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Lewis Base Catalyzed Addition of Trimethylsilyl Cyanide to Aldehydes

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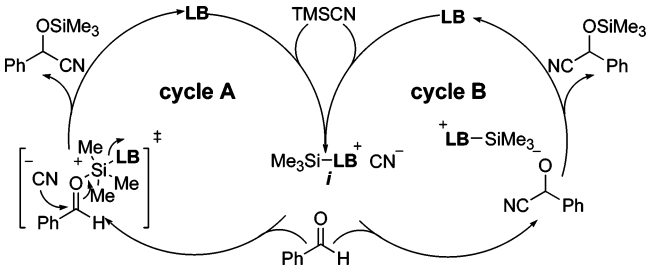
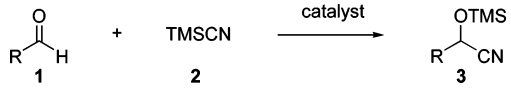


A variety of achiral Lewis bases were found to catalyze the addition of TMSCN to the aldehydes. Among them, phosphines and amines were the most efficient catalysts. In addition, several chiral amines and phosphines were examined in a catalytic, asymmetric addition of TMSCN to benzaldehyde albeit with low enantioselectivity. A mechanistic study revealed that the reaction was first order in aldehyde, first order in Lewis base, and zeroth order in TMSCN, suggesting the complex formation of TMSCN and Lewis base formation of complex ***i***. However, there are at least two possible scenarios for this catalytic process, and in view of the low selectivities observed, it is not clear which mechanism is operative.

The addition of cyanide to aldehydes and ketones is one of the oldest known carbon−carbon bond-forming reactions. First reported in 1832 by Winkler,[1] this reaction is the foundation of the Kiliani−Fisher synthesis of carbohydrates and as such also represents one of the first stereoselective reactions.[2] Over the intervening decades, cyanohydrins have demonstrated considerable synthetic potential as useful building blocks in organic synthesis.[3] Both the hydroxyl and nitrile groups of the cyanohydrins can be further transformed into a variety of useful functional units. After activation, the hydroxyl group can be displaced by a wide range of nucleophiles to form functionalized nitriles.[4] Furthermore, the nitrile function can be hydrolyzed to create many different types of α-hydroxy carbonyl compounds or reduced to form 1,2-amino alcohol derivatives.[5]

In light of the synthetic utility of this class of compounds, the preparation of enantiomerically enriched cyanohydrins has been extensively investigated and comprehensively reviewed.[6] The reagents (catalysts) that effect enantioselective cyanation of carbonyl compounds fall into four main classes: (1) enzymes (oxynitrilase), (2) peptides, (3) Lewis acids (primarily transition metal complexes), and (4) combinations of Lewis acids and Lewis bases. The majority of these synthetic agents have been developed for the addition of trimethylsilyl cyanide (TMSCN) as a safer alternative to HCN or KCN.[7] The enantioselective silylcyanation of aldehydes **1** can be promoted by many chiral Lewis acidic complexes to provide products with good yields and enantioselectivities (Scheme 1).[6] Typically, these catalysts are generated by the combination of a strong Lewis acid with a chiral ligand either in situ or in a separate preparation. The complexation of the Lewis acid and chiral ligand usually leads to deactivation of the catalyst due to the basicity of the donor atoms of the ligands. Therefore, these catalytic systems often suffer from low reaction rates.

SCHEME 1



In recent years, Shibasaki and co-workers developed Lewis acid−Lewis base bifunctional catalysts for the addition of TMSCN to aldehydes.[8] This new bifunctional catalyst consists of a Lewis acidic Al(III) center and Lewis basic phosphine oxide functionality. The catalyst is designed to activate both the electrophile and nucleophile at defined positions simultaneously. The authors suggest that the aluminum moiety electrophilically activates the aldehyde by complexation, and the phosphine oxide moiety activates the TMSCN by hypercoordination. These combined effects lead to excellent chemical yields and high enantioselectivities of the cyanohydrin product. However, the reaction requires very long reaction times, and TMSCN must be added slowly via syringe pump for several hours to achieve high enantioselectivity.

