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ASYMMETRIC TRIMETHYLSILYLCYANATION OF ACETOPHENONE CATALYZED BY CINCHONA ALKALOIDS

Michael C.K. Choi, [1]* Shu-Sun Chan, [1] Man-Kong Chan ,[1] Jong Chul Kim,[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: bckchoi@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 - Six cinchona alkaloids were used as catalysts for the study of addition of TMSCN to acetophenone (**1**) at atmospheric and pressurized conditions. Only the about 10% *ee* was attained either in hexane or ethyl acetate using quinine or cinchonine. The enantiomeric excesses (*ee*'s) of the cyanohydrin (**3)** were found to be decreased with pressure in the presence of alkaloids. The rationale of these reactions was discussed.

INTRODUCTION

A whole series of procedures have been developed in the past decade for the transformation of optically active cyanohydrins.[1] Upon the transformations, chiral cyanohydrins yield useful intermediates for fine chemicals such as pharmaceuticals, pesticides, vitamins and food additives. Asymmetric syntheses of aldehyde cyanohydrins have been investigated extensively.[2] There is an increasing interest of synthesis of optically active ketone cyanohydrins.[3] Shibasaki *et al.* achieved the first general and practical catalytic addition of trimethylsilyl cyanide (TMSCN) to ketones using their bifunctional catalyst.[3c]

We are of interest to investigate the asymmetric trimethylsilylcyanation of acetophenone (**1**) in the

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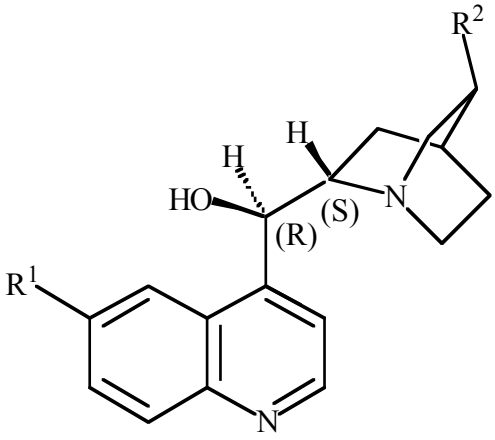
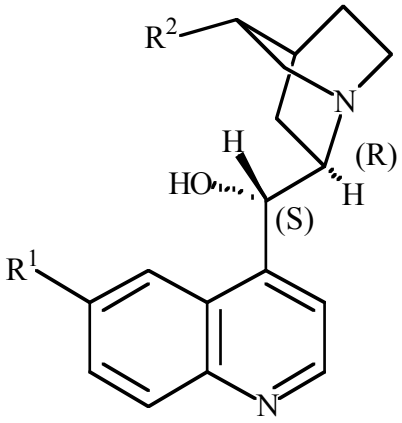
Dedicated to Professor A. I. Meyers on the occasion of his 70th birthday

presence of chiral catalysts under atmospheric and pressurized conditions. The chiral catalysts employed were cinchona alkaloids such as cinchonidine (CD), cinchonine (CN), dihydroquinidine (DHQD), dihydroquinine (DHQN), quinidine (QD), and quinine (QN).





R^1 = OMe, R^2 = vinyl, QN

R^1 = OMe, R^2 = Et, DHQN

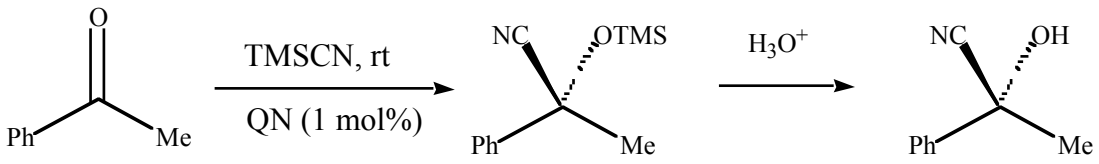
R^1 = H, R^2 = vinyl, CD

R^1 = OMe, R^2 = vinyl, QD

R^1 = OMe, R^2 = Et, DHQD

R^1 = H, R^2 = vinyl, CN

ASYMMETRIC TRIMETHYLSILYLCYANATION OF ACETOPHENONE (1) CATALYZED BY CINCHONA ALKALOIDS AT 10^{-4} GPa



1 **2** **3**

Scheme 1

Firstly, amongst the six cinchona alkaloids, QN was chosen as a catalyst in the addition of TMSCN to acetophenone (**1**) at 10^{-4} GPa (Scheme 1) in order to study effect of solvents as well as effect of structure of cinchona alkaloids.

