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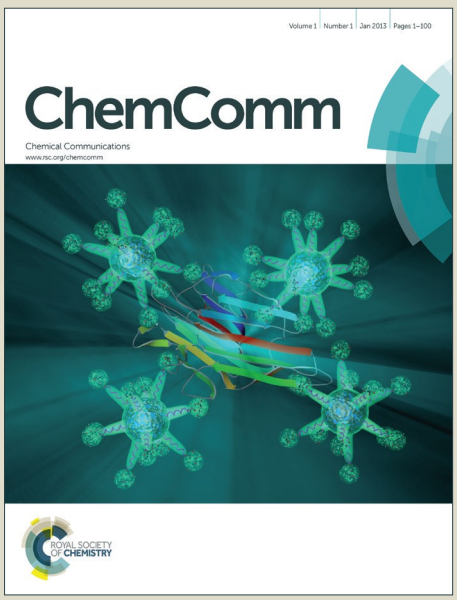

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ARTICLE TYPE

Regioselective direct oxidative C–H cyanation of quinoline and its derivatives catalyzed by vanadium-containing heteropoly acids†

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A direct oxidative C–H cyanation of quinoline and its derivatives using trimethylsilyl cyanide as the cyano source and molecular oxygen as the terminal oxidant has been developed. In the presence of catalytic amounts of vanadium-containing heteropoly acids, e.g., $H_7PV_4Mo_8O_{40}$, cyanation of various quinoline and its derivatives preferentially took place at the 4-position, affording the corresponding substituted 4-cyanoquinolines as the major products.

The cyano group is one of the most important functional groups, and aryl and heteroaryl nitriles have widely been applied in production of the corresponding carboxylic acids, amides, amines, aldehydes, ketones, and a variety of heterocyclic compounds.[1] In addition, they are often found as integral parts of pharmaceuticals, agrochemicals, dyes, fine chemicals, and natural products.[1] Currently, benzonitrile and cyanopyridines have industrially been produced by ammoxidation of toluene and methylpyridines, respectively, under rather harsh reaction conditions.[2] Even now, the Sandmeyer reaction[3] and the Rosenmund–von Braun reaction[4] using copper(I) cyanide (CuCN) as the cyano source are two of the most frequently utilized choices for laboratory scale synthesis of aryl and heteroaryl nitriles.[1] Concequently, the development of the efficient alternative synthetic procedures is still a subject of urgency.

To date, several efficient catalytic procedures for synthesis of nitriles have been developed.[5–10] For example, aerobic oxidative dehydrogenation of primary amines,[5] dehydration of primary amides or aldoximes,[6] and ammoxidation of primary alcohols[7] are the attractive routes because only water is formed as the co-product in these systems. The transition metal-catalyzed (in particular palladium-catalyzed) nucleophilic cyanation of aryl and heteroaryl halides, triflates, or boronic acids using various cyano sources such as metal cyanides, trimethylsilyl cyanide (TMSCN), and acetone cyanohydrin has emerged as the attractive procedures for late-stage cyano group installation.[8] Although the nucleophilic cyanation can precisely give the desired nitrile products, it usually utilize pre-activated substrates, which concurrently generate (super)stoichiometric amounts of metal salts as the wastes.[8] To overcome the problem, the transition metal-catalyzed direct C–H cyanation of aromatic compounds with suitable directing groups has been developed.[9] As an alternative to nuclephilic cyanation, electrophilic cyanation reagents, e.g., hypervalent iodine(III) reagents, have also been designed.[10]

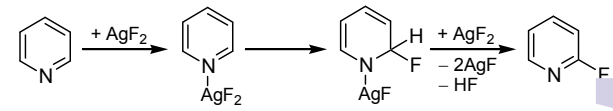


Fig. 1 Proposed reaction mechanism for the fluorination of pyridines with AgF_2 (Hartwig fluorination).[11]

