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Screening of a modular sugar-based phosphoroamidite ligand library in the asymmetric nickel-catalyzed trialkylaluminium addition to aldehydes

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ABSTRACT

A modular sugar-based phosphoroamidite ligand library for the Ni-catalyzed trialkylaluminium addition to aldehydes has been synthesized and screened. After systematic variation of the sugar backbone, the substituents at the phosphoroamidite moieties and the flexibility of the ligand backbone, the monophosphoroamidite ligand 3-amine-3-deoxy-1,2:5,6-di-*O*-isopropylidene-((3,3′-di-trimethylsilyl-1,1′-biphenyl-2,2′-diyl)phosphite)-α-D-glucofuranose **1d** were found to be optimal. Activities were high and enantioselectivities were good (ees up to 78%) for several aryl aldehydes.

1. Introduction

The catalytic addition of organoaluminium reagents to aldehydes as a route to chiral alcohols has attracted considerable attention, since many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products.[1] Although organoaluminium reagents can be economically obtained on an industrial scale,[2] they are rarely used.[3–5] In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminium to aldehydes can be grouped into two types. The first type is the titanium complexes. Although they usually afford high enantioselectivities, they have slow turnover rates that restrict their potential utility and also require high catalyst loadings (10–20 mol %).[3a–d] The second type is the recently studied nickel complexes that provide enantioselectivities similar to those that are obtained with titanium complexes but with low catalyst loadings (0.05–1 mol %).[3e,4,5a] For the latter nickel catalysts, only two types of ligands have been successfully applied. The first application was reported by Woodward et al. using monophosphoroamidite ligands as the chiral source.[3e,4] The second application used a series of sugar-based monophosphite ligands.[5a] On the basis of this structure and in an attempt to expand the range of ligands for this process, a new ligand library in which the phosphite group is replaced by a phosphoroamidite group (Fig. 1) has been designed and is reported herein. This ligand library combines the advantages of both types of successful ligands (phosphoroamidite and monodentated sugar).

The synthesis and application of 35 potential chiral monophosphoroamidite ligands **1–5a–g** (Fig. 1) in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminium to several aldehyde types are reported. These ligands, derived from D-glucose, D-fructose, and D-galactose, also have the advantages of carbohydrates and phosphoroamidite ligands: they are cheap, easily constructed with modules, and highly resistant to oxidation.[6] All these features enable series of chiral ligands to be synthesized and screened in the search for high activity and selectivity. The effects of systematically varying the configurations of the ligand backbone at C-3 (**1–2**), the substituents/configurations in the biaryl phosphite moiety (**a–g**), the carbohydrate ring size (**1–3**), and the flexibility of the ligand backbone (**3–5**) were fully explored with this library. By carefully selecting these elements, we achieved good enantioselectivities and activities for different substrate types.

2. Results and discussion

2.1. Synthesis of ligands

Ligands **1–5** were efficiently synthesized in one step by reaction of the corresponding sugar amines **6–10** with 1 equiv of the phosphorochloridite [ClP(OR)$_2$; (OR)$_2$ = **a–g**] formed in situ in the presence of pyridine (Scheme 1). Sugar alcohols **5–8** were easily prepared on a large scale from D-(+)-glucose, D-(−)-fructose, and D-(+)-galactose (Scheme 1). All the ligands were purified on neutral alumina under an atmosphere of argon and isolated in moderate yields as white solids or colorless liquids. The elemental analyses were in agreement with the assigned structures. The ^{1}H, ^{31}P, and ^{13}C NMR spectra were as expected for these C_1 ligands (see Section 4). One singlet for each compound was observed in the ^{31}P NMR spectrum (see Section 4). Rapid ring inversions (atropoisomerization) in the biphenyl-phosphorus moieties **a-e** occurred on the NMR time scale since the expected diastereoisomers were not detected by low-temperature phosphorus NMR.[7]

