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High enantio- and diastereoselective induction of BINOL- and TADDOL-modified vinyloxy ethoxides in C–C coupling reactions with aldehydes

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Abstract—The basic reagent vinyloxyethoxy titanium trisisopropyloxide, easily modified by replacing two of the isopropyloxides with the optically active diol (*R*)- or (*S*)-BINOL, reacts with simple, prochiral aldehydes to give chiral β-hydroxy-1,3-dioxolanes with enantiomeric ratios up to 99:1. The same reagents, (*R*)- or (*S*)-configured, react with the chiral 2,3-*O*-isopropylidene-D-glyceraldehyde to give the corresponding open chain pentose derivatives. The main components have opposite descriptors at the newly created stereogenic center, indicating strong reagent control. A comparable system, modified by (*R*,*R*)- or (*S*,*S*)-TADDOL shows a weaker induction with the chiral aldehyde, but now with the same product configuration for both reagents, indicating predominant substrate control.

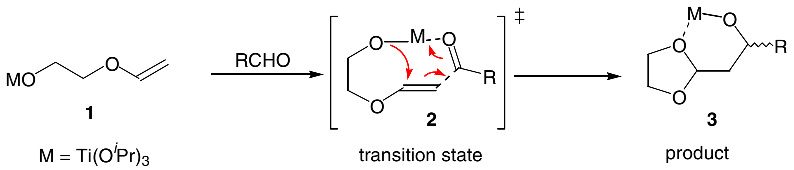
1. Introduction

Vinyloxy ethoxides with a Lewis acidic and/or coordinating counter ion react with aldehydes to yield β-hydroxy-1,3-dioxolanes (Scheme 1).

Experimental and also theoretical considerations of this new reaction principle are in agreement with the idea, that the reaction proceeds via a transition state, in which the metal coordinates the educts to a cyclic nine-membered arrangement, resulting in C–C and C–O σ-bond formation.[1,2] The stereochemical course of the reaction can be affected independently by chiral induction from an aldehyde,[2] by (*E*/*Z*)-configurations in the vinyloxy moiety,[2] and by C_2-symmetry[3] in the underlying diols of the reagent. We now report the observation that (*R*)- or (*S*)-BINOL[4] and (*R*,*R*)- or (*S*,*S*)-TADDOL[5] modified trisisopropyloxy titanium+ exhibits a fourth independent very simple possibility to influence the stereochemical course of the reaction.

Scheme 2 describes the formal generation of the reagents. While the reaction of $ClTi(O^iPr)_3$ with sodium vinyloxy ethoxide **8** generates the basic reagent **1**, now in a separate step, the chiral diols (*R*)- or (*S*)-BINOL or (*R*,*R*)- or (*S*,*S*)-TADDOL are set into equilibrium with the chloro titanium alcoholate. Molecular sieves promote faster equilibration of the reaction mixture. This solution is then treated in the usual way.

The structure of the chiral reagents, described as monomers in Scheme 2 is not proven, due to the dynamic equilibrium, titanium alcoholates may undergo. Also dimeric structures for Ti-species as described here have



Scheme 1. General scheme for the reaction of vinyloxy ethoxides with aldehydes.

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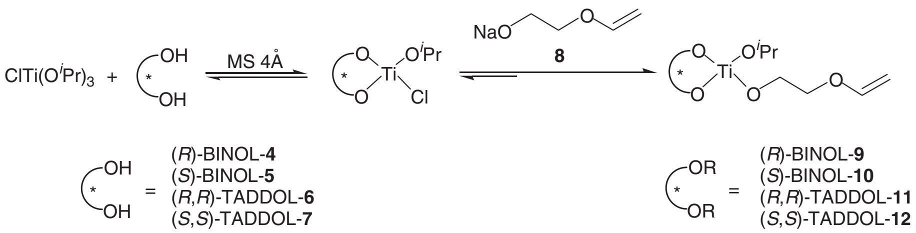


Scheme 2. Formation of the reagents **9**–**12**.

