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Screening of a Modular Sugar-Based Phosphite Ligand Library in the Asymmetric Nickel-Catalyzed Trialkylaluminum Addition to Aldehydes

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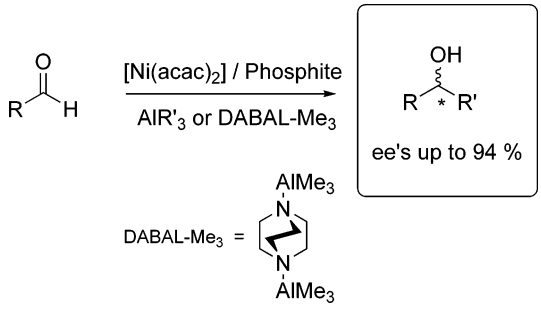

We synthesized a modular sugar-based phosphite ligand library for the Ni-catalyzed trialkylaluminum addition to aldehydes. This library has been designed to rapidly screen the ligands to uncover their important structure features and determine the scope of the phosphite ligands in this catalytic reaction. After systematic variation of the sugar backbone, the substituents at the phosphite moieties, and the flexibility of the ligand backbone, the monophosphite ligand 1,2:5,6-di-*O*-isopropylidene-3-*O*-((3,3′;5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite)-α-D-glucofuranose **1c** was found to be optimal, yielding high activities and enantioselectivities (ee's up to 94%) for several aryl aldehydes.

Introduction

Catalytic asymmetric carbon−carbon bond formation is one of the most actively pursued areas of research in the field of asymmetric catalysis. In this context, catalytic addition of dialkylzincs to aldehydes as a route to chiral alcohols has attracted much attention since many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products.[1] For alkylation reagents, trialkylaluminum compounds are more interesting than other organometallic reagents because they are economically obtained on an industrial scale from aluminum hydride and olefins.[2] Despite this advantage, their use is rare.[3] In this respect, the few most successful catalysts for the enantioselective addition of trialkylaluminum to aldehydes have been titanium complexes bearing chiral diols or *N*-sulfonylated amino alcohols as ligands.[3a−d] However, the high catalyst loadings needed and the slow turnover rate[4] hamper the potential utility of these catalytic systems. Recently, Woodward and co-workers reported the first report of the asymmetric addition of a trialkylaluminum to aldehydes employing a nickel catalyst, containing a phosphoroamidite ligand. Excellent enantioselectivities with low catalyst loadings were attained.[3e]

To further expand the range of ligands and performance of this asymmetric nickel-catalyzed addition of organoaluminum reagents to the aldehydes process, we designed a library of chiral monophosphite ligands **1**−**5** (Figure 1). These ligands are derived from natural D-glucose, D-galactose, and D-fructose and have the advantage of carbohydrate and phosphite ligands, such

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(4) Addition reactions of AlR_3 to an aldehyde normally require catalyst loadings of 10−20%, see refs 3a−d.

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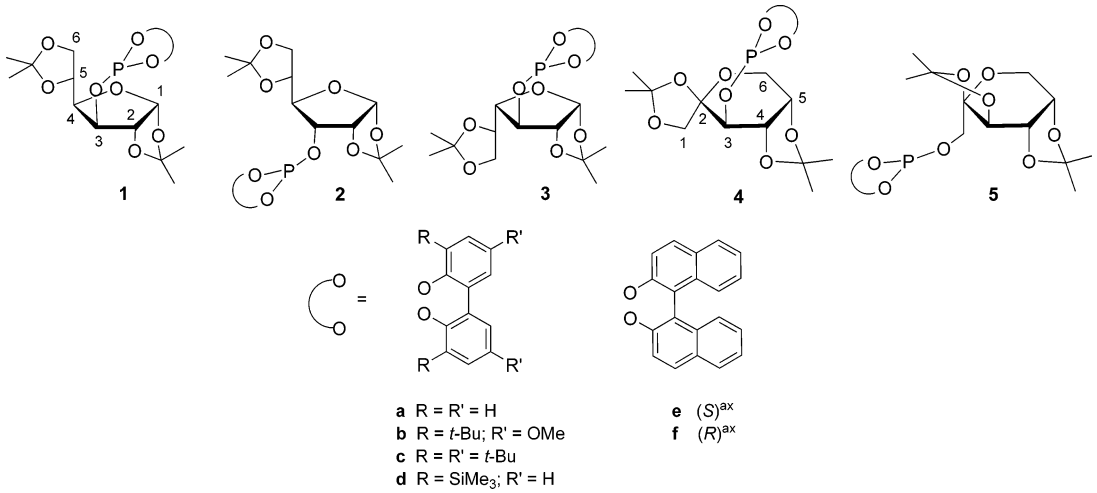


FIGURE 1. Carbohydrate-based phosphite ligands **1**−**5**.

as availability at a low price from readily available alcohols and facile modular constructions.[5] In addition, they are less sensitive to air than typical phosphines, widely used as ligands in asymmetric catalysis. All these favorable features enable series of chiral ligands to be synthesized and screened in the search for high activity and selectivity.[5] Although carbohydrate-based bidentate ligands have been successfully used in some enantioselective reactions (mainly hydrogenation and allylic alkylation),[5] few good monodentate chiral ligands have been reported based on carbohydrates.[6]

We report here the design of a library of 60 potential sugar-based chiral phosphite ligands and screen their use in the nickel-catalyzed addition of organoaluminum reagents to aldehydes. The synthesis and screening of the library were performed using a series of parallel reactors each equipped with 12 different positions. With this library we fully investigated the effects of systematically varying the configurations at C-3 and C-4 of the ligand backbone (**1**−**3**), different substituents/configurations in the biaryl phosphite moiety (**a**−**f**), the carbohydrate ring size (**1**−**4**), and the flexibility of the ligand backbone (**4**, **5**). By carefully selecting these elements we achieved high enantioselectivities and activities in different substrate types. To the best of our knowledge, this is the first example of phosphite ligands applied to this process.

