A General Method for the Preparation of Chiral TREN Derivatives

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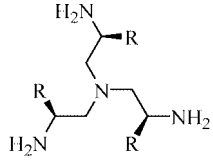
A general procedure for the preparation of C_3-symmetric TREN derivatives with backbone chirality has been developed. Stereo- and regioselective ring opening by ammonia of (*S*)-*N*-tosyl-2-isopropylaziridine, obtained starting from either the corresponding amino alcohol or amino acid, followed by deprotection of the amino groups afforded the parent chiral TREN compound in high overall yield. In addition to TREN compounds with primary amino groups, the synthetic method employed provides easy access to a variety of *N*,*N*′,*N*′′-substituted derivatives.

Introduction

Tris(2-aminoethyl)amine, TREN (**1**, R = H), and its *N*,*N*′,*N*′′-substituted derivatives are widely employed as ligands for both transition metals[1] and main group elements.[2] Several of the TREN containing compounds exhibit properties which make them useful for a variety of applications. Thus, proazaphosphatranes have been shown to be extremely strong bases with wide synthetic applications[3] at the same time as they serve as ligands for metals in catalytic processes.[4] Molybdenum complexes of *N*,*N*′,*N*′′-aryl-substituted TREN[5] have been found to activate dinitrogen.[6] Other recent applications include the fixation of CO_2 by zinc complexes[7] and the use of uncomplexed TREN derivatives as receptors for anions.[8] In addition, TREN has been used as a structural motif for the preparation of a variety of more elaborate tripodal ligands (Figure 1).[9]

Due to our interest in C_3-symmetric ligands[10] we wanted to have easy access to chiral TREN compounds for further functionalization. Therefore, we developed a procedure for the preparation of chiral *N*,*N*′,*N*′′-substituted TREN derivatives, with the chirality residing in the ligand backbone, through aziridine ring opening by ammonia.[11] Our synthesis was followed by the preparation by Yamamoto and co-workers of another chiral TREN compound starting from proline using a stepwise procedure.[12] Subsequently less rigid derivatives, with chiral substituents attached to the equatorial nitrogen atoms, were described by Verkade and co-workers.[13] Raymond and co-workers developed a method for the preparation of TREN compounds with backbone chirality employing reductive amination of α-amino aldehydes as the key step, which provided access to derivatives with primary amino groups, isolated as their trihydrochloride salts.[14] A recent report from Verkade's group[15] on the preparation of chiral TREN derivatives, using the procedure developed by Raymond, prompts us to report improvements on our previously disclosed procedure, resulting in experimentally simple and convenient methods for the preparation of parent chiral TREN compounds **1** (R = Me, *i*Pr) as well as chiral *N*,*N*′,*N*′′-alkyl and -aryl derivatives.



1
a: R = *i*Pr
b: R = Me

Figure 1. Chiral TREN compounds.

Results and Discussion

Chiral enantiopure aziridines are valuable synthetic building blocks due to their ability to undergo stereo- and regioselective ring opening reactions.[16] The aziridines are conveniently accessible by a variety of methods.[17] Starting from chiral amino alcohols, commonly derived from natural or synthetic amino acids, enantiopure aziridines are obtained in high yields without the use of additional chiral reagents. *N*-activated aziridines, such as *N*-sulfonylaziridines, undergo regioselective ring opening using a wide range

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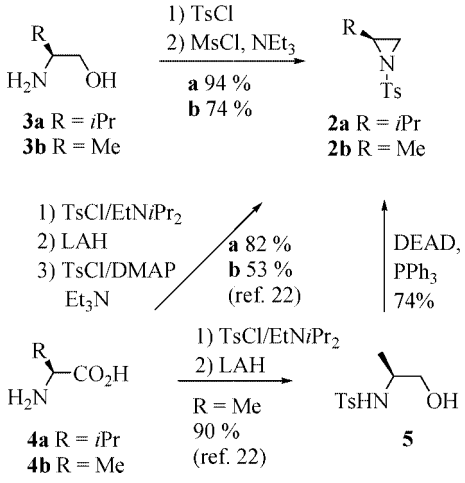
of nucleophiles to provide ring-opened products in enantiopure form. For the preparation of chiral TREN compounds we therefore found that a method based on aziridines would be highly attractive. Our synthetic method thus uses the ring opening of three equivalents of an *N*-(arylsulfonyl)aziridine by ammonia as the key step.

