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Mechanistic Insights into the Aerobic Cu(I)-Catalyzed Cross-Coupling of S-Acyl Thiosalicylamide Thiol Esters and Boronic Acids

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Abstract

The Density Functional Theory (DFT) method is used to elucidate the nature of the active species and the mechanism of the aerobic Cu^I-catalyzed cross-coupling of S-acyl thiosalicylamide thiol esters and boronic acids reported previously (*J. Am. Chem. Soc.* **2007**, *129*, 15734–15735; *Angew. Chem., Int. Ed.* **2009**, *48*, 1417–1421). The energetically lowest isomer of the proposed active species [LC(O)R¹]Cu-(O₂)-Cu[LC(O)R¹]²⁺, **2a**, (where L = thiolatosalicylamide) is found to be **I**_(OO,OO) with a μ - η^2 : η^2 -peroxo Cu₂O₂-core, while its isomers **I**₂_(OO,OO) with a *bis*-(μ -O) Cu₂O₂-core and **I**₃_(OO,OO) with a (μ - η^1 : η^1) Cu₂O₂-core lie only a few kcal/mol higher and separated by 4–7 kcal/mol energy barriers. In all these isomers, the thiol ester is coordinated to the Cu-centers via its two O-ends. Isomers with (SO,OO) and (SO,SO) coordination modes of the thiol esters lie slightly higher and are separated with moderate energy barriers. We found the latter isomers to be vital for the reported Cu^I-templated cross-coupling of S-acyl thiosalicylamide thiol esters and boronic acids under aerobic conditions. The presence of an anion (halide, carboxylate modeled as formate) in the reaction medium is found to be necessary. Its coordination to the active catalyst **I**_(SO,SO) is the first step of the proposed anion-assisted transmetalation by boronic acid. Overall the transmetalation reaction requires 34.0 kcal/mol and is 24.0 kcal/mol exergonic. This conclusion is in reasonable agreement with available experiments. The C-C bond formation in the transmetalation product requires a 6.3 kcal/mol lower energy barrier and is highly exergonic.

Introduction

Transition-metal-catalyzed C-C and C-X (X = N, O, etc.) cross-coupling reactions are among the most powerful of modern methods of organic synthesis and have had a significant impact on the basic and applied synthetic chemical sciences.^{1–4} Recently, Liebeskind and co-workers⁵ reported an unprecedented reaction for the construction of C-C bonds: the Cu^I-templated coupling of a thiol ester and a boronic acid that was rendered catalytic under aerobic conditions. This new reaction type evolved from a mechanistically distinct earlier anaerobic transformation⁶ that required catalytic quantities of Pd and at least a stoichiometric quantity of a Cu^I-carboxylate as a reaction mediator. The proposed⁵

Electronic Supplementary Information (*total of 47 pages*) includes: 1. Calculated Cartesian coordinates (in Å) of all reported structures (Table S1); 2. Absolute energies of different isomers of **2a** (Table S2); 3. Relative energies of different isomers of **2a** (Table S3); 4. Absolute energies for the species involved in the cross-coupling process (Table S4); 5. Relative energies for the species involved in the cross-coupling process (Table S5); 6. Geometrical parameters for the minimum and transition-state structures involved in the transmetalation step (Table S6); 7. Geometrical parameters for the minimum and transition-state structures involved in the C-C bond formation step (Table S7) and 8. Completed Reference 22.

mechanism of this aerobic cross-coupling process includes several elementary reactions and an active catalyst containing only Cu-centers (Scheme 1).

As seen in Scheme 1, the first step of the proposed mechanism is an aerobic activation of $\text{XCu}^{\text{I}}\text{-LC(O)R}^1$, **1**, by coordination of an O_2 molecule to form a $(\text{X})[\text{LC(O)R}^1]\text{Cu-(O}_2\text{)-Cu(X)[LC(O)R}^1]$, **2**, active catalyst (where L = thiolatosalicylamide). In the second stage, transmetalation of the boronic acid $\text{R}^2\text{-B(OH)}_2$ occurs to give X-B(OH)_2 , the ketone $(\text{OC})\text{R}^1\text{R}^2$, and a Cu-thiolate $\text{L}'\text{Cu-(O}_2\text{)-CuL}'$ (where L' = thiolatosalicylamide), **3**. The catalytic cycle is completed by reaction of the Cu-thiolate **3**, with the second (sacrificial) equivalent of the boronic acid. This would regenerate the requisite Cu(I) complex **1** for reentry into the catalytic cycle and simultaneously remove the thiolate ligand from the reaction system by producing the weakly coordinating S-aryl ether. However, until now, neither the true nature of the active catalyst **2** and the intermediate **3**, nor the factors controlling the thermodynamics and kinetics of the proposed steps are known.

In general, the active catalyst **2** may have several distinct isomers. Extensive research on the structure of $\text{L}^1\text{Cu(O}_2\text{)CuL}^1$ systems has shown that an O_2 molecule can bind to two Cu-centers (as well as other transition metals) in numerous ways,^{7,8} among which the side-on $\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo}$, **I1**, *bis*-($\mu\text{-O}$), **I2**, and trans end-on $\mu\text{-}\eta^1\text{:}\eta^1\text{-superoxo}$, **I3**, are dominant bonding motifs (see Scheme 2).

Of course, the relative stability of these binding motifs of O_2 to two Cu centers depends on the nature of the ligand L.^{1,8,9,10} For example, in hemocyanin, where each copper atom of the active center is coordinated by three histidines, O_2 binds between the two Cu^{II} centers via a $\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo}$ manner.¹¹ However, Masuda and colleagues¹² have demonstrated that two Cu^{I} -complexes with *cis,cis*-1,3,5-triaminocyclohexane ligands bind O_2 via a *bis*-($\mu\text{-O}$) fashion.

