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Diamidophosphites with remote *P**-stereocentres and their performance in Pd-catalyzed enantioselective reactions

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ABSTRACT

Diamidophosphite ligands based on 1,1′-bis(hydroxymethyl)ferrocene or N^1,N^2-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)oxalamide and bearing 1,3,2-diazaphospholidine rings with stereogenic phosphorus atoms were obtained. The use of these ligands provides up to 96% ee in Pd-catalyzed asymmetric allylations of (*E*)-1,3-diphenylallyl acetate, up to 70% ee in Pd-catalyzed desymmetrizations of *N*,*N*′-ditosyl-*meso*-cyclopent-4-ene-1,3-diol bis-carbamate and up to 80% ee in Pd-catalyzed allylic alkylations of cinnamyl acetate with ethyl 2-oxocyclohexane-1-carboxylate. Results obtained with a diamidophosphite containing an oxalamide framework show the considerable potential of such ligands in enantioselective catalysis.

1. Introduction

Despite impressive advances in the preparation and application of asymmetric transition-metal catalysis of large libraries of different phosphorus-based chiral ligands,[1–16] the development of efficient enantioselective catalytic systems based on novel inexpensive phosphorus-containing stereoselectors easily synthesized from available enantiopure synthons remains a challenge.[16–18] The overwhelming majority of known ligands in the composition of the corresponding metal complexes are able to catalyze (with different enantioselectivities) either a certain type of chemical transformation, or one certain reaction. There are very few versatile (the so-called 'privileged') ligands, and their high cost significantly limits their wide application.[16,19]

From a practical point of view, air-stable, inexpensive, and easily accessible ligands are highly desirable.[20] Optically active phosphite-type compounds satisfy these criteria, since they are favorably distinguished by stability to oxidation, pronounced π-acidity, and are inexpensive. It should also be noted that they can be easily obtained by simple condensation processes, including those involving parallel and solid-phase synthetic procedures.[8,12,18,21–35]

Among the phosphite-type chiral ligands, diamidophosphites (one P—O bond and two P—N bonds) are a relatively small but very promising group.[1,36–42] It should be noted that these compounds have different properties from more common phosphites (three P—O bonds) or phosphoramidites (two P—O bonds and one P—N bond). For example, nitrogen substituents create more steric bulk around the phosphorus than the oxygen atom, since nitrogen substitution may be greater. Furthermore, replacing the oxygen atom in the first coordination sphere of the phosphorus with a nitrogen atom increases the electron density on the phosphorus center.[1,42] The *P*,*P*-bidentate diamidophosphites $\mathbf{L_{A–D}}$ (Fig. 1) have been successfully applied in asymmetric Pd-catalyzed cycloadditions and Rh-catalyzed hydrogenations.[42–45]

Diamidophosphites with 1,3,2-diazaphospholidine rings and asymmetric phosphorus atoms have emerged as efficient stereoinducers.[46–48] In particular, these compounds display balanced electronic characteristics since they are both good π-acceptors (due to the accessibility of low-lying π^*_{PN} orbitals) as well as good σ-donors. The inclusion of the phosphorus atom in the five-membered ring enhances the resistance of the ligands to oxidation and hydrolysis, and the possibility of varying the nature of the substituents at the nitrogen and phosphorus atoms allows control over the steric and electronic parameters. Their modular nature also allows a facile systematic variation of the configuration at the *P**- and *C**-stereocenters in the phospholidine rings.[48,49] The presence of a stereogenic donor phosphorus atom significantly promotes successful asymmetric induction in the key step of the

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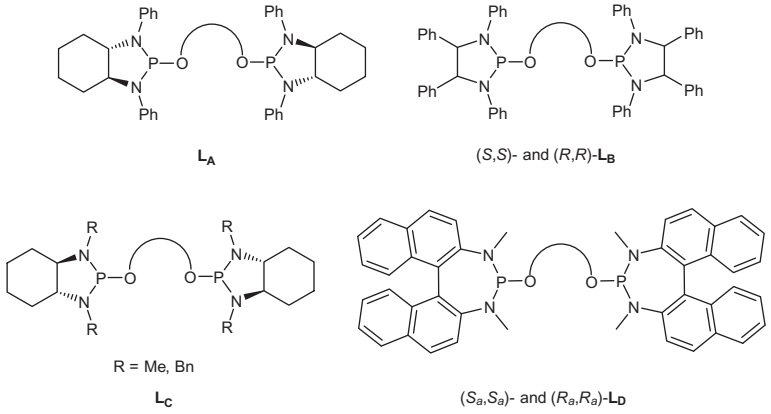


