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Solvent free aerobic oxidation of alcohols with 1-methyl-2-azaadamantane N-oxyl as a recyclable catalyst through phase separation

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An expedient, non-metallic green protocol for aerobic oxidation of alcohols was established. 1-Methyl-2-azaadamantane N-oxyl was used as the core catalyst due to its superior chemical stability and catalytic performance. The catalyst can be easily reused through phase separation by taking advantage of its solubility feature, which varies with its oxidation state.

Selective oxidation of alcohols to the corresponding aldehydes or ketones is one of the most fundamental transformations in organic synthesis.^{1,2} Molecular oxygen is obviously superior to other conventional stoichiometric oxidants, from both the viewpoints of green chemistry and economy.^{3,4} In the past decades, numerous catalytic systems, mostly based on noble metal catalysts, have been developed to harness the power of molecular oxygen for the oxidation of alcohols. Notably, there is another category, which is non-metallic and uses carbon materials^{5,6} or organic compounds, *e.g.* IBX^{7,8} and TEMPO⁹⁻¹² as core catalysts. As typical stable nitroxide radicals, TEMPO and its derivatives have been found to be very active towards the specific transformation of hydroxyl groups to carbonyl groups. However, the homogeneous nature and relatively high prices make them less attractive for large scale applications. Thus, many efforts have been devoted to improve their reusability. Most endeavours were focused on changing their homogeneous nature to heterogeneous *via* immobilization on certain supporting materials, such as organic polymers¹³⁻¹⁸ and silicas,^{19,20} particularly mesoporous structured silicas.²¹⁻²³ Other attempts include tagging TEMPO with fluoruous^{24,25} or ionic^{26,27} chains of small molecular weights to facilitate catalyst separation. We are also interested in developing green, economical and efficient oxidation systems. Herein, we report a green protocol for aerobic alcohol oxidation, which also utilizes a nitroxide radical 1-Me-AZADO as a homogenous catalyst, and the recycling of 1-Me-AZADO by taking advantage of the change of its solubility with oxidation state.

This research was inspired by the catalytic mechanism of nitroxide radical catalyzed oxidation of alcohols.²⁸ The mechanism involves an intermediate cation, which is oxidized from the starting nitroxide radical and serves as the real oxidant for alcohols. To complete the catalytic cycle, the cation oxidizes an alcohol to a carbonyl compound with itself reduced to a hydroxyamine, which is then oxidized by a bulk oxidant to regenerate the nitroxide radical. We noted that during the process, the catalyst first has limited solubility in water in its radical form, then it becomes soluble in water and insoluble in organic phase when oxidized to a cation, and finally it reverts to water insoluble upon reduction to the hydroxyamine form. And we postulated that this unique feature could be used to facilitate the catalyst recycling, promising a much simpler solution than immobilization. Therefore, we designed a two phase oxidation system with diluted HNO₃ solution as the aqueous phase and the alcohol substrate as the organic phase, without use of any organic solvents. Because diluted nitric acid is not able to oxidize hydroxyamines, a catalytic amount of NaNO₂ was added to generate stronger oxidants, *i.e.*, HNO₂ and further NO₂, which is also a key component for O₂ activation.

To find an appropriate nitroxide radical for this system, two main factors were taken into consideration. One is, of course, the catalytic performance, and the other is the stability of the corresponding cation. This is because an important step in the recycling process is the separation of the cations with the aqueous phase. This requires the catalysts to be able to remain stable in the ion form for a long enough time. If the cation is a short-lived intermediate, then a considerable amount of the catalyst will be decomposed during recycling, leading to the failure of this method. Three nitroxide radicals were chosen to be evaluated, *i.e.*, TEMPO, 1-Me-AZADO, and ABNO. TEMPO is the most commonly used one in this field. 1-Me-AZADO has been recently reported to show remarkably higher performance than TEMPO.²⁹ ABNO is reported to possess activity comparable to 1-Me-AZADO; moreover, its synthetic route is much simpler and shorter than that of 1-Me-AZADO, indicating a lower cost if adopted on a large scale.³⁰ To examine the stabilities of the corresponding cations, we prepared the ionic solutions by dissolving the three nitroxide radicals into 30% nitric acid, where the radicals were immediately oxidized to cations, and the changes in cationic concentrations with time were determined using UV-Vis spectroscopy. As shown in Fig. 1,

