Enantioselective Synthesis of Cyanohydrins by a Novel Aluminum Catalyst

Barry M. Trost,* Silvia Martínez-Sánchez

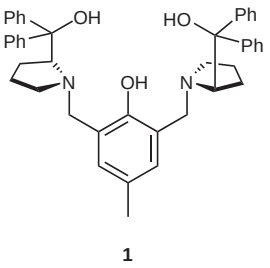
Department of Chemistry, Stanford University, Stanford, California 94305-5080, USA
Fax +1(650)7250002; E-mail: bmtrost@stanford.edu

Received 3 December 2004

Abstract: The development of a new chiral aluminum catalyst is reported. This catalyst has been applied efficiently to the asymmetric cyanosilylation of aldehydes.

Key words: aldehyde, cyanohydrin, trimethylsilylcyanide, asymmetric addition, aluminum

In recent years, we developed a dinuclear zinc catalyst based on the chiral ligand **1** (Figure 1). This system was very effective in different asymmetric processes, for instance the aldol reaction, a Mannich-type transformation, the nitro aldol reaction and the desymmetrization of *meso*-1,3-diols.[1] As part of our study on this chiral ligand, we have explored other catalytic processes and we report herein its effectiveness in the enantioselective cyanosilylation of aldehydes, a highly atom economical reaction.[2]

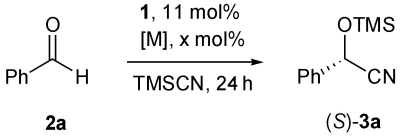


1

Figure 1

Cyanohydrins have a high synthetic potential as chiral building blocks in organic synthesis and they can be easily converted into a wide variety of compounds, including α-hydroxy acids, β-amino alcohols and α-amino acids.[3] Numerous methods, both enzymatic and chemical, have been reported for the asymmetric synthesis of cyanohydrins.[4] In particular, the development of new enantioselective catalysts has been extensively investigated; for instance, chiral aluminum complexes catalyze the addition of TMSCN to carbonyl derivatives, showing excellent enantioselectivity in most cases.[5]

Initially, we focused on the addition of TMSCN to benzaldehyde using different metal sources (Scheme 1, Table 1). The catalyst was prepared always by stirring ligand **1** with an organometallic reagent at room temperature in methylene chloride for 30 minutes. A little excess of ligand was used to avoid traces of the metal complex, which could also catalyze the reaction. Divalent metals did not generate an effective catalyst (entries 1–4). Thus, when the dinuclear zinc catalyst was used, the conversion of the reaction at 4 °C (temperature of the reaction)[6] was very low and silylation of the ligand was observed (entry 1). Dibutylmagnesium (one or two equivalents per ligand) or a mixed complex (one equivalent of both $ZnEt_2$ and $MgBu_2$) generated the silylated cyanohydrin as a racemic mixture (entries 3 and 4) or with very low ee (entry 2). A complex derived from titanium, a tetravalent metal, was also studied but the product was obtained with low ee (entries 5, 6). Trimethylaluminum was found to be the best metal source for this transformation. The addition of one equivalent of $AlMe_3$ per ligand led to an active species, which catalyzed the formation of silylated cyanohydrin (*S*)-**3a** in 60% yield and 80% ee (entry 7). The reaction did not proceed when two equivalents of $AlMe_3$ per ligand were used (entry 8) and only 26% ee was obtained when Cl_2AlMe was used instead of $AlMe_3$ (entry 9).



2a (*S*)-**3a**

Scheme 1

Table 1 Influence of the Metal in the Catalytic Enantioselective Addition of TMSCN to Benzaldehyde with Ligand **1**, in CH_2Cl_2, 4 °C

Entry	[M]	x [M] (%)	Yield of **3a** (%)	ee (%)[a]
1	$ZnEt_2$	20	4 [b]	–
2	$MgBu_2$	10	44	15 (*R*)
3	$MgBu_2$	20	43	0
4	$ZnEt_2$ + $MgBu_2$	20	39	0
5	$Ti(O\textit{i}\text{-}Pr)_4$	10	32	21 (*R*)
6	$Ti(O\textit{i}\text{-}Pr)_4$	20	50	31 (*R*)
7	$AlMe_3$	10	60	80 (*S*)
8	$AlMe_3$	20	3	0
9	Cl_2AlMe	10	20	26 (*S*)

[a] Enantioselectivity determined by HPLC analysis.
[b] Silylated ligand was isolated.

SYNLETT 2005, No. 4, pp 0627–0630
Advanced online publication: 22.02.2005
DOI: 10.1055/s-2005-863716; Art ID: S11104ST

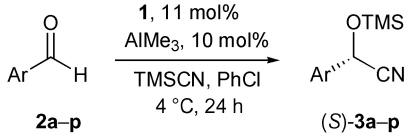
Table 2 Optimization of the Cyanosilylation of Benzaldehyde in Presence of the Aluminum Catalyst ([M] = $AlMe_3$).

