Indium tribromide: a highly effective catalyst for the addition of trimethylsilyl cyanide to α-hetero-substituted ketones

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Abstract—The catalytic addition of trimethylsilyl cyanide (TMSCN) to a large variety of hetero-substituted ketones promoted by anhydrous $InBr_3$ has been studied. The low catalytic loading (0.1–1 mol%) and the mild experimental conditions required represent the key features of this novel catalytic system. © 2001 Elsevier Science Ltd. All rights reserved.

Cyanation reactions of carbonyl compounds is one of the most powerful procedures for the synthesis of poly-functionalized molecules. In fact, the cyano moiety has considerable synthetic potential as a building block in organic synthesis (Fig. 1).[1] For this purpose, several useful cyanating reagents were introduced.[2] Among them, trimethylsilyl cyanide (TMSCN) seems to be one of the more effective and safe cyano anion sources for nucleophilic addition to carbonyl compounds.

Generally, in the absence of a catalyst, no reaction occurs between TMSCN and carbonyl compounds. Several additives and Lewis acids, both in stoichiometric and catalytic amounts, have been tested as promoting agents for such reactions.[3] The addition of TMSCN to aldehydes[4] and imines[5] (Strecker reaction) has been largely studied, whereas the cyanation reaction of less reactive substituted and unsubstituted ketones has not been extensively exploited.[6]

Our ongoing interest in the design and development of new and high-performance mild cyanation procedures prompted us to screen a large variety of Lewis acids as catalysts (10 mol%) for the addition of TMSCN to the commercially available α-methoxy acetophenone **1** (Scheme 1).

The choice of an α-alkoxy ketone as the model substrate was due to its known low reactivity towards Lewis acid-mediated addition reactions of trialkylsilyl cyanides.[3d] Among all the reactions carried out, higher

isolated yields of trimethylsilyloxy cyanohydrine **2** were recorded employing ZnI_2 (97%), $InCl_3$ (90%), $InBr_3$ (99%), $Sc(OTf)_3$ (91%), $Sn(OTf)_2$ (93%) as promoting agents.

Particularly interesting are the results obtained with $InBr_3$. Despite the mild Lewis acid character usually shown by indium salts, we found that anhydrous In(III) bromide effectively promotes the addition of TMSCN[7] to substituted ketones in CH_2Cl_2 and maintains its performance even at lower catalytic loading (1 mol%, yield = 99%; 0.1 mol%, yield = 90%; 0.05 mol%, yield = 70%; entries 3–5, Table 1). It should be noted that performing the cyanation in the absence of the catalyst gave the silyloxy nitrile in 7% yield after a reaction time of 48 h (Table 1, entry 1).
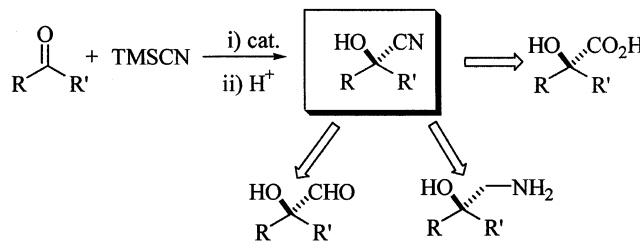
Figure 1. Cyanohydrins as intermediates in organic synthesis.

1: R=Ph, R'=H, X=OMe

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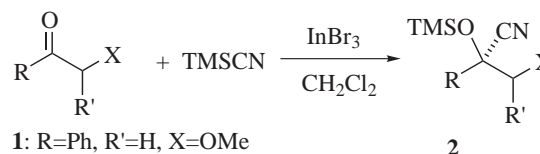
Scheme 1. Cyanation reaction of **1** mediated by Lewis acids.

