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Catalytic Enantioselective Allylation of Ketones via a Chiral Indium(III) Complex

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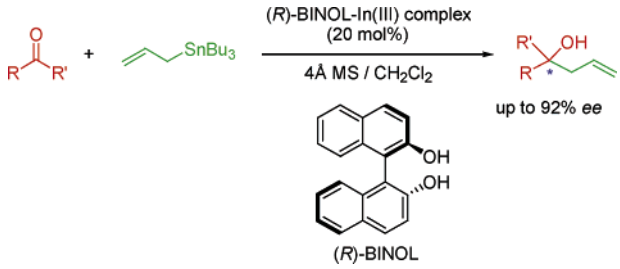
ABSTRACT



A chiral indium complex has been discovered to effect high enantioselectivities in the addition of allyltributylstannanes to ketones. The allylation of a variety of aromatic, α,β-unsaturated and aliphatic ketones resulted in good yields and high enantioselectivities (up to 92% ee).

The utilization of indium(III) complexes as efficient Lewis acid catalysts for organic synthesis,[1] particularly to the ends of forming C−C bond(s), has been well established. However, efforts to develop an efficient chiral indium Lewis acid for enantioselective organic transformations has been achieved with limited success. Therefore, developing new chiral indium complexes continues to pose a challenge to synthetic chemists.

The enantioselective allylation of carbonyl functionality to furnish homoallylic alcohols has acquired a major role due to the versatility of the products, which are important building blocks for the synthesis of many natural products and pharmaceuticals.[2] The development of asymmetric catalytic processes for obtaining secondary homoallylic alcohols from aldehydes and allyltrialkylstannanes[3] or allyltrialkylsilanes[4] greatly enhances the potential of this synthetic tool. However, the catalytic asymmetric allylation of ketones to generate enantiopure tertiary homoallylic

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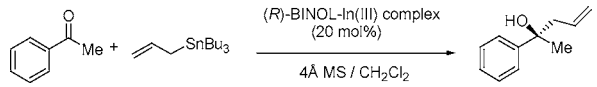
alcohols has proven to be a more challenging transformation owing to the significant difference in reactivity between aldehydes and ketones. As is anticipated by the lesser reactivity of ketones toward nucleophilic addition, the number of methods for enantioselective construction of tertiary alcohols by this approach is very limited.[5] Moreover, to the best of our knowledge, these methods require the strong allylating reagent, tetraallylstannane, in the process and possess limited substrate scope in some cases. In this paper, we report the first efficient asymmetric allylation of ketones using the less reactive allyltributylstannane as the allylating reagent catalyzed by a chiral (*R*)-BINOL−In(III) complex.

Recently, we have reported a practical catalytic asymmetric allylation of aldehydes with allyltributylstannanes in the presence of an indium(III) catalyst as a chiral Lewis acid which has proven to be efficient and especially convenient.[6] The chiral indium(III) catalyst was prepared by simply mixing (*R*)-BINOL with $InCl_3$ in CH_2Cl_2 at room temperature for 2 h. However, the reaction of acetophenone with allyltributylstannane using the optimum conditions previously described for the corresponding allylstannane reaction afforded the homoallylic alcohol in low yield and good enantiomeric excess (Table 1, entry 1). This result prompted us to utilize a stronger indium-based lewis acid in an attempt to increase both the chemical yield and enantioselectivity of the allylation reaction. The results from our efforts to optimize the reaction are shown in Table 1. The reaction carried out using 3 equiv of allyltributylstannanes leads to an increase in conversion with retention of enantiomeric excess (entry 2). To compensate for the reduced reactivity of ketones, we attempted to use $InBr_3$ as the indium reagent for the catalyst preparation due to its higher Lewis acidity. The reaction proceeded at ambient temperature, and the homoallylic alcohol was isolated in 76% yield and 82% enantioselective excess (entry 4). It is noteworthy that the chiral ligand, (*R*)-BINOL, can be easily recovered by silica gel chromatography in almost quantitative yield (94%).

Having optimized the reaction parameters for the allylation process, we extended the catalytic enantioselective addition of allyltributylstannane to a selection of ketones. The results are shown in Table 2.

