Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron: Asymmetry 17 (2006) 3282–3287

Tetrahedron: Asymmetry

Pyranoside phosphite–phosphoroamidite ligands for Pd-catalyzed asymmetric allylic alkylation reactions

Yvette Mata, Carmen Claver, Montserrat Diéguez* and Oscar Pàmies*

Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo s/n, 43007 Tarragona, Spain

Received 3 November 2006; accepted 23 November 2006

Abstract—We have designed and synthesized a new family of readily available phosphite–phosphoroamidite ligands for Pd-catalyzed allylic substitution reactions of several substrates with different steric and electronic properties. These ligands are derived from D-glucosamine and contain several substituents in the biphenyl moieties, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that enantioselectivities are mainly affected by the substituents at the *para*-positions of the biphenyl moieties. Enantiomeric excesses of up to 89% with high activities were obtained for *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**, *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S2** and *rac*-3-acetoxycycloheptene **S5**.

1. Introduction

Palladium-catalyzed asymmetric allylic alkylation is a versatile, widely used process in organic synthesis for the enantioselective formation of C–C and C-heteroatom bonds.[1] Many chiral ligands, bidentate nitrogen and phosphorus donors (both homo- and heterodonors), have been successfully applied.[1] Over the last few years, a group of less electron-rich phosphorus compounds, phosphite[2] and phosphoroamidite[3] ligands, have also demonstrated their potential utility in this process. The π-acceptor ability of these types of ligands have overcome the common limitation of low reaction rates observed for this process.

Following our interest in modular ligands and encouraged by the success of π-acceptor ligands,[2–4] we herein report the development of a new class of chiral phosphite–phosphoroamidite ligands **1**–**3** (Fig. 1), which have the advantages of both types of ligands, for the enantioselective Pd-catalyzed allylic alkylation reactions of several substrates with different electronic and steric properties. These ligands are derived from natural D-glucosamine so they also have the advantages of carbohydrates, such as availability at a low price and facile modular construction, which makes tedious optical resolution procedures unnecessary.[5] These ligands differ in the introduction of several substituents in the biphenyl moieties, with different steric and electronic properties, whose effect on the catalytic performance can be studied. As far as carbohydrate ligands are concerned, despite their advantages, they have only very recently shown their huge potential as a source of highly effective chiral ligands in this process.[2a,b,4b,6]

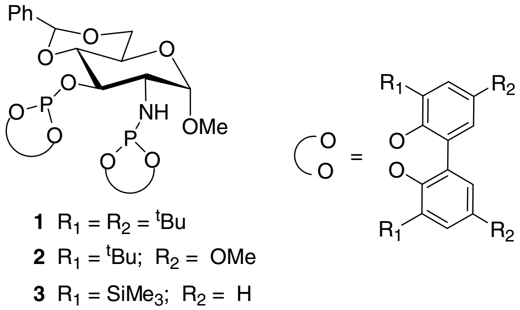


Figure 1. Phosphite–phosphoroamidite ligands **1**–**3**.

2. Results and discussion

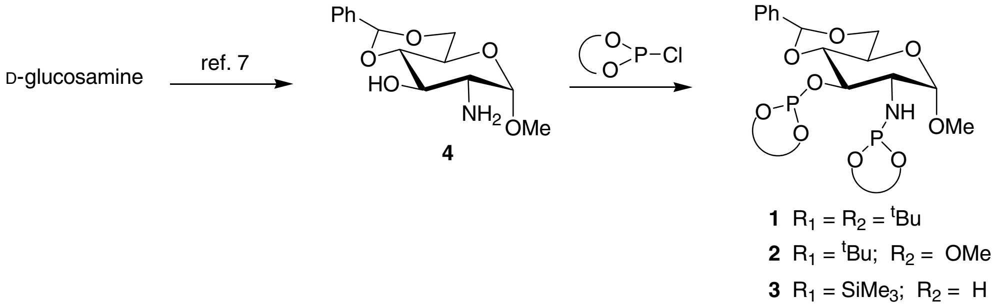
2.1. Synthesis of the chiral phosphite–phosphoroamidite ligands

