Role of Electronic Asymmetry in the Design of New Ligands: The Asymmetric Hydrocyanation Reaction

T. V. RajanBabu* and Albert L. Casalnuovo*,†

Department of Chemistry, The Ohio State University
100 West 18th Avenue, Columbus, Ohio 43210
Central Research and Development
Experimental Station, The DuPont Company
Wilmington, Delaware 19880

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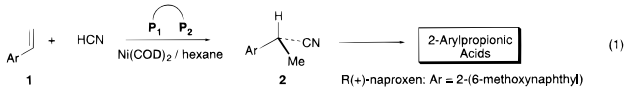
The concepts of C_2 symmetry and catalyst−substrate steric interactions have played an important role in the design and understanding of asymmetric catalysts and stereoselective reagents.[1,2] The C_2 symmetry element often simplifies the synthesis of the reagents and serves to reduce the number of competing diastereomeric intermediates in reactions involving their use.[3,4] Most often, the models[5] which adequately predict the stereochemical outcome of these reactions are based on the spatial orientation of groups within the disymmetric environment of the auxiliary or catalyst. Such steric-based, heuristic models are used not only to rationalize results but also to design more effective catalysts.[6] Even so, examples of the electronic tuning of asymmetric catalysts are appearing in the literature with increasing frequency.[7−12] Furthermore, in several cases, good enantioselectivities were obtained using chiral ligands without C_2 symmetry.[7,10−12]

The underlying reasons for the dependence of enantioselectivity on ligand electronics are only poorly understood. Nonetheless, the mechanistic and structural information that has become available in these cases suggests that a rationale based on steric effects alone does not adequately explain the stereochemical outcome. For reactions under the Curtin−Hammett regime, stereoelectronics may well play a determining role in the relative transition-state energies involved in the enantioselective step(s).[13−15] Thus, a transition metal complex with a bidentate ligand in which the two ligating atoms are electronically different could impart stereoelectronic control in the formation of a specific product, resulting in enhanced selectivity.[14] Indeed such effects may be responsible for the high enantioselectivity observed in a number of asymmetric reactions wherein different chelating atoms are used.[11,12] Unfortunately, a clear delineation of the steric and electronic effects is not possible in many of these systems. Ligands specifically designed to probe pure electronic asymmetry gave only moderate improvements over the more symmetric analogs.[19] To the best of our knowledge such ligands have not been tested in asymmetric carbon−carbon bond-forming reactions. Here we report on the use of an electronically unsymmetrical bis-3,4-diarylphosphinite ligand derived from an α-D-fructofuranoside (**3**) to achieve the highest enantioselectivity (*R*/*S*: 97.5/2.5) ever recorded for the asymmetric hydrocyanation reaction. In addition, the concept is further illustrated with the use of one of the simplest C_2-symmetric systems, viz., a bis-phosphinite derived from (S,S)-tartranil (**6**).

Vinylarenes react with HCN in the presence of Ni(0) complexes of vicinal diarylphosphinites to give exclusively the branched nitriles, which are potential intermediates for the synthesis of arylpropionic acids (eq 1). The enantioselectivity depends on the phosphorus substituents, and we have previously shown that electron-withdrawing substituents on phosphorus in a D-glucose-derived phosphinite system gave high ee's (∼91%) for this reaction,[10a,c] in which the major product is the *S*-



(1)

enantiomer. A serious limitation of ligand design based on natural products such as sugars is that often only one of the enantiomers is readily available.[20] In preliminary screening of various sugar-derived ligands, we discovered that 3,4-phosphinites from D-fructofuranoside derivatives gave the *R*-enantiomer of the 2-arylpropionitrile, albeit in low ee's. In an attempts to fine-tune this readily available ligand system, we prepared (eq 2) a series of ligands **5** where steric effects are

† Current address: DuPont Agricultural Products, Stine-Haskell Research Center S300/124, Newark, DE 19714.

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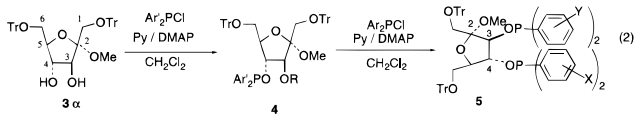
Table 1. Effect of Electronic Asymmetry on MVN Hydrocyanation

entry/ligand	X	Y	% ee of *R* nitrile
1/**5a**	H	H	43
2/**5b**	3,5-$(CF_3)_2$	3,5-$(CF_3)_2$	56
3/**5c**	H	3,5-$(CF_3)_2$	58
4/**5d**	3,5-$(CF_3)_2$	H	**89 (95 at 0 °C)**
5/**5e**	4-CH_3O	4-CH_3O	25
6/**5f**	3,5-$(CF_3)_2$	4-CH_3O	84
7/**5g**	3,5-$(CF_3)_2$	4-F	88
8/**5h**	3,5-$(CH_3)_2$	3,5-$(CH_3)_2$	40
9/**5i**	3,5-$(CF_3)_2$	3,5-$(CH_3)_2$	78
10/**5j**	3,5-F_2	3,5-F_2	45
11/**5k**	H	3,5-F_2	40
12/**5l**	3,5-F_2	H	63
13/**5m**	3,5-F_2	3,5-$(CF_3)_2$	42
14/**5n**	3,5-$(CF_3)_2$	3,5-F_2	78

largely kept constant and electronic effects systematically varied. The widely different reactivities of the 3- and 4-hydroxyl groups of the fructofuranoside system can be exploited to prepare electronically unsymmetrical bis(diaryl)phosphinites (eq 2). Hydrocyanation of 6-methoxy-2-vinylnaphthalene was carried out as described earlier,[10c] and the products were analyzed by HPLC (Table 1).



