

# Halide-Promoted Dioxygenolysis of a Carbon–Carbon Bond by a Copper(II) Diketonate Complex

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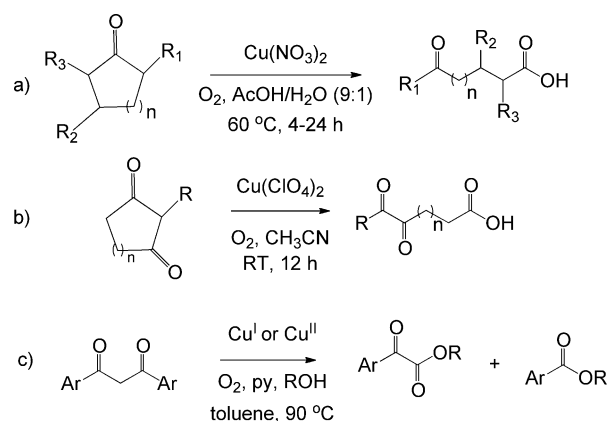
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**S** Supporting Information

**ABSTRACT:** A mononuclear Cu(II) chlorodiketonate complex was prepared, characterized, and found to undergo oxidative aliphatic carbon–carbon bond cleavage within the diketonate unit upon exposure to O<sub>2</sub> at ambient temperature. Mechanistic studies provide evidence for a dioxygenase-type C–C bond cleavage reaction pathway involving trione and hypochlorite intermediates. Significantly, the presence of a catalytic amount of chloride ion accelerates the oxygen activation step via the formation of a Cu–Cl species, which facilitates monodentate diketonate formation and lowers the barrier for O<sub>2</sub> activation. The observed reactivity and chloride catalysis is relevant to Cu(II) halide-catalyzed reactions in which diketonates are oxidatively cleaved using O<sub>2</sub> as the terminal oxidant. The results of this study suggest that anion coordination can play a significant role in influencing copper-mediated oxygen activation in such systems.

One of the most important challenges for chemists in the 21st century is to develop new ways for converting chemical feed stocks (including biomass) into useful products, including pharmaceuticals, polymers, and fuels, in an environmentally benign and cost-efficient manner.<sup>1</sup> Still underdeveloped and of relevance to this goal are methods for the selective oxidative cleavage of carbon–carbon bonds.<sup>2</sup> Of particular current interest in this area are reactions catalyzed by earth-abundant metals where O<sub>2</sub> is used as the terminal oxidant.<sup>3</sup> In this regard, a few reports have appeared demonstrating aliphatic C–C bond cleavage mediated by copper and O<sub>2</sub> at room temperature and above.<sup>4</sup> For example, oxidative cleavage reactions involving cyclic ketones (Scheme 1a) and cyclic 1,3-diones (Scheme 1b) catalyzed by simple Cu(II) salts and O<sub>2</sub> have been reported.<sup>5</sup> The reaction pathway proposed in these systems involves the generation of a Cu(I)–ketonyl radical pair which intercepts dioxygen. A very recent report outlines the copper-catalyzed oxidative cleavage of acyclic β-diketones (Scheme 1c) in a dioxygenase-type pathway.<sup>6</sup> This reaction proceeds in moderate to high yield by combining a catalytic amount of CuBr or CuBr<sub>2</sub> salt, pyridine, the diketone substrate, and oxygen in toluene/methanol at 90 °C.

