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Diastereoselective addition of trimethylsilyl cyanide to chiral *O*-, *S*- and *N*-heterocyclic aldimines

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Systematic investigation of asymmetric trimethylsilylcyanation of heterocyclic azomethines has been realized. The addition of trimethylsilyl cyanide to optically active furan, thiophene and pyridine aldimines, derived from (*R*)- and (*S*)-1-phenylethylamine, was studied in the presence of Lewis acids, and a series of the corresponding *α*-amino nitriles was obtained in fair to good yields (up to 91%). Unsaturated nitriles were also formed from pyridine imines. The sense of asymmetric induction and the degree of diastereoselectivity in the synthesis of *α*-amino nitriles were determined by means of ^{1}H NMR. The stereochemical outcome is a result of the same sense of asymmetric induction: *Re* face attack to the (*S*)-imines and *Si* face addition to the (*R*)-imines took place. The (*R,R*)- (up to 81%) or (*S,S*)- (up to 87%) *α*-amino nitriles predominated in the products obtained from the all furan, thiophene and pyridine (*R*)- or (*S*)-imines respectively. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: asymmetric synthesis; trimethylsilylcyanation; catalysis by Lewis acids; heterocyclic Schiff bases; α-amino nitriles

INTRODUCTION

Asymmetric cyanation of imines (Strecker reaction) provides an important tool for construction of optically active nitrogen-containing molecules (for recent reviews, see Refs 1–5). The cyanation of imines derived from chiral amines is an example of substrate-controlled diastereoselectivity (first-generation asymmetric synthesis[6]). In this diastereoselective reaction, the formation of a new chiral centre is under the control of an existing centre in the same molecule.

The first asymmetric Strecker synthesis was reported in 1963 by Harada.[7] Since that time, the general strategy for the induction of asymmetry in this reaction has been to generate a chiral Schiff base from the condensation of an aldehyde and an optically active primary amine. The diastereoselective addition of a nitrile source introduces a new chiral centre forming stereoenriched α-amino nitriles. One of the most suitable auxiliaries for asymmetric Strecker reactions are benzyl amines (for general examples see Refs 8–15). The use of trimethylsilyl cyanide (Me_3SiCN) in combination with a Lewis acid is preferable over the conventional NaCN/AcOH(cat.) method.[16–23]

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The asymmetric synthesis of α-amino nitriles using (*R*)- and (*S*)-1-phenylethylamine as a chiral matrix and a collection of aldehydes has been examined in numerous papers cited above. These studies have shown that the sense and the degree of stereoselectivity are dependent on the nature of both the aldimine and the catalytic system. Nevertheless, the reported data involve addition to imines obtained mainly from aromatic and aliphatic aldehydes. Only one heterocyclic aldehyde (3-pyridinealdehyde) was used recently as a starting substrate in these investigations.[15]

In previous work[24–26] we studied the asymmetric addition of Me_3SiCN to (hetero)aromatic aldehydes and to achiral heterocyclic imines. Herein we report the results of catalytic Me_3SiCN addition to imines prepared specially from the reactions of furan, thiophene and pyridine aldehydes with (*R*)- and (*S*)-1-phenylethylamine. By performing the reaction in both enantiomeric series we are able to compare the results and to obtain the corresponding diastereomeric compounds for further investigation of their biological activity.

EXPERIMENTAL

General

The solvents were dried (dichloromethane over P_2O_5 and benzene over CaH_2) and distilled prior to use. Me_3SiCN

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(Aldrich) was used without further purification. $AlCl_3$, $AlBr_3$ and the chemicals for the synthesis of imines were received from commercial sources (Fluka, Aldrich). 4 Å molecular sieves (VEB Laborchemie Apolda) and silica gel for column chromatography (Kieselgel 60, 0.063–0.200 mm, Merck) were used. Thin-layer chromatography (TLC) was performed on a Merck silica gel 60 F_{254} with various eluents.

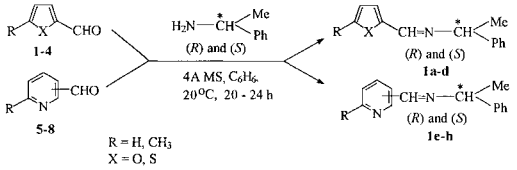
^{1}H NMR spectra were recorded on Bruker WH-90/DS (90 MHz) and Varian Mercury (200 MHz) spectrometers using $CDCl_3$ as a solvent and HMDSO as internal standard. The mass spectra were obtained on an HP 6890 GC/MS instrument. Optical rotation was determined by means of a Polamat A (Carl Zeiss, Jena) instrument. Elemental analysis was performed using Carlo Erba EA-1108 apparatus. Melting points were determined with a Kofler instrument.

Synthesis of imines (*R*)- and (*S*)-1a–h

Imines **1a–h** were synthesized by the reactions of the corresponding heterocyclic aldehydes (**1–8**) with (*R*)- and (*S*)-1-phenylethylamine. The aldehyde (5 mmol) was mixed with the amine (5 mmol) in dry benzene (20 ml) at ambient temperature in the presence of 4 Å molecular sieves (2.0 g). After some time (20–24 h) the molecular sieves were removed by filtration, the reaction mixture was concentrated, and imine was isolated by recrystallization from hexane or by vacuum distillation.

