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Screening of a modular sugar-based phosphite ligand library in the Cu-catalyzed asymmetric 1,4-addition reactions

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Abstract

A sugar-based monophosphite ligand library **L1**–**L5** was screened in the Cu-catalyzed asymmetric 1,4-addition to cyclic and aliphatic linear enones. These ligands are derived from D-glucose, D-galactose and D-fructose, which lead to a wide range of sugar backbones, and contain several substituents/configurations in the biaryl moiety, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that the catalytic performance (activities and enantioselectivities) is highly affected by the configuration of C-4 of the carbohydrate backbone, the size of the ring of the sugar backbone and the cooperative effect between configurations of C-3 and of the binaphthyl phosphite moiety. Good activities and enantioselectivities up to 57% and 51% were achieved for cyclic and aliphatic linear enones, respectively.

Keywords: Sugar-based phosphite ligands; Copper; Asymmetric catalysis; 1,4-Addition

1. Introduction

The asymmetric copper-catalyzed conjugate addition is, nowadays, a well-developed methodology to create chiral C–C bonds [1]. Many efforts have been made in designing efficient systems and identifying new ligands to improve enantioselectivities with specific classes of substrates [1]. Among the most efficient ligands, phosphite and phosphoroamidites based on biaryl moieties have played a prominent role [1g,2]. Although Michael additions of organolithium, Grignard and diorganozinc reagents to enones have been widely studied in the last decade [1], less attention has been paid to trialkylaluminium reagents [3]. Trialkylaluminum reagents has been recently appeared as an interesting alternative to organozinc reagents since the potential exists to more easily extend their range by technically simple hydro- and carboalumination reactions. Additionally, they allow Cu-catalyzed 1,4-addition to very challenging substrates (i.e. β-trisubstituted enones) which are inert to organozinc methodologies [3]. On the other hand, linear aliphatic enones is another class of substrate for which the development of more active and enantioselective catalysts is still needed [1].

Encouraged by the success of monophosphite ligands in this process, we report here the use of a highly modular sugar-based monophosphite ligand library (**L1**–**L5a**–**f**) in the Cu-catalyzed asymmetric 1,4-addition of trialkylaluminium to cyclic and aliphatic linear enones. These ligands have the advantage of carbohydrate and phosphite ligands, such as availability at low price from readily available alcohols, high resistance to oxidation and facile modular constructions [4]. Therefore, with this library we fully investigated the effects of systematically varying the configurations at C-3 and C-4 of the ligand backbone (**L1**–**L3**), different substituents/configurations in the biaryl phosphite moiety (**a**–**f**), the carbohydrate ring size (**L1**–**L4**) and the flexibility of the ligand backbone (**L4**–**L5**) (Fig. 1).

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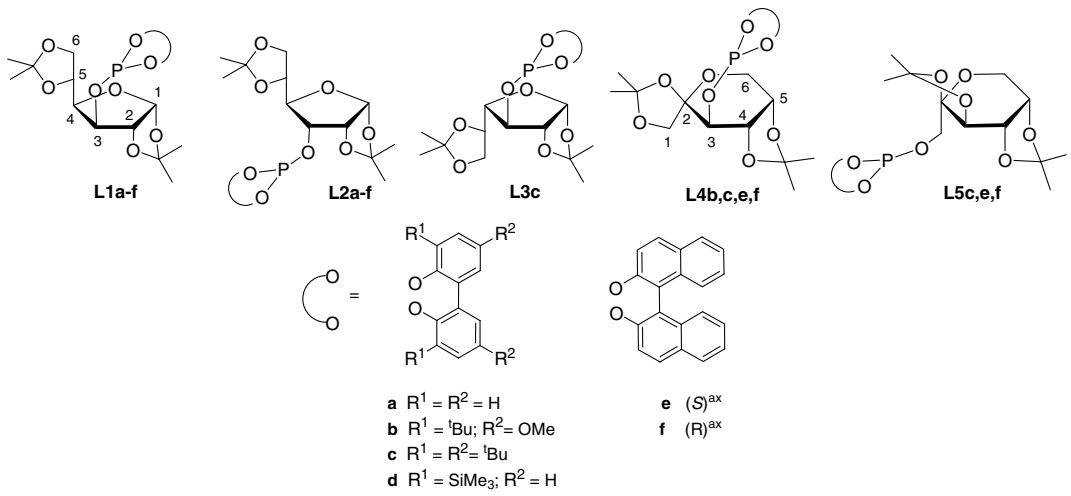


Fig. 1. Carbohydrate-based phosphite ligands **L1**–**L5a**–**f**.