Table 1. Effect of Solvent on the Enantioselective Addition of TMSCN to Acetophenone (**1**) Catalyzed by QN at 10^{-4} GPa[a]

Solvent	% of Conversion[b)]	% Ee[c) ,d)]
n-Hexane	32.4	9.3
Carbon Tetrachloride	40.5	6.6
Benzene	68.3	6.2
Toluene	30.9	7.5
Carbon Disulfide	74.1	4.3
Chloroform	78.5	6.0
Dichloromethane	84.3	4.6
Ether	49.7	7.4
Ethyl Acetate	9.8	9.1
Tetrahydrofuran	6.7	6.0
Acetonitrile	73.7	0.7
1,2-Dichloroethane	71.1	3.8
2,2-Dimethoxypropane	30.0	7.1

a) Reaction Conditions: 0.05 mmol of QN, 5 mmol of acetophenone, 6 mmol of TMSCN, 2.5 mL of solvent, ambient temperature, 2 d. b) Determined by ^{1}H NMR spectrometry. c) Determined by chiral GC after derivatisation with acetic anhydride. d) Configuration of the cyanohydrin is *R*.

Effect of Solvent

The above reaction was carried out in 13 solvents, varying from *n*-hexane to 2,2-dimethoxypropane. The solvent, the % of conversion and the *ee* were given in Table 1. It was evident that the reaction rates and the *ee*'s were strongly dependent upon the nature of the solvent.

The reaction took place smoothly when dichloromethane, chloroform, carbon disulfide, and acetonitrile were employed as the reaction medium, while ethyl acetate and THF gave the smallest % of conversion. Although it is quite difficult to account for the solvent effect on the reaction rate, the competition of the solvent molecules with acetophenone for the catalytic site of the QN can account for the slowest reaction for THF and ethyl acetate. Amongst the 13 solvents, *n*-hexane and ethyl acetate gave the highest *ee* but acetonitrile gave racemic product.

Effect of Structure of Cinchona Alkaloids

n-Hexane was employed as the reaction medium and the acetophenone/catalyst ratio was kept at 100:1. The configuration of the product formed in excess depends upon the cinchona alkaloids employed. The results were listed in Table 2. The alkaloids QN, DHQN and CD having C(8)-*S*, C(9)-*R* configurations gave (*R*)-**2** in excess, while the diastereomeric alkaloids QD, DHQD and CN with opposite configurations at C(8)-*R*, C(9)-*S* gave (*S*)-**2** in excess. In agreement with all the cinchona alkaloid catalyzed reactions reported to date, the configuration of the carbon atom C-8 and C-9 of the catalyst determines the configuration of the product formed in excess.[5] Although CN-catalyzed reaction gave a somewhat higher *ee* than QD-catalyzed reaction, the *ee*'s obtained on use of QN and CD were comparable. Unfortunately, the six cinchona alkaloids used gave only the low ee's of **3**. It was apparent that the conversions were highly dependent on the cinchona alkaloids (Table 2). One might speculate that the solubility of the intermediate could play an important role for the rate of reaction in n-hexane.

