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Furanoside phosphite–phosphoroamidite: new ligand class for the asymmetric nickel-catalyzed trialkylaluminium addition to aldehydes

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ABSTRACT

We have described the first successful application of bidentate ligands in the asymmetric Ni-catalyzed trialkylaluminium addition to several aldehydes. The ligands are prepared from inexpensive D-(+)-xylose and D-(+)-glucose and have the advantage of carbohydrate and phosphite/phosphoroamidite moieties. After systematic variation of the position of the phosphoroamidite group at either C5 or C-3, the configuration of C-3 and the substituents in the biaryl phosphite/phosphoroamidite moieties, enantioselectivities up to 84% and high yields were obtained in the Ni-catalyzed trialkylaluminium addition to several aldehydes.

One of the main goals of modern synthetic organic chemistry is the catalytic enantioselective formation of carbon–carbon bonds. In this context, the 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, trialkylaluminium compounds are more interesting than other organometallic reagents because they can be economically obtained on an industrial scale from aluminium hydride and olefins.[2] Despite this advantage they are little used.[3,4] 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 %).[3] The second type are 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 %).[4] For the latter nickel catalysts, only two types of ligands have been successfully applied. The first application was reported by Woodward and co-workers using monophosphoroamidite ligands as the chiral source.[4a,b] The second application used a series of sugar-based monophosphite ligands.[4c] To further expand the range of ligands and encouraged by the success of phosphite and phosphoroamidite ligands in this process, we report here the application of phosphite–phosphoroamidite ligands (**L1**–**L4a–e**, Fig. 1) in the Ni-catalyzed 1,2-addition of trialkylaluminium to aldehydes.[5,6] These ligands combine a priori the advantage of both types of successful ligands. They also have the advantages of carbohydrates and phosphite/phosphoroamidite ligands: they are cheap, easily constructed with modules and highly resistant to oxidation.[7] With these ligands, then, we investigated the effect of systematically varying the position of the phosphoroamidite group at either C-5 (ligands **L1** and **L2**) or C-3 (ligands **L3** and **L4**) of the furanoside backbone, the configuration at C-3 of the furanoside backbone and the substituents in the biaryl phosphite/phosphoroamidite moieties (**a–e**). By carefully selecting the ligand parameters, we achieved high enantioselectivities. To the best of our knowledge this is the first successful application of a bidentate ligand in this process.

To make the initial evaluation of this new type of ligands (**L1**–**L4a–e**), we chose the nickel-catalyzed asymmetric addition of trimethylaluminium to benzaldehyde, which was used as a model substrate (Table 1). The catalytic system was generated in situ by adding the corresponding phosphite–phosphoroamidite ligand to a suspension of the catalyst precursor [Ni(acac)$_2$] (acac = acetylacetonate).[8] The results indicate that enantioselectivity is affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3 and the substituents in the biaryl phosphite/phosphoroamidite moieties (**a–e**).

We first studied the effect of the position of the phosphoroamidite group at either C-5 (ligands **L1** and **L2**) or C-3 (ligands **L3** and **L4**) of the furanoside backbone and the configuration of C-3. We observed a co-operative effect between the position of the phosphoroamidite group and the configuration of carbon atom C-3 of the furanoside backbone (Table 1, entries 1, 3, 5 and 10). Therefore, the

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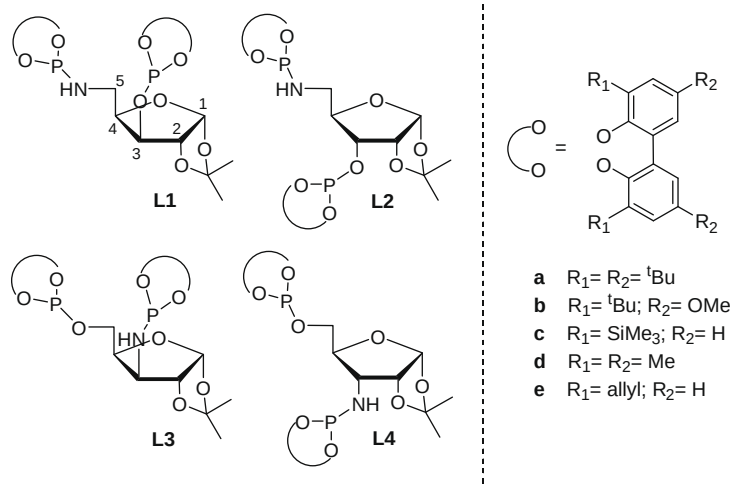
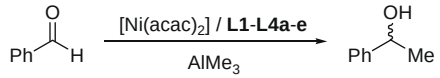


Figure 1. Carbohydrate-based phosphite–phosphoroamidite ligands **L1**–**L4a–e**.

