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Design of a new class of chiral quinoline–phosphine ligands. Synthesis and application in asymmetric catalysis

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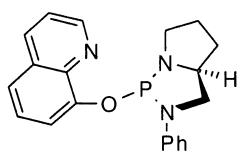
Abstract—The design and synthesis of a new class of chiral quinoline–phosphine ligands has been achieved. Their efficiency as asymmetric ligands in enantioselective palladium-catalyzed allylic substitution reactions and in the asymmetric copper-catalyzed addition of diethylzinc to enones was also investigated. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

In recent years, various C_2-symmetric and non-symmetric chiral ligands bearing phosphine, nitrogen and/or sulfur residues have been developed and used in numerous transition-metal-catalyzed reactions[1] such as hydrogenation[2] and allylic substitution.[3] Thus, a wide class of non-symmetric chiral PN- and SN-type compounds were found to be efficient ligands for catalytic asymmetric reactions on the basis of their electronic and steric properties.[4,5] In almost all cases, the phosphorus atom is not stereogenic but chiral oxazoline or imidazoline moieties impart the chirality and have been recognized as being important for inducing high enantioselectivities.[4b] In the context of our studies, we have recently described the synthesis of the new non-symmetric homochiral *P*-quinoline phosphine ligand, (2*R*,5*S*)-2-(8-quinolinoxy)-3-phenyl-1,3-diaza-2-phosphabicyclo-[3.3.0]octane (QUIPHOS), with chirality at the phosphorus atom (Scheme 1).[6]

Due to its high stability, this ligand has been successfully used in asymmetric palladium-catalyzed allylic substitutions,[7] copper-catalyzed Diels–Alder reactions[8] and the enantioselective conjugate addition of diethylzinc to enones.[9] Herein, we report our investigations into the synthesis of a new class of chiral quinoline–phosphine ligands analogous to QUIPHOS **1**, varying the nature of the chiral moiety and/or the substituents attached to the quinoline group.

QUIPHOS **1**



Scheme 1.

2. Results

The synthesis of this new class of bidentate chiral ligands was easily achieved by an exchange reaction between tris(dimethylamino)phosphine and a chiral auxiliary such as a diamine, a diol or an aminoalcohol in refluxing toluene followed by addition of 1 equiv. of the desired substituted hydroxyquinoline (Scheme 2).

Thus, we first modified the structure of the chiral moiety attached to the phosphorus atom of the original QUIPHOS compound. In this case, the desired ligands **2**–**7** were easily obtained in workable yields varying from 48 to 62% (Scheme 3).

Modification of the quinoline structure was also envisaged[10] and was completed as outlined above. Ligands **8**–**14**, analogous to the QUIPHOS structure, were synthesized in moderate to good yields and characterized by NMR spectroscopy (Table 1).

The catalytic properties of the palladium complexes formed in situ from these ligands and $[Pd(allyl)Cl]_2$ in an allylic substitution of 1,3-diphenyl-2-propenyl acetate **15** by benzylamine or a nucleophile generated from dimethylmalonate with bis(trimethylsilyl)acetamide (BSA) and a small amount of potassium acetate were investigated under the best reported[7] experimental conditions (Table 2).

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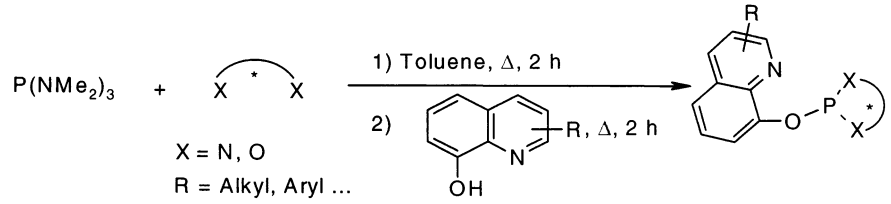
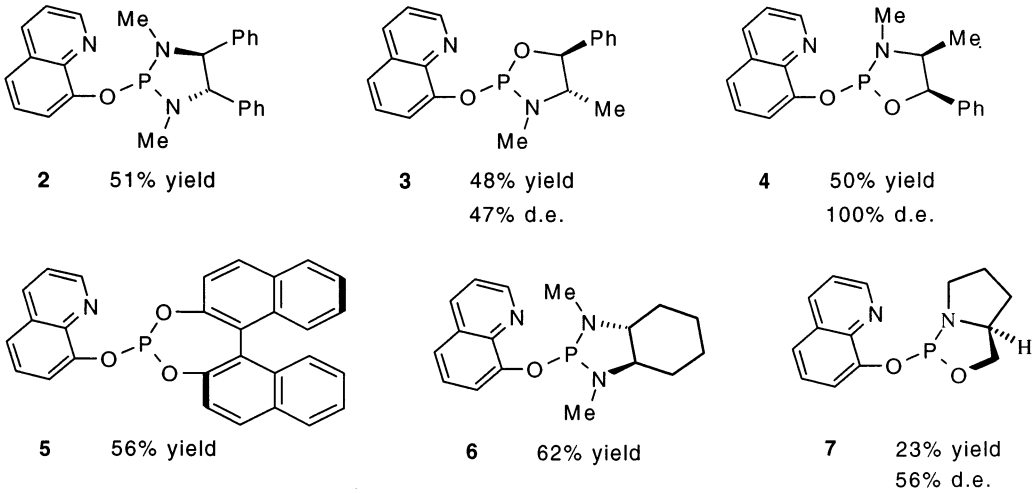
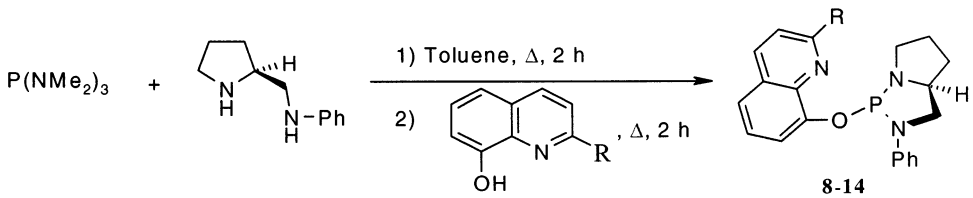


