Phenolic *N*-Oxide as a Highly Efficient Organocatalyst for Cyanosilylation of Ketones

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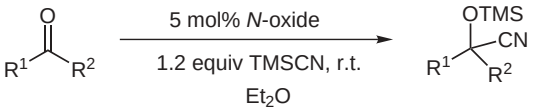
Abstract: The use of an inexpensive, easy to handle and readily available chemical, 5 mol% phenolic *N*-oxide, alone as a catalyst for cyanosilylation of ketones gave the corresponding products in 78–99% yield with reaction times of 0.5–16 hours.

Key words: catalysis, cyanohydrins, achiral *N*-oxides, ketones, organocatalysis

The addition of TMSCN to ketones is the most popular strategy to afford cyanohydrins, which can be conveniently converted into various important polyfunctionalized building blocks, including α-hydroxyl carbonyl compounds and β-amino alcohols, for the synthesis of many natural products and bioactive molecules.[1] The reaction is well known, yet its course is very dependent on the catalyst that is used. No reaction is observed in the absence of catalyst. A plethora of catalytic agents, including Lewis acid and Lewis base,[2] solubilized anionic species (KCN/18-crown-6),[3] inorganic solid acid and base,[4] have been employed. Since the first example of a novel bifunctional catalyst for this reaction was reported by Shibasaki,[5] our group developed a bifunctional catalyst with *N*-oxide dipolar moieties[6] and a double activation method (CDAM).[7] However, there are still many unsolved problems such as the expensive catalysts, troublesome procedures, and unsatisfactory substrate tolerance. For these purposes, new catalytic methods based on metal-free organic molecules have been developed in the last few years.[8] However, there are few reported examples of the cyanosilylation of ketones employing organocatalysts.[9] Herein, we reported the use of phenolic *N*-oxide as a catalyst for the cyanosilylation of ketones (Scheme 1).



Scheme 1

Chiral *N*-oxides have been used in several asymmetric synthetic procedures, including the allylation of aldehydes,[10] the addition of Et_2Zn to aldehydes,[11] the enantioselective reduction of ketones,[12] the enantioselective epoxide openings,[13] the asymmetric aldol reaction[14] and the Strecker reaction.[15] Intrigued by the significant nucleophilicity of amine *N*-oxides toward the silicon atom, we speculated that this reaction could be efficiently promoted by a lone *N*-oxide with proper structure. From our previous study on *N*-oxides as promoters for cyanation, we considered that the stronger a Lewis base is, the higher its reactivity is. Therefore, we proposed that aliphatic-type *N*-oxide is better than aromatic-type *N*-oxide and pyridine-type *N*-oxide with regard to this reaction. In the preliminary study, we investigated the addition of TMSCN to acetophenone in the presence of a series of easily prepared *N*-oxides with different stuctures to probe the relationships between the stucture of *N*-oxides and the reaction rate (Figure 1). The results are summarized in Table 1.

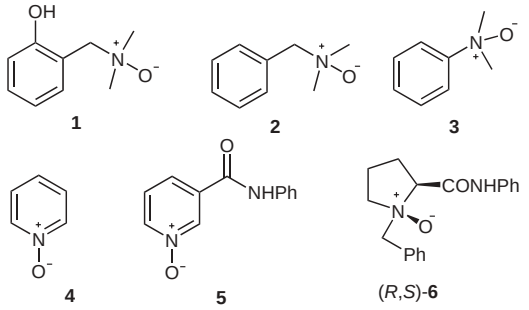


Figure 1

The catalytic activity of pyridine-type *N*-oxide is inferior to aromatic-type *N*-oxide (Table 1, entries 3–5) and aromatic-type *N*-oxide is inferior to aliphatic-type *N*-oxide (Table 1, entries 2 and 3). This agrees with our previous hypothesis. However, catalyst **2** is too sensitive to moisture and is difficult to handle. To smooth this trouble, catalyst **1**, with a hydroxyl moiety on the ortho position of the aromatic ring, was synthesized. Catalyst **1** was found to be more stable than catalyst **2** as a result of the intramolecular hydrogen bond. Fortunately, further experiments showed that the hydroxyl moiety on the aromatic ring is advanta-

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Table 1 Catalytic Addition of TMSCN to Acetophenone[a]

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	**1** (5)	CH_2Cl_2	0	26	80
2	**2** (5)	CH_2Cl_2	0	26	63
3	**3** (5)	CH_2Cl_2	0	26	15
4	**4** (5)	CH_2Cl_2	0	54	0
5	**5** (5)	CH_2Cl_2	0	54	8
6	**1** (5)	CH_2Cl_2	23	6	99
7	**1** (5)	Et_2O	23	6	99
8	**1** (5)	THF	23	7.5	82
9	**1** (5)	Toluene	23	7.5	96
10	**1** (1)	Et_2O	23	9	43

[a] TMSCN/acetophenone = 2, substrate concentration = 1 M.
[b] Isolated yields.

geous concerning both the catalytic activity and stabilization of the catalyst (Table 1, entries 1 and 2). Subsequent studies were performed with catalyst **1**.

