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# Short communication

# Phosphine and palladium-free synthesis of aryl and alkenyl boronates: A nano-catalytic approach



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# ABSTRACT

Superparamagnetic copperferrite nanoparticle is employed as an environmentally benign and efficient catalyst to affect the borylation of aryliodides yielding the corresponding arylboronates at low catalyst loading under mild reaction conditions. This protocol tolerates various substituents present in aryl iodides and also could be extended to beta bromostyrenes in the absence of phosphine and palladium.

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# 1. Introduction

Arylboronic esters are important class of benchmark reagents with broad utility in the area of organic synthesis. Because of their unique chemical properties such as broad functional group availability, air stability, and ease of handling, they have been considered as important building blocks in organic synthesis, and as a consequence, they undergo a wide range of transformations that lead to the formation of C—C and C—X (X = heteroatom) bonds. The phenylboronic acid skeleton is a privileged structure in medicinal chemistry for the discovery of pharmaceutical leads. Boron-based compounds exhibit various important biological activities [1]. Kong and colleagues utilized boronic acids as antimitotic agents (I and II) and bortezomib (III), a proteasome inhibitor, has been well known for anticancer therapy (Fig. 1) [2].

The traditional synthesis of arylboronic acids was accomplished via the reaction of aromatic organomercury compounds with borane solution followed by hydrolysis furnish arylboronic acids [3]. Various studies have reported that direct synthesis of arylboronic acids from aryl halides employing homogeneous palladium complex [4–9]. Compared to boronic acids, boronates are environmental friendly, easy to handle, air and chromatography-stable.

\* Corresponding author. *E-mail address:* chemistry@pusan.ac.kr (K.H. Park). Heise et al. successfully prepared the boronate derivatives with the reaction of glycol borates and Grignard reagents at room temperature under mild conditions [10]. Chavant et al. described the synthesis of aryl boronic esters through metal-halogen exchange reaction between iPrMgCl·LiCl and aryl iodides at 0 °C using cyclic borate esters [11]. Alternate approaches admit transition-metal catalysts for syntheses of arylboronic acid esters via activation of C—H and C—X bonds. Among those, palladium, nickel, iridium and recently copper complexes or salts in combination with toxic phosphine ligands was employed for borylation to take place [12–21]. Notably, Zhang and co-workers were noticed the borylation of aryl iodides through cesium effect under transition-metal free conditions [22], followed by Kiatiesevi et al. employed palladium as catalyst along with copper co-catalyst and triphenylphosphine to effect borylation take place at C—I bond of aromatics [23].

Conversely, there is significant interest in the development of transition metal nanoparticles for technological applications in various areas such as chemical sensors, electrocatalysts for fuel cells, and heterogeneous catalysts for organic transformations. We wondered if the nanocatalytic system could be complementary to aforementioned protocols that involved phosphine and overcome by means of a spinel bimetallic nanoparticles as catalysts to effect borylation of haloarenes. Since the catalytic activities of nanoparticles largely dependent on the surface design of the support along with the size and shape of the metal nanoparticles, the quest for more suitable solid supports for copper nanoparticles to provide highly active and selective catalyst is a challenging problem.



Fig. 1. Some biologically active organoboron compounds.

In the course of a program devoted to the discovery in designing a new nanoparticle catalysts for efficient organic transformations [24–31], we were interested in the synthesis of arylboronates using cost-

effective, readily available and magnetically recoverable copper ferrite nanoparticles is used as a catalyst to prepare arylboronates from aryl iodides under mild conditions. Of particular importance, we discovered

#### Table 1

Optimization of reaction conditions.



<sup>a</sup> Determined by GC–MS.

<sup>b</sup> Reaction with micro copper powder catalyst.

<sup>c</sup> CuO nanopowder.

<sup>d</sup> CuO hollow spheres.

<sup>e</sup> Cu<sub>2</sub>O nanocubes.

<sup>f</sup> Copper nanoparticles.

<sup>g</sup> Iron oxide nanoparticles.

#### Table 2

Evaluation of substrate scope.



#### R = electron donating or withdrawing

Entry	Arylhalide	Product	Yield (%) <sup>a</sup>
1		BPin	71
2		BPin	72
	Me	Me	
3		BPin	89
4	✓ Me	BPin Me	77
	Me	Me	
5		BPin	62
		$\bigcirc$	
6	OMe Me	OMe Me	40
		BPin	
7		BPin	45
		$\bigcirc$	
0	COOCH <sub>2</sub> Me	COOCH <sub>2</sub> Me	12
8		NC	42
9	F <sub>3</sub> CI	F <sub>3</sub> C BPin	81
10		BPin	59
11	CF <sub>3</sub>	CF <sub>3</sub> BPin	32
12			68
12		PinB-BPin	08
13		BPin	58
14	F I	F-BPin	81
15	Meo	MeO	Trace <sup>b</sup>
16			Trace <sup>c</sup>
17	MeO	MeOBNeop	ND
17	MeO	MeO-BPin	ND.