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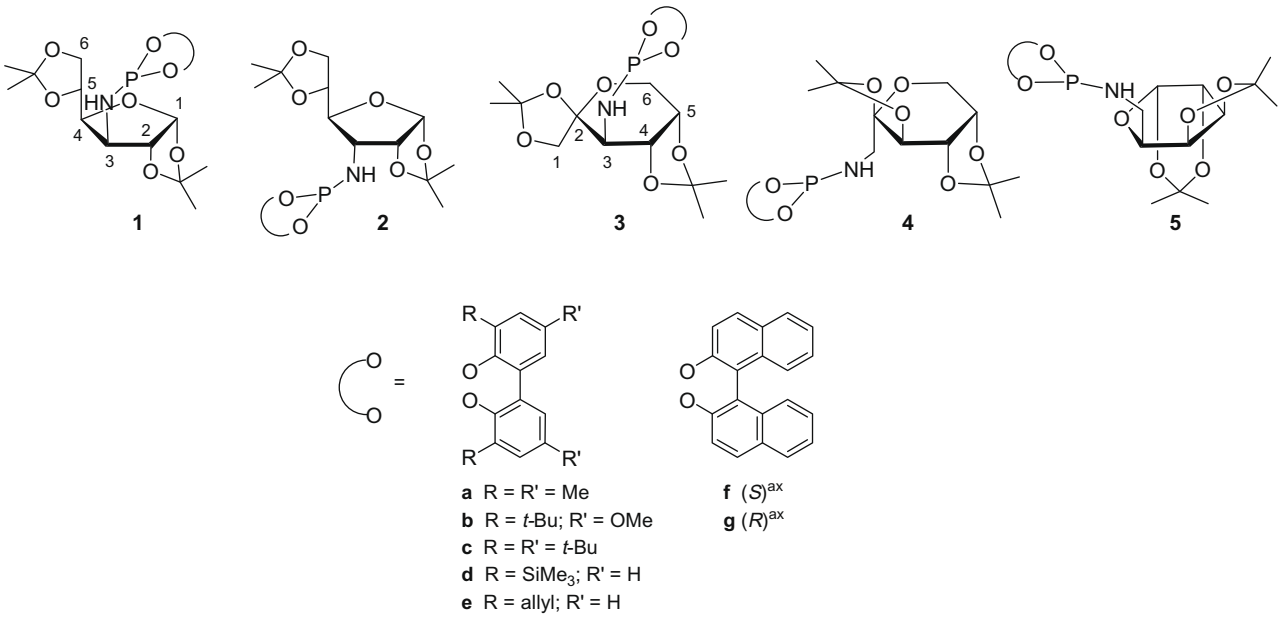
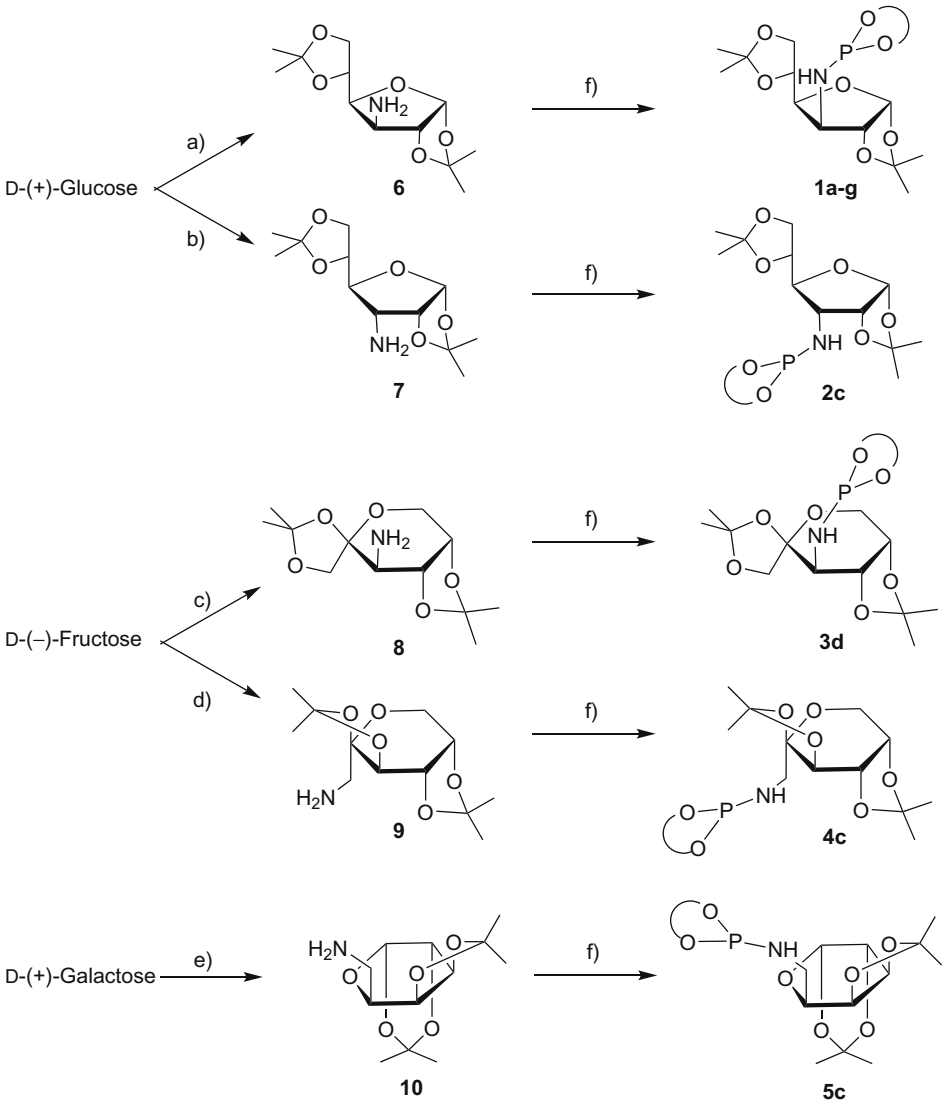


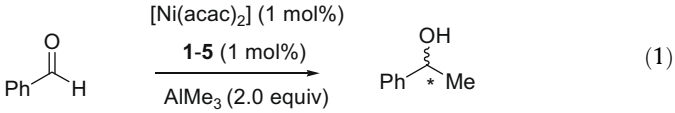
Figure 1. Carbohydrate-based phosphoroamidite ligands **1**–**5a**–**g**.



