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Directed Hydroxylation of sp^2 and sp^3 C−H Bonds Using Stoichiometric Amounts of Cu and H_2O_2

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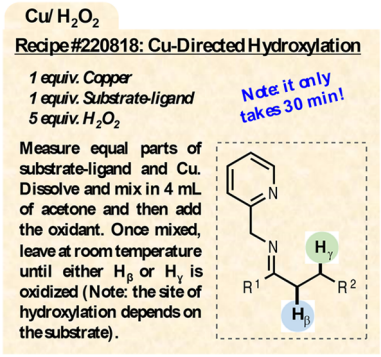
Supporting Information

ABSTRACT: The use of copper for C−H bond functionalization, compared to other metals, is relatively unexplored. Herein, we report a synthetic protocol for the regioselective hydroxylation of sp^2 and sp^3 C−H bonds using a directing group, stoichiometric amounts of Cu and H_2O_2. A wide array of aromatic ketones and aldehydes are oxidized in the carbonyl γ-position with remarkable yields. We also expanded this methodology to hydroxylate the β-position of alkylic ketones. Spectroscopic characterization, kinetics, and density functional theory calculations point toward the involvement of a mononuclear $LCu^{II}(OOH)$ species, which oxidizes the aromatic sp^2 C−H bonds via a concerted heterolytic O−O bond cleavage with concomitant electrophilic attack on the arene system.



1. INTRODUCTION

Synthetic methods that use 3d metals to carry out regioselective C−H hydroxylations are scarce.[1] One of the main challenges of this approach is to overcome the tendency of these metals to generate radical species, which usually lead to unselective C−H oxidations and functional group degradation.[2] Metalloenzymes have evolved to bypass these issues by developing active centers that can regulate the redox reactivity of the metal−O_2 intermediates and to control the substrate spatial orientation for site selectivity.[3,4] Que, Costas, and White have shown that non-heme Fe complexes catalyze the regioselective hydroxylation of complex organic molecules with H_2O_2 via formation of Fe−oxo intermediates.[5−7] On the other hand, our research group has recently reported that analogous Cu catalysts react with H_2O_2 to generate unselective hydroxyl radicals (Fenton-like chemistry).[8] The use of directing groups (DGs) is an elegant method for circumventing regioselectivity issues in organic synthesis.[9] We have recently studied the mechanism by which Cu promotes the intramolecular γ sp^3 C−H hydroxylation of steroidal imino-pyridine substrates,[10] a reaction first developed by Schönecker[11−13] and later optimized by Baran[14] (Figure 1A). On the basis of our findings, we were able to redesign the reaction conditions to use cheaper reagents with shorter reaction times under milder conditions.[10] In this work, we take advantage of this knowledge to carry out the functionalization of a wide array of substrates containing sp^2 and sp^3 C−H bonds (Figure 1B).

o-Acylphenols are commonly found in several bioactive natural products and drugs and are widely used as building blocks in the synthesis of pharmaceuticals and oxygen-containing heterocycles.[15] A classic approach for the synthesis of *o*-acylphenols is a two-step procedure that entails acylation of the phenols followed by Fries rearrangement' however, this method is not selective, and the substrate scope is limited.[16] A very attractive synthetic route is the direct regioselective hydroxylation of arylketones. Catalytic amounts of precious metals (Pd, Rh, and Ru) have been used for this purpose, but their reactivity often relies on harsh reaction conditions and the use of expensive hypervalent iodine oxidants [i.e., $PhI(CF_3CO_2)_3$].[17−19] The Yu research lab showed that Cu can promote intramolecular *ortho* hydroxylation of phenylamides at high temperatures by using excess amounts of a metal source and adding external oxazoline ligands and various additives.[19] Very recently, Uchiyama reported the directed *ortho* hydroxylation of *N*,*N*-diisopropylamides by deprotonation using excess amounts of a cuprate base followed by

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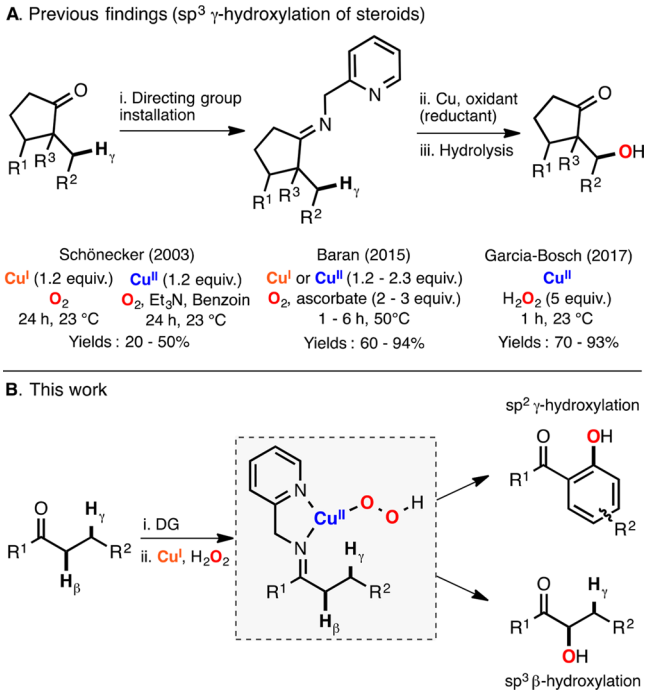


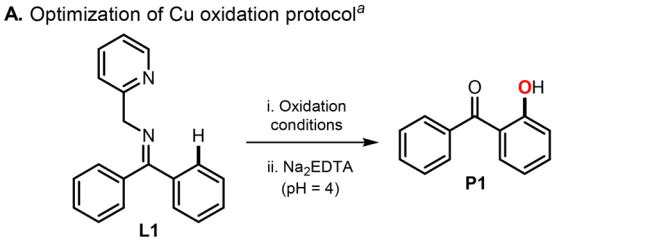
Figure 1. Cu-directed hydroxylation of sp^2 and sp^3 C−H bonds.

oxidation with ^{t}BuOOH.[20] Inspired by our findings on Cu-directed hydroxylation of sp^3 C−H bonds using H_2O_2 as an oxidant (see Figure 1A), we decided to determine if a similar methodology could be used for the synthesis of *o*-acylphenols under mild conditions.