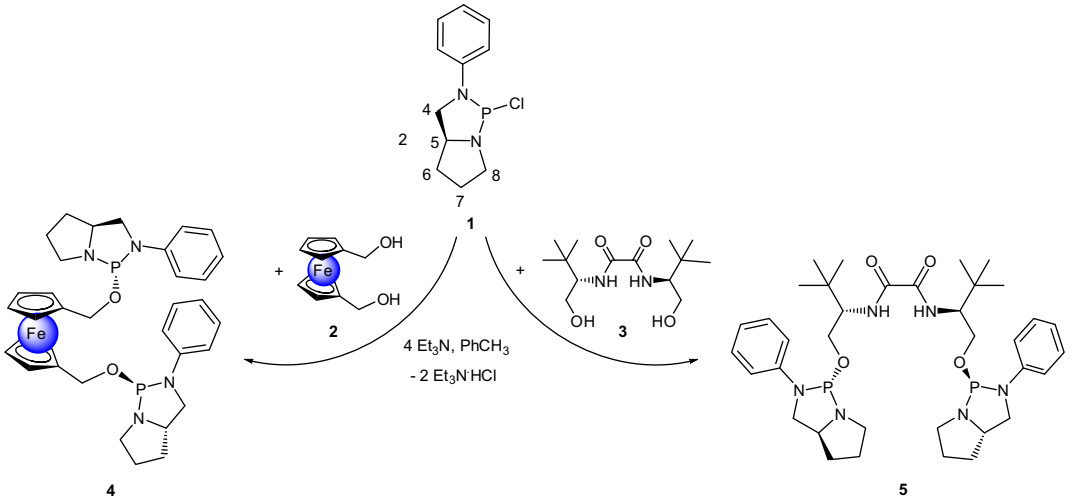
Figure 1. *P*,*P*-Bidentate diamidophosphite ligands.

catalytic cycle. Since this atom is directly bonded to the central metal atom (ion), it is positioned very close to the coordinated substrate. This factor suppresses any potential inefficient secondary transfer of chirality from the ligand framework and provides a more efficient chiral environment at the site where the enantioselection originates.[4,19,49,50] Along these lines, we have reported on an asymmetric Pd-catalyzed allylation and Rh-catalyzed hydrogenation and addition using some *P**,*P**-bidentate diamidophosphites containing 1,3,2-diazaphospholidine rings.[51–54]

Herein we have dedicated our efforts to synthesizing novel ligands containing remote diamidophosphite moieties and their exploration in Pd-catalyzed asymmetric allylation and desymmetrization reactions. The Pd-catalyzed allylic substitution is a powerful and well-established synthetic tool, which is tolerant of various functional groups in the substrate and which operates with a wide range of C-, N-, O-, S-, and P-nucleophiles. As a consequence, Pd-catalyzed allylic substitution is a versatile process that is widely used in the total synthesis of useful enantiomerically pure natural and unnatural compounds.[2,5,50,55–61] This is a common benchmark test for initial ligand screening and the enantiomeric excesses obtained are the simplest scale for evaluating new chiral ligands.[2,20,60] It should be noted that the Pd-catalyzed enantioselective synthesis of a quaternary carbon center is a formidable challenge.[62] The Pd-catalyzed desymmetrization of *N*,*N*′-ditosyl-*meso*-cyclopent-4-ene-1,3-diol bis-carbamate has been successfully used as a key step in the synthesis of mannostatin A and (−)-swainsonine.[5,56]

2. Results and discussion

As shown in Scheme 1, diamidophosphites **4** and **5** were synthesized in one step from the suitable diols **2** or **3** and phosphorylating reagent **1**. The reactions were performed in the presence of excess Et_3N as a HCl scavenger in toluene. Ligands **4** and **5** were purified by flash chromatography on Al_2O_3 or by crystallization and obtained in reasonable yields as an orange oil and white solid, respectively. The new stereoselectors could be prepared on a gram scale. They can be stored under dry conditions at room temperature for at least a few months with minimal degradation. Ligand **4** readily forms a solvate with toluene. Therefore, lengthy high vacuum drying is required for the preparation of analytically pure material. The elemental analyses, ^1H, ^{13}C, and ^{31}P NMR spectra and MALDI TOF/TOF mass spectra, were consistent with the expectation for these ligands. Thus, during the phosphorylation, the exclusive formation of stereospecific diamidophosphites **4** and **5** with an (*R*)-configuration at the *P**-stereocentres occurred. The ^{31}P NMR spectra of their solutions in $CDCl_3$ exhibited narrow singlets at δ_P 121.9 and 124.0, respectively. The ^{13}C NMR spectra of these compounds were characterized by large spin–spin coupling constants $^2J_{C(8),P}$ (38.7 and 38.3 Hz, see Section 4), which are indicative of the *syn*-orientation of the phosphorus lone pair with respect to the C(8) atom. The pseudoequatorial exocyclic substituent at the phosphorus atom and the $-(CH_2)_3-$ part of the pyrrolidine fragment of the phosphabicyclic skeleton are in the *anti*-arrangement (Fig. 2).[46–48,51–54,63,64]



Scheme 1. Synthesis of diamidophosphites **4** and **5**.

