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Synthesis of Heterofunctionalized Multidentate Diphosphines

Michael Quirmbach,[a] Jens Holz,[a] Vitali I. Tararov[a,b] and Armin Börner[a,*]

[a]*Institut für Organische Katalyseforschung an der Universität Rostock e.V., Buchbinderstr. 5/6, D-18055 Rostock, Germany*
[b]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilova 28, 117813 Moscow, Russian Federation*

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Abstract—The synthesis of new chiral multidentate amino- and amidophosphine ligands bearing up to six potential coordination sites were synthesized starting from L-valine. Based on these compounds chiral Ru(II) complexes were prepared, characterized and tested in the asymmetric transfer hydrogenation of aryl–alkyl ketones. In all cases investigated the catalyst bearing additional hydroxy groups gave lower conversions than the complex without hydroxy groups. Highest enantioselectivity was achieved with isobutyrophenone as substrate (69%ee).

Introduction

The catalytic asymmetric hydrogenation of prochiral ketones to chiral alcohols using transition metal complexes has gained increasing interest during recent years.[1] In particular, catalytic asymmetric transfer hydrogenation using 2-propanol has been shown to be an elegant and economic method due to the cheap hydrogen source employed and the avoidance of high pressure equipment. The mechanism for the transfer of hydrogen differs to that of hydrogenations utilizing molecular hydrogen. Therefore this approach can be used alternatively and may provide for higher enantioselectivity and productivity. During the last decade much effort has been directed towards the development of efficient catalytic systems but only recently success has been reported. Thus, ligands and corresponding metal complexes disclosed by Lemaire,[2] Noyori,[3] Helmchen,[4] Knochel,[5] and Zhang[6] have been shown to be efficacious. Noteworthy, are observations by Noyori[7] and Lemaire[8] that a NH moiety in the ligand is crucial for the achievement of high activity and selectivity. It was explained that the NH group promotes a cyclic transition state by formation of a hydrogen bond with the carbonyl group of the substrate.

For a couple of years we have been interested in the construction of chiral bifunctional HO-bearing phosphine ligands and their application in rhodium catalysed asymmetric hydrogenations.[9] We and others showed that in several instances the enantioselectivity of the parent catalyst could be significantly improved due to the additional functional group.[10] This effect is caused likely by the dual property of the HO group to act as a hemilabile ligand and to establish secondary interactions with the substrate by hydrogen bonds.

In an extension of this work, currently we are investigating the effect caused by hydroxy groups in phosphine metal complexes upon other asymmetric reactions. Herein we describe our first results obtained in the synthesis of new polyfunctionalized phosphines and their application in the transfer hydrogenation with Ru(II) complexes.

Due to the multifunctionality of the target compounds the synthesis of chiral functionalized phosphines requires a careful retrosynthetic planning.[11] Furthermore, in order to obtain a simple and economic pathway we focused our effort on the development of a modular approach allowing the simultaneous synthesis of a range of different ligands. We anticipated that β-aminoalkylphosphines could serve as appropriate templates. By the reaction of the amino group with, e.g. functionalized carboxylic acid chlorides or aldehydes additional functional groups can be easily incorporated affording multidentate ligands.

Results and Discussion

The synthesis of aminophosphine **4** ('ValPHOS') representing our building block for subsequent transformations was carried out as detailed in Scheme 1. This synthetic pathway is similar to the previously described approach by Hirol and Achiwa.[12] Thus, L-valinol available by the reduction of L-valine with $LiAlH_4$ was converted quantitatively into *N*-Boc-valinol by protection of the amino group with di-*tert*-butyl dicarbonate. Subsequent esterification with *p*-toluenesulfonyl chloride in pyridine gave tosylate **2**. In contrast to the synthesis described in the literature[12] we deprotected the amino group prior to the introduction of

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* Corresponding author. Tel.: +49-381-4669-310/350; fax: +49-381-4669-324/10; e-mail: armin.boerner@ifok.uni-rostock.de

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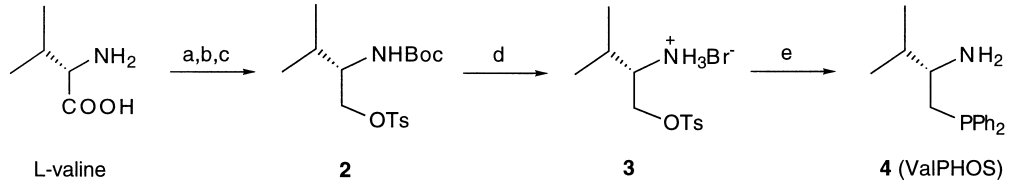
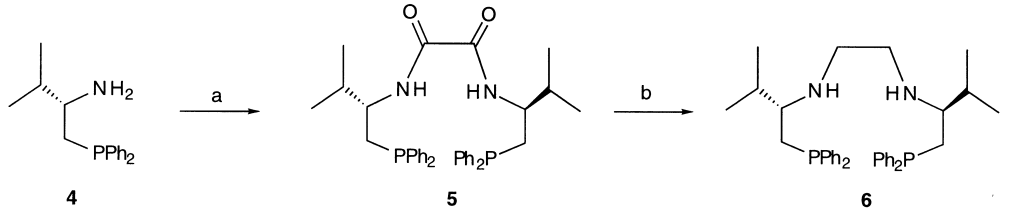


Scheme 1. Synthesis of the aminophosphine ValPHOS: 9a) 2.5 equiv. $LiAlH_4$, THF, 6 h, reflux, 60%; (b) 1.0 equiv. Boc_2O, Et_3N, dioxane/H_2O 1:1, 12 h, RT, 95%; (c) 1.0 equiv. TsCl, pyridine, 0°C, 12 h, 80%; (d) 30% HBr/HOAc, 0.5 h, 95%; (e) 2.1 equiv. $LiPPh_2$, THF, RT, 3 h, 43%.

