Pure & Appl. Chem., Vol. 66, No. 7, pp. 1535–1542, 1994.
Printed in Great Britain.

Electronic effects in asymmetric catalysis: enantioselective carbon–carbon bond forming processes

T. V. (Babu) RajanBabu and Albert L. Casalnuovo

DuPont Central Research and Development , Experimental Station, E328, Wilmington, Delaware 19880-0328, USA. (Contribution no. 8619)

Abstract. Transition metal complexes of 1,2-diol phosphinites and phosphites derived from readily available sugars catalyze a variety of asymmetric reactions of prochiral olefins including the asymmetric Makovnikov addition of HCN to vinyl arenes. The enantioselectivity of this reaction can be optimized by steric and electronic tuning of a readily available carbohydrate-derived ligand system. Both R and S enantiomers of a prototypical 2-arylpropionitrile, a precursor to widely used 2-arylpropionic acids, can thus be synthesized over 90 % enantiomeric excess at or below room temperature. An unusual electronic effect on the selectivity of this reaction may have wider implications for other related reactions.

Introduction

Starting with the pioneering studies of Emil Fischer, carbohydrates have historically played an important role in the development of organic chemistry. Over the past 4 or 5 years we have been interested in new methods for carbon-carbon bond forming reactions via organometallic reagents. In this context we have studied functional group compatibilities and stereochemical aspects of several new reactions using readily available carbohydrate-derived model compounds. We hoped that under the best of circumstances, the chemistry we uncover would also add to our synthetic methodology in the chiron approach to natural product synthesis. This expectation was indeed borne out in a number of instances.[1]

However, for the installation of new asymmetric centers, the chiron approach is not the most economic one because of the near stoichiometric nature of the chirality transfer involved in the production of new molecules. An ideal chemical solution would be one involving chiral multiplication such as asymmetric catalysis by enzymes or chiral metal complexes.[2]

Asymmetric Catalysis of C-C Bond Formation

The organometallic approach relies on the ability of transition metal complexes to accelerate certain reactions by several orders of magnitude. Further, activation of abundantly available small molecules such as CO, HCN, H_2 and simple olefins, and their conversion to value-added products by these complexes have been amply demonstrated. High stereoselectivity in the incorporation of these molecules would further enhance the value of these processes. If we set our goal in enantioselective catalysis as 95 % ee, the differentiation of diastereomeric transition states involving a chiral metal complex with $\Delta\Delta G^{\#}$ of at least 2.3 kcal/mole is needed. The factors which affect the necessary diastereoselective recognition are critically dependent on the nature of the ligand. A priori, these factors, which include both attractive and repulsive (steric) interactions, are still largely unpredictable. Thus the development of an easily modifiable ligand system would be key to success in this area; especially so in the present case, since we decided to study the hydrocyanation reaction (Fig. 1) for which a

practical asymmetric variant was not known when we started this work.[3] During this talk I will review the recent progress we have made in the design, synthesis and applications of new

