

A Convenient Catalytic Procedure for the Addition of Trimethylsilyl Cyanide to Functionalised Ketones, Mediated by InBr₃ – Insight into the Reaction Mechanism

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Dedicated to Prof. Gianfranco Cainelli on the occasion of his 70th birthday

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This paper describes a useful and practical methodology for the addition of trimethylsilyl cyanide (TMSCN) to a large variety of functionalised and unfunctionalised ketones in the presence of catalytic amounts of anhydrous InBr₃. The optimum procedure involves low catalyst loading (1 mol %) and appears general in scope and applicability for aromatic and aliphatic ketones. The desired cyanohydrins were typically

isolated as their O-silyl ethers in good to excellent chemical yields (up to 99%). Kinetic and spectroscopic studies suggest that a catalytically active dimeric indium species is involved in the reaction mechanism.

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Introduction

Cyanation is one of the most powerful procedures for the synthesis of functionalised compounds containing the cyano moiety, and has considerable synthetic potential in organic synthesis (Figure 1).^[1]

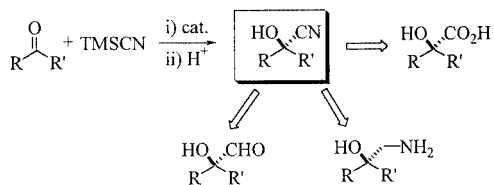


Figure 1. The versatility of the cyano group as a synthon in organic chemistry

Moreover, α -hydroxy nitriles or cyanohydrins are useful starting materials for the synthesis of biologically active compounds. For these reasons, cyanation methodologies are attracting increasing interest in organic synthesis.^[2] Generally, in the absence of a catalyst, no reaction occurs between TMSCN (a common cyano anion source) and carbonyl compounds. However, smooth reaction takes place in the presence of several promoting agents used both in

stoichiometric and in catalytic amount. Among these, Yb(CN)₃,^[3] Yb(OTf)₃,^[4] Cu(OTf)₂,^[5] ZnI₂,^[6] KCN/18-crown-6,^[7] LiClO₄,^[8] R₂SnCl₂,^[9] and Zr(KPO₄)₂^[10] appeared to be the most effective. Nevertheless, the scope of these procedures appears quite limited. In fact, only ZnI₂ and KCN/18-crown-6 are known to be moderately active as catalysts in the cyanation of heterosubstituted ketones. Low chemical yields, the lack of broad tolerance of functional groups and the high loading of catalyst required to perform this transformation on substituted ketones were the factors that prompted us to investigate a new catalytic system for the addition of trimethylsilyl cyanide to functionalised ketones.

Indium salts have some interesting features, namely their low environmental impact, high chemoselectivity, and tolerance toward aqueous media. These characteristics make indium salts unique in their group of the periodic table and justify the growing employment of InCl₃,^[11] InBr₃,^[12] and In(OTf)₃^[13] in organic synthesis. In this context, the low heterophilicity exhibited by indium salts^[14] (oxygen- and nitrogen-containing moieties) allows their employment in the performance of chemoselective transformations of polyfunctionalised compounds.

We have recently reported a high-yield InBr₃-catalysed cyanation of unfunctionalised and α -amino, α -thio, α -oxo, and α -nitro ketones.^[15] In this paper we report a full account of our results, stressing the remarkable generality of the procedure. Moreover, some example cyanation reactions were carried out on enantiomerically pure ketones and *N*-acyliminium ions, furnishing the corresponding cyano de-

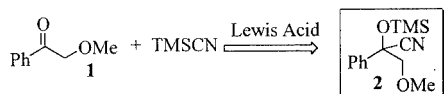
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derivatives with moderate to excellent diastereoselectivity. Finally, experimental observations derived from detailed kinetic and spectroscopic studies provided some information for the understanding of the reaction mechanism.

Results and Discussion

The addition of cyanide to aldehydes in the presence of organometallic catalysts, enzymes and biocatalytic systems is a well-known procedure.^[1] The corresponding reaction of the less reactive ketones, on the other hand, has been much less exploited.^[16] Our ongoing interest in the design and development of a new, mild, high-performance cyanation procedure prompted us to screen a large variety of metal salts as catalysts for the addition of TMSCN to the commercially available α -methoxyacetophenone (**1**) (Scheme 1).



Scheme 1. Screening of different Lewis acids in the catalytic addition of TMSCN to **1**

The choice of an α -alkoxy ketone as the model substrate was due to its known low reactivity toward Lewis acid mediated addition of trialkylsilyl cyanides.^[6,17] The results obtained with 10 mol % of catalyst are summarised in Table 1. Firstly, from analysis of the results it appears clear that a narrow connection between yield and Lewis acidity of the metal salts can be discerned.

