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# Ferrocene-Labelled Carbon-Encapsulated Iron Nanoparticles: The First Magnetic Nanocatalysts for C-H Arylation Toward 1,1'-Biphenyl Formation

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#### **ABSTRACT**:

The first magnetic nanocatalysts for C-H arylation toward 1,1'-biphenyl formation are described. The nanocatalysts are based on the conjugates of ferrocene and carbon-encapsulated iron nanoparticles. The highest catalytic activity was found for ferrocene conjugated to carbon-encapsulated iron nanoparticles via the *N*-methylpyrrolidine moiety. In the presence of the nanocatalyst, various 1,1'-biphenyls can be obtained with high yields (84-90%). The effect of substitution of the aniline's phenyl ring on the reaction yield is also included in this work. The nanocatalyst can be easily separated from the reaction mixture and can be reused up to four reaction cycles without any loss of its high catalytic activity. Our work sheds a light on potential application of functionalized carbon-encapsulated iron nanoparticles in modern, industrial organic processes towards more economical manufacturing of organic compounds.

KEYWORDS: C-H arylation, carbon-encapsulated iron nanoparticles, magnetic nanocatalyst, ferrocene, graphene-related material

#### **INTRODUCTION:**

The undoubted importance of 1,1'-biphenyls synthesis results from their various applications, for example in medicinal chemistry<sup>1</sup> and other applied sciences.<sup>2</sup> A number methods for 1,1'-biaryl formation have been reported, mainly metal-catalyzed homogeneous processes, such as Suziki-Miyaura coupling<sup>3</sup> (Pd-catalyzed), Kumada coupling<sup>4</sup> (Pd- or Ni-catalyzed), Negishi coupling<sup>5</sup> (Pd- or Ni-catalyzed) or Ullmann reaction<sup>6</sup> (Cu-catalyzed). These methods have been reported to produce the desired 1,1'-biaryls with high yields. Commonly, in these processes the specific and harmful reactants need to be used, such as presynthesized organozinc- or Griniard-type reagents, that require special handling under inert

conditions. Importantly, such synthetic methodologies require the use of metal-based coupling partners or metal-bearing homogeneous catalysts. This is an issue from the practical point of view, mainly because of difficult catalyst separation and recycling.<sup>7</sup> The industrial production of 1,1'-biaryls may require the use of significant amounts of highly toxic metal-containing compounds, what raises the key-issues associated with enlarging the reaction scale. This feature is also unfavorable in the field of medicinal chemistry. From the point of drug synthesis there is an urgent need to avoid the time-consuming removal of the metal artifacts from the obtained 1,1'-biaryl.<sup>8</sup> These drawbacks have stimulated the exploration of new ways of the 1,1'-biaryl synthesis, also including the methods using metal-free catalysts.<sup>9–11</sup> The immobilization of a metal-based catalyst on solid supports (including zeolites and carbon materials) is one of the most emerging concepts that enable the facile separation and recycling of the catalyst.<sup>12–15</sup> However, from the practical and industrial point of view, the common drawbacks of such concepts are (i) the complexity of the solid support preparation, as well as (ii) the requirement of applying harsh reaction conditions because of the limited contact time between the reagents and the heterogeneous catalyst.

The application of ferrocene (Fc) derivatives in catalysis is intensively studied.<sup>16,17</sup> Because of the reversible red-ox reactions of this organometallic compound, Fc may act as a catalyst in reaction paths based on various single-electron transfer oxidation or reduction processes.<sup>18–21</sup> One of the most emerging areas of catalytic applications of Fc-based compounds is the carbon-carbon bond formation toward the synthesis of biaryl motifs, termed as C-H arylation or arene C-H insertion. Several methodologies employing the Fc-based palladium complexes as the catalysts were developed.<sup>22–24,10,11</sup> In these processes a crosscoupling partner and a specific aryl derivative together with a catalysts of relatively sophisticated structure, is required. Very recently, native Fc<sup>25–28</sup> or the conjugate of Fc and graphene oxide<sup>29</sup> were reported as the catalysts for the diverse C-H arylation reactions. These

catalysts enabled the synthesis of various 1,1'-biphenyls in high yields, about 80 %. This disclosure shows a potential of Fc in modern homogenous and heterogeneous catalysis.