Ligands **1**–**3** were synthesized very efficiently in one step from the corresponding aminoalcohol **4**, which itself was

---

* Corresponding authors. Fax: +34 977559563; e-mail addresses: montserrat.dieguez@urv.cat; oscar.pamies@urv.cat

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.11.039



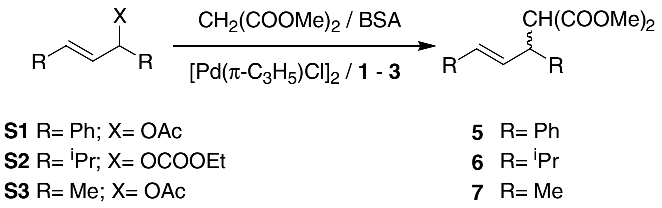
Scheme 1. Synthesis of ligands **1**–**3**.

easily prepared on a large scale from D-glucosamine using a standard procedure (Scheme 1).[7] Reaction of **4** with 2 equiv of the corresponding phosphorochloridite in dry toluene, under argon and in the presence of pyridine, provided the desired ligands **1**–**3** as white solids.

All ligands were stable during purification on neutral alumina under an atmosphere of argon. The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these C_1 ligands (see Section 4).

2.2. Allylic alkylation of disubstituted linear substrates

In this section, we report the use of the chiral phosphite–phosphoroamidite ligands **1**–**3** in the Pd-catalyzed allylic alkylation (Eq. 1) of three linear substrates with different steric properties: *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** (widely used as a model substrate), *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S2** and *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S3**. In all the cases, the catalysts were generated in situ from π-allyl-palladium chloride dimer $[Pd(\pi\text{-}C_3H_5)Cl]_2$ and the corresponding ligand. The nucleophile was generated from dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)-acetamide (BSA).



(1)

2.3. Allylic alkylation of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene S1 (Eq. 1)

We first investigated the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** with dimethyl malonate using the chiral phosphite–phosphoroamidite ligands **1**–**3** (Eq. 1).

The effect of the solvent and the ligand-to-palladium ratio were investigated using the catalyst precursor containing ligand **1** (Table 1, entries 1–4).

Table 1. Pd-catalyzed allylic alkylation of **S1**–**S3** using ligand **1**–**3**[a]

Entry	Ligand	Substrate	Solvent	Ratio L/Pd	% Conv[b] (h)	% ee[c]
1	**1**	**S1**	CH_2Cl_2	1.1	100 (0.5)	74 (*R*)
2	**1**	**S1**	DMF	1.1	100 (0.5)	73 (*R*)
3	**1**	**S1**	Toluene	1.1	89 (0.5)	84 (*R*)
4	**1**	**S1**	THF	1.1	100 (0.5)	84 (*R*)
5	**1**	**S1**	THF	0.75	100 (0.5)	85 (*R*)
6	**1**	**S1**	THF	2	100 (0.5)	84 (*R*)
7	**2**	**S1**	THF	1.1	100 (0.5)	76 (*R*)
8	**3**	**S1**	THF	1.1	100 (0.5)	81 (*R*)
9	**1**	**S2**	THF	1.1	100 (18)	89 (*S*)
10	**2**	**S2**	THF	1.1	100 (18)	81 (*S*)
11	**3**	**S2**	THF	1.1	100 (18)	87 (*S*)
12	**1**	**S3**	THF	1.1	100 (0.5)	43 (*R*)
13	**2**	**S3**	THF	1.1	100 (0.5)	45 (*R*)
14	**3**	**S3**	THF	1.1	100 (0.5)	61 (*R*)

[a] 0.5 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol % ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature.

[b] Reaction time in hours shown in parentheses.

[c] Absolute configuration drawn in parentheses.

Our results indicate the solvent affected catalytic performance. Tetrahydrofuran (THF) as a solvent provided the best combination of activity and enantioselectivity (Table 1, entries 1–4). The enantiomeric excess obtained with toluene was comparable to that with THF, but the activity was lower. On the other hand, the use of dichloromethane (CH_2Cl_2) and dimethylformamide (DMF) gave the same activities as that of THF, but their ee's were the lowest of the four solvents. In conclusion, a high activity ($TOF > 200$ mol **S1** $\times (\text{mol Pd} \times h)^{-1}$) and good enantioselectivity (84% (*R*) ee) were obtained.

