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SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
Ch6. Phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries
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6.2. Sugar-phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries for Cu-catalyzed asymmetric 1,4-addition reactions

Abstract. The phosphite-oxazoline **L1**-**L5a-g** and phosphite-phosphoroamidite **L6a-c** ligand libraries were also tested in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of cyclic and acyclic enones. Systematically varying the electronic and steric properties of the oxazoline and the biaryl phosphite substituents and the functional groups attached to the basic sugar-backbone had a strong effect on catalytic performance. In general, good activities and enantioselectivities were obtained. The enantioselectivity (up to 80%) was optimized with catalyst precursors containing the phosphite-oxazoline ligand **L1c** and **L1f**, that contains encumbered biaryl phosphite moieties and a phenyl oxazoline group.

6.2.1. 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] Most of the chiral ligand developed for this process are P-donor and mixed P,N-donor ligands.[1f-h,2] Among those, phosphite and phosphoramidite have played a dominant role.[1f-h] A prominent position in the rapid development of this process is occupied by the copper-catalyzed, ligand-accelerated, 1,4-addition of organozinc reagents.[1] Tryalkylalumium reagents have recently appeared as an interesting alternative to organozinc reagents since they are also readily available and also offer additional hydro- and carboalumination possibilities for their preparation.[3] Most of the chiral ligands have been developed for the enantioselective conjugate addition of organozinc reagents and less work has been devoted to the design of ligands for the conjugate addition of organoaluminium reagents. Additionally, linear aliphatic

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enones are another class of substrate for which the development of more active and enantioselective catalysts are still needed. Expansion of the range of ligands used for Cu-catalyzed addition of organoaluminium reagents to cyclic and linear substrates is desirable. For this purpose, carbohydrates are particularly advantageous because they are available at low price and because their modular constructions are easy.[4]

Encouraged by the success of phosphite and phosphoroamidite ligands in this process, we report here the application in the copper 1,4-addition of trialkylaluminium reagents to cyclic and linear enones of two sugar ligand libraries: (a) phosphite-oxazoline **L1-L5a-g** and (b) phosphite-phosphoroamidite **L6a-c** (Figure 1). These libraries combine a priori the advantages of both types of successful ligands.
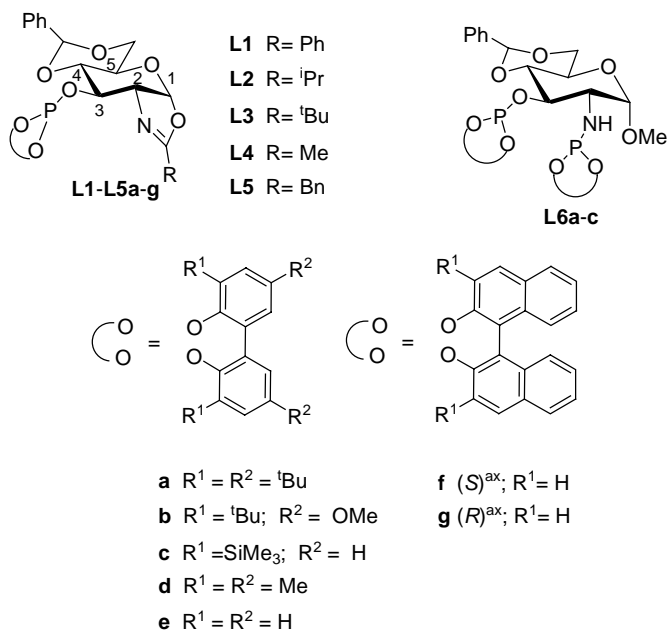

L1 R= Ph
L2 R= ^{i}Pr
L3 R= ^{t}Bu
L4 R= Me
L5 R= Bn

L1-L5a-g

L6a-c

a $R^1 = R^2 = {}^{t}Bu$
b $R^1 = {}^{t}Bu;\ R^2 = OMe$
c $R^1 = SiMe_3;\ R^2 = H$
d $R^1 = R^2 = Me$
e $R^1 = R^2 = H$

f $(S)^{ax};\ R^1 = H$
g $(R)^{ax};\ R^1 = H$

Figure 1. Phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries.

