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Phosphino-carboxamide hybrid ligands with a camphane scaffold for Pd-catalyzed asymmetric allylic alkylation

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Dedicated to Acad. Dimiter Ivanov on the occasion of his 120th birth anniversary

Condensation of *ortho*-diphenylphosphino benzoic acid with 3-*exo*-aminoisoborneol, isobornylamine and bornylamine afforded three new ligands, which were evaluated in the palladium-catalyzed allylic alkylation of (*E*)-1,3-diphenyl-2-propen-1-yl acetate. The catalytic performance strongly depended on the system used to generate the dimethyl malonate anion. The best enantioselectivity was achieved with the 3-*exo*-aminoisoborneol derived ligand when Cs_2CO_3 was used as a base. The isobornylamine and bornylamine derived ligands gave generally low enantioselectivities.

Key words: (+)-camphor, phosphino-carboxamides, P,O-ligands, allylic substitution

INTRODUCTION

Palladium-catalyzed asymmetric allylic alkylation has proven to be a powerful method for the preparation of a wide variety of chiral compounds and the rapid assembly of complex molecular architecture from simple starting materials [1]. While many types of catalyst systems have been successfully employed with certain systems, diphenylphosphino benzoic acid (DPPBA) based ligands have found use over a broad range of substrate classes [2].

Over the years, there has been a steady interest in the synthesis and application of simple, hybrid, hemilabile, P,O-type ligands [3]. Among the latter compounds, phosphino-carboxamides evolved into a specific class of structurally diverse molecules, bearing the combination of weak and strong donor heteroatom pairs, which enables them to bind to almost any metal, generating electronic asymmetry [4]. Another privilege is their stability and the ease with which they could be accessed. The advantages presented above and the unambiguous proof that P,O-mode of coordination with palladium center is giving catalytically active complex (Fig. 1, **I**) [5-7] justify the efforts to the development and application of amido-phosphine ligands in asymmetric allylic alkylation (AAA) [8-17].

A number of simple phosphino-carboxamides have been studied. For example, Marinho *et al.* [18, 19] have prepared a series of phosphino-amide ligands bearing a free hydroxyl function (Fig. 1, **II**).

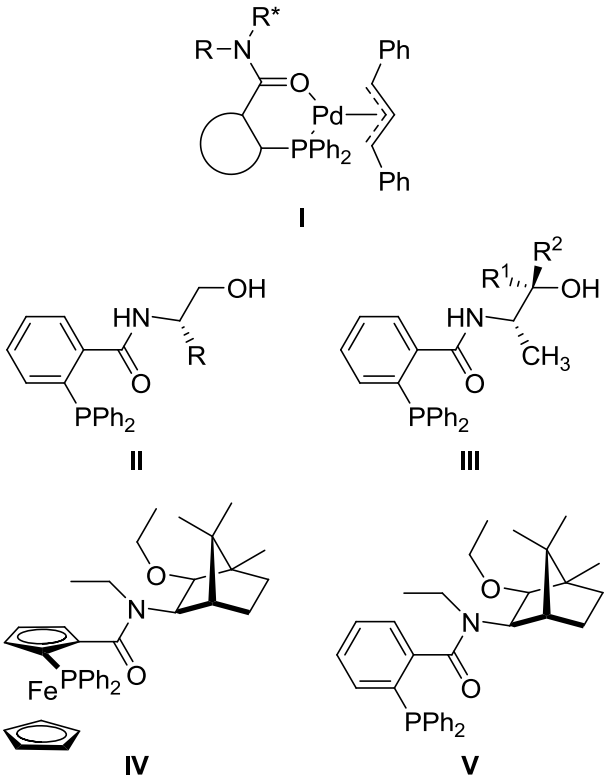

Fig. 1. Phosphino-carboxamides as hybrid, hemilabile, P,O-type ligands.

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The application of the ligands in AAA resulted in moderate enantioselectivities (up to 62% ee) and the authors hypothesized that the free-OH group was also coordinating with Pd, resulting in a deactivation of the latter. Mahadik *et al*. [20-22] reported the synthesis and application of norephedrine and pseudonorephedrine analogues (Fig. 1, **III**) that furnished slightly better enantioselectivities (up to 75% ee). Noteworthy is that in both cases the ligands are secondary amides.

