DOI: 10.1002/adsc.201000409

Dibutyltin Dimethoxide-Catalyzed Cyano Transfer to Aldehydes and Imines

Akira Yanagisawa,[a,]* Takuya Matsumoto,[a] Naoyuki Kushihara,[a]
and Kazuhiro Yoshida[a]

[a] Department of Chemistry, Graduate School of Science, Chiba University, Inage, Chiba 263-8522, Japan
Fax: (+81)-43-290-2789; e-mail: ayanagi@faculty.chiba-u.jp

Received: May 25, 2010; Revised: September 13, 2010; Published online: November 12, 2010

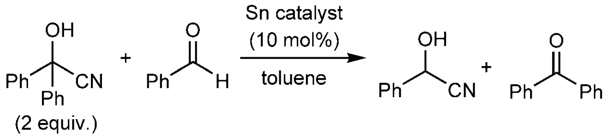
Abstract: A novel reaction involving cyano transfer from benzophenone cyanohydrin to aldehydes and imines was realized by using dibutyltin dimethoxide as a catalyst. Various cyanohydrins and α-amino nitriles were obtained in moderate to high yields by this reaction. Ketimines also showed remarkable reactivity as cyano acceptors under conventional reaction conditions. This catalytic reaction was further applied to a three-component condensation reaction of aldehydes, aniline, and benzophenone cyanohydrin in the presence of Drierite®.

Keywords: aldehydes; α-amino nitriles; cyanation; cyanohydrins; imines; tin

The cyanation of aldehydes and imines is a convenient method for preparing cyanohydrins and α-amino nitriles, respectively, which are further transformed into synthetically useful compounds, such as α-hydroxy carboxylic acids and α-amino acids.[1] As a cyanating agent, trimethylsilyl cyanide (Me_3SiCN) is frequently utilized in the reaction with aldehydes to afford trimethylsilylated cyanohydrins.[2] Besides Me_3SiCN, acetone cyanohydrin is known as a useful cyanide source. For example, acetone cyanohydrin undergoes cyano transfer to aldehydes in the presence of a catalytic amount of an oxovanadium(V)(salen) complex.[3] Zirconium alkoxide complexes[4] and organosamarium complexes[5] have also been employed as catalysts. In addition, acetone cyanohydrin is applicable to the cyano transfer reaction with imines. Indeed, a three-component Strecker-type reaction with acetone cyanohydrin has been achieved in the presence of triethylamine as catalyst.[6] Here we describe a novel reaction involving the cyano transfer from benzophenone cyanohydrin to aldehydes and imines catalyzed by dibutyltin dimethoxide (Scheme 1).

We have previously found that dibutyltin oxide acts as a catalyst in the allyl transfer reaction of tertiary homoallylic alcohols with aldehydes in which a catalytic amount of an allylic tin species is generated *in situ*.[7] We envisioned that Bu_2SnO would also catalyze the cyano transfer to aldehydes if a tin cyanide species were formed from a ketone cyanohydrin, according to a similar catalytic mechanism to that for the

Table 1. Screening of tin catalysts for the cyano transfer from benzophenone cyanohydrin to benzaldehyde.[a]



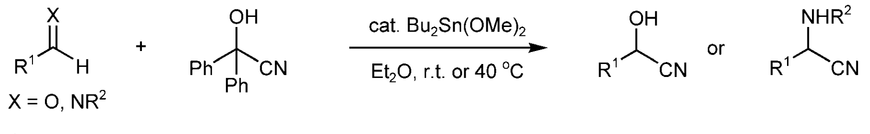
Entry	Catalyst	Temp. [°C]	*t* [h]	Yield[b] [%]
1	Bu_2SnO	100	3	<1
2	Bu_2SnBr_2	r.t.–120	24	<1
3[c]	Bu_2SnBr_2	r.t.–70	26	<1
4	$Bu_2Sn(OMe)_2$	r.t.	20	66
5[d]	$Bu_2Sn(OMe)_2$	r.t.–120	32	<1

[a] Unless otherwise noted, the reaction was performed using tin catalyst (10 mol%), benzophenone cyanohydrin (2 equiv.), and benzaldehyde (1 equiv.) in dry toluene at the specified temperature for 3–32 h.

