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Highly (*Z*)-Selective Synthesis of β-Monosubstituted α,β-Unsaturated Cyanides Using the Peterson Reaction

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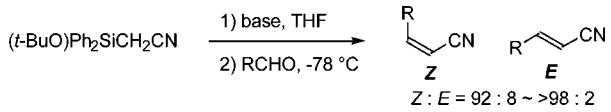
ABSTRACT



The Peterson reaction between (*t*-BuO)Ph_2SiCH_2CN and various aldehydes furnishes the corresponding β-monosubstituted α,β-unsaturated cyanides with high *Z* selectivity (*Z*:*E* = 92:8 to >98:2).

Since α,β-unsaturated carbonyl compounds are multifunctional, they are considered to be versatile building blocks in organic synthesis. For the efficient preparation of the thermodynamically less stable disubstituted (*Z*)-olefins from aldehydes, a few methods based upon Wittig-type[1−5] and Peterson-type[6−8] reactions have been reported. The cyano group functions similarly to carbonyls, but the inherent small size of the substituent allows for chemistry of its own.[9] As for methods for the selective preparation of (*Z*)-α,β-unsaturated cyanides, there are a few based upon phosphorus[10,11] and silicon[12,13] chemistry and there are interesting reports that describe the use of cross-metathesis.[14] Other than multistep methods,[13] however, reactions involving aromatic aldehydes have been less successful, giving products with only up to ca. 3:1 selectivity.

Previously, we reported that α-triphenylsilylacetamides ($Ph_3SiCH_2CONR'_2$) were useful reagents for the preparation

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(1) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.
(2) (a) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105−4108. (b) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934−1939. (c) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411−8416. (d) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406−8408. (e) Kokin, K.; Motoyoshiya, J.; Hayashi, S.; Aoyama, H. *Synth. Commun.* **1997**, *27*, 2387−2392.
(3) (a) Kojima, S.; Takagi, R.; Akiba, K.-y. *J. Am. Chem. Soc.* **1997**, *119*, 5970−5971. For related mechanistic studies, see: (b) Kojima, S.; Akiba, K.-y. *Tetrahedron Lett.* **1997**, *38*, 547−550. (c) Kojima, S.; Kawaguchi, K.; Akiba, K.-y. *Tetrahedron Lett.* **1997**, *38*, 7753−7756. (d) Kojima, S.; Kawaguchi, K.; Matsukawa, S.; Akiba, K.-y. *Tetrahedron* **2003**, *59*, 255−265.
(4) Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett.* **1999**, *40*, 6725−6728.
(5) (a) Ando, K. *Synlett* **2001**, 1272−1274. (b) Kojima, S.; Hidaka, T.; Ohba, Y.; Ohkata, K. *Phosphorus Sulfur Silicon* **2002**, *177*, 729−732. (c) Kojima, S.; Hidaka, T.; Ohba, Y. *Heteroatom Chem.* In press.
(6) For reviews on the Peterson reaction: (a) Ager, D. J. *Synthesis* **1984**, 384−398. (b) Ager, D. J. *Org. React.* **1990**, *42*, 1−223. (c) van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195−200.
(7) (a) Larcheveque, M.; Debal, A. *J. Chem. Soc., Chem. Commun.* **1981**, 877−878. (b) Matsuda, I.; Izumi, Y. *Tetrahedron Lett.* **1981**, *19*, 1805−1808. (c) Arai, S.; Tsuzuki, Y.; Matsuda, S.; Kitagaki, S.; Kita, Y. *Synlett* **1991**, 911−912.
(8) (a) Kojima, S.; Inai, H.; Hidaka, T.; Ohkata, K. *Chem. Commun.* **2000**, 1795−1796. (b) Kojima, S.; Inai, H.; Hidaka, T.; Fukuzaki, T.; Ohkata, K. *J. Org. Chem.* **2002**, *67*, 4093−4099.
(9) Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035−2077.
(10) Zhang, T. Y.; O'Toole, J. C.; Dunigan, J. M. *Tetrahedron Lett.* **1998**, *39*, 1461−1464.
(11) Kojima, S.; Kawaguchi, K.; Matsukawa, S.; Uchida, K.; Akiba, K.-y. *Chem. Lett.* **2002**, 170−171.
(12) (a) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568−5570. (b) Haruta, R.; Ishiguro, M.; Furuta, K.; Mori, A.; Ikeda, N.; Yamamoto, H. *Chem. Lett.* **1982**, 1093−1096. (c) Furuta, K.; Ishiguro, M.; Haruta, R.; Mori, A.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768−2776. (d) Palomo, C.; Aizpurua, J. M.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 2209−2210.
(13) (a) Sato, Y.; Niinomi, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 56−57. (b) Matsuda, I.; Okada, H.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 528−532.
(14) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162−5163; Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430−432.