Table 1. Screening of Lewis acids as catalysts for the addition reaction of TMSCN to α -methoxyacetophenone (**1**)

Entry ^[a]	Lewis acid	<i>t</i> [h]	Yield [%] ^[b]
1	ZnBr ₂	20	88
2	ZnI ₂	20	97
3	NiCl ₂	20	— ^[c]
4	NiBr ₂	20	— ^[c]
5	FeCl ₂	20	—
6	SbCl ₃	20	—
7	MgI ₂	20	55 ^[c]
8	AgF	20	—
9	InF ₃	20	19
10	InCl ₃	3	90
11	InBr ₃	0.5 ^[d]	99
12	MnBr ₂	20	60
13	Sc(OTf) ₃	20	91
14	Sn(OTf) ₂	20	93
15	La(OTf) ₃	20	15
16	Yb(OTf) ₃	20	18

^[a] All the reactions were carried out in anhydrous CH₂Cl₂ at room temperature, with 10 mol % of catalyst. The uncatalysed reaction proceeded to 10% conversion after 48 h reaction time. ^[b] The chemical yields given are of the isolated product after chromatographic purification. ^[c] A large amount of silyl enol ether was observed as a side product. ^[d] The reaction was carried out with 1 mol % of catalyst.

In fact, weak Lewis acids such as NiCl₂, NiBr₂, AgF, FeCl₂, SbCl₃, and InF₃ afforded the desired 3-methoxy-2-phenyl-2-(trimethylsilyloxy)propionitrile (**2**) only in traces (Entries 3–6, 8–9). Contrary to a previously reported study,^[6] the corresponding α -methoxy nitrile **2** was isolated in quantitative yield (97%, Entry 2) when ZnI₂ was employed as the catalyst. Finally, the use of lanthanide salts as catalysts afforded the products with poor levels of conversion (Entries 15 and 16, Table 1).^[3,18]

Of particular interest were the results obtained with InBr₃. Despite the mild Lewis acid character usually displayed by indium salts, we were delighted to find that TMSCN reacted smoothly with **1** in the presence of 10 mol % of anhydrous In^{III} bromide. Moreover, the isolated yields were excellent even at lower catalyst loadings (1 mol %, yield = 99%; 0.1 mol %, yield 90%; 0.05 mol %, yield = 70%; Entries 3–5 Table 2).^[19]

Table 2. Anhydrous InBr₃-mediated catalytic addition of TMSCN to **1**

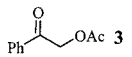
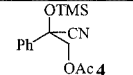
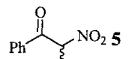
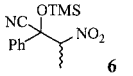
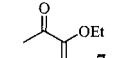
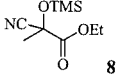
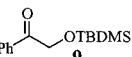
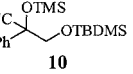
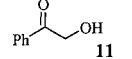
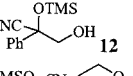
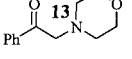
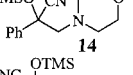
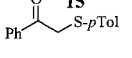
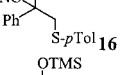
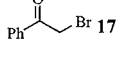
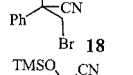
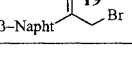
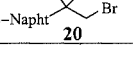
Entry ^[a]	Solvent	InBr ₃ [mol %]	<i>t</i> [h]	Yield [%] ^[b]
1	CH ₂ Cl ₂	—	48	7
2	CH ₂ Cl ₂	10	0.5	99
3	CH ₂ Cl ₂	1	0.5	99
4	CH ₂ Cl ₂	0.1	3	90 ^[c]
5	CH ₂ Cl ₂	0.05	72	70 ^[d]
6	THF	10	3	7
7	Et ₂ O	10	3	85
8	<i>n</i> -pentane	10	3	71
9	CH ₃ CN	10	3	85
10	toluene	10	3	90

^[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 used. ^[d] For this reaction a solution of InBr₃ (0.02 M) in dry CH₃CN was used.

It should be noted that, when the cyanation was performed in the absence of the catalyst, the silyloxy nitrile was isolated only in 7% yield after 48 h reaction time (Entry 1, Table 2). To optimise the experimental conditions, the influence of the solvent on the effectiveness of the catalytic system was briefly investigated. Several anhydrous solvents (Et₂O, *n*-pentane, CH₃CN, THF, toluene) were examined (Entries 6–10, Table 2), but the highest reaction rate was obtained with the use of DCM as the reaction medium.^[20]

The optimised procedure was carried out with a large variety of α -hetero-substituted ketones, showing the generality of the procedure, and the corresponding *O*-silyl cyanohydrins were isolated in excellent yields (Table 3). To the best of our knowledge, this is the first significant example of cyanation reaction carried out on amino-, thio- and halo-substituted ketones (Entries 6–9, Table 3). In fact, α -morpholinoacetophenone (**13**), α -(*p*-tolyl)acetophenone (**15**), and α -bromoacetophenone (**17**) furnished the desired *O*-silylated cyanohydrins **14**, **16**, and **18**, respectively, in moderate to superb isolated yields (71%, 95%, 85%; Table 3).

