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One-Pot Diastereoselective Synthesis of α-Aminonitriles from Aldehydes, Chiral Amines, and Trimethylsilyl Cyanide under Solvent-Free Conditions*

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Abstract—Treatment of aliphatic and aromatic aldehydes with chiral amines and trimethylsilyl cyanide in the absence or in the presence of Lewis acids (including lithium perchlorate) under solvent-free conditions afforded the corresponding α-aminonitriles in good yields and with a diastereoselectivity of 68 to 86%.

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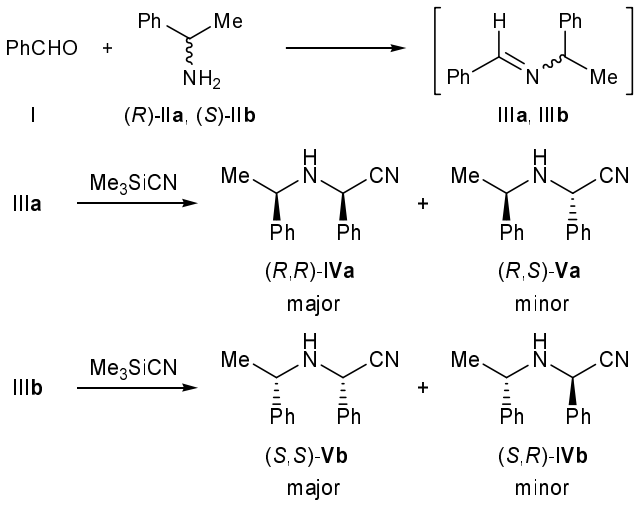
α-Aminonitriles constitute an important class of organic compounds, which can readily be transformed into α-amino acids and their derivatives [1]. The classical Strecker reaction underlies one of the most general methods for the preparation of α-aminonitriles on both laboratory and industrial scales [2]. Strecker reaction typically involves addition of cyanide ion to Schiff bases. Chiral α-aminonitriles were shown to be useful synthons; therefore, development of procedures for asymmetric synthesis of α-aminonitriles is strongly desirable. A number of methods have been proposed for enantioselective preparation of α-aminonitriles [3, 4], e.g., via nucleophilic addition of trimethylsilyl cyanide to Schiff bases generated *in situ* from carbonyl compounds and primary amines in the presence of a chiral Lewis acid or chiral complex [5–10]. We recently reported on the Mannich aminoalkylation of aldehydes with chiral amines in diethyl ether in the presence of lithium perchlorate [11–13]. The present communication describes a simple and efficient one-pot three-component asymmetric synthesis of α-aminonitriles in the absence of a solvent and expensive chiral Brønsted base with moderate diastereoselectivity.

In the first step, we examined the Strecker reaction of benzaldehyde (**I**) and accessible optically pure (*R*)-1-phenylethylamine (**IIa**) and (*S*)-1-phenylethylamine (**IIb**) in the presence of various Lewis acids and in the absence of a catalyst at room temperature to obtain chiral Schiff base **III** as intermediate. Addition of trimethylsilyl cyanide to the reaction mixture led to formation of chiral α-aminonitriles **IV** and **V** in high yields and a diastereoselectivity (diastereoisomer ratio) of 68 to 86% (Scheme 1, Table 1).

In the presence of small amounts of different Lewis acids (~50 mol %), such as $LiClO_4$, ZnI_2, $ZnBr_2$, $ZnCl_2$, $BF_3 \cdot OEt_2$, $AlCl_3$, and L-proline, without any solvent, the yields of α-aminonitriles **IV** and **V** in the Strecker reaction of benzaldehyde (**I**) with (*R*)-1-phenylethylamine (**IIa**) or (*S*)-1-phenylethylamine (**IIb**) were 65–98%, and the diastereoisomer ratio varied from 70:30 to 80:20. In the absence of Lewis acid, the reaction of trimethylsilyl cyanide with chiral Schiff base prepared *in situ* from benzaldehyde (**I**) and (*R*)-1-phenylethylamine (**IIa**) afforded almost pure α-aminonitriles with a diastereoisomer ratio of 72:28. In analogous reaction with (*S*)-1-phenylethylamine (**IIb**),

Scheme 1.