Graphene-related nanostructures are the essential class of solid supports in heterogeneous catalysis, owing to their high chemical inertness, high surface area and high surface electron density resulting in a  $\pi$ - $\pi$  staking phenomenon.<sup>30–32</sup> Carbon-encapsulated iron nanoparticles (CEINs) are the unique core-shell carbon nanomaterial. The iron core in CEINs is covered by a carbon shell comprising the curved graphene layers.<sup>33–35</sup> The mean diameter of CEINs is 30-50 nm. The carbon shell in CEINs prevents the metallic core after oxidation and limits spontaneous aggregation of nanoparticles. CEINs have similar surface properties as, e.g., few-layer graphene. The presence of magnetic core makes this material mobile at an external magnetic field and facilities its separation from solutions.<sup>33</sup> Many diverse synthetic methodologies for the surface functionalization of CEINs have been reported<sup>34,36–39</sup>, enabling new and prospective applications of CEINs. Importantly, CEINs-based materials meet the concept of magnetic nanocatalysis, which has been intensively explored research area in recent years.<sup>40–44</sup> The magnetic nanocatalysis enables to omit the drawbacks of homogenous catalysis, such as time-consuming recovery and reuse of a catalyst and sophisticated experimental procedures. The recent literature points many examples of catalytic applications of carbon-encapsulated magnetic nanoparticles<sup>35,38,40,45,46</sup>, elucidating a great potential of these materials in modern synthetic chemistry.

Here we report the conjugates of Fc and CEINs as a new nanocatalyst for C-H arylation reaction toward 1,1'-biphenyl formation. To the best of our knowledge, this study reports for the first time the catalytically active magnetic materials for this process. The synthesis of the nanocatalyst is simple, as well as the 1,1'-biphenyls can be produced in high yields from the commercially-available reactants.

#### **EXPERIMENTAL DETAILS**

Full experimental details are listed in the Experimental Section (see Section S1 in Supplementary Information).

General procedure for 1,1'-biphenyls formation using **CEINs-Fc-1-CEINs-Fc-3** as the nanocatalyst:

A flask equipped with a stirring bar was charged with aniline or given aniline derivative (0.8 mmol; 2 eq), HCl<sub>aq</sub> (168  $\mu$ L, 200.0 mg, 2 mmol; 12M HCl<sub>aq</sub> added; 2.5 eq per 1 eq of aniline) and acetone (1.5 mL). The content of the flask was cooled to 0°C using an ice bath. A solution of NaNO<sub>2</sub> (56.3 mg, 0.816 mmol; 1.02 eq per 1 eq of aniline) in a minimal amount of distilled water was slowly added at 0-5°C. The mixture was stirred for 7.0 min at 0-5°C. The as-obtained benzenediazonium salt was subjected to the reaction flask containing benzene (35.7  $\mu$ L, 31.3 mg, 0.4 mmol; 1 eq) and the given amount of nanocatalyst (**CEINs-Fc-1** - **CEINs-Fc-3**; 0.05 eq of ferrocene) in acetone (3 mL). The reaction mixture was sonicated at 25 °C for 5 hours. The nanocatalyst was then separated from the reaction mixture using a neodymium magnet. The supernatant was separated from the nanocatalyst. The supernatant was diluted with hexane (10 mL) and washed with saturated NaHCO<sub>3</sub> (2 mL), water (3 mL) and brine (2 mL). The organic layer was dried with anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure. After purification of the product by means of PTLC, 1,1'-biphenyl or a desired derivative of 1,1'-biphenyl was obtained (see data in Tables 1-4 for the reaction yields and conditions).

#### **RESULTS AND DISCUSSION**

The synthesis of Fc-labelled CEINs was performed employing the protocols previously reported by our group. The structures of the materials (CEINs-Fc-1-CEINs-Fc-3)

are presented in **Fig. 1**. The materials were obtained (i) via the one-step cycloaddition reaction (**CEINs-Fc-1**<sup>47</sup>, **CEINs-Fc-2**)<sup>48</sup>, or (ii) employing the three-step protocol (**CEINs-Fc-3**)<sup>49</sup>. Note that the materials differ in the type of linker between CEINs and Fc, as well as in content of Fc moiety: 21.2 wt%, 16.3 wt% and 6.3 wt%, for **CEINs-Fc-1**, **CEINs-Fc-2** and **CEINs-Fc-3**, respectively. Importantly, the cyclic voltammetry studies revealed the electrochemical activity of the nanoconjugates, because the fully reversible red-ox processes for Fc ligand attached to CEINs was observed.<sup>47–49</sup> Note that the microscopic studies (TEM) of various functionalized CEINs (including **CEINs-Fc-2**) revealed that the core-shell morphology of the obtained materials is retained after their surface modification, as well as no surface degradation after the functionalization is observed.<sup>39,45,48,50</sup>



Fig. 1. Structures of studied conjugates.

