Design and Synthesis of a Water-Tolerant Chiral Indium Complex: Application to One-Pot Three-Component Mannich-Type Reactions in Water

Jian Xiao, Teck-Peng Loh*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 639798, Singapore
Fax +65(6316)6984; E-mail: teckpeng@ntu.edu.sg

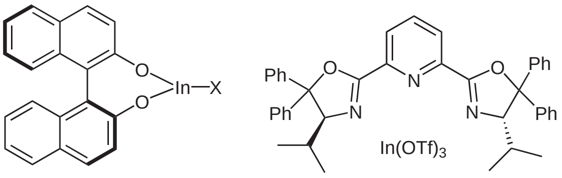
Received 14 December 2006

Abstract: A novel chiral indium(III) camphorsulfonate complex prepared from indium trichloride, allyltributylstannane and (1*S*)-(+)-10-camphorsulfonic acid has been developed as a water-tolerant Lewis acid to afford high yields (up to 99%) in one-pot three-component Mannich-type reactions in a true water environment.

Key words: chiral indium complex, one-pot three-component Mannich-type reaction, allyltributylstannane

In recent years, organic reactions in aqueous media have attracted a great deal of attention.[1] This is because water is a cheap, safe and environmentally benign solvent. Furthermore, reactions carried out in aqueous media provide opportunity to discover new concepts in organic synthesis. In the course of our investigations to develop efficient organic reactions in water, we have discovered that indium complexes are water-tolerant Lewis acids which can be used to catalyze a wide variety of organic transformations in aqueous media.[2]

Recently, two new chiral indium complexes, 1,1′-bi-2-naphthol (BINOL)–In(III) **1a**–**c** and 2,6-bis[4′(*S*)-isopropyloxazolin-2′-yl]pyridine (PYBOX)–In(III) complexes **2** (Figure 1) have been discovered in our group to effect a series of reactions in high enantioselectivities.[3]



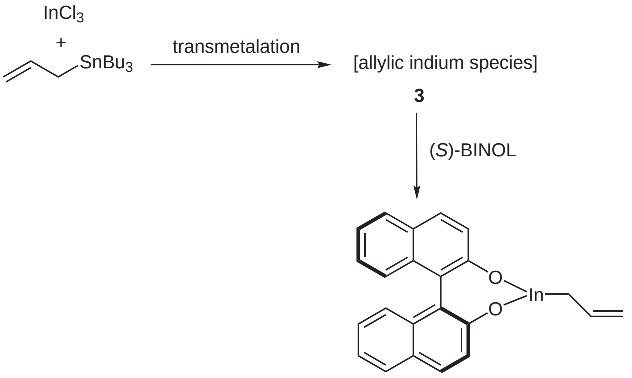
X = Cl (**a**), Br (**b**), allyl (**c**)
BINOL–In(III) complex **1a**–**c**

PYBOX–In(III) complex **2**

Figure 1

However, the extension of these catalytic systems to aqueous media was not successful.[4] Accordingly, the design of new water-tolerant chiral indium complex poses additional challenges. Therefore, in this paper we report our effort towards the development of a new water-tolerant indium complex which can catalyze organic transformations in aqueous media.

Previous studies on the synthesis of chiral BINOL–In(III) complex revealed that allylic indium species could be obtained from transmetalation of indium trichloride with allyltributylstannane. This indium species facilitate the formation of the BINOL–In(III) complex **1c**[3a] (Scheme 1).



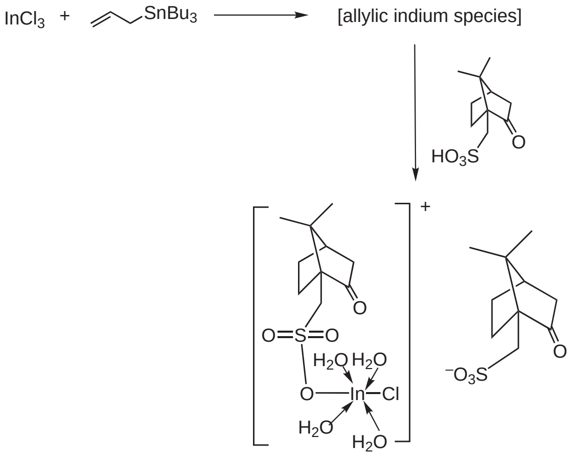
Scheme 1 Synthesis of BINOL–In(III) complex **1c**

Based on this result, we envisaged that the resulting indium species **3** can also react with more acidic (1*S*)-(+)-10-camphorsulfonic acid to produce a more reactive water-tolerant chiral indium complex. Herein, we report the synthesis of this chiral water-tolerant In(III)–camphorsulfonate complex obtained from transmetalation of allylic stannane with indium trihalides. Preliminary studies were directed towards the application of this catalyst for the one-pot three-component Mannich-type reaction in water.

