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TEMPO-catalyzed Aerobic Oxygenation and Nitrogenation of Olefins via C=C Double-Bond Cleavage

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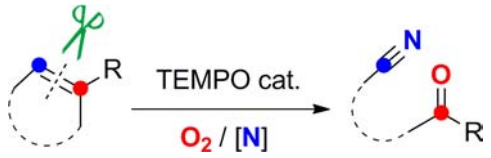
Supporting Information

ABSTRACT: A novel TEMPO-catalyzed aerobic oxygenation and nitrogenation of hydrocarbons via C=C double-bond cleavage has been disclosed. The reaction employs molecular oxygen as the terminal oxidant and oxygen-atom source by metal-free catalysis under mild conditions. This method can be used for the preparation of industrially and pharmaceutically important N- and O-containing motifs, directly from simple and readily available hydrocarbons.

The alkene functionalization is an essential functional group interconversion for organic synthesis.[1] The resulting compounds from alkene functionalization take a privileged position in the fields of pharmaceuticals, agrochemicals, and materials. Among intensive research in olefin chemistry, transition-metal-catalyzed C=C double-bond cleavage is a fundamental method in building complex molecules that would be unapproachable by other methods.[2] For example, the venerable ring-closing metathesis (RCM) processes offer an efficient approach to various medium and large cyclic hydrocarbons with transition-metal catalysts.[3] Although significant progresses have been made, some crucial issues have remained fairly unaddressed: (1) there are restrictions in terms of substrate scopes; (2) expensive and toxic metals are often employed; and (3) for oxidative transformation, unattractive stoichiometric oxidants are sometimes utilized. Therefore, the development of a promising access toward alkene functionalization associated with these challenges is highly desired.

Organocatalysis has attracted considerable attention and has been significantly developed.[4] Organic radicals have similar behavior to that of high-valent metals, but the attractive features of these compounds have not been identified as efficient catalysts due to instability issues. Notably, a representative stable radical, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), has been reported as a nonmetal catalyst in C−C bond formations[5] with molecular oxygen as the terminal oxidant.[6] Herein, we report a TEMPO catalyzed C=C double-bond cleavage to produce oxo nitriles using molecular oxygen as the terminal oxidant and a useful reagent $TMSN_3$ as the nitrogen source (Scheme 1).[7] The current protocol has many advantages and can be summarized as follows: (1) Variant alkenes, including terminal, di- and trisubstituted alkenes, are compatible. (2) A simple and readily available TEMPO has emerged as an efficient organocatalyst. (3) The incorporation of O- and N-atoms into simple hydrocarbons is achieved to convert alkenes to highly useful N- and O-containing building blocks for synthesis. (4) The TEMPO-O_2 system is inexpensive, mild, and easily handled with high catalytic efficiency and safety.

Scheme 1. Our Strategy of Olefins Direct Oxidative Nitrogenation via C=C Double-Bond Cleavage



Recently, we developed several approaches to N-containing compounds via oxidative nitrogenation involving C−C bond cleavage.[8] This is conceived and of long-standing interest by us. Among a number of failed attempts, an intriguing result attracted our attention. When α-methylstyrene **1** was submitted to catalytic amount of TEMPO in the presence of $TMSN_3$ under oxygen, acetophenone **2** was detected by GC-MS. This result indicates that the nitrogen source may play an important role in C=C double-bond cleavage, albeit the nitrogenation products are not observed. Hence, 1*H*-indene **3** was selected as the substrate for the model reaction. As expected, even at ordinary pressure, the reaction gave the nitrogenation product **3a** in good yield with high regioselectivity (entry 1, Table 1; optimization details, see SI). The reaction of **3** in gram scale (1.16 g) afforded **3a** in 76% yield (Table S5). Therefore, the present protocol concurrently realizes oxygenation and nitrogenation of C=C double bonds with high efficiency.

Subsequently, the scope of this oxidative oxygenation and nitrogenation transformation was investigated (Table 1). Some benzocycloalkenes gave the desired products in moderate yields (entries 1−3). The regioselectivity of these substrates is very high with oxygenation occurring at the benzylic site. The reactivity of aliphatic olefins is much lower than benzylic substrates. Upon testing a number of different additives, however, we found that inclusion of phenyliodiodiacetate (PIDA) enabled formation of the oxo nitrile products in moderate yield with simple cyclic olefins (entries 4−7). Although the exact role of PIDA is not clear yet, the presence of PIDA could improve the efficiency significantly. For example, the reaction in the presence of PIDA produced **7a** in 60% yield (entry 6, Table 1). However, only trace amount of **7a** was obtained in the absence of PIDA (entry 1, Table S3).