Results and Discussions

Ligand Design. Ligands **1**−**5** consist of chiral di-*O*-protected either furanoside (ligands **1**−**3**) or pyranoside (ligands **4** and **5**) backbones, which determine their underlying structure, and one hydroxyl group. Several phosphoric acid biaryl esters (**a**−**f**) were attached to these basic frameworks (Figure 1).

The influence of the different groups attached to the ortho and para positions of the biphenyl moieties on enantioselectivity was investigated using ligands **1a**−**d**, which have the same configuration on carbon atom C-3. To determine whether there is a cooperative effect between the stereocenters of the ligand backbone and the configuration of the biaryl phosphite moieties, we prepared a series of enantiomerically pure binaphthol-based ligands **1e**,**f** and **2e**,**f**.

We studied the effects of the stereogenic carbon atom C-3 on enantioselectivity by comparing diastereomeric ligands **1** and **2**, which have opposite configuration at C-3. The influence of the configuration of carbon atom C-4 on the catalytic performance was studied using ligands **1** and **3**, which only differ in the configuration at C-4.

The influence of the carbohydrate ring size in the catalytic performance of the nickel catalysts was studied with ligands **4**, which have a pyranoside backbone and the same configuration at C-3 as ligand **1**. Finally, with ligands **5** we studied how the flexibility of the ligand backbone may affect the catalytic performance of the nickel catalysts. These ligands have a pyranoside backbone like ligands **4** but differ from the rest of the ligands in the phosphite moiety attached to a primary alcohol, providing a more flexible ligand.

Synthesis of Ligands. Ligands **1**−**5**[7] were efficiently synthesized in one step by reaction of the corresponding sugar alcohols (**6**−**10**) with 1 equiv of PCl_3 and subsequent addition of the biaryl alcohols (**a**−**f**) in the presence of triethylamine using a series of parallel reactors each equipped with 12 positions (Scheme 1).[6c] Sugar alcohols **6**−**10** were easily prepared on a large scale from inexpensive D-(+)-glucose, D-(+)-galactose, and D-(−)-fructose (Scheme 1). All ligands were stable during purification on neutral silica under an atmosphere of argon and isolated in moderate yields as white solids. The ^{1}H, ^{31}P, and ^{13}C NMR spectra were as expected for these C_1 ligands (see Experimental Section).

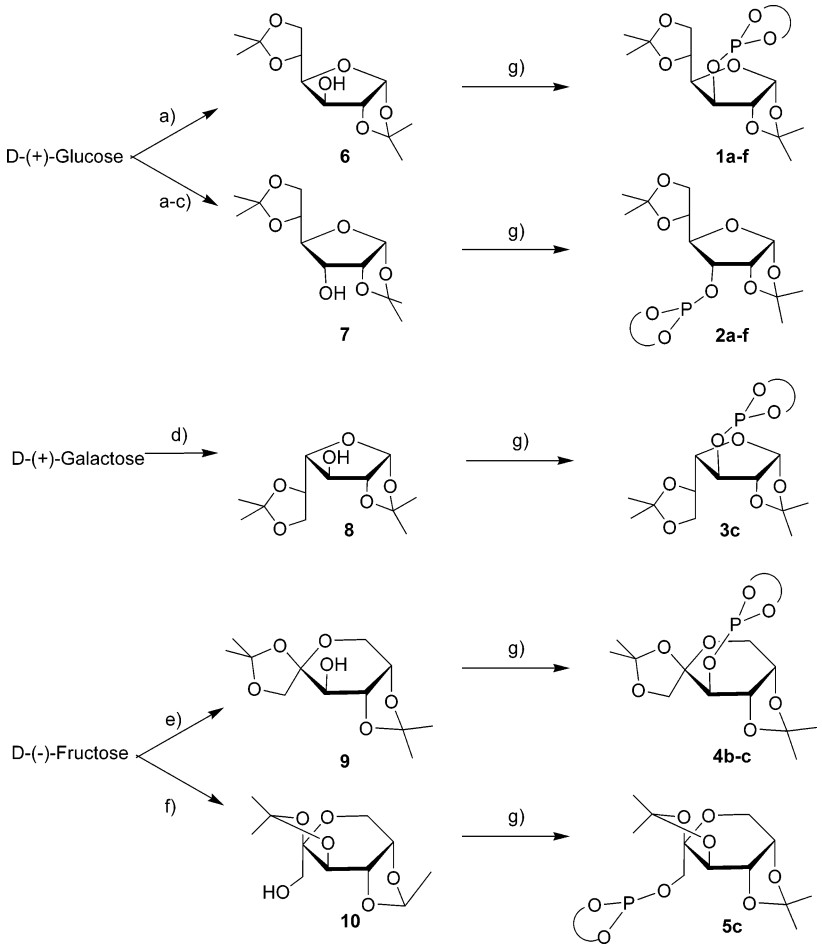
Asymmetric Addition of AlR_3 to Aldehydes. In a first set of experiments, we evaluated the phosphite ligand library (Figure 1)

(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 instance: (a) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889. (b) Reet, M. T.; Goossen, L. J.; Meiswinkel, A.; Paetzold, J.; Jense, J. F. *Org. Lett.* **2003**, *5*, 3099. (c) Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *Org. Lett.* **2003**, *5*, 4137. (d) Huang, H.; Liu, X.; Chen, S.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 2011. (e) Huang, H.; Liu, X.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 693.

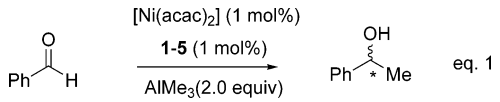
(7) Ligands **1a**,**c**,**e**,**f**, **2e**,**f**, and **4e**,**f** have been previously synthesized, see: (a) Suárez, A.; Pizzano, A.; Fernández, I.; Khiar, N. *Tetrahedron: Asymmetry* **2001**, *12*, 633 and refs 6b,c.

