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Modular Phospholane Ligands in Asymmetric Catalysis

MARK J. BURK
Chirotech Technology Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0WE, U.K.

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ABSTRACT
This Account outlines the preparation and application of a class of phosphine ligands based upon the *trans*-2,5-disubstituted phospholane moiety. The modular nature of these ligands has allowed facile variation of both phospholane substituent and backbone structure, thus providing access to a series of ligands. Bidentate bis(phospholane) ligands have been found to be very useful in asymmetric catalytic hydrogenation reactions. In particular, we highlight the versatility of highly efficient bis(phospholane)rhodium catalysts that allow enantioselective hydrogenation to produce a diverse range of compounds containing C−N, C−O, and C−C stereogenic centers.

Introduction

Asymmetric catalysis increasingly impacts life on earth. While this preamble may appear bold, its validity may be glimpsed through consideration of just one of the numerous beneficiaries of asymmetric catalysis, the pharmaceutical industry. Over 50% of the world's top-selling drugs are single enantiomers,[1] and it has been estimated that up to 80% of all drugs currently entering development are chiral and will be marketed as single-enantiomer entities.[2] The manufacture of single-enantiomer drugs ineluctably requires the synthesis of high-value, enantiomerically pure materials for construction of the final bulk active compound. As we will see throughout this special issue of *Accounts of Chemical Research*, asymmetric catalysis has come to the fore and now provides one of the most cost-effective and environmentally responsible methods for production of a truly vast array of structurally diverse, enantiomerically pure compounds. Such economic manufacture of key intermediates necessarily will allow provision of drugs displaying higher potency, greater specificity, and fewer side effects, but at lower cost to us, the consumers. In addition to pharmaceutical applications, asymmetric catalytic methods are being employed to great avail in the flavor and fragrance, agrochemical, animal health, polymer, and liquid crystal industries.[3] Given such pervasive utility, the opening statement perhaps does not sound so audacious.

An important area of asymmetric catalysis research involves the design of chiral ligands and transition metal catalysts that can effect a desired transformation with both high efficiency and high selectivity. While selectivity in asymmetric catalysis often refers to control of absolute stereochemistry, other types of selectivity such as diastereoselectivity, chemoselectivity, and regioselectivity also can play a crucial role in the development of a viable synthetic method based upon chiral transition metal catalysts. Because of the catalytic nature of the system, the intrinsic chirality of an asymmetric catalyst can be used effectively through many cycles, allowing many moles of a desired product to be generated from scant quantities of catalyst. Herein lies the economically and environmentally attractive features of asymmetric catalysis.

In this Account, we will outline our efforts to design a class of chiral phosphine ligands that are broadly useful in asymmetric catalysis.[4] In the construction of our ligands, we hoped to confer the characteristic of versatility through the introduction of "informative modularity". A well-conceived ligand class should possess one or more structural and/or electronic features (modules) that may be varied readily in a systematic fashion in order to optimize the design for a given purpose. A design is informative to the extent that variations in the ligand modules can be correlated to changes in the reactivity or selectivity of the catalyst. Many ligands are modular in that various different facets of the ligands may be transmuted easily, but quite frequently it is difficult to extract useful information concerning how those modifications influenced the results achieved in catalysis.

Phospholane Ligands

Auxiliaries, reagents, and catalysts based upon C_2-symmetric *trans*-2,5-disubstituted five-membered nitrogen and boron heterocycles are well-documented to render very high levels of absolute stereocontrol in numerous reactions.[5] These systems furnished the primal inspiration for our studies. Brunner and Sievi had prepared *trans*-3,4-disubstituted phospholanes, but these ligands proved relatively ineffectual in catalysis.[6] In this case, presumably the chiral environment was too distant from the metal coordination sphere to exert significant influence. In 1989, we envisaged that the analogous five-membered *trans*-2,5-disubstituted phospholane groups, possessing di- or trialkyl-substituted phosphorus atoms, may provide access to a series of new electron-rich chiral phosphine ligands.[7]

Ligand electronic properties can dramatically influence the reactivity and selectivity of transition metal catalysts, and the electron-rich nature of phospholanes was a unique feature that we anticipated may differentiate these systems from most other chiral ligands available at the time. Another important attribute of phospholanes was

Mark J. Burk was born 14 July 1959 in southern New Jersey near Philadelphia, PA. He received a B.A. degree from Rutgers University in 1982 and a Ph.D. from Yale University with Professor Robert Crabtree in 1986. After an NIH postdoctoral appointment with Professor K. Barry Sharpless at Massachusetts Institute of Technology from 1986 to 1988, he spent five years in the Central Research and Development Department of DuPont in Wilmington, DE. He joined the faculty of the Department of Chemistry of Duke University in 1993. Then, in 1996 he moved to Chirotech Technology Limited in Cambridge, England, where he is currently Director of Research. His research interests encompass the areas of organic synthesis, organometallic chemistry, homogeneous catalysis, and asymmetric catalysis. A main focus is the cultivation of new synthetic methodologies, including design of new chiral ligands and the development of new catalytic transformations. Significant effort currently is devoted to developing asymmetric catalytic methodology into commercially practicable technology.

