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Asymmetric Reformatsky reaction: application of mono- and dihydroxy carbohydrate derivatives as chiral ligands

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Abstract—This work describes for the first time the use of eight mono- and dihydroxy carbohydrate derivatives as ligands in the asymmetric Reformatsky reaction. The enantiomeric excess of the β-hydroxy ester obtained was 30% and the chemical yield was 50% on average. © 2002 Elsevier Science Ltd. All rights reserved.

The introduction of effective stereocontrolling features in a molecule is one of the most prominent subjects in modern stereoselective organic synthesis, and the preparation of novel chiral auxiliaries or catalysts is one of the most important areas of research within this field. Although many existing chiral auxiliaries and catalysts can induce useful levels of diastereoselection or enantioselectivity, making the preparation of many chiral compounds with high enantiomeric purity possible, it is still desirable to find new effective chiral compounds for the asymmetric catalysis of practical carbon–carbon bond-forming reactions. In this context, the Reformatsky reaction employing zinc metal, α-bromo esters, and a carbonyl compound is one of the most important methods for obtaining α-hydroxy carboxylic esters.[1] Since this reaction generates at least one stereogenic center, many methods using chiral substrates or chiral α-halo esters[2] have been examined in order to achieve high enantiomeric excess.

Recently, the use of chiral diamines, amino alcohols, aminodiols, and other chiral complexing agents have been thoroughly investigated.[3,4] Up to now approximately 50 ligands have been used in the asymmetric Reformatsky reaction. In most of the cases, the chemical yield has been on average 70%, whilst only ten ligands led to enantiomeric excesses in the range of 70–90%.

It is widely recognised that a number of carbohydrate-based templates, which in many cases exist in acyclic pentofuranose or hexopyranose forms, have been thoroughly investigated and can serve as effective chiral auxiliaries or catalysts as a consequence of forming a stereochemically biased spatial environment.[5,6] Their pronounced complexing ability towards cations make them very attractive as chiral auxiliaries in reactions such as aldol condensations,[6] cyclopropanations,[7] carbonyl group reductions,[8] the preparation of chiral sulfoxides,[9] Lewis acid-catalysed cycloadditions[10] and Reformatsky reactions, which involve positive ions in the transition state.[11]

Our interest is focused on the synthesis and use of carbohydrate derivatives as chiral auxiliaries in several organic reactions in order to broaden the application of these readily available chiral natural products.[12]

The relatively low enantioselectivity from asymmetric Reformatsky reactions using chiral ligands[4] means that there is a lack of good chiral catalysts for this reaction. Prior to this study, carbohydrate derivatives had never been investigated as chiral ligands for this reaction. Thus, the study of readily available carbohydrate derivatives as ligands in this reaction is of potential interest. Herein, we describe the results of the enantioselective Reformatsky reaction in the presence of a variety of monocyclic-hydroxy and acyclic carbohydrates derivatives as chiral ligands.

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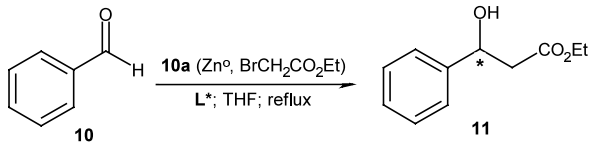
To examine the feasibility and enantioselectivity of carbohydrate-based ligands in the Reformatsky reaction, we decided to study a variety of cyclic and acyclic carbohydrates having a different number of free hydroxy groups (Scheme 1). The derivatives **3**, **4**, **6** and **7** are primary alcohols and **1**, **2** and **5** are secondary alcohols. The derivatives **1**–**9** were readily obtained in one or few steps by standard procedures described in the literature,[13] from D-glucose (derivatives **1**[13a] and **2**[13b,c]), D-ribose (derivative **3**[13d]), D-fructose (derivatives **4**[13a] and **5**[13a]), D-galactose (derivative **6**[13a]), and from D-mannitol (derivatives **7**,[13e] **8**,[13f] and **9**[13g]).

