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Oxidation of Primary Amines to Oximes with Molecular Oxygen using 1,1-Diphenyl-2-picrylhydrazyl and WO_3/Al_2O_3 as Catalysts

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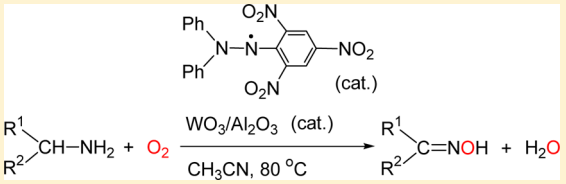
Supporting Information

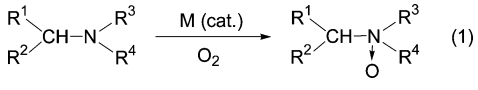
ABSTRACT: The oxidative transformation of primary amines to their corresponding oximes proceeds with high efficiency under molecular oxygen diluted with molecular nitrogen (O_2/N_2 = 7/93 v/v, 5 MPa) in the presence of the catalysts 1,1-diphenyl-2-picrylhydrazyl (DPPH) and tungsten oxide/alumina (WO_3/Al_2O_3). The method is environmentally benign, because the reaction requires only molecular oxygen as the terminal oxidant and gives water as a side product. Various alicyclic amines and aliphatic amines can be converted to their corresponding oximes in excellent yields. It is noteworthy that the oxidative transformation of primary amines proceeds chemoselectively in the presence of other functional groups. The key step of the present oxidation is a fast electron transfer from the primary amine to DPPH followed by proton transfer to give the α-aminoalkyl radical intermediate, which undergoes reaction with molecular oxygen and hydrogen abstraction to give α-aminoalkyl hydroperoxide. Subsequent reaction of the peroxide with WO_3/Al_2O_3 gives oximes. The aerobic oxidation of secondary amines gives the corresponding nitrones. Aerobic oxidative transformation of cyclohexylamines to cyclohexanone oximes is important as a method for industrial production of ε-caprolactam, a raw material for Nylon 6.



INTRODUCTION

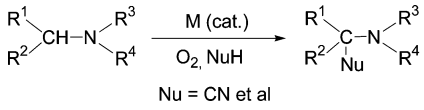
Catalytic oxidation of amines is of fundamental importance from both bioorganic and synthetic aspects.[1,2] Therefore, various methods have been reported. However, useful methods for catalytic oxidation are limited, because the selective oxidation of amines is extremely difficult as a result of amine sensitivity. Using peroxides as oxidants, various transition-metal-catalyzed oxidative transformations of amines have been explored. Tertiary amines are converted to *N*-oxides.[3] Secondary amines can be oxidized to either nitrones[4] or imines.[5] Primary amines are oxidized to nitroso intermediates, which are converted to various compounds, such as nitro compounds[6] and oximes.[7]

In the catalytic oxidation of amines, the use of molecular oxygen as an environmentally benign terminal oxidant under mild conditions is extremely important in view of environmental, economical, and synthetic aspects;[8] however, few catalytic aerobic oxidative transformations have been reported.[9] Aerobic catalytic oxidation of tertiary amines with transition-metal catalysts proceeds to give *N*-oxides (eq 1).[10]



(1)

Aerobic catalytic oxidative transformations of tertiary amines by α-C–H activation adjacent to nitrogen give the corresponding α-substituted products such as aminonitriles (eq 2).[2c,11]



(2)

Aerobic catalytic oxidative transformations of secondary amines give either imines or nitrones selectively, depending on the reaction conditions employed. Thus, transition-metal-catalyzed aerobic catalytic oxidation of secondary amines gives imines (eq 3).[12] In contrast, flavin-catalyzed aerobic oxidation of secondary amines selectively gives nitrones (eq 4).[13]

Aerobic catalytic oxidation of primary amines gives the corresponding imine intermediates that undergo either extensive dehydrogenation to give nitriles (eq 5)[14] or addition of the starting amine to give N-substituted imines (eq 6).[15] In particular, benzylamines undergo oxidative dimerization to give the corresponding imines with[15] or without[16] catalysts.

Primary amines can be oxidized to oximes. Catalytic oxidative transformations of primary amines with oxidants such as

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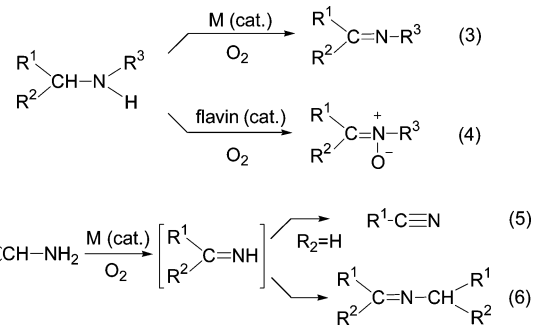
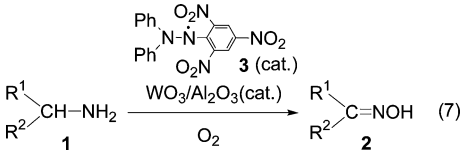


hydrogen peroxide have been reported with transition-metal catalysts.[7] However, aerobic catalytic oxidative transformations are limited to a few reactions. Vapor-phase aerobic oxidations in the presence of SiO_2-gel, γ-Al_2O_3, or WO_3/Al_2O_3 catalyst[17a] and a polyoxometal catalyst[17b] at extremely high temperatures give the corresponding oximes in low yields and with low selectivity. Titanium oxide catalyzed aerobic oxidation of cyclohexylamine occurs with low conversion.[17c]

Oximes are useful intermediates for the synthesis of commodity products, fine chemicals, medicines, and biologically active compounds.[18] Therefore, we aimed to explore an efficient and environmentally benign method for aerobic oxidative transformation of primary amines to oximes.

After many attempts, we discovered a highly selective and efficient method for oxidative transformation of primary amines (**1**) to oximes (**2**) by employing 1,1-diphenyl-2-picrylhydrazyl (DPPH; **3**) catalyst, a tungusten oxide/alumina (WO_3/Al_2O_3) cocatalyst, and molecular oxygen as the terminal oxidant under mild conditions (eq 7).[19] DPPH has been employed as a standard substrate for ESR spectroscopy[20a] and as a radical scavenger;[20b] however, it has never been used as an organic catalyst for organic synthesis.



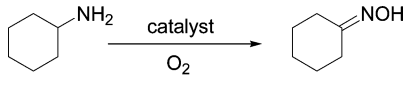
Full details regarding the scope and reaction mechanism of the aerobic oxidation of primary amines to oximes catalyzed by DPPH and WO_3/Al_2O_3 are described.

