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Diastereoselective Formation of Cyanohydrins from α-Alkoxy Aldehydes

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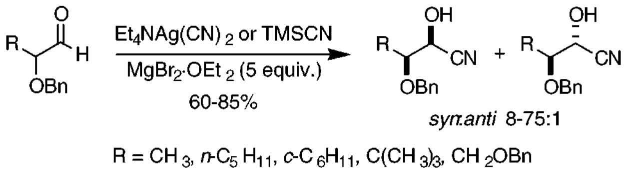
ABSTRACT



The reaction of α-alkoxy aldehydes with Et$_4$NAg(CN)$_2$ or Me$_3$SiCN in the presence of MgBr$_2$·OEt$_2$ in CH$_2$Cl$_2$ at 0 °C gives the corresponding syn cyanohydrins in good yield with high diastereoselectivity. Excess MgBr$_2$·OEt$_2$ (typically 5 equiv) is required for high diastereoselectivity. Et$_4$NAg(CN)$_2$ (but not Me$_3$SiCN) is sufficiently reactive to give cyanohydrins at −78 °C, and higher diastereoselectivity is obtained at this temperature.

Cyanohydrins are versatile synthetic intermediates for the preparation of a variety of useful compounds.[1] The enantioselective formation of cyanohydrins from achiral aldehydes has been extensively investigated in recent years, and several highly selective methods have been reported.[2,3] By contrast, cyanohydrins are often formed with poor diastereoselectivity from chiral aldehydes.[4] More than a century ago, Fischer reported that addition of HCN to L-arabinose gave a 2:1 mixture of cyanohydrins in favor of the manno (i.e., 2,3-anti) diastereomer.[5] Subsequently, diastereoselectivities of 1.5−5:1 in favor of the syn isomer have been reported for cyanohydrin formation from α-alkoxy aldehydes using trimethylsilyl cyanide (TMSCN) in the presence of various Lewis acids.[6] Our ongoing interest in the design and development of enantiotopic group selective reactions prompted an examination of cyanohydrin formation from α-alkoxy aldehydes.[7] However, the poor diastereoselectivity

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(2) Review: North, M. *Synlett* **1993**, 807. See also ref 1c.

(3) See inter alia: (a) Hwang, C.-D.; Hwang, D.-R.; Uang, B.-J. *J. Org. Chem.* **1998**, *63*, 6762. (b) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibisaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641. (c) Belokon′, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968.

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(7) (a) Ward, D. E.; Liu, Y.; Rhee, C. K. *Can. J. Chem.* **1994**, *72*, 1429. (b) Ward, D. E.; How, D.; Liu, Y. *J. Am. Chem. Soc.* **1997**, *119*, 1884. (c) Ward, D. E.; Lu, W.-L. *J. Am. Chem. Soc.* **1998**, *120*, 1098

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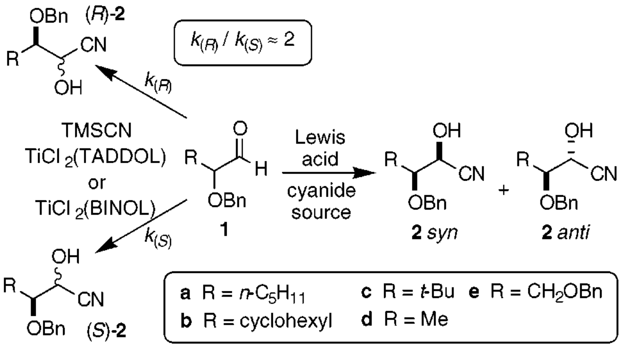
noted above did not bode well for this process, and not unexpectedly,[8] attempted kinetic resolution of **1a** using known *enantiotopic face* selective methods resulted in very low *enantiotopic group* selectivity (Scheme 1).[9] Thus, it seemed apparent that conditions to achieve cyanohydrin formation with much higher diastereoselectivity were required. In this paper, we report the development of such a process.