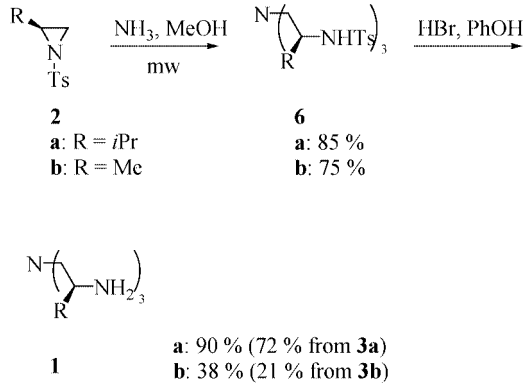
For the synthesis of substituted TREN derivatives **1a** and **1b**, (*S*)-*N*-tosyl-2-isopropylaziridine (**2a**) and (*S*)-*N*-tosyl-2-methylaziridine (**2b**) were required. By a recently published method these compounds were obtained in one step in 82 and 73% yield from commercially available (*S*)-valinol (**3a**) and (*S*)-alaninol (**3b**), respectively, using tosyl chloride, triethylamine, and DMAP.[18] A two-step procedure, using two equivalents of tosyl chloride, was reported to result in even higher yields of the same compounds, 90 and 88%.[19] In our hands, this latter procedure afforded **2a** and **2b** in considerably lower yields. However, a slight modification, whereby the second equivalent of tosyl chloride was replaced by mesyl chloride, afforded higher yields of the desired compounds. The isopropylaziridine **2a** was thus obtained in a one-pot procedure by treatment of (*S*)-valinol (**3a**) with 1.15 equivalents of tosyl chloride followed by 1.05 equivalents of mesyl chloride in the presence of four equivalents of triethylamine in 94% yield (Scheme 1). The same procedure applied to (*S*)-alaninol (**3b**) gave **2b**, albeit in lower yield, 74%.



Scheme 1. Synthesis of chiral tosylaziridines.

Although the amino alcohols are commercially available, the corresponding amino acids are less expensive and may therefore be found to be more suitable starting materials. The amino alcohols employed can be obtained from the corresponding amino acids. BH_3 reduction of (*S*)-valine (**4a**) has been reported to afford (*S*)-valinol (**3a**) in 95% yield,[20] which is a considerable improvement of previously reported 44%.[21] However, to avoid difficulties encountered during isolation of the water soluble products, we preferred to employ a method published by Berry and Craig providing direct access to tosylaziridines from amino acids.[22] By this method the desired aziridines were obtained from (*S*)-valine (**4a**) and (*S*)-alanine (**4b**) by a three-step procedure consisting of *N*-tosylation, LAH reduction, and *O*-tosylation accompanied by base-mediated ring closure. The overall yield of **2a** was 82%, which is lower than that obtained starting from the amino alcohol. Although tosylation of **4b** and reduction of the carboxylic acid function were reported to proceed smoothly (90% yield of **5** based on **4b**), mesylation and ring closure of the *N*-tosylated amino alcohol afforded merely 59% of **2b** (i.e. 53% based on **4b**).[22] We found, however, that under Mitsunobu conditions,[23] **5** was transferred to **2b** in 74% yield, thus resulting in an overall yield of **2b** from **4b** of 67%, which is lower than that obtained in the one-pot procedure starting with (*S*)-alaninol. Scheme 1 summarizes the methods for the preparation of aziridines **2a** and **2b** from either the amino alcohols or the amino acids which we found most suitable.

Our first published conditions for the stereo- and regioselective aziridine ring opening by ammonia resulted in a rather sluggish reaction, requiring four days at 40 °C to obtain a 70% yield of C_3-symmetric **6b** from **2b**.[11] We later found that efficient ring opening occurred when a 4:1 mixture of **2a** and ammonia in methanol was subjected to microwave irradiation for 75 minutes, while the temperature was maintained at 160 °C (Scheme 2).[24] We were particularly pleased to find that cooling of the reaction mixture led to the precipitation of white crystals, consisting of pure **6a**, according to NMR spectrosopy, in 85% yield. The same procedure applied to **2b** required chromatographic purification of the product (**6b**), which did not precipitate after reaction. Heating at 50 °C for four days in place of using microwave irradiation resulted in a similar yield (75%).

