ORGANOMETALLICS
Article
Cite This: Organometallics XXXX, XXX, XXX−XXX
pubs.acs.org/Organometallics

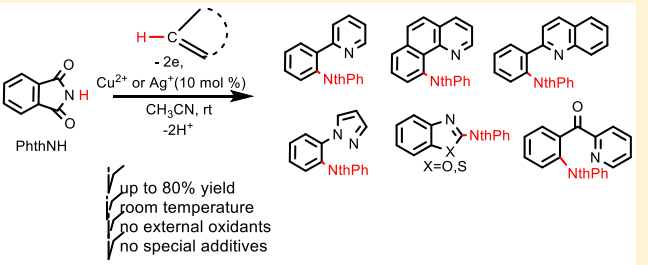
Copper or Silver-Mediated Oxidative C(sp^2)−H/N−H Cross-Coupling of Phthalimide and Heterocyclic Arenes: Access to *N*-Arylphthalimides

Tatyana V. Gryaznova, Kirill V. Kholin, Elizaveta O. Nikanshina, Vera V. Khrizanforova, Sofia O. Strekalova, Robert R. Fayzullin, and Yulia H. Budnikova*

Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center, Russian Academy of Sciences, Arbuzov str. 8, Kazan 420088, Russian Federation

Supporting Information

ABSTRACT: Copper or silver-catalyzed direct C(sp^2)−H/N−H electrochemical cross-coupling of phthalimide and heterocyclic arenes (2-phenylpyridine, benzo[*h*]quinoline, benzoxazole, and benzothiazole, etc.) for the efficient synthesis of phthalimide derivatives is described. This reaction features good yield, mild conditions, and broad substrate scope, which provides an efficient and straightforward protocol to access this type of tertiary amines. For the first time, the proposed protocol is based not only on a copper catalyst but also on silver, which has never been used for this purpose before, and both give comparable results. Mechanistic investigations (voltammetry, ESR studies) disclosed that a free-radical pathway might be excluded in this process accomplished through Cu(I)/Cu(II)/Cu(III) or Ag(I)/Ag(III) cycles.



INTRODUCTION

The aromatic and heteroaromatic amines are ubiquitous in naturally occurring compounds, bioactive compounds (pharmaceuticals, agrochemicals) and organic materials (polymers, dyes), ligands for catalysts, and flavors, as important intermediates, which has inspired synthetic chemists to develop new more efficient synthetic methodologies for constructing C−N bonds.[1] Metal-catalyzed C−N cross-coupling name reactions, such as the Buchwald−Hartwig, Ullman, or Chan−Evans−Lam couplings, have been developed as a powerful tool for organic chemists.[1f,2] Despite the apparent advances, the prefunctionalization of arenes by (pseudo)halides or boronic acids as substituents is required and results in the production of substantial quantities of waste.

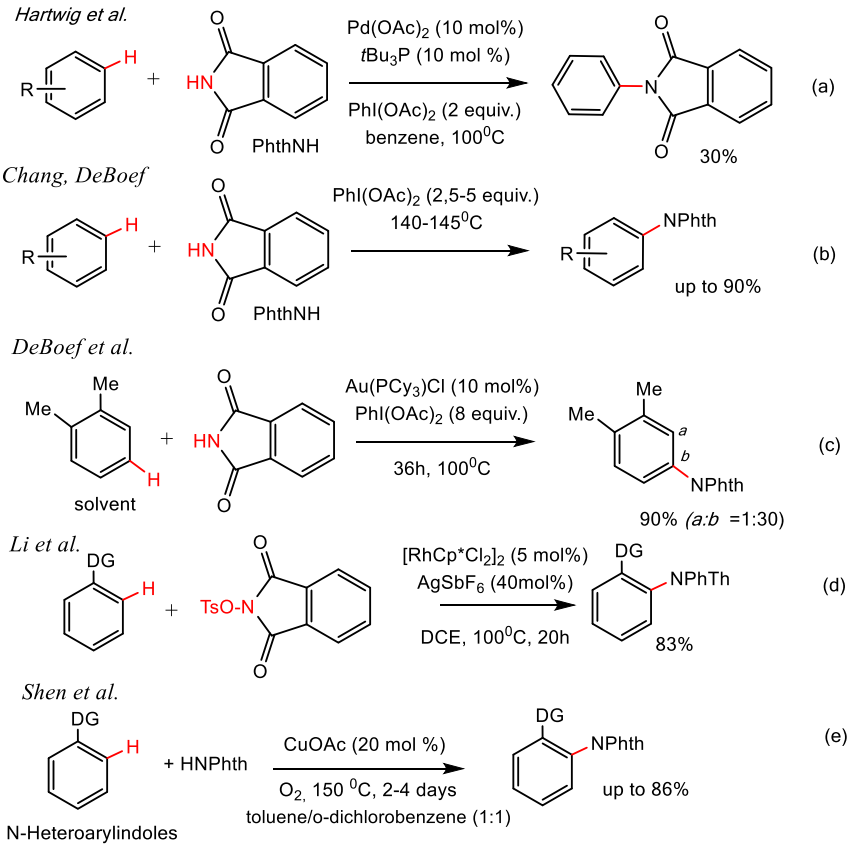
Recently, the dehydrogenative C−H/N−H cross-coupling of amines and aromatic C−H partners has emerged as a straightforward pathway for the synthesis of (hetero)-arylamines, which has been an atom-economic and more effective process for the formation of C−N bonds.[3] However, most cases of metal-catalyzed C−H/N−H cross-coupling reactions are related to expensive precious metals, such as Pd, Rh, and Ru,[3,4] but the use of readily available widely used transition metals such as Cu, Ni, Co is crucial and promising.[3] In the past few years silver is extensively used in homogeneous and heterogeneous catalysis for organic synthesis owing to its Lewis acidity, and as not only a powerful one-electron, but also two-electron oxidant.[9] Silver has provided a unique opportunity in organic catalytic reactions owing to its more economical than other expensive transition metals, excellent selectivity and stability, and environmentally benign nature. The higher reactivity exhibited by silver derivatives in the activation of various organic substrates place them among the most prominent reagents in free radical reactions. Silver catalysts are used much less frequently in C−H amination reactions than copper, rhodium, cobalt, and most other known catalysts for these reactions. There are reports of the cooperative action of silver and other metals—rhodium,[4i] palladium,[5,6] nickel[7] or copper,[8] and so on. Successful examples of the use of silver catalysts are often associated with nitrene transfer reactions, at which the amination of C(sp^3)−H bonds occurs;[9] most often this is an intramolecular reaction. Silver-catalyzed amination of aromatic C(sp^2)−H bonds has been described only in single papers.[10]

The amine reagents used in the amination reactions are amines, amides, sulfonamides, N−O reagents and N−X (X = halogen) reagents,[3] but the amines themselves, not their derivatives, are the most interesting as aminating agents. Interestingly, phthalimide, which is a valuable ammonia equivalent and used to synthesize primary amines, by a reaction called the Gabriel reaction,[11] has recently captured much attention from chemists. Phthalimide, in particular, is known as an ideal starting point for the development of the amination technology, because it is commercially available, inexpensive, and easy to handle, and once coupled, its derivative can be readily converted to a primary amine,

Received: July 2, 2019

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

Scheme 1. Known Approaches toward *N*-Arylphthalimides



which can be further derivatized. Recently, a number of phthalimide derivatives, thalidomide, and others have been found to have several important biological activities, including the inhibition of tumor necrosis factor-α (TNF-α) production, as well as the highest in vivo anti-inflammatory activity, antiangiogenic, and cyclooxygenase inhibitory activities.[12] A number of *N*-arylphthalimides have been shown to have anticancer activity[13] and anti-inflammatory activity.[14] The photoreactions of substituted phthalimides can be used to efficiently construct a number of interesting heterocyclic structures.[15] It has recently been shown that some phthalimide derivatives form highly concentrated eutectic electrolytes promising for creating organic redox flow batteries with enhanced reversibility.[16] Therefore, the search for a new direct atom-saving option of obtaining *N*-arylphthalimides is relevant and in demand. However, all known methods for the synthesis of *N*-arylphthalimides have a number of disadvantages, and there are virtually no convenient atom-saving, relatively environmentally acceptable methods, based on direct cross-dehydrative C(sp^2)−H/H−N combination (phthalimide itself, not its derivative) without using excess organic oxidants $PhI(OAc)_2$, with the participation of catalysts based on cheaper and more common metals such as Cu, Ag, Ni, Co, and not the most expensive noble Pd, Rh, Ru, under mild conditions at room temperature, eliminating toxic solvents (toluene, *o*-dichlorobenzene, etc.).

For example, Hartwig and co-workers documented a Pd-catalyzed ($Pd(OAc)_2$ with *t*-Bu_3P ligand) intermolecular C−H amination reaction of arenes with phthalimide to form *N*-aryl phthalimides using 6 equiv of $PhI(OAc)_2$ as an oxidant in benzene at 100 °C with a yield of 30% (Scheme 1, a).[17]

Similar works reported by Chang (140 °C)[18] and DeBoef (145 °C, MW)[19] were performed in the presence of $PhI(OAc)_2$ (2.5−5 equiv) (Scheme 1, b). The DeBoef group[20] reported the Au(I)-catalyzed ($Au(PCy_3)Cl$) oxidative C−H amidation of alkylbenzenes by using phthalimide as an aminating source with high yields, but using 8 equiv of $PhI(OAc)_2$ at 100 °C (Scheme 1, c).

