Stereoselective Synthesis of Tetrahydropyran-2,4-diols by a Simple Domino Aldol-Aldol Hemiacetal One-Pot Reaction

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Dedicated to Professor Rüchardt on the occasion of his 70th birthday

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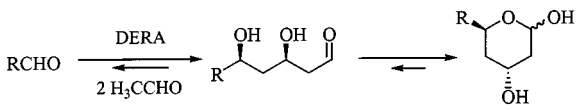
A new metal-directed (Ti, Zr, Al, In, Sn) domino aldol-aldol hemiacetal reaction is presented that can be used for the highly stereoselective de-novo synthesis of tetrahydropyran-2,4-diols containing five stereogenic centers.

Introduction

Over the last few years, the aldolases, a group of enzymes with a huge potential for C−C-bond formation, have been successfully introduced to organic synthesis,[1] especially for the stereoselective formation of carbohydrates and related compounds. While most of these enzymes catalyze the formation of β-hydroxy ketones by a simple aldol addition, 2-deoxyribose-5-phosphate aldolase (DERA)[2] is able to trigger the sequential aldol addition of one aldehyde with two equivalents of another aldehyde (or ketone). By this means, the stereoselective formation of tetrahydropyran-2,4-diols[3] − a ring system that is a part of many biologically active natural products, such as the denticulatins A and B[4] − can be readily accomplished.



The recent report of an artificial, DERA[5]-imitating system prompts us to publish the results of our studies starting twelve months ago about a domino aldol-aldol hemiacetal reaction[6] of metal bis(enolates) that can likewise be used to assemble tetrahydropyran-2,4-diols. While up to now the Cp_2Ti^{II}-based[5] system exclusively works in one single transformation, a formal trimerization of phenylacetaldehyde, our method opens up a completely new construction set to form tetrahydropyran-2,4-diols in a highly stereoselective manner, where the enolate and aldehyde components as well as the metal fragments can be varied.

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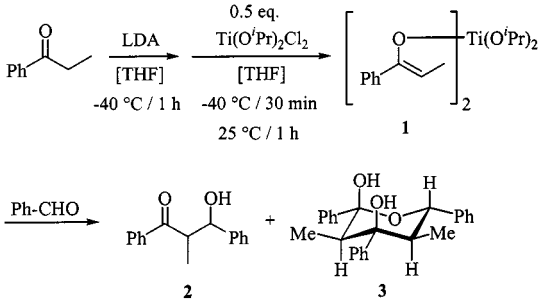
Results and Discussion

We came across this new reaction when we turned our attention from odd-electron[7] to closed-shell electrophiles

in C−C bond-forming reactions of titanium bis(enolates).[8]

For the first test, we chose to use the configurationally well-defined (*Z*)-enolate of propiophenone[9] as the enolate ligand at the titanium fragment.[10] Therefore, propiophenone was deprotonated by LDA in THF and subsequently treated with half an equivalent of $(i\text{PrO})_2TiCl_2$.



Scheme 1. Domino reaction with titanium bis(enolate) **1** and benzaldehyde

The reaction of **1** with a stoichiometric amount of benzaldehyde under the initially choosen conditions (−40 °C, 2 h) led only to the formation of the monoaldol product **2**. Obviously, the conditions were too mild for a successful attack of the second enolate at the titanium-bound **2**. As soon as the reaction mixture was heated to 67 °C for 2 h, the new diastereomerically pure product **3** was obtained. According to NMR-spectroscopic and X-ray analysis,[11] compound **3** was assigned to a tetrahydropyran-2,4-diol structure. It is important to note that all the large substituents occupy equatorial positions whereas the hydroxy groups are placed

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in axial positions in 3,5-dimethyl-2,4,6-triphenyltetrahydropyran-2,4-diol (**3**).

To check the tolerance of the above reaction with regard to other substrates, various aldehydes were used as electrophiles, whereas acetophenone and butyrophenone were employed as alternative enolate precursors (Table 1). While the aldehyde can be altered, there are obviously restrictions concerning the enolate part as long as we use the titanium metal fragment. This can be seen by the failure of the reaction with acetophenone. In all other cases, the tetrahydropyran-2,4-diol with the bulky groups in equatorial positions is the main product.

