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# Indium-catalyzed Barbier allylation reaction

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**Abstract**

Barbier allylation reaction of carbonyl compounds with allyl bromide was investigated using a catalytic amount of indium (0), indium (I) or indium (III) salts in the presence of a reducer and chlorotrimethylsilane (TMSCl). The Mn/TMSCl couple turned out to be the most efficient system to regenerate active indium in the allylation reaction of various carbonyl compounds including α- and β-oxygenated aldehydes.


*Keywords:* Indium; Manganese; Catalysis; Allylation reaction; Homocoupling

## 1. Introduction

Indium-mediated reactions have elicited considerable interest [1] in various reactions such allylation [2], propargylation [3], alkynylation [4], Reformatsky [5] reactions, cyclopropanations [6], reductions [7] and oxidations [8]. Indium was generally used in a stoichiometric amount but in some cases, catalytic versions were proposed [9]. We have recently investigated the use of the Mn/TMSCl (chlorotrimethylsilane) system as a possible regenerator of indium [10]. In this report, we describe alternative systems for regenerating active indium species along with the scope and limitations of the Mn/TMSCl system in allylation of various carbonyl compounds.

## 2. Results and discussion

The allylation reaction of benzaldehyde as the model was studied with different additives in the presence of allyl bromide (Table 1).

Manganese in particular conditions is an efficient metal in various reactions [11]. In THF, manganese has to be activated by TMSCl to be reactive but the yield


after 3 h remained low (Table 1, entry 2). Combined with $PbCl_2$ [12] or $GeI_2$ (Table 1, entry 3) the reaction was then effective. Mischmetall is also an efficient reducer [13] and the combination of mischmetall with TMSCl allowed to perform the reaction within 24 h (Table 1, entry 4). Either with manganese or mischmetall in combination with TMSCl, a catalytical amount of indium allowed to accelerate and increase the yield of the reaction (compare entries 2 and 7, entries 4 and 8 in Table 1). Aluminium, which was recently used as the anode in an indium electrochemical process [15], turned out to be less efficient as the reducer in the chemical process using TMSCl (Table 1, entry 9). If an organometallic species is involved in the mechanism, it could be either an indium (III) sesquihalide [16] or an allylindium (I) species [17]. The reactivity of such species could give rise to an indium alkoxide which could undergo a transmetallation to indium alkoxide by trimethylsilyl chloride. The liberating indium trichloride could be reduced by a mild reducer metal, such as manganese or mischmetall. In that hypothesis, indium trichloride should be an alternative catalyst. Surprisingly in that

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Table 1
Barbier allylation reaction of benzaldehyde with allyl bromide

| Entry | Conditions | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | Mn stoich. | 24 | 0 |
| 2 | Mn/TMSCl | 3 | 14 |
| 3 | Mn/TMSCl/10%$GeI_2$ | 8 | 94 |
| 4 | Mischmetal stoich./TMSCl | 24 | 77 |
| 5 | In stoich. | 3 | 32 |
| 6 | In stoich./TMSCl | 3 | 77 |
| 7 | Mn/TMSCl/10%In | 3 | 88 |
| 8 | Mischmetal/TMSCl/10%In | 8 | 77 |
| 9 | Al/TMSCl/10%In | 3 | 41 |
| 10 | Fe/TMSCl/10%In | 24 | 0 |
| 11 | InCl stoich. | 24 | 57 |
| 12 | InCl stoich./TMSCl | 3 | 90 |
| 13 | Mn/TMSCl/10%$InCl_3$ | 28 | 54 |
| 14 | Mn/TMSCl/10%$InBr_3$ | 3 | 61 |
| 15 | Mn/TMSCl/10%$In(OH)_3$ | 28 | 13 |
| 16 | Mn/TMSCl/10%$In_2O_3$ | 3 | 64 |
| 17 | Mn/TMSCl/10%InCl | 22 | 77 |
| 18 | Mn/TMSCl/10%InBr | 3 | 67 |
| 19 | Mn/TMSCl/10%InI | 4 | 47 |
| 20 | TDAE/TMSCl/10%In | 6 | 57 |

All reactions were performed in THF at room temperature except the last one which was performed in DMF at 50 °C.

case, the yield in the homoallylic alcohol decreased (Table 1, entry 13) owing to the formation of benzpinacol as a side-product in these conditions. Indium (III) bromide or indium (III) oxide as catalysts were more efficient (Table 1, entries 14–16).