Scheme 1



The low diastereoselectivity observed for cyanohydrin formation from α-alkoxy aldehydes on reaction with TMSCN in the presence of various Lewis acids is in stark contrast to the excellent selectivity often associated with nucleophilic additions to these aldehydes under chelation-controlled conditions.[10] Several Lewis acids were screened for their ability to promote diastereoselective cyanohydrin formation from **1a** using Et_4NCN (compared to TMSCN) as a readily available soluble cyanide source (Table 1). Low yields of the cyanohydrins were noted (except with $MgBr_2 \cdot OEt_2$), and this was attributed to the rapid formation of a precipitate upon addition of Et_4NCN to the reaction mixture indicating that the Lewis acid reacted with Et_4NCN to form a species incapable of generating cyanohydrins.

Table 1. Diastereoselectivity of Lewis Acid Mediated Hydrocyanation of **1a**

entry	Lewis acid (1 equiv)	CN⁻ source (1.1 equiv)	*T* (°C) (time (h))	% yield[a] of **2a** (syn/anti)[b]
1	$TiCl_4$	TMSCN	−78 (4)	70 (4:1)[c]
2	$SnCl_4$		−78 (2)	75 (6:1)[c]
3	$MgBr_2 \cdot OEt_2$		−78 (4)	*d*
4	$MgBr_2 \cdot OEt_2$		0 (1)	85 (6:1)[c]
5	$ZnBr_2$	Et_4NCN	−78 (4)	*d,e*
6	$TiCl_4$	*e*	−78 (4)	40 (6:1)
7	$SnCl_4$	*e*	−78 (4)	20 (2:1)
8	$MgBr_2 \cdot OEt_2$		−78 (4)	85 (3:1)

[a] Isolated yield. [b] Measured by ^{1}H NMR. [c] Cf. ref 6a. [d] **2a** not detected. [e] 3 equiv of Et_4NCN; **2a** not detected using 1 equiv.

Hydrocyanation mediated by $MgBr_2 \cdot OEt_2$ was studied further (Table 2). Despite the low solubility of $MgBr_2 \cdot OEt_2$ in CH_2Cl_2,[11] the diastereoselectivity of the reaction of **1a** with Et_4NCN was clearly dependent on the amount of $MgBr_2 \cdot OEt_2$ present. Surprisingly, **2a** was produced even in the absence of Lewis acid (Table 2, entry 1).[12] Although slower than with the other Lewis acids examined, a deleterious reaction of $MgBr_2 \cdot OEt_2$ with Et_4NCN was indicated by the much lower yield of **2a** obtained upon mixing these reagents for 1 h prior to addition of **1a**. Optimization[13] of this reaction gave **2a** in 65% isolated yield as a 12:1 mixture of syn/anti diastereomers, a level of stereoselectivity markedly superior to previous reports.[6] Similar results were obtained with **1b** and **1c**.[14]

Table 2. Diastereoselectivity of Hydrocyanation of **1** with Et_4NCN in the Presence of $MgBr_2 \cdot OEt_2$

entry	substrate	Mg(II) (equiv)	CN⁻ (equiv)	*T* (°C) (time (h))	% yield[a] of **2** (syn/anti)[a]
1	**1a**	0	1.1	−78 (1)	50 (1.5:1)
2		1	1.1	−78 (1)	95 (3:1)
3		5	1.1	−78 (1)	95 (5:1)
4		1	1.1	0 (0.5)	85 (1.3:1)
5		2.5	1.1	0 (0.5)	75 (2:1)
6		5	1.1	0 (0.5)	65 (4:1)
7		5	1.1[b]	0 (0.5)	25 (7:1)
8		5	2[c]	−78 (2.5)	65[d] (12:1)
9	**1b**	5	2[c]	−78 (2.5)	60[d] (>19:1)
10	**1c**	5	4[c]	−78 (2.5)	65[d] (12:1)

[a] Measured by ^{1}H NMR. [b] The mixture of Et_4NCN and $MgBr_2 \cdot OEt_2$ was stirred for 1 h prior to addition of **1a**. [c] See ref 13 for procedure. [d] Isolated yield (conversion ca. 85%).