2. Results and discussion

2.1. Ligand design

The sugar-based monophosphite ligands are derived from D-glucose, D-galactose and D-fructose, which lead to a wide range of sugar backbones (**L1**–**L5**), and contain several substituents/configurations in the biaryl moiety (**a**–**f**), with different steric and electronic properties, whose effect on the catalytic performance will be studied. Therefore, ligands **L1**–**L5a**–**f** consist of chiral di-O-protected either furanoside (ligands **L1**–**L3**) or pyranoside (ligands **L4** and **L5**) backbones, which determine their underlying structure, and one hydroxyl group. Several phosphoric acid biaryl esters (**a**–**f**) were attached to these basic frameworks (Fig. 1).

The influence of the different groups attached to the *ortho*- and *para*-positions of the biphenyl moieties on enantioselectivity was investigated using ligands **L1a**–**d**, which have the same configuration on the 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 **L1e**–**f** and **L2e**–**f**.

We studied the effects of the stereogenic carbon atom C-3 on enantioselectivity by comparing diastereomeric ligands **L1** and **L2** which have opposite configuration at C-3. The influence of the configuration of carbon atom C-4 in the catalytic performance was studied using ligands **L1** and **L3** which only differ in the configuration at C-4.

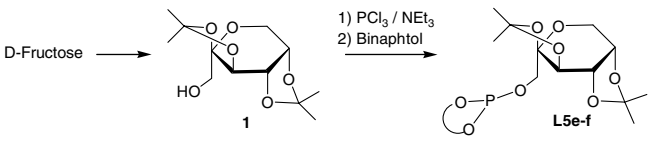
The influence of the carbohydrate ring size in the catalytic performance of the Pd-catalysts was studied with ligands **L4**, which have a pyranoside backbone and the same configuration at C-3 than furanoside ligand **L1**. Finally, with ligands **L5** we studied how the flexibility of the ligand backbone may affect the catalytic performance. These ligands have a pyranoside backbone as ligands **L4**, but differs from the rest of ligands in a phosphite moiety attached to a primary alcohol, providing a more flexible ligand.

2.2. Synthesis of ligands

Ligands **L5e** and **L5f** were efficiently synthesized in one step using the methodology previously described for related ligands **L1**–**L2a**–**f**, **L3c**, **L4b**,**c**,**e**,**f** and **L5c** [5]. Therefore, these ligands were achieved by reaction of the corresponding sugar alcohol (**1**) with 1 equiv. of PCl_3 and subsequent addition of the binaphthyl alcohols (**e** and **f**) in the presence of triethylamine (Scheme 1) [5]. Compound **1** was easily prepared on a large scale from inexpensive D-(−)-fructose [6]. Ligands **L5e** and **L5f** were stable during purification on neutral silica under an atmosphere of argon and isolated in low yields (14%) as white solids. The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these C_1 ligands (see Section 4).

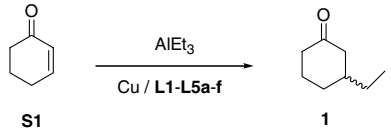
2.3. Asymmetric conjugated 1,4-addition of $AlEt_3$ to 2-cyclohexenone S1 (Eq. 1)

In a first set of experiments, we tested ligands **L1**–**L5** in the copper-catalyzed conjugated addition of triethylaluminium to 2-cyclohexenone **S1** (Eq. (1)). The latter was used as a substrate because this reaction has been performed with a wide range of ligands with several donor groups enabling to direct comparison of the efficiency of various ligand systems [1]. The catalytic system was



Scheme 1. Synthesis of phosphite ligands **L5e** and **L5f**.

generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor.



(1)

The effect of several reaction parameters, such as catalyst precursor, solvent, ligand-to-copper ratio and temperature, were studied using ligand **L1f** (Table 1). The best result was obtained using dimethoxyethane (DME) as solvent, $Cu(OAc)_2$ as catalyst precursor and a ligand-to-copper ratio of 4 at −30 °C (Table 1, entry 9).