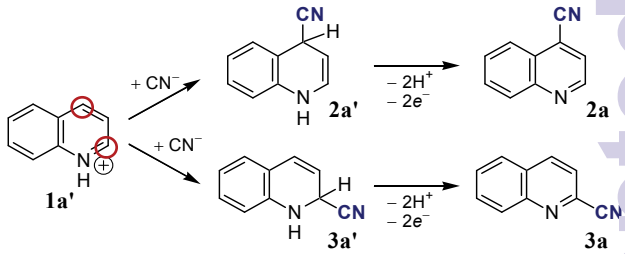
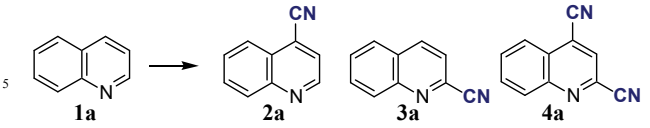


Fig. 2 Our strategy for direct oxidative C–H cyanation of quinoline derivatives. The cyanation possibly proceeds at the 2- and 4-positions (red circles).

Herein, we report a direct oxidative C–H cyanation of quinoline and its derivatives using TMSCN as the cyano source and molecular oxygen as the terminal oxidant. Our catalytic reaction design is inspired by the fluorination of pyridines with silver(II) fluoride (AgF_2) (Hartwig fluorination).[11] The reaction mechanism of the Hartwig fluorination is intrinsically similar to that of the Chichibabin reaction[12] (Fig. 1). In the Hartwig fluorination, the coordination of pyridine to AgF_2 initially takes place, followed by dearomative nucleophilic addition of the F species to the neighboring 2-position to form an amide-silver(II) fluoride complex. Finally, the abstraction of one proton and two electrons from the complex proceeds with the help of additional AgF_2, giving the corresponding 2-fluoropyridine together with two equivalents of silver(I) fluoride (AgF) and one equivalent of HF. Our strategy is shown in Fig. 2. The electron density of quinoline (in particular its 2- and 4-positions) can be lowered by protonation, which facilitates the nucleophilic addition of CN^- to form dearomatized intermediates. Then, the corresponding cyanoquinolines can be obtained by two electron oxidation of these intermediates. In order to realize the reaction in Fig. 2 as the efficient catalytic system, both *acidic* and *oxidation* properties should be needed for the catalysts, and we expect that heteropoly acids (HPAs) can satisfy this requirement.[13]

Table 1 Oxidative C–H cyanation of quinoline (**1a**) using various catalysts[a]



1a **2a** **3a** **4a**

Entry	Catalyst	Yield (%)			4-/2-CN ratio[b]
		2a	**3a**	**4a**	
1	$H_3PMo_{12}O_{40}$	22	<1	2	12.0
2	$H_4PVMo_{11}O_{40}$	20	<1	4	5.0
3	$H_5PV_2Mo_{10}O_{40}$	53	<1	4	13.3
4	$H_6PV_3Mo_9O_{40}$	51	2	7	6.4
5	$H_7PV_4Mo_8O_{40}$	59	3	4	9.0
6[c,d]	$H_7PV_4Mo_8O_{40}$	23	1	2	8.3
7	$H_4SiMo_{12}O_{40}$	3	<1	<1	–
8	$H_5SiVMo_{11}O_{40}$	28	<1	3	9.3
9	$H_3PW_{12}O_{40}$	3	<1	<1	–
10	$H_4PVW_{11}O_{40}$	16	<1	2	8.0
11	$H_5PV_2W_{10}O_{40}$	20	<1	2	10.0
12	$H_6PV_3W_9O_{40}$	28	<1	2	14.0
13	$H_7PV_4W_8O_{40}$	46	<1	4	11.5
14	$H_4SiW_{12}O_{40}$	6	1	<1	6.0
15	$H_5SiVW_{11}O_{40}$	12	<1	2	6.0
16[d,e]	V_2O_5	4	<1	1	5.0
17[d,e]	$NaVO_3$	2	<1	<1	–
18[d,e]	$VO(acac)_2$	7	<1	3	3.3
19[d,f]	$V_2O_5 + H_3PMo_{12}O_{40}$	6	<1	1	7.0
20[d,f]	$NaVO_3 + H_3PMo_{12}O_{40}$	8	<1	<1	–
21[d,f]	$VO(acac)_2 + H_3PMo_{12}O_{40}$	18	<1	3	7.0
22[d,g]	HNO_3	31	19	3	1.5
23[h]	$H_7PV_4Mo_8O_{40}$ + TBAOH	11	<1	2	6.5
24[d]	None	<1	<1	<1	–

