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Selective Oxidation of Exogenous Substrates by a Bis-Cu(III) Bis-Oxide Complex: Mechanism and Scope

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Abstract

Cu(III)₂(μ-O)₂ bis-oxides (**O**) form spontaneously by direct oxygenation of nitrogen-chelated Cu(I) species and constitute a diverse class of versatile 2e⁻/2H⁺ oxidants, but while these species have attracted attention as biomimetic models for dinuclear Cu enzymes, reactivity is typically limited to intramolecular ligand oxidation, and systems exhibiting synthetically useful reactivity with exogenous substrates are limited. **O**_{TMPD} (TMPD = N¹, N¹, N³, N³-tetramethylpropane-1,3-diamine) presents an exception, readily oxidizing a diverse array of exogenous substrates, including primary alcohols and amines selectively over their secondary counterparts in good yields. Mechanistic and DFT analyses suggest substrate oxidation proceeds through initial axial coordination, followed by rate limiting rotation to position the substrate in the Cu(III) equatorial plane, whereupon rapid deprotonation and oxidation by net hydride transfer occurs. Together, the results suggest the selectivity and broad substrate scope unique to **O**_{TMPD} are best attributed to the combination of ligand flexibility, limited steric demands, and ligand oxidative stability. In keeping with the absence of rate limiting C–H scission, **O**_{TMPD} exhibits a marked *insensitivity* to the strength of the substrate C^α–H bond, readily oxidizing benzyl alcohol and 1 octanol at near identical rates.

Graphical Abstract

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Declarations of interest
none

Keywords

Copper-dioxygen; Selective oxidation; Alcohol oxidation; Amine oxidation; Aerobic oxidation; C–H bond activation

1. Introduction

$\text{Cu(III)}_2(\mu\text{-O})_2$ bis-oxide (**O**) species formed through the direct oxygenation of nitrogen-ligated Cu(I) complexes have attracted attention over the past several decades as systems biomimetic of binuclear copper enzymes. This class of Cu/O₂ intermediates is the most prevalent in synthetic systems, stabilized by bi-, tri- and tetra-dentate amine ligands [1, 2]. Though established as powerful and versatile $2\text{e}^-/2\text{H}^+$ oxidants, their activity of characterized **O** species is limited largely to thermal decomposition via intramolecular oxidation of the supporting ligands. Systems reported to effect reactivity directed towards *exogenous* substrates are limited and focus on net O-atom transfer and oxidation of non-coordinating substrates or anions [2, 3]. Whereas mechanisms have been proposed for oxygenations [4–6] and oxidations of hydrocarbons [7] and phenols ($1\text{e}^-/1\text{H}^+$ C–C coupling) [8], detailed mechanistic studies are absent for substrates such as alcohols and amines. While mechanistic understanding lags substrate scope, promising developments raise the prospect of extension to catalytic oxidations as well. Itoh has reported catalytic hydrocarbon oxidation by an **O** species using H₂O₂ [9], and Lumb has reported catalytic reactivity with phenols using a $\mu\text{-}\eta^2, \eta^2\text{-(O}_2\text{)}$ dicopper(II) (***S*P**) species, which is known to exist in equilibrium with its Cu(III) **O** isomer when weakly coordinating anions are used (*e.g.*, SbF₆[−]) [10]. Learning how intermolecular oxidation of more coordinating substrates by **O** species occurs will allow further exploitation of their oxidizing potential in synthetic transformations.

We report herein a more detailed study of the reactivity of **O**_{TMPD} with exogenous substrates, including a proposed mechanism of selective alcohol and amine oxidation [11]. **O**_{TMPD} exhibits not only relatively high stoichiometric conversions of alcohol and alkoxide substrates to the corresponding ketone and aldehyde products (Fig. 1), but also high selectivity for primary alcohols over secondary alcohols in the presence of NEt₃. While the rate of alcohol oxidation by **O**_{TMPD} exhibits a marked *insensitivity* to the strength of the C^α–H bond, no appreciable over oxidation beyond the ketone or aldehyde products is observed.

Similar selectivity is observed with primary amines, which react 100 times faster than secondary amines at 193 K.

The broad scope of reactivity and high selectivity exhibited by **O_{TMPD}** remain unprecedented among the limited number of **O** species reported to exhibit exogenous substrate reactivity to date, and inform on the use of the Cu(III)₂O₂ core in effecting the versatile and highly selective stoichiometric oxidation of a wide variety of exogenous substrates *using O₂ as the terminal oxidant*.

2. Experimental

2.1 Chemicals

Solvent purification was performed using a Pure-Solv 400 system (Innovative Technology) or as reported previously [11]. All solvents were stored under a N₂ atmosphere. [Cu^I(MeCN)₄](X) (X = CF₃SO₃⁻, ClO₄⁻, SbF₆⁻, PF₆⁻, BF₄⁻) and [Cu^I(PhCN)₄](X) (X = CF₃SO₃⁻, ClO₄⁻) were synthesized by a variation of literature methods [12]. Preparation and manipulation of Cu(I) complexes was performed in a N₂ dry box with [O₂] < 1.0 ppm (Braun). Low-temperature UV/Vis spectra were collected using a Varian Cary 50 Scan spectrophotometer fitted with fiber-optic leads and custom-designed quartz probes (1 cm and 0.1 cm pathlengths, Hellma) in custom-designed sample cells (ChemGlass). Variable low temperature studies used an FTS cooling bath (Kinetics Thermal Systems, MC480A1). Solution ¹H NMR measurements were performed using a Varian XL 400 MHz spectrometer using TMS as an internal reference. GC-MS analysis was performed using an HP 5970 instrument equipped with an AT-5 (ALLTECH) column and mass-selective detector. The purity of ligands and quantification of reaction products were assessed by GC using an HP-5890 instrument equipped with an HP DB1 column and FID detector. Benzonitrile was used as an internal standard for alcohols, and acetophenone for amines.

N¹, N¹, N³, N³-tetramethylpropane-1,3-diamine (LTMPD): LTMPD (Sigma-Aldrich, 99%) was stirred overnight over sodium hydride and distilled under vacuum (0.1 mm Hg). The ligand purity was >99.5% by GC/GC-MS. GC-MS: [60 °C (1 min) to 180 °C (2 min) at 30 °C • min⁻¹]; t_r = 4.5 min (130, M⁺).

N¹, N¹, N³, N³, 2, 2-hexamethylpropane-1,3-diamine (LHMPD): 2,2-dimethylpropane-1,3-diamine (5.0 g, Aldrich) was added to a solution of HCOOH (10 equiv) and HCHO (37% aqueous solution, 10 equiv), and was heated at reflux overnight, whereupon the solution was made basic by addition of NaOH (2 M, aqueous) and extracted into diethyl ether (4 × 25 mL). The ether solution was dried over K₂CO₃, and the solvent removed by rotary evaporation. The resulting oil was distilled *in vacuo* from CaH₂ to afford the product as a colorless oil (75%). ¹H NMR(CDCl₃, 400 MHz): δ 0.9 (m, 6 H); 2.0 (m, 4 H); 2.2 (m, 12 H). GC-MS: [60 °C (1 min) to 180 °C (2 min) at 30 °C • min⁻¹]; t_r = 5.2 min (158, M⁺).