A significant further improvement was achieved with the serendipitous preparation of $Et_4NAg(CN)_2$ (Table 3).[15,16] This reagent did not react appreciably with $MgBr_2 \cdot OEt_2$ (Table

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[8] Enantiotopic group selectivity (*E*) can be estimated from the following equation where *r* is the reagent-controlled selectivity (i.e., enantioselectivity from achiral substrate with chiral reagent) and *s* is the substrate-controlled selectivity (i.e., the diastereoselectivity from chiral substrate with achiral reagent): $E = (rs + 1)/(r + s)$. For a discussion, see ref 7a.

[9] $TiCl_2$(TADDOL)/TMSCN: (a) Narasaka, K.; Minamikawa, H.; Hayakawa, S.; Yamada, T.; Iwasawa, N. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379. (b) Narasaka, K.; Yamada, T.; Minamikawa, H. *Chem. Lett.* **1987**, 2073. $TiCl_2$(BINOL)/TMSCN: (c) Mori, M.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6229.

[10] Devant, R. M.; Radunz, H.-E. In *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 2, pp 1196−1216.

[11] Ca. 8.5 mg/mL (0.033 M) at ambient temperature.

[12] The origin of this result is unclear but may be due to adventitious moisture despite our efforts to maintain anhydrous conditions; however, cyanohydrin formation by addition of the HCN formed upon quenching the reaction with CF_3CO_2H (TFA) may be ruled out because rapid quenching or addition of TFA before Et_4NCN failed to give **2a**.

[13] Slow addition of Et_4NCN (0.4 M in CH_2Cl_2, 2 equiv over 2 h) to a stirred suspension of $MgBr_2 \cdot OEt_2$ (5 equiv) and **1** (0.05 M) in CH_2Cl_2 at −78 °C. After further reaction for 0.5 h, the reaction was quenched by sequential addition of TFA (10 equiv) and then water followed by standard aqueous workup and, if necessary, silica gel chromatography. Control experiments established that addition of TFA did not induce cyanohydrin formation (i.e., addition of HCN)[12] or affect the diastereomer distribution.

[14] The relative stereochemical configurations of **2** were determined as follows: **2a** and **2c** in analogy to Reetz et al.[6a] by ^{1}H NMR (NOE) analysis of the acetonide derivatives of the diols resulting from hydrolysis ($TiCl_4$) of the benzyl ethers; **2d** is known;[6a] **2e** by conversion ((1) TIPSCl, DMAP; (2) DIBAL; (3) $NaBH_4$; (4) TBAF; (5) H_2/Pd−C; (6) Ac_2O, pyridine; ca. 30% overall yield) to the known threitol tetraacetate (Vogel, P.; Jeganathan, S. *J. Org. Chem.* **1991**, *56*, 1133); **2b** by analogy.

Table 3. Diastereoselectivity of Hydrocyanation of **1** with $Et_4NAg(CN)_2$ in the Presence of $MgBr_2 \cdot OEt_2$[a]

entry	substrate	Mg(II) (equiv)	$(CN)_2$[b] (equiv)	*T* (°C) (time (h))	% yield[c] of **2** (syn/anti)[c]
1	**1a**	0	1.1	0 (1)	*d*
2		0.5	1.1	0 (1)	60 (2:1)
3		1	1.1	0 (1)	95 (3:1)
4		2	1.1	0 (1)	95 (7:1)
5		5	1.1	0 (1)	95 (9:1)
6		5	1.1[e]	0 (0.5)	95 (9:1)
7		5	0.55	0 (1)	70 (7:1)
8		5	1.1	0 (1)	85[f] (9:1)
9		5	2	−78 (1)[g]	85[f] (24:1)[h]
10	**1b**	5	1.1	0 (1)	85f (75:1)[h]
11	**1c**	5	1.1	0 (1)	80[f] (>19:1)
12	**1d**	5	1.1	0 (1)	80[f] (5:1)
13	**1d**	5	2	−78 (1)[g]	75[f] (8:1)
14	**1e**	5	1.1	0 (1)	65[f] (11:1)[h]
15	**1e**	5	2	−78 (1)[g]	60[f] (18:1)[h]