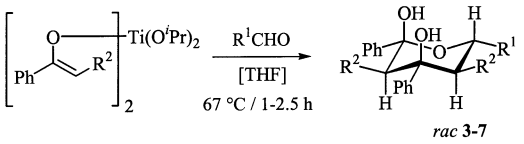

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Table 1. Domino reaction of the different titanium bis(enolate) with aldehydes

R^1	R^2	Product	Yield (%)[a]	Other diastereomers (%)[b]
Ph	Me	**3**	90	–
*i*Pr	Me	**4**	35	6
*n*Pr	Me	**5**	16	15
Ph	Et	**6**	40	–
Ph	H	**7**	–	–

[a] After chromatographic purification; isolated product. – [b] Tetrahydropyran-2,4-diols.

To better understand the reaction mechanism we investigated the temperature dependence of the domino reaction using **1** and benzaldehyde. After separation of the products, their structures were clearly assigned on the basis of NMR-spectroscopic data, even though the relative configuration of two additional diastereomers of **1a** (diastereomer I, II) could not yet be determined.

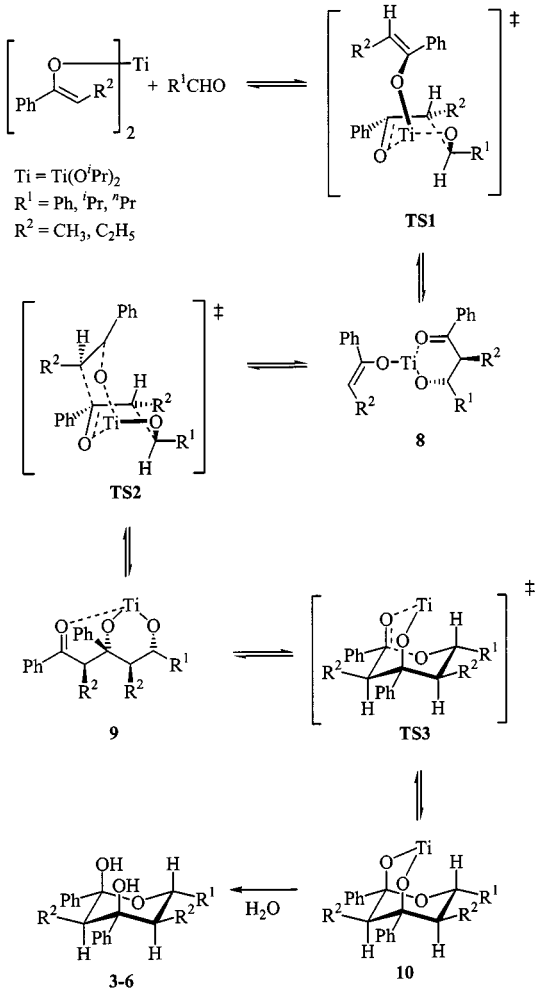
Table 2. Temperature dependence of the domino reaction of **1** with benzaldehyde

T [°C]	*t* [h]	**3** (%)	Diastereomer I (%)	Diastereomer II (%)	**2** (%)[12]
0	2	24	2	7	67
25	2.5	59	8	11	20
67	2	90	–	–	–

Interestingly, the reaction exhibits a higher diastereoselectivity the higher the temperature is, which suggests thermodynamic control of the product formation. As a consequence, the following mechanism seems to be plausible: The first step of the reaction involves an *anti*-selective aldol addition to form **8**[12] (cf. Scheme 2) which even at low temperatures proceeds via a boatlike transition state[13] (**TS1**). Only at higher temperatures will the remaining enolate attack the titanium-coordinated monoaldolate. In the course of the reaction a bicyclic transition state (**TS2**), characterized by one chair- and one boatlike six-membered ring, is likely to form. This transition state allows all large substituents to occupy equatorial positions. In the last step, the titanium alkoxide **9** attacks the carbonyl group by forming the titanium-bound hemiacetal **10**.