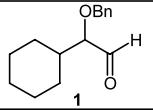
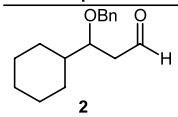
Other indium species, in particular indium (I) species as catalysts were tested with success (Table 1, entries 17–19); we report also the first Barbier reaction with stoichiometric indium (I) chloride alone or with combination of TMSCl (Table 1, entries 11 and 12). In these particular conditions an allylindium (I) species is precluded [18]. Another interesting experiment (Table 1, entry 20) deals with the use of tetrakis dimethylamino ethylene (TDAE) as an organic reducer [20]. The reaction was performed in DMF at 50 °C. Although

Table 2
Indium-catalyzed allylation of carbonyl compounds

| Entry | $R_1$, $R_2$ | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | Ph, H | 3 | 88 |
| 2 | $nC_7H_{15}$, H | 1.5 | 77 |
| 3 | $^t$Bu, H | 16 | 57 |
| 4 | $C_6H_{11}$, H | 4 | 83 |
| 5 | PhCH=CH, H | 4 | 39 |
| 6 | $CH_3CH$=CH, H | 4 | 32 |
| 7 | $-(CH_2)_5-$ | 16 | 91 |
| 8 | $CH_3(CH_2)_3$, H | 6 | 74 |
| 9 | Ph, Ph | 4 | 98 |
| 10 | Ph, $CH_3$ | 6 | 80 |

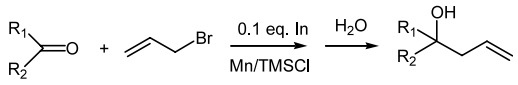
Conditions: 0.1 eq. In, 5 eq. Mn and TMSCl, room temperature, THF.

Table 3
Allylation of α- and β-oxygenated aldehydes

| | In (eq.) | Time (h) | Allylation product syn/anti ratio | yield | Ref. |
|---|---|---|---|---|---|
|  1 | 0.1 | 22 | 33 / 67 | 68 | |
| | | | **3** | | |
| | 1.1 | 12.5 | 25/75 | 81 | 23 |
|  2 | 0.1 | 19 | 32 / 68 | 46 | |
| | | | **4** | | |

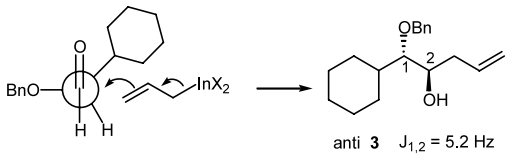
the yield is only moderate, this experiment evidences the regeneration of indium (0) by this powerful reducer.

The more favourable conditions to achieve indium-catalyzed allylation reaction were obtained when a catalytic amount of indium (0.1 equivalent) was used with the Mn/TMSCl system. Even if we cannot exclude the direct involvement of manganese activated by indium in these conditions, the role of manganese could be related to its reducing character allowing the regeneration of an indium reactive species. This regeneration system was applied to the allylation of various aldehydes and ketones (Table 2).



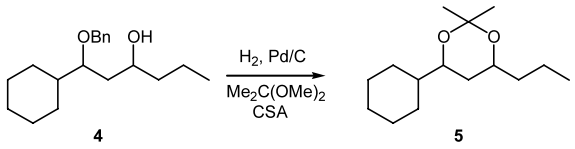

The same conditions were also tested in the allylation of α- and β-oxygenated aldehydes to evaluate the diastereoselectivity of the reaction (Table 3).

