Bidentate ligand promoted palladium-catalyzed C–H olefination of aromatic compounds

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CHAPTER 4

S,O-BIDENTATE LIGAND PROMOTED PALLADIUM-CATALYZED C–H OLEFINATION OF NON-DIRECTED ARENES WITH ALLYLIC SUBSTRATES

Part of this chapter has been published in:
4.1 Introduction
Palladium-catalyzed C–H olefination of simple arenes with unactivated alkenes is an almost unexplored research area.\(^1\) A few transformations using allylic substrates have been reported.\(^2\) One of the major challenges is to control the selectivity of these processes. For example, using allyl acetate as substrate, several isomers can be formed as shown in Scheme 4.1.\(^3\) On top of this, the site selectivity of C–H activation using undirected arenes is, as illustrated in Chapter 3, difficult to control.

Some examples of C–H olefination of simple arenes with allylic substrates are shown in Schemes 4.2. C–H Olefination of arenes with allyl acetate was achieved by using Pd(OAc)\(_2\) in combination with \(n\)-BuCO\(_2\)H as additive using Ag\(_2\)CO\(_3\) and BQ as oxidants (Scheme 4.2, a).\(^2d\) The reaction conditions were compatible with benzene, electron-rich and poor arenes giving the allylated products in moderate yields with good regioselectivities towards the styrenyl products. Regarding the site selectivity when using substituted arenes, a mixture of isomers was detected in all cases. Gigant and Bäckvall reported the C–H olefination of non-directed arenes with allyl acetate and \(N\)-allylphthalimide using Pd(OAc)\(_2\), iron phthalocyanine, BQ and acridine, for the reaction with \(N\)-allylphthalimide, under oxygen atmosphere (Scheme 4.2, b).\(^2c,2g\) Under these conditions, the desired styrenyl products were obtained in moderate yields and poor site selectivities. Law and co-workers described the C–H olefination of arenes with allylarenes using Pd(TFA)\(_2\) as a catalyst, AgOAc as an oxidant and pivalic acid as an additive (Scheme 4.2, c).\(^2i\) The reaction conditions were applied to benzene, electron rich and halogenated arenes providing the allylated products in moderate yields as a mixture of isomers.
S,O-Ligand promoted C–H olefination of arenes with allylic substrates

As described in Chapter 3, we have discovered that S,O-bidentate ligands are capable of promoting Pd-catalyzed C–H olefination reactions of non-directed arenes with activated alkenes. Under the conditions developed in Chapter 3, the reaction using unactivated alkenes, including allylic substrates, was inefficient. We speculated that by tuning the reaction conditions, a broader alkene scope can be achieved. This chapter deals with the development of a new catalytic system based on Pd/S,O-ligand that permits the C–H olefination of non-directed arenes with allylic substrates to occur in fair yields.

4.2 Results and discussion

Optimization of reaction conditions for C–H allylation of benzene

We started the investigation by applying our standard conditions for C–H olefination of non-directed arenes with activated alkenes as reported in Chapter 3. To allylbenzene, Pd(OAc)₂/L (5 mol%) and 1 equiv of PhCO₂t-Bu in acetic acid as the solvent, an excess of benzene was added and the reaction mixture was stirred at 100 °C for 6 h (Scheme 4.3). Unfortunately, the desired product 1a was obtained in a yield of only 15%.

![Scheme 4.3 C–H Olefination of benzene with allylbenzene.](image)
We then altered the reaction conditions to 10 mol% of Pd/L catalyst, 1 equiv of allylbenzene, and 66 equiv of benzene and stirring at 80 °C overnight. Under these conditions and using AgOAc as an oxidant, we observed an increase in yield of 1a to 38% (Table 4.1, entry 1). The yield was improved to 54% when DCE was used as solvent (entry 2). Other solvents including CHCl₃, hexafluorobenzene and methyl t-butyl ether were tried (entries 3–5). However, none of them gave a better result than using DCE. We also performed the C–H olefination using different oxidants including Cu(OAc)₂, CsOAc, Cs₂CO₃, BQ and PhCO₃t-Bu (entries 6–10). Again, no improvement was observed as compared to the reaction using AgOAc (entry 2). Finally, we tested different temperatures ranging from 60 to 150 °C (entries 2 and 11–14) and found that 80 °C was the optimal temperature.

Table 4.1 Screening of solvents, oxidants and temperatures.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Oxidant</th>
<th>Temperature (°C)</th>
<th>NMR yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>AgOAc</td>
<td>80</td>
<td>38%</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>AgOAc</td>
<td>80</td>
<td>54%</td>
</tr>
<tr>
<td>3</td>
<td>CHCl₃</td>
<td>AgOAc</td>
<td>80</td>
<td>38%</td>
</tr>
<tr>
<td>4</td>
<td>C₆F₆</td>
<td>AgOAc</td>
<td>80</td>
<td>23%</td>
</tr>
<tr>
<td>5</td>
<td>Methyl t-butyl ether</td>
<td>AgOAc</td>
<td>80</td>
<td>17%</td>
</tr>
<tr>
<td>6</td>
<td>DCE</td>
<td>Cu(OAc)₂</td>
<td>80</td>
<td>15%</td>
</tr>
<tr>
<td>7</td>
<td>DCE</td>
<td>CsOAc</td>
<td>80</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>DCE</td>
<td>Cs₂CO₃</td>
<td>80</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>DCE</td>
<td>BQ</td>
<td>80</td>
<td>13%</td>
</tr>
<tr>
<td>10</td>
<td>DCE</td>
<td>PhCO₃t-Bu</td>
<td>80</td>
<td>5%</td>
</tr>
<tr>
<td>11</td>
<td>DCE</td>
<td>AgOAc</td>
<td>60</td>
<td>19%</td>
</tr>
<tr>
<td>12</td>
<td>DCE</td>
<td>AgOAc</td>
<td>100</td>
<td>36%</td>
</tr>
<tr>
<td>13</td>
<td>DCE</td>
<td>AgOAc</td>
<td>120</td>
<td>30%</td>
</tr>
<tr>
<td>14</td>
<td>DCE</td>
<td>AgOAc</td>
<td>150</td>
<td>25%</td>
</tr>
</tbody>
</table>

Yield was determined by ¹H NMR analysis of the crude mixture using CH₂Br₂ as an internal standard. NR = no reaction.

Next, we screened the reaction with different palladium sources including Pd(OAc)₂, Pd(TFA)₂, Pd(ACN)₂Cl₂, PdCl₂ and Pd(PPh₃)₂Cl₂ (Table 4.2). Nevertheless, Pd(OAc)₂ still gave the best result.
Table 4.2 Screening of palladium sources.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source</th>
<th>NMR yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>39%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(TFA)$_2$</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>Pd(ACN)$_2$Cl$_2$</td>
<td>36%</td>
</tr>
<tr>
<td>4</td>
<td>PdCl$_2$</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$</td>
<td>25%</td>
</tr>
</tbody>
</table>

Yield was determined by $^1$H NMR analysis of the crude mixture using CH$_2$Br$_2$ as an internal standard. NR = no reaction. Note: All reactions were performed at the same time for comparison.