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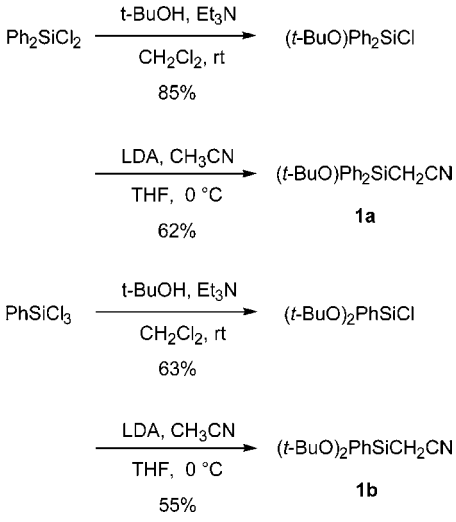
of (*Z*)-*β*-monosubstituted α,*β*-unsaturated amides, whereas a reagent bearing a less electronegative trimethylsilyl group either exhibited (*E*)-selectivity or gave no olefinic product.[8] Based upon this finding, we investigated the reactions of **1a** and **1b** with various aldehydes. Here the silyl group is even more electronegative than a triphenylsilyl due to the presence of the alkoxy groups in the place of the phenyl groups. We have found that the reagents bearing the electronegative silyl groups also produce (*Z*)-olefination products with high selectivity from various aldehydes. Even aromatic aldehydes give (*Z*)-α,*β*-unsaturated cyanides with good levels of selectivity, with **1a** being the better of the two. Herein we describe our results.

Reagents **1a** and **1b** were prepared in moderate yields (62 and 53%, respectively) as chromatographable compounds by the reaction of $(t\text{-BuO})_n\text{Ph}_{3-n}\text{SiCl}$[15] with the lithium enolate of acetonitrile. The two starting halides were prepared from $\text{Ph}_{3-n}\text{SiCl}_{n+1}$ and *t*-BuOH (Scheme 1). The preparations of

Scheme 1



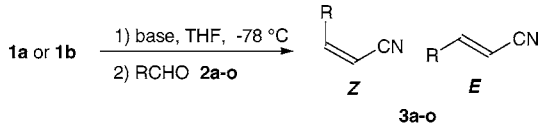
(MeO)$\text{Ph}_2\text{SiCH}_2\text{CN}$ and (*i*-PrO)$\text{Ph}_2\text{SiCH}_2\text{CN}$ were also attempted. However, these compounds were prone to decomposition and difficult to purify. Therefore, these compounds were not pursued any further.

All the reactions were carried out in THF at −78 °C (Scheme 2). Benzaldehyde and 3-phenylpropionaldehyde were the first aldehydes examined using reagent **1a** with KHMDS (which was the optimal base for the reactions of previously investigated $\text{Ph}_3\text{SiCH}_2\text{CONR}'_2$) (Table 1, entries 1 and 7). Both substrates gave the expected (*Z*)-olefin with selectivity as high as 96:4.