Starting from cyclohexanecarboxaldehyde, the known aldehyde **1** [21,22] was prepared according the following sequence: addition of vinylmagnesium bromide [23], benzylation (NaH, $PhCH_2Br$, 82% yield), osmylation (4% $OsO_4$, NMO, 80% yield) and periodate cleavage ($NaIO_4$, 86% yield). The stereochemistry of the allylation product **3**, arising from the α-oxygenated aldehyde **1**, was determined from the data of the literature [22]. The main difference between the *syn* and *anti* products is relative to the chemical shifts and coupling constants of the $H_1$ proton. The $H_1$ proton of the *anti* isomer is more deshielded and appeared as a triplet whereas the $H_1$ proton of the *syn* isomer appeared as a doublet of doublet. The coupling constants $J_{1,2}$ of the *anti* and *syn* isomers have different values, 5.2 and 3.6 Hz respectively. The selectivity of the indium-catalyzed allylation reaction was in favour of the *anti* isomer, arising from a non-chelation controlled transition state as observed in the stoichiometric process [23]. The dominant effect comes from a lowering C–O antibonding orbital bringing about an increased stabilisation of a Felkin-Anh antiperiplanar nucleophilic addition of the organoindium species to the aldehyde carbonyl [24].




anti **3** $J_{1,2}$ = 5.2 Hz

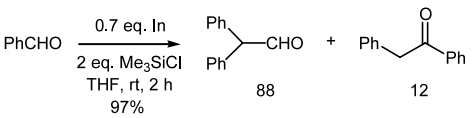
The β-oxygenated aldehyde **2** was also prepared from cyclohexanecarboxaldehyde according a similar sequence: allylation (AllylBr, In/Mn/TMSCl, 83%), benzylation (NaH, $PhCH_2Br$, 87% yield), osmylation (4% $OsO_4$, NMO, 61% yield) and periodate cleavage ($NaIO_4$, 86% yield). To elucidate the stereochemistry of the allylation product **4** we have transformed it into 1,3-diol acetonide **5** by hydrogenation followed by acetalisation and then analyzed the crude mixture according to the method proposed by Rychnovsky et al. [25].




**4** **5**

In this method the exploration of $^{13}C$-NMR spectrum in the region ranging from 19 to 30 ppm gives an evidence of the *syn* or *anti* configuration of the 1,3-diol acetonides. Unfortunately the signals of $^{13}C$ for the cyclohexyl group are also visible in that region. According to the authors, the quaternary C-acetal $^{13}C$ chemical shift is also indicative of the change in conformation, where typical *syn*- and *anti*-acetonides have $^{13}C$ chemical shifts of 98.5 and 100.4 ppm, respectively. Since the spectrum of our sample displayed two signals at 98.15 and 100.11 ppm, we have concluded that the major peak at 100.11 ppm should correspond to the *anti*-acetonide whereas the minor one at 98.15 ppm should correspond to the *syn*-acetonide. Based upon these considerations, we were then able to attribute the $^{1}H$ and $^{13}C$ chemical shifts of the *syn* and *anti* isomers of the allylation compound **4** and to determine the syn:anti ratio (Table 3).

With aromatic aldehydes we have sometimes detected pinacols. This observation prompted us to investigate more precisely the indium-mediated pinacolisation of benzaldehyde. Thus a solution of benzaldehyde and TMSCl (2 molar amounts) dissolved in tetrahydrofuran was added dropwise to indium (0.7 molar amount); the mixture was stirred for 2 h at room temperature and gave 97% of conversion: diphenylacetaldehyde and desoxybenzoin were obtained in the ratio 88/12 as evidenced by gas chromatography.




