

# Microwave-Assisted, Copper-Catalyzed Domino O–H/C–H Arylation Reaction toward the Synthesis of Oxygen-Doped Polyaromatic Molecules

Entzy Kaplanai, Efstathios Tonis, Maria Drymona, Yulian Zagranyski, Demeter Tzeli, and Georgios C. Vougioukalakis\*



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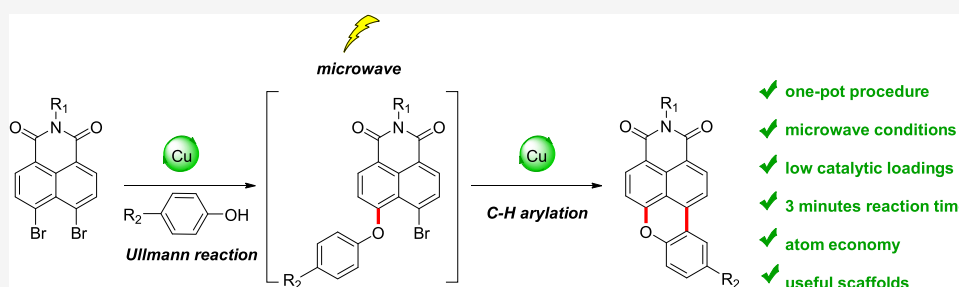
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**ABSTRACT:** Benzoxanthenes and their analogues are a very important class of compounds mainly due to their wide range of biological and technological applications. The development of a new methodology for their synthesis, involving an Ullmann-type coupling followed by an intramolecular C–H arylation, catalyzed by copper in a domino fashion, is reported. A variety of *para*-substituted phenols are amenable to this methodology, affording the desired products in moderate to good yields. Our protocol is expedient and practical and is carried out under microwave irradiation in only 3 min under air. A plausible catalytic cycle is proposed based on experimental mechanistic investigations and density functional theory (DFT) calculations.

## INTRODUCTION

The Ullmann reaction enables the synthesis of biaryl compounds through the cross-coupling of aryl halides.<sup>1–3</sup> This transformation is traditionally catalyzed by copper-based catalysis, involving an earth-abundant, low-cost, and biocompatible metal. The great impact of the Ullmann reaction in industry toward the preparation of pharmaceuticals,<sup>4</sup> agrochemicals,<sup>5</sup> and polymers<sup>6</sup> has led to an expanded version of the classic methodology, in which the reaction between an aryl halide and an amine, a phenol, or a thiophenol provides the corresponding aryl-amine, -ether, or -thioether, respectively.<sup>7–9</sup> Thus, the Ullmann-type reactions, as they are widely called, are a very powerful tool for the formation of various heterocycles.<sup>10</sup>

The direct arylation of arenes with aryl halides has also attracted a lot of attention because, in many cases, it provides, among others, step economy and can be used as a useful tool for the synthesis of novel building blocks.<sup>11,12</sup> This usually involves a C–H bond activation, promoted by high-cost noble metals, such as Pd,<sup>13</sup> Rh,<sup>14</sup> Ru,<sup>15</sup> and Ir.<sup>16</sup> However, especially during the last decade, catalysts based on first-row transition metals, such as Ni,<sup>17</sup> Fe,<sup>18</sup> and Co,<sup>19</sup> have been proven suitable for these transformations. Cu has also been employed in C–H activation protocols.<sup>20–23</sup> Cu salts are used without or in combination with various types of ligands for the direct

arylation of activated or nonactivated benzenes.<sup>24</sup> However, the use of high catalyst loadings, extremely high temperatures (<200 °C), and long reaction times comprise significant drawbacks.

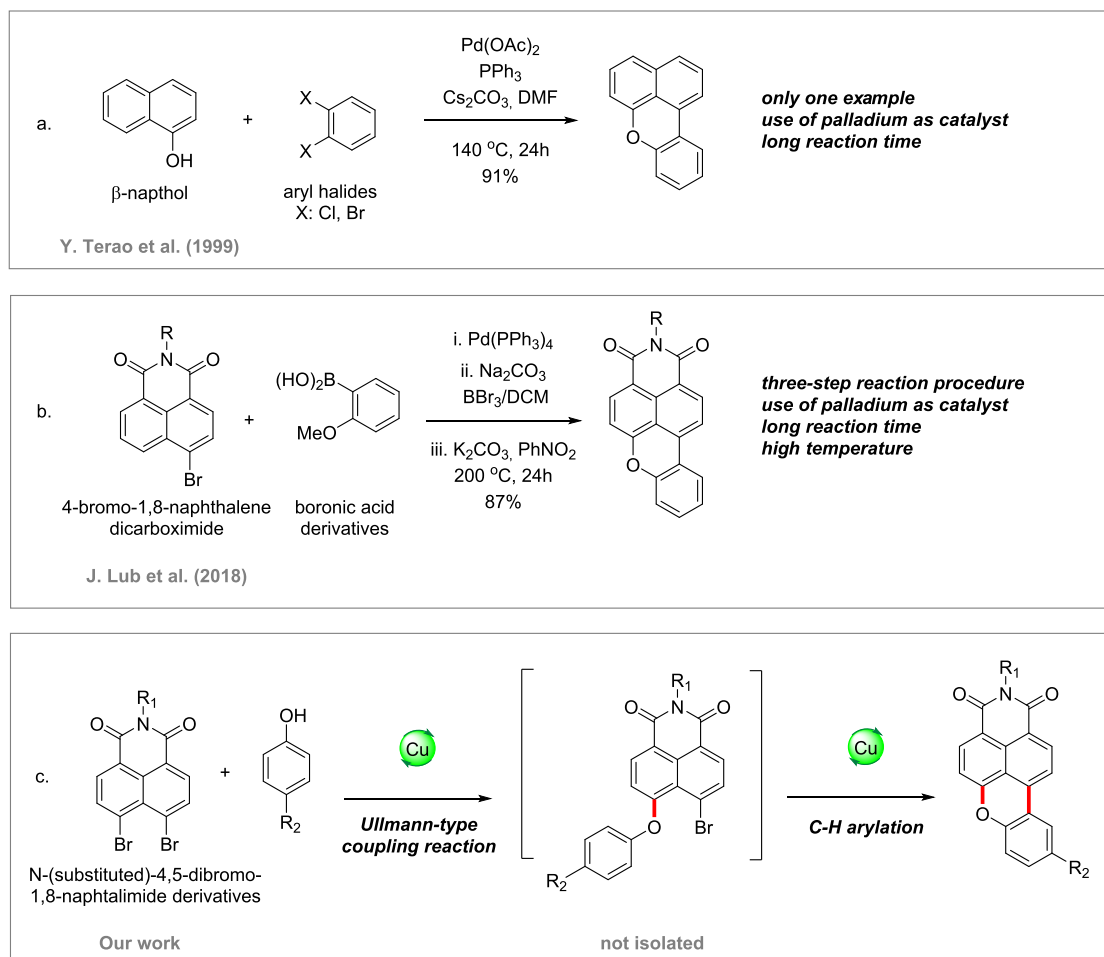
On a different note, benzoxanthenes are a class of oxygen-containing heterocyclic compounds rarely found in nature.<sup>25–27</sup> Multiple biological properties of benzoxanthenes as antiviral,<sup>28,29</sup> anticancer,<sup>30–32</sup> and anti-inflammatory<sup>33,34</sup> agents are well documented. In addition, their derivatives, which are strongly fluorescent, find uses in laser technologies, solar cells, or are used as dyes for the visualization of biomolecules.<sup>26,35–38</sup> A well-known synthetic methodology toward benzoxanthenes is the one-pot multicomponent reaction between naphthol and aryl halides in the presence of palladium (Scheme 1a).<sup>39</sup> However, the poor reaction scope (only one example has been mentioned) along with the necessity of the expensive and nonabundant palladium limits

