*J. Am. Chem. Soc.* **2000,** *122,* 402−403

# Organic Reactions in Aqueous Media. Cyclopentadienylindium(I) as the First Example of Organoindium(I) Reagent for Carbon−Carbon Bond Formation and the Demonstration of One-Pot Tandem Addition/Intramolecular Diels−Alder Reaction in Aqueous Media

Yang Yang and Tak Hang Chan*

*Department of Chemistry, McGill University*
*Montreal, Quebec, Canada H3A 2K6*

*Received July 26, 1999*

Because of the concern for the environment and the search for synthetic efficiency, organic reactions in aqueous media have attracted considerable recent interest in organic synthesis.[1] A seminal observation was the fact that Diels−Alder reactions,[2] and subsequently many pericyclic reactions,[3] proceed faster in water than in organic solvents. The discovery of water-stable lanthanide Lewis acids which can serve as catalysts for the Diels−Alder reactions in aqueous media further enhances the potential usefulness of these reactions.[4] In parallel, organometallic reactions in aqueous media have been developed and their application in organic synthesis has been increasingly recognized.[5] In this connection, indium chemistry has captured much recent attention[6] largely due to the discovery that indium can mediate the smooth coupling of allylic halides with aldehydes to give the corresponding homoallylic alcohols in aqueous media.[7] The reaction has been applied extensively to the synthesis of carbohydrates[8] and other natural products.[9] Despite such interest, the nature of the allylindium intermediate was not well characterized.[10] Recently, we established through indirect evidence that the allylindium intermediate in indium-mediated Barbier-type allylation reaction is allylindium(I).[11] This conclusion is somewhat unexpected since much of the current organoindium chemistry[12] has been focused on the many known indium(III) compounds.[13] In contrast, there are few examples of organoindium(I) compounds which are all derivatives of cyclopentadienylindium(I) (**1**).[14] We are therefore interested in examining the possibility of using **1** as organometallic reagent in aqueous media and its synthetic potential.

Cyclopentadienylindium(I) (**1**) was first synthesized by Fischer and Hofmann in 1957.[15] Its synthesis, structural characterization, and derivatives have been well studied by many researchers.[16] There were however hardly any reference to its application as an organometallic reagent in organic synthesis, especially in aqueous media.[17] Herein we report that addition reaction of aldehydes (**2**) can be realized by using cyclopentadienylindium(I) as nucleophilic reagent in aqueous media according to Scheme 1.[18,19] The expected products **3** however rearranged via the well-established 1,5-hydrogen shift to give the isomeric compounds **4** and **5** as a mixture (usually in a ratio of 1:1 as determined from $^1$H and $^{13}$C NMR).[20] The structures of the alkylated cyclopentadienes **4** and **5** can be further confirmed by reacting the resultant aqueous reaction mixture with dimethyl acetylenedicarboxylate (**6**) at room temperature in the presence of ytterbium triflate.[4] The two alkylated cyclopentadienes **4** and **5** were "captured" as the corresponding Diels−Alder adducts (**7** and **8**) which can be separated and fully characterized.

It can be seen from Table 1 that the yields of the addition of aldehydes with **1** ranged from moderate to good (entries 1−6). The reaction can be performed in organic solvent with similar yield. In the aqueous media, the main byproduct observed was from the hydrolysis of cyclopentadienylindium(I). Apparently, there was a competition between the addition reaction and hydrolysis in aqueous media. Consequently, when more reactive aldehydes were employed, higher yields of the adducts were obtained (entries 3 and 4). With the less reactive ketone, no

---

(1) For review, see: (a) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. (b) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic & Professional: Glasgow, 1998.

(2) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.

(3) See for examples: (a) Gajewski, J. J.; Brichford, N. L. *J. Am. Chem. Soc.* **1994**, *116*, 3165. (b) Lubineau, A.; Bouchain, G.; Queneau, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2433.