With the optimal conditions in hand, we compared the reaction of benzene and allylbenzene with and without ligand (Scheme 4.4). The reaction without ligand provided product 1a in 35% yield while the reaction with ligand resulted in an improved isolated yield of 52%. To prove that the increase in yield was due to an acceleration of the reaction, we studied the kinetic profile of the reactions in the absence and presence of ligand L. The curves clearly indicated that ligand L increases the reaction rate. However, this acceleration is less pronounced than in the reaction reported in Chapter 3.

Scheme 4.4 C–H Olefination of benzene and allylbenzene with and without ligand L.

C–H Olefination of non-directed arenes and allylic substrates

With the optimal conditions for the reaction of benzene with allylbenzene in hand, we explored the C–H olefination reaction with other substrates (Table 4.3). The reaction of naphthalene, o-xylene and anisole with allylbenzene provided the desired allylated products 2, 3 and 4 in 89%, 62% and 68% isolated yields, respectively (entries 1–3). We next studied the generality of this reaction using other allylic substrates such as allyl acetate and N-allylphthalimide. Using our methodology, the reaction of allyl acetate with benzene, naphthalene, o-xylene, m-xylene or mesitylene provided the desired allylated products 5–9 in 53–75% isolated yields (entries 4–8). Other arenes with different electronic properties such as anisole, 4-chloroanisole and 1,3,5-trifluorobenzene were also evaluated in the reaction with allyl acetate (entries 9–11). For these substrates, the allylated products 10–12 were obtained in moderate to good yields (40–82%). The reaction of N-allylphthalimide with mesitylene and 1,3,5-trimethoxybenzene furnished the allylated products 13 and 14 in 73% and 61% yields, respectively (entries 12 and 13). Importantly, in all cases, the reaction in the presence of the
S, O-ligand \( \textbf{L} \) provided a higher yield than the reaction without ligand. Overall, the new catalytic system promotes the olefination of a wide variety of arenes including bulky, electron-rich and electron-poor arenes.

Table 4.3 Substrate scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield(^a)</th>
<th>( a/\beta ) or ( o/m/p ) (^d)</th>
<th>( a/a' ) or ( b/b' ) or ( c/c' ) (^e)</th>
<th>( E/Z ) (^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a/a'</td>
<td>89%</td>
<td>64/36(^d)</td>
<td>42/58(^d)</td>
<td>-(^g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
<td>32/68(^d)</td>
<td>48/52(^d)</td>
<td>-(^g)</td>
</tr>
<tr>
<td>2</td>
<td>3a/a'</td>
<td>62%</td>
<td>38/62(^d)</td>
<td>50/50(^d)</td>
<td>-(^g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37%</td>
<td>13/87(^d)</td>
<td>54/46(^d)</td>
<td>-(^g)</td>
</tr>
<tr>
<td>3</td>
<td>4a/a'</td>
<td>68%</td>
<td>62/4/34(^d)</td>
<td>65/35(^d)</td>
<td>-(^g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37%</td>
<td>30/10/60(^d)</td>
<td>55/45(^d)</td>
<td>-(^g)</td>
</tr>
<tr>
<td>4</td>
<td>5b/b'</td>
<td>65%</td>
<td>-</td>
<td>92/8</td>
<td>90/10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35%(^b)</td>
<td>-</td>
<td>96/4</td>
<td>95/5</td>
</tr>
<tr>
<td>5</td>
<td>6b/b'</td>
<td>75%</td>
<td>60/40(^g)</td>
<td>95/5</td>
<td>-(^g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55%(^b)</td>
<td>34/66(^g)</td>
<td>97/3</td>
<td>-(^g)</td>
</tr>
<tr>
<td>6</td>
<td>7b/b'</td>
<td>74%</td>
<td>36/64</td>
<td>91/9</td>
<td>-(^g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38%(^b)</td>
<td>17/83</td>
<td>96/4</td>
<td>-(^g)</td>
</tr>
<tr>
<td>7</td>
<td>8b/b'</td>
<td>53%</td>
<td>33/60/7</td>
<td>85/15</td>
<td>-(^g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36%(^b)</td>
<td>33/60/7</td>
<td>85/15</td>
<td>-(^g)</td>
</tr>
<tr>
<td>8</td>
<td>9b/b'</td>
<td>67%</td>
<td>-</td>
<td>71/29</td>
<td>86/14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12%(^b)</td>
<td>-</td>
<td>75/25</td>
<td>71/29</td>
</tr>
<tr>
<td>9</td>
<td>10b/b'</td>
<td>78%</td>
<td>68/0/32(^g)</td>
<td>93/7</td>
<td>-(^g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38%(^b)</td>
<td>37/0/63(^g)</td>
<td>98/2</td>
<td>-(^g)</td>
</tr>
<tr>
<td>10</td>
<td>11b/b'</td>
<td>82%</td>
<td>17/83</td>
<td>91/9</td>
<td>-(^g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30%</td>
<td>12/88</td>
<td>95/5</td>
<td>-(^g)</td>
</tr>
</tbody>
</table>
Regarding the site selectivity of the process (see α/β or o/m/p values in Table 4.3), the allylation reaction in the presence of the S,O-ligand \( \text{L} \) took place preferentially at the most \( \text{electron-rich} \) position in the arene. A similar trend was observed in the olefination reactions described in Chapter 3. Concerning the selectivity of \( \beta \)-hydride elimination (see \( \text{a/a}', \text{b/b}' \) and \( \text{c/c}' \) values in Table 4.3), a ca. 1:1 mixture of isomers in both reactions with and without ligand was observed using allylbenzene (entries 1–3). For the olefination reactions with allyl acetate or \( \text{N}-\text{allylphthalimide} \), only the products from internal carbopalladation were observed (entries 4–13). After the carbopalladation step, \( \beta\)-\text{OAc} [or \( \beta\)-(NPhth)] or \( \beta\)-hydride elimination can take place. However, under our reaction conditions, we did not detect the products derived from \( \beta\)-\text{OAc} [or \( \beta\)-(NPhth)] elimination. Furthermore, with respect to the \( \beta\)-hydride elimination pathway, although two possible products can be formed, we observed, with and without ligand, mainly the products from the \( \beta\)-hydride elimination that leads to the double bond in conjugation with the arene. This high regioselectivity has been previously attributed to the chelation between the O and the Pd atom (Scheme 4.5).\(^{2a,2d,3} \) This chelation impedes rotation around the C–C bond and therefore, hinders the \( \text{syn} \) relationship between the Pd and H\(_b\). It can also be rationalized that the most stable product, with the conjugation between the double bond and the arene, is the one that forms.

In line with this general trend, we found that the reactions of mesitylene and 1,3,5-trifluorobenzene afforded the allylated products 9, 12 and 13 with moderate regioselectivity (71/29 for mesitylene and 62/38 for 1,3,5-trifluorobenzene; entries 8, 11 and 12). In addition, isomerization of the double bond to the \( \text{Z} \) configuration occurred in the reaction of these arenes with allyl acetate (see \( \text{E/Z} \) value, entries 8 and 11). Similar behavior was observed in the reaction without ligand. The low regioselectivity observed can be explained by steric hindrance of the mesitylene, which hampers rotation around the C–C bond, disfavouring the \( \text{syn} \) relationship between the Pd and H\(_b\). Another explanation is that the \( \text{ortho} \)-methyl substituent of mesitylene prevents coplanarity of the double bond to the aromatic ring thus making the styrenyl isomer less stable. However, the reason why the allylation reaction of 1,3,5-trifluorobenzene provided the olefinated product with low regioselectivity (b/b' and \( \text{E/Z} \)) is still unclear to us.