With the (*Z*)-selective $\text{Ph}_3\text{SiCH}_2\text{CONR}'_2$ we had observed a countercation effect, i.e., selectivity in the order of $K^+ > Na^+ > Li^+$. To see whether a similar tendency could be observed, NaHMDS and *n*-BuLi were also examined with

(15) (*t*-BuO)Ph_2SiCl: Gillard, J. W.; Fortin, R.; Morton, H. E.; Yoakim, C.; Quesnelle, C. A.; Daignault, S.; Guindon, Y. *J. Org. Chem.* **1988**, *53*, 2602−2608.

Scheme 2

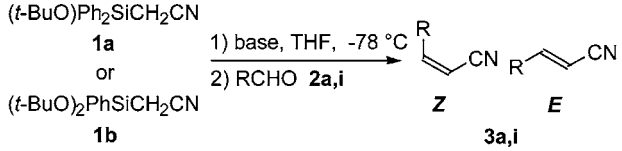


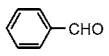
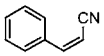
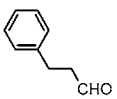
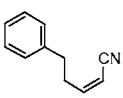
2a: R=Ph
2b: R=4-MeOC$_6$H$_4$
2c: R=3-MeOC$_6$H$_4$
2d: R=2-MeOC$_6$H$_4$
2e: R=4-ClC$_6$H$_4$
2f: R=2-ClC$_6$H$_4$
2g: R=2-Furyl
2h: R=2-Pyridyl
2i: R=PhCH$_2$CH$_2$
2j: R=*c*-Hexyl
2k: R=Ph(CH$_3$)CH
2l: R=*t*-Bu
2m: R=Ph(CH$_3$)$_2$C
2n: R=(*E*)-PhCH=CH
2o: R=TBSC≡C

the same two aldehydes. It was found that for the aromatic aldehyde and the aliphatic aldehyde, *n*-BuLi (entry 5) and NaHMDS (entry 9) gave the best results, respectively. However, the differences in selectivity upon changing the countercation were minute compared with the reactions of $\text{Ph}_3\text{SiCH}_2\text{CONR}'_2$. Other commonly used bases such as *t*-BuOK led to lower yields and selectivity. Reagent **1b** was similarly surveyed (even-numbered entries), and it was found to furnish comparable selectivity. However, reduction in yields was observed. Thus, we decided to focus on reagent **1a** for ensuing investigations.

Various aromatic aldehydes were now examined (Table 2). Since the differences in selectivity with the various bases used were small for **2a**, all three bases (KHMDS, NaHMDS, and *n*-BuLi) were surveyed for typical aromatic aldehydes. For all the substrates examined, (*Z*)-selectivity exceeded 9:1. Again, the countercation effect was found to be minimal and no particular trend could be deduced from the results. Where

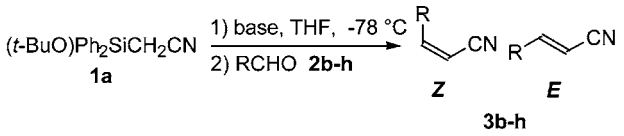
Table 1. Reaction of **1a** and **1b** with Aldehydes **2a** and **2i**[a]

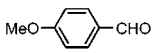
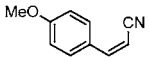
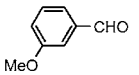
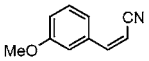
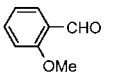
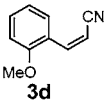
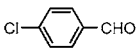
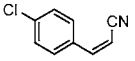
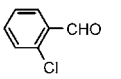
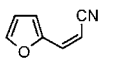
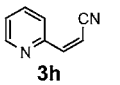


