

Indium-Mediated Organometallic Reactions in Aqueous Media: The Nature of the Allylindium Intermediate

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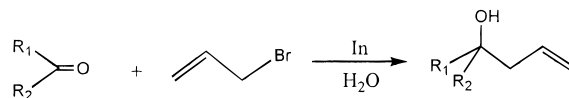
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Indium-mediated organometallic reactions have elicited considerable interest recently,¹ especially with the discovery that many of the indium-mediated reactions can be carried out in aqueous media.² In particular, the reaction of carbonyl compounds with allyl bromide and indium in water³ (Scheme 1) has been examined extensively because of its synthetic advantages⁴ as well as its potential as an environmentally benign chemical process.⁵ The reaction shows good regioselectivity,⁶ diastereoselectivity,^{6,7} and long-range stereoselection through chelation control.⁸ Because the reaction can be carried out in aqueous media, it has been particularly useful in the synthesis of carbohydrates and their analogues without the need for the protection–deprotection protocol common in conventional carbohydrate chemistry.⁹

Despite the extensive interest, little is known about the nature of the allylindium intermediate. Because organoindium compounds are known to be hydrolyzed by water,¹⁰ it has been proposed that the aqueous indium-mediated allylation reaction proceeds on the metal surface⁴ without the involvement of a discrete allylindium intermediate.¹¹ More recently, it is accepted that an allylindium intermediate is involved on the basis of the observation of Whitesides et al.¹² Reaction of allylmagnesium bromide and indium trichloride in ether generated the presumed allylindium dichloride (**1**, X = Cl) which reacted with carbohydrates in ethanol/water (10/1) to give the corresponding homoallylic alcohols. On the other hand, it has been reported that allyl halides reacted with indium in organic solvents to give the structurally not well-defined allylindium sesquihalides (**2**).¹³ Most investiga-

Scheme 1



tors have used the sesquihalide formulation to describe the allylindium intermediate in the indium-mediated allylation reactions in organic solvents.^{1,14} It has not been established whether allyl bromide reacts with indium in water to give the allylindium dibromide (**1**, X = Br) or diallylindium bromide (**3**) or indeed allylindium sesquibromide (**2**, X = Br) which can be considered as an aggregate of **1** and **3**.

We have now found that when allyl bromide reacted with indium in D₂O and the reaction was followed by ¹H NMR, the allylic proton signal of the bromide at 4.0 ppm quickly declined in intensity, and a new signal at 1.7 ppm (d, *J* = 8 Hz) appeared. The new signal reached a maximum in about 20–30 min and then slowly declined in intensity to disappear completely overnight. The mixture was left with unreacted allylic bromide and a new product which was identified as allyl alcohol.¹⁵ We attributed the signal at 1.7 ppm to an allylindium intermediate. When the reaction mixture was quenched with benzaldehyde at a time when the signal at 1.7 ppm was maximal, the product homoallylic alcohol **4** was obtained in 99% yield. These experiments prove that a discrete allylindium intermediate is formed in the reaction of allyl bromide with indium in water. Furthermore, this allylindium species cannot have the sesquibromide structure **2** because that would necessitate the presence of two sets of allylic signals.¹³

We then tried to see if the allylindium intermediate could have either structure **1** or **3**. Reactions of allylmagnesium bromide with indium tribromide in various proportions in ether, followed by efforts to isolate the products in vacuo did not lead to any pure, isolable allylindium compound. Extraction of the presumed allylindium bromides from the reaction mixture (after the removal of most of the ether solvent) into CDCl₃ and examination of the ¹H NMR showed the presence of allylic signals at both δ 1.7 and 2.15 in varying ratios. This led us to question the structural assignment for **2** (X = Br), the allylindium species from the reaction of allyl bromide and indium in DMF. When allyl bromide and indium were reacted at room temperature in DMF for 5 min, and the mixture was examined by ¹H NMR, two sets of allylic signals at δ 1.7 and 2.15 were observed at a ratio of about 1:2, consistent with those reported in the literature.¹³ However, when the mixture was left overnight, the signal at 1.7 was greatly reduced, and the signal at 2.15 was enhanced. Quenching of the reaction mixture after 5 min of reaction into D₂O and examination of the products by ¹H NMR showed the signal at 1.7 ppm only. This suggests that, in the reaction of allyl bromide with indium in DMF, at least two allylindium compounds were formed, one of which is the same as the compound formed in aqueous media.

