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TI-TRIOL CATALYSED TRIMETHYLSILYLCYANATION OF ACETOPHENONES UNDER HIGH PRESSURE

Michael C.K. Choi,[*1] Shu-Sun Chan,[1] Man-Kong Chan,[1] Jong Chul Kim,[2] Hirokazu Iida,[2†] and Kiyoshi Matsumoto*[2]

[1] Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis[††] and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China (e-mail: bcckchoi@polyu.edu.hk) [2] Graduate School of Human & Environmental Studies, Kyoto University, Kyoto 606-8501, Japan (**e-mail:Kiyoshi.Matsumoto@ma1.seikyou.ne.jp**)

Abstract—The first trimethylsilylcyanation of acetophenone to the corresponding (*S*)-cyanohydrin was accomplished with e.e. up to 60% in 93% yield at 0.8 GPa, using 0.01 eq. of a *reusable* catalyst prepared from (*S*)-3,3-dimethyl-1,2,4-butanetriol and titanium isopropoxide. Reactions of 4'-substituted acetophenones to the corresponding cyanohydrins gave lower e.e. and yields.

INTRODUCTION

Cyanohydrins now occupy a fascinating niche at the interface between chemistry and biology,[1,2] whether they are enantiopure or not. In the synthesis of non-asymmertic cyanohydrins, Singh[3] reported copper(II) triflate catalyzed addition to carbonyl compounds. Enantiomerically pure cyanohydrins are Important synthetic intermediates in the synthesis of other chiral compounds, including □-hydroxy acids,

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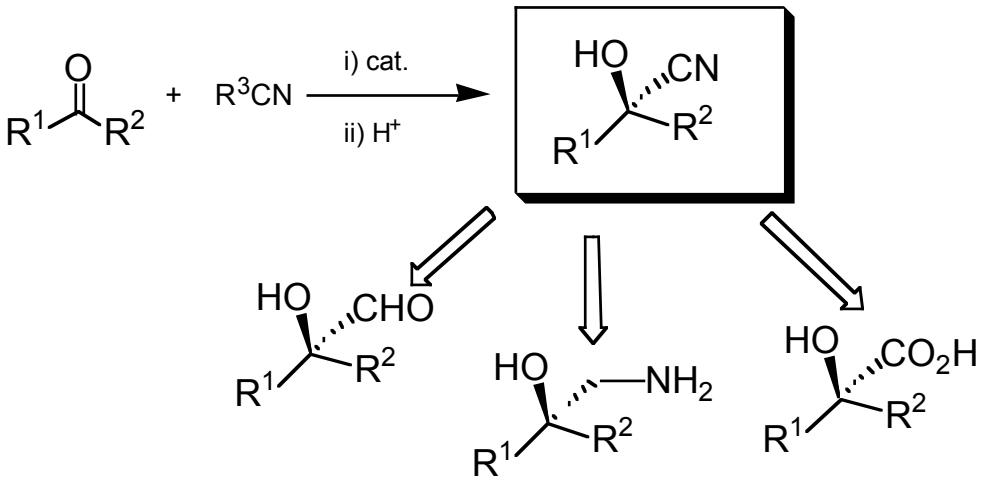
Dedicated to Professor Leo A. Paquette on the occasion of his 70th birthday



Scheme 1

-hydroxy aldehydes, amino alcohols, -hydroxy ketones, tetronic acids and -amino acids (Scheme1).[4]

In addition, they are of significant industrial importance. For instance, the arylethylamines that can be synthesized from the corresponding aromatic cyanides are an important framework in medicinal chemistry, as this synthetic route has provided ligands for a number of receptors such as those for dopamine, serotonin and melatonin.[2] Cyanohydrins are usually synthesized by addition of trimethylsilyl cyanide(TMSCN) to carbonyl groups *via* cyanohydrin trimethylsilyl ether in the presence of a catalyst, e.g. Lewis acids.[5]

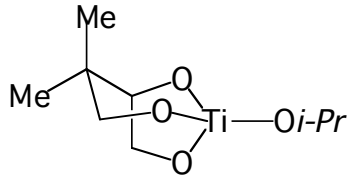
On the other hand, trialkylsilyl groups behave as bulky, hydrophobic (non-hydrogen-bonding), polarizable hydrogens, as clarified and codified by Fleming.[6] These conclusions have arisen from many seminal papers that are summarized elsewhere.[7,8]