Table 3. Catalytic cyanation of α -substituted ketones with InBr_3 as the Lewis acid^[a]

$\text{R}-\text{C}(=\text{O})-\text{X} + \text{TMSCN} \xrightarrow[\text{CH}_2\text{Cl}_2 / \text{RT}]{\text{InBr}_3} \text{R}-\text{C}(\text{OTMS})(\text{CN})-\text{X}$				
Entry	Ketone	Product	<i>t</i> [h]	Yield [%] ^[b]
1			3	97
2			2.5	77 ^[c]
3			3	91
4			24	27
5			24	traces
6			3	71
7			3	95
8			3	85
9			3	91

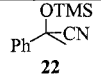
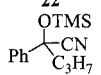
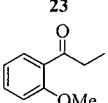
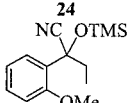
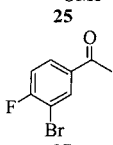
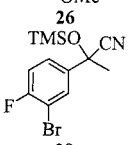
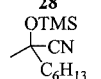
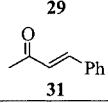
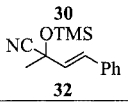
^[a] All the reactions were carried out in anhydrous CH_2Cl_2 at room temperature, with 10 mol % of catalyst. ^[b] The given chemical yields are of the isolated *O*-silylated product after chromatographic purification. ^[c] The cyanohydrin was isolated in a 61:39 diastereoisomeric ratio. The diastereoisomer ratio was determined from ^1H NMR analysis of the crude product.

On the other hand, the α -hydroxy ketone **11** and α -(*tert*-butyldimethylsilyloxy)acetophenone (**9**) are poor substrates for this procedure. As a matter of fact, while a complex mixture of undefined products was detected by GC analysis in the case of **12**, the presence of a highly steric hindering group (TBDMS) in proximity to the carbonyl moiety of the substrate **9** effects the efficacy of the process strikingly. Moreover, it should be mentioned that no product deriving from enolisation of the ketones was detected during the course of the reaction (checked by ^1H NMR).^[21]

This indium catalytic system was also applied to aromatic and aliphatic unsubstituted ketones. The corresponding cyanohydrins were obtained in high isolated yields (75–96%; see Table 4). In addition, it is important to stress the remarkable chemoselectivity observed for the α,β -unsaturated ketone **31**. In this case, in fact, only the product derived from 1,2-addition was obtained (Entry 6, Table 4).

Finally, several optically pure ketones were treated with TMSCN in the presence of InBr_3 , and the results are collected in Table 5. Commercially available (*S*)-(–)-menthone (**33**) and (1*R*)-(+)-camphor (**35**) afforded the corresponding cyanohydrins **34** and **36** in good yields (85%, 88%) and

Table 4. Catalytic cyanation of unsubstituted ketones with InBr_3 as the Lewis acid^[a]

$\text{R}-\text{C}(=\text{O})-\text{R}' + \text{TMSCN} \xrightarrow[\text{CH}_2\text{Cl}_2 / \text{RT}]{\text{InBr}_3} \text{R}-\text{C}(\text{OTMS})(\text{CN})-\text{R}'$				
Entry	Ketone	Product	<i>t</i> [h]	Yield [%] ^[b]
1			3	90
2			3	94
3			3	85
4			2.5	96
5			3	75
6			3	83

^[a] All the reactions were carried out in anhydrous CH_2Cl_2 at room temperature, with 1 mol % of catalyst. ^[b] The given chemical yields are of the isolated *O*-silylated product after chromatographic purification.

moderate diastereoisomeric ratios (*drs*) of 1.6:1 and 3.5:1, respectively (Entries 1–2, Table 5). The stereoselectivity appeared to be strongly correlated to the bulkiness in proximity to the carbonyl moiety. In fact, the chiral α -(*S*)-*O*-*tert*-butyldimethylsilyloxy ketones (Me)-**37**, (Bn)-**39**, and (Ph)-**41**^[22] afforded, in the presence of InBr_3 (10 mol %), the desired 1,2-disilyloxy nitriles (**40**, **42**, **44**) with an increasing diastereoselectivity from 53:47 to 82:18 (Table 5, Entries 3–5).

