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Palladium(0) nanoparticles-catalyzed ligand-free direct arylation of benzothiazole via C–H bond functionalization

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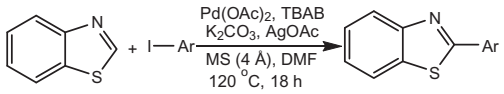
ABSTRACT

Palladium nanoparticles, generated in situ efficiently catalyzes direct 2-C–H arylation of benzothiazole without requirement of any ligand. A wide range of substituted aryl and heteroaryl iodides participate in this reaction producing a series of 2-aryl/heteroaryl-benzothiazoles in high yields.

The heteroaromatics are of much importance in organic synthesis as they constitute the core unit of many natural bioactive products[1] and are extensively utilized in pharmaceutical and material industries.[2] A typical approach to connect one heteroarene and arene nuclei via cross-coupling reaction of metalated arene/heteroarene and halogenated heteroarene/arene is widely utilized.[3] However, the direct arylation of heteroarenes by catalytic C–H activation is a more convenient process and has received considerable attention in recent times as an effective means for the synthesis of functionalized heteroarenes.[4] Several procedures using a variety of catalysts such as $Ni(OAc)_2$/bipy,[4a] $[RhCl(coe)_2]$/phosphepine ligand,[4b] $Pd(TMHD)_2$,[4c] $Pd(OAc)_2$/1-(benzhydryl)-3-(alkyl)benzimadazolium salts,[4d] $[Pd(dppf)Cl_2]\cdot CH_2Cl_2/PPh_3$,[4e] $Pd(OAc)_2$/P(biphenyl-2-yl)(*t*-Bu)$_2$,[4f] $PdCl_2(PPh_3)_2$/CuCl/polymethylhydrosiloxane,[4g] $Pd(OAc)_2/PPh_3$,[4h] CuI/PPh_3,[4i] and CuI/LiO^{t}Bu[4j] have been developed. All these procedures except one[4j] use a metal salt and a ligand for an effective reaction and most of these ligands are expensive, air sensitive and toxic and their preparation also involved tedious processes.

The use of metal nanoparticles as catalysts in organic reactions has attracted considerable attention in recent times in the context of green chemistry because of their benign character and ease of preparation.[5] Moreover, they show enhanced catalytic efficiency because of their better ability to transfer electrons and large surface area to volume ratio.[6] As a part of our continuing program to explore the novel applications of metal nanoparticles[7] we report herein C–H functionalization of benzothiazole by aryl iodides catalyzed by in situ generated palladium nanoparticles without the use of any ligand (Scheme 1).

To standardize the reaction conditions, a series of experiments were carried out using different solvents and varied reaction parameters for a representative reaction of 4-iodoanisole and benzothiazole. The uses of base and additive have much effect on this reaction. After trying combinations of several bases, solvents and additives, it was found that assembly of K_2CO_3/AgOAc/molecular sieves (4 Å) in DMF (18 h) produced the best results (Table 1, entry 9). In the absence of molecular sieves, the yield of product is reduced substantially (Table 1, entry 10). The use of Ag_2CO_3 in place of K_2CO_3 and AgOAc also reduced the yield of product appreciably (Table 1, entry 12). The absence of TBAB (tetrabutylammonium bromide) has a profound effect on this reaction (Table 1, entry 14). It is believed that TBAB acts as a stabilizer for Pd nanoparticles formed in situ, preventing them from fast agglomerization and thus helps in the progress of the reaction.[5d] The preformed Pd nanoparticles are not equally active in this reaction (Table 1, entry 16) possibly due to their inherent tendency for agglomerization. The amount of $Pd(OAc)_2$ generating Pd nanoparticles[7g,8] was optimized to 6.6 mol % for an effective reaction. Very



Scheme 1.

