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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 998–1004

Experimental and theoretical studies on the asymmetric cyanosilylation of C_2-symmetric hydrazones

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Received 29 February 2008; accepted 20 March 2008

Abstract—The Et_2AlCl-promoted asymmetric cyanosilylation of (2*S*,5*S*)-1-amino-2,5-diphenylpyrrolidine-derived aliphatic hydrazones affords the corresponding hydrazino nitriles with high diastereoselectivity (dr 91:9 to >99:1). The resolving properties of the auxiliary allowed the isolation of the adducts as single diastereoisomers (dr >99:1) in good yields (80–84%) after chromatography. Ab initio MO calculations indicated that the formation of the hydrazone-promoter complex inhibits n→π conjugation and increases the nucleophilicity of the dialkylamino nitrogen, enabling the basic activation of TMSCN. The calculated geometries for these complexes show the shielding of the *Si* face of the C=N bond by one of the phenyl groups in the auxiliary, providing an explanation for the observed absolute configuration.

1. Introduction

The Strecker reaction is an industrially relevant reaction useful for the synthesis of α-amino nitriles and derivatives thereof.[1] A number of efficient diastereoselective Strecker syntheses based on diverse chiral auxiliaries and/or chiral substrates have been described. More recently, investigations have led to efficient enantioselective metal Lewis acid-catalyzed processes, as well as a number of successful asymmetric organocatalytic approaches.[2] However, one of the limitations of the Strecker reaction is related to the difficult preparation and storage of the imines, particularly in the aliphatic series, due to the poor stability of such substrates, in part associated to the formation of enamine tautomers and their subsequent transformations.

Over the last few years, our research group has been investigating the chemistry of aldehyde *N,N*-dialkylhydrazones and their use in asymmetric synthesis. These compounds exhibit hybrid properties between those of imines and enamines, constituting a singular case of ambiphilic reactivity that can be exploited in different contexts. For instance, *N,N*-dialkylhydrazones have been used as nucleophilic, d^1 reagents for the enantioselective formylation and cyanation of a wide range of electrophilic substrates,[3] as chiral ligands in asymmetric catalysis,[4] as stable imine surrogates in Mannich-type addition of ketene silyl acetals and thioacetals,[5] and in asymmetric Staudinger-like cycloadditions.[6] The higher stability and lower tendency to tautomerize of aliphatic *N,N*-dialkylhydrazones with respect to simple imines were found to be the key characteristics for a qualitatively better performance in this last imine-type reactivity. These facts and the availability of several hydrazones containing tunable chiral auxiliaries prompted us to further explore the usefulness of these compounds as *N*-amino-substituted imines in Strecker-type cyanosilylation reaction. The use of hydrazones as substrates in this reaction is of particular interest for the synthesis of α-hydrazino acids, valuable precursors of conformationally restricted,[7,8] protease-resistant[9] peptidomimetics. Additionally, cyclic α-hydrazino acids such as piperazic acids are present in several bioactive peptides, and constitute useful intermediates in medicinal chemistry.[10] In spite of

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doi:10.1016/j.tetasy.2008.03.020

the above remarks, there are few examples reported for the synthesis of enantiomerically pure α-hydrazino acids, essential for biological studies.[11]

The use of *N,N*-dialkylhydrazones as starting materials in the Strecker synthesis leading to α-hydrazino nitriles has scarcely been studied. The stereoselective addition of trimethylsilyl cyanide (TMSCN) to chiral hydrazones was first described by Kim using (*S*)-1-amino-2-methoxymethylindoline aldehyde hydrazones,[12] and more recently by Enders using hydrazones derived from (*S*)-1-amino-2-methoximethylpyrrolidine (SAMP).[13] In both cases, the corresponding α-hydrazino nitriles were obtained in good yields and diastereoselectivities (de 88–96%), but always as mixtures of diastereoisomers.

