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Iron(III) Nitrate/TEMPO-Catalyzed Aerobic Alcohol Oxidation: Distinguishing between Serial versus Integrated Redox Cooperativity

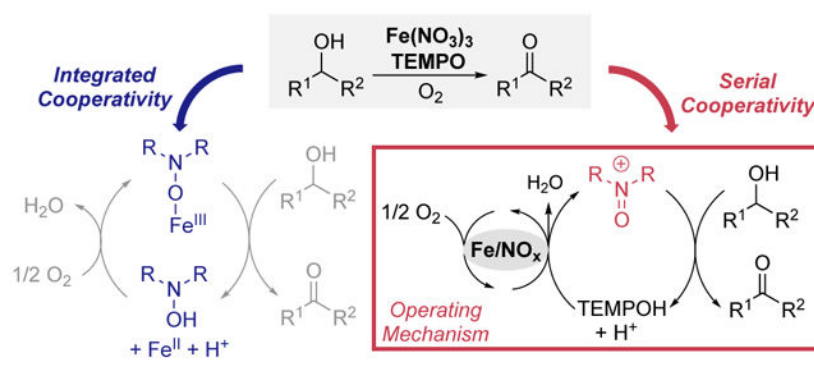
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Abstract

Aerobic alcohol oxidation catalyzed by transition-metal salts and aminoxyls are prominent examples of cooperative catalysis. Cu/aminoxyl catalysts have been studied previously and feature “integrated cooperativity”, in which Cu^{II} and the aminoxyl participate together to mediate alcohol oxidation. Here, we investigate a complementary Fe/aminoxyl catalyst system and provide evidence for “serial cooperativity”, involving a redox cascade in which alcohol is oxidized by in situ-generated oxoammonium species, which is directly detected in the catalytic reaction mixture by cyclic step chronoamperometry. The mechanistic difference between the Cu and Fe-based catalysts arises from the use iron(III) nitrate, which initiates a NO_x-based redox cycle for oxidation of aminoxyl/hydroxylamine to oxoammonium. The different mechanisms for the Cu- and Fe-based catalyst systems are manifested in different alcohol oxidation chemoselectivity and functional group compatibility.

Graphical Abstract



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Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/jacs.1c05224](https://doi.org/10.1021/jacs.1c05224)
Experimental details, additional electrochemical data, and compound characterization data with NMR spectra (PDF).

The authors declare no competing financial interest.

Aminoxyl radicals, such as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), are highly effective (co)catalysts for alcohol oxidation.¹⁻⁷ They are used in the industrially important Anelli oxidation, which uses NaOCl as the oxidant,^{8,9} serve as effective electrocatalysts,⁷ and are key components in numerous aerobic alcohol oxidation catalysts.³⁻⁶ The Anelli and electrochemical oxidation methods are initiated by one-electron oxidation of TEMPO to TEMPO⁺, and the oxoammonium species promotes alcohol oxidation, generating TEMPOH as byproduct (Scheme 1). Catalytic turnover proceeds via two-electron oxidation of TEMPOH to TEMPO⁺ with NaOCl or at an electrode. Aerobic oxidation methods feature different mechanisms, depending on the cocatalyst used to promote oxidation of TEMPOH (Scheme 2A). Cu/aminoxyl cocatalyst systems have been developed for aerobic alcohol oxidation,^{4,5} and mechanistic studies reveal “integrated cooperativity” between Cu^{II} and an aminoxyl radical. Each component serves as a one-electron oxidant to support the two-electron oxidation reaction (Scheme 2B).¹⁰⁻¹³ Electrochemical studies confirm that the high-potential oxoammonium species is not formed in these reactions.¹⁴ A different class of aerobic alcohol oxidation catalysts employ NO_x-based cocatalysts,⁶ derived from NaNO₂, HNO₃, or organic nitrites (Scheme 2A). Mechanistic studies show that these reactions feature a redox cascade involving “serial cooperativity”, in which O₂ reacts with NO to generate NO₂, and NO₂ oxidizes TEMPOH to TEMPO⁺ (Scheme 2C).^{15,16} The final step closely resembles other TEMPO-catalyzed alcohol oxidation reactions that generate TEMPO⁺ as the reactive oxidant (e.g., using NaOCl or an electrode). Fe/TEMPO represents a third set of cocatalyst systems that show excellent aerobic alcohol oxidation reactivity.¹⁷⁻²³ The mechanism of these reactions has not yet been characterized, but postulated pathways include both integrated and serial cooperativity.^{5,17,19-21,23} Stoichiometric alcohol oxidation reactions observed with FeCl₃-TEMPO adducts are consistent with an “integrated” mechanism.²⁴⁻²⁶ On the other hand, nearly all Fe/TEMPO catalysts use iron nitrates or include another NO_x source that could contribute to a “serial” pathway. In the present study, we probe the mechanism of Fe/TEMPO-catalyzed alcohol oxidation by operando electrochemical analysis, and the data provide evidence for serial cooperativity. This mechanism is further evident from reactions with substrates that reveal different chemoselectivity and synthetic scope relative to Cu/TEMPO-catalyzed alcohol oxidation.

