

Catalytic asymmetric dienylation of achiral aldehydes using buta-2,3-dienylstannane in the presence of chiral Lewis acid and synergetic reagent

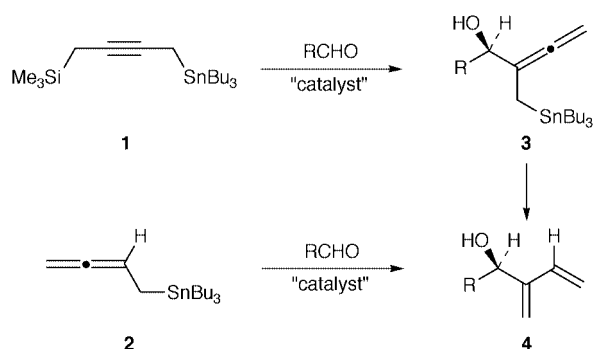
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Efficient catalytic asymmetric dienylation of achiral aldehydes with buta-2,3-dienyltributylstannane promoted by a BINOL-Ti^{IV} complex is achieved with high enantioselectivity by the utilization of Et₂BSP^r.

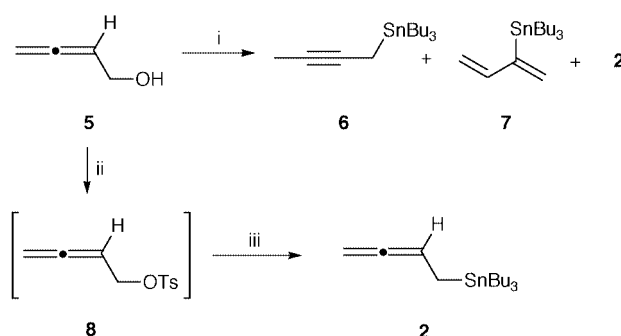
The development of catalytic asymmetric methods for carbonyl addition reactions is an important research area of current organic chemistry.¹ Recent efforts by several research groups to activate chiral catalysts to reach maximum selectivity and reactivity through the use of additives and cocatalysts have led to impressive advances in carbonyl addition reactions.² Recent reports from this laboratory have shown that the utilization of molecular synergetic reagents can provide highly enantioselective versions of allylic transfer reactions³ of achiral aldehydes including allylation, propargylation and allenylation.⁴ More recently, we demonstrated the enantioselective synthesis of dienyl alcohols by a two step sequence employing (4-trimethylsilylbut-2-ynyl)tributylstannane (**1**) as an allylic transfer reagent as depicted in Scheme 1.⁵ The efficiency of this



Scheme 1 Catalytic asymmetric dienylation routes.

protocol in terms of enantioselectivity and catalytic ability has encouraged us to develop a direct method for the catalytic asymmetric dienylation process which would expand the utility and practicability of allylic transfer reactions.⁶

The starting point of this investigation was the availability of the reagent **2** in a regiochemically pure form. Initial attempts on the synthesis of **2** using allenyl alcohol **5**⁷ afforded discouraging results since the products were formed as a mixture of regioisomers. We were surprised to find that the reaction performed under conditions i as described in Scheme 2 gave repeatedly **6** as a major component (*ca.* **6**:**7**:**2** = 2:0.1:1). The formation of but-2-ynylstannane **6** from **5** was attributed to basic media in the reaction mixture. As a consequence, we speculated that the formation of **6** could be avoided by small changes in the reaction conditions to minimize basic media in the reaction mixture. Indeed we were delighted to find that the tin reagent **2**, a crucial compound for this investigation, can be prepared by the following sequence: i) addition of allenyl alcohol **5** to a mixture of *p*-TsCl and NaH in THF at $-78\text{ }^\circ\text{C}$ for 1 h then $-20\text{ }^\circ\text{C}$ for 1 h resulted in the formation of the tosylate **8** which was used for



Scheme 2 Reagents and conditions: i) a. NaH, $0\text{ }^\circ\text{C}$, THF; b. *p*-TsCl, THF, $0\text{ }^\circ\text{C}$; c. Bu₃SnLi, $-78\text{ }^\circ\text{C}$. ii) NaH, *p*-TsCl, -78 to $-20\text{ }^\circ\text{C}$, THF. iii) Bu₃SnLi, $-78\text{ }^\circ\text{C}$, 1 h.

the next operation without isolation; ii) subsequent treatment of tosylate **8** with Bu₃SnLi at $-78\text{ }^\circ\text{C}$ for 1 h and then work up (quenching with pH 7 buffer solution followed by extraction with hexanes) afforded the crude product. After removal of base line impurities by filtration through Et₃N-pretreated silica gel with hexanes, final purification was effected by bulb to bulb distillation (0.1 mmHg, $150\text{ }^\circ\text{C}$, 54% yield).⁸ The stage was thus set for the dienylation of **2** with aldehydes promoted by a chiral Lewis acid catalyst.