(4) For Dies−Alder reaction in aqueous media catalyzed by lanthanide triflates, see: Kobayashi, S. *Synlett* **1994**, 689 and references therein.

(5) See for examples: (a) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181.(b) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023

(6) For review, see: (a) Cintas, P. *Synlett* **1995**, 1087. (b) Li, C. J. *Tetrahedron*, **1996**, *52*, 5643. (c) Chan, T. H.; Isaac, M. B. *Pure Appl. Chem.* **1996**, *68*, 919. (d) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P., Williamson, T., Eds.; Oxford University Press: New York, 1998.

(7) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017.

(8) (a) Chan, T. H.; Lee, M. C. *J. Org. Chem.* **1995**, *60*, 4228. (b) Schmid, W.; Whitesides, M. *J. Am. Chem. Soc.* **1991**, *113*, 6674. (c) Chan, T. H.; Xin, Y. C.; von Itzstein, M. *J. Org. Chem.* **1997**, *62*, 3500.

(9) For some recent examples of indium-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.

(10) Most investigators have used the sesquihalide formulation to describe the allylindium intermediate in the indium-mediated allylation reactions in organic solvents, see: (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.

(11) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228.

(12) For recents examples see: (a) Hirashita, T.; Kamei, T.; Horie, T.; Yamamura, H.; Kawai, M.; Arake, S. *J. Org. Chem.* **1999**, *64*, 172. (b) Araki, S.; Nakano, H.; Subburaj, K.; Hirashita, T.; Shibutani, K.; Yamamura, H.; Kawai, M.; Butsugan, Y. *Tetrahedron Lett.* **1999** *39*, 6327. (c) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4095.

(13) (a) Nesmeyanov, A. N.; Sokolik, R. A. *The Organic Compounds of Boron, Aluminum, Gallium, Indium and Thallium*; North-Holland Publishing Company; Amsterdam, 1967. (b) Tuck, D. G. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1987; Vol. 1. (c) Tuck, D. G. *Pure. Appl. Chem.* **1983**, *55*, 1477. (d) Tuck, D. G. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Sone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 1.

(14) For the review of lower valent indium chemistry see: Tuck, D. G. *Chem. Soc. Rev.* **1993**, *22*, 269.

(15) Fischer, E. O.; Hoffmann, H. P. *Angew Chem.* **1957**, 69, 639.

(16) (a) Peppe, C.; Tuck, D. G.; Victoriano, L. *J. Chem. Soc., Dalton* **1981**, 2592. (b) Beachley, O. T., Jr.; Churchill, M. R.; Fettinger, J. C.; Pazik, J. C.; Victoriano, L. *J. Am. Chem. Soc.* **1986**, *108*, 4666. (c) Schumann, H.; Haniak, C.; Gorlitz, F.; Loebel, J. *J Organomet. Chem.* **1989**, *363*, 243. (d) Beachley, O. T., Jr.; Pazik, J. C.; Glassman, T. E.; Chruchill, M. R.; Fettinger, J. C.; Blom, R. *Organometallics* **1988**, *7*, 1051.

(17) As far as we can determine, the only reported reaction of **1** is its Diels−Alder reaction with maleic anhydride. It is quite possible that the reaction is actually not due to **1** but due to cyclopentadiene released from **1**. See: Contreras, J. G.; Tuck, D. G. *Inorg. Chem.* **1973**, *12*, 2596.

(18) The detailed reaction procedure is as follow: aldehyde (0.5 mmol) was dissovled in a mixture of 3 mL of THF and $H_2O$ (4:1) with stirring at 0 °C. Freshly made cyclopentadienylindium(I) (1.0 mmol) was added and the mixture was stirred at 0 °C for 4 h under the protection of argon. The reaction mixture was extracted directly with diethyl ether (3 × 15 mL) and washed with saturated sodium bicarbonate aqueous solution. After evaporation of the solvent, the purified products were obtained from flash chromatography on silica gel using a mixture of hexane and ethyl acetate (10:1) as eluent.

