PERKIN 1

Cycloadducts from highly functionalized nitrones and oximes as ligands in the enantioselective addition of diethylzinc to benzaldehyde

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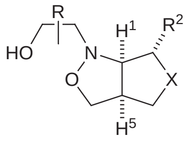
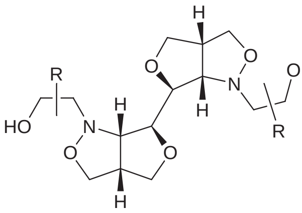
Highly diastereoselective intramolecular cycloaddition of nitrones **5**–**7** and **16**, as well as oximes **11**–**13** that are easily accessible from diethyl (*R*,*R*)-tartrate, affords bicyclic compounds **8**–**10** and **17**. The tetracyclic compound **14** is formed as the main product by an intramolecular domino reaction of dioxime **11**. Some of the bicyclic compounds and the tetracyclic compound **14** are tested as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde. An ee of 93% was achieved in the presence of the best ligand.

Introduction

Enantioselective catalysis is the most effective method for the synthesis of chiral non-racemic compounds.[1] Thus, intensive efforts have been made during recent years to discover new chiral catalysts for this purpose.[2] One of the most studied enantioselective reactions is the addition of dialkylzinc compounds to aldehydes in the presence of various polyfunctional compounds such as α,β-diamines, β-amino alcohols and α,β-diols that act as ligands for the formation of catalytically active zinc complexes.[3] Recently, we found that some of the 3,7-dioxa-2-azabicyclo[3.3.0]octanes with β-hydroxy alkyl groups at the 2-position such as **A** catalyze the reaction in this way, yielding the product with an enantiomeric excess exceeding 90%.[4]

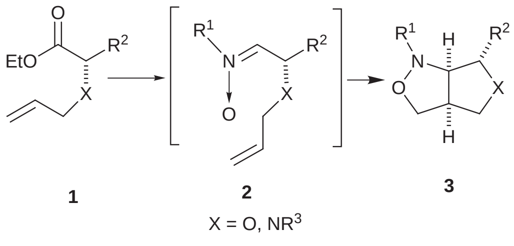


A



B

Thus, the question arose as to whether compounds such as **B**, in which two such fragments are joined, would display a *synergetic* effect enhancing the enantioselectivity of the reaction. Enantiopure 3,7-dioxa-2-azabicyclo[3.3.0]octanes **3** are easily accessible from α-hydroxy carboxylic esters.[5] *O*-allylation of the hydroxy esters gave compounds **1** which in turn were converted to nitrones **2** by reduction with diisobutylaluminium hydride (DIBAL-H) followed by treatment with *N*-β-hydroxyalkyl-substituted hydroxylamines (Scheme 1). Nitrones **2** underwent spontaneously an intramolecular cycloaddition affording the bicyclic compounds **3**. The same reaction sequence performed with the doubly functionalized ethyl tartrate should yield the desired compounds **B**.[6] Although we could not make any prediction on the molecular structure of the catalytically active zinc complex, it would be desirable to get at least some insight into the preferred conformation of the pure ligand by an X-ray analysis. Herein we present the results of our studies on the synthesis of compounds **B** and related products and their application in the enantioselective addition of diethylzinc to benzaldehyde.



Scheme 1

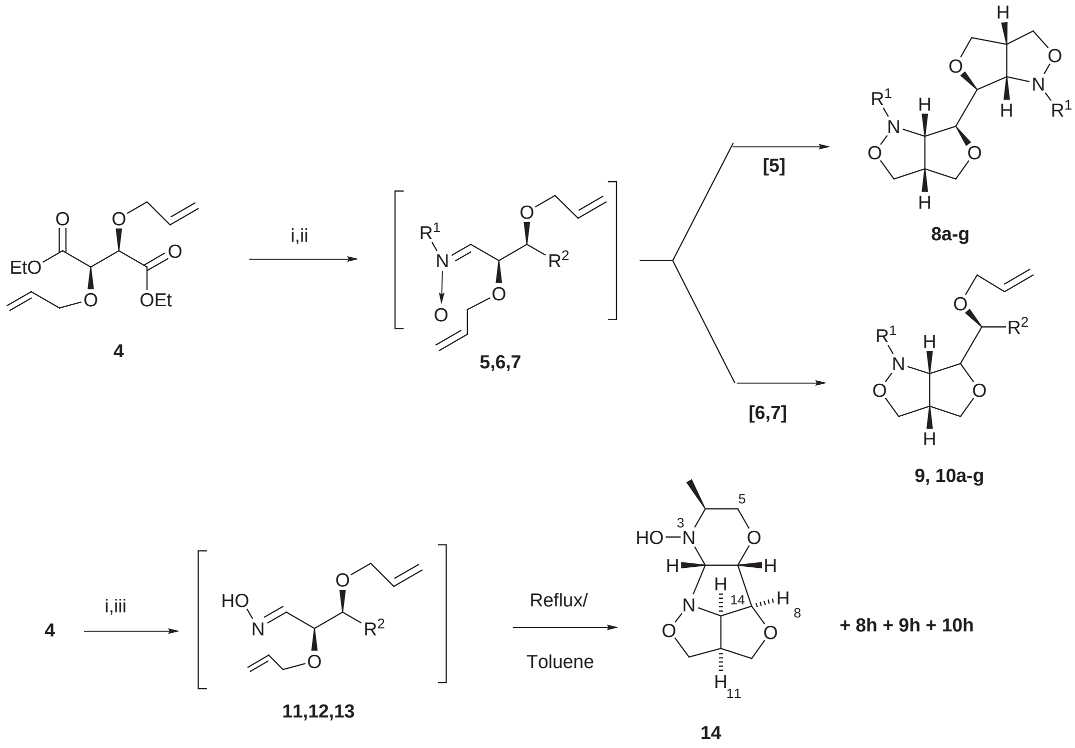
Results and discussion

Formation of the cycloadducts derived from diethyl (*R*,*R*)-tartrate

Compound **4** was prepared from diethyl (*R*,*R*)-tartrate without racemization by treatment with allyl bromide in the presence of silver(I) oxide.[6] Reduction of **4** by DIBAL-H was the most problematic step in the reaction sequence. The corresponding dialdehyde could not be prepared without the formation of a monoaldehyde possessing either an unreduced ester or a hydroxymethyl group arising from more extensive reduction, or both of the undesired by-products.

To avoid racemization of the unstable reaction products during work-up we decided to treat the reaction mixture directly with *N*-alkylhydroxylamines[7a] to give a mixture of the nitrones **5**, **6** and **7**. Under these reaction conditions the dinitrones **5** underwent a two-fold intramolecular cycloaddition affording the desired products **8**,[6] whereas compounds **9** and **10** were formed by a single intramolecular cycloaddition of **6** or **7**, respectively (Scheme 2). Separation by column chromatography provided the diastereomerically pure compounds **8** as well as **9** and **10** (see Table 1)[7b] which were all found to be optically active. This means that they are also enantiopure. Since the starting compound **4** contains two independent stereogenic centers, diastereomers would have been formed if partial racemization had taken place. Furthermore, in a number of the products the group R^1 contains additional stereogenic centers.

However, if the unsubstituted hydroxylamine was used instead of R^1NHOH in this reaction sequence the dioxime **11** was formed along with oximes **12** and **13**. Refluxing the reaction mixture in toluene afforded the tetracyclic compound **14** as the major product together with compounds **8h**, **9h** and **10h**.[8]



5-10	R^1
a	$CH_2C_6H_5$
b	CH_2-C_6H_4-OMe-4
c	C*H(Me)Ph[*S*]
d	$C(Me)_2CH_2OH$
e	C*H(Et)CH_2OH[*R*]
f	C*H(Me)C*H(Ph)OH[1*S*,2*R*]
g	C*H(Me)C(Ph)$_2$OH[*S*]
h	H

	R^2
5	CH=N(O)R^1
6,9,12	COOEt
7,10,13	CH_2OH
11	CH=N-OH

$$9 \xrightarrow{\text{i, ii or iii}} 8 \xleftarrow{\text{iv, ii or iii}} 10$$

Scheme 2 *Reagents and conditions*: i, DIBAL-H/CH_2Cl_2/−78 °C; ii, $R^1NHOH·HCl/Et_3N$; iii, $NH_2OH·HCl/Et_3N$; iv, DMSO $(COCl)_2$, Et_3N.