We have previously used cyclic step chronoamperometry (CSCA) to probe TEMPO-catalyzed alcohol oxidation reactions with NaOCl as the oxidant.²⁷ This analytical technique detects redox active species in solution without influencing their bulk concentration. Use of a rotating disk electrode (RDE) avoids mass-transfer limitations at the electrode and provides real-time insights into the analytes in solution. The CSCA experiments were conducted by cycling the RDE between potentials above and below the TEMPO⁺/TEMPO redox couple ($E_{1/2} = 0.24$ V vs Fc⁺⁰). When the RDE potential is above 0.24 V, positive current is detected from oxidation of TEMPO in solution and the magnitude of the current is proportional to [TEMPO]. When the RDE is below 0.24 V, negative current arises from reduction of TEMPO⁺ with a magnitude proportional to [TEMPO⁺].

Studies were initiated by analyzing TEMPO speciation in the presence of HCl and HNO₃ in order to establish CSCA benchmarks for the investigation of Fe/TEMPO-catalyzed aerobic alcohol oxidation (Figure 1). The conditions were derived from a previously reported

catalytic NO_x/TEMPO method for alcohol oxidation.²⁸ Addition of 1 equiv HCl to a solution of TEMPO initiates TEMPO disproportionation into a 1:1 mixture of TEMPO^+ and TEMPOH_2^+ .^{29–31} TEMPOH_2^+ is electrochemically inactive at these potentials and measured currents solely arise from TEMPO and TEMPO^+ . During a period of 12 min ($t = 1\text{--}13$ min), TEMPO disappearance and TEMPO^+ appearance proceeds with the expected 2:1 stoichiometry (Figure 1B). Addition of HNO_3 (1 equiv) at this point initiates oxidation of all of the TEMPO and TEMPOH_2^+ to TEMPO^+ , reflecting the $\text{TEMPOH}/\text{NO}_x/\text{O}_2$ portion of the mechanism in Scheme 2C.

We then used CSCA to probe TEMPO speciation in the presence of $\text{Fe}(\text{NO}_3)_3$ under air in CH_3CN (Figure 2). $\text{Fe}(\text{NO}_3)_3$ is electroactive and is reduced at a potential similar to TEMPO^+ . Nonetheless, it was possible to subtract the background current of $\text{Fe}(\text{NO}_3)_3$ in the absence of TEMPO (see Supporting Information for details; while this issue affects quantitative precision, the resulting data provide clear insights). An induction period is evident over the first 2 min of the reaction, during which time TEMPO disproportionation is evident from the 2:1 stoichiometry associated with TEMPO disappearance and TEMPO^+ appearance). This phase is followed by a rapid oxidation of TEMPO species, resulting in depletion of TEMPO together with the formation of TEMPO^+ . These data show that, unlike the (bpy)Cu/NMI cocatalyst system,^{14, 32} $\text{Fe}(\text{NO}_3)_3$ is capable of generating TEMPO^+ and implicate a serial cooperativity mechanism similar to Scheme 2C.

Additional experiments were conducted to gain additional insights into the origin of TEMPO disproportionation and redox behavior in the presence of $\text{Fe}(\text{NO}_3)_3$. $\text{Fe}(\text{OTf})_3$ and $\text{Al}(\text{OTf})_3$ represent M^{3+} Lewis acids, similar to $\text{Fe}(\text{NO}_3)_3$, and these species show very similar reactivity with TEMPO (Figures 3A and 3B). CSCA analysis reveals rapid formation of 0.5 equiv of TEMPO^+ , consistent with Lewis acid-promoted disproportionation of TEMPO. TEMPO disproportionation was independently confirmed by following the $\text{Al}(\text{OTf})_3/\text{TEMPO}$ reaction by UV-visible spectroscopy (see Figure S6 in the Supporting Information).³³ The anodic CSCA current in Figures 3A and 3B (blue traces) is assigned to “[TEMPO]” because the current at the anodic potential could include oxidation of species other than TEMPO (e.g., TEMPO-M adducts, $\text{M} = \text{Fe}^{\text{III}}, \text{Al}^{\text{III}}$). Weaker Lewis acids, $\text{Zn}(\text{NO}_3)_2$ and $\text{Al}(\text{OTf})_3/3 \text{NBu}_4\text{NO}_3$, are less effective in promoting TEMPO disproportionation (Figures 3C and 3D). Negligible or slower formation of TEMPO^+ is observed in these experiments.

