Asymmetric catalytic routes to chiral building blocks of medicinal interest

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Abstract: Asymmetric hydrogenation reactions can provide practical access to a diverse array of chiral building blocks. We have developed a variety of highly selective rhodium and ruthenium hydrogenation catalysts based on chiral 1,2-bis(phospholano)benzene (**1**; DuPHOS) and 1,2-bis(phospholano)ethane (**2**; BPE) ligands. The expanding utility of these catalyst systems is revealed through highly enantioselective syntheses of α-amino acids, β-branched amino acids, and β-hydroxy esters. The versatility of the catalysts derives from our ligand design which allows variation of the steric environment imposed by the phospholane ligands such that they can accomodate the different steric demands of each substrate class of interest.

INTRODUCTION

The synthesis of many pharmaceutical agents and complex natural products relies on the availability of chiral intermediates that can serve as building blocks for further structural and stereochemical elaboration. Asymmetric catalytic synthesis has emerged as one of the most efficient methods to prepare a wide variety of small molecules in highly enantiomerically-enriched form.[1] Accordingly, asymmetric catalysis is playing an increasingly important role in drug design and development.

Within this framework, the focus of our research is development of new asymmeric catalytic methodologies that may be applied to the synthesis of molecules of biological or medicinal interest. Toward this goal, we recently have designed a new class of 1,2-bis(phospholano)benzene (DuPHOS) ligands **1** and 1,2-bis(phospholano)ethane (BPE) ligands **2** that have been found to produce a series of extraordinarily effective Rh- and Ru-based hydrogenation catalysts.[2-4] We herein provide an overview of these studies and outline the utility of these catalyst systems for the highly enantioselective synthesis of α-amino acids, β-branched amino acids, and β-hydroxy esters.

1; DuPHOS   2; BPE
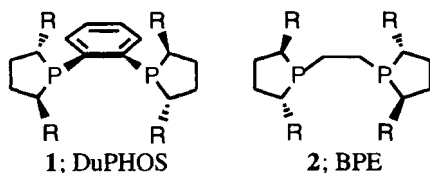
CHIRAL BUILDING BLOCKS

1. α-Amino Acid Derivatives

α-Amino acids are one of the most widely used chiral building blocks in organic synthesis.[5] We recently have reported that cationic rhodium complexes [(COD)Rh(DuPHOS)]⁺OTf⁻ bearing our Et-DuPHOS or Pr-DuPHOS ligands (**1**; R = Et or Pr) are precursors to highly enantioselective (≥98% ee) catalysts for the hydrogenation of α-enamide esters and acids (**3**) (eq. 1).[3a,c] These reactions proceed under mild conditions (15-30 psi H$_2$, 25 °C, MeOH) and the catalysts are extremely efficient (substrate-to-catalyst ratios (S/C) up to 50,000 have been demonstrated). The DuPHOS-Rh catalysts yield reduction products with highly predictable absolute configurations; (*R,R*)-Pr-DuPHOS-Rh consistently affords products **4** of (*R*)-absolute configuration, while (*S,S*)-Pr-DuPHOS-Rh provides (*S*)-**4**. In terms of stability, the solid DuPHOS-Rh catalysts are resistant to air oxidation for short periods, and thus may be weighed in the atmosphere. In solution, the catalysts are more readily oxidized, and deoxygenated solvents must be employed for the hydrogenation reactions.

