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Flavin Nitroalkane Oxidase Mimics Compatibility with NOx/TEMPO Catalysis: Aerobic Oxidization of Alcohols, Diols, and Ethers

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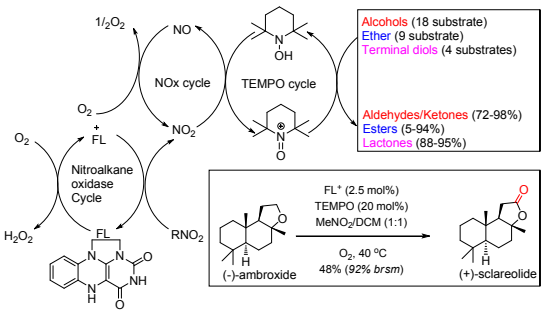
Department of Chemistry and Biochemistry, The University of Texas at Arlington, TX, 76019-0065



ABSTRACT: Biomimetic flavin organocatalysts oxidize nitromethane to formaldehyde and NO_x—providing a relatively non-toxic, non-caustic, and inexpensive source for catalytic NO_2 for aerobic TEMPO oxidations of alcohols, diols, and ethers. Alcohols were oxidized to aldehydes or ketones, cyclic ethers to esters, and terminal diols to lactones. In situ trapping of NO_x and formaldehyde suggest an oxidative Nef process reminiscent of flavoprotein nitroalkane oxidase reactivity, which is achieved by relatively stable 1,10-bridged flavins. The metal-free flavin/NOx/TEMPO catalytic cycles are uniquely compatible, especially compared to other Nef and NOx-generating processes, and reveal selectivity over flavin-catalyzed sulfoxide formation. Aliphatic ethers were oxidized by this method, as demonstrated by the conversion of (−)-ambroxide to (+)-sclareolide.

Keywords: *aerobic oxidation, flavin mimics, nitroalkane oxidase, oxidative Nef*

▪ INTRODUCTION

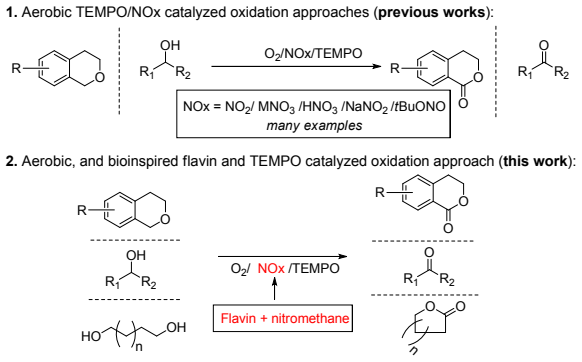
Flavins are attractive azaquinone-like species that perform a surprising array of organocatalytic oxidations and photocatalytic transformations as coenzymes in nature. Unlike many quinone oxidants, reduced flavins are efficiently reoxidized by molecular oxygen at ambient temperatures.[1] The development of new methodologies using robust and tunable flavin mimics has been demonstrated for half a century, since initial bioorganic investigations,[2] including recent biomimetic amine oxidation, photocatalytic oxidations, and cycloaddition processes.[3] Flavoprotein nitroalkane oxidases (NAO), a class of oxidoreductases, catalyze the oxidative Nef reaction of nitroalkanes to produce aldehydes along with nitrite ions and hydrogen peroxide; the overall conversion implies a significant defense mechanism and approach for nitrogen metabolism in organisms.[4] We hoped to investigate riboflavin-inspired catalysts to perform the transformation of nitroalkanes into useful carbonyl products and nitrite feedstock for catalytic reactions.

Nitroalkanes are privileged building blocks in synthetic organic chemistry. Formation of their nitronate salt allows for the modification of the α-carbon position, as demonstrated by Henry-like reactions.[5] Various transformations of the nitro group can then be performed.[6] Among them, the Nef reaction is a powerful transformation that converts the nitro group to a carbonyl functional group, reversing the polarity of the neighboring carbon atom. Initially performed by strong acid treatment of the nitronate salt,[7] the oxidative Nef reaction provides an often milder transformation.[8] Nitroalkane reactivity continues to inspire chemists for their versatility in organic synthesis and we took note that nitromethane itself has recently been investigated as a less toxic, more stable, and inexpensive NOx source—as compared to inorganic reagents—for nitrosation,[9] nitration,[10] alkylation,[11] and cyanation.[10, 12] Here we demonstrate a significant advance in flavin catalysis for synthetically useful oxidative Nef reactions. Furthermore, we report the use of metal-free, flavin-generated NOx for green cooperative catalysis and the compatibility of flavin- and existing NOx/TEMPO-catalytic cycles, to address challenges in fundamental oxidation reactions.[13]

Selective oxidations of alcohols to aldehydes or ketones is a pivotal and widely studied transformation.[14] Direct oxidation of cyclic ethers to esters and oxidative cyclization of terminal diols represent important classes of oxidation for generating functionalized bioactive structures.[15] Chemists have developed the aerobic NO_x/TEMPO system as a more sustainable approach.[16] TEMPO in the presence of co-catalytic NO_x is desirable because they offer selective and efficient transformations for practical considerations.[15c, 16e, 16i, 17] The majority of NO_x sources, however, are toxic or corrosive inorganic or gaseous sources. Though MNO_x,[18] HNO_x,[17b, 19] or NO_x[20] are widely used as stoichiometric oxidants or catalysts/cocatalysts in oxidation reactions (**Scheme**

1.1), many efforts have sought alternative reagents as NOx sources.[9-10, 21]

Scheme 1: Aerobic TEMPO Catalyzed Oxidations with NOx Cocatalysts: 1) Common NOx source 2) Nitroalkane Oxidase Inspired approach.

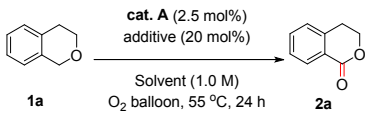


Motivated by NAO transformations of nitroalkanes to aldehydes and inorganic nitrite/nitrate ions, we found that very early reports described NAO reactivity in buffered media by flavin analogues, confirming the reactivity of unusually electron deficient, covalently bound flavin coenzymes in these biotransformation. However, these results did not yield synthetically useful methods due to flavin instability.[22] We hypothesized that more stable flavinium organocatalysts could achieve NAO activity for synthetically useful purposes, as nitrite ions and aldehydes are concomitantly generated from inexpensive 1-nitroalkanes. Here we report the enhanced activity of 1,10-bridged flavinium catalysts[23] in performing the oxidative Nef reaction, along with current limitations. We also show that nitrite ions generated from organic CH_3NO_2 (**Scheme 1.2**) are useful in contemporary TEMPO-mediated reactions, and that flavin catalysts are compatible with TEMPO oxidation of alcohols and ethers. CH_3NO_2 can be used neat, or in mixed solvent systems. We believe this NAO biomimetic approach demonstrates advances in aerobic organocatalytic Nef reactions, non-metal NOx sources, and cooperativity in aerobic TEMPO reactions.

