Catalytic Asymmetric Synthesis of Homoallylic Alcohols: Chiral Amplification and Chiral Poisoning in a Titanium/BINOL Catalyst System

J. W. Faller,* D. W. I. Sams, and X. Liu

Department of Chemistry, Yale University
New Haven, Connecticut 06511-8118

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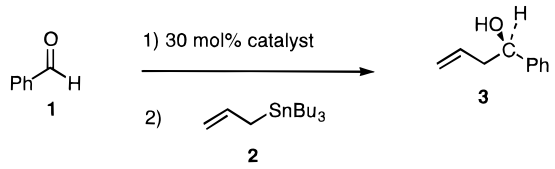
Efficient methods for the enantioselective Lewis acid-catalyzed syntheses of homoallylic alcohols have been discussed in four recent reports.[1] In each case, the catalyst employed was derived from the reaction of $Ti(O\text{-}i\text{-}Pr)_4$ or $TiCl_2(O\text{-}i\text{-}Pr)_2$ with *(R)*- or (*S*)-BINOL. These reactions are synthetically very useful, as all the reagents are readily available from commercial sources; however, the high cost of the resolved *(R)*- or (*S*)-BINOL employed in these reactions is a practical consideration despite one's ability to recycle some of the ligand.[2] We have focused on the reaction of benzaldehyde with allyl tributyltin *via* a modification of a method of Keck employing such a titanium/BINOL catalyst and have found that this system displays chiral amplification and chiral poisoning phenomena.[1b] The chiral poisoning strategy allows the use of the much less expensive racemic form of BINOL[2] in this reaction while still producing a homoallylic alcohol with high enantiomeric purity.

We began by investigating the reaction in which partially resolved BINOL (0.6 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (0.6 mmol) were heated under reflux in CH_2Cl_2 (4 mL) in the presence of 800 mg of 4 Å molecular sieves (ms) for 1 h before addition of benzaldehyde **1** (2 mmol) at room temperature and subsequent addition of allyltributyltin **2** (2.2 mmol) at −78 °C. Under these conditions, the catalysts are employed at 30 mol % (titanium to aldehyde).[3] The reaction was allowed to proceed for 70 h at −23 °C before the product was isolated by a modification of the method of Keck.[4] The results, as summarized in Table 1, show a positive nonlinear effect (NLE) in correlating product enantiomeric purity with the ee of the BINOL, i.e., *chiral amplification*. Keck also observed a NLE in an analogous system.[1c] Mikami and Nakai *et al.* have observed a similar NLE in the glyoxylate ene reaction catalyzed by a catalyst derived from $TiX_2(O\text{-}i\text{-}Pr)_2$ (X = Cl or Br) and enantiomerically enriched BINOL.[5] Based on molecular weight studies, they attribute the NLE in this reaction to the formation of dimeric structures of general formula $Ti_2X_4[BINOL]_2$. This suggests that the *meso* dimer, $Ti_2X_4[(R)\text{-BINOL}][(S)\text{-BINOL}]$, has a lower activity than either of the homochiral dimers, $Ti_2X_4[(R)\text{-BINOL}]_2$ or $Ti_2X_4[(S)\text{-BINOL}]_2$. Although the mechanism is uncertain,[6−12] one can rationalize the result by assuming that the dimers are the principal active species and that each reaction occurs at only one titanium center during each cycle. It would follow that the reactivity of a given center is modified by the presence of the other metal. *In effect, one can consider the other end of the dimer as a titanium-containing ligand which modifies the reactivity of the center directly involved in the reaction.* When enantiomerically enriched BINOL is employed in the glyoxylate ene reaction, the monomeric unit formed from the enantiomer of BINOL in lower concentration is effectively sequestered through the formation of the unreactive *meso* dimer. This leaves the remaining BINOL, now in effectively much greater enantiomeric excess (ee), to be contained in homochiral dimers of much greater activity. Thus, relatively small ee's in the BINOL can produce much greater ee's in the product. While we have not carried out molecular weight determinations, it is probable that a similar mechanism is involved in the chiral amplification found in the asymmetric allylation reaction. This suggests that the *meso* dimer $Ti_2(O\text{-}i\text{-}Pr)_4[(R)\text{-BINOL}][(S)\text{-BINOL}]$ is less competent as a catalyst than the homochiral dimers $Ti_2(O\text{-}i\text{-}Pr)_4[(R)\text{-BINOL}]_2$ or $Ti_2(O\text{-}i\text{-}Pr)_4[(S)\text{-BINOL}]_2$, and thus chiral amplification is observed.