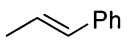
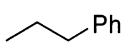
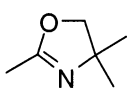
Scheme 2.



Scheme 3.

Table 1. Synthesis of various substituted QUIPHOS ligands

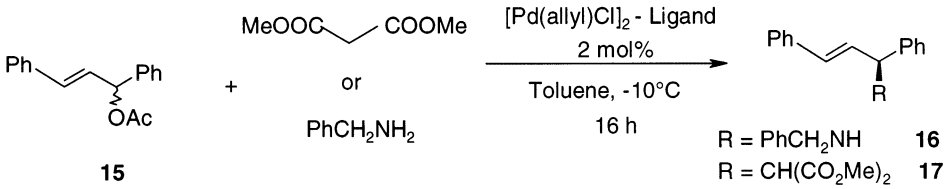


Entry	Ligand	R	Yield (%)[a]	Diastereomeric ratio (*anti*/*syn*)[b]
1	**8**	Me	49	100 / 0
2	**9**	Ph	45	100 / 0
3	**10**	*tert*-Bu	35	100 / 0
4	**11**	CN	72	100 / 0
5	**12**		22	92 / 8
6	**13**		51	97 / 3
7	**14**		46	77 / 23

[a] Isolated yield.
[b] Diastereomeric ratio determined by ^{31}P NMR spectroscopy analysis (see Ref. 11).

Replacement of the (*S*)-2-anilinomethyl pyrrolidine moiety in ligands **2**–**7** led to a significant decrease in catalytic efficiency. Poor conversions and low e.e.s were observed, demonstrating the importance of this structure on the outcome of the reaction. On the other hand, slight modifications at the quinoline group led in almost

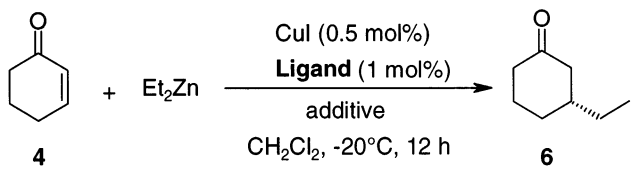
Table 2. Enantioselective catalytic palladium allylic substitution using various substituted QUIPHOS ligands



Entry[a]	Ligand	**16**		**17**	
		Yield (%)	E.e. (%)	Yield (%)	E.e. (%)
1	**1**	100	93 (*S*)	100	85 (*R*)
2	**2**	78	12 (*S*)	94	15 (*R*)
3	**3**	81	6 (*S*)	68	10 (*R*)
4	**4**	86	35 (*S*)	79	27 (*R*)
5	**5**	91	33 (*S*)	89	31 (*R*)
6	**6**	0	0	56	29 (*R*)
7	**7**	2	n.d.	0	–
8	**8**	60	38 (*S*)	100	42 (*R*)
9	**9**	100	72 (*S*)	100	64 (*R*)
10	**10**	100	59 (*S*)	100	41 (*R*)
11	**11**	15	60 (*S*)	95	74 (*R*)
12	**12**	100	76 (*S*)	75	41 (*R*)
13	**13**	83	78 (*S*)	75	36 (*R*)
14	**14**[b]	100	50 (*S*)	93	48 (*R*)

[a] Conversion and e.e. determined by HPLC analysis on a Daicel Chiralcel OD-H column using hexane/*i*-PrOH (200:1) as eluent (254 nm, 1 mL/min; see Section 4).
[b] Mixture of diastereomeric ligands (77:23).

Table 3. Enantioselective Cu(I)-catalyzed additions of Et_2Zn to cyclohexenone using ligands **1**–**14**



Entry[a]	Ligand	No additive		$Zn(OH)_2$ (0.25 equiv.)	
		Yield (%)	E.e. (%)	Yield (%)	E.e. (%)
1	**1**	100	7	100	53
2	**2**	84	25	91	20
3	**3**	100	0	68	2
4	**4**	64	0	67	1
5	**5**	0	–	0	–
6	**6**	84	27	89	25
7	**7**	100	2	98	2
8	**8**	100	35	100	42
9	**9**	100	30	100	29
10	**10**	97	25	97	15
11	**11**	95	38	95	44
12	**12**	100	40	100	50
13	**13**	100	41	100	51
14	**14**[b]	96	46	96	55

[a] Conversion and e.e. determined by GC analysis on a Macherey Nagel FS-Lipodex E column, 25 m×0.25 mm, He pressure 60 kPa, 58–115°C, 3°C/min (see Section 4).
[b] Mixture of diastereomeric ligands (77:23).

all cases to good conversions varying from 75 to 100% (entries 8–14). Depending on the nature of the substituent attached to the quinoline ring, poor to moderate enantioselectivities were seen and enantioselectivities were less good than those seen using QUIPHOS **1**. At this time it is difficult to correlate the influence of the structural features and the observed e.e.s.