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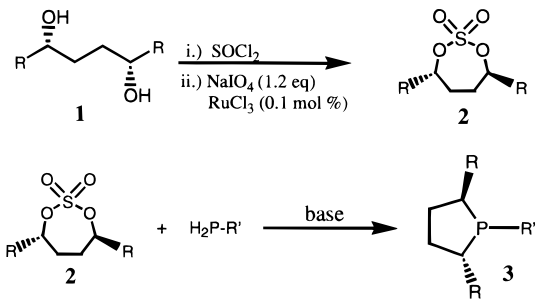
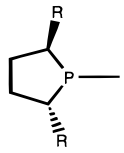
Scheme 1. General Synthesis of Phospholanes 3



associated with the modularity of these systems. We believed that the ability to vary the phospholane R-substitutents in a systematic fashion should allow valuable information to be gathered concerning the steric requirements of the catalytic process. In this manner, the steric environment imposed by the ligand could be tuned to ideally accommodate the steric demands of the reactants, and thus facilitate optimization of catalyst efficacy.



Trans-2,5-disubstituted Phospholanes Allow Systematic Variation of R-Substituents

Entry to *trans*-2,5-disubstituted phospholanes **3** was achieved conveniently through the use of chiral 1,4-diols **1** (Scheme 1).[8] Originally, the requisite series of 1,4-diols was prepared via electrochemical Kolbe coupling of enantiomerically pure α-hydroxy acids.[9] Commercially, the Kolbe procedure was not practical, and much more attractive routes involving biocatalytic methodologies currently are used to produce the needed 1,4-diols.[7,11a]

The availability of enantiomerically pure 1,4-diols **1** allowed assembly of phospholanes possessing a range of R-substituents through base-induced reaction between 1,4-diol cyclic sulfates **2** and primary phosphines. Because the chirality of phospholanes resides within the phosphorus heterocycle, the R′ group of **3** represents another module that may be varied to create a diverse collection of chiral phospholane ligands. In the event that R′ possesses one or more additional primary phosphine groups ($-PH_2$ units), chelating ligand structures are possible.[9,10] In this case, the backbone unit of the multidentate ligand may be explored as an element of diversity in an effort to control ligand electronic and conformational properties.[11] Figure 1 displays representative examples of this growing family of phospholane ligands.

The effectiveness of chiral ligand design can be measured only through applications in asymmetric catalysis. In this context, the bidentate DuPHOS and BPE ligands[12] have displayed patent advantages in asymmetric catalytic hydrogenation reactions. A visual sense of the asymmetric environment imposed by these diphosphines may be gained by observing the X-ray crystal structure of the hydrogenation precursor [(COD)Rh-((*R*,*R*)-Me-DuPHOS)]$^+SbF_6^-$ (Figure 2). In this view of the complex, one can appreciate the rigid C_2-symmetric

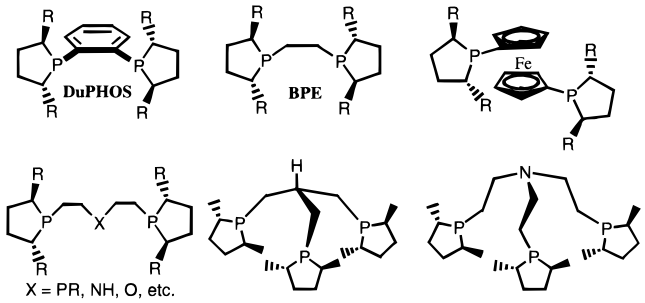


FIGURE 1. Chiral phospholane ligands showing backbone diversity.

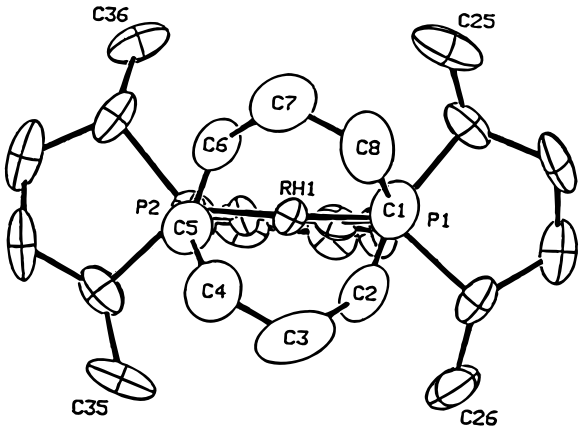


FIGURE 2. ORTEP drawing of cationic fragment [(COD)Rh((*R*,*R*)-Me-DuPHOS)]$^+$ showing orientation of the phospholane rings and C_2-symmetry of the Me-DuPHOS ligand (ref 18).

nature of the ligand, as well as the fact that systematic steric changes may be brought about through introduction of increasingly large phospholane R-substituents.

Asymmetric Catalytic Hydrogenations

Asymmetric catalysis is a vehicle for commercial manufacture of single-enantiomer compounds. Asymmetric hydrogenation reactions are ideal in this regard due to the ease with which these robust processes are scaled up, and because of the cleanliness of these transformations—few byproducts are generated. Exceedingly high enantioselectivities and catalytic efficiencies have been realized in enantioselective hydrogenation reactions.[13] Of any asymmetric catalytic method currently available, asymmetric hydrogenation technology is capable of directly producing the most diverse range of chiral compounds. In fact, asymmetric hydrogenation technology now has evolved to the point that the greatest obstacle to production often is development of an efficient substrate synthesis. The versatility of phospholane ligands in asymmetric catalytic hydrogenations may be highlighted through a survey of the different types of stereogenic centers that can be created using this technology.