**Scheme 1. Examples of Oxidative Aliphatic Carbon–Carbon Bond Cleavage Catalyzed by Cu(II) Salts and O<sub>2</sub>**

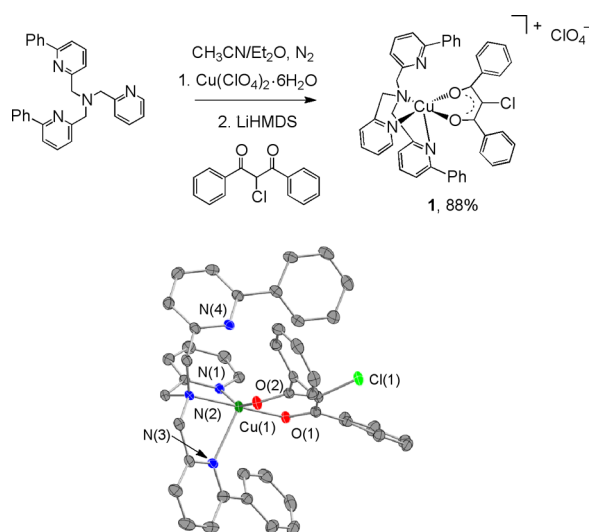


Almost no mechanistic details are currently known for the reactions shown in Scheme 1. Of particular note is the complete lack of understanding of the role of counterion or coligands in allowing the reaction to proceed in a facile manner. In fact, mechanistic studies of oxidative C–C bond cleavage reactions using copper and O<sub>2</sub> have been limited to model complexes for copper-containing quercetin dioxygenase (QDO).<sup>7</sup> Herein we report our discovery of dioxygenase-type aliphatic C–C bond cleavage reactivity involving a Cu(II) chlorodiketonate complex upon reaction with O<sub>2</sub> at ambient temperature. Importantly, initial mechanistic and computational studies of this reaction indicate that chloride ion can serve as a catalyst to lower the barrier of the rate-determining oxygen activation step in the reaction pathway. This is an intriguing result that suggests that simple anions can play a key role in Cu(II)/O<sub>2</sub> systems that promote oxidative C–C bond cleavage reactivity.

The Cu(II) chlorodiketonate complex [(6-Ph<sub>2</sub>TPA)Cu(PhC(O)CClC(O)Ph)]ClO<sub>4</sub> (**1**)<sup>8</sup> was assembled as shown in Figure 1 (top). X-ray crystallographic studies revealed a five-coordinate copper center in which one of the phenyl-appended pyridyl arms of the chelate ligand is dissociated from the metal

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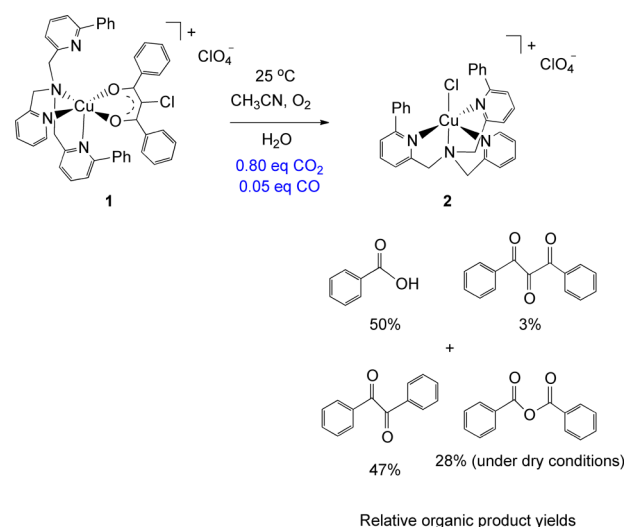
**Figure 1.** (Top) Synthetic route for the preparation of 1. (Bottom) A thermal ellipsoid representation of the cationic portion of 1. Ellipsoids are plotted at the 50% probability level. Hydrogen atoms are omitted for clarity.

center (Figure 1, bottom), and the second phenyl-appended pyridyl arm is elongated relative to the other nitrogen donors. The geometry of the center is a distorted square-based pyramid ( $\tau = 0.40$ ).<sup>9</sup> Bond distances within the six-membered diketonate chelate ring are consistent with a fully delocalized monoanion, and the C–Cl bond distance (1.747(2) Å) is in the range typically found for other chlorodiketonates (1.739–1.755 Å).<sup>10</sup>

