Enantioselective allylation of ketones catalyzed by chiral In(III)-PYBOX complexes†

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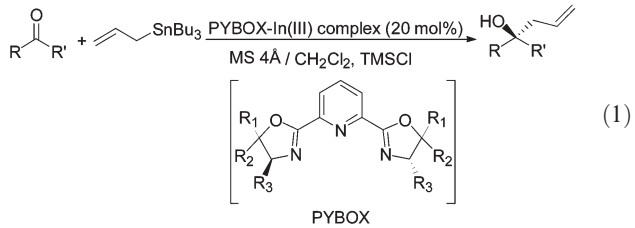
In the presence of 20 mol% of chiral catalytic complex prepared from $In(OTf)_3$ and chiral PYBOX, allyltributylstannane reacted with achiral ketones to afford the corresponding homoallylic alcohols in moderate to high enantioselectivities (54–95% ee), which constitutes the first example of enantioselective allylation of ketones catalyzed by the chiral In(III)-PYBOX complex.

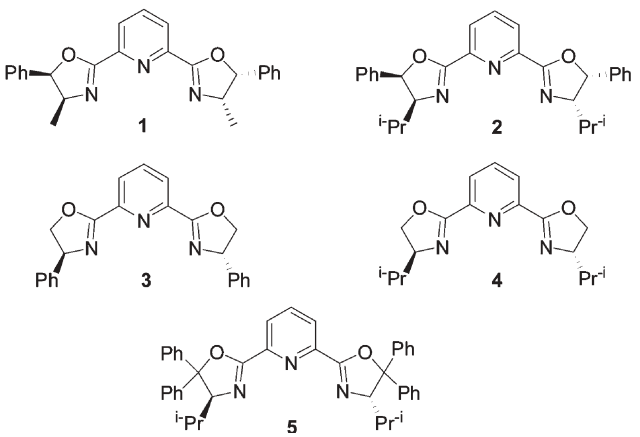
Enantioselective allylation of carbonyl compounds is one of the most useful tools in synthetic organic chemistry, due in part to the fact that chiral homoallylic alcohols are very useful intermediates for the enantioselective synthesis of complex chiral substances.[1] The potential of this synthetic tool has been enhanced by newly developed enantioselective versions, especially chiral Lewis acid-catalyzed addition of the allyl transfer reagent to the carbonyl functionality. It has been demonstrated that many catalysts promote the enantioselective allylation of aldehydes to give secondary homoallylic alcohols with excellent enantioselectivities.[2] However, very few enantioselective allylation of ketones have been successful[3] owing to the significant differences in reactivity between aldehydes and ketones. To compensate for the reduced reactivity of ketones, a more reactive allylating agent is needed.

In recent years, indium(III) complexes have gained widespread applications as efficient Lewis acids for various carbon–carbon bond forming reactions and other synthetic transformations.[4] Based on our previous work on the asymmetric allylation of aldehydes,[5] we have developed the first catalytic asymmetric allylation of ketones using allyltributylstannane as an allylating reactant based on catalytic amounts of chiral In(III)-PYBOX complex (eqn. (1)).



(1)

In the development of this methodology, we had screened several variants of the PYBOX ligand using the following standard protocol. To an oven dried 5 mL round-bottom flask equipped with a magnetic stirring bar was added $In(OTf)_3$ (0.2 equiv.) and 4 Å molecular sieve (120 mg). The solids were azeotropically dried with anhydrous tetrahydrofuran twice (2 mL × 2) prior to the addition of 1 mL of dichloromethane. Chiral PYBOX (0.22 equiv.) was added and the mixture was stirred under nitrogen at room temperature for 2 h to afford a white suspension. A mixture of ketone **6** (0.15 mmol, 1 equiv.) and TMSCl (1.2 equiv.) in dichloromethane (0.2 mL) was added to the resulting suspension and stirred for 10 min. The mixture was then cooled to 0 °C for 15 min followed by the addition of allyltributylstannane (1.2 equiv.). The reaction mixture was stirred at 0 °C for 70 h, and was subsequently treated with 2 mL saturated sodium bicarbonate solution at room temperature for 30 min. The product was extracted with dichloromethane, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified *via* silica gel chromatography to afford the homoallylic alcohol **7**. The results for chiral PYBOX **1–5** are summarized in Table 1.



