

A New Lithium Alkoxide Accelerated Diastereoselective Cyanation of Ketones

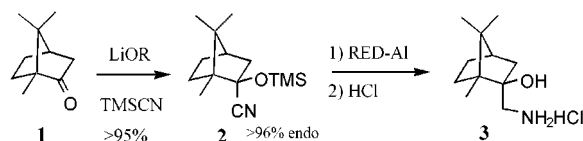
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ABSTRACT



A remarkably general lithium heteroatom assisted TMSCN or TBSCN addition to aldehydes and ketones has been discovered. The process provides excellent selectivities and high rates. Conformationally constrained ketones such as camphor, fenchone, and nopinone give excellent diastereoselectivities with TMSCN. Reduction of **2** provided diastereopure amino alcohol **3** in good yield. α - and β -Methyl cyclohexanones with TBSCN–LiOR afford high diastereoselectivities and yields.

The development of practical technology for the preparation of α -hydroxy- α -substituted acids, ketones, aldehydes, and β -hydroxy amines from readily available carbonyl compounds is an extremely important area of organic chemistry. One of the most straightforward entries to the above-mentioned building blocks is via cyanohydrins.¹ Preparation of cyanohydrins from ketones is well documented, and limited enantioselective methods are available.² The most commonly used method is through the use of the Lewis acid

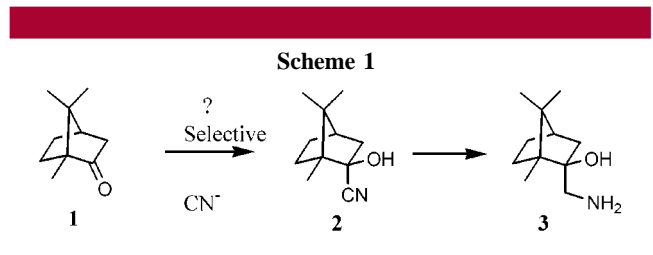
catalyzed addition of TMSCN to ketones.³ However, general, mild, high-yielding, and selective processes for cyanation of hindered carbonyl groups are still lacking.

In our efforts to synthesize conformationally constrained, enantiomerically pure amino alcohols for use in asymmetric synthesis, we required a practical procedure for the preparation of camphor-derived amino alcohol **3**. We envisaged that compound **2**, derived from a selective cyanide addition would provide an easy access to the desired amino alcohols.⁴ Herein, we disclose the development of a new and neutral diastereoselective cyanation process for the generation of the silyl ethers of cyanohydrins from ketones using cyanosilanes and a lithium heteroatom catalyst. The method is applied to the synthesis of enantiomerically pure amino alcohol **3** in a convenient, high yielding procedure.

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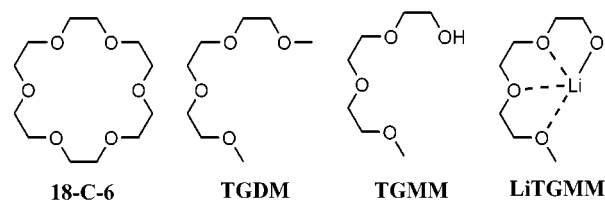


Figure 1.

Initially, we investigated the well-known Evans ZnI_2 -catalyzed addition of TMSCN to the hindered ketone camphor (**1**).⁴ This process has been reported to provide 5:3 diastereoselectivity. As a result of the diastereoselectivity observed with the ZnI_2 process, the 18-C-6/ KCN catalyzed addition of TMSCN to camphor was examined.⁵ The reaction of 5 mol % of 18-C-6/ KCN in THF with 1.2 equiv of TMSCN at room temperature, followed by the addition of 1 equiv of camphor, provided **2** in a diastereomeric ratio of 94:6 favoring the endo isomer. However, while the diastereoselectivity was high, the rate of the reaction was extremely slow, requiring 3 days to reach 35% conversion. Another drawback of the 18-C-6/ KCN system is that 18-C-6 is expensive and toxic. Therefore, our goal was to develop a selective cyanation system like 18-C-6/ KCN with the emphasis on generality and practicality. First, we explored the 18-C-6 replacement hoping to find a nontoxic ligand that can accelerate the cyanation process while maintaining the diastereoselectivity. We systematically examined several available bismethylated and monomethylated glymes with KCN , NaCN , LiCN in DMF, or TMSCN in THF under various conditions.

