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Application of novel phosphine oxazoline ligands in asymmetric allylations of 4-acyloxy-2-pentene derivatives

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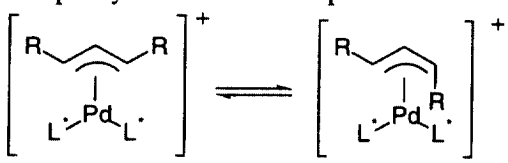
Abstract

A library of novel phosphine oxazoline ligands **2** was tested in the asymmetric allylation of 4-acyloxy-2-pentenes **1**. High throughput screening techniques were employed to accelerate this process. The data accumulated allowed the extent of asymmetric induction to be correlated with the ligand substituent R and ligand-to-metal ratios.

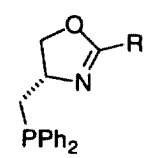
1. Introduction

Highly enantioselective, palladium-mediated allylation reactions[1] are only possible if there is a favorable synergy between several kinetic and thermodynamic factors. For reactions involving the symmetrical intermediates **1**, the most obvious of these parameters is the reaction rate ratio corresponding to addition at the π-allyl termini. However, equilibration rates and positions for interconversion of the *syn,syn* and *syn,anti* forms also have a bearing on the stereoselectivities obtained. It has been proposed that the latter effects are more important if the substituent R is small, and this explains the general observation that enantioselective allylations via the methyl-substituted intermediates **1a** are harder to achieve than for the phenyl-substituted complexes **1b**.[2]



syn, syn *syn, anti*

1a, R = Me; **1b**, R = Ph



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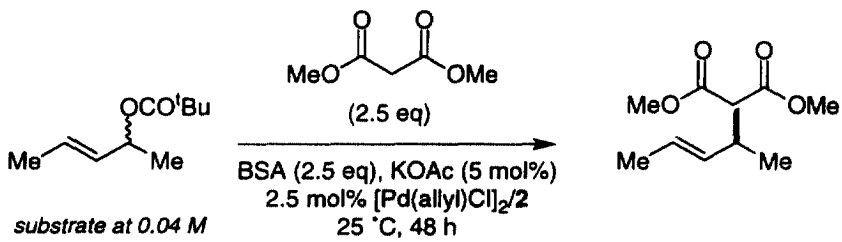
A library of the novel phosphine oxazoline ligands **2** was recently prepared in our laboratories.[3] This paper describes how the performance of ligands **2** in an asymmetric allylation reaction of substrate **1a** was evaluated. An improved procedure for high throughput screening of catalyst libraries[3–6] was used to do this; that protocol is also outlined here.

2. Results and discussion

Scheme 1 summarizes the conditions used for all the allylations described in this paper. Seven different ligands were screened at two different ligand:metal ratios in CH_2Cl_2. In fact, allylations under other conditions were also attempted (eg NaH as base, THF as solvent), but the data obtained were uniformly inferior.



Scheme 1.

The library screen was performed by running all the reactions in parallel in a dry box, then measuring enantioselectivities via automated GC analysis, using a chiral column. The apparatus used for this was a 34-well or a 27-well plate as shown in Fig. 1. This consists of an aluminum block with a U-shaped internal channel through which cooling fluid can be circulated from a cryostat. A thermocouple was used to check that a uniform temperature was obtained across the plate. The block has the same base size as a 96 well microtitre plate, and was agitated on a microtitre plate shaker. Glass vials contained the reaction mixtures in each well, and a small glass bead was also added to improve agitation. The particular plate used for this screen had 27 wells.

Fig. 2 summarizes the results obtained using the conditions shown in Scheme 1. Three generalizations can be made from this data. First, better results were obtained when the ligand:metal ratio was kept below 1:1. Second, the electron-releasing and the electron-withdrawing aryl substituents, 4-MeO-C_6H_4 and 4-NO_2-C_6H_4, both performed better than phenyl. However, the spread of enantioselectivities for these aryl groups was not large, i.e. within 30% *ee* in the lower enantiomeric excess range that corresponds to relatively small kinetic differences. Third, ligands with larger R groups tended to give better enantioselectivities.

