Communications

Enantioselective Addition of Trimethylsilyl Cyanide to Aldehydes Induced by a New Chiral Ti(IV) Complex

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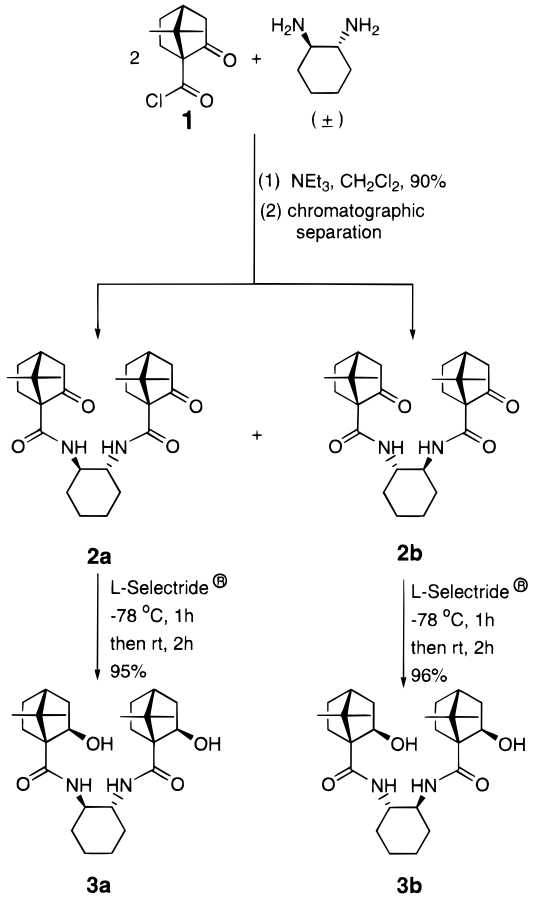
Optically active cyanohydrins are synthetic precursors of α-hydroxy carboxylic acids, α-amino carboxylic acids, *β*-hydroxy amines, and several other classes of organic compounds of biological importance. Existing methods for the preparation of chiral cyanohydrins include both enzymatic[1,2] and chemical processes.[1,3] Chemically, several efficient methods have been developed. In most of these methods, however, the chiral ligands are rather unstable and cannot be easily recovered. We now describe a new chiral Ti(IV) catalyst with dihydroxy-*trans*-1,2-diamide **3a** as the ligand**,** which effects the enantioselective addition of trimethylsilyl cyanide to aldehydes.

Ligand **3a** and its diastereoisomer **3b** were prepared from ketopinic acid chloride **(1)**[4] according to the Scheme 1. On treatment with optically pure (+)- or (−)-*trans*-1,2-diaminocyclohexane in dichloromethane in the presence of triethylamine, ketopinic acid chloride was converted to the *trans*-diketoamide **2a** or **2b**, respectively. Diketoamide **2a** and **2b** could also be obtained in pure form by reacting ketopinic acid chloride with (+)-*trans*-1,2-diaminocyclohexane in the same fashion as above followed by separation of the resulting diastereomeric mixture by column chromatography on silica gel. Subsequent reduction of **2a** and **2b** using L-selectride in tetrahydrofuran at −78 °C for 1 h and then at room temperature for 2 h gave **3a** and **3b**, respectively

Scheme 1



with the hydroxy group at the *exo* position.[5] The absolute stereochemistry of ligand **3a** was further determined by X-ray crystallographic analysis.

Ligand **3a** was found to be an useful chiral ligand for asymmetric induction (eq 1). In conjunction with titanium tetraisopropoxide, ligand **3a** was shown to effect the enantioselective addition of trimethylsilyl cyanide to benzaldehyde **4a** (Table 1). Optimum results were obtained when the reaction was carried out at −78 °C in dichloromethane using the complex prepared from 16.5 mol % of ligand **3a** and 15 mol % of titanium tetraisopropoxide in the presence of 4 Å molecular sieves (entry 6). Under these conditions, the desired cyanohydrin was isolated in 79% yield and 94% ee after hydrolysis (1 *N* HCl, rt, 6 h) of the initial addition product. At the same time, chiral ligand **3a** was recovered in 92% yield. Interestingly, in the absence of molecular sieves, the reaction was extremely slow and no sign of reaction was observed in 24 h at −30 °C (entry 2). This observation is in agreement with those reported previously

