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Practical One-Pot Multistep Synthesis of 2H-1,3-Benzoxazines Using Copper, Hydrogen Peroxide, and Triethylamine

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In this article, we describe simple one-pot syntheses of 2H-1,3-benzoxazines from ketones utilizing an imino-pyridine directing group (R^1R^2-C=N–CH_2-Pyr), which promotes a Cu-directed sp^2 hydroxylation using H_2O_2 as oxidant and followed by an oxidative intramolecular C–O bond formation upon addition of NEt_3. This synthetic protocol is utilized in the gram scale synthesis of the 2H-1,3-benzoxazine derived from benzophenone. Mechanistic studies reveal that the cyclization occurs via deprotonation of the benzylic position of the directing group to produce a 2-azallyl anion intermediate, which is oxidized to the corresponding 2-azaallyl radical before the C–O bond formation event. Understanding of the cyclization mechanism also allowed us to develop reaction conditions that utilize catalytic amounts of Cu.

2H-1,3-Benzoxazines are common motifs in bioactive molecules that have multiple applications including pharmaceutics (e.g., TCV-295 is used as a potassium channel-activating agent to treat asthma, hypertension, etc.) and as bactericides (Figure 1A).[1] Despite their relevance only a handful of synthetic routes have been reported, which usually entail tedious multistep procedures with poor overall yields and limited product scope.[2] Our research lab is interested in developing practical synthetic protocols inspired by the oxygenase and oxidase reactivity of Cu-dependent metalloenzymes by which challenging functionalization reactions (e.g., selective C–H hydroxylation) can be achieved using cheap reagents under mild conditions (e.g., Cu and H_2O_2 at room temperature).[3] In 2017, we reported the intramolecular γ-hydroxylation of sp^3 C–H bonds via installation of a directing group (DG) to ketone substrates and selective hydroxylation using Cu^{II} and H_2O_2 (Figure 1B).[4] To our delight, this protocol has been recently used in the total synthesis of nortriterpenoids and ritterazine B.[5] In 2019, we described that this methodology can also be applied to the β-hydroxylation of sp^3 C–H bonds and the γ-hydroxylation of sp^2 C–H bonds.[6] In the hydroxylation of substrate-ligand derived from benzophenone using Cu, H_2O_2 and triethylamine (NEt_3), we observed the formation of an unknown product. This unidentified product, which is formed by exposing the hydroxylation product to NEt_3 in the presence of Cu^{II}, was characterized by NMR as the 2H-1,3-benzoxazine heterocycle produced via intramolecular C–O bond formation between the benzylic position of the DG and the phenolic moiety (Figure 1C). This serendipitous finding triggered the work that we present in this paper, in which describe that 2H-1,3-benzoxazine products can be generated in one-pot syntheses using cheap reagents (Cu^{II}, H_2O_2 and NEt_3) under mild and practical reaction conditions.

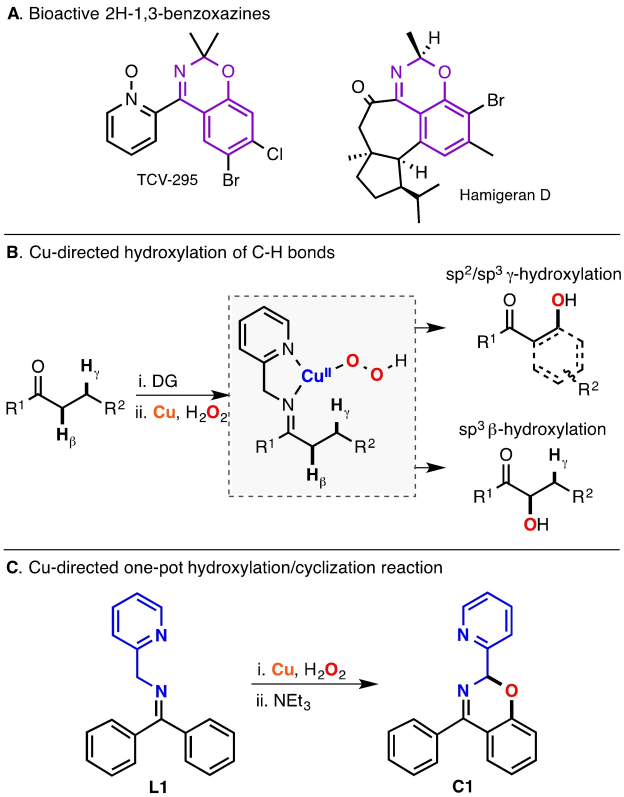

Figure 1. Structure of relevant 2H-1,3-benzoxazines (A), Cu-directed hydroxylation of C–H bonds (B) and serendipitous Cu-promoted hydroxylation/cyclization reactions observed in the oxidation of L1 (C).

