

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

Abstract. The sugar-based monophosphite ligand library **L7-L11a-f** was also tested 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.

6.3.1. 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 phosphoramidites based on biaryl moieties have played a prominent role.^{1f-h,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 (**L7-L11a-f**) in the Cu-catalyzed asymmetric 1,4-addition of trialkylaluminum 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 (**L7-L9**), different substituents/configurations in the biaryl phosphite moiety (**a-f**), the carbohydrate ring size (**L7-L10**) and the flexibility of the ligand backbone (**L10-L11**) (Figure 1).

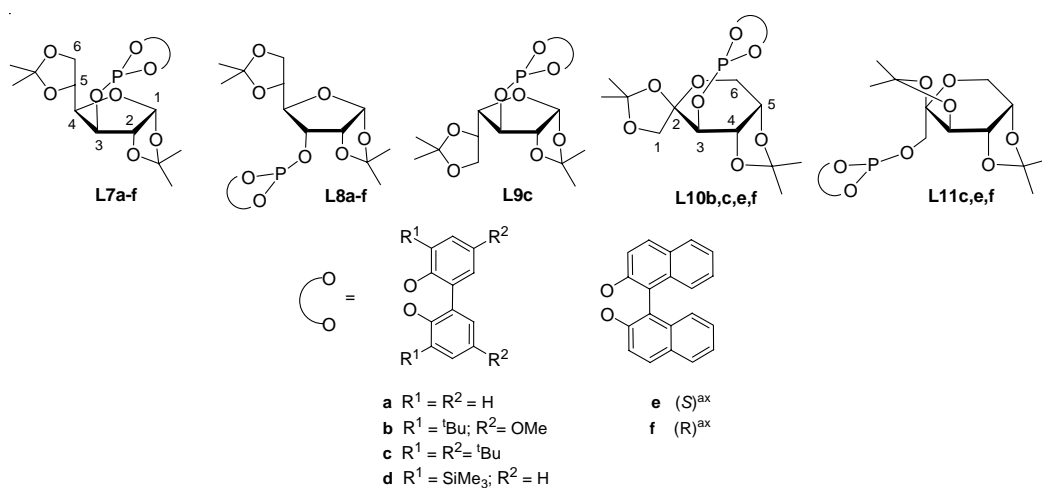
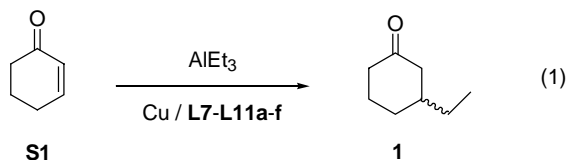


Figure 1. Carbohydrate-based phosphite ligands **L7-L11a-f**.

6.3.2. Results and Discussion

6.3.2.1. Asymmetric conjugated 1,4-addition of AlEt_3 to 2-cyclohexenone **S1** (equation 1)

In a first set of experiments, we tested ligands **L7-L11a-f** 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 generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor.



The effect of several reaction parameters, such as catalyst precursor, solvent, ligand-to-copper ratio and temperature, were studied using ligand **L7f** (Table 1). The best result was obtained using dimethoxyethane (DME) as solvent, $\text{Cu}(\text{OAc})_2$ as catalyst precursor and a ligand-to-copper ratio of 4 at $-30\text{ }^\circ\text{C}$ (Table 1, entry 9).

Table 1. Selected results for the copper-catalyzed conjugate 1,4-addition of **S1** using ligand **L7f**. Effect of the catalyst precursor, solvent, temperature and ligand-to-copper ratio.

Entry	Solvent	Precursor	T (°C)	%Conv ^b	%Yield ^c	%ee ^d
1	Et ₂ O	CuTC	-30	99	8	4 (<i>R</i>)
2	Et ₂ O	Cu(OTf) ₂	-30	96	21	9 (<i>R</i>)
3	Et ₂ O	Cu(OAc) ₂	-30	88	31	14 (<i>R</i>)
4	Et ₂ O	[Cu(MeCN) ₄]BF ₄	-30	98	18	5 (<i>R</i>)
5	Et ₂ O	CuI	-30	90	10	5 (<i>R</i>)
6	^t BuOMe	Cu(OAc) ₂	-30	84	40	1 (<i>R</i>)
7	CH ₂ Cl ₂	Cu(OAc) ₂	-30	100	9	13 (<i>R</i>)
8	THF	Cu(OAc) ₂	-30	83	8	35 (<i>R</i>)
9	DME	Cu(OAc) ₂	-30	96	77	48 (<i>R</i>)
10 ^e	DME	Cu(OAc) ₂	-30	87	16	12 (<i>R</i>)
11 ^f	DME	Cu(OAc) ₂	-30	98	24	28 (<i>R</i>)
12	DME	Cu(OAc) ₂	-20	99	10	36 (<i>R</i>)
13	DME	Cu(OAc) ₂	-40	95	29	10 (<i>R</i>)

^a Reaction conditions: Cu-precursor (1 mol%), **L7f** (4 mol%), AlEt₃ (1.4 eq, 0.4 mmol), **S1** (0.28 mmol), solvent (2 mL). ^b % Conversion determined by GC using undecane as internal standard after 2 hours. ^c % Yield determined by GC using undecane as internal standard after 2 hours. ^d Enantiomeric excess measured by GC using Lipodex A column. ^e ligand (1 mol%). ^f ligand (2 mol%).

