Electronic Amplification of Selectivity in Rh-Catalyzed Hydrogenations: D-Glucose-Derived Ligands for the Synthesis of D- or L-Amino Acids

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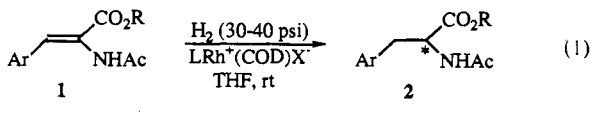
Asymmetric catalysis by transition-metal complexes has made enormous progress during the past decade,[1] yet the factors that are important for achieving high enantioselectivity remain the subject of speculation even in reactions that have been extensively studied.[2] Most often, heuristic models based on steric arguments are used in the rationalization of results[3] and in the design of more selective catalysts.[4] Electronic effects have seldom been employed as a *control element for enantioselectivity*, even though such effects have long been recognized as being important in primary organometallic processes such as oxidative addition and reductive elimination.[5,6] Only a few examples have been documented where electronic tuning of a ligand system has resulted in an enhancement of enantioselectivity.[7-10] Previously we demonstrated that the enantioselectivity of the Ni(0)-catalyzed asymmetric hydrocyanation of olefins was dramatically improved when phosphinites with electron-withdrawing substituents at phosphorus were employed as ligands.[8] In this communication we report our findings on the electronic effects[10] in the Rh(I)-catalyzed asymmetric hydrogenation of acetamidoacrylates **1** (eq 1).[11] In this instance, *electron-rich* phosphinites provide a highly

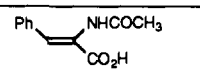
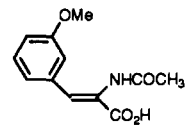
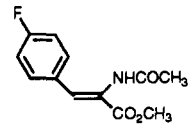
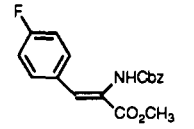


(1)

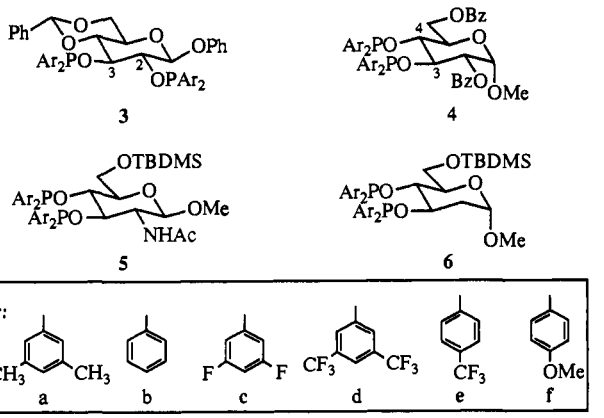
practical route to a wide spectrum of amino acid derivatives. We also describe how the sense of chirality of the products **2** is dependent on the relative juxtaposition of the vicinal diphosphinites *on a given sugar backbone*. Thus, both L- and D-amino acids can be synthesized in excellent enantioselectivity using the *same* sugar, D-glucose.

The application of simple diphenylphosphinites such as **3b** as ligands in the Rh-catalyzed hydrogenation of dehydrophenylalanine **1** (Ar = Ph) has been reported to give good selectivities.[12] However, we and others[13] have found that the scope of **3b** was severely limited for the synthesis of substituted phenylalanines, as enantiomeric excesses (ee's) ranged from 62 to 94% (Table 1, under **3b**).[14]

Table 1. Substituent Effects on Rh-Catalyzed Hydrogenation of Dehydroamino Acids **1**[a]

entry	substrate	ee[b] (%), ligand 3a	3b	3c	3d
1		99.0	94.0	60.0	71.0
2		97.0	91.0	53.0	5.0
3		97.2	85.0	13.0	9.0
4		97[c]	62[c]	<1[c]	54[c]

[a] Reaction conditions: 0.05–0.1 mol % $LRh^+(COD)SbF_6^-$, 30–40 psi H_2, in THF, room temperature (see supplementary material for details). [b] Enantiomeric excesses determined by GC (Chirasil S-Val) on methyl esters. [c] Enantiomeric excess determined after reduction on alcohols by HPLC (Chiracel-OB).



In sharp contrast to the hydrocyanation reaction,[8] the use of phosphinites **3c** and **3d** with electron-withdrawing substituents resulted in a dramatic *decrease* in the enantioselectivity of the hydrogenation reaction (see under **3c** and **3d**, Table 1).[14] For example, in the preparation of methyl (4-fluorophenyl)alaninate

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(14) See supplementary material for a more extensive list of other amino acids and for the detailed synthesis of **4a**.

