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Alkenyl bromides: useful coupling partners for the palladium-catalysed coupling with heteroaromatics via a C–H bond activation

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Abstract

Alkenyl bromides were found to be useful reactants for the palladium-catalysed direct C–H activation/functionalisation reaction of heteroaromatics such as benzoxazole or benzothiazole. Moderate to good yields of coupling products were obtained using both α- and β-substituted alkenyl bromides or even the trisubstituted alkenyl bromide 2-bromo-3-methylbut-2-ene. This reaction is environmentally attractive as it provides only HX associated to the base as a by-product.
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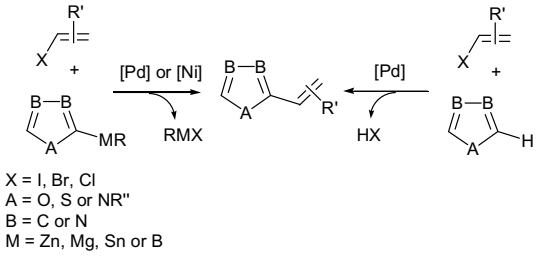
Keywords: C–H bond activation; Vinyl halides; Palladium; Catalysis; Benzoxazole

The palladium-catalysed alkenylation reaction of heteroaromatics is one of the most powerful methods for the preparation of alkenyl-substituted heteroarenes.[1] The efficiency of several methods such as palladium or nickel catalysed Stille,[2] Negishi,[3] Kumada[4] or Suzuki[5] cross-couplings for the reaction of alkenyl halides with thiophenes, furans, thiazoles or oxazoles has been described. However, these reactions require the prior preparation of an organometallic derivative of a heteroaromatic, and provide an organometallic salt (MX) as a by-product (Scheme 1).



Scheme 1.

Since a few years, a new palladium-catalysed procedure for the functionalisation of heteroaromatics has emerged. It consists in directly functionalising the heteroaromatics via a C–H bond activation of the heteroarene. This procedure proceeds nicely for the coupling of several heteroaromatics with aryl or heteroaryl iodides, bromides and chlorides, or even triflates.[6–13] For such couplings, no preparation of an organometallic derivative is required. Moreover, this reaction provides only HX associated to a base, instead of a metallic salt as a by-product and therefore is very interesting in terms of both atom-economy and non-toxic wastes (Scheme 1). However, so far, most of the results for this reaction were obtained with aryl halides or triflates. To our knowledge, only a few results employing other functionalisation reactants have been described. For example, the synthesis of a range of pyrroloquinolines via

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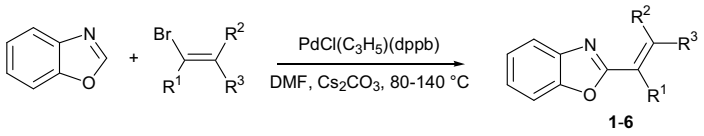


Scheme 2.

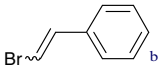
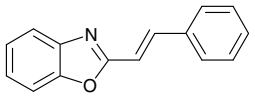
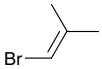
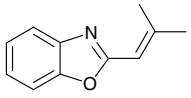
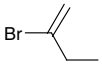
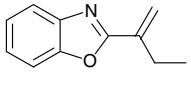
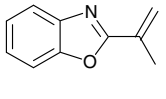
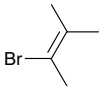
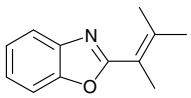
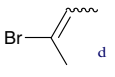
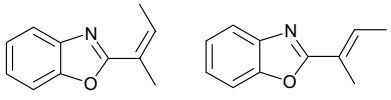
C–H bond activation/functionalisation using norbornadiene was described by Hulcoop and Lautens employing $Pd(OAc)_2/PPh_3$ as the catalytic system.[14] Recently, Ma and co-workers described the direct 3-allylation of indole derivatives with electron-deficient allyl acetates in the presence of $Pd(dba)_2$/2,2′-bipyridine as the catalyst.[15] The palladium-catalysed direct alkynylation of N-fused heterocycles using terminal alkynes has also been reported recently.[16]

The extension of heteroaromatic C–H bond activation/functionalisation procedure to a wider diversity of substrates both at the laboratory scale and in the industry would be a considerable advantage for sustainable development because of the lower cost, lower mass and the wider diversity of reactants, as well as for the treatment of the relatively nontoxic waste.