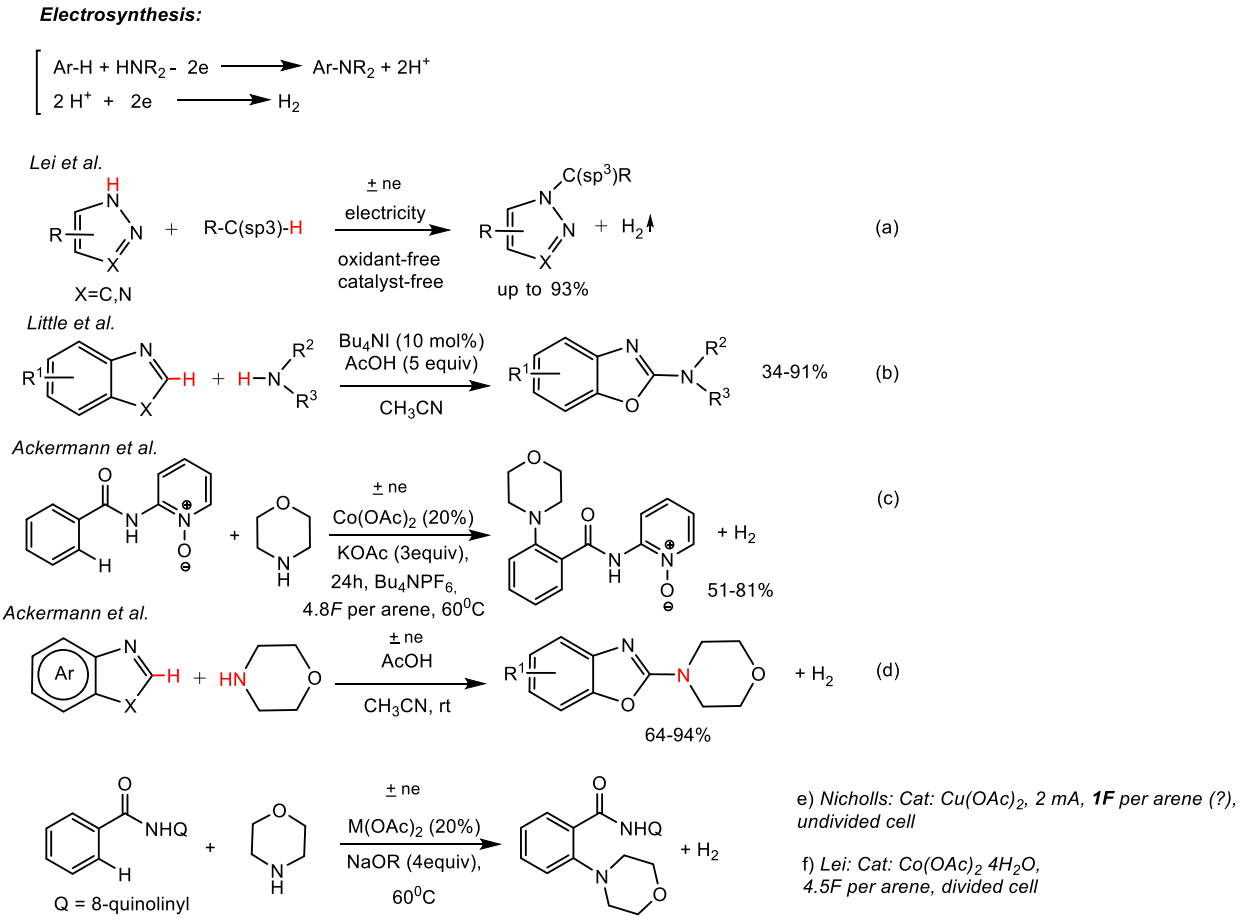
At the same time, Li et al.[21] demonstrated an Rh(III) and Ag cocatalyzed C−H amination of arenes bearing directing groups using *N*-OTs phthalimide as an amidating reagent (Scheme 1, d). In all of the examples above, the choice of arenes is rather limited; the best yields are given by substituted toluenes.

In 2015, Shen documented a Cu(I)-catalyzed C−H amidation of *N*-pyrimidyl(pyridyl) indoles and 2-arylpyridines under oxygen using phthalimide as an aminating source (Scheme 1, e).[22] The best results were obtained at high temperatures, at 150 °C, in solvents that are not "green", toluene/*o*-dichlorobenzene (1:1), at that, with CuOAc being more effective than $Cu(OAc)_2$, the content of the catalyst is relatively high, 20 mol %, and requires 2−4 days to reach completion.

In many recent studies on the introduction of phthalimide moiety on the aromatic C−H bond, it is not phthalimide itself that is used, but its derivatives. For example, *N*-(arylthio)i(a)-mides PhthN-S-Ph,[5] *N*-acyloxyphthalimides PhthN-OCF_3,[23] *N*-hydroxyphthalimide PhthN-OH,[24] PhthN-OTs[25,26] or *N*-chlorophthalimides[27] were used in metal-catalyzed cross-coupling reactions. Although this technique is convenient for increasing the reactivity of phthalimide, it adds new stages to the synthesis of *N*-arylphthalimides.

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

Scheme 2. Electrochemical Examples of CH/NH Cross-Coupling



There are some successful recently published examples of electrochemical amination of heterocyclic substrates.[3e,h] For example, Lei described electrooxidative C(sp^3)−H amination of azoles via intermolecular oxidative C(sp^3)−H/N−H cross-coupling[28] (Scheme 2, a). Aromatic C(sp^2)−H bonds are not aminated under these conditions.

Little suggested using an I^-/I_2 pair as a mediator in the combination of secondary amines and benzoxazole[29] (Scheme 2, b). Ackermann[30] selected the conditions for electrochemical ligand-directed amination−the $Co(OAc)_2{\cdot}4H_2O$ catalyst, KOAc and Bu_4NPF_6 in γ-valerolactone (GVL) as a solvent; however, the choice of reagents is limited to arenes with directing groups including pyridine oxide (PyO = pyridine-1-oxide), and secondary amines are only cyclic aliphatic ones (Scheme 2, c). The key importance of N,O bidentate coordination mode for electrochemical C−H nitrogenation was discovered (Scheme 2, b). It is noteworthy that N,N bidentate chelation and electron deficient amides did not facilitate the cobalt catalyzed C−H amination.

Recently, Ackermann[31] described electrochemical amination of morpholine benzoxazoles without a catalyst; AcOH (Scheme 2, d) plays the role of electrolyte. Recently, Lei[32] and Nicholls[33] groups (Scheme 2, e,f) independently developed metal(II)-catalyzed electrooxidative chelate-promoted ortho-C−H amination with cyclic amines (such as morpholine, etc.) under conditions similar to those proposed by Ackermann[30] (Scheme 2, c). However, Lei[33] used $Co(OAc)_2$, like Ackermann,[30] and Nicholls[33] used $Cu(OAc)_2$. It should be noted that the synthesis conditions in the work of Nicholls[33] were very unusual, since the process progressed at a scaled-down current of 2 mA, and the passage of 1 *F* electricity only in an undivided cell yielded up to 79% of product, while the material and electronic balance of the reaction according to the equation (see the general scheme reported throughout the literature, Scheme 2) requires at least 2 F of electricity per mole of the arene (amine is taken in excess). In similar reactions by Ackermann[30] or Lei,[32,4] 8 and 4.5 *F* are required, respectively. Usually, in an undivided cell, the current efficiencies are lower than in a divided one, considering side reactions on both electrodes are unavoidable. The given voltamperometric data[33] for each of the components and given mechanisms leave much to be desired, since it is known that $Cu(OAc)_2$ is oxidized at high anodic potentials, and water and NaOAc (the known Kolbe reaction) are oxidized much earlier, so cyclic voltammetry of the mixture of these components cannot describe oxidation of $Cu^{II/III}$ as the authors believe, thus building on their reaction mechanism, but without evidence.[33]

However, in no case in the above-described conditions of electrosynthesis was phthalimide used as an aminating agent, as some authors specifically mentioned, for example, Little.[29]

Earlier, we proposed an electrocatalytic approach to the direct aromatic C(sp^2)−H functionalization (phosphonation or fluoroalkylation) using transition metal complexes and salts as catalysts.[34−48] The authors confirmed the success of electrochemically inducing C−H/P−H cross-coupling of dialkyl-*H*-phosphonate with different (hetero)aromatic molecules, such as benzenes bearing electron donor and electron withdrawing substituents in the ring or coumarins under the

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

action of Ni, Co or Mn catalysts and the mixtures of metal complexes,[35−38,40] and azole derivatives (benzo-1,3-azoles, 3-methylindole, 4-methyl-2-acetylthiazole) under the action of Ag catalyst.[48] Mention may be made of electrooxidative coupling of diphenylphosphine oxide with acetylenes in the presence of catalytic amounts of Ag^+ resulting in the formation of benzo[*b*]phosphole oxides.[39] The authors have proven that electrochemical transfer of an electron to (from) metal phosphonate generates a phosphonyl radical, which can then react with different arenes giving the products of aromatic C−H phosphonation in some cases,[37−39] but ligand-directed C−H functionalization includes high oxidation states of metal catalysts, Ni^{III} or $Pd^{III/IV}$.[34,42,44−47]

Thus, the purpose of this study is to develop a method for the synthesis of *N*-arylphthalimides by direct C(sp^2)−H/N−H cross-coupling of phthalimide and heterocyclic arenes under mild electrochemical conditions involving copper or silver salts, affordable and relatively inexpensive catalysts (10 mol %) under mild reaction conditions at room temperature, without chemical oxidants, using environmentally benign electricity. We also propose to develop a universal method for amination with phthalimide of arenes of various nature such as 2-phenylpyridine, benzo[*h*]quinoline, benzoxazole, and benzothiazole, etc., which, according to the authors' data, have never before been able to engage in a direct reaction with phthalimide at all or only under harsh conditions.

RESULTS AND DISCUSSION

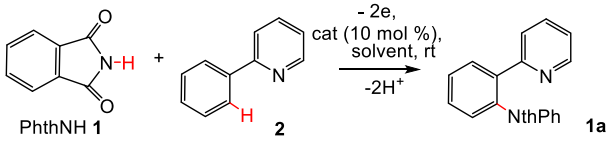
The study commenced with the reaction of phthalimide (PhthNH) **1** with 2-phenylpyridine **2** as the model reaction (Table 1). The desired product **1a** was obtained at 78% yield by using $Cu(OAc)_2$ (10 mol %) as the catalyst in CH_3CN (entry 1). Further evaluation of different catalysts, solvents, and additives revealed that the reaction proceeded efficiently also with Ag_2O or AgOAc as a catalyst to afford the product **1a**, but any additives were useless.

Acetonitrile as a solvent is much better than DMF (entries 4 and 10). Palladium and cobalt salts or complexes (entries 12 and 13−14, where bpy is added for better solubility of the catalyst) could not give a higher yield than copper or silver salt (or oxide), but Ni(bpy)$(BF_4)_2$ proved to be an ineffective catalyst (entry 15).

Without a catalyst, the reaction does not proceed (entry 16), and in an undivided cell, the yields are much lower or no product is formed at all (entries 5 and 8).