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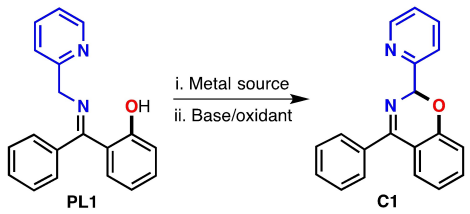
The cyclization reaction was optimized for the substrate-ligand derived from 2-hydroxybenzophenone **PL1** (Figure 2). The reactions were carried out at room temperature and under air by mixing solutions of **PL1** with the metal source and base. We found that 1 equiv. of $Cu^{II}(CF_3SO_3)_2$ and 5 equiv. of NEt_3 were optimal for the formation of the cyclic product (Figure 2, entries 1 to 4). We also observed that other bases such as TMG (1,1,3,3-tetramethylguanidine), DBU (1,8-diazabicyclo[5,4,0] undec-7-ene), TBD (1,5,7-triazabicyclo[4,4,0]dec-5-ene) or pyridine produced the 2H-1,3-benzoxazine product with smaller yields (Figure 2, entries 5 to 8). Other Cu^{II} sources were also utilized and we found that $Cu^{II}(NO_3)_2 \cdot 3H_2O$ (cheapest Cu salt) reached the highest yields. Other metal sources (Fe^{II}, Mn^{II}, Ni^{II}, Zn^{II} and Pd^{II}) did not form the cyclization product or did in very minor yields. Interesting, cyclization in other solvents (THF, CH_2Cl_2 and CH_3CN) led to similar yields to the ones obtained in acetone.

After optimizing the cyclization reaction, we decided to develop a one-pot synthetic protocol to oxidize a series of substrate-ligands (**LX**) to the corresponding hydroxylation products (**PLX**) and cyclization products (**CX**) (Figure 3A). The hydroxylation of the **LX** systems was performed utilizing 1 equiv. of $Cu^{II}(NO_3)_2 \cdot 3H_2O$, 1 equiv. of NMe_4OH and 5 equiv. of H_2O_2, which allowed to obtain the **PLX** products with good yields. 4,4′-substituted benzophenones were oxidized with yields similar to the ones reported in our previous work (see **PL1-PL5** in Figure 3A). In this paper, we also analyzed the hydroxylation of unsymmetric 2-susbtituted benzophenones (**PL6-PL9**), which were functionalized at the *ortho*-position of the unsubstituted ring in a selective fashion (see S.I. for synthesis of L6-L9). The hydroxylation products derived from 4-substituted acetophenones (**PL10-PL13**) and acetonaphthones (**PL14** and **PL15**) were also obtained with moderate yields (20–40%). 4-substituted benzaldehydes could also be oxidized but did not produce the resulting **PL** products (**PL16-PL18**) since these were hydrolyzed to the corresponding 4-substituted 2-hydroxy-benzaldehydes (see S.I. for details). The products derived from sp^2 C–H hydroxylation of butyrophenone (**PL19**) and 2-methyl-1-tetralone (**PL20**) were obtained with excellent selectivity (i.e., no sp^3 C–H hydroxylation).