Intriguingly, $\text{L}^1\text{Cu(O}_2\text{)CuL}^1$ complexes with different O_2 coordination motifs show quite different reactivity. In particular, complexes with the $\{\text{Cu-(}\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2\text{)-Cu}\}$ bonding motif have been characterized as basic and nucleophilic,¹³ but not particularly electrophilic. In contrast, complexes with the $\{\text{Cu-(}\mu\text{-}\eta^1\text{:}\eta^1\text{-O}_2\text{)-Cu}\}$ bonding motif fail to exhibit basic character and instead enhance the electrophilicity of the bound dioxygen molecule.¹³ Finally, complexes with the $\{\text{Cu-(}\mu\text{-O)}_2\text{-Cu}\}$ bonding motif exhibit strongly electrophilic character, and can oxidize both activated and aliphatic C-H bonds, hydroxylate aromatic rings, and serve as oxidizing agents in electron-transfer reactions.¹³ Thus, elucidation of the true nature of **2** is important in clarification of the real mechanism of Cu^{I} -catalyzed thioorganic and boronic acid coupling reaction under aerobic conditions.

As a first task we used computational approaches to reveal the structure and relative energy of various isomers of **2**, as well as the energy barriers separating those isomers. The second task of this paper is to elucidate the mechanism and factors controlling the kinetics and thermodynamics of the aerobic cross-coupling reaction. For this purpose, we calculated all possible reactants, intermediates, transition states and products of the reaction (1):

Computational Procedure

Computational Models Used

Liebeskind and co-workers have demonstrated⁵ that all sources of Cu^{I} tested in catalytic amounts are able to produce the cross-coupling reaction under aerobic conditions

independently of the counterion. This finding suggests that the active species of reaction (1) could be the same regardless of the counterion used. Therefore, in our computational study we model the active species **2** by the dicationic complex **2a** (see Scheme 3).

For the sake of computational efficiency in our modeling of the studied cross-coupling reaction we used $R^1=Me$ and $R^2=Ph$ as the substituents on the thiol ester and the boronic acid, respectively. The R' substituent attached to the N-atom of the thiosalicylamide ligand has been modeled as an H atom.

Computational Methods Used

The complexes containing Cu_2O_2 -cores have been the subject of many previous computational studies.^{9,14,15} Cramer, Gagliardi and coworkers have concluded^{9,14} that the better description of such systems requires the use of Completely Renormalized Coupled Cluster (CR-CC) and Restricted Active Space (RAS) approaches. However, application of these methods to large systems, such as those presented in this paper, is not practical. Therefore, the use of relatively less time-consuming approaches, such as various DFT functionals is necessary. Previously, various density functionals were used to study complexes with Cu_2O_2 -cores. Cramer and Gagliardi have reported that local functionals are, in general, more suitable to study the transformations in these systems,^{9,14} while one should use them, as well as hybrid functionals, with caution. Therefore, in this paper we use a local density functional approach, BLYP,¹⁷ in conjunction with the 6-31G(d,p) [C, H, O, N, S and B atoms]¹⁸ and LANL08(f) [Cu atoms] basis sets.¹⁹ Geometries all reported structures were fully optimized without any symmetry restrains. For all reported species, Hessian matrices were calculated, and all transition states confirmed to have one imaginary frequency corresponding to the reaction coordinates. Their nature was confirmed by performing IRC (intrinsic reaction coordinate) calculations. The thermodynamic properties of the reported reactions were computed at 298.15 K and 1 atm employing the usual rigid rotor and harmonic oscillator models.²⁰ Solvent effects were estimated at the PCM level using gas-phase optimized geometries and dimethylformamide (DMF) as a solvent.²¹ All calculations were performed with the Gaussian 09 suite of programs.²²

Results and Discussion

Part-1: Structure and Stability of Isomers of Complex 2a

As mentioned above, the Cu_2O_2 -core of **2a** has many isomeric forms, including **I1**, **I2** and **I3** presented in Scheme 2, above. In addition, for each given Cu_2O_2 -core, **2a** may have several structures which differ by the coordination modes of the *S*-acyl thiosalicylamide ligands to the Cu-centers. Indeed, each *S*-acyl thiosalicylamide ligand could coordinate to the Cu-center either via its S and O³ ends (termed SO-coordination) or with its O³ and O⁵ atoms (termed OO-coordination). All possible isomers of **2a**, as well as the located transition state structures connecting those isomers are schematically presented in Scheme 4. The calculated relative energies of these structures are given in Scheme 5 as $\Delta H(\Delta G)[\Delta G_{solv}]$, where ΔH and ΔG are gas-phase enthalpy and Gibbs free energies. The ΔG_{solv} is calculated as $\Delta G_s + [\Delta G - \Delta E]$, where ΔG_s is the PCM calculated free energy in DMF solution and ΔE is the gas-phase total energy. The full geometry parameters, as well as absolute and relative energies of these structures are given in Tables S1, S2 and S3 of the Supporting Information, respectively. Their calculated important geometry parameters are given in Tables 1 and 2, while Mulliken spin densities of their important atoms are included to Scheme 4. Despite extensive attempts we were not able to locate all required transition states at their lowest singlet and triplet electronic states, especially those involved in the **I1**($\mu-\eta^2:\eta^2$) $\rightarrow$ **I3**($\mu-\eta^1:\eta^1$) isomerization. This failure is a result of the fact that the barriers associated with these transition states are very small.

As seen from the calculated data, all located isomers of **2a** are thermodynamically accessible. The most stable isomer of **2a** is **I1**_(OO,OO) with a μ - η^2 : η^2 -peroxo Cu₂O₂-core. In this isomer, both substrate molecules are coordinated to Cu-centers by their O-ends (the oxygen of the thiol ester and the oxygen of the amide group). Thermodynamically, the less stable isomer of **2a** is **I2**_(SO,SO), which lies 13.7 kcal/mol higher than the **I1**_(OO,OO) isomer (throughout the paper we discuss only solvation free energies ΔG_{solv}). Isomer **I3**_(SO,SO) has a μ - η^1 : η^1 -superoxo, Cu₂O₂-core, where both substrates are in SO- coordination modes.