[a] Reaction conditions: **1a** (0.5 mmol), TMSCN (2 mmol), HPA (10 mol%), DMSO (2 mL), O_2 (1 atm), 100 °C, 24 h. Yields were determined by GC using naphthalene as the internal standard. [b] 4-Cyanation/2-cyanation ratio = (sum of **2a** and **4a** (mol))/(sum of **3a** and **4a** (mol)). [c] Ar (1 atm). [d] 48 h. [e] Vanadium (20 mol%). [f] Vanadium (20 mol%) + $H_3PMo_{12}O_{40}$ (4 mol%). [g] HNO_3 (70 mol%). [h] $H_7PV_4Mo_8O_{40}$ (10 mol%) + TBAOH (70 mol%).

Our initial experiments focused on the cyanation of quinoline (**1a**) under various conditions using $H_6PV_3Mo_9O_{40}$ (Table S1, ESI†).[14] We chose TMSCN as the cyano source. The preliminary solvent screening showed that dimethyl sulfoxide (DMSO) was the best for the cyanation among the solvents examined. The yields of the cyanation products increased with an increase in the reaction temperature up to 100 °C. The effects of amounts of the catalyst and TMSCN are summarized in Table S2 (ESI†). The color of the reaction solution changed from orange (the color of $H_6PV_3Mo_9O_{40}$, fully oxidized form) to dark green immediately at the beginning of the reaction. This suggests that $H_6PV_3Mo_9O_{40}$ is somewhat reduced during the cyanation. The reduction color gradually changed to almost the original color (chrome yellow) toward the end of the reaction.

Next, the catalytic activities of various kinds of HPAs (10 mol%) were examined for the cyanation of **1a** in DMSO at 100 °C in 1 atm of molecular oxygen (Table 1). The reaction hardly proceeded in the absence of the catalysts under the present conditions (Table 1, entry 24). It should be noted that the HPA-catalyzed cyanation preferentially proceeded at the 4-position to give 4-cyanoquinoline (**2a**) as the major product in all cases. In contrast, it has been reported that 2-cyanoquinoline (**3a**) is typically obtained in several nucleophilic cyanation systems.[15] While the cyanation proceeded to some extent in the presence of an acidic oxidant, nitric acid (HNO_3), commonly utilized for numerous oxidation reactions, the 4-cyanation/2-cyanation ratio (= (sum of **2a** and **4a**)/(sum of **3a** and **4a**)) was 1.5 and much lower than those with HPAs (Table 1, entry 22). The desired cyanation products were significantly obtained when the reaction was performed using vanadium-containing HPAs such as phospho(or silico)vanadomolybdic acids (Table 1, entries 2–5 and 8) and phospho(or silico)vanadotungstic acids (Table 1, entries 10–13 and 15). With regard to polyatoms of vanadium-containing HPAs, molybdenum was slightly better than tungsten (Table 1, entries 2–5 *vs.* entries 10–13). It is well known that molybdic acids possess higher oxidation potentials in comparison with tungstic acids.[16]

Under an argon atmosphere using $H_7PV_4Mo_8O_{40}$, almost the stoichiometric amount of the cyanation products with respect to vanadium species employed (40 mol%, theoretical production 20%, Fig. 2) was produced (Table 1, entry 6), and the dark green color of the reaction solution almost unchanged during the reaction, indicating that molecular oxygen can act as the terminal oxidant for the present oxidative cyanation. The catalytic activities of vanadium-containing HPAs were significantly higher than those of vanadium-free HPAs such as $H_3PMo_{12}O_{40}$, $H_4SiMo_{12}O_{40}$, $H_3PW_{12}O_{40}$, and $H_4SiW_{12}O_{40}$ (Table 1, entries 1, 7, 9, and 14). These results indicate that vanadium is an indispensable component to attain the high yields of cyanation products. However, simple vanadium compounds such as V_2O_5, $NaVO_3$, and $VO(acac)_2$ (acac = acetylacetonate) hardly catalyzed the cyanation (Table 1, entries 16–18). In addition, the cyanation did not proceed effectively in the presence of simple mixtures of V_2O_5 and $H_3PMo_{12}O_{40}$, $NaVO_3$ and $H_3PMo_{12}O_{40}$, and $VO(acac)_2$ and $H_3PMo_{12}O_{40}$ (Table 1, entries 19–21). Therefore, the substitution of vanadium into HPA frameworks is important to obtain the high catalytic performance. It has been reported that phosphovanadomolybdic acids can generate cation radical species from various substrates and that the vanadium sites play important roles in the single-electron oxidation.[13,17] Moreover, the reduced (vanadium) species in (or interacting with) HPAs is known to be readily reoxidized by molecular oxygen.[13,17,18]

