

Synthesis and application of new (*threo*)- and (*erythro*)-amino alcohols based on the octahydro-cyclopenta[*b*]pyrrole system in the catalytic enantioselective addition of diethylzinc to benzaldehyde

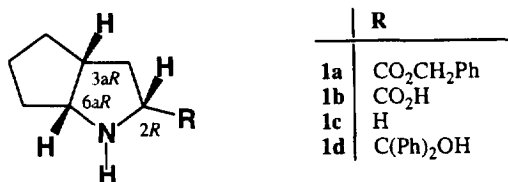
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Abstract: Asymmetric catalytic ethylation of benzaldehyde utilizing a series of new, artificial β -amino alcohols based on the octahydro-cyclopenta[*b*]pyrrole system is presented. A systematic investigation on the inductive correlation of up to four catalyst-internal stereogenic centers and on steric aspects of these structures has been conducted with diastereomerically pure, bicyclic (*erythro*)- and (*threo*)-compounds **2–13**. Chiral ligands have been developed reaching excellent enantioselectivities, e.g. enantiomeric excesses up to 91% with a favored (*R*)-induction. © 1997 Elsevier Science Ltd

Introduction

New artificial auxiliaries with catalytic efficiency suitably designed for the catalyst-controlled, enantioselective addition of diethylzinc to benzaldehyde¹ have been synthesized based on the enantiomerically pure (*2R,3aR,6aR*)-octahydro-cyclopenta[*b*]pyrrole system starting from the industrial waste material (*all-R*)-**1a** (Scheme 1).²



Scheme 1. Derivatives of the (*2R,3aR,6aR*)-octahydro-cyclopenta[*b*]pyrrole system.

Diastereomerically pure, bicyclic (*erythro*)- and (*threo*)-*sec*-amino-*sec*-alcohols **2–8** and the corresponding *tert*-amino-*sec*-alcohols **9–13**, e.g. frameworks with four spatial packed stereogenic centers — including four diastereomeric configurations with ($\alpha R, \beta R$)-, ($\alpha S, \beta R$)-, ($\alpha S, \beta S$)-, and ($\alpha R, \beta S$)-stereochemistry — were tested concerning their catalytic and inductive ability at room temperature.

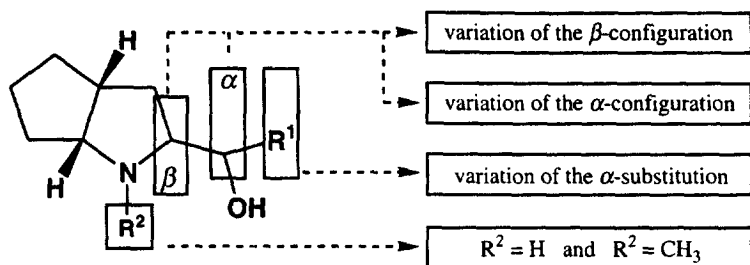
A systematic empirical investigation changing the stereochemical properties of the *sec*- and *tert*-amino alcohol structures has been conducted. Concentration was focussed on the stereochemical correlation of the (ligand-) internal stereogenic centers in addition to steric aspects of the catalyst structure (Scheme 2: additional *N*-methylation, variation of the substitution pattern in α -position) to improve the enantioselective and catalytic efficiency.

For comparison, related structures with various α -*bis*-substitution patterns including cycloalkanol fragments have also been tested as auxiliaries in this reaction.²⁰

Synthesis of catalysts

In the context of our studies on the utilization of industrial waste materials² we used the enantiomerically pure, bicyclic (*all-R*)-**1a**,³ -**1b** or -**1d**^{2p} as starting materials for the synthesis of

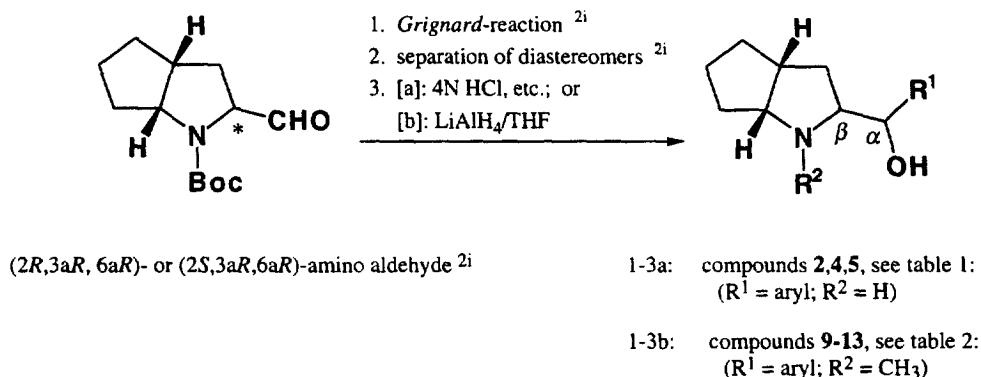
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Scheme 2. Description of the general structure of amino alcohols 2–13 (for R^1 and R^2 see Tables 1 and 2).

new β -amino alcohol structures employing different methods: The diastereo- and regioselective α -hydroxyalkylation of the *N*-nitroso derivative of (*all-R*)-**1d**^{2b} or Grignard additions to diastereomeric (*2R,3aR,6aR*)- and (*2S,3aR,6aR*)- α -amino aldehydes²ⁱ of **1a**.

The previously published preparation of (*threo*)- and (*erythro*)-*sec*-amino-*sec*-alcohols **2,4,5** by the diastereodivergent conversion of octahydro-cyclopenta[*b*]pyrrole-based (*2R,3aR,6aR*)- and (*2S,3aR,6aR*)-amino aldehydes with aromatic Grignard reagents²ⁱ was extended by the LiAlH_4 reduction of the *N*-Boc-protected intermediates (Scheme 3, reaction step 3b) yielding the corresponding *N*-methylated structures ($\alpha R, \beta R$)-**9**, ($\alpha S, \beta R$)-**9,10,12,13**, ($\alpha S, \beta S$)-**9,11** and ($\alpha R, \beta S$)-**9,10,13** with a secondary alcohol function (the respective aryl substituent and the stereochemistry of these products are given in Table 2).