More detailed analyses of these three isomeric forms show that:

1. At their singlet electronic states all isomers with a μ - η^2 : η^2 -peroxo Cu₂O₂-core, **I1**, can be better described as a peroxo (O₂²⁻) species with no unpaired spins, and longer, 1.504–1.508 Å, O-O bond distances. At their triplet states these isomers are superoxide (O₂⁻) species with almost one α -spin (0.90–0.99 e) on the O₂-ligand and 0.3–0.4 α -spins on the Cu-centers, and with 1.441–1.448 Å (shorter than that in their singlet states) O-O bond distances. Based on these findings one may assign +2 and +1.5 oxidation states to the Cu-centers at singlet and triplet state of **I1** isomers, respectively. Also, the singlet and triplet states of all **I1** isomers are very close to each other in energy.
2. In their singlet electronic states all isomers with a *bis*-(μ -O) Cu₂O₂-core, **I2**, contain two oxo groups (O²⁻) with no unpaired spins. While in their triplet states every oxygen atom of the *bis*-(μ -O)-core in **I2** isomers is a monoanion (O⁻) with significant (0.66 - 0.90 e) α -spins. It is interesting to note that the spin density of the (μ -O)-centers reduces significantly upon changing coordination modes of the thiol ester via (OO,OO) > (SO,OO) > (SO,SO). Thus, coordination of the S-atom of the thiol ester reduces spin density of the (μ -O)-center. Based on these findings we could assign +3 and +2 oxidation states for the Cu-center of the singlet and triplet **I2** species. Furthermore, based on the reported difference in the nature of the (μ -O)-centers in singlet and triplet **I2** isomers, we should expect their singlet states to be more stable than their triplet states: this is consistent with their energy presented in Scheme 4. The O-O distances on the **I2** isomers are calculated to be long, 2.250–2.357 Å, which indicates a lack of O-O interaction.
3. The **I3** isomers with a (μ - η^1 : η^1) Cu₂O₂-core can be best characterized as superoxide (O₂⁻) complexes in both the singlet and triplet electronic states. At their triplet states, the O₂-moiety of the **I3** isomers contain 1.07–1.17 |e⁻| α -spin and the O-O distance ranges from 1.349–1.363 Å. The geometries of the singlet structures mirror the triplet ones. For the singlet states, the calculated spin densities, 0.26–0.27 |e⁻|, on the O₂-moiety are notably smaller than those for triplet states. Based on these findings, we assigned +1.5 oxidation states to the Cu-centers of the **I3** isomers, regardless of the electronic state of the complex.

The second interesting finding in the calculated energies of the studied isomers of **2a** is the thermodynamic stability of the substrate coordination modes to the Cu-centers, which decreases via (OO,OO) > (SO,OO) > (SO,SO) regardless of the O₂-moiety within the Cu₂O₂-core. Thus, coordination of the thiol ester to the Cu-centers via its S-end is thermodynamically slightly less favorable. However, this coordination mode of the thiol ester is expected to be vital for the reported⁵ Cu^I-templated coupling of the S-acyl thiosalicylamide and the boronic acid under aerobic conditions (see below).

Indeed, it is reasonable to expect that those isomers of **2a** with a strongly activated S-C(O)Me bond will be more prone to cross-coupling product with the boronic acid. Analyses of geometries of the isomers of **2a** show that the S-C(O)Me bond is strongly activated only in isomers with (SO,OO) and/or (SO,SO) coordination of the thiol ester. As seen in Table 1,

the calculated S-C(O)Me bond distances are: in **I1**-type of isomers, 1.787 - 1.789 Å for **I1**_(OO,OO), 2.069–2.074 and 1.790–1.792 Å for **I1**_(SO,OO), and 2.026 - 2.072 Å for **I1**_(SO,SO); In **I2**-type of isomers, 1.781–1.786 Å for **I2**_(OO,OO), 2.109–2.127, and 1.783–1.791 Å for **I2**_(SO,OO), and 2.091 - 2.121 for **I2**_(SO,SO); In **I3**-type of isomers, 1.790 - 1.797 Å for **I3**_(OO,OO) and (2.015 - 2.037 Å for **I3**_(SO,SO).

The oxidation state of the Cu is another factor that can influence the activation of the S-C(O)Me bond. Indeed, as seen in Table 1 the average S-C(O)Me bond distances are: 2.049 and 2.028 Å for **³I1**_(SO,SO) and **³I3**_(SO,SO), respectively; 2.057 Å for **¹I1**_(SO,SO) and (2.121 Å) for **¹I2**_(SO,SO), where the oxidation states of Cu atoms are +1.5, +2 and +3, respectively. Thus, the higher the oxidation state of Cu the more activated the S-C bond in S-C(O)Me. As mentioned above all reported isomers of **2a** are energetically close and could easily transform among each other. We were not able to locate all required transition state structures because the barriers associated with these transition states are very small. Among the numerous barriers located, the highest ones, 19.1 and 15.5 kcal/mol, are that associated with the **³TS1-2**_(OO,OO) and the **¹TS2**_(OO,OO) transition states, respectively. Even this barrier can be considered as moderate.

In summary, the above-presented data clearly show that all isomers of **2a** are close in energy and can rearrange to each other with moderate energy barriers. The energetically lowest isomer is **I1**_(OO,OO) with a $\mu\text{-}\eta^2\text{:}\eta^2$ -peroxo Cu₂O₂-core, while isomer **I2**_(OO,OO) with a *bis*-($\mu\text{-O}$) Cu₂O₂-core and isomer **I3**_(OO,OO) with a ($\mu\text{-}\eta^1\text{:}\eta^1$) Cu₂O₂-core lie only a few kcal/mol higher and are separated with 4–7 kcal/mol energy barriers. In all of these isomers, the thiol ester is coordinated to the Cu-centers via its two O-ends. Their counterparts with the (SO,OO) and (SO,SO) coordination modes of the thiol esters lie somewhat higher in energy (maximum of 13.7 kcal/mol) and are separated from the former with moderate energy barriers (maximum of 19.1 kcal/mol). However, these high energy isomers are vital for the reported⁵ Cu^I-templated coupling of the S-acyl thiosalicylamide thiol ester and boronic acid under aerobic conditions, because the coordination of the thiol ester to the Cu-centers via its S-end results in a significant elongation of S-C(O)R bond distance that makes the next step of the reaction (i.e. the C-C coupling) a facile.