The study of the oxidative properties of LCu/O_2 species has led to a better understanding of the reactivity of Cu-dependent monooxygenase enzymes.[21−24] For several examples, the formation of a metastable LCu/O_2 intermediate is followed by the intramolecular oxidation of the ligand scaffold, including ligand hydroxylation,[25,26] sulfoxidation,[27] and N-dealkylation.[28] In selected examples, Cu complexes have been used to promote the intermolecular oxidation of external substrates,[29] with a focus on mimicking the tyrosinase-like *ortho* hydroxylation of phenolates, including stoichiometric[30−32] and catalytic transformations.[33,34] Despite the rich reactivity of Cu/O_2 species in the synthetic inorganic literature, their use in synthetic organic chemistry has been restricted to a handful of examples.[23] Among these, it is worth mentioning Lumb's reports on Cu-catalyzed aerobic functionalization of phenols.[35−37] Réglier pioneered the field of Cu-directed oxidation of C−H bonds,[38,39] an approach that inspired the work of Schönecker[11−13] on steroid sp^3 hydroxylation. Using a similar methodology, Schindler has also shown that bidentate amines can direct the hydroxylation of sp^2 and sp^3 C−H bonds employing Cu^I and O_2 with modest oxidation yields (<50%).[40] On the basis of these precedents, we report the Cu-directed hydroxylation of sp^2 and sp^3 C−H bonds in which unprecedented regioselectivity and a deeper mechanistic understanding of the reaction mechanism are achieved (Figure 1B).

2. RESULTS AND DISCUSSION

2.1. Synthesis and Oxidation of Imino-Pyridine Substrates. Condensation of benzophenone, **S1**, with 2-picolylamine led to the formation of the substrate−ligand system **L1** (Figure 2A; see also the Supporting Information for



Entry	Metal source[b]	Oxidant[c]	Solvent	Yield **P1** (%)[d]
1	$[Cu^I(CH_3CN)_4]PF_6$	H_2O_2 (1.5 equiv.)	acetone	65
2	$[Cu^I(CH_3CN)_4]PF_6$	H_2O_2 (2.5 equiv.)	acetone	78
3	$[Cu^I(CH_3CN)_4]PF_6$	H_2O_2 (5 equiv.)	acetone	85
4	$[Cu^I(CH_3CN)_4]PF_6$	H_2O_2 (10 equiv.)	acetone	80
5	$[Cu^I(CH_3CN)_4]PF_6$	O_2, -20 °C	acetone	7
6	$[Cu^I(CH_3CN)_4]PF_6$	O_2, 0 °C	acetone	8
7	$[Cu^I(CH_3CN)_4]PF_6$	O_2, 20 °C	acetone	12
8	$[Cu^I(CH_3CN)_4]PF_6$	O_2, 50 °C	acetone	46
9	$[Cu^I(CH_3CN)_4]PF_6$	H_2O_2	CH_3CN	44
10	$[Cu^I(CH_3CN)_4]PF_6$	H_2O_2	THF	66
11	$[Cu^I(CH_3CN)_4]PF_6$	H_2O_2	CH_2Cl_2	49
12	$[Cu^I(CH_3CN)_4]PF_6$	^{t}BuOOH	acetone	0
13	$[Cu^I(CH_3CN)_4]PF_6$	CumOOH	acetone	0
14	$Cu^I(OAc)$	H_2O_2	acetone	0
15	$[Cu^I(CH_3CN)_4](CF_3SO_3)$	H_2O_2	acetone	76
16	$Cu^{II}(CF_3SO_3)_2$	H_2O_2	acetone	45
17	$Cu^{II}Cl_2$	H_2O_2	acetone	6
18	$Cu^{II}(OAc)_2$	H_2O_2	acetone	0
19	$Ni^{II}(CF_3SO_3)_2$	H_2O_2	acetone	0
20	$Fe^{II}(CF_3SO_3)_2$	H_2O_2	acetone	0
21	$Mn^{II}(CF_3SO_3)_2$	H_2O_2	acetone	0
22	$[Cu^I(CH_3CN)_4]PF_6$	H_2O_2	acetone	70[e]
23	$Cu^{II}(NO_3)_2{\cdot}3H_2O$	H_2O_2	acetone	22
24	$Cu^{II}(NO_3)_2{\cdot}3H_2O$	H_2O_2	THF	37
25	$Cu^{II}(NO_3)_2{\cdot}3H_2O$	H_2O_2/OH^-	acetone	80[f]

[a] All reactions were performed with **[L1]** = 40 mM. [b] 1 equiv. [c] 5 equiv. of 30% H_2O_2 (aq.) were used unless stated (30 min, r.t.). [d] Yields were determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [e] Oxidation of isolated $[(\boldsymbol{L1})Cu^I(CH_3CN)](PF_6)$. [f] 1 equiv. of $NMe_4OH{\cdot}5H_2O$

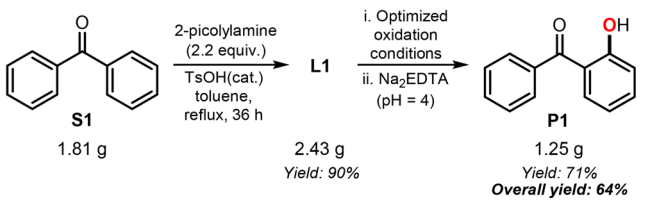


Figure 2. (A) Optimization of the reaction conditions for the hydroxylation of **L1**. (B) Gram scale oxidation of **S1** using the optimized Cu^I/H_2O_2 conditions. See the Supporting Information.

experimental details). The Cu-promoted oxidation of **L1** was optimized under various reaction conditions (Figure 2A). One-pot mixing of equimolar amounts of **L1** and $[Cu^I(CH_3CN)_4]$-(PF_6) in acetone followed by addition of 5 equiv of H_2O_2 produced the hydroxylation product **P1** in excellent yields (Figure 2A, entry 3). The use of various Cu sources was tested (Figure 2A, entries 14−18) with $[Cu^I(CH_3CN)_4](PF_6)$ reaching the highest yields (≤85%). Acetone was found to be the best solvent, followed by THF, CH_2Cl_2, and CH_3CN (Figure 2A, entries 3 and 9−11). We also analyzed the use of O_2 as an oxidant. We observed that an increase in the reaction temperature from −20 to 50 °C (Figure 2A, entries 5−8) afforded higher yields (from 7% to 46%). A similar effect was observed in the oxidation of sp^3 steroidal systems and was attributed to the formation of H_2O_2 via reduction of O_2 by Cu^I (i.e., formation of Cu^{II} and superoxide) and subsequent oxidation of the solvent, which is favored at high temperatures.[10] The efficiency of other oxidants such as cumyl

