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Direct Catalytic Aldol-Type Reactions Using RCH_2CN

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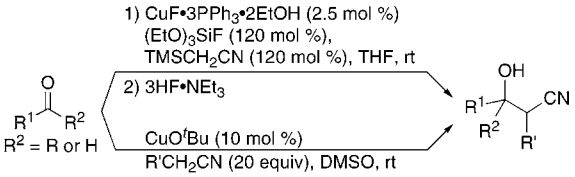
ABSTRACT

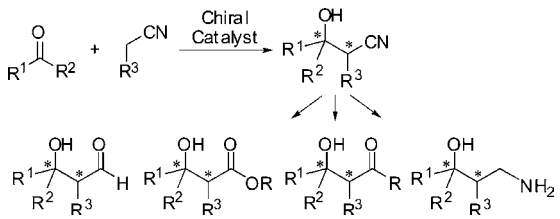


A copper fluoride-catalyzed cyanomethylation that can be applied to a wide range of ketones and aldehydes was developed using $TMSCH_2CN$ as a nucleophile. The reaction was extended to a conceptually more advanced copper alkoxide-catalyzed direct addition of alkylnitriles to aldehydes, which can act as a surrogate direct catalytic aldol reaction of esters. These reactions can be applied to the first catalytic enantioselective cyanomethylation of ketones and direct catalytic enantioselective cyanomethylation of aldehydes.

Because of the versatility of the nitrile group, cyanomethylation of carbonyl compounds is a surrogate ester enolate aldol reaction. The product, β-hydroxy nitriles, can be easily converted to useful building blocks, such as β-hydroxycarboxylic acid derivatives and γ-amino alcohols.[1] During our development of a direct catalytic enantioselective aldol reaction (catalytic on metal),[2,3] we focused on the use of alkylnitriles as donors (Scheme 1). Alkylnitriles contain an α-proton with a pK_a value close to that of an acetylenic proton (∼25),[4] which should be more easily deprotonated via an interaction of the nitrile with a soft Lewis acid. A strong interaction between a nitrile and a soft metal would be advantageous for chemoselective deprotonation in the presence of aliphatic aldehydes. We report here the CuO^{t}Bu-catalyzed direct aldol-type addition of alkylnitriles to aldehydes. This reaction was developed on the basis of the CuF-catalyzed cyanomethylation of ketones and aldehydes using $TMSCH_2CN$ as a nucleophile. These two reactions can, in principle, be extended to catalytic enantioselective aldol-type reactions.

Examples of the catalytic cyanomethylation reactions are significantly more scarce than those of catalytic aldol reactions: Palomo et al. reported a TASF- or alkaline metal alkoxide-catalyzed cyanomethylation using $TMSCH_2CN$ as a nucleophile.[5] More recently, Verkade et al. reported a direct

Scheme 1. Direct Catalytic Enantioselective Addition of Nitriles



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[‡] PRESTO.

(1) For examples of cyanomethylation in natural product synthesis, see: (a) Corey, E. J.; Wu, Y.-J. *J. Am. Chem. Soc*. **1993**, *115*, 8871. (b) Fukuda, Y.; Okamoto, Y. *Tetrahedron* **2002**, *58*, 2513.

(2) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc*. **1999**, *121*, 4168.

(3) For a review on direct catalytic enantioselective aldol reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573.

(4) For a direct catalytic enantioselective alkynylation, see: Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.

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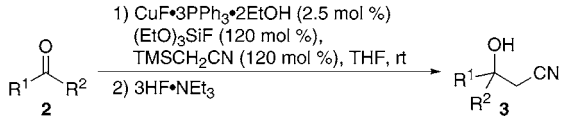
addition of acetonitrile to aldehydes and ketones using proazaphosphatranes as a Brönsted base catalyst in the presence of magnesium sulfate.[6] In these precedent examples, however, the substrate generality is not necessarily high, especially for ketones. There is only one catalytic enantioselective cyanomethylation of an aldehyde reported so far, using cyanomethylzinc bromide as a nucleophile.[7]