Plausible Mechanism for the Catalytic Asymmetric Trimethylsilylcyanation of Acetophenone

The initial reaction of TMSCN with QN would afford the corresponding trimethylsilyl ether.The hydrogen cyanide produced would protonate the tertiary amine of QN and at the same time the generated cyanide ion would attack the carbonyl group of acetophenone (Scheme 2).The two possible orientations of acetophenone in the transition states of the QN-catalyzed addition of HCN were shown in Scheme 2. The addition of cyanide to the *si* face of acetophenone gave (*R*)- **2** whereas that to the *re* face

Table 2. Effect of Structure of Cinchona Alkaloids on the Enantioselective Addition of TMSCN to Acetophenone at 10^{-4} GPa[a)]

Catalyst	% of Conversion[b)]	% Ee[c)] (Config.)
QN	32.4	9.3 (*R*)
QD	79.8	6.6 (*S*)
CD	64.4	9.0 (*R*)
CN	39.6	9.3 (*S)*
DHQN	91.1	8.7 (*R*)
DHQD	85.8	7.3 (*S*)

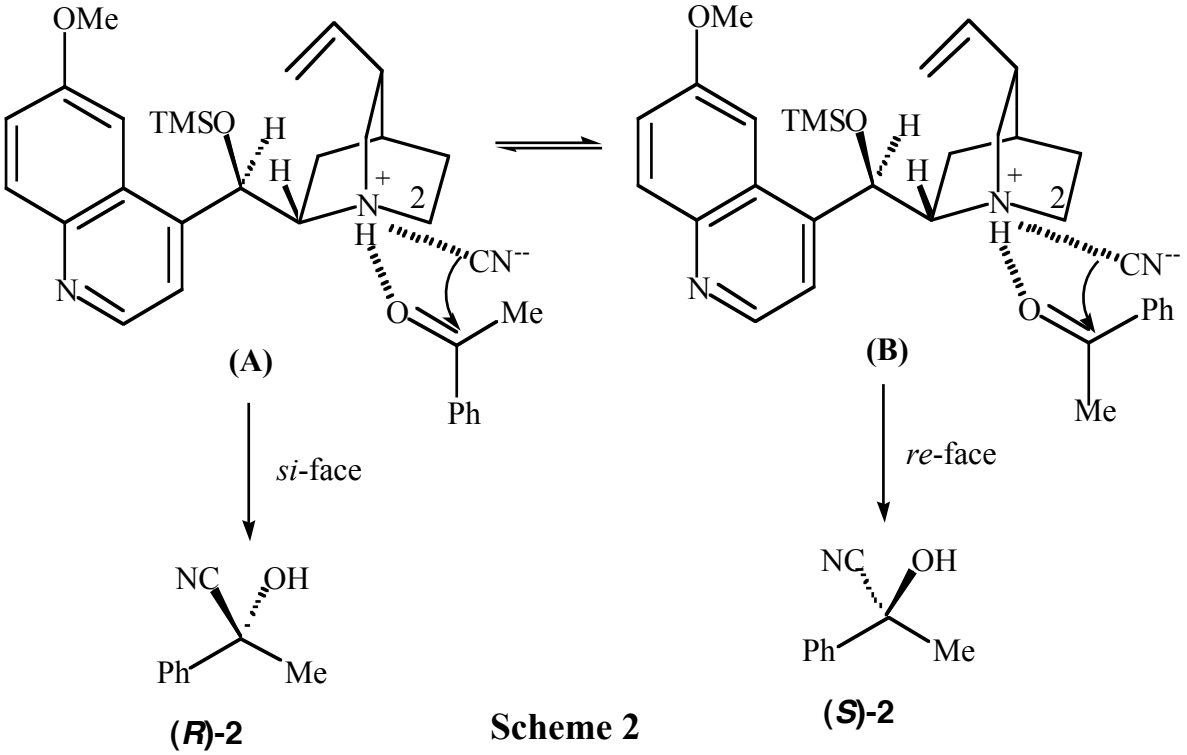
a) Reaction Conditions: 0.05 mmol of catalyst, 5 mmol of acetophenone, 6 mmol of TMSCN, 2.5 mL of *n*-hexane, ambient temperature, 2 d. b) Determined by ^{1}H NMR spectrometry. c) Determined by chiral GC after derivatisation with acetic anhydride.

of acetophenone (**1**) gave (*S*)- **2**. By considering the steric interaction between the C_2 methylene group of QN and the phenyl group of acetophenone, the addition of cyanide to the *si* face of acetophenone was considered to be slightly more favorable, so the (*R*)-**2** was produced in a little excess.

