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Tetrahedron
Tetrahedron 63 (2007) 12655–12664

Synthesis and dynamics of atropisomeric (*S*)-*N*-(α-phenylethyl)benzamides

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Received 9 August 2007; revised 29 September 2007; accepted 2 October 2007
Available online 6 October 2007

Abstract—The synthesis of atropisomeric 2-substituted benzamides **2a–e**, **3a–e**, and **4a–e**, and characterization by X-ray structure analysis of **2d**, **2e**, **3c**, **3e**, **4c**, and **4e** are reported. Dynamic ^{1}H NMR spectroscopic studies of benzamides **2b–d**, **3b–d**, and **4b–d** indicate that only two of the four possible rotamers are present in solution, with population ratios ranging between 1.5:1 and 4.1:1. The measured free energy of activation to interconversion of the rotamers ranged from 12.4 to 18.9 kcal mol^{-1}. Benzamides ArCON[(*S*)-phenethyl]$_2$ (**2e**, **3e**, and **4e**), exhibited atropisomer ratios between 1.7:1 and 1:1, and free energies of interconversion of the rotamers ranged from 11.5 to 17.6 kcal mol^{-1}. The highest rotation barriers were observed for the *ortho*-nitro derivatives **2a–e**. Molecular calculations at the semiempirical level (PM3MM) gave free energies of activation for benzamides **2e** and **3e** of 23.6 and 12.4 kcal mol^{-1}, respectively, which are comparable to the experimental values.

1. Introduction

Compounds presenting chiral axes, such as BINOL and BINAP, have played an important role in the development of asymmetric catalysis and are considered to be privileged ligands.[1–3] These ligands are chiral due to restricted rotation about the central C–C bonds, whose rotational barriers are sufficiently high to allow isolation and use at high temperatures without racemization.[4–7]

In contrast to atropisomeric biaryl ligands, efforts to perform catalytic asymmetric reactions with non-biaryl atropisomers have attracted less attention. The perpendicular architecture of atropisomeric anilides, benzamides, and naphthamides effectively exert control over the formation of new stereogenic centers.[8–11] The most common route to atropisomeric anilides, benzamides, and naphthamides entails diastereoselective reactions with stoichiometric chiral auxiliaries.[12–15] Enantioselective methods to prepare such compounds, however, are emerging[16–21] and will likely inspire new investigations in this area.

One of the aims of our research is to prepare non-biaryl atropisomeric benzamides that are suitable ligands for use in asymmetric catalysis. The most significant hurdle in the application of such ligands is the preparation of chiral building blocks that contain enantioenriched atropisomers.[13,22,23] A strategy that has been successfully utilized to circumvent this synthetic challenge involves installation of a stereogenic center near an axis that exhibits hindered rotation. Ideally, the rotational barrier is not sufficiently high to allow isolation of stereochemically stable atropisomers at temperatures necessary to perform enantioselective reactions. The central chirality will influence the relative energies of the interconverting diastereomeric conformations of the atropisomers. If the bound ligand's chiral axis is positioned close to the metal center, it may have a significant impact on the enantioselectivity of reactions at the metal. In other words,

Keywords: Atropisomers; Chiral ligands; Variable temperature NMR; Semiempirical theoretical calculations.
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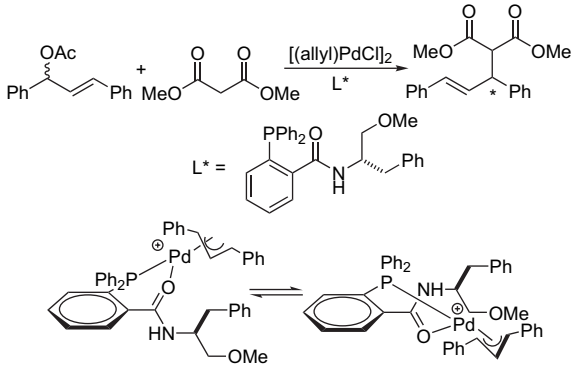
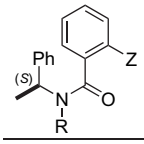
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.10.010

the central chirality can cause the atropisomeric group to preferentially adopt one of the chiral conformations and this chiral conformation can be used in the transfer of asymmetry to the substrate.[7,24–26] In their pioneering work, Mino et al. prepared chiral P/O chelating ligands containing secondary amides and a phosphine (Scheme 1).[27] Although the stereogenic center is far removed from the metal binding site, the ligated catalyst gave up to 85% enantioselectivity in the palladium catalyzed asymmetric allylation reaction. This enantioselectivity is impressive, especially when compared to the slightly lower enantioselectivity observed when a closely related PO ligand with a fixed atropisomeric amide was used in this reaction.[23]



Scheme 1.

In this work, we set out to prepare a series of N/O ligands that would bind to metals upon deprotonation. Given the importance of the (*S*)-α-phenylethylamino group in asymmetric synthesis,[28,29] we chose to use this chiral auxiliary as the source of central chirality. We report herein the synthesis of *ortho*-substituted benzamides **2a–e**, **3a–e**, and **4a–e** (Fig. 1) from secondary *N*-[(*S*)-α-phenylethyl]amines **1a–e**. The structures of benzamides **2d**, **2e**, **3c**, **3e**, **4c**, and **4e** were determined by X-ray crystallography, allowing assignment of the absolute configuration of the chiral axis in the solid state. We have also studied the dynamics of atropisomerization in these compounds, both by variable temperature ^{1}H nuclear magnetic resonance spectroscopy (VT ^{1}H NMR), and computationally using semiempirical methods (PM3MM).



2a–e; Z = NO_2
3a–e; Z = NH_2
4a–e; Z = $NHSO_2$-*p*-C_6H_4-*t*-Bu

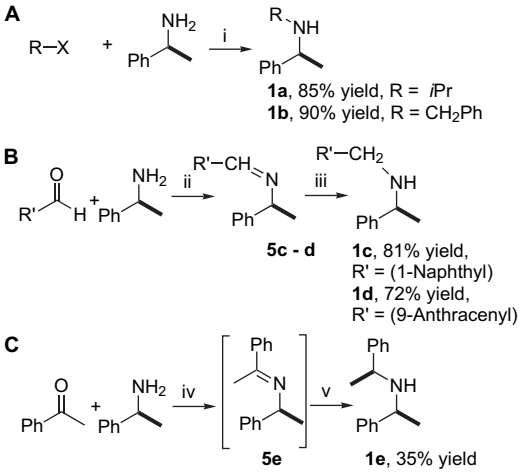
Benzamide	R
a	*i*-Pr
b	$PhCH_2$
c	(1-Naphthyl)CH_2
d	(9-Anthracenyl)CH_2
e	(*S*)-PhMeCH

Figure 1. *ortho*-Substituted *N*-[(*S*)-α-phenylethyl]benzamides.

2. Results and discussion

2.1. Synthesis of (*S*)-*N*-(α-phenylethyl)benzamides 2a–e, 3a–e, and 4a–e

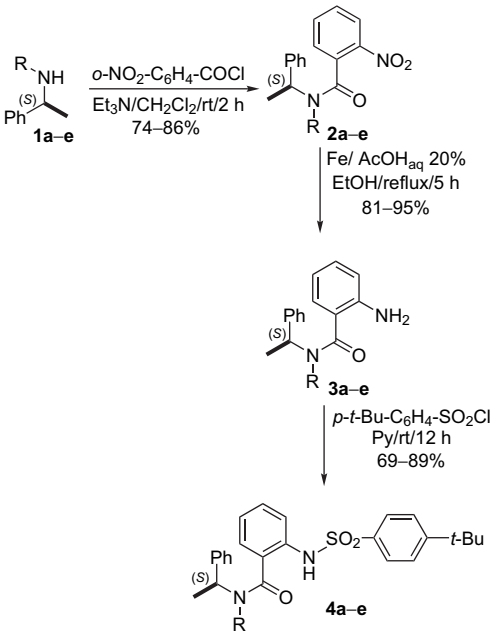
The secondary amines **1a** and **1b** were prepared from (*S*)-α-phenylethylamine by N-alkylation with 2-iodo-propane and benzyl bromide, respectively. Reactions were performed in DMPU in the presence of Na_2CO_3, according to the procedure described in the literature (85–90% yield, Scheme 2, A).[30]



Scheme 2. *Reagents and conditions*: (i) Na_2CO_3, DMPU, Δ; (ii) K_2CO_3/EtOH–H_2O (80:20), rt, 12 h; (iii) $NaBH_4$/MeOH, rt, 6 h; (iv) (1) Ti(O*i*-Pr)$_4$ (3 equiv); (2) H_2/Pd–C 10% (0.5 mol %), 12 h; (v) (1) HCl 5% aq, Δ, recrystallization; (2) NaOH 1 M.