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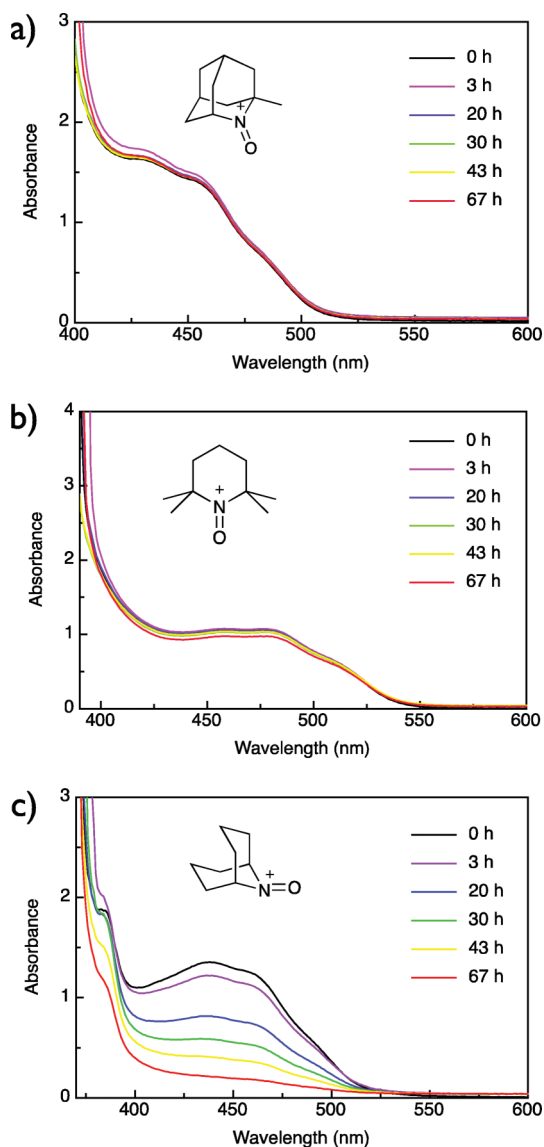


Fig. 1 Chemical stabilities of 1-Me-AZADO⁺, ABNO⁺ and TEMPO⁺. a), b) and c) 0.05 M of nitroxides in 30% HNO₃ solutions, measured by UV-Vis spectroscopy.

1-Me-AZADO⁺ and TEMPO⁺ were satisfactorily stable over a period of three days, and in contrast, ABNO⁺ decomposed rapidly, and its characteristic adsorption (438 nm) decreased by 84% after 67 h. Their relative catalytic performances were compared in the oxidation of benzyl alcohol under the same reaction conditions. Preliminary results, shown in Fig. 2, indicated that 1-Me-AZADO is slightly more active than ABNO, and is far more active compared with TEMPO. Thus, it seemed to us that 1-Me-AZADO is the best candidate for our system in terms of chemical stability and catalytic performance, and it was therefore chosen as the core catalyst for our subsequent studies.

In a typical reaction, 1-Me-AZADO was first dissolved in alcohol substrate to give a red solution. Upon the addition of dilute nitric acid, the radicals were oxidized to cations, which is supposed to give a yellowish green color. However, such color was not observed since the cations were immediately reduced by alcohols to colorless hydroxyamines. Following the atmosphere