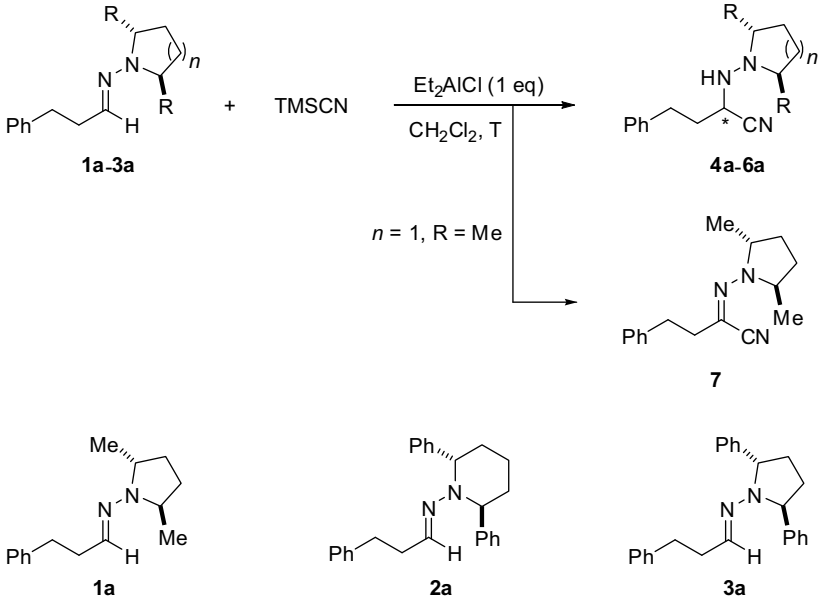
Herein we report the results collected by using (2*S*,5*S*)-2,5-diphenylpyrrolidine as a suitable auxiliary in the diastereoselective Et_2AlCl–mediated addition of TMSCN to hydrazones **3**, together with theoretical considerations providing an explanation for the high inductions achieved with this auxiliary and for the observed absolute configuration.

2. Results and discussion

Hydrazones derived from C_2-symmetric *N,N*-dialkylhydrazines were chosen as substrates in order to circumvent any consideration related to the loss of a suitable chiral environment associated with free rotation around the N–N bond. It was also considered that the geometry of such auxiliaries have been found to effect excellent stereocontrol in different reactions such as asymmetric Diels–Alder cycloadditions of 1-amino dienes,[14] radical additions to methacrylamides,[15] asymmetric thio-Claisen rearrangements,[16] α-hydrazination of α,β-unsaturated amides[17] and 1,3-dipolar cycloadditions.[18] Moreover, it should also be noted that 2,5-diphenylpyrrolidine has found application as a highly selective organocatalyst in the α-halogenation of aldehydes,[19] where the reactive enamine intermediates are isoelectronic with the hydrazones used in this study.

Initial experiments were performed using dihydrocinnamaldehyde-derived C_2-symmetric *N,N*-dialkylhydrazones **1a**–**3a** as model reactants and TMSCN as the cyanide source. Reactivity screening revealed that the best results correspond to reactions performed in dry CH_2Cl_2 using Et_2AlCl as a Lewis acid promoter (Scheme 1). One of the expected effects of the substitution at C-2 and C-5(6) is the steric inhibition of the planar conformations required for an efficient n→π conjugation in the N–N=C system. Such a steric effect is therefore expected to increase the electrophilicity of the substrate, while some stabilizing effect could be maintained.[20] In the six-membered hydrazone **2a**, derived from (2*S*,6*S*)-1-amino-2,6-diphenylpiperidine, the combination of bulky substituents at the 2- and 6-positions and a preferred chair-like conformation of the six-membered piperidine ring, this effect should be even more marked.

The preliminary screening performed with hydrazones **1a**–**3a** confirmed this hypothesis: the less hindered hydrazone **1a**, derived from (2*R*,5*R*)-1-amino-2,5-dimethylpyrrolidine, showed a relatively poor reactivity, requiring 7 days at −78 °C to reach a conversion of 70%. Moreover, the expected product **4a** could not be obtained; cyano hydrazone **7**, presumably formed after the oxidation of **4a**, was isolated instead as the only reaction product in 68% yield (Table 1). The more hindered diphenyl substituted substrates **2a** and **3a** exhibited, as expected, a much better reactivity. In particular, hydrazone **2a**, derived from (2*S*,6*S*)-1-amino-2,6-diphenylpiperidine reacted much faster (>99% conversion after 2 days at −78 °C), but the corresponding product **5a** was obtained as a mixture of diastereomers in a near 1:1 ratio, even at this temperature. Finally, the best result was obtained with hydrazone **3a**,



Scheme 1. Cyanosilylation of hydrazones **1a**–**3a**.