Scheme 1. Synthesis of monophosphoroamidite ligand library **L1**–**L5a**–**g**. (a) Ref. 8; (b) Ref. 9; (c) Ref. 10; (d) Ref. 11; (e) Ref. 12; (f) $ClP(OR)_2$; $(OR)_2$ = **a**–**g**/Py/toluene.

2.2. Asymmetric addition of AlR_3 to aldehydes

In the first set of experiments, the phosphoroamidite ligand library (Fig. 1) was used in the nickel-catalyzed asymmetric addition of trimethylaluminium to benzaldehyde, which is used as a model substrate (Eq. 1). The catalytic system was generated in situ by adding the corresponding phosphoroamidite ligand to a suspension of the catalyst precursor $[Ni(acac)_2]$ (acac = acetylacetonate).



(1)

The results, which are summarized in Table 1, indicate that the catalytic performance (activities and enantioselectivities) strongly affected by the configuration of carbon atom C-3, the size of the ring of the sugar backbone and the substituents of the biaryl moieties.

With ligands **1a–e** we studied how the substituents of the biaryl phosphoroamidite moiety affect the product outcome. The results indicated that the substituents at the *ortho*-positions of the biphenyl moiety mainly affected activities, while enantioselectivitites are affected by the substituents at both *ortho* and *para* positions. Activities were controlled by the steric properties of the *ortho* substituents (Table 1, entries 1–5). They were higher when more sterically demanding substituents were present (i.e., ^tBu = $SiMe_3$ > allyl > Me). For high enantioselectivities, the bulky substituents at the *ortho* position need to be combined with small substituents at the *para* positions of the biaryl moiety (Table 1, entries 2–4). Therefore, activities and enantioselectivities were best with ligand **L1d**, which contain trimethylsilyl groups at the *ortho* positions of the biaryl phosphoroamidite moiety (Table 1, entry 4). This behavior contrasts with the effect of the biaryl-substituents on related monophosphite counterparts, for which enantioselectivities were higher when *tert*-butyl groups were present at both *ortho* and *para* positions.[5a]

We used ligands **1f** and **1g** to study the possibility of a cooperative effect between the stereocenters of the ligand backbone and the configuration of the biaryl phosphite moieties (Table 1, entries 6 and 7). The results indicated that the matched combination is achieved with ligand **1f**, which has an (*S*)-configuration at carbon atom C-3 and also in the biaryl phosphoroamidite moiety. However, the enantioselectivities obtained with **1f** are lower than those obtained using bulky *ortho*-substituted biphenyl ligand **1d**. This contrasts with the higher enantioselectivites obtained when enantiopure unsubstituted binaphthyl phosphoroamidite moieties are present in related Feringa-type phosphoroamidites.[3e,4]

With ligands **2**, whose configuration at C-3 is opposite to that of ligands **1**, the effect of this configuration on the product outcome was studied. The results indicated that the C-3 configuration affects enantioselectivity (Table 1, entries 8 and 9). Ligands **2** with an (*R*)-configuration at C-3 provided lower enantioselectivities than when ligands **1** were used. Ligand **3d** which has a pyranoside backbone provided slightly lower enantioselectivitities (up to 43%) than their related furanoside ligand **1d** (Table 1, entry 10 vs entry 4). Finally, the most flexible ligands **4** and **5**, the phosphoroamidite moiety of which is attached to a primary carbon, provided the lowest enantioselectivities (Table 1, entries 11 and 12).

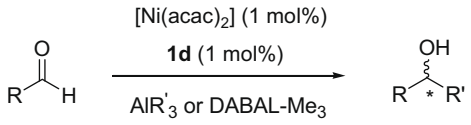
Next, we used the ligand **1d** that provided the best results to study the effect of the ligand-to-nickel ratio on the product outcome. Our results show that an excess of ligand is not needed for yields and enantioselectivities to be high (Table 1, entries 4, 13, and 14). To further investigate the catalytic efficiency of these Ni/**1–5** systems, they were tested in the nickel-catalyzed addition of several trialkylaluminium sources (AlR'_3, R′ = Me or Et; and DABAL-Me_3) to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 2. We found that enantioselectivity for $AlMe_3$ addition is hardly affected by the presence of electron-donating groups at the *para* position of the phenyl group (Table 2, entries 1, 3, 5, and 9). However, the presence of electron-withdrawing groups at the *para* position has a negative effect on enantioselectivity (Table 2, entry 7). The enantioselectivity of the reaction is also significantly influenced by steric factors (Table 2, entries 11 and 12). The results of using triethylaluminium as alkylating reagent indicated that the catalytic performance follows the same trend as for the trimethylaluminium addition. However, enantioselectivities are slightly better (Table 2, entries 1, 3, 5, 7, and 9 vs entries 2, 4, 6, 8, and 10).