$$(1)$$
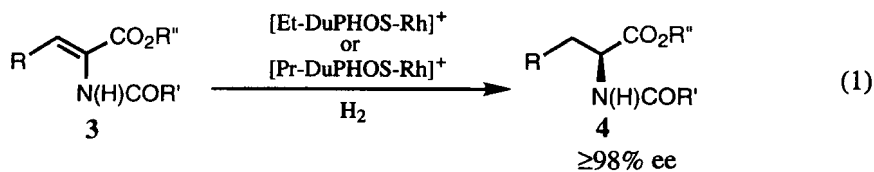
Two significant features of these catalysts are: (i) extremely high enantioselectivites have been achieved over a very broad range of α-enamide substrates, and (ii) a wide variety of organic functionality is tolerated in these reactions. Accordingly, one of the most important applications of the Et-DuPHOS-Rh and Pr-DuPHOS-Rh catalysts likely will lie in the production of highly functionalized, nonproteinogenic amino acid derivatives of type 4. A representative list of amino acid derivatives that we have prepared in ≥98% ee using the Pr-DuPHOS-Rh catalyst is shown in Figure 1. Thus, an array of arylalanines were obtained, including substituted phenylalanines, 1- and 2-naphthylalanine, 2- and 3-thienylalanine, 2-furanylalanine, and ferrocenylalanine derivatives. In contrast to most other catalysts developed for α-enamide hydrogenations, the DuPHOS-Rh catalysts provide invariably high ee's with both ester and free carboxylic acid derivatives, and with α-enamides possessing a variety of N-protecting groups, including N-acetyl, N-benzoyl, N-Cbz, and N-Boc. Similarly, a series of branched alkyl-, linear alkyl-, and perfluoroalkyl-substituted α-enamides were hydrogenated with very high enantioselectivities.
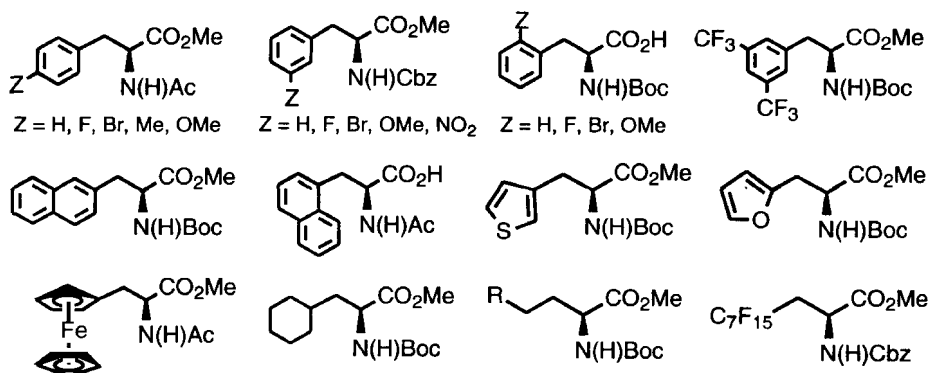

Figure 1. Representative α-amino acids generated in ≥98% ee using the Pr-DuPHOS-Rh catalyst

As outlined above, our DuPHOS-Rh catalysts provide one of the most convenient routes to a large number of novel amino acids. In terms of efficiency, however, our asymmetric hydrogenation process requires that individual enamides must be prepared for each new α-amino acid desired. In the design and optimization of peptide and peptidomimetic therapeutics, countless variations of a particular amino acid moiety are often necessary in order to obtain optimum activity, bioavailablity, and resistance to metabolic breakdown.[6,7] For example, many *o*-, *m*-, and *p*-substituted phenylalanine (Phe) derivatives are known and have found extensive application in the synthesis of biologically active compounds.[5,8] The position and type of substituent present on the phenyl ring often significantly impacts the biological activity of peptides containing phenylalanine derivatives. Currently, however, substituted phenylalanine derivatives generally are prepared individually by either optical or enzymatic resolution methods,[9] or by stoichiometric chiral auxiliary chemistry.[5] The synthesis of each derivative needed for such structure-activity relationship (SAR) studies can be a momumental task. To address this problem, we have developed a new tandem catalysis procedure for the preparation of a diverse range of aromatic amino acids and peptides.[10]

Scheme 1 depicts the general features of the two-step process for the preparation of ring-substituted phenylalanine derivatives. The first step involves the use of our asymmetric hydrogenation
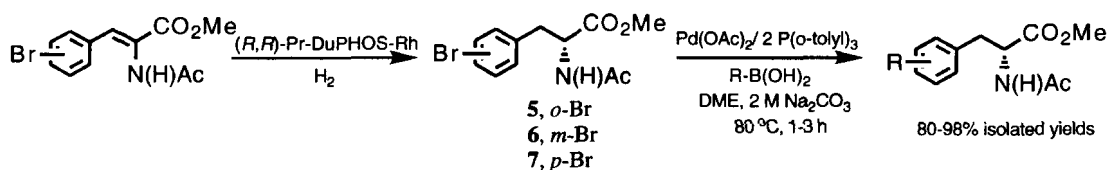
Scheme 1. Synthesis of substituted phenylalanine derivatives via tandem catalysis procedure