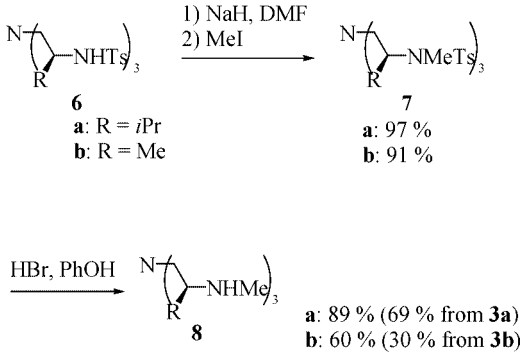


Scheme 2. Synthesis of chiral TREN derivatives by aziridine ring opening.

Deprotection of compounds containing several *N*-sulfonyl functions has occasionally been connected with problems.[25] In our previous procedure we employed *N*-nosylaziridines.[26] Deprotection was achieved using mercaptoacetic acid and LiOH,[27] thiophenol and sodium carbonate,[27] or sodium in ammonia.[28] However, yields were not satisfactory and not always reproducible, and for reasons which are unknown to us, **1a** and **1b** were obtained at best only in very low yields by any of these methods. We have now found that the desired compounds are conveniently obtained in higher and reproducible yields from the tosylated amines using 48% HBr/phenol[29] for the deprotection. Thus, deprotection of compounds **6a** and **6b** in refluxing

HBr led to the parent chiral TREN derivatives **1a**[30] and **1b** in 90 and 38% yields, respectively (Scheme 2).

With tosylated compounds **6a** and **6b** as well as deprotected TREN derivatives **1a** and **1b** in hand, we decided to prepare different types of *N*,*N*′,*N*′′-substituted derivatives. For this purpose, three different routes were employed. The first consisted of *N*-alkylation of tosyl-protected TREN derivatives **6a** and **6b**. Treatment of **6a** and **6b** with sodium hydride and methyl iodide gave **7a** and **7b** in yields of 97 and 91%, respectively (Scheme 3). Deprotection, again using HBr and phenol, gave the desired methylated derivatives **8a** and **8b** in 89 and 60% yields (69 and 30% from **3a** and **3b**, respectively). Compound **8a** was previously obtained from the corresponding nosyl derivatives,[11] although in lower yield [53% from (*S*)-valine as compared to 60% employing the present method].



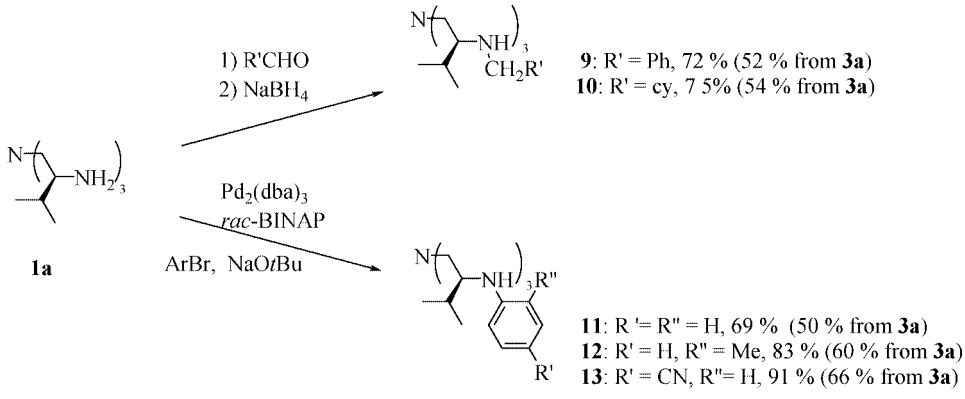
Scheme 3. Synthesis of chiral *N*-alkylated TREN derivatives.

N,*N*′,*N*′′-Tribenzyl derivative **9** was previously prepared by an analogous procedure (45% from **3a**).[11] However, somewhat higher yield of the same compound was achieved by reductive amination of three equivalents of benzaldehyde with **1a** and $NaBH_4$ (72%, 52% from **3a**, Scheme 4). Reductive amination using cyclohexanecarboxaldehyde afforded **10** (75%, 54% from **3a**). Finally, palladium-catalyzed arylation of **1a** using bromobenzene, 2-methylbromobenzene, or 4-cyanobromobenzene and a catalyst prepared from trisbenzylideneacetonedipalladium and *rac*-BINAP provided *N*-aryl derivatives **11**–**13** in 69, 83 and 91% yields (50, 60 and 66% overall from **3a**), respectively.