Therefore, the reaction of one equivalent of indium trichloride with two equivalents of allyltributylstannane to generate allylic indium species **3**, followed by the addition of (1*S*)-(+)-10-camphorsulfonic acid produced a new chiral indium complex **4** (Scheme 2). The structure of this indium complex was confirmed by X-ray crystal structure analysis (Figure 2).[5]

To check the catalytic activity of this new indium complex **4** in water, the three-component reaction of benzaldehyde (0.5 mmol), aniline (0.5 mmol) and l-methoxy-2-methyl-l-trimethylsiloxypropene (1 mmol) was examined.[6] To our delight, this indium complex afforded the Mannich product in good yield even when 5 mol% of the catalyst was used (when the catalyst loading was 20%, 10%, 5%, and 1%, the yield was 69%, 69%, 69%, and

SYNLETT 2007, No. 5, pp 0815–0817
Advanced online publication: 08.03.2007
DOI: 10.1055/s-2007-970774; Art ID: D38706ST



Scheme 2 Synthesis of indium complex **4**

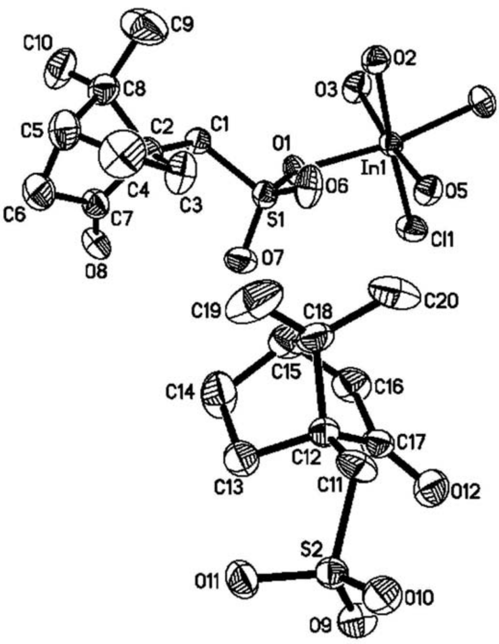
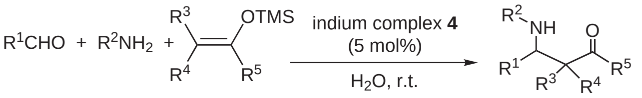


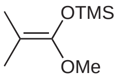
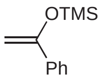
Figure 2 X-ray crystal structure of indium complex **4**

24%, respectively). With these optimized conditions, the reactions were carried out using different aldehydes, amines and the results are shown in Table 1.[7]

In all cases, the reactions proceeded smoothly in water to afford the desired products in moderate to good yields. Furthermore, this new indium complex **4** showed higher catalytic activity as compared with the reactions carried out using 20 mol% of indium trichloride (yields are shown in parenthesis).[8] Unfortunately, we did not observe any enantioselectivity with this chiral indium complex. An important observation made from these experiments was that no deamination or other side reactions commonly associated with Mannich-type reactions were observed. When 10 mol% of the indium complex was employed in the reaction conditions described in entry 1 of Table 1, the catalyst could be recycled at least five times without a significant loss in catalytic activity (1st cycle: 69%, 2nd cycle: 69%, 3rd cycle: 60%, 4th cycle: 50%, 5th cycle: 50%).[9]

Table 1 Three-Component Mannich-Type Reactions Catalyzed by Indium Complex **4** in Water[a]



Entry	Aldehyde (R^1)	Amine (R^2)	Silyl ether	Yield (%)[b]
1	Ph	Ph	 OTMS OMe	69 (54)
2	Ph	4-ClC_6H_4		71 (23)
3	Ph	4-$MeOC_6H_4$		60 (30)
4	2-Py	Ph		99 (92)
5	2-Py	4-ClC_6H_4		99 (90)
6	2-Py	4-$MeOC_6H_4$		99[c] (90)
7	H	Ph		46 (30)
8	H	4-ClC_6H_4		28 (21)
9	H	4-$MeOC_6H_4$		40 (35)
10	H	Ph	 OTMS Ph	99 (91)
11	H	4-ClC_6H_4		99 (85)
12	Ph	4-ClC_6H_4		71 (60)
13	2-Py	4-$MeOC_6H_4$		99 (90)

[a] Reaction conditions: aldehyde (1.0 equiv), amine (1.2 equiv), ketene silyl ether (2 equiv) in H_2O (5 mL) and 5% indium complex **4** stirred for 1 d.