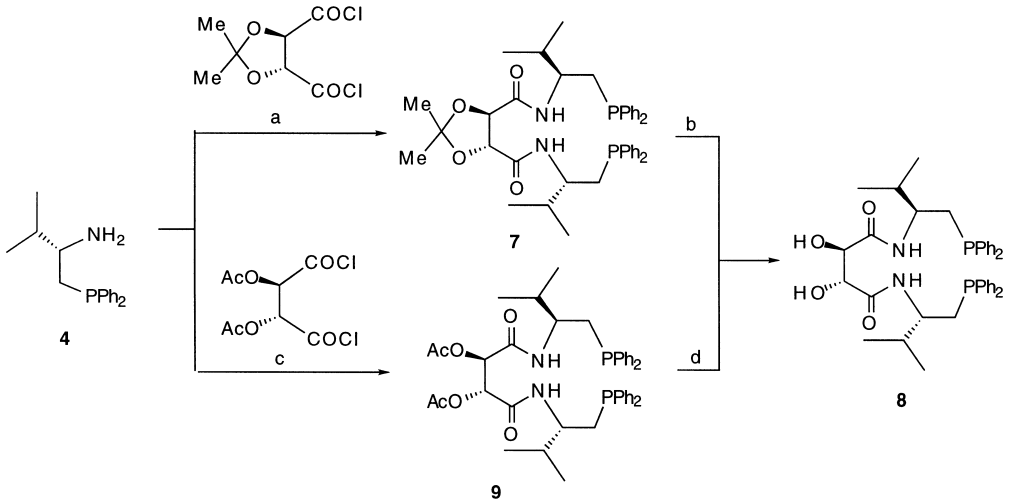
the phosphino group. Removal of the Boc-group was carried out by treatment of **2** with HBr/HOAc yielding ammonium salt **3**. This procedure revealed to be more advantageous because the formation of byproducts frequently observed in the reaction of **2** with $LiPPh_2$ was prevented. The subsequent phosphinylation of **3** took place under consumption of 2 equiv. of $LiPPh_2$ to give ValPHOS **4** in 43% yield. In turn we investigated exemplarily the potential of chiral amino phosphine **4** to serve as building block for the construction of chiral multidentate phosphine ligands. Thus, the reaction of 2 equiv. of **4** with oxalic chloride yielded diamide **5** (Scheme 2). The reduction of the amido groups with $LiAlH_4$ furnished the diamine **6** in an overall yield of 47% based on ValPHOS.

More challengingly, it revealed the preparation of the hydroxy amidophosphine **8**. Two synthetic routes were encountered (Scheme 3). Both have in common the use of HO-protected tartaric acid dichlorides. In our first approach **4** was treated with 2,3-*O*-isoproylidene-L-tartaric acid dichloride prepared according to Choi et al.[13] in three steps starting from dimethyl 2,3-*O*-isopropylidene-L-tartrate, to yield **7**. Surprisingly, the cleavage of the isopropylidene acetal under acidic conditions required rather severe conditions and long reaction time. The desired hydroxy amidophosphine **8** was finally obtained in 60% yield. The second approach that started from 2,3-*O*-diacetyl-L-tartaric acid-dichloride[14] was more advantageous, because the cleavage of the acetyl groups in **7** under basic conditions occurred smoothly and fast, and afforded **8** in 79% overall yield based on **4**.

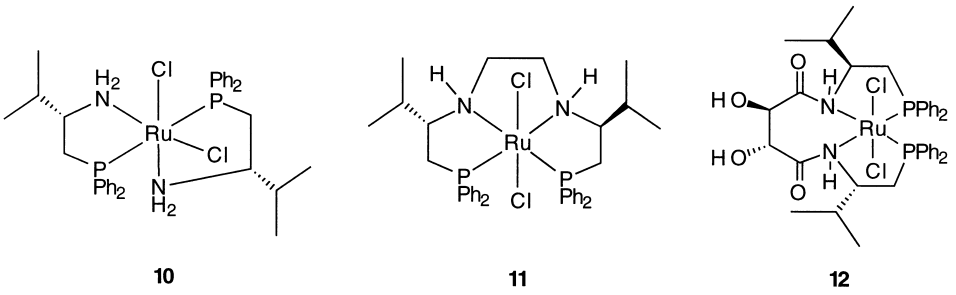
As a starting material for the synthesis of the Ru(II) catalysts *trans*-$RuCl_2(DMSO)_4$[15] was chosen. The reaction of 2 equiv. of **4** with $RuCl_2(DMSO)_4$ in toluene furnished after 18 h a C_1-symmetrical Ru complex. It is important to note that the phosphine groups were situated *trans* at the ruthenium centre. The ^{31}P–^{31}P-coupling constants of 295.5 Hz derived from the $^{31}P\{^1H\}$ NMR spectrum gave unambiguous proof for this coordination mode (δ 22.2 and



