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Enantioselective synthesis of 1-vinyltetrahydroisoquinolines through palladium-catalysed intramolecular allylic amidation with chiral PhthalaPhos ligands

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ABSTRACT

The PhthalaPhos ligands, chiral BINOL monophosphites endowed with a phthalamide group, have been screened in the synthesis of 1-vinyltetrahydroisoquinolines by intramolecular palladium-catalysed asymmetric allylic amidation (AAA) of achiral tosylamidocarbonates. Identification of the best ligand followed by optimisation of the reaction conditions allowed the desired product to be obtained with up to 83% ee. Remarkably, the reaction is stereoconvergent, affording the same enantiomer of the desired product regardless of the geometry of the allylic carbonate's double bond, which allows, in principle, the use of *E*/*Z* mixtures.

1. Introduction

Chiral 1-vinyltetrahydroisoquinolines are important synthetic targets, that are the key-precursors of the tetrahydroisoquinoline core of several pharmacologically active molecules (i.e., Schulzeines A–C, Almorexant).[1] Efficient synthetic alternatives to traditional routes (i.e., enantioselective Pictet–Spengler and Bischler–Napieralski reaction)[1] are based on asymmetric intramolecular allylic amidations (AAA) using a metal catalyst such as iridium[2] or palladium.[3] In particular, the palladium-catalysed asymmetric substitution of allylic alcohol derivatives with an amine, amide or carbamate has become a powerful tool for the construction of nitrogen heterocycles.[4]

Two research groups have applied this methodology to synthesise 1-vinyltetrahydroisoquinolines (Fig. 1): Katsuki et al. reported that palladium complexes generated from chiral 2-(phosphinophenyl)pyridines as P,N-ligands promote the cyclisation of achiral *cis*-allylic acetates (Fig. 1A) leading to the product with good enantiomeric excess (88%), albeit at a very slow rate (12 day reaction time required for synthetically useful conversion).[3a] Improved reaction rates (10 h for full conversion) and enantioselectivities (up to 96% ee) were achieved by Ojima et al. when they used

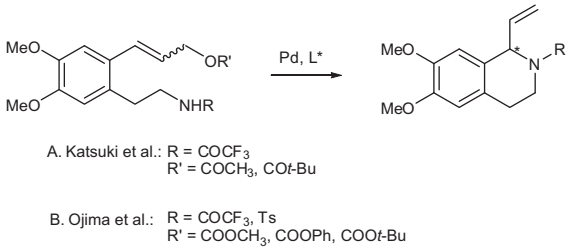

Figure 1. Previously reported syntheses of 1-vinyltetrahydroisoquinolines by Pd-catalysed intramolecular allylation.[3a,b]

cis-allylic carbonates as substrates and chiral biphenol-based monophosphoramidites as ligands (Fig. 1B).[3b]

The same authors also published the catalytic applications of structurally related chiral monodentate phosphites,[5,6] but no results in intramolecular allylic substitutions were reported with these ligands. To the best of our knowledge, the only examples of asymmetric C—N bond forming allylic substitutions promoted by monophosphite Pd-complexes have been reported by Lyubimov, Gavrilov, Tsarev et al., who described the intermolecular AAA of 1,3-diphenyl-3-acetoxyprop-1-ene with nitrogen nucleophiles (up to 74% ee)[7a–d] and the desymmetrisation of a *meso*-1,3-diol biscarbamate (up to 67% ee).[7e]

Our research group has recently developed a new class of chiral BINOL-derived monophosphites, named PhthalaPhos (Fig. 2),[8] which possess a phthalamide functional group capable of supra-

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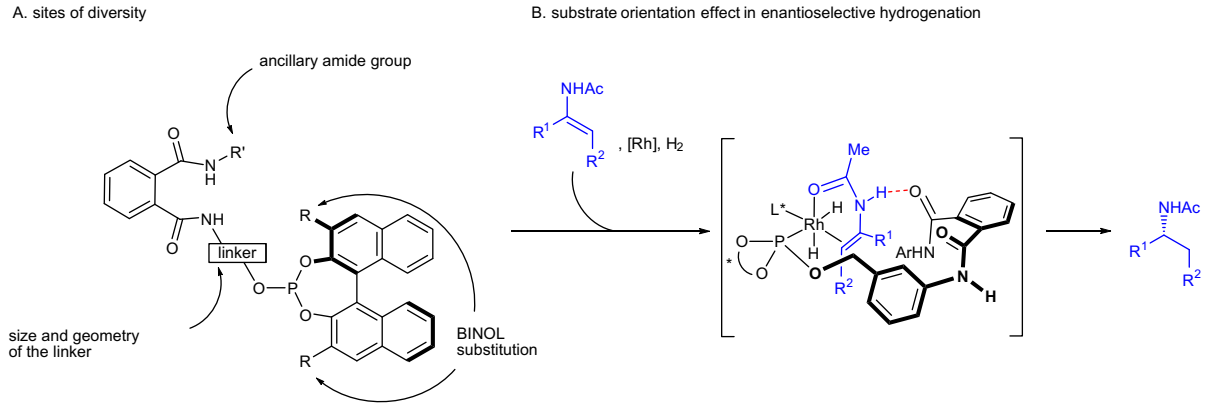


