Regioselective oxidative Pd-catalysed coupling of alkylboronic acids with pyridin-2-yl-substituted heterocycles†

Julian Wippich, Ingo Schnapperelle and Thorsten Bach*

A total of 19 alkylated heterocycles (thiophenes, benzothiophenes, pyrroles, furans) were prepared (36–99% yield) from the respective pyridin-2-yl-substituted precursors employing alkylboronic acids as the C–H alkylating reagents in an oxidative (Ag$_2$CO$_3$ and 2,6-dimethyl-1,4-benzoquinone as oxidants) Pd-catalysed coupling reaction.

Despite considerable progress in recent years, the direct C–H alkylation of aromatic heterocycles by transition-metal catalysis remains a considerable challenge. An appropriate option to achieve the desired regioselectivity in this process is based on the use of directing groups. In the thiophene series the pyridin-2-yl group has frequently served to mediate a reaction at position C3 if it was attached as a directing group to carbon atom C2. Upon Pd(II) catalysis, oxidative dimerization of 2-pyridin-2-ylthiophene (1) proceeded selectively at C3 as did the oxidative arylation with arylboronic acids. The Pd(II)-catalysed arylation of 1 with aryl bromides proceeded preferentially at C5 although the regioselectivity was variable.

In this communication we disclose our results on the regioselective oxidative Pd-catalysed coupling of alkylboronic acids with 2-pyridin-2-yl-substituted thiophenes and related heterocycles (benzothiophene, furan, pyrrole).

The starting point of our study was a report by the Yu group, who found that 2-phenylpyridine could be alkylated with alkylboronic acids (3.0 eq.) employing a reagent combination of Pd(OAc)$_2$ (10 mol%), Ag$_2$O (1 eq.) and 1,4-benzoquinone (0.5 eq.) at 100 °C in tert-amyl alcohol (tAmOH). Yields varied between 51 and 75% (six examples) depending on the alkyl group. When applying the same conditions to 2-pyridin-2-ylthiophene (1) and butylboronic acid we recorded a conversion of 34% after 14 hours and a product yield of 30% (determined by GLC with dodecane as internal standard). Raising the silver concentration and replacing Ag$_2$O by Ag$_2$CO$_3$ as the silver source increased the conversion to 90% and the yield to 58%. Despite this significant improvement, it was notable that the butylboronic acid was largely consumed by an undesired alkylation reaction, which occurred at 1,4-benzoquinone. Indeed, it has been reported that 1,4-benzoquinone can be alkylated by alkylboronic acids under oxidative conditions in the presence of a Pd(II) catalyst. If 1,4-benzoquinone was omitted in the present reaction, the turnover was retarded (37% conversion after 14 h), which confirmed the importance of 1,4-benzoquinone to complete the catalytic cycle. In order to find a 1,4-benzoquinone, which would be less susceptible towards alkylation, various substituted derivatives were screened (see the ESI† for further information). The study revealed that 2,6-dimethyl-1,4-benzoquinone (2) was a superior co-catalyst for the desired reaction as compared to unsubstituted 1,4-benzoquinone. Applying it to the otherwise unchanged reactions conditions, the yield for the desired butylated product increased according to GLC to 70% (92% conversion). On preparative scale, the reaction delivered an almost identical result and 3-butyliothiophene 3a was isolated in 71% yield (Table 1).

Oxidative dimerisation (dehydrogenative coupling) to the respective 5,5′-dithiophene was a notable side reaction, which may at least partially account for the moderate yields, which were recorded for products 3b–3e. Indeed, it was shown that 5,5′-dithiophene 4 was formed in 60% yield from product 3a if the latter was subjected to oxidative coupling conditions (Scheme 1). Even in the presence of butylboronic acid, the dimer was the only product isolated. Applying exactly the reaction conditions used for the alkylation (Table 1), product 4 was obtained from 3a in 59% yield. A further alkylation was not observed.

When the 5-position in the thiophene was blocked the reaction outcome significantly improved (Table 2). For ethyl 2-(pyridin-2-yl)-5-thiophene carboxylate, alkylation reactions proceeded cleanly and delivered products 5a–5d in yields of 71–97%. The reactions conditions were compatible with ketone (product 5e) and aldehyde (product 5f) functional groups at position C5 of the thiophene core. Remarkably, more electron rich thiophenes also withstood the oxidative conditions of the coupling reaction. Product 5g was isolated in almost quantitative yield and even the 5-methoxythiophene 5h
could be obtained with good chemoselectivity. Moreover, it was possible to extend the reaction to 2-pyridin-2-ylbenzothiophene resulting in the alkylation products 5i and 5j. Commercially available boronic acids were used in all experiments and it was secured by NMR that no condensation to the corresponding boroxines had occurred upon storage. In the course of the reaction the initially green suspension turned black possibly due to metal precipitation.