The nanoconjugates were tested as nanocatalysts for C-H arylation in formation of 1,1'-biphenyl (**Table 1**). The reaction conditions were optimized using the **CEINs-Fc-1** material as the nanocatalyst and benzene and aniline as the reactants. The experimental details are given in the experimental section.<sup>51</sup> In brief, the first step involved the treatment of aniline (1) with sodium nitrite in the presence of hydrochloric acid. The as-obtained benzenediazonium salt (2) was subjected to a reaction flask containing benzene and the nanocatalyst in organic solvent.<sup>52</sup> The obtained results are summarized in Table 1. The highest reaction yield (90%) was observed for the reaction of 2 eq of aniline and 1 eq of benzene in

the presence of 0.05 eq of Fc-labelled nanocatalyst in acetone (Table 1, entry 6).<sup>53</sup> It is noteworthy that no product was formed without a catalyst added (Table 1, entry 1). Secondly, the usage of pristine CEINs as a nanocatalyst did not result in formation of the product (Table 1, entry 2). It means that the presence of Fc moiety on the surface of CEINs is essential for the desired reaction path.

*Table 1*. Optimization of the reaction conditions using CEINs-Fc-1 material as the nanocatalyst.

	NH <sub>2</sub>	NaNO <sub>2,</sub> H( 0-5 °C H <sub>2</sub> O/solve	$\frac{CI}{nt} \begin{bmatrix} N_2^+ CI^- \\ 0 \end{bmatrix} \frac{1}{5 \text{ mol}\%}$	Fc (CEINs-Fc-1) 25 °C solvent	3	
Entry	Benzene	Aniline	Fc (mass of the	Solvent [first	Reaction time	Reaction
	[eq]	[eq]	nanocatalyst)	step mL +	[h] <sup>b</sup>	yield [%] <sup>c</sup>
			[eq]([mg]) <sup>a</sup>	second step		
				mL]		
1	1 <sup>d</sup>	1	- (no catalyst added)	Acetone	9e	0
				(1.5+3)		
2	1 <sup>d</sup>	1	- (30 mg of native	Acetone	9e	0
			CEINs used)	(1.5+3)		
3	2	1 <sup>d</sup>	- (30 mg of native	Acetone	9e	0
			CEINs used)	(1.5+3)		
4	1 <sup>d</sup>	1	0.05 (17.5)	Acetone	6	75
				(1.5+3)		
5	2	1 <sup>d</sup>	0.10 (35.0)	Acetone	5	87
				(1.5+3)		
6	<b>1</b> <sup>d</sup>	2	<b>0.05</b> (17.5)	Acetone	5	90
				(1.5+3)		
7	2	1 <sup>d</sup>	0.05 (17.5)	DMSO	7	75
				(1.5+3)		
8	4	1 <sup>d</sup>	0.05 (17.5)	Acetone	6	84
				(1.5+3)		
9	2	1 <sup>d</sup>	0.05 (17.5)	Acetone	9	79
				(1.5+3)		

<sup>a</sup> calculations based on TGA data for Fc content in CEINs-Fc-1,

<sup>b</sup> reaction progress tracked with TLC,

- <sup>c</sup> isolated yields,
- <sup>d</sup> 1 molar equivalent refers to 0.4 mmol of reactant,
- <sup>e</sup> no conversion of reactants into desired product observed.

