A Widely Applicable Regioselective Aerobic α-Cyanation of Tertiary Amines Heterogeneously Catalyzed by Manganese Oxides
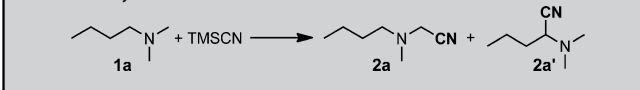
Kazuya Yamaguchi, Ye Wang, and Noritaka Mizuno*[a]

α-Amino nitriles are an important class of compounds and have been utilized as versatile synthetic intermediates for value-added products, such as α-amino acids, α-amino aldehydes, α-amino alcohols, vicinal amines, and alkaloids.[1] Classically, α-amino nitriles have been synthesized by wasteful and substrate-limited procedures.[1] As an alternative, cross-dehydrogenative coupling-type α-cyanation of (tertiary) amines by activation of C(sp³)–H bonds adjacent to amino groups is now emerging as one of the most green and straightforward synthetic procedures for α-amino nitriles.[2–9] To date, several stoichiometric, catalytic, and photocatalytic procedures using various oxidants such as singlet oxygen,[2] chlorine dioxide,[3] hypervalent iodines,[4] tropylium ion,[5] tert-butyl (hydro)peroxide,[6] hydrogen peroxide,[7] and molecular oxygen (triplet oxygen)[8,9] have been reported (Table S1). However, in almost all cases, the substrate scopes are limited only to reactive N,N-dialkylanilines (including N-aryltetrahydroisoquinolines) and the recovery and reuse of the (homogeneous) catalysts are quite difficult (Table S1).[2–9] Therefore, the development of efficient and widely applicable α-cyanation systems is an important subject. The use of heterogeneous catalysts and molecular oxygen as a terminal oxidant would be more desirable from the standpoint of green chemistry.[10]

Manganese oxide-based octahedral molecular sieves, in particular OMS-2 (2×2 hollandite structure, $KMn_8O_{16}\cdot nH_2O$, Figure S1),[11] have been recognized as efficient oxidation catalysts, owing to their excellent properties, such as large (external) surface areas, redox ability, electron-conducting properties, and oxygen reduction abilities.[11–15] By using OMS-2, various catalytic oxidation systems, e.g., dehydrogenation of alcohols,[12] dehydrogenation and oxygenation of primary amines,[13] oxygenation of alkylarenes,[14] and oxidative amidation of primary alcohols and methylarenes,[15] have been developed to date.[16] Herein, we demonstrate for the first time that OMS-2 can act as an efficient reusable heterogeneous catalyst for the regioselective α-cyanation of tertiary amines using trimethylsilyl cyanide (TMSCN) as a cyano source and molecular oxygen as a terminal oxidant. Various structurally diverse tertiary amines can

be applied to the present cyanation, giving the corresponding α-amino nitriles in moderate to high yields.

Initially, the cyanation of N,N-dimethyl-1-butylamine (**1a**) was performed in the presence of various of catalysts (Table 1).[17,18] Compound **1a** was chosen as a model substrate

Table 1. α-Cyanation of **1a** under various conditions.[a]

Entry	Catalyst	Conv. of **1a** [%]	Total yield (**2a**+**2a'**) [%]	**2a**/**2a'** ratio
1	OMS-2[b]	89	88	95/5
2	OMS-2 + BHT[c]	25	23	95/5
3	β-MnO₂	90	79	97/3
4	amorphous MnO₂	80	66	91/9
5	δ-MnO₂	38	34	83/17
6	Co₃O₄	36	5	94/6
7	CeO₂	19	10	79/21
8	V₂O₅	5	4	82/18
9	RuCl₃·nH₂O[d]	15	11	80/20
10	CuCl₂[d]	11	6	86/14
11	FeCl₃[d]	34	15	88/12
12	MoO₂(acac)₂[d]	10	7	86/14
13	AIBN[d]	56	42	57/43
14	I₂[d]	18	8	87/13
15	none	4	2	45/55