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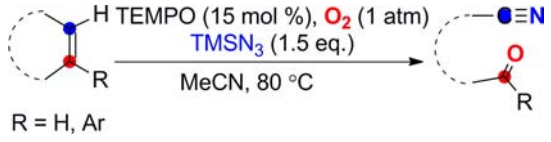
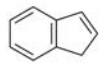
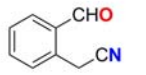
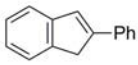
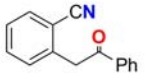
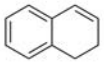
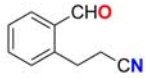
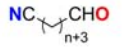
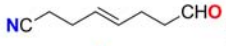
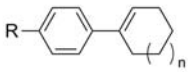
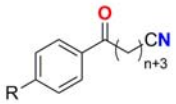
Table 1. TEMPO-Catalyzed Oxidative Nitrogenation of Diverse Olefins[a]



entry	substrate		product		yield	(%)[b]
1[c]		3			3a	82
2[c]		4			4a	50
3		5			5a	38
4[d]		n = 1 6			6a	30
5[d]		n = 3 7			7a	60
6[d]		n = 7 8[e]			8a	43
7[f]		9			9a	34
						
8	R = H, n = 1	10			10a	90
9	R = Me, n = 1	11			11a	82
10	R = OMe, n = 1	12			12a	52
11	R = F, n = 1	13			13a	83
12	R = Cl, n = 1	14			14a	95
13	R = Br, n = 1	15			15a	56
14	R = H, n = 2	16			16a	91
15	R = H, n = 3	17			17a	70

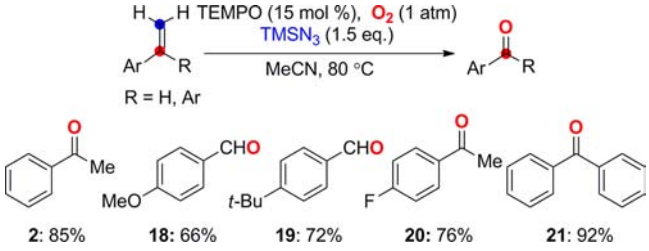
[a]Reaction conditions: olefin (0.3 mmol), $TMSN_3$ (0.45 mmol), TEMPO (0.045 mmol) in MeCN (2.0 mL) at 80 °C for 36 h under oxygen (1 atm). [b]Isolated yields. [c]Reation was carried out for 24 h. [d]10 mol % PIDA was added. [e]With *cis* and *trans* mixture. [f]10 mol % TBHP (5.5 M in decane) was added.

Furthermore, the reaction with PIDA in the absence of TEMPO catalyst only afforded the desired product in 13% yield (entry 13, Table S3). Interestingly, even a large ring like **8** gave the desired long-chain oxo nitriles **8a** in 43% yield (entry 6). It is noteworthy that (1*z*,5*z*)-cycloocta-1,5-diene (COD) gave **9a** in 34% yield with one double bond retained (entry 7). Trisubstituted cyclic olefins, such as 1-arylcycloalkenes, react smoothly under the standard conditions (entries 8−15). The substitution effect is not obvious among these substrates. However, 1-methyl cyclohexene did work under the standard conditions. Notably, **14a** was obtained in 95% yield (entry 12), and larger cyclic olefins were also tolerant in this transformation (entries 14 and 15).

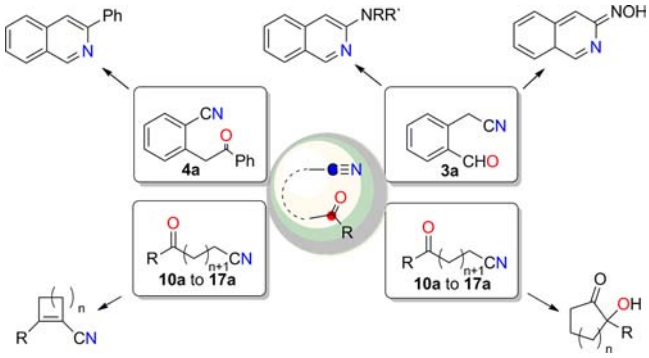
Terminal alkenes, such as styrenes, gave the corresponding carbonyl compounds in good yields (Scheme 2). Benzophenone **21** was obtained in 92% yield from 1,1-diphenylethylene. To investigate the possible one carbon product, α-methyl styrene was carried out under the standard conditions. After the reaction, HCN as another product has been detected in the solvent by GC-MS (see SI).