[(LTMPD)Cu^I(MeCN)](X) (X = CF₃SO₃⁻, ClO₄⁻, SbF₆⁻, PF₆⁻, BF₄⁻);
[(LTMPD)Cu^I(PhCN)](X) (X = CF₃SO₃⁻, ClO₄⁻): Equimolar amounts of either [Cu^I(MeCN)₄](X) or [Cu^I(PhCN)₄](X) and **L_{TMPD}** were combined as CH₂Cl₂ solutions in a

N_2 dry box immediately before use. $[(\text{LTMPD})\text{Cu}^{\text{I}}(\text{MeCN})](\text{CF}_3\text{SO}_3)$: ^1H NMR(CDCl_3 , 400 MHz), δ 1.7 (m, 4 H); 2.1 (s, 9 H); 2.5 (s, 14 H); 2.65 (m, 3 H).

O Species, $[\text{L}_2\text{Cu}(\text{III})_2(\text{O})_2]^{2+}$: $\text{OTMPD}^{\text{MeCN}}(\text{X})_2$, LTMPD , MeCN , $\text{X} = (\text{CF}_3\text{SO}_3^-, \text{ClO}_4^-, \text{SbF}_6^-, \text{PF}_6^-, \text{BF}_4^-)$

$\text{OTMPD}^{\text{PhCN}}(\text{X})_2$, LTMPD , PhCN , $\text{X} = (\text{CF}_3\text{SO}_3^-, \text{ClO}_4^-, \text{SbF}_6^-)$

$\text{OHMPD}^{\text{MeCN}}(\text{X})_2$, LHMPD , MeCN , $\text{X} = (\text{CF}_3\text{SO}_3^-)$

A 1.0 or 0.1 mM solution of pre mixed 1:1 $[\text{Cu}^{\text{I}}(\text{MeCN})_4](\text{X})$ or $[\text{Cu}^{\text{I}}(\text{PhCN})_4](\text{X})$ and diamine ligand in CH_2Cl_2 was oxygenated by bubbling O_2 through a needle at 193 K, generating the **O** species as intense yellow solutions with characteristic optical features at *ca.* 300 nm and *ca.* 400 nm (Table 1). **O** species can be obtained in higher yields when pre-mixed 1:1 Cu(I)-ligand solutions are injected into pre-oxygenated solvent, though this methodology is not always practical for many of the experiments reported herein.

PhCH₂OD, PhCD₂OH, PhCH(D)OH, and PhCH(D)O⁻: PhCH₂OD: NaH (1.1 equiv) was added to PhCH₂OH (neat) and stirred until H₂ evolution ceased. The resulting solution was quenched using excess D₂O (99.9%). The alcohol was extracted into dry ether, the ether extract was dried over K₂CO₃, and the solvent was removed to afford PhCH₂OD (>98% D by ^1H NMR). PhCD₂OH, PhCH(D)OH, and PhCH(D)O⁻ salts were prepared by literature methods [11, 13].

2.2 Oxidation of Exogenous Substrates

Solutions of $\text{OTMPD}^{\text{MeCN}}(\text{X})_2$ and $\text{OTMPD}^{\text{PhCN}}(\text{X})_2$ (10 mM, 5 mL in CH_2Cl_2) were prepared from the pre-mixed 1:1 Cu(I)-ligand precursors by addition of excess O_2 (1 atm) at 193 K. Two equiv of substrate per oxidant were used unless otherwise noted. For anaerobic substrate oxidations, excess O_2 was removed and the solution was flushed with N_2 prior to substrate addition. Similar product distributions were obtained for alcohol oxidation reactions performed under O_2 and N_2 at 233 K. Alcohol oxidations without NEt₃ were carried out at 233 K, and all other reactions were carried out under N_2 at 193 K unless otherwise noted. The resulting reaction mixtures were quenched by dropwise addition of aqueous ammonia (30%) until the CH_2Cl_2 layer turned colorless, and passed through a column of neutral activated alumina (Brockmann I, ~150 mesh, 58 Å) followed by MeOH (2 mL). The copper product is retained, and the organic products elute. The reaction mixture was analyzed by GC/GC-MS. Mass recovery of the products was greater than 90% based on addition of an internal calibrant (benzonitrile for alcohols, acetophenone for amines).

Substrate chase experiments were performed at 293 K in the presence of NEt₃ (2 equiv), or at 233 K in the absence of NEt₃. In each experiment, a second alcohol substrate was injected 2 min after addition of the first. The relative amounts of the corresponding substituted benzaldehyde products were analyzed by GC-MS.

2.3 Kinetic Isotope Effects

The intramolecular kinetic isotope effect (KIE) for benzyl alcohol oxidation by $\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ was determined from the product ratio of PhCDO and PhCHO using PhC(H)(D)OH (2 equiv, >98% D as determined by GC-MS) as the substrate. The product ratio was determined by a least-squares component analysis of the product aldehyde, using the 105–108 peak intensities and component spectra of authentic samples. The intramolecular KIE for the sodium salt of PhC(H)(D)O[−] was determined using the same method. The intermolecular KIE was obtained by addition of a 1:1 mixture of PhCH₂OH:PhCD₂OH to $\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ at varied temperatures (193 – 253 K). The mixture of PhCDO and PhCHO products was analyzed as above for three independent reaction mixtures. The decay of the *ca.* 400 nm optical band of O_{TMPD} (0.1 mM) was used to determine the relative rates of oxidation for PhCH₂OH ($k_H = 3.9 \times 10^{-4} \text{ s}^{-1}$) relative to PhCD₂OH ($k_D = 3.6 \times 10^{-4} \text{ s}^{-1}$) (KIE = 1.1 at 253 K, CH₂Cl₂, 40 equiv substrate), and PhCH₂OH ($k_H = 3.5 \times 10^{-4} \text{ s}^{-1}$) relative to PhCH₂OD ($k_D = 3.7 \times 10^{-4} \text{ s}^{-1}$) (KIE = 1 ± 0.1 at 233 K, 40 equiv substrate). Each rate constant is reported as the average of two independent reactions. The same methodology was used to determine the rates of oxidation of PhCH₂OH ($k_H = 4.7 \times 10^{-4} \text{ s}^{-1}$) and PhCH₂OD ($k_D = 1.3 \times 10^{-4} \text{ s}^{-1}$) in the presence of 2 equiv NEt₃ (KIE = 3.6 at 213 K, 20 equiv substrate), the rates of oxidation of PhCH₂OH and PhCD₂OH in the presence of 2 equiv NEt₃ (KIE = 1 at 193 K, 2 equiv substrate), and the rates of oxidation of PhCH₂ONa ($3.7 \times 10^{-1} \text{ s}^{-1}$) and PhCD₂ONa ($9.0 \times 10^{-2} \text{ s}^{-1}$) at 193 K (KIE = 4.1, 2 equiv substrate).

