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Enantioselective Preparation of C_2-Symmetrical 1,4-Diols

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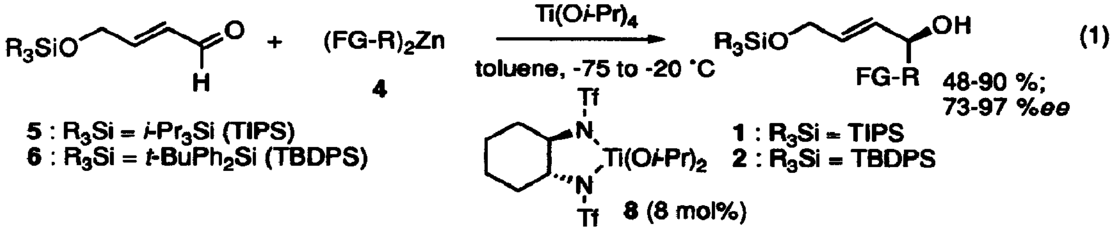
*Summary: The catalytic enantioselective addition of functionalized dialkylzincs to the γ-alkoxyaldehydes 5, 6 and 7 provides 1,4-diols 1-3 with 73-99 %ee. After a simple reaction sequence, these diols are converted to chiral γ-alkoxyaldehydes which undergo a second catalytic enantioselective addition of the same diorganozinc providing C_2-symmetrical 1,4-diols **10a-f** with excellent diastereoselectivity (up to 97 : 3).*

C_2-Symmetrical molecules are important chiral building blocks and C_2-symmetrical 1,4-diols have been especially useful for the preparation of new chiral phosphine ligands of interest for asymmetric catalysis.[1] These 1,4-diols have been prepared by enzymatic reductions[2] or by transformations of molecules from the chiral pool.[3] Herein, we wish to report a new catalytic asymmetric preparation of 1,4-diols of type **1**, **2** or **3** involving addition of functionalized diorganozincs **4** to γ-alkoxyaldehydes **5**, **6** or **7** in the presence of the chiral catalyst **8**[4] (eq 1 and 2). The aldehydes **5**, **6** and **7** were prepared in 2 steps from (*Z*)-2-butene-1,4-diol[5] and 1,4-butanediol in 56-73 % overall yield. The functionalized dialkylzincs **4** were conveniently obtained by treating the corresponding alkyl iodides FG-RI with Et_2Zn (1.3 equiv, neat, 55 °C, 3-18 h) in the presence of CuI or CuCN (0.3 mol %).[6] The addition of $(FG\text{-}R)_2Zn$ (2.5 - 3.0 equiv) to the aldehydes **5-7** (1.0 equiv) in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ (2 equiv) and the catalyst **8** (8 mol%) is complete within a few hours at temperatures between -75 to -15 °C and produces the protected 1,4-diols **1-3** with good enantioselectivity (Table I). Whereas the addition of unfunctionalized zinc reagents proceeds with uniformly high enantiomeric excesses (entries 1, 2, 10 and 11), differences are observed with functionalized dialkylzincs and an interference of the functional group present in the organometallic reagent is observed.



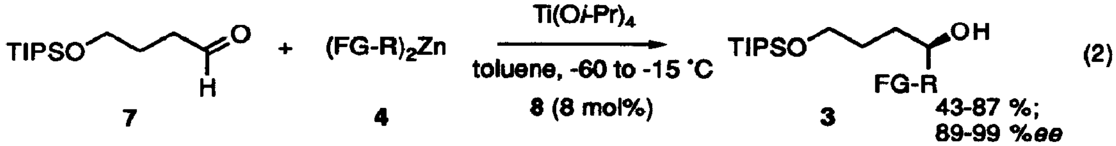
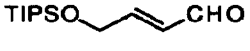
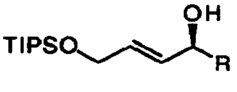
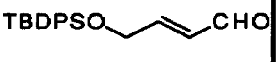
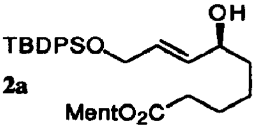
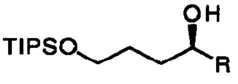