The results in Figures 2 and 3 reveal that neither Fe^{III} [e.g., in the form of $\text{Fe}(\text{OTf})_3$] nor nitrate salts alone can account for the TEMPO reactivity and cocatalytic role of $\text{Fe}(\text{NO}_3)_3$ in aerobic alcohol oxidation reactions. A rationale for the observations is that Fe^{III} -promoted TEMPO disproportionation generates TEMPO anion, which will coordinate to Fe^{III} and provide reducing equivalents needed to convert nitrate into catalytically relevant NO_x species. The iron species likely play an active role in nitrate reduction³⁴ and initiation of catalysis.

The results above show that $\text{Fe}(\text{NO}_3)_3$ and Brønsted-acid NO_x -based catalyst systems feature similar mechanisms for aerobic alcohol oxidation, involving serial cooperativity (Scheme 2C). This pathway, which contrasts the integrated cooperativity of (bpy)Cu

cocatalyst systems (Scheme 2B), has important synthetic implications. A series of substrate probes and kinetic comparisons were used to illuminate the similarities and differences among three prototypical catalyst systems for aerobic alcohol oxidation: Cu/TEMPO,³⁵ Fe(NO₃)₃/TEMPO,^{20,21} and H⁺/NO_x/TEMPO.³⁶ These efforts prioritized mechanistic insights over synthetic optimization as the latter has been emphasized in previous reports. The diol substrates in Figures 4A and 4B feature an electronically activated 2° benzylic alcohol with a sterically less hindered 1° benzylic or aliphatic alcohol. In both cases, the Cu/TEMPO catalyst shows a preference for 1° alcohol oxidation. The Fe(NO₃)₃ and NaNO₂/HNO₃ cocatalyst systems exhibit similar reactivity, with little selectivity between 1°/2° benzylic alcohols (Figure 4A) but high selectivity for 2° benzylic over 1° aliphatic alcohol oxidation (Figure 4B). This selectivity contrasts that observed with the Cu/TEMPO catalyst system but matches that expected from oxoammonium-mediated alcohol oxidation under acidic conditions, aligning with the serial mechanistic pathway in Scheme 2C.^{37,38}

To compare 1° and 2° aliphatic alcohols, cyclohexanol and cyclohexylmethanol oxidation were monitored via gas-uptake methods (Figure 4C).³⁹ Reaction time courses show that Cu/TEMPO oxidizes cyclohexylmethanol approximately two-fold faster than cyclohexanol. In contrast, Fe(NO₃)₃/TEMPO oxidizes cyclohexanol approximately three-fold faster than cyclohexylmethanol, following an induction period at the start of the reaction (attributed to in situ generation of NO_x species as discussed above). The NaNO₂/HNO₃ system shows poor reactivity with aliphatic alcohols and kinetic data were not recorded. The latter observation highlights a benefit of the Fe(NO₃)₃-based catalyst system relative to other NO_x-based catalysts that use a similar mechanism.

The Cu/TEMPO and Fe(NO₃)₃/TEMPO catalyst systems show complementary features with other substrates (Figure 4D). For example, Cu/TEMPO catalysts show good tolerance of basic and oxidatively sensitive functional groups.^{35,40–42} This feature is evident in oxidation of the quinoline- and aniline-containing substrates **9** and **11**. In contrast, little reactivity for these substrates is observed with the Fe(NO₃)₃ catalyst system, probably arising from interference of the basic functional groups with the Lewis acidity of Fe^{III} and/or generation of the NO_x cocatalyst species. The Fe(NO₃)₃ catalyst system can be advantageous in other cases. Cu/TEMPO reacts poorly with 1° alcohol **13**, which has a terminal alkyne; a mixture of unreacted starting material and products, including the aldehyde, are observed. In contrast, **13** shows good reactivity with the Fe(NO₃)₃/TEMPO catalyst system, affording the carboxylic acid **15** in good yield. This result highlights another complementary feature of Cu and Fe(NO₃)₃-based catalyst systems: Cu/TEMPO catalysts convert 1° alcohols to aldehydes and are poisoned by acidic functional groups, such as carboxylic acids. The Fe(NO₃)₃ system not only tolerates acidic groups but can also oxidize 1° alcohols to the carboxylic acid products.²⁰

The substrate reactivity data in Figure 4 pairs with the mechanistic data in Figures 1–3 to support serial cooperativity between Fe(NO₃)₃ and TEMPO during catalytic aerobic alcohol oxidation (Scheme 2C). The combination of Fe³⁺ and nitrate represents an appealing NO_x cocatalyst system capable of generating oxoammonium species with O₂ (Scheme 3). We anticipate that aerobic alcohol oxidation catalysts that feature nitrate or other NO_x components also take advantage of similar reactivity. Examples include recently reported