In order to further extend the scope of the functionalisation of heteroaromatics via C–H bond activation, we herein report on the coupling of α- or β-substituted alkenyl bromides with benzoxazole, benzothiazole or 2-*n*-propylthiazole. A simple access to 2-alkenyloxazole or thiazole derivatives would be useful due to their anticancer, anti-HIV or antimicrobial properties.[17]

For this study, based on the previous results,[11,12] DMF or DMAc was chosen as the solvent and K_2CO_3, Cs_2CO_3 or KOAc as the base. The reactions were conducted at 80–140 °C under argon in the presence of $PdCl(C_3H_5)(dppb)$[18] as the catalyst. For low boiling point alkenyl bromides, the reactions were performed in autoclaves. The reactions were performed using 2 equiv of heterocyclic coupling partner, due to partial decomposition of these substrates at elevated temperatures. However, in most cases, a large amount of these substrates was recovered unreacted allowing to perform these reactions with a smaller excess of the reactant.

Table 1
Direct arylations of alkenyl bromides with benzoxazole catalysed by $PdCl(C_3H_5)(dppb)$ complex (Scheme 2)[20,21]

Entry	Alkenyl bromide	Reaction temp (°C)	Product	Yield[a] (%)
1	 [b]	100	 **1**	100 (61)
2		140	 **2**	77 (54)[c]
3		140	 **3**	64 (47)[c]
4		140	 **4**	68 (58)[c]
5		140	 **5**	73 (51)[c]
6	 [d]	140		87 (55 of **6b**)[c]
7		80	*Z*: **6a** and *E*: **6b**	50[c]

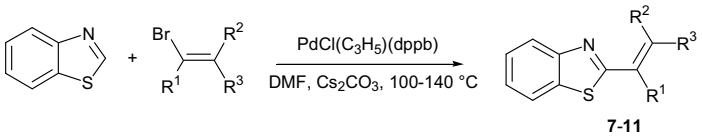
Conditions: catalyst $PdCl(C_3H_5)(dppb)$ (0.05 equiv), see Ref. 18, alkenyl bromide (1 equiv), benzoxazole (2 equiv), Cs_2CO_3 (2 equiv), DMF, 20 h, under argon, GC and NMR yields.

[a] Yields in parentheses correspond to isolated yields.

[b] Ratio of stereoisomers *Z*/*E*: 9/91.

[c] Reaction performed in autoclave, 4% of **6a** was also observed in GC/MS and NMR of the crude mixture.

[d] Ratio of stereoisomers *Z*/*E*: 50/50.



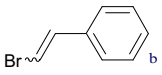
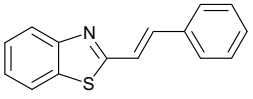
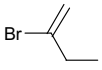
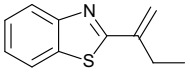
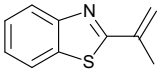
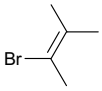
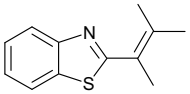
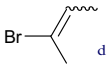
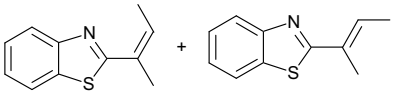
Scheme 3.

In order to determine the most suitable reaction conditions for this reaction, we studied the reactivity of benzoxazole with β-bromostyrene in the presence of 5 mol % $PdCl(C_3H_5)(dppb)$ using various bases and solvents (Scheme 2 and Table 1). Employing K_2CO_3 as the base and DMF as the solvent at 100 °C, the expected product **1** was not observed. Using KOAc under similar conditions, **1** was obtained in a very low yield. The most suitable base appears to be Cs_2CO_3. With this base, using DMF at 100 °C as reaction conditions, **1** was obtained selectively in 61% isolated yield. At a slightly higher temperature (120 °C), the dimerisation of β-bromostyrene was observed in relatively large amounts, especially when traces of oxygen were present in the reaction mixture. On the other hand, at 80 °C relatively low yields of product **1** were obtained due to moderate conversion of β-bromostyrene. DMAc as the solvent gave a mixture of **1** and β-bromostyrene dimers. Several other catalytic systems such as $Pd(OAc)_2$, or $[PdCl(C_3H_5)]_2$ associated to PPh_3, dppe or in the absence of ligand have been employed for this reaction, using Cs_2CO_3 as the base in DMF at 100 °C. However, they led to very low to moderate yields of **1**. A yield of 39% was obtained using $Pd(OAc)_2$ in the presence of dppb.