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Scheme 1. Known Approaches toward Benzoxanthene Derivatives and Our Strategy



the use of this protocol. Another way to approach the synthesis of this kind of compound is by a three-step reaction procedure, involving a Suzuki–Miyaura cross-coupling reaction of 4-bromo-1,8-naphthalenedicarboximide analogues with 2-methoxyphenylboronic acid, followed by the removal of the protecting group, and finally, an intramolecular oxidative cyclization (Scheme 1b).<sup>36</sup> Along with these lines, a swift, straightforward, practical access to benzoxanthene compounds is highly desired and can find many applications.

Herein, we report the development of a new synthetic strategy toward benzoxanthenes, involving an Ullmann-type coupling between phenols and *N*-(substituted-4,5-dibromo-1,8-naphthalimide) derivatives, followed by an intramolecular C–H arylation step, catalyzed by copper in a domino fashion (Scheme 1c). An analogous approach has previously found success in a domino *N*–H/C–H activation process, involving aromatic amines under dual palladium catalysis.<sup>40</sup> To the best of our knowledge, this is the first copper-catalyzed domino O–H/C–H arylation process for the synthesis of the benzoxanthene core.

## RESULTS AND DISCUSSION

We initiated our investigation employing the model reaction of *N*-propyl-4,5-dibromo-1,8-naphthalimide (**1a**) and 1*H*-phenol to optimize the critical reaction parameters (Table 1). Based on analogous works, we began by using CuI (20%), 2,2'-dipyridine-4,4'-dicarboxylic acid (**L1**, 20%), and K<sub>2</sub>CO<sub>3</sub> (3

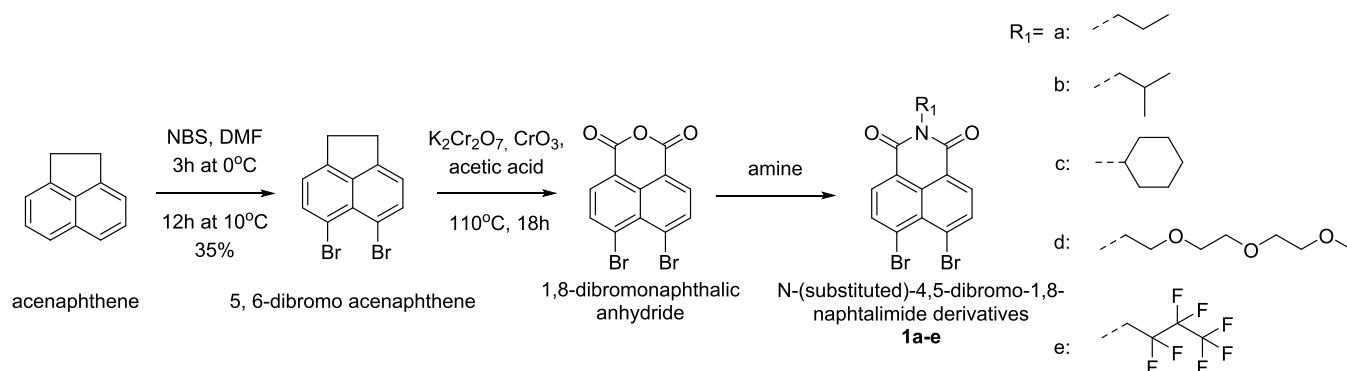
equiv) in DMSO at 160 °C, in an oil bath, for 24 h, under conventional heating (entry 1). Under these reaction conditions, the desired cyclized product **3a** was not obtained. Instead, we observed the formation of side products **4a** and **5b** (isolated and characterized). These are probably generated via the dehalogenation of the monosubstituted product **2a** and a second Ullmann coupling of product **2a** with phenol, respectively. Furthermore, we also observed the formation of the hydroxylated side product **6a**. When the reaction was carried out under microwave irradiation at 190 °C for 30 min, we obtained the desired **3a** in 20% yield (entry 2). Several copper sources (in different oxidation states) were then screened, such as CuCl, Cu(CH<sub>3</sub>COO), CuO, and CuCl<sub>2</sub>, but they either did not improve the reaction yield or did not lead to any product formation at all (entries 3–6). Additionally, we screened a lot of monodentate ligands, such as phosphines (PPh<sub>3</sub>, PCy<sub>3</sub>), *N*-heterocyclic carbenes (IMes, IPr), as well as several bidentate nitrogen-containing ligands, such as oxalamides, phenanthrolines, and dipyridines. The most successful results were obtained upon using dipyridines. Besides 2,2'-dipyridine-4,4'-dicarboxylic acid (**L1**), 4,4'-dibromo-2,2'-dipyridine (**L3**), 4,4-dimethyl-2,2'-dipyridine (**L4**), and 4,4'-di-*tert*-butyl-2,2'-dipyridine (**L2**) were also utilized, with the latter providing the best results, leading to **3a** in 31% yield (entries 7–9). Among the aprotic polar solvents utilized, including DMSO, DMF, and NMP, and the aromatic solvent *cymene*, DMA, was the most suitable, affording **3a** in 64% yield (entries