The catalytic performance of CEINs-Fc-1 was compared with CEINs-Fc-2 and CEINs-Fc-3 (Table 2). All the nanocatalysts had the catalytic activity in formation of 1,1'biphenyl. Noteworthy, CEINs-Fc-2 exhibited similar catalytic activity as CEINs-Fc-1 (Table 2, entries 2-3). This feature can be ascribed to the similar Fc content in these materials and to the similar linkage between Fc ligand and the surface of CEINs. Interestingly, the catalytic performance for CEINs-Fc-3 (Table 2, entries 4-5) was lower than for CEINs-Fc-1 and CEINs-Fc-2. The first reason of this phenomenon might be associated with the lower content of Fc ligand for CEINs-Fc-3 than for the other materials. Thus, higher mass of the catalyst lowers dispersion stability of the material in organic solvent, because of the higher tendency of the nanoparticles to aggregate. Note that the yield of the process did not change after increasing twice the volume of the solvent for the reaction (Table 2, entry 5). The longer aliphatic linker between Fc and CEINs might enable the attack of the as-generated aryl radicals to the graphene-like surface of CEINs. Graphene-related surfaces are indeed known to readily reacts with radicals.<sup>54–56</sup> This hypothesis was evidenced via the analysis of FT-IR spectra. The spectrum of CEINs-Fc-3 after the catalytic reaction clearly differs from the spectrum of the material before the process.<sup>57</sup> The new absorption bands located at 1595 and 695-620 cm<sup>-1</sup> were indeed ascribed to the introduction of benzene-type moieties on the surface of CEINs. Importantly, such difference in the FT-IR spectra of the nanocatalyst after the reaction was observed neither for CEINs-Fc-1 nor for CEINs-Fc-2.58 This means that these materials did no undergo any side-processes with the aryl radicals, most plausibly because of higher 'packing' of the CEINs' structure with Fc moieties for CEINs-Fc-1 and CEINs-Fc-2 than for CEINs-Fc-3. The performed DLS measurements revealed that the **CEINs-Fc-1** nanocatalyst exhibit the lowest mean hydrodynamic diameter (560 nm) among all the studied materials (**CEINs-Fc-2**: 680 nm, **CEINs-Fc-3**: 880 nm) (size distribution diagrams are presented in Section S5 in Supplementary Information). This feature can be further ascribed to higher catalytic activity of **CEINs-Fc-1** material in comparison to other nanocatalysts, because of the higher surface area, easier accessibility of the Fc ligand and the lower tendency of the nanocatalyst to aggregate.

*Table 2*. Catalytic performance of CEINs-Fc-1, CEINs-Fc-2 and CEINs-Fc-3, together with a reference test for pristine CEINs.



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- <sup>a</sup> calculations based on TGA data for Fc content in the given nanocatalyst,
- <sup>b</sup> reaction progress tracked with TLC,
- <sup>c</sup> isolated yields,
- <sup>d</sup> acetone (1.5+3 mL) used as solvent,
- <sup>e</sup> no conversion of reactants into desired product observed,
- <sup>f</sup> acetone (3+6 mL) used as solvent.

The results for the designed coupling reaction using **CEINs-Fc-1** as the catalyst were compared with the catalytic activity of previously reported homogenous and heterogeneous catalysts for desired C-H arylation (**Table 3**). The direct comparison of these data brings a conclusion that the herein developed nanocatalyst provides the highest reaction yield in the shortest reaction time and under the mildest conditions. Note that this conclusion is also true for the application of native Fc as the catalyst (Table 3, entry 2). Our method does not require (i) the use of high molar equivalents of other additives (Table 3, entry 3) or (i) the use of high mass of a catalyst (Table 3, entry 5). It is noteworthy that in a contrary to the method employing the catalyst of relatively sophisticated structure (Table 3, entry 4), **CEINs-Fc-1** preparation method is a simple one-step process, employing commercially available and low-cost reactants. Thus, our synthetic methodology enables more economical manufacturing of biphenyls. Additionally, the magnetic properties of the developed catalyst allow for its easy separation from the reaction mixture (**Fig. 2a**). This feature makes our nanocatalyst easy to recover and recycle, which are very important topics in terms of potential application of this material in industrial processes.

After separation of **CEINs-Fc-1** from the reaction mixture, the nanocatalyst was washed with acetone, dried in oven at 50 °C for 1 day and reused. The recyclability studies with **CEINs-Fc-1** revealed that the developed nanocatalyst can be used up to four reaction

cycles without any loss of its activity (**Fig. 2b**). For the fifth cycle a 6% decrease in the reaction yield was observed.<sup>59</sup> It is likely that this slight loss of activity after recycle #4 might be associated with lowering of the dispersion stability of the nanocatalyst after the reaction cycles.<sup>60</sup> It should be highlighted that no changes in the FT-IR spectrum for **CEINs-Fc-1** between the reaction cycles were observed.<sup>61</sup>



*Fig. 2.* (a) Dispersion of CEINs-Fc-1 in acetone (2 mg/mL) (left) and magnetic response in presence of neodymium magnet (right), (b) recyclability study of CEINs-Fc-1 (for the reaction scheme, see Table 2)

#### Table 3. Comparison of catalytic performance CEINs-Fc-1 with previously reported catalysts

for 1,1-biphenyl (3) formation using aniline and benzene as the reactants.

