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Enantioselective synthesis of 1-(1,3-dioxolan-2-yl)-3-pentanol from 3-(1,3-dioxolan-2-yl)-propanal by catalytic ethylation†

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Abstract

The catalytic enantioselective ethylation of 3-(1,3-dioxolan-2-yl)-propanal by diethylzinc in the presence of various β-aminoalcohol precatalysts is presented. The enantiocontrolled alkylation step was accomplished with enantiomeric ratios of up to 86:14 and chemical yields ranging from 38 to 81% for the resulting 1-(1,3-dioxolan-2-yl)-3-pentanol.

1. Introduction

Acetals are one of the most widely used and versatile protecting groups in organic synthesis with broad applications in the protection of carbonyl, hydroxyl and diol functions.[1] The versatility of acetals prompted us to use 1,3-dioxolan-2-yl-substituted aliphatic aldehydes as precursors for the synthesis of potential chiral building blocks such as (γ-hydroxyalkyl)aldehydes containing a stereogenic secondary alcohol function. The results published in this paper are an extension of our previous studies on the diethylzinc addition to 1,3-dithian-2-yl substituted aldehydes.[2]

2. Results and discussion

For the ethylation of straight chain aliphatic aldehydes possessing a cyclic *O*,*O*-moiety, 3-(1,3-dioxolan-2-yl)-propanal was chosen as a model substrate. The precatalysts tested in this reaction are: (+)-*N*-methyl-ephedrine (ligand *A*),[3] (*all-R*)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane (*B*),[4] (*all-R*)-3-(dibenzylhydroxymethyl)-2-azabicyclo[3.3.0]octane (*C*)[5] and (*S*)-*N*-methyl-2-(diphenylhydroxymethyl)azetidin (*D*).[6]

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Besides the often substantially diminished enantioselectivities observed with aliphatic substrates,[7] a significant 'ligand acceleration' caused by the 1,3-dioxolane substructure[8] had to be taken into account.

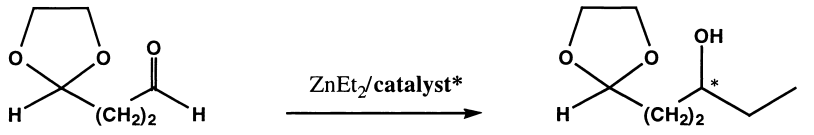
The results and further experimental details of the process optimization utilizing precatalyst *A* are displayed in Table 1 (entries 1–8). Yield, reaction rate and enantioselectivity of the alkylation product-1-(1,3-dioxolan-2-yl)-3-pentanol are dependent on the molar ratios of diethylzinc to aldehyde: only an almost racemic reaction product (entry 5; *e.r.*: 53: 47) is obtained in 51% yield when 1 equiv. of diethylzinc is employed (Scheme 1)

To get this yield the reaction time had to be increased to 120 h. With 2 equiv. of diethylzinc (entry 7; yield: 63%, reaction time: 48 h) an improved enantiomeric ratio of 76:24 is reached. The

Table 1
Enantioselective addition of diethylzinc to 3-(1,3-dioxolan-2-yl)-propanal[9] at room temperature (20–25°C) catalyzed by ligands *A*, *B*, *C* and *D*; product: 1-(1,3-dioxolan-2-yl)-3-pentanol

Entry	Ratios of aldehyde : $ZnEt_2$[a]	Ligand*[b]	Conc. [mol%]	Time [h]	Yield[c] [%]	*e.r.*[d]
1	1 : 1	*A*	3	24	10	-[e]
2	1 : 1	*A*	3	48	25	-[e]
3	1 : 1	*A*	3	72	29	-[e]
4	1 : 1	*A*	3	96	43	-[e]
5	1 : 1	*A*	3	120	51	53 : 47
6	1 : 2	*A*	3	24	53	-[e]
7	1 : 2	*A*	3	48	63	76 : 24
8	1 : 4	*A*	3	48	81	78 : 22
9	1 : 2	*B*	3	40	60	83 : 17
10	1 : 4	*B*	3	40	53	84 : 16
11	1 : 2	*C*	3	40	53	76 : 24
12	1 : 2	*D*	3	40	38	86 : 14

