

## Article

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# Direct C–H Arylation of Heteroarenes with Copper Impregnated on Magnetite as a Reusable Catalyst: Evidence for CuO Nanoparticle Catalysis in Solution

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**ABSTRACT:** A reusable copper-based catalyst system was employed for the direct arylation of electron-rich heteroarenes. Under mild and operationally simple reaction conditions good yields and selectivities were obtained using diaryliodonium salts as coupling partners. A combination of experimental methods including kinetic studies, filtration tests, and a series of analytical tools (TXRF, ICP-MS, SEM, XPS, TEM, EFTEM) provide evidence for catalytically active soluble nanoparticles formed from an amorphous heterogeneous precursor. Mechanistic studies hint at a redox-neutral process which promotes counterion dissociation from the diaryliodonium salt by a copper(II)oxide species.

*KEYWORDS*: reusable copper catalyst, direct C–H arylation, electron-rich heteroarenes, nanoparticle catalysis, leaching-redeposition.

#### INTRODUCTION

The regioselective construction of aryl-aryl bonds is of fundamental importance in organic synthesis and compounds containing polyaryl moieties are ubiquitious in natural products and pharmaceuticals.<sup>1</sup> To accomplish biaryl or heteroaryl-aryl bond formation, cross-coupling methods have been developed and broadly employed over the past century.<sup>2</sup> Among them, the Ullmann,<sup>3</sup> Stille,<sup>4</sup> Suzuki<sup>5</sup> and Kumada-Corriu<sup>6</sup> couplings are some of the most important and highly utilized methods. However, the need for pre-functionalized starting materials compromises the efficiency of these processes as their synthesis can be a significant challenge.7 Transition-metalcatalyzed C-H activation is a powerful and efficient tool for the modification of organic molecules<sup>8</sup> and the direct arylation (DA) of (hetero)arenes remains one of the most useful methodologies in organic synthesis.<sup>9</sup> Most catalytic DA processes are conducted with late transition metals such as rhodium, ruthenium, iridium and, most commonly, with palladium.9 The use of more abundant first-row transition metals in DA catalysis is still limited.<sup>10</sup> Direct arylation with simple, abundant copper salts represents an economically viable alternative to precious metal catalysis and yet remains a challenge in industry and academia. From the pioneering work of Daugulis," Gaunt,<sup>12</sup> You<sup>13</sup> and more recently, Greaney,<sup>14</sup> the use of homogeneous copper salts as precatalysts became relevant. The need for coordinating ligands and/or bases, high catalyst loadings and temperatures, however, hinder the practical use of these methodologies (Scheme 1). A potential alternative which enables mild and direct arylation of heteroarenes has emerged in the field of photocatalysis. However, these reactions require a large excess of starting materials compromising their utility from an economic standpoint.<sup>15</sup>



(+) Recyclable catalyst (+) Additive free (+) General methodology

Scheme 1. Copper-catalyzed direct arylation of electron-rich heteroarenes

Along the same lines, transition-metal-free alternatives are gaining relevance. These reactions, however, generally involve the *in situ* formation of free radicals and thus

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display a limited functional group tolerance as well as regioselectivity issues.<sup>16</sup>

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Heterogeneous catalysis has several potential advantages over homogeneous catalysis. The reactions are usually unaffected by air or moisture and the catalyst can be easily removed from the reaction mixture which enables its reuse.<sup>17</sup> Our group has recently contributed to the area of heterogeneous C-H functionalization. Employing simple Pd/C and Pd/Al<sub>2</sub>O<sub>2</sub> catalyst systems, we developed the direct C-H thiolation and arylation of electron-rich heterocycles and polyaromatics.<sup>18</sup> However, the reaction yields were highly variable depending on the commercial catalyst source and these supported palladium-based catalysts could not be easily recycled. Considering these limitations in addition to the need for the development of synthetic methodologies using recyclable, sustainable and abundant metal catalysts, we decided to explore heterogeneous copper sources as potential alternatives.

