Catalytic Asymmetric Synthesis of Homoallylic Alcohols

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Here we present a novel procedure for the synthesis of highly enantiomerically enriched homoallylic alcohols by the reaction of aldehydes with allyltributyltin in the presence of a catalytic amount of an (*S*)-(1,1′-binaphthalene)-2,2′-diol–titanium complex (BINOL–$TiCl_2$, *S*-**1**).

The synthesis of enantiomerically enriched homoallylic alcohols has represented a main goal in asymmetric synthesis thanks to the broad availability of allylmetal compounds and to the extreme versatility of the products, which can be considered precursors of aldols, saturated alcohols, 1,3- and 1,4-diols, etc. Very important results have been obtained from the use of a stoichiometric amount of η^1-allylmetal compounds bearing chiral ligands. Among them allyl boranes[1a] and boronates,[1b] allyl boradiazolidines,[1c] allyl titanates,[1d] and allyl and aluminum[1e] derivatives have been reported, each affording high levels of enantioselectivity.

On the other hand, very little is known about general methodologies for the allylation of aldehydes based on the use of chiral Lewis acids as the source of stereoselectivity.[2] Apart from the very important finding of the glyoxylate ene reaction catalyzed by complex **1**[3] (which is limited to glyoxylic aldehyde and 2,2-disubstituted alkenes as substrates), good enantioselectivities have been obtained by Yamamoto et al.[4] from the allylation reaction of aromatic aldehydes with allyltrimethylsilanes catalyzed by a chiral acyloxyborane (CAB). In this case, however, aliphatic aldehydes proved to be unsuitable substrates affording poor yields. This last drawback has been partially overcome by the recent finding of Marshall et al.,[5] appearing while the present work was already in progress, who used a combination of an allyltributyltin and trifluoroacetic anhydride together with a stoichiometric amount of the CAB promoter to obtain homoallylic alcohols in very good yields and stereoselectivities ranging from 70 to 95%.

Our procedure for the enantioselective allylation of aldehydes **2a–f** is based on the use of allyltributyltin **3**[6] and is promoted and stereochemically controlled by a *catalytic amount* (20 mol%) of the BINOL–$TiCl_2$ complex *S*-**1**[7] in the presence of activated 4-Å molecular sieves (MS), as summarized in Scheme I.

Data shown in Table I relate to the reactions of octanal **2a**, which was chosen as a model substrate. The enantioselectivity

Scheme I

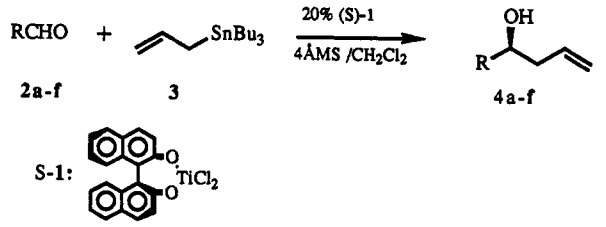

Table I. Reactions of Octanal (**2a**) with Allyltributyltin (**3**) Catalyzed by Complex *S*-**1**[a]

entry	catalyst (mol %)[b]	4-Å MS[c]	*T* (°C)[d]	*t* (h)	yield (%)[e]	ee (%)[f]
1	$TiCl_2(OiPr)_2$ (20)[g]	D	–20 → RT		0	
2	*S*-**1** (20)	D	–20	24	83	97.4
3	*R*-**1** (20)	D	–20	24	81	97.4
4	*S*-**1** (20)	D	–20 → RT	12	75	94
5	*S*-**1** (20)	U	–20 → RT	90	62	94
6	*S*-**1** (20)[h]	D	–20 → RT	24	72	13.5
7	*S*-**1** (20)	F	–20 → RT	24	70	82