Table 1. Optimization of the Reaction Conditions

entry <sup>a</sup>	catalyst	ligand	base	solvent	T (°C)	time	yield <sup>c</sup> (%)
1	CuI (20%)	L1 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMSO	160/conv. heating <sup>b</sup>	24 h	N.P.
2	CuI (20%)	L1 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMSO	190/MW	30 min	20%
3	CuCl (20%)	L1 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMSO	190/MW	30 min	19%
4	Cu(CH <sub>3</sub> COO) (20%)	L1 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMSO	190/MW	30 min	N.P.
5	CuO (20%)	L1 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMSO	190/MW	30 min	N.P.
6	CuCl <sub>2</sub> (20%)	L1 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMSO	190/MW	30 min	N.P.
7	CuI (20%)	L2 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMSO	190/MW	30 min	31%
8	CuI (20%)	L3 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMSO	190/MW	30 min	24%
9	CuI (20%)	L4 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMSO	190/MW	30 min	22%
10	CuI (20%)	L2 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMF	190/MW	30 min	22%
11	CuI (20%)	L2 (20%)	K <sub>2</sub> CO <sub>3</sub>	NMP	190/MW	30 min	traces
12	CuI (20%)	L2 (20%)	K <sub>2</sub> CO <sub>3</sub>	cymene	190/MW	30 min	N.P.
13	CuI (20%)	L2 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMA	190/MW	30 min	64%
14	CuI (20%)	L2 (20%)	-	DMA	190/MW	30 min	N.R.
15	CuI (20%)	L2 (20%)	NaOH	DMA	190/MW	30 min	N.P.
16	CuI (20%)	L2 (20%)	NafBuO	DMA	190/MW	30 min	N.P.
17	CuI (20%)	L2 (20%)	K <sub>2</sub> CO <sub>3</sub>	DMA	170/MW	3 min	64%
18	CuI (30%)	L2 (30%)	K <sub>2</sub> CO <sub>3</sub>	DMA	170/MW	3 min	10%

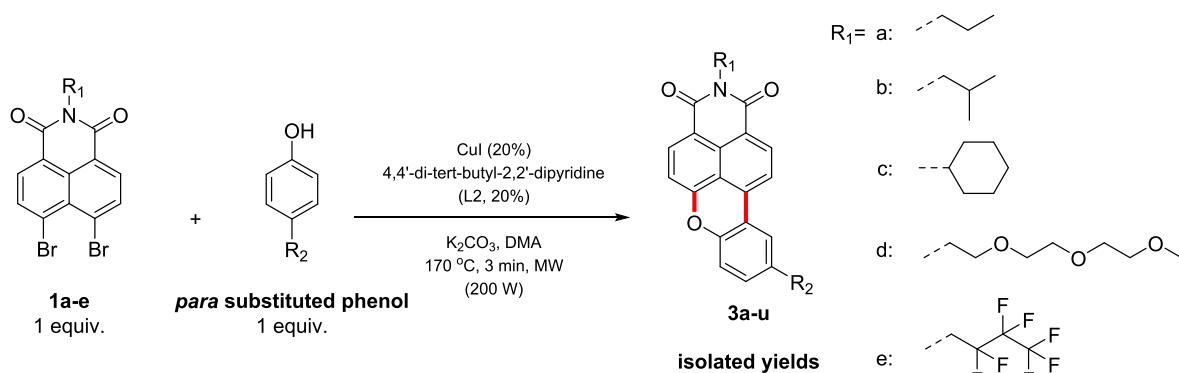
<sup>a</sup>Reaction conditions: 1a (0,126 mmol, 1 equiv), 1H-phenol (0,126 mol, 1 equiv), [Cu] source (% mol), ligand (% mol), base (3 equiv), solvent (0, 5 mL), under air, MW (200 Watt). <sup>b</sup>Heating source: oil bath. <sup>c</sup>Yield: isolated yield.