With the optimized conditions at hand, we proceeded in exploring the scope of arenes (Scheme 3, Table 2) with two of the best catalysts, $Cu(OAc)_2$ and Ag_2O. Phthalimide as an aminating reagent was tested in electrocatalytic amination of arenes and heterocyclic compounds, as ligand-directed, using 2-phenylpyridine and benzo[*h*]quinoline, 1-phenylpyrazole, 2-phenylquinoline, benzoylpyridine, and heteroazole substrates: benzoxazole and benzothiazole.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	additive	divided or undivided cell	yield of **1a**, %[b]
1	$Cu(OAc)_2$	CH_3CN	–	divided	**78**
2	$Cu(OAc)_2$	CH_3CN	K_2CO_3	divided	45
3	$Cu(OAc)_2$	CH_3CN	KOAc	divided	45
4	$Cu(OAc)_2$	DMF	–	divided	20
5	$Cu(OAc)_2$	CH_3CN	–	undivided	5
6	CuI	CH_3CN	–	divided	0
7	Ag_2O	CH_3CN	–	divided	**76**
8	Ag_2O	CH_3CN	–	undivided	0
9	Ag_2O	CH_3CN	KOAc	divided	38
10	Ag_2O	DMF	–	divided	5
11	AgOAc	CH_3CN	–	divided	**72**
12	$Pd(OAc)_2$	CH_3CN	–	divided	56
13	$Co(OAc)_2$	CH_3CN	–	divided	62
14	Co(bpy)$(BF_4)_2$	CH_3CN	–	divided	64
15	Ni(bpy)$(BF_4)_2$	CH_3CN	–	divided	0
16	without catalyst	CH_3CN	–	divided	0

[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), catalyst (0.1 mmol), solvent (15 mL) at 25 °C under Ar, 2*F* electricity (54 mA·h). [b]Isolated.

Scheme 3. C−H/N−H Cross-Coupling of Phthalimide with Various Heteroarenes

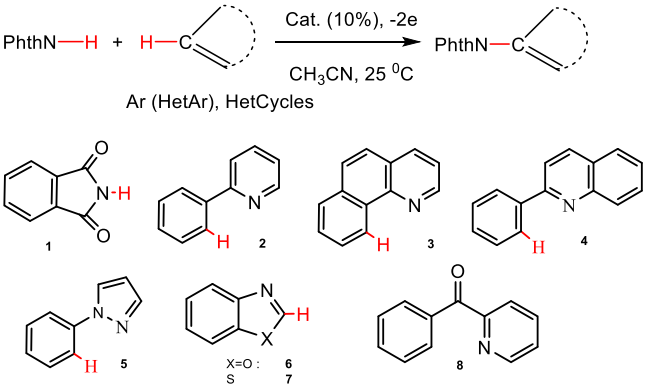


Table 2. Yields of Cross-Coupling Product for Various Aromatic and Heterocyclic Partners[a]

entry	C(sp^2)−H partner	catalyst, 10 mol %	yield of cross-coupling, %[b]
1	**2**	$Cu(OAc)_2$	78
2		Ag_2O	76
3	**3**	$Cu(OAc)_2$	80
4		Ag_2O	74
5	**4**	$Cu(OAc)_2$	67
6		Ag_2O	64
7	**5**	$Cu(OAc)_2$	63
8		Ag_2O	65
9	**6**	$Cu(OAc)_2$	29
10		Ag_2O	25
11	**7**	$Cu(OAc)_2$	39
12		Ag_2O	36
13	**8**	$Cu(OAc)_2$	50
14		Ag_2O	54

[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), catalyst (0.1 mmol), CH_3CN (15 mL) at 25 °C under Ar, 2*F* electricity (54 mA·h), divided cell. [b]Isolated.

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

As shown in Table 2, the electrochemical approach to the amination of 2-phenylpyridine with phthalimide proved to be effective; the yield of the ortho-aminated derivative of 2-phenylpyridine was 78%. With good yield (80%), benzo[*h*]-quinoline is also aminated under the same conditions. In the case of using 2-benzoylpyridine as the substrate, the yield of the aminated product was about 50%.

In all reactions of ligand-directed (pyridine-directed) amination, 2-aminated derivatives are formed, in the cases of benzoxazole-2-(benzo[*d*]oxazol-2-yl)isoindoline-1,3-dione and benzothiazole-2-(benzo[*d*]thiazole-2-yl) isoindoline-1,3-dione. Regardless of the catalyst used, benzoxazole and benzothiazole are aminated to approximately the same yield (entries 9−12, Table 2).

Electrochemical Study. Different techniques were applied to monitor the changes in the key components over the course of these homogeneous reactions. For a detailed investigation of the reaction pathway, the cyclic voltammetry (CV) and electron paramagnetic resonance spectroscopy (EPR) methods were applied.

The redox properties of all participants in the catalytic CH/NH cross-coupling were studied using cyclic voltammetry and electrochemical data, which are summarized in Table 3.

Table 3. Electrochemical Data for Participants of Catalytic C−H/N−H Cross-Coupling[a]

	E_p of oxidation (V)	
compound	Pt w.e., CH_3CN	CPE, CH_3CN
1	3.00	1.00
	1.10 (in DMF)	–
2	2.2	–
3	1.945	–
4	2.06	–
5	1.88	–
6	2.26	–
7	2.13	–
8	2.56	–
$Cu(OAc)_2$	2.4	–
$Co(OAc)_2$	insoluble	1.35
$Cobipy(BF_4)_2$	1.50	–
$Nibipy(BF_4)_2$	1.83	–
Ag_2O	insoluble	1.25
AgOAc	1.89	–
$Pd(OAc)_2$	1.90	

[a]CH_3CN (or DMF), Pt (or CPE) w.e., 0.1 M Bu_4NBF4, 100 mV/s, Ag/AgCl reference electrode.

CH_3CN. Both aromatic reaction partners and phthalimide and $Cu(OAc)_2$ in acetonitrile on a platinum electrode are oxidized in the high potential region (Figures 1 and 2). In the presence of $Cu(OAc)_2$ (1:1), E_{p1}^{ox} 2-PhPy (**2**) shifts to lower potentials and an increase in the oxidation current at this potential by two in comparison with diffusion indicates the coordination of 2-phenylpyridine **2** with Cu^{II} (Figure 1). $Cu(OAc)_2$ itself is more difficult to oxidize, at ∼2.4 V ref Ag/AgCl. If there was no coordination, one would observe the superposition of independent Cu^{II} and arene **2** peaks, that is, the current would increase approximately at the potential of the second oxidation peak **2**. The addition of amine−phthalimide (1:1:1), which is not electrochemically active in CH_3CN up to 3.0 V, leads to the appearance of a complex

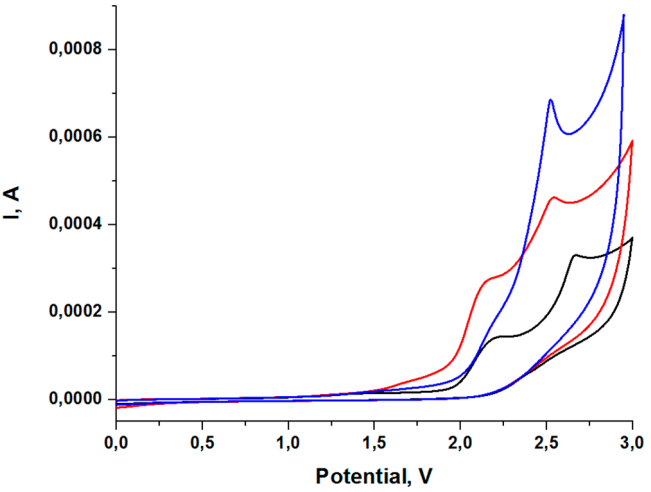


Figure 1. Cyclic voltammograms (CVs) for **2** (black), mixture of **2** with $Cu(OAc)_2$ (1:1) (red), mixture of **1** and **2** with $Cu(OAc)_2$ (1:1:1) (blue). Concentration 5×10^{-3} M for all compounds, CH_3CN, Bu_4NBF_4 (10^{-1} M). Ref. Ag/AgCl, 100 mV/s, Pt w.e.

wave, approximately 7 electrons in total, which indicates a catalytic reaction with Cu^{II} regeneration.

Analysis of the redox behavior of the PhthNH with $Cu(OAc)_2$ system (Figure 2) shows that the addition of phthalimide to $Cu(OAc)_2$ has little effect on the cyclic voltammetry of the latter.

Ag_2O is insoluble in CH_3CN; therefore, it is impossible to determine the potential for oxidation of the latter in solution. However, during the oxidative electrolysis of the studied mixtures, very fast dissolution of Ag_2O is observed, its black precipitate quickly disappears. In order to assess the redox properties of insoluble or poorly soluble participants in this reaction, a carbon paste electrode (CPE) with an ionic liquid as a binder was used, allowing the study of redox properties in a wide range of potentials.[47,49] Phthalimide is oxidized in CPE at ∼1.0 V (Figure S1), and Ag_2O at 1.25 V (Table 3).

DMF. Phthalimide is oxidized in a solution of DMF at ∼1.1 V (Figure S2), that is, much easier than in CH_3CN, and that is closer to the potentials of solid-phase oxidation in CPE. However, a small window of available DMF potentials (DMF is oxidized at ∼1.5 V) usually prevents the use of this solvent in oxidative electrosynthesis. Our results confirm that, under the conditions studied, DMF is not indifferent, oxidizes, and participates in the functionalization of arenes, even at lower potentials, reducing the overall yield of the desired product of the C−H/N−H coupling (Table 1). Therefore, this paper will consider only current−voltage data in the available area of the DMF oxidation potentials.

Voltammetric studies of the reaction mixtures in the presence of silver catalysts proved difficult, since Ag_2O is not soluble in CH_3CN, AgOAc is poorly soluble, and no effects as well as no catalytic current increases or significant shifts in the oxidation potentials of arenes in their presence were observed (Figure S3).

However, during the coelectrolysis of 1 and 2 and Ag_2O catalyst (1:1:1), a decrease in the oxidation current of 2-phenylpyridine, **2**, was observed; that is, it was consumed, Ag_2O dissolved, and new waves of intermediate compounds appeared, possibly coordinated with Ag^+, oxidized at about 1.5 V (Figure S4).

