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Enantioselective alkylation of aldehydes promoted by (*S*)-tyrosine-derived β-amino alcohols

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Abstract—Two (*S*)-tyrosine-derived β-amino alcohols exhibiting a secondary and tertiary amino moiety, respectively, were employed in the enantioselective alkylation of aldehydes using diethylzinc. The enantioselectivity, catalytic activity and substrate specificity of these precatalysts were compared by high-throughput screening of benzaldehyde, cyclohexanecarboxaldehyde and hexanal. The homochiral catalysts were found to exhibit opposite chiral induction. The secondary amino alcohol favors the formation of (*S*)-alcohols, whereas the tertiary amino alcohol provides (*R*)-alcohols. Enantioselectivity and sense of chiral induction obtained with the secondary amino alcohol was proven to depend on the choice of solvent and experimental procedure. The mechanism of the enantioselective ethylation of benzaldehyde promoted by (*S*)-tyrosine-derived β-amino alcohols was studied by stoichiometric experiments and MM2 computations. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The enantioselective alkylation of aldehydes promoted by β-amino alcohols is one of the most important C–C bond forming reactions.[1] Due to the slow achiral background reaction and the ease of operation, a variety of catalysts that utilize organozinc reagents to produce chiral secondary alcohols from aldehydes have been developed in recent years.[2] To date, the catalytic performance of a number of β-amino alcohols derived from amino acids has been investigated.[3] In general, solvents such as hexanes, toluene, dichloromethane or diethyl ether can be used at ambient temperature without compromising yield and enantioselectivity. Therefore, the enantioselective alkylation of aldehydes provides an excellent opportunity for developing soluble nanosize catalysts for continuous operation in a membrane reactor.[4] Thus, advantages of homogeneous catalysis (high yield, selectivity, reproducibility and catalyst activity under mild reaction conditions) may be combined with those of heterogeneous catalysis (simple product isolation and catalyst recycling). Incorporation of a catalyst into a dendrimer or polymer support requires an additional functional group within the catalyst for immobilization. An important feature of tyrosine-derived catalysts is that the phenol group provides an anchor remote from the asymmetric center, which might allow one to covalently attach such a catalyst to a soluble support without decreasing its activity or stereoselectivity.

To investigate the potential of tyrosine-derived β-amino alcohols as catalyst precursors for the enantioselective alkylation of aliphatic and aromatic aldehydes using diethylzinc, we synthesized (2*S*)-3-(4-benzyloxyphenyl)-2-butylamino-1,1-diphenylpropanol, **1**, and (2*S*)-3-(4-benzyloxyphenyl)-2-dibutylamino-1,1-diphenylpropanol, **2** (Fig. 1). Reductive cleavage of the benzyl group of **1** and **2**, respectively, would allow immobilization of the β-amino alcohol on a suitable dendrimer or polymer support.

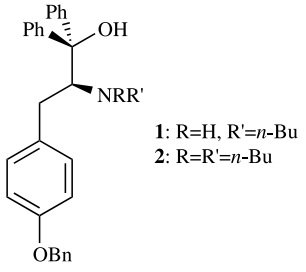

Figure 1. Structure of tyrosinols **1** and **2**.

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The ability of catalyst precursors **1** and **2** to promote the enantioselective alkylation of linear and branched aliphatic as well as aromatic aldehydes with diethylzinc was investigated. Benzaldehyde, **3**, cyclohexanecarboxaldehyde, **4**, and hexanal, **5**, were chosen as representative substrates that exhibit a wide range of different reactivity and steric demand (Fig. 2).

2. Results and discussion

Both catalyst precursors **1** and **2** were synthesized in five steps from (*S*)-tyrosine methyl ester, **9** (Fig. 3). The use of standard Boc_2O protection/deprotection procedures allowed selective benzylation of the phenol moiety of **9** in high yields. Alkylation of (*S*)-*O*-benzyltyrosine methyl ester hydrochloride, **10**, using butyl iodide afforded a 1:1 mixture of (*S*)-*N*-butyl-*O*-benzyltyrosine methyl ester, **11**, and (*S*)-*N*,*N*-dibutyl-*O*-benzyltyrosine methyl ester, **12**, in 70% overall yield. Flash chromatography allowed purification of the amino esters **11** and **12** and recovery of 25% starting material **10**. Amino esters **11** and **12** were converted to β-amino alcohols **1** and **2**, respectively, using phenylmagnesium chloride. The Grignard reaction was carried out under mild reaction conditions to avoid racemization.

We have recently reported a high-throughput screening (HTS) protocol that allows rapid evaluation of enantioselective catalysts.[5] Following this procedure, we determined the enantioselectivity, substrate specificity, sense of chiral induction and catalytic activity of amino alcohols **1** and **2** in a single screening experiment using representative aldehydes **3**–**5** at room temperature (Table 1). Each run was performed in a mixture of diethyl ether and hexanes (1:2) and quenched after 16 h to allow comparison of catalytic activity and substrate

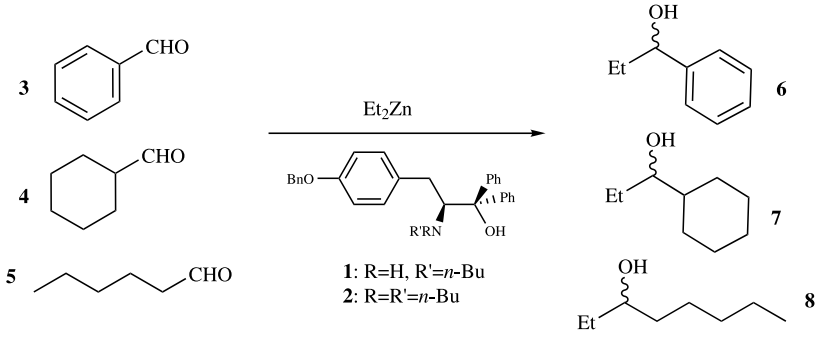


Figure 2. Enantioselective alkylation of aldehydes **3**–**5** promoted by precatalysts **1** and **2**.

