Aldolases as Leitmotiv – A Nonenzymatic Domino Aldol Reaction Triggered by Zinc Bisenolate and Polyenolate (ate) Complexes

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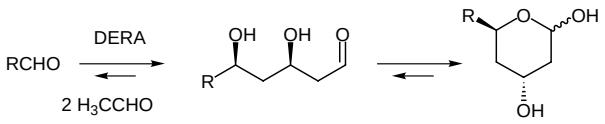
This paper is dedicated to Prof. Dr. M. Christl on the occasion of his 60th birthday

Abstract: A new zinc(II) mediated sequential aldol reaction is described for the diastereoselective one-pot synthesis of tetrahydropyran-2,4-diols. The dependence of the yield on the ratio Zn^{2+}/enolate proposes that zinc(II) polyenolate and ate complexes may be involved.

Key words: aldol reactions, domino reactions, zinc, stereoselective synthesis, hemiacetal

Aldolases are attractive enzymes for synthetic chemistry as they catalyze a variety of C–C bond formation and cleavage reactions, most often with exquisite stereochemical control. Two categories are known: class I aldolases use Schiff base formation with an active-site lysine whereas class II enzymes require a divalent metal ion, in particular zinc. While both protocols have been used frequently for monoaldol formation, the deoxyribose phosphate aldolase (DERA, class I aldolase, see Equation)[1] and its combination with RAMA[2] are able to even catalyze a sequential aldol-aldol addition by reacting two equivalents of an enolizable carbonyl compound with an aldehyde as electrophile to afford tetrahydropyran-2,4-diols that are a part of various important natural products.[3]

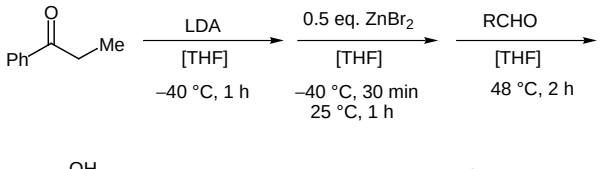


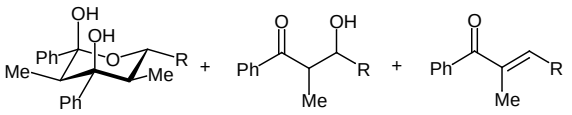
Equation

It is well known that in class II aldolases[4] a zinc ion plays a pivotal role to activate the deprotonation of the carbonyl components and to bind the enol.[5] This simple picture and our recent success with titanium bisenolates[6] suggested to treat in a biomimetic fashion two equivalents of an enolate with an appropriate electrophile in the presence of Zn^{2+} as Lewis acid, despite the fact that zinc(II) has a poor history in aldol reactions,[7,8] and that the naked Zn^{2+} ion makes a poor model for zinc aldolases.[9]

To test our idea we prepared zinc bisenolate **4** from propiophenone by deprotonation with LDA in THF and subsequent reaction with 0.5 equivalents of $ZnBr_2$. The resultant clear solution was subsequently treated with a stoichiometric amount of benzaldehyde (r.t., 2 h) yielding after aqueous work-up **1a** as a single diastereomer besides **2a** and **3a** (see Table 1 and Table 2).[10]

Table 1 Reaction of various Aldehydes with Propiophenone Enolate in the Presence of $ZnBr_2$





1a-i **2a-i** **3a-i**

	Aldehyde RCHO	R	Yield[a] of **1a–i**[b] [%]	Yield[a] of **1a–i**[c] [%]
a	benzaldehyde	H_5C_6-	50	75
b	dimethylaminobenzaldehyde	4-$Me_2NC_6H_4$-	37	62
c	methoxybenzaldehyde	4-$MeOC_6H_4$-	44	69
d	fluorobenzaldehyde	4-FC_6H_4-	45	82
e	furfural	furfuryl-	42	
f	cinnamaldehyde	C_6H_5CH=CH-	10	
g	anthracenecarbaldehyde	9-$C_{10}H_9$-	40	
h	nitrobenzaldehyde	4-$NO_2C_6H_4$-	20	46
i	*iso*-butyraldehyde	*i*-Pr	10	

[a] Yield is based on aldehyde.
[b] Using one equivalent of **4**.
[c] Using two equivalents of **4**.