Table 1
Selected results for the nickel-catalyzed asymmetric addition of AlMe3 to benzaldehyde using the phosphoroamidite library **1–5a–g**[a]

Entry	Ligand	L/Ni	% Conv[b]	% Yield[c]	% ee[d]
1	**1a**	1	12	11	28 (*R*)
2	**1b**	1	100	100	12 (*S*)
3	**1c**	1	99	98	21 (*S*)
4	**1d**	1	100	99	69 (*R*)
5	**1e**	1	48	48	53 (*R*)
6	**1f**	1	100	100	35 (*R*)
7	**1g**	1	100	98	23 (*S*)
8	**2b**	1	100	100	8 (*R*)
9	**2c**	1	100	100	10 (*R*)
10	**3d**	1	100	97	43 (*R*)
11	**4c**	1	100	97	6 (*R*)
12	**5c**	1	92	91	5 (*R*)
13	**1d**	2	100	100	67 (*R*)
14	**1d**	0.5	100	99	65 (*R*)

[a] Reaction conditions: $T = -20$ °C, $[Ni(acac)_2]$ (1 mol %), $AlMe_3$ (2 equiv), substrate (0.25 mmol), THF (2 mL).
[b] % Conversion determined by GC.
[c] % Yield determined by GC using dodecane as internal standard.
[d] Enantiomeric excess measured by GC using Cyclodex-B column.

Table 2
Selected results for the nickel-catalyzed asymmetric addition of (AlR'_3 (R′ Me or Et) and DABAL-Me_3 to aldehydes using ligand **1d**[a]



Entry	R	R′	% Conv.[b]	Yield[c]	% ee[d]
1	C_6H_5	Me	100	99	69 (*R*)
2	C_6H_5	Et	95	93	78 (*R*)
3	4-CH_3–C_6H_4	Me	100	95	62 (*R*)
4	4-CH_3–C_6H_4	Et	98	96	65 (*R*)
5	4-OMe–C_6H_4	Me	99	98	64 (*R*)
6	4-OMe–C_6H_4	Et	100	95	69 (*R*)
7	4-CF_3–C_6H_4	Me	28	26	41 (*S*)
8	4-CF_3–C_6H_4	Et	33	29	42 (*S*)
9	4-F–C_6H_4	Me	98	97	60 (*S*)
10	4-F–C_6H_4	Et	100	94	62 (*S*)
11	3-OMe–C_6H_4	Me	100	94	37 (*R*)
12	2-OMe–C_6H_4	Me	20	17	37 (*R*)
13[e]	C_6H_5	Me	85	82	67 (*R*)
14[e]	4-CH_3–C_6H_4	Me	84	80	60 (*R*)
15[e]	4-CF_3–C_6H_4	Me	16	15	43 (*S*)
16[e]	3-OMe–C_6H_4	Me	67	62	33 (*R*)

[a] Reaction conditions: $T = -20$ °C, $[Ni(acac)_2]$ (1 mol %), **1d** (1 mol %), (AlR'_3 (2 equiv), substrate (0.25 mmol), THF (2 mL).
[b] % Conversion determined by GC after 1 h.
[c] % Yield determined by GC using dodecane as internal standard.
[d] Enantiomeric excess measured by GC using Cyclodex-B column.
[e] DABAL-Me_3 (1.3 equiv), $T = 5$ °C.

Recently, Woodward et al. reported for the first time the advantages of using DABAL-Me_3 as an air-stable methylating reagent in nickel-catalyzed additions to aldehydes.[3e] Our results using this reagent indicate that the catalytic performance follows the same trend as for the trimethylaluminium addition to aldehydes, which is not unexpected because the reactions have a similar mechanism. However, the yields were lower than in trimethylaluminium addition (Table 2, entries 13–16).

3. Conclusions

A library of readily available monophosphoroamidite ligands has been synthesized and applied in the Ni-catalyzed trialkylaluminium addition to several aldehydes. By carefully designing this library it was possible to systematically investigate the effect of varying the sugar backbone, the configuration at carbon C-3 of the ligand backbone and the type of substituents/configurations in the biaryl phosphoroamidite moiety. By judicious choice of the ligand components good enantioselectivities (ee values up to 78%) and high activities in several aryl aldehydes, with low catalyst loadings (1 mol %) and no excess of ligand were obtained.