This protocol of oxidative cleavage of olefins may have profound implications of synthesis, since it offers facile approaches to many valuable compounds (Scheme 3). For

Scheme 2. TEMPO-Catalyzed Oxidative Nitrogenation of Some Terminal Alkenes



Scheme 3. The Profound Implications of Oxo Nitriles in Organic Synthesis

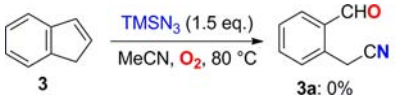


instance, 2-arylacetonitriles, such as **3a**, are versatile building blocks in the synthesis of isoquinoline derivatives.[9] Benzonitrile derivatives, such as **4a**, are reported as synthetic precursors of isoquinolines.[10]

In addition, oxo nitriles derived from 1-arylcyclic olefins (such as **10**−**17**) have been used to produce α-hydroxyketones which are present in a multitude of natural products.[11,12] Furthermore, these oxo nitriles (such as **10a**−**17a**) are utilized as key intermediates to synthesize alkenenitriles.[13]

It should be mentioned that this protocol establishes more efficient and concise synthetic methodologies. For example, as common synthons, **6a** is often produced through multisteps from pentane-1,5-diol.[14] After careful unilateral bromination, cyanation, and oxidation, the target product is isolated in 13% overall yield. In contrast, it can be easily produced simply from cyclohexene **6** by this present approach (Scheme 4i). Moreover, the current method is also attractive due to its mild conditions and convenient operations. Another convincing example is the synthesis of previously mentioned aliphatic oxo nitriles (such as **10a**, Scheme 4ii). Traditional condensations need strict inert gas protection for the sake of moist-sensitive bases with cumbersome operations.[15] Conversely, under the present conditions, these compounds have been smoothly produced in 50−95% yields starting from simple and readily available 1-arylcyclic alkenes.

Many control experiments have been investigated to probe the mechanism of this TEMPO-catalyzed oxygenation and nitrogenation chemistry. The results indicate that TEMPO is required for this transformation (eq 1). The result of ^{18}O-



(1)

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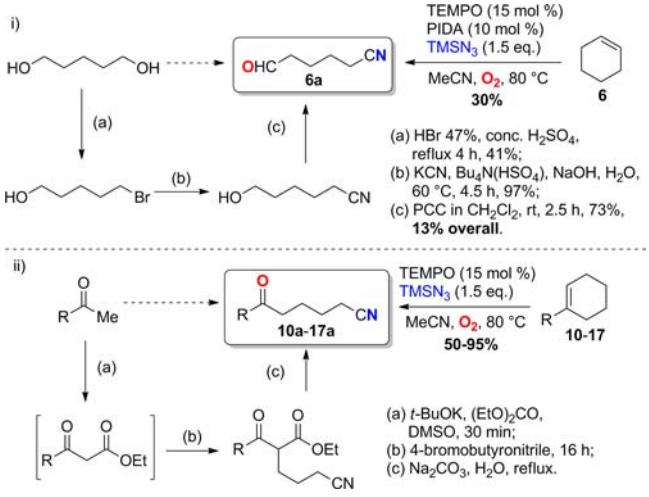
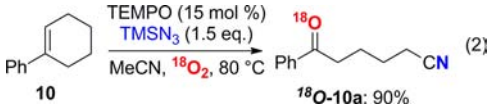
Scheme 4. A Concise Approach to Synthetic Important Oxo Nitriles



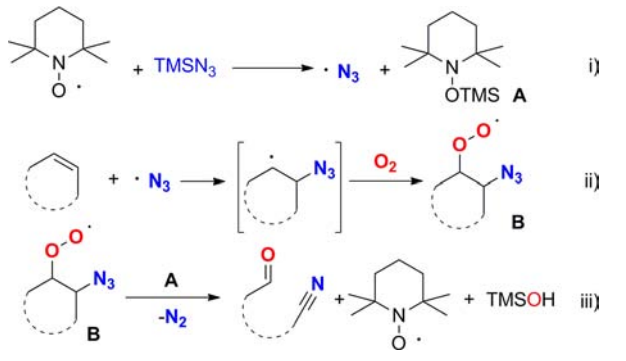
labeling experiment proves the dual functions of molecular oxygen as both an oxidant to reoxidize the catalyst and an oxygen source for the oxygenation process (eq 2). The reaction



is not sensitive to water and the isolated yield of product insensitive to the presence of 2 equiv of water. No product was observed in the presence of water under argon (eq 3).