On the basis of our recent results,[9] we tested these ligands in the asymmetric copper-catalyzed addition of diethylzinc to cyclohexenone as test substrate[12] (Table 3).

Irrespective of the experimental conditions applied, good conversions (>90%) were seen in all cases. A significant improvement in the product e.e. from 7 to 53% was observed when the reaction was completed in the presence of $Zn(OH)_2$ (Table 2, entry 1). The beneficial effect on the selectivity of the reaction using the $Zn(OH)_2$ additive can be rationalized on the basis of its Lewis acid properties. Thus, it can be postulated that complexation of Zn to the enone carbonyl group increases the enantiofacial differentiation and enhances the enantioselectivity of the reaction. As discussed above, ligands **2**–**7** led to poor results in terms of enantioselectivity, varying from 2 to 12% e.e. (Table 2, entries 2–7). Ligands **8**–**14** led to lower or similar e.e.s and yields to those previously obtained using QUIPHOS **1**, underlining the importance of the ligand structure on the enantioselectivity of the reaction.

3. Conclusion

The design and synthesis of a new class of chiral quinoline–phosphine ligands has been achieved and their efficiency in both enantioselective palladium-catalyzed allylic substitution reactions and enantioselective copper-catalyzed diethylzinc addition to enones has been investigated. Further studies are now in progress in order to extend the use of these ligands to other catalytic asymmetric reactions.

4. Experimental

Tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone ketyl immediately prior to use. Ethyl acetate and petroleum ether (35–60°C) were purchased from SDS and used without any further purification. Column chromatography was performed on SDS silica gel (70–230 mesh). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200.00 and 50.30 MHz on a Bruker AC200 instrument; ^{31}P NMR spectra were recorded in $CDCl_3$ solution at 40.50 MHz on a Bruker AC100 (the usual abbreviations are used: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet). The positive chemical shift values are given in ppm, while the coupling constants are in hertz. Specific rotations were determined with a Perkin–Elmer 341 polarimeter.

4.1. Synthesis of 2-substituted-8-hydroxyquinoline

4.1.1. 2-Phenyl-8-hydroxyquinoline. 2-Phenyl-8-hydroxyquinoline was synthesized following a modification of the procedure reported by Merritt et al.[13] To a stirred suspension of lithium metal (0.841 g, 0.121 mol) in diethyl ether (50 mL) under argon was added dropwise bromobenzene (9.09 g, 57.9 mmol). After stirring the mixture for 40 min, a solution of 8-hydroxyquinoline (4.00 g, 27.6 mmol) in diethyl ether (80 mL) was slowly added. The solution was then stirred under reflux for 1 h, cooled to rt and air was bubbled through the mixture for 2 h. Water (40 mL) and diethyl ether (80 mL) were slowly added and the solution was neutralized (HCl 33%). The two phases were separated and the aqueous layer was extracted with dichloromethane (4×40 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was distilled at reduced pressure (0.03 mbar, 160–165°C) to afford 2-phenyl-8-hydroxyquinoline (4.34 g, 56%) as a pale yellow solid; mp 55°C; IR (KBr): ν 3396 (O–H str.), 3076–3046 (C–H str. Ar); ^1H NMR: δ 8.25–8.50 (s large, 1H), 8.12–8.19 (m, 3H), 7.85 (d, 1H, $J=8.6$ Hz), 7.49–7.60 (m, 3H), 7.43 (d, 1H, $J=7.4$ Hz), 7.32 (dd, 1H, $J=1.3$, 8.2 Hz), 7.26 (dd, 1H, $J=1.4$, 7.4 Hz); ^{13}C NMR: δ 154.7, 152.1, 138.5, 137.8, 136.8, 129.4, 128.7, 127.3, 127.2, 119.3, 117.5, 110.0.

4.1.2. 2-*tert*-Butyl-8-hydroxyquinoline. 2-*tert*-Butyl-8-hydroxyquinoline was synthesized from *tert*-BuLi (24.3 mL, 1.7 M in pentane, 41.3 mmol) and 8-hydroxyquinoline (2.00 g, 13.7 mmol) according to the same procedure previously described. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 20:1) to afford 2-*tert*-butyl-8-hydroxyquinoline as a clear liquid (1.16 g, 42% yield); IR (neat): ν 3395 (O–H str.), 3056–3000 (C–H str. Ar), 2964–2872 (C–H str. Al); ^1H NMR: δ 8.20–8.55 (s large, 1H), 8.06 (d, 1H, $J=8.7$ Hz), 7.50 (d, 1H, $J=8.7$ Hz), 7.37 (t, 1H, $J=7.8$ Hz), 7.25 (dd, 1H, $J=1.4$, 8.2 Hz), 7.14 (dd, 1H, $J=1.4$, 7.3 Hz), 1.45 (s, 9H); ^{13}C NMR: δ 167.2, 151.9, 136.8, 136.2, 126.7, 126.5, 119.0, 117.3, 109.4, 37.9, 30.0.

