UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
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6. Cu-catalyzed asymmetric 1,4-conjugated addition of trialkylaluminium reagents to enones

6.1. Background

The last decade has seen an important breakthroughs in what is possible in the area of catalytic asymmetric 1,4-addition of alkyl organometallic nucleophiles to enones. Most of the succesfull asymmetric versions of this chemistry have made use of diorganozinc reagents, specially $ZnEt_2$, a trend started by Alexakis (Cu-catalysis) and Soai (Ni-catalysis).[1] Viable ligand classes affording > 90% ee for the addition of diorganozinc to several types of cyclic and chalcone substrates are now available.[2] However, relatively few publications describing highly enantioselective addition of organometallics to linear aliphatic enones and using trialkylaluminium reagents as alternative to organozincs have appeared.[2] This justify to expand the range of ligands for the Cu-catalyzed addition of organoaluminium reagents to enones and more specifically to the linear aliphatic ones. For this purpose, carbohydrates are particularly advantageous because they are available at low price and because their modular constructions are easy.

In this chapter, we report the application of the three carbohydrate-based ligand libraries described in Chapter 3 (phosphite-oxazoline (**L1**-**L5a-i**), phosphite-phosphoroamidite (**L6a-c**) and monophosphite (**L7**-**L11a-f**) in the asymmetric Cu-catalyzed 1,4-addition of trialkylaluminium reagents to enones. More specifically, in section 6.2 we report the application of the glucopyranoside phosphite-oxazoline (**L1**-**L5a-i**) and phosphite-phosphoroamidite (**L6a-c**) ligand libraries. 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. In general, good activities and enantioselectivities were obtained. The best enantioselectivities (ee's up to 78%) were obtained using the catalysts precursor

containing the phosphite-oxazoline ligand **L1c** in the 1,4-addition to aliphatic linear substrates. In section 6.3, we report the application of the modular sugar-based monophosphite ligand library **L7**-**L11a**-**f** for the Cu-catalyzed 1,4-addition of trialkylaluminium reagents to enones. 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.

6.1.1. References

[1] a) Alexakis, A.; Vastra, J.; Burton, J.; Mangeney, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3193. b) Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc. Chem. Commun.* **1989**, 516.

[2] See for instance: a) Alexakis, A. in *Methodologies in Asymmetric Catalysis*; Chapter 4, American Chemical Society, Washington DC, **2004**. b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002,** 3211.