

RSC Advances



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

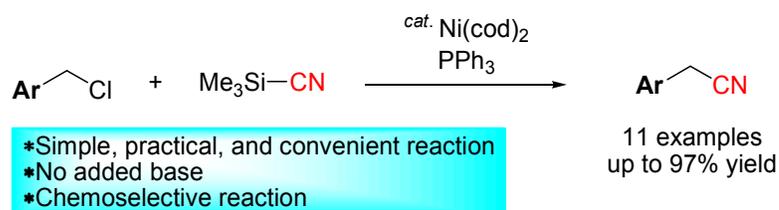
Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Table of Contents

Simple and practical method of cyanation reaction of benzyl chlorides and trimethylsilyl cyanide was achieved, using Ni(cod)₂/PPh₃ catalyst system, to give arylacetonitriles.



Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Synthesis of arylacetonitrile derivatives: Ni-catalyzed reaction of benzyl chlorides with trimethylsilyl cyanide under base-free conditions[†]

Yasushi Satoh and Yasushi Obora*

Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

DOI: 10.1039/b000000x

We developed a simple strategy for the synthesis of arylacetonitriles from benzyl chlorides and trimethylsilyl cyanide using a Ni(cod)₂/PPh₃ catalyst.

Arylacetonitriles are very important units for synthesizing 10 carboxylic acids, amides, aldehydes, and azaheterocyclic compounds.¹ Additionally, these compounds are key structures in many natural products and biologically active substances,² including verapamil, anastrozole, cilomilast, and piritramide (Figure 1). Furthermore, transformation of 15 arylacetonitriles using transition-metal catalysts has been investigated,^{3–5} such as cycloaddition of alkynes and nitriles,³ carbocyanation of alkynes,⁴ and synthesis of 3,4-disubstituted 2-aminonaphthalenes and 1,3-benzoxazines by the Pd-catalyzed annulation of alkynes using (2-iodophenyl)acetonitriles.⁵ 20 Arylacetonitriles have attracted considerable attention from synthetic chemists for use in various reaction conditions.⁶

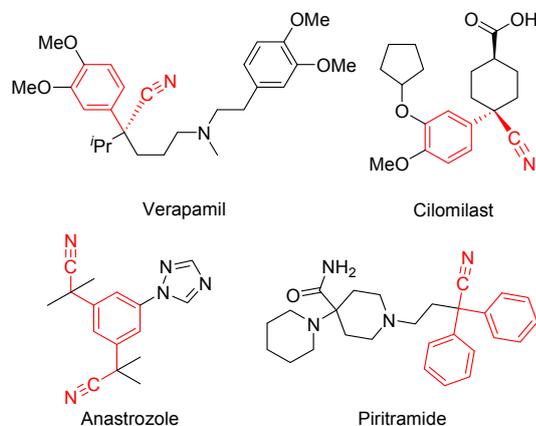


Fig. 1. Biologically active compounds containing arylacetonitriles (red).

A strategy for preparing arylacetonitriles from aryl halides using transition-metal catalysts has been reported.⁷ For example, cyanomethylation of aryl halides by the Pd-catalyzed reaction with 4-isoxazolyl boronate,^{7a} cyanoacetate 30 salts,^{7b} cyanoesters,^{7c} or trimethylsilylacetonitrile^{7d} used as the cyanomethyl source has been reported. Recently, Wang reported the cyanation of the benzylic position by the Cu-catalyzed reaction of benzyl chlorides with K₄[Fe(CN)₆] as the cyanating reagent.⁸ This cyanation reaction is attractive in 35 terms of using a non-toxic cyanating reagent. However, 4-

methoxybenzyl chloride and 1-phenylethyl chloride give the corresponding cyanation products in low yield (33% and 8%, respectively).

