Modular multidentate phosphine ligands: application to palladium-catalyzed allylic alkylations

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Multidentate phosphines were readily obtained by reaction of chiral multidentate amines, prepared *via* ring opening of (*S*)-*N*-tosyl-2-isopropylaziridine with ammonia, primary, and secondary amines, with achiral phosphorus containing building blocks. The phosphines were used in palladium-catalyzed alkylation of *rac*-3-cyclohexenyl and cyclopentenyl carbonates. The enantioselectivity and reactivity were largely dependent on the structure of the amine core of the ligands. Up to 88% ee was observed in reactions with the six-membered substrate.

Introduction

The design and synthesis of new chiral ligands are urged by the demand for reactive and selective asymmetric metal catalysts.[1] Ligands which can be prepared from cheap and easily available starting materials in few synthetic steps, and which are designed to allow for facile structural variations, are particularly useful since efficient transfer of chirality in catalytic reactions usually requires optimization of the ligand structure for each particular reaction and each substrate.

We have recently developed a modular approach for the preparation of multidentate nitrogen ligands.[2] The synthesis is based on the nucleophilic ring opening of activated chiral aziridines, obtained from easily available amino acids, by amines. By employing ammonia, primary and secondary monoamines and diamines as nucleophiles, chiral ligand backbones with easily variable structures are obtained. Thus, C_3-symmetric[3] amines can be prepared from ammonia,[4,5] whereas compounds with C_2 and C_1 symmetry are obtained from primary and secondary amines, respectively.[6] The multidentate product amines can be employed directly as chiral nitrogen ligands[7] or the amino groups can serve as attachment points for suitable achiral or chiral donor functions, thus providing access to various types of multidentate ligands.

We were particularly interested in studying whether chiral information may be delivered from the chiral core to achiral catalytically active sites on the periphery of the ligand and whether the structure of the amine containing core and the size of the chiral pockets would influence the enantioselectivity in catalytic reactions. If that would be the case, facile structural variations would permit tuning of the catalytic properties. We present here the preparation of polydentate chiral amines and their functionalization with achiral phosphorus containing building blocks to provide polydentate phosphine ligands. The new ligands were applied in palladium-catalyzed asymmetric allylic alkylations of *rac*-methyl 3-cyclohexenyl and *rac*-ethyl 3-cyclopentenyl carbonate.

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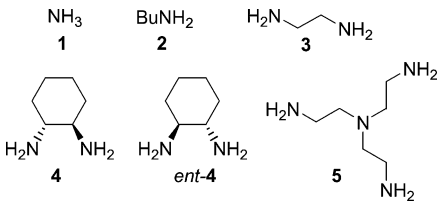
Results and discussion

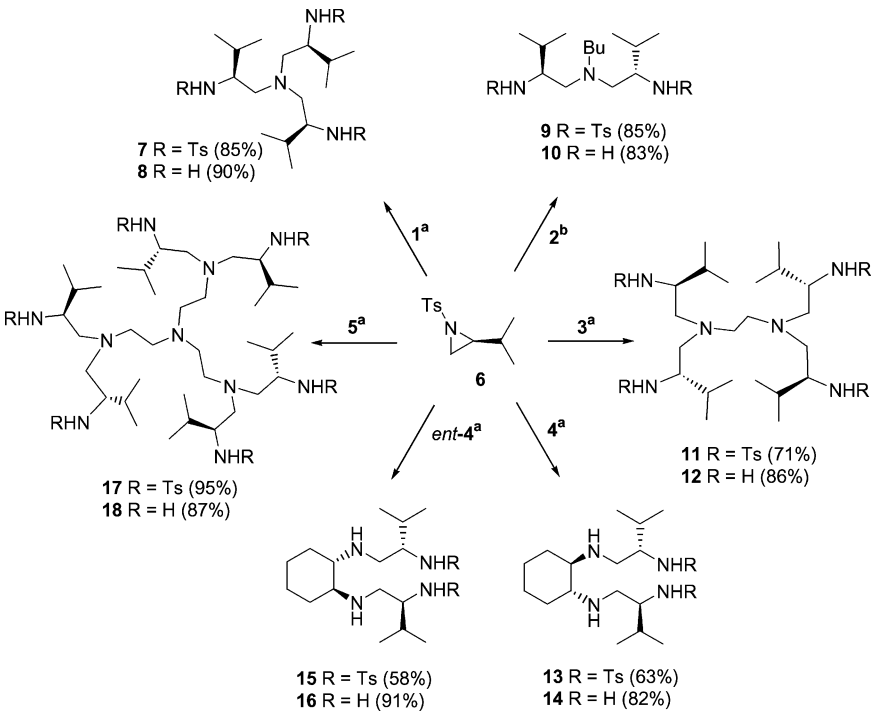
Ligand design and preparation

To achieve the desired structural variation, we used ammonia (**1**), butylamine (**2**), 1,2-diaminoethane (**3**), (*R*,*R*)-1,2-diaminocyclohexane (**4**), (*S*,*S*)-1,2-diaminocyclohexane (*ent*-**4**), and tris(2-aminoethyl)amine (TREN, **5**) as nucleophiles for the ring opening of a chiral aziridine. An activated aziridine is required for the reactions to proceed readily. (*S*)-*N*-Tosyl-2-isopropylaziridine (**6**) was selected since the activating group can be easily removed subsequent to the ring opening.



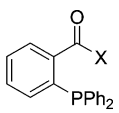
We have previously shown that ammonia and butylamine react with three and two equivalents, respectively, of the aziridine to afford **7** and **9**, which after deprotection using HBr and phenol, gave **8** and **10** (Scheme 1). Diamine **3** reacted smoothly with four equivalents of the aziridine, providing **11** and, after deprotection, **12**. In contrast, the more sterically hindered chiral amines **4** and *ent*-**4** reacted with only two molecules of the aziridine to yield secondary amines **13** and **15**, in analogy to what we have previosuly observed in the ring opening of *N*-triflic aziridine.[2] Although the yields in these reactions were somewhat lower than those in reactions with other amines, deprotection occurred smoothly to provide **14** and **16** in acceptable overall yields. Finally, we were pleased to discover that reaction of TREN provided a high yield of hexasubstituted product **17** and, after removal of the tosyl group, **18**.