Table I. 1,4-Diols **1**-**3** obtained by the catalytic asymmetric addition of dialkylzincs **4** to the aldehydes **5**-**7**.

entry	aldehyde	$(FG\text{-}R)_2Zn$ FG-R	product	yield[a] (%)	*ee*[b] (%)
					
1	**5**	Et	**1a**: R = Et	90	94
2	**5**	Oct	**1b**: R = Oct	88	90
3	**5**	$(CH_2)_3OPiv$	**1c**: R = $(CH_2)_3OPiv$	63	97
4	**5**	$(CH_2)_4OAc$	**1d**: R = $(CH_2)_4OAc$	60	87
5	**5**	$(CH_2)_4OPiv$	**1e**: R = $(CH_2)_4OPiv$	58	95
6	**5**	$(CH_2)_4Cl$	**1f**: R = $(CH_2)_4Cl$	76	96
7	**5**	$(CH_2)_3N(Tf)Bn$	**1g**: R = $(CH_2)_3N(Tf)Bn$	48	73
8	**5**	$(CH_2)_4CO_2Ment$	**1h**: R = $(CH_2)_4CO_2Ment$	50 (48)[c]	56 (81)[c]
9	 **6**	$(CH_2)_4CO_2Ment$	 **2a**	68	78
					
10	**7**	Et	**3a**: R = Et	77	96
11	**7**	Pent	**3b**: R = Pent	87	99
12	**7**	$(CH_2)_3OPiv$	**3c**: R = $(CH_2)_3OPiv$	62	96
13	**7**	$(CH_2)_4OAc$	**3d**: R = $(CH_2)_4OAc$	65	89
14	**7**	$(CH_2)_4OPiv$	**3e**: R = $(CH_2)_4OPiv$	69	95
15	**7**	$(CH_2)_5OPiv$	**3f**: R = $(CH_2)_5OPiv$	43	96
16	**7**	$(CH_2)_4Cl$	**3g**: R = $(CH_2)_4Cl$	72 (58)[c]	93 (96)[c]

[a] Isolated yield of analytically pure products. [b] Determined by preparing the corresponding *O*-acetylmandelates using (*S*)-(+)-*O*-acetylmandelic acid. In each case, a calibration sample using (±)-*O*-acetylmandelic acid was prepared (ref. 10). [c] $Ti(Ot\text{-}Bu)_4$ was used instead of $Ti(Oi\text{-}Pr)_4$ and the reaction was performed at 0 °C.

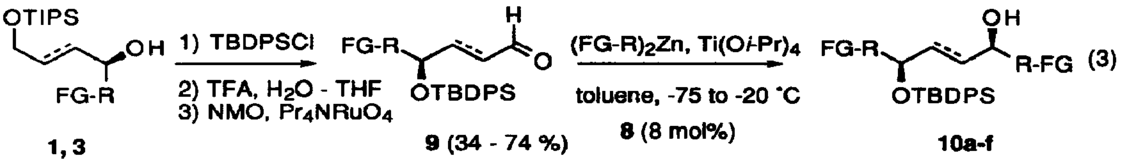
Thus, bis(4-acetoxybutyl)zinc adds to the aldehyde **5** with 87 %*ee* (entry 4) and aldehyde **7** with 89 %*ee* (entry 13), whereas the sterically more demanding bis(4-pivaloxybutyl)zinc adds to the same aldehydes with 95 %*ee* (entries 5 and 14). This difference is attributed to the poorer chelating ability of the pivaloxy group with the zinc metallic center compared to that of the acetoxy group. A chelating functionality deactivates the zinc reagent and will slow down alkoxy ligand exchange processes at the chiral titanium center. These are vital for the *catalytic* nature of the enantioselective addition. The alkoxide exchange kinetics may also be reflected by the temperature dependence of the enantioselectivity of the addition reaction. We found that sterically non-demanding zinc reagents, such as Et_2Zn, show the usual temperature dependence of the enantiomeric excess. Thus, the addition of Et_2Zn to the aldehyde **5** at -50 °C gives 85 %*ee*, whereas at -75 °C, an enantioselectivity of 94 %*ee* is observed. In the case of less reactive dialkylzincs (Oct_2Zn and ester functionalized diorganozincs), an inverse temperature dependence is observed (Table II) and a higher enantioselectivity is obtained at higher temperature. In these cases, a reaction temperature between -30 and -15 °C furnishes the highest enantiomeric excess. Higher reaction temperatures again lead to lower enantioselectivities. This behavior can be explained by assuming, that with less reactive dialkylzincs the exchange processes at the chiral titanium are slow compared to the addition rate and higher temperatures are required to regenerate the chiral titanium catalyst. In the case of the addition of a nitrogen containing zinc reagent (eg. $Zn((CH_2)_3N(Tf)Bn)_2$) a deactivation of the zinc reagent by the basic nitrogen atom occurs and an enantioselectivity of only 73 %*ee* is obtained (entry 7).