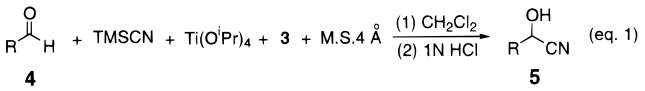


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Table 1. Enantioselective Trimethylsilylcyanation of Benzaldehyde Using 3/Ti(O^{i}Pr)$_4$ with TMSCN

entry	ligand (mol %)	Ti(O^{i}Pr)$_4$ mol %	MS 4 Å,[a] mg	temp, °C	time, h	yield,[b] %	ee,[c] %	config[d]
1	**3a** (22)	20	–	0	10	78	20	*S*
2	**3a** (22)	20	–	−30	24	0	–	–
3	**3a** (11)	10	130	30	6	78	48	*S*
4	**3a** (11)	10	130	−30	24	74	55	*S*
5	**3a** (22)	20	130	−30	18	75	71	*S*
6	**3a** (16.5)	15	130	−78	48	79	94	*S*
7	**3b** (16.5)	15	130	−78	48	77	4	*R*

[a] Powder, dried at 300 °C/0.1 mmHg for 24 h before use. [b] Isolated yield. [c] Determined by HPLC with Chiracel OD column (^{i}PrOH/hexane = 0.25/100, 1 mL/min) after being protected as TBDMS ether. [d] Absolute configurations were determined by comparison of optical rotations with literature values.

Table 2. Enantioselective Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by 3a/Ti(O^{i}Pr)$_4$ Catalyst at −78 °C

entry	aldehyde	time, h	yield,[a] %	ee,[b] %	config[c]
1	3-phenoxybenzaldehyde (**4b**)	120	57 (76)	97.2	*S*
2	4-methoxybenzaldehyde (**4c**)	120	53 (75)	96.6	*S*
3	2-naphthaldehyde (**4d**)	120	76 (85)	96.2	*S*
4	(*E*)-cinnamaldehyde (**4e**)	120	51 (80)	95.1	*S*
5	3-phenylpropionaldehyde (**4f**)	120	62 (78)	97.5	*S*
6	2-methylbenzaldehyde (**4g**)	120	68 (85)	96.8	*S*
7	cyclohexanecarboxaldehyde (**4h**)	60	94	87.2	*S*
8	valeraldehyde (**4i**)	36	96	88.5	*S*

[a] Numbers in parentheses are percent conversions. [b] Enantiomeric excess were determined by HPLC with Chiracel OD column after protected as acetyl ester. [c] Absolute configurations were determined by comparison of optical rotations with literature values.

by Narasaka.[6] The exact function of molecular sieves, however, remains unclear at the present time. It is also noteworthy that the degree of enantioselectivity appears to be proportional to the amount of the complex employed. Thus, when the amount of the complex used was reduced by a half, the enantioselectivity of the reaction was found to depreciate considerably (entries 4 and 5). The selectivity was also found to be temperature dependent as expected; when the reaction was carried out at −30 °C, mandelonitrile was obtained in 71% ee after hydrolysis (entry 5). This level of enantioselectivity was considerably inferior to that observed for the addition reaction carried out at −78 °C. Not surprisingly, however, the improved selectivity was at the expense of the reaction rate. Ligand **3b** was not a useful ligand when applied in the same reaction conditions; only 4% ee was observed in this case (entry 7).

To examine the efficacy of this catalytic process with regards to substrate structure, a variety of aromatic and aliphatic aldehydes were subjected to the conditions optimized in the case of benzaldehyde, employing **3a** with titanium tetraisopropoxide as the catalyst, and the results are summarized in Table 2. The asymmetric induction achieved in both aromatic (>94%) and aliphatic aldehydes (>87%) is quite high. This compares favorably with other organometallic processes reported in the literature thus far. The catalytic nature of the reaction coupled with the high stability and recovery rate of chiral ligand **3a** constitutes the major improvement on existing methods.

In conclusion, a new and efficient catalytic process for the synthesis of chiral cyanohydrins in high enantiomeric excess has been developed. In comparison with previously reported methods, our process is advantageous in both stability of ligand and high levels of enantiocontrol.

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Supporting Information Available: Experimental procedures and spectral data for compounds **2** and **3**, detailed conditions for the analysis of chiral cyanohydrins **5a**−**i**, and X-ray crystallographic data for **3a** (22 pages).

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