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Sugar-based phosphite and phosphoroamidite ligands for the Cu-catalyzed asymmetric 1,4-addition to enones

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ABSTRACT

A modular sugar-based phosphoroamidite **L1**–**L5a**–**g** and phosphite **L6**–**L9a**–**g** ligand library was tested in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of β-substituted (cyclic and linear) and β,β′-disubstituted (cyclic) enones. The selectivity depended strongly on the configuration of carbon atom C-3, the size of the sugar backbone ring, the flexibility of the ligand backbone, the substituents and configurations in the biaryl phosphoroamidite moieties **a**–**g**, the type of functional group attached to the ligand backbone and the substrate structure. Therefore, by carefully selecting the ligand parameters, enantioselectivities of up to 60% for cyclic substrates and 72% for linear ones were achieved.

1. Introduction

Nowadays, asymmetric copper-catalyzed conjugate addition is a well-developed methodology for creating C–C bonds stereoselectivity.[1] The last decade has seen important breakthroughs in what is possible in the area of catalytic asymmetric 1,4-addition of alkyl organometallic nucleophiles to enones. Most of the successful asymmetric versions of this chemistry have made use of diorganozinc reagents, particularly $ZnEt_2$, a trend started by Alexakis (Cu-catalysis) and Soai (Ni-catalysis).[2] Viable ligand classes are now available that give >90% ee for the addition of diorganozinc to several types of cyclic and chalcone substrates.[1] Phosphites and phosphoroamidites based on biaryl moieties are amongst the most efficient ligands.[1j,k,3] Despite all these advances, there have been relatively few publications describing the highly enantioselective addition of organometallics to linear aliphatic enones or the use of trialkylaluminium reagents as an alternative to organozincs.[4] Additionally, trialkylaluminium reagents allow Cu-catalyzed 1,4-addition to very challenging substrates (i.e., β,β′-disubstituted enones), which are inert to organozinc methodologies.[1j,4h,k] This justifies expanding the range of ligands for the Cu-catalyzed addition of organoaluminium reagents to enones, in particularly to linear aliphatic and β,β′-disubstituted enones. Carbohydrates are particularly useful for this purpose because they are inexpensive and because their modular constructions are easy.[5] In this context and encouraged by the success of monophosphoroamidite ligands in this process, we herein report the use of a highly modular sugar-based monophosphoroamidite ligand library (Fig. 1, **L1**–**L5a**–**g**) in the Cu-catalyzed asymmetric 1,4-addition of organometallic reagents to cyclic and linear enones. We also compare the effectiveness of this phosphoroamidite ligand library with the results obtained using related monophosphite ligands (Fig. 1, **L6**–**L9a**–**g**).[6] To do so, we have also expanded our previous work on monophosphite ligands **L6**–**L9a**–**g** to other challenging classes of substrates (i.e., nitroolefins and β,β′-disubstituted enones). Using these ligands, we fully investigated the effects of systematically varying the configuration of the carbon atom C-3 (ligands **L1**, **L2**, **L6** and **L7**), the size of the sugar backbone ring (ligands **L3** and **L8**), the flexibility of the ligand backbone (ligands **L4**, **L5** and **L9**), the substituents and configurations in the biaryl phosphoroamidite moieties **a**–**g** and the type of functional group attached to the ligand backbone (X = O or NH).

2. Results and discussion

2.1. Ligand synthesis

The new phosphoroamidite ligands **L2b**–**e** and **L4**–**L5b**–**e** were synthesized very efficiently in one step from the corresponding sugar amines, which were prepared on a large scale from D-glucose, D-fructose and D-galactose, as previously described (Scheme 1).[7] Therefore, the reaction of the corresponding amine with 1 equiv of the desired in situ formed phosphorochloridite in the presence of pyridine afforded the desired ligands.

The new ligands **L2a**–**e** and **L4**–**L5d**–**e** were purified on neutral alumina under an atmosphere of argon and were isolated as white solids or colourless viscous liquids. They were stable at room temperature and very stable to hydrolysis. Elemental analyses agreed

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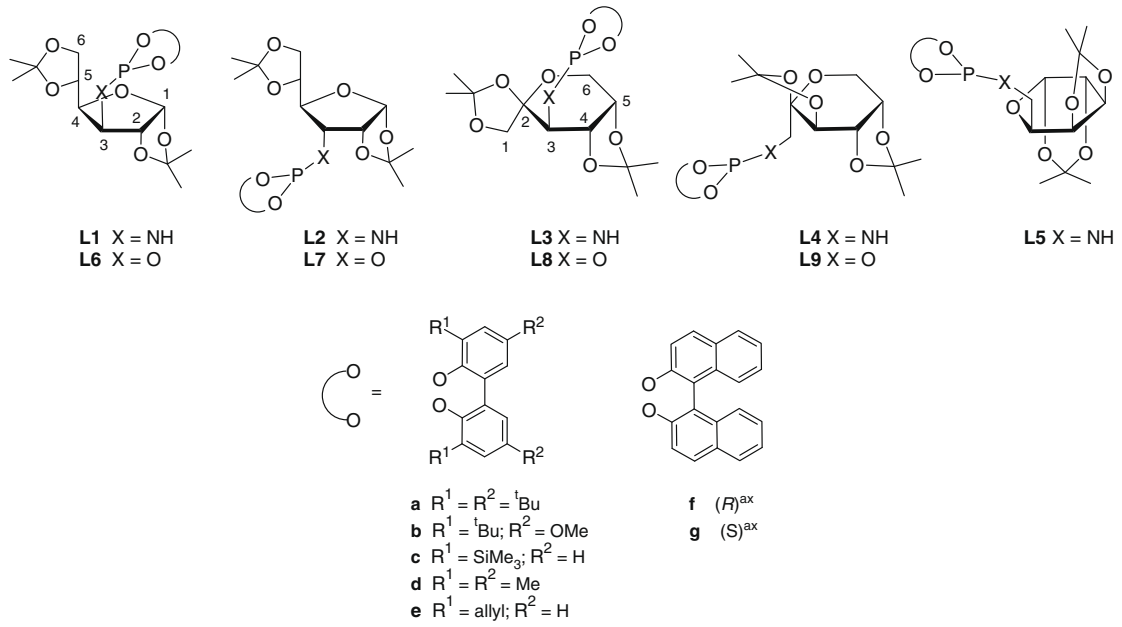
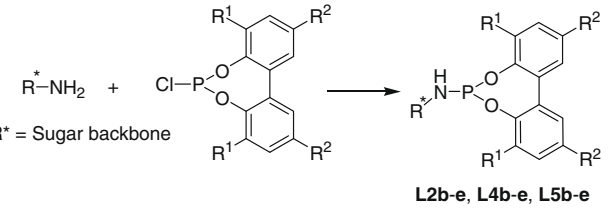