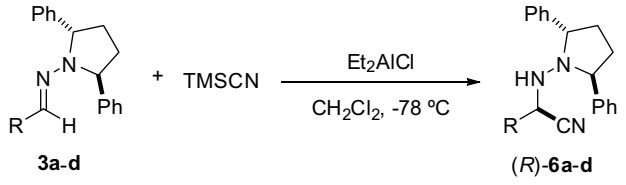
Table 1. Addition of TMSCN to hydrazones **1a**–**3a** in presence of Et_2AlCl

Entry	Hydrazone	T (°C)	t (d)	Product	Conversion[a] (%)	dr[a]
1	**1a**	−78	7	**4a**	70	—[b]
2	**2a**	−78	2	**5a**	>98	50:50
3	**3a**	rt	1	**6a**	>98	60:40
4	**3a**	−78	3	**6a**	>98	91:9

[a] Determined by ^1H and ^{13}C NMR analyses of crude reaction mixtures.
[b] Not determined. Cyano hydrazone **7** was obtained as the only reaction product.

derived from (2*S*,5*S*)-1-amino-2,5-diphenylpyrrolidine. When the reaction was performed at room temperature, complete conversion and a 60:40 dr were observed after 24 h. The diastereoselectivity was dramatically improved to 91:9 dr when the reaction was performed at −78 °C. Additionally, the 2,5-diphenylpyrrolidine auxiliary also served as a resolution agent, allowing the isolation of the major diastereoisomer (*R*)-**6a** as a pure enantiomer in 87% yield after simple chromatographic purification. No oxidation products related to **7** were observed in this case, presumably due to a steric protection of the hydrazine moiety.

Table 2. Addition of TMSCN to hydrazones **3a**–**d** in presence of Et_2AlCl



3a-d (*R*)-**6a-d**

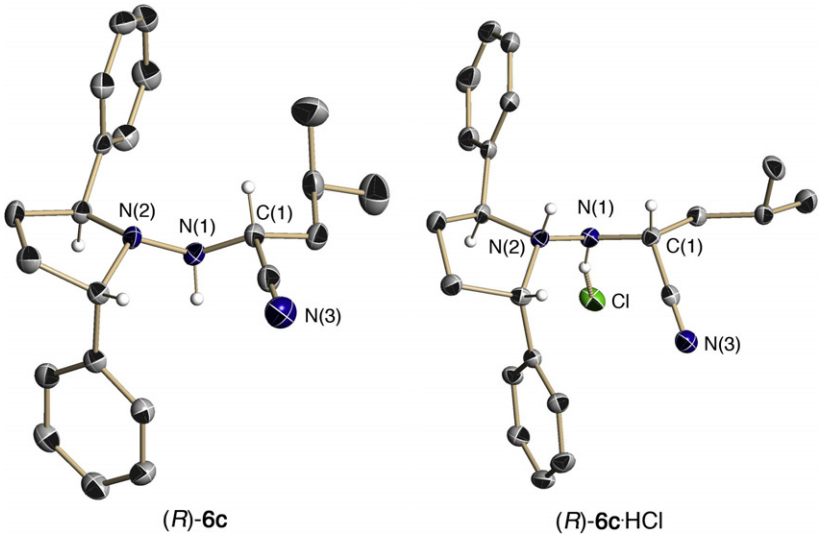
Entry	Hydrazone	R	t (d)	dr[a] (%)	Product	Yield[b] (%)
1	**3a**	$PhCH_2CH_2$	3	91:9	(*R*)-**6a**	82 (>99:1)
2	**3b**	^{i}Pr	1	98:2	(*R*)-**6b**	80 (>99:1)
3	**3c**	^{i}Bu	3	99:1	(*R*)-**6c**	83 (>99:1)
4	**3d**	n-C_5H_{11}	3	97:3	(*R*)-**6d**	84 (>99:1)

[a] Determined by ^1H and ^{13}C NMR analyses of crude reaction mixtures.
[b] Isolated yield of major isomer. In parentheses dr of enantiomerically pure major compound isolated in all cases after column chromatography.