Figure 2. (A) Modular structure of PhthalaPhos ligands; (B) proposed substrate orientation effect in Rh-catalysed hydrogenation (see Ref. 8b).

molecular hydrogen bonding interactions.[9] The PhthalaPhos ligand library has been screened in the rhodium-catalysed hydrogenation of olefins, and has shown excellent levels of enantioselectivity with several dehydroamino ester and enamide substrates. Mechanistic, spectroscopic and computational studies strongly suggest that the phthalamide moiety exerts a substrate orientation effect in the hydrogenation catalytic cycle (Fig. 2B),[8b] which explains their superior enantioselectivity compared to structurally related phosphites devoid of hydrogen bonding groups.

Air-stable and easy to prepare (see below), the PhthalaPhos ligands possess a modular structure featuring the following sites of diversity (Fig. 2A): (i) the linker between the phosphite and the phthalamide moieties; (ii) the substitution on the binaphtholic portion; and (iii) the ancillary amide, namely the amide group which is not connected to the phosphite moiety.

Herein we report the use of the PhthalaPhos ligands in the synthesis of 1-vinyltetrahydroisoquinolines **P1** and **P2** (Fig. 3) by palladium-catalysed intramolecular amidation of allylic carbonates **1** and **2**, as a benchmark reaction to evaluate the catalytic potential of ligands in the enantioselective synthesis of heterocycles.

2. Results and discussion

2.1. Ligand synthesis

The PhthalaPhos ligands can be synthesised via a straightforward four-step protocol,[8] which is exemplified by the preparation of ligand **L4** (Scheme 1).[10]

2.2. PhthalaPhos ligand library screening

The PhthalaPhos library was initially screened in the cyclisation of the *trans*-allylic carbonate (*E*)-**1a** (Fig. 3)[3b] in order to select the most promising ligand, to be used for further optimisation of the reaction conditions. In each experiment, substrate (*E*)-**1a** was treated with a catalytic amount of the palladium complex generated

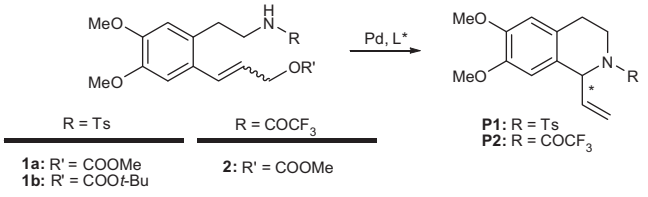
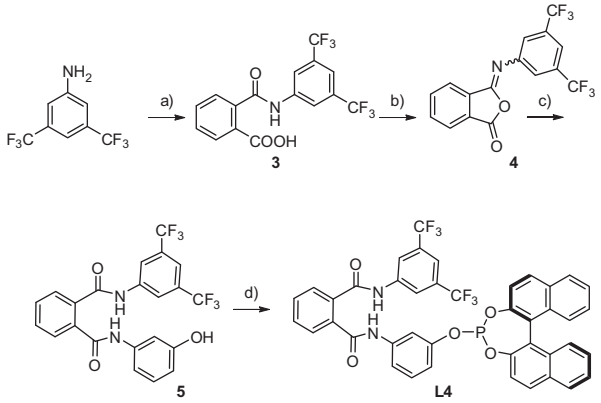


Figure 3. Synthesis of 1-vinyltetrahydroisoquinolines using PhthalaPhos ligand palladium complexes.



Scheme 1. Synthesis of ligand **L4**. Reagents and conditions: (a) Phthalic anhydride, $CHCl_3$, reflux, 98%; (b) $(CF_3CO)_2O$, TEA, THF, 0 °C to rt, 99%; (c) 3-aminophenol, THF, rt, quantitative; (d) (*S*)-BINOL-PCl, TEA, THF, rt, 68%.