SCHEME 1. Synthesis of Phosphite Ligands 1−5



(a) Acetone, I_2, 6 h.[8] (b) PCC, CH_2Cl_2, NaOAc, 16 h.[9] (c) $NaBH_4$, EtOH, −20 °C to room temperature overnight.[9] (d) DMF, acetone, Dowex H^+, reflux 48 h.[10] (e) $HClO_4$, dimethoxypropane, 0 °C, 6 h.[11] (f) $HClO_4$, dimethoxypropane, rt, 16 h.[12] (g) PCl_3, NEt_3, THF, biaryl alcohol (**a**−**f**), rt.[6c]

in the nickel-catalyzed asymmetric addition of trimethylaluminum to benzaldehyde, which is used as a model substrate (eq 1). The catalytic system was generated in situ by adding the corresponding phosphite ligand to a suspension of the catalyst precursor [Ni(acac)$_2$] (acac = acetylacetonate).



The results, which are summarized in Table 1, indicate that the catalytic performance (activities and enantioselectivities) is highly affected by the configuration of carbon atoms C-3 and C-4, the size of the ring of the sugar backbone, and the substituents of the biaryl moieties.

With ligands **1a**−**f** we studied how the biaryl phosphite moieties affects the product outcome. We found that the substituents at the ortho positions of the biaryl phosphite moiety affected yield, while enantioselectivities were mainly affected by the substituents at the para positions of the biaryl phosphite group. Therefore, for high yields bulky substituents in the ortho position of the biaryl phosphite moiety are necessary (entries 1, 5, and 6 vs 2−4). Regarding enantioselectivities, these are better when *tert*-butyl groups are present in the para position of the biphenyl phosphite moiety (entries 3 vs 2 and 4). The best tradeoff between yield and enantioselectivity was therefore obtained using ligand **1c**.

With ligands **2**, whose configuration at C-3 is opposite those of ligands **1**, we studied the effect of this configuration on the product outcome. The results indicated that there is an influence of this configuration on enantioselectivity (entries 7−12). Therefore, use of ligands **2** with an *R* configuration at C-3 provided lower enantioselectivities than using ligands **1**. Concerning the effect of the biaryl substituents, the results using ligands **2a**−**d** confirm the previous trends observed with ligands **1**. Therefore, yields and enantioselectivities were best using the ligand that contains *tert*-butyl groups at both the ortho and para positions of the biphenyl phosphite moiety (ligand **2c**).

With ligands **1e**, **1f**, **2e** and **2f**, we studied the possibility of a cooperative effect between the stereocenters of the ligand backbone and the configuration of the biaryl phosphite moieties (entries 5, 6, 11, and 12). The results indicated that the matched

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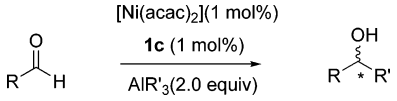
TABLE 1. Selected Results for the Nickel-Catalyzed Asymmetric Addition of $AlMe_3$ to Benzaldehyde Using Phosphite Library (1−5)[a]

entry	ligand	L*/Ni	*t* (h)	% conv.[b]	% yield[c]	% ee[d]
1	1a	2	3	16	15	27 (*R*)
2	1b	2	3	89	80	82 (*S*)
3	1c	2	3	100	85	89 (*S*)
4	1d	2	3	100	87	52 (*S*)
5	1e	2	3	14	11	41 (*R*)
6	1f	2	3	17	12	10 (*R*)
7	2a	2	3	15	12	5 (*R*)
8	2b	2	3	98	95	41 (*R*)
9	2c	2	3	100	100	44 (*R*)
10	2d	2	3	100	86	17 (*R*)
11	2e	2	3	29	22	6 (*R*)
12	2f	2	3	12	3	5 (*S*)
13	3c	2	3	100	60	70 (*R*)
14	4b	2	3	99	58	9 (*S*)
15	4c	2	3	100	64	52 (*S*)
16	5c	2	3	83	52	36 (*R*)
17	1c	2.5	3	100	68	88 (*S*)
18	1c	1	3	100	100	89 (*S*)
19	1c	1	1	100	100	90 (*S*)
20	1c	1	1	100	96	88 (*S*)
21	2c	1	1	100	95	45 (*R*)

[a] Reaction conditions: $T = -20$ °C, [Ni(acac)$_2$] (1 mol %), $AlMe_3$ (2 equiv), substrate (0.25 mmol), solvent THF (2 mL). [b] Percent conversion determined by GC. [c] Percent 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) to Aldehydes Using Ligand 1c[a]



entry	R	R′	% conv.[b]	yield[c]	% ee[d]
1	C_6H_5	Me	100	100	90 (*S*)
2	C_6H_5	Et	100	96	88 (*S*)
3	4-Cl-C_6H_4	Me	100	82	91 (*S*)
4	4-Cl-C_6H_4	Et	100	83	90 (*S*)
5	4-OMe-C_6H_4	Me	93	53	94 (*S*)
6	4-CF_3-C_6H_4	Me	100	95	93 (*S*)
7	4-CF_3-C_6H_4	Et	100	96	94 (*S*)
8	4-Me- C_6H_4	Me	94	84	91 (*S*)
9	4-Me- C_6H_4	Et	98	85	88 (*S*)
10	4-Br-C_6H_4	Me	98	86	92 (*S*)
11	3-Cl-C_6H_4	Me	95	73	74 (*S*)
12	2-Cl-C_6H_4	Me	97	85	41 (*R*)
13[e]	$PhCH_2CH_2$	Me	100	89	25 (*S*)
14[f]	PhCH=CH	Me	97	44	25 (*R*)

[a] Reaction conditions: $T = -20$ °C, [Ni(acac)$_2$] (1 mol %), **1c** (1mol %), AlR'_3 (2 equiv), substrate (0.25 mmol), solvent THF (2 mL). [b] Percent conversion determined by GC after 1 h. [c] Percent yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Cyclodex-B column. [e] **1c** (2 mol %), reaction time 6 h. [f] **1c** (2 mol %), reaction time 5 h.

combination is achieved with ligand **1e**, which has an *S* configuration at carbon atom C-3 and in the biaryl phosphite moiety.

