Room temperature Palladium-Catalyzed C–H Functionalization of Benzothiazole with Iodo(Hetero)Arenes.

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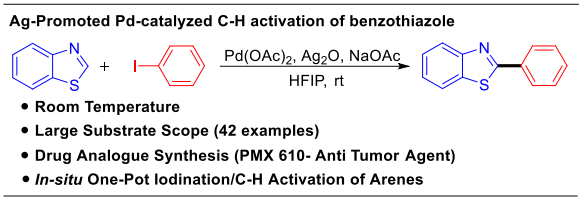


ABSTRACT:A versatile synthetic protocol involving the room temperature direct arylation of benzothiazole with a wide variety of iodo(hetero)arenes under palladium-catalyzed conditions and promoted by HFIP as the reaction solvent has been presented herewith. An in-situ one-pot sequential HFIP promoted selective iodination of (hetero)arenes followed by Pd-catalyzed direct arylation of benzothiazole has also been disclosed.

2-(Hetero)arylbenzothiazole[1] is an important structural motif having significant occurrence in a wide variety of biologically relevant compounds exhibiting activity ranging from anti-bacterial[1], anti-tumor (PMX 610)[2b] to radio tracer ability for the detection of β-amyloid plaques.[1] Presence of the 2-aryl benzothiazole moiety in the commercially available anti-tumor drug, Phortress[3] further emphasizes the importance of the 2-(hetero)arylbenzothiazole structural motif (Figure 1).

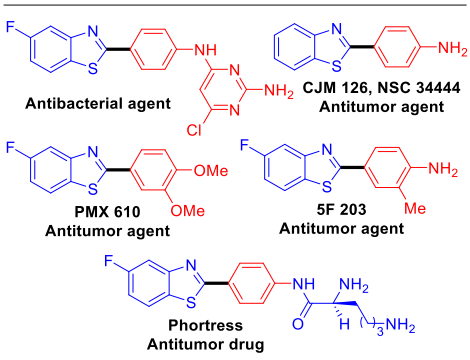


Figure 1: Bio-active 2-(hetero)arylbenzothiazoles.

Given the importance of 2-(hetero)arylbenzothiazoles on the commercial front, development of sustainable and efficient synthetic protocols becomes a necessity. Most common synthetic strategy employed for the synthesis of 2-aryl benzothiazoles involves the cyclisation of 2-aminothiophenol and related substrates with different benzaldehydes or aldehyde precursors in the presence of catalysts and oxidants[4] (**Strategy A**, Figure 2). Although, higher temperatures necessary for effecting the cyclisation combined with poor reactivity hinders further application of such a strategy. Cross-dehydrogenative coupling (CDC) is a useful synthetic option allowing unfunctionalized benzothiazole to be directly coupled with a variety of arenes[5] (**Strategy B**, Figure 2). Several protocols have been reported in recent years however, regioselectivity is of major concern alongside the problem of high reaction temperature.

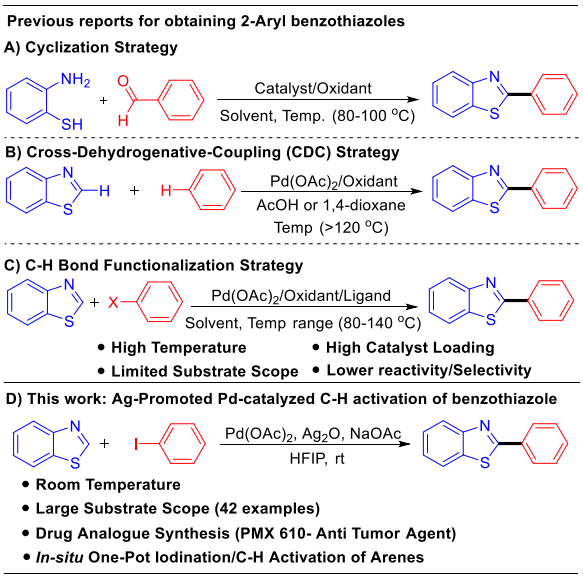


Figure 2: Strategies for the synthesis of 2-arylbenzothiazoles.