Amines **1c**, **1d**, and **1e** were prepared from 1-naphthylaldehyde, 9-anthracenylaldehyde, and acetophenone, respectively, via the corresponding imines **5c**, **5d**, and **5e** followed by reduction. Thus, reaction of 1-naphthylaldehyde or 9-anthracenylaldehyde with (*S*)-α-phenylethylamine and K_2CO_3 in EtOH/H_2O (80:20) at room temperature afforded intermediate aldimines **5c** and **5d**. The aldimines were reduced with $NaBH_4$ in MeOH at room temperature (overall yield 72–81%, Scheme 2, B). According to the procedure described in the literature,[31] reaction of acetophenone with (*S*)-α-phenylethylamine in the presence of 3 equiv of Ti(O*i*-Pr)$_4$, followed by in situ reduction of the ketimine **5e** with H_2/Pd–C (5 mol %), afforded a diastereomeric mixture (78:22 dr). The ammonium chloride salts were formed and the (*S*,*S*)-product was obtained by fractional crystallization of the diastereomeric mixture. The free amine **1e** was liberated upon reaction with 1 M NaOH (35% overall yield, Scheme 2, C).

ortho-Nitrobenzamides **2a–e** were prepared by addition of the secondary amines **1a–e** (1 equiv) to *ortho*-nitrobenzoyl chloride (1.4 equiv) in dichloromethane in the presence of triethylamine (74–86% yield, Scheme 3). The resulting nitro derivatives **2a–e** were reduced to the corresponding anilines **3a–e** with iron powder (16 equiv) in 20% aqueous acetic acid in EtOH (81–95% yield, Scheme 3). Finally, *ortho*-(sulfonamido)benzamides **4a–e** were prepared by addition of *para-tert*-butylbenzensulfonyl chloride (2 equiv) to a solution of anilines **3a–e** (1 equiv) in pyridine at 25 °C, affording **4a–e** in 69–89% yield (Scheme 3).



Scheme 3.

Benzamides **2d**, **2e**, **3c**, **3e**, **4c**, and **4e** were crystallized and afforded X-ray quality crystals. The solid state structures were determined and are illustrated in Figure 2 (**2d**, **3c**, and **4c**) and Figure 3 (**2e**, **3e**, and **4e**). Each compound was detected in the collected crystallized material as a single diastereomer in the solid state. The configurations about the atropisomeric axes were assigned from the solid state structures as (R_a,*S*,*E*) for **2d**, **3c**, and **4c**. The configurations of **2e**, **3e**, and **4e** were assigned as (S_a,*S*,*S*), (R_a,*S*,*S*), and (S_a,*S*,*S*), respectively.

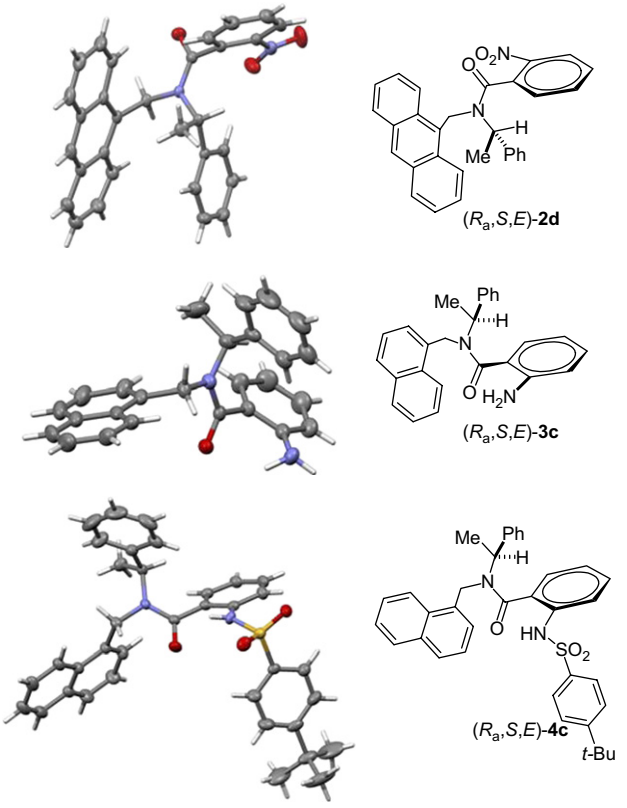


Figure 2. Solid state structures of (R_a,*S*,*E*)-*N*-(anthracen-9-ylmethyl)-2-nitro-*N*-(α-phenylethyl)benzamide **2d**, (R_a,*S*,*E*)-2-amino-*N*-(naphthalen-1-ylmethyl)-*N*-(α-phenylethyl)benzamide **3c**, and (R_a,*S*,*E*)-2-(4-*tert*-butylphenylsulfonamido)-*N*-(naphthalen-1-ylmethyl)-*N*-(α-phenylethyl)benzamide **4c** illustrating the conformations about the atropisomeric amides. Compound **4c** crystallized with acetone included in the unit cell, which is omitted for clarity.

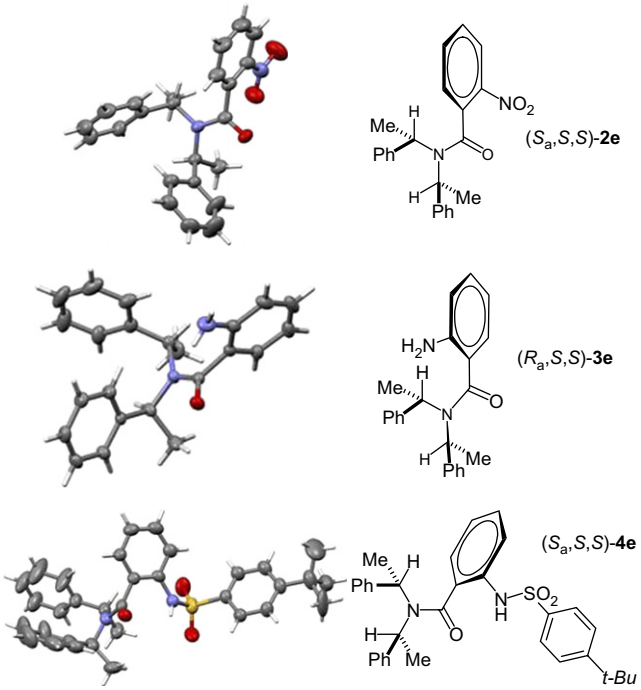


Figure 3. Solid state structures of (S_a,*S*,*S*)-2-nitro-*N*,*N*-bis-(α-phenylethyl)-benzamide **2e**, (R_a,*S*,*S*)-2-amino-*N*,*N*-bis(α-phenylethyl)benzamide **3e**, and (S_a,*S*,*S*)-2-(4-*tert*-butylphenylsulfonamido)-*N*,*N*-bis(α-phenylethyl)benzamide **4e** illustrating the conformations about the atropisomeric amides. Disorder in the *t*-Bu group of **4e** is not shown, but can be found in the structure report.

2.2. VT NMR experiments on *ortho*-substituted benzamides

With the tertiary amides in hand, we initiated studies to examine their solution dynamics. Variable temperature ^{1}H NMR spectroscopy was performed on *ortho*-substituted benzamide derivatives **2a–e**, **3a–e**, and **4a–e** to determine the number of conformers observable in solution and their relative populations. The NMR spectra of the benzamides containing *Ni*-Pr groups (**2a**, **3a**, and **4a**) were complicated due to overlapping resonances and were not amenable to our analysis.

Each of the *ortho*-substituted benzamides **2b–d**, **3b–d**, and **4b–d** potentially has four diastereomers, by a possible restriction in the rotation around the Ph–CO and NH–CO bonds. These conformers interconvert by rotation about the N–CO amide bond and/or rotation about the Ar–CO bond (Fig. 4). In contrast, rotation about the [(*S*)-phenylethyl]$_2$N–CO amide bond in **2e**, **3e**, and **4e** is degenerate and only two diastereomers are possible (Fig. 5).

