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Catalytic enantioselective addition of diethylzinc to 1,3-dithian-2-yl substituted aliphatic aldehydes: a new approach to optically active 2-(hydroxyalkyl)-1,3-dithianes†

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Abstract

Asymmetric synthesis of 2-(hydroxyalkyl)-1,3-dithianes was achieved in good yields of up to 81% by using various 1,3-dithian-2-yl-substituted aliphatic aldehydes as substrates in the catalytic enantioselective addition of diethylzinc. With fair enantiomeric ratios of up to 85:15 in the enantiocontrolled ethylation step this synthetic approach provides an entry towards potential chiral building blocks.

1. Introduction

The broad application of 1,3-dithianes as protecting groups for the carbonyl functionality,[1] as nucleophilic acyl anion equivalents,[2] or as masked methylene functions,[3] prompted us to develop a general synthetic approach to chiral 2-(hydroxyalkyl)-1,3-dithianes which give access to highly versatile chiral building blocks such as (hydroxyalkyl)aldehydes or -ketones with a stereogenic secondary alcohol function. The enantiocontrolled catalytic dialkylzinc reaction seemed to hold considerable promise in this direction since the starting materials—1,3-dithian-2-yl substituted aldehydes—are readily available from 1,3-dithianes,[4] and deprotection of the resulting alkylation products **2** accomplished by various methods[5] should result in the desired products.

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2. Results and discussion

Initial experiments were focused on the evaluation of some general aspects of the diethylzinc reaction: looking at the results displayed in Tables 1 and 2 it becomes apparent that the ethylation of short chain aliphatic aldehydes possessing a cyclic *S,S*-moiety would pose difficulties. The problems in reaching satisfactory enantioselectivities in the reaction of short, straight chain aldehydes[6] are displayed in Table 1 (four examples, maximum e.r.: 83:17, entry 4).

Table 1
Enantioselective addition of diethylzinc to aliphatic aldehydes at room temperature catalyzed by ligands *A* and *B*

Entry	Substrate	Equiv. of $ZnEt_2$	Solvent	Ligand*[a]	Conc. [mol%]	Product	Yield[b] [%]	*e.r.*[c]
1	ethanal	1	hexane	*A*	3	2-butanol	24	71 : 29
2	propanal	1	hexane	*A*	3	3-pentanol	40	-[d]
3	hexanal	1	hexane	*A*	3	3-octanol	77	78 : 22
4	heptanal	1	toluene	*B*	5	3-nonanol	78	83 : 17

[a]: *A*: (+)-*N*-methyl-ephedrine[10a], *B*: (*all-R*)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane[10b]; [b]: Isolated yield after 48 h reaction time; [c]: Determination of the enantiomeric ratio by NMR spectroscopy after derivatization with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride[7]; [d] *e.r.* not measured.

Table 2
Addition of diethylzinc to benzaldehyde at room temperature (20–25°C) catalyzed by 1,3-dioxane, 1,3-dithiane and 2-methyl-1,3-dithiane; product: (*RS*)-1-phenylpropan-1-ol; reaction time: 24 h

Entry	Substrate	Equiv. of $ZnEt_2$	Solvent	Catalyst	Conc. [mol%]	Yield[a] [%]
5	benzaldehyde	1	toluene	1,3-dioxane	50	50
6	benzaldehyde	1	toluene	1,3-dioxane	100	54
7	benzaldehyde	1	toluene	1,3-dithiane	50	41
8	benzaldehyde	1	toluene	2-methyl-1,3-dithiane	50	67

[a]: Isolated yield of (*RS*)-1-phenylpropan-1-ol after fractional distillation.

Table 2 demonstrates a significant 'ligand acceleration' for the otherwise very slow diethylzinc addition to benzaldehyde[7] caused by substrate-like structures such as 1,3-dithiane (or 1,3-dioxane). Thus, the reaction rate of the catalyst-promoted ethylation reaction, which has to be considerably faster than the competing substrate-catalyzed pathway (yielding the corresponding racemic secondary alcohols and responsible for low *e.r.*s), is of utmost importance for an efficient stereoselective conversion of 1,3-dithian-2-yl substrates.

To slow down the unwanted side reaction and to enhance the accelerating effect and the stereocontrol of the catalyst a non-polar solvent—hexane—was chosen. Due to the precipitation of a diethylzinc/dithiane complex in hexane/toluene mixtures (Table 3, entry 9)—significantly diminishing the aldehyde concentration in solution—the isolated yield after 48 h reaction time is

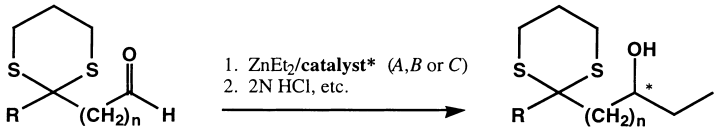
Table 3
Enantioselective addition of diethylzinc to 1,3-dithian-2-yl-substituted aliphatic aldehydes (substrate **1a–c**[11–13]) at room temperature (20–25°C) catalyzed by ligands *A*, *B* and *C*; products: **2a–c**