As a phosphorus containing achiral moiety, 2-(diphenylphosphino)benzoic acid (**19a**) was used and attached to the primary amino groups, *via* amide formation links, as previously achieved for the preparation of **20** and **21** from **8** and **10**, respectively.[8] The amines prepared were thus reacted with **19a** using either DCC–DMAP or EDC·HCl–HOBt, affording



Scheme 1 Reagents and conditions: (a) (i) amine, MeOH, microwaves 160 °C; (ii) HBr (48% aq.), PhOH, reflux; (b) (i) amine, MeOH, 0–55 °C; (ii) HBr (48% aq.), PhOH, reflux.

phosphines **20**–**25**, with structures analogous to that of the Trost ligand **28**.[9] We anticipated that the properties of the ligand might be influenced by the nature of the linker. In order to explore this possibility, C_3-symmetric imine **26** and amine **27**, with a larger degree of freedom, were also prepared. For the condensation between the chiral TREN derivative **8** and 2-(diphenylphosphino)benzaldehyde (**19b**), several different reaction conditions were attempted. In acetonitrile at room temperature, only 50% conversion was achieved after 48 h, as determined by ^{31}P NMR spectroscopy, and at reflux temperature the ligand underwent degradation. However, in CH_2Cl_2–CH_3OH (1 : 3)[10] the aldehyde was totally consumed after 72 h at room temperature, and the desired ligand **26** was isolated as a yellow solid.



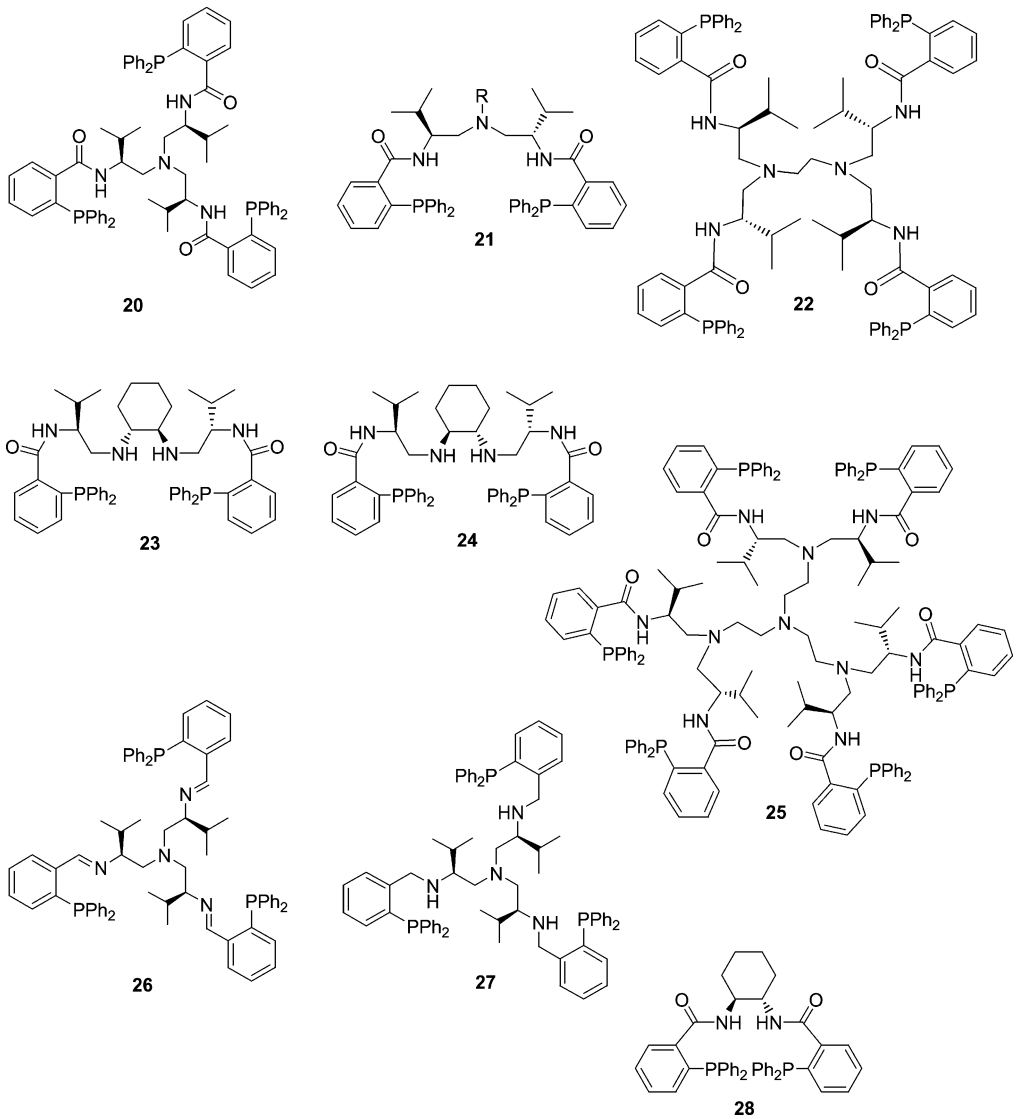
19a X = OH
19b X = H

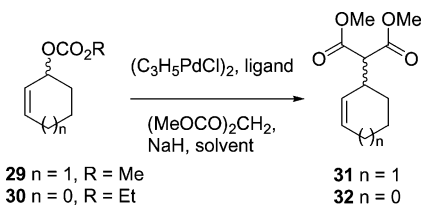
Finally, the imine functions in **26** were reduced by sodium borohydride[11] to yield phosphine amine ligand **27** in 70%.