RESULTS AND DISCUSSION

DPPH-Catalyzed Oxidative Transformation of Primary Amines with Molecular Oxygen. Aerobic catalytic oxidation of primary amines using transition-metal catalysts usually gives either nitriles[14] or *N*-alkylimines,[15] as shown in eqs 5 and 6. Furthermore, dehydration of aldoximes at higher temperature gives nitriles.[21] We attempted to discover a method for aerobic oxidative transformation of primary amines to oximes using transition-metal catalysts. However, all attempts failed. The aerobic oxidation of cyclohexylamines in the presence of a transition-metal catalyst such as $TiO(acac)_2$, $VO(acac)_2$, $FeCl_3$, $Co(acac)_2$, $CuCl_2$, $MoO_2(acac)_2$, $RuCl_2(PPh_3)_3$, Na_2WO_4, WO_3, and WO_3/Al_2O_3 gave no oxime, and a complex mixture of nitriles, *N*-alkylimines, and carbonyl compounds was obtained.

We next examined the aerobic oxidation of primary amines using various organocatalysts. 2,2,6,6-Tetramethylpiperidine-*N*-oxyl (TEMPO) has been used as a highly efficient catalyst for the aerobic oxidation of various substrates such as alcohols.[22] *N*-Hydroxyphthalimide (NHPI) is also an excellent catalyst for aerobic oxidation of a broad range of organic substrates such as alkanes and alkyl aromatics.[23] Flavin is an efficient catalyst for the aerobic oxidation of secondary amines to nitrones.[13] All attempts at the aerobic oxidation of primary amines using the organocatalysts mentioned above failed. The aerobic oxidations for cyclohexylamine in the presence of such catalysts are summarized in Table 1. Combining catalysts such as TEMPO with $RuCl_2(PPh_3)_3$[22] and NHPI with $Co(acac)_2$[23] showed excellent catalytic activity for the aerobic oxidation of alcohols or hydrocarbons. However, these catalysts showed no effective activity (entries 1 and 2). It is noteworthy that when WO_3/Al_2O_3, which was prepared according to the literature procedure,[19] was used instead of $RuCl_2(PPh_3)_3$ and $Co(acac)_2$, the oxime was obtained in low yields (entries 3 and 4). WO_3/Al_2O_3 alone is not effective (entry 5).

Table 1. Activity of Catalysts for the Aerobic Oxidative Transformation of Cyclohexylamine (1a)[a]



1a **2a**

entry	catalyst	conversion of amine **1a** (%)[b]	selectivity for oxime **2a** (%)[b]
1[c]	TEMPO-$RuCl_2(PPh_3)_3$	21	0
2[d]	NHPI-$Co(acac)_2$	36	0
3	TEMPO-WO_3/Al_2O_3	4	2
4	NHPI-WO_3/Al_2O_3	7	3
5	WO_3/Al_2O_3	7	0
6	DPPH	21	3
7	DPPH-WO_3/Al_2O_3	59	95

[a]Reaction conditions: **1a** (5 mmol), organocatalyst (2.5 mol %), WO_3/Al_2O_3 (W: 1 mol %) in acetonitrile (3 mL), O_2 (O_2/N_2 = 7/93 v/v, 5 MPa) at 80 °C for 4 h. [b]Determined by GC analysis using an internal standard. [c]TEMPO (3 mol %)-$RuCl_2(PPh_3)_3$ (1 mol %). [d]NHPI (10 mol %)-$Co(acac)_2$ (0.5 mol %).

DPPH is well-known as a stable radical and has been used as an ESR standard,[20a] polymerization inhibitor,[20b] and monitor of chemical reactions involving radicals.[20c,d] However, it has never been used as an organocatalyst for organic synthesis. DPPH can be readily prepared by oxidation of 1,1-diphenyl-2-picrylhydrazine, which is prepared from diphenylhydrazine and picryl chloride.[24] Therefore, we examined the catalytic activity of DPPH. The reaction with DPPH alone gave cyclohexanone and polymeric compounds in addition to a small amount of cyclohexanone oxime (Table 1, entry 6). The combination of DPPH and WO_3/Al_2O_3 was found to give an excellent result (entry 7). Thus, the reaction of cyclohexylamine (**1a**) in the presence of DPPH (2.5 mol %)−WO_3/Al_2O_3 (W; 1 mol %) in acetonitrile at 80 °C under molecular oxygen (O_2/N_2 = 7/93 v/v, 5 MPa, outside flammability limits) for 4 h gave cyclohexanone oxime (**2a**) with 95% selectivity and 59% conversion. No decomposition or deterioration of DPPH was observed under the reaction conditions. Molecular oxygen diluted with nitrogen (O_2/N_2 = 7/93 v/v, 5 MPa), which corresponds to air diluted with molecular nitrogen, was used outside flammability limits using an autoclave at all times. In

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industry pure oxygen cannot be used, and air diluted with molecular nitrogen is used. This is such a case. This method is convenient for a large-scale closed system and also for a flow system. Oxidation with molecular oxygen (1 atm, balloon) gave excellent results; therefore, this method is convenient for laboratory organic synthesis.

We examined the catalytic activity of cocatalysts. Representative results are shown in Table 2. DPPH alone exhibited low catalytic activity for the aerobic oxidation of amines to oximes (entry 1). Amines were converted to the carbonyl compound and a mixture of unidentified byproducts.

Table 2. Aerobic Catalytic Oxidative Transformation of Cyclohexylamine (1a): Catalytic Activity of Cocatalysts[a]

entry	transition-metal catalyst	conversion of amine **1a** (%)[b]	selectivity for oxime **2a** (%)[b]
1	none	21	3
2	WO_3/Al_2O_3	59	95
3	WO_3/ZrO_2	63	86
4	WO_3/TiO_2	22	64
5	WO_3	15	6
6	TiO_2	36	90
7	TS-1	14	93
8	$Ti(OiPr)_4$	67	88
9	$TiO(acac)_2$	61	89
10	Nb_2O_5	50	80
11	$MoO_2(acac)_2$	17	2
12	$VO(acac)_2$	21	1
13	$Fe(acac)_3$	6	44
14	$RuCl_2(PPh_3)_3$	4	19

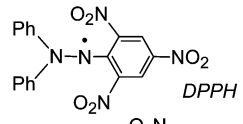
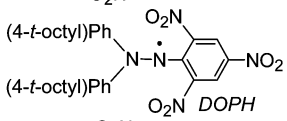
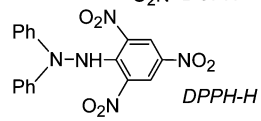
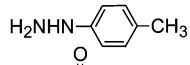
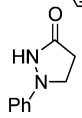
[a]Reaction conditions: **1a** (5 mmol), DPPH (2.5 mol %), cocatalyst (metal: 1 mol %) in acetonitrile (3 mL), O_2 (O_2/N_2 = 7/93 v/v, 5 MPa) at 80 °C for 4 h. [b]Determined by GC analysis using an internal standard.

