CHAPTER 3

SYNTHESIS OF S,O-BIDENTATE LIGANDS AND THEIR APPLICATION IN PALLADIUM-CATALYZED C–H OLEFINATION OF NON-DIRECTED ARENES WITH ACTIVATED ALKENES

Part of this chapter has been published in:
3.1 Introduction
Design of S,O-bidentate ligands
As mentioned in Chapter 1, our design for the development of new ligands for Pd-catalyzed C–H functionalization reactions is based on the combination of a Lewis base and a carboxylic acid unit. Following this design, in our group, we recently demonstrated that picolinic acid ligands promote the Pd-catalyzed C–H acetoxylation of simple arenes.\(^1\) Both reactivity and selectivity were enhanced by the presence of the N,O-bidentate ligand. We postulate that the carboxylic acid functionality promotes C–H bond cleavage and the chelating ability of the nitrogen atom of the pyridine enhances the stability of the catalyst. We observed that during the reaction, an insoluble palladium complex precipitates. This inactive complex was isolated and identified as palladium complex I bearing two picolinic acid molecules (Figure 3.1).

![Figure 3.1 Structure of an inactive complex I.](image)

We envisioned that a bidentate ligand with weaker coordination ability to Pd(OAc)\(_2\) than the bidentate picolinic acid ligand would lead to a more efficient catalyst. Indeed, it has been reported by Stahl et al. that bidentate ligands with weaker coordination abilities (i.e. DAF) than traditional bidentate ligands (i.e. bpy) are effective in promoting several Pd-catalyzed reactions.\(^2\) With this information in mind, we decided to investigate the performance of bidentate thioethercarboxylic acids ligands L (S,O-ligands), which have hemilabile behavior in palladium chemistry (Figure 3.2).\(^3\) It is worthy to mention that, to the best of our knowledge, this type of ligands has never been used in metal-catalysis.

![Figure 3.2 Structures of bidentate ligands.](image)

General overview of Pd-catalyzed C–H olefination of non-directed arenes
The first C–H olefination of benzene using a stoichiometric amount of palladium was reported by Fujiwara and Moritani in 1967.\(^4\) Later on, several research groups developed the catalytic version of this reaction.\(^5\) In general, the substrate scope is limited to neutral or electron-rich arenes\(^6\) and a mixture of regioisomers is observed.\(^6a-c\) To overcome these limitations, directing groups or templates have been used.\(^7\) Various directing groups such as carboxylic acid,\(^8\) pyridine,\(^9\) nitrile,\(^10\) thiol,\(^11\) sulfonamide\(^12\) or silanol\(^13\) have been reported to promote this transformation providing the desired products in good yields and selectivities. However, as mentioned in Chapter 1, this strategy suffers from a few drawbacks such as the synthesis of...
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complicated templates or directing groups, and the requirement to introduce and remove the directing group.

An attractive alternative to the use of directing groups and templates is the development of suitable ligands. In this context, only few ligands have been successfully applied in Pd-catalyzed C–H olefination of non-directed arenes.14 In 2009, Yu et al. described the first selective C–H olefination of electron-poor arenes by using a bulky pyridine ligand (Scheme 3.1).14a This ligand promoted the aerobic C–H olefination of various electron-deficient arenes, providing the products in good yields and selectivities towards meta olefinated arenes.

![Scheme 3.1 Pyridine ligand promoted Pd-catalyzed C–H olefination of electron-poor arenes.](image1)

Subsequent investigations from Sanford’s group identified the beneficial effect of the commercially available 3,5-dichloropyridine ligand as a promoter of the Fujiwara-Moritani reaction (Scheme 3.2).14b The reaction conditions were compatible with both electron-rich and electron-poor arenes to give the olefinated products in moderate to good yields. Mixtures of isomers were detected with preferential functionalization at the most electronic-rich position on the arene.

![Scheme 3.2 Pyridine ligand promoted Pd-catalyzed C–H olefination of simple arenes.](image2)

In 2014, Duan and co-workers showed that 2-hydroxy-1,10-phenanthroline ligand promoted the C–H alkenylation of a variety of arenes (Scheme 3.3).14c Good yields and mixtures of isomers were obtained. Interestingly, the reaction occurs with a preference towards the meta position independently of the nature of the substituent.

![Scheme 3.3 Phenanthroline promoted Pd-catalyzed C–H olefination of simple arenes.](image3)

The mono-protected amino acid (MPAA), Ac-Ile-OH, was also described as an efficient ligand to promote the Fujiwara-Moritani reaction (Scheme 3.4).14d This catalytic system was applied...
to benzene and electron-poor substrates providing the olefinated products in moderate to
good yields and good site selectivities towards the meta products.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
(1 \text{ equiv}) & \quad \text{EWG} \\
\text{excess} & \quad \text{Pd(2OAc)}_2 (10 \text{ mol\%}) \\
& \quad \text{Ac-Ile-OH (20 \text{ mol\%})} \\
& \quad \text{KHCO}_3 (40 \text{ mol\%}) \\
\end{align*}
\]

\[
\begin{align*}
& \quad \text{O}_2 (1 \text{ atm}) , \text{t-AmylOH} \\
& \quad 90 ^\circ \text{C}, 36 \text{ h} \\
& \quad \text{47-96\%} \\
\end{align*}
\]

\text{Scheme 3.4 MPAA promoted Pd-catalyzed C–H olefination of electron-poor arenes.}

Although these examples showed that ligands can promote the Pd-catalyzed C–H olefination of arenes, moderate to good yields and low site selectivities are generally obtained. Moreover, these catalytic systems required an excess of arenes and high catalyst loading. After the completion of the research presented in this Chapter, two new catalytic systems using 1 equiv of arene were published (Scheme 3.5).\textsuperscript{15} C–H Olefination of electron rich and poor arenes was achieved in good yields and selectivities using Pd/pyridone ligand catalyst (Scheme 3.5, a).\textsuperscript{15a} At the same time, van Gemmeren and co-workers showed that a pyridine derivative in the combination with a MPAA promoted the C–H olefination of simple arenes (Scheme 3.5, b).\textsuperscript{15b} In both examples, the reaction took place at the most electron rich and sterically least hindered position.

\text{Scheme 3.5 Pyridine ligand promoted Pd-catalyzed C–H olefination of simple arenes.}

In this chapter, we describe the synthesis of a variety of S,O-ligands, namely thioethercarboxylic acids L. The beneficial effect of the S,O-ligands in promoting the Pd-catalyzed C–H olefination of non-directed arenes is also presented. Finally, the applicability of the new methodology in late-stage functionalization of complex molecules and in preparative scale is demonstrated.
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3.2 Results and discussion
3.2.1 Synthesis of S,O-bidentate ligands
Thioethercarboxylic acid ligands L can be easily synthesized in two steps from commercially available carboxylic acids via α-bromination followed by nucleophilic substitution with thiols (Scheme 3.6).

Scheme 3.6 General scheme for the synthesis of thioethercarboxylic acid ligands L.

Bromination of butyric acid (1a) and 3,3-dimethylbutanoic acid (1b) using N-bromosuccinimide (NBS) in acidic conditions at 85 °C provided 2-bromobutanoic acid (2a) and 2-bromo-3,3-dimethylbutanoic acid (2b) in 87% and 81% yields, respectively (Table 3.1, entries 1 and 2). 2-Bromo-3-methylbutanoic acid (2c) and 2-bromo-2-methylpropanoic acid (2d) were purchased from commercially available sources.

Table 3.1 Synthesis of α-bromocarboxylic acids 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>2</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>H</td>
<td>2a</td>
<td>87%</td>
</tr>
<tr>
<td>2</td>
<td>t-Bu</td>
<td>H</td>
<td>2b</td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>H</td>
<td>2c</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Me</td>
<td>2d</td>
<td></td>
</tr>
</tbody>
</table>

To synthesize the target S,O-bidentate ligands L, a nucleophilic substitution reaction of α-brominated compounds 2 with different thiols in the presence of NaOH was performed (Table 3.2). Ligands L1–L3 were obtained in good yields by reacting compounds 2a–2c with thiophenol in EtOH (entries 1–3). However, when the same reaction conditions were applied to compound 2d, a mixture of the desired ligand L4 together with 2-ethoxy-2-methylpropanoic acid, arising from nucleophilic substitution of EtOH to 2-bromo-2-methylpropanoic acid (2d), was observed (entry 4). t-BuOH was then used as a solvent providing the desired product L4 in excellent yield (84%, entry 5). Next, the reactions of 2-bromo-3-methylbutanoic acid (2c) with different thiols were performed. When using bulky thiols such as 2,4,6-trimethylthiophenol and triphenylmethanethiol, the S,O-ligands L5 and L6 were obtained in moderate yields (entries 6 and 7). The reactions with thiols bearing electron-rich (entries 8 and 9) and electron-poor (entries 10 and 11) substituents in the aromatic ring as well as aliphatic thiols (entries 12 and 13) provided the desired ligands L7–L12 in good to excellent yields.
Table 3.2 Nucleophilic substitution of α-bromocarboxylic acids 2 with thiols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>L</th>
<th>Solvent</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>H</td>
<td>Ph</td>
<td>L1</td>
<td>EtOH</td>
<td>81%</td>
</tr>
<tr>
<td>2</td>
<td>t-Bu</td>
<td>H</td>
<td>Ph</td>
<td>L2</td>
<td>EtOH</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>H</td>
<td>Ph</td>
<td>L3</td>
<td>EtOH</td>
<td>73%</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>L4</td>
<td>EtOH</td>
<td>53%</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>L4</td>
<td>t-BuOH</td>
<td>84%</td>
</tr>
<tr>
<td>6</td>
<td>i-Pr</td>
<td>H</td>
<td>Tr</td>
<td>L5</td>
<td>EtOH</td>
<td>39%</td>
</tr>
<tr>
<td>7</td>
<td>i-Pr</td>
<td>H</td>
<td>p-OMe- C₆H₄</td>
<td>L6</td>
<td>EtOH</td>
<td>94%</td>
</tr>
<tr>
<td>8</td>
<td>i-Pr</td>
<td>H</td>
<td>2,4,6-(OMe)₃- C₆H₂</td>
<td>L7</td>
<td>EtOH</td>
<td>94%</td>
</tr>
<tr>
<td>9</td>
<td>i-Pr</td>
<td>H</td>
<td>C₆F₅</td>
<td>L8</td>
<td>EtOH</td>
<td>94%</td>
</tr>
<tr>
<td>10</td>
<td>i-Pr</td>
<td>H</td>
<td>p-CF₃-C₆H₄</td>
<td>L9</td>
<td>t-BuOH</td>
<td>94%</td>
</tr>
<tr>
<td>11</td>
<td>i-Pr</td>
<td>H</td>
<td>Bn</td>
<td>L10</td>
<td>EtOH</td>
<td>59%</td>
</tr>
<tr>
<td>12</td>
<td>i-Pr</td>
<td>H</td>
<td>i-Pr</td>
<td>L11</td>
<td>EtOH</td>
<td>90%</td>
</tr>
<tr>
<td>13</td>
<td>i-Pr</td>
<td>H</td>
<td>i-Pr</td>
<td>L12</td>
<td>t-BuOH</td>
<td>89%</td>
</tr>
</tbody>
</table>

*A mixture of the desired ligand L4 and α-ethoxycarboxylic acid byproduct was obtained. *A mixture of the desired ligand L and α-ethoxycarboxylic acid byproduct was obtained when using EtOH as a solvent.

The synthesis of the ligand bearing a cyclopropane in α-position L13 was synthesized in three steps from acrolein (3) following reported procedures (Scheme 3.7). The reaction of acrolein and thiophenol in the presence of SnCl₄ as a catalyst at room temperature gave compound 4 in 96% yield. Thioketal 4 was then reacted with TMEDA and MeLi at 0 °C for 3 h providing compound 5 in moderate yield, which then reacted with lithium naphthalenide and CO₂ to obtain product L13 in 33% yield.

As shown in Scheme 3.8, 2-(phenylthio)benzoic acid (L14) was synthesized by refluxing 2-bromobenzoic acid (6) with thiophenol under basic conditions in the presence of copper and cuprous oxide. After 4 h, the desired product was obtained in 26% yield.
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Scheme 3.8 Synthesis of L14.

The synthesis of tetrahydro-2-thiophenecarboxylic acid ligand L15 was achieved in three steps following a literature procedure (Scheme 3.9). Compound 8 was obtained in 52% yield by reacting chloroacetonitrile (7) and 3-chloropropane-1-thiol in the presence of potassium carbonate at 45 °C overnight. Cyclization of compound 8 using benzyltriethylammonium chloride (TEBA) and NaOH in aqueous solution provided compound 9 in good yield. Hydrolysis of compound 9 by refluxing in hydrochloric acid (6 M) for 3 h gave ligand L15 in 61% yield.

Scheme 3.9 Synthetic route for the synthesis of L15.

3.2.2 S,O-Ligand promoted Pd-catalyzed C–H olefination of non-directed arenes with activated alkenes

S,O-Ligands in Pd-catalyzed C–H olefination of benzene

With the S,O-ligands in hand, we first investigated the influence of these ligands in the Pd(II)-catalyzed C–H olefination reaction employing benzene and ethyl acrylate as model substrates under standard conditions for C–H olefination (Table 3.3). In the absence of ligand, the reaction with 5 mol% of Pd(OAc)₂, 1 equiv of t-butyl peroxybenzoate, 1 equiv of olefin and excess of benzene in acetic acid at 100 °C provided olefinated product 12a in only 16% yield after 2 h (entry 1). In contrast, the presence of 5 mol% of 2-ethyl-2-(phenylthio)acetic acid (L1) improved the product yield to 64% (entry 2). Similar yields were obtained with ligands bearing aliphatic chains at α-position (L2 and L3), including the gem-dimethyl (L4) and cyclopropane (L13) ligands (entries 3–6). 2-(Phenylthio)acetic acid (L16) and 2-phenyl-2-(phenylthio)acetic acid (L17) furnished the olefinated product 12a in 40% and 20% yield, respectively (entries 7 and 8). Next, the reaction with 2-(phenylthio)benzoic acid (L14), which could form a 6-membered palladacycle intermediate, provided the product in 16% yield (entry 9). We explored the effect on the reactivity of S,O-ligands with different substituents attached to the sulfur atom, including electron rich, electron poor and bulky aromatic (L5–L10) and aliphatic substituents (L11 and L12) (entries 10–17). Unfortunately, all these ligands provided similar or slightly lower yields than those obtained with L3, with the exception of the bulky ligand L6.
which did not furnish any product. The reaction with tetrahydro-2-thiophenecarboxylic acid (L15) and 2-thiophenecarboxylic acid (L18) which are more rigid than other ligands described previously provided the desired product in 61% and 26% yields, respectively (entries 18 and 19). From these initial studies, we concluded that, in general, thioethercarboxylic acid ligands bearing aliphatic substituents at α-position along with a neutral aromatic ring attached to the sulfur atom constitute the most active ligand for the Pd-catalyzed C–H olefination of benzene.

Having established the positive effect of the S,O-ligand in the reaction, different experiments were conducted to ascertain the role of each functionality in the ligand. First, we performed the reaction with the corresponding sulfoxide (L19) and sulfone (L20) to confirm that these species are not responsible for the observed catalytic activity. Indeed, the reaction in the presence of either of these ligands (entries 20 and 21) provided a similar outcome as the reaction without ligand. The use of thioanisole (L21) and methyl 2,2-dimethyl-2-(phenylthio)acetate (L22) as ligands furnished the olefinated product 12a in 27% and 37% yields, respectively (entries 22 and 23). Reactions using bidentate ligands with selenium (L23), oxygen (L24) or nitrogen (L25) atoms instead of sulfur, gave ethyl cinnamate (12a) in 17–47% yield (entries 24–26). These results confirmed that the presence of both functionalities, thioether and carboxylic acid, is crucial for the acceleration of this reaction.

**Table 3.3 Ligand optimization.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>NMR yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No ligand</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>R(^1)</td>
<td>R(^2)</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>H</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu</td>
<td>H</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr</td>
<td>H</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>H</td>
</tr>
<tr>
<td>9</td>
<td>R(^2)</td>
<td>L14</td>
</tr>
<tr>
<td>10</td>
<td>i-Pr</td>
<td>L5</td>
</tr>
<tr>
<td>11</td>
<td>Tr</td>
<td>L6</td>
</tr>
<tr>
<td>12</td>
<td>p-OMe-C(_6)H(_4)</td>
<td>L7</td>
</tr>
<tr>
<td>13</td>
<td>2,4,6-(OMe)(_2)-C(_6)H(_2)</td>
<td>L8</td>
</tr>
<tr>
<td>14</td>
<td>C(_6)F(_5)</td>
<td>L9</td>
</tr>
<tr>
<td>15</td>
<td>p-CF(_3)-C(_6)H(_4)</td>
<td>L10</td>
</tr>
<tr>
<td>16</td>
<td>Bn</td>
<td>L11</td>
</tr>
<tr>
<td>17</td>
<td>i-Pr</td>
<td>L12</td>
</tr>
</tbody>
</table>
Table 3.3 Ligand optimization (continued).

