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Trimethylsilylcyanation of Aldehydes and Ketones Catalyzed by Diorganotin Dichlorides

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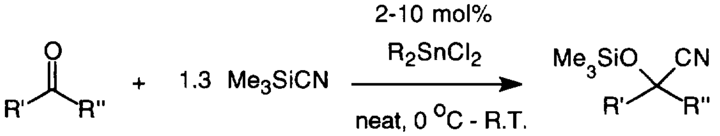
Abstract: Dibutyltin dichloride and diphenyltin dichloride functioned as effective catalysts for the trimethylsilylcyanation of aldehydes and ketones. Isolated yields ranged from 71% to 97%. Copyright © 1996 Elsevier Science Ltd

The development of catalysts for the addition reaction of cyanotrialkylsilanes with carbonyl compounds is an area of active study[1, 2] due to the synthetic versatility of *O*-silylated cyanohydrins.[3] Although diorganotin dihalides offer several attractive features[4] which could be exploited in catalytic systems (for example: mild Lewis acidity; ease of synthesis; generally monomeric solution state structures; strong carbon-metal bonds relative to many organometallics; and relative stability to air), the use of these organometallic compounds as catalysts in preparative organic reactions is surprisingly uncommon.[5] Recently, Scholl and Fu reported that tributyltin cyanide was an efficient catalysts for the trialkylsilylcyanation of aldehydes and activated ketones.[1a] As part of an ongoing program to develop practical, enantioselective, catalytic reactions based on diorganotin dihalides, we have found dibutyltin dichloride and diphenyltin dichloride to function as effective catalysts for the addition of trimethylsilyl cyanide (TMSCN) to aldehydes and unactivated ketones.



(1)

Treatment of a variety of aldehydes and ketones with TMSCN and a catalytic amount of diorganotin dihalide neat at 0 °C followed by warming to room temperature[6] furnished the expected *O*-silylated cyanohydrins in good yield (Eq. 1, Table 1).[7] Both sterically hindered and conjugated aldehydes were suitable substrates (entries 2-6, and 8), as were dialkyl and aryl alkyl ketones (entries 10-12). Diphenyltin dichloride was a more reactive catalyst than dibutyltin dichloride (entries 4, 5 and 11, 12). All uncatalyzed reactions exhibited less than 4% conversion under otherwise identical conditions except for pivaldehyde, which showed 20% conversion.[8] In the case of benzaldehyde, freshly-distilled dibutyltin dichloride afforded results (entry 3) comparable to those obtained with dibutyltin dichloride which was used as received and handled in an air atmosphere (entry 2), demonstrating that the catalyst is air-tolerant and suggesting that catalytic activity is not due to an inorganic impurity in the commercial organotin.

Table 1. Yields and reaction times for the diorganotin dihalide-catalyzed trimethylsilylcyanation of aldehydes and ketones.

		R_2SnCl_2 catalyst			
Entry	Substrate	R=	Mol%	Time (h)	Yield(%)[a]
1[b]	c-$C_6H_{11}CHO$	Bu	10	0.5	83[c]
2	PhCHO	Bu	10	0.5	90
3[d]	PhCHO	Bu	10	0.5	97
4	PhCHO	Bu	2	0.5	75[e]
5	PhCHO	Ph	2	0.5	90
6[b,f]	t-BuCHO	Bu	10	5.5	71
7[b]	PhCHMeCHO	Bu	10	1.5	78[g]
8	(E)-PhCH=CHCHO	Bu	10	0.5	86[h]
9[b]	n-$C_7H_{15}CHO$	Bu	10	0.2	85
10	n-$C_6H_{13}COMe$	Bu	10	22	93
11	PhCOMe	Bu	10	45	93[e]
12	PhCOMe	Ph	4[i]	1.8	95

a) Isolated yields of spectroscopically pure products are reported unless otherwise noted. All reactions were run to 100% conversion as determined by ^1H NMR of the crude product unless otherwise noted. All products were identified by comparison of their ^1H and ^{13}C NMR spectra with samples prepared with ZnI_2 catalyst.[9] b) The aldehyde was treated as described in reference 8. c) Traces of an unidentified impurity were present in the isolated product. d) The catalyst was distilled before use. e) Because of incomplete conversion, yield was estimated from the ^1H NMR spectrum of the crude reaction mixture. f) The uncatalyzed reaction proceeded to 20% conversion. g) A 1:1 ratio of diasteriomers was obtained. h) Exclusive 1,2-addition was observed. i) This loading represents the solubility limit of the catalyst in the reaction medium.

