

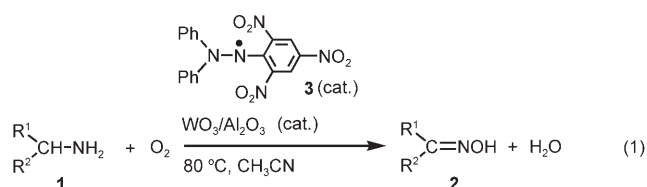
# Aerobic Oxidation of Primary Amines to Oximes Catalyzed by DPPH and WO<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub>

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Since the catalytic oxidation of amines is important for enzymatic<sup>[1]</sup> and synthetic processes,<sup>[2]</sup> various methods have been examined; however, useful methods for the oxidation of amines are limited because of the sensitivity of amines. Selective catalytic oxidative transformations of secondary amines to nitrones<sup>[3,4]</sup> and imines<sup>[5,6]</sup> 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.<sup>[7]</sup> Catalytic oxidation of primary amines with hydrogen peroxide gives oximes along with by-products such as nitroalkanes, carbonyl compounds, and imines.<sup>[8–12]</sup>

Aerobic oxidation under mild conditions is one of the current challenges in view of environmental and economical aspects;<sup>[13,14]</sup> however, aerobic oxidative transformations of amines are limited to a few reactions, which include the ruthenium-catalyzed oxidative cyanation of tertiary amines,<sup>[15]</sup> transition-metal-catalyzed oxidation of secondary amines to imines<sup>[6]</sup> and of primary amines to nitriles,<sup>[16]</sup> and flavin-catalyzed oxidation of secondary amines to nitrones.<sup>[4]</sup> 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 SiO<sub>2</sub> gel at higher temperature (>150 °C) gives oximes only in low yields.<sup>[17]</sup> 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**)<sup>[18]</sup> and tungstated alumina (WO<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub>) 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



complexes as catalysts was found to give nitriles resulting from extensive oxidative dehydration.<sup>[16]</sup> Furthermore, dehydration of aldoximes occurs at higher temperatures to give nitriles.<sup>[19]</sup> Next, we examined organocatalysts. Attempts using typical catalysts such as flavin,<sup>[4]</sup> 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO),<sup>[20]</sup> and phthalimide-*N*-oxyl (PINO) derived from *N*-hydroxyphthalimide (NHPI)<sup>[21]</sup> failed. We then focused on DPPH, which had never been used for catalytic oxidation. Ultimately, the combination of DPPH and WO<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub> 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 WO<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub> proved to be the best catalyst (Table 1, entry 1). The reaction of cyclohexylamine in the presence of DPPH (2.5 mol %) and WO<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub> (1 mol %) under molecular oxygen diluted with molecular nitrogen for safety (O<sub>2</sub>/N<sub>2</sub> = 7:93 v/v, 5 MPa, under the explosion limit) in acetonitrile at 80 °C for 4 h gave cyclohexanone oxime with 95 % selectivity

**Table 1:** The aerobic oxidation of cyclohexylamine to cyclohexanone oximes using various catalysts.<sup>[a]</sup>

| Entry             | Catalyst                                                    | Conversion of amine [%] <sup>[b]</sup> | Selectivity for oxime [%] <sup>[b]</sup> |
|-------------------|-------------------------------------------------------------|----------------------------------------|------------------------------------------|
| 1                 | DPPH–WO <sub>3</sub> /Al <sub>2</sub> O <sub>3</sub>        | 59                                     | 95                                       |
| 2                 | DPPH                                                        | 21                                     | 3                                        |
| 3                 | WO <sub>3</sub> /Al <sub>2</sub> O <sub>3</sub>             | 7                                      | 0                                        |
| 4                 | DPPH–WO <sub>3</sub> /ZrO <sub>2</sub>                      | 63                                     | 86                                       |
| 5                 | DPPH–TS-1                                                   | 14                                     | 93                                       |
| 6                 | DPPH–[Ti(OiPr) <sub>4</sub> ]                               | 67                                     | 88                                       |
| 7                 | DPPH–[TiO(acac) <sub>2</sub> ]                              | 61                                     | 89                                       |
| 8                 | DPPH–Nb <sub>2</sub> O <sub>5</sub>                         | 50                                     | 80                                       |
| 9                 | DPPH–H–WO <sub>3</sub> /Al <sub>2</sub> O <sub>3</sub>      | 41                                     | 96                                       |
| 10                | DOPH–WO <sub>3</sub> /Al <sub>2</sub> O <sub>3</sub>        | 62                                     | 96                                       |
| 11                | TEMPO–WO <sub>3</sub> /Al <sub>2</sub> O <sub>3</sub>       | 4                                      | 2                                        |
| 12                | NHPI–WO <sub>3</sub> /Al <sub>2</sub> O <sub>3</sub>        | 7                                      | 3                                        |
| 13 <sup>[c]</sup> | TEMPO–[RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub> ] | 21                                     | 0                                        |
| 14 <sup>[d]</sup> | NHPI–[Co(acac) <sub>3</sub> ]                               | 36                                     | 0                                        |