The best result was obtained from the use of the chiral tetraphenyl substituted (*S*)-*i*-PrPYBOX 5 with 80% yield and 62% ee (Table 1, entry 5).

Under the optimal conditions described above, other ketones were examined, and the results are collected in Table 2. The reactions of ketones with allyltributylstannane gave the corresponding chiral homoallylic alcohols with moderate to good yields (40–90%) and moderate to high enantioselectivities (up to 95% ee, Table 2, entry 6). Attention is drawn to entries 1 and 2 in which practically no attenuation of catalytic efficiency and enantioselectivity was observed by reusing the recovered chiral ligand.

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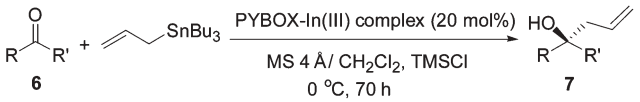
† Electronic supplementary information (ESI) available: Spectroscopic and analytical data for all compounds and the representative procedure. See http://dx.doi.org/10.1039/b507768k

Table 1 Evaluation of various chiral indium(III) complexes for the asymmetric allylation reaction

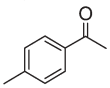
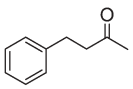
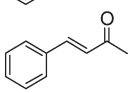
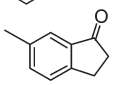


Entry	PYBOX	Ketone	Yield (%)[a]	ee (%)[b]
1	**1**	$PhCOCH_3$	20	20
2	**2**	$PhCOCH_3$	10	26
3	**3**	$PhCOCH_3$	30	27
4	**4**	$PhCOCH_3$	34	31
5	**5**	$PhCOCH_3$	80	62

[a] Isolated yield. [b] ee determined by HPLC.

The conjugated enone undergoes exclusively 1,2-addition in good yield and with fair enantiomeric excess (Table 2, entry 5), the saturated derivative reacted to give the homoallylic alcohol with nearly the same enantiomeric excess (Table 2, entry 4). Excellent results were obtained when cyclic ketones were used as starting materials (Table 2, entries 6, 7, 8). During the study, we found the role of TMSCl was crucial for the reaction, the absence of which will result in a dramatic decrease in enantioselectivity and yield of product. It is worthy to note that the catalytic allylation of ketones for our chiral indium complex can be accomplished simply by using allyltributyl stannane unlike other catalytic systems that require stronger allylating reagents such as tetraallylstannanes.

Table 2 Enantioselective allylation of ketones catalyzed by $In(OTf)_3$-PYBOX **5** complex[a]

Entry	Ketone	Yield (%)[b]	ee (%)[c]
1		80[d]	62 *R*
2		79	63[e] *R*
3		85	67 *R*
4		80	55 *S*
5		71	54 *R*
6		90	95 *R*
7		40	90 *R*
8		68	84 *R*

[a] All the reactions were carried out with ketone (1 equiv.), TMSCl (1.2 equiv.) and allyltributylstannane (1.2 equiv.) using $In(OTf)_3$ (0.2 equiv.) and (*S*)-*i*-PrPYBOX **5** (0.22 equiv.) in the presence of activated MS 4 Å in anhydrous CH_2Cl_2. The reaction mixture was kept for 70 h at 0 °C. [b] Isolated yield. [c] ee determined by HPLC, the absolute configuration of products was assigned by comparison with optical rotation and/or retention time on chiral HPLC in ref. 6. For further details see supporting information. [d] 85% of chiral ligand was recovered. [e] Recovered (*S*)-*i*-PrPYBOX **5** was used for the reaction.

In summary, we have developed a novel and practical enantioselective catalytic system for the allylation of ketones that provides tertiary homoallylic alcohols with moderate to high enantiomeric excess using a catalytic amount of chiral In(III)-PYBOX complex. In some cases, the corresponding allylation products could be obtained in $\geqslant$90% *ee*. Further efforts are being directed toward exploring the utility of this novel approach and the mechanism of the chiral indium–PYBOX complex catalysed allylation reaction.†

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