88 12

It is worthy to note that any attempt to isolate the products led to a loss of material since diphenylacetaldehyde is unstable in the air. Thus a flash chromatography allowing to isolate the coupling compounds of benzaldehyde yielded to only 47% of diphenylacetaldehyde, along with 12% of desoxybenzoin and 20% of benzophenone. We think that diphenylacetaldehyde could be oxidized in the air into a carboxylic acid, then into an α-peroxyacid which underwent a decarboxylation leading to benzophenone. We then discovered that the commercial sample of diphenylacetaldehyde we purchased contained a small amount of benzophenone; this proportion increases rapidly if no precaution is taken. Use of stilbene epoxide as the substrate in the conditions of the reductive coupling (In/TMSCl in THF) led to diphenylacetaldehyde and trans stilbene in a small amount; desoxybenzoin was not detected, which could rule out the epoxide as the main intermediate in the reductive coupling of benzaldehyde in THF. Contrary to the reductive coupling with zinc–copper which involves a transient epoxide [26], the indium coupling is mainly processing via a pinacol-type intermediate, since benzpinacol in the presence of 0.7 molar amount of indium and 2 molar amounts of TMSCl in THF led after 11 min to diphenylacetaldehyde and desoxybenzoin in the 85:15 ratio. This rearrangement is slower in the absence of indium affording 56% of diphenylacetaldehyde and 10% of desoxybenzoin after 7 h; as far as we know, it is the first time such a TMSCl-promoted rearrangement is mentioned [27]. By contrast, when indium is activated under ultrasound conditions in the absence of TMSCl the coupling reaction of benzaldehyde gives benzpinacol in aqueous solvents [29].

## 3. Conclusion

Catalytic amounts of zero, mono or trivalent indium were used in the Barbier allylation of carbonyl compounds to afford the corresponding homoallylic alcohols. Indium was regenerated with a mild reducer, such as manganese, in the presence of an oxophile such as chlorotrimethylsilane in order to cleave the carbon–oxygen bond of the indium alcoolate arising from the nucleophilic attack of an organoindium intermediate upon the carbonyl function.

## 4. Experimental

### 4.1. General reaction conditions

All reactions were carried out under argon using Schlenk techniques. Solvents were distilled prior to use: THF from Na-benzophenone. Preparative flash column chromatographies were carried out using SDS silicagel 60 (6–35 μ); solvent composition are quoted as v/v. $^{1}H$- and $^{13}C$-NMR spectra were recorded on a Brucker

Advance DPX 250 spectrometer (250 MHz for $^1$H and 62.5 MHz for $^{13}$C); chemical shifts were expressed in parts per million downfield from tetramethylsilane.

### 4.2. General procedure for indium-catalyzed allylation of aldehydes and ketones

As a typical experiment, indium (23 mg, 0.2 mmol) and manganese (550 mg, 10 mmol) were placed in a Schlenk tube. The mixture was stirred under vacuum for 30 min. THF (12.5 ml) was then added under argon and the mixture stirred vigorously; allyl bromide (432 μl, 5 mmol), benzaldehyde (203 μl, 2 mmol), TMSCl (1.27 ml, 10 mmol) were successively added under argon. The mixture was allowed to react at room temperature for 3 h under a vigorous stirring; it turned progressively from black to gray and then white. After 3 h, a saturated solution of ammonium chloride (12 ml) was added and the adduct extracted with ethyl acetate. The organic layers were dried, filtered off and then evaporated to afford after silicagel chromatography 1-phenyl-but-3-en-1-ol in 88% yield.

#### 4.2.1. 1-benzyloxy-1-cyclohexylpent-4-en-2-ol (**3**)

$^1$H-NMR ($CDCl_3$, 250 MHz): $\delta$ 1–1.9 (m, 11H, c-Hex), 2–2.4 (m, 3H, O*H* and H-3), 2.95 (dd, 0.33H, *J* 5.7, $J_{1,2}$ 3.6, H-1, *syn*), 3.06 (t, 0.67H, $J_{1,2}$ 5.2, H-1, *anti*), 3.6 (m, 0.33H, H-2, *syn*), 3.66 (ddd, 0.67H, $J_{2,3}$ 8.7, $J_{1,2}$ 5.2, $J_{2,3'}$ 3.9, H-2, *anti*), 4.31 (d, 0.33H, *J* 11.8, PhC$H_2$, *syn*), 4.47 (d, 0.67H, *J* 11.4, PhC$H_2$, *anti*), 4.54–4.55 (2d, 1H, PhC$H_2$, *syn* and *anti*), 4.91–5.06 (m, 2H, H-5 and H-5′), 5.63–5.83 (m, 1H, H-4), 7.1–7.3 (m, 5H).

