.3, 78.8, 61.5, 56.4, 55.6, 14.2.

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