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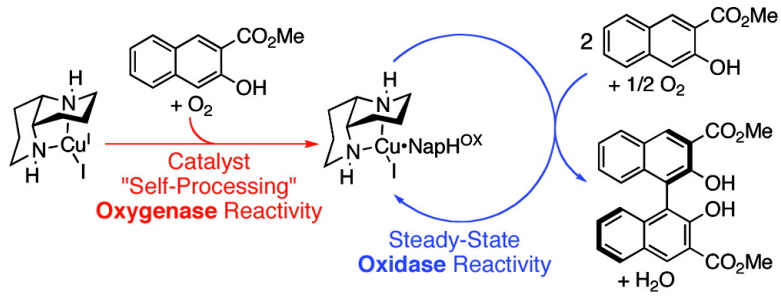
J. Am. Chem. Soc., **2008**, 130 (37), 12232-12233 • DOI: 10.1021/ja804570b • Publication Date (Web): 19 August 2008



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Mechanistic Study of Asymmetric Oxidative Biaryl Coupling: Evidence for Self-Processing of the Copper Catalyst to Achieve Control of Oxidase vs Oxygenase Activity

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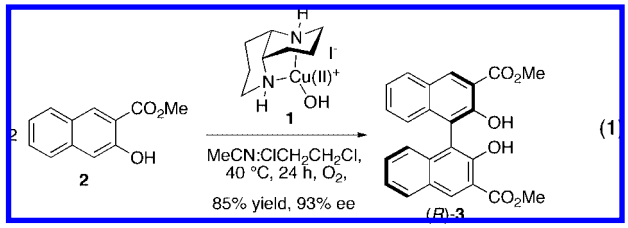
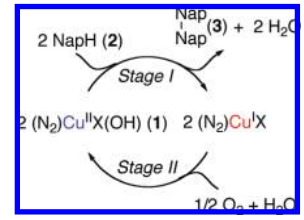
The mechanistic understanding of dioxygen activation and reactivity in biological copper-containing oxidases has grown substantially in recent years.[1] Application of these insights to the development of new catalytic oxidation reactions, however, has been much more limited.[2,3] We recently reported the development of an effective chemical oxidase system that achieves aerobic oxidative biaryl coupling (OBC) in high yield and enantioselectivity with a 1,5-diaza-*cis*-decalin copper(II) complex, $(N_2)Cu^{II}(OH)I$ (**1**), as the catalyst (eq 1).[4,5] This chemistry has enabled the enantioselective synthesis of a variety of chiral 3,3′-disubstituted BINOL derivatives,[4b] binaphthyl polymers,[4c] and perylenequinone natural products.[4d−f] To facilitate ongoing efforts to develop new reactions, we have initiated a mechanistic study of this catalytic process. Either Cu^{I} or Cu^{II} catalyst precursors can be used to initiate the catalytic reaction, but in both cases, we have observed an unusual kinetic "burst" phase. Mechanistic studies under presteady-state and steady-state reaction conditions provide intriguing insights into similarities and differences between this synthetic catalyst system and biological copper oxidases, including the ability to avoid undesired oxygen-atom-transfer ("oxygenase") reactivity under aerobic conditions.



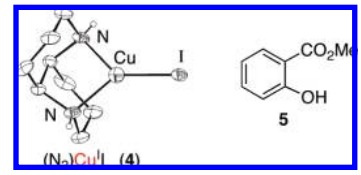
Many biological oxidase reactions proceed by a two-stage "ping-pong" mechanism consisting of two separate half-reactions: (1) substrate oxidation by the oxidized catalyst and (2) dioxygen-coupled oxidation of the reduced catalyst. Our initial studies supported such a mechanism for the OBC reaction (Scheme 1). Copper(II)-hydroxide complex **1** has been characterized crystallographically and exists as a trimer in the solid state.[6] This complex is an effective copper source for catalytic OBC (eq 1) and promotes stoichiometric substrate oxidation under anaerobic conditions. Product **3** forms in a 1:2 ratio with respect to the copper concentration, indicating that **1** serves as a one-electron oxidant. The enantioselectivity of the stoichiometric reaction (91% ee) is virtually identical to that observed under catalytic conditions.

