A Theoretical and Experimental Study of the Asymmetric Addition of Dialkylzinc to *N*-(Diphenylphosphinoyl)benzalimine

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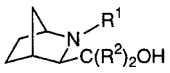
Abstract: The mechanism of the enantioselective addition of diethylzinc to *N*-(diphenylphosphinoyl)benzalimine with catalysis by bicyclic 2-azanorbornyl-3-methanols was studied by quantum chemical calculations. The mechanism proved to differ from that of the addition of diethylzinc to aldehydes and also from an earlier proposed mechanism. The results of the calculations were used to identify several factors responsible for the selectivity. The theoretical evaluation was performed in connection with an experimental study of the effects of introducing an additional stereocenter in the ligand. An efficient route to both diastereomers of new bicyclic 2-azanorbornyl-3-methanols with an additional chiral center (the secondary alcohol group) is also presented. In the best case, an enantiomeric excess of up to 97% was obtained with these new ligands.

Keywords: ab initio calculations · amino alcohols · asymmetric catalysis · nucleophilic additions · zinc

Introduction

Carbon–carbon bond formation plays an important role in synthetic organic chemistry, and addition of organometallic reagents to carbonyl groups is one of the most popular methods for achieving this purpose.[1, 2] In modern organic chemistry many of these addition reactions were performed with high asymmetric induction by using chiral auxiliaries or ligands. Among the most successful classes of ligands are optically active β-amino alcohols, which are easily synthesized from the corresponding α-amino acids and are extremely useful in many asymmetric reactions.[3] In particular, ligands derived from proline have been successfully used in a variety of transformations,[4] a fact that inspired us to search for even more powerful ligands based on the proline backbone. We are especially interested in the synthesis of chiral, nonnatural β-amino alcohols possessing the 2-azanorbornyl skeleton **1** and their applications in asymmetric catalysis.[5]



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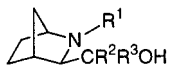

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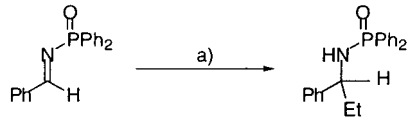
Such bicyclic ligands with a primary alcohol group ($R^1 = R^2 = H$) are effective in the ruthenium-catalyzed asymmetric transfer hydrogenation of ketones,[6] and their tertiary analogues ($R^1 = H$, $R^2 = Ar$) are good promotors in the asymmetric reduction of ketones via the corresponding in-situ-generated oxazaborolidines.[7] High enantioselectivities in the nucleophilic addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines[8] (Scheme 1) were also attained in the presence of stoichiometric or catalytic amounts of the *N*-substituted 2-azanorbornyl-3-methanols ($R^1 = Bn$; $R^2 = H$, Me, *i*Pr, or Ph).[9]

To obtain more knowledge about the factors governing the selectivity, we performed a quantum chemical investigation of



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Scheme 1. a) Et_2Zn (3 equiv), chiral amino alcohol (1 equiv), toluene, 0 °C to room temperature.

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Supporting information for this article is available on the WWW under http://www/wiley-vch.de/home/chemistry/ or from the author.

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the reaction mechanism of the latter reaction. By combining new experimental results with the results of the calculations, we were able to reach several conclusions about the selectivity process. We also report an efficient route to both diastereomers of bicyclic 2-azanorbornyl-3-methanol compounds with an additional stereocenter (**2**), that is, a secondary alcohol group, and their ability to mediate the formation of chiral amines in the addition of dialkylzinc to prochiral imines (Scheme 1).

Results and Discussion

Reaction Mechanism

Successful rationalizations of enantioselectivity depend on comprehensive knowledge about the reaction mechanism. The mechanism of amino alcohol catalyzed addition of dialkylzinc reagents to aldehydes was recently investigated by quantum chemical methods.[10] This reaction take places via a [2.2.0] bicyclic transition state (TS) analogous to **A** in Figure 1. With this structure as a starting point, we evaluated five types of TS for the addition of diethylzinc to *N*-(diphenylphosphinoyl)benzalimine (Figure 1).

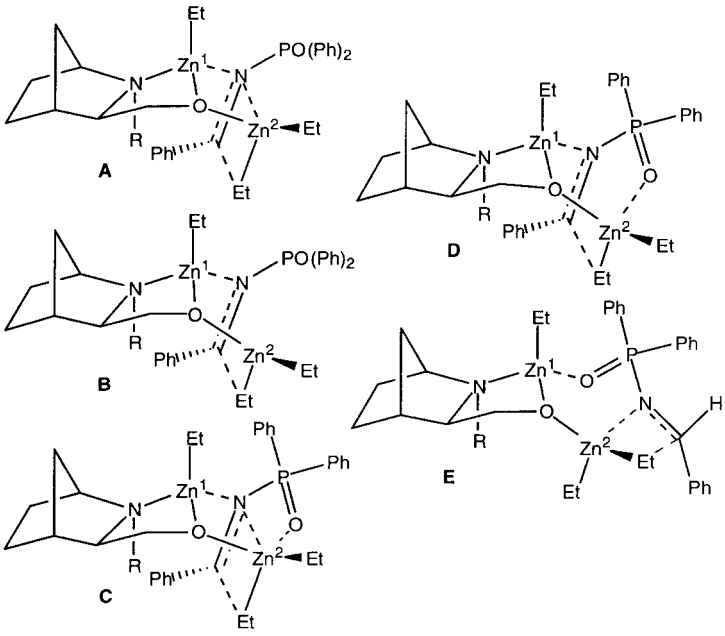

Figure 1. Five different types of transition states (TS) evaluated for the addition of diethylzinc to *N*-(diphenylphosphinoyl) benzalimine.

As shown in Table 1a [2.2.0] bicyclic TS **A**, as in the case of the analogous aldehyde reaction, can be excluded from the potential energy surface of the imine reaction. The two reactions evidently differ in reaction mechanism. Structure **B**, a ring-opened analogue of **A**, could not be located for our large model system and instead optimized to structure **A**. For a smaller model system this TS was about 3 kcal mol^{-1} higher in energy than **D** (see Supporting Information). Structure **C**, which contains an even more tightly bound substrate, optimized to structure **D** and could not be located in any of the calculations. A transition state such as **D** was earlier invoked to explain the stereochemical outcome of the reaction.[11a] As shown in Table 1 an analysis based on this TS indeed results in a correct prediction of the enantioselectivity. This TS is also considerably lower in energy than **A**. However, a TS in which the phosphinoyl oxygen atom coordinates to the Zn center of the catalyst is even lower in energy. In addition, the calculated energy difference between the two lowest energy TSs that lead to opposite enantiomers of the product fits accurately to the experimental value of the enantioselectivity (91 % *ee*).[9] The energy barrier calculated from precoordinated *N*-(dimethylphosphinoyl)benzalimine for this TS (Table 1, entry 5) is 12.7 kcal mol^{-1} at the HF/3-21G level and 14.9 kcal mol^{-1} for the application of B3PW91 to the HF geometry. This barrier is reasonably low, and the conclusion must be that the reaction occurs via a TS of type **E**. The driving forces calculated similarly from the same precoordinated complex are -54.8 kcal mol^{-1} and -40.1 kcal mol^{-1}, respectively. One reason for this TS being lower in energy than **D** is probably that it avoids major steric repulsion between the ligand and the aryl group of the imine. Calculations on a smaller model system with the sterically unhindered *N*-(dimethylphosphinoyl)formimine support this conclusion (see Supporting Information).[2]

Origin of the selectivity: In rationalizing the enantioselectivity of the addition of diethylzinc to *N*-(diphenylphosphinoyl)-benzalimine, 16 possible diastereomeric transition states of type **E** must be considered. To perform this extensive analysis, the TSs were categorized according to four different geometrical parameters, each capable of blocking a specific set of diastereomeric routes.

Table 1. Relative transition state energies [kcal mol^{-1}] for the addition of dimethylzinc to *N*-(dimethylphosphinoyl)benzalimine with ligand **1** ($R^1 = Me$, $R^2 = H$) as catalyst.