Figure 1. Phosphite and phosphoroamidite ligands **L1**–**L9a**–**g**.



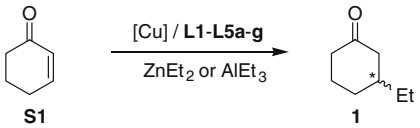
Scheme 1. Synthesis of the new phosphoroamidite ligands **L2b**–**e** and **L4**–**L5b**–**e**.

with the assigned structures. The ^{1}H and ^{13}C NMR spectra were as expected for these C_1 ligands. Two signals for each compound were observed in the ^{31}P NMR spectrum (see Section 4). Rapid ring inversions (atropoisomerization) in the biphenyl-phosphorus moieties **b**–**e** occurred on the NMR time scale instead of the expected diastereoisomers, which were not detected by low-temperature phosphorus NMR.[8]

2.2. Asymmetric conjugate 1,4-addition to cyclic enones

2.2.1. Asymmetric conjugated 1,4-addition of $ZnEt_2$ and $AlEt_3$ to cyclohexenone S1

In the first set of experiments, we tested the new phosphoroamidite ligands **L1**–**L5a–g** in the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone **S1** (Eq. 1). The latter was chosen as a substrate because this reaction has already been performed with a wide range of ligands with several donor groups, thus enabling the efficiency of the various ligands systems to be directly compared.[1]



(1)

The catalytic system was generated in situ by adding the corresponding ligand to a suspension of catalyst precursor under standard conditions.[9] The results are shown in Table 1. They indicate that the enantioselectivity is highly affected by the configuration of carbon atom C-3, the size of the sugar backbone ring, the flexibility of the ligand backbone and the substituents and configurations in the biaryl phosphoroamidite moieties **a**–**g**. The best enantioselectivities (ee's up to 56%; Table 1, entry 7) were obtained using ligand **L1g**, which has the appropriate combination of ligand parameter.

Table 1
Selected results for the Cu-catalyzed asymmetric 1,4-addition to S1 using ligands **L1**–**L9a**–**g**[a]

Entry	L	% Conv[b] (h)	% Yield[b]	% ee[c]
1	**L1a**	100 (18)	85	26 (*R*)
2	**L1b**	100 (18)	79	24 (*S*)
3	**L1c**	100 (18)	82	32 (*S*)
4	**L1d**	99 (18)	77	10 (*R*)
5	**L1e**	100 (18)	85	4 (*S*)
6	**L1f**	100 (18)	89	14 (*R*)
7	**L1g**	100 (18)	88	56 (*S*)
8	**L2a**	95 (18)	75	18 (*S*)
9	**L2b**	100 (18)	89	9 (*S*)
10	**L2c**	100 (18)	76	5 (*S*)
11	**L3c**	100 (18)	87	21 (*S*)
12	**L4a**	100 (18)	92	20 (*R*)
13	**L4b**	100 (18)	95	22 (*R*)
14	**L4d**	100 (18)	87	10 (*R*)
15	**L5a**	100 (18)	78	11 (*S*)
16	**L5b**	100 (18)	89	10 (*S*)
17	**L5d**	100 (18)	85	8 (*R*)
18	**L5e**	100 (18)	67	8 (*S*)
19[d]	**L6g**	98 (2)	24	20 (*S*)
20[d]	**L7a**	99 (2)	28	23 (*S*)
21[d]	**L8a**	94 (2)	8	4 (*S*)
22[d]	**L9a**	99 (2)	18	8 (*S*)
23[e]	**L1g**	100 (18)	69	35 (*S*)
24[f]	**L1g**	100 (18)	74	20 (*S*)

[a] Reaction conditions: CuTC (2 mol %), ligand (2 mol %), $ZnEt_2$ (1.5 equiv, 0.62 mmol), **S1** (0.415 mmol), Et_2O (2.5 mL) at −30 °C.
[b] Conversion and yields determined by GC using undecane as internal standard after 18 h.
[c] Enantiomeric excess measured by GC using Lipodex A column.
[d] Reported in the literature, see Ref. 6.
[e] Using $AlEt_3$ (1.5 equiv, 0.62 mmol).
[f] Using $Cu(OTf)_2$ in CH_2Cl_2 at 0 °C.