To probe the catalyst reoxidation step, the corresponding diaza-*cis*-decalin copper(I) complex, $(N_2)Cu^{I}I$, **4**, was prepared. This crystallographically characterized complex is an effective copper source for the aerobic OBC reaction providing the identical

Scheme 1. Hypothetical "Ping-Pong" Mechanism for Copper-Catalyzed Aerobic Oxidative Biaryl Coupling



enantioselectivity (93% ee) as **1**. Furthermore, treatment with molecular oxygen converts **4** into **1**. In the absence of the naphthol substrate **2**, O_2-uptake measurements reveal a **4**/O_2 stoichiometry of 4:1 with or without unreactive substrate analogue **5**. Although details of the copper(I)-dioxygen reaction pathway remain to be elucidated, these observations, together with the substrate oxidation reaction, support the proposed oxidase pathway in Scheme 1.



The kinetics of the catalytic reactions were analyzed by HPLC measurement of substrate and product concentrations and by continuous gas manometry. When the reaction was initiated with Cu^{II} complex **1**, the time course (Figure 1A) revealed an initial burst of product formation followed by slower steady-state turnover. The burst reflects stoichiometric oxidation of the substrate by **1**, resulting in formation of ∼0.5 equiv of product. The slower steady-state rate suggests that the chemistry of OBC (Stage I, Scheme 1)

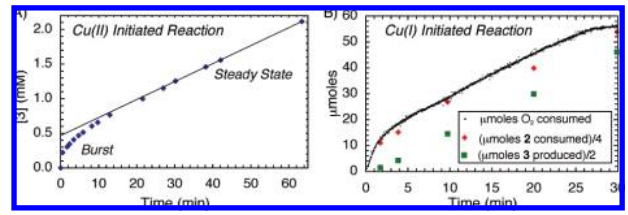


Figure 1. (A) Kinetic time course for product (**3**) formation in the OBC with catalyst **1** from HPLC. Conditions: [**2**] = 94 mM, [4-biphenyl phenyl ether] = 23 mM, [**1**] = 2 mM, atmospheric O_2, MeCN, 40 °C. (B) Kinetic time course for the OBC with catalyst **4**. (Blue) Actual O_2 uptake; (red) μmols [**2**] consumed divided by 4; (green) μmols [**3**] formed divided by 2. Conditions: [**2**] = 151 mM, [**4**] = 10 mM, pO_2 = 840 Torr, [4-biphenyl phenyl ether] = 42 mM, 6 mL of MeCN, 40 °C. Concentrations of **2** and **3** determined by GC.

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10.1021/ja804570b CCC: $40.75

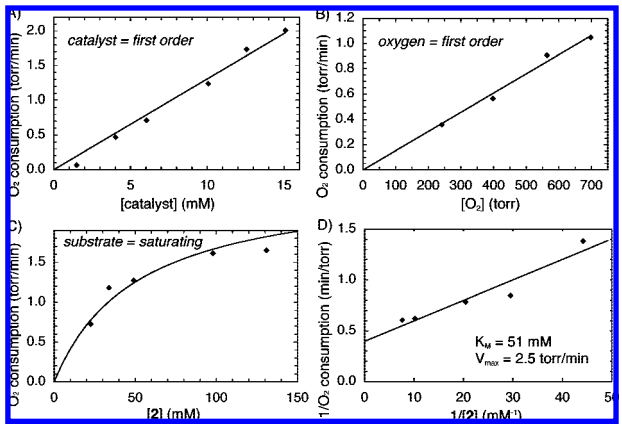


Figure 2. Dependencies of steady-state rate in MeCN at 40 °C. (A) Dependence on catalyst **4** concentration: [**2**] = 120 mM, pO_2 normalized to 849 Torr. (B) Dependence on initial O_2 pressure: [**2**] = 190 mM, [**4**] = 10 mM. (C) Dependence on substrate **2** concentration: [**4**] = 13 mM, pO_2 normalized to 849 Torr. (D) Lineweaver−Burk plot of Figure 2C.

is not rate determining and points to reoxidation of the catalyst by O_2 (Stage II, Scheme 1) as the rate-determining step.

