Effect of Water on Keck's Catalytic Asymmetric Allylations of Aldehydes

Michio Kurosu,* Miguel Lorca

Department of Chemistry and Biochemistry, The Florida State University, Tallahassee, FL 32306, USA
E-mail: mkurosu@fas.harvard.edu

Received 5 January 2005

Abstract: The complex generated from BINOL, Ti(*i*-PrO)$_4$, and unactivated or a large amount of activated 4 Å MS in toluene is very effective in catalytic allylations of aldehydes using allyltributyltin. Allylations with 2.5 mol% of the catalyst provide homoallylic alcohols with greater than 95% ee. Very high *syn*-selective allylations of protected b-hydroxyaldehydes are achieved with 5 mol% of the BINOL/Ti(*i*-PrO)$_4$ complex.

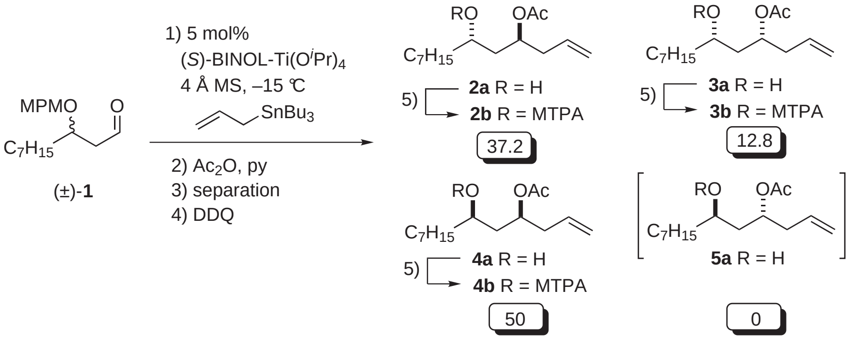
Key words: catalytic asymmetric allylation, 4 Å molecular sieves, BINOL, Ti(*i*-PrO)$_4$, allyltributyltin

The additions of the acetate unit to aldehydes plays an important role in the syntheses of most natural products of polyketide origin.[1] In a number of total syntheses of such molecules asymmetric allylations of aldehydes are often the start in constructing 1,3-polyol units. The asymmetric allylations via stoichiometric amount of chiral allyldialkylboranes[2] and allyldialkoxylboranes[3] have been widely utilized.[4] Although impressive advances have been achieved in Lewis acid and Lewis base-catalyzed catalytic asymmetric allylation of aromatic and reactive aldehydes,[5] few procedures can be applied to the synthesis of large quantities of optically active homoallylic alcohols from various types of aldehydes. Among the catalytic asymmetric allylation reactions developed so far, the catalysts prepared from BINOL)/Ti(*i*-PrO)$_4$ (Keck's conditions),[6] BINOL /TiCl$_2$(*i*-PrO)$_2$,[7] and BINOL/Zr species[8] using allyltributyltin would be applicable to a variety of aldehydes including chiral aldehydes. The active catalysts for allylstannations of aldehydes can be generated reproducibly by mixing a 1:1 mixture of BINOL and Zr species in the presence of 4 Å molecular sieves (MS).[8c] However, in our hands a 1:1 mixture of BINOL and Ti(*i*-PrO)$_4$ did not form an effective complex that catalyzed allylstannations of aldehydes in a catalytic manner with a useful level of enantioselectivity. Keck originally reported that a 1:1 mixture of BINOL and Ti(*i*-PrO)$_4$ in the presence of 4 Å MS under reflux in CH$_2$Cl$_2$ or a 2:1 mixture of BINOL and Ti(*i*-PrO)$_4$ in the presence of 4 Å MS and a catalytic amount of TfOH in CH$_2$Cl$_2$ afforded effective catalysts.[6a] Later, Keck modified the procedures in which allylstannations of the aromatic and aliphatic aldehydes via 20 mol% of the complex generated from a 2:1 mixture of BINOL and Ti(*i*-PrO)$_4$ in the absence of MS afforded the corresponding homoallylic alcohols in 89–96% ee at 0–23 °C.[6b] Brückner observed large deviations of yield and selectivity from the reported results by Keck, and developed a reliable procedure for allylstannation reactions in which the allylation of hydrocinnamaldehyde using the catalyst generated from a 2:1 mixture of (*R*)-BINOL and Ti(EtO)$_4$ in the absence of MS in CH$_2$Cl$_2$ afforded (*S*)-1-phenylhex-5-en-3-ol in 72% yield with 97.6% ee after 12 days at –40 °C.[9] Although Brückner's conditions provide homoallylic alcohols with excellent enantiomeric excess the method needed to be further developed, because: (1) 20 mol% of the catalyst is required (with respect to BINOL); (2) the reactions require very long reaction times at controlled temperatures; and (3) no generalization has been possible for catalytic asymmetric allylation reactions of chiral aldehydes. We now wish to report a very practical catalytic asymmetric allylation of aldehydes with the catalyst generated from a 2:1 mixture of BINOL and Ti(*i*-PrO)$_4$ (Keck's conditions) in the presence of unactivated or a large amount of activated 4 Å MS, and its application to the syntheses of *syn*-1,3-polyol units.