[a] Reaction conditions: Catalyst (50 mg), **1a** (0.2 mmol), TMSCN (0.4 mmol), acetonitrile (2 mL), 80°C, O₂ (1 atm), 2 h. Yields were determined by GC analysis using biphenyl as an internal standard. [b] The isolated yield of products (**2a**+**2a'**, **2a**/**2a'**=95/5) was 85% in the cyanation for 4 h. [c] BHT (0.2 mmol). [d] Catalyst (10 mol%).

because it is relatively less reactive in comparison with frequently utilized N,N-dialkylanilines and has never been utilized in the previously reported α-cyanation systems.[2–9] Under the present conditions, the reaction hardly proceeded in the absence of the catalysts (Table 1, entry 15). Among various catalysts examined, OMS-2 showed the highest catalytic performance; regioselective cyanation efficiently proceeded to afford the corresponding α-amino nitriles **2a** and **2a'** in 88% total yield and occurred at the α-methyl position (**2a**/**2a'**=95/5, Table 1, entry 1). Other manganese-based oxides, such as β-MnO₂, amorphous MnO₂, and δ-MnO₂ (birnessite), gave the corresponding α-amino nitriles in moderate to high yields (Table 1, entries 3–5). In these cases, the regioselective cyanation also occurred at the α-methyl position. Co₃O₄ and CeO₂ showed much lower catalytic activities than those of manganese-based oxides (Table 1, entries 6 and 7). Although V₂O₅,[8b]

[a] Dr. K. Yamaguchi, Dr. Y. Wang, Prof. Dr. N. Mizuno
Department of Applied Chemistry, School of Engineering
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
Fax: (+81) 3-5841-7220
E-mail: tmizuno@mail.ecc.u-tokyo.ac.jp

RuCl$_3\cdot n$H$_2$O,[7a, 8a] CuCl$_2$,[8f] FeCl$_3$,[8g] MoO$_2$(acac)$_2$ (acac = acetylacetonato),[8d] 2,2'-azobis(isobutyronitrile) (AIBN),[8c] and I$_2$[8e] have been reported to be active for α-cyanation of N,N-dialkylanilines, these catalysts were not effective for the cyanation of the trialkylamine **1a** (Table 1, entries 8–14). The OMS-2-catalyzed cyanation was significantly suppressed in the presence of a radical scavenger of dibutylhydroxytoluene (BHT) (Table 1, entry 2), suggesting that radical intermediates are involved in the present cyanation. When using a carbon-centered radical generator of AIBN (by means of hydrogen atom abstraction), the cyanation was not regioselective and gave a 57:43 mixture of **2a** and **2a'** (Table 1, entry 13).

To verify whether the observed catalysis is derived from solid OMS-2 or leached manganese species, the cyanation of **1a** was performed, and OMS-2 was removed from the reaction mixture by hot filtration at approximately 50% conversion of **1a**. Then, the filtrate was again heated at 80°C in 1 atm of O$_2$ (1 atm = 0.101 MPa). In this case, further production of **2a** and **2a'** was hardly observed (Figure S2). It was confirmed by the inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis that manganese species was hardly detected in the filtrate (below 0.055%). These results can rule out any contribution to the observed catalysis from manganese species that leached into the reaction solution, and the observed catalysis for the present cyanation is truly heterogeneous.[19] After the cyanation was completed, OMS-2 could easily be retrieved from the reaction mixture by simple filtration with >95% recovery. The retrieved OMS-2 catalyst could be reused at least five times for the cyanation of **1a**; even for the fifth reuse experiment, 90% total yield of **2a** and **2a'** (**2a/2a'** = 97/3) was still obtained (Table S2).