2.4 O_{TMPD} Thermal Decomposition

The decomposition kinetics of $\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{X})_2$ and $\text{O}_{\text{TMPD}}^{\text{PhCN}} \cdot (\text{X})_2$ in the absence of added substrate were measured by monitoring the decay of their characteristic 400 nm optical features (0.1 mM or 1.0 mM) in CH₂Cl₂. $\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{X})_2$ and $\text{O}_{\text{TMPD}}^{\text{PhCN}} \cdot (\text{X})_2$ were generated by oxygenation at 193 K, and then transferred to a second cooling bath at a predetermined temperature. Thermal equilibration from 193 K to 253 K required *ca.* 2 min as assessed by an OMEGA temperature probe inserted directly into the solution. Data for kinetic analysis were collected only after thermal equilibration was complete. The rate constants for thermal decomposition were obtained using SPECFIT [14] through a multi wavelength (300–500 nm) component analysis. Among all data sets, the number of significant eigenvectors calculated was generally two. For all data sets, good first order (A → B) fits were obtained. Thermal decomposition products were isolated by the method described previously (Section 2.2). The ligand products were analyzed by GC/GC MS. In all cases, ligand mass recovery was >90% relative to internal standards added to the solutions. Only a small amount of ligand dealkylation was observed (<5%). L_{TMPD} : [60 °C (1 min) to 180 °C (2 min) at 30 °C • min^{−1}]; $t_r = 4.5 \text{ min}$ (130, M⁺). $\text{L}_{\text{monodemethylated TMPD}}$: [50 °C (1 min) at 20 °C • min^{−1} to 120 °C (1 min)]; $t_r = 2.4 \text{ min}$ (116, M⁺).

2.5 Computational Methods

DFT calculations were performed using Gaussian 09, Revision D.01 [15]. Optimizations were performed using the ω B97-xD functional [16] and def2TZVP basis set [17] with SMD implicit solvation in CH₂Cl₂ [18], and minima verified by frequency calculations by the same method. Single point energy calculations were performed using analogous

methodology with the inclusion of Douglas-Kroll-Hess second-order (DKH2) scalar relativistic corrections [19–23]. Natural Bonding Orbitals were calculated using NBO version 3.1 [24], and orbital visualization was performed in GaussView 5 and LUMO [25]. Preliminary transition state searches were performed using the ω B97-xD functional and def2SVP basis set with SMD implicit solvation in CH_2Cl_2 . Transition states were verified by IRC calculations using the same methodology.

3. Results

3.1. Characterization

Reaction of Cu(I) precursors $[(\text{L}_{\text{TMPD}})\text{Cu}^{\text{I}}(\text{MeCN})](\text{X})$ ($\text{X} = \text{CF}_3\text{SO}_3^-$, ClO_4^- , SbF_6^- , PF_6^- , BF_4^-) and $[(\text{L}_{\text{TMPD}})\text{Cu}^{\text{I}}(\text{PhCN})](\text{X})$ ($\text{X} = \text{CF}_3\text{SO}_3^-$, ClO_4^-) with O_2 at 193 K in aprotic solvents yielded yellow-brown solutions typical of $[\text{L}_2\text{Cu}(\text{III})_2\text{O}_2]^{2+}$ (**O**) complexes, featuring intense LMCT features at *ca.* 300 nm ($16,000 \text{ M}^{-1} \text{ cm}^{-1}$) and *ca.* 400 nm ($24,000 \text{ M}^{-1} \text{ cm}^{-1}$) characteristic of **O**_{TMPD} (Table 1).

3.2. **O**_{TMPD} and **O**_{HMPD} Thermal Decomposition

Thermal decomposition of alkylamine-ligated **O** species generally occurs at temperatures greater than 233 K, proceeding typically through oxidative N-dealkylation of the ligand. The mechanism of this reaction is generally ascribed to rate-limiting HAT from an $\text{NC}^\alpha\text{--H}$ bond to a bridging oxide ligand of the Cu_2O_2 core [26–28].

Thermal decomposition of **O**_{TMPD}^{MeCN}·(CF_3SO_3)₂ (193 K – 253 K) yielded Eyring activation parameters $H^\ddagger = 13.1 \text{ kcal} \cdot \text{mol}^{-1}$ and $S^\ddagger = 22 \text{ cal} \cdot \text{mol}^{-1}$ ($[\text{Cu}] = 0.1 \text{ mM}$, CF_3SO_3^- , CH_2Cl_2). Analysis of the ligand decomposition products, however, revealed only 5% ligand dealkylation, as compared with the 50% yield anticipated for a $2e^-/2\text{H}^+$ oxidant. Apart from the monodemethylated ligand, no other ligand oxidation product was detected by GC. The thermal decay rates were found to be independent of the weakly coordinating counteranions examined, as well as the nitrile ligands used in the Cu(I) precursors (MeCN, PhCN; Fig. 2). The analogous **O**_{HMPD} species formed with **L**_{HMPD} was found to decompose nearly 5 times faster than **O**_{TMPD}^{MeCN}·(CF_3SO_3)₂ or **O**_{TMPD}^{PhCN}·(CF_3SO_3)₂ under similar conditions.

3.3 Reactivity with PPh_3 , Phenols, Catechols, and Hydrocarbons

Complexes **O**_{TMPD}^{MeCN}·(**X**)₂ and **O**_{TMPD}^{PhCN}·(**X**)₂ act as mild oxidants toward a variety of bonds. **O**_{TMPD}^{MeCN}·(CF_3SO_3)₂ reacts efficiently with PPh_3 under N_2 to form PPh_3O , with 2,4-di-*tert*-butylphenol to generate the C–C coupled bis-phenol, with 2,4-di-*tert*-butylcatechol to generate 3,5-di-*tert*-butylbenzoquinone, and with 4-methylthiocrisol to generate 1,2-di-*p*-tolyl disulfane (Fig. 3) [11]. Though the reactions observed with thiols and phenols are consistent with a HAT mechanism, **O**_{TMPD}^{MeCN}·(CF_3SO_3)₂ exhibits no apparent reactivity over hrs with even weak C–H bonds [29] such as N-methyl-9,10-dihydroacridine (C–H BDE = $80 \text{ kcal} \cdot \text{mol}^{-1}$), dihydroanthracene (C–H BDE = $78 \text{ kcal} \cdot \text{mol}^{-1}$), and 1,4 cyclohexadiene (C–H BDE = $76 \text{ kcal} \cdot \text{mol}^{-1}$).

3.4 Alcohol Oxidation

$\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ reacts with a variety of alcohols to selectively generate aldehyde and ketone products, with 60–70% product yields after *ca.* 5 h at 233 K (2:1 substrate:oxidant ratio, CH_2Cl_2 , yields based on oxidant) (Fig. 4 and Fig. 5).

While independent of counteranion, these yields exhibit a surprising dependence on the choice of Cu(I) precursor (Fig. 5); whereas the reaction of benzyl alcohol with $\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ ($[(\text{L}_{\text{TMPD}})_2\text{Cu}_2\text{O}_2](\text{CF}_3\text{SO}_3)_2$), prepared from $[(\text{L}_{\text{TMPD}})\text{Cu}^{\text{I}}(\text{MeCN})](\text{CF}_3\text{SO}_3)$, proceeds with 60% substrate conversion, these yields increase to 90% with $\text{O}_{\text{TMPD}}^{\text{PhCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ ($[(\text{L}_{\text{TMPD}})_2\text{Cu}_2\text{O}_2](\text{CF}_3\text{SO}_3)_2$), prepared from $[(\text{L}_{\text{TMPD}})\text{Cu}^{\text{I}}(\text{PhCN})](\text{CF}_3\text{SO}_3)$. These yields do not change appreciably using deuterated PhCN-d_5 or MeCN-d_3 in the oxidant preparation.