With ligands **L1a–g** we studied the effects of the biaryl phosphoroamidite moiety on enantioselectivity. We found that the presence of bulky substituents at the *ortho* positions of the biphenyl phosphite moiety had a positive effect on the enantioselectivity (Table 1, entries 1–3 vs entries 4 and 5). We also observed a cooperative effect between the configuration of the biaryl moieties and the configuration of carbon atom C-3 in the sugar backbone (Table 1, entries 6 and 7). The results indicate that the matched combination is achieved with ligand **L1g**, which has an (*S*)-configuration at both the carbon atom C-3 and in the binaphthyl phosphoroamidite moiety (Table 1, entry 7).

With ligands **L2**, whose configuration at C-3 is the opposite of that of ligands **L1**, we studied the effect of this configuration in the product outcome. The results indicated that this configuration influences the enantioselectivity (Table 1, entries 8–10 vs entries 1–3). Therefore, ligands **L2** with an (*R*) configuration at C-3 provided lower enantioselectivities than ligands **L1**.

Ligands **L3**, which have a pyranoside backbone, provided lower enantioselectivitities than the related furanoside ligands **L1** (Table 1, entry 3 vs entry 11).

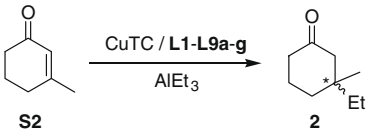
Using the most flexible ligands **L4** and **L5**, which have the phosphoroamidite moiety attached to a primary carbon, provided lower enantioselectivities than ligands **L1** (Table 1, entries 12–18).

Finally, after comparing these results with those from the related phosphite ligands **L6**–**L9**, we found that replacing the phosphite moiety with a phosphoroamidite group had a positive effect on the enantioselectivity (Table 1, entries 7, 8, 11 and 12 vs entries 19–22).[6]

We next used the ligand that provided the best results (ligand **L1g**) to study the effect of several reaction parameters (i.e., catalyst precursor, solvent, alkylating reagent and temperature) on the enantioselectivity. However, enantioselectivities did not improve (Table 1, entries 7, 23 and 24).

2.2.2. Asymmetric conjugate 1,4-addition of 3-methyl-cyclohexenone S2

To study further the potential of ligands **L1**–**L9a**–**g**, we tested them in the copper-catalyzed conjugated addition of triethylaluminum to 3-methyl-cyclohexenone **S2** (Eq. 2). The conjugate addition of this type of substrate provides an efficient way to build stereogenic quaternary centres into a compound.[1]



(2)

For a long time, the 1,4-addition of β,β′-disubstituted enones (such as **S2**) was unsuccessful because of the low reactivity of these substrates with dialkylzinc reagents. Recently, Alexakis et al. have disclosed that a combination of more reactive trialkylaluminum reagents and appropriately chosen reaction parameters would be efficient in the 1,4-addition to this type of challenging substrate.[10] The latter conditions were used for testing our ligand library in the Cu-conjugated addition of substrate **S2**. The results are summarized in Table 2. We found that enantioselectivity is highly affected by the configuration of carbon atom C-3, the size of the sugar backbone ring, the flexibility of the ligand backbone, the substituents and configurations in the biaryl phosphoroamidite moieties **a**–**g** and the type of functional group attached to the ligand backbone. However, the effect of these parameters on the conjugate addition of substrate **S2** was different from their effect on the conjugate addition of substrate **S1**. As for substrate **S1**, the presence of bulky substituents at the *ortho* position of the biphenyl moiety usually had a positive effect on the enantioselectivity (Table 2, entries 7 vs 8 and 9); however, ee's are negatively affected by replacing the phosphite moiety with a phosphoroamidite group (Table 2, entries 15 and 18 vs entries 1 and 7). Also, in contrast to **S1**, the enantioselectivity in phosphoroamidite ligands **L1**–**L5a** is hardly affected by the flexibility of the ligand backbone (Table 2, entries 1, 7, 11 and 14), whereas for phosphite ligands **L6**–**L9**, increasing the flexibility of the ligand negatively affected ee's (Table 2, entries 15, 18, 21 and 22).

Table 2
Selected results for the Cu-catalyzed asymmetric 1,4-addition to **S2** using ligands **L1**–**L9a**–**g**[a]

Entry	L	% Conv[b] (h)	% Yield[b]	% ee[c]
1	**L1a**	40 (18)	31	9 (*S*)
2	**L1b**	23 (18)	19	5 (*S*)
3	**L1c**	12 (18)	8	4 (*S*)
4	**L1d**	48 (18)	32	15 (*S*)
5	**L1e**	22 (18)	14	25 (*S*)
6	**L1g**	32 (18)	22	41 (*S*)
7	**L2a**	25 (18)	19	49 (*S*)
8	**L2d**	25 (18)	18	23 (*S*)
9	**L2e**	18 (18)	11	6 (*S*)
10	**L3c**	15 (18)	13	2 (*S*)
11	**L4a**	8 (18)	7	43 (*S*)
12	**L4d**	20 (18)	11	15 (*S*)
13	**L4e**	5 (18)	3	4 (*S*)
14	**L5a**	12 (18)	9	35 (*S*)
15	**L6a**	12 (18)	9	50 (*R*)
16	**L6f**	12 (18)	10	8 (*S*)
17	**L6g**	18 (18)	13	30 (*S*)
18	**L7a**	51 (48)	49	60 (*S*)
19	**L7f**	18 (18)	12	20 (*S*)
20	**L7g**	40 (18)	33	42 (*S*)
21	**L8a**	10 (18)	7	5 (*S*)
22	**L9a**	12 (18)	8	3 (*S*)

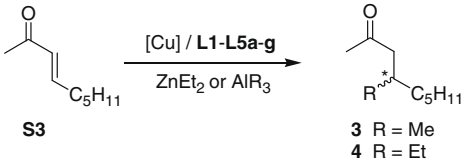
[a] Reaction conditions: CuTC (4 mol %), ligand (4 mol %), $AlEt_3$ (1.5 equiv, 0.62 mmol), **S2** (0.415 mmol), Et_2O (2.5 mL), $T = -30$ °C.
[b] Conversion and yields determined by GC using undecane as internal standard after 18 h.
[c] Enantiomeric excess measured by GC using Lipodex E column.

