Aerobic Catalytic Oxidation
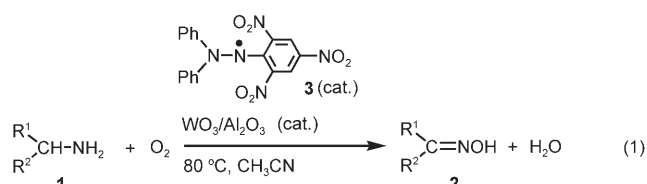
Aerobic Oxidation of Primary Amines to Oximes Catalyzed by DPPH and WO₃/Al₂O₃

Ken Suzuki,* Tomonari Watanabe, and Shun-Ichi Murahashi*

Since the catalytic oxidation of amines is important for enzymatic[1] and synthetic processes,[2] various methods have been examined; however, useful methods for the oxidation of amines are limited because of the sensitivy of amines. Selective catalytic oxidative transformations of secondary amines to nitrones[3,4] and imines[5,6] have been explored. However, selective catalytic oxidation of primary amines **1** to oximes **2** [see Eq. (1)] has been not achieved, although oximes are useful intermediates for the synthesis of fine chemicals, medicines, and biologically active compounds.[7] Catalytic oxidation of primary amines with hydrogen peroxide gives oximes along with by-products such as nitroalkanes, carbonyl compounds, and imines.[8–12]

Aerobic oxidation under mild conditions is one of the current challenges in view of environmental and economical aspects;[13,14] however, aerobic oxidative transformations of amines are limited to a few reactions, which include the ruthenium-catalyzed oxidative cyanation of tertiary amines,[15] transition-metal-catalyzed oxidation of secondary amines to imines[6] and of primary amines to nitriles,[16] and flavin-catalyzed oxidation of secondary amines to nitrones.[4] There is no efficient method so far for the *aerobic* oxidation of primary amines to oximes. The reported method employing a heterogeneous catalyst such as SiO₂ gel at higher temperature (>150°C) gives oximes only in low yields.[17] Herein, we report a highly selective and efficient catalytic method for the oxidation of primary amines to oximes by employing 1,1-diphenyl-2-picrylhydrazyl (DPPH; **3**)[18] and tungstated alumina (WO₃/Al₂O₃) as the catalyst and molecular oxygen as the terminal oxidant [Eq. (1)].

We sought to find a catalyst for the aerobic catalytic oxidation of cyclohexylamine. Attempts at transition-metal-catalyzed oxidation of amines to oximes failed. Aerobic catalytic oxidation of primary amines with transition-metal

$$
\begin{array}{c}
\text{Ph} \\
\diagdown \\
\text{N–N}^\bullet \\
\diagup \\
\text{Ph}
\end{array}
\begin{array}{c}
\text{O}_2\text{N} \\
\diagup \\
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\text{O}_2\text{N}
\end{array}
\text{NO}_2 \quad \mathbf{3} \text{ (cat.)}
$$

$$
\underset{\mathbf{1}}{\overset{R^1}{\underset{R^2}{\diagup}}}\text{CH–NH}_2 + \text{O}_2 \xrightarrow[80\,°C,\ CH_3CN]{WO_3/Al_2O_3\ (cat.)} \underset{\mathbf{2}}{\overset{R^1}{\underset{R^2}{\diagup}}}\text{C=NOH} + \text{H}_2\text{O} \qquad (1)
$$

complexes as catalysts was found to give nitriles resulting from extensive oxidative dehydration.[16] Furthermore, dehydration of aldoximes occurs at higher temperatures to give nitriles.[19] Next, we examined organocatalysts. Attempts using typical catalysts such as flavin,[4] 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO),[20] and phthalimide-N-oxyl (PINO) derived from N-hydroxyphthalimide (NHPI)[21] failed. We then focused on DPPH, which had never been used for catalytic oxidation. Ultimately, the combination of DPPH and WO₃/Al₂O₃ proved to be an excellent catalyst.

The catalytic activity of various catalysts for the aerobic oxidation of cyclohexylamine is summarized in Table 1. Among the catalysts examined, the system of DPPH and WO₃/Al₂O₃ proved to be the best catalyst (Table 1, entry 1). The reaction of cyclohexylamine in the presence of DPPH (2.5 mol%) and WO₃/Al₂O₃ (1 mol%) under molecular oxygen diluted with molecular nitrogen for safety (O₂/N₂ = 7:93 v/v, 5 MPa, under the explosion limit) in acetonitrile at 80°C for 4 h gave cyclohexanone oxime with 95% selectivity

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author. DPPH = 1,1-diphenyl-2-picrylhydrazyl.