Table 1
Selected results for the nickel-catalyzed asymmetric addition of $AlMe_3$ to benzaldehyde using ligands **L1**–**L4a–e**[a]



Entry	Ligand	L/Ni	Conv.[b] (%)	Yield[c] (%)	ee[d] (%)
1	**L1a**	1	53	52	4 (*R*)
2	**L1b**	1	67	67	15 (*R*)
3	**L2a**	1	66	66	56 (*R*)
4	**L2b**	1	98	95	20 (*R*)
5	**L3a**	1	100	99	84 (*R*)
6	**L3b**	1	95	95	6 (*S*)
7	**L3c**	1	34	30	11 (*R*)
8	**L3d**	1	68	64	11 (*S*)
9	**L3e**	1	15	15	4 (*S*)
10	**L4a**	1	100	98	25 (*S*)
11	**L4b**	1	90	90	36 (*S*)
12	**L4c**	1	86	84	17 (*S*)
13	**L3a**	2	100	100	84 (*R*)
14	**L3a**	0.5	100	100	76 (*R*)

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

matched combination is achieved with ligands **L3**, the phosphoroamidite moiety of which is attached to C-3 and an *S* configuration of carbon atom C-3 in the tetrahydrofuran ring (Table 1, entry 5).

The effect of the substituents in the biaryl phosphite/phosphoroamidite moieties was studied using ligands **L1–L4a–e** (Table 1). The results indicate that bulky substituents need to be present at both *ortho* and *para* positions of the biaryl moieties if enantioselectivities are to be high. Therefore, ligands **L1**–**L4a** provide higher enantioselectivites than ligands **L1**–**L4b–e** (Table 1, entries 1, 3, 5 and 10 vs 2, 4, 6–9, 11 and 12).

We also used ligand **L3a** to study the effect of the ligand-to-nickel ratio on the product outcome. Our results show that no excess of ligand is needed for yields and enantioselectivities to be high (Table 1, entries 5 vs 13 and 14).

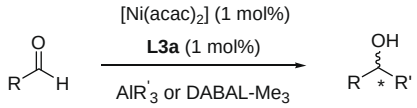
In summary, the result was the best with ligand **L3a** (Table 1, entry 5, ees up to 84%), which contains the optimal combination of ligand parameters (position of the phosphoroamidite group, configuration at C-3 of the furanoside backbone and the substituents in the biaryl phosphite/phosphoroamidite moieties). These results clearly show the efficiency of using highly modular scaffolds in the ligand design.

To further investigate the catalytic efficiency of these Ni/**L1**–**L4a–e** systems, we tested them 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 negatively affected by the presence of electron-donating groups at the *para* position of the phenyl group (Table 2, entry 1 vs 3, 5 and 8). However, the presence of electron-withdrawing groups at the *para* position has little effect on enantioselectivity (Table 2, entry 6). The enantioselectivity of the reaction is also negatively influenced by steric factors (Table 2, entries 9 and 10).

The results of using triethylaluminium as the alkylating reagent indicated that the catalytic performance follows the same trend as for the trimethylaluminium addition. The enantioselectivities, however, were lower (Table 2, entries 2, 4 and 7).

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 **L3a**[a]



Entry	R	R′	Conv.[b] (%)	Yield[c] (%)	ee[d] (%)
1	C_6H_5	Me	100	99	84 (*R*)
2	C_6H_5	Et	95	92	69 (*R*)
3	4-CH_3–C_6H_4	Me	100	98	79 (*R*)
4	4-CH_3–C_6H_4	Et	98	94	53 (*R*)
5	4-OMe–C_6H_4	Me	98	93	67 (*R*)
6	4-CF_3–C_6H_4	Me	100	96	82 (*R*)
7	4-CF_3–C_6H_4	Et	100	93	68 (*R*)
8	4-F–C_6H_4	Me	99	94	67 (*R*)
9	3-OMe–C_6H_4	Me	100	96	53 (*R*)
10	2-OMe–C_6H_4	Me	65	63	0
11[e]	C_6H_5	Me	86	79	82 (*R*)
12[e]	4-CH_3–C_6H_4	Me	82	80	76 (*R*)
13[e]	4-CF_3–C_6H_4	Me	92	85	80 (*R*)

[a] Reaction conditions: $T = -20$ °C, $[Ni(acac)_2]$ (1 mol %), **L3a** (1 mol %), AlR'_3 (2 equiv), substrate (0.25 mmol), THF (2 mL).
[b] Percentage conversion determined by GC after 1 h.
[c] Percentage 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 and co-workers reported for the first time the advantages of using DABAL–Me_3 as an air-stable methylating reagent in nickel-catalyzed additions to aldehydes.[4a] 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 11–13).

In summary, we have described the first successful application of bidentate ligands in the asymmetric Ni-catalyzed trialkylaluminium addition to several aldehydes. These phosphite–phosphoroamidite ligands have the advantage that they are easily prepared in a few steps from commercial D-xylose and D-glucose, inexpensive natural chiral feedstocks. In addition, their furanoside backbone and biaryl moieties can be easily tuned so that their effect on catalytic performance can be explored. By carefully selecting the ligand components, we obtained high activities and enantioselectivities. These results open up a new class of ligands (bidentated phosphite–phosphoroamidite) for the nickel-catalyzed trialkylaluminium addition to aldehydes. Mechanistic studies and further modifications in both the sugar backbone and the functional groups are currently being made.