[a] Reaction conditions: Cyclohexylamine (5 mmol), organocatalyst (2.5 mol %), transition-metal catalyst (metal: 1 mol %) in acetonitrile (3 mL), O<sub>2</sub> (O<sub>2</sub>/N<sub>2</sub> = 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 % [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>]. [d] 10 mol % NHPI, 0.5 mol % [Co(acac)<sub>3</sub>]. acac = acetylacetonate.

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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.

and 59% conversion. Control experiments showed that DPPH and  $\text{WO}_3/\text{Al}_2\text{O}_3$  alone exhibited no catalytic activity, and the coexistence of DPPH and  $\text{WO}_3/\text{Al}_2\text{O}_3$  is necessary for the high catalytic activity (Table 1, entries 2 and 3).  $\text{WO}_3/\text{ZrO}_2$ , TS-1,  $[\text{Ti}(\text{O}i\text{Pr})_4]$ ,  $[\text{TiO}(\text{acac})_2]$ , and  $\text{Nb}_2\text{O}_5$  can be used as the cocatalyst of DPPH (Table 1, entries 4–8), while  $\text{MoO}_3/\text{Al}_2\text{O}_3$ ,  $[\text{MoO}_2(\text{acac})_2]$ ,  $[\text{VO}(\text{acac})_2]$ ,  $[\text{Fe}(\text{acac})_3]$ , and  $[\text{Co}(\text{acac})_2]$  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<sup>[20a]</sup> 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  $[\text{RuCl}_2(\text{PPh}_3)_3]$ <sup>[20]</sup> or NHPI with  $[\text{Co}(\text{acac})_2]$ ,<sup>[21]</sup> 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  $\text{WO}_3/\text{Al}_2\text{O}_3$  (1 mol %) in acetonitrile under  $\text{O}_2/\text{N}_2$  (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  $\text{WO}_3/\text{Al}_2\text{O}_3$  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  $\epsilon$ -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-hydroxycyclohexylamine proceeded chemoselectively to afford the corresponding oxime in 82 % yield (Table 2, entry 8). Chemoselective oxidation of 5-hydroxypentylamine was also observed (Table 2, entry 10). The reaction of tertiary amines such as *tert*-butylamine did not occur.

Importantly, the DPPH- $\text{WO}_3/\text{Al}_2\text{O}_3$  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- $\text{WO}_3/\text{Al}_2\text{O}_3$ .<sup>[a]</sup>

| Entry | Substrate                                                                         | <i>t</i> [h] | Conversion [%] <sup>[b]</sup> | Yield of oxime [%] <sup>[b]</sup> |
|-------|-----------------------------------------------------------------------------------|--------------|-------------------------------|-----------------------------------|
| 1     |  | 8            | 98                            | 90 (85) <sup>[c]</sup>            |
| 2     |  | 16           | 98                            | 89 <sup>[d]</sup>                 |
| 3     |  | 8            | 97                            | 82                                |
| 4     |  | 48           | 96                            | 73                                |
| 5     |  | 48           | 95                            | 80                                |
| 6     |  | 48           | 90                            | 72                                |
| 7     |  | 8            | 97                            | 85                                |
| 8     |  | 48           | 97                            | 82                                |
| 9     |  | 36           | 94                            | 73 <sup>[e]</sup>                 |
| 10    |  | 48           | 95                            | 75 <sup>[e]</sup>                 |

