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Selfcondensation of 2-methylpropanal with homochiral BINOL catalysts as a model asymmetric aldol–Tishchenko reaction

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Abstract

Binaphtholate catalysts were used to investigate the stereochemistry of 2-methylpropanal selfcondensation. Several steps of this condensation were found to be affected weakly or moderately by homochiral catalysts, but with opposite enantioselectivities.

The classic aldol–Tishchenko reaction[1] is used to obtain 1,3-diol monoesters from the selfcondensation of aldehydes with at least one α-hydrogen. In the first step of this reaction, two molecules of aldehyde are condensed to the aldol product, which is further reduced by the third molecule of aldehyde to give 1,3-diol monoester. In addition, the latter could be subjected to acyl migration. Although the aldol–Tishchenko reaction has been known for more than 100 years,[1a] and the aldol condensation thoroughly studied, there is still little information about the stereochemistry of the Tishchenko reaction and the acyl migration.

The mechanism of the Tishchenko reaction was not clear until Burkhardt[2] and Evans[3] proposed in 1990 the idea of 6+6 bicyclic activated complexes, where the hydride transfer occurs intramolecularly in the hemiacetal formed from the aldehyde and the β-hydroxy carbonyl compound. This idea was later supported by other authors and the reaction has been used for the diastereoselective reduction of some β-hydroxy carbonyl compounds.[4,5] The acyl migration of the first formed monoester occurring after disproportionation has been described,[2–7] but the stereochemistry of this isomerisation was discussed only in our recent short report[8] considering its enantioselectivity.

Our goal in this study was to investigate the mechanism and stereochemical aspects of the aldol–Tishchenko reaction and to evaluate its suitability for the enantioselective synthesis of 1,3-diol derivatives. We used 2-methylpropanal **1** as a simple starting compound (aldol **2** contains only one stereogenic centre), and binaphtholates as chiral catalysts in solvents such as THF, DMF and DMSO. In all experiments the reaction products consisted mainly of monoesters **3** and **4** and aldoxanes **5** and **6**, without substantial variations in proportions. The shortest reaction times and the highest ees were obtained with (*S*)-1,1′-binaphthalene-2-ol-2′-oxylithium **7** in THF.

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The results of the first experiments with **1** in the presence of catalyst **7** (Table 1) indicate that there are at least two steps with different enantiomeric discriminations. A small excess of (*R*)-**2** after 70 minutes (entry b) indicates some discrimination in the aldol condensation step. In another experiment[8] we found that the chiral catalyst **7** affects the stereochemistry of reversible acyl migration (in both directions), but with a preference for the *S* isomer. The large amount of aldoxanes, considered as the by-products of the aldol–Tishchenko reaction,[9] is probably due to their relative stability at ambient temperature.

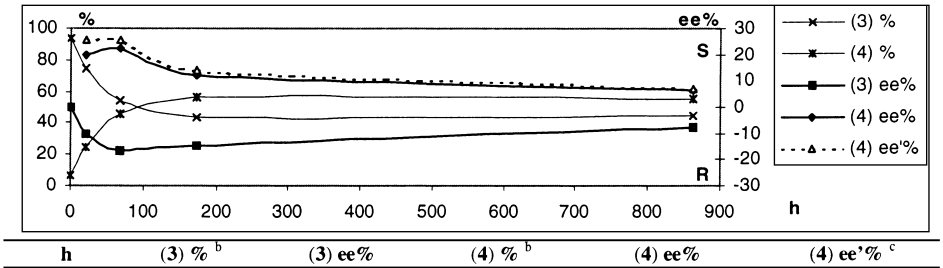
Table 1
Results of selfcondensation of **1**[a]

Entry (time)	**a** (214 h)		**b** (1.2 h)	
Compound [b]	**%** [c]	**ee%** [d]	**%**	**ee%**
2	5	-	76	12.9 *R*
3	24	3.5 *S*	7	-
4	28	18.7 *S*	0	-
5 + **6** [e]	43	19.4 *R*	11	-

[a] Reactions were performed at room temperature, **7**:**1** molar ratio 1:10.
[b] Reaction products were separated from catalyst by distillation *in vacuo* and individual components were separated with column chromatography on silica gel. Compounds were identified by ^{1}H NMR.
[c] Ratio of reaction products was determined from GLC data.
[d] **3** and **4** were hydrolyzed and **2** and **5** + **6** were reduced to 2,2,4-trimethylpentane-1,3-diol **10**, where diacetate ee was determined by GLC on Chiraldex™ B-PH. The absolute configuration was assigned according to the retention times of enantiomers ((*S*)-**10**, prepared by Harada[10] method, diacetate eluted first from Chiraldex™ B-PH).
[e] Aldoxane diastereomers **5** and **6** were not separable by column chromatography and by GLC (SGE BP10). In all experiments **5**:**6** ≈ 3:2 was determined by ^{1}H NMR.