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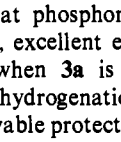
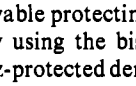
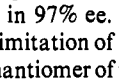
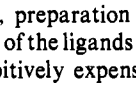
(entry 3), the ee drops from 85% using the diphenylphosphinite **3b** to 9.0% with the bis[3,5-bis(trifluoromethyl)phenyl]phosphinite **3d** as the ligand. Remarkably, the use of phosphinite **3a** with the comparatively more electron-donating 3,5-dimethylphenyl groups at phosphorus increased the ee to 97.2%. More importantly, excellent ee's are obtained over a wide range of substrates when **3a** is the ligand. Furthermore, successful asymmetric hydrogenation of dehydroamino acid derivatives with easily removable protecting groups on nitrogen is rare.[11b,13] We find that by using the bis(3,5-dimethylphenyl)phosphinite **3a**, even the Cbz-protected derivative of (4-fluorophenyl)alanine can be prepared in 97% ee.

A major limitation of carbohydrate-derived ligands is that the unnatural enantiomer of the ligand is usually not readily available. In our case, preparation of D-amino acids would require the enantiomers of the ligands of type **3**—ligands that must be derived from prohibitively expensive L-glucose.[15] We discovered that readily available 3,4-diphosphinite ligands (**4**, prepared from methyl α-D-glucopyranoside in two steps)[14,16] provide D-amino acids in the hydrogenation reaction.[17,18] As before, the bis(3,5-dimethylphenyl)phosphinite **4a** gives the highest ee's (>96%) for a variety of substituted phenylalanine derivatives (Table 2).[14] *From a practical standpoint, this is a remarkably useful result, since both* D- *and* L-*amino acids can now be prepared in excellent enantioselectivity by using ligands from one of the most abundantly available sugars,* D-*glucose.*[15] A more detailed study of the electronic effect was conducted with ligand **4** using a range of electronically different phosphinites (Table 2, entries 7–12), including bis[4-(trifluoromethyl)phenyl]phosphinite **4e** and bis-(4-methoxyphenyl)phosphinites **4f**. Note that once again the electronic effect is incontrovertible, with the ee's ranging from 0 to 93% on going from electron-withdrawing to electron-donating substituents at phosphorus.

Finally, a brief examination of structural changes in the sugar backbone was conducted to evaluate the steric requirements of the 3,4-system. The widely available 2-deoxy-2-acetamido-D-glucose system **5** was found to be an equally effective ligand for the production of D-amino acids, providing, for example, methyl D-phenylalaninate (**2**, Ar = Ph, R = Me) in 98.3% ee (entry 5). However, it does appear that an equatorial substituent at the 2-position is crucial for high ee's, because the use of the simple 2-deoxy derivative **6a** provided only 65.1% ee for the same compound (entry 6).

Table 2. Synthesis of D-Amino Acids Using Glucose 3,4-diphosphinites[a]

entry	Ar in **1**	L(SbF_6)[b]	ee (%)	entry	Ar in **1**	L(BF_4)[b]	ee (%)
				5	Ph	**5a**	98.3
1		**4a**	96.2	6	Ph	**6a**	65.1
				7	Ph	**4a**	93.0[c]
2		**4a**	96.0	8	Ph	**4f**	84.7
				9	Ph	**4b**	71.1
3		**4a**	97.0	10	Ph	**4c**	1.0
				11	Ph	**4d**	2.3
4		**4a**	96.4	12	Ph	**4e**	2.0

[a] See Table 1 for reaction conditions. [b] Denotes counterion in $LRh^+(COD)X^-$. [c] 96.0% ee with $LRh^+(COD)SbF_6^-$.

The origin of the enhancement of enantioselectivity as a function of the electronic nature of the ligand remains speculative. As indicated by recent ^{103}Rh NMR data, the electron density on Rh may have a bearing on the relative rates of H_2 addition to the intermediate diastereomeric Rh(L)–cinnamate complexes.[19] The ligand electronic effects on the intrinsic stabilities and reactivities of the two intermediate diastereomeric complexes[2a,20] remain to be evaluated.[21]

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Supplementary Material Available: Typical procedures and GC and HPLC conditions for analysis (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) For example, D-glucose and methyl α-D-glucopyranoside are two of the cheapest starting materials (<$1.00/kg). By comparison, L-glucose costs $23 000.00/kg.

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(17) The highest ee reported to date for the preparation of D-amino acids using a sugar diphosphinite is only 63%. Habus, I.; Raza, Z.; Sunjic, V. *J. Mol. Catal.* **1987**, *42*, 173.

(18) The change in the product's sense of chirality can be explained by the pseudoenantiomeric relationship of the glucose 2,3- and 3,4-configurations. We believe, conceptually, this dependence can be exploited for catalyst design in other asymmetric reactions.

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(21) We have demonstrated similar electronic effects in the reduction of several *N*-acetamidocinnamates using *trans*-(1*S*,2*S*)-cyclohexane-1,2-diphosphinites. Further mechanistic studies using this simplified system are in progress.