Table 1 Yields[a] of the isolated compounds **8**–**10** (%)

Entry	8	9	10	Total yield (%)
a[b]	9	—	—	9
b[b]	21	—	—	21
c[c]	29	—	14	43
d[c]	28	14	14	56
e[c]	23	11	11	45
f[c]	15	30	—	45
g[c]	35	17	—	52
h[d]	14	9	9	56

[a] Ratios and overall yields calculated from the *O*,*O*′-diallylated tartrate **4**. [b] For reaction conditions see ref. 6. [c] −78 °C; molar ratio of **4**: DIBAL-H : R^1NHOH, 1 : 2.5 : 2.5. [d] 24% of compound **14** was formed in addition. Molar ratio of **4**: DIBAL-H : NH_2OH, 1 : 4 : 4, see also ref. 8.

Obviously, the latter were formed from **11**, **12** and **13** *via* the tautomeric nitrones **5h**, **6h** and **7h**,[9] respectively (Scheme 2). The main reaction pathway of compound **11**, however, is the formation of **14** by a domino reaction.[10] Again, **14** as well as **8h**, **9h** and **10h** were found to be optically active.

Most of the compounds **9d**–**g** as well as **10c**–**e** were also converted to **8c**–**g** *via* the corresponding aldehydes which were formed by DIBAL-H reduction in the former and by Swern oxidation in the latter case. Subsequent treatment of the aldehydes with the respective *N*-alkylhydroxylamines afforded compounds **8** in the usual way. Compound **8h** was isolated as the single product either from reduction of **9h** or from Swern oxidation of **10h** followed by reaction with unsubstituted hydroxylamine and refluxing the resulting oxime in toluene. Since no tetracyclic compound **14** could be detected under these conditions it was excluded that the formation of **14** from **11** starts with an intramolecular 1,3-dipolar cycloaddition to give first the 3,7-dioxa-2-azabicyclo[3.3.0]octane moiety with generation of the six-membered ring in one of the subsequent reaction steps.[8]

Finally, the monoallylated compound **15** was converted to **17** (Scheme 3). In the preparation of **15** the ratio of diethyl (*R*,*R*)-tartrate, allyl bromide and silver(I) oxide was reduced to 1 : 1 : 1 but the diallylated compound **4** was formed along with **15** in a ratio of 1 : 1. Several attempts failed to obtain only **15** by varying the ratio of the reactants. Separation of compounds **4** and **15** was performed by column chromatography.

In the same way as described before, compound **15** was reduced by DIBAL-H followed by treatment with *N*-alkylhydroxylamine R^1NHOH [R^1 = -$C(CH_3)_2CH_2OH$] (Scheme 3). Compound **17** was the only cycloadduct that could be isolated from the reaction mixture in 52% yield. Thus, nitrone **16** must be assumed to be the intermediate from which **17** was formed by an intramolecular 1,3-dipolar cycloaddition. This means that preponderantly only one of the two ester groups was reduced although four equivalents of DIBAL-H were used. However, nitrones such as **18** undergo intramolecular cyclo-

Table 2 Selected ^{1}H NMR data of compounds **8a**–**h** in $CDCl_3$ (δ values,[a,b] *J* in Hz)

	8a	**8b**	**8c**	**8d**	**8e**	**8f**	**8g**	**8h**
1′-H	3.74	3.77	4.23	4.00	4.05	4.18	4.01	4.11
4′α-H[c]	4.12	4.14	3.94	3.63	3.83	3.82	3.85	3.89
4′β-H	3.62	3.67	3.61	3.59	3.62	3.69	3.48	3.49
5′-H	3.27	3.31	3.41	3.23	3.24	3.31	3.21	3.16
6′α-H	4.07	4.11	4.33	4.06	4.16	4.25	4.17	4.21
6′β-H	3.53	3.59	3.53	3.59	3.56	3.59	3.40	3.43
8′-H	3.61	3.64	3.98	3.88	3.79	3.91	3.63	3.55
1′/5′-H	8.0	8.5	7.2	7.5	8.6	8.5	8.1	8.8
1′/8′-H	4.3	5.0	7.2	3.8	4.9	5.3	5.3	4.6
4′α/5′-H	7.6	7.5	6.5	7.2	7.0	6.8	6.7	6.1
4′β/5′-H	3.0	3.0	<1.0	3.3	3.1	2.3	2.3	<1.0
5′/6′α-H	7.1	7.2	7.7	8.2	7.9	8.1	8.0	8.5
5′/6′β-H	5.7	5.4	7.4	5.0	6.0	6.5	6.7	8.0

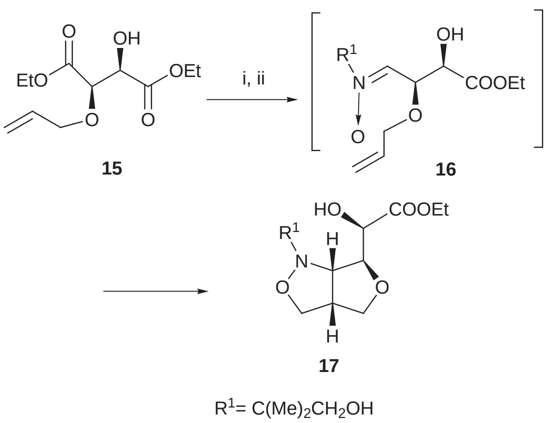
[a] For additional chemical shifts, see Experimental section. [b] For the numbering system used in compounds **8**, see Experimental section. [c] See ref. 14.

Table 3 Selected ^{1}H NMR data of compounds **9d**–**h** and **17** in $CDCl_3$ (δ values, *J* in Hz)

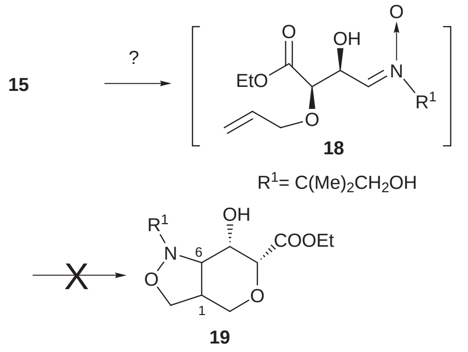
				4			6								
Compd	OCH_2CH_3 (*H*$_2$)	OCH_2CH_3 (*H*$_3$)	2	4a	4b	5	*cis*	*trans*	1′	4′α	4′β	5′	6′α	6′β	8′
9d	4.22	1.25	4.01	3.84	4.27	5.88	5.24		4.19	4.05	3.63	3.23	4.15	3.58	4.06
9e	4.18	1.21	4.05	3.87	4.21	5.83	5.16		4.21	3.84	3.60	3.21	4.17	3.54	4.02
9f	4.19	1.20	4.10	3.85	4.25	5.95	5.13	5.20	4.33	3.78	3.67	3.29	4.23	3.55	4.04
9g	4.16	1.22	3.97	3.94	4.19	5.72	5.13		4.27	3.81	3.42	3.14	4.14	3.38	3.84
9h	4.10	1.13	3.97	3.77	4.1	5.75	5.03	5.08	4.10	3.77	3.44	3.09	4.1	3.30	3.17
17	4.22	1.21	4.21	—	—	—	—		4.10	4.04	3.63	3.25	4.14	3.58	4.06

Compd	1′/5′	1′/8′	4′α/5′	4′β/5′	5′/6′α	5′/6′β	OCH_2CH_3	2/8′	4a/5	4b/5
9d	8.8	5.6	7.9	4.3	6.9	5.7	7.1	2.8	5.2	6.3
9e	—[a]	8.6	6.9	—[a]	6.9	5.9	7.0	3.9	5.5	6.7
9f	8.5	5.1	6.4	<1.8	7.4	6.2	7.1	3.3	5.4	6.9
9g	8.6	5.8	6.9	1.6	—[a]	2.6	7.2	3.4	4.9	6.8
9h	8.1	6.3	6.4	2.9	8.0	7.0	7.1	4.9	—[a]	—[a]
17	8.8	4.3	7.6	4.8	7.2	5.4	7.2	1.9	—	—

[a] Could not be determined (not well resolved).