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**Table 4.3 Substrate scope (continued).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>( \text{b/b}' )</th>
<th>( \text{c/c}' )</th>
<th>( \text{d/d}' )</th>
<th>( \text{e/e}' )</th>
</tr>
</thead>
</table>
| 11    | \[
\begin{array}{c}
\text{F} \\
\text{Me}
\end{array}
\] | 40% \( ^{a} \) | - | 62/38 | 69/31 |
|       | \[
\begin{array}{c}
\text{F} \\
\text{Me}
\end{array}
\] | 25% \( ^{b} \) | - | 65/35 | 73/27 |
| 12    | \[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\] | 73% \( ^{c} \) | - | 71/29 | 93/7 |
|       | \[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\] | 20% \( ^{b} \) | - | 90/10 | 90/10 |
| 13    | \[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\] | 61% \( ^{d} \) | - | 98/2 | \( ^{f} \) |
|       | \[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\] | 36% \( ^{e} \) | - | 97/3 | - |

\(^{a}\text{Isolated yield.} \ ^{b}\text{Calculated yield based on } ^{1}\text{H NMR using CHBr}_{2} \text{as an internal standard.} \ ^{c}\text{Determined by } ^{1}\text{H NMR analysis of the isolated mixture.} \ ^{d}\text{Determined by GC analysis.} \ ^{e}\text{Traces of } \text{Z} \text{isomer were detected.} \ ^{f}\text{No } \text{Z} \text{isomer was detected.} \ ^{g}\text{Ratio measured from the } \text{b} \text{isomer.} \)
Finally, we applied the developed methodology to the late-stage functionalization of a complex molecule (Scheme 4.6). In this case, we minimized the amount of the arene to 1 equiv. Under these conditions, the reaction of O-methylestrone (1 equiv) with allyl acetate (1.5 equiv) and Pd(OAc)$_2$ (10 mol%) without ligand provided the desired product in only 10% yield, as determined by NMR. To our delight, the same reaction in the presence of L furnished the olefinated product 15 in 55% isolated yield as a mixture of ortho-olefinated isomers (a:b = 60:40).

Scheme 4.6 Late-stage C–H alkylation of estrone.

4.3 Conclusions
The Pd/S,O-ligand catalytic system is capable of promoting C–H olefination of arenes with different allyl substrates in the presence of silver acetate, providing the desired allylated products in good yields. We have observed that acceleration of the reaction with allyl substrates in the presence of the S,O-ligand is less pronounced than in the reaction with activated alkenes as reported in Chapter 3. A wide range of arenes including bulky, electron-rich and electron-poor arenes are suitable substrates for this transformation. The olefination reactions occur preferentially at the most electron-rich position of the arene similar to the reaction using activated alkenes. Regarding the regioselectivity of the β-hydride elimination, mixtures of isomers are obtained in the reaction with allylbenzene. However, in the reaction with allyl acetate and N-allylphthalimide mainly one isomer is formed. The applicability of the new catalytic system is demonstrated in the late-stage functionalization of a complex molecule.

4.4 Acknowledgements
Dr. Yolanda Álvarez-Casao, Michiel Uiterweerd, Nick Westerveld and Simone Sozzi are kindly acknowledged for their contributions to this chapter. Ed Zuidinga and Dorette Tromp are thanked for the high-resolution mass measurements.
4.5 Experimental section

General information
Chromatography: Silicycle Silica Flash P60 size 40–63 µm (230–400 mesh), TLC: Merck silica gel 60 (0.25mm). Visualization of the TLC was performed by UV, phosphomolybdic acid, KMnO₄ or oleum staining. Mass spectra were recorded on AccuTOF GC v 4g and JMS-T100GCV mass spectrometers. ¹H and ¹³C NMR were recorded on a Bruker 400 and a Bruker DRX 300, using CDCl₃ as a solvent. Chemical shift values are reported in ppm with the solvent resonance as an internal standard (CDCl₃: δ 7.26 for ¹H, δ 77.16 for ¹³C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, bs = broad singlet, m = multiplet), coupling constants (Hz), and integration.

Infrared spectra were recorded on a Bruker IFS 28 FT-spectrophotometer and wavelengths are reported in cm⁻¹. Meltin points were measured in a POLYThERM A Heiztisch Mikroskop. GC analysis was performed on a Shimadzu GC-2010 Plus Gas Chromatograph, using a SH-Rxi-5HT (30 m, 0.25 mm, D 0.25 µm) column. All reagents and solvents were used as received. Pd(OAc)₂ was purchased from Strem. 3-Methyl-2-(phenylthio)butanoic acid (L) was prepared according to the procedure described in Chapter 3. N-Allylphthali mid was prepared according to the literature. Reference compounds were synthesized following procedures described in literature for similar compounds: 2α₇, 2αβ₇, 2α’α₉, 2α’β₉, 3α₉, 3αβ₉, 3α’α₉, 3α’β₉, 3a’α₉, 3a’β₉, 4αo₁₁, 4am₁₂, 4ap₁₂, 4a’m₁₃, 4a’p₁₃.

Pd-Catalyzed C–H olefination of benzene with allylbenzene

Screening of solvents
A stock solution of ligand L (0.0846 M in CH₂Cl₂) (300 µL, 25 µmol, 10 mol%) was added to a pressure tube and the solvent was allowed to evaporate at room temperature. Then, allylbenzene (33 µL, 0.25 mmol, 1 equiv), Pd(OAc)₂ (5.6 mg, 25 µmol, 10 mol%), silver acetate (62.8 mg, 0.375 mmol, 1.5 equiv), benzene (1.5 mL, 16.5 mmol, 66 equiv) and the corresponding solvent (0.5 mL, 0.5 M) were added. The pressure tube was sealed with a screw cap and the reaction was placed in an 80 °C pre-heated oil bath and stirred overnight. The resulting reaction mixture was filtered through a pad of Celite, rinsed with CH₂Cl₂ and then concentrated under reduced pressure. The ¹H NMR yield was determined by adding CH₂Br₂ (17.5 µL, 0.25 mmol, 1 equiv) as an internal standard.

Screening of oxidants
A stock solution of ligand L (0.0846 M in CH₂Cl₂) (300 µL, 25 µmol, 10 mol%) was added to a pressure tube and the solvent was allowed to evaporate at room temperature. Then, allylbenzene (33 µL, 0.25 mmol, 1 equiv), Pd(OAc)₂ (5.6 mg, 25 µmol, 10 mol%), the corresponding oxidant (0.375 mmol, 1.5 equiv), benzene (1.5 mL, 16.5 mmol, 66 equiv) and DCE (0.5 mL, 0.5 M) were added. The pressure tube was sealed with a screw cap and the reaction was placed in an 80 °C pre-heated oil bath and stirred overnight. The resulting reaction mixture was filtered through a pad of Celite, rinsed with CH₂Cl₂ and then concentrated under reduced pressure. The ¹H NMR yield was determined by adding CH₂Br₂ (17.5 µL, 0.25 mmol, 1 equiv) as an internal standard.
Table 4.4 Screening of oxidants.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Amount of oxidant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOAc</td>
<td>62.8 mg</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)$_2$</td>
<td>68.1 mg</td>
</tr>
<tr>
<td>3</td>
<td>CsOAc</td>
<td>72.0 mg</td>
</tr>
<tr>
<td>4</td>
<td>Cs$_2$CO$_3$</td>
<td>122.2 mg</td>
</tr>
<tr>
<td>5</td>
<td>BQ</td>
<td>40.5 mg</td>
</tr>
<tr>
<td>6</td>
<td>PhCO$_3$t-Bu</td>
<td>70 µL</td>
</tr>
</tbody>
</table>

