Tailor-made Catalysts Immobilised on Silica.

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Silica immobilised palladium phosphine complexes as recyclable, regioselective catalysts for the allylic alkylation

Abstract

The covalent immobilisation of palladium phosphine complexes on silica is demonstrated to be a viable method for the recovery of allylic alkylation catalysts. Both bidentate and monodentate phosphine ligands form stable palladium catalysts that could be recycled without catalyst deterioration. The regioselectivity of the immobilised catalysts for the alkylated products showed the same trend as the homogeneous analogues. A pre-modification of the silica surface using dichlorodimethylsilane was crucial, though, for the recycling properties of the catalyst system. The morphology of the silica support did not have impact on the catalyst performance in the alkylation of 3-methyl-but-2-enyl trifluoroacetate with sodium diethyl 2-methylmalonate; amorphous silica and MCM-41 supported Pd(I) gave a similar product distribution.

8.1 Introduction

Palladium catalysed C-C bond formation reactions are powerful tools in organic synthesis, providing mild and selective methods to a great variety of valuable chemicals from basic precursors. An intriguing example of such a reaction is the allylic substitution reaction. After the discovery by Tsuji, further development of this reaction by Trost and others led to catalyst systems that are extensively used in modern organic synthesis.¹ For applications in the fine chemical industry it is of great importance that these palladium containing catalysts are completely and conveniently separated from the product and, preferably, reused in numerous catalytic runs thereby increasing the number of turnovers. The vast amount of research devoted to the Trost-Tsuji reaction also stimulated the investigation of several approaches to the immobilisation of alkylation catalysts on organic polymers.² Despite the advantages (i.e. chemical and mechanical inertness) there is surprisingly little reported on the covalent anchoring of this type of catalysts on inorganic supports.³,⁴ Sinou et al. investigated the application of a two phase H₂O-nitrile catalyst system, using Pd(TPPTS), as the water soluble catalyst. This enabled a straightforward catalyst recovery via phase-separation.⁵ The use of this catalyst in a set-up involving a Supported Aqueous Phase Catalyst resulted in an important increase in catalyst performance and catalyst recovery compared to the two phase system.⁶ The activity and recycling of these systems were found to be largely dependent on the miscibility of the two phases and on the water content on the silica support, respectively.⁷,⁸ As part of an ongoing research toward sustainable and recyclable catalyst systems⁹ we studied the covalent immobilisation of palladium catalysts on silica. In this chapter, it is reported that the immobilisation of palladium-phosphine complexes to silica, tethered via the phosphine ligand, enables an easy and complete separation of the active catalyst from the products. Moreover, it will be shown that the regioselectivity of the alkylation reaction is influenced by the nature of the phosphine ligand similar to the homogeneous analogues.

8.2 Results and discussion

8.2.1 Ligand immobilisation

Three different trialkoxysilane functionalised phosphine ligands were used in this study: N-(3-trimethoxysilane-n-propyl)-4,5-bis(diphenylphosphino)-phenoxazine 1, N-(3-triethoxysilane-n-propyl)N',N'-bis(2-(diphenylphosphino)ethyl) urea 2, and 2-(diphenylphosphino)ethyltrimethoxysilane 3 (Chart 8.1). The synthesis of ligand 1 and 2 were reported in Chapter 3 and ligand 3 was obtained commercially.
Ligands were tethered to the support-surface by stirring a toluene suspension of the ligand and silica at 65°C for 2 hours. Subsequently, the remaining silanols on the silica were modified to alkylsilyl species by treatment with dichlorodimethylsilane. This "capping" of silanols is done in order to avoid side reactions during catalysis. The efficiency of this modification is clearly visible in the IR spectra, which show that the broad OH band at 3000-3300 cm\(^{-1}\) is decreased to a large extent (Figure 8.1). The obtained supported ligand systems can be stored for months under an inert atmosphere.