reaction to produce appropriately functionalized α-amino acids. For example, we have prepared enantiomerically pure (*R*)-*o*-bromo-, (*R*)-*m*-bromo-, and (*R*)-*p*-bromophenylalanine derivatives (5-7), via (*R,R*)-Pr-DuPHOS-Rh-catalyzed hydrogenation.[3a,3c] These bromophenylalanines subsequently were employed as key intermediates from which a wide variety of substituted phenylalanine derivatives could be readily obtained through Pd-catalyzed cross-coupling reactions with a range of boronic acid derivatives. A series of *ortho*-substituted analogs, derived from (*R*)-*o*-Br-Phe (5) and the corresponding boronic acids, are shown in Figure 2. The *meta* and *para* series of Phe derivatives, as well as a variety of other substituted N-acetyl- and N-Boc-arylalanine and heteroarylalanine derivatives, were prepared with equal facility through this cross-coupling procedure.[10]
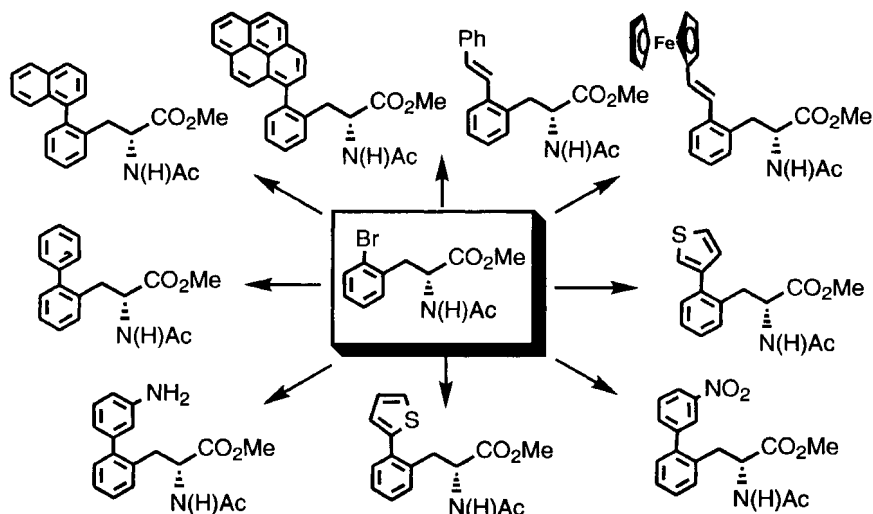

Figure 2. *Ortho*-substituted Phe derivatives obtained through tandem catalysis procedure

One limitation of the above strategy is the requisite synthesis of each boronic acid needed for incorporation through cross-coupling. We reasoned that a more efficient and versatile approach would involve preparation of dihydroxyboryl-substituted phenylalanine derivatives that could be coupled directly with a large number of readily available aromatic and vinylic bromides or triflates. Dihydroxyboryl-Phe derivatives are of interest for application in boron neutron capture therapy,[11] and both *m*- and *p*-dihydroxyborylphenylalanines previously have been prepared through enzymatic resolution procedures using α-chymotrypsin.[12] We have sought to apply our enantioselective hydrogenation process to the preparation of the desired boronic acid-Phe derivatives. Initially, we successfully synthesized the *p*-dihydroxyboryl α-enamide **8** through Schmidt's Horner-Emmons reagent.[13] Upon attempted hydrogenation of **8** under our standard conditions with the Pr-DuPHOS-Rh catalyst in methanol, however, we unexpectedly observed reductive deborylation to afford exclusively the parent phenylalanine derivative (Scheme 2). Deborylation was found to predominate regardless of the nature of the solvent or Rh catalyst used. The reason for facile deborylation of **8** under these conditions and the mechanism involved remain uncertain.
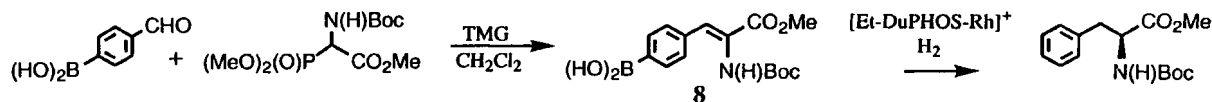