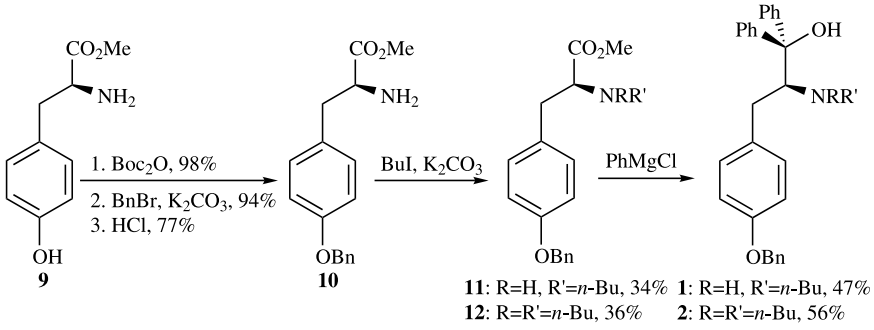


Figure 3. Synthesis of β-amino alcohols **1** and **2**.

Table 1. High-throughput screening of precatalysts **1** and **2** using aldehydes **3**–**5**

Run	β-Amino alcohol	Aldehyde	% Yield[a]	% ee[b]	Configuration[b]
1	**1**	**3**	>99[c]	59	(*S*)
1	**1**	**4**	86	26	(*S*)
1	**1**	**5**	96	60	(*S*)
2	**2**	**3**	89	22	(*R*)
2	**2**	**4**	84	32	(*R*)
2	**2**	**5**	88	18	(*R*)

[a] Yields are calculated based on GC analysis using naphthalene as the internal standard.
[b] The enantiomeric excess of alcohols **6**–**8** was determined by enantioselective GC using octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin as the chiral stationary phase. The elution order of enantiomers of alcohols **6**–**8** was known from previous studies.[5]
[c] No starting material was detected.

specificity of β-amino alcohols **1** and **2**. Both catalysts were found to exhibit high activity towards aromatic and linear aliphatic aldehydes. Employing tyrosinol **1** as the precatalyst gave benzaldehyde, **3**, and hexanal, **5**, in almost quantitative yield within 16 h. Slightly lower yields, i.e. 89 and 88%, were observed for the ethylation of aldehydes **3** and **5** using precatalyst **2**. Both catalysts afford decreased catalytic activity towards cyclohexanecarboxaldehyde, **4**, which may be attributed to increased steric hindrance in the transition state. However, employing amino alcohol **1** and **2**, respectively, in the alkylation of aldehydes with diethylzinc provides only moderate to good enantioselectivities. Precatalyst **1** affords (*S*)-1-phenylpropanol, **6**, and (*S*)-3-octanol, **8**, with 59 and 60% ee, whereas (*S*)-1-cyclohexylpropanol, **7**, was obtained in only 26% ee. By contrast, β-amino alcohol **2** exhibits higher enantioselectivity for branched aliphatic aldehydes such as **4** than for less sterically hindered substrates **3** and **5**. However, ees observed are only moderate. A decrease in temperature to 0°C did not improve enantioselectivities of both catalysts. Notably, the homochiral tyrosinols afford opposite chiral induction under the same reaction conditions. The use of β-amino alcohol **1** favors *Si*-face attack of diethylzinc on the prochiral aldehyde resulting in formation of the corresponding (*S*)-alcohols, whereas **2** affords (*R*)-alcohols **6**–**8**. Moreover, the chirality induced by the catalyst derived from β-amino alcohol **1** was found to depend significantly on the solvents used. In hexanes, (*S*)-**6** and (*S*)-**8** were obtained with only 23 and 46% enantioselectivity, respectively, whereas (*R*)-**7** was produced in 8% ee. In addition, employing **1** in the enantioselective alkylation of prochiral aldehydes requires the use of freshly distilled aldehydes since small amounts of impurities exhibit dramatic effects on the catalytic performance resulting in reversed chiral induction. Enantioselectivity and sense of chiral induction of the alkylation of aldehydes **3**–**5** was also found to depend on the experimental procedure. Treatment of a solution of precatalyst **1** in diethyl ether with diethylzinc prior to addition of the aldehyde mixture resulted in formation of (*S*)-alcohols (Table 1). By contrast, reversal of the addition order, i.e. addition of aldehydes **3**–**5** prior to addition of diethylzinc, led to formation of (*R*)-alcohols with low enantioselectivity. This might be attributed to the formation of catalytically active enamine derivatives of **4** and **5** that promote the alkylation of aldehydes **3**–**6** with opposite enantioselectivity. To prove this hypothesis we performed an individual screening experiment in which tyrosinol **1** was treated with benzaldehyde, **3**, at room temperature for 1 h prior to the addition of diethylzinc at 0°C. Since benzaldehyde and β-amino alcohol **1** cannot undergo reaction to form an enamine, the formation of (*S*)-**6** was still favored, i.e. the observed yield and enantioselectivity did not depend on the experimental procedure.

Based on the low enantioselectivity and opposite chiral induction observed with β-amino alcohols **1** and **2**, we decided to verify the HTS results by individual screening of each aldehyde (Table 2). Again, high catalytic activity but only moderate to good enantioselectivities were observed. Yields and enantioselectivities obtained by simultaneous screening of aldehydes **3**–**5** using precatalyst **2** are in excellent agreement with individual screening results. However, tyrosinol **1** showed significantly better enantioselectivity for aldehyde **3** in the absence of aldehydes **4** and **5**. Given the sensitivity of β-amino alcohol **1** to small amounts of impurities and reaction conditions as described above, the variations in enantioselectivity observed following different screening protocols were somehow expected.