The InBr_3 was also able to catalyse the cyanation reaction of 4-acetoxy- β -lactams. The (3*R*,4*R*,1'*R*)-4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (**43**) was easily converted into the (3*S*,4*R*,1'*R*)-4-cyano derivative **44** in good yield (75%) and excellent diastereomeric ratio (98:2; Entry 6, Table 5).^[23]

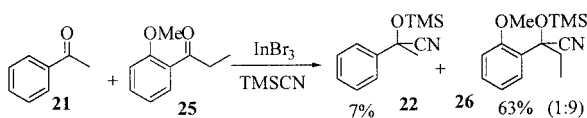
A discriminating experiment between bidentate and monodentate carbonyl substrates was carried out by treatment of an equimolar mixture of **21** and **25** with 10 mol % of InBr_3 in CH_2Cl_2 at room temperature for 30 min, and subsequent addition of 1.05 equiv. of TMSCN (Scheme 2). After a reaction time of 24 h, the competitive cyanation reaction had given rise to an excess of the α -methoxy cyanohydrin **26**, accompanied by **22** in a 9:1 ratio.^[24]

Since the indium(III) salts are commonly identified as chelating Lewis acids,^[25] the result of the competition experiment could be a consequence of a preferred initial

Table 5. Stereoselectivity in the catalytic cyanation of optically active ketones^[a]

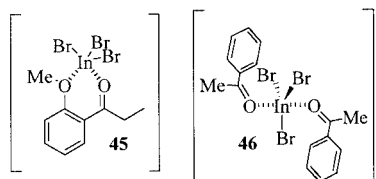
Entry	Ketone	Product	<i>T</i> [°C]	Yield [%] ^[b]	d.r. ^[c]
1			r.t.	85	62:38
2			r.t.	88	78:22
3			-20	96	53:47
4			-20	77	58:42
5			-40	81	82:18
6			r.t.	75	98:2

^[a] All the reactions were carried out in anhydrous CH₂Cl₂ with 10 mol % of catalyst. ^[b] The given chemical yields are of the isolated *O*-silylated product after chromatographic purification. ^[c] The diastereoisomeric ratio was determined by GC and NMR analysis of the crude mixture.



Scheme 2. The competitive experiment between mono- and bidentate carbonyl substrates

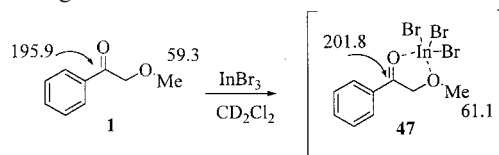
formation of a pentacoordinate indium species^[26] **45** with respect to the unchelated adduct **46** (Scheme 3).



Scheme 3

To validate the former statement regarding chelate organisation, a ¹³C NMR investigation of the reaction mixture was performed (with CDCl₃ as solvent). Scheme 4 shows the more diagnostic chemical shifts of the complex **47** (InBr₃/1, 1:1 ratio) in comparison with the signals of the ketone **1**. The recorded spectra displayed that a single species is present in solution. Moreover, the chemical shift vari-

ations of the signals of the carbonyl and methoxy carbon atoms indicate that indium bromide is involved in a two-side-binding interaction with the heterosubstituted ketone.

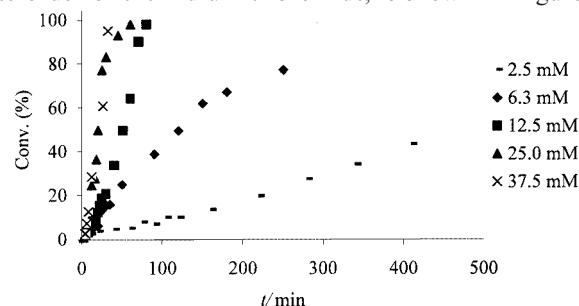


Scheme 4

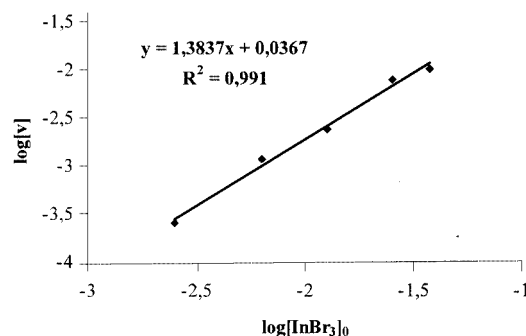
Reaction Mechanism

To make reactions available for kinetic studies requires the identification of experimental conditions under which the transformation rate is sufficiently slow. For our purposes, α -morpholinoacetophenone (**13**) guaranteed feasible monitoring of the initial reaction rates of the cyanation by GC. A solution of naphthalene in dry CH₂Cl₂ was used as the internal standard. The reaction rates were measured monitoring each run from 8% completion to 18–25% conversion and all the cyanation reactions were monitored up to at least 75% conversion.

