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The first example of catalytic asymmetric allylation of aldehydes in a tin(II) mediated Barbier reaction †

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Abstract: Catalytic asymmetric allylation of achiral aldehydes promoted by chiral titanates has been examined. Modest enantiomeric excess of the homoallylic alcohol was observed in a Barbier protocol involving Sn(II)–Group 16 complexes. © 1997 Elsevier Science Ltd

Control of stereoselectivity in the addition reactions of performed allyl stannanes[1] and allyl silanes[2] to aldehydes has been intensely studied by various groups in the past decade. The accrued knowledge has led to the development of stoichiometric,[3] and more recently catalytic[4] asymmetric allylation (CAA) protocols from preformed allyl-organometallics. Inspite of many variants of Barbier type allylation reactions in the literature,[5] a CAA protocol has yet to be developed. In view of our continuing interest in the organic reactivity of allyl-tin complexes,[6] we wished to attempt the title reaction in order to obviate the need to pre-synthesizing allyl-organometallic reagents vis-a-vis widening the scope of classical Barbier reaction.

The key issues considered by us in building a CAA strategy under the Barbier frame-work are: (a) facile generation of allyltin reagent in-situ from readily available and cheap starting materials, (b) decreased Lewis acidity at the tin(IV) centre to inhibit aldehyde co-ordination, (c) utilization of a chiral Lewis acid catalyst to promote aldehyde co-ordination and hence asymmetric induction. In-situ generation of allyl stannanes can be achieved by a variety of reagent combinations;[7] starting either from Sn or Sn^{II} and allyl halide, alcohol, acetate, mesylate etc. After preliminary exploration with respect to reaction times and product yield we chose Sn(II)cat.CuCl/allyl bromide/aldehyde combination for our reaction. In order to reduce the Lewis acidity at the tin centre, we have synthesised various complexes[8] of Sn(II) with Group-16 donor ligands (Figure 1, **1**–**5**). Finally, chiral Ti(IV) catalysts were selected by us bearing in mind their high Lewis acidity and proved record in asymmetric allylation with preformed allyl stannanes. Initial results from the reaction of **5** demonstrating successful delineation of our strategy is presented herein.

In a typical experiment, (R)-(+)-1,1′-bi (2-naphthol) (0.2 mM) and $Ti(O^iPr)_4$ (0.2 mM) in dichloromethane (1 ml) was stirred under nitrogen for 1 h at room temperature, after which 3-phenylpropanaldehyde (2 mM) was added and stirring was continued for further 10 mins to obtain a dark orange solution (solution A). In a separate two-necked round bottom flask; **5**[10] (2 mM), CuCl (0.2 mM) and allyl bromide (3 mM) in dry tetrahydrofuran (5 ml) were stirred under nitrogen for 1 h after which solution A was introduced via cannula and the resulting mixture was stirred for 3 h

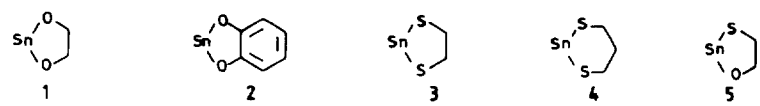

Figure 1.

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Table 1. Enantioselective allylation of aldehydes with allyl bromide and reagent **5** promoted by chiral titanium-binol complex[a]

Entry	Aldehyde	Isolated[b] yield %	$[\alpha]_D$ (c, solvent)	e.e.%[c] (configuration)
1.	3-Phenylpropanal	49	$[\alpha]_D^{25}$ + 13.3 (1.0, $CHCl_3$)	63.4 (R)
2.		52[d]	$[\alpha]_D^{25}$ - 13.1 (1.2, $CHCl_3$)	62.5 (S)
3.	4-Chlorobenzaldehyde	46	$[\alpha]_D^{23}$ + 5.9 (2.0, PhH)	17.6 (R)
4.	4-Methoxybenzaldehyde	49	$[\alpha]_D^{25}$ + 17.4 (1.5, PhH)	21.2 (R)
5.	3-Phenyl-2-propenal	42	$[\alpha]_D^{21}$ - 7.6 (3.5, Et_2O)	52.0 (R)
6.	Benzaldehyde	51	$[\alpha]_D^{21}$ + 14.8 (4.0, PhH)	31.2 (R)

a) Unless otherwise stated, reactions were carried out with Ti-(R)-(+)-1,1′-bi(2-naphthol) complex. b) All compounds were fully characterised by ^1H NMR (200 MHz), EIMS (70ev) and by comparison with authentic samples. c) The enantiomeric exess and absolute configurations were determined by a comparison with the values reported in literature[9]. d) Reaction was performed with Ti-(S)-(-)-1,1′-bi(2-naphthol) complex.