Scheme 2. Synthesis of **6**: (a) 0.5 equiv. $(COCl)_2$, 1.6 equiv. Et_3N, Et_2O, −78°C to RT, 5 h, 63%; (b) 6 equiv. $LiAlH_4$, THF, reflux, 24 h, 75%.



Scheme 3. Synthesis of hydroxy amidophosphine **8**: (a) 1.6 equiv. Et_3N, Et_2O, −78°C to RT, 5 h, 90%; (b) 8 equiv. TFA, MeOH/H_2O 10:1, 4 d, 60°C, 60%; (c) 1.6 equiv. Et_3N, Et_2O, −78°C to RT, 5 h, 83%; (d) cat. NaOMe, MeOH, RT, 3 h, 95%.



10 11 12

Scheme 4. New Ru(II) complexes prepared.

δ 32.8). Due to this feature we ascribe structure **10** to the formed complex (Scheme 4). Under the same reaction conditions *trans*-$RuCl_2(DMSO)_4$ was treated with the tetradentate ligand **6**, to give complex **11** featuring C_2-symmetry. The $^{31}P\{^1H\}$ NMR spectrum of the complex was characterized by a single resonance at δ 51.0. When **8** reacted with *trans*-$RuCl_2(DMSO)_4$ the C_2-symmetric complex **12** was formed. The geometry was derived from the $^{31}P\{^1H\}$ NMR spectrum where a singlet at δ 47.6 was observed. It is noteworthy, that exclusively amido and phosphine groups were bound to the ruthenium. Proof for this coordination mode came from the $^{13}C\{^1H\}$ NMR spectrum where the resonance of the C=O group in the ligand **8** shifted by complexation downfield from δ 171.0 to 181.7. The coordination of the HO groups was excluded due to the nearly unchanged shift of the resonance of the carbon attached to the HO group. Unfortunately, attempts to synthesize a ruthenium complex based on the amidophosphine **7** failed. This is probably due to the rigid backbone of **7** preventing the simultaneous complexation of all four ligating atoms.

The new ruthenium complexes **10**–**12** were tested in the asymmetric transfer hydrogenation of several aryl–alkyl ketones employing 2-propanol as a hydrogen source. All Ru(II) complexes catalysed the reaction. With the exception of **10**, affording racemic product, other Ru(II) complexes gave the corresponding alcohols in moderate enantioselectivities. Highest ee was achieved with isobutyrophenone as substrate (69%ee). It is interesting to note that the complex **12** bearing two hydroxy groups performed in all trials rather sluggish and required prolonged reaction time to achieve some conversion. Unfortunately, an increase of the enantioselectivity due to the additional hydroxy groups was not observed.

The decelerating effect of HO groups described above was already noted several times in the Rh(I) catalysed hydrogenation with hydroxy phosphines as ligands in methanol as solvent.[9,16] NMR spectroscopic studies gave proof that this effect is due to the intermediate coordination of the hemilabile hydroxy group on the rhodium and the formation of a coordinatively saturated metal centre.[17] Apparently, also during the Ru(II) catalysed transfer hydrogenation in 2-propanol such interactions come into play and affect the rate of the reaction. Further investigations are in progress to verify the utility of the new ligands also in other catalytic reactions.

Experimental

General procedures

All solvents were dried and distilled under argon. Reactions involving phosphines and organometallic compounds were performed under an Ar atmosphere by using standard Schlenk techniques. Tetrahydrofuran (THF), diethyl ether (Et_2O) and toluene were distilled from sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from CaH_2. Commercial reagents were used without further purification. Thin-layer chromatography was performed on pre-coated TLC plates (silica gel 60 F_{254}, Merck). Flash chromatography was carried out with silica gel 60 (particle size 0.040–0.063 mm, Merck). Melting points are corrected. The optical rotation was measured on a 'gyromat-HP' instrument (Fa. Dr. Kernchen). NMR spectra were recorded on a Bruker ARX 400 instrument at 303 K. Spectra were obtained at the following frequencies: 400.13 (^1H), 100.63 (^{13}C), 161.98 (^{31}P). Chemical shifts of ^1H and ^{13}C NMR spectra are given relative to the residual solvent peak (δ). Chemical shifts of ^{31}P NMR spectra are reported in ppm referred to H_3PO_4 as external standard. The mass spectra were recorded on an AMD 402 instrument (Fa. Intectra).

