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Acyclic Stereocontrol in the Addition of Trimethylsilyl Cyanide to *N*-substituted Imines of (2*S*)-Lactic Aldehyde.

Gianfranco Cainelli*, Daria Giacomini*, Alessandra Treré, Paola Galletti.

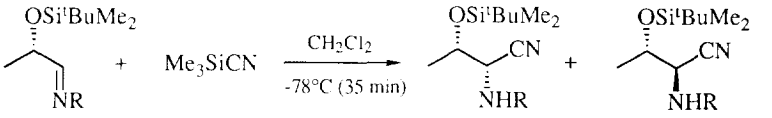
Dipartimento di Chimica "G.Ciamician" Università di Bologna
Via Selmi 2, I-40126 Bologna, Italy.

Abstract: The cyanosilylation of a series of *N*-substituted lactaldehyde imines is reported. The trimethylsilylcyanide addition affords optically active α-amino nitriles. All the imines show a *syn* diastereofacial selectivity that is maintained irrespective to the nature of the Lewis acid employed and even remains in the noncatalyzed reaction.

α-Amino nitriles are important intermediates in the synthesis of nitrogen containing compounds[1] and considerable attention has been given to stereoselective methods for their preparation because of the possibility of tranformation into enantiopure α-amino acids. In this field, asymmetric Strecker syntheses have been widely used for the preparation of α-amino acids *via* hydrolysis of the corresponding α-amino nitriles obtained by hydrocyanation of aldimines with chiral *N*-substituents[2]. In spite of the well documented addition of trimethylsilyl cyanide (TMS-CN) to aldehydes[3], little attention has been devoted to imines[4]. Recently Reetz and coworkers described the reaction of α-*N*,*N*-dibenzylamino aldimines with trimethylsilyl cyanide in presence of Lewis acids as promoters[5] leading to α,β-diaminonitriles with high *anti* diastereoselectivity, and Herranaz prepared cyanomethylene pseudopeptides by the acid catalyzed addition of TMS-CN to unstable aldimine intermediates[6].

In a series of our studies, we have demonstrated the usefulness of α-alkoxy metallo imines in the control of the 1,2-asymmetric induction in nucleophilic addition by lithiumalkyls[7a], organomagnesium[7a] and organocopper reagents[7b]. Now we would like to report a study on the cyanosilylation of *N*-substituted imines derived from the *O*-protected (2*S*)-lactic aldehyde by means of trimethyl silyl cyanide (TMS-CN), describing herein the influence of reaction conditions and substrates on the stereochemical outcome.

Scheme 1



1a-c **2a-c** **3a-c**

1a: R= p-MeOPhenyl **1b:** R=Diphenylmethyl
1c: R= $SiMe_3$ **2c,3c:** R=H

The products in these Strecker-type reactions are *N*-protected α-amino-β-alkoxy nitriles which are potential building blocks for further synthetic elaboration (Scheme 1).

Results and discussion

The enantiomerically pure *O*-protected imines **1a-b** are prepared from *2(S)-O-(t*-butyldimethylsilyloxy)propanal[8] with *p*-methoxyphenyl-amine or diphenylmethyl-amine in anhydrous CH_2Cl_2 and $MgSO_4$ as dehydrating agent, while metalloimine **1c** has been prepared according to our already described procedure[9] and used generally as such. In a typical procedure 1 mmol of the imine was reacted with TMS-CN (1.1 mmol) in anhydrous CH_2Cl_2 (12mL) at -78°C with or without a Lewis acid under inert atmosphere for 0.5 hour, then the reaction mixture was quenched at -78°C with a saturated aqueous solution of NH_4Cl. The *syn/anti* ratio (**2a-c**: **3a-c**) was determined directly on the crude product by ^{1}H-NMR analysis. Results are collected in Table 1.