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6.2.2. Results and Discussion

6.2.2.1. Ligand design

Ligand libraries **L1-L5a-g** and **L6a-c** consist of a 4,5-*O*-protected glucopyranoside backbone with a phosphite moiety at C-3 position, which determine their underlying structure, and either oxazoline (ligands **L1-L5a-g**) or phosphoroamidite (ligands **L6a-c**) groups attached to this basic backbone. The synthesis of the phosphite-oxazoline **L1-L5a-g** and the phosphite-phosphoroamidite **L6a-c** ligand libraries (Figure 1) have been previously described in Chapter 3.

We studied the influence of systematically varying the electronic and steric properties of the oxazoline substituents and different substituents/configurations in the biaryl phosphite moiety using ligands **L1-L5a-g**.

We then used both ligand libraries **L1-L5a-g** and **L6a-c** to study how a phosphoroamidite rather than an oxazoline functionality affected catalytic performance. We also studied the effect of the substituents in the phosphoroamidite moiety in catalytic performance using ligands **L6a-c**.

6.2.2.2. Asymmetric conjugated 1,4-addition of AlEt₃ and ZnEt₂ to 2-cyclohexenone S1 (equation 1)

In a first set of experiments, we tested ligands **L1-L5a-g** and **L6a-c** in the copper-catalyzed conjugated addition of triethylaluminium and diethylzinc to 2-cyclohexenone **S1** (equation 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]

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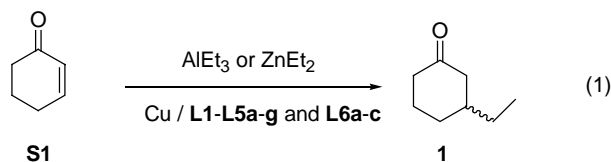
The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor under standard conditions.[1] The results are shown in Table 1.

Table 1. Selected results for the copper-catalysed conjugate 1,4-addition of **S1** using ligands **L1-L5a-g** and **L6a-c**.[a]

Entry	Ligand	T (ºC)	%Conv[b]	%Yield[c]	%ee[d]
1	**L1a**	-30	85	36	6 (*S*)
2	**L1b**	-30	95	20	27 (*S*)
3	**L1c**	-30	99	50	64 (*S*)
4	**L1f**	-30	88	61	64 (*S*)
5	**L1g**	-30	75	55	15 (*S*)
6	**L2a**	-30	99	70	5 (*S*)
7	**L3a**	-30	95	39	7 (*S*)
8	**L4a**	-30	91	27	3 (*S*)
9	**L5a**	-30	96	43	5 (*S*)
10[e]	**L1c**	-30	88	42	6 (*R*)
11[e]	**L1c**	0	80	18	5 (*R*)
12	**L6c**	-30	89	22	17 (*S*)

[a] Reaction conditions: $Cu(OAc)_2$ (1 mol%), ligand (4 mol%), $AlEt_3$ (0.4 mmol), **S1** (0.28 mmol), diethylether (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] $ZnEt_2$ (0.4 mmol).

They indicated that enantioselectivity is mainly affected by the substituents/configuration at the biaryl phosphite moiety, while the oxazoline groups have little effect (Table 1, entries 1-9). The results were therefore best using

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ligands **L1c** and **L1f**, that contain trimethylsilyl substituents at the *ortho* positions of the biphenyl phosphite moiety and an (*S*)-binaphtyl phosphite moiety, respectivelly (ee's up to 64%). In addition, the replacement of the oxazoline by a phosphoroamidite moiety had a negative effect on yield and enantioselectivity (Table 1, entry 3 vs 12). Comparing the results using triethylaluminium with the results of using diethylzinc, we can conclude that yields and enantioselectivities were lower using diethylzinc (Table 1, entries 3 vs 10 and 11).

In addition to the effect of structural parameters on catalytic performance, the reaction parameters can also be controlled to further improve yields and selectivity. Therefore, the effect of several reaction parameters, such as catalyst precursor, solvent and ligand-to-copper ratio, were studied using ligand **L1b** (Table 2). However, yields and enantioselectivities did not improved.

