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Synthesis and conformational analysis of novel tertiary amides derived from *N*-[(*S*)-α-phenylethyl]-1,3-Imidazolidine

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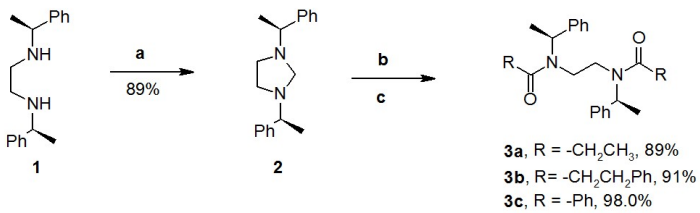
Abstract

The synthesis of three chiral tertiary amides by ring opening of the symmetric 1,3-imidazolidine **2** under mild conditions is described. ^{1}H NMR dynamics studies were performed to identify three rotamers present in solution, which were also examined by DFT calculations.



3a, R = -CH_2CH_3, 89%
3b, R= -CH_2CH_2Ph, 91%
3c, R = -Ph, 98.0%

Reagents and conditions: a) K_2CO_3/$MgSO_4$/ $CHCl_3$, CH_2O-H_2O (37% v/v).
b) *n*-BuLi (1.2 equiv), 0 °C, c) RCOCl (2.2 equiv), – 78 °C

Keywords: Tertiary amides, variable temperature RMN, theoretical analysis, *Z*- and *E*-rotamer

Introduction

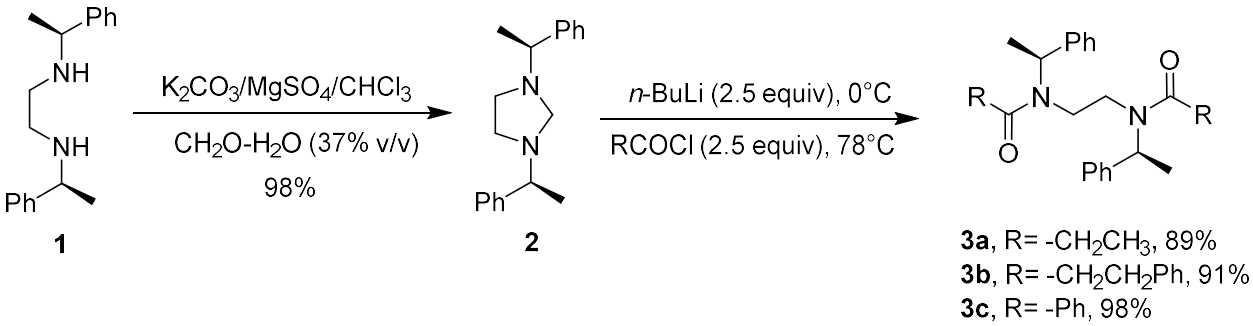
Amide bond formation is one of the most often used transformations in organic synthesis, and amides are frequently employed as building blocks for the synthesis of biologically active compounds[1-3] such as anti-inflammatory and analgesic agents,[4,5] fungicides antibiotics, parasiticides and antivirals.[6,7] The synthetic route used most frequently for amide formation involves the combination of an amine (including ammonia) with an activated carboxylic acid derivatives[8] or directly with the carboxylic acid in a reaction mediated by a coupling reagent.[9] The existing methods have several drawbacks in common, such as poor atom-efficiency, the use of hazardous reagents, and the generation of waste that not only reduce the process efficiency but also impose environmental problems. To address these challenging problems in amide synthesis, a plethora of novel amide formation reactions have been developed,[10] i.e. catalytic acylation of amines with carboxylic acids,[11] dehydrogenative amidation of alcohols,[12-14] amino carbonylation of aryl chlorides,[15,16] hydroamination of alkynes,[17,18] transamidation of primary amides,[19,20] and oxidative amidation of aldehydes.[21,22]

Fife and Perillo have reported a ring-opening reaction starting from 1,3-imidazolidines via acid catalysis and a mechanism has been proposed.[23] The structural features of amides have been widely studied by NMR spectroscopy and molecular modeling studies, among others because they represent model compounds for peptides and proteins.[24-26]

As part of an ongoing project involving chiral diamines as chiral ligand adjuvants,[27,28] herein we have also examined the E/Z equilibrium of tertiary amides **3a-3c**, which were prepared by a ring-opening reaction of 1,3-imidazolidine **2** with *n*-BuLi and different acyl chlorides.