4. Experimental

4.1. General considerations

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Compounds **6–10** were prepared by previously described methods.[8–12] Phosphorochloridites were easily prepared in one step from the corresponding biaryls.[13] All other reagents were used as commercially available. ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. The chemical shifts are referenced to tetramethylsilane (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. The ^{1}H and ^{13}C NMR spectral assignments were determined by ^{1}H–^{1}H and ^{1}H–^{13}C correlation spectra.

4.2. General procedure for the preparation of phosphoroamidite ligands 1–5a–g

Phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL) and pyridine (0.18 mL, 2.3 mmol) was added. Amine (1 mmol) was azeotropically dried with toluene (3 × 1 mL) and then dissolved in toluene (10 mL), to which pyridine (0.18 mL, 2.3 mmol) was added. The amine solution was transferred slowly at 0 °C to the solution of phosphorochloridite. The reaction mixture was warmed to 80 °C and stirred overnight, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified in a short path of alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as white powder or colorless liquid.

Compound ***1a***: Yield: 206 mg (39%). ^{31}P NMR (C_6D_6), δ: 145.4 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.12 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.21 (m, 1H, NH), 4.01 (m, 1H, H-6′), 4.12 (m, 1H, H-6), 4.21 (m, 1H, H-3), 4.26 (m, 1H, H-4), 4.32 (m, 1H, H-5), 4.42 (d, 1H, H-2, $^3J_{2-1}$ = 3.6 Hz), 5.71 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.7–7.3 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 16.9 (CH_3), 17.3 (CH_3), 19.9 (CH_3), 21.1 (CH_3), 25.2 (CH_3), 26.1 (CH_3), 26.6 (CH_3), 27.2 (CH_3), 58.1 (d, C-3, J_{C-P} = 7.0 Hz), 68.0 (C-6), 73.1 (C-5), 81.1 (C-4), 85.3 (d, C-2, J_{C-P} = 8.2 Hz), 105.0 (C-1), 109.9 (CMe_2), 111.2 (CMe_2), 128.3 (CH=), 128.5 (CH=), 130.1 (CH=), 134.8 (C), 134.9 (C), 143.2 (C), 143.4 (C), 152.1 (C), 152.5 (C). Anal. Calcd (%) for $C_{28}H_{36}NO_7P$: C, 63.51; H, 6.85; N, 2.64. Found: C, 63.54; H, 6.87; N, 2.61.

Compound ***1b***: Yield: 277 mg (43%). ^{31}P NMR (C_6D_6), δ: 149.8 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.08 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.49 (s, 9H, CH_3, *t*-Bu), 1.54 (s, 9H, CH_3, *t*-Bu), 3.18 (m, 1H, NH), 3.27 (s, 3H, CH_3–O), 3.36 (s, 3H, CH_3–O), 4.03 (m, 1H, H-6′), 4.09 (m, 1H, H-6), 4.17 (m, 1H, H-3), 4.24 (m, 1H, H-4), 4.30 (m, 1H, H-5), 4.47 (d, 1H, H-2, $^3J_{2-1}$ = 3.6 Hz), 5.70 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.69 (m, 2H, CH=), 7.15 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 25.6 (CH_3), 26.2 (CH_3), 26.9 (CH_3), 27.3 (CH_3), 31.3 (CH_3, *t*-Bu), 31.5 (CH_3, *t*-Bu), 35.6 (C, *t*-Bu), 35.7 (C, *t*-Bu), 55.3 (CH_3–O), 58.2 (d, C-3, J_{C-P} = 9.8 Hz), 68.1 (C-6), 73.2 (C-5), 81.3 (d, C-4, J_{C-P} = 3.0 Hz), 85.8 (d, C-2, J_{C-P} = 9.8 Hz), 105.2 (C-1), 109.7 (CMe_2), 111.6 (CMe_2), 113.2 (CH=), 113.5 (CH=), 114.8 (CH=), 115.2 (CH=), 134.8 (C), 134.9 (C), 143.2 (C), 143.5 (C), 156.4 (C), 156.5 (C). Anal. Calcd (%) for $C_{34}H_{48}NO_9P$: C, 63.24; H, 7.49; N, 2.17. Found: C, 63.28; H, 7.46; N, 2.15.

