solvent. The measured molecular weights for the individual species of 5827 ± 2 Da (I) and 6410 ± 2 Da (II) were consistent with the sequence within experimental uncertainty. The measured molecular weight of the duplex (12 297 ± 10 Da) is higher than that calculated ($M_r$ 12 237.1). This may be the result of insufficient desolvation of these higher molecular weight, lower charge state ions compared to their single-stranded counterparts or the result of greater counterion association (e.g., residual $Na^+$, $NH_4^+$, etc., which may remain and indeed may be necessary to stabilize the duplex structure in the gas phase).

The present results are the first observation of duplex oligonucleotides from solution by mass spectrometry, a potentially significant first step toward the study of oligonucleotide and nucleic acid associations. The results show that careful choice of both solution and ESI-MS interface conditions are crucial, consistent with earlier reports for the analysis of noncovalent complexes.[2,3] An extended $m/z$ range ($>m/z$ 2000) may also be useful for such observations since the intact duplex is observed with significant intensity only in relatively low charge states. It is uncertain whether the monomeric constituents observed in the mass spectra are representative of the solution or whether they are products of dissociation of Coulombically destabilized higher charge states of the duplex. Indeed, one expects decreased stability for the gas-phase duplex in higher charge states as desolvation removes the dielectric shielding provided by the solvent. Higher charge state ions are also collisionally activated to a greater extent in the interface than lower charge state ions[6] and so are subject to dissociation by the same processes required to desolvate the lower charge state ions. Further studies of larger duplex structures and other noncovalent nucleotide complexes are in progress.

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## Chiral Poisoning: A Novel Strategy for Asymmetric Catalysis

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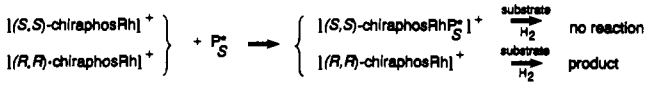
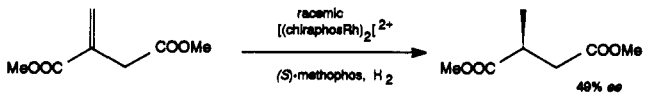
Asymmetric synthesis is an important goal in contemporary pharmaceutical and agricultural chemistry.[1] Catalytic asymmetric hydrogenation in particular has proven useful in many situtations, such as the industrial production of L-Dopa.[2] Asymmetric chelating bisphosphines, the key ligands in many of these metal-catalyzed reactions, are costly and can degrade with time. Our new approach offers the possibility of using the readily available racemic ligands and selectively poisoning one hand of the chiral catalyst with an inexpensive chiral poison.

We have investigated the racemic version of [(chiraphos)Rh(NBD)]$BF_4$, which was developed and extensively studied in the enantiomerically pure form by Bosnich [chiraphos = $Ph_2P(CHMe)_2PPh_2$].[3] Reduction with hydrogen releases a catalytically active species [(chiraphos)Rh]$^+$, which may be solvated or a dimer, [(chiraphos)Rh]$_2^{2+}$.[4,5] The dimer can be isolated and is a useful catalyst precursor, as it can dissociate in solution to yield [(chiraphos)Rh]$^+$. If racemic chiraphos is used to prepare the dimer, dissociation should provide equal amounts of [(*S*,*S*)-chiraphosRh]$^+$ and [(*R*,*R*)-chiraphosRh]$^+$. If a poison selectively deactivated all of one enantiomer, then the hydrogenation due to the remaining active catalyst would yield a product of high enantiomeric purity. In the ideal case one-half an equivalent of poison per equivalent of racemic catalyst would leave one-half of an equivalent of active homochiral catalyst.




In our initial screening, we found an effective poison for the asymmetric hydrogenation of dimethyl itaconate. It demonstrates the principles involved, and we report our observations here since we believe the strategy will be applicable to many asymmetric catalyst systems. Our chiral poison, which we call (*S*)-methophos, (*S*)-[$Ph_2POCH_2CH(NMe_2)CH_2CH_2SMe$], is readily prepared from methionine.[7] Although this ligand can be effective in other types of asymmetric synthesis, it is a very poor ligand for the asymmetric hydrogenation of dimethyl itaconate and yields dimethyl methylsuccinate in <2% ee. We find that it can act as an effective chiral poison, however.