## Scheme 2. Synthetic Pathway for Substrates 1a–e

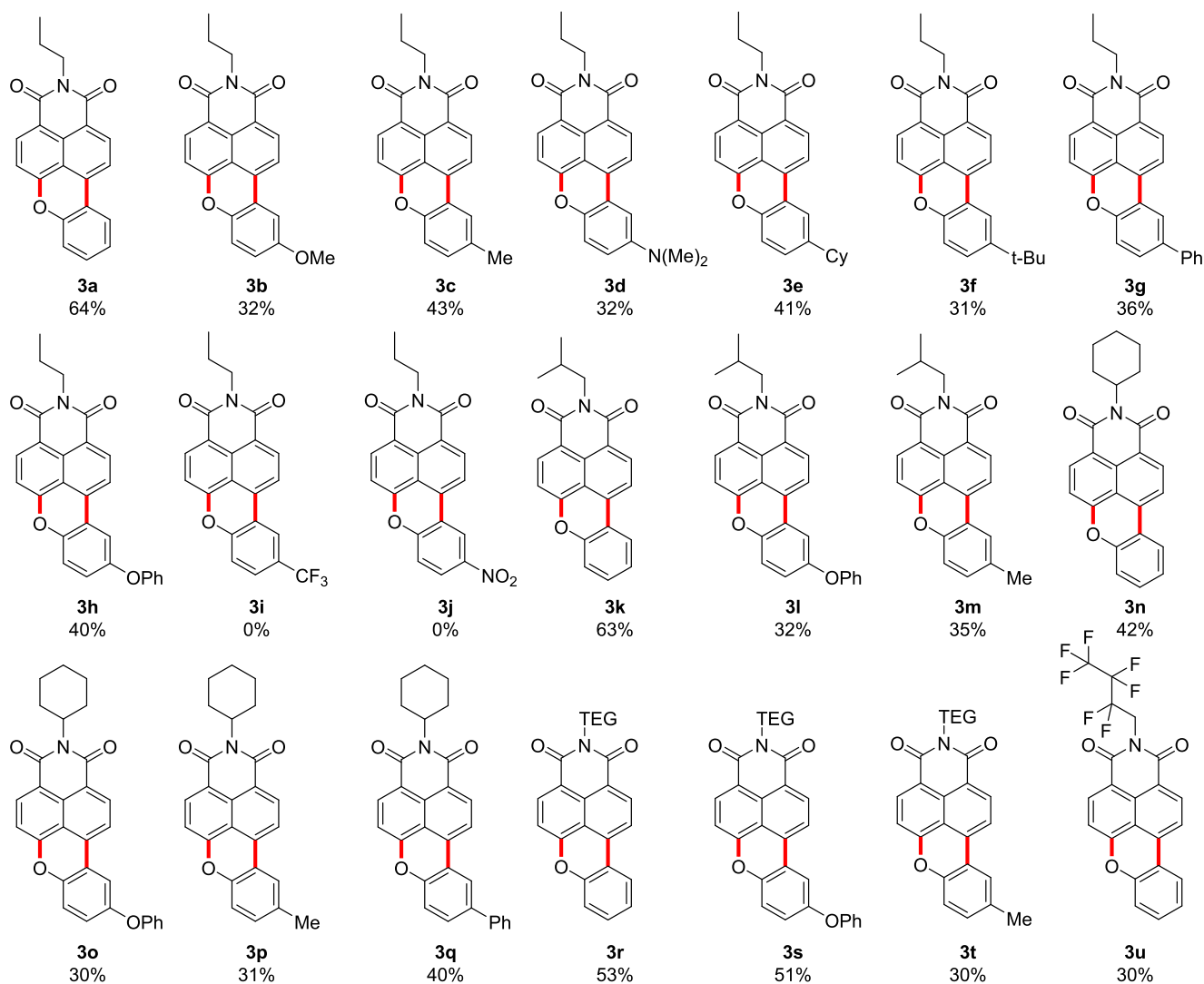


10–13). As anticipated, the base has a crucial role in the reaction. No product formation was detected in the absence of a base (entry 14), while K<sub>2</sub>CO<sub>3</sub> was the optimal choice. When K<sub>2</sub>CO<sub>3</sub> was replaced, under these conditions, by NaOH or NafBuO (entries 15 and 16), no desired product was formed. Upon carrying out some time-dependent experiments, we found that only 3 min under microwave irradiation at 170 °C is enough (entry 17). We also increased the amounts of catalyst

and ligand, but this was deleterious for the reaction (entry 18). In a nutshell, after probing a variety of copper sources, bases, solvents, and copper and ligand loadings, we concluded that the combination of 20 mol % CuI and 20 mol % 4,4'-di-*tert*-butyl-2,2'-bipyridine (L2), along with 3 equiv of K<sub>2</sub>CO<sub>3</sub> in DMA at 170 °C for 3 min under microwave irradiation, comprises the optimum reaction conditions for this transformation.

Table 2. Substrate Scope with Substituted Phenols<sup>a</sup>

## Scope:

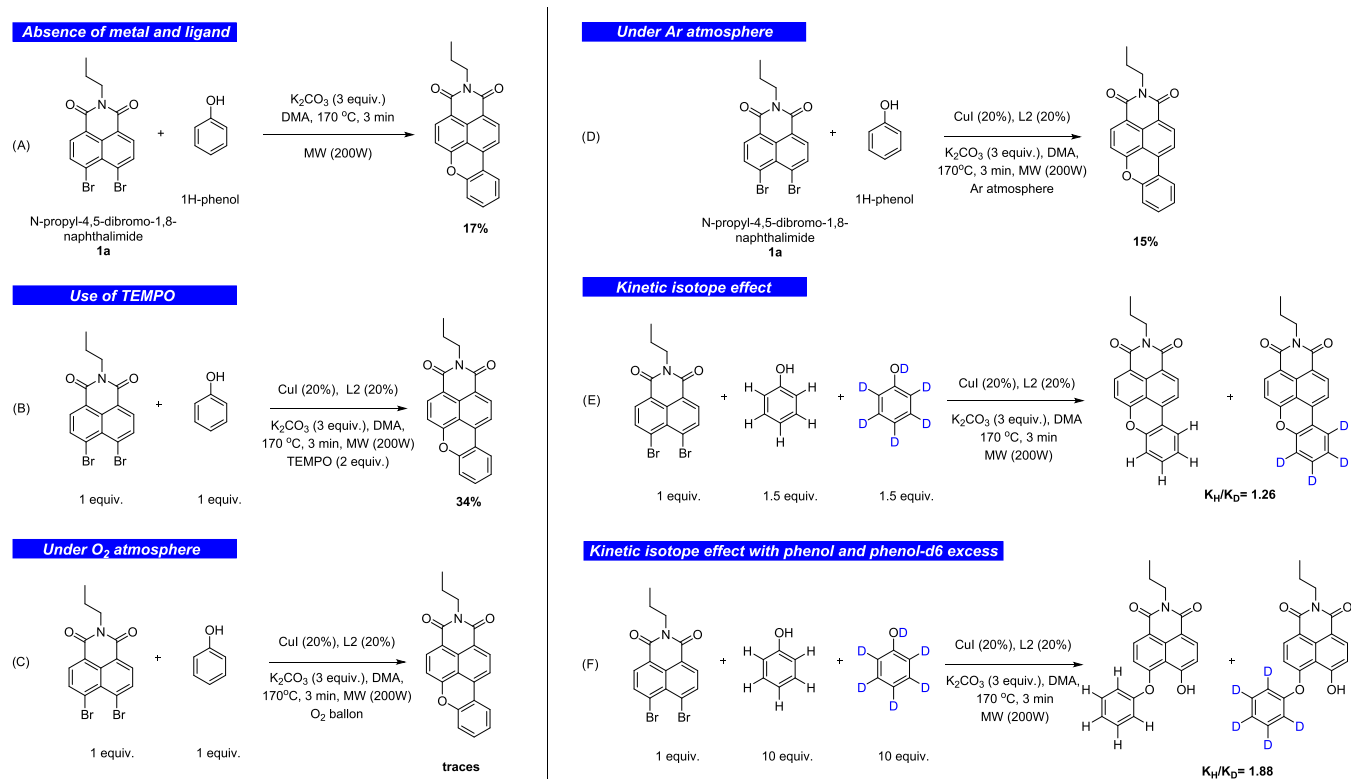


<sup>a</sup>Reaction conditions: 1a–e (0,126 mmol, 1 equiv), 1*H*-phenol (0,126 mol, 1 equiv), CuI (20%), 4, 4'-di-*tert*-butyl-2, 2'-dipyridine (L2, 20%), K<sub>2</sub>CO<sub>3</sub> (3 equiv), DMA (0,5 mL), 170 °C, 3 min, under air, MW (200 Watt).