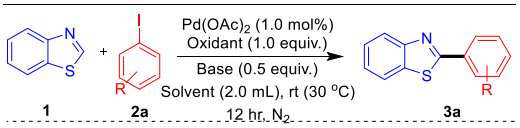
C–H bond functionalization strategy involving the reaction of heteroarenes with aryl halides as the coupling partners have found wide applications as it helps overcome the regioselectivity problem and many research groups have reported protocols

for the synthesis of 2-arylbenzothiazoles (**Strategy C**, Figure 2).[6] However, several shortcomings of the known protocols in the form of high catalyst loading, higher reaction temperatures (>80 °C) and lower reactivity provides further impetus to researchers to address these issues.

In this regards, we report herein a room temperature synthetic protocol involving the palladium-catalyzed C─H functionalization of benzothiazole with a wide variety of (hetero)aryl iodides (**Strategy D**, Figure 2). Mild nature of the catalytic protocol promoted in (hexafluoro-2-propanol) HFIP with Ag_2O as the oxidant provides an ideal opportunity to develop an one-pot iodination of (hetero)arene/C─H functionalization of benzothiazole protocol.

At the outset of our studies, it was decided to investigate the well-known synergistic behavior[7] of Pd and Ag in catalyzing C─H functionalization of a variety of substrates as Ag additives could perform a role either as an oxidants or scavenging halides from the Pd centre (Scheme 1).[8] Accordingly, a catalytic system involving $Pd(OAc)_2$ and Ag_2O as the oxidant in DMF as the solvent with NaOAc as the base was employed for the functionalization of benzothiazole with iodobenzene. With absolutely no product formation observed for the above system, solvent study was undertaken. Non polar solvents such as THF, PhMe, 1,4-dioxane failed to furnish the desired product possibly due to the poor solubility of substrates. Similarly, no product formation was observed when EtOH or CH_3CN were employed as solvents. Fluorinated solvents[9] in recent years have found a lot of importance in C─H functionalization,[10] especially the fluorinated alcohols such as TFE and HFIP[11]. In this regards, TFA with higher acidity value than TFE or HFIP again failed to provide any product. Fluorinated alcohols such as TFE and HFIP however, were successful in promoting the C─H functionalization reaction with best results obtained with HFIP.

Scheme 1: Optimization table for C─H functionalization of benzothiazoles.