Table II. Temperature dependence of the enantiomeric excess in the addition of a dialkylzinc to the aldehyde **5**.

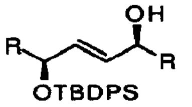
Oct_2Zn						$(PivO(CH_2)_3)_2Zn$			
T (°C)	-75	-65	-50	-45	-45 to -25	T (°C)	-50	-25	-20
ee (%)	42	60	83	90	90	*ee* (%)	44	95	97

Usually, ester substituted zinc reagents of the type $Zn((CH_2)_nCO_2R)_2$ (n = 2-4) give moderate enantioselectivities,[6a,7] however, an enantiomeric excess of 81 %*ee* can be reached by using a menthyl ester and $Ti(Ot\text{-}Bu)_4$ instead of $Ti(Oi\text{-}Pr)_4$.[8] The use of the sterically highly hindered aldehyde **6** gives similar results (entries 8 and 9). Finally, a variety of dialkylzincs add to the *saturated* γ-alkoxyaldehyde **7** with excellent enantioselectivity (entries 10-15). A yield erosion occurs with the less reactive functional dialkylzincs. It seems to be due to a competitive enolization of the aldehyde **7**. These addition reactions can be scaled up, and bis(3-pivaloxypropyl)zinc (3 equiv) has been added to the aldehyde **5** (1 equiv) on a 30 mmol-scale affording **1c** in 63 % yield (7.31 g) with 97 ± 1%*ee*.[9]

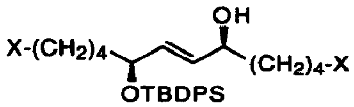
The products **1** and **3** can be readily converted, via a simple reaction sequence ((i) TBDPSCl, imidazole, DMF (ii) TFA, H_2O-THF (iii) NMO, Pr_4NRuO_4 cat, CH_2Cl_2), into γ-alkoxyaldehydes **9**, which, after the addition of a second equivalent of $(FG\text{-}R)_2Zn$ in the presence of **8**, furnish the C_2-symmetrical 1,4-diol derivatives **10a**-**10f** with an excellent diastereoselectivity determined by ^1H- and ^{13}C-NMR (eq 3).



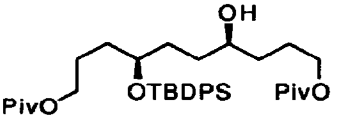
1, 3 **9** (34 - 74 %) **10a-f** (3)



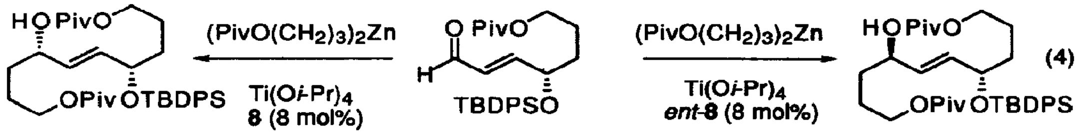
10a : R = Et; 66 % (96: 4)
10b : R = Oct; 70 % (97: 3)