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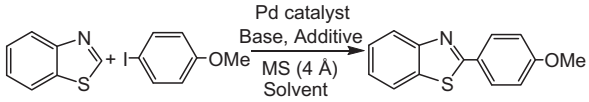
Table 1
Standardization of reaction conditions



	Pd catalyst	Base	Additive	Solvent	Temp (°C)	Time (h)	Yield (%)
1	$Pd(OAc)_2$, TBAB	K_2CO_3	—	THF	75	9	0
2	$Pd(OAc)_2$, TBAB	K_2CO_3	—	THF	75	18	10
3	$Pd(OAc)_2$, TBAB	K_2CO_3	—	NMP	120	18	0
4	$Pd(OAc)_2$, TBAB	K_2CO_3	—	DMF	120	9	20
5	$Pd(OAc)_2$, TBAB	K_2CO_3	—	DMF	120	18	30
6	$Pd(OAc)_2$, TBAB	Cs_2CO_3	—	DMF	120	18	0
7	$Pd(OAc)_2$, TBAB	KO^tBu	—	DMF	120	18	10
8	$Pd(OAc)_2$, TBAB	K_3PO_4	—	DMF	120	18	0
9	**$Pd(OAc)_2$, TBAB**	**K_2CO_3**	**AgOAc**	**DMF**	**120**	**18**	**78**
10[a]	$Pd(OAc)_2$, TBAB	K_2CO_3	AgOAc	DMF	120	18	50
11	$Pd(OAc)_2$, TBAB	K_2CO_3	AgOAc	THF	75	18	35
12	$Pd(OAc)_2$, TBAB	Ag_2CO_3	—	DMF	120	18	45
13	$Pd(OAc)_2$, TBAB	AgOAc	—	DMF	120	18	40
14	$Pd(OAc)_2$	K_2CO_3	AgOAc	DMF	120	18	45
15	$Pd(PPh_3)_4$	K_2CO_3	AgOAc	DMF	120	18	15
16	Preformed Pd nps	K_2CO_3	AgOAc	DMF	120	18	35

The bold signifies that the entry 9 provides the best result.
[a] The reaction was carried out in the absence of 4 Å molecular sieves.

interestingly, Pd(0) [$Pd(PPh_3)_4$] under identical reaction conditions virtually failed to catalyze the reaction (Table 1, entry 15).

Thus, in a typical experimental procedure a mixture of iodoarene, benzothiazole, $Pd(OAc)_2$, tetrabutylammonium bromide (TBAB), potassium carbonate, silver acetate, 4 Å molecular sieves in DMF was heated with stirring at 125 °C under argon for 18 h (TLC). The standard work-up and purification by column chromatography provided the pure product.

To determine the active catalytic species in this reaction, an extract from the reaction mixture of iodoarene and benzothiazole after 4 h from the start of the reaction was found to indicate the formation of nanoparticles of 2–3 nm size by TEM (Transmission Electron Microscope) image (Fig. 1). The identity of these particles as Pd was confirmed by the selected area electron diffraction (SAED) pattern (Fig. 2) which exhibited four diffused rings due to (1, 1, 1), (2, 0, 0), (2, 2, 0), and (3, 1, 1) reflections of fcc Pd and indicated the crystalline nature of nanoparticles.

A wide range of diversely substituted aryl iodides underwent reactions with benzothiazole by this procedure[9] to produce the corresponding 2-substituted benzothiazoles. The results are summarized in Table 2. The electron-donating as well as electron-withdrawing substituents on the aryl iodides are uniformly compatible

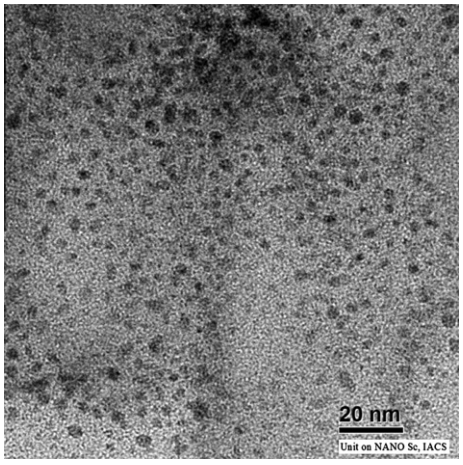


Figure 1. TEM image of Pd nps.