In the third experiment the course of acyl migration in racemic **3** was monitored. When the concentration of **4** in the reaction mixture is low (Table 2), then it has a relatively high ee, which gradually decreases afterwards. The maximum ee of **3** appears after some time, and then also starts to decrease. The closer the reaction is to equilibrium, the lower the ee becomes in both monoesters.

Table 2
Changes in the regioisomeric and enantiomeric composition as a consequence of acyl migration[a]

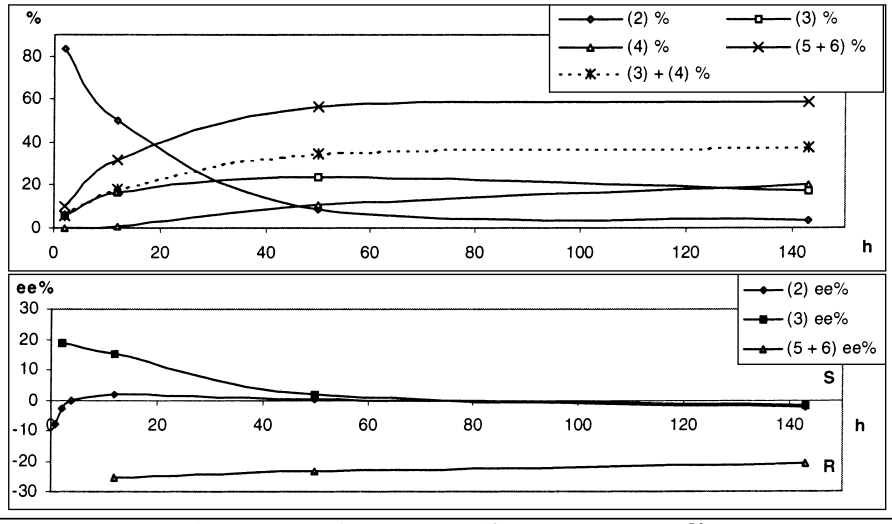


h	**(3) %** [b]	**(3) ee%**	**(4) %** [b]	**(4) ee%**	**(4) ee'%** [c]
0	94	0	6	(0)	-
20	75	10.1 *R*	25	19.5 *S*	25.8
68	54	16.6 *R*	46	22.1 *S*	25.4
172	44	14.8 *R*	56	12.4 *S*	13.9
862	45	7.7 *R*	55	6.2 *S*	7.0

[a] **7**:**3** mole ratio 1:3.
[b] Individual components were separated with column chromatography on silica gel. See also footnotes for Table 1.
[c] Adjusted ee% considering 6% of racemic **4** in starting material.

In another experiment the course of the whole reaction was monitored. After a few hours, when the major condensation product was **2** (Table 3), the enantiomeric enrichment of the *R* isomer decreases rapidly, most probably due to a fast retroaldol reaction. After 12 h, **2** is already enriched very slightly in the *S* isomer, probably because of the quicker formation of (*R*)-aldoxanes. Afterwards, as the amount

Table 3
Changes in reaction products relative composition and in their ee%



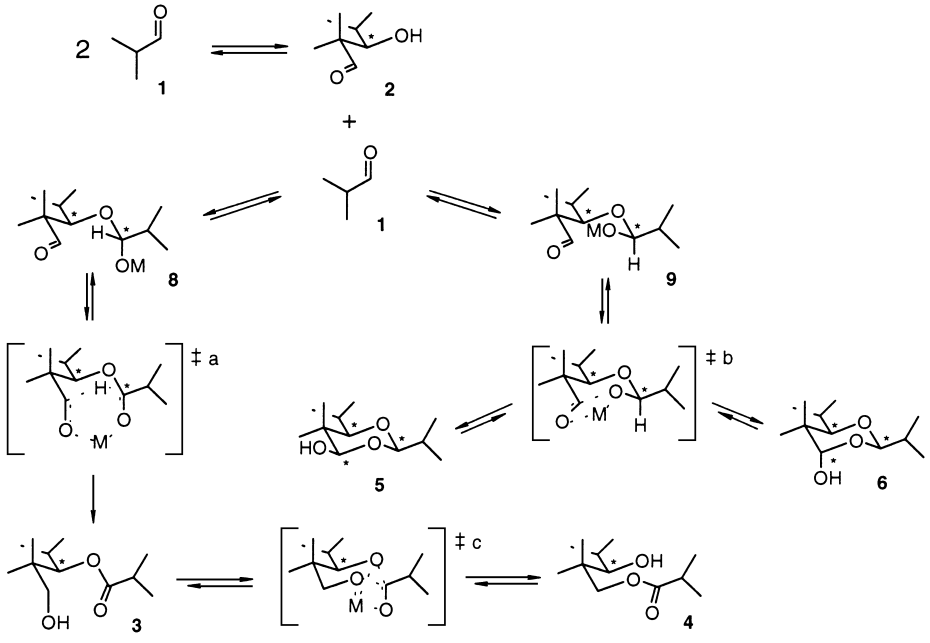
h	1	2		4	12		50		143	
Compound [a]	**ee%**	**%**	**ee%**	**ee%**	**%**	**ee%**	**%**	**ee%**	**%**	**ee%**
2	8 *R*	84	2.9 *R*	0.3 *R*	50	1.7 *S*	9	0.3 *S*	3.5	2.4 *R*
3	-	6	18.6 *S*	-	17	15.1 *S*	24	2.0 *S*	17	1.7 *R*
4	-	0	-	-	1	-	11	-	20.5	33.0 *S*
5 + 6	-	10	-	-	32	25.6 *R*	56	23.4 *R*	59	21.0 *R*
(**3 + 4**)		6			18		35		37.5	