Heterogeneous copper catalysts are recognized for their applications in oxidation, click chemistry and Ullmann and Goldberg coupling reactions.<sup>19</sup> Their use in C–H functionalization, however, is much less developed and comprehensive studies on the active catalytic species of copper-based systems has only recently started to be explored.<sup>20</sup> For example, Corma and co-workers reported on the elucidation of clusters as active catalytic species in "homogeneous" copper-catalyzed cross-coupling reactions.<sup>21</sup> However, to the best of our knowledge, similar studies targeting elucidation of active catalytic species on solid or supported copper-catalysts, in the area of direct C–H functionalization, have yet to be described.

Herein, we report a reusable magnetic copper-based catalyst for the regioselective direct arylation of a variety of electron-rich heteroarenes with diaryliodonium salts (Scheme 1).<sup>22</sup> These reactions proceed in good yields under mild, operationally simple conditions. Moreover, a combination of experimental methods including kinetic studies, mass spectrometry, filtration tests, transmission electron microscopy (TEM), total X-ray fluorescence (TXRF), X-ray photoelectron spectroscopy (XPS), energyfiltered transmission electron microscopy (EFTEM) provide a better understanding of the active catalytic species in the reaction. Additionally, mechanistic data preclude a radical pathway and suggest a copper(II)oxide-promoted electrophilic aromatic substitution.

#### RESULTS AND DISCUSSION

We commenced our exploration of heterogeneous copper catalysts using Cu/C (Sigma-Aldrich) in the reaction of 2*n*-butylthiophene (1a) with diphenyliodonium salts, 2. The desired C5-arylated product, 3a, was obtained in 20% yield using toluene as the solvent (Table 1, entry 1). Reducing the reaction temperature from 80 to 60 °C improved the product yield (Table 1, entry 2) and using a nanoparticle-based catalyst such as CuO (nanopowder, 50 nm, Sigma-Aldrich, Table 1, entry 3) resulted in an increase in the formation of 3a.

Unfortunately, CuO nanopowder failed to catalyze the reaction of other substituted thiophene moieties along with different electron-rich heterocycles such as furan and benzofuran. We observed mostly decomposition of starting material after a low conversion (10-20 %) was obtained. We speculated that the acid generated in situ from the counterion of the iodonium salt promoted starting material decomposition and thus tested different supports that could neutralize the reaction media and allow for the arylation reaction to take place. Moreover, a support could also improve reusability. Due to the ease of preparation, separation and high optical basicity,<sup>23</sup> we decided to explore a superparamagnetic support. CuO/Fe<sub>3</sub>O<sub>4</sub>, easily prepared from a basified mixture of  $CuCl_2$  and  $Fe_3O_4$ ,<sup>24</sup> gave **3a** in 17% yield (Table 1, entry 4). Changing the solvent to 1,2-dichloroethane (DCE) (Table 1, entry 5) and then to dichloromethane (Table 1, entry 6), as well as changing the counterion of the iodonium salt from triflate to tetrafluoroborate gave the desired product in 70% yield (Table 1, entry 7). The optimized conditions were found by modifying the stoichiometry of the reaction and adding 2 equivalents of the heteroarene to avoid the formation of the bisarylated byproduct. 2-n-Butyl-5phenylthiophene (3a) was isolated in 78% yield with a selectivity of  $90:10 (C_5/C_4)$  (Table 1, entry 8).