C−N Stereogenic Centers. The advent of asymmetric catalytic homogeneous hydrogenation may be traced to the pursuit of economic routes to unnatural α-amino acids more than 30 years ago.[14] Notwithstanding impressive initial success achieved with rhodium complexes bearing chiral diphosphines such as DIOP[15] and DIPAMP,[16] general catalysts for the enantioselective hydrogenation of a range

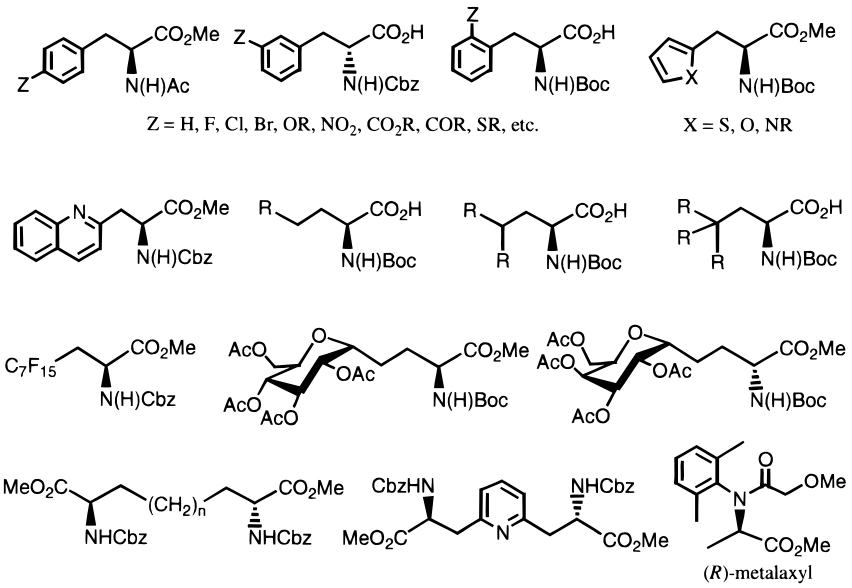
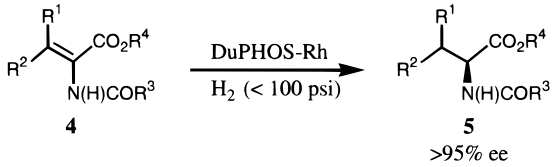


FIGURE 3. Amino acid derivatives produced via DuPHOS-Rh catalysts.

of different α-enamide substrates **4** had remained elusive, even in 1990.

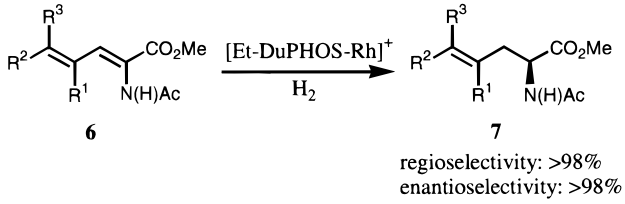


Cationic rhodium complexes of the type [(COD)Rh-(DuPHOS)]$^+X^-$ (X = weakly or noncoordinating anion) serve as highly efficient catalyst precursors for the low-pressure hydrogenation of α-enamides of type **4**.[17] For substrates that possess a single β-substituent (e.g., R^1 = H), the Me-DuPHOS-Rh and Et-DuPHOS-Rh catalysts were found paramount, rendering a multitude of amino acid derivatives with enantioselectivities 95−99% ee. A variety of N-acyl protecting groups may be employed, and enamides **4** may be used either as carboxylic esters or as acids. Moreover, the substrates may be present as mixtures of *E* and *Z* geometric isomers with little detrimental effect. The commercial viability of these robust catalysts is evinced by the high catalyst activities (turnover frequencies >5000 h^{-1}) and catalyst productivities (substrate-to-catalyst (S/C) ratios up to 50 000) displayed by these systems.[18]

Figure 3 reveals the wide selection of β-substituents and organic functional groups that are tolerated by these catalysts in the production of novel amino acids. Virtually any substituted aromatic, heteroaromatic, alkyl, fluoroalkyl, or other functionalized organic group may be incorporated into the amino acid product.[17−21] Assorted C-glycopeptide intermediates were generated in reactions whereby the catalyst displayed high levels of reagent control.[22] Polyamino acids of different sorts have been synthesized with very high selectivities.[23] Finally, the highly active fungicide, (*R*)-metalaxyl, has been produced efficiently using this technology.[13d]

The advantages of modularity inherent to the DuPHOS ligand series became apparent during attempts to hydrogenate enamides **4** possessing two β-substituents (R^1, $R^2 \neq$ H). Enantioselective hydrogenation of tetrasubstituted alkene units of this type had presented a significant challenge for all known catalysts, and the highest selectivity reported prior to our work was 55% ee using a DIPAMP-Rh catalyst.[24] We found that the rates and enantioselectivities were dramatically dependent upon the properties of the phospholane ligand.[25] In contrast to the pre-eminence of Et-DuPHOS-Rh for enamides containing a single β-substituent, sterically less encumbered catalysts were required for hydrogenation of sterically congested β,β-disubstituted enamides. In particular, the Me-DuPHOS-Rh and more electron-rich Me-BPE-Rh catalysts have been found superior for the production of multifarious β-branched amino acids.[26]

The DuPHOS-Rh catalysts also offer excellent regioselectivity in asymmetric hydrogenation reactions.[18,27] Selective hydrogenation of one alkene function within substrates possessing two or more different alkene groups can be a significant challenge, particularly if the most highly substituted alkene is targeted for reduction.