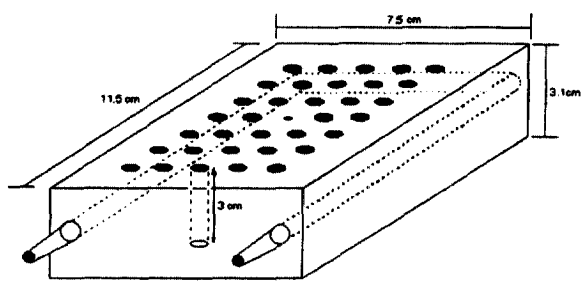


Fig. 1. Apparatus used for high throughput screening

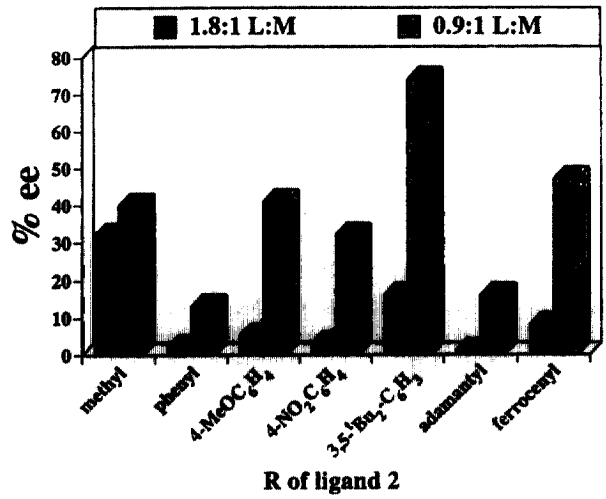


Fig. 2. Enantioselectivities obtained in the reaction (Scheme 1) as a function of ligand substituent and ligand-to-metal ratio (L:M)

Several inferences can be drawn from the data presented above. First, diminished enantioselectivities at higher ligand-to-metal ratios are symptomatic of equilibria between weak ligand chelates and non-chelated complexes of type ML_2 (where L is a bidentate ligand coordinated through one ligating site). In this study, this may be a consequence of excessive strain in the 5-membered rings formed on chelation of the ligand to palladium.[3] Analogous ligands that could form larger ring chelates may be better. Nevertheless, the best enantioselectivity obtained in this work (74% *ee* as part of the screen, 75% *ee* when repeated on a larger scale in the conventional way) is marginally better than that observed in other studies,[7,8] except for one of Trost's ligands for which 92% *ee* has been obtained.[2] Second, the electron withdrawing or releasing properties of R are less important than the bulkiness of this substituent. However, the exact dependence of enantioselectivity on R was more complex than just a size effect. The 3,5-^{t}Bu$_2$-C$_6$H$_3$, adamantyl, or ferrocenyl substituents are all large, but the first of these gave a markedly better enantioselectivity than the rest. In fact, the 3,5-^{t}Bu$_2$-C$_6$H$_3$ ligand accounted for the best enantioselectivity observed in this work whereas the adamantyl substituent gave only 16% *ee*. Thus it appears that the absolute size of the ligand substituent was less critical than its topography.

3. Conclusions

Relatively simple equipment can be used for high throughput screening of catalyst libraries. The screens are rapid and efficient, and allow more data to be accumulated in a shorter period of time than would otherwise be possible. In this study it was possible to probe the effects of two variables (ligand substituent R and ligand-to-metal ratio) simultaneously. In general, optimization and discovery of catalyst systems is complicated by mutually dependent variables, hence interpretation of small data sets from serial screens can be difficult or impossible. High throughput screening facilitates collection of enough data to address this type of problem.