#### Table 1. Optimization of reaction conditions<sup>a</sup>

T V	. Db-IV		catalyst	ſ ≫_{ ∧	
Bu S	+ F121A 2a	solvent temperature		Bu S	
Entry	Catalyst (y mol%)	X	Solvent	Temp. (°C)	Yield <sup>b</sup>
1	Cu/C (10)	OTf	Toluene	80	20%
2	Cu/C (10)	OTf	Toluene	60	39%
3	CuO (5) <sup>c</sup>	OTf	Toluene	60	44%
4	CuO/Fe <sub>3</sub> O <sub>4</sub> (5.6)	OTf	Toluene	60	17%
5	CuO/Fe <sub>3</sub> O <sub>4</sub> (5.6)	OTf	DCE	70	55%
6	CuO/Fe <sub>3</sub> O <sub>4</sub> (5.6)	OTf	$CH_2Cl_2$	70	62%
7	CuO/Fe <sub>3</sub> O <sub>4</sub> (5.6)	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	70%
<b>8</b> <sup>d</sup>	CuO/Fe <sub>3</sub> O <sub>4</sub> (5.6)	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	84% (78%) <sup>e</sup>
9 <sup>d</sup>	Fe <sub>3</sub> O <sub>4</sub>	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	о%
10 <sup>d</sup>	-	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	о%
nd	Cu/C (10)	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	44%
12 <sup>d</sup>	CuO/Al <sub>2</sub> O <sub>3</sub> (10)	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	33%
13 <sup>d</sup>	CuCl <sub>2</sub> (10)	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	51%
14 <sup>d</sup>	Cu(OTf) <sub>2</sub> (10)	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	56%
15 <sup>d</sup>	CuBr (10)	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	7%
16 <sup>d</sup>	Cul (10)	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	о%
17 <sup>d</sup>	Cu <sub>2</sub> O	BF <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70	71%

<sup>a</sup>Reaction conditions: 2-*n*-butylthiophene (1.0 equiv.), diphenyliodonium salt (1.0 equiv., 0.10 mmol), solvent (0.50 mL) for 22 h. <sup>b</sup>GC-FID yield. <sup>c</sup>Nanopowder (50 nm). <sup>d</sup>2.0 equiv. of 1a. <sup>e</sup>Isolated yield.

Running this reaction in the absence of copper either with or without the magnetite support failed to afford the

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59 60 desired product (Table 1, entries 9-10). Also, the magnetite proved superior to other supports (Table 1, entries 11-12). This  $CuO/Fe_3O_4$  catalyst system outperformed a series of commonly employed homogeneous Cu(II) and Cu(I)salts (Table 1, entries 13-17 and Table S1, page S9) and furthermore, showed better tolerance when diverse electron-rich heteroarenes such as indole, furan and benzofuran were employed (*vide infra*). Additionally, other catalysts with magnetic support failed to catalyze this reaction (Table S2, page S9).



Scheme 2. Substrate scope of different heterocycles<sup>a</sup> Isolated yields are given. <sup>a</sup>General procedure: heteroarene (2.0 equiv.), diphenyliodonium salt (1.0 equiv., 0.30 mmol), CuO/Fe<sub>3</sub>O<sub>4</sub> (5.6 mol%), in CH<sub>2</sub>Cl<sub>2</sub> at 70 °C, 22 h. <sup>b</sup>5.0 mmol. <sup>c</sup>Isolated as a mixture of isomers. <sup>d</sup>2.5 equiv. of heteroarene. <sup>e</sup>50 °C in CH<sub>2</sub>Cl<sub>2</sub>.

With the optimized conditions in hand, we focused on the exploration of the reaction scope. First, different heteroarenes were investigated (Scheme 2). Electron donating (3a, 3b) and withdrawing (3e, 3g) substituted thiophenes were found to be suitable substrates for the reaction. The C5-regioselectivity was maintained for 2substitued thiophenes. Notably, a disubstituted thiophene could be employed in the reaction (3c). We observed that the 3-substitued thiophenes proved to be more challenging substrates under the reaction conditions and usually lower yields were obtained (3f) (see SI, page S29 for further details). 2-n-Butylfuran underwent C5-arylation with perfect selectivity albeit in low yield (3h).