(*S*)-1-(*p*-Toluenesulfonylmethyl)-2-methyl-propylammonium bromide (3). The Boc-protected amine **2** (87 mmol, 31.0 g) was slowly added to a 2 M solution of HBr in HOAc (72 mL) at room temperature. After completion of the gas evolution stirring was continued for a further hour followed by the addition of Et_2O (400 mL). The precipitated product was filtered off, washed with Et_2O (3×200 mL) and dried in vacuo yielding **3** as a colourless solid. Yield 28.0 g (95%); mp 125°C; $[\alpha]_D^{25}$=10.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=8.30 (br, 3H, NH_3^+), 7.89 (d, ^3J=8.4 Hz, 2H, Ph), 7.34 (d, ^3J=8.4 Hz, 2H, Ph), 4.45 (dd, ^3J=3.7 Hz, ^2J=11.3 Hz, H_b–CH_2), 4.35 (dd, ^3J=5.9 Hz, ^2J=11.3 Hz, H_a–CH_2), 3.43 (m, 1H, CHN), 2.43 (s, 3H, CH_3–Ph), 2.20 (m, 1H, $CH(CH_3)_2$), 1.10 (d, ^3J=6.9 Hz, 3H, CH_3), 0.96 (d, ^3J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ=145.4, 131.7, 130.1, 128.3 (Ph), 69.9 (CH_2), 56.6 (CHN), 27.9 ($CH(CH_3)_2$), 21.7 (CH_3–Ph), 19.1 (CH_3), 18.4 (CH_3); IR (KBr) $\tilde{\nu}$ = 3192, 3161, 3137 (m, NH_3^+), 2995, 2974, 2918, 2886, 2846 (s, C–H), 1594 (m), 1575 (w), 1492 (s), 1361, 1190, 1176 (s, SO_2–OR), 1002, 950 (s), 853, 817 (s, C–H_{arom}), 773 (m), 669 (s), 622 (m); MS (EI, 70 eV) [*m*/*z*] (rel. int.%): 259 [M^+-Br^-] (3), 122 (90), 72 (100), 43 [$C_3H_7^+$] (90); calcd: $C_{12}H_{20}BrNO_3S$ (338.26) C 42.61, H 5.96, N 4.14; found: C 42.77, H 6.08, N 4.19.

(*S*)-1-(Diphenylphosphinomethyl)-2-methyl-propylamine (4), ValPHOS. A solution of lithium diphenylphosphide, prepared from *p*-chlorodiphenylphosphine (40.4 mmol, 8.91 g) and lithium metal (132 mmol, 0.91 g), was slowly added to a suspension of **3** (13.0 mmol, 4.40 g) in THF (50 mL) at 0°C. The reaction mixture was then warmed to room temperature, stirred for 5 h followed by removal of the solvent under reduced pressure. The obtained red residue was dissolved in water (20 mL) and CH_2Cl_2 (40 mL). The organic layer was separated, dried (Na_2SO_4) and the solvent evaporated. The obtained crude product was purified by flash chromatography (*n*-hexane/EtOAc/Et_3N 1:2:0.02, R_f=0.2) yielding a colourless oil. Yield 1.5 g (43%); $[\alpha]_D^{25}$=84.4 (*c*=1.0, $CHCl_3$); ^{31}P NMR ($CDCl_3$) δ=−21.0 (s, PPh_2); ^{1}H NMR ($CDCl_3$) δ=7.50–7.29 (m, 10 H, Ph), 2.63 (m, 1H), 2.32 (m, 1H), 1.95 (m, 1H), 1.71 (m, 1H), 1.35 (brs, 2H, NH_2), 0.89 (d, ^3J=6.7 Hz, 3H, CH_3), 0.87 (d, ^3J=6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ=139.8–128.7 (Ph), 54.0 (d, $^2J_{PC}$=13.4 Hz, CHN), 34.5 (d, $^1J_{PC}$=12.4 Hz, CH_2), 34.2 (d, $^3J_{PC}$=7.6 Hz, $CH(CH_3)_2$), 18.9 (CH_3), 17.1 (CH_3); IR (neat): $\tilde{\nu}$ = 3372, 3305 (w, NH_2), 3070, 3053 (s, C–H), 2957 (vs), 2930 (sh, C–H), 1585 (m), 1480 (s), 1465 (sh), 1434 (vs, P–C), 1385, 1366 (m, $CH(CH_3)_2$), 1185, 1095 (w), 1027 (w), 863 (br), 740, 697 (vs, C–H_{arom}); MS (EI, 70 eV) [*m*/*z*] (rel. int.%): 271 [M^+] (11), 254 [M^+-NH_3] (18), 200 (100), 183 (57), 72 (46); calcd: $C_{17}H_{22}NP$ (271.34) C 75.25, H 8.17, N 5.16; found: C 74.87, H 7.96, N 5.05.