Complex 1 has a prominent absorption feature at 363 nm ( $\epsilon = 10\,200 \text{ M}^{-1} \text{ cm}^{-1}$ ) that is likely due to a  $\pi\text{--}\pi^*$  transition within the diketonate, but also may include some LMCT character. The X-band EPR spectrum of 1 at 20 K (Figures S1 and S2) is consistent with retention of the distorted square pyramidal geometry in solution.<sup>11</sup>

Exposure of a wet  $\text{CH}_3\text{CN}$  solution of 1 to  $\text{O}_2$  leads to the decay of the 363 nm absorption band (Figure S3) within 1 h at ambient temperature, which is consistent with destruction of the diketonate unit.<sup>12</sup> Vapor diffusion of  $\text{Et}_2\text{O}$  into a concentrated  $\text{CH}_2\text{Cl}_2$  solution of the product mixture generated crystals of  $[(6\text{-Ph}_2\text{TPA})\text{CuCl}]\text{ClO}_4$  (2). Complex 2 contains a five-coordinate Cu(II) center in a distorted trigonal bipyramidal geometry ( $\tau = 0.61$ , Figure S4).<sup>9</sup> The Cu–Cl bond distance in 2 (2.1989(7) Å) is the shortest reported for a mononuclear Cu(II)–Cl complex ligated by a tris(2-methylpyridyl)amine-based ligand.<sup>13</sup> A comparison of the EPR spectra of the crude product mixture and independently synthesized 2 (Figure S5) indicated that complex 2 was the only Cu(II)-containing product generated in the reaction.

The fate of the diketonate ligand was determined by GC-MS analysis of the products.<sup>14</sup> In the presence of water, analysis revealed the formation of benzoic acid, benzil and diphenylpropanetrione (Figure 2). Under dry conditions, an additional product, benzoic anhydride, was identified. GC analysis of the headspace of the reaction mixture revealed the formation of  $\text{CO}_2$  (0.80 equiv) and  $\text{CO}$  (0.05 equiv).  $^{18}\text{O}_2$ -labeling studies revealed the incorporation of at least one labeled oxygen atom into 60% of the benzoic acid, while an  $^{16}\text{O}_2/\text{H}_2^{18}\text{O}$  experiment shows incorporation of labeled oxygen into 30% of the benzoic acid (Figure S6). Combined, these results strongly suggest a reaction pathway in which an  $\alpha$ -substituted diketonate reacts



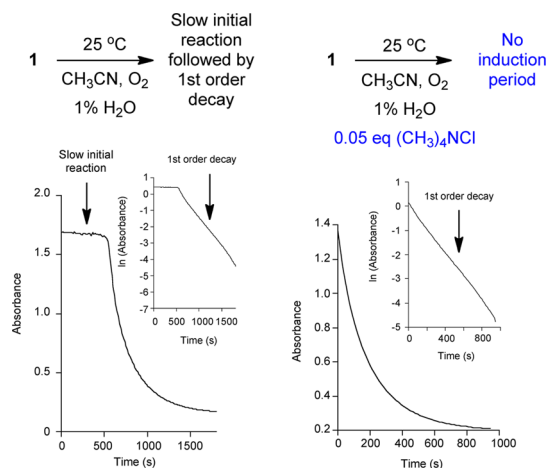
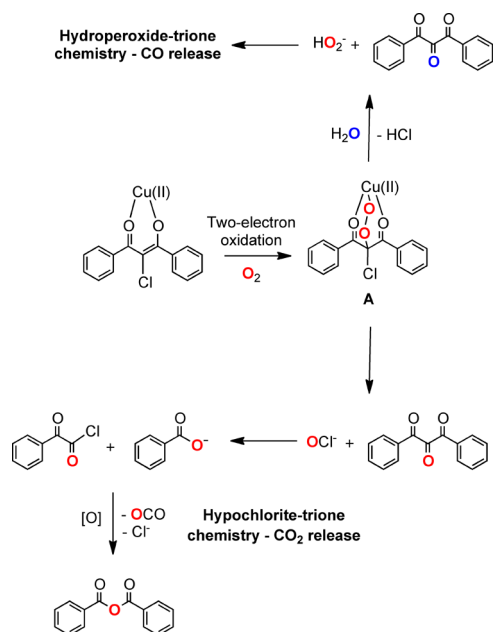
**Figure 2.** Reaction of 1 with  $\text{O}_2$  in  $\text{CH}_3\text{CN}$  at 25 °C. Benzil ( $\text{PhC(O)C(O)Ph}$ ) is generated via Lewis acid-promoted migration chemistry of diphenylpropanetrione.<sup>15,16</sup> The formation of this byproduct provides evidence for the involvement of the trione in the reaction. Previous studies have shown that divalent metal complexes of the 6- $\text{Ph}_2\text{TPA}$  ligand promote this type of migration chemistry.<sup>17</sup>