Similarly, a disubstituted furan afforded the desired arylated product with high regioselectivity (3i). Where lower yields were obtained, we observed either starting material decomposition (acid-sensitive substrates such as furans 3h, 3i) or an influence of electronic effects when electron withdrawing groups were directly attached to the heteroarene (3g), probably indicating an electrophilic type of mechanism. The versatility of the magnetic catalyst was not limited to thiophenes and furans. We were pleased to find that unprotected indoles as well as *N*-methylindoles reacted highly selectively and in acceptable to good yields under our optimized conditions (3k-3o).

The C<sub>3</sub>-arylation of the indole in a thiophene-indole moiety (**3j**) highlights the regioselectivity of our catalytic system. Moreover, functional groups were tolerated such as 5-iodo- and 5-benzyloxyindole, which would allow for further derivatization of these compounds (**3m**, **3o**). Unsubstituted benzofurans were selectively arylated at the C<sub>2</sub>-position (**3r**) and, remarkably, the arylation took place at C<sub>3</sub>-position when C<sub>2</sub>-substituted benzofurans were employed (**3q**). To our surprise, when benzo[*b*]thiophene was tested under our conditions, no product was observed (**3s**).

The importance of the support was once again highlighted when we observed that unsupported CuO nanopowder performed poorly in the arylations of 2-*n*-butylfuran and benzofuran (**3h**, **3r**). Furthermore, CuO/Fe<sub>3</sub>O<sub>4</sub> proved superior to commonly employed homogeneous copper sources, especially in the reaction with oxygen-containing heterocycles such as benzofuran and furan derivatives. The copper salts failed to achieve high yields (o to 20%) in the reaction primarily due to acid-promoted starting material decomposition, as was observed in kinetic measurements comparing CuO/Fe<sub>3</sub>O<sub>4</sub> to 3 different copperbased catalysts (See SI pages S<sub>3</sub>O-S<sub>3</sub>I for further detail). The utility of the catalytic system was tested on a 5 mmol scale reaction and we were pleased to obtain **3a** in 75%.

Next, we explored the scope of the diaryliodonium salt (Scheme 3). Electronically diverse iodonium salts were found to be efficient coupling partners, although a clear preference for electon-poor iodonium salts was observed in reactions with 1a (4a, 4d). Diaryliodonium salts containing meta or para-substitution on the arene were welltolerated as were arenes with electron withdrawing groups such as -Br, -F, -NO<sub>2</sub> and -CO<sub>2</sub>Et (4a, 4h, 4j, 4d, 4e, 4k, 4l) which would allow for further functionalization of the products. Notably, this simple catalytic system enabled the reaction of electronically diverse, unsymmetrical iodonium salts containing a cheap, non-transferable arene (2,4,6-triisopropylphenyl, TRIP) (4d, 4k). A modified robustness screen was applied for further exploration of functional group tolerance of the reaction (see SI, pages S32-S33).25



Scheme 3. Substrate scope of the iodonium salt<sup>a</sup>

Isolated yields are given. For 2-*n*-butylthiophenes selectivities refer to C<sub>5</sub>/C<sub>4</sub>, C<sub>2</sub>/C<sub>3</sub> for benzofurans and C<sub>3</sub>/C<sub>2</sub> for indole. <sup>a</sup>General procedure: heteroarene (2.0 equiv.), diphenyliodonium salt (1.0 equiv., 0.30 mmol), CuO/Fe<sub>3</sub>O<sub>4</sub> (5.6 mol%), in CH<sub>2</sub>Cl<sub>2</sub> at 70 °C, 22 h. <sup>b</sup>Isolated as a mixture of isomers. <sup>c</sup>2.5 equiv. of heteroarene. <sup>d</sup><sub>5</sub>O °C in CH<sub>2</sub>Cl<sub>2</sub>.

We were pleased to find that the catalyst could be easily recovered using a magnet and reused. The reusability experiments showed no loss in reactivity over five consecutive cycles, however, after the 5<sup>th</sup> cycle, a loss of reactivity was observed (Scheme 4).