Recently, we have accomplished practical synthesis of camphane based planar chiral diphenylphosphino-ferrocenecarboxamide (Fig. 1, **IV**) and diphenylphosphino-benzenecarboxamide ligands (Fig. 1, **V**) [23-25]. Application of these ligands in the Pd-catalyzed AAA as P,O-chelates proceeded with promising degree of enantio-selectivity (up to 92%) [25]. The use of camphane based chiral auxiliary proved to be the major contributor to the asymmetric induction in the catalytic process.

Encouraged by these results, we dedicated our efforts toward the synthesis of secondary benzenecarboxamides. A switch of tertiary to secondary amides gave us the opportunity to investigate the influence of the amide hydrogen in the catalytic process. Furthermore, examination of the effect of the OH-function on the ligand structure/activity study, made us interested in the synthesis of secondary amide analogue of **V** (Fig 1.), bearing a free hydroxyl group. Herein, we report a practical synthesis of new camphor derived phosphinobenzenecarboxamide ligands and their application in Pd-catalyzed asymmetric allylic alkylation.

EXPERIMENTAL

Reagents were commercial grade and used without further purification. CH_2Cl_2 was distilled from CaH_2. THF and Et_2O were distilled over sodium/benzophenone. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with Merck Kieselgel 60 F_{254} 0.25 mm (Merck). Flash column chromatography was carried out using Silica Gel 60 230-400 mesh (Fluka). Melting points of the compounds were determined using "Electrothermal" MEL-TEMP apparatus (uncorrected). Optical rotations ($[\alpha]_D^{20}$) were measured on Perkin–Elmer 241 polarimeter. The NMR spectra were recorded on a Bruker Avance II+ 600 (600.13 for ^{1}H NMR, 150.92 MHz for ^{13}C NMR and 242.92 MHz for ^{31}P NMR) spectrometer with TMS (85% H_3PO_4 for ^{31}P) as internal standard for chemical shifts (δ, ppm). ^{1}H and ^{13}C NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration and identification. The assignment of the ^{1}H and ^{13}C NMR spectra was made on the basis of DEPT, COSY, HSQC, HMBC and NOESY experiments. Mass spectra (MS) were recorded on a Thermo Scientific DFS (High Resolution Double Focusing Magnetic Sector) mass spectrometer (Bremen, Germany) and are reported as fragmentation in m/z with relative intensities (%) in parentheses. The high performance liquid chromatography (HPLC) separations were performed with an Agilent 1100 System fitted with diode array detector and manual injector with a 20 μl injection loop Chiralpak IA, 250x4.6mm particle size 5 μm, and Chiralpak IC 250x4.6mm, particle size 5 μm stainless-steel columns from Chiral Technologies Europe LTD were used. The analyses were performed at 25°C. Elemental analyses were performed by Microanalytical Service Laboratory of Faculty of Chemistry, University of Sofia, using Vario EL3 CHNS(O) and Microanalytical service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Science.

*General Procedure for the preparation of the amides **2**, **4** and **6** (GP)*

1-Hydroxybenzotriazole (HOBt) (1.1 equiv) and 2-diphenylphosphinobenzoic acid (1 equiv) were suspended in dichloromethane, and the mixture was stirred for 5 min. Then, *N*-[3-(dimethylamino) propyl]-*N*-ethylcarbodiimide (EDC) (1.1 equiv) was added, followed by the appropriate amine, diluted with a small amount of dichloromethane (1.1 equiv). Stirring was continued for 24 h at room temperature until the starting material was completely consumed (TLC). Then the mixture was directly subjected to flash column chromatography.

*Synthesis of 2-(diphenylphosphino)-N-((1S,2R,3S,4R)-3-hydroxy-4,7,7-trimethylbicyclo [2.2.1]heptan-2-yl)benzamide **2***

