Synthesis of a Silanol-substituted Proline Analog as Organocatalyst

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A proline-derived silanol, was designed as a novel potential organocatalyst, and synthesized starting from the tetrazole **3**. The central idea was the combination of an acidic (tetrazole) and a basic functionality (pyrrolidine) with a silanol moiety in the same molecule. The synthesis of **7** was performed in four reaction steps starting with the tetrazole **3**. In the solid state (X-ray crystal structure analysis) the crucial functional groups show a favorable orientation. A chiral HPLC method and a chiral capillary electrophoresis method have been established for the investigation of the kinetic resolution of the racemic alcohols **9** and **11**. Acetylation reactions of alcohols were not accelerated by the organocatalyst **7**, and the produced *ee* values were rather low.

Key words: Proline-derived Tetrazole, Silanol, Organocatalyst, Kinetic Resolution of Alcohols, Chiral HPLC, Chiral Capillary Electrophoresis

Introduction

Catalysts employed for enantioselective syntheses of organic compounds, *e. g.* pharmaceutical products, agrochemicals, or fine chemicals, generally fall into three categories: transition metal complexes, enzymes and organocatalysts. Organocatalysts represent small organic molecules, which are able to catalyze a particular organic reaction. In contrast to transition metal complexes, the catalytic activity of organocatalysts resides in the low molecular weight organic molecule itself. Usually, organocatalysts are inexpensive, nontoxic and, in comparison with enzymes, stable under most reaction conditions and readily available in both enantiomeric forms [1].

Proline belongs to the most widely used organocatalysts in chemistry, because it is able to catalyze intermolecular Michael additions [2], Mannich reactions [3], inter- [4] and intramolecular aldol reactions [5], and addition reactions on N=N [6] and N=O double bonds [7]. (*R*)-and (*S*)-proline are both commercially available in bulk quantities and thus represent particularly attractive amino acid organocatalysts.

In the field of enantioselective syntheses the kinetic resolution of secondary alcohols using organocatalysts represents an interesting strategy of accessing enantiomerically pure compounds [8]. The idea of this project was the combination of the crucial basic and acid functional groups of the proline system (**1**) with a silanol moiety [9] in the same molecule (**2**) to get a new type of catalyst for enantioselective acylation reactions (Fig. 1).

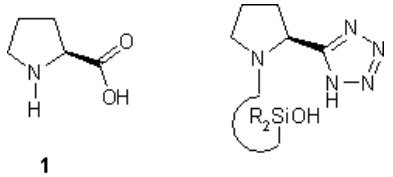

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Fig. 1. The organocatalyst (*S*)-proline (**1**) compared with the designed silanol-modified derivatives **2**.

Results ans Discussion

The silanol moiety was expected to bind the acylating agent, *i. e.* the acetyl group transferred from acetic anhydride or an enol acetate. Thereby one enantiomer of a racemic alcohol should be preferably fixed and activated by two hydrogen bonds to the acidic and basic functional groups of the catalyst. The high order of this