Unfortunately, none of these systems mediated the cyanide addition to camphor. Significantly, deprotonation of inexpensive triglyme monomethyl ether (TGMM, 5 mol %) with LiH (5 mol %) or $n\text{-BuLi}$ (5 mol %) in THF at 0 °C provided a soluble and remarkable lithium alkoxide (LiTGMM, 5 mol %). The addition of 5 mol % LiTGMM to 1.2 equiv of TMSCN , followed by the addition of 1.0 equiv of camphor gave a quantitative conversion of camphor to the desired silyl-cyanohydrin with 96:4 diastereoselectivity (Table 1, entry 4).⁶

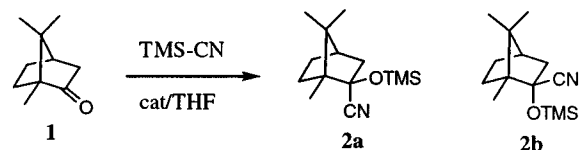
Increasing the temperature (up to 60 °C) decreases the diastereoselectivity and increases the rate of the reaction (entry 10). On the other hand, decreasing the temperature to -10 °C did not change the diastereoselectivity but did, however, decrease the rate of the reaction dramatically (entry 11). Increasing the catalytic loading increases the rate of reaction while maintaining the diastereoselectivity (entry 9). *Surprisingly, the sodium, potassium, or magnesium salt of TGMM does not catalyze this important transformation*

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(6) Other solvents such as CH_2Cl_2 , MTBE, and toluene can be used in this reaction. Preferred solvent is dry THF. It is important to note that premixing LiOR and TMSCN is critical before addition of ketone or aldehyde.

Table 1^a



entry	catalyst (mol%)	temp (°C)	time (h)	% yield (% conv)	dr (2a:2b)
1	ZnI_2 (5)	22	24	(98)	72:27
2	$\text{KCN}/18\text{-C-6}$ (5)	22	72	(35)	94:6
3	TGMM (5)	22	12	(0)	
4	LiTGMM (5)	22	4	95 (>99)	96:4
5	NaTGMM (5)	22	12	(0)	
6	KTGMM (5)	22	12	(0)	
7	MgTGMM (5)	22	12	(0)	
8	TGMM/LiCl (5)	22	24	(0)	
9	LiTGMM (50)	22	1	96 (>99)	96:4
10	LiTGMM (5)	60	1	96 (>99)	86:14
11	LiTGMM (5)	-10	16	(40)	96:4
12	LiOMe (5)	22	4	95 (>99)	96:4
13	LiOBu (5)	22	4	(>99)	96:4
14	LiNEt_2 (5)	22	7	(>99)	96:4
15	LiPPh_2 (5)	22	10	(>99)	96:4
16	LiSPh (5)	22	24	(>99)	96:4

^a Selectivities were determined by GC%.

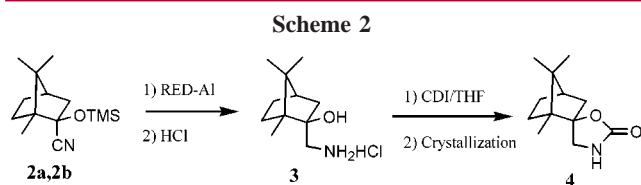
(Table 1, entries 5–7).⁷ It is important to point out that LiCl/TGMM does not catalyze the reaction; only lithium alkoxide promotes the cyanation process. We were intrigued to determine if a polyether-derived lithium alkoxide was necessary for this catalytic process. Therefore, we examined other alkoxides, such as LiOMe , LiOEt ,⁸ and LiOBu . Interestingly, all of the alkoxides promoted the reaction to the same degree. A study was conducted to understand the other lithium-heteroatom effects on the TMSCN addition to camphor. Other lithium anions such as LiNEt_2 , LiPPh_2 , and LiSPh also promoted the reaction with a similar diastereoselectivity to alkoxides, but at reduced rates (entries 14–16).