Entry	Aldehyde	Reagent	Base	Product	*Z* : *E*[b]	Yield[c]
1		**1a**	KHMDS		96: 4	74
2		**1b**	KHMDS		95: 5	39
3	**2a**	**1a**	NaHMDS	**3a**	98: 2	79
4		**1b**	NaHMDS		97: 3	54
5		**1a**	*n*-BuLi		**99: 1**	93
6		**1b**	*n*-BuLi		97: 3	49
7		**1a**	KHMDS		96: 4	99
8		**1b**	KHMDS		97: 3	37
9		**1a**	NaHMDS		**>98: 2**	88
10	**2i**	**1b**	NaHMDS	**3i**	97: 3	53
11		**1a**	*n*-BuLi		96: 4	99
12		**1b**	*n*-BuLi		66:34	24

[a] In all the reactions, the aldehyde (0.34 mmol) was dissolved in THF (3 mL) and the reactions were run for 3 h at −78 °C. [b] Determined by ^{1}H NMR (500 MHz) measurement of the crude mixture. [c] Combined isolated yield of (*Z*)- and (*E*)-olefins.

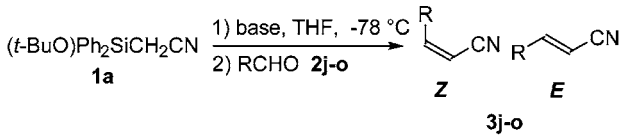
Table 2. Reaction of **1a** with Aromatic Aldehydes **2b**−**h**[a]

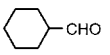
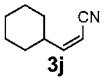
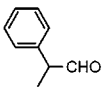
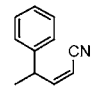
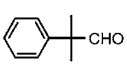
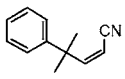
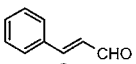
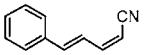
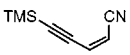


Entry	Aldehyde	Base	Product	$Z:E$[b]	Yield[c]
1		KHMDS		96: 4	94
2	**2b**	*n*-BuLi	**3b**	98: 2	79
3	 **2c**	KHMDS	 **3c**	97: 3	79
4	 **2d**	KHMDS	 **3d**	96: 4	91
5		KHMDS		97: 3	68
6		NaHMDS		98: 2	72
7	**2e**	*n*-BuLi	**3e**	96: 4	94
8		KHMDS		93: 7	74
9		NaHMDS		92: 8	71
10		*n*-BuLi		87:13	63
11	**2f**	*n*-BuLi[d]	**3f**	89:11	78
12		KHMDS		98: 2	62
13		NaHMDS		94: 6	85
14	**2g**	*n*-BuLi	**3g**	97: 3	90
15		KHMDS		92: 8	88
16		NaHMDS		90:10	75
17		*n*-BuLi		87:13	63
18	**2h**	*n*-BuLi[d]	**3h**	91: 9	71

[a] In all the reactions, the aldehyde (0.34 mmol) was dissolved in THF (3 mL) and the reactions were run for 3 h at −78 °C. [b] Determined by ^{1}H NMR (500 MHz) measurement of the crude mixture. [c] Combined isolated yield of (*Z*)- and (*E*)-olefins. [d] TMEDA was used as an additive.

Table 3. Reaction of **1a** with Aliphatic Aldehydes **2j**−**o**[a]



Entry	Aldehyde	Base	Product	$Z:E$[b]	Yield[c]
1	 **2j**	KHMDS	 **3j**	>98: 2	(quant)[e,f]
2		KHMDS		>98: 2	20
3		NaHMDS		96: 4	55
4		*n*-BuLi		97: 3	72
5	**2k**	*n*-BuLi[d]	**3k**	>98: 2	60
6		KHMDS		88:12	(quant)[e]
7	**2l**	*n*-BuLi	**3l**	94: 6	52(quant)
8		KHMDS[g]		86:14	93
9		NaHMDS[g]		95: 5	85
10	**2m**	*n*-BuLi[g]	**3m**	95: 5	87
11		KHMDS		93: 7	83
12		NaHMDS		94: 6	85
13	**2n**	*n*-BuLi	**3n**	92: 8	89
14		KHMDS		94: 6	75
15		NaHMDS		93: 7	98
16	**2o**	*n*-BuLi	**3o**	95: 5	93