Catalytic reactions

Having access to phosphine ligands **20**–**27**, we decided to study the influence of the chiral core on the reactivity and selectivity in catalytic reactions. Palladium-catalyzed asymmetric allylic alkylation of *rac*-methyl 3-cyclohexenyl and *rac*-ethyl 3-cyclopentenyl carbonate with malonate was selected as a suitable reaction (Scheme 2), providing the opportunity to compare the behavior of the new ligands with that of Trost's ligand **28**.[12] With the latter ligand, the nature of the counter ion of the nucleophile and the solvent was shown to be of significant importance due to a memory effect.[13] Reactions run in methylene chloride using the tetrahexylammonium salt of the malonate exhibited the highest enantioselectivity. These conditions were therefore used in reactions employing **20**–**27** as ligands. The amount of ligand used was adjusted to maintain a phosphorus–palladium ratio of 3 : 1 in all reactions.[14]

Use of a catalyst (2.5 mol%, *i.e.* 5% Pd) containing C_3-symmetric ligand **20** in the alkylation of **29** resulted in full conversion to product **31** with high enantioselectivity (85% ee) within less than 50 min at room temperature (entry 1, Table 1). A lower reaction temperature did not provide any advantage (entry 2). A catalyst containing ligand **21** exhibited somewhat lower reactivity and selectivity (entry 3). Ligand **22** was also slightly less selective than **20**, and the selectivity decreased with the temperature (entries 4–6). In analogy to what was observed with ligand **28**, reactions in THF in place of methylene chloride (entry 7) and without addition of tetrahexylammonium bromide (entry 8) resulted in lower enantioselectivity. The ligands obtained from chiral 1,2-diaminocyclohexanes and containing secondary amine functions, **23** and **24**, resulted in catalysts with poor reactivity (entries 9 and 10). In contrast to these ligands, C_3-symmetric ligand **25** resulted in rapid formation of highly enantioenriched product (entry 11). Ligands **26** and **27**, having the amide group replaced by an imino or amino function, provided inferior results (entries 12–15). Under the conditions we used for ligands **20**–**27**, Trost's ligand **28** gave the product with 93% ee at room temperature, which is somewhat higher then that observed with the most selective ligand **20** at the same temperature (85%). The reactivity of **28** was however somewhat lower than that of, *e.g.*, **25**, which afforded full conversion after 10 min at room temperature.





Scheme 2 Allylic alkylation of cyclohexenyl and cyclopentenyl carbonate.

Alkylation of cyclopentenyl carbonate (**30**) with tetrahexylammonium malonate occurred with the same high rate as the alkylation of the six-membered carbonate, but with considerably lower enantioselectivity, the highest ee, 53%, being observed using ligand **25** (entries 17–19).

The influence of the amount of catalyst was then investigated. It was found that decreasing the amount of catalyst led to slightly improved results, although somewhat longer reaction times were required (Table 2). Thus, up to 88% ee and full conversion were observed for ligand **20** when merely 1.25 mol% palladium (0.63 mol% of the dimer) was used (entry 10).

Conclusions

We have demonstrated that chiral multidentate phosphines are readily obtained by a modular ligand synthesis. Ring opening of a chiral activated aziridine with ammonia, primary amines, diamines, or triamines was used as a key step to provide multidentate amines, which were substituted with achiral phosphine building blocks *via* amide or imine formation. Since a large variety of amines can be used in the aziridine ring opening, extensive variation of the ligand structures is possible. In palladium-catalyzed asymmetric allylic alkylations it was demonstrated that the structure of the chiral nucleus has a profound influence on the catalytic properties of metal complexes of the ligands.

Experimental

All reactions were run under an atmosphere of dry nitrogen unless otherwise indicated. Anhydrous solvents were transferred using oven-dried syringes. Glassware was oven- or flame-dried. Triethylamine was distilled from CaH_2. Dichloromethane, diethyl ether, THF, and DMF were taken from Meyer's

Table 1 Allylic alkylation of methyl 3-cyclohexenyl carbonate and ethyl 3-cyclopentenyl carbonate with sodium dimethyl malonate[a]

Entry	Ligand	Substrate	Solvent	Temp (°C)	Time	Conversion (%)[b]	ee (%)[c]
1	**20**	**29**	DCM	rt	20 min	96	85 (*S*)
					50 min	100	85 (*S*)
2	**20**	**29**	DCM	−3	1 h	99	85 (*S*)
3	**21**	**29**	DCM	rt	10 min	58	79 (*S*)
					40 min	83	76 (*S*)
					1 h	93	76 (*S*)
					2 h	97	75 (*S*)
4	**22**	**29**	DCM	rt	10 min	100	81 (*S*)
5	**22**	**29**	DCM	−3	30 min	59	76 (*S*)
					70 min	100	71 (*S*)
6	**22**	**29**	DCM	−20 to −8	100 min	53	62 (*S*)
7	**22**	**29**	THF	rt	15 min	100	36 (*S*)
8[d]	**22**	**29**	THF	rt	15 min	71	37 (*S*)
					1 h	100	30 (*S*)
9	**23**	**29**	DCM	rt	70 h	5	—
10	**24**	**29**	DCM	rt	43 h	52	31 (*R*)
11	**25**	**29**	DCM	rt	10 min	100	72 (*S*)
12	**26**	**29**	DCM	rt	30 min	100	5 (*S*)
13	**26**	**29**	DCM	−3	30 min	43	16 (*S*)
14	**27**	**29**	DCM	rt	30 min	100	5 (*R*)
15	**27**	**29**	DCM	−78	6 h	14	5 (*R*)
16	**28**	**29**	DCM	rt	20 min	85	93 (*R*)
					60 min	95	93 (*R*)
17	**20**	**30**	DCM	rt	30 min	100	31 (*S*)
18	**22**	**30**	DCM	rt	20 min	100	18 (*S*)
19	**25**	**30**	DCM	rt	10 min	100	53 (*S*)

[a] NaH: 0.5 mmol, DMM: 0.6 mmol, THAB: 0.52 mmol, $(C_3H_5PdCl)_2$: 4.2 μmol (2.5 mol%), ligand: 12.5 (**21**, **23**, **24**); 8.3 (**20**, **26**, **27**); 6.3 (**22**); 4.2 (**25**) μmol, carbonate: 0.165 mmol, solvent: 3 mL. [b] Determined by GC-MS. [c] Determined by HPLC (**30**) or the combination of optical rotation data[15] and ^{1}H NMR chiral shift experiments (**31**).[13] [d] No THAB added.

