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Furanoside phosphite–phosphoroamidite and diphosphoroamidite ligands for Cu-catalyzed asymmetric 1,4-addition reactions

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ABSTRACT

A sugar-based phosphite–phosphoroamidite and diphosphoroamidite ligand library **L1**–**L5a**–**g** was tested in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of β-substituted and β,β′-disubstituted enones. Our results indicated that the selectivity was strongly dependent on the ligand parameters and on the substrate structure. Moderate-to-good enantioselectivities (ees up to 84%) were obtained in the 1,4-addition of several types of β-substituted cyclic and linear substrates. Of particular note is the high enantioselectivity (ees up to 90%) obtained for the more challenging β,β′-disubstituted 3-methylcyclohexenone.

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1. Introduction

The enantioselective conjugate addition of organometallic reagents to α,β-unsaturated substrates catalyzed by chiral transition metal complexes is a useful synthetic process for asymmetric carbon-carbon bond formation.[1] The design of the chiral ligands together with the reaction conditions is perhaps the key to attaining high asymmetric induction in this process. Subtle changes in the conformational, steric, and/or electronic properties of the chiral ligand have led to dramatic variation in the reactivity and enantioselectivity. Since in most cases there is a strong substrate dependence, tunable and readily synthesized ligand series are desirable if high enantioselectivities are to be obtained for a wide range of substrates.[1] Among the most efficient ligands, phosphites and phosphoroamidites based on biaryl moieties have played a prominent role.[1f–h,j,2] Although Michael additions of organolithium, Grignard, and diorganozinc reagents to enones have been widely studied over the last decade,[1] less attention has been paid to trialkylaluminum reagents.[3] Trialkylaluminum reagents have recently appeared as an interesting alternative to organozinc reagents because their range can be more easily extended by technically simple hydro- and carboalumination reactions. Additionally, the Cu-catalyzed 1,4-addition of trialkylaluminum reagents can be carried out on very challenging substrates (i.e., β-trisubstituted enones) which are inert to organozinc methodologies.[1] On the other hand, linear aliphatic enones are another class of substrates for which more active and enantioselective catalysts still need to be developed.[1]

Following our interest in modular ligands and encouraged by the success of phosphite and phosphoroamidite ligands in this process, we herein report the application of a sugar-based phosphite–phosphoroamidite[4] and diphosphoroamidite[5] ligand library (**L1**–**L5a**–**g**; Fig. 1) to the Cu-catalyzed asymmetric 1,4-addition of organometallic reagents to cyclic and aliphatic linear enones. These ligands have the same advantages as carbohydrate and phosphite/phosphoroamidite ligands, that is, they are available at a low price from readily available feedstocks, they have high resistance to oxidation, and have straightforward modular constructions.[6] Therefore, with this library we fully investigated the effects of systematically varying the position of the phosphoroamidite group at both C-5 (ligands **L1** and **L2**) and C-3 (ligands **L3** and **L4**) of the furanoside backbone, as well as effects of the configuration at C-3 of the furanoside backbone, the introduction of a second phosphoroamidite moiety (ligands **L5**) and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties (**a**–**g**).

2. Results and discussion

2.1. Ligand design

Ligands **L1**–**L5a**–**g** were synthesized very efficiently in one step from the corresponding sugar aminoalcohols **1**–**4** or diamine **5**, which were prepared on a large scale from D-xylose and D-glucose, as previously described (Scheme 1).[4a,c,d,5] Therefore, the reaction of the corresponding aminoalcohol or diamine with 2 equiv of the desired in situ-formed phosphorochloridite **6a**–**g** in the presence of a base afforded the desired ligands.

