Camphane-based phosphino-carboxamide ligands as P,O-chelates in Pd-catalyzed enantioselective allylic alkylation

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A B S T R A C T

A practical synthesis for new chiral phosphino-carboxamide ligands has been accomplished. These ligands were effectively modified both on the amide moiety and the phosphine atom. Application of these ligands in the Pd-catalyzed allylic alkylation of \((E)-1,3\)-diphenyl-2-propenyl acetate proceeded with excellent conversions and with ee’s of up to 92%. The use of a camphane based chiral auxiliary was found to be crucial for the asymmetric induction.

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1. Introduction

Phosphino-carboxamides have emerged as a specific class of molecules, finding manifold use in various fields, particularly in coordination chemistry, biomedical sciences, and in catalysis. 1 The structure of phosphino-carboxamide ligands bearing the combination of weak and strong donor heteroatom pairs enables them to bind to almost any metal, thus generating electronic asymmetry. 2 The different donor moieties also allow independent modifications, thus ensuring the possibility for unlimited variations. 1 Another privilege is their stability and the ease with which they can be accessed.

Despite all of the advantages presented above and the unambiguous proof that the P,O-mode of coordination with the palladium center gives catalytically active complex (Fig. 1. I), 3a–c the application of amido-phosphine ligands in the asymmetric allylic alkylation (AAA) has been rarely studied. 3 Recently, we accomplished the practical synthesis of planar chiral phosphino-ferrocenecarboxamide ligands via highly diastereoselective amide-directed ortho-metallation (Fig. 1. II). 4 Camphane-based skeletons, available inexpensively through the ‘chiral pool’, were found to be excellent auxiliaries for the diastereoselective deprotonation of ferrocene. The synthesized (+)-camphor derived ligands, possessing both planar and central chirality (Fig. 1. II), proved to be effective for the AAA. 4b We were thus inspired to examine which of the two chiral elements is the major contributor to asymmetric induction in the catalytic process. The synthesis of analogous structures lacking planar chirality was a logical extension of our investigations (Fig. 1. III). Herein, we report a further development of the camphane-based chiral template for the design of phosphino-carboxamide ligands.

2. Results and discussion

Our aim was to obtain the target structures using simple and effective synthetic procedures. The construction of the required phosphino-carboxamides was performed in three straightforward steps starting from readily available (+)-camphor derived aminooalcohols 5 and amines. 6 Condensation of (2S)-(−)-3-exo-aminosoborneol with 2-bromobenzoyl chloride afforded benzamide 1 (Scheme 1). 7 The corresponding tertiary amides 2a–c were achieved by N-alkylation and a simultaneous O-alkylation with NaH as the deprotonating reagent followed by the addition of an

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appropriate haloalkane. In addition to the ethyl group 2a, we also introduced butyl 2b and benzyl groups 2c in order to investigate the influence of their steric effects on the undertaken ligand structure/activity study. A consecutive brom-lithium exchange followed by reaction with ClPPh2 gave a set of the desired phosphine-carboxamide ligands 3a–c. Changing the electrophile to ClPCy2 afforded 3d (Scheme 1). The latter was selected as an electronically and sterically varied analogue, opening up the possibility for additional tuning.

Another aspect of our work was the synthesis of structures containing a bulky iPr-group on the amide nitrogen. The tertiary amide 5 was synthesized following the already described procedure, starting from secondary amine 4, which was prepared by reductive amination with acetone. Subsequent alkylation of the OH-group with MeI gave 6. The Br–Li exchange/electrophile quench sequence furnished ligand 7 (Scheme 2). Attempts to synthesize the O-ethyl analogue of 6 were unsuccessful. Over the course of the reaction, decomposition of the starting amide 5 was observed, probably due to steric hindrance.

Further investigation of the influence of the camphane chiral element forced us to synthesize ligands based on the endo-amino-diastereoisomer of 3-aminoborneol. The formation of the amide linkage was accomplished by the reaction of (2R)-3-endo-amino-borneol in an analogous fashion to the previous series 8 (Scheme 3). The N,O-bis-ethylated compound 9 and the phosphine-amide 10 were synthesized following the above described protocol.