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L15</td>
<td>61%</td>
</tr>
<tr>
<td>L18</td>
<td>26%</td>
</tr>
<tr>
<td>L19</td>
<td>16%</td>
</tr>
<tr>
<td>L20</td>
<td>20%</td>
</tr>
<tr>
<td>L21</td>
<td>27%</td>
</tr>
<tr>
<td>L22</td>
<td>37%</td>
</tr>
<tr>
<td>L23</td>
<td>47%</td>
</tr>
<tr>
<td>L24</td>
<td>17%</td>
</tr>
<tr>
<td>L25</td>
<td>31%</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.

To prove that the higher yield observed in the presence of the S,O-ligand corresponds to an acceleration of the reaction, we studied the kinetics of the reaction in the absence and in the presence of S,O-ligand L3 (Scheme 3.10). The curves clearly indicated that ligand L3 increased the reaction rate dramatically when compared with the conditions without ligand. Interestingly, in both cases deactivation of the catalyst occurs after ca. 2 h, suggesting that the ligand does not stabilize the catalyst.

Scheme 3.10 Kinetic profile with and without L3.

**Optimization of the reaction conditions of Pd-catalyzed C–H olefination of benzene**

Ligand L3 was selected for further optimization of other parameters in the reaction. First, the effect on the reaction of different amounts of ligand L3, varying from 2.5–15 mol%, was studied (Table 3.4). The best result was obtained using a 1:1 ratio of Pd:ligand, suggesting that only one ligand is involved in the active catalyst.
Table 3.4 Optimization of Pd:L3 ratio.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L3 (mol%)</th>
<th>Pd:L3 ratio</th>
<th>NMR yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>1:0.5</td>
<td>36%</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>1:1</td>
<td>63%</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>1:2</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>1:3</td>
<td>11%</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.

We performed different C–H olefination reactions varying the catalyst loading (Table 3.5). Although the best result was obtained using 5 mol% of catalyst, we were pleased to observe that the reaction proceeded in fair yield using only 2 mol%.

Table 3.5 Catalyst loading.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>NMR yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>63%</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>55%</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>46%</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>43%</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.

In previous experiments, we used an excess of benzene. With the idea to apply the new catalyst to more complex arenes, we tried to minimize the amount of benzene in the reaction (Table 3.6). Unfortunately, when we decreased the amount of benzene from 11.2 to 2 equiv, we observed a significant decrease in the yield of the reaction. As we will see later on, the amount of other arenes can be reduced without negatively affecting the yields (see Scheme 3.12).
Table 3.6 Optimization of the amount of benzene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzene (equiv)</th>
<th>NMR yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.2</td>
<td>63%</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>46%</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>32%</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>23%</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>10%</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.

We also studied the effect of other oxidants including $t$-butyl hydroperoxide, peracetic acid, oxygen, benzoquinone, silver-based oxidants, persulfate and peroxymonosulfate in the reaction (Table 3.7). However, no improvement was observed when compared with the reaction using PhCO$_3$t-Bu.

Table 3.7 Screening of oxidants.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>NMR yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCO$_3$t-Bu</td>
<td>63%</td>
</tr>
<tr>
<td>2</td>
<td>$t$-BuOOH</td>
<td>49%</td>
</tr>
<tr>
<td>3</td>
<td>AcOOH</td>
<td>5%</td>
</tr>
<tr>
<td>4</td>
<td>O$_2$ (1 atm)</td>
<td>12%</td>
</tr>
<tr>
<td>5</td>
<td>BQ</td>
<td>19%</td>
</tr>
<tr>
<td>6</td>
<td>AgOAc</td>
<td>39%</td>
</tr>
<tr>
<td>7</td>
<td>Ag$_2$CO$_3$</td>
<td>25%</td>
</tr>
<tr>
<td>8</td>
<td>Na$_2$S$_2$O$_8$</td>
<td>17%</td>
</tr>
<tr>
<td>9</td>
<td>K$_2$S$_2$O$_8$</td>
<td>24%</td>
</tr>
<tr>
<td>10</td>
<td>Oxone</td>
<td>39%</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.

Finally, we screened different solvents as shown in Table 3.8. The reaction using a more acidic solvent such as TFA provided the olefinated product in only 10% NMR yield (entry 2). We tested the reaction using different alcohols (entries 3–6), including HFIP that is nowadays widely used in C–H functionalization reactions; however, low yields were obtained. Other non-protic solvents were tested (entries 7–12) but none of them gave better result than using acetic acid.
Table 3.8 Screening of solvents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>NMR yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH</td>
<td>63%</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>HFIP</td>
<td>38%a</td>
</tr>
<tr>
<td>4</td>
<td>TFE</td>
<td>39%a</td>
</tr>
<tr>
<td>5</td>
<td>MeOH</td>
<td>2%</td>
</tr>
<tr>
<td>6</td>
<td>t-AmylOH</td>
<td>34%</td>
</tr>
<tr>
<td>7</td>
<td>MeCN</td>
<td>5%</td>
</tr>
<tr>
<td>8</td>
<td>DCE</td>
<td>9%</td>
</tr>
<tr>
<td>9</td>
<td>1,4-dioxane</td>
<td>11%a</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>25%</td>
</tr>
<tr>
<td>11</td>
<td>DME</td>
<td>6%</td>
</tr>
<tr>
<td>12</td>
<td>DMF</td>
<td>NR</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. *Traces of ethyl 3,3-diphenylacrylate were observed. NR = no reaction.

Pd-Catalyzed C–H olefination of naphthalene

To analyze the effect of the new catalytic system on the site selectivity of the reaction, we applied our optimal reaction conditions for benzene to naphthalene. The reaction with ligand L3 showed an increase of yield from 57% to 87% yield, as determined by NMR (76% isolated yield), compared to the reaction without ligand. To our delight, we observed that the ligand influences the site selectivity of the reaction, going from equimolecular mixtures of regioisomers without ligand to a ratio of 2:1 in favor of the α-olefinated product (Table 3.9, entries 1 and 2). In attempts to improve the site selectivity of the reaction, we tried the reaction with other S,O-ligands. The reaction with L4, which bears two methyl groups at the α-position, provided similar yield and site selectivity to ligand L3 (entry 3). Next, we tested several ligand with different substituents attached to the sulfur atom. Using L8 or L12, with a 2,4,6-trimethoxyphenyl group or an i-propyl group attached to the sulfur atom, respectively, the reactivity was slightly decreased while the selectivity was slightly improved (entries 4 and 5). The reaction using the more rigid ligand L15 showed no improvement on the site selectivity (entry 6). Finally, the reaction using L26, with an O-methylhydroxamic acid group, gave equimolecular mixtures of olefinated products (entry 7).
Table 3.9 Effect of ligand in the C–H olefination of naphthalene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>NMR yield (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No ligand</td>
<td>57% (1:1.1)</td>
</tr>
<tr>
<td>2</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>87% (2:1)</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>89% (2.2:1)</td>
</tr>
<tr>
<td>4</td>
<td>2,4,6-(OMe)&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>66% (2.4:1)</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr</td>
<td>77% (2.3:1)</td>
</tr>
<tr>
<td>7</td>
<td>L26</td>
<td>62% (1:1.1)</td>
</tr>
</tbody>
</table>

Yield and site selectivity were determined by <sup>1</sup>H NMR analysis of the crude mixture using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. Isolated yield of all isomers was given in square bracket.

In a desperate attempt to improve the selectivity of the reaction, we decided to add different type of additives (Table 3.10). Additives including BF<sub>3</sub>·OEt<sub>2</sub>, TMSCl, ZnCl<sub>2</sub>, Yb(OTf)<sub>3</sub>, Cu(OTf)<sub>2</sub>, benzoquinone or PPh<sub>3</sub> among others were tested, but unfortunately, none of them gave a better result.

Table 3.10 Effects of additives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>NMR yield (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>87% (2:1)</td>
</tr>
<tr>
<td>2</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;·OEt&lt;sub&gt;2&lt;/sub&gt;</td>
<td>25% (2.6:1)</td>
</tr>
<tr>
<td>3</td>
<td>TMSCl</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>AlCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>ZnCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>NaCl</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>KBr</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>TMSOTf</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>Yb(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>15% (1.6:1)</td>
</tr>
<tr>
<td>10</td>
<td>Bu&lt;sub&gt;4&lt;/sub&gt;NOTf</td>
<td>90% (2.1:1)</td>
</tr>
<tr>
<td>11</td>
<td>Zn(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>19% (1.7:1)</td>
</tr>
</tbody>
</table>
Table 3.10 Effects of additives (continued).

<table>
<thead>
<tr>
<th>No.</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>Site Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Cu(OTf)_2</td>
<td>9% (1:4:1)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>AgOTf</td>
<td>73% (1:7:1)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>AgClO_4</td>
<td>80% (1:7:1)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>CuSO_4</td>
<td>65% (1:9:1)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>ZnSO_4.7H_2O</td>
<td>82% (1:9:1)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>AgBF_4</td>
<td>92% (2:1:1)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>NaBF_4</td>
<td>73% (1:9:1)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Fe(BF_4)_2.6H_2O</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>KPF_6</td>
<td>76% (2:1)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>NH_4PF_6</td>
<td>31% (2:1)</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>BQ</td>
<td>48% (2.8:1)</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>PPh_3</td>
<td>77% (1:8:1)</td>
<td></td>
</tr>
</tbody>
</table>

Yield and site selectivity were determined by ^1H NMR analysis of the crude mixture using CH_2Br_2 as an internal standard. ^5 5 mol% of additive was used. NR = no reaction.

Pd-Catalyzed C–H olefination of non-directed arenes with activated alkenes

We explored the substrate scope of this transformation with different arenes using the optimized conditions (5 mol% of catalyst, 1 equiv of t-butyl peroxybenzoate, 1 equiv of olefin and excess of arene in acetic acid at 100 °C for 6 h) (Table 3.11). The reaction in the presence of L3 of arenes with alkyl substituents, ortho-, meta- and para-xylene and mesitylene, provided the alkenylated products 12c, 12d, 12e and 12f with excellent yields (76%, 83%, 75% and 84%, respectively). Regarding the site selectivity, the ortho-xylene provided a 1:1.9 ratio of α(a) and β(b) isomers, respectively, and the meta-xylene provided a mixture of isomers (a:b:c = 4.9:1:1.3 ratio) in favor of the less sterically hindered ortho-olefinated product. We also tested the reaction of arenes bearing strong electron-donating groups including anisole, 1,2- and 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene giving the products in excellent yields (70–82%) (12g–j). Anisole provided a 1.5:1 ratio of the ortho and para isomers and traces of the meta isomer were detected in the crude reaction mixture. 1,2-Dimethoxybenzene gave a 1:4.9 ratio of the corresponding α(a) and β(b) isomers. Similarly, C–H olefination of 1,3-dimethoxybenzene occurred mainly at the less sterically hindered C–H bond at the ortho position of the methoxy group (6:1 ratio). Moreover, unprotected phenol was also tested providing the ortho- and para-olefinated products 12k in excellent yield (82%) with a ratio of 1.9 to 1, respectively. Taking into consideration that only few reports deal with the direct functionalization of phenols, both the yield obtained and the preference for the ortho olefination are remarkable. The C–H olefination of various electron-deficient arenes was also explored. Larger amounts of arene were required in some of these cases to increase the yields. The reaction of ethyl benzoate provided the desired olefinated products 12l in moderate yield as a mixture of isomers in favor of the meta olefinated product (o:m:p = 1.2:3.3:1). When 1,2-, 1,3- and 1,4-dichlorobenzene were employed as starting materials, the desired products 12m–12o were obtained as a mixture of regioisomers in good yields (60–78%). The reaction with 1,3,5-trifluorobenzene furnished the desired product 12p in 77% yield. Furthermore, when 4-chloroanisole was subjected to the standard reaction conditions, the olefinated product 12q was obtained in 60% yield with a 4:3:1 ratio in favor of the ortho product with respect to the methoxy substituent. We found that arenes bearing
strong electron-withdrawing substituents such as cyano, trifluoromethyl and nitro (12r–12t) were olefinated with low yields.

As shown in the Table 3.11, the reaction in the presence of the S,O-ligand L3, provided in most cases higher yields than the reaction in the absence of the ligand. Regarding the site selectivity, our results indicated that it is mainly dictated by the substrate and controlled by electronic factors, with preferential functionalization at the most electron-rich position in the arene. However, by comparing the site selectivity of the reactions with and without L3, it is evident that ligand L3 influences the site selectivity in most cases. Interestingly, a different trend in site selectivity was observed when the reaction was performed in the presence and absence of L3 using anisole (10g) or phenol (10k) as substrates. The reactions without ligand provided a mixture of ortho- and para-products with a clear preference for the latter. In contrast, in the presence of L3, the ortho-olefinated products were preferred.

Table 3.11 Substrate scope.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>(a:b) Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>12c</td>
<td>88%</td>
<td>1:1.9</td>
</tr>
<tr>
<td>12d</td>
<td>88%</td>
<td>4.9:1:1.3</td>
</tr>
<tr>
<td>12e</td>
<td>75%</td>
<td>1:1.3</td>
</tr>
<tr>
<td>12f</td>
<td>88%</td>
<td>1:1.9</td>
</tr>
<tr>
<td>12g</td>
<td>80%</td>
<td>1.5:1</td>
</tr>
<tr>
<td>12h</td>
<td>82%</td>
<td>1:1.4</td>
</tr>
<tr>
<td>12i</td>
<td>81%</td>
<td>6:1</td>
</tr>
<tr>
<td>12j</td>
<td>70%</td>
<td>1:1.3</td>
</tr>
<tr>
<td>12k</td>
<td>78%</td>
<td>1:1.9</td>
</tr>
<tr>
<td>12l</td>
<td>45%</td>
<td>1.2:3.3:1</td>
</tr>
<tr>
<td>12m</td>
<td>60%</td>
<td>1:1.2</td>
</tr>
<tr>
<td>12n</td>
<td>78%</td>
<td>1:4.4:1:4.6</td>
</tr>
</tbody>
</table>

*Note: a, b, and c refer to the positions of the substituents.*
Table 3.11 Substrate scope (continued).

Table 3.12 Olefin scope.

Yield and selectivity were determined by $^1$H NMR analysis of the crude mixture using CH$_2$Br$_2$ as an internal standard. Isolated yield of all isomers is given in square brackets. $^a$Traces of meta isomer was detected. $^b$25 equiv of arene was used. $^c$32 equiv of arene was used. $^d$Mainly 1 isomer was observed.

We next explored the olefin scope in the reaction with benzene (Table 3.12). The reactions with and without L3 were again performed. Using activated alkenes, the product yield was improved in the presence of ligand L3 in all cases. The reactions with methyl acrylate and ethyl cinnamate furnished the olefinated products 14a and 14b, respectively, in high yields. Other electrophilic alkenes such as vinyl phosphonate, vinyl amide, vinyl nitrile and vinyl sulfonate reacted efficiently with benzene, leading to the olefinated products 14c–f in good yields (42–78%). However, we observed low yields using non-activated alkenes such as allylbenzene or allyl acetate without any improvement when ligand L3 was used.
Table 3.12 Olefin scope (continued).

<table>
<thead>
<tr>
<th>Olefin scope</th>
<th>Yield</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>14g</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>14h</td>
<td>35%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Yield and selectivity were determined by $^1$H NMR analysis of the crude mixture using CH$_2$Br$_2$ as an internal standard. Isolated yield of all products is given in square brackets. *The reaction was performed overnight.

Finally, the C–H olefination in preparative scale using mesitylene (3.5 mmol) and 1,3,5-trifluorobenzene (1.75 mmol) as starting materials afforded the corresponding olefinated products 12f and 12p with good isolated yields without any significant erosion from the original values (Scheme 3.11).

Scheme 3.11 C–H Olefination of simple arenes in preparative scale.

Comparison of catalytic systems

As mentioned in the introduction, pyridine-based ligands are efficient ligands in promoting C–H olefination of non-directed arenes. In Table 3.13, we show the comparison of the results reported by Sanford using 3,5-dichloropyridine\textsuperscript{14b} with the results previously presented using L3 and without ligand (see Table 3.11). The reaction of naphthalene without ligand and in the presence of 3,5-dichloropyridine provided an equimolecular mixture of isomers versus the 2:1 ratio obtained in the presence of L3 in favor of the α-olefinated product. The reaction of anisole without ligand and with 3,5-dichloropyridine provided a mixture of ortho and para products, with a clear preference for the latter. In contrast, in the presence of L3, the ortho-olefinated product was preferred. The reaction of phenol using 3,5-dichloropyridine provided a mixture of ortho and para products with a small preference for the ortho product (1.4:o:1:p) when compared to ligand L3 (1.9:o:1:p). These results indicate that the S,O-ligand has stronger influence on the site selectivity of the C–H olefination reaction than the pyridine based ligand.
Table 3.13 Comparison of catalytic systems.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>12b (a:b)</th>
<th>12g (o:m:p)</th>
<th>12k (o:p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ligand</td>
<td>(1:1)</td>
<td>(1:0:1.7)</td>
<td>(1:1.3)</td>
</tr>
<tr>
<td>L3</td>
<td>(2:1)</td>
<td>(1.5:0:1)</td>
<td>(1.9:1)</td>
</tr>
<tr>
<td>3,5-Dichloropyridine</td>
<td>(1.1:1)²</td>
<td>(4.1:1:7.4)²</td>
<td>(1.4:1)²</td>
</tr>
</tbody>
</table>

Site selectivity was determined by ¹H NMR analysis of the crude mixture. ²Site selectivity reported previously in ref 14b.