Trimethylsilylcyanation of chiral heterocyclic aldimines

In a typical procedure, in a 5 cm^3 Pierce reaction vial, 1.0 equivalent of imine in dichloromethane (2 ml) reacted with 1.2 equivalents of Me_3SiCN (CAUTION: toxic!) in the presence of catalytic amounts of $AlBr_3$ (10 mol%) and 4 Å molecular sieves (0.5 g) at 20 or 40 °C under an argon atmosphere. When the reaction was complete [monitored by TLC and gas chromatography–mass spectrometry (GC–MS)], conversion of starting imine was determined by ^{1}H NMR. Then saturated aqueous $NaHCO_3$ was added, and the organic compounds were extracted with diethyl ether. After the organic layer was dried over $MgSO_4$ and evaporated, the products were isolated by column chromatography on silica gel using various eluents. The ^{1}H NMR spectra of isolated products were recorded and optical rotation determined.



Scheme 1. Synthesis of imines (*R*)- and (*S*)-**1a–h**.

RESULTS AND DISCUSSION

Synthesis of chiral heterocyclic imines

A series of optically active heterocyclic Schiff bases was synthesized by the reactions of aldehydes **1–8** with (*R*)- and (*S*)-1-phenylethylamine in the presence of 4 Å molecular sieves (Scheme 1, Table 1). The spectral and analytical data for all the imines were in good agreement with their structure (Tables 2–4).

Table 1. Characteristics of aldimines **1a–h**

Imine[a]	R	X	Pyridine isomer	Isolated yield (%)	M.p. (°C)	$[\alpha]_{546}^{20-23}$(deg) (*c* in benzene)	Colour	Lit. [α] (deg)
(*R*)-**1a**	H	O	–	78	oil	−72.2 (7.4)	yellow	$[\alpha]_D^{20}$ − 66.1 (*c* 6.4, benzene)[28]
(*S*)-**1a**	H	O		78	oil	+71.6 (8.0)	yellow	$[\alpha]_D^{25}$ + 76.4 (*c* 1.1, $CHCl_3$)[29]
(*R*)-**1b**	CH_3	O	–	80	oil	−123.4 (8.1)	yellow	
(*S*)-**1b**	CH_3	O		79	oil	+125.3 (7.7)	yellow	
(*R*)-**1c**	H	S	–	83	44–45	−155.3 (7.3)	white	
(*S*)-**1c**	H	S		85	47	+159.6 (3.6)	white	$[\alpha]_{546}^{20}$ + 183.4 (*c* 9.7, acetone)[30]
(*R*)-**1d**	CH_3	S	–	78	40	−229.2 (4.7)	white	
(*S*)-**1d**	CH_3	S		81	39	+225.5 (4.2)	white	
(*R*)-**1e**	H	–	α	79	oil	−55.4 (6.3)	yellow	
(*S*)-**1e**	H	–	α	78	oil	+55.8 (4.4)	yellow	$[\alpha]_D^{25}$ + 37 (*c* 2.24, $CHCl_3$)[29]
(*R*)-**1f**	H	–	β	76	oil	−92.0 (6.7)	white	$[\alpha]_{546}^{20}$ + 55.7 (*c* 51.0, acetone)[30]
(*S*)-**1f**	H	–	β	81	oil	+92.1 (6.6)	white	$[\alpha]_D^{25}$ + 62.1 (*c* 2.1, $CHCl_3$)[29]
(*R*)-**1g**	H	–	γ	80	oil	−66.1 (6.7)	white	
(*S*)-**1g**	H	–	γ	84	oil	+66.2 (8.6)	white	$[\alpha]_D^{25}$ + 27.1 (*c* 1.1, $CHCl_3$)[29]
(*R*)-**1h**	CH_3	–	α	82	28	−20.2 (5.0)	white	
(*S*)-**1h**	CH_3	–	α	89	oil	+21.0 (10.1)	yellow	$[\alpha]_{546}^{20}$ + 29.6 (*c* 10.0, acetone)[30]

[a] Racemic compounds **1a–d** were synthesized previously.[27] The data of the ^{1}H NMR and MS spectra given for them were identical with the spectra of (*R*)- and (*S*)-isomers.

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Table 2. ^{1}H NMR spectra of pyridine aldimines **1e–h**

Imine[a,b]	Chemical shift (ppm), *J* (Hz)					
	CH_3CH, d	MeC*H*, q	CH_3-ring, s	Ph, m	Protons of pyridine ring	CH—N, s
1e	1.61	4.64	–	7.2–7.5	7.29, ddd, *J* = 7.7, 4.9, 1.4, PyH-5	8.46
	J = 6.9				7.72, m, *J* = 7.7, 1.8, PyH-4	
					8.09, ddd, *J* = 7.7, 1.4, 1.0, PyH-3	
					8.63, m, *J* = 4.9, 1.7, 1.0, PyH-6	
1f	1.57	4.55	–		7.2–7.5, m, 6H, Ph, PyH-5	8.39
	J = 6.6				8.14, dt, *J* = 8.0, 2.0, PyH-4	
					8.61, dd, *J* = 5.2, 2.0, PyH-6	
					8.88, d, *J* = 2.4, PyH-2	
1g	1.58	4.57	–	7.2–7.5	7.60, dd, *J* = 6.0, 2.0, PyH-3,5	8.33
	J = 6.4				8.67, dd, *J* = 6.0, 2.0, PyH-2,6	
1h	1.60	4.62	2.58	7.2–7.4	7.16, d, *J* = 7.7, PyH-5	8.44
	J = 6.8				7.61, t, *J* = 7.7, PyH-4	
					7.92, d, *J* = 7.7, PyH-3	

[a] Identical spectra of the (*R*)-and (*S*)-isomers for all the compounds were found.
[b] Spectra of **1e–h** were comparable with those given in Refs 29, 30 for these imines.