Varying the ligand-to-palladium ratio showed that excess ligand was not needed to obtain good enantioselectivities and activities (Table 1, entries 4–6).

Under the optimized conditions, we studied how the biphenyl substituents at the phosphite moieties affected the catalytic performance with ligands **2** and **3** (Table 1, entries 7 and 8).

The use of ligand **2** with methoxy substituents at the *para*-position of the biphenyl moieties showed the same activity but lower asymmetric induction than those obtained with the catalytic system Pd/**1** (Table 1, entry 7). The use of ligand

3 with a trimethylsilyl substituents at the *ortho*-positions of the biphenyl moiety and no substituents at the *para*-positions showed slightly lower asymmetric induction than the catalytic system containing ligand **1** (Table 1, entry 8).

2.4. Allylic alkylation of *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate S2 (Eq. 1)

We also evaluated the phosphite–phosphoroamidite ligands **1**–**3** in the allylic substitution process of **S2** using dimethyl malonate as a nucleophile (Eq. 1). This substrate is more sterically demanding than the previously used substrate **S1**.[1] The most remarkable results are shown in Table 1 (entries 9–11). In general, they follow the same trends as for the allylic alkylation of **S1**. However, the enantiomeric excesses were slightly higher (ee's up to 89%). As expected, the activities were lower than in the alkylation reaction of **S1**, but were good for this type of substrate.[1] Again, the catalyst precursor containing the phosphite–phosphoroamidite ligand **1** provided the best enantioselectivity (Table 1, entry 9). The stereoselectivity of the alkylation of **S2** was the same as for the alkylation reaction of **S1**, although the CIP descriptor was inverted due to the change in priority of the groups.

2.5. Allylic alkylation of *rac*-1,3-dimethyl-3-acetoxyprop-1-ene S3 (Eq. 1)

We also screened ligands **1**–**3** in the allylic alkylation of linear substrate **S3** (Eq. 1). This substrate is sterically less demanding than the previously used substrates **S1** and **S2**. Enantioselectivity for **S3** is therefore more difficult to control than with hindered substrates, such as **S1** and **S2**.[1] The results of using the phosphite–phosphoroamidite ligands are summarized in Table 1 (entries 12–14). High activities (TOF > 200 mol **S3** × (mol Pd × h)$^{-1}$) and moderate enantioselectivities (ee's up to 61%) were obtained. The general trends that controlled the enantioselectivity were different from those that controlled **S1** and **S2**. Therefore, the best enantioselectivity was obtained with ligand **3**, which contained bulky trimethylsilyl groups at the *ortho*-positions and small hydrogens at the *para*-positions of the biphenyl moiety (Table 1, entry 14). These results show the importance of using modular scaffolds in ligand design.

2.6. Allylic alkylation of cyclic substrates

As for the unhindered substrate **S3**, enantioselectivity in cyclic substrates is difficult to control, mainly because of the presence of less sterically demanding *syn*-substituents. These *syn* substituents are thought to play a crucial role in the enantioselection observed with acyclic substrates in the corresponding Pd–allyl intermediate.[1] To obtain high ee's, the ligand must create a small chiral pocket (the chiral cavity where the allyl group is embedded) around the metal center.[1]

In this section, we report the use of the chiral phosphite–phosphoroamidite ligands **1**–**3** in the Pd-catalyzed allylic alkylation of two cyclic substrates (Eq. 2): *rac*-3-acetoxycyclohexene **S4** (which is widely used as a model substrate) and *rac*-3-acetoxycycloheptene **S5**.