The opposite chiral induction observed for the enantioselective alkylation of aldehydes **3**–**5** prompted us to further investigate the mechanism of the ethylation of benzaldehyde promoted by β-amino alcohols **1** and **2**. First, the effect of the stoichiometry of β-amino alcohol, benzaldehyde and diethylzinc on reactivity was examined (Table 3). No sign of reaction was observed using equimolar amounts of amino alcohol and diethylzinc (entries 1 and 3). Both precatalysts **1** and **2** require 3 equiv. of organozinc reagent to promote the alkylation of 2 equiv. of benzaldehyde (entries 2 and 5). Our findings are in good agreement with similar studies

Table 2. Individual screening results of precatalysts **1** and **2**

β-Amino alcohol	Aldehyde	% Yield[a]	% ee[b]	Configuration[b]
1	**3**	97	85	(*S*)
1	**4**	69	19	(*S*)
1	**5**	88	63	(*S*)
2	**3**	>99[c]	22	(*R*)
2	**4**	79	34	(*R*)
2	**5**	90	18	(*R*)

[a] Yields are calculated based on GC analysis using naphthalene as the internal standard.

[b] The enantiomeric excess of alcohols **6**–**8** was determined by enantioselective GC using octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin as the chiral stationary phase. The elution order of enantiomers of alcohols **6**–**8** was known from previous studies.[5]

[c] No starting material was detected.

Table 3. Effect of stoichiometry of β-amino alcohol, aldehyde **3** and diethylzinc on reactivity

Entry	β-Amino alcohol	Ratio (β-amino alcohol/**3**/Et_2Zn)	% Yield	% ee
1	**1**	1/2/1	No reaction	–
2	**1**	1/2/3	94	86 (*S*)
3	**2**	1/2/1	No reaction	–
4	**2**	1/2/2	50	28 (*R*)
5	**2**	1/2/3	92	31 (*R*)

reported by Kitamura et al. using of (–)-3-*exo*-(dimethylamino)isoborneol as the precatalyst.[1a] Accordingly, the first equivalent of diethylzinc is required to form the active catalyst, whereas the second equivalent can undergo reaction with an aldehyde upon activation. An important atom economical limitation of the investigated reaction is that only one alkyl group of diethylzinc can be utilized (compare entries 4 and 5). Our stoichiometric experiments also show that the proton of the secondary amine moiety of precatalyst **1** does not react with diethylzinc. Similarly, ^{1}H NMR studies using tyrosinols **1** and **2**, respectively, and various amounts of dimethyl zinc revealed formation of 1 equiv. of methane in both cases. Attempts to elucidate the structure of active catalyst species by ^{1}H and ^{13}C NMR spectroscopy were not successful due to the fluxional behavior of organozinc species in solution.

Recently, the origin of enantioselectivity observed in β-amino alcohol catalyzed alkylations of aldehydes using organozinc reagents has been rationalized by computational studies.[6] Following a qualitative approach to better understand the opposite chiral induction obtained with homochiral precatalysts **1** and **2**, we optimized the structure of the five-membered chelate ring that is formed upon reaction of the β-amino alcohol with 1 equiv. of diethylzinc using MM2 computations. It is assumed that coordination of the second equivalent of diethylzinc and benzaldehyde, **3**, results in a tricyclic transition state. The geometry of the four-membered μ-oxo ring as well as the approach of the aldehyde was adapted from computations reported by Vidal-Ferran and co-workers (Fig. 4).[7]

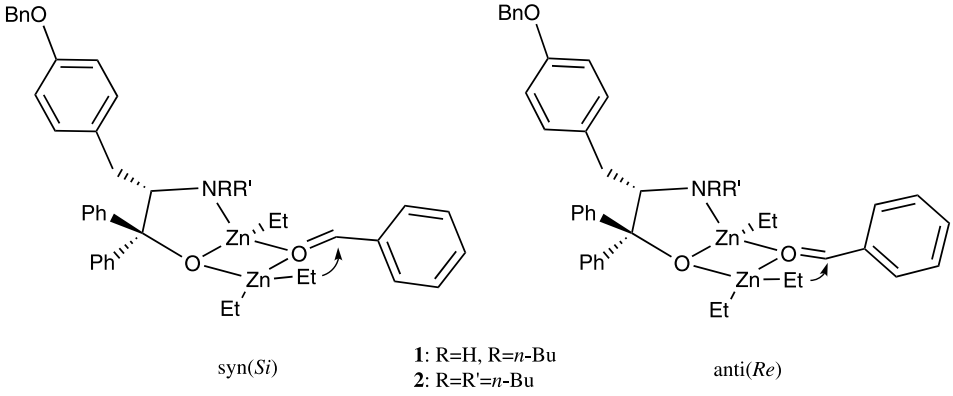
It is assumed that the approaching aldehyde preferentially coordinates from the less hindered face of the five-membered chelate ring.[6,7] Thus, aldehyde **3** forms a μ-oxo four-membered ring opposite to the 4-benzyloxybenzyl moiety of the chiral amino alcohol. Based on the geometry of the four-membered ring, one can imagine two low energy μ-oxo transition states exhibiting the bulky phenyl group of **3** in less crowded positions to minimize steric repulsion with the ethyl group attached to the zinc atom in the five-membered ring and the *n*-butyl group(s) attached to the nitrogen atom, respectively.[8] Thus, both the electrophilicity of the aldehyde and the nucleophilicity of one alkyl group of diethylzinc are increased in the *syn*(*Si*) and *anti*(*Re*) transition states.[9]

Optimization of the favored diastereomeric transition states by MM2 computations allows rationalization of chiral induction and selectivity of both tyrosinol-derived catalysts. Comparison of transition states derived from **1** reveals that the *syn*(*Si*) geometry should indeed be significantly more stable than the *anti*(*Re*) structure. The latter exhibits enhanced steric repulsion between aldehyde **3** and both the ethyl group on the zinc atom in the five-membered ring and the *n*-butyl moiety on the ring nitrogen (Fig. 5). The preference for the *syn* transition state favors a *Si*-face attack on benzaldehyde and thus explains the observed formation of (*S*)-1-phenylpropanol with good enantioselectivity.