Pd-Catalyzed C–H olefination of complex molecules

Having revealed the high reactivity of the new catalytic system in simple arenes, we assessed the suitability of this methodology for late-stage functionalization of complex molecules (Scheme 3.12). To the best of our knowledge, when we performed these experiments, the intermolecular Fujiwara-Moritani reaction using the arene as a limiting reagent was not reported.¹⁵ We found out that increasing the amount of catalyst from 5 to 10 mol% and extending the reaction time from 6 h to 16 h permitted the use of only 1 equiv of starting material. The reaction of O-methylestrone (10u) (1 equiv) with ethyl acrylate (1.5 equiv) and Pd(OAc)₂ (10 mol%) provided the desired product 12u in only 10% conversion. In contrast, when the reaction was carried out in the presence of L3, the olefinated product 12u was obtained in 88% yield as a mixture of ortho-olefinated isomers respect to the methoxy substituents (a:b = 3:1). As a comparison, we performed the reaction using Pd/3,5-dichloropyridine catalyst¹⁴b but only 30% conversion was detected under the same reaction conditions. Similarly, when the reaction of the naproxen derivative 10v was carried out in the absence of ligand, only traces of olefinated product 12v was detected by ¹H NMR. The same reaction in the presence of L3 furnished a mixture of products with a combined isolated yield of 88%, being the main isomer the ortho-olefinated product respect to the methoxy substituent (a:others = 3:1). Again, for comparison, we performed the reaction of the naproxen derivative 10v using 3,5-dichloropyridine as a ligand. Under the standard conditions, we obtained a mixture of olefinated products in 27% NMR yield. To further prove the applicability of the new catalytic system, the C–H olefination in preparative scale of O-methylestrone (10u) (1.75 mmol) was performed. To our delight, the yield was comparable with the original value.
3.3 Conclusions
In summary, we have synthesized a variety of S,O-ligands in two steps from commercially available starting materials. The new catalytic system based on Pd/S,O-ligand is successful in promoting the C–H olefination of arenes. We have proven by comparing the reaction with and without ligand that the S,O-ligand is responsible for the high reactivity of the catalyst, promoting the C–H olefination of both electron-rich and electron-poor arenes in high yields. For all these substrates, the olefination reactions occur preferentially at the most electron-rich position of the arene. Remarkably, the Pd/S,O-ligand system has shown higher activity and influence in the site selectivity than the well-established Pd/pyridine-based catalytic system. In addition, we have demonstrated that the developed methodology is applicable on preparative scale and in late-stage functionalization of complex molecules.

3.4 Acknowledgements
Dr. Carolina Valderas, Dr. Melania Gómez-Martínez, Dr. Yolanda Álvarez-Casao and Daniël Verdoorn are kindly acknowledged for their contributions to this chapter. Ed Zuidinga and Dorette Tromp are thanked for the high-resolution mass measurements.

3.5 Experimental section
General information
Chromatography: Silicyle Silica Flash P60 size 40–63 µm (230–400 mesh), TLC: Merck silica gel 60 (0.25 mm). Visualization of the TLC was performed by UV, phosphomolybdic acid, KMnO₄ or oleum staining. Mass spectra were recorded on AccuTOF GC v 4g, JMS-T100GCV mass spectrometers. ¹H, ¹³C and ¹⁹F NMR were recorded on Bruker 500 AMX, 400 and Bruker DRX 300 using CDCl₃ as a solvent, unless otherwise mentioned. 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 $^{13}$C; DMSO-d$_6$: δ 2.50 for $^1$H). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, 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$^{-1}$. Melting points were measured in a POLYTHERM A Heiztisch Mikroskop. GC analysis was performed on a Shimadzu GC-2010 Plus Gas Chromatograph, using SH-Rxi-5HT (30 m, 0.25 mm, D 0.25 μm) column. THF was dried over sodium/benzophenone and used freshly distilled. Acetonitrile was dried over CaH$_2$ and distilled. The glassware was preheated for moisture-sensitive reactions. All reagents and solvents were used as received. Pd(OAc)$_2$ was purchased from Strem. (Phenylthio)acetic acid (L16), α-(phenylthio)phenylacetic acid (L17), 2-thiophenecarboxylic acid (L18) and thioanisole (L21) were purchased from commercial suppliers.

3.5.1 Synthesis of ligands

**Procedure for the synthesis of ligands L1–L12**

**General procedure for α-bromination of carboxylic acids**

α-Bromocarboxylic acids were prepared following the procedure described in the literature.$^{16a}$ A solution of the corresponding carboxylic acid (1 equiv), N-bromosuccinimide (1.5 equiv), conc. H$_2$SO$_4$ and trifluoroacetic acid was heated at 85 °C overnight. The reaction was concentrated under reduced pressure. The crude residue was purified by distillation.

**2-Bromobutanoic acid (2a)**

2-Bromobutanoic acid (2a) was prepared following the general procedure using butyric acid (2.5 g, 28.37 mmol, 1 equiv), N-bromosuccinimide (7.57 g, 42.56 mmol, 1.5 equiv), conc. H$_2$SO$_4$ and trifluoroacetic acid (15 mL). The crude residue was purified by distillation under reduced pressure (3 mbar, 93 °C) providing the titled compound as a yellow liquid (4.12 g, 87% yield). $^1$H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.$^{22}$ $^1$H NMR (300 MHz) δ = 9.80 (bs, 1H), 4.20 (t, $J = 7.2$ Hz, 1H), 2.19 – 1.98 (m, 2H), 1.07 (t, $J = 7.3$ Hz, 3H).

**2-Bromo-3,3-dimethylbutanoic acid (2b)**

2-Bromo-3,3-dimethylbutanoic acid (2b) was prepared following the general procedure using 3,3-dimethylbutyric acid (2.5 g, 21.52 mmol, 1 equiv), N-bromosuccinimide (5.75 g, 32.28 mmol, 1.5 equiv), conc. H$_2$SO$_4$ (0.57 mL) and trifluoroacetic acid (11 mL). The crude residue was purified by distillation under reduced pressure (2 mbar, 100 °C) providing the titled compound as a yellow solid (3.42 g, 81% yield). $^1$H NMR (400 MHz) δ = 4.10 (s, 1H), 1.15 (s, 9H), $^{13}$C NMR (101 MHz) δ = 175.4, 57.9, 34.4, 26.9; IR ν = 2960, 2916, 2871, 1703, 1418, 1367, 1268, 1179, 1164, 922, 884, 699, 501, 412 cm$^{-1}$; HRMS (FD) calcd for C$_6$H$_{11}$BrO$_2$ [M]$^+$: 193.9942; found: 193.9947; mp 55 – 58 °C.
General procedure for the addition of thiols to α-bromocarboxylic acids

S,O-ligands were prepared following the procedure described in the literature. To a solution of the corresponding α-bromocarboxylic acid (1 equiv) and NaOH (2 or 2.5 equiv) in EtOH or t-BuOH (0.16–0.33 M), the corresponding thiol (1 equiv) was added at room temperature. The reaction was refluxed overnight and concentrated under reduced pressure. The resulting crude was dissolved in water (10 mL) and acidified by 6 M aqueous HCl solution until pH = 1. The aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (3 x 10 mL). Then, the combined NaHCO₃ aqueous layers were acidified by 6 M aqueous HCl solution until pH = 1. The aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were dried over anh. MgSO₄, filtered and concentrated under reduced pressure to obtain the desired product.

2-(Phenylthio)butanoic acid (L1)

Ligand L1 was prepared following the general procedure using 2-bromobutanoic acid (2a) (0.84 g, 5 mmol, 1 equiv), NaOH (0.4 g, 10 mmol, 2 equiv) and thiophenol (0.51 mL, 5 mmol, 1 equiv) in EtOH (15 mL), providing the titled compound as a yellow oil (0.8 g, 81% yield). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound. ¹H NMR (300 MHz) δ = 7.49 – 7.46 (m, 2H), 7.35 – 7.26 (m, 3H), 3.57 (dd, J = 7.9, 7.0 Hz, 1H), 1.98 – 1.77 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H).

3,3-Dimethyl-2-(phenylthio)butanoic acid (L2)

Ligand L2 was prepared following the general procedure using 2-bromo-3,3-dimethylbutanoic acid (2b) (0.49 g, 2.5 mmol, 1 equiv), NaOH (0.2 g, 5 mmol, 2 equiv) and thiophenol (0.26 mL, 2.5 mmol, 1 equiv) in EtOH (7.5 mL), providing the titled compound as a yellow solid (0.45 g, 80% yield). ¹H NMR (300 MHz) δ = 11.58 (bs, 1H), 7.55 – 7.52 (m, 2H), 7.36 – 7.25 (m, 3H), 3.56 (s, 1H), 1.24 (s, 9H); ¹³C NMR (75 MHz) δ = 179.0, 135.2, 131.8, 129.2, 127.6, 63.3, 34.5, 27.6; IR ν = 3077, 3059, 2964, 2905, 2870, 2667, 2562, 1694, 1271, 1182, 1026, 739, 689, 483 cm⁻¹; HRMS (EI) calcd for C₁₂H₁₆O₂S [M⁺]: 224.0871; found: 224.0887; mp 50 – 53 °C.

3-Methyl-2-(phenylthio)butanoic acid (L3)

Ligand L3 was prepared following the general procedure using 2-bromo-3-methylbutanoic acid (2c) (0.91 g, 5 mmol, 1 equiv), NaOH (0.4 g, 10 mmol, 2 equiv) and thiophenol (0.51 mL, 5 mmol, 1 equiv) in EtOH (15 mL), providing the titled compound as a colorless oil (0.76 g, 73% yield). ¹H NMR (400 MHz) δ = 7.48 – 7.46 (m, 2H), 7.32 – 7.26 (m, 3H), 3.43 (d, J = 8.5 Hz, 1H), 2.20 – 2.11 (m, 1H), 1.18 (d, J = 6.7 Hz, 3H), 1.10 (d, J = 6.7 Hz, 3H); ¹³C NMR (75 MHz) δ = 178.7, 134.0, 132.3, 129.1, 127.8, 59.0, 30.3, 20.5, 20.1; IR ν = 2963, 2931, 2872, 1701, 1284, 1220, 1186, 743, 690 cm⁻¹; HRMS (EI) calcd for C₁₁H₁₄O₂S [M⁺]: 210.0715; found: 210.0719.
2-Methyl-2-(phenylthio)propanoic acid (L4)

Ligand L4 was prepared following the general procedure using 2-bromo-2-methylpropionic acid (2d) (0.84 g, 5 mmol, 1 equiv), NaOH (0.5 g, 12.5 mmol, 2.5 equiv) and thiophenol (0.51 mL, 5 mmol, 1 equiv) in t-BuOH (15 mL), providing the titled compound as a pale yellow solid (0.82 g, 84% yield). \(^1\)H NMR (300 MHz) \(\delta = 7.53 – 7.50\) (m, 2H), 7.40 – 7.31 (m, 3H), 1.50 (s, 6H); \(^1\)C NMR (75 MHz) \(\delta = 180.3, 136.8, 131.1, 129.6, 128.8, 50.7, 25.5\); IR \(\nu = 3055, 2974, 2932, 2650, 2545, 1688, 1283, 1164, 751, 691\) cm\(^{-1}\); HRMS (EI) calcd for C\(_{10}\)H\(_{12}\)O\(_2\)S \([M]+\): 196.0558; found: 196.0560; mp 45 – 48 °C.

2-(Mesitylthio)-3-methylbutanoic acid (L5)

Ligand L5 was prepared following the general procedure using 2-bromo-3-methylbutanoic acid (2c) (100 mg, 0.55 mmol, 1 equiv), NaOH (44 mg, 1.1 mmol, 2 equiv) and 2,4,6-trimethylbenzenethiol (0.1 mL, 0.55 mmol, 1 equiv) in EtOH (1.7 mL), providing the titled compound as a white solid (73 mg, 53% yield). \(^1\)H NMR (300 MHz) \(\delta = 6.91\) (s, 2H), 3.12 (d, \(J = 8.9\) Hz, 1H), 2.48 (s, 6H), 2.25 (s, 3H), 2.19 – 2.11 (m, 1H), 1.22 (d, \(J = 6.7\) Hz, 3H), 1.09 (d, \(J = 6.7\) Hz, 3H); \(^1\)C NMR (101 MHz) \(\delta = 179.1, 143.4, 138.9, 129.3, 128.1, 58.0, 30.7, 21.9, 21.2, 20.7, 20.4\); IR \(\nu = 2967, 2924, 2874, 1696, 1281, 852, 690, 555, 496\) cm\(^{-1}\); HRMS (EI) calcd for C\(_{14}\)H\(_{20}\)O\(_2\)S \([M]+\): 252.1184; found: 252.1184; mp 118 – 123 °C.

3-Methyl-2-(tritylthio)butanoic acid (L6)

Ligand L6 was prepared following the general procedure using 2-bromo-3-methylbutanoic acid (2c) (0.26 g, 1.45 mmol, 1 equiv), NaOH (0.15 g, 3.63 mmol, 2.5 equiv) and triphenylmethanethiol (0.4 g, 1.45 mmol, 1 equiv) in EtOH (7.25 mL), providing the titled compound as a white solid (0.21 g, 39% yield). \(^1\)H NMR (300 MHz) \(\delta = 7.54 – 7.50\) (m, 6H), 7.32 – 7.19 (m, 9H), 2.80 (d, \(J = 6.3\) Hz, 1H), 2.03 – 1.92 (m, 1H), 1.04 (d, \(J = 6.7\) Hz, 3H), 0.97 (d, \(J = 6.7\) Hz, 3H); \(^1\)C NMR (75 MHz) \(\delta = 178.9, 144.4, 129.7, 128.0, 126.9, 68.1, 54.0, 31.7, 20.5, 19.7\); IR \(\nu = 2964, 1697, 1470, 1419, 1255, 1184, 745, 676, 528\) cm\(^{-1}\); HRMS (FD): calcd for C\(_{24}\)H\(_{24}\)O\(_2\)S \([M]+\): 376.1497; found 376.1495. mp 164 – 167 °C.

2-[(4-Methoxyphenylthio)-3-methylbutanoic acid (L7)

Ligand L7 was prepared following the general procedure using 2-bromo-3-methylbutanoic acid (2c) (0.45 g, 2.5 mmol, 1 equiv), NaOH (0.2 g, 5 mmol, 2 equiv) and 4-methoxythiophenol (0.31 mL, 2.5 mmol, 1 equiv) in EtOH (7.5 mL), providing the titled compound as a colorless oil (0.56 g, 94% yield). \(^1\)H NMR (400 MHz) \(\delta = 7.44\) (d, \(J = 8.9\) Hz, 2H), 6.84 (d, \(J = 8.9\) Hz, 2H), 3.79 (s, 3H), 3.24 (d, \(J = 8.9\) Hz, 1H), 2.11 – 2.03 (m, 1H), 1.18 (d, \(J = 6.7\) Hz, 3H), 1.07 (d, \(J = 6.7\) Hz, 3H); \(^1\)C NMR (101 MHz) \(\delta = 178.4, 159.9, 135.8, 123.6, 114.5, 60.0, 55.1, 29.7, 20.5, 20.0\); IR \(\nu = 2962, 2936, 2872, 2836, 1699, 1591, 1493, 1285, 1244, 1172, 1030, 827\) cm\(^{-1}\); HRMS (EI) calcd for C\(_{12}\)H\(_{16}\)O\(_3\)S \([M]+\): 240.0820; found: 240.0825.
3-Methyl-2-[(2,4,6-trimethoxyphenyl)thio]butanoic acid (L8)

Ligand L8 was prepared following the general procedure using 2-bromo-3-methylbutanoic acid (2c) (0.14 g, 0.8 mmol, 1 equiv), NaOH (0.08 g, 2 mmol, 2.5 equiv) and 2,4,6-trimethoxybenzenethiol (0.16 g, 0.8 mmol, 1 equiv) in EtOH (5 mL), providing the titled compound as a pale brown solid (0.16 g, 66% yield). \[^1\]H NMR (400 MHz) δ = 6.12 (s, 2H), 3.84 (s, 6H), 3.82 (s, 3H), 3.27 (d, J = 7.6 Hz, 1H), 2.23 – 2.17 (m, 1H), 1.17 (d, J = 6.7 Hz, 3H), 1.10 (d, J = 6.7 Hz, 3H); \[^13\]C NMR (101 MHz) δ = 177.3, 162.6, 162.1, 99.8, 91.0, 59.4, 56.1, 55.4, 30.6, 20.7, 19.8; IR ν = 3001, 2981, 2958, 2838, 1691, 1578, 1467, 1405, 1366, 1121, 951, 802 cm\(^{-1}\); HRMS (FD): calcd for C\(_{14}\)H\(_{20}\)O\(_5\)S \([\text{M}]^+: 300.1031\); found 300.1031; mp 131 – 136 °C.

