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A Mild TEMPO-Catalyzed Aerobic Oxidative Conversion of Aldehydes into Nitriles

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Abstract: An efficient method to prepare nitriles from aldehydes using hexamethyldisilazane (HMDS) as the nitrogen source has been developed. The reactions were performed with 2,2,6,6-tetramethylpiperidine l-oxyl (TEMPO) as the catalyst, $NaNO_2$ or TBN as the co-catalyst, and molecular oxygen as the terminal oxidant under mild conditions. A variety of aromatic, heteroaromatic, aliphatic and allylic aldehydes could be converted into their corresponding nitriles in good to excellent yields.

Keywords: aldehydes; hexamethyldisilazane (HMDS); nitriles; oxidation; oxygen; 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)

As a useful intermediate,[1] the nitrile moiety is one of the most important functional groups[2] and can be easily converted into corresponding amines,[3] amides,[4] ketones,[5] carboxylic acids[6] and esters.[7] Furthermore, it is also a key motif in numerous useful compounds such as bioactive natural products,[8] pharmaceuticals,[9] and functional materials.[10] The Sandmeyer reaction was used as the classical synthetic method for aromatic nitriles, while toxic metal cyanides were always required to undergo a cross-coupling with aryl halides.[11] Later on, a large number of new methods such as ammoxidation of alcohols,[12] oxidation of amines,[13] and dehydration of amides[14] or aldoximes[15] have been developed as alternative pathways for the synthesis of nitriles. These methods offer great improvements, but always need high temperature or pressure, stoichiometric or excess amount of highly reactive oxidants, transition metal catalysts or metal complex catalysts.

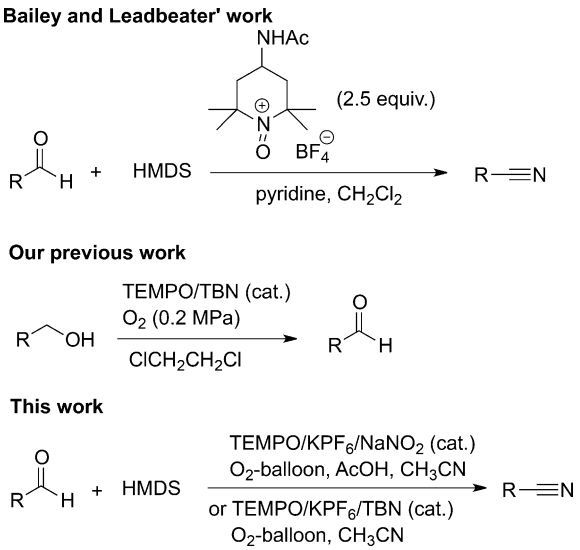
Because of the ready availability of aldehydes, they have been utilized as attractive starting materials for synthesis of nitriles, and several methods have been reported with different compounds as nitrogen sources.[16] However, these reported methods all have some drawbacks: (i) stoichiometric oxidants, like TBHP and $NaICl_2$, were needed; (ii) limited substrates could be used; (iii) transition metal catalysts were essential in most cases. Thus, developing an economical, environmentally friendly and efficient method for the direct synthesis of nitriles from aldehydes still remains a great challenge. Recently, Bailey, Leadbeater and co-workers have provided a new metal-free route to prepare an array of nitriles from aldehydes mediated by an oxoammonium salt (4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, AcNH-TEMPO$^+BF_4^-$) with hexamethyldisilazane (HMDS) as the nitrogen source.[17] This oxidation system is quite simple and can be operated under mild conditions. Nevertheless, 2.5 equiv. of the oxoammonium salt must be employed as the oxidant and 1.1 equiv. of pyridine was used to absorb the highly toxic by-product BF_3.