Our method thus provides easy access to chiral TREN compounds **1a** and **1b** in three steps in 72 and 21% overall yields from (*S*)-valinol (**3a**) and (*S*)-alaninol (**3b**), respectively. Alternatively, starting from the corresponding amino acids, the same compounds are obtained in five steps in overall yields of 63 and 19%, respectively. The procedures are experimentally simple. The preparation of **1a** from **3a** requires column chromatography only after the first step, the remaining purifications being accomplished by filtration or extraction. In contrast to some of the previous methods affording chiral TREN compounds with the stereocenters located in the *N*-substituents[13] or in which the nitrogen atoms form part of a pyrrolidine ring,[12] our method gives access to chiral parent TREN derivatives with primary amino groups. In addition, a variety of *N*,*N*′,*N*′′-substituted derivatives, which are of interest for various potential applications, are accessible in reasonable overall yields, as demonstrated by the syntheses of *N*,*N*′,*N*′′-substituted compounds **8**–**13**.

The location of chirality in the ligand backbone is expected to add rigidity to metal complexes and main group element derivatives of the chiral TREN compounds, thereby favoring one of the possible diastereomeric twisted conformations. The stereocenters are, however, situated remote from the metal center. Model studies indicate that in **1a** and **1b** as well as in *N*,*N*′,*N*′′-alkyl derivatives, chiral transfer to the region of a coordinated metal ion may be inefficient. In contrast, aryl groups on nitrogen are thought to serve as efficient transmittors of chirality. We therefore consider the introduction of aryl groups on nitrogen by Pd-catalyzed C–*N* coupling to be of special interest.

Our new method should be compared to that recently published by Raymond[14] and subsequently extended by Verkade.[15] Raymond prepared the parent compounds as their hydrochloride salts in moderate overall yields from the amino alcohols, whereas Verkade prepared an *N*,*N*′,*N*′′-alkylsubstituted analogue of **1** (R = Bn) in five step from (*S*)-phenylalanine in an overall yield of 48%. Our method thus results in higher overall yields of the *N*,*N*′,*N*′′-substituted compounds starting from either (*S*)-valine (**4a**) or (*S*)-valinol (**3a**). We have also demonstrated that derivatives with a large variety of substituents on nitrogen are easily access-



Scheme 4. *N*-Functionalization of chiral TREN.

ible. With the method based on reductive amination,[14] there is a potential risk for epimerization of intermediates having the stereocenter next to a carbonyl group, even if that was not observed in the present case. In contrast, our procedure gives access to stereochemically well-defined parent chiral TREN compounds and their *N*,*N*′,*N*′′-substituted derivatives in high yields.

In addition to C_3-symmetric tripodal amines, our synthetic strategy provides access also to C_2-symmetric compounds by employing primary amines for the initial aziridine ring opening, or by using appropriate nucleophile/aziridine ratios.[24,31] Alternatively, as was recently demonstrated, the formation of products from single or double ring-opening can be controlled by the choice of solvent.[32]

The presently described compounds are expected to serve as useful ligands for metal ions and main group elements in catalytic applications. In addition, the chiral TREN derivatives constitute versatile building blocks for different types of ligands, as demonstrated for example by the preparation of phosphanylamides with rotational symmetry.[33]

Conclusions

An efficient and experimentally simple route for the preparation of enantiopure C_3-symmetric TREN analogues has been developed starting from the appropriate amino alcohol or amino acid. The synthesis proceeds via *N*-sulfonylaziridines, which are ring-opened by ammonia. In addition to tripodal compounds with primary amino functions, a variety of *N*,*N*′,*N*′′-alkyl- and aryl-substituted derivatives are conveniently accessible using our method.

Experimental Section

General Remarks: All reactions were run under dry nitrogen unless otherwise indicated. Glassware was oven- or flame-dried. Sodium *tert*-butoxide was sublimated before use. Dichloromethane, triethylamine, and toluene were distilled from CaH_2. Methanol and all other reagents were used as received.