$ \begin{array}{c} & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & $								
Entry	Catalyst/additives	Molar	Reaction	Reaction	Reaction	Reference		
		equivalent	time [h]	temperature	yield			
		of the		[°C]	[%]			
			catalyst					
		[eq]						
1	Fe CEINS-Fc-1	0.05ª	5	0-25	90	This work		
2	ferrocene	0.10	8	rt	84	25		
3	p-toluenesulfonic acid	2.00	30	50	55	62		
	triethylorthoformate	1.00						
	copper (I) chloride	0.10						
4	phenalenyl based-catalyst <sup>b</sup>	0.025	12	rt	78	63		
	tetrakis(dimethylamino)ethylene	0.05						
5	K-10 montmorillonite	_c	15	110	90	64		

<sup>a</sup> it refers to 17.5 mg of material,

<sup>b</sup> 9-methylamino-1-ethoxyphenalenium tetrafluoroborate,

<sup>c</sup> 2 g of the catalyst per 1 mmol of aniline.

In order to explore the effect of substitution on the yield of the designed catalytic reaction, various anilines were used in the **CEINs-Fc-1**-catalyzed process (**Table 4**). The anilines bearing the electron donating (i.e.  $CH_3$ ,  $OCH_3$ , Br; Table 4, entries 1-4) or electron withdrawing (i.e.  $NO_2$ , Table 4 entries 5-6) substituents were tested. The reaction yields with nitroanilines (93-90%) were slightly higher than for the native aniline (90%). The presence of the electron donating group in the phenyl ring provided slightly lower reaction yields (88-84%). Such a trend is in a good agreement with the data for the reactions catalyzed by the

native Fc.<sup>25</sup> The reaction yields for *para*-substituted anilines were slightly higher (1-2%) than for the respective *orto*-derivatives, most plausibly due to the steric effect of the substituent.

 Table 4. The effect of aniline substitution on the yield of the developed CEINs-Fc-1 

 catalyzed reaction.



<sup>a</sup> for the native aniline (1,1'-biphenyl obtained) the yield of the reaction is 90%,

<sup>b</sup> isolated yields,

<sup>c</sup> reaction time: 5 h, 0.05 eq of the nanocatalyst.

The proposed reaction mechanism is presented in **Fig. 3**.<sup>25,28</sup> It involves a single electron transfer that take place between the aryldiazonium salt and Fc-templated nanocatalyst with subsequent formation of an aryl radical (Fig. 3a). In the second step, the aryl radical intermediate with benzene is formed (Fig. 3b). Finally, a single-electron oxidation reaction followed by acid-base reaction with Cl<sup>-</sup> (generated in the first step) restores the Fc catalyst and provides the desired 1,1'-biphenyl (Fig. 3c). The first factor that influences on the high catalytic activity of the studied materials is clearly ascribed to the presence of Fc moieties on surface of CEINs. Adsorption of reactants on graphene-like surface of CEINs during the chemical reaction<sup>30,65,66</sup> is believed to be a synergistic interface effect that increases the catalytic activity of the studied materials.



*Fig. 3.* Proposed reaction mechanism: (a) generation of aryl radical, (b) formation of aryl radical intermediate with benzene, (c) formation of 1,1'-biphenyl.

#### CONCLUSIONS

In conclusion, we presented high catalytic activity of CEINs grafted with Fc in formation of various 1,1'-biphenyls employing the C-H arylation process with commercially available reactants. The highest catalytic activity was found for the nanoconjugate bearing the *N*-methylpyrrolidine moiety. The synthesis path for this material is simple and is based on the one-step reaction. The pure 1,1'-biphenyl was obtained in 90% yield under mild conditions at short reaction time (5 h) using 0.05 molar equivalent of Fc-templated nanocatalyst. The substitution of the aniline's phenyl ring with electron-withdrawing groups provided higher reactions (93-91%) in comparison to the electron-donating groups (88-84%). The catalyst can be easily separated from the reaction mixture, as well as can be used up to four reaction cycles without any loss of its activity. This work lays sheds a new light on the C-H arylation reactions employing the magnetic nanocatalysts, towards their application in modern, industrial organic processes.

#### ASSOCIATED CONTENT

#### **Supporting Information**

Experimental	section,	NMR	and	FT-IR	data.
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The Supporting Information is available free of charge on the ACS Publications website.

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#### **AUTHOR CONTRIBUTIONS**

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

#### NOTES

The authors declare no competing financial interests.

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