Acknowledgements

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References and notes

1. Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757.
2. Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; Wiley: New York, 1988.
3. (a) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc.* **1997**, *119*, 4080; (b) Pagenkopf, B. L.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 9593; (c) Lu, J.-F.; You, J.-S.; Gau, H.-M. *Tetrahedron: Asymmetry* **2000**, *11*, 2531; (d) You, J.-S.; Hsieh, S.-H.; Gau, H.-M. *Chem. Commun.* **2001**, 1546.
4. (a) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2232; (b) Biswas, K.; Chapron, A.; Cooper, T.; Fraser, P. K.; Novak, A.; Prieto, O.; Woodward, S. *Pure Appl. Chem.* **2006**, *78*, 511; (c) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *J. Org. Chem.* **2006**, *71*, 8159; (d) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *Inorg. Chim. Acta* **2008**, *361*, 1381.
5. Ligands **L1**-**L4a–c** have been successfully applied in the Pd-catalyzed allylic substitution reaction and in the Rh-catalyzed hydrogenation. See: (a) Diéguez, M.; Ruiz, A.; Claver, C. *Chem. Commun.* **2001**, 2702; (b) Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2827; (c) Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49; (d) Raluy, E.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* doi:10.1002/adsc.200900073.
6. The new ligands **L3d** and **L3e** were prepared following the same procedure as for the preparation of **L1**–**L4a–c**. Ligand **L3d**: yield: 0.42 g, 57%. ^{31}P NMR (C_6D_6), δ: 136.7 (s), 144.2 (s). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.07 (s, 6H, CH_3), 2.08 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.29 (s, 6H, CH_3), 2.32 (s, 3H, CH_3), 3.03 (m, 1H, NH), 3.79 (m, 1H, H-3), 4.16 (m, 1H, H-5), 4.23 (m, 2H, H-4, H-5′), 4.32 (d, 1H, H-2, $^3J_{1-2}$ = 4.0 Hz), 5.59 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.7–7.2 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 17.1 (CH_3), 17.2 (CH_3), 17.3 (CH_3), 21.2 (CH_3), 26.8 (CH_3), 27.2 (CH_3), 58.2 (d, C-3, J_{C-P} = 6.8 Hz), 63.8 (C-5), 79.3 (C-4), 87.0 (C-2), 105.0 (C-1), 112.1 (CMe_2), 126.0 (CH=), 128.9 (CH=), 129.7 (CH=),130.3 (C), 130.4 (C), 130.5 (C), 131.6 (CH=), 131.8 (CH=), 132.3 (CH=), 133.8 (C), 134.1 (C), 134.3 (C), 147.1 (C), 147.2 (C), 147.3 (C), 147.5 (C). Anal. Calcd for $C_{40}H_{45}NO_8P_2$: C, 65.84; H, 6.22; N, 1.92. Found: C, 65.76; H, 6.19; N, 1.90. Ligand **L3e**: yield: 0.39 g, 50%. ^{31}P NMR (C_6D_6), δ: 142.3 (s), 145.2 (s). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 3.11 (m, 1H, NH), 3.43 (m, 1H, H-3), 3.58 (m, 5H, H-4, CH_2), 4.08 (m, 1H, H-5), 4.19 (m, 2H, H-4, H-5′), 4.42 (d, 1H, H-2, $^3J_{1-2}$ = 3.6 Hz), 5.09 (m, 4H, CH_2=), 5.48 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 5.94 (m, 2H, CH=), 6.8–7.2 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 26.8 (CH_3), 27.3 (CH_3), 35.0 (CH_2), 35.1 (CH_2), 35.3 (CH_2), 35.6 (CH_2), 53.6 (d, C-3, J_{C-P} = 7.2 Hz), 63.9 (d, C-5, J_{C-P} = 3.6 Hz), 80.6 (C-4), 85.6 (C-2), 104.9 (C-1), 112.5 (CMe_2), 116.7 (CH_2=), 116.8 (CH_2=), 125.6 (CH=), 125.9 (CH=), 129.0 (CH=) 129.4 (CH=), 129.6 (CH=), 130.3 (CH=), 132.6 (C), 132.8 (C), 133.2 (C), 136.9 (CH = allyl), 137.7 (CH = allyl), 137.9 (CH = allyl), 138.1 (CH = allyl), 148.7 (C), 149.1 (C), 149.3 (C). Anal. Calcd for $C_{44}H_{45}NO_8P_2$: C, 67.95; H, 5.83; N, 1.80. Found: C, 67.99; H, 5.86; N, 1.81.
7. See for instance: (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346; (b) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; (c) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165; (d) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957; (e) Pàmies, O.; Diéguez, M.; Ruiz, A.; Claver, C. *Chemistry Today* **2004**, 12; (f) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. In *Methodologies in Asymmetric Catalysis*; Malhotra, S. V., Ed.; American Chemical Society: Washington DC, 2004; (g) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113; (h) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem.* **2007**, 4621; (i) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267; (j) Börner, A. *Phosphorous Ligands in Asymmetric Catalysis*; Wiley-VCH: Weinheim, 2008.
8. In a typical experiment: [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.