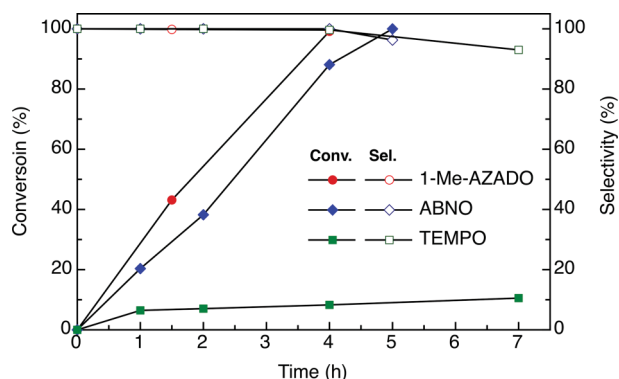
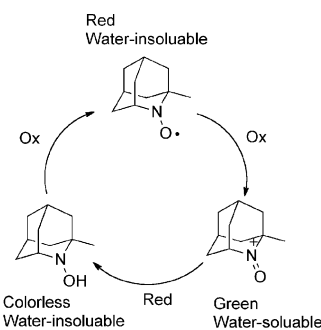
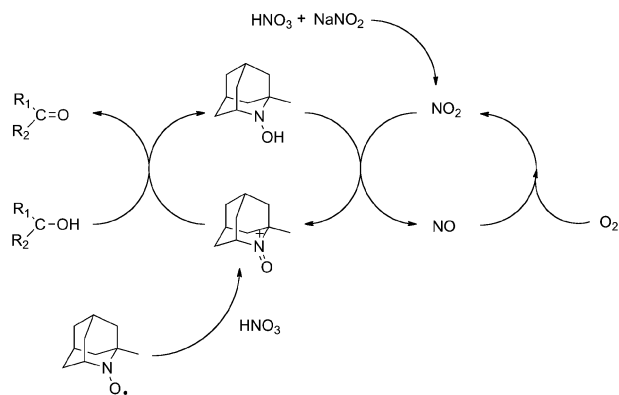


Fig. 2 Comparison of catalytic performances among 1-Me-AZADO, ABNO and TEMPO. Reaction conditions: benzyl alcohol (40 mmol), nitroxide radicals (0.2 mmol), 5% HNO₃ (4 mmol), NaNO₂ (4 mmol), 40 °C, O₂ (balloon pressure).

being replaced by O₂, NaNO₂ solution was added using a hypodermic syringe. After the completion of reaction, the lower aqueous phase was observed to display a green color, contrasted to the upper colorless organic phase, suggesting a very large solubility difference of 1-Me-AZADO⁺ in the two phases. Such interesting color and solubility changes are summarized in Scheme 1. A full picture of the overall mechanism underlying this oxidation system is proposed and depicted in Scheme 2, where two redox cycles are combined to activate molecular oxygen for alcohol oxidation.



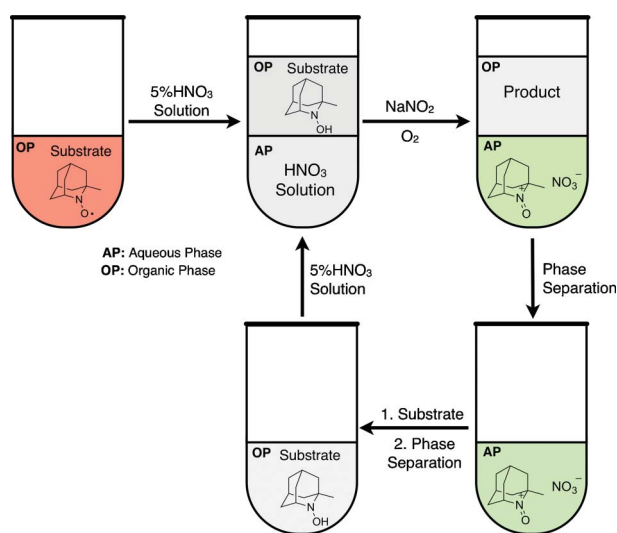
Scheme 1 Solubility changes of 1-Me-AZADO with oxidation state.



Scheme 2 Proposed mechanism.