Entry	TS type enantiomer	Product at Zn1	Configuration	eq/ax[a]	HF/3-21G	B3PW91/[b] //HF/3–21G	B3PW91/[b] //B3PW91/[c]
1	**A**	*S*	*R*		34.8	22.4	
2	**D**	*S*	*R*		12.7	12.2	11.7
3	**D**	*S*	*S*		21.2	16.5	
4	**D**	*R*	*R*		18.0	15.2	
5	**E**	*S*	*R*	eq	0.0	0.0	0.0
6	**E**	*S*	*S*	eq	2.2	2.7	
7	**E**	*R*	*R*	ax	7.7	9.5	
8	**E**	*R*	*R*	eq	1.1	1.8	1.4
9	**E**	*R*	*S*	eq	2.5	2.6	

[a] Orientation of the aryl substituent of the imine in the TS of type **E**. [b] The basis set was 6–311 + G* for Zn and 6–31G* for P, C, N, O, and H. [c] The basis set was 6–311 + G for Zn and 6–31G for P, C, N, O, and H.

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General ligand effects: Coordination of the nitrogen atom of the ligand to zinc (Zn^1, Figure 1) requires an *R* configuration at this position that places the alcohol group and the coordinated zinc center in a *syn* arrangement. This lowers the number of energetically viable TSs to eight.

The second diastereo-differentiating component in the reaction can be referred to as equatorial/axial selectivity, in which the geometrical distinction concerns the orientation of the aryl substituent of the imine in the TS. Figure 2 illustrates

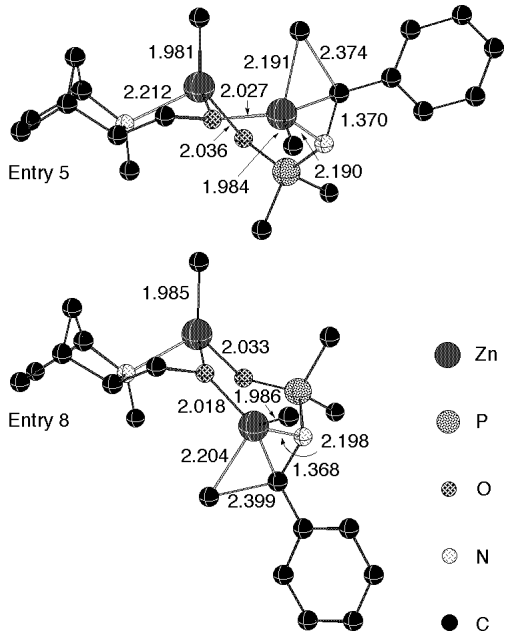


Figure 2. The two lowest transition states found for the addition of dimethylzinc to *N*-(dimethylphosphinoyl)benzalimine (entries 5 and 8 in Table 1), optimized at the B3PW91 level with the basis sets 6–311 + G for Zn and 6–31G for other atoms. Hydrogen atoms omitted for clarity.

two TSs with an equatorial-type orientation of the aryl group. This effect proved to be very strong and was estimated to be about 7 kcal mol^{-1} in favor of an equatorial configuration (Table 1, entries 7 and 8). The number of TSs to be included in the analysis of the enantioselectivity is thus reduced to four.

The preference for an *R* configuration at Zn^1 is due to the steric requirements of the ligand in the back-folded (*S*)-Zn^1-TS. This effect can be estimated to be around 3 kcal mol^{-1} (Table 1, entries 5 and 6) and thus may leave room for competitive pathways.

Finally, the face selectivity at the imine determines the enantioselectivity of the reaction. The calculations correctly predict a preferential formation of the *S* product, and the energy difference calculated by B3PW91 on the HF geometry is 1.8 kcal mol^{-1} (Table 1). Experimentally, this energy difference was estimated at about 2 kcal mol^{-1} for a measured *ee* of 91 %.[9] The main difference between the lowest (*R*)- and the lowest (*S*)-TS concern the orientation of the four-membered ring (Zn2-C-C-N), where an *exo* orientation is favored (Figure 2).

Substituent effects: As we reported before,[9] the use of a tertiary alcohol group (**1**; R^1 = Bn, R^2 = Ph) led to a poor *ee* (16 %), and the best result (91 % *ee*) for this bicyclic amino alcohol was obtained with a primary alcohol group (**1**; R^1 = Bn, R^2 = H). The best result so far was achieved with an aziridino alcohol (94 % *ee*).[11a]

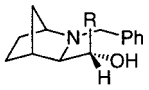
A potential site for introducing new substituents is the position α to the alcohol in the 2-azanorbornyl-3-methanol ligand. A series of such ligands **5**–**8** was synthesized with the intention of studying the effects of substituents on the enantioselectivity of the reaction, and the results are listed in Table 2. Ligand **5** gave the highest enantiomeric excess

Table 2. Addition of diethylzinc to *N*-(diphenylphosphinoyl)benzalimine.

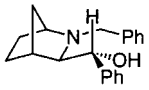
Entry	Chiral ligand	Yield [%][a]	*ee* [%][b]	Abs. config.[c]
1	**5**	70	97	*S*
2	**6**	68	93	*S*
3	**7**	59	79	*S*
4	**8**	52	71	*S*

[a] Yield of isolated product after flash chromatography (silica gel; pentane/acetone). [b] Determined by HPLC analysis on a chiral column (ChiralCel OD-H). [c] Determined as described in ref. [11].

reported so far (97 % ee) and thus makes this reaction an even more powerful tool for the synthesis of chiral amines. All of these reactions were performed with a stoichiometric amount of the chiral ligand under the conditions previously reported.[9,11]



5 R = Ph
6 R = Me
7 R = *i*Pr



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To identify the factors responsible for the increase in *ee* with ligand **5**, we performed two large calculations on this system (Table 3). The calculated energies correlate well with the

Table 3. Substituent effects on energies [kcal mol^{-1}] and selected geometrical parameters.[a]

Chiral ligand	Product enantiomer	B3PW91/[b] //HF/3–21G	Out-of-plane angle (Zn^1-O-Zn^2-C_α)	Dihedral angle Δ(C-Zn^2-N-C)
1	(*S*)	0.0	140°	8°
5	(*S*)	0.0	168°	4°
1	(*R*)	1.8	−153°	−9°
5	(*R*)	2.8	−155°	−12°

[a] The comparison refers to the lowest (*S*)- and the lowest (*R*)-TS in Table 1. [b] The basis set was 6-311 + G* for Zn and 6-31G* for P, C, N, O, and H.

experimental results in Table 2 and thus allow a deeper analysis of the selectivity-determining process. The main structural differences between TS structures with unsubstituted and substituted ligands concern the out-of-plane torsional angle Zn^1-O-Zn^2-C_α (α to the alcohol) and the dihedral angle C-Zn^2-N-C in the four-membered ring of the TS. These parameters are affected oppositely by the substituent in the

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two diastereomeric TSs. Perhaps the most important of these effects is the deviation from planarity of the four-membered ring. Comparing, for example, entries 6 and 9 in Table 1, for which the main differences are the *exo*/*endo* relationship of the four-membered ring (*endo* for entry 6) this effect seems to be efficiently compensated by the difference in planarity. The TS in entry 6 is almost completely planar whereas that of entry 9 is puckered (C-Zn^2-N-C $-31°$).

Ligand synthesis

The synthetic approach to the key intermediate **12** is outlined in Scheme 2. Compound **9** was obtained by a diastereoselective aza-Diels–Alder reaction between cyclopentadiene and the imine derived from ethyl glyoxylate and (*S*)-1-phenylethylamine.[13] After purification by flash chromatography the major exo cycloadduct was hydrogenated under an atmosphere of molecular hydrogen in the presence of Pd/C (10 wt%) to yield the N-protected amino ester **10**. Reduction with $LiAlH_4$ and subsequent oxidation of **11** under Swern conditions led to the α-amino aldehyde **12** as a yellow oil in excellent yield.[14] Treatment of **12** with Grignard reagents afforded adduct **13** in low yield, even when reverse addition was used.[15] Addition of Grignard reagents to carbonyl groups can be promoted by addition of anhydrous cerium chloride, which presumably forms highly oxophilic organocerium reagents.[16, 17] These intermediates were generated in situ and treated at low temperature with **12** to give the desired secondary alcohols with good selectivity (85:15) and in up to almost quantitative yield. The diastereomeric mixture could be easily purified by flash chromatography and the major isomers isolated as white solids. The stereoselective introduction of the second chiral center into the bicyclic compound was thus achieved. The high selectivity of the reaction is due to preferential approach of the nucleophile from the less hindered side of the nonchelated[15] α-amino aldehyde (Figure 3).