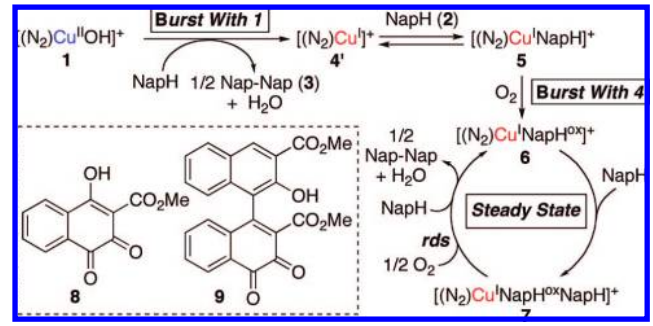
Reactions with Cu^I complex **4** were examined with the expectation of a linear product-formation profile associated with the steady-state rate in Figure 1A. However, another burst phase was observed, this time corresponding to the rapid consumption of 0.25 equiv of molecular oxygen (Figure 1B). Formation of product **3** was not observed until *after* the oxygen-uptake burst. The steady-state catalytic turnover rate is identical for both catalyst precursors, and kinetic analysis reveals that this rate exhibits a first-order dependence on [**4**] and [O_2] (Figure 2A and 2B). Taken together, these data indicate that aerobic oxidation of the catalyst is indeed the turnover-limiting step of the reaction (Stage II, Scheme 1). The gas-uptake burst observed with **4** as the catalyst precursor, however, indicates that **4** itself cannot be the catalyst resting state.

The burst behavior with Cu^I complex **4** provides a clue into the identity of the actual catalyst. Figure 1B reveals that substrate **2** is consumed in the burst; however, this material is not transformed into product **3** but instead yields a substrate oxygenation product, designated **NapH^{OX}**. This *oxygenase* reactivity is not observed after the burst phase is complete. During steady-state turnover, substrate **2** is converted exclusively into product **3** (Figure 1B). These results suggest selective *oxidase* reactivity arises from enlistment of a cofactor, **NapH^{OX}**, formed in a catalyst "self-processing" event analogous to that characterized in biological catalysts, such as amine oxidases.[7] We speculate that the combination of **NapH^{OX}** with the (N_2)Cu complex forms the kinetically competent catalyst (e.g., **6**, Scheme 2) that effects the highly selective *oxidase* activity observed in the OBC reaction (Scheme 2). **NapH^{OX}** is likely a quinone as supported by the isolation of *ortho*-quinones **8** and **9** from reaction mixtures that were halted within the first turnover (5 min).

Oxidation of a substrate/Cu-cofactor complex, such as **7**, is proposed to be the rate-determining step under steady-state conditions. The "sequential" mechanism in Scheme 2 differs from the "ping-pong" mechanism often encountered in biological oxidase catalysis; however, this proposal accounts for the first-order dependencies of catalyst precursor [**4**] and [O_2] and the saturation dependence on the substrate [**2**] (Figure 2).

In conclusion, several unique features of the catalytic OBC with 1,5-diaza-*cis*-decalin copper complexes have been identified. Copper complexes **1** and **4** are effective precatalysts for the OBC reaction, but they do not comprise the active redox couple under steady-state conditions. Copper(I) complex **4** exhibits presteady-state *oxygenase*

Scheme 2. "Sequential" Mechanism for Copper-Catalyzed Aerobic OBC Consistent with the Kinetic Data



activity in the presence of substrate **2** to produce a cofactor that alters the reactivity of the Cu catalyst. The modified catalyst reacts somewhat more slowly with O_2 than **4**, but it exhibits exclusive *oxidase* activity, achieving C−C bond formation with enantioselectivities nearly identical to those obtained in the stoichiometric oxidative coupling reaction promoted by Cu^{II} complex **1**. Further studies are needed to elucidate the precise identity of the cofactor **NapH^{OX}** and the steady-state catalyst **7**, but the present results highlight important opportunities to achieve selective modulation of oxidase vs oxygenase activity in aerobic oxidation reactions.

Acknowledgment. Financial support was provided by the NSF (M.C.K.: CHE-0616885), the NIH (M.C.K.: CA109164), and the DOE (S.S.S.: DE-FG02-05ER15690). The invaluable assistance of Dr. Patrick Carroll in obtaining the X-ray structure is gratefully acknowledged. We thank B. A. Steinhoff for helpful discussions and assistance with gas-uptake kinetics experiments.

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

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JA804570B