▪ RESULTS AND DISCUSSION

Our investigation commenced by direct oxidation of cyclic ether isochroman (**1a**) as a model substrate. Previously, Zhang and coworkers demonstrated its oxidation by catalytic TEMPO, $NaNO_2$, and HCl in aerobic acetonitrile (35 °C, 8h, 80% yield).[15c] When nitromethane was used as a solvent in the presence of 2.5 mol% flavinium catalyst **A** at 55 °C under aerobic conditions, no isochroman-1-one (**2a**) was observed (Table 1, **entry 1**). However, the addition of TEMPO (20 mol%) gave **2a** in 68% NMR yield with 70% conversion (**entry 2**). No product was observed in the absence of flavinium catalyst (**entry 3**) and removal of nitromethane halted the reaction, with only trace product formed in MeCN (**entry 4**).

Table 1: Initial Studies[a]



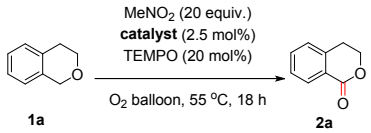
Entry	Catalyst (2.5 mol%)	Solvent (1 M)	Additive (20 mol%)	Yield (Conversion)
1	A	$MeNO_2$	-	0
2	A	$MeNO_2$	TEMPO	68 (70)
3	-	$MeNO_2$	TEMPO	0
4	A	-	TEMPO	0[b], 0[c], 5[d]

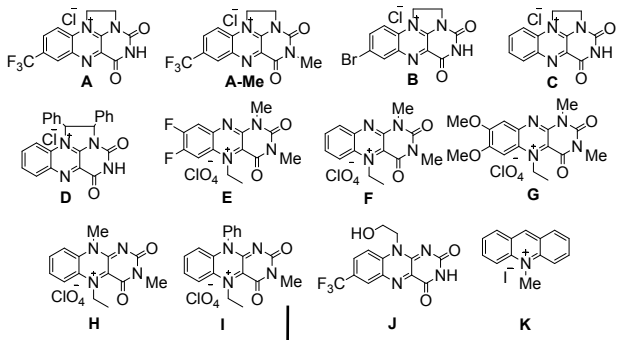
[a]Reaction Conditions: **1a** (0.2 mmol), cat. A (2.5 mol%), TEMPO (20 mol%), solvent (1.0 M), 55 °C, 24 h, O_2 balloon; [b]neat, [c]in DMSO, toluene, DCE, or 1,4-dioxane solvents; [d]in MeCN solvent; Yields and conversions calculated from ^{1}H NMR experiments.

A range of flavin catalysts were prepared and investigated, primarily as their flavinium salts. All 1,10-disubstituted "bridged" flavinium catalysts **A-D** were productive, albeit with varied efficiency related to their relative redox potentials (**Table 2**, **entry 1-5**). More electron rich, **C** and **D** were superior to their substituted and electron poor variants **A**, **A-Me**, and **B**—these substitution patterns usual indicate lower barriers for flavin reoxidation by O_2.[2b, 24] In contrast, tricyclic isoalloxazinium and alloxazinium flavin mimics **E**, **F**, and **G**—similar to those initially reported in kinetic study of NAO reactivity—were significantly less productive (**entry 7-9**). Control reactions with alloxan, H_2O_2, DDQ, $SOCl_2$, and HCl ruled out non-flavinium based reactivities (**entry 13-17**) Moreover, recently used catalysts like $Cu(OTf)_2$, DBU, and PIFA for NOx generation from nitromethane were inefficient in this comparison (**entry 18-22**).

Reaction time, temperature, and external conditions were studied with catalyst **C** (**Table 3**). Lower loading of either TEMPO or nitromethane led to moderate activity (**entry 4** and **5**). Oxygen and water are imperative for the reaction, and elevated temperatures in neat nitromethane provided convenient reaction times (**entry 6-10**). Freshly dried nitromethane led to poor yields (**entry 9**). However, trace addition of water (0.25% or 2.5% by volume) restored reactivity (**entry 10**). The reaction was also found to be compatible, albeit slower, with one equivalent of nitromethane in dicholoromethane solvent (**entry 11**). Evaluating different nitroalkane sources found that nitromethane and α-nitrotoluene outperformed other nitroalkane sources; moderate yields were still encountered with nitroethane (**Table S1**). Interestingly, replacing nitromethane (CH_3NO_2) with deuterated nitromethane (CD_3NO_2) reduced the turnover rate, as indicated by four-hour reaction yields (**Table S1**). CD_3NO_2 yields were comparable to the non-deuterated reaction with a 24-hour reaction period, and a primary kinetic isotope effect was observed (K_H/K_D = 3.3). Overall, either one mol% catalyst **C** for 10 hours or 2.5 mol% catalyst **C** for four hours were effective with 10 mol% loading of TEMPO at 40 °C under O_2 balloon in excess CH_3NO_2 (**entries 2** and **3**).

Table 2: Catalyst Investigation[a]



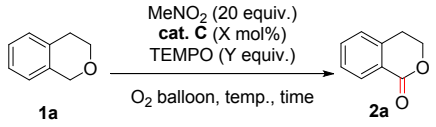


Entry	Catalyst (X mol%)	Yield	Entry	Catalyst (X mol%)	Yield
1	A (2.5)	71	12	K (2.5)	trace
2	A-Me (2.5)	74	13	alloxan (5)	0
3	B (2.5)	21	14	H_2O_2 (10)	0
4	C (2.5)	96 (100)	15	DDQ (5)	0[b]
5	D (2.5)	94 (100)	16	$SOCl_2$ (5)	0[b]
6	E (5)	16	17	HCl (10)	0[b]
7	F (5)	11	18	DBU (5)	0[b]
8	G (5)	10	19	$FeCl_3.6H_2O$ (5)	trace[b]
9	H (2.5)	7	20	$Cu(OTf)_2$ (5)	trace[b,c]
10	I (2.5)	6	21	PIFA (5)	0[b]
11	J (2.5)	trace	22	Guanidine Hydrochloride (5)	0[b]

[a]Reaction Conditions: **1a** (0.2 mmol), $MeNO_2$ (20 equiv.), catalyst (2.5 mol%), TEMPO (20 mol%), 55 °C, 18 h, O_2 balloon. [b]6 hours reaction times. [c]0.5 equiv. DBU added. Numbers in the parenthesis represent NMR conversion

