Effects of Subjoin Lewis Acid on the Catalytic Asymmetric Allylic Transfer Reactions of Aldehydes Promoted by BINOL-Ti(IV) Complex

Chan-Mo Yu,* Ha-Soon Choi, Sook-Kyung Yoon, and Won-Hyuk Jung
Department of Chemistry, Sung Kyun Kwan University, Suwon 440-746, Korea
Fax 82-331-290-7075; E-mail cmyu@chem.skku.ac.kr
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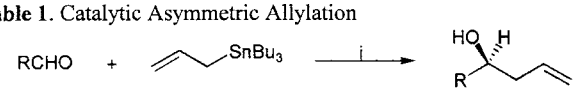
Abstract: Practical and efficient catalytic asymmetric allylic transfer reactions of achiral aldehydes with tin reagents promoted by BINOL-Ti(IV) complex are achieved with high enantioselectivity by the utilization of subjoined Lewis acid, $B(OMe)_3$.

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 because such structures are featured in many biologically relevant substances.[1] Of particular interest is chiral modified ligand accelerating strategy which, mainly due to the stereoselective pathway, could dominate over the nonselective route.[2] Furthermore, this system can be allowed to use extra reagent to regulate reaction pathway. For example, dialkylzinc addition to aldehydes catalyzed by chiral bissulfonamide-Ti(IV) complex was achieved in high levels of enantioselectivity by the utilization of large excess $Ti(O\textit{i}\text{-}Pr)_4$.[3] The BINOL-Ti(IV) complex prepared from the reaction of BINOL and $Ti(O\textit{i}\text{-}Pr)_4$ has proven to be ligand accelerating catalyst in comparison with $Ti(O\textit{i}\text{-}Pr)_4$ as a role of Lewis acid catalyst.[4] This enhanced Lewis acidity may be interpreted by assuming that the favorable angular change of Ti(IV) species caused by chelation of sterically demanding BINOL into the pentacoordinate from the tetracoordinate resulted in the formation of vacant orbital to accommodate aldehyde.[5] Even though there have been several elegant reports regarding chiral Lewis acid promoted allylation reaction in the literature,[6] the lack of data concerning the additive effects to increase catalytic ability surprised us, in view of the expected similarity of such system to the well defined catalytic carbonyl addition reactions.[3,7] During the course of our research program aimed at finding a new catalytic system for the enantioselective allylic transfer reactions,[8] we became quite interested in the systematic study on the effect of appendant Lewis acid into the BINOL-Ti(IV) catalyst system. This research led to the discovery of the remarkable effects by subjoining Lewis acid, which expedites the catalytic process of asymmetric allylation and propargylation with high levels of enantioselectivity.

The first study for orienting experiments focused on the feasibility of subjoined Lewis acid for the catalytic asymmetric allylation of achiral aldehydes. Our initial studies were carried out with **1** (R = CH_2CH_2Ph) and allyltributylstannane (**2**) in the presence of (*S*)-BINOL-Ti(IV) complex along with various less reactive Lewis acids. After surveying numerous conditions, several key findings emerged: (i) the use of excess $Ti(O\textit{i}\text{-}Pr)_4$ did not affect catalytic process, and slightly declined enantioselectivity was observed; (ii) $Al(OR^1)_3$ were proved to be unpromising mainly due to lower enantioselectivity; (iii) $B(OR^1)_3$ exhibited efficiency for the catalytic process; (iv) a 2 : 1 mixture of the BINOL-$Ti(O\textit{i}\text{-}Pr)_4$ complex in the presence of 4 A molecular sieves proved to be the most efficient catalyst.[9] (v) the reaction performed at 0 °C in CH_2Cl_2 resulted in optimal chemical yields and enantioselectivities.

The remarkable observation has been made that the use of $B(OMe)_3$ led to increasing reaction rate and catalytic capability in comparison with that of non-additive systems[6e]: this was generally superior to others such as $B(OEt)_3$ and $B(O\textit{i}\text{-}Pr)_3$ and was chosen for systematic studies.[10] The allylation reaction was performed according to the following procedure: The (*S*)-BINOL-Ti(IV) complex was prepared from the reaction of (*S*)-BINOL with $Ti(O\textit{i}\text{-}Pr)_4$ in the presence of activated powdered 4 A molecular sieves at 20 °C for 3 h. To a solution of **1** (R = CH_2CH_2Ph, 1 eq) and $B(OMe)_3$ (0.5 eq) in the presence of (*S*)-BINOL-Ti(IV) complex (5 mol%) in CH_2Cl_2 at 0 °C was added dropwise allyltributylstannane (**2**, 1.2 eq) in CH_2Cl_2. After 9 h at 0 °C, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$. Workup and silica gel chromatography afforded the alcohol **4** (R = CH_2CH_2Ph) in 91% isolated yield with 96% ee. This discovery prompted us to carry out more experiments under the reduced amounts of chiral catalyst with various aldehydes. The representative results are summarized in Table 1.

