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Short communication

# Diverse catalytic efficiency of nitroxyl radicals tuned by Lewis acids in the oxidation of hydrocarbons

Lu Jia [a], Kexian Chen [b], Lingyao Wang [a], Renfeng Du [a], Congmin Wang [a], Jia Yao [a], Haoran Li [a,b,*]

[a] *Department of Chemistry, ZJU-NHU United R&D Center, Zhejiang University, Hangzhou 310027, PR China*
[b] *State Key Laboratory of Chemical Engineering, Department of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310027, PR China*

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ABSTRACT

Aerobic oxidation of α-isophorone catalyzed by 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) has achieved comparable performance to that catalyzed by phthalimide-*N*-oxyl (PINO) with the assistance of Lewis acids (LAs), but the latter efficiency is depressed by LAs. Remarkably changed structural and thermochemical properties of nitroxyl radicals induced by LAs cause the diversely altered reactivity. Persistent and nonconjugated nitroxyl radicals with alkyl groups around N–O parts like TEMPO can be activated, whereas non-persistent ones, with N–O parts conjugated with carbonyl groups like PINO are deactivated by LAs. TEMPO analogues combined with strong but less steric-hindrance LAs exhibit the highest catalytic activity.

## 1. Introduction

Oxidation of hydrocarbons with the molecular oxygen as oxidant has received considerable attention in both academic research and chemical industry [1–3]. Generally, metallic catalysts and harsh conditions are required in these processes. Environment friendly catalysts are hence particularly desirable, especially the fascinating organocatalysts nitroxyl radicals [4–7]. For instance, the phthalimide-*N*-oxyl (PINO) is recognized as a powerful catalyst for the oxidation of hydrocarbons [8–11]. However, its facile thermal deactivation limits its applications at high temperatures [12,13]. This drawback could be overcome partly under mild conditions [14,15]. The 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), accepted as "golden" catalyst for the oxidation of alcohols, phenols, and amines [16–18], also has superiors to overcome this drawback of PINO [3,4]. Nevertheless, it is not effective in the oxidation of hydrocarbons.

The efficient utilization of TEMPO in the oxidation of hydrocarbons is highly attractive [3]. There are successful cases for TEMPO to promote this oxidation under appropriate conditions. High temperature or binding with metal centered complexes facilitate the hydrogen-transfer by TEMPO, which is a crucial step in the oxidation of hydrocarbons [19,20]. Besides, the oxidation of active C–H bonds can be smoothly catalyzed by TEMPO [21]. Recently, Hayton and co-workers showed that the TEMPO-$MCl_3$ (M = Fe, Al) system was active towards the oxidation of 9,10-dihydroanthracene [22], opening a new opportunity to improve the reactivity of nitroxides. To our interests, both applying persistent nitroxyl radicals in the oxidation of hydrocarbons and comparing them with the non-persistent ones are significantly important in organocatalysis. Herein, we report that TEMPO exhibits comparable catalytic efficiency to PINO in the oxidation of α-isophorone (α-IP) with the assistance of Lewis acids (LAs), in which the activity of PINO is unexpectedly depressed. Corresponding mechanisms and catalytic activity of analogous nitroxyl radials tuned by LAs are investigated.

## 2. Experimental section

Reagents were purchased from commercial suppliers and used as received. The solvent toluene was distilled. Detailed procedures for the oxidation of α-IP and its control reaction without oxygen were provided in the supporting information. Reactions were performed under anhydrous conditions. With desired amounts of α-IP, catalysts and toluene in a dry three-neck flask fitted with a magnetic stirrer, the mixture was stirred at 80 °C for 24 h under a balloon filled with oxygen or nitrogen. Products were confirmed using standard chemicals. The conversion of α-IP and selectivity of ketoisophorone (KIP) were determined by gas chromatography using ethyl benzoate as an internal standard.

## 3. Computational details

All geometry optimizations, frequencies and energy calculations were carried out within Gaussian 03 software using B3LYP method, and the 6-31 + G* and LANL2DZ basis sets were used for non-metal atoms and metal atoms, respectively. Stationary points were minima without any imaginary frequency, while the transition states had only

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* Corresponding author at: Department of Chemistry, ZJU-NHU United R&D Center, Zhejiang University, Hangzhou 310027, PR China.
*E-mail address:* lihr@zju.edu.cn (H. Li).