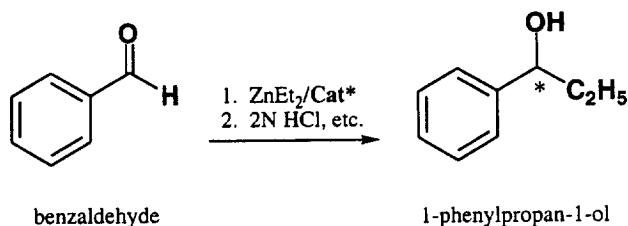


Scheme 3. Synthesis of catalysts **2,4,5** and **9-13**.

Several ($\alpha R, \beta S$)-configured *sec*-amino systems ($\alpha R, \beta S$)-**3,6-8** were prepared by an alternative synthetic approach using the enantiomerically pure heterocyclic amine (*all-R*)-**1d**²ⁱ as starting material in a diastereoselective α -hydroxyalkylation with aromatic aldehydes.^{2g}

Results and discussion

The stereodifferentiating ability of selected (*erythro*)- and (*threo*)-amino-*sec*-alcohols—combining an ephedrine-analogue building block and a highly rigid, five-membered prolinol fragment—with a secondary or tertiary amino function have been tested in the enantioselective addition of diethylzinc to benzaldehyde at room temperature (Scheme 4). For these series of β -amino alcohols (Tables 1 and 2) concentration was focussed on the systematic modification of stereochemical properties, e.g. the inductive correlation between the fixed stereogenic centers in the bridged C3a- and C6a-positions of the octahydro-cyclopenta[*b*]pyrrole-basis and the newly generated stereogenic center in α -position. Furthermore, the correlation between the stereogenic centers in α - and β -position (on the “ethylene” bridge between the *N* and *O*-coordination centers of the ligand) were changed.



Scheme 4. Enantioselective catalytic ethylation of benzaldehyde in the presence of optical active catalysts (Cat*): **2–13** (the results are summarized in Tables 1 and 2).

Table 1. Enantioselective addition of diethylzinc to benzaldehyde, product: 1-phenylpropan-1-ol

Catalyst*	<i>N</i> -substituent R ²	substituent R ¹	conc. [mol %]	temp. [°C]	yield [%]	<i>e.e.</i> [%] ^a	config.
($\alpha R, \beta R$)-2	H	4-methyl-phenyl	5	20	67	8	<i>S</i>
($\alpha S, \beta R$)-2	H	4-methyl-phenyl	10	22	83	5	<i>S</i>
($\alpha S, \beta S$)-2	H	4-methyl-phenyl	5	23	74	13	<i>R</i>
($\alpha R, \beta S$)-2	H	4-methyl-phenyl	10	24	71	43	<i>R</i>
($\alpha R, \beta S$)-3	H	4-(<i>i</i> -propyl)-phenyl	10	24	67	35	<i>R</i>
($\alpha R, \beta S$)-4	H	1-naphthyl	5	22	73	75	<i>R</i>
($\alpha S, \beta R$)-4	H	1-naphthyl	10	21	74	13	<i>S</i>
($\alpha R, \beta S$)-5	H	2,5-dimethyl-phenyl	5	20	68	70	<i>R</i>
($\alpha R, \beta S$)-6	H	2,4-dichloro-phenyl	5	22	71	46	<i>R</i>
($\alpha R, \beta S$)-7	H	4-methoxy-phenyl	10	20	64	70	<i>R</i>
($\alpha R, \beta S$)-8	H	benzyl	5	25	68	16	<i>R</i>

a. Enantiomeric excess determined by GC analysis (SGE Cydec-B, chiral). Absolute configuration determined by optical rotation.

First experiments²ⁿ utilizing various *sec*-amino-*sec*-alcohols gave — independent of the stereochemical properties — only poor to mediocre enantioselectivities ranging between 5 and 75% *e.e.* [selected results with these α -*mono*-aryl ligands are given in Table 1: ($\alpha R, \beta R$)-catalyst: 8% *e.e.*; ($\alpha S, \beta R$)-catalysts: 5–13% *e.e.*, ($\alpha S, \beta S$)-catalyst: 13% *e.e.* and ($\alpha R, \beta S$)-catalysts: 16–75% *e.e.*].

Best results are obtained with (*erythro*)-($\alpha R, \beta S$)-compounds. Generally the bulkier the α -substituent, the more (*R*)-selectivity is favored (Table 1: R¹=benzyl: 16% *e.e.*; R¹=4-methyl-phenyl: 43% and R¹=1-naphthyl: 75%). Consequently, the corresponding *N*-methylated structures **9–13** were employed for this asymmetric process (Table 2).

With each *N*-methylated α -*mono*-aryl structure the α -stereochemistry determines the absolute

Table 2. Enantioselective addition of diethylzinc to benzaldehyde, product: 1-phenylpropan-1-ol

Catalyst*	<i>N</i> -substituent R ²	substituent R ¹	conc. [mol %]	temp. [°C]	yield [%]	<i>e.e.</i> [%] ^a	config.
($\alpha R, \beta R$)- 9	CH ₃	4-methyl-phenyl	2	23	81	83	<i>R</i>
($\alpha R, \beta R$)- 9	CH ₃	4-methyl-phenyl	5	21	86	91	<i>R</i>
($\alpha R, \beta S$)- 9	CH ₃	4-methyl-phenyl	5	23	76	83	<i>R</i>
($\alpha R, \beta S$)- 9	CH ₃	4-methyl-phenyl	10	20	78	77	<i>R</i>
($\alpha S, \beta R$)- 9	CH ₃	4-methyl-phenyl	5	25	69	51	<i>S</i>
($\alpha S, \beta S$)- 9	CH ₃	4-methyl-phenyl	5	22	72	54	<i>S</i>
($\alpha R, \beta S$)- 10	CH ₃	2,5-dimethyl-phenyl	5	20	70	62	<i>R</i>
($\alpha S, \beta R$)- 10	CH ₃	2,5-dimethyl-phenyl	5	24	73	61	<i>S</i>
($\alpha S, \beta S$)- 11	CH ₃	phenyl	5	24	69	61	<i>S</i>
($\alpha S, \beta R$)- 12	CH ₃	2,4,6-trimethyl-phenyl	5	20	76	35	<i>R</i>
($\alpha R, \beta S$)- 13	CH ₃	1-naphthyl	5	20	71	50	<i>R</i>
($\alpha S, \beta R$)- 13	CH ₃	1-naphthyl	5	21	67	88	<i>R</i>

a. Enantiomeric excess determined by GC analysis (SGE Cydec-B, chiral). Absolute configuration determined by optical rotation.