at 0°C and then at ambient temperature for 50 h. After solvent removal the mixture was subjected to column chromatography over silica-gel (60–120 mesh) using hexane–acetone (24:1) as eluent to afford (R)-(+)-6-phenyl-1-hexene-3-ol in 42% isolated yield and 63.4% enantiomeric purity (Table 1, entry 1). In an independent experiment, reaction of allyl bromide with 3-phenylpropanaldehyde in the presence of Ti–S(−)binol complex afforded the corresponding S-(−) alcohol in 62.5% ee. (Table 1, entry 2). Similar reactions of allyl bromide with various aldehydes provided corresponding alcohols in 17.6–52.0% ee (Table 1, entry 3–6).

Control experiments further reveal that, in the absence of CuCl, the reactions are extremely slow,[11] the product yield being <10% after 50 h. Furthermore, solvents play a crucial role in facilitating the reaction in terms of both chemical and optical yield of the alcohol. In these respects THF is found to be better when compared to DCM, DMF and MeCN. Influence of the tin reagent was tested by us in the reaction of benzaldehyde with allyl bromide (Table 2). It is noteworthy that reagents **1** and **2** afford comparatively better yields of the homoallylic alcohols, but the asymmetric yields are very poor. On the other hand reagent **4** offers better enantioselectivity, however, the product yield is extremely low. In this regard, reagent **5** is the best candidate to date. These results suggest that both reactivity and enantioselectivity are crucially dependent on the donor atom bound to tin. Further work is warranted in this direction. We have also iniated preliminary studies in evaluating the influence of chiral ligands (Table 3). Tartrate derivatives **6** and **7**; are known chelators to titanium;[12] however they exist in equilibrium between free ligand and ligand-bound complex. Chiral tertiary amino alcohols **8** and **9** are proven anchors in asymmetric alkylation.[13] In our hand **6–9** found to be ineffective in promoting CAA as compared to binol. Moreover, use of preformed Ti-binol catalyst in Ti:binol ratio of 1:2 did not improve the %ee over the catalyst in Ti:binol ratio of 1:1.

In summary, the present work clearly demonstrated the asymmetric induction can be achieved in a Barbier protocol. Mechanism based investigations might unfurl the reasons for moderate enantioselectivity in our protocol. Further work is underway in this direction and in utilizing the methodology towards the synthesis of chiral ipsdienol, ipsenol, lavandulol and artemisia alcohol.

Acknowledgements

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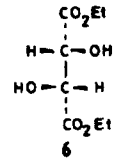
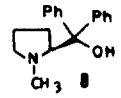
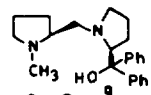
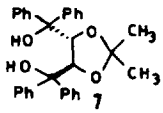
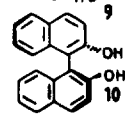
Table 2. Enantioselective allylation of benzaldehyde with allyl bromide promoted by chiral titanium–R(+) binol complex: influence of tin reagent

Tin reagent	Isolated yield %	e.e. %	Tin reagent	Isolated yield %	e.e. %
$SnCl_2$	76	1.1 (R)	**3**	18	5.6 (R)
1	38	5.5 (R)	**4**	8	20.1 (R)
2	48	5.2 (R)	**5**	51	31.2 (R)

Table 3. Enantioselective allylation of benzaldehyde with allyl bromide, reagent **5** and chiral titanium complexes: influence of chiral ligands

Ligand	Isolated Yield %	e.e. %	Ligand	Isolated Yield %	e.e. %
 **6**	32	11.0 (S)	 **8**	28	2.3 (S)
			 **9**	25	1.8 (S)
 **7**	36	3.5 (S)	 **10**	52	29.6 (S)

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10. Synthesis of reagent **5**: Triethylamine (23.3 ml, 0.16 mol) was added to a stirred solution of anhydrous $SnCl_2$ (15.12g, 0.08 mol) in methanol (250 ml). After 30 minutes, 2-mercaptoethanol (6.25 g, 0.08 mol) was added and stirring was continued for another 2 h. The light yellow product was filtered, washed with methanol, diethyl ether and finally air-dried for 24 h. The yield was almost quantitative. Under normal circumstances the compound retains activity for one month.
11. Similar observation was earlier made: See ref.[7a]
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