Next, the substrate scope of the present OMS-2-catalyzed cyanation was examined (Figures 1 and 2).[17] As shown in Figure 1, various structurally diverse trialkyl and benzylic amines could be converted into the corresponding monocyanated products without formation of di- and tricyanated products in all cases. Selective cyanation of N-methylalkylamines occurred at the α-methyl positions, giving the corresponding α-amino nitriles in moderate to high yields (Figure 1, entries 1–5). Even in the case of a sterically hindered trialkylamine, the cyanation efficiently proceeded, affording the corresponding α-amino nitrile in a high yield (Figure 1, entry 6). The present OMS-2-catalyzed system was applicable to substrates containing ester and diamino groups (Figure 1, entries 7 and 8). With regard to trialkylamines, the order of regioselectivity was methyl > methylene ≫ methine. Regioselective cyanation of N,N-dialkylbenzylamines occurred at the α-methyl positions, giving the corresponding α-amino nitriles (Figure 1, entries 9–11). OMS-2 also showed high catalytic performance for cyanation of N,N-dimethylanilines (Figure 2). N,N-Dimethylanilines, which contain electron-donating as well as electron-withdrawing substituents at the para-positions, gave the corresponding α-cyanated anilines in high yields (Figure 2, entries 1, 2, and 5–8). The amounts of OMS-2 could be reduced, though the longer reaction times were required to attain high yields (Figure 2, entries 2 and 6). In the cyanation of ortho-, meta-, and para-toluidines, the steric effect was observed; the reac-
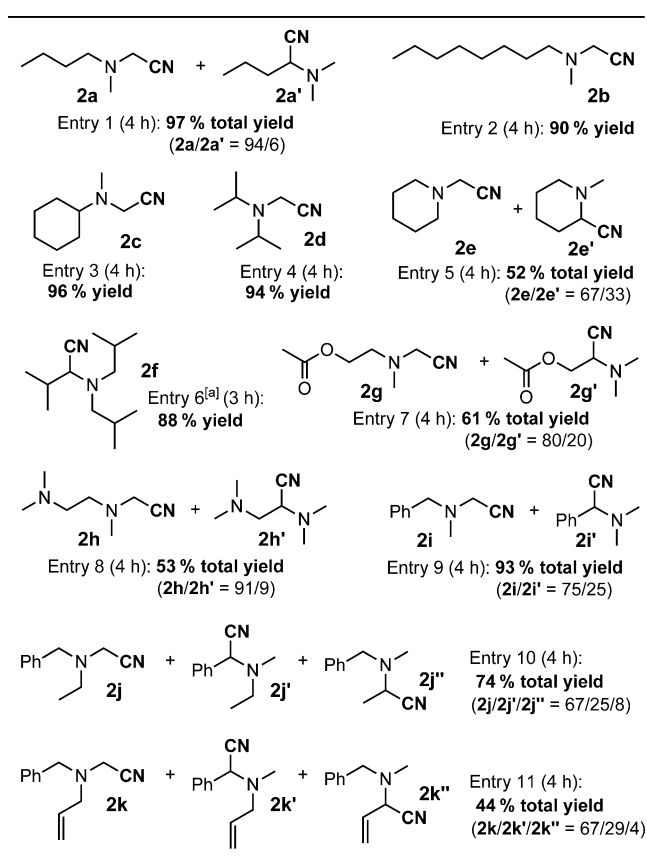