Bu 1 (2 c	−S + la equiv.)	Ph <sub>2</sub> IBF <sub>4</sub> -	CuO/Fe <sub>3</sub> C CH <sub>2</sub> Cl <sub>2</sub> , 70 22 h	04 → °C Bu	S Sa	
Cycle	1	2	3	4	5	6
Yield	78 %	76 %	77 %	77 %	78%	68 %
Scheme 4. Reusability study of the copper-based catalyst system <sup>a</sup>						

Isolated yields are given. <sup>a</sup>General procedure: See Scheme 2 and SI. The catalyst was washed with  $CH_2Cl_2$  (4 times) and dried at 75 °C for 45 min after every cycle.

# STUDIES TOWARDS ELUCIDATING THE ACTIVE CATALYTIC SPECIES

Next, we were interested in understanding whether the catalysis was taking place on the surface of the magnetically recoverable heterogeneous catalyst or if the active catalytic species was in solution. Therefore, we started our investigation into the details of the reaction through a series of kinetic measurements, high-resolution mass spectrometry, heterogeneity tests, poisoning experiments and catalyst analyses with XPS, SEM, TXRF, ICP-MS, TEM, EFTEM and diffraction pattern.

The kinetics of the standard reaction providing 2-*n*-butyl-5-phenyl-thiophene (**3a**) showed an induction period of 2

hours and a sigmoidal reaction profile (Figure 1). These results are indicative of the in situ formation of a new active catalytic species derived from the heterogeneous catalyst.<sup>18c</sup> The presence of an induction period was also detected when other common copper sources such as CuO nanopowder, CuCl<sub>2</sub>, or Cu(OTf)<sub>2</sub> were employed. One of most common methods to differentiate between heterogeneous surface catalysis and solution-phase catalysis is the hot filtration test.<sup>26</sup> We decided to apply this technique to our reaction at various stages of the reaction. Filtration of the crude reaction through Celite at 15% conversion showed a 5% increase after allowing the filtrate to stir at 70 °C for the remainder of the standard reaction time. Intrigued by this result, the reaction was filtered at 45% conversion. After the standard 22 hours of reaction time, GC-FID analysis of the filtrate showed that the yield had increased to 84%, clearly indicating the formation of a soluble active species. In further kinetic analysis of the separated filtrate, we observed no induction period for the formation of product 3a, strongly indicating the presence of the active catalytic species in solution (Figure 1). Moreover, the separated solid catalyst still presented an induction period but produced 3a in the same yield as the filtrate after the standard reaction time. These results support the formation of a soluble active species from the heterogeneous precursor. A leachingredeposition mechanism would be in accordance with the recycling results observed for the catalyst.<sup>27</sup> If such a phenomenon was operational, a variation of the metal content in solution should be observed throughout the reaction and the copper content on the solid catalyst should remain fairly constant at the end of the reaction time.



**Figure 1.** Kinetic results for the reaction of 2-*n*-butylthiophene (**1a**) and diphenyliodonium tetrafluoroborate (**2a**) catalyzed by CuO/Fe<sub>3</sub>O<sub>4</sub>. The line represents the moment when the reaction mixture was filtered.

In order to verify this "boomerang" phenomena, a series of TXRF measurements were conducted to determine the abundance of metal in solution (Table 2). In line with a leaching-redeposition mechanism, TXRF results confirmed the presence of metal (predominantly copper) in solution. Additionally, an increase in the metal concentration after the induction period and a decrease towards the end of the reaction time was observed. ICP-MS analysis of the catalyst showed a loss of 13% in mass of copper after