By contrast, transition states derived from tyrosinol **2** are more sterically crowded and do not differ significantly in stability. The two *n*-butyl groups seem to shield the chiral information of **2** and therefore diminish chiral induction. Repulsion between the ethyl group on the five-membered ring zinc atom and the adjacent *n*-butyl group on the nitrogen atom should equally destabilize both transition states. As a consequence of the overcrowded structure, the *syn*(*Si*) geometry is further destabilized by repulsive interactions between one *n*-butyl group and the adjacent aldehyde moiety. Similarly, the *anti*(*Re*) geometry suffers from repulsion between the adjacent zinc ethyl moiety and the coordinating benzaldehyde (Fig. 6). As a result, the *anti*(*Re*) transition state is slightly preferred, i.e. **2** favors formation of (*R*)-1-phenylpropanol with moderate enantioselectivity.

3. Conclusion

Tyrosinols **1** and **2** exhibiting a secondary and tertiary amino function, respectively, were prepared from (*S*)-tyrosine in good overall yields and employed in the enantioselective alkylation of benzaldehyde, cyclohexanecarboxaldehyde, and hexanal using diethylzinc. High yields but only moderate to good enantioselectiv-



syn(*Si*) **1**: R=H, R=*n*-Bu **2**: R=R'=*n*-Bu anti(*Re*)

Figure 4. Postulated favored transition states derived from β-amino alcohols **1** and **2**.

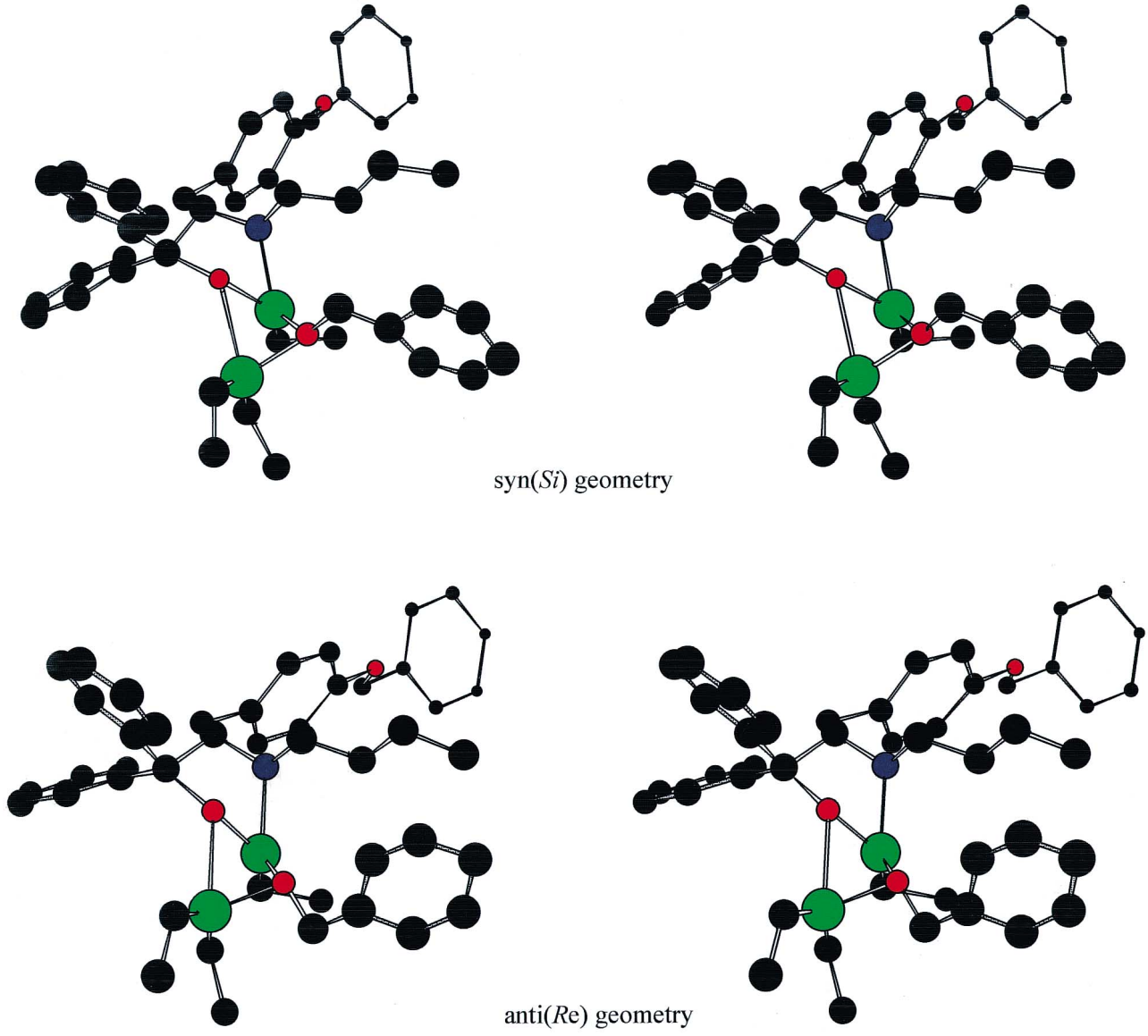


Figure 5. Stereoview of *syn*(*Si*) and *anti*(*Re*) geometry of transition states derived from precatalyst **1** obtained by MM2 calculations. Hydrogens are omitted for clarity.