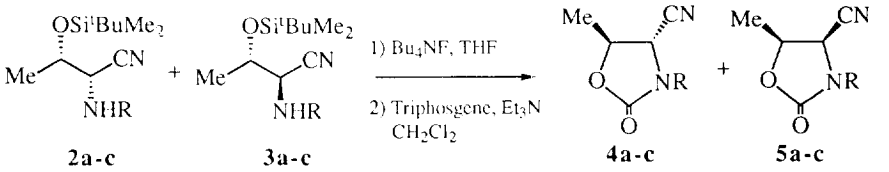
Table 1

Entry	imine	Lewis acid	yield %	syn:anti
1	**1a**	-	40	86:14
2	"	ZnI_2 (0.1eq)	95	80:20
3	"	$ZnMe_2$ (0.1eq)	82	79:21
4	"	$AlMe_3$ (0.1eq)	62	81:19
5	"	$LiClO_4$ (1.1eq)	23	74:26
6	"	Et_2AlCl (1.2eq)	23	80:20
7	"	Me_3SiOTf(2eq)	92	53:47
8	"	ZnI_2 (2eq)	97	90:10
9		-	51	78:22*
10	**1b**	-	67	67:33
11	"	ZnI_2(0.1eq)	93	74:26
12	"	$ZnMe_2$(0.1eq)	97	65:35
13		$AlMe_3$(0.1eq)	89	63:37
14	**1c**	-	80	79:21
15		ZnI_2(0.1)	-	-
16		ZnI_2(2eq)	16	77:23
17		Me_3SiOTf(2eq)	90	64:36

* 2eq. of TMS-CN were used

The assignment of the absolute configuration at the new stereogenic center in epimers **2a-c** and **3a-c** was established by the $J_{4,5}$ value in the ^{1}H-NMR spectra of the corresponding oxazolidin-2-ones obtained from the respective *O*- deprotected aminonitriles, after reaction with triphosgene. The *cis* oxazolidin-2-ones showed a $J_{4,5}$ value of 7.9 Hz consistent with a H_4,H_5 *cis* disposition, while in the *trans* isomer the value of this coupling constant was 5.1-5.6 Hz (scheme 2).[10]

Scheme 2



2a-c **3a-c** **4a-c** **5a-c**

a: R= p-MeOPhenyl **b**: R=Diphenylmethyl **c**: R=H

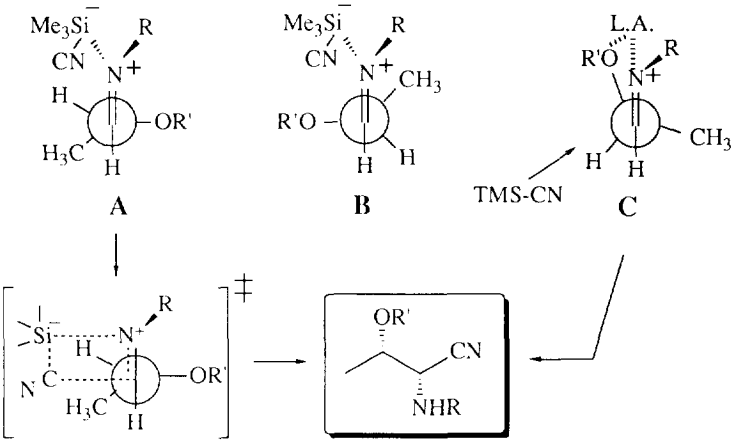
When the imine **1a** is submitted to a reaction with TMS-CN, the Lewis acids ZnI_2 and Me_3SiOTf proved to be the best promoters leading to a quantitative conversion into the corresponding aminonitriles (entries 2 and 7), while $LiClO_4$ and Et_2AlCl are the worst (entries 5 and 6). Interestingly the reaction proceeds in considerable yields (40%) even without any catalyst (entry 1). With a 10 mol % of a Lewis Acid the *syn* isomer is preferred, but higher *syn* diastereoselectivity is reached by the noncatalyzed reaction. Increasing the amount of ZnI_2 until 2 equivalents (entry 8) raises the **2a**:**3a** ratio to 90:10. Using a non-chelating catalyst, such as Me_3SiOTf, the diastereoselectivity drops to 53:47 (entry 7). The *N*- diphenylmethylimine **1b** is more reactive than **1a**, in fact without catalyst the yield is 67% while with $ZnMe_2$ the conversion is quantitative (entries 10 and 12). In this case however the stereoselectivity is lower irrespective of the nature of the Lewis acid. The *N*-trimethylsilyl imine **1c** shows the highest reactivity affording, in the noncatalyzed reaction, the *N*-unsubstituted aminonitriles **2c** and **3c** in a 80% yield (entry 14), with a 79:21 *syn/anti* ratio. With this substrate, ZnI_2, but not Me_3SiOTf, appears to be detrimental to the yield while the diastereoselectivity remains unchanged (77:23 entry 16).