In summary, the best results (ee's up to 60%) were obtained with phosphite ligand **L7a** (Table 1, entry 18), which has bulky *tert*-butyl groups at both the *ortho*- and *para*-positions of the biphenyl moiety and a furanoside sugar-backbone.

2.3. Asymmetric conjugate 1,4-addition to linear enones

2.3.1. Asymmetric conjugated 1,4-addition of $ZnEt_2$ and $AlEt_3$ to *trans*-3-nonen-2-one S3

We have also screened the new phosphoroamidite ligands **L1**–**L5a**–**g** in the copper-catalyzed conjugated addition of several alkylating reagents to the linear substrate: *trans*-3-nonen-2-one **S3** (Eq. 3). This enone, possessing only aliphatic substituents, is a more demanding substrate class for asymmetric conjugated addition than **S1**. The high conformational mobility of this substrate together with the presence of only subtle substrate-catalyst steric interactions makes the design of effective enantioselective systems a real challenge.[4e,h,11]



(3)

The most representative results are shown in Table 3. In general the ligand requirements were the same as those for the 1,4-addition to **S1** except for those regarding the substituents and configurations in the biaryl phosphoroamidite moieties **a**–**g**. Therefore, enantioselectivities were best (ee's up to 49%) when

Table 3
Selected results for the Cu-catalyzed asymmetric 1,4-addition to **S3** using ligands **L1**–**L9a**–**g**[a]

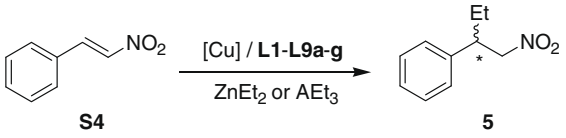
Entry	L	Precursor	Alkylating reagent	% Conv[b] (h)	% Yield[b]	% ee[c]
1	**L1a**	CuTC	$AlMe_3$	85 (18)	72	38 (*R*)
2	**L1b**	CuTC	$AlMe_3$	97 (18)	83	49 (*R*)
3	**L1c**	CuTC	$AlMe_3$	78 (18)	65	23 (*R*)
4	**L1d**	CuTC	$AlMe_3$	78 (18)	61	14 (*R*)
5	**L1e**	CuTC	$AlMe_3$	36 (18)	26	8 (*R*)
6	**L1g**	CuTC	$AlMe_3$	45 (18)	33	26 (*S*)
7	**L2a**	CuTC	$AlMe_3$	91 (18)	76	23 (*S*)
8	**L3c**	CuTC	$AlMe_3$	84 (18)	77	14 (*S*)
9	**L4a**	CuTC	$AlMe_3$	90 (18)	79	4 (*S*)
10	**L5a**	CuTC	$AlMe_3$	94 (18)	81	6 (*S*)
11[d]	**L6a**	CuTC	$AlMe_3$	99 (2)	79	18 (*R*)
12[d]	**L7a**	CuTC	$AlMe_3$	72 (2)	65	8 (*S*)
13	**L1d**	$Cu(OTf)_2$	$AlMe_3$	87 (18)	80	12 (*R*)
14	**L1d**	$[Cu(CH_3CN)_4]BF_4$	$AlMe_3$	84 (18)	79	6 (*R*)
15	**L1d**	CuTC	$AlEt_3$	99 (18)	84	4 (*R*)
16	**L1d**	CuTC	$ZnEt_2$	97 (18)	89	8 (*R*)

[a] Reaction conditions: Cu-precursor (2 mol %), ligand (2 mol %), alkylating reagent (1.5 equiv, 0.62 mmol), **S3** (0.415 mmol), Et_2O (2.5 mL), $T = -30$ °C.
[b] Conversion and yields determined by GC using undecane as internal standard after 18 h.
[c] Enantiomeric excess measured by GC using 6-Me-2,3-pe-γ-CD column.
[d] Reported in the literature, see Ref. 6.

using ligand **L1b**, which has *tert*-butyl groups at the *ortho* positions and methoxy substituents at the *para*-positions of the biphenyl moiety (Table 3, entry 2). We also studied the effect of several reaction parameters (i.e., catalyst precursor, solvent, alkylating reagent and temperature) on the enantioselectivity. However, the enantioselectivities did not improve (Table 3, entry 2 vs entries 13–16).

2.3.2. Asymmetric conjugated 1,4-addition of $ZnEt_2$ and $AlEt_3$ to *trans*-nitrostyrene S4

Finally, we applied the ligand library **L1**–**L9a**–**g** in the copper-catalyzed conjugated addition of several alkylating reagents to the linear nitrolefin *trans*-nitrostyrene **S4** (Eq. 4). The nitro group is of particular synthetic importance, as it can be transformed into a variety of valuable organic compounds such as aldehydes, carboxylic acids, nitriles, nitrooxides and amines.[1j,12]



S4 **5** (4)

The results are summarized in Table 4. We found that the presence of bulky substituents at the biaryl moiety had a negative effect on the enantioselectivity (Table 4, entries 1–6). However, for the most flexible ligands **L5**, enantioselectivities were better with bulky substituents at these positions (Table 4, entries 13–15). We also found that phosphite ligands provided better enantioselectivities than their phosphoroamidite counterparts. Therefore the best results (ee's up to 72%) were obtained with ligand **L6g** (Table 4, entry 18). The reaction parameters (i.e., catalyst precursor, solvent, alkylating reagent and temperature) also indicated that diethylzinc can also be successfully used and that it provides the same enantioselectivities as when triethylaluminum is used (Table 4, entries 18 and 22), whereas the use of trimethylaluminum reduces ee's (Table 4, entry 24).