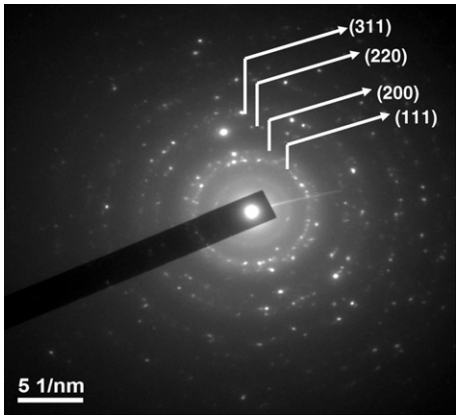


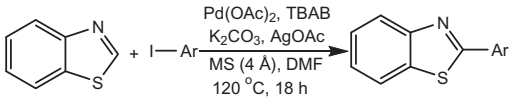
Figure 2. SAED pattern of Pd nps.

in this reaction. The F, Cl, Br groups remained inactive in the reaction with benzothiazole (Table 2, entries 2, 3, 8, and 9). The pharmaceutically important trifluoromethyl and trifluoromethoxy moieties-substituted aryl iodides participated in this reaction without any difficulty. The pyridyl iodides (Table 2, entries 18 and 19) also underwent reactions with benzothiazole to provide bis-heteroaryl systems which are also of much potential in pharmaceutical industries.

In general, the reactions are clean and high yielding. Several sensitive functionalities such as F, Cl, Br, OMe, OCF_3, CF3, CN, NO_2, COMe, CO_2Et, and heterocyclic system, pyridinyl unit are compatible in this reaction. Very significantly, as mentioned earlier, when this reaction was performed under identical conditions in the presence of tetrakis(triphenylphosphine)palladium, no appreciable reaction was observed (Table 1, entry 15). This demonstrates the importance of Pd(0) nanoparticles for this C–H functionalization.

It is suggested that Pd(0) nanoparticles generated in situ undergo oxidative addition with the aryl iodide in the usual way to provide an intermediate Ar–Pd–I which on reaction with benzothiazole in presence of K_2CO_3 and AgOAc leads to σ-adduct of arylpalladium(II) (**A**)[4h,10] with insertion of Ar moiety. This complex **A** via deprotonation produces an intermediate **B** which on reductive elimination provides the product regenerating Pd(0) (Fig. 3).

Table 2
Arylation of benzothiazole



Entry	Ar	Yield[a] (%)	Ref.
1	C_6H_5	81	4a
2	3-Cl–C_6H_4	72	11
3	4-Cl–C_6H_4	83	4a
4	3-Me–C_6H_4	80	4a
5	4-Me–C_6H_4	85	4a
6	3-MeO–C6H4	75	12
7	4-MeO–C_6H_4	78	4a
8	3-F–C6H4	81	13
9	4-Br–C_6H_4	70	14
10	3-F_3C–C_6H_4	84	4a
11	4-F_3CO–C_6H_4	82	—
12	3,5-Me_2–C_6H_3	72	—
13	4-NC–C_6H_4	79	4a
14	4-O_2N–C_6H_4	73	14
15	4-MeOC–C_6H_4	70	4d
16	4-EtO_2C–C_6H_4	84	—
17	1-Naphthyl	81	4a
18	2-Pyridyl	75	14
19	3-Pyridyl	78	4a

[a] Yields refer to those of purified isolated products characterized by spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR).

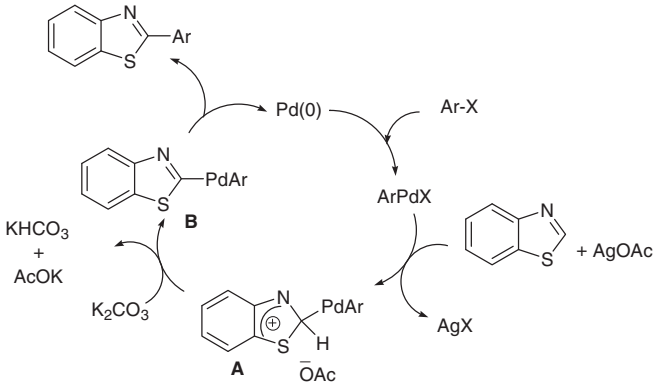


Figure 3. Plausible mechanism.

The role of AgOAc in this reaction is also very significant. Possibly, Ag(I) abstracts the I^- from the Pd(II) complex thereby generating an electrophilic-cationic-Pd intermediate[15] and thus accelerates the reaction. Moreover, I^- might have an inhibitory effect and Ag^+ minimizes this effect by removing I^- from the system.[4e]

In conclusion, we have developed a simple and efficient palladium(0) nanoparticles-catalyzed direct arylation and heteroarylation of benzothiazole based on C–H activation under ligand-free condition. This protocol provides an easy access to a wide range of 2-substituted benzothiazoles.