It is well known that molecular oxygen is an ideal terminal oxidant due to its remarkable advantages, including cleanness, great abundance, inexpensiveness and high atom efficiency. Previously, our group reported a 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)/*tert*-butyl nitrite (TBN)/O_2 catalytic oxidation system for the aerobic oxidation of alcohols, in which TEMPO was employed as the catalyst, TBN as the co-catalyst, and molecular oxygen as the terminal oxidant.[18] In this metal-free system, the key point is that TBN served as the NO equivalent to activate molecular oxygen. In fact, this system was expanded from our previous catalytic oxidation systems, such as TEMPO/Br_2/$NaNO_2$/O_2,[19] TEMPO/HBr/TBN/O_2,[20] TEMPO/1,3-dibromo-5,5-dimethylhydantoin/$NaNO_2$/

O_2,[21] and extended to the TEMPO/DDQ/TBN/O_2 system[22].

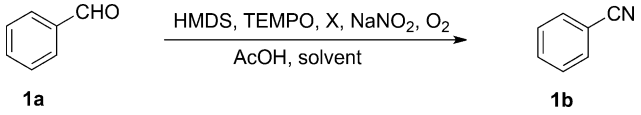
Inspired by our previous work, we attempted to replace the stoichiometric oxidant AcNH-TEMPO$^+BF_4^-$ by the TEMPO/$NaNO_2$ (or TBN)/O_2 system. During the compilation of this present work, Kim et al. reported an aerobic oxidative conversion of aldehydes into nitriles catalyzed by a nitroxyl radical/NO_x system.[23] Unfortunately, aliphatic aldehydes were not suitable for use in their reaction system. Herein we report an efficient methodology for the synthesis of nitriles from aldehydes with HMDS as the nitrogen source using TEMPO as the catalyst, $NaNO_2$ or TBN as the co-catalyst and O_2 as the terminal oxidant under mild conditions (Scheme 1).

Initially, we started to optimize the reaction conditions with benzaldehyde (**1a**) as the model substrate (Table 1).The reaction was carried out with 10 mol% of TEMPO, 10 mol% of $NaNO_2$, 10 mol% of $NaBF_4$, 2.5 equiv. of HMDS in the solution of acetic acid and acetonitrile with an oxygen balloon at 50 °C. Benzonitrile (**1b**) could be obtained with 58% yield as determined by GC using an internal standard method in 8 h (entry 1). When the reaction temperature was decreased from 50 °C to 30 °C, the GC yield of **1b** increased dramatically to 81% (entry 3). Then the additive, $NaBF_4$, was removed from the catalytic system, but the GC yield of **1b** dropped into 65 % (entry 4). This phenomenon suggested that $NaBF_4$ had played an important role in this reaction and we just won-



Scheme 1. The new methodology for the synthesis of nitriles from aldehydes

Table 1. Optimization of the direct synthesis of benzonitrile from benzaldehyde.[a]