WO_3/Al_2O_3, WO_3/ZrO_2, Ti $(OiPr)_4$, $TiO(acac)_2$, and Nb_2O_5 proved to be excellent cocatalysts for the aerobic oxidation of **1a** (Table 2, entries 2, 3, and 8−10), while WO_3/TiO_2 TiO_2, and titanium silicate-1 (TS-1) showed low catalytic activity (entries 4, 6, and 7). Tungsten catalysts such as WO_3 and Na_2WO_4 and other transition-metal catalysts such as MoO_3/Al_2O_3, $MoO_2(acac)_2$, Na_2MoO_4, $VO(acac)_2$, $Fe(acac)_3$, $Co(acac)_2$, and $RuCl_2(PPh_3)_3$ showed poor catalytic activity (entries 5 and 11−14).

Next, we examined the catalytic activity of the hydrazyl radical, hydrazine, and hydrazide in combination with WO_3/Al_2O_3. Representative results are summarized in Table 3. DPPH and its derivatives, such as 1,1-bis(4-*tert*-octylphenyl)-2-picrylhydrazyl (DOPH) and 1,1-diphenyl-2-picrylhydrazine (DPPH-H), showed high catalytic activity (entries 1−3). Hydrazide compounds such as *p*-methylphenylhydrazine and hydrazide compounds such as 1-phenyl-3-pyrazolidone can be used as catalysts (entries 4 and 5). 1,2-Dihydroindazol-3-one, benzoic hydrazine, *N*,*N*′-dibenzoylhydrazine, and phthalhydrazide showed low catalytic activity. It is noteworthy that, with the exception of DPPH, DOPH, and DPPH-H, the organic catalysts undergo decomposition and deterioration under the reaction conditions. Therefore, DPPH is the best catalyst because of its high catalytic activity, stability, and ease of handling.

The solvent effect of the aerobic oxidation of primary amine catalyzed by DPPH−WO_3/Al_2O_3 is very important. Representative results are shown in Table 4. Acetonitrile and *N*,*N*-dimethylformamide (DMF) were the best solvents among those examined (entries 1 and 2). Nitriles such as propionitrile and benzonitrile and amides such as *N*,*N*-dimethylacetamide and *N*,*N*-dimethylpropionamide also gave high conversions. However, slight formation of *N*-alkylformamide derived from primary amines when using DMF was observed under the reaction conditions. The reactions in nonpolar solvents, such as toluene, showed low conversions (entry 3). Use of a protic solvent such as methanol, *tert*-butyl alcohol, and H_2O resulted in low conversions (entries 4−6).

Table 3. Effect of Organocatalyst on the Organocatalyst−WO_3/Al_2O_3-Catalyzed Aerobic Oxidative Transformation of 1a[a]

entry	organocatalyst	conversion of amine **1a** (%)[b]	selectivity for oxime **2a** (%)[b]
1	 DPPH	59	95
2	 DOPH	62	96
3	 DPPH-H	41	96
4		32	87
5		30	80

[a]Reaction conditions: **1a** (5 mmol), organocatalyst (2.5 mol %), WO_3/Al_2O_3 (W: 1 mol %) in acetonitrile (3 mL), O_2 (O_2/N_2 = 7/93 v/v, 5 MPa) at 80 °C for 4 h. [b]Determined by GC analysis using an internal standard.

Table 4. Effect of Solvent on the DPPH−WO_3/Al_2O_3-Catalyzed Aerobic Oxidative Transformation of 1a[a]

entry	solvent	conversion of amine **1a** (%)[b]	selectivity for oxime **2a** (%)[b]
1	acetonitrile	59	95
2	*N*,*N*-dimethylformamide	77	94
3	toluene	6	92
4	methanol	14	91
5	*tert*-butyl alcohol	9	93
6	H_2O	5	83

[a]Reaction conditions: **1a** (5 mmol), DPPH (2.5 mol %), WO_3/Al_2O_3 (W: 1 mol %) in solvent (3 mL), O_2 (O_2/N_2 = 7/93 v/v, 5 MPa) at 80 °C for 4 h. [b]Determined by GC analysis using an internal standard.

Representative results of the aerobic oxidation of primary amines in acetonitrile at 80 °C in the presence of the DPPH−WO_3/Al_2O_3 catalyst under molecular oxygen are summarized in Table 5. The oxidation of **1a** gave **2a** (90%) along with small amounts of nitrocyclohexane (4%), cyclohexanone (2%), and *N*-cyclohexylidene−cyclohexylamine (1%) (entry 1). In the gram scale reaction, cyclohexanone oxime was obtained in 85% isolated yield. No decomposition of DPPH was observed under

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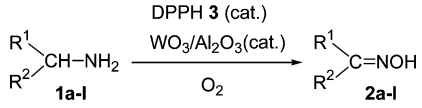
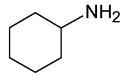
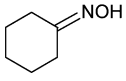
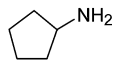
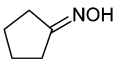
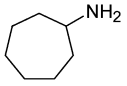
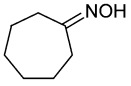
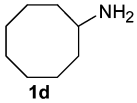
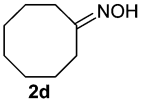
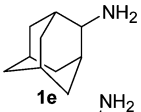
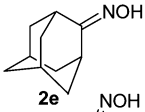
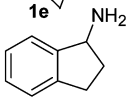
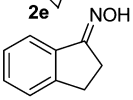
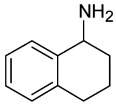
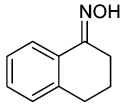
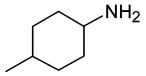
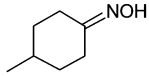
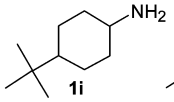
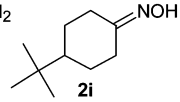
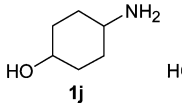
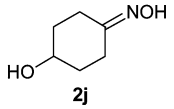
Table 5. DPPH−WO_3/Al_2O_3-Catalyzed Aerobic Oxidative Transformation of Primary Amines to Oximes[a]