Nucleophilic activation of TMSCN with triphenylphosphine was first reported by Evans in 1977.[9] A systematic investigation of Lewis base catalysis of this reaction was carried out by Mukaiyama and co-workers.[10] These studies demonstrated that achiral Lewis bases such as amines, phosphines, arsines, and stibines can catalyze the addition of TMSCN to aldehydes. Subsequently, Kagan showed that chiral lithium alkoxides derived from binol and salens can catalyze the asymmetric

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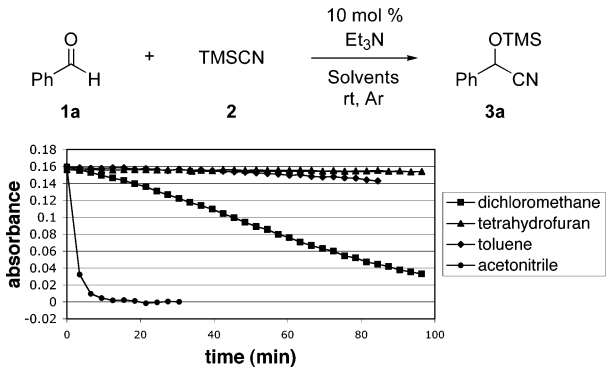

FIGURE 1. Solvent survey for the addition of TMSCN to benzaldehyde.

addition of TMSCN to aldehydes albeit with highly variable enantioselectivities.[11] More recently, Deng and co-workers reported the use of cinchona alkaloids as chiral Lewis bases for trimethylsilylcyanation of activated carbonyl compounds.[12,13] All of these developments have significantly advanced the frontier of enantioselective cyanohydrin synthesis. However, there still is room for improvement, particularly with regard to catalyst simplicity, reaction generality, and especially reaction rate. In view of our continuing interest in the use of chiral Lewis bases for asymmetric transformations,[14] we have undertaken the development of a general Lewis base catalyzed asymmetric trimethylsilylcyanation of aldehydes. Our initial efforts to develop a novel catalytic system, focused on a thorough and quantitative survey of various Lewis bases to establish their relative catalytic efficiency. The rate equation was also of interest to clarify the role of each component and determine if, mechanistically, nucleophilic catalysis was amenable to asymmetric induction. It was hoped that these fundamental investigations would guide the design of an effective chiral Lewis base catalyst.

1. Survey of the Solvent. To develop an effective Lewis base catalyzed process for the addition of TMSCN to aldehydes, several experimental variables were investigated. Foremost among the factors that can influence the rate of the reaction are the solvents and catalyst structures. Therefore, a systematic study of these two variables was performed. Initially, various solvents were surveyed to determine what effect polarity and donicity[15] have on the rate of addition of TMSCN to benzaldehyde (**1a**). Triethylamine, which had been successfully employed previously, was chosen as the catalyst for these reactions.[10] Both the catalyzed and the uncatalyzed reaction rates were measured in situ using a ReactIR instrument, and the catalyzed reaction profiles are shown in Figure 1. Unfortunately, no clear trend emerges from these data, as the relative rates do not correlate with the polarity or the basicity of solvents.[15,16] Nevertheless, the rapid rate of the addition in acetonitrile compared to other solvents clearly identified it as the solvent of choice for this transformation. Furthermore, no reaction was observed in the absence of triethylamine, thus demonstrating that CH_3CN was not catalyzing the reaction.

2. Survey of the Lewis Base Catalyst. A wide range of functionally and structurally diverse Lewis bases were examined in acetonitrile. Included in this survey were tri-*n*-butylphosphine (*n*-Bu_3P), *N*,*N*-(dimethylamino)pyridine (DMAP), triethylamine (Et_3N), *N*-methylimidazole (NMI), hexamethylphosphoric triamide (HMPA), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine *N*-oxide, triphenylphosphine oxide, thiourea, and tetramethylurea. The rate of trimethylsilylcyanation of benzaldehyde (**1a**) in the presence of these Lewis bases was again measured in situ using a ReactIR instrument (Figure 2). Although *n*-Bu_3P was the most effective catalyst found, amines such as DMAP, Et_3N, and NMI were comparable. With the exception of HMPA, oxygen centered bases showed poor catalytic activities. Clearly, the rate of reaction correlates well with the donor ability of the Lewis bases.[17]