According to NMR- and X-ray investigations[11] all large substituents in **1a** occupy equatorial positions with only the hydroxyl groups being placed in axial positions.[12] Hence, in this reaction 5 new stereogenic centers are generated in a highly diastereoselective manner giving rise to only 1 out of 16 possible stereoisomers.

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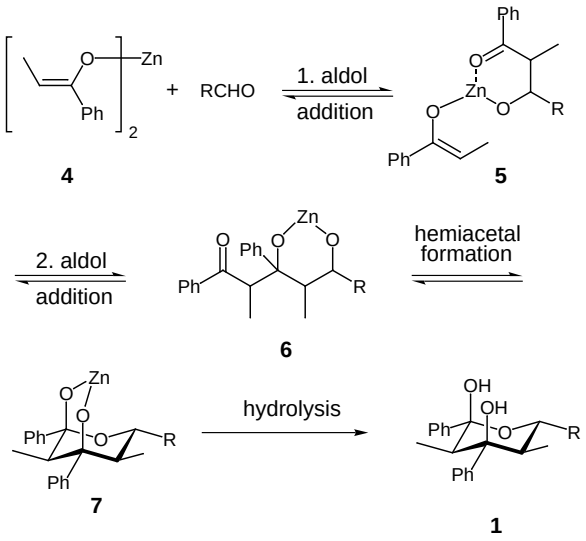
To improve the yields of the domino aldol product **1a** the reaction was studied at various temperatures, i.e. 0 °C, 25 °C, 48 °C and 67 °C. While refluxing the reaction mixture at 67 °C led exclusively to the formation of monoaldol condensation product **3a**, addition of benzaldehyde at room temperature followed by heating of the reaction mixture at 48 °C for 2 hours provided the highest yield of **1a** (50%, see Table 1). Hence, a number of additional aldehydes was studied using the optimized conditions (Table 1).

A straightforward mechanistic proposal for tetrahydropyran-2,4-diol formation is depicted in Scheme 1. At first, a zinc bisenolate **4** is formed that undergoes an aldol reaction with the aldehyde. The resultant zinc aldolate **5** subsequently is attacked intramolecularly by the second enolate. Finally, zinc bound tetrahydropyran-2,4-diol **7** is afforded by intramolecular hemiacetal formation. Under thermodynamic control all large substituents (methyl, phenyl, R) are placed in the equatorial position.



Scheme 1

However, following the mechanism proposed in Scheme 1 it is astounding that only yields of ≤ 50% (with 1 equiv of $ZnBr_2$/2 equiv of enolate) are obtained, which led us to consider the structure of the putative zinc bisenolate in solution. From solid state investigations on related zinc alkoxides[13] and zinc enolate[14] one has to assume that, in solution, dimeric species should prevail with THF acting as additional ligand.

To investigate the role of zinc enolate aggregation we varied the amount of propiophenone enolate with regard to zinc(II) to 3:1 which increased the yield of **1a** (64%; Table 2, entry 3). Further increase of the propiophenone enolate/zinc(II) ratio to 4:1 (entry 2), however, ensued in a sharp decline in the yield. Moreover, the yield of **1a** decayed rapidly (entries 5–7) when the molar amount of aldehyde exceeded the amount of zinc(II). While, at first, this finding indicates that a catalytic route cannot be realized, it also makes clear that with excess aldehyde the equilibrium is shifting from the domino product to the monoaldol products **2a** and **3a**.

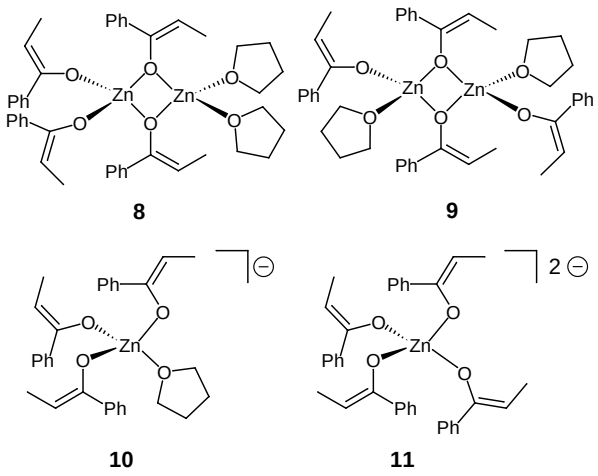
Table 2 Varying the Ratio of Propiophenone Enolate to $ZnBr_2$ in Presence of Benzaldehyde at 48 °C