According to GP, a mixture of 2-diphenyl-phosphinobenzoic acid (0.100 g, 0.326 mmol), HOBt (0.049 g, 0.359 mmol), EDC (0.069 g, 0.359 mmol) and (1*R*,2*S*,3*R*,4*S*)-3-amino-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol [26] (0.061 g, 0.359 mmol) afforded after column chromatography (silica gel, CH_2Cl_2/Et_2O, 100:1) 0.127 g (85% yield) of **2** as a white solid; mp >89°C decomp. $[\alpha]^{20}_D$ +16.0 (c 0.53, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.76 (s, 3H, 9-H), 0.91 (s, 3H, 10-H), 0.97 (s, 3H, 8-H), 1.01-1.07 (m, 1H, 6-H$_{endo}$), 1.12-1.16 (m, 1H, 5-H$_{endo}$), 1.44-1.49 (m, 1H, 6-H$_{exo}$), 1.65-1.70 (m, 1H, 5-H$_{exo}$), 1.68 (d, *J* 2.3 Hz, 1H, 4-H), 2.23 (d, *J* 2.6 Hz, 1H, OH), 3.78 (dd, *J* 7.2, 3.4 Hz, 1H, 2-H),

3.80-3.83 (m, 1H, 3-H), 6.40 (d, *J* 5.9 Hz, 1H, NH), 6.98 (ddd, *J* 7.6, 4.0, 1.0 Hz, 1H, arom.), 7.27-7.31 (m, 5H, arom.), 7.32-7.34 (m, 6H, arom.), 7.37 (dt, *J* 7.5, 1.3 Hz, 1H, arom.), 7.55 (ddd, *J* 7.5, 3.8, 1.2 Hz, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 11.32 (10-C), 20.94 (8-C), 21.37 (9-C), 26.23 (5-C), 33.23 (6-C), 46.93 (7-C), 49.10 (1-C), 50.03 (4-C), 58.41 (3-C), 80.09 (2-C), 127.35 (d, $J_{P,C}$ 5.3 Hz, 1 arom. CH), 128.48 (d, $J_{P,C}$ 7.1 Hz, 2 arom. CH), 128.57 (d, $J_{P,C}$ 7.1 Hz, 2 arom. CH), 128.73 (2 arom. CH), 128.83 (1 arom. CH), 130.00 (1 arom. CH), 133.71 (d, $J_{P,C}$ 19.8 Hz, 2 arom. CH), 133.95 (d, $J_{P,C}$ 20.1 Hz, 2 arom. CH), 134.27 (1 arom.CH), 135.84 (d, $J_{P,C}$ 19.4 Hz, 2 arom. C), 136.92 (d, $J_{P,C}$ 9.8 Hz, 2 arom. C), 137.21 (d, $J_{P,C}$ 11.0 Hz, 2 arom. C), 141.95 (d, $J_{P,C}$ 26.7 Hz, 2 arom. C), 169.14 (CO) ppm. ^{31}P NMR ($CDCl_3$, 242.92 MHz): δ -10.44 (s) ppm. MS (ESI): *m*/z 458 (100, $[M+1]^+$). $C_{29}H_{32}NO_2P$ (457.54): calcd. C 76.13, H 7.05, N 3.06, found C 76.24, H 7.13, N 3.10.

*Synthesis of 2-(diphenylphosphino)-N-((1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)benzamide **4***

