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New Homochiral Cyclic Diol Ligands for Titanium Alkoxide Catalyzed Phosphonylation of Aldehydes

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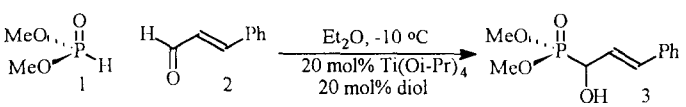
Abstract: An investigation of the structural effects of chiral diol ligands on the enantioselectivity of phosphonylation was performed. Cyclic diols, and cyclohexanediol in particular, were identified as effective ligands for titanium alkoxide catalyzed asymmetric phosphonylation.

Chiral α-hydroxyphosphonates are biologically active,[1] and are flexible precursors for other α and γ substituted phosphonates.[2] The fact that the biological activity is often dependent on the absolute configuration of the α-position has resulted in a growing interest in methods for the asymmetric synthesis of hydroxyphosphonates.[3-5] Potentially, the most efficient and economic route to these compounds involves enantioselective catalysis.[4,5] Recently, the research of our group and others has been directed toward the development of metal alkoxide based catalytic systems for the Pudovik reaction,[5] and has resulted in the introduction of lanthanide,[5a-d] titanium,[5d,e] and aluminum[5f] catalyst systems.

In 1993, Shibuya reported[5d] that complexes of $Ti(O^iPr)_4$ and Binol or Taddol were ineffective asymmetric catalysts for hydrophosphonylation. However, the complex formed by mixing $Ti(O^iPr)_4$ and diisopropyl L-tartrate (1:1) catalyzed the addition of diethyl phosphite to benzaldehyde with 53% ee and 75% yield. We had observed similarly low enantiomeric excesses with Binol and Taddol,[6] and the intriguing success of the tartrate ligand prompted us to investigate the effect of ligand structure on the level of asymmetric induction.



The addition of dimethyl phosphite **1** to cinnamaldehyde **2** was selected as the reaction system for screening catalysts. The allylic hydroxy phosphonate **3** has been well characterized in our own laboratories[7] and the enantiomers are easily separated by HPLC.[8a] As a starting point, the complex formed by mixing

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diisopropyl tartrate **4** and $Ti(O^iPr)_4$ was examined (Table 1). In contrast to the reported reactions with aromatic aldehydes, the product was formed with a disappointingly low enantiomeric excess (13%).[9] Changing the ester group from isopropyl (**4**) to benzyl (**5**) led to a marked improvement in enantiomeric excess. It has been shown that the ester groups of the tartrate coordinate to the titanium and help to define the complex structure.[10] Diols **6** and **7**, prepared by the Sharpless asymmetric dihydroxylation reaction,[11] were examined to investigate the effect of deleting one or both esters groups. Loss of one ester group had little effect on the enantioselectivity (38%), whereas loss of both ester groups had dramatic effect (7%). Indeed we have observed that acyclic diols are typically a poor choice of ligand for asymmetric phosphonylation.[12] Thus, it appears that acyclic diols require at least one adjacent ester group for effective asymmetric induction.

Carbohydrates are naturally occurring cyclic polyols, which by selective protection, can provide a large number of cyclic diols as potential ligands.[13] Diols **8-13** were obtained by hydrogenation of triacetyl glucal, methanolysis and selective re-protection of the primary (C-6) hydroxyl.

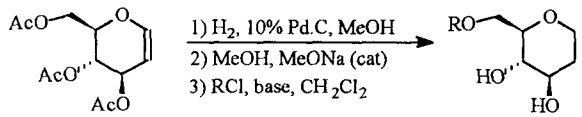
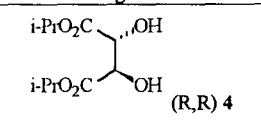
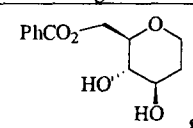
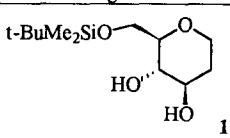
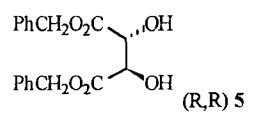
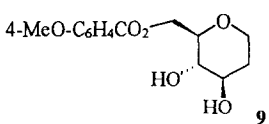
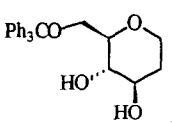
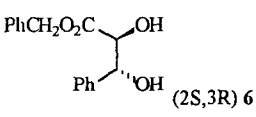
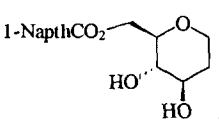
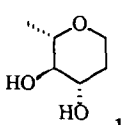
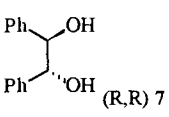
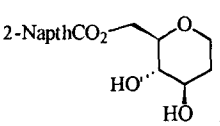
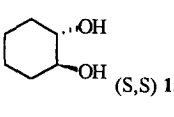