The generality of this trend (increasing reaction rate with increasing nucleophilicity of the Lewis base) was examined for three additional aldehydes (*E*)-cinnamaldehyde (**1b**), hydrocinnamaldehyde (**1c**), and phenylpropagyl aldehyde (**1d**) with a limited selection of Lewis bases (Figure 2). Hydrocinnamaldehyde and phenylpropagyl aldehyde were very reactive substrates, and these reactions had to be carried out at −30 °C using 0.1 mol % of catalyst to allow for differences in the efficiency of the catalysts to be discerned. Interestingly, the trend in catalytic activity with respect to the donor character of the Lewis base remained consistent with all of these aldehydes, namely *n*-Bu_3P > DMAP > Et_3N.

As the initial survey clearly showed, *n*-Bu_3P was a highly effective catalyst for the trimethylsilylcyanation of all classes of aldehydes surveyed. To determine the structural and chemical requirements of an efficient catalyst, several phosphorus-containing Lewis bases were investigated. The catalytic activities of triphenylphosphine, triethyl phosphite, and hexamethylphosphorous triamide (HMPT) in the addition of TMSCN to benzaldehyde **1a** were measured in situ using a ReactIR instrument. Triphenylphosphine and triethyl phosphite showed moderate reactivity, while HMPT showed reactivity similar to *n*-Bu_3P.

3. Kinetic Study. To gain insight into the origin of the significant catalysis by Lewis bases, a kinetic analysis of the silylcyanation reaction was carried out. The integral method and the method of initial rates were employed to determine the order of the individual reagents in this reaction. First, to determine the overall reaction order, the concentration of **1a** was plotted against time for three different scenarios; [**1a**], 1/[**1a**], and ln[**1a**]. The best fit was obtained in plotting ln [**1a**] vs time. Therefore, the overall reaction order is first order (see the Supporting Information).

By varying the amount of **1a**, the initial rates at different concentrations of **1a** could be measured. Examination of the initial rates revealed that the reaction was first order in **1a**. Similar studies were done for the Et_3N and TMSCN. The kinetic plots revealed that the reaction was first order in Et_3N and zeroth order in TMSCN (see the Supporting Information).

4. Mechanism. On the basis of the results from these kinetic studies, two catalytic cycles can be proposed (Figure 3). Catalytic cycle A involves an ionized cyanide intermediate ***i*** held in a tight ion pair. After the silyl cation coordinates to the