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

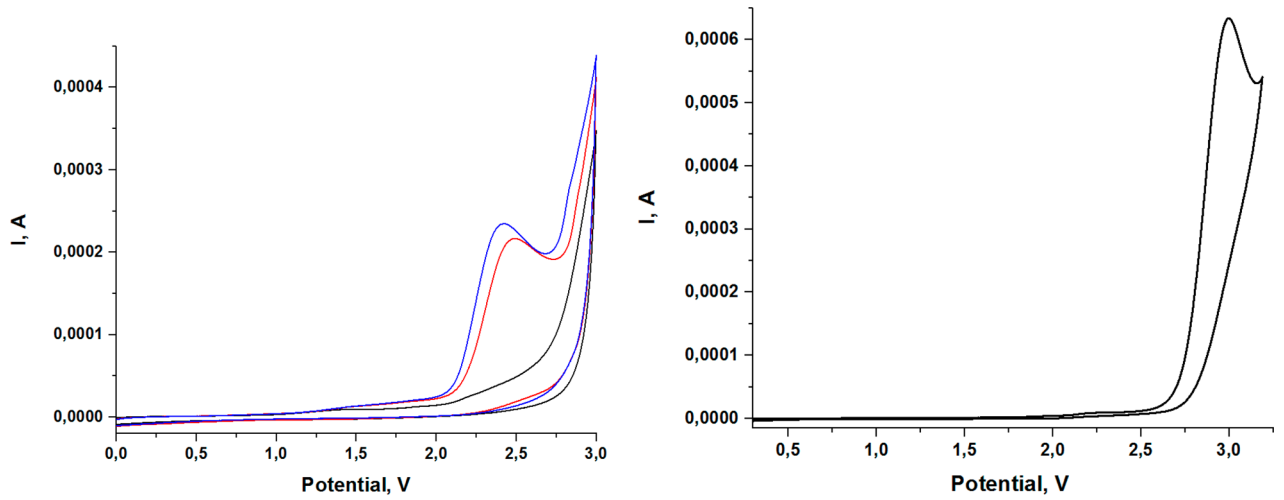


Figure 2. CVs for **1** (black), mixture of **1** with $Cu(OAc)_2$ (1:1) (red), mixture of **1** with excess $Cu(OAc)_2$ (1:6) (blue). Concentration 5×10^{-3} M, CH_3CN, Bu_4NBF_4 (10^{-1} M). Ref. Ag/AgCl, 100 mV/s, Pt w.e.

Electron Paramagnetic Resonance Spectroscopy (EPR). The changes in the copper (or silver) oxidation state and/or nuclearity and other expectative paramagnetic species were monitored by electron paramagnetic resonance (EPR) spectroscopy.

Solutions without Catalyst. When oxidizing phthalimide solution in DMF at 0.9 V (ref Pt wire), the EPR spectrum of radical **1** is observed (Figure 3). The resulting spectrum was simulated (Figure 3):

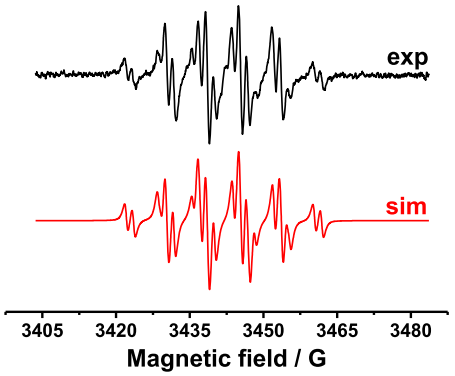


Figure 3. EPR spectrum of phtalimide **1** oxidation in DMF recorded at 293 K with simulations. g = 2.0071, a_N = 8.26 G, a_{H1} = 8.21 G, a_{H2} = 7.04 G, a_{H3} = 6.53 G, a_{H4} = 1.46 G, ΔH = 0.6 G.

The magnetic resonance parameters of the EPR spectrum during oxidation **1** are somewhat similar to the parameters of the anion radical observed during the reduction **1**.[50] In Torzo's study,[50] hyperfine splitting constant (hps) on nitrogen is very close to that proposed by the authors (8.2 G) and the hps constants from 4 protons are also observed. However, the two protons have greater constants, 20 and 31 G, but the oxidation and reduction products **1** cannot coincide.

Surprisingly, despite numerous talks about the imidyl radicals chemistry including the phthalimide radical,[15,51,52] there is no description of the EPR spectrum of the latter and the corresponding magnetic resonance parameters in the literature, that is, the authors recorded it for the first time.

The combined oxidation of phthalimide and phenylpyridine in DMF at a potential of 0.9 V (ref Pt wire) in the EPR cell gives a similar spectrum, but with broadened lines (Figure 4):

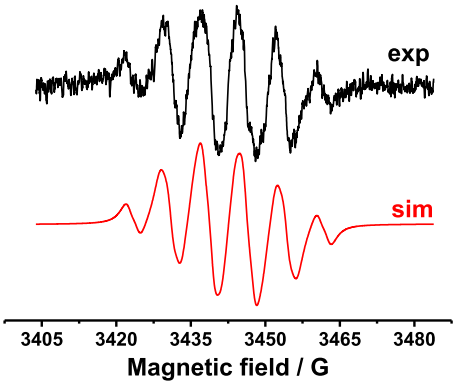


Figure 4. EPR spectrum recorded during joint oxidation of **1** and **2** in DMF solution. ΔH = 1.8 G.

The causes of broadening could be numerous, for example, the existence of several similar radical forms of the molecule. That is, during oxidation of **1** in the presence of 2-phenylpyridine **2** in the absence of a catalyst, the EPR signal does not disappear (at least for a day), which indirectly confirms the absence of a fast reaction between the oxidized form of PhthNH (its radical cation or radical after the loss of a proton) and an arene.

Phthalimide oxidation in an EPR cell in CH_3CN also gives a signal, but its magnetic resonance parameters are somewhat different (see Figure S5). Apparently, there is a signal of a radical product with the solvent.

$Cu(OAc)_2$ Solutions. Initially, the $Cu(OAc)_2$ solution does not deliver EPR spectra, which indicates that the Cu(II) is in a dimeric form in solution. Earlier, it was shown that the EPR signal of the copper(II) acetate dimer $[Cu_2(OAc)_4(H_2O)_2]$ in CH_3CN was undetectable at room temperature[53] (week ERP). Adding to $Cu(OAc)_2$ both **1** and **2**, or a mixture of them does not lead to the appearance of the EPR signal of the monomeric Cu(II), the solutions are EPR silent.

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

During the co-oxidation of $Cu(OAc)_2$ and2-phenylpyridine in CH_3CN at a potential of ~1.8 V (ref Pt wire) in the EPR cell, the EPR spectrum of the metal complex shown in (Figure 5) begins to appear. There are the lines with the different

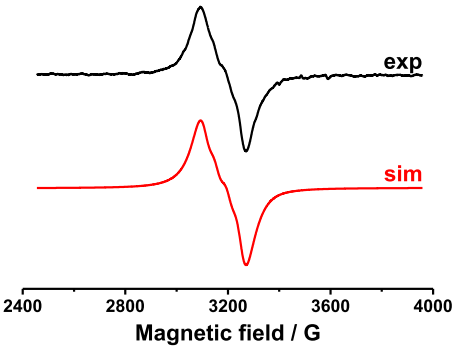


Figure 5. EPR spectrum registered during joint oxidation of $Cu(OAc)_2$ and phenylpyridine **2** in CH_3CN solution

widths in the low-field and high-field parts of the signal, while the width is quite significant and the lines overlap. The lines (4 pcs), in turn, arise due to the splitting on the Cu(II) nucleus with a nuclear spin 3/2. Thus, the formation of mononuclear copper(II) complexes in oxidizing conditions is observed. The spectrum was simulated and the following parameters were obtained: g = 2.17, a_{Cu} = 45 G; ΔH = 49 ÷ 53 G.

The EPR spectrum of the solution obtained as a result of preparative joint electrolysis of $Cu(OAc)_2$ and 2-phenylpyridine **2** in CH_3CN is characterized by the same signal, but of greater intensity. Since the concentration of mononuclear copper(II) complexes is much higher, the lines are even more significantly broadened and the signal degenerates into a single irregular line (Figure 6). Preservation of the signal for a long time (several hours, at least) indicates the stability of the formed mononuclear Cu(II).

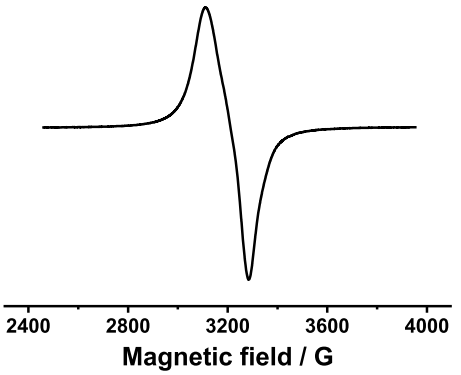
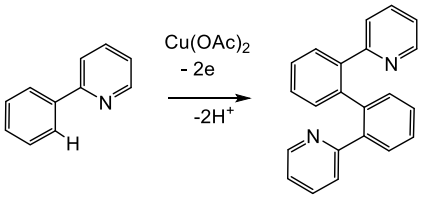


Figure 6. EPR spectrum recorded after joint preparative electrolysis of $Cu(OAc)_2$ and **2**.

Analysis of the products of joint electrolysis of $Cu(OAc)_2$ and **2** in CH_3CN shows the formation of the known dimer 2,2′-bis(pyridin-2-yl)biphenyl according to the following Scheme 4 with the yield of the isolated product about 40%, at a conversion of **2** about 60% after 2 F per mol of **2**.

Co-oxidation of $Cu(OAc)_2$, 1, and 2 (1:1:1) in CH_3CN or DMF. At a potential of up to 1.0 V, no EPR signals appear, including those corresponding to organic radicals. This indirectly indicates that phthalimide **1** does not exist here in

Scheme 4. Cu-Electrocatalyzed Homo-Cross-Dehydrogenative Coupling of 2-Phenylpyridine



free-form, but is coordinated with Cu(II). The results of all three EPR experiments on the oxidation in DMF solution are summarized in one Figure S6.

At high potentials, the EPR signal begins to show some growth in CH_3CN, similar to that shown in Figure 6, corresponding its g-factor to the spectrum of the mononuclear Cu(II) complex. With a further increase in potential (at least up to +2.2 V), the intensity of the signal increases.

Thus, under the conditions of electrolysis, organic radical particles in the presence of $Cu(OAc)_2$ are not detected, catalytic regeneration of Cu(II) is observed at potentials of about 2 V, and monomerization of the Cu(II) complex during oxidation with **2** (or also **1**) is observed. Likewise monomerization of palladium dimeric complexes with 2-phpy, $[Pd(phpy)P(O)(OEt)_2]_2$ during the electrochemical oxidative C−H phosphonation was observed earlier.[45,47]

Considering the fact that the reaction being studied goes best with CH_3CN, whereas phthalimide itself is more difficult to oxidize than other participants in the reaction—both $Cu(OAc)_2$ and 2-phenylpyridine—it should be recognized that the first stage of the catalytic cycle is not radical in nature. The EPR data in DMF also confirm that in the presence of Cu(II), phthalimide **1** itself does not oxidize and its radical cations or radicals are not formed, apparently due to the coordination of **1** in complex with Cu(II).