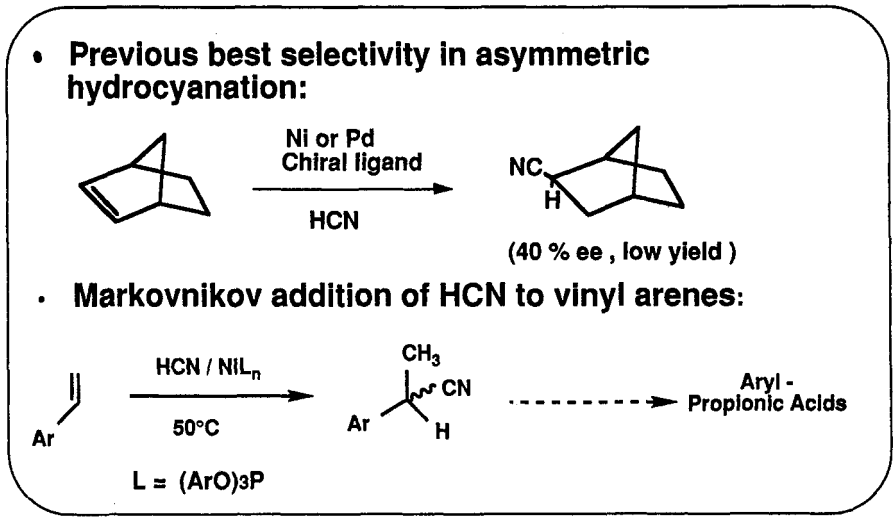

Fig. 1. The hydrocyanation reaction.

ligands derived from carbohydrates and the use of their Ni(0) complexes in the asymmetric hydrocyanation reaction.[4] We were especially attracted to phosphinites[5] derived from readily available carbohydrate diols, since they satisfied our basic criteria of tunability (Fig. 2) and ease of preparation (Fig. 3). We reasoned that in this ligand system, steric and electronic factors could be *systematically* changed in order to optimize high enantioselectivity.

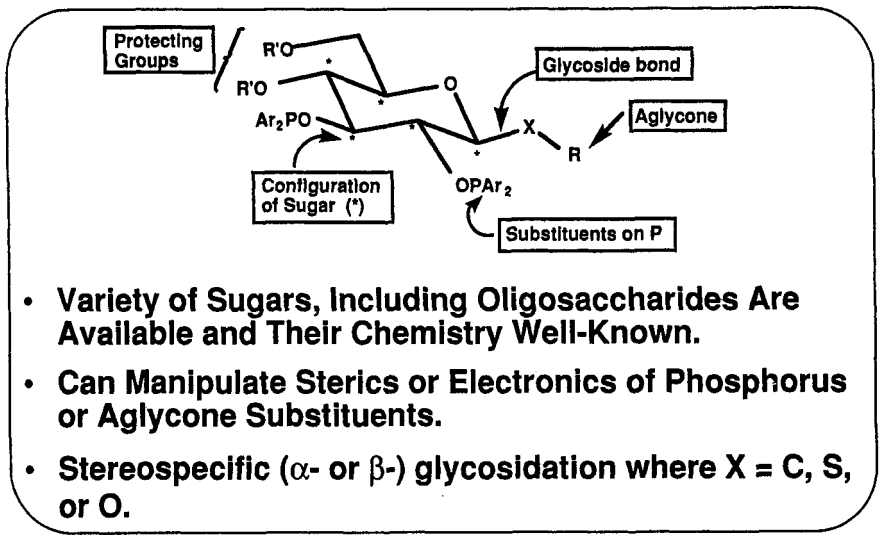

Fig. 2. Design of 1,2-diol phosphinite ligands from sugars.

The Asymmetric Hydrocyanation Reaction

Why the hydrocyanation reaction? (a) Arguably the most important bond construction in organic chemistry is that of the C-C bond. Yet it is precisely in this area that the limitations of