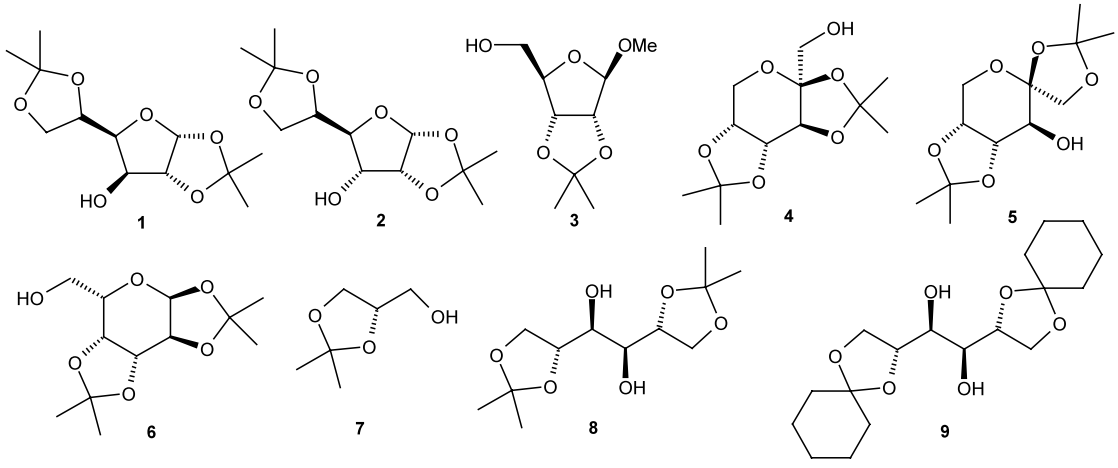
The Reformatsky reaction using these catalysts was completed using the following general procedure: A mixture of benzaldehyde **10** (1 mmol), Reformatsky reagent **10a** (3 mmol; 2-bromoethylacetate and zinc powder) and the carbohydrate **1**–**9** as the chiral ligand (**L***) was heated under reflux in THF (Eq. (1)).[14]



(1)

The reaction conditions as well as the enantiomeric excess (e.e.) of the β-hydroxy ester **11** are indicated in Table 1.

As shown in Table 1 (entries 1–9), the chemical yields are similar to those described in the literature with a 1:3:1 molar relationship. No appreciable enantiomeric excess was obtained for the monohydroxy ligands **1**–**7**. It should be noted that the secondary monohydroxy ligands **2** and **5** (entry 2 and 5) showed slightly better performance producing 3-hydroxy-3-phenylpropanoate **11** in 18 and 19% e.e. On the other hand, the dihydroxy ligands **8** and **9** furnished the adduct with the best enantiomeric excess, indicating that the complexating



Scheme 1. Carbohydrate derivatives used in asymmetric Reformatsky reaction.

Table 1. Enantioselective Reformatsky reactions of benzaldehyde catalysed by **1**–**9**

Entry	Ligand (**L***)	Molar ratio **10**:**10a**:**L***	Reaction time (h)	Yield **11** (%)[a]	% e.e. **11**[b] (config.)[c]
1	**1**	1:3:1	2.5	56	10 (*S*)
2	**2**	1:3:1	3.0	47	18 (*R*)
3	**3**	1:3:1	3.0	42	0
4	**4**	1:3:1	2.5	46	3 (*S*)
5	**5**	1:3:1	3.0	52	19 (*S*)
6	**6**	1:3:1	2.0	53	4 (*R*)
7	**7**	1:3:1	3.0	60	<3 (*R*)
8	**8**	1:3:1	2.0	58	30 (*R*)
9	**9**	1:3:1	3.0	60	20 (*R*)
10	**5**	1:3:0.5	3.0	45	<3 (*S*)
11	**5**	1:3:2	3.0	45	22 (*S*)
12	**5**	1:3:3	2.5	10	24 (*S*)
13	**5**	1:2:2	2.5	20	9 (*S*)
14	**8**	1:3:0.5	3.0	50	8 (*R*)
15	**8**	1:3:2	3.0	52	30 (*R*)
16	**8**	1:3:3	3.0	48	30 (*R*)