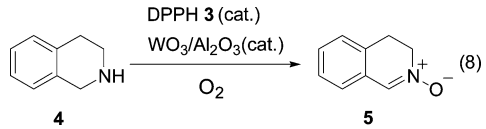
entry	substrate	product	conversion (%)[b] / yield (%)[b] / time (h)
1 2[d]	 1a	 2a	98/90 (85)[c]/8 98/89/16
3	 1b	 2b	97/82/8
4	 1c	 2c	96/73/48
5[e]	 1d	 2d	93/66/36
6	 1e	 2e	95/80/48
7	 1f	 2f	90/72/48
8	 1g	 2g	87/63/48
9	 1h	 2h	97/85/8
10	 1i	 2i	98/75/16
11	 1j	 2j	97/82/48
12[e]	$CH_3(CH_2)_6CH_2NH_2$ 1k	$CH_3(CH_2)_6CH{=}NOH$ 2k	94/73/36
13	$HO(CH_2)_4CH_2NH_2$ 1l	$HO(CH_2)_4CH{=}NOH$ 2l	95/75/48

[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 v/v, 5 MPa) at 80 °C. [b]Determined by GC analysis using an internal standard. [c]The isolated yield obtained from a gram-scale reaction is shown in parentheses. [d]O_2 atmosphere (1 atm, balloon) at 80 °C. [e]10 mol % DPPH.

the reaction conditions. The WO_3/Al_2O_3 catalyst was separated by filtration, after which tungsten was not observed in the filtrate by induced coupled plasma (ICP) analyses. The oxidation proceeded efficiently under an atmosphere pressure of molecular oxygen (1 atm, balloon) (entry 2). The reaction did not occur in the absence of molecular oxygen. A manometric measurement of the oxygen uptake revealed that an equimolar amount of molecular oxygen was consumed for the oxidation of primary amines.

Alicyclic amines (**1b−i**) were converted to the corresponding oximes (**2b−i**) in excellent yields (Table 5, entries 3−10). The reactions of aliphatic amines also gave their corresponding oximes in good yields. In a typical example, the oxidation of octylamine (**1k**) gave the corresponding oxime (**2k**) in 73% yield (entry 12). The reaction tolerates other oxidizable groups. Thus, the oxidation of 4-hydroxylcyclohexylamine (**1j**) proceeded chemoselectively to afford the corresponding oxime (**2j**) in 82% yield (entry 11). Oxidation of 5-hydroxylpentylamine (**1l**) proceeded chemoselectively (entry 13).

DPPH-Catalyzed Aerobic Oxidation of Secondary Amines with Molecular Oxygen. The aerobic oxidation of secondary amines gave their corresponding nitrones. Typically, the oxidation of 1,2,3,4-tetrahydroisoquinoline (**4**) with molecular oxygen in the presence of DPPH−WO_3/Al_2O_3 catalyst in acetonitrile at 80 °C gave 3,4-dihydroisoquinoline *N*-oxide (**5**) with 61% selectivity and 28% conversion (eq 8). The low conversion of the starting amines is the result of the



spin-trapping ability of nitrones.[25] A similar oxidation of dibutylamine gave *N*-butylidenebutylamine *N*-oxide with 72% selectivity. Dibenzylamine and 2-methylpiperidine can also be converted into their corresponding nitrones; however, the selectivity of nitrones decreased at high conversion. The reaction of *tert*-butylamine did not occur.

Recyclability of DPPH−WO_3/Al_2O_3 Catalyst. Stability and recyclability is a key issue in catalysis. The DPPH−WO_3/Al_2O_3 catalyst can be reused without loss of catalytic activity or selectivity. After the reaction, the 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 the solvent, the product, and the DPPH residue **3**. The recovered **3** was reused directly. The results obtained in a stability study of DPPH−WO_3/Al_2O_3-catalyzed aerobic oxidation of **1a** are shown in Figure 1. The yield of cyclohexanone oxime was maintained at a similar value for at least three rounds of recycling.

Evaluation of the Production of Cyclohexanone Oxime. Oximes are usually synthesized by condensation of aldehydes or ketones with hydroxylamine, which is toxic and thermally unstable. Cyclohexanone oxime is an intermediate for the industrial production of ε-caprolactam, a precursor to

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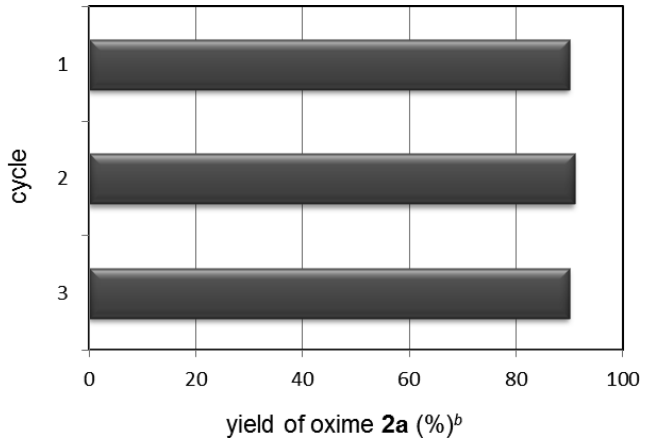
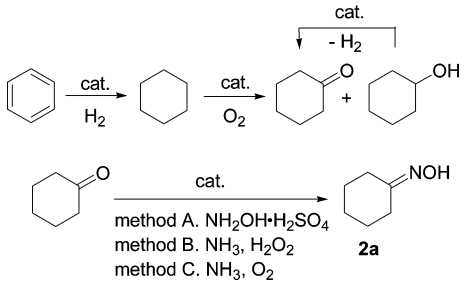


Figure 1. Recycling of the DPPH–WO_3/Al_2O_3 catalyst for the aerobic oxidation of **1a**. Reaction conditions: **1a** (5 mmol), DPPH (5 mol %), WO_3/Al_2O_3 (W: 1 mol %) in acetonitrile (3 mL) under O_2 (O_2/N_2 = 7/93 v/v, 5 MPa) at 80 °C for 8 h. Yields were determined by GC analysis using an internal standard.

Nylon 6. The industrial route for cyclohexanone oxime is oximation of cyclohexanone with hydroxylamine sulfate, the sulfuric acid liberated being neutralized by ammonia, with coproduction of large amounts of ammonium sulfate (method A), as shown in Scheme 1.[26] Therefore, various methods for the

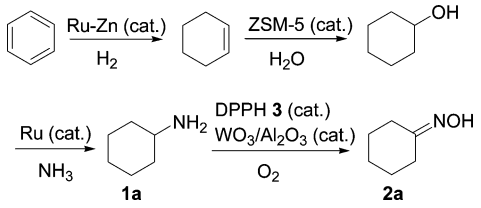
Scheme 1. Conventional Route to 2a from Benzene



synthesis of cyclohexanone oxime from cyclohexanone have been developed. Ammoximation of cyclohexanone with ammonia and hydrogen peroxide catalyzed by titanium silicate-1 (TS-1) (method B)[27a] and ammoximation with ammonia and molecular oxygen using SiO_2–Al_2O_3 and $Co^{II}Co^{III}$AlPO-36 (method C)[27b,c] were explored. However, these methods require cyclohexanone, which is supplied by aerobic oxidation of cyclohexane, giving a mixture of cyclohexanone and cyclohexanol (K/A oil) with 70–80% selectivity and very low conversion (3–6%).[28]