Compound ***1c***:Yield: 271 mg (39%). ^{31}P NMR (C_6D_6), δ: 148.7 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.21 (s, 9H, CH_3, *t*-Bu), 1.29 (s, 9H, CH_3, *t*-Bu), 1.32 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.47 (s, 9H, CH_3, *t*-Bu), 1.51 (s, 9H, CH_3, *t*-Bu), 3.23 (m, 1H, NH), 4.08 (m, 2H, H-6′ and H-6), 4.13 (m, 1H, H-3), 4.19 (m, 1H, H-4), 4.27 (m, 1H, H-5), 4.33 (d, 1H, H-2, $^3J_{2-1}$ = 4.0 Hz), 5.79 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.79 (m, 2H, CH=), 7.21 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 25.9 (CH_3), 26.1 (CH_3), 26.4 (CH_3), 27.2 (CH_3), 31.3 (CH_3, *t*-Bu), 31.5 (CH_3, *t*-Bu), 31.8 (CH_3, *t*-Bu), 35.6 (C, *t*-Bu), 35.7 (C, *t*-Bu), 36.0 (C, *t*-Bu), 58.0 (d, C-3, J_{C-P} = 12.0 Hz), 68.3 (C-6), 73.0 (C-5), 81.7 (d, C-4, J_{C-P} = 3.2 Hz), 86.3 (d, C-2, J_{C-P} = 9.2 Hz), 105.8 (C-1), 109.9 (CMe_2), 112.3 (CMe_2), 124.5 (CH=), 124.7 (CH=), 127.1 (CH=), 127.6 (CH=), 133.9 (C), 134.2 (C), 144.9 (C), 145.6 (C), 150.2 (C). Anal. Calcd (%) for $C_{40}H_{60}NO_7P$: C, 68.84; H, 8.67; N, 2.01. Found: C, 68.88; H, 8.69; N, 2.03.

Compound ***1d***: Yield: 276 mg (45%). ^{31}P NMR (C_6D_6), δ: 151.6 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.35 (s, 3H, CH_3-Si), 0.39 (s, 3H, CH_3-Si), 1.01 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 3.19 (m, 1H, NH), 3.96 (m, 1H, H-6′), 4.03 (m, 1H, H-6), 4.12 (m, 1H, H-3), 4.19 (m, 1H, H-4), 4.26 (m, 1H, H-5), 4.54 (d, 1H, H-2, $^3J_{2-1}$ = 4.0 Hz), 5.71 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.7–7.4 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 0.5 (CH_3-Si), 0.6 (CH_3-Si), 25.8 (CH_3), 26.4 (CH_3), 26.9 (CH_3), 27.4 (CH_3), 58.5 (d, C-3, J_{C-P} = 8.4 Hz), 68.0 (C-6), 73.4 (C-5), 81.3 (C-4), 86.2 (d, C-2, J_{C-P} = 11.4 Hz), 105.3 (C-1), 109.9 (CMe_2), 111.9 (CMe_2), 121.8 (CH=), 125.2 (CH=), 132.3 (C), 132.5 (C), 133.0 (CH=), 133.7 (C), 135.7 (CH=), 136.5 (C), 136.9 (C), 154.9 (C). Anal. Calcd (%) for $C_{30}H_{44}NO_7PSi_2$: C, 58.32; H, 7.18; N, 2.27. Found: C, 58.34; H, 7.17; N, 2.26.

Compound ***1e***: Yield: 265 mg (48%). ^{31}P NMR (C_6D_6), δ: 150.6 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.08 (m, 1H, NH), 3.57 (CH_2 allyl), 3.98 (m, 1H, H-6′), 4.02 (m, 1H, H-6), 4.11 (m, 1H, H-3), 4.20 (m, 2H, H-4, H-5), 4.43 (d, 1H, H-2, $^3J_{2-1}$ = 3.2 Hz), 5.03 (m, 4H, CH_2= allyl), 5.46 (d, 1H, H-1, $^3J_{1-2}$ = 3.2 Hz), 5.98 (m, 2H, CH= allyl), 6.9–7.2 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 25.9 (CH_3), 26.4 (CH_3), 27.1 (CH_3), 27.5 (CH_3), 35.2 (CH_2 allyl), 35.3 (CH_2 allyl), 58.4 (d, C-3, J_{C-P} = 24.0 Hz), 67.9 (C-6), 73.4 (C-5), 81.1 (d, C-4, J_{C-P} = 4.6 Hz), 86.7 (d, C-2, J_{C-P} = 6.1 Hz), 105.1 (C-1), 109.8 (CMe_2), 112.1 (CMe_2), 116.6 (CH_2 allyl), 116.7 (CH_2 allyl), 125.1 (CH=), 125.4 (CH=), 126.0 (C), 128.9 (CH=), 129.0 (CH=), 129.6 (C), 130.3 (CH=), 132.9 (C), 133.0 (C), 133.2 (C), 137.3 (CH= allyl), 137.4 (CH= allyl). Anal. Calcd (%) for $C_{30}H_{36}NO_7P$: C, 65.09; H, 6.55; N, 2.53. Found: C, 65.13; H, 6.59; N, 2.49.