Table 3. Mass spectra of pyridine aldimines **1e–h**

Imine[a,b]	GC–MS, *m/z* (I_{rel}, %)[c]
1e	210 (12, M^+), 209 (9, $[M-H]^+$), 195 (51, $[M-Me]^+$), 181 (6), 168 (7), 133 (10, $[M-Ph]^+$), 118 (2), 105 (100, $[Ph(Me)HC]^+$, $[C_5H_4NCH{=}N]^+$), 92 (18), 79 (22, $[PyH]^+$), 78 (18, Py^+), 77 (35, Ph^+), 65 (12), 51 (21), 39 (13), 28 (22)
1f	210 (18, M^+), 209 (4, $[M-H]^+$), 195 (17, $[M-Me]^+$), 183 (6), 167 (14), 133 (4, $[M-Ph]^+$), 132 (3, $[M-Py]^+$), 115 (3), 106 (23), 105 (100, $[Ph(Me)HC]^+$, $[C_5H_4NCH{=}N]^+$), 103 (10), 91 (16), 79 (28, $[PyH]^+$), 78 (18, Py^+), 77 (34, Ph^+), 63 (16), 51 (33), 39 (11)
1g	210 (15, M^+), 195 (12, $[M-Me]^+$), 183 (12), 167 (10), 131 (5), 106 (18), 105 (100, $[Ph(Me)HC]^+$, $[C_5H_4NCH{=}N]^+$), 103 (9), 91 (5), 91 (4), 79 (27, $[PyH]^+$), 78 (19, Py^+), 77 (31, Ph^+), 63 (13), 51 (37), 39 (10)
1h	224 (29, M^+), 223 (15, $[M-H]^+$), 210 (15), 209 (95, $[M-Me]^+$), 182 (35), 132 (12), 121 (20), 106 (21), 105 (100, $[Ph(Me)HC]^+$), 103 (22), 94 (13), 79 (21), 78 (12), 77 (45, Ph^+), 65 (15), 51 (17), 39 (20)

[a] Identical spectra of the (*R*)- and (*S*)-isomers for all the compounds were found.
[b] Spectra of **1e–g** were comparable with those given in Ref. 29 for these imines.
[c] Py = pyridyl.

Table 4. Elemental analysis of the solid aldimines obtained

Imine	Mol. formula	Found/calculated (%)			
		C	H	N	S
(*R*)-**1c**	$C_{13}H_{13}NS$	72.26/72.52	6.00/6.09	6.40/6.50	14.77/14.89
(*S*)-**1c**	$C_{13}H_{13}NS$	72.53/72.52	6.11/6.09	6.47/6.50	14.88/14.89
(*R*)-**1d**	$C_{14}H_{15}NS$	73.22/73.32	6.58/6.59	6.06/6.11	13.89/13.98
(*S*)-**1d**	$C_{14}H_{15}NS$	73.13/73.32	6.52/6.59	6.05/6.11	13.87/13.98
(*R*)-**1h**	$C_{15}H_{16}N_2$	80.33/80.32	7.19/7.19	12.54/12.49	–
(*S*)-**2d**	$C_{15}H_{16}N_2S$	71.02/70.28	6.40/6.29	10.46/10.93	11.93/12.51

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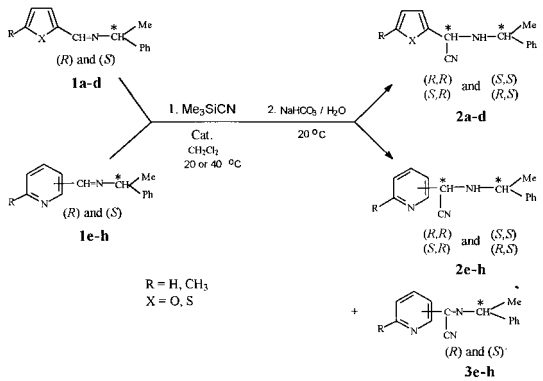
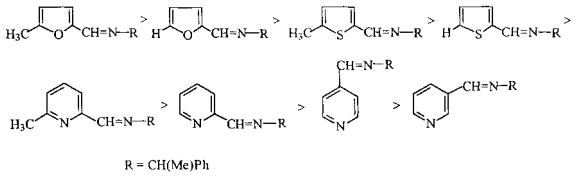


Scheme 2. Trimethylsilylcyanation of the optically active heterocyclic imines.



Scheme 3. Reactivity order of heterocyclic imines in the Strecker reaction.