Screening of temperatures
A stock solution of ligand L (0.0846 M in CH$_2$Cl$_2$) (300 µL, 25 µmol, 10 mol%) was added to a pressure tube and the solvent was allowed to evaporate at room temperature. Then, allylbenzene (33 µL, 0.25 mmol, 1 equiv), Pd(OAc)$_2$ (5.6 mg, 25 µmol, 10 mol%), silver acetate (62.8 mg, 0.375 mmol, 1.5 equiv), benzene (1.5 mL, 16.5 mmol, 66 equiv) and DCE (0.5 mL, 0.5 M) were added. The pressure tube was sealed with a screw cap and the reaction was placed in a 60–150 °C pre-heated oil bath and stirred overnight. The resulting reaction mixture was filtered through a pad of Celite, rinsed with CH$_2$Cl$_2$ and then concentrated under reduced pressure. The $^1$H NMR yield was determined by adding CH$_2$Br$_2$ (17.5 µL, 0.25 mmol, 1 equiv) as an internal standard.

Screening of palladium sources
A stock solution of ligand L (0.0846 M in CH$_2$Cl$_2$) (300 µL, 25 µmol, 10 mol%) was added to a pressure tube and the solvent was allowed to evaporate at room temperature. Then, allylbenzene (33 µL, 0.25 mmol, 1 equiv), the corresponding Pd source (25 µmol, 10 mol%), silver acetate (62.8 mg, 0.375 mmol, 1.5 equiv), benzene (1.5 mL, 16.5 mmol, 66 equiv) and DCE (0.5 mL, 0.5 M) were added. The pressure tube was sealed with a screw cap and the reaction was placed in an 80 °C pre-heated oil bath and stirred overnight. The resulting reaction mixture was filtered through a pad of Celite, rinsed with CH$_2$Cl$_2$ and then concentrated under reduced pressure. The $^1$H NMR yield was determined by adding CH$_2$Br$_2$ (17.5 µL, 0.25 mmol, 1 equiv) as an internal standard.

Table 4.5 Screening of palladium sources.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source</th>
<th>Amount of Pd (mg)</th>
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<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>5.6</td>
</tr>
<tr>
<td>2</td>
<td>Pd(TFA)$_2$</td>
<td>8.3</td>
</tr>
<tr>
<td>3</td>
<td>Pd(ACN)$_2$Cl$_2$</td>
<td>6.5</td>
</tr>
<tr>
<td>4</td>
<td>PdCl$_2$</td>
<td>4.4</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$</td>
<td>17.5</td>
</tr>
</tbody>
</table>

Kinetic profile of the Pd-catalyzed C–H allylation of benzene with and without ligand L
Ligand L (10.5 mg, 0.05 mmol, 10 mol%), Pd(OAc)$_2$ (11.2 mg, 0.05 mmol, 10 mol%), silver acetate (125 mg, 0.75 mmol, 1.5 equiv), allylbenzene (66 µL, 0.5 mmol, 1 equiv), benzene (3 mL, 33.3 mmol, 66 equiv) and DCE (1 mL, 0.5 M) were added into a pressure tube. The pressure tube was sealed with a crimp cap with septa and the reaction was placed in an 80 °C
S,O-Ligand promoted C–H olefination of arenes with allylic substrates

Pre-heated oil bath. The reaction was monitored during time by sampling 0.1 mL. PhCl (20 µL) was added in each sample as an internal standard and diluted with EtOAc (1 mL). The organic layer was filtered through a plug of Celite and analyzed by GC.

A parallel reaction without ligand was also performed to compare the kinetic profile. Pd(OAc)2 (11.2 mg, 0.05 mmol, 10 mol%), silver acetate (125 mg, 0.75 mmol, 1.5 equiv), allylbenzene (66 µL, 0.5 mmol, 1 equiv), benzene (3 mL, 33.3 mmol, 66 equiv) and DCE (1 mL, 0.5 M) were added into a pressure tube. The pressure tube was sealed with a crimp cap with septa and the reaction was placed in an 80 °C pre-heated oil bath. The reaction was monitored during time by sampling 0.1 mL. PhCl (20 µL) was added in each sample as an internal standard and diluted with EtOAc (1 mL). The organic layer was filtered through a plug of Celite and analyzed by GC.

Table 4.6 Kinetic profile of the Pd-catalyzed C–H allylation of benzene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction time</th>
<th>GC yield (L)</th>
<th>GC yield (no ligand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 min</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>2</td>
<td>15 min</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>3</td>
<td>30 min</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td>4</td>
<td>45 min</td>
<td>20%</td>
<td>7%</td>
</tr>
<tr>
<td>5</td>
<td>1 h</td>
<td>26%</td>
<td>10%</td>
</tr>
<tr>
<td>6</td>
<td>1.5 h</td>
<td>31%</td>
<td>15%</td>
</tr>
<tr>
<td>7</td>
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<td>9</td>
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<td>10</td>
<td>8 h</td>
<td>54%</td>
<td>28%</td>
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</tbody>
</table>

Note: The reactions with and without L were performed at the same time to compare the kinetic profiles.

Pd-Catalyzed C–H olefination of simple arenes with allylic substrates

General procedure A
A stock solution of ligand L (0.0846 M in CH2Cl2) (300 µL, 25 µmol, 10 mol%) was added to a pressure tube and the solvent was allowed to evaporate at room temperature. Then, allylbenzene (33 µL, 0.25 mmol, 1 equiv) or N-allylphthalimide (46.8 mg, 0.25 mmol, 1 equiv), Pd(OAc)2 (5.6 mg, 25 µmol, 10 mol%), silver acetate (62.8 mg, 0.375 mmol, 1.5 equiv), the corresponding arene (66 equiv) and DCE (0.5 mL, 0.5 M) were added. The pressure tube was sealed with a screw cap and the reaction was placed in a 100 °C pre-heated oil bath and stirred for 24 h. The resulting reaction mixture was filtered through a pad of Celite, rinsed with CH2Cl2 and then concentrated under reduced pressure. The 1H NMR yield was determined by adding CH2Br2 (17.5 µL, 0.25 mmol, 1 equiv) as an internal standard. The crude residue was purified by column chromatography to obtain the desired product.

General procedure B
A stock solution of ligand L (0.0846 M in CH2Cl2) (300 µL, 25 µmol, 10 mol%) was added to a pressure tube and the solvent was allowed to evaporate at room temperature. Then, allyl acetate (27 µL, 0.25 mmol, 1 equiv), Pd(OAc)2 (5.6 mg, 25 µmol, 10 mol%), silver acetate (62.8 mg, 0.375 mmol, 1.5 equiv), the corresponding arene (33 equiv) and DCE (0.5 mL, 0.5
M) were added. The pressure tube was sealed with a screw cap and the reaction was placed in an 80 °C pre-heated oil bath and stirred for 20 h. The resulting reaction mixture was filtered through a pad of Celite, rinsed with CH₂Cl₂ and then concentrated under reduced pressure. The ¹H NMR yield was determined by adding CH₂Br₂ (17.5 µL, 0.25 mmol, 1 equiv) as an internal standard. The crude residue was purified by column chromatography to obtain the desired product.