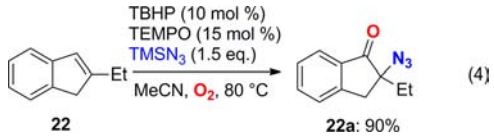
On the basis of the preliminary results, a plausible pathway is proposed for this oxygenation and nitrogenation reaction (Scheme 5). Initially, $TMSN_3$ generates azido free radical associated with the formation of intermediate **A**[16] (Scheme 5i), which is detected by GC-MS (see SI). The azido free radical subsequently attacks the alkene and terminates with molecular oxygen to form peroxide radical **B** (Scheme 5ii). Subsequently, the peroxyl radical **B** reacts directly with the TEMPO-TMS species **A**, followed by a continuous rearrangement and

Scheme 5. Proposed Mechanism of This Oxidative Nitrogenaion of Olefins



heterolysis of the O−O bond to form the desired oxo nitrile product, with the regeneration of the catalyst, the release of N_2 and the formation of TMSOH (GC-MS detected, see SI) (Scheme 5iii). Although the precise process from **B** to product is not completely clear yet, α-azido ketone and β-hydroxyl azide were excluded as the intermediates involved in this process by the control experiments (see SI).

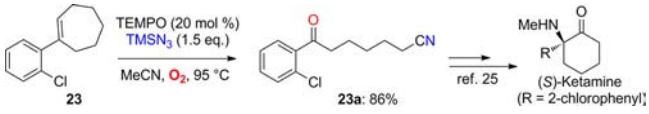
The regioselectivity of this transformation may be interpreted by the stability of the possible α-azido radical intermediates. This hypothesis was further confirmed by parallels between 2-phenyl-1*H*-indene **4** (entry 2, Table 1) and its analogue **22** (eq 4). When phenyl was replaced by ethyl,



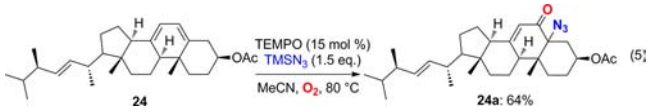
the regioselectivity led to a Wacker-type oxidation product **22a** in 90% yield. *t*-Butyl hydroperoxide (TBHP) was identified as an essential additive in this reaction; low efficiency was observed in its absence.

The current method provides many opportunities to synthesize useful intermediates. For instance, the widely used anesthetic and analgesic medicine, the (*S*)-ketamine, was enantiomerically prepared from oxo nitrile **23a** in many steps.[17] As previously mentioned, it is inevitable to undergo trivial manipulations to obtain **23a**. Alternatively, with our concise strategy, this compound has been prepared in 86% yield with readily available alkenes (Scheme 6).

Scheme 6. Synthesis of Key Intermediate of Ketamine



To our delight, this kind of TEMPO-$TMSN_3$ system could be executed in the oxidation of steroids (eq 5). Ergosterol is a



vital steroid as the precursor of vitamin D. In this case, the α-oxo azide product **24a** was obtained in 64% yield without further Schmidt rearrangement due to the polysubstituents (eq 5). Despite rarely reported in preparation,[18] many studies in steroid chemistry have shown that α-azido steroidal ketones like **24a** are key intermediates to α-aminoalcohols,[19] α-aminoketones,[20] and bis-steroidal pyrazines.[21]

In conclusion, selective C−C bond functionalization has been considered as one of the most challenging and attractive process because it enables the straightforward utilization of hydrocarbons in organic synthesis. This chemistry provides an efficient and concise strategy for the synthesis of various oxo nitriles, which can be used for the further preparation of industrially and pharmaceutically important N- and O-containing compounds, directly from simple and readily available hydrocarbons. The metal-free catalysis and aerobic oxidation under mild conditions could make it significant and attractive in chemical synthesis.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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