^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance 400 or a Bruker DMX 500 instrument at room temperature in $CDCl_3$, using the residual signals from $CHCl_3$ (^{1}H: δ = 7.27 ppm; ^{13}C: δ = 77.2 ppm) as internal standard. Microwave heating was performed in a SmithCreator™ single-mode cavity from Biotage AB, Sweden. Optical rotations were recorded with a Perkin–Elmer 343 polarimeter at the sodium D line at ambient temperature. Flash chromatography was carried out using SDS silica gel 60 (40–63 μm). Melting points were measured in open capillary tubes using an Electrothermal instrument and are uncorrected. Elemental analyses were performed by Analytische Laboratorien, Lindlar, Germany. The preparation of **6a**[24] and **6b**[11] from **2a** and **2b**, respectively, has been described previously.

Aziridine 2a: TsCl (7.90 g, 41.4 mmol) was added to a solution of Et_3N (20.2 mL, 144 mmol) and (*S*)-valinol (**3a**, 3.72 g, 36 mmol) in CH_2Cl_2 (300 mL) at –25 °C. The reaction mixture was first stirred for 45 min in the cooling bath, then for another 2.5 h at room temperature. MsCl (2.93 mL, 37.8 mmol) was then added dropwise over 10 min at –25 °C. The reaction was run for 24 h in the cooling bath, which was slowly warmed to room temperature. The wine-red reaction mixture was washed with 0.5 M HCl (2 × 225 mL). The organic phase was washed with saturated aqueous Na_2CO_3 (2 × 225 mL) and dried with $MgSO_4$. The solvent was removed in vacuo. Purification by flash chromatography (silica gel, 10% EtOAc in hexanes) afforded **2a** (8.12 g, 94%) as white needles. The ^{1}H NMR and ^{13}C NMR spectroscopic data agreed with those published for the same compound.[34]

Compound 2b (from 3b): The previously published method was used.[11] By employing an exact 3:1 ratio of aziridine and ammonia (concentration of ammonia in methanol determined by titration using HCl, with methyl red as an indicator) the yield was increased from 70 to 74%.

Compound 2b (from 5): DEAD (0.39 mL, 2.48 mmol) was added dropwise to a solution of *N*-tosylalaninol[22] (500 mg, 2.18 mmol) and PPh_3 (629 mg, 2.40 mmol) in THF (20 mL) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 3 h, and then the solvent was evaporated. The crude product was purified by chromatography (silica gel, hexane/EtOAc, 3:2) to give **2b** (343 mg, 74%). The ^{1}H NMR and ^{13}C NMR spectroscopic data agreed with those published for the same compound.[34]

Compound 1a: Deprotection of the tosyl functions was achieved according to a modified literature procedure.[29] HBr (48% aq., 64 mL) was added to a flask containing **6a** (3.69 g, 5.02 mmol) and phenol (4.56 g, 48.44 mmol) and the mixture was refluxed for 48 h. Water (88 mL) and 2 M NaOH (38 mL) were added at room temperature to adjust the pH to about 1. The aqueous phase was washed with EtOAc (3 × 50 mL), then its pH adjusted with 2 M NaOH (about 350 mL) to > 13. The aqueous phase was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic phases were dried with Na_2SO_4. The solvent was removed in vacuo to give **1a** (1.24 g, 90%) as a light yellow oil. $[\alpha]_D^{20}$ = +179 (*c* = 0.72, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.72–2.67 (m, 3 H), 2.29–2.26 (m, 6 H), 1.89 (br. s, 6 H), 1.50 (octet, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 9 H), 0.90 (d, *J* = 6.7 Hz, 9 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 59.6, 53.5, 32.3, 19.3, 18.4 ppm. $C_{15}H_{36}N_4$ (272.47): calcd. C 66.12, H 13.32, N 20.56; found C 65.93, H 13.28, N 20.42.

Compound 1b: Tetraamine **1b** was prepared analogously to tetraamine **1a** from tris(sulfonamide) **6b** (3.50 g, 5.38 mmol). Distillation (105–110 °C/0.13 Torr) gave the product in 38% yield (0.39 g) as a clear oil which partly solidified upon standing. $[\alpha]_D^{20}$ = +183 (*c* = 0.73, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.09–3.04 (m, 3 H), 2.24–2.14 (m, 6 H), 1.57 (br. s, 6 H), 0.98 (d, *J* = 6.3 Hz, 9 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 64.1, 43.9, 24.4 ppm.