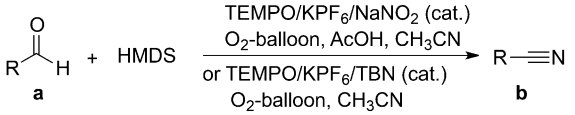


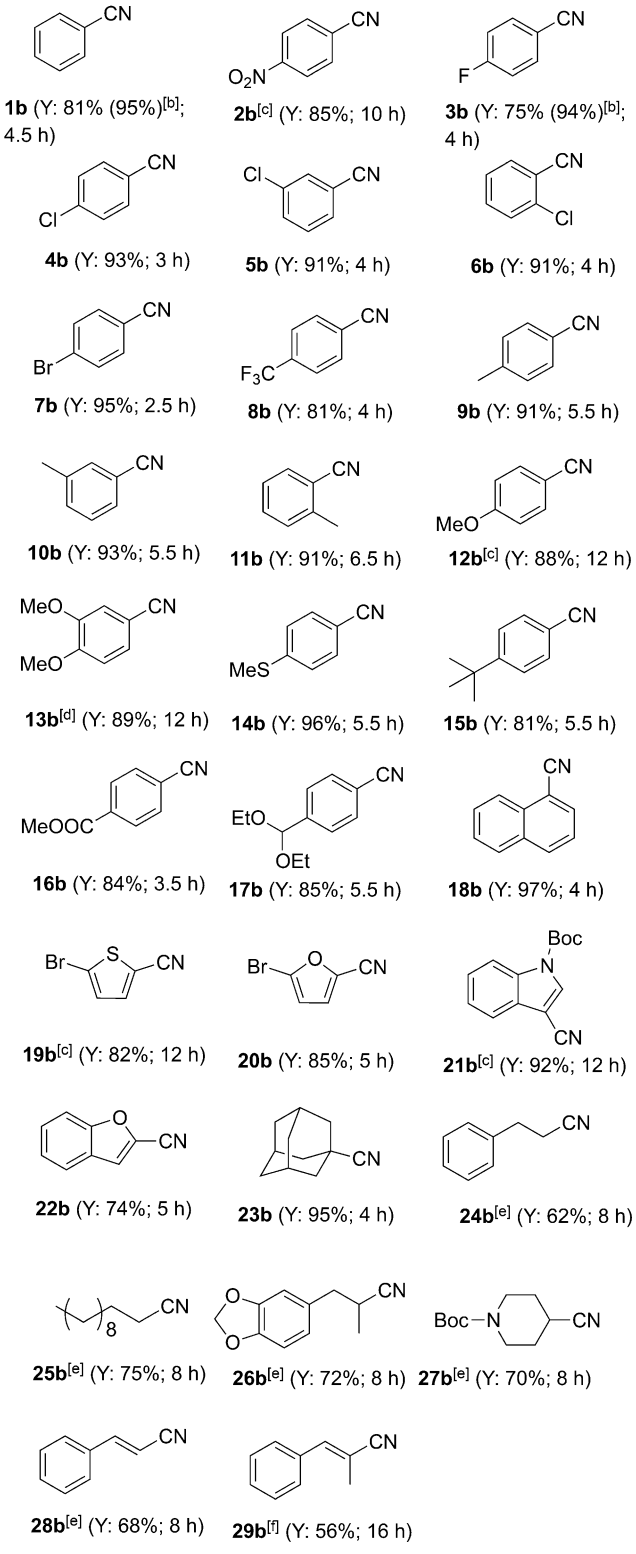
1a **1b**

Entry	HMDS [equiv.]	TEMPO [mol%]	$NaNO_2$ [mol%]	X (mol%)	Solvent	Temp. [°C]	Yield [%][b]
1	2.5	10	10	$NaBF_4$ (10)	CH_3CN	50	38
2	2.5	10	10	$NaBF_4$ (10)	CH_3CN	40	52
3	2.5	10	10	$NaBF_4$ (10)	CH_3CN	30	81
4	2.5	10	10	–	CH_3CN	30	65
5	2.5	10	10	NaCl (10)	CH_3CN	30	67
6	2.5	10	10	KPF_6 (10)	CH_3CN	30	95
7	2.5	10	10	KSCN (10)	CH_3CN	30	20
8	2.5	10	10	KPF_6 (10)	$PhCH_3$	30	trace
9	2.5	10	10	KPF_6 (10)	PhCl	30	trace
10	2.5	10	10	KPF_6 (10)	THF	30	trace
11	2.5	10	10	KPF_6 (10)	EtOAc	30	trace
12	2.5	10	10	KPF_6 (10)	DCM	30	trace
13	2.5	10	10	KPF_6 (10)	DMF	30	23
14	2.5	10	10	KPF_6 (10)	DMSO	30	37
15	2.0	10	10	KPF_6 (10)	CH_3CN	30	80
16	1.5	10	10	KPF_6 (10)	CH_3CN	30	72
17	1.0	10	10	KPF_6 (10)	CH_3CN	30	50
18	2.5	5	10	KPF_6 (10)	CH_3CN	30	77
19	2.5	5	5	KPF_6 (10)	CH_3CN	30	69
20	2.5	5	5	KPF_6 (5)	CH_3CN	30	60
21[c]	**2.5**	**10**	**10**	**KPF_6 (10)**	**CH_3CN**	**30**	**95**

