Enantioselective synthesis of homoallylic alcohols *via* a chiral In(III)–PYBOX complex†

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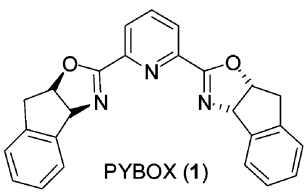
In the presence of 20 mol% of a chiral catalytic complex prepared from $In(OTf)_3$ and chiral PYBOX, allyltributylstannane reacted with aldehydes to afford the corresponding homoallylic alcohols in moderate to high enantioselectivities (60–93% ee).

Catalytic enantioselective synthesis is a valuable method for the preparation of optically active compounds.[1] In connection, the enantioselective allylation of carbonyl functionality to furnish homoallylic alcohols has become one of the most useful tools in modern organic synthesis;[2] thanks to the chiral homoallylic alcohols which are very useful intermediates enjoying a wide application in chemical synthesis.[3] Although significant results have been obtained by using a stoichiometric amount of allylmetal compounds bearing chiral ligands, such as allyl boranes and boronates, allyl boradiazolidines, allyl titanates, allyl and aluminium derivatives,[4] there are only a few methods available for the catalytic enantioselective allylation of aldehydes based on the use of chiral Lewis acids as the source of stereoselectivity.[5]

In recent years, indium complexes have attracted great attention among the synthetic community. This is because indium complexes have been found to catalyze a wide variety of organic transformations under very mild reaction conditions including carrying out reactions in aqueous media.[6] Accordingly, much effort has been directed towards the development of an efficient chiral indium complex for asymmetric transformations but with little success.[7] This aim continues to pose a challenge to synthetic chemists.[8]

In this paper, we report the enantioselective allylation reaction of aldehydes catalyzed by a new chiral indium(III)–PYBOX complex, which was prepared from indium triflate and chiral PYBOX (**1**).



PYBOX (**1**)

During the process of optimizing the reaction conditions using benzaldehyde as a starting material, we were gratified to find that the reaction proceeded smoothly to afford the homoallylic alcohol with the best result (87% ee, Table 1, entry 1) in dichloromethane at −60 °C in the presence of powdered activated 4 Å molecular sieves.

The standard protocol is as follows. To an oven dried round-bottom flask was added $In(OTf)_3$ (0.2 equiv.) and powdered activated 4 Å molecular sieves. The solid was azeotropically dried with anhydrous tetrahydrofuran twice prior to the addition of dichloromethane. Chiral PYBOX (**1**) (0.22 equiv.) was added and the mixture was stirred under nitrogen at room temperature for 2 hours to afford a white suspension. A mixture of aldehyde (**2**) (1 equiv.) and TMSCl (1.2 equiv.) in dichloromethane was added to the resulting suspension and stirred for 10 minutes. The mixture was then cooled to −60 °C followed by the addition of allyltributylstannane (1.2 equiv.). After stirring at −60 °C for 30 hours, the homoallylic alcohol (**3**) was then obtained by aqueous workup and column chromatography.

The optimized reaction conditions found for the allylation of benzaldehyde were applied to other aldehydes. The results are summarised in Table 1.

As shown in Table 1, in all cases, the homoallylic alcohols were obtained in good yields and high enantioselectivities (up to 93% ee) not only with aromatic aldehydes but also with α,β-unsaturated and aliphatic aldehydes. In the reaction with α,β-unsaturated aldehydes, the 1,2-addition reaction proceeded exclusively. It should be emphasized that chiral PYBOX (**1**) could be recovered easily from the reaction mixture in almost quantitative yield after the usual workup, and could be reused in this enantioselective allylation reaction without loss of enantioselectivity.

Meanwhile, it is noteworthy that the chiral steroidal aldehyde (**4**) could be allylated to give (**5**) with excellent enantioselectivity ($22S : 22R = 100 : 0$) and in good yield in the presence of a catalytic amount of the indium(III)–PYBOX (**1**) complex (Scheme 1). Furthermore, the reaction was highly chemoselective, reacting only with the aldehyde functionality. No reaction was observed with the enone functionality in the ring labelled A.