ites were obtained with both catalysts following a high-throughput screening protocol that allows simultaneous screening of representative substrates. Tyrosinol **1** was found to promote formation of (*S*)-alcohols, whereas tertiary amino alcohol **2** favors (*R*)-alcohols. However, precatalyst **1** yielded (*R*)-alcohols in low ees when hexane was used as the reaction solvent. Also, addition of enolizable aldehydes to **1** prior to addition of diethylzinc was found to induce (*R*)-configuration. This was attributed to the formation of enamine derivatives that exhibit some catalytic activity but opposite chiral induction than β-amino alcohol **1**. Stoichiometric experiments and ^{1}H NMR experiments revealed that both amino alcohols utilize 1 equiv. of the dialkyl zinc reagent to form the active catalyst species. The catalyst takes advantage of only one alkyl moiety of the organozinc reagent to alkylate the aldehyde, i.e. the atom economy of this reaction is inherently limited to 50%. MM2 computational analysis suggests that the catalyst derived from **1** and 1 equiv. of diethylzinc favors formation of a *syn*(*Si*) transition state with a second equivalent of diethylzinc and benzaldehyde **3** to yield (*S*)-1-phenylpropanol with good enantioselectivity. By contrast, the *anti*(*Re*) transition state derived from tyrosinol **2** is slightly favored over the diastereomeric *syn*(*Si*) geometry. Accordingly, **2** promotes the formation of (*R*)-1-phenylpropanol with low enantioselectivity.

4. Experimental

All chemicals were of reagent grade and were purchased from Aldrich. Flash chromatography was carried out on silica gel (Merck Kieselgel 60, particle size 0.032–0.063 mm). NMR spectra were obtained at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) on a Varian FT NMR spectrometer using $CDCl_3$ as the solvent, if not stated otherwise.

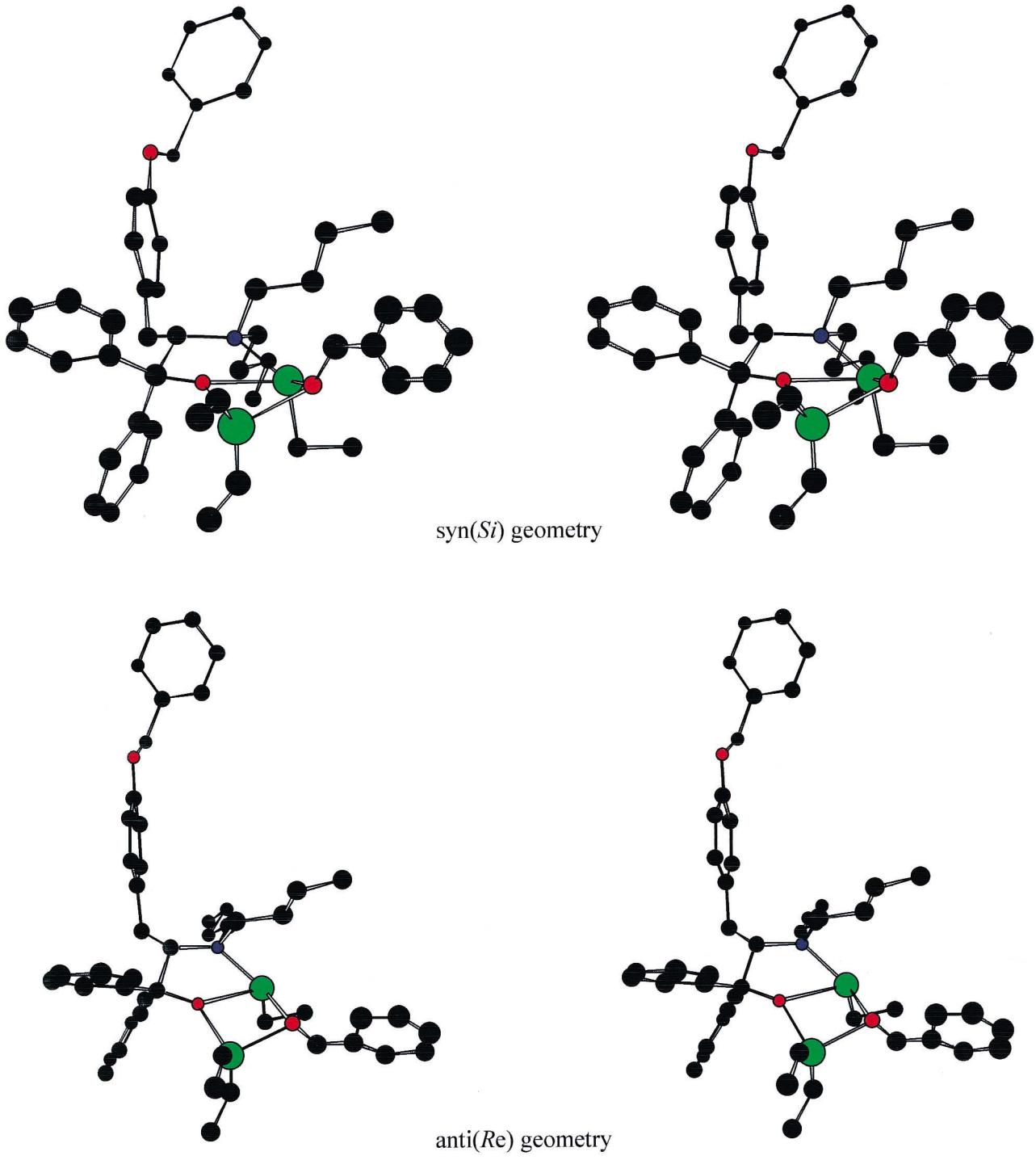


Figure 6. Stereoview of *syn*(*Si*) and *anti*(*Re*) geometry of transition states derived from precatalyst **2** obtained by MM2 calculations. Hydrogens are omitted for clarity.

4.1. General procedure for the enantioselective alkylation of aldehydes

To a solution of the catalyst (0.02 mmol, 8 mol%) in anhydrous diethyl ether (1 ml) was added diethylzinc (1 M in hexanes, 1.1 mmol). After 40 min, the solution was cooled to 0°C and a mixture of naphthalene and the aldehyde (0.26 mmol) in hexanes (1 ml) was added dropwise. The reaction mixture was stirred for 16 h at room temperature and quenched with saturated NH_4Cl (5 ml). The aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined analysed by GC.