Figure 1. Cyanation of various trialkyl and benzylic amines. Reaction conditions: OMS-2 (50 mg), amine (0.2 mmol), TMSCN (0.4 mmol), acetonitrile (2 mL), 80°C, O$_2$ (1 atm). Yields were determined by GC analysis using biphenyl or naphthalene as an internal standard. [a] OMS-2 (100 mg).
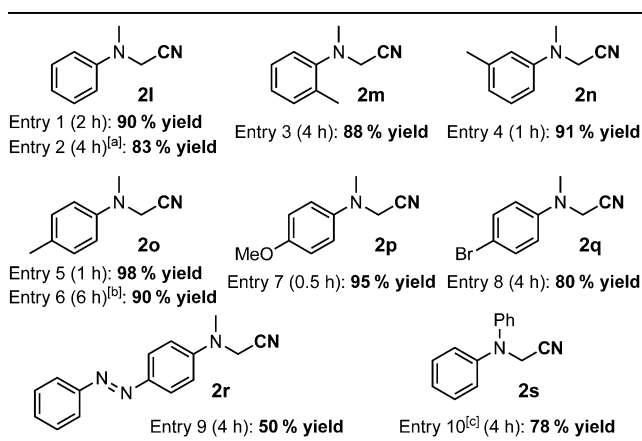
Figure 2. Cyanation of various N,N-dimethylanilines. Reaction conditions: OMS-2 (50 mg), aniline (0.2 mmol), TMSCN (0.4 mmol), acetonitrile (2 mL), 80°C, O$_2$ (1 atm). Yields were determined by GC analysis using biphenyl or naphthalene as an internal standard. The corresponding demethylated products were formed as byproducts to some extent (<5% for entries 1–6 and 8, 5% for entry 7, 17% for entry 9, 7% for entry 10). [a] OMS-2 (80 mg), **2l** (0.4 mmol), TMSCN (0.8 mmol). [b] OMS-2 (20 mg). [c] OMS-2 (100 mg), TMSCN (0.8 mmol).

tion rate of ortho-toluidine was smaller than those of meta- and para-derivatives (Figure 2, entries 3–5). Similarly, a sterically

hindered *N,N*-diphenyl-substituted amine required a longer time and larger amounts of OMS-2 and TMSCN to attain a high yield (Figure 2, entry 10). Methyl yellow gave the corresponding α-cyanated product without affecting the azo group (Figure 2, entry 9). Notably, larger scale reactions were also successful; for example, when the gram scale cyanation of **1o** was performed, 0.99 g of **2o** could be obtained (Scheme 1).
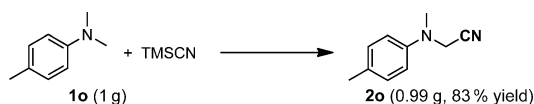
Scheme 1. Larger scale cyanation. Reaction conditions: OMS-2 (2 g), **1o** (1 g, 7.4 mmol), TMSCN (14.8 mmol), acetonitrile (50 mL), 80 °C, O$_2$ (1 atm), 2 h.

The OMS-2-catalyzed competitive cyanations of *para*-substituted *N,N*-dimethylanilines gave the following reactivity order; *p*-OMe (18) > *p*-Me (3.0) > *p*-H (1.0) > *p*-Br (0.27) > *p*-NO$_2$ (0.0082), where the values in the parentheses are the relative rates, and the formation rate of **2l** (*p*-H) is taken as unity. The slope of the linear line of the Hammett plot using Brown-Okamoto σ$^+$ values gave a Hammett ρ value of −2.2 (Figure 3).
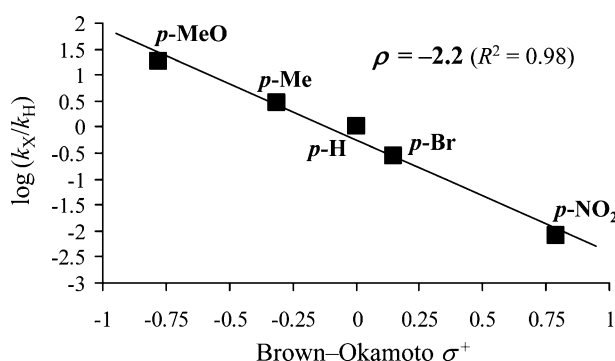
Figure 3. Hammett plot for the OMS-2-catalyzed competitive cyanation: Reaction conditions: OMS-2 (50 mg), *N,N*-dimethylaniline (0.1 mmol), *para*-substituted derivative (0.1 mmol), TMSCN (0.4 mmol), acetonitrile (2 mL), 80 °C, O$_2$ (1 atm).