In conclusion, the chiral indium(III)–PYBOX complex prepared from indium triflate and C_2-symmetric chiral PYBOX (**1**) was found to be an effective chiral ligand for the enantioselective allylation reaction of aldehydes with allyltributylstannane giving high enantioselectivity. In some cases, the corresponding allylation products were obtained in >90% ee. These results open a novel way to design and synthesize new chiral ligands for enantioselective reactions.[9]

The main features of our new reaction are as follows: (1) the procedure is operationally simple and can furnish a wide variety of homoallylic alcohols in good yields with high levels of enantioselectivities; (2) the allylation can be performed exclusively by using commercially available chemicals; (3) the chiral ligand can be

† Electronic supplementary information (ESI) available: spectroscopic and analytical data for all compounds and the representative procedure. See http://www.rsc.org/suppdata/cc/b4/b415550e/

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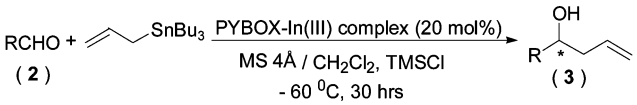
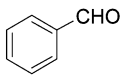
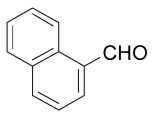
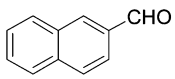
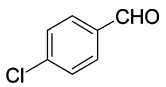
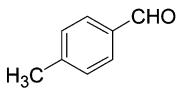
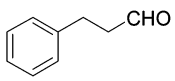
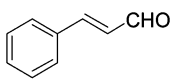
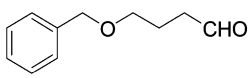
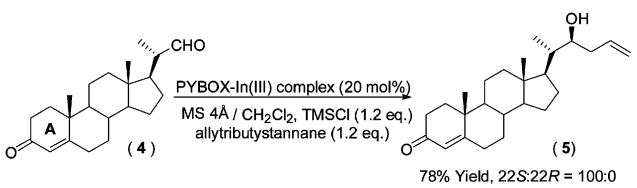
Table 1 $In(OTf)_3$–PYBOX (**1**) catalyzed allylation of aldehyde[a]



Entry	RCHO	Yield (%)[b]	Ee (%)[c]
1		65	87
2		83	90
3		72	85
4		47	93
5		96	83
6		77	60
7		62	67
8		72	63

[a] All reactions were carried out with aldehyde (1 equiv.), TMSCl (1.2 equiv.) and allyltributylstannane (1.2 equiv.) using $In(OTf)_3$ (0.2 equiv.) and PYBOX (**1**) (0.22 equiv.) in the presence of activated 4 Å MS in anhydrous CH_2Cl_2. The reaction mixture was kept for 30 h at −60 °C. [b] Isolated yield. [c] Ee determined by HPLC. For further details see ESI.

recovered in high yield thus making this method attractive for the scale-up preparation of homoallylic alcohols with high enantioselectivities. Further work on redesigning high affinity chiral PYBOX applicable to the allylation reaction as well as for other organic transformations is in progress.



Scheme 1 Application to the steroid side-chain synthesis.

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Notes and references

1 (*a*) N. Jacobsen, A. Pfaltz and H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Springer-Verlag, Berlin, 1999; (*b*) I. Ojima, *Catalytic Asymmetric Synthesis*, VCH Publishers, Cambridge, 1993; (*c*) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, 1994.

2 (*a*) S. C. Denmark and J.-P. Fu, *Chem. Rev.*, 2003, **103**, 2752; for some examples see: (*b*) G. E. Keck, K. H. Tarbet and L. S. Geraci, *J. Am. Chem. Soc.*, 1993, **115**, 8467; (*c*) A. L. Cosata, M. G. Piazza, E. Tagliavini, C. Trombini and A. U. Ronchi, *J. Am. Chem. Soc.*, 1993, **115**, 7001; (*d*) A. Yanagisawa, H. Nakashima, A. Ishiba and H. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 4723; (*e*) A. Yanagisawa, A. Ishiba, H. Nakashima and H. Yamamoto, *Synlett*, 1996, 88; (*f*) A. Yanagisawa, H. Nakashima, Y. Nakatsuka, A. Ishiba and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 1129; (*g*) H. Hanawa, T. Hashimoto and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 1708; (*h*) P. G. Cozzi, P. Orioli, E. Tagliavini and A. Umani-Ronchi, *Tetrahedron Lett.*, 1997, **38**, 145.

3 (*a*) K. C. Nicolaou, D. W. Kim and R. Baati, *Angew. Chem., Int. Ed.*, 2002, **41**, 3701; (*b*) K. R. Hornberger, C. L. Hamblet and J. L. Leighton, *J. Am. Chem. Soc.*, 2000, **122**, 12894; (*c*) F. X. Felpin and J. Lebreton, *J. Org. Chem.*, 2002, **67**, 9192; (*d*) Y. Yamamoto, *Acc. Chem. Res.*, 1987, **20**, 243.

4 (*a*) H. C. Brown and K. J. Parabhakar, *J. Am. Chem. Soc.*, 1983, **105**, 2092; (*b*) W. R. Roush, L. K. Hoong and M. A. Palmer, *J. Org. Chem.*, 1990, **55**, 4109; (*c*) E. J. Corey, Y. Chan-Mo and S. K. Sung, *J. Am. Chem. Soc.*, 1989, **111**, 5496; (*d*) M. Riediker and R. O. Duthaler, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 494; (*e*) A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit and F. Schwarzenbach, *J. Am. Chem. Soc.*, 1992, **114**, 2321.