Scheme 3 *Reagents and conditions*: i, DIBAL-H/CH_2Cl_2/−78 °C; ii, $R^1NHOH{\cdot}HCl/Et_3N$.



Scheme 4

addition to give 3,8-dioxa-7-azabicyclo[4.3.0]nonanes (*e.g.* **19**) only at elevated temperatures (Scheme 4)[11a] whereas the reaction of nitrones affording 3,7-dioxa-2-azabicyclco[3.3.0]octanes (*e.g.* **16**→**17**) is known to occur at room temperature or even at lower temperatures. Thus, it is expected that nitrone **18**, if formed at all, cannot undergo an intramolecular cycloaddition under the reaction conditions.

The structure of the bicyclic compounds

The structure determination of all new compounds is mainly based on their ^{1}H and ^{13}C NMR data. Selected ^{1}H NMR data of compounds **8** and **9** are summarized in Tables 2 and 3, respectively. In the ^{1}H NMR spectrum of **8c** line broadening was observed at 273 K. At 223 K, however, all signals were clearly distinguishable (see Table 2). It is of note that the data for compound **17** are in full agreement with those of the corresponding compounds **9** as well as **8**. On this basis, an alternative structure **19** could be excluded for this cycloadduct.[11b]

X-Ray analysis of compound **8b** that crystallized as its monohydrate confirmed the conclusions drawn from the NMR spectra and provided additional information on the conformation of this compound in the solid state. The structure of compound **14**, in particular the configuration at the six stereo-

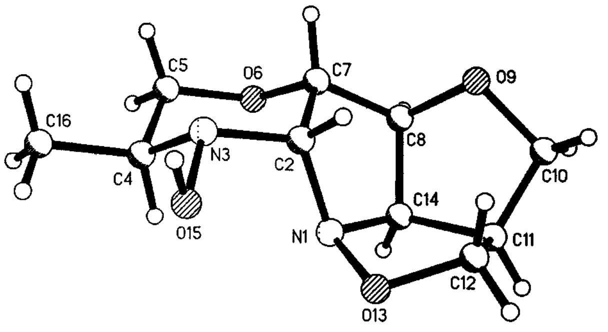


Fig. 1 Molecular plot of (1*R*,2*S*,3*R*,4*S*,7*S*,8*S*,11*S*,14*R*)-(−)-3-hydroxy-4-methyl-6,9,13-trioxa-1,3-diazatetracyclo[6.5.1.$0^{2,7}$.$0^{11,14}$]-tetradecane **14**. Selected bond lengths (Å): N1–O13 1.436(4), N1–C2 1.481(4), N1–C14 1.485(5). C2–N3 1.445(4), C2–C7 1.524(5), N3–O15 1.447(4), N3–C4 1.462(4), C4–C5 1.516(7), C5–O6 1.427(6), O6–C7 1.427(4), C7–8 1.512(5), C8–O9 1.421(5), C8–C14 1.530(6), O9–C10 1.437(6), C10–C11 1.513(6), C11–C12 1.511(8), C11–C14 1.540(5), C12–O13 1.428(6). Selected bond angles (°): O13–N1–C14 105.4(3), C2–N1–C14 107.4(3), N3–C2–C7 110.9(3), N1–C2–C7 103.6(3), C2–N3–C4 112.5(3), N3–C4–C5 105.3(3), O6–C5–C4 112.0(3), C7–O6–C5 111.5(3), O6–C7–C8 105.8(3), O6–C7–C2 111.3(3), C8–C7–C2 103.1(3), O9–C8–C7 109.2(3), C7–C8–C14 104.6(3), O9–C8–C14 105.6(3), C7–C8–C14 104.6(3), C8–O9–C10 106.5(3), O9–C10–C11 104.5(4), C12–C11–C14 102.6(4) C10–C11–C14 102.8(4), O13–C12–C11 105.6(4), C12–O13–N1 106.7(3), N1–C14–C8 106.6(3), N1–C14–C11 106.6(3), C8–C14–C11 105.0(3).

Table 4 Selected torsional angles of compound **8b** and comparison of ^{1}H NMR coupling constants *J* (Hz) with theoretical values calculated from the torsional angles with the aid of the Karplus equation.[a]

Selected *J* values between the protons		Torsional angles (°)	J_{calc}	J_{found}
H1–C1–C5–H5		11.4	7.9	8.5
H4α–C4–C5–H5		13.4	7.8	7.5
H4β–C4–C5–H5		107.1	0.6	3.0
H1–C1–C8–H8	**(A)**	−150.7	7.0	5.0
	(B)	−124.4	2.8	
H5–C5–C6–H6α	**(A)**	18.5	7.4	7.2
	(B)	−24.5	6.8	
H5–C5–C6–H6β	**(A)**	138.7	5.1	5.6
	(B)	94.8	0	
H8A–C8–C8a–H8a	**A**	85.1	0	<1
H8A–C8–C8a–H8a	**B**	58.8	2.0	
H8B–C8–C8a–H8a	**A**	58.8	2.0	
H8B–C8–C8a–H8a	**B**	32.6	5.8	

[a] Ref. 13

genic centers of the molecule, was also confirmed by an X-ray analysis (Fig. 1).

Usually the two five-membered rings of 3,7-dioxa-2-azabicyclo[3.3.0]octanes **3** (X = O) exist in an envelope form, in which the two oxygen atoms protrude from the respective plane formed by the four other ring atoms.[4] In those compounds that are unsubstituted at positions 4, 5 and 6, the O-3 atom (isoxazolidine ring) occupies a position *anti* to the protons 1-H and 5-H at the bridgehead positions, whereas the O-7 atom (tetrahydrofuran ring) is *syn*-oriented to these protons. A similar situation arises for the corresponding 3-oxa-2,7-diazabicyclo[3.3.0]-octanes[12] in which the N-7 atom (pyrrolidine ring) is *syn*-oriented to 1-H and 5-H. From the torsional angles formed by the neighbouring hydrogen atoms that were determined by X-ray analyses, theoretical ^{1}H NMR coupling constants with the aid of the Karplus equation[13] were calculated.[4,12] In all these cases a good accordance with the experimentally determined coupling constants was found, indicating that there is a rough agreement of the conformation in the solid state and in solution.

As the X-ray analysis reveals, the situation is somewhat different in compound **8b** in which two bicyclic units are joined at position 8 and 8a (Fig. 2). In this compound the O-7 atoms of the two tetrahydrofuran rings occupy a position either *syn*- or *anti*-oriented to the bridgehead protons 1-H and 5-H. While in the isoxazolidine rings the O-3 atom is fixed in an *anti*-position to 1-H/5-H, the O-7 atoms change their position between the *syn*- and *anti*-orientation. With this interconversion of the tetrahydrofuran rings there is a change in the position of protons 6α-H, 6β-H[14] and 8-H, accompanied by a change in the relative positions of protons 8-H and 8a-H, whereas the atoms of the isoxazolidine rings do not change their position.