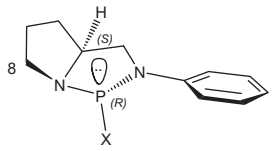
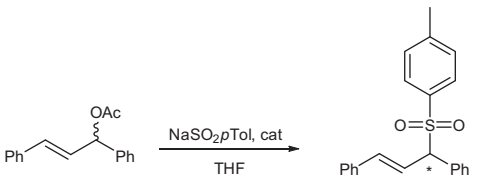


Figure 2. Stereochemistry of the phosphabicyclic part in ligands **4** and **5** (X = exocyclic substituent).

In order to explore the application of the new stereoinducers **4** and **5** in Pd-catalyzed asymmetric allylic substitutions, we evaluated the interaction of (*E*)-1,3-diphenylallyl acetate **6** with various nucleophiles. As stated above, compound **6** was chosen as a substrate because this model process is very convenient for the direct comparison of the efficiency of different stereoselectors. These reactions were carried out at room temperature in the presence of catalysts formed from $[Pd(allyl)Cl]_2$ as a palladium source. Results are summarized in Tables 1–3.

In a first set of experiments, we tested the new diamidophosphites in the allylic sulfonylation of **6** with sodium *para*-toluene sulfinate as the S-nucleophile in THF as the solvent (Table 1). The

Table 1
Pd-catalyzed allylic sulfonylation of (*E*)-1,3-diphenylallyl acetate **6** with sodium *para*-toluene sulfinate[a]

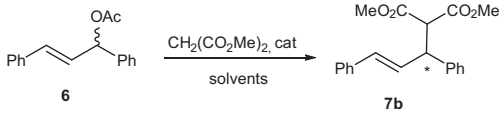


6 **7a**

Entry	Ligand	L/Pd	Yield (%)	ee[b] (%)
1	**4**	1	70	23 (*S*)
2	**4**	2	87	77 (*S*)
3	**5**	**1**	**42**	**86 (*R*)**
4	**5**	2	35	61 (*R*)

[a] All reactions were carried out with 2 mol % of $[Pd(allyl)Cl]_2$ in THF at room temperature for 48 h.
[b] Enantiomeric excess of **7a** was determined by HPLC (Daicel Chiralcel OD-H, C_6H_{14}/*i*-PrOH = 4:1, 0.5 mL/min, 254 nm, $t(R)$ = 16.3 min, $t(S)$ = 18.5 min).

Table 2
Pd-catalyzed allylic alkylation of (*E*)-1,3-diphenylallyl acetate **6** with dimethyl malonate[a]

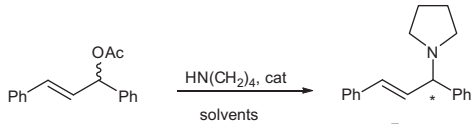


6 **7b**

Entry	Ligand	L/Pd	Solvent	Conversion (%)	ee[b] (%)
1	**4**	1	CH_2Cl_2	100	92 (*S*)
2	**4**	2	CH_2Cl_2	62	91 (*S*)
3	**4**	1	THF	100	87 (*S*)
4	**4**	2	THF	78	73 (*S*)
5	**5**	1	CH_2Cl_2	96	88 (*S*)
6	**5**	2	CH_2Cl_2	92	93 (*S*)
7	**5**	1	THF	90	88 (*S*)
8	**5**	**2**	**THF**	**99**	**94 (*S*)**

[a] All reactions were carried out with 2 mol % of $[Pd(allyl)Cl]_2$ at room temperature for 48 h (BSA, KOAc).
[b] The conversion of substrate **6** and enantiomeric excess of **7b** were determined by HPLC (Daicel Chiralcel OD-H, C_6H_{14}/*i*-PrOH = 99:1, 0.3 mL/min, 254 nm, $t(R)$ = 28.0 min, $t(S)$ = 29.3 min).

Table 3
Pd-catalyzed allylic amination of (*E*)-1,3-diphenylallyl acetate **6** with pyrrolidine[a]



6 **7c**

Entry	Ligand	L/Pd	Solvent	Conversion (%)	ee[b] (%)
1	**4**	1	CH_2Cl_2	100	87 (*R*)
2	**4**	2	CH_2Cl_2	100	87 (*R*)
3	**4**	1	THF	100	85 (*R*)
4	**4**	2	THF	100	79 (*R*)
5	**5**	1	CH_2Cl_2	100	62 (*R*)
6	**5**	2	CH_2Cl_2	100	27 (*R*)
7	**5**	1	THF	95	85 (*R*)
8	**5**	**2**	**THF**	**85**	**96 (*R*)**

[a] All reactions were carried out with 2 mol % of $[Pd(allyl)Cl]_2$ at room temperature for 48 h.
[b] The conversion of substrate **6** and enantiomeric excess of **7c** were determined by HPLC (Daicel Chiralcel OD-H, C_6H_{14}/*i*-PrOH/$HN(Et)_2$ = 200:1:0.1, 0.9 mL/min, 254 nm, $t(R)$ = 5.0 min, $t(S)$ = 6.1 min).

reaction product (*R*)-**7a** was obtained with good enantioselectivity (up to 86% ee) when diamidophosphite **5** was employed as the chiral auxiliary; the molar ratio L/Pd = 1 is undoubtedly preferable (Table 1, entries 3 and 4). At the same time, ligand **4** afforded sulfone (*S*)-**7a** with a lower enantiomeric purity (up to 77% ee, Table 1, entries 1 and 2), but with higher yields.