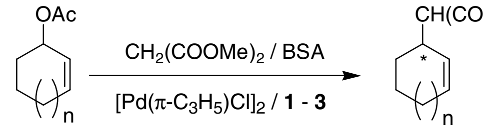
Table 2. Pd-Catalyzed allylic alkylation of **S4** and **S5** using ligands **1**–**3**[a]

Entry	Ligand	Substrate	Solvent	Ratio L/Pd	% Conv[b] (h)	% ee[c]
1	**1**	**S4**	CH_2Cl_2	1.1	100 (2)	37 (*S*)
2	**1**	**S4**	DMF	1.1	100 (2)	26 (*S*)
3	**1**	**S4**	Toluene	1.1	32 (2)	35 (*S*)
4	**1**	**S4**	THF	1.1	100 (2)	48 (*S*)
5	**1**	**S4**	THF	0.75	100 (2)	47 (*S*)
6	**1**	**S4**	THF	2	100 (2)	48 (*S*)
7	**2**	**S4**	THF	1.1	100 (2)	46 (*S*)
8	**3**	**S4**	THF	1.1	100 (2)	22 (*S*)
9	**1**	**S5**	THF	1.1	17 (2)	82 (*S*)
10	**2**	**S5**	THF	1.1	16 (2)	81 (*S*)
11	**3**	**S5**	THF	1.1	12 (2)	42 (*S*)

[a] 0.5 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature and CH_2Cl_2 as solvent.

[b] Measured by GC. Reaction time in hours shown in parentheses.

[c] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses.



(2)

S4 n=1
S5 n=2

8 n=1
9 n=2

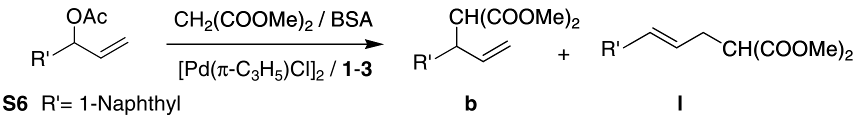
We initially studied the allylic alkylation of *rac*-3-acetoxycyclohexene **S4** using ligands **1**–**3**. Preliminary investigations into the solvent effect and ligand-to-palladium ratio provided the same trends as those with the previously tested linear substrate **S1** (Table 2, entries 1–6). The optimal trade-off between enantioselectivities and reaction rates was therefore optimum with THF and a ligand-to-palladium ratio of 1.1. The results of using the rest of the phosphite–phosphoroamidite ligands under the optimized conditions are shown in Table 2 and indicate that substituents at the *para*-positions of the biphenyl moieties are needed for better enantioselectivities (Table 2, entries 5 and 7 vs 8). Thus, ligands **1** and **2** with *tert*-butyl and methoxy substituents at the *para*-positions of the biphenyl moieties, respectively, provided higher asymmetric induction than ligands **3** with small hydrogen substituents in these positions.

With these ligands, we also studied the Pd-catalyzed allylic alkylation of the seven-membered ring substrate **S5** (Table 2, entries 9–11). Interestingly, high enantioselectivities (ee's up to 82%) were obtained using ligands **1** and **2** (Table 2, entries 9 and 10).

2.7. Allylic substitution of monosubstituted linear substrates

Finally, we also examined the regio- and stereoselective allylic alkylation of 1-(1-naphthyl)allyl acetate **S6** with dimethyl malonate. For this substrate, the development of highly regio- and enantioselective Pd-catalysts is still a challenge.[8,4] The results obtained with the phosphite–phosphoroamidite ligands **1**–**3** are summarized in Table 3. Unfortunately, the regioselectivity for the branched products was not high. However, good enantioselectivities

Table 3. Selected results for the Pd-catalyzed allylic alkylation of **S6**[a]



Entry	Ligand	Solvent	% Conv.[b] (*t*/h)	**b**/**l**[b]	% ee[c]
1	**1**	CH_2Cl_2	100 (2)	20/80	72 (*S*)
2	**1**	DMF	100 (2)	21/79	54 (*S*)
3	**1**	Toluene	34 (2)	15/75	68 (*S*)
4	**1**	THF	100 (2)	12/88	38 (*S*)
5	**2**	CH_2Cl_2	100 (2)	25/75	28 (*S*)
6	**3**	CH_2Cl_2	100 (2)	40/60	41 (*S*)

[a] 1 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 2.2 mol % ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature.