Asymmetric addition of Me_3SiCN to optically active heterocyclic imines

Two chiral imines (*R*)- and (*S*)-**1a–h** prepared were tested in the Strecker synthesis catalysed by Lewis acids: $AlCl_3$ or $AlBr_3$ (5–20 mol%). The addition of Me_3SiCN to imines was carried out in methylene chloride at 20 or 40 °C until imine conversion was mainly 78–100% (monitored by TLC and GC–MS and determined by ^1H NMR). Some of products

Table 5. Characteristics of the trimethylsilylcyanation reactions and the products

Run	Starting imine	Catalyst (mol%)	Temp. (°C)	Time (h)	Conversion (%)[a,b]	Col. Chrom. eluent	Product[c,d]	Yield (%)	d.r.[a,e]	$[\alpha]_{546}^{20-23}$(deg) (*c* in benzene)
1	(*R*)-**1a**	$AlCl_3$ (5)	20	25	n.d.	C_6H_6:EtOAc = 9:1	**2a**(*R*)	43	78:22	+88.9 (0.84)
2	(*S*)-**1a**	$AlCl_3$ (5)	20	20	n.d.	C_6H_6:EtOAc = 9:1	**2a**(*S*)	38	67:33	−80.6 (0.5)
3	(*R*)-**1b**	$AlBr_3$ (20)	20	1	∼100	–	**2b**(*R*)	82	74:26	+105.5 (0.7)
4	(*S*)-**1b**	$AlBr_3$ (20)	20	1	∼100	–	**2b**(*S*)	80	74:26	−103.2 (0.7)
5	(*R*)-**1c**	$AlBr_3$ (10) + MS 4Å	20	6.5	80	Hex:EtOAc = 5:1	**2c**(*R*)	75	79:21	+119.4 (2.1)
6	(*S*)-**1c**	$AlBr_3$ (10) + MS 4Å	20	6.5	78	Hex:EtOAc = 5:1	**2c**(*S*)	72	78:22	−103.2 (1.8)
7	(*R*)-**1d**	$AlBr_3$ (20)	20	1	80	Hex:EtOAc = 5:1	**2d**(*R*)	58	77:23	+69.1 (1.3)
8	(*S*)-**1d**	$AlBr_3$ (20)	20	1	87	Hex:EtOAc = 5:1	**2d**(*S*)	62	75:25	−69.1 (1.3)
9	(*R*)-**1e**	$AlCl_3$ (20)	40	19	75	–	**2e**(*R*)	n.d.	71:29	
10	(*R*)-**1e**	$AlBr_3$ (10) + MS 4Å	40	2	87	$CHCl_3$:MeOH = 9.5:0.5	**2e**(*R*)	40	78:22	+55.8 (1.2)
						$CHCl_3$:MeOH = 9.5:0.5	(*R*)-**3e**	33	–	+43.8 (0.8)
11	(*S*)-**1e**	$AlCl_3$ (20)	40	19	n.d.	$CHCl_3$:MeOH = 9:1	**2e**(*S*)	61	74:26	−45.5 (1.2)
						$CHCl_3$:MeOH = 9:1	(*S*)-**3e**	10	–	
12	(*S*)-**1e**	$AlBr_3$ (10)	20	41	40	–	**2e**(*S*)	–	71:29	
13	(*S*)-**1e**	$AlBr_3$ (10) + MS 4Å	40	8.5	96	$CHCl_3$:MeOH = 9.5:0.5	**2e**(*S*)	73	79:21	−47.3 (1.3)
						$CHCl_3$: MeOH = 9.5:0.5	(*S*)-**3e**	18	–	−42.8 (0.5)
14	(*R*)-**1f**	$AlBr_3$ (10) + MS 4Å	40	21	95	CH_2Cl_2:MeOH = 10:1	**2f**(*R*)	70	75:25	+93.4 (1.8)
						CH_2Cl_2: MeOH = 10:1	(*R*)-**3f**	15	–	
15	(*S*)-**1f**	$AlBr_3$ (10) + MS 4Å	40	22.5	82	CH_2Cl_2:MeOH = 10:1	**2f**(*S*)	75	80:20	−89.7 (2.5)
16	(*R*)-**1g**	$AlBr_3$ (10) + MS 4Å	20	8.5	97	CH_2Cl_2:MeOH = 10:1	**2g**(*R*)	60	81:19	+72.4 (1.8)
						CH_2Cl_2: MeOH = 10:1	(*R*)-**3g**	25	–	+38.3 (0.8)
17	(*S*)-**1g**	$AlBr_3$ (10) + MS 4Å	20	6	91	CH_2Cl_2:MeOH = 10:1	**2g**(*S*)	64	87:13	−82.3 (1.2)
						CH_2Cl_2: MeOH = 10:1	(*S*)-**3g**	12	–	
18	(*R*)-**1h**	$AlBr_3$ (10) + MS 4Å	20	2	98	CH_2Cl_2:MeOH = 20:1	(*R*)-**2h**	70	80:20	+85.1 (1.4)
						CH_2Cl_2: MeOH = 20:1	(*R*)-**3h**	20	–	+77.7 (0.6)
19	(*S*)-**1h**	$AlBr_3$ (10) + MS 4Å	20	2.5	∼100	–	**2h**(*S*)	85	76:24	−92.6 (3.7)

[a] Determined by ^1H NMR.
[b] n.d.: not determined.
[c] Configuration of the newly formed stereocentre is given.
[d] All the compounds were oils except **2d**(*S*): solid, m.p. 48–49 °C.
[e] d.r.: diastereoisomeric ratio.