As O_{TMPD} does not react appreciably with either aldehydes or ketones, synthetically useful yields (>90%) are accessible using an excess of oxidant per substrate; 1-octanol, for instance, yielded >95% octaldehyde using 2.5 equiv of $\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ relative to 1-octanol. Under the excess oxidant conditions, at most 5% over-oxidized products were detected by GC.

$\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ also exhibits a *ca.* 2:1 selectivity for primary over secondary alcohols assessed by intermolecular competitions (1-octanol versus 2-octanol, Fig. 6). Addition of 2 equiv of NEt_3 increases this selectivity to 18:1, and accelerates the reaction substantially such that reaction proceeds with high yields within 3 h at 193 K rather than 3–5 h at 233 K. 2 equiv of 2,6-lutidine also increases the selectivity in favor of primary alcohols, but to a more staid 7:1 ratio.

Whereas $\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ exhibits uniform selectivity for primary over secondary alcohols, a remarkable *absence* of discrimination is observed *among* primary alcohols. While 1-octanol is generally regarded as less oxidizable than benzyl alcohol due to its substantially stronger $\text{C}^\alpha\text{--H}$ BDE [29], the reaction of $\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ with a 1:1 alcohol mixture affords a 1:1 mixture of 1-octaldehyde and benzaldehyde at an overall conversion of 60%, comparable to that observed for the oxidation of benzyl alcohol alone (Fig. 6).

Intramolecular competition experiments among primary alcohols and between primary and secondary alcohols afforded similar results (Fig. 6). Oxidation of 1,4-benzylidimethanol in the absence of NEt_3 yielded a statistical 2:1 mixture of the mono-aldehyde and di-aldehyde; addition of excess oxidant (4 equiv per substrate) affords exclusive di-aldehyde product in a 60% overall yield based on substrate. Likewise, oxidation of 1,5-hexanediol by $\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ with 2 equiv of NEt_3 per diol affords 5-hydroxyhexanal and 5-hydroxy-2-hexanone in a 20:1 ratio, along with some lactone product generated by a secondary oxidation of the cyclized 5-hydroxyhexanal (Fig. 6). This indicates > 25:1 primary:secondary selectivity in oxidizing 1,5-hexanediol under these conditions. By contrast, the selectivity using a Swern oxidation, a standard organic transformation of alcohols to aldehydes, is in our hands only 2:1. Near-complete conversion of 1,5-hexanediol to the lactone is possible using excess $\text{O}_{\text{TMPD}}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ (4 equiv per diol).

3.5 Reactivity with Amines

In addition to alcohols, $\text{OTMPD}^{\text{MeCN}}\text{-(CF}_3\text{SO}_3)_2$ reacts selectively with primary and secondary amines to generate both $4\text{e}^-/4\text{H}^+$ and $2\text{e}^-/2\text{H}^+$ oxidation products, respectively. Primary amines, such as benzylamine and benzyldiethylamine, react in a 1:1 substrate:oxidant ratio to yield their nitrile products, benzonitrile and benzyldiethylcyanide, respectively, consistent with the intermediacy of an imine product (Fig. 7). As observed among alcohols, secondary benzylamines react 100 times more slowly than a primary benzylamine. No appreciable tertiary amine oxidation is observed.

3.6 Mechanistic Studies of Alcohol Oxidation

3.6.1 Kinetic Model and Biphasic Reaction Kinetics—The reaction rate of $\text{OTMPD}^{\text{MeCN}}\text{-(CF}_3\text{SO}_3)_2$ with benzyl alcohol under pseudo-first order conditions of substrate (20 equiv) at 233 K increased linearly with the concentration of both $\text{OTMPD}^{\text{MeCN}}\text{-(CF}_3\text{SO}_3)_2$ and benzyl alcohol (Fig. 8), consistent with a first-order rate dependence of each species. The optical traces of the decay of $\text{OTMPD}^{\text{MeCN}}\text{-(CF}_3\text{SO}_3)_2$ over time fit best an $\text{A} \rightarrow \text{B} \rightarrow \text{C}$ kinetic model involving an initial slower step preceding a rate limiting step, yielding pseudo first order rate constants $k_{\text{obs}} = 1.5 \times 10^{-3} \text{ s}^{-1}$ for the initial $\text{A} \rightarrow \text{B}$ step, and $k_{\text{obs}} = 5.3 \times 10^{-4} \text{ s}^{-1}$ for the second step ($\text{B} \rightarrow \text{C}$).

3.6.2. Chase Experiments—The biphasic kinetics observed suggest an initial, fast substrate coordination step. A series of substrate chase experiments probed the reversibility of this postulated substrate binding step in the presence and absence of added NEt_3 . In each set of experiments, $\text{OTMPD}^{\text{MeCN}}\text{-(CF}_3\text{SO}_3)_2$ was allowed to react with a twofold excess of total alcohol to assure incomplete substrate conversion. The alcohols were added sequentially, 2 min apart, with the product ratio determined by GC (Table 2).

Whereas the reaction of **1** with a 1:1 mixture of *p*-CF₃ benzyl alcohol: *p*-H benzyl alcohol yields a nearly equimolar mixture of the respective oxidation products (0.9:1.1), chasing *p*-H benzyl alcohol with its *p*-CF₃ analog afforded a 1.6:1 excess of the *p*-H product, and chasing *p*-CF₃ benzyl alcohol with *p*-H benzyl alcohol afforded a similar 1.5:1 excess of the *p*-CF₃ product. Similar selectivity was observed upon addition of NEt_3 : chasing *p*-H benzyl alcohol with *p*-CF₃ benzyl alcohol afforded a 1.4:1 excess of the *p*-H product, as compared to a slightly higher 2:1 excess of the *p*-CF₃ product for the reverse experiment.

3.6.3. Kinetic Isotope Effects and Hammett Analysis—Under the hypothesis that $\text{C}^{\alpha}\text{-H}$ cleavage might prove rate limiting, the *intermolecular* competition of PhCH_2OH with PhCD_2OH was examined over a temperature range of 193–253 K. Independent optical monitoring of the pseudo first order decay of $\text{OTMPD}^{\text{MeCN}}\text{-(CF}_3\text{SO}_3)_2$ (1 equiv) in the presence of excess PhCH_2OH or PhCD_2OH (40 equiv) gave nearly identical rates with a KIE ($k_{\text{H}}/k_{\text{D}}$) of 1.1 at 253 K. Comparable KIEs were obtained for an *intermolecular* competitive experiment using a 1:1 mixture of PhCH_2OH with PhCD_2OH over a temperature range of 193–253 K. A primary *intramolecular* KIE occurs in the oxidation of PhC(H)(D)OH over a similar temperature range ($k_{\text{H}}/k_{\text{D}} = 4.8$ at 233 K), and an identical primary *intramolecular* KIE was observed using the sodium salt of PhC(H)(D)O^- (Fig. 9). In light of the rate acceleration observed in the presence of base, the involvement of

rate-limiting O–H bond cleavage was interrogated as well; competition of PhCH₂OH with PhCH₂OD in independent absolute rate experiments yielded a KIE (k_H/k_D) of 1 ± 0.1 at 233 K (0.05 mM **O**^{MeCN}_{TMPD}·(CF₃SO₃)₂, 40 equiv alcohol per complex).

