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5.2. Phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries in the asymmetric Ni-catalyzed trialkylaluminium addition to aldehydes

Abstract. The phosphite-oxazoline **L1**-**L5a-c** and phosphite-phosphoroamidite **L6a-c** ligand libraries were also tested in the asymmetric Ni-catalyzed 1,2-addition reactions to aldehydes. Systematically varying the electronic and steric properties of the oxazoline and biaryl phosphite substituents and the functional groups attached to the basic sugar-backbone, we found a strong influence of the oxazoline and the functional groups of the sugar backbone on catalytic performance. Enantioselectivity (ee's up to 59%) was best with the catalysts precursor containing the phosphite-oxazoline ligand **L3a**, that contains an sterically hindered *tert*-butyl oxazoline group.

5.2.1. Introduction

Nucleophilic 1,2-addition of organometallic reagents to carbonyl compounds constitutes one of the most fundamental operations in organic synthesis for the formation of chiral secondary alcohols.[1] For alkylation reagents, trialkylaluminium compounds are more interesting than other organometallic reagents because they are economically available on industrial scales from aluminium hydride reagents and olefins.[2] Despite this advantage trialkylaluminium is less documented.[3,4] In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminium to aldehydes can be grouped in two types. A first group are titanium complexes that although they usually afford high enantioselectivities, but have slow turnover rates hampering their potential utility and requiring high catalyst loadings (10-20 mol %).[3a-d] The second type are recently studied nickel complexes that provide enantioselectivities similar to those using titanium complexes but with low catalyst loadings (0.05 - 1 mol %).[3e,4] For the latter nickel

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catalysts, only Woodward and co-workers reported the successful use of phosphoroamidite ligands as chiral source. Despite this success, the results indicate that an excess of ligand (L/Ni = 2) is necessary for high ee's to be achieved.[3e] More research is therefore needed to study the possibility offered by other ligands for this transformation.

To further expand the range of ligands in this process we report here the screening of the chiral phosphite-oxazoline **L1**-**L5a-c** and phosphite-phosphoroamidite **L6a-c** ligand libraries (Figure 1), described in the previous Chapter 3, in the asymmetric Ni-catalyzed addition of trialkylaluminium reagents to aldehydes. These ligands, derived from D-glucosamine, have the advantage of carbohydrates, such as availability at low price from readily available alcohols, facile modular constructions and high resistance to oxidation.[5] All these favourable features enable series of chiral ligands to be synthetized and screened in the search for high activity and selectivity. Therefore, with these libraries we fully investigated the effects of systematically varying the electronic and steric properties of the oxazoline substituent (**L1**-**L5**), the functional group attached to the basic sugar-backbone (**L5** and **L6**) and different substituents in the biaryl phosphite moiety (**a-c**).

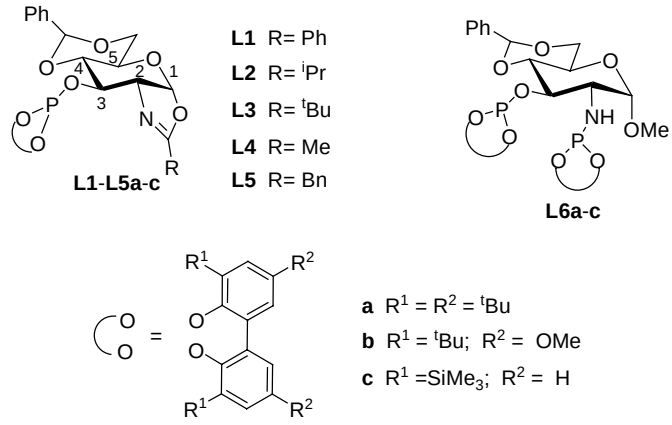

Figure 1. Phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña

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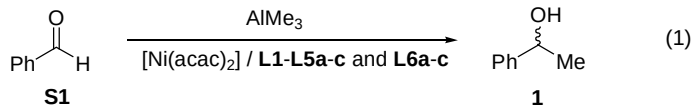
5.2.2. Results and Discussion

5.2.2.1. Asymmetric addition of AlR_3 to aldehydes

In a first set of experiments, we evaluated the phosphite-oxazoline (**L1-L5a-c**) and phosphite-phosphoroamidite (**L6a-c**) ligand libraries in the Ni-catalyzed asymmetric addition of trimethylaluminium to benzaldehyde **S1**, which is used as a model substrate (eq. 1). The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of the catalyst precursor [$Ni(acac)_2$] (acac= acetylacetonate).