4.1.1. GC analysis. Naphthalene, aldehydes **3**, **4** or **5** as well as the enantiomers of the corresponding alcohols **6**–**8** were separated in one GC run using octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin (60% in OV

1701, 30 m) as the chiral stationary phase.[10] Temperature program: 90°C for 5 min, then 7°C/min to 115°C. Enantioselectivity α: 1.02 (**6**), 1.02 (**7**), 1.04 (**8**). Individual response factors [area(aldehyde)×mg(standard)/area(standard)×mg(aldehyde)] were determined for all three aldehydes by GC analysis of the individual reaction mixtures containing one aldehyde and naphthalene as the internal standard. Determination of the ratio of the area of the aldehyde to the area of naphthalene obtained from a second GC run of the product mixture containing naphthalene, the remaining aldehyde and the corresponding chiral alcohol allowed the calculation of yields. Dilution experiments revealed excellent linearity of aldehyde responses over the concentration range obtained in reaction and product mixtures. Since the total area% of side products proved to be less than 2% in all cases, we were able to calculate chemical yields based on aldehyde conversion.

4.2. Preparation of (*S*)-*N*-(*tert*-butoxycarbonyl)tyrosine methyl ester

To a solution of (*S*)-tyrosine methyl ester hydrochloride, **9** (10.0 g, 43.2 mmol) and $NaHCO_3$ (7.25 g, 86 mmol) in THF/methanol (200 ml/60 ml) was added di-*tert*-butyl dicarbonate (9.40 g, 43.2 mmol) dissolved in THF (20 ml). The solution was stirred at room temperature for 22 h. The solvents were removed in vacuo. The residue was dissolved in CH_2Cl_2, washed with water and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure. Recrystallization of the residue from CH_2Cl_2 provided white crystals (12.5 g, 42.3 mmol, 98%). ^{1}H NMR: $\delta = 1.42$ (s, 9H), 3.08 (m, 2H), 3.71 (s, 3H), 4.59 (m, 1H), 5.00 (bs, 1H), 5.10 (bs, 1H), 6.76 (d, $J = 8.4$, 2H), 6.98 (d, $J = 8.4$, 2H). ^{13}C NMR: 28.4, 37.6, 52.3, 54.6, 80.2, 115.4, 127.2, 130.2, 155.0, 155.2, 172.5.

4.3. Preparation of (*S*)-*N*-(*tert*-butoxycarbonyl)-*O*-benzyltyrosine methyl ester

To a solution of (*S*)-*N*-(*tert*-butoxycarbonyl)tyrosine methyl ester (10.19 g, 34.5 mmol) dissolved in acetone (30 ml) was added K_2CO_3 (5.32 g, 38 mmol) and benzyl bromide (4.68 ml, 39.4 mmol). The reaction mixture was heated to reflux for 6 h. Acetone was removed and the residue was partitioned between CH_2Cl_2 and 5% NaOH. The combined organic layers were dried over $MgSO_4$ and CH_2Cl_2 was evaporated. Purification by flash chromatography (CH_2Cl_2) yielded white crystals (12.5 g, 32.4 mmol, 94%). ^{1}H NMR: $\delta = 1.42$ (s, 9H), 3.03 (m, 2H), 3.71 (s, 3H), 4.54 (m, 1H), 4.97 (bs, 1H), 5.04 (s, 2H), 6.90 (d, $J = 8.7$, 2H), 7.04 (d, $J = 8.7$ Hz, 2H), 7.40 (m, 5H). ^{13}C NMR: 28.3, 37.5, 52.2, 54.5, 69.9, 79.8, 114.8, 127.3, 127.8, 128.1, 128.4, 130.1, 136.8, 154.9, 157.7, 172.2.

4.4. Preparation of (*S*)-*O*-benzyltyrosine methyl ester hydrochloride, 10

(*S*)-*N*-(*tert*-Butoxycarbonyl)-*O*-benzyltyrosine methyl ester (12.1 g, 31.5 mmol) was dissolved in 4 M HCl in dioxane (130 ml) and stirred for 2 h. The precipitate was washed with dioxane and dried in vacuo to give white crystals (7.8 g, 24.3 mmol, 77%). ^{1}H NMR (DMSO-d_6): $\delta = 3.13$ (m, 2H), 3.67 (s, 3H), 4.24 (t, $J = 7.4$ Hz, 1H), 5.08 (s, 2H), 6.96 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 7.18 (m, 5H), 8.42 (bs, 3H). ^{13}C NMR (DMSO-d_6): 35.1, 52.7, 53.5, 69.3, 114.9, 126.7, 127.7, 127.9, 128.5, 130.6, 137.1, 157.5, 169.3.

4.5. Preparation of (*S*)-*N*-butyl-*O*-benzyltyrosine methyl ester, 11 and (*S*)-*N*,*N*-dibutyl-*O*-benzyltyrosine methyl ester, 12

To a solution of (*S*)-*O*-benzyltyrosine methyl ester, **10** (4.93 g, 15 mmol) in anhydrous acetonitrile (120 ml) was added K_2CO_3 (12.65 g, 90 mmol). The reaction mixture was heated to 60°C and butyl iodide (5.94 g, 32.3 mmol) was added. The mixture was heated under reflux for 24 h, acetonitrile was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and water. The combined organic layers were dried over $MgSO_4$ and CH_2Cl_2 was removed in vacuo. After purification by flash chromatography (CH_2Cl_2/EtOAc, 20:1) **11** (1.76 g, 5.15 mmol, 34%) and **12** (2.17 g, 5.4 mmol, 36%) were obtained as light yellow oils.

