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Reactivity of a Stable Copper-Dioxygen Complex

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We report the isolation of a room temperature stable dipyrromethene $Cu(O_2)$ complex featuring a side-on O_2 coordination. Reactivity studies highlight the unique ability of the dioxygen adduct for both hydrogen-atom abstraction and acid/base chemistry towards phenols, demonstrating that side-on superoxide species can be reactive entities.

Activation of dioxygen by copper systems plays an essential role in both biological[1-3] and abiological[4-6] transformations. Studies on natural enzymes and synthetic complexes have identified structural motifs of mono-, di-, and tri-copper sites with varying degrees of dioxygen activation (superoxide, peroxide, oxo), and consequently distinct reactivity profiles.[7-11] As such, elucidating the correlation between the initially generated 1:1 $Cu(O_2)$ adduct and the subsequent reactivity of this intermediate towards substrates is essential for rationally designing synthetic systems competent for selective oxidation chemistry.

Among the $Cu(O_2)$ adducts isolated to date,[12-27] both end-on and side-on coordination of dioxygen have been observed to afford a Cu^{II}-superoxide unit that features either a triplet (end-on bound)[12-21] or a diamagnetic (side-on bound)[22-25, 27] ground state. Reactivity studies identified the ability of terminally bound $Cu(O_2)$ complexes to engage in hydrogen-atom abstraction (HAA)[12, 14-18] from weak C–H and phenol O–H bonds or acid/base chemistry,[14, 19] whereas no such transformations can be effected at a side-on $Cu(\kappa^2\text{–}O_2)$ complex.[23] In line with these observations, DFT investigations suggested that less electron donating ligands could increase the oxidative potency of such $Cu(O_2)$ complexes by inducing a Cu superoxide and, therefore, electrophilic character.[23]

Using weak-field dipyrromethene ligands, our group has demonstrated the stabilization of a unique ferric iminyl species that is competent for C–H amination.[28, 29] Encouraged by these results, we set out to probe the potential of this weakly donating scaffold to similarly stabilize a dipyrrin copper superoxide complex and explore its reactivity. Herein, we report the isolation of a side-on $Cu(\kappa^2\text{–}O_2)$ complex that persists at room temperature and yet manifests both HAA and acid/base chemistry towards phenolic O–H bonds.

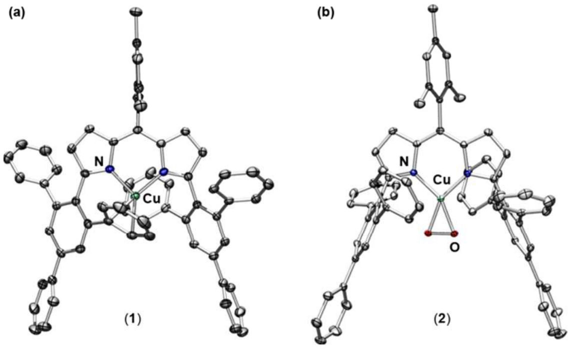

Fig. 1 Solid state molecular structures for (a) $(^{Ar}L)Cu$ (**1**) and (b) $(^{Ar}L)Cu(O_2)$ (**2**) with thermal ellipsoids at 50% probability level. Color scheme: Cu, aquamarine; N, blue; O, red. Hydrogens and solvent molecules are omitted for clarity.

Metalation of $(^{Ar}L)Li$ with CuCl in tetrahydrofuran affords $(^{Ar}L)Cu^{I}$ (**1**) (^{Ar}L: 5-mesityl-1,9-(2,4,6-Ph_3-C_6H_2)dipyrrin[28]). X-ray diffraction studies on single crystals obtained from a concentrated hexanes solution of **1** reveal a three-coordinate copper centre featuring an η^2-interaction with one of the *ortho*-phenyl groups of the 2,4,6-Ph_3-C_6H_2 substituent (Fig. 1a). Treatment of **1** with strongly donating functionalities such as acetonitrile or ammonia displaces the bound arene to afford the corresponding solvento adducts (Fig. S7, ESI†). Upon exposure to vacuum, however, complete removal of