S1 **1** (1)

The results, which are summarized in Table 1, indicate that for phosphite-oxazoline ligands the enantioselectivities are mainly affected by the steric properties of the substituent at the oxazoline moiety while the substituents at the phosphite moiety hardly affected it at all. The results were therefore best using ligand **L3a** that contains a bulky *tert*-butyl oxazoline group (Table 1, entries 1-6). Interestingly, lowering the ligand-to-nickel ratio increased activity, yield and enantioselectivity (Table 1, entry 5 *vs* 8). In addition, comparing the results obtained with ligands **L1-L5a-c** and **L6a-c**, we found that the replacement of the *tert*-butyl oxazoline function by a phosphoroamidite moiety did not improve enantioselectivities (Table 1, entries 8 *vs* 9-11).

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Table 1. Selected results for the Ni-catalyzed asymmetric addition of $AlMe_3$ to **S1** using **L1-L5a-c** and **L6a-c** ligand libraries.[a]

Entry	Ligand	L*/Ni	t (h)	% Conv.[b]	% Yield[c]	% ee[d]
1	**L1a**	2	3	60	59	4 (*S*)
2	**L1b**	2	3	67	64	2 (*S*)
3	**L1c**	2	3	51	47	1 (*S*)
4	**L2a**	2	3	30	16	4 (*S*)
5	**L3a**	2	3	43	20	37 (*S*)
6	**L4a**	2	3	35	22	2 (*S*)
7	**L3a**	1	3	49	24	48 (*S*)
8	**L3a**	0.75	3	70	44	52 (*S*)
9	**L6a**	0.75	3	99	40	6 (*S*)
10	**L6b**	0.75	3	91	40	41 (*S*)
11	**L6c**	0.75	3	86	32	1 (*S*)

[a] Reaction conditions: T= -20 ^oC, $[Ni(acac)_2]$ (1 mol%), $AlMe_3$ (2 equiv.), **S1** (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 3 hours. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column.

We next tested the ligand that provided the best results (**L3a**) in the Ni-catalyzed addition of trimethylaluminium to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 2. We found that enantioselectivity is mainly affected by the electronic properties of the groups at the phenyl moiety. Therefore, the presence of electrondonating groups at the *para* position of the phenyl group decreases enantioselectivity (Table 2, entries 1 and 4 *vs* 2, 3 and 6). As expected, we also found that the enantioselectivity was lower when a more flexible substrate **S9** was used (Table 2, entries 1 *vs* 9).

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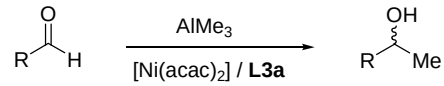
Table 2. Selected results for the nickel-catalyzed asymmetric addition of $AlMe_3$ to aldehydes using ligand **L3a**.[a]

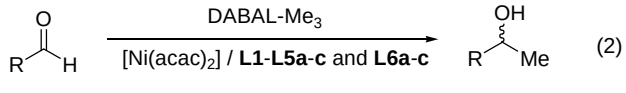


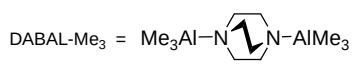
Entry	Substrate	R	% Conv.[b]	Yield[c]	% ee[d]
1	**S1**	C_6H_5	70	44	52 (*S*)
2	**S2**	4-Cl-C_6H_4	64	25	35 (*S*)
3	**S3**	4-OMe-C_6H_4	29	26	32 (*S*)
4	**S4**	4-CF_3-C_6H_4	25	19	53 (*S*)
5	**S5**	4-Br-C_6H_4	55	22	40 (*S*)
6	**S6**	4-Me- C_6H_4	61	24	37 (*S*)
7	**S7**	3-Cl-C_6H_4	47	23	30 (*S*)
8	**S8**	2-Cl-C_6H_4	35	24	33 (*S*)
9[e]	**S9**	PhCH=CH	34	30	4 (*R*)

[a] Reaction conditions: T= -20 °C, [Ni(acac)$_2$] (1 mol%), **L3a** (0.75 mol%), $AlMe_3$ (2 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 3 hour. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column. [e] Reaction time 5 hours.