4.1.3. 2-Cyano-8-hydroxyquinoline. 2-Cyano-8-hydroxyquinoline was prepared from 8-hydroxyquinoline in 37% yield according to the reported procedure.[14] Spectral data were in agreement with those reported in the literature.[15]

4.1.4. 2-(4′,4′-Dimethyl-2′-oxazoline)-8-hydroxyquinoline. A mixture of 2-cyano-8-hydroxyquinoline (500 mg, 2.94 mmol), 2-amino-2-methylpropanol (593 mg, 6.65 mmol) and powdered 4 Å molecular sieves (1.00 g) in 1,2-dichlorobenzene (5 mL) was stirred under reflux for 60 h under argon. The mixture was cooled to rt, diluted with dichloromethane (30 mL), filtered and evaporated. The evaporation residue was purified by silica gel chromatography (petroleum ether/THF, 2:1) to afford 2-(4′,4′-dimethyl-2′-oxazoline)-8-hydroxyquinoline as a yellow solid (485 mg, 68% yield); mp 97°C; IR (KBr): ν 3376 (O–H str.), 3087–3046 (C–H str. Ar), 2987–2877 (C–H str. Al); ^1H NMR: δ 8.22–8.60 (s large, 1H), 7.91

(d, 2H, $J=3.8$ Hz), 7.26 (d, 1H, $J=7.9$ Hz), 7.07 (d, 2H, $J=7.9$ Hz), 4.04 (s, 2H), 1.26 (s, 6H); ^{13}C NMR: δ 161.0, 152.9, 143.8, 137.4, 136.0, 128.8, 128.6, 120.6, 117.1, 110.8, 79.2, 67.4, 27.9.

4.1.5. (*E*)-2-(2-Phenylethenyl)-8-hydroxyquinoline. (*E*)-2-(2-Phenylethenyl)-8-hydroxyquinoline was synthesized following a procedure reported by Merritt et al.[13] Spectral data were in agreement with those reported in the literature.[15]

4.1.6. (*E*)-2-(2-Phenylethyl)-8-hydroxyquinoline. A mixture of (*E*)-2-(2-phenylethenyl)-8-hydroxyquinoline (1.00 g, 4.04 mmol) and 5% Pd/C (861 mg, 0.404 mmol) in ethyl acetate was stirred at rt under hydrogen at atmospheric pressure for 12 h. The mixture was then filtered through Celite and evaporated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 10:1) to afford (*E*)-2-(2-phenylethyl)-8-hydroxyquinoline (515 mg, 51% yield) as a pale yellow oil; IR (neat): ν 3397 (O–H str.), 3070–3002 (C–H str. Ar), 2971–2861 (C–H str. Al); ^{1}H NMR: δ 8.15–8.50 (s large, 1H), 8.04 (d, 1H, $J=8.4$ Hz), 7.22–7.49 (m, 9H), 3.18–3.39 (m, 4H); ^{13}C NMR: δ 159.4, 151.8, 141.3, 137.6, 136.2, 128.4 (×2), 126.8, 126.7, 126.0, 122.3, 117.6, 109.8, 39.9, 35.2.

4.2. General procedure for the synthesis of ligands

Diamine or aminoalcohol (3 mmol) was placed in a 25 mL two-necked round-bottomed flask under argon. Dry toluene (3 mL) and tris(dimethylamino)phosphine (3 mmol) were added. The solution was heated under reflux for 2 h and cooled to rt. A solution of 8-hydroxyquinoline or 2-substituted-8-hydroxyquinoline (3 mmol) in dry toluene (1 mL) was added under argon. The solution was then heated under reflux for 2 h and then cooled to rt. Purification was achieved by precipitation at the end of the reaction or by silica gel chromatography as described for each compound.

4.2.1. (3*R*,4*R*)-3,4-Diphenyl-2,5-dimethyl-1-(8-quinolinoxy)-2,5-diaza-1-phosphacyclopentane 2. Purified by precipitation at the end of the reaction by the addition of hexane (0.2 mL). The mixture was filtered and the filter cake dried to afford **2** as a pale yellow solid (51% yield); mp 86°C; $[\alpha]_D=+17.2$ (c 1.02, CH_2Cl_2); IR (neat): ν 3084–3006 (C–H str. Ar), 2987–2807 (C–H str. Al); ^{31}P NMR (C_6D_6): δ 139.9; ^{1}H NMR (C_6D_6): δ 8.77 (dd, 1H, $J=1.5$, 3.9 Hz), 7.74 (dd, 1H, $J=1.5$, 8.1 Hz), 7.55–7.63 (m, 3H), 7.16–7.45 (m, 10H), 6.92–7.01 (m, 1H), 4.82 (dd, 1H, $J=3.9$, 9.0 Hz), 4.48 (dd, 1H, $J=3.3$, 9.3 Hz), 3.14 (d, 3H, $J=10.8$ Hz), 3.85 (d, 3H, $J=14.7$ Hz); ^{13}C NMR (C_6D_6): δ 153.8 (d, $J=2.0$ Hz), 148.6, 142.8, 140.8, 140.2 (d, $J=5.2$ Hz), 135.6, 130.3, 128.7, 128.6 (×2), 128.5, 127.9, 127.6, 127.2, 121.3, 121.2, 119.1 (d, $J=3.6$ Hz), 79.3 (d, $J=10.3$ Hz), 77.7 (d, $J=8.8$ Hz), 33.8 (d, $J=28.6$ Hz), 32.6 (d, $J=12.9$ Hz).