*It is noteworthy that all the imines **1a-d** are more reactive than the common starting aldehyde* since attempted reaction of the 2(*S*)-*O*-(*t*-butyldimethylsilyloxy)propanal in a noncatalyzed reaction with TMS-CN at -78°C gave only traces of the corresponding cyanohydrin.[11]

A mechanism consistent with our results has been considered. Recently it has been reported that trimethylsilyl cyanide smoothly reacts with aldehydes in the presence of a catalytic amount of a Lewis base such as amine, phosphine, arsine or antimony compounds to afford the corresponding cyanohydrin trimethyl silyl ethers in excellent yields.[12] In this reaction the Lewis bases would coordinate to TMS-CN to form a reactive intermediate, a pentacoordinated silicate, which has the potential for reacting with aldehydes. In our case, in absence of any catalyst, the first event could be the coordination of the trimethylsilyl cyanide with the lone pair on the nitrogen atom of the imine generating the intermediate depicted in Scheme 3. In this structure the highly coordinated silicon enhances the nucleophilicity of the cyanide as well as the electrophilicity of the imine carbon favoring the intramolecular transfer of the cyanide group in an autocatalytic manner.[13] Assuming an open chain model, the intermediate **A** and **B** could be formulated.[14] The **B** adduct appears to be destabilized by a non bonded interaction betweeen *N*-substituents and the imine side chain; the rotamer **A** does not have this unfavorable interaction and the following intramolecular attack of the

cyanide group occurs in an antiperiplanar fashion to the alkoxy-group, leading to the syn isomer. In presence of an external Lewis acid the cyanosilylation probably proceeds through the chelation complex **C** to give the *syn* adduct selectively. This hypothesis is substantiated by the little diastereoselectivity shown by Me_3SiOTf in agreement with his non-chelation properties.

Scheme 3



In conclusion, the present work shows that enantiopure *O*-(*t*-butildimethylsilyloxy) imines of (2*S*)-lactic aldehyde are easily reacted with TMS-CN. A *syn* diastereofacial selectivity is observed in each case in the presence of a Lewis acid as well in the noncatalized reaction. The method was applied to the synthesis of chiral *N*-substituted and *N*-unsubstituted α-amino nitriles, useful starting materials for α-amino acids.[15]

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Experimental

Commercially available compounds were used without further purification. Solvents were dried and purified by standard methods. Melting points were recorded on a Buchi apparatus and were uncorrected. IR spectra were recorded on a FT-IR Nicolet 205. NMR spectra were performed in $CDCl_3$ solution on Varian Gemini 300 and Gemini 200 instruments with TMS as internal standard. Mass spectra were recorded at an ionization energy of 70 eV on a HP-5971. Exact mass were recorded on VG 7070 E; optical rotation was recorded on Perkin Elmer polarimeter 241. TLC were performed on silica gel 60 F-254 plates and column chromatography on Merck Kieselgel 60 (230-400 mesh). *N*-(Trimethylsilyl)-imine **1c** was prepared as described in the literature.[9]

Imines **1a-b** were prepared as follows: To a stirred solution of aldehyde (10mmol), in dry CH_2Cl_2 (15mL) at 0°C were added the amine (10 mmol) and a large excess of anhydrous $MgSO_4$ successively. The resulting mixture was stirred for 2h at room temperature. The filtered solution was evaporated to give the crude imine.

(2S)-2-(t-butyl-dimethylsilyloxy)-N-(p-methoxyphenyl)-propanal imine (**1a**).

1a (1.24 mmol, 0.36 g), was obtained as a brown oil following the general procedure, yield=62%

IR (film) : 1658, 1250 cm^{-1}

m/e: 293 (M^+, 1), 278(3), 236(100), 221(12), 206(7), 134(8), 73(21), 57(6).