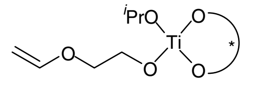
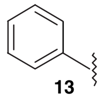
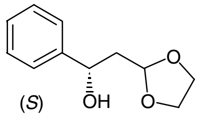
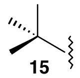
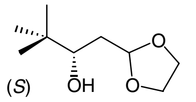
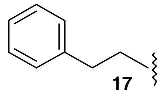
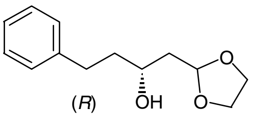
been proposed.[6] The structures of the reagent in Scheme 2 may be regarded as proposals, derived from the stoichiometric composition of the solution.

2. Results and discussion

(*R*)-BINOL **4** reacts with the prochiral benzaldehyde **13** to the corresponding β-hydroxy-1,3-dioxolane **14** (Table 1). The enantiomeric ratio is 92.5:7.5 in favor for the (*S*)-configuration at C-3. With 2,2-dimethylpropanal **15**, bearing the bulky *tert*-butyl group, the e.r. is 95.5:4.5 also with (*S*)-configuration at C-3 for the main compound **16**. 3-Phenylpropanal **17** shows the best stereochemical result with an e.r. of 99:1. The descriptor of the main product **18** is now (*R*) at C-3, according to the CIP-rules, but the absolute configuration is the same as in the examples given before, D with regard to 1,3-dioxolane.

The reaction of the chiral 2,3-*O*-isopropylidene-D-glyceraldehyde **19** with the reagent modified with (*R*)-BINOL **4** leads in an excellent yield of 95% to the corresponding diastereomers with a diastereomeric ratio of 94:6 in favor of the (3*S*)-configured open chain 2-deoxypentose derivative (3*S*)-**20** (Table 2). Nearly the same d.r. of 93:7 is found, now with (3*R*)-configuration at C-3 of (3*R*)-**20**, when (*S*)-BINOL **5** is applied, indicating strong reagent control for the C–C and C–O bond forming process to yield the β-hydroxy-1,3-dioxolane. The reactions of (*R*,*R*)- or (*S*,*S*)-TADDOL-**11**, respectively, **-12** with the glyceraldehyde derivative **19** are lower in yield (77%, respectively, 85%) and induction (d.r. 82:18 for (*R*,*R*)-TADDOL-**11** and 71:29 for (*S*,*S*)-TADDOL-**12**). Interestingly for both enantiomeric reagents they show the same configuration (3*R*) for the predominant stereoisomer (3*R*)-**20**. Figure 1 describes the assumed situation leading to the transition state. The bulky phenyl substituents shield the Ti^{4+}-cation in such a strong way, that the aldehyde function of **19** can only contact the Ti^{4+} by approaching with the less hindered side to one of the phenyl groups (see arrows). As a consequence of this, the mobile vinyloxy moiety has to enter the C–C bond forming trajectory from the opposite side. The stereochemical situation is nearly identical for both TADDOLato-configurations. There should be a slight difference, due to the fact, that for the (*R*,*R*)-TADDOL-**11** the destabilizing interactions with the aldehyde **19** should be lower, than for the (*S*,*S*)-TADDOL-**12** (compare red bonds in Fig. 1). This might be reflected in the small differences for the diastereomeric ratios, found experimentally. Here, straight substrate control seems to operate.

Table 1. Results of the enantioselective C–C coupling reactions

Chiral Ti-reagent[a]	R	Products[b,c]		Yield (%)[d]
 (*R*)-BINOL-**9**	 **13**	 **14**	e.r. 92.5:7.5	70
	 **15**	 **16**	e.r. 95.5:4.5	54
	 **17**	 **18**	e.r. 99:1	62

[a] BINOL: 1,1′-Binaphthyl-2,2′-diol.

[b] Enantiomeric ratios determined by GC-analysis of the crude product.

[c] The assignments of the configurations were established by chiroptical methods (CD of the corresponding methyl xanthogenate).[7,8]

[d] Isolated yield.