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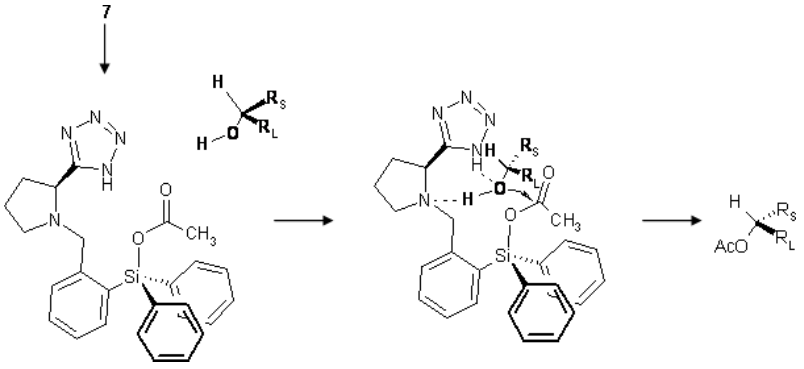
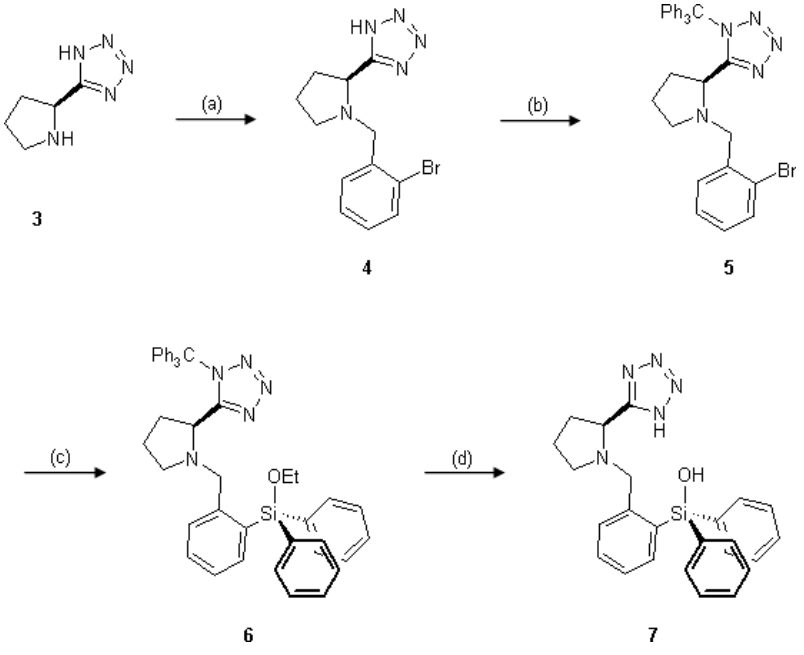


Fig. 2. Postulated catalytic mechanism of the designed organocatalyst **7** during acetylation of racemic alcohols.



Scheme 1. Reagents and reaction conditions: (a) 2-Bromobenzaldehyde, $NaBH(OAc)_3$, THF, 2 h, r. t., 88 %; (b) Ph_3CCl, NEt_3, THF, 2 h, r. t., 93 %; (c) *n*-BuLi, −78 °C, THF, 30 min, −78 °C, then $Ph_2Si(OEt)_2$, 2 h, −78 °C, 36 h, r. t., (d) HCl, 14 h, r. t., 35 %.

intermediate complex should result in a kinetic resolution of the racemic alcohol, *i. e.* one enantiomer should be acetylated much faster than the other enantiomer, which should thus be left unchanged (Fig. 2).

The synthesis of the silanol-modified proline analog **7** started with the tetrazole **3**, which is available from the natural amino acid (*S*)-proline (**1**) in five reaction steps [10]. Reductive alkylation of the secondary amine **3** with 2-bromobenzaldehyde and $NaBH(OAc)_3$ [11] led to the bromobenzyl derivative **4** in 88 % yield. Since a halogen-metal exchange was planned for the introduction of the silanol moiety, the tetrazole system of **4** was protected with trityl chloride to give the trityl derivative **5** in 94 % yield. Halogen-metal exchange with *n*-butyllithium and subsequent reaction with diethoxydiphenylsilane provided the silyl ether **6**, which was hydrolyzed without isolation with diluted HCl to give the triarylsilanol **7** (Scheme 1).

Recrystallization of the proline-derived silanol **7** from a mixture of cyclohexane and CH_2Cl_2 provided crystals, which were suitable for an X-ray crystal structure analysis. The structure shown in Fig. 3 clearly demonstrates that the three important functional groups, the silanol moiety, the basic pyrrolidine N atom and the acidic tetrazole proton, have a favorable orientation, which is an ideal condition for the enantioselective acetyl group transfer.

For purpose of comparison the tetrazolylpyrrolidine **8** bearing only a small methyl group instead of the silanol moiety at the pyrrolidine N atom was synthe-

Table 1. Kinetic resolution of racemic alcohol **9** using the organocatalysts **7** and **8**.

