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Predictably Selective (sp^3)C–O Bond Formation through Copper Catalyzed Dehydrogenative Coupling: Facile Synthesis of Dihydro-oxazinone Derivatives

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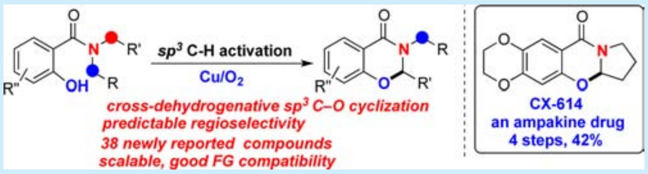
Supporting Information

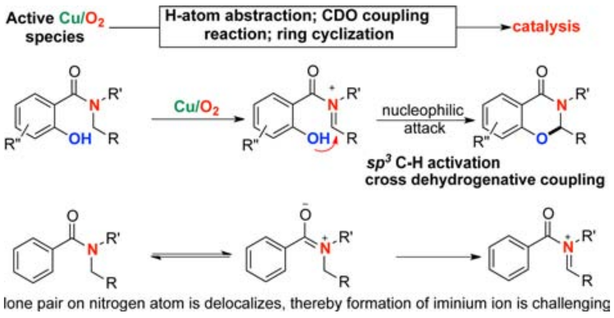
ABSTRACT: An intramolecular dehydrogenative (sp^3)C–O bond formation in salicylamides can be initiated by an active Cu/O$_2$ species to generate pharamaceutically relevant dihydro-oxazinones. Experimental findings suggest that stereoelectronic parameters in both coupling partners are controlling factors for site selectivity in bond formation. Mechanistic investigations including isotope labeling, kinetic studies helped to propose a catalytic cycle. The method provides a convenient synthesis of an investigational new medicine CX-614, which has potential in finding treatment for Parkinson's and Alzheimer's diseases.



Over the past decade, substantial research interest has been focused on developing selective C–C bond formation reactions through Cu-catalyzed cross-dehydrogenative coupling.[1] The basis of this waste-minimized approach, popularized by the Chao-Jun Li group,[2] lies in the oxidative C–H activation of both of the coupling partners. In most of the cases, a tertiary amine has been used as one of the partners where a C–H bond next to the heteroatom has been activated.[3] During the course of these reactions, an iminium intermediate formed, which is subsequently trapped by a carbon-centered nucleophile.[4] Despite the significant advances made in this greener side of the cross-coupling chemistry, application of this strategy in intramolecular C–heteroatom bond formation to synthesize pharmaceutically important and synthetically challenging heterocycles is far less studied.[5]

In this context, we planned to study cross-dehydrogenative sp^3 C–O bond formation involving an amide and phenol under an O$_2$ atmosphere with a Cu-based small molecule catalyst (Scheme 1). Formation of an iminiun ion from amide, which is essential to implement such a strategy, is challenging due to delocalization of the nitrogen lone pair to the carbonyl oxygen (Scheme 1). To overcome this difficulty, we thought to develop a highly reactive catalyst system, which will generate an iminiun ion transiently, followed by an intramolecular phenolic moiety intercepting this intermediate to generate medicinally relevant heterocyclic scaffolds (Scheme 1). The power of this strategy is described herein by generating an exemplary set of dihydro-oxazinone compounds (38 examples), most of which represent new chemical entities. The dihydro-oxazinone moiety is found in a number of pharmaceutically relevant scaffolds such as CX-614[6] and DRF-2519.[7] Optimized conditions[8] with the diethyl amide of salicylic acid in the presence of 5 mol % of CuCl$_2$ in *m*-xylene produced cyclic compound **2b** (isolated, 80%; GC yield, 85%) by employing active Cu/O$_2$ species.

Scheme 1. Synthetic Design



The scope of the reaction was investigated by varying both the amine and the acid part. A gram scale reaction gave a 75% isolated yield (**2b**) of the cyclized product. Amides synthesized from cyclic amines such as pyrrolidine (**2d**, 83%), piperidine (**2e**, 77%), and azepane (**2f**, 71%) also underwent C–O bond formation in preparatively useful yields. The relative ease of product formation observed upon varying substituents at the 5-position of the salicylic acid unit (e.g., **2a**, **2i**–**2l**, and **2n**) suggests that stereoelectronic parameters are strong contributing factors in these C–O bond formation reactions. Specifically a strong electron-withdrawing group, such as nitro, in a salicylic acid moiety deactivates the nucleophile, thereby decreasing the efficiency of the cyclization reaction considerably (**2i** and **2n**).

