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ENANTIOSELECTIVE CONVERSION OF ALDEHYDES TO CYANOHYDRINS BY A CATALYTIC SYSTEM WITH SEPARATE CHIRAL BINDING SITES FOR ALDEHYDE AND CYANIDE COMPONENTS

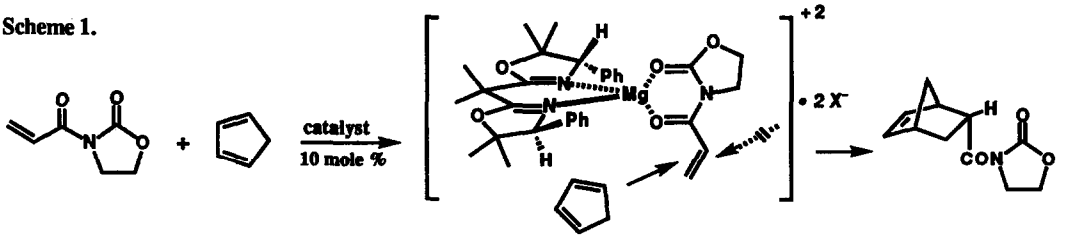
E. J. Corey and Zhe Wang

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

Summary: *A new enantioselective method for the synthesis of chiral cyanohydrins from aldehydes and trimethylsilyl cyanide is described which uses a pair of synergistic chiral reagents, one to activate the aldehyde and the other to provide an equivalent of chiral cyanide ion.*

We recently described the application of chiral bisoxazoline-iron[1] or magnesium[2] complexes to the catalytic enantioselective Diels-Alder reaction as illustrated in Scheme 1.[3] This paper concerns the study of

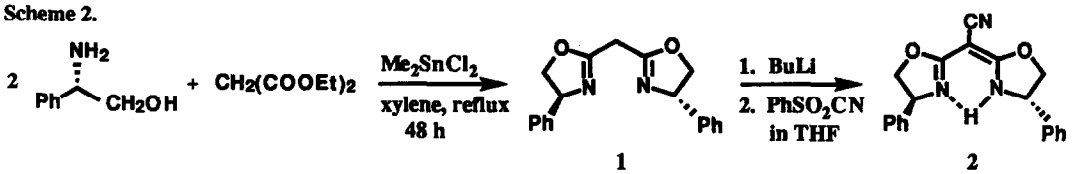
Scheme 1.



magnesium complexes of related bisoxazolines as catalysts for the enantioselective conversion of aldehydes to cyanohydrins. The importance of chiral cyanohydrins in synthesis has motivated the investigation of a wide variety of other catalysts for enantioselective synthesis.[4,5] Despite considerable research, the ultimate goal of developing practical and highly effective catalytic systems for enantioselective cyanohydrin formation has remained elusive.

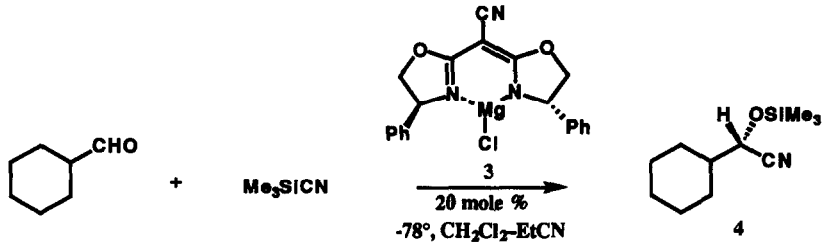
The (*S*,*S*)-bisoxazoline **1** was synthesized from (*S*)-phenylglycinol[6] and diethyl malonate using Masamune's method[3a] (Scheme 2) and converted without purification[7] to the cyanobisoxazoline **2** by sequential treatment with 1 equiv of *n*-BuLi and 1 equiv of tetramethylethylenediamine in tetrahydrofuran (-78 °C for 1 h then 0 °C for 0.5 h) and benzenesulfonyl cyanide[8] (-78 °C for 1.5 h and 0 °C for 1 h). After chromatography on neutral alumina (3 : 2 hexane–ethyl acetate as eluant) and recrystallization from ethyl acetate–hexane, pure **2** (70% overall) was obtained as a stable colorless solid, mp 146.4 - 147.2 °C, $[\alpha]_D^{23}$ + 454° (c=1, $CHCl_3$), HRMS (EI) 331.1322 (calcd for **2**, 331.1321).[9]

Scheme 2.