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the 6<sup>th</sup> catalytic cycle. These results could help explain the drop in reactivity observed when the catalyst was used for a 6<sup>th</sup> reaction cycle and are in accordance with the findings of the hot filtration test. Furthermore, after the 6<sup>th</sup> catalytic cycle SEM and XPS analysis revealed an extensive coverage of the catalyst surface by a fluorinated compound, likely deposited tetrafluoroborate on the surface of the CuO/Fe<sub>3</sub>O<sub>4</sub> (see SI, pages S<sub>35</sub>-S<sub>39</sub>). This effect could either slowly prevent the redeposition of CuO onto the support or block the release of the metal oxide from the surface and thus prevent the formation of the active catalytic species.<sup>28</sup> The coverage of the surface changed the morphology of the magnetic catalyst as observed in Figure 2.

Table 2. Abundance of metal in solution at differentreaction times according to TXRF measurements

Reaction time	Cu (mg/L)	Cu in solution <sup>a</sup>	Fe (mg/L)	Conversion by GC-FID
2 h	2.34	< 1 %	1.58	о%
7 h	323.42	45 %	2.27	40%
11 h	88.14	12 %	0.57	75%
22 h	0.50	< 1 %	0.24	84%

<sup>a</sup>With respect of starting percentage of copper (5.6 mol%).



**Figure 2.** SEM images of fresh catalyst (A) and the reused catalyst after 6<sup>th</sup> catalytic cycle (B) showing change in morphology.

Intrigued by these results, we decided to further investigate the nature of the active soluble catalytic species and thus TEM, EFTEM and diffraction pattern measurements were conducted for a sample with a 40% conversion. TEM-images showed a series of aggregates ranging from small (10-100 nm) to significantly larger (100-400 nm) (Figure 3.). We wondered whether these aggregates could contain embedded nanoparticles in an amorphous layer of organic material and hence, EFTEM studies were conducted.



**Figure 3.** TEM-images of the nanoparticles, which are embedded into an amorphous layer. A and B show the aggregates after 40% conversion. The size of the aggregates varied from small (10-100 nm, **A**) to large (100-400 nm, **B**).

EFTEM-images confirmed the presence of an amorphous layer surrounding the particles. The electron beam from the EFTEM destroyed the outer layer completely, revealing the underlying nanoparticles. The difference between the exposed nanoparticles (Figure 4B) and those embedded in an amorphous layer (Figure 4A) can be seen by laying the TEM and EFTEM-images side-by-side. Also, EFTEM measurements showed a homogeneous distribution of the nanoparticles throughout the analyzed sample (see SI, pages S41-S47).





**Figure 4.** TEM-images of the nanoparticles, which are embedded into an amorphous layer before (**A**) and after the EFTEM measurements (**B** and **C**). During the measurements the electron beam destroys the outer layer, which reveals the underlying nanoparticles. The particles give a high contrast both in bright field (**B**) and dark field (**C**) TEM-images.

Additionally, the corresponding diffraction pattern supports these findings (Figure 5).<sup>29</sup> Prior to EFTEM, no signals could be detected. After destroying the outer layer that covers the nanoparticles, however, a crystalline structure was observed and hkl planes for CuO and  $Fe_3O_4$  were found. The copper within the nanoparticles was identified as only copper(II)oxide (Figure 5). These results strongly

indicate that CuO nanoparticles are present in the active catalytic species.

According to literature reports,<sup>30</sup> changes in nanoparticle structure could be induced by irradiation with high energy electron beams from transmission electron microscopy techniques however, during our measurements we did not observe any changes in the morphology or structure of the nanoparticles.



**Figure 5.** Diffraction pattern of the nanoparticles. A diffraction pattern could only be detected after the organic layer was destroyed. The most prominent hkl planes are marked for CuO.

Recently, a study from Ananikov and coworkers<sup>31</sup> showed the formation of soluble copper-thiolate as the active catalytic species in the cross-coupling reaction of thiols and arylhalides using CuO nanoparticles as precatalyst. Inspired by their ability to observe their catalytically active leached copper species by mass spectrometry, we wondered if similar analysis could provide us with the same insight. A series of ESI-MS, MALDI-TOF and HPLC-MS measurements showed no evidence of ionizable copper and/or copper oxide species in solution.

