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Concerning the Mechanism of the $FeCl_3$-Catalyzed α-Oxyamination of Aldehydes: Evidence for a Non-SOMO Activation Pathway

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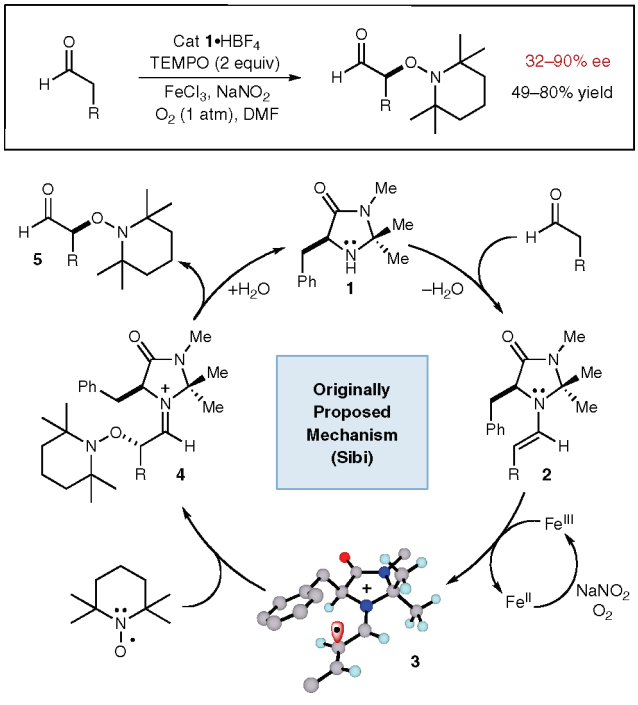
Abstract: The mechanism of a recently reported aldehyde α-oxyamination reaction has been studied using a combination of kinetic, spectrometric, and spectrophotometric techniques. Most crucially, the use of a validated cyclopropane-based radical-clock substrate has demonstrated that carbon−oxygen bond formation occurs predominantly through an enamine activation manifold. The mechanistic details reported herein indicate that, as has been proposed for previously studied alcohol oxidations, complexation between TEMPO and a simple metal salt leads to electrophilic ionic reactivity.

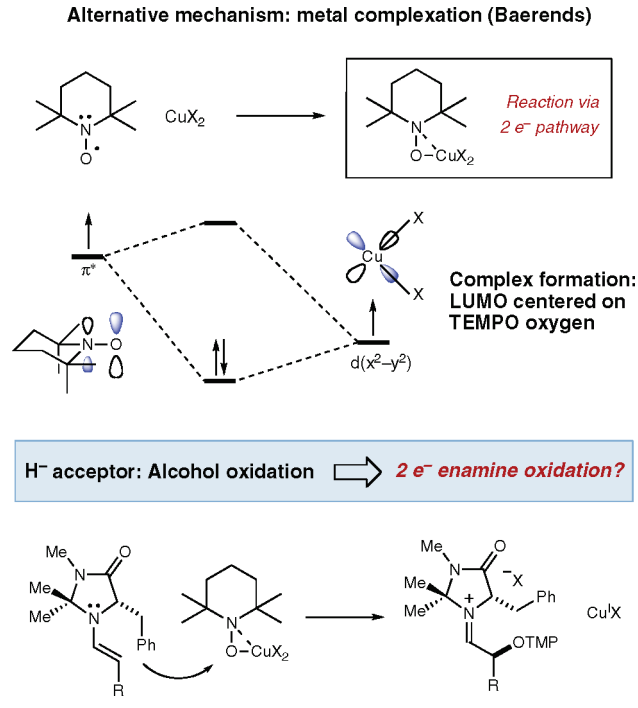
In 2007, simultaneous publications from MacMillan and Sibi described the progression of organocatalysis beyond closed-shell bond-forming pathways, as each report detailed the α-functionalization of aldehydes via a radical cation intermediate.[1] Our laboratory has further developed this catalysis manifold, termed singly occupied molecular orbital (SOMO) activation, to enable a wide range of transformations, including aldehyde α-alkylation,[1a] enolation,[2a] vinylation,[2b] nitroalkylation,[2c] arylation,[2d] carbo-oxidation,[2e] and polyene cyclization.[2f] During the course of these studies, however, we have continually met with failure when attempting to translate the Sibi oxidative conditions[3] ($FeCl_3$, $NaNO_2$, and O_2) to catalytic bond constructions beyond the initial report. This is intriguing, given that the key activated intermediate should be identical in each case (an imidazolidinone-derived radical cation); however, the observed reactivity of these species appears related to the manner in which they are generated. In an effort to understand this mechanistic discrepancy, we initiated an investigation into the role of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a purported SOMO-phile in the α-oxyamination catalytic cycle. Surprisingly, our findings revealed that the Sibi reaction does not operate by a SOMO activation mechanism but instead proceeds via a more traditional enamine catalysis pathway.