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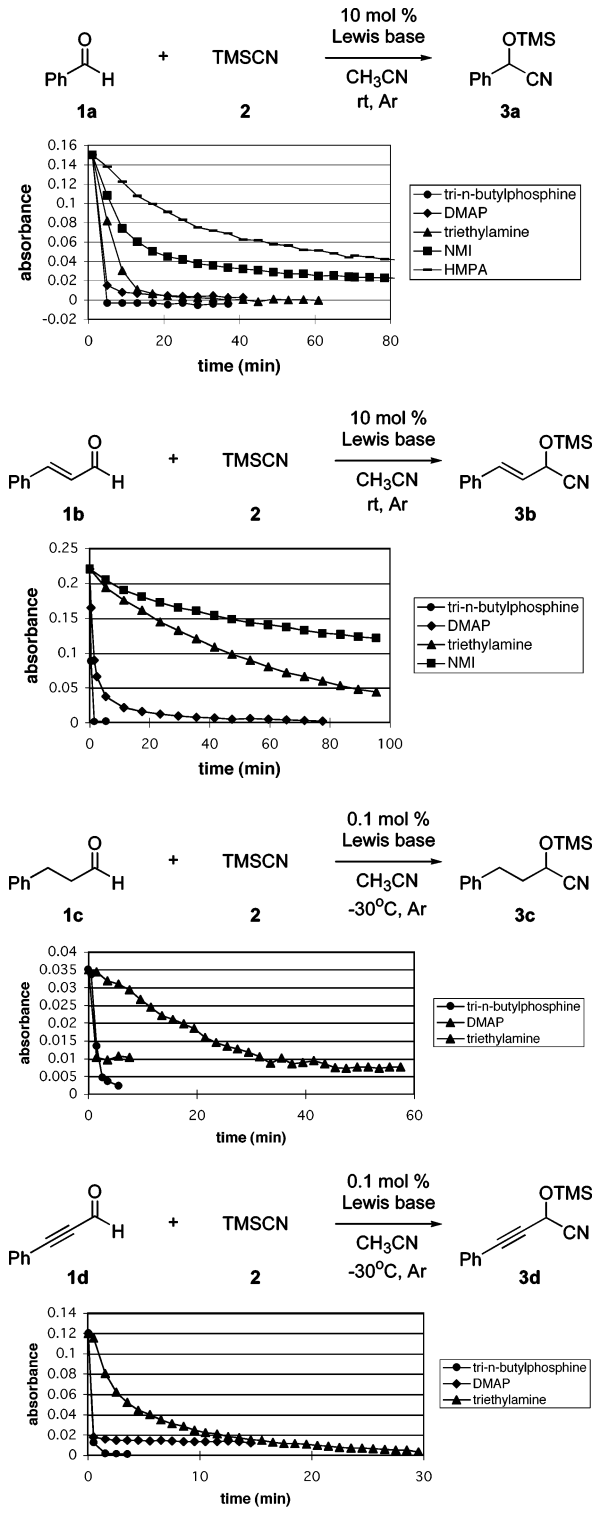


FIGURE 2. Lewis base survey for the addition of TMSCN to various aldehydes (only efficient Lewis bases are shown for **1b**−**d**).

aldehyde, cyanide addition can occur under influence of the chiral Lewis base. In this cycle, the chiral information from the Lewis base can be transferred to the newly forming chiral center. If the binding of the Lewis base to TMSCN is irreversible or the equilibrium lies on the ion pair ***i***, the reaction will be first order in catalyst and zeroth order in TMSCN. If the coordination of silyl group to aldehyde is the rate-determining step, the reaction will be first order in aldehyde.

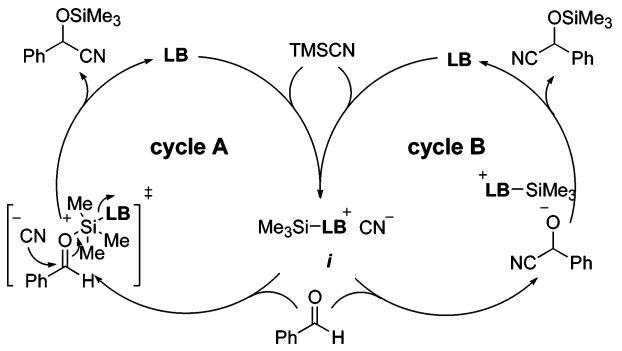


FIGURE 3. Proposed catalytic cycles.

Catalytic cycle B involves formation of a free cyanide anion that can add to the aldehyde without influence of the silyl cation bound Lewis base. In this cycle, the chiral information on the Lewis base is not transferred to the newly forming stereocenter. If the Lewis base−cyanide exchange is irreversible or the equilibrium lies on the free cyanide anion, the reaction will be first order in catalyst and zeroth order in TMSCN. Furthermore, if the addition of the free cyanide to aldehyde is the rate determining step, the reaction will be first order in aldehyde.

Therefore, to obtain asymmetric induction, the ion pair should be stabilized to prevent dissociation, thereby allow for the reaction to proceed through catalytic cycle A. The stability of the ion pair ***i*** can be greatly influenced by changing reaction conditions such as solvent, Lewis base, and temperature. Studies of trimethylsilylcyanation of aldehydes in the presence of various chiral Lewis bases is described below.