[b] Isolated yield.

[c] THF was used as solvent.

[d] Acetone cyanohydrin was used as cyanide source.



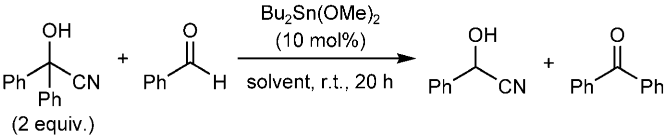
Scheme 1. $Bu_2Sn(OMe)_2$-catalyzed cyano transfer from benzophenone cyanohydrin to aldehydes and imines.

allyl transfer reaction.[7] We attempted to react benzaldehyde with benzophenone cyanohydrin in the presence of Bu_2SnO in toluene at 100 °C for 3 h, but were not able to obtain the target benzaldehyde cyanohydrin at all (entry 1, Table 1). Then, we tested the catalytic ability of Bu_2SnBr_2, which effectively catalyzes the trimethylsilylcyanation of aldehydes,[8] but the reaction did not proceed in both toluene and THF (entries 2 and 3). Surprisingly, $Bu_2Sn(OMe)_2$ promoted the cyano transfer.[9] When benzaldehyde was treated with two equivalents of benzophenone cyanohydrin under the influence of 10 mol% of $Bu_2Sn(OMe)_2$ in toluene at room temperature for 20 h, the desired adduct was formed in 66% yield (entry 4). Employment of acetone cyanohydrin in place of benzophenone cyanohydrin resulted in a significant deceleration of the cyano transfer (entry 5).

In order to improve the chemical yield, we next examined solvent effects (Table 2). Among the solvents used, diethyl ether gave a better result than toluene (compare entry 4 with entry 1). Dichloromethane, THF, and acetonitrile were less effective solvents in the present cyanation (entries 2, 3, and 5).

The alkyl substituents of an organotin dimethoxide are considered to affect its electronic and/or steric properties. Thus, we further carried out the screening of organotin dimethoxides, that were generated *in situ* from the corresponding dialkyltin dihalides (X = Cl or Br) and sodium methoxide, in the reaction involving cyano transfer from benzophenone cyanohydrin to benzaldehyde in diethyl ether (Table 3). As a result, $Me_2Sn(OMe)_2$ exhibited higher reactivity than $Bu_2Sn(OMe)_2$ (compare entry 1 with entry 2). There seems to be essentially no difference in reactivity between commercially available $Bu_2Sn(OMe)_2$ and the *in situ* prepared one (entries 2 and 3). A bulky organotin dimethoxide also efficiently catalyzed the reaction (entry 5), whereas $Ph_2Sn(OMe)_2$ afforded the desired product in low yield (entry 4). Based on these results, we concluded that commercial dibutyltin dimethoxide is the tin catalyst of choice because its catalytic activity is almost equivalent to that of the *in situ* generated dialkyltin dimethoxide, and it is easy to handle.

Table 2. Solvent effect on the cyano transfer from benzophenone cyanohydrin to benzaldehyde catalyzed by $Bu_2Sn(OMe)_2$.[a]

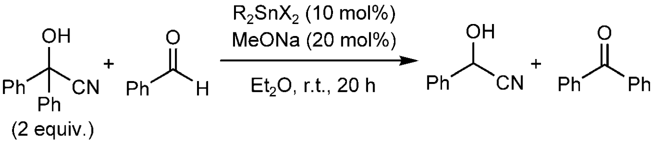


Entry	Solvent	Yield [%][b]
1	toluene	66
2	CH_2Cl_2	58
3	THF	42
4	Et_2O	74
5	MeCN	58

[a] The reaction was performed using $Bu_2Sn(OMe)_2$ (10 mol%), benzophenone cyanohydrin (2 equiv.), and benzaldehyde (1 equiv.) in a specified dry solvent at room temperature for 20 h.

[b] Isolated yield.