Three discoveries of historical significance are noted: (1) Replacing OH with $OSiMe_3$ group decreases the boiling points of polar compounds such as sugars,[9] (2) bulky silyl groups are good protecting groups for organic functional groups, particularly alcohols, as demonstrated by Stork and Corey,[10] and (3) under acidic conditions, silyl-protected enolates can react with many different electrophilic partners, as shown by Mukaiyama.[11]

While organosilyl groups are as easy to work with as traditional organic compounds, they change the selectivity of organic functional groups to certain reagents. Above all, they may be removed from organic frameworks under conditions that do not affect normal organic functional groups.

As a result of these properties, trialkylsilyl groups have been increasingly exploited in organic synthesis. However, asymmetric synthesis with trialkylsilyl groups under high pressure have been less studied.

Quite recently, since cinchona alkaloids are commercially available and cheap, six cinchona alkaloids were used as catalysts for the study of addition of TMSCN to acetophenone under atmospheric and pressurized conditions.[12] Unfortunately, only the about 10% e.e. was attained either in hexane or ethyl acetate using quinine or cinchonine. The enantiomeric excesses (e.e.'s) of the cyanohydrin were found to be decreased with pressure in the presence of alkaloids. Similar results have been observed in the high pressure mediated asymmetric Henry, [13] Michael[14] and Baylis-Hillman reactions. [15]



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In particular, regarding to the synthesis of optically active cyanohydrins,[1] (*R*)-oxynitrilase catalysed decyanation of racemic 2-alkanone cyanohydrins to give the (*S*)-cyanohydrins,[16] and addition of HCN to 3-alkanones forms the (*R*)-cyanohydrins with good enantiomeric excesses (e.e.).[17] Recombinant hydroxynitrile lyase acted on acetophenone with HCN to give (*S*)-acetophenone cyanohydrin in 13% yield with 78% e.e..[18] Benzaldehyde cyanohydrin *via* a chiral phosphate auxiliary agent gave eventually (*R*)-acetophenone cyanohydrin in an overall 17% yield with e.e. > 96%.[19]

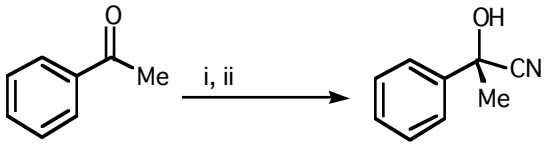
Asymmetric syntheses of aldehyde cyanohydrins have been investigated extensively.[20] Specifically, there is a growing interest in achieving catalytic addition of cyanotrialkylsilanes with ketones to give enantiopure cyanohydrins.[21] Recently, asymmetric trimethylsilylcyanation of benzaldehyde by chiral titanium catalysts was reported to give cyanohydrin products with moderate to good e.e. values.[22-26] However, there is no mention in the literature of asymmetric trialkylsilylcyanation of ketones, even

though non-racemic chiral diorganotin dihalides were predicted to be effective catalysts for enantioselective silylcyanations of ketones.[27] Although Ti-triol (**1**) prepared from (*S*)-3,3-dimethyl-1,2,4-butanetriol and titanium isopropoxide showed quite good enantioselectivity in the asymmetric trimethylsilylcyanation of benzaldehyde,[22] it is necessary to use a stoichiometric amount and it showed detrimental effect upon the e.e. in the presence of a catalytic amount.[22] Furthermore, attempted silylcyanations of 4'-isobutylacetophenone using the catalyst (**1**) were unsuccessful under a number of different conditions,[22] thus these two disadvantages attracted our attention so we examined the catalytic activity of Ti-triol (**1**) on acetophenone cyanohydrins formation under high pressure.