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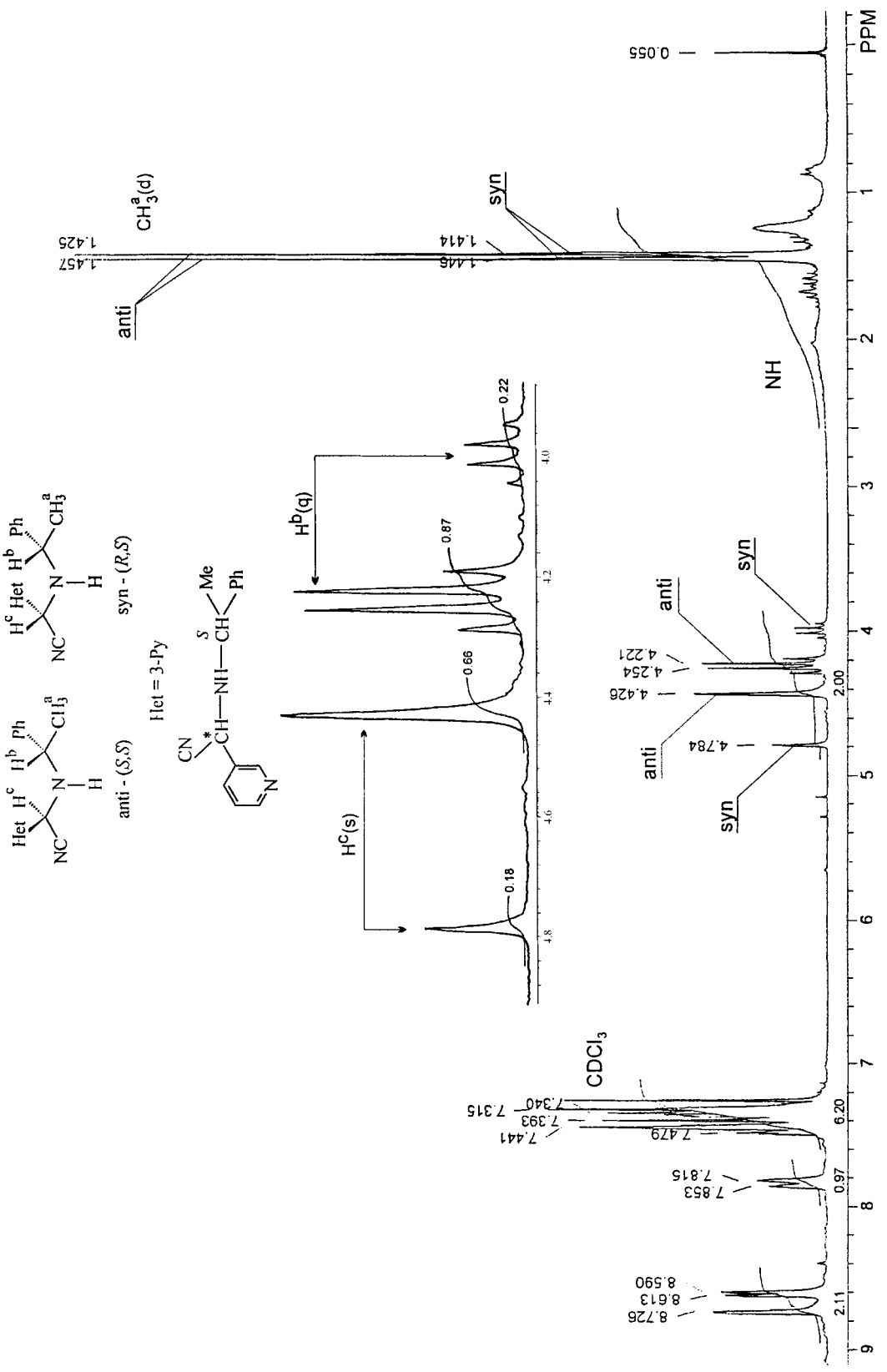

Figure 1. ^{1}H NMR spectrum of α-amino nitrile **2f** obtained from imine (*S*)-**1f**.

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Table 6. ^{1}H NMR spectra of nitriles **2** and **3**