[a] Procedure as in ref 13 except $Et_4NAg(CN)_2$ solution was added dropwise in <3 min. [b] Molar equiv of $Et_4NAg(CN)_2$. [c] Measured by ^1H NMR. [d] **2a** not detected; **1a** recovered unchanged. [e] The mixture of $Et_4NAg(CN)_2$ and $MgBr_2 \cdot OEt_2$ was stirred for 3 h prior to addition of **1a**. [f] Isolated yield. [g] Reaction mixture allowed to slowly warm to −20 °C over 2 h before quenching. [h] Measured by HPLC.

3, cf. entries 5 and 6) and did not react with **1a** in the absence of $MgBr_2 \cdot OEt_2$ (Table 3, entry 1; cf. Table 2, entry 1). The diastereoselectivity of hydrocyanation of **1a** with $Et_4NAg(CN)_2$ was dependent on the amount of $MgBr_2 \cdot OEt_2$, and with 5 equiv at 0 °C, the cyanohydrins **2a** were isolated in good yield as a 9:1 mixture of syn and anti diastereomers, respectively; the diastereoselectivity improved to 24:1 at −78 °C.[17] Similar results could be obtained with the more soluble MgI_2,[18] but using $Mg(OTf)_2$ and $Mg(ClO_4)_2$ did not give cyanohydrins. Reaction of aldehydes **1b**−**e** with $Et_4NAg(CN)_2$ also produced the corresponding syn cyanohydrins **2b**−**e** with excellent diastereoselectivity under the above conditions (Table 3).[14] In contrast, poor syn diastereoselectivities were previously reported for the hydrocyanations of **1d**[6a,g] (3−4:1) and **1e**[6a,i] (5:1) with TMSCN in the presence of various Lewis acids ($TiCl_4$, $SnCl_4$, $MgBr_2$; 1 equiv) at low temperature (−78 to −30 °C).

For comparison, the stereoselectivity of hydrocyanation of **1** with TMSCN mediated by $MgBr_2 \cdot OEt_2$ was investigated (Table 4). As with $Et_4NAg(CN)_2$, the diastereoselectivity of addition of TMSCN to **1a** was dependent on the amount of $MgBr_2 \cdot OEt_2$ present, and the reaction was very slow in the absence of Lewis acid. Even with excess $MgBr_2 \cdot OEt_2$, negligible reaction occurred at −78 °C. When a mixture of TMSCN and $MgBr_2 \cdot OEt_2$ was "aged" prior to addition of **1a**, a marked reduction in the yield of **2a** resulted but without deterioration of diastereoselectivity. In no case were trimethylsilyl ethers of the cyanohydrins **2** detected and, because they were demonstrated to be stable to the reaction conditions and the workup, their intermediacy was ruled out.[19] With 5 equiv of $MgBr_2 \cdot OEt_2$ at 0 °C, the results of hydrocyanation of **1a**−**d** with TMSCN were remarkably similar to those with $Et_4NAg(CN)_2$ and much more stereoselective than previously reported.[6] The comparatively low diastereoselectivity observed for the reaction of **1e** with $Et_4NAg(CN)_2$ is attributed to the propensity of **2e** to undergo epimerization in the presence of Et_4NBr.[20]