Alternatively, trimethylsilyl cyanide (TMSCN) has been 40 widely used as a cyanating reagent.⁹ Many reactions have been reported using TMSCN in the presence of transition-metal catalysts, such as trimethylsilylcyanation of aldehydes,^{9a} ketones,^{9a} and hydrazones,^{9b} conjugated addition of cyanide to enones,^{9c} aminocyanation of alkenes,^{9d} and hydrocyanative 45 cyclization of allene-ynes and bis-allenes.^{9e}

However, to our knowledge, transition-metal-catalyzed cyanation of benzyl halides with TMSCN has not been reported. The reaction of benzyl halides with TMSCN in the presence of a stoichiometric amount of tetrabutylammonium 50 fluoride (F⁻ source) to give benzyl cyanides via hypervalent silicate intermediates was reported by Deshong.¹⁰ However, this reaction requires a stoichiometric amount of strong base and some organic transformations are triggered by bases. Additionally, F⁻ also sets off various reactions involving 55 Hiyama coupling¹¹ and desilylation.¹²

In light of previous methods of cyanation, we have developed a reaction scheme for the cyanation of benzyl chlorides without base and F⁻. We herein describe a convenient synthetic method for producing arylacetonitriles 60 by the reaction of benzyl chlorides with TMSCN catalyzed by a Ni complex under base-free and mild conditions. Additionally, the reactants, catalysts, and ligands used are all commercially available compounds.

Initially, benzyl chloride (**1a**) and TMSCN (**2**) were used as 65 model reactants for the optimization of the cyanation reaction conditions, and the results are shown in Table 1. When **1a** (1 mmol) was reacted with **2** (2 mmol) in the presence of Ni(cod)₂ (0.1 mmol, 10 mol%) (cod: 1,5-cyclooctadiene) in toluene (1 mL) at 60 °C for 16 h, the reaction produced benzyl 70 cyanide (**3a**) in 29% yield (Table 1, entry 1). We next examined using Ni(cod)₂/PPh₃ as a catalyst and found that the reaction proceeded to give **3a** in 93% yield, as well as 1,2-diphenylethane in 6% yield (Table 1, entry 2). The results of the investigation of various ligands, such as phosphine ligands 75 (PPh₃, PCy₃, PCy₂Ph, dppe (ethylenebis(diphenylphosphine))), and dppf (1,1'-ferrocenebis(diphenylphosphine)), Table 1, entries 2–6), the 2,2'-bipyridyl ligand (Table 1, entry 7), and the NHC ligand (IMes, Table 1, entry 8), showed that the best ligand is PPh₃. It also should be noted that **3a** was not

obtained without catalyst and ligand (Table 1, entry 9).

We next examined Ni(0) precursors not containing Ni(cod)₂ for the reaction (Table 1, entries 10 and 11). When NiCl₂(PPh₃)₂/Zn¹³ and NiBr₂(DME)/Zn¹⁴ were used as the Ni(0) precursor in the reaction, benzyl cyanide (**3a**) was not obtained. When Pd(dba)₂ was used as the catalyst, the cyanation product **3a** was not formed (entry 12). In these reactions, benzyl chloride (**1a**) was observed by GC. Therefore, we selected Ni(cod)₂ as a model catalyst for the reaction.

Additionally, we found that the optimized reaction ratio of **1a**:**2a** was 1:4, with which **3a** was obtained in 97% yield with excellent chemoselectivity (Table 1, entry 13).

Under the optimized reaction conditions (Table 1, entry 13), we investigated the scope of the Ni-catalyzed cyanation reaction using various substituted benzyl chlorides (Table 2). Various electron-withdrawing and -donating groups at the *para* position of the benzyl chlorides were investigated (Table 2, entries 1–5).

Table 1 Optimization of model reaction^a

			
Entry	Catalyst	Ligand (x mmol)	Yield (%) ^b
1	Ni(cod) ₂	–	29
2 ^c	Ni(cod) ₂	PPh ₃ (0.2)	93
3	Ni(cod) ₂	PCy ₃ (0.2)	85
4 ^d	Ni(cod) ₂	PCy ₂ Ph (0.2)	89
5	Ni(cod) ₂	dppe (0.1)	77
6	Ni(cod) ₂	dppf (0.1)	55
7	Ni(cod) ₂	2,2-bipyridyl (0.1)	59
8	Ni(cod) ₂	IMes (0.1)	78
9	–	–	n.d. ^g
10 ^e	NiCl ₂ (PPh ₃) ₂ /Zn	PPh ₃ (0.2)	n.d. ^g
11 ^e	NiBr ₂ (DME)/Zn	PPh ₃ (0.2)	n.d. ^g
12	Pd(dba) ₂	PPh ₃ (0.2)	n.d. ^g
13 ^f	Ni(cod) ₂	PPh ₃ (0.2)	97(83)

