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$Pd(OAc)_2$ catalyzed synthesis of 2-aryl- and 2-heteroaryl-benzoxazoles and benzothiazoles in imidazolium ionic liquids (ILs) without additives and with recycling/reuse of the IL

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ABSTRACT

A facile, high yielding, method for the synthesis of a library of 2-aryl- and 2-heteroaryl-benzoxazoles and benzothiazoles from readily available Schiff bases is reported employing catalytic amounts of $Pd(OAc)_2$ in imidazolium ionic liquids (bmim)BF_4 and (bmim)PF_6 without ligands and/or additives. Simple product isolation and recycling/re-use of the IL are additional advantages of this method.

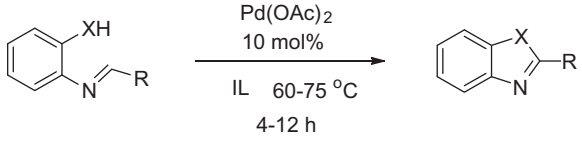
Due to their widespread presence in biologically active natural products and pharmaceuticals benzoxazole and benzothiazole structural motifs have received considerable attention from the synthetic/medicinal chemistry community.[1] Fluorinated 2-aryl-benzothiazoles exhibit notable antitumor and metabolic activities,[2] and it has been suggested that this class of compounds are metabolized by cytochrome-P450 to reactive nitrenium ions.[2b] Apart from their importance in medicinal chemistry, the 2-aryl-benzoxazoles and benzothiazoles have also been applied in materials chemistry.[3]

Transition metal-catalyzed C–H arylation of azoles constitutes a major strategy in the synthesis of the 2-aryl derivatives.[4] The nickel-catalyzed reactions use ligands and additives and are performed in solvents such as dioxane and DMF at high temperatures.[4a,b] The $Pd(OAc)_2$-catalyzed reactions also employ ligands and additives, and are typically performed in DMF, or are used without ligands in the presence base and various additives.[4c–f] A copper-mediated version with Ar-I employed CuI/PPh_3/base with DMF as solvent.[4g]

Another widely employed method for the synthesis of benzoxazoles and benzothiazoles is via condensation of amino-phenols and amino-thiols with aldehydes or carboxylic acids, employing PPA,[5a] or Lewis acids in solvents such as dioxane, and toluene[5b] EtOAc/molecular sieves/heat,[5c] or by using KCN/DMF,[5d] with one reported example using $FeCl_3{\cdot}6H_2O$ with (bmim)BF_4 as co-catalyst.[5e]

Oxidative cyclization of phenolic and thiophenolic Schiff bases constitutes another strategy for the synthesis of substituted benzoxazoles and benzothizaoles. For this transformation reagents such as IBX,[5c] $Pd(OAc)_2/CsCO_3/DMF/O_2$,[6a] or PCC/silica/DCM[6b] have been employed. Cyclization of benzothioamides and benzothioureas using $CuCl_2$/BINAM/base/MeCN,[6c] $Pd_2(dba)_3$/monophosphine,[6d] and DDQ/DCM,[6e] or by photolysis using chloranil in DCE/toluene,[6f] have also been reported.

In reviewing these literature methods and considering the reagents, solvents, and conditions that have been employed, it is clear that despite reasonable diversity, development of less reagent



Where, R = Aryl, Heteroaryl
X = O, S
IL = (bmim)BF_4 or (bmim)PF_6

Scheme 1. $Pd(OAc)_2$-catalyzed synthesis of 2-aryl- and 2-heteroaryl-benzoxazoles and benzothiazoles.