[a] Individual components were separated with column chromatography on silica gel. See also footnotes for Table 1.

of **2** decreases, the ee changes very slowly towards a very slight excess of the *R* isomer. This may be explained assuming that a certain amount of **2** originates from the degradation of aldoxanes. The change in percentages of monoesters and aldoxanes with time are quite similar, only the percentage of aldoxanes is proportionally larger than that of monoesters. However, a closer examination reveals that the ratio gradually increases in favour of the monoesters relative to the aldoxanes once the rapid increase of both the materials has ceased (at about 50 h). This could be due to the slow degradation of aldoxanes or to the reversibility of their formation. The latter proposal is also supported by the slow decrease in the ees of the aldoxanes with time. The changes of amounts of **3** and **4** in the products and the change in the ee of **3** and also the relatively high ee of **4** (at 143 h) are in good agreement with the results of the acyl migration experiment described above.

From the results of these experiments and previous reports[2,3,5b] the following scheme can be drawn (Scheme 1) for the selfcondensation of **1** in the presence of **7**. The reaction starts with the rapid formation of **2**, so that the rate of formation of the *R* isomer is somewhat higher. Soon excess of the *R* enantiomer decreases close to zero, because of the reverse aldol reaction. At the same time **2** starts to react with **1** to form two diastereomeric hemiacetals **8** and **9**. We propose that both diastereomers react differently: **8** seems to be more able to form the activated complex **‡a** for hydride transfer (as proposed by Evans[3] for Tishchenko-type reactions) and gives **3**, while **9** is more suitable to form the hypothetical activated complex **‡b** for the formation of aldoxanes. The ratio of aldoxanes and monoesters in the experiments is about 3:2, but it is not clear whether this arises from the diastereoselectivity of the formation of hemiacetals or from the limitations in hydride transfer. Both trimerisation paths also have opposite enantioselectivities, so that **3** is enriched with the *S* isomer and the aldoxanes with the *R* isomer. The

possibility that only one of them is enantioselective and the other uses the starting material left enriched with the opposite enantiomer is avoided, because of the rapid equilibration of the aldol reaction. This is also consistent with the observed ee of **2** throughout most of the reaction. However, it is not obvious from these experiments at which point exactly the discrimination takes place — at the hemiacetal formation or at the following Tishchenko reaction and aldoxane formation. The intramolecular acyl migration, preferring the *S* isomer, begins after the formation of **3** and leads to the formation of a mixture of **3** and **4** in the reaction products. In the beginning, it also causes quite large differences in the ee values of **3** and **4**, but afterwards, the differences slowly decrease due to the reversibility of this isomerisation.



Scheme 1. Selfcondensation of **1** in the presence of binaphtholate catalysts (only the *R* series of **2**–**8** is depicted)

In this work we have shown that several steps in the selfcondensation of **1** proceed with low to moderate enantioselectivity in the presence of catalyst **7**. To our knowledge, this is the first time that the enantioselectivity has been studied in the one-pot aldol–Tishchenko reaction, and if the different steps are considered separately, then the chiral discrimination in the formation of secondary 1,3-diol monoesters and aldoxanes is also novel. The use of this multi-step condensation to prepare enantiomerically pure 1,3-diol derivatives seems to be limited (at least under the conditions described here), because of the various equilibrium reactions and opposite selectivities. However, some single steps of this condensation could be useful separately under other conditions, or the reaction toward the aldoxanes may be more promising to obtain products with high ee.

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