Chiral ferrocene-based phosphine-imine and sulfur-imine ligands for palladium-catalyzed asymmetric allylic alkylation of cycloalkenyl esters

Xiangping Hu, Changmin Bai, Huicong Dai, Huilin Chen, Zhuo Zheng∗

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, PR China

Received 2 January 2004; received in revised form 13 April 2004; accepted 14 April 2004

Abstract

Chiral ferrocene-based phosphine-imine ligands 1–3 and sulfur-imine ligand 4 were applied in the palladium-catalyzed asymmetric allylic alkylation of cycloalkenyl esters. The results revealed that the substituents in aryl ring, ferrocenylmethyl and benzylene position strongly affected the enantioselective induction of phosphine-imine ligands, and the most stereoselective ligand was ferrocenylphosphine-imine 1b with a nitro group in the meta-position of phenyl ring. Under the optimized condition, up to 91% (enantiomeric excesses) e.e. of cyclic alkylation product was obtained by the use of 1b.

© 2004 Elsevier B.V. All rights reserved.

Keywords: Ferrocene; Phosphine-imine ligands; Asymmetric; Allylic alkylation; Cycloalkenyl esters

1. Introduction

Palladium-catalyzed allylic substitutions have been one of the most intensely studied topics in asymmetric synthesis during the past two decades [1]. Specifically, various ligands have been successfully applied to the enantioselective alkylation of cycloalkenyl esters. The results revealed that the substituents in aryl ring, ferrocenylmethyl and benzylicene position strongly affected the enantioselective induction of phosphine-imine ligands, and the most stereoselective ligand was ferrocenylphosphine-imine 1b with a nitro group in the meta-position of phenyl ring. Under the optimized condition, up to 91% (enantiomeric excesses) e.e. of cyclic alkylation product was obtained by the use of 1b.
In addition, to compare the catalytic activity between \( P \)-imine and \( S \)-imine, the synthesis of ferrocenylsulfur-imine ligand 4 and its application in this reaction were also described (Fig. 1).

2. Experimental

2.1. General methods

Melting points were measured on a Yanaco micro melting point apparatus (uncorrected). Optical rotations were measured on a HORIBA SEPA-200 high sensitive polarimeter (uncorrected). Optical rotations were measured on a BRUKER DRX 400 system with TMS as an internal standard. The 31P NMR spectra were recorded on a BRUKER DRX 400 system with 85% phosphoric acid as the external standard. The \( \text{H} \) NMR spectra were recorded on a BRUKER DRX 400 system with CDCl 3 as an internal standard. The 13C NMR spectra were recorded on a BRUKER DRX 400 system with TMS as an internal standard. The percentage of e.e. were determined by HPLC (Agilent 1100 series) analysis using a chiral column. All experiments were carried out under an argon atmosphere. All solvents were dried using standard procedures.

2.2. Synthesis of ferrocenylphosphine-imine ligands

2.2.1. Synthesis of \((R,S)_2\)-\((3\text{-nitrobenzylidene})-1-(S)\text{-}(2\text{-phenylthio})\text{ferroceny}l\text{ethylamine }[\text{(RS}_2)_2\text{-}2\)]

To a solution of \((R,S)_2\)-PPFNH 2 (413 mg, 1.0 mmol) in ethanol (10.0 ml) were added 3-nitrobenzaldehyde (120 mg, 1.0 mmol) and anhydrous MgSO 4 (200 mg). The reaction mixture was then heated to reflux. After the reaction was complete (detected by TLC after 24 h), the reaction mixture was diluted with CH 2 Cl 2:CH 3 OH (10:2). 1H NMR measurements were carried out on a BRUKER DRX 400 system with TMS as an internal standard. The 31P NMR spectra were recorded on a BRUKER DRX 400 system with 85% phosphoric acid as the external standard. The percentage of e.e. were determined by HPLC (Agilent 1100 series) analysis using a chiral column. All experiments were carried out under an argon atmosphere. All solvents were dried using standard procedures.