To examine the efficiency with which the central chirality biases the stereochemistry of the atropisomeric axes, the

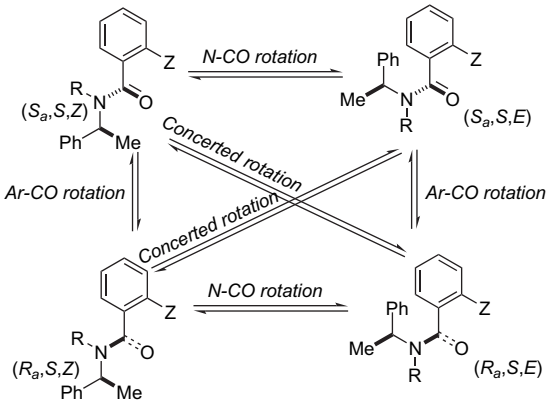


Figure 4. Conformational interconversions of **2a–d**, **3a–d**, and **4a–d**.

Figure 5. Conformational interconversions of **2e**, **3e**, and **4e**.

NMR spectra were recorded at temperatures that freeze out individual conformers. The 200 MHz ^{1}H NMR spectra of the *ortho*-nitrobenzamides exhibited resonances for two diastereomers at room temperature (Table 1, entries 1–4). The ratio of the diastereomers in DMSO-d_6 was found to range from about 1:1 for **2e** to 3:1 for **2d**. At room temperature, only a single species was observed for compounds **3b–d** and **4b–d**, suggesting that interconversion of the conformers was rapid at this temperature on the NMR timescale. The ratios of diastereomers of the *ortho*-amino- and *ortho*-sulfonylaminobenzamides were, therefore, measured in $CDCl_3$ at temperatures between −50 and −60 °C (Table 1, entries 5–12). Although there are four possible diastereomeric atropisomers for each benzamide **2b–d**, **3b–d**, and **4b–d**, we observed only two of them by VT NMR (Fig. 4). In these cases the ratio of conformers ranged from 1:1 to 1:4. The higher rotational barriers of the *ortho*-nitrobenzamides are primarily attributed to the effective size of the *ortho*-nitro group, which lies roughly in the plane of the aryl ring, over the amino and sulfonamido groups. Rotation about the Ar–CO bond probably causes simultaneous rotation of the Ar–NO_2 from the electronically preferred orientation parallel to the aromatic ring. In contrast, the bulky sulfonyl group can orient away from the amide carbonyl to avoid unfavorable interaction during the Ar–CO rotation. Another contributing factor could be stabilization of the transition state to rotation about the Ar–CO bond by formation of a hydrogen bond between the N–H of the *ortho*-substituent (H_2N– or H–N–SO_2Tol and the amide carbonyl).

Free energy of activation of interconversion of configurationally labile compounds has been investigated by means of dynamic NMR spectroscopy.[32,33] To measure the free energy of activation ($\Delta G^{\ddagger}$) by variable temperature ^{1}H NMR, the coalescence temperature method can be used. The coalescence temperature (T_c, K) is the lowest temperature at which the two rotamers merge (Table 2). The free energy of activation ($\Delta G^{\ddagger}$, kcal mol^{-1}) is derived using the Eyring equation and the rate constant (k_c, s^{-1}, Eqs. 1 and 3).[32]

$$k_c = \pi\Delta\nu/\sqrt{2} = 2.22\Delta\nu \quad (1)$$

$$\Delta G^{\ddagger} = 2.303RT_c(10.319 + \log T_c/k_c) \quad (2)$$

$$\Delta G^{\ddagger} = 4.569 \times 10^{-3}T_c(10.319 + \log T_c/k_c) \quad (3)$$

The ^{1}H NMR experiments with *ortho*-nitrobenzamides **2b–e** were conducted in DMSO-d_6. At room temperature, resonances for two diastereomers were observed. The coalescence temperatures for *ortho*-nitrobenzamides **2b–e** were reached upon heating the sample in the probe of the NMR spectrometer to temperatures between 75 and 105 °C. The measured free energies of activation ranged from 17.6 to 18.9 kcal mol^{-1} (Table 2, entries 1–4). The coalescence temperatures for *ortho*-amino- and *ortho*-sulfonylaminobenzamides **3b–e** and **4b–e** were reached on cooling samples in $CDCl_3$ between −40 and 0 °C. On the basis of these VT NMR experiments, free energies of activation were calculated for **3b–e** and **4b–e** and found to be 11.5–13.5 kcal mol^{-1} (Table 2, entries 5–12).

Table 1. Populations of diastereoisomeric atropisomers of amides **2b–e**, **3b–e**, and **4b–e**

Entry	Z	R	Solvent	T (°C)	Ratio
1, **2b**	NO_2	CH_2Ph	DMSO-d_6	+25	0.60:0.40
2, **2c**	NO_2	CH_2(1-naphthyl)	DMSO-d_6	+25	0.67:0.33
3, **2d**	NO_2	CH_2(9-anthracenyl)	DMSO-d_6	+25	0.75:0.25
4, **2e**	NO_2	(*S*)-$CHCH_3Ph$	DMSO-d_6	+25	0.56:0.44
5, **3b**	NH_2	CH_2Ph	$CDCl_3$	−50	0.73:0.27
6, **3c**	NH_2	CH_2(1-naphthyl)	$CDCl_3$	−53	0.71:0.29
7, **3d**	NH_2	CH_2(9-anthracenyl)	$CDCl_3$	−60	0.67:0.33
8, **3e**	NH_2	(*S*)-$CHCH_3Ph$	$CDCl_3$	−60	0.50:0.50
9, **4b**	$NHSO_2p$-C_6H_4-*t*-Bu	CH_2Ph	$CDCl_3$	−50	0.60:0.40
10, **4c**	$NHSO_2p$-C_6H_4-*t*-Bu	CH_2(1-naphthyl)	$CDCl_3$	−50	0.58:0.42
11, **4d**	$NHSO_2p$-C_6H_4-*t*-Bu	CH_2(9-anthracenyl)	$CDCl_3$	−60	0.65:0.35
12, **4e**	$NHSO_2p$-C_6H_4-*t*-Bu	(*S*)-$CHCH_3Ph$	$CDCl_3$	−60	0.56:0.44

Table 2. VT NMR studies of benzamides **2b–e**, **3b–e**, and **4b–e**

Entry	Solvent	δ_1 (ppm)	δ_2 (ppm)	$\Delta\nu$ (Hz)	k_c (s^{-1})	T_c (°C)	$\Delta G^{\ddagger}$ (kcal mol^{-1})[a]
1, **2b**	DMSO-d_6	1.642	1.443	39.8	88.4	105	18.9
2, **2c**	DMSO-d_6	1.694	1.473	44.2	98.1	95	18.3
3, **2d**	DMSO-d_6	7.442	7.167	55.0	122.1	85	17.6
4, **2e**	DMSO-d_6	4.847	4.710	27.4	60.8	75	17.6
5, **3b**	$CDCl_3$	1.588	1.381	41.4	91.9	−20	12.4
6, **3c**	$CDCl_3$	4.600	4.222	75.6	167.8	−10	12.6
7, **3d**	$CDCl_3$	4.830	4.714	23.2	51.5	−20	12.7
8, **3e**	$CDCl_3$	1.929	1.736	38.6	85.6	−40	11.5
9, **4b**	$CDCl_3$	3.904	3.725	35.8	79.5	0	13.5
10, **4c**	$CDCl_3$	1.304	1.265	7.8	17.3	−10	13.8
11, **4d**	$CDCl_3$	4.842	4.747	19.0	42.2	−20	12.8
12, **4e**	$CDCl_3$	1.392	1.324	13.6	30.2	−40	12.5

[a] Error±0.3 kcal mol^{-1}.

2.3. Computational calculations of bond rotation on tertiary aromatic amides

To gain further insight into the dynamic processes observed by VT NMR, we performed computations on benzamides **2e** and **3e**. These benzamides were chosen because they have very different barriers to interconversion of the diastereomeric atropisomers. Furthermore, the calculations are simplified by the equivalence of the two *N*,*N*-dialkyl groups on the amide nitrogens. The structures were calculated at the semiempirical PM3MM level, implemented in Gaussian '03.[34] The transition state for rotation of the Ar–CO bond of **3e** was found to contain a hydrogen bond between the oxygen of the carbonyl and the amino N–H. Hydrogen bond distances for the O···H and N–H bonds of 2.48 and 1.71 Å, respectively, were used.

Table 3. Relative energies of diastereomeric conformations and comparison of experimental and calculated barriers of interconversion[a]

Entry	E (S_a,*S*,*S*)	E (R_a,*S*,*S*)	$\Delta G^{\ddagger}_{exp}$ [b]	$\Delta G^{\ddagger}_{calcd}$
1, **2e**	0	1.709	17.6	23.6
2, **3e**	0.0917	0	11.5	12.4

[a] All the values are given in kcal mol^{-1}.
[b] The experimental data were obtained by VT NMR spectroscopy.