* The text was submitted by the authors in English.

Table 1. Yields and ratios of diastereoisomeric 2-phenyl-2-(1-phenylethylamino)acetonitriles in the reactions of benzaldehyde with (*R*)- and (*S*)-1-phenylethylamines and trimethylsilyl cyanide in the presence of various Lewis acids without a solvent at room temperature

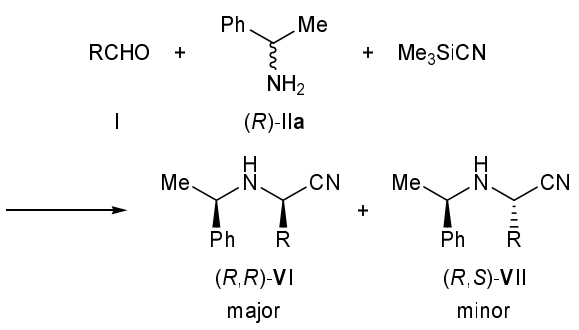
Lewis acid	Reaction with (*R*)-1-phenylethylamine (*R*)-(**IIa**)		Reaction with (*S*)-1-phenylethylamine (*S*)-(**IIb**)	
	yield, %	diastereoisomer ratio **IVa**:**Va**	yield, %	diastereoisomer ratio **Vb**:**IVb**
–	96	72:28	96	69:31
$LiClO_4$	98	78:22	94	76:24
ZnI_2	96	77:23	96	77:23
$ZnBr_2$	93	76:24	88	76:24
$ZnCl_2$	96	78:22	90	78:22
$BF_3 \cdot OEt_2$	98	76:24	88	75:25
$AlCl_3$	65	80:20		
L-Proline	85	70:30		

α-aminonitriles **IV** and **V** were formed at almost the same ratio (69:31). The results are summarized in Table 1. It is seen that the diastereoisomer ratio does not change to a considerable extent in the presence of an achiral Lewis acid, though $LiClO_4$, ZnI_2, and $BF_3 \cdot Et_2O$ give better yields and disatereoselectivity, as compared to the other Lewis acids.

In the second step, various Schiff bases generated *in situ* from aliphatic and aromatic aldehydes and chiral amine were reacted with trimethylsilyl cyanide in the absence of Lewis acid and solvent at room temperature. As a result, the corresponding α-aminonitriles were formed in good to excellent yields in a short time (~10 min). The diastereoisomer ratio varied from 86:14 to 68:32 (Scheme 2, Table 2); it was determined from the CH signal intensities in the ^{1}H NMR spectra of the crude products, δ ~4.70 (**IV**) and 4.40 ppm (**V**). The configuration of both diastereoisomers was established on the basis of their IR and ^{1}H NMR spectra and published data [14–16].

To conclude, it should be emphasized that the proposed one-pot procedure ensures preparation of almost pure α-aminonitriles with a relatively high diastereoselectivity from aliphatic or aromatic aldehydes, (*R*)-1-phenylethylamine, and trimethylsilyl cyanide in the absence of Lewis acid under solvent-free conditions at room temperature in a short time. The use of achiral Lewis acids, as well as carrying out the reaction without a catalyst, does not change the product yield and diastereoisomer ratio to an appreciable extent [14–16]. To the best of our knowledge, the proposed procedure is the first example of one-pot solvent-free asymmetric Strecker synthesis.

Scheme 2.



For R, see Table 2.

EXPERIMENTAL

General procedure for the synthesis of α-aminonitriles IV and V in the absence of solvent and Lewis acid. A mixture of 2 mmol of the corresponding aldehyde and 3 mmol of (*R*)-1-phenylethylamine (**Ia**) was stirred for 1 min at room temperature in a 25-ml flask. Trimethylsilyl cyanide, 2.1 mmol, was then added through a syringe, the mixture was stirred for 10 min at room temperature, 10 ml of water was added, and the mixture was extracted with methylene chloride (3×2 ml). If necessary, the crude product was purified by column chromatography using hexane–ethyl acetate (6:1) as eluent. The products were identified by the IR, NMR, and mass spectral data and by comparison with authentic samples.