Further studies showed that several parameters were important for the reactivity. At room temperature, the reaction proceeded in higher yield and shorter reaction time (Table 1, entries 1 and 6). Then, a solvent study showed that CH_2Cl_2 and Et_2O provided better results than THF and toluene (Table 1, entries 6–9). Considering environmental factors, we chose Et_2O as the preferred solvent. The amount of the catalyst was also revealed to be an important parameter for the attainment of high yield in short time. Further reducing the amount of the catalyst led to a much longer reaction time (Table 1, entry 10). It should be noted that when the ratio of TMSCN to acetophenone was reduced to 1.2, there was no obvious effect on the reaction time and yield. So we obtained the following optimal conditions: 5 mol% **1**, 23 °C, concentration of ketones = 1 M in Et_2O, TMSCN/ketone = 1.2 equivalents. Additionally, this reaction was found to be insensitive to air and moisture. Hence, there was no need for an inert atmosphere.

Encouraged by the results obtained for acetophenone, we investigated a number of other ketones to probe their behavior under the optimal conditions outlined above, the results are given in Table 2.[16]

Aromatic, conjugated and aliphatic ketones afforded the corresponding products in excellent isolated yields (Table 2, entries 1–16). Furthermore, the reaction rate of cyanosilylation of heterocyclic ketone is also fast (Table 2, entry 16). The substituents on the aromatic ring had a slight influence on reactivity (Table 2, entries 3–7) with one exception (Table 2, entry 8). β-Tetralone was more active than α-tetralone (Table 2, entries 12 and 13). The α,β-unsaturated ketone gave the product more rapidly than the α,β-saturated one (Table 2, entries 10 and 11).

Table 2 Catalytic Addition of TMSCN to Ketones Using Compound **1**[a]

Entry	Ketone	Time (h)	Yield (%)[b]
1	Acetophenone	6	99
2	2-Acetonaphthone	3	99
3	Propiophenone	3	99
4	*n*-Butyrophenone	3	99
5	3-Chloroacetophenone	4.5	99
6	4-Chloroacetophenone	5	99
7	4-Methoxyacetophenone	5	99
8	4-Nitroacetophenone	0.5	98
9	4-Fluorobenzophenone	1	99
10	*trans*-4-Phenyl-3-buten-2-one	0.5	98
11	Benzylacetone	1.5	99
12	α-Tetralone	16	82
13	β-Tetralone	5	78
14	2-Heptanone	0.5	99
15	Cyclohexanone	0.5	99
16	2-Acetylthiophene	4.5	96

[a] Conditions: 5 mol% **1**, substrate concentration = 1 M in Et_2O, 23 °C, TMSCN = 1.2 equiv.
[b] Isolated yields.

Additionally, we attempted to investigate the enantioselective cyanosilylation of ketones by using chiral *N*-oxide alone. In CH_2Cl_2 solvent and at 0 °C, the use of 10 mol% chiral *N*-oxide **6** as catalyst for cyanosilylation of acetophenone gave the 2-trimethylsilyloxy-2-phenylpropanenitrile in 99% isolated yield with 21% ee after 100 hours.

In conclusion, we have developed a mild and highly efficient protocol for the synthesis of racemic OTMS cyanohydrins from ketones and TMSCN catalyzed by phenolic *N*-oxide. The mild experimental conditions, shorter reaction time, inexpensive organic catalyst and the wide substrate applicability represent the notable features of this procedure. Future efforts will be devoted to further searches for effective chiral *N*-oxides as catalysts for the asymmetric cyanosilylation of ketones and investigating the mechanism of this reaction.

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(16) **General Procedure for Cyanosilylation of Ketones:** To a mixture of ketone (0.5 mmol) and phenolic *N*-oxide (4.2 mg, 0.025 mmol) in Et_2O (0.5 mL) was added trimethylsilyl cyanide (83 μL, 1.2 equiv) at r.t. The reaction was monitored by TLC, and after the reaction period described in Table 2, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography with Et_2O–petroleum ether (1:100, v/v) to give the pure product.

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