The design of phosphino-carboxamides derived from isobornylamine and bornylamine as the source of chirality, was considered as an alternative to the above described structures. The reaction with 2-bromobenzoyl chloride afforded the corresponding amides 11 and 14 in excellent yields (Scheme 4). Conversion to the tertiary amides 12 and 15 was accomplished by an ethylation protocol. The lithiation-quench sequence resulted in the desired 13 and 16. In all cases, the oxidation of phosphines to the corresponding phosphine oxides was minimized by using a non-aqueous work-up procedure.

![Scheme 1](image1)

![Scheme 2](image2)

![Scheme 3](image3)

![Scheme 4](image4)

The chiral phosphine-amide ligands were tested in the Pd-catalyzed AAA of racemic (E)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate using [Pd(η^3-C_5H_5)Cl]_2 as the palladium source (Scheme 5). The nucleophile was generated in situ by Trost’s procedure using N,O-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of alkali metal acetate.12

Initially, the reaction was performed with ligand 3a, as a representative, using BSA/KOAc in toluene.13 Under these conditions the alkylated product was isolated in excellent yield and with an enantiomeric excess of 76% in favor of the (∈)-enantiomer (Table 1, entry 1). By using LiOAc as a base additive, the enantioselectivity increased to 91% ee (entry 2). Upon testing different solvents, it was found that the selectivity in Et_2O remains high (91% ee, entry 3) but slightly decreased in THF and CH_2CN (entries 4 and 5). Surveying the reaction conditions we selected LiOAc as the base additive and Et_2O as the solvent to estimate the whole series of ligands.  

Table 1 Palladium-catalyzed AAA of racemic (E)-1,3-diphenyl-2-propenyl acetate with dimethylmalonate

<table>
<thead>
<tr>
<th>Entry</th>
<th>L^+</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>PhCH_3</td>
<td>KOAc</td>
<td>99</td>
<td>76 (R)</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>PhCH_3</td>
<td>LiOAc</td>
<td>99</td>
<td>91 (R)</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>THF</td>
<td>LiOAc</td>
<td>96</td>
<td>90 (R)</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>CH_2CN</td>
<td>LiOAc</td>
<td>99</td>
<td>89 (R)</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>Et_2O</td>
<td>LiOAc</td>
<td>99</td>
<td>92 (R)</td>
</tr>
<tr>
<td>6</td>
<td>3c</td>
<td>CH_2CN</td>
<td>LiOAc</td>
<td>99</td>
<td>91 (R)</td>
</tr>
<tr>
<td>7</td>
<td>3d</td>
<td>Et_2O</td>
<td>LiOAc</td>
<td>99</td>
<td>91 (R)</td>
</tr>
<tr>
<td>8</td>
<td>3d</td>
<td>Et_2O</td>
<td>LiOAc</td>
<td>99</td>
<td>54 (S)</td>
</tr>
<tr>
<td>9</td>
<td>3t</td>
<td>Et_2O</td>
<td>LiOAc</td>
<td>99</td>
<td>68 (S)</td>
</tr>
<tr>
<td>10</td>
<td>3t</td>
<td>Et_2O</td>
<td>LiOAc</td>
<td>99</td>
<td>30 (R)</td>
</tr>
<tr>
<td>11</td>
<td>13</td>
<td>Et_2O</td>
<td>LiOAc</td>
<td>99</td>
<td>30 (R)</td>
</tr>
<tr>
<td>12</td>
<td>16</td>
<td>Et_2O</td>
<td>LiOAc</td>
<td>99</td>
<td>0</td>
</tr>
</tbody>
</table>

a Reaction conditions: 1 equiv of substrate, 0.03 equiv of [Pd(η^3-C_5H_5)Cl]_2 (5 equiv). The mixture was stirred for 30 min at rt and then RX (5 equiv) (RX = EtI, nBuBr, BnBr) was added. The reaction was stirred at rt until the starting material was completely consumed (TLC). Next, it was cooled to 0 °C and treated sat. aq. NH_4Cl. The organic phase was separated and the aqueous phase was extracted three times with EtO. The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel. Data for 2-bromo-N-(15,28,35,48)-3-ethoxy-4,7,7-trimethylbicyclo[2.2.2]hept-2-enylamide 2a: mp 82–84 °C (from EtOH).

b Isolated pure products after column chromatography.

c Enantiomeric excess was determined by HPLC analysis (Chiralpak IA chiral column). The absolute configuration was determined by comparison of the specific rotation with the literature.11