Fig. 3a shows the ^{1}H NMR spectrum of a DMSO-d_6 solution of **1a** (0.1 M). Upon addition of an equimolar amount of $H_7PV_4Mo_8O_{40}$ with respect to **1a** to this solution, **1a** was protonated to form the qunolinium cation species **1a'** (Fig. 3b). The importance of the protonation was evidenced by the fact that the in situ neutralization with tetra-*n*-butylammonium hydroxide (TBAOH) significantly lowered the efficiency of the cyanation of **1a** (Table 1, entry 23). It is clear that the electron densities at the 2- and 4-positions of **1a'** (**1a**) are significantly lower than those of the other positions. In addition, if the dearomative nucleophilic addition takes place at the 3-position, the intermediate is relatively unstable in comparison with **2a'** and **3a'**. Therefore, the 2- and 4-positions are possibly the expected cyanation sites.

The positive-ion cold spray ionization mass (CSI-MS) spectrum of a DMSO solution of $H_3PMo_{12}O_{40}$ (5.5 mM)[19]

showed sets of signals centered at *m/z* 2139, 2217, and 2295 assignable to $[H_4PMo_{12}O_{40}(DMSO)_4]^+$, $[H_4PMo_{12}O_{40}(DMSO)_5]^+$, and $[H_4PMo_{12}O_{40}(DMSO)_6]^+$, respectively (Fig. 4a), indicating the coordination of DMSO molecules onto HPAs. When an equimolar amount of **1a** with respect to $H_3PMo_{12}O_{40}$ was added to this solution, the CSI-MS spectrum became complicated, but we could assigned several sets of signals; for example, the signal sets centered at 2190, 2241, 2267, 2319, and 2370 were assignable to $[H_3PMo_{12}O_{40}(DMSO)_3(\mathbf{1a'})]^+$ $[H_2PMo_{12}O_{40}(DMSO)_2(\mathbf{1a'})_2]^+$, $[H_3PMo_{12}O_{40}(DMSO)_4(\mathbf{1a'})]^+$, $[H_2PMo_{12}O_{40}(DMSO)_3(\mathbf{1a'})_2]^+$, and $[HPMo_{12}O_{40}(DMSO)_2(\mathbf{1a'})_3]^+$, respectively (Fig. 4b).

From the above ^{1}H NMR and CSI-MS observations, it is likely that the protonation of quinolines affords the quinolinium cation species which are stabilized on HPAs and that DMSO molecules also co-exist on HPAs. Not only HPA frameworks but also the DMSO molecules may cause the steric crowing around the 2-position of quinolines, and thereby the dearomative nucreaphilic addition of CN^- to the 2-position is possibly prevented to give the corresponding 4-cyanoquinolines as the preferential products (Fig. 5).

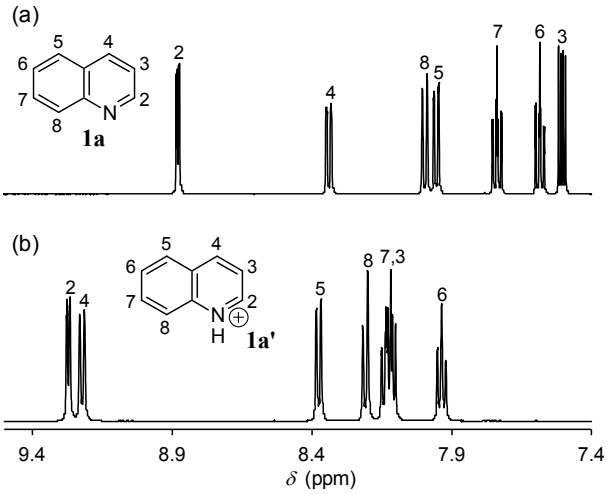


Fig. 3 ^{1}H NMR spectra of DMSO-d_6 solutions of (a) **1a** (0.1 M) and (b) **1a** and $H_7PV_4Mo_8O_{40}$ (0.1 M both). See also Figs. S1 and S2 (NOESY spectra) in ESI†.