RESULTS AND DISCUSSION

Effect of Solvent and Pressure

The reactions of TMSCN with acetophenone (Scheme 2), at 18°C catalysed by 0.01 equivalent of **1,** in seven solvents (Table 1, Entries 1-7) at 0.8 GPa for 18 h gave the (*S*)-acetophenone cyanohydrin (**2**),



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Scheme 2 : i, TMSCN, **1**, solvents, 0.8 GPa, 18 h; ii 2M HCl

after acidic hydrolysis, in 5-93% yields and e.e. up to 60%. Among the solvents employed, highest yield and appreciable e.e. were obtained by using dichloromethane (Entries 7 and 8). Essentially, no difference is observed between commercially available dichoromethane and purified one distilled off calcium hydride. In the case of other solvents such as benzene, THF, ether ethyl acetate, the catalyst (**1**) remains presumably undissolved at high pressures, so giving the low yields of **2**. In haxane, **1** remains largely undissolved even at atmospheric pressure. The reaction in dichloromethane for 18 h at atmospheric pressure gave the cyanohydrin (**2**) in 23% yield and 7% e.e. (Entry 9). On leaving the reaction for 11 days at atmospheric pressure gave cyanohydrin (**2**) in 81% yield and 3% e.e. (Entry 10). At 0.8 GPa for 1 h in dichloromethane, the e.e. (Entry 11) was similar as in Entry 7 indicating that high pressure might suppress the racemization which took place at atmospheric pressure. Indeed, at 0.4 GPa for 18 h, both the yield and e.e.decreased (62% yield and 38% e.e.). The catalyst was precipitated by adding hexane and

recovered by centrifugation. The catalyst could be reused under the conditions of Entry 7 and gave (*S*)-cyanohydrin (**2**) in similar e.e. (59%) but in lower yield (69%) (Entry 12).

Table 1. Trimethylsilylcyanation of Acetophenone

Entry	Conditions[a]	Yield[b] (%)	E.e. (%)
1	Acetonitrile	52	0
2	Hexane[c]	12	1
3	Benzene	25	2
4	THF	5	32
5	Ether	10	52
6	Ethyl acetate	6	56
7	CH_2Cl_2	93	60
8	CH_2Cl_2 (distilled over calcium hydride)	94	57
9	CH_2Cl_2 (1 atmosphere 18 h)	23	7
10	CH_2Cl_2 (1 atmosphere, 11 days)	81	3
11	CH_2Cl_2 (1 h)	23	60
12	CH_2Cl_2 , reused catalyst	69	59

[a]Reaction at 18°C with 0.01 eq. of the catalyst (**2**) to acetophenone and 1.2 eq. TMSCN at 0.8 GPa for 18 h unless otherwise indicated. [b]Determined by ^{1}H NMR. (Brüker DPX-400 instrument). [c]Catalyst remains largely undissolved.

Effect of Amount of Catalyst (1)

The effect of different amount of catalyst (**1**) on the enantioselective addition of acetophenone at 18°C with 1.2 eq. of TMSCN in dichloromethane for 18 h at 0.8 GPa was also investigated (Table 2). Less satisfactory results in terms of the yields and e.e. values were obtained when 0.003 eq. of the catalyst was

used, whereas, when more than 0.01 eq. of the catalyst was used, the yields were slightly increased but the e.e. values were decreased predumably due to racemization by the catalyst.

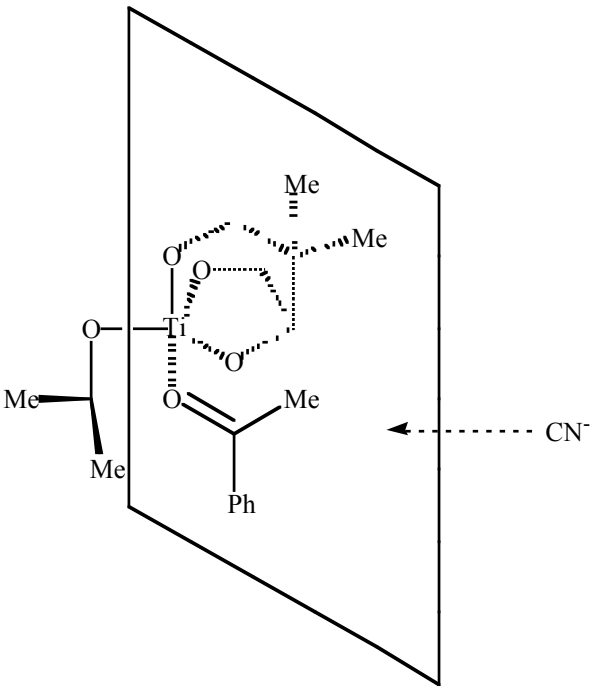
Table 2. Effect of Different Amount of Catalyst (**1**)

Amount of Catalyst (eq.)	Yield (%)	E.e. (%)
0.0033	38	59
0.02	97	56
0.10	98	47

Reactions of 4'-chloro, 4'-methoxy and 4'-methylacetophenones with TMSCN under the conditions of Entry 7 (Table 1) gave the corresponding cyanohydrins in 39, 24, and 27% yields with 32, 36 and 45% e.e., respectively.