Tris(sulfonamide) 7a: A solution of **6a** (4.00 g, 5.44 mmol) in DMF (33 mL) was added dropwise during 30 min via a cannula to NaH (1.43 g of a 60% dispersion in oil, 35.8 mmol, which had been washed with 3 × 10 mL of pentane) in DMF (20 mL) at 0 °C. The suspension was stirred for 10 min at this temperature and then MeI (2.03 mL, 32.7 mmol) was added during 10 min. The suspension was stirred overnight while the temperature was allowed to reach room temperature. The reaction was quenched by careful addition of water (40 mL). CH_2Cl_2 (50 mL) was added, the phases separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a sticky solid. The solid was washed with diethyl ether to yield **7a** (3.95 g, 97%), which was used directly in the next step. M.p. 172–174 °C. $[\alpha]_D^{20}$ = –32.1 (*c* = 0.70, CH_2Cl_2). R_f = 0.35 (40% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.2 Hz, 6 H), 7.27 (d, *J* = 8.2 Hz, 6 H), 3.75 (app q, *J* = 6.6 Hz, 3 H), 2.95 (dd, *J* = 13.6 and 6.7 Hz Hz, 3

H), 2.70 (s, 9 H), 2.41 (s, 9 H), 2.07 (dd, J = 13.6 and 6.7 Hz Hz, 3 H), 1.79 (octet, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 9 H), 0.85 (d, J = 6.9 Hz, 9 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 143.2, 137.3, 129.6, 127.5, 60.0, 55.2, 30.5, 30.2, 21.7, 20.6, 19.8 ppm. $C_{39}H_{60}N_4O_6S_3$ (777.12): calcd. C 60.28, H 7.78, N 7.21; found C 60.36, H 7.81, N 7.17.

Tris(sulfonamide) 7b: Compound **7b** was prepared analogously to compound **7a**. Trissulfonamide **6b** (1.51 g, 2.32 mmol) gave trimethylated **7b** as a white solid in 99% crude yield (1.59 g). The solid was pure enough to be used directly in the subsequent deprotection step. An analytical sample was obtained by flash chromatography (silica gel, 40% EtOAc in hexanes) in 91% yield (1.45 g). M.p. 57–59 °C. $[a]_D^{20}$ = –55.3 (c = 0.90, $CHCl_3$). R_f = 0.35 (30% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.2 Hz, 6 H) 7.30 (d, J = 8.1 Hz, 6 H), 4.00 (app sextet, J = 6.7 Hz, 3 H), 2.72 (s, 9 H), 2.51 (dd, J = 13.0 and 5.8 Hz Hz, 3 H), 2.42 (s, 9 H), 2.37 (dd, J = 12.9 and 8.4 Hz Hz, 3 H), 0.84 (d, J = 6.6 Hz, 9 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 143.3, 137.1, 129.8, 127.2, 59.2, 51.0, 28.4, 21.7, 15.1 ppm. $C_{33}H_{48}N_4O_6S_3$ (692.96): calcd. C 57.20, H 6.98, N 8.09; found C 57.39, H 7.10, N 8.02.

Tetraamine 8a: A mixture of tris(sulfonamide) **7a** (149 mg, 0.19 mmol), phenol (156 mg, 1.66 mmol), and HBr (2.3 mL, 48% in water) was refluxed for 24 h. Water and NaOH (s) were carefully added to the cooled dark red mixture until pH $\approx$ 1. The aqueous phase was washed with EtOAc (10 × 8 mL), the pH was increased to > 13 with NaOH (s), and the aqueous phase was extracted with CH_2Cl_2 (5 × 8 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated in vacuo leaving a pink oil. Addition of diethyl ether caused formation of a pink precipitate, which was filtered off leaving **8a** as a colourless oil in 89% yield (54 mg). Spectral data were in accordance with those previously published.[11]

Tetraamine 8b: Tetraamine **8b** was prepared analogously to compound **8a** from tris(sulfonamide) **7b** (4.34 g, 6.26 mmol). Distillation (110 °C/0.05 Torr) gave the gave tetraamine **8b** in 60% yield (0.87 g) as a colourless oil which partially solidified upon standing. $[a]_D^{20}$ = +155 (c = 0.26, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.62-2.58 (m, 3 H), 2.41 (s, 9 H), 2.33 (dd, J = 12.9 and 10.0 Hz Hz, 3 H), 2.19 (dd, J = 12.9 and 3.2 Hz Hz, 3 H), 1.75 (br. s, 3 H), 0.95 (d, J = 6.2 Hz, 9 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 63.2, 53.4, 35.4, 19.5 ppm. $C_{12}H_{30}N_4$ (230.39): calcd: C 62.56, H 13.12, N 24.32; found C 62.43, H 12.95, N 24.17.

