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Short communication

Atom economic palladium catalyzed novel approach for arylation of benzothiazole and benzoxazole with triarylbismuth reagents via C—H activation

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ABSTRACT

We have developed a novel method for the direct C—H functionalization of benzothiazole and benzoxazole using triarylbismuth reagents. The arylation proceeds using the homogeneous catalytic system $PdCl_2$, $Cu(OAc)_2$ and PPh_3 ligand. Triarylbismuthines, which act as threefold arylating reagents, have low toxicity, are green and ecofriendly. These methodologies are particularly useful to prepare arylated benzothiazoles and benzoxazoles.

1. Introduction

Transition-metal-catalyzed direct functionalization of C—H bonds represents a powerful approach for the development of more sustainable chemical processes [1]. Direct arylation of arenes is an attractive alternative to traditional cross-coupling reactions [2]. These arylation reactions of benzothiazoles and benzoxazoles achieve regioselectivity using transition metal catalysts [3–6]. These moieties are part of compounds having several biological properties such as antibacterial, antitumor and anti-inflammatory [7–9]. The synthesis of such heterocycles and their derivatives has been a topic of research as they have important applications in a variety of fields. Transition metal catalyzed C—H functionalization reactions of arenes and hetero arenes have gained more attention in the preparation of various organic and biologically important scaffolds [10]. A variety of aryl sources, such as aryl halides [11], arylboronic acids [12], iodobenzenediacetate [13], arenediazonium salts [14], aryl sulfamates [15], aryltrimethylammonium triflates [16], arene benzenesulfonyl chlorides [17] and substituted benzoic acids [18] have been used for the arylation of benzothiazoles and benzoxazoles. Some examples are given in Fig. 1.

We have used triarylbismuthines as the arylating agent for the direct C—H functionalization of benzothiazole and benzoxazole. Triarylbismuth compounds are stable, have low toxicity and can be easily prepared from aryl Grignard or lithium reagents and BiX_3 inorganic salts [19,20]. The major advantage of triarylbismuth compounds is the low Bi—C dissociation energy [21]. They also offer threefold coupling reactivity with other coupling partners under palladium catalyzed conditions [22]. They show various applications in organic transformations, either as reagents or catalysts [23].

Triarylbismuthines show various applications such as synthesis of unsymmetrical diaryl selenides [24], various arylation reactions [25,26], C—P bond formation [27] and cross-coupling with bromopyridines and bromoquinolines [28]. Organobismuth reagents are also used in S-arylation of diaryldisulfides [29], N-arylation of amines [30], azoles [31] and N-cyclopropylation of cyclic amides [32]. They also find important applications in O-arylation of N-protected 1,2-aminoalcohols [33], phenols [34], and in the synthesis of α-diimines from isocyanides [35].

To the best of our knowledge, this is the first report on the application of triarylbismuth as the arylating agent for the synthesis of benzothiazoles and benzoxazoles by C—H activation. Here, we developed a $PdCl_2$-$Cu(OAc)_2$-PPh_3 catalytic system for the arylation of benzothiazole and benzoxazole using triarylbismuth as the arylating agent.

2. Results and discussion

Initially, we have optimized various reaction parameters to develop this protocol. $PdCl_2$-$Cu(OAc)_2$ acts as a catalytic system over the model reaction of benzothiazole (**1a**) and only 0.33 equivalent of triphenylbismuth (**2a**) to get the arylated product (**3a**). The experimental results are summarized in Table 1. We first carried out the reaction