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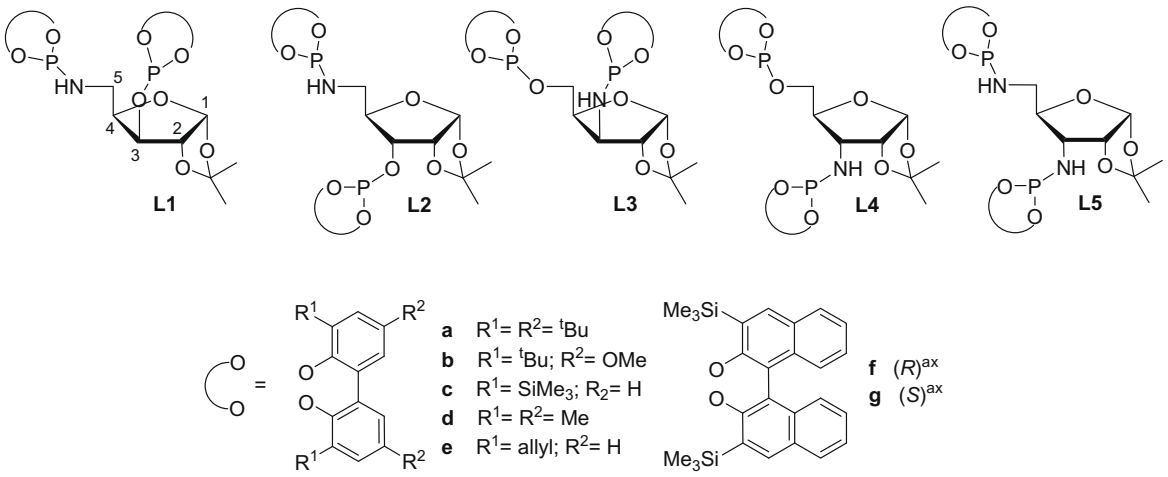
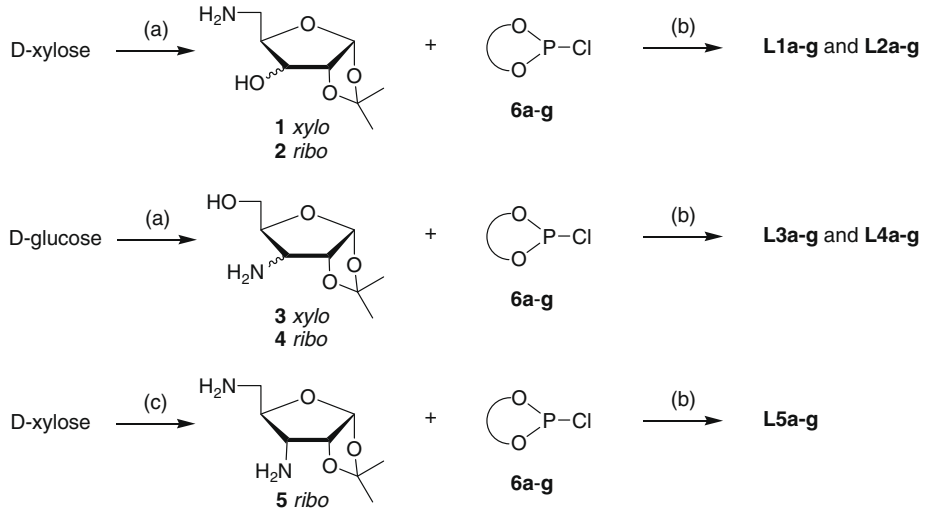


Figure 1. Phosphite–phosphoroamidite and diphosphoroamidite ligands **L1**–**L5a**–**g**.



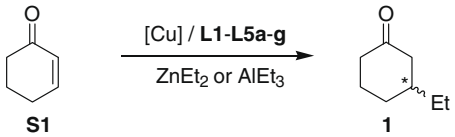
Scheme 1. Synthesis of ligands **L1**–**L5a**–**g**. Reagents and conditions: (a) Ref. 4d; (b) Py, toluene, and 80 °C; and (c) Ref. 5.

The new ligands, **L1d**–**e**, **L2d**–**e,** and **L4d**–**e**, were also stable during purification on neutral alumina under an argon atmosphere and were isolated as white solids. They were stable at room temperature and very stable to hydrolysis. Elemental analyses were in agreement with the assigned structure. 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 **d** and **e** occurred on the NMR time scale because the expected diastereoisomers were not detected by low-temperature phosphorus NMR.[7]

2.2. Asymmetric conjugate 1,4-addition to β-substituted enones

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

In the first set of experiments, we tested furanoside 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 been performed with a wide range of ligands with several donor groups, thus enabling the efficiency of the various ligand systems to be compared directly.[1]



(1)

The catalytic system was generated in situ by adding the corresponding ligand to a suspension of the catalyst precursor under standard conditions.[8] The results are shown in Table 1. They indicate that enantioselectivity is highly affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, by the configuration of C-3, the introduction of a second phosphoroamidite moiety, and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties **a**–**g**.