General procedure for the synthesis of α-aminonitriles IV and V in the absence of solvent in the presence of Lewis acid. A mixture of 2 mmol of the corresponding aldehyde, 50 mol % of Lewis acid, and 3 mmol of (*R*)-1-phenylethylamine (**Ia**) was stirred for 1 min at room temperature in a 25-ml flask. Trimethylsilyl cyanide, 2.1 mmol, was then added through

Table 2. Yields and ratios of diastereoisomeric α-aminonitriles in reactions of aliphatic and aromatic aldehydes with (*R*)- and (*S*)-1-phenylethylamines and trimethylsilyl cyanide in the absence of Lewis acid and solvent at room temperature

R in RCHO	Phenylethylamine	Yield,[a] %	Diastereoisomer ratio (*R*,*R*)-(**VI**):(*R*,*S*)-(**VII**)
4-FC_6H_4	(*R*)-(**IIa**)	98	72:28
2-Thienyl	(*R*)-(**IIa**)	85	76:24
4-Pyridyl	(*R*)-(**IIa**)	75	86:14
$C_6H_5CH{=}CH$	(*R*)-(**IIa**)	80	74:26
2-$MeOC_6H_4$	(*R*)-(**IIa**)	75	72:28
1-Naphthyl	(*R*)-(**IIa**)	79	70:30
2-Naphthyl	(*R*)-(**IIa**)	82	72:28
4-ClC_6H_4	(*R*)-(**IIa**)	88	68:32
2,4-$Cl_2C_6H_4$	(*R*)-(**IIa**)	90	72:28
$(CH_3)_2CH$	(*R*)-(**IIa**)	80	70:30
$C_6H_5CH_2CH_2$	(*R*)-(**IIa**)	85	75:25
4-FC_6H_4	(*S*)-(**IIb**)	90	68:32[b]
2-Thienyl	(*S*)-(**IIb**)	80	73:24[b]

[a] According to the ^{1}H NMR data (500 MHz, $CDCl_3$).
[b] (*S*,*S*):(*S*,*R*).

a syringe, the mixture was stirred for 10 min at room temperature, 10 ml of water was added, and the mixture was extracted with methylene chloride (2×10 ml). If necessary, the crude product was purified by column chromatography using hexane–ethyl acetate (6:1) as eluent. The products were identified by the IR, NMR, and mass spectral data and by comparison with authentic samples.

Caution! Although we had no accident while using lithium perchlorate, it is advisable to dry $LiClO_4$ in a fume hood using a suitable lab shield. All reactions were carried out in a fume hood.

Some spectral data for the major diastereoisomers are given below.

(*R*,*R*)-2-Phenyl-2-(1-phenylethylamino)acetonitrile (IVa) [16]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3323.4 (NH), 2248.2 (CN). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.48 d (3H, *J* = 6.5 Hz), 1.83 s (1H), 4.29 q (1H, *J* = 6.5 Hz), 4.41 s (1H), 7.23–7.62 m (10H). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 26.2 (CH_3), 52.8 (HNCH), 57.4 (H**C**CN), 119.5 (CN), 127.4 (CH), 127.5 (CH), 128.0 (CH), 128.4 (CH), 129.0 (CH), 129.2 (CH), 135.8 (C), 143.8 (C).

(*R*,*R*)-2-(4-Fluorophenyl)-2-(1-phenylethylamino)acetonitrile (VIa) [17]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3325.4 (NH), 2233.4 (CN). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.48 d (3H, *J* = 6.8 Hz), 1.98 s (1H), 4.29 q (1H, *J* = 6.7 Hz), 4.41 s (1H), 7.10–7.70 m (9H).