The minimum energies of the diastereoisomeric conformers were located by calculating the energies at different angles between the aryl and carbonyl groups. We observed that the lowest energy rotamer for compound **2e** had the (S_a,*S*,*S*) stereochemistry (Table 3). In contrast, the lowest energy conformation of benzamide **3e** exhibited the opposite configuration of the chiral axis (Table 3). The minimum energy conformers located computationally are the same as those found in the solid state structures of **2e** and **3e** (Fig. 6). The calculated relative energies (Table 3) are in agreement with

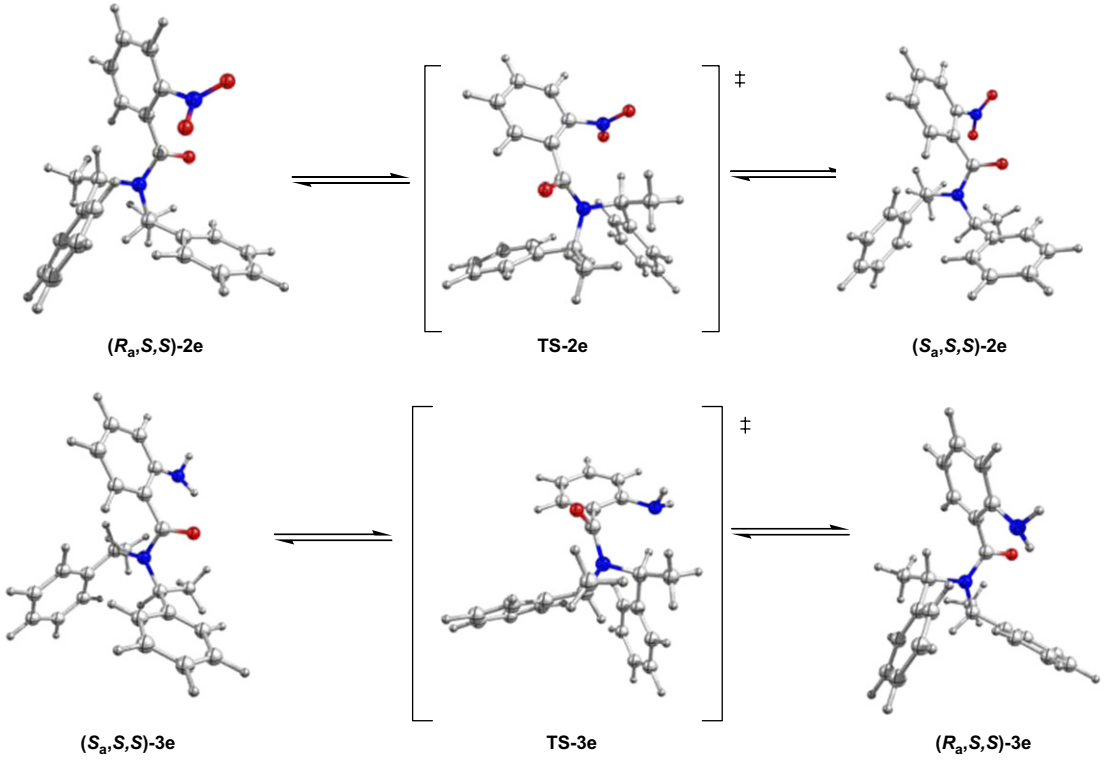


Figure 6. Calculated structures of diastereomeric conformations and transition states of benzamides **2e** and **3e**.

the populations of the diastereomers measured by ^{1}H NMR (Table 1, entries 4 and 8), which showed a preferential conformation for **2e**. The transition state structures were also calculated and the free energies of activation were found to be 23.6 and 12.4 kcal mol^{-1} for **2e** and **3e**, respectively (Table 3). The calculated free energies of activation showed a good correlation with the experimental values obtained by VT NMR.

Approach to the transition states **TS-2e** and **TS-3e** was found to occur with simultaneous rotation around the C_{aryl}–N bond of nitro and the amino groups (Fig. 6).

3. Conclusion

In summary, we prepared a series of atropisomeric benzamides (**2a–e**, **3a–e**, and **4a–e**) from secondary amines **1a–e** in overall yields of 41–72%. The dynamics of bond rotation have been evaluated by VT NMR techniques. In each case, only two of the four possible diastereoisomeric conformers were observed. We found that the rate of interconversion of the diastereoisomeric conformations is almost completely dependent on the nature of the *ortho*-substituent. The nature of the N–R group has little impact on the rotational barriers. Furthermore, simulation of rotational barriers about the Ar–CO and CO–NRR′ bonds at the PM3MM level suggests gearing of the *ortho*-substituent (NO_2 or NH_2) with rotation about the Ar–CO bond. We obtained only low to moderate diastereoselectivity and we surmise that the chiral amines are not enough stereo-differentiating to promote chiral atropisomerism. With a better understanding of the stereochemical dynamics of these atropisomeric benzamides, we are now positioned to prepare a second generation of atropisomeric benzamides and examine their use as ligands in catalytic asymmetric reactions.

4. Experimental section

4.1. General methods

NMR spectra were obtained on a 300 MHz Fourier transform spectrometer at the University of Pennsylvania and a 200 MHz at the Universidad de las Americas Puebla NMR facilities. ^{1}H NMR spectra were referenced to tetramethylsilane; ^{13}C{^{1}H} NMR spectra were referenced to residual solvent.

4.2. (*S*)-*N*-(*iso*-Propyl)-α-phenylethylamine (1a)

Amine **1a** was prepared according to the literature procedure.[30]

4.3. (*S*)-*N*-(Benzyl)-α-phenylethylamine (1b)

Amine **1b** was prepared according to the literature procedure.[30]

4.4. (*S*)-(Naphthalen-1-ylmethyl)-α-phenylethylamine (1c)[35,36]

(*S*)-α-Phenylethylamine (1.21 g, 10.0 mmol) and solid K_2CO_3 (1.38 g, 10.0 mmol) were dissolved in 13.5 mL of H_2O and 50.0 mL of EtOH. 1-Naphthaldehyde (1.56 g, 10.0 mmol) was then added and the mixture was stirred overnight at room temperature. The reaction mixture was evaporated under vacuum until the aldimine **5c** gets precipitated as a yellow solid, which was filtered and washed with a mixture of EtOH/H_2O (80:20) to provide 2.58 g of **5c** (9.90 mmol, 99% yield). A magnetically stirred suspension of **5c** (1.70 g, 6.50 mmol) in absolute methanol (30 mL) was cooled to 0 °C and treated with sodium borohydride (0.740 g, 19.5 mmol) for 15 min. The resulting mixture was stirred at rt for 6 h. The reaction was quenched by slow addition of water, washed with 25 mL of H_2O, extracted with 3×25 mL of dichloromethane, and the combined organic phase was dried with magnesium sulfate. The solvent was then removed under reduced pressure and the product **1c** (2.11 g, 81% yield) was recovered.

4.4.1. Data for (*S*)-(naphthalen-1-ylmethyl)-α-phenylethylamine (1c).[35] Afforded a pale yellow liquid (82% yield); $[\alpha]_D^{20}$ −31.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.36 (d, 3H, ^3J=6.6 Hz), 1.64 (br, 1H, NH), 3.86 (q, 1H, ^3J=6.6 Hz), 3.96 (d, 1H, ^2J=13.2 Hz), 4.05 (d, 1H, ^2J=12.8 Hz), 7.18–7.23 (m, 1H), 7.25–7.30 (m, 2H), 7.32–7.43 (m, 6H), 7.66–7.71 (m, 1H), 7.75–7.80 (m, 1H), 7.93–7.97 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz) δ=25.2, 50.0, 58.7, 123.5, 125.1, 125.3, 125.6, 125.8, 126.5, 126.7, 127.4, 128.1, 128.3, 131.4, 133.5, 135.8, 145.1; IR (film) cm^{-1}: 3318, 3048, 2966, 2907, 2849, 1596, 1508, 1490, 1449, 1396, 1367, 1302, 1261, 1202, 1161, 1114, 1079, 1020, 908, 855, 779, 697, 597, 550; HRMS-ES$^+$ *m*/*z* found 261.1516 [(M)$^+$; calcd 261.1517 for $C_{19}H_{19}N$].