Table 2 The influence of the amount of ligands and palladium to allylic alkylation of methyl 2-cyclohexenyl carbonate with sodium dimethyl malonate[a]

Entry	Ligand	$(C_3H_5PdCl)_2$[b] (mol%)	Time (min)	Conversion (%)[c]	ee (%)[d]
1	**22**	2.5	10	100	81 (*S*)
2	**22**	1.25	10	96	85 (*S*)
			30	100	84 (*S*)
3	**22**	0.63	30	91	84 (*S*)
			60	100	83 (*S*)
5	**25**	2.5	10	100	72 (*S*)
5	**25**	1.25	10	84	77 (*S*)
			40	100	75 (*S*)
7	**25**	0.63	10	76	75 (*S*)
			40	100	74 (*S*)
8	**20**	2.5	20	96	85 (*S*)
9	**20**	1.25	30	96	87 (*S*)
			60	100	86 (*S*)
10	**20**	0.63	40	95	88 (*S*)
			70	100	88 (*S*)

[a] NaH: 0.5 mmol, DMM: 0.6 mmol, THAB: 0.52 mmol, carbonate: 0.165 mmol, DCM: 3 mL, rt. [b] Pd : P ratio 1 : 3. [c] Determined by GC-MS. [d] Determined by HPLC.

Solvent Dispensing System. Sodium hydride was washed with pentane and dried *in vacuo*. Tetrahexylammonium bromide (THAB) was washed with diethyl ether and dried *in vacuo*. Methanol and all the other reagents were used as received.

^{1}H and ^{13}C spectra were recorded on a Bruker Advance 400 instrument or a Bruker DMX 500 instrument in $CDCl_3$, using the residual signals from $CHCl_3$ (^{1}H: δ 7.25 ppm; ^{13}C: δ 77.0 ppm) as internal standard. ^{31}P NMR spectra were recorded on a Bruker DMX 500 instrument in $CDCl_3$ using H_3PO_4 as external standard. Optical rotations were recorded with a Perkin-Elmer 343 polarimeter at the sodium D line at ambient temperature. Flash chromatography was carried out using SDS silica gel 60 (40–63 μm). Melting points were measured in open capillary tubes using an electrothermal instrument and were uncorrected. HRMS was carried out by Instrumentstationen, Kemicentrum, Lund University, Sweden.

Compounds **21**,[8] **6**,[2] **29**,[16] and **30**[16] were synthesized *via* published procedures. Aldehyde **19b** was prepared in a two-step reaction from 2-bromoiodobenzene, which was reacted with isopropylmagnesium bromide[17] to promote an aryl exchange, followed by

introduction of the phosphine using chlorodiphenylphosphine, to form 2-(diphenylphosphino)bromobenzene[18] in 60% yield. *o*-Lithiation and reaction with DMF afforded **19b**.[19]

Compound 9

Compound **9** was prepared following our previous procedure[2] using *n*-butylamine (1.34 mL, 13.6 mmol) and aziridine **6** (6.6 g, 27.4 mmol) in MeOH (18 mL), giving compound **9** as a white powder (7.02 g, 85%): R_f (hexane–EtOAc 7 : 3) 0.7; $[\alpha]_D^{25}$ +29.5 (*c* 1.09 in $CHCl_3$); mp 116–117 °C; δ_H (400 MHz, $CDCl_3$) 0.75 (6 H, d, *J* 7.0), 0.77 (6 H, d, *J* 7.0), 0.86 (3 H, t, *J* 7.2), 1.01–1.31 (4 H, m), 1.93 (2 H, dhept, *J* 7.0 and 4.0), 2.12–2.23 (1 H, m), 2.24–2.34 (1 H, m), 2.31 (2 H, dd, *J* 13.1 and 5.5), 2.38 (2 H, dd, *J* 13.1 and 8.8), 2.41 (6 H, s), 3.26–3.39 (2 H, m), 5.21 (2 H, br s), 7.27 (4 H, d, *J* 8.2), 7.79 (4 H, d, *J* 8.2); δ_C (125 MHz, $CDCl_3$) 14.0, 17.7, 20.5, 21.5, 27.1, 29.7, 53.0, 53.7, 56.0, 127.0, 129.5, 138.6, 143.0.

Compound 10

Compound **10** was prepared in the same way as described previously[5] from **9** (6.82 g, 12.36 mmol), phenol (7.51 g, 79.79 mmol), and HBr (48% aq., 104.5 mL), giving the product (2.49 g, 83%) as a light brown oil: $[\alpha]_D^{25}$ +106.5 (*c* 0.76 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.894 (3 H, t, *J* 7.3), 0.896 (6 H, d, *J* 6.8), 0.91 (6 H, d, *J* 6.8), 1.16–1.45 (4 H, m), 1.50 (2 H, octet, *J* 6.8), 1.82 (4 H, br s), 2.17–2.27 (1 H, m), 2.22 (2 H, dd, *J* 12.6 and 10.3), 2.30 (2 H, dd, *J* 12.6 and 3.0), 2.45–2.54 (1 H, m), 2.60–2.68 (2 H, m); δ_C (100 MHz, $CDCl_3$) 14.0, 18.7, 18.9, 20.6, 28.0, 31.0, 54.3, 54.6, 56.5.