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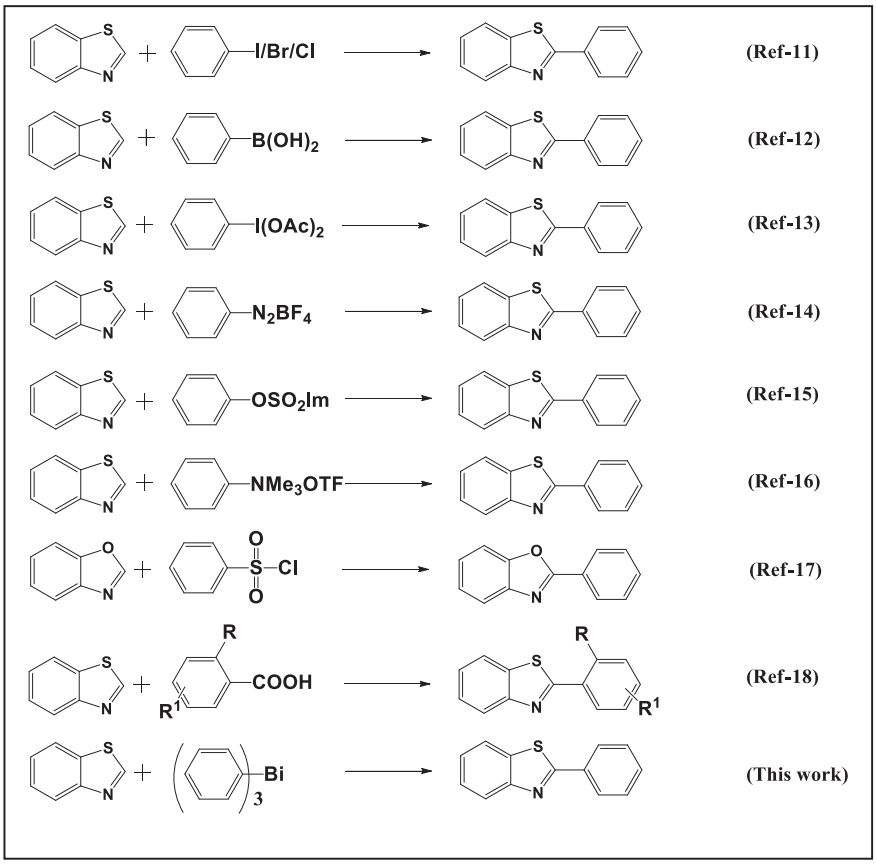
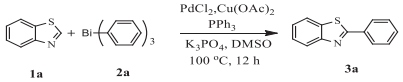


Fig. 1. Various methods for arylation of azoles via C—H activation using different arylating agents.

Table 1
Optimization of reaction parameters for benzothiazole with triphenylbismuth reagent.[a]



1a 2a 3a

Entry	Catalyst (mol%)	Ligand (mol%)	$Cu(OAc)_2$ (mol%)	Base	Solvent	Temperature	Time	Yield 3a (%)[b]
1	$PdCl_2$(5)	0	0	K_3PO_4	DMSO	100	12	6
2	0	0	10	K_3PO_4	DMSO	100	12	12
3	$PdCl_2$ (5)	0	10	K_3PO_4	DMSO	100	12	54
4	$PdCl_2$ (5)	2,2′-Bipyridine (30)	10	K_3PO_4	DMSO	100	12	16
5	$PdCl_2$ (5)	1,10-Phenathroline (30)	10	K_3PO_4	DMSO	100	12	66
6	$PdCl_2$ (5)	TMEDA (30)	10	K_3PO_4	DMSO	100	12	34
7	$PdCl_2$ (5)	DPPB (05)	10	K_3PO_4	DMSO	100	12	36
8	$PdCl_2$ (5)	DPPP (05)	10	K_3PO_4	DMSO	100	12	46
9	$PdCl_2$ (5)	DPPF (05)	10	K_3PO_4	DMSO	100	12	49
10	$PdCl_2$ (5)	PPh_3 (10)	10	K_3PO_4	DMSO	100	12	90 (87)
11	$Pd(PPh_3)_4$ (5)	0	10	K_3PO_4	DMSO	100	12	74
12	$Pd(dba)_2$ (5)	0	10	K_3PO_4	DMSO	100	12	48
13	$Pd(dppf)Cl_2$ (5)	PPh_3 (10)	10	K_3PO_4	DMSO	100	12	59
14	$Pd(PPh_3)_2Cl_2$ (5)	PPh_3 (10)	10	K_3PO_4	DMSO	100	12	72
15	$PdCl_2$ (5)	PPh_3 (10)	10	Cs_2CO_3	DMSO	100	12	34
16	$PdCl_2$ (5)	PPh_3 (10)	10	K_2CO_3	DMSO	100	12	21
17	$PdCl_2$ (5)	PPh_3 (10)	10	K_3PO_4	DMF	100	12	15
18	$PdCl_2$ (5)	PPh_3 (10)	10	K_3PO_4	water	100	12	22
19	$PdCl_2$ (5)	PPh_3 (10)	10	K_3PO_4	Dioxane	100	12	11
20	$PdCl_2$ (5)	PPh_3 (10)	10	K_3PO_4	DMA	100	12	10
21	$RuCl_2(PPh_3)_3$(5)	PPh_3 (10)	10	K_3PO_4	DMSO	100	12	15
22	$NiCl_2$ (5)	PPh_3 (20)	10	K_3PO_4	DMSO	100	12	8