4.4.2. Data for (*S*)-1-(naphthalen-1-ylmethylene)-α-phenylethylamine (5c).[36] Afforded a light yellow powder (99% yield), mp 59.8–60.0 °C; $[\alpha]_D^{20}$ − 49.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.58 (d, 3H, ^3J=6.6 Hz), 4.40 (q, 1H, ^3J=6.6 Hz), 7.14–7.17 (m, 1H), 7.26 (q, 4H, ^3J=7.4 Hz), 7.42 (t, 2H, ^3J=7.0 Hz), 7.62 (d, 1H, ^3J=8.2 Hz), 7.72 (d, 2H, ^3J=7.0 Hz), 8.72 (s, 1H), 8.97 (d, 1H, ^3J=8.6 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz) δ=25.9, 71.0, 124.2, 124.6, 125.5, 126.1, 126.3, 126.6, 128.0, 128.8, 130.4, 130.8, 131.0, 132.8, 137.9, 144.7, 158.4; IR (film) cm^{-1}: 3084, 3037, 2966, 2919, 2861, 1690, 1631, 1613, 1590, 1502, 1484, 1443, 1390, 1361, 1232, 1173, 1114, 1073, 1014, 973, 902, 832, 797, 767, 691; HRMS-ES$^+$ *m*/*z* found 259.1365 [(M)$^+$; calcd 259.1361 for $C_{19}H_{17}N$].

Secondary amine **1d** and aldimine **5d** were prepared according to the procedure outlined above.

4.4.3. Data for (*S*)-(anthracen-9-ylmethyl)-α-phenylethylamine (1d). Afforded a yellow powder (73% yield), mp 82.0 °C; $[\alpha]_D^{20}$ −37.3 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.37 (d, 3H, ^3J=6.6 Hz), 1.68 (br, 1H, NH), 4.02 (q, 1H, ^3J=6.6 Hz), 4.39 (d, 1H, ^2J=12.4 Hz), 4.49 (d, 1H, ^2J=12.2 Hz), 7.29–7.50 (m, 9H), 7.87–7.92 (m, 2H), 8.05–8.09 (m, 2H), 8.28 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz) δ=25.3, 44.6, 59.7, 123.9, 124.6, 125.7, 126.7, 126.8, 126.9, 128.3, 128.8, 129.9, 131.2, 131.5, 145.2; IR (film) cm^{-1}: 3343, 3047, 2960, 2910, 2848, 1613, 1601, 1582, 1507, 1488, 1447, 1364, 1326, 1214, 1126, 1102, 1039, 1020, 989, 958, 889, 845, 783, 759, 727, 702, 646, 603; HRMS-ES$^+$ *m*/*z* found 312.1737 [(M+H)$^+$; calcd 312.1752 for $C_{23}H_{22}N$].

4.4.4. Data for (*S*)-(anthracen-9-ylmethylene)-α-phenylethylamine (5d). Afforded a yellow powder (99% yield), mp 118.0 °C; $[\alpha]_D^{20}$ −12.4 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ=1.81 (d, 3H, ^3J=6.6 Hz), 4.84 (q, 1H, ^3J=6.6 Hz), 7.21–7.28 (m, 1H), 7.30–7.48 (m, 6H), 7.55–7.59 (m, 2H), 7.94–7.99 (m, 2H), 8.39–8.44 (m, 3H), 9.47 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ=26.0, 72.1, 124.5, 124.9, 126.3, 126.5, 126.8, 128.3, 128.5, 128.9, 129.6, 130.9, 140.5, 144.3, 158.2; IR (film) cm^{-1}: 3072, 3025, 2966, 2919, 2860, 1637, 1513, 1484, 1443, 1378, 1296, 1255, 1155, 1114, 1067, 1014, 961, 897, 867, 838, 791, 756, 732, 697, 657, 609; HRMS-ES$^+$ *m/z* found 310.1596 [(M+H)$^+$; calcd 310.1596 for $C_{23}H_{20}N$].

4.4.5. (*S*,*S*)-Bis(α-phenylethyl)amine (1e). Amine **1e** was prepared according to the literature procedure.[31]

4.5. General procedure for the preparation of 2-nitrobenzamides (2a–e)

A solution of the secondary amine **2a**–**e** (3.00 mmol), and triethylamine (6.00 mmol) in dichloromethane (10 mL) was slowly added to an ice cooled solution of 2-nitrobenzoyl chloride (4.20 mmol) in dichloromethane (10 mL). The resulting mixture was allowed to warm to rt and stirred for 2 h. The solution was quenched with 25 mL of H_2O, extracted with 3×25 mL of dichloromethane, and the combined organic phase was dried with magnesium sulfate. The solvent was then removed under reduced pressure and the 2-nitro-benzamides were recovered. The crude products were purified by flash chromatography on deactivated silica gel (Et_3N/SiO_2=2.5% v/v, hexanes/EtOAc (80:20) to afford **2a**–**e**.

4.5.1. Data for (*S*)-*N*-*iso*-propyl-2-nitro-*N*-(α-phenylethyl)benzamide (2a). Afforded white crystals (78% yield), mp 161.8–162.0 °C; $[\alpha]_D^{20}$ −112.3 (*c* 1, $CHCl_3$); ^1H NMR (DMSO-d_6, *T*=175 °C, 200 MHz) δ=1.21 (d, 3H, ^3J=7.4 Hz), 1.41 (d, 3H, ^3J=6.6 Hz), 1.76 (d, 3H, ^3J=6.6 Hz), 3.69 (m, 1H, ^3J=6.6 Hz), 4.79 (q, 1H, 7.0 Hz), 7.21–7.56 (m, 5H), 7.62–7.89 (m, 3H), 8.17 (t, 1H, ^3J=7.6 Hz); $^{13}C\{^1H\}$ NMR (DMSO-d_6, *T*=175 °C, 50 MHz) δ=17.5, 19.6, 19.7, 44.5, 53.8, 122.9, 125.2, 125.5, 126.0, 126.3, 128.0, 132.6, 170.1; IR (film) cm^{-1}: 3060, 2978, 2931, 2872, 1637, 1572, 1525, 1478, 1437, 1349, 1261, 1190, 1138, 1096, 1061, 1026, 967, 908, 850, 785, 756, 703, 662; HRMS-ES$^+$ *m/z* found 313.1540 [(M+H)$^+$; calcd 313.1552 for $C_{18}H_{21}N_2O_3$].

4.5.2. Data for (*S*)-*N*-benzyl-2-nitro-*N*-(α-phenylethyl)benzamide (2b). Afforded yellow crystals (82% yield), mp 92.0–92.3 °C; $[\alpha]_D^{20}$ −104.9 (*c* 1, $CHCl_3$); ^1H NMR (DMSO-d_6, *T*=175 °C, 200 MHz) δ=1.60 (d, 3H, ^3J=6.2 Hz), 4.23 (dd, 1H, J'=15.8 Hz, J''=2.8 Hz), 4.66 (d, 1H, ^2J=15.6 Hz), 5.32 (br, 1H), 7.16–7.34 (m, 10H), 7.46–7.50 (m, 1H), 7.55–7.70 (m, 2H), 8.09–8.13 (m, 1H); $^{13}C\{^1H\}$ NMR (DMSO-d_6, *T*=175 °C, 50 MHz) δ=17.1, 47.1, 55.0, 122.7, 125.0, 125.6, 125.9, 126.2, 126.5, 126.6, 128.2, 131.3, 132.2, 136.3, 138.5, 143.9, 165.6; IR (film) cm^{-1}: 3060, 3025, 2978, 2931, 2872, 1637, 1572, 1525, 1490, 1437, 1408, 1343, 1261, 1202, 1143, 1073, 1026, 991, 961, 914, 850, 785, 750, 697; HRMS-ES$^+$ *m/z* found 361.1568 [(M+H)$^+$; calcd 361.1552 for $C_{22}H_{21}N_2O_3$].

4.5.3. Data for (*S*)-*N*-(naphthalen-1-ylmethyl)-2-nitro-*N*-(α-phenylethyl)benzamide (2c). Afforded a pale yellow foamy solid (86% yield), mp 97.8–98.0 °C; $[\alpha]_D^{20}$ −71.0 (*c* 1, $CHCl_3$); ^1H NMR (DMSO-d_6, *T*=175 °C, 200 MHz) δ=1.62 (d, 3H, ^3J=4.8 Hz), 4.92 (d, 1H, ^2J=16.6 Hz), 5.17 (d, 1H, ^2J=17.2 Hz), 5.34 (br, 1H), 7.21–7.85 (m, 15H), 8.08 (br, 1H); $^{13}C\{^1H\}$ NMR (DMSO-d_6, *T*=185 °C, 50 MHz) δ=17.2, 44.1, 55.5, 121.0, 122.8, 123.3, 123.5, 123.7, 124.3, 125.6, 125.8, 126.4, 126.6, 126.8, 128.3, 129.0, 130.2, 131.3, 131.7, 132.2, 138.5, 143.8, 165.8; IR (film) cm^{-1}: 3060, 2990, 2931, 2872, 1631, 1572, 1525, 1484, 1443, 1408, 1378, 1343, 1314, 1261, 1208, 1149, 1073, 1020, 991, 850, 785, 756, 703; HRMS-ES$^+$ *m/z* found 433.1541 [(M+Na)$^+$; calcd 433.1528 for $C_{26}H_{22}N_2O_3Na$].