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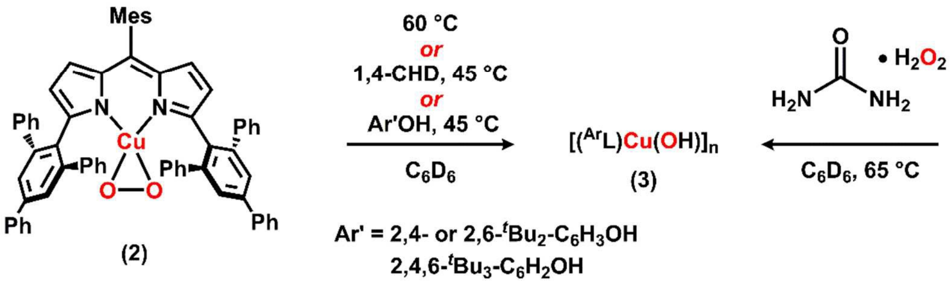
these exogenous ligands is observed, demonstrating the inherent stability of the η^2-coordination.

Addition of a stoichiometric amount of dioxygen to a frozen benzene solution of **1** results in immediate colour change from purple (λ_{max} 575 nm) to dark pink (λ_{max} 545 nm) upon thawing the reaction mixture, along with formation of new diamagnetic resonances in the ^{1}H NMR spectrum; however, full consumption of **1** is not observed (Fig. S9, ESI†). Diffusion of pentane into a saturated benzene solution of **1** under an atmosphere of O_2 afforded crystals suitable for X-ray diffraction, providing structural evidence for a side-on bound O_2 adduct (^{Ar}L)Cu(O_2) (**2**). The solid state molecular structure (Fig. 1b) displays an elongated O–O bond (1.383(2) Å) compared to typical superoxide moieties (1.2–1.3 Å),[9, 23, 30-34] more in line with a doubly reduced O_2 moiety (~1.4 Å).[9, 23, 30-34] The Cu–O bond lengths of 1.8306(11) and 1.8360(12) Å, respectively, are also indicative of a strong covalent interaction. Further, the average Cu–$N_{dipyrrin}$ bond lengths of **2** (1.878(2) Å) are significantly shorter compared to those observed in several authentic dipyrrinato Cu^{II} species ((^{Ar}L)CuCl: 1.890(2) Å; (^{Ar}L)Cu(OEt): 1.919(3) Å; (^{Ar}L)Cu(OPh): 1.904(1) Å, ESI†). However, an anilido imine supported side-on Cu(κ^2–O_2) species featuring an O–O bond length of 1.392(3) Å and similarly contracted Cu–O and Cu–N bond lengths[27] was recently reassigned as a Cu^{II} superoxide unit based on Cu K pre-edge XANES data as opposed to the originally proposed Cu^{III} peroxide formulation.[35] Finally, resonance Raman on **2** did not provide a definitive ν_{O-O} as the anticipated region[8] (Fig. S12-13, ESI†). As such, a definitive description of **2** as either a Cu^{III} peroxide or a Cu^{II} superoxide is not possible.

Preliminary DFT investigations[36] using crystallographically determined parameters identified a closed-shell singlet ground state with the lowest unoccupied molecular orbital (MO) depicting the σ* interactions between the d_{xz} orbital and both the dipyrrin ligand and the O_2 moiety. Given the weak ligand field of the dipyrrin scaffold and its influence on electronic structure evidenced in our previous studies[28, 29] as well as the multi-configurational character described for such side-on copper dioxygen species,[22, 24] we chose to further examine the electronic structure of **2**. As discussed in literature reports,[35] the broken symmetry (BS) approach fails to provide a satisfactory result for these Cu(O_2) systems, and indeed, we were unable to converge to a BS solution corresponding to a cupric centre antiferromagnetically coupled to a superoxide radical. However, following a similar protocol[35] applied for the two crystallographically characterized side-on Cu(κ^2–O_2) complexes,[22,24] the use of a complete active space self-consistent field (CASSCF) method reveals the complex electronic nature of **2**. A CAS(2,2) reference space on a truncated model of **2** (see ESI†) identified the two $\sigma(d_{xz} + \pi^*_{O2})$ and $\sigma^*(d_{xz} - \pi^*_{O2})$ active MOs (Fig. S8a, Table S2, ESI†). Subsequent localization of these MOs (Fig. S8b, ESI†) and analysis of the resulting wavefunctions with respect to a valence bond description unveiled 87.1% contributions from the $Cu^{II}(O_2^{\bullet-})$ configuration, with 9.4% and 3.5% participation of the $Cu^{I}(O_2^{0})$ and $Cu^{III}(O_2^{2-})$ states, respectively (Table S3, ESI†). These results are consistent with those calculated for the analogous *β*-diketiminato Cu(κ^2–O_2) adduct[35] and suggest a significant Cu^{II}-superoxide character for **2**.