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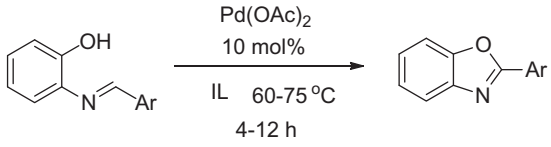
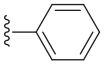
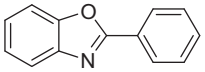
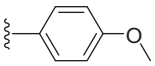
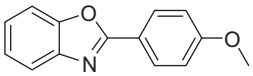
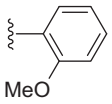
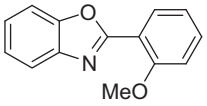
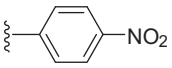
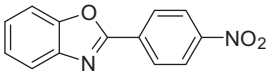
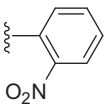
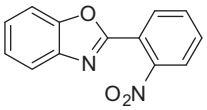
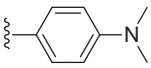
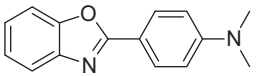
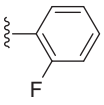
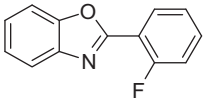
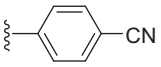
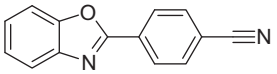
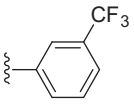
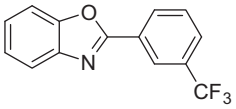
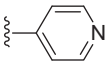
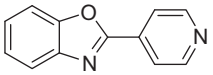
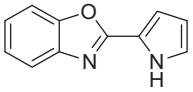
Table 1
$Pd(OAc)_2$-catalyzed synthesis of 2-aryl and 2-heteroaryl-benzoxazoles[a,b,c]



Entry	Ar	Product	IL	Time (h)	Isolated yield (%)
1[a]			$(bmim)PF_6$	6	84
2[a]			$(bmim)BF_4$	8	80
3[b]			$(bmim)BF_4$	4	77
4[c]			$(bmim)BF_4$	4	78
5[a]			$(bmim)BF_4$	9	80
6[b]			$(bmim)BF_4$	5	85
7[b]			$(bmim)PF_6$	8	72
8[c]			$(bmim)PF_6$	8	70
9[a]			$(bmim)PF_6$	12	74
10[b]			$(bmim)PF_6$	4	89
11[c]			$(bmim)PF_6$	12	68

[a] Fresh IL was used.
[b] 2nd cycle.
[c] 3rd cycle.

intensive methods that are also environmentally more acceptable is a desirable goal.

In continuation of our studies on electrophilic and onium ion chemistry in ionic liquids,[7] and in connection to recent works from our laboratory on $Pd(OAc)_2$-catalyzed Matsuda–Heck arylation,[8a] and cross-coupling of polyfluoroarenes with simple aromatics[8b] we wish to report a facile, high yielding, method for the synthesis of 2-aryl- and 2-heteroaryl-benzoxazoles and benzthiazoles starting from the Schiff bases, employing catalytic amounts of $Pd(OAc)_2$ in imidazolium ionic liquids $(bmim)BF_4$ and $(bmim)PF_6$ as solvent, under very mild conditions without the need for any other additive and with recycling and reuse of the ILs (see Scheme 1).[9,10]

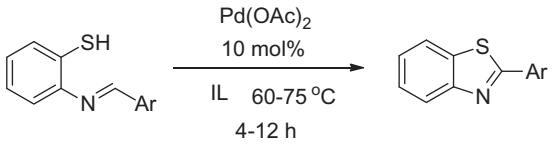
The results for benzoxazoles are summarized in Table 1, with isolated yields ranging from 68% to 85%. Table 2 summarizes the outcomes for benzothiazoles, with the isolated yields ranging from 68% to 88%.

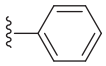
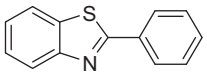
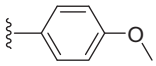
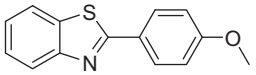
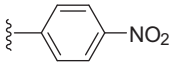
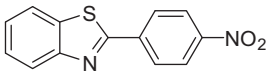
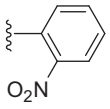
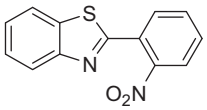
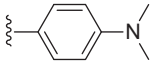
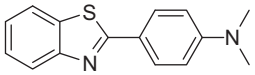
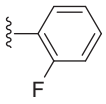
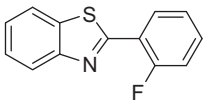
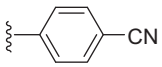
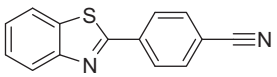
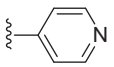
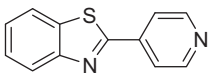
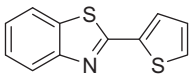
Typically, the recovered IL could be reused for up to 3 runs before it had to be set aside for 'clean-up', whereupon it could be recycled and used again in the reaction (see Ref. 10). Reactions performed in the recycled/reused IL led to slightly lower isolated yields in some cases (see Tables 1 and 2).