[a] *Reactions conditions:* **1a** (4 mmol, 0. 424 g), 1 mL of AcOH, 5 mL of solvent, oxygen balloon, 8 h.
[b] Yields were determined by GC using an internal standard method.
[c] Reaction time was 4.5 h.

Table 2. Oxidative conversion of aldehydes to nitriles.[a]





dered whether other salts have the same or much better effects. Thereby several salts, such as NaCl, KPF_6, and KSCN were tested (entries 5–7). We observed that the best GC yield of **1b** moved up to 95% on using KPF_6 (entry 6), while KSCN had a negative effect (entry 7). The effects of additives on the reaction might be relevant to the formal redox potential of $TEMPO^+$/TEMPO in the presence of different anions.[24] Several other solvents were also examined and the results showed a crucial effect of the solvent. When some strong polar solvents, like DMF and DMSO, were employed, **1b** was obtained in 23% and 27% GC yield, respectively (entries 12 and 13), whereas other less polar solvents, such as $PhCH_3$, PhCl, THF, EtOAc and dichloromethane, produced a negligible amount of nitrile (entries 8–12).

Encouraged by the above results, the loadings of TEMPO, $NaNO_2$, KPF_6 and HMDS were reduced. When the loading of TEMPO was reduced to 5 mol%, the GC yield of **1b** went down to 77% accordingly (entry 18). In addition, reducing the loading of $NaNO_2$ or KPF_6 could also lead to a lower yield of **1b** (entries 19 and 20). When the load of HMDS was reduced to 2.0, 1.5, and 1.0 equiv., the GC yield of **1b** was decreased to 80%, 72%, and 50%, respectively (entries 15–17). In addition, it was found that the full conversion of **1a** could be achieved with a 95% GC yield of **1b** in 4.5 h with 10 mol% of TEMPO, 10 mol% of $NaNO_2$, 10 mol% of KPF_6, 2.5 equiv. of HMDS in the mixture of acetic acid and acetonitrile at 30 °C (entry 21).

After getting the optimal reaction conditions, the substrate scope of this methodology was investigated and the results are summarized in Table 2. Initially, a series of benzaldehydes with a wide variety of substituent groups were tested. Results indicated that substrates with electron-withdrawing groups, most of which could be converted into their corresponding benzonitriles in 5 h (**3b–8b**), were more active than those with electron-donating ones in this transformation (**9b–15b**). Almost all of the substrates with electron-donating groups needed a longer reaction time or some promotions of the reaction conditions. For example, it was impossible to drive the conversion of

[a] *Reaction conditions:* aldehyde (4 mmol), HMDS (10 mmol), TEMPO (0.4 mmol), $NaNO_2$ (0.4 mmol), KPF_6 (0.4 mmol), 1 mL of AcOH, 5 mL of CH_3CN, O_2-balloon, 30 °C. Y = yield of the isolated product.

[b] Values in parentheses were determined by GC using an internal standard method.

[c] $NaNO_2$ (15 mol%), KPF_6 (15 mol%).

[d] TEMPO (15 mol%), $NaNO_2$ (15 mol%), and KPF_6 (15 mol%), 40 °C.

[e] TBN (15 mol%) without $NaNO_2$ and AcOH, 50 mL of CH_3CN.

[f] $NaNO_2$ (20 mol%), KPF_6 (20 mol%).