Results and Discussion

A series of convenient procedures for the preparation of *N*,*N*'-ethylene-bis[(*S*)-1-phenylethyl]amine **1** are available in the literature.[29] Accordingly, 1,3-imidazolidine **2** was prepared in excellent yield (98%) by condensation of diamine **1** with aqueous formaldehyde following the general procedure reported by Coldham *et al*.[30,31] (Scheme 1). An important observation for this reaction is that the use of formaldehyde (37% aq. v/v) instead of paraformaldehyde resulted in higher yields (98% versus 80%).



Scheme 1. Reaction sequence for the synthesis of **3a-3c**.

For the ring-opening reaction of 1,3-imidazolidine **2,** with a series of different bases were tested, including *sec*-BuLi (1.2 equiv), NaHMDS (1.2 equiv), DBU (1.2 equiv), DMPA (1.2 equiv), DMPA-Et_3N (0.05:1.3), and Py (1.2 equiv). The optimal conditions for the preparation of **3a-3c** were observed in the presence of *n*-BuLi (2.5

equiv, 1.0 M solution in hexane).[32] After the addition of *n*-BuLi at 0 °C the reaction mixture was stirred for 0.5 h, whereupon 2.5 equivalents of the corresponding acyl chloride (propionyl, hydrocinamoyl and benzoyl chloride) were added at -78 °C. After chromatographic purification, the tertiary amides **3a-3c** were afforded in yields ranging from 89 to 98% (Scheme 1).

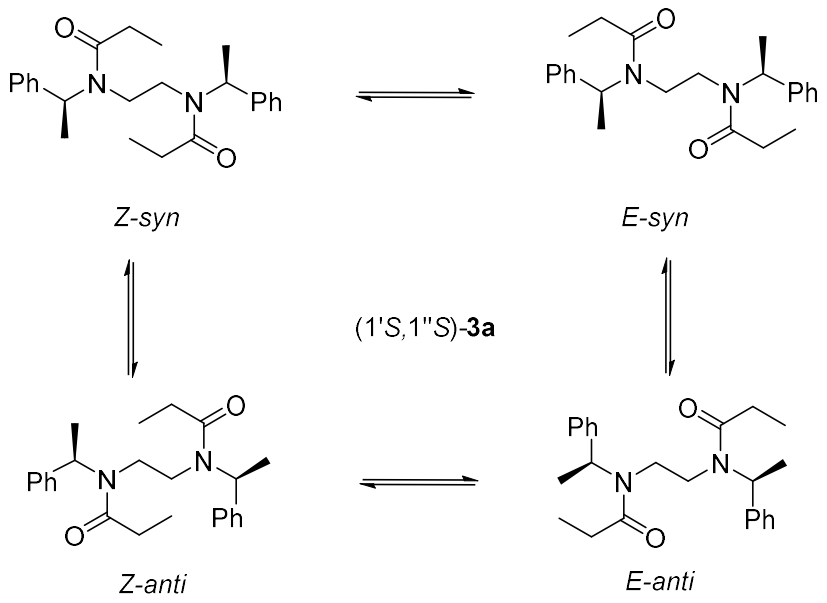


Figure 1. Conformational interconversion reactions for compound **3a**.