Entry	Metal source[b]	Base/oxidant[c]	Solvent	Yield **C1** (%)[d]
1	$Cu^{II}(CF_3SO_3)_2$	NEt_3 (1 equiv)	acetone	42
2	$Cu^{II}(CF_3SO_3)_2$	NEt_3 (2.5 equiv)	acetone	46
3	$Cu^{II}(CF_3SO_3)_2$	NEt_3	acetone	58
4	$Cu^{II}(CF_3SO_3)_2$	NEt_3 (10 equiv)	acetone	56
5	$Cu^{II}(CF_3SO_3)_2$	TMG[g]	acetone	29
6	$Cu^{II}(CF_3SO_3)_2$	DBU[h]	acetone	0
7	$Cu^{II}(CF_3SO_3)_2$	TBD[i]	acetone	2
8	$Cu^{II}(CF_3SO_3)_2$	Pyridine	acetone	11
9	$Cu^{II}(CF_3SO_3)_2$	NEt_3	THF	59
10	$Cu^{II}(CF_3SO_3)_2$	NEt_3	CH_2Cl_2	55
11	$Cu^{II}(CF_3SO_3)_2$	NEt_3	CH_3CN	41
12	$Cu^{II}(CH_3CO_2)_2$	NEt_3	acetone	13
13	$Cu^{II}Cl_2$	NEt_3	acetone	44
14	$Cu^{II}(ClO_4)_2 \cdot 6H_2O$	NEt_3	acetone	44
15	$Cu^{II}(NO_3)_2 \cdot 3H_2O$	NEt_3	acetone	67
16	$Cu^{II}(NO_3)_2 \cdot 3H_2O$	NEt_3	THF	41
17	$[Cu^{I}(CH_3CN)_4]PF_6$	NEt_3	acetone	2
18	$Fe^{II}(CH_3CO_2)_2$	NEt_3	acetone	7
19	$Fe^{II}(CF_3SO_3)_2$	NEt_3	acetone	12
20	$Mn^{II}(CH_3CO_2)_2$	NEt_3	acetone	5
21	$Ni^{II}(CH_3CO_2)_2$	NEt_3	acetone	0
22	$Zn^{II}(CH_3CO_2)_2$	NEt_3	acetone	0
23	$Pd^{II}(CH_3CO_2)_2$	NEt_3	acetone	0

[a] All reactions were performed with [**PL1**] = 40 mM. [b] 1 equiv of metal source. [c] 5 equiv of base under air, unless stated (30 min, r.t.). [d] Yields were determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [e] Reaction and work-up under anaerobic conditions. [f] Oxidation carried out in an O_2-saturated acetone solution. [g] 1,1,3,3-tetramethylguanidine. [h] 1,8-diazabicyclo[5,4,0]undec-7-ene. [i] 1,5,7-triazabicyclo[4,4,0]dec-5-ene.

Figure 2. Optimization of the cyclization reaction conditions.

The one-pot sequential hydroxylation-cyclization of the **LX** systems to **CX** was accomplished by performing the hydroxylation with Cu^{II}, NMe_4OH and H_2O_2 and, after 30 minutes, adding 5 equiv. of NEt_3 (Figure 3A). The cyclization products were obtained with modest overall yields (ca. 35%) partially attributed to hydrolysis of the imine bond in **LX** and **PLX**. These overall yields are also in agreement with the average yield obtained in the sp^2 hydroxylation (ca. 60%) and the optimized cyclization (ca. 70%). Despite the yields, the **CX** products were obtained as sole products by filtering the solutions obtained after work-up through a basic alumina plug. Using this one-pot methodology, we synthesized and characterized 15 novel 2-H-1,3-benzoxazines derived from 4-substituted benzophenones (**C1-C5**), 2-substituted benzophenones (**C6-C9**), 4-substituted acetophenones (**C10-C13**), acetonaphthones (**C14** and **C15**), butyrophenone (**C19**) and 2-methyl-1-tetralone (**C20**) (see Figure 3). For 4-substituted benzaldehydes, we did not observe the formation of the corresponding cyclization products (**C16-C18**) since we believe the **PLX** imine products are hydrolyzed in the reaction crude. We attempted to carry out the cyclization of the independently synthesized **PL16** using Cu^{II} and NEt_3 but no cyclization was observed and only the products derived from **PL16** hydrolysis could be isolated (see SI).