Scheme 2. Preparation and hydrogenation of *p*-boronic acid enamide **8**

Recently, we have discovered that deborylation can be avoided through the use of 1,3-propanediol-protected boryl derivatives (Scheme 3). Thus, Pr-DuPHOS-Rh-catalyzed hydrogenation of the borylpropanediolate analog **9** in methylene chloride or ethyl acetate afforded the desired *p*-boronate phenylalanine derivative **10** in high enantiomeric excess (98.7% ee), and with no evidence of deborylation. The propanediol protecting group may be removed readily with mild acid or base to afford the boronic acid analog. Alternatively, for cross-coupling reactions, the propanediolboronate **10** may be used directly under the standard basic conditions which presumably allow hydrolysis of **10** to the boronic acid *in situ*. Thus, reaction between **10** and bromobenzene catalyzed by the combination Pd(OAc)₂/tri(*o*-tolyl)phosphine in DME with 2 M Na₂CO₃ afforded the *p*-biphenylalanine derivative **11** in 75% isolated yield (Scheme 3). In a similar fashion, cross-coupling between **10** and 4'-bromobenzo-18-crown-6 or *p*-bromophenylalanine **7** yielded the benzo-18-crown-6-phenylalanine (**12**) or *p*-diphenylalanine (**13**) derivatives, respectively.

2. β-Branched α-Amino Acids

During an examination of substrate scope in the hydrogenation of α-enamides **3**, we have observed that our cationic Et-DuPHOS-Rh catalysts are uniquely capable of hydrogenating both (*E*)- and (*Z*)-isomeric α-enamides with high enantiomeric excesses.[3c,14] Moreover, for a given catalyst configuration, the same product absolute configuration is obtained, regardless of the α-enamide configuration (i.e., *E* or *Z*). These results suggested that our catalysts may allow the highly enantioselective hydrogenation of α-enamides possessing substituents in both the (*E*)- and (*Z*)-positions (i.e., β,β-disubstituted α-enamides).
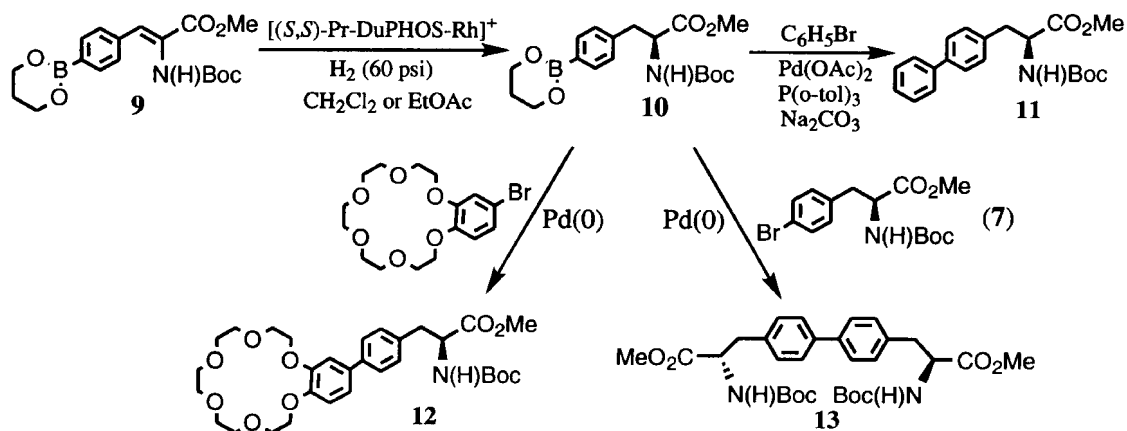
Scheme 3. Synthesis and use of *p*-boronate-phenylalanine derivative **10**