We first studied the configuration of C-3 and 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. We observed a cooperative effect between the position of the phosphoroamidite group and the configuration of carbon atom at C-3 of the furanoside backbone. These results indicate that the matched combination is achieved with ligands **L4**, whose phosphoroamidite moiety is attached to C-3 and which have an (*R*)-configuration of the carbon atom at C-3 on the tetrahydrofuran ring (Table 1, entries 16–22).

Table 1
Cu-catalyzed asymmetric 1,4-addition of diethylzinc to **S1** using ligands **L1**–**L5a**–**g**[a]

Entry	L	% Conv[b]	% Yield[b]	% ee[c]
1	**L1a**	100	95	10 (*R*)
2	**L1b**	84	80	2 (*R*)
3	**L1c**	99	92	1 (*R*)
4	**L1d**	95	93	51 (*S*)
5	**L1e**	100	96	41 (*S*)
6	**L2a**	100	92	20 (*S*)
7	**L2b**	99	90	10 (*S*)
8	**L2c**	96	88	11 (*S*)
9	**L2d**	100	93	55 (*R*)
10	**L2e**	100	91	37 (*R*)
11	**L3a**	97	89	28 (*S*)
12	**L3b**	97	93	18 (*S*)
13	**L3c**	100	96	18 (*S*)
14	**L3d**	100	92	12 (*R*)
15	**L3e**	100	90	6 (*R*)
16	**L4a**	99	94	38 (*S*)
17	**L4b**	97	90	28 (*S*)
18	**L4c**	100	91	15 (*S*)
19	**L4d**	100	89	53 (*R*)
20	**L4e**	100	84	30 (*R*)
21	**L4f**	100	86	16 (*R*)
22	**L4g**	100	90	64 (*S*)
23	**L5a**	100	92	12 (*S*)
24	**L5b**	100	87	29 (*S*)
25	**L5d**	100	96	32 (*R*)

[a] Reaction conditions: CuTC (2 mol %), ligand (2 mol %), $ZnEt_2$ (1.5 equiv, 0.62 mmol), **S1** (0.415 mmol), and Et_2O (2.5 mL).
[b] Conversion and yields determined by GC analysis using undecane as the internal standard after 18 h.
[c] Enantiomeric excess measured by GC using Lipodex A column.

We next studied the effects of the biaryl phosphite/phosphoroamidite moieties using ligands **L1**–**L4a**–**g** (Table 1). We found that enantioselectivity was negatively affected by the presence of sterically hindered substituents at the *ortho*-positions and either methoxy or hydrogen substituents at the *para*-position of the biphenyl moieties (Table 1, entries 16–20). We also observed a cooperative effect between the configuration of the biaryl moieties and the configuration of the carbon atom at C-3. The results indicate that the matched combination is achieved with ligand **L4g**, which has an (*R*)-configuration at carbon atom C-3 and an (*S*)-configuration in the binaphthyl phosphite/phosphoroamidite moieties (Table 1, entry 22).

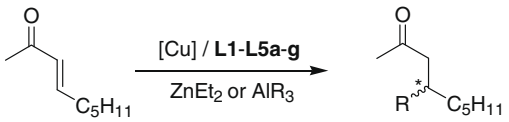
We then used ligands **L5** to study how replacing the phosphite moiety with a phosphoroamidite group affected catalytic performance. The results indicated that the presence of a second phosphoroamidite moiety in the ligands had a negative effect on enantioselectivity (Table 1, entries 9 and 19 vs 25).

In summary, the best result was obtained with ligand **L4g** (Table 1, entry 22), which contains the optimal combination of ligand parameters (position of the phosphoroamidite group, configuration at C-3 of the furanoside backbone, and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties).

In addition to controlling the effect of the structural parameters on the catalytic performance, the reaction parameters can also be controlled to further improve yields and selectivities. Therefore, the effects of several reaction parameters, such as catalyst precursor, solvent, alkylating reagent, and temperature, were studied using ligands **L4f** and **L4g** (Table 2). In this case, the enantioselectivity was further improved (ees up to 84%) with ligand **L4g** by using copper triflate and diethylzinc in dichloromethane at 0 °C (Table 2, entry 6).[9]

2.2.2. Asymmetric conjugate 1,4-addition of $ZnEt_2$, $AlEt_3$, and $AlMe_3$ to *trans*-3-nonen-2-one S2

We have also screened the use of ligands **L1**–**L5a**–**g** in the copper-catalyzed conjugate addition of several alkylating reagents to the linear substrate: *trans*-3-nonen-2-one **S2** (Eq. 2). This enone, possessing only aliphatic substituents, is a more demanding substrate class for asymmetric conjugate addition than **S1**. The high conformational mobility of this substrate together with the presence of only subtle substrate-catalyst steric interactions makes designing effective enantioselective systems very challenging.[3e,h,10]

