New aspects of palladium-catalysed carbon-carbon bond formation reactions
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SELECTIVE PALLADIUM-CATALYSED OXIDATIVE COUPLING OF ANILIDES WITH OLEFIN S THROUGH C-H BOND ACTIVATION AT ROOM TEMPERATURE

Abstract

Using a high throughput experimentation approach, a selective and mild palladium-catalysed oxidative coupling reaction between anilide derivatives and acrylates was found that occurs through ortho C-H bond activation. This reaction provides a novel, promising method for synthesising valuable functionalised arylalkenes without the formation of halide-waste. The reaction is carried out in an acidic environment under mild conditions. Using the cheap oxidant benzoquinone yields up to 91% are obtained at ambient temperature. At elevated temperatures, even oxygen can be used as the oxidant, resulting in water as the only side-product. The reaction is insensitive towards water and can be performed in the presence of non-coordinating solvents. It exhibits first order kinetics in acetanilide, as well as a strong electronic dependence, with electron-rich aromatic compounds reacting faster than electron-poor arenes. A plot of the observed reaction rates $k_{obs}$ for a series meta-substituted acetanilides against the Hammett $\sigma_m$ parameter yields an approximately linear correlation with a $\rho$-value of $-2.2$. Furthermore, a kinetic isotope effect is observed ($k_{H^*} / k_{H} = 3$). These results are interpreted in terms of a mechanism of the coupling in which the key step of the catalytic cycle is believed to be the electrophilic attack by a [PdOAc]$^-$ complex on the $\pi$-system of the arene. This step is likely to be rate-limiting.

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7.1 Introduction

The palladium-catalysed arylation of olefins (better known as the Heck-Mizoroki reaction) is now recognised to be a key reaction for constructing new carbon-carbon bonds.\cite{1-4} Being a very mild method and showing compatibility with many functional groups, it is a very attractive tool for the production of aromatic fine chemicals.\cite{5} In recent years, much progress has been reported on the development of new catalysts for this reaction, that show high stability and reactivity, even towards relatively unreactive starting compounds (e.g. aryl chlorides). Still, a major drawback accompanying this procedure is the restriction of possible substrates to mainly organic halides, which leads to the coproduction of a significant amount of halide salt. For industrial application, this large waste stream poses environmental problems. Promising examples have been reported in which alternative leaving groups have been employed, such as organic anhydrides, which produce the corresponding acid as the side-product (together with carbon monoxide) that can be recycled to the anhydride again.\cite{6} Nevertheless, a clear need remains for alternative Heck-type coupling reactions that enable production of functionalised aromatic compounds with reduced waste formation. C-H activation reactions, one of the most challenging fields in modern chemistry\cite{7-10} could provide such a methodology.

Many late transition metals are known to be able to form efficient catalysts for functionalising aromatic compounds through C-H bond cleavage.\cite{11-16} Coupling reactions of arenes bearing an ortho-directing group (e.g. α-aryl ketones) with olefins can be performed selectively and smoothly using ruthenium-catalysts in refluxing toluene, as shown by Murai in the early 90’s (see scheme 1).\cite{17,24} In these cases, addition of the C-H bond to the double bond takes place, producing alkylarenes. Experimental and theoretical considerations suggest that the oxygen of the carbonyl functionality coordinates strongly to the Ru-centre, followed by the breaking of the closest (ortho-) C-H bond.\cite{25}

Examples of the oxidative catalytic coupling of aromatic compounds are much less abundant. Åkermark reported the inter- and intramolecular coupling of diphenylamine and quinone derivatives using palladium as the catalyst.\cite{26,27} Fujiwara\cite{9,28-31} and later others\cite{32-36} have exemplified the palladium-catalysed oxidative coupling of arenes and olefins, both in a

\begin{Scheme}
\begin{center}
\begin{tikzpicture}
\node[above] at (0,0) {Scheme 1. General representation of addition-type (a) and oxidative (b) coupling reactions between arenes and alkenes.};
\end{tikzpicture}
\end{center}
\end{Scheme}
stochiometric and a catalytic fashion. In these cases, the required presence of peroxides as the oxidant in combination with strong acidic media and or elevated temperatures is still a major drawback. Recently, Milstein and co-workers reported the use of ruthenium catalysts and molecular oxygen as oxidant in the coupling of benzene with alkenes. This reaction produces only water as the side product. Unfortunately, this procedure shows moderate selectivity in some cases and requires high temperatures (180 °C). We decided to study the functionalisation of aniline derivatives with alkenes through C-H bond activation. This type of reaction would produce valuable aromatic compounds, and can function as a model reaction for other coupling reactions, e.g. the intramolecular synthesis of indoles. In this chapter, we report a mild method for such functionalisation of anilines with alkenes using Pd(OAc)$_2$ as the catalyst together with cheap oxidants and solvents.