[b] Conversion percentage and linear-to-branched ratio determined by ^1H NMR.

[c] Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.

can be obtained (ee's up to 72%). The results also indicate that regio- and enantioselectivities are highly affected by the substituents at the *para*-position of the biphenyl moieties (Table 3, entries 1, 5, and 6). However, whereas the best enantioselectivities were obtained when bulky substitutents in the *para*-positions of the biphenyl moieties were present (ligand **1**, Table 3, entry 1), regioselectivities are better when unhindered hydrogens are present at these positions (ligand **3**, Table 3, entry 6).

3. Conclusions

We have designed and synthesized a new family of readily available phosphite–phosphoroamidite ligands for Pd-catalyzed allylic substitution reactions of several substrates with different steric and electronic properties. These ligands are derived from D-glucosamine and contain several substituents in the biphenyl moieties, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that enantioselectivities are mainly affected by the substituents at the *para*-positions of the biphenyl moieties. However, these effects are different depending on the substrate under study. Therefore, for the hindered disubstituted linear substrates **S1** and **S2**, and the cyclic substrates **S4** and **S5**, we found the best enantioselectivities (ee's up to 89%) with ligand **1**, contained bulky *tert*-butyl group at the *para*-positions of the biaryl groups while for the unhindered disubstituted linear substrate **S3** the best selectivity (ee's up to 61%) was obtained with ligand **3**, that has small hydrogens at these *para*-positions. For the monosubstituted linear substrate **S6**, these ligands proved to be inadequate in terms of regioselectivities. However, we obtained good enantioselectivity by carefully selecting the substituents on the *para*-position of the biphenyl moieties (ee's up to 72%). It should be noted that high activities were obtained in all cases, due to the π-acceptor capacity of these phosphite–phosphoroamidite ligands.

We are confident that further development of new ligands, taking advantage of the modularity of this family of ligands, will improve selectivities so far obtained in unhindered disubstituted linear substrate and monosubstituted substrates. Such mechanistic studies are currently underway.

4. Experimental

4.1. General

All syntheses were performed using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Compound **4**[7] and phosphorochloridites[9] were prepared by previously described methods. All other reagents were used as commercially available. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. Chemical shifts are relative to $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. All assignments in NMR spectra were determined by ^1H–^1H and ^{13}C–^1H spectra. Racemic substrates **S1**–**S6** were prepared as reported previously.[10–13]

4.2. Synthesis of the chiral phosphite–phosphoroamidite ligands

The corresponding phosphorochloridite (2.25 mmol) produced in situ was dissolved in toluene (10.0 mL), and pyridine (0.60 mL, 7.4 mmol) was added. Amino-alcohol **4** (0.28 g, 1.0 mmol) was azeotropically dried with toluene (3 × 2 mL) and then dissolved in toluene (10.0 mL) to which pyridine (0.60 mL, 7.4 mmol) was added. The solution was transferred slowly at 0 °C to a solution of phosphorochloridite. The reaction mixture was stirred overnight at 80 °C, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash column chromatography (eluent: toluene/hexane/Et_3N = 50:75:2) to produce the desired ligand as a white powder.