**Figure 8.1:** Infrared spectra of silica (bottom) and silica modified with dimethyldichlorosilane (top).

### 8.2.2 Catalysis

The palladium phosphine catalysts Pd(1), Pd(2) and Pd(3) were prepared *in situ* by stirring a mixture of silica immobilised ligand in a solution of Pd\((\text{dba})_2\) in THF. This resulted in a decoloration of the solution within 5 minutes (from purple to colorless) and at the same time the silica turned yellow. When no ligand is present on the silica no adsorption of the Pd precursor on the silica surface takes place and the Pd\((\text{dba})_2\) remained in solution. After
washing the catalyst containing silica, the systems were used in the allylic alkylation of 3-phenyl-prop-2-enyl trifluoroacetate (A) using sodium diethyl 2-methylmalonate as the nucleophile (Scheme 8.1). In this reaction three alkylated products can be formed, the linear (E), the linear (Z) and the branched product.

All catalyst systems were very active in this reaction; turnover frequencies (TOFs, determined as average turnover frequencies by means of GC-analysis) ranged from 17*10^3 mol.mol^{-1}.h^{-1} for Pd(1) to 10*10^3 mol.mol^{-1}.h^{-1} for Pd(3) (Table 8.1). In all cases the linear (E) product is the main product (~ 95%). The amount of branched product formed increases in the order Pd(2)<Pd(3)<Pd(1) (2.5%, 3.4%, 5.3% respectively). The differences, however, are very small because the linear (E) product, in which the conjugation is maintained, is more stable and thus the nature of the catalyst influences the product distribution only marginally.

Table 8.1: Results from the allylic alkylation of A with sodium diethyl 2-methylmalonate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion (%)</th>
<th>TOF (*10^4)</th>
<th>Linear product (%)</th>
<th>Branched product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(1)</td>
<td>54</td>
<td>1.7</td>
<td>94.6</td>
<td>5.3</td>
</tr>
<tr>
<td>2</td>
<td>Pd(2)</td>
<td>28</td>
<td>1.2</td>
<td>97.5</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>Pd(3)</td>
<td>30</td>
<td>1.0</td>
<td>96.6</td>
<td>3.4</td>
</tr>
<tr>
<td>4</td>
<td>No Pd</td>
<td>1.7</td>
<td>-</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

a Reactions were run in 2 ml of THF, using 5*10^{-2} mol of Pd(dba)_3, 50 mg silica immobilised ligand, 1.0 mmol of substrate and 0.5 mmol of sodium diethyl 2-methylmalonate at room temperature. b Determined after 1 minute. c The average turnover frequency calculated after 1 minute in mol.mol^{-1}.h^{-1}. d Determined by means of GC-analysis. e A blanc reaction with all components present in the reaction mixture, including silica, but without the presence of the catalyst.
The sterically more hindered substrate 3-methyl-but-2-enyl trifluoroacetate (B) was converted somewhat more slowly compared to A (Table 8.2). Also for B the reaction rate is dependent on the nature of the phosphine ligand, the xanthene based diphosphine again forming the fastest catalyst. Using substrate B, the differences in reaction rate are more pronounced; Pd(1) (TOF of 6800 mol·mol⁻¹·h⁻¹) is nearly three times faster than the other catalysts. Pd(2) showed a TOF of 1800 mol·mol⁻¹·h⁻¹ and Pd(3) showed a TOF of 2700 mol·mol⁻¹·h⁻¹. The higher catalyst activity of Pd(1) compared to Pd(2) is ascribed to the larger P-Pd-P bite angle, which was calculated to be 108° for ligand 1 and 93° for ligand 2. This bite angle effect was previously observed for the homogeneous catalysed alkylation of B using the same nucleophile. Ligands containing a wide bite angle were found to decrease the back-bonding to the substituted site of the allyl moiety, which results in a pronounced effect on the reactivity of the allylic carbon atoms and also on the regioselectivity of this reaction. Using the silica immobilised systems, the differences in regioselectivity for the branched product were also clearly observed. Pd(1) produced the branched product with 58.3 percent selectivity whereas Pd(2) and Pd(3) formed only 11.6 and 10.7 percent of the branched product, respectively. As was observed for comparable homogeneously catalysed experiments, the larger bite angle of 1 enhances the electronic preference for nucleophilic attack on the branched position. The current results clearly indicated that the catalyst performance of this type of systems remain largely intact upon immobilisation to a silica support. Ligand 2, having a non-rigid backbone with a small bite angle, induces a selectivity similar as monophosphine containing Pd(3).

