Bifunctional molecular accelerator for catalytic asymmetric allylation: R_2MSR' (M = B, Al) as a useful synergetic reagent

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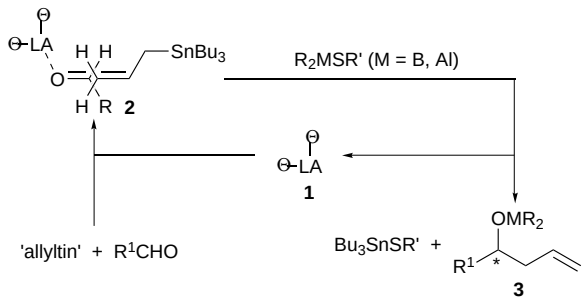
Dramatic acceleration of the catalytic process of asymmetric allylation of achiral aldehydes is observed by the utilization of the bifunctional synergetic reagents R_2MSR' (M = B, Al).

Chiral homoallyl alcohols are very useful intermediates for the enantioselective synthesis of complex chiral substances.[1] The exceptional power of the allyl transfer reaction to aldehydes in forming optically active homoallylic alcohols has been enhanced by newly developed enantioselective versions, especially chiral Lewis acid-catalysed addition of the allyl transfer reagent to a carbonyl functionality.[2] The development of synthetic methods for achieving absolute stereoselection by the utilization of chiral catalysts increasingly requires precise control of the reaction pathway based on mechanistic behaviour and the rational design of new reagents and processes.[3] The geometrical possibilities offered by chemical transformation together with the predictable power of mechanistic behaviour can allow the design of new catalytic systems. Recently, we demonstrated the utilization of the molecular accelerator Me_3SiSPr^i, designed on the basis of mechanistic speculation, for catalytic asymmetric allylation that resulted in not only a significant increase in the reaction rate but also a reduced dosage of chiral catalyst.[4] Described herein is an extension of the molecular accelerating strategy aimed at finding new reagents and realizing useful and practical asymmetric syntheses. This research led to the discovery of the remarkable synergetic reagent $R_2M–SR'$ (M = B, Al), which expedites the catalytic process of asymmetric allylation with high levels of enantioselectivity. In the present research, two major advances have been made in the enantioselective synthesis of homoallylic alcohols: (i) this system exhibited a dramatic increase in catalytic ability; (ii) alkylthioborane has advantages over alkylthiosilane in terms of efficacy, stereoselectivity and applicability to other systems.

Our rationale for the introduction of a molecular accelerator into the catalytic system was based on speculation illustrated in Scheme 1. In order to increase catalytic ability, regeneration of chiral catalyst **1** as a consequence of dissociation of product **3** from the reaction complex must be achieved. We reasoned that if a bifunctional synergetic reagent, *i.e.* R_2MSR'(M = B, Al), could control the catalytic allylation process *via* the Sn–S (enhancement of Sn–C bond breaking) and M–O (dissociation of product **3**) bond forming steps to reinforce regeneration of catalyst **1**, practical and efficient catalytic asymmetric allylation might be realized in a predictable fashion. The key to this prediction is the strong Sn–S and M–O bonds relative to the weaker M–S bond.

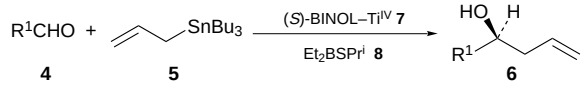


Scheme 1

The starting point of this present research was the availability of R_2BSR'; alkylthioboranes are readily prepared in quantity, easily purified by distillation and stable to storage.[5] Several alkylthioboranes (R_2BSR': R = Et, Bu; R′ = Et, Pr^i, Bu, Bu^t, Ph) were prepared and examined for their abilities as synergetic reagents in the allylation of hydrocinnamaldehyde with allyltributylstannane in the presence of (*S*)-BINOL–Ti^{IV} complex **7** (10 mol%).† Preliminary investigations indicated that efficient allylation was realized with Et_2BSPr^i at −20 °C for 5 h (93% isolated yield; 97% ee); this result is superior to the control system (−20 °C for 70 h, 78% isolated yield with 94% ee). Upon optimisation, the catalytic allyl transfer reaction was conducted by dropwise addition of Et_2BSPr^i (**8**, 1.2 equiv.) in CH_2Cl_2 at −20 °C to the mixture of **4** (R^1 = CH_2CH_2Ph, 1.0 equiv.) and **5** (1.3 equiv.) in the presence of chiral catalyst **7** (10 mol%) and 4 Å molecular sieves. After 5 h at −20 °C, the resulting reaction mixture was treated with aqueous $NaHCO_3$. After work up, the final purification of the homoallyl alcohol can be effected by silica gel chromatography.