Isochroman substrates are not widely available from commercial sources; however, eight diverse substrates demonstrate their general reactivity and limitations (**Table 4**), with functional group compatibility being explored further by alcohol substrates and mixed experiments. Overall results show good reactivity for benzylic and cyclic ethers (**entry 1a-1f**). Excellent isolated yields were achieved with electron-neutral and -rich aromatic substrates under the standard condition (**entry 2a-2d**). On the other hand, electron-poor substrate **1e** afforded slightly reduced yield of 67%. Starting material **1e** was also isolated in 28%, along with the product **2e**, showing a useful mass balance. Xanthene **1f** reacted smoothly to give corresponding xanthone product **2f** in excellent yield. Non-arene cyclic ethers containing relatively inert sp^3 C-H bonds were also challenged for their scope. Tetrahydrofuran gave 79% NMR yield of desired butyrolactone **2g** in a 70-hour reaction with higher loading of flavin catalyst **C**, TEMPO, and nitromethane. However,

Table 3: Initial Component Optimization[a]

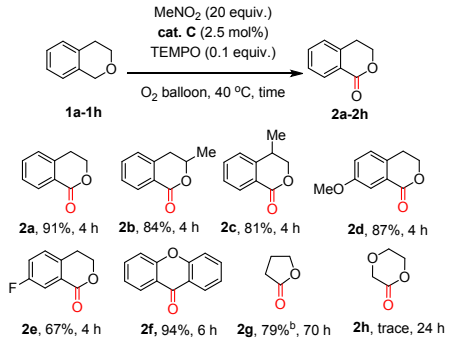


Entry	Catalyst C (X mol%)	TEMPO (Y mol%)	Temp. (°C)	Time (h)	NMR yield
1	2.5	20	40	4	93
2	2.5	10	40	4	91
3	1	10	40	10	98
4	1	2	40	24	39
5	1	10	40	24	36[b]
6	1	10	40	10	trace[c]
7	1	10	RT	10	18
8	1	10	40	24	8[d]
9	1	10	40	10	7[e], trace[f]
10	1	10	40	10	95[g], 94[h]
11	2.5	10	55	48	81[i]

[a]Reaction Conditions: **1a** (0.2 mmol) and $MeNO_2$ (20 equiv.); [b]2 equiv. of $MeNO_2$ was used; [c]N_2 balloon instead of O_2 balloon; [d]in a closed vessel without O_2 balloon. [e]Molecular sieves were added; [f]freshly dried $MeNO_2$ was used; [g]0.25% by volume of H_2O was added in freshly dried $MeNO_2$; [h]2.5% by volume of H_2O was added in freshly dried $MeNO_2$; [i]1 equiv. of $MeNO_2$ was used in 0.2 mL DCM solvent.

substrate **1h** was relatively inert and provided trace yields by NMR analysis. We previously summarized the disparate stabilization of oxidized byproducts for these two substrates, attributable to strain effects and the β-effect in dioxane.[25]

Table 4: Substrate Scope for Cyclic Ether Substrates

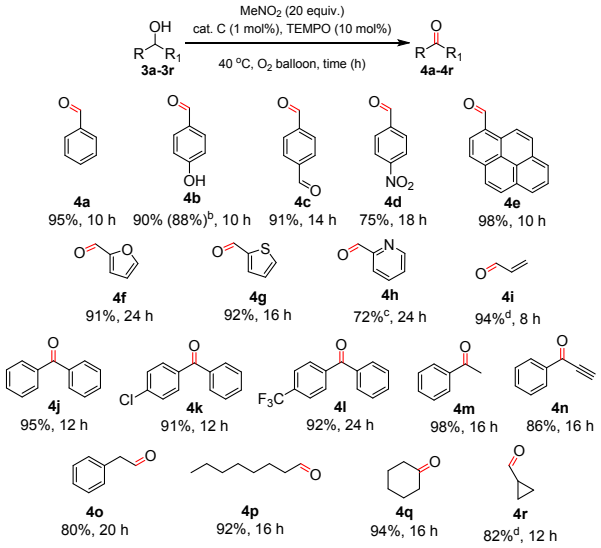


[a]Reaction Conditions **1a-1h** (2.0 mmol), $MeNO_2$ (20 equiv.), catalyst **C** (0.05 mmol), TEMPO (0.2 mmol), 40 °C, O_2 balloon; [b]NMR yield and reaction condition: **2g** (0.2 mmol), $MeNO_2$ (40 equiv.), catalyst **C** (0.005 mmol), TEMPO (0.05 mmol), 40 °C, O_2 balloon

A range of alcohol substrates including aromatic, heteroaromatic, and aliphatic primary and secondary alcohols were chosen. The results are summarized in **Table 5**. Electronic effects were evident. Benzyl alcohol (**entry 4a**) and 4-hydroxy benzyl alcohol (**entry 4b**) gave excellent isolated yields, without the observation of over-oxidized products, even with prolonged time. This highlights the

selectivity of the TEMPO oxidation method, even though peroxide byproducts are likely present from the flavin catalytic cycle. Alcohols containing electron withdrawing groups like -CHO (**entry 4c**) and -NO_2 (**entry 4d**) furnished aldehydes in good yields. For the later substrate, 22% of the remaining starting material **3d** was recovered. 1-Pyrene methanol (**entry 4e**) was an excellent substrate for the method. Similarly, heteroaromatic benzylic alcohol substrates like furanyl (**entry 4f**) and thiophenyl (**entry 4g**) also gave satisfying yields. Even in the case of electron deficient pyridinyl substrate (**entry 4h**), 72% of the desired aldehyde product was obtained. Allyl alcohol (**3i**) yielded corresponding aldehyde product **4i** in excellent yield and shorter time. Secondary and aromatic substrates (**entry 4j-4m**) were also highly effective at forming ketones. The alkyne functional group was also well-tolerated (**entry 4n**). The method was also suitable for primary and secondary aliphatic substrates. For example, 1-octanol, cyclohexanol, cyclopropyl alcohol, and phenylethyl alcohol all gave corresponding oxidized products in useful yields, which further strengthens the utility of this biomimetic oxidation method (**entry 4o-4r**).

