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# Mechanistic Understanding of the Unexpected Meta Selectivity in Copper-Catalyzed Anilide C–H Bond Arylation

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*Supporting Information*

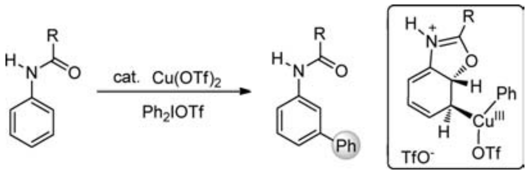
**ABSTRACT:** DFT calculations suggest that the unexpected meta product in the copper-catalyzed arylation of anilide is formed via a Heck-like four-membered-ring transition state involving a $Cu^{III}-Ph$ species. A competitive electrophilic substitution mechanism delivers the ortho product when a methoxy group is present at the meta position of pivanilide. A series of experiments including kinetic studies support the involvement of a $Cu^{I}$ catalyst.

Transition-metal-catalyzed functionalization of aromatic C–H bonds is of great synthetic and theoretical value.[1] Regioselectivity can be achieved by using directing groups,[2] steric-sensitive catalysts,[3] or rationally designed ligands[4] or by the nature of the C–H bond.[5] In contrast to the well-established method of functional-group-directed ortho C–H bond functionalization through cyclometalation,[2] meta-selective C–H bond functionalization is rare.[3,4] Recently, Phipps and Gaunt[6] reported the arylation of anilides by copper(II) catalysts (Scheme 1). This simple process proceeds under mild conditions and forms unexpected meta-arylated products for a broad scope of substrates, violating the traditional rule that anilides favor electrophilic aromatic substitution at the ortho or para position. In addition, the regioselectivity can be switched to afford the ortho-arylated product for *m*-methoxypivanilide.

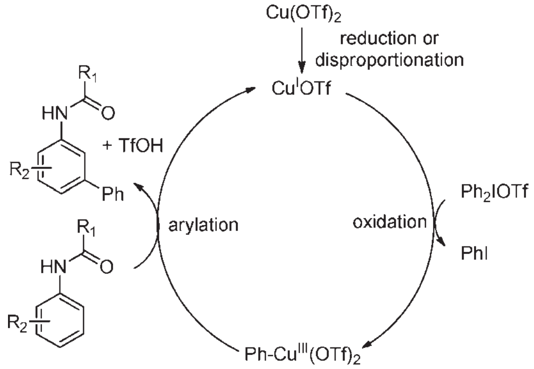
Phipps and Gaunt proposed an anti-oxycupration mechanism involving a $Cu^{III}$–aryl species to explain the regioselective meta arylation (Scheme 1); however, the exact mechanism remains unclear. Besides, there must be another pathway to produce the ortho-arylated product for *m*-methoxypivanilide. Herein we communicate our theoretical study using density functional theory (DFT) calculations[7] as well as experimental investigations of the novel mechanism of the copper-catalyzed anilide meta C–H bond arylation reaction.

A $Cu^{I}/Cu^{III}$ cycle[8] is proposed for the transformation (Scheme 2). The active $Cu^{I}$ species can be initially formed through either the reduction of $Cu^{II}$ by the nucleophile or the disproportionation of $Cu^{II}$.[9] Oxidative addition to the $Cu^{I}$ species by the diaryliodonium salt reagent[10] gives a $Cu^{III}$–aryl species,[9c,d,11] which transfers the aryl group to the anilide. In this step, the $Cu^{I}$ species is regenerated and an acid is formed. On the basis of this catalytic cycle, an exhaustive computational study was carried out using the substrate with $R_1$ = Me and $R_2$ = H. The key results for the pathways leading to the meta- and ortho-arylated products are illustrated in Figures 1 and 2.[12]

**Scheme 1. Gaunt's Copper-Catalyzed Meta Arylation of Anilide and the Anti-Oxycupration Mechanism**



**Scheme 2. $Cu^{I}/Cu^{III}$ Catalytic Cycle**



The highly electrophilic $Ph-Cu(OTf)_2$ species tends to bind the acetanilide at the electron-rich carbonyl oxygen or the ortho and para carbon sites, forming carbonyl-coordinated (**1** and **2**) and aromatic–copper (**3**) complexes. The former two are much more stable because the $Cu^{III}$–O interaction (hard acid–hard base) is stronger than $Cu^{III}$–aromatic interaction (hard acid–soft base). The energy of the most stable *E*-type carbonyl-coordinated complex, **1**, was set as the reference zero of energy in this study.