(19) The reaction is to be distinguished from the reaction of cyclopentadiene itself with aldehydes in aqueous basic conditions which gave the corresponding fulvenes. See: (a) Little, W. F.; Koestler, R. C. *J. Org. Chem.* **1961**, *26*, 3247 (b) Ziegler, K.; Gellet, H. G.; Martin, H.; Schnider, J. *Justus Liebigs Ann. Chem.* **1954**, *589*, 91.

(20) About hydrogen migration in substituted cyclopentadienes see: (a) McLean, S.; Haynes, P *Tetrahedron* **1965**, *21*, 2329. (b) McLean, S.; Haynes, P *Tetrahedron* **1965**, *21*, 2343.

10.1021/ja9928778 CCC: $19.00

## Scheme 1

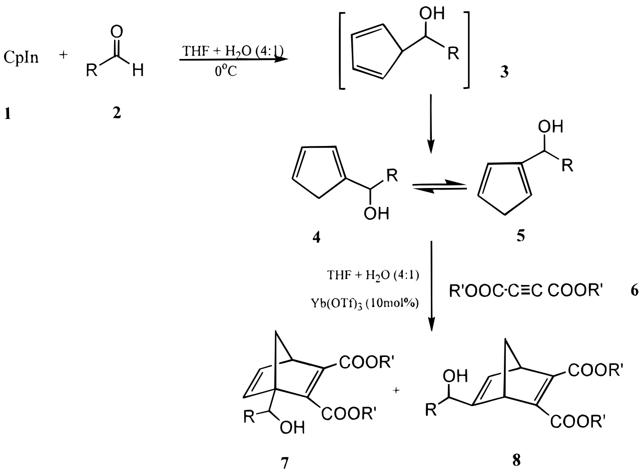
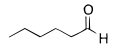
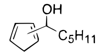
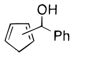
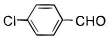
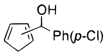
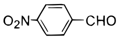
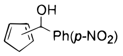
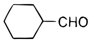
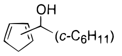
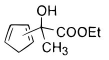
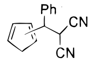
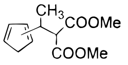


**Table 1.** Addition Reaction of Aldehydes and Electron-Deficient Alkenes with Cyclopentadienyindium(I) in Aqueous Media[18]

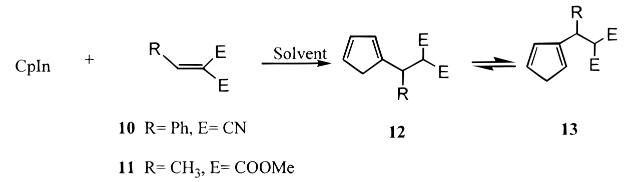
| Entry | Substrates | Product | Yield[a] (%) |
|---|---|---|---|
| 1 |  |  | 51 (55)[b] |
| 2 | PhCHO |  | 60 (46)[c] |
| 3 |  |  | 66 (48)[c] |
| 4 |  |  | 76 |
| 5 |  |  | 51 |
| 6 | $CH_3COCOOEt$ |  | 59 |
| 7 | Ph(Me)C=O | - | 0 |
| 8 | $PhCH=C(CN)_2$ |  | 61[e] (67)[d] |
| 9 | $CH_3CH=C(COOMe)_2$ |  | 21[e] (64)[d] |

[a] Isolated yields. [b] The reaction was performed in THF at 0 °C. [c] The reaction was performed in water alone at room temperation. [d] The reaction was performed in $CH_2Cl_2$ at room temperature. [e] The reaction was performed in THF + $H_2O$ (1:1) at room temperature.

