Pyridyl Phosphinites and Pyridyl Phosphites from Chiral Pyridyl Alcohols — A Modular Approach

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Chiral arylated pyridyl alcohols, pyridyl phosphinites and pyridyl phosphites were prepared by Suzuki arylation and/or *O*-functionalization with a chlorodiarylphosphane or a chlorodiarylphosphite of chiral 2-bromo-6-(1-hydroxyalkyl)pyridines or 2-(1-hydroxyalkyl)pyridines, with the chirality originating from the chiral pool. The pyridyl alcohols were assessed as catalysts for the addition of diethylzinc to benzaldehyde and the P,N-ligands were employed in the palladium-catalysed substitutions of *rac*-1,3-diphenyl-2-propenyl acetate and *rac*-2-cyclohexenyl acetate with dimethyl malonate. Moderate enantioselectivities were observed in the catalytic reactions. We observed kinetic resolution of the racemic acetate when using one of the phosphite ligands.

Introduction

Recent progress in asymmetric synthesis has provided powerful catalytic procedures for the preparation of a wide variety of organic compounds in enantiopure or enantioenriched forms.[1] This development has been based on combinations of trial-and-error and attempted rational catalyst design. To meet the increasing demand for enantiopure or enantioenriched products, more efficient methods are required for catalyst development and screening of metal complexes.[2,3] Today, high-throughput screening technologies — whereby a combination of synthetic procedures and efficient analytical methods allow on-line determination of yield[4] and enantioselectivity[5] — are being explored, together with methods that allow downsizing.[6] Simple variation of catalyst structure can sometimes be achieved by the use of additives or activators,[7] but structural variations of the ligand responsible for chirality transfer is usually required to achieve high selectivity. Efficient methods are required for their preparation of chiral ligands having the desired structural variations.[8] Modular approaches are widely employed for this purpose.[9] Such methods are particularly important when they permit the preparation of different types of ligands, for example, those containing different sets of donor atoms, starting from the same basic skeleton.

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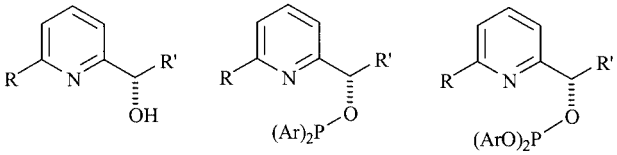
Previously, we developed a simple methodology for the preparation of chiral enantiopure pyridyl alcohols [**1**, R = H, Br; R′ = neomenthyl,[10] (*S*)-methoxybenzyl, (*S*)-1-methoxyethyl][11] that employs cheap and readily available compounds that originate from the chiral pool. Here we describe the transformation of the pyridyl alcohols into 6-aryl-substituted pyridyl alcohols (**1**, R = Ar), chiral pyridyl phosphinites (**2**, R = H, Ar) and pyridyl phosphites (**3**, R = H).



1 **2** **3**

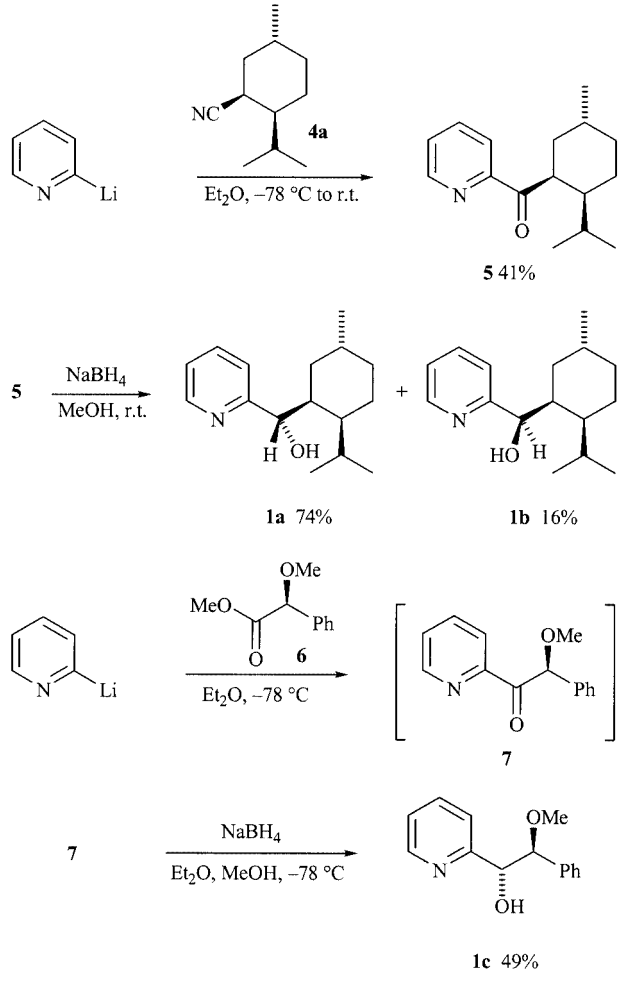
Chiral pyridyl alcohols have found extensive use in catalytic applications, in particular for the addition of diethylzinc to aldehydes and the conjugate addition to α,β-unsaturated carbonyl compounds.[12] Achiral[13] as well as chiral[14] pyridinophosphinites and a tridentate bisphosphinated 2,6-bis(1-hydroxyethyl)pyridine[15] have been prepared and used in palladium-catalysed allylations, rhodium-catalysed hydroformylations, and Rh- and Ir-catalyzed hydrogenations of prochiral imines,[16] respectively. Pyridinophosphites have recently also been applied to a variety of catalytic processes.[17]

We have applied the pyridyl alcohols described here as catalysts for the addition of diethylzinc to benzaldehyde and we have used the P,N derivatives in palladium-catalysed allylic alkylations.

Results and Discussion

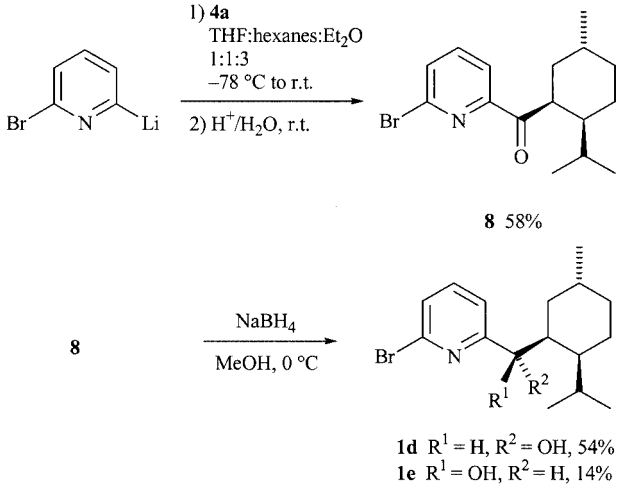
Preparation of Ligands

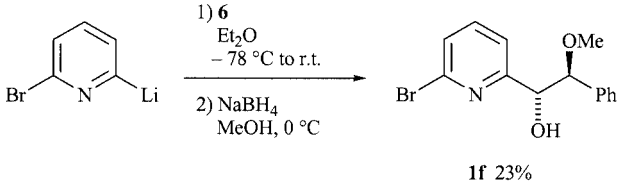
Diastereoisomeric alcohols **1a** and **1b** were obtained as described previously from reaction of (1*S*,2*S*,5*R*)-1-cyano-2-isopropyl-5-methylcyclohexane (neomenthyl-1-nitrile, **4a**) with 2-lithiopyridine, followed by reduction of the ketone **5** obtained using sodium borohydride, and chromatographic separation of the products;[10] the analogous reactions of mandelic acid methyl ester derivative **6** afforded the ketone **7**, which upon reduction yielded pyridyl alcohol **1c** as a single diastereoisomer (Scheme 1).[11]



Scheme 1

The derivatives **1d** and **1e** were prepared by reaction of 2-bromo-6-lithiopyridine, obtained by lithiation of 2,6-dibromopyridine in THF/hexane/diethyl ether (1:1:3), with **4a** to give the ketone **8** (58%), which was reduced with sodium borohydride to give a ca. 4:1 ratio of the (*S*) and (*R*) isomers in a total isolated yield of 68% (Scheme 2). Compound





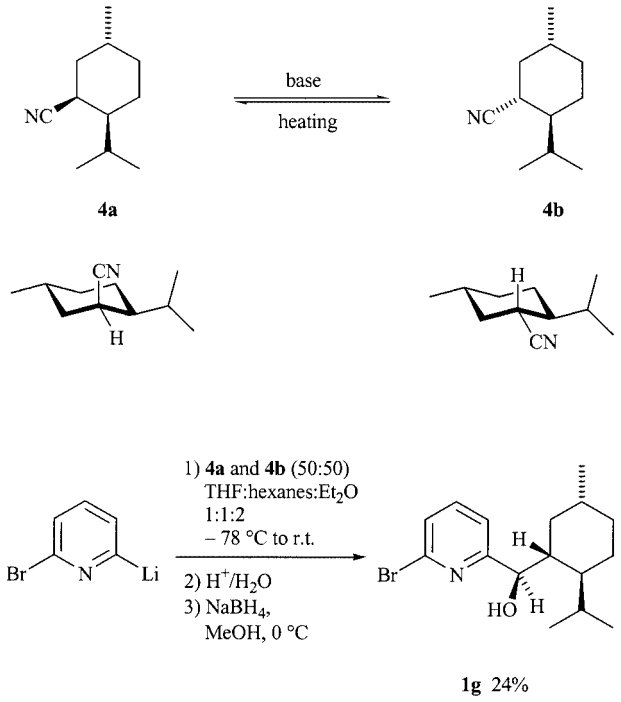
Scheme 2

1f was obtained analogously starting from 2,6-dibromopyridine and **6**.[11]