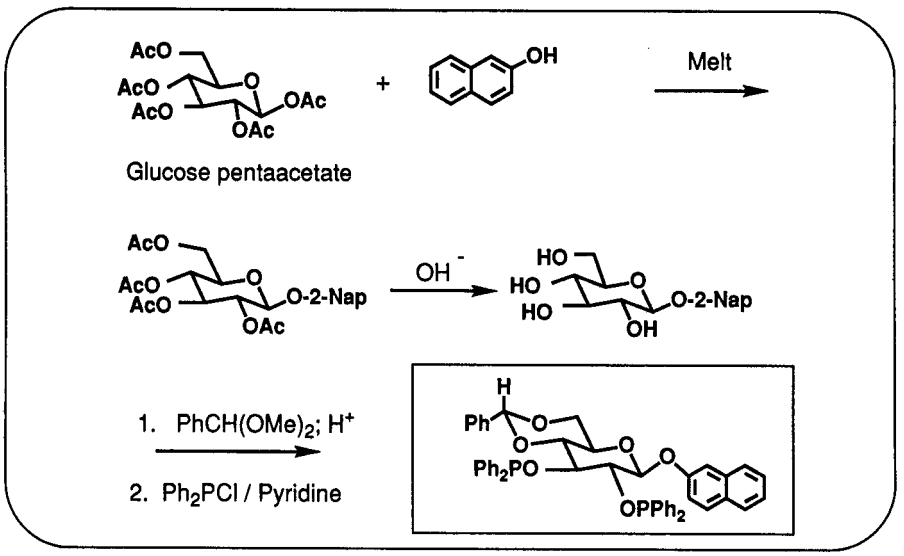

Fig. 3. Synthesis of prototypical sugar diol phosphinites.

the current asymmetric synthesis technology are most evident (Fig. 1). Truly *practical* asymmetric C-C bond forming reactions are rare and to our knowledge only one metal-catalyzed asymmetric C-C bond forming reaction is currently practiced on an industrial scale - the copper-catalyzed cyclopropanation of isobutylene.[6] (b) The resulting nitriles are easily

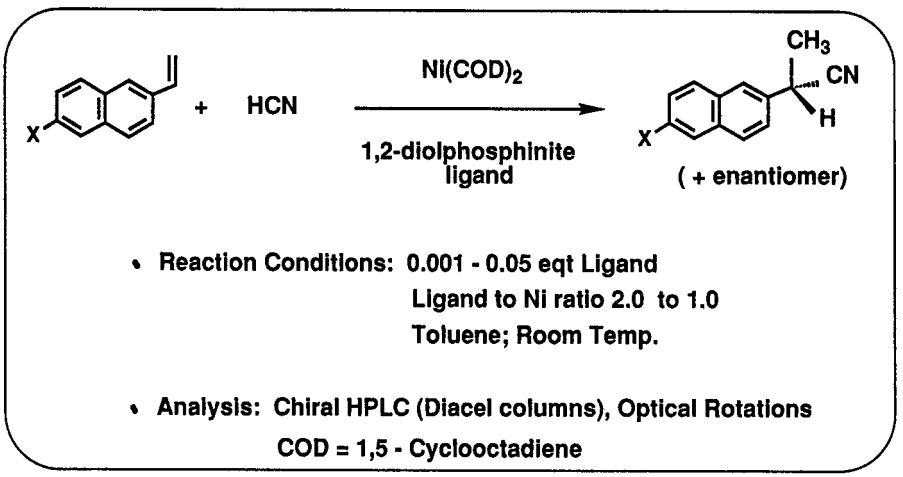

Fig. 4. The protocol for the Ni(0)- catalyzed hydrocyantion of vinylarenes.

transformed into amines, aldehydes, acids and a variety of other valuable intermediates. Vinyl arenes were chosen as prototypical substrates, since Markovnikov addition of HCN to these compounds results in 2-aryl-2-propionitriles.[7] The acids derived from these nitriles make up an important class of widely marketed non-steroidal antiinflammatory profen agents. Naproxen is particularly topical because the R enantiomer has a number of undesirable health effects.

The addition of HCN to 6-methoxy-2-vinylnaphthalene was carried out at room temperature in the presence of catalytic amounts of bis(1,5-cyclooctadiene)Ni(0) and a carbohydrate-derived diol phosphinite to give the corresponding arylpropionitrile in excellent yields (up to 99 % conversion) and with unprecedented enantioselectivity (Fig. 4). In sharp contrast to the well-known Pt or Rh-catalyzed hydrocarbonylation of these vinyl arenes,[8] no trace of the linear products were detected under these conditions. Further, the inherent enantioselectivity is