We also performed the one-pot synthesis of **C1** from **L1** at a gram scale (Figure 3B). After hydroxylation with copper, tetramethylammonium hydroxide and hydrogen peroxide and cyclization with triethylamine, we were able to isolate **C1** by stirring the reaction crude overnight with a saturated aqueous solution of Na_4EDTA and purifying the resulting organic products by flash column chromatography in basic alumina (yield: 26%, 575 mg). The isolated **C1** product was transferred inside the glovebox and it was reacted with 1 equiv. of $[Cu^{I}(CH_3CN)_4]PF_6$ to produce the corresponding cuprous complex (Figure 3B, right). The resulting complex, $[(\mathbf{C1})Cu^{I}(CH_3CN)]PF_6$, was characterized by X-ray diffraction analysis and the C–N distances and N–C–O angles measured were consistent with the formulation of **C1** as 2H-1,3-benzoxazine product.[7] We also noticed that in this cuprous complex, the directing group and the Cu ion were oriented towards the phenyl ring that was not oxidized, which suggested that after the cyclization reaction a second hydroxylation process could be promoted. In fact, hydroxylation of the cyclization product of **C1** to **PC1** was accomplished by adding stoichiometric amounts of [Cu^{I}-

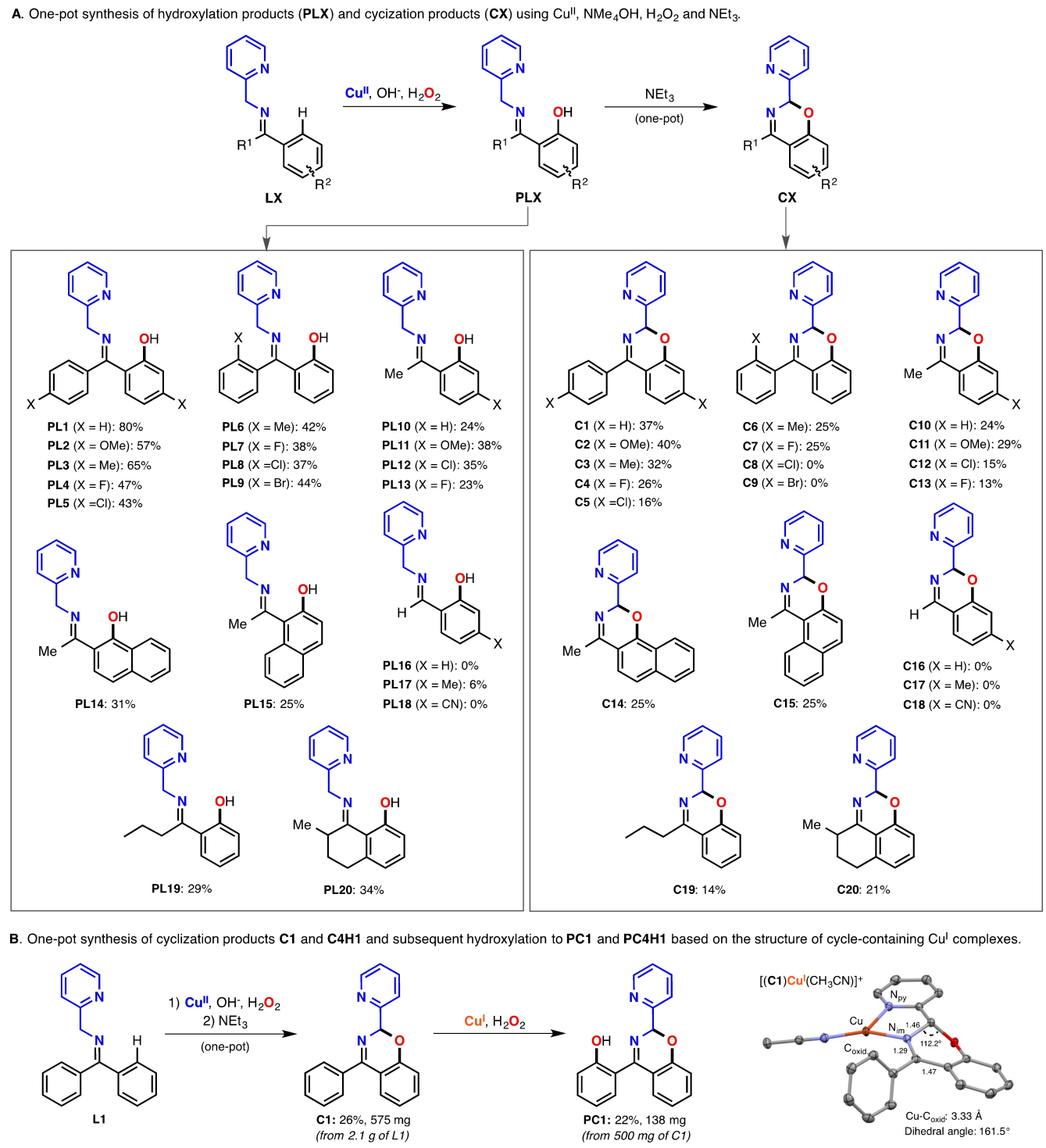
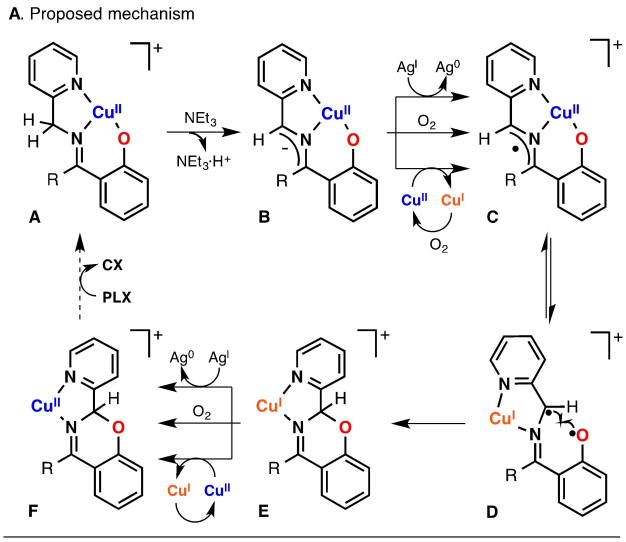