Entry	Substrate [**1a-c**]	Equiv. of $ZnEt_2$	Solvent	Ligand*[a]	Conc. [mol%]	Time [h]	Yield[c] [%]	*e.r.*[d]
9	**1a**[11]	4	hexane[b]	*A*	3	48	6	53 : 47
10	**1a**	2	toluene	*A*	3	10	31	-[e]
11	**1a**	2	toluene	*A*	3	20	69	-[e]
12	**1a**	4	toluene	*A*	3	20	63	-[e]
13	**1b**[12]	2	toluene	*A*	3	20	69	72 : 28
14	**1b**	2	toluene	*B*	3	20	76	85 : 15
15	**1b**	2	toluene	*C*	3	20	67	75 : 25
16	**1c**[13]	2	toluene	*A*	3	20	72	71 : 29
17	**1c**	2	toluene	*B*	3	20	81	77 : 23
18	**1c**	2	toluene	*C*	3	20	80	76 : 24

[a]: *A*: (+)-*N*-methyl-ephedrine[10a], *B*: (*all-R*)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane[10b], *C*: (*all-R*)-3-(dibenzylhydroxymethyl)-2-azabicyclo[3.3.0]octane[10c]; [b] Entry 9: a solution of diethylzinc in hexane (1M) was used with addition of toluene (hexane:toluene = 1:1); [c]: Isolated yield after flash chromatography on silica gel, eluent: dichloromethane; products **2a-c** are obtained as colorless to slightly colored oils; [d]: Determination by NMR spectroscopy after derivatization with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride[7]; [e] *e.r.* not measured.

only 6%. The molar ratio of diethylzinc to 3-(2-methyl-1,3-dithian-2-yl)propanal had to be increased to 3:1 to get a detectable conversion of the substrate. An excess of more than 4 equiv. diethylzinc in hexane does not increase the yield any further (entry 9).

As a consequence, toluene was chosen as the solvent for the following experiments. An excess of 2 equiv. of diethylzinc in toluene,[8] and a reaction time of 20 h at room temperature, proved to be sufficient for the conversion of 1,3-dithian-2-yl substituted aldehydes (entries 10–12): 1-(2-methyl-1,3-dithian-2-yl)-3-pentanol (product **2a**, Scheme 1), 1-(1,3-dithian-2-yl)-3-pentanol (product **2b**) and 1-(2-phenyl-1,3-dithian-2-yl)-2-butanol (product **2c**) are obtained in maximum yields of 69, 76 and 81% (Table 3, entries 11, 14 and 17), respectively. The limitations in terms of enantioselectivity using (+)-*N*-methyl-ephedrine (Table 3, ligand *A*: entries 9, 13 and 16) as the catalyst precursor prompted us to test other ligands (*B* and *C*)[9] to improve the stereocontrol in the ethylation reaction. The results obtained with these ligands are also given in Table 3: With *e.r.*s ranging



1a (R = CH_3 , n = 2)
1b (R = H , n = 2)
1c (R = Phenyl , n = 1)

2a (R = CH_3 , n = 2)
2b (R = H , n = 2)
2c (R = Phenyl , n = 1)

Scheme 1.

from 75:25 to 85:15 (Table 3, entries 14, 15, 17 and 18) structures *B* and *C* exhibit a very good performance—considering the low ligand concentration of only 3 mol% used in these reactions.

In conclusion, the catalytic enantioselective addition of diethylzinc to 1,3-dithian-2-yl-substituted aliphatic aldehydes provides a practical method for the preparation of highly versatile, enantiomerically enriched building blocks. With enantiomeric ratios of up to 85:15 (for 1-(1,3-dithian-2-yl)-3-pentanol **2b**) promising results were obtained utilizing only 3 mol% of the catalyst precursor. A process optimization focused on the reaction temperature, catalyst concentration and ligand structure is currently under way.

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9. The following solvents were also tested for the ethylation of 1,3-dithian-2-yl substituted aldehydes: ether, acetonitrile, tetrahydrofurane, acetone, dichloromethane.
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11. Synthesis of 3-(2-methyl-1,3-dithian-2-yl)-propanal **1a** via lithiation of 2-methyl-1,3-dithiane with *n*-butyllithium, alkylation with 2-(2-bromoethyl)-1,3-dioxolane (yield after flash chromatography: 91%) and, finally, removal of the aldehyde-protecting group by hydrolysis with 2N HCl (yield after distillation: 95%), a colorless oil (b.p.: 110°C at 0.2 torr), product characterization by ^{1}H and ^{13}C NMR spectroscopy.

12. Synthesis of 3-(1,3-dithian-2-yl)-propanal **1b** via lithiation of 1,3-dithiane with *n*-butyllithium, alkylation with 2-(2-bromoethyl)-1,3-dioxolane (yield: 88%) and treatment with 2N HCl (yield after distillation: 92%); product: a colorless oil, characterization by ^{1}H and ^{13}C NMR spectroscopy.
13. Synthesis of 2-(2-phenyl-1,3-dithian-2-yl)-ethanal **1c** via lithiation of 2-phenyl-1,3-dithiane with *n*-butyllithium, alkylation with bromoacetaldehyde diethyl acetal (yield: 73%) and treatment with 2N HCl (yield after crystallization from methanol: 71%); product: slightly green crystals; product m.p.: 62°C, characterization by ^{1}H and ^{13}C NMR spectroscopy.