Compound[a]		Chemical shift (ppm), *J* (Hz)					
		CH_3CH, d	CH_3-ring	NH	CHCN	CHMe, q	Ring protons
2a(*R*)	major	1.43, *J*=6.4	–	2.0, br s	4.43, br s	4.19, *J*=6.4	6.3–6.4, m, FurH-3,4; 7.2–7.4, m, FurH-5, Ph
2a(*S*)	minor	1.37, *J*=6.4	–	2.0, br s	4.68, br s	3.92, *J*=6.4	6.3–6.4, m, FurH-3,4; 7.2–7.4, m, FurH-5, Ph
2b(*R*)	major	1.43, *J*=6.4	2.28	1.9, br s	4.35, br s	4.18, *J*=6.4	5.92, m, *J*=2.2, FurH-4; 6.25, m, *J*=2.2, FurH-3; 7.2–7.4, m, Ph
2b(*S*)	minor	1.37, *J*=6.4	2.28	1.9, br s	4.61, br s	3.93, *J*=6.4	5.92, m, *J*=2.2, FurH-4; 6.20, m, *J*=2.2, FurH-3; 7.2–7.4, m, Ph
2c(*R*)	major	1.37, *J*=7.0	–	1.95, d, *J*=12.0	4.49, d, *J*=12.0	4.15, *J*=7.0	6.8–7.5, m, ThH-3,4, Ph; 7.64, m, ThH-5
2c(*S*)	minor	1.35, *J*=7.0	–	1.95, d, *J*=12.0	4.49, d, *J*=12.0	3.99, *J*=7.0	6.8–7.5, m, ThH-3,4, Ph; 7.64, m, ThH-5
2d(*R*)	major	1.35, *J*=6.6	2.42	1.95, d, *J*=11.6	4.45, d, *J*=11.6	4.16, *J*=6.6	6.57, d, *J*=3.4, ThH-4; 6.94, d, *J*=3.4, ThH-3; 7.2–7.4, m, Ph
2d(*S*)	minor	1.33, *J*=6.6	2.42	1.9, br d	4.46, d, *J*=11.6	4.00, *J*=6.6	6.57, d, *J*=3.4, ThH-4; 6.94, d, *J*=3.4, ThH-3; 7.2–7.4, m, Ph
2e(*R*)	major	1.45, *J*=6.6	–	2.5, br s	4.44, s	4.27, *J*=6.6	7.2–7.4, m, PyH-3,5, Ph; 7.70, td, *J*=6.0, 1.2, PyH-4; 8.61, m, *J*=4.6, PyH-6
2e(*S*)	minor	1.41, *J*=6.6	–	2.5, br s	4.76, s	3.98, *J*=6.6	7.2–7.4, m, PyH-3,5, Ph; 7.70, td, *J*=6.0, 1.2, PyH-4; 8.61, m, *J*=4.6, PyH-6
(*R*)-**3e**		1.64, *J*=6.4	–	–	–	5.25, *J*=6.4	7.3–7.5, m, PyH-5, Ph; 7.73, td, *J*=7.0, 1.6, PyH-4; 8.12, d, *J*=7.0, PyH-3; 8.69, m, *J*=4.8, PyH-6
(*S*)-**3e**							
2f(*R*)	major	1.44, *J*=6.6	–	2.0, br s	4.43, s	4.24, *J*=6.6	7.2–7.5, m, PyH-5, Ph; 7.83, dt, *J*=8.0, 2.2, PyH-4; 8.60, dd, *J*=5.0, 1.6, PyH-6; 8.73, d, *J*=2.4
2f(*S*)	minor	1.43, *J*=6.6	–	2.0, br s	4.78, s	3.99, *J*=6.6	7.2–7.5, m, PyH-5, Ph; 7.83, dt, *J*=8.0, 2.2, PyH-4; 8.60, dd, *J*=5.0, 1.6, PyH-6; 8.73, d, *J*=2.4
(*R*)-**3f**		1.58, *J*=6.6	–	–	–	5.20, *J*=6.6	7.2–7.5, m, PyH-5, Ph; 8.17, dt, *J*=7.8, 2.2, PyH-4; 8.75, dd, *J*=5.0, 1.6, PyH-6; 8.87, d, *J*=2.2
2g(*R*)	major	1.47, *J*=7.0	–	2.1, br s	4.41, s	4.24, *J*=7.0	7.3–7.6, m, Ph, PyH-3,5; 8.62, dd, *J*=6.0, 2.0, PyH-2,6
2g(*S*)	minor	1.44, *J*=7.0	–	2.1, br s	4.78, s	4.02, *J*=7.0	7.3–7.6, m, Ph, PyH-3,5; 8.62, dd, *J*=6.0, 2.0, PyH-2,6
(*R*)-**3g**		1.67, *J*=7.2	–	–	–	5.22, *J*=7.2	7.2–7.6, m, Ph; 7.84, dd, *J*=6.0, 2.0, PyH-3,5; 8.78, dd, *J*=6.0, 2.0, PyH-2,6
(*S*)-**3g**							
2h(*R*)	major	1.47, *J*=6.6	2.56	2.3, br s	4.37, s	4.27, *J*=6.6	7.09, d, *J*=7.6, PyH-5; 7.15, d, *J*=7.6, PyH-3; 7.2–7.5, m, Ph; 7.59, t, *J*=7.6, PyH-4
2h(*R*)	minor	1.41, *J*=6.4	2.55	2.3, br s	4.70, s	3.98, *J*=6.4	7.09, d, *J*=7.6, PyH-5; 7.15, d, *J*=7.6, PyH-3; 7.2–7.5, m, Ph; 7.59, t, *J*=7.6, PyH-4
(*R*)-**3h**		1.64, *J*=6.4	2.62	–	–	5.25, *J*=6.4	7.23, d, *J*=6.5, PyH-5; 7.3–7.5, m, Ph; 7.63, t, *J*=6.5, PyH-4; 7.93, d, *J*=6.5, PyH-3

[a] Configuration of the CH(Me)Ph group is given.