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hydroperoxide (CumOOH) and *tert*-butyl hydroperoxide (^{t}BuOOH) was also studied (Figure 2A, entries 12 and 13, respectively), but only H_2O_2 produced the oxidation product **P1**. Noticeably, when other first-row transition metal sources were used (e.g., Mn^{II}, Fe^{II}, and Ni^{II}), **P1** was not formed and only starting material was recovered (Figure 2A, entries 19–21). We performed the oxidation of **L1** on a gram scale using the optimized conditions (1 equiv of Cu^I and 5 equiv of H_2O_2), which afforded the hydroxylation product, **P1**, in 71% yield (Figure 2B; note that a 64% overall yield includes the installation of the directing group).

With the most suitable oxidation conditions in hand, we explored the hydroxylation of the substrate–ligand systems derived from the condensation of 2-picolylamine with various benzophenones, acetophenones, and benzaldehydes (Figure 3A). For all of these systems, we obtained the oxidation products derived from the γ-hydroxylation of the sp^2 C–H bond (**P1**–**P13**) with moderate to excellent yields (30–85%). Substrates in which the oxidation can occur at multiple sites (e.g., 2-acetonaphthone can be oxidized at the β sp^3 position or two different γ sp^2 positions) were also tested. Oxidation of 2-acetonaphthone occurred selectively at position 1 of the naphthyl ring with remarkable yields (**P14**, 84%). Similarly, the oxidation of the imino-pyridine substrate derived from 1-acetonaphthone led to the sp^2 hydroxylation product (**P15**, 33%). We also aimed to verify that our oxidation conditions did not generate overoxidation products. To do so, we synthesized the imino-pyridine system derived from **P1** and subjected it to oxidation with Cu^I and H_2O_2, which led to recovery of **P1** (**P16**, 0%) and differed from other Cu/O_2 systems in which intramolecular hydroxylation of phenol substituents was observed.[41]

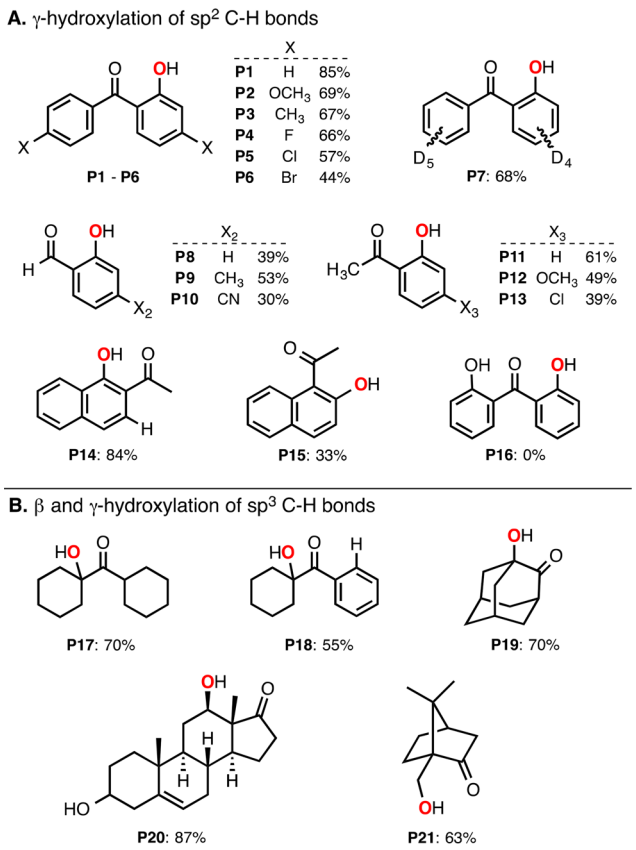

Figure 3. (A) γ-Hydroxylation of sp^2 C–H bonds. (B) β- and γ-hydroxylation of sp^3 C–H. (C) Divergent regioselectivity: γ-sp^2 hydroxylation described this work (DG, 2-picolylamine) vs β-sp^3 hydroxylation reported by Schoenebeck.[42] All reactions were performed with 40 mM **LX** using 5 equiv of 30% H_2O_2 (2.5 equiv for sp^2 C–H hydroxylation) for 30 min at room temperature in acetone. See the Supporting Information for further details.

A new set of sp^3 C–H bond-containing systems were also oxidized using Cu^I and H_2O_2 (Figure 3B). The substrate–ligand system derived from dicyclohexyl ketone was selectively oxidized at the β position in high yields (**P17**, 70%). This selectivity differs from previous findings in which the sp^3 C–H hydroxylation occurred at the γ position. Like in previous reports, the systems derived from dehydro-*epi*-androsterone and *R*-camphor were selectively oxidized at the γ site (**P20** and **P21**).[10−14] The β selectivity was also observed by the oxidation of the asymmetric system derived from cyclohexyl phenyl ketone (**P18**, 55%). More importantly, our methodology allowed synthesis of the β-hydroxylation product of 2-adamantanone with remarkable yields (**P19**, 70%), which is inaccessible using classic silyl enol ether/peroxyacid oxidations and other base-triggered oxidation reactions.[42−45] Our methodology also resulted in the γ sp^2 hydroxylation of cyclic ketones such as 2-methyl-1-tetralone with good yields (Figure 3C, **P22**, 54%). Interestingly, this regioselectivity differs from the reactivity observed by Schoenebeck and co-workers, in which a combination of Cu_2O, a strong base, and O_2 led to the oxidation of the β-sp^3 C–H bond (**P23**, 92%).[42]

2.2. Synthesis of Copper Complexes. With the substrate–ligand systems in hand, we synthesized and characterized cuprous complexes in which one or two ligand scaffolds are bound to the metal ion (Figure 4A; see also the