4.2.2. (3*S*,4*S*)-2,3-Dimethyl-4-phenyl-1-(8-quinolinoxy)-2-aza-5-oxa-1-phosphacylopentane 3. Purified by silica gel chromatography (THF/petroleum ether, 1:5). The major eluting band was evaporated to afford **3** as a colorless oil in 48% yield (ratio *anti*:*syn* = 73:26); $[\alpha]_D=+42.1$ (c 1.30, CH_2Cl_2); IR (neat): ν 3062–3038 (C–H str. Ar), 2977–2898 (C–H str. Al); ^{31}P NMR: δ 138.1 (*anti*), 144.1 (*syn*); ^{1}H NMR: δ (*anti*) 8.80 (dd, 1H, $J=4.2$, 16.4 Hz), 8.12 (d, 1H, $J=8.3$ Hz), 7.14–7.54 (m, 10H), 4.70 (dd, 1H, $J=2.4$, 9.5 Hz), 2.90 (d, 3H, $J=13.5$ Hz), 1.21 (d, 3H, $J=5.7$ Hz); ^{13}C NMR: δ (*anti*) 152.2, 149.1, 149.0, 139.6, 135.7, 129.8, 128.4, 128.1, 127.6, 126.7, 121.9, 121.3, 118.6 (d, $J=7.1$ Hz), 91.5 (d, $J=10.5$ Hz), 61.2 (d, $J=5.9$ Hz), 29.5 (d, $J=12.9$ Hz), 14.9 (d, $J=6.3$ Hz).

4.2.3. (3*S*,4*R*)-2,3-Dimethyl-4-phenyl-1-(8-quinolinoxy)-2-aza-5-oxa-1-phosphacylopentane 4. Purified by silica gel chromatography (THF/petroleum ether, 1:5) in 50% yield (100% *anti* diastereomer) as a colorless oil; $[\alpha]_D=+30.5$ (c 0.38, CH_2Cl_2); IR (neat): ν 3062–3033 (C–H str. Ar), 2971–2813 (C–H str. Al); ^{31}P NMR: δ 137.5; ^{1}H NMR: δ 8.93 (d, 1H, $J=4.4$ Hz), 8.12 (d, 1H, $J=7.8$ Hz), 7.34–7.48 (m, 10H), 5.96 (d, 1H, $J=7.2$ Hz), 2.98 (d, 3H, $J=12.2$ Hz), 0.71 (d, 3H, $J=6.5$ Hz); ^{13}C NMR: δ 150.6, 149.1, 147.8, 138.0, 135.7, 129.6, 128.0 (×2), 127.6, 126.7 (d, $J=8.1$ Hz), 122.0, 121.3, 118.8 (d, $J=7.2$ Hz), 84.7 (d, $J=8.7$ Hz), 57.6 (d, $J=5.8$ Hz), 29.5 (d, $J=17.3$ Hz), 14.7 (d, $J=3.7$ Hz).

4.2.4. (*R*)-4-(8-Quinolinoxy)-3,5-dioxa-4-phosphacyclohepta-[2,1-a;3,4-a′]binaphthalene 5. Purified by silica gel chromatography (THF/petroleum ether, 1:6) in 56% yield as a colorless oil; $[\alpha]_D=-155$ (c 0.23, THF); IR (neat): ν 3060–3021 (C–H str. Ar), 2967–2891 (C–H str. Al); ^{31}P NMR (C_6D_6): δ 141.3; ^{1}H NMR (C_6D_6): δ 8.76–8.80 (dd, 1H, $J=1.5$, 4.2 Hz), 7.47–7.69 (m, 7H), 7.15–7.40 (m, 6H), 6.93–7.10 (m, 3H), 6.71–6.80 (m, 1H); ^{13}C NMR (C_6D_6): δ 153.6, 150.6, 150.3, 149.3, 149.0, 148.6, 135.9, 134.4, 133.4 (d, $J=14.1$ Hz), 131.8 (d, $J=18.6$ Hz), 130.6, 129.9, 129.8, 128.7 (d, $J=2.7$ Hz), 127.4, 127.0, 126.6, 126.4, 125.1, 125.0, 123.8, 123.0, 122.7, 122.5, 121.8, 118.8 (d, $J=2.1$ Hz), 118.4.

4.2.5. (1*R*,5*R*)-2,4-Dimethyl-3-(8-quinolinoxy)-2,4-diaza-3-phosphabicyclo[4.3.0]nonane 6. Purified by silica gel chromatography (THF/petroleum ether, 1:2) in 61% yield as a colorless oil; $[\alpha]_D=-9.83$ (c 0.60, CH_2Cl_2); IR (neat): ν 3052–3010 (C–H str. Ar), 2936–2801 (C–H str. Al); ^{31}P NMR: δ 147.5; ^{1}H NMR: δ 8.64 (dd, 1H, $J=1.5$, 4.2 Hz), 7.97 (dd, 1H, $J=1.5$, 8.3 Hz), 7.05–7.34 (m, 4H), 2.98 (d, 3H, $J=12.8$ Hz), 2.66 (d, 3H, $J=15.1$ Hz), 2.07–1.94 (m, 2H), 1.65–1.73 (m, 2H), 0.95–1.28 (m, 4H); ^{13}C NMR: δ 152.5 (d, $J=2.3$ Hz), 148.5, 141.9 (d, $J=1.7$ Hz), 135.6, 129.6, 126.6, 121.1, 121.0, 119.1 (d, $J=4.0$ Hz), 69.6 (d, $J=8.0$ Hz), 65.2 (d, $J=7.5$ Hz), 33.4 (d, $J=32.7$ Hz), 30.4 (d, $J=10.9$ Hz), 29.4, 28.7 (d, $J=3.4$ Hz), 24.1 (×2).