Table 1. Catalytic Asymmetric Allylation



1 **2** **4**

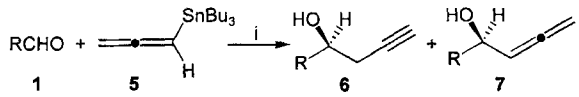
i. (*S*)-BINOL-Ti(IV) (**3**), $B(OMe)_3$, 0 °C, CH_2Cl_2

entry	aldehyde	**3** (mol%)[a]	t/h	yield, %[b]	ee, %[c]
1	$PhCH_2CH_2$	5	9	91	96
2		2	9	78	93
3		1	11	73	92
4	*n*-C_6H_{13}	5	9	83	93
5		2	12	69	93
6		1	24	59	88
7	Ph	5	11	85	91
8		2	26	77	90
9		1	44	64	83
10	*c*-C_6H_{11}	5	10	71	90
11		2	24	62	89
12		1	44	47	81

[a] (*S*)-BINOL-$Ti(O\textit{i}\text{-}Pr)_4$ = 2:1 ratio. [b] Yields refer to isolated and purified products. [c] Enantiomeric excesses were determined using chiral shift reagent [Eu(hfc)$_3$] and by preparation of (+)-MTPA ester derivatives, analysis by ^1H NMR spectroscopy and comparison with authentic samples.

With our research scope of the asymmetric allylation reaction, we turned our attention next to examine possibility of this approach with less reactive allenyltin reagent[11] for the catalytic asymmetric propargylation reaction of aldehydes.[12] Treatment of **5**[13] with **1** (R = CH_2CH_2Ph, 1 eq) in the presence of (*S*)-BINOL-Ti(IV) complex (10 mol%) and $B(OMe)_3$ (0.5 eq) in CH_2Cl_2 for 9 h afforded the alcohol **6** (R = CH_2CH_2Ph) in 72 % isolated yield and >97% ee. From Table 2 it can be seen that asymmetric propargylations were conducted on a variety of aldehydes under identical conditions to furnish alcohols **6** with excellent enantioselectivities. The absolute configuration and enantioselectivity of the predominating enantiomer for each adduct were unambiguously established by the conversion to the corresponding (+)-MTPA esters, analysis of ^1H NMR spectroscopy, and comparison with authentic samples. Reaction times and chemical yields were dependent on the steric environment of the substrates. It is worthy of note that the reaction also produced considerable amounts of isomeric allenyl alcohols **7** which might be originated from equilibrium between allenyl- and propargyl-tin under the reaction condition.

Table 2. Catalytic Asymmetric Propargylation



i. (*S*)-BINOL-Ti(IV) (**3**, 10 mol%)[a], $B(OMe)_3$, 0 °C, CH_2Cl_2

entry	aldehyde	t/h	**6** : **7**	yield, %[b]	ee, %[c]
1	$PhCH_2CH_2$	9	98 : 2	72	> 97
2	n-C_6H_{13}	9	94 : 6	71	94
3	Ph	22	90 : 10	57	92
4	c-C_6H_{11}	22	78 : 22	44	95

[a] (*S*)-BINOL-Ti(O*i*-Pr)$_4$ = 2:1 ratio. [b] Yields refer to isolated and purified products. [c] Enantiomeric excesses were determined by preparation of (+)-MTPA ester derivatives, analysis by ^{1}H NMR spectroscopy (C*H*OR) and comparison with authentic samples.

The exact mechanistic behavior of $B(OMe)_3$ has not been rigorously elucidated. However, this enhanced catalytic ability by the utilization of subjoining Lewis acid may be explained by assuming that the role of $B(OMe)_3$ must be a consequence of the dissociation of product from the reaction complex to facilitate regeneration of chiral catalyst.

In summary, this paper describes a new process for the enantioselective allylic transfer reactions in high levels of enantioselectivity. The method described herein is innovative and practical in terms of reaction conditions and availability of reagents. Further applications to more complicated systems are in progress.

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