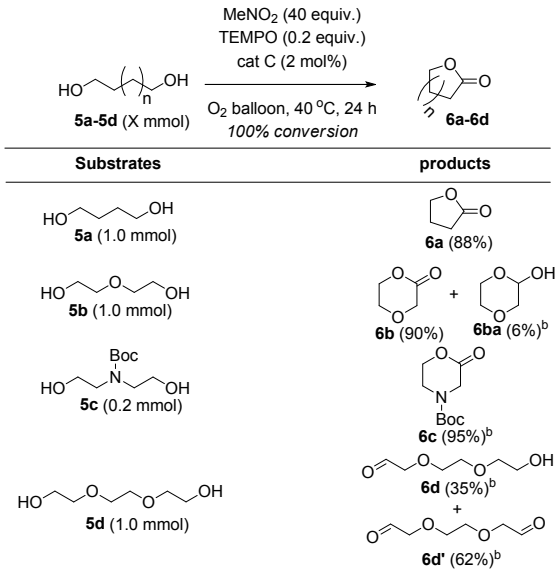
Table 5: Substrate Scope for Alcohol Oxidation[a]



[a]Reaction Conditions: **3a-3r** (1.0 mmol), $MeNO_2$ (20 equiv.), catalyst C (1 mol%), TEMPO (10 mol%); [b]Isolated yield for 24-hour reaction; [c]**3h** (0.25 mmol), catalyst C (2.5 mol%) and TEMPO (20 mol%); [d]NMR Yield from crude reaction mixture

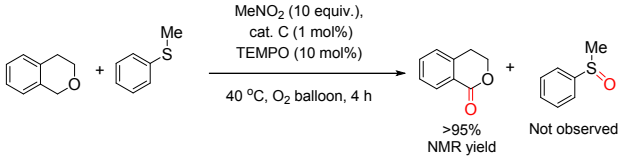
The flavin/TEMPO method oxidized terminal diols, leading to the formation of lactones in one step (**Table 6**). Six- or seven-membered diols (**5a-5c**) reacted smoothly at 2 mol% loading of catalyst **C** and 20 mol% loading of TEMPO catalyst in excess CH_3NO_2 to give the desired corresponding lactone products in excellent yields. Longer triethylene glycol **5d** did not give cyclized product. Nevertheless, smooth oxidation of alcohol groups was encountered with full conversion of alcohol starting material. Sulfur oxidation to sulfoxides often predominates in flavin-catalyzed oxidations.[1a, 1b, 26] In **Scheme 2,** isochroman **1a** was selectively oxidized in competition with thioanisole under the standard reaction conditions.

Table 6: Substrate Scope for Terminal Diols[a]



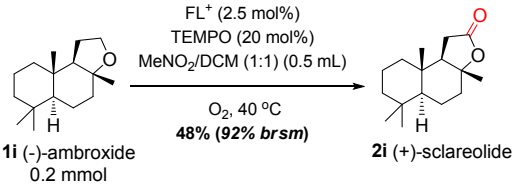
[a]Reaction Conditions: $MeNO_2$ (20 equiv), TEMPO (20 mol%), Catalyst C (2 mol%), 40 °C, O_2 balloon, 24 h. [b]NMR yields of crude reaction mixture

Scheme 2: Selectivity of the method: Sulfur oxidation vs Isochroman oxidation



Synthetic utility of the method was investigated further by oxidation of chiral cyclic ether (−)-ambroxide (**Scheme 3**). The oxidation gave moderate yields of the desired (+)-sclereolide product, no sign of stereochemical degradation, and tolerated the addition of dichloromethane as a cosolvent, used to incorporate the fairly non-polar substrate. Combined with the functional group tolerability above, this shows the efficacy of the method for the late stage oxidation.

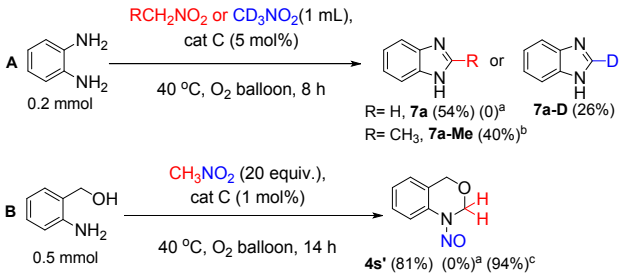
Scheme 3: Synthetic Application of the Method



To understand the flavin mediated nitroalkane transformation more thoroughly, catalyst **C** and 1-nitroalkanes were investigated in the absence of TEMPO and the substrates above (**Scheme 4**). In the presence of *o*-phenylenediamine, an aldehyde trap, corresponding benzimidazoles were formed from nitromethane or nitroethane. Deuterated nitromethane CD_3NO_2 gave 2-deuterobenzimidazole **7a-D**. No benzimidazole products were observed in the absence of flavin catalyst. Aminoalcohol **3t** yielded exclusively *N*-nitrosobenzo[1,3]oxazine **4s'** (**Scheme 4B**). The reaction outcome was similar with added catalytic TEMPO. Additionally, benzaldehyde was observed in crude NMR experiments of α-nitrotoluene and catalyst **C**, when substrates were removed (**Figure S5**). These results are evidence of nitroalkane's reactivity with

flavinium catalysts and potential for further development focusing on efficient oxidative Nef reactivity.

Scheme 4: Evidence of Nitromethane Derived Products (unoptimized results). [a]Yields without flavin catalyst. [b]14 h ^{1}H NMR yield. [c]isolated yield with 10 mol% TEMPO



NO_x species were qualitatively characterized by ion chromatography[27] by comparing the retention time of the observed ions with the standard ions i.e. chloride, nitrite, bromide and nitrate (**Figure 1**, purple trace). Reaction samples were reconstituted in water after nitromethane evaporation, following standard reaction condition. Nitrate was detected in samples lacking TEMPO (**Figure 1**, pink trace). Nitrite ions were detected in the presence of TEMPO with (red trace) and without substrate (light blue traces). This shows that TEMPO is crucial for generating persistent nitrite ions, which are known to oxidize TEMPOH to TEMPO$^+$. Residual chloride ions were detected in control water samples (**Figure S4**).

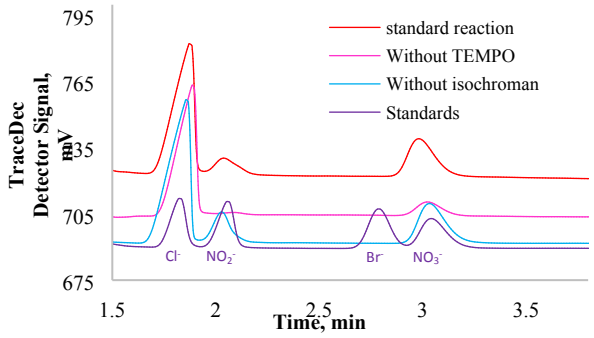


Figure 1: Extracted Ion Chromatogram: Comparison of analyte samples with the standards: Open Tubular Ion Chromatographic Conditions as follows. Column: AS 18 Anion Exchange latex coated silica columns (25 µm i.d., 360 µm o.d., Effective length: 40 cm); Eluent: 1 mM sodium benzoate; Injection volume: 4 nL; Flow rate: 150 nL/min; Detection: TraceDec Detector (Frequency: 150 KHz, Gain: 200%, Voltage: 0 dB, Offset: 0).