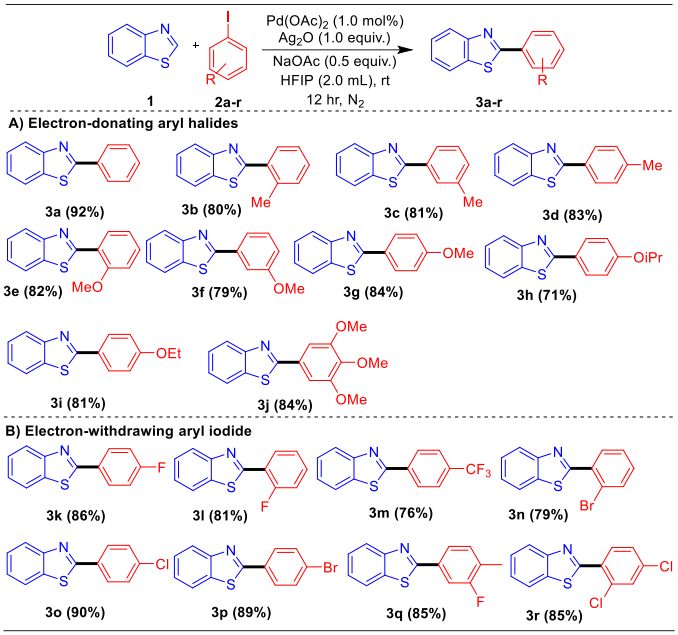


Entry	Pd precursor	Oxidant	Base	Solvent	%Yield
1.	$Pd(OAc)_2$	Ag_2O	NaOAc	DMF	0
2.	$Pd(OAc)_2$	Ag_2O	NaOAc	THF	0
3.	$Pd(OAc)_2$	Ag_2O	NaOAc	PhMe	0
4.	$Pd(OAc)_2$	Ag_2O	NaOAc	dioxane	0
5.	$Pd(OAc)_2$	Ag_2O	NaOAc	EtOH	0
6.	$Pd(OAc)_2$	Ag_2O	NaOAc	CH_3CN	0
7.	$Pd(OAc)_2$	Ag_2O	NaOAc	TFA	0
8.	$Pd(OAc)_2$	Ag_2O	NaOAc	TFE	59
9.	$Pd(OAc)_2$	Ag_2O	NaOAc	**HFIP**	95
10.	$Pd(OAc)_2$	Ag_2O	NaOAc (1.0)	HFIP	83
11.	-	Ag_2O	NaOAc	HFIP	0
12.	$Pd(OAc)_2$	-	NaOAc	HFIP	0
13.	$Pd(OAc)_2$	Ag_2O	K_2CO_3	HFIP	0
14.	$Pd(OAc)_2$	Ag_2O	Na_2CO_3	HFIP	0
15.	$Pd(OAc)_2$	O_2	NaOAc	HFIP	63
16.	$Pd(OAc)_2$	Air	NaOAc	HFIP	54
17.	$Pd(OAc)_2$	$Cu(OAc)_2$	NaOAc	HFIP	78
18.	$Pd(OAc)_2$	AgOAc	NaOAc	HFIP	87

Increase in the concentration of base was found to be detrimental for the catalytic reaction as was the case with the removal of either $Pd(OAc)_2$ or Ag_2O. Alteration in the base from NaOAc to K_2CO_3 or Na_2CO_3 also brought about reduction in catalytic activity. Replacement of Ag_2O with terminal oxidant such as dioxygen or air brought about reduction in yield which was also observed in the case of $Cu(OAc)_2$. AgOAc however, worked in a similar fashion to Ag_2O providing some insight into the possible role of Ag in promoting the catalytic reaction.

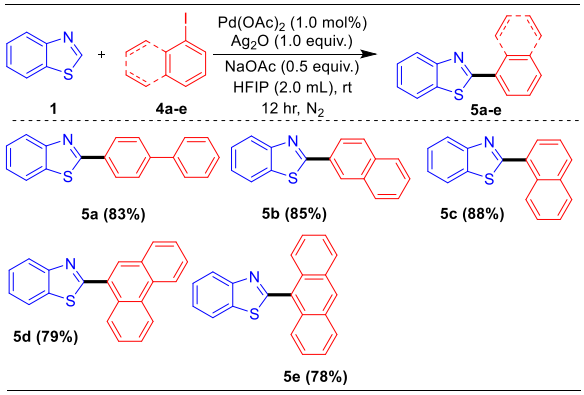
With an efficient catalytic system in hand, extensive substrate scope was undertaken employing first aryl iodides having electron-releasing substituents (**Part A**, Scheme 2). In most cases good reactivity was observed while *ortho*-substituted aryl iodides were also well tolerated (**3a-j**, Scheme 2). Aryl halide coupling partners with electron-attracting substituents were next to be tested (**Part B**, Scheme 2). Good to excellent yields of the functionalized products signifies little effect of electron-attracting substituents on catalytic activity (**3k-r**, Scheme 2).

Scheme 2: Substrate scope for room temperature C–H functionalization of benzothiazoles.



Polyaromatic aryl halides are useful synthetic coupling partners for the introduction and improvement of photophysical properties[12] due to enhanced conjugation. Substrates ranging from simple biphenyl, naphthyls or phenanthrenyls to anthracenyl were tested with most providing good yields of the the C─H functionalized benzothiazole derivatives (Scheme 3).