Ligands **3**, whose configuration at C-4 is opposite those of ligands **1**, afforded lower enantioselectivity than the catalytic system Ni/**1** (entry 3 vs 13) but higher than the catalytic system Ni/**2** (entry 9 vs 13). From these results we can conclude that the effect of the configuration of carbon C-3 is more important than the effect of C-4 on the catalytic performance.

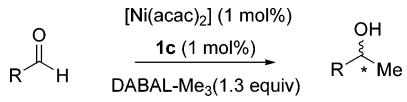
Ligands **4**, which have a pyranoside backbone, provided lower yields and enantioselectivities (up to 52% (*S*)) than their related furanoside ligands **1** (entries 2 and 3 vs 14 and 15).

TABLE 3. Selected Results for the Nickel-Catalyzed Asymmetric Addition of DABAL-Me_3 to Benzaldehyde[a]

entry	ligand	L*/Ni	DABAL (equiv)	*t* (h)	% conv.[b]	% yield[c]	% ee[d]
1	1a	2	1.3	3	75	36	18 (*R*)
2	1b	2	1.3	3	63	35	86 (*S*)
3	1c	2	1.3	3	85	40	87 (*S*)
4	1d	2	1.3	3	73	60	46 (*S*)
5	1e	2	1.3	3	59	37	47 (*R*)
6	1f	2	1.3	3	60	5	0
7	2a	2	1.3	3	74	43	5 (*S*)
8	2b	2	1.3	3	90	51	47 (*S*)
9	2c	2	1.3	3	90	27	58 (*S*)
10	2d	2	1.3	3	70	38	17 (*S*)
11	2e	2	1.3	3	88	38	11 (*S*)
12	2f	2	1.3	3	83	29	4 (*S*)
13	1c	2	0.6	3	61	40	84 (*S*)
14	1c	1	1.3	1.5	97	78	88 (*S*)

[a] Reaction conditions: $T = 5$ °C, Ni(acac)$_2$ (1 mol %), substrate (0.25 mmol), solvent THF (2 mL). [b] Percent conversion determined by GC. [c] Percent yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Cyclodex-B column.

TABLE 4. Selected Results for the Nickel-Catalyzed Asymmetric Addition of DABAL-Me_3 to Aldehydes Using Ligand 1c[a]



entry	R	% conv.[b]	yield[c]	% ee[d]
1	C_6H_5	85	78	88 (*S*)
2	4-Cl-C_6H_4	99	64	91 (*S*)
3	4-OMe-C_6H_4	92	25	78 (*S*)
4	4-CF_3-C_6H_4	100	53	82 (*S*)
5	4-Br-C_6H_4	93	69	90 (*S*)
6	4-Me- C_6H_4	96	68	88 (*S*)
7	3-Cl-C_6H_4	90	58	67 (*S*)
8	2-Cl-C_6H_4	90	62	35 (*R*)
9[e]	PhCH=CH	86	22	30 (*R*)

[a] Reaction conditions: $T = 5$ °C, Ni(acac)$_2$ (1 mol %), **1c** (1mol %), DABAL-Me_3 (1.3 equiv), substrate (0.25 mmol), solvent THF (2 mL). [b] Percent conversion determined by GC after 1.5 h. [c] Percent yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Cyclodex-B column. [e] **1c** (2mol %).

Finally, the most flexible ligand **5**, which has the phosphite moiety attached to a primary carbon, provided the lowest enantioselectivities (entry 16 vs 3, 9, 13, and 15).

With the ligand that provided the best results (ligand **1c**) we next studied the effect of the ligand-to-nickel ratio in the product outcome. Our results show that no excess of ligand is needed for high yields and enantioselectivities (entry 17 vs 3 and 16).[13] Finally, we optimized the reaction time and found complete reaction after 1 h (entry 18 vs 3).

To further investigate the catalytic efficiency of these Ni/**1**−**5** systems, we then tested them in the nickel-catalyzed addition of trialkylaluminum (AlR'_3; R′ = Me or Et) to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 2.

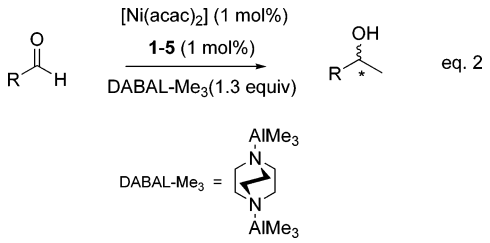
We found that enantioselectivity for $AlMe_3$ addition is hardly affected by the presence of electron-withdrawing or electron-donating groups at the para position of the phenyl group (entries 1, 3, 5, 6, 8, and 10). However, the best yield was achieved using benzaldehyde as substrate, while substrate 4-OMe-Ph gave

(13) At high ligand-to-nickel ratio the disproportionation of benzaldehyde to benzoic acid and benzyl alcohol takes place.

the poorest (entry 1 vs 5). Enantioselectivity of the reaction is also significantly influenced by steric factors. Therefore, enantioselectivities are better when para-substituted aryl aldehydes were used as substrates (entries 3, 11, and 12). We also found that enantioselectivity was more difficulty to control when a more flexible substrate is used (entries 13 and 14).

The results of using triethylaluminum as alkylating reagent indicated that the catalytic performance followed the same trend as for the trimethylaluminum addition (entries 1, 3, 6, and 8 vs 2, 4, 7, and 9).

Asymmetric Addition of DABAL-Me$_3$ to Aldehydes. Recently, Woodward and co-workers reported for the first time the advantages of using DABAL-Me$_3$ as air-stable methylating reagent in the nickel-catalyzed additions to aldehydes.[3e] Encouraged by the excellent results obtained using trialkylaluminum reagents to aldehydes, we decided to also test the phosphite library **1**−**5** in the nickel-catalyzed addition of DABAL-Me$_3$ to aldehydes (eq 2).