Compound ***1f***: Yield: 223 mg (39%). ^{31}P NMR (C_6D_6), δ: 154.4 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.03 (m, 1H, NH), 4.05 (m, 2H, H-6, H-6′), 4.13 (m, 1H, H-3), 4.25 (m, 2H, H-4, H-5), 4.57 (d, 1H, H-2, $^3J_{2-1}$ = 3.6 Hz), 5.39 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.9–7.8 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 25.4 (CH_3), 26.0 (CH_3), 26.3 (CH_3), 27.0 (CH_3), 57.8 (d, C-3, J_{C-P} = 26.3 Hz), 67.6 (C-6), 73.6 (C-5), 80.6 (C-4), 86.8 (d, C-2, J_{C-P} = 12.0 Hz), 106.3 (C-1), 109.6 (CMe_2), 111.7 (CMe_2),

121.8 (CH=), 122.6 (CH=), 125.0 (CH=), 125.6 (C), 126.5 (CH=), 127.1 (CH=), 127.2 (CH=), 128.5 (CH=), 129.1 (CH=), 130.8 (CH=), 131.4 (C), 131.8 (C), 133.3 (C). Anal. Calcd (%) for $C_{32}H_{32}NO_7P$: C, 67.01; H, 5.62; N, 2.44. Found: C, 66.98; H, 5.63; N, 2.42.

Compound ***1g***:Yield: 199 mg (35%). ^{31}P NMR (C_6D_6), δ: 152.2 (s, 1P). ^1H NMR (C_6D_6), δ: 1.09 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.13 (m, 1H, NH), 4.03 (m, 1H, H-6), 4.06 (m, 1H, H-6′), 4.18 (m, 1H, H-3), 4.24 (m, 2H, H-4, H-5), 4.54 (d, 1H, H-2, $^3J_{2-1}$ = 4.0 Hz), 5.29 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.9–7.8 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 25.3 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 27.2 (CH_3), 57.8 (d, C-3, J_{C-P} = 7.8 Hz), 67.8 (C-6), 73.9 (C-5), 80.8 (C-4), 86.3 (d, C-2, J_{C-P} = 6.8 Hz), 105.8 (C-1), 109.3 (CMe_2), 111.6 (CMe_2), 121.9 (CH=), 122.8 (CH=), 125.0 (CH=), 125.4 (C), 126.1 (CH=), 126.7 (CH=), 127.0 (CH=), 128.4 (CH=), 129.6 (CH=), 131.5 (C), 131.9 (C), 133.3 (C). Anal. Calcd (%) for $C_{32}H_{32}NO_7P$: C, 67.01; H, 5.62; N, 2.44. Found: C, 67.09; H, 5.66; N, 2.41.

Compound ***2c***: Yield: 334 mg (48%). ^{31}P NMR (C_6D_6), δ: 149.4 (s, 1P). ^1H NMR (C_6D_6), δ: 1.11 (s, 3H, CH_3), 1.24 (s, 9H, CH_3, *t*-Bu), 1.26 (s, 9H, CH_3, *t*-Bu), 1.29 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.57 (s, 9H, CH_3, *t*-Bu), 1.63 (s, 9H, CH_3, *t*-Bu), 3.11 (m, 1H, H-3), 3.22 (m, 1H, NH), 3.56 (m, 1H, H-2), 3.91 (m, 2H, H-6′, H-6), 4.02 (m, 1H, H-4), 4.51 (m, 1H, H-5), 5.45 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.8–7.2 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 26.3 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 31.8 (CH_3, *t*-Bu), 31.9 (CH_3, *t*-Bu), 32.0 (CH_3, *t*-Bu), 34.8 (C, *t*-Bu), 35.0 (C, *t*-Bu), 35.8 (C, *t*-Bu), 56.1 (d, C-3, J_{C-P} = 9.2 Hz), 64.4 (C-6), 76.0 (C-5), 79.9 (C-4), 80.5 (C-2), 104,4 (C-1), 109.8 (CMe_2), 112.4 (CMe_2), 124.4 (CH=), 124.8 (CH=), 125.3 (CH=), 125.5 (C), 125.6 (C), 128.9 (CH=), 138.2 (C), 146.8 (C), 147.3 (C). Anal. Calcd (%) for $C_{40}H_{60}NO_7P$: C, 68.84; H, 8.67; N, 2.01. Found: C, 68.91; H, 8.71; N, 1.99.