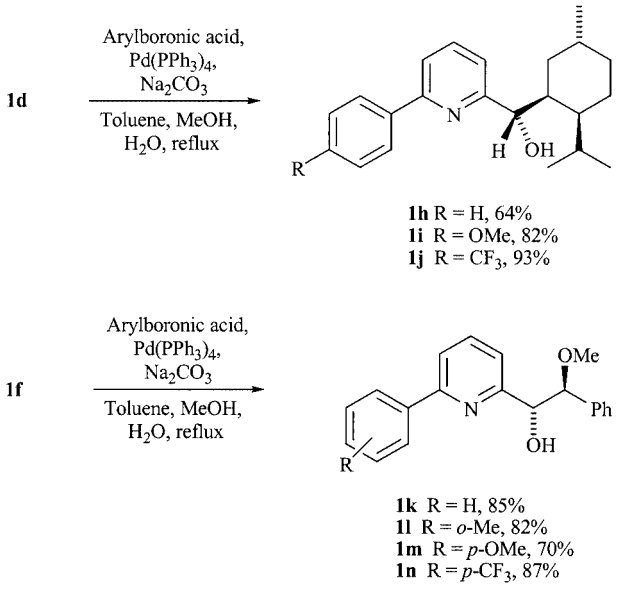
To gain access to menthyl derivatives, a variety of conditions were tested for the epimerization of (1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexane-1-carbonitrile. With the cyano group in the axial position, proton abstraction is highly disfavoured and rather drastic conditions are required for epimerization to occur. Microwave irradiation at 160 °C over a period of 20 min in 0.1 M NaOEt in ethanol afforded a 1:1 mixture of the epimers **4a** and **4b**,[18] which could not be separated by chromatography (Scheme 3).

Some epimerization occurred in the reactions of 2-bromo-6-lithiopyridine and **4a** and we isolated products that seemingly were obtained from **4b**. Use of a solvent consisting of a 1:1:2 mixture of THF/hexane/diethyl ether, in place of the 1:1:3 mixture normally employed, increased the degree of epimerization, although at the expense of the total yield of the reaction. To optimize the formation of menthyl alcohols, the 1:1 mixture of epimeric nitriles was treated with 2-bromo-6-lithiopyridine in the 1:1:2 mixture of solvents. From this reaction, we isolated in a pure form only the isomer with absolute (*R*) configuration at the carbinol carbon atom (**1g**; 24% yield from the nitrile, Scheme 3).

6-Aryl-substituted pyridyl alcohols were conveniently accessible by Suzuki coupling of bromo derivatives **1d** and **1f** using tetrakis(triphenylphosphane)palladium and sodium carbonate. Phenylboronic acid, *o*-methylphenylboronic acid, *p*-methoxyphenylboronic acid, and *p*-(trifluoromethyl)-phenylboronic acid were selected as reagents to allow us to study the effects of electron-withdrawing and electron-donating substituents on the subsequent catalytic reactions.



Scheme 3

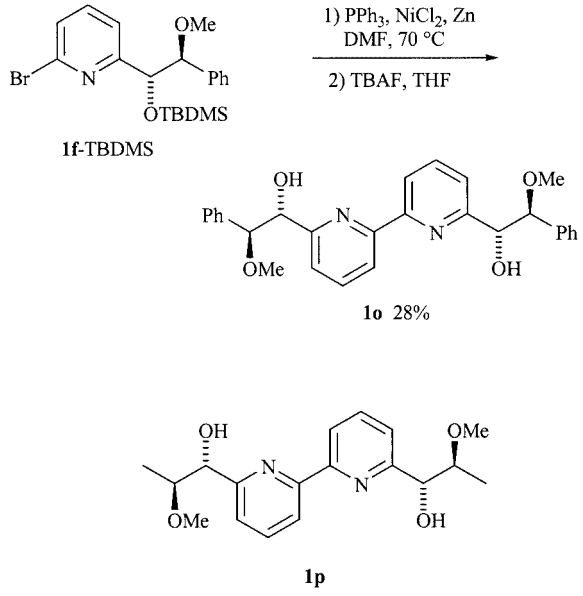


Scheme 4

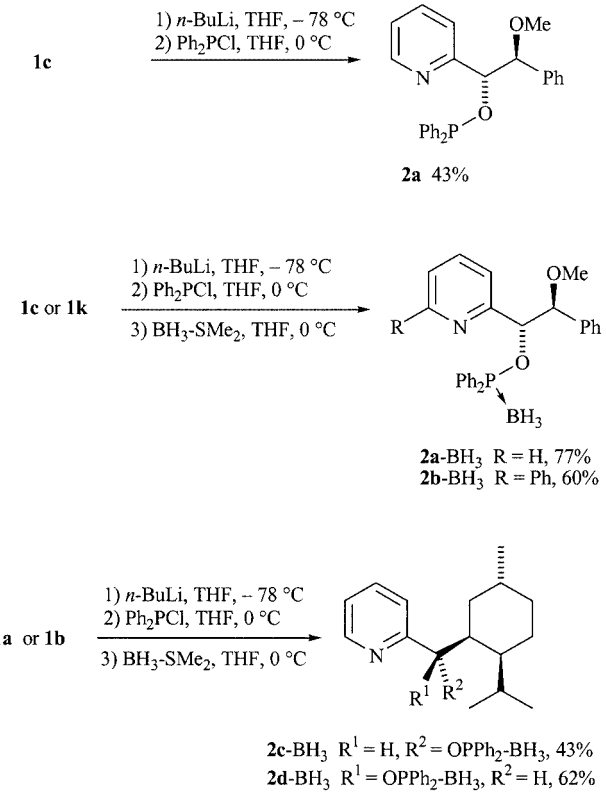
The reactions afforded good-to-high yields (64−93%) of products **1h**−**1n** (Scheme 4).

Nickel-mediated dimerization of TBDMS-protected **1f** and the analogous lactic acid derivative afforded, after deprotection, bipyridine compounds **1o** and **1p** (Scheme 5).[11]

We prepared phosphinites from the appropriate pyridyl alcohols by deprotonation with *n*BuLi, followed by reaction with chlorodiphenylphosphane (Scheme 6). The desired phosphinite was obtained from mandelic acid derivative **1c** in 43% yield. In situ protection of the labile product by using BH_3·SMe_2 increased the yield to 77% and, therefore,



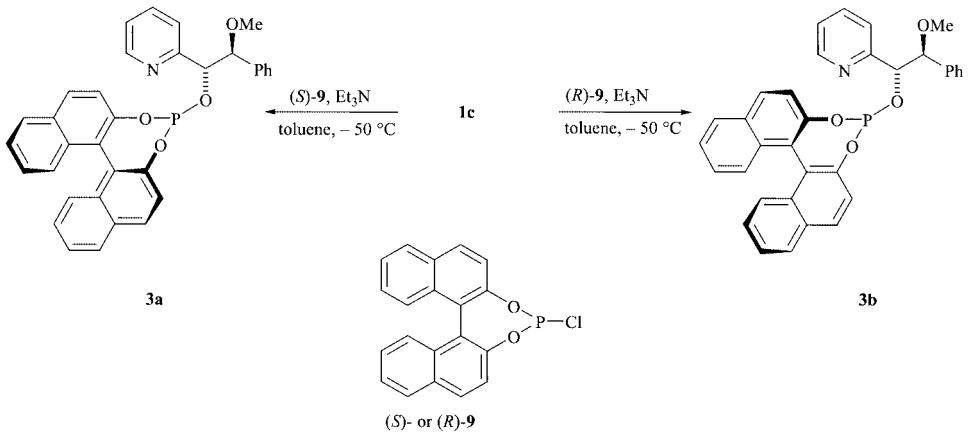
Scheme 5



Scheme 6

we employed this method for the preparation of the arylated analogue **2b**−BH_3 as well as for neomenthyl ligands **2c**−BH_3 and **2d**−BH_3.

Finally, we prepared the phosphites **3a** and **3b** from pyridyl alcohol **1c** and (*S*)- and (*R*)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-*a*:3,4-*a*′]binaphthalenes [(*S*)-**9** and (*R*)-**9**], respectively, in the presence of triethylamine (Scheme 7).



Scheme 7

Assignment of Absolute Configuration

Previously, we assigned the absolute configuration of the pyridyl alcohols **1a** and **1b** from NMR spectroscopic data of their Mosher ester derivatives.[10] Grayson and co-workers,[19] however, prepared compounds **1a** and **1b** by an alternative procedure and showed by X-ray crystallography that the absolute configuration at the carbinol carbon atoms is opposite to that assigned by us and, thus, **1a** has an (*S*) and **1b** an (*R*) absolute configuration. From these assignments, it follows that **1d** should have an (*S*) and **1e** an (*R*) absolute configuration at the epimeric centres, as judged by the similarities of their NMR spectra to those of **1a** and **1b**, respectively. This assumption is supported by the expected formation of the (*S*) isomer as the major compound upon reduction of ketone **8**. For the same reasons, compound **1g** is believed to have an (*R*) absolute configuration at the centre formed upon reduction of the ketone.

The assignment of an (*S*) absolute configuration at the carbinol carbon atom in compound **1c** was previously deduced from NOEs observed in the Mosher ester derivative.[11] To support this assignment, the compound was crystallized and its structure determined by X-ray crystallography (Figure 1). It was shown that, for this compound also, the absolute configuration was opposite to that assigned from the NMR spectroscopic data. It is still unclear whether the failure of the Mosher method in the present cases is due to the preference of an unexpected conformation[20] of the esters or to some other effect; compounds containing substituents having additional chiral centres should anyway be treated with caution.[21] Finally, the absolute configuration of compound **1f** was correlated to that of **1c** by debromination and, thus, it is (*R*).