Entry	Catalyst, amount	Ac_2O (equiv.)	NEt_3 (equiv.)	Solvent	Temp. (°C)	Time (h)	Conv. (%)	*ee* of **10** (%)
1	–	1	–	CH_2Cl_2	2	36	5	0
2	**7**, 5 mol-%	1	–	CH_2Cl_2	20	36	22	8
3	–	0.75	0.75	CH_2Cl_2	20	20	12	0
4	**7**, 5 mol-%	0.75	0.75	CH_2Cl_2	20	20	24	4
5	**8**, 5 mol-%	2	2	CH_2Cl_2	20	2	66	11

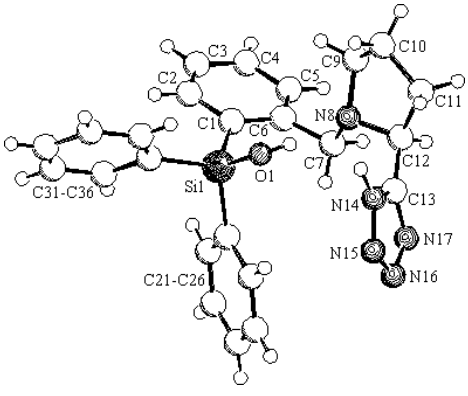
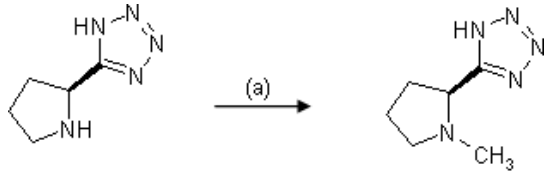


Fig. 3. Molecular structure of one of the two crystallographically independent molecules of the organocatalyst **7** in the solid state showing a favorable orientation of the three crucial functional groups.



3 **8**

Scheme 2. Reagents and reaction conditions: (a) Formalin, CH_3OH, H_2, 1 bar, Pd/C, r. t., 12 h, 84 %.

sized. The methylation of the secondary amine **3** was performed under reductive conditions with formaldehyde and H_2, Pd/C (Scheme 2).

With the new organocatalysts **7** and **8** in hand their catalytic properties for the kinetic resolution were investigated with the standard racemic alcohol 1-phenylethanol (**9**). Within this project a novel chiral HPLC method was developed, which allows the simultaneous separation of both pairs of enantiomers in a single run. Thus the ratio of enantiomers of the alcohol **9** and the acetate **10** as well as the conversion can be directly determined (Fig. 4). In this method the chiral stationary phase Chiralcel AD-H® containing modified amylose as chiral selector, and the mobile phase *n*-hexane/ethanol were used [12].

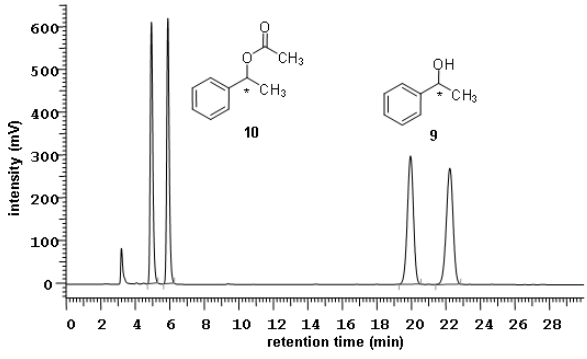


Fig. 4. Chiral HPLC analysis of racemic alcohol **9** and acetate **10**: Chiralcel AD-H, 5 μm, *n*-hexane/ethanol 99/1, flow rate 1.0 mL min^{-1}, UV detection at 220 nm.

Some of the performed experiments are summarized in Table 1. In the first control experiment, racemic phenylethanol (**9**) was reacted with Ac_2O in CH_2Cl_2 which resulted in very low conversion (5 %) and no differentiation of the enantiomers (Table 1, entry 1). Addition of 5 mol-% of the organocatalyst **7** (entry 2) led to an increase of the conversion by 22 % and a slight enantiomeric excess of the formed acetate **10** (*ee* 8 %). Whereas the reaction rate was increased upon addition of NEt_3, the enantiomeric excess of **10** was reduced due to increased uncatalyzed background acetylation (entries 3, 4). Acetylation of the alcohol **9** in the presence of the methylated proline derivative **8** resulted in 66 % conversion with low enantiomeric excess of the produced acetate **10** (*ee* 11 %, entry 5).

Since we are interested in bicyclic compounds as novel κ-receptor agonists [13], the organocatalyst **7** was applied on the kinetic resolution of the bicyclic *endo*-configurated alcohol **11** [13b]. The progress of the acetylation was observed using a chiral capillary electrophoresis method, which has been developed starting with a reported method [14]. In Fig. 5 a typical electropherogram is shown. With hydroxypropyl-β-cyclodextrin as chiral selector, the alcohol **11** and the acetate **12** as well as their enantiomers were separated in a single capillary electrophoresis run.