7.2 Results and Discussion

7.2.1 Initial Screening and Optimisation Experiments. To find a lead, we first employed rapid screening experiments using a parallel synthesis apparatus and tested several potential catalyst precursors with different functionalised substrates (a schematic overview of the experimental set-up is shown in the Experimental Section). The reactions were performed under an inert atmosphere using 1 mol% of the catalyst on a 2 mmol scale of the substrates in various solvents at 80 °C. Analysis of the results was performed after 16 hours reaction time by GC and GC/MS. From these experiments, the coupling of styrene with acetanilide in the presence of Pd(OAc)$_2$ and an equimolar amount of benzoquinone (BQ) emerged as a 'hit', resulting in the predominant formation of a single product in ca. 20% yield (estimated by GC). Isolation of the product and subsequent characterisation revealed that the compound was $(E)$-2-acetylaminostilbene, resulting from the oxidative coupling of the aromatic compound with the alkene. This lead prompted us to further research.

Since in general acrylate substrates are more reactive in Heck reactions than styrene, further screening experiments were carried out using n-butyl acrylate. The results hereof are summarised in Table 1. As found in the parallel experiments using styrene, aniline derivatives 4 and 5 are not reactive under the conditions tested. The reaction of acetanilide (1) with n-butyl acrylate proceeds smoothly and selectively at 80 °C using 2 mol% Pd(OAc)$_2$ and benzoquinone as oxidant to yield the common Heck product $(E)$-3-(2-acetylamino)phenylpropenoic acid butyl ester exclusively (3 in Scheme 2), in somewhat higher yield than in the reaction using styrene (entry 3). No $\alpha$-substitution or Z-product formation was observed, in correspondence with the characteristics of acrylate couplings in Heck type chemistry in general. Furthermore, no formation of 3- or 4-substituted coupling products was observed in any of the reactions performed. This shows the
Scheme 2. Palladium-catalysed reaction of acetanilide with \(n\)-butyl acrylate to yield (E)-3-(2-acetylamino)phenyl)propenoic acid butyl ester (3).

Importance of the ortho-directing effect of the amide group, analogously to the selective C-H activation of \(\alpha\)-arylketones in 'Murai-type' catalysis. We did not detect any trace of products resulting from N-H bond activation. Under the acidic conditions employed, the deprotonation of the amide nitrogen is probably an unfavourable reaction pathway.

Remarkably, lowering the reaction temperature to 20 °C results in higher yields (Table 1, entries 3-4). Acetic acid proved to be the solvent of choice, but using mixtures (up to 1:1 v/v) of HOAc with

Table 1. Coupling of aniline derivatives with \(n\)-butyl acrylate using Pd(OAc)$_2$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Additives</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>80</td>
<td>HOAc</td>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>80</td>
<td>HOAc</td>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>80</td>
<td>HOAc</td>
<td>none</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>20</td>
<td>HOAc</td>
<td>none</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>20</td>
<td>HOAc / Toluene$^b$</td>
<td>TsOH$^d$</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>20</td>
<td>HOAc / NMP$^b$</td>
<td>TsOH$^d$</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>20</td>
<td>HOAc / Toluene$^b$</td>
<td>H$_2$O (5% v/v)</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>20</td>
<td>HOAc / Toluene$^b$</td>
<td>NaCl$^d$</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>20</td>
<td>CF$_3$COOH</td>
<td>none</td>
<td>61</td>
</tr>
<tr>
<td>10$^d$</td>
<td></td>
<td>20</td>
<td>HOAc / Toluene$^b$</td>
<td>TsOH$^d$</td>
<td>29</td>
</tr>
</tbody>
</table>

*a* substrate (3.0 mmol), \(n\)-butyl acrylate (3.3 mmol), Pd(OAc)$_2$ (0.06 mmol), BQ (3.0 mmol). Yields are isolated yields. See the Experimental Section for more details. $^b$ 1:2 ratio (v/v). NMP = \(N\)-methyl pyrrolidinone. $^d$ 1.5 mmol$^d$ performed using H$_2$O$_2$ as the oxidant.

\(\text{CH}_2\text{Cl}_2\) or THF does not affect the yields to a large extent. Products arising from coupling of the alkene with aromatic solvents used (e.g. toluene) are not observed. When benzene-$d_6$ is used, no incorporation of H-atoms occurs, indicating that C-H activation of aromatic compounds without
Oxidative Coupling of Anilides with Olefins

coordinating substituent does not take place under these conditions. Solvents with coordinating abilities like NMP hamper the catalytic reaction (entry 6). This indicates that competitive coordination of the substrate and solvent occurs in these cases, effectively blocking the C-H bond breaking. Water or oxygen do not have a disadvantageous effect on the conversion, enabling the reactions to be conveniently performed under air atmosphere. The presence of a substoichiometric amount (0.5-1.0 equiv.) of para-toluenesulfonic acid (TsOH) has a large beneficial effect, resulting in an increased yield, up to 72 %, when acetanilide is employed as the substrate (Table 1, entry 5). Larger amounts of TsOH do not further improve the yields, but instead promote a side reaction of the alkene, probably an acid-catalysed polymerisation.