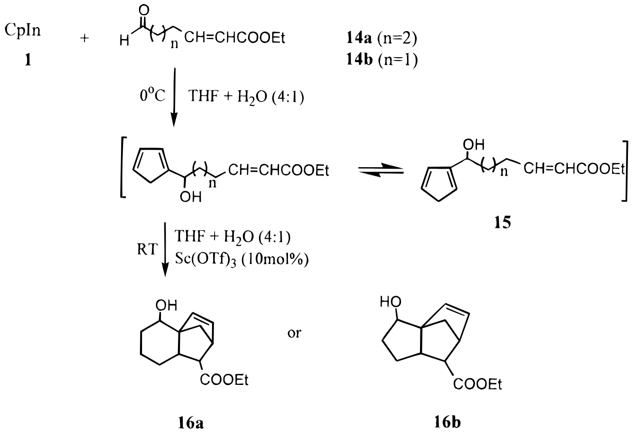
addtion product was obtained (entry 7). On the other hand, when the ketone function was activated, additon reaction can also occur and the corresponding cyclopentadienyl derivative can be formed (entry 6). It should be noted that the nitro function was not reduced under the reaction conditions[21] and additon at the aldehyde function occurred uneventfully (entry 4). The facile reaction of cyclopentadienylindium(I) with aldehydes is to be contrasted with the lack of reaction of tris-cyclopentadienylindium(III) (**9**)[22] with aldehydes under the same reaction conditions.[23]

With electron-deficient alkenes (**10** and **11**), compound **1** underwent additon in the Michael fashion to give the adducts, again as a mixture of 1- and 2-substituted cyclopentadienes (**12** and **13**) (entries 8 and 9)[24] (Scheme 2).

## Scheme 2



## Scheme 3



Alkylated cyclopentadienes have been widely used as synthons in organic synthesis. The intramolecular Diels–Alder reaction of these compounds represents an important strategy in the total synthesis of natural products which contain two or more fused carbocycles.[25] The facile reaction of **1** with aldehydes provides a novel way to prepare such precursors and we demonstrated further that intramolecular Diels–Alder reaction can also be realized in aqueous media in the presence of a catalytic amount of scandium triflate.[4] By using 7-oxo-2-heptenoic acid ethyl ester (**14a**) as the aldehyde, the substituted cyclopentadiene **15a** can be readily obtained. Compound **15a** underwent intramolecular Diels–Alder reaction to give the fused tricyclic compound **16a** in good yield (77%).[26] Moreover, since the intramolecular Diels–Alder reaction can be performed in similar aqueous conditions, the two reactions can be realized in tandem in a *one-pot* process without purification of the intermediate alkylated cyclopentadiene **15a** (Scheme 3). Similarly, by starting with 6-oxo-2-hexenoic acid ethyl ester (**14b**), the tricyclic compound **16b** can be obtained in a one-pot process in 54% overall yield.

In summary, cyclopentadienylindium(I) has been demonstrated to be an effective organometallic reagent that can react with aldehydes or electron-deficient alkenes in aqueous media to give highly functionalized substituted cyclopentadienes. This reaction with the appropriate substrates can be followed by an intramolecular Diels–Alder reaction in the same pot to provide complex tricyclic structures in a synthetically efficient manner.[27]

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

**Supporting Information Available:** Experimental details and characterization of compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA9928778

---

[21] Chan, T. H.; Yang, Y.; Li, C. J. *J. Org. Chem.* **1999**, *64*, 4452.

[22] Prepared and characterized according to literature procedures. See: Poland, J. S.; Tuck, D. G *J. Organomet. Chem.* **1972,** *42*, 307.

[23] Unreacted aldehydes were recovered from the reaction mixture. The tris-cyclopentadienylindium(III) could not be recovered, presumably due to its facile hydrolysis under the reaction conditions.

[24] Wang, L.; Sun, X.; Zhang, Y *Synth. Commun.* **1998**, *28*, 3263.

[25] For review see: Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671.

[26] For some examples, see: (a) Berube, G.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 4045. (b) Nystrom, J.-E.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 4695. (c) Corey, E. J.; Munroe, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 6129.

[27] Trost, B. M. *Science* **1991**, *254*, 1471.