Complex **2** exhibits interesting properties and reactivity profile. Unlike the previously characterized Cu(O_2) species, which tend to decay above –25 °C,[2, 9, 14, 17, 19, 22-24] **2** is surprisingly persistent in solution at room temperature. However, despite the relatively strong Cu(O_2) interaction, the η^2-arene association is still preferred; exposure of *in situ* generated **2** to vacuum results in conversion to the starting Cu^{I} complex **1** (Fig. S9, ESI†), akin to the behaviour reported for a tris(pyrazolyl)borate side-on bound Cu^{II} superoxide.[22] Additionally, variable temperature ^{1}H NMR studies identified an equilibrium between **1** and **2**, justifying the incomplete generation of **2** at room temperature even in the presence of excess dioxygen. O_2 binding is favoured at lower temperatures, with full conversion to **2** observed *in situ* at –15 °C (Fig. S10, ESI†) and oxygen release noted upon warming the reaction mixture back to room temperature. Such temperature dependent reversible O_2 binding has been previously described for a tris(tetramethylguanidino)tren end-on Cu^{II} superoxide.[12]

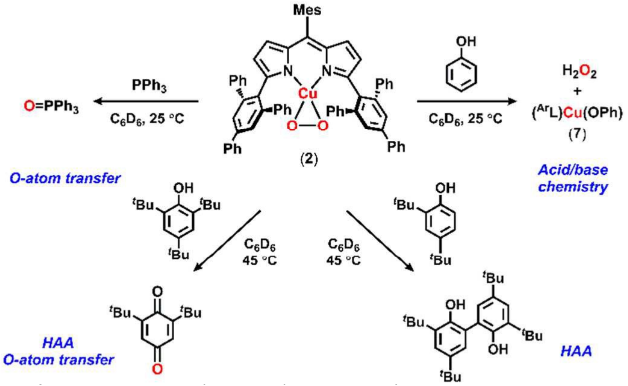
Despite its robust nature, **2** is not inert. Heating a benzene solution of the *in situ* generated **2** at 60 °C results in full consumption of the dioxygen adduct, giving rise to a ^{1}H NMR spectrum with no well-defined features (Scheme 1). Notably, no ligand hydroxylation was observed. Unfortunately, structural confirmation of the final Cu complex (**3**) has been unsuccessful. A frozen toluene EPR spectrum of **3** collected at 77 K identifies an $S = {}^1/_2$ signal consistent with a Cu^{II} formulation (g_{Cu} = 2.24, A_{Cu} = 543 MHz, Fig. S14, ESI†). O–O



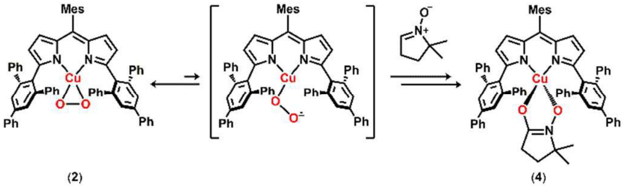
Scheme 1 Reactions leading to formation of complex **3**.

bond cleavage and decay of **2** into a copper hydroxide is possible, likely forming $[(^{Ar}L)Cu(OH)]_n$ units, as a three-coordinate, terminal copper hydroxide would be unstable.[37] A tri-copper formulation would be more plausible than a dimeric motif given the cupric EPR signature of **3**. Interestingly, the same product was detected upon treatment of **1** with excess urea hydroperoxide at 65 °C (Scheme 1 and Fig. S15, ESI†), suggesting that a Cu hydroperoxide species may form during the thermal decomposition of **2**. Such an intermediate would arise upon a HAA step, transformation which has been previously described for terminal Cu^{II} superoxide complexes,[12, 14-18] albeit not for side-on bound $Cu(O_2)$ adducts.[23] Indeed, in the presence of a weak hydrogen atom source such as 2-hydroxy-2-azaadamantane **2** rapidly undergoes HAA at room temperature to afford the corresponding *N*-oxide organic radical as confirmed via EPR spectroscopy (Fig. S17, ESI†). Further, reaction of **2** with 1,4-cyclohexadiene (bond dissociation energy (BDE) = 77 $^{kcal}/_{mol}$)[38] proceeds at 45 °C, generating a Cu^{II} species with an EPR signal not well defined, but similar to that of **3** (Scheme 1 and Fig. S18, ESI†), suggesting that HAA from the allylic C–H bond may occur. Following a similar HAA step, exposure of **2** to 2,4-di-*tert*-butylphenol at 45 °C furnishes the expected C–C coupled dimeric product quantitatively.