3-Methyl-2-[(perfluorophenyl)thio]butanoic acid (L9)

Ligand L9 was prepared following the general procedure using 2-bromo-3-methylbutanoic acid (2c) (0.18 g, 1 mmol, 1 equiv), NaOH (0.1 g, 2.5 mmol, 2.5 equiv) and 2,3,4,5,6-pentafluorothiophenol (0.13 mL, 1 mmol, 1 equiv) in t-BuOH (3.5 mL), providing the titled compound as a pale yellow oil (0.28 g, 94% yield). \[^1\]H NMR (300 MHz) δ = 8.82 (bs, 1H), 3.32 (d, J = 8.9 Hz, 1H), 2.17 – 2.05 (m, 1H), 1.22 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H); \[^13\]C NMR (75 MHz) δ = 177.2, 148.5 (d, J\(_{C-F} = 247.3\) Hz), 142.4 (d, J\(_{C-F} = 257.3\) Hz), 137.4 (d, J\(_{C-F} = 256.0\) Hz), 107.4 – 106.8 (m, 58.4, 30.3, 20.6, 19.9); \[^19\]F NMR (282 MHz) δ = -130.99 (d, J\(_{F-F} = 18.3\) Hz), -150.30 (t, J = 20.8 Hz), -160.57 – -160.74 (m); IR ν = 2969, 1706, 1512, 1486, 1289, 1092, 980, 862 cm\(^{-1}\); HRMS (EI) calcd for C\(_{11}\)H\(_{9}\)F\(_5\)O\(_2\)S \([\text{M}]^+: 300.0243\); found: 300.0256.

2-[(4-Trifluoromethylphenyl)thio]-3-methylbutanoic acid (L10)

Ligand L10 was prepared following the general procedure using 2-bromo-3-methylbutanoic acid (2c) (0.45 g, 2.5 mmol, 1 equiv), NaOH (0.2 g, 5 mmol, 2 equiv) and 4-(trifluoromethyl)thiophenol (0.32 mL, 2.5 mmol, 1 equiv) in EtOH (7.5 mL), providing the titled compound as a pale yellow oil (0.41 g, 59% yield). \[^1\]H NMR (300 MHz) δ = 7.57 – 7.50 (m, 4H), 3.55 (d, J = 8.4 Hz, 1H), 2.26 – 2.14 (m, 1H), 1.18 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H); \[^13\]C NMR (75 MHz) δ = 178.5, 139.8, 130.5, 129.2 (q, J\(_{C-F} = 32.8\) Hz), 126.0 (q, J\(_{C-F} = 3.7\) Hz), 122.3, 57.8, 30.6, 20.5, 20.0; \[^19\]F NMR (282 MHz) δ = -62.64; IR ν = 2966, 2933, 2875, 1705, 1607, 1323, 1164, 1123, 1094, 1063, 1014, 828 cm\(^{-1}\); HRMS (EI) calcd for C\(_{12}\)H\(_{13}\)F\(_3\)O\(_2\)S \([\text{M}]^+: 278.0588\); found: 278.0595.
2-(Isopropylthio)-3-methylbutanoic acid (L12)

Ligand L12 was prepared following the general procedure using 2-bromo-3-methylbutanoic acid (2c) (0.91 g, 5 mmol, 1 equiv), NaOH (0.5 g, 12.5 mmol, 2.5 equiv) and 2-propanethiol (0.46 mL, 5 mmol, 1 equiv) in t-BuOH (15 mL), providing the titled compound as a colorless oil (0.79 g, 89% yield).

1H NMR (400 MHz) δ = 10.86 (bs, 1H), 3.06 – 3.00 (m, 2H), 2.05 – 2.01 (m, 1H), 1.28 (d, J = 6.5 Hz, 3H), 1.26 (d, J = 6.5 Hz, 3H), 1.08 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H); 13C NMR (75 MHz) δ = 179.7, 53.9, 36.2, 30.3, 23.6, 23.4, 20.9, 20.1; IR ν = 2962, 2928, 2869, 1698, 1461, 1367, 928, 699 cm⁻¹; HRMS (FD): calcd for C₁₂H₁₆O₂S [M]+: 224.0871; found 224.0878.

Procedure for the synthesis of 1-(phenylthio)cyclopropanecarboxylic acid (L13)

1,1,3-(Trisphenylthio)propane (4)

1,1,3-(Trisphenylthio)propane (4) was synthesized following the procedure described in the literature.¹⁷a Acrolein (3) (1.34 mL, 20 mmol, 1 equiv) and thiophenol (6.4 mL, 62 mmol, 3.1 equiv) were stirred in dry acetonitrile (10 mL) under nitrogen atmosphere at -50 °C. SnCl₄ (0.47 mL, 4 mmol, 20 mol%) was added to the reaction at -50 °C and stirred overnight at room temperature. The reaction was quenched with aqueous NaOH solution (0.5 M, 25 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with aqueous NaOH solution (0.5 M, 3 x 20 mL), dried over anh. MgSO₄, filtered and concentrated under reduced pressure to afford 1,1,3-(trisphenylthio)propane (7.09 g, 96% yield).

1H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.²⁶ 1H NMR (400 MHz) δ = 7.47 – 7.44 (m, 3H), 7.32 – 7.20 (m, 12H), 4.64 (t, J = 6.8 Hz, 1H), 3.22 (t, J = 6.9 Hz, 2H), 2.20 – 2.13 (m, 2H).

1,1-Bis(phenylthio)cyclopropane (5)

1,1-Bis(phenylthio)cyclopropane (5) was synthesized following the procedure described in the literature.¹⁷b TMEDA (1.70 mL, 11.2 mmol, 2 equiv) was added to a solution of 1,1,3-(trisphenylthio)propane (2.06 g, 5.6 mmol, 1 equiv) in dry THF (30 mL) under nitrogen atmosphere. The reaction was cooled to 0 °C. MeLi (1.6 M, 5.6 mL, 8.96 mmol, 1.6 equiv) was added to the mixture and the reaction was stirred for 3 h at 0 °C. The mixture was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anh. MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography using Et₂O:petroleum ether (1:49 v/v) as an eluent to afford 1,1-bis(phenylthio)cyclopropane (0.71 g, 49% yield). 1H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.²⁷ 1H NMR (400 MHz) δ = 7.51 – 7.48 (m, 4H), 7.38 – 7.34 (m, 4H), 7.30 – 7.26 (m, 2H), 1.52 (s, 4H).
1-(Phenylthio)cyclopropanecarboxylic acid (L13)

Ligand L13 was synthesized following the procedure described in the literature.\(^{17c}\) The solution of lithium naphthalenide (0.5 M, 8.4 mL, 4.2 mmol, 1.8 equiv) in dry THF (10 mL) under nitrogen atmosphere was cooled to -70 °C [synthesis of lithium naphthalenide: dry THF (10 mL) was added to freshly prepared Li (52 mg, 7.5 mmol, 1.5 equiv) and naphthalene (0.64 g, 5 mmol, 1 equiv) under nitrogen atmosphere. The reaction was sonicated at maximum energy for 5 min at room temperature to afford a green solution. The reaction was stirred for another 1 h at room temperature to give a dark green solution]. The solution of 1,1-(phenylthio)cyclopropane (5) (0.6 g, 2.32 mmol, 1 equiv) in dry THF (3 mL) was added to the reaction and stirred for 15 min. Dry CO\(_2\) (s) (excess) was added and the mixture was stirred at -70 °C for 5 min and then at room temperature for 3 h. The reaction was quenched by adding saturated aqueous ammonium chloride (25 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anh. MgSO\(_4\), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:4 v/v) as an eluent to afford 1-(phenylthio)cyclopropanecarboxylic acid (L13) as a pale yellow solid (0.15 g, 33% yield).

\[\text{L13} \quad \text{CO}_2\text{H} \quad \text{SPh} \]

1\(^{H}\) NMR (300 MHz) \(\delta = 7.39 – 7.28 \text{ (m, 4H)}, 7.28 – 7.20 \text{ (m, 1H)}, 1.92 – 1.88 \text{ (m, 2H)}, 1.51 – 1.45 \text{ (m, 2H)}\); 13\(^{C}\) NMR (75 MHz) \(\delta = 179.0, 135.8, 129.1, 128.4, 126.4, 26.9, 21.9\); IR \(\nu = 3059, 3017, 2924, 2853, 1689, 1439, 1302, 930, 737, 690 \text{ cm}^{-1}\); HRMS (FD): calcd for C\(_{10}\)H\(_{10}\)O\(_2\)S [M]+: 194.0402; found 194.0407; mp 77 – 83 °C.

**Procedure for the synthesis of 2-(phenylthio)benzoic acid (L14)**

Ligand L14 was synthesized following the procedure described in the literature.\(^{18}\) A mixture of thiophenol (0.34 mL, 3.25 mmol, 1.3 equiv), 2-bromobenzoic acid (6) (0.5 g, 2.5 mmol, 1 equiv), potassium carbonate (0.35 g, 5 mmol, 1 equiv), copper powder (14.3 mg, 0.23 mmol, 9 mol%) and copper oxide (16.1 mg, 0.11 mmol, 4.5 mol%) in EtOH (1 mL) was refluxed for 4 h. Then, the reaction was cooled to room temperature and the solvent was concentrated under reduced pressure. The residue was poured into water (15 mL) and acidified with diluted hydrochloric acid until pH = 5 giving a precipitate, which was dissolved in aqueous Na\(_2\)CO\(_3\) solution (5%). The solution was filtered through Celite, acidified again with diluted HCl and filtered giving 2-(phenylthio)benzoic acid (L14) as a white solid (0.15 g, 26% yield). \(^{1}H\) NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.\(^{18}\) \(^{1}H\) NMR (400 MHz) \(\delta = 8.16 \text{ (dd, } J = 7.8, 1.6 \text{ Hz, 1H)}, 7.63 – 7.60 \text{ (m, 2H)}, 7.49 – 7.46 \text{ (m, 3H)}, 7.33 – 7.29 \text{ (m, 1H)}, 7.18 \text{ (td, } J = 7.6, 1.2 \text{ Hz, 1H}), 6.84 \text{ (dd, } J = 8.2, 1.1 \text{ Hz, 1H}).

**Procedure for the synthesis of tetrahydrothiophene-2-carboxylic acid (L15)**

2-[(3-Chloropropyl)thio]acetonitrile (8)

2-[(3-Chloropropyl)thio]acetonitrile (8) was synthesized following the procedure described in the literature.\(^{19}\) Potassium carbonate (0.87 g, 6.33 mmol, 1 equiv) was added in one portion to a solution of chloroacetonitrile (7) (0.8 mL, 12.66 mmol, 2 equiv) in acetonitrile (7 mL). The reaction was heated at 40 °C and a solution of 3-chloropropanethiol (0.7 mL, 6.33 mmol, 1 equiv) in
Acetonitrile (2 mL) was added dropwise to the reaction. Then, the reaction mixture was heated at 45 °C overnight. The inorganic salts were filtered off and the solvent was removed under reduced pressure. The crude residue was purified by Kugelrohr distillation (760 mmHg, 220 °C) giving 2-[(3-chloropropyl)thio]acetonitrile (8) as a colorless oil (0.49 g, 52% yield). \(^1\)H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.\(^1\)\(^9\) \(^1\)H NMR (400 MHz) \(\delta = 3.62 (t, J = 6.2 \text{ Hz}, 2 \text{H}), 3.29 (s, 2 \text{H}), 2.83 (t, J = 7.0 \text{ Hz}, 2 \text{H}), 2.09 - 2.02 (m, 2 \text{H}).

**Tetrahydrothiophene-2-carbonitrile (9)**

Tetrahydrothiophene-2-carbonitrile (9) was synthesized following the procedure described in the literature.\(^1\)\(^9\) Aqueous NaOH solution (50% v/v, 2.2 mL) was added dropwise to the mixture of 2-[(3-chloropropyl)thio]acetonitrile (8) (0.49 g, 3.27 mmol, 1 equiv) and benzyltriethylammonium chloride (TEBA) (22.5 mg, 98.6 µmol, 3 mol%). The mixture was stirred for 1 h. The reaction was extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL). The combined organic layers were washed with aqueous HCl solution (10%, 15 mL) and water (15 mL). The organic layers were dried over anh. MgSO\(_4\), filtered and evaporated under reduced pressure. The crude residue was purified by Kugelrohr distillation (760 mmHg, 220 °C) giving tetrahydrothiophene-2-carbonitrile (9) as a colorless oil (0.28 g, 76% yield). \(^1\)H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.\(^1\)\(^9\) \(^1\)H NMR (400 MHz) \(\delta = 3.95 - 3.93 (m, 1 \text{H}), 3.06 - 3.03 (m, 1 \text{H}), 2.91 - 2.88 (m, 1 \text{H}), 2.29 - 2.26 (m, 1 \text{H}), 2.17 - 2.07 (m, 3 \text{H}).

**Tetrahydrothiophene-2-carboxylic acid (L15)**

Aqueous HCl solution (6 M, 1.5 mL) was added to tetrahydrothiophene-2-carbonitrile (9) (0.28 g, 2.48 mmol, 1 equiv) and the reaction was refluxed for 3 h. Then, the reaction mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anh. MgSO\(_4\), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:4 v/v) as an eluent to obtain tetrahydrothiophene-2-carboxylic acid (L15) as a white solid (0.2 g, 61% yield). \(^1\)H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.\(^1\)\(^9\) \(^1\)H NMR (400 MHz) \(\delta = 11.92 (bs, 1 \text{H}), 3.94 (dd, J = 7.2, 4.4 \text{ Hz}, 1 \text{H}), 3.01 - 2.96 (m, 1 \text{H}), 2.91 - 2.85 (m, 1 \text{H}), 2.30 - 2.27 (m, 1 \text{H}), 2.18 - 1.98 (m, 3 \text{H}).
Procedure for the synthesis of methyl 2-methyl-2-(phenylthio)propanoate (L22), 2-methyl-2-(phenylsulfinyl)propanoic acid (L19) and 2-methyl-2-(phenylsulfonyl)propanoic acid (L20)

**Scheme 3.13** Synthetic route for the synthesis of methyl 2-methyl-2-(phenylthio)propanoate (L22), 2-methyl-2-(phenylsulfinyl)propanoic acid (L19) and 2-methyl-2-(phenylsulfonyl)propanoic acid (L20).

**Methyl 2-methyl-2-(phenylthio)propanoate (L22)**

A solution of 2-methyl-2-(phenylthio)propanoic acid (L4) (0.69 g, 3.52 mmol, 1 equiv) and p-TsOH·H2O (0.67 g, 3.52 mmol, 1 equiv) in MeOH (10 mL) was refluxed overnight. The reaction was evaporated to dryness. The crude obtained was dissolved in a NaOH solution until pH = 14 and extracted with CH2Cl2 (3 x 10 mL). The combined organic layers were dried over anh. MgSO4, filtered and concentrated under reduced pressure to afford methyl 2-methyl-2-(phenylthio)propanoate (L22) as a white solid (0.64 g, 86% yield).

**General procedure for the oxidation of methyl 2-methyl-2-(phenylthio)propanoate (L22)**

m-CPBA (77%, 1 or 3 equiv) was added to a solution of methyl 2-methyl-2-(phenylthio)propanoate (L22) (1 equiv) in CH2Cl2 at 0 °C. The reaction was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous Na2SO3 (10 mL) and extracted with CH2Cl2 (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaHCO3 (30 mL), dried over anh. MgSO4, filtered and concentrated under reduced pressure. The crude residue was purified as specified in each case to obtain the desired product.

**Methyl 2-methyl-2-(phenylsulfinyl)propanoate**

Methyl 2-methyl-2-(phenylsulfinyl)propanoate was synthesized following the general procedure using m-CPBA (0.36 g, 1.62 mmol, 1 equiv) and methyl 2-methyl-2-(phenylthio)propanoate (L22) (0.34 g, 1.62 mmol, 1 equiv) in CH2Cl2 (7 mL). The crude residue was purified by column chromatography using EtOAc:petroleum ether (3:7 v/v) as an eluent providing the titled compound as a white solid (0.15 g, 41% yield).
H NMR (300 MHz) \( \delta = 7.65 - 7.48 \) (m, 5H), 3.65 (s, 3H), 1.58 (s, 3H), 1.29 (s, 3H); \(^{13}\)C NMR (75 MHz) \( \delta = 171.4, 140.2, 131.9, 128.8, 125.7, 66.5, 52.7, 20.7, 16.1; \) IR \( \nu = 2953, 2926, 2852, 1724, 1460, 1444, 1272, 1154, 1081, 1049, 751, 692 \) cm\(^{-1}\).