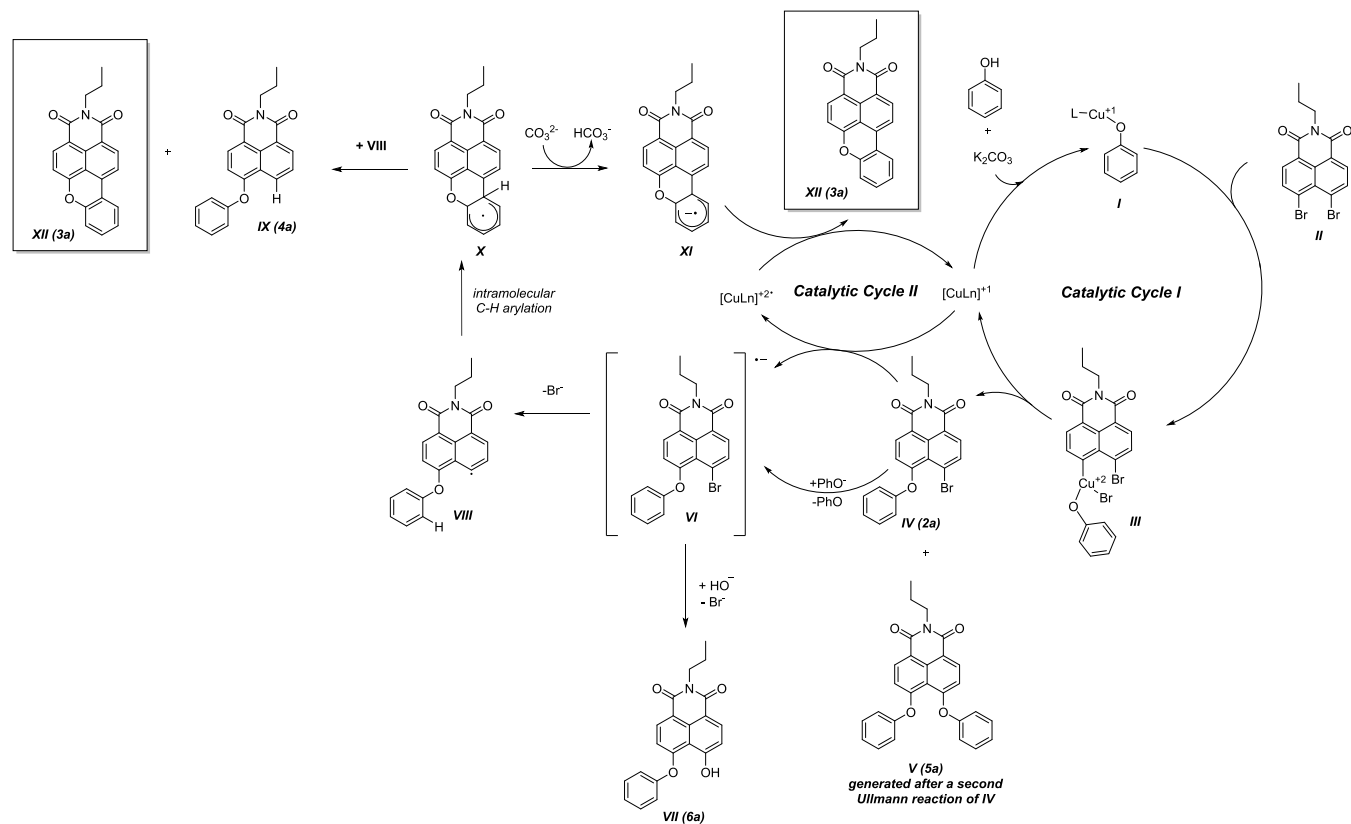
With the optimum conditions in hand, we studied the substrate scope. Five different 4,5-dibromo-1,8-naphthalimide derivatives (1a–e), bearing different substituents on the nitrogen atom, were designed and synthesized through a three-step synthetic route (Scheme 2) and then tested with several substituted phenols. It turned out that our method is

particularly suitable for nonsubstituted or electron-rich phenols. The position of the phenol substituent dramatically affects the yield of the reaction, as only *para*-substituted phenols lead to the desired product. The best results were obtained when substrates 1a–e were reacted with non-substituted phenol, affording the desired cyclized products

## Scheme 3. Experiments Carried Out to Shed Light on the Mechanism of the Transformation



## Scheme 4. Proposed Reaction Mechanism



3a, 3k, 3n, 3r, and 3u in moderate to good isolated yields (30–64%) (Table 2). *N*-propyl-4,5-dibromo-1,8-naphthalimide's (1a) activity was examined with a wide range of electron-

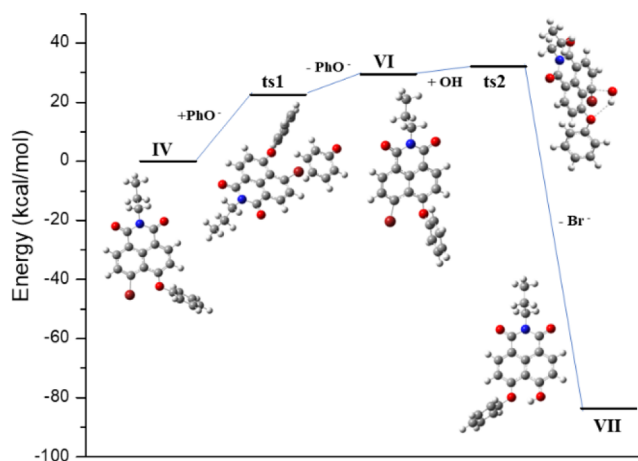
rich *para*-substituted phenols. Phenols bearing methoxy, methyl, dimethyl amino, cyclohexyl, *tert*-butyl, phenyl, or phenoxy groups afforded products 3b–h in isolated yields



ranging from 31 to 43%. On the contrary, phenols bearing electron withdrawing *para* substituents, such as trifluoromethyl or nitro, did not afford the corresponding cyclized products **3i** and **3j**, respectively. Furthermore, phenols bearing halogen atoms in *para* positions, such as chlorine and bromine, were dehalogenated during the reaction, providing **3a** instead of the corresponding cyclized products. *Para*-substituted fluorophenol remained unreactive in this transformation, also not leading to the desired product formation. Substrates **1b–d** were also utilized, bearing *para* methyl, *para* phenoxy, or *para* phenyl substituents, leading to products **3l**, **3m**, **3o–q**, **3s**, and **3t** in isolated yields between 30 and 53%.