However, from a stoichiometric experiment, we were able to detect that a positively charged dimeric diaryliodonium species appeared after heating the catalyst with the diaryliodonium salt. This suggests an activation process that is not observed when the iodonium salt is heated in the absence of the catalyst. Moreover, formation of nanoparticles was observed by TEM when a stoichiometric amount of the diaryliodonium salt was heated with the catalyst, strongly suggesting the need for an interaction between these components in order to achieve nanoparticle formation.

Although the exact scenario for the formation of nanoparticles is difficult to describe, the combination of data collected from the several characterization and kinetic measurements allows us to propose a CuO nanoparticle formation mechanism. The formation of the particles is initiated by ripening of CuO from the surface by interaction with the diphenyliodonium salt and consequent agglomeration. The likely-formed negatively-charged nanoparticles would promote removal of the counterion from the I(III) salts and consequently favor stabilization by the cationic diaryliodonium species. Once the starting material (diaryliodonium) is consumed, the particles could deaggregate and redeposit on the support.

The original description of the magnetic catalyst by Yus and co-workers<sup>24</sup> mentions a homogeneous distribution of copper on the magnetite and the absence of nanoparticles by TEM imaging. Hence, our findings suggest that the observed particles could be formed *in situ* during the reaction. To the best of our knowledge, this phenomenon has not yet been described for copper-based amorphous heterogeneous precursors in direct C–H functionalization reactions.<sup>32,33</sup>

#### **REACTION MECHANISM**

To gain more insight into the reaction mechanism we considered 3 main pathways:

- a) A single electron transfer (SET) from Cu(II) to promote the homolytic reduction of the diaryliodonium salt with a concomitant formation of a phenyl radical.<sup>34</sup>
- b) A Cu(I)/Cu(III) cycle initiating with a Cu(I) species from the Cu(II) precursor through either reduction by the nucleophile or disproportionation of Cu(II).<sup>12</sup>
- c) A Cu(II) induced dissociation of the counterion of the diaryliodonium salt generating a highly electrophilic aromatic species followed by attack from the heteroarene.<sup>12c</sup>

Copper-catalyzed Meerwein C-H arylation reactions are known to involve the generation of an aryl radical species from suitable precursors such as diazonium salts.<sup>35</sup> In a similar fashion, we considered that an SET from Cu(II) to the diaryliodonium salt could induce the formation of an aryl radical. In order to determine if this pathway was operative, we prepared radical clock substrate 3cyclopropylthiophene (1j) to use as a probe for the wellestablished radical clock reaction (Scheme 5).<sup>36</sup> Under our standard reaction conditions we observed a mixture of both the C2- and C5-monoarylated regioisomeric products (3j and 3j' in a 2:1 ratio respectively) as well as the C2,5-bisarylated product. These three arylated products were obtained in 52% combined yield. The mixture was isolated by preparative HPLC and fully characterized as the corresponding arylated cyclopropylthiophenes (3j, 3j' and 3j"), strongly suggesting that the arylation reaction is not operating via a radical mechanism. Moreover, addition of radical inhibitors such as dibutylhydroxytoluene (BHT) and 1,1-diphenylethylene did not affect the reaction yield.

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<sup>a</sup>For reaction conditions see Scheme 2 and SI.