Table 3. Screening of organotin dimethoxide catalysts for the cyano transfer from benzophenone cyanohydrin to benzaldehyde.[a]



Entry	R	X	Yield [%][b]
1	Me	Cl	84
2	Bu	Br	72
3[c]	Bu	–	74
4	Ph	Cl	45
5	Bn	Br	76

[a] Unless otherwise noted, the reaction was performed using R_2SnX_2 (10 mol%), MeONa (20 mol%), benzophenone cyanohydrin (2 equiv.), and benzaldehyde (1 equiv.) in dry diethyl ether at room temperature for 20 h.

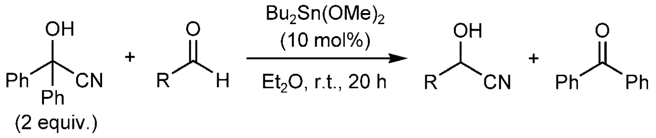
[b] Isolated yield.

[c] Commercial $Bu_2Sn(OMe)_2$ was used as an organotin dimethoxide catalyst.

With the optimized catalyst and solvent in hand, we performed the cyano transfer from benzophenone cyanohydrin to various aldehydes. The results are summarized in Table 4. Not only aromatic aldehydes but an α,β-unsaturated aldehyde and aliphatic aldehydes also underwent the cyanation under conventional reaction conditions and the corresponding cyanohydrins were obtained in moderate to high yields. The substituent at the *para*-position of benzaldehyde to a large extent influenced its reactivity (compare entries 2–4 with entry 1). As for the *p*-trifluoromethyl derivative, the isolated yield of the product reached 90% (entry 3). In the reaction with cinnamaldehyde, a 1,2-adduct was formed predominantly (entry 9).

The above-mentioned results further prompted us to use $Bu_2Sn(OMe)_2$ as a catalyst for the cyano transfer from benzophenone cyanohydrin to aldimines. Treatment of *N*-benzylideneaniline (1 equiv.) with benzophenone cyanohydrin (2 equiv.) in the presence of dibutyltin dimethoxide (10 mol%) in diethyl ether at 40 °C for 20 h gave the target α-amino nitrile in 94% combined yield (Table 5, entry 1). Then, we attempted the cyanation of diverse aldimines under these reaction conditions and Table 5 shows selected examples. Worthy of note is that the reaction with electron-rich imines gave reactivities that were higher

Table 4. $Bu_2Sn(OMe)_2$-catalyzed cyano transfer from benzophenone cyanohydrin to various aldehydes.[a]

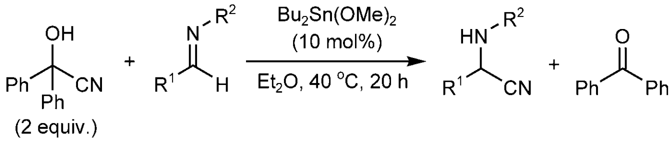


Entry	R	Yield [%][b]
1	Ph	74
2	4-$NO_2C_6H_4$	65
3	4-$CF_3C_6H_4$	90
4	4-$MeOC_6H_4$	29
5	2-$MeOC_6H_4$	50
6	1-naphthyl	84
7	2-naphthyl	59
8	2-thienyl	32
9	(*E*)-PhCH=CH	45
10	$PhCH_2CH_2$	90
11	*n*-C_5H_{11}	64
12	*c*-C_6H_{11}	87

[a] The reaction was performed using $Bu_2Sn(OMe)_2$ (10 mol%), benzophenone cyanohydrin (2 equiv.), and aldehyde (1 equiv.) in dry ether at room temperature for 20 h.

[b] Isolated yield.

Table 5. $Bu_2Sn(OMe)_2$-catalyzed cyano transfer from benzophenone cyanohydrin to various aldimines.[a]



Entry	R^1	R^2	Yield [%][b]
1	Ph	Ph	94
2	4-$MeOC_6H_4$	Ph	>99
3	2-$MeOC_6H_4$	Ph	>99
4	4-$CF_3C_6H_4$	Ph	73
5	1-naphthyl	Ph	86
6	2-furyl	Ph	96
7	4-$MeOC_6H_4$	4-BrC_6H_4	93
8	Ph	4-$MeOC_6H_4$	97
9	Ph	4-BrC_6H_4	83

[a] The reaction was performed using $Bu_2Sn(OMe)_2$ (10 mol%), benzophenone cyanohydrin (2 equiv.), and aldimine (1 equiv.) in dry diethyl ether at 40 °C for 20 h.