^a Reaction conditions: **1a** (1 mmol), **2** (2 mmol), catalyst (0.1 mmol) and ligand (x mmol) in toluene (1 mL) at 60 °C for 16 h under Ar. ^b Yields were determined by gas chromatography on the basis of the quantity of **1a** used. The number in parentheses shows the isolated yield. ^c In addition to **3a**, 1,2-diphenylethane (6%) was formed. ^d The reaction was performed at 100 °C. ^e Zn (0.2 mmol) was used. ^f **2** (4 mmol) was used. dppe = Ethylenebis(diphenylphosphine), dppf = 1,1'-Ferrocenebis(diphenylphosphine), IMes = 1,3-Dimesitylimidazol-2-ylidene. ^g Not detected by GC.

4-Methylbenzyl chloride (**1b**), 4-(chloromethyl)anisole (**1c**), 4-fluorobenzyl chloride (**1d**), and methyl-4-(chloromethyl)benzoate (**1e**) were used in the reaction and the corresponding benzyl cyanide derivatives (**3b–3e**) were obtained in 85–96% yield (Table 2, entries 2–5).

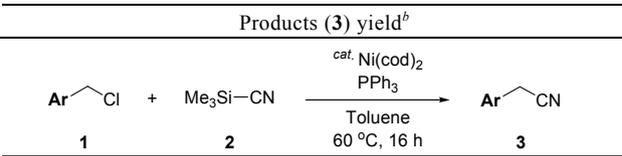
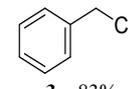
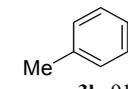
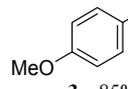
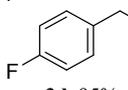
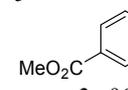
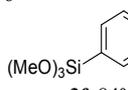
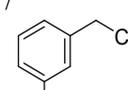
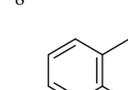
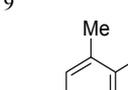
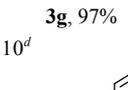
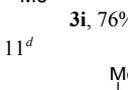
The reaction was successful using benzyl chloride with an alkoxy-silane substituent. When 4-(chloromethyl)phenyltrimethoxysilane (**3f**) was used, the

desired cyanation product (**3f**), which can be used in the Hiyama-coupling reaction, was obtained in 84% yield (Table 2, entry 6). It is noteworthy that the desilylation products were not all observed by gas chromatography because this reaction does not use base or acid.

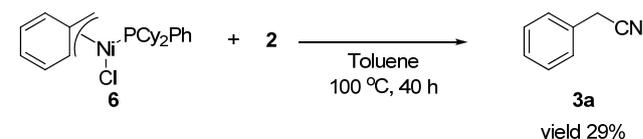
The position of the methyl substituent on the phenyl ring had an effect on the yield (Table 2, entries 2, 7–9). When 4-methylbenzyl chloride (**1b**) and 3-methylbenzyl chloride (**1g**) were used in place of benzyl chloride in this reaction, **1b** and **1g** smoothly converted to the desired benzyl cyanide derivatives. Benzyl chloride with *ortho*-Me substituents, such as 2-methylbenzyl chloride (**1h**) and 2,4,6-trimethylbenzyl chloride (**1i**), were applied to the reaction. 2-Methylbenzyl cyanide (**3h**) and 2,4,6-trimethylbenzyl cyanide (**3i**), were not obtained in high yield (72% and 76%, respectively) because of steric hindrance on the phenyl ring.

Additionally, 2-(chloromethyl)naphthalene (**1j**) was applied to the reaction, and the corresponding product (**3j**) was obtained in 96% yield (Table 2, entry 10). Furthermore, we found that 2-phenylpropanenitrile (**3k**) was obtained in 93% yield with excellent chemoselectivity (Table 2, entry 11).

Table 2 Scope of the reaction of **1** with **2**^a

			
1	2	3	Yield (%)
			3a , 83%
			3b , 91% 3c , 85% 3d , 95% 3e , 96% 3f , 84%
			3g , 97% 3h , 72% 3i , 76%
			3j , 96% 3k , 93%

^a For reaction conditions, see optimized conditions (Table 1, entry 13). ^b Isolated yields. ^c Dioxane (2 mL) was used as solvent. ^d The reaction was performed at 100 °C. ^e **2** (2 mmol) was used.