A Hammett analysis further probed the nature of the rate limiting transition state in the oxidation. A series of *para*-substituted benzyl alcohols (*p*-F, *p*-Cl, *p*-H, *p*-Me, *p*-OMe) [30] yielded a small negative ρ value of -0.2 (Fig. 9).

3.6.4. Radical Clocks—Radical clocks provide an opportunity to probe the involvement of a substrate radical following a putative product-determining C–H scission. With the intermediacy of a long-lived radical intermediate, ring-opened products are anticipated [31–33]. Cyclobutanol and cyclopropyl(phenyl)methanol (2 equiv) are oxidized efficiently by **O**^{MeCN}_{TMPD}·(CF₃SO₃)₂ (1 equiv) at 233 K to their carbonyl products (Fig. 4). In both cases, no radical rearrangement products could be detected by GC.

3.6.5 Reactivity Summary—**O**_{TMPD} formed by the direct oxygenation of Cu(I) in the presence of **L**_{TMPD} reacts selectively with primary alcohols and amines to yield their respective 2e[−]/2H⁺ and 4e[−]/4H⁺ oxidation products (aldehydes and nitriles) in 60–90% yields (Section 3.4 and Section 3.5). With alcohols, higher yields are possible using either **O**^{PhCN}_{TMPD}·(CF₃SO₃)₂, in which the Cu(I) precursor is ligated by benzonitrile rather than acetonitrile, or an excess of **O**^{MeCN}_{TMPD}·(CF₃SO₃)₂. While the reaction is highly selective for primary substrates over their secondary congeners, a striking lack of discrimination is observed between 1-octanol and benzyl alcohol, despite the dramatically different C^α–H bond strengths. Oxidation of tertiary amines, tertiary alcohols, and hydrocarbons is not observed. The oxidation reaction is dramatically accelerated and its selectivity enhanced by the addition of NEt₃, with reactions complete in 3 h at 193 K. Indeed, 1,5-hexanediol can be oxidized to its lactone product in high yields (4e[−]/4H⁺ oxidation) with a primary-to-secondary selectivity of >25:1 using a twofold excess of oxidant and 2 equiv of NEt₃.

Kinetic studies by optical spectroscopy suggest an initial binding event prior to the rate-limiting step, and mechanistic studies with deuterated benzyl alcohols indicate that the rate-limiting step (RLS) in the absence of NEt₃ does not involve O–H or C–H bond cleavage. Intramolecular KIEs indicate that the product determining step (PDS) does involve C–H bond cleavage, through either a net hydride transfer or short lived radical intermediate (Section 3.6).

4. Discussion

4.1. Exogenous Reactivity

While several earlier studies probed the reactivity of equilibrium mixtures of **O** and isomeric side-on peroxide μ - η^2, η^2 -(O₂)dicopper(II) (**^SP**) species [2, 34], the first detailed reactivity study of a characterized “spectroscopically pure” Cu(III)₂(μ -O)₂ species with exogenous substrates used the bidentate diamine ligand **L**_{TMPD} of this study [11]. While the ability of an **O** species to effect *intramolecular* ligand oxidation is well established [2], the **L**_{TMPD} **O** species (**O**_{TMPD}) efficiently projects its oxidizing ability to *exogenous* substrates, evidenced

by limited intramolecular ligand demethylation upon thermal decomposition (Section 3.2) [27].

More recent reports extend the oxidative substrate scope of **O** species: *ortho* hydroxylation of phenolic substrates to catechols and quinones, the oxidative reactivity effected by the binuclear copper enzyme tyrosinase [6, 8]; oxidation of weak O–H and C–H bonds [7, 35–38]; catalytic oxidation of cyclohexane to cyclohexanol and cyclohexanone using H₂O₂ as the oxidant [9] and stoichiometric oxidation of THF to THF-OH and γ -butyrolactone [39], as well as oxidation of toluene to benzyl alcohol [40]. Regioselective and enantioselective oxidative dearomatization reactions (net O-atom transfer) are also possible, including the first asymmetric synthesis of the azaphilone natural products (+)-sclerotiorin and (+)-8-*O*-methylsclerotiorinamine and the preparation of several unnatural azaphilones, with asymmetric induction achieved using sparteine ligands [41–43]. The reactions of characterized **O** species are joined by numerous catalytic oxidations involving Cu(I) salts and O₂ in which the active oxidant species remain unclear [44]. Yet despite ongoing discovery of new reactivity, a dearth of detailed mechanistic studies of exogenous substrate oxidation by **O** species persists [2].

Most **O** species formed with peralkylated amines have a limited stability at 233 K, the temperature investigated for the initial alcohol oxidations in this study. Yet, **O**_{TMPD} in CH₂Cl₂ is remarkably stable at 233 K relative to other **O** species, which correlates with its stronger methyl NC ^{α} –H bonds as compared to other alkyl substituents. Indeed, **O** species with ligands possessing weaker NC ^{α} –H bonds thermally decay faster, consistent with rate-limiting *intramolecular* HAT to the oxide ligand of the Cu₂O₂ core. To our knowledge, the only more thermally stable dicationic **O** species is **OTMCHD** [45].

An Eyring analysis of the first order thermal decay rates of **OTMPD**^{MeCN}·(CF₃SO₃)₂ (193–253 K, [Cu] = 0.1 mM, CH₂Cl₂) provides activation parameters of $H^\ddagger = 13.1 \text{ kcal mol}^{-1}$ and $S^\ddagger = -22 \text{ cal} \cdot \text{mol}^{-1}$. While the enthalpic term is lower than other systems, the large negative entropic term contributes substantially to the barrier of ligand C–H activation [45, 46]. Ligand product analysis following thermal decay reveals only 5% ligand demethylation, rather than 50% assuming the Cu₂O₂ core serves as a 2e[−]/2H⁺ oxidant. At parity of N-alkyl substituents, three major factors may influence the decay mechanism: exogenous nitrile ligands (MeCN/PhCN) from the Cu(I) starting material, weakly coordinating counteranions, and the structure of the ligating diamine. The decay rates of **OTMPD**^{MeCN}(X)₂ and **OTMPD**^{PhCN}(X)₂ are effectively identical across all anions investigated (Fig. 2), excluding the first two possibilities. A reduction in ligand flexibility at parity of donor moieties is possible by introduction of two methyl groups in the propylene backbone; **OHMPD**^{MeCN}(CF₃SO₃)₂ decomposes nearly 5 times faster than **OTMPD**^{MeCN}·(CF₃SO₃)₂ under similar reaction conditions (Fig. 2). An increase in ligand conformational flexibility offers one explanation for the increase in thermal stability with **L**_{TMPD}, presumably through attenuation of ligand self oxidation, allowing oxidizing capacity to be directed instead towards exogenous substrates. Indeed, alcohol oxidation yields with **OHMPD**^{MeCN}·(CF₃SO₃)₂ are at best one third those with **OTMPD**^{MeCN}·(CF₃SO₃)₂.