4. Experimental

4.1. General

Optical rotations were measured on Jasco DIP-360 digital polarimeter at 25°C. Thin layer chromatography was performed using silica gel 60 F_{254} plates. Flash chromatography was performed using silica gel (230–600 mesh). CH_2Cl_2 was distilled over CaH_2 and THF over Na/benzophenone. 1,3-Dimethylpropenyl pivalate was synthesized following a literature procedure.[9] Other chemicals were purchased from commercial suppliers and used as received. GC analyses were performed on a Hewlett Packard 6890 Series gas chromatograph equipped with 6890 Series automatic sampler, and an in-house chiral column was used for the GC analysis (prepared by Vigh et al.,[10] Texas A & M; 30.7 m×0.25 mm, 30% β-*tert*-butyldimethylsilyl cyclodextrin derivative in OV-1701-vi of 0.25 μm film thickness).

4.2. Description of high throughput screen

In a nitrogen atmosphere, allylpalladium chloride dimer (0.36 mg, 0.001 mmol) was weighed into glass half dram vials, each equipped with a small glass bead to enhance agitation. Stock solutions (0.004 M) of the ligands were prepared, appropriate amounts were added to each well via a micropipette, and the solutions were diluted to a total volume of 200 μl by adding additional solvent. The solutions were set at a temperature of 25±1°C in the block apparatus. After 0.5 h equilibration time, a 0.2 M stock solution of 1,3-dimethylpropenyl pivalate (200 μl, 0.04 mmol) was added to each well, followed by neat dimethyl malonate (12 μl, 0.1 mmol), *O,N*-bis(trimethylsilyl)acetamide (25 μl, 0.1 mmol), and solid potassium acetate (0.5 mg, 0.005 mmol). The block was agitated for 48 h on a horizontal shaker designed for 96 well microtiter plates. A 20 μl aliquot from each reaction was removed and passed through a short silica plug (40% EtOAc/hexanes); this operation was done manually. The reactions were then analyzed via GC (80°C; retention times, t_1=41.7 min, t_2=42.3 min). The GC separation was calibrated using racemic material.

4.3. Preparative scale reaction with ligand (R)-2-(3,5-di-tert-butylphenyl)-4-[(diphenylphosphino)-methyl]oxazoline

In an inert atmosphere, (*R*)-2-(3,5-di-*tert*-butylphenyl)-4-[(diphenylphosphino)methyl]oxazoline (4.1 mg, 0.009 mmol) and allylpalladium chloride dimer (1.83 mg, 0.005 mmol) were dissolved in 5 ml of dichloromethane and stirred for 0.5 h. A 0.2 M stock solution of 1,3-dimethylpropenyl pivalate (5 ml, 1.0 mmol) was added to this solution, followed by dimethyl malonate (225 μl, 2.0 mmol), *O,N*-bis(trimethylsilyl)acetamide (BSA, 500 μl, 2.0 mmol), and solid potassium acetate (1.0 mg, 0.01 mmol). The solution was stirred for 48 h. The solvent was removed and purified directly via flash chromatography on silica gel (95:5 hexanes:EtOAc) providing 209 mg (77%) of **3** as a colorless oil in 75% ee.

Acknowledgements

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References

1. Trost, B. M.; Vranken, D. L. V. *Chem. Rev.* **1996**, *96*, 395.
2. Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520.
3. Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, submitted.
4. Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220.
5. Burgess, K.; Moye-Sherman, D.; Porte, A. M. Libraries of Transition-Metal Catalysts. High-Throughput Screening of Catalysts for Synthetic Organic Methodology, in *Molecular Diversity and Combinatorial Chemistry*; I. M. Chaiken and K. D. Janda, eds; ACS, 1996; p. 128.
6. Burgess, K.; Porte, A. M. Accelerated Syntheses and Screening of Stereoselective Transition Metal Catalysts, in *Advances in Catalytic Processes*; M. P. Doyle, ed.; JAI Press, Inc.: Greenwich, CT, 1997; p. 69.
7. Matt, P. V.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566.
8. Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179.
9. Matt, P. V.; Loiseleur, O.; Koch, G.; Pfaltz, A. *Tetrahedron* **1994**, *5*, 573.
10. Shitangkoon, A.; Vigh, G. *J. Chromatography A* **1996**, *738*, 31.