Acknowledgement

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References


8. A typical procedure for the preparation of tertiary amides 2a–c was as follows: In DMF at 0 °C was added NaH (5 equiv.). The mixture was stirred for 30 min at rt and then RX (5 equiv) (RX = EtI, nBuBr, BnBr) was added. The reaction was stirred at rt until the starting material was completely consumed (TLC). Next, it was cooled to 0 °C and treated sat. aq. NH_4Cl. The organic phase was separated and the aqueous phase was extracted three times with EtO. The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel. Data for 2-bromo-N-(15,28,35,48)-3-ethoxy-4,7,7-trimethylbicyclo[2.2.2]hept-2-enylamide 2a: mp 82–84 °C (from EtOH).
9. Typical procedure for the preparation of ligands 3a–d, 7, 10, 13, and 16: n-Butyllithium (1.2 equiv) was added to a solution of benzamides 2a–c, 6, 9, 12, and 15 (1 equiv) in THF at −78 °C. After stirring for 30 min Ph2PCl or Cy2PCl (1.5 equiv.) was added. The reaction was stirred at −78 °C for 1.5 h. Next, it was poured quickly through a pad of Celite. The flask and the Celite were washed with ether, and the filtrate was concentrated under reduced pressure. The resulting sticky oil was purified by flash column chromatography. Data for 2-(diphenylphosphino)-N-((1S,2R,3S,4R)-3-ethoxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-N-ethylbenzamide 3a: mp >64 °C decomp. ½ 20 D ¼+ 58:8 (c 0.148, CHCl3). 1H NMR (CDCl3, 600 MHz) δ = 0.82 (s, 3H, 9-H), 0.94 (s, 3H, OCH2CH3), 1.09 (t, JH,H = 7.0 Hz, 3H, NCH2CH3), 1.13–1.7 (m, 1H, 6-Hendo), 1.20–1.25 (m, 1H, 5-Hendo), 1.46–1.50 (m, 1H, 6-Hexo), 1.75–1.79 (m, 1H, 5-Hexo), 2.06 (d, JH,H = 4.0 Hz, 1H, 4-H), 3.22–3.26 (m, 1H, NCH2CH3), 3.36–3.39 (m, 1H, OCH2CH3), 3.43 (dq, JH,H = 15.0, 7.2 Hz, 1H, OCH2CH3), 3.52 (d, JH,H = 7.0 Hz, 1H, 2-H), 4.08 (d, JH,H = 7.0 Hz, 1H, 3-H), 7.20 (dd, JH,H = 7.4 Hz, 1H, arom.), 7.27–7.30 (m, 11H, arom.), 7.36 (t, JH,H = 7.4 Hz, 1H, arom.). 7.48 (dd, JH,H = 7.2, 3.1 Hz, 1H, arom.) ppm. 13C NMR (CDCl3, 150.9 MHz) δ = 11.67 (C-10), 15.85 (OCH2CH3), 16.60 (NCH2CH3), 21.29 (C-9), 21.52 (C-8), 27.58 (C-5), 32.28 (C-6), 42.96 (NCH2CH3), 45.90 (C-4), 47.64 (C-7), 49.47 (C-1), 62.62 (C-3), 89.56 (C-2), 127.85 (CDC), 127.93 (1 arom. CH), 128.06 (d, J31P,13C = 6.6 Hz, 2arom. CH), 128.28 (2arom. CH), 128.30 (d, J31P,13C = 8.2 Hz, 2arom. CH), 128.73 (2arom. CH), 133.20 (d, J31P,13C = 17.8 Hz, 2arom. CH), 133.65 (d, J31P,13C = 19.7 Hz, 2arom. CH), 135.49 (d, J31P,13C = 2.9 Hz, 1arom. CH), 137.44 (d, J31P,13C = 10.1 Hz, 1arom. C), 138.96 (d, J31P,13C = 12.7 Hz, 1arom. C), 145.06 (d, J31P,13C = 34.1 Hz, CPh2), 172.45 (CO) ppm. 31P NMR (CDCl3, 242.92 MHz): δ = −13.14 (s) ppm. MS (Cl m/z (rel. int.) = 514 (100) [M+H]+, C33H40NO2P (513.65): calcd. C 77.16, H 7.85, N 2.73, found C 77.24, H 7.79, N 2.75.