Entry	x $AlMe_3$ (%)	Solvent	Temp (°C)	Yield of **3a** (%)	ee (%)[a]
1	10	CH_2Cl_2	4	60	80
2	10	CH_2Cl_2	–25	42	58
3	10	CH_2Cl_2	25	79	55
4	10	$CHCl_3$	4	60	27
5	10	PhCl	4	76	86
6	10	Toluene	4	50	33
7	10	THF	4	38	0
8	10	MeCN	4	59	5
9	7 [b]	PhCl	4	70	77

[a] Enantioselectivity determined by HPLC analysis.[8,9]
[b] 7.8 mol% of **1**.

The addition of TMSCN to benzaldehyde in presence of the aluminum catalyst (generated at r.t.) was then optimized (Scheme 1, Table 2). First, it was observed that any change in the temperature of reaction produced lower ee (see entries 1–3). On the other hand, the choice of solvent influenced the degree of enantioselectivity (entries 4–8). Chlorobenzene was the most effective solvent, generating the product in high yield and 86% ee (entry 5). Finally, a lower catalyst loading was also tested, but poorer ee was observed (entry 9).

The scope of the reaction was then investigated with different aldehydes using the optimized conditions (11 mol% catalyst generated at r.t., 4 °C, chlorobenzene).[7] Aromatic aldehydes gave better results, with high yields and up to 86% ee, as shown in Scheme 2 and Table 3. In general, alkyl, alkynyl and halogen groups at the *meta*-position of the aromatic ring were tolerated well (entries 2–8), whereas substituents at the *para*-position gave slightly lower ee (entries 9–11). Among the heterocyclic aldehydes studied (entries 14–16) 3-thienylcarboxaldehyde performed best, forming the silylated cyanohydrin in 75% yield and 84% ee (entry 16).



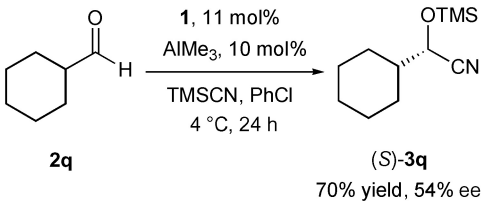
Scheme 2

An aliphatic aldehyde was also studied (Scheme 3). Cyclohexanecarboxaldehyde reacted well with TMSCN in presence of our aluminum catalyst, leading to the silylated cyanohydrin in 70% yield and moderate ee. The absolute configuration of the products was determined by comparison of optical rotations to known products[8] and by analogy in the other cases.[9]

Table 3 Asymmetric TMSCN Addition to Aromatic Aldehydes Catalyzed by (*S*,*S*)-**1**

Entry	ArCHO	Product	Yield of **3** (%)	ee (%)[a]
1	Benzaldehyde	**3a**	76	86
2	3-Tolualdehyde	**3b**	72	80
3	3,5-Dimethylbenzaldehyde	**3c**	68	57[b]
4	3-Chlorobenzaldehyde	**3d**	80	86
5	3-Bromobenzaldehyde	**3e**	76	82
6	3,5-Dichlorobenzaldehyde	**3f**	78	80[b]
7	3,5-Dibromobenzaldehyde	**3g**	74	85[b]
8	3-(Hex-1-ynyl)benzaldehyde	**3h**	74	82[b]
9	4-Tolualdehyde	**3i**	54	77
10	4-Anisaldehyde	**3j**	68	62
11	Biphenyl-4-carboxaldehyde	**3k**	56	60
12	2-Naphthaldehyde	**3l**	73	84
13	1-Naphthaldehyde	**3m**	68	73
14	2-Furaldehyde	**3n**	50	60[c]
15	3-Furaldehyde	**3o**	66	71
16	3-Thienylcarboxaldehyde	**3p**	75	84

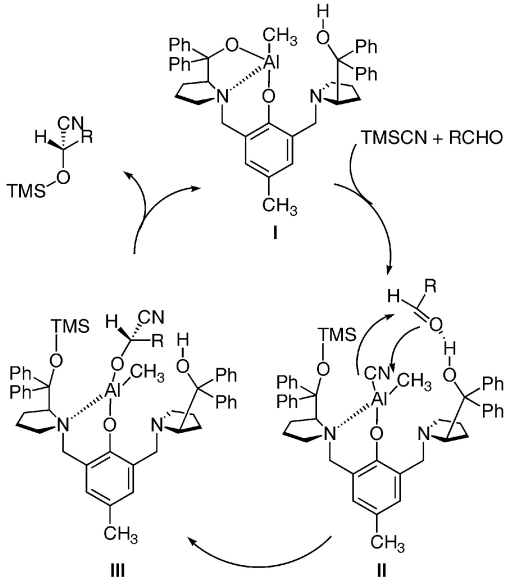
[a] Enantioselectivity determined by HPLC analysis. Absolute configuration assigned as *S* by comparison to known compounds unless otherwise indicated.
[b] Absolute configuration assigned by analogy.
[c] *R*-isomer as a result of a change in the priority of the substituents.