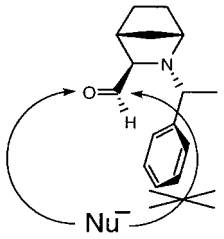
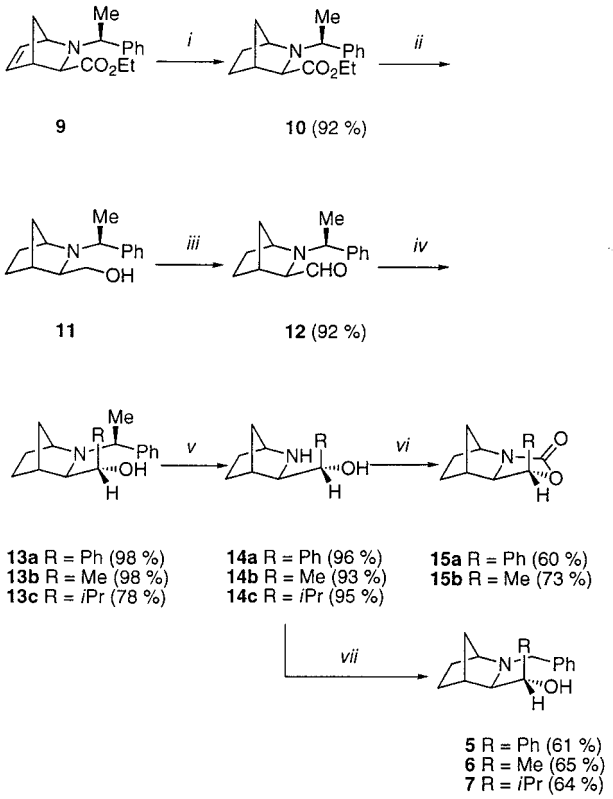


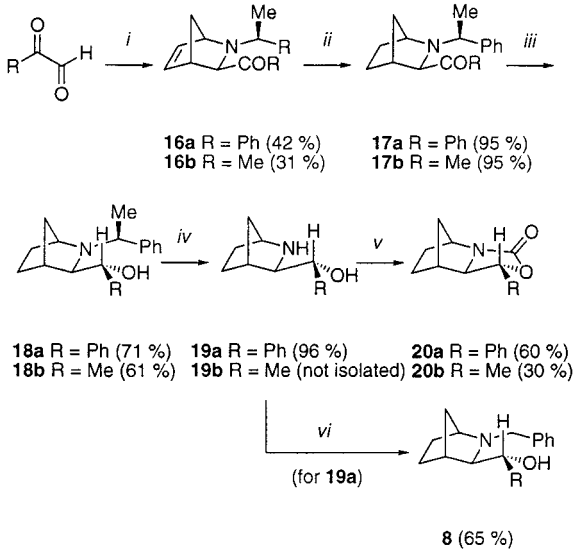
Figure 3. Preferential approach of the nucleophile from the less hindered side of the aldehyde.

Hydrogenolysis of **13** was first attempted with a catalytic amount of Pd/C,[18] but this did not yield the desired product. However, treatment of the same compound under 20 atm H_2 in presence of catalytic amounts of Pearlman's catalyst ($Pd(OH)_2$/C) gave the free amino alcohols **14** as white solids in excellent yield.

Having isolated the diastereomers **14**, we thought the Mitsunobu reaction[19] would be suitable for inverting the absolute configuration at the stereocenter of the secondary alcohol. However, the reaction did not take place, probably due to steric hindrance. Instead we developed another short and straightforward route to the diastereomers starting from prochiral bicyclic ketones (Scheme 3).



Scheme 2. i) H_2 (1 atm), Pd/C (10 wt%), EtOH, room temperature. ii) $LiAlH_4$, THF, room temperature. iii) Swern oxidation. iv) RMgX/$CeCl_3$, THF, $-78°$C. v) H_2 (300 psi), $Pd(OH)_2$/C (20 wt%), EtOH, room temperature. vi) Cl_2CO, NEt_3, THF, 0 °C. vii) BnCl, K_2CO_3, MeCN, room temperature.



Scheme 3. i) (*S*)-1-phenylethylamine, CH_2Cl_2, 0 °C; TFA, $BF_3 \cdot OEt_2$, cyclopentadiene, CH_2Cl_2, $-78°$C. ii) H_2 (1 atm), Pd/C (10 wt%), MeOH, K_2CO_3, room temperature. iii) $LiAlH_4$, THF, $-78°$C. iv) H_2 (300 psi), $Pd(OH)_2$/C (20 wt%), EtOH, room temperature. v) Cl_2CO, NEt_3, THF, 0 °C. vi) BnCl, K_2CO_3, MeCN, room temperature.

The prochiral ketones were obtained by a diastereoselective aza-Diels–Alder reaction analogous to that described for the synthesis of the ester **9**. Treatment of cyclopentadiene with the imines prepared from (*S*)-1-phenylethylamine and phenylglyoxal or pyruvic aldehyde resulted in the cycloadducts

16. Hydrogenation of **16** under an atmosphere of hydrogen in presence of 10% Pd/C gave the α-amino ketones **17.** Reduction of these intermediates with $NaBH_4$ was unsuccessful (20% yield after 2 d at 20 °C), but with $LiAlH_4$ the corresponding alcohols were obtained in good yields and high selectivity (80:20). With diisobutylaluminum hydride (DIBAL) a similar yield was obtained but the selectivity was slightly lower (70:30). The N-protected β-amino alcohols **18** were subsequently hydrogenolyzed and benzylated under the conditions employed for the diastereomers **13**.[18]

Determination of stereochemistry

Relative stereochemistry: Treatment of **14** and **19** with phosgene furnished the corresponding *N,O*-carbamates **15** and **20** (Schemes 2 and 3). The relative configuration of these compounds was determined by NOE difference spectroscopy (Figure 4).

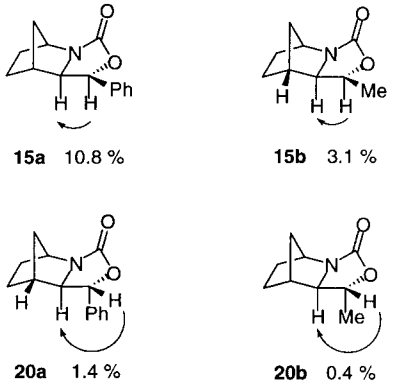
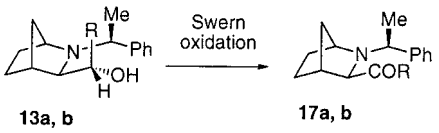


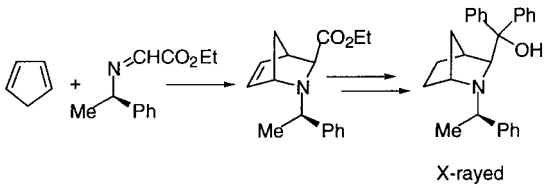
Figure 4. NOE difference spectroscopy of the *N,O*-carbamates **15** and **20** confirming the relative stereochemistry of the α-substituents.

Absolute stereochemistry: Further clues to the absolute stereochemistry of the compounds **19** was obtained by performing a Swern oxidation on the 2-azanorbornyl-3-methanols **13** to give the β-amino ketones **17** (Scheme 4). Since all spectroscopic data were in complete agreement with that observed for the ketones derived from the usual aza-Diels–Alder reaction followed by hydrogenation, it could be concluded that the two compounds have the same absolute configuration.



Scheme 4.

The chiral induction by the (*R*)-1-phenylethylamine in the aza-Diels–Alder reaction between cyclopentadiene and the imine derived from ethyl glyoxylate and (*R*)-1-phenylethylamine was assigned by means of X-ray crystallography (Scheme 5).[20] Since **16a** and **16b** have the same absolute stereochemistry as the 2-azanorbornyl-3-methanols **13**, an assignment of the absolute stereochemistry could be made for all compounds derived from these intermediates.