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.

Table 2. Selected results for the copper-catalysed conjugate 1,4-addition of **S1** using ligands **L7-L11a-f**.

Entry	Ligand	%Conv ^b	%Yield ^c	%ee ^d
1	L7a	99	61	21 (<i>R</i>)
2	L7b	99	61	37 (<i>R</i>)
3	L7c	98	10	8 (<i>R</i>)
4	L7d	99	61	21 (<i>R</i>)
5	L7e	98	24	20 (<i>S</i>)
6	L7f	96	77	48 (<i>R</i>)
7	L8a	92	23	6 (<i>S</i>)
8	L8b	98	31	15 (<i>S</i>)
9	L8c	99	28	23 (<i>S</i>)
10	L8d	91	15	14 (<i>S</i>)
11	L8e	99	55	57 (<i>R</i>)
12	L8f	93	17	7 (<i>S</i>)
13	L9c	99	23	4 (<i>R</i>)
14	L10b	98	11	8 (<i>S</i>)
15	L10c	94	8	4 (<i>S</i>)
16	L10e	99	56	12 (<i>S</i>)
17	L10f	100	33	2 (<i>S</i>)
18	L11c	99	18	8 (<i>S</i>)
19	L11e	99	18	23 (<i>S</i>)
20	L11f	100	46	33 (<i>R</i>)

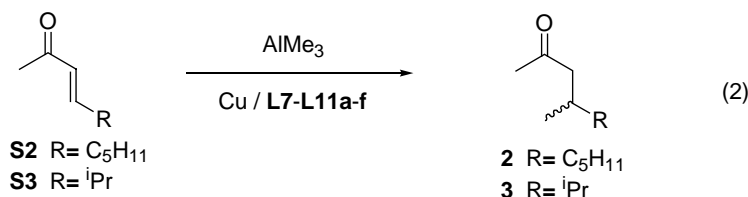
^a Reaction conditions: Cu(OTf)₂ (1 mol%), ligand (4 mol%), AlMe₃ (1.4 eq, 0.4 mmol), **S1** (0.28 mmol), Me₂O (2 mL). ^b % Conversion determined by GC using undecane as internal standard after 2 hours. ^c % Yield determined by GC

The results using ligands **L7a-f** and **L8a-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 **L8e** (Table

2, entry 11). In addition, we also found that the biphenyl phosphite moieties in ligands **L7a-d** adopted an *R* configuration (Table 2, entries 1-4 vs 5 and 6), while in ligands **L8a-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 **L7** with **L9**, that only differ in the configuration at C-4, we found that ligands **L9** with an *S* configuration at C-4 gave lower enantioselectivities than ligands **L7** with an opposite configuration at this position (Table 2, entries 1-6 and 13). In addition, ligands **L10** and **L11** which have a pyranoside backbone provided lower yields and enantioselectivities than furanoside ligands (Table 2, entries 14-20). In summary, the best results was obtained with ligand **L8e** that contains the optimal combination of the ligand parameters (ee's up to 57%; Table 2, entry 11).

6.3.2.2. Asymmetric conjugated 1,4-addition of AlMe_3 to linear substrates **S2** and **S3** (equation 2)

In this section, we report the use of ligands **L7-L11a-f** in the copper-catalyzed conjugated addition of trimethylaluminium (equation 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.^{3d,5}



We first investigated the copper-catalyzed 1,4-addition of *trans*-3-nonen-2-one **S2** (equation 2, R= C₅H₁₁) 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).

Table 3. Selected results for the copper-catalysed conjugate 1,4-addition of **S2** using ligands **L7c**.

Entry	Solvent	Precursor	T (°C)	%Conv ^b	%Yield ^c	%ee ^d
1	Et ₂ O	CuTC	-30	97	21	3 (S)
2	Et ₂ O	Cu(OTf) ₂	-30	99	79	18 (R)
3	Et ₂ O	Cu(OAc) ₂	-30	93	31	7 (S)
4	Et ₂ O	[Cu(MeCN) ₄]BF ₄	-30	85	25	4 (S)
5	^t BuOMe	Cu(OTf) ₂	-30	95	62	11 (S)
6	CH ₂ Cl ₂	Cu(OTf) ₂	-30	95	55	19 (S)
7	THF	Cu(OTf) ₂	-30	31	7	3 (S)
8 ^e	Et ₂ O	Cu(OTf) ₂	-30	90	48	15 (R)
9 ^f	Et ₂ O	Cu(OTf) ₂	-30	91	51	15 (R)
10	Et ₂ O	Cu(OTf) ₂	-20	88	52	15 (R)
11	Et ₂ O	Cu(OTf) ₂	-40	93	56	18 (R)

^a Reaction conditions: Cu(OTf)₂ (1 mol%), **L7c** (4 mol%), AlMe₃ (1.4 eq, 0.4 mmol), **S2** (0.28 mmol), solvent (2 mL). ^b % Conversion determined by GC using undecane as internal standard after 2 hours. ^c % Yield determined by GC using undecane as internal standard after 2 hours. ^d Enantiomeric excess measured by GC using 6-Me-2,3-pe-δ-CD column. ^{3h} ^e ligand (1 mol%). ^f ligand (2 mol%).