Part-II. Mechanistic Details of the Cross-Coupling

Having elucidated the structures and energies of the different isomers of **2a**, in this section we discuss the possible mechanisms and factors controlling the kinetics and thermodynamics of the cross-coupling reaction of **2a** with boronic acid, i.e. reaction (1), above. In these studies, we use the **I1**_(SO,SO) isomer of **2a** with a $\mu\text{-}\eta^2\text{:}\eta^2$ -peroxo Cu₂O₂-core as an active specie (see the discussion above for additional details). Formate anion is included into our calculations to mimic of presence of the 3-methylsalicylate anion present in the original reaction medium.⁵ For simplicity, we organize our analysis and discussion to cover two steps: (1) the transmetalation assisted by formate (as a representative anion), which facilitates the transfer of a Ph-group of Ph-B(OH)₂ to one of the Cu centers, and (2) the C-C bond formation leading to the ketone product. All calculated intermediates, transition states and products of these steps are schematically given in Scheme 6. Their important geometry parameters and the Mulliken atomic spin densities of selected atoms are given in Tables 3 and 4. Their total and relative energies are given in Tables S4 and S5 of the Supporting Materials. Tables S6 and S7 include important geometries of these structures.

II.1 The Transmetalation Step

A free energy profile of this step is given in Scheme 7, where the reference was set to be the energy of the **I1**_(OO,OO) + PhB(OH)₂ + HCO₂[−] dissociation limit. Since this reaction involves negatively (formate) and positively (**2a**) charged fragments, here we only discuss

the free energies in solution. Furthermore, since the electronic ground states of all structures (except structures **IVa2** and **IVb**) involved in this step are the triplet states, here we discuss only the triplet state potential energy surface and the triplet state structures of related reactants, intermediates, transition states and products. All data concerning the singlet states are given in supporting materials. Since this step of reaction (1) includes three fragments - **2a**, formate and boronic acid - it may, in general, proceed via two different pathways. The first pathway starts with formate anion coordination to **2a**, while the second pathway is initiated by boronic acid addition to **2a**.

Pathway-1

The addition of formate anion to the **II**_(SO,SO) isomer of **2a** leads to formation of **IIa** and is calculated to be exergonic by 40.4 kcal/mol (i.e. 34.3 kcal/mol, relative to **II**_(OO,OO) + PhB(OH)₂ + HCO₂⁻). In the resulting intermediate **IIa**, the formate is bidentate coordinated to the Cu^I-center forcing the S^I-atom of the thiol ester to be detached from Cu^I and coordinate to Cu² via the carbonyl oxo-end of the -S-C(R^I)O group. Furthermore, the O₂ molecule of the Cu₂O₂-core changes its coordination mode from a (μ-η²:η²)-peroxo to (μ-η¹:η¹)-superoxo.

The next step of the reaction is coordination of the boronic acid to intermediate **IIa**. This process leads to formation of several weakly bound complexes (see the Supporting Information) among which complex **IIIa** is energetically most favorable. However, even complex **IIIa** is thermodynamically less stable (by 4.2 kcal/mol) than the dissociation limit of the reaction, **IIa** + Ph-B(OH)₂. In this intermediate, Ph-B(OH)₂ is coordinated to the Cu^I-center with its OH-group: the calculated Cu^I-O⁶ bond distance is 2.146 Å. This interaction forces the formate to rearrange its coordination to Cu^I from bidentate to monodentate. Such structural arrangement in intermediate **IIIa** makes available two pathways for formate-assisted Ph-B bond cleavage. The first of them starts with interaction of the B-center with the coordinated μ₂-O atom of formate, while the second one starts by interaction of boron with the carbonyl oxygen of formate (which is not coordinated to Cu-center). Calculations show that the rate-determining step of both pathways is the B-Ph cleavage step (see Figure 1 for transition states associated with these steps), that requires 1.3 kcal/mol more energy for the former than for the latter process. Furthermore, these two processes proceed through similar intermediates and transition states. For the sake of simplicity, we discuss in detail below only the second pathway, while energies and geometries of all intermediates and transition states of the first pathway are given in the Supporting Information. In **IIIa**, the formate oxygen O⁸ is coordinated to the Cu^I atom [d(Cu^I-O⁸) = 2.074 Å]. The O⁷ atom of formate is coordinated to the B-center [d(B-O⁷) = 1.599 Å] and makes it a pseudotetrahedral four coordinated center. At the same time, the Ph-group of Ph-B(OH)₂ interacts with the Cu^I center [d(Cu^I-C¹) = 2.182 Å]. This interaction induces an elongation of the B-C¹(Ph) bond to 1.648 Å. At the transition state (see Figure 1) **TS(IIIa-IVa1)**, which is the B-Ph cleavage transition state, the B-C¹(Ph) bond is elongated even further to 2.240 Å. Simultaneously, the Cu^I-C¹ bond starts forming: the calculated Cu^I-C¹ bond distance is 1.982 Å.

The free energy barrier height for this step is calculated to be 34.0 kcal/mol measured from **IIa** (Scheme 7). Considering the thermal condition of the reported experiments (50 °C), free energy calculations at 1 atm pressure, and the accuracy of the used computational methods (which overestimate the barriers),²¹ one may assume a satisfactory agreement between computation and experiment.⁵

Overcoming **TS(IIIa-IVa1)** leads to the intermediate **IVa1**, where the formation of the Cu^I-C¹ bond is completed. The Cu^I-C¹ bond distance is calculated to be 1.940 Å. At this stage, the byproduct B(O₂CH)(OH)₂, weakly interacting with the catalyst, is formed. Dissociation

of the byproduct from the di-Cu complex generates the intermediate **IVa**. Geometry parameters of **IVa** and **IVa1** are very close (see Table 3). This indicates a weak bonding between **IVa** and $\text{B}(\text{O}_2\text{CH})(\text{OH})_2$; the calculated free energy of the reaction **IVa1** $\rightarrow$ **IVa** + $\text{B}(\text{O}_2\text{CH})(\text{OH})_2$ is 11.0 kcal/mol. Next, **IVa** rearranges to **V** with only a 1.7 kcal/mol energy gain. As seen in Scheme 7, the overall reaction of $\text{II}_{(\text{OO},\text{OO})} + \text{PhB}(\text{OH})_2 + \text{HCO}_2^- \rightarrow + \text{B}(\text{O}_2\text{CH})(\text{OH})_2$ is 24 kcal/mol exergonic and proceeds via the 34 kcal/mol rate-determining barrier at transition state **TS(IIIa-IVa1)**. The first step of this reaction, formate coordination to **II**, is a highly exergonic process.