[a] In all the reactions, the aldehyde (0.34 mmol) was dissolved in THF (3 mL) and the reactions were run for 3 h (expect where noted otherwise) at −78 °C. [b] Determined by ^{1}H NMR (500 MHz) measurement of the crude mixture. [c] Combined isolated yield of (*Z*)- and (*E*)-olefins with NMR yields in parentheses. [d] TMEDA was used as an additive. [e] Could not be separated from toluene, the solvent of the commercial KHMDS used here. [f] Run using *t*-BuOK allowed isolation in 51% (96:4) yield. [g] Reaction was run for 6 h.

selectivity was somewhat low using *n*-BuLi, the effect of TMEDA as an additive was examined (entries 11 and 18). In these runs, a slight increase in selectivity was seen.

As for aliphatic aldehydes other than 3-phenylpropionaldehyde, examinations were carried out in connection with steric bulk α to the formyl group (Table 3). With cyclohexanecarboxyaldehyde, the formation of the (*Z*)-olefin was exclusive using KHMDS (entry 1). 2-Phenylpropionaldehyde, which did not give any olefinic product due to enolization in the case of $Ph_3SiCH_2CONR'_2$, was also found to give the desired (*Z*)-olefin exclusively with KHMDS, although in low yield (entry 2). However, changing the base to NaHMDS and then to *n*-BuLi led to a progressive increase in yield with only a small decrease in selectivity (entries 3 and 4). Applying TMEDA to the reaction using *n*-BuLi as the base led to a small decrease in yield. However, the (*Z*)-olefin was the exclusive product.

This difference in reactivity compared with the corresponding amide-type reagent is probably due to the difference in size between the cyano group and an amide group, allowing the reagent with the former group to react more readily. The propensity for aliphatic aldehydes (without too much steric hindrance, vide infra) to give (*Z*)-olefins with higher selectivity than aromatic aldehydes parallels that of previous examinations with phosphorus- and silicon-based reagents.[10−12]

The reactions of the aldehydes with a quaternary carbon α to the formyl group were found to be somewhat sluggish, and in the case of 2-methyl-2-phenylpropionaldehyde, longer reaction times were required (entries 8−10). The selectivity dropped notably upon using KHMDS (entries 6 and 8) but increased to an acceptable level upon using NaHMDS or *n*-BuLi. The propensity for the less bulky aliphatic aldehyde to give higher selectivity is opposite to what has been observed with the corresponding (*Z*)-selective Horner−Wadsworth−Emmons reagent.[10]

Conjugated aliphatic aldehydes were also found to give good results, furnishing the corresponding products from *trans*-cinnamaldehyde and 3-trimethylsilylprop-2-yn-1-one with selectivity up to 94:6 and 95:5, respectively. Therefore, this reagent should be useful for the preparation of extended conjugated alkenes of defined geometry.

Although the (*t*-BuO)Ph_2Si group worked extremely well for the acetonitrile-derived reagent, the same could not be said for the ethyl acetate derivative. In this case, yields and selectivity were low. Since there is no reason to believe that the small perturbation in the electronic nature of the enolate of the silyl compound, from carbonitrile-stabilized anion to ester-stabilized anion, should change the electronic reactivity of the reagent, we believe the cause of this difference between the two reagents could be attributed to the steric bulk of the reagent. The fact that the presumably bulkier (*t*-BuO)$_2$PhSiCH_2CN (**1b**) was less effective in the reaction also supports this notion.

In summary, we have developed a Peterson reagent, (*t*-BuO)Ph_2SiCH_2CN (**1a**), that has generality for the preparation of (*Z*)-β-monosubstituted α,β-unsaturated cyanides from both aromatic and aliphatic aldehydes. Further investigations on substituent effects involving the silyl moiety and mechanistic studies of the reaction are currently underway.

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Supporting Information Available: Experimental procedures and characterization data for the product (*Z*)-β-monosubstituted α,β-unsaturated cyanides. This material is available free of charge via the Internet at http://pubs.acs.org.

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