Iron(II)-Catalyzed Aerobic Biomimetic Oxidation of Amines using a Hybrid Hydroquinone/Cobalt Catalyst as Electron Transfer Mediator

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Abstract: Herein we report the first Fe(II)-catalyzed aerobic biomimetic oxidation of amines. This oxidation reaction involves several electron transfer steps and is inspired by biological oxidation in the respiratory chain. The electron transfer from the amine to molecular oxygen is aided by two coupled catalytic redox systems, which lower the energy barrier and improve the selectivity of the oxidation reaction. An iron hydrogen transfer complex was utilized as the substrate-selective dehydrogenation catalyst along with a bifunctional hydroquinone/cobalt Schiff base complex as a hybrid electron transfer mediator. Various primary and secondary amines were oxidized in air to their corresponding aldimines or ketimines in good to excellent yield.

Oxidation processes constitute an important fundamental class of transformations in organic chemistry. Although numerous oxidation reactions have been developed over the years, the demand for milder, more efficient, and sustainable methods has increased in recent times with the growing interest in green chemical procedures.[11] With regard to green methods, of particular interest are those inspired by biological processes, where environmentally friendly and inexpensive oxidants such as molecular oxygen (O₂) or hydrogen peroxide (H₂O₂) are often used. However, direct selective oxidation of an organic substrate by H₂O₂ or O₂ remains an unmet challenge because of the large energy barriers and low selectivity of such direct oxidations. The use of a substrate-selective redox catalyst (SSRC) may solve this problem, where the reduced form of the SSRC (i.e. SSRC_red) is re-oxidized by H₂O₂ or O₂. However, direct re-oxidation of the SSRC_red to SSRC by O₂ or H₂O₂ may still be too slow and there are only a limited number of examples known in the literature of direct reoxidation of an SSRC_red by O₂ or H₂O₂.[2-3] In Nature this oxidation problem is solved by enlisting multiple enzymes and co-enzymes as electron transfer mediators (ETMs), which lower the overall barrier for electron transfer from the SSRC_red to H₂O₂ or O₂ as shown in Scheme 1. In natural aerobic systems, these ETMs are part of the respiratory chain, which is responsible for producing ATP in many organisms. The overall process of the respiratory chain is analogous to the process shown in Scheme 1 and ends with reduction of O₂ to H₂O.[4] Over the years we have developed a number of biomimetic oxidations that work according to the principle shown in Scheme 1, where ruthenium,[5] palladium,[6] and osmium,[7] have been used as substrate-selective redox catalysts.[8]

Recently the groups of Beller and Bolm declared that the age of iron had begun, and it is certainly true that the field has advanced rapidly since then.[9] Over the past two decades, inexpensive iron catalysts have been employed in many elegant synthetic transformations which have traditionally been dominated by noble transition metal catalysts, such as cross-coupling and transfer hydrogenation, among many others.[10-12] We have recently developed iron-catalyzed reactions including DKR of sec-alcohols, cycloisomerization of functionalized allenes, and biomimetic aerobic oxidation of alcohols.[13-14] In the present work we have developed a novel iron-catalyzed aerobic oxidation of amines via the biomimetic approach in Scheme 1, where ETM and ETM are merged into the bifunctional ETM_I, which acts as a hybrid catalyst (Scheme 2).

A prominent class of iron catalysts that have been used for transfer hydrogenation are the (cyclopentadienone)iron tricarbonyl complexes II, originally synthesized by Reppe and Vetter in the 1950’s (Scheme 3).[15] Iron hydride complex III was first prepared and isolated by the group of Knöllker.[16,17] Knöllker’s complex III and its related iron tricarbonyl complexes II have found extensive use in transfer hydrogenation reactions.[18,19] The first use of complex III in catalysis was reported by the group of Casey in 2007 for the...
hydrogenation of ketones.\[19\] Later, the group of Funk reported the DMPh (DMPh = 3,5-dimethylphenyl) tricarbonyl variant IIa of these complexes,\[18a\] which was found to be more active in redox reactions than all other tricarbonyl complexes II tested. Complex IIa can be activated in situ to generate intermediate IIa', which in turn can be reduced to iron hydride IV in the presence of a hydrogen source (Scheme 3).\[20\] The activation of the catalyst (IIa ! IIa') is done through oxidative decarbonylation induced by trimethylamine N-oxide (TMANO).\[21\] Our group has recently applied these types of iron complexes in several iron-catalyzed reactions.\[13,14\]