^1H NMR : (300 MHz , $CDCl_3$) : 7.75 (d, *J*=5.0 Hz, 1H, **H**C=N); 6.85- 7.10 (m, 4H, Ar**H**); 4.48 (dq, J_1=5.0 Hz, J_2=6.3 Hz, 1H, **CH**OSi); 3.80 (s, 3H, O**CH**$_3$); 1.39 (d, *J*=6.3 Hz, 3H, **CH**$_3$); 0.91 (s, 9H, (**CH**$_3$)$_3$C); 0.11 (s, 3H, **CH**$_3$Si); 0.09 (s, 3H, **CH**$_3$Si).

(2S)-2-(t-butyl-dimethylsilyloxy)-N-(diphenylmethyl) propanal imine (**1b**).

1b (1.4 mmol, 0.49 g), was obtained as clear oil, yield=70%

m/e : 353 (M^+ 1), 296(4), 221(23), 167(100), 115(4), 73(20).

IR (film) : 3050, 2960, 2860, 1672, 1250 cm^{-1}

^1H NMR : (300 MHz, $CDCl_3$) : 7.78 (d, *J*=6.3 Hz, 1H, **H**C=N); 7.50-7.10 (m, 10H, Ar**H**); 5.21 (s, 1H, Ph_2**CH**); 4.45 (quintet, *J*=6.3 Hz, 1H, **CH**OSi); 1.38 (d, *J*=6.3 Hz, 3H, **CH**$_3$); 0.90 (s, 9H, (**CH**$_3$)$_3$C); 0.11 (s, 3H, **CH**$_3$Si); 0.09 (s, 3H, **CH**$_3$Si).

General procedure for the synthesis of protected aminonitriles

To a solution of imine **1a-c** (1 mmol) in anhydrous CH_2Cl_2 (12 ml) at -78°C, under inert atmosphere, 1.1 eq of Me_3SiCN was added. After being stirred for 35 min, at -78°C a saturated acqueous solution of NH_4Cl (10mL) was added, warming to room temperature the aqueous phase was re-extracted with CH_2Cl_2 (2x20mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated.

General procedure for the synthesis of protected aminonitriles in presence of a Lewis acid.

To a solution of the Lewis acid (0.1 mmol) in anhydrous CH_2Cl_2 (10 ml) at -78°C under inert atmosphere, was added the imine **1a-c** (1 mmol) in 2mL of CH_2Cl_2 and after 10 min. Me_3SiCN (1.1 mmol). After being stirred for 35 min, at -78°C a saturated aqueous solution of NH_4Cl (10 mL) was added, warming to room temperature the aqueous phase was re-extracted with CH_2Cl_2 (2x20 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated.

(2S,3S) and (2R,3S)-3-(t-butyldimethylsilyloxy)-2-N-(p-methoxyphenyl)-butanonitrile (**2a**)*and* (**3a**)

The residue obtained with the general procedure was purified by silica-gel column cromatography (cyclohexane/AcOEt=9/1) obtaining the mixture of the two diastereoisomers. Using ZnI_2 (2 eq. entry 8 Table 1) **2a** was obtained pure by crystallization with CH_2Cl_2 / pentane.