2.2.2. Synthesis of \((S,S)_2\)-\((3\text{-nitrobenzylidene})-1-(S)\text{-}(2\text{-phenylthio})\text{ferroceny}l\text{ethylamine }[\text{(SS}_2)_2\text{-}4\)]

Ferrocenylphosphine-imine \((S,S)_2\)-1b was prepared as a foam solid in a way similar to that described for \((R,S)_2\)-1f except for using \((S,S)_2\)-PPFNH 2 instead of \((R,S)_2\)-PPFNH 2 , 3-nitrobenzaldehyde instead of 3-methylbenzaldehyde. [\(\alpha\)D] 25 = -49.8 (c 0.31, CH 2 Cl 2 ); \(\text{H} \) NMR (DMSO-d 6 ) \(\delta\) 2.16 (d, \(J = 6.4 \text{ Hz}, 3 \text{H})

2.2.3. Synthesis of \((R,S)_2\)-\((3\text{-nitrobenzylidene})-1-(S)\text{-}(2\text{-phenylthio})\text{ferroceny}l\text{ethylamine }[\text{(RS}_2)_2\text{-}3\)]

Ferrocenylphosphine-imine \((R,S)_2\)-3b was prepared as a foam solid in a way similar to that described for...

2.3.1. Synthesis of (R)-1-[(S)-2-(phenylthio)ferrocenyl]-ethylyamine ([RS]p-10)

To a solution of (R)-N,N-dimethyl-1-[(S)-2-(phenylthio)ferrocenyl]ethylamine 8 (3.65 g, 10 mmol) in 25 ml of CH2Cl2 at 0 °C was dropwise added MeI (1.25 ml, 2.84 g, 20 mmol). After the addition was complete, the solution was allowed to warm slowly to room temperature. After the reaction was complete (detected by TLC), all of the volatiles were removed under reduced pressure to afford 4.18 g (94.9% yield) of ammonium salt 9. To ammonium salt 9 (1.40 g, 2.68 mmol) was added a solution of 10 ml of 25% aqueous NH3 in 20 ml of CH3CN (8.0 ml). The mixture was then placed in a 100 ml autoclave and heated at 70-80 °C overnight. The mixture was diluted with 10 ml of CH2Cl2, and then all of the volatiles were removed under reduced pressure. The resulting residue was purified by column chromatography on a silica gel column modified with 2.0% of Et3N (eluted by hexanes:ethyl acetate:Et3N, 10:1:0.1) to afford 0.65 g (72.0% yield) of 3-methylbenzaldehyde. mp 137-138 °C; [α]D25 = -468 (c 0.26, CHCl3); 1H NMR (DMSO-d6) δ 1.60 (d, J = 6.4 Hz, 3H); 3.64 (s, 1H), 4.41 (s, 1H), 4.71 (s, 1H), 4.90-4.92 (m, 1H), 6.62-6.66 (m, 1H), 6.79-6.89 (m, 4H), 7.36-7.38 (m, 5H), 8.32 (s, 3H), 8.74 (s, 1H); 13C NMR δ = -23.1. HRMS calculated for C19H16FeO2P: 348.0751, found 348.0745.

2.4. General procedure for Pd-catalyzed asymmetric allylic alkylation of cycloalkenyl esters 5

A solution of [Pd(η3-C5H5)Cl]2 (3.7 mg, 0.01 mmol) and chiral ferrocenylphosphine-imine 1-3 or sulfur-imine 4 (0.025 mmol) in toluene (1.5 ml) was stirred at room temperature for 1 h under argon atmosphere. To this Pd-catalyst was added cycloalkenyl esters 5 (0.50 mmol) in toluene (1.5 ml), followed by dimethyl maleate (170 ul, 1.5 mmol) or diethyl methylmalonate (260 ul, 1.5 mmol), NaO-bis(trimethylsilyl)acetamide (BSA, 0.37 ml, 1.5 mmol), and a catalytic amount of LiOAc (0.01 mmol) sequentially. After stirring for 24 h at room temperature, the reaction mixture was quenched with saturated aqueous NH4Cl solution and diluted with CH2Cl2. The organic layer was separated, dried over MgSO4, and concentrated under reduced pressure. The residue was purified by column chromatography on a silica gel column (eluted by hexanes:ethyl acetate, 2011) to afford the pure product 7, e.e.-value for 7 was determined by GC (B-390 stationary capillary column). The absolute configuration was determined by the specific rotation with a literature value [9].