configuration of the predominately formed enantiomer, regardless of other stereogenic centers in C3a-, C6a- or C2-position: (αS)-configured β -amino alcohols preferentially yield the (*S*)-enantiomer of 1-phenylpropan-1-ol whereas with (αR)-ligands the (*R*)-addition product is preferred (for comparison, with the *sec*-amino-*sec*-alcohols the β -located stereogenic center dominates the sense of asymmetric induction, see Table 1). An exception to this rule are the results with the homochiral ($\alpha S, \beta R$)-configured amino alcohols ($\alpha S, \beta R$)-**12** and **-13**: For these compounds with a sterically demanding α -substitution (Table 2: R¹=2,4,6-trimethyl-phenyl and 1-naphthyl) the formation of (*R*)-configured product alcohols is observed instead of the expected (*S*)-ethylation product as obtained with ($\alpha S, \beta R$)-**9** and ($\alpha S, \beta R$)-**10** (Table 2: R¹=4-methyl-phenyl and 2,5-dimethyl-phenyl). Therefore the stereochemical course of this reaction utilizing ($\alpha S, \beta R$)-catalysts is not generally predictable but dependent on the steric properties of the α -substituent.

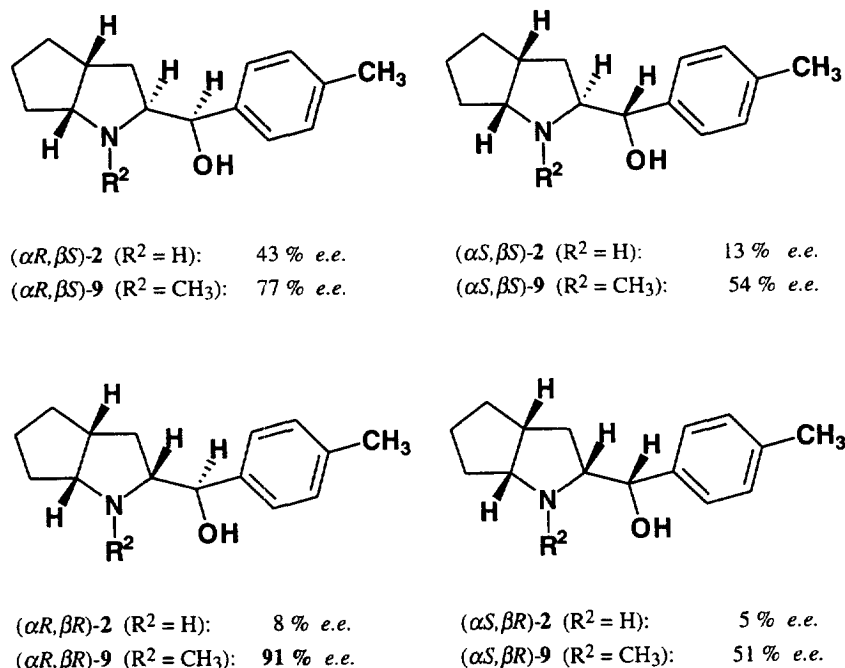
Remarkable for this series of *tert*-amino-*sec*-alcohols is the inconsistency of the enantioselectivities obtained with homochiral catalysts dependent on generally small changes of the steric demand in the α -position (Table 2, for example catalysts ($\alpha S, \beta R$)-**9**, **-10**, **-12**, **-13**: *e.e.* ranging between 88 and 35%).

The (*all-R*)-configured (*threo*)-compound ($\alpha R, \beta R$)-**9** (R¹=4-methyl-phenyl, Table 2) with an enantiomeric excess of 83% (catalyst concentration: 2 mol %) and 91% (catalyst concentration: 5 mol %), respectively, gives the best results. In case of suitable steric information provided by the α -

substituent — independent of an (αR)- or (αS)-configuration — a highly efficient stereoselection of the product formation is possible (Table 2, ligand ($\alpha S, \beta R$)-**13**: 88% *e.e.*, again the catalyst is based on a ($2R, 3aR, 6aR$)-backbone).

The additional *N*-methylation generally leads to a significant improvement in the enantioselectivity of the ethylation step (see Tables 1 and 2). In some cases a drastic increase is observed (for example, see compounds ($\alpha R, \beta R$)-**2** and ($\alpha R, \beta R$)-**9** or ($\alpha S, \beta R$)-**4** and ($\alpha S, \beta R$)-**13** with an increase from 8 to 91% and from 13 to 88% *e.e.*, respectively). One exception is ligand ($\alpha R, \beta S$)-**13**: Compared to the corresponding *sec*-amino-*sec*-alcohol ($\alpha R, \beta S$)-**4** the stereocontrol is diminished (50 and 75% *e.e.*).

Scheme 5 gives a survey of the stereochemical variation of the α -(4-methyl-phenyl)-*mono*-substituted compounds ($\alpha R, \beta R$)-**2**, ($\alpha S, \beta R$)-**2**, ($\alpha S, \beta S$)-**2** and ($\alpha R, \beta S$)-**2** as well as the corresponding *N*-methylated structures ($\alpha R, \beta R$)-**9**, ($\alpha S, \beta R$)-**9**, ($\alpha S, \beta S$)-**9** and ($\alpha R, \beta S$)-**9**. For this particular stereoselective transformation the *tert*-amino-*sec*-alcohol ($\alpha R, \beta R$)-**9** is — concerning the stereochemical properties — the most effective catalyst structure based on the octahydro-cyclopenta[*b*]pyrrole system: The *N*-methyl compound ($\alpha R, \beta R$)-**9** with its ($1'R, 2R, 3aR, 6aR$)-configuration provides the most favourable inductive correlation between the four ligand-internal stereogenic centers. With catalysts **2** and **9** the distinct influence of the *N*-alkylation can be observed: whereas the reaction of benzaldehyde and diethylzinc in the presence of catalyst ($\alpha R, \beta R$)-**9** leads to the (*R*)-enantiomeric product in high *e.e.*, the secondary amine, e.g. catalyst ($\alpha R, \beta R$)-**2** gives the corresponding (*S*)-enantiomer with a very low enantioselectivity.



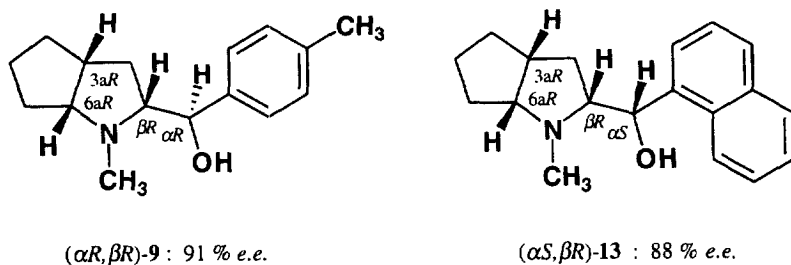
Scheme 5. Schematic survey on results obtained with stereoisomeric (*threo*)- and (*erythro*)-amino alcohols in the enantioselective catalyzed addition of diethylzinc to benzaldehyde.