Table 2. Selected results for the copper-catalysed conjugate 1,4-addition of **S1** using ligand **L1b**. Effect of the catalyst precursor, solvent and ligand-to-copper ratio.[a]

Entry	Solvent	Precursor	T (ºC)	%Conv[b]	%Yield[c]	%ee[d]
1	Et_2O	$Cu(OAc)_2$	-30	95	20	27 (*S*)
2	Et_2O	$Cu(OTf)_2$	-30	97	10	26 (*S*)
3	Et_2O	CuTC	-30	96	17	27 (*S*)
4	Et_2O	$[Cu(MeCN)_4]BF_4$	-30	94	17	25 (*S*)
5	Et_2O	CuI	-30	94	13	21 (*S*)
6	^tBuMeO	$Cu(OAc)_2$	-30	92	42	0
7	DCM	$Cu(OAc)_2$	-30	100	13	13 (*S*)
8	THF	$Cu(OAc)_2$	-30	95	17	20 (*S*)
9	Me_2O	$Cu(OAc)_2$	-30	90	20	17 (*S*)
10[e]	Et_2O	$Cu(OAc)_2$	-30	90	26	14 (*S*)
11[f]	Et_2O	$Cu(OAc)_2$	-30	90	26	15 (*S*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), ligand (4 mol%), $AlEt_3$ (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%).

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6.2.2.3. Asymmetric conjugated 1,4-addition of AlMe$_3$ to linear substrates S2 and S3 (equation 2)

We have also screened the use of ligands **L1-L5a-g** and **L6a-c** 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]

$$
\text{S2} \quad R= C_5H_{11} \qquad\qquad \text{2} \quad R= C_5H_{11}
$$
$$
\text{S3} \quad R= {}^iPr \qquad\qquad \text{3} \quad R= {}^iPr
$$
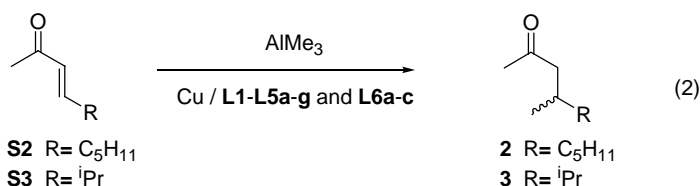
We first investigated the copper-catalyzed 1,4-addition of *trans*-3-nonen-2-one **S2** (equation 2, R= C$_5$H$_{11}$) with trimethylaluminium under standard conditions. The results are summarized in Table 3. In contrast to **S1**, the results indicated that yields and enantioselectivities are affected by the substituents at both the biaryl phosphite and oxazoline moieties (Table 3, entries 1-10). Therefore the best yield (up to 85%) and enantioselectivities (up to 62%) were obtained again with ligands **L1c** and **L1f**, that contain sterically demanding substituents in biaryl phosphite moiety and a phenyl oxazoline group. Again, the replacement of the oxazoline by a phosphoroamidite moiety did not improve yields or enantioselectivities (Table 3, entry 2 vs 11).

We next studied by one of the best ligands (**L1c**) the effect of several reaction parameters, such as catalyst precursor (i.e. Cu(OTf)$_2$, CuTC, Cu(OAc)$_2$,

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CuI and [Cu(MeCN)$_4$]BF$_4$), solvent (i.e. diethylether, CH$_2$Cl$_2$, THF, *tert*-butylmethylether) and ligand-to-copper ratio. Interestingly, in contrast to the conjugate addition to **S1**, we found an important positive effect using [Cu(MeCN)$_4$]BF$_4$ as a catalyst precursor on enantioselectivity. Therefore, enantioselectivity increased from 51% to 78% (Table 3, entry 3 vs 12). The rest of reactions parameters did not improve the catalytic performance.

Table 3. Selected results for the copper-catalysed conjugate 1,4-addition of **S2** using ligands **L1-L5a-g** and **L6a-c**.

Entry	Ligand	Precursor	T (ºC)	%Conv[b]	%Yield[c]	%ee[d]
1	**L1a**	Cu(OTf)$_2$	-30	92	29	31 (*R*)
2	**L1b**	Cu(OTf)$_2$	-30	60	32	32 (*R*)
3	**L1c**	Cu(OTf)$_2$	-30	97	51	51 (*R*)
4	**L1d**	Cu(OTf)$_2$	-30	76	50	45 (*R*)
5	**L1f**	Cu(OTf)$_2$	-30	92	85	62 (*R*)
6	**L1g**	Cu(OTf)$_2$	-30	90	78	52 (*R*)
7	**L2a**	Cu(OTf)$_2$	-30	93	46	40 (*R*)
8	**L3a**	Cu(OTf)$_2$	-30	97	48	33 (*R*)
9	**L4a**	Cu(OTf)$_2$	-30	76	16	49 (*R*)
10	**L5a**	Cu(OTf)$_2$	-30	68	26	34 (*R*)
11	**L6b**	Cu(OTf)$_2$	-30	80	32	26 (*S*)
12	**L1c**	[Cu(MeCN)$_4$]BF$_4$	-30	94	48	78 (*R*)