Since it was not possible to isolate any complexes suitable for X-ray analysis from the mixtures of reaction participants, the authors analyzed the EPR spectra of solid powders isolated from acetonitrile, after mixing the reaction participants, before and after electrochemical oxidation. The results are shown in Figure 7.

As is known, $Cu(OAc)_2$ in solid form is a paramagnetic compound with anomalous magnetic properties,[54] which can

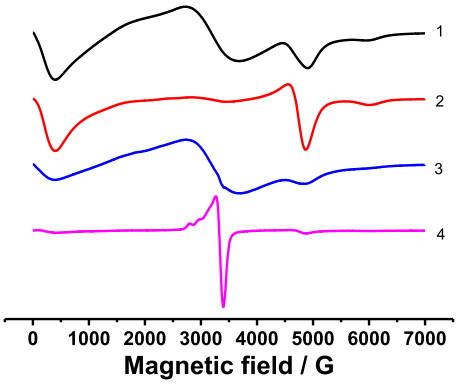
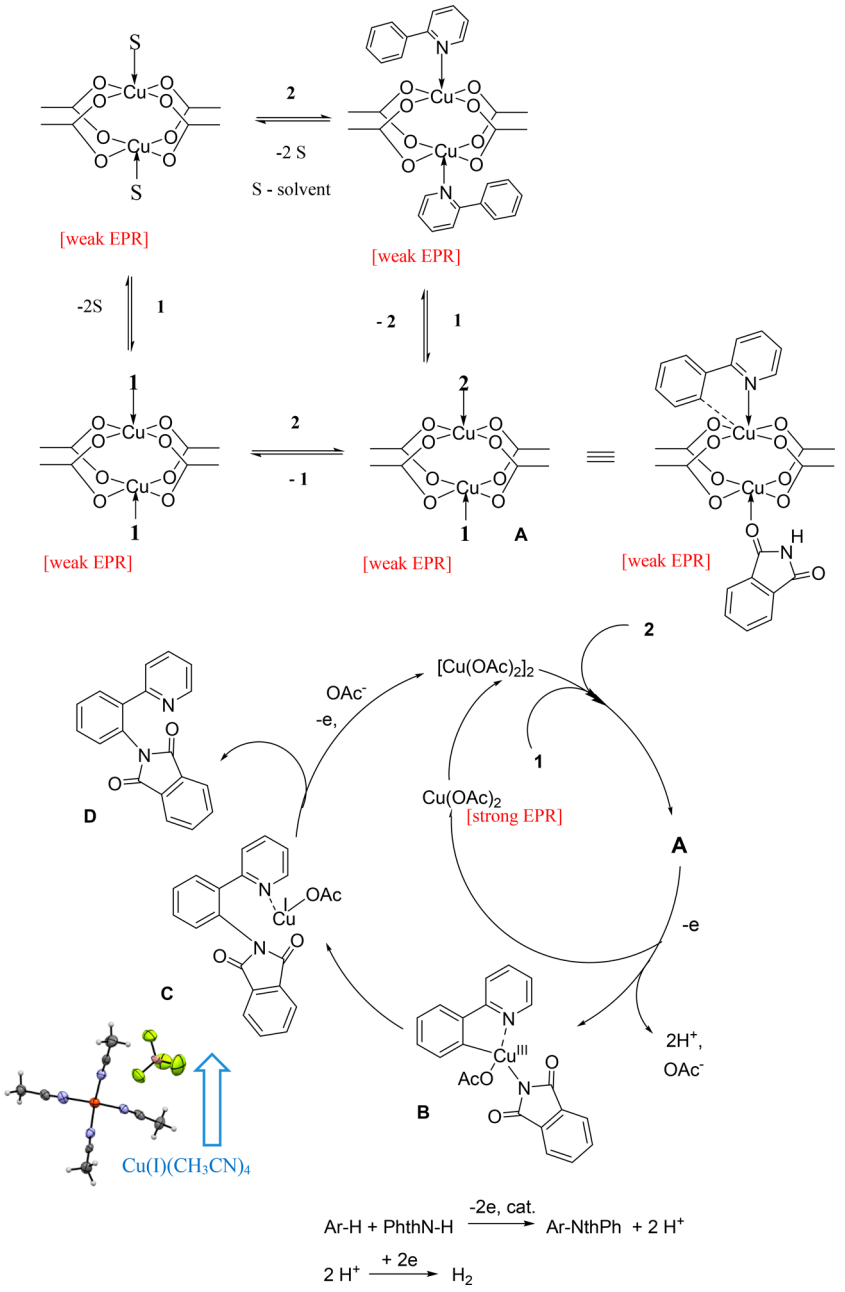


Figure 7. EPR spectra for powders: $Cu(OAc)_2$ pure (1, black), and precipitates in CH_3CN after mixture $Cu(OAc)_2$ with **2** (2, red), with **1** (3, blue) and after joint oxidation of $Cu(OAc)_2$ with **2** (4, pink) in CH_3CN.

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

Scheme 5. Proposed Catalytic Cycle



be explained if one assumes that copper atoms are pairwise coupled by the exchange interaction of an antiferromagnetic character, leading to a singlet ground state with S = 0 and an excited paramagnetic triplet with S = 1. Copper acetate monohydrate is a dual-nucleus compound the molecules of which contain 2 copper ions bound by 4 carboxyl groups of acetate ions and two water molecules. The closest 6 neighbors of each copper ion are 4 oxygen atoms belonging to 4 different carboxyl groups, a copper atom and an oxygen water molecule. The EPR spectrum of $Cu(OAc)_2$ observed by us (Figure 7, 1) coincides with the previously published.[54,55] The spectrum is the sum of copper acetate signals and a wide isotropic line in medium fields with parameters g = 2.17, ΔH_{iso} = 965 G. Apparently, this line belongs to some copper clusters—it has a considerable width, as one can observe the envelope from Cu(II) ions in a cluster, each of which is in its effective magnetic field, and also experiences interaction with the neighboring copper ions.

The precipitate after copper acetate is mixed with **2** in acetonitrile is characterized by an EPR signal (Figure 7, 2) close to the copper acetate signal; that is to say, it is also a dimeric complex of Cu(II). The EPR of the precipitate obtained after mixing copper acetate with phthalimide in acetonitrile (Figure 7, 3) has the parameters of a broad line in the middle fields with g = 2.17, ΔH_{iso} = 960 G, which is close to the values characteristic of copper acetate, although there are certain differences in the waveform, partial separation occurs. However, oxidation of the amine under the action of Cu(II) or disproportionation to Cu(I) and Cu(III), which is sometimes stated in the aforementioned literature, is not observed.[56]

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

The EPR spectrum of the precipitate obtained after mixing $Cu(OAc)_2$ with phthalimide in acetonitrile and their combined oxidation is characterized by a signal characteristic of mononuclear Cu(II) complexes in the low-spin state of 3d.[9] The spectrum was simulated and the parameters of the spin Hamiltonian were obtained, which characterize the slightly distorted axial symmetry of the complex (Figure 7, 4, and Figure S7): g_1 = 2.27, a_{Cu} = 170 G, ΔH_1 = 90 G; g_2 = 2.10, ΔH_2 = 120 G; g_3 = 2.04, ΔH_3 = 70 G; $\langle g \rangle \approx 2.14$. The complex possesses axial symmetry, since g2 and g3 are close, while g1 is very different. Splittings on the Cu(II) nucleus with a nuclear spin of 3/2 are also observed.

The EPR spectrum of the precipitate obtained after mixing $Cu(OAc)_2$ with 2-phenylpyridine **2** in acetonitrile and their combined oxidation is characterized by a signal that is closely related with that described above for the solution (Figure 6). Thus, the electrochemical oxidation of $Cu(OAc)_2$ with each of the participants in the cross-coupling under investigation proceeds with the regeneration of Cu(II) and the formation of monometallic intermediate complexes.

The EPR studies of the joint oxidation of a mixture of AgOAc + **1** and AgOAc + **1** + **2** during oxidation of up to 3 V in CH_3CN showed that no paramagnetic particles are formed under these conditions. This fact may indicate the occurrence of a catalytic process using the $Ag^{I/III}$ mechanism.

Mechanistic Considerations. Thus, the obtained EPR and CV data confirm the binding of 2-phenylpyridine and phthalimide to copper, the oxidation of which leads to catalytic regeneration of Cu(II), while organic radical particles in the presence of copper are not detected under electrolysis conditions, but the monomerization of Cu(II) takes place. It should be noted that the mechanism of the transformation of the reagents (arene, amine, metal-catalyst, oxidant (chemical or electron)) in the catalytic reaction of the CH/NH coupling has not yet been established, but, as a rule, it is postulated that intermediates have not been identified and their reactivity has not been studied, although different assumptions are made for compounds of different nature and catalysts.

So, Yu et al.[57] proposed a single electron transfer (SET) pathway of pyridine-directed Cu-catalyzed ortho- C−H functionalizations (amination or acetoxylation). A SET from the aryl ring to the coordinated Cu(II) leading to the cation-radical intermediate as the rate-limiting step was supposed and the coordination of Cu(II) to the pyridine was necessary for the SET process. The observed *ortho*-selectivity was explained by an intramolecular anion transfer from a nitrogen-bound Cu(I)"ate" complex.

Nicholls[33] proposed that electrooxidative C−H amination proceeds through a Cu^I/Cu^{III} catalytic cycle, where R_2NH cyclic amine reacts only with Cu(III) species yielding Cu(III)-N key intermediate, which after reductive elimination produces Cu(I) complex of aryl amide, etc. Ackermann[30] surmises a catalytic cycle to initiate the electrochemical formation of the catalytically active cobalt(III)carboxylate species or radical-cation of arene (benzamide bearing pyridine-oxide substituent for coordination with cobalt) by anodic oxidation. Thereafter, the steps of carboxylate-assisted C−H activation, subsequent to salt metathesis and reductive elimination from the cobalt(IV) amido species produces C−N target molecules.

