Asymmetric Synthesis of 1,2-Diamino-4,5-dimethylcyclohexanes by Zirconium-Catalyzed and -Promoted Reductive Cyclization Reactions

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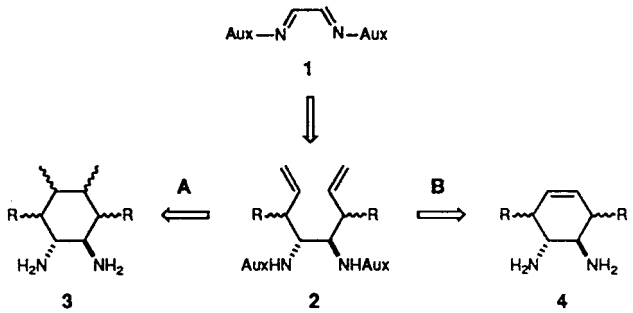
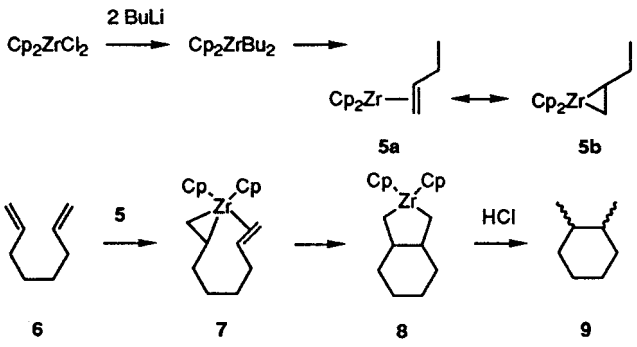
The asymmetric synthesis of 1,2-diamino-4,5-dimethylcyclohexanes was achieved by the zirconium-catalyzed and -promoted reductive cyclization of *N*,*N*′-di[(*S*)-1-phenylethyl]-4(*R*),5(*R*)-diamino-1,7-octadiene. The reaction of the diene with 5 equiv of butylmagnesium chloride and 0.1 mol % of bis(cyclopentadienyl)zirconium dichloride in diethyl ether at 0−20 °C gave mainly the 1(*R*),2(*R*)-diamino-4(*S*),5(*S*)-dimethylcyclohexane derivative having C_2 symmetry, but the reaction with 4 equiv of dibutylzirconocene in tetrahydrofuran at −78 to −50 °C gave prevalently the diastereomer with the 4(*R*),5(*S*) configuration. By reductive cleavage of the auxiliary, followed by sulfonylation reaction, 1(*R*),2(*R*)-di(4-toluenesulfonyl)amino)-4(*S*),5(*S*)-dimethylcyclohexane was prepared.

Transition metal catalyzed or promoted cyclization[1] and ring-closing metathesis[2] reactions of 1,*ω*-dienes, -enynes, and -diynes have emerged in the past decade as powerful tools for the synthesis of carbocyclic and heterocyclic compounds. We envisioned that 1,2-diaminocyclohexanes **3** and -cyclohex-4-enes **4**[3] and ring-substituted analogues could be prepared applying those cyclization methodologies to homoallylic 1,2-diamines **2**, which are in turn available from a homochiral glyoxal diimine **1** (Scheme 1). Now we report the results of the zirconium-promoted[4] or -catalyzed reductive cyclizations[5,6] of compounds **2** to give substituted cyclohexanes **3**, in which the absolute and relative configuration of the newly formed stereocenters is controlled by the auxiliary as well as the experimental conditions.

Scheme 1



Scheme 2



It has been reported that the zirconium-promoted reductive cyclization of 1,7-octadiene **6** affords 1,2-dimethylcyclohexane **9**. The presumed mechanism,[4] described in Scheme 2, involves the transmetalation of zirconocene dichloride with butyllithium to give dibutylzirconocene, which decomposes by loss of butane to give the active organometallic species, i.e., zirconocene-

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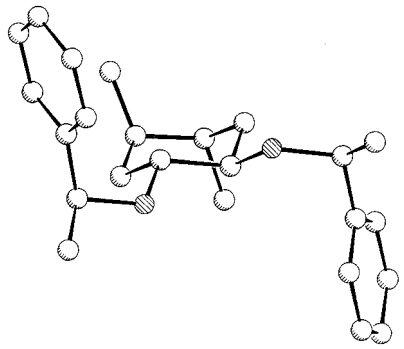


Figure 1.

