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Catalytic asymmetric prop-2-ynylation involving the use of the bifunctional synergetic reagent Et_2BSPr^i

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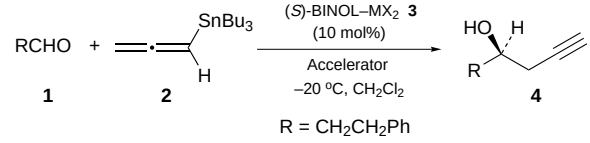
Efficient catalytic asymmetric prop-2-ynylation of achiral aldehydes with allenyltributylstannane promoted by a BINOL–Ti^{IV} complex (10 mol%) is achieved with high enantioselectivity by the use of Et_2BSPr^i.

We report here a useful catalytic method for the enantioselective synthesis of but-3-yn-1-ols from the reaction of an allenyltin reagent with achiral aldehydes promoted by a chiral Lewis acid together with a synergetic reagent. Among the fundamental asymmetric reactions, allylic transfer from chiral reagents to a carbonyl functionality, forming enantiomeric rich homoallylic alcohols, attracts considerable attention from the synthetic community since the resulting products serve as chiral building blocks for multi-step syntheses.[1] In spite of the structural versatility of the prop-2-ynylic system, there have been few reports in this area compared with the allylic system, mainly due to a lack of reactivity and regiochemical problems.[2] While a couple of chiral allenyl reagents employing chiral auxiliaries have been developed to realize a highly enantio- and regio-selective synthesis of but-3-yn-1-ols,[3] catalytic chiral Lewis acids have been introduced in the reaction of aldehydes with allenylstannane.[4] Nonethless, the method for catalytic asymmetric prop-2-ynylation employing chiral Lewis acids is not ideal, mainly due to poor catalytic ability (50–100 mol%) and long reaction times (72–100 h). The method described herein is successful with a variety of aldehydes in the presence of a catalyst employing a bifunctional synergetic reagent and affords products of high enantiomeric purity. The process utilizes a readily available alkylthioborane as a synergetic reagent.

Our initial studies began with hydrocinnamaldehyde **1** and allenyltributylstannane **2**.[5] Treatment of **1** with **2** in the presence of (*S*)-BINOL–Ti^{IV} (10 mol%) in CH_2Cl_2 at −20 °C for 24 h afforded only a barely detectable amount of adduct **4**. We subsequently observed that synergetic reagents, which were previously utilized for catalytic asymmetric allylation,[6] can also be employed for catalytic asymmetric prop-2-ynylation. After surveying series of alkylthioboranes and alkylthiosilanes, several key points emerged: (i) Et_2BSPr^i was generally superior to other reagents, including Me_3SiSPr^i; (ii) a 1 : 1 mixture of the BINOL–$Ti(OPr^i)_4$† or BINOL–$Zr(OPr^i)_4$‡ complexes proved to be the most effective catalyst; (iii) the new systems exhibited a dramatic acceleration of the reaction rate as well as significantly increasing catalytic ability in comparison with the non-accelerator system;[4] (iv) optimal chemical yields and enantioselectivities were observed with the use of CH_2Cl_2 as a solvent compared to other solvents such as toluene, diethyl ether or propionitrile. Selected results for the preliminary studies are summarised in Table 1. Especial encouraging were entries 2 and 5; therefore, chiral catalysts BINOL–Ti^{IV} and –Zr^{IV} with Et_2BSPr^i were chosen for systematic studies because they exhibited high level of enanatioselectivity with reasonable chemical yields.

The prop-2-ynylation reaction was performed according to the following procedure: all reactions were carried out in the presence of 4 Å molecular sieves to remove any trace of water. To a solution of **1** (R = CH_2CH_2Ph, 1 equiv.) and **2** (1.3 equiv. in the presence of (*S*)-BINOL–Ti^{IV} **5** (10 mol%) at −20 °C was added dropwise Et_2BSPr^i (1.2 equiv.) in CH_2Cl_2. After 9 h at −20 °C, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$. Work up and silica gel chromatography (SiO_2, deactivated with 1% of Et_3N in hexane; eluent, hexane–EtOAc) afforded the alcohol **4** (R = CH_2CH_2Ph) in 86% isolated yield and 94% ee. Using these optimal conditions, a range of experiments on the catalytic asymmetric prop-2-ynylation of aldehydes was carried out. From Table 2 it can be seen that asymmetric prop-2-ynylations were conducted on a variety of aldehydes under identical conditions to furnish alcohols **4** with excellent enantioselectivities. Reaction times and chemical yields, as indicated in Table 2, were dependent on the steric environment of the substrates. It is worthy of note that the reaction also produced trace amounts of isomeric allenyl alcohol (< 2%) according to analysis of the ^1H NMR spectra of the crude products. A reduced dosage of chiral catalyst **5**

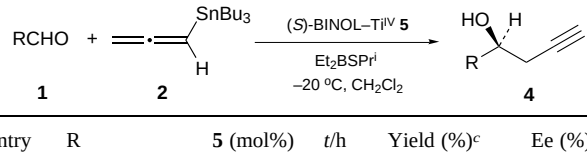
Table 1 Selected data for preliminary investigations