Apparently a sterically demanding α -*bis*-substitution (for comparison see previously published results:²⁰ analogous α -*bis*-substituted compounds gave *e.e.* values between 91 and 96%⁴) seems to be more important for the enhancement of the stereocontrol originating from the ($2R, 3aR, 6aR$)-fragment than additional α -located chiral information.

This is demonstrated by the results obtained with the ($2R, 3aR, 6aR$)-systems ($\alpha R, \beta R$)-**9** and ($\alpha S, \beta R$)-

13 (Table 2): in spite of a reversed α -configuration both are equally effective catalysts, both with an (*R*)-induction for the formation of 1-phenylpropan-1-ol. This observation is further confirmed by the results of *sec*-amino-*sec*-alcohols containing an α -*mono*-aryl-substituent ($\alpha R, \beta R$)-**2** (Table 1: 8% *e.e.*), ($\alpha S, \beta R$)-**2** (Table 1: 5% *e.e.*) and the related α -*bis*-phenyl-system (βR)-**1d**^{2p} (in this case without an additional α -located stereogenic center, results: 96% *e.e.* and 97% *e.e.* using 5 and 10 mol % of (*all-R*)-**1d**, respectively⁴).

In conclusion, Scheme 6 shows the most efficient catalyst precursors based on the (*all-R*)-octahydro-cyclopenta[*b*]pyrrole-2-carboxylic acid benzyl ester (*all-R*)-**1a**. Noteworthy is the significant importance of the (2*R*,3*aR*,6*aR*)-framework, the tertiary amino function as well as the influence of a bulky α -hydroxy-substitution on the inductive efficiency of these auxiliaries. By comparison with earlier results,^{2o} additional chiral information in the α -position and the configuration of this stereogenic center — as discussed above — seem to play a less important role.



Scheme 6.

These (*R*)-inducing structures are similarly highly efficient, complementary catalysts with regard to several (*S*)-proline-derived catalysts with favored (*S*)-induction reported by Soai *et al.* (for example: (*S*)-diphenyl-(1-methylpyrrolidin-2-yl)-methanol).⁵

Experimental section

All reactions were carried out in oven-dried glassware under an argon atmosphere using anhydrous solvents. Melting points were taken on a melting point apparatus according to Dr Linström and are uncorrected. Optical rotations were measured on a Perkin–Elmer automatic polarimeter. IR spectra were recorded on a Philips PU 9706 spectrophotometer. The ¹H-NMR and ¹³C-NMR spectra were registered on a Bruker AM 300 spectrometer using TMS as the internal standard. Mass spectra were recorded on a Finnigan-MAT 212 (data system 300; CI, isobutane). Elemental analyses (C, H, N) were performed on a Carlo Erba Stumentalione (MOD 1104) analyzer. Gas chromatography (GC) was performed using a Shimadzu (GC-15A) instrument, 25 m column: SGE Cydex-B (chiral), *w*_i=0.25 mm, film thickness 0.25 μ m, 1 μ l product in *n*-hexane, detection: FID, carrier gas: nitrogen. Commercially available chemicals were used. The *N*-Boc-protected amino alcohols, e.g. the starting materials for the synthesis of compounds **9–13** were prepared according to a previously published procedure.^{2g, 2i, 2n} Furthermore, structures **2–8**^{2g, 2i, 2n} were also tested in the enantioselective ethylation of benzaldehyde.

General procedure 1

Reduction of *N*-Boc-protected amino alcohol structures with LiAlH₄ affording the corresponding *N*-methylated *tert*-amino alcohols **9–13**.

To a suspension of 1.1 g (29.4 mmol) lithium aluminium hydride in 70 ml THF — stirred for 1 h under reflux then cooled down to room temperature — 3.0 mmol of the respective *N*-*tert*-butoxycarbonyl derivative (dissolved in 10 ml of THF) are added dropwise within 30 min at room temperature under argon atmosphere. Then the reaction mixture is heated under reflux for 18 h. The heating bath is removed and 5% aqueous KOH is added cautiously at room temperature to destroy the excess reducing reagent. After two additional hours under reflux, the resulting white suspension is filtered,

the solids are intensively washed with additional solvent (THF or MTBE) and the combined organic phases are concentrated *in vacuo* after drying with MgSO₄ to afford colourless or slightly yellow oils as crude products. In all cases further purification of the crude products is accomplished by flash-chromatography or shortway distillation ("bulb-to-bulb" distillation utilizing a Büchi GKR-51 system) under reduced pressure. A more detailed description of the individual work-up is given below under the name of each compound. According to this general procedure the following products were prepared.

(α R, β R)-(1-Methyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(4-methyl-phenyl)-methanol (α R, β R)-9

Starting material: 1.0 g (3.0 mmol) (α R, β R)-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(4-methyl-phenyl)-methanol;²ⁱ work-up: purification by flash-chromatography (silica gel 60, eluents: *n*-hexane/EtOAc 2:8, addition of 40 ml triethylamine per liter of the solvent mixture, TLC: R_f-value: 0.40); yield: 0.57 g (77%), product: colourless oil; [α]_D²⁰ = -22.9 (*c*=0.88, CH₂Cl₂); IR (NaCl): ν =3600–3210 cm⁻¹ (OH), ¹H-NMR (CDCl₃): δ =1.17–1.68 (m, 7H, H3a, 2×H4, 2×H5, 2×H6), 1.94 (s, 3H, ArCH₃), 2.03–2.14 (m, 1H, 1×H3), 2.27 (s, 3H, NCH₃), 2.33–2.46 (m, 1H, 1×H3), 2.72–2.90 (m, 2H, H6a, H2), 3.86 (s, br., 1H, ArCHOH), 4.49 (s, 1H, ArCHOH), 7.07 (d, *J*=7.7 Hz, 2H, aromat.-H), 7.23 (d, *J*=8.2 Hz, 2H, aromat.-H); ¹³C-NMR (CDCl₃): δ =21.02 (1C, ArCH₃), 24.08, 32.98, 33.48, 37.98 (4C, C3, C4, C5, C6), 39.73 (1C, C3a), 41.59 (1C, NCH₃), 72.17, 72.33 (2C, C6a, C2), 74.09 (1C, ArCHOH), 125.15, 128.72 (4C, aromat.-C), 135.97, 141.95 (2C, q. aromat.-C); MS (CI, *i*-butane): 246 (MH⁺, 100%), 121 (C₈H₉O⁺, 23%); Anal. calc. for C₁₆H₂₃NO (245.2): C, 78.31; H, 9.45; N, 5.71; found: C, 78.22; H, 9.38; N, 5.73.