Table 4
Selected results for the Cu-catalyzed asymmetric 1,4-addition to **S4** using ligands **L1**–**L9a**–**g**[a]

Entry	L	Precursor	Alkylating reagent	% Conv[b] (h)	% Yield[b]	% ee[c]
1	**L1a**	CuTC	$AlEt_3$	100 (18)	87	20 (*S*)
2	**L1b**	CuTC	$AlEt_3$	100 (18)	79	13 (*S*)
3	**L1c**	CuTC	$AlEt_3$	100 (18)	93	18 (*S*)
4	**L1d**	CuTC	$AlEt_3$	100 (18)	89	26 (*S*)
5	**L1e**	CuTC	$AlEt_3$	100 (18)	90	35 (*S*)
6	**L1g**	CuTC	$AlEt_3$	100 (18)	86	30 (*S*)
7	**L2a**	CuTC	$AlEt_3$	100 (18)	78	14 (*R*)
8	**L2d**	CuTC	$AlEt_3$	100 (18)	91	32 (*R*)
9	**L2e**	CuTC	$AlEt_3$	100 (18)	86	45 (*R*)
10	**L3c**	CuTC	$AlEt_3$	100 (18)	91	13 (*S*)
11	**L4d**	CuTC	$AlEt_3$	100 (18)	84	6 (*R*)
12	**L4e**	CuTC	$AlEt_3$	100 (18)	90	4 (*R*)
13	**L5a**	CuTC	$AlEt_3$	100 (18)	93	32 (*R*)
14	**L5d**	CuTC	$AlEt_3$	100 (18)	90	8 (*R*)
15	**L5e**	CuTC	$AlEt_3$	100 (18)	89	6 (*R*)
16	**L6a**	CuTC	$AlEt_3$	100 (18)	85	2 (*S*)
17	**L6f**	CuTC	$AlEt_3$	100 (18)	90	10 (*R*)
18	**L6g**	CuTC	$AlEt_3$	100 (18)	88	72 (*R*)
19	**L7g**	CuTC	$AlEt_3$	100 (18)	89	24 (*S*)
20	**L8f**	CuTC	$AlEt_3$	100 (18)	84	56 (*R*)
21	**L9f**	CuTC	$AlEt_3$	100 (18)	84	10 (*S*)
22	**L6g**	CuTC	$ZnEt_2$	100 (18)	93	72 (*R*)
23[d]	**L6g**	$Cu(OTf)_2$	$ZnEt_2$	100 (18)	92	0
24	**L6g**	CuTC	$AlMe_3$	98 (18)	57	56 (*R*)

[a] Reaction conditions: Cu-precursor (2 mol %), ligand (2 mol %), alkylating reagent (1.5 equiv, 0.62 mmol), **S4** (0.415 mmol), Et_2O (2.5 mL), $T = -30$ °C.
[b] Conversion and yields determined by GC using undecane as internal standard after 18 h.
[c] Enantiomeric excess measured by GC using Lipodex E column.
[d] $T = 0$ °C.

3. Conclusions

A sugar-based phosphoroamidite **L1**–**L5a**–**g** and phosphite **L6**–**L9a**–**g** ligand library has been tested in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of cyclic and acyclic enones. Our results indicated that the selectivity depended strongly on the configuration of the carbon atom C-3, the size of the sugar backbone ring, the flexibility of the ligand backbone, the substituents and configurations in the biaryl phosphoroamidite moieties **a**–**g**, the type of functional group attached to the ligand backbone and the substrate structure. Therefore, by carefully selecting the ligand parameters, we achieved enantioselectivities of up to 60% for cyclic substrates and 72% for linear substrates.

4. Experimental section

4.1. General considerations

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified using standard procedures. Sugar amines were prepared from D-glucose, D-fructose and D-galactose as described.[7] Ligands **L1a–g**,[7] **L2a**,[7] **L3c**,[7] **L4**–**L5a**[7] and **L6**–**L9a–g**[13] were prepared as previously described. All other reagents were used in their commercially available form. ^{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 the internal standard or to H_3PO_4 (^{31}P) as the 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 ligands L1–L5a–g

Phosphorochloridite (2.2 mmol) produced in situ was dissolved in toluene (5 mL) before pyridine (0.36 mL, 4.6 mmol) was added. The amine (2 mmol) was azeotropically dried with toluene (3 × 1 mL) and then dissolved in toluene (10 mL), to which pyridine (0.36 mL, 4.6 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 a white powder or colourless liquid.