Cu(NO₃)₂/TEMPO⁴³ and Fe(NO₃)₃/bpy/TEMPO⁴⁴ systems.⁴⁵ The mechanism in Scheme 3 contrasts the integrated cooperativity mechanism of Cu/aminooxyl catalysts. These divergent modes of cooperativity are manifested by different chemoselectivity and synthetic scope for the catalytic reactions. The user-friendly and complementary synthetic features of both catalyst systems should contribute to broader adoption of aerobic alcohol oxidation methods in organic synthesis, including large scale applications.^{22,46–48}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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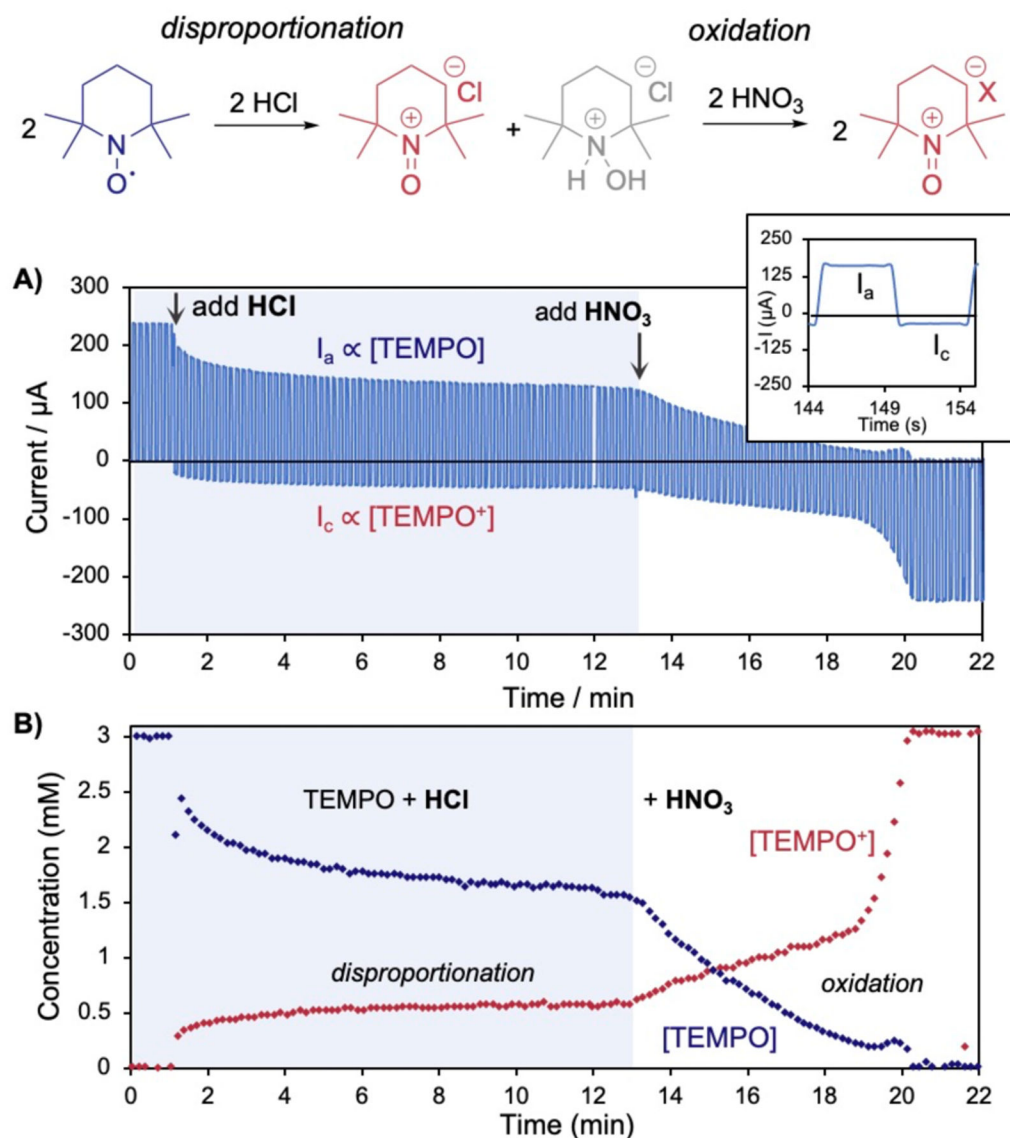


Figure 1.

A) Cyclic step chronoamperometric (CSCA) analysis of TEMPO (3 mM), following sequential addition of 1 equiv HCl (at 1 min) and HNO_3 (at 13 min) to the aerobic reaction mixture. Inset shows representative limiting anodic and cathodic currents for two CSCA steps. B) Concentration profiles of TEMPO and TEMPO⁺ based on the median I_c and I_a measured at -0.18 and 0.52 V vs. $\text{Fc}^{0/+}$, respectively, for each potential step in (A). Conditions: 0.1 M NBu_4PF_6 , CH_3CN , 1000 RPM.