To demonstrate the recycling method of 1-Me-AZADO by phase separation is of practical use, we conducted recyclability

studies with the substrate of benzyl alcohol. The procedure is briefly illustrated in Scheme 3. After the completion of a previous reaction, the green aqueous phase is transferred to a new vessel, followed by the addition of a new batch of alcohol substrate. Upon shaking, 1-Me-AZADO⁺ is reduced to hydroxyamine as the green color vanishes, and transfers to the organic phase due to the change of solubility. Subsequent removal of the aqueous phase and addition of fresh nitric acid take it back to the starting point that is ready for conducting a second reaction. The amounts of catalysts being recovered are calculated from the UV-Vis adsorption (430.2 nm) of 1-Me-AZADO⁺ after reaction, based on a previously-made calibration curve. As shown in Fig. 3, for a fixed reaction time, the conversion of substrate can still reach around 90% in the eighth run, with over half of the catalysts being recovered after eight cycles. Besides the inevitable loss during the recycling process, the consumption of catalysts may also come from the oxidative decomposition during the reaction. If the reactions were conducted on a larger scale, the catalyst loss during recycling could be further reduced. Although 1-Me-AZADO is not fully recovered, a total turn over number (TON) of over 600 could be easily delivered along with practical catalytic performances, which is comparable to those supported nitroxyl radicals under aerobic oxidation conditions.



Scheme 3 Illustration of recycling of 1-Me-AZADO by phase separation.

The current system can be simply applied to various benzylic alcohols. The alcohols chosen to be investigated here all have melting points lower than the reaction temperature (40 °C), so the use of any organic solvents can be avoided. The results are shown in Table 1. Most of these benzylic alcohols have substituents either at *ortho* position or *meta* position. No significant substituent effects on the oxidation reactivities were observed except for 4-methoxybenzyl alcohol (entry 6) and 3-nitrobenzyl alcohol (entry 7). The strong electron withdrawing effect of nitro group largely reduces the reactivity as expected. Interestingly, the methoxy group at *para* position, which is electron donating, was unexpectedly observed to show an adverse effect in our system. To achieve good conversions for these less active substrates, double amounts of catalysts were employed. Our system also works well with heteroaromatic

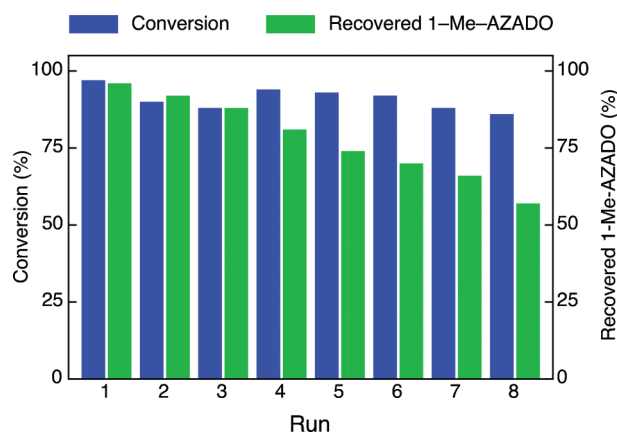


Fig. 3 Recycling of 1-Me-AZADO in the oxidation of benzyl alcohol. Reaction conditions: benzyl alcohol (20 mmol), 1-Me-AZADO (0.2 mmol), 5% HNO₃ (2 mmol), NaNO₂ (2 mmol), 40 °C, O₂ (balloon pressure), 2–2.5 h.

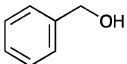
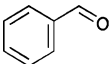
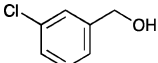
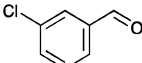
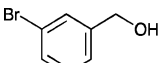
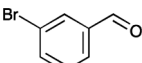
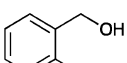
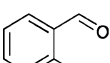
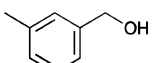
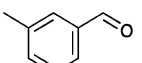
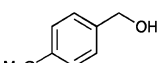
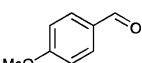
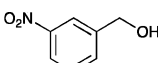
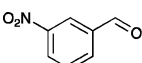


