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Sugar–phosphite–oxazoline and phosphite–phosphoroamidite ligand libraries for Cu-catalyzed asymmetric 1,4-addition reactions

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Abstract—Sugar–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. Systematically varying the electronic and steric properties of the oxazoline and biaryl phosphite substituents and the functional groups attached to the basic sugar-backbone had a strong effect on the catalytic performance. In general, good activities and enantioselectivities were obtained. The enantioselectivity (up to 80%) was optimized with catalyst precursors containing the phosphite–oxazoline ligands **L1c** and **L1f** that contain encumbered biaryl phosphite moieties and a phenyl oxazoline group.

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 ligands developed for this process are P-donor and mixed P,N-donor ligands.[1f–h,2] Amongst 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] Trialkylaluminium reagents have recently appeared as interesting alternatives to organozinc reagents since they are also readily available and 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 while less work has been devoted to the design of ligands for the conjugate addition of organoaluminium reagents. Additionally, linear aliphatic enones are another class of substrate, for which the development of more active and enantioselective catalysts are still needed. The 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 their modular constructions are easy.[4]

Encouraged by the success of phosphite and phosphoroamidite ligands in this process, we herein report the application in 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** (Fig. 1). These libraries combine a priori the advantages of both types of successful ligands.

2. Results and discussion

2.1. Ligand design

The sugar-based phosphite–oxazoline **L1**–**L5a**–**g** and phosphite–phosphoroamidite **L6a**–**c** ligand libraries are derived from D-glucosamine and consist of a 4,5-O-protected glucopyranoside backbone with a phosphite moiety at the C-3 position, which determine their underlying structure, with either the oxazoline (ligands **L1**–**L5a**–**g**) or phosphoroamidite (ligands **L6a**–**c**) groups attached to this basic backbone.

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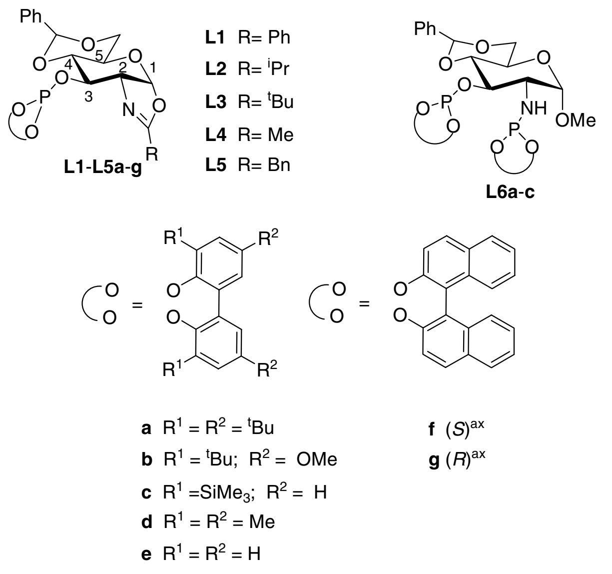


Figure 1. Phosphite–oxazoline and phosphite–phosphoroamidite ligand libraries.

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

Entry	Ligand	*T* (°C)	% 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 the internal standard after 2 h.

[c] % Yield determined by GC using undecane as the internal standard after 2 h.

[d] Enantiomeric excess measured by GC using Lipodex A column.

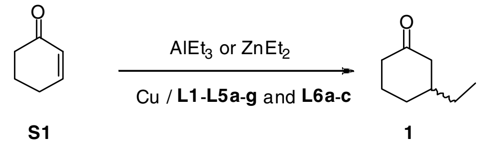
[e] $ZnEt_2$ (0.4 mmol).

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 the catalytic performance. We also studied the effect of the substituents in the phosphoroamidite moiety in catalytic performance using ligands **L6a**–**c**.

2.2. Asymmetric conjugate 1,4-addition of $AlEt_3$ and $ZnEt_2$ to 2-cyclohexenone S1

In the 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** (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 a direct comparison of the efficiency of various ligand systems.[1]

 (1)

The catalytic system was generated in situ by adding the corresponding ligand to a suspension of the catalyst precursor under standard conditions.[1] The results are shown in Table 1. 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 best results were obtained when using ligands **L1c** and **L1f**, which contain trimethylsilyl substituents at the *ortho* positions of the biphenyl phosphite moiety and an (*S*)-binaphthyl phosphite moiety, respectively (ee values up to 64%). In addition, the replacement of the oxazoline by a phosphoroamidite moiety had a negative effect on the 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 when using diethylzinc (Table 1, entry 3 vs entries 10 and 11).