Proposed Mechanism

The catalytic asymmetric trimethylsilylcyanation of acetophenone proceeds by the coordination of to Ti-



Scheme 3

triol (**1**) followed by addition of TMSCN. The stereochemical outcome observed in the present

asymmetric trimethylsilylcyanation could be explained by considering the mechanism as shown in Scheme 3. TMSCN would attack the *Re* face of the activated acetophenone leading to the formation of (*S*)-acetophenone cyanohydrin as the isopropyl group would block the *Si* face of acetophenone. On the other hand, the coordination of acetophenone to the other apical positions, that is, below the six or the seven-membered ring is considered to be less favorable.

No promotion effects due to the 4-substituents on the benzene ring on the enantioselectivities were observed for the reactions of 4'-chloroacetophenone, 4'-methoxyacetophenone and 4'-methylacetophenones with TMSCN.

CONCLUSION

Using Ti-triol (**1**) as catalyst at 0.4 to 0.8 GPa gave cyanohydrins at a higher reaction rate and e.e. than at atmospheric condition. This is the first enantioselective reaction of TMSCN with ketone. Furthermore, it is quite intriguing that high pressure can suppress the racemization which took place at atmospheric pressure as there are only few examples where the e.e. values are increased with pressure.[26,28-30]

EXPERIMENTAL

Reagents and Materials

Acetophenones were obtained from Peking Chemical Works and TMSCN was purchased either from Acros or Fluka. Stocks from suppliers were used directly without further distillation.

Instrumentation

NMR spectrometer, IR spectrometer, gas chromatography, chiral gas chromatography, capillary column, polarimeter and column chromatography were employed as described before.[12] High pressure reactions were performed on a Model HR 15-B3 (Hikari-Kouatsu, Hiroshima, Japan).

General Procedure for the Enantioselective Addition of TMSCN to Acetophenone

To a mixture of catalyst (0.05 mmol) and **1** (0.60 g, 5 mmol) in 2.5 mL of solvent was added TMSCN

(0.60 g, 6 mmol). After mixing the reaction mixture thoroughly, it was either transferred to the Teflon capsule and was pressurized or left stirring under atmospheric pressure. The reaction mixture was poured into a mixture of dichloromethane (20 mL) and 0.5M hydrochloric acid (20 mL), and then the organic layer was removed. The resulting acid layer was further extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and dichloromethane was removed under reduced pressure affording a yellow liquid. The % of conversion was determined by recording the ^{1}H NMR spectrum of the yellow liquid. Subsequently the crude reaction product was purified by column chromatography (*n*-hexane: EtOAc 5:1) and afforded a colorless liquid. The purified reaction mixture in EtOAc (40 mL) was stirred with 3M hydrochloric acid (20 mL) for 3 h. After usual workup, the acetophenone cyanohydrin was obtained as a pale yellow liquid which was analyzed by chiral GC after derivation with Ac_2O to determine the e.e.

Determination of Enantiomeric Excess of Acetophenone Cyanohydrin

Resolution of Racemic Acetophenone Cyanohydrin Acetates by Chiral Gas Chromatography Capillary Column

A catalytic amount of DMAP was added to a mixture of 0.05 g (0.3 mmol) of ketone cyanohydrin, 0.5 mL of pyridine and 0.5 mL of Ac_2O in 1 mL of dichloromethane and the resulting mixture was stirred overnight. After usual workup, the residual was purified by column chromatography (*n*-hexane: EtOAc 5:1) affording a pale yellow liquid. The acetates were then analysed by chiral gas chromatography capillary column, a WCOT fused silica 25 m × 0.25 mm coating CP Chirasil-Dex capillary column. The enantiomers of the ketone cyanohydrin acetates were separated such that they were near to base line. The conditions for the resolution of the acetate were as follows. Acetophenone cyanohydrin acetate: the oven temperature: 150 °C; t_R of (*S*)-enantiomer: 6.52 min, t_R of (*R*)-enantiomer: 6.72 min.

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† Present address: Tokushima University School of Dentistry, Tokushima, 770-8504, Japan

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