## A Mild and Efficient Cyanosilylation of Ketones Using In Situ Generated *N*-oxides-Ti(*i*PrO)<sub>4</sub> Complexes as Catalysts

Yongcun Shen,<sup>b</sup> Xiaoming Feng,\*a Yan Li,<sup>a</sup> Guolin Zhang,<sup>c</sup> Yaozhong Jiang\*<sup>b</sup>

<sup>c</sup> Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China

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**Abstract:** The addition of TMSCN to ketones catalyzed by complex of racemic N-(2'-pyridylmethyl)-2-diphenylhydroxymethyl-pyrrolidine *N*-oxide (rac-1) or *N*-benzyl-*N*,*N*-dihydroxyethylamine *N*-oxide and Ti(*i*PrO)<sub>4</sub> affords the racemic O-TMS cyanohydrins in good to excellent isolated yields (up to 97%) under mild reaction conditions.

Key words: catalysis, cyanosilylation, ketones, N-oxides, complex



Figure

Cyanation reaction of carbonyl compounds is one of the most powerful procedures for the synthesis of polyfunctionalized molecules. In fact, cyanohydrins are highly versatile synthetic intermediates, which can easily be converted to various important building blocks including  $\alpha$ -hydroxy carbonyl derivatives and  $\beta$ -aminoalcohols.<sup>1</sup> The addition of TMSCN to ketones catalyzed by Lewis acids or Lewis bases is the most used strategy for the synthesis of cyanohydrins.<sup>2</sup> Generally, in the absence of catalyst, no reaction occurs between TMSCN and carbonyl compounds. Additives and Lewis acids have been examined as promoters for such reactions. A variety of Lewis acids and Lewis bases have been employed successfully as promoters in cyanosilylation of ketones.<sup>2</sup> However, the number of methods for effecting catalytic cyanosilylation of ketones remains quite limited, and to the best of our knowledge, although chiral amine N-oxides were used in asymmetric synthesis, such as allylation of aldehydes<sup>3</sup> and reduction of ketones and addition of ZnEt<sub>2</sub> to aldehydes,<sup>4</sup> there is no report about the application of N-oxides in nucleophilic addition of cyanide to ketones. Herein, we wish to report the first example about cyanosilylation reaction of ketones using N-oxides-Ti(iPrO)<sub>4</sub> complexes as promoters (Scheme 1) to afford racemic O-TMS cyanohydrins in high isolated yields (up to 97%).





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We have recently reported that chiral N-oxides are highly effective catalysts for enantioselective Strecker reaction,<sup>5</sup> which prompted an investigation of addition of TMSCN to ketones employing chiral N-oxides, however, no cyanosilylation adduct was obtained with (+)-S-3,3'-dimethyl-2,2'-biquinoline-N,N'-dioxide. This could be due to the poor activities of ketones. Although (+)-S-3,3'-dimethyl-2,2'-biquinoline- N,N'-dioxide can activate TMSCN, it is still difficult for addition of TMSCN to ketones. We envisaged that compounds with N-oxide moiety and available multiple coordination sites to metal ion, coordinating with metal, would catalyze cyanosilylation reaction of ketones. For testing this assumption, a series of racemic Noxides were synthesized.<sup>6</sup> With N-oxides in hand, and acetophenone as a test substrate, a rac-1-Ti(*i*PrO)<sub>4</sub> complex system was found to be the most promising catalyst for this reaction.<sup>7</sup> In CH<sub>2</sub>Cl<sub>2</sub> at 0 °C, 20 mol% rac-1-Ti(*i*PrO)<sub>4</sub> (2:1 ratio) complex used as catalyst, acetophenone gave racemic O-TMS cyanohydrin in 82% isolated yield (Table 1, entry 1). Further studies showed that there was no difference in catalytic activities between two diastereoisomer<sup>8</sup> and several factors were important for isolated yield. The best results were obtained when 2 equiv. of rac-1 (Figure) were used per Ti and concentration of substrates was 0.34 M. A solvent study showed that CH<sub>2</sub>Cl<sub>2</sub> provided the best results (Table 1).<sup>9</sup> It is noteworthy that, when the reaction was carried out in CH<sub>3</sub>CN, product was found to be trace. Such a low conversion is probably due to a strong coordination interaction between Ti and CH<sub>3</sub>CN. This result was different from that reported by Saravanan, using Cu(OTf)2 as catalyst for the addition of TMSCN to carbonyl compounds.<sup>2e</sup>