(1-butene) **5**, which is better represented by the zirconaciclopropane resonance structure **5b**. Ligand exchange of the complex **5** with the diene **6** gives the alkene−zirconacyclopropane **7**; then insertion of the alkene into a Zr−C bond leads to the zirconabicycloalkane **8**, from which the hydrocarbon **9** is obtained after acidic quenching. Later, a more convenient procedure was described,[5] which allowed the use of a catalytic amount of the zirconocene complex, exploiting an excess of butylmagnesium chloride in substitution for butyllithium, as dibutylzirconocene was regenerated by transmetalation of the zirconabicycloalkane **8**.

We have carried out the reaction of the diaminodiene **10**[7] with an excess of butylmagnesium chloride and a catalytic amount of zirconocene dichloride in diethyl ether at 0−20 °C (route **A**) and obtained a mixture of the three diastereomers **11a**−**c** with a ratio of 82:5:13 in order of increasing retention time by GC-MS analysis. It is noteworthy that it was not necessary to protect the amino functions to accomplish the desired transformation. The ^{1}H NMR spectrum of the crude product revealed that the major and minor diastereomers **11a** and **11b** had C_2 symmetry and consequently the *trans* relationship of the methyl substituents at C-4 and C-5, whereas the isomer **11c** gave distinct absorptions for the nonequivalent methyl groups. The prevalent diastereomer **11a** was obtained pure through treatment of the mixture with excess hydrochloric acid and crystallization of the dihydrochloride **11a(HCl)$_2$** from methanol, followed by treatment with base. The ditosylamide **13** was also prepared from **11a(HCl)$_2$** by reductive removal of the auxiliary and routine disulfonylation of the intermediate primary diamine dihydrochloride **12** in basic medium.

The crystals of the salt **11a(HCl)$_2$** were not suitable for the X-ray structure analysis, which was necessary to unambiguously determine the absolute configuration of the newly formed stereocenters. We then prepared the dipicrate of **11a**, which nicely crystallized from methanol, incorporating a molecule of solvent. The structure of the dication (Figure 1) shows the (*S*) configuration of the C-4 and C-5 stereocenters and the preferred chair conformation of the cyclohexane ring, with the methyl and amino substituents in axial and equatorial position, respectively. It is worth nothing how the basic unit in the crystal packing of the salt **[11a($C_6H_3N_3O_7$)$_2$(CH_3OH)]** results from direct hydrogen bond association of one cation and one CH_3OH solvent molecule (Figure 2). The -NH_2^+ groups on the cations are hydrogen bonded to the -O^- groups belonging to the picrate anions (N- - -O 2.726, 2.762 Å). In addition to this, the CH_3OH molecule interacts via the OH function with both the -NH_2^+ groups and with the -O^- group of one picrate (O- - -N 2.797, 2.853 Å; O- - -O 2.665 Å). This arrangement allows the "segregation" of the charged portions of the salt components, and the resulting solvated supramolecular unit can then be packed in the solid as a pure van der Waals object.[8]