A plausible mechanism is presented in **Figure 2** based on preliminary mechanistic studies and consistent with NAO and TEMPO literature precedent.[18a, 22a, 28] In general, three catalytic cycles are speculated to be crucial for the overall oxidation process. First, nitromethane oxidation by flavinium species releases nitrite ion, formaldehyde, and then hydrogen peroxide during flavin catalytic turnover by O_2. Hydrogen peroxide, or activated flavohydroperoxide, oxidizes nitrite to nitrate[29] as observed by ion chromatography in the absence of TEMPO (**Figure 1**, pink trace). Nitrite and nitrate ions may undergo various oxidation transformations; however, they are known to comproportionate to form nitrogen dioxide (NO_2)—the likely source of the observed brown reaction color—that can facilitate the oxidation of TEMPO to TEMPO$^+$.[30] The NO_2 that is reduced by TEMPOH, is then reoxidized by NO's facile reactivity with molecular oxygen as demonstrated in previous NOx/TEMPO reactions. Finally, the ultimate oxidization of substrates to products takes place by the standard TEMPOH and TEMPO$^+$ redox couple, which were detected by mass spectrometry analysis (**Figure S6 and S7**) of crude reaction samples. TEMPO$^+$ was persistent when no substrate was present (**Figure S6**). Focusing on the flavin/CH_3NO_2 cycle, the possible N5-adduct (**C-A**) of flavin with nitronate ion was not directly observed. While examples of such adducts are well-understood in biological models,[4c, 28, 31] N5 adducts are more rarely observed in non-biological models.[32] It should be noted that the bisiminium nature of flavinium catalysts present multiple electrophilic sites to nucleophiles achievable under altered reaction conditions.[33] Bridged flaviniums were ultimately observed to react with peroxide at the C10a position by isotopically labeled NMR experiments.[34] Given that the sterically congested **catalyst D** near C10a also gives the product equally well as compared to less sterically congested **catalyst C**, the traditional NAO-like event may take place at N5; however, C10a addition cannot be overlooked. Ongoing studies will hopefully illuminate this mechanistic question and lend aid to broadening the scope of oxidation Nef reactions. Finally, the relative rates of oxygen consumption are currently unknown, but appear to be mainly centered at the redox cycle of NO/NO_2.

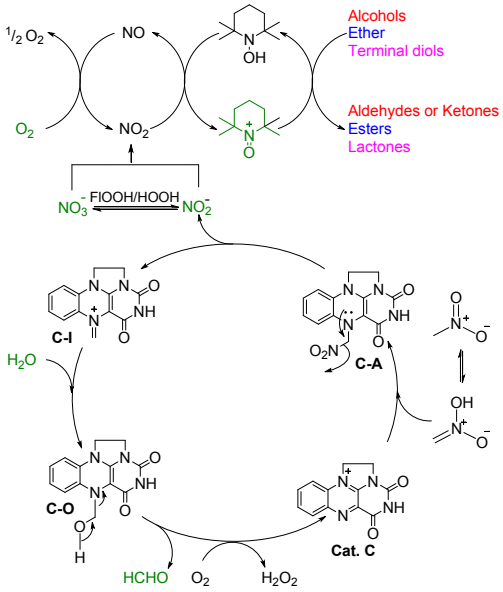


Figure 2: Plausible Mechanism. Green highlighted species were directly or indirectly observed and critical for the reaction.

▪ CONCLUSION

In conclusion, we have demonstrated a multicatalytic approach to the metal-free, aerobic oxidation of various alcohols and ethers. Flavoprotein nitroalkane oxidase chemistry was mimicked by robust 1,10-bridged flavinium organocatalysts to produce NO_x by an oxidative Nef reaction. The organically sourced NOx system is compatible with TEMPO/NOx oxidations and converts cyclic ethers to esters, alcohols to aldehydes/ketones, and terminal diols to lactones. To the best of our knowledge, the catalytic Nef and TEMPO cycles have not been combined; common Nef reaction were incompatible with TEMPO when attempted under similar conditions. Not only do flavin catalysts provide synthetically useful NOx from nitroalkanes, but it seems possible that further development may lead to an organocatalytic oxidative Nef reaction.

▪ EXPERIMENTAL SECTION

General comments: All reagents were used as purchased from Alfa Aesar, Acros Organics, and Sigma Aldrich. Nitromethane was purchased as 98% grade from Alfa Aesar and was used without further purification. All reactions were performed under atmospheric conditions unless otherwise specified. ^{1}H NMRs were recorded on 300 MHz and 500 MHz spectrometers and referenced to the internal solvent signals (7.26 ppm in $CDCl_3$ or 2.5 ppm in DMSO-d_6 or 3.3 ppm in CD_3OD or 2.0 ppm in CD_3COOD or 1.9 ppm in CD_3CN). $^{13}C\{^1H\}$ NMRs were recorded on 75 MHz and 125 MHz spectrometers referenced to the internal solvent signals (central peak 77.00 ppm in $CDCl_3$ or 39.5 in DMSO-d_6 or 39.0 in CD_3OD or 20.0 ppm in CD_3COOD or 1.3 ppm in CD_3CN). Data are reported as follows: chemical shift (in ppm, δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (in Hz). DMSO was used as internal standard for investigating NMR yields and KIE measurement. Thin layer chromatography was performed in silica gel coated aluminum plates (EMD Merck F254, 250 mm thickness). TLC spots were visualized using 254 nm ultraviolet light and Chemical stains. Flash chromatography was performed over Silicycle Silicaflash P60 silica gel (mesh 230-400). Mel-Temp II apparatus was used to record melting points in capillary tubes and were uncorrected. Bruker Alpha-P FT-IR Spectrometer was used for recording IR spectra with attenuated total reflectance on a diamond sample plate. Open tubular ion chromatography was performed over AS 18 Anion Exchange latex coated silica columns. Shimadzu TOF spectrometer in the Shimadzu Center for Advanced Analytical Chemistry at UT Arlington was used for obtaining HRMS data.

Flavin based catalysts (**A-J**) were synthesized following previously reported methods.[2d, 23b, 35] Catalyst **K** was synthesized following a method described in a literature.[35d] Starting materials **1a-D$_2$**, **1b**, **1c**, **1d**, **1e**, **3c**, **3e,** and **3r** were synthesized following established protocols.[36] Other starting materials were commercially available and used without further purification.