(*S*,*S*)-*N*,*N*′-Bis(1-diphenylphosphinomethyl-2-methyl-propyl)oxaldiamide (5). A solution of oxalyl chloride (4.49 mmol, 0.57 g) in Et_2O (20 mL) was added dropwise via syringe to a stirred solution of **4** (9.20 mmol, 2.49 g) and triethylamine (14.4 mmol, 2.0 mL) in Et_2O (50 mL) at −78°C. When the addition was completed the reaction mixture was allowed to warm to room temperature with continuous stirring at ambient temperature for an additional 5 h. After evaporation of the solvent the residue was dissolved in CH_2Cl_2 (20 mL), washed with water (2×20 mL) and then the organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure and the obtained crude product was purified by flash chromatography (*n*-hexane/EtOAc 4:1, R_f=0.4) yielding a colourless solid. Yield 1.7 g (63%); mp 63–65°C; $[\alpha]_D^{25}$=−3.8 (*c*=1.1, $CHCl_3$); ^{31}P NMR ($CDCl_3$) δ=−22.6 (s, PPh_2); ^{1}H NMR ($CDCl_3$) δ=7.40–7.21 (m, 20 H, Ph), 3.77 (m, 2H, CHN), 2.21 (m, 4H), 1.94 (m, 2H), 0.81 (d, ^3J=6.3 Hz, 6 H, CH_3), 0.81 (d, ^3J=6.3 Hz, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ=158.2 (C=O), 137.3–127.5 (Ph), 52.8 (d, $^2J_{PC}$=15.3 Hz, CHN), 31.9 (d, $^3J_{PC}$=8.6 Hz, $CH(CH_3)_2$), 31.8 (d, $^1J_{PC}$=14.3 Hz, CH_2), 19.2 (CH_3), 16.9 (CH_3); IR (nujol): $\tilde{\nu}$ = 3268 (br, CONH), 1652 (s, amide), 1433 (s, P–C), 1377 (m), 737, 695 (m, C–H_{arom}); MS (EI, 70 eV) [*m*/*z*] (rel. int.%): 596 [M^+] (19), 325 (100), 202 (69); calcd: $C_{36}H_{42}N_2O_2P_2$ (596.27) C 72.47, H 7.09, N 4.69; found: C 71.98, H 7.18, N 4.63.

(*S*,*S*)-*N*,*N*′-Bis(1-diphenylphosphinomethyl-2-methyl-propyl)ethylen-1,2-diamine (6). $LiAlH_4$ (52.7 mmol, 2.00 g) were added in small portions to a stirred solution of **5** (8.25 mmol, 5.0 g) in THF (75 mL) at room temperature. The resulting reaction mixture was refluxed for 24 h followed by slow addition of water (20 mL). The residue was extracted several times with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvent the residue was purified by flash chromatography giving a viscous oil (*n*-hexane/EtOAc 1:1, R_f=0.35). Yield 3.5 g (75%); $[\alpha]_D^{25}$=56.4 (*c*=1.4, $CHCl_3$); ^{31}P NMR ($CDCl_3$) δ=−21.1 (s, PPh_2); ^{1}H NMR ($CDCl_3$) δ=7.49–7.24 (m, 20H, Ph), 2.46 (m, 4H, CH_2N), 2.29 (m, 2H, CHN), 2.11 (ddd, $^2J_{PH}$=1.8 Hz, ^3J=4.9 Hz, ^2J=13.9 Hz, 2H, H_b–CH_2), 1.95 (ddd, $^2J_{PH}$=1.6 Hz, ^3J=8.5 Hz, ^2J=13.9 Hz, 2H, H_a–CH_2), 1.85 (m, 2H, CH), 0.87 (d, ^3J=6.7 Hz, 6H, CH_3), 0.82 (d, ^3J=6.7 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ=139.6–128.2 (Ph), 60.3 (d, $^2J_{PC}$=14.3 Hz, CHN), 47.8 (CH_2N), 31.2 ($CH(CH_3)_2$), 30.6 (d, $^1J_{PC}$=13.4 Hz, CH_2), 18.1 (CH_3), 17.7 (CH_3); IR (neat): $\tilde{\nu}$ = 3371 (w, NH_2), 3070, 3053 (s, C–H_{arom}), 2955 (vs), 2930 (sh, C–H), 1585 (m), 1480 (s), 1465 (sh), 1433 (vs, P–C), 1384, 1366 (m, $CH(CH_3)_2$), 1182 (w), 1097 (m), 1068 (m), 1027, 999 (w), 739, 696 (vs, C–H_{arom}); MS (CI, isobutane) [*m*/*z*] (rel. int.%): 625 [M+$C(CH_3)_3$] (3), 569 [M+H] (100), 297 (20); calcd: $C_{36}H_{46}N_2P_2$ (568.72) C 76.03, H 7.99, N 4.93; found: C 75.57, H 8.15, N 4.50.