4-methylbenzaldehyde (**9a**) to be finished essentially under the optimized conditions until the reaction time was prolonged to 5.5 h. More than that, extending reaction time was an invalid means for some benzaldehydes, such as 4-methoxybenzaldehyde (**12a**) and 3,4-dimethoxybenzaldehyde (**13a**). Both of them needed higher loadings of catalysts to complete their conversions. Besides, the steric hindrance of substituent groups also had an effect on reaction rate. The *ortho*-position substituted substrates accomplished their transformation more difficultly than those with *meta*- or *para*-positioned groups, which was evidenced by the comparison of **9a**, **10a** and **11a**. In order to know the applicability of the protocol for acid labile groups, two acid-sensitive substrates (**16a**, **17a**) were tested. To our delight, **16b** and **17b** were obtained in satisfying yields.

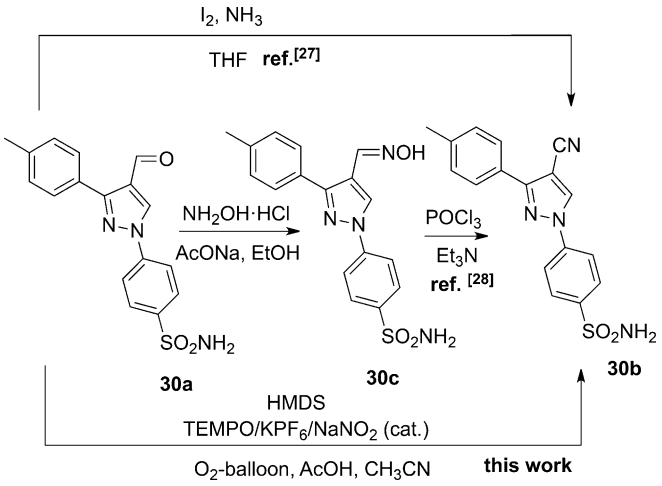
Next, the feasibility for the nitrile formation of polycyclic and heterocyclic systems was examined. A representative polycyclic substrate tolerated our catalytic system giving the product **18b** in excellent yield. Analogously, some heterocyclic examples containing sulfur, oxygen and nitrogen atoms were also verified to give high yields of nitriles (**19b**–**22b**). However, the S-containing substrate **19a** and N-containing substrate **21a** required a longer reaction time and extra 5% of $NaNO_2$ and KPF_6 for full conversions.

Adamantane-1-carbaldehyde (**23a**), an α-saturated aliphatic aldehyde, gave the desired nitrile **23b** in 95% yield. Aliphatic aldehydes with α-H atoms could undergo a self-aldol condensation easily in the presence of silylated amines.[25] This result was proved by the representative aliphatic aldehyde, 3-phenylpropanal (**24a**), which did not afford the target product under our optimized reaction conditions. According to Kelly's work,[17] adding HMDS slowly to the reaction solution was an effective way to avoid this unwanted side reaction. But unfortunately, it did not work in our reaction system, and the same result was observed on adding aldehyde **24a** slowly into the reaction solution. However, to our surprise, when $NaNO_2$ was replaced by the equal amount of TBN and the acetic acid was removed from the reaction mixture, an about 20% yield of **24b** was obtained. With this encouraging finding in hand, the final yield of **24b** reached up to 62% by adding aldehyde slowly into the reaction mixture with a ten-fold amount of solvent. The above results demonstrated that there was a competitive relationship between the oxidation reaction and the self-aldol condensation of **24a** under alkaline conditions. When in acidic solution, the rate of self-aldol condensation remained overwhelmingly superior to the desired oxidation reaction. Much to our delight, some other α-unsaturated aldehydes, such as undecanal, helional and *N*-Boc-piperidin-4-ylformaldehyde also could be converted into the desired nitriles with satisfying yields in this promoted method (**25b**–**27b**). The reactions of allylic aldehydes were also studied. Aerobic oxidation converison of cinnamaldehyde (**28a**) to cinnamonitrile (**28b**) could be successfully performed with the TEMPO/KPF_6/TBN catalytic system, while (*E*)-2-methyl-3-phenylacrylaldehyde (**29a**) could be oxidized to (*E*)-2-methyl-3-phenylacrylonitrile (**29b**) with the TEMPO/KPF_6/$NaNO_2$ catalytic system.