Table 4. Diastereoselectivity of Hydrocyanation of **1** with TMSCN in the Presence of $MgBr_2 \cdot OEt_2$[a]

entry	substrate	Mg(II) (equiv)	CN[b] (equiv)	*T* (°C) (time (h))	% yield[c] of **2** (syn/anti)[c]
1	**1a**	0	1.1	0 (1)	*d*
2		0.5	1.1	0 (1)	75 (6:1)
3		1	1.1	0 (1)	95 (7:1)
4		2.5	1.1	0 (1)	95 (9:1)
5		5	1.1	0 (1)	95 (9:1)
6		5	1.1	−78 (1)	*d*
7		5	1.1[e]	0 (3)	50 (9:1)
8		5	1.2	0 (1)	85[f] (9:1)
9	**1b**	5	1.2	0 (1)	85[f] (75:1)[g]
10	**1c**	5	1.2	0 (1)	80[f] (>19:1)
11	**1d**	5	1.2	0 (1)	75[f] (5:1)
12	**1e**	5	1.2	0 (1)	65[f] (24:1)[g]

[a] Procedure: TMSCN was added to a stirred suspension **1** (0.05 M) and $MgBr_2 \cdot OEt_2$ in CH_2Cl_2 at the indicated temperature, and after the indicted time, the reaction was quenched and processed as described in ref 13. [b] Molar equiv of TMSCN. [c] Measured by ^1H NMR. [d] **2a** not detected; **1a** recovered unchanged. [e] The mixture of TMSCN and $MgBr_2 \cdot OEt_2$ was stirred for 3 h prior to addition of **1a**. [f] Isolated yield. [g] Measured by HPLC.

The mechanistic details of hydrocyanation in the presence of excess $MgBr_2 \cdot OEt_2$ are uncertain, but some conclusions can be drawn. Our current working hypothesis is outlined in Scheme 2. For all three cyanide reagents, the dependence of hydrocyanation stereoselectivity on the amount of $MgBr_2 \cdot$

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(15) Preparation of $Et_4NAg(CN)_2$: A solution of Et_4NBr (1.72 g, 8.2 mmol) in H_2O (30 mL) was added to AgCN (2.73 g, 20.4 mmol; prepared from $AgNO_3$ and KCN), and the resulting stirred suspension was heated under reflux in the dark for 16 h. The cooled (rt) mixture was filtered and the precipitate washed with water. The combined filtrate and washings was concentrated to dryness, and the solid obtained was suspended in benzene and the mixture concentrated to dryness. The resultant white solid was taken up in CH_2Cl_2 and filtered, and the filtrate was concentrated and dried under high vacuum to give a white granular solid (2.10 g, 88%). Anal. Calcd for $C_{10}H_{20}AgN_3$: C, 41.40; H, 7.96; N, 14.48; Ag, 37.17. Found: C 41.59; H, 7.34; N, 13.98; Ag, 36 (by precipitation of AgCl).

(16) The formation of $Et_4NAg(CN)_2$ is consistent with the relative solubilities of AgCN ($K_s = 1.2 \times 10^{-16}$), AgBr ($K_s = 5.2 \times 10^{-13}$), and $Ag[Ag(CN)_2]$ ($K_s = 5\times 10^{-12}$) (*Handbook of Analytical Chemistry*; Meites, L., Ed.; McGraw-Hill: New York, 1963; Section 1, p 13), and the empirical formula is consistent with the elemental analysis (note 15).

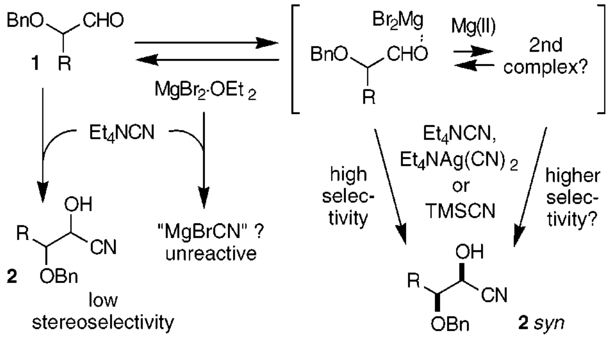
(17) This increase is consistent with a simple temperature effect [i.e., dr at 195 K = (dr at 273 K) exp(273/195)].

