Catalytic Asymmetric Hydrogenation[1]

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Summary An efficient direct route to optically active α-amino acids has been achieved by a catalytic asymmetric reduction of α-acylaminoacrylic acids.

RECENT publications[2] have shown that fairly efficient catalytic asymmetric hydrogenation can be accomplished using a rhodium complex with a chiral phosphine or amide ligand. These results prompt us to report the reduction of α-acylaminoacrylic acids. This technique, and the fact that excess L or D amino-acid derivatives are often easily separated from DL, now provides a practical synthesis of these compounds without the usual resolution step.

In previous work phosphine ligands in which the asymmetry is in the side chain have been used.[2a,b] We describe cases in which the chirality is on the phosphorus. The Table shows the results obtained with various phosphines and substrates. The considerable variation of yields with phosphine structure clearly shows the need for a match of catalyst and substrate. Of particular interest are the high optical purities obtained with *o*-anisylmethylcyclohexylphosphine when applied to various acylphenylalanine precursors. These yields in the 85—90% range, and the probability that our phosphine was only 95% optically pure, show that we have achieved almost complete stereospecificity.

With acylaminocinnamic acids our catalyst system was very active, the above results being obtained in 3 h at 25° with 500 mm H_2 and 0·05% metal. A successful catalyst can be made in a variety of ways. Rhodium(I)–diene complexes of the type $[Rh(1,5\text{-hexadiene})Cl]_2$ mixed with two chiral ligands and prehydrogenated for 5 min at 1 atm H_2 work well. $RhCl_3,3H_2O$ and two ligands with a more vigorous prehydrogenation is also quite effective.

Our contention[1b] that optimum results are obtained with exactly two ligands is confirmed by preparation of a crystalline compound [Rh(1,5-cyclo-octadiene)(Cl)L] (L = *o*-anisylmethylphenylphosphine). The mono-ligand derivative gave slow hydrogenation and low optical bias. Adding *in situ* another mole of chiral L gave fast rates and high optical purities. If non-chiral dimethylphenylphosphine is used as the extra ligand, fast rates but only half the optical yield is obtained. A crystalline two-ligand compound $[Rh(1,5\text{-cyclo-octadiene})L_2]^+(C_6H_5)_4B^-$ or BF_4^- gave identical results suggesting that the catalyst is cationic. These solid derivatives are air-stable and convenient to use. They absorb hydrogen readily in methanol solution at 25° and at 1—2 atm to form the active catalyst.

The *o*-anisylmethylphenylphosphine was made according to Mislow[4] by reaction of *o*-anisylmagnesium bromide with resolved menthyl methylphenylphosphinate followed by

TABLE. *Hydrogenation of α-acylaminoacrylic acids*

Chiral phosphine R^1–P(R^2)–R^3				Substrate $R^4CH{=}C(NHCOR^5)CO_2H$		Product $R^4CH_2{-}CH(NHCOR^5)CO_2H$
R^1	R^2	R^3	Approx Optical purity %	R^4	R^5	Optical purity %[a]
o-Anisyl	Me	Ph	95	3-MeO-4-(OH)C_6H_3	Ph	58[b]
Me	Ph	Pr^n	90	3-MeO-4-(OH)C_6H_3	Ph	28[c]
Me	Ph	Pr^i	90	3-MeO-4-(OH)C_6H_3	Ph	28[c]
m-Anisyl	Me	Ph	80	3-MeO-4-(OH)C_6H_3	Ph	1[c]
o-Anisyl	Cyclohexyl	Me	95	3-MeO-4-(OH)C_6H_3	Ph	87[d]
o-Anisyl	Cyclohexyl	Me	95	3-MeO-4-(OH)C_6H_3	Ph	90[e]
Cyclohexyl	Me	Ph	75	3-MeO-4-(OH)C_6H_3	Ph	32[c]
o-Anisyl	Ph	Pr^i	80	3-MeO-4-(OH)C_6H_3	Ph	1[c]
o-Anisyl	Me	Ph	95	3-MeO-4-(AcO)C_6H_3	Me	55[b]
o-Anisyl	Me	Pr^n	95	3-MeO-4-(AcO)C_6H_3	Me	20[c]
o-Anisyl	Cyclohexyl	Me	90	3-MeO-4-(AcO)C_6H_3	Me	77[f]
o-Anisyl	Cyclohexyl	Me	95	3-MeO-4-(AcO)C_6H_3	Me	85[d]
o-Anisyl	Cyclohexyl	Me	95	3-MeO-4-(AcO)C_6H_3	Me	88[e]
o-Anisyl	Cyclohexyl	Me	95	Ph	Me	85[d]
o-Anisyl	Cyclohexyl	Me	95	Ph	Ph	85[d]
o-Anisyl	Cyclohexyl	Me	95	H	Me	60[d]

[a] All optical purities were determined by direct comparison of the total reaction mixture with a blank made from authentic acylated amino acid in order to avoid any enrichment from work-up or slight contribution from the catalyst. [b] In a stirred autoclave in methanol at 55 p.s.i. (abs.) of hydrogen at 50° with one equivalent of NaOH added. The molar ratio of substrate to catalyst was 3000 : 1. [c] In a Parr shaker in methanol at 55 p.s.i. (abs.) at 25°. [d] As c in 95% ethanol at 10 p.s.i. (abs.). [e] As d in propan-2-ol. [f] As b using 0·05% triethylamine instead of NaOH.

reduction with $HSiCl_3$. The other phosphines were made similarly. *o*-Anisylcyclohexylmethylphosphine was prepared by selective reduction of *o*-anisylmethylphenylphosphine oxide with 5% Rh on carbon followed by $HSiCl_3$ reduction.

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[1] For previous papers in series see: (a) W. S. Knowles and M. J. Sabacky, *Chem. Comm.*, **1968**, **1445**; (b) W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *Ann. New York Acad. Sci.*, **1970**, **172**, 232; (c) patents pending.

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