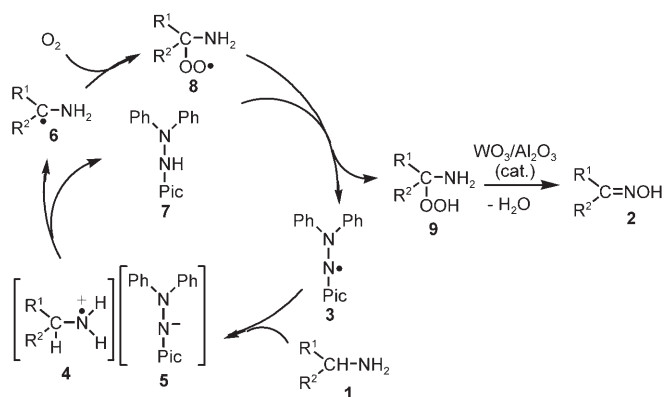
[a] Reaction conditions: primary amine (5 mmol), DPPH (5 mol %),  $\text{WO}_3/\text{Al}_2\text{O}_3$  (W: 1 mol %) in acetonitrile (3 mL),  $\text{O}_2$  ( $\text{O}_2/\text{N}_2$  = 7:93; 5 MPa) at 80 °C. [b] Determined by GC analysis using an internal standard. [c] The yield of isolated product obtained from a gram-scale reaction is in parentheses. [d]  $\text{O}_2$  atmosphere (1 atm, balloon) at 80 °C. [e] 10 mol % DPPH.

**Table 3:** Recycling of the catalyst DPPH- $\text{WO}_3/\text{Al}_2\text{O}_3$  for the aerobic oxidation of cyclohexylamine.<sup>[a]</sup>

| Cycle | Conversion [%] <sup>[b]</sup> | Yield of oxime [%] <sup>[b]</sup> |
|-------|-------------------------------|-----------------------------------|
| 1     | 98                            | 90                                |
| 2     | 97                            | 91                                |
| 3     | 99                            | 90                                |

[a] Reaction conditions: cyclohexylamine (5 mmol), DPPH (5 mol %),  $\text{WO}_3/\text{Al}_2\text{O}_3$  (W: 1 mol %) in acetonitrile (3 mL) under  $\text{O}_2/\text{N}_2$  (7:93; 5 MPa) at 80 °C for 8 h. Recycling of the catalyst: after the reaction,  $\text{WO}_3/\text{Al}_2\text{O}_3$  could be easily separated from the reaction mixture by filtration, and the isolated  $\text{WO}_3/\text{Al}_2\text{O}_3$  was reused. Kugelrohr distillation (100 °C, 30 mmHg) gave cyclohexanone, 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**.<sup>[22]</sup> 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  $\alpha$ -aminoalkyl radical **6**. The latter undergoes reaction with molecular oxygen to afford the  $\alpha$ -aminoalkylperoxyl radical **8**, which undergoes abstraction of hydrogen from **7** to give  $\alpha$ -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- $\text{WO}_3/\text{Al}_2\text{O}_3$ -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  $\text{WO}_3/\text{Al}_2\text{O}_3$  catalyst. Indeed, when 1-hydroperoxycyclohexylamine, which was prepared from cyclohexanone,  $\text{NH}_3$ , and  $\text{H}_2\text{O}_2$ ,<sup>[23]</sup> was allowed to react with the  $\text{WO}_3/\text{Al}_2\text{O}_3$  catalyst at room temperature, cyclohexanone oxime was obtained in 75 % yield. It is noteworthy that the same reaction in the absence of  $\text{WO}_3/\text{Al}_2\text{O}_3$  catalyst gave cyclohexanone in 90 % yield.

In conclusion, we have found that a novel, efficient, aerobic oxidative transformation of primary amines with DPPH- $\text{WO}_3/\text{Al}_2\text{O}_3$  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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