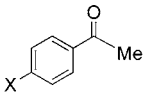
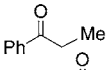
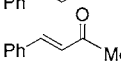
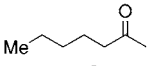
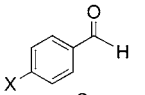
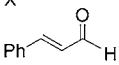
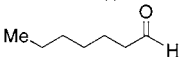
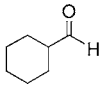
We first planned to develop a general catalytic cyanomethylation method using $TMSCH_2CN$, on the basis of our recent findings of the CuF-catalyzed aldol reaction for ketones using ketene trimethylsilyl acetal as a nucleophile.[8] In this reaction, a stoichiometric addition of $(EtO)_3SiF$ was the key for generating the active catalyst, $[(EtO)_3SiF_2]^-\cdot[Cu(PPh_3)_3]^+$ (**1**), as well as the catalyst turnover. The fluoride transfer from **1** to trimethylsilyl enolate initiates the catalytic cycle, which induces active copper enolate formation through a dynamic ligand exchange between silicon and copper atoms. The highly robust feature of the reaction prompted us to investigate the catalytic cyanomethylation of ketones using $TMSCH_2CN$ as a nucleophile. A possible difficulty was the higher stability of $TMSCH_2CN$ against fluoride activation (C−Si activation) compared to that of trimethylsilyl enolates (O−Si activation).[9]

When we applied the optimized aldol reaction conditions to cyanomethylation of *p*-methoxyacetophenone (**2d**) [2.5 mol % CuF·3PPh$_3$·2EtOH,[10] 120 mol % $(EtO)_3SiF$, THF as a solvent at room temperature for 24 h], the reaction did not go to completion and product **3d** was obtained in only 40% yield after deprotection.[11] Kinetic studies of the aldol reaction indicated that a silyl enolate is an inhibitor of the reaction.[8] The initial reaction rate possesses an order of −0.8 with regard to the silyl enolate concentration. On the basis of the analogy of the cyanomethylation to the aldol reaction, we expected that a slow addition of $TMSCH_2CN$, keeping the silicon concentration sufficiently low, would improve reactivity. As expected, the yield of **3d** improved to 75% when $TMSCH_2CN$ was added slowly (4.5 h)[12] to a solution of the catalyst, $(EtO)_3SiF$, and **2d** (Table 1, entry 4).

Under the optimized reaction conditions, the present catalytic cyanomethylation was generally applicable to a wide range of ketones and aldehydes (Table 1).[13] For reactive substrates such as **2a** and **2b** (entries 1 and 2) or aldehydes (entries 8−12), high yields were obtained even under a one portion addition of $TMSCH_2CN$. Specifically, the reaction

Table 1. CuF-Catalyzed Cyanomethylation by $TMSCH_2CN$



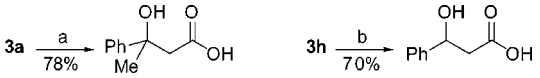
entry	substrate		time (h)	yield (%)[a]
1		X = H (**2a**)	12	93
2		X = Cl (**2b**)	2.5	92
3[b]		X = Me (**2c**)	24	80
4[b]		X = OMe (**2d**)	24	75
5[b]		**2e**	24	75
6[c]		**2f**	6	98
7[b]		**2g**	24	79
8		X = H (**2h**)	1.5	100
9		X = OMe (**2i**)	24	96
10		**2j**	1.5	92
11		**2k**	4	80
12		**2l**	6	86

[a] Isolated yield. [b] $TMSCH_2CN$ was added slowly over 4.5 h. [c] $TMSCH_2CN$ was added slowly over 1 h.

can be applied to an ethyl-substituted aromatic ketone **2e**, an enone **2f**, and an easily enolizable linear aldehyde **2k**.[14] Thus, this is the first example of a general catalytic cyanomethylation of carbonyl compounds.