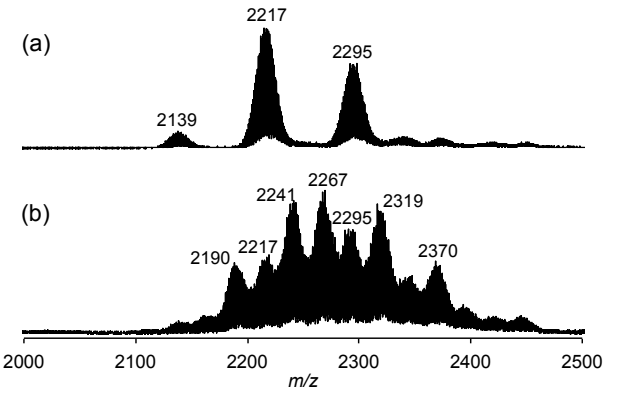


Fig. 4 CSI-MS spectra of DMSO solutions of (a) $H_3PMo_{12}O_{40}$ (5.5 mM) and (b) **1a** and $H_3PMo_{12}O_{40}$ (5.5 mM both) (see the text for their assignments).

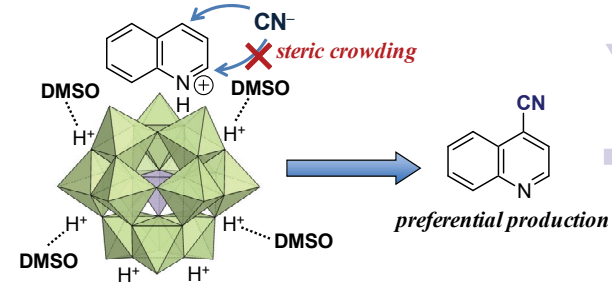


Fig. 5 Origin of the preferential production of 4-cyanoquinoline. The {MO_6} moieties (M = Mo, W, or V) occupy the green octahedra, and the {XO_4} moiety (X = P or Si) is shown as the internal gray tetrahedron.

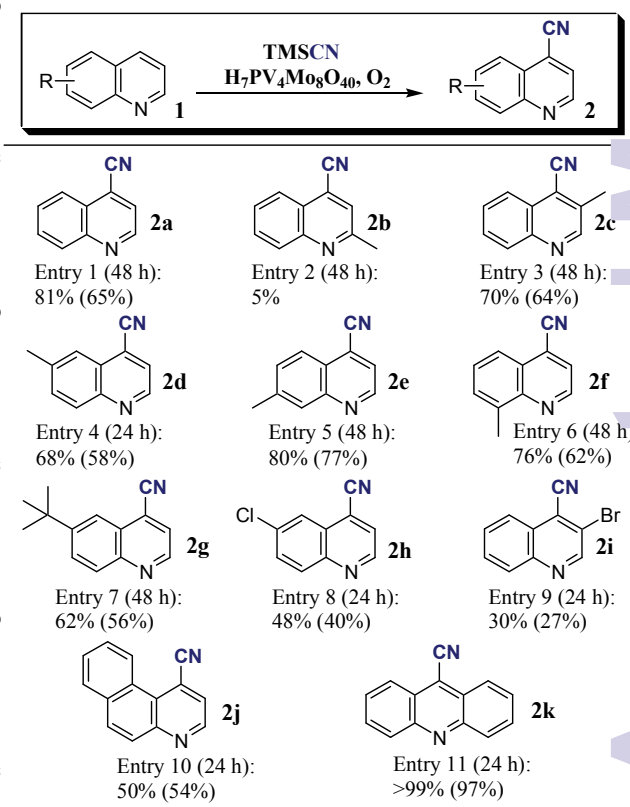


Fig. 6 Scope of the $H_7PV_4Mo_8O_{40}$-catalyzed oxidative C–H cyanation of quinoline and its derivatives. Reaction conditions: (0.5 mmol), TMSCN (2 mmol), $H_7PV_4Mo_8O_{40}$ (10 mol%), DMSO (2 mL), O_2 (1 atm), 100 °C, 24 or 48 h. Yields were determined by GC using naphthalene as the internal standard. The values in the parentheses are the isolated yields of **2**. See Table S3 in ESI† in more detail.