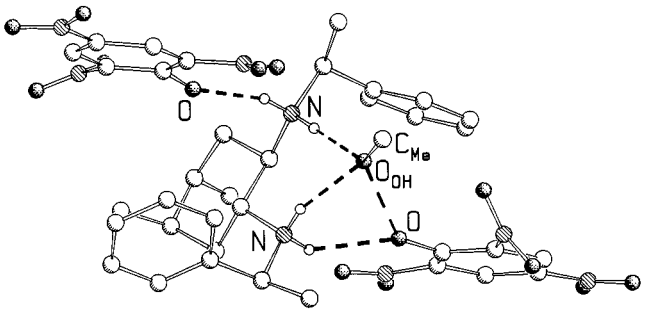
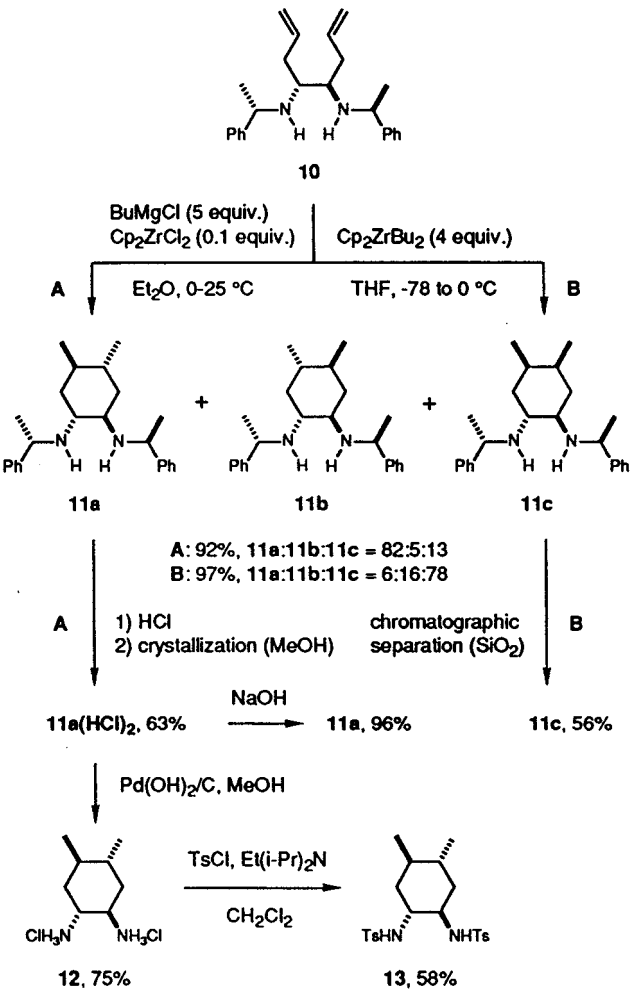


Figure 2.

Scheme 3



We also performed the cyclization of the diaminodiene **10** by reaction with 4 equiv of dibutylzirconocene, generated in situ at −78 °C from dichlorozirconocene and butyllithium in THF (route **B** in Scheme 3). Surprisingly, the reaction was complete after stirring for 2 h at −50 °C and afforded mainly the diastereomer **11c**, which was

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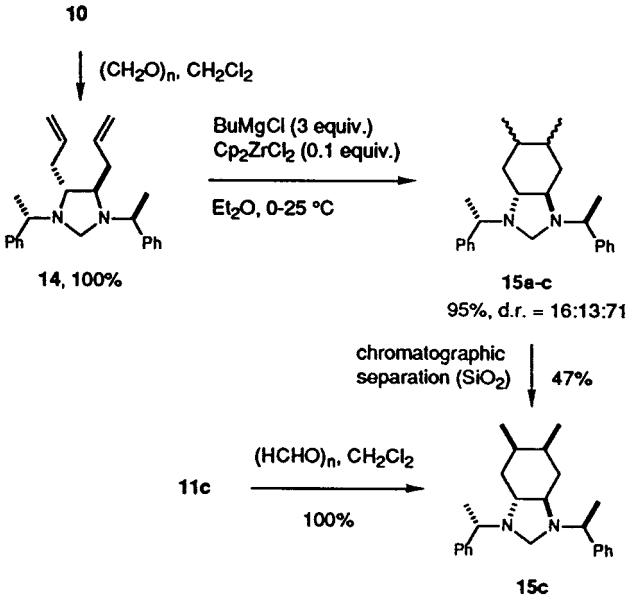
Scheme 4



obtained pure with good yield by chromatography. In a separate experiment we also observed that the diastereomeric ratio did not change by raising the temperature to 0 °C, but at reflux temperature the relative amount of the other diastereomers increased and some decomposition and polymerization occurred. It should also be observed that the cyclization took place only when an excess of dibutylzirconocene was used, the first 2 equiv being presumably consumed by complexation with the amino groups.