Recently, Fujiwara reported on the effective and mild palladium-catalysed coupling of electron-rich arenes with alkenes and alkynes, resulting in the reductive formation of arylalkanes and alkene respectively. These reactions could be performed both in an intramolecular and intermolecular way. The acidity of the solvent was shown to have a large influence on the reaction rate in these hydroarylation reactions, CF$_3$COOH being much more effective than HOAc. These observations could be explained in terms of increasing electrophilicity of the Pd(II) centre by replacement of AcO$^-$ by CF$_3$COO$^-$, caused by stronger electron-withdrawing capacity and weaker coordination of the trifluoroacetate anion. This renders the Pd-centre more cationic and therefore more electrophilic, resulting in faster metalation of the aromatic C-H bond. In our case, employing CF$_3$COOH as the solvent (without TsOH added) results in similar catalyst performance as the acetic acid - TsOH combination (entry 9, Table 1). Apparently, the increased acidity also results in protonation of a larger amount of the metal complex, thereby increasing the electrophilic character of the catalyst. Protonation of the anions can also influence the rate of subsequent alkene coordination and insertion in the catalytic cycle (vide infra).

Other metal complexes, e.g. Ru$_3$(CO)$_7$, [RuCl$_2$(η-cymene)$_2$], PtCl$_2$ and Ni(OAc)$_2$, showed no activity under the standard conditions used. Palladium sources such as PdCl$_2$, Pd[PPh$_3$]$_2$Cl$_2$ and palladium on charcoal resulted in no to low (<10%) conversions. Addition of inorganic acids (HCl, H$_2$SO$_4$) had a large detrimental effect on the catalytic performance. Ryabov and coworkers have shown that the stoichiometric reaction of the ortho-palladated anilide complex dimer [[(C$_6$O)$_2$C$_6$H$_4$NH(η-CH$_3$)Pd(η-μ-OAc)$_2$]$_2$ with styrenes is acid catalysed, and that protonation is likely to occur at the bridging acetate ligands. Similarly, the stoichiometric reaction of ortho-palladated N,N-dialkylbenzylamines with alkenes was shown to occur through initial protonation of the corresponding chloride-bridged Pd dimers. Subsequent alkene coordination, followed by insertion and β-H elimination yields the corresponding vinylated arene. Apparently, in our case halides block the preceding step of the catalytic cycle, i.e. coordination - cleavage of the C-H bond in the aromatic substrate, by coordinating to the Pd(II)-centre. This coordination will decrease the electrophilicity of the metal and thereby its reactivity (entry 8, Table 1). Furthermore, it is known that the presence of halide anions can favour protonolysis of Pd-alkyl bonds over β-H
This would result in the formation of alkylarenes as side-products in our system. However, no such addition products are observed in our reactions.

Table 2. Coupling of substituted amilide derivatives with \(n\)-butyl acrylate using Pd(OAc)\(_2\) in acetic acid\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>15</td>
<td>38(^b)</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>16</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>17</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>18</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>19</td>
<td>(29)</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>20</td>
<td>(&lt;5)</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>21</td>
<td>(28)</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>22</td>
<td>(26)</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>23</td>
<td>55</td>
</tr>
</tbody>
</table>

\(^a\) reactions performed as described in Table 1, entry 5. Yields in parentheses were determined by GC. \(^b\) determined by \(^1\)H NMR.

7.2.2 Scope of the Reaction: Substrates. To investigate the scope of the reaction, we tested several other substrates under the optimised reaction conditions. Substituents on the aromatic moiety of the acetanilide substrate were found to influence the efficiency of the coupling reaction significantly (see Table 2). As anticipated, ortho-substitution hampers the reaction to a large extent, as is shown by the lower yield with 2-methyl acetanilide (entry 1). It has been reported that the palladation of ortho-substituted acetanilides does not take place at all\(^{[2]}\) or at elevated temperatures only.\(^{[33]}\) Besides the statistical decrease in sites available for C-H activation, steric and electronic effects are likely to play a role herein. Using 3-methyl acetanilide (7; entry 2) the reaction efficiency is enhanced to give a 91% isolated yield of coupling product 16. No formation of the 6-substituted product is observed, probably due to steric reasons. Modification of the aromatic ring with substituents having electronically different properties has a large influence on the outcome of
the reaction (entries 3-5; also see below). Clearly, electron-donating meta-substituents result in higher yields. The inductive donating effect of the 3-methyl group makes the position para to it more susceptible to electrophilic attack, but the difference in yield with the 4-methyl substituted acetonilide is small, see entry 3. Multiply substituted substrates only yield small amounts of the desired product (entry 6).