Entry	MX_2	Accelerator	*t*/h	Yield (%)	Ee (%)
1	$Ti(OPr^i)_2$[a]	Control	20	Trace	—
2	$Ti(OPr^i)_2$[a]	Et_2BSPr^i	9	86	94
3	$Ti(OPr^i)_2$[b]	Et_2BSPr^i	9	84	93
4	$Ti(OPr^i)_2$[a]	Me_3SiSPr^i	9	57[c]	—
5	$Zr(OPr^i)_2$[d]	Et_2BSPr^i	8	72	92

[a] BINOL–$Ti(OPr^i)_4$ = 1 : 1. [b] BINOL–$Ti(OPr^i)_4$ = 2 : 1. [c] Isolated yield after desilylation (Bu_4NF). [d] BINOL + $Zr(OPr^i)_4$.

Table 2 Catalytic prop-2-ynylation promoted by the BINOL–Ti^{IV} complex[a,b]



Entry	R	**5** (mol%)	*t*/h	Yield (%)[c]	Ee (%)[d]
1	$PhCH_2CH_2$	10	9	86	94
2	$PhCH_2CH_2$	5	18	65	91
3	C_6H_{11}	10	9	75	92
4	C_6H_{11}	5	18	51	88
5	c-C_6H_{11}	10	15	73	91
6	Me_2CHCH_2	10	15	61	95
7	Ph	10	15	52	92

[a] All reactions were run at −20 °C. [b] Absolute configurations were verified by comparison of specific rotation sign with authentic and/or literature values. [c] Yields refer to isolated and purified products. [d] Enantiomeric excess values were determined by preparation of (+)-MTPA ester derivatives, analysis by ^1H NMR spectroscopy (C*H*OR) and comparison with authentic and racemic samples.

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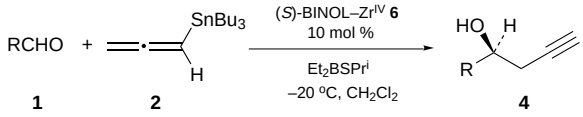
resulted in diminished chemical yields, longer reaction times and poorer stereoselectivites.

Catalytic asymmetric prop-2-ynylation promoted by the (*S*)-BINOL– Zr^{IV} ‡ complex was also investigated under similar conditions to those described above. Most of the isolated major alcohols were contaminated with a trace of the isomeric allenyl alcohol (< 3%), but in the case of cyclohexanecarbaldehyde the product ratio proved to be 93 : 7 as judged by ^{1}H NMR spectroscopic analysis of the crude products. The data summarised in Table 3 allow the following points to be stated: (i) as expected, the process using the molecular accelerator is effective in terms of reaction time as well as chemical yield; (ii) in general, the Zr^{IV} complex provides modest to excellent enantioselectivities, which are somewhat lower than those of the Ti^{IV} complex; (iii) the enantioselectivities correlate with the degree of steric hindrance in the substrates.

The work disclosed here is innovative mainly because of the reinforcement of catalytic ability outlined, especially with the less reactive allenylstannane.[8] However, further extension of the understanding of this chemistry is required in the following areas: (i) the exact mechanism by which Et_2BSPr^i accelerates the catalytic process,which involves dissociation of the product from the reaction complex and regeneration of the chiral catalyst; (ii) the origin of isomeric allenyl alcohols is also unclear, and may involve equilibration between allenyl- and prop-2-ynyl-tin reagents or α- and γ-orientation to tin in the transition state.

Table 3 Catalytic prop-2-ynylation promoted by the BINOL-Zr^{IV} complex



1 **2** **4**

Entry	R	*t*/h	Yield (%)	Ee (%)
1	$PhCH_2CH_2$	9	72	92
2	C_6H_{11}	9	71	87
3	c-C_6H_{11}	15	67	68
4	Me_2CHCH_2	15	65	91
5	Ph	15	44	71

[a] All conditions were identical with those of Table 2.

In conclusion, the enantioselective prop-2-ynylation of achiral aldehydes, a process of clear synthetic potential, has been advanced to a new level of practicality and stereoselectivity as a result of the utilization of a molecular accelerator to increase catalytic ability and reactivity. Studies are in progress to extend this chemistry to more highly functionalised tin reagents, including racemic allenylstannanes for kinetic resolutions. We believe that further studies will provide a better understanding of this chemical phenomenon.

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Footnotes

† The (*S*)-BINOL–Ti^{IV} complex was prepared from the reaction of (*S*)-BINOL with $Ti(OPr^i)_4$ in the presence of activated powdered 4 Å molecular sieves at 20 °C for 3 h (ref. 4).

‡ The (*S*)-BINOL–Zr^{IV} complex was prepared from the reaction of (*S*)-BINOL with $Zr(OPr^i)_4$ in the presence of activated powdered 4 Å molecular sieves at 20 °C for 2 h (ref. 7).

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