Characterization data of new catalyst:

9-Bromo-4,6-dioxo-2,4,5,6-tetrahydro-1H-benzo[g]imidazo[1,2,3-ij]pteridin-12-ium **(B):**

Prepared according to the reported procedure.[23b] Yield 69% (245 mg, 1.0 mmol scale); Yellow solid; mp decomposed at 310 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.91 (br, 1H), 8.66 (s, 1H), 8.49 (d, 1H, J = 8.5 Hz), 8.29 (d, 1H, J = 8.2 Hz), 5.34 (t, 2H, J = 9.3 Hz), 4.67 (t, , 2H, J = 9.3 Hz); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz): δ 158.3, 146.8, 145.3, 138.5, 135.3, 134.9, 134.0, 133.1, 129.8, 121.4, 51.4, 45.5; IR (neat, cm^{-1}): 3345, 3070, 2930, 1731, 1624, 1369; HRMS (IT-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_8BrN_4O_2$ 318.9825; Found 318.9822; UV/Vis (H_2O) λmax = 404 nm

5-ethyl-7,8-dimethoxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrobenzo[g]pteridin-5-ium perchlorate **(G):**

Prepared according to the reported procedure.[35b] Yield 83% (356 mg, 1.0 mmol scale); Yellow solid; mp 255-256 °C; ^{1}H NMR (CD_3CN, 500 MHz): δ 7.57 (s, 1H), 7.45 (s, 1H), 6.00 (br, 1H), 5.22 (br, 1H), 4.23 (s, 3H), 4.16 (s, 3H), 3.78 (s, 3H), 3.49 (s, 3H), 1.74 (t, 3H, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (CD_3CN, 125 MHz): δ 160.5, 159.9, 157.0, 150.1, 148.1, 147.6, 131.0, 116.6, 107.7, 97.5, 59.1, 58.6, 51.6, 31.1, 30.3, 14.8; IR (neat, cm-1): 3071, 2991, 1712, 1668, 1492; HRMS (IT-TOF) m/z: $[M]^+$ Calcd for $C_{16}H_{19}N_4O^4$ 331.1401; Found 331.1395; UV/Vis (CH_3CN) λmax = 412 nm.

5-ethyl-3-methyl-2,4-dioxo-10-phenyl-2,3,4,10-tetrahydrobenzo[g]pteridin-5-ium perchlorate **(I):**

Prepared according to the reported procedure.[35c] Yield 73% (315 mg, 1.0 mmol scale); Purple solid; mp decomposed >300 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.67 (d, 1H, J = 1.2 Hz), 7.56 (d, 2H, J = 5.4 Hz), 7.44 (d, 1H, J = 12.6 Hz), 7.27 (d, 1H, J = 7.9 Hz), 7.20 – 7.14 (m, 2H), 6.86 (t, 1H, J = 7.4 Hz), 6.35 (d, 1H, J = 7.9 Hz), 3.74 (m, 1H), 3.62 (s, 3H), 3.57 (m, 1H), 3.15 (s, 3H), 1.23 (t, 3H, J = 6.6 Hz); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz): δ 166.1, 159.3, 154.6, 138.0, 132.6, 130.5, 130.4, 130.1, 129.1, 128.2, 125.2, 120.9, 117.9, 117.3, 74.7, 43.7, 28.1, 14.0; IR (neat, cm-1): 3089, 2993, 1712, 1665, 1552; HRMS (IT-TOF) m/z: $[M]^+$ Calcd for $C_{19}H_{17}N_4O_2$ 333.1346; Found 333.1345; UV/Vis (DMSO) λmax = 352 nm

N.B. NMR spectral data for Catalyst **H** and **I** were taken in DMSO-d_6, which represent C4a-hydroxyflavin species. This was confirmed from NMR data observed for corresponding hydroxyflavin (**I$_{OH}$**) prepared separately from a known procedure (see NMR spectral figures for **I$_{OH}$** taken in methylene chloride-d_2).[35c]

10-(2-hydroxyethyl)-7-(trifluoromethyl)benzo[g]pteridine-2,4(3H,10H)-dione **(J):**

Prepared according to the reported procedure.[23b] Yield 65% (2.11 g, 10.0 mmol scale); Yellow solid; mp decomposed at 262 °C ; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.57 (br, 1H), 8.47 (s, 1H), 8.21 (dt, 2H, J = 9.1, 5.4 Hz), 4.97 (s, 1H), 4.70 (t, 2H, J = 5.7 Hz), 3.83 (t, 2H, J = 5.5 Hz); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz): δ 159.8, 156.0, 151.6, 140.8, 136.5, 134.4, 130.3 (q, J = 3.7 Hz), 129.1 (q, J = 3.7 Hz), δ 126.2 (q, J = 33.2 Hz), 124.0 (q, J = 272.2 Hz), 119.4, 57.9, 47.3; ^{19}F NMR (DMSO-d_6, 282 MHz): δ -60.5; IR (neat, cm-1): 3296, 3098, 2996, 1677, 1556; HRMS (IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{10}F_3N_4O_3$ 327.0700; Found 327.0691

1. General procedure for oxidation reaction catalysed by Flavin and TEMPO catalyst:

Flavin catalyst **C** (0.01 equivalent or 0.02 equivalent or 0.025 equivalent), TEMPO (0.1 equivalent or 0.2 equivalent) and Alcohols or Ethers or Terminal diols (1.0 equivalent) were added in an oven dried 2.0-dram vial fitted with septum and magnetic stirbar. The reaction vial was purged with O_2 before adding Nitromethane (20 or 40 equivalent). The reaction vial was heated in oil bath at a given temperature until the completion of reaction as indicated by TLC analysis. Then the solution was concentrated in rotary evaporator and the crude product was directly purified by column chromatography using hexanes and ethyl acetate as eluents without regular work up.

Procedure for measuring NMR yields of compound 2g, 4i, 4r, 6ba, 6c, 6d, 6d, 7a-Me: In a typical experiment with compound 2g, after the reaction was stopped at a given time, reaction mixture was added with one equivalent of internal standard dimethyl sulfoxide with respect to the compound 2g. For the preparation of NMR sample, 0.1 mL of this solution was added with 0.6 mL of $CDCl_3$. The integration value from a peak at 3.8 ppm was measured relative to the internal standard peak at 2.4 ppm to obtain NMR yields of the desired product from the crude reaction mixture.

Isochroman oxidation products:

isochroman-1-one **(2a)[15b]:**

Yield 91% (269 mg); Clear liquid; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80 (d, 1H, *J* = 7.6 Hz), 7.46 – 7.33 (m, 1H), 7.22 (t, 1H, *J* = 7.5 Hz), 7.14 (d, 1H, *J* = 7.5 Hz), 4.33 (t, 2H, *J* = 6.0 Hz), 2.89 (t, 2H, *J* = 6.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 165.0, 139.5, 133.5, 130.0, 127.4, 127.2, 125.0, 67.2, 27.6.