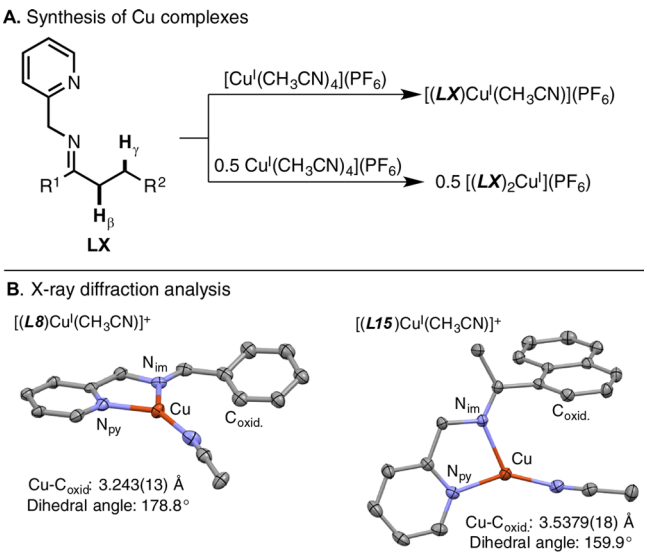

Figure 4. (A) Synthesis of Cu^I substrate–ligand complexes. (B) X-ray diffraction analyses of the systems derived from benzaldehyde (left) and 1-acetophenone (right). See the Supporting Information for further details.

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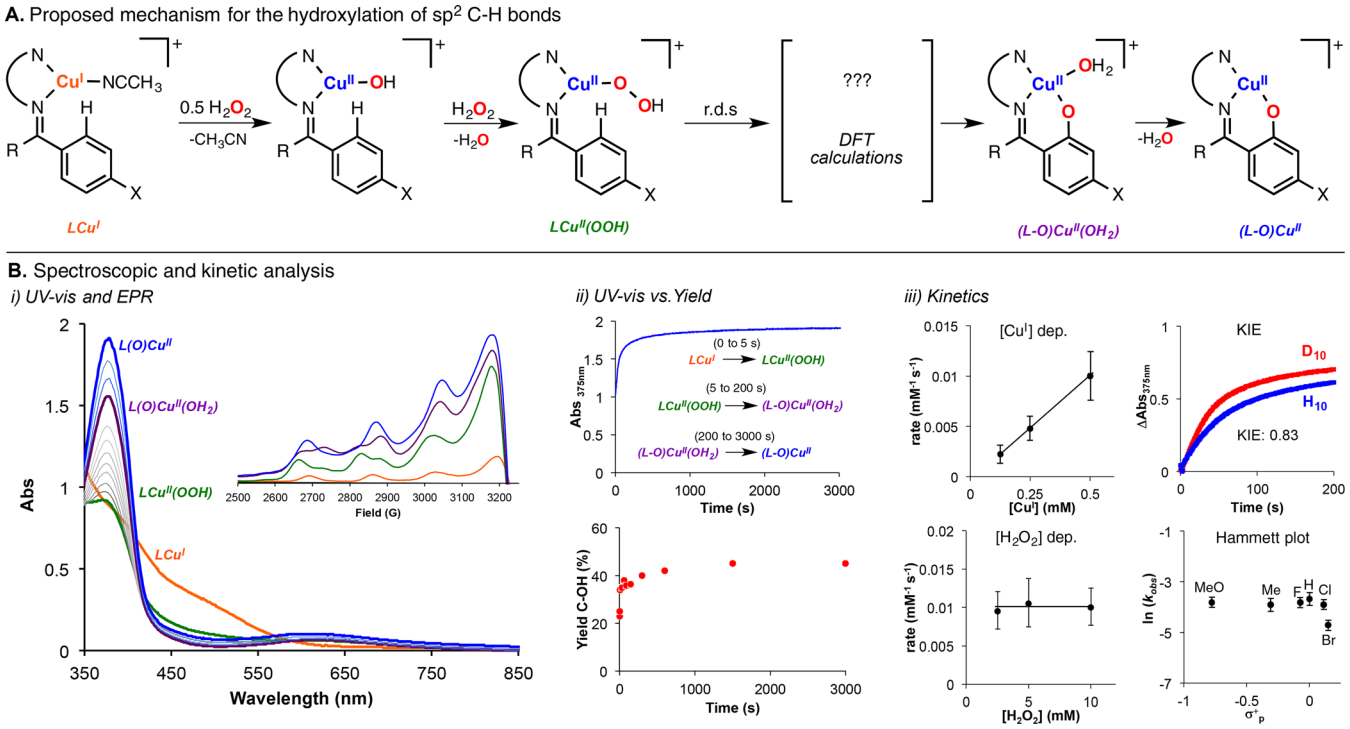

Figure 5. (A) Proposed reaction mechanism for the Cu-directed sp^2 C−H hydroxylation with H_2O_2. (B) (i) UV−vis and EPR characterization of the reaction intermediates formed upon addition of H_2O_2 (20 equiv) to the $[(L1)Cu^I(CH_3CN)]^+$ complex (0.5 mM) in acetone at −20 °C (note that the EPR shows mixtures of intermediates and only the main contributor is indicated; the $g_\perp$, $g_\parallel$, and $A_\parallel$ values can be found in the Supporting Information; also see the Supporting Information for Cu^{II} signal quantification). (ii) Evolution of the absorbance at 380 nm of the reaction (top) and analysis of the hydroxylation yields over time (bottom). (iii) Kinetic analysis of the reaction by varying $[Cu^I]_0$ and $[H_2O_2]_0$, KIE analysis, and a Hammett plot (see the text and Supporting Information for details).

Supporting Information). X-ray diffraction analysis of the isolated substrate−ligand Cu complexes provided structural information about the site of hydroxylation (Figure 4B; see also the Supporting Information). For example, analysis of the Cu^I system derived from 2-acetophenone (**L15**) showed that the γ sp^2 C−H position that will undergo oxidation ($C_{oxid.}$) is the closest to the Cu ion, with the CH_3 site pointed away from the CuN_3 T-shaped core.