Previous work by Gaunt and coworkers has suggested the possibility of a Cu(I)/Cu(III) catalytic cycle from the reduction or disproportionation of Cu(II).12 This proposal on the *meta*-arylation of acetanilides has been supported by density functional theory (DFT) calculations from the groups of Li and Wu.<sup>37</sup> Futhermore, Stahl and Ribas have achieved the isolation and characterization of Cu(III) complexes.<sup>38</sup> In the proposed Cu(I)/Cu(III) catalytic cycle, the diaryliodonium salt oxidatively adds to a Cu(I) species forming a putative highly electrophilic Cu(III)-aryl species. Reaction of this electrophilic species with the heteroarene would be facilitated by its intrinsic nucleophilicity. Reductive elimination would regenerate Cu(I) and release the product from the catalytic cycle. Alternatively, Gaunt and co-workers proposed a counterion dissociation facilitated by the metal to account for the selectivity that they observed in uncatalyzed reactions with diphenyliodonium salts.<sup>12C</sup> Hence, we conducted a series of experiments to gain a better understanding of the reaction mechanism. A competition experiment between an electron-rich and an electron-poor thiophene (1a and 1a") led to the preferential formation of 3b, indicating a preference for electron-rich heteroaryl-substrates (Scheme 6A). Moreover, a competition experiment between two electronically different iodonium salts (2b and 2c) favored formation of **4b**, suggesting a preferred reactivity with more electrophilic coupling partners (Scheme 6B). A competition KIE of 0.8 was observed for the standard reaction suggesting that C-H activation is not involved in the rate determining step.<sup>39</sup> Moreover, we observed the selective transfer of the least sterically hindered arene when employing unsymmetrical diaryliodonium salts. Together, these results suggest that an electrophilic aromatic substitution mechanism promoted by transition metal catalysis is taking place under our reaction conditions.



Scheme 6. Competition experiments between electronically distinct thiophenes (A) and electronically distinct iodonium salts (B)<sup>a</sup>

<sup>a</sup>For reaction conditions see SI. For experiment A, yields given are isolated. For experiment B, yields were determined by GC-FID.

We also observed a change in the reaction rate when we preheated the catalyst for 4 hours in the presence of diphenyliodonium tetrafluoroborate (2a). After adding 2-nbutylthiophene (1a), the induction period of the reaction was reduced to 30 min. TXRF measurements of the preheated solution showed a higher amount of dissolved copper compared to preheated solutions of only the catalyst or a mixture of CuO/Fe<sub>3</sub>O<sub>4</sub> and 2-n-butylthiophene (1a) (see SI, page S40). This result suggests an interaction between the catalyst and the iodonium salt being a critical step of the catalytic cycle. Although, we have no conclusive evidence of this interaction either resulting in an oxidative addition of the iodonium salt to the copper catalyst or a catalyst-promoted dissociation of the counterion, the results of EFTEM analysis showed the presence of only Cu(II) oxide species in solution. Several mass spectrometry techniques showed no evidence of copperaryl or any copper-based ionizable species in solution. Considering the combination of these results, it is likely that a redox-neutral process featuring a metal-promoted counterion dissociation is taking place in our reaction.

#### CONCLUSIONS

A reusable copper impregnated on magnetite system was used to catalyze the direct arylation of electron-rich heteroarenes. Under mild and operationally simple reaction conditions, acceptable to good yields and high regioselectivities were obtained using diaryliodonium salts as coupling partners. A radical clock experiment, KIE measurement and competition tests preclude a radical mechanism and suggest either a metal-promoted counterion dissociation from the iodonium salt or a Cu(I)/Cu(III) cycle as plausible reaction mechanisms.

Importantly, a series of experimental methods including kinetic studies, filtration tests and various analytical techniques indicate the formation of a soluble active catalytic species. Further characterization provided evidence for the likely generation of nanoparticles from the amorphous heterogeneous precursor. This finding represents a starting point on the comprehension of active catalytic species on C–H functionalization reactions using copperbased catalytic systems, and could be considered a beginning on questioning whether other copper-based transformations (regardless of being "homogeneous" or "heterogeneous") might be catalyzed by *in situ* generated nanoparticles.<sup>40</sup>

#### ASSOCIATED CONTENT

**Supporting Information**. Experimental details, characterization data, and copies of NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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