IR(film) : 3320, 3000, 2960, 2250, 1250 cm^{-1} m/e: 320 (M^+, 1); 293(2); 236(100); 221(11); 73(29)
HRMS: found 320.1919 (calculated 320.1920 for $C_{17}H_{28}N_2O_2Si$).
2a: m.p. 57-59°C; $[\alpha]_D^{25}$ +136.8 (c=2.96, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): 6.90-6.60 (m, 4H, Ar**H**); 4.31 (dq, J_1=2.8 Hz, J_2=6.2 Hz, 1H, **CH**OSi); 4.0 (d, J=2.8 Hz, 1H, **CH**CN); 3.78 (s, 3H, O**CH**$_3$); 2.5 (bs, 1H, N**H**); 1.36 (d, J=6.2 Hz, 3H, **CH**$_3$); 0.95 (s, 9H, (**CH**$_3$)$_3$C); 0.18 (s, 3H, **CH**$_3$Si); 0.12 (s, 3H, **CH**$_3$Si).
^{13}C NMR (300 MHz, $CDCl_3$): 153.83, 138.99 (**Ar**), 119.01 (**CN**); 116.05,114.99 (**Ar**); 68.72 (**CH**OSi); 55.64(O**CH**$_3$); 53.53(**CH**CN); 25.71((**CH**$_3$)$_3$C); 20.40(**CH**$_3$); 17.95 ((CH$_3$)$_3$**C**); -4.49(**CH**$_3$Si);-4.92 (**CH**$_3$Si).
3a: ^1H NMR (200 MHz, $CDCl_3$): 6.90-6.60 (m, 4H, Ar**H**); 4.17 (dq, J_1=3.6 Hz, J_2=6.2 Hz, 1H, **CH**OSi); 4.05 (d, J=3.6 Hz, 1H, **CH**CN); 3.78 (s, 3H, O**CH**$_3$); 2.5 (bs, 1H, N**H**); 1.42 (d, J=6.2 Hz, 3H, **CH**$_3$); 0.96 (s, 9H, (**CH**$_3$)$_3$C); 0.18 (s, 3H, **CH**$_3$Si); 0.12 (s, 3H, **CH**$_3$Si).
^{13}C NMR (300MHz, $CDCl_3$): 153.83, 138.99(**Ar**); 118.90 (**CN**); 116.08,114.99 (**Ar**); 68.54 (**CH**OSi); 55.64 (O**CH**$_3$); 54.80(**CH**CN); 25.71 ((**CH**$_3$)$_3$CH); 20.91 (**CH**$_3$); 17.94 ((CH$_3$)$_3$**C**); -4.87 (**CH**$_3$Si);-4.92 (**CH**$_3$Si).

(2S,3S) and (2R,3S)-3-(t-butyldimethylsilyloxy)-2-N-(diphenylmethyl)-butanonitrile (**2b**) *and* (**3b**)
The residue obtained with the general procedure was purified by silica-gel column cromatography (cyclohexane/AcOEt=9/1) R_f=0.6 obtaining a mixture of **2b** and **3b**.
for a mixture of **2b**:**3b**=70:30 (de=40%) we obtained $[\alpha]_D^{25}$ +36.0 (c=4.8, $CHCl_3$).
IR (film): 3325, 3100, 2230, 1250 cm^{-1}. m/e: 380 (M^+ 2), 296(5),221(12),167(100),115(5), 73(25)
HRMS: found 380.2282 (calculated 380.2284 for $C_{23}H_{32}N_2OSi$).
2b: ^1H NMR (300 MHz, $CDCl_3$): 7.55-7.20 (m, 10H, Ar**H**); 5.14 (s, 1H, Ph$_2$**CH**); 4.14 (dq, J_1=3.1 Hz, J_2=6.3 Hz, 1H, **CH**OSi); 3.34 (d, J=3.1 Hz, 1H, **CH**NH); 2.20 (bs, 1H, N**H**); 1.37 (d, J=6.3 Hz, 3H, **CH**$_3$); 0.89(s, 9H, (**CH**$_3$)$_3$C); 0.09 (s, 3H, **CH**$_3$Si); 0.08 (s, 3H, **CH**$_3$Si).
^{13}C NMR (300 MHz, $CDCl_3$): 143.28, 141.28, 128.72, 128.59, 127.38, 126.86 (**Ar**); 119.09 (**CN**); 68.75 (**CH**OSi); 64.93 (Ph$_2$**CH**); 54.99 (**CH**CN); 25.64 ((**CH**$_3$)$_3$C); 19.97 (**CH**$_3$); 17.87 ((CH$_3$)$_3$**C**) ; -4.67 (SiCH$_3$); -5.01 (SiCH$_3$).
3b: ^1H NMR (300 MHz, $CDCl_3$): 7.55-7.20 (m, 10H, Ar**H**); 5.15 (s, 1H, Ph$_2$**CH**); 4.09 (dq, J_1=3.9 Hz, J_2=6.3 Hz, 1H, **CH**OSi); 3.29 (d, J=3.9 Hz, 1H, **CH**CN); 2.20 (bs, 1H, N**H**); 1.31 (d, J=6.3 Hz, 3H, **CH**$_3$); 0.88 (s, 9H, (**CH**$_3$)$_3$C); 0.10 (s, 3H, **CH**$_3$Si); 0.09(s, 3H, **CH**$_3$Si).
^{13}C NMR (300 MHz, $CDCl_3$): 143.23, 141.40, 128.72, 128.59, 127.38, 126.86 (**Ar**); 118.08 (**CN**); 68.94 (**CH**OSi); 64.93 (Ph$_2$CH); 56.02 (**CH**CN); 25.59 ((**CH**$_3$)$_3$C); 20.96 (**CH**$_3$); 17.87 ((CH$_3$)$_3$**C**); -4.39 (SiCH$_3$); -4.85 (SiCH$_3$).