Compounds **3a-3c** are the result of a diacylation reaction of the nitrogen atoms leading to the ring-opening of the imidazolidine ring. This observation indicates that the C-N bonds are activated by coordination of the Lewis acid to the nitrogen.[33]

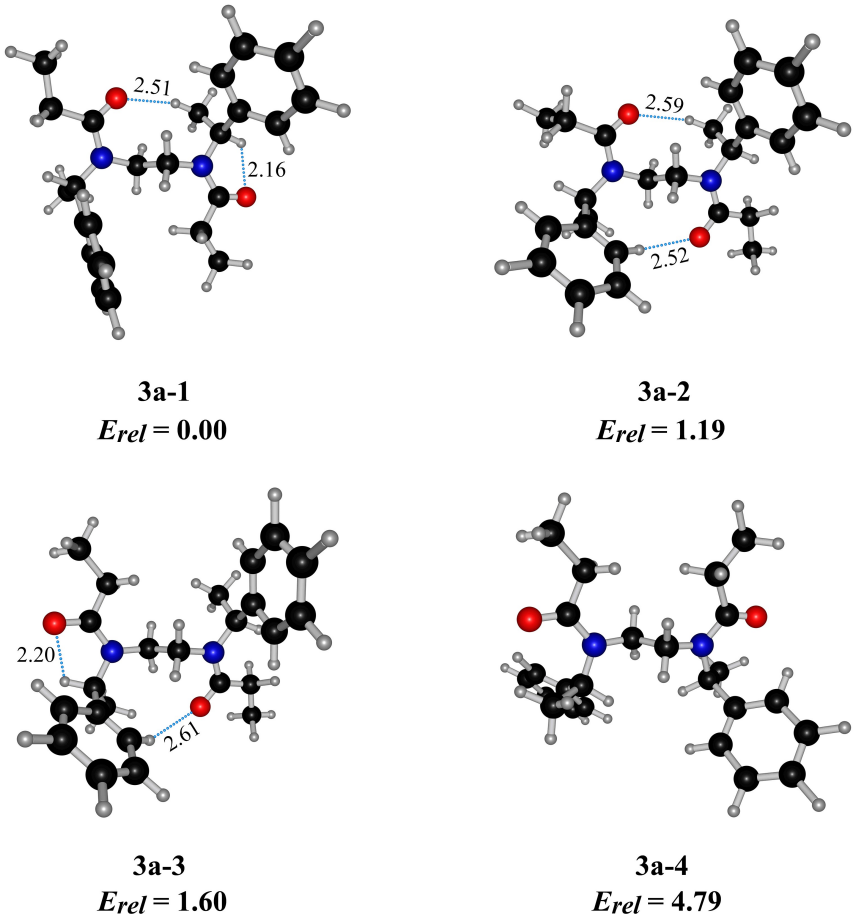
When smaller amounts of acyl chloride were employed, e.g. 1.2 equivalents, the imidazolidine ring opens forming **3a**-**3c** rotamers, but there were still traces of the starting material (**2**).

Even though, compounds **3a-3c** seem to be simple molecules, the ^{1}H and ^{13}C NMR spectra in $CDCl_3$ at room temperature show the presence of a dynamic equilibrium, giving a total of three sets of signals, which based on HSQC experiment are attributed to rotamers (*Z-syn, E-syn,* and *E-anti*, with population ratios of 1.4:1.5:0.3) (Figure 1). Interestingly the *Z-anti* rotamer was not observed, which was attributed to steric repulsion between the carbonyl group and the phenyl group. Variable temperature ^{1}H NMR spectra were also measured in DMSO-d_6 in a temperature range from 20 to 175 °C. In order to assign all signals unequivocally, COSY and HETCOR experiments were realized also at 175 °C (see Table 1).

In order to examine with more detail of the different rotamers present in solution, we explored the potential energy surface of **3a** by quantum mechanical DFT calculations, using the B3LYP/6-31G(d,p) method to optimize the geometries and to calculate the relative energies of all minima (see Figure 2). Of the four possible rotamers three (**3a-1**, **3a-2** and **3a-3**) had similar energy values, (Figure 2), which is in agreement with the NMR data. Rotamer **3a-4** has a significantly higher energy (4.79 kcal/mol) when compared to the most stable conformer **3a-1**.

