



### Development of efficient palladium catalysts for alkoxy-carbonylation of alkenes†

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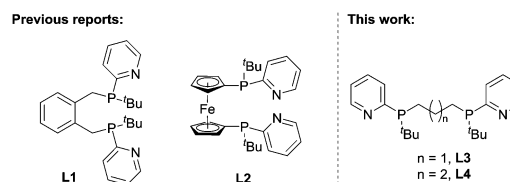
Herein, we report a general and efficient Pd-catalysed alkoxy-carbonylation of sterically hindered and demanding olefins including a variety of tri-, tetra-substituted and 1,1-disubstituted alkenes. In the presence of 1,3-bis(*tert*-butyl(pyridin-2-yl)phosphanyl)propane **L3** or 1,4-bis(*tert*-butyl(pyridin-2-yl)phosphanyl)butane **L4** the desired esters are obtained in good yields and selectivities. Similar transformation is obtained using tertiary ether as showcased in the carbonylation of MTBE to the corresponding linear ester in high yield and selectivity.

Transformations of alkenes continue to be a fundamental basis of the current chemical industry. Besides polymerizations and oxidations, transition-metal catalysed carbonylation reactions of alkenes are among the most important processes in the area of homogeneous catalysis and are widely used in industry as well as organic synthesis.<sup>1</sup> In this respect, a variety of value-added bulk and fine chemicals such as aldehydes,<sup>2</sup> acids,<sup>3</sup> amides,<sup>4</sup> imides<sup>5</sup> as well as esters,<sup>6</sup> are available *via* oxo methodologies. Despite important developments of novel catalytic protocols using CO surrogates,<sup>7</sup> applying more selective catalysts<sup>8</sup> or using different nucleophiles,<sup>9</sup> the carbonylation of more challenging alkenes such as internal olefins, 1,1-disubstituted olefins even tri- or tetra-substituted olefins remains an important and rewarding but difficult goal.

With regard to catalytic carbonylations, the reactivity order of diverse olefins is independent of the metal Co,<sup>10</sup> Rh,<sup>11</sup> or Pd.<sup>12</sup> For example, it is well known that ethylene and terminal olefins show high activity<sup>13</sup> in carbonylation reactions involving transition metal hydride complexes, while reactions of 1,1-disubstituted olefins require more severe reaction conditions or alternatively more active catalysts than terminal or internal olefins. Hence, not surprisingly most of the catalytic carbonylation reactions are limited to terminal olefins and the *n,m*-disubstituted internal alkenes R<sup>1</sup>-CH=CH-R<sup>2</sup>.

As for the tri- or tetra-substituted olefins with much lower activity, the carbonylation of the sp<sup>2</sup>-configured carbon-atoms is particularly difficult (Keulemans' rule)<sup>14</sup> mainly because of the low binding affinity of these substrates towards the metal centre and the sluggish migratory insertion of the metal complex.<sup>15</sup> On the other hand, certain tri-and/or tetra-substituted alkenes are attractive feedstocks and this structure motif is commonly found in natural products, pharmaceuticals, and petrochemicals. However, for further valorisation of such olefins, a significant amount of them cannot be further transformed, due to their low reactivity leading to useless waste.

In 2017, we developed phosphine-based ligands **L1**, **L2** (Scheme 1) bearing both *tert*-butyl and pyridine substituents on the phosphorous atom with different backbones to solve this problem,<sup>16</sup> and applied them in the palladium-catalysed alkoxy-carbonylation of challenging olefins and alcohols.<sup>17</sup> Here, the basic pyridine group improves the rate of the nucleophilic attack on the intermediate palladium acyl complex, which can be the rate-limiting step in these transformations. On the other hand, the nitrogen atom on the pyridine ring is able to improve the stability of the catalyst by hemilabile coordination to the palladium center in the catalytic cycle.<sup>18</sup> Due to the importance of 1,3-bis-diphenylphosphinopropane (**L7**) and 1,4-bis-diphenylphosphino-butane (**L8**), which represent privileged ligands for a variety of catalytic applications,<sup>19</sup> most recently we synthesized **L3** and **L4** (Scheme 1) and demonstrated their superior activity in alkyne carbonylations.<sup>20</sup> Herein, we present for the first time their usefulness in the alkoxy-carbonylation of



**Scheme 1** Recently reported ligands for Pd-catalysed alkoxy-carbonylation of tri- and tetra-substituted alkenes.

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all kinds of alkenes. Moreover, alkoxy-carbonylation of methyl *tert*-butyl ether (MTBE) was presented.