Table 8.2: Results from the allylic alkylation of B with sodium diethyl 2-methylmalonate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion%d</th>
<th>TOF%c</th>
<th>Linear productd</th>
<th>Branched productd</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(1)</td>
<td>68</td>
<td>6.8</td>
<td>41.7</td>
<td>58.3</td>
</tr>
<tr>
<td>2</td>
<td>Pd(2)</td>
<td>25</td>
<td>1.8</td>
<td>88.4</td>
<td>11.6</td>
</tr>
<tr>
<td>3</td>
<td>Pd(3)</td>
<td>20</td>
<td>2.7</td>
<td>89.3</td>
<td>10.7</td>
</tr>
<tr>
<td>4</td>
<td>Pd(1)/MCM</td>
<td>68</td>
<td>n.d.</td>
<td>41.6</td>
<td>58.4</td>
</tr>
</tbody>
</table>

Reactions were run in 2 ml of THF, using 5*10⁻³ mol of Pd(dba)₂, 50 mg of silica immobilised ligand, 1.0 mmol of substrate and 0.5 mmol of sodium diethyl 2-methylmalonate at room temperature. Determined after 5 minutes. The average turnover frequency calculated after 5 minutes in mol·mol⁻¹·h⁻¹. Determined by means of GC-analysis.

Johnson et al. showed that the use of MCM-41 as support can have a large impact on the enantioselectivity and regioselectivity in the allylic alkylation reaction (see also Chapter 1, section 1.6.2). The constrained catalyst environment gave a significant increase in the percentage of branched product in the alkylation of B. In contrast we observed that Pd(1) immobilised on MCM-41 gave the same regioselectivity as Pd(1) tethered to amorphous silica; 58.4 and 58.3 percent, respectively (Table 8.2, entries 4 and 1).
8.2.3 Recycling of the catalyst

The catalyst recovery was investigated by performing series of four consecutive catalytic runs using both A and B as the substrate. For A both the activity and the high regioselectivity for the linear product remained the same upon recycling catalyst Pd(1), Pd(2) and, surprisingly, also Pd(3) (Table 8.3). Neither a systematic drop in activity nor a decrease in selectivity was observed in four catalyst runs which indicates that a complete retention of the active catalyst on the silica support was obtained. Colourless product mixtures were separated from the solid catalyst and also no palladium black formation was observed. With AES experiments no significant palladium could be detected in the product phase, indicating that leaching was less than 1 percent per cycle of the total amount of palladium used. Even Pd(3), containing the monophosphine ligand, showed a full recovery of catalytic activity in these recycling experiments.

Table 8.3: Catalyst recycling experiments for the allylic alkylation of A with sodium diethyl 2-methylmalonate.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst [cycle]</th>
<th>Conversion\textsuperscript{b} (%)</th>
<th>Linear product\textsuperscript{c} (%)</th>
<th>Branched product\textsuperscript{c} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(1), [1]</td>
<td>81</td>
<td>94.3</td>
<td>5.7</td>
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<td>2</td>
<td>[2]</td>
<td>79</td>
<td>97.0</td>
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<td>[3]</td>
<td>82</td>
<td>96.9</td>
<td>3.1</td>
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<td>[4]</td>
<td>83</td>
<td>96.6</td>
<td>3.4</td>
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<tr>
<td>5</td>
<td>Pd(2), [1]</td>
<td>85</td>
<td>97.6</td>
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<td>[2]</td>
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<td>[3]</td>
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<td>2.7</td>
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<td>8</td>
<td>[4]</td>
<td>80</td>
<td>97.5</td>
<td>2.5</td>
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<tr>
<td>9</td>
<td>Pd(3), [1]</td>
<td>24</td>
<td>97.0</td>
<td>3.0</td>
</tr>
<tr>
<td>10</td>
<td>[2]</td>
<td>24</td>
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<td>0</td>
</tr>
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<td>11</td>
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<tr>
<td>12</td>
<td>[4]</td>
<td>34</td>
<td>98.9</td>
<td>1.1</td>
</tr>
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</table>

\textsuperscript{a} Reactions were run in 2 ml of THF, using \(5 \times 10^{-7}\) mol of Pd(dba)\textsubscript{2}, 50 mg silica immobilised ligand, 1.0 mmol of substrate and 0.5 mmol of sodium diethyl 2-methylmalonate at room temperature.\textsuperscript{b} Determined after 10 minutes.\textsuperscript{c} Determined by means of GC-analysis.