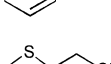
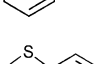
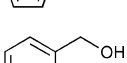
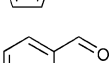
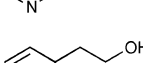
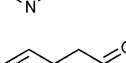
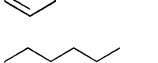
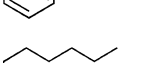
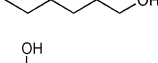
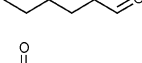
primary alcohols, which have been reported to be poisonous to noble metal catalysts. For instance, 2-thiophenemethanol was oxidized smoothly without any difficulty (entry 9). For basic substrates, such as 3-pyridinemethanol (entry 10), additional amounts of nitric acid are needed to improve reaction rates and to ensure good conversions. Notably, ideal selectivities to aldehydes were maintained for all primary alcohols. However, when applying our system to aliphatic alcohols, a problem of incomplete conversions of alcohols was encountered (entry 11–13). Actually, the decomposition of 1-Me-AZADO was limited during the reaction, since the catalysts were well recovered after reactions. Therefore it should not be the main reason for the low conversions. A plausible explanation might be the solvent effect. As there was no other organic solvent, the substrate itself also played as the solvent, and over the course of the reaction, the mixture composition changed due to the formation of aldehyde products, resulting in the unfavorable change of the chemical environment for the oxidation reaction.

In summary, a simple green method for the aerobic oxidation of alcohols has been disclosed by using a nitroxide radical 1-Me-AZADO as a recyclable catalyst. The concept of catalyst recycling by utilizing the unique solubility feature of 1-Me-AZADO was demonstrated to be practical, largely increasing the total TON of catalyst. Compared with those oxidation systems using supported nitroxide radicals, this method offers great ease of catalyst preparation as well as product purification, and is also more energy and material efficient. Moreover, the elimination of the use of organic solvent also affords great environmental benefit, embodying the notion of green chemistry.

Experimental

All alcohol substrates, TEMPO and 1-Me-AZADO were obtained from commercial suppliers and were used as received. ABNO was synthesized according to reported procedures.³⁰ UV-Vis spectra were recorded on a HITACHI U-2800 Spectrophotometer. Oxidation reactions were carried out using a SIBATA Chemist Plaza CP100 multi-reactor equipped with 30 × 200 mm sized test tubes as reaction vessels and separate magnetic stirrers.

Table 1 Aerobic oxidation of various alcohols

Entry ^a	Substrate	Product	t (h)	Conv. (%) ^d	Scl. (%) ^d
1			4	99	99
2			3	99	100
3			6	95	99
4			3	99	95
5			3	99	100
6 ^b			5	100	100
7 ^b			5	100	100
8			5	84	100
9 ^b			4	98	100
10 ^{b,c}			10	89	98
11 ^b			8	48	100
12 ^b			8	59	100
13 ^b			8	38	100

^a General conditions: substrate (40 mmol), 1-Me-AZADO (0.2 mmol, 0.5 mol%), 5% HNO₃ (4 mmol, 10 mol%), NaNO₂ (4 mmol, 10 mol%), 40 °C, O₂ (balloon pressure). ^b 1-Me-AZADO (0.4 mmol, 1 mol%). ^c 5% HNO₃ (8 mmol, 20 mol%), NaNO₂ (8 mmol, 20 mol%). ^d Determined by GC-MS, based on area normalization.

Samples were analyzed with a SHIMAZDU GCMS-QP2010 Plus, using a Restek Rxi-1 ms column. Quantitative analysis was based on area normalization.

Typical procedures for alcohol oxidations: 40 mmol of alcohol, 0.2–0.4 mmol of 1-Me-AZADO were added into a test tube, which was then sealed with a silicon septum, evacuated and backfilled with oxygen using an oxygen balloon. 4 mmol of 5% HNO₃ was charged using a hypodermic needle and the mixture was heated to 40 °C. After the mixture turned to colorless, 4 mmol of 0.5 M NaNO₂ was added using a hypodermic needle. Samples were taken at appropriate intervals and were analyzed with GC-MS.

Acknowledgements

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