As anticipated from our previous work,[10a] electron-donating substituents on the phosphorus aryl groups give the lowest ee's (entries 1, 5, and 8). Electron-deficient phosphinites increase the selectivity to some extent (entries 2 and 10). However, the most dramatic increase (entry 4) was noticed when the C_3-phosphinite is relatively electron-rich (Ph_2P) and the C_4-phosphinite is electron-deficient ($[3,5\text{-}(CF_3)_2C_6H_3)]_2P$). The relative juxtaposition of the electronically different phosphino groups seems to be important, since reversing the order (entry 3) produces no better selectivity than the symmetric electron-deficient phosphinite (entry 2). A similar, albeit, less dramatic, trend is observed with the pair of phosphinites with $[3,5\text{-}(F_2)C_6H_3]_2P$ and Ph_2P (entries 1, 10, 11, and 12). The unsymmetrical phosphinite with the more electron-deficient phosphorus at the C_4–position of fructose is clearly superior (63% ee, entry 12) to either of the symmetrical phosphinite (entries 1 and 10, 43 and 45%, respectively) or the one in which the more electron-deficient phosphorus is at C_3 (40% ee, entry 11). These results are difficult to rationalize on the basis of any steric arguments alone, and we suggest an electronic origin for these unusual observations. The general trend suggests that for high enantioselectivity, C_4 must carry the electron-deficient phosphinite and C_3, the electron-rich one. Other examples (entries 6, 7, and 9) verify this conjecture.

There is some evidence that similar electronic asymmetry can enhance enantioselectivity in other much simpler ligand systems. To probe this effect we chose a simple C_2-symmetric diol, (*S*,*S*)-tartranil (eq 3).[21] Diarylphosphinites (**8**) derived from this

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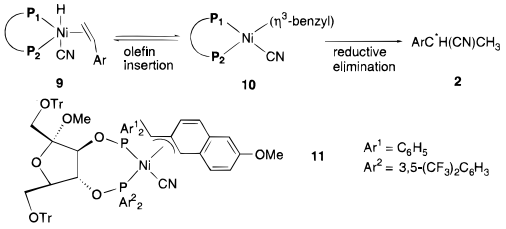
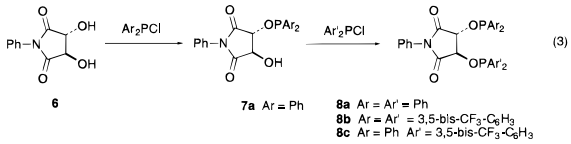


Figure 1. Abbreviated mechanism of asymmetric hydrocyanation.

molecule showed a similar, though less dramatic effect. Thus, the highest ee, 77% (*S*), was obtained with a mixed phenyl/3,5-bis(trifluoromethyl)phenyl derivative (**8c**), whereas the C_2-symmetric phenyl (**8a**) and 3,5-bis(trifluoromethyl)phenyl (**8b**) derivatives gave 54 and 70% ee respectively.



Based on kinetic and isotope labeling studies we proposed[10c] a mechanism (Figure 1) for the asymmetric hydrocyanation of vinyl arenes in which the intermediate **10** plays a key role. We proposed that the relative rates of formation of **10** and the subsequent reductive elimination, as a function of the ligand electronic properties, dictated the overall selectivity. If the primary effect of electron-withdrawing phosphorus aryl substituents is to accelerate the final reductive elimination,[22] then the enhancement of enantioselectivity may result because one of the diastereomers of **10** may be disproportionately affected. The precise factors favoring a particular diastereomer are presently unclear, but the results with the α-methyl fructofuranoside ligand frame strongly suggest the importance of a *stereoelectronic* component. For example, the effect of electronic asymmetry may reflect the importance of a trans relationship[23] between the η^3-aryl fragment and the phosphorus bearing the electron-withdrawing aryl groups (**11**).

These results clearly demonstrate that incorporation of electronically different phosphorus chelates can markedly enhance enantioselectivity with certain ligand frame works. Thus we have demonstrated that by appropriate electronic tuning of ligands derived from two of the most abundantly available sugars, viz., D-glucose[10c] and D-fructose, both enantiomers of naproxen nitrile (**2**) can be prepared in excellent enantioselectivity (91% *S*, 95% *R* at 0 °C) via a catalytic asymmetric hydrocyanation reaction. Elaboration of the concept of electronic asymmetry in other systems and applications of unsymmetrical diphosphinites and phosphines as ligands in other reactions will be the subject of future work.

Supporting Information Available: Details of the synthesis and spectroscopic characterization of ligands (7 pages). See any current masthead page for ordering and Internet access instructions.

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