[a] All the reactions were carried out on 1.5 mmol of **2a** using a **3**:**2a** = 2:1 molar ratio and in the presence of 1.5 g of powdered activated 4-Å MS in 7.5 mL of anhydrous CH_2Cl_2. [b] Moles % of catalyst with respect to **2a**. [c] D, dried for 12 h at 250 °C and 0.1 Torr. U, undried. F, dried, 4-Å MS were used in the preparation of the catalyst and then filtered off under Ar atmosphere. [d] –20 means that the reaction mixture is cooled at –20 °C 10 min after the addition of **3** and prior to the addition of **2a** and then kept at this temperature. –20 → RT means that after being kept at –20 °C for 4 h the reaction temperature is allowed to rise up to room temperature. [e] Yields are relative to the weight of the pure isolated product. [f] Determined by integration of the GC peaks of the two enantiomers separated on a chiral pentyldimethyl-β-cyclodextrin column. [g] Both catalytic and stoichiometric amounts of $TiCl_2(OiPr)_2$ were tested, but no product formation was observed. [h] The catalyst was prepared from 20 mol % BINOL and 100 mol % $TiCl_2(OiPr)_2$.

is very high (97%, entry 2), superior to all those reported for straight-chain aldehydes; chemical yields are also good. The better results were obtained when the catalyst was prepared from the reaction of equimolar quantities of $TiCl_2(Oi\text{-}Pr)_2$ and *S*-(–)-binaphthol (a slight excess of binaphthol is used) in CH_2Cl_2 at room temperature in the presence of 4-Å MS for 2 h.[3] Allyltributyltin (**3**) and, after cooling to –20 °C, octanal are added, and the mixture is kept at –20 °C under stirring. The homoallylic alcohol **4a** is then obtained by aqueous workup and column chromatography. It is worth note that binaphthol can be easily recovered from the column in ≥80% yield without racemization. This makes the cost of the chiral catalyst irrelevant.

The role of molecular sieves is crucial for the preparation of the catalyst, and no reaction occurs if 4-Å MS are not present at this stage, but they also partially affect the following allylation reaction[8] (entry 7). In particular, the conservation status of 4-Å MS must be taken into account: in fact, although just-opened packages of molecular sieves can be usefully employed, storing them in a desiccator with P_2O_5 results in progressive degradation of their performances (cf. entries 4 and 5), *so drying under conditions stated in the note to Table I is strongly recommended.* If these conditions are satisfied, an acceptable reaction rate can be achieved and complete conversion of **2a** is obtained in 24 h (entry 2); some improvement of the rate is obtained if the reaction temperature is raised to 20 °C (entry 4), the ee level being only

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(1) (a) Brown, H. C.; Parabhakar, K. J. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J. *J. Org. Chem.* **1990**, *55*, 4109. (c) Corey, E. J.; Chan-Mo, Y.; Sung, S. K. *J. Am. Chem. Soc.* **1989**, *111*, 5496. (d) Riediker, M.; Duthaler, R. O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 494. (e) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321. (f) Minowa, N.; Mukayama, T. *Bull. Chem. Soc. Jpn.* **1987**, *69*, 3697.

(2) The use of chiral Lewis acids in catalytic asymmetric reactions has been recently reviewed: Narasaka, K. *Synthesis*, **1991**, 1. Low stereoselectivities have been obtained from the allylation of 3-methybutanal promoted by various chiral titanium complexes: Ketter, A.; Hermann, R. *Z. Naturforsch.* **1990**, *45B*, 1684.

(3) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.

(4) Furuta, K.; Makoto, M.; Yamamoto, H. *Synlett* **1991**, 561.

(5) Marshall, J. A.; Tang, Y. *Synlett* **1992**, 653.

(6) The product **4a** did not form if allyltrimethylsilane was used instead of **2**.

(7) A ligand exchange between complex **1** and allyltributyltin was evidenced from the quantitative formation of Bu_3SnCl when equimolar amounts of *S*-**1** and **3** were mixed; nevertheless, the allyltitanium derivative thus formed did not afford any detectable amounts of product **4a** upon addition of an *equimolar amount* of octanal at RT after 48 h. So we can exclude that an allyl transfer from titanium to aldehyde is the actual reaction pathway. We suppose that a BINOL–TiCl–allyl complex acts as the chiral Lewis acid catalyst, but further mechanistic investigations are in course.

(8) No change in stereoselectivity has been observed in the glyoxylate ene reaction if 4-Å MS are filtered off (ref 3).