55

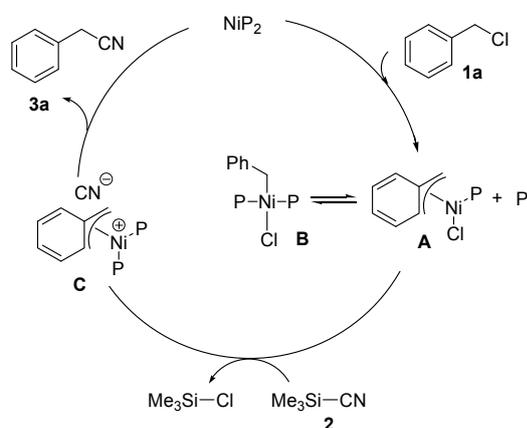
Previously, Jamison reported that Ni-catalyzed Heck-type reactions of benzyl chlorides with simple olefins gave functionalized allylbenzenes.¹⁵ This reaction initiates oxidative addition of benzyl chlorides to Ni(0) and forms the $\text{Ni}(\eta^3\text{-CH}_2\text{Ph})(\text{PCy}_2\text{Ph})\text{Cl}$ complex. Our developed cyanation method using benzyl chlorides might proceed in the same way.

Therefore, we performed the reaction of $\text{Ni}(\eta^3\text{-CH}_2\text{Ph})(\text{PCy}_2\text{Ph})\text{Cl}$ (**6**) (0.4 mmol) with TMSCN (**2**) (1.6 mmol) in toluene (3 mL) at 100 °C for 40 h to determine the reaction mechanism (Scheme 1). This reaction gave benzyl cyanide (**3**) in substantial yield (29%). The result of this experiment indicates that **6** is the intermediate of the cyanation reaction.

Based on these experiments, we propose the cyanation mechanism shown in Scheme 2. The reaction is initiated by oxidative addition of the $\text{NiP}_2(0)$ complex to benzyl chloride (**1a**) to form the $\text{Ni}(\eta^3\text{-CH}_2\text{Ph})(\text{dicyclohexylphosphine})\text{Cl}$ complex (**A**) and the $\text{Ni}(\eta^1\text{-CH}_2\text{Ph})\text{bis}(\text{dicyclohexylphosphine})\text{Cl}$ complex (**B**). In this case, **A** is more stable than **B**. Then, complex (**A**) rapidly reacts with trimethylsilyl cyanide (**2**), and the cross-coupling product (**3a**) is obtained via **C**. Furthermore, the reaction proceeds without base despite the existence of halogenated starting materials. We might expect that Me_3SiCl ¹⁶ is generated from the reaction of complex (**A**) with TMSCN (**2**).

In conclusion, we have discovered a practical, general, and efficient method for the synthesis of arylacetonitrile derivatives. This synthetic method is $\text{Ni}(\text{cod})_2/\text{PPh}_3$ -catalyzed cyanation of aryl chlorides with TMSCN under base- and F^- source-free condition to give arylacetonitriles with high chemoselectivity.

Scheme 2. Plausible reaction mechanism for the reaction of **1a** with **2**



This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, Kansai University, and MEXT-Supported Program for the Strategic Research Foundation at Private Universities (2010-2014).

Notes and references

Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Suita, Osaka 564-8680, Japan. Fax: +81-6-6339-4026; Tel: +81-6-6368-0876; E-mail: obora@kansai-u.ac.jp.

† Electronic Supplementary Information (ESI) available: Experimental procedures, and compound characterization data. See DOI:10.1039/b000000x/