According to GP, a mixture of 2-diphenylphosphinobenzoic acid (0.100 g, 0.326 mmol), HOBt (0.049 g, 0.359 mmol), EDC (0.069 g, 0.359 mmol) and (1*R*,2*R*,4*R*)-1,7,7-trimethyl bicyclo-[2.2.1]heptan-2-amine [27] (0.055 g, 0.359 mmol) afforded after column chromatography (silica gel, CH_2Cl_2/Et_2O, 100:1) 0.142 g (99% yield) of **4** as a white solid; mp 73-75 °C. $[\alpha]^{20}_D$ -58.1 (c 0.74, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.67 (s, 3H, 9-H), 0.78 (s, 3H, 8-H), 0.82 (s, 3H, 10-H), 1.09-1.14 (m, 1H, 5-H$_{endo}$), 1.27-1.31 (m, 1H, 6-H$_{endo}$), 1.39-1.43 (m, 1H, 3-H$_{exo}$), 1.50-1.55 (m, 1H, 6-H$_{exo}$), 1.64-1.66 (m, 1H, 5-H$_{exo}$), 1.66 (d, *J* 4.2 Hz, 1H, 4-H), 1.77 (dd, *J* 13.3, 9.1 Hz, 1H, 3-H$_{endo}$), 4.00 (dt, *J* 9.0, 5.1 Hz, 1H, 2-H$_{endo}$), 5.89 (d, *J* 8.3 Hz, 1H, NH), 6.94 (dd, *J* 7.0, 4.0 Hz, 1H, arom.), 7.22-7.29 (m, 4H, arom.), 7.31-7.34 (m, 7H, arom.), 7.38 (dt, *J* 7.5, 1.0 Hz, 1H, arom.), 7.57 (ddd, *J* 6.6, 3.8, 0.9 Hz, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 11.76 (10-C), 20.05 (9-C), 20.19 (8-C), 26.94 (5-C), 35.82 (6-C), 38.46 (3-C), 44.77 (4-C), 47.01 (7-C), 48.63 (1-C), 57.14 (2-C), 127.81 (d, $J_{P,C}$ 5.2 Hz, 1 arom. CH), 128.50 (d, $J_{P,C}$ 7.0 Hz, 2 arom. CH), 128.65 (d, $J_{P,C}$ 7.0 Hz, 2 arom. CH), 128.70 (1 arom. CH), 128.82 (1 arom. CH), 128.86 (1 arom. CH), 129.91 (1 arom. CH), 133.76 (d, $J_{P,C}$ 20.0 Hz, 2 arom. CH), 133.85 (d, $J_{P,C}$ 20.0 Hz, 2 arom. CH), 134.21 (1 arom. CH), 135.15 (d, $J_{P,C}$ 20.0 Hz, 1 arom. C), 136.87 (d, $J_{P,C}$ 11.3 Hz, 1 arom. C), 137.11 (d, $J_{P,C}$ 11.5 Hz, 1 arom. C), 142.31 (d, $J_{P,C}$ 27.0 Hz, 1 arom. C), 168.38 (CO) ppm. ^{31}P NMR ($CDCl_3$, 242.92 MHz): δ -11.37 (s) ppm. MS (ESI): *m*/z 442 (100, $[M+1]^+$). $C_{29}H_{32}NOP$ (441.54): calcd. C 78.88, H 7.30, N 3.17, found C 78.99, H 7.42, N 3.19.

*Synthesis of 2-(diphenylphosphino)-N-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)benzamide **6***

According to GP, a mixture of 2-diphenylphosphinobenzoic acid (0.100 g, 0.326 mmol), HOBt (0.049 g, 0.359 mmol), EDC (0.069 g, 0.359 mmol) and (1*R*,2*S*,4*R*)-1,7,7-trimethyl bicycle-[2.2.1]heptan-2-amine [28] (0.055 g, 0.359 mmol) afforded after column chromatography (silica gel, CH_2Cl_2/Et_2O 100:1) 0.140 g (97% yield) of **6** as a white solid; mp 71-72 °C. $[\alpha]^{20}_D$ +10.2 (c 0.47, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.63 (dd, $J_{H,H}$ = 13.4, 4.6 Hz, 1H, 3-H$_{endo}$), 0.77 (s, 3H, 10-H), 0.82 (s, 3H, 9-H), 0.85-0.89 (m, 1H, 5-H$_{endo}$), 0.91 (s, 3H, 8-H), 1.19-1.24 (m, 2H, 6-H$_{endo}$, 6-H$_{exo}$), 1.57 (d, *J* 4.5 Hz, 1H, 4-H), 1.60-1.66 (m, 1H, 5-H$_{exo}$), 2.24-2.29 (m, 1H, 3-H$_{exo}$), 4.30-4.34 (m, 1H, 2-H$_{exo}$), 6.02 (d, *J* 7.3 Hz, 1H, NH), 6.92 (ddd, *J* 7.7, 4.1, 1.0 Hz, 1H, arom.), 7.23-7.29 (m, 4H, arom.), 7.30-7.35 (m, 7H, arom.), 7.40 (dt, *J* 7.5, 1.2 Hz, 1H, arom.), 7.65 (ddd, *J* 7.6, 3.8, 1.2 Hz, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 13.61 (10-C), 18.66 (8-C), 19.74 (9-C), 28.06 (6-C), 28.12 (5-C), 37.00 (3-C), 44.71 (4-C), 47.99 (7-C), 49.36 (1-C), 54.51 (2-C), 127.30 (d, $J_{P,C}$ 5.3 Hz, 1 arom. CH), 128.60 (d, $J_{P,C}$ 6.9 Hz, 2 arom. CH), 128.82 (1 arom. CH), 128.90 (1 arom. CH), 128.92 (1 arom. CH), 129.97 (1 arom. CH), 133.79 (d, $J_{P,C}$ 18.6 Hz, 4 arom. CH), 134.10 (1 arom. CH), 134.43 (d, $J_{P,C}$ 19.6 Hz, 1 arom. C), 136.64 (d, $J_{P,C}$ 11.0 Hz, 1 arom. C), 136.93 (d, $J_{P,C}$ 11.4 Hz, 1 arom. C), 142.52 (d, $J_{P,C}$ 27.3 Hz, 1 arom. C), 169.10 (CO) ppm. ^{31}P NMR ($CDCl_3$, 242.92 MHz): δ -11.17 (s) ppm. MS (ESI): *m*/z 442 (100, $[M+1]^+$). $C_{29}H_{32}NOP$ (441.54): calcd. C 78.88, H 7.30, N 3.17, found C 78.96, H 7.25, N 3.21.