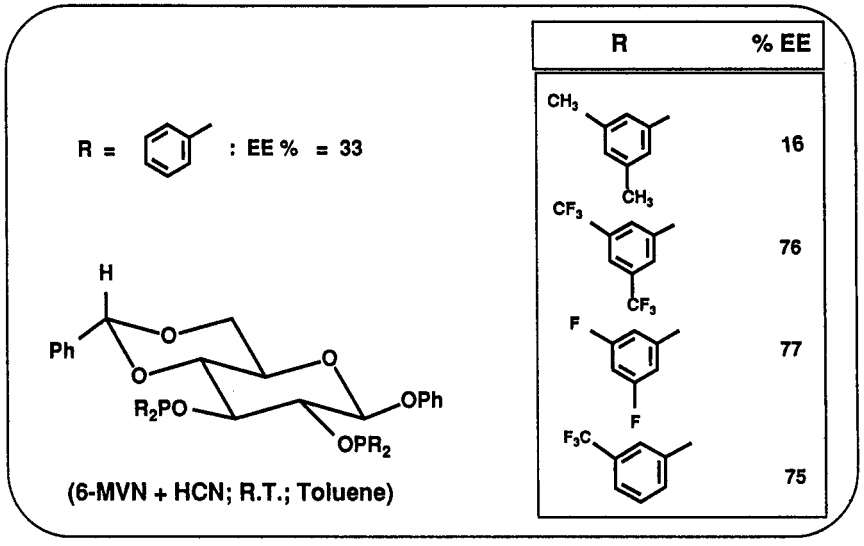

Fig. 5. Electronic effects of the P - substituents

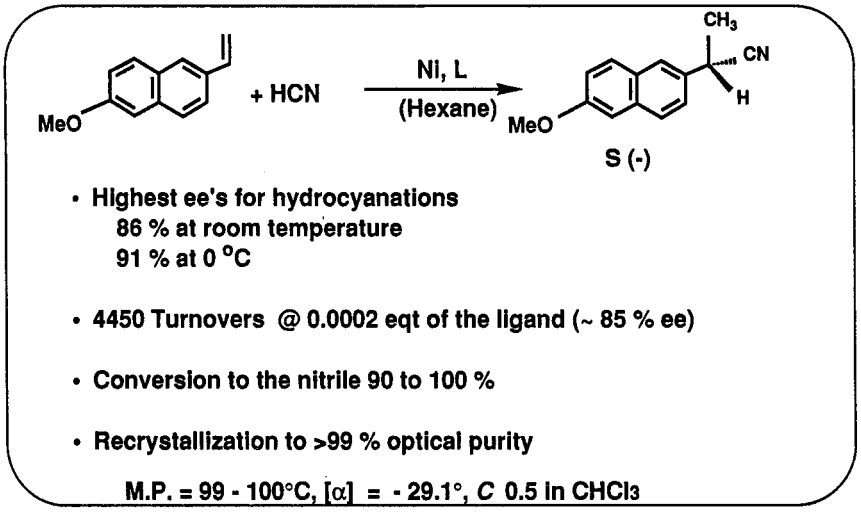

Fig. 6. Synthesis of naproxen nitrile.

independent of the extent of reaction or catalyst loading. A non-polar solvent like hexane gave the highest ee.

Sugar diolphosphinites as ligands

Initial screening of a number of 1,2- and 1,3- diolphosphinites prepared from readily available

diols indicated the overwhelming importance of the gluco-configuration of the sugar backbone for high enantioselectivity. The steric and electronic manipulations of the aglycone yielded a modest, yet discernable, improvement on the selectivity of this reaction. The substituents on the ligating phosphorus had a more dramatic effect. We found that electron-withdrawing groups like F or CF_3 on the phosphorus aryl groups (meta) gave the highest ee's as compared to the corresponding H-derivative (75% vs 33 % in toluene; Fig. 5). Remarkably, these catalysts also exhibited very high activity (552 turnovers/h) in the hydrocyanation of vinylnaphthalene. Using the bis-trifluoromethyl phosphinite, substrate to ligand ratios of 5000 can be used under conditions where the high ee's were maintained. These effects have since been confirmed in a number of other hydrocyanation reactions. Such electronic effects on the enantioselectivity have rarely been reported,[9] nevertheless we expect that they will play an increasingly important role in the design of future catalysts. A dramatic solvent effect was also observed in this reaction. Thus in hexane at 0°C, one can get ee's as high as 91% (i.e. S to R ratios 95.5 to 4.5) for naproxen nitrile (Fig. 6) using the bis-CF_3 -ligand. Simple recrystallization of the crude product yields optically pure (>99 % S-isomer) nitrile.[10] The optically pure drug can be prepared from this nitrile.