The present method for aerobic catalytic oxidative transformation of cyclohexylamine to cyclohexanone oxime is compatible with the methods mentioned above by combining the following simple catalytic reactions starting from benzene, as shown in Scheme 2. Thus, cyclohexylamine can be obtained by ruthenium-catalyzed amination of cyclohexanol in high selectivity.[29] Cyclohexanol is produced by partial hydrogenation of benzene to cyclohexene over a ruthenium–zinc catalyst,[30] followed by hydration of cyclohexene in the presence of a high-silica zeolite catalyst (ZSM-5).[31] Actually, the process for cyclohexanol from benzene has been applied industrially. These combined processes, that is, partial hydrogenation of benzene, hydration of cyclohexene, amination of cyclohexanol, and

Scheme 2. Proposed Route to 2a from Benzene



aerobic oxidation of cyclohexylamine, would be a useful method for the production of cyclohexanone oxime, a precursor of ε-caprolactam. It is noteworthy that recently attractive approaches to **2a** have been explored, including NHPI-catalyzed nitrosation of cyclohexane with *tert*-butyl nitrite followed by treatment with triethylamine[32a] and chemoselective hydrogenation of 1-nitro-1-cyclohexene.[32b]

Mechanistic Study. We investigated the effect of variables on kinetic factors for the DPPH–WO_3/Al_2O_3-catalyzed aerobic oxidation of cyclohexylamine. The effect of the DPPH and WO_3/Al_2O_3 concentrations on catalytic performance was examined. As shown in Figure 2a, a linear increase was observed with respect to the DPPH concentration in the range of 1–7.5 mol %. On the other hand, with respect to the effect of the WO_3/Al_2O_3 concentration, no significant increase in rate was observed above a W concentration of 0.5 mol % (Figure 2b). A kinetics study showed a first-order relationship for the amount of DPPH catalyst and a zero-order dependence of the reaction rate on the amount of WO_3/Al_2O_3 catalyst (W; 0.5–2 mol %).

The effect of reaction temperature in the range 60–110 °C on catalytic performance was investigated. A temperature of 80 °C was found to be optimal for the DPPH–WO_3/Al_2O_3-catalyzed aerobic oxidation of **1a**. Lower temperatures afforded a decrease in activity, and higher temperatures resulted in low selectivity. The conversion of **1a** increased exponentially with temperature, while the selectivity of the oxime **2a** decreased (Figure S1, Supporting Information). The dependence of the initial rate of oxidation on temperature determined the activation energy of the reaction. The initial rate for the DPPH–WO_3/Al_2O_3-catalyzed aerobic oxidation of **1a** vs the reaction temperature can be readily fitted to the familiar expression $k = A \exp(-E_a/RT)$ to give an activation energy (E_a) of 69.8 kJ/mol (Figure S2, Supporting Information).

The time course plotted for the aerobic oxidation of **1a** over DPPH–WO_3/Al_2O_3 catalyst at 80 °C showed that the conversion increased linearly with time during the initial 3 h of the reaction, and then the rate became slower. The initial conversion rate at 80 °C was calculated on the basis of the fraction after 1 h based on Figure S3 (Supporting Information) to be 12 g h^{-1} (g of DPPH)$^{-1}$.

The influence of oxygen pressure on catalytic performance for the aerobic oxidation of **1a** with the use of the DPPH–WO_3/Al_2O_3 catalyst at 80 °C was investigated using the O_2/N_2 (7/93 v/v) gas mixture between 3 and 10 MPa. The catalytic activity increased considerably upon going from low to high pressure, while the selectivity of **2a** decreased. The best results were obtained under 5 MPa of O_2/N_2 (7/93 v/v) (Figure S4, Supporting Information).

Next, we investigated the stoichiometric reaction of DPPH **3** with amine **1a** (eq 9). The electron transfers from **1a** to DPPH proceeded in an instant to give the DPPH anion (**6**). A solution of **3** in acetonitrile was allowed to react with an equimolar

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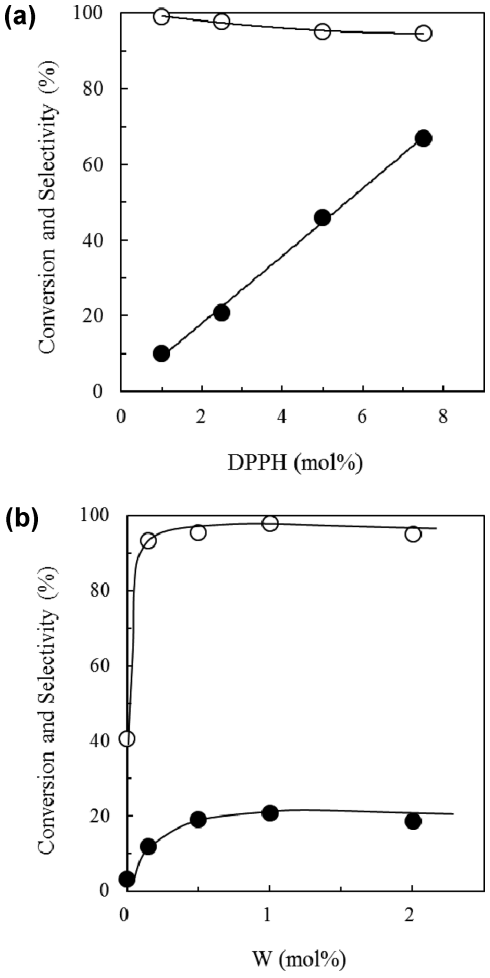
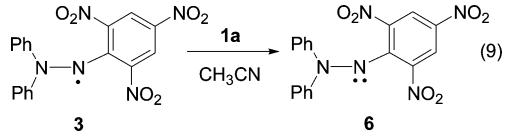
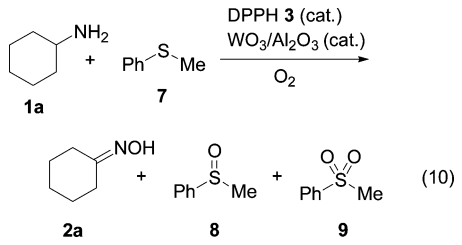


Figure 2. Effect of DPPH and WO_3/Al_2O_3 concentrations on the DPPH–WO_3/Al_2O_3-catalyzed aerobic oxidation of **1a**: (a) different concentrations of DPPH with WO_3/Al_2O_3 (W: 1 mol %); (b) different concentrations of WO_3/Al_2O_3(W) with DPPH (2.5 mol %). Symbols: (●) **1a** conversion, (○) **2a** selectivity. Conditions: **1a** (5 mmol), DPPH (1–7.5 mol %), WO_3/Al_2O_3 (W: 0–2 mol %) in acetonitrile (3 mL), O_2 (O_2/N_2 = 7/93 v/v, 5 MPa) at 80 °C for 2 h.



amount of **1a** under nitrogen at 25 °C; the color of the reaction mixture changed immediately from purple to brown, and the UV–vis absorption at 520 nm characteristic of **3** was not observed (Figure S5, Supporting Information). Amine **1a** was converted to a mixture of unidentified high-boiling products.