The recycling experiments were also adopted to the allylic alkylation of B (Table 8.4). Pd(1), Pd(2) and Pd(3) again showed a clean and straightforward catalyst recovery upon reuse of the catalysts in four consecutive catalytic runs. Pd(1) remained selective for the branched product up to the fourth catalyst runs (the regioselectivity varied between 56.7 and 58.4% (entries 1 to 4)). Also Pd(2), for which the regioselectivity ranged between 88.4 and 93.2% (entries 5 to 8) and Pd(3) with a regioselectivity ranging between 87.2 and 91.9% (entries 9 to
12) showed a good catalyst recovery in four consecutive catalytic runs. No systematic drop in catalyst activity was observed for the three catalyst systems, which was substantiated by the absence of significant Pd leaching.

Table 8.4: Catalyst recycling experiments for the allylic alkylation of B with sodium diethyl 2-methylmalonate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion(^b) (%)</th>
<th>Linear product(^c) (%)</th>
<th>Branched product(^c) (%)</th>
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<td>Pd(1), [1]</td>
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<td>[3]</td>
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<td>[4]</td>
<td>64</td>
<td>43.3</td>
<td>56.7</td>
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<td>Pd(2), [1]</td>
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<td>88.4</td>
<td>11.6</td>
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<td>[2]</td>
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<td>89.9</td>
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<td>89.3</td>
<td>10.7</td>
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<td>[2]</td>
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<td>27</td>
<td>91.9</td>
<td>8.1</td>
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<tr>
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<td>Pd(1)/MCM, [1]</td>
<td>68</td>
<td>41.6</td>
<td>58.4</td>
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<td>[2]</td>
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<td>58.6</td>
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<td>65</td>
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<td>58.1</td>
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<td>[4]</td>
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<td>58.8</td>
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<td>43.1</td>
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<td>20</td>
<td>[4]</td>
<td>19</td>
<td>83.2</td>
<td>16.8</td>
</tr>
</tbody>
</table>

\(^a\) Reactions were run in 2 ml of THF, using 5 \(\times 10^{-3}\) mol of Pd(dba)\(_3\), 50 mg of the above described immobilised ligand, 1.0 mmol of substrate and 0.5 mmol of sodium diethyl 2-methylmalonate at room temperature. \(^b\) Determined after 5 minutes. \(^c\) Determined by means of GC-analysis.

The recycling experiments were also adopted to Pd(1) immobilised on MCM-41 (Table 8.4, entries 13-16). The conversion of the alkylation of B remained the same in four consecutive catalytic runs (ranging between 65 and 71%) and also the selectivity for the branched product was virtually unaltered (ranging between 58.1 and 58.8%). Hence, the morphology of the silica support does not have any effect on the stability or recyclability of this type of catalyst.
It is concluded that these silica immobilised palladium phosphine catalysts are all very stable under catalytic conditions and that the palladium phosphine bond, even when monophosphines were used, is strong enough to fully maintain the palladium to the support.

The surface of the non-modified silica was found to have a major impact on the catalysis. When Pd(1) on non-modified silica (Pd(1)') was used in the alkylation of B, both the activity and selectivity of the catalyst decreased dramatically (Figure 8.2 and Table 8.4, entries 17-20). Using Pd(1)’ the selectivity for the branched product is already low compared to that of Pd(1) in the first run (43.1% and 58.3%, respectively) (entries 17 and 1)). The selectivity decreased further to 16.8% in the fourth run (entries 17 to 20). Moreover, the catalyst activity was observed to be a factor of three lower for Pd(1)’. This experiment clearly indicates that the silanols on the silica surface of Pd(1)’ strongly interfere with the catalyst. Hence, the modification of the silanols on the silica surface with dimethylsilane is crucial in the development of this type of selective and stable immobilised alkylation catalysts.