(*R*,*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diacid-bis{[(1′*S*)-1′-(diphenylphosphinomethyl)-2′-methyl-propyl]-amide} (7). Following the procedure described above for the preparation of **5** a solution of 2,3-*O*-isopropylidene-L-tartaric acid dichloride (0.80 mmol, 0.18 g) in Et_2O was allowed to react with **4** (1.60 mmol, 0.44 g) in the presence of triethylamine (2.15 mmol, 0.3 mL). After flash chromatography (*n*-hexane/EtOAc 1:2, R_f=0.7) a colourless solid was obtained. Yield 0.5 g (90%); mp 68°C; $[\alpha]_D^{25}$=37.4 (*c*=0.2, $CHCl_3$); ^{31}P NMR ($CDCl_3$) δ=−23.1 (s, PPh_2); ^{1}H NMR ($CDCl_3$) δ=7.50–7.27 (m, 20H, Ph), 7.12 (d, ^3J=9.35 Hz, 2H, NH), 4.30 (s, 2H, CHO), 3.95 (m, 2H, CHN), 2.32 (ddd, $^2J_{PH}$=1.9 Hz, ^3J=4.9 Hz, ^2J=14.0 Hz, 2H, H_b–CH_2), 2.20 (ddd, $^2J_{PH}$=1.5 Hz, ^3J=9.1 Hz, ^2J=14.0 Hz, 2H, H_a–CH_2), 1.98 (m, 2H, CH), 1.50 (s, 6H, CH_3), 0.92 (d, ^3J=6.9 Hz, 6H, CH_3), 0.90 (d, ^3J=6.9 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ=168.9 (NC=O), 138.4–128.5 (Ph), 112.0 ($C(CH_3)_2$), 77.6 (CHO), 51.8 (d, $^2J_{PC}$=14.3 Hz, CHN), 32.3 (d, $^3J_{PC}$=7.6 Hz, $CH(CH_3)_2$), 32.2 (d, $^1J_{PC}$=11.5 Hz, CH_2), 26.5 (CH_3), 26.4 (CH_3), 19.1 (CH_3), 17.5 (CH_3); IR (nujol): $\tilde{\nu}$ = 3277 (br, CONH), 1656 (s, amid I), 1559 (amid II), 1435 (s, P–C), 1377 (m), 742, 697 (m, C–H_{arom}); MS (EI, 70 eV) [*m*/*z*] (rel. int.%): 695 [M^++H] (1), 496 (3), 424 (100), 366 (11), 201 (59); calcd: $C_{41}H_{48}N_2O_4P_2$ (694.79) C 70.88, H 6.96, N 4.03; found: C 70.30, H 7.12, N 3.90.

(2*R*,3*R*)-*N*,*N*′-Bis[(1′*S*)-1′-(diphenylphosphinomethyl)-2′-methyl-propyl]-2,3-dihydroxy-succinediamide (8). From **7**. Trifluoracetic acid (TFA) (5.2 mmol, 0.4 mL) was added dropwise to a stirred solution of **7** (0.71 mmol, 0.50 g) in MeOH/water (10:1).The resulting reaction mixture was heated to 60°C and kept for 4 d at this temperature. After evaporation of the solvent the residue was dissolved in CH_2Cl_2 (40 mL), washed with saturated $NaHCO_3$ (2×20 mL), NaCl solution (40 mL), water (40 mL) and the organic layer was dried (Na_2SO_4).The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (*n*-hexane/EtOAc 1:2, R_f=0.5). Yield 0.27 g (60%).

From **9**. To a stirred solution of **9** (2.43 mmol, 1.80 g) in

methanol a solution of sodium methoxide (1.3 M, 0.3 mL) was added at room temperature. After stirring for 3 h the reaction mixture was hydrolysed with water (0.2 mL) and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (*n*-hexane/EtOAC 1:2, R_f=0.5) yielding a colourless solid. Yield 1.45 g (95%).

The succinediamide **8** obtained from **7** and **9**, respectively, featured the same physical properties: mp 60–62°C; $[\alpha]_D^{25}$=78.0 (*c*=1.0, $CHCl_3$); ^{31}P NMR ($CDCl_3$) δ=−22.5 (s, PPh_2); ^{1}H NMR ($CDCl_3$) δ=7.46–7.30 (m, 20H, Ph), 6.96 (d, ^3J=10.1 Hz, 2H, NH), 4.28 (brs, 4H, OH, CHOH),), 3.93 (m, 2H, NCH), 2.34 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 1.93 (m, 2H, CH), 0.87 (d, ^3J=6.7 Hz, 12 H, CH_3); ^{13}C NMR ($CDCl_3$) δ=171.0 (C=O), 137.8–128.5 (Ph), 71.6 (CHO), 51.6 (d, $^2J_{PC}$=14.3 Hz, CHN), 32.7 (d, $^3J_{PC}$=7.6 Hz, $CH(CH_3)_2$), 32.6 (d, $^1J_{PC}$=14.3 Hz, CH_2), 19.2 (CH_3), 17.6 (CH_3); IR (nujol): $\tilde{\nu}$ = 3382, 3288 (br, CONH), 1647 (s, amid I), 1523 (m, amid II), 1434 (s, P–C), 1377 (m); 739, 695 (m, C–H_{arom}); MS (EI, 70 eV) [*m*/*z*] (rel. int.%): 657 [M^++H] (3), 386 (43), 312 (13), 271 (29), 202 (100); calcd: $C_{38}H_{46}N_2O_4P_2$ (656.74) C 69.50, H 7.06, N 4.22; found: C 69.23, H 7.12, N 4.23.

