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# Enhanced regioselectivity in palladium-catalysed asymmetric methoxycarbonylation of styrene using phosphetanes as chiral ligands

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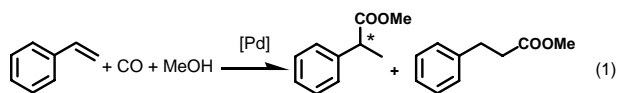
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**The palladium-catalysed asymmetric methoxycarbonylation of styrene has been investigated for the first time using phosphetanes as chiral ligands and showed good catalytic activity, excellent regioselectivity to the branched product and enantioselectivity up to 29%.**

Over the past two decades, the asymmetric methoxycarbonylation of styrene (equation 1) has been extensively studied as a route to obtain 2-arylpropionic acids, the most important class of non-steroidal anti-inflammatory drugs.<sup>1</sup>

Catalysts containing bidentate diphosphine ligands have been frequently used for this reaction, but generally afford low regio- and enantioselectivity to the branched product.<sup>2</sup> Only a few successful examples have been reported using these catalytic systems.<sup>3</sup> Monodentate phosphines have recently received more attention due to their significant potential in various catalytic processes.<sup>4</sup> In the palladium-catalysed methoxycarbonylation of styrene, their use provides high regioselectivities to the branched ester although the enantioselectivity is usually low. Cometti and Chiusoli<sup>5</sup> reported the use of neomenthylidiphenyl phosphine **A** (Fig. 1). Later Nozaki and coworkers<sup>6</sup> used the phospholane ligand **B** and recently the same authors reported on the application of palladium complexes with binaphthol-derived phosphines **C** in the methoxycarbonylation of vinylarenes achieving 53% ee with the branched ester as the only reaction product.<sup>7</sup> A similar behaviour was observed for related palladium-catalysed hydroxycarbonylations of styrene, where it has been found that palladium complex containing monodentate ligands produce excellent regioselectivity to the branched acids but low enantioselectivity, while systems containing bidentate ligands mainly produce linear acids.<sup>8</sup> The mechanistic aspects of hydroxycarboxylation and methoxycarbonylation of styrene have recently been reviewed.<sup>9</sup>

Phosphetane ligands have only recently been introduced in homogeneous catalysis.<sup>10</sup> Their restricted conformational freedom, due to the presence of a four-membered ring, is expected to enhance the chiral induction during the catalytic processes.<sup>11</sup> These highly hindered, chiral phosphines have been reported in asymmetric hydrogenation reactions catalysed by rhodium and ruthenium complexes.<sup>12</sup> Phosphetanes based palladium catalyst were also used in processes such as olefin hydrosilation and allylic nucleophilic substitutions.<sup>13</sup> Here, we report our preliminary results obtained in the asymmetric methoxycarbonylation of styrene catalysed by palladium complexes bearing monodentate chiral phosphetane ligands. This is the first time that such ligands are used in carbonylation reactions.



Scheme 1. Pd-catalysed methoxycarbonylation of styrene

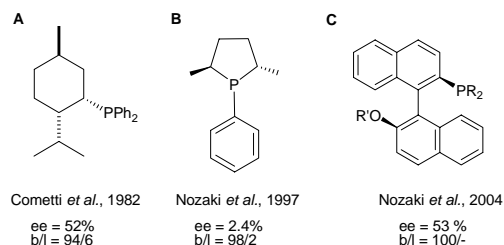


Fig. 1. Monodentate phosphines previously used in asymmetric methoxycarbonylation of styrene. (A) [5], (B) [6], (C) [7]

The syntheses of the phosphetane ligands **1-4** (Fig. 2) and palladium complexes PdCl<sub>2</sub>(**3**)<sub>2</sub> were performed according to the literature procedures.<sup>10,13a,13b,14</sup> The ligands **1-4** were first tested for catalysis using PdCl<sub>2</sub> as palladium precursor, under standard conditions. The results obtained are summarised in Table 1. When the phosphetane **1** was used, 97% conversion was obtained with a chemoselectivity to the esters of 99% and a regioselectivity to the branched product of 98% (run 1). Moreover, chirality was induced by the ligand **1** in this system and yielded an enantiomeric excess of 12%. However, when the bulkier ligands **2** and **3** were used for this reaction, the conversion was found to decrease considerably, although the

chemo- and regioselectivity of the reactions remained high (runs 2 and 3). It should be noted that the simple replacement of the two phenyl rings of **2** by methyl groups in **3** resulted in a substantial decrease in the activity of the catalyst and in the chemoselectivity of the reaction. The utilisation of the ferrocenylphosphetane **4** exhibited an even greater diminution in catalysts activity and chemoselectivity, although the ratio of branched to linear esters remained 99:1. In view of these results, the reaction conditions were optimised using ligand **1**.

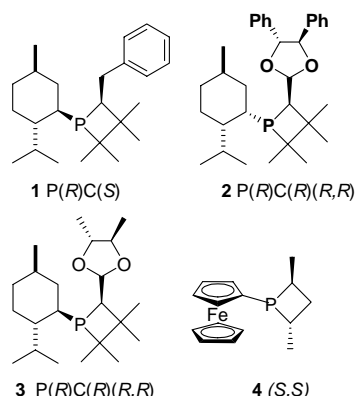


Fig. 2. Chiral phosphetanes used in this study.