To gain some insights into the reaction mechanism, we initially carried out some control experiments, as shown in Scheme 3. The reaction between **1a** and 1*H*-phenol in the absence of metal and ligand afforded **3a** in 17% yield (Scheme 3A). Therefore, the reaction of the specific substrate can proceed in the absence of the catalytic system but in a significantly lower yield. Control experiments were also performed in the presence of the radical scavenger 2,2,6,6-tetramethyl piperidine 1-oxyl (TEMPO). In this case, the reaction provided **3a** in 34% yield, about half of that was obtained in the absence of TEMPO (Scheme 3B). We furthermore observed that the existence of a small amount of oxygen that is trapped in a microwave tube is necessary for the reaction to proceed.<sup>41–43</sup> When the reaction was performed under an atmosphere of pure O<sub>2</sub>, only side products **2a**, **4a**, and **6a** were formed, along with traces of **3a** (Scheme 3C). We assume that Cu(I) is oxidized by the O<sub>2</sub> excess to Cu(II), shutting down completely the C–H arylation step. On the other hand, reactions performed under an argon atmosphere resulted in **3a** in a significantly lower yield (Scheme 3D). These observations suggest that the excess of O<sub>2</sub> might lead to extensive copper oxidation to Cu(II), whereas an argon atmosphere does not allow Cu to oxidize at all. In both cases, the C–H arylation step is blocked. Next, an intermolecular kinetic isotope effect (KIE) competition was performed. The reaction was carried out under the standard reaction conditions using **1a**, along with 1.5 equiv of 1*H*-phenol and 1.5 equiv of phenol-*d*<sub>6</sub> (Scheme 3E). The *k*<sub>H</sub>/*k*<sub>D</sub> ratio measured is 1.26, suggesting that the rate-determining step does not involve a C–H bond breaking. The use of a larger excess of 1*H*-phenol (10 equiv) and phenol-*d*<sub>6</sub> (10 equiv) leads to the isolation of the hydroxylated side product **6a**, as the main product, in 61% yield (the *k*<sub>H</sub>/*k*<sub>D</sub> ratio measured was 1.88). In this case, the formation of the desired product **3a** was not observed (Scheme 3F).

**Proposed Mechanism and DFT Calculations.** The synthesis of benzoxanthenes via an Ullmann reaction and an intramolecular C–H arylation step employing a copper catalyst was studied via density functional theory (DFT) calculations (Scheme 4). Detailed energy profiles are shown in Scheme 1S (Electronic Supporting Information, ESI). The dimer interaction energies of some molecules are also given. The activation energies are less than 26 kcal/mol and the dimerization energies can further ease the energy demands of the reaction paths (Figures 1–4 herein and 1S–3S in ESI). Almost in all dimers,  $\pi$ – $\pi$  stacking bonds are formed, with bond distances ranging from 3.28 to 3.59 Å (Figure 3S, ESI). Note that the typical  $\pi$ – $\pi$  stacking bond distances are about 3.5 Å.<sup>44</sup> In brief, the first cycle (catalytic cycle I) involves an Ullmann coupling reaction, in which phenol reacts with copper iodide, forming intermediate I. Subsequently, this undergoes



**Figure 1.** Calculated reaction path IV → VII at wB97XD/6-311+G(d,p) in DMA solvent.

oxidative addition with aryl halide **II**, forming intermediate **III**, which releases **IV** (**2a**), also regenerating the copper catalyst via a reductive elimination. Alternatively, oxidative addition with the aryl halide can occur first.<sup>45</sup> The formation of **IV** can be also achieved via a base-promoted aromatic nucleophilic substitution (S<sub>N</sub>Ar).<sup>46–49</sup> Then, intermediate **IV** can either be involved in a second Ullmann coupling reaction, affording the disubstituted product **V** (**5a**) or in the aromatic C–H arylation step (catalytic cycle II) toward the formation of the desired product **XII** (**3a**). In specific, a single-electron transfer (SET) reaction from [CuLn]<sup>+1</sup> to anion **VI** and the following C–Br bond breaking lead to the formation of intermediate **VIII**.<sup>19,50–52</sup> Alternatively, the electron transfer from **IV** to **VI** could be achieved through the phenoxide anion (PhO<sup>−</sup>). In parallel, the hydroxylation of anion **VI** in the presence of K<sub>2</sub>CO<sub>3</sub> and water (from the solvent) generates the side product **VII** (**6a**). Although a few Cu-catalyzed hydroxylations of aryl halides have been reported, the corresponding reaction mechanism remains unclear.<sup>53,54</sup> Intramolecular cyclization of aryl radical **X** results in the formation of cyclohexadienyl radical **X**, which can be deprotonated from K<sub>2</sub>CO<sub>3</sub>, forming biaryl radical **XI**, eventually leading to the side product **IX** and the desired product **XII** (**3a**). The latter is formed via a single-electron transfer to [CuLn]<sup>2+,•</sup>, regenerating the catalyst. The second catalytic cycle can alternatively proceed in the absence of a copper catalyst via a radical pathway promoted by K<sub>2</sub>CO<sub>3</sub> (base-promoted HAS).<sup>55–57</sup>