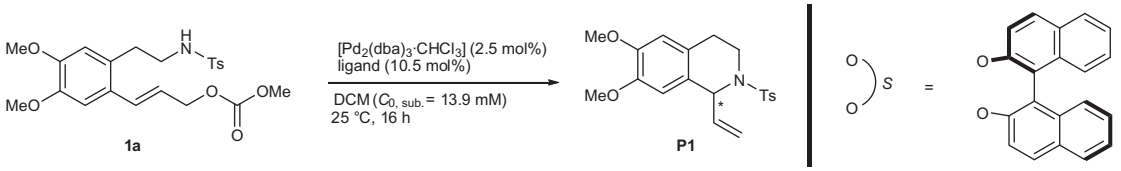
in situ from 2.5 mol % of $[Pd_2(dba)_3{\cdot}CHCl_3]$ (5 mol % of Pd) and 10.5 mol % of the selected ligand in DCM at 25 °C. The reaction conditions and results are shown in Table 1.

The size and geometry of the linker between the phosphite moiety and the diamide group turned out to strongly affect the catalytic properties. Phosphites **L1**, **L2** and **L4**, with a *meta*-substituted phenol linker, gave full conversion and moderate enantioselectivity (entries 3, 4 and 6), while ligand **L10**, featuring a *para*-substituted phenol linker, gave incomplete conversion and lower stereocontrol (entry 12). Benzyl phosphites **L5-7**, **L8-9** and **L11-15** led to full conversion in most cases (entries 7–9, 10–11 and 14–15), but with very low or no enantioselectivity. Finally, no reaction occurred in the presence of naphthyl phosphite ligands **L16-17** or with ligand **L18**, featuring an aliphatic linker (entries 18–20).

The ancillary amide (i.e., not bearing the phosphite group) strongly affects the catalytic behaviour, as can be observed by comparing the results obtained with ligands **L1**, **L3** and **L4**, which only differ in this structural element: an aromatic ancillary amide is necessary in order to achieve full conversion (entries 3 and 6), while only trace amounts of the desired product were formed with **L3**, possessing a *n*-butyl amide group (entry 5). The more acidic 3,5-bis(trifluoromethyl)phenyl group of **L4** gave a better enantioselectivity than the 4-butylphenyl amide of **L1** (entry 6 vs entry 3). No reaction took place when (*E*)-**1a** was treated with $[Pd_2(dba)_3{\cdot}CHCl_3]$ in the absence of any ligand (entry 21).

It is noteworthy that palladium complexes of ligands **L1**, **L2** and **L4** gave enantiomeric excesses which exceeded those obtained in

Table 1
Results of the screening of PhthalaPhos ligand library in the Pd-catalysed allylic amidation of (*E*)-**1a**



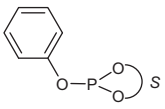
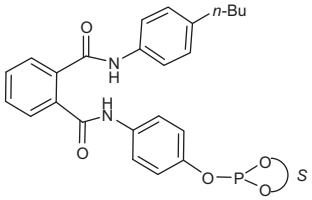
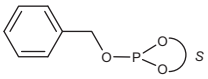
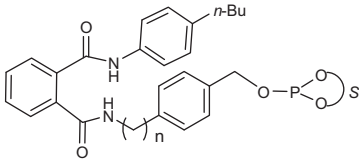
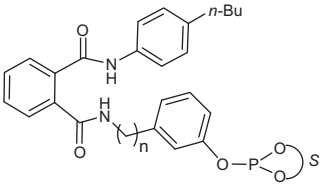
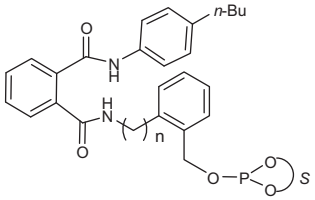
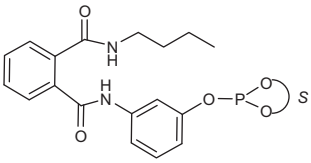
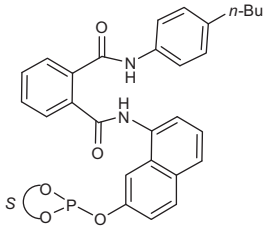
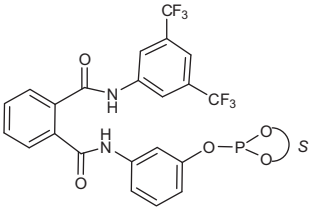
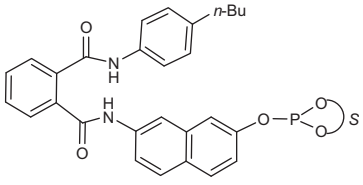
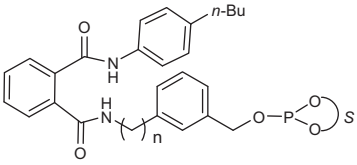
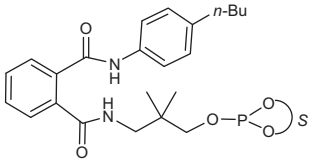
Entry	Ligand	Conv. (%)[a]	ee (%),[b] abs. conf.[c]	Entry	Ligand	Conv.[a] (%)	ee[b] (%), abs. conf.[c]
							