Aiming to obtain the other C_2-symmetric diastereomer **11b**, we attempted the reductive cyclization of the aminal **14**, which was easily prepared by condensation of the diamine **10** with paraformaldehyde, following the catalytic procedure (Scheme 4). We hoped that the tether linking the nitrogen atoms, resulting in the construction of a fused bicyclic molecule, would have been able to affect the stereochemistry of the cyclization process. As a matter of fact, by the catalytic procedure a mixture of the three diastereomers **15a**−**c** was obtained, the most abundant one being eluted later by GC-MS analysis. The *cis* relationship of the methyl substituents in the purified main diastereomer **15c** was then assessed by ^{1}H NMR analysis and by comparison with the authentic compound prepared from the diamine **11c** and paraformaldehyde.

The opposite stereochemical outcome of the zirconium-catalyzed cyclomagnesation and stoichiometric cyclozirconation reactions is in striking contrast with the previously reported cyclization of 1,7-octadiene **6**, which produced mainly the *cis*-fused zirconabicycloalkane **8**, and then *cis*-1,2-dimethylcyclohexane **9** by protonolysis, following the stoichiometric and catalytic procedures,[5d] although the more stable *trans* isomer was predominant at higher temperature, owing to the reversibility of the cyclozirconation step. Similarly, the cyclizations of hydroxy-substituted 1,7-dienes[4c,5c] and 4-oxa- and 4-aza-1,7-dienes[9] were highly *cis*-selective, but structural or steric factors favored the *trans* isomers in the construction of substituted six-membered carbo- and heterocycles.[9b,c]

At the moment, it is premature to advance hypotheses on the stereoelectronic factors which affect the relative stability of the chair and boat transition states which can be envisioned for the cyclozirconation step leading to the different diastereomers of the products **11** and **15**. At first, the mechanism of the reaction must be thoroughly clarified, identifying the real intermediates involved and consequently the nature of the substituents in the six-membered ring being constructed. They may be magnesium amides in the catalytic reaction and zirconium−amino complexes in the stoichiometric reaction. However, even by this assumption not all the results, particularly the formation of the bicyclic product **15c** from the diene **14**, could be explained.

We wish to underline that this is the first report on an enantioselective synthesis of ring-substituted 1,2-diaminocyclohexanes.[10] It should be observed that the enantiomer of the diamine **11a** and its derivatives can be obtained by the same synthetic sequence using (*R*)-1-phenylethylamine as the auxiliary. The previously reported asymmetric syntheses of 1,2-diaminocyclohexanes lacking ring substituents were plagued by the poor diastereoselectivity.[11] Hence, the development of new methods for the enantioselective synthesis of this class of compounds is a very important objective for the organic chemist, owing to the potential utility of such compounds in the fields of asymmetric synthesis[12] and medicinal chemistry. In fact, analogous ring-substituted 1,2-cyclohexanediamines, which have been prepared as racemic compounds, are selective κ-opioid agonists,[13] but in one case the enantiomers were resolved and their activity and selectivity were found to be dependent on both the absolute and relative stereochemistry of the ring substituents.[13a] Moreoveer, Pt(II) complexes of *cis*- and racemic *trans*-1,2-diaminocyclohexane, even containing hydroxy substituents on the ring, are used as antitumoral agents,[14] but it is noteworthy that (*R*,*R*)-1,2-diaminocyclohexane proved to be more active than its enantiomer.[14a]

Experimental Section

General. Solvents were distilled in an N_2 atmosphere prior to use: Et_2O and THF over sodium benzophenone ketyl and successively over $LiAlH_4$. Chromatographic purifications were carried on columns of silica gel (Merck, 230−400 mesh) at medium pressure. *n*-BuLi (1.6 M in hexane), *n*-BuMgCl (2 M in Et_2O), and bis(cyclopentadienyl)zirconium dichloride were purchased from Aldrich. All the organometallic reactions were performed in flame-dried apparatus under a static atmosphere of dry argon.