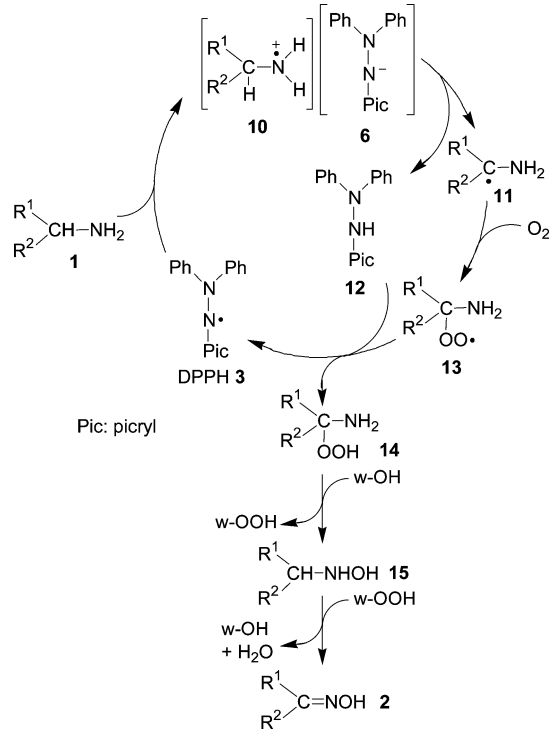
A competitive reaction of primary amines and sulfides was performed with the aim of preserving the reactive oxygen species generated by the DPPH–WO_3/Al_2O_3 catalyst system (eq 10). The aerobic oxidation of a mixture of amine **1a** and thioanisole (**7**) (1/1) in the presence of DPPH (5 mol %)–WO_3/Al_2O_3 catalyst in acetonitrile at 80 °C for 8 h gave the oxime **2a** (16% yield at 99% conversion of **1a**), sulfoxide **8** (40% yield at 58% conversion of **7**), and sulfone **9** (16% yield at 58% conversion of **7**), respectively. Control experiments showed that the oxidation product of **7** could not be detected in the absence of **1a**. Oxidation of sulfides can be achieved with



peroxides such as hydrogen peroxide in the presence of various transition metals.[33] Oxygen transfer from peroxy metal species to a sulfur atom takes place to give sulfoxides and sulfones. Apparently, hydroperoxy or peroxo tungsten species, which are electrophilic oxygen species, are generated by the DPPH–WO_3/Al_2O_3 catalyst system.

The reaction can be rationalized by assuming the mechanism shown in Scheme 3. Initially, fast electron transfer from primary

Scheme 3. Proposed Mechanism for DPPH–WO_3/Al_2O_3-Catalyzed Aerobic Oxidation of Primary Amines (1)



amine **1** to **3** occurs to give a complex of an aminium cation radical (**10**) and DPPH anion (**6**).[34] Fast electron transfers from the amine to DPPH were observed by the UV–vis spectral experiment. The aminium cation radical **10** thus formed undergoes deprotonation in the cage to give DPPH-H (**12**) and an α-aminoalkyl radical (**11**). The latter undergoes a reaction with molecular oxygen to afford an α-aminoalkylperoxy radical (**13**), which undergoes abstraction of hydrogen from DPPH-H (**12**) to give an α-aminoalkyl hydroperoxide (**14**) and regenerate **3** to complete the catalytic cycle. It is noteworthy that, as shown in Table 1, aerobic oxidation of cyclohexylamine does not take place with usual radical initiators such as TEMPO and NHPI. The unique property of DPPH is probably the result of the ability of DPPH to promote a fast electron transfer to amines. It is unlikely that the radical **11** is formed by direct hydrogen abstraction of

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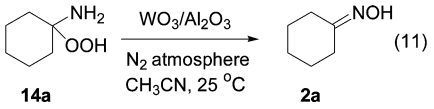
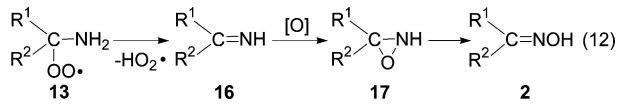
DPPH from the amine **1**. The reaction of alkyl hydroperoxide **14** with tungsten oxide/alumina (WO_3/Al_2O_3) gives hydroxylamine (**15**) and tungstate hydroperoxide w-OOH, where w may be WO_3^-, WO_4^-, or WO_6^-.[35] Further oxidation of **15** with w-OOH followed by dehydration would give **2** to complete the catalytic cycle.

Indeed, when 1-hydroperoxycyclohexylamine (**14a**), which was prepared from cyclohexanone, ammonia, and hydrogen peroxide,[36] was allowed to react with the WO_3/Al_2O_3 catalyst at room temperature under a nitrogen atmosphere, oxime **2a** was obtained in 75% yield (eq 11).[19] It is noteworthy that the same



reaction in the absence of the catalyst WO_3/Al_2O_3 gave cyclohexanone in 90% yield. It has been reported that **14a** undergoes decomposition to give **2a** in the presence of the catalyst Na_2WO_4 in EtOH.[36]

This one-step reaction is of considerable industrial interest, as it provides an alternative route to cyclohexanone oxime; therefore, a mechanistic study has been conducted. Hermans reported an alternative pathway from α-aminoperoxyl radical **13** to oxime **2** on the basis of computational treatment through various quantum-chemical methods.[37] As shown in eq 12,



elimination of HOO$^\bullet$ radical from **13** would give imine **16** and subsequent oxidation of **16** gives oxazirane **17**, which undergoes rearrangement to give oxime **2**. It is very difficult to distinguish these two pathways after the formation of **13**; however, the pathway shown in Scheme 3 seems to be reasonable. The present aerobic oxidation is unique to DPPH, and no reaction takes place with the usual radical initiators such as TEMPO and NHPI, indicating that the direct α-CH hydrogen abstraction from primary amines to give α-aminoalkyl radical **11** seems unlikely. In the presence of WO_3/Al_2O_3 alone and without DPPH, no oxime was formed. It was claimed that HOO$^\bullet$ elimination from **13** proceeds more quickly than hydrogen abstraction from amines; however, in the present catalytic system hydrogen abstraction from DPPH-H (**12**) would proceed much more quickly in comparison with hydrogen abstraction from the starting amine. The oxidation of the unstable intermediate imine **16** with HOO$^\bullet$ species to give oxazirane **17** would be difficult. Even if oxazirane **17** is formed from imine **16** under the reaction conditions, highly selective formation of oxime **2** (90% yield) from **17** would be very difficult, because there has been no report on the selective rearrangement of **17** to **2**. Furthermore, neither the amination product of **17** with the starting amine nor amides derived from rearrangement of **17** could be detected among the products. Oxazirane **17** is a very active amination reagent[38] and also undergoes rearrangement to amides.[39]