3. Results and discussion

3.1. Substituent effect of ferrocenylphosphine-imine ligands on the palladium-catalyzed asymmetric allylic alkylation of cyclohexenyl acetate 5a with dimethyl maleonate 6a

Initially, the substituent effect of ferrocenylphosphine-imine ligands on the Pd-catalyzed asymmetric allylic alkylation of cyclohexenyl acetate 5a with dimethyl maleonate 6a was examined (Eq. (1)). The reaction was carried out in toluene at room temperature in the presence of 2.0 mol% of [Pd(η3-C5H5)Cl]2, 5.0 mol% of chiral ligand, and a mixture of NaO-bis(trimethylsilyl)acetamide and 2.0 mol% of potassium acetate. The results were summarized in Table 1. The data indicated that the substituent in ferrocenophosphine-imine skeleton strongly affected the catalytic activity and enantioselectivity. Firstly, the effect of substituent in aryl ring was investigated (entries 1–7). The position of the substituent in phenyl ring had great effect in the catalytic reaction, and ligand with a meta-substituent tended to exhibit better enantioselectivity (entries 1–3). Thus, ligand 1a with an ortho-NO2 substituent gave the allylic alkylation product with only 32% yield and 59% e.e. (entry 1). However, if the NO2 group was in the catalytic reaction, and ligand with a meta-substituent tended to exhibit better enantioselectivity (entries 1–3).
gave allylic product with 81% yield and 83% e.e. (entry 2). Comparing to ligand 1b, ligand 1c with para-NO2 group exhibited the slightly lower enantioselectivity and catalytic activity (entry 3 versus entry 2). Changing the substituent in meta-position of phenyl ring resulted in the dramatic change of the reactivity and enantioselectivity, and all of the meta-substituted ligands 1d–1g gave the allylic product with lower enantioselectivity than the corresponding meta-NO2 substituted analogue (entries 4–7 versus entry 2). We next investigated the influence of substituent in benzylidene and ferrocenylmethyl position on the catalytic reaction, and found that introducing an ethyl group into ferrocenylmethyl position or introducing a methyl group into benzylidene position resulted in the remarkable increase of the catalytic activity and the observable decrease of the enantioselectivity (entries 8–10). However, a phenyl group in ferrocenylmethyl position caused the dramatic decrease of the activity and enantioselectivity (entry 11). Due to the good result obtained by the use of 1b with a meta-NO2 substituent, we then speculated that ligand 3 with two electron-withdrawing substituents was perhaps more effective ligands for this reaction. However, the results were proved to be very discouraged. Using 3,5-dinitro substituted ligand 3b, no allylic alkylation product was obtained (entry 13), while 3,5-bis(trifluoromethyl) substituted ligand 3a only gave the allylic product in <10% yield with 73% e.e. (entry 12). The absolute configuration of product 7a from these reactions was proven to be R by comparing the specific rotation with a literature value [9].

In order to investigate the diastereomeric effect of ferrocenylphosphate-imine ligands in the catalytic reaction, (S,S)-1b was synthesized and applied to the model reaction. Comparing to its (R,R)-analogue, (S,S)-1b gave the allylic product with lower yield and enantioselectivity but having the same configuration (entry 14 versus entry 2). This result suggested that (R)-central chirality and (S)-planar chirality in these ferrocenylphosphate-imine ligands was matched for this reaction.