4.5.4. Data for (R_a,*S*,*E*)-*N*-(anthracen-9-ylmethyl)-2-nitro-*N*-(α-phenylethyl)benzamide (2d). Afforded a pale yellow solid (74% yield), mp 161.8–162 °C; $[\alpha]_D^{20}$ −83.9 (*c* 1, $CHCl_3$); ^1H NMR (DMSO-d_6, *T*=165 °C, 200 MHz) δ=1.34 (br, 3H), 4.95 (br, 1H), 5.54 (d, 1H, ^2J=15.0 Hz), 5.74 (d, 1H, ^2J=15.0 Hz), 7.00–7.08 (m, 5H), 7.34–7.60 (m, 7H), 7.98–8.12 (m, 5H), 8.43 (s, 1H); $^{13}C\{^1H\}$ NMR (DMSO-d_6, *T*=165 °C, 50 MHz) δ=16.0, 40.7, 54.5, 122.5, 122.7, 123.2, 124.4, 125.1, 125.4, 125.8, 126.1, 126.2, 126.6, 127.2, 128.0, 129.3, 129.4, 131.5, 132.1, 137.9, 143.4, 165.6; IR (film) cm^{-1}: 3048, 2989, 1631, 1572, 1531, 1448, 1417, 1345, 1252, 1219, 1159, 1028, 991, 889, 854, 788, 734, 698, 624; recrystallized from hexanes/EtOAc (1:1); yellow prism, 0.60×0.38×0.28 mm^3, $C_{30}H_{24}N_2O_3$. Monoclinic, $P2_1$, *a*=12.0572(12), *b*=6.1558(13), *c*=15.8216(19) Å, β=95.225(7)°, *Z*=2, ρ_{calcd}=1.308 g cm^{-3}. A set of 6838 reflections was collected at *T*=296(1) K using Mo Kα radiation (λ=0.71073 Å, Bruker P4 diffractometer), corresponding to $2\theta_{max}$=55°. For the refinement of 318 parameters, 2923 independent reflections (Friedel pairs merged, R_{int}=0.0189) were used, without neither restraints nor constraints (SHELXTL 5.10 package).[37] All H atoms were placed in idealized positions and refined using a standard riding model. The absolute configuration of the chiral center was assigned as *S*-C11. Final *R* indices: R_1=0.0337 for 2509 reflections with $I>2\sigma(I)$ and wR_2=0.0923 for all data. CCDC deposition number: 601708. Structure factors and raw files are available on request to authors. HRMS-ES$^+$ *m/z* found 483.1698 [(M+Na)$^+$; calcd 483.1685 for $C_{30}H_{24}N_2O_3Na$].

4.5.5. Data for (S_a,*S*,*S*)-2-nitro-*N*,*N*-bis(α-phenylethyl)-benzamide (2e). Afforded colorless crystals (80% yield), mp 150.0–151.0 °C; $[\alpha]_D^{20}$ −48.9 (*c* 1, $CHCl_3$); ^1H NMR (DMSO-d_6, *T*=165 °C, 200 MHz) δ=1.56 (br, 1H), 1.80 (d, 5H, ^3J=6.6 Hz), 4.85 (br, 2H), 7.16 (d, ^3J=1.6 Hz, 8H), 7.25–7.55 (m, 3H), 7.70 (m, 1H), 7.82 (t, 1H, ^3J=7.8 Hz), 8.19 (d, 1H, ^3J=8.0 Hz); $^{13}C\{^1H\}$ NMR (DMSO-d_6, *T*=165 °C, 50 MHz) δ=17.6, 18.0, 54.7, 123.2, 125.3, 125.8, 125.9, 126.1, 126.3, 126.5, 126.6, 128.3, 132.1, 132.7, 132.9, 139.1, 164.4; IR (film) cm^{-1}: 3062, 3031, 2980, 2942, 1639, 1574, 1527, 1496, 1430, 1346, 1319, 1280, 1260, 1204, 1156, 1086, 1008, 1024, 964, 876, 853, 791, 753, 697, 666; recrystallized from hexanes/Et_2O (1:1); colorless block, 0.60×0.38×0.36 mm^3, $C_{23}H_{22}N_2O_3$. Orthorhombic, $P2_12_12_1$, *a*=8.669(4), *b*=12.327(7), *c*=18.410(8) Å, *Z*=4, ρ_{calcd}=1.264 g cm^{-3}.

A set of 4549 reflections was collected at T=296(2) K using Mo Kα radiation (λ=0.71073 Å, Siemens P4 diffractometer), corresponding to $2\theta_{max}$=52°. For the refinement of 256 parameters, 50 independent reflections 2276 (Friedel pairs merged, R_{int}=0.0651) were used, without neither restraints nor constraints (SHELXTL 5.10 package).[37] All H atoms were placed in idealized positions and refined using a standard riding model. The absolute configurations of the chiral centers were assigned as *S*-C8, *S*-C16 assuming an unchanged configuration for the chiral starting material during the synthesis. Final R indices: R_1=0.0511 for 1432 reflections with $I>2\sigma(I)$ and wR_2=0.1649 for all data. CCDC deposition number: 623376. Structure factors and raw files are available on request to authors. HRMS-ES$^+$ m/z found 375.1713 [(M+H)$^+$; calcd 375.1709 for $C_{23}H_{23}N_2O_3$].

4.6. General procedure for the preparation of 2-aminobenzamides (3a–e)

A solution of the 2-nitrobenzamides **2a**–**e** (1.00 mmol) and 5% acetic acid solution (17 mL) in EtOH/H_2O (80:20) was treated with iron powder (16.0 mmol). The resulting solution was then heated under reflux for 5 h with vigorous stirring. The mixture was cooled in an ice bath followed by addition of 20% aqueous $NaHCO_3$ (20 mL) and dichloromethane (50 mL). The resulting mixture was filtered over Celite, extracted with 3×25 mL of dichloromethane, and the combined organic phase was dried over magnesium sulfate. After filtration the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on deactivated silica gel (Et_3N/SiO_2=2.5% v/v, hexanes/EtOAc (80:20)) to afford the products **3a**–**e**.

4.6.1. Data for (*S*)-2-amino-*N*-*iso*-propyl-*N*-(α-phenylethyl)benzamide (3a). Afforded a colorless liquid (95% yield); $[\alpha]_D^{20}$ −140.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.05 (d, 3H, ^3J=6.7 Hz), 1.38 (d, 3H, ^3J=6.8 Hz), 1.60 (d, 3H, ^3J=6.9 Hz), 3.40 (br, 1H), 3.78 (br, 2H), 4.91 (q, 1H, ^3J=6.9 Hz), 6.65–6.71 (m, 2H), 7.05–7.09 (m, 2H), 7.17–7.18 (m, 1H), 7.19–7.23 (m, 2H), 7.26–7.33 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ=17.8, 20.5, 21.3, 48.3, 57.1, 117.2, 118.2, 126.2, 127.5, 127.7, 128.4, 130.0, 144.4, 170.9; IR (film) cm^{-1}: 3436, 3342, 3213, 3049, 2966, 2931, 2872, 1619, 1590, 1490, 1455, 1361, 1325, 1261, 1196, 1178, 1138, 1096, 1026, 967, 908, 855, 820, 785, 756, 697, 644; HRMS-ES$^+$ m/z found 305.1639 [(M+Na)$^+$; calcd 305.1630 for $C_{18}H_{22}N_2ONa$].

4.6.2. Data for (*S*)-2-amino-*N*-benzyl-*N*-(α-phenylethyl)-benzamide (3b). Afforded a colorless liquid (81% yield); $[\alpha]_D^{20}$ −127.7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.46 (d, 3H, ^3J=7.0 Hz), 3.91 (d, 1H, ^2J=15.4 Hz), 4.30 (br, 2H, NH), 4.84 (d, 1H, ^2J=15.0 Hz), 5.44 (br, 1H), 6.62–6.69 (m, 2H), 7.03–7.29 (m, 12H); ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz) δ=18.7, 46.3, 56.1, 116.6, 117.1, 120.6, 126.3, 126.4, 126.7, 126.9, 127.1, 127.8, 128.1, 130.0, 138.4, 139.6, 144.8, 171.3; IR (film) cm^{-1}: 3448, 3229, 3064, 3019, 2970, 2933, 1609, 1590, 1483, 1442, 1397, 1294, 1156, 1025, 751, 686; HRMS-ES$^+$ m/z found 353.1639 [(M+Na)$^+$; calcd 353.1631 for $C_{22}H_{22}N_2ONa$].

