

Catalytic Asymmetric Synthesis of (*S*)-Acetophenone Cyanohydrin under High Pressure

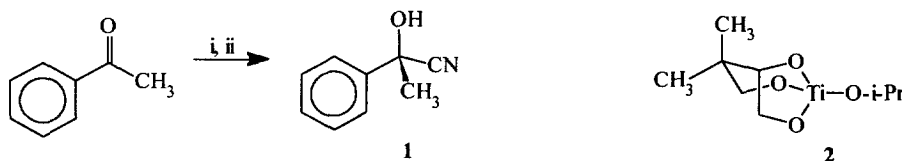
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Abstract : The first trimethylsilylcyanation of acetophenone to its (*S*)-cyanohydrin was accomplished with e.e. up to 60% in 93% yield at 0.8 GPa, using 0.01 eq. of a reusable catalyst prepared from (*S*)-3,3-dimethyl-1,2,4-butanetriol and titanium isopropoxide. Reactions of 4'-substituted acetophenones to the corresponding cyanohydrins gave lower e.e. and yields. © 1997 Elsevier Science Ltd.

Comprehensive reviews on synthesis and reactions of optically active cyanohydrins indicated that much less work was reported for ketone cyanohydrins^{1,2}. (*R*)-Oxynitrilase catalysed decyanation of racemic 2-alkanone cyanohydrins to give the (*S*)-cyanohydrins³ and addition of HCN to 3-alkanones to form the (*R*)-cyanohydrins with good enantiomeric excesses (e.e.)⁴. Recombinant hydroxynitrile lyase acted on acetophenone with HCN to give (*S*)-acetophenone cyanohydrin **1** in 13% yield with 78% e.e.⁵. Benzaldehyde cyanohydrin via a chiral phosphate auxiliary agent gave eventually (*R*)-acetophenone cyanohydrin in an overall 17% yield with e.e. > 96%⁶.



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

There is a growing interest in achieving catalytic addition of cyanotrialkylsilanes with carbonyl compounds to give enantiopure cyanohydrins. Recently, asymmetric trimethylsilylcyanation of benzaldehyde by chiral titanium catalysts were reported to give its cyanohydrins with moderate to good e.e. values.⁷⁻¹¹ Even though nonracemic chiral diorganotin dihalides were forecasted to be effective catalysts for enantioselective

silylcyanations of ketones¹², successful asymmetric trialkylsilylcyanation of ketone was not found in the literature. As attempted silylcyanations of 4'-isobutylacetophenone using the catalyst **2** prepared from (*S*)-3,3-dimethyl-1,2,4-butanetriol and titanium isopropoxide were unsuccessful⁷, application of high pressure in GPa range^{13,14} might be of use to investigate the asymmetric addition of trimethylsilyl cyanide (TMSCN) to ketones.

Reactions of TMSCN with acetophenone (Scheme) at 18°C catalysed by 0.01 equivalent of **2** in seven solvents¹⁵ (Table 1, entries 1-7) at 0.8 GPa for 18 hours giving the (*S*)-acetophenone cyanohydrin **1**¹⁶ after acidic hydrolysis with 5-93% yields and e.e.¹⁷ up to 60%. Similar yield and e.e. were obtained by using dichloromethane distilled over calcium hydride (entry 8). The reaction in dichloromethane for 18 hours at atmospheric pressure gave the cyanohydrin **1** with 23% yield and 7% e.e. (entry 9). On leaving the reaction for 11 days at atmospheric pressure gave the cyanohydrin **1** with 81% yield and 3% e.e. (entry 10). At 0.8 GPa for 1 hour 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. The catalyst was precipitated by adding hexane and recovered by centrifugation. The catalyst could be reused under the conditions of entry 7 gave the (*S*)-cyanohydrin **1** in similar e.e. (59%) but 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	Diethyl ether	10	52
6	Ethyl acetate	6	56
7	CH ₂ Cl ₂	93	60
8	CH ₂ Cl ₂ (distilled over calcium hydride)	94	57
9	CH ₂ Cl ₂ (1 atmosphere 18 hours)	23	7
10	CH ₂ Cl ₂ (1 atmosphere, 11 days)	81	3
11	CH ₂ Cl ₂ (1 hour)	23	60
12	CH ₂ Cl 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 hours unless otherwise indicated. ^b Determined by ¹H N.M.R. (Brüker DPX-400 instrument). ^c Catalyst remains largely undissolved.

The effect of different amount of catalyst **2** on the enantioselective addition of acetophenone at 18°C with 1.2 eq. of TMSCN in dichloromethane for 18 hours at 0.8 Gpa (entry 7, Table 1) was also investigated (Table 2). Less satisfactory results in terms of the yields and e.e. values were obtained for not using 0.01 eq. of the catalyst.

Table 2. Effect of different amount of catalyst **2**

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. As this is the first enantioselective reaction of TMSCN with ketone and together with the fact that there are only few examples where the e.e. values are increased with pressure^{13,18,19}, the scope of studying the TMSCN reactions involving the catalyst **2** and other chiral titanium catalysts as well as chiral crown ether cyanide complexes with other aromatic ketones is under investigation.

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15. **General procedure for the asymmetric trimethylsilylcyanation of acetophenone:** TMSCN (594 mg, 6 mmol) in particular solvent (2.5 ml) was added to the mixture of the catalyst **2** (11.9 mg, 0.05 mmol) and acetophenone (600 mg, 5 mmol). After mixing the reagents thoroughly, it was either left stirring under atmospheric condition or transferred to the teflon capsule to be kept at 0.8 GPa for the indicated period of time. The crude product was then poured into a mixture of CH₂Cl₂ (20ml) and 0.5 M HCL (20 ml). The usual extraction work-up to give a mixture of acetophenone and silylated acetophenone cyanohydrin from which the % yield was determined. The product was stirred in a mixture of 2 M HCl (20ml) and ethyl acetate (40 ml) for 3 h at room temperature. The usual extraction work-up and silica gel column chromatography (hexane: ethyl acetate, 5:1) of the residue gave a mixture of acetophenone and its cyanohydrins.
16. The cyanohydrin was hydrolyzed with conc. HCl to the corresponding 2-hydroxy-2-phenylpropionic acid and compared with the optical rotation value of the optically active acid (No. 8692) from Lancaster catalogue 95/96.
17. Enantiomeric excess was determined using G. C. on a WCOT fused silica 25m × 0.25mm coating CP chirasil-Dex capillary column after derivatization of the cyanohydrin with acetic anhydride.
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