Then, using the most suitable reaction conditions (DMF, Cs_2CO_3 and $PdCl(C_3H_5)(dppb)$), we examined the scope and limitation of the reaction using various mono-, bi- or trisubstituted alkenyl bromides (Scheme 2 and Table 1).

β-Disubstituted alkenyl bromide: 1-bromo-2-methylprop-1-ene gave the coupling product **2**. However, a higher reaction temperature (140 °C) was required in order to obtain a high conversion (77%) of 1-bromo-2-methylprop-1-ene and a moderate isolated yield of **2** (54%) (Table 1, entry 2). The α-substituted alkenyl bromides: 2-bromobut-1-ene and 2-bromoprop-1-ene gave **3** and **4** in 47 and 58% yields, respectively, revealing a low influence of the substituent position on alkenyl bromides on the yields (Table 1, entries 3 and 4). These results were confirmed using the α- and β-substituted alkenyl bromide: 2-bromo-3-methylbut-2-ene, which gave **5** in a similar yield of 51% (Table 1, entry 5). We also studied the reactivity of a mixture of (*Z*)- and (*E*)-2-bromobut-1-ene (50/50) (Table 1, entries 6 and 7). Coupling product **6b** was selectively obtained in 55% yield. The formation of 4% of the other stereoisomer **6a** was also observed. A small amount of the starting material 2-bromobut-2-ene in a ratio 69/31 of

Table 2
Direct arylations of alkenyl bromides with benzothiazole catalysed by $PdCl(C_3H_5)(dppb)$ complex (Scheme 3)[20,21]

Entry	Alkenyl bromide	Reaction temp (°C)	Product	Yield[a] (%)
1		100	 **7**	100 (69)
2		140	 **8**	53 (47)[c]
3		140	 **9**	46 (32)[c]
4		120	 **10**	67 (58)
5		120	 *Z*: **11a** and *E*: **11b**	35 (27) (ratio *Z*: **11a**/*E*: **11b** 9/91)[19]

Conditions: catalyst $PdCl(C_3H_5)(dppb)$ (0.05 equiv), see Ref. 18, alkenyl bromide (1 equiv), benzothiazole (2 equiv), Cs_2CO_3 (2 equiv), DMF, 20 h, under argon, GC and NMR yields.

[a] Yields in parentheses correspond to isolated yields.

[b] Ratio of stereoisomers *Z*/*E*: 9/91.

[c] Reaction performed in autoclave.

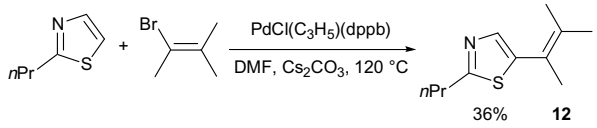
[d] Ratio of stereoisomers *Z*/*E*: 50/50.

Z/*E* stereoisomers was also recovered unreacted. These results indicate that there is apparently some isomerisation of the alkenyl double bond in the course of the reaction, and that both (*Z*)- and (*E*)-2-bromobut-1-ene can be converted to **6b**. (*E*) stereoisomer appears to be slightly more reactive than the (*Z*)-2-bromobut-1-ene.

Next, we examined the reactivity of benzothiazole (Scheme 3 and Table 2). The coupling with β-bromostyrene, 2-bromobut-1-ene, 2-bromoprop-1-ene or 2-bromo-3-methylbut-2-ene led selectively to the target products **7**–**10** in moderate to good yields (Table 2, entries 1–4). (*Z*)- and (*E*)-2-Bromobut-1-ene (ratio 50/50) led to a 9/91 mixture of **11a** and **11b** (Table 2, entry 5). It should be noted that for most of these reactions, no side products were formed. The moderate yields of some reactions arise mostly from incomplete conversions of the alkenyl bromides. Therefore, on a large scale, the recycling of unreacted alkenyl bromides should be possible.

Finally, we performed the selective 5-alkenylation of 2-*n*-propylthiazole using 2-bromo-3-methylbut-2-ene. This heteroarene was found to be slightly less reactive than benzoxazole or benzothiazole. The reaction gave product **12** in 36% isolated yield (Scheme 4). For this reaction, 48% of 2-bromo-3-methylbut-2-ene was recovered unreacted.