(18) This reagent (prepared from Mg and I_2 in ether) was capricious, and efficacy was seemingly sensitive to the amount of residual ether. Occasionally, results were equal to or better than with $MgBr_2 \cdot OEt_2$ but were not reproducible and often were inferior.

(19) Reaction of a 1:1 mixture of the TMS ether of **2a** (1.3: 1, syn/anti) and **1d** with TMSCN (1.2 equiv) in the presence $MgBr_2 \cdot OEt_2$ (5 equiv) at 0 °C for 1 h gave a 3:1:2 mixture of **2d** (5:1, syn/anti), **2a**, and the TMS ether of **2a** (1.3: 1, syn/anti), respectively.

(20) For example, addition of Et_4NBr (1 equiv) to a solution of **2e** (20: 1, syn/anti) in CH_2Cl_2 followed by concentration to dryness and then standard aqueous work up gave **2e** (1:1, syn/anti) in nearly quantitative yield. Other cyanohydrins gave similar results, but **2e** seemed to be particularly susceptible, and even failure to completely remove residual ammonium salts during workup of reactions of **1e** with $Et_4NAg(CN)_2$ gave **2e** with attenuated selectivity.

Scheme 2



OEt$_2$ implies multiple reaction pathways with different diastereoselectivities. With Et$_4$NCN, this is easily accommodated because reaction can occur in the absence of Lewis acid. Thus, the stereoselectivity in this case will be related to fraction of free versus Mg(II) coordinated aldehyde, which could be influenced by the amount Mg(II) present; however, because most of the Mg(II) is insoluble, this influence cannot be due to an increased concentration of Mg(II) but might involve coordination of aldehyde at the surface of the MgBr$_2$·OEt$_2$. The increase in selectivity observed with slow addition of Et$_4$NCN suggests that the rate of formation of coordinated aldehyde is slow relative to addition of CN$^-$ to the free aldehyde.

Neither Et$_4$NAg(CN)$_2$ nor TMSCN reacts appreciably with **1** in the absence of MgBr$_2$·OEt$_2$. With TMSCN, the dependence of stereoselectivity on the amount of MgBr$_2$·OEt$_2$ suggests the possible presence of more than one aldehyde·Mg(II) complex with the more selective (and more reactive?) complex being formed preferentially with increasing amounts of Mg(II). Compared to TMSCN, the greater sensitivity of the stereoselectivity for addition of Et$_4$NAg(CN)$_2$ to **1** with small amounts of MgBr$_2$·OEt$_2$ can be, in part, attributed to the in situ formation of Et$_4$NCN;[21] alternatively, the higher reactivity of Et$_4$NAg(CN)$_2$ might lead to a less selective partition of the reaction among multiple aldehyde·Mg(II) complexes. Although the observed syn diastereoselectivity is consistent with a chelated Mg(II) complex, a nonchelated complex is also possible.[22] Clearly, further work is required to differentiate among these mechanistic possibilities.

In conclusion, syn cyanohydrins are produced with excellent diastereoselectivity from various α-alkoxy aldehydes by reaction with Et$_4$NAg(CN)$_2$ or TMSCN in the presence of excess MgBr$_2$·OEt$_2$ in CH$_2$Cl$_2$ at 0 °C; higher diastereoselectivity can be obtained with Et$_4$NAg(CN)$_2$ (but not TMSCN) by reaction at −78 °C. Considering the widespread use of cyanohydrins in synthesis and the poor diastereoselectivity of previous examples, this method should find numerous synthetic applications. Work on developing an enantiotopic group selective process is underway.

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[21] Both cyanides from Et$_4$NAg(CN)$_2$ can add to **1** (Table 3, entry 7).

[22] For an example of high syn selectivity from a nonchelated complex, see: Mikami, K.; Matsukawa, S.; Sawa, E.; Harada, A.; Koga, N. *Tetrahedron Lett.* **1997**, *38*, 1951.