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Preparation of *N,N′*-Di-[(*S*)-1-phenylethyl)]-(1*R*,2*R*,-4*S*,5*S*)-1,2-diamino-4,5-dimethylcyclohexane 11a. To the solution of *N,N′*-di-[(*S*)-1-phenylethyl)]-4(*S*),5(*S*)-diaminoocta-1,7-diene **10** (0.174 g, 0.5 mmol) in anhydrous Et_2O in a dry apparatus under an Ar atmosphere was added *n*-BuMgCl (2 M in Et_2O, 1.25 mL, 2.5 mmol) dropwise with stirring. After 30 min, Cp_2ZrCl_2 (0.015 g, 0.051 mmol) was added and the mixture was stirred for 18 h at room temperature; then water was added and the organic phase was extracted with Et_2O, dried with Na_2SO_4, and concentrated to give **11a**−**c** as an oil (0.160 g, 91%). GC-MS analysis of the crude product allowed for the determination of an 82:5:13 ratio of three diastereomers in order of increasing retention time. The product was dissolved in MeOH (2 mL); then 37% HCl (1 mmol) was added to the solution cooled at 0−5 °C. Water was eliminated by adding benzene and concentrating at reduced pressure, and repeating this operation two times. The white solid obtained was washed with anhydrous cold CH_2Cl_2; then the residue was crystallized from MeOH to obtain pure **11a(HCl)$_2$** (0.133 g): mp 252 °C (dec); $[\alpha]^{20}_D$ −30 (*c* 1, MeOH); ^{1}H NMR (200 MHz, D_2O) δ 7.37 and 7.16 (2 m, 10 H), 4.30 (q, 2 H), 3.02 (m, 2 H), 1.95−1.15 (m, 6 H), 1.43 (d, J = 6.7 Hz, 6 H), 0.81 (d, J = 6.0 Hz, 6 H) ppm.

The salt was treated with 1 M NaOH (2 mL), and the free base was extracted with Et_2O; then the collected Et_2O layers were dried with Na_2SO_4 and concentrated to leave the pure diamine **11a** as an oil (0.105 g, 3 mmol, 60%): $[\alpha]^{20}_D$ −82.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.20 (m, 10 H), 3.75 (q, 2 H), 2.32 (m, 2 H), 1.6 (broad, 2 H), 1.50−1.30 (m, 6 H), 1.27 (d, J = 6.6 Hz, 6 H), 0.85 (d, J = 6.0 Hz, 6 H) ppm; MS, *m*/*z* (relative intensity) 105 (100, $PhCHCH_3$), 120 (36, PhCHMeNH), 245 (7, $M^+ - PhCHCH_3$). Anal. Found: C, 82.30; H, 9.74; N, 7.96. $C_{24}H_{34}N_2$ required: C, 82.23; H, 9.78; N, 7.99.

The dipicrate of **11a** was prepared by adding **11a** (0.455 g, 1.3 mmol) to a solution of picric acid (0.595 g, 2.6 mmol) in Et_2O (60 mL). The precipitate that was formed immediately was recrystallized from methanol to obtain crystals of **11a-($C_6H_3N_3O_7$)$_2$(CH_3OH)** suitable for X-ray analysis: mp 159−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$−D_2O) spectroscopy δ 9.02 (s, 4 H, picrate), 7.30 (m, 10 H), 4.54 (q, 2 H), 3.52 (s, 3 H, CH_3OH), 3.49 (m, 2 H), 1.67−2.16 (m, 6 H), 1.63 (d, J = 6.6 Hz, 6 H), 0.70 (d, J = 6.9 Hz, 6 H) ppm.

Crystal Structure Characterization of 11a($C_6H_3N_3O_7$)$_2$-(CH_3OH). All X-ray diffraction data collections were carried out on a NONIUS CAD-4 diffractometer equipped with an Oxford Cryostream liquid-N_2 device. Diffraction data were corrected for absorption by azimuthal scanning of high-χ reflections. SHELX86 (Sheldrick, G. M. *Acta Crystallogr.* **1990**, *146*, 467) and SHELXL92 (Sheldrick, G. M. SHELXL92, Program for Crystal Structure Determination; University of Goettingen: Goettingen, Germany, 1992) were used for structure solution and refinement based on F^2. SCHAKAL97 (Keller, E. SCHAKAL97, Graphical Representation of Molecular Models; University of Freiburg: Germany, 1997) was used for the graphical representation of the results. Mo Kα radiation: λ = 0.71069 Å, graphite monochromated , T = 273(2) K. All non-H atoms were refined anisotropically. The hydrogen atoms were added in calculated positions and refined anisotropically.