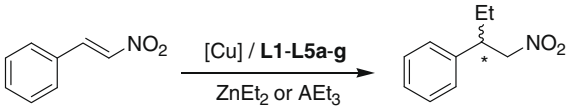


S2 **2** R= Me **3** R= Et (2)

Table 3 shows the most representative results. In general, the ligand requirements were the same as those for the 1,4-addition of **S1**. Again, the best enantioselectivity (ees up to 51%) was obtained with ligand **L4g** (Table 3, entry 10). However, the effects of the reaction parameters (catalyst precursor, solvent, alkylating reagent, and temperature) were different to those observed for **S1**. Therefore, the best enantioselectivities were obtained using CuTC and trimethylaluminum in diethylether at −30 °C (Table 3, entries 10 vs 12–15).

2.2.3. Asymmetric conjugate 1,4-addition of $ZnEt_2$ and $AlEt_3$ to *trans*-nitrostyrene S3

We next applied the ligand library **L1**–**L5a**–**g** to the copper-catalyzed conjugate addition of several alkylating reagents to the linear nitroolefin *trans*-nitrostyrene **S3** (Eq. 3). The nitro group is very important synthetically, because it can be transformed into a variety of valuable organic compounds, such as aldehydes, carboxylic acids, nitriles, nitro oxides, and amines.[11]



S3 **4** (3)

Table 2
Selected results for the Cu-catalyzed asymmetric 1,4-addition of **S1** using ligands **L4f** and **L4g**[a]

Entry	L	Precursor	Alkylating reagent	Solvent	*T*	% Conv[b] (h)	% Yield[b]	% ee[c]
1	**L4f**	CuTC	$ZnEt_2$	Et_2O	−30	100 (18)	86	16 (*R*)
2	**L4g**	CuTC	$ZnEt_2$	Et_2O	−30	100 (18)	90	64 (*S*)
3	**L4f**	CuTC	$AlEt_3$	Et_2O	−30	100 (18)	85	9 (*R*)
4	**L4g**	CuTC	$AlEt_3$	Et_2O	−30	100 (18)	81	36 (*S*)
5	**L4f**	$Cu(OTf)_2$	$ZnEt_2$	CH_2Cl_2	0	100 (0.5)	92	60 (*R*)
6	**L4g**	$Cu(OTf)_2$	$ZnEt_2$	CH_2Cl_2	0	100 (0.5)	94	84 (*S*)

Effect of the reaction parameters.
[a] Reaction conditions: Cu-precursor (2 mol %), ligand (2 mol %), alkylating reagent (1.5 equiv, 0.62 mmol), (0.415 mmol), and solvent (2.5 mL).
[b] Conversion and yields determined by GC analysis using undecane as the internal standard.
[c] Enantiomeric excess measured by GC using Lipodex A column.

Table 3
Selected results for the Cu-catalyzed asymmetric 1,4-addition of **S2** using ligands **L1**–**L5a**–**g**[a]

Entry	L	Precursor	Alkylating reagent	% Conv[b]	% Yield[b]	% ee[c]
1	**L1a**	CuTC	$AlMe_3$	90	76	7 (*R*)
2	**L2a**	CuTC	$AlMe_3$	100	74	11 (*S*)
3	**L3a**	CuTC	$AlMe_3$	92	81	14 (*R*)
4	**L4a**	CuTC	$AlMe_3$	95	74	23 (*S*)
5	**L4b**	CuTC	$AlMe_3$	91	69	14 (*S*)
6	**L4c**	CuTC	$AlMe_3$	87	67	17 (*S*)
7	**L4d**	CuTC	$AlMe_3$	75	68	44 (*R*)
8	**L4e**	CuTC	$AlMe_3$	83	71	5 (*R*)
9	**L4f**	CuTC	$AlMe_3$	88	74	32 (*R*)
10	**L4g**	CuTC	$AlMe_3$	91	79	51 (*S*)
11	**L5d**	CuTC	$AlMe_3$	81	72	39 (*R*)
12	**L4g**	$Cu(OTf)_2$	$AlMe_3$	91	83	35 (*S*)
13	**L4g**	$[Cu(CH_3CN)_4]BF_4$	$AlMe_3$	90	78	18 (*S*)
14	**L4g**	CuTC	$AlEt_3$	96	85	40 (*S*)
15	**L4g**	CuTC	$ZnEt_2$	66	59	5 (*S*)

[a] Reaction conditions: Cu-precursor (2 mol %), ligand (2 mol %), alkylating reagent (1.5 equiv, 0.62 mmol), **S2** (0.415 mmol), Et_2O (2.5 mL), and $T = -30$ °C.
[b] Conversion and yields determined by GC using undecane as the internal standard after 18 h.
[c] Enantiomeric excess measured by GC analysis using a 6-Me-2,3-pe-γ-CD column.