1	**6**	100	12, (*R*)	12	**L10**	90	8, (*S*)
							
				13	**L11** (*n* = 0)	19	0
				14	**L12** (*n* = 1)	100	5, (*R*)
2	**7**	17	0	15	**L13** (*n* = 2)	100	4, (*R*)
							
3	**L1** (*n* = 0)	100	30, (*R*)	16	**L14** (*n* = 1)	20	n. d.
4	**L2** (*n* = 2)	100	37, (*R*)	17	**L15** (*n* = 2)	<5	n. d.
							
5	**L3**	<5	n. d.	18	**L16**	<5	n. d.
							
6	**L4**	100	**43**, (*R*)	19	**L17**	<5	n. d.
							
7	**L5** (*n* = 0)	100	0				
8	**L6** (*n* = 1)	100	0				
9	**L7** (*n* = 2)	100	5, (*R*)	20	**L18**	<5	n. d.

Table 1 (*continued*)

Entry	Ligand	Conv. (%)[a]	ee (%),[b] abs. conf.[c]	Entry	Ligand	Conv.[a] (%)	ee[b] (%), abs. conf.[c]
10	**L8** (n = 0)	100	12, (*R*)	21	None	0	—
11	**L9** (n = 1)	100	0				

[a] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Determined by HPLC analysis (column: Chiralpak AD-H; eluent: 8:2 hexane/*i*-PrOH) of the product purified by flash chromatography.
[c] Assigned by comparison of the sign of the specific rotation with the literature data (see Ref. 3b).

the presence of reference (*S*)-BINOL-phosphites **6** and **7**, which lack the phthalamide fragment (entries 3, 4, 6 vs entries 1, 2). These results suggest that the diamide moiety plays an important role in determining the stereochemical course of the reaction. It is likely that, analogously to what we observed for rhodium-catalysed hydrogenations,[8b] the PhthalaPhos ligands' amide groups take part in guiding the approach of the substrate towards the metal through the formation of a hydrogen bonding interaction. These ligand–substrate secondary interactions[9] have already been suggested for palladium-catalysed allylations carried out in the presence of bidentate ligands possessing polar groups (such as Trost's[11] and Hayashi's-Ito's[9,12] ligands).

2.3. Reaction condition optimisation

Optimisation of the intramolecular palladium-catalysed AAA of (*E*)-**1a** in the presence of the best performing ligand **L4** began with solvent screening. Results reported in Table 2 show that aromatic solvents are best suited for this reaction. In particular, using toluene, benzene, *m*-xylene and chlorobenzene led to significantly improved ee values (entries 3–6) compared to DCM or 1,2-dichloroethane (entries 1–2). On the other hand, aliphatic hydrocarbons, such as hexane and cyclohexane, gave modest conversion and poor enantioselectivity (entries 8–9). The use of coordinating solvents (entries 10–12) resulted in high or complete substrate conversion but reduced enantioselectivity, which is consistent with the hypothesised occurrence of ligand–substrate hydrogen bonding interactions. Remarkably, reversed stereodiscrimination was observed in acetonitrile and isopropanol (entries 11–12). Accordingly, further optimisation of the reaction parameters was carried out in toluene, which is less toxic than benzene and more volatile than *m*-xylene and chlorobenzene.

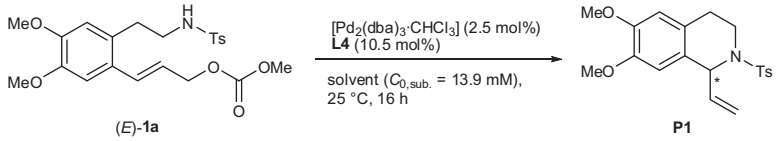
Results summarised in Table 3 indicate that a palladium-to-ligand ratio of 1/2 provides the best combination of activity and stereoselectivity (entry 3 vs entries 1–2). When the catalyst loading was reduced to 2.5 mol %, conversion turned out to be incomplete and the ee dropped to 50% (entry 4). Moreover, the use of a π–allylpalladium chloride dimer as the palladium source gave very low conversion and ee (entry 5). Finally, we observed that the enantioselectivity increased up to 73% when the reaction was carried out at 0 °C for 16 h (entry 6). Lowering the temperature to −10 °C made the reaction slower and less enantioselective (entry 7).

2.4. Impact of the substrate structure on the enantioselectivity

With the optimised reaction conditions established, we reacted the allylic carbonates (*Z*)-**1a**, (*Z*)-**2a** and (*E*)-**1b** (Fig. 3) to study the effect of their structural features on the reaction (Table 4).