Interestingly, application of several aromatic substrates possessing other potentially ortho-directing groups did not result in the desired coupling products (Figure 1). Thus, the reaction of N-methyl acetonilide (24) gave no conversion at all. Possibly, the coordinating ability of the amido group is reduced by the steric bulk of the methyl group, which forces the amide substituents to bend out-of-plane. Furthermore, the methyl group makes tautomerisation towards the enol form of the amide impossible. N-Methyl-2-phenyl acetamide (12) can be applied (entry 7, Table 2), as well as formanilide (entry 8), although the yields in these cases are only moderate. When benzanilide (14, entry 9) is subjected to the catalytic conditions, only the isomer arising from the C-H activation at the nitrogen-substituted aromatic ring is observed (as determined by NMR spectroscopy and GC/MS). This remarkable regioselectivity can be explained by the preferential formation of a six-membered palladacycle, which apparently is favoured over the isomeric five-membered intermediate. This is confirmed by the fact that N-methyl benzamide is not reactive under the standard conditions tested either. Since five-membered palladated complexes are known to be more stable than six-membered analogues,[44, 45] we suggest that the electronic properties of the carbonyl do not allow coordination and subsequent C-H activation in these five-ring cases. This was supported by the fact that no deuterium incorporation was observed when the unreactive substrates were treated with acetic acid-d_4 under catalytic conditions but in the absence of alkene. The subtlety of the factors governing the reactivity of the aromatic compounds is further illustrated by the lack of reactivity of phenyl acetate. Recently, the palladium-catalysed ortho-arylation of alkyl aryl ketones and related compounds has been reported to occur under basic conditions.[46, 47] This type of coupling reaction is likely to proceed through a different mechanism, but could have intermediates in which five-membered Pd(C,O) palladacycles play a role. In these studies, the authors suggest that the palladation occurs via initial enolate oxygen coordination.
One of the problems possibly arising in C-H bond activation chemistry is the formation of multiply substituted products since several C-H bonds are present. This complication often has to be suppressed by the use of a large excess of aromatic substrate. In our studies, only in a few cases minor amounts (<1%) of disubstitution are observed, even when a small excess (<1.5 equiv.) of alkene is employed. This indicates disfavoured electronic and steric properties of the primary product formed towards a second substitution.

\[
\begin{align*}
&\text{H} \\
\text{O} & + \text{\textendash} \text{R} \\
\text{Pd(OAc)}_2 & \text{BQ} \\
\text{HOAc} & \rightarrow \\
&\text{HN} \\
\text{O} & \text{R}
\end{align*}
\]

Table 3. Coupling of 3-methyl acetonilide with different alkenes using \(\text{Pd(OAc)}_2\) in acetic acid/toluene<sup>a</sup><sup>b</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R = \text{Ph})</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>(R = 4\text{-MeO-Ph})</td>
<td>29</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>(R = 4\text{-Cl-Ph})</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>(R = \text{OMe})</td>
<td>31</td>
<td>&lt;1&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>1,3-cyclohexadiene</td>
<td>32</td>
<td>&lt;1&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>(\text{EtOOCC} ≡\text{CH})</td>
<td>33</td>
<td>&lt;1&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: 5 mol % \(\text{Pd(OAc)}_2\), 0.5 equiv. \(\text{TsOH}\), 1.5 equiv. \(\text{BQ}\), reaction time 16 hrs. <sup>b</sup>2/1 (v/v) determined by GC. <sup>d</sup>unidentified by-products formed.

Other alkenes, like styrene, can also be applied, although less mild conditions are required in these cases (Table 3). For example, styrene reacts with 3-methyl acetonilide (7) using 5 mol % \(\text{Pd(OAc)}_2\), at 40 °C to give a 24 % yield of (E)-2-acetylamino stilbene. The coupling reactions are hampered by the increased amount of side product formed from olefin polymerisation on employing elongated reaction times. When electron-rich styrene derivatives are used, this polymerisation reaction is even dominant. The addition of radical scavengers as 4-tert-butylcatechol did not inhibit the consumption of the alkene. Styrenes with electron-withdrawing substituents give higher conversions towards the C-H activated coupling product. Thus, 4-chlorostyrene reacts with 3-methylacetonilide at 40 °C using 5 mol % palladium catalyst to the corresponding stilbene derivative in 58 % yield. Other alkenes, e.g. vinyl ethers gave no coupling to the desired product. Remarkably, application of ethyl propiolate does not result in the expected corresponding arylacetylene, but yields a complex mixture of several unidentified compounds.

7.2.3 Influence of the Oxidant. The coupling reactions described so far were performed using benzoquinone (BQ) as the oxidant. Use of other oxidants, e.g. hydrogen peroxide (see entry 10 of Table 1) or \(\text{Cu(II)(OAc)}_2\), give conversions that are significantly lower than those obtained
employing benzoquinone. The role of the BQ can be twofold. It serves as the oxidant, resulting in the formation of Pd(II) and hydroquinone. This reaction is known to be accelerated by acid.\textsuperscript{58, 49} In addition, BQ can act as a ligand, stabilizing the different Pd-species present during the catalytic cycle.\textsuperscript{59, 51} Addition of more than one equivalent of BQ does not improve the yield significantly in our reactions. Application of less than one equivalent of BQ lowers the conversion to a larger extent than expected on the basis of simple stoichiometry. These results indicate that the role of benzoquinone is beyond that of just being the oxidant.