Scheme 1. Proposed Mechanism for $FeCl_3$-Catalyzed Oxidation



The α-oxyamination mechanism proposed by Sibi (Scheme 1) begins with condensation of imidazolidinone catalyst **1** and an aldehyde to generate electron-rich enamine **2**. Oxidation of this intermediate with $FeCl_3$ was proposed to produce radical cation **3**, which would then combine with TEMPO to yield iminium ion **4**. Hydrolysis of such a species would liberate the observed α-oxygenated product **5**, while an oxygen atmosphere, assisted by catalytic $NaNO_2$, was believed to replenish the requisite Fe(III) species.

Given that the capture of α-carbonyl radicals by TEMPO has been known for more than a decade, this catalytic cycle appears to be more than reasonable.[4] Moreover, the α-oxyamination of aldehydes with TEMPO has been performed recently using both photoredox catalysis[5] and electrochemical techniques,[6] and in both cases an identical mechanism was suggested. However, a wealth of mechanistic studies pertaining to $CuCl_2$/TEMPO-catalyzed alcohol oxidations[7] has clearly demonstrated the capacity of TEMPO to undergo metal complexation[8] to form the reactive oxidant. Specifically, the recent theoretical work of Baerends has shown that CuX_2•TEMPO can behave as an ionic electrophile via single-electron pairing of CuX_2 and TEMPO,[9] while Sheldon's kinetic isotope studies[10] have shown that copper−TEMPO complexes do not generate free oxoammonium itself ($[R_2N{=}O]^+$). Thus, an alternative pathway for the



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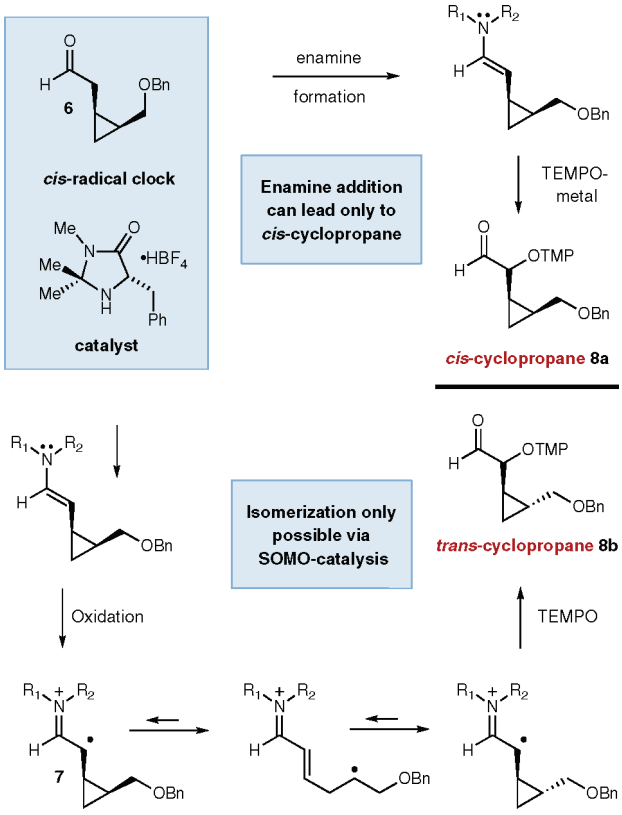
Scheme 2. Differentiating SOMO Activation and Enamine Addition