To elucidate the structure of this allylindium species, we turned to other methods for the preparation of organoindium compounds. It has been reported that organoindium compounds can be

(1) For some recent examples of indium-mediated reactions in organic solvents, see: (a) Araki, S.; Imai, A.; Shimizu, K.; Yamada, M.; Mori, A.; Butsugan, Y. *J. Org. Chem.* **1995**, *60*, 1841. (b) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2318. (c) Ranu, B. C.; Majee, A. *Chem. Commun.* **1997**, 1225. (d) Reetz, M. T.; Haning, H. *J. Organomet. Chem.* **1997**, *541*, 117. (e) For review, see Cintas, P. *Synlett*, **1995**, 1087.

(2) For some recent examples of In-mediated reactions in aqueous media, see: (a) Paquette, L. A.; Rothhaar, R. R.; Issac, M.; Rogers, L. M.; Rogers, R. D. *J. Org. Chem.* **1998**, *63*, 5463. (b) Chan, T. H.; Lu, W. *Tetrahedron Lett.* **1998**, *39*, 8605. (c) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C. J. *J. Org. Chem.* **1998**, *63*, 7472. (d) Loh, T.-P.; Cao, G.-Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1453, 1457. (e) For review, see: Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997.

(3) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7020.

(4) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181.

(5) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P., Williamson, T., Eds.; Oxford University Press: New York, 1998.

(6) (a) Issac, M. B.; Chan, T. H. *Tetrahedron Lett.* **1995**, *36*, 8957. (b) Issac, M. B.; Chan, T. H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003.

(7) Paquette, L.; Mitzel, T. M. *J. Org. Chem.* **1996**, *61*, 8799.

(8) Paquette, L. A.; Lobben, P. C. *J. Org. Chem.* **1998**, *63*, 5604. and references therein.

(9) For examples, see: (a) Chan, T. H.; Lee, M. C. *J. Org. Chem.* **1995**, *60*, 4228. (b) Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 7939. (c) Chan, T. H.; Xin, Y.-C.; von Itzstein, M. *J. Org. Chem.* **1997**, *62*, 3500. (d) Choi, S. K.; Lee, S.; Whiteside, G. M. *J. Org. Chem.* **1996**, *61*, 8739.

(10) Nesmeyanov, A. N.; Sokolik, R. A. *The Organic Compounds of Boron, Aluminum, Gallium, Indium and Thallium*; North-Holland Publishing Company: Amsterdam, 1967.

(11) Recently, allylation of aldehydes with magnesium in water has been observed. Both allylmagnesium intermediate and metal surface reaction have been proposed to account for the formation of products. See: Li, C.-J.; Zhang, W. C. *J. Am. Chem. Soc.* **1998**, *120*, 9102.

(12) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500.

(13) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831. As far as we can determine, the structure **2** (X = I) was assigned solely on the basis of ¹H NMR spectrum (DMF-*d*₇) which showed two sets of allyl signals at δ 1.75 (d, *J* = 8 Hz) and 2.02 (d, *J* = 8 Hz).

(14) (a) Araki, S.; Shimizu, T.; Johar, P. S.; Jin, S.-J.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538. (b) Bossard, F.; Damabrin, V.; Lintanf, V.; Beuchet, P.; Mosset, P. *Tetrahedron Lett.* **1995**, *36*, 6055. (c) Tussa, L.; Lebreton, C.; Mosset, P. *Chem.—Eur. J.* **1997**, *3*, 1064. (d) Lloyd-Jones, G. C.; Russell, T. *Synlett* **1998**, 903. (e) Araki, S.; Nakano, H.; Subburaj, K.; Hirashita, T.; Shibutani, K.; Yamamura, H.; Kawai, M.; Butsugan, Y. *Tetrahedron Lett.* **1998**, *39*, 6327. (f) Capps, S. M.; Lloyd-Jones, G. C.; Murray, M.; Peakman, T. M.; Walsh, K. E. *Tetrahedron Lett.* **1998**, *39*, 2853.