Scheme 5. Determination of the absolute stereochemistry.[20]

Conclusions

On the basis of quantum chemical investigations with the B3PW91[21] hybrid functional we conclude that the reaction mechanism, both for the reaction catalyzed by bicyclic 2-azanorbornyl-3-methanols and for the reaction catalyzed by aziridinoalcohols,[11] occurs via a TS of type **E** (Figure 1). This finding enabled the factors that govern the enantioselectivity of the reaction to be analyzed, and four elements of the selectivity process were identified. We improved the enantioselectivity of the reaction up to 97% *ee* by introducing an additional chiral center in the ligand. Work is now in progress to uncover the mechanistic details of the catalytic cycle. In addition, a TS molecular mechanics model is currently being developed to enable faster evaluations of substituent effects and rapid evaluation of new ligands.

Experimental Section

Methods of calculation: All calculations were performed with the Gaussian 94 program.[22] Geometry optimizations were performed by HF calculations with the 3-21G basis set. For some selected transition states, geometry optimizations were performed with B3PW91, a density functional type of calculation with a hybrid functional, together with the 6-31G basis set for all atoms except for zinc, for which 6-311 + G was used. The final energies were determined with B3PW91 and the 6–31G* basis set for all atoms except for zinc (6-311 + G*). The model used in the calculations was very close to the real system, although some truncations were necessary to reduce the size of the system. As the aim of the calculations was to rationalize the stereochemical outcome of the reaction, all stereocenters were left intact. The model system is depicted in Figure 5. The imine was considered to exist exclusively in a *trans* configuration.

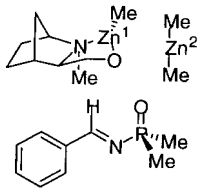


Figure 5. Model system used in the calculations.

General methods: For general experimental information, see ref. [23]. All reactions were performed under nitrogen or argon. Before use the reaction vessels were evacuated, heated, and flushed with inert gas. All commercially available reagents were employed as supplied, except for cyclopentadiene, which was freshly distilled prior to use. Flash chromatography was performed on silica gel (Matrex 60A, 37–70 μm). Deactivated silica gel was prepared by elution of the column with 5% Et_3N in pentane until the eluate was alkaline (pH paper). TLC was performed on precoated plates (SIL G-60 UV_{254}, Macherey-Nagel). Deactivated silica gel was obtained by eluting TLC plates with 5% Et_3N in pentane and drying before applying the sample. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer, a Varian XL 300 spectrometer, or a Varian Unity 400 spectrometer at 25 °C; the reference for ^1H chemical shifts was residual $CHCl_3$ ($\delta = 7.26$), and that for ^{13}C chemical shifts the ^{13}C signal of $CDCl_3$ ($\delta = 77.0$). Mass spectra were recorded at 70 eV with a Finnigan MAT GCQ instrument by direct inlet. IR spectra were recorded with a Perkin Elmer 1760 FTIR spectrometer and a Perkin Elmer 1600 series FTIR spectrom-

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eter. HPLC analysis of diethylzinc addition products was carried out on a chiral column (ChiralCel OD-H), with a UV detector and a flow rate of 0.5 mL min^{-1} of hexane/isopropyl alcohol (95/5). The retention times were 24.7 min for the *R* isomer and 36.9 min for the *S* isomer. Et_2Zn was purchased from Aldrich Co. Imine **1** was prepared according to a literature procedure.[9b]

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo[2.2.1]heptane-3-carboxaldehyde (12): To a solution of oxalyl chloride (4.82 g, 38 mmol) in dry CH_2Cl_2 (100 mL) at $-78\,^\circ C$ was added a solution of DMSO (6.39 g, 82.6 mmol) in CH_2Cl_2 (10 mL) over 5 min, and the reaction mixture was stirred for 10 min at $-78\,^\circ C$. The alcohol **11** (8.01 g, 34.4 mmol) was added as a solution in CH_2Cl_2 (10 mL) over 5 min. The reaction mixture was stirred for 15 min, and an excess of Et_3N (17.4 g, 120 mmol) was added over 5 min. The cooling bath was removed and the temperature raised to room temperature. Water (120 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were washed with brine (60 mL) and dried over $MgSO_4$. Filtration and evaporation afforded a residue that was purified by flash chromatography with Et_2O/pentane (1/4) as eluent to give a yellow oil. Yield: 92%; $R_f = 0.38$ (Et_2O/pentane 1/4); $[\alpha]_D^{25} = +78.6$ ($c = 2.00$ in $CHCl_3$); IR (neat): $\tilde{\nu} = 1721$, 2970, 3062 cm^{-1}; ^{1}H NMR: $\delta = 9.00$ (d, $^3J(H,H) = 2.90$ Hz, 1H), 7.33–7.17 (m, 5H), 3.81 (s, 1H), 3.52 (q, $^3J(H,H) = 6.56$ Hz, 1H), 2.41 (br s, 2H), 1.99–2.05 (m, 1H), 1.62–1.73 (m, 2H), 1.44–1.51 (m, 1H), 1.39 (d, $^3J(H,H) = 6.41$ Hz, 3H), 1.32 (d, $^3J(H,H) = 9.77$ Hz, 1H); ^{13}C NMR: $\delta = 205.0$, 144.8, 128.5, 127.9, 127.6, 75.7, 60.8, 58.3, 42.3, 36.4, 29.2, 22.6, 22.5; MS (70 eV, EI): *m/z* (%): 229 (10) [M^+], 200 (40) [$C_{14}H_{18}N^+$], 105 (100) [$C_8H_9^+$]; $C_{15}H_{19}NO$ (229.3): calcd: C 78.56, H 8.35, N 6.11, found: C 78.29, H 8.31, N 6.25.

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo[2.2.1]heptane-3-(*S*)-phenylmethanol (13a): At $-78\,^\circ C$ phenylmagnesium bromide (0.45 mL, 1.33 mmol, 3M in Et_2O) was added to a suspension of cerium chloride (327 mg, 1.33 mmol) in dry THF (3 mL). After stirring for 1 h the mixture was treated with a solution of **6** (100 mg, 0.44 mmol) in dry THF (2 mL), and the reaction vessel was allowed to reach room temperature overnight. Then brine (10 mL) was added and the product was extracted with CH_2Cl_2 (3 × 10 mL). After drying over Na_2SO_4 the solvent was evaporated and the residue was purified by flash chromatography. Yield: 98%; $R_f = 0.51$ (EtOAc/pentane 1/1); $[\alpha]_D^{25} = -83.4$ ($c = 1.00$ in $CHCl_3$); IR (neat): $\tilde{\nu} =$ 3421, 2972, 2871, 1494, 1451.6 cm^{-1}; ^{1}H NMR: $\delta = 7.45-6.95$ (m, 10H), 3.75 (s, 1H), 3.63 (q, $^3J(H,H) = 6.8$ Hz, 1H), 3.10 (d, $^3J(H,H) = 6.4$ Hz, 1H), 2.22 (d, $^3J(H,H) = 6.2$ Hz, 1H), 1.90–2.05 (m, 2H), 1.75 (br s, 1H), 1.20–1.50 (m, 5H), 1.05 (d, $^3J(H,H) = 8.1$ Hz, 2H); ^{13}C NMR: $\delta = 186.8$, 128.6, 127.8, 127.7, 126.3, 125.4, 107.9, 73.1, 71.9, 60.8, 58.7, 37.6, 36.1, 29.8, 22.5, 22.3; MS (70 eV, EI): *m/z* (%): 308 (< 1) [M^+], 106 (10) [$C_7H_6O^+$], 105 (100) [$C_8H_9^+$]; $C_{21}H_{25}NO$ (307.4): calcd: C 82.04, H 8.2, N 4.56; found: C 81.84, H 8.08, N 4.41.