Entry	PhCHO [equiv]	Propiophenone enolate [equiv]	$ZnBr_2$ [equiv]	**1a** [%]	**2a** [%]	**3a** [%]
1	1	4	2	75	14	1
2	1	4	1	36	35	10
3	1	3	1	64	15	5
4	1	2	1	50	31	7
5	1	2	0.75	32	43	9
6	1	2	0.5	2	36	19
7	1	2	0.25	–	23	7

The combined preparative results in Table 2 are indeed in line with a dimeric species having only one zinc bisenolate reacting to **1**. One could argue that yields ≤ 50% at an enolate to Zn^{2+} ratio of 2:1 (Table 2, entry 4) are due to incomplete enolate formation under our conditions, in particular since doubling the amount of zinc bisenolate leads to a sizeable increase in the yield of **1a** (75%, see Table 2, entry 1). However, three arguments can be raised against such a hypothesis: (i) Enolate formation from propiophenone proved to be quantitative in trapping reactions with trimethylsilylchloride. (ii) Doubling the amount of enolate while keeping the amount of Zn^{2+} constant led to a decrease in yield (36% of **1a**, see Table 2, entry 2). (iii) Keeping the enolate to Zn^{2+} ratio at 4:1 but now decreasing its overall amount by 50% (see Table 2, entry 6) entailed a sharp drop of the yield to 2%. Hence, there is no linear correlation of yield of **1a** and the amount of enolate.

Strong evidence for dimeric species emerges from the results of entries 2–4 in Table 2 as the yield changes from 50% (aldehyde:enolate:Zn^{2+} = 1:2:1) to 64% (1:3:1) and to 36% (1:4:1). Such a trend is most readily understood with structural changes of the reactive zinc(II) enolate species; i.e. a switch from a dimeric zinc bisenolate **8** and/or **9** (enolate:Zn^{2+} = 2:1) to a monomeric ate complex **10** (3:1) and finally to a zinc(II) tetrakisenolate dianion **11** (4:1) (Scheme 2). The latter species is expected to show a reduced reactivity for the sequential aldol reaction as coordination of the monoaldolate to the zinc(II) to activate the carbonyl for the second aldol reaction is certainly impeded.

Overall, the mechanistic investigation shows that the yield of **1** is coupled in a complex manner to the amount of enolate applied. Yields can be increased beyond those in the standard protocol (Zn^{2+}:enolate:aldehyde = 1:2:1) in two ways, both of which are in accordance with dimeric zinc species in solution: (i) Use of an enolate:Zn^{2+} ratio of 3:1 to operate via ate complexes, or (ii) doubling the amount



Scheme 2

of zinc bisenolate (see Table 1, right column) to make up for one unreactive bisenolate caught up in the dimeric Zn_2 species.

With regard to synthetic applications, the present approach is a good alternative to the DERA/RAMA[1,2] catalyzed reaction that has only a limited substrate tolerance. Although not catalytic in nature, various aromatic and aliphatic aldehydes, even containing strongly coordinating substituents and bulky groups, can be treated with zinc(II) bisenolate to afford the highly substituted tetrahydropyran-2,4-diols as one single diastereomer.

In conclusion, we have developed a new strategy using classical, nonbiological zinc(II) chemistry to perform a sequential double aldol reaction leading to heavily substituted tetrahydropyran-2,4-diols in a highly stereoselective manner. Control experiments suggest that dimeric zinc(II) species may play a pivotal role in the process.