General procedure for the palladium-catalyzed allylic alkylation

A: A mixture of chiral ligand (0.03 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (6.0 mg, 0.016 mmol), and LiOAc (0.05 mmol) in a dry solvent (3 mL) was stirred at rt in a Schlenk tube for 30 min. Then, rac- (*E*)-1,3-diphenylprop-2-en-1-yl acetate (126 mg, 0.5 mmol) was introduced followed, after stirring for another 5 min, by N,O-bis-(trimethylsilyl)acetamide (BSA; 0.37 mL, 1.5 mmol) and dimethyl malonate (0.17 mL, 1.5 mmol). The mixture was stirred at rt for 24 h, then the reaction mixture was diluted with

diethyl ether (10 mL) and washed consecutively with sat. aq. NH_4Cl and water. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 9:1).

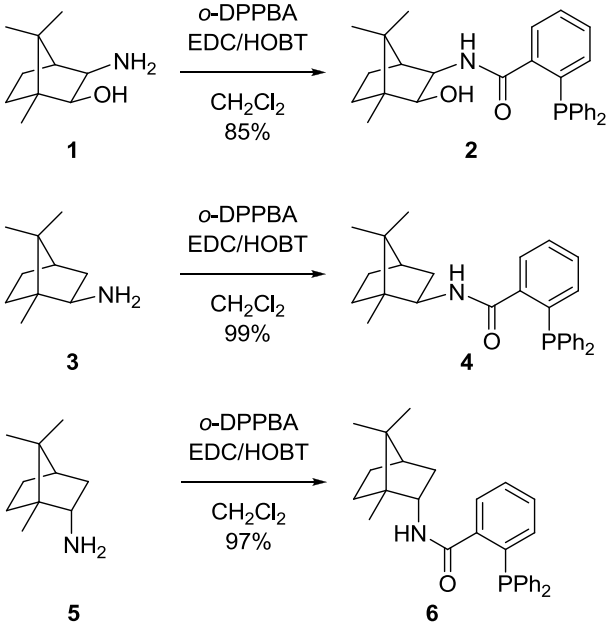
B: A mixture of chiral ligand (0.03 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (6.0 mg, 0.016 mmol), in a dry solvent (3 mL) was stirred at rt in a Schlenk tube for 30 min. Then, rac- 1,3-diphenylprop-2-en-1-yl acetate (126 mg, 0.5 mmol) was introduced followed, after stirring for another 5 min, by Cs_2CO_3 (0.326 g, 1.0 mmol) and dimethyl malonate (0.11 mL, 1.0 mmol). The mixture was stirred at rt for 24 h. The reaction was quenched with sat. aq. NH_4Cl, extracted with EtOAc (3×20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate, 9:1).

The enantioselectivity was determined by HPLC analysis with a chiral column (Chiralpak IA; hexane/*i*-PrOH, 95:5; flow rate, 0.7 mL/ min; t_R, 14.321; t_S, 17.871 min). The absolute configurations of the enantiomers were determined by comparison of the retention times with that of an authentic sample and by measurement of the optical rotation of the product.

RESULTS AND DISCUSSION

For the planned condensation reactions, readily available, 3-*exo*-aminoisoborneol [26], iso-bornylamine [27] and bornylamine [28] were selected as key (+)-camphor-derived starting compounds.