The conversion of the cyanomethylation products to *β*-hydroxycarboxylic acids was straightforward through hydrolysis under basic conditions.[15] The results indicate the equivalency of the cyanomethylation products to aldol products (Scheme 2).

Scheme 2. Hydrolysis of the Cyanomethylation Products[a]



[a] Conditions: (a) 3 M NaOH (aq)/30% H_2O_2 (aq), rt, 1 h; 35−45 °C, 15 h. (b) 3 M NaOH (aq)/30% H_2O_2 (aq), rt, 14 h.

Although investigations to clarify the reaction mechanism are currently ongoing, we propose the working hypothesis

(5) Palomo, C.; Aizpurua, J. M.; López, M. C.; Lecea, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1692.

(6) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 3090.

(7) Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron: Asymmetry* **1992**, *3*, 677. The product with 78% ee was obtained in 45% yield, using 30 mol % catalyst (only one example from benzaldehyde).

(8) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644.

(9) Allyltrimethylsilane is not reactive under conditions reported in ref 8; however, allyltrimethoxysilane can react with carbonyl compounds: Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. The degree of C−Si polarization should be larger in $TMSCH_2CN$ than in allyltrimethylsilane.

(10) Gulliver, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, *52*, 153.

(11) Initial product was the corresponding triethoxysilyl ether.

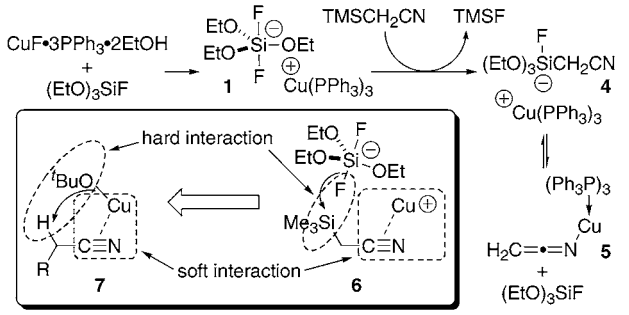
(12) Slow addition time is important for high chemical yield. See Supporting Information (SI) for details.

(13) **General Procedure for Copper Fluoride-Catalyzed Cyanomethylation by $TMSCH_2CN$ (Table 1, Entry 6).** To a solution of CuF·3PPh$_3$·2EtOH (9.6 mg, 0.01 mmol) in THF (0.4 mL) were added **2f** (58.5 mg, 0.40 mmol) and $(EtO)_3SiF$ (89 μL, 0.48 mmol) in an ice bath. To the mixed solution was added $TMSCH_2CN$ (66 μL, 0.48 mmol) slowly over 1 h with a syringe pump. After 6 h, 3HF·NEt$_3$ (0.3 mL) was added for desilylation (ca. 1 h).

(14) There are no previous examples of catalytic cyanomethylation of linear aldehydes, propiophenone, or enones.

(15) Davis, F. A.; Reddy, G. V.; Chen, B.-C.; Kumar, A.; Haque, M. S. *J. Org. Chem.* **1995**, *60*, 6148.

Scheme 3. Working Hypothesis of $TMSCH_2CN$ Activation by Fluorosilicate **1** (C−Si Activation) and Its Analogy to Deprotonation

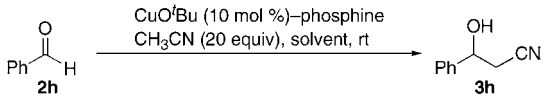


shown in Scheme 3, on the basis of the mechanism underlying the aldol reaction with ketones.[8] The first step should be ligand redistribution between silicate **1** and $TMSCH_2CN$ to give TMSF and silicate **4**.[16] The stable carbon−silicon bond is cleaved in this step. This is possible only by polarization of the carbon−silicon bond through coordination of the nitrile to the copper (**6**). The importance of the nitrile−copper interaction was suggested by the fact that the aldol reaction between *tert*-butyl α-*C*-trimethylsilyl acetate and acetophenone did not proceed under the present reaction conditions. Silicate **4** would exist under equilibrium with *N*-copper ketenimide **5**, which would be the actual nucleophile.