In Table 4 the torsional angles that are formed by the protons of the isoxazolidine rings and by those of the tetrahydrofuran rings are summarized, as well as those formed by the protons 8-H and 8a-H at the junction of the two bicyclic halves. Due to the two possible conformations of the tetrahydrofuran rings two values are given, (**A**: O-7 *syn* to 1-H/5-H, **B**: O-7 *trans* to 1-H/5-H). Accordingly, four possibilities for the angle 8-H/8a-H arise. A comparison between the coupling constants calculated from the torsional angles and those found experimentally indicates, however, that in solution most of the molecules should adopt a conformation in which both O-7 atoms are *syn*-orientated to the protons 1-H/5-H (**A**). This conformation is depicted in Fig. 2. In this case the two halves of the molecules are almost perpendicularly orientated to one another. The accordance of the ^{1}H coupling constants of compound **8b** with those of the other compounds **8** (see Table 2 for comparison of ^3J values) suggests a very similar conformation for all these compounds.

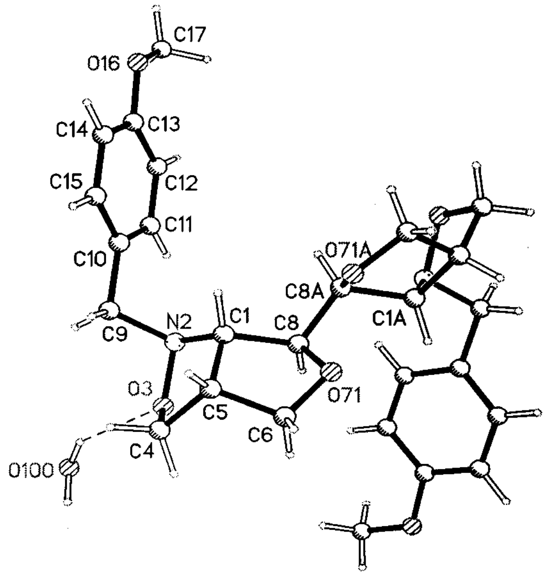


Fig. 2 Molecular plot of (1′*S*,5′*R*,8′*S*)-8,8′-bi[2′-(*p*-methoxybenzyl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octane] **8b**. Selected bond lengths (Å): C1–N2 1.456(5), C1–C8 1.513(5), C1–C5 1.553(5), N2–O3 1.446(3), N2–C9 1.468(5), C3–C4 1.446(5), C4–C5 1.519(6), C5–C6 1.505(6), C6–O71 1.340(6), C8–C8[a] 1.484(7), C8–O71 1.515(7); selected bond angles (°): N2–C1–C8 112.5(3), N2–C1–C5 107.6(3), C8–C1–C5 103.7(3), O3–N2–C1 103.0(3), O3–N2–C9 109.5(2), C1–N2–C9 112.5(3), C4–O3–N2 107.5(3), O3–C4–C5 105.7(3), C6–C5–C4 115.0(4), C6–C5–C1 103.8(3), C4–C5–C1 102.3(3), O71–C6–C5 106.4(4), C8[a]–C8–C1 115.1(4), C8[a] –C8–O71 98.4(3), C1–C8–O71 99.5(4), C6–O71–C8 106.1(4). [a] Symmetry transformations used to generate equivalent atoms: $-x,y,-z + 1$.

In view of the geometry of the parent molecules a *synergetic effect* by interaction of the two complex centers formed by addition of diethylzinc seems to be rather improbable at first glance. However, due to the conformative flexibility of compounds **8** such an effect cannot be excluded *a priori*. Moreover, the steric effect of the other half of the molecule on the reaction center should be quite different from that of the smaller groups of compounds **3** tested so far. For this reason, we decided to use not only compounds **8c–h** but also **9d–h**, **10h** and **17** as well as

Table 5 Enantioselectivities in the reaction of benzaldehyde with diethylzinc in the presence of a catalytic amount of chiral ligand[a]

Entry	Ligand	Conversion to **20** (%)[b]	Conversion to benzyl alcohol (%)	Ee[c,d]
1	**8c**	18	11	20
2	**8d**	23	3	82
3	**8e**	8	8	14
4	**8f**	26	5	55
5	**8g**	29	7	93[e]
6	**8h**	22	18	16
7	**9d**	41	3	71
8	**9e**	83	4	74
9	**9f**	41	8	63
10	**9g**	65	11	88[e]
11	**9h**	13	15	25
12	**10h**	25	10	20
13	**14**	35	10	30
14	**17**	35	8	54[e]

[a] Reaction conditions: 2.5 mmol benzaldehyde, 150 mol% of diethylzinc in hexane, 6 mol% of ligand (catalyst); reaction temperature 0 °C, reaction time 24 h. [b] Conversion calculated from ^{1}H NMR spectrum. [c] The alcohol **20** was converted to the diastereomeric forms of **21** by esterification with (*S*)-*O*-acetylmandelic acid, the de of **21** was evaluated by ^{1}H NMR. [d] The configuration of the major form of compound **20** was finally found to be *S* with all ligands. [e] The ee was found to be 88% for entry 5, 89% for entry 10 and 55% for entry 14 by GC of **20** on a chiral column.

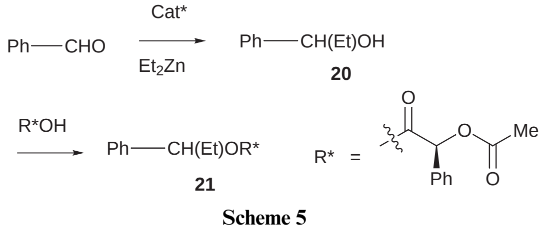
the hydroxylamine **14** with the heterocyclic diamino group as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde.

Enantioselective catalysis

The bicyclic compounds **8c–h**, **9d–h 10h** and **17** and the tetracyclic compound **14** were tested as chiral ligands in the enantioselective reaction of benzaldehyde with diethylzinc. The reaction was performed in hexane at 0 °C using 150 mol% of diethylzinc and 6 mol% of the chiral ligand. In the presence of compounds **8c–h** only 16 to 40% of the starting material was converted (Table 5). In addition to the expected 1-phenylpropan-1-ol **20** (8–29%), a relatively large amount of benzyl alcohol was formed. With compounds **9d–g** the yield of **20** increased and the relative amount of benzyl alcohol formed decreased.

In all cases the (*S*)-enantiomer of **20** was formed in excess. The ee values were determined by conversion into the diastereomeric esters **21** by reaction with (*S*)-*O*-acetylmandelic acid[15] and comparison of the intensities of the most characteristic ^{1}H NMR signal (triplet at δ 0.63 for *SR* diastereomer and at δ 0.88 for *SS* diastereomer). In the case of ligands **8g**, **9g** and **17**, the ee of **20** was also determined by GC on a chiral column (see Table 5, entries 5, 10 and 14).

The highest ee (93%) could be achieved with compound **8g** which possesses an additional stereogenic center and a tertiary alcohol group in the β-hydroxyalkyl moiety [$R^1 = CH(Me)C(Ph)_2OH$]. Almost the same ee (94%) was achieved with compound **3** [$R^1 = CH(Me)C(Ph)_2OH$], however, in this case the conversion to **20** was found be 100%.[16] On the other hand, ligand **8d** [$R^1 = C(Me)_2CH_2OH$] without an additional stereogenic center and with a primary alcohol group gave rise to formation of **20** with an ee of 82%, again less than compound **3** [$X = O, R^1 = C(Me)_2CH_2OH$] which yielded a slightly higher ee with 100% conversion.[4]



Scheme 5

Conclusion

Thus, as a result of these studies, it can be concluded that the use of ligands **8** in which two bicyclic ring systems are joined together does not afford a *synergetic effect* in the enantioselective catalysis of the reaction between diethylzinc and benzaldehyde. Rather, the nature of the R^1 substituent is crucial for the enantioselectivity as is indicated by comparison of the ee values (Table 5). However, the larger steric congestion in such molecules diminishes the reaction rate considerably, thus reducing the conversion of the starting material. In ligands **9d–h**, the steric congestion is decreased compared to compounds **8**. For this reason, with these ligands conversion is somewhat higher, however, the ee does not exceed 88% (**9g**).