4.2. Mechanistic Analysis with Exogenous Substrates

The ability of $\mathbf{O}_{\text{TMPD}}$ to effect such a broad range of selective and efficient oxidations, including oxidation of alcohols, stands in contrast with other known alkylamine-ligated $\mathbf{O}$ species [45]. The reactivity of $\mathbf{O}_{\text{TMPD}}$ is foremost consistent with increased ligand flexibility (*vide supra*) and axial substrate accessibility to the $\mathbf{O}_{\text{TMPD}}$ core.

This postulate is structurally supported by a fifth Cu–N/O scattering interaction needed in the EXAFS model at each Cu(III), consistent with association of a counteranion (2.32 Å, Fig. 10) [11]. A similar coordinated counteranion is observed by single crystal X-ray diffraction at the $\mathbf{L}_{\text{TMPD}}$ ligated Cu(III) in a mixed-ligand β -diketiminato/TMPD Cu(III)₂(μ -O)₂ structure (CF_3SO_3^- , Cu $\cdots$ O = 2.61 Å) [47]. Such axial coordination is not observed in more sterically congested diamine-ligated $\mathbf{O}$ species, and is consistent with a more sterically accessible axial approach for coordinating substrates in $\mathbf{O}_{\text{TMPD}}$.

The disposition of the N methyl groups of $\mathbf{O}_{\text{TMPD}}$, however, does preclude *direct* access to the electrophilic O–O σ^* LUMO, colinear with the O–O vector, thereby attenuating reactivity with non-coordinating substrates such as hydrocarbons (Fig. 11) [2, 24, 35]. $\mathbf{O}_{\text{TMPD}}$ reacts selectively with coordinating substrates such as alcohols and amines but exhibits no apparent reactivity with weak hydrocarbon C–H bonds. By contrast, $\mathbf{O}_{\text{PD}}$, with much reduced steric demands (Fig. 11), reacts with weak C–H bonds of exogenous substrates through a rate-limiting C–H scission at 150 K [36]. In this case, DFT calculations support direct access of the C H bond to the electrophilic O–O σ^* LUMO.

The axial accessibility of $\mathbf{O}_{\text{TMPD}}$ is consistent with the biphasic kinetics observed for $\mathbf{O}_{\text{TMPD}}^{\text{MeCN}}(\text{CF}_3\text{SO}_3)_2$ with benzyl alcohol if the fast, initial optical changes are interpreted as a substrate binding event. The small negative Hammett ρ value for *p*-substituted benzyl alcohol oxidations indicates faster reactivity with more donating alcohols, consistent with a stronger binding event as the benzyl alcohols become more electron rich. The significant rate enhancement observed with added alkoxides or added NEt_3 strongly suggests that the mechanism of neutral alcohol oxidation involves initial coordination of the *neutral* substrate. The product mixtures observed in substrate chase experiments, in which a second alcohol is injected 2 minutes after the first, support the reversibility of this binding event.

The LMCT energies of $\mathbf{O}$ species in the 250–400 nm range are most sensitive to equatorial ligation. Addition of an alcohol to $\mathbf{O}_{\text{TMPD}}$ solution slightly attenuates the intensity of the LMCT features, but without an appreciable energy shift (Fig. 12). Such optical behavior is consistent with initial alcohol coordination in an *axial* position. Itoh and Fukuzumi proposed a similar axially coordinated intermediate to an $\mathbf{O}$ species in the oxidation of sulfides to sulfoxides [4]. In this species as well, the initial intermediate exhibits a notable diminution in its LMCT intensities without a significant shift in energy.

The proclivity of $\mathbf{O}_{\text{TMPD}}$ to coordinate exogenous ligands in the axial position finds strong precedent in not only the close anion coordination of CF_3SO_3^- , but also the more recent discovery of facile ligand exchange upon addition of exogenous nitrogenous ligands to $\mathbf{O}_{\text{TMPD}}$ at 150 K [48]. Despite the ability of $\mathbf{O}_{\text{TMPD}}$ to oxidize primary amines at 193 K,

addition of 2 equiv of **L_{PD}** to **O_{TMPD}** at 150 K results in rapid ligand exchange to form **OPD** (Fig. 13). The lack of primary amine oxidation is rationalized by the disposition of the electrophilic **O** LUMO orthogonal to an axial position. A substantial structural reorganization would be required prior to substrate oxidation (Fig. 13). For **L_{PD}**, this reorganizational barrier is evidently sufficiently high to preclude oxidation before decomplexation of the initial ligand and chelation of the Cu(III).

An axially coordinated alcohol requires a similar rotation from its initial orientation into the equatorial Cu₂O₂ plane such that the alcohol C^α-H group is positioned appropriately for oxidation (Fig. 14). As *primary* C-H/D and O-H/D KIEs are not observed using suitably deuterated benzyl alcohols, neither C-H nor O-H cleavage appears ratelimiting. This stands in contrast to the reaction of **OTMED** (Fig. 11), in which C-H bond cleavage *is* rate-limiting [46]. The rate-limiting step for **O_{TMPD}** alcohol oxidation is proposed to be an axial-to-equatorial rotation of the ligated alcohol concurrent with the equatorial-to-axial positioning of one amine group of **L_{TMPD}**. As this axial amine will be associated weakly on the d⁸ Cu(III) center, it provides an incipient base to deprotonate an equatorially ligated alcohol, acidified relative to a free alcohol. The geometric acrobatics required in this rotation and ultimate alcohol deprotonation by one amine group of the ligand highlight an importance of flexibility in the ligand backbone.

This rate-limiting rotation is proposed to be followed by rapid O-H and C-H scission (Fig. 15). The identical primary *intramolecular* KIEs for PhCHDOH and PhCHDO⁻ Li⁺ ($k_H/k_D = 4.8$ at 233 K) are consistent with a shared PDS, which requires alcohol O-H deprotonation *prior* to C-H cleavage. The C-H bond cleavage could proceed through HAT with a triplet transition state, or remain on a single surface from the starting materials to proceed through a net hydride transfer to the Cu₂O₂ core. As cyclobutanol is oxidized cleanly to its ketone without detection of radical rearrangement products, net hydride transfer on a singlet surface is the simplest mechanistic interpretation.

Preliminary DFT calculations at the ωB97-xD/def2SVP level using ethanol as a model substrate are consistent with the mechanism proposed above, implicating an initial, reversible coordination of the neutral alcohol in the axial position, followed by a rate-limiting rotation of the neutral alcohol into the equatorial plane and release of one amine moiety of **L_{TMPD}**. This rate-limiting rotation is followed by a lower barrier deprotonation of the coordinated alcohol to form the equatorially coordinated alkoxide, hydrogen bonded to the protonated **L_{TMPD}** amine. A facile net hydride transfer from the coordinated alkoxide to the Cu₂O₂ core in a 5 membered transition state provides the carbonyl product and a (**L_{TMPD}**)₂Cu(II)₂(O)(OH)]²⁺ species on a singlet surface. Rapid proton transfer from the protonated amine of **L_{TMPD}** then affords the presumed [(**L_{TMPD}**)₂Cu(II)₂(OH)₂]²⁺ product. While analogous reactivity by HAT is possible, preliminary calculations place the barrier to a triplet pathway higher by 5 kcal•mol⁻¹.