(E)-3-(Phenyl)allyl benzene (1a)

General procedure A was followed using allylbenzene (33 µL, 0.25 mmol, 1 equiv) and benzene (1.5 mL, 16.5 mmol, 66 equiv), providing the titled compound as a yellow oil (25 mg, 52% yield). ¹H NMR spectra data of 1a matched the spectra data reported in the literature for this compound.¹¹ ¹H NMR (400 MHz) δ = 7.47 – 7.23 (m, 10H), 6.53 – 6.37 (m, 2H), 3.60 (d, J = 6.6 Hz, 2H).

A parallel reaction without ligand was also performed providing the titled compounds in 35% ¹H NMR yield.

3-(Naphthalenyl)allyl benzene (2aα), 3-(2-naphthalenyl)allyl benzene (2aβ), 1-cinnamyl-naphthalene (2a′α) and 2-cinnamyl-naphthalene (2a′β)

General procedure A was followed using allylbenzene (33 µL, 0.25 mmol, 1 equiv) and naphthalene (2.1 g, 16.5 mmol, 66 equiv). The crude residue was purified by column chromatography using petroleum ether to EtOAc:petroleum ether 1:19 as eluent providing the titled compounds as a yellow oil (50 mg as a mixture of isomers in a ratio 64α:36β, 2aα:2a′α = 42:58, determined by GC analysis; 89% yield). ¹H NMR spectra data of 2aα, 2aβ, 2a′α and 2a′β matched the spectra data reported in the literature for these compounds.¹⁰,¹⁴-¹⁵ ¹H NMR (400 MHz) of 2a δ = 8.17 – 8.12 (m, 1Hα), 7.96 – 7.70 (m, 6Hα+β), 7.68 – 7.17 (m, 18Hα+β), 6.82 – 6.18 (m, 3Hα+β), 3.73 (dd, J = 6.9, 1.6 Hz, 2Hα), 3.66 (d, J = 6.7 Hz, 2Hβ). Characteristic ¹H NMR signals for 2a′: 2a′α: 4.05 (d, J = 4.7 Hz, 2H), 2a′β: 3.76 (d, J = 6.2 Hz, 2H).

A parallel reaction without ligand was also performed providing the titled compounds in 50% isolated yield (32α:68β, 2aα:2a′α = 48:52, determined by GC analysis).

3-(2,3-Dimethylphenyl)allyl benzene (3aα), 3-(3,4-dimethylphenyl)allyl benzene (3aβ), 1-cinnamyl-2,3-dimethylbenzene (3a′α) and 4-cinnamyl-1,2-dimethylbenzene (3a′β)

General procedure A was followed using allylbenzene (33 µL, 0.25 mmol, 1 equiv) and o-xylene (2 mL, 16.5 mmol, 66 equiv). The crude residue was purified by column chromatography using petroleum ether to EtOAc:petroleum ether 1:19 as eluent providing the titled compounds as a yellow oil (34 mg as a mixture of isomers in a ratio 38α:62β, 3aα:3a′α = 50:50, determined by GC analysis; 62% yield). ¹H NMR spectra data of 3aβ, 3a′α and 3a′β matched the spectra data reported in the literature for these compounds.¹⁴,¹⁶-¹⁷ ¹H NMR (400 MHz) of 3aα δ = 7.50 – 7.30 (m, 6H), 7.18 (d, J = 4.6 Hz, 2H), 6.87 (d, J = 15.5 Hz, 1H), 6.30
(E)-3-(2-Methoxyphenyl)allyl benzene (4ao), \(^{18}\) (E)-3-(3-methoxyphenyl)allyl benzene (4am), \(^{19}\) (E)-3-(4-methoxyphenyl)allyl benzene (4ap), \(^{20}\) 1-cinnamyl-2-methoxybenzene (4a'0), \(^{13}\) 1-cinnamyl-3-methoxy-benzene (4a'm) \(^{13}\) and 1-cinnamyl-4-methoxybenzene (4a'p) \(^{13}\)

General procedure A was followed using allylbenzene (33 μL, 0.25 mmol, 1 equiv) and anisole (1.8 mL, 16.5 mmol, 66 equiv). The crude residue was purified by column chromatography using EtOAc:petroleum ether 1:49 to 1:24 as eluent providing the titled compounds as a yellow oil (37 mg as a mixture of isomers in a ratio 62:4:34p, 4a:4a' = 65:35, determined by GC analysis; 68% yield). \(^1\)H NMR spectra of 4ao, 4am and 4ap matched the spectra data reported in the literature for these compounds. \(^{13,18-20}\) \(^1\)H NMR (400 MHz) δ = 7.56 – 7.19 (m, 20H\textsubscript{α,α,α-mp}), 7.02 – 6.85 (m, 8H\textsubscript{α,α,α,α-mp}), 6.55 – 6.36 (m, 2H\textsubscript{mp}), 6.35 – 6.22 (m, 3H\textsubscript{α,α,α-mp}), 3.90 (s, 3H\textsubscript{α}), 3.85 (s, 3H\textsubscript{α,α-mp}), 3.68 – 3.52 (m, 6H\textsubscript{α,α-mp}). Characteristic \(^1\)H NMR signals for 4a': 4a'α: 3.68 – 3.52 (m, 2H), 4a'm: 3.68 – 3.52 (m, 2H), 4a'p: 3.68 – 3.52 (m, 2H).

A parallel reaction without ligand was also performed providing the titled compounds in 37% isolated yield (13a:87β, 2a:2a' = 54:46, determined by GC analysis).

(E)-Cinnamyl acetate (5b) \(^{21}\) and (E)-3-phenylpropenyl acetate (5b') \(^{22}\)

General procedure B was followed using benzene (0.75 mL, 8.25 mmol, 33 equiv), providing the titled compounds as a yellow oil (29 mg as a mixture of isomers in a ratio 5b:5b' = 92:8, \(Z/E = 10:90\), determined by \(^1\)H NMR; 65% yield). \(^1\)H NMR spectra of 5b and 5b' matched the spectra data reported in the literature for these compounds. \(^{21-22}\) \(^1\)H NMR (400 MHz) of \(E\)-5b δ = 7.45 – 7.26 (m, 5H), 6.66 (d, \(J = 15.9\) Hz, 1H), 6.29 (dt, \(J = 15.9, 6.4\) Hz, 1H), 4.73 (dd, \(J = 6.5, 1.3\) Hz, 2H), 2.10 (s, 3H). Characteristic \(^1\)H NMR signals for 5b/b': \(Z\)-5b: 4.87 (d, \(J = 6.6\) Hz, 2H), \(E\)-5b': 3.53 (d, \(J = 7.4\) Hz, 1H), \(Z\)-5b': 3.36 (d, \(J = 7.5\) Hz, 2H).