- 1 K. Friedrich, and K. Wallenfels, *The Chemistry of the Cyano Group*, Wiley-Interscience, New York, 1970.
- 2 (a) F. F. Fleming, *J. Med. Chem.*, 2010, **53**, 7902.
- 3 Reviews for the synthesis of pyridines from transition-metals-catalyzed [2+2] cycloaddition reaction: (a) K. P. C. Vollhardt, *Angew. Chem.*, 1984, **96**, 525; *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 539; (b) H. Bönnemann, *Angew. Chem.*, 1985, **97**, 264; *Angew. Chem. Int. Ed. Engl.*, 1985, **24**, 248; (c) J. A. Varela and C. Saá, *Chem. Rev.*, 2003, **103**, 3787; (d) P. R. Chopade and J. Louie, *Adv. Synth. Catal.*, 2006, **348**, 2307; (f) G. Domínguez and J. Pérez-Castells, *Chem. Soc. Rev.*, 2011, **40**, 3430.
- 4 (a) A. Yada, T. Yukawa, Y. Nakao and T. Hiyama, *Chem. Commun.*, 2009, 3931; (b) A. Yada, T. Yukawa, H. Idei, Y. Nakao and T. Hiyama, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 619.
- 5 (a) Q. Tian, A. A. Pletnev and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 339.
- 6 (a) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi and G. Tocco, *Org. Lett.*, 2000, **2**, 1737; (b) V. N. Telvekar and R. A. Rane, *Tetrahedron Lett.*, 2007, **48**, 6051; (c) C. O. Kangani, B. W. Day and D. E. Kelley, *Tetrahedron Lett.*, 2008, **49**, 914; (d) G. Chen, Z. Wang, J. Wu and K. Ding, *Org. Lett.*, 2008, **10**, 4573.
- 7 (a) J. Velcicky, A. Soicke, R. Steiner and H. -G. Schmalz, *J. Am. Chem. Soc.*, 2011, **133**, 6948. (b) R. Shang, D. -S. Ji, L. Chu, Y. Fu and L. Liu, *Angew. Chem. Int. Ed.*, 2011, **50**, 4470; (c) N. A. Beare and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 541; (d) L. Wu and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 15824.
- 8 Y. Ren, C. Dong, S. Zhao, Y. Sun, J. Wang, J. Ma and C. Hou, *Tetrahedron Lett.*, 2012, **53**, 2825.
- 9 (a) J. -M. Brunel and J. P. Holmes, *Angew. Chem. Int. Ed.*, 2004, **43**, 2752; (b) J. M. Keith and E. N. Jacobsen, *Org. Lett.*, 2004, **6**, 153; (c) Y. Tanaka, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2008, **130**, 6072; (d) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Hun, Q. Liu and Q. Zhang, *Angew. Chem. Int. Ed.*, 2013, **52**, 2529; (e) J. Shimokawa, T. Harada, S. Yokoshima and T. Fukuyama, *J. Am. Chem. Soc.*, 2011, **133**, 17634.
- 10 E. D. Soli, A. S. Manoso, M. C. Patterson and P. Deshong, *J. Org. Chem.*, 1999, **64**, 3171.
- 11 (a) T. Hiyama and E. Shirakawa, *Top. Curr. Chem.*, 2002, **219**, 61; (b) S. E. Denmark and R. F. Sweis, In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; A. de Meijere and F. Diederich, Eds., Wiley-VCH: Weinheim, Germany, 2004; pp163-216.
- 12 (a) T. D. Nelson and R. D. Crouch, *Synthesis*, 1996, 1031; (b) G. Satori, R. Ballini, F. Bigi, G. Bosica, R. Maggi and P. Righi, *Chem. Rev.*, 2004, **104**, 199.
- 13 D. K. Rayabarapu, C. -F. Chiou and C. -H. Cheng, *Org. Lett.*, 2002, **4**, 1679.
- 14 J. -C. Hsieh, Y. -C. Chen, A. -Y. Cheng, H. -C. Tseng, *Org. Lett.*, 2012, **14**, 1282.
- 15 (a) R. Matsubara, A. T. Gutierrez and T. F. Jamison, *J. Am. Chem. Soc.*, 2011, **133**, 19020; (b) E. A. Standley and T. M. Jamison, *J. Am. Chem. Soc.*, 2013, **135**, 1585.
- 16 Me_3SiCl was analyzed by using the ^{29}Si NMR (DEPT) analysis. After the model reaction (Table 1, entry 13), ^{29}Si NMR (DEPT) analysis of Me_3SiCl shows a peak at 27.1 ppm.¹⁵
- 17 J. Schraml, V. Chvalovsky, M. Magi and E. Lippmaa, *Collect. Czech. Chem. Commun.*, 1979, **44**, 854.