The results are summarized in Table 4. Again, activities and enantioselectivities were affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, and by the configuration of C-3, the introduction of a second phosphoroamidite moiety, and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties **a**–**g**. However, these parameters had a different effect on the conjugate addition of substrates **S1** and **S2**. Thus, the configuration of C-3 controls the sense of enantioselectivity. In this respect, whereas ligands **L1** and **L3** with an (*S*)-configuration at C-3 provide (*S*)-**4**, ligands **L2** and **L4** and **L5** with an opposite configuration at C-3 predominantly provide (*R*)-**4** (Table 4, entries 1 and 3 vs 2, 4, and 9). We also found that diphosphoroamidite ligands provide higher enantioselectivities than the phosphite–phosphoroamidite ligands (Table 4, entries 7 vs 1–6). The effect of the substituents and configurations of the biaryl phosphite/phosphoroamidite moieties **a**–**g** on the enantioselectivity depends of the type of ligand. Thus, in the case of phosphite–phosphoroamidite ligands, enantioselectivities are best when methyl substituents are present at both the *ortho*- and the *para*-positions of the biphenyl moieties, whereas in the case of the diphosphoroamidites, the best ees are obtained when bulky *tert*-butyl groups are present at the *ortho*-positions of the biphenyl moiety (Table 4, entries 7 and 8 vs 9). In summary, and in contrast to the substrates **S1** and **S2**, the best ees (up to 66%) were obtained with homodonor ligands **L5a**–**b** (Table 4, entries 7 and 8).

The effects of the reaction parameters (catalyst precursor, solvent, alkylating reagent, and temperature) were the same as those for the 1,4-addition of **S2**.

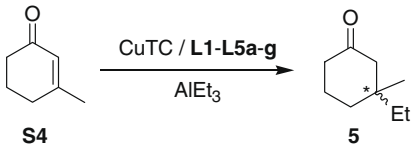
Table 4
Selected results for the Cu-catalyzed asymmetric 1,4-addition of **S3** using ligands **L1**–**L5a**–g[a]

Entry	L	Precursor	Alkylating reagent	% Conv[b]	% Yield[b]	% ee[c]
1	**L1d**	CuTC	$AlEt_3$	100	93	12 (*S*)
2	**L2d**	CuTC	$AlEt_3$	95	90	50 (*R*)
3	**L3d**	CuTC	$AlEt_3$	100	94	60 (*S*)
4	**L4d**	CuTC	$AlEt_3$	100	93	55 (*R*)
5	**L4f**	CuTC	$AlEt_3$	100	86	15 (*S*)
6	**L4g**	CuTC	$AlEt_3$	100	90	29 (*R*)
7	**L5a**	CuTC	$AlEt_3$	100	90	66 (*R*)
8	**L5b**	CuTC	$AlEt_3$	100	88	66 (*R*)
9	**L5d**	CuTC	$AlEt_3$	100	89	6 (*R*)
10[d]	**L5a**	CuTC	$AlEt_3$	80	74	40 (*R*)
11	**L4d**	CuTC	$ZnEt_2$	100	91	42 (*R*)
12	**L5a**	CuTC	$ZnEt_2$	98	87	24 (*R*)
13	**L5a**	$Cu(Otf)_2$	$ZnEt_2$	100	94	5 (*S*)

[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), and $T = -30$ °C.
[b] Conversion and yields determined by GC analysis using undecane as the internal standard after 18 h.
[c] Enantiomeric excess measured by GC analysis using a Lipodex E column.
[d] $T = -78$ °C.