A parallel reaction without ligand was also performed providing the titled compounds in 36% \(^1\)H NMR yield (5b:5b' = 96:4, \(Z/E = 5:95\), determined by \(^1\)H NMR).
3-(Naphthalenyl)allyl acetate (6bα),2β 3-(2-naphthalenyl)allyl acetate (6bβ),2β 3-(naphthalenyl)prope-nyl acetate (6b'α) and 3-(2-naphthalenyl)propenyl acetate (6b'β)

General procedure B was followed using naphtalene (1.1 g, 8.25 mmol, 33 equiv). The crude residue was purified by column chromatography using EtOAc:petroleum ether 1:19 as eluent providing the titled compounds as a colorless oil (42 mg as a mixture of isomers in a ratio 60bα:40bβ, 6b:6b' = 95:5, determined by 1H NMR; 75% yield). 1H NMR spectra data of 6bα and 6bβ matched the spectra reported in the literature for these compounds. 2β 1H NMR (400 MHz) of 6bα and 6bβ δ = 8.10 (d, J = 8.1 Hz, 1Hα), 7.86 (d, J = 7.1 Hz, 1Hβ), 7.84 – 7.77 (m, 4Hα+β), 7.42 (s, 1Hα), 7.63 – 7.40 (m, 8Hα+β), 6.82 (d, J = 15.8 Hz, 1Hδ), 6.42 (dt, J = 15.9, 6.5 Hz, 1Hδ), 6.32 (dt, J = 15.6, 6.4 Hz, 1Hδ), 4.85 (dd, J = 6.4, 1.3 Hz, 2Hδ), 4.79 (dd, J = 6.5, 1.3 Hz, 2Hδ), 2.14 (s, 3Hδ), 2.13 (s, 3Hδ). Characteristic 1H NMR signals for 6b': 3.67 (d, J = 7.5 Hz, 2Hα or β), 3.50 (d, J = 7.5 Hz, 2Hβ or α).

A parallel reaction without ligand was also performed providing the titled compounds in 55% 1H NMR yield (34bα:66bβ, 6b:6b' = 97:3, determined by 1H NMR).

3-(2,3-Dimethylphenyl)allyl acetate (7bα),2c 3-(3,4-dimethylphenyl)allyl acetate (7bβ),2c 3-(2,3-dimethylphenyl)propenyl acetate (7b'α) and 3-(3,4-dimethylphenyl)propenyl acetate (7b'β)

General procedure B was followed using α-xylene (1 mL, 8.25 mmol, 33 equiv). The crude residue was purified by column chromatography using EtOAc:petroleum ether 1:39 as eluent providing the titled compounds as a colorless oil (38 mg as a mixture of isomers in a ratio 36α:64β, 7b:7b' = 91:9, determined by 1H NMR; 74% yield). 1H NMR spectra data of 7bα and 7bβ matched the spectra reported in the literature for these compounds. 2c 1H NMR (400 MHz) of 7bα and 7bβ δ = 7.28 (dd, J = 6.8, 2.4 Hz, 1Hα), 7.18 (s, 1Hβ), 7.15 – 7.06 (m, 4Hα+β), 6.95 (d, J = 15.5 Hz, 1Hα), 6.60 (d, J = 15.9 Hz, 1Hβ), 6.24 (dt, J = 15.9, 6.6 Hz, 1Hβ), 6.10 (dt, J = 15.7, 6.5 Hz, 1Hα), 4.75 (dd, J = 6.5, 1.4 Hz, 2Hα), 4.72 (dd, J = 6.6, 1.3 Hz, 2Hδ), 2.29 (s, 3Hα), 2.26 (m, 9Hα+β), 2.11 (s, 3Hδ), 2.10 (s, 3Hβ). Characteristic 1H NMR signals for 7b': 3.34 (dd, J = 7.2, 1.5 Hz, 2Hα or β), 3.27 (d, J = 7.6 Hz, 2Hβ or α).

A parallel reaction without ligand was also performed providing the titled compounds in 38% 1H NMR yield (17α:83β, 7b:7b' = 96:4, determined by 1H NMR).

3-(2,6-Dimethylphenyl)allyl acetate (8bα),2b 3-(2,4-dimethylphenyl)allyl acetate (8b'α), 3-(3,5-dimethylphenyl)allyl acetate (8bβ), 3-(3,5-dimethylphenyl)propenyl acetate (8b'α),2b 3-(2,4-dimethylphe-nyl)propenyl acetate (8b'α) and 3-(3,5-dimethylphenyl)propenyl acetate (8b'β)

General procedure B was followed using m-xylene (1 mL, 8.25 mmol, 33 equiv). The crude residue was purified by column chromatography using EtOAc:petroleum ether 1:39 as eluent providing the titled compounds as a colorless oil (27 mg as a mixture of isomers in a ratio 13α:65α:22m, 8b:8b' = 85:15, determined by 1H NMR; 53% yield). 1H
NMR spectra data of 8bo and 8bo' matched the spectra data reported in the literature for these compounds.2b 1H NMR (400 MHz) of 8bo, 8bo' and 8bm δ = 7.35 (d, J = 7.7 Hz, 1Hβ), 7.10 – 6.94 (m, 7Hα,β,ε,γ,δ,ε,γ,δ), 6.91 (s, 1Hβ), 6.84 (d, J = 15.7 Hz, 1Hδ), 6.64 (d, J = 16.3 Hz, 1Hα), 6.59 (d, J = 16.0 Hz, 1Hβ), 6.26 (dt, J = 15.9, 6.4 Hz, 1Hγ), 6.14 (dt, J = 15.8, 6.6 Hz, 1Hε), 5.80 (dt, J = 16.4, 6.3 Hz, 1Hα,β,ε,γ,δ,ε,γ,δ), 4.79 – 4.68 (m, 6Hα,β,ε,γ,δ,ε,γ,δ), 2.34 – 2.29 (m, 18Hα,β,ε,γ,δ,ε,γ,δ), 2.19 – 2.09 (m, 9Hα,β,ε,γ,δ,ε,γ,δ). Characteristic signals for 7b': δ = 3.50 (dd, J = 7.0, 1.9 Hz, 2H1o,1o'), 3.34 (dd, J = 6.6, 1.7 Hz, 2H2o,2o') 3.28 (d, J = 7.1 Hz, 2H3o,3o').

A parallel reaction without ligand was also performed providing the titled compounds in 36% 1H NMR yield (33α:600:7m, 8b:8b' = 96:4, determined by 1H NMR).

3-Mesitylallyl acetate (9b)2c and 3-mesitylpropenyl acetate (9b')

General procedure B was followed using mesitylene (1.2 mL, 8.25 mmol, 33 equiv). The crude residue was purified by column chromatography using EtOAc:petroleum 1:39 as eluent providing the titled compounds as a colorless oil (37 mg as a mixture of isomers in a ratio 9b:9b' = 71:29, Z:E = 14:86, determined by 1H NMR; 67% yield). 1H NMR spectra data of E-9b matched the spectra data reported in the literature for this compound.2c 1H NMR (400 MHz) of 9b and 9b' δ = 7.06 (d, J = 6.3 Hz, 1Hε), 6.98 (d, J = 12.4 Hz, 1Hγ), 6.89 – 6.81 (m, 8Hb+b'), 6.63 (d, J = 16.1 Hz, 1Hε), 6.53 (d, J = 11.2 Hz, 1Hb), 5.89 (dt, J = 11.3, 6.7 Hz, 1Hγ), 5.79 (dt, J = 16.2, 6.3 Hz, 1Hε), 5.48 (dt, J = 12.8, 6.6 Hz, 1Hb), 4.85 – 4.78 (m, 1Hε), 4.75 (dd, J = 6.3, 1.4 Hz, 2Hε), 4.38 (dd, J = 6.6, 1.4 Hz, 2Hb), 3.47 (dd, J = 7.0, 1.8 Hz, 2Hε), 3.31 (dd, J = 6.6, 1.7 Hz, 2Hb), 2.29 – 2.25 (m, 36Hb+b'), 2.20 (s, 3Hε), 2.11 (s, 3Hε), 2.08 (s, 3Hε), 2.01 (s, 3Hb).