Other reaction conditions were briefly considered. Different solvents were examined (Table 1, entries 6–10); however, the highest reaction rate was obtained employing CH_2Cl_2.[8] It is noteworthy that when carrying out the reaction in THF, cyanohydrin **2** was isolated in only 7% yield. Such a low conversion is due to a strong interaction between the highly oxophilic indium tribromide and THF that decreases the Lewis acidity of the indium salt.
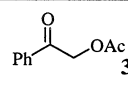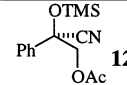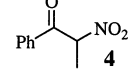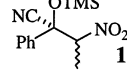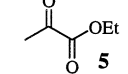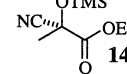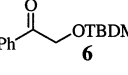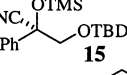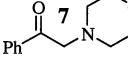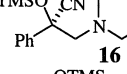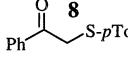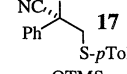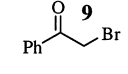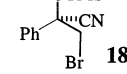
Having optimized the reaction protocol (InBr₃, 1 mol%), the indium-mediated cyanation of a wide range of α-hetero-substituted ketones[9] was investigated and the results are given in Table 2.

To our knowledge, this is the first significant example of a cyanation reaction carried out on amino-, thio- and halo-substituted ketones (entries 5–7, Table 2). In fact, α-morpholine acetophenone **7**, α-*p*-tolyl acetophenone **8** and α-bromo acetophenone **9** furnished the desired *O*-silylated cyanohydrins **16**, **17** and **18**, respectively, in good to excellent yields (51, 95 and 85%, respectively, Table 2). On the other hand, the α-*t*-butyldimethylsilyloxy acetophenone **6** represents a limitation for this procedure. As a matter of fact, the low conversion in **15** was probably a function of the high steric hindrance (*O*-TBDMS) of **6** in proximity to the carbonyl moiety.

Finally, it is noteworthy that this cyanation reaction is also able to convert unsubstituted ketones (**10** and **11**) to the corresponding silyl cyanohydrins in excellent yield (96%) with a low loading of InBr₃ (0.1 mol%) (entries 8 and 9, Table 2).

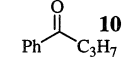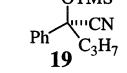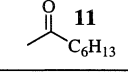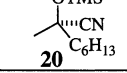In conclusion, we present a straightforward InBr₃-mediated cyanation methodology that allows the synthesis of cyanohydrins from substituted and unsubstituted ketones. The mild experimental conditions, the low loading of catalyst and the general applicability repre-

Table 2. Catalytic cyanation of hetero-substituted and unsubstituted ketones using InBr₃ as a Lewis acid[a]

Entry	Ketone	Product	t (h)	Yield (%)[b]
1	**3**	**12**	3	97
2	**4**	**13**	2.5	77[c]
3	**5**	**14**	3	91
4	**6**	**15**	24	27
5	**7**	**16**	24	51
6	**8**	**17**	3	95
7	**9**	**18**	3	85
8	**10**	**19**	16	96[d]
9	**11**	**20**	16	96

[a] All the reactions were carried out in anhydrous CH_2Cl_2 at room temperature, employing 1 mol% of catalyst.
[b] The chemical yields are given on the isolated *O*-silyl product after chromatographic purification.
[c] The cyanohydrin was isolated in a diastereomeric ratio of 61:39 (^{1}H NMR of the crude product).
[d] The reaction was carried out employing 1 mol% of InBr₃.

sent the notable features of such a procedure. Studies concerning the reaction mechanism, as well as the application of the catalytic protocol in the synthesis of biologically active compounds, are in progress.

A typical procedure for the catalytic cyanation reaction is as follows: To a flame-dried two-necked flask were added 2 mL of dry CH_2Cl_2, anhydrous InBr₃ (11 mg, 0.03 mmol) and **1** (460 μL, 3 mmol). After stirring for 10 min, TMSCN (560 μL, 4.5 mmol) was added by syringe to the clear solution. The reaction was stirred at room temperature until complete consumption of the ketone had occurred (as evidenced by TLC, ca. 30 min) and reaction was then quenched with a saturated solution of NaHCO₃ (4 mL). After the usual work-up (extraction with Et₂O (3×5 mL), anhydrification with Na₂SO₄ and evaporation of the solvent under reduced pressure), the crude product was purified by flash chromatography (cyclohexane:Et₂O 95:5) to afford the 3-methoxy-2-phenyl-2-trimethylsilyl propionitrile **2** as a pale yellow oil in 99% yield. ^{1}H NMR (300 MHz, CDCl₃): δ 0.18 (s, 9 H), 3.42 (s, 3 H), 3.57 (d, $J = 9.9$ Hz, 1 H), 3.64 (d, $J = 9.9$ Hz, 1 H), 7.35–7.72 (m, 3 H), 7.51–7.58 (m, 2 H). ^{13}C NMR (75 MHz, CDCl₃): δ 1.01, 59.86, 75.23, 80.58, 119.93, 125.53, 128.47, 129.01,