Although a detailed understanding of this reaction will require further studies, previous reports regarding organotin chemistry suggest that a tin cyanide may be a catalytically active species:[10] (1) dimethyltin dicyanide has been prepared from the reaction of dimethyltin dichloride and TMSCN;[11, 12] (2) tributyltin cyanide adds to aldehydes much more rapidly than does TMSCN;[13] and (3) organotin alkoxides react with trialkylsilyl halides to afford the organotin halide and silylated alcohol.[1a,14] A plausible catalytic cycle which takes these observations into account is depicted in Figure 1.

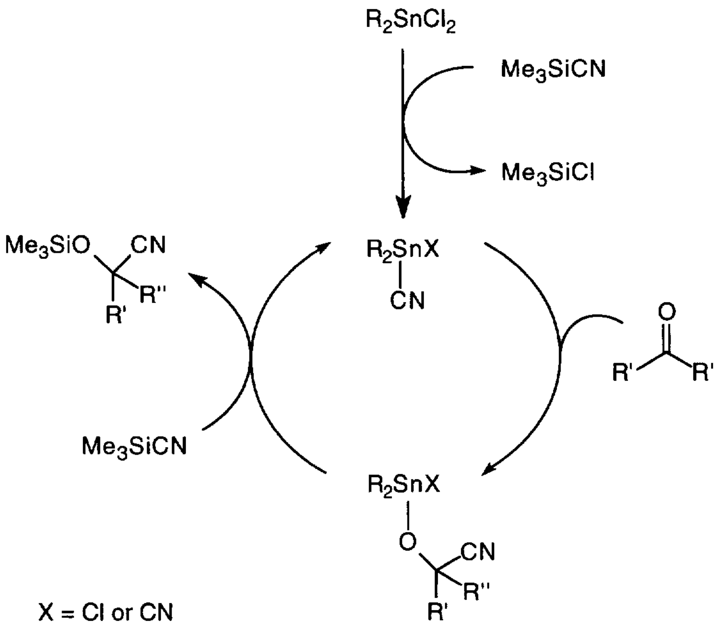


Figure 1. Possible catalytic cycle for the trimethylsilylcyanation of aldehydes and ketones catalyzed by diorganotin dichlorides.

Given our preliminary mechanistic considerations, the advantageous features of diorganotin dihalides, and the fact that a number of nonracemic chiral diorganotin dihalides have already been reported,[5a, 5f, 15] we believe that the development of an enantioselective version of this new catalytic system may be feasible. Efforts directed toward this end are in progress.

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6. Reactions with aldehydes were generally mildly exothermic. Initial cooling was employed to prevent significant temperature increase.

7. **General experimental procedure:** Trimethylsilyl cyanide (CAUTION: *Toxic!*, 3.20 mmol, 1.3 eq) was added to the untreated organotin catalyst at room temperature under nitrogen. The homogeneous mixture was frozen in an ice bath after which the untreated aldehyde or ketone (2.46 mmol, 1 eq) was added and the ice bath was removed. After the indicated time, the resulting oil was pipetted onto a short plug of Florisil® and eluted with Skelly B. The catalyst-free product was obtained by evaporation of the solvent at water aspirator pressure.

8. We believe that trace amounts of carboxylic acids resulting from air-oxidation of the starting aldehydes act as catalysts in the absence of organotins. We found that washing the aldehyde sequentially with equal volumes of saturated NaHCO$_3$, water, 5% HCl, and water followed by vacuum distillation (see: Perrin, D.D., Armarego, L.F., Perrin, D.R.; *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1966; p 350) minimized the uncatalyzed reaction. In the case of octanal, simply distilling the aldehyde had little effect. We observed substantial acceleration of the addition reaction of untreated octanal with TMSCN in the presence of 10 mol% acetic acid. There was no significant acceleration in the presence of 10 mol% ethanol. We also found that the reaction of untreated octanal with TMSCN alone could be inhibited by adding 4 mol% Me$_3$SiCl. This amount of additive had a negligable effect on the rate of the Bu$_2$SnCl$_2$-catalyzed reaction. The role Me$_3$SiCl in these reactions is not yet understood.

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