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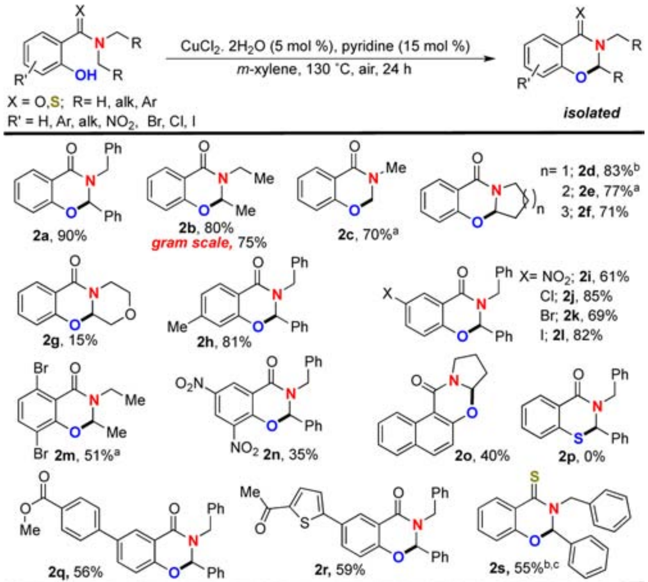
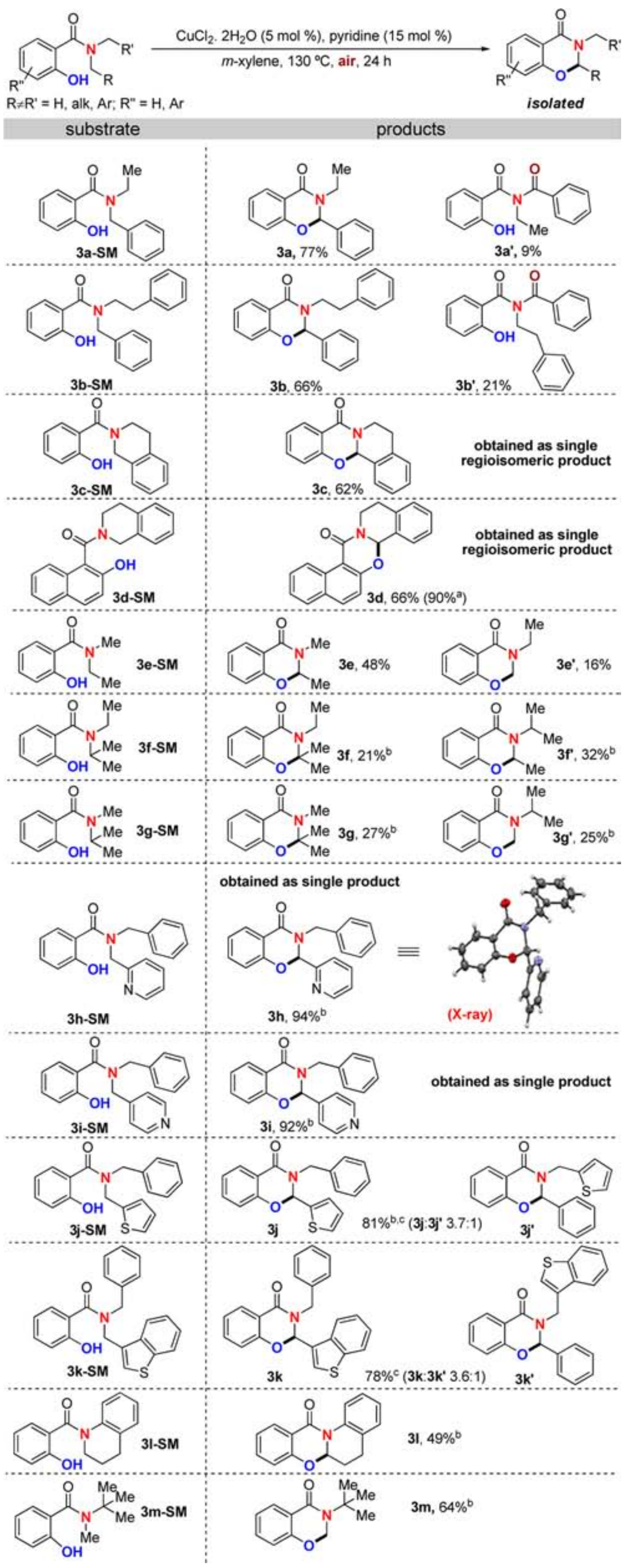
Scheme 2. Cyclization with Symmetric Amines