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Table 7. Mass spectra of nitriles **2** and **3**

Compound[a,b]	MS, m/z (I_{rel}, %)
2a	211 (15, $[M - Me]^+$), 200 (18), 199 (100, $[M - HCN]^+$), 198 (7), 185 (12), 184 (82, $[M - HCN - Me]^+$), 157 (17), 128 (16), 121 (18, $[M - Ph(Me)HC]^+$), 116 (15), 106 (56), 105 (100, $[Ph(Me)HC]^+$), 104 (25), 103 (32), 91 (10), 79 (47), 78 (30), 77 (73, Ph^+), 65 (12), 63 (10), 53 (15), 52 (32), 51 (55), 50 (17), 39 (50), 38 (12), 27 (65, $[HCN]^+$)
2e	236 (5, $[M - H]^+$), 235 (30, $[M - 2H]^+$), 234 (67, $[M - 3H]^+$), 220 (50, $[M - 2H - Me]^+$), 211 (15, $[M - CN]^+$), 210 (17, $[M - HCN]^+$), 209 (16, $[M - CN - 2H]^+$), 208 (30, $[M - HCN - 2H]^+$), 207 (15), 196 (25, $[M - CN - Me]^+$), 195 (100, $[M - HCN - Me]^+$), 194 (55, $[M - CN - Me - 2H]^+$), 168 (23), 167 (17), 159 (10, [M - Py]), 133 (20), 132 (18, [PyCH(CN)NH]), 131 (21), 130 (16), 121 (28), 120 (95, $[Ph(Me)CHNH]^+$), 118 (28), 117 (55, $[PyCHCN]^+$), 107 (30), 106 (93), 105 (100, $[Ph(Me)CH]^+$), 104 (50), 103 (54), 92 (80), 79 (70, $[PyH]^+$), 78 (68, Py^+), 77 (79, Ph^+), 63 (13), 52 (30), 51 (32), 43 (30), 39 (35), 27 (40, $[HCN]^+$)
3e	235 (24, M^+), 234 (8, $[M - H]^+$), 220 (20, $[M - Me]^+$), 208 (12), 193 (7), 158 (7, [M − Ph]), 157 (7, [M − Py]), 132 (5), 117 (25), 105 (100, $[Ph(Me)CH]^+$), 90 (17), 79 (28, $[PyH]^+$), 78 (21, Py^+), 77 (42, Ph^+), 63 (13), 51 (28), 39 (11)
2f	235 (2, $[M - 2H]^+$), 222 (7, $[M - Me]^+$), 211 (8, $[M - CN]^+$), 210 (30, $[M - HCN]^+$), 209 (16, $[M - CN - 2H]^+$), 183 (15), 168 (14), 167 (13), 117 (8, $[PyCHCN]^+$), 107 (17), 106 (60), 105 (100, $[Ph(Me)CH]^+$), 104 (20), 103 (25), 91 (19), 79 (38, $[PyH]^+$), 78 (48, Py^+), 77 (42, Ph^+), 63 (21), 52 (32), 51 (36), 50 (30), 39 (23), 27 (22, $[HCN]^+$)
3f	235 (19, M^+), 220 (18, $[M - Me]^+$), 192 (8), 166 (6), 157 (7, $[M - Py]^+$), 156 (10), 116 (5), 106 (10), 105 (100, $[Ph(Me)CH]^+$), 103 (15), 89 (9), 79 (15, $[PyH]^+$), 78 (12, Py^+), 77 (26, Ph^+), 63 (7), 51 (20), 39 (6)
2g	236 (2, $[M - H]^+$), 235 (25, $[M - 2H]^+$), 234 (2), 220 (20, $[M - 2H - Me]^+$), 210 (5, $[M - HCN]^+$), 195 (4), 193 (6), 192 (7), 183 (4), 167 (6), 166 (5), 157 (18), 156 (14), 131 (10), 120 (17), 117 (11, $[PyCHCN]^+$), 106 (52), 105 (100, $[Ph(Me)CH]^+$), 104 (20), 103 (22), 89 (15), 79 (40, $[PyH]^+$), 78 (42, Py^+), 77 (42, Ph^+), 63 (17), 53 (23), 52 (40), 51 (25), 39 (15), 27 (12, $[HCN]^+$)
3g	235 (25, M^+), 234 (5, $[M - H]^+$), 220 (18, $[M - Me]^+$), 208 (3), 192 (7), 157 (10, $[M - Py]^+$), 156 (8), 131 (3), 116 (4), 105 (100, $[Ph(Me)CH]^+$), 103 (13), 89 (7), 79 (14, $[PyH]^+$), 78 (15, Py^+), 77 (21, Ph^+), 63 (10), 51 (18), 39 (5)
3h	249 (30, M^+), 248 (95, $[M - H]^+$), 234 (36, $[M - Me]^+$), 223 (15), 222 (58), 221 (27), 209 (8), 131 (14), 119 (15), 106 (7), 105 (100, $[Ph(Me)CH]^+$), 104 (22), 103 (34), 92 (9), 79 (23, $[PyH]^+$), 78 (18, Py^+), 77 (55, Ph^+), 65 (20), 51 (20), 39 (15)

[a] Registration of the mass spectra for some α-amino nitriles was not successful since decomposition of these compounds took place.
[b] Identical spectra of the optical isomers were obtained.

were thermally unstable under GC analysis conditions. After hydrolysis of the reaction mixtures with aqueous $NaHCO_3$, the products were isolated by column chromatography. Besides the corresponding α-amino nitriles **2**, the formation of unexpected unsaturated nitriles **3** from all the pyridine imines was found (Scheme 2, Table 5).

