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Palladium-catalyzed direct functionalization of benzoxazoles with alkenyl iodides

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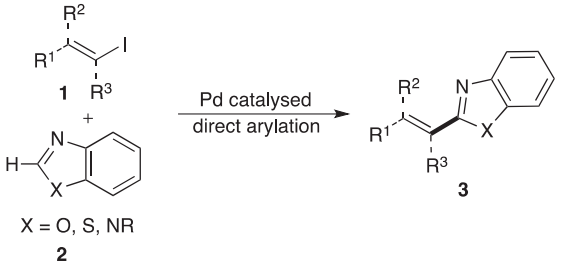
ABSTRACT

A straightforward procedure for the palladium-catalyzed direct functionalization of benzoxazoles with alkenyl iodides is described. The reactions employ a Pd(II)-precatalyst and use 'on water' conditions to achieve the ready union of a range of di- and tri-substituted alkenyl iodides with a small range of benzoxazoles.

Palladium-catalyzed cross-coupling reactions represent some of the most reliable, popular, and strategically important transformations available to synthetic chemists.[1] However, despite the many advantages associated with these methods, one limitation is the general need to employ an activating group on each coupling partner. This usually takes the form of one nucleophilic organometallic partner, such as an organo-tin or -boron reagent, together with an electrophilic reagent such as an aryl- or alkenyl halide (or pseudo-halide). To address this limitation, the last decade has seen enormous advances in the use of direct arylation methods based on C–H functionalization (or activation) chemistry.[2] These new technologies generally allow for one of the coupling partners to be employed without an activating group.[3] The major focus of these new methods has been in the development of aryl–aryl, or aryl–(hetero)aryl couplings, with examples of alkenyl- and alkyl-couplings being less prevalent.[4,5] Our laboratory has been interested in the development of intramolecular variants of direct arylation processes employing alkenyl halides and we have applied these methods to the synthesis of both carbocyclic and heterocyclic systems.[6] Therefore, when we required access to a series of 2-substituted benzoxazoles, the use of an intermolecular direct functionalization process employing alkenyl halides was an attractive proposition (Scheme 1). Employing alkenyl halide substrates would allow the flexibility afforded by the alkene functional group;



Scheme 1. A direct functionalization route to 2-alkenylbenzoxazoles (and related heterocycles).

that is, further transformations such as hydrogenation or dihydroxylation would allow access to a series of simple derivatives.

Although benzoxazoles have been employed in direct functionalization chemistries in combination with aryl halides,[7] their combination with alkenyl halides is poorly represented.[8] The procedures that have been described suffer from extended reaction times and/or moderate yields. Greaney has recently reported the direct arylation of a broad range of heterocycles employing palladium catalysis and 'on water' conditions.[9,10] Given the generality of this method with respect to substrate scope, the use of commercial catalyst systems, and the general ease of use, we elected to explore the Greaney method for the desired benzoxazole alkenylation (Table 1). We studied the coupling of benzoxazole (**2a**) and alkenyl iodide **1a** as a test system, and were pleased to observe that the application of the literature conditions [$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, PPh_3, Ag_2CO_3, H_2O, 60 °C] delivered the 2-alkenylated benzoxazole **3a** in a 35% yield

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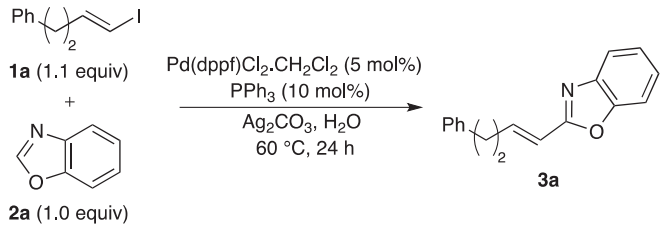
Table 1
Optimization of the preparation of 2-alkenylbenzoxazole **3a** from the coupling of benzoxazole **2a** and alkenyl iodide **1a**[a]