[a] Reaction conditions: Cu(OTf)$_2$ (1 mol%), ligand (4 mol%), AlMe$_3$ (1.4 eq, 0.4 mmol), **S2** (0.28 mmol), diethylether (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.

Finally, we investigated the copper-catalyzed 1,4-addition of *trans*-5-methyl-3-hexen-2-one **S3** (equation 2, R= ^{i}Pr) with trimethylaluminium. The results are summarized in Table 4. As for substrate **S2**, the results indicated that yields and enantioselectivities are affected by the substituents/configurations at the biaryl phosphite and by the oxazoline groups (Table 4, entries 1-10). Again, the best yield

(up to 94%) and enantioselectivity (up to 80%) was obtained with ligands **L1c** and **L1f**, that contain encumbered biaryl phosphite moieties and a phenyl oxazoline group. The replacement of the oxazoline by a phosphoroamidite moiety had a negative effect on yield and enantioselectivity (Table 3, entry 3 vs 11). The effect of several ligand parameters such as catalyst precursor (i.e. Cu(OTf)$_2$, CuTC, Cu(OAc)$_2$, CuI and [Cu(MeCN)$_4$]BF$_4$), solvent (i.e. diethylether, CH$_2$Cl$_2$, THF, *tert*-butylmethylether) and ligand-to-copper ratio were also studied. However, in contrast to the conjugate addition to **S2**, yields and enantioselectivities did not improve.

Table 4. Selected results for the copper-catalysed conjugate 1,4-addition of **S3** using ligands **L1-L5a-g** and **L6a-c**.

Entry	Ligand	Precursor	T (ºC)	%Conv[b]	%Yield[c]	%ee[d]
1	**L1a**	Cu(OTf)$_2$	-30	60	44	32 (*R*)
2	**L1b**	Cu(OTf)$_2$	-30	39	20	44 (*R*)
3	**L1c**	Cu(OTf)$_2$	-30	94	94	68 (*R*)
4	**L1d**	Cu(OTf)$_2$	-30	75	55	52 (*R*)
5	**L1f**	Cu(OTf)$_2$	-30	96	90	80 (*R*)
6	**L1g**	Cu(OTf)$_2$	-30	92	88	55 (*R*)
7	**L2a**	Cu(OTf)$_2$	-30	43	43	69 (*R*)
8	**L3a**	Cu(OTf)$_2$	-30	53	42	40 (*R*)
9	**L4a**	Cu(OTf)$_2$	-30	57	1	50 (*R*)
10	**L5a**	Cu(OTf)$_2$	-30	51	52	53 (*R*)
11	**L6c**	Cu(OTf)$_2$	-30	93	88	8 (*S*)

[a] Reaction conditions: Cu(OTf)$_2$ (1 mol%), ligand (4 mol%), AlMe$_3$ (1.4 eq, 0.4 mmol), **S3** (0.28 mmol), Et$_2$O (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.

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6.2.3. Conclusions

The phosphite-oxazoline **L1-L5a-g** and phosphite-phosphoroamidite **L6a-c** ligand libraries were 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 type of functional group attached to the carbohydrate backbone, on the electronic and steric properties of the oxazoline and biaryl phosphite substituents and on the substrate structure. Good enantioselectivities (up to 80%) were obtained using the catalyst precursors containing the phosphite-oxazoline ligands **L1c** and **L1f** in the 1,4-addition to aliphatic linear substrates.

6.2.4. Experimental Section

6.2.4.1. General Comments

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L1-L5a-g**[6] and **L6a-c**[7] and substrate **S3**[3d] were prepared as previously described. All other reagents were used as commercially available.

6.2.4.2. 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 μL) was added and the organic layer was filtered

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twice through a plug of silica. Yields and enantiomeric excesses were measured by GC.[3h]

6.2.5. Acknowledgements

6.2.6. References

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