We also studied the possibility to apply molecular oxygen as the oxidant in this catalytic system. In this case, the only side-product formed is water, resulting in a truly waste-free Heck-type coupling reaction (Scheme 4). Several examples exist in which Pd(II) is regenerated using oxygen, sometimes in combination with catalytic amounts of co-oxidants (e.g. Cu(II)), the most famous being probably the Wacker process.\textsuperscript{52} We tested the coupling of acetanilide with \textit{n}-butyl acrylate under an oxygen atmosphere (1 atmosphere) using 10 mol % of benzoquinone and 10 mol % of Cu(II)(OAc)\(_2\) at 70 °C. After two hours, GC analysis of the reaction mixture revealed more than 98 % yield of the desired coupling product. When the copper co-catalyst was omitted, the conversion reached 78 % after 4 hrs. Reactions run at room temperature did not result in formation of the product. Apparently the re-oxidation of the Pd(0) species formed after each catalytic cycle has a higher activation barrier when employing oxygen instead of BQ. Cu(II) lowers this barrier to some extent. These important results represent one of the first examples of an efficient oxidative coupling of arenes with alkenes at low temperatures using oxygen as the oxidant.

7.2.4 Mechanistic Aspects. To gain more insight into the mechanism of the oxidative coupling described here, we decided to investigate the electronic dependence of the aromatic substrate of the reaction. Competition experiments of a series of 4-substituted acetanilides show that electron-rich arenes react significantly faster ($k_{obs}(8) > k_{obs}(9) = k_{obs}(1) >> k_{obs}(10)$). The kinetic data resulting from these competition experiments give a Hammett-Brown plot showing the log ($k_{obs} / k_0$) vs. the $\sigma_\pi^*$ constants as depicted in Figure 2. Although the correlation is not conclusively linear, we estimate from the slope of this plot that $\rho = -2.2$. Similar $\rho$-values have been reported for

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_4.png}
\caption{Oxidative coupling of acetanilide with \textit{n}-butyl acrylate using oxygen as the oxidant.}
\end{figure}
electrophilic aromatic substitution reactions.\textsuperscript{[52]} Based on these results, a reaction pathway which involves slow attack of the electrophilic Pd\textsuperscript{I} species (presumably Pd(OAc)) on the arene $\pi$-system, resulting in a Wheland-type (arene ion) intermediate (see scheme 5), seems probable.\textsuperscript{[37]} An alternative mechanism, which involves oxidative addition of the C-H bond to Pd(II) to yield an (aryl)Pd(IV)(H) complex seems unlikely because the electronic dependence observed is not in accordance with such a mechanism. Furthermore, it has been argued that a Pd(II)/Pd(IV) mechanism is not likely to occur when using aryl substrates,\textsuperscript{[42]} although some controversy exists concerning this matter.\textsuperscript{[55]}

To test the electrophilic substitution mechanism hypothesis, the coupling was probed for the presence of a kinetic isotope effect, determined by division of the observed rate-constants ($k_{\text{obs}}$) obtained using acetanilide and 2,3,4,5,6-acetanilide-$d_5$ (see Figure 3). The reaction appears to follow pseudo first-order kinetics for both acetanilide-$h_5$ and acetanilide-$d_5$. From this we calculate $k'_{\text{obs},H} = 1.9 \times 10^2 \text{ mol}^{-1} \cdot \text{s}^{-1} \cdot \text{dm}^3$ and $k'_{\text{obs},D} = 6.4 \times 10^2 \text{ mol}^{-1} \cdot \text{s}^{-1} \cdot \text{dm}^3$. Thus, the reaction indeed exhibits a small but significant kinetic isotope effect ($k_{\text{H}}/k_{\text{D}} = 3$), indicating slow C-H bond activation. The value found here is similar to values reported for other palladium systems involved in electrophilic aromatic substitution.\textsuperscript{[54, 56]} Theoretically, one would expect no kinetic isotope effect for reactions in which the C-H-D bond breaking is not the slowest step. Since the electrophilic attack of the palladium centre on the $\pi$-system of the arene is likely to be the rate-limiting step of the catalytic cycle, (see above) the small isotope effect present can arise from the so-called partitioning effect.\textsuperscript{[57]} This effect can be kinetically deduced from the presence of a pre-equilibrium of the intermediate in aromatic electrophilic substitution (the earlier mentioned
Oxidative Coupling of Anilides with Olefins

areniu m ion) and the starting compounds. When the reverse reaction of this equilibrium is able to compete with the fast C-H(D) bond breaking step, the observed rate will depend to some extent on the rate constant of this irreversible step, resulting in a kinetic isotope effect.[55]

\[
y = -1.40 \times 10^{-4} x - 9.37 \times 10^{-3}
\]

\[
R^2 = 9.92 \times 10^{-1}
\]

\[
y = -4.22 \times 10^{-4} x + 4.55 \times 10^{-2}
\]

\[
R^2 = 9.92 \times 10^{-1}
\]

Figure 3. Logarithmic plot of the reaction rate for the reaction of acetanilide-\(h_5\) with \(n\)-butyl acrylate.