Under the optimized conditions, we evaluated the rest of ligands. The results, which are summarized in Table 2, indicated that selectivities are highly affected by the configuration of C-4 of the carbohydrate backbone, the size of the ring of the sugar backbone and the cooperative effect between the configurations of C-3 and of the binaphthyl phosphite moiety. In all cases, the formation of byproducts has been observed.

The results using ligands **L1a–f** and **L2a–f** allow us to study the influence of the substituents/configurations of the biaryl moiety and the effect of the configuration at C-3 on the product outcome (Table 2, entries 1–11). We found that there is a cooperative effect between the configuration of C-3 and the configuration of the biaryl moiety. This resulted in a matched combination for ligand **L2e** (Table 2, entry 11). In addition, we also found that the biphenyl phosphite moieties in ligands **L1a–d** adopted an *R* configuration (Table 2, entries 1–4 vs. 5 and 6), while in ligands **L2a–d** they adopted an *S* configuration (Table 2, entries 7–10 vs. 11 and 12) when coordinated to the copper-active species. Comparing the results using ligands **L1** with **L3**, that only differ in the configuration at C-4, we found that ligands **L3** with an *S* configuration at C-4 gave lower enantioselectivities than ligands **L1** with an opposite configuration at this position (Table 2, entries 1–6 and 13). In addition, ligands **L4** and **L5** which have a pyranoside backbone provided lower yields and enantioselectivities than furanoside ligands (Table 2, entries 14–20). In

Table 2
Selected results for the copper-catalyzed conjugate 1,4-addition of **S1** using ligands **L1–L5a–f**[a]

Entry	Ligand	% Conv[b]	% Yield[c]	% ee[d]
1	**L1a**	99	61	21 (*R*)
2	**L1b**	99	61	37 (*R*)
3	**L1c**	98	10	8 (*R*)
4	**L1d**	99	61	21 (*R*)
5	**L1e**	98	24	20 (*S*)
6	**L1f**	96	77	48 (*R*)
7	**L2a**	92	23	6 (*S*)
8	**L2b**	98	31	15 (*S*)
9	**L2c**	99	28	23 (*S*)
10	**L2d**	91	15	14 (*S*)
11	**L2e**	99	55	57 (*R*)
12	**L2f**	93	17	7 (*S*)
13	**L3c**	99	23	4 (*R*)
14	**L4b**	98	11	8 (*S*)
15	**L4c**	94	8	4 (*S*)
16	**L4e**	99	56	12 (*S*)
17	**L4f**	100	33	2 (*S*)
18	**L5c**	99	18	8 (*S*)
19	**L5e**	99	18	23 (*S*)
20	**L5f**	100	46	33 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), ligand (4 mol%), $AlMe_3$ (1.4 equiv., 0.4 mmol), **S1** (0.28 mmol), DME (2 mL).
[b] % Conversion determined by GC using undecane as internal standard after 2 h.
[c] % Yield determined by GC.
[d] Enantiomeric excess measured by GC using Lipodex A column.

Table 1
Selected results for the copper-catalyzed conjugate 1,4-addition of **S1** using ligand **L1f**[a]

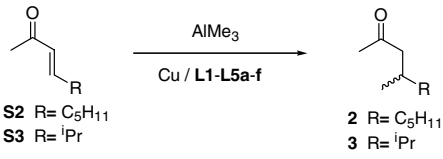
Entry	Solvent	Precursor	*T* (°C)	% Conv[b]	% Yield[c]	% ee[d]
1	Et_2O	CuTC	−30	99	8	4 (*R*)
2	Et_2O	$Cu(OTf)_2$	−30	96	21	9 (*R*)
3	Et_2O	$Cu(OAc)_2$	−30	88	31	14 (*R*)
4	Et_2O	$[Cu(MeCN)_4]BF_4$	−30	98	18	5 (*R*)
5	Et_2O	CuI	−30	90	10	5 (*R*)
6	^tBuOMe	$Cu(OAc)_2$	−30	84	40	1 (*R*)
7	CH_2Cl_2	$Cu(OAc)_2$	−30	100	9	13 (*R*)
8	THF	$Cu(OAc)_2$	−30	83	8	35 (*R*)
9	DME	$Cu(OAc)_2$	−30	96	77	48 (*R*)
10[e]	DME	$Cu(OAc)_2$	−30	87	16	12 (*R*)
11[f]	DME	$Cu(OAc)_2$	−30	98	24	28 (*R*)
12	DME	$Cu(OAc)_2$	−20	99	10	36 (*R*)
13	DME	$Cu(OAc)_2$	−40	95	29	10 (*R*)