As seen in Table 4, unpaired spins of the reported intermediates and transition states involved in this pathway are located, mostly, on the atoms of the Cu_2O_2 -core (1.75 – 1.86 | e^-), and have no significant effect on the reported mechanism of the reaction.

Pathway-2

This pathway starts with addition of the boronic acid to $\text{II}_{(\text{SO},\text{SO})}$ to generate the adduct **II** (see Scheme 6), which is 4.8 kcal/mol endergonic (10.9 kcal/mol, relative to $\text{II}_{(\text{OO},\text{OO})} + \text{PhB}(\text{OH})_2 + \text{HCO}_2^-$). The calculated $\text{Cu}^1\text{-C}^1(\text{Ph})$ and $\text{B-C}^1(\text{Ph})$ bond distances in **II** are 2.175 and 1.598 Å, respectively. This process may occur with some energy barrier, which was not located in present study because the existence of this barrier is not expected to affect our general conclusion (see below).

Formate coordination to **II** initiates the transmetalation process. In the resulting intermediate **III**, the formate molecule is coordinated to the tetrahedral B-center [$d(\text{B-O}^7) = 1.474$ Å], which results in elongation of the B-C^1 and $\text{Cu}^1\text{-C}^1(\text{Ph})$ bonds to 1.654 Å, and 2.307 Å, respectively, and formation of the $\text{Cu}^1\text{-O}^6$ bond. The reaction $\text{HCO}_2^- + \text{II} \rightarrow \text{III}$ is calculated to be 24.3 kcal/mol exergonic. Transmetalation in the resulting

intermediate **III** occurs via transition state **TS(III-IVb1)** (see Figure 1). As seen in Table 3, at this transition state the $\text{B-C}^1(\text{Ph})$ and $\text{Cu}^1\text{-O}^6$ bonds are elongated to 2.171 and 2.172 Å, respectively, and the $\text{Cu}^1\text{-C}^1$ bond is being formed with distance of 2.037 Å. These geometry changes are consistent with a transition state where the B-Ph bond cleaves as the Cu-Ph bond forms. The energy barrier associated with this transition state is calculated to be 12.8 kcal/mol (relative to the pre-reaction complex **III**). Overcoming this barrier leads to complex **IVb1** with a strong $\text{Cu}^1\text{-C}^1(\text{Ph})$ bond [$d(\text{Cu}^1\text{-C}^1) = 1.921$ Å], where the resulting Cu_2 -complex interacts with the byproduct $\text{B}(\text{O}_2\text{CH})(\text{OH})_2$. The byproduct dissociation from the Cu_2 -fragment of **IVb1** generates **IVb** complex. The **IVb1** $\rightarrow$ **IVb** + $\text{B}(\text{O}_2\text{CH})(\text{OH})_2$ process is found to be exergonic by 7.4 kcal/mol. Isomers **IVb** and **V** are very close in energy and are separated by a very small energy barrier.

Thus, if the formate-assisted transmetalation reaction starts with boronic acid addition to **2a**, **pathway-2**, then several (at least 10.9) kcal/mol of energy are required to initiate the process. Subsequent steps of this pathway are less energy demanding and occur very easily. The overall reaction $\text{II}_{(\text{OO},\text{OO})} + \text{PhB}(\text{OH})_2 + \text{HCOO}^- \rightarrow \text{V} + \text{B}(\text{O}_2\text{CH})(\text{OH})_2$ is exergonic by 24–25 kcal/mol.

Comparison of the above presented pathways 1 and 2 shows that transmetalation most likely will proceed via **pathway-1**. Indeed, **pathway-1** does not require any energy to initiate the reaction, while **pathway-2** requires several kcal/mol of energy for coordination of boronic acid to the active species **2a**. Thus, one may predict that formate-assisted transmetalation in **2a** starts with addition of formate to one of Cu-centers of **2a** to generate intermediate **IIa**. At the next step, the boronic acid coordinates to **IIa** via its OH-group to form intermediate **IIIa**. Interaction of the carbonyl oxygen of formate with the B-center facilitates the B-C(Ph) bond cleavage, which occurs via the rate-determining (34 kcal/mol) transition state **TS(IIa-IVa1)**

(see Figure 1) and leads to the final product **V**. The overall reaction is 24.0 kcal/mol exergonic. As we have noted above, the transmetalation reaction may also proceed via interaction of the B-center with the coordinated μ_2 -O atom of formate, a process that is only 1.3 kcal/mol higher energy and slightly less favorable than the process involving the carbonyl oxygen. This energetically reasonable transmetalation by interaction of the B-center with the coordinated μ_2 -O atom of formate is a likely model for the ability of a Cu^{I} -halide to also catalyze the aerobic cross coupling reaction of S-acyl thiosalicylamides and boronic acids (where the transmetalation is facilitated by prior coordination of halide).

The C-C Bond Formation Step

The final product of the above-presented transmetalation step, complex **V**, is well positioned for formation of the C-C bond that will generate the ketone product. Indeed, in **V**, the S^{I} atom is coordinated to Cu^{I} center and the $\text{S}^{\text{I}}\text{-C}^2(\text{O})\text{Me}$ bond is activated (1.925 Å, see Table 3). Furthermore, the $\text{C}^2(\text{O})\text{Me}$ fragment and phenyl group, which are expected to couple, are located in a suitable position with $d(\text{C}^1\text{-C}^2) = 3.702$ Å.