Figure 4. Reaction profile for the stoichiometric reaction of \(n\)-butyl acrylate and acetanilide using \([((C,O)-2-C_6H_4NHC(O)CH_3)Pd(II)(\mu-OAc)]_2\) (●) and Pd(OAc)_2 (○) under standard conditions.
Ryabov and coworkers have shown that in the (earlier mentioned) stoichiometric reaction of the palladated anilide complex dimer [(C₆H₄NHC(O)CH₃)Pd(II)(µ-OAc)]; with styrenes, the rate-limiting step is the insertion of alkene into the palladium-carbon bond. We tested this dimeric ortho-palladated anilide complex in the stoichiometric reaction with n-butyl acrylate (Figure 4). The reaction using the preformed complexes does not show a significant incubation period, in contrast to the in situ generated catalysts, which does exhibit a short incubation period (ca. 8 minutes) before gaining catalytic activity. These results also support a reaction pathway via slow electrophilic attack of cationic [PdOAc]⁺ species on the π-system of the arenes. The proposed mechanism is depicted in Scheme 5.

Scheme 5. Proposed mechanism for the C-H activating step of anilides via electrophilic attack of Palladium on the aromatic ring (for simplicity only monomeric Pd-species are depicted).

7.3 Conclusions

We have shown that the palladium-catalysed oxidative coupling of anilides with alkenes through C-H bond activation, producing arylalkenes, is feasible and can be carried out selectively under very mild conditions. Application of oxygen as the oxidant is possible, resulting in a waste-free Heck-type coupling reaction. Although the scope is somewhat limited so far to activated arenes and alkenes, and relatively high palladium loadings and media of high acidity are required,
the huge potential of this type of coupling has been shown. The results presented in this chapter strongly suggest that the reaction occurs through an electrophilic activation mechanism. Within this mechanism, the electrophilic attack on the π-system of the arene is rate-determining. However, some aspects of the reaction, such as the lack of reactivity for some substrates, remain puzzling and require further detailed mechanistic research. Extension of the scope towards other substrates and the intramolecular variant of the reaction, which would produce valuable indole-derivatives, is highly desirable.

7.4 Experimental Section

General Information. Experiments were carried out under air atmosphere using magnetic stirring unless otherwise noted. Solvents were obtained from commercial suppliers and used without further purification. n-Butylacrylate was purchased from Aldrich and used as received. Anilides were obtained from commercial suppliers (Acros) or synthesised by reaction of the corresponding aniline with acetic anhydride. \( \{\text{C(O)-2-C}_{2}\text{H}_{4}\text{NH}(\text{OH})\text{CH}_{3}\} \text{Pd}(\mu\text{-OAc})_{2} \) was prepared as reported by Fujiwara.\(^{[4]}\) \(^1\)H NMR spectra were recorded on a Varian Mercury 300 (300.1 MHz) spectrometer in CDCl\(_3\) and are reported in ppm using tetramethylsilane as external standard. Data are reported as follows: (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; integration; coupling constant(s) in Hz; assignment). \(^1\)C NMR spectra were recorded on the same spectrometer (75.5 MHz) in proton decoupled mode. GC measurements were performed on a Shimadzu GC-17A, equipped with a F.I.D. detector and a BPX35 column with an internal diameter of 0.22 mm and a film thickness of 0.25 μm. GC MS measurements (F.I. detection) were performed on a HP 5890 5971 apparatus, equipped with a ZB-5 column (5% a cross-linked phenyl polysiloxane) with an internal diameter of 0.25 mm and film thickness of 0.25 μm. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed at the Department of Microanalysis at the Rijksuniversiteit Groningen, The Netherlands.

Parallel Screening Experiments. Rapid screening experiments were carried out by using a commercially available automated parallel synthesis Chemspeed ASW 2000 apparatus. The reactions were performed under an inert atmosphere of nitrogen. Each reaction vessel was charged with 0.02 mmol (1 mol%) of the desired catalyst, 0.25 mL of dihexyl ether as internal standard and, if required, 216 mg (2.0 mmol) of benzoquinone (BQ), followed by 2.0 mL of a stock solution of the aniline-substrate (1.0 M) in the desired solvent. Next, the alkene was added (2.0 mmol), the reaction mixture heated to 80 °C and subsequently stirred under vortex agitation for 16 hrs.
Samples of the resulting reaction mixtures were diluted with hexanes and analyzed by GC MS. See Figure 5 for details on the reactions screened.