[a] Reaction conditions: benzothiazole (0.5 mmol, 1 equivalent), triphenylbismuth (0.167 mmol, 0.33 equivalent), base (1.5 mmol), ligand (mol%), solvent (3 mL), 100 °C, 12 h.
[b] GC yield based on **1a**. The yield of isolated product is shown in parenthesis. PPh_3- triphenylphosphine, TMEDA-tetramethylethylenediamine, DPPB-1,4-bis(diphenylphosphino)butane, DPPP-1,3-bis(diphenylphosphino)propane, DPPf-1,1′-ferrocenediyl-bis(diphenylphosphine), $Pd(dba)_2$-bis(dibenzylideneacetone)palladium(0), $Pd(dppf)Cl_2$–1,1′-bis(diphenylphosphino) ferrocenedichloropalladium(II).

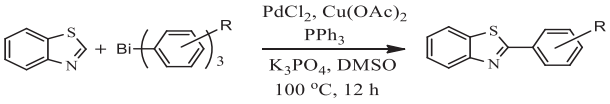
with $PdCl_2$ as a catalyst and obtained product **3a** with 6% GC yield (entry 1, Table 1). We also used $Cu(OAc)_2$ as a catalyst and obtained only 12% GC yield of **3a** (entry 2, Table 1). When we employed Pd/Cu (5:10 mol%) catalytic system, it gave 54% yield of **3a** (entry 3, Table 1). After getting these encouraging results, we tried to get better product yield of **3a** by employing various ligands. We screened various nitrogen containing ligands such as 2,2′-bipyridine, 1,10-phenanthroline and TMEDA. They showed 16%, 66% and 34% yield respectively (entries 4–6, Table 1). Phosphorus containing ligands such as DPPB, DPPP, and DPPF provided 36%, 46% and 49% yields of **3a** (entries 7–9, Table 1). We got very surprising results when we used 10 mol% PPh_3 as ligand. It offered 90% GC yield and 87% isolated yield of **3a** (entry 10, Table 1). We also tried some palladium species such as $Pd(PPh_3)_4$, $Pd(dba)_2$, $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$ along with $Cu(OAc)_2$ as a co-catalyst and PPh_3 as a ligand but obtained only 74%, 48%, 59% and 72% GC yield respectively (entries 11–14, Table 1). We also tried other bases such as Cs_2CO_3 and K_2CO_3 but got only 34% and 21% yield of **3a** (entries 15–16, Table 1). The model reaction was carried out using various solvents such as DMF, water, dioxane and DMA. The obtained results revealed that DMSO is the best solvent for this reaction (entries 17–20, Table 1). Reaction using $RuCl_2(PPh_3)_3$ and $NiCl_2$ afforded only 15% and 8% GC yield respectively (entries 21–22, Table 1). Optimized reaction parameters for the reaction between benzothiazole (0.5 mmol) and triphenylbismuth (0.167 mmol) include the catalytic system $PdCl_2$ (5 mol%), $Cu(OAc)_2$ (10 mol%), PPh_3 (10 mol%), K_3PO_4 base (1.5 mmol), DMSO (3 mL) as a solvent, at 100 °C for 12 h.