The results, which are summarized in Tables 3 and 4, indicate that the catalytic performance (activities and enantioselectivities) follows the same trend as for the trialkylaluminum addition to aldehydes, which is not unexpected because the reactions have a similar mechanism. However, the yields were lower than in trimethylaluminum addition. Again, the catalytic precursor containing the phosphite ligand **1c** provided the best enantioselectivity (87% ee). It is worth noting that in this case the negative effect on yields in the presence of an excess of ligand is more pronounced than when trimethylaluminum was used. Therefore, yields increased almost 100% by reducing the ligand-to-nickel ratio from 2 to 1 (entries 3 vs 14).

Conclusions

A library of readily available monophosphite ligands has been synthesized and applied for the first time in the Ni-catalyzed trialkylaluminum addition to several aldehydes. By carefully designing this library we were able to systematically investigate the effect of varying the sugar backbone, the configurations at carbon C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety. By judicious choice of the ligand components we obtained high enantioselectivities (ee values up to 94%) and high activities, in several aryl aldehydes, with low catalyst loading (1 mol %) and without excess of ligand.

To sum up, the combination of high activities and enantioselectivities with low catalyst loading and the low cost of these phosphite ligands open up a new class of ligands for the enantioselective Ni-catalyzed addition of trialkylaluminum reagents to aldehydes that competes favorably with the best ligands designed for this process.[3]

Experimental Section

General Considerations. All syntheses were performed using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Compounds **6**−**10** were prepared by previously described methods.[8−12] Ligands **1a**,**c**,**e**,**f, 2e**,**f**, and **4e**,**f** have been previously synthesized.[7] 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.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-((3,3′-di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)phosphite)-α-D-glucofuranose (1b). To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **6** (390 mg, 1.5 mmol) in THF (5 mL) was slowly added PCl_3 (132 μL, 1.5 mmol) as a solution in THF (4 mL), and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then cooled to −10 °C, and NEt_3 (1.07 mL, 4.5 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature, maintained under these conditions for 0.25 h, and then cooled to 0 °C. Solid 3,3′-di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diol (0.54 g, 1.5 mmol) was added, and the resulting mixture was allowed to warm to room temperature and stirred overnight. Diethyl ether was added; then the solid was removed by filtration through a pad of Celite, the solvent was removed in vacuo, and the residue was purified by flash chromatography (eluent CH_2Cl_2, R_f: 0.32) to produce 100 mg (11%) of a white solid. ^{31}P NMR (400 MHz, C_6D_6) δ 145.2 ppm. ^{1}H NMR (400 MHz, C_6D_6) δ 1.03 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.34 (s, 3H, CH_3,), 1.39 (s, 3H, CH_3), 1.49 (s, 18H, CH_3, ^{t}Bu), 3.31 (s, 6H, OMe), 4.01 (dd, 1H, H-6′, $^2J_{6'-6}$ = 8.4 Hz, $^2J_{6'-5}$ = 6.0 Hz), 4.10 (dd, 1H, H-6, $^2J_{6-6'}$ = 8.4 Hz, $^3J_{6-5}$ = 5.2 Hz), 4.27 (m, 1H, H-2), 4.44 (dd, 1H, H-4, $^3J_{4-3}$ = 2.4 Hz, $^3J_{4-5}$ = 8.0 Hz), 4.57 (m, 1H, H-5), 5.20 (dd, 1H, H-3, $^3J_{3-4}$ = 2.8 Hz, $^2J_{3-P}$ = 8.0 Hz), 5.83 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.66 (m, 1H, CH═), 6.72 (m, 1H, CH═), 7.14 (m, 2H, CH═). ^{13}C NMR (400 MHz, C_6D_6) δ 25.8 (CH_3), 26.4 (CH_3), 27.2 (CH_3), 27.5 (CH_3), 31.4 (CH_3,^{t}Bu), 31.5 (CH_3,^{t}Bu), 31.6 (CH_3,^{t}Bu), 36.2 (C ^{t}Bu), 36.3 (C ^{t}Bu), 55.4 (d, OCH_3, J_{c-p} = 3.7 Hz), 68.0 (C-6), 73.4 (C-5), 77.6 (C-3), 81.9 (d, C-4, J_{c-p} = 4.6 Hz), 85.0 (C-2), 106.1 (C-1), 112.2 (C), 113.7 (CH═), 114.0 (CH═), 115.2 (CH═), 143.1 (C), 154.1 (C), 155.6 (C), 157.0 (C). Anal. Calcd for $C_{34}H_{47}O_{10}P$: C, 63.15; H, 7.33. Found: C, 63.30; H 7.42.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-((3,3′-di-trimethylsilyl-1,1′-biphenyl-2,2′-diyl) phosphite)-α-D-glucofuranose (1d). Treatment of 3,3′-di-trimethylsilyl-1,1′-biphenyl-2,2′-diol (0.49 g, 1.5 mmol) and **6** (390 mg, 1.5 mmol), as described for compound **1b**, afforded phosphite **1d**, which was purified by flash chromatography (eluent CH_2Cl_2, R_f: 0.61) to produce 210 mg (22%) of a white solid. ^{31}P NMR (400 MHz, C_6D_6) δ 146.0 ppm. ^{1}H NMR (400 MHz, C_6D_6) δ 0.39 (s, 9H, CH_3−Si), 0.40 (s, 9H, CH_3−Si), 0.98 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 4.00 (dd, 1H, H-6′, $^2J_{6'-6}$ = 8.4 Hz, $^3J_{6'-5}$ = 6.0 Hz), 4.10 (m, 2H, H-6, H-2), 4.44 (m, 1H, H-4), 4.56 (m, 1H, H-5), 5.13 (m, 1H, H-3), 5.85 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 7.02 (m, 2H, CH═), 7.16 (m, 2H, CH═), 7.38 (m, 2H, CH═). ^{13}C NMR (400 MHz, C_6D_6) δ 0.4 (CH_3−Si), 25.8 (CH_3), 26.4 (CH_3), 27.1 (CH_3), 27.5 (CH_3), 67.9 (C-6), 73.4 (C-5), 77.4 (C-3), 81.8 (d, C-4, J_{c-p} = 4.6 Hz), 84.9 (C-2), 106.0 (C-1), 109.8 (C), 112.2 (C), 125.5 (CH═), 125.6 (CH═), 130.8 (C), 132.1 (C), 133.1 (CH═), 133.2 (CH═), 135.7 (CH═), 135.8 (CH═). Anal. Calcd for $C_{30}H_{43}O_8PSi_2$: C, 58.23; H, 7.00. Found: C, 58.43; H, 6.98.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-((1,1′-biphenyl-2,2′-diyl)-phosphite)-α-D-allofuranose (2a). Treatment of 1,1′-biphenyl-2,2′-diol (0.28 g, 1.5 mmol) and **7** (390 mg, 1.5 mmol), as described for compound **1b**, afforded phosphite **2a**, which was purified by flash chromatography (eluent CH_2Cl_2, R_f: 0.45) to produce 150 mg (22%) of a white solid. ^{31}P NMR (400 MHz, C_6D_6) δ 139.5 ppm. ^{1}H NMR (400 MHz, C_6D_6) δ 1.16 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.78 (m, 1H, H-6′), 3.93 (m, 1H, H-6), 4.11 (dd, 1H, H-2, $^3J_{2-3}$ = 4.2 Hz, $^3J_{2-1}$ = 3.6 Hz), 4.17 (m, 1H, H-5), 4.34 (m, 1H, H-4), 4.48 (m, 1H, H-3),