Table 1. The effect of ligand structure on the titanium akoxide catalyzed phosphonylation of cinnamaldehyde with $(MeO)_2P(O)H$

Ligand	E.e., %	Ligand	E.e., %	Ligand	E.e., %
 (R,R) **4**	13	 **8**	49 (S)	 **12**	40
 (R,R) **5**	43-51 (R)	 **9**	45	 **13**	50
 (2S,3R) **6**	38 (S)	 **10**	44	 **14**	39 (R)
 (R,R) **7**	7 (S)	 **11**	54	 (S,S) **15**	67-70 (R)

Enantiomeric excess was determined by HPLC on a Whelk-O column, EtOH/hexanes.

Catalysts formed by mixing the diols **8-13** with $Ti(O^iPr)_4$ in a 1.1:1 ratio proved to be effective for the phosphonylation of cinnamaldehyde providing hydroxyphosphonate **3** with uniformly modest enantiomeric excesses (40 to 54%). The enantiomeric excess appeared to be independent of the substituent at C-6. This

observation was given further support when complete removal of the oxygen atom at C-6 (from rhamnose **14**) caused only a marginal drop in stereoselectivity. Moreover, the least complex system of all, cyclohexanediol **15**,[15] gave an improved enantiomeric excess (70%).

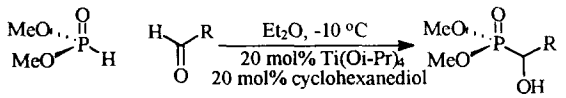
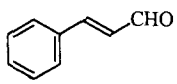
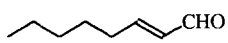
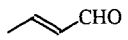
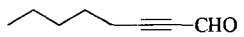
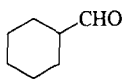


Table 2. The phosphonylation of aldehydes with $(MeO)_2P(O)H$ using (*S,S*) cyclohexanediol and $Ti(O^iPr)_4$

Entry	Aldehyde	Enantiomeric Excess,[a] %	Yield %	Configuration[c]
	X			
a	NO_2	52	58	R
b	CF_3	55	73	(R)[d]
c	F	62	44	R
d	Cl	53	66	R
e	H	64	51	R
f	Me	64	69	(R)[d]
g	OMe	57	65	R
h	NMe_2	64	61	R
i		67-70	45	R
j		60[b]	44	(R)[d]
k		65[b]	72	(R)[d]
l		49[b]	82	(R)[d]
m		42[b]	48	(R)[d]

a) Determined by HPLC on a Whelk-O column, EtOH/hexanes, 1:9. b) determined by ^1H NMR spectroscopy, see ref 14, c) determined by comparison of optical rotation and order of elution from HPLC column to known values, see ref 8; d) Inferred from NMR shift measurements and order of elution from HPLC column (ref 8).

The complex formed between (*S,S*) cyclohexanediol and $Ti(O^iPr)_4$ was investigated further. Dimethyl phosphite was added to a series of aldehydes (Table 2). Reaction with *para* substituted aromatic aldehydes showed that the electronic nature of the aldehyde had little effect on the stereoselectivity. In general, the selectivities using unoptimized conditions were within 50-60% e.e. for most of the aldehydes studied. Therefore, the catalysts prepared from cyclohexanediol appear to hold some promise. We are currently studying cyclohexanediol and other carbohydrate motifs in an effort to optimize the reaction conditions and stereoselectivity.

General Procedure: To anhydrous (*1S, 2S*)-*trans*-1, 2 cyclohexane diol (49.9 mg, 430 μmole) was added freshly distilled Et_2O (3.5 mL), followed by distilled $Ti(O^iPr)_4$ (116 μL, 391 μmole). The mixture was allowed to sit for 30 min. to insure complete complexation (diol dissolves). The aldehyde (2 mmole) was added, followed by distilled dimethyl phosphite (216 μL, 2.4 mmole). The flask was placed in the freezer at approximately -10 °C. After 13 hours, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with

deionized water (60 mL). The CH_2Cl_2 layer was collected and the aqueous layer was extracted a second time with CH_2Cl_2 (50 mL). The extracts were combined and washed with deionized water (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*.

Acknowledgments

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