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo[2.2.1]heptane-3-(*S*)-methylmethanol (13b): At $-78\,^\circ C$ methylmagnesium chloride (0.48 mL, 1.46 mmol, 3M in THF) was added to a suspension of cerium chloride (360 mg, 1.46 mmol) in dry THF (3 mL). After stirring for 1 h the mixture was treated with a solution of **6** (110 mg, 0.48 mmol) in dry THF (2 mL) and the reaction vessel was allowed to reach room temperature overnight. Then brine (10 mL) was added and the product was extracted with CH_2Cl_2 (3 × 10 mL). After drying over Na_2SO_4 the solvent was evaporated and the residue was purified by flash chromatography. Yield: 98%; $R_f = 0.40$ (EtOAc/pentane 1/1); $[\alpha]_D^{25} = -48.6$ ($c = 1.00$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} =$ 3695, 3383, 2962, 2874, 1602, 1309, 1277, 1054 cm^{-1}; ^{1}H NMR: $\delta = 7.40-7.20$ (m, 5H), 3.70 (s, 1H), 3.55 (q, $^3J(H,H) = 7.2$ Hz, 1H), 3.20 (br s, 1H), 2.35 (d, $^3J(H,H) = 4.8$ Hz, 1H), 2.20 (d, $^3J(H,H) = 4.8$ Hz, 1H), 2.10–1.80 (m, 2H), 1.70–1.15 (m, 5H), 1.38 (d, $^3J(H,H) = 6.5$ Hz, 3H), 0.90 (d, $^3J(H,H) =$ 6.9 Hz, 3H); ^{13}C NMR: $\delta = 146.0$, 128.5, 127.5, 127.5, 107.4, 72.9, 65.5, 60.9, 58.4, 36.6, 36.3, 29.8, 22.8, 22.4, 17.8; MS (70 eV, EI): *m/z* (%): 245 (23) [M^+], 105 (38) [$C_8H_9^+$], 91 (100), 69 (30) [$C_4H_5O^+$]; $C_{16}H_{23}NO$ (245.4): calcd: C 78.32, H 9.45, N 5.71; found: C, 78.21, H 9.62, N 5.84.

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo[2.2.1]heptane-3-(*S*)-isopropylmethanol (13c): At $-78\,^\circ C$ the Grignard reagent derived from isopropyl bromide (0.27 mL, 3 mmol) and magnesium (80 mg, 3 mmol) in dry THF (5 mL) was added to a suspension of cerium chloride (750 mg, 3 mmol) in dry THF (10 mL). After stirring for 1 h the mixture was treated with a solution of **6** (229 mg, 1 mmol) in dry THF (2 mL) and the reaction vessel was allowed to reach room temperature overnight. Then brine (10 mL) was added and the product was extracted with CH_2Cl_2 (3 × 10 mL). After drying over Na_2SO_4 the solvent was evaporated and the residue was purified by flash chromatography. Yield: 78%; $R_f = 0.20$ (EtOAc/pentane 1/1); $[\alpha]_D^{25} = -21.0$ ($c = 1.00$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} =$ 3055, 2987, 2306, 1424, 1271 cm^{-1}; ^{1}H NMR: $\delta = 7.40-7.20$ (m, 5H), 3.73 (br s, 1H), 3.57 (q, $^3J(H,H) = 6.4$ Hz, 1H), 3.45 (br s, 1H), 2.31 (br s, 1H), 1.95–2.15 (m, 2H), 1.90 (d, $^3J(H,H) = 9.8$ Hz, 1H), 1.80–1.55 (m, 2H), 1.42 (d, $^3J(H,H) = 6.4$ Hz, 5H), 1.35–1.15 (m, 3H), 0.75(d, $^3J(H,H) = 6.0$ Hz, 3H), 0.53 (d, $^3J(H,H) = 6.0$ Hz, 3H); ^{13}C NMR: $\delta = 145.5$, 128.3, 127.6, 127.4, 75.6, 70.1, 60.8, 58.2, 37.1, 36.4, 30.5, 30.0, 22.5, 22.2, 20.7, 17.9; MS (70 eV, EI): *m/z* (%): 274 (16) [M^+], 105 (100) [$C_8H_9^+$], 104 (15) [$C_8H_8^+$], 103 (23) [$C_8H_7^+$]; $C_{18}H_{27}NO$ (273.4): calcd: C 79.07, H 9.95, N 5.12; found: C 78.91, H 10.05, N 5.15.

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo[2.2.1]hept-5-ene-3-phenylketone (16a): Phenyl glyoxylate (2.0 g, 15 mmol) was dissolved in CH_2Cl_2 (15 mL), containing 3 g of activated 4 Å molecular sieves. The solution was cooled to $0\,^\circ C$, and (*S*)-1-phenylethylamine (2.0 mL, 15.7 mmol) was added. After 30 min, the solution was cooled to $-78\,^\circ C$, and trifluoroacetic acid (1.2 mL, 15.7 mmol), $BF_3 \cdot Et_2O$ (1.97 mL, 15.7 mmol), and cyclopentadiene (1.3 mL, 15.7 mmol) were added. The reaction was kept at $-78\,^\circ C$ for 5 h then allowed to warm to room temperature. The molecular sieves were removed, and the reaction mixture was washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4. Concentration and purification by flash chromatography (deactivated silica gel, pentane/Et_2O 95/5–80/20) afforded pure **16a**. Yield: 42%; $R_f = 0.45$ (Et_2O/pentane 1/4); $[\alpha]_D^{25} = +10.1$ ($c = 1.00$ in CH_2Cl_2); IR ($CHCl_3$): $\tilde{\nu} = 3680$, 3601, 2784, 1711, 1691, 1606 cm^{-1}; ^{1}H NMR: $\delta = 7.45-6.9$ (m, 10H), 6.5 (s, 1H), 6.00 (dd, $^3J(H,H) = 6.3$ Hz, $^3J(H,H) = 2.0$ Hz, 1H), 3.20 (s, 1H), 4.40 (s, 1H), 3.15 (q, $^3J(H,H) = 6.6$ Hz, 1H), 2.85 (s, 1H), 2.10 (d, $^3J(H,H) = 8.4$ Hz, 1H), 1.45 (d, $^3J(H,H) = 6.9$ Hz, 3H), 1.40 (d, $^3J(H,H) = 8.8$ Hz, 1H); ^{13}C NMR: $\delta = 145.1$, 137.3, 136.1, 133.6, 132.2, 128.2, 128.1, 128.0, 127.5, 127.0, 121.3, 66.9, 64.2, 62.7, 49.3, 44.5, 22.7; MS (70 eV, EI): *m/z* (%): 304 (5) [M^+], 105 (100) [$C_8H_9^+$], 104 (11) [$C_8H_8^+$], 94 (17) [$C_6H_7N^+$]; $C_{21}H_{21}NO$ (303.4): calcd: C 83.13, H 6.98, N 4.62; found: C 83.21, H 6.87, N 4.78.

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo[2.2.1]hept-5-ene-3-methylketone (16b): To a cooled solution ($0\,^\circ C$) of methyl glyoxylate (17.82 g, 41 mmol, 40% solution in H_2O) in H_2O (20 mL) was added dropwise an aqueous solution of (*S*)-1-phenylethylamine (10 g, 49.5 mmol) in 2M HCl (41 mL). After stirring for 30 min cyclopentadiene (10.84 g, 164 mmol) was added, stirring was continued overnight, and the solution was allowed to warm to room temperature. Then the reaction mixture was adjusted to pH 8 with NaOH. Extraction with CH_2Cl_2 (3 × 50 mL), drying over Na_2SO_4, concentration under reduced pressure, and purification by flash chromatography (deactivated silica gel, pentane/Et_2O 95/5–80/20) afforded pure **16b**. Yield: 31%; $R_f = 0.15$ (Et_2O/pentane 1/4); $[\alpha]_D^{25} = +10.8$ ($c = 0.50$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 2875$, 1721, 1693 cm^{-1}; ^{1}H NMR: $\delta =$ 7.40–7.20 (m, 5H), 6.50 (dd, $^3J(H,H) = 5.5$ Hz, $^3J(H,H) = 3.0$ Hz, 1H), 6.30 (dd, $^3J(H,H) = 5.5$ Hz, $^3J(H,H) = 1.5$ Hz, 1H), 4.37 (s, 1H), 3.03 (q, $^3J(H,H) = 6.4$ Hz, 1H), 2.85 (s, 1H), 2.35 (s, 1H), 2.00 (d, $^3J(H,H) =$ 8.5 Hz, 1H), 1.80–1.20 (m, 1H), 1.64 (s, 3H), 1.45 (d, $^3J(H,H) = 6.7$ Hz, 3H); ^{13}C NMR: $\delta = 145.2$, 136.5, 132.9, 128.3, 128.2, 127.3, 70.9, 63.8, 62.7, 48.5, 44.7, 28.0, 22.0; MS (70 eV, EI): *m/z* (%): 242 (15) [M^+], 198 (100) [$C_{14}H_{16}N^+$], 106 (96) [$C_8H_9^+$]; $C_{16}H_{19}NO$ (241.3): calcd: C 79.63, H 7.94, N 5.80; found: C 79.78, H 8.07, N 6.05.