Acknowledgement

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(10) **General Procedure**: A solution of diisopropylamine (1.26 mL, 9.0 mmol) in THF (30 mL) was treated at 0 °C with a solution of *n*-butyllithium (3.0 mL, 2.5 M in hexane, 7.5 mmol) and stirred for 15 min. After cooling to –40 °C propiophenone (1.01 mL, 7.50 mmol) was added and the mixture was stirred at –40 °C for 1 h. Then, the appropriate amount of zinc dibromide (usually 3.75 mmol) was added. The yellow reaction mixture was stirred for 30 min at –40 °C and for 1 h at r.t. Now, it was treated with a solution of the aldehyde (3.75 mmol) in THF (30 mL) and the temperature was raised to 48 °C (see Table 1), where it was stirred for 2 h. The reaction was quenched with sat. aq $NaHCO_3$ (50 mL). The layers were separated and the aq layer was extracted three times with diethylether. The combined organic layers were washed with sat. aq NaCl and dried with Na_2SO_4.
(11) The structural identification of the substrates is based on extensive NMR investigations (C,H- and H,H-COSY as well as NOESY), which will be discussed in more detail in the full paper. A X-ray analysis solved recently is in agreement with our assignment, s. Engelen, B.; Panthöfer, M. personal communication.
(12) **1c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.45 (d, ^3J = 7.0 Hz, 3 H), 0.60 (d, ^3J = 7.1 Hz, 3 H), 2.34 (dq, ^3J = 10.8 Hz, ^3J = 7.1 Hz, 1 H), 2.36 (qd, ^3J = 7.0 Hz, ^4J = 1.3 Hz, 1 H), 3.81 (s, 3 H), 3.90 (s, 1 H), 3.95 (s, 1 H), 5.02 (d, ^3J = 10.8 Hz, 1 H), 6.90 (d ^3J = 9.6 Hz, 2 H), 7.19–7.52 (m, 9 H), 7.60–7.82 (m, 3 H); **1d**: ^{1}H NMR (200 MHz, $CDCl_3$): δ =0.45 (d, ^3J = 7.1 Hz, 3 H), 0.60 (d, ^3J = 7.1 Hz, 3 H), 2.35 (dq, ^3J = 10.1 Hz, ^3J = 7.1 Hz, 1 H), 2.36 (qd, ^3J = 7.1 Hz, ^4J = 1.1 Hz, 1 H), 3.90 (s, 1 H), 3.99 (s, 1 H), 5.06 (d, ^3J = 10.1 Hz, 1H), 7.08 (m, 2 H), 7.19–7.52 (m, 9 H), 7.61–7.70 (m, 3 H); **1e**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.49 (d, ^3J = 6.7 Hz, 3 H), 0.56 (d, ^3J = 7.0 Hz, 3 H), 2.32 (q, ^3J = 7.0 Hz, 1 H), 2.70 (dq, ^3J = 11.0 Hz, ^3J = 6.7 Hz, 1 H), 3.82 (s, 1 H), 4.02 (s, 1 H), 5.14 (d, ^3J = 11.0 Hz 1 H), 6.35 (m, 2 H), 7.23–7.43 (m, 8 H), 7.65 (m, 3 H); **1f**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.45 (d, ^3J = 7.1 Hz, 3 H), 0.58 (d, ^3J = 6.9 Hz, 3 H), 2.35 (dq, ^3J = 10.4 Hz, ^3J = 7.1 Hz 1 H), 2.36 (qd, ^3J = 6.9 Hz, ^4J = 1.3 Hz 1 H), 3.66 (s, 1 H), 3.81 (s, 1 H), 4.61 (dd, ^3J = 10.4 Hz, ^3J = 7.1 Hz 1 H), 6.23 (dd, ^3J = 15.8 Hz, ^3J = 7.1 Hz), 6.63 (d, ^3J = 15.8 Hz 1 H), 7.12–7.32 (m, 12 H), 7.53–7.60 (m, 3 H); **1g**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.32 (d, ^3J = 6.8 Hz, 3 H), 0.72 (d, ^3J = 7.2 Hz, 3 H), 2.67 (dq, ^3J = 10.8 Hz, ^3J = 6.8 Hz 1 H), 3.65 (qd, ^3J = 7.2 Hz, ^4J = 1.3 Hz 1 H), 4.13 (d, ^4J = 1.7 Hz 1 H), 4.27 (s, 1 H), 6.9 (d, ^3J = 10.8 Hz 1 H), 7.36–7.41 (m, 8 H) 7.42–7.58 (m, 2 H), 7.67–7.80 (m, 4 H), 7.97–8.07 (m, 2 H), 8.44 (s, 1 H), 8.51 (d, ^3J = 8.6 Hz, 1 H), 9.41 (d, ^3J = 8.8 Hz, 1 H).
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