Compound ***3d***: Yield: 234 mg (38%). ^{31}P NMR (C_6D_6), δ: 154.3 (s, 1P). ^1H NMR (C_6D_6), δ: 0.31 (s, 9H, CH_3-Si), 0.42 (s, 9H, CH_3-Si), 1.09 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 3.82 (m, 1H, H-2), 3.98 (m, 2H, H-1, H-1′), 4.21 (d, 1H, H-6′, $^2J_{6'-6}$ = 12.0 Hz), 4.51 (m, 1H, H-3), 4.54 (m, 1H, H-4), 5.59 (d, 1H, H-6, $^2J_{6-6'}$ = 12.0 Hz), 7.28 (m, 1H, CH=), 7.32 (m, 1H, CH=), 7.54 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 0.5 (CH_3-Si), 0.6 (CH_3-Si), 26.0 (CH_3), 26.5 (CH_3), 28.2 (CH_3), 28.8 (CH_3), 60.9 (C-1), 71.3 (C-6), 72.4 (C-4), 74.7 (C-2), 77.1 (C-3), 104.9 (C-5), 109.6 (CMe_2), 112.5 (CMe_2), 124.8 (CH=), 124.9 (CH=), 126.2 (C), 127.3 (CH=), 127.9 (CH=), 133.7 (C), 134.9 (C), 140.9 (C), 141.0 (C), 146.8 (C). Anal. Calcd (%) for $C_{30}H_{44}NO_7PSi_2$: C, 58.32; H, 7.18; N, 2.27. Found: C, 58.26; H, 7.21; N, 2.31.

Compound ***4c***: Yield: 237 mg (34%). ^{31}P NMR (C_6D_6), δ: 147.1 (s, 1P). ^1H NMR (C_6D_6), δ: 1.02 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.24 (s, 18H, CH_3, *t*-Bu), 1.26 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.56 (s, 9H, CH_3, *t*-Bu), 1.59 (s, 9H, CH_3, *t*-Bu), 3.27 (m, 1H, H-6), 3.37 (m, 1H, H-6′), 3.56 (d, 1H, H-1, $^2J_{1-1'}$ = 9.2 Hz), 3.64 (d, 1H, H-1′, $^2J_{1-1'}$ = 9.2 Hz), 3.72 (m, 1H, H-4), 3.75 (m, 1H, NH), 4.31 (m, 1H, H-3), 4.37 (m, 1H, H-2), 7.0–7.2 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 24.5 (CH_3), 25.7 (CH_3), 26.6 (CH_3), 30.5 (CH_3), 31.7 (CH_3, *t*-Bu), 31.8 (CH_3, *t*-Bu), 32.0 (CH_3, *t*-Bu), 35.0 (C, *t*-Bu), 35.8 (C, *t*-Bu), 36.0 (C, *t*-Bu), 47.5 (C-6), 61.8 (C-1), 71.1 (C-3), 71.5 (C-4), 72.2 (C-2), 108.2 (CMe_2), 109.3 (CMe_2), 124.5 (CH=), 125.3 (CH=), 126.2 (CH=), 127.0 (CH=), 137.2 (C), 143.8 (C), 146.6 (C). Anal. Calcd (%) for $C_{40}H_{60}NO_7P$: C, 68.84; H, 8.67; N, 2.01. Found: C, 68.87; H, 8.69; N, 1.98.

Compound ***5c***: Yield: 306 mg (44%). ^{31}P NMR (C_6D_6), δ: 148.5 (s, 1P). ^1H NMR (C_6D_6), δ: 1.03 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.31 (s, 18H, CH_3, *t*-Bu), 1.42 (s, 3H, CH_3), 1.60 (s, 18H, CH_3, *t*-Bu), 3.17 (m, 2H, H-6, H-6′), 3.42 (m, 1H, NH), 3.79 (m, 1H, H-1), 3.81 (m, 1H, H-5), 4.12 (m, 1H, H-3), 4.40 (m, 1H, H-2), 5.41 (m, 1H, H-4), 7.2–7.6 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 24.7 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 30.2 (CH_3, *t*-Bu), 31.8 (CH_3, *t*-Bu), 35.6 (C, *t*-Bu), 35.9 (C, *t*-Bu), 41.4 (d, C-2, J_{C-P} = 12.0 Hz), 69.5 (C-5), 71.3 (C-3), 71.5 (C-2), 71.8 (C-1), 96.9 (C-4), 108.7 (CMe_2), 109.4 (CMe_2), 124.4 (CH=), 124.5 (CH=), 125.3 (C), 127.0 (CH=), 127.2 (CH=), 134.3 (C), 140.9 (C), 146.5 (C), 148.2 (C). Anal. Calcd (%) for $C_{40}H_{60}NO_7P$: C, 68.84; H, 8.67; N, 2.01. Found: C, 68.90; H, 8.65; N, 2.03.

4.3. General procedure for the Ni-catalyzed enantioselective 1,2-addition of trialkylaluminium reagents to aldehydes

$[Ni(acac)_2]$ (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at −20 °C for 10 min. Neat aldehyde (0.25 mmol) was then added and trialkylaluminium (0.5 mmol) was added dropwise after a further 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.

4.4. General procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me_3 to aldehydes

$[Ni(acac)_2]$ (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at 5 °C for 10 min. Neat aldehyde (0.25 mmol) was then added and trialkylaluminium (84 mg, 0.325 mmol, 1.3 equiv) was added after a further 10 min. After the desired reaction time, the reaction was quenched with 2 M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.

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