We observed that the olefin geometry did not affect the sense of enantiocontrol: (*E*)- and (*Z*)-isomers of **1a** both led to the (*R*)-enantiomer of **P1**, although in the latter case the reaction was slower

Table 2
Solvent effect on the intramolecular amidation of (*E*)-**1a** catalysed by the **L4**–Pd complex

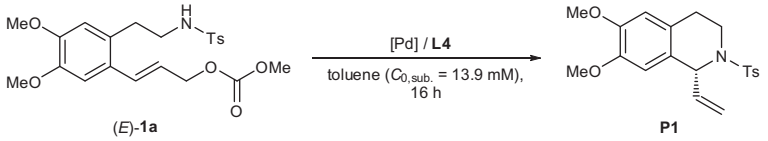


(*E*)-**1a** **P1**

Entry	Solvent	Conversion[a] (%)	ee (%), abs. conf. [b]
1	DCM	100	43, (*R*)
2	1,2-DCE	100	30, (*R*)
3	Toluene	100	**63**, (***R***)
4	Benzene	100	**64**, (***R***)
5	Chlorobenzene	100	**62**, (***R***)
6	*m*-Xylene	100	**64**, (***R***)
7	Anisole	100	50, (*R*)
8	Hexane	28	28, (*R*)
9	Cyclohexane	41	26, (*R*)
10	THF	100	7, (*R*)
11	*i*-PrOH	100	19, (*S*)
12	CH_3CN	95	23, (*S*)

[a] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] See the footnotes of Table 1.

Table 3
Effect of Pd/**L4** ratio, catalyst loading, Pd source and temperature in the AAA of (*E*)-**1a** in toluene



(*E*)-**1a** **P1**

Entry	Pd catalyst (mol %)	Pd/L	*T* (°C)	Conv.[a] (%)	ee[b] (%)
1[c]	$[Pd_2(dba)_3]\cdot CHCl_3$ (2.5)	1/2	25	100	63
2	$[Pd_2(dba)_3]\cdot CHCl_3$ (2.5)	1/1	25	100	59
3	$[Pd_2(dba)_3]\cdot CHCl_3$ (2.5)	1/3	25	85	59
4	$[Pd_2(dba)_3]\cdot CHCl_3$ (1.25)	1/2	25	90	50
5	$[Pd(allyl)Cl]_2$ (2.5)	1/2	25	53	50
6	$[Pd_2(dba)_3]\cdot CHCl_3$ (2.5)	1/2	0	**100**	**73**
7[d]	$[Pd_2(dba)_3]\cdot CHCl_3$ (2.5)	1/2	−10	75	61

[a] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] (*R*)-Configuration (determined as shown in Table 1) in all cases.
[c] No effect on conversion and ee was observed using a substrate concentration of 6.95 mm and 27.8 mm, respectively.
[d] Reaction time = 48 h.

Table 4
Cyclisation of structurally modified substrates

Entry	Substrate	*T* (°C)	*t* (h)	Conv.[a] (%)	ee (%), abs. conf.	Yield[b] (%)
1	(*E*)-**1a**	0	16	100	73, (*R*)[c]	82
2	(*Z*)-**1a**	0	104	100	62, (*R*)[c]	85
3	(*Z*)-**2**	25	20	100[d]	9,[e] (*R*)[f]	59
4	(*E*)-**1b**	0	44	**100**	**83**, (***R***)[c]	81

[a] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Isolated yields.
[c] See the footnotes of Table 1.
[d] 30% conversion after 104 h at 0 °C.
[e] Determined by HPLC analysis (column: Chiralpak OJ-H; eluent: 9:1 hexane/*i*-PrOH) of the product purified by flash chromatography.
[f] Assigned by comparison of the HPLC elution order with the literature data (see Ref. 2).

(entry 2 vs entry 1). The *cis*-isomer (*Z*)-**1a** gave the product in high yield and with slightly lower enantiopurity (62% ee) than the *trans* counterpart (73% ee). Since the reaction is stereoconvergent, substrates with low *E*/*Z* purity can in principle be employed without a significant erosion of the ee. On the contrary, Ojima reported that the reaction of the same substrates, in the presence of chiral monophosphoramidite ligands, is stereodivergent: (*E*)-**1a** affords (*R*)-**P1** with 71% ee, while (*Z*)-**1a** gives the opposite enantiomer (*S*)-**P1** with 74% ee.[3b]