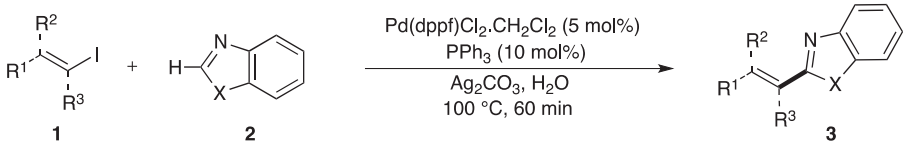
Entry	Variation from above	Yield[a] (%)
1	Original conditions	35
2	100 °C, 24 h	17
3	Microwave (MW), 100 °C, 1 h	58
4	MW, 120 °C, 1 h	49
5	MW, 100 °C, 1 h, + benzoquinone	23
6	MW, 100 °C, 1 h, no PPh_3	16
7	MW, 100 °C, 1 h, replace PPh_3 with dppf	28
8	100 °C, 1 h, **1a** (1 equiv), **2a** (2 equiv)	70

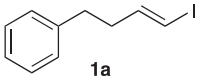
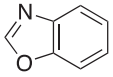
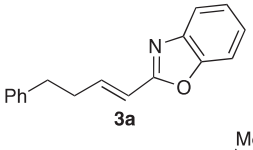
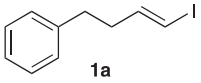
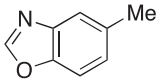
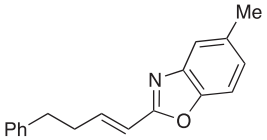
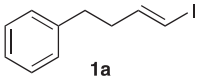
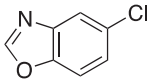
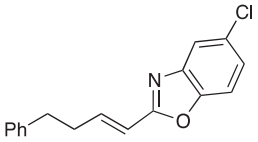
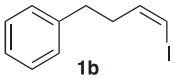
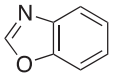
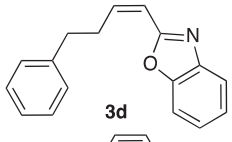
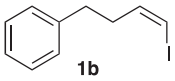
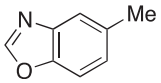
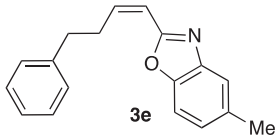
[a] Isolated yields.

(entry 1). With a modest yield of the target molecule achieved we set about exploring variations from these conditions to improve the yield of **3a**. Increasing the reaction temperature to 100 °C and maintaining a 24 h reaction reduced the efficiency; however, employing a microwave reactor and performing the transformation at 100 °C for only 1 h increased the yield of **3a** to 58% (entries 2 and 3). A further increase in temperature (to 120 °C), the addition of a re-oxidant (benzoquinone), and removal or replacement of the PPh_3 ligand all delivered less effective reactions (entries 4–7). Finally, using conventional heating in a sealed tube and employing benzoxazole in excess relative to the alkenyl iodide (**1a**:**2a** = 1:2), increased the yield to 70% (entry 8).

With an efficient and operationally simple protocol established we applied the method to a range of alkenyl iodides and benzoxazoles in order to assess the scope of the reaction (Table 2). In general, variation of the alkenyl iodide was tolerated well, with simple functional groups, such as methyl ethers (entries 6 and 7) and chloroalkanes (entries 8–10), as well as tri-substituted examples (entries 11–14) all performing well. It was notable that it was possible to employ successfully both the (*E*)- and (*Z*)-isomers of an alkene (**1a** and **1b**) and maintain the integrity of the alkene geometry in the products (entries 1 and 4). Alkenyl bromide substrates were unreactive under our optimized reaction conditions.[11] Simple variation of benzoxazole to include methyl- and chloro-substituents was also possible (entries 2 and 3, for example). We next turned our attention to the use of alternative heterocyclic coupling partners, particularly benzothiazole and *N*-methylbenzimidazole; although unsuccessful with the 1,2-disubstituted alkenyl iodide substrates, it was possible to couple trisubstituted alkenyl iodide **1e** to both of these heterocycles in moderate yield (entries 13 and 14). Other simple heterocycles, such as 2-phenyloxazole and 2-phenylthiazole, both of which have been successfully employed in direct functionalizations with aryl halides, were unreactive with