with dioxygen to produce a trione intermediate, as has been observed in model systems for Ni(II)- and Fe(II)-containing acireductone dioxygenases.<sup>17</sup> Importantly, under dry conditions, quantitative  $^{18}\text{O}$  incorporation was found in the diphenylpropanetrione intermediate. Additionally, we have found that admixture of equimolar amounts 6- $\text{Ph}_2\text{TPA}$ ,  $\text{Cu}(\text{ClO}_4)_2$ , diphenylpropanetrione, and sodium hypochlorite gave the same product mixture and  $\text{CO}_2$ : $\text{CO}$  ratio as the reaction starting from 1 and  $\text{O}_2$ .

Based on the observed  $\text{CO}_2$ : $\text{CO}$  ratio, the quantitative incorporation of a labeled oxygen into the trione intermediate, the observation of benzoic anhydride under dry conditions, and the congruence of products from the reaction of 1 with  $\text{O}_2$  and the independent 6- $\text{Ph}_2\text{TPA}/\text{Cu}(\text{II})/\text{diphenylpropanetrione}/\text{hypochlorite}$  reaction, we propose that aliphatic C–C bond cleavage in this system results primarily from the reaction of hypochlorite ion with diphenylpropanetrione, with these reagents being formed via O–O cleavage and O–Cl bond formation, respectively, within a Cu(II)–peroxo intermediate (A, Scheme 2). Notably, this hypochlorite pathway differs from the hydroperoxide pathway previously identified for aliphatic C–C bond cleavage involving a coordinated diketonate having a hydroxyl group in place of the chloride substituent.<sup>17</sup>

UV–vis kinetic studies of the reaction of 1 with  $\text{O}_2$  under pseudo-first-order conditions with respect to oxygen revealed a slow induction phase ( $k_{\text{obs}} \approx 3.0 \times 10^{-5} \text{ s}^{-1}$ , 21 °C) followed by a first-order decay process (Figure 3, left;  $k_{\text{obs}} \approx 3.5 \times 10^{-3} \text{ s}^{-1}$ , 21 °C). This behavior suggested that a product formed in the reaction could serve as a catalyst for the reaction. With that in mind, we found that the induction period is not observed in the presence of a catalytic amount of chloride ion (Figure 3, right). A linear dependence of the observed rate constant on chloride concentration was found (Figure S7). Overall, these initial kinetic studies suggest that chloride ion lowers the activation barrier for reaction of the Cu(II) diketonate complex with  $\text{O}_2$ . This is significant in terms of Cu(II) halide-mediated C–C bond cleavage reactions (Scheme 1) involving  $\text{O}_2$  in that, while