Compound **1**. Yield: 0.38 g (32%). ^{31}P NMR (400 MHz, C_6D_6): $\delta = 146.6$ (s, 1P), 152.7 (s, 1P). ^1H NMR (400 MHz, C_6D_6): $\delta = 1.24$ (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 18H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 3.00 (s, 3H, OMe), 3.23 (m, 1H, NH), 3.61 (m, 3H, H-1, H-4, H-6′), 3.76 (m, 1H, H-5), 4.04 (b, 1H, H-2), 4.13 (m, 1H, H-6), 4.73 (m, 1H, H-3), 5.53 (s, 1H, H-7), 7.00–7.8 (m, 13H, CH=). ^{13}C NMR (400 MHz, C_6D_6): $\delta = 30.9$ (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 54.1 (CH_3–O, C-2), 62.8 (C-5), 68.9 (C-6), 75.3 (d, C-3, $^2J_{\text{c–p}} = 21.3$ Hz), 80.7 (C-4), 100.5 (C-1), 101.4 (C-7), 123.8 (CH=), 123.9 (CH=), 124.1 (CH=), 124.3 (CH=), 126.2 (CH=), 126.6 (CH=), 126.8 (CH=), 126.9 (CH=), 127.0 (CH=), 128.0 (CH=), 128.4 (CH=), 128.8 (CH=), 129.2 (CH=), 132.5 (C), 133.4 (C), 134.1 (C), 134.6 (C), 137.7 (C), 140.1 (C), 140.5 (C), 141.0 (C), 141.5 (C), 145.3 (C), 145.6 (C), 146.2 (C), 146.3 (C), 146.9 (C). Anal. Calcd (%) for $C_{70}H_{97}NO_9P_2$: C, 72.57; H, 8.44; N, 1.21. Found: C, 72.63; H, 8.50; N, 1.22. Melting point: 181 °C.

Compound **2**. Yield: 0.22 g (21%). ^{31}P NMR (400 MHz, C_6D_6): $\delta = 147.0$ (s, 1P) 151.2 (s, 1P). ^{1}H NMR (400 MHz, C_6D_6): $\delta = 1.43$ (s, 18H, CH_3, ^{t}Bu), 1.48 (s, 18H, CH_3, ^{t}Bu), 2.99 (s, 3H, OMe), 3.30 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.32 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.52 (m, 3H, 1NH, H-4, H-6′), 3.77 (m, 1H, H-5), 3.98 (m, 1H, H-1), 4.11 (m, 2H, H-2, H-6), 4.76 (m, 1H, H-3), 5.44 (s, 1H, H-7), 6.60–7.75 (m, 13H, CH=). ^{13}C NMR (400 MHz, C_6D_6): $\delta = 31.3$ (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 35.7 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 54.7 (C-2), 55.3 (OCH_3), 55.4 (OCH_3), 55.5 (OCH_3), 55.6 (OCH_3), 63.5 (C-5), 69.3 (C-6), 75.9 (m, C-3), 81.1 (C-4), 101.2 (C-1), 101.8 (C-7), 112.8 (CH=), 113.5 (CH=), 113.7 (CH=), 113.8 (CH=), 114.7 (CH=), 115.0 (CH=), 115.2 (CH=), 126.0 (CH=), 127.0 (CH=), 128.6 (CH=), 128.9 (CH=), 129.3 (CH=), 129.7 (CH=), 134.8 (C), 135.0 (C) 138.2 (C), 142.8 (C), 143.1 (C), 143.5 (C) 144.0 (C), 156.3 (C), 156.5 (C), 156.6 (C), 156.8 (C). Anal. Calcd (%) for $C_{58}H_{73}NO_{13}P_2$: C, 65.08; H, 6.98; N, 1.33. Found: C, 66.14; H, 7.01; N, 1.36. Melting point: 150 °C.

Compound **3**. Yield: 0.30 g (30%). ^{31}P NMR (400 MHz, C_6D_6): $\delta = 149.6$ (s, 1P) 151.9 (s, 1P). ^{1}H NMR (400 MHz, C_6D_6): $\delta = 0.28$ (s, 9H, CH_3–Si), 0.39 (s, 9H, CH_3–Si), 0.40 (s, 9H, CH_3–Si), 0.42 (s, 9H, CH_3–Si), 2.94 (s, 3H, OMe), 3.36 (m, 1H, NH), 3.47 (m, 1H, H-6′), 3.67 (m, 1H, H-4), 3.83 (m, 1H, H-5), 3.90 (m, 1H, H-2), 4.04 (m, 1H, H-6), 4.07 (m, 1H, H-1), 4.82 (m, 1H, H-3), 5.42 (s, 1H, H-7), 6.99–7.70 (m, 17H, CH=). ^{13}C NMR (400 MHz, C_6D_6): $\delta = 0.4$ (CH_3–Si), 0.5 (CH_3–Si), 0.6 (CH_3–Si), 55.8 (OCH_3), 55.8 (C-2), 63.6 (C-5), 69.3 (C-6), 74.8 (m, C-3), 81.5 (C-4), 100.7 (C-1), 102.1 (C-7), 124.9 (CH=), 125.1 (CH=), 125.4 (CH=), 127.1 (CH=), 129.3 (CH=), 132.6 (CH=), 132.7 (CH=), 133.0 (CH=), 133.2 (CH=), 135.5 (CH=), 133.7 (CH=), 135.8 (CH=). Anal. Calcd (%) for $C_{50}H_{65}NO_9P_2Si_4$: C, 60.15; H, 6.56; N, 1.40. Found: C, 60.12; H, 6.59; N, 1.41. Melting point: 117 °C.