A screen of myriad chiral diphosphine rhodium and ruthenium catalysts showed that the cationic Et-DuPHOS-Rh catalysts are uniquely suited for hydrogenation of dienamides **6** with both high enantioselectivities (>98% ee) and high regioselectivities (>98%) to produce allylglycine derivatives **7**.[27] No other catalyst, including the closely related Me-DuPHOS-Rh and *i*-Pr-DuPHOS-Rh, has

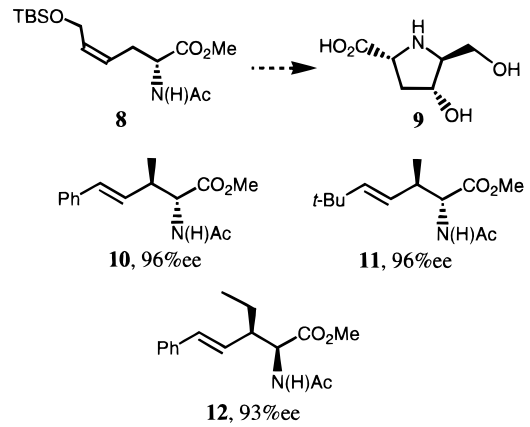
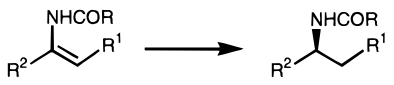


FIGURE 4. Functional allylglycine derivatives prepared through hydrogenation.

been found as effective for this transformation, demonstrating the benefits of modular ligand design. Enamide substrates are known to chelate to cationic diphosphine-Rh catalysts through the alkene and the carbonyl oxygen atom of the N-acyl group. Apparently, such chelation directs the hydrogenation to occur preferentially at the enamide alkene unit of **6**. In the case of the Et-DuPHOS-Rh catalyst system, hydrogenation of other alkene groups within the substrate is particularly unfavorable, regardless of whether the alkenes are conjugated, as in **6**, or more remote from the enamide function.[18]

Allylglycine derivatives are functionalized amino acids that serve as valuable synthetic intermediates. For instance, allylglycine **8** was prepared in 99% ee via the (*R,R*)-Et-DuPHOS-Rh catalyst and then conveniently converted to the complex natural product (+)-bulgecinine **9** (Figure 4).[27] Through use of the Me-BPE-Rh catalysts, hydrogenation of dienamides bearing an additional β-substitutent has allowed rapid access to β-branched allylglycines (**10**−**12**) possessing contiguous stereogenic centers.[28] These challenging examples demonstrate the powerful influence of substrate chelation, whereby the tetrasubstituted enamide alkene unit is reduced in preference to a disubstituted alkene function.

Hydrogenation of enamides using bis(phospholane)-based rhodium catalysts has been extended to include substrates previously considered intractable. Many enamides of general structure **13** now may be prepared readily from ketones and subsequently hydrogenated with the DuPHOS-Rh or BPE-Rh catalysts to provide simple access to a range of valuable amine derivatives **14**.



Hydrogenation of enamides **13** supporting different substitution patterns has permitted preparation of highly enantiomerically enriched amines, amino alcohols, and diamines (Figure 5). For example, the Me-DuPHOS-Rh and Et-DuPHOS-Rh catalysts provided facile access to structures **15**−**17** with enantioselectivities up to >99% ee.[29] The Me-DuPHOS-Rh and Me-BPE-Rh catalysts were found effective for reduction of α-aryl enamides (**13**, R^2 = aromatic group) to provide an array of α-1-arylalkylamine derivatives **18** (95−99% ee).[30] In an analogous fashion, arylglycinol derivatives **19** were synthesized conveniently and with high enantioselectivity (>97% ee) using the Me-DuPHOS-Rh catalysts.[31] As previously noted, the DuPHOS-Rh and BPE-Rh catalysts tolerate β-substituents in either the *E*- or *Z*-position of enamides **13**, converging the substrate mixture to product with high ee's. Cyclic amines, such as 1-aminoindane (**20**), have been prepared with enantioselectivities >99% ee.[32] Finally, enamides **13** possessing tertiary alkyl R^2-substituents are hydrogenated efficiently with the Me-DuPHOS-Rh catalysts to yield enantiomerically pure dialkylamine derivatives of structure **21**.[32]

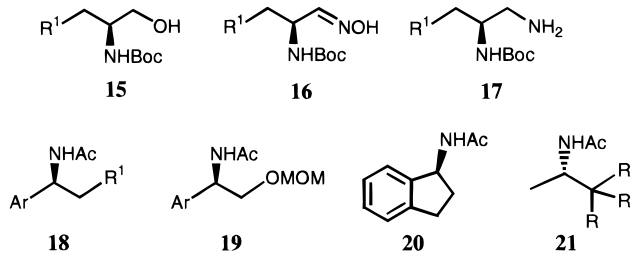
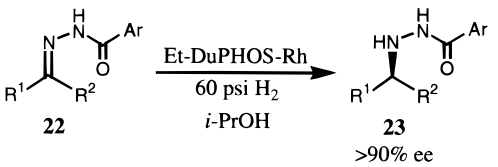


FIGURE 5. Amines, amino alcohols, and diamines available via DuPHOS-Rh-catalyzed enamide hydrogenation.

An alternative reduction method for generation of a C−N stereogenic center could entail hydrogenation of the C=N double bond. Thus far, catalysts bearing the DuPHOS and BPE ligands have been found ineffectual for hydrogenation of imines and oximes. However, hydrogenation of *N*-acylhydrazones of structure **22** is facile and can render a broad range of hydrazine derivatives **23**. The Et-DuPHOS-Rh catalysts were found consummate for this process, and a variety of hydrazines and hydrazino acids were prepared with high enantioselectivities (>90% ee).[33] Optically active amines also could be generated through this method by reductive cleavage of the N−N bond of hydrazines **23**.