Compound 9: Benzaldehyde (0.14 mL, 1.38 mmol) was added to tetraamine **1a** (89.7 mg, 0.33 mmol) in methanol (1.5 mL) and the reaction mixture was stirred at room temperature for 2 h. Sodium borohydride (92.4 mg, 2.44 mmol) was added and stirring was continued for an additional 20 h. Water (2 mL) was then carefully added and the methanol was evaporated on the rotary evaporator. The aqueous phase was extracted with CH_2Cl_2 (5 × 2 mL). The organic phase was washed with brine (5 mL) and dried with $MgSO_4$. The solvent was removed, the resulting crude product was dissolved in pentane and the formed colourless solid was filtered off. The filtrate was concentrated and the residue purified by column chromatography (silica gel, hexane/EtOAc, 7:3 + 1% triethylamine) to yield **9a** (127.8 mg, 72%) as a colourless solid. $[a]_D^{20}$ = +152.4 (c = 0.88, CH_2Cl_2) (this value was determined from an analytical sample and is higher than that previously published[11]). ^{1}H NMR and ^{13}C NMR spectroscopic data were in agreement with those previously published.[11] $C_{36}H_{54}N_4$ (542.84): calcd. C 79.65, H 10.03, N 10.32; found C 79.53, H 10.07, 10.29.

Compound 10: Cyclohexanecarboxaldehyde (0.16 mL, 1.32 mmol) was added to tetraamine **1a** (88.5 mg, 0.33 mmol) in methanol (2 mL) and the reaction mixture was stirred at room temperature for 3 h. Sodium borohydride (91 mg, 2.41 mmol) was added and the reaction mixture stirred at room temperature for an additional 3 d. Water (3 mL) was carefully added and the methanol was evaporated. The aqueous phase was extracted with CH_2Cl_2 (5 × 3 mL) and the organic phase was washed with brine (5 mL) and dried with $MgSO_4$. The solvent was removed and the resulting crude product was purified by column chromatography (silica gel, hexane/EtOAc, 7:3 + 1% triethylamine) to yield tetraamine **10** (136.4 mg, 75%) as a colourless solid. R_f = 0.4 (hexane/EtOAc, 7:3 + 1% triethylamine). $[a]_D^{20}$ = +142.5 (c = 0.57, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39–2.28 (m, 4 H), 2.38 (dd, J = 12.3, 1.9 Hz, 1 H), 1.91–1.81 (m, 2 H), 1.75–1.67 (m, 4 H), 1.36–1.15 (m, 5 H), 0.92–0.82 (m, 8 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 60.6, 56.6, 55.7, 39.3, 32.1, 28.8, 27.1, 26.4, 26.3, 19.2, 16.8 ppm.

Compound 11: *N*-Arylation was achieved by a modified literature procedure.[35] The Pd catalyst was pre-formed by vigorously stirring $Pd_2(dba)_3$ (27.6 mg, 0.03 mmol) and *rac*-BINAP (56 mg, 0.09 mmol) in toluene (11 mL) at room temperature for 3.5 h. A separate flask was charged with **1a** (544 mg, 2 mmol), bromobenzene (0.63 mL, 6 mmol), sodium *tert*-butoxide (669 mg, 6.96 mmol), and toluene (11 mL). The wine-red catalyst solution was added and the reaction mixture was heated at 80 °C for 20 h. The precipitate (NaBr) was removed by centrifugation. The organic phase was concentrated and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 9:1 + 0.5% Et_3N) to give **11** (687 mg, 69%) as a light yellow solid. R_f = 0.30 (hexane/EtOAc, 9:1 + 1.0% Et_3N and 1.0% MeOH). $[a]_D^{20}$ = –181.4 (c = 0.30, $CHCl_3$). M.p. 87–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (t, J = 7.9 Hz, 6 H), 6.64 (t, J = 7.2 Hz, 3 H), 6.26 (d, J = 7.8 Hz, 6 H), 3.53 (d, J = 5.5 Hz, 3 H), 3.43–3.28 (m, 3 H), 2.54 [dd (resolution enhancement), J = 12.7 and 11.0 Hz Hz, 3 H], 2.31 (dd, J = 12.7 and 3.9 Hz Hz, 3 H), 1.99–1.82 (m, J = 7.1 and 3.8 Hz Hz, 3 H), 0.89 (d, J = 7.1 Hz, 9 H), 0.79 (d, J = 7.1 Hz, 9 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 149.0, 129.7, 117.2, 113.4, 54.9, 54.4, 30.4, 18.8, 18.2 ppm. $C_{33}H_{48}N_4$ (500.76): calcd. C 79.15, H 9.66, N 11.19; found C 78.91, H 9.81, N 11.09.