A 1:1 mixture of BINOL and Ti(*i*-PrO)$_4$ in strictly anhydrous CH$_2$Cl$_2$ forms the BINOL/Ti(*i*-PrO)$_2$ complex which can be characterized by ^{1}H NMR spectroscopy;[10] however, this complex did not catalyze allylstannations of aldehydes. We observed that addition of unactivated 4 Å MS[11] to a 2:1 mixture of BINOL and Ti(*i*-PrO)$_4$ was very effective in the formation of an active catalyst; the allylstannation of hydrocinnamaldehyde using 10 mol% of the catalyst generated from a 2:1 mixture of (*S*)-BINOL and Ti(*i*-PrO)$_4$ in the presence of unactivated 4 Å MS (50 mg of unactivated 4 Å MS against 200 mg of BINOL) in CH$_2$Cl$_2$ afforded (*R*)-1-phenylhex-5-en-3-ol in 95% yield with 97.8% ee after 1.5 hours at –15 °C.[12] In our studies on the structure elucidation of the BINOL-group IVB transition metal complexes by Fourier transform ion cyclotron resonance (FT-ICR) mass spectroscopy,[13] a 2:1 mixture of BINOL and Ti(*i*-PrO)$_4$ in CH$_2$Cl$_2$ in the presence of unactivated 4 Å MS formed a large cluster which contains multiple Ti atoms (calculated mass = 1819.0445). ^{1}H NMR spectral analyses of the complex revealed that a mixture of an uncharacterizable BINOL/Ti complex and BINOLs exists in CD$_2$Cl$_2$; however, hydroxyl groups of unclustered BINOLs were shifted from 5.05 ppm to 5.12 ppm.[14] The low field change in chemical shift observed for BINOL-OHs indicates that unclustered BINOLs coordinate with the BINOL/Ti complex. Ti(*i*-PrO)$_4$ is known to form Ti-oxo species such as [Ti$_7$O$_4$](OR)$_{20}$, [Ti$_8$O$_6$](OR)$_{20}$, and [Ti$_{12}$O$_{16}$](OR)$_{16}$ with trace amounts of water through Ti(*i*-PrO)$_3$(OH).[15] On the

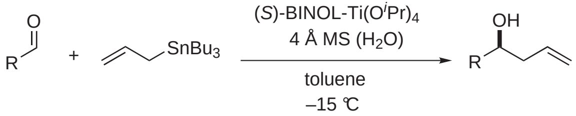
SYNLETT 2005, No. 7, pp 1109–1112
Advanced online publication: 14.04.2005
DOI: 10.1055/s-2005-865202; Art ID: S00205ST