<sup>a</sup> Yield was determined by GC–MS includes ArH side products.

<sup>b</sup> 4-lodoanisole (1 mmol), HBPin (1.5 mmol), NaH (1.5 mmol), CuFe<sub>2</sub>O<sub>4</sub> (5 mol%), THF (5 mL), RT for 12 h under argon with magnetic stirring.

<sup>c</sup> Bis(neopentyl glycolato)diboron was used as borylating agent under Table 1 conditions.

the beneficial synergistic effect of  $CuFe_2O_4$  nanoparticles on the reaction efficiency. In this letter, we only show the  $CuFe_2O_4$  NPs catalyzed borylation of iodoarenes in the combination of an inexpensive, environmentally benign boron source  $B_2Pin_2$  in air under ligand-free conditions. In addition, all reagents used in this paper are commercially available and bench stable, eliminating the use of glove box.

# 2. Experimental

# 2.1. General description

Reagents were purchased from Aldrich Chemical Co., TCI and Strem Chemical Co. and used as received. CuFe<sub>2</sub>O<sub>4</sub> nanoparticles were procured from Aldrich; Catalog No. 641723. All compounds reported have been well known and their mass splitting pattern consistent with existing literature. Reaction products were analyzed by GC–MS (Shimadzu-QP2010 SE).

#### 2.2. General procedure for borylation of iodoarenes

4-Iodo anisole (0.813 mmol, 200 mg), bis(pinacolato) diboron (1.219 mmol, 309 mg) were dissolved in 3 mL of dmf followed by copper ferrite nanoparticles (5 mol% with respect to 4-iodo anisole) and potassium tert-butoxide (1.219 mmol, 137 mg) were added to a 10 mL capped vial and stirred at RT for time indicated. After stirring, the mixture was diluted with diethyl ether and filtered through celite bed. The filtrate was extracted with water (3 times) and the organic phase was dried over anhydrous MgSO<sub>4</sub>. The crude product was subjected to analyze by GC–MS. The conversion yield is accurately measured based on the consumption of 4-iodo anisole and the side product formed due to protodeiodination.

# 3. Results and discussion

# 3.1. Catalytic activity

We began a careful optimization study with the arylation of 4iodoanisole (1 mmol) with bis(pinacolato)diboron (1.5 mmol) and base (1.5 mmol). No reaction was observed in the absence of copper catalyst (Table 1, entry 1). However, the use of 2.5 mol% of CuFe<sub>2</sub>O<sub>4</sub> NPs proved to be satisfactory, with moderate conversion being achieved (Table 1, entry 2). Slight increase to 5 mol% proved to be optimal, with good conversion (Table 1, entry 3). The use of a 10 mol% of catalyst gave a comparable yield to that of the 5 mol% of the copper ferrite NPs

#### Table 3

Br + B <sub>2</sub> Pin; E:Z 83:17	2 3mL dmf, 1d, RT 1.5eq base E:Z 89:11			
Entry	β-bromostyrene	Product		
1	Br	BPin		
2	Br	BPin		
3	Br	BPin		
4	Br	BPin		
5	Br	BPin		
6	Br	BPin		
7	CI Br	BPin		

CuFe<sub>2</sub>O<sub>4</sub> NPs catalyzed borylation of  $\beta$ -bromostyrene<sup>a</sup>.

a Reaction conditions: β-bromostyrene (1 mmol), B<sub>2</sub>Pin<sub>2</sub> (1.5 mmol), catalyst (5 mol% respect to β-bromostyrene), Base (1.5 mmol), dmf (3 mL), RT, 24 h.

<sup>b</sup> Determined by GC–MS includes side products from protodebromination.

<sup>c</sup> See the Supporting Information for selectivity.

<sup>d</sup> Me<sub>3</sub>COK used as base.

<sup>e</sup> LiOMe base was employed.

<sup>f</sup> 10 mol% of catalyst was used.

 $^{\rm g}$   $\beta$ -Bromostyrene was synthesized from known literature.

catalyst (not shown). Further optimization, by variation of the base, showed that lithium and sodium tertiary butoxide were produced less satisfactory results (Table 1, entries 4 and 5). Moderate yield was achieved with lithium methoxide (Table 1, entry 6). Solvents such as *N*,*N*′-dimethyl-*N*,*N*′-trimethylene urea (dmpu), dimethyl sulfoxide (dmso), tetrahydrofuran (thf), acetonitrile and toluene completely shut down the borylation and returned only unreacted starting material (Table 1, entries 7–11). Dimethylacetamide (dma) and N-methyl pyrrolidinone (nmp) were detrimental (Table 1, entries 12 and 13). Among the various sources of copper nanocatalysts examined such as micro-copper powder, commercially available CuO nanopowder [32], CuO hollow spheres, Cu<sub>2</sub>O nanocubes and Cu nanoparticles [24,33,34] were compared in order to prove superior catalytic activity and synergistic effect at the interface between copper and iron oxide nanoparticles (Table 1, entries 14-18) while borylation was ineffective with sole iron oxide nanoparticles catalyst (Table 1, entry 19).