2.3. Mechanistic Studies. With the isolated complexes $[(LX)Cu^I(CH_3CN)]^+$, we studied the mechanism by which the Cu-directed sp^2 hydroxylation takes place (Figure 5). In our previous study, we proposed that the reaction between LCu^I and O_2 generated LCu^{II} and superoxide that, upon oxidation of the solvent, formed H_2O_2.[10] Subsequent reaction of LCu^{II} and H_2O_2 would produce a mononuclear $LCu^{II}(OOH)$ intermediate before the rate-determining step (r.d.s.). We found that the same $LCu^{II}(OOH)$ species could also be formed by addition of H_2O_2 to the LCu^I or LCu^{II} complexes.[46] For the benzophenone-derived Cu^I complexes described herein, we suggest a similar hydroxylation pathway (Figure 5A). The reaction between LCu^I and H_2O_2 was followed by ultraviolet visible (UV−vis) and electron paramagnetic resonance (EPR) (Figure 5B, i). Addition of H_2O_2 (20 equiv) to a 0.5 mM acetone solution of $[(L1)Cu^I(CH_3CN)]^+$ at −20 °C (orange spectrum) generated a species with spectral features characteristic of $LCu^{II}(OOH)$ complexes (green spectrum, λ_{max} = 380−400 nm, ε = 2000 M^{-1} cm^{-1}).[46] Decomposition of the metastable $LCu^{II}(OOH)$ produced two mononuclear Cu^{II} species in a stepwise manner (λ_{max} ~ 380 nm), which we assign as Cu^{II} compounds in which the γ sp^2 C−H bond has been oxidized (purple and blue spectra in Figure 5B, i). We independently synthesized and characterized the Cu^{II}-bound hydroxylation product (ligand derived from **P1**), and its UV−vis spectrum overlaps with the species formed in the LCu^I/H_2O_2 reaction (see the Supporting Information). Fitting of the absorbance at 380 nm (Figure 5B, ii, top) suggested a three-step reaction in which the initial LCu^I is quickly transformed to the $LCu^{II}(OOH)$ complex (0−5 s), which evolves to generate two forms of the hydroxylation product [(L-O)$Cu^{II}(OH_2)$ from 5 to 200 s and (L-O)Cu^{II} from 200 to 3000 s]. The same species are observed by EPR, during which, upon addition of H_2O_2 to LCu^I, three distinctive mononuclear Cu^{II} complexes are consecutively formed (Figure 5B, i, inset). We confirmed that the hydroxylation of the substrate occurred at short reaction times (from 5 to 200 s after addition of H_2O_2) by analyzing the hydroxylation yields at different reaction times (Figure 5B, ii, bottom).

Kinetic analysis at different Cu and H_2O_2 concentrations indicated that the hydroxylation rate is first-order in $[LCu^I]_0$ and zero-order in $[H_2O_2]_0$, which suggested that the intramolecular hydroxylation is not a one-step bimolecular process between LCu^I and H_2O_2 and that the decay of the putative $LCu^{II}(OOH)$ intermediate occurs in the r.d.s. (Figure 5B, iii). The kinetic isotope effect (KIE) of the reaction was obtained by comparing the reaction rates of the benzophenone-derived ligand system **L1** with the benzophenone-d_{10} analogue **L7** (Figure 5B, iii; see also the Supporting Information). The KIE value (~0.83) indicates that during the r.d.s. the C−H bond that is oxidized undergoes sp^2 to sp^3 hybridization, which is consistent with an electrophilic attack of the $LCu^{II}(OOH)$ on the arene substrate.[47]

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We also obtained the reaction rates of Cu^I substrate–ligand systems derived from 4-substituted benzophenones (X = MeO, Me, F, Cl, or Br). The hydroxylation rates were found to be independent of the substituent (k_{obs} vs σ^+_p, Hammett plot, in Figure 5B, iii), which might appear to contradict the proposed direct electrophilic attack of the $LCu^{II}(OOH)$ on the aromatic system, because this reaction would be accelerated for electron-donating systems.[48] However, the possibility that the introduction of electron-donating or electron-withdrawing subtituents into the substrate–ligand structure might also affect the electrophilicity of the $LCu^{II}(OOH)$ cores should be considered: for example, the use of the 4-MeO substituent will produce a substrate more reactive toward electrophilic attack but will also lead to a more electron-rich $LCu^{II}(OOH)$ species, and hence less electrophilic (see Figure 6B), compensating for the substrate substituent effect.

To substantiate this mechanistic hypothesis, we measured the redox potentials of the benzophenone-derived Cu complexes (Figure 6). We found that the complex derived from benzophenone $[(L1)Cu^I(CH_3CN)]^+$ was reversibly oxidized in CH_3CN at −0.07 V versus ferrocene/ferrocenium ($Fc^{0/+}$). For the systems containing electron-donating groups, the Cu^I/Cu^{II} redox couple shifted to lower redox potentials (−0.11 V for 4-Me and −0.16 V for 4-MeO), while for the systems with electron-withdrawing substituents, the redox potentials were found at higher potentials (0.00 V for 4-F and 0.02 V for 4-Cl and 4-Br).

Overall, substitution of position 4 of the substrate–ligand phenyl substituent led to a change in the redox potentials of almost 0.2 V, with the 4-MeO system having the lowest redox potential and the 4-Br system having the highest, which we believe corroborates our hypothesis about the electrophilicity of the putative $LCu^{II}(OOH)$ reactive intermediates [i.e., 4-MeO substrate more prone to electrophilic attack but $LCu^{II}(OOH)$ less electrophilic].

2.4. Computational Studies. Density functional theory (DFT) calculations were carried out to improve our understanding of the mechanism by which the putative mononuclear $LCu^{II}(OOH)$ promotes intramolecular hydroxylation (Figure 7). Our calculations (including solvent and scalar relativistic corrections) at S12g/TZ2P//BP86-D3/TDZP showed that the end-on Cu^{II}–hydroperoxide intermediate (RC) undergoes heterolytic O–O cleavage with concomitant electrophilic attack of the phenyl substituent.[49] We found that the resulting Wheland-like intermediate[50] (INT1) isomerized to a Cu complex in which the H at the γ-carbon is transferred to the δ aromatic position (INT2).[51] This hydrogen shift could then trigger the deprotonation of the organic fragment by the Cu^{II}–OH core (TS3) to generate H_2O and recover the aromaticity of the ring (PC).