basis of the irreproducibility of the formation of an active catalyst in strictly anhydrous CH_2Cl_2 and by analyses of an active catalyst via FT-ICR and ^{1}H NMR spectroscopy, it was concluded that trace amounts of water contaminating the reaction mixture were responsible for the formation of an active catalyst. In active catalyst formation unactivated 4 Å MS were efficient as a water donor source. Interestingly, an active catalyst could also be generated with a large amount of activated 4 Å MS[16] (more than 200 mg of activated 4 Å MS against 200 mg of BINOL).[17] We observed pronounced solvent effect; when the reaction was carried out in toluene, the allylstannation of hydrocinnamaldehyde using 2.5 mol% catalyst generated in the presence of activated 4 Å MS afforded (*R*)-1-phenylhex-5-en-3-ol in 90% yield with 97.8% ee after 36 hours at –15 °C. On the other hand, the same reaction in CH_2Cl_2 required 5 mol% catalyst to attain the same conversion yield with comparable selectivity. We have applied the optimized conditions to structurally diverse aldehydes and representative results are summarized in Table 1. In most cases the enantioselectivities of the products were remarkably high; allylations of the achiral aldehydes were complete within 36 hours and the isolated products exhibited greater than 95% ee (entries 1–5). The allylation of the alkynal gave rise to the propargyl alcohol with satisfactory selectivity (entry 6); asymmetric allylations of alkynals that are controlled via the cyclic transition state usually result in unsatisfactory selectivities (75–85% ee). Thus, the catalytic asymmetric allylation reactions described here can be utilized for the syntheses of relatively large amounts of optically active homoallylic alcohols; we have demonstrated allylation of the aldehydes on a 10 g scale (Table 1, entries 1 and 2), however, theses conditions were not applicable to aromatic aldehydes and cinnamaldehyde (Table 1, entries 7–9).



Scheme 1 Catalytic allylstannation of (±)-**1**

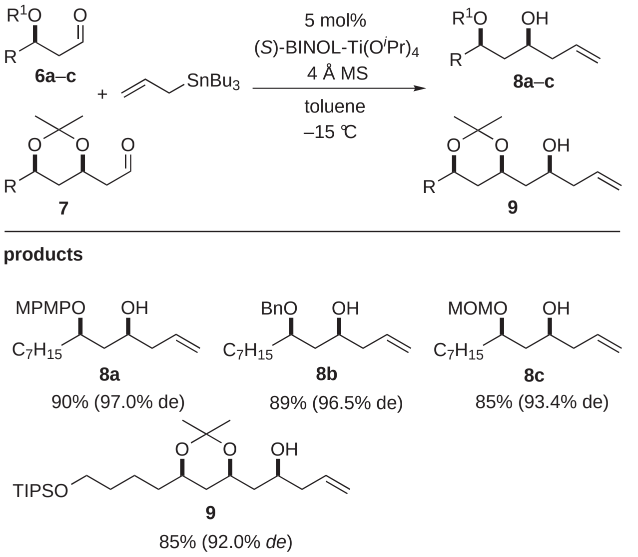
Table 1 Catalytic Asymmetric Allylstannations of Aldehydes[a]



Entry	Aldehyde (R)	Catalyst (mol%)	Time (h)	Yield (%)	ee (%)
1	$PhCH_2CH_2$	2.5	36	90	97.8[b]
2	C_8H_{17}	2.5	36	85	95.0[c]
3	$TBSOCH_2CH_2$	2.5	36	75	95.0[b]
4	$BnOCH_2CH_2$	2.5	36	90	95.5[b]
5	$TBDPSOCH_2(CH)_3CH_2$	2.5	36	93	97.5[b]
6	$C_5H_{11}C{\equiv}C$	2.5	24	85	90.0[c]
7	Ph	10	36	30	95.0[b]
8	*p*-MeOPh	10	36	10	–
9	*trans*-PhCH=CH	10	36	15	–

[a] All reactions were carried out at 2.0 M concentration.
[b] Determined by the HPLC analysis on a Chiralcel OD column.
[c] Determined by ^{1}H NMR spectroscopic analysis of its Mosher ester.

Although catalytic asymmetric allylations through acyclic transition states would be useful for chiral aldehydes such as β-hydroxyaldehydes, few such applications were found in the literature.[18] In addition, the diastereoselectivities of allylated products seem to be significantly influenced by the protecting groups used. As described above a 2:1 mixture of BINOL and Ti(*i*-PrO)$_4$ in the presence of unactivated 4 Å MS formed a rather large catalyst which might interact with the functional groups at the β-position of aldehydes. To investigate how the BINOL/Ti catalyst ignores the β-chiral center of aldehydes, we first conducted an allylation reaction of a racemic β-hydroxyaldehyde possessing a MPM protecting group, (±)-**1**. As illustrated in Scheme 1, the separation of diastereomers of the acetates **2a** and a mixture of **3a** and **4a** followed by analyses of their Mosher's esters revealed that catalytic allylation of (±)-**1** afforded 37.2:12.8 ratio of *anti*- and *syn*-products which originated from (*S*)-3-(4-methoxybenzyloxy) decanal [(*S*)-**1**]. On the other hand, under these conditions (*R*)-**1** was converted to the *syn*-product exclusively.[19] The *syn*-selective catalytic asymmetric allylation observed for a racemic aldehyde was confirmed by the catalytic asymmetric allylations of several optically pure (*R*)-3-hydroxylaldehyde derivatives, **6a**–**c** and **7** (Scheme 2).[20]