As shown for the prototypical phenylethanol (**9**), the acetylation rate of the conformationally more con-

Table 2. Kinetic resolution of racemic alcohol **11** using the organocatalysts **7** and **8**.

Entry	Catalyst, amount	Ac_2O (equiv.)	NEt_3 (equiv.)	Solvent	Temp. (°C)	Time (h)	Conv. (%)	*ee* of **12** (%)
1	–	2	2	CH_2Cl_2	20	36	5	0
2	**7**, 10 mol-%	2	2	CH_2Cl_2	20	36	8	3.8
3	**8**, 10 mol-%	2	2	CH_2Cl_2	20	36	11	4.5

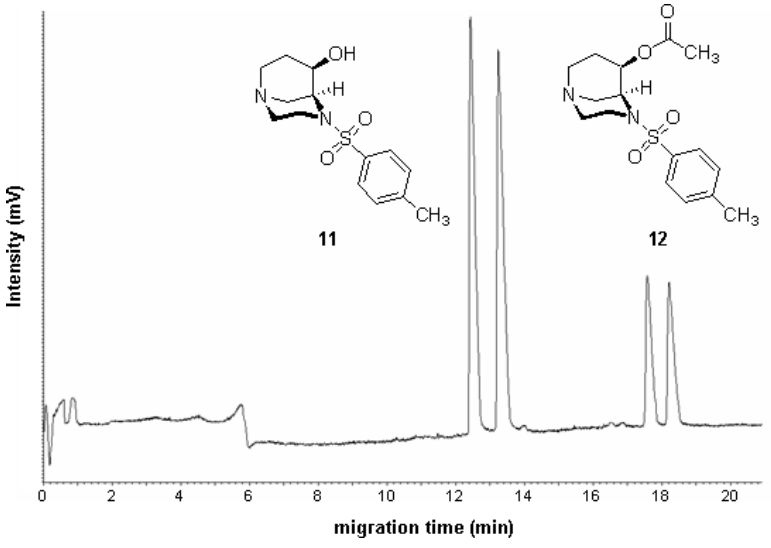


Fig. 5. Chiral CE analysis of racemic alcohol **11** and acetate **12**: Hydroxypropyl-β-cyclodextrin, 0.1 M phosphoric acid pH = 2.0, hydrodynamic injection for 5 s at 0.5 psi.

strained bicyclic alcohol **11** was only slightly increased by the organocatalyst **7** (see Table 2, entries 1 and 2). Moreover, the differentiation of the enantiomeric alcohols was negligible. Using the methylated derivative **8** as organocatalyst led to a similar observation (entry 3).

In conclusion, the synthesis of a novel potential organocatalyst derived from the proteinogenic amino acid (*S*)-proline is described. In the organocatalyst **7** the carboxylic acid moiety of proline is replaced by an acidic tetrazole system, and a silanol moiety is introduced into the N substituent. The X-ray crystal structure analysis of **7** shows a favorable orientation of the crucial functional groups. A novel chiral HPLC method (Chiralcel AD-H®) and a novel chiral capillary electrophoresis method (hydroxypropyl-β-cyclodextrin) were established to observe the kinetic resolution of racemic alcohols. Unfortunately, the reaction rate was not increased considerably by the designed organocatalyst **7**. Furthermore, the enantiomeric excess of the produced acetates **10** and **12** was rather low. The organocatalyst **8** with the small methyl group led to the same result indicating that the silanol moiety does not influence the enantioselective acetylation of secondary alcohols. In future work the catalytic activity of **7** in further reactions will be investigated.

Experimental Section

General marks

Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, height of SiO_2 column, fraction size, eluent, R_f value. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. Optical rotation: Polarimeter 341 (Perkin Elmer); 1.0 dm tube; concentration c in g/100 mL, optical rotation $[\alpha]$ in grad mL dm^{-1} g^{-1}. MS: MAT GCQ (Thermo-Finnigan); EI = electron impact, ESI = electrospray ionization. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury-400BB spectrometer (Varian); δ in ppm relative to tetramethylsilane; coupling constants J are given with 0.5 Hz resolution. HPLC: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 μm), 250–4 mm; flow rate: 1.00 mL min^{-1}; injection volume: 5.0 μL; detection at λ = 210 nm; solvents: A: water with 0.05 % (v/v) trifluoroacetic acid; B: acetonitrile with 0.05 % (v/v) trifluoroacetic acid; gradient elution: (A %): 0 min: 90 %, 4 min: 90 %, 29 min: 0 %, 31 min: 0 %, 31.5 min: 90 %, 40 min: 90 %.