In a typical experiment, a solution of the racemic dimeric catalyst was stirred in THF under nitrogen with 0.7 equiv of (*S*)-methophos ((*S*)-mtp:Rh = 0.7:1) for 2 h. Dimethyl itaconate (DMI:Rh ≈ 15:1) was then added and the reaction mixture was transferred to a pressure reactor. The reaction was complete within 3 h at moderate pressures (~800 psi). The enantiomeric purity of the dimethyl methylsuccinate product was determined by chiral NMR shift experiments using Eu(hfc)$_3$.




As expected [(chiraphos)Rh]$_2^{2+}$ dimers produced from racemic chiraphos and hydrogenation in the presence of achiral diphos produced dimethyl methylsuccinate in 0% ee. Since the [(*S*)-methophosRh]$^+$ produced a product with <2% ee, the poisonong has dramatically enhanced the enantioselectivity of the asymmetric catalysis.

Hydrogenation using the pure (*R*,*R*)-chiraphos rhodium complex yields the (*S*)-methylsuccinate in high enantiomeric purity (>98% ee). Since (*S*)-methylsuccinate predominates in our system, we assume that the principal hydrogenation path involves [(*R*,*R*)-chiraphosRh]$^+$ and that the primary role of the (*S*)-methophos is to bind to [(*S*,*S*)-chiraphosRh]$^+$ and so reduce its equilibrium concentration.[10]

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(4) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 936, 946. Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2121. (The counterion was often $ClO_4^-$ in these studies.)
(5) There are actually several dimers present here,[4] as well as in the diphos analogue.[6] In the dimers of chiraphos a phenyl group in one monomer bonds to the Rh of the other, which renders the phosphorus center chiral. This further complicates the $^{31}P$ NMR since diastereomers are formed owing to chirality at the carbon as well as at phosphorus. Studies of the poisoning are complicated by the multiplicity of diastereomeric species, as well as exchange phenomena which lead to broadening of the NMR spectra of species interacting with the methophos.
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Naturally one anticipates a large number of equilibria in this system, and the "poison" in reality operates by forming several complexes which have reduced rates of catalytic activity. The poison would be expected in practice to deactivate both enantiomers of the active species to some extent. The effectiveness of the poisoning would depend on the quality of the chiral discrimination of the poison.

There is at least one other factor, "chirality amplification", which can contribute significantly to the enantiomeric purity of the product. In our case it appears to be important at lower $H_2$ pressures. Once the poison preferentially sequesters one enantiomer of the catalyst, there are no longer equal amounts of [(*S*,*S*)-chiraphos]Rh$^+$ and [(*R*,*R*)-chiraphosRh]$^+$ in solution. This has an effect on the relative monomer and dimer populations because the stability of the mixed dimer is different than that for the dimer containing identical ligands.

$$|(S,S),(R,R)\text{-(chiraphosRh)}_2|^{2+} \rightleftharpoons |(R,R)\text{-chiraphosRh}|^+ + |(S,S)\text{-chiraphosRh}|^+$$

$$|(R,R),(R,R)\text{-(chiraphosRh)}_2|^{2+} \rightleftharpoons 2\,|(R,R)\text{-chiraphosRh}|^+$$

For example, if we consider the idealized case where the poison completely deactivated two-thirds of the [(*S*,*S*)-chiraphosRh]$^+$ in a racemic mixture, a 1:3 ratio of (*S*,*S*) to (*R*,*R*) would remain available for catalysis. Very little of the (*S*,*S*)-(*S*,*S*) dimer would be formed if the formation constant of the homodimer were much less than that of the heterodimer. This would also require that much of the (*R*,*R*)-(*S*,*S*) dimer would remain associated, whereas the (*R*,*R*)-(*R*,*R*) would mostly be dissociated. In effect some of the (*R*,*R*) monomer sequesters the (*S*,*S*) monomer, leaving the remaining pure (*R*,*R*) monomer available for catalysis. This idealized case illustrates how a catalyst of low enantiomeric purity could yield a product of higher enantiomeric purity. This type of nonlinear effect was originally investigated by Kagan[11] and recently shown to be important in chiral amino alcohol assisted dialkylzinc addition to carbonyls by Noyori.[12]

This chiral amplification effect contributes in our case under certain conditions. For example, we have found chiral amplification when using nonracemic chiraphos in the formation of dimers in the absence of poisons. The use of dimer prepared from a 1:2 mixture of (*S*,*S*)-chiraphos/(*R*,*R*)-chiraphos yields a 1:4 mixture of (*R*)-methylsuccinate to (*S*)-methylsuccinate.