(α S, β R)-(1-Methyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(4-methyl-phenyl)-methanol (α S, β R)-9

Starting material: 0.75 g (2.26 mmol) (α S, β R)-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(4-methyl-phenyl)-methanol;²ⁱ work-up: purification by flash-chromatography (silica gel 60, eluents: *n*-hexane/EtOAc 2:8, addition of 10 ml triethylamine per liter of the solvent mixture, TLC: R_f-value: 0.65); yield: 0.43 g (78%), product: colourless oil; [α]_D²⁰ = +67.8 (*c*=0.35, CH₂Cl₂); IR (NaCl): ν =3610–3180 cm⁻¹ (OH); ¹H-NMR (CDCl₃): δ =1.26–1.74 (m, 9H, H3a, 2×H4, 2×H5, 2×H6, 2×H3), 2.33 (s, 3H, ArCH₃), 2.40 (s, 3H, NCH₃), 2.51–2.62 (m, 1H, H6a), 2.94–3.03 (m, 1H, H2), 3.69 (s, br., 1H, ArCHOH), 4.81 (d, *J*=3.3 Hz, 1H, ArCHOH), 7.14 (d, *J*=7.7 Hz, 2H, aromat.-H), 7.23 (d, *J*=8.2 Hz, 2H, aromat.-H); ¹³C-NMR (CDCl₃): δ =21.06 (1C, ArCH₃), 24.04, 31.34, 32.87, 33.49 (4C, C3, C4, C5, C6), 38.64 (1C, C3a), 38.91 (1C, NCH₃), 68.79, 72.05 (2C, C6a, C2), 72.84 (1C, ArCHOH), 125.23, 128.66 (4C, aromat.-C), 136.16, 138.67 (2C, q. aromat.-C); MS (CI, *i*-butane): 246 (MH⁺, 100%), 121 (C₈H₉O⁺, 45%); Anal. calc. for C₁₆H₂₃NO (245.2): C, 78.31; H, 9.45; N, 5.71; found: C, 78.22; H, 9.40; N, 5.68.

(α S, β S)-(1-Methyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(4-methyl-phenyl)-methanol (α S, β S)-9

Starting material: 0.80 g (2.4 mmol) (α S, β S)-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(4-methyl-phenyl)-methanol;²ⁱ work-up: purification by flash-chromatography (silica gel 60, eluents: petrol ether/EtOAc 7:3, addition of 15 ml triethylamine per liter of the solvent mixture, TLC: R_f-value: 0.41); yield: 0.50 g (85%), product: colourless solid (slow crystallization at +4°C in the fridge); [α]_D²⁰ = -46.0 (*c*=3.67, CH₂Cl₂); IR (KBr): ν =3600–3180 cm⁻¹ (OH); ¹H-NMR (CDCl₃): δ =0.82–0.96, 1.08–1.28, 1.38–1.79 (m, 7H, H3a, 2×H4, 2×H5, 2×H6), 1.85–2.04 (m, 1H, 1×H3), 1.80–1.95 (m, 1H, 1×H3), 2.34 (s, 3H, ArCH₃), 2.43 (s, 3H, NCH₃), 2.72–2.84 (m, 1H, H6a), 3.68 (s, 1H, ArCHOH), 3.76–3.84 (m, 1H, H2), 4.83 (d, *J*=2.7 Hz, 1H, ArCHOH), 7.12 (d, *J*=8.2 Hz, 2H, aromat.-H), 7.25 (d, *J*=7.7 Hz, 2H, aromat.-H); ¹³C-NMR (CDCl₃): δ =21.05 (1C, ArCH₃), 25.71, 26.74, 31.86, 34.02 (4C, C3, C4, C5, C6), 34.62 (1C, C3a), 39.02 (1C, NCH₃), 67.60, 68.89 (2C, C6a, C2), 70.53 (1C, ArCHOH), 125.34, 128.66 (4C, aromat.-C), 136.15, 138.88 (2C, q. aromat.-C); MS (CI, *i*-butane): 246 (MH⁺, 100%), 121 (C₈H₉O⁺, 34%); Anal. calc. for C₁₆H₂₃NO (245.2): C, 78.31; H, 9.45; N, 5.71; found: C, 78.12; H, 9.52; N, 5.75.

($\alpha R, \beta S$)-(1-Methyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(4-methyl-phenyl)-methanol ($\alpha R, \beta S$)-9

Starting material: 0.96 g (2.9 mmol) ($\alpha R, \beta S$)-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(4-methyl-phenyl)-methanol;²ⁱ work-up: purification by flash-chromatography (silica gel 60, eluents: *n*-hexane/EtOAc 1:9, addition of 50 ml triethylamine per liter of the solvent mixture, TLC: R_f -value: 0.51); yield: 0.59 g (83%), product: colourless, viscous oil; $[\alpha]_D^{20} = -40.2$ ($c=0.46$, CH_2Cl_2); IR (NaCl): $\nu=3620\text{--}3180\text{ cm}^{-1}$ (OH); $^1\text{H-NMR}$ (CDCl_3): $\delta=0.71\text{--}0.80$, $0.96\text{--}1.09$, $1.17\text{--}1.60$ (m, 7H, H3a, 2×H4, 2×H5, 2×H6), $1.60\text{--}1.74$ (m, 1H, 1×H3), $1.80\text{--}1.95$ (m, 1H, 1×H3), 2.28 (s, 3H, ArCH₃), 2.37 (s, 3H, NCH₃), $2.63\text{--}2.74$ (ddd, $J=9.4$ Hz, 6.6 Hz, 3.3 Hz, 1H, H6a), 3.57 (s, 1H, ArCHOH), $3.66\text{--}3.74$ (m, 1H, H2), 4.74 (d, $J=3.3$ Hz, 1H, ArCHOH), 7.07 (d, $J=8.2$ Hz, 2H, aromat.-H), 7.18 (d, $J=8.4$ Hz, 2H, aromat.-H); $^{13}\text{C-NMR}$ (CDCl_3): $\delta=21.06$ (1C, ArCH₃), 25.72 , 26.72 , 31.82 , 34.02 (4C, C3, C4, C5, C6), 34.63 (1C, C3a), 38.96 (1C, NCH₃), 67.56 , 68.86 (2C, C6a, C2), 70.47 (1C, ArCHOH), 125.32 , 128.66 (4C, aromat.-C), 136.18 , 138.82 (2C, q. aromat.-C); MS (CI, *i*-butane): 246 (MH^+ , 100%), 121 ($\text{C}_8\text{H}_9\text{O}^+$, 45%); Anal. calc. for $\text{C}_{16}\text{H}_{23}\text{NO}$ (245.2): C, 78.31; H, 9.45; N, 5.71; found: C, 78.40; H, 9.49; N, 5.72.