^{a}10 mol % Cu. ^{b} 20 mol % Cu. ^{c} 10% **2a** isolated as side product.

Scheme 3. Cyclization with Unsymmetric Amines (SM, Starting Material)



^{a}Yield based on recovered starting materials. ^{b} 20 mol % Cu. ^{c} Total yield of two isomers.

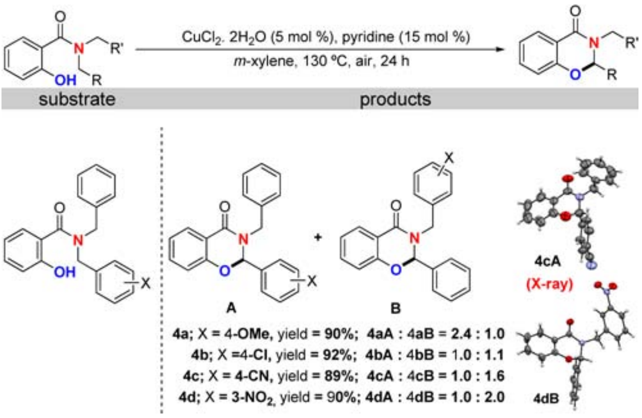
To examine the site selectivity aspect of this C−O coupling, a number of unsymmetrical amides were tested (Scheme 3). Despite having two possible *N*-methylene sites for cross-dehydrogenative sp^3 C−O bond formation in **3a-SM**, we observed cyclization only at the benzylic position in the presence of an *N*-ethyl moiety (**3a**). Specifically, complete selectivity for C−O bond formation was observed at the benzylic side of tetrahydroisoquinoline while incorporated either in salicylamide (**3c**) or in 2-hydroxy-1-naphthamide (**3d**). Consistent with this observation, not even a trace of C−O bond formation at the *N*-phenethyl arm was detected in the presence of a *N*-benzyl group (**3b**). A lower product yield in the case of **3b** (66%) can be attributed to the formation of ketone product **3b**′ (21%) via an oxygen rebound step (*vide infra*) originating from the active Cu/O$_2$ species.

Cyclization occurred preferentially at the more electron-rich (2°) C−H bonds (**3e**) compared to (1°) C−H bonds (**3e**′). But, in the case of ethyl (2°) vs isopropyl (3°) (**3f-SM**) or methyl (1°) vs isopropyl (**3g-SM**), the steric factor dominated over the electronic factor. The Cu catalyst even recognized subtle electronic differences in *N*-picolylamine versus *N*-benzylamine. Therefore, salicylamides generated from either 2-picolyl or 4-picolyl amine yielded the C−O coupled product exclusively at the pyridine end (**3h**, 94%, X-ray;[9] **3i**, 92%) in the presence of the *N*-benzyl moiety. Consistent with this observation, cyclization in **3j-SM** and **3k-SM** preferentially occurred at the heterocyclic end.

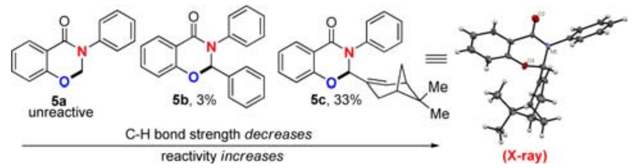
Encouraged by these results, we probed the electronic dependence of the method by incorporating either an electron-donating or -withdrawing group in the amine part (Scheme 4). A noticeable electronic bias was evident, as preferential cyclization occurred on the electron-rich side.[8,9] Consistent with this, regioselectivity followed the order of electron donating ability on phenyl substitution (OMe > H > Cl > CN > NO$_2$) of the dibenzylamine part (**4a**−**4d**).