Our initial studies commenced with tetramethylethylene **1a** as the model substrate under previously optimized carbonylation reaction conditions (0.5 mol% Pd catalyst, 40 bar CO, 120 °C) using the ligand **L3**. To our delight, the corresponding ester product **2a** was obtained in almost quantitative yield (99%) and the common ether by-product **3a** was not observed in GC analysis (Table 1, entry 1). Applying **L4** with an extended methylene chain also gave the desired product **2a** in 84% yield while a minor amount (7%) of **3a** was generated (Table 1, entry 2). Interestingly, when using ligands **L5** and **L6** with C5 and C6 chains, the desired product **2a** was observed only in trace amounts and both of the reactions gave **3a** in moderate yields (Table 1, entries 3 and 4). In addition, the commercially available bidentate ligands dppp **L7**, dppb **L8** and their derivatives **L9–L10** which have the same backbones to **L3** and **L4**, were also examined in this reaction. Except for **L8**, all the reactions afforded undesired **3a** in moderate yields and there were only trace amounts of the desired product **2a** detected (Table 1, entries 5–8). This clearly demonstrates the superiority of the novel ligands compared to previously privileged ligands.

Notably, decreasing the catalyst loading to 0.1 mol%, the reaction proceeded still smoothly to give the corresponding product **2a** in excellent yield (99%) and selectivity (Table 1, entry 9), which illustrates the high activity of the catalyst. To improve the reaction further on, the effects of other critical parameters including Pd precursor and acid co-catalyst were investigated for the methoxycarbonylation of **1a** in the presence of **L3** (see ESI† for details).

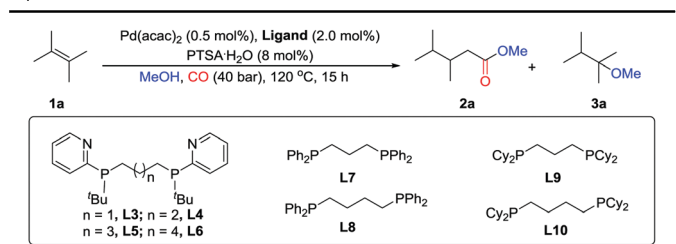
Then, under optimized reaction conditions, the scope of the reaction was studied with less reactive internal olefins

(**1r–1x**) including tri- and tetra-substituted ones (**1a–1d**, **1z**), and di-substituted terminal olefins (**1e–1m**, **1y**). As shown in Table 2, in all cases the corresponding ester products were afforded in high yields (61–99%) with good to very good selectivities. For example, tetra-substituted 9,10-octalin (**1b**) was transformed smoothly to **2b** in 92% yield (Table 2, entry 2).

Table 2 Pd-catalysed alkoxy-carbonylation of alkenes: substrate scope<sup>a</sup>

Entry	Olefin	Product	Yield/%	Selectivity <sup>b</sup>
1			99 <sup>c</sup>	> 99/1
2			92	1/2 89/11 syn/anti 67/33
3			95	> 99/1
4			90	97/3
5			96–99	> 99/1
6			95	97/3
7			99	> 99/1
8			95	> 99/1
9			95	> 99/1
10			94	94/6
11			79	94/6
12			99	99/1
13			93	55/45
14			93–95	1/2 70/30 2/1 94/6
15			91	94/6
16			98	—
17			94	—
18			61	1/2 97/3
18			95	1/2 94/6

Table 1 Palladium-catalysed alkoxy-carbonylation of tetramethylethylene: Optimization of the reaction conditions



Entry <sup>a</sup>	Ligand	Conv. <sup>b</sup> (%)	Yield of <b>2a</b> <sup>b</sup> (%)	Yield of <b>3a</b> <sup>b</sup> (%)
1	<b>L3</b>	> 99	99	0
2	<b>L4</b>	92	84	7
3	<b>L5</b>	49	4	41
4	<b>L6</b>	52	2	44
5	<b>L7</b>	48	2	43
6	<b>L8</b>	63	22	31
7	<b>L9</b>	54	0	45
8	<b>L10</b>	48	0	45
9 <sup>c</sup>	<b>L3</b>	> 99	99	0

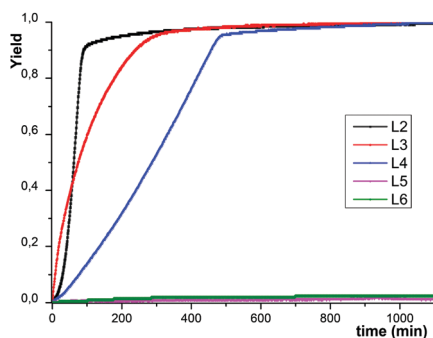
<sup>a</sup> Reaction conditions: **1a** (1.0 mmol), Pd(acac)<sub>2</sub> (1.52 mg, 0.5 mol%), **L** (2.0 mol%), PTSA·H<sub>2</sub>O (16.0 mg, 8.0 mol%), MeOH (2.0 mL), CO (40 bar), 120 °C, 15 h. <sup>b</sup> Conversion and yield were determined by GC analysis using isooctane as the internal standard. <sup>c</sup> 0.1/0.4/1.6 mol% of Pd(acac)<sub>2</sub>/**L3**/PTSA·H<sub>2</sub>O was used.