Treatment of **2** with either 2,6-di-*tert*-butylphenol or 2,4,6-tri-*tert*-butylphenol at 45 °C instead allows for isolation of 2,6-di-*tert*-butyl-1,4-benzoquinone (identified via GC–MS, major organic product, ESI†) along with detection of the same species **3** by EPR spectroscopy (Scheme 2 and Fig. S20, ESI†). Oxygenation of 2,6- and 2,4,6-substituted phenols to furnish 1,4-benzoquinone derivative products has been demonstrated with several Cu superoxide complexes.[12, 15, 16] Recent mechanistic investigations by Karlin et al.[16] have proposed that the Cu superoxide is involved in both HAA and subsequent reactivity with the phenoxyl radical to effect the overall four-electron oxygenation. The reactivity of **2** is noteworthy considering that the analogous side-on bound antiferromagnetically coupled Cu^{II} superoxide complexes reported display no such chemistry. Complex **2** could potentially rearrange to a terminal O_2 binding mode *in situ* which could then undergo HAA and O-atom transfer as described. Supporting this proposal, reaction of **2** with the radical trap 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) affords a new Cu^{II} species (Scheme 3 and Fig. S1, ESI†). That was identified via X-ray crystallography as the $(^{Ar}L)Cu(O–DMPO)$ adduct (**4**) (Fig. S28, ESI†). Although the mechanism of O–O bond cleavage and formation of **4** is unclear at the moment, this result is in line with a superoxide character of the bound O_2 moiety in **2**.



Scheme 2 Reactivity of $(^{Ar}L)Cu(O_2)$ (**2**).



Scheme 3 Proposed equilibrium between side-on / end-on O_2 bound in **2** and subsequent reaction with DMPO.

Interestingly, despite the electrophilic character inferred from the HAA ability of **2**, the Cu/O_2 adduct can also engage in acid/base chemistry (Scheme 2). Addition of dioxygen to a benzene solution of **1** and phenol furnishes two new Cu^{II} species as indicated by EPR spectroscopy (Fig. S23, ESI†). No C–C coupled product is detected by ^1H NMR or GC–MS, suggesting that a phenoxyl radical is not generated during the reaction. Instead, phenol deprotonation and formation of the corresponding $(^{Ar}L)Cu(OPh)$ (**7**) was confirmed via independent synthesis of the phenoxide complex (Figs. S4, S23, ESI†). Treatment of **2** with more acidic phenols such as 4-nitrophenol and 2-amino-4-*tert*-butylphenol produces a similar outcome, whereas addition of ammonium chloride furnishes the respective $(^{Ar}L)CuCl$ (**5**) (Figs. S2, S24, ESI†). Both Tolman[19] and Itoh[14] have reported formation of copper phenoxides upon reaction of copper superoxide complexes with *para* substituted phenols. In these instances, the hypothesized mechanism involves deprotonation of the phenol unit by the superoxide moiety followed by ligand exchange to arrive at a copper phenoxide and the hydroperoxide radical which subsequently disproportionates into hydrogen peroxide and water. Indeed, formation of hydrogen peroxide upon treatment of **2** with phenol was confirmed by iodometry (Fig. S25, ESI†), suggesting that the reaction likely follows an analogous mechanism as previously described.[14, 19]

The switch in the reactivity of **2** towards phenolic substrates reflects a unique property of the dipyrrin Cu/O_2 complex relative to other copper dioxygen species. The similar pK_a values (in DMSO) for phenol and 4-methoxyphenol or 2,4,6-tri-*tert*-butylphenol (~17-19)[39] suggest that deprotonation over HAA is dictated by the BDE of the O–H bond. As such, **2** undergoes HAA with substrates featuring BDEs[38] up to 83 $^{kcal}/_{mol}$ and deprotonates those phenols that necessitate higher oxidative potency for homolytic O–H cleavage, thus demonstrating both electrophilic and basic character. This is not a common feature for other mononuclear copper superoxide complexes in the literature which manifest either reactivity profile, but not both. The end-on Cu^{II} superoxide reported by Itoh is the only other example to date of a Cu/O_2 adduct engaging in acid/base chemistry with 4-*tert*-butyphenol and undergoing HAA activity from