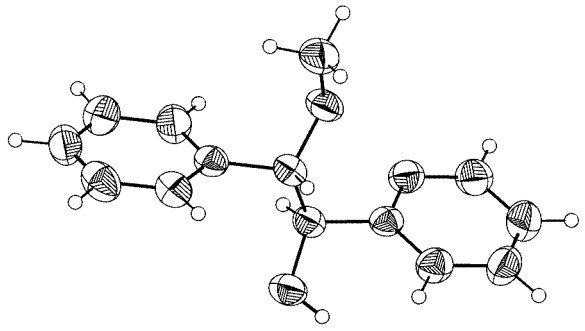


Figure 1. Crystal structure of **1c**; thermal ellipsoids are drawn at a 50% probability level

Addition of Diethylzinc to Benzaldehyde

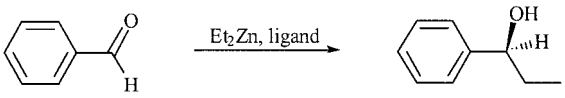
Chiral amino alcohols have been used extensively in the addition of diethylzinc to aldehydes, a reaction that is widely employed as a benchmark to compare the efficiency of these types of ligands. Among amino alcohols, several pyridyl alcohols have also been used previously in the catalytic reaction. We assessed the pyridyl alcohols **1a**−**1p** as catalysts for the addition of diethylzinc to benzaldehyde in toluene at 0 °C [Equation (1)]. The reaction conditions were not optimized because the purpose of this study was to investigate the effect of structural changes in the ligand on the enantioselectivity of the reaction. We found that the absolute configuration of the product alcohol is determined by the absolute configuration at the carbinol carbon atom of the ligand. Neomenthyl ligands **1a** and **1b** gave products with the same degree of enantioselectivity, but with different absolute configurations (64% *ee*; Table 1, Entries 1 and 2). The mandelic acid derivative **1c** provided the product with a slightly higher enantioselectivity (67% *ee*, Entry 3). For the 2-bromo derivatives **1d**, **1e** and **1g**, we found that the relative configuration of the stereocentres has a profound influence on the enantioselectivity (69%, 56% and 28% *ee*, respectively; Entries 4, 5 and 7). The selectivity in this case was more sensitive to the structure of the substituent. For **1e** and for the ligand derived from mandelic acid derivative **1f** , the presence of a bromine atom in the 2-position of the pyridine ring has a negative effect on the enantioselectivity (54% *ee* for **1f**, cf. 67% for **1c**; Entries 6 and 3), whereas we observed the opposite effect for **1d** and, previously, for 2-(1-hydroxy-2,2-dimethylpropyl)pyridine.[22] The introduction of a phenyl or a *p*-substituted aryl substituent in the 6-position of the pyridine ring in the neomenthyl derivatives (**1h**−**1j**) resulted in a somewhat increased enantioselectivity (Entries 8−10), whereas for the mandelic acid derivatives **1k**−**1n** we observed enantioselectivities

Table 1. Addition of diethylzinc to benzaldehyde in the presence of ligands **1**

Entry	Ligand[a]	Yield (%)[b]	*ee* (%)[c]
1	**1a**	94	64 (*S*)
2	**1b**	96	64 (*R*)
3	**1c**	94	67 (*S*)
4	**1d**	84	69 (*S*)
5	**1e**	88	56 (*R*)
6	**1f**	77	54 (*S*)
7	**1g**	94	28 (*R*)
8	**1h**	80	79 (*S*)
9	**1i**	96	79 (*S*)
10	**1j**	84	82 (*S*)
11	**1k**	93	67 (*S*)
12	**1l**	74	61 (*S*)
13	**1m**	85	66 (*S*)
14	**1n**	83	70 (*S*)
15	**1o**	90	83 (*S*)
16	**1p**	88	47 (*S*)

[a] The reactions were performed in toluene at 0 °C with 10 mol % ligand and 2.0 equiv. Et_2Zn (1.1 M in toluene). [b] GC yields. [c] Determined by GC using a chiral column (Chrompack CP-Cyclodextrin β-2,3,6-*m*-19).

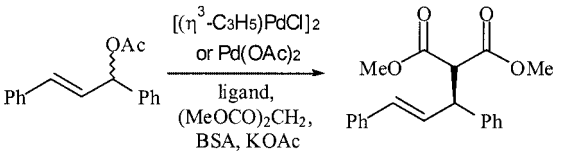
similar to that of **1c**, except for **1l**, having a methyl group in the *ortho* position, which resulted in a somewhat lower selectivity (Entries 11−14). The electronic properties, however, have a minor influence on the reactivity and selectivity in the catalytic reaction, as is shown by comparing ligands **1h**−**1j** and **1k**, **1m** and **1n** having hydrogen, methoxy and trifluoromethyl groups in the *para* position of the aromatic ring in the 6-position of the pyridine ring. This observation is in contrast to the situation with hydroxyalkylimidazolines, where electronic effects have been shown recently to exert a profound influence on the enantioselectivity.[23] The bipyridines **1o** and **1p**, derived from mandelic and lactic acid, respectively, exhibit marked differences in enantioselectivity (83 and 47%, respectively; Entries 15 and 16).



(1)

Palladium-Catalysed Substitution of *rac*-1,3-Diphenyl-2-propenyl Acetate with Malonate

We chose to study the performance of pyridinophosphinite ligands **2a**−**2d** in the palladium-catalysed alkylation[24] of *rac*-1,3-diphenyl-2-propenyl acetate by using dimethyl malonate as the nucleophile [Equation (2)].



(2)

Deprotection of the BH_3-protected ligands was achieved either with diethylamine prior to the catalytic reaction or in situ with palladium acetate,[25] which was employed simultaneously as the palladium source for the catalytic reaction.[26] Use of ligand **2a** and 4 mol % of bis(π-allylpalladium chloride) in a ratio of 1.5:1 resulted in full conversion within 4 h into the product in 46% *ee*, with the (*R*) enantiomer as the major isomer (Table 2, Entry 1). In situ deprotection with palladium acetate, which required a Pd:L ratio of 1:1, gave the same product with similar selectivity, but within a shorter period of time (48% *ee*; Entry 2). As expected, a prolonged reaction time was required for full conversion when using a lower amount of catalyst (Entry 3). Deprotection with diethylamine prior to reaction allowed us to study the influence of the ligand:palladium ratio. We found for **2a** that the reactivity and selectivity were

Table 2. Palladium-catalysed substitution of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of ligands **2** and **3**

Entry	Ligand[a]	Pd:L (% cat.)[a]	Pd source[a]	Time (h)	Conv. (%)[b]	*ee* (%)[c]
1	**2a**	1:1.5 (4)	$[(C_3H_5)PdCl]_2$	4	100	46 (*R*)
2	**2a**−BH_3	1:1 (4)	$Pd(OAc)_2$	1.5	100	48 (*R*)
3	**2a**−BH_3	1:1 (2)	$Pd(OAc)_2$	17	100	48 (*R*)
4	**2a**−BH_3 [d]	1:1 (4)	$[(C_3H_5)PdCl]_2$	8	100	48 (*R*)
5	**2a**−BH_3 [d]	1:1.5 (4)	$[(C_3H_5)PdCl]_2$	8	100	47 (*R*)
6	**2b**−BH_3	1:1 (2)	$Pd(OAc)_2$	189	36	52 (*R*)
7	**2b**−BH_3 [d]	1:1 (4)	$[(C_3H_5)PdCl]_2$	100	99	56 (*R*)
8	**2b**−BH_3 [d]	1:1.5 (4)	$[(C_3H_5)PdCl]_2$	4	100	10 (*R*)
9	**2c**−BH_3	1:1 (2)	$Pd(OAc)_2$	4	95	44 (*R*)
10	**2c**−BH_3	1:1 (4)	$Pd(OAc)_2$	1	100	44 (*R*)
11	**2d**−BH_3	1:1 (2)	$Pd(OAc)_2$	16	95	50 (*S*)
12	**3a**	1:1 (2)	$[(C_3H_5)PdCl]_2$	31	99	51 (*S*)
13	**3a**	1:1 (4)	$[(C_3H_5)PdCl]_2$	21	99	51 (*S*)
14	**3b**	1:1 (2)	$[(C_3H_5)PdCl]_2$	31	100	2 (*S*)
15	**3b**	1:1 (4)	$[(C_3H_5)PdCl]_2$	21	100	5 (*S*)

[a] The catalysts were generated in situ from the amounts of the ligand and the palladium source indicated. The reactions were performed in CH_2Cl_2 at room temp. [b] Determined by HPLC. [c] Determined by HPLC using a chiral column (Daicel Chiralcel OD-H). [d] The ligand was deprotected using Et_2NH.

essentially independent of this ratio (Entries 4 and 5). Ligand **2b**, with a phenyl substituent in the 6-position of the pyridine ring, exhibited lower reactivity than **2a**, but gave the product having slightly higher enantioselectivity (52% *ee*; Entry 6). Full conversion was reached when bis(π-allylpalladium chloride) was employed as the palladium source, although this process required a reaction time of 100 h (56% *ee*; Entry 7). It is interesting to note that using a 1:1.5 Pd:L ratio in this case resulted in a considerably lower enantioselectivity (10%; Entry 8), probably as a result of the formation of a 1:2 palladium−ligand complex. Ligands **2c** and **2d**, which differ only in their absolute configurations at the benzylic position, afforded products with different absolute configurations, but with similar enantioselectivities: 44% *ee* for the (*R*) enantiomer and 50% *ee* for the (*S*) enantiomer, respectively (Entries 9−11). The former ligand exhibits a higher reactivity, providing 95% conversion into the product within 4 h, cf. 16 h for **2d**.