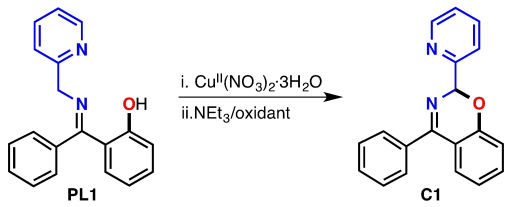
Figure 3. (A) One-pot hydroxylation of **LX** to **PLX** and hydroxylation/cyclization of **LX** to **CX** using Cu^{II}, hydroxide, H_2O_2 and NEt_3. (B) Gram-scale synthesis of cyclization products **C1** and subsequent hydroxylation to **PC1** based on the X-ray diffraction structure of $[(\mathbf{C1})Cu^{I}(CH_3CN)](PF_6)$ (see S.I. for details).

$(CH_3CN)_4](PF_6)$ and 5 equiv. of H_2O_2 (Figure 3B). **PC1** could be isolated after Na_4EDTA (pH:11)/EtOAc work-up followed by flash column chromatography (Figure 3B).

We have previously reported that for the sp^2 substrate-ligands (e.g. **L1**), the Cu-promoted hydroxylation of sp^2 C–H bonds involves the formation of mononuclear Cu^{II}-hydroperoxo species.[6] The proposed mechanism for the cyclization reaction is depicted in Figure 4A. Deprotonation of the Cu^{II}-PLX complex (**A**) by NEt_3 is proposed to produce a 2-azaallyl anion (**B**) that undergoes an intermolecular $1e^-$ oxidation event to generate a 2-azaallyl radical (**C**) before imine isomerization (**D**) and radical-radical C–O bond formation (**E**).[8] In order to support the



B. Mechanistic evidence: O_2, excess Cu^{II} and Ag^{I} as oxidants



Entry[a]	Cu^{II} equiv	Oxidant	Yield **C1** (%)[b]
1	1 equiv	Air	67
2	1 equiv	No air (under N_2)[c]	25
3	2 equiv	No air (under N_2)[c]	66
4	1 equiv	1 equiv $AgNO_3$ (under N_2)[c]	72
5	0.1 equiv	Air	15
6	0.1 equiv	1 equiv $AgNO_3$ (under N_2)[c]	27
7	0.1 equiv	2.5 equiv $AgNO_3$ (under N_2)[c]	57
8	0.1 equiv	2.5 equiv $AgNO_3$ (Air)	55
9	0.1 equiv	5 equiv $AgNO_3$ (Air)	50
10	0.01 equiv	5 equiv $AgNO_3$ (Air)	40

[a] All reactions were performed with [**PL1**] = 40 mM in acetone and using 5 equiv of NEt_3 (30 min, r.t.) [b] Yields were determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c]Reaction and work-up under anaerobic conditions.