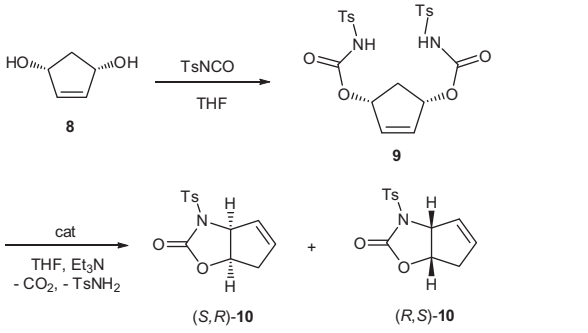
In the Pd-catalyzed allylic alkylation of **6** with dimethyl malonate as the C-nucleophile, diamidophosphites **4** and **5** were found to be the equally efficient stereoinducers, providing up to 92% and 94% ee, respectively (Table 2, entries 1 and 8). It should be noted that in all cases, the catalytic systems based on novel diamidophosphites led to product **7b** with an (*S*)-configuration. When the reaction was carried out using **4** as the ligand, the best ee values were observed in CH_2Cl_2, the L/Pd molar ratio had no effect on the enantioselectivity in this medium. Ligand **4** provided quantitative conversions of **6** in both solvents at the molar ratio L/Pd = 1 (Table 2, entries 1–4). It is noteworthy that for diamidophosphite **5**, the nature of the solvent did not have a significant effect on the reaction rate or the asymmetric induction, while an increase in the L/Pd molar ratio led to a slight increase in enantioselectivity (Table 2, entries 5–8).

We also investigated novel stereoinducers in the enantioselective Pd-catalyzed allylic amination of **6** with pyrrolidine. With diamidophosphite **4**, quantitative conversion of **6** and good enantioselectivities (79–87%) were achieved (Table 3, entries 1–4). Ligand **5** demonstrated higher asymmetric induction (up to 96% ee), but the nature of the solvent and the L/Pd molar ratio were found to have a significant effect on the reaction rate and enantioselectivity. In particular, the reaction in THF was more enantioselective, while a higher conversion was achieved in CH_2Cl_2 (Table 3, entries 5–8). As shown in Table 3, the resulting amination product **7c** proved to have the same (*R*)-configuration in all cases.

In the next step, stereoselectors **4** and **5** were studied in the Pd-catalyzed desymmetrization of *N*,*N*′-ditosyl-*meso*-cyclopent-4-ene-1,3-diol bis-carbamate **9** (Table 4). The reaction was performed in THF in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ as the catalytic precursor. Catalytic compositions based on ligand **4** showed mediocre yields and enantioselectivity (up to 46% ee, Table 4, entries 1 and 2) irrespective of the L/Pd molar ratio. Compound **5** produced significantly better chemical yields and asymmetric induction (up to 70% ee, Table 4, entries 3 and 4). In this case the molar ratio L/Pd = 1 was optimal.

Finally the Pd-catalyzed allylic alkylation of cinnamyl acetate **11** with ethyl 2-oxocyclohexane-1-carboxylate **12** (Table 5) was inves-

Table 4
Pd-catalyzed desymmetrization of *N*,*N*′-ditosyl-*meso*-cyclopent-4-ene-1,3-diol bis-carbamate **9**[a]

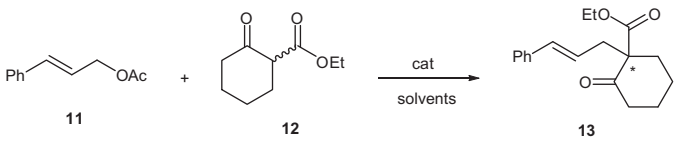


Entry	Ligand	L/Pd	Yield (%)	ee[b,c] (%)
1	**4**	1	49	45 (II)
2	**4**	2	52	46 (II)
3	**5**	**1**	**87**	**70 (II)**
4	**5**	2	90	56 (II)

[a] All reactions were carried out with 5 mol % of $[Pd_2(dba)_3]\cdot CHCl_3$ in THF at 35 °C for 24 h.
[b] The enantiomeric excess of **10** was determined by HPLC (Kromasil 5-CelluCoat, C_6H_{14}/*i*-PrOH = 9:1, 2 mL/min, 219 nm, *t*(I) = 13 min, *t*(II) = 17 min).
[c] The absolute configuration of product **10** was not assigned.