Compound **30b** displays appreciable anti-inflammatory and selective COX-2 inhibitory activity.[26] Generally, there used to be two common routes for the synthesis of **30b** (Scheme 2). In one route, aldehyde **30a** was oxidized by an excess amount of iodine with ammonia as the nitrogen source in THF to afford compound **30b** directly.[27] The other route included two steps, formation of the intermediate **30c** and then a subsequent dehydration process with $POCl_3$/TEA.[28] To further expand our newly developed method, compound **30b** was subjected to our oxidation system, the reaction was smoothly performed and a 95% isolated yield of **30c** was obtained.

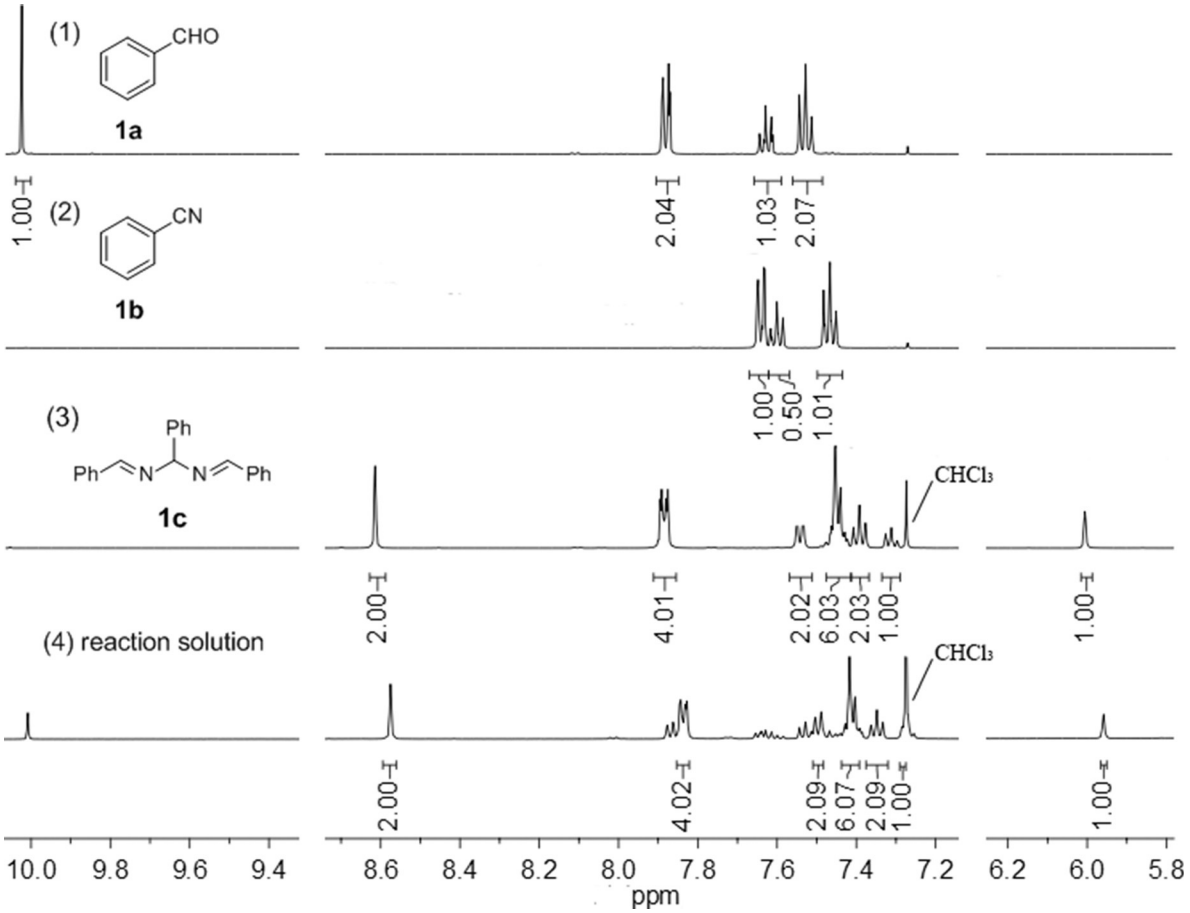
As mentioned in the above discussion, electron-withdrawing groups had a positive effect on the transformation of benzaldehydes to benzonitriles. It was assumed that the formation rate of 4-nitrobenzonitrile (**2b**) must be fast, but the reaction could not reach completion unless the loadings of $NaNO_2$ and KPF_6 were increased to 15 mol% and the reaction time prolonged to 10 h (Table 2). Meanwhile, a great deal of precipitate was generated shortly after the beginning of the reaction and disappeared very slowly. Hence, we speculated that the reaction might involve an intermediate which would be transformed to the final product. The poor solubility of the intermediate in the oxidation conversion of 4-nitrobenzaldehyde led to the lower rate of generation of **2b**.