(2*R*,3*R*)-Acetic acid-2-acetoxy-1,2-bis[(1′*S*)-1′-(diphenylphosphinomethyl)-2′-methyl-propyl-carbamoyl]ethyl-ester (9). Following the procedure described above for the preparation of **5** a solution of 2,3-*O*-diacetyl-L-tartaric acid dichloride (2.73 mmol, 0.74 g) in Et_2O was allowed to react with **4** (5.34 mmol, 1.45 g) in the presence of triethylamine (10.8 mmol, 1.5 mL). After flash chromatography (CH_2Cl_2/EtOAc 10:1, R_f=0.4) a colourless solid was obtained. Yield 1.68 g (83%); mp 116–118°C; $[\alpha]_D^{25}$=44.7 (*c*=1.0, $CHCl_3$); ^{31}P NMR ($CDCl_3$) δ=−23.9 (s, PPh_2); ^{1}H NMR ($CDCl_3$) δ=7.45–7.30 (m, 20H, Ph), 6.08 (d, ^3J=9.4 Hz, 2H, NH), 5.70 (s, 2H, CHO), 3.85 (m, 2H, CHN), 2.27 (ddd, $^2J_{PH}$=2.2 Hz, J=4.9 Hz, ^2J=13.8 Hz, 2H, H_b–CH_2), 1.91 (m, 2H,CH), 2.15 (m, 8H, CH_3CO, H_a–CH_2), 0.79 (d, ^3J=6.6 Hz, 6H, CH_3), 0.79 (d, ^3J=6.6 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ=169.4 (NC=O), 165.6 (C=O), 138.3–128.5 (Ph), 72.3 (CHO), 51.9 (d, $^2J_{PC}$=14.3 Hz, CHN), 32.1 (d, $^3J_{PC}$=7.6 Hz, $CH(CH_3)_2$), 31.9 (d, $^1J_{PC}$=14.3 Hz, CH_2), 21.1 (CH_3CO), 21.0 (CH_3CO), 18.8 (CH_3), 17.2 (CH_3); IR (nujol): $\tilde{\nu}$ = 3310, 3247 (br, CONH), 1749 (s, C=O), 1660 (s, amid), 1435 (s, P–C), 1377 (m), 739, 696 (m, C–H_{arom}); MS (EI, 70 eV) [*m*/*z*] (rel. int.%): 739 [M^+−H] (3), 696 [M^+−H−CH_3CO] (2), 636 (11), 620 (11), 468 (90), 270 (90), 201 (100); calcd: $C_{42}H_{50}N_2O_6P_2$ (740.82) C 68.09, H 6.80, N 3.78; found: C 67.70, H 6.61, N 3.72.

General procedure for the synthesis of Ru(II)-complexes using $RuCl_2$(DMSO)

A Schlenk tube was charged with 1.00 mmol of a tetradentate aminophosphine (2.00 mmol if a bidentate ligand was used) and dissolved in toluene. After complete dissolution of the phosphine $RuCl_2(DMSO)_4$ (1.00 mmol) was added at once. The suspension was heated to 75°C and kept for 18 h at this temperature. After this period the solution became nearly homogeneous. Filtration of the mixture followed by evaporation of the solvent gave the crude complex. It was washed with diethyl ether (5×10 mL) and dried in vacuo.

[Ru(4)$_2$Cl$_2$] Complex 10. According to the general procedure for preparation of Ru(II) complexes, ValPHOS (**4**) (0.49 mmol, 0.13 g) was treated with *trans*-$RuCl_2(DMSO)_4$ (0.25 mmol, 0.13 g) in toluene (3 mL). The complex was washed with diethyl ether and dried under reduced pressure affording yellow plates. Yield 0.16 g (91%); mp 105–108°C; ^{31}P NMR (CD_2Cl_2) δ=22.2 (d, $^2J_{PP}$=295.5 Hz), 32.8 (d, $^2J_{PP}$=295.5 Hz); ^{1}H NMR (CD_2Cl_2) δ=8.35–7.16 (m, 20H, Ph), 3.43 (m, 2H, CHN), 3.08 (m, 4H, CH_2P), 2.75 (m, 1H, CH), 2.00 (m, 1H, CH), 1.11 (d, ^3J=6.6 Hz, 3H, CH_3), 0.85 (d, ^3J=6.6 Hz, 3H, CH_3), 0.60 (d, ^3J=6.6 Hz, 3H, CH_3), 0.53 (d, ^3J=6.6 Hz, 3H, CH_3); ^{13}C NMR (CD_2Cl_2) δ=133.0–127.9 (Ph), 66.5 (br, CHN), 63.5 (br, CHN), 34.9 (d, $^1J_{PC}$=26.7 Hz, CH_2), 33.5 (d, $^3J_{PC}$=15.3 Hz, $CH(CH_3)$), 33.3 (d, $^3J_{PC}$=15.3 Hz, $CH(CH_3)$), 28.6 (d, $^1J_{PC}$=27.7 Hz, CH_2), 21.2, (CH_3), 21.8 (CH_3), 18.9 (CH_3), 18.8 (CH_3); IR (nujol): $\tilde{\nu}$ = 3317 (w, NH_2), 1572 (w), 1435 (s, P–C), 1074, 1019 (br), 742, 697 (s, C–H_{arom}); MS (EI, 70 eV) [*m*/*z*] (rel. int.%): 713 [M^++H] (100), 679 [M^+−Cl] (9), 642 (70), 557 (30), 244 (50); calcd: $C_{34}H_{44}Cl_2N_2P_2Ru$ (714.14) C 57.13, H 6.21, N 3.92; found: C 56.89, H 6.10, N 3.83.