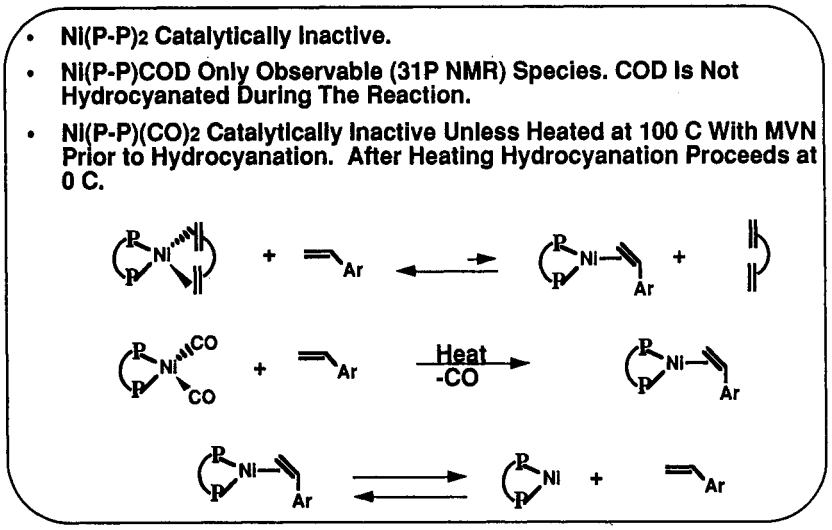

Fig. 7. Summary of some mechanistic studies.

Electronic Effects on Enantioselectivity: Mechanistic Considerations

Some of the initial mechanistic studies (Fig. 7) seem to suggest that the enantioselectivity has little to do with the initial π-facial selectivity. For example, variable temperature ^{31}P NMR suggest a fast rate of MVN exchange from the initially formed NiL(MVN) complex. Further the distribution of diastereomers, though complex, does not reflect the high ee's observed.

When electron-withdrawing substituents (for which best ee's were observed) are used, labelling studies using DCN indicate minimum incorporation of D into the olefin (and an attendant maximum into the product nitrile) (Fig. 8). We propose that the enantioselective step occurs in the insertion of the vinyl arene into the Ni-H with electron-withdrawing ligands (Figs. 9 and 10). The D-scrambling studies suggest that β–hydride elimination competes with reductive elimination in the case of electron-rich phosphinites (Fig. 10). *We believe that the electronic tuning of competing pathways could have broader implications in*

asymmetric catalysis and applications in other reactions are sure to follow. Our studies in hydroformylation, hydrogenation and cross-coupling reactions have confirmed this and that