In summary, the functionalisation of heteroaromatics via C–H bond activation is not limited to the use of aryl halides or triflates. We have demonstrated, for the first time to our knowledge, that alkenyl halides are also useful coupling partners in C–H bond activation. In the presence of $PdCl(C_3H_5)$(dppb), the reaction of the electron-rich heteroaromatic derivatives benzoxazole, benzothiazole or 2-*n*-propylthiazole with alkenyl bromides led to the coupling products in low to relatively high yields. Both α- and β-substituted alkenyl bromides have been employed successfully. Even a trisubstituted alkenyl bromide gave the expected coupling product. For this reason, this method is applicable to the coupling of a wide variety of alkenyl bromides. It should be noted that, despite their interest, most of the products prepared by this method are new, indicating a relatively limited access to such compounds using more traditional cross-coupling procedures. Moreover, due to environmental reasons, the advantage of such atom-economy and nontoxic wastes procedure, (formation of CsBr and CO_2 as side products) should become increasingly important for industrial processes. The extension of this procedure to other heterocycles such as furans or thiophenes and mechanistic studies are currently under investigation, and will be reported in due course.



Scheme 4.

Acknowledgements

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20. As a typical experiment (Table 1, entry 1), the reaction of β-bromostyrene (0.183 g, 1 mmol), benzoxazole (0.238 g, 2 mmol) and Cs_2CO_3 (0.652 g, 2 mmol) at 100 °C over 20 h in dry DMF (10 mL) in the presence of $PdCl(C_3H_5)$(dppb) complex (0.05 mmol) under argon afforded the corresponding product **1** after evaporation and filtration on silica gel in 61% (0.135 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81 (d, $J = 16.5$ Hz, 1H), 7.73 (m, 1H), 7.68–7.47 (m, 3H), 7.46–7.30 (m, 5H), 7.10 (d, $J = 16.5$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.6, 150.2, 142.0, 139.3, 135.0, 129.6, 128.8, 127.4, 125.1, 124.4, 119.7, 113.8, 110.2.
21. All new compounds gave satisfactory ^{1}H, ^{13}C and elementary analysis. ^{1}H NMR (200 MHz, $CDCl_3$) of new compounds: **2** δ 7.72 (m, 1H), 7.51 (m, 1H), 7.31 (m, 2H), 6.28 (s, 1H), 2.38 (s, 3H), 2.07 (s, 3H); **3** δ 7.74 (m, 1H), 7.53 (m, 1H), 7.33 (m, 2H), 6.30 (s, 1H), 5.62 (s, 1H), 2.71 (q, $J = 7.4$ Hz, 2H), 1.30 (t, $J = 7.4$ Hz, 3H); **4** δ 7.75 (m, 1H), 7.54 (m, 1H), 7.33 (m, 2H), 6.27 (s, 1H), 5.63 (s, 1H), 2.31 (s, 3H); **5** δ 7.73 (m, 1H), 7.53 (m, 1H), 7.33 (m, 2H), 2.28 (s, 3H), 2.21 (s, 3H), 2.00 (s, 3H); **6b** δ 7.73 (m, 1H), 7.50 (m, 1H), 7.31 (m, 2H), 6.96 (qq, $J = 7.0$ and 1.2 Hz, 1H), 2.21 (s, 3H), 1.95 (d, $J = 7.0$ Hz, 3H); **8** δ 8.04 (d, $J = 8.3$ Hz, 1H), 7.87 (d, $J = 8.3$ Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 1H), 5.99 (s, 1H), 5.52 (s, 1H), 2.79 (q, $J = 7.4$ Hz, 2H), 1.27 (t, $J = 7.4$ Hz, 3H); **9** δ 8.04 (d, $J = 8.3$ Hz, 1H), 7.86 (d, $J = 8.3$ Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 1H), 5.98 (s, 1H), 5.55 (s, 1H), 2.36 (s, 3H); **10** δ 8.03 (d, $J = 8.3$ Hz, 1H), 7.88 (d, $J = 8.3$ Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 1H), 2.20 (s, 3H), 2.06 (s, 3H), 1.96 (s, 3H); **12** δ 7.34 (s, 1H), 2.94 (t, $J = 7.4$ Hz, 2H), 2.00 (s, 3H), 1.87 (sext., $J = 7.4$ Hz, 2H), 1.84 (s, 3H), 1.82 (s, 3H), 1.05 (t, $J = 7.4$ Hz, 3H).