**General Procedure for the Coupling of Acetanilide Derivatives with n-Butylacrylate.** In a typical experiment, anilide (3.0 mmol), 13.5 mg (0.06 mmol) of Pd(OAc)$_2$, 324 mg (3.0 mmol) of BQ and 286 mg (1.5 mmol) of p-toluenesulfonylic acid monohydrate were weighed into a one-neck round-bottom flask charged with a stirring bar. Next, 4.5 mL of acetic acid was added, followed by a solution of 0.42 mL (3.0 mmol) n-butylacrylate in 2.25 mL of toluene. The flask was capped with a rubber septum, and the mixture stirred overnight. Aliquots of the mixture were taken and diluted in diethyl ether, washed with a saturated NaHCO$_3$ solution, dried over MgSO$_4$, followed by GC or GC MS analysis. After 16 hrs., the reaction mixture was diluted with 15 mL of ether, and carefully neutralized with a 2.5 M NaOH solution. After extraction of the aqueous phase with 15 mL of ether, the combined organic phases were washed with water (15 mL), dried (MgSO$_4$) and evaporated in vacuo. The resulting solids were purified by column chromatography to yield the corresponding product as a white powder. Recrystallization provided analytically pure product (except for 15).

**($E$)-3-(2-acetylamino-phenyl)-propenoic acid butyl ester (4).** $^1$H NMR (300 MHz, CDCl$_3$): δ 7.80 (d, 1H, J = 15.7 Hz, olefinic H), 7.73 (d, 1H, J = 8.4 Hz, ArH), 7.54 (d, 1H, J = 7.8 Hz, ArH), 7.40-7.37 (m, 2H, ArH), 7.20 (m, 1H, ArH), 6.39 (d, 1H, J = 15.7 Hz, olefinic H), 4.19 (t, 2H, J = 6.6 Hz, C(0)OC$_2$H$_5$), 2.22 (s, 3H, NHC(0)C$_2$H$_5$), 1.71-1.62 (m, 2H, OCH$_2$CH$_2$), 1.45-1.42 (m, 2H, CH$_2$CH$_2$CH$_2$), 0.95 (t, 3H, J = 7.5 Hz, CH$_3$). ($\text{The N-}\ Z$ resonance is not observed); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 169.2, 167.2, 139.5, 136.1, 131.0, 127.9, 127.3, 126.2, 125.6, 120.8, 64.9, 30.9, 24.4, 19.4, 14.0. Mp: 86 °C. Calcd. (%): C 68.94, H 7.33, N 5.36; found: C 68.96, H 7.40, N 5.34.

**($E$)-3-(2-acetylamino-5-methylphenyl)-propenoic acid butyl ester (13).** $^1$H NMR (300 MHz, CDCl$_3$): δ 7.76 (d, 1H, J = 16.0 Hz, olefinic H), 7.65 (bs, 1H, N-\text{H}), 7.55 (d, 1H, J = 8.2 Hz, ArH), 7.36 (s, 1H, ArH), 7.19 (d, 1H, J = 8.2 Hz, ArH), 6.38 (d, 1H, J = 16.0 Hz, olefinic H), 4.19 (t, 2H, J = 6.6 Hz, C(0)OCH$_2$), 2.33 (s, 3H, NHC(O)CH$_3$), 2.14 (s, 3H, ArC$_3$H$_3$), 1.70-1.63 (m, 2H, OCH$_2$CH$_2$), 1.46-1.38 (m, 2H, CH$_2$CH$_2$CH$_2$), 0.96 (t, 3H, J = 7.3 Hz, CH$_3$). ($\text{The N-}\ Z$ resonance is not observed); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 169.5, 167.3, 139.9, 136.0, 133.7, 131.8, 128.3, 127.5, 126.1, 120.1, 64.8, 30.9, 24.1, 21.2, 19.4, 14.0. Mp: 97 °C. Calcd. (%): C 69.79, H 7.69, N 5.09; found: C 69.65, H 7.82, N 5.08.

**($E$)-3-(2-acetylamino-4-methylphenyl)-propenoic acid butyl ester (14).** $^1$H NMR (300 MHz, CDCl$_3$): δ 7.95 (bs, 1H, N-\text{H}), 7.74 (d, 1H, J = 15.9 Hz, olefinic H), 7.40-7.35 (m, 2H, ArH), 6.94 (d, 1H, J = 8.0 Hz, ArH), 6.27 (d, 1H, J = 15.9 Hz, olefinic H), 4.12 (t, 2H, J = 6.6 Hz,
Oxidative Coupling of Anilides with Olefins

C(=O)OCH₂, 2.27 (s, 3H, NHC(=O)CH₂), 2.15 (s, 3H, ArCH₃), 1.64-1.59 (m, 2H, OCH₂CH₃), 1.40-1.35 (m, 2H, CH₂CH₂CH₂), 0.91 (t, 3H, J = 7.3 Hz, CH₃CH₂CH₂), \(^1^C\) NMR (75 MHz, CDCl₃): δ 169.4, 167.4, 141.7, 139.6, 136.0, 127.2, 127.0, 126.2, 125.2, 119.4, 64.8, 30.9, 24.3, 21.7, 19.4, 14.0. Mp: 127-128 °C. Caled. (% for C₁₅H₁₂NO₂): C 69.79, H 7.69, N 5.09; found: C 69.77, H 7.74, N 5.08.