The first mechanism that we investigated was the anti-oxycupration mechanism proposed by Phipps and Gaunt.[6] In their scheme (path ***a*** in Figure 1), the highly electrophilic $Cu^{III}$–aryl species activates the aromatic system as a Lewis acid, and then the carbonyl oxygen attacks the ortho position, pushing electrons out to form a C–Cu bond at the expected meta position. The aromaticity is broken in this process. Deprotonation with

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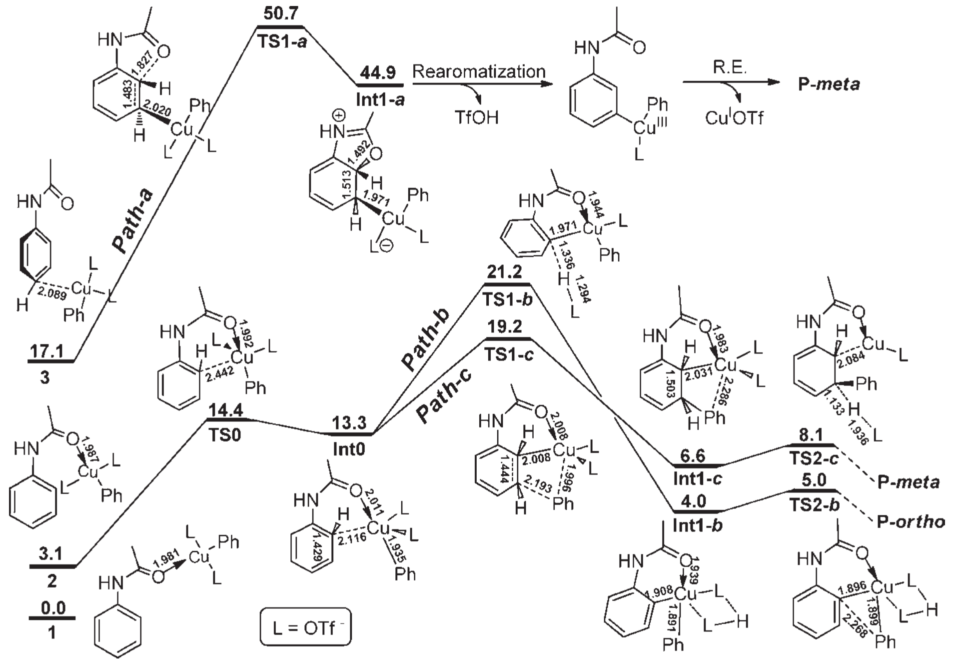


**Figure 1.** The three calculated reaction pathways. Relative free energies including the solvent effect ($\Delta G_{sol}$) are given in kcal/mol.

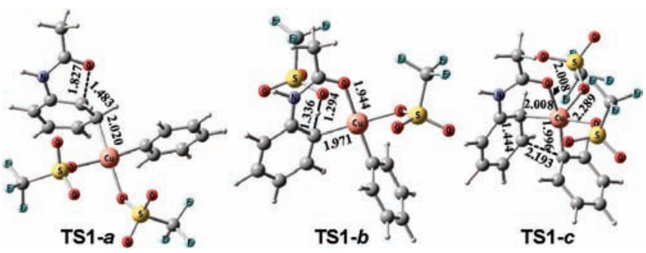


**Figure 2.** Optimized transition states of the rate-determining steps for the three pathways.

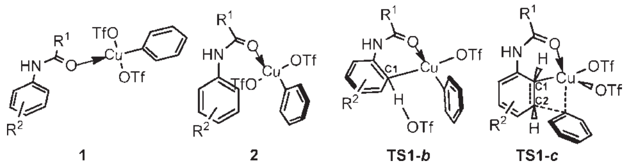
base results in rearomatization. Subsequent reductive elimination leads to the meta product. The calculated relative free energy of the anti-oxycupration transition state **TS1-*a*** (Figure 2) is 50.7 kcal/mol, indicating that path ***a*** is extremely unfavorable, perhaps for the following reasons: (a) the amide group is a weak $\pi$-electron donor, and the site being attacked is the unfavorable electron-rich ortho position; (b) copper shifts from the preferred electron-rich para position to the unfavorable meta position in this process; (c) the aromaticity is broken without adequate compensation because the newly formed $C_{ortho}-O$ bond is weak (1.49 Å) relative to a typical $C(sp^3)-O$ bond (1.45 Å). Another important reason may be that this step forms a zwitterionic intermediate with separated positive and negative charges, which cannot be well-stabilized in dichloroethane. Therefore, path ***a*** can be excluded.