In order to first determine the optimum reaction temperature for the PdCl<sub>2</sub>/1/*p*-TsOH system, the CO pressure was kept constant at 35 bars and the reaction temperature varied from 25 to 70 °C. Under these conditions, the highest selectivity was obtained at 50°C with both conversion and the branched to linear products ratio being superior to 99% and the ee of 10% (run 5). When the reaction was repeated with a lower concentration of PdCl<sub>2</sub> (run 7), the conversion was found to be 48%, but illustrating an increase in catalyst activity (TOF = 2 vs. 1.03 h<sup>-1</sup>). Raising the CO pressure resulted in the reduction of both conversion and enantioselectivity of the reaction (run 8). Increasing the acidity of the media was found to be beneficial to the activity of this system (run 9, TOF = 3.38 h<sup>-1</sup>).

Experiments were therefore performed using the isolated complex PdCl<sub>2</sub>(**3**)<sub>2</sub> as the catalyst precursor. The results obtained show that PdCl<sub>2</sub>(**3**)<sub>2</sub> is a convenient catalyst precursor for this reaction with the desired branched ester produced in higher yield and with higher chemoselectivity (run 10) than the selectivities obtained when the catalyst was prepared in situ (run 3). It is noteworthy that when the concentration of PdCl<sub>2</sub>(**3**)<sub>2</sub> was lowered to 0.5 mol% (run 11), the enantioselectivity of the reaction was improved significantly (ee = 29%).

Table 1. Methoxycarbonylation of styrene using PdCl<sub>2</sub>/phosphetane/*p*-TsOH system<sup>a</sup>

| Run <sup>a</sup> | Catalyst                                | Ligand   | P CO | T(°C) | %C  | %(b+l) | b:l  | %ee <sup>b</sup> |
|------------------|---|----------|------|-------|-----|--------|------|------------------|
| 1                | PdCl <sub>2</sub>                       | <b>1</b> | 35   | 70    | 97  | >99    | 98:2 | 12 ( <i>R</i> )  |
| 2                | PdCl <sub>2</sub>                       | <b>2</b> | 35   | 70    | 35  | 95     | 96:4 | 3 ( <i>S</i> )   |
| 3                | PdCl <sub>2</sub>                       | <b>3</b> | 35   | 70    | 19  | 62     | 99:1 | 0                |
| 4                | PdCl <sub>2</sub>                       | <b>4</b> | 35   | 70    | 5   | 21     | 99:1 | nd               |
| 5                | PdCl <sub>2</sub>                       | <b>1</b> | 35   | 50    | >99 | >99    | 99:1 | 10 ( <i>R</i> )  |
| 6                | PdCl <sub>2</sub>                       | <b>1</b> | 35   | 25    | <1  | -      | -    | -                |
| 7 <sup>c</sup>   | PdCl <sub>2</sub>                       | <b>1</b> | 35   | 50    | 48  | >99    | 98:2 | 14 ( <i>R</i> )  |
| 8 <sup>c</sup>   | PdCl <sub>2</sub>                       | <b>1</b> | 60   | 50    | 37  | 99     | 97:3 | 4 ( <i>R</i> )   |
| 9 <sup>c,d</sup> | PdCl <sub>2</sub>                       | <b>1</b> | 35   | 50    | 81  | 97     | 97:3 | 10 ( <i>R</i> )  |
| 10               | PdCl <sub>2</sub> (Ligand) <sub>2</sub> | <b>3</b> | 35   | 70    | 81  | 96-    | 96:4 | 0                |
| 11 <sup>e</sup>  | PdCl <sub>2</sub> (Ligand) <sub>2</sub> | <b>3</b> | 35   | 70    | 26  | 94     | 97:3 | 29( <i>R</i> )   |

<sup>a</sup> Reaction conditions: 4 mol% Pd (0.015 mmol), L/Pd = 2, 24h, MeOH:THF (1:1), 0.15 mmol *p*-TsOH.

<sup>b</sup>Enantiomeric excesses were determined by <sup>1</sup>H NMR spectroscopy using Eu(hfc)<sub>3</sub> as the chiral shift reagent and by HPLC analysis (Daicel CHIRACEL OJ, hexane/2-propanol = 95/5, 1.5 ml min<sup>-1</sup>). C, conversion; b, branched ester; l, linear ester.

<sup>c</sup> 1 mol% Pd.

<sup>d</sup> 1.5 mmol *p*-TsOH

<sup>e</sup> 0.5 mol% Pd

In conclusion, we have demonstrated that monodentate phosphetanes are suitable chiral ligands for the palladium-catalysed asymmetric methoxycarbonylation of styrene. Under mild conditions, the chemo- and regioselectivity of this reaction were found to be excellent, with production of the corresponding branched ester in high yield. The catalytic process takes place with fair stereoselectivity, with ee up to 29 % when the isolated complex PdCl<sub>2</sub>(**3**)<sub>2</sub> was used as the catalyst precursor. Further investigations on the coordination chemistry of these ligands and the catalytic activity of

the corresponding palladium complexes are currently on going and will be reported in due course. The tuning of their steric and electronic properties will be investigated in detail in order to optimise the enantioselectivity of the reaction.

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