Experimental

General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. All melting points are uncorrected. Elemental analysis: Division Routine Analytical Section, Fachbereich Chemie, University of Marburg, NMR: Bruker AMX 500, AM 400 and AC 300, using the residues of ^{1}H ($\delta = 7.24$) or ^{13}C ($\delta = 77.0$) of the solvent $CDCl_3$ as internal standard. Unless otherwise stated, the ^{1}H NMR spectra were recorded at 300 MHz, the ^{13}C NMR spectra at 75 MHz in $CDCl_3$, MS: Varian CH 7 (EI), IR: Beckman IR 33 and Bruker IFS 88-FT-IR. In some cases the enantiomeric excess (ee) was also determined by GC (Siemens SICHROMAT 3, Helium, 0.8 bar, 120 °C) on a chiral column (25 m × 0.25 mm, XE 60 PEA CHROMPACK). Optical rotation: Polarimeter Perkin-Elmer 241, at 589 nm. Diethyl (*R*,*R*)-tartrate was purchased from Merck and diethylzinc (1.0 M in hexane fraction) from Aldrich; both were used as received.

Compound **4** was prepared as described earlier.[6]

Diethyl (2*R*,3*R*)-2-allyloxy-3-hydroxybutane-1,4-dioate 15

A solution of diethyl (*R*,*R*)-tartrate (5.15 g, 25 mmol) and allyl bromide (2.6 ml, 31 mmol) in Et_2O (100 mL) was gently refluxed in the dark. Within 10 min, well-dried silver(I) oxide (5.8 g, 25 mmol) was added in three portions. After refluxing for 2 h the reaction mixture was stirred for 24 h. The solid residue was separated and washed repeatedly with Et_2O. The combined ethereal solutions were dried over $MgSO_4$. After removal of the solvent, the volatile components were removed at 0 °C under reduced pressure (*ca.* 0.1 mbar). Compounds **4** and **15** were separated by column chromatography [silica gel; EtOAc–light petroleum (bp 40–60 °C), 1 : 1], $[\alpha]_D^{19}$ +42.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ: 1.24 (t, 3H, *J* 7.6, OCH_2CH_3), 1.25 (t, 3H, *J* 7.0, OCH_2CH_3), 3.08 (d, 1H, *J* 8.6, OH), 3.84 (ddd, 1H, ^2J 12.6, ^3J 6.5, ^4J 1.1, CH_2-CH=), 4.20 (m, 6H, OCH_2CH_3, OCH_2CH_3, 2-H, CH_2-CH=), 4.54 (dd, 1H, *J* 8.6, 2.4, 3-H), 5.12 (m, 2H, =CH_2), 5.74 (m, 1H, CH=); ^{13}C NMR δ: 13.9 (2C, OCH_2CH_3), 61.3 (OCH_2), 61.9 (OCH_2), 72.0 (CH_2=), 72.2 (C-2), 78.2 (C-3), 118.0 (=CH_2), 133.3 (CH=), 169.1 (C=O), 171.0 (C=O).

Reduction of compound 4 and treatment of the resulting aldehydes with *N*-alkylhydroxylamines: general procedure

A 1 M solution of DIBAL-H in hexane (25 mL) was added dropwise to a solution of **4** (10 mmol) in Et_2O (30 mL) over 30 min at −78 °C. The reaction mixture was stirred for 80 min. Subsequently MeOH (0.2 mL, 5 mmol) was added and the mixture was warmed to 0 °C. Then water (1.5 mL, 83 mmol) was added dropwise to the mixture which was then stirred for 10 min at 0–5 °C.

A solution of *N*-alkylhydroxylamine hydrochloride (20 mmol) in Et_2O or CH_2Cl_2 was added. Then Et_3N (20 mmol) was added dropwise to the reaction mixture within 5 min at 0–5 °C. After 15 min, molecular sieves (4 g, 4 Å) were added. Subsequently, the mixture was stirred for 2 h at 0–5 °C and then for 2 days at room temperature. The solid residue was separated and washed several times with Et_2O or $CHCl_3$. The products were separated and purified by column chromatography [silica gel; EtOAc–light petroleum (bp 40–60 °C), 1 : 1].

A similar procedure was used for the DIBAL-H reduction of **9d**–**g**, and subsequent treatment with corresponding alkylhydroxylamines provided the compounds **8d**–**g**.

General procedure for Swern oxidation of compounds 10c–e

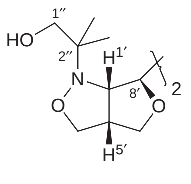
A solution of dimethyl sulfoxide (0.12 g, 1.46 mmol) in dichloromethane was added dropwise to a solution of oxalyl chloride (0.1 g, 0.76 mmol) in dichloromethane (5 mL) at −78 °C under nitrogen. After 10 min compound **10** (0.73 mmol) in dichloromethane (2 mL) was added dropwise. Stirring was continued for 2 h at −78 °C before triethylamine (0.19 g, 1.82 mmol) was added. Subsequently the temperature was raised to 0 °C before hydrolysis was performed by addition of water (0.1 mL). Successively $MgSO_4$ (approximately 1 g) and the *N*-alkylhydroxylamine hydrochloride (0.73 mmol) were added. The reaction mixture was stirred for 24 h at room temperature. After filtration the organic layer was washed twice with water and then dried with $MgSO_4$. Removal of the solvent was followed by column chromatography [silica gel; EtOAc–light petroleum (bp 40–60 °C), 1 : 1].

Crystals of **8b** suitable for X-ray analysis were obtained from a solution of Et_2O–light petroleum (bp 40–60 °C) (1 : 4) at ~−15 °C.

(1′*S*,1″*S*,5′*R*,8′*S*)-8,8′-Bi{2′-(1″-phenylethyl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octane} 8c

Yield: 29%, mp 126–128 °C; $[\alpha]_{\mathrm{D}}^{19}$ −14.4 (*c* 0.25, $CHCl_3$); ν_{max}(KBr) 2867, 1437, 1069 cm^{-1}; ^1H NMR (500 MHz) see Table 2. Additional data, δ: 1.36 (d, 2 × 3H, *J* 5.5, CH_3), 3.85 (q, 2 × 1H, *J* 5.5, N-CH), 7.2–7.37 (m, Ar-H); $J_{4'\alpha,4'\beta}$ 6.6, $J_{6'\alpha,6'\beta}$ 7.7; ^{13}C NMR δ: 21.5 (CH_3), 49.0 (C-5′), 63.2 (C-1″), 70.5 (C-1′), 70.6 (C-6′), 73.5 (C-4′), 83.2 (C-8′), 127.1–128.2 (Ar); MS (EI) *m*/*z* (rel. int.) 436 (5%), 105 (100).

(1′*S*,5′*R*,8′*S*)-8,8′-Bi{2′-(1″-hydroxy-2″-methylpropan-2″yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octane} 8d



Yield: 28%, mp 90–93 °C; $[\alpha]_{\mathrm{D}}^{19}$ +7.37 (*c* 0.19, $CHCl_3$); ν_{max}(KBr) 3446, 2987, 1478, 1398 cm^{-1}; ^1H NMR see Table 2. Additional data, δ: 1.00 (s, 2 × 3H, CH_3), 1.04 (s, 2 × 3H, CH_3), 2.09 (br s, 6H, 2 × OH and probably 2 × H_2O), 3.33 (d, 2 × 1H, $J_{1''a,1''b}$ 11.1, 1″a-H), 3.53 (d, 2 × 1H, $J_{1''a,1''b}$ 11.1, 1b″-H); $J_{4'\alpha,4'\beta}$ 8.7, $J_{6'\alpha,6'\beta}$ 8.2; ^{13}C NMR (75 MHz) δ: 18.3 (CH_3), 21.8 (CH_3), 50.4 (C-5′), 62.4 (C-2″), 67.3 (C-1′), 69.8 (C-1″), 72.7 (C-4′), 72.9 (C-6′), 84.05 (C-8′); MS (EI) *m*/*z* 341 (M^+ − 31, 100%).