On the basis of these results, O–O bond cleavage is the reaction step that requires more energy. This agrees with our kinetic measurements [i.e., first-order dependence of $[Cu]_0$, zero-order dependence of $[H_2O_2]_0$, and KIE (*vide supra*)] and spectroscopic characterizations, all of which suggested that the O–O bond cleavage, coupled with electrophilic attack, is rate-limiting. We also carried out the same calculations for the 4-substituted systems 4-MeO and 4-Br. We computed that the energetics of the rate-determining step for 4-MeO and 4-Br were very similar to the values found for the 4-H system (15.8 kcal/mol for 4-H, 16.2 kcal/mol for 4-MeO, and 14.6 kcal/mol for 4-Br). These findings (~1 kcal/mol difference between the 4-substituted systems) are in agreement with the kinetic data

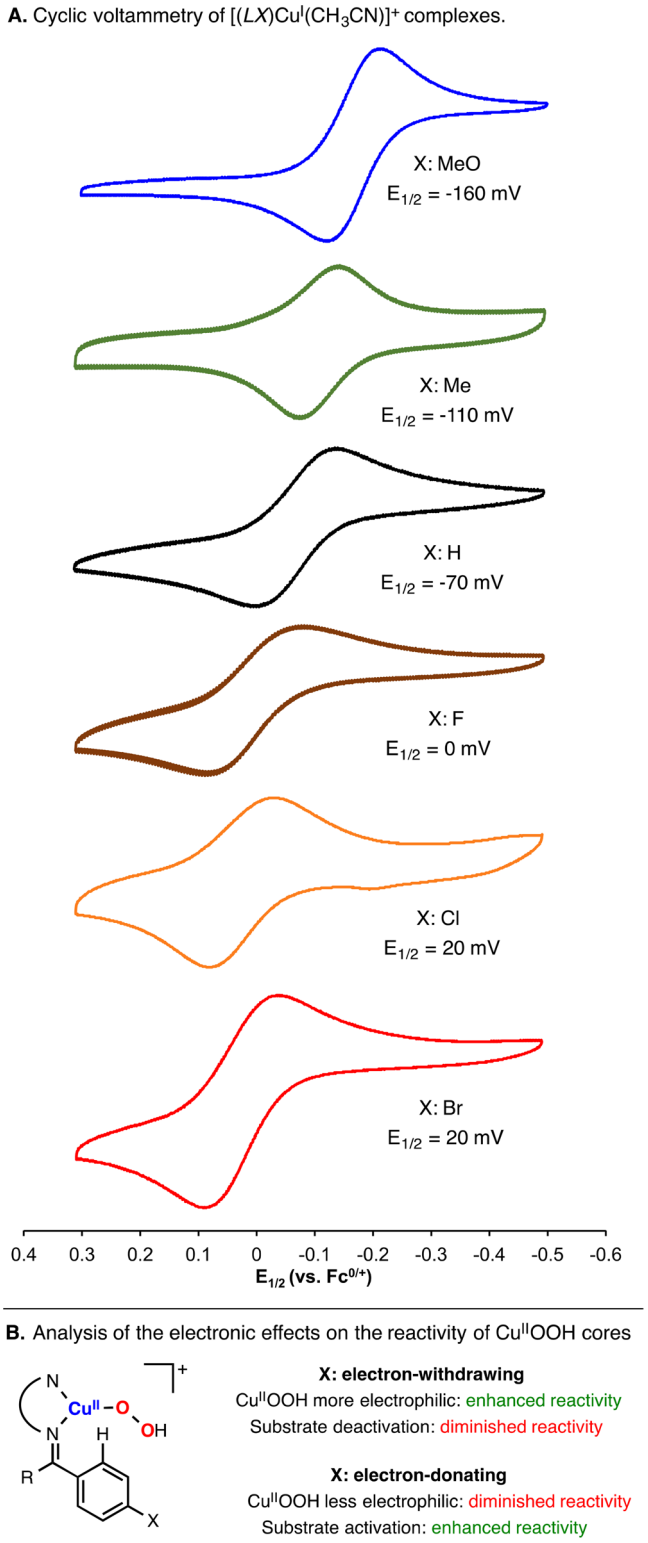

Figure 6. (A) Cyclic voltammetry measurements for the family of benzophenone-derived Cu^I complexes. (B) Effects on the reactivity of the putative $LCu^{II}(OOH)$ species.

described above in which similar reaction rates were observed for all of the 4-substituted benzophenone–ligand complexes.

2.5. Mechanistic Considerations. Copper(I) complexes react with O_2 to generate fleeting mononuclear Cu/O_2 species that are difficult to trap due to their tendency to react with other LCu^I equivalents and form more stable Cu_2O_2 cores.[21,52]

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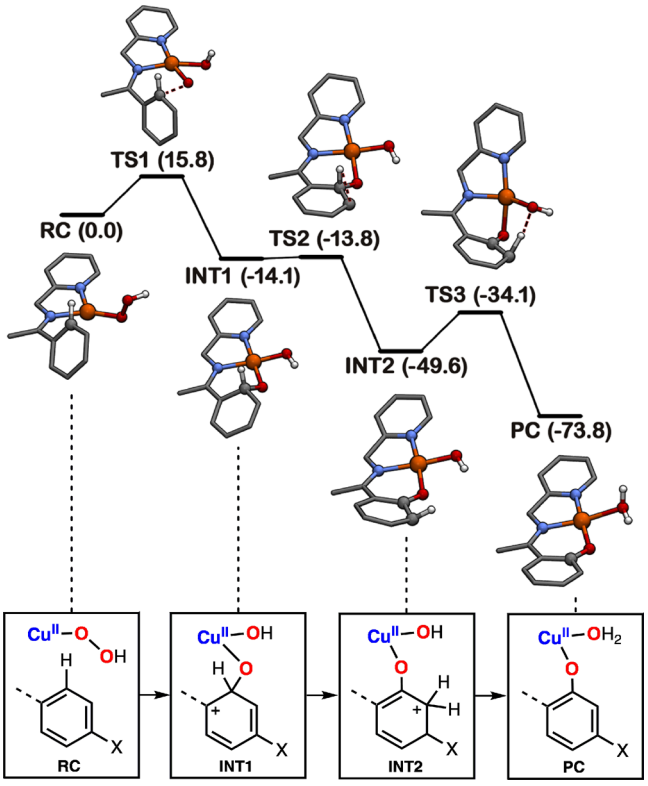

Figure 7. DFT calculations on the Cu-directed hydroxylation of sp^2 C−H bonds.