C−O Stereogenic Centers. The utility of chiral alcohols is manifest, and the ability to effectively produce chiral alcohol functionality is vital. We have investigated two different pathways to chiral alcohols, one involving alkene reduction and one through carbonyl hydrogenation.

Hydrogenation of enol acylates, formed from ketones and having the generic form **24**, proceeds efficiently and with high enantioselectivities using the DuPHOS-Rh and BPE-Rh catalyst systems (Figure 6). Again, use of substrates **24** as *E*/*Z*-isomeric mixtures does not debase enantioselectivities. Acid- or base-catalyzed hydrolysis of the acyl group of **25** renders simple access to the desired alcohol products.

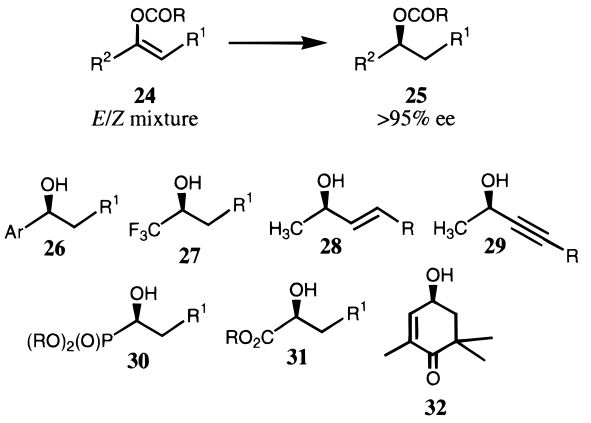
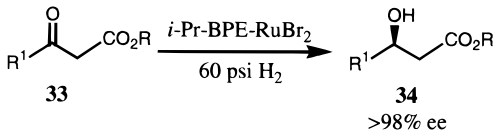


FIGURE 6. Alcohols produced through asymmetric hydrogenation of enol acylates **24**.

This strategy has been used to prepare numerous different types of alcohols, including aromatic alcohols **26** and trifluoromethyl-substituted derivatives **27**.[12] Alcohols of type **28** and **29**, respectively, were produced through highly enantioselective and regioselective hydrogenation of allylic and propargylic enol acetates.[34] Moreover, a wide range of α-hydroxyphosphonate esters **30**[35] and valuable α-hydroxycarboxylic esters **31**[36] have been prepared with high enantioselectivities (>95% ee) by this method. Rather than hydrolysis to **31**, direct hydride-mediated reduction of the initially formed acetate products (i.e., **25**; $R^2 = CO_2R$) affords chiral 1,2-diols in high yield.[36] Cyclic enol acetates also may be hydrogenated with high enantioselectivity. For instance, multikilogram quantities of the intermediate (*S*)-phorenol (**32**) have been manufactured through efficient (S/C = 20 000; 4 h) and highly enantioselective (98% ee) hydrogenation of the corresponding enol acetate using the (*R,R*)-Et-DuPHOS-Rh catalyst.[37]

Asymmetric hydrogenation of ketones represents a more direct approach to chiral alcohols. Thus far, DuPHOS-Rh and BPE-Rh catalysts have been found unavailing for efficient and selective hydrogenation of ketone functionality. However, ruthenium catalysts bearing the DuPHOS and BPE ligands are effective for the low-pressure (60 psi H_2) hydrogenation of β-keto esters **33**.[38] Using a catalyst precursor of general composition [*i*-Pr-BPE-$RuBr_2$], a wide selection of β-hydroxy esters **34** have been attained with very high enantioselectivities (>98% ee). More recently, we have found that the easily handled complex, [η^6-(C_6H_6)Ru(Me-DuPHOS)Cl]OTf, also may serve as a comparable precursor for highly enantioselective β-keto ester hydrogenations.[39]



C−C Stereogenic Centers. The creation of C−C stereogenic centers is an important and challenging area of asymmetric synthesis. The apparent need to synthesize geometrically pure alkenes that are devoid of attached

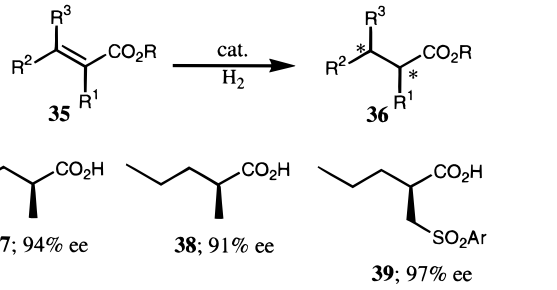
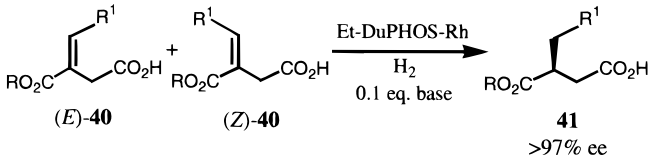


FIGURE 7. Carboxylic acid derivatives accessed by asymmetric hydrogenation.

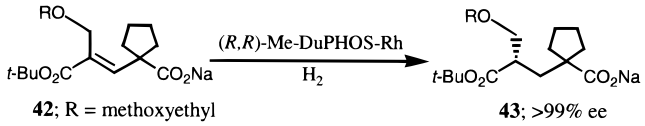
heteroatoms has served as one impediment to the development of practical hydrogenation processes for this purpose.