The transition state (see Figure 1) associated with the $\text{C}^1\text{-C}^2$ coupling is found to be **TS(V-VI)**. At this transition state, the $\text{Cu}^{\text{I}}\text{-C}^1$ and $\text{S}^{\text{I}}\text{-C}^2$ bonds (2.025 and 2.374 Å, respectively) are cleaved, and the $\text{C}^1\text{-C}^2$ bond (2.350 Å) is formed. Another interesting pattern observed at this transition state is the increase of the $\text{Cu}^{\text{I}}\text{-S}^{\text{I}}$ bond strength upon elongation of the $\text{S}^{\text{I}}\text{-C}^2$ bond distance ($\text{Cu}^{\text{I}}\text{-S}^{\text{I}}$ is 2.723 Å for **V** and 2.345 Å for **TS(V-VI)**). The barrier height associated with this transition state is 17.4 kcal/mol, which is calculated from the pre-reaction complex **V**. The calculated energy difference between **IIa**, the most stable structure along the reaction profile, and **TS(V-VI)** is 27.7 kcal/mol. In other words, the barrier required for the C-C bond formation is 6.3 kcal/mol smaller than the 34.0 kcal/mol barrier obtained for the transmetalation step.

Overcoming **TS(V-VI)** leads to intermediate **VI** with a real $\text{C}^1\text{-C}^2$ bond between the phenyl and acetyl groups [$d(\text{C}^1\text{-C}^2) = 1.482$ Å], a much stronger $\text{Cu}^{\text{I}}\text{-S}^{\text{I}}$ bond [$d(\text{Cu}^{\text{I}}\text{-S}^{\text{I}}) = 2.178$ Å], and the final ketone molecule interacting with the Cu^2 center [$d(\text{Cu}^{\text{I}}\text{-O}^4) = 2.116$ Å]. As expected, this process is strongly exergonic by 56.0 kcal/mol.

The last step of the reaction is dissociation of the ketone from **VI** that leads to the ketone and complex **VII**. This process releases 1.4 kcal/mol of free energy in solution, so the overall transformation, i.e. **2a** + $\text{PhB}(\text{OH})_2$ + $\text{HCO}_2^- \rightarrow \text{VII} + (\text{HCO}_2)\text{B}(\text{OH})_2 + \text{OC}(\text{R}^1)(\text{R}^2)$, is strongly exergonic: 57.4 kcal/mol relative to the most stable **II**_(OO,OO) isomer of **2a** and 23.0 kcal/mol relative to most stable intermediate of transmetalation step **IIa**.

As in the transmetalation process, a majority (1.55–1.66 $[\text{e}^-]$) of the two unpaired spins of the triplet states for all reported structures are always located at the Cu_2O_2 -core, and do not play significant role in the mechanism of reported reactions.

Conclusions

We can draw the following conclusions from the above-presented findings:

1. The energetically lowest isomer of $[\text{LC}(\text{O})\text{R}^1]\text{Cu}(\text{O}_2)\text{-Cu}[\text{LC}(\text{O})\text{R}^1]^{2+}$, **2a**, (where L = thiolatosalicylamide) is **II**_(OO,OO) with a $\mu\text{-}\eta^2\text{:}\eta^2$ -peroxo Cu_2O_2 -core, while isomers **I2**_(OO,OO) with a *bis*-(μ -O) Cu_2O_2 -core and **I3**_(OO,OO) with a (μ - $\eta^1\text{:}\eta^1$) Cu_2O_2 -core lie only a few kcal/mol higher and are separated from the former (and from each other) with 4–7 kcal/mol energy barriers. In all of these isomers, the S-acyl thiosalicylamide thiol ester is coordinated to the Cu-centers via its two O-ends. Their counterparts with the (SO,OO) and (SO,SO) coordination modes of the thiol

esters lie somewhat higher in energy (maximum of 7.3 kcal/mol) and are separated from the former by moderate energy barriers (maximum of 15.5 kcal/mol). In general, isomers with the (SO,OO) and (SO,SO) coordination modes of thiol esters are vital for the reported⁵ Cu^I-templated coupling of a thioorganic and boronic acid under aerobic conditions.

2. The Cu-centers are in their: (a) +2 and +1.5 oxidation states at singlet and triplet **I1** isomers with a μ - η^2 : η^2 -peroxo Cu₂O₂-core, respectively; (b) +3 and +2 oxidation states at singlet and triplet **I2** species with a *bis*-(μ -O) Cu₂O₂-core, and (c) +1.5 oxidation states at singlet and triplet **I3** species with a (μ - η^1 : η^1) Cu₂O₂-core.
3. The presence of an anion such as halide or carboxylate in the reaction medium (the latter modeled by formate in this paper) is necessary; coordination of this anion to the active catalyst is the first step of the proposed anion-assisted transmetalation in the active species **2a** by boronic acid. The overall formate-assisted reaction is 24.0 kcal/mol exergonic and proceeds via a moderate rate-determining energy barrier of 34.0 kcal/mol at the B-C(Ph) bond cleavage transition state **TS(IIa-IVa1)** leading to intermediate **V**. This conclusion is in reasonable agreement with available experiments.⁵
4. The C-C bond formation in intermediate **V** requires a 6.3 kcal/mol lower energy barrier and is highly exergonic.