Initial experiments on the dienylation of **2** with hydrocinnamaldehyde promoted by BINOL-Ti^{IV} complex indicated that the tin reagent **2** turned out to be less reactive than other allylic transfer reagents such as allyl-, propargyl- and allenylstannanes. After surveying numerous conditions, several key findings emerged: i) control experiment revealed that the reaction proceeded only marginally in the absence of synergetic reagent (10 mol% catalyst, $-20\text{ }^\circ\text{C}$, 30 h, <5% yield); ii) Et₂BSP^r exhibited moderate efficiency for the catalytic process in increasing reaction rate; iii) a 2:1 mixture of the BINOL and Ti(OP^r)₄ complex in the presence of 4 Å molecular sieves proved to be the most efficient catalyst; iv) the reaction performed at $-20\text{ }^\circ\text{C}$ in PhCF₃ resulted in optimal chemical yields and enantioselectivities in comparison with other solvents such as CH₂Cl₂ and toluene.⁹ Under optimal conditions, the allylic transfer reaction was conducted by the dropwise addition of Et₂BSP^r (1.2 equiv) in PhCF₃ at $-20\text{ }^\circ\text{C}$ to a mixture of **2** and hydrocinnamaldehyde in the presence of (*S*)-BINOL-Ti^{IV} (10 mol%)¹⁰ in PhCF₃. After 8 h at $-20\text{ }^\circ\text{C}$, the mixture was quenched by the addition of a saturated aqueous NaHCO₃. Work up and chromatography on triethylamine treated silica gel gave **4** (R = PhCH₂CH₂) in 74% yield with 97% ee. Additional experiments with various aldehydes were carried out and representative results are summarized in Table 1. It can be seen from Table 1 that the catalytic process is effective for a variety of aldehydes. It is noteworthy that the protocol using reagent **2** turned out to be more efficient than the two step operation employing reagent **1** in terms of enantioselectivities and chemical yields. The absolute configuration of

Table 1 Dienylation reactions of **2** with achiral aldehydes^{a,b}

Entry	RCHO	t/h	Yield (%) ^c	Ee (%) ^d
1	PhCH ₂ CH ₂	8	74	97
2	C ₆ H ₁₃	8	72	94
3	Ph	8	81	98
4	PhCH=CH	16	53	91
5	PhC≡C	16	61	93

^a All reactions were carried out at $-20\text{ }^{\circ}\text{C}$ in PhCF_3 . ^b BINOL:Ti(OPrⁱ)₄ = 2:1 (10 mol%). ^c Yields refer to isolated and purified products.

^d Enantiomeric excesses were determined by preparation of (+)-MTPA ester derivatives, analysis by 500 MHz ¹H NMR spectroscopy, and comparison with corresponding diastereomers which were prepared from (R)-BINOL-Ti^{IV}.

the predominating enantiomer of the adducts **4** was unambiguously established by comparison of their specific rotations with that of known alcohols.^{5,6}

In summary, an efficient method for the catalytic enantioselective addition of buta-2,3-dienyltributylstannane to aldehydes is described which employs a synergetic reagent, Et₂BSPriⁱ, and BINOL-Ti^{IV} complex, furnishing dienylation products in good yields with high levels of enantioselectivity. Studies are in progress to enlarge the scope of this protocol with more highly functionalized tin reagents, which will provide a better understanding of this chemical phenomenon.

Experimental

Typical procedure for the catalytic dienylation (entry 3 of Table 1): a flame-dried flask containing (S)-BINOL (57.3 mg, 0.2 mmol) and activated powdered 4 Å molecular sieves (0.7 g) was evacuated and carefully purged with nitrogen three times and then charged with dry PhCF₃ (2 mL) followed by freshly distilled Ti(OPrⁱ)₄ (freshly prepared 0.5 M in PhCF₃, 0.2 mL, 0.1 mmol). The mixture was allowed to proceed at 25 °C for 3 h. The red-brown mixture was cooled to $-20\text{ }^{\circ}\text{C}$ in a dry ice-CCl₄ bath, and benzaldehyde (**1**, R¹ = Ph, 0.11 g, 1.0 mmol) in PhCF₃ (0.5 mL) was added. To this mixture was added dropwise buta-2,3-dienyltributylstannane (**2**, 0.41 g, 1.2 mmol) in PhCF₃ (1 mL) followed by Et₂BSPriⁱ (0.18 g, 1.25 mmol) in PhCF₃ (1 mL) with a gas-tight syringe *via* a syringe pump over 1 h along the wall of the flask while keeping the temperature below $-20\text{ }^{\circ}\text{C}$. After stirring for 8 h at $-20\text{ }^{\circ}\text{C}$, aqueous NaHCO₃ (5 mL) was added to the reaction mixture, and then diluted with CH₂Cl₂ (10 mL). The molecular sieves were removed by filtration, and the aqueous layer was extracted with CH₂Cl₂ (*ca.* 20 mL). After drying the combined organic solution over anhydrous Na₂SO₄, the solvents were removed under reduced pressure. Flash column chromatography (Et₃N pretreated SiO₂, 10% EtOAc in hexanes) afforded **4** (R = Ph; 0.130 g, 0.81 mmol,

81%) as a colorless liquid: TLC, R_f 0.29 (9:1 hexane-EtOAc); $[\alpha]_{\text{D}}^{20} = -93.2$ (*c* 1.34 in CHCl₃); ν_{max} (neat)/cm⁻¹ 3386, 3088, 3030, 1594, 1452, 992, 736, 664; Found: C, 82.33; H, 7.69. Calc. for C₁₁H₁₂O: C, 82.46; H, 7.55; O, 9.99%; δ_{H} (500 MHz; CDCl₃; Me₄Si) 2.01 (1H, d, *J* 3.40, OH), 5.05 (1H, d, *J* 11.34, HC=CHH^c), 5.22 (1H, d, *J* 17.85, HC=CHHⁱ), 5.34 (1H, s, C=CHH), 5.41 (1H, s, C=CHH), 5.48 (1H, d, *J* 3.40, CHO), 6.31 (1H, dd, *J* 11.34 and 17.85, HC=CH₂), 7.25–7.40 (5H, m, PhH); δ_{C} (50 MHz; CDCl₃; Me₄Si) 74.03, 115.44, 115.61, 126.85, 127.79, 128.46, 135.80, 141.97, 147.68.

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