**Methyl 2-methyl-2-(phenylsulfonyl)propanoate**

Methyl 2-methyl-2-(phenylsulfonyl)propanoate was synthesized following the general procedure using \( m \)-CPBA (0.64 g, 2.85 mmol, 3 equiv) and methyl 2-methyl-2-(phenylthio)propanoate (L22) (0.20 g, 0.95 mmol, 1 equiv) in \( \text{CH}_2\text{Cl}_2 \) (5 mL), providing the titled compound as a white solid (0.2 g, 87% yield). \(^{1}H\) NMR (400 MHz) \( \delta = 7.84 \) (dd, \( J = 8.4, 1.2 \) Hz, 2H), 7.70 – 7.65 (m, 1H), 7.55 (dd, \( J = 10.7, 4.8 \) Hz, 2H), 3.68 (s, 3H), 1.61 (s, 6H); \(^{13}\)C NMR (101 MHz) \( \delta = 169.4, 135.8, 134.3, 130.5, 128.8, 69.3, 53.2, 20.4; \) IR \( \nu = 3001, 2957, 1736, 1448, 1301, 1276, 1152, 1123, 1075, 835, 765, 723, 695, 608, 563 \) cm\(^{-1}\).

**General procedure for the hydrolysis of methyl 2-methylpropanoate derivatives**

The corresponding methyl 2-methylpropanoate derivative (1 equiv) and NaOH (20 equiv) were added to a mixture of THF, MeOH and \( \text{H}_2\text{O} \) (1:1:1) and the reaction was stirred overnight at room temperature. Then, the reaction was evaporated to dryness. The obtained crude was dissolved in \( \text{H}_2\text{O} \) (10 mL) and washed with \( \text{CH}_2\text{Cl}_2 \) (3 x 10 mL). The aqueous layer was acidified by aqueous HCl solution (1 M) until pH = 1 and extracted with \( \text{CH}_2\text{Cl}_2 \) (3 x 15 mL). The combined organic layers were dried over anh. \( \text{MgSO}_4 \), filtered and concentrated under reduced pressure to afford the desired product.

**2-Methyl-2-(phenylsulfinyl)propanoic acid (L19)**

2-Methyl-2-(phenylsulfinyl)propanoic acid (L19) was synthesized following the general procedure using methyl 2-methyl-2-(phenylsulfinyl)propanoate (0.14 g, 0.62 mmol, 1 equiv) and NaOH (0.5 g, 12.4 mmol, 20 equiv) in a mixture of THF, MeOH and \( \text{H}_2\text{O} \) (1, 1 and 1 mL, respectively), providing the titled compound as a white solid (0.11 g, 84% yield). \(^{1}H\) NMR (300 MHz) \( \delta = 8.41 \) (bs, 1H), 7.63 – 7.47 (m, 5H), 1.43 (s, 3H), 1.42 (s, 3H); \(^{13}\)C NMR (75 MHz) \( \delta = 173.2, 138.0, 132.5, 129.1, 126.2, 65.0, 19.4, 18.6; \) IR \( \nu = 2982, 2936, 1712, 1440, 1225, 1145, 1120, 1011, 995, 749, 686, 591, 510, 485 \) cm\(^{-1}\); HRMS (FD) calcd for C\(_{10}\)H\(_{12}\)O\(_3\)S [M\(^{+}\)]: 212.0507; found: 212.0498; mp 131 – 134 °C.

**2-Methyl-2-(phenylsulfonyl)propanoic acid (L20)**

2-Methyl-2-(phenylsulfonyl)propanoic acid (L20) was synthesized following the general procedure using methyl 2-methyl-2-(phenylsulfonyl)propanoate (0.16 g, 0.66 mmol, 1 equiv) and NaOH (0.53 g, 13.2 mmol, 20 equiv) in a mixture of THF, MeOH and \( \text{H}_2\text{O} \) (1, 1 and 1 mL, respectively), providing the titled compound as a white solid (0.13 g, 86% yield). \(^{1}H\) NMR (300 MHz) \( \delta = 9.92 \) (bs, 1H), 7.89 (d, \( J = 7.6 \) Hz, 2H), 7.69 (t, \( J = 7.4 \) Hz, 1H), 7.56 (t, \( J = 7.6 \) Hz, 2H), 1.62 (s, 6H); \(^{13}\)C NMR (75 MHz) \( \delta = 175.2, 135.2, 134.5, 130.6, 129.0, 69.1, 20.3; \) IR \( \nu = 3066, 3002, 2918, 1700, 1284, 1128, 1073, 898, 723, 695, 606, 569, 532 \) cm\(^{-1}\); HRMS (FD) calcd for C\(_{10}\)H\(_{13}\)O\(_4\)S [M\(^{+}\)H\(^+\)]: 229.0535; found: 229.0526; mp 134 – 140 °C.
**Procedure for the synthesis of 3-methyl-2-(phenylselanyl)butanoic acid (L23)**

\[
\begin{array}{c}
\text{PhSeH (1 equiv)} \\
\text{EtOH, reflux, overnight} \\
\text{NaOH (2 equiv)} \\
\text{89%}
\end{array}
\]

**Scheme 3.14 Synthesis of ligand L23.**

Ligand L23 was prepared following the procedure described in the literature.\textsuperscript{16b} To a solution of 2-bromo-3-methylbutanoic acid (0.18 g, 1 mol, 1 equiv) and NaOH (0.1 g, 2.5 mmol, 2.5 equiv) in EtOH (3 mL), benzeneselenol (0.11 mL, 1 mmol, 1 equiv) was added at room temperature. The reaction was refluxed overnight and concentrated under reduced pressure. The resulting crude was dissolved in water (10 mL) and acidified by 6 M aqueous HCl solution until pH = 1. The aqueous layer was extracted with Et\(_2\)O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaHCO\(_3\) (3 x 10 mL). Then, the combined NaHCO\(_3\) aqueous layers were acidified by 6 M aqueous HCl solution until pH = 1. The aqueous layer was extracted with Et\(_2\)O (3 x 20 mL). The combined organic layers were dried over anh. MgSO\(_4\), filtered and concentrated under reduced pressure to obtain the desired product as a pale yellow oil (0.23 g, 89% yield).

\[\text{1H NMR (300 MHz) } \delta = 11.66 (bs, 1H), 7.79 - 7.60 (m, 2H), 7.40 - 7.28 (m, 3H), 3.38 (d, } J = 9.4 \text{ Hz, } 1H), 2.21 - 2.06 (m, 1H), 1.23 (d, } J = 6.7 \text{ Hz, } 3H), 1.13 (d, } J = 6.7 \text{ Hz, } 3H);\]

\[\text{13C NMR (75 MHz) } \delta = 179.7, 135.4, 129.2, 128.5, 128.5, 53.0, 30.0, 21.1, 20.9;\]

\[\text{IR } \nu = 3057, 2962, 2929, 2871, 1693, 1286, 1215, 1158, 737, 689, 469 \text{ cm}^{-1};\]

\[\text{HRMS (FD) ca} \text{ld for } C_{11}H_{14}O_2Se [M]^+: 258.0159; \text{ found: 258.0160.}\]

**Procedure for the synthesis of 3-methyl-2-phenoxybutanoic acid (L24)**

\[
\begin{array}{c}
\text{p-TsOH (1 equiv)} \\
\text{EtOH, } 80^\circ C, \text{ overnight} \\
\text{72%}
\end{array}
\]

**Scheme 3.15 Synthetic route for the synthesis of ligand L24.**

**Ethyl 2-bromo-3-methylbutanoate**

A solution of 2-bromo-3-methylbutanoic acid (0.91 g, 5 mmol, 1 equiv) and p-TsOH·H\(_2\)O (0.95 g, 5 mmol, 1 equiv) in EtOH (15 mL) was refluxed overnight. The reaction was evaporated to dryness. The crude obtained was dissolved in a NaOH solution until pH = 14 and extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL). The combined organic layers were dried over anh. MgSO\(_4\), filtered and concentrated under reduced pressure to afford ethyl 2-bromo-3-methylbutanoate as a pale yellow oil (0.76 g, 72% yield). \textsuperscript{1}H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.\textsuperscript{28} \textsuperscript{1}H NMR (400 MHz) \(\delta = 4.23 (q, } J = 7.1 \text{ Hz, } 2H), 4.03 (d, } J = 7.9 \text{ Hz, } 1H), 2.31 - 2.17 (m, 1H), 1.30 (t, } J = 7.1 \text{ Hz, } 3H), 1.10 (d, } J = 6.6 \text{ Hz, } 3H), 1.03 (d, } J = 6.7 \text{ Hz, } 3H).
Ethyl 3-methyl-2-phenoxybutanoate

Ethyl 3-methyl-2-phenoxybutanoate was prepared following the procedure described in the literature. A solution of ethyl 2-bromo-3-methylbutanoate (0.5 g, 2.39 mmol, 1 equiv), phenol (0.27 g, 2.87 mmol, 1.2 equiv) and K$_2$CO$_3$ (0.99 g, 7.17 mmol, 3 equiv) in acetone (8 mL) was refluxed overnight. The reaction was poured into H$_2$O and extracted with Et$_2$O two times. The combined organic layers were washed with saturated NaCl solution, dried over anh. MgSO$_4$, filtered and concentrated under reduced pressure. To drive the reaction to completion, phenol (0.27 g, 2.87 mmol, 1.2 equiv) and K$_2$CO$_3$ (2 g, 14.34 mmol, 6 equiv) were added to the solution of the crude residue in acetone (10 mL). The reaction was refluxed overnight and worked up as previously described. The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:4 v/v) as an eluent to obtain ethyl 3-methyl-2-phenoxybutanoate as a pale yellow oil (0.14 g, 27% yield).

$^1$H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.

$^1$H NMR (400 MHz) δ = 7.32 – 7.26 (m, 2H), 7.03 – 6.96 (m, 1H), 6.95 – 6.89 (m, 2H), 4.38 (d, $J = 5.7$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 2.37 – 2.26 (m, 1H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.12 (d, $J = 6.9$ Hz, 3H), 1.09 (d, $J = 6.9$ Hz, 3H).

3-Methyl-2-phenoxybutanoic acid (L24)

3-Methyl-2-phenoxybutanoic acid (L24) was prepared following the procedure described in the literature. Aqueous NaOH (2 M, 0.64 mL, 1.28 mmol, 2 equiv) was added dropwise to the solution of ethyl 3-methyl-2-phenoxybutanoate (0.14 g, 0.64 mmol, 1 equiv) in EtOH (1.6 mL) at 0 °C. The reaction was stirred at room temperature overnight and then concentrated under reduced pressure. The crude residue was dissolved in H$_2$O and the aqueous solution was washed with Et$_2$O two times. The aqueous layer was acidified with aqueous HCl (4 M) and extracted with Et$_2$O 2 times. The combined organic layers were washed with saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated under reduced pressure to afford 3-methyl-2-phenoxybutanoic acid (L24) as a white solid (0.11 g, 86% yield). $^1$H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.

$^1$H NMR (400 MHz) δ = 10.68 (bs, 1H), 7.34 – 7.27 (m, 2H), 7.05 – 6.99 (m, 1H), 6.97 – 6.90 (m, 2H), 4.47 (d, $J = 5.0$ Hz, 1H), 2.50 – 2.26 (m, 1H), 1.15 (d, $J = 6.9$ Hz, 3H), 1.13 (d, $J = 6.9$ Hz, 3H).

Procedure for the synthesis of dimethylvaline (L25)

Dimethylvaline (L25) was prepared following the procedure described in the literature. Pd/C (5%, 80 mg, 0.034 mmol, 2 mol%) was added to the solution of L-valine (0.2 g, 1.7 mmol, 1 equiv) in MeOH (80 mL). The atmosphere was changed to H$_2$ and aqueous formaldehyde...
(37%, 0.29 mL, 3.74 mmol, 2.2 equiv) was added. The reaction was stirred at room temperature overnight, then Pd/C was filtered off and washed with MeOH (3 x 20 mL). The filtrate was concentrated under reduced pressure to afford dimethylvaline (L25) as a white solid (0.24 g, 97% yield). $^1$H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound. $^{32}$ $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta = 2.64$ (d, $J = 9.4$ Hz, 1H), 2.28 (s, 6H), 1.98 – 1.81 (m, 1H), 0.92 (d, $J = 6.7$ Hz, 3H), 0.84 (d, $J = 6.7$ Hz, 3H).

Procedure for the synthesis of $N$-methoxy-3-methyl-2-(phenylthio)butanamide (L26)

Scheme 3.17 The synthesis of ligand L26.

$N$-Methoxy-3-methyl-2-(phenylthio)butanamide (L26) was prepared following the procedure described in the literature for similar compounds.$^{20a}$ 3-Methyl-2-(phenylthio)butanoic acid (L3) (0.46 g, 2.21 mmol, 1 equiv), HOBt (0.33 g, 2.43 mmol, 1.1 equiv) and EDC (0.47 g, 2.43 mmol, 1.1 equiv) were stirred in CH$_2$Cl$_2$ (9 mL). The reaction was cooled to 0 °C and then $O$-methylhydroxyamine hydrochloride salt (0.28 g, 3.31 mmol, 1.5 equiv) and N,N-diisopropylethylamine (0.55 mL, 3.31 mmol, 1.5 equiv) were added. The reaction was stirred at room temperature for 24 h. The reaction was poured into water (10 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over anh. MgSO$_4$, filtered and evaporated to dryness. The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:1 v/v) as an eluent to afford $N$-methoxy-3-methyl-2-(phenylthio)butanamide (L26) as a colorless solid (0.41 g, 77% yield). $^1$H NMR (400 MHz) $\delta =$ 9.50 (bs, 1H), 7.50 – 7.34 (m, 2H), 7.32 – 7.21 (m, 3H), 3.61 (s, 3H), 3.51 – 3.38 (m, 1H), 2.41 – 2.20 (m, 1H), 1.12 (d, $J = 6.7$ Hz, 6H); $^{13}$C NMR (75 MHz) $\delta =$ 168.6, 133.9, 131.6, 128.9, 127.2, 63.7, 57.4, 30.8, 20.5, 20.0; IR $\nu =$ 3115, 2962, 2932, 2871, 1573, 1508, 1360, 1025, 938, 747, 691, 637, 511 cm$^{-1}$; HRMS (FD) calcd for C$_{12}$H$_{17}$NO$_2$S [M]$^+$: 239.0980; found 239.0980; mp 48 – 52 °C.

3.5.2 Pd-Catalyzed C–H olefination of non-directed arenes with activated alkenes

Pd-Catalyzed C–H olefination of benzene

**Ligand optimization**

The corresponding ligand (12.5 µmol, 5 mol%) (some ligands were prepared in stock solution in CH$_2$Cl$_2$. In that case, the solution was added to the pressure tube and dried with nitrogen stream until dryness), Pd(OAc)$_2$ (2.8 mg, 12.5 µmol, 5 mol%), t-butyl peroxybenzoate (47 µL, 0.25 mmol, 1 equiv), ethyl acrylate (11a) (27 µL, 0.25 mmol, 1 equiv), benzene (10a) (0.25 mL, 2.8 mmol, 11.2 equiv) and AcOH (1.25 mL, 0.2 M) were added into a pressure tube. The pressure tube was sealed with a screw cap and the reaction was placed in a 100 °C preheated oil bath and stirred for 2 h. The resulting mixture was diluted with EtOAc and quenched with aqueous Na$_2$SO$_3$ solution (10%). The organic layer was washed with saturated
aqueous NaHCO₃ solution, dried over anh. MgSO₄, filtered and 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.

**Ethyl cinnamate (12a)**

¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.³³ ¹H NMR (300 MHz) δ = 7.69 (d, J = 16.0 Hz, 1H), 7.54 – 7.51 (m, 2H), 7.40 – 7.36 (m, 3H), 6.44 (d, J = 16.0 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H).