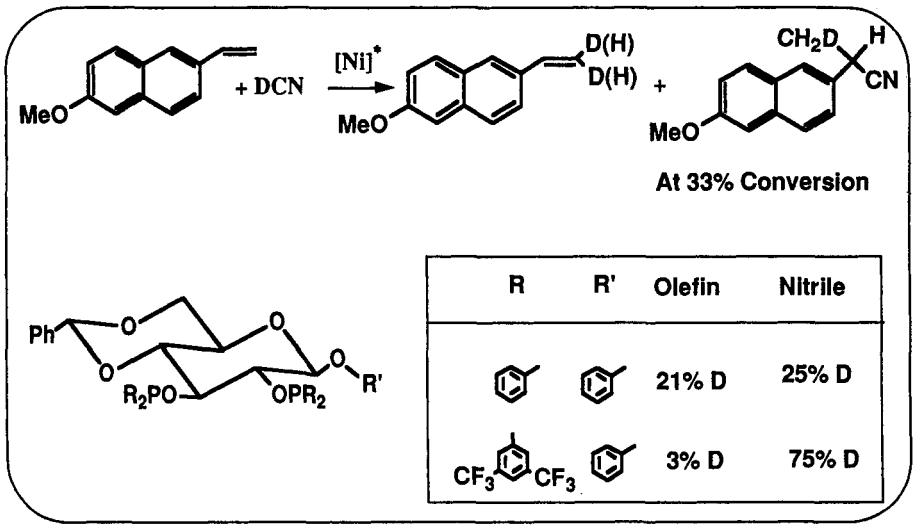

Fig. 8. Isotopic labelling studies.

will be the subject of future discussions. Asymmetric hydrosilylation is another reaction where these concepts could be applied.

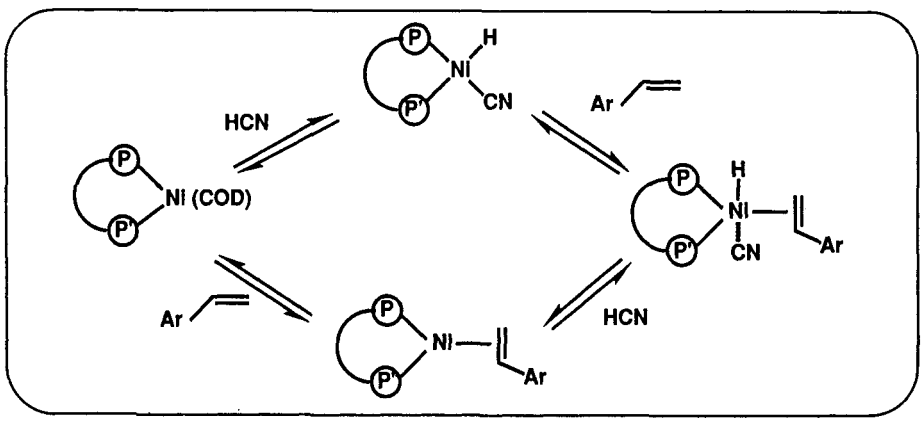

Fig. 9. Hydrocyanation mechanism I.

Further Fine-Tuning: The R-Nitrile

It is fortuitous that the D-glucose-derived ligands gave the desired S-isomer of the nitrile. In a more general context, one would like to prepare both R and S isomers from readily available sugars. Our search for a system to produce the R-isomers led to α-methylfructofuranoside. The results are shown in Fig. 11. The fructose-derived system provided, for the first time, an opportunity to introduce further elements of electronic asymmetry in the ligand by way of the different reactivities of the 3- (more hindered) and 4-hydroxyls. Now two different kinds of

phosphorus atoms can be attached to these oxygens. This fine tuning gave us the highest ee's (94%) to date for the asymmetric hydrocyanation reaction.