Unsaturated carboxylic acid derivatives of general structure **35** can be hydrogenated with a high degree of stereoselection to furnish products **36** with new C−C stereogenic centers at either the α- or the β-carbon (Figure 7). For example, carboxylic acid products **37** and **38** have been obtained with high enantioselectivities using an *i*-Pr-DuPHOS-Ru catalyst.[40] Unfortunately, this process is not general, as substitution with larger groups at either α- or β-positions led to serious diminution of selectivity and rates. More recently, functionalized carboxylic acids, such as **39**, were prepared directly and with high ee's through hydrogenation of the corresponding vinyl sulfones using Et-DuPHOS-Rh.[41]

Considerably improved scope was realized in the hydrogenation of itaconates **40**, which serve as useful substrates for production of 2-alkyl succinate peptidomimetics **41**. The Et-DuPHOS-Rh catalysts are superlative for asymmetric hydrogenation of a very broad range of itaconate substrates with exceedingly high enantioselectivities (>97% ee) and high efficiencies (S/C >5000).[42] Itaconates may be prepared effectively as *E*/*Z*-isomeric mixtures through Stobbe condensation between aldehydes and dialkyl succinates. Fortunately, the Et-DuPHOS-Rh catalysts once again tolerate geometrically impure substrates and converge the mixture to the desired product.

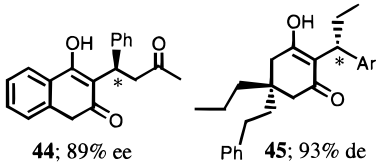


The unique substrate **42** has been hydrogenated efficiently and with high selectivity (>99% ee) using the (*R,R*)-Me-DuPHOS-Rh catalyst to afford **43**, an important intermediate for the drug candoxatril.[43]



Stereoselective hydrogenation also has been used successfully to introduce C−C stereogenic centers into two

related dihydropyrone derivatives. Both enantiomers of the anticoagulant warfarin (**44**) have been prepared in 89% ee through hydrogenation of the corresponding α,β-unsaturated ketone using the Et-DuPHOS-Rh catalysts.[44] More recently, the (*R,R*)-Me-DuPHOS-Rh catalyst furnished a key intermediate (**45**) for production of a new nonpeptidic HIV protease inhibitor.[45]



44; 89% ee **45**; 93% de

Stereochemical Model

Elegant mechanistic studies have unveiled some of the mysteries associated with asymmetric catalytic hydrogenation reactions, and yet we still do not fully comprehend many aspects of these processes. Gaining an appreciation for the origin of enantioselection can build intuition and guide future research efforts.

The success that we have achieved with each substrate class listed above may be attributed to the intrinsic advantages of substrate chelation. Chelation entails metal binding of the reducible functionality as well as an appropriately positioned secondary coordinating group within the substrate. The importance of this phenomenon in asymmetric hydrogenation reactions has been advanced in seminal work by Halpern, Brown, and others.[46] We also have observed and characterized catalytic intermediates in studies that strongly imply chelation of substrates such as enamides,[47] *N*-acylhydrazones,[33] and itaconates.[43]

The benefits of substrate chelation may be realized in various ways. Substrate chelation may lead to high catalytic rates due to the enhanced stability of catalytic intermediates (higher substrate binding constants) relative to nonchelating species. Higher enantioselectivities may be achieved due to the effects of chelation, which restricts the degrees of freedom available to a substrate. More strongly binding secondary coordinating groups appear to have a more pronounced effect upon absolute stereocontrol. Finally, substrate chelation may allow other types of selectivity, such as regioselectivity and chemoselectivity. For instance, chelate-directed hydrogenation is implicated in the regioselective DuPHOS-Rh-catalyzed hydrogenation of both dienamides **6**[27] and unsaturated enol acetates.[34]

A unique characteristic of the DuPHOS-Rh and BPE-Rh catalysts is the relative indifference they display toward β-substituents in the *E*- and/or *Z*-positions of trisubstituted olefinic substrates. High enantioselectivities are achieved in the hydrogenation of *E/Z* mixtures because the same absolute configuration of product is obtained independent of olefin geometry. For example, the (*R,R*)-Et-DuPHOS-Rh catalyst provides amino acids **5** and α-benzoyloxy esters **25** with (*R*)-absolute configuration, as well as succinates **41** with (*S*)-configuration, regardless