Once the best auxiliary and conditions were identified, we extended the addition of TMSCN to hydrazones **3b**–**d** bearing different aliphatic side chains. The results summarized in Table 2 indicate a uniform behaviour for the reaction of these substrates, which proceeded in all cases with very high diastereoselectivities (dr 97:3 to 99:1). Thanks again to the resolving properties of the chosen auxiliary, adducts **6b**–**d** were isolated in all cases as enantiomerically pure compounds and in good yields (80–84%) after purification by column chromatography.

The absolute (*R*)-configuration of the newly created stereogenic centre was unambiguously determined for (*R*)-**6c** and its corresponding hydrochloride (*R*)-**6c**·HCl by single-crystal X-ray techniques (Fig. 1).[21] The absolute configuration of products **6a**, **6b** and **6d** was assigned by analogy.

Ab initio MO calculations for the structures, stabilities and charges of the hydrazone and the complexes involved in the reaction have been carried out in order to help an understanding of the high inductions effected by the 2,5-diphenylpyrrolidine auxiliary and the observed sense of the facial discrimination. Acetaldehyde derived hydrazone from (2*S*,5*S*)-1-amino-2,5-diphenylpyrrolidine **H** and Me_2AlCl were chosen as suitable models for substrate and promoter. These keep the essential structural elements present in those used experimentally, while maintaining the computational cost at an acceptable level. All the calculations were performed using GAUSSIAN 03[22] with the standard 6-31G** basis set[23] and the B3-LYP[24] method. All the structures were fully characterized by harmonic analysis. As the formation of Me_2AlCl/hydrazone complexes is assumed to occur prior to the addition, we focused on a search of their possible structures. Two different geometries **A** and **B** were located (Fig. 2 and Table 3) at close energetic levels ($\Delta E \sim 1$ kcal/mol).



(*R*)-**6c** (*R*)-**6c**·HCl

Figure 1. ORTEP drawings for (*R*)-**6c** and (*R*)-**6c**·HCl. Thermal ellipsoids are drawn at the 50% probability level; most **H** atoms are omitted for clarity.

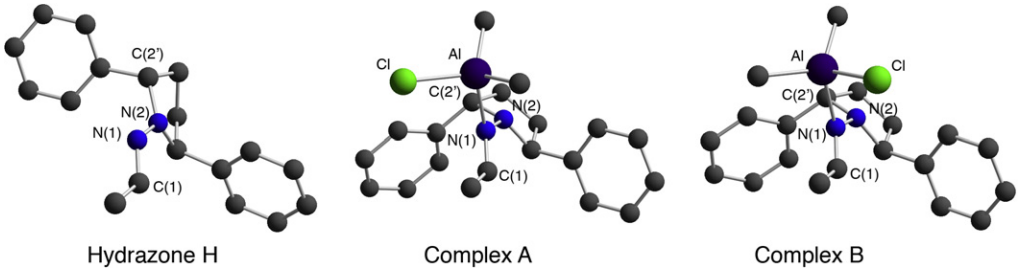


Figure 2. Calculated geometries of acetaldehyde hydrazone **H** and intermediate complexes **A** and **B**.

Table 3. Selected CHELPG charges, distances and angles calculated for hydrazone **H** and complexes **A** and **B**

	$q_{C(1)}$ (e)	$q_{N(1)}$ (e)	$q_{N(2)}$ (e)	$d_{C(1)–N(1)}$ (Å)	$d_{N(1)–N(2)}$ (Å)	C(1)–N(1)–N(2)–C(2′) (°)	Cl–Al–N(1)–C(1) (°)
H	0.265	−0.555	+0.270	1.29	1.35	+170.6	
A	0.092	−0.066	−0.208	1.29	1.40	+119.2	−70.7
B	0.117	−0.123	−0.178	1.29	1.40	+124.1	+53.9