Investigation of the scope of substrates was conducted under the optimized conditions as outlined above, the results were given in Table 1. The aromatic, conjugated and ali-

<sup>&</sup>lt;sup>a</sup> Sichuan Key Laboratory of Green Chemistry and Technology, The Faculty of Chemistry, Sichuan University, Chengdu 610064, China Fax +86(28)5412907; E-mail: xmfeng@pridns.scn.edu.cn

<sup>&</sup>lt;sup>b</sup> Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China

phatic ketones afforded the corresponding products in good to excellent isolated yields (Table 1, entries 1–10). The experimental results indicated that substituents on aromatic ring had slight influence on conversion. Especially, less reactive ketone such as 2-acetylthiophen gave the product in moderate isolated yield (Table 1, entry 12) by our procedure, this is the first example of cyanosilylation of 2-acetylthiophen. As a matter of fact, the low conversion of 2-acetylthiophen (Table 1, entry 12) was probably due to coordination between sulfur atom on the thiophen ring and titanium, which restricted the coordination between carbonyl group and titanium.

**Table 1**Cyanosilylation of Ketones ( $R^1COR^2$ ) Catalyzed by *rac*-1-Ti (*i*PrO)<sub>4</sub> (2:1 ratio) Complex<sup>a</sup>

Entry	$R^1$	R <sup>2</sup>	Time (h)	Isolated yield (%) <sup>b</sup>
1	Ph	CH <sub>3</sub>	62	82
2	$2-FC_6H_4$	CH <sub>3</sub>	68	85
3	$4-FC_6H_4$	CH <sub>3</sub>	68	84
4	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	CH <sub>3</sub>	96	93
5	C <sub>6</sub> H <sub>5</sub>	$C_2H_5$	72	87
6	$4-CH_3C_6H_4$	CH <sub>3</sub>	92	79
7	β-naphthyl	CH <sub>3</sub>	98	79
8	$4-NO_2C_6H_4$	CH <sub>3</sub>	80	86
9	C <sub>6</sub> H <sub>5</sub> CH=CH	CH <sub>3</sub>	96	80
10	$n-C_5H_{11}$	CH <sub>3</sub>	51	97
11	$4-NH_2C_6H_4$	CH <sub>3</sub>	98	54
12	2-thiophenyl	CH <sub>3</sub>	76	42

<sup>a</sup> All the reactions were carried out according to experimental procedure.<sup>10</sup>

<sup>b</sup> The isolated yields are given on the isolated O-TMS cyanohydrins after chromatographic purification, satisfactory spectral data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR) and elemental analysis were obtained for the new compounds.

Although *rac*-1 was easily synthesized, Grignard reaction conditions are severe in process of preparation. We attempted to employ more easily prepared *N*-oxide instead of *rac*-1. For this purpose, *N*-oxide 2 (Figure) was synthesized (Scheme 2)<sup>11</sup> and employed for cyanosilylation of ketones according to procedure described above, the results of representative substrates were shown in Table 2. Gratifyingly, the results indicated that catalytic activity of *N*-oxide 2-Ti(*i*PrO)<sub>4</sub> is similar to that of *rac*-1-Ti(*i*PrO)<sub>4</sub> for this reaction. So *N*-oxide 2 as more inexpensive ligand could be employed in this procedure, and make this procedure more practical.

To glean mechanistic insight into the cyanosilylation reaction of ketones and understand the role of *N*-oxide moiety, 20 mol% *rac*-**3**-Ti(*i*PrO)<sub>4</sub> (2:1 ratio) complex was used to catalyze cyanosilylation reaction of acetophenone

$$HN(CH_2CH_2OH)_2 \xrightarrow{BnBr/K_2CO_3} BnN(CH_2CH_2OH)_2$$

$$\xrightarrow{\text{mCPBA/K}_2\text{CO}_3} \xrightarrow{\text{O}^-}_{\text{I}} \text{BnN}(\text{CH}_2\text{CH}_2\text{OH})_2$$

Scheme 2

at 0 °C in CH<sub>2</sub>Cl<sub>2</sub>, after 76 h, no product was obtained. It showed that, although catalyst could activate the ketone, the reaction still proceeded difficultly. It revealed that Noxide moiety played an important role in this reaction. On the other hand, bases can catalyze the addition of TMSCN to carbonyl compounds.<sup>12</sup> However, in the absence of Ti(*i*PrO)<sub>4</sub>, 20 mol% *rac*-1 was used as catalyst for this reaction, after 70 h, no product was found. This result suggested that  $Ti(iPrO)_4$  was also necessary for this reaction. Although the mechanistic details of 20 mol% rac-1-Ti(iP $rO_4$  (2:1 ratio) complex catalyst accelerating cyanosilylation process of ketones are uncertain, from experimental results obtained, it could be postulated that Ti as a Lewis acid and N-oxide moiety as a Lewis base work cooperatively to activate the ketones and TMSCN, respectively. Therefore, rac-1-Ti(iPrO)<sub>4</sub> and N-oxide 2-Ti(iPrO)<sub>4</sub> complexes are probably the Lewis acid and Lewis base bifunctional catalysts.