5 (*a*) K. Ishibara, M. Mouri, Q. Gao, T. Maruyama, K. Furuta and H. Yamamoto, *J. Am. Chem. Soc.*, 1993, **115**, 11490; (*b*) J. A. Marshall and Y. Tang, *Synlett*, 1992, 653; (*c*) A. L. Costa, M. G. Piazza, E. Tagliavini, C. Trombini and A. Umani-Ronchi, *J. Am. Chem. Soc.*, 1993, **115**, 7001; (*d*) A. Yanagisawa, H. Nakashima, A. Ishiba and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 1129; (*e*) S. E. Demark and T. Wynn, *J. Am. Chem. Soc.*, 2001, **123**, 6199.

6 (*a*) K. K. Chauhan and C. G. Frost, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3015; (*b*) G. Babu and P. T. Perumal, *Aldrichimica Acta*, 2000, **33**, 16; for recent examples see: (*c*) T. Mukaiyama, T. Ohno, T. Nishimura, J. S. Han and S. Kobayashi, *Chem. Lett.*, 1990, 2239; (*d*) B. M. Trost, S. Sharma and T. Schmidt, *J. Am. Chem. Soc.*, 1992, **114**, 7903; (*e*) T.-P. Loh, J. Pei and G.-Q. Cao, *Chem. Commun.*, 1996, 1819; (*f*) T.-P. Loh, J. Pei and M. Lin, *Chem. Commun.*, 1996, 2315; (*g*) T.-P. Loh, G.-L. Chua, J. J. Vittal and M.-W. Wong, *Chem. Commun.*, 1998, 861; (*h*) T.-P. Loh and L.-L. Wei, *Tetrahedron Lett.*, 1998, **39**, 323; (*i*) T.-P. Loh, J.-M. Huang, S.-H. Goh and J. J. Vittal, *Org. Lett.*, 2000, **2**, 1291; (*j*) J. Yang and C.-J. Li, *Synlett*, 1999, 717; (*k*) G.-S. Viswanathan, J. Yang and C.-J. Li, *Org. Lett.*, 1999, **1**, 993; (*l*) B. C. Ranu and U. Jana, *J. Org. Chem.*, 1998, **63**, 8212; (*m*) B. C. Ranu, A. Hajra and U. Jana, *J. Org. Chem.*, 2000, **65**, 6270; (*n*) T. Ali, K. K. Chauhan and C. G. Frost, *Tetrahedron Lett.*, 1999, **40**, 5621; (*o*) K. K. Chauhan, C. G. Frost, I. Love and D. Waite, *Synlett*, 1999, 1743; (*p*) T. Tsuchimoto, T. Maeda, E. Shirakawa and Y. Kawakami, *Chem. Commun.*, 2000, 1573; (*q*) S. Gadhwal and J. S. Sandhu, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2827; (*r*) T.-P. Loh, Q.-Y. Hu and L.-T. Ma, *J. Am. Chem. Soc.*, 2001, **123**, 2450; (*s*) C.-J. Zhu, F. Yuan, W.-J. Gu and Y. Pan, *Chem. Commun.*, 2003, 692; (*t*) T.-P. Loh, in *Science of Synthesis*, ed. H. Yamamoto, Georg Thieme Verlag Stuttgart, New York, 2004, p. 413.

7 For reviews see: (*a*) C.-J. Li and T.-H. Chan, *Tetrahedron*, 1999, **55**, 11149; (*b*) C.-J. Li and T.-H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997; for recent examples see: (*c*) T.-P. Loh and J.-R. Zhou, *Tetrahedron Lett.*, 1999, **40**, 9115; (*d*) T.-P. Loh and X.-R. Li, *Tetrahedron*, 1999, **55**, 5611; (*e*) T.-P. Loh and X.-R. Li, *Eur. J. Org. Chem.*, 1999, 1893; (*f*) T.-P. Loh and J.-R. Zhou, *Tetrahedron Lett.*, 2000, **41**, 5261; (*g*) T.-H. Chan and Y. Yang, *J. Am. Chem. Soc*, 1999, **121**, 3228; (*h*) K.-T. Tan, S.-S. Chng, H.-S. Cheng and T.-P. Loh, *J. Am. Chem. Soc*, 2003, **125**, 2958; (*i*) M. Eda, H. Miyabe, A. Nishimura, O. Miyata, Y. Takemoto and T. Naito, *Org. Lett.*, 2003, **5**, 3835.

8 C.-J. Zhu, F. Yuan, W.-J. Gu and Y. Pan, *Chem. Commun.*, 2003, 692; G. Zhong, *Chem. Commun.*, 2004, 606.

9 Although we can speculate that In^{2+} may be involved in the transition, the exact transition state assembly of this reaction requires a more detailed investigation.