A simple reaction analysis with ball-stick models clearly indicates that the two transition states **TS1** and **TS2** are energetically not the most favorable ones. That leads at lower temperatures (kinetic control) to the formation of products diastereomeric to **3**–**6** with alkyl- and/or phenyl groups in axial positions. At higher temperatures with increasing reaction time the titanium-coordinated hemiacetal **10**, however, is formed with increasing stereoselectivity.

This mechanistic picture is supported by the fact that, in the series of electrophiles, viz. benzaldehyde, isobutyraldehyde and *n*-butyraldehyde, increasing amounts of other diastereomers are furnished besides the main products **3**–**5** (cf. Table 1). In the light of thermodynamic control, this result was to be expected because of decreasing A values[14] (in kcal·mol^{-1}: Ph: 2.8; *i*Pr: 2.2, *n*Pr: ca. 1.8).



Scheme 2. Proposed mechanism of the domino reaction

From the analysis of the mechanistic proposal in Scheme 2 the following preliminary requirement profile emerges for the metal fragment: a) it should exhibit Lewis acidity, b) it should be sufficiently electropositive so that both enolate moieties remain sufficiently nucleophilic, and c) it should have a large ion radius so that on its periphery the reaction

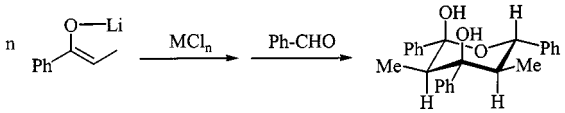


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Table 3. Variation of the metal fragments in the domino reaction of **1** with benzaldehyde

Metal fragment	Conditions[a]	EN[b]	Ion radius of M [pm][c]	Charge density z^2/r [e^{2}Å^{-1}][d]	Yield (%) of **3**[e]
$TiCl_4$	67°C, 2 h	1.32	65 (CN 5)	24.61	50
$ZrCl_4$	r.t., 2 h	1.22	80 (CN 5)	20	45
BCl_3	r.t., 2.5 h	2.01	25 (CN 4)	36	–
$AlCl_3$	r.t., 2.5 h	1.47	53 (CN 4)	16.98	64
$InCl_3$	r.t., 2.5 h	1.49	76 (CN 4)	11.84	85
$SiMe_2Cl_2$	0°C, 0.5 h	1.74	54 (CN 6)	29.63	–[f]
$SnCl_2$	0°C, 2 h	1.72	102 (CN 2)	3.92	–[g]
$SnCl_4$	r.t., 2 h	1.72	76 (CN 5)	21.05	34 (+ 37[h])

[a] Reaction conditions for the reaction with benzaldehyde. – [b] EN: electronegativity by Allred and Rochow.[15] – [c] Ion radius; CN: coordination number. – [d] Charge density, referring to the coordination number during the reaction. – [e] Yield with regard to benzaldehyde. – [f] 73% yield of **2**, when using reaction conditions by Mukaiyama[16] with 1 equiv. of $TiCl_4$. – [g] 69% yield of **2**. – [h] 29 and 8% of diastereomers I and II, respectively.

cascade can take place. To probe this conception various metal halides MCl_n (with $n \geq 2$) were treated with n equivalents of the enolate to the corresponding tris- or tetrakis(enolates). After addition of benzaldehyde these furnished product **3** (reaction analogous to Scheme 1). In Table 3 the optimized reaction conditions are provided.

The results of Table 3 demonstrate that indeed a general reaction takes place that is controlled by an interplay of electronegativity, ion radius and charge density of the metal fragment. Obviously, in boron(III) complexes the ion radius is too small, however, in this case not even the formation of monoaldol product **2** was observed. For silicon(IV) bis(enolates) the small ion radius in combination with the high electronegativity seems to be incompatible with this reaction, while for tin(II) bis(enolates) the charge density is not high enough to initiate the attack of the second enolate.