### 3.2. Ferrocenylsulfur-imine ligand for the palladium-catalyzed asymmetric alkylation of cyclohexenyl acetate with dimethyl malonate

The easy derivatization of the ferrocene skeleton stimulated us to synthesize ferrocenylsulfur-imine analogues to make a comparison between P-imine and S-imine in the catalytic activity. Ferrocenylsulfur-imine ligand 4 was easily synthesized according to the procedure outlined in Scheme 1. The initial step in the synthesis involved the methylation of (R)-(N,N-dimethyl-1-[(S)-2-(phenylthio)ferrocenyl]ethylamine 8 with MeI to generate an ammonium salt 9 [88]. Subsequent treatment of ammonium salt 9 with NH3 gave (R)-1-[(S)-2-(phenylthio)ferrocenyl]ethylamine 10 in 72.0% yield [10]. Treatment of 10 with 3-nitrobenzaldehyde in ethanol in the presence of MgSO4 at refluxing temperature gave S-imine 4 in 66.4% yield. The ferrocenylsulfur-imine 4 was then applied to the palladium-catalyzed asymmetric allylic alkylation of cyclohexenyl acetate 5a under the above-described conditions. Comparing to the corresponding phosphate-imine analogue, the rate of reaction intervened by sulfur-imine 4 was very slow, even after 7 days, only 32% yield of allylic product was obtained, although a good enantioselectivity (82% e.e.) was achieved.
Table 2
Pd-catalyzed asymmetric alkylation of cycloalkenyl esters using ferrocenylphosphine-imine ligand 1b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Nucleophile</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yield (%) b</th>
<th>% e.e. d (Configuration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>6a</td>
<td>BSA</td>
<td>CsOAc</td>
<td>Toluene</td>
<td>25</td>
<td>91 (R)</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td>6a</td>
<td>BSA</td>
<td>KOAc</td>
<td>Toluene</td>
<td>25</td>
<td>81 (R)</td>
</tr>
<tr>
<td>3</td>
<td>5a</td>
<td>6a</td>
<td>BSA</td>
<td>NaOAc</td>
<td>Toluene</td>
<td>25</td>
<td>94 (R)</td>
</tr>
<tr>
<td>4</td>
<td>5a</td>
<td>6a</td>
<td>BSA</td>
<td>LiOAc</td>
<td>Toluene</td>
<td>25</td>
<td>96 (R)</td>
</tr>
<tr>
<td>5</td>
<td>5a</td>
<td>6a</td>
<td>BSA</td>
<td>LiOAc</td>
<td>CH2Cl2</td>
<td>25</td>
<td>90 (R)</td>
</tr>
<tr>
<td>6</td>
<td>5a</td>
<td>6a</td>
<td>BSA</td>
<td>LiOAc</td>
<td>Ether</td>
<td>25</td>
<td>90 (R)</td>
</tr>
<tr>
<td>7</td>
<td>5a</td>
<td>6a</td>
<td>BSA</td>
<td>LiOAc</td>
<td>THF</td>
<td>25</td>
<td>97 (R)</td>
</tr>
<tr>
<td>8</td>
<td>5a</td>
<td>6a</td>
<td>BSA</td>
<td>LiOAc</td>
<td>Toluene</td>
<td>25</td>
<td>76 (R)</td>
</tr>
<tr>
<td>9</td>
<td>5a</td>
<td>6a</td>
<td>BSA</td>
<td>LiOAc</td>
<td>Toluene</td>
<td>10</td>
<td>91 (R)</td>
</tr>
<tr>
<td>10</td>
<td>5a</td>
<td>6a</td>
<td>BSA</td>
<td>LiOAc</td>
<td>Toluene</td>
<td>0</td>
<td>47 (R)</td>
</tr>
<tr>
<td>11</td>
<td>5a</td>
<td>6b</td>
<td>BSA</td>
<td>LiOAc</td>
<td>Toluene</td>
<td>25</td>
<td>78 (R)</td>
</tr>
<tr>
<td>12</td>
<td>5c</td>
<td>6a</td>
<td>BSA</td>
<td>LiOAc</td>
<td>Toluene</td>
<td>25</td>
<td>79 (R)</td>
</tr>
<tr>
<td>13</td>
<td>5d</td>
<td>6a</td>
<td>BSA</td>
<td>LiOAc</td>
<td>Toluene</td>
<td>25</td>
<td>95 (R)</td>
</tr>
</tbody>
</table>

a The reactions were carried out in the presence of 2.0 mol% \([\text{Pd}(\text{H}_2\text{C}3\text{H}_5)\text{Cl}]_2\), 5.0 mol% of chiral ligand, 3.0 eq. of dimethyl malonate or diethyl methylmalonate, 3.0 eq. of BSA and 2.0 mol% of metal acetate at room temperature for 24 h.
b Isolated yields.
c Determined by GC analysis using a \(-390°C\) stationary capillary column.
d The R-conformation was confirmed by comparing the specific rotation with a literature value [9].
e The reaction was carried out for 48 h.