Path ***b*** resembles the metal−ligand dual-participation C−H activation process termed concerted metalation deprotonation (CMD) by Fagnou[5b,13] or, more recently, ambiphilic metal−ligand activation (AMLA) by Davies and Macgregor.[14] However, the use of $Cu^{III}$ as the activating metal has rarely been seen in the literature.[15] Starting from the *Z*-type carbonyl-coordinated complex **2** with the copper at a suitable position, a facile intramolecular Friedel−Crafts-type electrophilic attack at $C_{ortho}$ takes place (**TS0**, 14.4 kcal/mol), forming a pentacoordinated copper intermediate with an $OTf^-$ anion at the apical position and the other four ligands roughly in a plane (**Int0**). In the next step, the apical $OTf^-$ anion disassociates from the copper and abstracts the proton from $C_{ortho}$ in an intermolecular fashion (**TS1-*b***, 21.2 kcal/mol).[16] The intramolecular version of **TS1-*b*** with the apical $OTf^-$ anion still coordinated to copper is only 0.8 kcal/mol higher in energy.[12] The formed six-membered cyclic copper intermediate **Int1-*b*** is relatively stable (4.0 kcal/mol). Subsequent reductive elimination (**TS2-*b***), which is easy because of the strong driving force for $Cu^{III}$ reduction, results in the ortho-arylated product.

Path ***c*** shares with path ***b*** the electrophilic-attack step from **2** to **Int0**. Afterward, the phenyl group bonded to copper is transferred to the meta position via the Heck-like four-membered-ring transition state **TS1-*c***, leading to intermediate **Int1-*c*** with $Cu^{III}$ and phenyl added at the ortho and meta positions, respectively. The $C_{ortho}-Cu$ bond distance is slightly longer in **Int1-*c*** (2.031 Å) than in **TS1-*c*** (2.008 Å), indicating a weaker $Cu-C_{ortho}$ interaction. The $C_{ortho}-C_{meta}$ bond distance in **TS1-*c*** (1.444 Å) is only 0.015 Å longer than that in **Int0** (1.429 Å) and much shorter than that in **TS1-*a*** (1.483 Å). Unlike **Int1-*a***, the benzene ring in **Int1-*c*** remains nearly planar. These structural features indicate that the aromaticity is not completely destroyed in path ***c***. This explains the favorable energies of **TS1-*c*** (19.2 kcal/mol) and **Int1-*c*** (6.6 kcal/mol). In the following step (**TS2-*c***), the $C_{ortho}-Cu$ bond breaks, converting $Cu^{III}$ to $Cu^{I}$. Meantime, a free $OTf^-$ anion abstracts the proton at the meta position, recovering the aromaticity and resulting in the meta-arylated product. The small barrier for this step (1.5 kcal/mol) again shows the strong driving force for $Cu^{III}$ reduction. Overall, path ***c*** is the most preferred pathway; however, path ***b*** is also kinetically accessible.

To obtain a deeper understanding of this reaction, the effects of the terminal $R^1$ group and the aromatic substituent $R^2$ group were studied (Table 1). The results showed that in all cases **TS1-*c*** is more favorable, indicating that the meta-arylation pathway is

**Table 1. Calculated Substituent Effects for $R^1$ and $R^{2a}$**



**1** **2** **TS1-*b*** **TS1-*c***

| entry | $R^1$ | $R^2$ | 1 | 2 | TS1-*b* | TS1-*c* |
|---|---|---|---|---|---|---|
| 1 | Me | H | 0.0 | 3.1 | 21.2 | 19.2 |
| 2 | $CMe_3$ | H | 0.0 | 0.2 | 18.0 | 16.1 |
| 3 | Ph | H | 0.0 | 2.5 | 20.9 | 18.0 |
| 4 | *p*-$MeC_6H_4$ | H | 0.0 | 3.0 | 21.0 | 19.1 |
| 5 | *p*-$OMeC_6H_4$ | H | 0.0 | 1.9 | 19.6 | 17.6 |
| 6 | *p*-$FC_6H_4$ | H | 0.0 | 2.7 | 20.4 | 18.4 |
| 7 | *p*-$CF_3C_6H_4$ | H | 0.0 | 3.0 | 21.6 | 18.6 |
| 8 | $CMe_3$ | *o*-OMe | 0.6 | 0.0 | 19.2 | 13.7 |
| 9 | $CMe_3$ | *o*-Me | 0.5 | 0.0 | 18.1 | 13.6 |
| 10 | $CMe_3$ | *o*-F | 0.0 | 0.0 | 19.0 | 17.8 |
| 11 | $CMe_3$ | *m*-OMe | 0.4 | 0.0 | 13.5 | 12.3 |
| 12 | $CMe_3$ | *m*-Me | 0.1 | 0.0 | 16.7 | 14.3 |
| 13 | $CMe_3$ | *m*-F | 0.0 | 0.1 | 17.8 | 16.8 |
| 14 | $CMe_3$ | *p*-OMe | 0.6 | 0.0 | 18.6 | 13.9 |
| 15 | $CMe_3$ | *p*-Me | 0.5 | 0.0 | 17.9 | 14.1 |
| 16 | $CMe_3$ | *p*-F | 0.0 | 0.4 | 19.9 | 17.8 |