The comparative analysis of the structural features of **A** and **B** reveals the dihedral angle Cl–Al–N(1)–C(1) (−70.7° and +53.9°, respectively) as the most significant geometric difference. The high deviation of planarity observed in both structures when compared with the starting hydrazone **H**, deduced from the dihedral angle C(1)–N(1)–N(2)–C(2′) (124.1° and 119.2°, respectively) indicates that the coordination of the former with the aluminium atom inhibits the conjugation between the amino nitrogen N(2) lone pair and the C=N double bond.[25] Although the C(1)–N(1) distance is not much affected by the formation of the complex, this loss of conjugation is also reflected in the N(1)–N(2) bond distance, which is longer in **A** and **B** (1.40 Å) than in **H** (1.35 Å) and in the degree of pyramidalization at N(2). A clearer diagnostic of this phenomenon is provided by the calculated CHELPG[26] charges on N(2), which increase from +0.270 e in **H** to −0.208 e and −0.178 e for complexes **A** and **B**, respectively (Table 3). These values also reflect the loss of the n→π conjugation, which, consequently, makes the amino N(2) lone pair clearly more basic. As the activation of TMSCN by Lewis bases is well established,[27] we assume that the *N*-dialkylamino group in the substrate effects the basic activation of TMSCN and, through a pentavalent silicon intermediate, drives the 'intramolecular' release of the cyanide to the neighbour azomethine carbon C(1) (Fig. 3).

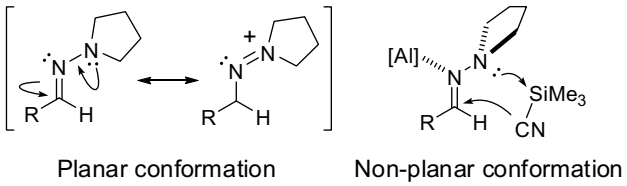


Figure 3. Activation of TMSCN by the dialkylamino group in the [Al]–coordinated substrate.

These calculations also offer an explanation for the observed absolute configuration. Both complexes **A** and **B** posses geometries characterized by the effective shielding of the *Re* face of the CN double bond by one of the Ph groups of the auxiliary, leaving the *Si* face available for the preferred attack of the nucleophile.

3. Conclusion

In conclusion, the excellent facial discrimination by the (2*S*,5*S*)-2,5-diphenylpyrrolidine group makes it a convenient auxiliary, which very efficiently controls the stereochemical course of the addition reactions of TMSCN to aliphatic hydrazones **3a**–**d**. The resolving properties of this auxiliary allow the synthesis of the corresponding enantiomerically pure α-hydrazino nitriles in very high yields.

4. Experimental

4.1. General experimental methods

Solvents were purified and dried by standard procedures. Flash chromatography was carried out on silica gel (0.063–0.200 mm, 0.040–0.063 mm or 0.020–0.045 mm). Melting points were recorded in a metal block and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz, 400 MHz or 500 MHz; ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz or 125 MHz with the solvent peak used as the internal reference.

4.2. Experimental procedures

4.2.1. Synthesis of hydrazones 3a–d. General procedure. To a stirred solution of (2*S*,5*S*)-1-amino-2,5-diphenylpyrrolidine[4a] (476 mg, 2 mmol) in CH_2Cl_2 (2.5 mL) were added the corresponding aldehyde (2.2 mmol) and Na_2SO_4. The reaction mixture was stirred at room temperature overnight, dried over Na_2SO_4, concentrated, and the residue purified by flash chromatography on silica gel (0.063–0.200 mm). Data of (2*S*,5*S*)-1-[(3-methyl)butylideneamine]-2,5-diphenylpyrrolidine **3c** were identical to those described in the literature.[6d]

Eluents, yields and spectral and analytical data for compounds **3a**, **3b** and **3d** are as follows.