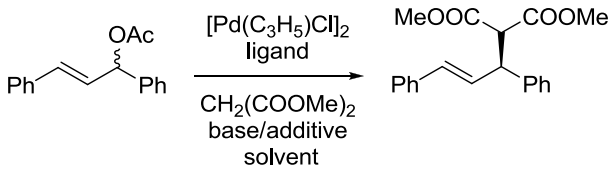
First, we synthesized the secondary amide analogue of **V** (Fig 1.), bearing a hydroxyl group on the camphane scaffold. Thus, we had the chance to exploit whether the presence of the free OH-group might serve as a third coordination site in the formation of more rigid chelates of the palladium catalyst, resulting in enhanced enantioselectivity, or will lead to a problem of deactivation of the palladium in the catalytic process [18-22]. One more aspect of our investigation was modification of the electronic properties of the amide carbonyl group as a coordination center. The desired diphenylphosphino-benzenecarboxamide ligand **2** was easily obtained by condensation of *o*-DPPBA with (2*S*)-(-)-3-*exo*-aminoisoborneol **1** in dry CH_2Cl_2 in the presence of *N*-[-3-(dimethyl amino)-propyl]-*N*'-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBT) (Scheme 1). The amide **2** was isolated by column chromatography as air stable white solid in 85% yield. The influence of the camphane chiral source was further investigated by the synthesis of diphenylphosphino-benzenecarboxamide ligands **4** and **6,** starting from isobornylamine or bornylamine, respectively. Thereby, we had the possibility to investigate how the difference in the camphor derived fragment influences the reactivity of the transition metal complexes and the asymmetric induction in the catalytic process. Moreover, the ligand structures lacking a hydroxyl function afforded an opportunity to examine additionally the effect of the latter. Formation of the amide linkage was accomplished by applying the EDC/HOBT/*o*-DPPBA coupling procedure to *exo*-bornylamine **3** and *endo*-bornylamine **5**. The desired products **4** and **6** were isolated in quantitative yields after purification (Scheme 1).



Scheme 1. Synthesis of diphenylphosphino-benzene-carboxamide ligands **2**, **4** and **6**.

In all cases the oxidation of the phosphines to the corresponding phosphine oxides was minimized by using a non-aqueous work-up procedure, subjecting the reaction mixtures directly to flash column chromatography on silica gel. The structures of the newly synthesized compounds were confirmed by 1D and 2D NMR spectra, MS data and elemental analysis.

The chiral diphenylphosphino-benzene carboxamide ligands **2**, **4** and **6** were evaluated in the palladium-catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenyl-2-propen-1-yl acetate with dimethyl malonate using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as a palladium source (Scheme 2).



Scheme 2. Pd-catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenyl-2-propen-1-yl acetate.

Initially, the reaction was performed with ligand **2** under our previously reported conditions [25]. The nucleophile was generated in situ by Trost's procedure [29] using N,O-bis(trimethylsilyl) acetamide (BSA) and a catalytic amount of LiOAc as a base additive (Table 1). The reaction carried out in Et_2O proceeded with excellent conversion but no asymmetric induction was observed (Table 1, entry 1). Performing the alkylation in THF instead of Et_2O led to enantioselectivity of 16% ee in favor of (*R*)-enantiomer (Table 1, entry 2). The best enantioselectivity of 52% ee was achieved when 2 equivalents of anhydrous cesium carbonate were employed as the base, instead of BSA/LiOAc, in CH_2Cl_2 (Table 1, entry 3). An interesting comparison can be made with the N,O-disubstituted analogue of ligand **2**. Both the reactions in Et_2O and in THF with ligand **V** (Fig. 1) proceeded with excellent enantioselectivity of 91% ee, favoring the same (*R*)-enantiomer [25]. Obviously, the presence of free-OH group greatly influences the catalytic performance, leading to substantial drop of enantioselectivity.

Applying the optimized for ligand **2** reaction conditions to the isobornylamine derived ligand **4** resulted in excellent conversion but lack of asymmetric induction (Table 1, entry 4). When a mixture of BSA and a catalytic amount of LiOAc in THF was used as the base instead of Cs_2CO_3, the enantioselectivity raised to 12% ee, favoring (*R*)-configuration of the substitution product (Table 1, entry 5). Performing the alkylation in Et_2O instead of THF did not influence the catalytic performance (13% ee, entry 6). In comparison, the N-ethylated analogue of ligand **4** afforded enantioselectivity of 30% favoring the same (*R*)-enantiomer [25]. Evidently, the secondary amide performs no better than the tertiary.