Nishiyama's group has synthesized a series of *N*′,*N*-disubstitued methanediamine derivatives from HMDS and aldehydes catalyzed by $ZnCl_2$,[29] *N*,*N*′-dibenzyli-

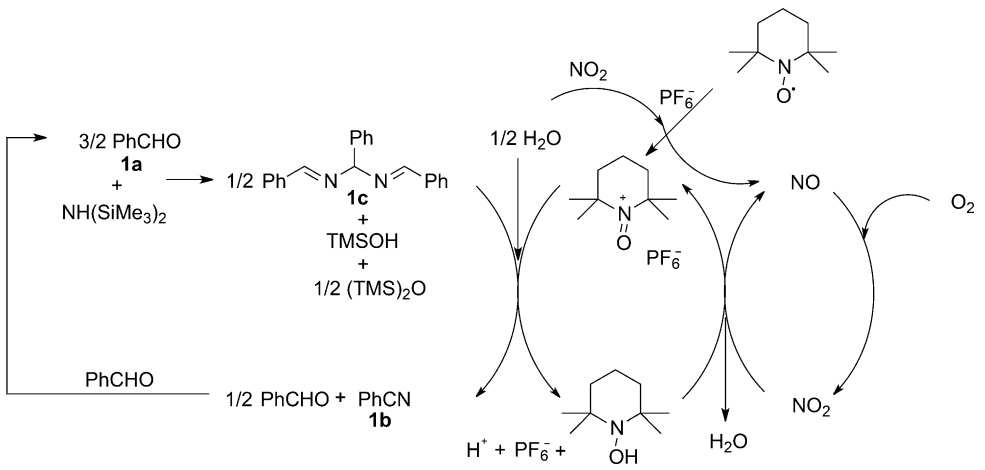


Scheme 2. Application of the TEMPO/KPF_6/$NaNO_2$/O_2 system.

dene-1-phenylmethanediamine (**1c**) was one of examples. We successfully synthesized and separated compound **1c** with benzaldehyde, HMDS and AcOH in CH_3CN. Then **1c** was submitted to our TEMPO/KPF_6/$NaNO_2$/O_2 oxidation system; to our delight, the expected product benzonitrile (**1b**) was detected and the only side product was benzaldehyde. Furthermore, when the reaction mixture of the oxidative conversion **1a** to **1b** was directly subjected to ^{1}H NMR analysis, **1c** could also be detected after reaction time of 1 h (Scheme 3). Thus we speculated that **1c** was the crucial intermediate for the current synthesis of **1b**.