Crystal data: orthorombic, space group $P2_12_12_1$, colorless crystals, a = 10.520(8), b = 13.151(6), and c = 29.43(2) Å, V = 4072(5) Å^3, Z = 4, d_c = 1.368 g cm^{-3}, $F(000)$ = 1760, μ = 0.108 mm^{-1}, θ range 3.0−23.0°, 3233 reflections measured, 3197 of which were independent, refinement on F^2 for 494 parameters, wR (F^2, all reflections) = 0.2524, $R_1(I > 2\sigma I)$ = 0.0758, S = 1.027.

Preparation of Aminals 15a−c from Aminal 14. The procedure previously described for the preparation of diamine **11a** was followed, but 3 equiv of *n*-BuMgCl was used.

Preparation of *N,N′*-Di-[(*S*)-1-phenylethyl)]-(1*R*,2*R*,-4*R*,5*S*)-1,2-diamino-4,5-dimethylcyclohexane 11c. A solution of Cp_2ZrBu_2 was prepared by adding dropwise *n*-BuLi (1.6 M in hexane, 5 mL, 8 mmol) to the stirred solution of Cp_2ZrCl_2 (1.16 g, 4 mmol) in anhydrous THF (10 mL), cooled to −78 °C in an Ar atmosphere, and stirring was continued for 1 h. Then the solution of the diamine **7** (0.350 g, 1 mmol) in THF (5 mL) was dropwise added, the cooling bath was removed, and stirring was continued while the temperature was allowed to reach 0 °C during 2 h. The reaction mixture was quenched by adding MeOH (5 mL) and aqueous $NaHCO_3$ (10 mL), the organic phase was extracted with Et_2O, and the collected Et_2O layers were dried with Na_2SO_4 and concentrated to leave an oil. GC-MS analysis showed that it was a mixture of diastereomers **11a**−**c** in a ratio of 6:16:78, in order of elution. The product was chromatographed on a SiO_2 column eluting with cyclohexanes−ethyl acetate 3:1 to give **11c** (0.200 g, 56%, >98% pure): $[\alpha]^{20}_D$ −146 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 10 H), 3.85 (m, 2 H), 2.10−1.60 (m, 8 H), 1.35 and 1.33 (2 d, 6 H, J = 6.9 Hz, 1.08 and 0.86 (2 m, 2 H), 0.79 and 0.64 (2 d, J = 6.9 Hz, 6 H) ppm. Anal. Found: C, 82.30; H, 9.76; N, 7.94. $C_{24}H_{34}N_2$ required: C, 82.23; H, 9.78; N, 7.99.

The dipicrate of **11c** was prepared and recrystallized from methanol, but the crystals were not suitable for X-ray-analysis: ^{1}H NMR (300 MHz, $CDCl_3$−D_2O) δ 9.03 (s, 4 H, picrate), 7.30 (m, 10 H), 4.51 (q, 2 H), 3.51 (s, 3 H, CH_3OH), 3.31 (m, 2 H), 2.18−1.83 (m, 6 H), 1.66 and 1.62 (2 d, J = 6.6 Hz, 6 H), 0.87 and 0.50 (2 d, J = 6.0 and 7.5 Hz, 6 H) ppm.

Preparation of *N,N′*-Di(4-toluenesulfonyl)-(1*R*,2*R*,-4*R*,5*R*)-1,2-diamino-4,5-dimethylcyclohexane 13. A Parr apparatus was filled with the salt **11a(HCl)$_2$** (0.45 g, 1.06 mmol), MeOH (35 mL), and Pd(OH)$_2$/C (0.150 g) and then submitted to a pressure of 48 psi of H_2 for 36 h. The solution was filtered through a small pad of Celite and then concentrated to leave the crude primary diamine dihydrochloride **12** as a glassy solid, which was rinsed with CH_2Cl_2 and dried at reduced pressure: 0.161 g, 75%; mp 220 °C (dec); $[\alpha]^{25}_D$ −18.7 (*c* 0.65, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (m, 2 H), 1.78, 1.60, and 1.37 (3 m, 6 H), 0.86 (d, J = 6.0 Hz, 6 H) ppm.