(2S,3S) and (2R,3S) -3-(t -butyldimethylsilyloxy)-2-amino-butanonitrile (**2c**) *and* (**3c**)
The residue obtained with the general procedure, was purified by silica-gel column cromatography (cyclohexane/AcOEt=7/3) and only **2c** was obtained pure in the early fraction, while **3c** was eluted as mixture.
IR(film) :3300,2850,2250,1250 cm-1. m/e: 214(M^+ 1),172(5); 157(11); 130(100); 115(16); 73(31).

HRMS: found 214.1502 (calculated 214.1501 for $C_{10}H_{22}N_2OSi$).

2c: clear oil, $[\alpha]_D^{25}$ +14.7 (c=3.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) : 4.02 (dq, J_1=4.2 Hz J_2=6.3 Hz, 1H, **CH**OSi); 3.60 (d, J_1=4.2 1H, **CH**CN); 1.80 (bs, 2H, NH_2); 1.27 (d, J=6.3 Hz, 3H, CH_3); 0.9 (s, 9H, $(CH_3)_3C$); 0.15 (s, 3H, CH_3Si); 0.14 (s, 3H, CH_3Si).

^{13}C NMR (300 MHz; $CDCl_3$): 120.64 (**C**N); 69.24 (**C**HOSi); 49.94 (**C**HCN); 25.48 ((**C**H_3)$_3$C); 19.28 (**C**H_3); 17.70 (CH$_3$)$_3$**C**); -4.86 (**C**H_3Si); -5.17 (CH$_3$Si).

3c: ^1H NMR (300 MHz, $CDCl_3$): 3.95 (dq, J_1=3.8Hz J_2=6.3 Hz, 1H, **CH**OSi); 3.57 (d, J=3.8, 1H, **CH**CN); 1.80 (bs, 2H, NH_2); 1.30 (d, J=6.3, 3H, CH_3); 0.9 (s, 9H, $(CH_3)_3C$); 0.15 (s, 3H, CH_3Si); 0.14 (s, 3H, CH_3Si).

^{13}C NMR (300 MHz, $CDCl_3$): 119.97 (**C**N); 69.42 (**C**HOSi); 50.65 (**C**HCN); 25.60 ((**C**H_3)$_3$C); 20.40 (**C**H_3); 17.70 ((CH$_3$)$_3$**C**); -4.73 (**C**H_3Si); -5.10 (**C**H_3Si).

General procedure for the synthesis of 1,3-oxazolidin-2-ones

To a solution of *O* -protected aminonitrile (0.53 mmol) in dry THF at room temperature and under argon atmosphere were added 0.8 mmol of tetrabutylammoniumfluoride (TBAF) solution (1.1M in THF). The mixture was stirred overnight and then quenched at O°C with a saturated $KHCO_3$ solution and extracted with ethylacetate (3x50ml). The organic phase dried over Na_2SO_4 and evaporated gave a crude product that was cyclized using triphosgene (0.25 mmol) in dry CH_2Cl_2 (6 ml) at O°C and Et_3N (0.76mmol). The mixture was stirred two days at 20°C. Quenching with a saturated solution of NH_4Cl, extraction with CH_2Cl_2 (3x20ml), drying over Na_2SO_4 and evaporation gave the crude product that was purified by silica gel cromatography (eluant: cyclohexane/ ethylacetate=1/1)

4a: IR (nujol): 2938, 2249, 1771 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$): 7.40-7.00 (m, 4H, Ar**H**); 4.88 (dq, J_1=5.1, J_2=6.3 Hz, 1H, CH_3**CH**); 4.56 (d, J=5.1 Hz, 1H, **CH**CN); 3.81 (s, 3H, O**CH**$_3$), 1.60 (d, J=6.3 Hz, 3H, **CH**$_3$).