4.2.6. (2*R*,5*S*)-2-(8-Quinolinoxy)-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octane 7. A solution of HCl (2 M in Et_2O, 7 mL, 14 mmol) and Et_2O (13 mL) was cooled to 0°C in a 50 mL two-necked round-bottomed flask under argon. A solution of (*S*)-prolinol (10 mmol) in Et_2O (2 mL) was slowly added. The mixture was stirred for 1 h at rt, then evaporated, washed with petroleum ether (3×7 mL) and dried under vacuum. Dry toluene

(12 mL) and tris(dimethylamino)phosphine (10 mmol) were added. The solution was stirred under reflux for 2 h and then cooled to rt. 8-Hydroxyquinoline (10 mmol) was added under argon. The solution was then stirred under reflux for 2 h and cooled to rt. After evaporation of the solvent, the residue was distilled under reduced pressure (5×10^{-3} mbar, 155–170°C) to afford compound **7** as a pale yellow oil (616 mg, 23%); $[\alpha]_D=+10.7$ (*c* 1.1, CH_2Cl_2); IR (neat): *v* 3074–3025 (C–H str. Ar), 2964–2873 (C–H str. Al); ^{31}P NMR: δ 152.2 (*anti*), 137.3 (*syn*); ^{1}H NMR: δ 8.00 (d, 1H, $J=8.3$ Hz), 7.09–7.45 (m, 5H), 3.75–4.07 (m, 3H), 2.95–3.19 (m, 2H), 1.41–2.02 (m, 4H); ^{13}C NMR: δ (*anti*) = 152.0, 148.4, 140.7, 135.5, 129.3, 126.5, 121.2, 120.9, 117.6 (d, $J=5.7$ Hz), 72.7 (d, $J=9.0$ Hz), 61.6 (d, $J=4.4$ Hz), 46.5 (d, $J=33.2$ Hz), 31.0, 26.1 (d, $J=2.5$ Hz).

4.2.7. (2*R*,5*S*)-3-Phenyl-2-(2-methyl-8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane 8. Purified by silica gel chromatography (THF/petroleum ether, 1:5) in 49% yield as a colorless oil (100% *anti* diastereomer); $[\alpha]_D=-388$ (*c* 1.15, CH_2Cl_2); IR (neat): *v* 3056–3010 (C–H str. Ar), 2964–2872 (C–H str. Al); ^{31}P NMR: δ 129.5; ^{1}H NMR: δ 8.00 (d, 1H, $J=8.4$ Hz), 7.45 (d, 1H, $J=7.6$ Hz), 7.1–7.35 (m, 7H), 6.86 (t, 1H, $J=6.9$ Hz), 4.00 (q, 1H, $J=6.4$ Hz), 3.71–3.83 (m, 2H), 3.40–3.50 (m, 1H), 3.22–3.32 (m, 1H), 2.76 (s, 3H), 1.55–2.02 (m, 4H); ^{13}C NMR: δ 157.8, 150.9, 145.6 (d, $J=14.6$ Hz), 141.83, 135.9, 129.0, 128.9, 127.9, 125.7, 122.0 (d, $J=5.2$ Hz), 120.2 (d, $J=3.9$ Hz), 119.0, 115.5 (d, $J=13.4$ Hz), 62.7 (d, $J=8.9$ Hz), 53.6 (d, $J=7.5$ Hz), 48.3 (d, $J=33.4$ Hz), 31.7, 26.5 (d, $J=4.2$ Hz), 25.4.

4.2.8. (2*R*,5*S*)-3-Phenyl-2-(2-phenyl-8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane 9. Purified by precipitation at the end of the reaction. The mixture was filtered and the filter cake dried to afford **9** as a white solid (100% *anti* diastereomer) in 45% yield; mp 145°C; $[\alpha]_D=-466$ (*c* 1.05, CH_2Cl_2); IR (KBr): *v* 3067–3000 (C–H str. Ar), 2977–2847 (C–H str. Al); ^{31}P NMR: δ 129.0; ^{1}H NMR: δ 8.30 (d, 1H, $J=7.9$ Hz), 8.28 (d, 1H, $J=7.0$ Hz), 8.18 (d, 1H, $J=8.6$ Hz), 7.89 (d, 1H, $J=8.6$ Hz), 7.45–7.60 (m, 4H), 7.30–7.45 (m, 1H), 7.20–7.30 (m, 5 H), 6.89–6.96 (q, 1H, $J=4.1$ Hz), 3.75–4.00 (m, 2H), 3.50–3.65 (m, 1H), 3.05–3.35 (m, 2H), 1.50–2.00 (m, 4H); ^{13}C NMR: δ 155.9, 151.4, 145.5 (d, $J=16.0$ Hz), 142.1, 139.5, 136.8, 129.3 (×2), 128.7, 127.9, 126.5, 122.1, 120.6 (d, $J=4.6$ Hz), 119.3, 118.8, 115.8 (d, $J=13.0$ Hz), 62.9 (d, $J=8.8$ Hz), 53.9 (d, $J=7.3$ Hz), 48.0 (d, $J=32.8$ Hz), 31.7, 26.6 (d, $J=4.0$ Hz).