4.5.1. (*S*)-*N*-Butyl-*O*-benzyltyrosine methyl ester, 11. ^{1}H NMR: $\delta = 0.87$ (t, $J = 7.2$ Hz, 3H), 1.29 (m, 2H), 1.39 (m, 2H), 2.46 (m, 1H), 2.56 (m, 1H), 2.89 (m, 2H), 3.47 (t, $J = 9.0$ Hz, 1H), 3.63 (s, 3H), 5.04 (s, 2H), 6.89 (d, $J = 8.5$ Hz, 2H), 7.09 (d, $J = 8.5$ Hz, 2H), 7.4 (m, 5H). ^{13}C NMR: 13.9, 20.3, 32.1, 38.8, 47.8, 51.5, 63.2, 69.8, 114.6, 127.2, 127.7, 128.3, 129.3, 129.9, 136.8, 157.3, 174.8.

4.5.2. (*S*)-*N*,*N*-Dibutyl-*O*-benzyltyrosine methyl ester, 12. ^{1}H NMR: $\delta = 0.88$ (t, $J = 7.2$ Hz, 6H), 1.32 (m, 8H), 2.43 (m, 2H), 2.62 (m, 2H), 2.77 (dd, $J = 7.0$ Hz, $J = 12.4$ Hz, 1H), 3.00 (dd, $J = 9.0$ Hz, $J = 12.4$ Hz, 1H), 3.53 (dd, $J = 7.0$ Hz, $J = 9.0$ Hz, 1H), 3.60 (s, 3H), 5.03 (s, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 7.10 (d, $J = 8.7$ Hz, 2H), 7.38 (m, 5H). ^{13}C NMR: 14.2, 20.4, 30.9, 35.2, 50.9, 65.4, 69.9, 114.4, 127.3, 127.7, 128.4, 130.0, 131.0, 137.0, 157.0, 172.9.

4.6. Preparation of (2*S*)-3-(4-benzyloxyphenyl)-2-butylamino-1,1-diphenylpropanol, 1

(*S*)-*N*-Butyl-*O*-benzyltyrosine methyl ester, **11** (300 mg, 0.88 mmol) was dissolved in anhydrous THF (3 ml) under a nitrogen atmosphere. A solution of PhMgCl (2 M in hexanes 1.8 ml, 3.6 mmol) was added dropwise at 0°C. The mixture was stirred for 4 h at 0°C and then quenched with saturated aqueous NH_4Cl at 0°C. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and CH_2Cl_2 was removed. Flash chromatography (CH_2Cl_2/EA/TEA, 200:1:1) gave light yellow crystals (190 mg, 0.41 mmol, 46.6%). ^{1}H NMR: $\delta = 0.60$ (t, $J = 6.9$ Hz, 3H), 0.93 (m, 4H), 2.83 (m, 1H), 2.97 (m, 1H), 2.23 (dd, $J = 10.6$ Hz, $J = 14.5$ Hz, 1H), 2.81 (dd, $J = 3.1$ Hz, $J = 14.5$ Hz, 1H), 3.81 (dd, $J = 3.1$ Hz, $J = 10.6$ Hz, 1H), 5.04 (s, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 7.08 (d, $J = 8.7$ Hz, 2H), 7.16 (dd, $J = 8.5$ Hz, $J = 8.5$ Hz, 2H), 7.38 (m, 9H), 7.61 (dd,

$J=1.5$ Hz, $J=8.4$ Hz, 2H), 7.70 (dd, $J=1.5$ Hz, $J=8.4$ Hz, 2H). ^{13}C NMR: 14.4, 20.4, 32.8, 37.5, 49.9, 66.8, 70.7, 115.5, 126.2, 126.5, 126.8, 127.0, 128.0, 128.4, 128.5, 128.6, 129.0, 130.3, 132.3, 137.5, 145.7, 148.3, 157.8. Anal. calcd for $C_{32}H_{35}NO_2$: C, 82.54; H, 7.58; N, 3.01. Found: C, 82.39; H, 7.37; N, 3.00%.

4.7. Preparation of (2*S*)-3-(4-benzyloxyphenyl)-2-dibutylamino-1,1-diphenylpropanol, 2

A solution of PhMgCl (2 M in hexanes, 1.0 ml, 2.0 mmol) was added dropwise to (*S*)-*N*,*N*-dibutyl-*O*-benzyltyrosine methyl ester, **12** (300 mg, 0.76 mmol) in anhydrous THF (3 ml) at 0°C under a nitrogen atmosphere. The solution was stirred for 5 h. Following the work-up procedure described for **1**, purification of the residue by flash chromatography (CH_2Cl_2/EA/TEA, 400:2:2) afforded a white oil (220 mg, 0.42 mmol, 56%). ^{1}H NMR: $\delta=0.77$ (t, $J=7.2$ Hz, 6H), 1.06 (m, 4H), 1.22 (m, 2H), 1.40 (m, 2H), 2.04 (m, 4H), 2.77 (dd, $J=12.4$ Hz, $J=15.9$ Hz, 1H), 3.06 (dd, $J=1.3$ Hz, $J=15.91$ Hz, 1H), 3.94 (dd, $J=1.3$ Hz, $J=12.4$ Hz, 1H), 5.04 (s, 2H), 6.18 (s, 1H), 6.88 (d, $J=8.8$ Hz, 2H), 7.11 (d, $J=8.8$ Hz, 2H), 7.35 (m, 11H), 7.56 (d, $J=8.4$ Hz, 4H). ^{13}C NMR: 14.1, 20.4, 31.9, 33.4, 52.7, 70.0, 71.4, 114.7, 126.6, 127.1, 127.3, 127.6, 127.8, 128.0, 128.4, 129.9, 136.9, 144.2, 145.8, 157.0. Anal. calcd for $C_{36}H_{43}NO_2$: C, 82.87; H, 8.31; N, 2.68. Found: C, 82.94; H, 7.99; N, 2.93%.