[Ru(6)(Cl)$_2$] Complex 11. According to the general procedure for the preparation of Ru(II)-complexes, aminophosphine **6** (0.49 mmol, 0.28 g) was treated with *trans*-$RuCl_2(DMSO)_4$ (0.49 mmol, 0.25 g) in toluene (6 mL). The complex yielded was washed with diethyl ether and dried under reduced pressure to give a light brown powder. Yield 0.27 g (75%); mp 183–185°C; ^{31}P NMR ($CDCl_3$) δ=51.0 (s, PPh_2); ^{1}H NMR (CD_2Cl_2) δ=7.55–6.97 (m, 20H, Ph), 4.55 (m, 1H), 3.97 (m, 1H), 3.23 (m, 6H), 2.93 (m, 4H), 1.22 (d, ^3J=6.9 Hz, 6H, CH_3), 0.98 (d, ^3J=6.9 Hz, 3H, CH_3); ^{13}C NMR (CD_2Cl_2) δ=134.8–127.0 (Ph), 63.6 (CHN), 49.0 (CH_2), 35.3 (d, ^1J=14.3 Hz, CH_2), 35.3 (d, ^1J=14.3 Hz, CH_2), 26.9 (d, ^3J=7.6 Hz, $CH(CH_3)_2$), 26.9 (d, ^3J=7.6 Hz, $CH(CH_3)_2$), 21.1 (CH_3), 13.3 (CH_3); IR (nujol): $\tilde{\nu}$ = 3433 (br, NH), 3208 (w, C–H_{arom}), 1434 (s, P–C), 1098, 1058, 1027 (m), 739, 695 (s, C–H_{arom}); MS (EI, 70 eV) [*m*/*z*] (rel. int.%): 740 [M^+] (100), 666 (61), 625 (29), 332 (22), 183 (52); calcd: $C_{36}H_{46}Cl_2N_2P_2Ru$ (740.68) C 58.38, H 6.26, N 3.78; found: C 57.83, H 6.12, N 3.65.

[Ru(8)Cl$_2$] Complex 12. According to the general procedure for the preparation of Ru(II) complexes, amidophosphine **8** (1.05 mmol, 0.69 g) was treated with *trans*-$RuCl_2(DMSO)_4$ (1.05 mmol, 0.69 g) in toluene (10 mL). The complex yielded was washed with diethyl ether and dried under reduced pressure to give a dark red powder. Yield 0.70 g (80%); mp >250°C; ^{31}P NMR (CD_2Cl_2) δ=47.6 (s, PPh_2); ^{1}H NMR (CD_2Cl_2) δ=7.71 (d, ^3J=4.9 Hz, 2H, NH), 6.90–7.40 (m, 20H, Ph), 5.70 (d, ^3J=6.4 Hz, 2H, CHO), 4.80 (d, ^3J=6.4 Hz, 2H, OH, exchangeable with D_2O), 3.84 (m, 2H, NCH), 3.17 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 1.79 (m, 2H, CH), 0.83 (d, ^3J=6.6 Hz, 6H, CH_3), 0.81 (d, ^3J=6.9 Hz, 6H, CH_3); ^{13}C NMR (CD_2Cl_2) δ=181.7 (NC=O), 139.9–125.3 (Ph), 72.7 (CHO), 52.4 (CHN), 34.3 (d, ^1J=13.4 Hz, CH_2), 34.3 (d, ^1J=13.4 Hz, CH_2), 33.6 (br, $CH(CH_3)_2$), 19.0 (CH_3), 15.9

(CH_3); IR (nujol): $\tilde{\nu}$3379, 3237, 3047 (br, CONH, OH), 1614 (s, amid I), 1550 (s, amid II), 1436 (s, P-C), 1376 (m), 1110 (m), 1094 (m), 801 (m), 696 (s, C–H_{arom}); MS (EI, 70 eV) [*m*/*z*] (rel. int.%): 712 [$M^+ - C_4H_4O_4$] (11), 614 (9), 368 (20), 255 (37), 199 (100); calcd: $C_{38}H_{46}N_2O_4P_2RuCl_2$ (828.72) C 55.08, H 5.59, N 3.38; found: C 54.98, H 5.55, N 3.30.

General procedure for transfer hydrogenation

A Schlenk tube was charged with isopropanol (5 mL), the chiral Ru(II) complex (0.01 mmol) and sodium hydroxide (5 mg). The solution was stirred for 20 min at room temperature followed by the addition of the appropriate ketone. Then the temperature was adjusted at 50°C and the solution kept for 1 to 144 h. After cooling to room temperature the mixture was passed through a plug of silica gel to remove the catalyst. Product analyses were performed by gas chromatography and by HPLC.

(*S*)-Isobutylphenyl carbinol. According to the general procedure for the transfer hydrogenation isobutyrophenone was reduced at 55°C for 3 h to give (*S*)-isobutylphenyl carbinol in 27% yield and 69%ee.

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