($\alpha S, \beta R$)-1'-(2,5-Dimethyl-phenyl)-(1-methyl-octahydro-cyclopenta[b]pyrrol-2-yl)methanol ($\alpha S, \beta R$)-10

Starting material: 0.80 g (2.32 mmol) work-up: ($\alpha S, \beta R$)-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(2,5-dimethyl-phenyl)-methanol;²ⁱ purification by flash-chromatography (silica gel 60, eluents: petrol ether/EtOAc 7:3, addition of 15 ml triethylamine per liter of the solvent mixture, TLC: R_f -value: 0.54); yield: 0.53 g (88%), product: colourless oil; $[\alpha]_D^{20} = +36.3$ ($c=0.69$, CH_2Cl_2); IR (NaCl): $\nu=3620\text{--}3100\text{ cm}^{-1}$ (OH); $^1\text{H-NMR}$ (CDCl_3): $\delta=1.34\text{--}1.79$ (m, 8H, H3a, 2×H4, 2×H5, 2×H6, 1×H3), 2.29 (s, 3H, ArCH₃), 2.36 (s, 3H, ArCH₃), 2.41 (s, 3H, NCH₃), $2.24\text{--}2.46$ (m, 1H, 1×H3), $2.53\text{--}2.64$ (m, 1H, H6a), $2.92\text{--}2.98$ (m, 1H, H2), 3.68 (s, br., 1H, ArCHOH), 5.06 (d, $J=3.3$ Hz, 1H, ArCHOH), 6.94 (m, 2H, aromat.-H), 7.37 (s, 1H, aromat.-H); $^{13}\text{C-NMR}$ (CDCl_3): $\delta=18.41$, 21.19 (2C, 2×ArCH₃), 24.11 , 31.37 , 32.91 , 33.53 (4C, C3, C4, C5, C6), 38.65 (1C, C3a), 39.03 (1C, NCH₃), 66.15 , 69.17 (2C, C6a, C2), 72.91 (1C, ArCHOH), 126.35 , 127.23 , 129.79 (3C, aromat.-C), 130.49 , 135.13 , 139.03 (3C, q. aromat.-C); MS (CI, *i*-butane): 260 (MH^+ , 100%), 135 ($\text{C}_9\text{H}_{11}\text{O}^+$, 42%); Anal. calc. for $\text{C}_{17}\text{H}_{25}\text{NO}$ (259.2): C, 78.71; H, 9.72; N, 5.40; found: C, 78.67; H, 9.65; N, 5.42.

($\alpha R, \beta S$)-1'-(2,5-Dimethyl-phenyl)-(1-methyl-octahydro-cyclopenta[b]pyrrol-2-yl)methanol ($\alpha R, \beta S$)-10

Starting material: 0.73 g (2.11 mmol) ($\alpha R, \beta S$)-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(2,5-dimethyl-phenyl)-methanol;²ⁱ work-up: purification by flash-chromatography (silica gel 60, eluent: petrol ether/EtOAc 7:3, addition of 15 ml triethylamine per liter of the solvent mixture, TLC: R_f -value: 0.46); yield: 0.41 g (75%), product: colourless, viscous oil; $[\alpha]_D^{20} = -17.1$ ($c=1.12$, CH_2Cl_2); IR (NaCl): $\nu=3600\text{--}3140\text{ cm}^{-1}$ (OH); $^1\text{H-NMR}$ (CDCl_3): $\delta=0.83\text{--}0.91$, $1.04\text{--}1.21$, $1.41\text{--}1.84$ (m, 7H, H3a, 2×H4, 2×H5, 2×H6), $2.02\text{--}2.16$ (m, 1H, 1×H3), 2.24 (s, 3H, ArCH₃), 2.31 (s, 3H, ArCH₃), $2.40\text{--}2.54$ (m, 1H, 1×H3), 2.46 (s, 3H, NCH₃), $2.78\text{--}2.86$ (m, 1H, H6a), 3.51 (s, 1H, ArCHOH), $3.73\text{--}3.86$ (m, 1H, H2), 5.10 (d, $J=2.8$ Hz, 1H, ArCHOH), $6.96\text{--}7.03$ (m, 2H, aromat.-H), 7.43 (s, 1H, aromat.-H); $^{13}\text{C-NMR}$ (CDCl_3): $\delta=18.48$, 21.15 (2C, 2×ArCH₃), 25.69 , 26.77 , 31.80 , 33.97 (4C, C3, C4, C5, C6), 34.56 (1C, C3a), 39.14 (1C, NCH₃), 64.65 , 66.12 (2C, C6a, C2), 70.46 (1C, ArCHOH), 126.45 , 127.20 , 129.81 (3C, aromat.-C), 130.51 , 135.06 , 139.24 (3C, q. aromat.-C); MS (CI, *i*-butane): 260 (MH^+ , 100%); Anal. calc. for $\text{C}_{17}\text{H}_{25}\text{NO}$ (259.2): C, 78.71; H, 9.72; N, 5.40; found: C, 78.86; H, 9.78; N, 5.38.