The solid (0.107 g, 0.5 mmol) was suspended in CH_2Cl_2 (5 mL), the mixture was cooled at 0−5 °C with an ice bath, and then ethyldiisopropylamine (1.06 mL, 6.3 mmol) was added. After stirring for 15 min at 25 °C, the mixture was again cooled to 0 °C, and then 4-toluenesulfonyl chloride (0.230 g, 1.2 mmol) was added. After stirring for a further 2 h, 2 N HCl (5 mL) was added and the organic phase was extracted with Et_2O. The collected ethereal layers were washed with brine, dried with Na_2SO_4, and concentrated to leave the diamide **13** as a white solid, which was crystallyzed two times from CH_2Cl_2−cyclohexane: 0.130 g (58%); mp 205−206 °C; $[\alpha]^{20}_D$ +65.8 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.8 Hz, 4 H), 7.32 (d, J = 8.1 Hz, 4 H), 4.71 (d, J = 5.7 Hz, 2 H), 3.37 (m, 2 H), 2.45 (s, 6 H), 1.65−1.10 (m, 6 H), 0.82 (d, J = 5.4 Hz, 6 H) ppm. Anal. Found: C, 63.17; H, 7.22; N, 6.66. $C_{22}H_{30}N_2O_4S_2$ required: C, 63.14; H, 7.23; N, 6.69.

Preparation of Aminals 14 and 15c from the Secondary Diamines 10 and 15c. General Procedure. Paraformaldehyde (0.100 g, 4 mmol), *p*-TsOH−H_2O (0.010 g), and $MgSO_4$ (0.5 g) were added to the solution of diamine **11c** (0.070 g, 0.2 mmol) in anhydrous CH_2Cl_2 (5 mL). The mixture was magnetically stirred at rt for 48 h and then filtered on Celite. The solution was washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated to leave the compound **15c** in quantitative yield (0.072 g): $[\alpha]^{25}_D$ −42.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.19 (m, 10 H), 3.88 and 3.85 (2 q, 2 H), 3.50 (s, 2 H), 2.45 and 2.32 (2 m, 2 H), 2.04−1.68 (m, 4 H), 1.50 (m, 1 H), 1.37 (d, J = 6.9 Hz), 1.27 (m, 1 H), 0.93 and 0.90 (2 d, J = 6.6 and 7.5 Hz, 6 H) ppm; MS, *m*/*z* (relative intensity) 105 (100, $PhCHCH_3$), 361 (45, $M^+ - 1$), 362 (18, M^+). Anal. Found: C, 82.78; H, 9.48; N, 7.70. $C_{25}H_{34}N_2$ required: C, 82.82; H, 9.45; N, 7.73.

1,3-Di[(*S*)-1-phenylethyl]-4(*R*),5(*R*)-di(2-propenyl)imidazolidine 14 (100%): $[\alpha]^{25}_D$ −33.1 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.06 (m, 10 H), 5.81−5.63 (m, 2 H), 5.05−4.92 (m, 4 H), 3.76 (m, 2 H), 3.36 (s, 2 H), 2.76 (m, 2 H), 2.24 and 2.14 (2 m, 4 H), 1.60 (s, ca. 1 H, NH, probably due to incorporated H_2O), 1.30 (m, 6 H) ppm; MS, *m*/*z* (relative intensity) 105 (100, $PhCHCH_3$), 319 (17), 69 (11), 79 (10), 173

(9). Anal. Found: C, 83.10; H, 8.99; N, 7.75. $C_{25}H_{32}N_2$ required: C, 83.28; H, 8.95; N, 7.77.

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Supporting Information Available: Tables of X-ray structural data, including data collection parameters, positional and thermal parameters, and bond distances and angles, plus ORTEP drawings and crystal packing for **11a($C_6H_3N_3O_7$)$_2$-(CH_3OH)**. This material is available free of charge via the Internet at http://pubs.acs.org.

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