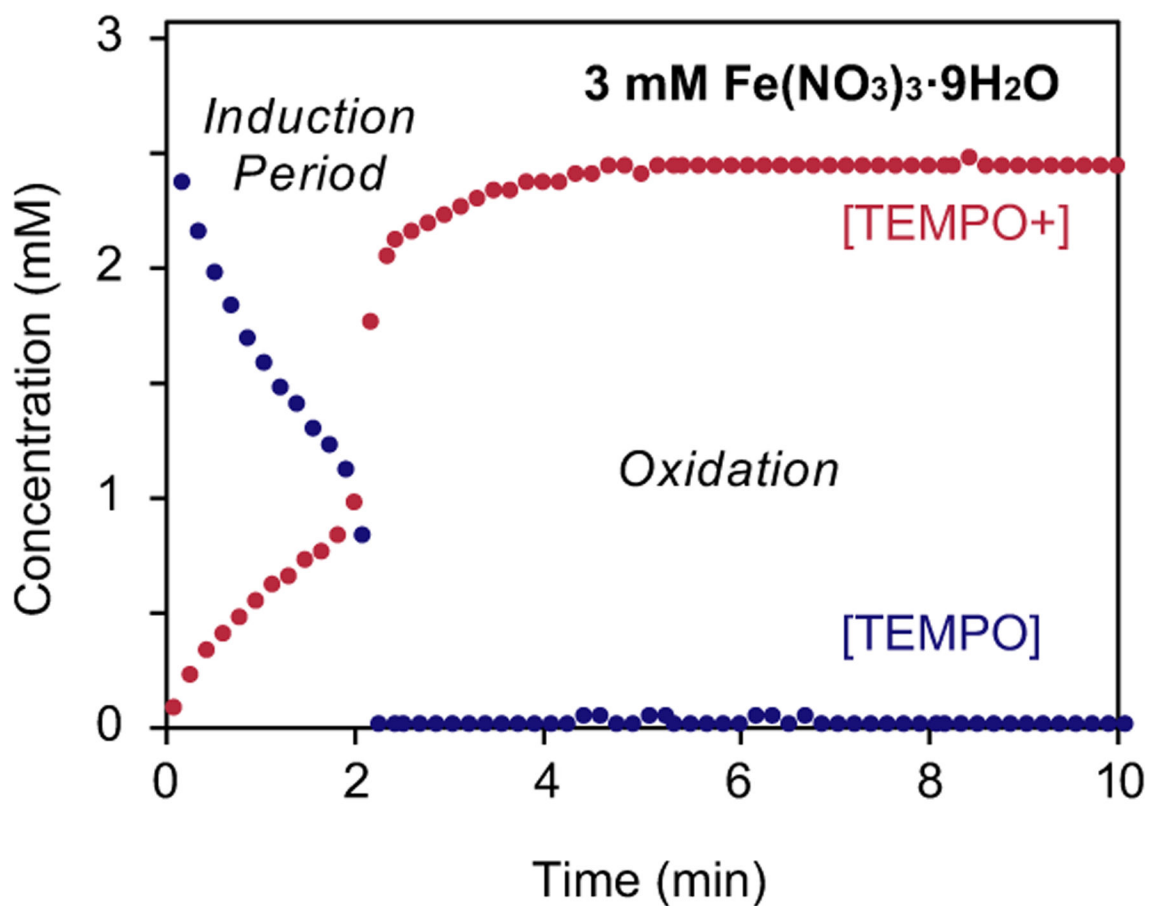


Figure 2. [TEMPO] (blue) and [TEMPO⁺] (red) obtained by using CSCA at a rotating disk electrode upon mixing CH₃CN solutions of TEMPO and Fe(NO₃)₃·9H₂O in the absence (A) and presence (B) of 1-phenylethanol (50 mM). Conditions: 3 mM [TEMPO] and [Fe], 0.1 M NBu₄PF₆ in CH₃CN; I_c and I_a measured at -0.16 and 0.64 V vs. Fc^{0/+}, respectively, 1000 RPM.