The reaction of **2** with 1 equiv of ethereal *n*-butylmagnesium chloride followed by removal of ether *in vacuo* produced the bisoxazoline–magnesium complex **3** which when dissolved in dichloromethane-propionitrile was effective in catalyzing the formation of cyanohydrin trimethylsilyl (TMS) ethers from aldehydes and TMSCN. Reaction of cyclohexane carboxaldehyde and 2 equiv of TMSCN in 3 : 1 CH_2Cl_2–C_2H_5CN in the presence of 20 mole % of **3** at -78 °C for 25 h afforded the chiral cyanohydrin TMS ether **4** in 85% yield with 82.5 : 17.5 *S*/*R* enantioselectivity (65% ee).[10,11] This modest level of enantioselectivity was much enhanced by

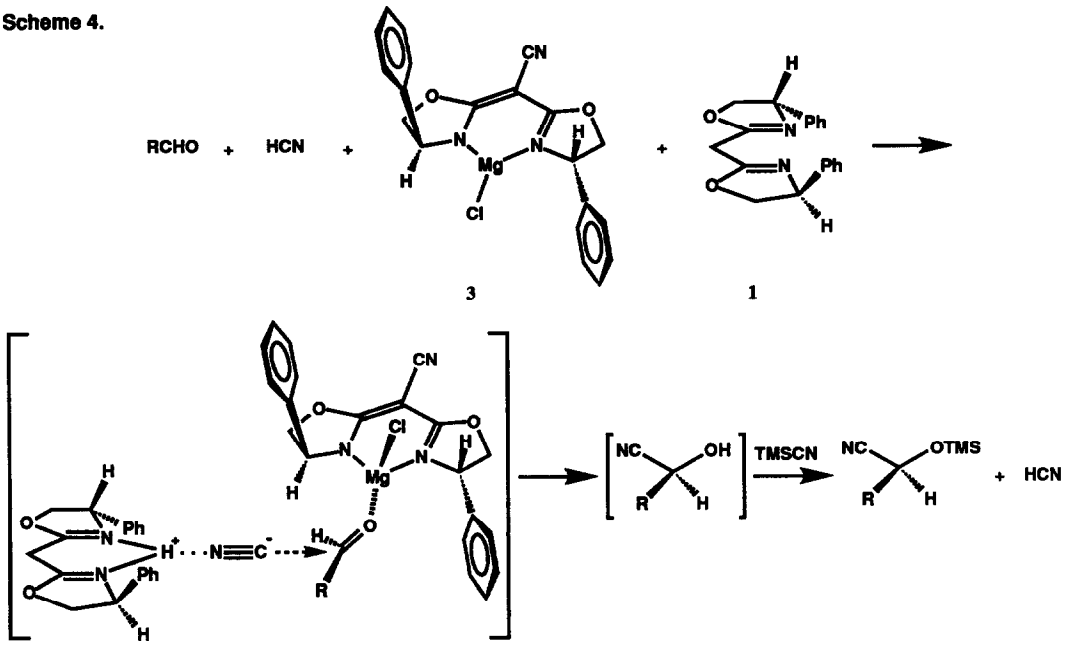
Scheme 3.