The salient feature of this catalytic cyanation process is the high diastereoselectivity, and the excellent rate of the reaction. The stereochemical outcome of the cyanide addition to camphor was unambiguously established by the reduction of cyanohydrin **2** with RED-Al in toluene, followed by crystallization of the HCl salt in MeOH to give amino alcohol **3** as a single diastereomer in a 72% yield. The amino alcohol was converted to new oxazolidinone **4**, and a single-crystal X-ray analysis of **4** indicated that the cyanide addition occurred mainly from the endo-face of the ring system (Scheme 2).⁹

(7) Sodium and potassium salt of TGMM were generated upon treatment of NaH and KH with TGMM, respectively. MgTGMM was produced simply by treatment of TGMM with EtMgBr .

(8) Available from Aldrich as a 1 M THF solution.

(9) (a) See Supporting Information for X-ray crystallography data of compound **4**. (b) The novel camphor-derived oxazolidinone **4** will be used as a chiral auxiliary for asymmetric synthesis.



The viability of this lithium heteroatom accelerated cyanide addition process was examined by applying the procedure to various ketones and benzaldehyde. As depicted in Table 2, nopinone and fenchone gave high selectivities in excellent yields with reasonable rates of reaction (entries 1 and 2). It

Table 2. Lithium Alkoxide Mediated TMSCN Addition to Ketones^a

entry	substrate	catalytic loading (mol%)	temp (°C)	time (h)	dr (GC%)	yield (%)
1		5	22	4	93:7	91
2		5	22	16	99:1	95
3		5	-78	12	77:23	97
4		5	-78	4	85:15	96
5		5	-78	12	82:18	94
6		5	22 -20	4 16	84:14 97:3	94
7		5*	22	2		96
8		1	22	2		95
9		0.1 0.025	22	2.5 24		95 94
10		1	22	0.2		96
11		5	22	4		95
12		1	22	0.2		98
13		5	22	4	>99:1	92**

^a All reactions were conducted in THF with LiTGMM and 1.2 equiv of TMSCN at the specified temperature unless otherwise specified. *Readily available 1 M THF solution LiOEt was used as the catalyst. **2.2 equiv of TMSCN was used. The extra 1 equiv of TMSCN is required for silylation of hydroxyl group. The product is bisilylated.

has been noted in the literature that α -methyl cyclohexanone cyanate gave an extremely low diastereoselectivity with ZnI_2 , KCN/18-C-6, or TMSOTf (2%, 4%, and 16%, respectively).¹⁰ Interestingly, α - and β -methyl cycloalkanones provided good selectivities and excellent yields at -78 °C with the current procedure (entries 3–5). It is important to note that α,β -unsaturated ketone carvone undergoes 1,2-addition only, with high diastereoselectivity (entry 6). The neutral nature of this cyanation system is exemplified by the high yielding processes of enolizable ketones, such as ethyl acetoacetate and ethyl cyclohexyl glyoxylate (entries 7 and 8).

Recently, Jenner reported that 4-amino acetophenone is a difficult substrate to cyanate with a ZnI_2 , $LiClO_4$, or LiF_4B protocol.¹¹ It is gratifying to mention the Li-alkoxide procedure afforded >95% yield (entry 11). Aldehydes and nonhindered ketones can be cyanated with extremely high yields. As revealed in Table 2, entry 9, cyclohexyl phenyl ketone can be converted to the desired cyanohydrin with very low catalytic loading (0.025 mol % of LiTGMM), while maintaining a reasonable reaction rate.

This important catalytic process is not only applicable for TMSCN addition to ketones. It can be extended to the sterically congested TBSCN addition to hindered ketones. As outlined in Table 3, the isolated yields of the reactions

Table 3. Lithium Alkoxide Mediated TBSCN Addition to Ketones^a

entry	ketone	time (h)	dr (GC%)	yield %
1		24	91:9	94
2		24	93:7	71*
3		18	96:4	94
4		15		98

^a All reaction were conducted in THF with 25 mol % of LiTGMM and 1.7 equiv of TBSCN at 22 °C. *50 mol % of LiTGMM was used.