Effect of the catalyst precursor, solvent, temperature and ligand-to-copper ratio.
[a] Reaction conditions: Cu-precursor (1 mol%), **L1f** (4 mol%), $AlEt_3$ (1.4 equiv., 0.4 mmol), **S1** (0.28 mmol), solvent (2 mL).
[b] % Conversion determined by GC using undecane as internal standard after 2 h.
[c] % Yield determined by GC using undecane as internal standard after 2 h.
[d] Enantiomeric excess measured by GC using Lipodex A column.
[e] Ligand (1 mol%).
[f] Ligand (2 mol%).

summary, the best results was obtained with ligand **L2e** that contains the best combination of the ligand parameters (ee values up to 57%; Table 2, entry 11).

2.4. Asymmetric conjugated 1,4-addition of $AlMe_3$ to linear substrates S2 and S3 (Eq. (2))

In this section, we report the use of ligands **L1**–**L5a**–**f** in the copper-catalyzed conjugated addition of trimethylaluminium (Eq. (2)) to two linear substrates with different steric properties: *trans*-3-nonen-2-one **S2** and *trans*-5-methyl-3-hexen-2-one **S3**. These enones possessing only aliphatic substituents are a more demanding substrate class for asymmetric conjugated addition than **S1**. The high conformational mobility of these substrates together with the presence of only subtle substrate–catalyst steric interactions makes the design of effective enantioselective systems a real challenge [3e,7].



(2)

We first investigated the copper-catalyzed 1,4-addition of *trans*-3-nonen-2-one **S2** (Eq. (1), $R = C_5H_{11}$) with trimethylaluminium. Table 3 summarized the preliminary investigations into the solvent effect, the catalyst precursor and the ligand-to-copper ratio. The results indicated that the optimum trade-off between yields and enantioselectivity was obtained when diethylether was used as a solvent, the ligand-to-copper ratio was 4 and $Cu(OTf)_2$ was used as a catalyst precursor (Table 3, entry 2).

Under optimized conditions, the results with the rest of ligands indicated that yield and enantioselectivities followed a different trend regarding the effect of the size of the ring of the sugar backbone and the cooperative effect between the configurations of C-3 and of the binaphthyl phosphite moiety to those observed for substrate **S1** (Table 4). Therefore, pyranoside ligands **L4** provided better enantioselectivities than their relative furanoside **L1** ligands and the cooperative effect between C-3 and binaphthyl moieties resulted in a matched combination for ligand **L1f**. In summary, the best result (ee values up to 52%) was obtained with ligand **L4f** that contains the best combination of the ligand parameters (Table 4, entry 17).

Table 4
Selected results for the copper-catalyzed conjugate 1,4-addition of **S2** using ligands **L1**–**L4a**–**f**[a]

Entry	Ligand	% Conv[b]	% Yield[c]	% ee[d]
1	**L1a**	32	6	8 (*R*)
2	**L1b**	66	48	18 (*R*)
3	**L1c**	99	79	18 (*R*)
4	**L1d**	93	51	4 (*R*)
5	**L1e**	95	53	42 (*S*)
6	**L1f**	96	51	48 (*R*)
7	**L2a**	38	9	10 (*S*)
8	**L2b**	77	83	8 (*S*)
9	**L2c**	72	65	8 (*S*)
10	**L2d**	95	52	13 (*S*)
11	**L2e**	97	40	24 (*S*)
12	**L2f**	98	50	28 (*R*)
13	**L3c**	89	63	1 (*R*)
14	**L4b**	87	49	7 (*S*)
15	**L4c**	87	49	8 (*S*)
16	**L4e**	99	61	46 (*S*)
17	**L4f**	91	66	52 (*R*)
18	**L5c**	92	64	9 (*S*)
19	**L5e**	40	11	13 (*S*)
20	**L5f**	26	4	7 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), ligand (4 mol%), $AlMe_3$ (1.4 equiv., 0.4 mmol), **S2** (0.28 mmol), Et_2O (2 mL).
[b] % Conversion determined by GC using undecane as internal standard after 2 h.
[c] % Yield determined by GC using undecane as internal standard after 2 h.
[d] Enantiomeric excess measured by GC using 6-Me-2,3-pe-δ-CD column [3h].