Overall, we can now place the aerobic, Cu-catalyzed coupling of boronic acids with S-acyl thiosalicylamides in mechanistic context with the earlier described Pd-catalyzed, Cu^I carboxylate-mediated desulfitative coupling reactions.⁶ In the original anaerobic desulfitative chemistry, which spans a wide variety of thioorganic substrates, palladium is required to affect an oxidative addition with the C-S bond to activate the thioorganic, which produces an intermediate, R-PdL_n-SR', able to undergo transmetalation with a boronic acid when mechanistically facilitated through the action of the Cu^I carboxylate.²⁴ In comparison, the S-acyl thiosalicylamide substrates described herein do not require prior activation by Pd in order to participate in Cu-mediated cross-coupling with boronic acids. Thus, coordination to Cu not only provides a template that orients a reactive R-Cu moiety (generated upon transmetalation from B to Cu) proximal to the thiol ester unit, but it also enhances the native electrophilicity of the thiol ester bond and facilitates the C-C bond forming step. However, the aerobic reaction conditions are not essential in order to induce ketone formation from an S-acyl thiosalicylamide and a boronic acid. In fact, treatment of an S-acyl thiosalicylamide and a boronic acid with stoichiometric quantities of a Cu^I carboxylate salt under anaerobic conditions slowly mediates the formation of ketone product in very good yields.²⁵ In comparison, under aerobic reaction conditions two changes occur: (1) the reaction is rendered catalytic in Cu, and (2) the ketone formation proceeds at a much faster observed rate when conditions catalytic in Cu are compared to the anaerobic reaction using stoichiometric quantities of Cu. Although the computational study described within does not address the fine mechanistic detail of the aerobic catalytic turnover step directly (see stage 3 of Scheme 1, above), it is clear that a second, sacrificial equivalent of the boronic acid is intimately involved in the turnover.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Calculated important transition states of the formate-assisted transmetalation in **2a** by boronic acid and the C-C bond cross-coupling reactions. Here, we also present the atomic notations used in this paper.

Scheme 1.

The proposed mechanism of the Cu^I-templated aerobic cross-coupling of thioorganic and boronic (see Ref. 5)

μ_2 -peroxo

I1

bis-(μ -O)

I2

μ_1 -superoxo

I3

Scheme 2.

Three possible O₂-coordination modes in Cu₂O₂-cores

Scheme 3.
Model of species **2**, as **2a**, used in this paper

Scheme 4.

Calculated isomers of **2a** and connecting transition states (in dashed boxes) studied in this paper. Mulliken spin densities (in |e|) are given with each structure. Values in red and blue are for triplet and singlet electronic states of the reported structures, respectively.

Scheme 5.

Calculated relative energies ($\Delta H(\Delta G)[\Delta G_{\text{solV}}]$ in kcal/mol) of various isomers of **2a** and connecting transition states. Values in red and blue are for triplet and singlet electronic states of the reported structures, respectively.

Scheme 6.

Schematic presentation of located important reactants, intermediates, transition states and products of formate-assisted transmetalation in **2a** by boronic acid and C-C bond cross-coupling reactions. For structures of the presented transition states see Figure 1. Full geometry parameters for all of these structures are given in the Supporting Information. Their important geometry parameters are given in Table 3.

Scheme 7.

Calculated potential energy surface of the formate-assisted transmetalation in **2a** by boronic acid and the subsequent C-C bond cross-coupling reactions. Presented energies are Gibbs free energies in solution (in kcal/mol). For notation of the structures, see Scheme 5 and Figure 1.

Table 1

The calculated important bond distances (in Å) of various isomers of **2a** studied in this paper, at their singlet and triplet electronic states. Full geometries of these isomers are included in supporting Materials.

Param.	I ₁ (oo,oo)	I ₁ (so,oo)	I ₁ (so,so)	I ₂ (oo,oo)	I ₂ (so,oo)	I ₂ (so,so)	I ₃ (oo,oo)	I ₃ (so,so)
Mult.	3	1	3	1	3	1	3	1
Cu ¹ -O ¹	2.012	1.940	1.966	1.935	1.929	1.908	1.846	1.818
Cu ¹ -O ²	2.038	1.943	2.127	1.959	2.209	2.003	1.846	1.820
Cu ² -O ¹	2.063	1.943	2.171	1.993	2.193	2.008	1.892	1.820
Cu ² -O ²	2.010	1.940	1.950	1.917	1.929	1.915	1.893	1.818
Cu ¹ -Cu ²	3.326	3.580	3.431	3.600	3.345	3.611	2.952	2.859
O ¹ -O ²	1.446	1.504	1.441	1.504	1.448	1.508	2.294	2.250
Cu ¹ -S ¹	3.693	3.736	2.335	2.299	2.347	2.327	3.708	3.700
Cu ¹ -O ³	1.976	1.961	1.912	1.908	1.905	1.920	1.963	1.948
Cu ¹ -O ⁵	1.981	1.965	4.002	4.014	-	-	1.967	1.952
S ¹ -CHO	1.788	1.787	2.069	2.074	2.072	2.045	1.783	1.781
Cu ² -S ²	-	-	3.830	3.766	2.367	2.313	-	-
Cu ² -O ⁴	1.954	1.961	1.941	1.957	1.915	1.911	1.979	1.952
Cu ² -O ⁶	1.983	1.965	2.006	1.976	3.848	4.000	1.982	1.948
S ² -CHO	1.789	1.787	1.792	1.790	2.026	2.069	1.786	1.781

The calculated important bond distances (in Å) of located transition states connecting various isomers of **2a** studied in this paper, at their singlet and triplet electronic states. Full geometries of these isomers are included in Supporting Materials.

Param.	TS1(00,00,00)	TS1(s0,00,s0)	TS2(00,00,s0)	TS1-2(00,00)	TS1-2(s0,00)	TS1-2(s0,s0)	TS1-3(00,00)
Mult.	1	1	3	1	3	1	3
Cu ¹ -O ¹	1.919	1.913	1.919	1.811	1.819	1.848	1.852
Cu ¹ -O ²	2.021	1.975	1.926	1.859	1.837	1.848	1.853
Cu ² -O ¹	1.957	2.106	1.812	1.825	1.872	1.982	1.854
Cu ² -O ²	1.924	1.889	1.820	1.818	1.794	1.971	1.852
Cu ¹ -Cu ²	3.580	3.625	2.912	2.887	2.871	3.061	3.207
O ¹ -O ²	1.490	1.490	2.286	2.221	2.268	1.893	1.855
Cu ¹ -S ¹	2.648	2.304	2.703	2.687	2.324	3.687	3.740
Cu ¹ -O ³	1.940	1.904	1.978	1.934	1.914	1.96	1.959
Cu ¹ -O ⁵	2.210	-	2.245	2.248	-	1.965	1.961
S ¹ -CHO	1.898	2.070	1.902	1.902	2.100	1.782	1.784
Cu ² -S ²	-	2.708	-	-	2.718	-	3.880
Cu ² -O ⁴	1.952	1.936	1.950	1.946	1.934	1.971	1.959
Cu ² -O ⁶	1.968	2.180	1.961	1.954	2.196	1.988	1.961
S ² -CHO	1.787	1.891	1.782	1.782	1.903	1.789	1.784

Table 3

The calculated important bond distances (in Å) of the located intermediates, transition states and products of the formate-assisted transmetalation in **2a** with boronic acid. Full geometries of these structures are included to Supporting Materials. Here, we report only the triplet ground states of these structures. Geometries of their singlet counterparts are given in Supporting Materials section. See Figure 1 for atomic notations and for reported transition states.