(15) The formation of allyl alcohol can be explained by the hydrolysis of allyl bromide under the Lewis acid influence of indium bromides formed in the reaction. This was verified by independent experiments.

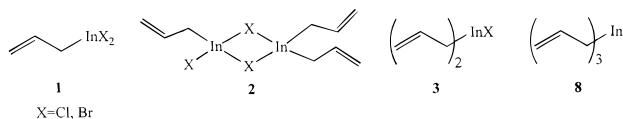
Table 1. Allylation Reactions of Carbonyl Compounds by Transmetalation Reaction in Aqueous Media

Entry	Carbonyl Compound	Reaction Condition ^a	Products	Yield ^b (%)
1		6:5 (1:1)	---	0
2	6	6:5:In (1:1:1)		90
3	6	6:5:In (1:1:0.5)	7	73
4	6	6:5:In (1:0.5:0.5)	7	47
5		10:5 (1:1)	---	0
6	10	10:5:In (1:1:1)		99 (a:b=84:16) ^c
7	10	10:5:InI (1:1:1)	11a + 11b	99 (a:b=84:16) ^c
8	10	10:Allylbromide:In (1:2:2)	11a + 11b	99 (a:b=84:16) ^c

^a All reactions were performed in pure water (3 mL) at rt overnight with carbonyl compound (0.5 mmol) and the other reagents in the indicated quantities. ^b The yields were determined by ¹H NMR. ^c The ratio between 11a and 11b was determined from ¹³C NMR, and their relative configurations were determined from NOE.

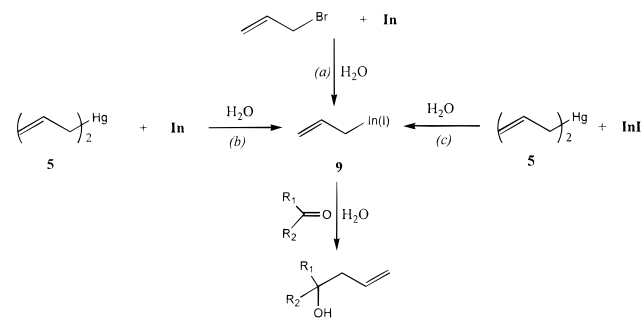
prepared by means of heating organomercury compounds with indium metal through a transmetalation reaction.^{16,17} However, following the procedure of heating a mixture of neat diallylmercury (**5**)¹⁸ with indium metal powder at 110 °C, the reaction gave mainly polymeric materials. Lowering the reaction temperature, or heating the mixture in DMF or other organic solvents did not lead to any change in **5**. On the other hand, mixing **5** with indium powder in D₂O led to release of heat and complete destruction of **5** without characterizable new product remaining in the D₂O solution. We therefore followed the reaction of **5** and indium in a solvent mixture of DMF/D₂O (6/1) at 0 °C by ¹H NMR and found that the allylic signal due to **5** (at 1.9 ppm) slowly declined and a new signal at 1.7 ppm appeared which over time also disappeared.¹⁹ The same transient allylindium species was formed, and since no bromide was involved in the transmetalation reaction, the allylindium species cannot be **1** or **2** or **3**. That the same allylindium species was formed in water was also demonstrated by its reaction with carbonyl compounds. Diallylmercury was unreactive toward acetophenone (**6**) in aqueous media.²⁰ However, addition of indium to a mixture of **5** and **6** in aqueous media gave a quantitative yield of the allylation product **7** (Table 1).

There remains the question of what, if not **1**, **2** or **3**, is the structure of the transient allylindium species in water? Since it is not bromide-containing, possible structures would be triallylindium (**8**) or allylindium(I) (**9**). Efforts to prepare pure **8** or **9** by



reacting excess allylmagnesium bromide with indium trihalides or indium(I) iodide in ether were not successful. Transmetalation using diallylmercury with indium halides was therefore examined. Reaction of **5** with indium(I) iodide in D₂O gave, in 15 min, the allylic signal at 1.7 ppm which slowly disappeared overnight.²¹ On the other hand, reaction of **5** with indium tribromide in D₂O did not give the signal at 1.7 ppm.²² We conclude, therefore, that the transient, ¹H NMR observable allylindium species in aqueous media is allylindium(I) (**9**).^{23,24}