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TEMPO–H (BDE ~ 70 $^{kcal}/_{mol}$),[38] albeit access to any stronger O–H or C–H bonds (BDE > 70 $^{kcal}/_{mol}$) was not demonstrated.[14]

Complementing the proton and HAA reactivity, **2** also promotes two-electron O-atom transfer chemistry to triphenylphosphine (Scheme 2). Upon addition of dioxygen to a benzene solution of **1** and substrate, regeneration of **1** was accompanied by quantitative formation of triphenylphosphine oxide as confirmed via both ^{31}P NMR and GC–MS. No O-atom transfer was detected when **2** was prepared in the presence of dimethylsulfide or alkene sources (i.e., styrene, 1,3-cyclohexadiene), most likely due to the high binding affinity of the copper(I) centre for these substrates.

The foregoing results showcase the isolation of a robust dipyrromethene copper dioxygen adduct. Despite the side-on coordination of O_2, this complex manifests unique reactivity compared to previously described mononuclear $Cu(O_2)$ species: both HAA and acid/base chemistry towards a range of phenolic substrates as well as O-atom transfer to triphenylphosphine. To account for the observed reactivity, we propose an *in situ* formation of a more reactive terminal superoxide complex may precede O-atom transfer, however, an unprecedented substrate activation at the side-on dioxygen moiety cannot be discounted. Overall, the data highlights the importance of the dipyrrin platform in stabilizing such reactive entities and promoting desirable transformations.