As can be seen from Table 1, the reactivity of copper ferrite NPs is 1 to 9 times higher than copper oxide nanoparticles and clearly underlines the effectiveness of the synergistic catalysis. We hypothesize that the high efficacy of the bimetallic catalyst can also be attributed to the presence of iron may play a crucial role in activation of C—I bond and as a consequence, conversion is better than sole copper catalysts. Recently, despite the synergistic effect and other parameters, Ranu and coworkers demonstrated the role of iron present in copper ferrite NPs in the synthesis of unsymmetrical 1,3-diynes. The Lewis acidity of the Fe<sup>III</sup> center significantly contributed to the enhanced activation of the C—Br bond, whereas the same reaction with CuO NPs was ineffective. It is noteworthy that the distinct role of iron is paramount important in the reaction specified [35]. Similarly, in our case the iron would have possibly involved synergistic catalysis with copper in enhancing the oxidative addition of C—I bond, which led to higher conversion.

Yield (%)<sup>b,c</sup>

61

62<sup>f</sup>

74<sup>g</sup>

60

75

83

To the best of our knowledge, the use of a nanoparticles based heterogeneous catalyst has never been described for the borylation of aryl iodides with  $B_2Pin_2$  under ligand-free conditions. After evaluation of numerous reaction parameters, we identified that arylboronate (**3a**) could be generated in 90% yield (GC–MS) by treatment of 4-iodoanisole (**1a**) and  $B_2Pin_2$  (**2a**) in the presence of 5 mol% CuFe<sub>2</sub>O<sub>4</sub> NPs and 3 mL dmf solvent at room temperature (RT) for 12 h. We believe this work will be useful to gain some insights into nanomaterials catalyzed borylation of aryliodides, although the substrate scope was not enough at this stage. Despite, several points regarding our optimized reaction conditions (30 °C); 2) short reaction time (12 h); 3) use of low copper loading; 4) ligand free.

With an optimized set of conditions in hand, we explored further the scope and limitations of this process. As it can be seen from Table 2, our protocol tolerated wide variety of substituents including electron-withdrawing and donating groups present in the aromatic ring and afforded corresponding boronates in moderate to good yields (entries 1–14, Table 2). Reactions with other boron sources such as pinacolborane and bis(neopentyl glycolato)diboron were unsuccessful (entries 15 and 16, Table 2). Shifting of the haloarene to 4-bromoanisole was not reactive under identical conditions (entry 17, Table 2). The yield denoted in Table 2 includes the side product stem from protodeiodination of starting precursor that usually observed during borylation reaction.

To further evaluate the versatility of our catalytic system, we shifted our attention to the viability of B-bromostyrenes. We were delighted to found that phenylvinyl boronates could be obtained in good yields with high regioselectivity. The reaction of  $\beta$ -bromostyrene with bis(pinacolato diboron) underwent smoothly affording borylated product with enhanced trans-selectivity from the starting precursor under mild conditions. In fact,  $\beta$ -bromostyrenes are less reactive with copper catalysts rather than palladium in borylation reactions and to the best of our knowledge, this is the first report of borylation of sp<sup>2</sup>-carbon having bromo substituent with nanocatalysts under ligand-free conditions. When the base potassium tertiary butoxide was used, low conversion was attained (entry 1, Table 3). On the contrary, a two-fold increase of substrate conversion was observed when the base lithium methoxide was employed (entry 2, Table 3). Moreover, increasing the catalyst loading from 5 to 10 mol% seems ineffective (entry 3, Table 3). An increase in vield was observed when  $\beta$ -bromostyrene was synthesized from known procedure and used as starting material (entry 4, Table 3). Relative to aryl iodide borylation, the functionalized B-bromostyrenes containing methyl, methoxy, and chloro groups having selectivities in the E:Z ratio of 99:1 were also borylated in good to moderate yields (entries 5-7, Table 3) with slight decrease in the selectivity (see Supporting Information).

#### 4. Conclusion

In conclusion, we disclosed a simple synthetic strategy for borylation of aryl iodides and  $\beta$ -bromostyrenes with easily available and environmental-friendly bis(pinacolato) diboron, catalyzed by commercially available, inexpensive copper ferrite nanoparticles at low catalyst loading under ligand free conditions. The role of Iron in the catalyst was exemplified in terms of higher yield of products.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx. doi.org/10.1016/j.catcom.2016.07.014.

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