The nature of the nucleophile greatly influences the reaction selectivity, as observed when switching from (*Z*)-**1a** to (*Z*)-**2**, containing the trifluoroacetyl group as a nitrogen substituent (Fig. 3): the latter underwent full conversion at 25 °C, and the desired tetrahydroisoquinoline (*R*)-**P2** was isolated in good yield but dramatically lower ee (entry 3 vs entry 2). By contrast, Ojima reported that the same substrate led to (*S*)-**P2** with 79% ee with monophosphoramidite ligands.[3b]

The size of the leaving group also has an impact on the stereochemical outcome of the reaction: allylic *t*-Bu-carbonate (*E*)-**1b** gave (*R*)-**P1** with higher ee (83%) compared to the corresponding Me-carbonate (*E*)-**1a** (entry 4 vs entry 1). Until now, this is the best result obtained in the synthesis of chiral *N*-Ts substituted tetrahydroisoquinolines.

3. Conclusion

In conclusion, we have shown that PhthalaPhos ligands[8] can be successfully employed in palladium-catalysed transformations: the screening of the library allowed the identification of an efficient ligand **L4** for the synthesis of *N*-tosyl-1-vinyltetrahydroisoquinoline **P1** by palladium-catalysed intramolecular asymmetric allylic amidation (AAA). For the first time, monophosphite ligands could be used for carrying out this transformation with full conversion and good enantioselectivity (up to 83% ee). The diamide functionality of the PhthalaPhos ligands plays a key role in determining their activity and stereoselectivity in this reaction, and it is likely involved in substrate orientation effects. We are currently exploring new applications of PhthalaPhos ligands in other palladium-catalysed enantioselective transformations.

4. Experimental

4.1. General

All reactions were carried out in flame-dried glassware with magnetic stirring under a nitrogen atmosphere, unless otherwise stated. Solvents for reactions were distilled over the following

drying agents and transferred under nitrogen: THF (Na), Et_3N (CaH_2). Dry Et_2O and DCM (over molecular sieves in bottles with crown cap) were stored under nitrogen. Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness). Visualisation was accomplished by irradiation with a UV lamp and/or staining with a ceric ammonium molybdate solution. Flash column chromatography was performed using silica gel (60 Å, particle size 40–64 μm) as stationary phase, following the procedure by Still and co-workers.[13] Proton NMR spectra were recorded on a spectrometer operating at 400.13 MHz. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm; CD_2Cl_2, δ = 5.32 ppm; $[D]_6$acetone, δ = 2.05 ppm; CD_3OD, δ = 3.33 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet–doublet, td = triplet–doublet. ^{13}C NMR spectra were recorded on a 400 MHz spectrometer operating at 100.56 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.23 ppm; CD_2Cl_2, δ = 54.00 ppm; $[D]_6$acetone, δ = 206.26 ppm and 29.84 ppm; CD_3OD, δ = 49.05 ppm). ^{31}P NMR spectra were recorded on a 400 MHz spectrometer operating at 162 MHz, with complete proton decoupling. ^{31}P NMR chemical shifts are reported in ppm (δ) relative to external 85% H_3PO_4 at 0 ppm (positive values downfield). ^{19}F NMR were recorded on a 300 MHz spectrometer operating at 282 MHz. ^{19}F NMR chemical shifts are reported in ppm (δ) relative to external $CFCl_3$ at 0 ppm (positive values downfield). The coupling constant values are given in Hz. Infrared spectra were recorded on a standard FT/IR spectrometer. Optical rotation values were measured on an automatic polarimeter with a 1 dm cell at the sodium D line (λ = 589 nm). High resolution mass spectra (HRMS) were performed on a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II and Xmass software (Bruker Daltonics)—4.7 T Magnet (Magnex) equipped with ESI source, available at CIGA (Centro Interdipartimentale Grandi Apparecchiature) c/o Università degli Studi di Milano.

The synthesis and characterisation of ligands **L1**-**3**/**L5**-**18** have been reported elsewhere.[8] Ligands **6** and **7** are known compounds,[14] that we prepared according to a published procedure.[15] Chlorophosphite (*S*)-BINOL-PCl was prepared from (*S*)-BINOL on a gram scale according to a literature procedure.[16] Substrates (*Z*)-**1a**, (*E*)-**1a**, (*E*)-**1b** and (*Z*)-**2a** were prepared following published procedures.[3b,c]