10c : X = Cl; 68 % (97: 3)
10d : X = OAc; 69 % (94: 6)



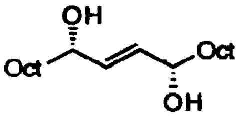
10e : 61 % (96 : 4)



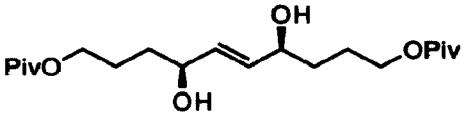
10f : 73 %; > 97: 3 **9a** **10g** : 64 %; > 97: 3

The configuration of newly formed chiral center depends only on the configuration of the titanium catalyst and *not* on the configuration of the chiral center already present in the molecule. Thus, the addition of a zinc reagent to the aldehyde **9a** in the presence of the (*R*,*R*)-catalyst **8** provides the C_2-symmetrical 1,4-diol derivative **10f** (73 %; >94 %*de*), whereas carrying out the same reaction in the presence of the (*S*,*S*)-catalyst (*ent*-**8**) produces the *meso*-1,4-diol derivative **10g** (64 %; >94 %*de*); eq 4. A similar selectivity is observed in the preparation of **10e**; the (*R*,*R*)-catalyst **8** leads to the (*S*,*S*)-diol derivative (61 %; 96 : 4), whereas the (*S*,*S*)-catalyst (*ent*-**8**) produces the corresponding *meso*-diol derivative (56 %; 96 : 4).[11] The removal of the Si-protecting group of compounds **10** (TBAF, THF, 55-65 °C, 12-21 h) gives the free 1,4-diols **11a** (96 % from **10b**) and **11b**

(66 % from **10f**). Further transformations of the C_2-symmetrical 1,4-diols, as well as applications of 1,4-diols in catalytic asymmetric synthesis, are underway in our laboratories.



11a



11b

Acknowledgments.

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9. *Typical procedure.* Preparation of (4*S*)-(*E*)-4-hydroxy-7-triisopropylsiloxy-5-heptenyl pivalate **1c** (30 mmol scale experiment).(a) Preparation of bis(3-pivaloxypropyl)zinc: A 250 mL three-necked flask was charged with 3-iodopropyl pivalate (180 mmol, 48.6 g), CuI (0.3 mol%, 0.54 mmol, 103 mg) and Et_2Zn (1.3 equiv., 234 mmol, 24.0 mL). The reaction mixture was warmed to 55 °C (oil bath temperature) and was stirred for 14 h. The flask was connected to the vacuum (0.1 mm Hg) and ethyl iodide and excess Et_2Zn were distilled off (55 °C, 2 h). Decane (10 mL) was added and pumping was continued for 1 h. This procedure was repeated twice and the zinc reagent was then diluted with toluene (60 mL).
   (b) Preparation of the alcohol **1c**. In a 250 mL three-necked flask, $Ti(Oi\text{-}Pr)_4$ (60 mmol, 17.9 mL) and catalyst **8** (8 mol%, 2.4 mmol, 908 mg) in toluene (20 mL) were warmed to 50 °C for 0.5 h. After cooling to -60 °C, the dialkylzinc solution, as prepared above, was slowly added. The mixture was stirred for 0.5 h and warmed to -20 °C. The aldehyde **5** (30 mmol, 7.27 g) in toluene (5 mL) was added and the reaction mixture was stirred for 12 h. After usual workup (Et_2O, 10% HCl), the organic layer was treated with 10% NaOH to remove the catalyst and was dried ($MgSO_4$). The resulting crude oil was purified by chromatography (hexanes - ether 4:1 to 1:1) to afford the pure product as a yellow oil (18.9 mmol, 7.31 g, 63%, 97%*ee* ; $[\alpha]^{25}_D = +1.1$ (c = 7.0, benzene)). The enantiomeric excess was determined by ^1H-NMR analysis of its derivative with (*S*)-(+)-*O*-acetylmandelic acid and comparison with the spectrum of the racemic material (ref.10).
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