4.2.1.1. (2*S*,5*S*)-1-[(3-Phenyl)propylideneamine]-2,5-diphenylpyrrolidine 3a. From dihydrocinnamaldehyde (0.32 mL, 2.2 mmol), flash chromatography (1:16 Et_2O–hexane) gave 461 mg (65%) of hydrazone **3a** as an oil: $[\alpha]_D^{20} = -163.9$ (*c* 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.70–1.80 (m, 2H), 2.32–2.67 (m, 6H), 4.98 (d, $J = 7.0$ Hz, 2H), 6.17 (t, $J = 5.4$ Hz, 1H), 6.95–7.39 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.5, 34.5, 34.6, 65.1, 125.7, 126.5, 126.7, 126.9, 128.3, 128.5, 128.6, 128.8, 134.8, 141.7, 144.1. IR (cm^{-1}) 3025, 2942, 1602, 1493, 1450, 1225, 1029, 749, 699. MS (EI) *m*/*z* (%) 355 [M^++1] (12), 354 [M^+] (40), 263 (100), 117 (60), 105 (67), 91 (71), 77 (18). HRMS calcd for $C_{25}H_{26}N_2$ 354.2096, found 354.2099.

4.2.1.2. (2*S*,5*S*)-1-[(2-Methyl)propylideneamine]-2,5-diphenylpyrrolidine 3b. From isobutyraldehyde (0.2 mL, 2.2 mmol), flash chromatography (1:16 Et_2O–hexane) gave 444 mg (76%) of hydrazone **3b** as an oil: $[\alpha]_D^{20} = -149.7$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, $J = 6.9$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H), 1.75–1.78 (m, 2H), 2.23–2.35 (m, 1H), 2.45–2.52 (m, 2H), 4.97 (d, $J = 6.9$ Hz, 2H), 6.02 (d, $J = 6.3$ Hz, 1H), 7.18–7.30 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 21.5, 31.7, 32.0, 65.2, 126.7, 126.9, 128.5, 128.7, 142.2, 144.3. MS (EI) *m*/*z* (%) 293 [M^++1] (19), 292 [M^+] (69), 104 (100), 91 (22), 77 (14). HRMS calcd for $C_{20}H_{24}N_2$ 292.1939, found 292.1943.

4.2.1.3. (2*S*,5*S*)-1-Hexylideneamine-2,5-diphenylpyrrolidine 3d. From hexanal (0.27 mL, 2.2 mmol), flash chromatography (1:16 Et_2O–hexane) gave 529 mg (75%) of hydrazone **3d** as an oil: $[\alpha]_D^{20} = -149.0$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, $J = 6.9$ Hz, 3H), 1.14–1.27 (m, 6H), 1.72–1.79 (m, 2H), 1.97–2.04 (m, 2H), 2.45–2.52 (m, 2H), 4.99 (d, $J = 7.2$ Hz, 2H), 6.13 (t, $J = 5.4$ Hz, 1H), 7.17–7.29 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.7, 28.1, 31.3, 31.6, 33.0, 65.1, 126.6, 126.6, 128.8, 136.6, 144.4. MS (EI) *m*/*z* (%) 321 [M^++1] (24), 320 [M^+] (100), 249 (46), 243 (34), 222 (7), 91 (34), 77 (15). HRMS calcd for $C_{22}H_{28}N_2$ 320.2252, found 320.2245.

4.2.2. Synthesis of hydrazino nitriles 6a–d. General procedure. In a Schlenk tube, Et_2AlCl (0.5 mmol, 500 μL of solution 1 M in hexane) was added to a solution of hydrazone **3a**–**d** (0.5 mmol) in dry CH_2Cl_2 (8 mL, 0.06 M) under an argon atmosphere. The mixture was stirred at rt for 20 minutes, cooled to −78 °C and TMSCN (1.5 mmol, 188 μL) was added. The mixture was stirred at −78 °C until total consumption of the starting material (**1**–**3d**, TLC). MeOH (2 mL) was added and the reaction mixture was allowed to warm to rt. The mixture was then washed with H_2O (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash chromatography. Starting material, eluents, yields and spectral and analytical data for compounds **6a**–**d** are as follows.