The initial reaction rates calculated at different concentrations ([C]₀) of InBr₃, **13**, and TMSCN furnished the overall kinetic equation of the cyanation process. An example of such a study, directed towards exploration of the rate order of the indium tribromide, is shown in Figure 2.

Figure 2. Degrees of conversion (%) versus time at different [InBr₃]₀

From the trends of the curves recorded at different indium concentrations (2.5–37.5 mM), it appears that the rate of cyanation was strongly affected by the total concentra-

Figure 3. Determination of the order dependence on the total concentration of InBr₃

tion of indium. The reaction orders with respect to all the cyanation components were obtained by plotting $\log[\text{rate}]$ versus $\log[C]_0$, and the case for InBr_3 is reported in Figure 3.

With $[\text{InBr}_3]_0$, $[\mathbf{13}]_0$, and $[\text{TMSCN}]_0$ indicating the initial concentrations of the pre-catalyst, α -morpholino ketone, and trimethylsilyl cyanide, respectively, the rate equation is described as $\text{rate} = 2.3 \cdot [\text{InBr}_3]_0^{1.4} \cdot [\text{TMSCN}]_0^{1.0} \cdot [\mathbf{13}]_0^0$. The rate was first-order depending on the concentration of the TMSCN and zero-order with respect to the concentration of the carbonyl compound.

In the first step of the catalytic cycle, the Lewis acid is assumed to coordinate the carbonyl compound **13**. As previously reported, a fractional order (1.4) for a catalytic species can be interpreted in terms of the presence of an equilibrium between a mononuclear (**A**) and a dinuclear indium/**13** complex (**B**) in which the dimeric aggregate is the catalytically active species (Figure 4).^[27] The hypothesis of a di-bromo-bridged structure for the dimeric indium aggregate is in agreement with several experimental data reported in the literature.^[28]

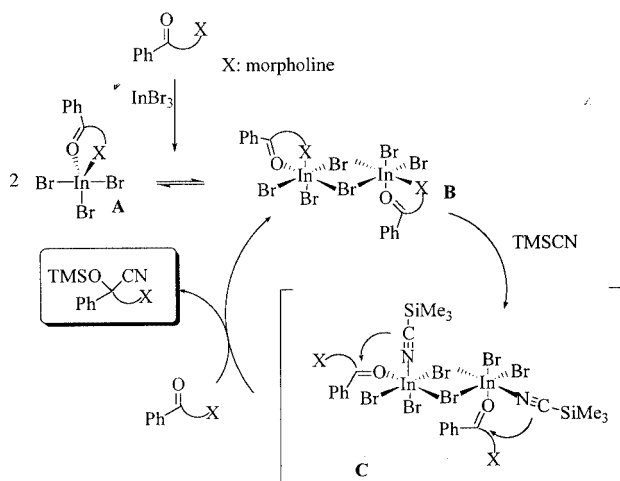
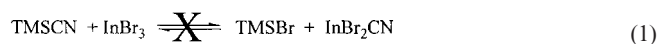


Figure 4. Hypothetical InBr_3 -promoted cyanation reaction mechanism

To provide additional evidence for the presence of such an equilibrium, we carried out some ^1H NMR complexation studies. InBr_3 and **13** were mixed (1:1 ratio, CD_2Cl_2) and some NMR spectra were recorded at room temp. and at -60°C . While the ^1H NMR spectra recorded at room temp. showed several sets of broad peaks, the ^{13}C NMR spectra showed the existence of a single species in which the ketone seems to be coordinated by a bidentate interaction with the indium metal centre (see Supporting Information).^[29]

In order to explain the first-order dependence on the TMSCN we suggest that the incoming nucleophile could interact with the metal atom to furnish an aggregate in which TMSCN and carbonyl compound are close to each other (**C**). At present, the true nature of the $\text{In}-[\text{CN}]$ interaction remains unclear. However, the hypothetical formation of an indium cyanide species by a fast transmetallation

reaction between InBr_3 and TMSCN [Equation (1)]^[30] was ruled out by spectroscopic investigations.



In fact, on monitoring of the reaction between TMSCN [^{13}C NMR (CD_2Cl_2 , TMS, 25°C): $\delta = 127.0$, -1.8 ppm] and InBr_3 (1:1 ratio) in anhydrous CD_2Cl_2 at 25°C by ^{13}C NMR, no formation of TMSBr ($\delta = 4.2$ ppm) was observed.^[31] On the other hand, the spectra showed the complete disappearance of the TMSCN signals, and a new peak appeared at $\delta = 1.9$ ppm.^[32] This shifting to lower field, in comparison to TMSCN, could indicate the presence of an $\text{In} \leftarrow \text{NC}$ species characterised by a dative interaction between the cyano group of the TMSCN and the indium metal centre.^[33] In support of this hypothesis, we recorded the ^{29}Si NMR spectra (in CD_2Cl_2) of interacting InBr_3 and TMSCN ($\delta = -11.1$ ppm), and only one signal appeared at $\delta = 7.4$ ppm. A tentative picture to account for the kinetic and spectroscopic investigations for the indium-mediated cyanation is suggested in Figure 4.