[a] The numerical values are relative free energies in solvent ($\Delta G_{sol}$) in kcal/mol.

dominant. The size of the $R^1$ group is crucial to the relative stabilities of **1** and **2**, which can affect the reaction barriers. The $CMe_3$ group (entry 2) destabilizes **1** by 2.9 kcal/mol relative to the Me group (entry 1). Consequently, the energy of **TS1-*c*** decreases by ~3.1 kcal/mol. A large $R^1$ group pushes copper to the trans position, facilitating the electrophilic attack at the ortho carbon. This is consistent with the experimental observations that the substrates with $R^1 = CMe_3$ gave the best yield. On the other hand, the electronic character of $R^1$ has a small effect on the reaction, as indicated by entries 3–7. The energies of **2** and **TS1-*c*** vary slightly within 1.1 and 1.5 kcal/mol, respectively.

The substituent $R^2$ on the aromatic ring has a larger effect on the reaction barrier than $R^1$ does. In comparison with entry 2 ($R^1 = CMe_3$, $R^2$ = H), all of the ortho, meta, and para electron-donating groups (EDGs) lower the barrier for path ***c*** (entries 8, 9, 11, 12, 14, 15) because they can increase the electron density at either C1 or C2 (Table 1, **TS1-*c***). However, only at the meta position can EDGs considerably increase the electron density of C1 and lower the barrier for path ***b*** (entries 11 and 12). Electron-withdrawing groups (EWGs) generally raise the barriers for both pathways (entries 10, 13, and 16, except for **TS1-*b*** in entry 13). Mechanistically, these results reflect the electrophilic character of the $Cu^{III}$–Ph species.

The calculated results in entry 11 are inconsistent with the experiments. The strong EDG *m*-OMe stabilizes **TS1-*b*** (4.5 kcal/mol) more than it stabilizes **TS1-*c*** (3.8 kcal/mol). However, this is not enough to reverse the regioselectivity. Since the two transition states involve different types of reactions, a calculation error may be inevitable. We also explored a more complicated model in which a HOTf molecule forms a hydrogen bond with the *m*-OMe group. The calculated barrier for path ***b*** is 0.9 kcal/mol lower than that for path ***c*** using the model.[12] Thus, the ortho-arylated anilide becomes the main product.

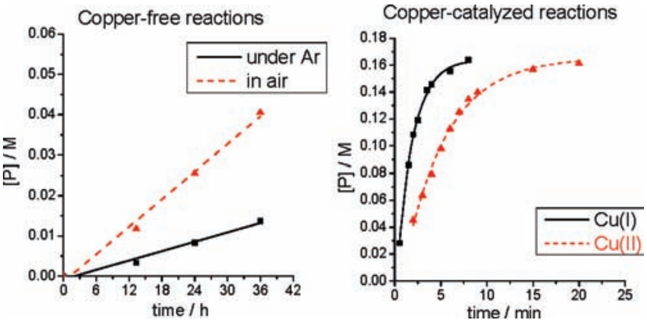


**Figure 3.** Plots of product concentration [P] vs time for the (left) copper-free and (right) copper-catalyzed reactions. Reaction conditions: [*o*-methylpivanilide] = 0.20 M; [catalyst] = 0.01 M; [$Ph_2IOTf$] equal to the saturated concentration, since it could not be fully dissolved; 90 °C in DCE.

We then repeated the experiment for the arylation of the *m*-methoxypivanilide substrate under the conditions described by Gaunt.[6] We found the formation of both ortho- and meta-arylated products in a ratio of 10:1.[17] Thus, the calculated small energy difference is in qualitative agreement with the experimental results. When base was added to the reaction, the ratio of ortho to meta product decreased to about 4:1. This result also supports the model involving a HOTf molecule.

Recently, Gaunt et al.[18] reported that this meta arylation and related reactions can happen without a copper catalyst. They observed a yield of 78% for *o*-methylpivanilide at 80 °C under copper-free conditions. These findings cast some doubt on our $Cu^{III}$–Ph model. However, when we ran this copper-free reaction, inconsistent results were initially obtained. Using carefully purified reactants and solvent and carefully cleaned apparatus, we found that *o*-methylpivanilide gave only a small amount of product at 90 °C in 24 h. Under the same conditions, the $Cu(OTf)_2$-catalyzed reaction finished in 20 min.

