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Guanidine-Catalyzed Asymmetric Trimethylsilylcyanation of Carbonyl Compounds

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Abstract: Several kinds of modified guanidines were applied to the trimethylsilylcyanation of 3-phenylpropanal, cylohexanecarboxaldehyde, pivalaldehyde, and 4-phenyl-2-butanone. Good to moderate enantioselectivity was obtained, even on a ketonic substrate, when a C_2-symmetrical bicyclic guanidine, (2*S*,3*S*,7*S*,8*S*)-tetraphenyl-1,4,8-triaza[2.2.0]bicyclooct-4-ene, was used as a base catalyst.

Keywords: asymmetric catalysis; cyanotrimethylsilane; guanidines; hydrocyanation; nitriles; organic catalysis

Introduction

Hydrocyanation of carbonyl compounds with hydrogen cyanide (HCN), leading to α-hydroxy acids by hydrolysis of the resulting addition products, is an important organic reaction for carbon-carbon bond formation.[1] Cyanotrimethylsilane (TMSCN)[2] can be used as the equivalent of HCN, in which a Lewis acid is basically needed as an additive in order to activate carbonyl substrates and the addition products are trimethylsilylated cyanohydrins (TMS-cyanohydrins). The use of chiral additives leads to TMS-cyanohydrins with good asymmetric induction.[1b,3] Guanidines can be characterized as superbases[4] in organic synthesis due to their strong basicity.[5] We have explored the possibility of readily available modified guanidines[6] as re-useable chiral superbases in asymmetric synthesis.[7] The reaction of carbonyl compounds with TMSCN in the presence of a modified guanidine was examined in the course of our studies on guanidine chemistry and reasonable asymmetric induction was observed when a newly prepared C_2-symmetrical bicyclic guanidine, (2*S*,3*S*,7*S*,8*S*)-tetraphenyl-1,4,8-triaza[2.2.0]bicyclooct-4-ene, was used as a catalyst. In this paper we present the guanidine-catalyzed asymmetric trimethylsilylcyanation (TMS-cyanation) of carbonyl compounds.

Results and Discussion

In this study five modified guanidines, **1**,[6a] **2**,[6a] **3**,[6b] **4**,[6c] and **5**, as shown in Figure 1, were examined in the TMS-cyanation as catalysts.

Corey et al.[8] had reported that a C_2-symmetrical bicyclic guanidine, (3*S*,7*S*)-1,4,6-triazabicylco[2.2.0]oct-4-ene, acted as an effective organic base catalyst in the asymmetric Strecker reaction of diphenylmethyliminobenzaldehyde with hydrogen cyanide (HCN) (96% yield, 86% ee). Thus, a structurally-related C_2-symmetrical bicyclic guanidine **5** was newly designed and prepared from (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**6**)