Scheme 3

In order to examine the structure of the catalyst, we stirred an equimolecular amount of ligand **1** and trimethylaluminum in deuterated methylene chloride (distilled from calcium hydride) for 30 minutes and obtained a ^{1}H NMR. Based on this spectrum, we suggest that the precatalyst could have the structure **I** represented in Scheme 4. There is a peak at $\delta = -1.18$ ppm assigned to a methyl group still remaining on the aluminum atom. In addition, two aromatic protons at $\delta = 6.24$ and 6.33 ppm, and two AB systems at $\delta = 3.41$ (1 H, d, $J = 12.3$ Hz), 2.96 (1 H, d, $J = 12.9$ Hz), 2.85 (1 H, d, $J = 12.9$ Hz) and 2.23 (1 H, d, $J = 12.3$ Hz), corresponding to the diastereotopic methylene groups, suggest a non-symmetrical structure. The real nature of the active catalyst awaits further investigation.

Tentatively, we propose an initial reaction of TMSCN to the aluminum alkoxide followed by hydrogen bonding of the aldehyde to the free hydroxy group, leading to structure **II** (Scheme 4). An internal delivery of the cyanide to the *re* face of the aldehyde to adduct **III**, followed by silylation of the alkoxy group would lead to the final product.



Scheme 4 Mechanism rationale

In summary, we have developed a novel aluminum catalyst based on our chiral ligand **1**, which lets us to carry out the enantioselective addition of TMSCN to aldehydes with reasonable yields and enantioselectivity. More experiments to determine the nature of the active catalyst and the mechanism of the reaction are currently underway.

Acknowledgment

We thank the National Science Foundation and the National Institute of Health, General Medical Sciences (GM13598), for their generous support of our programs. S.M.S thanks Fundación Ramón Areces for a postdoctoral fellowship.

References

(1) (a) Trost, B. M.; Yeh, V. S. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 861. (b) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (c) Trost, B. M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410. (d) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660.

(2) Atom economy in organic synthesis: (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(3) (a) Gaucher, A.; Ollivier, J.; Salaün, J. *Synlett* **1991**, 151. (b) Schwindt, M. A.; Belmont, D. T.; Carlson, M.; Franklin, L. C.; Hendrickson, V. S.; Karrick, G. L.; Poc, R. W.; Sobicray, D. M.; Van de Vusse, J. *J. Org. Chem.* **1996**, *61*, 9564. (c) Effenberger, F.; Jäger, J. J. *J. Org. Chem.* **1997**, *62*, 3867.

(4) For reviews on enantioselective synthesis and applications of cyanohydrins: (a) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555. (b) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649. (c) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147. (d) Brunel, J.-M.; Holmes, I. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2752.

(5) For aluminum-catalyzed TMSCN enantioselective addition to aldehydes see: (a) Iovel, I.; Popelis, Y.; Fleisher, M.; Lukevics, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1279. (b) Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 805. (c) Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589. (d) For aluminum-catalyzed TMSCN enantioselective addition to ketones see: Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 1009.

(6) Temperature of a cold room.

(7) **Typical Procedure**
Catalysis Generation: A 2 M solution of trimethylaluminum in toluene (25 μL, 0.05 mmol) was added dropwise to a solution of ligand **1** (36 mg, 0.056 mmol) in 1.0 mL of chlorobenzene at r.t. After stirring for 30 min at the same temperature, the resulting solution was cooled to 4 °C to be used as catalyst.
TMSCN Addition: Aldehyde **2** (0.5 mmol) was added in one portion to the catalyst solution at 4 °C and after 10 min TMSCN (73 μL, 0.55 mmol) was added over 2 min. The reaction mixture was stirred at the same temperature for 24 h. Then the reaction was quenched with 2.0 mL of pH 7 buffer phosphate solution (Na_2HPO_4/NaH_2PO_4) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated to give a colorless oil. The crude was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 5:1) to yield the corresponding silylated cyanohydrins.