L2b: Yield: 284 mg (44%). ^{31}P NMR (C_6D_6), δ: 148.7 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.02 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.48 (s, 9H, CH_3, *t*-Bu), 1.52 (s, 9H, CH_3, *t*-Bu), 3.04 (m, 1H, H-3), 3.24 (m, 1H, NH), 3.27 (s, 3H, CH_3–O), 3.29 (s, 3H, CH_3–O), 3.76 (m, 1H, H-2), 3.89 (m, 1H, H-6́), 3.92 (m, 1H, H-6), 4.00 (m, 1H, H-4), 4.52 (m, 1H, H-5), 5.33 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 Hz), 6.62 (m, 1H, CH=), 6.70 (m, 1H, CH=), 7.11 (m, 2H, CH=). ^{13}C NMR (C_6D_6), δ: 26.2 (CH_3), 26.4 (CH_3), 28.8 (CH_3), 28.9 (CH_3), 31.4 (CH_3, *t*-Bu), 31.6 (CH_3, *t*-Bu), 35.7 (C, *t*-Bu), 35.8 (C, *t*-Bu), 55.2 (CH_3–O), 55.4 (CH_3–O), 55.8 (d, C-3, J_{C-P} = 6.8 Hz), 64.0 (C-6), 75.7 (C-5), 79.8 (C-4), 80.3 (C-2), 104.3 (C-1), 109.6 (CMe_2), 112.2 (CMe_2), 112.5 (CH=), 113.8 (CH=), 114.9 (CH=), 115.0 (CH=), 134.8 (C), 134.9 (C), 143.0 (C), 143.2 (C), 156.4 (C), 156.7 (C). Anal. Calcd for $C_{34}H_{48}NO_9P$: C, 63.24; H, 7.49; N, 2.17. Found: C, 63.21; H, 7.52; N, 2.15.

L2c: Yield: 315 mg (51%). ^{31}P NMR (C_6D_6), δ: 149.7 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.35 (s, 3H, CH_3–Si), 0.42 (s, 3H, CH_3–Si), 1.04 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.87 (m, 1H, H-3), 3.12 (m, 1H, NH), 3.62 (m, 1H, H-2), 3.69 (m, 1H, H-6), 3.75 (m, 1H, H-6′), 3.97 (m, 1H, H-4), 4.65 (m, 1H, H-5), 5.26 (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), 0.7 (CH_3–Si), 26.5 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 55.4 (d, C-3, J_{C-P} = 1.6 Hz), 63.8 (C-6), 75.8 (C-5), 79.9 (d, C-4, J_{C-P} = 1.6 Hz), 80.6 (C-2), 104.3 (C-1), 109.8 (CMe_2), 112.4 (CMe_2), 125.2 (CH=), 126.0 (CH=), 131.9 (C), 132.0 (C), 132.2 (CH=), 132.3 (C), 132.4 (C), 133.2 (CH=), 135.4 (CH=), 136.0 (CH=), 136.5 (C), 138.2 (C), 155.7 (C), 155.9 (C). Anal. Calcd for $C_{30}H_{44}NO_7PSi_2$: C, 58.32; H, 7.18; N, 2.27. Found: C, 58.36; H, 7.20; N, 2.24.

L2d: Yield: 280 mg (53%). ^{31}P NMR (C_6D_6), δ: 150.2 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.05 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.16 (s, 6H, CH_3), 2.24 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.89 (m, 1H, H-3), 3.11 (m, 1H, NH), 3.64 (m, 1H, H-2), 3.72 (m, 1H, H-6), 3.78 (m, 1H, H-6′), 3.99 (m, 1H, H-4), 4.66 (m, 1H, H-5), 5.32 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.7–7.4 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 17.1 (CH_3), 17.7 (CH_3), 25.8 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 55.8 (d, C-3, J_{C-P} = 6.4 Hz), 63.9 (C-6), 74.7 (C-5), 79.7 (d, C-4, J_{C-P} = 3.2 Hz), 81.1 (C-2), 104.2 (C-1), 109.2 (CMe_2), 112.2 (CMe_2), 125.2 (CH=), 126.0 (CH=), 131.9 (C), 132.0 (C), 132.2 (CH=), 132.3 (C), 132.4 (C), 133.2 (CH=), 135.4 (CH=), 138.2 (C), 139.7 (C). Anal. Calcd for $C_{28}H_{36}NO_7P$: C, 63.51; H, 6.85; N, 2.64. Found: C, 63.48; H, 6.82; N, 2.65.

L2e: Yield: 237 mg (42%). ^{31}P NMR (C_6D_6), δ: 146.9 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.09 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.37 (m, 2H, NH, H-3), 3.69 (m, 5H, H-2, CH_2 allyl), 3.82 (m, 2H, H-6, H-6′), 3.91 (m, 1H, H-4), 4.34 (m, 1H, H-5), 5.13 (m, 4H, CH_2= allyl), 5.32 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.07 (m, 2H, CH= allyl), 6.9–7.2 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 25.5 (CH_3), 26.6 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 35.7 (CH_2 allyl), 58.6 (C-3), 68.0 (C-6), 78.0 (C-5), 80.9 (C-4), 81.6 (C-2), 104.8 (C-1), 109.9 (CMe_2), 112.6 (CMe_2), 115.8 (CH_2 allyl), 120.8 (CH=), 126.0 (C), 129.7 (C), 129.9 (CH=), 130.2 (CH=), 135.4 (C), 136.1 (C), 138.2 (CH= allyl). Anal. Calcd for $C_{30}H_{36}NO_7P$: C, 65.09; H, 6.55; N, 2.53. Found: C, 65.10; H, 6.53; N, 2.51.