[a] Yield after purification on silica gel column chromatography.
[b] Determined by ^{1}H NMR with Eu(hfc)$_3$.
[c] Determined on the basis of the sign of the specific rotation previously described.[15]

ability of the ligand in the transition state is an important factor for the enantioselectivity, probably due to the steric hindrance from the carbohydrate moiety.[16] In order to investigate if this complexation ability is related to the enantiomeric excess of the product, several reactions were carried out using **5** and **8** with different molar ratios. The conditions of these reactions and the results obtained are shown in Table 1 (entries 10–16).

From the results presented in Table 1 it can be observed that the ligand **5** increased the enantioselectivity to a maximum of 24% when the molar ratio was changed from 1:3:0.5 to 1:3:3 (benzaldehyde; Reformatsky reagent: ligand; entries 5, 10–12). These results indicate that the amount of ligand is an important factor for controlling the enantioselectivity. A slight improvement in e.e. was observed when the molar ratio was changed from 1:3:2 to 1:3:3, but the yield decreased (entries 11 and 12, respectively). When ligand **8** was used, varying the molar ratio from 1 to 3 equiv. (entries 8 and 14–16) no changes in the enantiomeric excess was observed. It is noteworthy, that the use of both ligands at a molar ratio below 1:3:1 (entries 10 and 15) led to drastic decreases in the e.e. values. The performance of these ligands was also examined at −78°C but no Reformatsky reaction was observed at this temperature.

The results obtained demonstrate that ligands with one free hydroxy group have good complexing ability to zinc with 2 M equiv. of ligand, while ligands with two free hydroxy groups have high complexing ability with an optimum of 1 M equiv.

In summary, this report describes for the first time the use of eight mono- and dihydroxy ligands based on carbohydrates as chiral ligands in the Reformatsky reaction. Besides the low enantioselectivity obtained with these catalysts, it was possible to show the importance of the relationship between the amounts of these chiral ligands and the number of hydroxy groups in transition state to the enantioselectivity of the reaction. We believe that this study might be very useful for designing new carbohydrate-based chiral catalysts having stronger complexing groups, which may give improved enantioselectivity in this reaction.

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14. *Typical experimental procedure*: A solution of **10** (1 mmol), chiral ligand (**L* 1–9**; Table 1 summarize molar ratio: 0.5, 1, 2 or 3 mmol) and ethyl α-bromoacetate (Table 1 summarize molar ratio: 2 or 3 mmol) in anhydrous THF (5 ml) was added to a slurry of Zn dust (Table 1 summarizes the molar ratio: either 2 or 3 mmol was used) in anhydrous THF (5 ml). The Zn dust was previously activated by washing it with aqueous HCl and acetone, and dried at 100°C for 30 min. The resulting solution was heated under reflux for the time indicated in Table 1. The reaction was quenched with 10% HCl, and the mixture was extracted with ethyl ether. The organic layer was washed with 10% aqueous $NaHCO_3$, water, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using 3% ethyl acetate: hexane. The ethyl 3-hydroxy-3-phenyl propanoate was obtained in 10–60% yield. Ethyl 3-hydroxy-3-phenylpropanoate **11**:[17] colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.27 (3H, t, $J=7.2$ Hz), 2.70 (1H, dd, $J=16.4$ Hz and 4.8 Hz), 2.77 (1H, dd, $J=16.4$ and 8.4 Hz), 3.27 (broad s, OH), 4.18 (2H, q, $J=7.2$ Hz), 5.13 (1H, dd, $J=8.4$ and 4.8 Hz), 7.26–7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 14.0, 43.2, 60.8, 70.2, 125.6, 127.7, 128.4, 142.4, 172.3; e.e. 30%, $[\alpha]_D^{21}=+13.6$ (*c* 1.1, $CHCl_3$); lit.[17] e.e. 98%, $[\alpha]_D^{20}=+44.0$ (*c* 1.013, $CHCl_3$).

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