**Kinetic profile of the Pd-catalyzed C–H olefination of benzene with and without ligand L₃**

Ligand L₃ (5.2 mg, 25 µmol, 5 mol%), Pd(OAc)₂ (5.6 mg, 25 µmol, 5 mol%), t-butyl peroxybenzolate (94 µL, 0.5 mmol, 1 equiv), ethyl acrylate (11a) (53 µL, 0.5 mmol, 1 equiv), benzene (10a) (0.5 mL, 5.6 mmol, 11.2 equiv) and AcOH (2.5 mL, 0.2 M) were added into a pressure tube. The pressure tube was sealed with a crimp cap with septa and the reaction was placed in a 100 °C pre-heated oil bath. The reaction was followed during time by sampling 0.1 mL. PhCl (20 µL) was added in each sample as an internal standard for quantitative GC analysis. The reaction mixture was diluted with EtOAc (1 mL). The organic layer was quenched with aqueous Na₂SO₃ solution (10%, 1 mL) and washed with saturated aqueous NaHCO₃ solution (2 x 2 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 (5.6 mg, 25 µmol, 5 mol%), t-butyl peroxybenzolate (94 µL, 0.5 mmol, 1 equiv), ethyl acrylate (11a) (53 µL, 0.5 mmol, 1 equiv), benzene (10a) (0.5 mL, 5.6 mmol, 11.2 equiv) and AcOH (2.5 mL, 0.2 M) were added into a pressure tube. The pressure tube was sealed with a crimp cap with septa and the reaction was placed in a 100 °C pre-heated oil bath. The reaction was followed during time by sampling 0.1 mL. PhCl (20 µL) was added in each sample as an internal standard for quantitative GC analysis. The reaction mixture was diluted with EtOAc (1 mL). The organic layer was quenched with aqueous Na₂SO₃ solution (10%, 1 mL) and washed with saturated aqueous NaHCO₃ solution (2 x 2 mL). The organic layer was filtered through a plug of Celite and analyzed by GC.
Table 3.14 Kinetic profile of the Pd-catalyzed C–H olefination of benzene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction time</th>
<th>GC yield (L3)</th>
<th>GC yield (no ligand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 min</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>10 min</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>3</td>
<td>15 min</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>4</td>
<td>30 min</td>
<td>26%</td>
<td>4%</td>
</tr>
<tr>
<td>5</td>
<td>45 min</td>
<td>38%</td>
<td>6%</td>
</tr>
<tr>
<td>6</td>
<td>1 h</td>
<td>50%</td>
<td>9%</td>
</tr>
<tr>
<td>7</td>
<td>1.5 h</td>
<td>65%</td>
<td>15%</td>
</tr>
<tr>
<td>8</td>
<td>2 h</td>
<td>69%</td>
<td>30%</td>
</tr>
<tr>
<td>9</td>
<td>3 h</td>
<td>67%</td>
<td>47%</td>
</tr>
<tr>
<td>10</td>
<td>5 h</td>
<td>67%</td>
<td>46%</td>
</tr>
<tr>
<td>11</td>
<td>8 h</td>
<td>69%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Note: The reactions with and without L3 were performed at the same time to compare the kinetic profiles.

Loading of the ligand
A stock solution of ligand L3 (0.0846 M in CH2Cl2) was added into a pressure tube and dried with nitrogen steam until dryness followed by Pd(OAc)2 (2.8 mg, 12.5 µmol, 5 mol%), t-butyl peroxybenzoate (47 µL, 0.25 mmol, 1 equiv), ethyl acrylate (11a) (27 µL, 0.25 mmol, 1 equiv), benzene (10a) (0.25 mL, 2.8 mmol, 11.2 equiv) and AcOH (1.25 mL, 0.2 M). 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 6 h. The resulting mixture was diluted with EtOAc and quenched with aqueous Na2SO3 solution (10%). The organic layer was washed with saturated aqueous NaHCO3 solution, dried over anh. MgSO4, filtered and 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 3.15 Loading of the ligand.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L3 (mol%)</th>
<th>A stock solution of L3 (µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>150</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>450</td>
</tr>
</tbody>
</table>

Loading of the catalyst
A stock solution of ligand L3 (0.0846 M in CH2Cl2) was added into a pressure tube and dried with nitrogen steam until dryness followed by the corresponding amount of Pd(OAc)2, t-butyl peroxybenzoate (47 µL, 0.25 mmol, 1 equiv), ethyl acrylate (11a) (27 µL, 0.25 mmol, 1 equiv), benzene (10a) (0.25 mL, 2.8 mmol, 11.2 equiv) and AcOH (1.25 mL, 0.2 M). 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 6 h. The resulting mixture was diluted with EtOAc and quenched with aqueous Na2SO3 solution (10%). The organic layer was washed with saturated aqueous NaHCO3 solution, dried over anh. MgSO4, filtered and concentrated under reduced pressure. The ¹H
NMR yield was determined by adding CH$_2$Br$_2$ (17.5 µL, 0.25 mmol, 1 equiv) as an internal standard.

<table>
<thead>
<tr>
<th>Table 3.16 Loading of the catalyst.</th>
</tr>
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<tbody>
<tr>
<td><strong>Entry</strong></td>
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<tr>
<td>1</td>
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<tr>
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</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

**Screening of the amount of benzene**

A stock solution of ligand L3 (0.0846 M in CH$_2$Cl$_2$) (150 µL, 12.5 µmol, 5 mol%) was added into a pressure tube and dried with nitrogen steam until dryness followed by Pd(OAc)$_2$ (2.8 mg, 12.5 µmol, 5 mol%), t-butyl peroxybenzoate (47 µL, 0.25 mmol, 1 equiv), ethyl acrylate (11a) (27 µL, 0.25 mmol, 1 equiv), benzene (10a) (11.2–2 equiv) and AcOH (1.25 mL, 0.2 M). 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 6 h. The resulting mixture was diluted with EtOAc and quenched with aqueous Na$_2$SO$_3$ solution (10%). The organic layer was washed with saturated aqueous NaHCO$_3$ solution, dried over anh. MgSO$_4$, filtered and 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>
<thead>
<tr>
<th>Table 3.17 Screening of the amount of benzene.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entry</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

**Screening of oxidants**

A stock solution of ligand L3 (0.0846 M in CH$_2$Cl$_2$) (150 µL, 12.5 µmol, 5 mol%) was added into a pressure tube and dried with nitrogen steam until dryness followed by Pd(OAc)$_2$ (2.8 mg, 12.5 µmol, 5 mol%), the corresponding oxidant (0.25 mmol, 1 equiv), ethyl acrylate (11a) (27 µL, 0.25 mmol, 1 equiv), benzene (10a) (0.25 mL, 2.8 mmol, 11.2 equiv) and AcOH (1.25 mL, 0.2 M). 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 6 h. The resulting mixture was diluted with EtOAc and quenched with aqueous Na$_2$SO$_3$ solution (10%). The organic layer was washed with saturated aqueous NaHCO$_3$ solution, dried over anh. MgSO$_4$, filtered and 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 3.18 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>PhCO\textsubscript{3}t-Bu</td>
<td>47 µL</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOOH</td>
<td>25 µL</td>
</tr>
<tr>
<td>3</td>
<td>AcOOH</td>
<td>17 µL</td>
</tr>
<tr>
<td>4</td>
<td>O\textsubscript{2}</td>
<td>1 atm</td>
</tr>
<tr>
<td>5</td>
<td>BQ</td>
<td>27 mg</td>
</tr>
<tr>
<td>6</td>
<td>AgOAc</td>
<td>41.7 mg</td>
</tr>
<tr>
<td>7</td>
<td>Ag\textsubscript{2}CO\textsubscript{3}</td>
<td>68.9 mg</td>
</tr>
<tr>
<td>8</td>
<td>Na\textsubscript{2}S\textsubscript{2}O\textsubscript{8}</td>
<td>59.5 mg</td>
</tr>
<tr>
<td>9</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8}</td>
<td>67.6 mg</td>
</tr>
<tr>
<td>10</td>
<td>Oxone</td>
<td>76.8 mg</td>
</tr>
</tbody>
</table>

Screening of solvents
A stock solution of ligand L\textsubscript{3} (0.0846 M in CH\textsubscript{2}Cl\textsubscript{2}) (150 µL, 12.5 µmol, 5 mol%) was added into a pressure tube and dried with nitrogen steam until dryness followed by Pd(OAc)\textsubscript{2} (2.8 mg, 12.5 µmol, 5 mol%), t-butyl peroxybenzoate (47 µL, 0.25 mmol, 1 equiv), ethyl acrylate (11a) (27 µL, 0.25 mmol, 1 equiv), benzene (10a) (0.25 mL, 2.8 mmol, 11.2 equiv) and the corresponding solvent (1.25 mL, 0.2 M). 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 6 h. The resulting mixture was diluted with EtOAc and quenched with aqueous Na\textsubscript{2}SO\textsubscript{3} solution (10%). The organic layer was washed with saturated aqueous NaHCO\textsubscript{3} solution, dried over anh. MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. The \textsuperscript{1}H NMR yield was determined by adding CH\textsubscript{2}Br\textsubscript{2} (17.5 µL, 0.25 mmol, 1 equiv) as an internal standard.

Pd-Catalyzed C–H olefination of naphthalene

Ligand optimization
The corresponding ligand (12.5 µmol, 5 mol%) (some ligands were prepared in stock solution in CH\textsubscript{2}Cl\textsubscript{2}. In that case, the solution was added to the pressure tube and dried with nitrogen stream until dryness), Pd(OAc)\textsubscript{2} (2.8 mg, 12.5 µmol, 5 mol%), t-butyl peroxybenzoate (47 µL, 0.25 mmol, 1 equiv), ethyl acrylate (11a) (27 µL, 0.25 mmol, 1 equiv), naphthalene (10b) (0.32 g, 2.5 mmol, 10 equiv) and AcOH (1.25 mL, 0.2 M) were added into a pressure tube. 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 6 h. The resulting mixture was diluted with EtOAc and quenched with aqueous Na\textsubscript{2}SO\textsubscript{3} solution (10%). The organic layer was washed with saturated aqueous NaHCO\textsubscript{3} solution, dried over anh. MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. The \textsuperscript{1}H NMR yield was determined by adding CH\textsubscript{2}Br\textsubscript{2} (17.5 µL, 0.25 mmol, 1 equiv) as an internal standard.

Screening of additives
A stock solution of ligand L\textsubscript{3} (0.0846 M in CH\textsubscript{2}Cl\textsubscript{2}) (150 µL, 12.5 µmol, 5 mol%) was added into a pressure tube and dried with nitrogen steam until dryness followed by Pd(OAc)\textsubscript{2} (2.8 mg, 12.5 µmol, 5 mol%), t-butyl peroxybenzoate (47 µL, 0.25 mmol, 1 equiv), ethyl acrylate (11a) (27 µL, 0.25 mmol, 1 equiv), naphthalene (10b) (0.32 g, 2.5 mmol, 10 equiv), AcOH
(1.25 mL, 0.2 M) and the corresponding additive (0.125 mmol, 0.5 equiv or indicated otherwise). 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 6 h. The resulting mixture was diluted with EtOAc and quenched with aqueous Na₂SO₃ solution (10%). The organic layer was washed with saturated aqueous NaHCO₃ solution, dried over anh. MgSO₄, filtered and 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 3.19 Screening of additives.

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<th>Entry</th>
<th>Additive</th>
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<tr>
<td>1</td>
<td>BF₃·OEt₂</td>
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</tr>
<tr>
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<td>Bu₄NOTf</td>
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</tr>
<tr>
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<td>Zn(OTf)₂</td>
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</tr>
<tr>
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</tr>
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<tr>
<td>22</td>
<td>PPh₃</td>
<td>3.3 mg, 12.5 µmol, 5 mol%</td>
</tr>
</tbody>
</table>

**General procedure for the Pd-catalyzed C–H olefination of simple arenes**

A stock solution of ligand L₃ (0.0846 M in CH₂Cl₂) (150 µL, 12.5 µmol, 5 mol%) was added to a pressure tube and dried with nitrogen steam until dryness followed by Pd(OAc)₂ (2.8 mg, 12.5 µmol, 5 mol%), t-butyl peroxybenzoate (47 µL, 0.25 mmol, 1 equiv), ethyl acrylate (11a) (27 µL, 0.25 mmol, 1 equiv), the corresponding arene (10) (10–32 equiv) and AcOH (1.25 mL, 0.2 M). 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 6 h. The resulting mixture was diluted with EtOAc and quenched with aqueous Na₂SO₃ solution (10%). The organic layer was washed with saturated aqueous NaHCO₃ solution, dried over anh. MgSO₄, filtered and 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 as specified in each case to obtain the desired product.

**(E)-Ethyl 3-(naphthalen-1-yl)acrylate (12ba) and (E)-ethyl 3-(naphthalen-2-yl)acrylate (12bb)**

General procedure was followed using naphthalene (10b) (0.32 g, 2.5 mmol, 10 equiv), providing the titled compounds in 87% ¹H NMR yield (a:b = 2:1). The crude residue was purified by column chromatography using petroleum ether as an eluent providing the titled compounds as a clear oil (43.2 mg, 76% yield). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds. ¹H NMR (400 MHz) δ = 8.56 (d, J = 15.9 Hz, 1H a), 8.23 (d, J = 7.8 Hz, 1H a), 7.95 – 7.84 (m, 7H a+b), 7.78 (d, J = 7.2 Hz, 1H a), 7.69 (dd, J = 8.7, 1.7 Hz, 1H b), 7.63 – 7.48 (m, 5H a+b), 6.58 (d, J = 16.0, 1H b), 6.56 (d, J = 15.9, 1H b), 4.39 – 4.29 (m, 4H a+b), 1.44 – 1.37 (m, 6H a+b).

A parallel reaction without ligand was also performed providing the titled compounds in 57% ¹H NMR yield (a:b = 1:1.1).

**(E)-Ethyl 3-(2,3-dimethylphenyl)acrylate (12ca) and (E)-ethyl 3-(3,4-dimethylphenyl)acrylate (12cb)**

General procedure was followed using o-xylene (10c) (0.3 mL, 2.5 mmol, 10 equiv), providing the titled compounds in 88% ¹H NMR yield (a:b = 1:1.9). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:19 v/v) as an eluent providing the titled compounds as a clear oil (37.8 mg, 76% yield). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds. ¹H NMR (300 MHz) δ = 8.10 (d, J = 15.8 Hz, 1H a), 7.67 (d, J = 16.0 Hz, 1H b), 7.41 (d, J = 7.6 Hz, 1H a), 7.40 – 7.11 (m, 5H a+b), 6.42 (d, J = 16.0 Hz, 1H b), 6.34 (d, J = 15.8 Hz, 1H a), 4.33 – 4.25 (m, 4H a+b), 2.35 (s, 3H a), 2.33 (s, 3H a), 2.30 (s, 6H b), 1.40 – 1.34 (m, 6H a+b).

A parallel reaction without ligand was also performed providing the titled compounds in 55% ¹H NMR yield (a:b = 1:3).

**(E)-Ethyl 3-(2,4-dimethylphenyl)acrylate (12da), (E)-ethyl 3-(3,5-dimethylphenyl)acrylate (12db) and (E)-ethyl 3-(2,6-dimethylphenyl)acrylate (12dc)**

General procedure was followed using m-xylene (10d) (0.31 mL, 2.5 mmol, 10 equiv), providing the titled compounds in 88% ¹H NMR yield (a:b:c = 4.9:1:1.3). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:19 v/v) as an eluent providing the titled compounds as a clear oil (42.3 mg, 83% yield). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds. ¹H NMR (300 MHz) δ = 7.97 (dd, J = 15.8, 2.8 Hz, 1H a), 7.86 (dd, J = 17.3, 1.9 Hz, 1H c), 7.66 (dd, J = 14.3, 3.0 Hz, 1H b), 7.50 – 7.47 (m, 1H b), 7.29 –
7.27 (m, 2H₀), 7.17 – 6.95 (m, 6Hₐ₋ₙ), 6.43 (dd, J = 16.0, 3.0 Hz, 1Hₖ), 6.35 (dd, J = 15.8, 2.9 Hz, 1Hₜ), 6.09 (dd, J = 17.3, 1.9 Hz, 1Hₜ), 4.32 – 4.26 (m, 6Hₐ₋ₙ), 2.43 – 2.28 (m, 18Hₐ₋ₙ), 1.39 – 1.34 (m, 9Hₐ₋ₙ).

A parallel reaction without ligand was also performed providing the titled compounds in 52% ¹H NMR yield (a:b:c = 3:0:1).

**Ethyl (E)-3-(2,5-dimethylphenyl)acrylate (12e)**

General procedure was followed using p-xylene (10e) (0.31 mL, 2.5 mmol, 10 equiv), providing the titled compound in 75% ¹H NMR yield. The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:19 v/v) as an eluent providing the titled compound as a clear oil (38.1 mg, 75% yield). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds.³⁶ ¹H NMR (400 MHz) δ = 7.96 (d, J = 15.9 Hz, 1H), 7.37 (s, 1H), 7.09 (d, J = 1.1 Hz, 2H), 6.36 (d, J = 15.9 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 2.33 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H).

A parallel reaction without ligand was also performed providing the titled compound in 47% ¹H NMR yield.

**Ethyl (E)-3-mesitylacrylate (12f)**

General procedure was followed using mesitylene (10f) (0.35 mL, 2.5 mmol, 10 equiv), providing the titled compound in 88% ¹H NMR yield. The product was obtained as a clear oil (46 mg, 84% yield). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.³⁷ ¹H NMR (400 MHz) δ = 7.85 (d, J = 16.3 Hz, 1H), 6.90 (s, 2H), 6.06 (d, J = 16.4 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.34 (s, 6H), 2.29 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H).