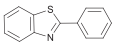
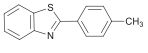
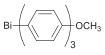
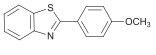
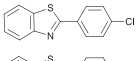
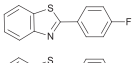
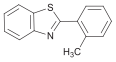
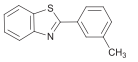
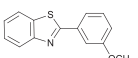
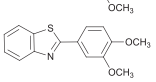
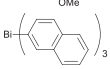
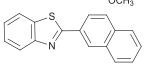
Under these optimized reaction conditions, a series of substituted triarylbismuth compounds were applied for C—H functionalization of benzothiazole. Initially, triphenylbismuth gave 87% isolated yield (entry 1, Table 2). When we used electron rich triarylbismuth derivatives such as 4-Me and 4-OMe, 78% and 86% yields were obtained (entries 2–3, Table 2). We also tested 4-chloro and 4-fluoro substituted triarylbismuth out of which 4-chloro substituted bismuth gave higher yield as compared to 4-fluoro (entries 4–5, Table 2). Sterically hindered 2-Me arylbismuth gave 62% yield (entry 6, Table 2), whereas 3-Me and 3-OMe arylbismuth afforded fairly good yields of desired products (entry 7–8, Table 2). Also, 3,4-OMe arylbismuth gave 82% yield whereas tris(2-napthyl)bismuth derivative provided 80% yield of the corresponding product (entry 9–10, Table 2).

The same reaction conditions were employed for the arylation of benzoxazole and the arylated products were obtained higher yields compared to benzothiazole derivatives. Initially, triphenylbismuth was used and offered 90% yield (entry 1, Table 3). Similarly, electron rich arylbismuth 4-Me and 4-OMe gave 85% and 90% yields respectively (entries 2–3, Table 3). Among the halo arylbismuth derivatives, arylation using 4-chloro gave good yield of the desired product whereas 4-fluoro afforded moderate yield with benzoxazole (entries 4–5, Table 3). Some sterically hindered bismuth derivatives showed 70% yield (entry 6, Table 3) whereas the 3-Me and 3-MeO afforded good yields (entries 7–8, Table 3). We also tried 3,4-MeO derivative and obtained the corresponding benzoxazole in 86% yield (entry 9, Table 3). We carried out the reaction using tris(2-napthyl)bismuth derivative which afforded good yield of the corresponding product (entry 10, Table 3). We also carried out the reaction with substituted benzoxazoles and obtained good yields of the respective arylated products (entry 11–12, Table 3).

The plausible mechanistic pathway for C—H functionalization reaction of benzothiazole is illustrated in Fig. 2. Initially, reaction between $PdCl_2$ and phosphine ligand results in the formation of complex (A) which subsequently reacts with $BiAr_3$ to form complex (B) [35]. Deprotonation of benzothiazole by K_3PO_4 and reaction with copper acetate then gives the corresponding heteroaryl copper intermediate (C) [10], which on reaction with (B) forms intermediate (D). Reductive elimination from (D) furnishes the desired arylated product (E), thus completing the catalytic cycle by regenerating complex (A).