Table 1. VT NMR experiments for the analysis of rotamers **3a**-**3c** in $CDCl_3$ and DMSO-d_6

Compound	R	Solvent	T (ºC)	Ratio *Z-syn, E-syn, E-anti*
3a	-CH_2CH_3	DMSO-d_6	25	1.4:1.5:0.3
		DMSO-d_6	170	2:1:0
		$CDCl_3$	-60	1:1
3b	-CH_2CH_2Ph	DMSO-d_6	25	1.4:1.5:0.3
		DMSO-d_6	170	2:1:0
		$CDCl_3$	-60	1:1
3c	-Ph	DMSO-d_6	25	1:0:0
		DMSO-d_6	75	1:0:0
		$CDCl_3$	-50	1:0:0



3a-1
***Erel* = 0.00**

3a-2
***Erel* = 1.19**

3a-3
***Erel* = 1.60**

3a-4
***Erel* = 4.79**

Figure 2. Optimized geometries for the four possible rotamers of **3a** using the B3LYP/6-31G(d,p) method. Relative energies are in kcal/mol.

The most stable structures **3a-1** and **3a-3**, exhibit two type of hydrogen bonds, the first one is between the carbonyl of the amide group and a hydrogen atom attached to the neighboring methine group with H···O distances of 2.16 and 2.20 Å, respectively, and the second one is in between the carbonyl groups and hydrogen atoms from methyl and phenyl groups, with H···O distances of 2.51 and 2.61 Å, respectively. On the contrary, **3a-2** showed two C-H···O interactions with hydrogen atoms from phenyl and methyl groups with H···O distances of 2.52 and 2.59 Å, which are significantly smaller than the sum of the van der Waals radii (2.80

Å). The importance of the C-H···O interactions for the molecular conformation of amides has been previously established also by other research group.[34]

The free energy of activation for the interconversion of compounds **3a-1** to **3a-4** has been investigated by means of dynamic NMR spectroscopy.[35,36] To measure the free energy of activation ($\Delta G^{\neq}$) by variable temperature ^{1}H NMR spectroscopy, the coalescence temperature method can be used. The coalescence temperature (T_c, K) is the lowest temperature at which the rotamers merge in the ^{1}H NMR spectrum (Table 2). The free energy of activation ($\Delta G^{\neq}$, kcal mol^{-1}) and the rate constant (kc, s^{-1}) can be derived from the Eyring equation (Eqs.1 and 3).[36]

$$k_c = \pi\Delta\nu/\sqrt{2} \quad [1]$$

$$\Delta G^{\neq} = 2.303RT_c\left(10.319+\log\left(T_c/k_c\right)\right) \quad [2]$$

$$\Delta G^{\neq} = 4.569\times10^{-3}T_c\left(10.319+\log\left(T_c/k_c\right)\right) \quad [3]$$

On the other hand, the rotational barrier for compounds **3a** and **3b** has been calculated both experimentally (Table 2) and theoretically (Table 3). The theoretical values were calculated in the gas phase with and without solvent (see Table 3). No significant changes were observed when comparing the experimental data with the theoretical values.

Table 2. Relative energies (in kcal/mol) of the barriers of interconversion between the diastereomeric conformations of **3a** and 3**b**, as established by VT-NMR experiments in $CDCl_3$ and DMSO-d_6

Comp.	Solvent	δ_1 (ppm)	δ_2 (ppm)	ν (Hz)	k_c (s^{-1})	T_c (K)	$\Delta G^{\neq}_{exp}$	$\Delta G^{\neq}_{calcd}$
3a	$CDCl_3$	1.41	1.38	6	13.31	85	17.14	15.23
3b	DMSO-d_6	1.37	1.25	24	53.28	358	16.95	17.03

Table 3. Relative energies of the barriers of interconversion between the diastereomeric conformations of the **3a** and **3b**, calculated at the B3LYP/6-31G(d,p) level of theory. Note: The experimental values are included for comparison

Compound	Solvent	$\Delta G^{\neq}_{calcd}$	$\Delta G^{\neq}_{exp}$
3a	---	22.47	---
3b	---	19.36	---
3a	$CDCl_3$	15.23	17.14
3b	DMSO-d_6	17.03	16.95

Additionally, for **3a** crystals suitable for single-crystal X-ray diffraction, analysis could be grown, which allowed to establish that the solid state structure contains only one of the three rotamers found in solutions (*Z-syn*) (Figure 3).