3-methylisochroman-1-one **(2b)[15b]:**

Yield 84% (272 mg); Clear liquid; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.09 (d, 1H, *J* = 7.7 Hz), 7.53 (t, 1H, 7.2 Hz), 7.38 (t,1H, *J* = 7.5 Hz), 7.23 (d, 1H, *J* = 7.6 Hz), 4.78 – 4.58 (m, 1H), 3.08 – 2.85 (m, 2H), 1.52 (d, 3H, *J* = 6.3 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 165.7, 139.2, 133.6, 130.2, 127.9, 127.8, 125.0, 74.6, 34.9, 20.9; HRMS (IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{11}O_2$ 163.0754; Found 163.0756

4-methylisochroman-1-one **(2c)[15b]:**

Yield 81% (262 mg); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (d, 1H, *J* = 7.7 Hz), 7.62-7.50 (m, 1H), 7.45-7.33 (m, 1H), 7.29 (d, 1H, *J* = 7.6 Hz), 4.51 (dd, 1H, *J* = 10.9, 4.0 Hz), 4.23 (dd, 1H, *J* = 10.9, 6.6 Hz), 3.25-3.06 (m, 1H), 1.36 (d, 3H, *J* = 7.1 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 165.2, 144.6, 133.9, 130.5, 127.5, 125.7, 124.4, 72.5, 31.7, 16.7.

7-methoxyisochroman-1-one **(2d)[15b]:**

Yield 87% (310 mg); Clear liquid; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.59 (d, 1H, *J* = 2.6 Hz), 7.17 (d, 1H, *J* = 8.4 Hz), 7.10 (dd, 1H, *J* = 8.4, 2.7 Hz), 4.52 (t, 2H, *J* = 6.0 Hz), 3.85 (s, 3H), 2.99 (t, 3H, *J* = 6.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 165.1, 158.8, 131.7, 128.2, 125.9, 121.5, 112.8, 67.5, 55.5, 26.8.

7-fluoroisochroman-1-one **(2e)[15b]:**

Yield 67% (222 mg); White solid; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82 (d, 1H, *J* = 8.1 Hz), 7.42 – 7.17 (m, 2H), 4.59 (t, 2H, *J* = 6.0 Hz), 3.09 (t, 2H, *J* = 6.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 164.2, 161.96 (d, *J* = 247.4 Hz), 135.41 (d, *J* = 3.3 Hz), 129.23 (d, *J* = 7.4 Hz), 127.07 (d, *J* = 7.6 Hz), 121.22 (d, *J* = 22.2 Hz), 116.89 (d, *J* = 23.1 Hz), 67.6, 27.2; ^{19}F NMR ($CDCl_3$, 282 MHz): δ -113.7 (dd, *J* = 14.6, 7.2 Hz).

9H-xanthen-9-one **(2f)[15c]:**

Yield 94% (368 mg); White solid; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.35 (dd, 2H, *J* = 8.0, 1.6 Hz), 7.73 (m 2H), 7.51 (d, 2H, *J* = 8.4 Hz), 7.44 – 7.36 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 177.4, 156.3, 134.9, 126.9, 124.0, 122.0, 118.1.

(3aR, 5aS, 9aS, 9bR)-3a,6,6,9a-tetramethyldecahydronaphtho[2,1-b]furan2(1H)-one ((+)-Sclareolide) **(2i)[37]:**

Yield 48% (24 mg, 0.2 mmol scale); White solid; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.41 (dd, 1H, *J* = 16.1, 14.9 Hz), 2.24 (dd, 1H, *J* = 16.2, 6.5 Hz), 2.08 (dt, 1H, *J* = 11.9, 3.3 Hz), 1.97 (dd, 1H, *J* = 14.8, 6.5 Hz), 1.92 – 1.84 (m, 1H), 1.74 – 1.65 (m, 2H), 1.47 – 1.31 (m, 7H), 1.23 – 1.18 (m, 1H), 1.06 (dd, 2H, *J* = 12.7, 2.8 Hz), 0.91 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 177.0, 86.5, 59.2, 56.7, 42.3, 39.6, 38.8, 36.1, 33.3, 33.2, 29.8, 28.8, 21.7, 21.0, 20.7, 18.2, 15.2; IR (neat, cm^{-1}): 2920, 1761, 1157; $[\alpha]_D^{28.0}$ = +46.7 (c = 1.00, $CHCl_3$) (reported: $[\alpha]_D^{28.7}$ = +46.9 (c = 1.00, $CHCl_3$)[37]

Alcohol Oxidation products:

Benzaldehyde **(4a)[16l]:**

Yield 95% (101 mg); Pale yellow liquid; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.86 (s, 1H), 7.77 (d, 2H, *J* = 7.4 Hz), 7.56 (t, 1H, *J* = 7.1 Hz), 7.45 (t, 2H, *J* = 7.3 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 191.4, 134.9, 133.0, 128.0, 127.5.

4-hydroxybenzaldehyde **(4b)[38]:**

Yield 90% (110 mg); White solid; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.86 (s, 1H), 7.82 (d, 2H, *J* = 7.2 Hz), 6.99 (d, 2H, *J* = 7.2 Hz), 6.48 (br, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 191.5, 161.8, 132.7, 129.9, 116.1.

Terephthalaldehyde **(4c)[39]:**

Yield 91% (122 mg); White solid; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.12 (s, 2H), 8.04 (s, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 191.6, 140.1, 130.2

4-nitrobenzaldehyde **(4d)[38]:**

Yield 75% (113 mg); Brown solid; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.16 (s, 1H), 8.40 (d, 2H, *J* = 8.6 Hz), 8.08 (d, 2H, *J* = 8.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 190.4, 151.2, 140.1, 130.6, 124.4.

pyrene-1-carbaldehyde **(4e)[36d]:**

Yield 98% (225 mg); Brown solid; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.75 (s, 1H), 9.37 (d, 1H, *J* = 9.3 Hz), 8.40 (d, 1H, *J* = 7.9 Hz), 8.28 (dd, 3H, *J* = 8.1, 4.4 Hz), 8.20 (dd, 2H, *J* = 8.3, 6.4 Hz), 8.06 (dd, 2H, *J* = 14.0, 8.2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 193.1, 135.6, 131.4, 131.1, 131.0, 130.9, 130.8, 130.5, 127.4, 127.2, 127.1, 126.9, 126.6, 124.7, 124.6, 124.1, 123.0

Furan-2-carboxylaldehyde **(4f)[16f]:**

Yield 91% (87 mg); Clear liquid; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.62 (s, 1H), 7.73 – 7.61 (m, 1H), 7.26 – 7.18 (m, 1H), 6.57 (dd, 1H, *J* = 3.6, 1.7 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 177.9, 153.0, 148.1, 121.2, 112.6.

Thiophene-2-carboxyldehyde **(4g)[16l]:**

Yield 92% (103 mg); Clear liquid; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.82 (s, *1*H), δ 7.67 (dd, 2H, *J* = 13.1, 4.0 Hz), 7.12 – 7.07 (m, 1H); $^{13}C\{^1H\}$ NMR (**(**$CDCl_3$, 125 MHz,): δ 182.8, 143.6, 136.4, 134.9, 128.2.