(*R*,*R*)-2-(1-Phenylethylamino)-2-(2-thienyl)acetonitrile (VIb) [7, 18]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3319.6 (NH), 2232.7 (CN). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.48 d (3H, *J* = 6.5 Hz), 2.08 s (1H), 4.25 q (1H, *J* = 6.5 Hz), 4.59 s (1H), 7.01–7.82 m (8H).

(*R*,*R*)-4-Phenyl-2-(1-phenylethylamino)-3-butenenitrile (VId) [7, 17, 19]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3361.1 (NH), 2227.9 (CN). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.48 d (3H, *J* = 6.7 Hz), 1.72 s (1H), 3.99 d.d (1H), 4.2 q (1H, *J* = 6.6 Hz), 6.10 d.d (1H), 6.30 d.d (1H), 7.15–7.75 m (10H).

(*R*,*R*)-2-(2-Methoxyphenyl)-2-(1-phenylethylamino)acetonitrile (VIe) [14]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3335.4 (NH), 2222.6 (CN). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.47 d (3H, *J* = 6.5 Hz), 2.30 s (1H), 3.81 s (3H), 4.31 q (1H, *J* = 6.5 Hz), 4.54 s (1H), 6.95–7.50 m (9H).

(*R*,*R*)-2-(1-Naphthyl)-2-(1-phenylethylamino)acetonitrile (VIf) [2]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3329.9 (NH), 2243.0 (CN). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.51 d (1H, *J* = 6.8 Hz), 1.81 d (1H, *J* = 11.5 Hz), 4.38 q (1H, *J* = 6.7 Hz), 4.91 d (1H, *J* = 11.3 Hz), 7.20–7.91 m (12H).

(*R*,*R*)-2-(2-Naphthyl)-2-(1-phenylethylamino)acetonitrile (VIg) [16]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3328.1 (NH), 2242.1 (CN). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.49 d (3H, *J* = 6.5 Hz),

1.91 d (1H, *J* = 11.9 Hz), 4.34 q (1H, *J* = 6.5 Hz), 4.59 d (1H, *J* = 11.9 Hz), 7.28–8.09 m (12H).

(*R*,*R*)-2-(4-Chlorophenyl)-2-(1-phenylethylamino)acetonitrile (VIh) [14]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3329.9 (NH), 2232.7 (CN). ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.47 d (3H, *J* = 6.8 Hz), 1.83 d (1H, *J* = 12.1 Hz), 4.27 q (1H, *J* = 6.8 Hz), 4.39 d (1H, *J* = 12.1 Hz), 7.22–7.65 m (9H).

(*R*,*R*)-2-(2,4-Dichlorophenyl)-2-(1-phenylethylamino)acetonitrile (VIi) [19]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3331.2 (NH), 2235.2 (CN). ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.47 d (3H, *J* = 6.6 Hz), 1.84 d (1H, *J* = 11.1 Hz), 4.25 q (1H, *J* = 6.5 Hz), 4.65 d (1H, *J* = 11.4 Hz), 7.22–7.59 m (8H).

(*R*,*R*)-3-Methyl-2-(1-phenylethylamino)butanenitrile (VIj) [20]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3332.6 (NH), 2251.2 (CN). ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.36 m (6H), 1.46 d (3H, *J* = 6.6 Hz), 1.71 m (1H), 2.11 s (1H), 3.6 d (1H, *J* = 6.4 Hz), 4.22 q (1H, *J* = 6.6 Hz), 7.21–7.45 m (5H).

(*R*,*R*)-4-Phenyl-2-(1-phenylethylamino)butanenitrile (VIk) [14]. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 3334.4 (NH), 2249.1 (CN). ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.48 d (3H, *J* = 6.5 Hz), 1.83 s (1H), 2.62 m (2H), 3.22 t (2H, *J* = 7.4 Hz), 3.71 t (1H, *J* = 7.2 Hz), 4.32 q (1H, *J* = 6.5 Hz), 7.23–7.58 m (10H).

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