L4b: Yield: 245 mg (38%). ^{31}P NMR (C_6D_6), δ: 147.8 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.49 (s, 9H, CH_3, *t*-Bu), 1.51 (s, 9H, CH_3, *t*-Bu), 3.28 (s, 3H, CH_3–O), 3.30 (s, 3H, CH_3–O), 3.43 (m, 1H, H-6), 3.57 (m, 1H, H-6′), 3.59 (m, 1H, H-1), 3.65 (m, 1H, H-1′), 3.72 (m, 1H, NH), 3.75 (m, 1H, H-4), 4.40 (m, 1H, H-3), 4.42 (m, 1H, H-2), 7.0–7.2 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 24.4 (CH_3), 25.7 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 31.6 (CH_3, *t*-Bu), 31.7 (CH_3, *t*-Bu), 35.0 (C, *t*-Bu), 35.3 (C, *t*-Bu), 47.5 (d, C-6, J_{C-P} = 12.1 Hz), 55.2 (CH_3–O), 55.3 (CH_3–O), 61.9 (C-1), 71.1 (C-3), 71.5 (C-4), 72.1 (C-2), 108.3 (CMe_2), 109.3 (CMe_2), 115.0 (CH=), 116.3 (CH=), 135.0 (C), 143.1 (C), 156.6 (C). Anal. Calcd for $C_{34}H_{48}NO_9P$: C, 63.24; H, 7.49; N, 2.17. Found: C, 63.19; H, 7.50; N, 2.14.

L4c: Yield: 228 mg (37%). ^{31}P NMR (C_6D_6), δ: 149.5 (s, 1P). ^{1}H NMR (C_6D_6), δ: 0.40 (s, 9H, CH_3–Si), 0.45 (s, 9H, CH_3–Si), 1.06 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.27 (m, 1H, H-6), 3.38 (m, 1H, H-6′), 3.60 (m, 1H, H-1), 3.67 (m, 1H, H-1′), 3.73 (m, 1H, NH), 3.79 (m, 1H, H-4), 4.34 (m, 1H, H-3), 4.41 (m, 1H, H-2), 6.8–7.4 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 0.4 (CH_3–Si), 0.5 (CH_3–Si), 24.3 (CH_3), 25.5 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 47.9 (d, C-6, J_{C-P} = 8.2 Hz), 61.8 (C-1), 71.0 (C-3), 71.4 (C-4), 72.2 (C-2), 108.3 (CMe_2), 109.2 (CMe_2), 124.9 (CH=), 126.0 (C), 129.6 (CH=), 131.9 (C), 132.0 (C), 135.8 (CH=), 135.9 (CH=), 136.5 (C), 138.2 (C), 155.7 (C). Anal. Calcd for $C_{30}H_{44}NO_7PSi_2$: C, 58.32; H, 7.18; N, 2.27. Found: C, 58.29; H, 7.16; N, 2.26.

L4d: Yield: 216 mg (41%). ^{31}P NMR (C_6D_6), δ: 144.4 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.42 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.49 (s, 6H, CH_3), 2.73 (s, 6H, CH_3), 3.74 (m, 1H, H-6), 3.94 (m, 1H, H-6′), 4.03 (m, 1H, H-1), 4.05 (m, 1H, H-1′), 4.08 (m, 1H, NH), 4.13 (m, 1H, H-4), 4.76 (m, 1H, H-3), 4.80 (m, 1H, H-2), 7.3–7.5 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 17.1 (CH_3), 21.1 (CH_3), 24.3 (CH_3), 25.6 (CH_3), 26.4 (CH_3), 26.8 (CH_3), 46.7 (d, C-6, J_{C-P} = 11.4 Hz), 61.9 (C-1), 71.1 (C-3), 71.4 (C-4), 71.8 (C-2), 108.4 (CMe_2), 109.3 (CMe_2), 128.3 (CH=), 128.6 (CH=), 131.6 (C), 131.7 (C), 133.6 (C). Anal. Calcd for $C_{28}H_{36}NO_7P$: C, 63.51; H, 6.85; N, 2.64. Found: C, 63.46; H, 6.81; N, 2.63.

L4e: Yield: 265 mg (48%). ^{31}P NMR (C_6D_6), δ: 146.3 (s, 1P). ^{1}H NMR (C_6D_6), δ: 1.06 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.30 (m, 1H, H-6), 3.44 (m, 1H, H-6′), 3.47 (m, 1H, H-1), 3.50 (m, 1H, H-1′), 3.57 (m, 5H, NH, CH_2 allyl), 4.41 (m, 2H, H-4, H-3), 5.07 (m, 5H, H-2, CH_2= allyl), 6.02 (m, 2H, CH= allyl), 6.9–7.4 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 24.3 (CH_3), 25.6 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 35.2 (CH_2 allyl), 35.4 (CH_2 allyl), 47.0 (d, C-6, J_{C-P} = 4.2 Hz), 61.8 (C-1), 71.0 (C-3), 71.4 (C-4), 71.9 (C-2), 108.3 (CMe_2), 109.2 (CMe_2), 116.4 (CH_2= allyl), 116.6 (CH_2= allyl), 124.9 (CH=), 125.0 (CH=), 126.3 (C), 128.8 (CH=), 130.3 (CH=), 133.1 (C), 133.2 (C), 137.3 (CH= allyl), 137.5 (CH= allyl).

Anal. Calcd for $C_{30}H_{36}NO_7P$: C, 65.09; H, 6.55; N, 2.53. Found: C, 65.12; H, 6.58; N, 2.56.

L5b: Yield: 309 mg (48%). ^{31}P NMR (C_6D_6), δ: 147.6 (s, 1P). ^1H NMR (C_6D_6), δ: 1.03 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.54 (s, 9H, CH_3, *t*-Bu), 1.56 (s, 18H, CH_3, *t*-Bu), 3.29 (m, 2H, H-6, H-6′), 3.33 (s, 3H,CH_3–O), 3.35 (s, 3H, CH_3–O), 3.49 (m, 1H, NH), 3.82 (m, 1H, H-1), 3.89 (m, 1H, H-5), 4.13 (m, 1H, H-3), 4.41 (m, 1H, H-2), 5.44 (m, 1H, H-4), 7.0–7.2 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 24.7 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 31,6 (CH_3, *t*-Bu), 34.8 (C, *t*-Bu), 41.4 (d, C-2, J_{C-P} = 12.1 Hz), 55.4 (CH_3–O), 69.5 (C-5), 71.3 (C-3), 71.5 (C-2), 71.8 (C-1), 97.0 (C-4), 108.7 (CMe_2), 109.5 (CMe_2), 115.2 (CH=), 115.5 (CH=), 129.6 (C), 135.0 (C), 135.1 (C), 142.9 (C), 156.4 (C). Anal. Calcd for $C_{34}H_{48}NO_9P$: C, 63.24; H, 7.49; N 2.17. Found: C, 63.26; H, 7.50; N, 2.19.