the addition of 12 mole % of the bisoxazoline **1** as a cocatalyst. Thus, at -78 °C in 3 : 1 CH_2Cl_2–C_2H_5CN with 20 mole % of **3** and 12 mole % of **1** as cocatalysts, the reaction of cyclohexane carboxaldehyde and TMSCN (2 equiv) produced the cyanohydrin TMS ether **4** after 4 h in 95% yield with 97 : 3 *S*/*R* enantioselectivity (94% ee). Equally dramatic results were obtained when this experiment was repeated with a single change, the replacement of 12 mole % of **1** by 12 mole % of the (*R*,*R*)-enantiomer of **1**, which provided after 8 h at -78 °C cyanohydrin TMS ether **4** in 90% yield but with only 69 : 31 *S*/*R* selectivity (38% ee). A control experiment involving the (*S*,*S*)-bisoxazoline **1**, TMSCN and cyclohexane carboxaldehyde showed very little reaction at -78 °C and a slow reaction at -50 °C to give *completely racemic* cyanohydrin TMS ether **4**. When considered together these results clearly indicate that the highly enantioselective (*ca.* 30 : 1) formation of cyanohydrin ether **4** when cocatalysts **1** and **3** are used together may involve activation of the aldehyde by coordination with **3** and subsequent reaction of that complex with a "chiral cyanide donor derived from the (*S*,*S*)-bisoxazoline" **1**. The simplest form which the "chiral cyanide" donor could take is a complex of **1** with HCN, traces of which can be expected to be present in reaction mixtures containing TMSCN as a result of hydrolysis caused by adventitious traces of water. If the complex of **1** with HCN is the cyanide source, reaction with aldehyde would produce cyanohydrin which would then be converted to cyanohydrin TMS ether by reaction with TMSCN with regeneration of HCN. This type of process is illustrated in a general way by Scheme 4.

The possibility that free cyanohydrin is produced as a primary product and subsequently silylated by TMSCN to form the product **4** was tested by a control experiment. Reaction of the cyanohydrin of cyclohexane carboxaldehyde with 2 equiv of TMSCN, even without catalyst **3** , in CH_2Cl_2–C_2H_5CN at -78 °C resulted in rapid and complete conversion to the cyanohydrin TMS ether **4**, as required for the reaction pathway summarized in Scheme 4. Also consistent with this pathway is the observation that the addition of HCN (generated from a measured amount of TMSCN and CH_3OH) to a mixture of aldehyde, TMSCN, and cocatalysts **1** and **3** accelerates the formation of chiral cyanohydrin TMS ether in proportion to the amount of HCN added. However, it has also been found that the addition of greater than a few mole % of HCN to the mixture of aldehyde, TMSCN, **1** and **3** results in decreased enantioselectivity. This decrease may be due to the promotion by HCN of another, less enantioselective pathway, for example involving $[C{\equiv}N{\bullet\bullet}HCN]^-$ as the nucleophile

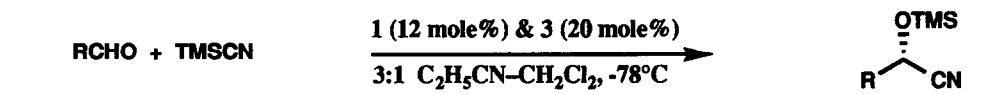
Scheme 4.



rather than the complex of **1** with HCN. In this connection, it is relevant that the reaction of cyclohexane carboxaldehyde with **1** and HCN (2 equiv) at -78 °C produces the cyanohydrin of cyclohexane carboxaldehyde with only 53 : 47 *S/R* enantioselectivity.