CONCLUSIONS

Efficient and selective aerobic oxidative transformation of primary amines to oximes proceeds with high efficiency under mild conditions in the presence of the catalyst 1,1-diphenyl-2-picrylhydrazyl (DPPH) and the cocatalyst tungsten oxide/alumina (WO_3/Al_2O_3). Various alicyclic and aliphatic amines can be converted to their corresponding oximes in excellent yields. In the DPPH–WO_3/Al_2O_3 system, DPPH acts as an electron transfer mediator, and an alkylhydroperoxide intermediate is transformed into an oxime by the WO_3/Al_2O_3 cocatalyst. This strategy provides an efficient and environmentally benign method for the synthesis of oximes. The principle of aerobic oxidation using DPPH will be particularly important for exploring further aerobic catalytic oxidations.

EXPERIMENTAL SECTION

General Methods. All the amines (**1a–l**) were commercially available and were used without further purification. 1,1-Diphenyl-2-picrylhydrazyl (DPPH), 1,1-diphenyl-2-picrylhydrazine (DPPH-H), 1,1-bis(4-*tert*-octylphenyl)-2-picrylhydrazyl (DOPH), *N*-hydroxyphthalimide (NHPI), 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), and all other reagents were obtained from commercial suppliers. GC measurements were carried out with a gas chromatograph (FID) equipped with a glass capillary column. GC-MS analyses were performed on a mass spectrometer equipped with a glass capillary column. Column chromatography was performed using silica gel columns. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer (^{1}H, 400 MHz; ^{13}C, 100 MHz). Chemical shifts are expressed in parts per million downfield from tetramethylsilane. HRMS analyses were performed on a time-of-flight mass spectrometer equipped with an ESI source. The known compounds **2a–i** and **5** were identified by comparison of the ^{1}H NMR and ^{13}C NMR spectra with those of the authentic samples obtained from the commercially available compounds or the compound prepared according to the literature.

General Procedure for the Catalytic Oxidation of Primary Amines to Oximes with Molecular Oxygen. A stainless steel autoclave (120 mL) equipped with a magnetic stirring bar was charged with a mixture of DPPH (**3**; 98.6 mg, 0.25 mmol), WO_3/Al_2O_3[19] (42 mg, W: 0.05 mmol), amine (5 mmol), and tetradecane (internal standard for GC analysis, 0.25 mmol) in acetonitrile (3 mL). The autoclave was pressurized to 5 MPa with an oxygen–nitrogen mixture (7/93 v/v), and the mixture was stirred (600 rpm) at 80 °C for 8 h. The reaction mixture was subjected to GC analysis using tetradecane as an internal standard. The products were also isolated and purified by column chromatography on silica gel with EtOAc and petroleum ether as eluent and identified by the usual methods: i.e., NMR, HRMS, etc.

*Cyclohexanone Oxime (**2a**).* Table 5, entries 1 and 2: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22 (1H, s), 2.51 (2H, t, J = 6.2 Hz), 2.21 (2H, t, J = 6.2 Hz), 1.63–1.62 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.6, 32.1, 26.8, 25.8, 25.5, 24.4; HRMS (ESI) calcd for $C_6H_{11}NO$ $[M + H]^+$ 114.0919, found 114.0922; mp 89–90 °C.

*Cyclopentanone Oxime (**2b**).* Table 5, entry 3: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.36 (1H, s), 2.46 (2H, t, J = 7.0 Hz), 2.37 (2H, t, J = 6.8 Hz), 1.84–1.73 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.3, 30.8, 27.1, 25.1, 24.5; HRMS (ESI) calcd for C_5H_9NO $[M + H]^+$ 100.0762, found 100.0757; mp 56–57 °C.

*Cycloheptanone Oxime (**2c**).* Table 5, entry 4: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.38 (1H, s), 2.58 (2H, t, J = 6.0 Hz), 2.38 (2H, t, J = 5.7 Hz), 1.71–1.56 (8H, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 164.3, 33.7, 30.4, 30.3, 28.5, 27.5, 24.5; HRMS (ESI) calcd for $C_7H_{13}NO$ $[M + H]^+$ 128.1075, found 128.1069.

*Cyclooctanone Oxime (**2d**).* Table 5, entry 5: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.23 (1H, s), 2.45 (2H, t, J = 6.3 Hz), 2.29 (2H, t, J = 6.6 Hz), 1.81–1.71 (4H, m), 1.54–1.50 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.0, 33.1, 27.2, 26.8, 26.6, 25.3, 24.6, 24.4; HRMS (ESI) calcd for $C_8H_{15}NO$ $[M + H]^+$ 142.1232, found 142.1226; mp 40–42 °C.

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*2-Adamantanone Oxime (**2e**).* Table 5, entry 6: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (1H, s), 3.58 (1H, s), 2.56 (1H, s), 2.00−1.82 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.7, 38.8, 37.4, 36.5, 36.2, 28.7, 27.8; HRMS (ESI) calcd for $C_{10}H_{15}NO$ $[M + H]^+$ 166.1232, found 166.1224; mp 165−166 °C.

*Indan-1-one Oxime (**2f**).* Table 5, entry 7: white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.83 (1H, s), 7.55 (1H, d, J = 7.8 Hz), 7.34 (2H, dd, J = 12.0, 4.3 Hz), 7.25 (1H, t, J = 7.2 Hz), 2.99 (2H, t, J = 6.7 Hz), 2.80−2.76 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.9, 147.6, 136.5, 129.6, 126.7, 125.6, 120.5, 27.8, 25.5; HRMS (ESI) calcd for C_9H_9NO $[M + H]^+$ 148.0762, found 148.0772; mp 145−146 °C.