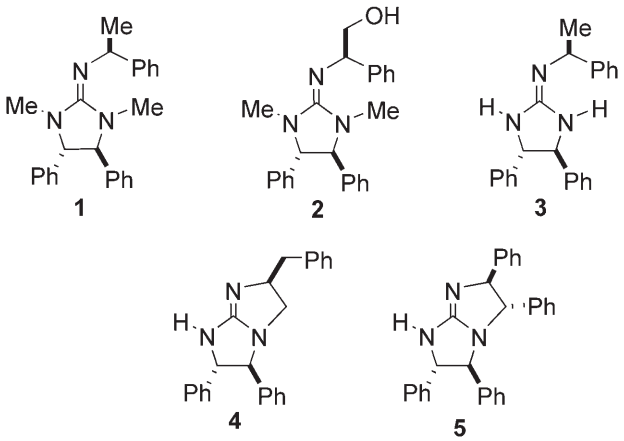
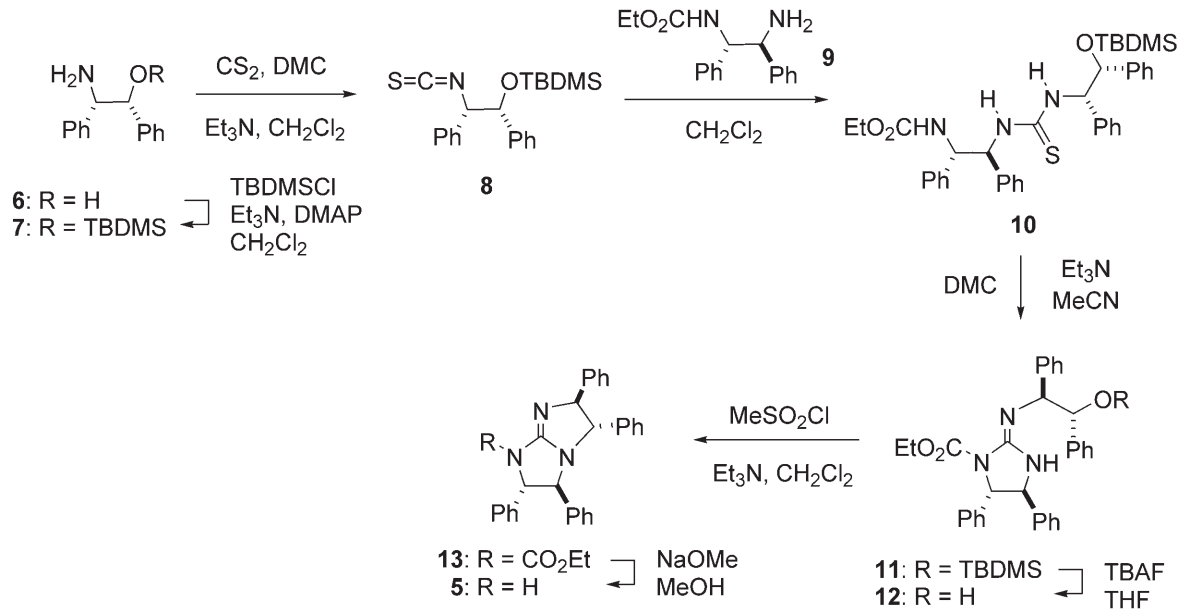
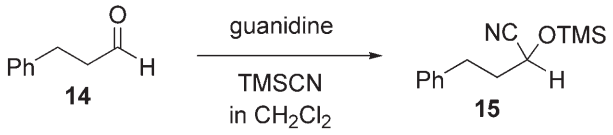


Figure 1. Modified guanidines **1**–**5** used for TMS-cyanations.



Scheme 1. Preparation of the C_2-symmetrical bicyclic guanidine **5**.

Table 1. Preliminary trials for the guanidine-catalyzed TMS-cyanation of 3-phenylpropanal (**14**).



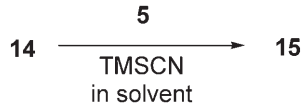
Run	Guanidine	Time [h]	**15**		Configuration
			Yield [%][a]	ee [%][b]	
1	**1**	2.5	95	3	*S*
2	**2**	2.0	94	1	*R*
3	**3**	2.0	97	3	*S*
4	**4**	2.0	95	5	*S*
5	**5**	2.5	96	12	*S*

[a] Estimated by ^{1}H NMR.
[b] Determined by chiral HPLC. Conditions, column: DAICEL CHIRALCEL OD-H; solvent: *n*-hexane:2-propanol = 15:1; flow rate: 0.5 mL/min; detection: UV (254 nm); (*R*)-derivative: 8.2 min; (*S*)-derivative: 8.8 min.

in good total yield by application of 2-chloro-1,3-dimethylimidazolium chloride (DMC)-mediated reactions[9] in the key steps (Scheme 1). The amino alcohol **6** was smoothly converted to isothiocyanate **8** by treatment with DMC[9a] after protection of the alcoholic function with *t*-butyldimethylsilyl (TBDMS) group. Modification of the isothiocyanate function in **8** with ethoxycarbonylated (1*S*,2*S*)-1,2-diphenylethylenediamine **9** afforded a thioamide derivative **10**. The DMC-induced intramolecular cyclization[9c] followed by deprotection of the silyl group with tetrabutylammonium fluoride (TBAF) yielded a monocyclic guanidine **12**. Treatment of **12** with methanesulfonyl chloride, in which intramolecular substitution of the corresponding methanesulfonate *in situ* formed occurred, gave a bicyclic system **13**. Finally, deprotection of the ethoxycarbonyl function in **13** with sodium methoxide afforded the desired C_2-symmetrical bicyclic guanidine, (2*S*,3*S*,7*S*,8*S*)-tetraphenyl-1,4,8-triaza[2.2.0]bicyclooct-4-ene (**5**), in overall 42% yield.