A plausible mechanism involving Pd-complexation to imine nitrogen followed by cyclization and elimination is outlined in Scheme 2.

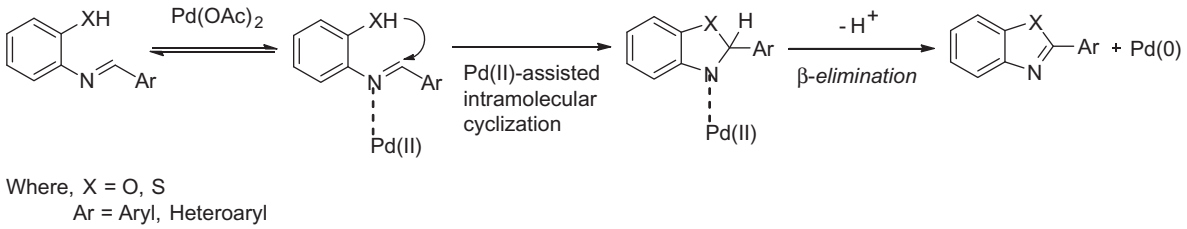
In summary, the present Pd-catalyzed approach provides rapid access to a host of 2-aryl and 2-heteroaryl-benzoxazoles and benzthiazoles from readily available Schiff bases, without the need for ligands, oxidants, additives, or hazardous solvents such as DMF and dioxane. Given the importance of functionalized 2-arylazoles

Table 2
$Pd(OAc)_2$-catalyzed synthesis of 2-aryl and 2-heteroaryl-benzothiazoles[a,b,c]



Entry	Ar	Product	IL	Time (h)	Isolated yield (%)
1[a]			$(bmim)PF_6$	10	88
2[b]			$(bmim)PF_6$	9	80
3[c]			$(bmim)PF_6$	8	75
4[a]			$(bmim)BF_4$	8	80
5[a]			$(bmim)PF_6$	8	70
6[b]			$(bmim)BF_4$	12	71
7[b]			$(bmim)PF_6$	12	75
8[c]			$(bmim)BF_4$	10	76
9[a]			$(bmim)BF_4$	12	68

[a] Fresh IL was used.
[b] 2nd cycle.
[c] 3rd cycle.



Scheme 2. Plausible mechanism for $Pd(OAc)_2$-catalyzed cyclization and β-elimination.

in medicinal chemistry, the present IL version offers an environmentally more acceptable alternative to the existing methods.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.155.

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9. *General procedure*: The desired Schiff base (1 mmol) was introduced into an oven-dried Schlenk tube charged with (bmim)PF_6 or (bmim)BF_4 ionic liquid (4–5 mL). Following efficient magnetic stirring (for 30 min) the reaction mixture was then charged with $Pd(OAc)_2$ (10 mol %). The reaction mixture was stirred at 60–75 °C and the progress of the reaction was monitored by TLC and GC–MS. The brown-colored reaction mass was cooled to rt and the products were extracted with dry diethyl ether (4 times). Removal of solvent under vacuum furnished the crude products which were chromatographed with hexane/ethyl acetate mixture (80:20) or DCM/methanol mixture (95:5) to afford the pure cyclized products which were characterized by NMR (^1H, ^{13}C, ^{19}F) and by GC–MS (see Supplementary data for characterization data). The brown colored IL was dried overnight under vacuum at 50 °C and reused in the next 2–3 run, after which it was set aside for recovery and recycling as outlined in Ref. 10.
10. *Procedure for recycling of ionic liquid*: The combined brown-colored ionic liquids recovered from several set of experiments were dissolved in MeCN, and filtered through Celite to remove insoluble black particles. After removal of solvent from the filtrate under vacuum, the recycled IL was dried overnight under vacuum at 50 °C and reused in subsequent runs.