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**Table 1**
The oxidation of α-IP.[a]

| Entry | Catalyst (10 mol%) | Conv. (%) | KIP Select. (%) |
|---|---|---|---|
| 1 | – | – | – |
| 2 | $ZnCl_2$ | – | – |
| 3 | $AlCl_3$ | 3 | – |
| 4 | TEMPO | 4 | – |
| 5 | TEMPO + $ZnCl_2$ | 11 | 10 |
| 6 | TEMPO + $AlCl_3$ | 29 | 33 |
| 7 | NHPI | 34 | 41 |
| 8 | NHPI + $ZnCl_2$ | 30 | 24 |
| 9 | NHPI + $AlCl_3$ | 27 | 16 |

[a] Reaction conditions: α-IP (20 mmol), solvent: toluene (10 mL), temperature: 80 °C, reaction time: 24 h.

one imaginary frequency. The intrinsic reaction coordinates were also performed. The hydrogen-transfer barriers were calculated at the B3LYP/LANL2DZ(6-311++G**)//B3LYP/LANL2DZ(6-31 + G*) level with a dielectric constant of 2.379 (toluene) using polarizable continuum model.

## 4. Results and discussion

### 4.1. Oxidation of α-IP catalyzed by nitroxyl radicals with LAs

The combination of LAs and catalytic amount of TEMPO promotes the oxidation of α-IP with molecular oxygen as oxidant. Especially with $AlCl_3$, TEMPO shows comparable performance to PINO. As displayed in Table 1, the oxidation of α-IP without catalysts or just with LAs does not occur smoothly. The catalytic efficiency of TEMPO is obviously lower than that of *N*-hydroxyphthalimide (NHPI). However, both the conversion of α-IP and selectivity of KIP increase when TEMPO combines with LAs. Besides, the reaction of α-IP, TEMPO and $AlCl_3$ under anaerobic condition shows that neither KIP nor the dimmer of α-IP radical and TEMPO is found. Both the experiment and computation indicate that the new oxygen atom of KIP mainly comes from the oxygen rather than TEMPO (Fig. S1). As NHPI is stable towards LAs in this system (Figs. S2 and S3), its usage with LAs is attempted. Unexpectedly, the reactivity of NHPI is depressed by LAs (Table 1). Systematic studies are performed to elucidate these observations.