The unique carbon−silicon bond activation step requires a focused discussion (Scheme 3, **6**). The high catalyst activity of **1** stems partly from the combination of a hard nucleophile (fluorosilicate) and a soft Lewis acid (Cu^+). The soft Lewis acid interacts with the soft nitrile of $TMSCH_2CN$ to polarize the α-carbon−silicon bond. Concomitant nucleophilic attack of the hard fluorosilicate onto the hard silicon atom of $TMSCH_2CN$ then leads to the facile activation of the intrinsically stable carbon−silicon bond. If another hard nucleophile (or Brönsted base)−soft Lewis acid combination (i.e., CuO^tBu[17]) is used, it might be possible to activate (i.e., deprotonate) simple alkylnitriles (Scheme 3, **7**). The soft interaction between copper and the nitrile should polarize the α-carbon−hydrogen bond of alkylnitriles and thus acidify the α-proton, while the hard alkoxide should attack the hard α-proton. This led us to investigate the conceptually more advanced direct catalytic addition of alkylnitriles.

Reaction conditions of the direct catalytic cyanomethylation were optimized for the acetonitrile (20 equiv) addition to benzaldehyde at room temperature in the presence of 10 mol % CuO^tBu and various phosphine ligands (Table 2).[18] The yield was improved using electron-rich phosphine ligands in polar solvents. The best results were obtained using

Table 2. Optimization of Direct Catalytic Cyanomethylation of Benzaldehyde



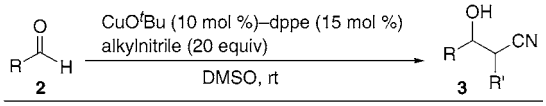
entry	phosphine (mol %)	solvent	time	yield[a]
1	Ph_3P (30)	THF	48	27
2	Bu_3P (30)	THF	48	34
3	$^c Hex_3P$ (30)	THF	48	34
4	$^t Bu_3P$ (30)	THF	48	17
5	$^c Hex_3P$ (30)	DMF	3	68
6	$^c Hex_3P$ (30)	^{t}BuOH	3	54
7	$^c Hex_3P$ (30)	CH_2Cl_2	24	3
8	dppe (15)	DMF	6	95
9	dppe (15)	DMSO	2	95

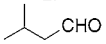
[a] Isolated yield.

a bidentate phosphine ligand (dppe) in DMSO solvent (entry 9), and the product was obtained in 95% yield in 2 h. This high reactivity should, in part, be due to the unique combination of the soft metal and hard alkoxide, because hard metal-containing bases (that generate hard metal aldolates during the reaction) such as KO^{t}Bu, KHMDS, NaHMDS, LiHMDS, and La(O^{i}Pr)$_3$ (10 mol %) could not efficiently promote the reaction (0−39% yield).

Substrate generality was investigated under the optimized reaction conditions (Table 3). High to excellent chemical

Table 3. Direct Catalytic Addition of Alkylnitriles



entry	substrate	alkylnitrile	time (h)	yield (%)[a]
1	**2h**	CH_3CN	2	95
2[b]	**2h**	CH_3CN	6	81
3	**2j**	CH_3CN	2	78
4	**2l**	CH_3CN	2	71
5	 **2m**	CH_3CN	2	71
6	**2h**	CH_3CH_2CN	2	90[c]
7	**2h**	$CH_3CH_2CH_2CN$	4	76[d]

[a] Isolated yield. [b] Performed using 5 mol % CuO^tBu, 7.5 mol % dppe, and 5 equiv CH_3CN. [c] Diastereomer ratio is 1.5:1 (syn major).[21] [d] Diastereomer ratio is 1.6:1 (syn major).[22]

yields were obtained from aromatic aldehydes, α,β-unsaturated aldehyde, and aliphatic aldehydes.[19] The applicability to the addition of other alkylnitriles such as propionitrile and butyronitrile is noteworthy, although the diastereoselectivity (1.5:1−1.6:1) remains to be optimized.[20]