General procedure for alkene reduction: 1 g of the 2-azanorbornene **16a** or **16b** was dissolved in MeOH (25 mL), and the solution added to a stirred suspension of Pd/C (100 mg, 10 wt%) and 200 mg K_2CO_3. After 3 h the solvent was evaporated. Then the residue was dissolved in H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated to give the white, low-melting solids **17a** and **17b**.

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo(2.2.1(heptane-3-phenylketone (17a): Yield: 95%; $R_f = 0.2$ (Et_2O/pentane 1/4); $[\alpha]_D^{25} =$ $+0.6$ ($c = 0.50$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3695$, 2963, 2874, 1691, 1600, 1312, 1228 cm^{-1}; ^{1}H NMR: $\delta = 7.40-6.90$ (m, 10H), 3.90 (s, 1H), 3.60 (q, $^3J(H,H) = 6.5$ Hz, 1H), 3.51 (s, 1H), 2.25 (d, $^3J(H,H) = 5.6$ Hz, 1H), 2.10–2.21 (m, 2H), 1.42–1.80 (m, 3H), 1.40 (d, $^3J(H,H) = 6.7$ Hz, 3H), 1.31 (d, $^3J(H,H) = 6.7$ Hz, 1H); ^{13}C NMR: $\delta = 200.6$, 144.8, 137.0, 132.0, 128.3, 128.0, 128.0, 127.4, 127.1, 72.3, 61.4, 58.2, 43.2, 35.3, 29.6, 22.6, 22.1; MS

(70 eV, EI): *m/z* (%): 306 (16) [M^+], 105 (100) [$C_8H_9^+$]; $C_{21}H_{23}NO$ (305.4): calcd: C 82.59, H 7.59, N 4.59; found: C 82.35, H 7.44, N 4.72.

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo[2.2.1]heptane-3-methylketone (17b): Yield: 95%; $R_f = 0.5$ (Et_2O/pentane 1/4); $[\alpha]_D^{25} = -23.2$ ($c = 0.50$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3695$, 2964, 2874, 1712, 1693, 1602, 1314, 1191 cm^{-1}; ^1H NMR: $\delta = 7.40-7.10$ (m, 5H), 3.80 (s, 1H), 3.45 (q, $^3J(H,H) = 6.6$ Hz, 1H), 2.65 (s, 1H), 2.21 (d, $^3J(H,H) = 3.6$ Hz, 1H), 2.11–1.90 (m, 2H), 1.82–1.21 (m, 4H), 1.50 (s, 3H), 1.36 (d, $^3J(H,H) = 6.5$ Hz, 3H); ^{13}C NMR: $\delta = 210.3$, 186.8, 145.0, 128.4, 128.2, 127.4, 76.6, 61.0, 58.1, 42.3, 35.5, 29.9, 27.3, 22.1, 22.0; MS (70 eV, EI): *m/z* (%): 244 (8) [M^+], 105 (100) [$C_8H_9^+$], 96 (16) [$C_6H_9N^+$]; $C_{16}H_{21}NO$ (243.3): calcd: C 78.97, H 8.7, N 5.74; found: C 79.10, H 8.85, N 5.58.

General procedure for ketone reduction: To a suspension of $LiAlH_4$ (250 mg, 6.55 mmol) in THF (20 mL) at −78 °C was added dropwise a solution (10 mL) of the ketone (1 g, 3.28 mmol) in THF by syringe. After 30 min the cooling bath was removed, and stirring was continued for 1 h. The reaction was quenched by adding H_2O (0.25 mL) and 2 M NaOH (0.5 mL) and then filtered through Celite. Evaporation afforded a residue, which was purified by flash chromatography on deactivated silica gel to give the protected β-amino alcohol.

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo[2.2.1]heptane-3-(*R*)-phenylmethanol (18a): Yield: 71%; $R_f = 0.51$ (EtOAc/pentane 1/1); $[\alpha]_D^{25} = -5.28$ ($c = 2.40$ in $CHCl_3$); IR (neat): $\tilde{\nu} = 3216$, 2958, 2875, 1603, 1442, 1309, 1204, 1061 cm^{-1}; ^1H NMR: $\delta = 7.21-7.40$ (m, 5H), 7.05–7.15 (m, 3H), 6.48–6.59 (m, 2H), 3.75 (d, $^3J(H,H) = 5.8$ Hz, 1H), 3.68 (s, 1H), 3.52 (q, $^3J(H,H) = 6.1$ Hz, 1H), 2.30 (d, $^3J(H,H) = 5.1$ Hz, 1H), 2.21–2.05 (br m, 1H), 2.26 (s, 1H), 1.60–1.80 (m, 2H), 1.45 (d, $^3J(H,H) = 6.80$ Hz, 3H), 1.35–1.20 (m, 3H); ^{13}C NMR: $\delta = 186.8$, 128.6, 127.8, 127.7, 126.3, 125.4, 107.9, 73.1, 71.9, 60.8, 58.7, 37.6, 36.1, 29.8, 22.5, 22.3; MS (70 eV, EI): *m/z* (%): 307 (2) [M^+], 274 (100) [$C_{20}H_{20}N^+$], 179 (75), 105 (18) [$C_8H_9^+$], 95 (23) [$C_6H_9N^+$]; $C_{21}H_{25}NO$ (307.4): calcd: C 82.04, H 8.2, N 4.56; found: C 82.17, H 8.13, N 4.65.

(1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo[2.2.1]heptane-3-(*R*)-methylmethanol (18b): Yield: 61%; $R_f = 0.40$ (EtOAc/pentane 1/1); $[\alpha]_D^{25} = -50.4$ ($c = 1.00$ in CH_2Cl_2); IR ($CHCl_3$): $\tilde{\nu} = 3260$, 3601, 1606, 1080 cm^{-1}; ^1H NMR: $\delta = 7.40-7.20$ (m, 5H) , 3.64 (s, 1H), 3.52 (q, $^3J(H,H) = 6.54$ Hz, 1H), 2.83 (dq, $^3J(H,H) = 4.14$ Hz, $^3J(H,H) = 2.2$ Hz, 1H), 2.11 (d, $^3J(H,H) = 4.08$ Hz, 2H), 1.99 (d, $^3J(H,H) = 3.84$ Hz, 1H), 1.60–1.82 (m, 2H), 1.45 (d, $^3J(H,H) = 6.54$ Hz, 3H), 1.45–1.20 (m, 3H), 0.33 (d, $^3J(H,H) = 6.36$ Hz, 3H); ^{13}C NMR: $\delta = 144.9$, 128.7, 128.4, 128.3, 127.6, 127.5, 72.1, 68.0, 60.9, 58.7, 42.9, 35.3, 27.8, 23.4, 22.3, 21.0; MS (70 eV, EI): *m/z* (%): 246 (21) [M^+], 79 (100); $C_{16}H_{23}NO$ (245.4): calcd: C 78.32, H 9.45, N 5.71; found: C 78.53, H 9.50, N 5.58.

General procedure for debenzylation: To a solution of the protected β-amino alcohol (1 g) in EtOH (50 mL) was added $Pd(OH)_2/C$ (200 mg, 20 wt%). The mixture was hydrogenated for 48 h at 20 atm pressure. The completeness of the reaction was monitored by NMR spectroscopy. The catalyst was filtered off on a bed of Celite, washed with CH_2Cl_2 (20 mL), and the combined filtrates were evaporated to dryness. The residue was triturated with pentane and dried to give the deprotected β-amino alcohols as off-white powders.