5.33 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.94−7.07 (m, 4H, CH═), 7.20 (m, 2H, CH═), 7.37 (m, 2H, CH═). ^{13}C NMR (400 MHz, C_6D_6) δ 25.9 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 27.3 (CH_3), 66.5 (C-6), 75.1 (C-3), 76.5 (C-5), 79.4 (C-4), 80.0 (C-2), 104.7 (C-1), 110.6 (CMe_2) 117.4 (CH═), 122.0 (C), 122.6 (C), 123.0 (CH═), 123.1 (CH═), 125.7 (CH═), 127.8 (CH═), 129.7 (CH═), 130.0 (CH═), 130.3 (C), 130.5 (CH═), 132.3 (CH═), 132.7 (C). Anal. Calcd for $C_{24}H_{27}O_8P$: C, 60.76; H, 5.74. Found: C, 60.82; H, 5.89.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-((3,3′-di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)phosphite)-α-D-allofuranose (2b). Treatment of 3,3′-di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diol (0.54 g, 1.5 mmol) and **7** (390 mg, 1.5 mmol), as described for compound **1b**, afforded phosphite **2b**, which was purified by flash chromatography (eluent CH_2Cl_2, R_f: 0.30) to produce 180 mg (19%) of a white solid. ^{31}P NMR (400 MHz, C_6D_6) δ 144.1 ppm. ^{1}H NMR (400 MHz, C_6D_6) δ 1.14 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.42 (s, 3H, CH_3,), 1.49 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 3.33 (s, 3H, OMe), 3.36 (s, 3H, OMe), 3.76 (m, 1H, H-6′), 3.82 (m, 1H, H-6), 4.03 (m, 1H, H-2), 4.17 (m, 1H, H-5), 4.41 (m, 1H, H-4), 4.46 (m, 1H, H-3), 5.42 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.71 (m, 2H, CH═), 7.15 (m, 2H, CH═). ^{13}C NMR (400 MHz, C_6D_6) δ 26.1 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 27.4 (CH_3), 31.6 (CH_3,^{t}Bu), 35.9 (C), 36.0 (C), 55.4 (OCH_3), 55.5 (OCH_3), 66.0 (C-6), 75.3 (C-3), 76.7 (C-5), 79.4 (d, C-4, J_{c-p} = 3.1 Hz), 79.6 (C-2), 104.8 (C-1), 110.1 (C), 113.4 (CH═), 113.6 (C), 114.0 (CH═), 115.0 (CH═), 142.8 (C), 143.7 (C), 143.8 (C), 156.9 (C). Anal. Calcd for $C_{34}H_{47}O_{10}P$: C, 63.15; H, 7.33. Found: C, 63.08; H, 7.42.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-((3,3′-5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl) phosphite)-α-D-allofuranose (2c). Treatment of 3,3′;5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diol (0.62 g, 1.5 mmol) and **7** (390 mg, 1.5 mmol), as described for compound **1b**, afforded phosphite **2c**, which was purified by flash chromatography (eluent CH_2Cl_2, R_f: 0.41) to produce 110 mg (12%) of a white solid. ^{31}P NMR (400 MHz, $CDCl_3$) δ 143.2 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.35 (s, 18H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 3H, CH_3), 3.62 (m, 1H, H-6′), 3.77 (m, 1H, H-6), 3.95 (m, 1H, H-2), 4.09 (m, 1H, H-4), 4.14 (m, 1H, H-5), 4.33 (m, 1H, H-3), 5.54 (d, 1H, H-1, $^3J_{1-2}$ = 3.2 Hz), 7.12 (m, 1H, CH═), 7.18 (m, 1H, CH═), 7.43 (m, 2H, CH═). ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.6 (CH_3), 26.4 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 31.1 (CH_3,^{t}Bu), 31.2 (CH_3,^{t}Bu), 31.4 (CH_3,^{t}Bu), 31.5 (CH_3,^{t}Bu), 34.6 (C), 34.7 (C), 35.4 (C), 65.1 (C-6), 73.5 (C-3), 75.3 (C-5), 77.7 (d, C-4, J_{c-p} = 3.9 Hz), 78.5 (C-2), 103.6 (C-1), 109.6 (C), 113.1 (C), 124.0 (CH═), 124.2 (CH═), 125.3 (CH═), 126.2 (CH═), 126.8 (CH═), 128.2 (CH═), 129.0 (CH═), 140.2 (C), 140.4 (C), 133.5 (C), 133.7 (C), 146.6 (C), 146.7 (C). Anal. Calcd for $C_{40}H_{59}O_8P$: C, 68.74; H, 8.51. Found: C, 68.89; H, 8.63.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-((3,3′-di-trimethylsilyl-1,1′-biphenyl-2,2′-diyl) phosphite)-α-D-allofuranose (2d). Treatment of 3,3′-di-trimethylsilyl-1,1′-biphenyl-2,2′-diol (0.49 g, 1.5 mmol) and **7** (390 mg, 1.5 mmol), as described for compound **1b**, afforded phosphite **2d**, which was purified by flash chromatography (eluent CH_2Cl_2, R_f: 0.68) to produce 180 mg (20%) of a white solid. ^{31}P NMR (400 MHz, C_6D_6) δ 143.4 ppm. ^{1}H NMR (400 MHz, C_6D_6) δ 0.43 (s, 9H, CH_3−Si), 0.45 (s, 9H, CH_3−Si), 1.11 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.66 (m, 2H, H-6′, H-2), 3.76 (m, 1H, H-6), 4.12 (m, 1H, H-5), 4.37 (m, 2H, H-3, H-4), 5.33 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 7.02 (m, 2H, CH═), 7.18 (m, 2H, CH═), 7.40 (m, 2H, CH═). ^{13}C NMR (400 MHz, C_6D_6) δ −0.1 (CH_3−Si), 25.7 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 65.4 (C-6), 74.6 (d, C-4, J_{c-p} = 8.4 Hz), 76.4 (C-5), 78.5 (d, C-3, J_{c-p} = 3.0 Hz), 78.9 (C-2), 104.2 (C-1), 113.2 (C), 124.9 (CH═), 125.0 (CH═), 130.3 (C), 130.5 (C), 132.2 (CH═),132.8 (CH═), 135.1 (CH═),135.3 (CH═). Anal. Calcd for $C_{30}H_{43}O_8PSi_2$: C, 58.23; H, 7.00. Found: C, 58.84; H, 7.17.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-((3,3′-5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite)-α-D-galactofuranose (3c). Treatment of 3,3′;5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diol (0.62 g, 0.5 mmol) and **8** (390 mg, 0.5 mmol), as described for compound **1b**, afforded phosphite **3c**, which was purified by flash chromatography (eluent CH_2Cl_2, R_f: 0.55) to produce 80 mg (23%) of a white solid. ^{31}P NMR (400 MHz, $CDCl_3$) δ 137.6 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.34 (s, 18H, CH_3, ^{t}Bu), 1.37 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.47 (s, 18H, CH_3, ^{t}Bu), 3.47 (m, 1H, H-6′), 3.91 (m, 2H, H-5, H-6), 4.19 (d, 1H, H-4, $^3J_{4-3}$ = 8 Hz), 4.27 (dd, 1H, H-2, $^3J_{2-1}$ = 5.2 Hz, J_{2-P} = 4.8 Hz), 4.55 (dd, 1H, H-3, $^3J_{3-4}$ = 8 Hz, J_{3-P} = 5.2 Hz), 5.47 (d, 1H, H-2, $^2J_{2-1}$ = 5.2 Hz), 7.14 (m, 2H, CH═), 7.41 (m, 2H, CH═). ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.6 (CH_3), 25.1 (CH_3), 26.2 (CH_3), 26.3 (CH_3), 31.2 (CH_3,^{t}Bu), 31.3 (CH_3,^{t}Bu), 31.7 (CH_3,^{t}Bu), 31.8 (CH_3,^{t}Bu), 34.8 (C), 35.5 (C), 35.6 (C), 62.9 (d, C-6, J_{c-p} = 2.2 Hz), 67.2 (d, C-5, J_{c-p} = 2.3 Hz), 70.6 (C-4), 70.7 (C-2), 70.8 (C-3), 96.4 (C-1), 108.8 (C), 109.6 (C), 124.4 (CH═), 124.4 (CH═), 125.5 (CH═), 126.7 (CH═), 128.5 (C), 129.2 (C), 129.3 (C), 133.3 (C), 138.3 (C), 140.0 (C), 140.1 (C), 146.5 (C), 146.6 (C). Anal. Calcd for $C_{40}H_{59}O_8P$: C, 68.74; H, 8.51. Found: C, 68.98; H, 8.62.