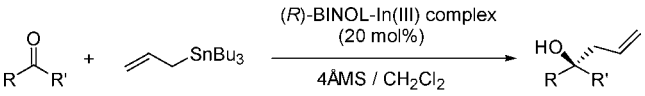
Table 1. Enantioselective Allylation of Acetophenone Catalyzed by Chiral (*R*)-BINOL−In(III) Complex[a]

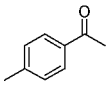
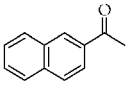
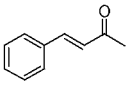
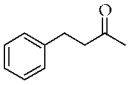
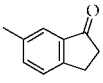


entry	indium reagent	allyl stannane (equiv)	*T* (°C)	yield[b] (%)	ee[c] (%)
1	$InCl_3$	2.0	−78 to rt	25	81
2	$InCl_3$	3.0	−78 to rt	46	81
3	$InCl_3$	3.0	rt	54	81
4	$InBr_3$[d]	3.0	rt	76	82

[a] Unless otherwise specified, the reaction was carried out using the chiral indium(III) catalyst prepared from (*R*)-BINOL (22 mol %) and $InCl_3$ (20 mol %) in the presence of 15 mg of powdered activated 4 Å molecular sieves in 1.0 mL of CH_2Cl_2. The reaction mixture was kept for 4 h at −78 °C and then 72 h at rt. [b] Isolated yield. [c] Please refer to the Supporting Information for enantiomeric excess determination. [d] The reaction was stirred at rt for 72 h.

Table 2. Enantioselective Allylations of Various Ketones Catalyzed by Chiral (*R*)-BINOL−In(III) Complex[a]



entry	ketone	yield (%)[b]	ee (%)[c]
1		74	82
2		41	84
3		80	84
4		82	90
5		60	80
6		61	90
7		50	92

[a] Unless otherwise specified, the reaction was carried out with allyltributyl stannane (1.5 mmol) and ketone (0.5 mmol) using the chiral indium(III) catalyst prepared from (*R*)-BINOL (22 mol %) and $InBr_3$ (20 mol %) in the presence of 15 mg of powdered activated 4 Å molecular sieves in 1.0 mL of CH_2Cl_2. The reaction mixture was stirred at rt for 72 h. [b] Isolated yield. [c] Please refer to the Supporting Information for enantiomeric excess determination.

In all cases, the homoallylic alcohols were obtained in good enantioselectivities (up to 92% ee) not only with aromatic ketones but also with aliphatic and cyclic aromatic ketones. The allylation reaction of acetophenone and 4-meth-

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ylacetophenone under the influence of the chiral indium catalyst furnished the homoallylic alcohols with 82% and 84% ee, respectively (Table 2, entries 1 and 2). Moreover, 2′-acetonaphthone also underwent the allylation reaction affording the product in 80% yield and 84% ee.

Allylation of a representative conjugated enone gave exclusively a 1,2-allylation product in good yield with high enantioselectivity (entry 4). Interestingly, while *trans*-4-phenyl-3-buten-2-one underwent allylation with 90% ee, the saturated derivative reacted to give the homoallylic alcohol with 80% ee (entry 5).

The ketones, 1-indanone and 6-methyl-1-indanone, both underwent the allylation reaction to afford the homoallylic alcohols in 90% and 92% ee, respectively, though the yield of the latter was only moderate (entries 6 and 7).

The absolute configuration of the tertiary homoallylic alcohol (Table 1, entry 1) was determined by comparison of the sign of the optical rotation with the literature value.[5d,7] The *re* face of the ketone is attacked when the (*R*)-catalyst is used, in agreement with the persistent preference shown by BINOL-based catalysts. The stereochemical course of the allylation process catalyzed by the chiral (*R*)-BINOL−In (III) complex can be envisaged in terms of the catalyst−ketone pre-transition state assembly depicted in Figure 1. In Figure

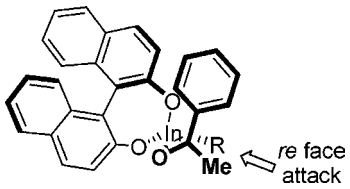

Figure 1. Proposed BINOL−In(III)−aldehyde pre-transition state.

1, the aromatic rings of the (*R*)-BINOL effectively screen the *si* face of the complexed ketone from attack by allyltributylstannanes. As such, this facilitated the addition of the allyl moiety to the *re* face of the ketone leading to the enantiomers shown in Tables 1 and 2.

It is worthy to note that the catalytic allylation of ketones for this chiral indium complex can be accomplished simply by using allyltributylstannane unlike most other asymmetric catalytic systems which require stronger allylation reagents such as tetraallylstannanes. In fact, as far as we know, this is the first example of catalytic enantioselective allylation of ketones using allyltributylstannanes as the allylation reagent.

In conclusion, we have demonstrated the first highly catalytic enantioselective allylation of ketones using a chiral indium(III) complex prepared from (*R*)-BINOL and $InBr_3$. The main features of this 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 enantioselectivites; (2) the allylation can be performed simply by using allyltributylstanannes and commercially available chemicals; (3) the chiral ligand can be recovered in high yield, thus making this method attractive for scale-up preparation of homoallylic alcohols with high enantioselectivities; Continuing investigations in this laboratory will attempt to elucidate the identity of the chiral BINOL−In(III) species and further expand the scope of the process.

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Supporting Information Available: Experimental details, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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