Table 2 (continued)

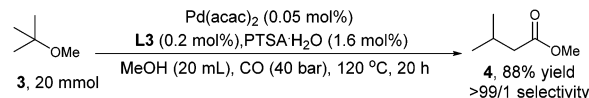
Entry	Olefin	Product	Yield/%	Selectivity <sup>b</sup>
19			99	2/1 >99/1
21			99	>99/1
22			75	98/2 68/32 dr

<sup>a</sup> Unless otherwise noted, all the reactions were performed in MeOH (2.0 mL) at 120 °C for 20 hours in the presence of **1** (1.0 mmol), Pd(acac)<sub>2</sub> (0.5 mol%), **L3** (2.0 mol%), PTSA·H<sub>2</sub>O (8.0 mol%), CO (40 bar) and isolated yields for all products. <sup>b</sup> The selectivity were determined by GC analysis using isooctane as the internal standard. <sup>c</sup> GC yield using isooctane as the internal standard.

Notably, methoxycarbonylation of the industrial feedstock diisobutene<sup>21</sup> (**1c**) and tri-substituted alkenes **1d** proceeded *via* sequential isomerization and carbonylation to afford the desired esters **2c** and **2d** in excellent yields and selectivities (Table 2, entries 3 and 4). The reactions of di-substituted terminal olefins including  $\alpha$ -methylstyrene derivatives with different substitutes on the phenyl ring (**1e–1i**) and (4-methylpent-1-ene-2,4-diyl)dibenzene (**1j**) as well as  $\alpha$ -phenylstyrene (**1k**) gave the desired terminal esters in no less than 96% yield with excellent selectivities (Table 2, entries 5–7). Furthermore, the notoriously unreactive push-pull olefin **1l** afforded the corresponding amino acid derivative in 95% yield (Table 2, entry 8). In addition, substrates bearing a variety of substituents such as fluoride, silyl, imide, and ester (**1m–1q**) reacted well in this protocol (Table 2, entries 9–13). To our delight, cycloalkenes, which often show low reactivity under traditional alkoxy carbonylation conditions, are transformed into the corresponding esters in high yields and selectivity (Table 2, entries 14–16). The reaction of stilbene (**1v**) and cinnamitrile (**1w**) which are not able to isomerize also provided the esters as well (Table 2, entries 17 and 18). Interestingly, the



**Fig. 1** Palladium-catalysed methoxycarbonylation of ethylene. Reaction conditions: ethylene (1.5 g, 54 mmol), Pd(acac)<sub>2</sub> (6.5 mg, 0.04 mol%), ligand (0.16 mol%), PTSA·H<sub>2</sub>O (61.1 mg, 0.6 mol%), MeOH (20.0 mL), CO (30 bar), 23 °C.



**Scheme 2** Pd-Catalysed carbonylation of MTBE to linear ester.

succinic acid diester derivative **2x**, which has been applied in the synthesis of rennin inhibitors,<sup>22</sup> and matrix metalloproteinase<sup>23</sup> as well as material science<sup>24</sup> was directly obtained from both methyl cinnamate (**1x**) and methyl 2-phenylacrylate (**1x'**) in high yield (Table 2, entries 19 and 20). Moreover, the diester **2y**, which is of interest for polymer chemistry, was obtained in quantitative yield and selectivity through the dimethoxycarbonylation of **1y** using our catalytic system (Table 2, entry 21). Finally, the methoxycarbonylation of a potent anti-tumor drug diethylstilbestrol (**1z**) afforded the ester **2z** in good yield, albeit as a mixture of diastereomers (Table 2, entry 22).

To demonstrate the relevance of our catalysts, the industrially important methoxycarbonylation of ethylene was performed with **L2–L6** as the ligand, respectively. As depicted in Fig. 1, ethylene was completely converted to the methyl-methacrylate, a feedstock of polymer chemistry, in the presence of Pd/**L3**/PTSA (0.04/0.16/0.6 mol%) at room temperature within 5 hours. Under the same reaction condition, ligand **L4** also gave the desired product in excellent yield albeit with longer time. Meanwhile, applying ligand **L5** or **L6** in this reaction, methyl methacrylate was observed in significantly lower yield. As a reference, the known ligand **L2** was also applied in this process, affording the corresponding product within 5 hours, which demonstrate the improved activity of ligand **L3** and **L4**. To show the usefulness of this palladium catalyst further on, we evaluated the carbonylation of the industrial bulk chemical methyl *tert*-butyl ether (MTBE) as a surrogate for isobutene. Gratifyingly, at low catalyst loading methyl 3-methylbutanoate (**4**) was achieved in 88% yield which demonstrates the principle possibility to perform such reactions in a 100% atom-efficient way (Scheme 2).

In conclusion, we demonstrated for the first time that analogous ligands compared to dppp and dppb with “built-in base” create favorable palladium catalyst systems, which allow for general alkoxy carbonylations of different olefin classes. These ligands are specifically advantageous for less reactive, sterically hindered and industrially important bulk alkenes to afford the corresponding products with high activity. Moreover, these catalytic systems can be also utilized in the alkoxy carbonylation of tertiary ethers as demonstrated in case of MTBE. Given its generality and efficiency, these catalysts provide a practical synthetic tool for the conversion of a wide variety of alkenes into versatile ester products.

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## Conflicts of interest

There are no conflicts to declare.

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