(1′*S*,2″*R*,5′*R*,8′*S*)-8,8′-Bi{2′-(1″-hydroxybutan-2″-yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octane} 8e

Yield: 23%, mp 110–112 °C; $[\alpha]_{\mathrm{D}}^{19}$ −11.82 (*c* 0.11, $CHCl_3$); ^1H NMR see Table 2. Additional data, δ: 0.87 (t, 2 × 3H, *J* 7.5, 4″-H), 1.49 (qdd, 2 × 1H, *J* 7.5, 14.0, 3.4, 3″a-H), 1.63 (qdd, 2 × 1H, *J* 7.5, 14.0, 8.9, 3″b-H), 2.57 (m, 2 × 1H, N-C*H*), 3.59 (m, 2 × 2H, 1″-H); $J_{4'\alpha,4'\beta}$ $J_{6'\alpha,6'\beta}$ 8.7; ^{13}C NMR δ: 10.6 (C-4″), 19.9 (C-3″), 49.1 (C-5′), 62.2 (C-1″), 66.0 (C-2″), 70.9 (C-4′), 71.1 (C-1′), 73.7 (C-6′), 83.4 (C-8′); MS (EI) *m*/*z* (rel. int.) 372 (M^+, 0.2%), 341 (100).

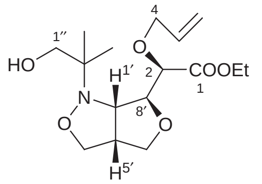
(1′*S*,1″*S*,2″*R*,5′R,8′S)-8,8′-Bi{2′-(1″-hydroxy-1″-phenylpropan-2″-yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octane} 8f

Yield: 15%, $[\alpha]_{\mathrm{D}}^{19}$ −21.42 (*c* 0.07, $CHCl_3$); ^1H NMR see Table 2. Additional data, δ: 0.82 (d, 2 × 3H, $J_{2'',3''}$ 6.5, 3″-H), 1.36 (s, 2 × 1H, OH), 2.91 (dq, 2 × 1H, $J_{1'',2''}$ 2.2, $J_{2'',3''}$ 6.5, 2″-H), 4.88 (d, 2 × 1H, $J_{1'',2''}$ 2.2, 1″-H), 7.40 (m, Ar-H); $J_{4'\alpha,4'\beta}$ 8.9, $J_{6'\alpha,6'\beta}$ 8.8; ^{13}C NMR δ: 8.4 (q), 48.7 (d), 64.6 (d), 71.0 (d), 71.2 (t), 73.0 (t), 73.8 (d), 82.5 (d), 125.8–140.0 (Ar); Anal. Calc. for $C_{28}H_{36}N_2O_6$ (496.6): C, 67.72; H, 7.31; N, 5.64. Found: C, 67.26; H, 7.49; N, 5.28%.

(1′*S*,2″*S*,5′*R*,8′*S*)-8,8′-Bi{2′-(1″,1″-diphenyl-1″-hydroxypropan-2″-yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octane} 8g

Yield: 35%, mp 174–177 °C; $[\alpha]_{\mathrm{D}}^{19}$ −57.0 (*c* 0.1, $CHCl_3$); ν_{max}(KBr) 3455, 2875, 1448, 1069 cm^{-1}; ^1H NMR (500 MHz) see Table 2. Additional data, δ: 0.89 (d, 2 × 3H, $J_{2'',3''}$ 6.7, 3″-H), 4.15 (q, 2 × 1H, $J_{2'',3''}$ 6.7, 2″-H), 7.30 (m, Ar-H); $J_{4'\alpha,4'\beta}$ 8.9, $J_{6'\alpha,6'\beta}$ 8.9; ^{13}C NMR δ: 14.1 (C-3″), 49.4 (C-5′), 65.3 (C-2″), 68.7 (C-1′), 71.1 (C-4′), 73.2 (C-6′), 79.8 (C-1″), 82.4 (C-8′), 125.6–147.5 (Ar).

Ethyl (1′*S*,2*R*,5′*R*,8′*S*)-2-[2′-(1″-hydroxy-2″-methylpropan-2″-yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octan-8′-yl]-3-oxahex-5-enoate 9d



Yield: 14%, $[\alpha]_{\mathrm{D}}^{19}$ +34.0 (*c* 0.13, $CHCl_3$); ν_{max}(neat) 3396, 2832, 1745, 1458, 1385 cm^{-1}; ^1H NMR (400 MHz): see Table 3. Additional data, δ: 1.03 (s, 6H, $2CH_3$), 3.34 (d, 1H, ^2J 11.1, 1″a-H), 3.57 (d, 1H, ^2J 11.1, 1″b-H); $J_{4'\alpha,4'\beta}$ 5.7, $J_{6'\alpha,6'\beta}$ 8.8, $J_{4a,4b}$ 12.3, $J_{5,6cis}$ 10.3, $J_{5,6trans}$ 17.2; ^{13}C NMR δ: 14.2 (OCH_2CH_3), 18.0 (CH_3), 23.3 (CH_3), 50.7 (C-5′), 61.2 (OCH_2CH_3), 61.9 (C-2″), 66.4 (C-1′), 70.0 (C-1″), 72.2 (C-4), 72.7 (C-4′), 73.0 (C-6′), 78.3 (C-2), 85.2 (C-8′), 118.4 (C-6), 133.7 (C-5), 170.1 (C-1); MS (EI) *m*/*z* (rel. int.) 329 (M^+, 1%), 298 (M^+ − 31, 100); Anal. Calc. for $C_{16}H_{27}NO_6$ (329.3): C, 58.34; H, 8.26; N, 4.25. Found: C, 58.59; H, 8.48; N, 4.56%.

Ethyl (1′*S*,2*R*,2″*R*,5′*R*,8′*S*)-2-[2′-(1″-hydroxybutan-2″-yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octan-8′-yl]-3-oxahex-5-enoate 9e

Yield: 11%; $[\alpha]_{\mathrm{D}}^{19}$ +20.90 (*c* 0.43, $CHCl_3$); ^1H NMR (500 MHz) see Table 3. Additional data, δ: 0.88 (t, 3H, *J* 7.5, 4″-H), 1.51 (m, 1H, 3″a-H), 1.64 (m, 1H, 3″b-H), 2.59 (m, 1H, 2″-H), 3.57 (dd, 1H, ^2J 11.9, ^3J 5.4, 1″a-H), 3.64 (dd, 1H, ^2J 11.9, ^3J 3.2, 1″b-H); ^{13}C NMR δ: 10.8 (C-4″), 14.3 (OCH_2CH_3), 19.8 (C-3″), 49.2 (C-5′), 61.3 (OCH_2CH_3), 62.1 (C-1″), 66.1 (C-2″), 70.2 (C-1′), 71.1 (C-4), 72.2 (C-4′), 73.8 (C-6′), 78.2 (C-2), 83.5 (C-8′), 118.7 (C-6) 133.6 (C-5), 170.3 (C=O); MS (EI) *m*/*z* (rel. int.) 329 (5%), 298 (100).