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

**Preparative scale synthesis**

Preparative scale synthesis was performed using 3-methyl-2-(phenyl-thio)butanoic acid (L₃) (36.8 mg, 0.175 mmol, 5 mol%), Pd(OAc)₂ (39.3 mg, 0.175 mmol, 5 mol%), t-butyl peroxybenzoate (0.66 mL, 3.5 mmol, 1 equiv), ethyl acrylate (0.37 mL, 3.5 mmol, 1 equiv), mesitylene (10f) (4.87 mL, 35 mmol, 10 equiv) and AcOH (9 mL, 0.1 M). The product was obtained as a clear oil (0.58 g, 76% yield).
**S,O-Ligands and their application in C–H olefination of arenes with activated alkenes**

**(E)-Ethyl 3-(2-methoxyphenyl)acrylate (12go), (E)-ethyl 3-(3-methoxyphenyl)acrylate (12gm) and (E)-ethyl 3-(4-methoxyphenyl)acrylate (12gp)**

General procedure was followed using anisole (10g) (0.27 mL, 2.5 mmol, 10 equiv), providing the titled compounds in 80% ¹H NMR yield (α:β = 1.5:1 and trace amount of m isomer). The crude residue was purified column chromatography using EtOAc:pentane ether (1:9 v/v) as an eluent providing the titled compounds as a clear oil (37.8 mg, 72% yield). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds.³⁸ ¹H NMR (400 MHz) δ = 7.99 (d, J = 16.2 Hz, 1Hα), 7.65 (d, J = 16.0 Hz, 1Hm), 7.64 (d, J = 16.0 Hz, 1Hp), 7.51 – 7.45 (m, 3Hα,β), 7.36 – 7.28 (m, 2Hα,m), 7.12 (d, J = 7.6 Hz, 1Hm), 7.04 (s, 1Hm), 6.98 – 6.88 (m, 5Hα,m,p), 6.53 (d, J = 16.2 Hz, 1Hα), 6.42 (d, J = 16.0 Hz, 1Hp), 6.31 (d, J = 16.0 Hz, 1Hm), 4.29 – 4.22 (m, 6Hα,m,p), 3.88 (s, 3Hβ), 3.83 (s, 6Hα,m,p), 1.35 – 1.31 (m, 9Hα,m,p).

A parallel reaction without ligand was also performed providing the titled compounds in 46% ¹H NMR yield (α:β = 1:1.7).

**(E)-Ethyl 3-(2,3-dimethoxyphenyl)acrylate (12ha) and (E)-ethyl 3-(3,4-dimethoxyphenyl)acrylate (12hb)**

General procedure was followed using 1,2-dimethoxybenzene (10h) (0.32 mL, 2.5 mmol, 10 equiv), providing the titled compounds in 82% ¹H NMR yield (a:b = 1:4.9). The crude residue was purified by column chromatography using EtOAc:pentane ether (1:19 v/v) as an eluent providing the titled compounds as a clear oil (50.9 mg, 81% yield). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds.³⁹ Isomer 12ha: ¹H NMR (300 MHz) δ = 7.99 (d, J = 16.2 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.48 (d, J = 16.2 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). Isomer 12hb: ¹H NMR (300 MHz) δ = 7.63 (d, J = 16.0 Hz, 1H), 7.10 (dd, J = 8.3, 2.0 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.31 (d, J = 15.9 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.91 (s, 6H), 1.34 (t, J = 7.1 Hz, 3H).

A parallel reaction without ligand was also performed providing the titled compounds in 40% ¹H NMR yield (a:b = 1:5.7).

**(E)-Ethyl 3-(2,4-dimethoxyphenyl)acrylate (12ia) and (E)-ethyl 3-(2,6-dimethoxyphenyl)acrylate (12ib)**

General procedure was followed using 1,3-dimethoxybenzene (10i) (0.33 mL, 2.5 mmol, 10 equiv). The crude residue was purified by column chromatography using EtOAc:pentane ether (1:9 v/v) as an eluent providing the titled compounds as a clear oil (48 mg, a:b = 6:1, 81% yield). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds.³⁹ ¹H NMR (400 MHz) δ = 8.13 (d, J = 16.3 Hz, 1Hβ), 7.90 (d, J = 16.1 Hz, 1Hα), 7.44 (d, J = 8.5 Hz, 1Hα), 6.88 (d, J = 8.1 Hz, 1Hβ), 6.62 (d, J = 16.1 Hz, 1Hβ), 6.30 (d, J = 8.1 Hz, 1Hβ), 4.22 (m, 6Hα,β, 3Hα,β), 1.34 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H).

(Abbreviations used in the paper: ¹H NMR: proton nuclear magnetic resonance, ¹³C NMR: carbon nuclear magnetic resonance, ppm: parts per million, δ: chemical shift, J: coupling constant, v(v): volume of solvent, m: multiplet, s: singlet, d: doublet, t: triplet, q: quartet, br: broad, s: singlet, dd: doublet of doublet, etc.)
Chapter 3

16.3 Hz, 1Hb), 6.56 (d, J = 8.5 Hz, 2Hb), 6.50 (dd, J = 8.5, 2.4 Hz, 2Hα+β), 6.45 (s, 1Hα), 6.43 (d, J = 16.2 Hz, 1Hα), 4.27 – 4.22 (m, 4Hα+β), 3.88 (s, 6Hb), 3.87 (s, 3Hα), 3.84 (s, 3Hα), 1.35 – 1.31 (m, 6Hα+β).

A parallel reaction without ligand was also performed providing the titled compounds in 28% isolated yield (a:b = 49:1).

(E)-Ethyl 3-(2,4,6-trimethoxyphenyl)acrylate (12j)

General procedure was followed using 1,3,5-trimethoxybenzene (10j) (0.42 g, 2.5 mmol, 10 equiv), providing the titled compound in 70% 1H NMR yield. The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:9 v/v) as an eluent providing the titled compound as a yellow solid (46.6 mg, 70% yield).

1H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.40 1H NMR (300 MHz) δ = 8.08 (d, J = 16.1 Hz, 1Ho), 6.75 (d, J = 16.1 Hz, 1Hp), 6.11 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

A parallel reaction without ligand was also performed providing the titled compound in 52% 1H NMR yield.

(E)-Ethyl 3-(2-hydroxyphenyl)acrylate (12ko) and (E)-ethyl 3-(4-hydroxyphenyl)acrylate (12kp)

General procedure was followed using phenol (10k) (0.24 g, 2.5 mmol, 10 equiv), providing the titled compounds in 87% 1H NMR yield (α:p = 1.9:1). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:4 v/v) as an eluent providing the titled compounds as a pale yellow oil (39.5 mg, 82% yield). 1H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds.41 1H NMR (400 MHz) δ = 8.05 (d, J = 16.2 Hz, 1Hα), 7.63 (d, J = 16.0 Hz, 1Hp), 7.46 (dd, J = 7.7, 1.6 Hz, 1Hα), 7.41 (d, J = 8.6 Hz, 2Hp), 7.23 (td, J = 7.7, 1.7 Hz, 1Hp), 6.92 – 6.87 (m, 4Hα+β), 6.64 (d, J = 16.2 Hz, 1Hα), 6.29 (d, J = 16.0 Hz, 1Hp), 4.32 – 4.24 (m, 4Hα+β), 1.36 – 1.32 (m, 6Hα+β).

A parallel reaction using 3,5-dichloropyridine (1.8 mg, 12.5 µmol, 5 mol%) was also performed providing the titled compounds in 50% 1H NMR yield (isomer α:p = 1.4:1).

A parallel reaction without ligand was also performed providing the titled compounds in 46% 1H NMR yield (α:p = 1:1.3).
Ethyl 2-[(E)-2-(ethoxycarbonyl)ethenyl]benzoate (12lo), ethyl 3-[(E)-2-(ethoxycarbonyl)ethenyl]benzoate (12lm) and ethyl 4-[(E)-2-(ethoxycarbonyl)ethenyl]benzoate (12lp)

General procedure was followed using ethyl benzoate (10l) (0.90 mL, 6.25 mmol, 25 equiv), providing the titled compounds in 45% $^1$H NMR yield ($o:m:p = 1:2:3:3:1$). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:20 v/v) as an eluent providing the titled compounds as a clear oil (26.0 mg, 42% yield). $^1$H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds. $^{42}$ $^1$H NMR (400 MHz) $\delta = 8.45$ (d, $J = 16.0$ Hz, 1H$_a$), 8.22 (s, 1H$_m$), 8.08 – 8.05 (m, 3H$_{m,p}$), 7.98 (dd, $J = 7.9$, 1.4 Hz, 1H$_b$), 7.75 – 7.69 (m, 4H$_{ax,m,p}$), 7.60 (td, $J = 5.2$, 2.7 Hz, 2H$_b$), 7.54 (td, $J = 7.5$, 1.2 Hz, 1H$_b$), 7.50 – 7.43 (m, 2H$_{am}$), 6.53 (d, $J = 16.1$ Hz, 2H$_{m,p}$), 6.31 (d, $J = 16.0$ Hz, 1H$_b$), 4.44 – 4.39 (m, 6H$_{ax,m,p}$), 4.32 – 4.27 (m, 6H$_{ox,m,p}$), 1.45 – 1.40 (m, 9H$_{ax,m,p}$), 1.38 – 1.31 (m, 9H$_{ox,m,p}$).

A parallel reaction without ligand was also performed providing the titled compounds in 22% $^1$H NMR yield ($o:m:p = 1:4.1:1.2$).

(E)-Ethyl 3-(2,3-dichlorophenyl)acrylate (12ma) and (E)-ethyl 3-(3,4-dichlorophenyl)acrylate (12mb)

General procedure was followed using 1,2-dichlorobenzene (10m) (0.9 mL, 8 mmol, 32 equiv), providing the titled compounds in 60% $^1$H NMR yield (a:b = 1:1.2). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:19 v/v) as an eluent providing the titled compounds as a clear oil (37 mg, 60% yield). $^1$H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds. $^{4b}$ $^1$H NMR (300 MHz) $\delta = 8.10$ (d, $J = 16.0$ Hz, 1H$_a$), 7.62 – 7.61 (m, 2H$_b$), 7.56 – 7.46 (m, 3H$_{a,b}$), 7.36 (dd, $J = 8.3$, 2.0 Hz, 1H$_a$), 7.24 (t, $J = 7.9$ Hz, 1H$_a$), 6.43 (d, $J = 16.0$ Hz, 2H$_{a,b}$), 4.34 – 4.25 (m, 4H$_{a,b}$), 1.39 – 1.33 (m, 6H$_{a,b}$).

A parallel reaction without ligand was also performed providing the titled compounds in 22% $^1$H NMR yield (a:b = 1:1.7).

(E)-Ethyl 3-(2,4-dichlorophenyl)acrylate (12na), (E)-ethyl 3-(3,5-dichlorophenyl)acrylate (12nb) and (E)-ethyl 3-(2,6-dichlorophenyl)acrylate (12nc)

General procedure was followed using 1,3-dichlorobenzene (10n) (0.92 mL, 8 mmol, 32 equiv), providing the titled compounds in 78% $^1$H NMR yield (a:b:c = 14.4:1:4.6). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:19 v/v) as an eluent providing the titled compounds as a clear oil (45.2 mg, 74% yield). $^1$H NMR spectra data of the isolated compounds 12na and 12nc matched with the spectra data reported in the literature for these compounds. $^{43}$ $^1$H NMR (300 MHz) $\delta = 8.02$ (d, $J = 16.1$ Hz, 1H$_a$), 7.80 (d, $J = 16.4$ Hz, 1H$_c$), 7.57 (d, $J = 8.5$ Hz, 1H$_a$), 7.45 (d, $J = 2.1$ Hz, 1H$_b$), 7.40 (d, $J = 1.7$ Hz, 1H$_b$), 7.37 (d, $J = 8.0$ Hz, 2H$_c$), 7.28 (dd, $J = 8.5$, 1.7 Hz, 1H$_a$), 6.61 (d, $J = 15.9$ Hz, 1H$_c$), 6.43 (d, $J = 16.1$ Hz, 1H$_a$), 4.30 – 4.27 (m, 4H$_{a,c}$), 1.39 – 1.34 (m, 6H$_{a,c}$). Traces amount
of isomer 12nb was also observed. Characteristic $^1$H NMR signal for 12nb: $^1$H NMR (300 MHz) $\delta$ = 7.55 (d, $J = 16.1$ Hz, 1H), 6.45 (d, $J = 16.1$ Hz, 1H).

A parallel reaction without ligand was also performed providing the titled compounds in 36% $^1$H NMR yield (a:b:c = 5.7:1:1.9).

**(E)-Ethyl 3-(2,5-dichlorophenyl)acrylate (12o)**

\[
\begin{align*}
\text{Cl} & \quad \equiv \quad \text{CO}_2\text{Et} \\
\text{12o} & \\
\end{align*}
\]

General procedure was followed using 1,4-dichlorobenzene (10o) (1.18 g, 8 mmol, 32 equiv), providing the titled compound in 66% $^1$H NMR yield. The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:19 v/v) as an eluent providing the titled compound as a clear oil (39.5 mg, 64% yield). $^1$H NMR (300 MHz) $\delta$ = 8.01 (d, $J = 16.0$ Hz, 1H), 7.61 (d, $J = 2.4$ Hz, 1H), 7.37 (d, $J = 8.6$ Hz, 1H), 7.29 (dd, $J = 9.2$, 1.5, Hz, 1H), 6.45 (d, $J = 16.0$ Hz, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 1.37 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (125 MHz) $\delta$ = 166.0, 139.1, 134.3, 133.1, 133.0, 131.2, 130.8, 127.4, 122.2, 60.9, 14.3; IR $\nu$ = 2995, 2912, 1722, 1643, 1460, 1316, 1185, 1094, 1026, 973, 861, 809 cm$^{-1}$; HRMS (FD) calcd for C$_{11}$H$_{10}$Cl$_2$O$_2$ [M]+: 224.0052; found: 224.0045; mp 34 – 38 °C.

A parallel reaction without ligand was also performed providing the titled compound in 30% $^1$H NMR yield.

**Preparative scale synthesis**

General procedure was followed using ligand L3 (18.4 mg, 87.5 µmol, 5 mol%), Pd(OAc)$_2$ (19.6 mg, 87.5 µmol, 5 mol%), t-butyl peroxybenzoate (0.33 mL, 1.75 mmol, 1 equiv), ethyl acrylate (0.19 mL, 1.75 mmol, 1 equiv), 1,3,5-trifluorobenzene (10p) (1.81 mL, 17.5 mmol, 10 equiv) and AcOH (8.75 mL). The product was obtained as a clear oil (0.27 g, 66% yield).
S,O-Ligands and their application in C–H olefination of arenes with activated alkenes

**(E)-Ethyl 3-(5-chloro-2-methoxyphenyl)acrylate (12qa) and (E)-ethyl 3-(2-chloro-5-methoxyphenyl)acrylate (12qb)**

General procedure was followed using p-chloroanisole (10q) (0.31 mL, 2.5 mmol, 10 equiv), providing the titled compounds in 64% $^1$H NMR yield (a:b = 4.3:1). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:9 v/v) as an eluent provided the titled compounds as a clear oil (36.2 mg, 60% yield). $^1$H NMR spectra data of the isolated compound 12qa matched with the spectra data reported in the literature for this compound.\(^{44}\) Isomer 12qa: $^1$H NMR (300 MHz) δ = 7.92 (d, $J = 16.1$ Hz, 1H), 7.49 (d, $J = 2.6$ Hz, 1H), 7.31 (dd, $J = 8.8, 2.6$ Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 1H), 6.52 (d, $J = 16.1$ Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 3.90 (s, 3H), 1.36 (t, $J = 7.2$ Hz, 3H). Trace amount of isomer 12qb was also observed. Characteristic $^1$H NMR signal for 12qb: $^1$H NMR (300 MHz) δ = 8.06 (d, $J = 16.1$ Hz, 1H), 6.43 (d, $J = 16.1$ Hz, 1H).

A parallel reaction without ligand was also performed providing the titled compounds in 20% $^1$H NMR yield (a:b = 4:1).

**(E)-Ethyl 3-(2-cyanophenyl)acrylate (12ro), (E)-ethyl 3-(3-cyanophenyl)acrylate (12rm) and (E)-ethyl 3-(4-cyanophenyl)acrylate (12rp)**

General procedure was followed using benzonitrile (10r) (0.26 mL, 2.5 mmol, 10 equiv), providing the titled compounds in <5% $^1$H NMR yield (mainly 1 isomer was observed). $^1$H NMR spectra data of the crude mixture matched with the spectra data reported in the literature for these compounds.\(^{45}\) Characteristic $^1$H NMR signal for 12r: 6.59 (d, $J = 16.0$ Hz, 1H).

A parallel reaction without ligand was also performed providing the titled compounds in <5% $^1$H NMR yield (mainly 1 isomer was observed).