Compound 11

Compound **11** was prepared analogously to **13** using diaminoethane (**3**, 30 mg, 0.5 mmol), **6** (718 mg, 3 mmol), and MeOH (2 mL). The precipitate formed was filtered off and rinsed with MeOH three times to give **11** as a white powder (359 mg, 71%): $[\alpha]_D^{25}$ +36.6 (*c* 0.66 in $CHCl_3$); mp 190–191 °C; δ_H (400 MHz, $CDCl_3$) 0.70 (12 H, d, *J* 6.9), 0.74 (12 H, d, *J* 6.9), 1.80 (4 H, dhept, *J* 6.9 and 4.0), 2.32–2.50 (10 H, m), 2.38 (12 H, s), 2.74–2.86 (2 H, m), 3.29–3.39 (4 H, m), 5.67 (4 H, d, *J* 6.3), 7.25 (8 H, d, *J* 8.3), 7.80 (8 H, d, *J* 8.3); δ_C (100 MHz, $CDCl_3$) 17.5, 18.0, 21.5, 30.0, 45.8, 51.9, 53.6, 56.5, 126.9, 129.4, 139.1, 142.8.

Compound 12

Compound **12** was prepared as described previously[5] from **11** (1.01 g, 1.0 mmol), phenol (1.21 g, 12.8 mmol), and HBr (48% aq., 17 mL), giving the product (343 mg, 86%) as a colorless oil: $[\alpha]_D^{25}$ +172.4 (*c* 0.52 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (12 H, d, *J* 6.8), 0.90 (12 H, d, *J* 6.8), 1.48 (4 H, octet, *J* 6.8), 1.5 (8 H, br s), 2.21 (2 H, dd, *J* 12.3 and 10.7), 2.33 (2 H, dd, *J* 12.3 and 2.3), 2.37–2.45 (2 H, m), 2.58–2.70 (6 H, m); δ_C (100 MHz, $CDCl_3$) 18.2, 19.3, 32.2, 52.8, 53.7, 60.0.

Compound 22

Ligand **22** was synthesized analogously to **23** using 2-(diphenylphosphino)benzoic acid (**19a**, 772 mg, 2.52 mmol), EDC·HCl (483 mg, 2.52 mmol,), HOBt (341 mg, 2.52 mmol), **12** (253 mg, 0.63 mmol), and DMF (11.2 mL). Purification by chromatography (silica gel, hexane–EtOAc 4 : 1 to hexane–EtOAc 3 : 1 + 0.25% Et_3N and 0.25% MeOH) gave **22** as a white foam (547 mg, 56%): R_f (hexane–EtOAc 3 : 1 + 6% Et_3N and 6% MeOH) 0.73; $[\alpha]_D^{25}$ −67.4 (*c* 0.26 in $CHCl_3$); mp 115–116 °C; δ_H (400 MHz, $CDCl_3$) 0.72 (12 H, d, *J* 6.8), 0.77 (12 H, d, *J* 6.8), 1.81 (4 H, octet, *J* 6.8), 2.39 (2 H, dd, *J* 12.5 and 3.9), 2.49–2.61 (2 H, m), 2.64–2.76 (2 H, m), 2.85 (4 H, app t, *J* 11.8), 4.02–4.15 (4 H, m), 6.38 (4 H, t, *J* 7.43), 6.55 (4 H, d, *J* 8.8), 6.77 (4 H, dd, *J* 6.9 and 3.9), 6.94 (4 H, t, *J* 7.2), 6.99 (8 H, t, *J* 6.9), 7.09 (8 H, t, *J* 6.8), 7.12–7.27 (28 H, m); δ_C (125 MHz, $CDCl_3$) 18.4, 19.3, 30.8, 48.2, 51.6, 55.4, 127.2, 127.3, 128.15–128.25 (multiple signals), 129.4, 133.4, 133.6, 134.0, 134.1, 136.9 (d, *J* 21.7), 138.3 (d, *J* 10.5), 138.6 (d, *J* 14.2), 141.3 (d, *J* 24.7), 169.0; δ_P (202 MHz, $CDCl_3$) −8.34 (s); HRMS (FAB+) calcd for $C_{98}H_{104}N_6O_4P_4$ [M + H] 1553.7148. Found: 1553.7151.

Compound 13

Compound **13** was synthesized in a similar way disclosed previously[2] using (1*R*,2*R*)-diaminocyclohexane (**4**, 173 mg, 1.52 mmol), aziridine **6** (731 mg, 3.05 mmol), and MeOH (2.0 mL). The mixture was exposed to microwave at 160 °C for 75 min. The solvent was removed and the brown solid obtained was purified by chromatography (hexane–EtOAc 3 : 1 + 0–1% Et_3N and 0–3% MeOH) to give the product as a yellow foam (578 mg, 63%): R_f (hexane–EtOAc 3 : 1 + 1% Et_3N and 3% MeOH) 0.13; $[\alpha]_D^{25}$ −51.6 (*c* 0. 69 in $CHCl_3$); mp 139–140 °C; δ_H (400 MHz, $CDCl_3$) 0.67 (6 H, d, *J* 6.8), 0.70 (6 H, d, *J* 6.8), 1.04–1.23 (4 H, m), 1.65 (2 H, octet, *J* 6.8), 1.54–1.74 (4 H, m), 1.88 (2 H, d, *J* 12.6), 2.17–2.27 (2 H, m), 2.40 (6 H, s), 2.57 (2 H, dd, *J* 11.8 and 7.1), 2.77 (2 H, dd, *J* 11.8 and 3.4), 3.12–3.19 (2 H, m), 6.14 (2 H, br s), 7.26 (4 H, d, *J* 8.3), 7.78 (4 H, d, *J* 8.3); δ_C (125 MHz, $CDCl_3$) 18.9, 19.0, 21.5, 25.1, 30.3, 31.8, 47.0, 60.15, 60.22, 126.9, 129.4, 139.0, 142.8.