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References

1. (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036; (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69; (c) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856.
2. (a) Reetz, M. T.; Kükenhöhner, T.; Weinig, P. *Tetrahedron Lett.* **1986**, *27*, 5711–5714; (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072; (c) Soai, K.; Yokohama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690–1691; (d) Soai, K.; Nishi, M.; Ito, Y. *Chem. Lett.* **1987**, 2405–2406; (e) Chaloner, P. A.; Perera, S. A. R. *Tetrahedron Lett.* **1987**, *28*, 3013–3014; (f) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233–5236; (g) Corey, E. J.; Yuen, P.-W.; Hannon, F. J.; Wierda, D. A. *J. Org. Chem.* **1990**, *55*, 784–786; (h) Soai, K.; Yokoyama, S.; Hayasaki, T. *J. Org. Chem.* **1991**, *56*, 4264–4268; (i) Soai, K.; Hirose, Y.; Ohno, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1473–1474; (j) Cho, B. T.; Kim, N. *Tetrahedron Lett.* **1994**, *35*, 4115–4118; (k) Cho, B. T.; Kim, N. *Synth. Commun.* **1996**, *26*, 855–865; (l) Soai, K.; Hayase, T.; Takai, K.; Sugiyama, T. *J. Org. Chem.* **1994**, *59*, 7908–7909; (m) Cho, B. T.; Kim, N. *Synth. Commun.* **1996**, *26*, 2273–2280; (n) Cho, B. T.; Kim, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2901–2907; (o) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1998**, *25*, 1489–1492; (p) Reddy, K. S.; Solà, L.; Moyano, M. A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 3969–3974; (q) Dangel, B. D.; Polt, R. *Org. Lett.* **2000**, *2*, 3003–3006; (r) Okamoto, K.; Kimachi, T.; Ibuka, T.; Takemoto, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 463–467; (s) Panev, S.; Linden, A.; Dimitrov, V. *Tetrahedron: Asymmetry* **2001**, *12*, 1313–1321; (t) Superchi, S.; Mecca, T.; Giorgio, E.; Rosini, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1235–1239; (u) Bastin, S.; Agbossou-Niedercorn, F.; Brocard, J.; Pelinski, L. *Tetrahedron: Asymmetry* **2001**, *12*, 2399–2408; (v) Liu, D. X.; Zhang, L. C.; Wang, Q.; Da, C. S.; Xin, Z. Q.; Wang, R.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2001**, *3*, 2733–2735; (w) Sato, I.; Urabe, H.; Ishii, S.; Tanji, S.; Soai, K. *Org. Lett.* **2001**, *3*, 3851–3854; (x) Le Goanvic, D.; Holler, M.; Pale, P. *Tetrahedron: Asymmetry* **2002**, *13*, 119–121; (y) Priego, J.; Mancheno, O. G.; Cabrera, S.; Carretero, J. C. *J. Org. Chem.* **2002**, *67*, 1346–1353; (z) Ruzziconi, R.; Piermatti, O.; Ricci, G.; Vinci, D. *Synlett* **2002**, 747–750.
3. (a) Soai, K.; Ookawa, A.; Ogawa, K.; Kaba, T. *J. Chem. Soc., Chem. Commun.* **1987**, 467–468; (b) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111–7115; (c) Soai, K.; Niwa, S. *Chem. Lett.* **1989**, 481–484; (d) Soai, K.; Watanabe, M.; Koyano, M. *J. Chem. Soc., Chem. Commun.* **1989**, 534–536; (e) Itsuno, S.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S.; Fréchet, J. M. J. *J. Org. Chem.* **1990**, *55*, 304–310; (f) Soai, K.; Watanabe, M.; Yamamoto, A.; Yamashita, T. *J. Mol. Catal.* **1991**, *64*, L27–L30; (g) Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L. *Tetrahedron* **1995**, *51*, 165–172; (h) Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712–7713; (i) Beliczey, J.; Giffels, G.; Kragl, U.; Wandrey, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1529–1539; (j) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1997**, *62*, 3770–3771; (k) Kossenjans, M.; Pennemann, H.; Martens, J.; Juanes, O.; Rodríguez-Ubis, J. C.; Brunet, E. *Tetrahedron: Asymmetry* **1998**, *9*, 4123–4125; (l) Solà, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078–7082; (m) Yang, X.; Shen, J.; Da, C.; Wang, R.; Choi, M. C. K. *Tetrahedron: Asymmetry* **1999**, *10*, 133–138; (n) Juanes, O.; Rodríguez-Ubis, J. C.; Brunet, E.; Pennemann, H.; Kossenjans, M.; Martens, J. *Eur. J. Org. Chem.* **1999**, 3323–3333.
4. (a) Kragl, U.; Dreisbach, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 642–644; (b) Kragl, U. *GIT Labor-Fachz.* **1997**, *41*, 814–815; (c) Giffels, G.; Beliczey, J.; Felder, M.; Kragl, U. *Tetrahedron: Asymmetry* **1998**, *9*, 691–696; (d) Rissom, S.; Beliczey, J.; Giffels, G.; Kragl, U.; Wandrey, C. *Tetrahedron: Asymmetry* **1999**, *10*, 923–928.

5. Wolf, C.; Hawes, P. A. *J. Org. Chem.* **2002**, *67*, 2727–2729.
6. Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998–9006 and references cited therein.
7. Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773–8776.
8. These unfavorable interactions would be significantly increased in the corresponding *syn*(*Re*) and *anti*(*Si*) geometries (not shown).
9. The *anti*/*syn* terminology refers to the relationship of the terminal rings in the tricyclic transition states. *syn*(*Si*) indicates *syn* geometry of the four-membered ring and *Si*-face attack on benzaldehyde. *anti*(*Re*) indicates *anti* geometry of the four-membered ring and *Re*-face attack on benzaldehyde.
10. König, W. A. *J. High Resolut. Chromatogr.* **1993**, *16*, 312–323.