A parallel reaction without ligand was also performed providing the titled compounds in 12% 1H NMR yield (9b:9b' = 75:25, Z:E = 29:71, determined by 1H NMR).

3-(2-Methoxyphenyl)allyl acetate (10bo),2b 3-(4-methoxyphenyl)allyl acetate (10bp),2b 3-(2-methoxy-phenyl)propenyl acetate (10bo') and 3-(4-methoxyphenyl)propenyl acetate (10bp')

General procedure B was followed using anisole (0.9 mL, 8.25 mmol, 33 equiv). The crude residue was purified by column chromatography using EtOAc:petroleum 1:79 as eluent providing the titled compounds as a colorless oil (40 mg as a mixture of isomers in a ratio 68bo:0bm:32bp, 10b:10bp' = 93:7, determined by 1H NMR; 78% yield). 1H NMR spectra data of 10bo and 10bp matched the spectra data reported in the literature for these compounds.2b 1H NMR (400 MHz) of 10bo and 10bp δ = 7.43 (dd, J = 7.6, 1.7 Hz, 1Hδ), 7.33 (d, J = 8.7 Hz, 1Hγ), 7.25 – 7.21 (m, 1Hδ), 6.98 (d, J = 16.0 Hz, 1Hε), 6.93 (t, J = 7.0 Hz, 1Hε), 6.95 – 6.83 (m, 4Hα,β,ε,γ), 6.60 (d, J = 15.7 Hz, 1Hε), 6.31 (dt, J = 16.0, 6.6 Hz, 1Hδ), 6.15 (dt, J = 15.9, 6.6 Hz, 1Hε), 4.74 (dd, J = 6.6, 1.4 Hz, 2Hε), 4.70 (dd, J = 6.7, 1.3 Hz, 2Hδ), 3.85 (s, 3Hδ), 3.81 (s, 3Hδ), 2.11 – 2.08 (m, 6Hα,β,ε,γ,δ,ε,γ,δ). Characteristic 1H NMR signals for 10bp': δ = 3.35 (d, J = 7.8, 2Hα,β,ε,γ,δ,ε,γ,δ), 3.30 (d, J = 7.0, 2Hα,β,ε,γ,δ,ε,γ,δ).
A parallel reaction without ligand was also performed providing the titled compounds in 38% \(^1\)H NMR yield (37bo:0bm:63bp, \textbf{10b:10b'} = 98:2, determined by \(^1\)H NMR).

3-(2-Chloro-5-methoxyphenyl)allyl acetate (11b\(\alpha\)),\(^{2c}\) 3-(5-chloro-2-methoxyphenyl)allyl acetate (11b\(\beta\)),\(^{2c}\) 3-(2-chloro-5-methoxyphenyl)propenyl acetate (11b\(\alpha\)) and 3-(5-chloro-2-methoxyphenyl)propenyl acetate (11b\(\beta\))

General procedure B was followed using p-chloroanisole (1 mL, 8.25 mmol, 33 equiv). The crude residue was purified by column chromatography using EtOAc:petroleum ether 1:9 to 3:7 as eluent providing the titled compounds as a yellow oil (48 mg as a mixture of isomers in a ratio \(17\alpha:83\beta\), \textbf{11b:11b'} = 91:9, determined by \(^1\)H NMR; 82% yield). \(^1\)H NMR spectra data of \textbf{11b} and \textbf{11b'} matched the spectra data reported in the literature for these compounds.\(^{2c}\) \(^1\)H NMR (400 MHz) of \textbf{11b\(\alpha\)} and \textbf{11b\(\beta\)} \(\delta = 7.39\) (d, \(J = 2.6\) Hz, \(1\text{H}_\alpha\)), 7.27 (d, \(J = 2.6\) Hz, \(1\text{H}_\beta\)), 7.20 (dd, \(J = 7.6, 2.7\) Hz, \(1\text{H}_\beta\)), 7.06 (d, \(J = 2.9\) Hz, \(1\text{H}_\beta\)), 7.02 (d, \(J = 16.0\) Hz, \(1\text{H}_\alpha\)), 6.91 (d, \(J = 16.0\) Hz, \(1\text{H}_\beta\)), 6.85 – 6.77 (m, \(2\text{H}_{b'\alpha}\)), 6.36 – 6.24 (m, \(2\text{H}_{b'\beta}\)), 4.78 (d, \(J = 6.2\) Hz, \(2\text{H}_\alpha\)), 4.74 (d, \(J = 6.4\) Hz, \(2\text{H}_\beta\)), 3.85 (s, \(3\text{H}_\alpha\)), 3.83 (s, \(3\text{H}_\beta\)), 2.14 (s, \(3\text{H}_\beta\)), 2.12 (s, \(3\text{H}_\beta\)). Characteristic \(^1\)H NMR signals for 11 b\(\beta\): 11b\(\alpha\): 3.44 (d, \(J = 7.5\) Hz, 2H), 11b\(\beta\): 3.28 (d, \(J = 7.6\) Hz, 2H).

A parallel reaction without ligand was also performed providing the titled compounds in 30% isolated yield (12a:88\%, \textbf{11b:11b'} = 95:5, determined by \(^1\)H NMR).

3-(2,4,6-Trifluorophenyl)allyl acetate (12b)\(^{23}\) and 3-(2,4,6-trifluorophenyl)propenyl acetate (12b\(\beta\))

General procedure B was followed using 1,3,5-trifluorobenzene (0.85 mL, 8.25 mmol, 33 equiv). The crude residue was purified by column chromatography using EtOAc:petroleum 1:19 as eluent providing the titled compounds as a yellow oil (23 mg, as a mixture of isomers in a ratio \(12b:12b' = 62:38\), \(Z:E = 31.69\), determined by \(^1\)H NMR; 40% yield). \(^1\)H NMR spectra data of \textbf{12b} matched the spectra data reported in the literature for this compound.\(^{23}\) \(^1\)H NMR (400 MHz) of \textbf{12b} and \textbf{12b'} \(\delta = 7.19\) (d, \(J = 12.5\) Hz, \(1\text{H}^b\)), 7.07 (d, \(J = 6.3, 1.4\) Hz, \(1\text{H}^E\)), 6.71 – 6.60 (m, \(6\text{H}^b\)), 6.59 – 6.48 (m, \(4\text{H}^b\)), 6.31 (d, \(J = 11.6\) Hz, \(1\text{H}^E\)), 6.03 (dt, \(J = 12.1, 6.3\) Hz, \(1\text{H}^E\)), 5.50 (dt, \(J = 12.4, 7.3\) Hz, \(1\text{H}^E\)), 5.06 – 4.93 (m, \(1\text{H}^E\)), 4.74 (d, \(J = 5.2\) Hz, \(2\text{H}^E\)), 4.57 (dd, \(J = 6.5, 1.6\) Hz, \(2\text{H}^Z\)), 3.46 (d, \(J = 7.5\) Hz, \(2\text{H}^E\)), 3.31 (d, \(J = 7.4\) Hz, \(2\text{H}^Z\)), 2.18 (s, \(3\text{H}^E\)), 2.11 (s, \(3\text{H}^E\)), 2.10 (s, \(3\text{H}^Z\)), 2.04 (s, \(3\text{H}^Z\)).