Compound 12: This compound was synthesized analogously to **11** using $Pd_2(dba)_3$ (201 mg, 0.22 mmol), *rac*-BINAP (410 mg, 0.66 mmol), **1a** (996 mg, 3.66 mmol), 2-bromotoluene (13.13 g, 76.75 mmol), sodium *tert*-butoxide (2.63 g, 27.41 mmol), and toluene (146 mL). The reaction mixture was heated at 100 °C for 96 h. The crude product was purified by flash chromatography with a gradient eluent (silica gel, hexane/EtOAc, 9:1 + 0.5% Et_3N and 0–1.0% MeOH) to give **12** (1.65 g, 83%) as a light yellow solid. R_f = 0.34 (hexane/EtOAc, 85:15 + 1.0% Et_3N and 1.0% MeOH). $[a]_D^{20}$ = –74.9 (c = 0.90, $CHCl_3$). M.p. 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (t, J = 7.2 Hz, 3 H), 6.97 (d, J = 7.3 Hz, 3 H), 6.64–6.53 (m, 6 H), 3.58–3.45 (m, 6 H), 2.64 (dd, J = 13.2 and 8.2 Hz Hz, 3 H), 2.57 (dd, J = 13.4 and 5.3 Hz Hz, 3 H), 2.24–2.13 (m, J = 7.0 and 4.1 Hz Hz, 3 H), 1.81 (s, 9 H), 0.97 (d, J = 7.0 Hz, 9 H), 0.84 (d, J = 7.0 Hz, 9 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 146.2, 131.3, 130.7, 128.0, 127.4, 122.9, 116.9, 116.6, 110.4, 56.4, 55.3, 31.7, 30.2, 29.7, 29.1, 18.2, 18.0, 17.5 ppm. $C_{36}H_{54}N_4$ (542.84): calcd. C 79.65, H 10.03, N 10.32; found C 79.47, H 9.92, N 10.22.

Compound 13: This compound was synthesized analogously to **11** using $Pd_2(dba)_3$ (24.7 mg, 0.027 mmol), *rac*-BINAP (50.4 mg, 0.081 mmol), **1a** (493 mg, 1.81 mmol), 4-bromobenzonitrile (988 mg, 5.43 mmol), sodium *tert*-butoxide (606 mg, 6.3 mmol) and

toluene (18.8 mL). The reaction mixture was heated at 80 °C for 24 h to yield a dark brown slurry. Toluene was removed and the residue was dissolved in $CHCl_3$. The precipitated fine powder (NaBr) was removed by centrifugation. The organic phase was concentrated and the crude product was purified by flash chromatography (hexane/EtOAc, 9:1 + 0.5% Et_3N, followed by $CHCl_3$) to give **13** (949 mg, 91%) as a light yellow solid. R_f = 0.1 (hexane/EtOAc, 3:1 + 2.0% Et_3N and 2.0% MeOH). $[\alpha]_D^{20}$ = –722 (c = 0.24, $CHCl_3$). M.p. 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.6 Hz, 6 H), 6.14 (d, J = 8.6 Hz, 6 H), 3.90 (d, J = 7.6 Hz, 3 H), 3.41 (ddd, J = 10.9, 4.1 and 4.0 Hz, 3 H), 2.49 (dd (resolution enhancement), J = 13.2 and 10.9 Hz Hz, 3 H), 2.41 (dd, J = 13.2 and 4.0 Hz Hz, 3 H), 1.97–1.83 (m, J = 6.9 and 4.1 Hz Hz, 3 H), 0.91 (d, J = 6.9 Hz, 9 H), 0.84 (d, J = 6.9 Hz, 9 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 151.7, 134.4, 120.5, 112.7, 99.0, 54.6, 30.6, 18.6, 18.3 ppm. $C_{36}H_{45}N_7$ (575.79): calcd. C 75.09, H 7.88, N 17.03; found C 74.85, H 7.77, N 16.76.

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