## Scheme 2. Hypochlorite versus Hydroperoxide Pathways for Aliphatic Carbon–Carbon Bond Cleavage

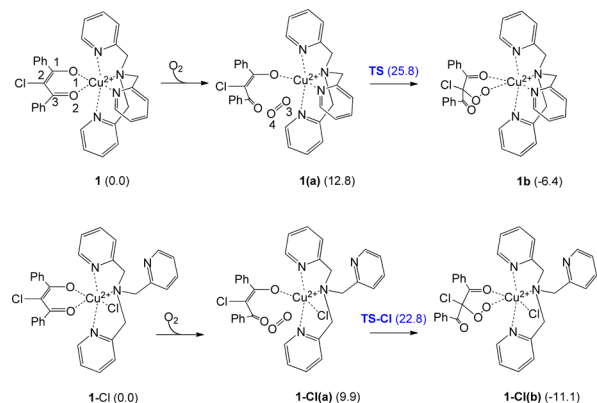


**Figure 3.** Absorbance (363 nm) versus time plots for reaction of **1** with  $\text{O}_2$  in the absence (left) and presence (right) of a catalytic amount of chloride ion. Insets:  $\ln(\text{Absorbance})$  vs time plots. Data were collected using  $\text{O}_2$ -purged solutions.

bulky carboxylate anions have been shown to accelerate model reactions for Fe(III)-containing QDOs, a similar anion effect has not been reported involving halides or in reactions involving a non-flavonol substrate.<sup>18</sup>

We have performed preliminary DFT studies to probe the reaction pathway leading to formation of the proposed bridging peroxy species **A** (Scheme 2) and to evaluate the effect of chloride ion on the oxygen activation chemistry. Using a truncated model wherein the phenyl appendages of the 6- $\text{Ph}_2\text{TPA}$  ligand were replaced by hydrogen atoms,<sup>19</sup> several different scenarios for  $\text{O}_2$  activation were probed both in the absence and in the presence of chloride ion, including (1) electronic excitation to a Cu(I)–enolate radical charge-transfer state followed by reaction with  $\text{O}_2$  and (2) direct attack of  $\text{O}_2$  on the central carbon of the enolate ligand. Additionally, we investigated whether dissociation of one of the pyridyl donors would lower the energy. The reaction pathway that was found

to be most feasible for the initial steps of the reaction involves the copper center exclusively in the Cu(II) oxidation state and parallels the mechanism proposed for Cu(II)-containing quercetin dioxygenase.<sup>20</sup> Thus, first the enolate ligand changes its coordination mode from bidentate to monodentate, which opens up a coordination site on the copper center for interaction with  $\text{O}_2$ . As shown in Scheme 3, opening the

Scheme 3. Comparison of the Lowest Energy  $\text{O}_2$  Activation Pathways for **1** and **1-Cl**

coordination site and binding of  $\text{O}_2$  in the second coordination sphere is less unfavorable for the chloride-binding complex **1-Cl**. This can be attributed, at least in part, to the different orientation of the Jahn–Teller axes in **1** and **1-Cl**. From the analysis of spin density plots (Figures S8 and S12), it follows that in **1** the doubly occupied  $d_{z^2}$  orbital is perpendicular to the  $\text{O1-Cu-O2}$  plane, whereas in **1-Cl** it points along the  $\text{Cu-O2}$  bond vector, and hence cleavage of the  $\text{Cu-O2}$  bond is promoted by the Jahn–Teller effect. Once the coordination site is open,  $\text{O}_2$  attacks the copper center and C2 in an asynchronous manner, first forming a bond to copper and partially oxidizing the enolate to enolate radical, and then developing a bond between C(2) and O(4). The computed Gibbs free energy of activation amounts to 25.8 and 22.8 kcal/mol for **TS** and **TS-Cl**, respectively, which through transition state theory corresponds to rate constants of  $7.8 \times 10^{-7}$  and  $1.3 \times 10^{-4} \text{ s}^{-1}$  ( $25^\circ \text{C}$ ), suggesting an expected >150-fold rate enhancement in the presence of  $\text{Cl}^-$ . The experimentally observed ~120-fold rate enhancement observed for the reaction of **1** with  $\text{O}_2$  following the slow induction phase is consistent with this proposal.