2,3:5,6-Di-*O*-isopropylidene-4-*O*-((3,3′-di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)phosphite)-β-D-fructopyranose (4b). Treatment of 3,3′-di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diol (0.54 g, 1.5 mmol) and **9** (390 mg, 1.5 mmol), as described for compound **1b**, afforded phosphite **4b**, which was purified by flash chromatography (eluent CH_2Cl_2, R_f: 0.55) to produce 270 mg (29%) of a white solid. ^{31}P NMR (400 MHz, C_6D_6) δ 149.8 ppm. ^{1}H NMR (400 MHz, C_6D_6) δ 1.13 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 3H, CH_3), 1.60 (s, 12H,, CH_3, CH_3 ^{t}Bu), 3.32 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.80 (m, 1H, H-2), 3.94 (m, 2H, H-1, H-1′), 4.15 (d, 1H, H-6′, $^2J_{6'-6}$ = 11.2 Hz), 4.48 (m, 1H, H-3), 4.56 (m, 1H, H-4), 4.65 (d, 1H, H-6, $^2J_{6-6'}$ = 11.6 Hz), 6.68 (m, 2H, CH═), 7.14 (m, 2H, CH═). ^{13}C NMR (400 MHz, C_6D_6) δ 26.1 (CH_3), 26.8 (CH_3), 27.8 (CH_3), 28.9 (CH_3), 31.3 (CH_3,^{t}Bu), 31.4 (CH_3,^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.8 (C), 36.1 (C), 55.4 (OCH_3), 55.5 (OCH_3), 60.7 (C-1), 71.8 (C-6), 72.9 (d, C-4, J_{c-p} = 9.2 Hz), 74.8 (C-2), 77.2 (C-3), 104.9 (C-5), 109.9 (CMe_2), 112.9 (CMe_2), 113.5 (CH═), 113.7 (CH═), 115.1 (CH═), 115.3 (CH═), 126.0 (C), 129.6 (C), 134.2 (C), 135.6 (C), 140.0 (C), 143.1 (C), 156.6 (C), 157.0 (C). Anal. Calcd for $C_{34}H_{47}O_{10}P$: C, 63.15; H, 7.33. Found: C, 63.44; H, 7.51.