One might consider that the (*R*)-BINOL−titanium moiety is deactivating the (*S*)-BINOL complex by forming the *meso* dimer, or *vice versa*. This suggested to us that we might be able to develop an even less active dimer by substituting an (*R*)- or (*S*)-BINOL−titanium moiety with a different resolved diol−titanium moiety in the dimeric species.

Table 1. Chiral Amplification in Catalysis with Nonracemic BINOL/Ti Catalysts



(*R*)-BINOL ee (%)[a]	yield of **3** (%)[b]	ee of **3** (%)[c]	configuration of **3**[d]
0	>90	0	
11	>95	26	(*R*)
20	>95	46	(*R*)
33	>95	76	(*R*)
50	>95	81	(*R*)
70, 90, 100	>95	>95	(*R*)

[a] In the nonracemic BINOL, (*R*)-BINOL was in excess. [b] Determined by ^1H NMR measurements on reaction mixtures (after 70 h). The reactions using lower ee catalysts proceeded more slowly. [c] Measured by GC using a cyclodex-B chiral column. [d] Determined *via* optical rotation measurements/GC retention times compared to pure samples of **3** prepared by the method of Keck.[1]

(1) (a) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (c) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543. (d) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827.

(2) For example, prices quoted in the Aldrich catalog (1995) are as follows: (*R*)-BINOL, $219.00 for 5 g; (*S*)-BINOL, $278.00 for 5 g; and racemic BINOL, $18.90 for 5 g.

(3) Keck[1] employs titanium/BINOL systems at 10 mol % (aldehyde to titanium). Since some of the titanium is in the form of reduced activity complexes in our experiments, we employ a higher titanium concentration in these reactions to ensure that the reaction proceeds to completion (see Table 2, entry 1).

(4) The workup procedure was identical to that described in ref 1b (method A), except that chromatographic separation was achieved using preparative TLC plates (silica gel 60 F_{254}) and 5% acetone in hexanes as eluant.

(5) (a) Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623. (b) Kitamoto, D. H.; Imma, H.; Nakai, T. *Tetrahedron. Lett.* **1995**, *36*, 1861−1864.

(6) NLEs can be explained by reactive dimers[7,8] or monomers.[8,9] Assuming that unreactive dimers dissociate into active monomers is also an attractive mechanism;[9] however, dimers as the principal active species have been implicated in some diolate−titanium reactions[5,10,11] owing to a first-order dependence on dimer.[10,11] It is also possible that even higher aggregates, such as trimers, could be important.[11,12]

(7) (a) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357. (b) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430−9439.

(8) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (b) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832−4842.

(9) Corey, E. J. *J. Org. Chem.* **1990**, *55*, 1693.

(10) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113.

(11) Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; Takasugawa, F. *Organometallics* **1994**, *13*, 2218−2229.

(12) Martin, C. Ph.D. Thesis, MIT, Cambridge, MA, 1990. Dimeric[5b] and trimeric structures[7] in crystal structures have been quoted as information from Prof. B. Sharpless. A solid state structure could be that of a more insoluble form and may not represent the nature of important oligomers in solution.

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Table 2. Chiral Poisoning of Racemic BINOL Titanium Isopropoxide

	poison[a] (mmol)					
entry no.	D-DIPT	Ti(O-*i*-Pr)$_4$	R in RCHO	yield of **3** (%)[b]	ee of **3** (%)[c]	configuration of **3**[d]
1	0.00	0.00	Ph	65	0	
2	0.24	0.20	Ph	44	19	(*S*)
3	0.30	0.20	Ph	40	39	(*S*)
4	0.40	0.20	Ph	47	81	(*S*)
5	0.60	0.20	Ph	63	91	(*S*)
6	0.60	0.20	*c*-C_6H_{11}	33	82	(*S*)
7	0.60	0.20	*trans*-PhCH=CH	25	86	(*S*)
8	0.60	0.20	2-furfuryl	37	92	nd[e]

[a] Each catalyst contained 0.4 mmol of racemic BINOL, 0.4 mmol of Ti(O-*i*-Pr)$_4$, 4 mL of CH_2Cl_2, and 800 mg of 4 Å molecular sieves in addition to the poison indicated in this column. [b] Determined by ^{1}H NMR measurements on crude reaction mixtures. [c] Entries 1−5 measured by GC using a cyclodex-B chiral column. Entries 6−8 determined by chiral shift reagent, Eu(hfc)$_3$. [d] Determined *via* optical rotation measurements/GC retention times compared to pure samples of **3** prepared by the method of Keck.[1] [e] Not determined.