4.2.2.1. (*R*)-2-[(2*S*,5*S*)-2,5-Diphenylpyrrolidin-1-ylamino]-4-phenylbutanenitrile (*R*)-6a. From hydrazone **3a** (170 mg, 0.48 mmol), flash chromatography on silica gel (0.020–0.045 mm) (3:1 toluene–hexane) gave 150 mg (82%) of (*R*)-**6a** as an oil: $[\alpha]_D^{20} = -138.0$ (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 1.45–1.61 (m, 2H), 1.92–2.09 (m, 2H), 2.21–2.40 (m, 2H), 2.41–2.52 (m, 2H), 2.85 (d, $J = 10.0$ Hz, 1H), 3.28–3.34 (m, 1H), 4.55 (br s, 2H), 6.76–7.42 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 31.1, 33.0, 51.8, 67.1, 122.3, 126.1, 127.6, 128.3, 128.4, 128.7, 140.1, 141.8. IR (cm^{-1}) 2925, 1726, 1454, 754, 701. MS (EI) *m*/*z* (%) 381 [M^+] (4), 355 (9), 354 (34), 263 (89), 237 (76), 117 (75), 105 (29), 104 (73), 91 (100), 77 (27). HRMS calcd for $C_{26}H_{27}N_3$ 381.2205, found 381.2189.

4.2.2.2. (*R*)-2-[(2*S*,5*S*)-2,5-Diphenylpyrrolidin-1-ylamino]-3-methylbutanenitrile (*R*)-6b. From hydrazone **3b** (138 mg, 0.47 mmol), flash chromatography on silica gel (0.020–0.045 mm) (toluene) gave 119 mg (80%) of (*R*)-**6b** as an oil: $[\alpha]_D^{20} = -125.3$ (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.61 (d, $J = 6.9$ Hz, 3H), 0.62 (d, $J = 6.9$ Hz, 3H), 1.42–1.51 (m, 1H), 1.98–2.09 (m, 2H), 2.43–2.52 (m, 2H), 2.85 (d, $J = 9.3$ Hz, 1H), 3.15 (dd, $J = 9.3$, 5.9 Hz, 1H), 4.53 (br s, 2H), 7.28–7.47 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 19.0, 29.8, 30.7, 59.4, 67.1, 121.5, 127.6, 128.6, 128.9, 141.8. IR (cm^{-1}) 3031, 2962, 2919, 1455, 754, 701. MS (CI) *m*/*z* (%) 320 [M^++1] (6), 319 [M^+] (11), 293 (98), 237 (100), 117 (30), 105 (35), 104 (50), 91 (25), 77 (6). HRMS calcd for $C_{21}H_{25}N_3$ 319.2048, found 319.2040.

4.2.2.3. (*R*)-2-[(2*S*,5*S*)-2,5-Diphenylpyrrolidin-1-ylamino]-4-methylpentanenitrile (*R*)-6c. From hydrazone **3c** (135 mg, 0.44 mmol), flash chromatography on silica gel (0.040–0.063 mm) (1:2→2:1 toluene–hexane) gave 120 mg (83%) of (*R*)-**6c** as a white solid. X-ray quality crystals were grown from a solution of (*R*)-**6c** in pentane at −20 °C: mp 108–110 °C. $[\alpha]_D^{20} = -142.8$ (*c* 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.38 (d, $J = 6.7$ Hz, 3H), 0.58 (d, $J = 6.7$ Hz, 3H), 1.01–1.14 (m, 2H), 1.29–1.39 (m, 1H), 1.97–2.03 (m, 2H), 2.40–2.50 (m, 2H), 2.71 (d, $J = 10.3$ Hz, 1H), 3.29 (c, $J = 8.3$ Hz, 1H), 4.52 (br s, 2H), 7.24–7.41 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 22.1, 24.3, 30.6, 40.3, 51.2, 67.1, 123.0, 127.5, 128.6, 128.7, 141.8. IR (cm^{-1}) 2957, 2931, 2871, 1728, 1455, 754, 702. MS (EI) *m*/*z* (%) 333 [M^+] (8), 307 (5), 306 (21), 237 (100), 117 (29), 105 (20), 104 (28), 91 (20), 77 (5). HRMS calcd for $C_{22}H_{27}N_3$ 333.2205, found 333.2194.