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Notes and references

1. R. A. Himes and K. D. Karlin, *Curr. Opin. Chem. Biol.* , 2009, **13**, 119.
2. K. D. Karlin and S. Itoh, *Copper-Oxygen Chemistry*, John Wiley & Sons, Hoboken, NJ, 2011.
3. E. I. Solomon, U. M. Sundaram and T. E. Machonkin, *Chem. Rev.*, 1996, **96**, 2563.
4. R. A. Himes and K. D. Karlin, *Proc. Natl. Acad. Sci. U.S.A.*, 2009, **106**, 18908.
5. L. Que and W. B. Tolman, *Nature*, 2008, **455**, 333.
6. A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem. Int. Ed.*, 2011, **50**, 11062.
7. L. Q. Hatcher and K. D. Karlin, *J. Biol. Inorg. Chem.* , 2004, **9**, 669.
8. E. A. Lewis and W. B. Tolman, *Chem. Rev.*, 2004, **104**, 1047.
9. L. M. Mirica, X. Ottenwaelder and T. D. P. Stack, *Chem. Rev.*, 2004, **104**, 1013.
10. E. I. Solomon, J. W. Ginsbach, D. E. Heppner, M. T. Kieber-Emmons, C. H. Kjaergaard, P. J. Smeets and J. S. Woertink, *Faraday Discuss.*, 2011, **148**, 11.
11. C. E. Elwell, N. L. Gagnon, B. D. Neisen, D. Dhar, A. D. Spaeth, G. M. Yee and W. B. Tolman, *Chem. Rev.*, 2017, **117**, 2059.
12. D. Maiti, D.-H. Lee, K. Gaotchenova, C. Würtele, M. C. Holthausen, A. A. N. Sarjeant, J. Sundermeyer, S. Schindler and K. D. Karlin, *Angew. Chem. Int. Ed.*, 2007, **47**, 82.
13. A. Kunishita, M. Kubo, H. Sugimoto, T. Ogura, K. Satto, T. Takui and S. Itoh, *J. Am. Chem. Soc.*, 2009, **131**, 2788.
14. T. Tano, Y. Okubo, A. Kunishita, M. Kubo, H. Sugimoto, N. Fujieda, T. Ogura and S. Itoh, *Inorg. Chem.*, 2013, **52**, 10431.
15. D. Maiti, C. Fry, J. S. Woertink, M. A. Vance, E. I. Solomon and K. D. Karlin, *J. Am. Chem. Soc.*, 2007, **129**, 264.
16. J. Y. Lee, R. L. Peterson, K. Ohkubo, I. Garcia-Bosch, R. A. Himes, J. S. Woertink, C. D. Moore, E. I. Solomon, S. Fukuzumi and K. D. Karlin, *J. Am. Chem. Soc.*, 2014, **136**, 9925.
17. S. Kim, J. Y. Lee, R. E. Cowley, J. W. Ginsbach, M. A. Siegler, E. I. Solomon and K. D. Karlin, *J. Am. Chem. Soc.*, 2015, **137**, 2796.
18. R. L. Peterson, R. A. Himes, H. Kotani, T. Suenobu, L. Tian, M. A. Siegler, E. I. Solomon, S. Fukuzumi and K. D. Karlin, *J. Am. Chem. Soc.*, 2011, **133**, 1702.
19. P. J. Donoghue, A. K. Gupta, D. W. Boyce, C. J. Cramer and W. B. Tolman, *J. Am. Chem. Soc.*, 2010, **132**, 15869.
20. C. Würtele, E. Gaoutchenova, K. Harms, M. C. Holthausen, J. Sundermeyer and S. Schindler, *Angew. Chem. Int. Ed.*, 2006, **45**, 3867.
21. M. Harata, K. Jitsukawa, H. Masuda and H. Einaga, *J. Am. Chem. Soc.*, 1994, **116**, 10817.
22. K. Fujisawa, M. Yoshihiko and N. Kitajima, *J. Am. Chem. Soc.*, 1994, **116**, 12079.
23. C. J. Cramer and W. B. Tolman, *Acc. Chem. Res.*, 2007, **40**, 601.
24. N. W. Aboelella, E. A. Lewis, A. M. Reynolds, W. W. Brennessel, C. J. Cramer and W. B. Tolman, *J. Am. Chem. Soc.*, 2002, **124**, 10660.
25. N. W. Aboelella, S. V. Kryatov, B. F. Gherman, W. W. Brennessel, V. G. Young, Jr., R. Sarangi, E. V. Rybak-Akimova, K. O. Hodgson, B. Hedman, E. I. Solomon, C. J. Cramer and W. B. Tolman, *J. Am. Chem. Soc.*, 2004, **126**, 16896.
26. D. J. E. Spencer, N. W. Aboelella, A. M. Reynolds, P. L. Holland and W. B. Tolman, *J. Am. Chem. Soc.*, 2002, **124**, 2108.
27. A. M. Reynolds, B. F. Gherman, C. J. Cramer and W. B. Tolman, *Inorg. Chem.*, 2005, **44**, 6989.
28. E. R. King, E. T. Hennessy and T. A. Betley, *J. Am. Chem. Soc.*, 2011, **133**, 4917.
29. D. A. Iovan and T. A. Betley, *J. Am. Chem. Soc.*, 2016, **138**, 1983.
30. L. Vaska, *Acc. Chem. Res.*, 1976, **9**, 175.
31. J. S. Valentine, *Chem. Rev.*, 1973, **73**, 235.
32. M. H. Gubelmann and A. F. Williams, *Struct. Bonding (Berlin, Ger.)*, 1983, **55**, 1.
33. H. A. O. Hill and D. G. Tew, *Comprehensive Coordination Chemistry*, Pergamon: Oxford, 1987.
34. C. J. Cramer, W. B. Tolman, K. H. Theopold and A. L. Rheingold, *Proc. Natl. Acad. Sci. U.S.A.*, 2003, **100**, 3635.
35. N. C. Tomson, K. D. Williams, X. Dai, S. Sproules, S. DeBeer, T. H. Warren and K. Wieghardt, *Chem. Sci.*, 2015, **6**, 2474.
36. F. Neese, *WIREs Comput. Mol. Sci.*, 2012, **2**, 73.
37. X. Dai and T. H. Warren, *Chem. Commun.*, 2001, 1998.
38. Y.-R. Luo, *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press LLC, Boca Raton, FL, 2003.
39. J. J. Warren, T. A. Tronic and J. M. Mayer, *Chem. Rev.*, 2010, **110**, 6961.

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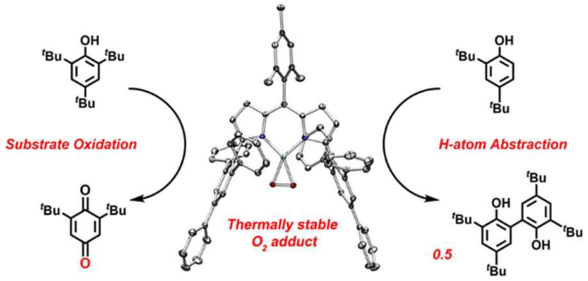

A stable Cu–dioxygen adduct is observed that effects both H–atom abstraction and O–atom transfer chemistry.