*(S)-5-[1-(2-Bromobenzyl)pyrrolidin-2-yl]-1H-tetrazole (**4**)*

Under Ar atmosphere, $NaBH(OAc)_3$ (318 mg, 1.5 mmol) was added to a solution of **3** (139 mg, 1.0 mmol) and 2-bromobenzaldehyde (175 μL, 1.5 mmol) in THF (10 mL). The reaction mixture was stirred at r. t. for 2 h. Then the solvent of the reaction mixture was removed *in vacuo*. The residue was purified by fc [3 cm, 15 cm, 10 mL, CH_2Cl_2/MeOH 9.5/0.5 → 9/1, R_f = 0.39 (CH_2Cl_2/MeOH 9/1)] to afford 272 mg (88 %) of **4** as a colorless solid, m. p. 181 °C. – $C_{12}H_{14}BrN_5$ (M_r = 308.2). – ^{1}H NMR ($CDCl_3$): δ = 1.89 – 2.00 (m, 2H, CH_2CH_2), 2.01 – 2.13 (m, 1H, CH_2CH_2), 2.38– 2.50 (m, 1H, CH_2CH_2), 2.78 (dd, J = 17.2/9.4 Hz, 1H, NCH_2), 3.43 – 3.52 (m, 1H, NCH_2), 3.88 (d, J = 13.3 Hz, 1H, PhCH_2N), 4.03 (d, J = 13.3 Hz, 1H, PhCH_2N), 4.45 (dd, J = 8.6/6.3 Hz, 1H, NCH), 6.57 (s broad, 1H, tetrazole-H), 7.11 (td, J = 7.8/1.6 Hz, 1H, 4′-H_{phenyl} or 5′-H_{phenyl}), 7.20 (td, J = 7.8/1.6 Hz, 1H, 4′-H_{phenyl} or 5′-H_{phenyl}), 7.31 (dd, J = 7.8/1.6 Hz, 1H, 6′-H_{phenyl}), 7.51 (dd, J = 7.8/1.6 Hz, 1H, 3′-H_{phenyl}). – IR (neat): ν (cm^{-1}) = 1473, 1444 and 1422 (m, N=N, C=N and C–H), 754 (s, arom. out of plane). – MS (EI): *m/z* (%) = 307 (5) [M, ^{79}Br]$^+$, 309 (6) [M, ^{81}Br]$^+$, 237 (64) [M–tetrazole, ^{79}Br]$^+$, 239 (63) [M–tetrazole, ^{81}Br]$^+$. – $[\alpha]_D^{20}$ = −16.4 (c = 0.59; MeOH). – HPLC: t_R = 11.1 min, purity 99.6 %.