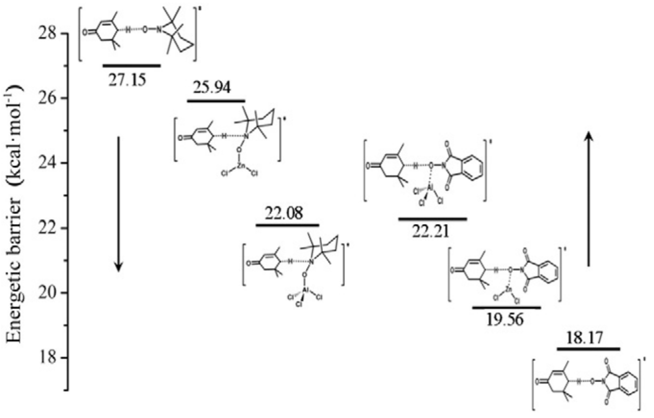

**Fig. 1.** Energetic barriers of hydrogen-transfer from α-IP to nitroxyl radicals with/without LAs.

The remarkably altered electronic configurations and thermochemical properties account for the changed catalytic efficiency of nitroxyl radicals. Geometric parameters of their active center N–O parts show that both TEMPO and PINO combined with LAs maintain radical characters on themselves (Table S1). This is beneficial to the oxidation which occurs mainly via a radical-based pathway [23,24]. More radical character on the terminal O atom and the higher >NO–H bond dissociation enthalpy (BDE) of NHPI enable PINO to perform excellently in its catalyzed oxidation [25]. For TEMPO, neither the equal radical characters of its O/N atoms nor the weaker O–H bond in TEMPOH is favorable for the oxidation of hydrocarbons. However, the electron spin density (SD) is obviously biased to the N atom of the activated TEMPO, which is unlike the primarily average one [16], enlarging the differences of SD on the N/O atoms (ΔSD). Notably, the ΔSD value of TEMPO is only 0.043, but it is increased to 0.414 by $AlCl_3$. This value is close to that of PINO [26], but the activated TEMPO has higher $SD_N$, contrary to PINO with higher $SD_O$ (Table 2). Thus, it is reasonable to conclude that the N atom is the active site of the activated TEMPO. These electron perturbations enhance the N–O bonds polarity, improving the reactivity of nitroxyl radicals [4]. Interestingly, the SD of PINO with LAs is also biased towards it N atom, but the ΔSD value is shrunk, inducing the decreased reactivity.

Besides, the N–H BDEs of TEMPOH′ (H atom linked to N atom of TEMPO, Fig. S4) modified by LAs are remarkably larger. It is 79.67 $kcal·mol^{-1}$ of TEMPOH′ modified by $AlCl_3$, which is close to the >NO–H BDE (85.12 $kcal·mol^{-1}$) of NHPI. This is thermally favorable for the hydrogen-transfer from normal C–H bonds with BDE about 80 $kcal·mol^{-1}$ [6]. The hydrogen-transfer barrier from α-IP to the N atom of TEMPO modified by $AlCl_3$ is notably lower than that to its O atom, supporting the shift of its active site (Fig. S4). This lower barrier is very close to that of PINO. Alternatively, the >NO–H BDEs of NHPI are reduced by LAs with higher hydrogen-transfer barriers from α-IP to PINO (Fig. 1). Above analysis on catalysts reactivity towards the well-established crucial step of the whole oxidation is helpful in understanding the experiments qualitatively.

### 4.2. Designing more active catalytic system

The reactivity of nitroxyl radical is related to its structure and the combined LAs. Persistent and nonconjugated ones with alkyl groups

**Table 2**
Key electronic structure and bond dissociation enthalpy (BDE) of TEMPO, PINO with and without LAs.

| Compound | $SD_O$ | $SD_N$ | ΔSD | >NO–H BDE[a] ($kcal·mol^{-1}$) | N–H BDE[b] ($kcal·mol^{-1}$) |
|---|---|---|---|---|---|
| TEMPO | 0.500<br>(0.500) | 0.457<br>(0.440) | 0.043<br>(0.060) | 67.82<br>(70.00) | – |
| T + $ZnCl_2$ | 0.414 | 0.580 | 0.166 | 59.02 | 71.18 |
| T + $AlCl_3$ | 0.257 | 0.671 | 0.414 | 57.04 | 79.67 |
| PINO | 0.631<br>(0.636) | 0.212<br>(0.200) | 0.419<br>(0.436) | 85.12<br>(88.00) | – |
| P + $ZnCl_2$ | 0.616 | 0.231 | 0.385 | 84.89 | 58.51 |
| P + $AlCl_3$ | 0.535 | 0.326 | 0.210 | 78.95 | 67.89 |

Data in parenthesis are taken from refs. [19] and [26].
[a] >NO–H bond of hydroxylamine.
[b] N–H bond of amine′.

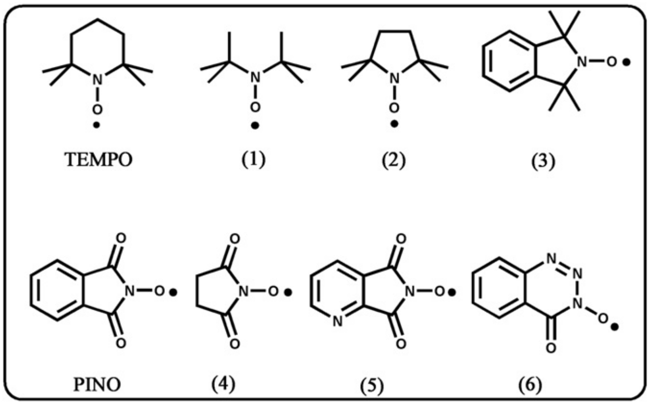

**Fig. 2.** Representative organocatalysts similar to TEMPO or PINO.