**Table 2** Cyanosilylation of Ketones (R<sup>1</sup>COR<sup>2</sup>) Catalyzed by *N*-Ox-ide (2)-Ti (*i*PrO)<sub>4</sub> (2:1 ratio) Complex<sup>a</sup>

Entry	<b>R</b> <sup>1</sup>	R <sup>2</sup>	Time (h)	Isolated Yield (%) <sup>b</sup>
1	Ph	CH <sub>3</sub>	68	80
2	$4-FC_6H_4$	CH <sub>3</sub>	68	84
3	$C_6H_5$	$C_2H_5$	80	87
4	$C_{6}H_{5}(CH_{2})_{2}$	CH <sub>3</sub>	96	93
5	$4-NO_2C_6H_4$	CH <sub>3</sub>	80	76

<sup>a</sup> All the reactions were carried out according to experimental procedure, but *rac*-1 was replaced by *N*-oxide **2**.<sup>10</sup>

<sup>b</sup> The isolated yields are given on the isolated O-TMS cyanohydrins after chromatographic purification, satisfactory spectral data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR) and elemental analysis were obtained for the new compounds.

In conclusion, we have developed a new, mild and highly efficient protocol for the synthesis of racemic O-TMS cyanohydrins from ketones and TMSCN catalyzed by *N*-oxides–titanium complexes generated in situ. The reported procedure clearly demonstrated that *N*-oxides–titanium complexes are good catalysts for the preparation of racemic O-TMS cyanohydrins. It compares favorably and represents a valid alternative to the existing methods. The important features of our method are: mild reaction conditions, simple work-up, inexpensive catalyst employed and

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wide substrate scope. Further efforts will be directed at understanding the catalytic mechanism, catalyst structure of this reaction and study of asymmetric cyanosilylation of ketones catalyzed by chiral *N*-oxide-metal complex.<sup>13</sup>

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- (7) N-(3'-Pyridylmethyl), N-(2'-methoxyphenylmethyl) and Nphenylmethyl-2- diphenylhydroxymethyl-pyrrolidine Noxides were screened.
- (8) With 20 mol% *rac*-1-Ti(*i*PrO)<sub>4</sub> (1:1.2 ratio) complex used as catalyst, acetophenone gave O-TMS cyanohydrin in 0% ee, but with 20 mol% (*S*)-1-Ti(*i*PrO)<sub>4</sub> (1:1.2 ratio) complex used as catalyst, acetophenone gave O-TMS cyanohydrin in 53.3% ee {GC [Varian, Chirasil DEX CB (0.25 mm × 25 m), Column temperature = 100 °C(isothermal), Injector temperature = 200 °C, Detector temperature = 250 °C,  $t_R(minor) = 26.3 min, t_R(major) = 27.8 min]$ }.
- (9) A series of solvents were examined including toluene, THF, Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub> and CH<sub>3</sub>CN.
- (10) A representative procedure: To a solution of rac-1 (12.2 mg, 0.034 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added Ti(*i*PrO)<sub>4</sub> (1 M in toluene, 17 µL, 0.017 mmol) at room temperature, and the mixture was stirred for 1 h, CH<sub>2</sub>Cl<sub>2</sub> was evaporated under reduced pressure. The resulting residue was further dried in vacuo for 30 min. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). To this solution, the ketone (0.17 mmol) was added under ice-water bath, followed by the addition of TMSCN (45 µL, 0.34 mmol) as shown in Table 1. The reaction was monitored by TLC, and after the reaction period described in Table 1, the solution was concentrated, usual work up and purification by silica gel chromatography gave the product. (11) *N*-oxide **2**:
- (11) *N*-oxide 2: White crystals; mp 135–137 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta = 3.46-3.47$ (t, J = 1.6 Hz, 4 H), 4.12(m, 4 H), 4.61(S, 2 H), 5.15(br, 2 H), 7.37–7.46(m, 5 H); MS *m/z*: 212(M<sup>+</sup> + H, 81%).
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