4.6.3. Data for (R_a,*S*,*E*)-2-amino-*N*-(naphthalen-1-ylmethyl)-*N*-(α-phenylethyl)benzamide (3c). Afforded a colorless solid (88% yield); $[\alpha]_D^{20}$ −52.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.43 (d, 3H, ^3J=7.0 Hz), 4.39–4.44 (m, 3H), 5.40 (d, 1H, ^2J=16.0 Hz), 5.57 (q, 1H, ^3J=6.2 Hz), 6.66–6.75 (m, 2H), 7.14 (t, 1H, ^3J=7.2 Hz), 7.21–7.47 (m, 9H), 7.71 (t, 1H, ^3J=4.8 Hz), 7.78–7.84 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz) δ=18.5, 44.3, 57.3, 116.9, 117.3, 120.6, 122.5, 123.7, 125.0, 125.3, 125.7, 126.6, 127.0 127.2, 127.3, 128.3, 128.5, 130.3, 133.3, 139.9, 145.3, 171.7; IR (film) cm^{-1}: 3412, 3331, 3248, 3048, 2978, 2931, 1613, 1596, 1490, 1449, 1408, 1308, 1261, 1149, 1073, 1026, 996, 791, 756, 650; recrystallized from hexanes/EtOAc (1:1); colorless prism, 0.6×0.4×0.2 mm^3, $C_{26}H_{24}N_2O$. Monoclinic, $P2_1$, a=9.2527(11), b=10.607(3), c=10.9807(12) Å, β=90.579(8)°, Z=2, ρ_{calcd}=1.173 g cm^{-3}. A set of 2664 reflections was collected at T=296(1) K using Mo Kα radiation (λ=0.71073 Å, Bruker P4 diffractometer), corresponding to $2\theta_{max}$=50°. For the refinement of 272 parameters, 2007 independent reflections (Friedel pairs merged, R_{int}=0.0123) were used, without neither restraints nor constraints (SHELXTL 5.10 package).[37] H atoms of the NH_2 functionality were found in a difference map and refined with free coordinates and isotropic displacement parameters. Other H atoms were placed in idealized positions and refined using a standard riding model. The absolute configuration of the chiral center was assigned as *S*-C11. Final R indices: R_1=0.0411 for 1689 reflections with $I>2\sigma(I)$ and wR_2=0.1166 for all data. CCDC deposition number: 601709. Structure factors and raw files are available on request to authors. HRMS-ES$^+$ m/z found 403.1774 [(M+Na)$^+$; calcd 403.1786 for $C_{26}H_{24}N_2ONa$].

4.6.4. Data for (*S*)-2-amino-*N*-(anthracen-9-ylmethyl)-*N*-(α-phenylethyl)benzamide (3d). Afforded a yellow solid (95% yield), mp 80.0–80.1 °C; $[\alpha]_D^{20}$ −144.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ=0.64 (d, 3H, ^3J=7.0 Hz), 4.47 (br, 2H, NH), 5.07–5.14 (m, 2H), 6.23 (d, 1H, ^2J=15.4 Hz), 6.59–6.74 (m, 2H), 6.94–6.98 (m, 2H), 7.06–7.20 (m, 5H), 7.27–7.42 (m, 4H), 7.89–7.93 (m, 4H), 8.32 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz) δ=17.7, 39.7, 57.1, 116.7, 117.3, 121.1, 124.2, 124.6, 125.7, 126.9, 127.0, 127.7, 128.0, 128.7, 129.2, 130.2, 130.5, 131.0, 139.0, 145.1, 172.0; IR (film) cm^{-1}: 3454, 3357, 3052, 2977, 1733, 1615, 1587, 1493, 1449, 1410, 1334, 1253, 1158, 1027, 992, 887, 843, 789, 731; HRMS-ES$^+$ m/z found 453.1922 [(M+Na)$^+$; calcd 453.1943 for $C_{30}H_{26}N_2ONa$].

4.6.5. Data for (R_a,*S*,*S*)-2-amino-*N*,*N*-bis(α-phenylethyl)-benzamide (3e). Afforded colorless crystals (82% yield), mp 115.0–116.0 °C; $[\alpha]_D^{20}$ −43.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.78 (d, 6H, ^3J=7.4 Hz) 3.92 (br, 2H, NH), 4.88 (q, 2H, ^3J=7.0 Hz), 6.67–6.76 (m, 2H); 7.07–7.15 (m, 12H) ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz) δ=19.3, 56.0, 116.5, 117.6, 123.2, 125.7, 126.8, 127.7, 129.4, 140.2, 143.8, 169.9; IR (film) cm^{-1}: 3444, 3348, 3060, 3029, 2977, 2939, 1616, 1494, 1452, 1430, 1320, 1206, 1156, 1096, 1024, 966, 884, 793, 749, 697; recrystallized from hexanes/Et_2O; colorless prism, 0.6×0.4×0.4 mm^3, $C_{23}H_{24}N_2O$. Monoclinic, $P2_1$, a=8.6721(17), b=9.555(2), c=12.031(2) Å, β=104.235(8)°, Z=2, ρ_{calcd}=1.184 g cm^{-3}. A set of 3847 reflections was collected at T=296(1) K using Mo Kα radiation (λ=0.71073 Å, Siemens

P4 diffractometer), corresponding to $2\theta_{max}$=49.98°. 1803 independent reflections (Friedel pairs merged, R_{int}=0.0241) were used for the refinement of 243 parameters, without neither restraints nor constraints (SHELXTL 5.10 package).[37] H atoms of the NH_2 functionality were found in a difference map and refined with free coordinates and isotropic displacement parameters. Other H atoms were placed in idealized positions and refined using a standard riding model. The absolute configurations of the chiral centers were assigned as *S*-C11, *S*-C19. Final *R* indices: R_1=0.0314 for 1737 reflections with $I>2\sigma(I)$ and wR_2=0.0861 for all data. CCDC deposition number: 623377. HRMS-ES$^+$ *m/z* found 367.1783 [(M+Na)$^+$; calcd 367.1786 for $C_{23}H_{24}N_2ONa$].

4.7. General procedure for preparation of 2-(4-*tert*-butylphenylsulfonamido)benzamides (4a–e)

para-*tert*-Butylbenzensulfonyl chloride (0.200 mmol) was added to a solution of **3a–e** (0.100 mmol) in pyridine (2 mL). The mixture was then stirred overnight at room temperature and the pyridine was removed under high vacuum. Aqueous HCl (0.20 M, 15 mL) was added to the residue, which was then extracted with 3×25 mL of dichloromethane and the combined organic phase was dried with magnesium sulfate. The solvent was then removed under reduced pressure. The crude product was purified by flash chromatography on deactivated silica gel (Et_3N/SiO_2=2.5% v/v, hexanes/EtOAc (91:9)) to afford the products **4a–e**.

4.7.1. Data for (*S*)-2-(4-*tert*-butylphenylsulfonamido)-*N*-*iso*-propyl-*N*-(α-phenylethyl)benzamide (4a). Afforded pale yellow crystals (69% yield), mp 78.3–78.5 °C; $[\alpha]_D^{20}$ −76.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.17 (d, 3H, ^3J=6.5 Hz), 1.26 (d, 3H, ^3J=6.0 Hz), 1.31 (s, 9H), 1.63 (br, 3H), 3.58 (br, 1H), 4.87 (br, 1H), 7.03 (t, 1H, ^3J=7.4 Hz), 7.22–7.36 (m, 6H), 7.48 (d, 2H, ^3J=8.6 Hz), 7.56 (d, 2H, ^3J=8.0 Hz), 7.86 (d, 2H, ^3J=8.0 Hz), 8.28 (br, 1H, NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ=18.2, 20.7, 21.5, 31.2, 35.3, 50.0, 123.4, 126.4, 127.2, 127.5, 128.7, 130.5, 136.1, 137.7, 156.9; IR (film) cm^{-1}: 3272, 3060, 2966, 2872, 1613, 1594, 1484, 1443, 1396, 1326, 1273, 1161, 1114, 1085, 1014, 926, 837, 756, 697, 620; HRMS-ES$^+$ *m/z* found 501.2196 [(M+Na)$^+$; calcd 501.2188 for $C_{28}H_{34}N_2O_3NaS$].