Recently we developed an iron-catalyzed biomimetic oxidation of alcohols employing two electron transfer mediators, 2,6-dimethoxy benzoquinone (DMBQ) and the cobalt Schiff-base catalyst Co(salmdpt).\[13a\] In that study alcohol 1 afforded ketone 2 in good yields in the aerobic oxidation. After the completion of that study, we envisioned that a similar iron-catalyzed biomimetic oxidation of amine substrates by molecular oxygen might be feasible, in particular since the corresponding ruthenium-catalyzed aerobic oxidation of amines had previously been realized with the same ETMs.\[5b\] Surprisingly, attempts to use these two ETMs (DMBQ and Co(salmdpt)) for the oxidation of 3a were unsuccessful and only trace amounts of imine 4a were obtained (Scheme 4). Apparently, the electron transfer to molecular oxygen is too slow in this case, resulting in predominating competing deactivation of the iron catalyst by molecular oxygen.

One way to circumvent this problem would be to increase the rate of the electron transfer from the iron catalyst to molecular oxygen. In previous studies we have obtained a faster electron transfer in oxidations by merging the two ETMs (the Co-Schiff base and the quinone) into a bifunctional ETM, which acts as a hybrid catalyst.\[22,23\] Interestingly, using such a bifunctional ETM (hybrid catalyst I in Scheme 2) in place of two separate ETMs (cf. Scheme 4) in the oxidation of 3a to 4a gave a 24% yield after 2 h (Table 1, entry 1). The

| Entry | Solvent | NMR Yield 1 h [%] | NMR Yield 2 h [%] |
|-------|---------|------------------|------------------|
| 1     | Anisole | 8                | 24               |
| 2     | Toluene | 18               | 25               |
| 3     | CPME    | 4                | 7                |
| 4     | 2-Me THF| 9                | 13               |
| 5     | 1,4-Diox| 21               | 40               |
| 6     | DCE     | 6                | 6                |
| 7     | DMSO    | 9                | 18               |
| 8     | DMF     | 3                | 8                |
| 9     | 1-Propanol | 10            | 19               |
| 10    | H2O     | 0                | 0                |
| 11    | Pentadecane | 3             | 3                |
| 12    | MeOH    | 20               | 41               |
| 13    | MeOH    | 26               | 69               |
| 14    | MeOH/1,4-Diox| 25          | 73 (> 95%)       |

[a] General reaction conditions: The reaction was conducted at 80°C with 0.25 mmol of 3a, 0.025 mmol of I, 0.05 mmol of IIa, 0.025 mmol of TMANO, and 2 mL of solvent. [b] Yields were determined by NMR analysis using 1,3,5-trimethoxybenzene. [c] Reaction was performed at 40°C. [d] 5 mol % of IIa, 5 mol % of TMANO and 10 mol % of I were used at 60°C. [e] NMR yield after 16 h. [f] MeOH and Dioxane were used in a 1:1 ratio. DCE = 1,2-dichloroethane.
efficient quenching of O₂ by oxidative degradation is not clear, but may be due to a more deactivation of the iron catalyst. The reason for this decreased meaning that the presence of somehow suppresses oxidative deactivation of the iron catalyst. The reason for this decreased oxidative degradation is not clear, but may be due to a more efficient quenching of O₂ by I and a more efficient reoxidation of IV to IIa'. This allows for a much longer reaction time, which is essential for the more electron-deficient (slower reacting) substrates, making the protocol broader in scope. Other solvents than anisole were screened as well (entries 2–11), and it was found that toluene and 1,4-dioxane gave the best results (entries 2 and 5). We next lowered the temperature and found that MeOH as solvent at 40°C gave an even better result (entry 12) than dioxane at 80°C (cf. entry 5). It is plausible that the cause of this improvement is the redox activity of MeOH, which could aid the overall oxidative process. Running the reaction at 60°C in MeOH allowed for a lowering of the catalyst loading of IIa to 5 mol% (entry 13). The optimal conditions were found to be a 1:1 mixture of MeOH and dioxane at 60°C and under these conditions 4a was obtained in 73% NMR yield after 2 h and in excellent yield (> 95%) after 16 h (entry 14).