Finally, the assumption that the rate-limiting step of the process is the approach of the TMSCN and the further nucleophilic addition could explain the independence of the reaction rate of the concentration of the carbonyl compound.

Conclusion

In conclusion, we have shown that InBr_3 can be effectively employed, at low catalytic loading, for promotion of the chemoselective addition of TMSCN to variously substituted and unsubstituted ketones. Such a procedure allows the isolation of the corresponding *O*-silylated cyanohydrins in high yields. In this context, an investigation of the reaction mechanism indicated the presence of an indium aggregate as the catalytically active species. Thanks to the mild experimental conditions required and due to its generality in scope and applicability, this procedure is probably one of the most straightforward catalytic systems for the synthesis of polyfunctionalised cyano compounds starting from carbonyls.

Experimental Section

General Remarks: ^1H NMR spectra were recorded with Varian Gemini 200 (200 MHz) or Varian INOVA 300 (300 MHz) spectrometers. Chemical shifts δ are given in ppm with respect to TMS, and coupling constants J are measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, br = broad, m = multiplet). ^{13}C NMR spectra were recorded with Varian Gemini 200 (50 MHz) or Varian INOVA 300 (75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent as the internal standard (deuteriochloroform: $\delta = 77.0$ ppm; deuteriodimethyl sulfoxide: $\delta = 39.0$ ppm). ^{29}Si NMR spectra were recorded with a Varian Gemini 300 (51.6 MHz) spec-

trometer. Chemical shifts δ are reported in ppm from tetramethylsilane as the external standard (TMS: δ = 0.0 ppm). GC-MS spectra were taken by EI ionization at 70 eV with a Hewlett–Packard 5971 with GC injection. They are reported as m/z (%). Flash column chromatography was performed on 270–400 mesh silica gel. Anhydrous CH_2Cl_2 , CH_3CN , Et_2O , THF, n -pentane, TMSCN, and **1** were purchased from the Fluka and Co. and from Aldrich and used as received. CDCl_3 and CD_2Cl_2 were dried over activated molecular sieves. Elemental analyses were carried out with an EACE 1110 CHNOS analyser. IR analysis was performed with an FT-IR NICOLET 205 spectrophotometer. IR spectra are expressed by wave-number in cm^{-1} . All the commercially available ketones were freshly distilled or crystallised before use. The azetidinone **43** was crystallised from n -pentane before use. The substituted ketones **3**,^[15] **5**,^[34a] **9**,^[15] **11**,^[34b] **13**,^[15] and **15**^[15] were prepared by literature procedures. The ketone **25** was synthesised by methylation of the commercially available ethyl (2-hydroxyphenyl) ketone (MeI/ K_2CO_3 , H_2O /acetone, yield 91%).

General Procedure for the InBr_3 -Mediated Catalytic Addition of TMSCN to Ketones: Anhydrous CH_2Cl_2 (2 mL), InBr_3 (11 mg, 0.03 mmol) and carbonyl compound (3 mmol) were placed, under nitrogen, in a flame-dried two-necked flask. The mixture was stirred until the indium tribromide was completely dissolved (5–10 min). Finally, TMSCN (4.5 mmol, 560 μL) was introduced dropwise by syringe. This clear solution was then stirred at room temperature until the disappearance of the ketone (1–3 h, checked by TLC). The reaction was then quenched with a saturated NaHCO_3 solution (3 mL) and extracted with Et_2O (3×3 mL). The organic portions were collected, dried (Na_2SO_4) and concentrated under reduced pressure, and the crude product mixture was purified by flash chromatography. For data of the different products, see Supporting Information.

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[1] R. J. H. Gregory, *Chem. Rev.* **1999**, 99, 3649–3682.

[2] A. Fujii, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2000**, 65, 6209–6212, and references cited therein.

[3] S. Matsubara, T. Takai, K. Utimoto, *Chem. Lett.* **1991**, 1447–1450.

[4] [4a] Y. Yang, D. Wang, *Synlett* **1997**, 861–868. [4b] Y. Yang, D. Wang, *Synlett* **1997**, 1379–1380.

[5] P. Saravanan, R. V. Anand, V. R. Singh, *Tetrahedron Lett.* **1998**, 39, 3823–3824.