^{13}C NMR (300 MHz, $CDCl_3$): 158.5 (**C**=O); 154.00, 129.5, 124.4, 114.8 (**Ar**); 111.90(**C**N); 72.87 (CH_3**C**H); 55.48 (O**C**H$_3$); 54.68 (**C**HCN); 20.01 (**C**H$_3$).

4b: IR (nujol): 2249, 1750 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): 7.20-7.50 (m, 10H, Ar**H**); 6.38 (s, 1H, Ph_2**CH**); 4.84 (quintet, 1H, J=6.4 Hz, CH_3**CH**); 3.73 (d, 1H,J=5.6 Hz, **CH**CN); 1.47(d, 3H, J=6.4 Hz, **CH**$_3$).

^{13}C NMR (200 MHz, $CDCl_3$): 155.65 (**C**=O), 136.6, 129.0, 128.7, 128.6, 128.4, 128.2, 127.8(**Ar**); 115.61(**C**N); 73.85 (CH_3**C**H); 62.14 (Ph_2**C**H); 50.98 (**C**HCN); 19.87 (**C**H$_3$).

5b: IR (nujol): 2249, 1750 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): 7.20-7.50 (m, 10H, Ar**H**); 6.30 (s,1H,Ph_2**CH**); 4.80 (m, 1H, CH_3**CH**);4.31 (d, 1H,J=7.9 Hz, **CH**CN); 1.66 (d, 3H, J=6.3 Hz, **CH**$_3$).

^{13}C NMR (200 MHz, $CDCl_3$): 155.64 (**C**=O), 137.11, 128.0, 128.7, 128.6, 128.4, 128.2, 127.8 (**Ar**); 113.75 (**C**N), 71.05 (CH_3**C**H); 61.93 (Ph_2**C**H); 50.63 (**C**HCN); 17.24 (**C**H$_3$).

4c:(IR (nujol): 3300, 2249, 1755 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$): 6.60 (bs, 1H, NH); 4.92 (m, 1H, **CH**CH_3); 4.26 (d, 1H,J=5.2 Hz, **CH**CN); 1.58 (d, 3H,J=6.4 Hz, **CH**$_3$).

^{13}C NMR (300 MHz, $CDCl_3$): 157.4 (**C**=O); 116.4 (**C**N); 76.32 (CH_3**C**H); 48.68 (**C**HCN); 19.93 (CH_3).

5c: (IR (nujol): 3300, 2249, 1755 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): 6.60 (bs, 1H, **NH**); 4.90 (m, 1H, **CH**CH_3); 4.72 (d, 1H,*J*=7.9 Hz, **CH**CN); 1.68 (d, 3H,*J*=6.4 Hz, CH_3).

^{13}C NMR (300 MHz, $CDCl_3$): 158.0 (**C**=O); 114.90 (**C**N); 73.41 (CH_3**C**H); 48.55 (**C**HCN); 17.32 (CH_3).

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10. See for instance ref.7c
11. When (2*S*)-*O*-protected lactic aldehyde (1 eq.) was reacted with 1eq. of TMS-CN in CH_2Cl_2 at -78°C, only starting aldehyde and traces of the corresponding cyanohydrin could be detected after 1h.
12. See ref.3d) and Kobayashi,S.; Tsuchiya,Y.; Mukaiyama,T. *Chemistry Lett.* **1991**, 537
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15. Preliminary experiments using adduct **2a** show that hydrolysis of the cyano group to form the corresponding carboxylic acid is possible (conc; HCl solution: 6h at reflux).

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