Table 3
Selected results for the copper-catalyzed conjugate 1,4-addition of **S2** using ligands **L1c**[a]

Entry	Solvent	Precursor	*T* (°C)	% Conv[b]	% Yield[c]	% ee[d]
1	Et_2O	CuTC	−30	97	21	3 (*S*)
2	Et_2O	$Cu(OTf)_2$	−30	99	79	18 (*R*)
3	Et_2O	$Cu(OAc)_2$	−30	93	31	7 (*S*)
4	Et_2O	$[Cu(MeCN)_4]BF_4$	−30	85	25	4 (*S*)
5	^tBuOMe	$Cu(OTf)_2$	−30	95	62	11 (S)
6	CH_2Cl_2	$Cu(OTf)_2$	−30	95	55	19 (*S*)
7	THF	$Cu(OTf)_2$	−30	31	7	3 (*S*)
8[e]	Et_2O	$Cu(OTf)_2$	−30	90	48	15 (*R*)
9[f]	Et_2O	$Cu(OTf)_2$	−30	91	51	15 (*R*)
10	Et_2O	$Cu(OTf)_2$	−20	88	52	15 (*R*)
11	Et_2O	$Cu(OTf)_2$	−40	93	56	18 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), **L1c** (4 mol%), $AlMe_3$ (1.4 equiv., 0.4 mmol), **S2** (0.28 mmol), solvent (2 mL).
[b] % Conversion determined by GC using undecane as internal standard after 2 h.
[c] % Yield determined by GC using undecane as internal standard after 2 h.
[d] Enantiomeric excess measured by GC using 6-Me-2,3-pe-δ-CD column [3h].
[e] Ligand (1 mol%).
[f] Ligand (2 mol%).

Table 5
Selected results for the copper-catalyzed conjugate 1,4-addition of **S3** using ligands **L1**–**L5a**–**f**[a]

Entry	Ligand	% Conv[b]	% Yield[c]	% ee[d]
1	**L1a**	14	3	9 (*R*)
2	**L1b**	26	23	20 (*R*)
3	**L1c**	96	96	39 (*R*)
4	**L1d**	95	95	21 (*R*)
5	**L1e**	90	77	30 (*S*)
6	**L1f**	56	39	29 (*R*)
7	**L2a**	10	3	4 (*S*)
8	**L2b**	95	95	12 (*S*)
9	**L2c**	95	95	7 (*S*)
10	**L2d**	82	77	3 (*S*)
11	**L2e**	95	91	48 (*S*)
12	**L2f**	42	32	17 (*R*)
13	**L3c**	96	96	22 (*R*)
14	**L4c**	96	96	33 (*R*)
15	**L4e**	98	98	48 (*S*)
16	**L4f**	97	97	52 (*R*)
17	**L5c**	98	98	12 (*R*)
18	**L5e**	40	40	14 (*S*)
19	**L5f**	6	4	10 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), ligand (4 mol%), $AlMe_3$ (1.4 equiv., 0.4 mmol), **S3** (0.28 mmol), Et_2O (2 mL).
[b] % Conversion determined by GC using undecane as internal standard after 2 h.
[c] % Yield determined by GC using undecane as internal standard after 2 h.
[d] Enantiomeric excess measured by GC using 6-Me-2,3-pe-δ-CD column [3h].

We finally studied the copper-catalyzed 1,4-addition of *trans*-5-methyl-3-hexen-2-one **S3** (Eq. (1), R = ^{i}Pr) with trimethylaluminium. The results are summarized in Table 5. Trends were similar to those observed for the previous substrate **S2**. Therefore, the best enantioselectivity (ee values up to 52%) was obtained with ligand **L4f** that contains an *R* binaphthyl phosphite moiety attached to the pyranoside backbone (Table 5, entry 16).

3. Conclusions

The sugar-based monophosphite ligand library **L1**–**L5a**–**f** was tested in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of cyclic and acyclic enones. Our results indicated that activity and selectivity depended strongly on the configuration of C-4 of the carbohydrate backbone, the size of the ring of the sugar backbone, the cooperative effect between configurations of C-3 and of the binaphthyl phosphite moiety and the substrate type. For cyclic substrate **S1**, enantioselectivities (up to 57%) were therefore best with ligand **L2e**, while for aliphatic linear substrates **S2** and **S3**, the best ligand was **L4f** (ee values up to 51%).