ASYMMETRIC TRIMETHYLSILYLCYANATION OF ACETOPHENONE (1) CATALYZED BY QN UNDER HIGH PRESSURE

The trimethylsilylcyanation of acetophenone catalyzed by QN in dichloromethane was performed under high pressure. The results were listed in Table 3.

The reaction rate was highly enhanced by pressure. At 1 GPa, the reaction proceeded in quantitative yield within 10 min. Even at 0.4 GPa, the reaction only required 80 min with 92.9 % of conversion. Two trends were observed: i) the *ee* decreased with the magnitude of pressure applied and ii) the *ee* decreased with the reaction time. The termolecular complex (**B**) is the sterically more congested and unfavored transition state. Pressure is expected to favor the formation of the enantiomer that is formed through a sterically more hindered transition state.[6] The observed decrease in *ee* can be explained by the difference in pressure effect on the two transition states. However, it is known that cyanohydrin would undergo racemization in the presence of cinchona alkaloids.[7] Thus, the increase in the rate of racemization under



Scheme 2

Table 3. Effect of Pressure and Time on the Enantioselective Addition of TMSCN to Acetophenone (**1**) Catalyzed by QN [a)]

Pressure (GPa)	Time	% of Conversion[b)]	% Ee [c), d)]
0.8	10 min	99.2	2.3
	1 h	99.9	2.8
	19 h	99.8	2.6
0.6	10 min	68.6	3.1
	27 min	94.6	2.8
	45 min	99.5	2.4
	1 h	99.8	2.7
0.4	10 min	21.4	3.4
	20 min	33.3	3.2
	30 min	60.5	3.5
	60 min	76.7	3.3
	80 min	92.9	3.1
10^{-4}	48 h	84.3	4.6

a) Reaction Conditions: 0.05 mmol of QN, 5 mmol of acetophenone, 6 mmol of TMSCN, 2.5 mL of dichloromethane. b) Determined by ^{1}H NMR spectrometry. c) Determined by chiral GC after derivatisation with acetic anhydride. d) Configuration of acetophenone cyanohydrin is *R*.

high pressure is presumably due to equilibrium control caused by cinchona alkaloids. Analogous but more remarkable results have been observed in the high pressure mediated asymmetric Henry, [8] Michael[9] and Baylis-Hillman reactions.[10] The variation of *ee* with pressure is illustrated in Figure 1. As suggested in the previous papers of ours and Marko *et al.*,[9, 10] the free hydroxy group might play an important role for effective asymmetric induction to lock the conformation of the ternary complex by hydrogen bonding to the carbonyl oxygen.

CONCLUSION

The addition of TMSCN to acetophenone (**1**) at atmospheric and pressurized conditions with six cinchona alkaloids was investigated. The *ee* of the cyanohydrin (**3**) was found to be decreased with pressure in the presence of alkaloids which is explained as the origin of the asymmetric induction in these reactions may

lie in the different in free energies of two transition state complexes leading to the (*R*) and (*S*) enantiomers. Although the *ee* is quite low at present, several important parameters have been delineated and the results of these investigations have provided useful insights into the understanding of this type of reactions at atmospheric and pressurized conditions.

