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Catalytic allylic transfer reactions of functionalized aldehydes promoted by BINOL-Ti(IV) with synergistic reagent

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Abstract—Practical and efficient catalytic asymmetric allylic transfer reactions of tin reagents promoted by BINOL-Ti[OCH(CF_3)$_2$]$_2$ complex by the utilization of *t*-BuSBEt_2 are successful with a variety of functionalized aldehydes containing ketone, aldehyde, ester, amide, or carbamoyl functionality and affords products in high levels of enantioselectivity. © 2003 Elsevier Science Ltd. All rights reserved.

The availability of efficient synthetic methods for achieving absolute stereoselectivity via catalytic process in the production of enantiomerically rich compounds is of considerable current interest in organic chemistry.[1] As a consequence, many advances in the catalytic asymmetric synthesis has been made through a variety of ways in synthetic strategy.[2] Of particular interest is an additive accelerating strategy to find practical ways of asymmetric routes mainly because the additive pathway could dominate over the non-additive routes in simple trials.[3] Recently, we reported a series of allylic transfer reactions of achiral aldehydes in forming corresponding secondary alcohols based on accelerating strategy. Our approach involves the use of BINOL-Ti(IV) complex as a chiral promoter along with *i*-PrSBEt_2or *i*-PrSSiMe_3 as an accelerating synergetic reagent that has recently been shown to provide highly catalytic versions of enantioselective allylic transfer reactions of achiral aldehydes such as allylation,[4] propargylation,[5] allenylation,[6] and dienylation.[7] Even though there have been several elegant reports regarding chiral Lewis acid-promoted allylation reactions in the literature,[8] the lack of data concerning the variation of aldehydes containing other carbonyl group surprised us, in view of the expected applicability of a carbonyl functionality.[9] During the course of our research program aimed at finding a new catalytic system for the enantioselective allylic transfer reactions, we became quite interested in the systematic study on the functionalized aldehydes for allylic transfer reactions. This research led to the discovery of the remarkable effects by synergistic reagent, which expedites the catalytic process for asymmetric allylation and propargylation of a variety of aldehydes containing additional carbonyl unit with high levels of enantioselectivity.

The first study for orienting experiments focused on the reactivity of the catalytic process with a functionalized aldehyde expected to be less reactive compared to a normal aldehyde mainly due to the inhibitory coordination with chiral catalyst by the additional carbonyl group. Several functionalized aldehydes listed in Figure 1 were examined as substrates for catalytic asymmetric allylation in order to evaluate issues of reactivity and stereoselectivity.

Our investigations began with allyltributylstannane and **1** in the presence of (*S*)-BINOL-Ti(IV) complex along with synergistic reagent. After surveying reaction conditions, several key findings emerged: (i) the control experiment revealed that the reaction proceeded only

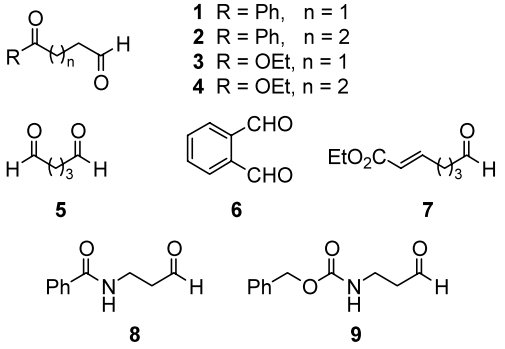

Figure 1.

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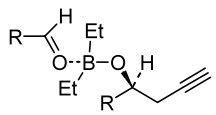
marginally in the absence of synergistic reagent (10 mol% of a 1:1 mixture of (*S*)-BINOL and Ti(O*i*-Pr)$_4$, –20°C, 56 h, 44% yield with 88% ee); (ii) *t*-BuSBEt$_2$ exhibited quite efficiency for the catalytic process to expedite reaction rate (3 mol%, 5 h, 86% yield with 97% ee);[10] (iii) the BINOL-Ti[OCH(CF$_3$)$_2$]$_2$ complex in the presence of 4 Å molecular sieves proved to be the most efficient catalyst;[11] (iv) the reaction performed at –20°C in PhCF$_3$ resulted in optimal chemical yields and enantioselectivities.[12] The reliability of the reaction was further examined with a variety of aldehydes of varying carbonyl functionalities as shown in Table 1. It is worthy of note that the bis-aldehydes **5** and **6** provided only mono-allylated products **12e** and **12f** presumably due to the formation of cyclic acetal. The absolute configuration of the predominating enantiomer for adduct was unambiguously established by comparison of values of specific rotation with an authentic sample.[13]

With our research scope of the asymmetric allylation reaction of functionalized aldehydes, we next turned our attention to examining the possibility of this approach with less reactive allenyltin reagent for the catalytic asymmetric propargylation reaction of functionalized aldehydes.[14] We were surprised to find that increased reactivity for the propargylation of functionalized aldehydes in comparison with normal aldehydes in the presence of chiral Lewis acid along with synergistic reagent *t*-BuSBEt$_2$ was observed. When aldehyde **1** was treated with allenyltributylstannane and thioborane **11** in the presence of 3 mol% of (*S*)-BINOL-Ti[OCH(CF$_3$)$_2$]$_2$ complex for 5 h at –20°C in PhCF$_3$, the corresponding propargylated alcohol **13a** was obtained in 83% isolated yield with 95% ee. This result was superior to those of normal aldehydes in terms of reaction times and catalytic ability (for example, PhCH$_2$CH$_2$CHO, 100 mol% of BINOL-Ti(IV) complex, 72 h, 80% yield with 92% ee and 4:1 isomeric mixture;[15] 10 mol% of catalyst, *i*-PrSBEt$_2$, 9 h, 86% yield with 94% ee).[5a] Crucial aspects for this transformation are as follows: (i) the reaction virtually did not proceed under 10 mol% of catalyst without the use of *t*-BuSBEt$_2$; (ii) the BINOL-Ti[OCH(CF$_3$)$_2$]$_2$ complex in the presence of 4 Å molecular sieves provided the best results. From Table 2 it can be seen that asymmetric propargylations were conducted on a variety of aldehydes to furnish alcohols **13** with excellent enantioselectivities. It is worthy of note that the reaction also produced none or less than 2% of isomeric allenyl alcohols except **13h** (95:5) according to analysis of the 500 MHz ^{1}H NMR spectra of the crude products.