We anticipate that these chiral poisons can be optimized for use in high-yield asymmetric hydrogenations. We are continuing to try to improve the process; however, at this time we have found that modest increases in the ee of the hydrogenation product were obtained by using THF in place of $CH_2Cl_2$, increasing the $H_2$ pressure, and increasing the poison to catalyst mole ratio to greater than ~50%. Increasing this ratio from ~50% to 200% appears to have only a modest effect on the ee. Increasing the temperature from 23 to 32 °C led to a decrease from 49% to 42% ee. These may well not be the optimum poisons nor the optimum conditions: it is plausible that many chiral ligands that have been dismissed in the past because their complexes were poor asymmetric catalysts may actually act as extremely effective poisons. It also follows that the approach described here can be applied to many other types of asymmetric catalysis.[14]

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**Supplementary Material Available:** Listing of experimental details of hydrogenations under several conditions (3 pages). Ordering information is given on any current masthead page.

(10) We have not yet elucidated the details of the poisoning.[5] An obvious choice would be the formation of a mixed [(bisphosphine)$_2$Rh]$^+$ complex with lower activity. [(bisphosphine)$_2$Rh]$^+$ complexes have seen limited use in chiral catalysis,[11] and to some extent, they may merely provide an alternative source for [(bisphosphine)Rh]$^+$. These bisphosphine complexes are moderately catalytically active, but there are indications that a different path may be involved;[11] nevertheless, they are less efficient catalysts. Regardless, the relative stabilities of {[(*S*)-methophos](*S*,*S*)-chiraphos]Rh}$^+$ and {[(*S*)-methophos](*R*,*R*)-chiraphos]Rh}$^+$ analogues would be different, which implies that (*S*)-methophos will effectively sequester one hand of the [chiraphosRh]$^+$ complex in preference to the other.

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## Biosynthesis of Taxoids. Mode of Formation of the Taxol Side Chain†

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Taxol[1] (**1**) and its semisynthetic analog, taxotere,[2] have attracted considerable attention because they show great promise as agents for the treatment of a variety of solid tumors.[3] A major impediment to their development has been the limited supply of these compounds; intensive research efforts are being directed toward finding long-term solutions to this problem. Since for the foreseeable future their commercial production will have to rely on biological systems as the source of at least the diterpene moiety of these compounds, an understanding of the chemistry employed by *Taxus* species to assemble these molecules is extremely pertinent. With this in mind we have embarked on studies on the biosynthesis of taxoids, and we report here on the origin of the phenylisoserine side chain which is essential for the antitumor activity of these compounds.

Leete and Bodem[4] have previously shown that the Winterstein's acid (3-(dimethylamino)-3-phenylpropanoic acid) moiety of taxine is derived from phenylalanine. A similar origin is likely for the phenylisoserine moiety of **1**. Scheme I shows two plausible pathways from phenylalanine to the *N*-benzoylphenylisoserine side chain of **1**, one via β-phenylalanine (path a) and one via cinnamic acid and its epoxide (path b); product stereochemistry would dictate that the latter route proceeds via *cis*-cinnamic acid. Haslam and co-workers[5] found that the conversion of phenylalanine into Winterstein's acid proceeds with retention of the *pro-S* and loss of the *pro-R* hydrogen from C-3 of the side chain, ruling out the involvement of phenylalanine:ammonia-lyase since this enzyme stereospecifically removes the *pro-S* hydrogen from C-3 of phenylalanine. To distinguish between the two pathways shown in Scheme I, we synthesized the possible intermediates **4**–**8** in deuterium-labeled form (**4a**–**8a**; **3a** is commercially available with 99.7 atom % D) (Chart I). Labeled side chain **6a** was prepared

† Dedicated to Professor Meinhart H. Zenk (Munich), a pioneer in plant secondary metabolite biosynthesis, on the occasion of his 60th birthday.

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