C. Mechanistic evidence: cyclization of substrate-ligand isomers

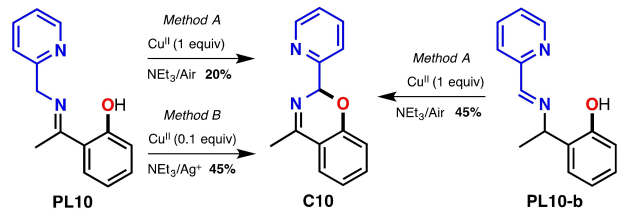


Figure 4. (A) Mechanistic proposal for the cyclization of **PLX** substrates. (B) Cyclization of **PL1** using stoichiometric and catalytic amounts of Cu^{II}. (C) Cyclization of **PL10** and its isomer **PL10-b** to **C10**.

mechanism, we performed the oxidation of **PL1** under different reaction conditions (Figure 4B). We found that when the reactions were carried out under anaerobic conditions, the reactions yield diminished (from 67% to 25%) but **C1** was still formed, which suggested that the oxidation of intermediate B did not require O_2. When the reaction was done under N_2 using 2 equiv. of Cu^{II} the yields were restituted, implying that the $1e^-$ oxidation of B did not involve the formation of a Cu/O_2 intermediate and that Cu^{II} could also act as $1e^-$ oxidant. In fact, the cyclization of **PL1** under anaerobic conditions using 1 equiv. of Cu^{II} and 1 equiv. of $AgNO_3$ ($1e^-$ oxidant) produced **C1** with excellent yields (72%).

The formation of the proposed 2-azaallyl radical was supported by the fact that the substrate derived from 2-hydroxyacetophenone **PL10** and its isomer **PL10-b** produced the same cyclization product (Figure 4C). For both substrates, the oxidation of the corresponding benzylic position generates a common 2-azaallyl radical intermediate that will undergo intramolecular C–O bond formation to product the same cyclic product.[9] Our mechanistic proposal also suggests that after C–O bond formation, the resulting cuprous product **E** can be oxidized and release copper(II), which could potentially oxidize another molecule of PLX. When the cyclization of **PL1** was carried out using catalytic amounts of Cu^{II} (10 mol%) under air, small amounts of **C1** were formed (Figure 4B, entry 5). However, when the reaction was performed with 0.1 equiv. of Cu^{II} under anaerobic conditions and using Ag^+ as oxidant, the product **C1** could be produced catalytically (Figure 4B, entry 6 and 7). For practical purposes, the reaction with Cu^{II} and Ag^+ was performed under air and we were able to utilize small amounts of Cu^{II} catalyst (1 mol%) to reach notable turnover numbers (Figure 4B, entry 10).

The development of these catalytic conditions, which required small amounts of Cu^{II}, prompted us to test if these could be applied in the cyclization of sensitive substrates such as **PL10** (Figure 4C). While in the cyclization of **PL10** performed using stoichiometric amounts of Cu^{II} and air we observed small yields (20%), when the reactions were done using 10 mol% of Cu^{II} and 5 equiv. of $AgNO_3$ the yields improved (45%).

To summarize, we have developed a one-pot practical and cheap method for the synthesis of 2H-1,3-benzoxazines utilizing a directing group as building block, Cu^{II}, H_2O_2 and NEt_3. Our findings suggest that the cyclization reactions entail the formation of Cu/2-azaallyl intermediates, which can also be formed using stoichiometric one-electron oxidants and catalytic amounts of Cu. Our current efforts are focused on expanding these one-pot cyclization reactions to substrate-ligands derived from alkylic ketones, aldehydes and other directing groups, along with the umpolung functionalization of amines and imines.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: 2-Azaallyl radicals · 2H-1,3-Benzoxazines · Copper · Cyclization · One-pot synthesis

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