4.2.9. (2*R*,5*S*)-3-Phenyl-2-(2-*tert*-butyl-8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane 10. Purified by silica gel chromatography (ethyl acetate/petroleum ether, 1:20) to afford **10** as a white solid in 35% yield (100% *anti* diastereomer); mp 110°C; $[\alpha]_D=-395$ (*c* 1.00, CH_2Cl_2); IR (KBr): *v* 3073–3054 (C–H str. Ar), 2978–2872 (C–H str. Al); ^{31}P NMR: δ 128.8; ^{1}H NMR: δ 9.48 (d, 1H, $J=8.7$ Hz), 8.95 (d, 1H, $J=8.7$ Hz), 8.89 (dd, 1H, $J=1$, 8.0 Hz), 8.68–8.75 (m, 2H), 8.62–8.67 (m, 3H), 8.55 (dd, 1H, $J=1.0$, 7.3 Hz), 8.27–8.35 (m, 1H), 5.16–5.35 (m, 2H), 4.97–5.13 (m, 1H), 4.50–4.72 (m, 2H), 3.04–3.40 (m, 4H), 2.95 (s, 9H); ^{13}C NMR: δ 168.1, 150.6, 145.5 (d, $J=14.9$ Hz), 141.4, 135.7, 129.0, 127.7, 125.5, 122.0, 120.4 (d, $J=4.6$ Hz), 119.1, 118.2, 115.5 (d, $J=12.3$ Hz), 62.7 (d, $J=8.7$ Hz), 53.7 (d, $J=7.0$ Hz), 48.0 (d, $J=33.6$ Hz), 38.3, 31.5, 30.2, 26.3 (d, $J=4.3$ Hz).

4.2.10. (2*R*,5*S*)-3-Phenyl-2-(2-cyano-8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane 11. Purified by silica gel chromatography (THF/petroleum ether, 1:5) to afford **11** as a colorless oil in 72% yield (100% *anti* diastereomer); $[\alpha]_D=-397$ (*c* 1.01, CH_2Cl_2); IR (neat): *v* 3067–3046 (C–H str. Ar), 2967–2877 (C–H str. Al), 2239 (CN str.); ^{31}P NMR: δ 134.3; ^{1}H NMR: δ 8.25 (d, 1H, $J=8.4$ Hz), 7.65 (d, 1H, $J=8.4$ Hz), 7.56 (d, 1H, $J=2.7$ Hz), 7.54 (s, 1H), 7.23–7.32 (m, 3H), 7.08–7.14 (m, 2H), 6.88 (t, 1H, $J=7.2$ Hz), 4.01–4.15 (m, 1H), 3.79–3.99 (m, 2H), 3.55–3.69 (m, 1H), 3.28–3.39 (m, 1H), 1.85–2.11 (m, 3H), 1.56–1.69 (m, 1H); ^{13}C NMR: δ 152.1, 145.1 (d, $J=15.0$ Hz), 142.3, 137.4, 132.0, 130.1, 129.9, 129.0, 123.4, 121.6, 121.4 (d, $J=3.4$ Hz), 119.3, 117.6, 115.4 (d, $J=14.1$ Hz), 62.7 (d, $J=8.8$ Hz), 53.4 (d, $J=7.9$ Hz), 48.0 (d, $J=32.4$ Hz), 31.7, 26.5 (d, $J=4.2$ Hz).

4.2.11. (2*R*,5*S*)-3-Phenyl-2-((*E*)-2-(2-phenylethenyl)-8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane 12. Purified by silica gel chromatography (THF/petroleum ether, 1:10) to afford **12** as a pale yellow solid in 22% yield (ratio *anti*:*syn* = 92:8); mp 52–65°C; $[\alpha]_D=-372$ (*c* 0.97, CH_2Cl_2); IR (KBr): *v* 3067–3047 (C–H str. Ar), 2967–2877 (C–H str. Al); ^{31}P NMR: δ 127.4 (*anti*), 122.4 (*syn*); ^{1}H NMR: δ (*anti*) = 8.07 (d, 1H, $J=8.6$ Hz), 7.16–7.76 (m, 15H), 6.85–6.96 (m, 1H), 3.60–3.95 (m, 3H), 3.20–3.45 (m, 2H), 1.55–2.05 (m, 4H); ^{13}C NMR: δ (*anti*) = 154.9, 151.1, 145.6 (d, $J=15.9$ Hz), 142.3, 136.6, 136.0, 133.8, 129.5, 129.0, 128.7 (×2), 128.5, 128.3, 127.1, 126.2, 122.0, 120.5 (d, $J=5.3$ Hz), 119.0 (d, $J=6.0$ Hz), 115.5 (d, $J=13.1$ Hz), 62.7 (d, $J=9.0$ Hz), 53.7 (d, $J=7.3$ Hz), 47.9 (d, $J=33.5$ Hz), 31.6, 26.5 (d, $J=4.2$ Hz).