Because of this, the reactivity of Cu_2O_2 species has been studied in detail, and it has been established that end-on dicopper(II)−peroxide intermediates are normally nucleophilic oxidants while side-on dicopper(II)−peroxide complexes and dicopper(III) bis-μ-oxo compounds are considered electrophilic oxidants.[32,53,54] On the other hand, mononuclear Cu/O_2 complexes are scarce and the study of their reactivity has been restricted to a few selected systems.[55−58]

Several research groups have reported that both mononuclear and dinuclear Cu/O_2 species can perform intramolecular C−H hydroxylations (Figure 8A). For example, Karlin and co-workers observed that a Cu complex bearing a superbasic tetradentate ligand (Figure 8A, i) could undergo intramolecular sp^3 C−H hydroxylation via formation of a putative mononuclear LCu^{II}−oxyl species.[25] The same research group also found that an $LCu^{II}(OOH)$ complex promoted the intramolecular sp^2 hydroxylation of a tmpa-derived tetradentate scaffold and showed that the corresponding $L_2Cu_2O_2$ adduct did not undergo intramolecular ligand oxidation (Figure 8A, ii).[59] Itoh and co-workers were able to generate and characterize a unique Cu^{II}−superoxide complex that underwent intramolecular C−H hydroxylation via H atom abstraction of the supporting tridentate ligand (Figure 8A, iii).[26,60] Réglier,[38] Schindler,[40,61] and Tolman[48] have reported that for some bidentate and tridentate ligands, these intramolecular hydroxylations entail the formation of Cu_2O_2 cores because N2 and N3 scaffolds usually favor their formation[52] [note that both Schindler and Tolman observed the formation of $L_2Cu^{III}{}_2(O^{2-})_2$ cores before ligand hydroxylation]. On the basis of reaction yields, a similar mechanistic scenario was hypothesized by Schönecker and co-workers for the intramolecular hydroxylation of sp^3 C−H bonds in steroid-derived bidentate ligands.[11−13] However, we have recently proposed that these ligand scaffolds are more likely oxidized via formation of mononuclear Cu/O_2 intermediates (Figure 8B).[10]

Our mechanistic findings supported the idea that H_2O_2 is the active oxidant in these intramolecular hydroxylations.[10] We proposed that the reaction between LCu^I and O_2 generated LCu^{II} and free superoxide, which was reduced to H_2O_2 via solvent oxidation. The resulting LCu^{II} would then react with H_2O_2 to produce a mononuclear $LCu^{II}(OOH)$ intermediate before ligand hydroxylation. We found that this $LCu^{II}(OOH)$ species could also be generated by adding H_2O_2 to LCu^I, which would form sequentially $LCu^{II}(OH)$ and $LCu^{II}(OOH)$. Alternatively, we observed that the $LCu^{II}(OOH)$ could also be formed by addition of H_2O_2 to the corresponding LCu^{II} complex in a presence of a base. On the basis of mechanistic evidence, we suggested that the mononuclear $LCu^{II}(OOH)$ complex underwent homolytic O−O bond cleavage to generate a hydroxyl radical, which would abstract a H atom from the γ sp^3 C−H bond of the ligand scaffold before C−O bond formation (Figure 8B). The mechanistic studies of sp^2 hydroxylation presented herein also support the formation of $LCu^{II}(OOH)$ intermediates. However, the reaction pathway for sp^2 C−H hydroxylation seems to entail a concerted C−O bond formation with heterolytic O−O bond cleavage as the rate-determining step of the reaction rather than homolytic cleavage.

As we have shown, the $LCu^{II}(OOH)$ complex is formed by addition of H_2O_2 to the copper(I) complex (see Figure 5B). We also tested if $LCu^{II}(OOH)$ could be generated by adding H_2O_2 to a solution of LCu^{II} and NMe_4OH (see the Supporting Information). Interestingly, we observe that the UV−vis changes and the rate of hydroxylation for **L1** with Cu^{II}, H_2O_2, and hydroxide were identical to those found in the oxidation of **L1** with Cu^I and H_2O_2 [note that the use of NMe_4OH also led to higher reaction yields in the oxidation of **L1** with $Cu^{II}(NO_3)$ (see entry 25 in Figure 2)]. We also carried out the oxidation of **L7** (deuterated version of **L1**) in the presence of Cu^{II}, H_2O_2, and HO^-, and the rates of hydroxylation were also similar to those calculated in Cu^I/H_2O_2, leading to an inverse kinetic isotope effect [KIE = 0.89 (see the Supporting Information)]. These findings suggest that under both oxidation conditions (Cu^I/H_2O_2 or $Cu^{II}/H_2O_2/HO^-$) the same reaction intermediates are formed.

It is worth mentioning that the formation of dinuclear Cu_2O_2 species under the reaction conditions presented here cannot be ruled out. However, the fact that the Cu^I complexes do not generate Cu_2O_2 cores at low temperatures upon reacting with O_2 suggests that these species are not involved in the oxidation of the ligand scaffold. The first-order dependence on $[LCu^I]_0$ and zero-order dependence on $[H_2O_2]_0$, the observed inverse kinetic isotope effect, and the spectroscopic characterization of the reaction intermediates point toward the involvement of a mononuclear species as the active hydroxylating agent. The formation of a Cu_2O_2 species after the rate-determining step and before C−H oxidation would not lead to a kinetic isotope effect (KIE = 1). The generation of a Cu_2O_2 core before the rate-determining step could also show a first-order dependence on $[LCu^I]_0$ and a zero-order dependence on $[H_2O_2]_0$, but if that were the case, the putative Cu_2O_2 species would accumulate before ligand oxidation (r.d.s.) and would be observed spectroscopically [$Cu^{II}{}_2(O_2{}^{2-})$ and $Cu^{III}{}_2(O^{2-})_2$ intermediates are EPR silent, and their UV−vis features are very intense and characteristic]. However, the possible involvement of dinuclear species was computed, and