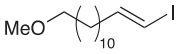
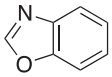
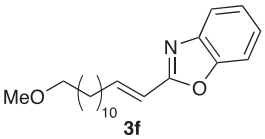
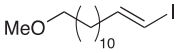
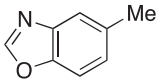
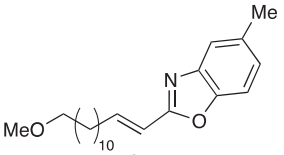
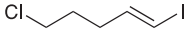
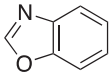
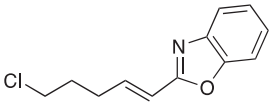
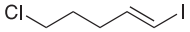
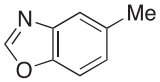
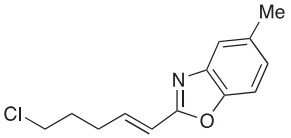
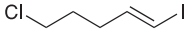
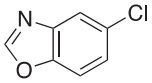
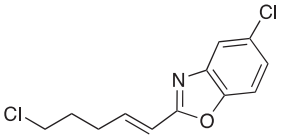
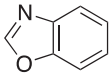
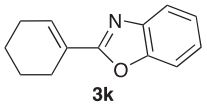
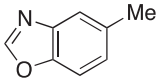
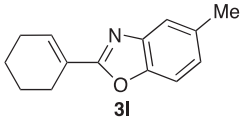
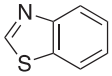
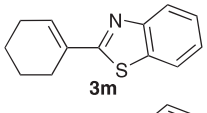
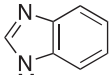
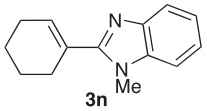
Table 2
Scope of the palladium-catalyzed direct functionalization of benzoxazoles (and related heterocycles) with alkenyl iodides using 'on water' conditions[a]



Entry	Alkenyl iodide	Heterocycle	Product	Yield[b] (%)
1	 **1a**		 **3a**	70
2	 **1a**		 **3b**	83
3	 **1a**		 **3c**	40
4	 **1b**		 **3d**	99
5	 **1b**		 **3e**	59

(*continued on next page*)

Table 2 (*continued*)

Entry	Alkenyl iodide	Heterocycle	Product	Yield[b] (%)
6	 **1c**		 **3f**	49
7	 **1c**		 **3g**	78
8	 **1d**		 **3h**	62
9	 **1d**		 **3i**	88
10	 **1d**		 **3j**	45
11	 **1e**		 **3k**	61
12	 **1e**		 **3l**	41
13	 **1e**		 **3m**	25
14	 **1e**		 **3n**	73

[a] Conditions: heterocycle (1.0 mmol), alkenyl iodide (0.5 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.025 mmol), PPh_3 (0.05 mmol), Ag_2CO_3 (1.0 mmol), H_2O (3.5 mL), 100 °C, 1 h, sealed tube.

[b] Isolated yields.

any of the alkenyl iodides employed in the present study. The apparent lower reactivity of alkenyl iodides relative to their aryl counterparts under the present reaction conditions may be due to the lower stability of alkenyl- versus aryl-metal intermediates.[12]

In conclusion, we have demonstrated a straightforward procedure for the direct functionalization of benzoxazoles with alkenyl iodides. The use of palladium catalysis and 'on water' conditions allows relatively short reaction times, and moderate to good yields to be achieved across a variety of substrates.

Acknowledgments

We would like to thank Syngenta and the EPSRC for their support of this study.

Supplementary data

Supplementary data (description of general experimental procedures, preparation of the vinyl iodides **1a–e** and spectroscopic data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.014.

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