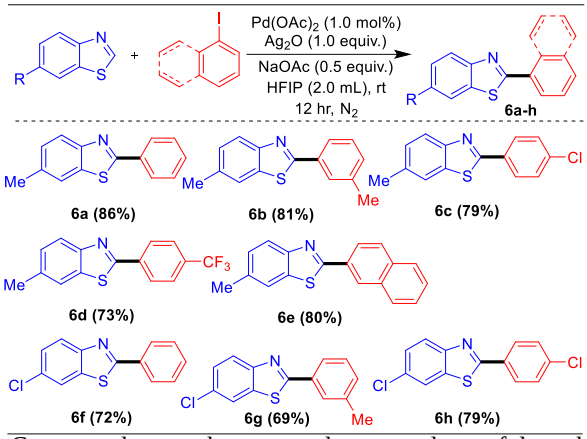
Scheme 3: Room temperature C–H functionalization of benzothiazoles using polyaromatics.



Substitution on the benzothiazole could influence the reactivity of the developed catalytic system. Benzothiazole con-

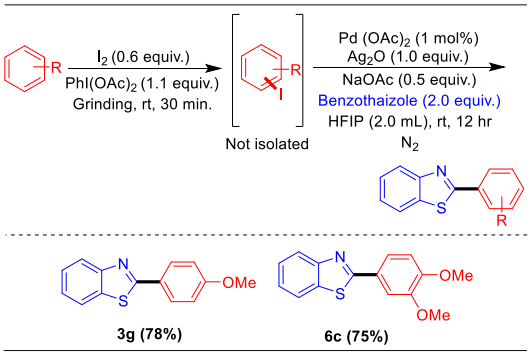
taining electron-releasing substituent (6-Me) as well as electron-attracting (6-Cl) both were employed as substrate with no appreciable change in reactivity was observed (**6a-h**, Scheme 4). These results further provide evidence about the high reactivity of the developed protocol,

Scheme 4: Substrate scope for room temperature C–H functionalization of substituted benzothiazoles.



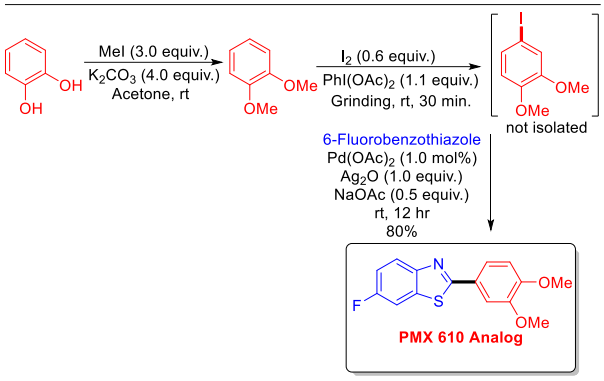
Crouse and co-workers, recently reported a useful synthetic strategy for carrying out regioselective halogenations of (hetero)arenes in HFIP as the solvent.[13] Taking advantage of this strategy we next envisaged a sequential tandem[14] protocol involving the HFIP promoted iodination of arenes (Crouse protocol) and combining it with our palladium-catalyzed C–H functionalization of benzothiazole in a tandem fashion. Although, conversion of the arene to aryl iodide was complete as described in the report by Crousse, further reaction did not proceed forward possibly due to the deactivation of the Pd catalyst[15] by the succinimide that is formed in solution. We therefore switched to another protocol by Karade and co-workers[16] (I_2/PhI(OAc)$_2$ and grinding) to get best results even with the sequential catalytic reaction. Methoxybenzene as well as 1,2-dimethoxybenzene was iodinated regioselectively and were directly employed as electrophilic partners for promoting the sequential iodination/C–H functionalization in good yields.