Although the role of synergistic reagent in accelerating the allylic transfer reaction must be a consequence of dissociation of the product through a favorable bond between B–O and Sn–S with regeneration of chiral catalyst, the coordination of borane product with a normal aldehyde shown as **14** could retard reaction rates. The enhanced reactivity of functionalized aldehydes especially for propargylation may be interpreted by assuming that the intramolecular and/or intermolecular coordination of an additional carbonyl unit **15** could reduce the above action.



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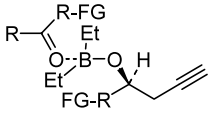

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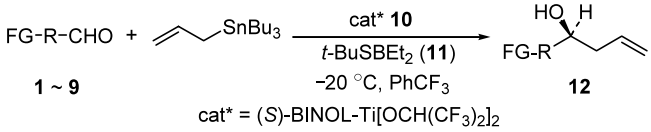
In summary, we have demonstrated the catalytic enantioselective addition of the allylic and propargylic moiety to functionalized aldehydes which employs a synergistic reagent, *t*-BuSBEt$_2$, and BINOL-

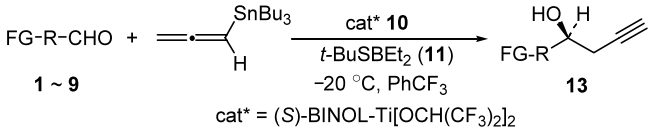
Table 1. Asymmetric allylation of functionalized aldehydes[a]



Entry	Aldehyde	Product	*t* (h)	Yield (%)[c]	Ee (%)[d]
1	**1**	**a**	5	86	97
2	**2**	**b**	5	83	95
3	**3**	**c**	6	81	98
4	**4**	**d**	6	79	98
5	**5**	**e**	6	87	92
6	**6**	**f**	6	71	89
7	**7**	**g**	12	94	92
8[b]	**8**	**h**	16	93	93
9[b]	**9**	**i**	16	78	91

[a] Reaction was run at –20°C in PhCF$_3$ with 3 mol% of **10**.
[b] Used 7 mol% of **10**.
[c] Yields refer to isolated and purified yield.
[d] Enantiomeric excesses were determined by preparation of (+)-MTPA ester derivatives, analysis by ^{1}H NMR (all entries, **12e** and **12f** were reduced to the corresponding diols and converted to bis-MTPA esters), and by HPLC analysis using chiral column (Chiracel OD-H, 3–5% *i*-PrOH in hexane, entries 1, 7, 8, 9).

Table 2. Asymmetric propargylation of functionalized aldehydes[a]



Entry	Aldehyde	Product	*t* (h)	Yield (%)[c]	Ee (%)[d]
1	**1**	**a**	6	83	93
2	**2**	**b**	6	82	95
3	**3**	**c**	12	80	94
4	**4**	**d**	12	83	96
5	**5**	**e**	12	58	91
6	**6**	**f**	12	73	92
7	**7**	**g**	6	84	92
8[b]	**8**	**h**	20	64	88
9[b]	**9**	**i**	20	54	84

[a] Reaction was run at −20°C in $PhCF_3$ with 3 mol% of **10**.
[b] Used 10 mol% of **10**.
[c] Yields refer to isolated and purified yield.
[d] Enantiomeric excesses were determined by preparation of (+)-MTPA ester derivatives, analysis by ^1H NMR (all entries, **13e** and **13f** were reduced to the corresponding diols and converted to bis-MTPA esters), and by HPLC analysis using chiral column (Chiracel OD-H, 3% *i*-PrOH in hexane, entries 8 and 9).

$Ti[OCH(CF_3)_2]_2$ complex. A variety of aldehydes containing ketone, aldehyde, ester, amide and carbamoyl functionality are converted to the corresponding secondary alcohols in good yields with high levels of enantioselectivity. Investigations into the versatility of this process including selective functional group transformations are currently underway.

Acknowledgements

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drying the combined organic solution over anhydrous Na_2SO_4, the solvents were removed under reduced pressure. Fresh column chromatography (SiO_2, 15% EtOAc in hexanes) afforded **12a** in 86% yield with 97% ee determined by HPLC using a Daicel OD-H column (hexane:*i*-PrOH 50:1; t_r (minor) = 15.3 min, t_r (major) 18.6 min). $[\alpha]_D^{23}$ +12.83 (*c* 0.9 in $CHCl_3$).

13. Compound **12a** was reduced by hydrazine hydrate in the presence of KOH to the corresponding (+)-(*4R*)-7-phenyl-hept-1-2n-4-ol in 41% yield. This alcohol has not only the same specific rotation sign but also identical NMR spectra of (+)-MTPA ester derivatives as compared with synthetic alcohol prepared by allyltributylstannane with 4-phenylbutanal in the presence of (*S*)-BINOL-Ti(VI) as described in Ref. 4a.
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