Compound 14

Compound **14** was prepared in the same way described previously[5] from **13** (1.40 g, 2.36 mmol), phenol (1.42 g, 15.1 mmol), and HBr (48% aq., 19.8 mL) giving the product (549 mg, 82%) as a pink thick oil: $[\alpha]_D^{25}$ −48.4 (*c* 0.79 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (6 H, d, *J* 6.8), 0.90 (6 H, d, *J* 6.8), 0.93–1.08 (2 H, m), 1.53–1.78 (4 H, m), 1.60 (2 H, dhept, *J* 6.8 and 5.5), 2.00–2.14 (4 H, m), 2.17 (2 H, dd, *J* 11.2 and 9.1), 2.46–2.54 (2 H, m), 2.85 (2 H, dd, *J* 11.2 and 3.5); δ_C (100 MHz, $CDCl_3$) 17.8, 19.5, 25.1, 32.1, 32.3, 51.8, 57.5, 62.7.

Compound 23

Ligand **23** was synthesized using a modified literature procedure.[20] 2-(Diphenylphosphino)benzoic acid (**19a**, 1.05 g, 3.33 mmol), 1-[3-(dimethylamino)propyl]3-ethylcarbodiimide hydrochloride (EDC·HCl) (638 mg, 3.33 mmol), and 1-hydroxylbenzotriazole hydrate (HOBt) (450 mg, 3.33 mmol) were stirred in DMF (46 mL) for 30 min at rt. **14** (473 mg, 1.66 mmol) was added, and the reaction mixture stirred for 24 h. 1 N HCl (92 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 90 mL). The combined organic phases were washed with brine (3 × 90 mL). The solvent was removed *in vacuo* and the crude product was purified by chromatography (silica gel, hexane–EtOAc 3 : 1, + 1–3% Et_3N and 2–3% MeOH) to give the **23** as a

white foam (808 mg, 56%): R_f (hexane–EtOAc 3 : 1 + 6% Et_3N and 6% MeOH) 0.43; $[\alpha]_D^{25}$ −81.4 (*c* 0.56 in $CHCl_3$); mp 88–90 °C; δ_H (400 MHz, $CDCl_3$) 0.77 (6 H, d, *J* 6.8), 0.81 (6 H, d, *J* 6.8), 0.83–0.94 (2 H, m), 1.16 (2 H, app t, *J* 10.2), 1.46 (2 H, br s), 1.58–1.71 (2 H, m), 1.76 (2 H, octet, *J* 6.8), 1.91–2.06 (4 H, m), 2.50 (2 H, dd, *J* 12.3 and 5.0), 2.67 (2 H, dd, *J* 12.3 and 4.7), 3.79–3.89 (2 H, m), 6.15 (2 H, d, *J* 8.8), 6.94 (2 H, dd, *J* 7.1 and 3.8), 7.18–7.37 (24 H, m), 7.58 (2 H, dd, *J* 6.8 and 3.5); δ_C (125 MHz, $CDCl_3$) 18.4, 19.5, 25.0, 29.2, 31.8, 47.5, 55.2, 62.0, 127.7, 127.8, 128.5, 128.59, 128.60, 128.7, 128.8, 128.9, 130.0, 133.6, 133.7, 133.8, 133.9, 134.3, 135.2 (d, *J* 20.2), 137.1 (d, *J* 11.2), 137.4 (d, *J* 12.0), 142.4 (d, *J* 27.7), 168.8; δ_P (202 MHz, $CDCl_3$) −10.4 (s); HRMS (FAB+) calcd for $C_{54}H_{62}N_4O_2P_2$ [M + H] 861.4426. Found: 861.4412.

Compound 15

Compound **15** was prepared analogously to **13** using (1*S*,2*S*)-diaminocyclohexane (*ent*-**4**, 173 mg, 1.52 mmol), compound **6** (731 mg, 3.05 mmol), and MeOH (2.0 mL). The brown solid obtained was purified by chromatography (silica gel, hexane–EtOAc 3 : 1 + 1% Et_3N and 2% MeOH) to give the product as a white-yellowish foam (519 mg, 58%): R_f (hexane–EtOAc 3 : 1 + 6% Et_3N and 6% MeOH) 0.38; $[\alpha]_D^{25}$ +4.5 (*c* 0.67 in $CHCl_3$); mp 45–46 °C; δ_H (400 MHz, $CDCl_3$) 0.64 (6 H, d, *J* 6.7), 0.75 (6 H, d, *J* 6.7), 0.93–1.07 (2 H, m), 1.14–1.23 (2 H, m), 1.56–1.81 (4 H, m), 1.72 (2 H, octet, *J* 6.7), 1.98 (2 H, d, *J* 13.1), 2.13–2.22 (2 H, m), 2.40 (6 H, s), 2.59 (2 H, dd, *J* 12.1 and 3.5), 2.87 (2 H, dd, *J* 12.1 and 5.0), 3.01–3.11 (2 H, m), 6.12 (2 H, br s), 7.26 (4 H, d, *J* 8.3), 7.80 (4 H, d, *J* 8.3); δ_C (125 MHz, $CDCl_3$) 18.9, 19.4, 21.5, 25.2, 29.8, 31.8, 47.1, 60.0, 61.0, 126.9, 129.5, 138.6, 142.9.

Compound 16

Compound **16** was prepared in the same way described previously[6] using compound **15** (1.29 g, 2.17 mmol), phenol (1.32 g, 14.0 mmol), and HBr (48% aq., 18.4 mL), giving the product (560 mg, 91%) as a clear light yellow oil: $[\alpha]_D^{25}$ +115. 9 (*c* 0.73 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (6 H, d, *J* 6.8), 0.90 (6 H, d, *J* 6.8), 0.92–1.04 (2 H, m), 1.16–1.25 (2 H, m), 1.39 (6 H, br s), 1.57 (2 H, dhept, *J* 6.8 and 5.0), 1.64–1.76 (2 H, m), 2.01–2.15 (4 H, m), 2.46 (2 H, dd, *J* 12.1 and 9.8), 2.55 (2 H, dd, *J* 12.1 and 3.5), 2.52–2.60 (2 H, m); δ_C (100 MHz, $CDCl_3$) 17.6, 19.5, 25.1, 31.8, 32.1, 50.9, 56.4, 61.2.