\((E)\)-3-(2-acetamino-3-methylphenyl)-propenoic acid butyl ester (15). \(^1^H\) NMR (300 MHz, CDCl₃): δ 7.79 (d, 1H, J = 15.9 Hz, olefinic H), 7.74 (bs, 1H, N-H), 7.30-7.22 (m, 3H, ArH), 6.38 (d, 2H, J = 6.5 Hz, C(=O)OCH₂), 2.10 (s, 3H, NHC(=O)CH₂), 2.00 (s, 3H, ArCH₃), 1.46-1.37 (m, 2H, OCH₂CH₂), 1.20 (t, 3H, J = 7.4 Hz, CH₃CH₂CH₂), \(^1^C\) NMR (75.5 MHz, CDCl₃): δ 169.9, 167.5, 140.7, 136.8, 134.7, 130.7, 129.9, 127.9, 123.9, 120.0, 64.7, 30.9, 23.3, 19.4, 18.6, 14.0. Compound contains a significant amount of starting compound (6), which could not be separated from the product.

\((E)\)-3-(2-acetamino-5-methoxyphenyl)-propenoic acid butyl ester (16). \(^1^H\) NMR (300 MHz, CDCl₃): δ 7.75 (d, 1H, J = 15.7 Hz, olefinic H), 7.48 (d, 1H, J = 8.8 Hz, ArH), 7.08-7.05 (m, 2H, N-H and ArH overlapping), 6.95-6.91 (m, 4H, ArH), 4.19 (t, 2H, J = 6.6 Hz, C(=O)OCH₂), 3.80 (s, 3H, OCH₃), 2.20 (s, 3H, NHC(=O)CH₂), 1.69-1.61 (m, 2H, OCH₂CH₂), 1.46-1.38 (m, 2H, CH₂CH₂CH₂), 0.92 (t, 3H, J = 7.4 Hz, CH₃CH₂CH₂), \(^1^C\) NMR (75 MHz, CDCl₃): δ 169.8, 167.1, 157.9, 139.7, 130.4, 129.3, 128.2, 120.5, 117.0, 111.3, 64.8, 55.8, 30.9, 23.9, 19.4, 14.0. Mp: 128-129 °C. Caled. (% for C₁₅H₁₂NO₂): C 65.96, H 7.27, N 4.81; found: C 66.04, H 7.29, N 4.85.

\((E)\)-3-(2-benzoylamino-phenyl)-propenoic acid butyl ester (20). \(^1^H\) NMR (300 MHz, CDCl₃): δ 8.04 (bs, 1H, N-H), 7.88-7.81 (m, 4H, ArH + olefinic H), 7.59-7.38 (m, 5H, ArH), 7.25-7.20 (m, 1H, ArH), 6.40 (d, 1H, J = 15.9 Hz, olefinic H), 4.13 (t, 2H, J = 6.6 Hz, C(=O)OCH₂), 1.65-1.58 (m, 2H, OCH₂CH₂), 1.41-1.33 (m, 2H, CH₂CH₂CH₂), 0.90 (t, 3H, J = 7.2 Hz, CH₃CH₂CH₂), \(^1^C\) NMR (75 MHz, CDCl₃): δ 167.0, 166.3, 139.4, 136.1, 134.4, 132.4, 131.0, 129.1, 128.4, 127.5, 126.3, 125.6, 121.1, 64.8, 30.9, 19.4, 14.0. Mp: 145 °C. Caled. (% for C₁₅H₁₄NO₂): C 74.28, H 6.55, N 4.33; found: C 73.98, H 6.48, N 4.40.

Kinetic Competition Experiments. These were performed as described above for the general catalysis procedures, but with a total Pd-loading of 34 mg (0.15 mmol: 5 mol\(^{-1}\)), equimolar amounts of competitive substrates (3.00 mmol in total) and at a reaction temperature of 40 °C. The conversion in acetanilide was determined by GC/MS using dihexylether as internal standard.

Deuterium Incorporation Experiments. These were performed as described above for the general catalysis procedures, but in CH₃COOD instead of CH₃COOH and without the addition of the alkene. The resulting reaction mixture was stirred for 24 hours at room temperature. After
standard workup, the mixture was analysed by GC/MS. No increase in the ion peaks belonging to mono- or dideterated amide was observed within experimental error.

Figure 5. Schematic overview of the experimental set-up of the rapid-screening experiments
References

[24] after the completion of this manuscript, a review on C-H activation followed by reaction with unsaturated substrates by Pfeffer and co-workers was published, see: V. Ritleng, C. Sirlin, M. Pfeffer, Chem. Rev. 2002, 102, 1731.
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