8.3 Conclusions

The covalent immobilisation of palladium phosphine complexes on silica is a viable approach to obtain recyclable allylic alkylation catalysts. Both bidentate and monodentate phosphine ligands form stable palladium catalysts that can be recycled with no significant catalyst deterioration and metal leaching. Catalyst performances were largely retained upon immobilisation but a pre-modification of the silanols on the silica surface using dichlorodimethylsilane was essential. The xanthene-based diphosphine 1, a ligand with a large natural P-Pd-P bite angle, gave rise to an increased regioselectivity for the branched product. The morphology of the silica support did not have an impact on the catalyst performance, amorphous silica and MCM-41 supported Pd(1) gave similar results.
8.4 Experimental section

General

N-(3-trimethoxysilane-n-propyl)-4,5-bis(diphenylphosphino)-phenoxazine (1)\(^{9a}\) and N-(3-triethoxysilane-n-propyl)-N',N'-bis(2-(diphenylphosphino)ethyl)-urea (2) were synthesised according to the procedures reported in Chapter 3. All other chemicals were purchased commercially and used without further purification. The type of silica was silica 60 A (70-200 \(\mu m\)). Hexane, pentane, diethyl ether, THF, toluene and benzene were distilled from sodium. Dichloromethane was distilled from calcium hydride. All reactions were performed using standard Schlenk techniques under Ar. All solutions and solvents not stated above were degassed prior to their use. NMR spectra were recorded on a Bruker AMX 300 or DRX 300 spectrometer. Chemical shifts are in ppm relative to TMS as external standard unless stated otherwise. FT-IR spectra were obtained on a Bio-Rad FTS-7 spectrophotometer. Mass spectra (FAB) were recorded on a JEOL JMS SX/SX102A. Elemental Analyses were performed on an Interscience Mega2 apparatus, equipped with a DBI column, length 30 m, inner diameter 0.32 mm, film thickness 3.0 \(\mu m\), and an F.I.D. detector.

Ligand immobilisation procedure

1 g of silica, which was dried at 180°C for several days, was further dried under reduced pressure at 180°C for 2 hours. After cooling down to room temperature, 100 mg ligand was added to a suspension of the silica in 20 ml of toluene. After the reaction mixture was stirred for 2 hours at 65°C, the silica was filtered and washed with three portions of toluene. The silica was suspended in a mixture of 20 ml of toluene and 2 ml of triethylamine and 0.5 ml of dichlorodimethylsilane were added to the mixture after stirring it for 5 minutes. The resulting mixture was stirred at room temperature for 1 hour and the silica was filtered and carefully washed with one portion of diethyl ether, two portions of methanol and again with two portions of diethyl ether. Finally, the product was dried under reduced pressure and stored under an inert atmosphere.

When MCM-41 was the support, the exterior of the material was pre-modified with dichlorodimethylsilane. To this end, 1 drop of dichlorodimethylsilane was added to a suspension of 1 g of MCM-41 in 20 ml of diethyl ether and the reaction mixture was stirred at room temperature for 1 h. After the MCM-41 was filtered and washed with diethyl ether the preparation was finished using the above described method.

Catalysis procedure

The catalytic experiments were performed in 2 ml of THF, using \(5\times10^{-7}\) mol of Pd(dba)_2, 50 mg of the above described immobilised ligand, 1.0 mmol of substrate and 0.5 mmol of
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sodium diethyl 2-methylmalonate at room temperature. A mixture of the palladium precursor and the silica-immobilised ligand were stirred in the THF for 30 minutes. After washing the catalyst with THF the catalysis was started by the addition of the substrate and the sodium diethyl 2-methylmalonate. The reaction was monitored by taking samples from the reaction mixture that, after aqueous work-up, were analysed by GC using decane as the internal standard. Subsequent catalytic runs were performed after removal of the products and washing of the catalyst with THF.

8.5 References and notes