Scheme 2 Catalytic asymmetric allylstannations of chiral aldehydes

In general due to the high oxophilicity of Lewis acids, allylstannations of chiral β-hydroxyaldehydes results in favor of chelation-controlled products (*anti*-products).[21] We reported that BINOL-Zr(*t*-BuO)$_4$ mediated *anti*-selective catalytic asymmetric allylstannations of β-hydroxyaldehydes protected with a variety of protecting groups. The diastereoselectivities observed in the allylation reactions of a series of chiral aldehydes using the BINOL/Zr complex clearly indicates that it is difficult to attain high *syn*-selectivity.[8c] Therefore, BINOL/Ti mediated *syn*-selective catalytic allylstannations of β-alkoxyaldehydes is complementary to the BINOL/Zr system; the BINOL-Zr system can be utilized for the syntheses of *anti*-1,3-diol units, on the other hand, the BINOL-Ti system furnishes high *syn*-1,3-diol products.

In conclusion, allylstannations of aldehydes can be achieved with low catalytic loading of the BINOL/Ti complex which is effectively generated from a 2:1 mixture of BINOL and Ti(*i*-PrO)$_4$ in the presence of unactivated or a large amount of activated 4 Å MS, which act as a controllable water donor source. The allylation reactions of achiral aldehydes proceeded within 36 hours at –15 °C and the enantiomeric excess of the homoallylic alcohols are greater than 95%. The catalytic asymmetric allylstannations via the BINOL-Ti(*i*-PrO)$_4$ system are very useful for the syntheses of *syn*-1,3-polyol units.

(*R*)-Undec-1-en-4-ol; Typical Procedure (Table 1, entry 2)

To a stirred mixture of (*S*)-BINOL[22] (560 mg, 1.96 mmol) and activated 4 Å MS (1.12 g) in anhyd toluene (150 mL) was added Ti(*i*-PrO)$_4$ (278 mg, 0.98 mmol). The reaction mixture was stirred for 2.5 h at r.t. At –15 °C allyltributyltin (39 g, 118 mmol) and octanal (10.0 g, 78.4 mmol) were added. After 36 h at –15 °C, a 2:1 mixture of powdered CsF/CsOH (20 g) and silica gel (40 g) were added.[23] The reaction mixture was stirred for an additional 2 h and all volatiles were evaporated in vacuo. Purification by silica gel chromatography (hexanes–EtOAc–CH_2Cl_2, 20:1:2 to 10:1:2) afforded (*R*)-undec-1-en-4-ol (11.4 g, 85%), $[a]_D^{27}$ +6.9 (*c* 1.0, $CHCl_3$).

Acknowledgment

This work was supported by The Florida State University. Dr. Alan Marshall and Mr. Robert Bossio are gratefully acknowledged for high-resolution mass spectral measurements. We thank Dr. Albet E. Stiegman for a useful discussion on the Ti oxides.

References

(1) (a) Heathcock, C. H. In *Asymmetric Synthesis*, Vol. 3; Morison, J. D., Ed.; Academic Press: New York, **1984**, 111. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203.

(2) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewiez, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.

(3) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J.-C. *J. Org. Chem.* **1990**, *55*, 4109.

(4) For other useful chiral allylating reagents see: (a) Riediker, M.; Duthaler, R. O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 494. (b) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *92*, 807. (c) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807; and references cited therein.

(5) (a) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *54*, 1481. (b) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561. (c) Marshall, J. A.; Tang, Y. *Synlett* **1992**, 653. (d) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490. (e) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161.
(f) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392. (g) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977. (h) Nakajima, M.; Saito, M.;

Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 641. (i) Chataigner, I.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, *120*, 6419. (j) Hanawa, H.; Kii, S.; Asao, N.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 5543. (k) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763; and references cited therein. (l) For catalytic asymmetric Barbier-type reactions see: Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248; and references cited therein.