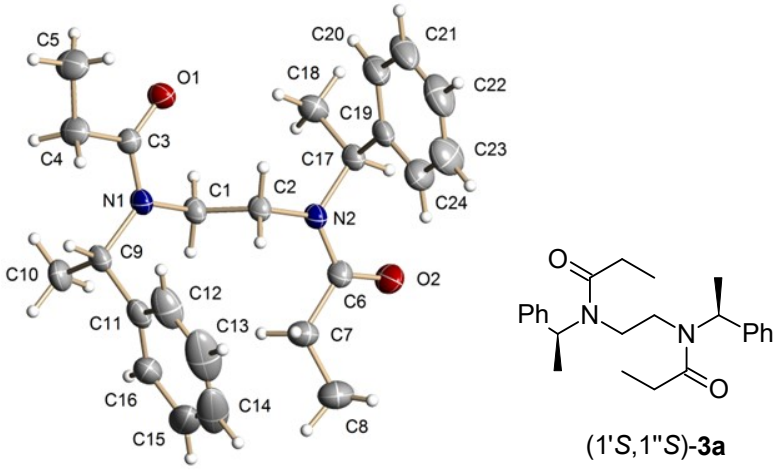


Figure 3. Molecular structure of *N,N*'-{di(propionyl)-di[(*S*)-1-phenylethyl]} ethylendiamine **3a** established by single crystal X-ray diffraction analysis.

Finally, the molecular structure of **3c** was optimized using the same computational method as described before, giving only one low-ebergy rotamer. In this derivative, the phenyl group attached to the diamide group restricts the rotation of the 1-phenylethyl substituents (Figure 4).

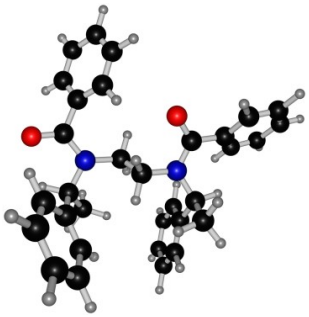


Figure 4. Molecular structure of **3c** calculated with the B3LYP/6-31G(d,p) method.

Conclusions

We reported on the synthesis of chiral symmetrically *N*,*N*'-trisubsituted-1,3-diamides **3a-3c** which have been prepared from the corresponding 1,2-diamines in excellent yields (89 – 98%). Diacylation of the nitrogen atoms induced ring-opening of 1,3-imidazolidine **2** even in the presence of mild bases. The conformational equilibria have been evaluated by VT NMR techniques and DFT calculations, showing that the rate of interconversion between rotamers is almost completely dependent on the nature of the substituent at the amide group.

Experimental Section

General. All experiments were carried out under an inert N_2 atmosphere. THF was distilled from sodium benzophenone. CH_2Cl_2 was dried from sodium hydride. Melting points were determined on a Fischer Jones

apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 881 spectrophotometer, using polystyrene as reference (1602 cm^{-1}). NMR spectra were obtained on Varian Mercury 200 or 400 equipments. ^1H NMR spectra were referenced to tetramethylsilane; $^{13}C\{^1H\}$ NMR spectra were referenced to residual non-deuterated solvent.

General Procedure for the Preparation of *N*-[(*S*)-α-phenylethyl]- 1,3-Imidazolidine (2). The *N*,*N*'-bis[(1*S*)-1-phenylethyl]ethane-1,2-diamine (1.81 g, 5.62 mmol) was added a mixture of 37% aqueous solution of formaldehyde (0.30 mL, 11.24 mmol), K_2CO_3 (2.00 g, 14.6 mmol), and $MgSO_4$ (2.00 g, 16.8 mmol) in $CHCl_3$ (25 mL) under inert atmosphere. The reaction mixture was stirred at room temperature for 24 h and then extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layer was dried with Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel [hexane-EtOAc; (10:1)].