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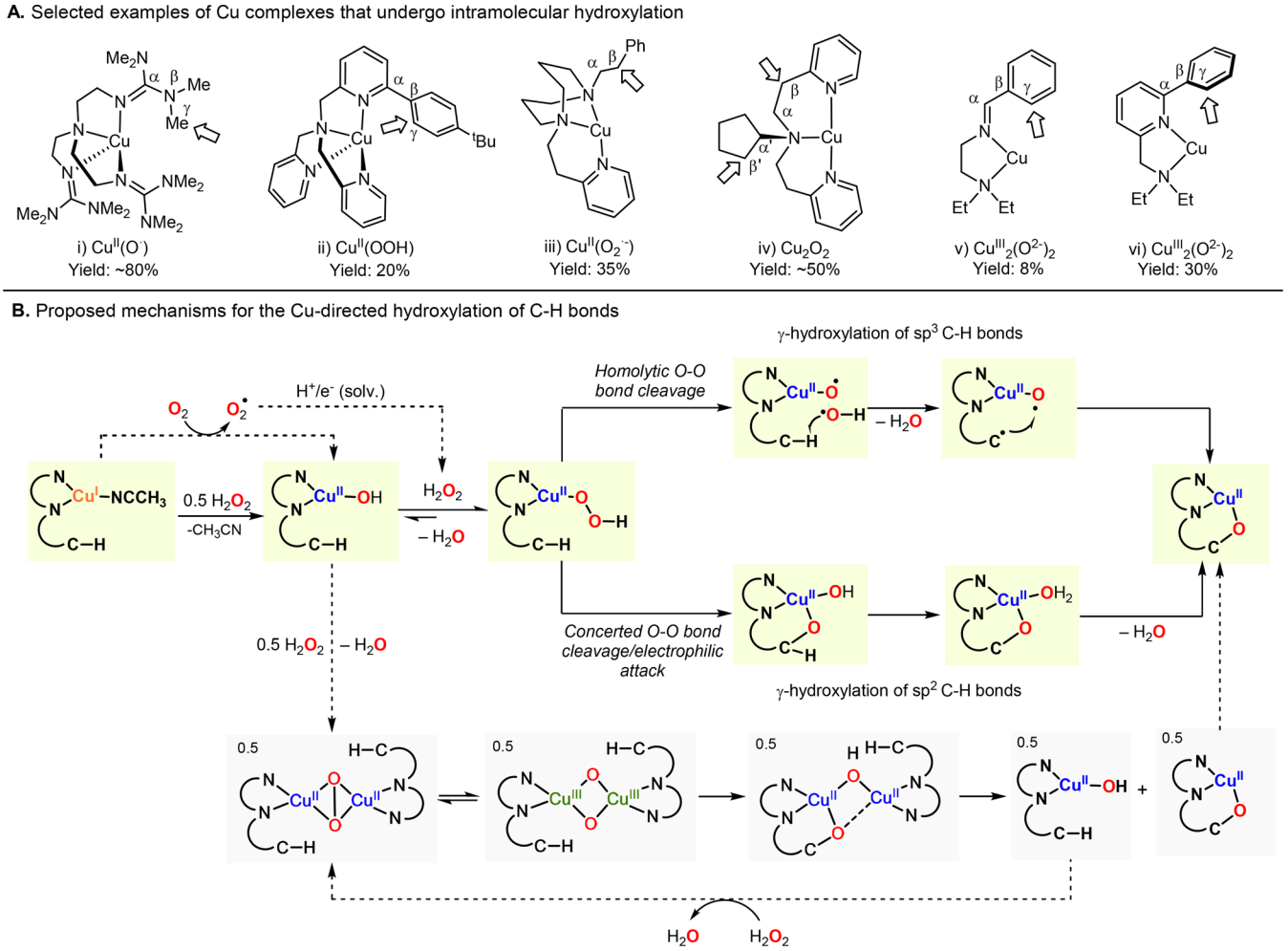

Figure 8. (A) Copper complexes that undergo intramolecular C−H hydroxylation via formation of mononuclear or dinuclear Cu/O_2 species. (B) Proposed reaction mechanisms for the intramolecular γ-hydroxylation of C−H bonds discussed herein.

we found that the activation energy for the intramolecular sp^2 C−H hydroxylation is slightly lower than that found for the $LCu^{II}(OOH)$ intermediate (see the Supporting Information). Our calculations also indicate that the generation of the $L_2Cu_2O_2$ cores from $LCu^{II}(OOH)$ is exergonic [$2LCu^{II}(OOH) \leftrightarrow L_2Cu^{II}_2(O_2^{2-}) + H_2O_2$ ($\Delta G \sim -7$ kcal/mol)], but the fact the reactions are carried out under excess amounts of H_2O_2 might favor the formation of the mononuclear $LCu^{II}(OOH)$ species, a behavior that has also been observed in the Cu-catalyzed hydroxylation of benzene by dicopper species with H_2O_2.[62]

3. CONCLUSIONS AND FUTURE PERSPECTIVES

In summary, we report here a synthetic protocol for the functionalization of ketones (and aldehydes) based on the use of directing groups (easily installed and removed), Cu, and H_2O_2, which resulted in hydroxylation products with remarkable yields and unprecedented selectivity (i.e., β-hydroxylation of sp^3 systems and selective hydroxylation in unsymmetric ketones). Close examination of the overall reaction mechanism led us to propose an $LCu^{II}(OOH)$ species as a key reaction intermediate, which has also been invoked in some Cu-containing metalloenzymes (e.g., lytic polysaccharide monooxygenases).[63] Inspired by these findings, our lab is now focused on rationally modifying the directing group to promote the hydroxylation of different substrate sites (β vs γ vs δ) and to generate a wide variety of Cu_n/O_2 species (mononuclear and dinuclear) that will lead to a better understanding of the reactivity of Cu-dependent monooxygenases.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.9b00901.

Experimental details, including substrate−ligand synthesis and oxidation, complex synthesis and characterization, kinetic analysis, spectroscopic characterization, and DFT calculations (PDF)

Accession Codes

CCDC 1880982−1880987 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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