2.3. Asymmetric conjugate 1,4-addition of β,β′-disubstituted enones

To study the potential of ligands **L1**–**L5a**–**g** further, we tested their effect on the copper-catalyzed conjugate addition of triethylaluminum to 3-methyl-cyclohexenone **S4** (Eq. 4). The conjugate addition of this type of substrates provides an efficient way to build stereogenic quaternary centers into a compound.[1]



(4)

For a long time, the 1,4-addition of β,β′-disubstituted enones was unsuccessful because of the low reactivity of these substrates with dialkylzinc reagents. Recently, Alexakis et al. have disclosed that the combination of more reactive trialkylaluminum reagents, together with an appropriate choice of the reaction parameters could be used efficiently for the 1,4-addition of this type of challenging substrates.[12] These latter conditions were used to test the effects of our ligand library on the Cu-conjugate addition of substrate **S4**. The results are summarized in Table 5. The position of the phosphoroamidite and the configuration at C-3 followed the same trends as those for the 1,4-addition of substrates **S1** and **S2** (Table 5, entries 1, 6, 7, and 11). However, the effect of the substituents and configurations on the biaryl phosphite/phosphoroamidite moieties **a**–**g** was different (Table 5, entries 2–6 and 8–13). Therefore, the best enantioselectivites (ees up to 90%) were obtained with ligand **L4e**, which has the phosphoroamidite attached to C-3, an (*R*)-configuration at carbon atom C-3, and allyl substituents at the *ortho*-positions of the biphenyl phosphite/phosphoroamidite moieties (Table 5, entry 11).

Table 5
Selected results for the Cu-catalyzed asymmetric 1,4-addition of **S4** using ligands **L1**–**L5a**–**g**[a]

Entry	L	% Conv[b]	% Yield[b]	% ee[c]
1	**L1e**	6	5	10 (*S*)
2	**L2a**	51	45	30 (*S*)
3	**L2b**	35	29	18 (*S*)
4	**L2c**	<5	—[d]	—[d]
5	**L2d**	<5	—[d]	—[d]
6	**L2e**	15	13	40 (*S*)
7	**L3e**	15	11	56 (*S*)
8	**L4a**	40	34	40 (*S*)
9	**L4b**	20	18	4 (*S*)
10	**L4c**	26	21	14 (*S*)
11[e]	**L4e**	60	52	90 (*S*)
12	**L4f**	18	14	18 (*R*)
13	**L4g**	15	11	33 (*S*)
14	**L5a**	20	15	32 (*S*)

[a] Reaction conditions: CuTC (4 mol %), ligand (4 mol %), $AlEt_3$ (1.5 equiv, 0.62 mmol), **S4** (0.415 mmol), Et_2O (2.5 mL), and $T = -30$ °C.
[b] Conversion and yields determined by GC analysis using undecane as the internal standard after 18 h.
[c] Enantiomeric excess measured by GC using a Lipodex E column.
[d] Not determined.

3. Conclusions

A modular-based phosphite–phosphoroamidite **L1**–**L4a**–**g** and diphosphoroamidite **L5a**–**g** ligand library was tested to determine its effects on the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of cyclic and acyclic enones. Our results indicated that the selectivity depended strongly on the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, as well as the configuration of C-3, the introduction of second phosphoroamidite moiety, the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties **a**–**g,** and on the substrate structure. For β-substituted cyclic **S1** and linear **S2** substrates, enantioselectivities (ees up to 84%) were best with ligand **L4g**, whereas for β-substituted nitro substrate **S3**, the best enantioselectivities (ees up to 66%) were obtained with ligands **L5a**–**b**. The high enantioselectivity (ees up to 90%) obtained for the more challenging β,β′-disubstituted enone **S4** using the CuTC/**L4e** catalytic system should also be noted.

4. Experimental

4.1. General considerations

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Aminoalcohols **1**–**4** and diamine **5** were prepared from D-xylose and D-glucose as described.[4d,5] Ligands **L1**–**L4a**–**c**,[4] **L3d**–**e**,[13] **L1**–**L4f**–**g,**[4d] and **L5a**–**g**[5] were prepared as previously described. All other reagents were used as commercially available. ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. The chemical shifts are referenced to tetramethylsilane (^1H and ^{13}C) as the internal standard or H_3PO_4 (^{31}P) as the external standard. The ^1H and ^{13}C NMR spectral assignments were determined by ^1H–^1H and ^1H–^{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) to which pyridine was added (0.36 mL, 4.6 mmol). Aminoalcohol (1 mmol) was azeotropically dried with toluene (3 × 1 mL) and then dissolved in toluene (10 mL), to which pyridine was added (0.36 mL, 4.6 mmol). The aminoalcohol solution was transferred slowly at 0 °C to the phosphorochloridite solution. The reaction mixture was warmed up 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 by flash chromatography (toluene/NEt_3 = 100/1) to produce the corresponding ligand in the form of a white powder.