Table 1. Catalytic addition of TMSCN to **1** mediated by anhydrous InBr₃[a]

Entry	Solvent	InBr₃ (mol%)	Time (h)	Yield (%)[b]
1	CH_2Cl_2	–	48	7
2	CH_2Cl_2	10	0.5	99
3	CH_2Cl_2	1	0.5	99
4	CH_2Cl_2	0.1	3	90[c]
5	CH_2Cl_2	0.05	72	70[d]
6	THF	10	3	7
7	Et₂O	10	3	85
8	*n*-Pentane	10	3	71
9	CH₃CN	10	3	85
10	Toluene	10	3	90

[a] All the reactions were carried out at room temperature.
[b] Isolated yields after flash chromatography.
[c] For this reaction a solution of InBr₃ (0.2 M) in dry CH₃CN was utilized.
[d] For this reaction a solution of InBr₃ (0.02 M) in dry CH₃CN was utilized.

138.18. GC–MS *m/z* (relative intensity): 59 (9), 73 (100), 91 (18), 103 (39), 135 (8), 147 (37), 193 (21), 207 (3), 277 (41), 292 (2). IR (neat): 3076, 2959, 2831, 2362, 2329, 1458, 1257, 854 cm^{-1}.

2-Methyl-2-trimethylsilyloxy-octanenitrile **20**: Pale yellow oil (96% yield). ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.24 (s, 9 H), 0.87–0.93 (m, 3 H), 1.30–1.36 (m, 4 H), 1.44–1.50 (m, 2 H), 1.57–1.58 (m, 4 H), 1.67–1.74 (m, 3 H). ^{13}C NMR (50 MHz, CDCl$_3$): δ 1.37, 14.10, 22.59, 24.28, 29.01, 30.97, 31.65, 43.39, 69.68, 122.16. GC–MS *m/z* (relative intensity): 55 (19), 69 (18), 73 (81), 75 (100), 100 (91), 115 (15), 127 (8), 142 (36), 185 (69), 212 (21), 227 (1). IR (neat): 2959, 2835, 2362, 2335, 1460, 1374, 1248, 837 cm^{-1}.

Acknowledgements

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6. (a) Garcia Ruano, J. L.; Martin Castro, A. M.; Rodriguez, J. M. *J. Org. Chem.* **1992**, *57*, 7235; (b) Golinski, M.; Brock, C. P.; Watt, D. S. *J. Org. Chem.* **1993**, *58*, 159. For catalytic enantioselective addition of TMSCN to ketones, see: Belokoń, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *40*, 8147; Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412. However, no examples of functionalized ketones were reported.
7. Performing the reaction with (Bu)$_3$SnCN as the cyanating agent, the product was isolated in lower yield: 62%, reaction time 72 h.
8. It is important to note that the success of this method depends on the use of rigorously anhydrous solvents. In fact, carrying out the cyanation of **1** in CH$_2$Cl$_2$ (99.6%, ACS reagent) the chemical yield significantly dropped to 28% (reaction time 48 h, InBr$_3$ 10 mol%).
9. The substituted ketones **3** and **6** were synthesized from the α-hydroxy acetophenone, see: (a) Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100 [**3**: Ac$_2$O/py/ CH$_2$Cl$_2$; **6**: TBDMSCl/imidazole/DMF]. Ketone **4** was prepared following a known procedure, see: (b) Ballini, R.; Bartoli, G.; Bosica, G.; Marcantoni, E.; Vita, P. *J. Org. Chem.* **2000**, *65*, 5854. Ketones **7** and **8** were obtained as follows: **7**: morpholine/Et$_3$N/**9** reflux in Et$_2$O; **8**: *p*-Tol-SH/ K$_2$CO$_3$/**9** in EtOH.