At first the reaction of 3-phenylpropanal[3a,c,g,i,k] (**14**) with TMSCN in dichloromethane (CH_2Cl_2) was preliminarily examined using modified guanidines (Table 1). A mixture of the aldehyde **14** (1 mol), TMSCN (1 mol), and a guanidine (0.1 mol) in CH_2Cl_2 (0.25 mol/L) was stirred at 0 °C until disappearance of **14** on TLC. The reactions were smoothly completed within 2.5 h, but low asymmetric inductions (up to 12% ee in run 5) were observed in all cases. The absolute stereochemistry of the major enantiomer of the TMS-cyanohydrin **15** was determined by chiral HPLC, even at the low ee achieved.

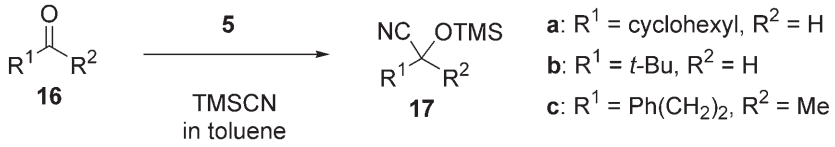
Table 2. The guanidine **5**-catalyzed TMS-cyanation of 3-phenylpropanal (**14**) under modified conditions.



Run	Solvent	Temperature [°C]	Time [h]	**15**	
				Yield [%][a]	ee [%]
1[b]	CH_2Cl_2	0	2.5	96	12
2	THF	0	5.0	53	20
3	toluene	0	2.5	96	25
4	none	0	1.5	quant.	6
5	CH_2Cl_2	−78	6.0	87	26
6	toluene	−78	6.0	85	50

[a] Estimated by ^{1}H NMR.
[b] The data cited from run 5 in Table 1.

Table 3. The TMS-cyanation of different carbonyl compounds in the presence of the guanidine **5**.



Run	**16**	Temperature [°C]	Time [h]	**17**		Configuration
				Yield [%][a]	ee [%]	
1	**a**	−78	1.5	93	70[b]	*S*
2	**b**	−78	7.0	92	43[c]	*S*
3	**c**	−40[d]	2.0	29	39	-[e]

[a] Estimated by ^{1}H NMR.
[b] Determined by chiral HPLC after conversion of **17a** to the benzoate. Conditions, column: DAICEL CHIRALPAK AD; solvent: *n*-hexane:2-propanol = 100:1; flow rate: 1.0 mL/min; detection: UV (254 nm); (*R*)-derivative: 8.4 min; (*S*)-derivative: 9.1 min.
[c] Determined by chiral HPLC after conversion of **17b** to the benzoate. Conditions, column: DAICEL CHIRALPAK AD; solvent: *n*-hexane:2-propanol = 150:1; flow rate: 0.2 mL/min; detection: UV (254 nm); (*R*)-derivative: 37.1 min; (*S*)-derivative: 43.5 min.
[d] No reaction occurred at −78 °C.
[e] Not determined.

No reaction occurred in the absence of a guanidine and no epimerization of the adduct was observed under the conditions used, indicating that guanidine plays the role of a catalyst and that this addition reaction is kinetically controlled.

We next attempted reactions in the presence of the C_2-symmetrical bicyclic guanidine **5**, which showed the best ee among the guanidines examined, for optimization of reaction conditions (Table 2). The use of tetrahydrofuran (THF) (run 2) and toluene (run 3) as solvent in place of CH_2Cl_2 led to slight improvements of asymmetric induction, whereas lowering the ee was observed in the reaction without solvent in spite of a rate acceleration (run 4). The reactions at −78 °C, as expected, resulted in an improvement of the asymmetric induction (run 1 *vs.* 5 and 3 *vs.* 6) and 50% ee was obtained with the use of toluene as solvent (run 6).

Finally the bicyclic guanidine **5** was applied to the TMS-cyanation under the estimated conditions using different carbonyl substrates (Table 3). In the use of cyclohexanecarbaldehyde[3b–e, g] (**16a**) not only satisfactory asymmetric induction (70% ee) but also smooth conversion to the adduct (< 1.5 h) was observed (run 1). Smooth reaction, even when needing longer reaction times, was also observed in the case of pivalaldehyde[3b–e,j,k,n] (**16b**); however, the ee was 43% (run 2). In these cases the ee of the adduct was determined after conversion to the corresponding benzoate.