The role of exogenous NEt₃ and 2,6-lutidine in increasing the rate and selectivity of alcohol oxidation is currently less clear, but one postulate is that these bases deprotonate the axially ligated alcohol, accelerating the previously rate-limiting rotation, and thereby enhancing the rate. Whereas the absence of a primary O-H/D KIE indicates that O-H/D cleavage is *not*

rate-limiting for neutral alcohols in the *absence* of NEt_3 , addition of 2 equiv NEt_3 leads not only to an accelerated rate, but also to a primary O–H/D KIE (Fig. 9). This result is consistent with deprotonation becoming the rate-limiting step. The reaction is further accelerated when the alcohol is fully deprotonated to yield the alkoxide, with a lower barrier to rotation suggested by the exceedingly fast reaction of alkoxides with O_{TMPD} at 233 K; the reaction occurs upon mixing. In the reaction of alkoxides, the emergence of a primary C–H/D KIE (observed for neutral alcohols in neither the absence nor presence of NEt_3) indicates that full deprotonation is required in order to accelerate the reaction to the point at which C–H/D cleavage becomes rate-limiting. A significant reduction of the rotational barrier upon deprotonation is recapitulated in DFT calculations as well. The dramatic increase in selectivity for primary versus secondary alcohols from 2:1 to 18:1 using NEt_3 (Fig. 6) would follow naturally from repulsion between the substrate, coordinated axially in a sterically congested environment, and the sterically demanding NEt_3 base. A reduction in steric demands, as with 2,6 lutidine, attenuates this selectivity to 7:1 (Fig. 6).

5. Conclusions

The bis-Cu(III) bis-(μ -O) complex O_{TMPD} effects the selective oxidation of exogenous primary alcohols to aldehydes and primary amines to nitriles in synthetically useful yields (up to >90%) using a twofold excess of this oxidant. In contrast with related O species, alcohol oxidation by O_{TMPD} exhibits not only high selectivity, but also a remarkable insensitivity to the strength of the $\text{C}^\alpha\text{--H}$ bond, oxidizing benzyl alcohol and 1-octanol at identical rates. Spectroscopic and kinetic analyses converge to a mechanism in which initial axial coordination of neutral alcohols is followed by rate-limiting rotation into the equatorial plane, whereupon rapid deprotonation and subsequent C–H scission by the bis oxide O--O_{σ^*} LUMO can occur. Radical clock experiments suggest that this reactivity takes place in the absence of long lived radical intermediates, consistent with a net hydride transfer on a singlet surface, a mechanistic postulate supported by DFT. The importance of ligand flexibility in enabling this reactivity is highlighted by comparison with related O species, which display an increasing competence in alcohol oxidation as the ligand backbone becomes more flexible and steric demands decrease. While this mechanistic analysis begins to illuminate the mechanism of neutral alcohol oxidation by O_{TMPD} , investigation into the origins of dramatic rate acceleration and enhanced selectivity in the presence of added NEt_3 , as well as substantially increased yields with oxidants prepared from PhCN versus MeCN precursors, remain ongoing.

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Abbreviations:

O_{TMPD}	$[(\text{L}_{\text{TMPD}})_2\text{Cu(III)}_2(\mu\text{-O})_2]^{2+}$
L_{TMPD}	N^1, N^1, N^3, N^3 -tetramethylpropane-1,3-diamine

OTMED	$[(\text{LTMED})_2\text{Cu(III)}_2(\mu\text{-O})_2]^{2+}$
LTMED	N^1, N^1, N^3, N^3 -tetramethylethane-1,2-diamine
OTMCHD	$[(\text{LTMCHD})_2\text{Cu(III)}_2(\mu\text{-O})_2]^{2+}$
LTMCHD	N^1, N^1, N^2, N^2 -tetramethyl-1 <i>R</i> ,2 <i>R</i> -diaminocyclohexane
OHMPD	$[(\text{LHMPD})_2\text{Cu(III)}_2(\mu\text{-O})_2]^{2+}$
LHMPD	$N^1, N^1, N^3, N^3, 2, 2$ -hexamethylpropane-1,3-diamine
OPD	$[(\text{LPD})_2\text{Cu(III)}_2(\mu\text{-O})_2]^{2+}$
LPD	propane-1,3-diamine
KIE	kinetic isotope effect
PDS	product determining step
RLS	rate-limiting step
DFT	density functional theory
MeCN	acetonitrile
PhCN	benzonitrile
LUMO	lowest occupied molecular orbital
LMCT	ligand-to-metal charge transfer
HAT	hydrogen atom transfer
EXAFS	extended X-ray absorption fine structure

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Highlights

- Bis-Cu(III) bis-oxides (**O**) form spontaneously from simple Cu(I) diamine complexes under O₂
- While powerful 2e⁻/2H⁺ oxidants, their reactivity with exogenous substrates is limited
- **O**_{TMPD} effects selective oxidation of alcohols and amines in >90% yields with excess oxidant
- Mechanistic analyses suggest alcohol oxidation occurs through net hydride transfer

Substrate	$\xrightarrow[\text{233 K, CH}_2\text{Cl}_2]{\text{O}_{\text{TMPD}}^{\text{PhCN}}-(\text{ClO}_4)_2}$	Product	Yield
90%
90%
60%
70%
60%

Fig. 1.
Reaction of $\text{O}_{\text{TMPD}}^{\text{PhCN}}-(\text{ClO}_4)_2$ ($[(\text{L}_{\text{TMPD}})_2\text{Cu}_2\text{O}_2](\text{ClO}_4)_2$, 1 equiv, 10 mM) with alcohols (2 equiv) at 233 K in CH_2Cl_2 . Yields based on oxidant.

Ligand	Counteranion	Nitrile	$k_{obs} (\times 10^4 \text{ s}^{-1})$	
HMPD	CF_3SO_3^-	MeCN	43	L_{HMPD}
TMPD	CF_3SO_3^-	MeCN	9.6	
TMPD	ClO_4^-	MeCN	9.2	L_{TMPD}
TMPD	ClO_4^-	PhCN	10	

Fig 2.

Optically measured thermal decomposition rate constants of **O** species at 263 K (1.0 mM Cu, CH_2Cl_2)

Fig. 3.
Reactivity of O_{TMPD} observed with exogenous substrates (substrate:oxidant 2:1). Yields based on oxidant.

Substrate	Product	% Yield
60
60
70
50
50
60
60
60
60
60
60
60

Fig. 4.

Alcohol oxidation by $\text{OTMPD}^{\text{MeCN}}(\text{CF}_3\text{SO}_3)_2$ at 233 K in CH_2Cl_2 after *ca.* 5 h (substrate:oxidant 2:1). Yields based on oxidant.