In the herein studied catalytic cycles, [CuL<sub>2</sub>]<sup>2+,1+</sup> and [CuL]<sup>2+,1+</sup> complexes were examined as catalysts, where L = 4,4′-diterbutyl-2,2′-dipyridine or phenoxy (PhO) (Scheme 1S, ESI). The use of [Cu(OPh)<sub>2</sub>]<sup>2+,1+</sup> in the catalytic cycles is favored energetically, when compared to [CuL<sub>2</sub>]<sup>2+,1+</sup> and [CuL]<sup>2+,1+</sup>, where L = 4,4′-di-*tert*-butyl-2,2′-dipyridine. In catalytic cycle I, for L = PhO, complex I is [CuL<sub>2</sub>]<sup>1+</sup>, which has been already formed in cycle II, while for L = 4,4′-di-*tert*-butyl-2,2′-dipyridine, the formation is an endothermic reaction, given that the PhO–H bond breaks homolytically. Regarding catalytic cycle II, no activation energy was found; the production of **XII** from **XI** and of **VI** from **IV** was smooth. The first reaction is energetically favored, while the reaction energy demands for the second one can be assisted by the energy gains of the first. Alternatively, the electron transfer from **IV** to **VI** can be done via the reaction IV + PhO<sup>−</sup> → VI + PhO. The energy demands are 29.2 kcal/mol. An intermediate

transition state (**ts1**) is formed with an activation energy of 22.5 kcal/mol (Figure 1), where Br interacts with the  $\pi$  electrons of the PhO moiety and a H atom of PhO with the PhO group of IV (Figure 3S, ESI). Note that the dimer interaction energies are  $-6.7$  kcal/mol, which can assist the reaction demands.

The substitution reaction of Br with OH, resulting in VII (6a), is an exothermic process with a very small activation energy of 2.9 kcal/mol, see Figure 1, **ts2**. In **ts2**, Br moves away from the plane of the aromatic moiety, and an O...C bond is formed between OH and VI, while a H...O bond further stabilizes the attached OH. The OCB r angle is  $99.86^\circ$  (Figure 2S in ESI). Although the substitution of Br with OH is an exothermic process, the withdrawal of Br<sup>-</sup> from VI, resulting in the VIII radical, is endothermic, i.e., +4.0 kcal/mol. The corresponding activation energy is 19.2 kcal/mol (**ts3**, Figure 2), where the Br<sup>-</sup> forms a weak bond at 2.316 Å. Note that in VI and IV, the corresponding C–Br bond distances are 1.916 and 1.904 Å, respectively.

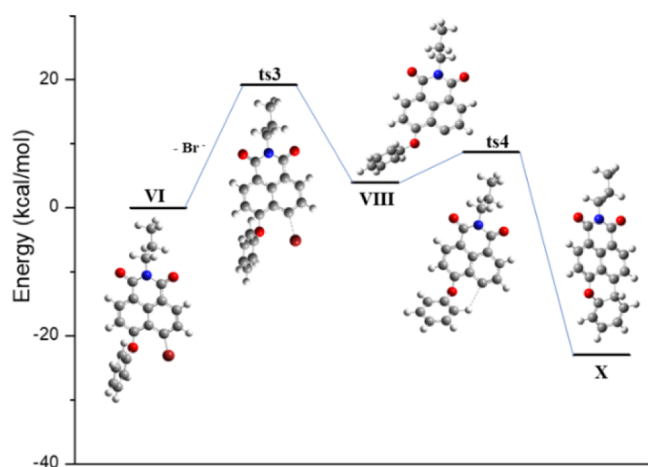


Figure 2. Calculated reaction path VI  $\rightarrow$  X at wB97XD/6-311+G(d,p) in DMA solvent.

The intramolecular C–H arylation of VIII is also an exothermic reaction with a small activation energy of 4.7 kcal/mol (**ts4**, Figure 2). In **ts4**, the PhO moiety has rotated around the O–C bond, while the H bond is formed (Figure 2). Then, the H transfer reaction occurs from X to VIII with an activation energy of 25.5 kcal/mol (**ts5**), with the reaction being exothermic, i.e.,  $-97.8$  kcal/mol (Figure 3). Note that a dimer is initially formed, between X and VIII, via  $\pi$ – $\pi$  bonds with bond distances at  $\sim 3.59$  Å. The dimerization energy is  $-21.9$  kcal/mol and the bond distance between the transferred H and the C $\cdot$  is 2.827 Å. Then, **ts5** is formed, where the H-transferred atom forms a H...C bond with a bond distance of 1.746 Å, while the  $\pi$ – $\pi$  bond distances are at  $\sim 3.39$  Å. Finally, XII(3a) + IX(4a) is formed (Figure 3).

Furthermore, as is shown in Scheme 4, an exothermic H<sup>+</sup> transfer to CO<sub>3</sub><sup>2-</sup> can take place, with radical XI leading to XII (3a) via catalytic cycle I. At first, X forms a dimer with CO<sub>3</sub><sup>2-</sup> with an interaction energy of  $-4.6$  kcal/mol, and the H...O bond distance is 1.861 Å. The activation energy of this reaction is 4.9 kcal/mol, corresponding to the formation of **ts6**, where the H-transferred atom forms H-bonds of 1.424 and 1.530 Å (Figure 4 herein and Figure 2S in ESI).

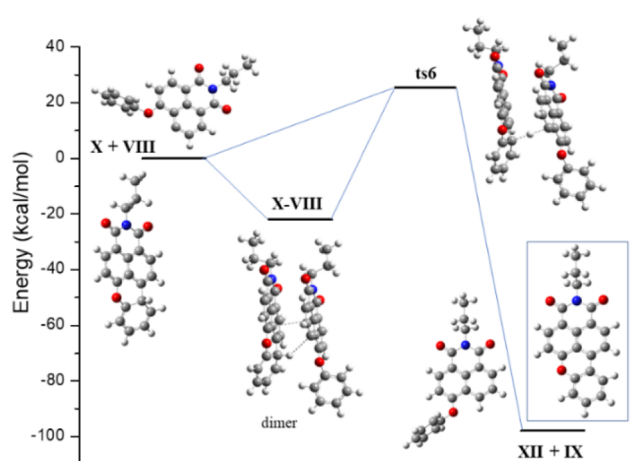


Figure 3. Calculated reaction path X + VIII  $\rightarrow$  XII + IX at wB97XD/6-311+G(d,p) in DMA solvent.