This discovery prompted us to carry out more experiments with reduced amounts of chiral catalyst. Indeed, we were delighted to find that the same reaction proceeds with 1 mol%

Table 1 Enantioselective allylation accelerated by Et_2BSPr^i [a,b]



Entry	R^1	Catalyst **7** (mol%)[c]	Yield (%)[d]	Ee (%)[e]
1	$PhCh_2CH_2$	10	93	97
2	$PhCH_2CH_2$	5	89	95
3	$PhCH_2CH_2$	2	81	93
4	$PhCH_2CH_2$	1	77	93
5	C_6H_{11}	10	87	97
6	C_6H_{11}	5	82	95
7	C_6H_{11}	2	75	91
8	C_6H_{11}	1	61	88
9	c-C_6H_{11}	10	77	93
10	c-C_6H_{11}	5	67	88
11	c-C_6H_{11}	2	53	85
12	c-C_6H_{11}	1	44	75
13	Ph	10	89	96
14	Ph	5	84	93
15	Ph	2	71	91
16	Ph	1	57	77

[a] All reactions were run at −20 °C in CH_2Cl_2. [b] Absolute configurations were determined by direct comparison with specific rotations of known alcohols. [c] BINOL–$Ti(OPr^i)_4$ = 2:1 ratio. [d] Chromatographed yields. [e] Enantiomeric exess was determined using chiral shift reagent [Eu(hfc)$_3$] and by preparation of (+)-MTPA ester derivatives, analysis by ^{1}H NMR spectroscopy and comparison with authentic samples.

(*S*)-BINOL–Ti^{IV} complex to give a 77% isolated yield with 93% ee. Additional experiments with various aldehydes were carried out and representative results are summarized in Table 1. The reactions are generally complete after 5–8 h at −20 °C. We observed that better enantioselectivities and chemical yields were obtained with less hindered aldehydes compared to the more substituted cyclohexanecarbaldehyde.

Although the role of Et_2BSPr^i in accelerating the allyl transfer reaction must be a consequence of the dissociation of the product from reaction complex with regeneration of chiral catalyst, the exact mechanism has not been rigorously elucidated, and may involve concerted or stepwise participation.[6]

We next turned our attention to examining the feasibility of this system using a alkylthioalane.[7] Several catalytic allylations of aldehydes employing R_2AlSR' were conducted under identical conditions to those described above, and the use of Et_2AlSPr^i **9** proved to be most effective. Representative results are listed in Table 2. It is worthy of note that the catalyst–Et_2AlSPr^i system affords high enantioselectivities and chemical yields with 10 mol% of catalyst after 5 h, while with reduced amount of catalyst, especially less than 5 mol%, sharply reduced levels of asymmetric induction are observed.‡

In conclusion, an efficient method for the catalytic enantioselective addition of allyltributylstannane to aldehyde is described which employs a molecular accelerator, R_2MSR', and 1–2 mol% of BINOL–Ti^{IV}, furnishing homoallylic alcohol in good yield with useful levels of enantioselectivity. We believe that this approach to increasing catalytic ability by the use of synergetic reagents could be widely applicable, not only in the field of asymmetric carbonyl addition, but also in other related reactions.

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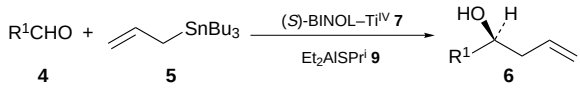
Table 2 Enantioselective allylation accelerated by Et_2AlSpr^i [a]



4 **5** **6**

Entry	R^1	Catalyst **7** (mol%)	Yield (%)	Ee (%)
1	$PhCh_2CH_2$	10	97	92
2	$PhCH_2CH_2$	5	91	63
3	C_6H_{11}	10	96	95
4	C_6H_{11}	5	83	85
5	c-C_6H_{11}	10	50	77
6	c-C_6H_{11}	5	45	57
7	Ph	10	92	93
8	Ph	5	81	79

[a] All conditions are the same as in Table 1.

Footnotes

† For the allylation reaction described herein, optimal enantioselectivity are observed with 2 : 1 BINOL–$Ti(OPr^i)_4$ in the presence of activated 4 Å molecular sieves.

‡ According to the results of control experiments under identical condition except for the use of catalyst, Et_2BSPr^i did not catalyse allyl transfer, while Et_2AlSPr^i turned out to be a very weak promoter. We did not observe any transmetallation reactions between Sn and B or Al.

References

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