4.7.2. Data for (*S*)-*N*-benzyl-2-(4-*tert*-butylphenylsulfonamido)-*N*-(α-phenylethyl)benzamide (4b). Afforded a yellow powder (70% yield), mp 80.2–80.5 °C; $[\alpha]_D^{20}$ −85.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.28 (s, 9H), 1.50 (d, 3H, ^3J=6.6 Hz), 3.64 (m, 1H), 3.93 (d, 1H, ^2J=15.8 Hz), 5.38 (br, 1H), 6.96 (m, 1H), 7.13–7.38 (m, 14H), 7.55 (d, 1H, ^3J=7.6 Hz), 7.74–7.79 (m, 2H), 8.42 (br, 1H, NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz) δ=19.3, 31.9, 35.9, 49.8, 57.8, 119.9, 122.8, 125.8, 126.6, 126.8, 127.6, 128.2, 128.5, 130.6, 135.9, 136.6, 137.6, 139.3, 156.0, 170.2; IR (film) cm^{-1}: 3272, 3049, 3025, 2954, 2872, 1619, 1596, 1490, 1449, 1402, 1331, 1279, 1202, 1161, 1085, 920, 750, 697, 620; HRMS-ES$^+$ *m/z* found 549.2205 [(M+Na)$^+$; calcd 549.2188 for $C_{32}H_{34}N_2O_3NaS$].

4.7.3. Data for (R_a,*S*,*E*)-2-(4-*tert*-butylphenylsulfonamido)-*N*-(naphthalen-1-ylmethyl)-*N*-(α-phenylethyl)-benzamide (4c). Afforded a yellow powder (89% yield), mp 88.2–88.3 °C; $[\alpha]_D^{20}$ −21.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.22 (s, 9H) 1.38–1.43 (m, 3H), 4.43 (d, 1H, ^2J=16.8 Hz), 5.40 (br, 1H), 6.62–6.71 (m, 1H), 7.17–7.41 (m, 15H), 7.41–7.67 (m, 4H), 8.51 (br, 1H, NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ=18.3, 29.9, 31.2, 35.3, 58.6, 117.7, 123.2, 125.5, 126.0, 126.2, 126.4, 127.2, 127.4, 127.6, 127.8, 127.9, 128.2, 128.8, 129.1, 131.3, 132.7, 133.8, 137.3, 140.1, 156.9, 171.2; IR (film) cm^{-1}: 3272, 3060, 2966, 2872, 1619, 1602, 1490, 1449, 1396, 1337, 1267, 1208, 1161, 1108, 1090, 1020, 920, 791, 756, 697, 620; recrystallized from hexanes/acetone (2:1); colorless plate, 0.60×0.38×0.06 mm^3, $C_{36}H_{36}N_2O_3S$ $(C_3H_6O)_{1.5}$. Monoclinic, $P2_1$, a=14.1816(19), b=9.4551(17), c=15.476(3) Å, β=106.429(15)°, Z=2, ρ_{calcd}=1.108 g cm^{-3}. A set of 9391 reflections was collected at T=296(1) K using Mo Kα radiation (λ=0.71073 Å, Bruker P4 diffractometer), corresponding to $2\theta_{max}$=50°. Raw data were corrected for a significant intensity decay of ca. 16% suffered by the sample during data collection, and absorption effects. 3733 independent reflections (Friedel pairs merged, R_{int}=0.0482) were used for the refinement of 455 parameters, corresponding to a model including restrained geometry for the solvent molecules (SHELXTL 5.10 package).[37] H atoms were placed in idealized positions and refined using a standard riding model. The absolute configuration of the chiral center was assigned as *S*-C11. Final *R* indices: R_1=0.0741 for 2522 reflections with $I>2\sigma(I)$ and wR_2=0.1822 for all data. CCDC deposition number: 601710. Structure factors and raw files are available on request to authors. HRMS-ES$^+$ *m/z* found 599.2366 [(M+Na)$^+$; calcd 599.2344 for $C_{36}H_{36}N_2O_3NaS$].

4.7.4. Data for (*S*)-*N*-(anthracen-9-ylmethyl)-2-(4-*tert*-butylphenylsulfonamido)-*N*-(α-phenylethyl)benzamide (4d). Afforded a yellow powder (77% yield), mp 116.0–116.5 °C; $[\alpha]_D^{20}$ −127.6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ=0.61(d, 3H, ^3J=6.5 Hz), 1.22 (s, 9H), 4.96 (q, 1H, ^3J=6.5 Hz), 5.21 (d, 1H, ^2J=14.5 Hz), 6.08 (d, 1H, ^2J=14.5 Hz); 6.98–7.03 (m, 3H), 7.23–7.33 (m, 6H), 7.47–7.58 (m, 8H), 7.91–7.02 (m, 4H), 8.43 (s, 1H), 8.65 (br, 1H, NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ=17.1, 29.9, 31,2, 35.3, 56.9, 118.8, 122.8, 124.1, 124.9, 125.2, 126.5, 126.7, 127.1, 127.2, 127.5, 128.3, 128.7, 129.4, 131.1, 131.2, 131.5, 136.9, 137.3, 139.2, 157.0, 171.5; IR (film) cm^{-1}: 3327, 3056, 3023, 2966, 2872, 1613, 1539, 1493, 1449, 1399, 1334, 1254, 1169, 1113, 1082, 1027, 993, 925, 834, 755, 733, 699; HRMS-ES$^+$ *m/z* found 649.2532 [(M+Na)$^+$; calcd 649.2501 for $C_{40}H_{38}N_2O_3NaS$].

4.7.5. Data for (S_a,*S*,*S*)-2-(4-*tert*-butylphenylsulfonamido)-*N*,*N*-bis(α-phenylethyl)benzamide (4e). Afforded colorless crystals (79% yield), mp 153.0–154.0 °C; $[\alpha]_D^{20}$ −38.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.31 (s, 9H), 1.73 (d, 6H, ^3J=7.0 Hz), 4.91 (q, 2H, ^3J=6.6 Hz), 7.00–7.04 (m, 2H), 7.08–7.17 (m, 4H), 7.19–7.28 (m, 8H), 7.42–7.48 (m, 2H), 7.77–7.82 (m, 2H), 8.60 (br, 1H, NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz) δ=19.6, 31.7, 35.8, 56.4, 119.8, 122.9, 126.0, 126.1, 126.7, 127.2, 127.3, 128.0, 129.9, 135.2, 137.1, 139.6, 156.0, 168.6; IR (film) cm^{-1}: 3060, 3031, 2965, 2869, 1598, 1493, 1451, 1435, 1324, 1281, 1203, 1166, 1113, 1087, 1024, 968, 925, 792, 757, 698; recrystallized from hexanes/Et_2O; colorless irregular, 0.6×0.6×0.4 mm^3, $C_{33}H_{36}N_2O_3S$. Tetragonal, $P4_12_12$,

a=13.3920(13), b=13.3920(13), c=34.679(4) Å, Z=8, ρ_{calcd}=1.155 g cm^{-3}. A set of 10,777 reflections was collected at T=296(1) K using Mo Kα radiation (λ= 0.71073 Å, Siemens P4 diffractometer), corresponding to $2\theta_{max}$=50.02°. For the refinement of 388 parameters, 5301 independent reflections (R_{int}=0.0670) were used (SHELXTL 5.10 package).[37] H atoms were placed in idealized positions and refined using a standard riding model. The *t*-Bu group is strongly disordered and was modeled with two positions for each methyl group. The absolute configurations of the chiral centers were assigned as *S*-C11, *S*-C19, and confirmed by refinement of a Flack parameter, x=0.08(17), based on non-merged Friedel pairs. Final R indices: R_1=0.0637 for 2908 reflections with $I>2\sigma(I)$ and wR_2=0.1900 for all data. CCDC deposition number: 623378. Structure factors and raw files are available on request to authors. HRMS-ES$^+$ m/z found 563.2350 [(M+Na)$^+$; calcd 563.2344 for $C_{33}H_{36}N_2O_3NaS$].

Acknowledgements

We thank CONACYT, Consejo Nacional de Ciencia y Tecnología (Project No. V39500-Q). C.A.P. thanks the Petroleum Research Fund (Summer Scholar Grant No. 41805-AC-1), and G.H. thanks CONACYT Grant No 144893. P.J.W. acknowledges the US National Science Foundation (CHE-0615210) for support of this work.

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