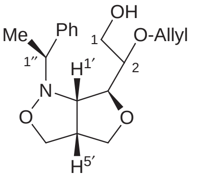
Ethyl (1′*S*,1″*S*,2*R*,2″*R*,5′*R*,8′*S*)-2-[2′-(1″-hydroxy-1″-phenylpropan-2″-yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octan-8′-yl]-3-oxahex-5-enoate 9f

Yield: 30%; $[\alpha]_{\mathrm{D}}^{19}$ −10.65 (*c* 0.31, $CHCl_3$); ^1H NMR see Table 3. Additional data, δ: 0.87 (d, 3H, $J_{2'',3''}$ 6.5, 3″-H), 2.93 (dq, 1H, $J_{2'',3''}$ 6.5, $J_{1'',2''}$ 1.8, 2″-H), 4.87 (d, 1H, $J_{1'',2''}$ 1.8, 1″-H), 7.3 (m, Ar-H); $J_{4'\alpha,4'\beta}$ 8.8, $J_{6'\alpha,6'\beta}$ 8.9, $J_{4a,4b}$ 12.4; ^{13}C NMR δ: 8.2 (C-3″), 14.0 (OCH$_2$*C*H$_3$), 48.4 (C-5′), 61.1 (O*C*H$_2$CH$_3$), 64.6 (C-2″), 70.4 (C-1′), 70.9 (C-4), 72.1 (C-4′), 73.5 (C-1″), 73.8 (C-6′), 77.3 (C-2), 83.0 (C-8′), 118.8 (C-6), 125.7, 126.5, 127.0, 128.0, 128.3 (Ar), 133.3 (C-5), 140.5 (Ar), 170.0 (C=O); Anal. Calc. for $C_{21}H_{29}NO_6$ (343.4): C, 64.43; H, 7.47; N, 3.58. Found: C, 64.64; H, 7.36; N, 3.89%.

Ethyl (1′*S*,2*R*,2″*S*,5′*R*,8′*S*)-2-[2′-(1″,1″-diphenyl-1″-hydroxypropan-2″-yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octan-8′-yl]-3-oxahex-5-enoate 9g

Yield: 17%; $[\alpha]_D^{19}$ −28.5 (*c* 0.34, CHCl$_3$); ^{1}H NMR see Table 3. Additional data, δ: 0.91 (d, 3H, $J_{2'',3''}$ 6.6, 3″-H), 4.07 (q, 1H, $J_{2'',3''}$ 6.6, 2″-H), 7.0–7.5 (m, Ar-H); $J_{4'\alpha,4'\beta}$ $J_{6'\alpha,6'\beta}$ 9.0; ^{13}C NMR δ: 14.3 (OCH$_2$*C*H$_3$), 14.7 (CH$_3$), 49.3 (C-5′), 61.2 (O*C*H$_2$CH$_3$), 64.6 (C-2″), 68.7 (C-1′), 71.1 (C-4′), 72.2 (C-4), 73.9 (C-6′), 77.3 (C-2), 79.7 (C-1″), 83.6 (C-8′), 118.8 (C-6), 125.9–128.01 (Ar), 133.6 (C-5), 145.7, 148.0 (Ar), 170.2 (C=O).

(1′*S*,1″S,2*S*,5′*R*,8′*S*)-2-[2′-(1″-Phenylethyl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octan-8′-yl]-3-oxahex-5-en-1-ol 10c



Yield: 14% mp 74–78 °C; $[\alpha]_D^{19}$ −14.62 (*c* 0.13, CHCl$_3$); ν_{max}(KBr) 3495, 2934, 1459 cm^{-1}; ^{1}H NMR δ: 1.39 (d, 3H, *J* 6.5, CH$_3$), 3.30 (m, 1H, 5′-H), 3.56 (m, 3H, 2-H, 4′α-H, 6′α-H), 3.93 (m, 5H, 6′β-H, 8′-H, 1″-H, 1-H), 4.09 (dd, 1H, *J* 12.7, 6.6, 4a-H), 4.12 (dd, 1H, *J* 8.3, 6.3, 1′-H), 4.24 (dd, 1H, *J* 12.7, 5.5, 4b-H), 4.29 (dd, 1H, *J* 8.1, 8.7, 4′β-H), 5.17 (m, 2H, 6-H), 5.84 (m, 1H, 5-H), 7.26–7.37 (m, Ar-H); ^{13}C NMR δ: 21.7 (q), 48.3 (d), 62.4 (t), 63.0 (d), 70.3 (t), 70.5 (d), 71.3 (t), 74.0 (t), 78.1 (d), 84.8 (d), 117.0 (t), 127.2–128.4 (Ar), 134.9 (d); MS (EI) *m*/*z* (rel. int.) 319 (3.5%), 104 (100); Anal. Calc. for $C_{18}H_{25}NO_4$ (319.4): C, 67.69; H, 7.89; N 4.39. Found: C, 67.23; H, 7.45; N, 4.48%.

(1′*S*,2*S*,5′*R*,8′*S*)-2-[2′-(1″-Hydroxy-2″-methylpropan-2″-yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octan-8′-yl]-3-oxahex-5-en-1-ol 10d

Yield: 14%; $[\alpha]_D^{19}$ +12.85 (*c* 0.07, CHCl$_3$); ν_{max}(neat) 3468, 2936, 1468 cm^{-1}; ^{1}H NMR δ: 0.81 (s, 3H, CH$_3$), 0.89 (s, 3H, CH$_3$), 3.17 (m, 1H, 5′-H), 3.31 (d, 1H, $J_{1''a,1''b}$ 11.0, 1″a-H), 3.52 (d, 1H, $J_{1''a,1''b}$ 11.0, 1″b-H), 3.58 (m, 2H, 4′α/6′α-H), 3.75 (dd, 1H, $J_{1a,1b}$ 11.3, $J_{1a,2}$ 3.7, 1a-H), 3.83 (dd, 1H, $J_{1a,1b}$ 11.3, $J_{1b,2}$ 4.8, 1b-H), 3.9 (m, 2H, 4′β or 6′β-H, 4a-H), 4.01 (m, 3H, 1′-H, 4′β or 6′β-H, 8′-H), 4.16 (m, 2H, 4b-H, 2-H), 5.18 (m, 2H, 6-H), 5.86 (m, 1H, 5-H); ^{13}C NMR δ: 18.4 (q), 23.2 (q), 50.3 (d), 61.9 (s), 62.0 (t), 66.9 (d), 70.1 (t), 71.2 (t), 72.9 (t), 73.1 (t), 77.8 (d), 86.1 (d), 117.4 (t), 134.0 (d).

(1′*S*,2*S*,2″*R*,5′*R*,8′*S*)-2-[2′-(1″-Hydroxybutan-2″-yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octan-8′-yl]-3-oxahex-5-en-1-ol 10e

Yield: 11%; $[\alpha]_D^{19}$ +13.50 (*c* 0.23, CHCl$_3$); ^{1}H NMR δ: 0.92 (t, 3H, *J* 7.5, 4″-H), 1.54 (m, 1H, 3″a-H), 1.70 (m, 1H, 3″b-H), 2.63 (m, 1H, 1″a-H), 3.28 (m, 1H, 1″b-H), 3.57–4.26 (m, 13H), 5.23 (m, 2H, 6-H), 5.91 (m, 1H, 5-H); ^{13}C NMR δ: 10.5, 19.9, 48.7, 61.1, 62.3, 65.6, 70.6, 70.7, 71.4, 73.6, 78.1, 84.2, 117.7, 134.4; MS (EI) *m*/*z* 287 (M$^+$); Anal. Calc. for $C_{14}H_{25}NO_5$ (287.4): C, 58.52; H, 8.77; N, 4.87. Found: C, 58.23; H, 8.55; N, 4.38%.

Ethyl (1′*S*,2*R*,5′*R*,8′*S*)-hydroxy[2′-(1″-hydroxy-2″-methylpropan-2″-yl)-3′,7′-dioxa-2′-azabicyclo[3.3.0]octan-8′-yl]acetate 17

Yield: 52% mp 104–106 °C; $[\alpha]_D^{19}$ −4.3 (*c* 0.28, CHCl$_3$); ν_{max}(KBr) 3485, 2972, 2929, 1742 cm^{-1}; ^{1}H NMR (300 MHz) see Table 3. Additional data, δ: 1.03 (s, 3H, CH$_3$), 1.04 (s, 3H, CH$_3$), 2.0 (s, 2H, OH), 3.33 (d, 1H, $J_{1''a,1''b}$ 10.8, 1″a-H), 3.55 (d, 1H, $J_{1''a,1''b}$ 10.8, 1″b-H); $J_{4'\alpha,4'\beta}$ 8.2, $J_{6'\alpha,6'\beta}$ 8.9; ^{13}C NMR δ: 14.1 (C-OCH$_2$*C*H$_3$), 17.9 (CH$_3$), 23.3 (CH$_3$), 50.6 (C-5′), 62.1 (C-2″), 62.3 (C-O*C*H$_2$CH$_3$), 66.5 (C-1′), 70.1 (C-1″), 71.3 (C-2), 72.8 (C-4′), 73.5 (C-6′), 85.5 (C-8′), 172.7 (C=O).