Subsequently we tested the salicylamide of *N*-methyl aniline, which was found to be unreactive (**5a**) under the standard reaction conditions (Scheme 5). Even the corresponding *N*-phenyl benzyl salicylamide failed to provide the desired cyclic product (**5b**, 3%). This lack of reactivity of *N*-phenyl amides may be attributed to the additional delocalization of the *nitrogen* lone pair into the phenyl ring, which in turn failed to stabilize the

Scheme 4. Electronic Dependence



Scheme 5. Reactivity Depends on C−H Bond Strength

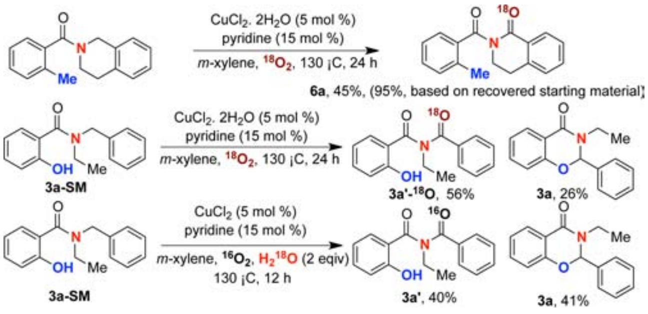


incipient iminium intermediate. To validate this hypothesis, an allylic moiety was incorporated (**5c**) into one end of the amine, as allylic C−H bonds are comparably weaker than the rest. In this case, C−O bond formation occurred in 33% yield without an allylic C−H shift in the cyclized product (X-ray).[9]

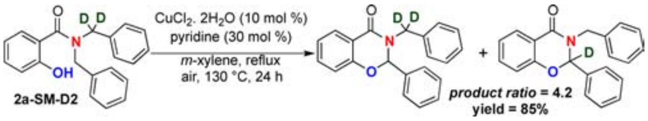
To elucidate mechanistic details, a crossover experiment was performed. A mixture of two amides, generated from piperidine and pyrrolidine, did not produce even a trace amount of the crossover compounds in either the starting materials or product.[8] Control experiments carried out under N_2 failed to produce the cyclized product.[8] Formation of **2b** decreased from 85% to 20% upon addition of TEMPO.[8] Furthermore, the detection of the homocoupling product from 2,4-di-*tert*-butyl phenol indicates that a radical is likely.[8]

Replacement of the hydroxyl moiety with a methyl group resulted in formation of the keto product **6a**, (Scheme 6; also see **3c-SM**, Scheme 3). A labeling study with $^{18}O_2$ further confirmed the Cu/O_2 species as being the active intermediate since ∼98% O-18 incorporation was observed in the product **8a**. As anticipated, a similar experiment with **3a-SM** and Cu/$^{18}O_2$ resulted in >99% O-18 labeling in **3a′-^{18}O** (Scheme 6). Please note that the O-18 labeling experiment was carried out upon evacuating the reaction flask and subsequent injection of $^{18}O_2$ by syringe. Under these conditions (compared to the reaction under air), cyclized product **3a** formation decreased to 26% and the keto product **3a′** increased to 56%. A first-order rate dependence (rate order = 1.33)[8] on *N*,*N*′-diethylsalicylamide (**2b-SM**) was established which is consistent with an intramolecular reaction. Further insights came by setting up an intramolecular substrate competition, −N(CH$_2$Ph) versus −N(CD$_2$Ph) cross-dehydrogenative sp^3 C−O cyclization in **2a-SM-D2** (Scheme 7). It has been observed that the C−H bond is more facile for cyclization over the C−D bond with a resultant product ratio of 4.2 (Scheme 7).[4d]