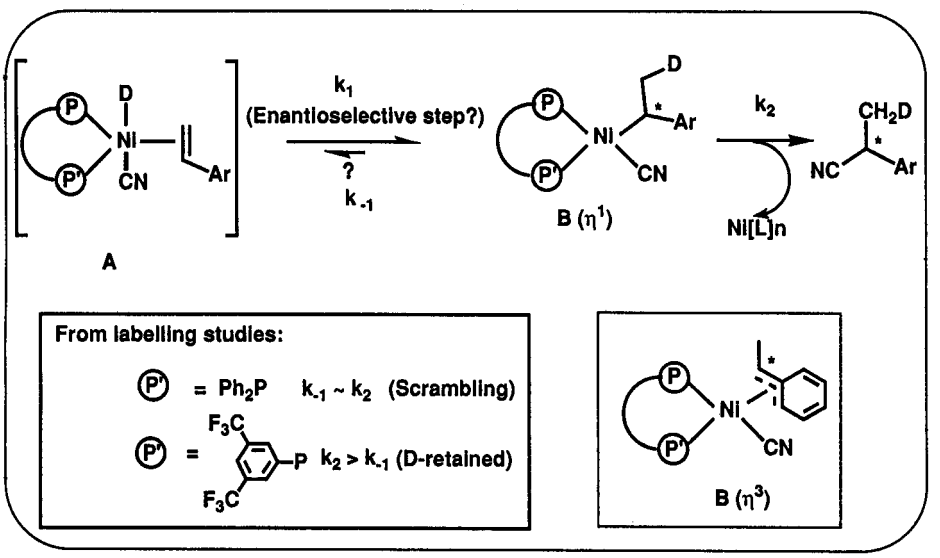

Fig. 10. Hydrocyanation mechanism II.

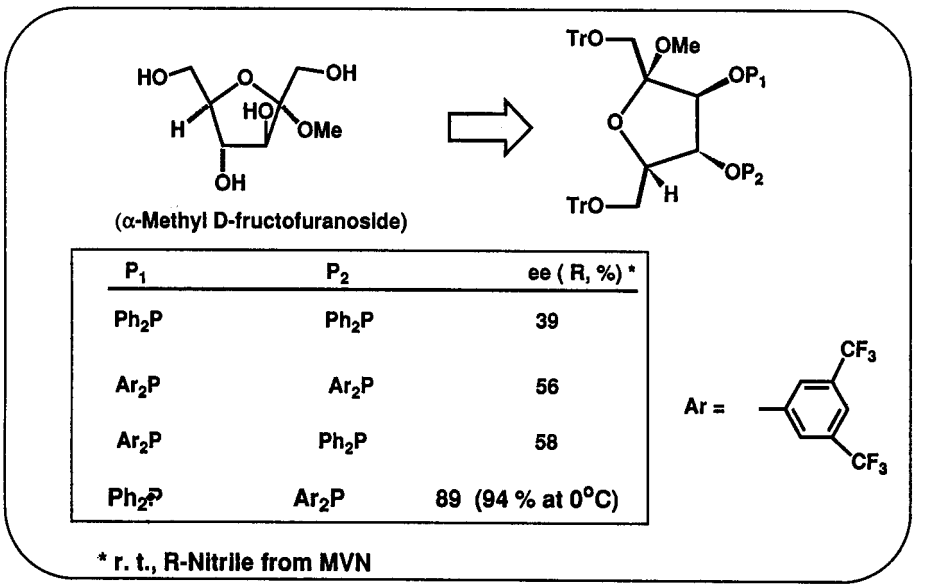

Fig. 11. The R-nitrile: Fine-tuning of a new ligand sytem.

Conclusions

In this exercise of semiempirical ligand design, we have only optimized the enantioselectivity for one reaction. We have shown that by electronic and steric tuning of readily available ligands from two of the most abundantly available sugars (glucose and fructose), one can produce both enantiomers of a key 2-arylpropionitrile (Fig. 12). Experiments under way suggest that the lessons learned here can be applied to other substrates and ultimately to other reactions as well.