In order to compare the rates of the copper-free and copper-catalyzed reactions, we monitored the kinetics of these reactions (Figure 3). Under copper-free conditions, we observed a yield of only 6.9% after 36 h when the reaction was run at 90 °C under argon, while the yield increased to 20.3% when the reaction was exposed to air. In the copper-catalyzed reaction, a yield of 20% was achieved in ~2 min. For a rough estimation, 5 mol % copper catalyst increased the reaction rate by ~3 orders of magnitude, unambiguously demonstrating the catalytic activity of copper catalysts. We also found that a $Cu^I$ catalyst was more active than a $Cu^{II}$ catalyst by a factor of ~2.5,[12] which can be explained on the basis of the proposed $Cu^I/Cu^{III}$ cycle in Scheme 2. In view of the fact that $Cu^I$ is directly involved in the $Cu^I/Cu^{III}$ cycle while $Cu^{II}$ has to be transformed to $Cu^I$ before it can enter the $Cu^I/Cu^{III}$ cycle, a lower rate for the $Cu^{II}$ catalyst is expected.

While monitoring the $Cu(OTf)_2$ catalyzed reaction, we observed that the reaction mixture turned purple as the reaction progressed. This purple species was not iodine (it did not react with the potassium iodide–amylum test paper) but probably was a $Cu^I$ complex. This color change phenomenon can also be understood on the basis of the catalytic cycle in Scheme 2. $Cu^{II}$ is initially transformed to $Cu^I$ and enters the cycle. As the reaction proceeds, $Ph_2IOTf$ runs out, resulting in a rate decrease for the oxidation step. Consequently, $Cu^I$ starts to accumulate, producing the purple color.

The transformation of $Cu^{II}$ to $Cu^I$ and then to $Cu^{III}$ by oxidation with a diaryliodonium salt was studied in detail by

Lockhart in 1983.[10a] In his study, $\mathrm{Cu^{I}}$ was firmly established as the reactive form of copper. A color change and a higher rate for the $\mathrm{Cu^{I}}$ catalyst than for the $\mathrm{Cu^{II}}$ catalyst were observed. In addition, inhibition of the reaction by cuproin, which acts as a $\mathrm{Cu^{I}}$ trap, was observed. In view of that work and our observations, it seems that the $\mathrm{Cu^{III}{-}Ph}$ mechanism is most likely to be operative in the current meta arylation reaction.

In summary, the mechanism of copper-mediated anilide meta arylation has been studied both theoretically and experimentally. DFT calculations suggest that meta-arylated products are formed via a Heck-like four-membered-ring transition state through a $\mathrm{Cu^{III}{-}Ph}$ intermediate. The involvement of the $\mathrm{Cu^{III}{-}Ph}$ species is supported by (1) the good agreement between the calculated and experimental reactivity and regiochemistry; (2) the large rate acceleration by $\mathrm{Cu^{I}}$ and $\mathrm{Cu^{II}}$ catalysts relative to the Cu-free reaction; (3) the change in color as reaction proceeds; and (4) the somewhat higher reactivity of $\mathrm{Cu^{I}}$ relative to $\mathrm{Cu^{II}}$.

## ■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Details (procedures, 3D structures, and coordinates) of calculations and experiments on *m*-methoxypivanilide and *o*-methylpivanilide. This material is available free of charge via the Internet at http://pubs.acs.org.

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## ■ ACKNOWLEDGMENT

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(8) Other cycles seem less possible. For example, the radical-containing $\mathrm{Cu^{I}/Cu^{II}}$ and $\mathrm{Cu^{II}/Cu^{III}}$ cycles are unlikely because radical inhibitors had no effect on the analogous arylation reaction of indole (see ref 9a). The $\mathrm{Cu^{0}/Cu^{II}}$ cycle is also excluded because the calculated activation energy for the $\mathrm{Cu^{0}/Cu^{II}}$ cycle was 28.0 kcal/mol, which is higher than the value of 19.2 kcal/mol for the $\mathrm{Cu^{I}/Cu^{III}}$ cycle in Figure 1.

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(17) The formation of the meta product for *m*-methoxypivanilide was not reported in ref 6. We found that the meta product was inseparable from the unreacted reactant by flash column chromatography. It was identified by NMR analysis of the mixture, separated by HPLC, and fully characterized. See the Supporting Information for details.

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