Shen et al.[22] in Cu-catalyzed direct amidation of aromatic C−H bonds of *N*-pyrimidyl(pyridyl) indoles and 2-arylpyridines concluded that the radical inhibitors, such as TEMPO, decrease in yield insignificantly, and suggested that a radical pathway for the C−H amination reaction is possibly unlikely, but nevertheless, a single electron transfer (SET) pathway as proposed by Yu et al. cannot be completely excluded. Ribas et al. opined that the Ag(I)/Ag(III) catalytic cycle and the elusive aryl-Ag(III) species as key intermediates in silver(I)-catalyzed C−X, C−C, C−N, and C−O cross couplings using the aminoquinoline directing group.[58]

In accordance with our results of the CV and EPR experiments, a mechanism has been suggested for the formation of tertiary amines, as outlined in Scheme 5. Initially, Cu(II) is coordinated with the nitrogen of the pyridine fragment **2**. The formation of a cyclometalated intermediate with activation of the adjacent $C(sp^2)$−H bond, similar to well-established palladium, nickel, and other cycles[34,41,42,44−47] is unlikely, since the dimeric structures of copper acetate are preserved at this stage, as shown by ESR studies. Changes in the voltammograms of individual compounds $Cu(OAc)_2$ and partners **1** and **2**, as well as in the EPR spectrum of $Cu(OAc)_2$ with additions of **1** and **2**, confirm their interaction and coordination, but, apparently, the complexes are labile. PhthNH **1** also interacts with the metal center, leading to the formation of intermediate **A**, which is subsequently converted to copper amide intermediate **B** during electro-oxidation.

Reductive elimination provides the target cross-coupling product **D** with C−N bond with the regeneration of the copper agent, Cu(I), which after one-electron oxidation gives the active catalyst Cu(II). The total reaction involves the transfer of 2 electrons (Scheme 5, general reaction below). Organic radical intermediates are not detected in this reaction. The formation of intermediate Cu(I) particles is confirmed by X-ray analysis of crystals precipitated from the reaction mixtures, if electrolysis is not fully carried out, but stopped after passing 1 *F* electricity, or by simulating a reaction with an equivalent ratio Cu(II): **1**:**2**. The isolated crystal structures correspond to the previously known $Cu(CH_3CN)_4(BF_4)$[59] (Scheme 5). The tetrafluoroborate anion appears to diffuse from the cathode space, where the electrolyte is $PyHBF_4$.

Thus, the Cu(I)/Cu(II)/Cu(III) mechanism works in this scheme. Anodic oxidation allows avoiding sacrificial stoichiometric oxidants. The proposed electrochemical CH/NH cross-coupling method does not require the pyridine-1-oxide or 8-aminoquinoline coordinating group, which is required for the metal-catalyzed reactions of Ackermann,[25] Lei,[27] and Nicholls[28] for ligand-directed reaction, the traditional excess of additional bases like NaOAc (NaOPiv), or heating, but, most importantly, it allows the use of phthalimide as an aminating agent, which has never previously reacted with the substrates studied under such mild conditions. The process is effective at relatively high current densities, 3.0 mA/cm^2—for comparison, Ackermann[25] states 0.83 mA/cm^2 and Nicholls[28] states 0.44 mA/cm^2—which makes it possible to quickly get the product in an atom-economical way and realize the reaction on a gram scale.

In conclusion, the ability to oxidatively couple phthalimide to various arenes is a useful method for synthesizing tertiary amines that is orthogonal to conventional amination techniques. Phthalimide, as we said earlier, is an ideal starting point for the development of the aforementioned oxidative amination technology. It is commercially available, inexpensive, and easy to handle, and once coupled, it can be readily converted to a primary amine. The proposed protocol for the preparation of *N*-arylphthalimides is for the first time based not

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

only on a copper catalyst but also on silver, which has never been used for this purpose before, and both give comparable results. Silver catalysis for C−H amination has exceptionally inspiring prospects, although it has so far been rarely used for these purposes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.9b00443.

Experimental procedures for all experiments and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yulia@iopc.ru.

ORCID

Robert R. Fayzullin: 0000-0002-3740-9833

Yulia H. Budnikova: 0000-0001-9497-4006

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the Russian Science Foundation, Grant No. 19-13-00016, for financial support of this research.

■ REFERENCES

(1) (a) Ricci, A., Ed.; *Amino Group Chemistry: From Synthesis to the Life Sciences*; Wiley-VCH: Weinheim, 2007. (b) Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J. *Modern Heterocyclic Chemistry*; Wiley-VCH: Weinheim, 2011. (c) Hili, R.; Yudin, A. K. Making Carbon-Nitrogen Bonds in Biological and Chemical Synthesis. *Nat. Chem. Biol.* **2006**, *2*, 284−287. (d) Hartwig, J. F. Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halides. *Acc. Chem. Res.* **2008**, *41*, 1534−1544. (e) Valente, C.; Pompeo, M.; Sayah, M.; Organ, M. G. Carbon-Heteroatom Coupling Using Pd-PEPPSI Complexes. *Org. Process Res. Dev.* **2014**, *18*, 180−190. (f) Surry, D. S.; Buchwald, S. L. Biaryl phosphane ligands in palladium-catalyzed amination. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361.

(2) (a) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116* (19), 12564−12649. (b) Muci, A. R.; Buchwald, S. L. Practical Palladium Catalysts for C-N and C-O Bond Formation. *Top. Curr. Chem.* **2002**, *219*, 131−209. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. Rational Development of Practical Catalysts for Aromatic Carbon-Nitrogen Bond Formation. *Acc. Chem. Res.* **1998**, *31*, 805−818. (d) Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.; Heydari, M.; Malmir, M. Buchwald-Hartwig reaction: An overview. *J. Organomet. Chem.* **2018**, *861*, 17−104. (e) Monnier, F.; Taillefer, M. Catalytic C-C, C-N, and C-O Ullmann-type coupling reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954−6971. (f) Armstrong, A.; Collins, J. C. Direct azole amination: C-H functionalization as a new approach to biologically important heterocycles. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282−2285. (g) Collet, F.; Dodd, R. H.; Dauban, P. Catalytic C-H amination: recent progress and future directions. *Chem. Commun.* **2009**, 5061−5074. (h) Muller, P.; Fruit, C. Enantioselective Catalytic Aziridinations and Asymmetric Nitrene Insertions into CH Bonds. *Chem. Rev.* **2003**, *103*, 2905−2920. (i) Hartwig, J. F. Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halides. *Acc. Chem. Res.* **2008**, *41*, 1534−1544. (j) Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. Pd-Catalyzed C-N Coupling Reactions Facilitated by Organic Bases: Mechanistic Investigation Leads to Enhanced Reactivity in the Arylation of Weakly Binding Amines. *ACS Catal.* **2019**, *9*, 3822−3830. (k) Uehling, M. R.; King, R. P.; Krska, S. W.; Cernak, T.; Buchwald, S. L. Pharmaceutical diversification via palladium oxidative addition complexes. *Science* **2019**, *363*, 405−408.

(3) Recent reviews on C−H activation and amination, see: (a) Wang, H.; Gao, X.; Lv, Z.; Abdelilah, T.; Lei, A. Recent Advances in Oxidative R1 -H/R2 -H Cross-Coupling with Hydrogen Evolution via Photo-/Electrochemistry. *Chem. Rev.* **2019**, *119*, 6769−6787. (b) Kim, H.; Chang, S. Transition-Metal-Mediated Direct C-H Amination of Hydrocarbons with Amine Reactants: The Most Desirable but Challenging C-N Bond-Formation Approach. *ACS Catal.* **2016**, *6*, 2341−2351. (c) Jiao, J.; Murakami, K.; Itami, K. Catalytic Methods for Aromatic C-H Amination: An Ideal Strategy for Nitrogen-Based Functional Molecules. *ACS Catal.* **2016**, *6* (2), 610−633. (d) Kalck, P.; Urrutigoïty, M. Tandem Hydroaminomethylation Reaction to Synthesize Amines from Alkenes. *Chem. Rev.* **2018**, *118*, 3833−3861. (e) Kärkäs, M. D. Electrochemical strategies for C-H functionalization and C-N bond formation. *Chem. Soc. Rev.* **2018**, *47*, 5786−5865. (f) Sauermann, N.; Meyer, T. H.; Qiu, Y. I.; Ackermann, L. Electrocatalytic C-H Activation. *ACS Catal.* **2018**, *8*, 7086−7103. (g) Meyer, T. H.; Finger, L. H.; Gandeepan, P.; Ackermann, L. Resource Economy by Metallaelectrocatalysis: Merging Electrochemistry and C-H Activation. *Trends in Chemistry* **2019**, *1* (1), 63−76. (h) Zhang, L.; Liardet, L.; Luo, J.; Ren, D.; Grätzel, M.; Hu, X. Photoelectrocatalytic arene C-H amination. *Nature Catalysis* **2019**, *2*, 366−373. (i) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C-H Activation. *Chem. Rev.* **2019**, *119* (4), 2192−2452. (j) Pototschnig, G.; Maulide, N.; Schnürch, M. Direct Functionalization of C-H Bonds by Iron, Nickel, and Cobalt Catalysis. *Chem. - Eur. J.* **2017**, *23*, 1−28. (k) Usman, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. Recent Developments in Cobalt Catalyzed Carbon-Carbon and Carbon-Heteroatom Bond Formation via C-H Bond Functionalization. *Synthesis* **2017**, *49*, 1419−1443.

(4) Selected examples of Pd, Rh, Ru-catalyzed C−H amination: (a) Timsina, Y. N.; Gupton, B. F.; Ellis, K. C. Palladium-Catalyzed C−H Amination of C(sp2) and C(sp3)−H Bonds: Mechanism and Scope for N-Based Molecule Synthesis. *ACS Catal.* **2018**, *8* (7), 5732−5776. (b) Yedage, S. L.; Bhanage, B. M. Palladium-Catalyzed Deaminative Phenanthridinone Synthesis from Aniline via C-H Bond Activation. *J. Org. Chem.* **2016**, *81* (10), 4103−4111. (c) Tan, Y.; Hartwig, J. F. Palladium-Catalyzed Amination of Aromatic C-H Bonds with Oxime Esters. *J. Am. Chem. Soc.* **2010**, *132*, 3676−3677. (d) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. Pd-Catalyzed Intermolecular C-H Amination with Alkylamines. *J. Am. Chem. Soc.* **2011**, *133*, 7652−7655. (e) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. Intermolecular Amidation of Unactivated sp2 and sp3 C-H Bonds via Palladium-Catalyzed Cascade C-H Activation/Nitrene Insertion. *J. Am. Chem. Soc.* **2006**, *128*, 9048−9049. (f) Pan, J.; Su, M.; Buchwald, S. L. Palladium(0)-Catalyzed Intermolecular Amination of Unactivated Csp3-H Bonds. *Angew. Chem., Int. Ed.* **2011**, *50*, 8647−8651. (g) Shrestha, R.; Mukherjee, P.; Tan, Y.; Litman, Z. C.; Hartwig, J. F. Sterically Controlled, Palladium-Catalyzed Intermolecular Amination of Arenes. *J. Am. Chem. Soc.* **2013**, *135*, 8480−8483. (h) Mei, T.-S.; Wang, X.; Yu, J.-Q. Pd(II)-Catalyzed Amination of C-H Bonds Using Single-Electron or Two-electron Oxidants. *J. Am. Chem. Soc.* **2009**, *131*, 10806−10807. (i) Park, Y.; Jee, S.; Kim, J. G.; Chang, S. Study of Sustainability and Scalability in the Cp*Rh(III)-Catalyzed Direct C-H Amidation with 1,4,2-Dioxazol-5-ones. *Org. Process Res. Dev.* **2015**, *19* (8), 1024−1029. (j) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. Rhodium(III)-Catalyzed Intermolecular Direct Amination of Aromatic C-H Bonds with N-Chloroamines. *Org. Lett.* **2012**, *14*, 272−275. (k) Wang, S.-B.; Gu, Q.; You, S.-L. Cp*Rh^{III}-Catalyzed C-H Amidation of Ferrocenes. *Organometallics* **2017**, *36* (22), 4359−4362. (l) Hu, X.-H.; Yang, X.-F.; Loh, T.-P. Chelation-Assisted Rhodium-Catalyzed Direct Amidation with Amidobenziodoxolones: C(sp2)-H, C(sp3)-H and Late-Stage Functionalizations. *ACS Catal.* **2016**, *6* (9), 5930−5934. (m) Nguyen, T. H. L.; Gigant, N.; Joseph, D. Advances in Direct Metal-Catalyzed Functionalization of