This is effectively a chiral poisoning strategy[13,14] for this reaction, *i.e.*, utilizing a catalyst synthesized from racemic BINOL and then selectively deactivating one enantiomeric moiety of the catalyst with a poison. The utility of such a strategy has previously been demonstrated by us with asymmetric hydrogenation catalysts prepared from racemic phosphines.[13] *The important feature of the model described above to explain the NLE is that one titanium monomer unit can act as a poison to deactivate another. This suggests that the best poison would be a titanium complex, not a purely organic inhibitor.*

The poisons chosen were derived from Ti(O-*i*-Pr)$_4$ and an enantiopure chiral diol in a 1:1 to 1:3 stoichiometry and were generated *in situ* during the preparation of the catalyst. In a typical reaction, racemic BINOL (0.4 mmol), diisopropyl D-tartrate (DIPT) (0.2−0.6 mmol), and Ti(O-*i*-Pr)$_4$ (0.6 mmol) were heated under reflux in CH_2Cl_2 (4 mL) in the presence of 4 Å molecular sieves (800 mg) for 1 h. Benzaldehyde **1** (2 mmol) was then added at room temperature before addition of allyltributyltin **2** (2.2 mmol) at −78 °C. The resulting mixture was kept at −23 °C for 70 h before workup as previously described.[1] Our results are summarized in Table 2. Moderate to good ee's were observed in **3** depending upon the specific diol employed. Diethyl L-tartrate gave the (*R*)-product with PhCHO; whereas (2*R*,3*R*)-(−)-2,3-butanediol gave the (*S*)-product in 68% ee. The best results were obtained with a poison produced from DIPT and Ti(O-*i*-Pr)$_4$. *It should be noted that the Ti(O-i-Pr)$_4$/tartrate poison mixtures displayed no catalytic activity on their own in the reaction of **1** with **2**.*

In an effort to understand the mechanism of this poisoning phenomenon, we carried out a series of reactions employing resolved BINOL under a protocol similar to that for the poisoning reactions discussed above. When (*R*)-BINOL, DIPT, and Ti(O-*i*-Pr)$_4$) were heated under reflux for 1 h before addition of **1** and **2**, no product **3** was observed after 70 h at −20 °C. In contrast, when (*S*)-BINOL, DIPT, and Ti(O-*i*-Pr)$_4$ were heated under reflux for 1 h before addition of **1** and **2**, the chiral alcohol **3** was observed in 20% yield (>95% ee) after 70 h at −20 °C. The addition of the DIPT/Ti(O-*i*-Pr)$_4$ poison therefore appears to deactivate the (*R*)-BINOL catalyst more effectively than the (*S*)-BINOL catalyst. Hence, addition of this poison to a catalyst derived from racemic BINOL leads to preferential deactivation of the (*R*)-BINOL catalyst and the observed ee's of **3**.[15] We attribute the chiral poisoning behavior to the probable formation of the mixed dimeric species Ti$_2$(O-*i*-Pr)$_4$[(*R*)-BINOL][DIOL] and Ti$_2$(O-*i*-Pr)$_4$[(*S*)-BINOL][DIOL]. When the diol is diisopropyl D-tartrate, the mixed dimer containing (*R*)-BINOL is less active than that containing (*S*)-BINOL, and this leads to the observed ee's observed in **3**.[16]

The Ti(O-*i*-Pr)$_4$/[DIPT] complex did not catalyze the reaction, whereas the Ti(O-*i*-Pr)$_4$/[(*rac*)-BINOL] was a rather poor catalyst and gave racemic product. A fascinating feature of this system is that mixing two mediocre catalysts produces a new one of reasonable activity that gives a high ee.

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(15) In an alternative procedure, the titanium tartrate poison was prepared separately and then added to the titanium catalyst prepared from racemic BINOL. This catalyst also showed chiral poisoning phenomena, but the best results were obtained by preparing the mixture *in situ*.

(16) The role of the excess tartrate is unclear. We presume that *n* is probably 2, but could possibly be 1 in the Ti$_2$(O-*i*-Pr)$_{2n}$[BINOL][DIOL]$_{3-n}$. Depending on relative equilibrium constants, (DIPT)$_x$Ti$_y$(O-*i*-Pr)$_z$ complexes would make a portion of the total number of (DIPT)Ti monomeric units unavailable to form dimers containing (*R*)-BINOL (analogous to the "reservoir effect" [7b]). We presume that the improvements in ee with higher concentrations of DIPT are a consequence of shifting equilibria to produce more deactivated Ti$_2$(O-*i*-Pr)$_4$[(*R*)-BINOL][DIPT]. Although displacing two O-*i*-Pr from Ti(O-*i*-Pr)$_4$ is straightforward,[10] removing all of the *i*-OPr groups from the titanium should be more difficult.[5b] Excess tartrate could also potentially slow other acid-catalyzed routes that might competitively yield low ee product. We are continuing our efforts to determine the nature of the various complexes in these mixtures.