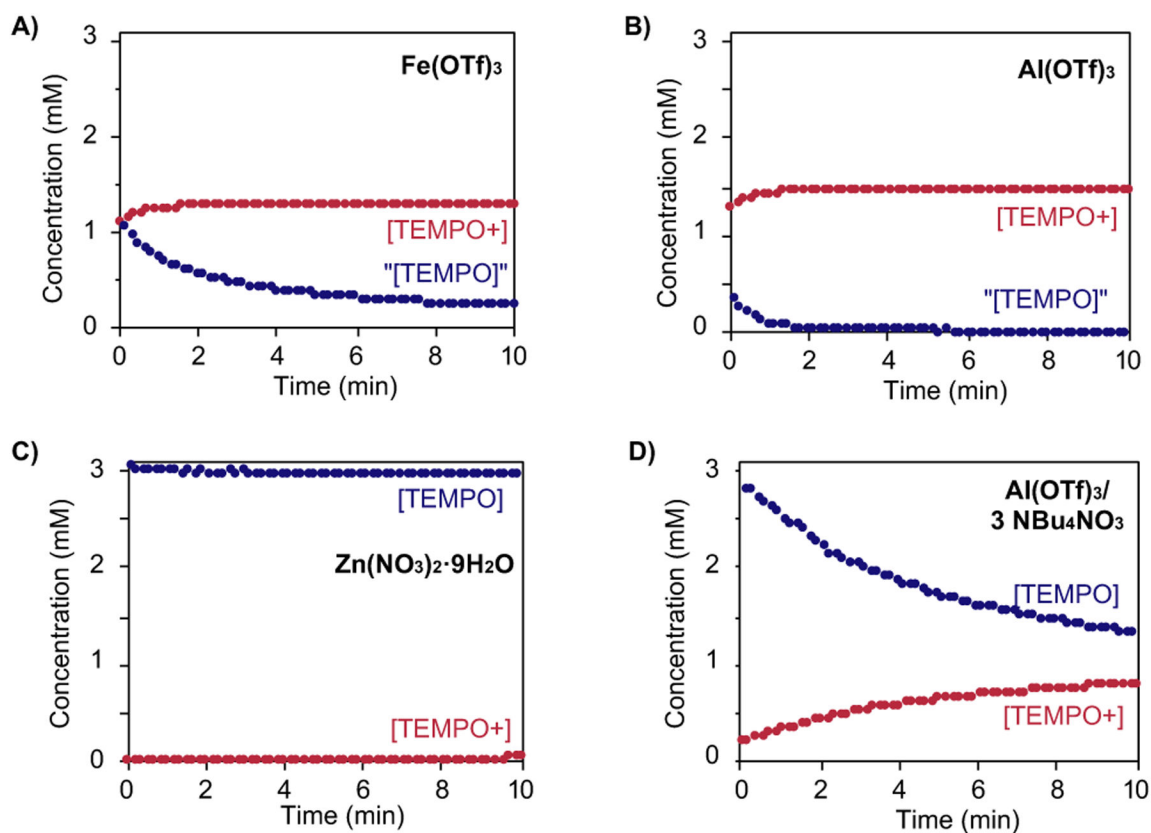
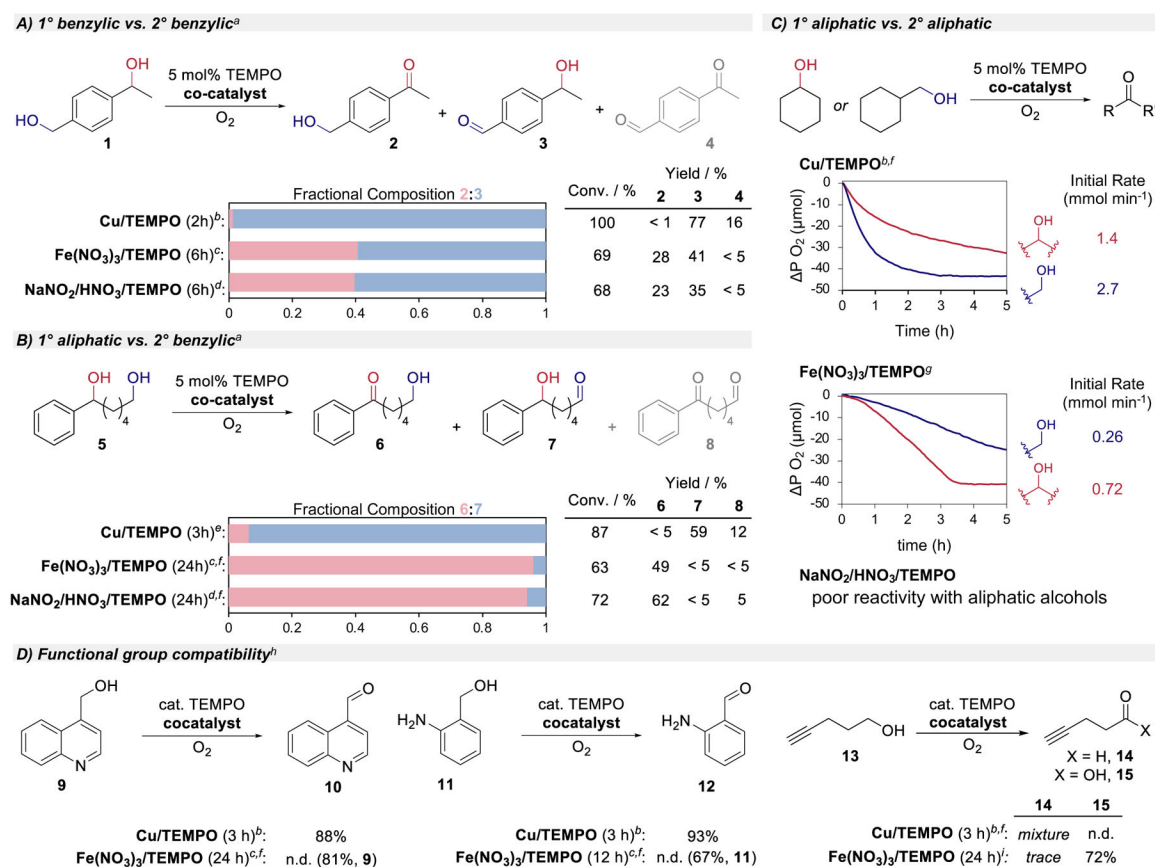
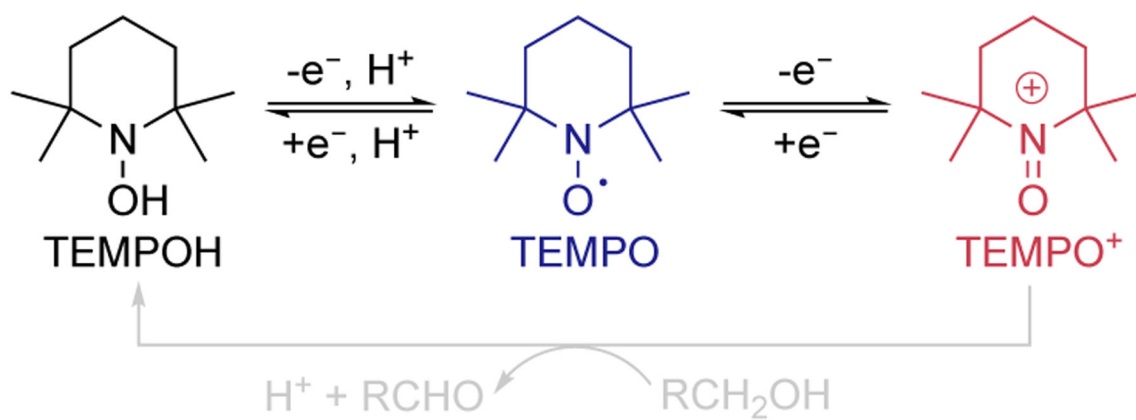