In the case of the reaction with unsubstituted hydroxylamine the mixture of compounds **11h**, **12h** and **13h** was refluxed in toluene. The formation of a mixture of products was shown by TLC (100% EtOAc; R_f **9h** = 0.55, **14** = 0.22, **10h** = 0.16, **8h** = 0.07). Separation of four compounds (**8h**, **9h**, **10h** and **14**) was achieved by column chromatography [silica gel; EtOAc–light petroleum (bp 40–60 °C), 1 : 1] and traces of another two products could not be isolated. Spectral and other data of compounds **8h** and **14** are given in reference 8.

Ethyl (1′*S*,2*R*,5′*R*,8′*S*)-2-(3′,7′-dioxa-2′-azabicyclo[3.3.0]-octan-8′-yl)-3-oxahex-5-enoate 9h

Yield: 9%, mp 65–68 °C; $[\alpha]_D^{19}$ +76.4 (*c* 1.0, CHCl$_3$); ν_{max}(KBr) 3395, 2965, 2935, 1738 cm^{-1}; ^{1}H NMR (500 MHz) see Table 3. Additional data, $J_{4'\alpha,4'\beta}$ $J_{6'\alpha,6'\beta}$ 8.8; ^{13}C NMR δ: 14.0 (CH$_3$), 49.3 (C-5′), 60.9 (O*C*H$_2$CH$_3$), 67.2 (C-1′), 71.9 (C-4), 73.7 (C-6′), 75.9 (C-4′), 77.6 (C-2), 84.1 (C-8′), 118.1 (C-6), 133.6 (C-5), 169.9 (C=O); MS (EI) *m*/*z* (rel. int.) 257 (M$^+$, 5%), 41 (100); Anal. Calc. for $C_{12}H_{19}NO_5$ (257.3): C, 56.02; H, 7.44; N, 5.44. Found: C, 56.34; H, 7.69; N, 5.21%.

(1′*S*,2*S*,5′*R*,8′*S*)-2-(3′,7′-Dioxa-2′-azabicyclo[3.3.0]octan-8′-yl)-3-oxahex-5-en-1-ol 10h

Yield: 9%; $[\alpha]_D^{19}$ +47.76 (*c* 0.67, CHCl$_3$); ^{1}H NMR δ: 3.16 (m, 1H, *J* 8.6, 8.6, 7.4, 7.2, 5′-H), 3.4 (dd, 1H, *J* 8.6, 7.4, 6′β-H), 3.51 (dt, 1H, *J* 4.8, 4.4, 2-H), 3.53 (dd, 1H, *J* 8.9, 7.2, 4′β-H), 3.62 (dd, 1H, *J* 6.5, 4.8, 8′-H), 3.74 (ddd, 2H, *J* 10, 4.4, 4.8, 1-H), 3.87 (d, 1H, *J* 8.9, 4′α-H), 4.01 (dd, 1H, *J* 8.6, 6.5, 1′-H), 4.1 (m, 2H, 4-H), 4.24 (t, 1H, *J* 8.6, 6′α-H), 5.15 (m, 2H, 6-H), 5.86 (m, 1H, 5-H); ^{13}C NMR δ: 49.1 (C-5′), 62.1 (C-1), 67.9 (C-1′), 71.6 (C-4), 73.6 (C-6′), 75.9 (C-4′), 78.7 (C-2), 84.8 (C-8′), 117.4 (C-6), 134.8 (C-5); MS (EI) *m*/*z* 215 (M$^+$); Anal. Calc. for $C_{10}H_{17}NO_4$ (215.2): C, 55.80; H, 7.96; N, 6.50. Found: C, 55.44; H, 7.62; N, 6.34%.

Catalysis of the reaction of diethylzinc with benzaldehyde

Freshly distilled benzaldehyde (0.25 mL, 2.5 mmol) was added to the catalyst (0.15 mmol) in a 10 mL flask under argon. The clear solution was cooled to 0 °C, then a 1.0 M solution of diethylzinc in hexane (3.75 mL, 3.75 mmol) was added within a period of 20 min. The reaction mixture was stirred for 12 h at 0 °C, then the reaction was quenched with 1.5 M hydrochloric acid (10 mL). Subsequently the mixture was extracted three times with diethyl ether. The combined organic layer was dried with MgSO$_4$. After filtration and removal of the solvent at 30 °C/500 mm Hg, a non-racemic mixture of (*R*)- and (*S*)-1-phenylpropan-1-ol **20** was obtained in the yields as presented in Table 5. At this stage a small amount of the crude mixture was analysed by ^{1}H NMR spectroscopy to determine the degree of conversion to **20** and benzyl alcohol. After this determination, the mixture was concentrated *in vacuo* in order to remove excess benzaldehyde and benzyl alcohol. Compound **20** was converted to the ester **21** for ee determination as described below. In addition, for some probes ee values were determined by GC on a chiral column.

Determination of the enantiomeric excess of 1-phenylpropanol 20 by preparation of diastereomeric esters 21 obtained by reaction with (*S*)-(+)-*O*-acetylmandelic acid

1-Phenylpropan-1-ol, **20** (from the above concentrated mixture) (94.3 mg, 0.69 mmol) was dissolved in dichloromethane (10 mL) under nitrogen. The solution was cooled to −10 °C. Successively DMAP (5 mg), (*S*)-(+)-*O*-acetylmandelic acid (134 mg, 0.69 mmol) and DCC (143 mg, 0.69 mmol) were added. The reaction mixture was stirred for 2 h at −10 °C and an additional 12 h at 20 °C. Then the solution was separated from the precipitate and the solvent removed by distillation to yield crude **21** which was analysed by ^{1}H NMR spectroscopy; the de was determined from the corresponding triplets at δ 0.63 (for *RS*) and δ 0.88 ppm (for *SS*).

Crystal data for 8b

$C_{26}H_{34}N_2O_7$, $M_r = 486.55$, $F(000) = 520$, monoclinic, $a = 11.444(1)$, $b = 6.006(1)$, $c = 18.591(1)$ Å, $\beta = 91.67(1)°$, $V = 1277.4(3)$ Å^3, space group $I2$ (no. 5), $Z = 2$, $D_x = 1.265$ g cm^{-3}, μ(Cu-Kα) = 7.57 cm^{-1}. The experimental data were collected at room temperature on a Nonius CAD4 diffractometer using graphite monochromated Cu-Kα radiation ($\lambda = 1.5478$ Å). An absorption correction was not applied. The structure was solved by direct methods.[17] Full matrix refinement on F^2 values[18] led to the final R values $wR_2 = 0.140$ (all independent 1589 data) and the conventional $R = 0.054$ [1430 reflections > $2\sigma(I)$].†

Crystal data for 14

$C_{10}H_{16}N_2O_4$, $M_r = 228.25$, $F(000) = 488$, orthorhombic, $a = 5.968(1)$, $b = 8.448(1)$, $c = 21.719(1)$ Å, $V = 1095.0(2)$ Å^3, space group $P2_12_12_1$ (no. 19), $Z = 4$, $D_x = 1.385$ g cm^{-3}, μ(Cu-Kα) = 9.03 cm^{-1}. The experimental data were collected at room temperature on a Nonius CAD4 diffractometer using graphite monochromated Cu-Kα radiation ($\lambda = 1.5478$ Å). An absorption correction was not applied. The structure was solved by direct methods.[17] Full matrix refinement on F^2 values[18] lead to the final R values $wR_2 = 0.195$ (all independent 1760 data) and the conventional $R = 0.064$ [1640 reflections > $2\sigma(I)$].†

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