Pyridyl phosphites have been shown to serve as monodentate P-ligands as well as bidentate P,N-ligands.[17] According to NMR spectroscopy, both donor atoms take part in coordination to the metal in an allyl−palladium(II) complex,[17a] whereas a ligand obtained from (*S*)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]binaphthalene and 8-hydroxyquinoline is able of coordinate to Ru^{II} and Rh^{III} in both fashions.[17c]

Ligands **3a** and **3b**, each of which has a centre and an axis of chirality, were next assessed in the palladium-catalysed allylations. Ligand **3a** turned out to be the diastereoisomer that affords the highest enantioselectivity: 51% *ee*, cf. 2−5% *ee* for **3b** (Table 2, Entries 12−15).

A ligand analogous to **3**, but having a binaphthyl group as the only element of chirality, has previously been employed by Arena et al. in the same palladium-catalysed process and it was found to yield racemic product.[17a] Introduction of a substituent (Me, Ph or Br) in the 6-position of the pyridine ring resulted in 7−11% enantioselectivity in the catalytic reaction.[17b] The authors suggest that the lack of chiral induction is due in part to flexible conformations of the six-membered chelate formed upon coordination to palladium. This assumption is corroborated by the observation of higher enantioselectivity in reactions employing a five-membered analogue, which is believed to have a more rigid structure. The more rigid quinoline-containing ligand has also been used in palladium-catalysed aminations and alkylations of *rac*-1,3-diphenyl-2-propenyl acetate to afford products with moderate enantioselectivities.[27]

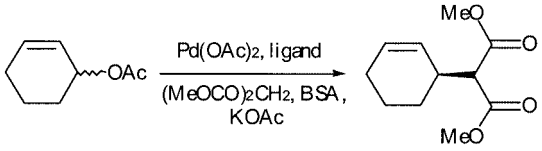
The methoxybenzyl substituent in our ligands is situated far from the substrate in the palladium−allyl complex. Because of the bulkiness of the substituent, however, we believe that it prefers a pseudoequatorial position in the six-membered chelate, which thereby increases the rigidity of the complex and, consequently, the chiral induction in the catalytic process. The absolute configurations of the products observed are those expected from the commonly used model for product formation.[28]

Ligands **3a** and **3b** were also employed in the substitution of *rac*-2-cyclohexenyl acetate [Equation (3)], but they were found to induce only moderate enantioselectivities in the product: **3a** afforded the (*S*) isomer in 31% *ee* and **3b** the opposite enantiomer in 17% *ee*, both in moderate yields even after extended reaction times (Table 3).

Table 3. Palladium-catalysed substitution of *rac*-2-cyclohexenyl acetate with dimethyl malonate in the presence of ligands **3**.

Entry	Ligand[a]	Pd:L (% cat.)[a]	Time (h)	Yield. (%)	*ee* (%)
1	**3a**	1:1 (4)	112	61	31 (*S*)
2	**3b**	1:1 (4)	143	58	17 (*R*)

[a] The catalysts were generated in situ from the amounts of the ligand and the palladium source indicated. The reactions were performed in CH_2Cl_2 at room temp.



(3)

Conclusion

Chiral 6-arylpyridyl alcohols, pyridyl phophinites and pyridyl phosphites were prepared by employing a modular approach starting from chiral pyridyl alcohols whose chirality originates from the chiral pool. The methodology we have employed allows wide structural variations of the ligands to be made. We employed the new ligands in the addition of diethylzinc to benzaldehyde and in the palladium-catalysed substitution of allylic acetates with malonate.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded with a Bruker DMX 500 instrument or with a Bruker Avance 400 instrument at 25 °C in $CDCl_3$, with residual $CHCl_3$ (^1H: δ = 7.26 ppm; ^{13}C: δ = 77.0 ppm) used as the internal standard. ^{31}P NMR spectra were recorded by using a Bruker DMX 500 instrument with 85% phosphoric acid as an external standard. Tetrahydrofuran (THF), toluene, and diethyl ether were distilled from sodium benzophenone ketyl. CH_2Cl_2 and Et_3N were distilled from CaH_2.

Determination of the Crystal Structure of 1c: $C_{14}H_{15}NO_2$, M = 229.28, orthorhombic, space group $P2_12_12_1$, a = 788.98(4), b = 818.73(5), c = 1919.15(1) pm, V = 1239.7(1) × 10^6 pm^3. Density (calcd.) = 1.228 $g{\cdot}cm^{-3}$. Crystal size 0.2 × 0.4 × 0.5 mm^3. $2\Theta_{max.}$ = 36.32°. Ag-K_α radiation, λ = 56.085 pm, T = 299 K. Diffraction data were collected with a Bruker−Nonius KappaCCD diffractometer. All non-hydrogen atoms were refined with anisotropic temperature parameters. Hydrogen atoms were localized from difference-Fourier syntheses and refined using a riding model. Structure solution: SHELXS-97, structure refinement on F^2 by using SHELXL-97. Final R values: R_1 = 0.0518, wR_2 = 0.119,

GooF = 1.167 for 1736 unique reflections and 154 parameters. Residual electron density: 0.18/−0.26. CCDC-211551 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (internat.) +44(1223)-336033 or E-mail: deposit@ccdc.cam.ac.uk.

(1*S*,2*S*,5*R*)-(6-Bromopyridin-2-yl)(2-isopropyl-5-methylcyclohexyl)-methanone (8): 2,6-Dibromopyridine (1403 mg, 5.80 mmol) in THF/hexane/diethyl ether (1:1:3, 15 mL) was added dropwise during 10 min to a solution of butyllithium (2.43 mL, 2.5 M in hexane, 6.08 mmol) at −78 °C under nitrogen. After 10 min, a solution of nitrile **4a** (872 mg, 5.28 mmol) in THF/hexane/diethyl ether (1:1:3, 4 mL) was added and the reaction mixture was stirred at −78 °C for 2.5 h followed by another 1.5 h at room temperature. The reaction was quenched by the addition of aqueous sulfuric acid (7 mL, 2 M). After vigorous stirring for 2 h, water (15 mL) and diethyl ether (15 mL) were added and the phases were separated. The aqueous phase was extracted with diethyl ether (2 × 15 mL), the combined organic phases were washed with saturated aqueous Na_2CO_3 (20 mL) and dried (Na_2SO_4). Evaporation under reduced pressure gave a brown oil that was purified by MPLC on silica gel (3 × 8.5 cm column; hexane/EtOAc continuous gradient: 0.375−2.5% EtOAc) to give **8** (989 mg, 58%) as a colourless oil that slowly crystallized upon standing. $[\alpha]_D^{22} = +37.0$ (c = 1.63 in CH_2Cl_2). ^{1}H NMR (400 MHz): δ = 0.789 (d, J = 6.5 Hz, 3 H, Me), 0.792 (d, J = 6.5 Hz, 3 H, Me), 0.90 (d, J = 6.5 Hz, 3 H, Me), 0.93−0.98 (m, 1 H), 1.12−1.47 (m, 3 H), 1.53−1.62 (m, 1 H), 1.73−2.00 (m, 4 H), 4.51 (br. s, 1 H, neomenthyl-1-H), 7.63 (dd, J = 7.6, 1.3 Hz, 1 H, 3- or 5-pyridyl), 7.69 (t, J = 7.6 Hz, 1 H, 4-pyridyl), 7.95 (dd, J = 7.6, 1.3 Hz, 1 H, 3- or 5-pyridyl) ppm. ^{13}C NMR (100.6 MHz): δ = 21.54, 21.62, 22.28, 26.27, 27.14, 30.14, 35.45, 37.36, 40.70, 46.84, 120.87, 131.30, 139.16, 141.17, 154.55, 202.99 ppm.