Mechanistically, it is assumed that the reaction follows the pathway previously proposed for the alkylation of benzenes. A mechanistic scheme is given in Scheme 2 for the transformation 1 → 3a. In the event, Pd(OAc)₂ attacks the thiophene core at position C3 leading to cyclopalladated intermediate 6. Transmetallation generates the precursor 7 for the reductive elimination step, in which a reduced palladium species (Pd⁰) is formed. Reoxidation to the reactive PdX₂ catalyst occurs stoichiometrically by the silver salt with possible assistance by benzoquinone 2. As pointed out earlier, benzoquinone may also be involved as ligand in the transmetallation and reductive elimination step. In addition, it appears as if the 2-pyridin-2-yl group facilitates transmetalation. After primary alkylation at C3, palladation occurs at position C5 and oxidative dimerisation prevails over oxidative coupling (vide supra).

### Table 1
Regioselective oxidative Pd-catalysed coupling of alkylboronic acids with 2-pyridin-2-ylthiophene (1)

<table>
<thead>
<tr>
<th>RB(OH)₂ (3.0 eq.)</th>
<th>2 (0.5 eq.)</th>
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<tbody>
<tr>
<td>10 mol% Pd(OAc)₂</td>
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<tr>
<td>Ag₂CO₃ (2 eq.)</td>
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<tr>
<td>100 °C, 14 h (AmOH)</td>
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Scheme 1 Oxidative dimerisation of 3-butylated product 3a to the 3,3'-dibutyl-5,5'-dithiophene 4.

a The substrate (c = 0.2 M) and all reagents were dissolved in dry tert-amyl alcohol. Upon stirring for five minutes at ambient temperature, the sealed reaction tube was placed in a pre-heated oil bath (100 °C). Work-up was performed with CH₂Cl₂ and aqueous Na₂S solution. Yields are given for isolated products after chromatographic purification.

### Table 2
Regioselective oxidative Pd-catalysed coupling of alkylboronic acids with 2-pyridin-2-yl-substituted thiophene and with 2-pyridin-2-ylbenzothiophene

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<th>RB(OH)₂ (3.0 eq.)</th>
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Scheme 2 Mechanistic proposal for the oxidative cross-coupling with 2-pyridin-2-ylthiophenes such as 1 (X = anionic ligand, L = neutral ligand).

Given the strong directing power of the 2-pyridin-2-yl group it was probed whether a selective alkylation was also possible at other positions of the thiophene ring and with other 2-(pyridin-2-yl)-substituted heterocycles as substrates. Butylboronic acid was used in these reactions as the nucleophile (Scheme 3). Gratifyingly, it was found that alkylation at position C4 of 3-pyridin-2-ylthiophene 8 was indeed possible employing the
conditions previously established. Product 9 was obtained in moderate yield. In the pyrrole series, it was observed that – in analogy to product formation 3a vs. 5d – the alklylation reaction of the 5-ethoxy carbonyl-substituted pyrrole 11 (Y = COOEt) gave a better yield than the reaction of the unsubstituted compound 10 (Y = H). Products yields for 12 and 13 were recorded as 58% and 90%. In the former case, competitive oxidative dimerisation at position C5 is likely the reason for the lower yields. Regarding the nitrogen protecting group, the benzyl group was shown to be superior as compared to methanesulfonyl (Ms), toluenesulfonyl (Ts) and para-methoxybenzyl (PMB). The respective 2-pyridin-2-ylpyroles gave lower yields in the oxidative coupling reactions. The oxidation sensitive 2-pyridin-2-ylfurans gave only traces of coupling product under the standard reaction condition. The less electron rich ethyl 5-furan carboxylate 14, however, could be converted into the respective alklylation product 15 albeit in relatively low yield.

In summary, it was shown that the pyridin-2-y1 group exerts a powerful directing influence on the Pd-catalysed C–H alkylation of five-membered heterocycles with alkyboronic acids. The alkylation reactions occur exclusively in ortho-position to the directing group resulting in the formation of the respective 3-substituted (pyridin-2-yl at C2) or 4-substituted (pyridin-2-yl at C3) products. 2,6-Dimethyl-1,4-benzoquinone (2) was found to be a superior co-reagent to promote in combination with Ag2CO3, the oxidative coupling. If the ortho-positions relative to the directing group are substituted, oxidative dimerisation occurs under the oxidative reaction conditions at position C5 of 3-alkyl(2-(pyridin-2-yl)thiophenes).

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Notes and references
7 For a recent report on the C5-selective arylation at substrate 1, see: R. Srivinasan, R. S. Kumaran and N. S. Nagarajan, RSC Adv., 2014, 4, 47697–47700.
15 The use of cyclopropyl boronic acid led to an inseparable mixture of product and substrate (35% conversion after 14 h).