Overall, the studies reported herein provide evidence for an intriguing role for chloride ion in Cu(II)/ $\text{O}_2$ -promoted oxidative carbon–carbon bond cleavage reactions involving a diketone substrate. The well-defined nature of **1** bodes well for further systematic kinetic and mechanistic investigations of analogues that will provide additional insight into the reaction pathways involved in Cu(II)/ $\text{O}_2$ -promoted oxidative cleavage chemistry.

## ■ ASSOCIATED CONTENT

## S Supporting Information

Details of experimental procedures; crystallographic files in CIF format for **1** and **2**; results of EPR experiments/simulations and isotope labeling studies; absorption spectra for the reaction of **1** with  $\text{O}_2$ ; thermal ellipsoid representation of **2**; chloride dependence studies of reaction of **1** with  $\text{O}_2$ ; spin density

plots. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

- (1) (a) Gettys, N. S. *J. Chem. Educ.* **1998**, *75*, 665. (b) National Research Council. *Bioinspired Chemistry for Energy: A Workshop Summary to the Chemical Sciences Roundtable*; The National Academies Press: Washington, DC, 2008. (c) National Research Council. *Health and Medicine: Challenges for the Chemical Sciences in the 21st Century*; The National Academies Press: Washington, DC, 2004.
- (2) (a) Allpress, C. J.; Berreau, L. M. *Coord. Chem. Rev.* **2013**, *257*, 3005. (b) Crabtree, R. H. *Nature* **2000**, *408*, 415. (c) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610.
- (3) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
- (4) Zhang, L.; Bi, X.; Guan, X.; Li, X.; Liu, Q.; Barry, B.-D.; Liao, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 11303.
- (5) (a) Atlamsani, A.; Brégeault, J.-M. *Synthesis* **1993**, 79. (b) Cossy, J.; Belotti, D.; Bellosta, V.; Brocca, D. *Tetrahedron Lett.* **1994**, *35*, 6089. (c) Brégeault, J.-M.; Launay, F.; Atlamsani, A. *C. R. Acad. Sci., Ser. IIC: Chim.* **2001**, *4*, 11. (d) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozłowski, M. C. *Chem. Rev.* **2013**, *113*, 6234.
- (6) Zhang, C.; Feng, P.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 15257.
- (7) (a) Kaizer, J.; Pap, J. S.; Speier, G. In *Copper Oxygen Chemistry*; Karlin, K. D., Itoh, S., Eds.; John Wiley & Sons, Inc.: New York, 2011; pp 23–52. (b) Pap, J. S.; Kaizer, J.; Speier, G. *Coord. Chem. Rev.* **2010**, *254*, 781.
- (8) 6-Ph<sub>2</sub>TPA = *N,N*-bis((6-phenyl-2-pyridyl)methyl)-*N*-((2-pyridyl)methyl)amine.
- (9) Addison, A. W.; Rao, T. N.; Reedijk, J.; van Rijn, J.; Verschoor, G. *J. Chem. Soc., Dalton Trans.* **1984**, 1349.