(*S*)-[(1′*S*,2′*S*,5′*R*)-1′-(2′-Isopropyl-5′-methyl)cyclohexyl](6′′-bromo-2′′-pyridyl)methanol (1d), and (*R*)-[(1′*S*,2′*S*,5′*R*)-1′-(2′-Isopropyl-5′-methyl)cyclohexyl](6′′-bromo-2′′-pyridyl)methanol (1e): $NaBH_4$ (83 mg, 2.15 mmol) was added at −78 °C to a solution of ketone **5** (116 mg, 0.36 mmol) in MeOH (6 mL). The reaction mixture was stirred for 114 h during which time it was warmed room temperature. Water (5 mL) and CH_2Cl_2 (10 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic phases were dried ($MgSO_4$) and the solvent was then evaporated under reduced pressure to give an oil. Purification by MPLC on silica gel (1 × 4 cm column; hexane/EtOAc continuous gradient: 0.375−5% EtOAc) yielded **1d** (63 mg, 54%) and **1e** (17 mg, 14%) as white solids. **1d:** $C_{16}H_{24}BrNO$ (326.3): calcd. C, 58.90, H 7.41, N 4.29; found C 58.68, H 7.47, N 4.28. $[\alpha]_D^{22} = -9.1$ (c = 1.25 in CH_2Cl_2). M.p. 64−66 °C. ^{1}H NMR (400 MHz): δ = 0.67 (d, J = 6.5 Hz, 3 H, Me), 0.84−0.96 (m, 2 H), 0.92 (d, J = 6.5 Hz, 3 H, Me), 1.04 (d, J = 6.5 Hz, 3 H, Me), 1.03−1.17 (m, 2 H), 1.38−1.56 (m, 2 H), 1.76−1.86 (m, 2 H), 2.00−2.09 (m, 1 H), 2.32−2.35 (m, 1 H, neomenthyl-1-H), 2.67 (d, J = 8.5 Hz, 1 H, OH), 4.91 (t, J = 8.5 Hz, 1 H, C*H*OH), 7.22 (dd, J = 7.7, 0.8 Hz, 1 H, 3- or 5-pyridyl), 7.37 (dd, J = 7.7, 0.8 Hz, 1 H, 3- or 5-pyridyl), 7.51 (t, J = 7.7 Hz, 1 H, 4-pyridyl) ppm. ^{13}C NMR (100.6 MHz): δ = 22.20, 22.53, 22.65, 24.87, 27.04, 30.02, 35.91, 38.93, 42.26, 49.79, 74.44, 120.32, 126.72, 138.56, 141.64, 165.06 ppm. **1e:** $[\alpha]_D^{22} = -6.4$ (c = 0.95 in CH_2Cl_2). M.p. 79−80 °C. ^{1}H NMR (400 MHz): δ = 0.74 (d, J = 6.6 Hz, 3 H, Me), 0.76−0.86 (m, 2 H), 0.99 (d, J = 6.6 Hz, 6 H, 2 × Me), 1.11−1.18 (m, 1 H), 1.32−1.38 (m, 1 H), 1.64−1.76 (m, 3 H), 1.77−1.84 (m, 1 H), 1.88−1.98 (m, 1 H), 2.18−2.22 (m, 1 H, neomenthyl-1-H), 3.56 (d, J = 5.5 Hz, 1 H, OH), 5.06 (dd, J = 5.5, 3.4 Hz, 1 H, C*H*OH), 7.22 (dd, J = 7.6, 0.8 Hz, 1 H, 3- or 5-pyridyl), 7.37 (dd, J = 7.6, 0.8 Hz, 1 H, 3- or 5-pyridyl), 7.53 (t, J = 7.6 Hz, 1 H, 4-pyridyl) ppm. ^{13}C NMR (125.8 MHz): δ = 21.57, 21.70, 23.34, 26.25, 28.18, 29.36, 35.86, 40.69, 47.82, 73.21, 119.16, 126.09, 138.77, 140.79, 165.06 ppm.

(*R*)-[(1′*R*,2′*S*,5′*R*)-1′-(2′-Isopropyl-5′-methyl)cyclohexyl](6′′-bromo-2′′-pyridyl)methanol (1g): 2,6-Dibromopyridine (804 mg, 3.33 mmol) in THF/hexane/diethyl ether (1:1:2, 9 mL) was added dropwise during 10 min to a solution of butyllithium (1.35 mL, 2.5 M in hexane, 3.38 mmol) at −78 °C under nitrogen. After 15 min, a solution of a mixture of nitriles **4a** and **4b** (500 mg, 3.03 mmol, 1:1) in THF/hexane/diethyl ether (1:1:2, 4 mL) was added and the reaction mixture was stirred at −78 °C for 2 h followed by another 2 h at room temperature. The reaction was quenched by the addition of aqueous hydrochloric acid (6 mL, 2 M). After vigorous stirring for 2 h, water (25 mL) and diethyl ether (25 mL) were added and the phases were separated. The aqueous phase was extracted with diethyl ether (2 × 25 mL) and the combined organic phases were dried ($MgSO_4$). Evaporation under reduced pressure gave a brown oil that was purified by column chromatography on silica gel (3 × 6 cm column; hexane/EtOAc, 95:5) to yield a ketone together with an unidentified byproduct (670 mg) as a colourless oil. This oil was dissolved in THF/MeOH (10:1, 33 mL) and cooled to 0 °C before $NaBH_4$ (254 mg, 0.66 mmol) was added in a few portions. After stirring at 0 °C for 31 h, the reaction was quenched by the addition of water (20 mL) and aqueous hydrochloric acid (10 mL, 0.5 M) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 30 mL), the combined organic phases were washed with brine (50 mL) and dried ($MgSO_4$) and then the solvents were evaporated under reduced pressure to give a slightly yellow oil. Purification by column chromatography on silica (3 × 5 cm column, hexane/EtOAc 95:5) yielded alcohol **1g** (240 mg, 24% over two steps) as a colourless oil. $[\alpha]_D^{22} = -35.8$ (c = 0.83 in CH_2Cl_2). ^{1}H NMR (400 MHz): δ = 0.24 (app q, J = 12.2 Hz, 1 H), 0.62−0.74 (m, 1 H), 0.78 (d, J = 6.9 Hz, 3 H, Me), 0.81 (d, J = 6.6 Hz, 3 H, Me), 0.94 (d, J = 6.9 Hz, 3 H, Me), 0.97−1.11 (m, 2 H), 1.26−1.38 (m, 1 H), 1.62−1.67 (m, 2 H), 1.78−1.83 (m, 1 H), 1.86−1.93 (m, 1 H), 2.25 (dsept, J = 6.9, 2.3 Hz, 1 H, C*H*Me$_2$), 3.67 (d, J = 5.8 Hz, 1 H, OH), 4.98 (dd, J = 5.8, 3.3 Hz, 1 H, C*H*OH), 7.17 (d, J = 7.7 Hz, 1 H, 3- or 5-pyridyl), 7.37 (d, J = 7.7 Hz, 1 H, 3- or 5-pyridyl), 7.52 (t, J = 7.7 Hz, 1 H, 4-pyridyl) ppm. ^{13}C NMR (100.6 MHz): δ = 15.24, 21.36, 22.59, 24.21, 26.75, 32.59, 34.88, 35.65, 43.56, 46.22, 72.51, 119.80, 126.23, 138.31, 140.60, 162.53 ppm.

(*S*)-[(1′*S*,2′*S*,5′*R*)-1′-(2′-Isopropyl-5′-methyl)cyclohexyl](6′′-phenyl-2′′-pyridyl)methanol (1h): Na_2CO_3 (39 mg, 0.37 mmol) in water (0.7 mL) and phenylboronic acid (27 mg, 0.22 mmol) in MeOH (2 mL) were added to a solution of pyridyl alcohol **1d** (60 mg, 0.18 mmol) and $[Pd(PPh_3)_4]$ (8.5 mg, 0.007 mmol, 4 mol %) in toluene (2 mL). The reaction mixture was heated under reflux and the reaction was monitored by TLC. After 20 h, saturated aqueous Na_2CO_3 (5 mL) and CH_2Cl_2 (5 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were dried (Na_2SO_4). Evaporation under reduced pressure gave yellow crystals that were purified by recrystallization from hexane to yield **1h** (38 mg, 64%) as a slightly yellow solid. $[\alpha]_D^{22} = -16.1$ (c = 0.78 in CH_2Cl_2). M.p. 115−116 °C. ^{1}H NMR (400 MHz): δ = 0.71 (d, J = 6.5 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H, Me), 0.87−0.98 (m, 2 H), 1.07 (d, J = 6.7 Hz, 3 H, Me), 1.11−1.19 (m, 1 H), 1.25−1.31 (m, 1 H),

1.47−1.58 (m, 1 H), 1.58−1.69 (m, 1 H), 1.80−1.88 (m, 2 H), 2.10−2.19 (m, 1 H), 2.38−2.43 (m, 1 H), 3.47 (d, J = 8.2 Hz, 1 H, OH), 5.02 (t, J = 8.2 Hz, 1 H, C*H*OH), 7.19 (dd, J = 7.6, 1.0 Hz, 1 H, 3-or 5-pyridyl), 7.42 (m, 1 H, Ph), 7.49 (m, 2 H, Ph), 7.64 (dd, J = 7.6, 1.0 Hz, 1 H, 3-or 5-pyridyl), 7.71 (t, J = 7.6 Hz, 1 H, 4-pyridyl), 8.03 (m, 2 H, Ph) ppm, ^{13}C NMR (100.6 MHz): δ = 22.29, 22.50, 22.79, 25.05, 27.16, 30.06, 36.12, 39.10, 42.55, 50.02, 74.42, 118.93, 120.00, 126.81, 128.70, 129.05, 136.92, 139.01, 156.29, 163.04 ppm.

(*S*)-[(1′*S*,2′*S*,5′*R*)-1′-(2′-Isopropyl-5′-methyl)cyclohexyl][6′′-(4′′′-methoxy-phenyl)-2′′-pyridyl]methanol (1i): Compound **1i** was synthesized from **1d** (80 mg, 0.245 mmol) and *p*-methoxyphenylboronic acid (41 mg, 0.26 mmol) in an manner analogous to that of **1h**. Purification by column chromatography on silica (2 × 8 cm column; hexane/EtOAc, 9:1) yielded **1i** (71 mg, 82%) as a white solid. $C_{23}H_{31}NO_2$ (353.5): calcd. C 78.15, H 8.84, N 3.96; found C 77.87, H 8.90, N 3.86. $[\alpha]_D^{22}$ = −32.4 (c = 0.54 in CH_2Cl_2). M.p. 122−123 °C. ^{1}H NMR (400 MHz): δ = 0.71 (d, J = 6.6 Hz, 3 H, Me), 0.93 (d, J = 6.4 Hz, 3 H, Me), 0.85−0.98 (m, 2 H), 1.06 (d, J = 6.4 Hz, 3 H, Me), 1.10−1.17 (m, 1 H), 1.25−1.31 (m, 1 H), 1.46−1.68 (m, 2 H), 1.79−1.87 (m, 2 H), 2.09−2.18 (m, 1 H), 2.35−2.41 (m, 1 H), 3.47 (d, J = 8.2 Hz, 1 H, OH), 3.87 (s, 3 H, OMe), 4.99 (t, J = 8.2 Hz, 1 H, C*H*OH), 7.01 (d, J = 9.1 Hz, 2 H, Ph), 7.11 (dd, J = 7.6, 0.8 Hz, 1 H, 3- or 5-pyridyl), 7.57 (dd, J = 7.6, 0.8 Hz, 1 H, 3- or 5-pyridyl), 7.67 (t, J = 7.6 Hz, 1 H, 4-pyridyl), 7.98 (d, J = 9.1 Hz, 2 H, Ph) ppm. ^{13}C NMR (100.6 MHz): δ = 22.29, 22.50, 22.79, 25.05, 27.16, 30.06, 36.14, 39.09, 42.52, 50.05, 55.35, 74.36, 114.09, 118.13, 119.26, 128.05, 131.65, 136.82, 155.96, 160.54, 162.80 ppm.