**(E)-Ethyl 3-(2,5-bis(trifluoromethyl)phenyl)acrylate (12s)**

General procedure was followed using 1,4-bis(trifluoromethyl)benzene (10s) (0.39 mL, 2.5 mmol, 10 equiv), providing the titled compound in traces amount. Characteristic $^1$H NMR signal for 12s: 6.56 (d, $J = 15.8$ Hz, 1H).

A parallel reaction without ligand was also performed providing the titled compound in traces amount.
(E)-Ethyl 3-(2-nitrophenyl)acrylate (12to), (E)-ethyl 3-(3-nitrophenyl)acrylate (12tm) and (E)-ethyl 3-(4-nitrophenyl)acrylate (12tp)

General procedure was followed using nitrobenzene (10t) (0.26 mL, 2.5 mmol, 10 equiv), providing the titled compounds in 6% $^1$H NMR yield (mixture of 3 isomers). $^1$H NMR spectra data of the crude mixture matched with the spectra data reported in the literature for these compounds.\(^{46}\) Characteristic $^1$H NMR signal for 12t: 12to: 6.31 (d, $J = 15.7$ Hz, 1H), 12tm: 6.49 (d, $J = 16.0$ Hz, 1H), 12tp: 6.51 (d, $J = 16.1$ Hz, 1H).

A parallel reaction without ligand was also performed providing the titled compounds in 10% $^1$H NMR yield (mixture of 3 isomers).

General procedure for the Pd-catalyzed C–H olefination of benzene with activated alkenes

A stock solution of ligand L3 (0.0846 M in CH$_2$Cl$_2$) (150 µL, 12.5 µmol, 5 mol%) was added to a pressure tube and dried with nitrogen steam until dryness followed by Pd(OAc)$_2$ (2.8 mg, 12.5 µmol, 5 mol%), t-butyl peroxybenzoate (47 µL, 0.25 mmol, 1 equiv), the corresponding olefin (11) (0.25 mmol, 1 equiv), benzene (10a) (0.25 mL, 2.8 mmol, 11.2 equiv) and AcOH (1.25 mL, 0.2 M). The pressure tube was sealed with a screw cap and the reaction was placed in a 100 °C pre-heated oil bath over the time period indicated for each reaction. The resulting mixture was diluted with EtOAc and quenched with aqueous Na$_2$SO$_3$ solution (10%). The organic layer was washed with saturated aqueous NaHCO$_3$ solution, dried over anh. MgSO$_4$, filtered and 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. The crude residue was purified as specified in each case to obtain the desired product.

Methyl cinnamate (14a)

General procedure was followed using methyl acrylate (22.5 µL, 0.25 mmol, 1 equiv). The reaction was stirred for 6 h, providing the titled compound in 79% $^1$H NMR yield. The product was obtained as a pale yellow oil (31.4 mg, 76% yield). $^1$H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound.\(^{47}\) $^1$H NMR (300 MHz) $\delta = 7.70$ (d, $J = 16.0$ Hz, 1H), 7.54 – 7.51 (m, 2H), 7.40 – 7.38 (m, 3H), 6.45 (d, $J = 16.0$ Hz, 1H), 3.81 (s, 3H).

A parallel reaction without ligand was also performed providing the titled compound in 64% $^1$H NMR yield (mono:di = 9.7:1).

Ethyl 3,3-diphenylacrylate (14b)

General procedure was followed using ethyl cinnamate (42 µL, 0.25 mmol, 1 equiv). The reaction was stirred for 6 h, providing the titled compound in 72% $^1$H NMR yield. The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:49 v/v) as an eluent providing the titled compound as a clear oil (34.8 mg, 56% yield).
$^1$H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound. $^{14b}$$^1$H NMR (400 MHz) $\delta = 7.42 - 7.33$ (m, 8H), 7.26 – 7.23 (m, 2H), 6.40 (s, 1H), 4.07 (q, $J = 7.2$ Hz, 2H), 1.14 (t, $J = 7.1$ Hz, 3H).

A parallel reaction without ligand was also performed providing the titled compound in 60% $^1$H NMR yield.

**(E)-Dimethyl styrylphosphonate (14c)**

![Chemical structure of (E)-Dimethyl styrylphosphonate (14c)](image)

General procedure was followed using 1-dimethoxyphosphonate (30 µL, 0.25 mmol, 1 equiv). The reaction was stirred for 6 h, providing the titled compound in 78% $^1$H NMR yield. The product was obtained as a pale yellow oil (37.1 mg, 68% yield). $^1$H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound. $^{48}$ $^1$H NMR (400 MHz) $\delta = 7.58 - 7.48$ (m, 3H), 7.41 – 7.28 (m, 3H), 6.23 (t, $J = 17.7$ Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H).

A parallel reaction without ligand was also performed providing the titled compound in 49% $^1$H NMR yield.

**N,N-Dimethylcinnamamide (14d mono) and N,N-dimethyl-3,3-diphenylacrylamide (14d di)**

![Chemical structures of N,N-Dimethylcinnamamide (14d mono) and N,N-dimethyl-3,3-diphenylacrylamide (14d di)](image)

General procedure was followed using N,N-dimethylacetamide (26 µL, 0.25 mmol, 1 equiv). The reaction was stirred for 6 h, providing the titled compounds in 56% $^1$H NMR yield (mono:di = 4.6:1). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:1 v/v) as an eluent providing the titled compounds as a pale yellow oil (18.7 mg, mono 34% and di 6% yield). $^1$H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds. $^{49}$ $^1$H NMR (400 MHz) $\delta = 7.69$ (d, $J = 15.4$ Hz, 1H mono), 7.56 – 7.54 (m, 2H mono), 7.41 – 7.28 (m, 2H mono), 6.37 (s, 1H di), 3.19 (s, 3H mono), 3.09 (s, 3H mono), 2.85 (s, 3H mono), 2.77 (s, 3H mono).

A parallel reaction without ligand was also performed providing the titled compounds in 24% $^1$H NMR yield (mono:di = 2.4:1).

**(E)-3-Phenylacrylonitrile (14e trans), (Z)-3-phenylacrylonitrile (14e cis), 3,3-diphenylacrylonitrile (14e di) and cinnamamide (14e amide)**

![Chemical structures of (E)-3-Phenylacrylonitrile (14e trans), (Z)-3-phenylacrylonitrile (14e cis), 3,3-diphenylacrylonitrile (14e di) and cinnamamide (14e amide)](image)

General procedure was followed using acrylonitrile (16.5 µL, 0.25 mmol, 1 equiv). The reaction was stirred overnight, providing the titled compounds in 64% $^1$H NMR yield (cis:trans:amide = 1.1:2.8:1). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:4 v/v) and then
MeOH:CH₂Cl₂ (3:7 v/v) as an eluent providing the titled compounds. Traces amount of di-alkenylation product was observed in ¹H NMR after purify by column chromatography. ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds.⁵⁰ ¹H NMR (400 MHz) δ = 7.82 – 7.80 (m, 2Hcis), 7.47 – 7.39 (m, 17Hcis-trans-diy), 7.31 – 7.29 (m, 2Hdi), 7.13 (d, J = 12.2 Hz, 1Hcis), 5.89 (d, J = 16.6 Hz, 1Htrans), 5.74 (s, 1Hdi), 5.45 (d, J = 12.2 Hz, 1Hdi). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for these compounds.⁵¹ ¹H NMR (400 MHz) δ = 7.97 – 7.94 (m, 2H), 7.69 (d, J = 15.4 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.42 – 7.37 (m, 3H), 6.86 (d, J = 15.4 Hz, 1H). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound. A parallel reaction without ligand was also performed providing the titled compound in 34% ¹H NMR yield (cis:trans:amide = 1:2.8:3).

**(E)**-[2-(Phenylsulfonyl)vinyl]benzene (14f)

(E)-Cinnamyl acetate (14h)

A parallel reaction without ligand was also performed providing the titled compound in 29% ¹H NMR yield.

**General procedure** was followed using phenyl vinyl sulfone (42 mg, 0.25 mmol, 1 equiv). The reaction was stirred overnight, providing the titled compound in 42% ¹H NMR yield. The crude residue was purified by column chromatography using EtOAc:petroleum ether (3:7 v/v) as an eluent providing the titled compound as a pale yellow oil (22.3 mg, 36% yield). ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound. ¹H NMR (400 MHz) δ = 7.97 – 7.94 (m, 2H), 7.69 (d, J = 15.4 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.42 – 7.37 (m, 3H), 6.86 (d, J = 15.4 Hz, 1H).

A parallel reaction without ligand was also performed providing the titled compound in 15% ¹H NMR yield. ¹H NMR spectra data of the crude mixture matched with the spectra data reported in the literature for this compound. ¹H NMR (400 MHz) δ = 7.97 – 7.94 (m, 2H), 7.69 (d, J = 15.4 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.42 – 7.37 (m, 3H), 6.86 (d, J = 15.4 Hz, 1H).

**General procedure** was followed using allyl acetate (27 µL, 0.25 mmol, 1 equiv). The reaction was stirred for 6 h, providing the titled compound in 35% ¹H NMR yield. ¹H NMR spectra data of the crude mixture matched with the spectra data reported in the literature for this compound. ¹H NMR spectra data of the isolated material matched with the spectra data reported in the literature for this compound. ¹H NMR (400 MHz) δ = 4.76 (dd, J = 6.5, 1.2 Hz, 1H).
General procedure for the Pd-catalyzed C–H olefination of estrone and naproxen derivatives

A stock solution of ligand L3 (0.0846 M in CH₂Cl₂, 10 mol%) was added to a pressure tube and dried with nitrogen steam until dryness followed by Pd(OAc)₂ (10 mol%), the corresponding arene (10) (1 equiv), t-butyli peroxybenzoate (1 equiv), ethyl acrylate (11a) (1.5 equiv) and AcOH (0.2 M). 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 16 h. The resulting mixture was diluted with EtOAc and quenched with aqueous Na₂SO₃ solution (10%). The organic layer was washed with saturated aqueous NaHCO₃ solution, dried over anh. MgSO₄, filtered and concentrated under reduced pressure. The crude mixture was purified as specified in each case to obtain the desired product.

(E)-2-(2-Ethoxycarbonylvinyl)estrone methyl ether (12ua) and (E)-4-(2-ethoxycarbonylvinyl)estrone methyl ether (12ub)

General procedure was followed using ligand L3 (0.0846 M in CH₂Cl₂) (300 µL, 25 µmol, 10 mol%), Pd(OAc)₂ (5.6 mg, 25 µmol, 10 mol%), estrone 3-methyl ether (10u) (71 µg, 0.25 mmol, 1 equiv), t-butyli peroxybenzoate (47 µL, 0.25 mmol, 1 equiv), ethyl acrylate (40 µL, 0.375 mmol, 1.5 equiv) and AcOH (1.25 mL). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:4 v/v) as an eluent providing the titled compounds as a clear oil (84 mg, a:b = 3:1, 88% yield). ¹H NMR (400 MHz) δ = 7.94 (d, J = 16.1 Hz, 1Hₐ), 7.87 (d, J = 16.2 Hz, 1H₃), 7.42 (s, 1Hₐ), 7.28 (d, J = 8.7 Hz, 1H₃), 6.80 (d, J = 8.7 Hz, 1H₃), 6.64 (s, 1Hₐ), 6.63 (d, J = 16.1 Hz, 1H₃), 6.51 (d, J = 16.1 Hz, 1Hₐ), 4.30 – 4.23 (m, 4Hₐ₃), 3.86 (s, 6Hₐ₃), 2.94 (dd, J = 8.8, 4.2 Hz, 4Hₐ₃), 2.52 (dd, J = 18.8, 8.6 Hz, 2Hₐ₃), 2.46 – 2.38 (m, 2Hₐ₃), 2.27 – 1.97 (m, 1OHₐ₃), 1.69 – 1.39 (m, 12Hₐ₃), 1.37 – 1.32 (m, 6Hₐ₃), 0.92 (s, 6Hₐ₃); ¹³C NMR (75 MHz) δ = 220.9, 220.8, 168.1, 167.8, 157.0, 156.5, 140.7, 140.4, 138.5, 137.7, 132.6, 132.1, 127.5, 126.3, 123.0, 121.1, 117.9, 111.5, 108.7, 60.4, 60.3, 55.6, 50.4, 48.0, 48.0, 44.3, 43.8, 38.3, 37.5, 36.0, 35.9, 31.7, 31.6, 30.0, 28.1, 26.6, 26.5, 26.3, 26.0, 21.7, 14.5, 13.9; IR ν = 2930, 2858, 1737, 1704, 1622, 1460, 1269, 1157, 1036, 864, 728 cm⁻¹; HRMS (EI) calcd for C₂₄H₃₀O₄ [M⁺]: 382.2144; found: 382.2129.

A parallel reaction using 3,5-dichloropyridine (3.7 mg, 25 µmol, 10 mol%) was also performed providing the titled compounds in 30% conversion.

A parallel reaction without ligand was also performed providing the titled compounds in 10% conversion.

Preparative scale synthesis

General procedure was followed using ligand L3 (36.8 mg, 0.18 mmol, 10 mol%), Pd(OAc)₂ (39.3 mg, 0.18 mmol, 10 mol%), estrone 3-methyl ether (10u) (0.5 g, 1.75 mmol, 1 equiv), t-butyli peroxybenzoate (0.33 mL, 1.75 mmol, 1 equiv), ethyl acrylate (11a) (0.28 mL, 2.63 mmol, 1.5 equiv) and AcOH (8.75 mL). The crude residue was purified by column
chromatography using EtOAc:petroleum ether (1:4 v/v) as an eluent providing the titled compounds as a clear oil (0.5 g, a:b = 3:1, 75% yield).

ocha (S,E)-5-(2-ethoxycarbonylvinyl)naproxen methyl ester (12va) and (S,E)-8-(2-ethoxycarbonylvinyl) naproxen methyl ester (12vb)

General procedure was followed using ligand L3 (0.0846 M in CH2Cl2) (415 µL, 35 µmol, 10 mol%), Pd(OAc)2 (7.8 mg, 35 µmol, 10 mol%), methyl ester of (S)-naproxen54 (10v) (85.5 mg, 0.35 mmol, 1 equiv), t-butyl peroxycarboxylate (66 µL, 0.35 mmol, 1 equiv), ethyl acrylate (11a) (56 µL, 0.52 mmol, 1.5 equiv) and AcOH (1.75 mL). The crude residue was purified by column chromatography using EtOAc:petroleum ether (1:15 v/v) as an eluent providing the titled compounds as a clear oil (76.1 mg, a:others = 3:1, 88% yield). Isomer 24v: 1H NMR (400 MHz) δ = 8.32 (d, J = 16.2 Hz, 1H), 8.16 (d, J = 8.9 Hz, 1H), 7.82 (d, J = 9.1 Hz, 1H), 7.68 (s, 1H), 7.47 (dd, J = 8.9, 1.9 Hz, 1H), 7.28 (d, J = 9.1 Hz, 1H), 6.75 (d, J = 16.2 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.00 (s, 3H), 3.93–3.83 (m, 1H), 3.67 (s, 3H), 1.58 (d, J = 7.2 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H); 13C NMR (101 MHz) δ = 175.0, 168.0, 156.8, 137.7, 136.0, 132.0, 131.5, 129.1, 127.4, 126.8, 123.9, 123.5, 116.7, 113.1, 60.5, 56.3, 52.2, 45.2, 18.6, 14.5; IR ν = 2978, 2939, 2843, 1732, 1704, 1620, 1592, 1267, 1250, 1154, 1041, 803 cm−1; HRMS (FD) calcd for C20H22O5 [M]+: 342.1467; found: 342.1471. Isomer 24v: 1H NMR (400 MHz) δ = 8.45 (d, J = 15.7 Hz, 1H), 7.78–7.68 (m, 3H), 7.38 (d, J = 2.2 Hz, 1H), 7.21 (dd, J = 8.9, 2.1 Hz, 1H), 6.57 (d, J = 15.7 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 3.95–3.86 (m, 1H), 3.70 (s, 3H), 1.60 (d, J = 7.2 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H); 13C NMR (101 MHz) δ = 175.0, 167.1, 158.6, 141.7, 135.4, 132.1, 131.2, 130.3, 129.5, 128.7, 125.6, 120.9, 119.4, 101.9, 60.8, 55.7, 52.3, 45.3, 18.7, 14.5; IR ν = 2979, 2932, 2851, 1735, 1713, 1604, 1260, 1175, 1032 cm−1; HRMS (FD) calcd for C20H22O5 [M]+: 342.1467; found: 342.1463.

A parallel reaction using 3,5-dichloropyridine (5.2 mg, 35 µmol, 10 mol%) was also performed providing the titled compounds in 30% NMR yield.

A parallel reaction without ligand was also performed providing the titled compounds in trace amount.

3.6 References


S,O-Ligands and their application in C–H olefination of arenes with activated alkenes