Ligand **6**, the *endo*-diastereoisomer of **4,** also afforded low level of enantioselectivity favoring the same (*R*)-enantiomer (12% ee, entry 7). Surprisingly, a change of the configuration at the carbon atom bonded to the amide nitrogen did not influence the enantioselectivity and the configuration of the products obtained.

Table 1. Palladium-catalyzed AAA of racemic (*E*)-1,3-diphenyl-2-propen-1-yl acetate with dimethyl malonate[a].

Entry	L*	Solvent	Base/Additive	Yield (%)[b]	ee (%), conf[c]
1	**2**	Et_2O	BSA/LiOAc	99	1, *R*
2	**2**	THF	BSA/LiOAc	99	16, *R*
3	**2**	CH_2Cl_2	Cs_2CO_3	99	52, *R*
4	**4**	CH_2Cl_2	Cs_2CO_3	99	1, *S*
5	**4**	THF	BSA/LiOAc	99	12, *R*
6	**4**	Et_2O	BSA/LiOAc	99	13, *R*
7	**6**	Et_2O	BSA/LiOAc	99	12, *R*

[a]Reaction conditions: **A** 1 equiv. substrate, 0.03 equiv $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 0.06 equiv. ligand, 3 equiv. N,O-bis(trimethylsilyl) acetamide (BSA), 3 equiv. dimethylmalonate, catalytic amount of additive salts, 24 h. **B** 1 equiv. substrate, 0.03 equiv $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 0.06 equiv. ligand, 2 equiv. Cs_2CO_3 2 equiv. dimethylmalonate, 24 h; [b]Isolated pure products after column chromatography; [c]Enantiomeric excess determined by HPLC analysis (Chiralpak IA chiral column). The absolute configuration was determined by comparison of the specific rotation to the literature value, see Ref [30].

The low enantio-selectivity made us forsake further optimizations. Quite controversial was also the result obtained with its N-ethylated analogue. No asymmetric induction was detected when employing the latter in the AAA, under the same reaction conditions [25]. Obviously, in the case of the bornylamine derived ligands the secondary amide is more potential than the tertiary. The opposite result was observed for the isobornylamine derived ligands.

CONCLUSION

New ligands were synthesized by condensation reactions of 3-*exo*-aminoisoborneol, isobornyl amine and bornylamine with *ortho*-diphenyl phosphino benzoic acid and evaluated in the palladium-catalyzed asymmetric allylic alkylation. The system used to generate the dimethyl malonate anion strongly determined the catalytic perfor-mance of 3-*exo*-aminoisoborneol derived ligand **2**. The best enantioselectivity of 52% ee was achieved when Cs_2CO_3 was used as a base. The combination of secondary amide with a free-OH group led to a drop of enantioselectivity compared to tertiary amide alkoxy analogues. The isobornylamine and bornylamine derived ligands gave generally low enantioselectivities of 13% ee and 12% ee, respecttively. A comparison with their tertiary amide analogues revealed that the electronic properties of the amide carbonyl group greatly influenced the asymmetric induction.

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ФОСФИН-КАРБОКСАМИДИ С КАМФАНОВ СКЕЛЕТ КАТО ЛИГАНДИ ЗА Pd-КАТАЛИЗИРАНО АСИМЕТРИЧНО АЛКИЛИРАНЕ

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(Резюме)

Чрез кондензация на *орто*-дифенилфосфино бензоена киселина с 3-*екзо*-аминоизоборнеол, изоборниламин и борниламин са получени три нови фосфин-карбоксамиди, които са изследвани като лиганди в Pd-катализирано асиметрично алилово алкилиране на (*E*)-1,3-дифенил-2-пропен-1-ил ацетат. Каталитичното действие силно зависи от условията използвани за получаване на диметил малонатния анион. Най-висока енантиоселективност е постигната с лиганд производен на 3-*екзо*-аминоизоборнеол и използването на Cs_2CO_3 като база. Лигандите, производни на изоборниламин и борниламин, индуцират по-ниска енантиоселективност.