tigated; this is a reaction where a quaternary stereogenic center is generated in the nucleophile. The catalysts were generated from the complex $[Pd(allyl)Cl]_2$ and the corresponding ligand in CH_2Cl_2 and toluene as the medium. Enantioselection occurred when the π-allyl-ligand complex differentiates between the prochiral faces of the approaching reagent. In this mechanism, where the nucleophile attacks on the face of the π-allyl system opposite to that of the chirality inducing metal–ligand complex, the generation of asymmetry appears to be relatively challenging.[5] Ligand **5** is a relatively good stereoselector, but **4** provided much lower asymmetric induction: quaternary-substituted product (*S*)-**13** was obtained in 80% and 37% ee, respectively (Table 5, entries 8 and 4). For diamidophosphite **5** toluene is the solvent of choice and L/Pd = 1:2 is the preferred molar ratio (Table 5, entries 5–10).

Table 5
Pd-catalyzed allylic alkylation of cinnamyl acetate **11** with ethyl 2-oxocyclohexane-1-carboxylate **12**[a]



Entry	Ligand	L/Pd	Solvent	Conversion (%)	ee[b] (%)
1	**4**	1	CH_2Cl_2	77	28 (*S*)
2	**4**	2	CH_2Cl_2	84	25 (*S*)
3	**4**	1	$PhCH_3$	82	33 (*S*)
4	**4**	2	$PhCH_3$	63	37 (*S*)
5	**5**	1:2	CH_2Cl_2	99	58 (*S*)
6	**5**	1	CH_2Cl_2	100	57 (*S*)
7	**5**	2	CH_2Cl_2	95	16 (*S*)
8	**5**	**1:2**	**$PhCH_3$**	**83**	**80 (*S*)**
9	**5**	1	$PhCH_3$	85	73 (*S*)
10	**5**	2	$PhCH_3$	100	21 (*S*)

[a] All reactions were carried out with 2 mol % of $[Pd(allyl)Cl]_2$ at room temperature for 48 h (BSA, $Zn(OAc)_2$).
[b] The conversion of substrate **11** and enantiomeric excess of **13** were determined by HPLC (Kromasil 5-CelluCoat, C_6H_{14}/*i*-PrOH = 95:5, 0.4 mL/min, 254 nm, *t*(*R*) = 14.3 min, *t*(*S*) = 16.4 min).

3. Conclusion

In summary, the following conclusions can be drawn: (i) we have designed and synthesized some novel readily accessible phosphorus-containing stereoinducers. These ligands have the following key advantages: the diamidophosphite nature of their remote phosphite-type moieties, the *P**-chirogenic phosphorus atoms and the 1,3,2-diazaphospholidine rings with balanced electronic characteristics; (ii) these ligands demonstrate moderate to high levels of asymmetric induction in Pd-catalyzed enantioselective allylations of (*E*)-1,3-diphenylallyl acetate, desymmetrizations of *N*,*N*′-ditosyl-*meso*-cyclopent-4-ene-1,3-diol bis-carbamate and in the asymmetric construction of quaternary carbon stereocenters; (iii) overall, diamidophosphite **5** with an oxalamide backbone is a more efficient stereoselector than its ferrocene-based analogue **4**. As a result, studies aimed at estimating the potential of the chiral phosphite-type ligands based on bis(aminoalcohol)oxalamides in asymmetric transition-metal catalysis are currently in progress.

4. Experimental

4.1. General

^{31}P, ^{13}C and ^{1}H NMR spectra were recorded on a Bruker AMX 400 (162.0 MHz for ^{31}P, 100.6 MHz for ^{13}C and 400.13 MHz for ^{1}H) or a Bruker Avance III 600 (242.9 MHz for ^{31}P, 150.9 MHz for ^{13}C and 600.13 MHz for ^{1}H) instrument. The complete assignment of all of the resonances in the ^{1}H and ^{13}C NMR spectra was achieved by the use of APT, DEPT, COSY, HSQC, and NOESY techniques and published data.[46,47,63] Chemical shifts (ppm) are given relative to Me_4Si (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P NMR). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, m = multiplet); coupling constants ^{n}J in Hertz (Hz) integration, '*n*' values are reported in the case of their unambiguous determination. Mass spectra were recorded on a Bruker Daltonics Ultraflex spectrometer (MALDI TOF/TOF). Optical rotations were measured on an Atago AP-300 polarimeter. HPLC analyses were performed on Agilent 1100 and Stayer instruments using Chiralcel® and Kromasil® columns. Elemental analyses were performed on a CHN-microanalyzer Carlo Erba EA1108 CHNS-O.