[a] A solution of diethylzinc in hexane (1M) with addition of toluene (hexane:toluene = 1:1) was used; [b]: *A*: (+)-*N*-methyl-ephedrine[3], *B*: (*all-R*)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane[4], *C*: (*all-R*)-3-(dibenzylhydroxymethyl)-2-azabicyclo[3.3.0]octane[5], *D*: (*S*)-*N*-methyl-2-(diphenylhydroxymethyl)-azetidine[6]; [c]: Isolated yield after flash chromatography on aluminium oxide, eluent: dichloromethane; the product is obtained as colorless oil; [d]: Determination by NMR spectroscopy after derivatization with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride[10]; [e] *e.r.* not measured.



3-(1,3-dioxolan-2-yl)-propanal 1-(1,3-dioxolan-2-yl)-3-pentanol

Scheme 1.

chemical yield is further increased to 81% (entry 8) when an excess amount of 4 equiv. of diethylzinc is used, while on the other hand, the enantiomeric ratio is only slightly influenced (entries 7 and 8, *e.r.* values: 76:24 versus 78:22). The same—in terms of enantioselectivity—applies to ligand *B* (entries 9 and 10).

With *e.r.* values of 84:16 and 86:14 (entries 10 and 12), structures *B* and *D* exhibit a fair performance—considering the low precatalyst concentration of only 3 mol% used in these reactions. On the other hand, the isolated yield of the addition product (38%) reached with ligand *D* is disappointingly low.

In conclusion, the catalytic enantioselective addition of diethylzinc to aliphatic 1,3-dioxolan-2-yl aldehydes provides a practical method for the preparation of enantiomerically enriched γ-hydroxy-substituted building blocks. A significant improvement of this process by further variation of the chiral ligand and by increasing the precatalyst concentration should be possible.

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8. A significant 'ligand acceleration' for the otherwise very slow diethylzinc addition to benzaldehyde caused by substrate-like compound 1,3-dioxane was observed, yielding the corresponding racemic secondary alcohol. With a concentration of 50 and 100 mol% 1,3-dioxane (*RS*)-1-phenylpropan-1-ol is obtained in 50 and 54% yield, respectively, after a reaction time of 24 h.
9. The starting material 3-(1,3-dioxolan-2-yl)-propanal was synthesized by a new approach via selective dethioacetalization of 1-(1,3-dioxolan-2-yl)-2-(1,3-dithian-2-yl)-ethane according to a method published by: Vedejs, E.; Fuchs, P. L. *J. Org. Chem*. **1971**, *36*, 366. The reaction product 1-(1,3-dioxolan-2-yl)-3-pentanol has, so far, only been described as a racemic compound: Ponglux, D.; Wongseripipatane, S.; Aimi, N.; Nishimura, M.; Ishikawa, M.; Sada, H.; Haginawa, J.; Sakai, S. *Chem. Pharm. Bull*. **1990**, *38*, 573. Here we describe, for the first time, the NMR data of 1-(1,3-dioxolan-2-yl)-3-pentanol: ^{1}H NMR ($CDCl_3$): 4.82 (t, $J=4.5$ Hz, 1H, OC*H*O), 3.85 (m, 4H, OCH_2CH_2O), 3.65–3.30 (m, 1H, C*H*OH), 2.42 (s, 1H, O*H*), 2.00–1.30 (m, 6H, $3\times CH_2$), 0.91 (t, $J=7.5$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 104.73 (OCHO), 72.86 (*C*HOH), 64.96 (2C, OCH_2CH_2O), 31.08 (C1), 30.30 (C2), 30.20 (C4), 9.88 (C5).
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