Pyridine-2-carboxyldehyde **(4h)[14l]:**

Yield 72% (77 mg); Pale brown liquid; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.93 (s, 1H), 8.65 (d, 1H, *J* = 4.6 Hz), 7.81 (d, 1H, *J* = 7.6 Hz), 7.75 (t, 1H, *J* = 7.6 Hz), 7.47 – 7.30 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 193.3, 152.7, 150.1, 137.0, 127.9, 121.6.

Benzophenone **(4j)[40]:**

Yield 95% (173 mg); White solid; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.66 (d, 4H, *J* = 7.5 Hz), 7.51 (t, 2H, *J* = 7.2 Hz), 7.40 (t, 4H, *J* = 7.4 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 195.0, 135.7, 130.9, 128.2, 126.7

(4-chlorophenyl)(phenyl)methanone **(4k)[40]:**

Yield 91% (197 mg); White solid; ^1H NMR (CD_3OD, 500 MHz) δ 7.78 – 7.71 (m, 4H), 7.63 (t, 1H, *J* = 7.5 Hz), 7.55 – 7.48 (m, 4H); $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ 197.1, 140.0, 138.4, 137.3, 133.9, 132.6, 130.9, 129.7, 129.6.

phenyl(4-(trifluoromethyl)phenyl)methanone **(4l)[40]:**

Yield 92% (230 mg); White solid; ^1H NMR (CD_3OD, 500 MHz): δ 7.91 (d, 2H, *J* = 8.1 Hz), 7.83 (d, 2H, *J* = 8.1 Hz), 7.80 – 7.75 (m, 2H), 7.65 (t, 1H, *J* = 7.5 Hz), 7.53 (t, 2H, *J* = 7.7 Hz); $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ 195.7, 140.9, 136.7, 133.3 (q, *J* =39 Hz), 133.0, 130.0, 129.7, 128.3, 125.1 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 324 Hz); 19F NMR (CD_3OD, 282 MHz): δ -64.4

Acetophenone **(4m)[18a]:**

Yield 98% (118 mg); White solid; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.79 (d, 2H, *J* = 7.6 Hz), 7.44 (t, 1H, *J* = 7.2 Hz), 7.33 (t, 2H, *J* = 7.5 Hz), 2.42 (s, 3H).

1-phenylprop-2-yn-1-one **(4n)[41]:**

Yield 86% (112 mg); White solid; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.24 – 8.12 (m, 2H), 7.64 (t, 1H, *J* = 7.4 Hz), 7.51 (t, 2H, *J* = 7.8 Hz), 3.44 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 177.5, 136.2, 134.6, 129.8, 128.8, 80.8, 80.4.

2-phenylacetaldehyde **(4o)[42]:**

Yield 80% (96 mg); Clear liquid; ^1H NMR (CD_2Cl_2, 500 MHz): δ 9.72 (t, 1H, *J* = 2.0 Hz), 7.36 (t, 2H, *J* = 7.4 Hz), 7.29 (t, 1H, *J* = 7.4 Hz), 7.21 (d, 2H, *J* = 7.1 Hz), 3.68 (d, 1H, *J* = 2.0 Hz); $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 125 MHz): δ 200.1, 132.8, 130.1, 129.2, 127.6, 50.7.

1-octanal **(4p)[18a]:**

Yield 92% (118 mg); Clear liquid; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.54 (m, 1H), δ 2.27 (t, 2H, *J* = 7.1 Hz), 1.49 – 1.41 (m, 2H), 1.21 – 1.07 (m, 8H), 0.73 (t, 3H, *J* = 6.4 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 202.3, 42.2, 30.1, 27.5, 27.5, 21.0, 20.5, 12.2.

Cyclohexanone **(4q)[18a]:**

Yield 94% (92 mg); Pale yellow liquid; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.31 – 2.18 (m, 4H), 1.83 – 1.74 (m, 4H), 1.68 – 1.59 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 212.3, 41.8, 26.9, 24.9.

1-nitroso-2,4-dihydro-*1H*-benzo[*d*][1,3]oxazine **(4s'):**

Yield 81% (66 mg, 0.5 mmol scale); Pale yellow solid; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, 1H, *J* = 8.2 Hz), 7.38 (t, 1H, *J* = 7.8 Hz), 7.28 (t, 1H, *J* = 7.5 Hz), 7.15 (d, 1H, *J* = 7.5 Hz), 5.43 (s, 2H), 4.86 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 135.0, 128.8, 126.5, 125.2, 122.7, 115.4, 73.7, 67.8; IR (neat, cm^{-1}): 3071, 2971, 2867, 2853, 1458; HRMS (IT-TOF) m/z: $[M+H]^+$ Calcd for $C_8H_9N_2O_2$ 165.0659; Found 165.0654

Diol oxidation products:

dihydrofuran-2(3H)-one **(6a)[15e]:**

Yield 88% (76 mg, 1 mmol scale); Clear liquid; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.27 (t, 2H, *J* = 7.1 Hz), 2.41 (t, 2H, *J* = 8.2 Hz), 2.30 – 2.11 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 177.8, 68.5, 27.7, 22.0.

1,4-dioxan-2-one **(6b)[15e]:**

Yield 90% (92 mg, 1 mmol scale); Clear liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.52 – 4.44 (m, 2H), 4.37 (s, 2H), 3.90 – 3.82 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 166.6, 68.6, 66.4, 62.7.

Other compounds:

1H-benzo[d]imidazole **(7a)[43]:**

Yield 54% (13 mg, 0.2 mmol scale); Brown solid; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (s, 1H), 7.71 – 7.62 (m, 2H), 7.34 – 7.27 (m, 2H), 5.62 (br, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 140.7, 137.7, 123.0, 115.6

1D-benzo[d]imidazole **(7a-D):**

Yield 26% (6 mg, 0.2 mmol scale); Brown solid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (dd, 2H, J = 5.9, 3.1 Hz), 7.30 (dd, 2H, J = 6.1, 3.1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 139.0, 123.0, 115.7; ^{2}H NMR (NONE, 46 MHz) δ 8.32; IR (neat, cm^{-1}): 3138, 3025, 2960, 2767, 2597, 1619, 1435; HRMS (IT-TOF) m/z: $[M+H]^+$ Calcd for $C_7H_8N_2$ 120.0682; Found 120.0676

ASSOCIATED CONTENT

Supporting Information.

NMR spectral figures and details of the deuterium KIE measurement and ion chromatography

AUTHOR INFORMATION

Corresponding Author

* Email for FWF: ffoss@uta.edu

Notes

The authors declare no competing financial interest**.**

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