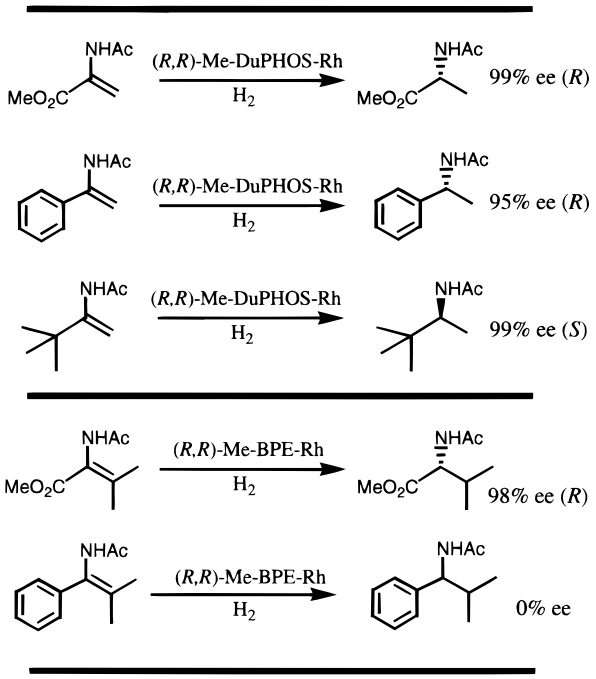


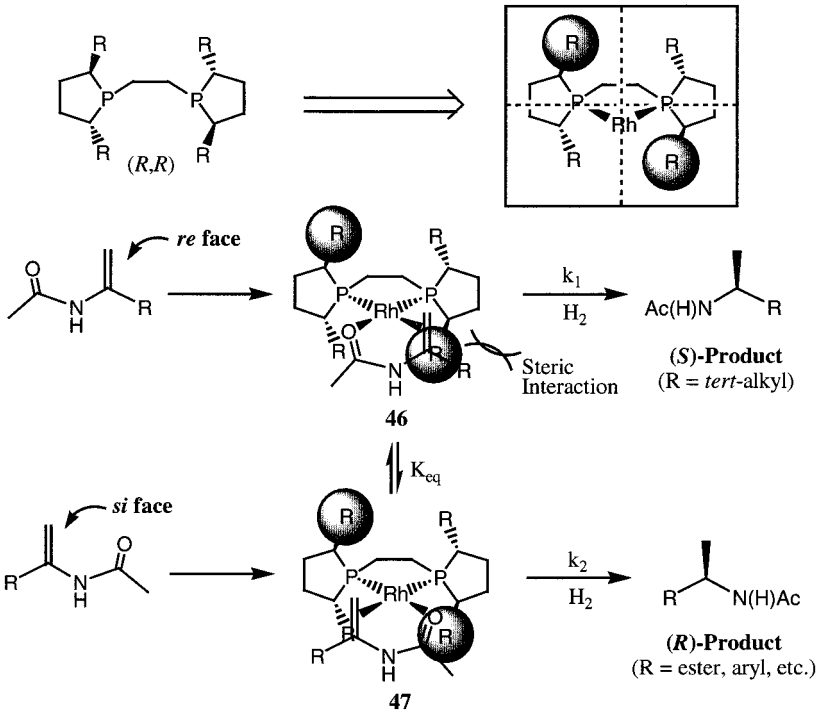
FIGURE 8. Stereochemical influence of α-substituents in hydrogenation.

of the *E/Z*-isomeric composition of the substrates. Deuteration studies involving different types of geometrically pure substrates have eliminated olefin isomerization as a possible explanation for these observations.[18,36]

While β-substituents impose little consequence, substituents located at the α-position of chelating olefinic substrates appear most influential in determining the stereochemical outcome of hydrogenation reactions. The results depicted in Figure 8 provide cogent evidence supporting this notion. The top experiments performed under identical conditions show a dramatic reversal of product absolute stereochemistry provoked simply by varying the enamide α-substituent from an ester or aryl group to a tertiary alkyl substituent.[30,32] Hydrogenation of β,β-disubstituted enamides also reveals the compelling influence of the α-substituent (lower half of Figure 8).

To facilitate our understanding of these results, we have developed a heuristic stereochemical model that incorporates the above information (Scheme 2). It is important to recognize that this is merely a simplistic model that is meant to serve as a didactic guide. Various assumptions are outlined below, and the actual mechanism of these reactions is far more complex than indicated in Scheme 2. We consider only interactions that may occur within the relevant diastereomeric catalytic intermediates. For clarity, the cationic species are represented without charge. A crucial assumption is that all enamide substrates chelate to rhodium in the expected fashion through the alkene unit and the *N*-acetyl carbonyl oxygen atom. The model also presumes that the rate- and stereochemistry-determining steps are the same and entail oxidative addition of hydrogen to the rhodium center of intermediate diastereomeric enamide complexes, analogous to that previously demonstrated for enamide esters.[46,47]

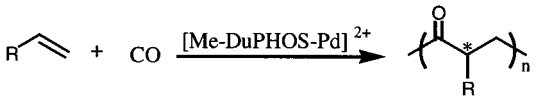
Scheme 2. Stereochemical Model for Asymmetric Hydrogenation of Enamides



Under these constraints, we envisioned that binding of the *re* face of a prototypical enamide to the (*R,R*)-DuPHOS-Rh or (*R,R*)-BPE-Rh catalyst should afford an intermediate complex of structure **46**, whereas coordination of the *si* face of the same enamide should yield the diastereomeric intermediate **47**. Intermediate **46** would experience an ostensibly severe steric interaction between the phospholane R-substituent and the α-substituent on the enamide, whereas intermediate **47** appears devoid of such presumably unfavorable van der Waals repulsions. The addition of hydrogen to each of the proposed intermediates **46** and **47** will occur with rate constants k_1 and k_2, respectively. Since intermediates **46** and **47** are diastereomers, k_1 and k_2 may be quite different; this situation can lead to substantial enantiomeric enrichment through the predominance of one pathway (K_{eq} also contributes). In the present case, the data suggest that $k_1 \gg k_2$ when the enamide α-R group is a bulky tertiary alkyl substituent such as *t*-Bu or 1-adamantyl, whereas $k_2 \gg k_1$ when the α-substituent is almost any other group, including carboxylic acid or ester, aromatic, phosphonate ester, hydroxymethyl, or oxime functionality.

By viewing the intermediate complexes **46** and **47**, we can envisage why enamide α-substituents may have a dominant role in the course of the reaction. Facially differentiating steric interactions occur principally between the phospholane R-groups and the α-substituent of the substrate. Moreover, β-substituents placed on the enamide have little impact on the reaction, as only minimal steric interactions would appear to occur between substrate *E*- and/or *Z*-groups and the phospholane ligand R-groups. However, the actual mechanism appears to be an intricate interplay of numerous factors that are substrate dependent, as can be seen in the bottom two examples of Figure 8. The above stereochemical paradigm qualitatively allows one to appreciate the critical interactions that may be involved between ligand and substrate. However, a clear and detailed understanding of these reactions will require rigorous mechanistic characterization, including kinetic analysis with a range of different substrates.