In principle, it should be possible in the cases of Ti^{IV}, Zr^{IV} and Sn^{IV} to form two molecules of **3** per metal fragment. We have increased the amount of benzaldehyde from one to two equivalents without noting an increase in the yield. It seems that by forming **3** in the hemisphere of the metal the steric hindrance increases so much that the reaction cascade cannot occur a second time.

Our investigations clearly indicate that this new metal-mediated domino aldol-aldol hemiacetal reaction constitutes a highly stereoselective de-novo synthesis of tetrahydropyran-2,4-diols (deoxy sugars), which is even superior to the enzymatic reactions[3] with regard to the substrate tolerance. As in the tandem-aldol Tishchenko reaction sequence[17] all the steps are reversible with the main diastereomer being formed under thermodynamic control. The aforementioned reaction sequence allows a much higher substrate variation than the catalytic pathway, for which only one example is described.[5] In addition, the mechanism of the catalytic route remains unclear and should not include metal bis(enolates).

In a much larger set of experiments we need to clarify to what extent the enolate or the carbonyl component can be varied in this multidimensional reaction array (e.g. different metals, different ligands). Noticeably, from some preliminary investigations it has already become clear that even aldehydes with polar or complexating functionalities such as methoxy or dimethylamino groups are tolerated without any complications.

Experimental Section

General Procedure: Preparation of 6-isopropyl-3,5-dimethyl-2,4-diphenyltetrahydropyran-2,4-diol (**4**): To a solution of diisopropylamine (0.75 mL, 5.5 mmol) in dry THF (30 mL), 3.3 mL of a 1.5 M *n*-butyllithium solution (5.0 mmol) was added at 0 °C. After 15 min, the solution was cooled down to −40 °C, propiophenone (0.67 mL, 5.0 mmol) was added and stirred for 1 h at −40 °C. After addition of neat diisopropoxytitanium dichloride (593 mg, 2.50 mmol), the mixture was stirred for another 30 min at −40 °C as well as 1 h at room temperature. Afterwards, a solution of isobutyraldehyde (0.23 mL, 2.5 mmol) in 20 mL of dry THF was added at room temperature. Then the reaction mixture was refluxed for 1 h and quenched by addition of a saturated solution of ammonium chloride. After the layers had been separated, the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried with sodium sulfate. After removal of the solvent, the crude product was purified by column chromatography on silica gel, first using cyclohexane/ethyl acetate (4:1; $R_f = 0.30$) and then petroleum ether/dichloromethane/ethyl acetate (20:10:1; $R_f = 0.20$). **4** (298 mg, 875 μmol, 35%) was obtained as a colorless solid. Selected spectroscopic data of **4**: ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.53 (d, ^3J = 7.1 Hz, 3 H), 0.61 (d, ^3J = 6.8 Hz, 3 H), 1.02 (d, ^3J = 6.9 Hz, 3 H), 1.06 (d, ^3J = 6.9 Hz, 3 H), 2.00 (dqq, ^3J = 6.9 Hz, ^3J = 6.9 Hz, ^3J = 2.1 Hz, 1 H), 2.06 (dq, ^3J = 7.1 Hz, ^4J = 1.1 Hz, 1 H), 2.17 (qd, ^3J = 10.5 Hz, ^3J = 6.8 Hz, 1 H), 3.55 (d, ^4J = 1.1 Hz, OH), 3.75 (s, 1 H, OH), 3.97 (dd, ^3J = 10.5 Hz, ^3J = 2.1 Hz, 1 H), 7.12−7.17 (br. m, 1 H), 7.19−7.23 (m, 1 H), 7.27−7.38 (m, 5 H), 7.58−7.62 (m, 2 H), 7.66−7.72 (br. m, 1 H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ = 9.5, 10.2, 14.5, 20.7, 28.4, 42.0, 48.0, 74.5, 78.4, 100.5, 123.8, 126.1, 126.3, 126.5, 127.7, 127.8, 127.9, 128.2, 144.2, 144.9.

Acknowledgments

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