*Tetralone 1-Oxime (**2g**).* Table 5, entry 8: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41 (1H, s), 7.89 (1H, d, J = 4.5 Hz), 7.29−7.25 (1H, m), 7.22−7.14 (2H, m), 2.83 (2H, t, J = 6.7 Hz), 2.77 (2H, t, J = 6.1 Hz), 1.92−1.85 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.3, 139.8, 130.4, 129.2, 128.63, 126.5, 124.0, 29.8, 23.9, 21.3; HRMS (ESI) calcd for $C_{10}H_{11}NO$ $[M + H]^+$ 162.0919, found 162.0915; mp 101−103 °C.

*4-Methylcyclohexanone Oxime (**2h**).* Table 5, entry 9: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (1H, s), 3.29−3.22 (1H, m), 2.38 (1H, d, J = 12.9 Hz), 2.10 (1H, dt, J = 19.7, 6.8 Hz), 1.89−1.75 (3H, m), 1.70−1.58 (1H, m), 1.22−1.06 (2H, m), 0.95 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.4, 34.8, 33.6, 31.9, 31.4, 23.7, 21.5; HRMS (ESI) calcd for $C_7H_{13}NO$ $[M + H]^+$ 128.1075, found 128.1071.

*4-tert-Butylcyclohexanone Oxime (**2i**).* Table 5, entry 10: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 (1H, s), 3.36 (1H, d, J = 16.3 Hz), 2.43 (1H, dd, J = 13.8, 2.3 Hz), 2.06 (1H, td, J = 12.2, 3.9 Hz), 1.95−1.91 (2H, m), 1.69 (1H, td, J = 13.7, 5.0 Hz), 1.26−1.16 (3H, m), 0.87 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.8, 47.5, 32.4, 31.9, 27.5, 26.3, 24.3; HRMS (ESI) calcd for $C_{10}H_{19}NO$ $[M + H]^+$ 170.1545, found 170.1535; mp 135−136 °C.

*4-Hydroxycyclohexanone Oxime (**2j**).* Table 5, entry 11: white solid; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 4.86 (2H, s), 3.89−3.85 (1H, m), 2.94−2.88 (1H, m), 2.42−2.36 (1H, m), 2.25−2.10 (2H, m), 1.93−1.88 (2H, m), 1.60−1.49 (2H, m); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 160.0, 68.8, 35.4, 34.0, 29.2, 21.5; HRMS (ESI) calcd for $C_6H_{11}NO_2$ $[M + H]^+$ 130.0868, found 130.0860; mp 80−82 °C.

*Octanal Oxime (**2k**).* Table 5, entry 12: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.99 (1H, s), 6.71 (1H, t, J = 5.5 Hz), 2.37 (2H, td, J = 7.5, 5.4 Hz), 1.48 (2H, dd, J = 14.8, 7.2 Hz), 1.31−1.29 (8H, m), 0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.9, 31.7, 29.3, 28.9, 26.0, 25.0, 22.6, 14.0; HRMS (ESI) calcd for $C_8H_{17}NO$ $[M + H]^+$ 144.1388, found 144.1380; mp 58−59 °C.

*5-Hydroxylpentanal Oxime (**2l**).* Table 5, entry 13: white solid; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 6.65 (1H, t, J = 5.5 Hz), 4.85 (2H, s), 3.57 (2H, t, J = 6.2 Hz), 2.37 (2H, td, J = 7.3, 5.5 Hz), 1.58−1.55 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 152.8, 62.5, 33.3, 25.6, 23.6; HRMS (ESI) calcd for $C_5H_{11}NO_2$ $[M + H]^+$ 118.0868, found 118.0862; mp 85−86 °C.

General Procedure for the Catalytic Oxidation of Secondary Amines to Nitrones with Molecular Oxygen. As a typical example, the aerobic oxidation of 1,2,3,4-tetrahydroisoquinoline (**4**) is described. A stainless steel autoclave (120 mL) equipped with a magnetic stirring bar was charged with a mixture of DPPH (**3**; 98.6 mg, 0.25 mmol), WO_3/Al_2O_3 (42 mg, W: 0.05 mmol), 1,2,3,4-tetrahydroisoquinoline (**4**; 666 mg, 5 mmol), and tetradecane (internal standard for GC analysis, 50 mg, 0.25 mmol) in acetonitrile (3 mL). The autoclave was pressurized to 5 MPa with an oxygen−nitrogen mixture (7/93 v/v), and the mixture was stirred (600 rpm) at 80 °C for 8 h. The reaction mixture was analyzed by GC using tetradecane as an internal standard. 3,4-Dihydroisoquinoline *N*-oxide (**5**)[13a] was obtained with 61% selectivity at 28% conversion.

*3,4-Dihydroisoquinoline N-oxide (**5**):*[13a] white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.20 (2H, t, J =7.78 Hz), 4.12 (2H, dt, J = 0.92 and 7.3 Hz), 7.12−7.15 (1H, m), 7.22−7.23 (1H, m), 7.28−7.30 (2H, m), 7.77 (1H, s); ^{13}C NMR (126 MHz, CDCh) δ (ppm) 27.7, 57.9, 125.4, 127.2, 127.6, 128.3, 129.4, 130.0, 134.1; MS (CI) m/z 148 $(M + H^+)$.

Recycling of the Catalyst. The first run was carried out under the same reaction conditions described in the general procedure for aerobic oxidation under O_2/N_2 (7/93 v/v, 5 MPa). After the reaction, the spent 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 the solvent and the product, and the residue of DPPH (**3**) was reused. These recycling procedures were repeated three times in the same manner as in the first run.

Competitive Reaction of Cyclohexylamine and Thioanisole for the DPPH−WO_3/Al_2O_3-Catalyzed Aerobic Oxidation. A mixture of DPPH (**3**; 98.6 mg, 0.25 mmol, 5 mol %), WO_3/Al_2O_3 (42 mg, W: 0.05 mmol, 1 mol %), cyclohexylamine (**1a**; 0.25 g, 2.5 mmol), thioanisole (**7**; 0.31 g, 2.5 mmol), and tetradecane (internal standard for GC analysis, 50 mg, 0.25 mmol) in acetonitrile (3 mL) was stirred under an oxygen−nitrogen mixture (7/93 v/v, 5 MPa) at 80 °C for 8 h. The reaction mixture was analyzed by GC using tetradecane as an internal standard, and the products were identified by GC-MS.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Kinetic data (Figure S1, effect of reaction temperature; Figure S2, correlation of initial rate and temperature; Figure S3, time course for aerobic oxidation, Figure S4, effect of oxygen pressure on catalytic performance) for the DPPH−WO_3/Al_2O_3-catalyzed aerobic oxidation of primary amine, UV−vis spectra (Figure S5) for the stoichiometric reaction of DPPH with primary amine, and figures giving the ^{1}H NMR, ^{13}C NMR and HRMS spectra of the new compounds **2j**−**l**. 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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