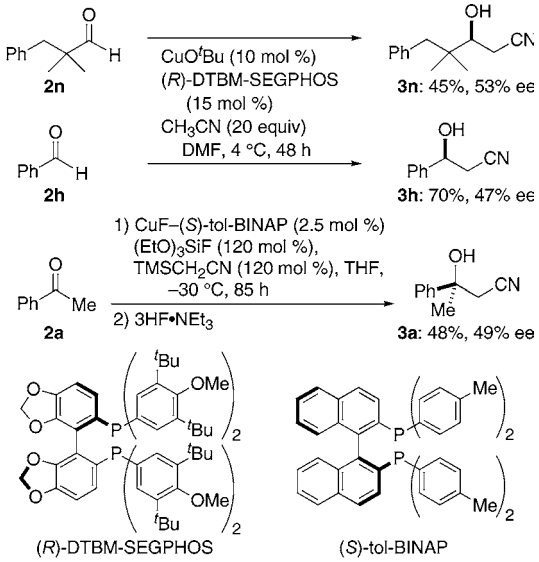
(16) Generation of TMSF in this step was confirmed by ^{1}H and ^{19}F NMR.

(17) Alkaline metal free CuO^tBu was prepared by adding 1 equiv of ^{t}BuOH to mesitylcopper generated by Saegusa's method: Tsuda, T.; Watanabe, K.; Miyata, K.; Yamamoto, H.; Saegusa, T. *Inorg. Chem.* **1981**, *20*, 2728. CuO^tBu can be stored as a THF solution (0.5 M) at −30 °C in a freezer under an argon atmosphere for at least two months without any activity loss.

(18) In the previous study of ketone aldol reaction (ref 8), we noticed the importance of the phosphine ligand in the catalyst turnover step, in which a copper aldolate traps the silicon to form the silyl aldolate. This step might mimic the alkylnitrile deprotonation by the copper aldolate in the direct catalytic addition.

The described reactions could, in principle, be extended to catalytic enantioselective reactions using chiral diphosphines as ligands (Scheme 4). Using the CuF−(*S*)-tol-BINAP complex (2.5 mol %) led to the addition of $TMSCH_2CN$ to **2a** at −30 °C in THF, and **3a** was obtained in 49% ee. Using the CuO^{t}Bu-(*R*)-DTBM-SEGPHOS[23] complex (10 mol %) led to the direct catalytic enantioselective cyanomethylation of aldehydes, and the products were obtained with up to 53% ee. Although the enantioselectivity is not in a satisfactory range, these reactions are the first examples of catalytic enantioselective cyanomethylation of ketones and direct catalytic enantioselective cyanomethylation of aldehydes. Specifically, considering the equivalency of the cyanomethylation products to the aldol products, the latter reaction would be considered as a direct catalytic enantioselective aldol reaction using a donor containing the carboxylic acid oxidation state.[24] The donor (acetonitrile), the substrate (aldehyde), and a catalytic amount of the chiral metal complex are required, and the overall reaction is a simple proton transfer from the donor to the acceptor.

Scheme 4. Application to Direct Catalytic Enantioselective Cyanomethylation of Aldehydes and Catalytic Enantioselective Cyanomethylation of Ketones



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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035206U

(19) **General Procedure for CuO^{t}Bu-Catalyzed Direct Cyanomethylation of Aldehyde (Table 3, Entry 6).** CuO^{t}Bu (0.03 mmol, 60μL in THF) and dppe (18 mg, 0.045 mmol) were mixed and dried under vacuum for 1 h. To the residue were added DMSO (0.3 mL), propionitrile (0.3 mL), and **2h** (30 μL, 0.3 mmol) to start the reaction.

(20) Catalytic addition of alkylnitriles other than acetonitrile is novel. The reaction with ketones has not yet been achieved.

(21) Canceill, J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1970**, 2180.

(22) Gotor, V.; Dehli, J. R.; Rebolledo, F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 307.

(23) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(24) For recent advances, see: (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2001**, *124*, 392. (b) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127. (c) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706.