Figure 3. [TEMPO] (blue) and [TEMPO⁺] (red) obtained by using CSCA at a rotating disk electrode upon mixing CH₃CN solutions of TEMPO and Fe(OTf)₃, Al(OTf)₃, Zn(NO₃)₂, and Al(OTf)₃/3 NBu₄NO₃. Conditions otherwise consistent with those in Figure 2.

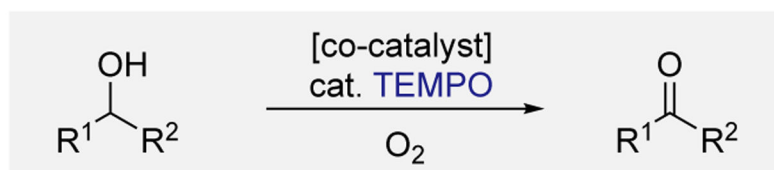
**Figure 4.**

Comparison of chemoselectivity and functional compatibility with different aminoxyl cocatalyst systems for aerobic alcohol oxidation: A) intramolecular competition between 1° and 2° benzylic alcohols, B) intramolecular competition between 1° aliphatic and 2° benzylic alcohols, C) independent rate comparison of cyclohexanol and cyclohexanemethanol (for Cu/TEMPO, initial rates determined from the first 20 min; for Fe(NO₃)₃, rates determined from 40–60 min, i.e., after induction period), D) additional substrate probes. Conditions: rt, 5 mol% TEMPO unless noted otherwise. (A), (B), (C): 0.1 mmol substrate (0.1 M), (D): 1.0 mmol substrate (0.2 M). ^aRatios, yields determined by ¹H NMR spectroscopy. ^b5 mol% [Cu(CH₃CN)₄]BF₄, 5 mol% bpy, 10 mol% *N*-methylimidazole (NMI), CH₃CN, air. ^c5 mol% Fe(NO₃)₃, CH₃CN, air. ^d10 mol% NaNO₂, 20 mol% HNO₃, CH₃CN, air. ^e5 mol% CuBr, 5 mol% bpy, 10 mol% NMI, CH₃CN, air. ^f1 atm O₂ rather than ambient air. ^g5 mol% Fe(NO₃)₃, 5 mol% KCl, 1,2-dichloroethane, 1 atm O₂. ^hIsolated yields. ⁱ10 mol% TEMPO, 10 mol% Fe(NO₃)₃, 10 mol% KCl, 1,2-dichloroethane, 1 atm O₂.



Scheme 1.
Aminoxy-based redox reactions.