General Procedure for Ring Opening of Imidazolidine (2). Imidazolidine **2** (0.3 g, 1.06 mmol) was placed in a dry two-necked flask fitted with a condenser and magnetic stirrer in THF under argon atmosphere. The reaction mixture was cooled to 0 °C on an ice bath, whereupon *n*-BuLi (0.66 mL, 1.6 M in cyclohexane) was added dropwise. After stirring for 30 min, the reaction mixture was cooled to – 78 °C. Then acyl chloride (2.33 mmol) was added dropwise. After stirring for 2 h, the reaction was quenched with NH_4Cl (10 mL, saturated aqueous solution), and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was dried with Na_2SO_4, and evaporated under reduced pressure. The product was purified by column chromatography on silica gel [hexane-EtOAc; (3:1)].

***N,N'*-{Di(propionyl)-di[(*S*)-1-phenylethyl]}ethylenediamine (3a).** The product was isolated in form of colorless crystalline powder. mp 69-71 °C. (0.45 g, 89% yield). $[\alpha]_D^{20}$ -100.8 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.12 (t, *J* 7.4 Hz, 3H, H-3*E*), 1.19 (t, *J* 7.2 Hz, 3H, H-3*Z*), 1.38 (d, *J* 4.2 Hz, 3H, H-H''), 1.41 (m, *J* 4.0 Hz, 3H, H-2'), 1.74 (d, *J* 7.0 Hz, 2H, H-3*Z*'), 2.15 (c, *J* 7.4 Hz, 2H, H-2*E*), 2.55 (m, 2H, H-2*Z*), 2.75 (m, 2H, H-1a', H-1a"), 3.18 (m, 2H, H-1a', H1a"), 5.08 (c, *J* 6.6 Hz, 1H, H-1"), 5.92 (c, *J* 7.0 Hz, 1H, H-1'), 7.28 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 9.4 (CH_3, C-3*Z*), 9.8 (CH_3, C-3*E*), 16.3 (CH_3, C-2'), 17.0 (CH_3, C-2"), 18.0 (CH_3, C-2'"), 25.7 (CH_2, C-2*Z*), 26.6 (CH_2, C-2*E*), 26.8 (CH_2, C-2*E*'), 40.8 (CH_3, C-1a'), 41.1 (CH_2, 1a'"), 42.6 (CH_2, 1a"), 49.8 (CH, C-1'), 54.0 (CH, C-1"), 54.9 (CH, C-1'"), 126.2 (Ar-CH), 126.5 (Ar-CH), 126.7 (Ar-CH), 126.8 (Ar-CH), 127.4 (Ar-CH), 127.7 (Ar-CH), 128.0 (Ar-CH), 128.2 (Ar-CH),139.1 (C-*ipso*), 140.0 (C-*ipso*), 141.0 (C-*ipso*), 173.3 (CO), 174.0 (CO). Crystal suitable for single-crystal X-ray diffraction analysis were grown from a solvent mixture ethanol and dichloromethane (3:1 v/v). Crystal data for $C_{24}H_{32}N_2O_2$, Mr = 380.52, 0.46 x 0.52 x 0.54 mm^3, monoclinic, space group $P2_1$, a = 8.9726(10) Å, b = 12.2364(14) Å, c = 10.1590(11) Å, β = 96.084(2)°, *V* = 1109.1(2) Å3, Z = 2, δ_{calcd} = 1.139 g/cm^3, μ = 0.072 mm^{-1}, $2\theta_{max}$ = 26, 11639 reflections collected, 2290 independent reflections (R_{int} = 0.0259), R_1 = 0.0443 for 2290 reflections with I > 2σ(I) and *w*R_2 = 0.1186 for all data, 257 parameters, GOF = 1.21. CCDC 1519415. FAB$^+$-MS *m/z* found: 381.2541 $[M]^+$ (calcd. for $C_{24}H_{33}O_2N_2$ 381.2542). Anal. calcd C, 75.75; H, 8.48; N, 7.36. Found: C, 75.96; H, 8.68; N, 7.42.