[b] Purified yield after column chromatography and the yield in parenthesis refers to the same reaction carried out using 20 mol% of indium trichloride in water.

[c] Yield for the mixture with tertiary Mannich product.

Thus the specificity of the reaction pathway, the high product yields, the ease and convenience of the experimental procedure, in addition to the many advantages of using water as a solvent for the reaction, make this methodology a very attractive synthetic route for β-aminocarbonyl compounds.

In summary, we have designed and synthesized a novel chiral indium complex and found that it is an excellent water-tolerant Lewis acid and could efficiently catalyze the one-pot three-component Mannich-type reactions in water using 5 mol% catalyst loading. Although control of chirality was not possible in these aqueous reactions, this study provides useful information on designing new water-tolerant chiral indium catalyst. The success of this design will open a new area of producing chiral water-tolerant Lewis acid catalysts. Further studies to apply this novel indium complex to other reactions in water as well as designing other water-stable chiral indium complexes are in progress.

Acknowledgment

We wish to thank the Nanyang Technological University and BMRC for their generous financial support.

References and Notes

(1) (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, **1997**. (b) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blacky Academic and Professional: London, England, **1998**.

(2) Loh, T.-P.; Chua, G.-L. *Chem. Commun.* **2006**, 2739.

(3) (a) Teo, Y.-C.; Tan, K.-T.; Loh, T.-P. *Chem. Commun.* **2005**, 1318. (b) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743. (c) Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539. (d) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (e) Lu, J.; Hong, M.-L.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, 1010. (f) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 7435.

(4) Teo, Y.-C.; Goh, E.-L.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 6209.

(5) Crystal Data: $C_{21}H_{39}C_4InO_{12}S_2$, M = 804.26, colorless prism. Crystal dimensions: 0.20 × 0.15 × 0.04 mm, monoclinic, space group $P2(1)$, a = 6.9145(2) Å, b = 15.3916(6) Å, c = 15.5826 (6) Å, V = 1657.02(10) Å^3, Z = 2, D_c = 1.612 Mg/m^3. Reflections collected: 34477; independent reflections: 7580 (R_{int} = 0.0432), final $R[I > 2\sigma(I)]$ = 0.0428, R (all data) = 0.0535, R_w = 0.1327. Crystallographic data for this crystal has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 624125. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road Cambridge CB2, 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

(6) Reactions with aliphatic aldehydes or aliphatic amines afforded the products in low yields.

(7) **Typical Reaction Procedure**: Anhydrous benzaldehyde (0.05 mL, 0.5 mmol) and indium complex **4** (20 mg, 0.025 mmol) were mixed and stirred at r.t. in H_2O (5 mL) for 10 min before the addition of anhyd aniline (0.06 mL, 0.6 mmol). The resulting mixture was stirred at r.t. for 30 min. 1-Methoxy-1-trimethylsilyloxypropene (0.2 mL, 1 mmol) was then added. The suspension was stirred at r.t. for 1 d and then extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with brine (5 mL), dried over anhyd $MgSO_4$, and concentrated under reduced pressure. The product was obtained in 69% yield after silica gel column chromatography as a yellowish wet solid; R_f 0.61 (hexane–EtOAc, 4:1). ^{1}H NMR ($CDCl_3$): δ = 7.23–7.31 (m, 5 H), 7.03–7.10 (m, 2 H), 6.50–6.65 (m, 3 H), 4.53 (s, 1 H), 3.67 (s, 3 H), 1.30 (s, 3 H), 1.20 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ = 176.97, 146.86, 139.17, 128.95, 128.21, 127.93, 127.38, 117.22, 113.34, 64.30, 52.01, 46.95, 24.48, 20.65. FTIR (thin film): 1715.8 cm^{-1}. HRMS: m/z calcd for $C_{18}H_{21}NO_2$: 283.1572; found: 283.1568.

(8) (a) Loh, T.-P.; Liung, S. B. K. W.; Tan, K.-L.; Wei, L.-L. *Tetrahedron* **2000**, *56*, 3227. (b) Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.* **1998**, *39*, 323.

(9) The drop in reactivity by the fourth or fifth cycle may be attributed to loss of catalyst due to organic extraction.