[b] Isolated yield.

than that of the reaction with *N*-benzylideneaniline (compare entries 2, 3, and 8 with entry 1) and an almost quantitative yield was attained in the case of 4-MeO and 2-MeO derivatives (entries 2 and 3). In contrast, electron-deficient imines gave the corresponding cyanated products in low yields (entries 4 and 9). Furthermore, we investigated the reactivity of ketimines derived from ketones and aniline under the conventional reaction conditions (40 °C, 20 h) and found that their reaction with benzophenone cyanohydrin proceeded smoothly to afford the desired products in satisfactory yields (Scheme 2).

We further applied the present catalytic process to a three-component cyano transfer from benzophenone cyanohydrin to *in situ* generated aldimines. The three-component coupling procedure that employs a cyanide source, an aldehyde, and an amine is superior to the two-component one that employs a cyanide source and an imine because the former does not require the tedious preparation of imines and is applicable to unstable imines. Under the typical reaction conditions for the two-component coupling procedure, good chemical yields were obtained when a mixture of benzophenone cyanohydrin (2 equiv.), an aldehyde (1 equiv.), and aniline (1 equiv.) was treated with 10 mol% of $Bu_2Sn(OMe)_2$ in the presence of Drierite® as a drying agent in ether at 40 °C for 20 h (entries 1 and 2 in Table 6).

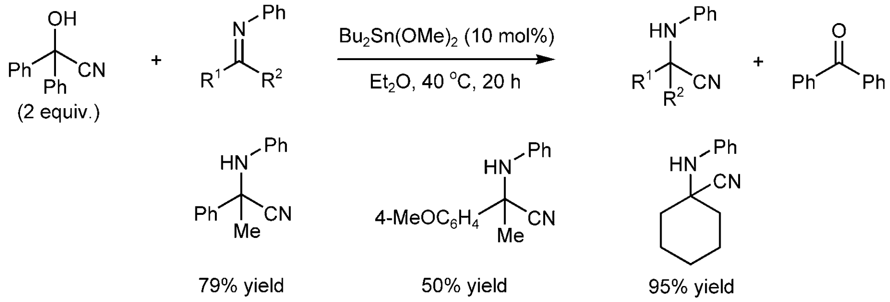
A plausible catalytic mechanism for the cyano transfer to aldehydes is illustrated in Figure 1. First of all, $Bu_2Sn(OMe)_2$ reacts with benzophenone cyanohydrin to yield the tin alkoxide of cyanohydrin **1** and MeOH. Tin alkoxide **1** then coordinates with aldehyde **2** to afford the tin alkoxide-aldehyde complex **3**. This is followed by the intramolecular cyano transfer to the aldehyde to give the tin alkoxide of cyanohydrin **4** and benzophenone. Finally, protonation of tin alkoxide **4** with benzophenone cyanohydrin results in the formation of the desired product **5** and the regeneration of the tin alkoxide of cyanohydrin **1**.

In summary, we have presented an example of a cyano transfer from benzophenone cyanohydrin to aldehydes and imines catalyzed by $Bu_2Sn(OMe)_2$. The main features of the present reaction are as follows: (i) it employs readily available chemicals and can provide various cyanohydrins and α-amino nitriles in high yields of up to 99%; (ii) ketimines can be also converted into the corresponding α-aminonitriles by applying this reaction; and (iii) a three-component coupling procedure has been developed for α-aminonitrile synthesis as a more efficient alternative.