There are not so many examples[3j,l,m] on asymmetric TMS-cyanation of ketones to our knowledge. Thus, we

tried the guanidine-catalyzed TMS-cyanation using 4-phenyl-2-butanone (**16c**) as substrate (run 3). The reaction was carried out at $-40\,^{\circ}C$ because of a lack of reaction at $-78\,^{\circ}C$. Although conversion was low (29%) even after stirring for a longer time (21 h), moderate asymmetric induction (39%) was observed.

Conclusion

In summary, it was found that a C_2-symmetrical bicyclic guanidine effectively catalyzed the asymmetric TMS-cyanation of carbonyl substrates. Especially reasonable ee was observed in cyclohexanecarbaldehyde (**16a**) and moderate asymmetric induction was attained even in a ketonic substrate. These guanidine-catalyzed asymmetric TMS-cyanations could contribute to the development of green chemistry,[10] because modified guanidines are considered to be re-useable (economically favored) and easily functionalizable (widely applicable) artificial organic bases. Thus, further examination on this guanidine chemistry is in progress in our laboratory.

Experimental Section

General

All melting points were measured on a Büchi 535 melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-700 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL JNM GSX-300. Optical rotations were recorded in chloroform ($c = 1.0$) on a JASCO DIP-140 digital polarimeter. Column chromatography was performed on silica gel 60 (70–230 mesh, Merck).

(1*R*,2*S*)-2-Amino-1-*t*-butyldimethylsilyloxy-1,2-diphenylethane (7)

A mixture of (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**6**; 10.0 g, 46.9 mmol), *t*-butylchlorodimethylsilane (7.07 g, 46.9 mmol), triethylamine (4.74 g, 46.9 mmol), and 4-dimethylaminopyridine (1.15 g, 9.38 mmol) in chloroform (200 mL) was stirred at room temperature for 41 h and then heated (bath temperature, 40 °C) for 6 h with stirring. The mixture was washed with H_2O, dried over $MgSO_4$, and evaporated. Purification of the residue by column chromatography ($CHCl_3$:MeOH = 50:1) afforded **7** as a colorless viscous oil; yield: 15.6 g (quant); $[\alpha]_D$: −32.3; ^1H NMR: δ = −0.32, −0.25 (each 3H, s, SiMe), 0.75 (9H, s, *t*-Bu), 1.53 (2H, br s, NH_2), 4.02, 4.63 (each 1H, d, $J = 6.5$ Hz, 1-, 2-H), 7.13–7.30 (10H, br s, ArH); ^{13}C NMR: δ = −5.55, −4.95, 18.01, 25.68, 62.90, 80.16, 127.10, 127.22, 127.48, 127.82, 127.94, 142.02, 142.66.

(1*R*,2*S*)-1-*t*-Butyldimethylsilyloxy-1,2-diphenyl-2-isothiocyanatoethane (8)

To a solution of the silyl ether **7** (15.1 g, 46. 2 mmol), carbon disulfide (3.51 g, 46.2 mmol), and triethylamine (15.4 g, 152 mmol) in CH_2Cl_2 (100 mL) was added DMC (9.38 g, 55.5 mmol) and the whole was stirred at room temperature for 1 h. After evaporation of the solvent the resulting insoluble material was washed with hexane. The washings were combined and evaporated. The residue was subjected to column chromatography (hexane:ethyl acetate = 20:1) to afford **8** as a colorless solid; yield: 14.1 g (82%); mp 37–40 °C; $[\alpha]_D$: −32.3; ^1H NMR: δ = −0.47, −0.28 (each 3H, s, SiMe), 0.78 (9H, s, *t*-Bu), 4.77 (1H, d, $J = 6.1$ Hz, 1- or 2-H), 4.82 (1H, d, $J = 6.1$ Hz, 2- or 1-H), 7.14–7.20 (4H, br s, ArH), 7.24–7.32 (6H, br s, ArH); ^{13}C NMR: δ = −5.49, −4.98, 17.98, 25.62, 68.18, 78.89, 127.10, 127.70, 128.03, 128.16, 128.25, 128.37, 135.87, 139.89; IR (KBr): $\nu_{max} = 2080\ cm^{-1}$.