4. Experimental

4.1. General comments

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L1**–**L2a**–**f**, **L3c**, **L4b**,**c**,**e**,**f** and **L5c** [5] and substrate **S3** [3e] were prepared as previously described. All other reagents were used as commercially available.

4.2. Synthesis of the chiral monophosphite ligands

4.2.1. Ligand *L5e*

To a stirred solution of **1** (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 (*S*)-binaphthol (1.5 mmol) was added and the resulting mixture was allowed to warm to room temperature and stirred overnight. Diethyl ether was added and 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 120 mg (14%) of a white solid. ^{31}P NMR (C_6D_6) $\delta = 137.7$ (s). ^{1}H NMR (C_6D_6) $\delta = 1.20$ (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.60 (s, 6H, CH_3), 3.74 (m, 2H), 3.90 (m, 2H), 4.44 (m, 1H), 4.56 (m, 1H), 4.73 (d, 1H, $J = 2.4$ Hz), 7.03–7.76 (m, 12H, CH=). ^{13}C NMR ($CDCl_3$) $\delta = 24.0$ (CH_3), 25.5 (CH_3), 25.6 (CH_3), 26.6 (CH_3), 61.1 (CH), 64.9 (d, CH, $J_{c\text{-}p} = 4$ Hz), 69.7 (CH), 70.1 (CH), 70.8 (CH), 101.9 (C), 108.9 (C), 109.0 (C), 117.8 (C), 121.7 (CH=), 121.9 (CH=), 122.5 (C), 124.0 (C), 124.9 (CH=), 125.1 (CH=), 126.2 (CH=), 126.3 (CH=), 126.9 (CH=), 127.0 (CH=), 128.4 (CH=), 130.2 (CH=), 130.4 (CH=), 131.0 (C), 131.6 (C), 132.5 (C), 132.8 (C), 147.3(C), 148.6(C). Anal. Calc. for $C_{32}H_{31}O_8P$: C, 66.89; H, 5.44. Found: C, 66.93; H, 5.32%.

4.2.2. Ligand *L5f*

Treatment of (*R*)-binaphthol (1.5 mmol) and **1** (390 mg, 1.5 mmol), as described for compound **L5e**, afforded phosphite **L5f**, which was purified by flash chromatography (eluent CH_2Cl_2, R_f: 0.28) to produce 110 mg (12%) of a white solid. ^{31}P NMR (C_6D_6) $\delta = 140.5$ (s). ^{1}H NMR (C_6D_6) $\delta = 1.12$ (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.55 (m, 1H), 3.70 (m, 2H), 4.06 (m, 1H), 4.38 (m, 2H), 4.55 (d, 1H, $J = 3.2$ Hz), 6.85–7.58 (m, 12H, CH=). ^{13}C NMR ($CDCl_3$) $\delta = 24.1$ (CH_3), 25.3 (CH_3), 26.0 (CH_3), 26.5 (CH_3), 61.2 (CH), 64.8 (CH), 69.8 (CH), 70.2 (CH), 70.8 (CH), 101.9 (C), 108.8 (C), 109.0 (C), 117.8 (C), 120.5 (C), 121.5 (CH=), 122.0 (CH=), 123.1 (C), 124.0 (C), 125.0 (CH=), 125.1 (CH=), 126.3 (CH=), 127.0 (CH=), 128.3 (CH=), 128.4 (CH=), 130.2 (CH=), 130.4 (CH=), 131.0 (C), 131.5 (C), 132.8 (C), 147.1 (C), 148.5 (C). Anal. Calc. for $C_{32}H_{31}O_8P$: C, 66.89; H, 5.44. Found: C, 66.78; H, 5.48%.

4.3. General procedure for the 1,4-addition to substrates *S1–S3*

In a typical procedure, a solution of copper-catalyst precursor (1 mol%) and the corresponding ligand (4 mol%) in 2 mL of solvent was stirred for 30 min at room temperature. Then, the substrate (0.28 mmol) was added at the corresponding temperature and next the desired alkylating organometallic reagent (1.4 equiv., 0.4 mmol) was added dropwise. After 2 h, the reaction was quenched with HCl (5 mL, 2 M). Then, undecane (50 μL) was added and the organic layer was filtered twice through a plug of silica. Yields and enantiomeric excesses were measured by GC [3h].

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