The negative ρ value can be interpreted the formation of a cationic intermediate,[20] i.e., an iminium cation intermediate. The formation of an iminium cation was further evidenced by the fact that **3f** could be trapped by the reaction of **1f** with LiBF$_4$ in the presence of OMS-2 (Scheme 2, Figure S3).[5]

With regard to formation of an iminium cation from a tertiary amine, the following three pathways can be considered;
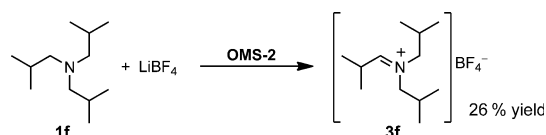
Scheme 2. Detection of an iminium cation intermediate. Reaction conditions: OMS-2 (100 mg), **1f** (0.2 mmol), LiBF$_4$ (0.4 mmol), [D$_3$]acetonitrile (2 mL), 80 °C, O$_2$ (1 atm), 15 h. The yield of **3f** was determined by ¹H NMR analysis (Figure S3).

A) direct hydride abstraction, **B**) hydrogen atom abstraction, followed by single-electron transfer (SET), and **C**) SET to form an amine cation radical, followed by deprotonation and the second SET. The pathway **A** can be excluded because the present OMS-2-catalyzed cyanation was significantly suppressed in the presence of the radical scavenger (Table 1, entry 1 vs. entry 2). In addition, the regioselectivity of OMS-2 was much different from that of the carbon-centered radical generator of AIBN; in the case of **1a**, the relative reactivity of methyl and methylene C−H bonds normalized with their numbers (R_{methyl}/$R_{methylene}$) was 6.3 for OMS-2, and the R_{methyl}/$R_{methylene}$ value was 0.44 for AIBN (Table 1, entry 1 vs. entry 13). This result suggests that the first step of the present cyanation is not a hydrogen atom abstraction. As above-mentioned, the order of regioselectivity was methyl > methylene ≫ methine, which is the opposite of that expected from the stability of alkyl radicals, but in accord with that expected from the stereoelectronically controlled deprotonation of amine cation radicals.[21] As for deprotonation of amine cation radicals, the overlap between the half-vacant nitrogen p orbital and the generating carbon radical p orbital is required, resulting in selective deprotonation of the less substituted α-C−H bond, i.e., methyl > methylene > methine.[21] A similar stereoelectronic effect has also been reported for photochemical addition of tertiary amines to *trans*-stilbene, where the proton transfer from amine cation radicals to a stilbene anion radical is included as a key step.[21] Therefore, the pathway **C** is the most plausible for formation of an iminium cation in the present case.

On the basis of the above-mentioned experimental evidences, we here propose a possible reaction mechanism for the present OMS-2-catalyzed α-cyanation of tertiary amines (Scheme 3). The overall equation is also shown in Scheme 3.[17]
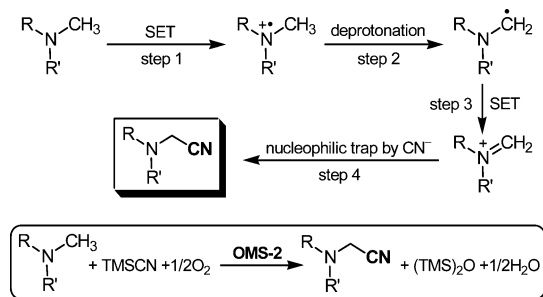
Scheme 3. Possible reaction mechanism for the present OMS-2-catalyzed α-cyanation of tertiary amines.

Firstly, an amine cation radical is formed by SET from an amine to OMS-2 (step 1). Then, deprotonation of the cation radical to form an α-aminated carbon radical (step 2). This step is stereoelectronically controlled and determines the regioselectivity.[21] The α-aminated carbon radical is a strongly reducing species. Thus, the second SET readily proceeds to form an iminium cation (step 3), followed by nucleophilic trap by CN$^-$ species to afford the corresponding α-amino nitrile. The reduced OMS-2 is reoxidized by molecular oxygen.