4.2.12. (2*R*,5*S*)-3-Phenyl-2-((*E*)-2-(2-phenylethyl)-8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane 13. Purified by silica gel chromatography (THF/petroleum ether, 1:8) to afford **10** as a pale yellow solid in 51% yield (ratio *anti*:*syn* = 97:3); mp 112°C; $[\alpha]_D=-341$ (*c* 1.07, CH_2Cl_2); IR (KBr): *v* 3067–3047 (C–H str. Ar), 2967–2847 (C–H str. Al); ^{31}P NMR: δ 129.1 (*anti*), 122.6 (*syn*); ^{1}H NMR: δ (*anti*) 8.03 (d, 1H, $J=8.4$ Hz), 7.48 (d, 1H, $J=8.0$ Hz), 7.21–7.40 (m, 12H), 6.80–7.00 (m, 1H), 4.04 (q, 1H, $J=6.5$ Hz), 3.65–3.90 (m, 2H), 3.15–3.52 (m, 6H), 1.80–2.10 (m, 3H), 1.55–1.72 (m, 1H); ^{13}C NMR: δ (*anti*) = 160.6, 150.9, 145.5 (d, $J=15.9$ Hz), 141.9, 141.6, 135.9, 128.9, 128.4, 128.3 (×2), 128.1, 125.8 (d, $J=4.1$ Hz), 122.0, 121.4, 120.2 (d, $J=4.6$ Hz), 119.0, 115.5 (d, $J=13.2$ Hz), 62.7 (d, $J=8.8$ Hz), 53.6 (d, $J=7.3$ Hz), 48.0 (d, $J=33.4$ Hz), 40.9, 35.8, 31.6, 26.4 (d, $J=4.1$ Hz).

4.2.13. (2*R*,5*S*)-3-Phenyl-2-(2-(4′,4′-dimethyl-2′-oxazoline)-8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane oxazoline 14. Purified by silica gel chromatography (THF/petroleum ether, 1:2) to afford **14** as a pale yellow

solid in 46% yield (ratio *anti*:*syn* = 77:23); mp 50–55°C; $[\alpha]_D = -277$ (*c* 0.86, CH_2Cl_2); IR (KBr): *v* 3067–3046 (C–H str. Ar), 2977–2877 (C–H str. Al); ^{31}P NMR: δ 128.9 (*anti*), 123.6 (*syn*); ^1H NMR: δ (*anti*) 8.14 (s, 2H), 6.75–7.50 (m, 8H), 4.22 (s, 2H), 3.55–3.90 (m, 2H), 3.10–3.40 (m, 1H), 1.40–2.05 (m, 6H), 1.42 (s, 6H); ^{13}C NMR: δ (*anti*) 162.0, 151.8, 146.0, 145.3 (d, $J = 15.4$ Hz), 141.6, 136.1, 129.8, 129.1, 128.8, 127.9, 121.8, 120.9, 118.9, 115.4, (d, $J = 13.2$ Hz), 79.3, 67.7, 62.6 (d, $J = 8.9$ Hz), 53.5 (d, $J = 7.5$ Hz), 47.6 (d, $J = 33.4$ Hz), 31.5, 28.4, 28.2, 26.3 (d, $J = 4.4$ Hz).

4.3. General procedure for asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate

A mixture of $[Pd(allyl)Cl]_2$ (3 mg, 8.2×10^{-3} mmol, 2 mol%) and the desired ligand (33×10^{-3} mmol) in anhydrous CH_2Cl_2 was stirred at rt for 15 min. A solution of 1,3-diphenylprop-3-en-1-yl acetate (100 mg, 0.396 mmol) was added and stirring was maintained for 5 min. Dimethylmalonate (157 mg, 1.18 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 241 mg, 1.18 mmol) and a catalytic amount of potassium acetate (KOAc) were subsequently added. The resulting solution was stirred at 25°C for 12 h. The solution was diluted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a pale yellow oil that solidified on standing. The e.e.s were determined by HPLC analysis of the crude mixture on a Daicel Chiralcel OD-H column ($\lambda = 254$ nm; flow rate 1 mL/min; eluent: hexane/*iso*-PrOH 200:1, $t_R = 19.57$ min, $t_S = 18.18$ min).

4.4. General procedure for asymmetric allylic amination of 1,3-diphenyl-2-propenyl acetate

A mixture of $[Pd(allyl)Cl]_2$ (3 mg, 8.2×10^{-3} mmol (2 mol%)) and the desired ligand (33×10^{-3} mmol) in anhydrous CH_2Cl_2 was stirred at rt for 15 min. A solution of 1,3-diphenylprop-3-en-1-yl acetate (100 mg, 0.396 mmol) was added and stirring was maintained for 5 min. Benzylamine (126 mg, 1.18 mmol) was subsequently added. The resulting solution was stirred at 25°C for 12 h. The solution was diluted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a pale yellow oil. The e.e. was determined on the crude mixture by HPLC analysis on a Daicel Chiralcel OD-H column ($\lambda = 254$ nm; flow rate 1 mL/min; eluent: hexane/*iso*-PrOH 200:1, $t_R = 19.7$ min, $t_S = 21.70$ min).

4.5. General procedure for asymmetric conjugate addition of Et_2Zn to 2-cyclohexenone

A solution of copper salt (5.20 μmol) and ligand (10.4 μmol) in dry solvent was stirred for 45 min at rt under argon. To this solution was added $Zn(OH)_2$ (25.8 mg, 0.52 mmol). The mixture was then cooled at −20°C. Et_2Zn (1.0 M in hexane, 2.1 mL) and 2-cyclohexanone (100 μL, 1.04 mmol) were added. After stirring for 12 h at −20°C, aqueous HCl solution (5N, 2 mL) was added and the mixture was extracted with Et_2O (3×10 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and filtered on silica gel (dichloromethane, 20 mL). Conversion and e.e.s were determined by gas chromatography on a Macherey Nagel FS-Lipodex E column, 25 m×0.25 mm, He pressure 60 kPa, 58–115°C, 3°C/min; $t_R = 14.8$ (2-cyclohexenone), 16.2 (*R*), 16.6 min (*S*).

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