L1d: Yield: 0.30 g, 42%. ^{31}P NMR (C_6D_6), δ: 135.3 (s), 145.1 (s). ^1H NMR (C_6D_6), δ: 1.07 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.10 (s, 6H, CH_3), 2.11 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.08 (m, 1H, NH), 3.29 (m, 2H, H-5 and H-5′), 4.03 (m, 1H, H-4), 4.45 (d, 1H, H-2, $^3J_{2-1}$ = 4.0 Hz), 4.53 (m, 1H, H-3), 5.74 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.8–7.2 (m, 8H, CH=). ^{13}C NMR (C_6D_6), δ: 17.4 (CH_3), 17.7 (CH_3), 17.9 (CH_3), 21.1 (CH_3), 26.3 (CH_3), 27.9 (CH_3), 28.1 (CH_3), 58.5 (m, C-3), 64.1 (C-5), 79.5 (C-4), 86.8 (C-2), 105.1 (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, 65.81; H, 6.26; N, 1.90.

L1e: Yield: 0.32 g, 41%. ^{31}P NMR (C_6D_6), δ: 141.3 (s), 146.1 (s). ^1H NMR (C_6D_6), δ: 0.98 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 3.11 (m, 1H, NH), 3.25 (m, 2H, H-5 and H-5′), 3.33–3.62 (m, 8H, CH_2), 4.11 (m, 1H, H-4), 4.37 (d, 1H, H-2, $^3J_{2-1}$ = 4.0 Hz), 4.50 (m, 1H, H-3), 4.99 (m, 8H, CH_2=), 5.72 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 5.91 (m, 4H, CH=), 6.8–7.2 (m, 12H, CH=). ^{13}C NMR(C_6D_6), δ: 26.0 (CH_3), 26.7 (CH_3), 34.6 (CH_2), 34.7 (CH_2), 34.9 (CH_2), 39.5 (d, C-5, J_{C-P} = 15.2 Hz), 77.4 (C-3), 80.9 (C-4), 84.9 (C-2), 105.0 (C-1), 111.6 (CMe_2), 115.8 (CH_2=), 116.0 (CH_2=), 116.3 (CH_2=), 116.8 (CH_2=), 124.4 (CH=), 125.2 (CH=), 128.4 (CH=), 128.6 (CH=), 129.4 (CH=), 129.5 (CH=), 130.3 (CH=), 130.5 (CH=), 131.4 (C), 131.9 (C), 132.1 (C), 132.4 (C), 132.5 (C), 136.2 (CH= allyl), 136.8 (CH= allyl), 136.9 (CH= allyl), 147.8 (C), 149.0 (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, 68.02; H, 5.87; N, 1.82.

L2d: Yield: 0.42 g, 57%. ^{31}P NMR (C_6D_6), δ: 136.9 (s), 144.9 (s). ^1H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.11 (s, 6H, CH_3), 2.19 (s, 6H, CH_3), 2.28 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.95 (m, 1H, NH), 3.69 (m, 1H, H-3), 4.13 (m, 1H, H-5'), 4.22 (m, 2H, H-4, H-5), 4.35 (m, 1H, H-2), 5.52 (d, 1H, H-1, $^3J_{1-2}$ = 4.0 Hz), 6.8–7.2 (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), 40.4 (m, C-5), 68.9 (C-3), 76.3 (C-4), 78.4 (C-2), 104.2 (C-1), 111.1 (CMe_2), 126.0 (CH=), 128.9 (CH=), 129.7 (CH=), 130.3 (C), 130.2 (C), 130.5 (C), 131.6 (CH=), 131.9 (CH=), 132.5 (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, 65.88; H, 6.24; N, 1.89.