All manipulations were carried out under a dry argon atmosphere in flame-dried glassware and in freshly dried and distilled solvents. For example, toluene and tetrahydrofuran were freshly distilled from sodium benzophenone ketyl before use; dichloromethane was distilled from NaH. Triethylamine and pyrrolidine were distilled over KOH and then over a small amount of $LiAlH_4$ before use. Thin-layer chromatography was performed on E. Merck pre-coated silica gel 60 F254 and Macherey-Nagel Alugram Alox N/UV_{254} plates. Column chromatography was performed using silica gel MN Kieselgel 60 (230–400 mesh) and MN-Aluminum oxide, basic, Brockmann Activity 1. Phosphorylating reagent (5*S*)-2-chloro-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane **1**, 1,1′-bis(hydroxymethyl)ferrocene **2** and N^1,N^2-bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)oxalamide **3** were prepared analogously to known procedures.[47,65–69] The $[Pd(allyl)Cl]_2$, starting substrate **6**, and $[Pd_2(dba)_3]\cdot CHCl_3$ were obtained as published.[70,71] Pd-catalyzed reactions: allylic sulfonylation of (*E*)-1,3-diphenylallyl acetate **6** with sodium *para*-toluene sulfinate, alkylation with dimethyl malonate, amination with pyrrolidine; desymmetrization of *N*,*N*′-ditosyl-*meso*-cyclopent-4-ene-1,3-diol biscarbamate **9** and allylic alkylation of cinnamyl acetate **11** with ethyl 2-oxocyclohexane-1-carboxylate **12** were performed according to the literature procedures.[47,72,54,62]

Sodium *para*-toluene sulfinate, dimethyl malonate, BSA (*N*,*O*-bis(trimethylsilyl)acetamide), *meso*-cyclopent-4-ene-1,3-diol

8, tosyl isocyanate, cinnamyl acetate **11** and ethyl 2-oxocyclohexane-1-carboxylate **12** were purchased from Aldrich and Acros Organics and used without further purification.

4.2. General procedure for the preparation of ligands 4 and 5

To a vigorously stirred solution of phosphorylating reagent **1** (0.49 g, 2 mmol) and Et_3N (0.56 mL, 4 mmol) in toluene (20 ml) was added the relevant diol **2** or **3** (1 mmol) in one portion. The mixture obtained was stirred for 24 h at 20 °C, then heated to 45 °C, and stirred at this temperature for 1 h, and then cooled to 20 °C. The resulting suspension was filtered through a short plug of aluminum oxide, the column was washed twice with toluene (5 mL), and the solvent was evaporated under reduced pressure (40 Torr). The residue was dried in vacuo (1 Torr) for 1 h. Products **4** and **5** were purified by flash chromatography on aluminum oxide (toluene) and by crystallization from heptane, respectively.

4.2.1. 1,1′-Bis[((2*R*,5*S*)-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octyloxy)methyl]ferrocene 4

Orange viscous oil (0.45 g, yield 68%). $[\alpha]_D^{25} = -284.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400.13 MHz, $CDCl_3$, 26 °C): δ = 1.63–1.70 (m, 2H, C(6)H_2), 1.74–1.81 (m, 2H, C(7)H_2), 1.83–1.91 (m, 2H, C(7)H_2), 2.02–2.11 (m, 2H, C(6)H_2), 3.15–3.24 (m, 4H, C(4)H_2 and C(8)H_2), 3.55–3.63 (m, 2H, C(8)H_2), 3.76–3.80 (m, 2H, C(4)H_2), 3.98–4.0 (m, 2H, CH_{Fc}), 4.01–4.03 (m, 2H, CH_{Fc}), 4.04–4.06 (m, 2H, CH_{Fc}), 4.10–4.12 (m, 2H, CH_{Fc}), 4.15–4.22 (m, 2H, C(5)H), 4.30 (dd, J = 11.3 Hz, J = 6.0 Hz, 2H, CH_2O), 4.49 (dd, J = 11.4 Hz, J = 6.5 Hz, 2H, CH_2O), 6.85 (t, ^3J = 7.4 Hz, 2H, CH_{Ph}), 7.04 (br d, $^3J \sim$ 7.8 Hz, 4H, CH_{Ph}), 7.24 (t, ^3J = 7.6 Hz, 4H, CH_{Ph}). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 26.1 (d, ^3J = 3.5 Hz, C(7)), 31.9 (s, C(6)), 48.7 (d, ^2J = 38.7 Hz, C(8)), 54.9 (d, ^2J = 6.5 Hz, C(4)), 60.1 (d, ^2J = 3.1 Hz, CH_2O), 63.1 (d, ^2J = 8.8 Hz, C(5)), 68.6 (s, CH_{Fc}), 68.7 (s, CH_{Fc}), 69.1 (s, CH_{Fc}), 69.2 (s, CH_{Fc}), 85.0 (s, C_{Fc}), 114.8 (d, ^3J = 11.5 Hz, CH_{Ph}), 118.7 (s, CH_{Ph}), 129.0 (s, CH_{Ph}), 145.7 (d, ^2J = 15.7 Hz, C_{Ph}). MS (MALDI TOF/TOF): *m*/*z* (%) = 677 (15) $[M+Na]^+$, 177 (100) $[C_{11}H_{16}N_2+H]^+$. Anal. Calcd for $C_{34}H_{40}FeN_4O_2P_2$: C, 62.39; H, 6.16; N, 8.56. Found: C, 62.60; H, 6.22; N, 8.21.