Finally, we turned our attention to the examination of the substrate scope for the present oxidative C–H cyanation using $H_7PV_4Mo_8O_{40}$. Various kinds of quinoline and its derivatives could be converted into the corresponding cyanoquinolines, and the cyanation preferentially took place at 4-position in all cases (Fig. 6, Table S2, ESI†).[20] The cyanation products could readily be isolated by extraction followed by column chromatography on silica gel using a mixed solvent of toluene and diethyl ether as the eluent.[14] As above-mentioned, the cyanation of **1a** preferentially gave **2a** in a high yield (Fig. 6, entry 1). The cyanation of alkyl-

substituted quinolines (except for 2-methylquinoline) efficiently proceeded to give the corresponding alkyl-substituted 4-cyanoquinolines (**2c**–**2g**) in moderate to good yields (Fig. 6, entries 3–7). On the other hand, the cyanation of 2-methylquinoline was not successful likely because of the steric reason (Fig. 6, entry 2). The chloro- and bromo-substituted quinolines afforded the corresponding 4-cyanoquinolines (**2h** and **2i**) in moderate yields without dehalogenation (Fig. 6, entries 8 and 9) Thus, it would be possible to utilize these halo-functionalities for further modification of the cyanoquinoline molecules. A benzo-fused quinoline also gave the corresponding 4-cyanoquinoline (**2j**) (Fig. 6, entry 10). Notably, acridine was quantitatively be converted into 9-cyanoacridine (**2k**) without any formation of other byproducts (Fig. 6, entry 11).

In conclusion, we have successfully developed for the first time the direct oxidative C–H cyanation of quinoline and its derivatives by vanadium-containing HPAs using TMSCN as the cyano source and molecular oxygen as the terminal oxidant. The present cyanation was highly regioselective to the 4-position likely caused by the steric crowding due to HPA frameworks and the solvent molecules coordinated onto HPAs.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, data of **2a**–**2k**, Tables S1–S3, and Figs. S1–S4. See DOI: 10.1039/b000000x/

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18 We confirmed the reoxidation of HPAs by O_2 by means of ^{51}V NMR and UV-Vis. In order to simplify the NMR studies, we utilized $H_4PVMo_{11}O_{40}$. The ^{51}V NMR spectrum of the fresh $H_4PVMo_{11}O_{40}$ (oxidized form) in DMSO-d_6 showed a main signal at −527 ppm (Fig. S3a, ESI†). To this solution, **1a** and TMSCN were added, and the solution was stirred at 100 ºC under an argon atmosphere for 20 h. The orange color of the solution changed to dark green, and the intensity of the signal became weaker (Fig. S3b, ESI†). Molecular oxygen was then introduced to the system, and the solution was stirred at 100 ºC for 0.5 h. By this treatment, the dark green color changed to the near original orange, and the intensity of the ^{51}V NMR signal was somewhat restored (Fig. S3c, ESI†). These results indicate that the HPA (vanadium species) is reduced by **1a** and TMSCN and that the reduced HPA can be reoxidized by molecular oxygen. The UV-vis studies also support the idea (Fig. S4, ESI†).

19 Vanadium-containing HPAs are intrinsically a mixture of various regioisomers and HPAs with different vanadium contents, and their CSI-MS spectra are very complicated. Thus, in order to simplify the CSI-MS studies, we utilized $H_3PMo_{12}O_{40}$ instead of vanadium containing HPAs.

20 Although the present system was applicable to a range of quinolines, the cyanation of pyridines was unsucessful likely because of the difficulty in the dearomative nucleophilic addition.