In summary, we have successfully developed a widely applicable, heterogeneously OMS-2-catalyzed system for α-cyanation of various tertiary amines. In comparison with the previously reported systems (Table S1),[2–9] the present OMS-2-catalyzed system has the following significant advantages; 1) a broad substrate scope including trialkyl, benzylic, and *N,N*-dialkylaniline derivatives, 2) the use of molecular oxygen as a terminal oxidant, 3) no additives, 4) an easy catalyst/product(s) separation, 5) the reusability of OMS-2, and/or 6) the use of relatively inexpensive manganese-based oxides as catalysts.

Keywords: cyanation · heterogeneous catalysis · manganese oxides · oxygen · tertiary amines

[1] a) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698; b) D. Enders, J. P. Shilvock, *Chem. Soc. Rev.* **2000**, *29*, 359; c) M. North, *Angew. Chem.* **2004**, *116*, 4218; *Angew. Chem. Int. Ed.* **2004**, *43*, 4126; d) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633; e) M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th ed.*, Wiley, Hoboken, NJ, **2007**; f) M. North, *Comprehensive Organic Functional Group Transformations, Vol. 3*, (Eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees, G. Pattenden), Pergamon, Oxford, **1995**, pp. 611–617.

[2] Using singlet oxygen: C. Ferroud, P. Rool, J. Santamaria, *Tetrahedron Lett.* **1998**, *39*, 9423.

[3] Using chlorine dioxide: C.-K. Chen, A. G. Hortmann, M. R. Marzabadi, *J. Am. Chem. Soc.* **1988**, *110*, 4829.

[4] Using hypervalent iodines: a) X.-Z. Shu, X.-F. Xia, Y.-F. Yang, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2009**, *74*, 7464; b) V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, B. Mismash, J. K. Woodward, A. J. Simonsen, *Tetrahedron Lett.* **1995**, *36*, 7975.

[5] Using tropylium ion: J. M. Allen, T. H. Lambert, *J. Am. Chem. Soc.* **2011**, *133*, 1260.

[6] Using *tert*-butyl hydroperoxide or di-*tert*-butyl peroxide: a) W. Han, A. R. Ofial, *Chem. Commun.* **2009**, 5024; b) Y. Zhang, H. Peng, M. Zhang, Y. Cheng, C. Zhu, *Chem. Commun.* **2011**, *47*, 2354; c) K. Tirumala, V. Rao, B. Haribabu, P. S. S. Prasad, N. Lingaiah, *ChemCatChem* **2012**, *4*, 1173; d) Z. Li, C.-J. Li, *Eur. J. Org. Chem.* **2005**, 3173; e) K. Harha, V. Reddy, G. Satish, V. P. Reddy, B. S. P. A. Kumar, Y. V. D. Nageswar, *RSC Adv.* **2012**, *2*, 11084; f) P. Liu, Y. Liu, E. L.-M. Wong, S. Xiang, C.-M. Che, *Chem. Sci.* **2011**, *2*, 2187.

[7] Using hydrogen peroxide: a) S.-I. Murahashi, T. Nakae, H. Terai, N. Komiya, *J. Am. Chem. Soc.* **2008**, *130*, 11005; b) S.-I. Murahashi, N. Komiya, H. Terai, *Angew. Chem.* **2005**, *117*, 7091; *Angew. Chem. Int. Ed.*

[2] **2005**, *44*, 6931; c) S. Verma, S. L. Jain, B. Sain, *Catal. Lett.* **2011**, *141*, 882; d) S. Singhal, S. L. Jain, B. Sain, *Adv. Synth. Catal.* **2010**, *352*, 1338; e) S. Verma, S. L. Jain, B. Sain, *ChemCatChem* **2011**, *3*, 1329.

[8] Using molecular oxygen: a) S.-I. Murahashi, N. Komiya, H. Terai, T. Nakae, *J. Am. Chem. Soc.* **2003**, *125*, 15312; b) S. Singhal, S. L. Jain, B. Sain, *Chem. Commun.* **2009**, 2371; c) L. Liu, Z. Wang, X. Fu, C.-H. Yan, *Org. Lett.* **2012**, *14*, 5692; d) K. Alagiri, K. R. Prabhu, *Org. Biomol. Chem.* **2012**, *10*, 835; e) J. Dhineshkumar, M. Lamani, K. Alagiri, K. R. Prabhu, *Org. Lett.* **2013**, *15*, 1092; f) E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317; g) S. Murata, K. Teramoto, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1297.