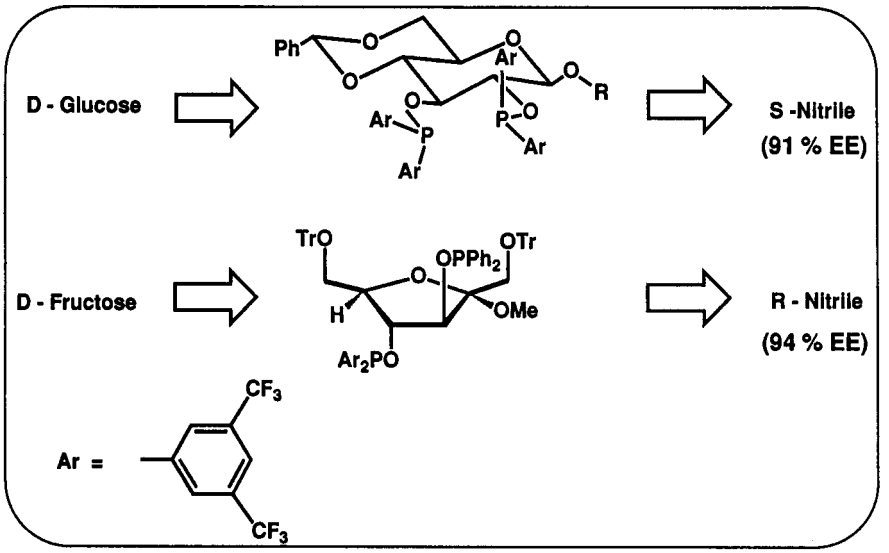

Fig. 12. Summary: Sugar ligands and asymmetric hydrocyanation.

Acknowledgements.
We gratefully acknowledge the invaluable technical assistance of M. S. Beattie, D. Johnson, G. H. Halliday, E. A. Duvall and K. G. Messner.

REFERENCES AND NOTES

1. T. V. RajanBabu, *Acc. Chem. Res.* **24**, 139 (1991); T. V. RajanBabu, W. A. Nugent and M. S.Beattie, *J. Am. Chem. Soc.*, **112**, 6408 (1990); T. V. RajanBabu, W. A. Nugent, D. F. Taber and P. J. Fagan, *J. Am. Chem. Soc.* **110**, 7128 (1988) and references cited therein.
2. For a critical account of this area and of DuPont's contributions see: W. A. Nugent, T. V. RajanBabu and M. J. Burk, *Science*, **259**, 479 (1993).
3. M. J. Barker, P. G. Pringle, *J. Chem. Soc., Chem. Commun.* 1292 (1991) and references cited therein.
4. For a preliminary account: T. V. RajanBabu and A. L. Casalnovo, *J. Am. Chem. Soc.* **114**, 6265 (1992).
5. The use of phosphinites have so far been largely limited to Rh-catalyzed hydrogenation of dehydroaminoacids. R. Selke; K. Haupke and H. W. Krause, *J. Mol. Catal.* **56**, 315 (1989).
6. T. Aratani, *Pure App. Chem.* **57**, 1837 (1985). Cyclic-dipeptide catalyzed HCN addition to aromatic aldehydes (J. Oku and S. Inoue, *J. Chem. Soc., Chem. Commun.* 229 (1981)) and amine mediated ketene-olefin cycloaddition (H. Wynberg and E. G. J. Staring, *J. Am. Chem. Soc.* **104**, 166 (1982)) are notable exceptions. Among the hundreds of other reactions reported, reactions of aldehydes with organo-zinc reagents (amino-alcohol or transition metal promoted) and with isonitriles (in the presence of gold complexes) have considerable potential for being practical.
7. W. A. Nugent and R. J. McKinney, *J. Org. Chem.* **50**, 5370 (1985).
8. J. K. Stille, H. Su, P. Brechot, G. Parrinello and L. S. Hegedus, *Organometallics* **10**, 1183 (1991).
9. For other recent examples, see: H. Takahashi, N. Yamamoto, H. Takeda, and K. Achiwa, *Chem. Lett.* 559 (1989); E. N. Jacobsen, W. Zhang and M. L. Guler *J. Am. Chem. Soc.* **113**, 6703 (1991); H. Nishiyama, S. Yamaguchi, M. Kondo and K. Itoh, *J. Org. Chem.* **57**, 4306 (1992).
10. For a more circuitous route to this compound, see: E. K. A. Wolber and C. Ruchardt, *Chem. Ber.* **124**, 1667 (1991).