Scheme 3. Enantioselective Copolymerization Using Me-DuPHOS-Pd Catalyst



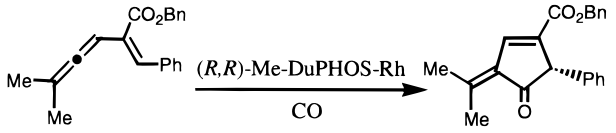
Other Applications of Phospholane Ligands

In addition to hydrogenation reactions, modular phospholane ligands are being applied in a growing rank of other useful asymmetric catalytic transformations. For instance, Jiang and Sen have reported the discovery of a dicationic Me-DuPHOS-Pd catalyst for the alternating copolymerization of aliphatic α-olefins and carbon monoxide (Scheme 3).[48]

Analysis with chiral NMR shift reagents revealed that the isotactic poly(1,4-ketone) products were formed with an average ee or overall degree of enantioselectivity that was >90%. Employing the same catalyst, Jiang and Sen also described the first example of alternating copolymerization between an internal alkene (2-butene) and carbon monoxide to form an isotactic, optically active poly(1,5-ketone).

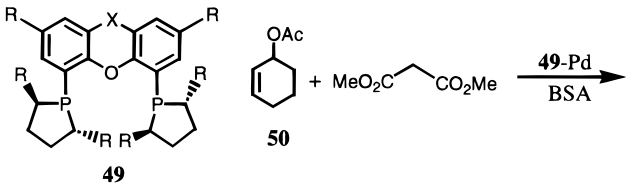
Murakami et al. have expounded upon the utility of cationic Me-DuPHOS-Rh catalysts for novel asymmetric [4 + 1] cycloaddition reactions between vinylallenes and

carbon monoxide.[49] Complex cyclopentenone derivatives such as **48** have been constructed in a single step and with enantioselectivities up to 95% ee in this process.

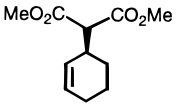


48; 95% ee

The modular nature of the phospholane series of ligands allows different backbone structures to be explored. Recently, the group of Osborn and van Leeuwen have reported bis(phospholane) ligands **49** possessing dibenzo[*b*,*d*]pyran and dibenzo-1,4-thioxin backbones which have large P−M−P bite angles.[11b] Preliminary studies using ligands possessing 2,5-dimethylphospholane units have affirmed that these systems are useful in asymmetric Pd-catalyzed allylic substitution reactions. Even notoriously difficult substrates, such as *O*-acetylcyclohexenol **50**, reacted with dimethyl malonate to yield substitution products (e.g., **51**) with high enantioselectivities.

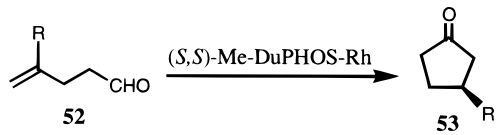


49 **50**



51; 93% ee

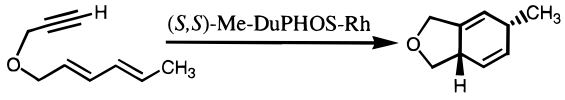
Two different reports have illustrated that cationic Me-DuPHOS-Rh serves as an excellent catalyst for asymmetric C−C bond-forming cyclization reactions. In the first example, Bosnich and co-workers discovered that valuable 3-substituted cyclopentanones **53** can be prepared simply by treatment of 4-pentenal derivatives **52** with the Me-DuPHOS-Rh catalyst.[50] Asymmetric intramolecular hydroacylation furnished the product cyclopentanones **53** in high yield and with enantioselectivities ranging from 93% to 98% ee.



52 **53**

93-98% ee

Finally, Gilbertson et al. have revealed that cationic Me-DuPHOS-Rh catalysts effect asymmetric [4 + 2] cycloisomerization of standard dieneynes such as **54** to afford bicyclic products **55**, whereupon two stereogenic centers are established with high levels of absoute stereocontrol.[51]



54 **55**; 95% ee

Conclusions

Modular phospholane ligands are finding useful applications in a growing number of catalytic reaction types. Catalysts derived from the bidentate DuPHOS and BPE ligands exhibit particularly high efficiency and selectivity in a wide spectrum of asymmetric hydrogenation reactions. These processes provide access to a diverse range of chiral compounds containing C−N, C−O, and C−C stereogenic centers. The versatility of these catalyst systems emanates from the modular nature of the ligands, which allows ready adjustment of their steric, electronic, and conformational properties. Optimal results have been achieved through the ability to systematically vary both the phospholane R-substituents and the ligand backbones. To date, only a limited number of phospholane-based ligands have been prepared and studied. It is likely that many new and interesting catalytic processes will be discovered and developed as this series of novel ligands is extended.

This work has been carried out over the past 10 years at three different research institutions. This Account is a testament to the diligence, skill, and intellectual prowess of the many excellent colleagues with whom I have had the great fortune to associate. I first would like to thank John Feaster, Bill Tumas, Tom Baker, Paul Fagan, Bill Nugent, and T. V. RajanBabu for the tremendous support and inspiration that they provided at DuPont CR&D, where this work began. Those were the days. I also would like to express deep gratitude to my indefatigable students at Duke University, where many of the exciting catalytic applications were discovered. Finally, I would like to warmly acknowledge my current colleagues at ChiroTech, where together we are experiencing the true commercial potential of asymmetric catalysis technology.

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