(*S*)-[(1′*S*,2′*S*,5′*R*)-1′-(2′-Isopropyl-5′-methyl)cyclohexyl][6′′-(4′′′-trifluoromethyl-phenyl)-2′′-pyridyl]methanol (1j): Compound **1j** was synthesized from **1d** (110 mg, 0.34 mmol) and *p*-(trifluoromethyl)-phenylboronic acid (78 mg, 0.40 mmol) in a manner analogous to that of **1h**. The product was obtained as a white solid (123 mg, 93%) after filtration through a silica plug using CH_2Cl_2 as the eluent. $C_{23}H_{28}F_3NO$ (391.5): calcd. C 70.57, H 7.21, N 3.58; found C 70.49, H 7.21, N 3.52. $[\alpha]_D^{22}$ = −11.1 (c = 1.23 in CH_2Cl_2). M.p. 107−108 °C. ^{1}H NMR (400 MHz): δ = 0.70 (d, J = 6.5 Hz, 3 H, Me), 0.94 (d, J = 6.4 Hz, 3 H, Me), 0.87−0.98 (m, 2 H), 1.07 (d, J = 6.4 Hz, 3 H, Me), 1.12−1.19 (m, 1 H), 1.21−1.26 (m, 1 H), 1.46−1.68 (m, 2 H), 1.80−1.87 (m, 2 H), 2.08−2.17 (m, 1 H), 2.38−2.42 (m, 1 H), 3.25 (d, J = 8.1 Hz, 1 H, OH), 5.04 (t, J = 8.1 Hz, 1 H, C*H*OH), 7.27 (dd, J = 7.7, 1.0 Hz, 1 H, 3- or 5-pyridyl), 7.67 (dd, J = 7.7, 1.0 Hz, 1 H, 3- or 5-pyridyl), 7.74 (dd, J = 8.1, 0.8 Hz, 2 H, Ph), 7.76 (t, J = 7.7 Hz, 1 H, 4-pyridyl), 8.13 (dd, J = 8.1, 0.8 Hz, 2 H, Ph) ppm. ^{13}C NMR (100.6 MHz): δ = 22.27, 22.48, 22.76, 25.03, 27.17, 30.11, 36.07, 39.06, 42.56, 50.01, 74.56, 119.34, 120.92, 124.16 (q, $J_{C,F}$ = 272.0 Hz), 125.68 (q, $J_{C,F}$ = 3.7 Hz), 127.09, 130.89 (q, $J_{C,F}$ = 32.4 Hz), 137.24, 142.20, 154.80, 163.59 ppm.

(1*R*,2*S*)-2-Methoxy-2-phenyl-1-(6′-phenyl-2′-pyridyl)ethan-1-ol (1k): Compound **1k** was synthesized from **1f** (144 mg, 0.47 mmol) and phenylboronic acid (64 mg, 0.51 mmol) in a manner analogous to that of **1h**. Purification by column chromatography on silica gel (1.5 × 9 cm column; hexane/EtOAc, 9:1) yielded **1k** (121 mg, 85%) as a white solid. $[\alpha]_D^{22}$ = +29.8 (c = 1.56 in CH_2Cl_2). M.p. 91−92 °C. ^{1}H NMR (400 MHz): δ = 3.23 (s, 3 H, OMe), 4.38 (d, J = 6.0 Hz, 1 H, OH), 4.45 (d, J = 6.0 Hz, 1 H, C*H*OMe), 4.99 (t, J = 6.0 Hz, 1 H, C*H*OH), 7.11 (d, J = 7.7 Hz, 1 H, 3- or 5-pyridyl), 7.20−7.30 (m, 5 H, Ph), 7.37−7.45 (m, 3 H, Ph), 7.59 (d, J = 7.7 Hz, 1 H, 3- or 5-pyridyl), 7.64 (t, J = 7.7 Hz, 1 H, 4-pyridyl), 7.90 (d, J = 7.1 Hz, 2 H, Ph) ppm. ^{13}C NMR (100.6 MHz): δ = 57.09, 75.48, 87.25, 119.27, 129.73, 126.86, 127.79, 127.90, 127.99, 128.66, 129.04, 136.85, 137.96, 138.86, 155.55, 158.44 ppm.

(1*R*,2*S*)-2-Methoxy-1-[6′-(2′′-methyl-1′′-phenyl)-2′-pyridyl]-2-phenylethan-1-ol (1l): Compound **1l** was synthesized from **1f** (62 mg, 0.20 mmol) and *o*-methylphenylboronic acid (29 mg, 0.21 mmol) in a manner analogous to that of **1h**. Purification by column chromatography on silica gel (1.5 × 4 cm column; hexane/EtOAc, 4:1) yielded **1l** (53 mg, 82%) as a colourless oil. $[\alpha]_D^{22}$ = +15.8 (c = 0.52 in CH_2Cl_2). ^{1}H NMR (400 MHz): δ = 2.23 (s, 3 H, Me), 3.26 (s, 3 H, OMe), 4.40−4.42 (m, 2 H, C*H*OMe and OH), 5.05 (t, J = 5.9 Hz, 1 H, C*H*OH), 7.16 (d, J = 7.7 Hz, 1 H, 3- or 5-pyridyl), 7.19−7.31 (m, 10 H), 7.69 (t, J = 7.7 Hz, 1 H, 4-pyridyl) ppm. ^{13}C NMR (100.6 MHz): δ = 20.28, 57.05, 75.38, 87.18, 120.12, 122.87, 125.80, 127.79, 127.89, 127.97, 128.34, 129.60, 130.76, 135.96, 136.37, 137.54, 139.79, 157.58, 158.18 ppm.

(1*R*,2*S*)-2-Methoxy-1-[6′-(2′′-methoxy-1′′-phenyl)-2′-pyridyl]-2-phenylethan-1-ol (1m): Compound **1m** was synthesized from **1f** (90 mg, 0.29 mmol) and *p*-methoyphenylboronic acid (54 mg, 0.35 mmol) in a manner analogous to that of **1h**. Purification by column chromatography on silica gel (1.5 × 7 cm column; hexane/EtOAc, 4:1) yielded **1f** (68 mg, 70%) as a white solid. $[\alpha]_D^{22}$ = +36.7 (c = 0.57 in CH_2Cl_2). M.p. 108−109 °C. ^{1}H NMR (400 MHz): δ = 3.26 (s, 3 H, CHO*Me*), 3.87 (s, 3 H, Ph-O*Me*), 4.38 (d, J = 6.1 Hz, 1 H, OH), 4.50 (d, J = 6.1 Hz, 1 H, C*H*OMe), 4.99 (t, J = 6.1 Hz, 1 H, C*H*OH), 6.98 (d, J = 9.1 Hz, 2 H, Ph), 7.09 (d, J = 7.7 Hz, 1 H, 3-or 5-pyridyl), 7.23−7.33 (m, 5 H, Ph), 7.56 (d, J = 7.7 Hz, 1 H, 3-or 5-pyridyl), 7.65 (t, J = 7.7 Hz, 1 H, 4-pyridyl), 7.88 (d, J = 9.1 Hz, 2 H, Ph) ppm. ^{13}C NMR (100.6 MHz): δ = 55.33, 57.06, 75.32, 87.24, 113.99, 118.48, 119.97, 127.45, 127.89, 127.95, 128.09, 131.41, 136.78, 137.95, 155.13, 158.10, 160.47 ppm.

(1*R*,2*S*)-2-Methoxy-2-phenyl-1-[6′-(2′′-trifluoromethyl-1′′-phenyl)-2′-pyridyl]ethan-1-ol (1n): Compound **1n** was synthesized from **1f** (179 mg, 0.58 mmol) and *p*-(trifluoromethyl)phenylboronic acid (135 mg, 0.71 mmol) in a manner analogous to that of **1h**. Purification by column chromatography on silica gel (3 × 5 cm column; hexane/EtOAc, 9:1) yielded **1n** (188 mg, 87%) as a white solid. $[\alpha]_D^{22}$ = +11.5 (c = 2.18 in CH_2Cl_2). M.p. 93−94 °C. ^{1}H NMR (500 MHz): δ = 3.28 (s, 3 H, OMe), 4.29 (br. d, J = 5.1 Hz, 1 H, OH), 4.44 (d, J = 5.1 Hz, 1 H, C*H*OMe), 5.05 (br. t, J = 5.1 Hz, 1 H, C*H*OH), 7.19 (d, J = 7.7 Hz, 1 H, 3- or 5-pyridyl), 7.23 (app d, J = 8.1 Hz, 2 H, Ph), 7.28−7.33 (m, 3 H, Ph), 7.66 (d, J = 7.7 Hz, 1 H, 3- or 5-pyridyl), 7.71−7.74 (m, 3 H, Ph and 5-pyridyl), 8.02 (d, J = 8.1 Hz, 2 H, Ph) ppm. ^{13}C NMR (125.8 MHz): δ = 57.09, 75.63, 87.10, 119.64, 121.59, 124.23 (q, $J_{C,F}$ = 272.2 Hz), 125.58 (q, $J_{C,F}$ = 3.8 Hz), 127.13, 127.86, 127.88, 128.01, 130.81 (q, $J_{C,F}$ = 32.2 Hz), 137.07, 137.64, 142.14, 154.03, 158.88 ppm.