Experimental Section

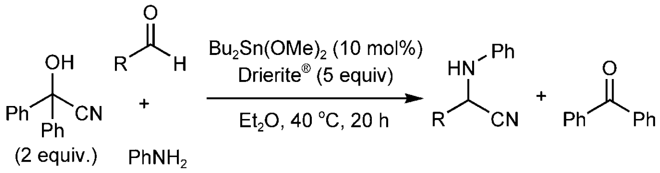
General Remarks

Column chromatography was conducted with 63–230 mesh silica gel. All experiments were carried out under an atmosphere of standard grade argon gas (oxygen <10 ppm). Benzophenone cyanohydrin was prepared by treating benzophenone with trimethylsilyl cyanide in the presence of a catalytic amount of ZnI_2 in CH_2Cl_2 followed by acid hydrolysis (3N HCl/THF).[10] Aldimines were prepared from the corresponding aldehydes and amines in the presence of anhy-



Scheme 2. $Bu_2Sn(OMe)_2$-catalyzed cyano transfer from benzophenone cyanohydrin to ketimines.

Table 6. Three-component cyano transfer from benzophenone cyanohydrin to *in situ* generated aldimines catalyzed by $Bu_2Sn(OMe)_2$.[a]



Entry	R	Yield [%][b]
1	Ph	78
2	(*E*)-PhCH=CH	72

[a] The reaction was performed using $Bu_2Sn(OMe)_2$ (10 mol%), benzophenone cyanohydrin (2 equiv.), aldehyde (1 equiv.), aniline (1 equiv.), and Drierite® (5 equiv.) in dry ether at 40 °C for 20 h.

[b] Isolated yield.

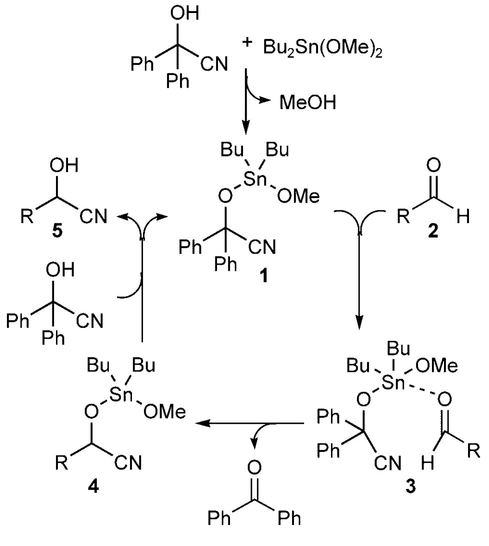


Figure 1. Plausible catalytic mechanism for the cyano transfer to aldehydes catalyzed by $Bu_2Sn(OMe)_2$.

drous $MgSO_4$ in dry THF. Other chemicals were used as purchased.

Caution! HCN is generated through the present catalytic reactions

Typical Experimental Procedure for Cyano Transfer from Benzophenone Cyanohydrin to Aldehydes: Synthesis of 2-Hydroxy-2-phenylacetonitrile (entry 4 in Table 2, entry 3 in Table 3, entry 1 in Table 4)[11]

A mixture of benzophenone cyanohydrin (209.2 mg, 1.0 mmol) and benzaldehyde (51 μL, 0.50 mmol) was dissolved in dry diethyl ether (2 mL) under an argon atmosphere. To the resulting solution was added dibutyltin dimethoxide (11.5 μL, 0.050 mmol) at room temperature. After stirring for 20 h at this temperature, the mixture was concentrated under vacuum. The residual crude product was purified by column chromatography on silica gel to afford 2-hydroxy-2-phenylacetonitrile; yield: 49.0 mg (74%).

Typical Experimental Procedure for Cyano Transfer from Benzophenone Cyanohydrin to Imines: Synthesis of 2-(*N*-Anilino)-2-phenylacetonitrile (entry 1 in Table 5)[12]

A mixture of benzophenone cyanohydrin (209.2 mg, 1.0 mmol) and *N*-benzylideneaniline (90.6 mg, 0.50 mmol) was dissolved in dry diethyl ether (2 mL) under an argon atmosphere. To the resulting solution was added dibutyltin dimethoxide (12.0 μL, 0.052 mmol) at room temperature. After stirring for 20 h at 40 °C, the mixture was concentrated under vacuum. The residual crude product was purified by column chromatography on silica gel to afford 2-(*N*-anilino)-2-phenylacetonitrile; yield: 97.9 mg (94%).