4.2.2. N^1,N^2-Bis[(*S*)-1-((2*R*,5*S*)-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octyloxy)-3,3-dimethylbutan-2-yl]oxalamide 5

White powder (0.53 g, yield 76%). $[\alpha]_D^{25} = +208.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400.13 MHz, $CDCl_3$, 27 °C): δ = 0.93 (s, 18H, CH_3), 1.59–1.66 (m, 2H, C(6)H_2), 1.68–1.79 (m, 2H, C(7)H_2), 1.82–1.90 (m, 2H, C(7)H_2), 2.03–2.11 (m, 2H, C(6)H_2), 3.15–3.24 (m, 4H, C(4)H_2 and C(8)H_2), 3.49–3.57 (m, 2H, C(8)H_2), 3.63–3.71 (m, 2H, CH_2O), 3.74 (t, J = 7.8 Hz, 2H, C(4)H_2), 3.78–3.85 (m, 4H, CH_2O and CHN), 4.11–4.18 (m, 2H, C(5)H), 6.84 (t, ^3J = 7.4 Hz, 2H, CH_{Ph}), 7.01 (br d, $^3J \sim$ 8.1 Hz, 4H, CH_{Ph}), 7.24 (t, ^3J = 8.0 Hz, 4H, CH_{Ph}), 7.61 (br d, $^3J \sim$ 9.8 Hz, 2H, NH). ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 26.2 (d, ^3J = 3.8 Hz, C(7)), 26.9 (s, CH_3), 32.1 (s, C(6)), 34.3 (s, C), 48.6 (d, ^2J = 38.3 Hz, C(8)), 54.9 (d, ^2J = 6.9 Hz, C(4)), 57.8 (d, ^3J = 2.3 Hz, CHN), 61.2 (d, ^2J = 4.1 Hz, CH_2O), 63.3 (d, ^2J = 8.8 Hz, C(5)), 114.8 (d, ^3J = 11.6 Hz, CH_{Ph}), 119.0 (s, CH_{Ph}), 129.1 (s, CH_{Ph}), 145.5 (d, ^2J = 15.8 Hz, C_{Ph}), 159.8 (s, CO). MS (MALDI TOF/TOF): *m*/*z* (%) = 719 (10) $[M+Na]^+$, 177 (100) $[C_{11}H_{16}N_2+H]^+$. Anal. Calcd for $C_{36}H_{54}N_6O_4P_2$: C, 62.05; H, 7.81; N, 12.06. Found: C, 62.31; H, 8.02; N, 12.14.

4.3. Catalytic reactions

4.3.1. The Pd-catalyzed allylic sulfonylation of (*E*)-1,3-diphenyl allyl acetate 6 with sodium *para*-toluene sulfinate

A solution of $[Pd(allyl)Cl]_2$ (0.0019 g, 0.005 mmol) and the appropriate ligand (0.01 mmol or 0.02 mmol) in THF (1.5 mL) was stirred for 40 min. Next, (*E*)-1,3-diphenylallyl acetate (0.05 mL, 0.25 mmol) was added and the solution stirred for 15 min, then sodium *para*-toluene sulfinate (0.089 g, 0.5 mmol) was added. The reaction mixture was stirred for a further 48 h, quenched with brine (3 mL) and extracted with THF (3 × 2 mL). The organic layer was washed with brine (2 × 2 mL) and dried over $MgSO_4$. The solvent was evaporated at reduced pressure (40 Torr). Crystallization of the residue from EtOH, followed by desiccation in a vacuum (10 Torr, 12 h), gave (*E*)-1,3-diphenyl-3-tosylprop-1-ene **7a** as white crystals.[73,74] The enantiomeric excess of **7a** was determined by HPLC (Daicel Chiralcel OD-H column, C_6H_{14}/*i*-PrOH = 4:1, 0.5 mL/min, 254 nm, t(*R*) = 16.3 min, t(*S*) = 18.5 min).

4.3.2. The Pd-catalyzed allylic alkylation of (*E*)-1,3-diphenylallyl acetate 6 with dimethyl malonate

A solution of $[Pd(allyl)Cl]_2$ (0.0019 g, 0.005 mmol) and the appropriate ligand (0.01 mmol or 0.02 mmol) in the appropriate solvent (1.5 mL) was stirred for 40 min. Next, (*E*)-1,3-diphenylallyl acetate (0.05 mL, 0.25 mmol) was added and the solution stirred for 15 min. after which dimethyl malonate (0.05 mL, 0.44 mmol), BSA (0.11 mL, 0.44 mmol) and potassium acetate (0.002 g) were added. The reaction mixture was then stirred for 48 h, diluted with CH_2Cl_2 or THF (2 mL) and filtered through a thin layer of silica gel. The filtrate was evaporated at reduced pressure (40 Torr) and dried in vacuo (10 Torr, 12 h) to afford a residue containing (*E*)-dimethyl 2-(1,3-diphenylallyl)malonate **7b**.[75,76] In order to evaluate the ee and conversion, the residue obtained was dissolved in an appropriate eluent mixture (8 mL) and a sample was taken for HPLC analysis (Daicel Chiralcel OD-H column, C_6H_{14}/*i*-PrOH = 99:1, 0.3 mL/min, 254 nm, t(*R*) = 28.0 min, t(*S*) = 29.3 min).