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

Azobenzenes. *ACS Catal.* **2018**, *8* (2), 1546−1579. (n) Banerjee, S.; De, P. B.; Pradhan, S.; Shah, T. A.; Punniyamurthy, T. Ru^{II}-Catalysed Regioselective C-N Bond Formation of Indolines and Carbazole with Acyl Azides. *Eur. J. Org. Chem.* **2019**, *7*, 1677−1684. (o) Ma, W.; Weng, Z.; Fang, X.; Gu, L.; Song, Y.; Ackermann, L. Ruthenium-Catalyzed C-H Selenylations of Benzamides. *Eur. J. Org. Chem.* **2019**, *1*, 41−45.

(5) Chaitanya, M.; Anbarasan, P. Lewis Acid/Brønsted Acid Controlled Pd(II)-Catalyzed Chemodivergent Functionalization of C(sp2)-H Bonds with N-(Arylthio)i(a)mides. *Org. Lett.* **2018**, *20*, 3362−3366.

(6) Kao, I.-H.; Wang, C.-Y.; Chang, Y.-C.; Wu, C.-L.; Chiu, Y.-J.; Hong, F.-E. Palladium-catalyzed phosphination and amination through C-H bond functionalization on biphenyl: Amido-substituent as directing group. *Tetrahedron* **2019**, *75*, 387−397.

(7) Zhao, R.; Yang, Y.; Wang, X.; Ren, P.; Zhang, Q.; Li, D. An efficient nickel/silver co-catalyzed remote C-H amination of 8-aminoquinolines with azodicarboxylates at room temperature. *RSC Adv.* **2018**, *8*, 37064.

(8) Tran, L. D.; Roane, J.; Daugulis, O. Directed Amination of Non-Acidic Arene C-H Bonds by a Copper-Silver Catalytic System. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043−6046.

(9) (a) Corbin, J. R.; Schomaker, J. M. Tunable differentiation of tertiary C-H bonds in intramolecular transition metal-catalyzed nitrene transfer reactions. *Chem. Commun.* **2017**, *53*, 4346−4349. (b) Dolan, N. S.; Scamp, R. J.; Yang, T.; Berry, J. F.; Schomaker, J. M. Catalyst-Controlled and Tunable, Chemoselective Silver-Catalyzed Intermolecular Nitrene Transfer: Experimental and Computational Studies. *J. Am. Chem. Soc.* **2016**, *138*, 14658−14667. (c) Chen, Z.; Ren, N.; Ma, X.; Nie, J.; Zhang, F.-G.; Ma, J.-A. Silver-Catalyzed [3 + 3] Dipolar Cycloaddition of Trifluorodiazoethane and Glycine Imines: Access to Highly Functionalized Trifluoromethyl-Substituted Triazines and Pyridines. *ACS Catal.* **2019**, *9* (5), 4600−4608. (d) Alderson, J. M.; Corbin, J. R.; Schomaker, J. M. Tunable, Chemo- and Site-Selective Nitrene Transfer Reactions through the Rational Design of Silver(I) Catalysts. *Acc. Chem. Res.* **2017**, *50*, 2147−2158. (e) Huang, M.; Yang, T.; Paretsky, J. D.; Berry, J. F.; Schomaker, J. M. Inverting Steric Effects: Using "Attractive" Noncovalent Interactions To Direct Silver-Catalyzed Nitrene Transfer. *J. Am. Chem. Soc.* **2017**, *139*, 17376−17386. (f) Alderson, J. M.; Corbin, J. R.; Schomaker, J. M. Investigation of transition metal-catalyzed nitrene transfer reactions in water. *Bioorg. Med. Chem.* **2018**, *26*, 5270−5273.

(10) Zhu, H.; Sun, S.; Qiao, H.; Yang, F.; Kang, J.; Wu, Y.; Wu, Y. Silver(I)-Catalyzed C4-H Amination of 1-Naphthylamine Derivatives with Azodicarboxylates. *Org. Lett.* **2018**, *20* (3), 620−623. (b) Cho, S. H.; Kim, J.; Lee, S. Y.; Chang, S. Silver-Mediated Direct Amination of Benzoxazoles: Tuning the Amino Group Source from Formamides to Parent Amines. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127−9130. (c) Kim, J.; Cho, S. H.; Joseph, J.; Chang, S. Cobalt- and Manganese-Catalyzed Direct Amination of Azoles under Mild Reaction Conditions and the Mechanistic Details. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899−9903.

(11) Osby, J. O.; Martin, M. G.; Ganem, B. An Exceptionally Mild Deprotection of Phthalimides. *Tetrahedron Lett.* **1984**, *25*, 2093−2096. (b) Khan, M. N. Kinetic Evidence for the Occurrence of a Stepwise Mechanism in the Hydrazinolysis of Phthalimide. *J. Org. Chem.* **1995**, *60*, 4536−4541.

(12) Casal, J. J.; Bollini, M.; Lombardo, M. E.; Bruno, A. M. Thalidomide analogues: Tumor necrosis factor-alpha inhibitors and their evaluation as anti-inflammatory agents. *Eur. J. Pharm. Sci.* **2016**, *83*, 114−119.

(13) Capitosti, S. M.; Hansen, T. P.; Brown, M. L. Thalidomide analogues demonstrate dual inhibition of both angiogenesis and prostate cancer. *Bioorg. Med. Chem.* **2004**, *12*, 327−336.

(14) Bhat, M. A.; Al-Omar, M. A.; Ansari, M. A.; Zoheir, K. M. A.; Imam, F.; Attia, S. M.; Bakheet, S. A.; Nadeem, A.; Korashy, H. M.; Voronkov, A.; Berishvili, V.; Ahmad, S. F. Design and Synthesis of N-Arylphthalimides as Inhibitors of Glucocorticoid-Induced TNF Receptor-Related Protein, Proinflammatory Mediators, and Cytokines in Carrageenan-Induced Lung Inflammation. *J. Med. Chem.* **2015**, *58*, 8850−8867.

(15) Yoon, U. C.; Mariano, P. S. The Synthetic Potential of Phthalimide SET Photochemistry. *Acc. Chem. Res.* **2001**, *34*, 523−533.

(16) Zhang, C.; Niu, Z.; Ding, Y.; Zhang, L.; Zhou, Y.; Guo, X.; Zhang, X.; Zhao, Y.; Yu, G. Highly Concentrated Phthalimide-Based Anolytes for Organic Redox Flow Batteries with Enhanced Reversibility. *Chem.* **2018**, *4* (12), 2814−2825.

(17) Shrestha, R.; Mukherjee, P.; Tan, Y.; Litman, Z. C.; Hartwig, J. F. Sterically Controlled, Palladium-Catalyzed Intermolecular Amination of Arenes. *J. Am. Chem. Soc.* **2013**, *135*, 8480−8483.

(18) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. Intermolecular Oxidative C-N Bond Formation under Metal-Free Conditions: Control of Chemoselectivity between Aryl sp2 and Benzylic sp3 C-H Bond Imidation. *J. Am. Chem. Soc.* **2011**, *133* (41), 16382−16385.

(19) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. Tandem C-H and N-H Bond Functionalization. *J. Am. Chem. Soc.* **2011**, *133* (49), 19960−19965.

(20) Marchetti, L.; Kantak, A.; Davis, R.; DeBoef, B. Regioselective Gold-Catalyzed Oxidative C-N Bond Formation. *Org. Lett.* **2015**, *17*, 358−361.

(21) Yu, S.; Wan, B.; Li, X. Rhodium(III)-Catalyzed C-H Activation and Amidation of Arenes Using N-Arenesulfonated Imides as Amidating Reagents. *Org. Lett.* **2013**, *15*, 3706−3709.

(22) Xu, H.; Qiao, X.; Yang, S.; Shen, Z. Cu-Catalyzed Direct Amidation of Aromatic C-H Bonds: An Access to Arylamines. *J. Org. Chem.* **2014**, *79* (10), 4414−4422.

(23) Allen, L. J.; Cabrera, P. J.; Lee, M.; Sanford, M. S. N-Acyloxyphthalimides as Nitrogen Radical Precursors in the Visible Light Photocatalyzed Room Temperature C-H Amination of Arenes and Heteroarenes. *J. Am. Chem. Soc.* **2014**, *136* (15), 5607−5610.

(24) Patil, M. R.; Dedhia, N. P.; Kapdi, A. R.; Kumar, A. V. Cobalt(II)/N-Hydroxyphthalimide-Catalyzed Cross-Dehydrogenative Coupling Reaction at Room Temperature under Aerobic Condition. *J. Org. Chem.* **2018**, *83*, 4477−4490.

(25) Yadav, M. R.; Shankar, M.; Ramesh, E.; Ghosh, K.; Sahoo, A. K. Ruthenium-Catalyzed ortho-C-H Mono- and Di-Imidation of Arenes with N-Tosyloxyphthalimide. *Org. Lett.* **2015**, *17*, 1886−1889.

(26) Yu, S.; Wan, B.; Li, X. Rhodium(III)-Catalyzed C-H Activation and Amidation of Arenes Using N-Arenesulfonated Imides as Amidating Reagents. *Org. Lett.* **2013**, *15*, 3706−3709.

(27) Kim, H.; Kim, T.; Lee, D. G.; Roh, S. W.; Lee, C. Nitrogen-Centered Radical-Mediated C-H Imidation of Arenes and Heteroarenes via Visible Light Induced Photocatalysis. *Chem. Commun.* **2014**, *50*, 9273−9276.