[9] Photocatalytic systems: a) Y. Pan, S. Wang, C. W. Kee, E. Dubuisson, Y. Yang, K. P. Loh, C.-H. Tan, *Green Chem.* **2011**, *13*, 3341; b) D. P. Hari, B. König, *Org. Lett.* **2011**, *13*, 3852; c) M. Rueping, S. Zhu, R. M. Koenigs, *Chem. Commun.* **2011**, *47*, 12709; d) M. Rueping, J. Zoller, D. C. Fabry, K. Poscharny, R. M. Koenigs, T. E. Weirich, J. Mayer, *Chem. Eur. J.* **2012**, *18*, 3478.

[10] a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, London, **1998**; b) R. A. Sheldon, *Green Chem.* **2000**, *2*, G1; c) P. T. Anastas, L. B. Bartlett, M. M. Kirchhoff, T. C. Williamson, *Catal. Today* **2000**, *55*, 11; d) R. A. Sheldon, H. van Bekkum, *Fine Chemicals through Heterogeneous Catalysis*, Wiley, Weinheim, **2001**.

[11] a) S. L. Suib, *Acc. Chem. Res.* **2008**, *41*, 479; b) R. N. DeGuzman, Y.-F. Shen, E. J. Neth, S. L. Suib, C.-L. O'Young, S. Levine, J. M. Newsam, *Chem. Mater.* **1994**, *6*, 815.

[12] a) Y.-C. Son, V. D. Makwana, A. R. Howell, S. L. Suib, *Angew. Chem.* **2001**, *113*, 4410; *Angew. Chem. Int. Ed.* **2001**, *40*, 4280; b) V. D. Makwana, Y.-C. Son, A. R. Howell, S. L. Suib, *J. Catal.* **2002**, *210*, 46.

[13] Y. Wang, H. Kobayashi, K. Yamaguchi, N. Mizuno, *Chem. Commun.* **2012**, *48*, 2642.

[14] N. N. Opembe, Y.-C. Son, T. Sriskandakumar, S. L. Suib, *ChemSusChem* **2008**, *1*, 182.

[15] a) K. Yamaguchi, H. Kobayashi, T. Oishi, N. Mizuno, *Angew. Chem.* **2012**, *124*, 559; *Angew. Chem. Int. Ed.* **2012**, *51*, 544; b) K. Yamaguchi, H. Kobayashi, Y. Wang, T. Oishi, Y. Ogasawara, N. Mizuno, *Catal. Sci. Technol.* **2013**, *3*, 318; c) Y. Wang, K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2012**, *124*, 7362; *Angew. Chem. Int. Ed.* **2012**, *51*, 7250.

[16] Quite recently, the MnO₂/CH₃SO₃H-promoted dehydrogenative alkylation of isochroman derivatives with carbon nucleophiles (not catalytic) has been reported: X. Liu, B. Sun, Z. Xie, X. Qin, L. Liu, H. Lou, *J. Org. Chem.* **2013**, *78*, 3104.

[17] Di(trimethylsilyl)ether was formed as a coproduct in all cases.

[18] Effects of solvents (Table S3), temperatures (Table S4), and amounts of TMSCN (Table S5) on the cyanation of **1a** were summarized in the Supporting Information.

[19] R. A. Sheldon, M. Wallau, I. W. C. E. Arends, U. Schuchardt, *Acc. Chem. Res.* **1998**, *31*, 485.

[20] K. A. Connors, *Chemical Kinetics, The Study of Reaction Rates in Solution*, VCH Publishers, Inc., New York, **1990**.

[21] a) F. D. Lewis, T.-I. Ho, J. T. Simpson, *J. Org. Chem.* **1981**, *46*, 1077; b) F. D. Lewis, *Acc. Chem. Res.* **1986**, *19*, 401.