Param.	IIa	II	IIIa	III	TS(IIIa-IVa1)	TS(IIIa-IVa2)	TS(III-IVb1)	IVa1	IVb1	IVa	IVb	V	TS(V-VI)	VI	VII
Cu ¹ -O ¹	1.957	2.042	1.964	1.923	1.986	2.043	1.991	1.973	2.064	1.978	2.051	2.030	1.978	1.857	1.897
Cu ¹ -O ³	2.030	1.969	2.068	2.113	2.205	2.023	2.080	2.203	2.005	2.114	2.016	2.126	2.236	2.134	2.189
Cu ¹ -O ⁶	-	3.486	2.146	1.986	-	2.845	2.172	-	3.176	-	-	2.723 ^{d)}	2.345 ^{a)}	2.178 ^{a)}	2.170 ^{a)}
Cu ¹ -O ⁷	2.073	-	2.004	-	-	2.435	-	-	-	-	-	-	-	-	-
Cu ¹ -O ⁸	2.144	-	-	-	2.096	-	-	2.412	-	-	-	2.279 ^{b)}	2.184 ^{b)}	2.192 ^{b)}	2.133 ^{b)}
Cu ¹ -C ¹	-	2.175	3.801	2.307	1.982	1.988	2.037	1.940	1.921	1.919	1.906	1.930	2.025	-	-
Cu ² -O ²	1.980	2.020	1.989	1.984	1.962	1.943	1.928	1.970	1.937	1.950	1.965	1.910	1.924	1.957	1.971
-Cu ² -O ⁴	2.081	2.080	2.065	2.069	2.092	2.126	2.149	2.093	2.143	2.322	2.140	-	-	2.116	-
Cu ² -O ⁵	2.060	1.989	2.042	2.051	2.085	2.027	2.021	2.076	2.025	1.988	2.088	2.019	2.035	2.095	2.051
Cu ² -S ²	2.401	2.404	2.414	2.403	2.380	2.448	2.461	2.384	2.428	2.628	2.357	2.470	2.470	2.749	2.457
O ¹ -O ²	1.345	1.324	1.327	1.357	1.353	1.341	1.357	1.364	1.338	1.349	1.340	1.379	1.385	1.355	1.389
B-O ⁶	-	1.365	1.429	1.570	1.423	1.441	1.448	1.378	1.386	-	-	-	-	-	-
B-O ⁷	-	-	3.967	1.474	1.474	1.491	1.426	1.440	1.402	-	-	-	-	-	-
B-C ¹	-	1.598	1.563	1.654	2.240	2.156	2.171	3.371	4.123	-	-	3.702 ^{c)}	2.350 ^{c)}	1.482 ^{c)}	-
S ¹ -C ²	1.799	1.780	1.801	1.791	1.801	1.803	1.804	1.801	1.807	1.819	1.807	1.925	2.374	-	-

^{a)} For Cu¹-S¹ distance;

^{b)} For Cu²-O³ distance;

^{c)} For C¹-C² distance.

Table 4

The calculated Mulliken spin densities (in |e|) of the located intermediates, transition states and products of the formate-assisted transmetalation in **2a** with boronic acid. Here, we report only the triplet ground states of these structures. See Figure 1 for used atomic notations used.

Atom	IIa	II	IIIa	III	TS(IIIa-IVa1)	TS(IIIa-IVa2)	TS(III-IVb1)	IVa1	IVb1	IVa	IVb	V	TS(V-VI)	VI	VII
Cu ¹	0.38	0.15	0.34	0.35	0.39	0.31	0.33	0.46	0.32	0.34	0.31	0.36	0.30	0.26	0.28
Cu ²	0.20	0.31	0.22	0.23	0.19	0.20	0.20	0.20	0.21	0.26	0.17	0.24	0.24	0.31	0.26
O ¹	0.63	0.67	0.67	0.61	0.60	0.66	0.61	0.58	0.67	0.60	0.68	0.62	0.56	0.51	0.52
O ²	0.58	0.69	0.62	0.57	0.57	0.56	0.53	0.57	0.57	0.61	0.57	0.44	0.45	0.55	0.50
O ³	0.03	0.01	0.02	0.03	0.02	0.01	0.01	0.03	0.00	0.03	0.01	0.02	0.03	0.06	0.05
O ⁴	0.02	0.03	0.01	0.02	0.02	0.02	0.02	0.01	0.02	0.00	0.01	0.00	0.03	0.02	-
O ⁵	0.01	0.06	0.02	0.01	0.00	0.01	0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.01	0.01
O ⁶	-	0.00	0.01	0.03	0.01	0.00	0.05	0.00	0.00	-	-	-	-	-	-
O ⁷	0.09	-	0.06	0.00	0.05	0.02	0.00	0.00	0.00	-	-	-	-	-	-
O ⁸	0.05	-	0.01	0.00	0.00	0.01	0.00	0.02	0.00	-	-	-	-	-	-
S ¹	0.01	0.01	0.00	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.10	0.18	0.24
S ²	0.00	0.03	0.01	0.00	0.00	0.20	0.01	0.01	0.02	0.03	0.00	0.05	0.05	0.03	0.07
C ¹	-	0.01	0.00	0.04	0.10	0.10	0.14	0.09	0.14	0.07	0.16	0.21	0.15	0.00	-
C ²	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.00	-
B	-	0.00	0.00	0.00	0.01	0.01	0.01	0.00	0.00	-	-	-	-	-	-