*(S)-5-[1-(2-Bromobenzyl)pyrrolidin-2-yl]-1-trityl-1H-tetrazole (**5**)*

Trityl chloride (257 mg, 0.92 mmol) was added to a solution of **4** (260 mg, 0.84 mmol) and triethylamine (350 μL, 2.5 mmol) in THF (10 mL). The reaction mixture was stirred at r. t. for 2 h, and filtered, and the solvent removed *in vacuo*. The residue was purified by fc (4 cm, 15 cm, 15 mL, *n*-hexane/ethyl acetate 9/1, R_f = 0.38) to afford 431 mg (93 %) of **5** as a colorless solid, m. p. 152 °C. – $C_{31}H_{28}BrN_5$ (M_r = 550.5). – ^{1}H NMR ($CDCl_3$): δ = 1.81 – 1.92 (m, 1H, CH_2CH_2), 1.96 – 2.08 (m, 1H, CH_2CH_2), 2.18– 2.33 (m, 2H, CH_2CH_2), 2.51 (dd, J = 17.2/8.6 Hz, 1H, NCH_2), 3.05 (ddd, J = 11.7/8.6/3.1 Hz, 1H, NCH_2), 3.58 (d, J = 14.1 Hz, 1H, PhCH_2N), 3.78 (d, J = 14.1 Hz, 1H, PhCH_2N), 4.12 (t, J = 7.0 Hz, 1H, NCH), 7.01 (td, J = 7.8/1.6 Hz, 1H, 4′-H_{phenyl} or 5′-H_{phenyl}), 7.05 – 7.10 (m, 6H, H_{trityl}), 7.15 (td, J = 7.8/1.6 Hz, 1H, 4′-H_{phenyl} or 5′-H_{phenyl}), 7.24 – 7.36 (m, 10H, 6′-H_{phenyl} and H_{trityl}), 7.44 (dd, J = 7.8/1.6 Hz, 1H, 3′-H_{phenyl}). – IR (neat): ν (cm^{-1}) = 1492, 1467 and 1445 (m, N=N, C=N and C–H), 757, 746 and 697 (m, arom. out of plane). – MS (ESI): *m/z* (%) = 1125 (48) [2M + Na, 2x ^{81}Br]$^+$, 1123 (86) [2M + Na, ^{79}Br/^{81}Br]$^+$, 1121 (45) [2M + Na, 2x ^{79}Br]$^+$, 552 (49) [M + H, ^{81}Br]$^+$, 550 (50) [M + H, ^{79}Br]$^+$, 243 (100) [CPh_3]$^+$. – $[\alpha]_D^{20}$ = −33.9 (c = 0.59; CH_2Cl_2).

*Diphenyl-{2-[(S)-2-(1H-tetrazol-5-yl)pyrrolidin-1-ylmethyl]phenyl}silanol (**7**)*

Under N_2, **5** (235 mg, 1.1 mmol) was dissolved in THF (20 mL), and the solution was cooled to −78 °C. Then a 1.6 M solution of *n*-butyllithium in *n*-hexane (690 μL, 1.1 mmol) was added slowly. The reaction mixture was stirred for 30 min at −78 °C. Then diphenyldiethoxysilane (400 μL, 1.5 mmol) was added dropwise. After stirring at −78 °C for 2 h, the mixture was allowed to warm to r. t. After 36 h (product **6**) 1 M aqueous HCl (10 mL) was added, and the resulting mixture was stirred at r. t. for additional 14 h. Then pH = 7 was adjusted by addition of 0.5 M aqueous NaOH, and the reaction mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo*. The residue was purified by fc [4 cm, 15 cm, 20 mL, CH_2Cl_2/MeOH 9.5/0.5 → 9/1, R_f = 0.38 (CH_2Cl_2/MeOH 9/1)] to afford 149 mg (35 %) of **7** as a colorless solid, m. p. 212 °C. – $C_{24}H_{25}N_5OSi$ (M_r = 427.6). – ^{1}H NMR ($CDCl_3$): δ = 1.74 – 1.86 (m, 2H, CH_2CH_2), 1.98 – 2.10 (m, 1H, CH_2CH_2), 2.22 – 2.34 (m, 1H, CH_2CH_2), 2.55 (dd, J = 18.8/8.6 Hz, 1H, NCH_2), 2.96 – 3.06 (m, 1H, NCH_2), 3.58 (d, J = 12.5 Hz, 1H, PhCH_2N), 3.93 (d, J = 12.5 Hz, 1H, PhCH_2N), 4.37 (t, J = 7.8 Hz, 1H, NCH), 7.15 – 7.40 (m, 12H, arom. H), 7.50 (d, J = 6.3 Hz, 2H, arom. H). The signals for the tetrazole-H and the SiOH could not be detected. – IR (neat): ν (cm^{-1}) = 1457, 1427 and 1445 (m, N=N, C=N and C–H), 763, 739 and 699 (m, arom. out of plane). – MS (ESI): *m/z* (%) = 428 (100) [M + H]$^+$, 877 (21) [2M + Na]$^+$. – $[\alpha]^{20}{}_D$ = +17.5 (c = 0.48; CH_2Cl_2). – HPLC: t_R = 18.9 min, purity 100 %.