(8) (a) Brusse, J.; Roos, E. C.; Van der Gen, A. *Tetrahedron Lett.* **1988**, *29*, 4485. (b) Almsick, A.; Buddrus, J.; Hoenicke-Schmidt, P.; Laumen, K.; Schneider, M. *J. Chem. Soc., Chem. Commun.* **1989**, *18*, 1391. (c) Effenberger, F.; Hörsch, B.; Förster, S.; Ziegler, T. *Tetrahedron Lett.* **1990**, *31*, 1249. (d) Effenberg, R.; Gutterer, B.; Ziegler, T. *Liebigs Ann. Chem.* **1991**, 269. (e) Dhanoa, D.; Bagley, S. W.; Chang, R. S. L.; Lotti, V. J.; Chen, T.-B. *J. Med. Chem.* **1993**, *36*, 3738. (f) Effenberger, F.; Eichhorn, J. *Tetrahedron: Asymmetry* **1997**, *8*, 469. (g) Hwang, C. D.; Hwang, D.-R.; Uang, B.-J. *J. Org. Chem.* **1998**, *63*, 6762. (h) Yang, W. B.; Fang, J. M. *J. Org. Chem.* **1998**, *63*, 1356. (i) Abiko, A.; Wang, G. *Tetrahedron* **1998**, *54*, 11405. (j) Liang, S.; Bu, X. R. *J. Org. Chem.* **2002**, *67*, 2702. (k) Nogami, H.; Motomu, K.; Shibasaki, M. *Chem. Pharm. Bull.* **2003**, *51*, 702.

(9) **Characterization of the New Compounds:**
Compound **3c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (s, 2 H), 7.26 (s, 1 H), 5.66 (s, 1 H), 2.59 (s, 3 H), 0.48 (s, 9 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 138.8, 136.2, 131.0, 124.2, 119.5, 63.8, 21.3, –0.1 ppm. IR (neat): 2960, 2921, 1612, 1464, 1255, 1159, 1101, 846, 754, 692 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NOSi$: C, 66.90; H, 8.21; N, 6.00. Found: C, 66.67; H, 7.95; N, 5.95. Enantiomer separation by HPLC (Daicel Chiralpak AD, λ = 250 nm, heptane–*i*-PrOH = 99.95:0.05; 1.0 mL/min; 57% ee): t_R = 6.83 (major) and 7.98 min. $[\alpha]_D$ –16.28 (*c* 2.12, $CHCl_3$).
Compound **3f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (m, 3 H), 5.43 (s, 1 H), 0.27 (s, 9 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 139.5, 135.7, 129.6, 124.8, 118.3, 62.4, –0.2 ppm. IR (neat): 3083, 2961, 2901, 1592, 1574, 1435, 1259, 1202, 1119, 872, 805, 754 cm^{-1}. Anal. Calcd for $C_{11}H_{13}Cl_2NOSi$: C, 48.18; H, 4.78; N, 5.11. Found: C, 48.61; H, 5.17; N, 5.03. Enantiomer separation by HPLC (Daicel

Chiralpak AD, λ = 235 nm, heptane–*i*-PrOH = 99.5:0.5; 0.6 mL/min; 80% ee): t_R = 9.80 and 10.48 (major) min. $[\alpha]_D$ –12.52 (*c* 2.91, $CHCl_3$).
Compound **3g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (m, 1 H), 7.55 (m, 2 H), 5.43 (s, 1 H), 0.27 (s, 9 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 139.9, 135.1, 128.1, 123.5, 118.2, 62.2, –0.2 ppm. IR (neat): 3076, 2959, 1589, 1562, 1427, 1256, 1193, 1118, 1095, 848, 742 cm^{-1}. Anal. Calcd for $C_{11}H_{13}Br_2NOSi$: C, 36.38; H, 3.61; N, 3.86. Found: C, 36.01; H, 2.99; N, 3.94. Enantiomer separation by HPLC (Daicel Chiralcel OD, λ = 235 nm, heptane–*i*-PrOH = 99.8:0.2, 1.0 mL/min; 85% ee): t_R = 11.69 (major) and 16.01 min. $[\alpha]_D$ –9.39 (*c* 2.53, $CHCl_3$).

Compound **3h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, 1 H), 7.39–7.32 (m, 3 H), 5.45 (s, 1 H), 2.44 (t, *J* = 6.9 Hz, 2 H), 1.60–1.47 (m, 4 H), 0.98 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 136.4, 132.5, 129.5, 128.9, 125.4, 125.0, 119.0, 91.6, 79.9, 63.4, 30.8, 22.1, 19.1, 13.7, –0.2 ppm. IR (neat): 2959, 2934, 2873, 2230, 1603, 1482, 1431, 1330, 1256, 1108, 1082, 860, 848 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NOSi$: C, 71.53; H, 8.12; N, 4.91. Found: C, 70.98; H, 8.51; N, 5.05. Enantiomer separation by HPLC (Daicel Chiralcel OD, λ = 250 nm, heptane–*i*-PrOH = 99.7:0.3; 1.0 mL/min; 82% ee): t_R = 18.16 (major) and 30.05 min. $[\alpha]_D$ –9.11 (*c* 0.26, $CHCl_3$).