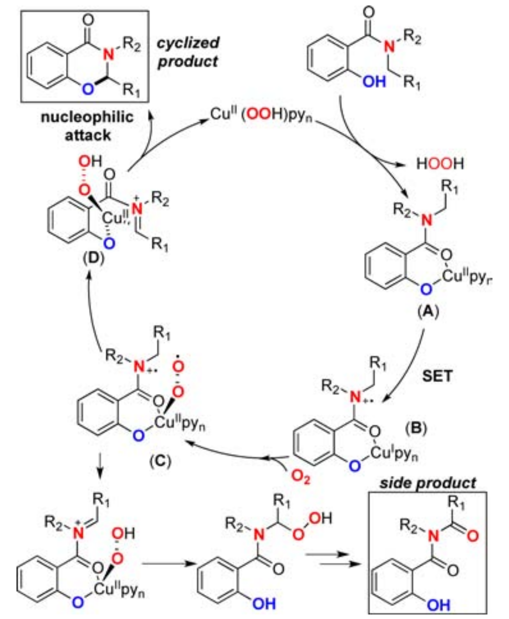
Scheme 6. O-18 Labeling Experiment



Scheme 7. Kinetic Isotope Effect Study



Scheme 8. Proposed Mechanism

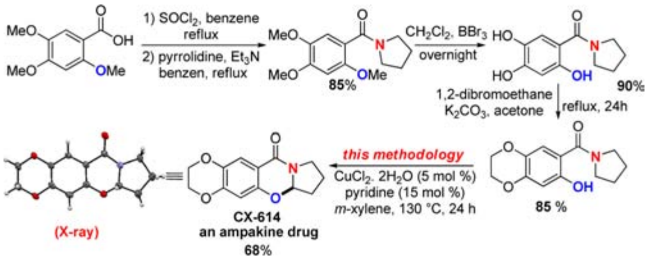


Based on these findings and from literature precedence,[1b,2b,4c,d] a probable mechanism has been depicted in Scheme 8. A substrate-bound Cu(II) center **A** is likely to be responsible for the single electron oxidation of the amide-nitrogen to form **B**.[4d,10] Subsequently, Cu(II)-superoxo species **C** is formed via Cu(I)/O_2 interaction.[11,12] This reactive intermediate **C** can abstract an H atom from the oxidized amide residue to form Cu(II)-hydroperoxo complex **D** along with generation of an iminium ion intermediate.[11] Subsequently, nucleophilic attack of the phenolate oxygen at the iminium carbon center provided the desired cyclic product. A resultant Cu(II)-hydroperoxo complex is thought to undergo an anion exchange with the substrate, and thereby, the catalyst center can be regenerated.

A minor amount of keto-product, as observed in **3a′** and **3b′**, may be caused by the adventitious water present in the solvent or by the Cu(II)-hydroperoxo species. No O-18 incorporation into the ketone product (e.g., **3a′**, Scheme 6) was observed upon addition of $H_2{}^{18}O$ either in trace amount or in excess. Therefore, water may be ruled out as the source of ketonic oxygen. Further, the $^{18}O_2$ labeling studies suggested involvement of a Cu/O_2 reactive intermediate for the ketone product as well as the cross-dehydrogenative sp^3 C−O bond formation.

Investigational new medicine CX-614, developed by Cortex Pharmaceuticals, and its derivatives have attracted extensive attention because of their activity on AMPA receptor and their ability to increase the synthesis of the brain-derived neurotrophic factor.[6] We have designed a four-step synthesis (Scheme 9); which resulted in a 44% (overall) yield of CX-614.[8,9]

Scheme 9. Synthesis of CX-614



In conclusion we have synthesized medicinally relevant dihydro-oxazinone derivatives through a Cu-based small molecule catalyst that uses O_2 to promote a direct and operationally simple cross-dehydrogenative coupling. The site of sp^3 C−O bond formation can be predicted based on electronic differences between the amide *N*-substituents. This scalable method uses an inexpensive catalyst and is applicable to a broad range of substrates.[13] Mechanistic studies including O-18 labeling, kinetic experiments, and deuterium labeling suggested that a Cu/O_2 based active species is responsible for the chemistry described herein. Such a method has potential to enable cross-dehydrogenative sp^3 C−O bond formation as a tool to synthesize complex heterocyclic compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare the following competing financial interest(s): A provisional patent on this work has been filed.

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(8) See Supporting Information for detailed description.

(9) CCDC-976164 (entry **3h**), CCDC-978672 (entry **4cA**), CCDC-976163 (entry **4dB**), CCDC-976165 (entry **5c**) and CCDC-978671 (**CX-614**) contain the supplementary crystallographic data for this paper,[8] and data can be obtained via http://www.ccdc.cam.ac.uk/data_request/cif.

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(12) A dimeric Cu_2O_2 species cannot be ruled out as a possible intermediate.[11c,d]

(13) A provisional patent on this work has been filed.