A: Aerobic Alcohol Oxidation Systems



Cu/TEMPO

Cu: (bpy)Cu^IX,
N-methylimidazole (NMI)

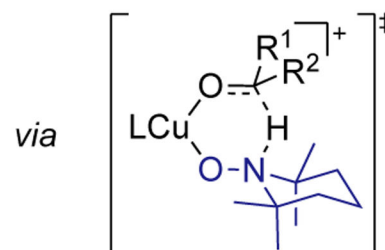
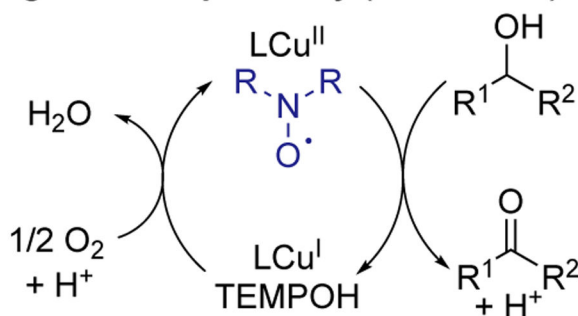
NO_x/TEMPO

NO_x: NaNO₂, HNO₃,
and/or *t*BuONO

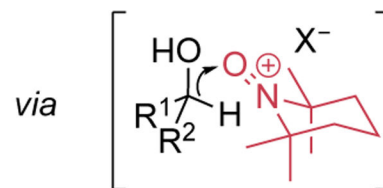
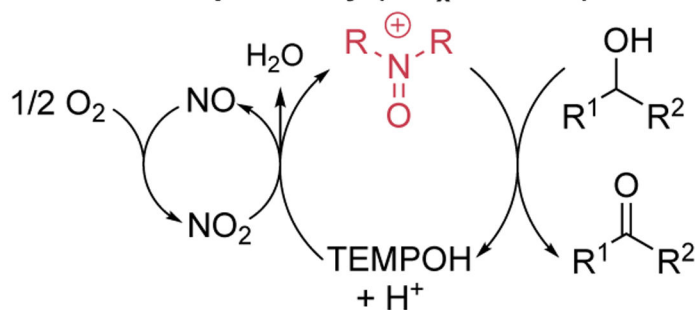
Fe/TEMPO

Fe: Fe(NO₃)₃·9H₂O

B: Integrated Cooperativity (Cu/TEMPO):

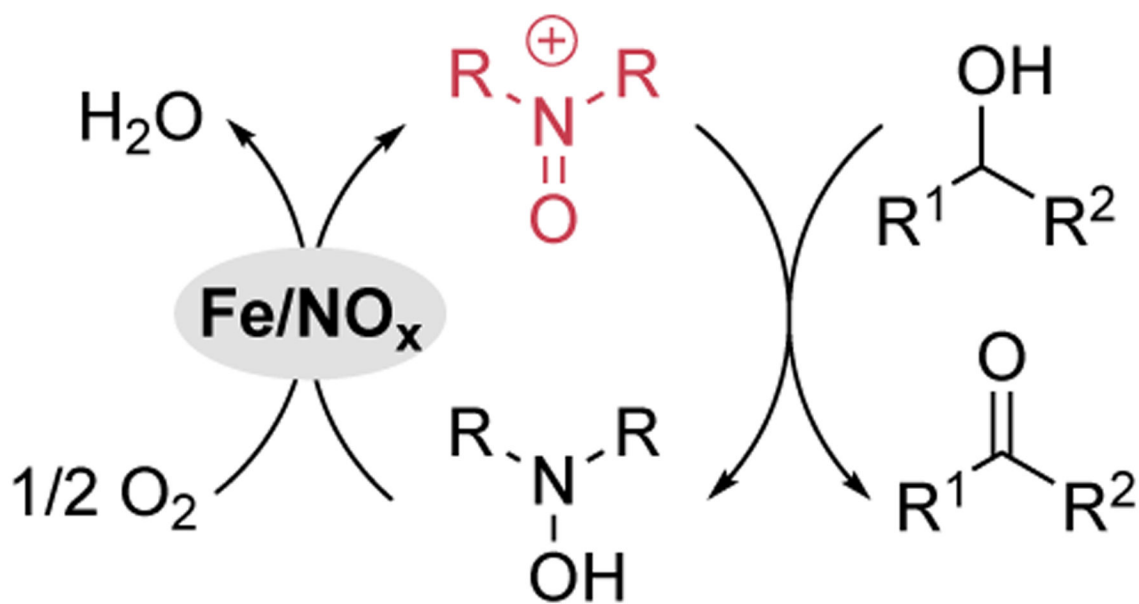


C: Serial Cooperativity (NO_x/TEMPO):



Scheme 2.

Aminoxyl co-catalyst systems for aerobic alcohol oxidation.



Scheme 3.
Simplified mechanism for $\text{Fe}(\text{NO}_3)_3$ /aminoxylcatalyzed aerobic alcohol oxidation.