L5c: Yield: 234 mg (38%). ^{31}P NMR (C_6D_6), δ: 149.7 (s, 1P). ^1H NMR (C_6D_6), δ: 0.31 (s, 3H, CH_3–Si), 0.40 (s, 3H, CH_3–Si), 1.05 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.28 (m, 1H, H-6), 3.31 (m, 1H, H-6′), 3.42 (m, 1H, NH), 3.86 (m, 1H, H-1), 3.92 (m, 1H, H-5), 4.11 (m, 1H, H-3), 4.40 (m, 1H, H-2), 5.42 (m, 1H, H-4), 7.0–7.2 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 0.5 (CH_3–Si), 0.7 (CH_3–Si), 24.7 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 26.9 (CH_3), 69.9 (C-5), 71.2 (C-3), 71.9 (C-2), 72.4 (C-1), 97.3 (C-4), 108.7 (CMe_2), 109.9 (CMe_2), 125.1 (CH=), 125.8 (CH=), 131.9 (C), 132.1 (C), 132.2 (CH=), 132.3 (C), 132.8 (C), 133.1 (CH=), 135.5 (CH=), 136.0 (CH=), 136.5 (C), 138.2 (C), 155.7 (C). Anal. Calcd for $C_{30}H_{44}NO_7PSi_2$: C, 58.32; H, 7.18; N, 2.27. Found: C, 58.33; H, 7.22; N, 2.25.

L5d: Yield: 269 mg (51%). ^{31}P NMR (C_6D_6), δ: 145.3 (s, 1P). ^1H NMR (C_6D_6), δ: 0.99 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.36 (s, 6H, CH_3), 3.32 (m, 2H, H-6, H-6′), 3.50 (m, 1H, NH), 3.61 (m, 1H, H-1), 3.88 (m, 1H, H-5), 4.12 (m, 1H, H-3), 4.34 (m, 1H, H-2), 5.44 (m, 1H, H-4), 7.0–7.2 (m, 4H, CH=). ^{13}C NMR (C_6D_6), δ: 17.2 (CH_3), 17.3 (CH_3), 21.2 (CH_3), 24.5 (CH_3), 25.3 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 40.9 (d, C-2, J_{C-P} = 7.6 Hz), 69.7 (C-5), 71.4 (C-3), 71.5 (C-2), 71.7 (C-1), 97.0 (C-4), 108.8 (CMe_2), 109.5 (CMe_2), 128.3 (CH=), 128.7 (CH=), 129.2 (CH=), 131.6 (C), 131.7 (C), 133.6 (C). Anal. Calcd for $C_{28}H_{36}NO_7P$: C, 63.51; H, 6.85; N, 2.64. Found: C, 63.53; H, 6.87; N, 2.62.

L5e: Yield: 260 mg (47%). ^{31}P NMR (C_6D_6), δ: 147.8 (s, 1P). ^1H NMR (C_6D_6), δ: 0.98 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.18 (m, 2H, H-6, H-6′), 3.44 (m, 1H, NH), 3.48 (m, 1H, H-1), 3.57 (m, 4H, CH_2 allyl), 3.76 (m, 1H, H-5), 4.07 (m, 1H, H-3), 4.32 (m, 1H, H-2), 5.01 (m, 4H, CH_2= allyl), 5.38 (m, 1H, H-4), 5.97 (m, 2H, CH= allyl), 6.9–7.2 (m, 6H, CH=). ^{13}C NMR (C_6D_6), δ: 24.6 (CH_3), 25.3 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 35.2 (CH_2 allyl), 35.3 (CH_2 allyl), 41.1 (d, C-2, J_{C-P} = 9.2 Hz), 69.6 (C-5), 71.3 (C-3), 71.5 (C-2), 71.8 (C-1), 97.0 (C-4), 108.8 (CMe_2), 109.5 (CMe_2), 116.5 (CH_2= allyl), 116.7 (CH_2= allyl), 124.8 (CH=), 125.0 (CH=), 126.0 (C), 129.6 (C), 130.2 (CH=), 132.5 (C), 133.0 (C), 137.4 (CH= allyl). Anal. Calcd for $C_{30}H_{36}NO_7P$: C, 65.09; H, 6.55; N, 2.53. Found: C, 65.12; H, 6.57; N, 2.54.

4.3. Typical procedure for the catalytic conjugate addition of alkylating reagents to enones

In a typical procedure, a solution of copper-catalyst precursor (8.3 μmol) and furanoside ligand (16.6 μmol) in the appropriate solvent (2 mL) was stirred for 30 min at room temperature. After cooling to the desired temperature, the alkylating reagents (0.62 mmol) were added. A solution of the desired enone (0.415 mmol) and undecane as the GC internal standard (0.25 mL) in dichloromethane (0.5 mL) was then added at the corresponding reaction temperature. The reaction was monitored by GC. The reaction was quenched with HCl (2 M) and filtered twice through flash silica. Conversion, chemoselectivity and enantioselectivity were obtained by GC.[4i]

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