*(S)-5-(1-Methylpyrrolidin-2-yl)-1H-tetrazole (**8**)*

Aqueous formaldehyde (40 %, 415 μL, 6.0 mmol) was added to a solution of **3** (417 mg, 3.0 mmol) in methanol (10 mL). Then 10 % Pd/C (200 mg) was added, and the resulting mixture was stirred under an H_2 atmosphere at r. t. for 12 h. The reaction mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. Addition of Et_2O led to a precipitate which was recrystallized from MeOH/Et_2O to afford 386 mg (84 %) of **8** as colorless solid, m. p. 225 °C. – $C_6H_{11}N_5$ (M_r = 153.2). – ^{1}H NMR (CD_3OD): δ = 2.23 – 2.33 (m, 2H, CH_2CH_2), 2.38 – 2.57 (m, 2H, CH_2CH_2), 2.80 (s, 3H, NCH_3), 3.22 – 3.30 (m, 1H, NCH_2), 3.58 – 3.68 (m, 1H, NCH_2), 4.66 (t, J = 8.6 Hz, 1H, NCH). A signal for the tetrazole H atom could not be detected. – IR (neat): ν (cm^{-1}) = 2962 (w, C–H), 1458, 1430 and 1417 (m, N=N, C=N and C–H). – MS (EI): *m/z* (%) = 153 (98) [M, 3]$^+$, 84 (98) [M–tetrazole]$^+$. – $[\alpha]_D^{20}$ = −28.7 (c = 0.58; MeOH).

*(1RS,5SR,6RS)-4-Tosyl-1,4-diazabicyclo[3.3.1]nonan-6-yl acetate (**12**)*

Under N_2 atmosphere, acetic anhydride (140 μL, 1.50 mmol) was added to a solution of **11** [13b] (90 mg, 0.30 mmol), NEt_3 (210 μL, 1.50 mmol) and DMAP (4 mg, 0.03 mmol) in CH_2Cl_2 (15 mL). After 2 h at r. t. a saturated $NaHCO_3$ solution was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo*. The residue was purified by fc [2 cm, 10 mL, CH_2Cl_2/MeOH 9.5/0.5, R_f = 0.26 (CH_2Cl_2/MeOH 9.5/0.5)] to afford 94 mg (92 %) of **11** as a colorless solid, m. p. 168 °C. – $C_{16}H_{22}N_2O_4S$ (M_r = 338.4). – ^{1}H NMR ($CDCl_3$): δ = 1.79 – 1.89 (m, 1H, 7-H), 1.93 – 2.04 (m, 1H, 7-H), 2.09 (s, 3H, O_2CCH_3), 2.40 (s, 3H, $ArCH_3$), 2.76 – 2.84 (m, 2H, NCH_2), 2.88 (dd, J = 14.1/5.5 Hz, 1H, NCH_2), 2.93 – 3.03 (m, 1H, NCH_2), 3.04 – 3.08 (m, 2H, NCH_2), 3.18 – 3.26 (m, 1H, NCH_2), 3.50 – 3.60 (m, 1H, NCH_2), 4.04 – 4.09 (m, 1H, 5-H), 4.95 (ddd, J = 11.7/7.0/3.9 Hz, 1H, 6-H), 7.26 (d, J = 7.8 Hz, 2H, 3′-$H_{tosylate}$, 5′-$H_{tosylate}$), 7.67 (d, J = 7.8 Hz, 2H, 2′-$H_{tosylate}$, 6′-$H_{tosylate}$). – IR (neat): ν (cm^{-1}) = 1736 (s, C=O), 1158 (s, S=O), 816 (m, arom. out of plane). – MS (EI): *m/z* (%) = 338 (19) $[M]^+$, 183 (100) $[M–SO_2C_6H_4CH_3]^+$. – HPLC: t_R = 15.1 min, purity 99.7 %.

*X-Ray crystal structure analysis of **7***

Recrystallization of **7** from cyclohexane/CH_2Cl_2 gave single crystals suitable for X-ray crystal structure analysis. $C_{24}H_{25}N_5OSi$, M_r = 427.58; crystal size 0.30 × 0.08 × 0.05 mm^3; T = 223(2) K, CuK_α radiation, λ = 1.54178 Å; monoclinic crystal system, space group $P2_1$ (no. 4); unit cell dimensions a = 9.5694(4), b = 15.0095(6), c = 16.1055(7) Å, β = 102.251(2)°, V = 2260.6(2) $Å^3$, Z = 4, $D_{calcd.}$ = 1.256 mg m^{-3}, μ(CuK_α) = 11.17 cm^{-1}, F(000) = 904 e; θ range: 4.07 – 67.62°, *hkl* range: ±11, −15/+17, −18/+19; reflections collected / unique: 17837 / 6920, R_{int} = 0.048, completeness to θ_{max} = 98.0 %; absorption correction: semi-empirical from equivalents, T_{max} / T_{min} = 0.946 / 0.731; refinement: full-matrix least-squares on F^2; data / restraints / parameters: 6920 / 1 / 567; goodness-of-fit on F^2 = 1.039; final R indices [$I \geq 2(I)$]: $R1$ = 0.041, $wR2$ = 0.104; R indices (all data): $R1$ = 0.044, $wR2$ = 0.107; Flack parameter x = 0.03(2); $\Delta\rho_{fin}$ (max / min) = 0.21 / −0.23 e $Å^{-3}$. *Comments*: Data were collected on a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction DENZO-SMN [15], absorption correction DENZO [16], structure solution SHELXS-97 [17], structure refinement SHELXL-97 [18], graphics SCHAKAL [19].