A number of different aldehydes were converted to the corresponding cyanohydrin TMS ethers under the conditions described above for **4**, with the results summarized in the Table below. In general, very good enantioselectivities were observed for aliphatic, non-conjugated aldehydes; however, slower reaction rates and considerably lower enantioselectivities were found for benzaldehyde and certain α,β-unsaturated aldehydes.[11]

Catalytic Enantioselective Cyanohydrin Synthesis



Aldehyde	Time (h)	Yield, %	ee, %	$[\alpha]_D$ (R–OTMS)	$[\alpha]_D$ (ROH)	Config.
n-$C_6H_{13}CHO$	10	88	95	–26.9	–18.0	S
$(C_2H_5)_2CHCHO$	6	86	91	–28.2	–14.2	S
c-$C_6H_{11}CHO$	<5	94	94	–35.0	–6.8	S
t-BuCHO	30	57	90	–16.7	–18.1	S
2-*E*-C_5H_9CHO	28	59	87	+3.7	+21.1	S
Sorbaldehyde	24	24	84	+23.7	+22.0	S
Geranial	45	31	63	+23.0	+35.4	S
Benzaldehyde	26	88	52	-27.4	-18.7	S

In summary, the experiments described above demonstrate the enhancement of the enantioselectivity of conversion of aldehydes to cyanohydrins by means of a new catalytic system in which *both* reactants are activated by binding to chiral sites. Although enzymic catalysis of bimolecular reactions frequently involves the binding of both substrates, most of the synthetic molecular catalysts which have been developed thus far for enantioselective reactions bind and activate only one reactant. In that respect the present work can serve as a model for the invention of more sophisticated and effective enantioselective catalysts.[12]

References and Notes

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6. Prepared by reduction of (*S*)-phenylglycine (Aldrich) with $LiAlH_4$ in THF at 0 °C initially and at reflux for 26 h.
7. Crude **1** was satisfactory for the preparation of **2**. Chromatographic purification of **1** is possible but care must be taken to prevent decomposition. On a 1-2 g scale **1** was purified by flash chromatography on silica gel pretreated with Et_3N using $CHCl_3$–MeOH–Et_3N (100 : 5 : 1) as eluant and was obtained in 83% yield from phenylglycinol as a colorless liquid after short-path distillation at 131-134 °C (0.01 mm Hg); $[\alpha]_D^{23}$ -78.8° (c=1, $CHCl_3$); HRMS (EI) 306.1321 (calcd for **1**, 306.1368); IR (cm^{-1}): 1666.9, 1591.9, 1578.4, 1493.6, 1067.6, 986.8; ^1H NMR (500.135 MHz, $CDCl_3$): δ 7.41 - 7.22 (10H, m), 5.26 (2H, dd, J = 10.0, 8.4 Hz), 4.70 (2H, dd, J = 10.0, 8.4 Hz), 4.29 (2H, dd, J = 8.4 Hz), 3.58 (2H, s); ^{13}C NMR (125.759 MHz, $CDCl_3$): 163.1, 142.1, 128.8, 127.7, 126.7, 75.4, 69.9, 28.5.
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9. Spectral data for **2**: IR (cm^{-1}): 2206.0, 1642.1, 1592.0, 1578.8, 1457.3, 1055.0; ^1H NMR (500.135 MHz, $CDCl_3$): δ 7.38 - 7.23 (10H, m), 5.18 (2H, dd, J = 9.2, 7.6 Hz), 4.83 (2H, dd, J = 9.2, 8.3 Hz), 4.29 (2H, dd, J = 8.3, 7.6 Hz); ^{13}C NMR (125.759 MHz): δ 167.8, 140.5, 129.1, 128.6, 126.5, 116.6, 76.1, 64.5.
10. The use of 3 : 1 CH_2Cl_2–C_2H_5CN as solvent is preferable to CH_2Cl_2 alone since the reaction in CH_2Cl_2 is not completely homogeneous and the product **4** is obtained with somewhat lower enantioselectivity (50% ee).
11. Enantioselectivity was determined by conversion to the cyanohydrin (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate esters and analysis of the 500 MHz ^1H NMR spectra. Absolute configuration was determined from measurement of the optical rotation of the cyanohydrin and comparison with literature[4,5] values.

12. This research was supported by grants from the National Institutes of Health and the National Science Foundation.

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