4.3.3. The Pd-catalyzed allylic amination of (*E*)-1,3-diphenylallyl acetate 6 with pyrrolidine

A solution of $[Pd(allyl)Cl]_2$ (0.0019 g, 0.005 mmol) and the appropriate ligand (0.01 mmol or 0.02 mmol) in the appropriate solvent (1.5 mL) was stirred for 40 min. Next, (*E*)-1,3-diphenylallyl acetate (0.05 mL, 0.25 mmol) was added and the solution stirred for 15 min, after which freshly distilled pyrrolidine (0.06 mL, 0.75 mmol) was added. The reaction mixture was stirred for 48 h, diluted with CH_2Cl_2 or THF (2 mL) and filtered through a thin layer of silica gel. The filtrate was evaporated at reduced pressure (40 Torr) and dried in vacuo (10 Torr, 12 h) to afford a residue containing (*E*)-1-(1,3-diphenylallyl)pyrrolidine **7c**.[77,78] In order to evaluate the ee and conversion, the residue obtained was dissolved in an appropriate eluent mixture (8 mL) and a sample was taken for HPLC analysis (Daicel Chiralcel OD-H column, C_6H_{14}/*i*-PrOH/HN(Et)$_2$ = 200:1:0.1, 0.9 mL/min, 254 nm, t(*R*) = 5.0 min, t(*S*) = 6.1 min).

4.3.4. The Pd-catalyzed desymmetrization of *N*,*N*′-ditosyl-*meso*-cyclopent-4-ene-1,3-diol biscarbamate 9

A solution of $[Pd_2(dba)_3]\cdot CHCl_3$ (0.005 g, 0.005 mmol) and the appropriate ligand (0.01 mmol or 0.02 mmol) in THF (1 mL) was stirred for 40 min. The resulting solution was brought to the 35 °C and a solution of *N*,*N*′-ditosyl-*meso*-cyclopent-4-ene-1,3-diol biscarbamate **9** and Et_3N (14 μL, 0.099 mmol) in THF (0.5 mL) was added [compound **9** was prepared in situ as follows: to a solution of the *meso*-cyclopent-4-ene-1,3-diol **8** (0.01 g, 0.099 mmol) in THF (0.5 mL), tosyl isocyanate (35 μL, 0.232 mmol) was added; the mixture was stirred at room temperature for 15 min, heated to 55 °C for 1 h and cooled down to room temperature]. The reaction mixture was then stirred for 24 h. The solvent was removed at reduced pressure (40 Torr) and the residue was purified by flash chromatography on a short pad of silica gel (EtOAc/hexane, 1:4) and dried in vacuo (1 Torr) for 2 h to give the desired product **10** as a slightly brown solid.[79] The enantiomeric excess of **10** was determined by HPLC (Kromasil 5-CelluCoat column, C_6H_{14}/*i*-PrOH = 9:1, 2 mL/min, 219 nm, t(I) = 13 min, t(II) = 17 min).

4.3.5. The Pd-catalyzed allylic alkylation of cinnamyl acetate 11 with ethyl 2-oxocyclohexane-1-carboxylate 12

A solution of $[Pd(allyl)Cl]_2$ (0.0019 g, 0.005 mmol) and the appropriate ligand (0.01 mmol or 0.02 mmol) in the appropriate solvent (1.5 mL) was stirred for 40 min. Next, cinnamyl acetate (0.04 mL, 0.25 mmol) was added and the solution stirred for 15 min. after which ethyl 2-oxocyclohexane-1-carboxylate (0.06 mL, 0.375 mmol), BSA (0.25 mL, 1 mmol), and zinc acetate (0.005 g) were added. The reaction mixture was stirred for 48 h, diluted with CH_2Cl_2 or toluene (2 mL), and filtered through a thin layer of silica gel. The filtrate was evaporated at reduced pressure (40 Torr) and dried in vacuo (10 Torr, 12 h) to afford a residue containing ethyl 1-cinnamyl-2-oxocyclohexanecarboxylate **13**.[62] In order to evaluate the ee and conversion, the residue obtained was dissolved in an appropriate eluent mixture (8 mL) and a sample was taken for HPLC analysis (Kromasil 5-CelluCoat, C_6H_{14}/*i*-PrOH = 95:5, 0.4 mL/min, 254 nm, $t(R)$ = 14.3 min, $t(S)$ = 16.4 min).

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