These results are summarized in Scheme 2. Allylindium(I) can be generated in aqueous media via three different pathways from (a) allyl bromide and indium, (b) diallylmercury and indium, and

Scheme 2

(c) diallylmercury and indium(I) iodide. The following experiments further support the conclusion that the same allylindium species is formed from the three different routes. 2-Methylcyclohexanone (**10**) was allylated under the three different conditions to give the addition product alcohols **11**. The ratios of the two diastereomeric alcohols in **11** were the same (84:16 in favor of the trans isomer) in all three cases (Table 1). It has been suggested that the diastereomeric ratio in this reaction is sensitive to the structure of the allylmetal species.^{1d}

The formation of indium(I) instead of indium(III) compound from the reactions of indium metal is consistent with the fact that indium has a relatively low first ionization potential but relatively high second or third ionization potentials.^{3,25} Furthermore, even though we have not ruled out a parallel process involving the metal surface mediated allyl radical anions,¹¹ the indium metal surface is not essential for the aqueous Barbier reaction since the same allylindium(I) can be generated as well by pathway c without the intervention of metallic indium.

Acknowledgment. We thank NSERC for financial support of this research.

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(17) Gilman, H.; Jones, R. G. *J. Am. Chem. Soc.* **1940**, *62*, 2353

(18) (a) Borisov, A. E.; Savel'eva, I. S.; Serdyuk, S. R. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1965**, 896. (b) Ziegler, H. E.; Roberts, J. D. *J. Org. Chem.* **1969**, *34*, 2826. (c) Lochynski, S.; Shine, H. J.; Soraka, M.; Venkatachalam, T. K. *J. Org. Chem.* **1990**, *55*, 2702.

(19) The experiment was performed in the following manner. To a mixture of diallylmercury (140 mg, 1 mmol) and indium powder (114 mg, 1 mmol) was added a solution of dimethylformamide (3 mL) and D₂O (0.5 mL) at 0 °C. The mixture was stirred, and aliquots (0.05 mL) were taken every 5 min and quenched in CDCl₃. The CDCl₃ solution was examined by ¹H NMR.

(20) Although diallylmercury is unreactive towards ketones, it reacts with aldehydes in aqueous media to give the corresponding homoallylic alcohols. Chan, T. H.; Yang, Y., manuscript to be published.

(21) Only signals attributed to allylindium(I) (**9**) were observed. The formation of allylmercury iodide was not observed, presumably because of further reaction with InI to give **9** and HgI₂.

(22) Diallylmercury did react with indium tribromide in D₂O to give an allylmetal compound with an allylic signal at 2.8 ppm. We are in the process of deducing its structure. However, if an allylindium species were generated under such conditions, we demonstrated that it was not able to allylate acetophenone and therefore it cannot be the reactive allylindium intermediate responsible for the allylation reaction.

(23) While lower oxidation state inorganic compounds of indium are well-known, there are only a few examples of organoindium(I) compounds. They are all derivatives of cyclopentadienylindium. The parent compound was reported to be extremely sensitive to atmospheric oxygen but is stable to water. Fischer, E. O.; Hofmann, H. P. *Angew Chem.* **1957**, *69*, 639.

(24) The ¹H NMR of allylindium(I) in D₂O at room temperature is more compatible with a σ -bonded allylindium structure than a π -bonded structure or rapidly equilibrating allylic isomers.

(25) In organic solvents, further reaction of In(I) compounds with allyl halide can lead to In(III) species. See: Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291. This paper reported the formation of allylindium diiodide from allyl iodide and indium(I) iodide in THF and that the allylic signal of allylindium diiodide was at about 2.1 ppm in THF-*d*₆. One can suggest that the reaction of allyl bromide and indium in DMF gives, instead of the previously suggested sesquibromide **2** (X = Br), a mixture of allylindium(I) (**9**) and allylindium dibromide (I, X = Br). Similarly, allylmagnesium bromide reacts with indium trihalide to give **1** and **9**. The formation of **9** is due to the reduction of **1** by the Grignard reagent or decomposition as observed in the formation of cyclopentadienylindium(I) from the reaction of cyclopentadienylsodium and indium trichloride.²²