(1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-(*S*)-phenylmethanol (14a): Yield: 96%; $[\alpha]_D^{25} = +13.2$ ($c = 0.50$ in $CHCl_3$); IR (neat): $\tilde{\nu} = 3312$, 2933 cm^{-1}; ^1H NMR: $\delta = 7.38-7.10$ (m, 5H), 4.27 (d, $^3J(H,H) = 6.2$ Hz, 1H), 3.40 (s, 1H), 2.85 (d, $^3J(H,H) = 6.2$ Hz, 1H), 2.25 (br s, 3H), 1.65–1.10 (m, 5H), 1.05 (d, $^3J(H,H) = 8.1$ Hz, 1H); ^{13}C NMR: $\delta = 128.3$, 127.3, 126.6, 107.4, 107.3, 75.6, 65.9, 55.8, 37.6, 34.8, 32.7, 29.4; MS (70 eV, EI): *m/z* (%): 202 (90) [M^+], 186 (18) [$C_{13}H_{17}N^+$], 69 (100); $C_{13}H_{17}NO$ (203.3): calcd: C 76.81, H 8.43, N 6.89; found: C 76.88, H 8.52, N 6.85.

(1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-(*S*)-methylmethanol (14b): Yield: 93%; $[\alpha]_D^{25} = +17.1$ ($c = 0.50$ in $CHCl_3$); IR (neat): $\tilde{\nu} = 3268$, 2954, 2364 cm^{-1}; ^1H NMR: $\delta = 4.63$ (br s, 2H), 3.50 (q, $^3J(H,H) = 6.4$ Hz, 1H), 3.49 (s, 1H), 2.70 (s, 1H), 2.59 (d, $^3J(H,H) = 7.1$ Hz, 1H), 2.52 (s, 1H), 1.78–1.20 (m, 5H), 1.17 (d, $^3J(H,H) = 7.9$ Hz, 3H), 1.09 (d, $^3J(H,H) = 1.1$ Hz, 1H); ^{13}C NMR: $\delta = 69.4$, 66.7, 55.8, 36.9, 34.8, 32.3, 29.3, 19.4; MS (70 eV, EI): *m/z* (%):141 (18) [M^+], 96 (47) [$C_6H_{10}N^+$], 68 (100); $C_8H_{15}NO$ (141.2): calcd: C 68.04, H 10.71, N 9.92; found: C 67.89, H 10.77, N 9.95.

(1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-(*S*)-isopropylmethanol (14c): Yield: 95%; $[\alpha]_D^{25} = -10.0$ ($c = 1.00$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3680$, 3601, 2873, 1730, 1607 cm^{-1}; ^1H NMR: $\delta = 3.51$ (br s, 3H), 3.02 (pseudo-t, $^3J(H,H) = 5.7$ Hz, 1H), 2.75 (d, $^3J(H,H) = 5.7$ Hz, 1H), 2.46 (s, 1H), 1.85–1.10 (m, 7H), 0.90 (d, $^3J(H,H) = 6.8$ Hz, 3H), 0.86 (d, $^3J(H,H) = 6.8$ Hz, 3H); ^{13}C NMR: $\delta = 77.1$, 63.0, 55.7, 36.9, 35.0, 31.2, 29.5, 29.2, 19.4, 17.4; MS (70 eV, EI): *m/z* (%): 168 (9) [$M^+ - H$], 96 (28) [$C_6H_{10}N^+$], 68 (100); $C_{10}H_{19}NO$ (169.3): calcd: C 70.96, H 11.31, N 8.27; found: C 71.10, H 11.45, N 8.21.

(1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-(*R*)-phenylmethanol (19a): Yield: 96%; $[\alpha]_D^{25} = +30.4$ ($c = 1.00$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3680$, 3601, 2874, 1730, 1691, 1607 cm^{-1}; ^1H NMR: $\delta = 7.40-7.20$ (m, 5H), 4.11 (d, $^3J(H,H) = 8.5$ Hz, 1H), 3.55 (s, 1H), 3.32 (br s, 2H), 2.78 (d, $^3J(H,H) = 8.2$ Hz, 1H), 2.01 (s, 1H), 1.80–1.22 (m, 5H), 1.20 (d, $^3J(H,H) = 10.2$ Hz, 1H); ^{13}C NMR: $\delta = 143.5$, 128.4, 127.5, 126.7, 107.3, 75.3, 67.7, 56.2, 39.0, 34.4, 28.3; MS (70 eV, EI): *m/z* (%): 204 (100) [M^+], 186 (19) [$C_{13}H_{15}N^+$], 96 (74) [$C_6H_{10}N^+$]; $C_{13}H_{17}NO$ (203.3): calcd: C 76.81, H 8.43, N 6.89; found: C 76.73, H 8.56, N 6.93.

General procedure for carbamate formation: At 0 °C phosgene (0.46 mL, 1.93 M solution in toluene, 0.89 mmol) was added to a solution of the β-amino alcohol (105 mg, 0.75 mmol) in THF (20 mL). After 10 min Et_3N (3.0 equiv) was added. Then after 10 min the cooling bath was removed, and stirring was continued at room temperature for 30 min. Evaporation of the solvent under reduced pressure afforded the crude carbamates, which were purified by flash chromatography on silica gel.

(1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-(*S*)-phenylmethanol *N*,*O*-carbamate (15a): Yield: 60%; $R_f = 0.70$ (pentane/EtOAc 1/1); $[\alpha]_D^{25} = +64.0$ ($c = 1.00$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3659$, 2954, 1730, 1755, 1602, 1319 cm^{-1}; ^1H NMR: $\delta = 7.52-7.30$ (m, 5H), 4.95 (d, $^3J(H,H) = 8.0$ Hz, 1H), 4.35 (s, 1H), 3.45 (d, $^3J(H,H) = 8.0$ Hz, 1H), 2.60 (s, 1H), 1.80–1.35 (m, 8H); ^{13}C NMR: $\delta = 138.4$, 128.9, 128.8, 125.8, 83.5, 70.2, 61.0, 40.7, 36.4, 27.8, 27.6; MS (70 eV, EI): *m/z* (%): 229 (52) [M^+], 184 (77) [$C_{13}H_{15}N^+$], 168 (100), 95 (48) [$C_6H_9N^+$]; $C_{14}H_{15}NO_2$ (229.3): calcd: C 73.34, H 6.59, N 6.11; found: C 73.21, H 6.80, N 6.35.

(1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-(*S*)-methylmethanol *N*,*O*-carbamate (15b): Yield: 30%; $R_f = 0.70$ (pentane/EtOAc 1/1); $[\alpha]_D^{25} = +12.7$ ($c = 1.00$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3054$, 2988, 2307, 1424, 1271 cm^{-1}; ^1H NMR: $\delta = 4.85$ (dq, $^3J(H,H) = 9.2$ Hz, $^3J(H,H) = 9.2$ Hz, 1H), 4.26 (s, 1H), 3.53 (d, $^3J(H,H) = 9.1$ Hz, 1H), 2.52 (s, 1H), 1.75–1.55 (m, 3H), 1.20–1.40 (m, 3H), 1.21 (d, $^3J(H,H) = 6.7$ Hz, 1H); ^{13}C NMR: $\delta = 163.2$, 106.5, 77.2, 74.9, 64.9, 60.6, 38.1, 37.6, 28.7, 27.2, 16.3; MS (70 eV, EI): *m/z* (%): 168 (63) [M^+], 105 (100); HRMS calcd for $C_9H_{13}NO_2$: 167.0946; found: 167.0945.