(28) Wu, J.; Zhou, Y.; Zhou, Y.; Chiang, Ch.-W.; Lei, A. Electrooxidative C(sp3)-H Amination of Azoles via Intermolecular Oxidative C(sp3)-H/N-H Cross-Coupling. *ACS Catal.* **2017**, *7* (12), 8320−8323.

(29) Gao, W.-J.; Li, W.-C.; Zeng, C.-C.; Tian, H.-Y.; Hu, L.-M.; Little, R. D. Electrochemically Initiated Oxidative Amination of Benzoxazoles Using Tetraalkylammonium Halides As Redox Catalysts. *J. Org. Chem.* **2014**, *79*, 9613−9618.

(30) Sauermann, N.; Mei, R.; Ackermann, L. Electrochemical C-H Amination by Cobalt Catalysis in a Renewable Solvent. *Angew. Chem., Int. Ed.* **2018**, *57*, 5090−5094.

(31) Qiu, Y.; Struwe, J.; Meyer, T. H.; Oliveira, J. C. A.; Ackermann. Catalyst- and Reagent-Free Electrochemical Azole C-H Amination. L. *Chem. - Eur. J.* **2018**, *24*, 12784−12789.

(32) Gao, X.; Wang, P.; Zeng, L.; Tang, S.; Lei, A. Cobalt(II)-Catalyzed Electrooxidative C-H Amination of Arenes with Alkylamines. *J. Am. Chem. Soc.* **2018**, *140*, 4195−4199.

(33) Kathiravan, S.; Suriyanarayanan, S.; Nicholls, I. A. Electrooxidative Amination of sp2 C-H Bonds: Coupling of Amines with Aryl Amides via Copper Catalysis. *Org. Lett.* **2019**, *21* (7), 1968−1972.

(34) Dudkina, Y. B.; Fayzullin, R. R.; Lyssenko, K. A.; Gubaidullin, A. T.; Kholin, K. V.; Levitskaya, A. I.; Balakina, M. Yu.; Budnikova, Y. H. Cyclometalated Nickel Complexes as Key Intermediates in

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX

C(sp2)-H Bond Functionalization: Synthesis, Catalysis, Electrochemical Properties, and DFT Calculations. *Organometallics* **2019**, *38* (6), 1254−1263.
(35) Budnikova, Y. H.; Gryaznova, T. V.; Grinenko, V. V.; Dudkina, Y. B.; Khrizanforov, M. N. Eco-efficient Electrocatalytic C-P bond Formation. *Pure Appl. Chem.* **2017**, *89* (3), 311−330.
(36) Budnikova, Y. H.; Dudkina, Y. B. Progress of electrochemical C(sp2)-H phosphonation. *Phosphorus, Sulfur Silicon Relat. Elem.* **2019**, *194* (4−6), 415−441.
(37) Khrizanforov, M. N.; Strekalova, S. O.; Kholin, K. V.; Khrizanforova, V. V.; Kadirov, M. K.; Gryaznova, T. V.; Budnikova, Y. H. Novel approach to metal-induced oxidative phosphorylation of aromatic compounds. *Catal. Today* **2017**, *279*, 133−141.
(38) Khrizanforov, M.; Strekalova, S.; Khrizanforova, V.; Dobrynin, A.; Kholin, K.; Gryaznova, T.; Grinenko, V.; Gubaidullin, A.; Kadirov, M. K.; Budnikova, Y. Cobalt-Catalyzed Green Cross-Dehydrogenative C(sp2)-H/PH Coupling Reactions. *Top. Catal.* **2018**, *61*, 1949−1956.
(39) Khrizanforova, V. V.; Kholin, K. V.; Khrizanforov, M. N.; Kadirov, M. K.; Budnikova, Yu. H. Electrooxidative CH/PH functionalization as a novel way to benzo[*b*]phosphole oxides mediated by catalytic amounts of silver acetate. *New J. Chem.* **2018**, *42*, 930−935.
(40) Budnikova, Y. H. Opportunities and challenges for combining electro- and organometallic catalysis in C(sp2)-H phosphonation. *Pure Appl. Chem.* **2019**, *91*, 17−31.
(41) Dudkina, Yu. B.; Gryaznova, T. V.; Sinyashin, O. G.; Budnikova, Yu. H. Ligand-directed electrochemical functionalization of C(sp2)—H bonds in the presence of the palladium and nickel compounds. *Russ. Chem. Bull.* **2015**, *64* (8), 1713−1725.
(42) Dudkina, Y. B.; Mikhaylov, D. Y.; Gryaznova, T. V.; Sinyashin, O. G.; Vicic, D. A.; Budnikova, Y. H. M^{II}/M^{III}-Catalyzed *ortho*-Fluoroalkylation of 2-Phenylpyridine. *Eur. J. Org. Chem.* **2012**, *2012*, 2114−2117.
(43) Mikhaylov, D. Yu.; Budnikova, Yu. H. Fluoroalkylation of organic compounds. *Russ. Chem. Rev.* **2013**, *82* (9), 835−864.
(44) Dudkina, Y. B.; Mikhaylov, D. Y.; Gryaznova, T. V.; Tufatullin, A. I.; Kataeva, O. N.; Vicic, D. A.; Budnikova, Y. H. Electrochemical Ortho Functionalization of 2-Phenylpyridine with Perfluorocarboxylic Acids Catalyzed by Palladium in Higher Oxidation States. *Organometallics* **2013**, *32*, 4785−4792.
(45) Grayaznova, T. V.; Dudkina, Y. B.; Islamov, D.R.; Kataeva, O.N.; Sinyashin, O.G.; Vicic, D. A.; Budnikova, Y. H. Pyridine-directed palladium-catalyzed electrochemical phosphonation of C-(sp2)-H bond. *J. Organomet. Chem.* **2015**, *785*, 68−71.
(46) Dudkina, Y. B.; Kholin, K. V.; Gryaznova, T. V.; Islamov, D. R.; Kataeva, O. N.; Rizvanov, I. Kh.; Levitskaya, A. I.; Fominykh, O. D.; Balakina, M. Yu.; Sinyashin, O. G.; Budnikova, Y. H. Redox Trends in Cyclometalated Palladium(II) Complexes. *Dalton Trans.* **2017**, *46*, 165−177.
(47) Gryaznova, T.; Dudkina, Y.; Khrizanforov, M.; Sinyashin, O.; Kataeva, O.; Budnikova, Y. Electrochemical properties of diphosphonate-bridged palladacycles and their reactivity in arene phosphonation. *J. Solid State Electrochem.* **2015**, *19*, 2665−2672.
(48) Yurko, E. O.; Gryaznova, T. V.; Kholin, K. V.; Khrizanforova, V. V.; Budnikova, Y. H. External Oxidant-Free Cross-Coupling: Electrochemically Induced Aromatic C-H Phos-phonation of Azoles with Dialkyl-H-Phosphonates Under Silver Catalysis. *Dalton Trans.* **2018**, *47*, 190−196.
(49) Khrizanforov, M. N.; Arkhipova, D. M.; Shekurov, R. P.; Gerasimova, T. P.; Ermolaev, V. V.; Islamov, D. R.; Miluykov, V. A.; Kataeva, O. N.; Khrizanforova, V. V.; Sinyashin, O. G.; Budnikova, Y. H. Novel paste electrodes based on phosphonium salt room temperature ionic liquids for studying the redox properties of insoluble compounds. *J. Solid State Electrochem.* **2015**, *19*, 2883−2890.
(50) Farnia, G.; Romanin, A.; Capobianco, G.; Torzo, F. Electrochemical reduction mechanism of phthalimide and some of its N-derivatives in DMF. *J. Electroanalyt. Chem. J. Electroanal. Chem. Interfacial Electrochem.* **1971**, *33* (1), 31−44.
(51) Cho, D. W.; Mariano, P. S.; Yoon, U. C. Direct and indirect single electron transfer (SET)-photochemical approaches for the preparation of novel phthalimide and naphthalimide-based lariat-type crown ethers. *Beilstein J. Org. Chem.* **2014**, *10*, 514−527.
(52) Syroeshkin, M. A.; Krylov, I. B.; Hughes, A. M.; Alabugin, I. V.; Nasybullina, D. V.; Sharipov, M. Yu.; Gultyai, V. P.; Terent'ev, A. O. Electrochemical behavior of N-oxyphthalimides: Cascades initiating self-sustaining catalytic reductive N-O bond cleavage. *J. Phys. Org. Chem.* **2017**, *30*, No. e3744.
(53) Sreenath, K.; Yuan, Z.; Macias-Contreras, M.; Ramachandran, V.; Clark, R. J.; Zhu, L. Dual Role of Acetate in Copper(II) Acetate Catalyzed Dehydrogenation of Chelating Aromatic Secondary Amines: A Kinetic Case Study of Copper-Catalyzed Oxidation Reactions. *Eur. J. Inorg. Chem.* **2016**, *2016*, 3728−3743.
(54) Bleaney, B.; Bowers, K. D. Anomalous paramagnetism of copper acetate. *Proc. R. Soc. London, Ser. A* **1952**, *214* (1119), 451−465.
(55) Chavan, S.; Srinivas, D.; Ratnasamy, P. The structural basis for the enhanced oxygenase activity of copper acetate dimers encapsulated in zeolites. *Top. Catal.* **2000**, *11* (1−4), 359−367.
(56) Kim, H.; Heo, J.; Kim, J.; Baik, M.-H.; Chang, S. Copper-Mediated Amination of Aryl C-H Bonds with the Direct Use of Aqueous Ammonia via a Disproportionation Pathway. *J. Am. Chem. Soc.* **2018**, *140* (43), 14350−14356.
(57) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. Cu(II)-Catalyzed Functionalizations of Aryl C-H Bonds Using O_2 as an Oxidant. *J. Am. Chem. Soc.* **2006**, *128* (21), 6790−6791.
(58) Capdevila, L.; Andris, E.; Bris, A.; Tarres, M.; Roldán-Gómez, S.; Roithová, J.; Ribas, X. Silver(I)-catalyzed C-X, C-C, C-N and C-O cross couplings using aminoquinoline directing group via elusive aryl-Ag(III) species. *ACS Catal.* **2018**, *8* (11), 10430−10436.
(59) Jones, P. G.; Crespo, O. Tetrakis(acetonitrile-N)copper(I) Tetrafluoroborate. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1998**, *C54*, 18−20.

DOI: 10.1021/acs.organomet.9b00443
Organometallics XXXX, XXX, XXX−XXX