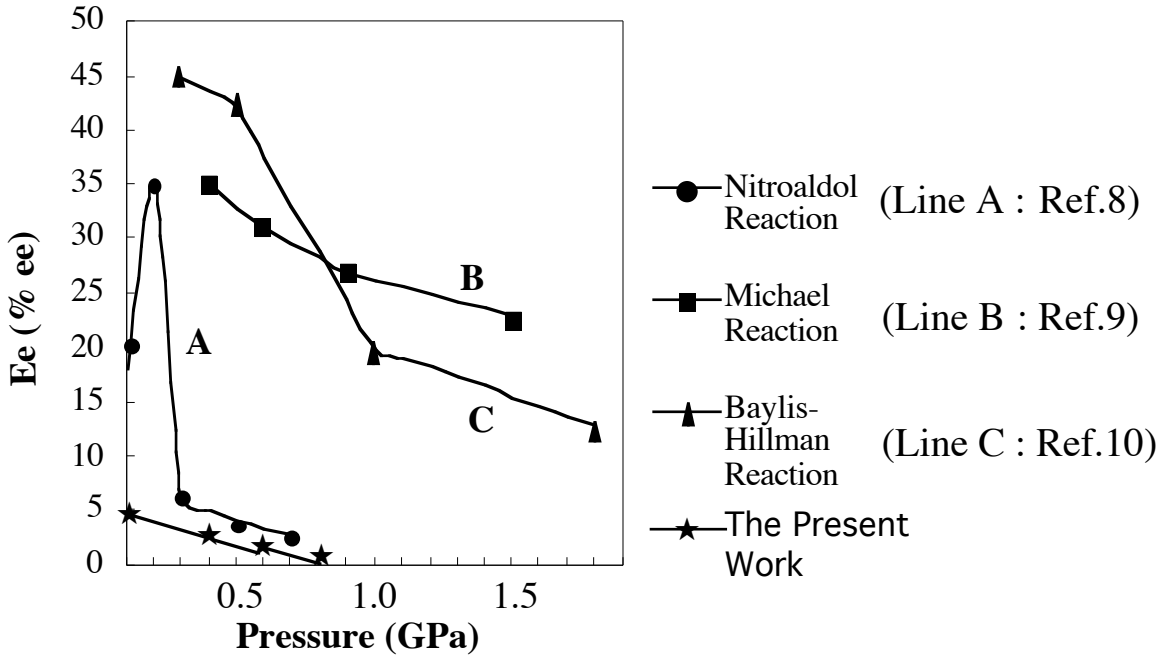


Figure 1. Variation of *ee* with pressure

EXPERIMENTAL

Reagents and Materials

Acetophenone (**1**) was obtained from Peking Chemical Works and TMSCN was purchased either from Acros or Fluka. Both of them were used directly without further distillation. CD, CN, DHQD, DHQN, QD, and QN were purchased from Aldrich Chemical Company.

Instrumentation

Nuclear Magnetic Resonance Spectrometer: NMR spectra were recorded in deuterated-chloroform, 99.8% deuterium (Aldrich Chemical Company or Acros Chemical Company) either on Bruker DPX-400 NMR Spectrometer at 400 MHz or JEOL JNM-A500 Spectrometer at 500 MHz with tetramethylsilane or

residual chloroform as internal standard. All chemical shifts (□) and J are quoted in ppm and Hz, respectively.

Infrared Spectrometer: Infrared absorption spectra of liquids were recorded neat on KBr plates and solids were recorded on KBr pellets by using Nicolet Magna-IR^{TM} Spectrometer 750 with Hewlett Packard Laser Printer.

Gas Chromatography: Gas chromatograms were recorded by using Hewlett Packard 5890 series II Gas Chromatography and Hewlett Packard HP 3395 integrator. The injector temperature was 250 °C and the detector temperature was 270 °C. Nitrogen was used as carrier gas and the flow rate was 100 mL/min.

Chiral Gas Chromatography Capillary Column: A WCOT fused silica 25 m □ 0.25 mm coating CP Chirasil-Dex capillary column was used.

Polarimeter: Optical rotations were measured on a Perkin-Elmer 341 polarimeter at the sodium D line, 589 nm for solutions in a 1 dm cell.

High Pressure Reactor: Model HR 15-B3 (Hikari-Kouatsu, Hiroshima, Japan).

Column Chromatography: Silica gel (Kieselgel 60, 230-400 mesh) was used for column chromatography.

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 to the 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. Then the crude reaction product was purified by column chromatography (*n*-hexane: EtOAc 5:1) affording a colorless liquid. The purified reaction mixture in EtOAc (40 mL) was stirred with 3M hydrochloric acid (20 mL) for 3 h. After normal workup, the the acetophenone cyanohydrin was obtained as pale yellow liquid which was analyzed by chiral GC after derivation with Ac_2O to determine the *ee*.

Determination of Enantiomeric Excess of Acetophenone Cyanohydrin

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

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 normal 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 to and 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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