Table 1: The aerobic oxidation of cyclohexylamine to cyclohexanone oximes using various catalysts.[a]

Entry	Catalyst	Conversion of amine [%][b]	Selectivity for oxime [%][b]
1	DPPH–WO₃/Al₂O₃	59	95
2	DPPH	21	3
3	WO₃/Al₂O₃	7	0
4	DPPH–WO₃/ZrO₂	63	86
5	DPPH–TS-1	14	93
6	DPPH–[Ti(O*i*Pr)₄]	67	88
7	DPPH–[TiO(acac)₂]	61	89
8	DPPH–Nb₂O₅	50	80
9	DPPH-H–WO₃/Al₂O₃	41	96
10	DOPH–WO₃/Al₂O₃	62	96
11	TEMPO–WO₃/Al₂O₃	4	2
12	NHPI–WO₃/Al₂O₃	7	3
13[c]	TEMPO–[RuCl₂(PPh₃)₃]	21	0
14[d]	NHPI–[Co(acac)₂]	36	0

[a] Reaction conditions: Cyclohexylamine (5 mmol), organocatalyst (2.5 mol%), transition-metal catalyst (metal: 1 mol%) in acetonitrile (3 mL), O₂ (O₂/N₂ = 7:93; 5 MPa) at 80°C for 4 h. [b] Determined by GC analysis using an internal standard. [c] 3 mol% TEMPO, 1 mol% [RuCl₂(PPh₃)₃]. [d] 10 mol% NHPI, 0.5 mol% [Co(acac)₂]. acac = acetylacetonate.

and 59% conversion. Control experiments showed that DPPH and WO_3/Al_2O_3 alone exhibited no catalytic activity, and the coexistence of DPPH and WO_3/Al_2O_3 is necessary for the high catalytic activity (Table 1, entries 2 and 3). WO_3/ZrO_2, TS-1, $[Ti(OiPr)_4]$, $[TiO(acac)_2]$, and Nb_2O_5 can be used as the cocatalyst of DPPH (Table 1, entries 4–8), while MoO_3/Al_2O_3, $[MoO_2(acac)_2]$, $[VO(acac)_2]$, $[Fe(acac)_3]$, and $[Co(acac)_2]$ are ineffective. The use of 1,1-diphenyl-2-picrylhydrazine (DPPH-H) or 1,1-di(4-tert-octylphenyl)-2-picrylhydrazyl (DOPH) instead of DPPH gave good results (Table 1, entries 9 and 10), while N-oxyl radicals[20a] such as TEMPO and PINO showed very low catalytic activity (Table 1, entries 11 and 12). Catalysts which show excellent activity for aerobic oxidation of alcohols or hydrocarbons, such as TEMPO with $[RuCl_2(PPh_3)_3]$[20] or NHPI with $[Co(acac)_2]$,[21] are inactive (Table 1, entries 13 and 14).

The choice of a solvent is also important. The reaction in a polar aprotic solvent such as acetonitrile or N,N-dimethylformamide gave a high conversion, while the reaction in a nonpolar solvent such as toluene or chlorobenzene gave a low conversion. Use of a protic solvent such as water, methanol, or tert-butanol resulted in low conversions.

The results of the oxidation of various primary amines catalyzed by DPPH (5 mol%) and WO_3/Al_2O_3 (1 mol%) in acetonitrile under O_2/N_2 (7:93 v/v, 5 MPa) at 80°C for 8 h are summarized in Table 2. The oxidation of cyclohexylamine gave cyclohexanone oxime (90%) along with nitrocyclohexane (4%) and cyclohexanone (2%; Table 2, entry 1). From a gram-scale reaction cyclohexanone oxime was obtained in 85% yield of isolated product. No decomposition of DPPH was observed under the reaction conditions. The WO_3/Al_2O_3 catalyst was separated by filtration, after which tungsten was not observed in the filtrate by ICP analyses. The oxidation proceeded efficiently under atmospheric pressure of molecular oxygen (1 atm, balloon; Table 2, entry 2), whereas the reaction did not occur in the absence of molecular oxygen. A manometric measurement of oxygen uptake revealed that an equimolar amount of molecular oxygen was consumed for the oxidation of the amine. The cyclohexanone oxime thus obtained is an important precursor of ε-caprolactam, a raw material of nylon 6. Alicyclic amines can be converted into the corresponding oximes in excellent yields (Table 2, entries 3–7). The aerobic oxidation of aliphatic amines also gave the corresponding oximes in good yields. Typically, the oxidation of octylamine gave the corresponding oxime (73%) and nitrile (7%; Table 2, entry 9). The reaction can tolerate other oxidizable groups and seems to be quite selective for amines. Thus, the oxidation of 4-hydroxylcyclohexylamine proceeded chemoselectively to afford the corresponding oxime in 82% yield (Table 2, entry 8). Chemoselective oxidation of 5-hydroxylpentylamine was also observed (Table 2, entry 10). The reaction of tertiary amines such as tert-butylamine did not occur.

Importantly, the DPPH–WO_3/Al_2O_3 catalyst could be reused without loss of catalytic activity or selectivity. The yield of cyclohexanone oxime could be kept at a similar value through three cycles of catalyst recycling (Table 3).