5. Survey of Chiral Lewis Bases. 5.1. Amines. On the basis of the results from the survey of catalysts, chiral amines and phosphines were investigated as potential candidates for asymmetric trimethylsilylcyanation of benzaldehyde **1a**. Because amines are easier to handle than oxidation sensitive phosphines, several readily available chiral amines were examined. Unfortunately, trimethylsilylcyanation performed in the presence of chiral amines, (*S*)-α-methylbenzylamine (**4**), (1*S*,2*R*)-*N*-methylephedrine (**5**), (−)-strychnine (**6**), $(DHQ)_2PHAL$ (**7**), and $(DHQD)_2PHAL$ (**8**) afforded only racemic product (Chart 1). Although there are many reasons why a catalyzed reaction displays no enantioselectivity, two explanations immediately come to the fore: (1) the high reactivity of TMSCN in CH_3CN, which

CHART 1

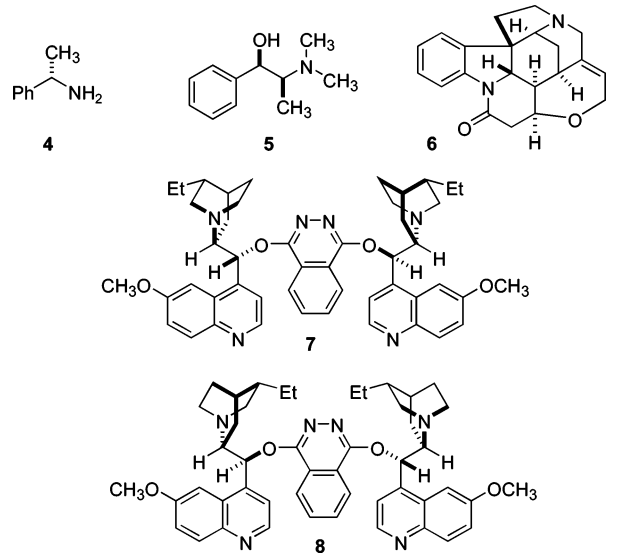


TABLE 1. Asymmetric Trimethylsilylcyanation of 1a with $(DHQ)_2PHAL$ in Various Solvents[a]

1a 2 3a

entry	solvent	ϵ_r[b]	time, h	yield, %	er[c]
1	hexane	1.88	17.8	63	49/51
2	toluene	2.38	16.7	59	34/66
3	1,4-dioxane	3.31	14.8	37	41/59
4	diethyl ether	4.20	18.2	53	51/49
5	$CHCl_3$	4.81	15.1	73	37/63
6	ethyl acetate	6.02	17.3	21	46/54
7	THF	7.58	13.7	54	48/52
8	CH_2Cl_2	8.93	5.0	57	40/60
9[d]	CH_2Cl_2	8.93	5.3	17	42/58
10	CH_3CN	35.94	4.0	74	51/49

[a] All reactions employed 1.05 equiv of TMSCN at 0.16 M concentration. [b] Dielectric constant. [c] Determined by CSP-GC with G-TA column; the absolute configuration was not determined. [d] Reaction at −78 °C.

would be characterized by an early transition state with little steric interaction between the aldehyde and chiral catalyst or (2) the ionization of the TMSCN by the Lewis base catalyst, thus generating free cyanide which can add to the aldehyde in an achiral addition reaction. Both of these pathways may be rendered selective the use of other solvents that would either slow the reaction or stabilize a hypervalent silicon intermediate and disfavor ionization.

To test this hypothesis, several solvents were examined in the addition of TMSCN to benzaldehyde **1a** in the presence of $(DHQ)_2PHAL$ (Table 1). Although moderate enantioselectivities were achieved in several cases (entries 2, 5, and 8), the increase in selectivity could not be related to the reaction rate or polarity of the solvents.