Typical Experimental Procedure for Three-component Cyano Transfer from Benzophenone Cyanohydrin to *in situ* Generated Aldimines: Synthesis of 2-(*N*-Anilino)-2-phenylacetonitrile (entry 1 in Table 6)[12]

A mixture of benzaldehyde (51 μL, 0.50 mmol), aniline (46 μL, 0.50 mmol), and Drierite® (340.4 mg, 2.5 mmol) in dry diethyl ether (2 mL) was stirred under an argon atmosphere at room temperature for 30 min. To the resulting solution were added benzophenone cyanohydrin (209.2 mg, 1.0 mmol) and dibutyltin dimethoxide (12.0 μL, 0.052 mmol) in that order. After stirring for 20 h at 40 °C, the mixture was concentrated under vacuum. The residual crude product was purified by column chromatography on silica gel to afford 2-(*N*-anilino)-2-phenylacetonitrile; yield: 81.5 mg (78%).

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Priority Area "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We also thank Professor Takayoshi Arai at Chiba University for helpful discussions.

References

[1] Reviews of cyanation of aldehydes: a) M. North, *Synlett* **1993**, 807; b) F. Effenberger, *Angew. Chem.* **1994**, *106*, 1609; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555; c) R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649; d) M. North, *Tetrahedron: Asymmetry* **2003**, *14*, 147. Reviews of cyanation of imines: e) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; f) H. Gröger, *Chem. Rev.* **2003**, *103*, 2795; g) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491.

[2] Reviews: a) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989; b) J.-M. Brunel, I. P. Holmes, *Angew. Chem.* **2004**, *116*, 2810; *Angew. Chem. Int. Ed.* **2004**, *43*, 2752; c) T. R. J. Achard, L. A. Clutterbuck, M. North, *Synlett* **2005**, 1828. See also ref.[1g] For a catalytic addition of Me_3SiCN to ketones, see: d) Y. Li, B. He, X. Feng, G. Zhang, *Synlett* **2004**, 1598; e) B. He, Y. Li, X. Feng, G. Zhang, *Synlett* **2004**, 1776; f) F.-X. Chen, X. Feng, *Synlett* **2005**, 892; g) L. Wang, X. Huang, J. Jiang, X. Liu, X. Feng, *Tetrahedron Lett.* **2006**, *47*, 1581. For a catalytic Strecker reaction using Me_3SiCN, see: h) Y. Wen, Y. Xiong, L. Chang, J. Huang, X. Liu, X. Feng, *J. Org. Chem.* **2007**, *72*, 7715.

[3] A. Watanabe, K. Matsumoto, Y. Shimada, T. Katsuki, *Tetrahedron Lett.* **2004**, *45*, 6229.

[4] T. Ooi, K. Takaya, T. Miura, H. Ichikawa, K. Maruoka, *Synlett* **2000**, 1133.

[5] Y. Kawasaki, A. Fujii, Y. Nakano, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **1999**, *64*, 4214.

[6] A. S. Paraskar, A. Sudalai, *Tetrahedron Lett.* **2006**, *47*, 5759.

[7] A. Yanagisawa, T. Aoki, T. Arai, *Synlett* **2006**, 2071.

[8] A. Yanagisawa, T. Matsumoto, T. Arai, K. Yoshida, *Chem. Lett.* **2009**, *38*, 336.

[9] $Bu_2Sn(OMe)_2$ acts as an efficient catalyst for the aldol reaction of alkenyl trichloroacetates: A. Yanagisawa, T. Sekiguchi, *Tetrahedron Lett.* **2003**, *44*, 7163.

[10] P. G. Gassman, J. J. Talley, *Tetrahedron Lett.* **1978**, 3773.

[11] W.-B. Yang, J.-M. Fang, *J. Org. Chem.* **1998**, *63*, 1356.

[12] Z.-L. Shen, S.-J. Ji, T.-P. Loh, *Tetrahedron* **2008**, *64*, 8159.