(α S, β S)-(1-Methyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-phenyl-methanol (α S, β S)-I1

Starting material: 0.45 g (1.4 mmol) (α S, β S)-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-phenyl-methanol;²ⁱ yield: 0.27 g (82%), product: colourless oil; $[\alpha]_D^{20} = -44.8$ ($c=0.56$, CH₂Cl₂); IR (NaCl): $\nu=3620\text{--}3120$ cm⁻¹ (OH); ¹H-NMR (CDCl₃): $\delta=1.22\text{--}1.93$ (m, 8H, H3a, 2×H4, 2×H5, 2×H6, 1×H3), 2.21 (s, 3H, NCH₃), 2.41–2.58 (m, 1H, 1×H3), 2.93–3.11 (m, 1H, H6a), 3.48 (s, 1H, ArCHOH), 3.58–3.72 (m, 1H, H2), 4.56 (d, $J=3.9$ Hz, 1H, ArCHOH), 7.18–7.42 (m, 5H, aromat.-H); ¹³C-NMR (CDCl₃): $\delta=25.30, 27.29, 33.26, 37.50$ (4C, C3, C4, C5, C6), 37.72 (1C, C3a), 39.99 (1C, NCH₃), 68.45, 71.06 (2C, C6a, C2), 73.99 (1C, ArCHOH), 125.70, 126.78, 128.04 (5C, aromat.-C), 144.49 (1C, q, aromat.-C); MS (CI, *i*-butane): 232 (MH⁺, 100%), 107 (C₇H₇O⁺, 35%); Anal. calc. for C₁₅H₂₁NO (231.2): C, 77.87; H, 9.16; N, 6.06; found: C, 77.69; H, 9.05; N, 5.94.

(α S, β R)-(1-Methyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(2,4,6-trimethyl-phenyl)-methanol (α S, β R)-I2

Starting material: 1.0 g (2.78 mmol) (α S, β R)-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(2,4,6-trimethyl-phenyl)-methanol;²ⁱ work-up: purification by flash-chromatography (silica gel 60, eluents: *n*-hexane/EtOAc 8:2, addition of 15 ml triethylamine per liter of the solvent mixture, TLC: R_f-value: 0.51); yield: 0.73 g (96%), product: colourless oil; $[\alpha]_D^{20} = +50.5$ ($c=0.95$, CH₂Cl₂); IR (NaCl): $\nu=3610\text{--}3170$ cm⁻¹ (OH); ¹H-NMR (CDCl₃): $\delta=1.36\text{--}1.77$ (m, 8H, H3a, 2×H4, 2×H5, 2×H6, 1×H3), 2.20 (s, 3H, ArCH₃), 2.36 (s, 3H, NCH₃), 2.38–2.47 (m, 1H, 1×H3), 2.44 (s, 6H, 2×ArCH₃), 2.51–2.66 (m, 1H, H6a), 2.89–2.99 (m, 1H, H2), 3.32 (s, 1H, ArCHOH), 5.24 (d, $J=3.3$ Hz, 1H, ArCHOH), 6.94 (s, 2H, aromat.-H); ¹³C-NMR (CDCl₃): $\delta=21.25, 23.97$ (3C, 3×ArCH₃), 29.66, 32.77, 33.00, 33.47 (4C, C3, C4, C5, C6), 38.99 (1C, C3a), 39.16 (1C, NCH₃), 69.63, 70.56 (2C, C6a, C2), 72.61 (1C, ArCHOH), 130.32 (2C, aromat.-C), 133.57, 135.66, 136.05 (4C, q, aromat.-C); MS (CI, *i*-butane): 274 (MH⁺, 100%); Anal. calc. for C₁₈H₂₇NO (273.2): C, 79.06; H, 9.96; N, 5.13; found: C, 79.21; H, 9.89; N, 5.08.

(α S, β R)-(1-Methyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(1-naphthyl)-methanol (α S, β R)-I3

Starting material: 1.0 g (2.72 mmol) (α S, β R)-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(1-naphthyl)-methanol;²ⁱ work-up: purification by flash-chromatography (silica gel 60, eluents: *n*-hexane/EtOAc 8:2, addition of 15 ml triethylamine per liter of the solvent mixture, TLC: R_f-value: 0.42); yield: 0.51 g (67%), product: colourless solid; mp: 106°C; $[\alpha]_D^{20} = -55.2$ ($c=0.52$, CH₂Cl₂); IR (KBr): $\nu=3620\text{--}3260$ cm⁻¹ (OH); ¹H-NMR (CDCl₃): $\delta=1.34\text{--}1.91$ (m, 7H, H3a, 2×H4, 2×H5, 2×H6), 2.08 (s, 3H, NCH₃), 2.38–2.59 (m, 2H, 2×H3), 2.88–2.94 (m, 1H, H6a), 3.08–3.14 (m, 1H, H2), 4.67 (s, 1H, ArCHOH), 5.32 (s, 1H, ArCHOH), 7.42–7.55 (m, 3H, aromat.-H), 7.76–7.80 (m, 1H, aromat.-H), 7.85–7.96 (m, 3H, aromat.-H); ¹³C-NMR (CDCl₃): $\delta=24.07, 33.05, 33.45, 38.54$ (4C, C3, C4, C5, C6), 39.69 (1C, C3a), 41.80 (1C, NCH₃), 70.26, 70.94 (2C, C6a, C2), 74.42 (1C, ArCHOH), 122.96, 123.04, 125.17, 125.50, 126.12, 127.18, 128.94 (7C, aromat.-C), 129.99, 133.80, 140.37 (3C, q, aromat.-C); MS (CI, *i*-butane): 282 (MH⁺, 100%); Anal. calc. for C₁₉H₂₃NO (281.2): C, 81.09; H, 8.2; N, 4.98; found: C, 80.95; H, 8.17; N, 4.87.

(α R, β S)-(1-Methyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(1-naphthyl)-methanol (α R, β S)-I3

Starting material: 1.0 g (2.72 mmol) (α R, β S)-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[b]pyrrol-2-yl)-1'-(1-naphthyl)-methanol;²ⁱ work-up: purification by flash-chromatography (silica gel 60, eluent: *n*-hexane/EtOAc 8:2, addition of 15 ml triethylamine per liter of the solvent mixture, TLC: R_f-value: 0.42); yield: 0.71 g (93%), product: colourless, viscous oil; $[\alpha]_D^{20} = -129.5$ ($c=2.37$, CH₂Cl₂); IR (NaCl): $\nu=3590\text{--}3100$ cm⁻¹ (OH); ¹H-NMR (CDCl₃): $\delta=0.62\text{--}0.74, 1.02\text{--}1.16, 1.31\text{--}1.79$ (m, 7H, H3a, 2×H4, 2×H5, 2×H6), 1.98–2.17 (m, 1H, 1×H3), 2.40–2.59 (m, 1H, 1×H3), 2.66 (s, 3H, NCH₃), 3.11–3.22 (m, 1H, H6a), 3.83–3.94 (m, 1H, H2), 5.71 (d, $J=2.8$ Hz,

¹H, ArCHOH), 7.44–7.58 (m, 3H, aromat.-H), 7.78–7.96 (m, 4H, aromat.-H); ¹³C-NMR (CDCl₃): δ=25.65, 26.82, 32.17, 33.90 (4C, C3, C4, C5, C6), 34.74 (1C, C3a), 39.12 (1C, NCH₃), 65.64, 65.83 (2C, C6a, C2), 70.66 (1C, ArCHOH), 122.46, 123.07, 125.12, 125.53, 125.63, 127.17, 128.92 (7C, aromat.-C), 130.16, 133.55, 137.02 (3C, q. aromat.-C); MS (CI, *i*-butane): 282 (MH⁺, 100%); Anal. calc. for C₁₉H₂₃NO (281.2): C, 81.09; H, 8.24; N, 4.98; found: C, 81.21; H, 8.29; N, 4.90.