Scheme 3. ^{1}H NMR spectral evidence for the mechanism: (1) **1a**; (2) **1b**; (3) **1c**; (4) the reaction mixture of oxidative conversion **1a** after a reaction time of 1 h.



Scheme 4. A proposed overall reaction mechanism.

The overall reaction mechanism for the present aerobic oxidative conversion of benzaldehyde to benzonitrile is described in Scheme 4. Under the acidic conditions, $NaNO_2$ can release NO, which will be easily oxidized into NO_2 by O_2. Benzaldehyde reacts with HMDS to give *N*,*N*′-dibenzylidene-1-phenylmethanediamine (**1c**), which can be oxidized by $TEMPO^+$ to give benzaldehyde and benzonitrile in the presence of H_2O. At the same time $TEMPO^+$ is reduced to TEMPOH. TEMPOH is subsequently regenerated to $TEMPO^+$ by NO_2, which turns into NO immediately.

In conclusion, we have successfully developed an efficient methodology for the aerobic oxidative conversion of aldehydes to their corresponding nitriles with HMDS as the nitrogen source using TEMPO as the catalyst, $NaNO_2$ or TBN as the co-catalyst. The homogeneous catalytic system is practical, environmentally friendly as it is performed at low temperature under atmospheric pressure without any transition metal catalysts and accommodates a broad range of substrates including aromatic, heteroaromatic, aliphatic and allylic aldehydes with good to excellent yields. This protocol has been successfully applied in the synthesis of a biological compound. In addition, an overall reaction mechanism has also been proposed.

Experimental Section

General Procedure for the Synthesis of Nitriles from α-Saturated Aldehydes as Exemplified for Benzonitrile (1b)

To a 20-mL, two-necked, round-bottom flask equipped with a magnetic stirring bar and a thermometer, were added 0.424 g (4 mmol) of **1a**, 5 mL of CH_3CN, 1.62 g (10 mmol) of HMDS, 0.0624 g (0.4 mmol) of TEMPO, 0.0268 g (0.4 mmol) of $NaNO_2$ and 0.0737 g (0.4 mmol) of KPF_6. Then the flask was sealed by a rubber plug after being charged with oxygen to replace the air in it. The flask was placed into a preheated water bath (30 °C). After that, 1.0 mL of glacial acetic acid was injected to the solution, and the mixture was stirred under a dioxygen atmosphere (balloon). After the reaction was finished (as determined by GC), to the reaction mixture were added 10 mL of 5% of $Na_2S_2O_3$ solution and stirred for 15 min. Then the mixture was transferred into a separation funnel, and 150 mL of diethyl ether were also added to the separation funnel. The two-phase mixture was washed with saturated sodium bicarbonate solution (25 mL × 2). Then the organic layer was dried with Na_2SO_4, concentrated on a rotary evaporator and the residue was purified by column chromatography on silica gel using hexanes/EtOAc (200:1) as eluent to afford **1b** as a colorless liquid; yield: 0.324 g (81%).

General Procedure for the Synthesis of Nitriles from α-Unsaturated Aldehydes as Exemplified for Undecanedinitrile (25b)

To a 100-mL, two-necked, round-bottom flask equipped with a magnetic stirring bar and a thermometer, were added 50 mL of CH_3CN, 1.62 g (10 mmol) of HMDS, 0.0624 g (0.4 mmol) of TEMPO and 0.1106 g (0.6 mmol) of KPF_6. Then the flask was sealed by a rubber plug after being charged with oxygen to replace the air in it. The flask was placed into a preheated water bath (30 °C). Meanwhile, 72 μL (0.6 mmol) of TBN were injected to the solution followed by stirring for 5 min under a dioxygen atmosphere (balloon). After that, 0.681 g (4 mmol) of undecanal was injected into the solution slowly (25 times, every 10 min once). The work-up procedure was as same as that for the synthesis of **1b**, and **25b** was obtained as a colorless liquid; yield: 0.380 g (62%).

Acknowledgements

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