1-[(1*R*,2*S*)-(2-*t*-Butyldimethylsilyloxy-1,2-diphenylethyl)]-2-[(1*S*,2*S*)-(1,2-diphenylethyl-2-ethoxycarbonylamino)]thioamide (10)

A mixture of the isothiocyanate **8** (13.3 g, 36.0 mmol) and 2-amino-1,2-diphenyl-1-ethoxycarbonylaminoethane (**9**; 10.2 g, 36.0 mmol) in CH_2Cl_2 (200 mL) was stirred at room temperature for 65 h. After evaporation of the solvent the residue was subjected to column chromatography (hexane:ethyl acetate = 5:1) to afford **10** as a colorless powder; yield: 22.0 g (94%); mp 85–90 °C; $[\alpha]_D$: −52.1; ^1H NMR[11]: δ = −0.27, −0.07 (each 3H, s, Me), 0.83 (9H, s, *t*-Bu), 1.18 (3H, br, CH_2CH_3), 4.07 (2H, br, OCH_2CH_3), 4.73, 5.02 (each 1H, br, CH), 5.63 (2H, br, CH × 2), 6.62 (1H, br, NH), 7.01 (10H, br s, ArH), 7.17 (10H, br s, ArH); ^{13}C NMR: δ = −5.23, −4.83, 14.56, 18.08, 25.78, 60.40, 60.76, 61.42, 64.33, 126.71, 127.35, 127.47, 127.98, 128.57, 136.59, 138.10, 140.23, 157.52, 181,11; IR (KBr): $\nu_{max} = 1690, 1530\ cm^{-1}$.

(4*S*,5*S*)-2-[(1*S*,2*R*)-(2-*t*-Butyldimethylsilyloxy-1,2-diphenylethyl)]imino-4,5-diphenyl-1-ethoxycarbonylimidazolidine (11)

To a solution of the thioamide **10** (21.4 g, 32.8 mmol) and triethylamine (9.94 g, 98.4 mmol) in acetonitrile (150 mL) was added DMC (6.65 g, 39.4 mmol) and the whole was refluxed for 17 h. After cooling the mixture was partitioned with CH_2Cl_2. The residue obtained after conventional work-up was subjected to column chromatography (hexane:ethyl acetate = 5:1) to afford **11** as a colorless amorphous solid; yield: 18.6 g (92%); $[\alpha]_D$: −21.0; ^1H NMR: δ = −0.20, −0.00 (each 3H, s, SiMe), 0.89 (9H, s, *t*-Bu), 0.95 (3H, t, $J = 6.8$ Hz, CH_2CH_3), 3.99 (2H, q, $J = 6.8$ Hz, OCH_2CH_3), 4.74, 4.77 (each 2H, d, $J = 4.1$ Hz, CH), 5.22 (1H, dd, $J = 8.6$, 4.7 Hz, 4-H), 5.23 (1H, d, $J = 4.7$ Hz, 5-H), 7.12–7.37 (20H, m, ArH), 7.95 (1H, br s, NH); ^{13}C NMR: δ = −5.31, −4.79, 13.83, 18.12, 25.83, 61.91, 63.14, 70.25, 73.94, 125.88, 126.12, 126.99, 127.12, 127.14, 127.20, 127.52, 127.58, 128.51, 128.52, 128.65, 138.43, 141.60, 142.58, 144.59, 152.78, 153.18; IR (KBr): $\nu_{max} = 3370, 1710, 1640, 1520\ cm^{-1}$.

(4*S*,5*S*)-4,5-Diphenyl-2-[(1*S*,2*R*)-(1,2-diphenyl-2-hydroxyethyl)]imino-1-ethoxycarbonylimidazolidine (12)

A solution of the protected imidazolidine **11** (18.1 g, 29.2 mmol) and a 1 M solution of tetrabutylammonium fluoride (38.0 mL, 38.0 mmol) in tetrahydrofuran (76 mL) were stirred at room temperature for 24 h. After partitioning with CH_2Cl_2, the residue was subjected to column chromatography (hexane:ethyl acetate = 3:1) to afford **12** as a colorless solid; yield: 10.5 g (71%); mp 74–77 °C; $[\alpha]_D$: −54.8; ^{1}H NMR: δ = 0.90 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.93 (2H, m, OCH_2CH_3), 4.73, 4.83 (each 1H, d, J = 4.4 Hz, CH), 5.15 (1H, d, J = 3.8 Hz, 5-H), 5.52 (1H, dd, J = 7.5, 3.8 Hz, 4-H), 7.06–7.39 (20H, m, ArH), 7.80 (1H, br s, NH); ^{13}C NMR: δ = 13.74, 62.20, 63.15, 70.47, 73.58, 78.40, 125.90, 126.13, 127.29, 127.46, 127.50, 127.56, 127.66, 127.72, 128.26, 128.74, 138.28, 139.82, 142.13, 143.77, 153.25, 154.34; IR (KBr): ν_{max} = 3340, 1710, 1640, 1530 cm^{-1}.