A parallel reaction without ligand was also performed providing the titled compounds in 25% \(^1\)H NMR yield (12b:12b' = 65:35, \(Z:E = 27:73\), determined by \(^1\)H NMR).
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3-(1,3,5-Trimethylphenyl)allyl phthalimide (13c) and 2-(3-mesitylpropenyl)isoindoline-1,3-dione (13c')

General procedure A was followed using N-allylphthalimide (46.8 mg, 0.25 mmol, 1 equiv) and mesitylene (2.3 mL, 16.5 mmol, 66 equiv). The crude residue was purified by column chromatography using EtOAc:petroleum ether 1:19 as eluent providing the titled compounds as a white solid (55 mg as a mixture of isomers in a ratio 13c:13c' = 71:29, Z:E = 7:93, determined by 1H NMR; 73% yield). 1H NMR (400 MHz) of 13c δ = 7.89 – 7.85 (m, 2H), 7.75 – 7.70 (m, 2H), 6.83 (s, 2H), 6.62 (d, J = 16.1 Hz, 1H), 5.70 (dt, J = 16.1, 6.3 Hz, 1H), 4.47 (dd, J = 6.2, 1.5 Hz, 2H), 2.24 (s, 3H), 2.23 (s, 6H); 13C NMR δ = 168.08, 136.56, 136.00, 134.10, 133.16, 131.79, 131.66, 128.59, 127.56, 123.44, 40.26, 21.06, 20.91. IR ν = 2920, 2855, 1707, 1389, 1335, 940, 850, 715, 527 cm⁻¹; HRMS (EI) calcd for C₂₀H₁₉NO₂ [M]+: 305.1416; found: 305.1425; mp 100 – 104 °C. Characteristic 1H NMR signals for 13c': E-13c' 3.51 (dd, J = 6.3, 1.7 Hz, 2H), Z-13c' 4.13 (dd, J = 6.1, 1.9 Hz, 2H).

A parallel reaction without ligand was also performed providing the titled compounds in 20% 1H NMR yield (13c:13c' = 90:10, Z:E = 10:90, determined by 1H NMR).

3-(1,3,5-Trimethoxyphenyl)allyl phthalimide (14c) and 2-(3-(2,4,6-trimethoxyphenyl)propenyl)isoindoline-1,3-dione (14c')

General procedure A was followed using N-allylphthalimide (46.8 mg, 0.25 mmol, 1 equiv) and 1,3,5-trimethoxybenzene (2.78 g, 16.5 mmol, 66 equiv). The crude residue was purified by column chromatography using CH₂Cl₂ as eluent providing the titled compounds as a yellow solid (54 mg, as a mixture of isomers in a ratio 14c:14c' = 98:2, determined by 1H NMR; 61% yield). 1H NMR spectra data of 14c matched the spectra data reported in the literature for this compound. 1H NMR (400 MHz) of 14c δ = 7.87 – 7.85 (m, 2H), 7.72 – 7.70 (m, 2H), 6.99 (d, J = 16.0 Hz, 1H), 6.62 – 6.54 (m, 1H), 6.11 (s, 2H), 4.44 (d, J = 6.8 Hz, 2H), 3.82 (s, 9H). Characteristic 1H NMR signal for 14c' δ = 3.42 (d, J = 7.3 Hz, 2H).

A parallel reaction without ligand was also performed providing the titled compounds in 36% isolated yield (14c:14c' = 97:3, determined by 1H NMR).

Procedure for the Pd-catalyzed C–H olefination of estrone 3-methyl ether with allyl acetate

(E)-3-(2-Estrone methyl ether)allyl acetate (15a) and (E)-3-(4-estrone methyl ether)allyl acetate (15b)

A stock solution of ligand L (0.0846 M in CH₂Cl₂) (300 µL, 25 µmol, 10 mol%) was added to a pressure tube and the solvent was allowed to evaporate at room temperature. Then, allyl acetate (27 µL, 0.25 mmol, 1 equiv), Pd(OAc)₂ (5.6 mg, 25 µmol, 10 mol%), silver acetate (62.8 mg, 0.375 mmol, 1.5 equiv),
estrone 3-methyl ether (71 mg, 0.25 mmol, 1 equiv), and DCE (0.5 mL, 0.5 M) were added. The pressure tube was sealed with a screw cap and the reaction was placed in an 80 °C preheated oil bath and stirred for 24 h. The resulting reaction mixture was filtered through a pad of Celite, rinsed with CH2Cl2 and then concentrated under reduced pressure. The crude residue was purified by column chromatography using EtOAc:pentane ether 1:9 to 3:7 as eluent providing the titled compounds as a colorless oil (51 mg as a mixture of isomers in a ratio 60a:40b, determined by 1H NMR; 55% yield). 1H NMR (400 MHz) δ = 7.35 (s, 1Hα), 7.21 (d, J = 8.6 Hz, 1Hβ), 6.92 (d, J = 16.0 Hz, 1Hα), 6.77 (d, J = 8.7 Hz, 1Hβ), 6.65 – 6.57 (m, 2Hα,b), 6.32 – 6.18 (m, 2Hα,b), 4.75 (d, J = 6.4 Hz, 2Hα), 4.72 (d, J = 6.4 Hz, 2Hβ), 3.82 (s, 3Hδ), 3.81 (s, 3Hβ), 2.96 – 2.86 (m, 4Hα,b), 2.55 – 2.45 (m, 2Hα,b), 2.46 – 2.35 (m, 2Hα,b), 2.32 – 2.21 (m, 2Hα,b), 2.20 – 2.12 (m, 2Hα,b), 2.10 (s, 3Hδ), 2.09 (s, 3Hα), 1.46 – 1.45 (m, 12Hα,b), 0.91 (s, 3Hβ), 0.91 (s, 3Hα). 13C NMR (101 MHz) δ = 220.9, 220.8, 170.9, 170.8, 155.5, 154.9, 137.7, 135.9, 132.3, 131.7, 129.5, 128.6, 127.8, 125.2, 124.2, 123.9, 122.8, 122.7, 111.1, 108.5, 66.0, 65.8, 55.5, 55.4, 50.4, 50.3, 47.9, 47.8, 44.3, 43.8, 38.3, 37.5, 35.8, 35.8, 31.6, 31.5, 29.6, 28.0, 26.6, 26.5, 26.1, 25.9, 21.5, 21.5, 21.0, 13.8, 13.76. IR ν = 2928, 2861, 1733, 1454, 1223, 1022, 969, 729 cm−1; HRMS (EI) calcd for C24H30O4 [M]+: 382.2144, found: 382.2161.

A parallel reaction without ligand was also performed providing the titled compounds in 10% 1H NMR yield.

4.6 References

(5) It has been postulated that Ag(I) salts can play a significant role in promoting β-hydride elimination and that might be the reason for the improvement in yield observed when using AgOAc. See reference 2d.
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(13) Zhang, Z.; Xu, L.; Chen, Z.; Liu, Z.; Miao, M.; Song, J.; Ren, H. Synlett 2015, 26, 2784-2788.