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

3. Pd-catalyzed asymmetric allylic substitution

3.1. Background

As we discussed in the introduction, most of the chiral ligands developed for asymmetric allylic substitution are mixed bidentated donor ligands (such as P-N, P-S and S-N). The efficiency of this type of hard-soft heterodonor ligands has been mainly attributed to the different electronic effects of the donor atoms. Mixed phosphorus-nitrogen ligands have played a dominant role among the heterodonor ligands. Among those, catalysts containing phosphine-oxazoline ligands have played a key role in the success of this process. Recently, a group of less electron-rich phosphorus compounds–biaryl phosphite ligands–have also demonstrated their potential utility in this process. In this context, our group have successfully reported the use of a phosphite-oxazoline ligand family **1** that overcomes the most common limitations of this process, such as low reaction rates and high substrate specificity (Figure 1).[1] Despite this success, reports on their use are rare.[1,2] This encourages further research into phosphite-oxazoline ligands.

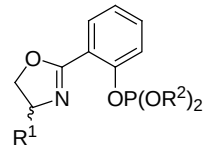

Figure 1. Phosphite-oxazoline ligands **1**.

Other heterodonor ligands, such as phosphite-phosphoroamidite, have recently demonstrated their potential utility in asymmetric catalysis. To our knowledge, only our group have recently reported the successful use of this type of ligands for asymmetric allylic substition (Figure 2).[3] More research is therefore

needed to study the scope for phosphite-phosphoroamidite as a new class of ligands for this process.

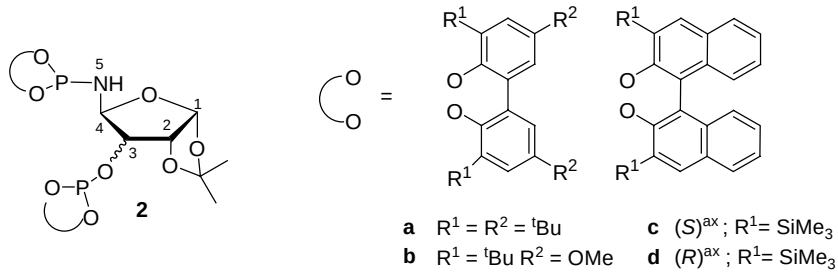

Figure 2. Phosphite-phosphoroamidite ligands **2** derived from D-xylose.

Less attention has been paid to catalysts containing monodentated ligands in asymmetric allylic substitution reactions. However, the groups of RajanBabu and Zhang obtained an enantioselectivity of 94% with catalysts precursors containing monophospholane ligands **3**-**5** (Figure 3).[4] This encourages further research into monophosphorous ligands.

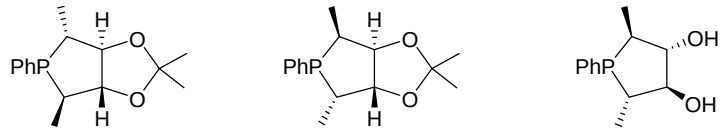

Figure 3. Monophospholane ligands developed by the groups of RajanBabu and Zhang.

In this chapter, we therefore report the synthesis of three carbohydrate-based ligand libraries: phosphite-oxazoline (**L1**-**L5a**-**i**), phosphite-phosphoroamidite (**L6a**-**c**) and monophosphite (**L7**-**L11a**-**f**). We also report their use as catalysts precursors in asymmetric allylic substitution reactions. More specifically, in section 3.2 we report the synthesis and application of a glucopyranoside phosphite-oxazoline ligand library (**L1**-**L5a**-**i**) in the Pd-catalyzed allylic substitution of several substrate types. This ligand library has four main advantages: (1) they can

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

be prepared in a few steps from readily available D-glucosamine; (2) the π-acceptor character of the phosphite moiety increases reaction rates; (3) the flexibility and larger bite angle created by the biaryl phosphite moiety increases versatility and (4) their modular nature enables the substituents in the oxazoline moiety and the substituents/configurations in the biaryl phosphite moiety to be easily and systematically varied. Thus, by carefully selecting the ligand components, high enantioselectivities (ee's up to 99%) and good activities have been achieved in a wide range of substrates with different steric and electronic properties. The study of the Pd-1,3-diphenyl, 1,3-dimethyl and 1,3-cyclohexenyl allyl intermediates by NMR spectroscopy makes it possible to understand the catalytic behaviour observed. This study also indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphite moiety. On the basis of the previous ligand library, in next section 3.3, we designed a new glucopyranoside ligand family (phosphite-phosphoroamite; **L6a-c**) in which the oxazoline moiety is replaced by a phosphoroamidite group. These ligands were applied to the Pd-catalyzed allylic alkylation of several substrates types. Systematic variation of the ligand parameters indicates that enantioselectivities are mainly affected by the substituents at the *para* positions of the biphenyl moieties. However, these effects are different depending on the substrate in study. Enantiomeric excesses of up to 89% with high activities were obtained for *rac*-1,3-diphenyl-3-acetoxyprop-1-ene, *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate and *rac*-3-acetoxycycloheptene. For the monosubstituted linear substrate 1-(1-naphthyl)allyl acetate, these ligands proved to be inadequate in terms of regioselectivities. However, we obtained good enantioselectivity by carefully selecting the substituents on the *para* position of the biphenyl moieties (ee's up to 72%). Finally, in section 3.4, we report the synthesis of a modular sugar-based monophosphite ligand library (**L7-L11a-f**) for the Pd-catalyzed allylic substitution reactions of several substrates. These ligands are derived from D-glucose, D-galactose and D-fructose, which lead to a wide range of sugar

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
ISBN:978-84-691-0367-6/DL:T-2193-2007

backbones, and contain several substituents/configuration 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 sugar backbone, the configurations at carbon C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety. Unfortunately, low-to-moderate enantioselectivities were obtained (ee's up to 46%).

3.1.1. References

[1] Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646.

[2] a) Prétôt, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 323. b) Gavrilov, K. N.; Tsarev, V. N.; Zheglov, S. V.; Lyubimov, S. E.; Shyryaev, A. A.; , Petrovskii, P. V.; Davankov, V. A. *Mendeleev Commun.* **2004**, 260.

[3] Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49.

[4] a) Yan, Y. Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 199. b) Zhang, X. WO Patent 03/040149 A2, 2003.