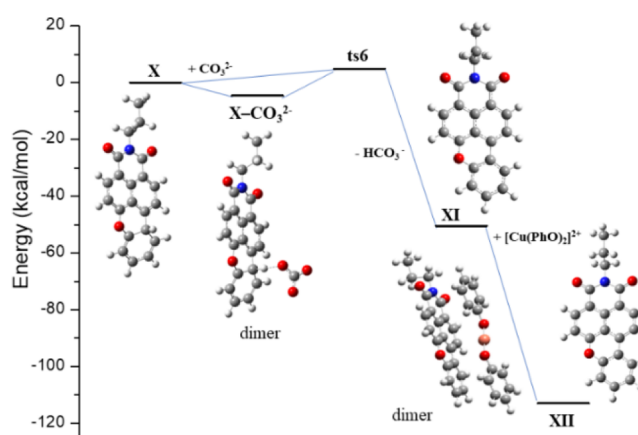


Figure 4. Calculated reaction path X  $\rightarrow$  XII at wB97XD/6-311+G(d,p) in DMA solvent.

To sum up, the energies calculated (Scheme S1, ESI) show clearly why all four compounds, 3a, 4a, 5a, and 6a, are products, taking into account the small, similar activation energies in all reaction steps. As a result, small changes in the conditions can alter the yields and the outcome of the reactions. Furthermore, compound 3a is the main product and can be produced via two routes. This is in accordance with the significant reduction of its yield in the absence of the Cu catalyst, where 3a is formed only via the electron transfer route from XI to XII (3a). The reaction path is smooth, as is shown in Figure 4 (herein) and Figure 3S (ESI). Finally, CuI is a better copper source than the other monohalides, given that CuI has the largest bond length and a significantly smaller bond dissociation energy; thus, it is released easier, forming the required complexes with L ligands in solution.<sup>58</sup>

## CONCLUSIONS

We herein report a sustainable, copper-catalyzed methodology for the synthesis of oxygen-containing polyaromatic molecules through an Ullmann reaction, followed by an intramolecular C–H arylation step, in a domino fashion. The use of microwave irradiation makes this methodology expedient, as it requires only 3 min, and the fact that it works under air makes it user-friendly. A variety of *para*-substituted phenols are amenable to this transformation, affording the desired products

in moderate to good yields. Mechanistic studies suggest the involvement of free radicals. A possible mechanism is proposed based on control experiments and kinetic isotope effect measurements. DFT calculations were also carried out, supporting the proposed mechanistic pathway.

## EXPERIMENTAL SECTION

**General Procedure for the Synthesis of Oxygen-Containing Polyaromatic Molecules.** A high-pressure 10 mL microwave vessel, equipped with a magnetic stir bar, was loaded with 50 mg of *N*-(substituted)-4,5-dibromo-1,8-naphthalimide (**1a–e**) (1 equiv) and phenol (1 equiv),  $K_2CO_3$  (3 equiv), CuI (20%), and 4,4'-di-*tert*-butyl-2,2'-dipyridine (**L2**) (20%) in DMA (0.5 mL). The reaction vessel was sealed and placed in the microwave apparatus for 3 min at 170 °C (200 Watt). After the reaction was completed, the organic products were extracted with DCM and thoroughly washed with water. The organic phase was dried over anhydrous  $Na_2SO_4$  and filtered. The solvent was removed in vacuo, and the product was further purified with silica gel column chromatography, affording the desired products **3a–u**.

**Computational Details.** The geometries of the minima, intermediates, and transition states involved in the synthetic procedures were fully energetically optimized by DFT calculations in *N,N'*-dimethylacetamide (DMA) solvent. The B3LYP<sup>59,60</sup> and wB97XD functionals<sup>61</sup> were employed in conjunction with the 6-311G+(d,p)<sup>59,60</sup> basis sets. The transition states were calculated by employing the STQN method for locating transition structures.<sup>62</sup> Both functionals are regarded as adequate for the calculation of catalytic reactions,<sup>63</sup> and their effectiveness has been checked in various cyclization reactions and systems with dispersion forces.<sup>64–66</sup> They gave similar results. However, the wB97XD functional, which uses a version of Grimme's D2 dispersion model, is regarded as the best one, as dispersion forces exist in some transition states.<sup>66</sup> For all minima structures and transition states, their frequencies were calculated to confirm that they are true minima and transition states, respectively. The solvent has been included as a dielectric constant,  $\epsilon = 37.781$ . Specifically, the polarizable continuum model was employed,<sup>67</sup> which has been proved to reproduce good solvent effects.<sup>68,69</sup> All calculations were performed using the Gaussian 16 program package.<sup>70</sup>

## ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

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Experimental procedures, additional optimization experiments, mechanistic experiments, computational information, compound characterization data, and copies of spectra (PDF)

## AUTHOR INFORMATION

### Corresponding Author

Georgios C. Vougioukalakis – Department of Chemistry, National and Kapodistrian University of Athens Panepistimiopolis, 15771 Athens, Greece; [orcid.org/0000-0002-4620-5859](https://orcid.org/0000-0002-4620-5859); Phone: +30-210-7274230; Email: [vougiouk@chem.uoa.gr](mailto:vougiouk@chem.uoa.gr); Fax: +30-210-7274761

### Authors

Enayaz Kaplanai – Department of Chemistry, National and Kapodistrian University of Athens Panepistimiopolis, 15771 Athens, Greece

Efstathios Tonis – Department of Chemistry, National and Kapodistrian University of Athens Panepistimiopolis, 15771 Athens, Greece

Maria Drymona – Department of Chemistry, National and Kapodistrian University of Athens Panepistimiopolis, 15771 Athens, Greece

Yulian Zagranyski – Department of Chemistry and Pharmacy, “St. Kliment Ohridski” University of Sofia, 1164 Sofia, Bulgaria

Demeter Tzeli – Department of Chemistry, National and Kapodistrian University of Athens Panepistimiopolis, 15771 Athens, Greece; Theoretical and Physical Chemistry Institute, National Hellenic Research Foundation, 11635 Athens, Greece; [orcid.org/0000-0003-0899-7282](https://orcid.org/0000-0003-0899-7282)

Complete contact information is available at:

<https://pubs.acs.org/doi/10.1021/acs.joc.3c00830>

### Author Contributions

This manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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