In addition to the effect of the 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 the catalyst precursor, solvent and ligand-to-copper ratio, were studied using ligand **L1b** (Table 2). However, yields and enantioselectivities did not improve.

2.3. Asymmetric conjugate 1,4-addition of $AlMe_3$ to linear substrates S2 and S3

We also screened the use of ligands **L1**–**L5a**–**g** and **L6a**–**c** 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 the asymmetric conjugate 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]

 (2)

Table 2. Selected results for the copper-catalyzed conjugate 1,4-addition of **S1** using ligand **L1b**[a]

Entry	Solvent	Precursor	*T* (°C)	% Conv[b]	% Yield[c]	% ee[d]
1	Ether	$Cu(OAc)_2$	−30	95	20	27 (*S*)
2	Ether	$Cu(OTf)_2$	−30	97	10	26 (*S*)
3	Ether	CuTC	−30	96	17	27 (*S*)
4	Ether	$[Cu(MeCN)_4]BF_4$	−30	94	17	25 (*S*)
5	Ether	CuI	−30	94	13	21 (*S*)
6	^{t}BuMeO	$Cu(OAc)_2$	−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	DME	$Cu(OAc)_2$	−30	90	20	17 (*S*)
10[e]	Ether	$Cu(OAc)_2$	−30	90	26	14 (*S*)
11[f]	Ether	$Cu(OAc)_2$	−30	90	26	15 (*S*)

Effect of the catalyst precursor, solvent and ligand-to-copper ratio.

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol %), ligand (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 the internal standard after 2 h.

[c] % Yield determined by GC using undecane as the internal standard after 2 h.

[d] Enantiomeric excess measured by GC using Lipodex A column.

[e] Ligand (1 mol %).

[f] Ligand (2 mol %).

We first investigated the copper-catalyzed 1,4-addition of *trans*-3-nonen-2-one **S2** (Eq. 2, $R = C_5H_{11}$) 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 yields (up to 85%) and enantioselectivities (up to 62%) were again obtained with ligands **L1c** and **L1f**, which contain sterically demanding substituents in the biaryl phosphite moiety and phenyl oxazoline group. Again, the replacement of the oxazoline by a phosphoroamidite moiety did not improve either the yields or enantioselectivities (Table 3, entry 2 vs 11).

We next studied, with one of the best ligands **L1c**, the effect of several reaction parameters, such as catalyst precursor (i.e., $Cu(OTf)_2$, CuTC, $Cu(OAc)_2$, CuI and $[Cu(MeCN)_4]BF_4$), solvent (i.e., diethylether, CH_2Cl_2, THF and *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 the reactions parameters did not improve the catalytic performance.

Finally, we investigated the copper-catalyzed 1,4-addition of *trans*-5-methyl-3-hexen-2-one **S3** (Eq. 2, $R = {}^i$Pr) with trimethylaluminium. The results are summarized in Table 4. For substrate **S2**, the results indicated that yields and enantioselectivities are affected by the substituents/configurations at the biaryl phosphite moiety and by the oxazoline groups (Table 4, entries 1–10). Again, the best yields (up to 94%) and enantioselectivities (up to 80%) were obtained with ligands **L1c** and **L1f**, which contain encumbered biaryl phosphite moieties and a phenyl oxazoline group. The replacement of the oxazoline by a phosphoroamidite moiety had a negative effect on the 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., dieth-

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

Entry	Ligand	Precursor	*T* (°C)	% 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 equiv, 0.4 mmol), **S2** (0.28 mmol), diethylether (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-β-CD column.[3h]

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

Entry	Ligand	Precursor	*T* (°C)	% 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 equiv, 0.4 mmol), **S3** (0.28 mmol), solvent (2 mL).

[b] % Conversion determined by GC using undecane as the internal standard after 2 h.

[c] % Yield determined by GC using undecane as the internal standard after 2 h.

[d] Enantiomeric excess measured by GC using 6-Me-2,3-pe-β-CD column.[3h]

ylether, CH$_2$Cl$_2$, THF and *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.

3. Conclusions

Modular-based 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 (ee values 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.

4. Experimental

4.1. General comments

All syntheses were performed by using standard Schlenk techniques under an 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.

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

In a typical procedure, a solution of the 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 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). Undecane (50 µL) was then added and the organic layer filtered twice through a plug of silica. Yields and enantiomeric excesses were measured by GC.[3h]

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