Although the addition to **1a** proceeded with low enantioselectivity, other aldehyde structures were also tested to ensure that this phenomenon was not substrate specific. Therefore, the same solvents were surveyed in the addition to **1b** and **1c** in the presence of $(DHQ)_2PHAL$. For **1b**, the products were always racemic. However, for **1c**, moderate enantioselectivity was observed in 1,4-dioxane (65/35).[18]

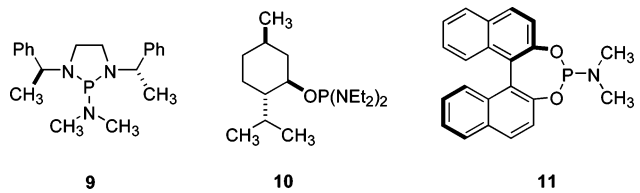
5.2. Phosphines. Although trialkylphosphines are air-sensitive, aminophosphines are less prone to oxidation and easier to prepare. Therefore, chiral aminophosphines were the first choice as chiral, phosphorus containing Lewis bases (Chart 2). Due to the strong influence of solvent on the enantioselectivity that was observed when catalyzed by amines, these reactions were performed in a range of solvents. Chiral aminophosphines **9**[19] and **10**[20] were synthesized and used as catalysts in the trimethylsilylcyanation of **1a** in various solvents. However, under these reaction conditions no enantioselectivity was observed.

The lack of asymmetric induction could result from the strong nucleophilicity of the aminophosphine, generating free cyanide ion from the ion pair. Therefore, the nucleophilicity of phosphines was attenuated through introducing oxygens in place of the nitrogens.

Although both compounds showed appreciable catalytic activity, there was no asymmetric induction as racemic products were isolated. Phosphoramidite **11**[19] and phosphite **12**[20b] were also surveyed, but no addition product could be isolated.

Despite unsatisfactory results from chiral Lewis base catalyzed reactions, the nonracemic product obtained suggests that improving enantioselectivity is mechanistically possible. Whereas cinchona alkaloid monomers provided only racemic products, modest enantioselectivity could be obtained with cinchona alkaloid dimers. Because the reaction was first order in catalyst, it is reasonable to assume that only one of the cinchona units in the dimer is needed to catalyze the reaction. Therefore, it can be postulated that only one cinchona alkaloid of the dimer activates TMSCN and the other cinchona alkaloid transfers chiral information to the reaction center, probably by shielding one side of aldehyde. This design will be pursued.

CHART 2



9 10 11

Experimental Section

General Experimental Procedures. See the Supporting Information.

DMAP-Catalyzed Addition of TMSCN to Benzaldehyde. Acetonitrile (20 mL) was added to a flame-dried, 50 mL flask containing DMAP (12 mg, 0.098 mmol, 0.01 equiv) with magnetic stir bar under N_2. Benzaldehyde (1 mL, 9.841 mmol) and TMSCN (1.325 mL, 9.939 mmol, 1.01 equiv) were added to the solution. After 1 h, the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 10/1) to give 1.920 g (95%) of **3a** as a clear, colorless oil.[21] Data for **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.49−7.39 (m, 5 H), 5.50 (s, 1 H), 0.24 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) 136.2, 129.6, 129.5, 126.6, 119.4, 63.9, −0.0; GC (G-TA column, 110 kPa, 90 °C) t_R 13.3 min (50%), 14.3 min (50%).

DMAP-Catalyzed Addition of TMSCN to Hydrocinnamaldehyde. Acetonitrile (3 mL) was added to a flame-dried, 10 mL flask containing DMAP (1.9 mg, 0.015 mmol, 0.01 equiv) with a magnetic stir bar under N_2. Hydrocinnamaldehyde (200 μL, 1.519 mmol) and TMSCN (205 μL, 1.534 mmol, 1.01 equiv) were added to the solution. After 20 min, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate, 10/1) to give 301 mg (85%) of **3c** as a clear, colorless oil.[21] Data for **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.33−7.19 (m, 5 H), 4.37 (dd, J = 6.4, 6.4, 1 H), 2.80 (dd, J = 3.8, 3.8, 2 H), 2.09−2.15 (m, 2 H), 0.21 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.9, 128.6, 128.4, 126.4, 119.9, 60.6, 37.6, 30.6, −0.4; GC (G-TA column, 110 kPa, 110 °C) t_R 12.5 min (50%), 13.5 min (50%).

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Supporting Information Available: Full experimental procedures and characterization data (including representative 2D NMR spectra) for all addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Me_3NO is as effective as DMAP catalyst for the trimethylsilylcyanation. A few chiral trialkylamine *N*-oxides were prepared, and they have appreciable catalytic activity; no significant asymmetric induction was observed.

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