Compound 24

Ligand **24** was synthesized analogously to **23** using 2-(diphenylphosphino)benzoic acid (**19a**, 472 mg, 1.54 mmol), EDC·HCl (295 mg, 1.54 mmol,), HOBt (208 mg, 1.54 mmol), **16** (218 mg, 0.77 mmol), and 19 mL DMF. Purified by chromatography (silica gel, hexane–EtOAc 3 : 1 + 1–6% Et_3N and 2–6% MeOH) to give **24** as a white foam (309 mg, 47%): R_f (hexane–EtOAc 3 : 1 + 6% Et_3N and 6% MeOH) 0.24; $[\alpha]_D^{25}$ −6.8 (*c* 0.30 in $CHCl_3$); mp 81–82 °C; δ_H (400 MHz, $CDCl_3$) 0.69 (6 H, d, *J* 6.8), 0.78 (6 H, d, *J* 6.8), 0.80–0.91 (2 H, m), 1.18 (2 H, app t, *J* 10.2), 1.52–1.81 (4 H, m), 1.75 (2 H, octet, *J* 6.8), 1.99 (2 H, d, *J* 12.8), 2.08–2.18 (2 H, m), 2.43 (2 H, dd, *J* 12.4 and 5.0), 2.30 (2 H, dd, *J* 12.4 and 6.7), 3.84–3.95 (2 H, m), 6.11 (2 H, d, *J* 8.8), 6.89–6.97 (2 H, m), 7.15–7.37 (24 H, m), 7.53–7.61 (2 H, m); δ_C (125 MHz, $CDCl_3$) 17.8, 19.4, 24.9, 29.4, 31.4, 47.5, 54.8, 61.2, 127.82, 127.86, 128.50, 128.55, 128.60, 128.65, 128.73, 128.81, 130.0, 133.70, 133.74, 133.86, 133.89, 134.32, 135.5 (d, *J* 21.1), 137.2 (d, *J* 11.5), 137.4 (d, *J* 11.5), 143.4 (d, 25.9), 168.9; δ_P (202 MHz, $CDCl_3$) −9.98 (s).

Compound 17

Compound **17** was prepared analogously to **13** using TREN (**5**, 48.3 mg, 0.33 mmol), **6** (718 mg, 3 mmol), and MeOH (2 mL). The crude product was purified by chromatography (silica gel, hexane–EtOAc 4 : 1 to hexane–EtOAc 3 : 1 + 3–6% Et_3N and 3–6% MeOH) to give **17** as a white foam (370 mg, 95%): R_f (hexane–EtOAc 3 : 1 + 6% Et_3N and 6% MeOH) 0.10; $[\alpha]_D^{25}$ +34.5 (*c* 1.49 in $CHCl_3$); mp 85–87 °C; δ_H (400 MHz, $CDCl_3$) 0.71 (18 H, d, *J* 6.9), 0.74 (18 H, d, *J* 6.9), 1.85 (6 H, dhept, *J* 6.9 and 3.7), 2.33 (6 H, dd, *J* 13.5 and 4.1), 2.37 (18 H, s), 2.40–2.47 (3 H, m), 2.44 (6 H, dd, *J* 13.5 and 10.2), 2.47–2.57 (6 H, m), 2.72–2.86 (3 H, m), 3.29–3.40 (6 H, m), 5.81 (6 H, br s), 7.23 (12 H, d, *J* 8.2), 7.77 (12 H, d, *J* 8.2); δ_C (125 MHz, $CDCl_3$) 17.2, 18.1, 21.5, 30.0, 51.5, 51.7, 53.2, 56.1, 127.0, 129.4, 139.0, 142.7.

Compound 18

Compound **18** was prepared in the same way described previously[5] using compound **17** (1.84 g, 1.16 mmol), phenol (2.11 g, 22.4 mmol), and HBr (48% aq., 30 mL), giving the product (663 mg, 87%) as a whitish semisolid: $[\alpha]_D^{25}$ +155.0 (0.40 in MeOH); δ_H (400 MHz, $CDCl_3$) 0.89 (18 H, d, *J* 6.8), 0.90 (18 H, d, *J* 6.8), 1.48 (6 H, octet, *J* 6.8), 1.5 (12 H, br s), 2.20 (6 H, dd, *J* 12.5 and 10.3), 2.35 (6 H, dd, *J* 12.5 and 2.8), 2.29–2.41 (3 H, m), 2.47–2.59 (6 H, m), 2.59–2.68 (9 H, m); δ_C (100 MHz, $CDCl_3$) 18.3, 19.4, 32.2, 53.1, 53.4, 53.8, 60.2.