Phosphinite 2c−BH$_3$: *n*BuLi (134 μL, 2.5 M in hexane, 0.34 mmol) was added to a solution of pyridyl alcohol **1a** (69 mg, 0.28 mmol) in THF (3 mL) at −78 °C under nitrogen. After stirring for 30 min, the temperature was increased to 0 °C. Chlorodiphenylphosphane (58 μL, 0.30 mmol) was added and the reaction mixture was stirred at 0 °C for 3 h. BH_3·SMe_2 (154 μL, 2.0 M in THF, 0.31 mmol) was added and the stirring was continued at 0 °C overnight (15 h). Water (5 mL) and CH_2Cl_2 (5 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 7 mL), the combined organic phases were dried ($MgSO_4$) and then

the solvents were evaporated under reduced pressure to give an oil. Purification by column chromatography on silica gel (3 × 7 cm; hexane/EtOAc, 19:1) yielded **2c**−BH_3 (77 mg, 62%) as a colourless oil. $[\alpha]_D^{22}$ = −8.6 (*c* = 1.1 in CH_2Cl_2). ^{1}H NMR (400 MHz): δ = 0.42 (d, *J* = 6.2 Hz, 3 H, Me), 0.63 (d, *J* = 6.2 Hz, 3 H, Me), 0.65 (d, *J* = 6.5 Hz, 3 H, Me), 0.68−1.30 (m, 8 H, including broad signal from BH_3), 1.34−1.45 (m, 1 H), 1.64−1.71 (m, 1 H), 1.79−1.90 (m, 2 H), 2.08−2.14 (m, 1 H), 2.87 (dd, *J* = 8.2, 3.8 Hz, 1 H, neomenthyl-1-H), 5.69 (t, *J* = 8.2 Hz, 1 H, C*H*OP), 6.98 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1 H, 5-pyridyl), 7.15 (td, *J* = 7.1, 2.0 Hz, 2 H, Ph), 7.24−7.29 (m, 2 H), 7.34−7.50 (m, 6 H), 7.75 (ddt, *J* = 10.8, 7.1, 2.0 Hz, 2 H, Ph), 8.47 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1 H, 6-pyridyl) ppm. ^{13}C NMR (125.8 MHz): δ = 21.01, 21.81, 22.59, 25.11, 26.98, 28.67, 35.85, 37.57, 39.62 (d, $J_{C,P}$ = 6.7 Hz), 49.02, 81.07 (d, $J_{C,P}$ = 3.0 Hz), 122.69, 124.23, 127.88 (d, $J_{C,P}$ = 11.2 Hz), 128.36 (d, $J_{C,P}$ = 10.5 Hz), 131.00 (d, $J_{C,P}$ = 2.2 Hz), 131.33 (d, $J_{C,P}$ = 5.2 Hz), 131.45 (d, $J_{C,P}$ = 5.2 Hz), 131.58 (d, $J_{C,P}$ = 2.2 Hz), 132.26 (d, $J_{C,P}$ = 6.0 Hz), 132.91 (d, $J_{C,P}$ = 15.7 Hz), 135.65, 149.21, 159.79 ppm. ^{31}P{^{1}H} NMR (202 MHz): δ = 106.12 (app d, $J_{P,B}$ = 81.0 Hz) ppm.

Phosphinite 2d−BH_3: Compound **2d**−BH_3 was synthesized from pyridyl alcohol **1b** (84 mg, 0.34 mmol) in a manner analogous to that of **2c**−BH_3. Purification by column chromatography on silica gel (3 × 6 cm; hexane/EtOAc, 9:1) yielded **2d**−BH_3 (66 mg, 43%) as a white solid. $[\alpha]_D^{22}$ = +18.9 (*c* = 1.1 in CH_2Cl_2). M.p. 121−122 °C. ^{1}H NMR (400 MHz): δ = 0.56 (d, *J* = 6.4 Hz, 3 H, Me), 0.73 (d, *J* = 6.4 Hz, 3 H, Me), 0.88 (d, *J* = 6.5 Hz, 3 H, Me), 0.80−0.98 (m, 3 H), 1.04−1.49 (m, 5 H, including broad signal from BH_3), 1.53−1.62 (m, 1 H), 1.65−1.74 (m, 1 H), 1.78−1.82 (m, 2 H), 2.93 (dd, *J* = 9.4, 3.4 Hz, 1 H, neomenthyl-1-H), 5.76 (dd, *J* = 9.4, 8.4 Hz, 1 H, C*H*OP), 6.95 (dd, *J* = 7.6, 4.8 Hz, 1 H, 5-pyridyl), 7.10 (td, *J* = 7.8, 2.0 Hz, 2 H, Ph), 7.17 (d, *J* = 7.6 Hz, 1 H, 3-pyridyl), 7.21 (t, *J* = 7.8 Hz, 1 H, Ph), 7.33 (td, *J* = 7.6, 1.1 Hz, 1 H, 4-pyridyl), 7.38−7.48 (Ph, 5 H), 7.78 (dd, *J* = 11.1, 7.8 Hz, 2 H, Ph), 8.47 (dt, *J* = 4.8, 1.1 Hz, 1 H, 6-pyridyl) ppm. ^{13}C NMR (100.6 MHz): δ = 22.21, 22.34, 22.64, 24.62, 26.72, 29.31, 35.92, 38.55, 39.97 (d $J_{C,P}$ = 6.8 Hz), 49.94, 81.46 (d $J_{C,P}$ = 3.0 Hz), 122.64, 123.73, 127.7 (d, $J_{C,P}$ = 10.6 Hz), 128.20 (d, $J_{C,P}$ = 11.3 Hz), 130.86 (d, $J_{C,P}$ = 2.3 Hz), 131.27 (d, $J_{C,P}$ = 11.3 Hz), 131.46 (d, $J_{C,P}$ = 11.3 Hz), 131.55 (d, J_{C-P} = 2.3 Hz), 131.91, 132.42 (d, $J_{C,P}$ = 14.4 Hz), 135.73, 149.40, 158.85 ppm. ^{31}P{^{1}H} NMR (202 MHz): δ = 103.44 (app d, $J_{P,B}$ = 82.3 Hz) ppm.

Phosphinite 2a: Pyridyl alcohol **1c** (40 mg, 0.17 mmol) was dissolved in THF (2.5 mL) and then cooled to −78 °C and placed under nitrogen. *n*BuLi (84 μL, 2.5 M in hexane, 0.21 mmol) was added and after stirring at −78 °C for 15 min the temperature was raised to 0 °C. Chlorodiphenylphosphane (36 μL, 0.19 mmol) was added and the reaction mixture was stirred at 0 °C for 8 h. Evaporation of the solvent under reduced pressure gave an oil that was purified by column chromatography on silica gel (1 × 4 cm column; hexane/EtOAc, 4:1) to yield **2a** (31 mg, 43%) as a colourless oil. $[\alpha]_D^{22}$ = −8.7 (*c* = 0.52 in CH_2Cl_2). ^{1}H NMR (400 MHz): δ = 3.16 (s, 3 H, OMe), 4.71 (d, *J* = 6.5 Hz, 1 H, C*H*OMe), 5.17 (dd, *J* = 9.8, 6.5 Hz, 1 H, C*H*OP), 7.13−7.28 (m, 17 H), 7.51 (td, *J* = 7.7, 1.8 Hz, 1 H, 4-pyridyl), 8.59 (dd, *J* = 5.4, 1.8 Hz, 1 H, 6-pyridyl) ppm. ^{13}C NMR (125.8 MHz): δ = 56.87, 85.08 (d, $J_{C,P}$ = 18.9 Hz), 86.16 (d, $J_{C,P}$ = 6.0 Hz), 122.61, 123.02, 127.79, 127.81, 127.90 (d, $J_{C,P}$ = 1.5 Hz), 127.95 (d, $J_{C,P}$ = 1.5 Hz), 128.92, 129.01, 130.43 (d, $J_{C,P}$ = 21.9 Hz), 130.74 (d, $J_{C,P}$ = 21.9), 131.62 (d, $J_{C,P}$ = 10.6 Hz), 131.85 (d, $J_{C,P}$ = 10.6 Hz), 135.99, 138.06, 148.93, 159.36 ppm. ^{31}P{^{1}H} NMR (202 MHz): δ = 116.0 ppm.