% Yield
$\text{O}_{\text{TMPD}}^{\text{MeCN}}\text{-(SbF}_6\text{)}_2$	MeCN	60
$\text{O}_{\text{TMPD}}^{\text{PhCN}}\text{-(SbF}_6\text{)}_2$	PhCN	90
$\text{O}_{\text{TMPD}}^{\text{MeCN}}\text{-(ClO}_4\text{)}_2$	MeCN	60
$\text{O}_{\text{TMPD}}^{\text{PhCN}}\text{-(ClO}_4\text{)}_2$	PhCN	90
$\text{O}_{\text{TMPD}}^{\text{MeCN}}\text{-(CF}_3\text{SO}_3\text{)}_2$	MeCN	60
$\text{O}_{\text{TMPD}}^{\text{PhCN}}\text{-(CF}_3\text{SO}_3\text{)}_2$	PhCN	90

Fig. 5.

Dependence of yield on counteranion and Cu(I) precursor in benzyl alcohol oxidation in CH_2Cl_2 (substrate:oxidant 2:1). Yields based on oxidant.

	Substrate(s)	Base	Selectivity
1		—	1 : 1
2	1-Octanol 2-Octanol	— NEt ₃	2 : 1 18 : 1
3	1-Octanol 2-Hexanol	NEt ₃ 2,6-lutidine	20 : 1 7 : 1
4		NEt ₃	20 : 1
5	1-Octanol	NEt ₃	15 : 1
6	1-Octanol	NEt ₃	15 : 1
7		—
8		NEt ₃

Fig. 6.

Intermolecular and intramolecular competitive alcohol oxidation by $\text{O}_{\text{TMPD}}^{\text{MeCN}}$ - $(\text{CF}_3\text{SO}_3)_2$ under excess substrate conditions in the absence (233 K for *ca.* 5 h) or presence (193 K, *ca.* 3 h) of base (NEt₃ or 2,6-lutidine, 2 equiv) in CH₂Cl₂.

	Amine	$\xrightarrow{\text{N}_2, 193 \text{ K}}$	Product(s)	% Yield
1		$\xrightarrow{k_1}$		75 (5) ^a
2		$\longrightarrow$		70 (2) ^a
3		$\xrightarrow{k_2}$	+	25 (4) ^a 25
4		$\not\longrightarrow$	NR	—
5		$\longrightarrow$		60 (3) ^a

Fig. 7.

Oxidation of amines (1 equiv, 20 mM) by $\text{OTMPD}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ (1 equiv, 20 mM) at 193 K in CH_2Cl_2 . Yields after aqueous workup (NR = no reaction). $k_1/k_2 = 100$ by optical spectroscopy. ^[a] Number of independent experiments. Yields based on oxidant.

Fig. 8.

Dependence of initial rates on initial concentrations of $OTMPD^{MeCN}_2(CF_3SO_3)_2$ (**left**) and benzyl alcohol (**right**). Linear fits to the data give $\log(k_{obs}) = 0.99 \cdot \log([Cu]) - 1.82$ ($R^2 = 0.98$) and $\log(k_{obs}) = 0.74 \cdot \log([benzyl\ alcohol]) - 5.2$ ($R^2 = 0.99$).

Substrate(s)	KIE (k_H/k_D)	T (K)
PhCH ₂ OH / PhCD ₂ OH (Intermolecular)	1.1	233
PhC(H)(D)OH (Intramolecular)	4.8	233
PhC(H)(D)O [•] (Intramolecular)	4.8	233
PhCH ₂ O [•] / PhCD ₂ O [•] (Absolute Rates)	4	193
PhCH ₂ OH / PhCH ₂ OD (Absolute Rates)	1 ± 0.1	233
PhCH ₂ OH / PhCH ₂ OD (Absolute Rates, NEt ₃)	3.6	213
PhCH ₂ OH / PhCD ₂ OH (Absolute Rates, NEt ₃)	1.1	213

Fig. 9. (Left) Kinetic isotope effects measured for oxidation of benzyl alcohol and derivatives by **OTMPD^{MeCN}-(CF₃SO₃)₂**, and (right) Hammett linear free energy relationship for the oxidation of *para*-substituted benzyl alcohol derivatives by **OTMPD^{MeCN}-(CF₃SO₃)₂**. For the Hammett plot [30], a linear fit gives $\log(k/k_0) = 0.215 \cdot \sigma - 0.00366$ ($R^2 = 0.99$, $\rho = -0.2$).

Fig. 10. Close counteranion association observed by EXAFS for $\text{OTMPD}^{\text{MeCN}} \cdot (\text{CF}_3\text{SO}_3)_2$ and by single crystal X-ray diffraction for the L_{TMPD} -ligated Cu(III) site in a mixed-ligand **O** system [11, 47].

Fig. 11.
Natural Bonding Orbitals for the electrophilic $\text{O}-\text{O}_{\sigma^*}$ LUMOs and space-filling representations of O_{TMPD} , O_{TMED} , and O_{PD} .

Fig. 12. Optical spectra of $\text{OTMPD}^{\text{MeCN}}(\text{CF}_3\text{SO}_3)_2$ (black trace) and putative substrate-coordinated intermediate (red trace) upon injection of benzyl alcohol (100 equiv) at 193 K in CH_2Cl_2 .

Fig. 13.

Reactivity of O_{TMPD} with monodentate amines (substrate oxidation) and concerted core capture by chelating propylenediamine at 150 K.

Fig. 14. Electrophilic O_{TMPD} LUMOs calculated with methanol (**A**) and methoxide (**B**) model substrates coordinated axially (**top**) versus equatorially (**bottom**).

Fig. 15.

Proposed mechanism of neutral alcohol oxidation by O_{TMPD} involving net hydride transfer ($2\text{e}^-/1\text{H}^+$) on a singlet surface to the Cu_2O_2 core.

Table 1.

Absorption maxima of **O**_{TMPD} varying counteranions and nitrile ligands (1 mM Cu, CH₂Cl₂, 193 K).

Counteranion	Absorption Maxima (nm)		
SbF ₆ ⁻	248	299	397
CF ₃ SO ₃ ⁻	249	299	397
PF ₆ ⁻	249	301	400
BF ₄ ⁻	249	301	400
ClO ₄ ⁻ (MeCN)	248	299	400
ClO ₄ ⁻ (PhCN)	248	299	400

Table 2.

Relative amounts of benzaldehyde products, *p*-CF₃ and *p*-H, obtained in chase experiments (2 equiv total alcohol) with **OTMPD**^{MeCN} (**CF**₃**SO**₃)₂ (1 equiv) in the absence (**A**, 233 K) or presence (**B**, 293 K) of NEt₃ (2 equiv). Substrate 2 was added 2 minutes after substrate 1.

	Substrate 1	Substrate 2	<i>p</i> -CF ₃	:	<i>p</i> -H
(A)	<i>p</i> -H + <i>p</i> -CF ₃	--	0.9	:	1.1
	<i>p</i> -H	<i>p</i> -CF ₃	1	:	1.6
	<i>p</i> -CF ₃	<i>p</i> -H	1.5	:	1
(B)	<i>p</i> -H	<i>p</i> -CF ₃	1	:	1.4
	<i>p</i> -CF ₃	<i>p</i> -H	2.0	:	1