Compound 25

Ligand **25** was synthesized analogously to **23** using 2-(diphenylphosphino)benzoic acid (**19a**, 184 mg, 0.6 mmol), EDC·HCl (115 mg, 0.6 mmol,), HOBt (81 mg, 0.6 mmol), **18** (66 mg, 0.1 mmol), and 2.8 mL DMF. The purification by chromatography (silica gel, hexane–EtOAc 3 : 1 + 0.5% Et_3N and 0.5% MeOH) gave **25** as a white foam (56 mg, 24%): R_f (hexane–EtOAc 3 : 1 + 6% Et_3N and 6% MeOH) 0.71; $[\alpha]_D^{25}$ −190.5 (0.23 in CH_2Cl_2); mp 127.3–129.5 °C; δ_H (400 MHz, $CDCl_3$) 0.67 (18 H, d, *J* 6.8), 0.71 (18 H, d, *J* 6.8), 1.50–1.63 (6 H, m), 2.02–2.14 (3 H, m), 2.27 (6 H, dd, *J* 12.5 and 3.4), 2.37–2.49 (3 H, m), 2.58–2.70 (6 H, m), 2.82 (6 H, app t, *J* 11.7), 3.92–4.04 (6 H, m), 6.29 (6 H, t, *J* 7.4), 6.75 (6 H, dd, *J* 7.3 and 4.0), 6.89 (12 H, t, *J* 7.2), 6.98 (12 H, t, *J* 7.7), 7.05 (12 H, t, *J* 7.2), 7.13–7.29 (42 H, m); δ_C (100 MHz, $CDCl_3$) 18.9, 19.2, 30.2, 51.9, 52.7, 53.3, 56.1, 127.42, 127.45, 128.0, 128.1, 128.23–128.32 (multiple signals), 129.1, 133.6, 133.8, 133.9, 134.1, 134.3, 136.9 (d, *J* 22.4), 138.2 (app t, *J* 14.2 and 12.7), 141.3 (d, *J* 22.4), 169.0; δ_P (202 MHz, $CDCl_3$) −8.0 (s); HRMS (FAB+) calcd for $C_{150}H_{162}N_{10}O_6P_6$ [M + H] 2386.1183. Found: 2386.1196.

Compound 26

Under nitrogen atmosphere, **8** (0.5 mmol, 0.136 g) and diphenylphosphine benzaldehyde **19b** (1.55 mmol, 0.5 g) were

dissolved in a solution of anhydrous CH_2Cl_2–CH_3OH (1 : 3) (100 mL). The homogeneous solution was stirred at room temperature for 72 h. The solvents were then evaporated under vacuum until a yellow precipitate appeared. This was filtered, washed with cold methanol to yield **26** (60%) as a yellow solid: $[a]_D^{25}$ −44.5 (*c* 0.49 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.54 (9 H, d, *J* 6.8), 0.62 (9 H, d, *J* 6.8), 1.57–1.71 (3 H, m), 2.28 (3 H, dd, *J* 13.5 and 7.4), 2.42 (3 H, dd, *J* 13.5 and 4.5), 2.88–2.99 (3 H, m), 6.80–6.88 (3 H, m), 7.17–7.31 (36 H, m), 7.42–7.47 (3 H, m), 8.51 (3 H, d, *J* 4.3); δ_C (100 MHz, $CDCl_3$) 17.7, 20.1, 30.6, 59.2, 75.2, 128.3–128.5 (multiple signals), 129.11, 129.14, 129.4, 133.5, 133.8, 133.99, 134.04,134.2, 137.1 (d, *J* 21.7), 137.6 (d, *J* 9.8), 137.8 (d, *J* 11.9), 139.8 (d, *J* 17.2), 158.7 (d, *J* 14.9); δ_P (202 MHz, $CDCl_3$) −11.0.

(*S*,*S*,*S*)-Tris[2-(2′-diphenylphosphinobenzamino)-3-methylbutyl]amine (27)

$NaBH_4$ (3.3 mmol, 0.125 g) was added in two portions to phosphine imine ligand **26** (1 mmol, 1.09 g) in anhydrous CH_2Cl_2–CH_3OH (1 : 2) (20 mL). After stirring overnight at room temperature, diethyl ether (20 mL) and saturated aqueous $NaHCO_3$ were added. The aqueous phase was extracted with diethyl ether. The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. A pale yellow solid corresponding to the amine ligand was obtained in 70%: $[a]_D^{25}$ +5.4 (*c* 0.26 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.65 (9 H, d, *J* 6.9), 0.71 (9 H, d, *J* 6.9), 1.67 (3 H, s br), 1.7–1.87 (3 H, m), 2.16 (3 H, dd, *J* 12.8 and 5.0), 2.25 (3 H, dd, *J* 12.8 and 7.8), 2.38–2.47 (3 H, m), 3.86 (6 H, s), 6.74–6.81 (3 H, m), 6.98–7.11 (6 H, m), 7.13–7.30 (3 H, m), 7.40–7.45 (30 H, m); δ_C (100 MHz, $CDCl_3$) 17.6, 17.8, 28.1, 50.2, 50.5, 56.2, 60.0, 126.7, 128.4–128.5 (multiple signals), 128.76, 128.81, 128.9, 133.2, 133.7, 133.8, 133.92, 133.98, 135.1 (d, *J* 13.6), 137.0 (d, *J* 11.2), 137.2 (d, *J* 11.2), 145.6 (d, *J* 23.2); δ_P (202 MHz, $CDCl_3$) −14.8.

Typical procedure for catalytic asymmetric allylic alkylation

Allylic alkylation followed Trost's procedure[12] with a slight modification. DCM (0.5 mL) was added to a flask charged with allylic palladium chloride dimer (4.2 μmol, 1.5 mg) and ligand **22** (6.3 μmol, 9.6 mg). The mixture was stirred for 5 min at rt before methyl 3-cyclohexenyl carbonate (**29**, 0.165 mmol, 26 mg) was added; 2.5 mL DCM was added to another flask charged with sodium hydride (0.5 mmol, 12 mg) and THAB (0.52 mmol, 225 mg). Then dimethyl malonate (0.6 mmol, 81 mg) was added dropwise to generate a solution of tetrahexylammonium dimethyl malonate. The catalytic solution was added to it at once. The reaction was monitored by GC-MS. The enantiomeric excess was determined by HPLC (**31**: 0.25% ^{i}PrOH in hexane, 0.5 mL min^{-1}, Chiralcel OD–H, wavelength: 220 nm, t_R = 28.3 min, t_S = 29.8 min, rt).

The same procedure was used for ethyl 3-cyclopentenyl carbonate (**30**) except the enantiomeric excess was determined by the combination of optical rotation data[15] and ^{1}H NMR chiral shift study (**32**).[13]

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