4.2. Synthesis of ligand L4

4.2.1. N^1-(3,5-Bis(trifluoromethyl)phenyl)-N^2-(3-hydroxyphenyl) phthalamide 5

Phthalisoimide **4**[8] (184.2 mg, 0.513 mmol, 1 equiv) was added to a stirred 0.11 M solution of 3-aminophenol (67.2 mg, 0.6154 mmol, 1.2 equiv) in THF. The mixture was stirred overnight at rt. The mixture was diluted with AcOEt (triple volume with respect to THF) and washed three times with 1 M HCl. The organic phase was dried over Na_2SO_4 and evaporated. Purification by flash chromatography (9:1 and then 8:2 DCM/AcOEt) afforded the product as a white solid. Yield: 240 mg (quantitative). mp = 134–135 °C; ^1H NMR (400 MHz, CD_3OD): δ = 8.32 (s, 2H), 7.77 (m, 2H), 7.68 (s, 1H), 7.67 (m, 2H), 7.27 (t, ^4J(H,H) = 1.6 Hz, 1H), 7.14 (t, ^3J(H,H) = 8.1 Hz, 1H), 7.04 (d, ^3J(H,H) = 8.1 Hz, 1H), 6.59 (dd, ^3J(H,H) = 8.1 Hz, ^4J(H,H) = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 170.1, 169.4, 158.9, 142.1, 140.8, 137.6, 137.0, 133.2 (q, ^2J(C,F) = 33.3 Hz), 131.8, 131.6, 130.5, 129.1, 129.1, 124.7 (q, ^2J(C,F) = 272.0 Hz), 121.1, 117.9, 113.2, 112.8, 109.1; ^{19}F NMR (282 MHz, CD_3OD): δ = −65.0 (s); IR (KBr): ν = 3270.7, 1644.0, 1416.5, 1382.7, 1277.6, 1129.1, 886.1 cm^{-1}; HRMS (ESI−): *m*/*z* 467.08378 $[M-H]^-$ (calcd for $C_{22}H_{13}N_2O_3F_6$: 467.08359).

4.2.2. N^1-(3,5-Bis(trifluoromethyl)phenyl)-N^2-(3-((11b*S*)-dinaphtho [2,1-d:1′,2′-*f*][1,3,2]dioxaphosphepin-4-yloxy)phenyl)phthalamide L4

(*S*)-BINOL-PCl (96.4 mg, 0.274 mmol, 1 equiv) was added to a stirred 0.1 M solution of alcohol **5** (128.3 mg, 0.274 mmol, 1 equiv) and Et_3N (0.115 mL, 83.2 mg, 0.822 mmol, 3 equiv) in THF. The obtained mixture was stirred overnight and then filtered through a pad of Celite (rinsing with THF). The solvent was evaporated under reduced pressure and the crude product was purified by trituration with 4:1 Et_2O/DCM, which gave a white solid. Yield: 146.1 mg (68%). Mp = 167–168 °C; $[\alpha]_D^{20}$ = +43.3 (*c* 0.96, acetone); ^1H NMR (400 MHz, $[D]_6$acetone): δ = 10.27 (s, 1H), 9.85 (s, 1H), 8.46 (s, 2H), 8.18 (d, ^3J(H,H) = 8.8 Hz, 1H), 8.09 (d, ^3J(H,H) = 8.2 Hz, 1H), 8.03 (d, ^3J(H,H) = 8.8 Hz, 1H), 8.01 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.89 (s, 1H), 7.81–7.74 (m, 2H), 7.70 (s, 1H), 7.67 (d, ^3J(H,H) = 8.8 Hz, 1H), 7.62–7.48 (m, 6H), 7.39–7.32 (m, 5H), 7.00 (dd, ^3J(H,H) = 8.1 Hz, ^4J(H,H) = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $[D]_6$acetone): δ = 168.5, 167.6, 152.6, 148.5, 147.8, 142.2, 141.8, 137.4, 137.1, 133.6, 133.3, 132.8, 132.6 (q, ^2J(C,F) = 33.0 Hz), 131.8, 131.4, 131.2, 131.0, 131.0, 129.6, 129.4, 128.9, 127.5, 127.4, 127.4, 127.3, 126.4, 126.1, 125.1, 124.4 (q, ^2J(C,F) = 272.2 Hz), 123.5, 122.7, 122.5, 120.4, 117.4, 116.7, 116.6, 116.5, 112.8; ^{31}P NMR (162 MHz, $[D]_6$acetone): δ = 144.6 (s); ^{19}F NMR (282 MHz, $[D]_6$acetone): δ = −64.0 (s); IR (KBr): ν = 3248.5, 3057.1, 1648.8, 1585.7, 1472.4, 1438.5, 1382.7, 1277.6, 1133.9, 948.8 cm^{-1}; HRMS (ESI+): *m*/*z* 805.12915 $[M+Na]^+$ (calcd for $C_{42}H_{25}N_2O_5F_6PNa$: 805.12975).