2,3:5,6-Di-*O*-isopropylidene-4-*O*-((3,3′-5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl) phosphite)-β-D-fructopyranose (4c). Treatment of 3,3′;5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diol (0.62 g, 1.5 mmol) and **9** (390 mg, 1.5 mmol), as described for compound **1b**, afforded phosphite **4c**, which was purified by flash chromatography (eluent CH_2Cl_2, R_f: 0.43) to produce 290 mg (28%) of a white solid. ^{31}P NMR (400 MHz, C_6D_6) δ 151.7 ppm. ^{1}H NMR (400 MHz, C_6D_6) δ 1.05 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 3H, CH_3), 1.64 (s, 12H, CH_3, CH_3 ^{t}Bu), 3.80 (m, 1H, H-2), 3.94 (m, 2H, H-1, H-1′), 4.12 (d, 1H, H-6′,$^2J_{6'-6}$ = 9.6 Hz), 4.50 (m, 1H, H-3), 4.54 (m, 1H, H-4), 5.58 (d, 1H, H-6, $^2J_{6-6'}$ = 9.6 Hz), 7.28 (m, 1H, CH═), 7.33 (m, 1H, CH═), 7.55 (m, 2H, CH═).^{13}C NMR (400 MHz, C_6D_6) δ 26.2 (CH_3), 26.8 (CH_3), 28.0 (CH_3), 29.0 (CH_3), 31.5 (CH_3,^{t}Bu), 31.6 (CH_3,^{t}Bu), 31.9 (CH_3,^{t}Bu), 32.0 (CH_3,^{t}Bu), 32.1 (CH_3,^{t}Bu), 34.9 (C), 35.0 (C), 35.9 (C), 36.1 (C), 60.6 (C-1), 71.8 (C-6), 72.8 (d, C-4, J_{c-p} = 8.3 Hz), 74.8 (C-2), 77.2 (C-3), 104.9 (C-5), 109.9 (CMe_2), 112.9 (CMe_2), 124.5 (CH═), 124.9 (CH═), 126.0 (C), 127.3 (CH═), 127.6 (CH═), 133.7 (C), 134.9 (C), 138.2 (C), 140.9 (C), 141.0 (C), 146.8 (C), 147.3 (C). Anal. Calcd for $C_{40}H_{59}O_8P$: C, 68.74; H, 8.51. Found: C, 68.69; H, 8.62.

2,3:4,5-Di-*O*-isopropylidene-6-*O*-((3,3′-5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite)-β-D-fructopyranose (5c). Treatment of 3,3′;5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diol (0.62 g, 1.5 mmol) and **10** (390 mg, 1.5 mmol), as described for compound **1b**, afforded phosphite **5c**, which was purified by flash chromatography (eluent toluene/NEt_3 (100:1), R_f: 0.55) to produce 140 mg (15%) of a white solid. ^{31}P NMR (400 MHz, C_6D_6) δ 135.9

ppm. ^{1}H NMR (400 MHz, C_6D_6) δ 0.70 (s, 3H, CH_3), 0.83 (s, 9H, CH_3, ^{t}Bu), 0.86 (s, 9H, CH_3, ^{t}Bu), 0.95 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.20 (s, 9H, CH_3, ^{t}Bu), 1.21 (s, 9H, CH_3, ^{t}Bu), 3.14 (d, 1H, H-6′, $^1J_{6'-6}$ = 16.8 Hz), 3.31 (m, 2H, H-6, H-4), 3.60 (m, 1H, H-1′), 3.94 (m, 1H, H-1), 4.00 (dd, 1H, H-3, $^3J_{3-2}$ = 14.0 Hz, $^3J_{3-4}$ = 3.6 Hz), 4.18 (d, 1H, H-2, $^2J_{2-1}$ = 3.6 Hz), 6.80 (d, 1H, CH═), 6.90 (d, 2H, CH═), 7.16 (m, 1H, CH═). ^{13}C NMR (400 MHz, C_6D_6) δ 24.7 (CH_3), 26.1 (CH_3), 26.6 (CH_3), 27.1 (CH_3), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 34.9 (C), 35.0 (C), 36.0 (C), 61.8 (C-6), 64.9 (C-1), 70.4 (C-2), 71.0 (C-3), 71.8 (C-4), 102.9 (C-5), 109.0 (CMe_2), 109.3 (CMe_2), 124.7 (CH═), 124.8 (CH═), 126.0 (C), 127.3 (CH═), 128.6 (CH═), 128.9 (C), 129.6 (C),133.9 (C), 140.6 (C), 140.8 (C), 147.1 (C), 147.3 (C). Anal. Calcd for $C_{40}H_{59}O_8P$: C, 68.74; H, 8.51. Found: C, 68.99; H, 8.71.

General Procedure for the Ni-Catalyzed Enantioselective 1,2-Addition of Trialkylaluminum 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 an argon atmosphere at −20 °C for 10 min. Neat aldehyde (0.25 mmol) was then added, and trialkylaluminum (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.

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 an argon atmosphere at 5 °C for 10 min. Neat aldehyde (0.25 mmol) was then added, and trialkylaluminum (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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