General procedure 2

Enantiocontrolled addition of diethylzinc to benzaldehyde in the presence of catalytic amounts of amino alcohols **2–13** generally based on the octahydro-cyclopenta[*b*]pyrrole system (the results are summarized in Tables 1 and 2).

Under an argon atmosphere a solution of 0.5 mmol of the respective catalyst precursor (alternatively 0.2 or 1 mmol, e.g. utilizing **2**, **5** or **10** mol % of amino alcohols **2–13**) in 20 ml of anhydrous toluene is prepared. After cooling to –40°C (with ethanol/liquid nitrogen) 18.2 ml (20 mmol) of a 1.1 M diethyl zinc solution in toluene are added within 10 minutes. After 30 minutes with stirring at constant temperature the clear solution is allowed to warm to room temperature. Then 1.06 g (10 mmol) of freshly distilled benzaldehyde, dissolved in 20 ml of anhydrous toluene, are added over a 30 min period. The mixture is stirred for an additional 40 h (at least 16 h) and quenched at 0°C by the addition of 60 ml 2 N aqueous HCl. After separation of the layers the water phase is extracted with diethyl ether (3×40 ml) and the combined organic extracts are subsequently washed with 3.9% NaHSO₃ solution (3×40 mL), saturated aqueous NaHCO₃ solution and finally with brine. After drying with MgSO₄ solvents are removed under reduced pressure and the residual oil is purified by distillation *in vacuo* (chemical yields: between 86 and 64%). The enantiomeric excess was determined by chiral GC analysis (SGE Cydec-B, chiral).

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References

1. For representative references about enantioselective dialkylzinc addition to aldehydes, see: (a) M. Kitamura, S. Suga, K. Kawai, R. Noyori, *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072. (b) M. Kitamura, S. Okada, S. Suga, R. Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036. (c) D. Seebach, A. K. Beck, B. Schmidt, Y. M. Wang, *Tetrahedron* **1994**, *50*, 4363–4384. (d) for a review, see: K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833–856.
2. (a) K. Stingl, J. Martens, *Liebigs Ann. Chem.* **1994**, 243–250. (b) K. Stingl, J. Martens, *Liebigs Ann. Chem.* **1994**, 479–484. (c) K. Stingl, J. Martens, *Liebigs Ann. Chem.* **1994**, 485–490. (d) K. Stingl, J. Martens, *Liebigs Ann. Chem.* **1994**, 491–496. (e) V. Peper, K. Stingl, H. Thümler, W. Saak, D. Haase, S. Pohl, S. Jugé, J. Martens, *Liebigs Ann.* **1995**, 2123–2131. (f) J. Wilken, S. Wallbaum, W. Saak, D. Haase, S. Pohl, L. N. Patkar, A. N. Dixit, P. Chittari, S. Rajappa, J. Martens, *Liebigs Ann.* **1996**, 927–934. (g) J. Wilken, J. Martens, *Liebigs Ann./Recueil* **1997**, 563–571. (h) J. Wilken, M. Kossenjans, W. Saak, D. Haase, S. Pohl, J. Martens, *Liebigs Ann./Recueil* **1997**, 573–579. (i) The new β-amino alcohols were prepared by usual addition of 2.2 eq. of Grignard reagent in *abs.* THF to 1 eq. of the *N*-Boc-aminoaldehyde at a temperature between –20°C and +40°C. After 18 h reaction time and work up with saturated NH₄Cl the resulting diastereomers were separated by flash-chromatography. A more detailed description of this procedure is described in: J. Wilken, C. Thorey, H. Gröger, D. Haase, W. Saak, S. Pohl, J. Muzart, J. Martens, *Liebigs Ann./Recueil* **1997**, *in print*. (j) J. Eilers, J. Wilken, J. Martens, *Tetrahedron: Asymmetry* **1996**, *8*, 2343–2357. (k) J. Wilken, J. Martens, *Synth. Commun.* **1996**, *26*, 4477–4485. (l) S. Wallbaum, T. Mehler, J. Martens, *Synth. Commun.* **1994**, *24*, 1381–1387. (m) S. Wallbaum, *Ph.D. thesis*, Universität Oldenburg, **1994**. (n) J. Wilken, *Ph.D. thesis*, Universität Oldenburg, **1997**. (o) J. Wilken, M. Kossenjans, H.

- Gröger, J. Martens, *Tetrahedron: Asymmetry* **1997**, *8*, 2007–2015. (p) S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1993**, *4*, 637–649.
3. The compound (*all-R*)-**1a** is a non-recyclable, enantiomerically pure waste material which is obtained in the process of synthesizing the ACE-inhibitor ramipril by Hoechst AG: (a) V. Teetz, R. Geiger, H. Gaul, *Tetrahedron Lett.* **1984**, *25*, 4479–4482. (b) H. Urbach, R. Henning, *Heterocycles* **1989**, *28*, 957–965.
 4. In this earlier publication^{20,2p} we used the optical purity *o.p.* instead of the enantiomeric excess *e.e.* to describe the catalytic efficiency of the amino alcohols in the diethylzinc addition to benzaldehyde. For the reason we observed a linear correlation between the *o.p.* and *e.e.* value for 1-phenylpropan-1-ol, in this paper we use for a better survey the correlated *e.e.* In general, the determination of optical purity is affected by a systematic error in the range of 2–4%; see: V. Schurig in: *Houben-Weyl, Methods of Organic Chemistry, Workbench—Edition E21*, Vol. 1; Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann, Thieme, Stuttgart, **1996**, p. 151–157.
 5. K. Soai, A. Ookawa, T. Kaba, K. Ogawa, *J. Am. Chem. Soc.* **1987**, *109*, 7111–7115.

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