4.3. Allylic amination cyclisation experiments

4.3.1. General procedure for the ligand screening in the allylation of substrate (*E*)-1a (Table 1)

In each vessel of a carousel multireactor at 25 °C, [$Pd_2(dba)_3$·$CHCl_3$] was added as a 2.781 mM DCM stock solution (0.2 mL, 0.556 μmol, 0.025 equiv), followed by the selected ligand (2.336 μmol, 0.105 equiv) and by 1.3 mL of DCM. The resulting mixture was stirred for 10 min and then a 0.222 M DCM solution of substrate (*E*)-**1a** (0.1 mL, 22.2 μmol, 1 equiv) was added. The reaction mixture was stirred overnight (conversion was monitored by TLC with 7:3 hexane/AcOEt eluent), then the solvent was quickly evaporated. The conversion was determined by proton NMR analysis of the residue.[17] Reaction product **P1**[3b] was purified by flash chromatography (eluent: DCM), and then analysed by chiral HPLC for determining the enantiomeric excess (column: Daicel Chiralpak AD-H; eluent: 8:2 hexane/*i*-PrOH; flow: 0.8 mL/min; λ = 210 nm; t_R = 23.5 min [(*S*)-enantiomer] and 33.4 min [(*R*)-enantiomer][18]). R_f 0.29 (DCM). ^1H NMR of product **P1**[3b] (400 MHz, CD_2Cl_2): δ = 7.64 (d, ^3J(H,H) = 7.5 Hz, 2H), 7.22 (d, ^3J(H,H) = 7.5 Hz, 2H), 6.53 (s, 1H), 6.47 (s, 1H), 5.89 (ddd, ^3J(H,H) = 17.0, 10.2, 5.8 Hz, 1H), 5.40 (d, ^3J(H,H) = 5.8 Hz, 1H), 5.15 (d, ^3J(H,H) = 10.2 Hz, 1H), 5.05 (d, ^3J(H,H) = 17.0 Hz, 1H), 3.83 (dd, ^3J(H,H) = 13.7, 6.0 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.30 (m, 1H), 2.64 (m, 1H), 2.50 (m, 1H), 2.37 (s, 3H).

4.3.2. General procedure for the next catalytic tests (Tables 2–4)

In each vessel of a carousel multireactor at 25 °C, [$Pd_2(dba)_3$·$CHCl_3$] was added as a 2.781 mM DCM stock solution (0.2 mL, 0.556 μmol, 0.025 equiv). Next, DCM was evaporated off under high vacuum and then the residue was re-dissolved in the selected solvent (0.5 mL). Ligand **L4** (1.8 mg, 2.336 μmol, 0.105 equiv) was added, followed by 1 mL of the selected solvent. The resulting mixture was stirred for 10 min and then the temperature was set to the selected value (if different from 25 °C). A 0.222 M DCM solution

of substrate (0.1 mL, 22.2 μmol, 1 equiv) was then added. The reaction mixture was stirred overnight (conversion was monitored by TLC with 7:3 hexane/AcOEt eluent), then the solvent was quickly evaporated. The residue was dissolved in CD_2Cl_2[17] and the conversion was determined by proton NMR. For product **P1**, the purification and determination of the ee were carried out as described above. Product **P2**[2,3b] was purified by flash chromatography (eluent: 3:1 hexane/AcOEt), and then analysed by chiral HPLC for determining the enantiomeric excess (column: Daicel Chiralcel OJ-H; eluent: 9:1 hexane/*i*-PrOH; flow: 0.7 mL/min; $\lambda = 210$ nm; $t_R = 19.5$ min [*S* enantiomer] and 24.5 min [*R* enantiomer][19]). R_f of **P2** 0.25 (3:1 hexane/AcOEt). ^{1}H NMR of product **P2** (400 MHz, CD_2Cl_2): mixture of rotamers A and B (6:4). $\delta = 6.69$ (s, 1H, rotamer B), 6.67 (s, 1H, rotamer A), 6.65 (s, 1H, rotamer A), 6.61 (s, 1H, rotamer B), 6.07–5.94 (m, 2H), 5.47–5.32 (m, 1H, overlapped with the solvent peak), 5.20–5.06 (m, 1H), 4.48 (m, 1H, rotamer B), 4.02 (m, 1H, rotamer A), 3.84 (s, 3H), 3.83 (s, 3H, rotamer B), 3.82 (s, 3H, rotamer A), 3.58 (m, 1H, rotamer A), 3.29 (m, 1H, rotamer B), 2.99 (m, 1H), 2.78 (m, 1H).

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17. The use of $CDCl_3$ led to acid-catalysed non-stereoselective cyclisation to **P1** or **P2**.
18. The absolute configuration was assigned by comparison of the specific rotation with the literature data (see Ref. 3b).
19. Assigned by comparison of HPLC elution order with the literature data (see Ref. 2).