[6] P. G. Gassman, J. J. Talley, *Tetrahedron Lett.* **1978**, 19, 3773–3776.

[7] W. J. Greenlee, D. G. Hangauer, *Tetrahedron Lett.* **1983**, 24, 4559–4560.

[8] G. Jenner, *Tetrahedron Lett.* **1999**, 40, 491–494.

[9] J. K. Whitesell, R. Apodaca, *Tetrahedron Lett.* **1996**, 37, 2525–2528.

[10] M. Curini, F. Epifanio, M. C. Marcotullio, O. Rosati, M. Rossi, *Synlett* **1999**, 315–316.

[11] [11a] Diels–Alder reaction: T.-P. Loh, J. Pei, M. Lin, *Chem. Commun.* **1996**, 2315–2316. [11b] Aldol reaction: T.-P. Loh, J. Pei, G.-Q. Cao, *Chem. Commun.* **1996**, 1819–1820. S. Kobaya-

shi, T. Busujima, S. Nagayama, *Tetrahedron Lett.* **1998**, 39, 1579–1582; T.-P. Loh, L.-L. Wei, *Tetrahedron Lett.* **1998**, 39, 323–326. [11c] Friedel–Crafts reaction: J. S. Yadav, S. Abraham, B. V. S. Reddy, G. Sabitha, *Synthesis* **2001**, 2165–2168. [11d] Aziridiation: S. Sengupta, S. Mondal, *Tetrahedron Lett.* **2000**, 41, 6245–6248. [11e] Allylation reaction: T. Miyai, K. Inoue, M. Yasuda, A. Baba, *Synlett* **1997**, 699–700. [11f] Biginelli reaction: B. C. Ranu, A. Hajra, U. Jana, *J. Org. Chem.* **2000**, 65, 6270–6272. [11g] Azidolysis of epoxycarboxylic acids: F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2001**, 66, 3554–3558. [11h] Y. Onishi, T. Ito, M. Yasuda, A. Baba, *Eur. J. Org. Chem.* **2002**, 1578–1581. [11i] Sakurai reaction: P. H. Lee, K. Lee, S. Sung, S. Chang, *J. Org. Chem.* **2001**, 66, 8646–8649. K. Inoue, A. Sawada, I. Shibata, A. Baba, *J. Am. Chem. Soc.* **2002**, 124, 906–907.

[12] [12a] Dithioacetalization: M. A. Ceschi, L. de Araujo Felix, C. Peppe, *Tetrahedron Lett.* **2000**, 41, 9695–9699. [12b] Tandem nucleophilic addition: M. Bandini, P. G. Cozzi, M. Giacomini, P. Melchiorre, S. Selva, A. Umani-Ronchi, *J. Org. Chem.* **2002**, 67, 3700–3704. [12c] Michael addition: M. Bandini, P. Melchiorre, A. Melloni, A. Umani-Ronchi, *Synlett* **2002**, 1110–1114. [12d] Stereoselective ring-opening of epoxides: M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *J. Org. Chem.*, **2002**, 67, 5386–5389.

[13] [13a] Rearrangement of homoallylic alcohols: T.-P. Loh, K.-T. Tan, Q.-Y. Hu, *Angew. Chem. Int. Ed.* **2001**, 40, 2921–2922. [13b] Cyclization: T.-P. Loh, Q.-Y. Hu, K.-T. Tan, H.-S. Cheng, *Org. Lett.* **2001**, 3, 2669–2672. [13c] Synthesis of tetrahydrofurans: T.-P. Loh, Q.-Y. Hu, L.-T. Ma, *J. Am. Chem. Soc.* **2001**, 123, 2450–2451.

[14] [14a] B. C. Ranu, *Eur. J. Org. Chem.* **2000**, 2347–2356. [14b] K. K. Chauhan, C. G. Frost, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015–3019. [14c] G. Babu, P. T. Perumal, *Aldrichimica Acta* **2000**, 33, 16–22.

[15] M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *Tetrahedron Lett.* **2001**, 42, 3041–3043. InF_3 has already been studied as a catalyst (30 mol %) in the cyanation of aldehyde compounds in water (see: T.-P. Loh, K.-C. Xu, D. S.-C. Ho, K.-Y. Sim, *Synlett* **1998**, 369–370); aliphatic and aromatic ketones did not undergo cyanation with TMSCN in this catalytic procedure, however.

[16] For a recent example of catalytic cyanation of ketones by LiOR, see: H. S. Wilkinson, P. T. Grover, C. P. Vandenbossche, R. P. Bakale, N. N. Bhongle, S. A. Wald, C. H. Senanayake, *Org. Lett.* **2001**, 3, 553–556.