4.3. Typical procedure for allylic alkylation of substrates S1–S5

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite–phosphoroamidite (0.0055 mmol) in THF (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in THF (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract was dried over $MgSO_4$. For substrate **S1**, the conversion was measured by ^{1}H NMR and the enantiomeric excess was determined by HPLC (Chiralcel-OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min). For substrate **S2**, conversion was measured by ^{1}H NMR and enantiomeric excess was determined by ^{1}H NMR using Eu(hfc)$_3$ as a resolving agent. For substrates **S3** and **S4**, conversion and enantiomeric excess were determined by GC using a FS-Cyclodex β-I/P 25 m column, internal diameter 0.2 mm, film thickness 0.33 mm, carrier gas: 100 kPa He, FID detector. For substrate **S5**, the conversion was determined by GC and the enantiomeric excess was determined by ^{1}H NMR using Eu(hfc)$_3$.

4.4. Typical procedure of allylic alkylation of monosubstituted linear substrate S6

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite–phosphoroamidite ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the substrate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion and regioselectivity were measured by ^{1}H NMR. To determine the ee by HPLC (Chiralcel-OJ, 3% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.

Acknowledgements

We thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2004-04412/BQU and Ramon y Cajal fellowship to O.P.) and the Generalitat de Catalunya (2005SGR007777 and Distinction to M.D.) for financial support.

References

1. For recent reviews, see: (a) Tsuji, J. *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; Wiley: New York, 1995; (b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395; (c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689; (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A.,

Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, Chapter 24; (e) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

2. (a) Diéguez, M.; Jansat, S.; Gomez, M.; Ruiz, A.; Muller, G.; Claver, C. *Chem. Commun.* **2001**, 1132; (b) Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1257; (c) Diéguez, M.; Pàmies, O.; Claver, C. *J. Org. Chem.* **2005**, *70*, 3363.
3. Raluy, E.; Claver, C.; Diéguez, M.; Pàmies, O. *Org. Lett.*, in press.
4. (a) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646; (b) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943.
5. See for instance: (a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; (b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165; (c) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957; (d) Pàmies, O.; Diéguez, M.; Ruiz, A.; Claver, C. *Chem. Today* **2004**, 12; (e) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. In *Methodologies in Asymmetric Catalysis*; Malhotra, S. V., Ed.; American Chemical Society: Washington, DC, 2004; (f) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113.
6. See, for example: (a) Yan, Y. Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 199; (b) Liu, D.; Li, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4471; (c) Albinati, A.; Pregosin, P. S.; Wick, K. *Organometallics* **1996**, *15*, 2419; (d) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 959; (e) Yonehara, K.; Jashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 9374; (f) Boog-Wick, K.; Pregosin, P. S.; Trabesinger, C. *Organometallics* **1998**, *17*, 3254.
7. Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Tetrahedron: Asymmetry* **2005**, *16*, 213.
8. For recent successful applications of Pd-catalysts, see: (a) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471; (b) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323; (c) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814.
9. (a) Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625; (b) Buisman, G. J. H.; van der Veen, L. A.; Klootwijk, A.; de Lange, W. G. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Organometallics* **1997**, *16*, 2929.
10. Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.
11. Jia, C.; Müller, P.; Mimoun, H. *J. Mol. Cat. A: Chem.* **1995**, *101*, 127.
12. Lehman, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863.
13. Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem.* **1989**, *111*, 6301.