CCDC 739292 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the catalytic kinetic resolution of racemic 1-phenylethanol

Acetic anhydride (150 μL, 1.6 mmol) was added to a solution of (±)-1-phenylethanol (100 μL, 0.8 mmol) and the respective catalyst candidate **7** or **8** (5 mol-% = 0.04 mmol) in CH_2Cl_2 (5 mL). When tlc control showed an adequate conversion, the reaction was stopped by the addition of a saturated solution of $NaHCO_3$ (10 mL). The organic layer was separated, dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo*. The crude product was dissolved in 2 mL of cyclohexane/ethyl acetate [2/1]. In order to remove the catalyst from the reaction mixture, this solution was filtered through a pad of silica gel, washed with cyclohexane/ethyl acetate [2/1], and concentrated under reduced pressure. The conversion and the enantiomeric excess were directly analyzed by a chiral HPLC method which separated the enantiomers of both compounds in one HPLC experiment.

Separation of enantiomers by chiral HPLC

Equipment (all Merck-Hitachi): pump: L-6200A; UV detector: L-7400; data transfer: l V interface of an A/D-converter; data acquisition: HSM-Software; column: Chiralcel AD-H, 5 μm, ∅ 4.6 mm, 25 cm, Daicel Chemical Industries, Japan; mobile phase: *n*-hexane/ethanol 99/1 at a flow rate of 1.0 mL/min; detection: UV absorption at 220 nm; retention times t(*R*-**10**) = 5.0 and t(*S*-**10**) = 5.8 min, t(*R*-**9**) = 19.5 and t(*S*-**9**) = 21.4 min.

*General procedure for the catalytic kinetic resolution of the racemic bicyclic alcohol **11***

Acetic anhydride (10 μL, 0.1 mmol) was added to a solution of **11** [13b] (15 mg, 0.05 mmol), NEt_3 (14 μL, 0.1 mmol) and the respective catalyst candidate **7** or **8** (10 mol-%) in CH_2Cl_2 (3 mL). The conversion was monitored by tlc. After 36 h at r. t., 0.1 mL of the reaction mixture was diluted with DMSO (2 mL). The resulting solution was diluted with H_3PO_4 (0.1 M) to 5 mL. The conversion and the enantiomeric excess were directly analyzed by a CE method, which separated the enantiomers of the alcohol **11** and the acetate **12** in one single CE experiment.

CE method modified according to ref. [14]

CE apparatus: Beckman P/ACE™ Capillary Electrophoresis System; data acquisition: Beckman Carat-software; capillary: bare fused-silica capillaries (effective length 30 cm, total length 40 cm, diameter 50 μm); detection: DAD detector at 190 nm; injection: hydrodynamic pressure injection (5 s, 0.5 psi). The background electrolyte was prepared from 0.1 M phosphoric acid adjusted to pH = 2.0 by dropwise addition of NEt_3. Hydroxypropyl-β-cyclodextrin was dissolved in this phosphate-NEt_3 buffer at a concentration of 0.65 mg/mL (0.45 mM). Prior to the injection of each

sample solution, the capillary was rinsed for 3 min with background electrolyte. The samples were injected hydrodynamically for 5 s at 0.5 psi. Separation was carried out by applying a voltage of 25 kV with normal polarity. The temperature of the capillary was kept at 20 °C during the separation by a liquid cooling system. After each run, the capillary was rinsed with methanol for 2 min, water for 30 s, 0.1 M NaOH for 2 min, and again water for 30 s.

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