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Table II. Allylation Reactions of Aldehydes with Allyltributyltin Catalyzed by Complex *S*-1[a]

entry	R	T (°C)[b]	t (h)	yield (%)[b]	ee (%), conf[c]	$[\alpha]^{25}_D$ (c, solv)
1	C_7H_{15} (**2a**)	−20	24	83	97.4, (*R*)	+6.51 (1.04, $CHCl_3$)
2	C_5H_{11} (**2b**)	−20	24	75	98.4, *R*	+8.3 (1.40, $CHCl_3$)
3	c-C_6H_{11} (**2c**)	−20	90	36	89.1, *S*	−8.60 (0.56, EtOH)
4	c-C_6H_{11} (**2c**)	RT	24	75	92.6, *S*	−8.94 (0.56, EtOH)
5	PhCH=CH (**2d**)	−20	90	38	94, *S*	+15.3 (1.32, Et_2O)
6	PhCH=CH (**2d**)	RT	24	85	88.8, *S*	+13.9 (1.53, Et_2O)
7	Ph (**2e**)	RT	48	96	82.0, *S*	−40.4 (2.58, PhH)
8	4-Py (**2f**)	RT	48	90	80.2, (*S*)	−35.9 (2.5, PhH)
9	PhCH=CH (**2d**)[d]	−20	24	95	66.8, *S*	+10.3 (1.53, Et_2O)
10	4-Py (**2f**)[e]	−20	20	83	47.6, (*S*)	−21.3 (2.5, PhH)

[a] All the reactions were carried out on 1.5 mmol of aldehyde using a 3:2 = 2:1 molar ratio in the presence of 20 mol % of catalyst *S*-1 (previously prepared at RT) and of 1.5 g of powdered activated 4-Å MS in 7.5 mL of anhydrous CH_2Cl_2. [b] Yields are relative to the weight of the pure isolated product. [c] Determined by integration of the GC peaks of the two enantiomeric alcohols or TMS ethers (R = Ph, 4-Py) separated on a chiral pentyldimethyl-β-cyclodextrin column. Configuration was determined by comparison of the sign of optical rotation with reported values: Riediker, M.; Duthaler, R. O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 494. Minowa, N.; Mukayama, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3697. Tamao, K.; Kanatani, R.; Kumada, M. *Tetrahedron Lett.*, **1984**, *25*, 1913; configurations in parentheses have been deduced assuming a constant preference for the *Si* face of the aldehyde. [d] 1.5 mmol of TMSCl was added. [e] 1.5 mmol of $(CF_3CO)_2O$ was added.

marginally affected. Since $TiCl_2(OiPr)_2$ cannot promote the allylation reaction[9] (entry 1), we tried to increase the reaction rate using an excess of $TiCl_2(OiPr)_2$ with respect to BINOL (entry 6), but a dramatical drop in stereoselectivity resulted.[10]

The extension of the reaction to different aldehydes afforded the data collected in Table II. Hexanal (**2b**) gave results very similar to those with **2a**, indicating a general trend for aliphatic straight-chain substrates, but when passing to α-branched or unsaturated compounds like **2c** and **2d** (entries 3 and 5), the reaction rate drops to unacceptable levels at −20 °C and the reaction must be run at room temperature. However, a very high stereoselectivity is still maintained. The addition of external electrophiles like TMSCl or $(CF_3CO)_2O$ strongly accelerates the reactions, but low ees are obtained (entries 9 and 10).[11] Aromatic aldehydes can be allylated in good yields with our method, ee values being slightly inferior to those of aliphatic substrates.

In conclusion, our catalytic allylation reaction represents a general procedure for the enantioselective synthesis of homoallylic alcohols. It makes use of a catalytic amount of a commercially available and simply recoverable chiral ligand (BINOL) and constitutes the best catalytic asymmetric methodology presently available for the allylation of aliphatic straight-chain aldehydes.

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Supplementary Material Available: Experimental procedures and data (2 pages). Ordering information is given on any current masthead page.

(9) This behavior is completely different from that of the glyoxylate ene reaction, catalyzed by the same complex **1** (ref 3), and from cycloaddition reaction, catalyzed by chiral $TiCl_2$-1,4-diol complex: Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, 1581. In all these cases $TiCl_2(OiPr)_2$ is at least as active as the chiral complex.

(10) Since the result of entry 1 (Table I) has been confirmed in three different runs, we must conclude that in this case a "new" unselective catalyst did form.

(11) Both TMSCl and $(CF_3CO)_2O$ partially promote the allylation of octanal by allyltributyltin.