- (10) (a) Taylor, J. C.; McLaren, A. B. *J. Chem. Soc., Dalton Trans.* **1979**, *3*, 460. (b) Isakova, V. G.; Baidina, I. A.; Morozova, N. B.; Igumenov, I. K. *Polyhedron* **2000**, *19*, 1097. (c) Ware, D. C.; Wilson, W. R.; Denny, W. A.; Rickard, C. E. *J. Chem. Soc., Chem. Commun.* **1991**, 1171. (d) Vock, C. A.; Renfrew, A. K.; Scopelliti, R.; Juillerat-Jeanerret, L.; Dyson, P. J. *Eur. J. Inorg. Chem.* **2008**, *10*, 1661. (e) Estes, E. D.; Scaringe, R. P.; Hatfield, W. E.; Hodgson, D. J. *Inorg. Chem.* **1976**, *15*, 1179. (f) Kavounis, C. A.; Tzavellas, L. C.; Cardin, C. J.; Zubavichus, Y. *Struct. Chem.* **1999**, *10*, 411. (g) Sans-Lenain, S.; Gleizes, A. *Inorg. Chim. Acta* **1993**, *211*, 67. (h) Sharutin, V. V.; Sharutina, O. K.; Zadachina, O. P.; Zakharova, A. N.; Reutov, V. A.; Shapkin, N. P.; Velsky, V. K. *Russ. J. Gen. Chem.* **2000**, *70*, 1672. (i) Allpress, C. J.; Arif, A. M.; Houghton, D. T.; Berreau, L. M. *Chem.—Eur. J.* **2011**, *17*, 14962.
- (11) (a) Peisach, J.; Blumberg, W. E. *Arch. Biochem. Biophys.* **1974**, *165*, 691. (b) Bubacco, L.; van Gastel, M.; Groenen, E. J. J.; Vijgenboom, E.; Canters, G. W. *J. Biol. Chem.* **2003**, *278*, 7381.
- (12) The reaction proceeds in the presence or absence of light.
- (13) (a) Harata, M.; Jitsukawa, K.; Masuda, H.; Einaga, H. *Chem. Lett.* **1995**, *24*, 61. (b) Lucchese, B.; Humphreys, K. J.; Lee, D.-H.; Incarvito, C. D.; Sommer, R. D.; Rheingold, A. L.; Karlin, K. D. *Inorg. Chem.* **2004**, *43*, 5987.
- (14) Diketonate-derived products were separated via a short silica column with >80% recovery; see Supporting Information for further details.
- (15) Roberts, J. D.; Smith, D. R.; Lee, C. C. *J. Am. Chem. Soc.* **1951**, *73*, 618.
- (16) Hydrated triketone may also be present in the reaction mixture. Lewis acid-promoted migration chemistry involving this intermediate would result in the formation of CO<sub>2</sub> and benzoin, the latter of which would be oxidized to benzil in the presence of OCl<sup>-</sup>.<sup>15</sup>
- (17) (a) Berreau, L. M.; Borowski, T.; Grubel, K.; Allpress, C. J.; Wikstrom, J. P.; Germain, M. E.; Rybak-Akimova, E. V.; Tierney, D. L. *Inorg. Chem.* **2011**, *50*, 1047. (b) Allpress, C. J.; Grubel, K.; Szajna-Fuller, E.; Arif, A. M.; Berreau, L. M. *J. Am. Chem. Soc.* **2013**, *135*, 659.
- (18) Baráth, G.; Kaizer, J.; Speier, G.; Párkányi, L.; Kuzmann, E.; Vértés, A. *Chem. Commun.* **2009**, 3630.
- (19) Preliminary calculations on the full cation (containing the 6-Ph<sub>2</sub>TPA ligand) provide evidence that the use of the smaller TPA model is valid. Specifically, geometry optimized structures of both **1** and its smaller TPA analog both exhibit two axial Cu(II)–N(pyridyl) (or phenyl–pyridyl) bonds. However, in both cases there are two distinct Cu–N distances, with the longer bond in the 6-Ph<sub>2</sub>TPA-ligated model structure corresponding to the pyridyl appendage that is dissociated in the X-ray structure of **1**. This being the case, the X-ray structure was used to guide the computations: e.g., the pyridyl donor that is dissociated in the crystal structure was rotated away to make space for O<sub>2</sub> binding in the next step. Overall, our computational studies thus far suggest that while the inaccuracy of the geometry optimized TPA structures may affect the energies to some extent, the qualitative conclusions drawn likely have substantial validity.
- (20) Siegbahn, P. E. M. *Inorg. Chem.* **2004**, *43*, 5944.