(2*S*,3*S*,7*S*,8*S*)-6-Ethoxycarbonyl-2,3,7,8-tetraphenyl-1,4,6-triazabicyclo[2.2.0]oct-4-ene (13)

To a solution of the deprotected imidazolidine **12** (9.97 g, 19.7 mmol) and triethylamine (8.80 g, 87.1 mmol) in CH_2Cl_2 (100 mL) was added methanesulfonyl chloride (5.97 g, 33.4 mmol) and the whole was stirred at room temperature for 24 h. After partitioning with CH_2Cl_2, acetonitrile was added to the residue and the product **13** (3.04 g) was precipitated. The filtrate was evaporated and the residue was subjected to column chromatography (hexane:ethyl acetate = 1 : 1) to afford additional product **13** (5.60 g) as colorless solid; total yield: 8.64 g (90%); mp 162–164 °C; $[\alpha]_D$: −25.2; ^{1}H NMR: δ = 1.17 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.99, 5.36 (each 1H, d, J = 8.8 Hz, CH), 4.14, 5.44 (each 1H, d, J = 2.4 Hz, CH), 4.24 (2H, m, OCH_2CH_3), 7.11–7.50 (20H, m, ArH); ^{13}C NMR: δ = 14.23, 62.78, 64.33, 69.65, 72.94, 84.10, 126.02, 126.99, 127.08, 127.15, 127.91, 128.23, 128.32, 128.69, 128.88, 128.91, 129.22, 137.49, 139.01, 140.31, 142.75, 151.13, 159.56; IR (KBr): ν_{max} = 1720, 1660 cm^{-1}.

(2*S*,3*S*,7*S*,8*S*)-2,3,7,8-Tetraphenyl-1,4,6-triazabicyclo[2.2.0]oct-4-ene (5)

A solution of the protected bicyclic guanidine **13** (8.10 g, 16.6 mmol) and sodium methoxide (6.48 g, 119 mmol) in methanol (32 mL) was stirred at room temperature for 1 h. After partitioning with CH_2Cl_2, acetonitrile was added and the whole was left to stand at −20 °C for 2 days. The precipitates were collected by filtration to give **5** as a colorless solid; yield: 6.25 g (91%); mp 157–162 °C; $[\alpha]_D$: −158.0; ^{1}H NMR: δ = 4.05, 4.99 (each 2H, d, J = 5.5 Hz, CH × 2), 6.66 (1H, br, NH), 7.11–7.14 (4H, m, ArH), 7.20–7.30 (16H, m, ArH); ^{13}C NMR: δ = 67.72, 126.62, 127.27, 127.40, 127.95, 128.42, 128.62, 138.99, 142.78, 167.34; IR (KBr): ν_{max} = 1670 cm^{-1}; anal. calcd. for $C_{29}H_{25}N_3$: C 83.82, H 6.06, N 10.11; found: C 83.33, H 6.05, N 10.17.

TMS-Cyanation of Cyclohexanecarbaldehyde (16a): 2-Cyclohexyl-2-hydroxyacetonitrile (Typical Procedure)

Caution: TMSCN can be absorbed through the skin and is extremely toxic.

A mixture of cyclohexanecarbaldehyde (**16a**; 0.05 mL, 0.41 mmol), TMSCN (0.05 mL, 0.38 mmol), and the guanidine **5** (17.5 mg, 0.04 mmol) in toluene (0. 5 mL) was stirred at 0 °C for 1.5 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 10% aqueous HCl, dried over $MgSO_4$, and evaporated to dryness. Purification of the crude product by SiO_2 column chromatography (hexane:ethyl acetate = 5:1) afforded 2-cyclohexyl-2-hydroxyacetonitrile; yield: 94.2 mg (82%). The ee was determined by chiral HPLC after derivatization to the benzoate.

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