Phosphinite 2a−BH_3: Compound **2a**−BH_3 was synthesized from pyridyl alcohol **1c** (102 mg, 0.44 mmol) in a manner analogous to that of **2c**−BH_3. Purification by column chromatography on silica gel (1.5 × 8.5 cm; hexane/EtOAc, 4:1) yielded **2a**−BH_3 (146 mg, 77%) as a colourless oil. $[\alpha]_D^{22}$ = −3.0 (*c* = 0.74 in $CHCl_3$). ^{1}H NMR (400 MHz): δ = 1.40−1.26 (m, 3 H, BH_3), 3.09 (s, 3 H, OMe), 4.81 (d, *J* = 7.1 Hz, 1 H, C*H*OMe), 5.60 (dd, *J* = 9.8, 7.1 Hz, 1 H, C*H*OP), 7.11 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1 H, 5-pyridyl), 7.21−7.51 (m, 17 H), 8.54 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1 H, 6-pyridyl) ppm. ^{13}C NMR (100.6 MHz): δ = 56.90, 81.71 (d, $J_{C,P}$ = 1.5 Hz), 85.03 (d, $J_{C,P}$ = 8.2 Hz), 127.98, 128.01, 128.08, 128.14 (d, $J_{C,P}$ = 4.5 Hz), 128.37, 131.30, 131.31, 131.38, 131.41, 131.42, 132.03 (d, $J_{C,P}$ = 4.5 Hz), 135.95, 137.69, 149.12, 156.99 ppm. ^{31}P{^{1}H} NMR (202 MHz): δ = 109.05 (app d, $J_{P,B}$ = 79.4 Hz) ppm.

Phosphinite 2b−BH_3: Compound **2b**−BH_3 was synthesized from pyridyl alcohol **1k** (45 mg, 0.15 mmol) in a manner analogous to that of **2c**−BH_3. Purification by column chromatography on silica gel (2 × 4 cm; hexane/EtOAc, 19:1) yielded **2b**−BH_3 (44 mg, 60%) as a colourless oil. $[\alpha]_D^{22}$ = −92.2 (*c* = 1.60 in CH_2Cl_2). ^{1}H NMR (500 MHz): δ = 0.64−1.36 (m, 3 H, BH_3), 3.14 (s, 3 H, OMe), 4.96 (d, *J* = 6.6 Hz, 1 H, C*H*OMe), 5.71 (dd, *J* = 9.5, 6.6 Hz, 1 H, C*H*OP), 7.15−7.19 (m, 3 H), 7.28−7.54 (m, 10 H), 7.40−7.54 (m, 8 H), 7.94 (d, *J* = 7.0 Hz, 2 H, Ph). ^{13}C NMR (100.6 MHz): δ = 57.03, 82.15 (d, $J_{C,P}$ = 2.2 Hz), 85.15 (d, $J_{C,P}$ = 7.5 Hz), 119.45, 122.43, 126.93, 127.95 (d, $J_{C,P}$ = 2.2 Hz), 128.04, 128.16, 128.45, 128.55, 128.82, 131.33 (d, $J_{C,P}$ = 2.2 Hz), 131.42 (d, $J_{C,P}$ = 7.5 Hz), 131.53 (d, $J_{C,P}$ = 7.5 Hz), 131.65, 132.08, 132.29, 132.77, 136.50, 137.92, 139.25, 156.28, 156.77; ^{31}P{^{1}H} NMR (202 MHz): δ = 108.61 (app d, $J_{P,B}$ = 75.1 Hz).

Phosphite 3b: (*R*)-4-Chloro-3,5-dioxa-4-phosphacyclohepta[2,1-*a*:3,4-*a*′]binaphthalene, obtained according to a published procedure,[15b] but with toluene as the solvent (330 mg, 0.884 mmol) was dissolved in toluene (7 mL) under nitrogen and cooled to −50 °C. Et_3N (0.124 mL, 0.884 mmol) was added followed by a solution of pyridyl alcohol **1c** (203 mg, 0.884 mmol) in toluene (13 mL). The reaction mixture was stirred on the thawing ice bath for 17 h. The suspension was filtered under nitrogen, the filter cake was washed with toluene (4 mL) and the filtrate was evaporated under reduced pressure to yield **3b** (520 mg, 84%) as a yellow solid contaminated by **1c** and toluene. ^{1}H NMR (500 MHz): δ = 3.28 (s, 3 H, OMe), 4.65 (d, *J* = 5.6 Hz, 1 H, C*H*OMe), 5.63 (dd, *J* = 10.6, 5.6 Hz, 1 H, C*H*OP), 6.71 (d, *J* = 8.8 Hz, 1 H, 1 H), 7.03 (d, *J* = 7.7 Hz, 1 H), 7.17−7.38 (m, 9 H), 7.40−7.43 (m, 4 H), 7.57 (td, *J* = 7.7, 1.5 Hz, 1 H, 4-pyridyl), 7.68 (d, *J* = 8.8 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.91 (d, *J* = 7.7 Hz, 1 H), 7.94 (d, *J* = 8.8 Hz, 1 H), 8.66 (d, *J* = 4.8 Hz, 1 H, 6-pyridyl) ppm. ^{13}C NMR (125.8 MHz): δ = 57.09, 79.59 (d, $J_{C,P}$ = 16.6 Hz), 85.62 (d, $J_{C,P}$ = 3.0 Hz), 121.96 (d, $J_{C,P}$ = 2.3 Hz), 122.36, 122.81, 124.25 (d, $J_{C,P}$ = 5.3 Hz), 124.70, 124.94, 125.94, 126.12, 126.99 (d, $J_{C,P}$ = 4.5 Hz), 127.77, 127.83, 127.95, 128.03, 128.16, 128.54, 129.20, 130.13, 131.00, 131.49, 132.55 (d, $J_{C,P}$ = 1.5 Hz), 132.76 (d, $J_{C,P}$ = 1.5 Hz), 136.26, 136.55, 147.44 (d, $J_{C,P}$ = 2.3 Hz), 147.82 (d, $J_{C,P}$ = 3.8 Hz), 148.61, 158.26 (d, $J_{C,P}$ = 3.0 Hz) ppm. ^{31}P{^{1}H} NMR (202 MHz): δ = 151.64 ppm.

Phosphite 3a: Compound **3a** was synthesized from pyridyl alcohol **1c** (240 mg, 1.05 mmol) and (*S*)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-*a*:3,4-*a*′]binaphthalene (370 mg, 1.05 mmol) in a manner analogous to that of **3b**. Yield: 560 mg (95%), contaminated by **1c** and toluene. ^{1}H NMR (500 MHz): δ = 3.31 (s, 3 H, OMe), 4.69 (d, *J* = 5.1 Hz, 1 H, C*H*OMe), 5.69 (dd, *J* = 9.9, 5.1 Hz, 1 H, C*H*OP), 6.92 (d, *J* = 7.7 Hz, 1 H), 7.02 (d, *J* = 8.8 Hz,

1 H), 7.13−7.25 (m, 9 H), 7.32−7.37 (m, 2 H), 7.40−7.44 (m, 3 H), 7.73 (d, J = 8.4 Hz, 1 H), 7.88−7.92 (m, 3 H), 8.57 (d, J = 4.8 Hz, 1 H, 6-pyridyl) ppm. ^{13}C NMR (125.8 MHz): δ = 57.05, 79.33 (d, $J_{C,P}$ = 11.3 Hz), 85.53 (d, $J_{C,P}$ = 4.5 Hz), 121.84 (d, $J_{C,P}$ = 2.3 Hz), 122.16, 122.34, 122.61, 124.22 (d, $J_{C,P}$ = 5.3 Hz), 124.72, 124.95, 125.92, 126.13, 127.00 (d, $J_{C,P}$ = 7.6 Hz), 127.72, 127.77, 127.89, 128.20, 128.30, 128.51, 129.33, 130.15, 130.98, 131.47, 132.47 (d, $J_{C,P}$ = 1.5 Hz), 132.78 (d, $J_{C,P}$ = 1.5 Hz), 136.24, 136.79, 137.86, 147.38 (d, $J_{C,P}$ = 2.3 Hz), 148.10 (d, $J_{C,P}$ = 5.3 Hz), 148.56, 158.26 (d, $J_{C,P}$ = 1.5 Hz) ppm. ^{31}P{^{1}H} NMR (202 MHz): δ = 147.63 ppm.

General Procedure for the Addition of Diethylzinc to Benzaldehyde: Benzaldehyde (61 μL, 0.60 mmol) and the ligand (0.06 mmol, 10 mol %) were dissolved in toluene (1 mL) under nitrogen and the solution was then cooled to 0 °C. After stirring for 30 min, Et_2Zn (1.09 mL, 1.1 M in toluene, 1.2 mmol) was added dropwise and the stirring was continued at 0 °C for 20 h. The reaction was quenched by the addition of aqueous HCl (5 mL, 0.25 M). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and the solvents evaporated under reduced pressure.

General Procedure for the Palladium-Catalysed Allylic Alkylation of *rac*-1,3-Diphenyl-2-propenyl Acetate: The appropriate amounts of the ligand and the palladium source were dissolved in CH_2Cl_2 (1 mL) together with the allyl acetate (121 mg, 0.48 mmol) under nitrogen. The solution was stirred at room temperature for 1 h and then cooled to −78 °C. Dimethyl malonate (123 μL, 1.08 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (375 μL, 1.44 mmol), KOAc (a few crystals) and CH_2Cl_2 (1 mL) were added. The reaction mixture was stirred at room temperature and monitored by HPLC (Chiracel OD-H column; hexane/*i*PrOH, 99:1; 0.5 mL·min^{-1}).

General Procedure for the Palladium-Catalysed Allylic Alkylation of *rac*-2-Cyclohexenyl Acetate: The same procedure was employed as that used for *rac*-1,3-diphenyl-2-propenyl acetate. The reaction mixture was stirred at room temperature and the conversion was monitored by GC/MS. The reaction mixture was filtered through a silica plug using CH_2Cl_2. The solvent was evaporated and the crude oil was purified by column chromatography on silica gel (1.5 × 7 cm column; hexane/EtOAc, 39:1).

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