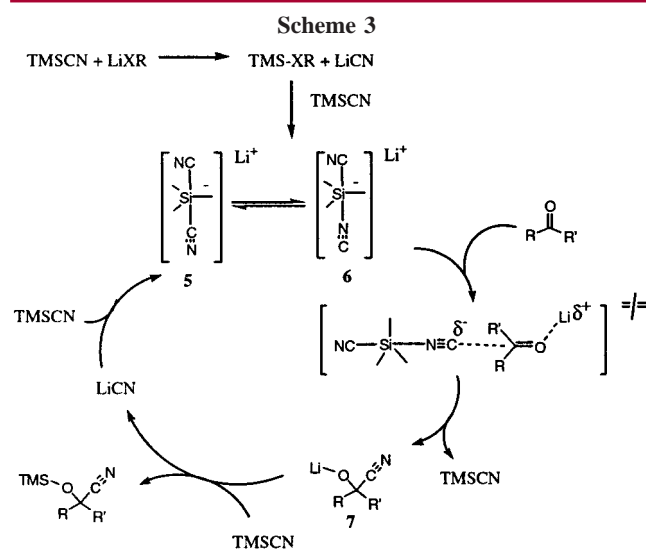
are high. Several interesting observations were noted when comparing the selectivities obtained from our TMSCN additions to those reported previously. For instance, Watt and co-workers reported that cyanation of camphor with TBSCN in the presence of either ZnI_2 or 18-C-6/KCN provided low diastereoselectivity (67:33 and 62:38, respectively).¹² When utilizing Li-alkoxide in the reaction, the diastereoselectivity is much higher (91:9, entry 1) than with

(10) Matsubara, S.; Takai, T.; Utimoto, K. *Chem. Lett.* **1991**, 1447.

(11) ZnI_2 provided a complex product mixture and $LiBF_4$ or $LiClO_4$ gave <15% yield. See: Jenner, G. *Tetrahedron Lett.* **1999**, 40, 491.

Watt's procedure; however, it was a slightly diminished diastereoselectivity compared to our TMS-CN addition process (96:4) (Table 1, entry 4). It is gratifying to disclose that the α - and β -methyl cyclohexanones provided an outstanding diastereoselectivity and complimentary results to TMS-CN process (Table 2, entries 3 and 4 and Table 3, entries 2 and 3).

The mechanistic details of this lithium alkoxide accelerated silyl cyanation process are uncertain, but literature precedence¹³ coupled with our reported data leads to the working hypothesis illustrated in Scheme 3. We propose that TMS-CN



reacts with LiXR (X = heteroatom) to generate lithium cyanide (the catalyst for the reaction sequence). Lithium cyanide then reacts with TMS-CN to form a pentavalent silicon species **5**, which is in equilibrium with isocyanide intermediate **6**. Then as shown in the transition state,

isocyanide delivers to activated ketone to provide lithio-cyanated adduct **7** and TMS-CN. The adduct **7** then reacts with TMS-CN to produce TMS cyanohydrin and regenerate LiCN for the next catalytic cycle.

In conclusion, we have demonstrated a remarkable lithium heteroatom accelerated TMS-CN or TBSCN addition to aldehydes and ketones with high yields. This process is inexpensive and provides good-to-excellent diastereoselectivity. Conformationally constrained structures such as camphor, fenchone, and nopinone give excellent selectivities. These adducts could be conveniently converted to their corresponding amino alcohols and derivatives thereof, which are currently being evaluated in asymmetric synthesis and will be forthcoming. The mechanism of this reaction and the asymmetric version of this important transformation are currently being investigated. Li-alkoxides are inexpensive and readily available, and this process does not require any heavy metals or toxic additives. We believe that this remarkable, efficient, and general *neutral-cyanation* method is a significant addition to synthetic organic chemistry.

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Supporting Information Available: Experimental procedures and analytical data for compounds **2**, other silyl cyanohydrin adducts, and synthetic procedures for **3** and **4** (including X-ray data). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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