Scheme 5: Sequential HFIP-promoted iodination/Pd-catalyzed C–H functionalization strategy



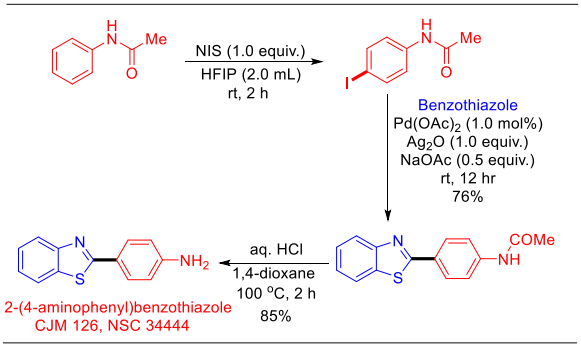
The developed one-pot synthetic procedure for the C–H functionalization of benzthiazoles is a highly desirable strategy as it allows the *in situ* generated aryl iodide (obtained regioselectively) to be utilized directly without isolation in the subsequent sequential C–H functionalization step. To demonstrate the synthetic potential of the developed strategy it was decided to synthesize PMX 610[2] analog, a potent antitumor agent (Scheme 6). At the start of the synthesis, catechol was converted into 1,2-dimethoxybenzene via simple methylation using methyl iodide. Next, *in situ* regioselective iodination using Karade method with iodine/PhI(OAc)$_2$ and grinding at ambient temperature was followed by GCMS for completion and subsequent addition of benzothiazole, Pd(OAc)$_2$ and other reagents for performing the sequential iodination/C–H functionalization thus providing an analog of antitumor agent, PMX 610 in 80% yield.

Scheme 6: Synthesis of PMX 610 analog (antitumor agent).



2-(4-Aminophenyl)benzothiazoles[2a] are important structural feature has found applicability as antitumor agents and showed potent inhibitory activity in the nanomolar range. The basic structure of 2-(4-aminophenyl)benzothiazoles designated as CJM 126 (also known as NSC 34444)[2b] exhibiting excellent antitumor activity could therefore be an interesting target for the application of our develop methodology. We envisaged the synthesis starting from a cheap starting material such as acetanilide, which on selective iodination at the para position and then subjected to the developed C–H functionalization conditions providing 78% of the N-acyl protected 2-(4-aminophenyl)benzothiazoles (Scheme 7).

Scheme 7: Synthesis of CJM126 (NSC 3444).



Silver salts have been known to play an important role in C–H functionalization methodologies with the likes of Sanford and co-workers[17] providing evidence for such behavior and Houk[7] summarizing elegantly in a recent review as well as others[8]. We also envisage a crucial role of the addition of Ag salt (Ag_2O or AgOAc) for assisting both the oxidative addition and transmetallation step in the catalytic cycle while HFIP assists the abstraction of the proton from benzothiazole resulting into the formation of the silver salt of benzothiazole. An intermediate similar to that proposed by Sanford could certainly be acting in our case too. Catalytic efficiency of the developed protocol allowing the reactions to be performed at ambient temperature could thus be attributed to the combination of all these factors.

In conclusion, a highly efficient room temperature palladium-catalyzed C─H functionalization of benzthiazoles has been developed exhibiting wide substrate scope while no effect of the electronic factors of substituents present either on the aryl iodide coupling partner or benzothiazole was observed on the catalytic activity. Assisted by the activating role of HFP and silver salts, allows the catalytic protocol to be employed in a sequential iodination/C─H functionalization tandem which was further applied towards the synthesis of an antitumor agent PMX 610. Another antitumor agent, CJM 126 was also synthesized using the developed C─H functionalization strategy in good yield.

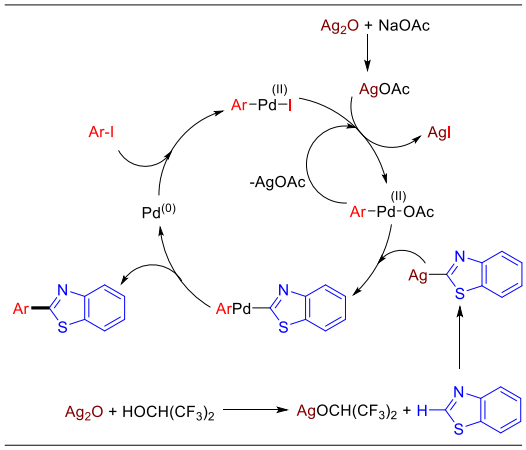


Figure 3: Plausible mechanism for C─H functionalization of benzothiazoles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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