[17] V. I. Cohen, R. E. Gibson, L. H. Fen, R. De la Cruz, M. S. Gitter, E. Harimen, R. C. Rebe, *J. Med. Chem.* **1991**, 34, 2989–2993.

[18] A. E. Vougioukas, H. B. Kagan, *Tetrahedron Lett.* **1987**, 28, 5513–5516.

[19] When tributyltin cyanide was used as the cyano source, **2** was obtained in lower yield (62%).

[20] The chemical yields obtained by the solvent screening are as follow: Et_2O : 85%; CH_3CN : 81%; n -pentane: 71%; THF: 7%; toluene: 90%. It is important to note that the success of this method depends on the use of rigorously anhydrous solvents. In fact, if the cyanation reaction of **1** was carried out in CH_2Cl_2 that had not been dried or distilled, the chemical yield dropped significantly, to 28% (reaction time 48 h, InBr_3 10 mol %).

[21] L. H. Foley, *J. Org. Chem.* **1985**, 50, 5204–5209.

[22] R. Martín, P. Romea, C. Tey, F. Urpí, J. Vilarrasa, *Synlett* **1997**, 1414–1415.

[23] D. Russowsky, R. Z. Petersen, M. N. Godoi, R. A. Pilli, *Tetrahedron Lett.* **2000**, 41, 9939–9942.

[24] The composition of the reaction product was determined by ^1H NMR analysis of the crude mixture. The higher reaction rate of **21** in comparison with **25** is explained in terms of a reduction in the transition state energy associated with preformation of the indium/**25** complex. The more selective substrate is therefore the more reactive.

- [25] The capability of the indium(III) species to bind multidentate substrates persists even in aqueous media, see: [25a] L. A. Paquette, T. M. Mitzel, *J. Am. Chem. Soc.* **1996**, *118*, 1931–1937. [25b] T.-P. Loh, K.-Y. Sim, S.-C. Ho, *Synlett* **1996**, 263–264. [25c] T.-P. Loh, X.-R. Li, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 980–982. [25d] L. A. Paquette, R. R. Rothhaar, *J. Org. Chem.* **1999**, *64*, 217–224.
- [26] A pentacoordinate trigonal-bipyramidal complex of InCl_3 salt with PhCOMe has been isolated and characterised; see: S. Jin, V. McKee, M. Nieuwenhuyzen, W. T. Robinson, C. J. Wilkins, *J. Chem. Soc., Dalton Trans.* **1993**, 3111–3116.
- [27] For an elegant discussion and interpretation of fractional reaction orders in catalytic enantioselective cyanation reactions, see: Y. N. Belokon', B. Green, N. S. Ikinnikov, V. S. Larichev, B. V. Lokshin, M. A. Moscalenko, M. North, C. Orizu, A. S. Peregudov, G. I. Timofeeva, *Eur. J. Org. Chem.* **2000**, 2655–2661.
- [28] [28a] O. T. Beachley Jr., R. N. Rusinko, *Inorg. Chem.* **1979**, *18*, 1966–1968. [28b] D. G. Tuck, in: *Comprehensive Coordination Chemistry*, vol. 3 (Ed.: G. Wilkinson), **1987**, pp.153–176 and references cited therein. All our attempts to obtain suitable crystals for an X-ray analysis were unsuccessful.
- [29] This result does not rule out the existence of a dimeric adduct; in fact, it is possible that the active dimeric species is an equilibrium intermediate present in a low concentration below the sensitivity of the NMR measurement.
- [30] For experimental evidence of transmetallation reactions between indium(III) salts and tetraalkyltin compounds, see ref. [15] and: J. Cossy, C. Rasamison, D. G. Pardo, J. A. Marshall, *Synlett* **2001**, 629–633.
- [31] M. S. Samples, C. H. Yoder, *J. Organomet. Chem.* **1986**, *312*, 149–153.
- [32] No transmetallation reaction was observed even under forcing experimental conditions with an excess of TMSCN.
- [33] Although it has been clearly documented that trimethylsilyl cyanide and isocyanide exist in labile equilibrium in solution (*normalliso* $\approx$ 90:10), no evidence of the active isocyanide form was observed in our spectroscopic investigations: [33a] M. R. Booth, S. G. Frankiss, *Spectrochim. Acta* **1970**, *26A*, 859–869. [33b] J. A. Seckar, J. S. Thayer, *Inorg. Chem.* **1976**, *15*, 501–504.
- [34] [34a] M. A. Aswell, R. F. W. Jackson, *Synthesis* **1988**, 229–231. [34b] G. Zhu, A. L. Casalnuovo, X. Zhang, *J. Org. Chem.* **1998**, *63*, 8100–8101.

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