(1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-(*R*)-phenylmethanol *N*,*O*-carbamate (20a): Yield: 60%; $R_f = 0.70$ (pentane/EtOAc 1/1); $[\alpha]_D^{25} = +6.1$ ($c = 1.00$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3659$, 2953, 2881, 1756, 1728, 1603, 1316, 1236 cm^{-1}; ^1H NMR: $\delta = 7.50-7.20$ (m, 5H), 5.75 (d, $^3J(H,H) = 9.2$ Hz, 1H), 4.25 (s, 1H), 3.85 (d, $^3J(H,H) = 9.2$ Hz, 1H), 2.05 (d, $^3J(H,H) = 3.2$ Hz, 1H), 1.70–1.35 (m, 5H), 1.00 (s, 1H); ^{13}C NMR: $\delta = 163.1$, 136.3, 128.4, 128.1, 125.2, 79.2, 66.3, 59.8, 38.8, 36.7, 28.4, 27.7; MS (70 eV, EI): *m/z* (%): 229 (55) [M^+], 184 (66) [$C_{13}H_{15}N^+$], 168 (100), 95 (40) [$C_6H_9N^+$]; $C_{14}H_{15}NO_2$ (229.3): calcd: C 73.34, H 6.59, N 6.11; found: C 73.42, H 6.55, N 5.97.

(1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-(*R*)-methylmethanol *N*,*O*-carbamate (20b): Yield: 73%; $R_f = 0.70$ (pentane/EtOAc 1/1); $[\alpha]_D^{25} = +1.1$ ($c = 0.28$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3055$, 2987, 2306, 1424, 1271 cm^{-1}; ^1H NMR: $\delta = 4.23$ (s, 1H), 4.11 (dq, $^3J(H,H) = 8.0$, $^3J(H,H) = 8.0$ Hz, 1H), 2.07 (s, 1H), 2.44 (s, 1H), 1.70–1.30 (m, 5H), 1.50 (dd, $^3J(H,H) = 8.0$, $^3J(H,H) = 8.0$ Hz, 3H); ^{13}C NMR: $\delta = 78.6$, 69.5, 60.5, 40.4, 36.4, 27.7, 27.7, 20.3; MS (70 eV, EI): *m/z* (%): 168 (62) [M^+], 105 (100); $C_9H_{13}NO_2$ (167.2): calcd: C 64.65, H 7.84, N 8.28; found: C 64.82, H 7.71, N 8.24.

General procedure for the benzylation of the NH β-amino alcohols: Benzylations of NH β-amino alcohols were performed according to a literature procedure.[11]

(1*S*,3*R*,4*R*)-2-(Benzylamino)-2-azabicyclo[2.2.1]heptane-3-(*S*)-phenylmethanol (5): Yield: 61%; $R_f = 0.30$ (pentane/EtOAc 4/1); $[\alpha]_D^{25} = -6.1$ ($c = 0.4$ in CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu} = 3602$, 3408, 2873, 1606, 1495, 1070, 1014 cm^{-1}; ^1H NMR: $\delta = 7.38-7.21$ (m, 10H), 4.39 (d, $^3J(H,H) = 4.8$ Hz, 1H), 3.66 (br s, 2H), 3.30–3.50 (m, 1H), 3.26 (br s, 1H), 2.30 (d, $^3J(H,H) = 4.8$ Hz, 1H), 2.05–1.90 (m, 1H), 1.88 (br d, $^3J(H,H) = 9.2$ Hz, 1H), 1.52–1.38 (m, 1H), 1.37–1.21 (m, 1H), 1.20–1.08 (m, 1H), 1.08 (br d, $^3J(H,H) = 9.6$ Hz, 1H), 1.05 (br s, 1H); ^{13}C NMR: $\delta = 141.7$, 139.4, 128.9, 128.5, 128.3, 128.0, 127.1, 126.8, 125.9, 73.5, 72.7, 58.9, 53.9, 38.2, 36.4, 30.0, 21.9; MS

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(70 eV, EI): *m/z* (%): 293 (6) [M^+], 186 (17) [$C_{13}H_{14}N^+$], 158 (100); HRMS calcd for $C_{20}H_{21}NO$: 293.1779; found: 293.16780.

(1*S*,3*R*,4*R*)-2-(Benzylamino)-2-azabicyclo[2.2.1]heptane-3-(*S*)-methylmethanol (6): Yield: 65%; $R_f = 0.43$ (pentane/EtOAc 7/3); $[\alpha]_D^{24} = +38.6$ ($c = 1.1$ in CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu} = 3623$, 3408, 2872, 2807, 1754, 1726, 1704, 1691, 1679, 1051 cm^{-1}; ^1H NMR: $\delta = 7.40-7.20$ (m, 5H), 3.75 (d, $^3J(H,H) = 13.2$ Hz, 1H), 3.65 (d, $^3J(H,H) = 13.2$ Hz, 1H), 3.51–3.45 (m, 1H), 3.19 (brs, 1H), 2.95–3.20 (m, 1H), 2.41 (brs, 1H), 2.10–1.85 (m, 2H), 1.82–1.68 (m, 1H), 1.62–1.56 (m, 1H), 1.40–1.10 (m, 3H), 1.14 (d, $^3J(H,H) = 6.8$ Hz, 3H); ^{13}C NMR: $\delta = 128.7$, 128.3, 127.0, 73.3, 66.4, 58.4, 54.0, 37.3, 36.7, 30.3, 22.0, 18.4; MS (70 eV, EI): *m/z* (%): 232 (5) [M^+], 186 (82) [$C_{11}H_{12}N^+$], 158 (100); HRMS calcd for $C_{15}H_{21}NO$: 231.1623; found: 231.1623.

(1*S*,3*R*,4*R*)-2-(Benzylamino)-2-azabicyclo[2.2.1]heptane-3-(*S*)-isopropylmethanol (7): Yield: 64%; $R_f = 0.46$ (pentane/EtOAc 7/3); $[\alpha]_D^{24} = +38.5$ ($c = 1.2$ in CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu} = 3623$, 3407, 2872, 2808, 1721, 1709, 1027 cm^{-1}; ^1H NMR: $\delta = 7.40-7.20$ (m, 5H), 3.73 (d, $^3J(H,H) = 13.2$ Hz, 1H), 3.61 (d, $^3J(H,H) = 13.2$ Hz, 1H), 3.18 (brs, 1H), 3.00–2.90 (m, 1H), 2.38 (brs, 1H), 2.11 (brs, 1H), 2.02–1.92 (m, 1H), 1.80–1.54 (m, 3H), 1.38–1.20 (m, 2H), 1.10 (d, $^3J(H,H) = 9.6$ Hz, 1H), 1.05 (d, $^3J(H,H) = 6.8$ Hz, 3H), 0.82 (d, $^3J(H,H) = 6.8$ Hz, 3H); ^{13}C NMR: $\delta = 128.9$, 128.3, 127.0, 75.3, 70.0, 57.9, 53.3, 37.4, 36.9, 30.9, 30.6, 21.7, 20.7, 18.3; MS (70 eV, EI): *m/z* (%): 259 (<1) [M^+], 186 (100) [$C_{13}H_{16}N^+$]; HRMS calcd for $C_{17}H_{25}NO$: 259.1936; found: 259.1935.

(1*S*,3*R*,4*R*)-2-(Benzylamino)-2-azabicyclo[2.2.1]heptane-3-(*R*)-phenylmethanol (8): Yield: 61%; $R_f = 0.42$ (pentane/EtOAc 4/1); $[\alpha]_D^{25} = -67.2$ ($c = 0.64$ in CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu} = 3603$, 3408, 2873, 1606, 1495, 1070, 1014 cm^{-1}; ^1H NMR: $\delta = 7.37-7.23$ (m, 10H), 4.35–4.80 (m, 1H), 4.30 (d, $^3J(H,H) = 6.8$ Hz, 1H), 3.77 (d, $^3J(H,H) = 13.3$ Hz, 1H), 3.60 (d, $^3J(H,H) = 13.3$ Hz, 1H), 3.23 (brs, 1H), 2.25–2.34 (m, 2H), 2.11–1.97 (m, 1H), 1.85 (brd, $^3J(H,H) = 9.7$ Hz, 1H), 1.70–1.55 (m, 1H), 1.35–1.20 (m, 3H); ^{13}C NMR: $\delta = 144.6$, 139.0, 128.7, 128.4, 128.2, 127.0, 125.9, 75.4, 75.4, 74.8, 57.9, 55.4, 42.1, 35.6, 28.4, 22.3; MS (70 eV, EI): *m/z* (%): 294 (3) [M^+], 186 (7) [$C_{13}H_{14}N^+$], 91 (100) [$C_7H_7^+$]; HRMS calcd for $C_{20}H_{21}NO$: 293.1779; found: 293.1678.

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