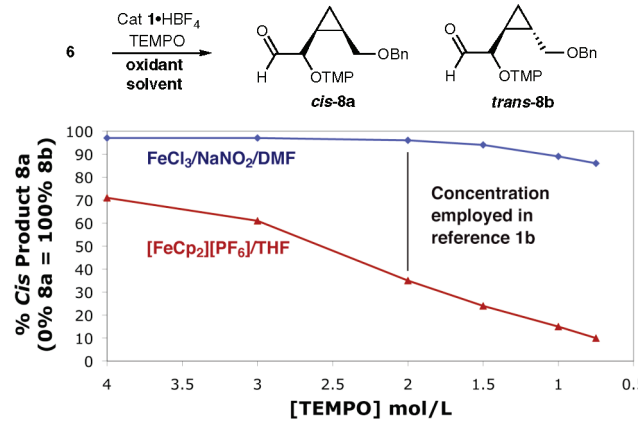
α-oxyamination reaction wherein enamine addition to an Fe(III)-bound TEMPO species is operative must be considered (see the alternative mechanism). With this in mind, we have undertaken several mechanistic studies to determine whether the Sibi reaction proceeds via a SOMO activation pathway involving a radical cation (as originally proposed) or by direct enamine addition to an iron−TEMPO complex.

Design Plan. We recognized that implementation of a suitable radical-clock-containing substrate should allow the detection of a SOMO-activated pathway (Scheme 2).[11] The *cis*-cyclopropane-substituted aldehyde **6** was chosen as a mechanistic probe, as the corresponding cyclopropylcarbinyl radical **7** should undergo rapid ring opening and ring closing[12] prior to C−O bond formation (an equilibration step that would predominantly lead to *trans*-cyclopropyl oxyamination products). In contrast, such radical intermediates would be absent from an enamine addition mechanism, so only cis-substituted cyclopropane products should be observed if an ionic pathway dominates.

Results. To test the validity of this radical-clock study, we exposed the *cis*-cyclopropyl substrate **6** to established SOMO activation conditions (specifically, $[FeCp_2][PF_6]$ in THF, a reliable outer-sphere oxidant) (Scheme 3). It should be noted that this oxidation system was initially employed in the original Sibi publication[1b] but did not become the optimized or preferred protocol. As expected, initial experiments with high concentrations of TEMPO (4.0 M) delivered a mixture of nonisomerized cis product **8a** (71%) and trans product **8b** (29%). As the concentration of TEMPO was decreased to 0.75 M, direct radical trapping to yield **8a** became a minor pathway (10%) while cyclopropyl rearrangement to the trans adduct **8b** became dominant. Having validated the use of formyl-cyclopropane **6** as a mechanistic probe, we next focused on the Sibi protocol. Indeed, when the optimal conditions from the initial study were employed ($FeCl_3$/$NaNO_2$, DMF, 2.0 M TEMPO), we observed that cis product **8a** was delivered in 95% yield. In contrast, the use of $[FeCp_2][PF_6]$ in THF yielded only a minor amount of the cis adduct (35%).