The reaction can be rationalized by assuming the mechanism shown in Scheme 1. Initially, fast electron transfer from

Table 2: Aerobic oxidation of primary amines to oximes catalyzed by DPPH–WO_3/Al_2O_3.[a]

| Entry	Substrate	t [h]	Conversion [%][b]	Yield of oxime [%][b]
1	(cyclohexylamine, NH_2)	8	98	90 (85)[c]
2	(cyclopentylamine, NH_2)	16	98	89[d]
3	(NH_2)	8	97	82
4	(NH_2)	48	96	73
5	(NH_2)	48	95	80
6	(NH_2)	48	90	72
7	(NH_2)	8	97	85
8	(HO–, NH_2)	48	97	82
9	(NH_2)	36	94	73[e]
10	(HO–, NH_2)	48	95	75[e]

[a] Reaction conditions: primary amine (5 mmol), DPPH (5 mol%), WO_3/Al_2O_3 (W: 1 mol%) in acetonitrile (3 mL), O_2 ($O_2/N_2 = 7:93$; 5 MPa) at 80°C. [b] Determined by GC analysis using an internal standard. [c] The yield of isolated product obtained from a gram-scale reaction is in parentheses. [d] O_2 atmosphere (1 atm, balloon) at 80°C. [e] 10 mol% DPPH.

Table 3: Recycling of the catalyst DPPH–WO_3/Al_2O_3 for the aerobic oxidation of cyclohexylamine.[a]

Cycle	Conversion [%][b]	Yield of oxime [%][b]
1	98	90
2	97	91
3	99	90

[a] Reaction conditions: cyclohexylamine (5 mmol), DPPH (5 mol%), WO_3/Al_2O_3 (W: 1 mol%) in acetonitrile (3 mL) under O_2/N_2 (7:93; 5MPa) at 80°C for 8 h. Recycling of the catalyst: after the reaction, WO_3/Al_2O_3 could be easily separated from the reaction mixture by filtration, and the isolated WO_3/Al_2O_3 was reused. Kugelrohr distillation (100°C, 30 mmHg) gave cyclohhexanone, acetonitrile, and the residue of DPPH, which was reused. [b] Determined by GC analysis using an internal standard.

primary amine **1** to DPPH occurs to give a complex of aminium cation radical **4** and DPPH anion **5**.[22] Fast electron transfer from amine to DPPH was observed by UV spectra obtained in nitrogen atmosphere. The aminium cation radical **4** thus formed undergoes deprotonation to give DPPH-H (**7**) and α-aminoalkyl radical **6**. The latter undergoes reaction with molecular oxygen to afford the α-aminoalkylperoxyl radical **8**, which undergoes abstraction of hydrogen from **7** to give α-aminoalkylhydroperoxide **9** and DPPH (**3**) to complete the catalytic cycle. The high efficiency of DPPH in comparison with other typical radical catalysts such as TEMPO and PINO is probably due to the fast electron transfer from DPPH to amines. It is unlikely that radical **6** is formed by direct hydrogen abstraction of DPPH from amine **1**.
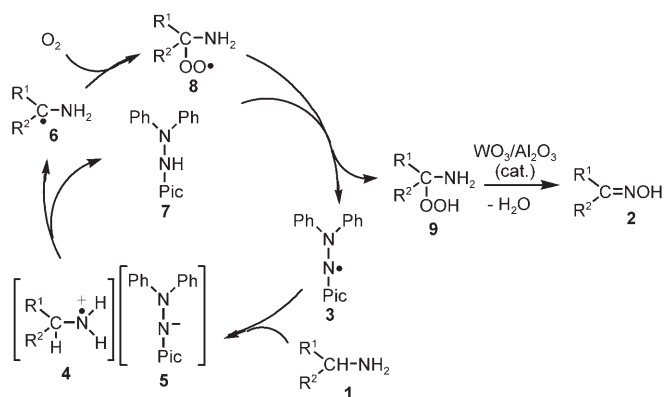
Scheme 1. Proposed mechanism for the DPPH–WO$_3$/Al$_2$O$_3$-catalyzed aerobic oxidation of primary amines to oximes. Pic = picryl.

The alkylhydroperoxide **9** thus formed is converted into the oxime **2** by reaction with the WO$_3$/Al$_2$O$_3$ catalyst. Indeed, when 1-hydroperoxycyclohexylamine, which was prepared from cyclohexanone, NH$_3$, and H$_2$O$_2$,[23] was allowed to react with the WO$_3$/Al$_2$O$_3$ catalyst at room temperature, cyclohexanone oxime was obtained in 75 % yield. It is noteworthy that the same reaction in the absence of WO$_3$/Al$_2$O$_3$ catalyst gave cyclohexanone in 90 % yield.

In conclusion, we have found that a novel, efficient, aerobic oxidative transformation of primary amines with DPPH–WO$_3$/Al$_2$O$_3$ catalyst affords oximes under mild conditions. We are currently working on the reaction mechanism and on the extension of this catalytic system to the other oxidation reactions.

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