$^{13}$C-NMR ($CDCl_3$, 62.5 MHz): $\delta$ = 25.7, 25.8, 25.9, 26.0, 26.1, 26.3, 28.4, 28.5, 29.8 (syn), 30.1 (*anti*), 36.8 (*anti*), 39.3 (*syn*), 39.7 (*anti*), 39.9 (*syn*), 70.5 (C-2, *syn*), 70.7 (C-2, *anti*), 74.6 (Ph*C*H2), 85.4 (C-1, *syn*), 86.5 (C-1, *anti*), 116.9 (C-5, *syn*), 117. 5 (C-5, *anti*), 127.3, 127.4, 127.5, 127.7, 128.1, 128.2 (Ph*C*H), 135.0 (C-4, *syn*), 135.3 (C-4, *anti*), 138.3 (Ph*C*, *syn*), 138.7 (Ph*C*, *anti*).

#### 4.2.2. 1-benzyloxy-1-cyclohexylhex-5-en-3-ol (**4**)

$^1$H-NMR ($CDCl_3$, 250 MHz): $\delta$ 1–2.2 (m, 15H, c-Hex, H-2 and H-4), 3.4 (m, 0.68H, H-1, *anti*), 3.6 (m, 0.32H, H-1, *syn*), 3.7 (m, 0.68H, H-3, *anti*), 3.9 (m, 0.32H, H-3, *syn*), 4.4 (m, 2H, PhC$H_2$), 5.0 (m, 2H, H-6 and H-6′), 5.7 (m, 1H, H-5).

$^{13}$C-NMR ($CDCl_3$, 62.5 MHz): $\delta$ 25.9, 26.5, 28.5, 28.9, 29.5, 32.7, 32.9, 38.6, 40.4, 71.2 (Ph$CH_2$, syn), 72.1 (Ph$CH_2$, anti), 79.7, 116.5 (C-6, *syn*), 117.2 (C-6, *anti*), 127.3, 127.7, 128.2 (Ph*C*H), 134.9 (C-5), 138.8 (Ph*C*).

Anal. Calc. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78; O, 11.09. Found: C, 78.23; H, 9.87; O, 10.81%.

#### 4.2.3. 1-cyclohexyl-1,3-O-isopropylidenehexane (**5**)

$^1$H-NMR ($CDCl_3$, 250 MHz): $\delta$ 0.7–2 (m, 26H), 3.2–3.8 (m, 3H, H-1 and H-3).

$^{13}$C-NMR ($CDCl_3$, 62.5 MHz): $\delta$ 14 (C-6), 18.2 (C-5), 18.6 (C-4), 19.8 (Me-acetal, *syn*), 24.3 and 24.6 (2Me-acetal, *anti*), 25.6-38 (c-Hex), 42.6, 42.7, 43.6, 98.1 (C-acetal, *syn*), 100.1 (C-acetal, *anti*).

### 4.3. Homocoupling of benzaldehyde

Indium (804 mg, 7 mmol) was placed in a Schlenk tube. The mixture was stirred under vacuum for 30 min. THF (60 ml), benzaldehyde (1.06 g, 10 mmol) and TMSCl (2.17 g, 20 mmol) were successively added. The mixture was allowed to react at room temperature for 4 h under a vigorous stirring. After adding 20 ml of ethyl acetate and 50 ml of water, the mixture was extracted three times with 20 ml of ethyl acetate. The organic layers were washed with 50 ml of a saturated solution of sodium bicarbonate and dried over magnesium sulphate. After evaporation of the solvents, the residue was chromatographed (cyclohexane–ethyl acetate, 95:5, v/v) to give diphenylacetaldehyde **5** (461 mg, 47%), desoxybenzoin **6** (118 mg, 12%) and benzophenone (182 mg, 20%).

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