These results can be explained by one of three scenarios:

Scheme 3. Radical-Clock Investigation of the Oxygenation Mechanism

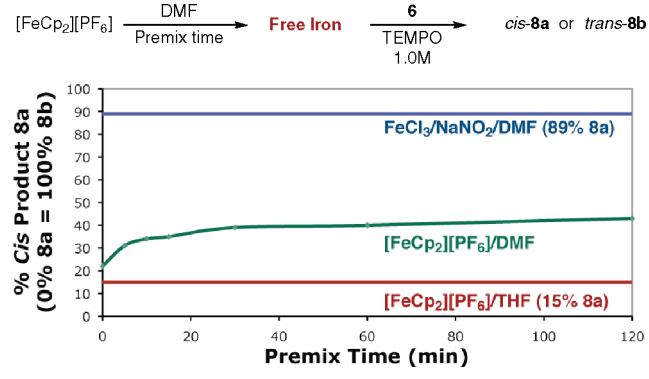


(i) The identity of the solvent (DMF vs THF) has a significant effect on the relative rates of TEMPO radical trapping versus cyclopropane isomerization. Direct comparison of $[FeCp_2][PF_6]$ and $FeCl_3$ in the same solvent is complicated by two factors: $FeCl_3$ delivers only traces of product in THF,[1b] while ferrocenium species are known to steadily decompose in DMF to liberate Fe(III),[13] which in turn could activate TEMPO toward enamine addition (resulting in a net increase in **8a** formation). In the present work, we were able to qualitatively account for the liberation of free iron in the following comparison experiment (Scheme 4). $[FeCp_2][PF_6]$ and catalyst **1**·HBF_4 were aged in DMF for various periods of time prior to the addition of TEMPO and aldehyde **6**. Since the amount of free iron should increase with the duration of premixing, we could assume that the amount of direct enamine trapping to generate cis product **8a** should increase accordingly. Indeed, this is exactly what was observed. However, when no aging step was employed, there was almost no difference between the product distributions obtained using ferrocenium in DMF and THF (15% **8a** in THF, 22% **8a** in DMF).

(ii) The 2.0 M ferrocenium case involves a diminished concentration of free TEMPO in comparison with the 2.0 M Sibi protocol. ReactIR experiments clearly demonstrated that the in situ concentration of free TEMPO was effectively 2.0 M for both the $FeCl_3$/$NaNO_2$/DMF and $[FeCp_2][PF_6]$/THF cases (see the Supporting Information).

(iii) The $FeCl_3$ system acts by enamine addition rather than a SOMO-type pathway. These combined results clearly indicate that whereas the ferrocenium case predominantly leads to radical-clock opening in DMF, the preferred Sibi protocol does not, which implies that the latter does not involve a radical cation as the major reaction pathway. Importantly, the observation of small amounts of rearranged product when $FeCl_3$ was used at low TEMPO concentration (15% trans product at 0.75 M TEMPO) was shown to arise from increased content of the unbound iron oxidant (see the Supporting Information).

Scheme 4. Product Distribution Using $[FeCp_2][PF_6]$ in DMF



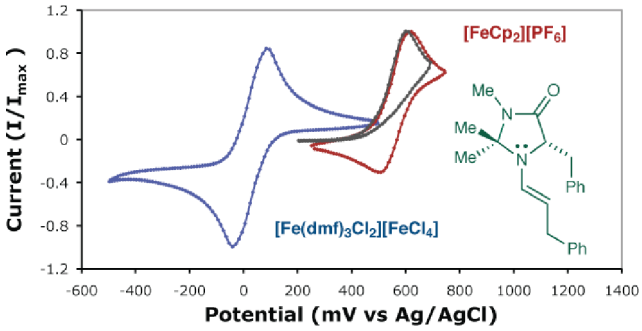
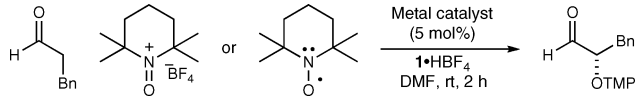


Figure 1. Cyclic voltammetry measurements in DMF.

Evidence for a TEMPO complexation/enamine addition pathway was further substantiated by consideration of the oxidation potentials of the reagents and intermediates involved (Figure 1). It is well-established that DMF solvation of $FeCl_3$ induces disproportionation to $[Fe(dmf)_3Cl_2][FeCl_4]$,[14a] a salt which is less oxidizing than $FeCl_3$ by ~0.5 V.[14b] We measured the irreversible oxidation potential of enamine **2** (derived from catalyst **1**) and found that it is well-matched for oxidation with $[FeCp_2][PF_6]$, while oxidation by $[Fe(dmf)_3Cl_2][FeCl_4]$ is endergonic by ~0.5 V.