3,3'-Diphenyl-*N,N'*-{di(propionyl)-di[(*S*)-1-phenylethyl]}ethylenediamine (3b). The product was recovered as a yellow liquid (0.09 g, 91%). $[\alpha]_D^{20}$ -185.7 (*c* 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.25 (d, *J* 7.0 Hz, 3H), 1.37 (d, *J* 7.0 Hz, 3H), 1.66 (d, *J* 7.0 Hz, 2H), 2.47 (m, 3H), 2.63 (m, 1H), 2.79 (m, 3H), 2.96 (m, 1H), 3.14 (m, 6H), 4.92 (m, 2H), 5.89 (c, *J* 7.0 Hz, 1H), 6.9 (m, 1H), 7.04 (m, 1H), 7.20 (m, 18H). ^{13}C NMR (50 MHz, $CDCl_3$) δ_c 17.3 (CH_3, C-2''), 18.1 (CH_3, C-2'), 18.9 (CH_3, C-2'''), 32.3 (CH_2, 1''a), 32.4 (CH_2, 1'a), 34.5 (CH_2, 2*E*), 35.9 (CH_2, 2*Z*), 36.3 (CH_2, 2*Z*'), 41.7 (CH_2, 3*E*), 42.1 (CH_2, 3*Z*'), 43.4 (CH_2, 3*Z*), 50.9 (CH, 1''), 54.9 (CH, 1'), 55.9 (CH, 1'''), 125.7 (Ar-CH), 125.8 (Ar-CH), 125.9 (Ar-CH), 126.5 (Ar-CH), 126.7 (Ar-CH), 126.9 (Ar-CH), 127.1 (Ar-CH), 127.5 (Ar-CH), 127.9 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.6 (Ar-CH), 139.0 (Ar-C), 140.5 (Ar-C), 140.8 (Ar-C), 140.9 (Ar-C), 171.5 (Ar-C), 172.3 (Ar-C). FAB$^+$-MS *m/z* found: 533.3176 $[M]^+$ calcd. for $C_{36}H_{41}O_2N_2$ 533.3168.

***N,N'*-{Di(benzoyl)-di[(*S*)-1-phenylethyl]}ethylenediamine (3c).** The product was isolated in form colorless crystalline powder. mp 135-137 °C; (0.86g, 98% yield). $[\alpha]_D^{20}$ -128.8 (*c* 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.28 (s a, 3H), 3.29 (s a, 2H), 5.10 (s a, 1H), 7.37 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ_c 17.7 (CH_3), 40.9 (CH_2), 57.2 (CH), 126.39 (Ar-CH), 127.1 (Ar-CH), 127.6 (Ar-CH), 128.2 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 129.4 (Ar-CH), 129.4 (Ar-CH), 137.0 (Ar-C), 140.0 (Ar-C), 172.4 (Ar-CH). FAB^+-MS *m/z* found: 477.2536 $[M]^+$ calcd. for $C_{32}H_{33}O_2N_2$ 477.2542.

Single-crystal X-ray diffraction analysis. Single–crystal X-ray diffraction studies were performed on a Bruker-APEX diffractometer with a CCD area detector ($\lambda_{MoK\alpha}$ = 0.71073 Å, monochromator: graphite). Frames were collected at *T* 293 K via *ω/φ*-rotation at 10 s per frame (SMART).[37] The measured intensities were reduced to F^2 and corrected for absorption with SADABS (SAINT-NT).[38] Corrections were made for Lorentz and polarization effects. Structure solution, refinement and data output were carried out with the SHELXTL-NT program package.[39,40] Non hydrogen atoms were refined anisotropically, while hydrogen atoms were placed in geometrically calculated positions using a riding model.
Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-**1489379-1489381**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk, website http://www.ccdc.cam.ac.uk).

Computational details. The geometries of all structures were fully optimized by using density functional theory (DFT) with the hybrid-functional B3LYP[41,42] in combination with the 6-31G(dp)[43] basis set implemented in the Gaussian 09 software package.[44] In order to characterize all structures as minima, their vibrational frequencies were calculated at the same level of theory. The Polarizable Continuum Model (PCM)[45] was used to compute energies in chloroform and DMSO with electrostatic dielectric constants, ε 4.9 and ε 46.7, respectively. This calculation was performed in the presence of a solvent by placing the solute in a cavity within the solvent reaction field via a set of overlapping spheres. Results were visualized with the Chemcraft program v1.6. The utility of the B3LYP functional for the theoretical characterization of organic systems has been widely explored in previous publications, showing good results.[46]

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