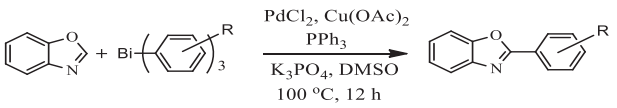
Table 2
Arylation of benzothiazole with triarylbismuth reagents.[a]

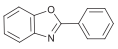
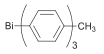
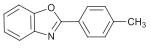
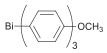
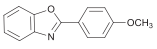
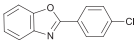
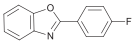
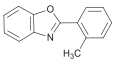
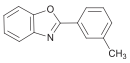
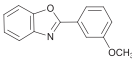
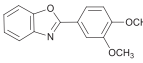
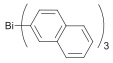
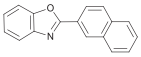
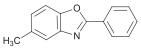
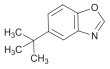
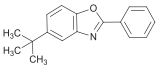


Entry	Benzothiazole	Triarylbismuth	Product	Yield[b] (%)
1				87
2				78
3				86
4				84
5				40
6				62
7				75
8				78
9				82
10				80

[a] Reaction conditions: benzothiazole (0.5 mmol), triarylbismuth (0.167 mmol), $PdCl_2$ (5 mol%), $Cu(OAc)_2$ (10 mol%), K_3PO_4 (1.5 mmol), PPh_3 (10 mol%), DMSO (3 mL), 100 °C, 12 h;
[b] Isolated product yield.

Table 3
Arylation of benzoxazole with triarylbismuth reagents.[a]



Entry	Benzoxazole	Triarylbismuth	Product	Yield[b] (%)
1				90
2				85
3				90
4				87
5				57
6				70
7				82
8				84
9				86
10				83
11				79
12				81

[a] Reaction conditions: benzoxazole (0.5 mmol), triarylbismuth (0.167 mmol), $PdCl_2$ (5 mol%), $Cu(OAc)_2$ (10 mol%), K_3PO_4 (1.5 mmol), PPh_3 (10 mol%), DMSO (3 mL), 100 °C, 12 h.
[b] Isolated product yield.

3. Conclusion

In conclusion, we have developed an effective and readily available $PdCl_2$-$Cu(OAc)_2$-PPh_3 catalytic system for the C—H functionalization of benzothiazoles and benzoxazoles with a variety of triarylbismuth compounds. The triarylbismuth reagents are stable, green, low toxic, eco-friendly and act as threefold arylating agents.

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Note: All compounds are well known and confirmed by GC–MS analysis. ^1H and ^{13}C spectra of the representative products are provided in the Supporting information.

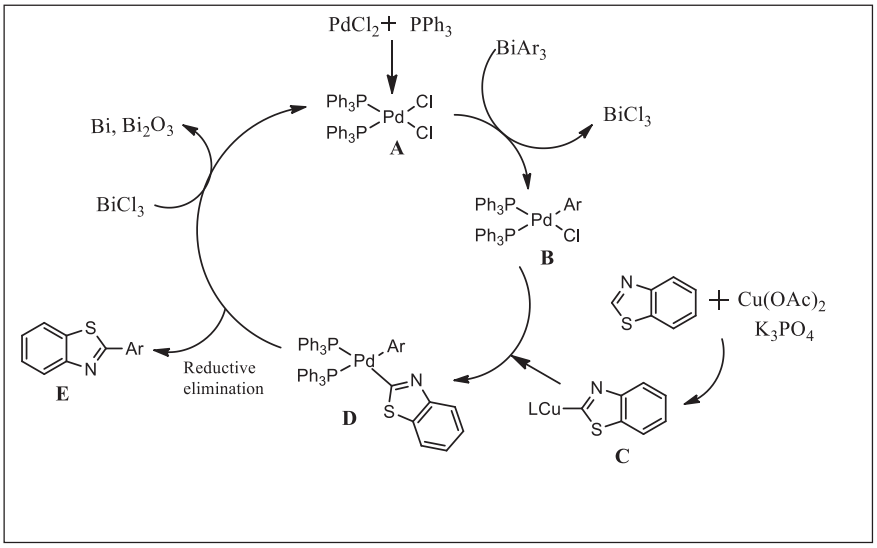

Fig. 2. Proposed mechanistic pathway for C—H functionalization reaction of benzothiazole.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2016.10.005.

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