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 **L10** provided better enantioselectivities than their relative furanoside **L7** ligands and the cooperative effect between C-3 and binaphthyl moieties resulted in a matched combination for ligand **L7f**. In summary, the best result (ee's up to 52%) was obtained with ligand **L10f** that contains the optimal 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 **L7-L11a-f**.

Entry	Ligand	%Conv ^b	%Yield ^c	%ee ^d
1	L7a	32	6	8 (<i>R</i>)
2	L7b	66	48	18 (<i>R</i>)
3	L7c	99	79	18 (<i>R</i>)
4	L7d	93	51	4 (<i>R</i>)
5	L7e	95	53	42 (<i>S</i>)
6	L7f	96	51	48 (<i>R</i>)
7	L8a	38	9	10 (<i>S</i>)
8	L8b	77	83	8 (<i>S</i>)
9	L8c	72	65	8 (<i>S</i>)
10	L8d	95	52	13 (<i>S</i>)
11	L8e	97	40	24 (<i>S</i>)
12	L8f	98	50	28 (<i>R</i>)
13	L9c	89	63	1 (<i>R</i>)
14	L10b	87	49	7 (<i>S</i>)
15	L10c	87	49	8 (<i>S</i>)
16	L10e	99	61	46 (<i>S</i>)
17	L10f	91	66	52 (<i>R</i>)
18	L11c	92	64	9 (<i>S</i>)
19	L11e	40	11	13 (<i>S</i>)
20	L11f	26	4	7 (<i>R</i>)

^a Reaction conditions: Cu(OTf)₂ (1 mol%), ligand (4 mol%), AlMe₃ (1.4 eq, 0.4 mmol), **S2** (0.28 mmol), Et₂O (2 mL). ^b % Conversion determined by GC using undecane as internal standard after 2 hours. ^c % Yield determined by GC using undecane as internal standard after 2 hours. ^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** (equation 2, R= ⁱPr) 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's up to 52%) was obtained with ligand **L10f** that contains an *R* binaphthyl phosphite moiety attached to the pyranoside backbone (Table 5, entry 16).

Table 5. Selected results for the copper-catalysed conjugate 1,4-addition of **S3** using ligands **L7-L11a-f**.

Entry	Ligand	%Conv ^b	%Yield ^c	%ee ^d
1	L7a	14	3	9 (<i>R</i>)
2	L7b	26	23	20 (<i>R</i>)
3	L7c	96	96	39 (<i>R</i>)
4	L7d	95	95	21 (<i>R</i>)
5	L7e	90	77	30 (<i>S</i>)
6	L7f	56	39	29 (<i>R</i>)
7	L8a	10	3	4 (<i>S</i>)
8	L8b	95	95	12 (<i>S</i>)
9	L8c	95	95	7 (<i>S</i>)
10	L8d	82	77	3 (<i>S</i>)
11	L8e	95	91	48 (<i>S</i>)
12	L8f	42	32	17 (<i>R</i>)
13	L9c	96	96	22 (<i>R</i>)
14	L10c	96	96	33 (<i>R</i>)
15	L10e	98	98	48 (<i>S</i>)
16	L10f	97	97	52 (<i>R</i>)
17	L11c	98	98	12 (<i>R</i>)
18	L11e	40	40	14 (<i>S</i>)
19	L11f	6	4	10 (<i>R</i>)

^a Reaction conditions: Cu(OTf)₂ (1 mol%), ligand (4 mol%), AlMe₃ (1.4 eq, 0.4 mmol), **S3** (0.28 mmol), Et₂O (2 mL). ^b % Conversion determined by GC using undecane as internal standard after 2 hours. ^c % Yield determined by GC using undecane as internal standard after 2 hours. ^d Enantiomeric excess measured by GC using 6-Me-2,3-pe- δ -CD column.^{3h}

6.3.3. Conclusions

The sugar-based monophosphite ligand library **L7-L11a-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 **L8e**, while for aliphatic linear substrates **S2** and **S3**, the best ligand was **L10f** (ee's up to 51%).

6.3.4. Experimental Section

6.3.4.1. General Comments

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L7-L11a-f**⁶ and substrate **S3**^{3d} were prepared as previously described. All other reagents were used as commercially available.

6.3.4.2. 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 minutes at room temperature. Then, the substrate (0.28 mmol) was added at the corresponding temperature and next the desired alkylating organometallic reagent (1.4 eq., 0.4 mmol) was added dropwise. After 2 hours, the reaction was quenched with HCl (5 mL, 2M). Then, undecane (50 μ L) was added and the organic layer was filtered

twice through a plug of silica. Yields and enantiomeric excesses were measured by GC.^{3h}

6.3.5. Acknowledgements

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6.2.6. References

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