(6) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8268. (b) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827. (c) Yu, C.-M.; Choi, H.-S.; Yoon, S.-K.; Jung, W.-H. *Synlett* **1997**, 889.

(7) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001.

(8) (a) Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897. (b) Casolari, S.; Cozzi, G. C.; Orioli, P.; Tagliavini, E.; Umani-Ronchi, A. *Chem. Commun.* **1997**, 2123. (c) Kurosu, M.; Lorca, M. *Tetrahedron Lett.* **2002**, *43*, 1765.

(9) Weigand, S.; Brückner, R. *Chem.–Eur. J.* **1996**, *2*, 1077.

(10) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, *296*, 267.

(11) Powdered 4 Å MS (available from Aldrich) were used for this study.

(12) In our hands the same reaction under the reported conditions by Keck[6b] afforded (*R*)-1-phenylhex-5-en-3-ol in 50% yield with 75.0% ee. For an analogous observation see reference 9.

(13) Senko, M. W.; Hendrickson, C. L.; Emmett, M. R.; Shi, S. D. H.; Marshall, A. *J. Am. Soc. Mass Spectrom.* **1997**, *8*, 970.

(14) ^{1}H NMR spectra (300 MHz, CD_2Cl_2) of (*S*)-BINOL and the active BINOL/Ti complex.

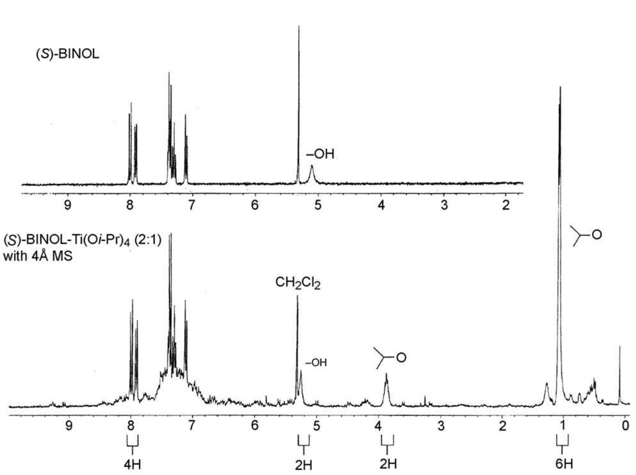


Figure 1

(15) (a) Jones, A. C.; Leedham, T. J.; Wright, P. J.; Crosbie, M. J.; Fleeting, K. A.; Otway, D. J.; O'Brien, P.; Pemble, M. E. *J. Mater. Chem.* **1998**, *8*, 1773. (b) Hubert-Pfalzgraf, L. G. *J. Mater. Chem.* **2004**, *14*, 3113; and references cited therein.

(16) Powdered 4 Å MS (available from Aldrich) were activated at 200 °C under high vacuum for 12 h, it is believed that water still remained inside activated 4 Å MS. Activated 3 Å and 5 Å MS were less effective in the formation of an active catalyst than 4 Å MS.

(17) The allylstannation of hydrocinnamaldehyde using the complex generated in the presence of 50–100 mg of activated 4 Å MS [against 200 mg of (*S*)-BINOL] afforded (*R*)-1-phenylhex-5-en-3-ol in 70–80% yields with 60–70% ee. The same scale experiment using the complex generated with 150 mg of activated 4 Å MS afforded the product in 82% yield with 85% ee.

(18) (a) Molinski, T. F.; Searle, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 9422. (b) Roush, W. R.; Champoux, J.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989.

(19) We believe that the procedures described here are an expeditious method for the analysis of selectivity of chiral reagent against chiral substrates. For an analogous concept for resolutions of chiral racemic ketons via a chiral reducing reagent see: Kurosu, M.; Kishi, Y. *J. Org. Chem.* **1998**, *63*, 6100.

(20) Stereochemistry of the skipped-triols were confirmed by using Kishi's universal NMR databases see: (a) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 4279. (b) Higashibayashi, S.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1437; and references cited therein.

(21) (a) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (b) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.

(22) (*S*)-BINOL was purchased from Kankyo Kagaku Center Co. Ltd.

(23) A mixture of powdered CsF/CsOH (2:1) and silica gel was effective to remove both Sn and Ti species see: Edelson, B. J.; Stoltz, B. M.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 6729.