4.2.2.4. (*R*)-2-[(2*S*,5*S*)-2,5-Diphenylpyrrolidin-1-ylamino]-heptanenitrile (*R*)-6d. From hydrazone **2d** (130 mg, 0.41 mmol), flash chromatography on silica gel (0.020–0.045 mm) (1:3→3:1 toluene–hexane) gave 106 mg (84%) of (*R*)-**6d** as an oil: $[\alpha]_D^{20} = -152.3$ (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.75 (t, $J = 7.3$ Hz, 3H), 0.83–0.99 (m, 4H), 1.00–1.12 (m, 2H), 1.17–1.26 (m, 2H), 1.97–2.06 (m, 2H), 2.43–2.52 (m, 2H), 2.81 (br s, 1H), 3.30 (t, $J = 7.0$ Hz, 1H), 4.54 (br s, 2H), 7.28–7.47 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.3, 24.8, 30.7, 30.8, 31.2, 52.6, 67.1, 122.6, 127.6, 128.6, 128.7, 141.9. IR (cm^{-1}) 2927, 1455, 754, 701. MS (EI) *m*/*z* (%) 347 [M^+] (4), 321 (21), 320 (85), 249 (42), 237 (86), 194

(23), 117 (46), 105 (25), 104 (100), 91 (45), 77 (18). HRMS calcd for $C_{23}H_{29}N_3$ 347.2361, found 347.2362.

4.2.3. Synthesis of hydrazino nitrile hydrochloride (*R*)-6c·HCl. HCl was bubbled into a solution of (*R*)-**6c** (20 mg, 0.06 mmol) in pentane. THF was added and the mixture was cooled to −20 °C to obtain X-ray quality crystals. $[\alpha]_D^{25} = -106.1$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.41 (d, $J = 6.5$ Hz, 3H), 0.62 (d, $J = 6.5$ Hz, 3H), 1.05–1.32 (m, 3H), 2.30–2.45 (m, 2H), 2.68 (br s, 2H), 3.59–4.00 (m, 1H), 4.78 (br s, 2H), 7.40–7.61 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 22.2, 24.4, 29.1, 41.1, 49.2, 69.4, 121.1, 129.3, 129.9, 136.5. IR (cm^{-1}) 3031, 2957, 1456, 754, 701. MS (CI) *m*/*z* (%) 334 [M^++1] (3), 333 [M^+] (4), 307 (100), 306 (50), 237 (34), 117 (9), 105 (8), 104 (12), 91 (7). HRMS calcd for $C_{22}H_{28}N_3$ 334.2283, found 334.2280.

4.2.4. *N*-[(2*R*,5*R*)-2,5-Dimethylpyrrolidin-1-yl]-3-phenylpropanimidoyl cyanide 7. Starting from hydrazone **1a** (115 mg, 0.5 mmol) and following the general procedure described above for **6a**–**d**, purification by flash chromatography on silica gel (0.063–0.200 mm) (1:20→1:10 EtOAc–hexane) gave 10.3 mg (9%) of unreacted starting material **1a** and 87 mg (68%) of **7** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (d, $J = 6.5$ Hz, 6H), 1.52–1.59 (m, 2H), 2.09–2.17 (m, 2H), 2.71 (dd, $J = 9.3$, 6.8 Hz, 2H), 2.92 (dd, $J = 8.8$, 6.8 Hz, 2H), 4.12–4.21 (m, 2H), 7.17–7.30 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 29.0, 33.9, 38.4, 57.0, 104.1, 117.0, 126.2, 128.5, 128.7, 140.9. MS (CI) *m*/*z* (%) 256 [M^++1] (11), 255 [M^+] (34), 240 (49), 164 (100), 91 (24). HRMS calcd for $C_{16}H_{21}N_3$ 255.1735, found 255.1732.

Acknowledgements

We thank the Spanish 'Ministerio de Ciencia y Tecnología' (Grants CTQ2007-61915, CTQ2004-00241, CTQ2007-60244) and the Junta de Andalucía (Grant 2005/FQM-658) for financial support. E.M.-L. and J.I.-S. thank the 'Ministerio de Educación y Ciencia' for predoctoral fellowships.

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