5.2.2.2. Asymmetric addition of DABAL-Me_3 to aldehydes

Recently, Woodward and co-workers reported for the first time the advantages of using DABAL-Me_3 as air-stable methylating reagent in the nickel-catalyzed additions to aldehydes.[3e] Therefore, we decided to also tested the phosphite-oxazoline (**L1**-**L5a**-**c**) and phosphite-phosphoroamidite (**L6a**-**c**) ligand libraries in the nickel-catalyzed addition of DABAL-Me_3 to aldehydes (eq. 2).





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The results, which are summarized in Tables 3 and 4, indicate that the catalytic performance (activities and enantioselectivities) follows the same trend as for the trialkylaluminium addition to aldehydes, which is not unexpected because the reactions have a similar mechanism. However, the yields were lower than in trimethylaluminium addition and enantioselectivities were slightly better. Again the best enantioselectivities (ee's up to 59%) were obtained with ligand **L3a**, which contains the most sterically demanding oxazoline substituent.

Table 3. Selected results for the nickel-catalyzed asymmetric addition of DABAL-Me_3 to **S1** using **L1-L5a-c** and **L6a-c** ligand libraries.[a]

Entry	Ligand	L/Ni	t (h)	% Conv.[b]	% Yield[c]	% ee[d]
1	**L1a**	1	3	32	3	31 (*S*)
2	**L1c**	1	3	52	3	25 (*S*)
3	**L2a**	1	3	42	1	25 (*S*)
4	**L3a**	1	3	24	8	59 (*S*)
5	**L4a**	1	3	42	7	19 (*S*)
6	**L5a**	1	3	52	11	24 (*S*)
7	**L6a**	1	3	53	6	14 (*S*)
8	**L6b**	1	3	53	3	27 (*S*)
9	**L6c**	1	3	49	4	7 (*S*)

[a] Reaction conditions: T= 0-5 ^{o}C, $Ni(acac)_2$ (1 mol%), **S1** (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 3 hours. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column.

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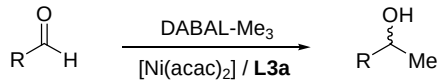
Table 4. Selected results for the nickel-catalyzed asymmetric addition of DABAL-Me_3 to aldehydes using ligand **L3a.**[a]



Entry	Substrate	R	% Conv.[b]	Yield[c]	% ee[d]
1	**S1**	C_6H_5	24	8	59 (*S*)
2	**S2**	4-Cl-C_6H_4	6	2	9 (*S*)
3	**S3**	4-OMe-C_6H_4	38	1	19 (*S*)
4	**S4**	4-CF_3-C_6H_4	22	2	4 (*S*)
5	**S5**	4-Br-C_6H_4	15	4	11 (*S*)
6	**S6**	4-Me- C_6H_4	39	3	34 (*S*)
7	**S7**	3-Cl-C_6H_4	14	3	6 (*S*)
8	**S8**	2-Cl-C_6H_4	6	4	16 (*S*)

[a] Reaction conditions: T= 0-5 ^oC, $Ni(acac)_2$ (1 mol%), **L3a** (1mol%), Dabal-Me_3 (1.3 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 3 hours. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column.

5.2.3. Conclusions

The phosphite-oxazoline **L1-L5a-c** and phosphite-phosphoroamidite **L6a-c** ligand libraries were tested in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminium reagents to aldehydes. Our results indicated that selectivity depended strongly on the type of functional group attached to the carbohydrate backbone, on steric properties of the oxazoline substituents and on the substrate structure. Moderate enantioselectivities (ee's up to 59%) were obtained using the catalysts precursor containing the phosphite-oxazoline ligand **L3a** in the 1,2-addition to several *para*-substituted aryl aldehydes.

ISBN:978-84-691-0375-3/DL:T.2193-2007

5.2.4. Experimental section

5.2.4.1. General comments

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L1-L5a-c**[6] and **L6a-c**[7] were prepared as previously described. All other reagents, including DABAL-Me_3, were used as commercially available.

5.2.4.2. General procedure for the Ni-catalyzed enantioselective 1,2-addition of trialkylaluminium reagents to aldehydes

Anhydrous [$Ni(acac)_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at -20 ^oC for 10 min. Neat aldehyde (0.25 mmol) was then added and trialkylaluminium (0.5 mmol) was added dropwise after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[3e]

5.2.4.3. General procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me_3 to aldehydes

Anhydrous [$Ni(acac)_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at 5 ^oC for 10 min. Neat aldehyde (0.25 mmol) was then added and DABAL-Me_3 (84 mg, 0.325 mmol, 1.3 equiv) was added after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20

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μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[3e]

5.2.5. Acknowledgements

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