3.3. Pd-catalyzed asymmetric allylic alkylation of cycloalkenyl esters by the use of (R,S)-1b

The above results revealed that the most stereoselective ligand was ferrocenylphosphine-imine 1b with a nitro group in meta-position of phenyl ring. We then used this ligand to carry out the following research. Optimization of the reaction conditions was first performed, and the results were summarized in Table 2. The metal acetate had important influence in the catalytic reaction. Using CsOAc as the additive gave the allylic product with slightly lower enantioselectivity but higher yield comparing to that using KOAc (entry 1 versus entry 2). Upon use of NaOAc or LiOAc instead of KOAc, the yield increased observably and the enantioselectivity was raised to 86% e.e. (entries 3 and 4). The effect of solvents on this reaction was also investigated and a significant variation in the catalytic activity was observed. Using CH2Cl2 as solvent, the reaction gave the product with the similar reactivity but lower enantioselectivity to that using toluene as solvent (entry 5). However, using Et2O as solvent slowed down the reaction rate dramatically, only 63% yield with 71% e.e. of allylic product was obtained (entry 6). THF proved to be an inferior solvent for this reaction. When the reaction carried out in this solvent, only 23% yield and 73% e.e. of allylic product was obtained (entry 7). Replacing acetate 5a with pivalate 5b as substrate resulted in a slight increase of enantioselectivity to 89% e.e. and a marked drop of yield to 76% (entry 8). When the reaction temperature was lowered to 10°C, an increase of the enantioselectivity to 90% e.e. was obtained but longer time was required to complete the reaction (entry 9). Lowering the reaction temperature to 0°C could further improve the enantioselectivity to 91% e.e. but decrease the reaction rate dramatically (entry 10).

To extend the validity of ferrocenylphosphine-imine ligand in this enantioselective reaction, the applications of 1b for other substrates or nucleophiles were then examined. The cyclohexenyl acetate 5a underwent alkylation with diethyl methylmalonate 6b to give allylic product 7b in 78% yield and 81% e.e. (entry 11). The alkylation of cyclohexenyl pivalate 5c gave 82% ee of 7c in 89% yield (entry 12), and an e.e.-value of 89% e.e. with 95% yield was observed in the alkylation of the cycloheptenyl acetate 5d (entry 13).

\[
\text{R}^1\text{CO}_2\text{R}^2 + [\text{Pd}(\text{H}_2\text{C}3\text{H}_5)\text{Cl}]_2 \rightarrow \text{R}^1\text{CO}_2\text{R}^2 + \text{CO}_2\text{R}^2
\]

5a: n = 1, R = CH3;
5b: n = 1, R = CH2CH3;
5c: n = 0, R = CH3;
5d: n = 2, R = CH3;
6a: R1 = H, R2 = Me;
6b: R1 = H, R2 = Et;
7a: n = 1, R1 = H, R2 = Me;
7b: n = 1, R1 = Me, R2 = Et;
7c: n = 0, R1 = H, R2 = Me;
7d: n = 2, R1 = H, R2 = Me;

(2)
4. Summary

In summary, we have reported the new use of ferrocenyl-phosphine-imine ligands 1-3 and sulfur-imine 4 in the asymmetric catalysis and found ligand 1b with a nitro group in meta-position of phenyl ring was effective for Pd-catalyzed asymmetric allylic alkylation of acyclic and cyclic substrates. In this paper, an e.e.-value of 91% for cyclic alkylation product was achieved.

Acknowledgements

The authors would like to thank the National Natural Science Foundation of China for financial support of this work (29933050).

References

(m) Y. Hamada, K. Sakaguchi, K. Hatano, O. Han, Tetrahedron Lett. 42 (2001) 1297;