With the fully optimized reaction conditions in hand, we next turned our attention to investigating the substrate scope of various benzylamine derivatives (Table 2). Electron-donating and electron-withdrawing substituents on the benzylamine had little effect on the reaction and products 4a–4f were obtained in good to excellent yields (entries 1–6, Table 2). It should be noted that the p-MeO-substituted benzylamine 3b, was fully converted to 4b (> 95% NMR yield) but the isolated yield was only 82% due to decomposition on purification (entry 2). Introducing a more sterically hindered o-methyl substituent on the benzylamine caused a drop in conversion but as expected the desired product 4f was stable and could be isolated in 68% yield (entry 6). Naphthyl-substituted product 4g was also obtained in an excellent yield (entry 7). 2-Furylmethylamine derivative 3h was well tolerated and aldimine product 4h was isolated in 60% yield (entry 8). Pyrrolidine substrate 3i could be oxidized to the corresponding ketimine in 56% isolated yield (entry 9). It became apparent that the substituent on the nitrogen is crucial for the success of the reaction, with the electron-rich PMP group giving the best result. Changing this group to Ph led to a significant loss in conversion with only 25% NMR yield of 4j being observed (entry 10). Amines with other protecting groups such as Ms, Ts or tert-butyl were all unreactive. Amines bearing a methyl group at the R₂-position were also tested but were found to give complex mixtures. Presumably oxidation of the α-proton occurs in these cases, resulting in highly reactive enamines. A notable exception to this limitation, however, is the oxidation of 3i to product 4j (entry 9).

Based on our results, a plausible mechanism is proposed in Scheme 5. The initially activated iron complex IIa is formed by reaction with TMANO via oxidative decarbonylation as shown in Scheme 3. After that, the active catalyst species IIa’ reacts with substrate 3 to generate 4 and hydride intermediate

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**Table 2: Substrate scope.**

| Entry | Substrate | Product | Yield [%] |
|-------|-----------|---------|-----------|
| 1     | ![3a](Image) | ![4a](Image) | 95% (> 95%) |
| 2     | ![3b](Image) | ![4b](Image) | 82 (> 95%) |
| 3     | ![3c](Image) | ![4c](Image) | 85% (85%) |
| 4     | ![3d](Image) | ![4d](Image) | 83% (87%) |
| 5     | ![3e](Image) | ![4e](Image) | 89% (91%) |
| 6     | ![3f](Image) | ![4f](Image) | 68% (73%) |
| 7     | ![3g](Image) | ![4g](Image) | 90% (95%) |
| 8     | ![3h](Image) | ![4h](Image) | 60% (70%) |
| 9     | ![3i](Image) | ![4i](Image) | 56% (95%) |
| 10    | ![3j](Image) | ![4j](Image) | (25%) |

Substrate scope. General reaction conditions: The reaction was conducted under air at 60°C for 16 h with 0.25 mmol of 3, 0.0125 mmol of IIa, 0.0125 mmol of TMANO, 0.025 mmol of I, 1 mL of 1,4-dioxane and 1 mL of MeOH. [a] Isolated yields. [b] NMR yield determined by using 1,3,5-trimethoxybenzene as internal standard.
Intermediate IV is then oxidized by the benzoquinone fragments of the oxidized hybrid catalyst (VII), resulting in the regeneration of IIa’ and I. Reaction of I with molecular oxygen results in the generation of Co(III)-superoxide adduct V. Intramolecular electron transfer from one of the hydroquinone fragments to Co with concomitant proton abstraction produces Co-quinone species VI and water. A second intramolecular electron transfer from hydroquinone to Co together with a proton transfer gives VII and water. Further investigations into the nature of the mechanism are underway in our laboratory.

Although the mechanism of the electron transfer from the hydroquinone in I to molecular oxygen has not been studied in detail, a similar mechanism for electron transfer-mediated reactions has been studied by the group of Stahl where cobalt(salen) and hydroquinone were used as separate ETMs. In this study it was proposed that the hydroquinone interacts with the Co(III)-superoxide intermediate (cf. V in Scheme 5) via hydrogen bonding, finally leading to a proton coupled electron transfer. This mechanism seems less likely with the bifunctional hybrid catalyst I, where an intramolecular electron transfer coupled with proton transfer probably occurs.

In conclusion, we have developed the first biomimetic oxidation of amines using an iron(II) catalyst together with a bifunctional hybrid catalyst. A hybrid hydroquinone/cobalt Schiff base was used as the ETM and was unexpectedly found to extend the lifetime of the iron catalyst and protect it from oxidative deactivation. The electron transfer system is reminiscent of that occurring in the respiratory chain (Fe catalyst vs. NADH and hybrid catalyst I vs. the ubiquinone-cytochrome c system). Various amines were oxidized to their corresponding imines in good to excellent yields using this biologically inspired method.

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** aerobic oxidation · amines · electron transfer · homogeneous catalysis · iron

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