L2e: Yield: 0.33 g, 43%. ^{31}P NMR (C_6D_6), δ: 139.8 (s), 143.3 (s). ^1H NMR (C_6D_6), δ: 1.12 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.94 (m, 1H, NH), 3.13 (m, 1H, H-5), 3.25 (m, 1H, H-5'), 3.32–3.64 (b, 8H, CH_2), 4.02 (m, 3H, H-2, H-3, H-4), 5.03 (m, 8H, CH_2=), 5.27 (d, 1H, H-1, $^3J_{1-2}$ = 4.2 Hz), 5.92 (m, 4H, CH=), 6.8–7.2 (m, 12H, CH=). ^{13}C NMR (C_6D_6), δ: 26.6 (CH_3), 26.9 (CH_3), 34.2 (CH_2), 34.4 (CH_2), 34.6 (CH_2), 34.9 (CH_2), 40.3 (m, C-5, J_{C-P} = 15.2 Hz), 69.3 (C-3), 75.3 (C-4), 79.4 (C-2), 103.2 (C-1), 112.3 (CMe_2), 115.8 (CH_2=), 116.0 (CH_2=), 116.2 (CH_2=), 116.4 (CH_2=), 124.0 (CH=), 124.5 (CH=), 128.2 (CH=) 128.4 (CH=), 129.1 (CH=), 129.3 (CH=), 129.9 (CH=), 130.0 (CH=), 131.2 (C), 131.4 (C), 131.8 (C), 131.9 (C), 132.3 (C), 135.4 (CH= allyl), 135.6 (CH= allyl), 135.7 (CH= allyl), 135.9 (CH= allyl), 147.7 (C), 149.1 (C), 149.2 (C). Anal. Calcd for $C_{44}H_{45}NO_8P_2$: C, 67.95; H, 5.83; N, 1.80. Found: C, 68.01; H, 5.81; N, 1.82.

L4d: Yield: 0.35 g, 49%. ^{31}P NMR (C_6D_6), δ: 139.3 (s), 143.9 (s). ^1H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.05 (s, 3H,

CH_3), 2.07 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.30 (s, 6H, CH_3), 2.33 (s, 3H, CH_3), 3.35 (m, 1H, NH), 3.54 (m, 1H, H-4), 3.61 (m, 1H, H-3), 3.88 (m, 1H, H-2), 4.05 (m, 1H, H-5), 4.31 (m, 1H, H-5′), 5.43 (d, 1H, H-1, $^3J_{1-2}$ = 3.6 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), 17.5 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 26.8 (CH_3), 27.1 (CH_3), 53.4 (d, C-3, J_{C-P} = 14.4 Hz), 62.6 (d, C-5, J_{C-P} = 5.3 Hz), 80.8 (C-2), 81.0 (C-4), 104.8 (C-1), 112.3 (CMe_2), 126.0 (CH=), 128.7 (CH=), 128.8 (CH=), 129.6 (CH=), 130.2 (C), 130.6 (C), 130.7 (C), 131.4 (CH=), 131.6 (CH=), 131.8 (CH=), 131.9 (CH=), 132.2 (C), 132.4 (C), 133.9 (C), 134.0 (C), 146.9 (C), 147.2 (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, 65.86; H, 6.24; N, 1.94.

L4e: Yield: 0.29 g, 39%. ^{31}P NMR (C_6D_6), δ: 142.3 (s), 145.8 (s). ^{1}H NMR (C_6D_6), δ: 1.04 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 3.24 (m, 1H, H-3), 3.36 (m, 1H, H-4), 3.58 (m, 5H, NH, CH_2), 3.78 (m, 1H, H-2), 3.92 (m, 1H, H-5), 4.21 (m, 1H, H-5′), 5.01 (m, 4H, CH_2=), 5.42 (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: 26.7 (CH_3), 27.0 (CH_3), 35.1 (CH_2), 35.2 (CH_2), 35.3 (CH_2), 35.5 (CH_2), 53.6 (d, C-3, J_{C-P} = 12 Hz), 63.3 (d, C-5, J_{C-P} = 6.2 Hz), 80.6 (C-2 and C-4), 104.7 (C-1), 112.3 (CMe_2), 116.7 (CH_2=), 116.8 (CH_2=), 125.2 (CH=), 125.4 (CH=), 128.9 (CH=) 129.6 (CH=), 129.7 (CH=), 130.1 (CH=), 132.6 (C), 132.8 (C), 133.3 (C), 136.8 (CH= allyl), 137.1 (CH= allyl), 137.2 (CH= allyl), 137.3 (CH= allyl), 148.8 (C), 149.2 (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, 67.94; H, 5.82; N, 1.84.

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 (8.3 μmol) in the appropriate solvent (2 mL) was stirred for 30 min at room temperature. After cooling to the desired temperature, the alkylating reagent (0.62 mmol) was added. A solution of the desired enone (0.415 mmol) and undecane as a 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.[3i]

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