Table 1. Other Systems for Catalytic Aldehyde α-Oxyamination



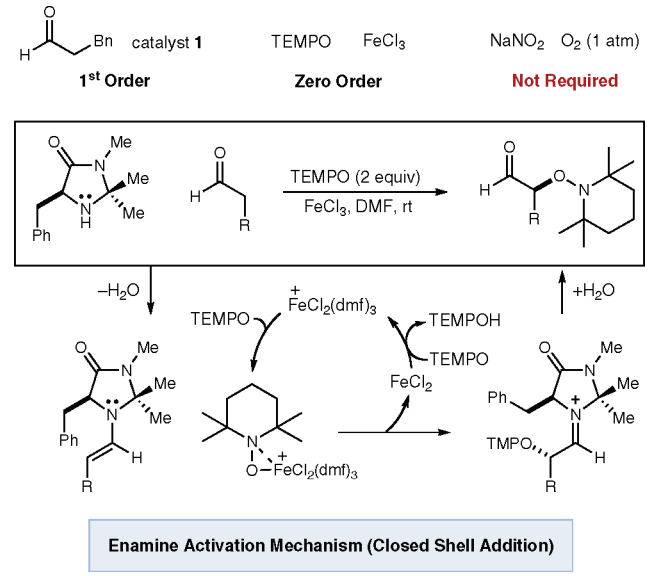
entry	oxygen source	metal catalyst	% yield[a]
1	TEMPO	none	11
2	oxoammonium[b]	none	19
3	TEMPO	$Sc(OTf)_3$	17
4	TEMPO	$Zn(NTf_2)_2$	12
5	TEMPO	$[Fe(dmf)_3Cl_2][FeCl_4]$	72
6	TEMPO	Co(salen)	75
7	TEMPO	$CuCl_2$	82

[a] Yield determined by ^1H NMR analysis relative to an internal standard. [b] Added as a solution in DMF over 1 h using syringe pump.

Because our mechanistic picture of enamine addition was founded upon previous studies of TEMPO−metal coordination,[7−10] a number of further predictions could be made. First, metal complexes known to bind TEMPO in a manner similar to $[Fe(dmf)_3Cl_2]^+$ (including $CuCl_2$) should effect the desired transformation. Second, Lewis acids that do not have an empty d orbital and thus cannot participate in TEMPO binding should not be effective. As shown in Table 1, these predictions were comprehensively confirmed. Most notably, the use of TEMPO or oxoammonium without metal additives[15] gave results similar to those for the $Sc(OTf)_3$ and $Zn(NTf_2)_2$ cases.

Finally, kinetic measurements revealed that the initial rate of reaction depends exclusively on the amine catalyst and aldehyde concentrations, indicating that enamine formation is rate-determining (Scheme 5). Moreover, while $FeCl_3$ is essential, identical levels of conversion were obtained without $NaNO_2$ and O_2 [the oxidant for the Sibi protocol is likely to be TEMPO,[16] which is known to reoxidize Cu(I) to Cu(II) in related alcohol oxidations[17]]. The sum of our results indicate that a significant revision of the proposed mechanism for the $FeCl_3$-catalyzed α-oxyamination of aldehydes is required. The mechanistic picture that best fits literature precedent and the results contained herein is shown in Scheme 5.[18] While the results of our investigations suggest that $FeCl_3/NaNO_2/O_2$ will not find application in SOMO catalysis, we expect that activation of TEMPO by metal complexation will lead to several new and efficient oxygenation protocols.

Scheme 5. Revised Mechanism for α-Oxygenation of Aldehydes



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Supporting Information Available: Experimental procedures, kinetic investigations, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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