To the best of our knowledge, this is the first report of benzothiazole arylation using palladium(0) nanoparticles. Significantly, Pd(0) is not effective for this reaction and this demonstrates the potential and distinction of Pd(0) nanoparticles over Pd(0).

Acknowledgments

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9. *Representative procedure for the reaction of benzothiazole and iodobenzene* (Table 2, entry 1): a mixture of iodobenzene (245 mg, 1.2 mmol), benzothiazole (135 mg, 1 mmol), $Pd(OAc)_2$ (15 mg, 6.6 mol %), tetrabutylammonium bromide (350 mg, 1.08 mmol), potassium carbonate (300 mg, 2.17 mmol), silver acetate (332 mg, 2 mmol), activated (preheated for 5 min in domestic microwave oven) 4 Å MS (0.75 g) in DMF (4 mL) was heated with stirring at 125 °C under argon for 18 h (TLC). The reaction mixture was extracted with Et_2O (4 × 15 mL). The extract was washed with water, brine and then dried (Na_2SO_4). Evaporation of solvent left the crude product, which was purified by column chromatography over silica gel (60–120 mesh) (hexane/ether 98:8) to provide 2-phenylbenzothiazole (171 mg, 81%) as a white solid. The mp and spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR) of this compound are in good agreement with those reported earlier.[4a]
This procedure was followed for the synthesis of all the products listed in Table 2. Many of these products are known compounds and were identified by comparison of their spectra with those reported earlier (see references in Table 2). The new compounds were characterized by their IR, ^{1}H NMR and ^{13}C NMR and HRMS spectroscopic data which are provided below in order of their entries in Table 2.
2-(4-(Trifluoromethoxy)phenyl)benzo[d]thiazole (Table 2, entry 11): white solid; mp 97 °C; IR (KBr) 3059, 2993, 1913, 1607, 1593, 1556, 1516, 1483, 1437, 1410, 1273, 1257, 1224, 1203, 1157 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.41(m, 3H), 7.46–7.49 (m, 1H), 7.89 (d, J = 7.95 Hz, 1H), 8.05–8.12 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.3, 121.8, 122.2, 123.5, 125.6 (2C), 126.6, 129.2 (2C), 132.3, 135.3, 151.1, 154.2, 166.3; HRMS Calcd for $C_{14}H_8F_3NOS$ $(M+H)^+$ 296.0357; Found 296.0351.
2-(3,5-Dimethylphenyl)benzo[d]thiazole (Table 2, entry 12): yellow liquid; IR (neat) 3059, 3030, 3009, 2957, 2918, 2862, 2733, 1716, 1684, 1601, 1558, 1506, 1456, 1435 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 6H), 7.13 (1H, s), 7.38 (t, J = 8 Hz, 1H), 7.49 (t, J = 8.5 Hz), 7.73 (s, 2H), 7.90 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3 (2C), 121.7, 123.2, 125.2, 125.5 (2C), 126.4, 132.9, 133.5, 135.1, 138.9 (2C), 154.1, 168.7; HRMS Calcd for $C_{15}H_{13}NS$ $(M+H)^+$ 240.0847; Found 240.0843.
Ethyl-4-(benzo[d]thiazole-2-yl)benzoate (Table 2, entry 16): white solid; mp 118 °C; IR (KBr) 3057, 3022, 2960, 2926, 2903, 2872, 2854, 1709, 1666, 1607, 1479, 1452, 1435, 1406 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (t, J = 6.75 Hz, 3H), 4.40 (t, J = 6.75 Hz, 2H), 7.39 (t, J = 7 Hz, 1H), 7.50 t, J = 7.5 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 1H), 8.08–8.13 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 61.3, 121.8, 123.7, 125.8, 126.7, 127.4 (2C), 130.3 (2C), 135.4, 137.4, 144.4, 154.2, 166.4, 166.7; HRMS Calcd for $C_{16}H_{13}NO_2S$ $(M+H)^+$ 284.0745; Found 284.0741.

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