Usually, reactions of Me_3SiCN with imines lead to α-amino nitriles and not to the unsaturated nitriles (in particular, this is so for the furan and thiophene derivatives; see above). This fact suggests that the pyridine N-atom plays some role in the formation of products **3** (yields in our conditions were up to 33% — run 10, Table 5). Comparable results were obtained in previous investigations[25,26] of Me_3SiCN addition to imines (produced from reactions of furan, thiophene and pyridine aldehydes with unchiral amines), and were also accompanied by the formation of the corresponding unsaturated compounds from pyridine imines only. Apparently, the pathway to unsaturated nitriles is achieved *via* formation of the intermediate σ-complex of AlX_3 with imine (through the N-atom of the pyridine ring) leading to an increase in the hydrogen atom mobility in the CH=N group. The proposed scheme of trimethylsilylcyanation of pyridine imines is given in Ref. 26.

It is interesting to compare this with the results of diastereoselective addition of methyllithium to aldimines (including some heterocyclic ones) derived from (*S*)-1-phenylethylamine.[31] Analogous formation of unsaturated byproducts — ketimines in this case — was found by these authors, who proposed a radical mechanism for these reactions. One can notice that the corresponding ketimine has been formed from the 4-pyridine derivative and not in the case from the 2-furyl compound.

$AlBr_3$ was more active than $AlCl_3$ in the Strecker synthesis with the heterocyclic imines studied. It was found that the reactions proceeded most smoothly under the action of a catalyst together with 4 Å molecular sieves. Furan imines were more active in the addition of Me_3SiCN than for thiophene and pyridine imines. The reactivity of methyl derivatives was higher than that of the heterocyclic azomethines themselves. The aldimines studied are arranged with respect to their reactivity according to Scheme 3.

All the products obtained were characterized by ^1H NMR, polarimetry and GC–MS (Tables 5–7). The reactions in all cases afforded mixtures of the α-amino nitrile diastereomers, with one diastereomer predominating, that being shown by

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the ^{1}H NMR spectra (Tables 5 and 6). All the spectra were found to have two quartets of benzylic protons and two signals of methine protons. The diastereoisomeric ratios obtained were determined by means of ^{1}H NMR using the signals of benzyl protons as key signals. A typical ^{1}H NMR spectrum is shown in Fig. 1 (for the product of Me_3SiCN addition to imine (*S*)-**1f** as an example). The signals of benzyl protons C<u>H</u>(Me)Ph appeared as well-separated quartets: the downfield (major) at δ 4.15–4.27 and the upfield (minor) at δ 3.92–4.02 ppm for all compounds **2** obtained from (*R*)- and from (*S*)-imines. The signals were assigned analogously in recent work[15] on the basis of the study by Ogura and coworkers[14] and taking into consideration the data in Refs 11, 12, 29 as follows: downfield to (*R,R*)- and (*S,S*)-anti-diastereomers and upfield to (*R,S*)- and (*S,R*)-syn-isomers. The signs of optical rotation (Table 5) correlated with ^{1}H NMR data. The α-amino nitriles obtained from all the (*S*)-imines were laevorotatory, whereas the (*R*)-isomers afforded (+)-products. The addition of Me_3SiCN to all the imines studied followed the same sense of asymmetric induction. When the configuration of the nitrogen auxiliary was *R*, the (*R,R*)-α-amino nitriles predominated over the (*S,R*)-isomer, whereas the (*S,S*)-products of addition formed mainly from (*S*)-imines. Thus, *Re* face attack to the (*S*)-imines and *Si* face addition to the (*R*)-imines occurred in all cases. All α-amino nitriles **2** were obtained with moderate diastereopurity: up to 81% for (*R,R*)- and up to 87% for (*S,S*)-isomers. Almost the same values of diastereoisomeric ratio were obtained in both enantiomeric series. Some differences appeared; these were generally in the isolation step of the products by column chromatography.

The thermodynamic/kinetic possibilities in the asymmetric Strecker synthesis with a number of aldimines based on 1-phenylethylamine (using HCN or NaCN in MeOH without any catalyst) were investigated in Refs 12, 14. Formation of amino nitriles has been found to occur under thermodynamic control. Equilibrium between the diastereomers was established in *ca* 0.5 h[12] or 3 h[14] for derivatives of aromatic and aliphatic aldehydes respectively.

Comparable results were obtained in the present work and in Ref. 15. The diastereoisomeric ratio was 80:20 in the synthesis of **2f** from (*S*)-**1f** (Table 5) and 79:21 (in the reaction without catalyst, 6 days).[15] In our opinion, this fact demonstrates that complete equilibrium between the diastereomers was reached in our experiments.

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