While the ability to hydrogenate β,β-disubstituted α-enamides **14** with high ee's could provide practical access to an array of valuable, constrained β-branched α-amino acids of type **15**, little success has been reported for enantioselective reduction of this substrate class.[1,15]
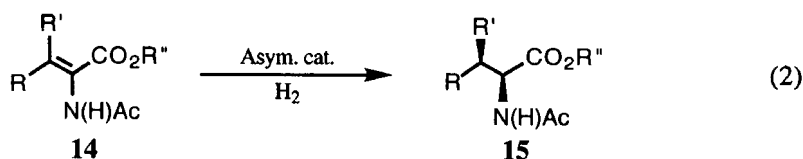
Our initial studies in this area were aimed at identifying an efficacious catalyst for enantioselective hydrogenation of substrates **14**.[16] Thus, we performed hydrogenations using a series of DuPHOS-Rh and BPE-Rh catalysts under a standard set of reaction conditions (MeOH, 25 °C, 60 psi H_2, S/C = 500, 24 h) and the α-enamide bearing two β-Me groups (**14a**; R, R', R" = Me). The results of these studies are shown in Table 1 and were somewhat surprising in that the Et-DuPHOS-Rh and Pr-DuPHOS-Rh catalysts were not suitable, despite their superiority with both (*E*)- and (*Z*)-α-enamides **3**. Of the DuPHOS-Rh catalysts, the least sterically-congested species, Me-DuPHOS-Rh, afforded the valine derivative **15a** with the highest enantioselectivity at 91.9% ee. A similar trend was observed with the BPE-Rh catalyst series, where the Me-BPE-Rh catalyst provided **15a** in 96.6% ee. Further optimization revealed that higher enantioselectivity could be achieved at 90 psi H_2 in benzene solvent. Under these conditions, Me-DuPHOS-Rh and Me-BPE-Rh produced **15a** in 96.0% ee and 98.2% ee, respectively. Significantly, the highest enantioselectivity previously reported for the hydrogenation of **14a** was 55% ee.[15b]

Using the (*R,R*)-Me-BPE-Rh catalyst under our optimized hydrogenation conditions (C_6H_6, 25 °C, 90 psi H_2, S/C = 500, 12 h) was found to provide a highly enantioselective route to a variety of β-branched amino acid derivatives of type **15** (Figure 3). Importantly, hydrogenation of enamides **14** possessing dissimilar β-substituents (R ≠ R') should allow the generation of an additional new β-stereogenic center in the product **15**. Thus, we have found that both *erythro* and *threo* diastereomers of the amino acid β-methylhomophenylalanine were produced in 96.2% ee and 95.8% ee, respectively, through hydrogenation of the corresponding (*E*)- and (*Z*)-enamides using (*R,R*)-Me-BPE-Rh (Figure 3).

Table 1. Enantioselectivities in the Hydrogenation of **14a** $(R,R',R'' = Me)^a$

Catalyst	$\% \ ee^b$ (Config.)^c
(S,S)-Me-DuPHOS-Rh	91.9% ee (S)
(S,S)-Et-DuPHOS-Rh	74.4% ee (S)
(R,R)-Pr-DuPHOS-Rh	45.2% ee (R)
(R,R)-i-Pr-DuPHOS-Rh	13.6% ee (S)
(R,R)-Me-BPE-Rh	96.6% ee (R)
(S,S)-Et-BPE-Rh	89.3% ee (S)
(R,R)-i-Pr-BPE-Rh	11.8% ee (S)

^{a}Reactions were conducted at 25 °C and an initial H_2 pressure of 60 psig using 0.25 M methanol solutions of substrate **14a** and the catalyst precursors $[DuPHOS-Rh(COD)]^+OTf^-$ or $[BPE-Rh(COD)]^+OTf^-$ (0.2 mol %), unless otherwise noted. Reaction time was 24 h and complete (100%) conversion was observed in all cases. ^{b}Enantiomeric excesses were determined by chiral capillary GC usi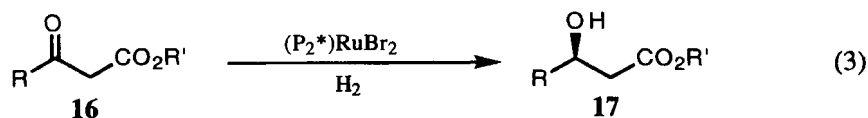ng Chrompack's Chirasil-L-Val column (25 m). ^{c}Absolute configurations were assigned by comparing the sign of optical rotation with that of authentic N-acetylvaline methyl ester.
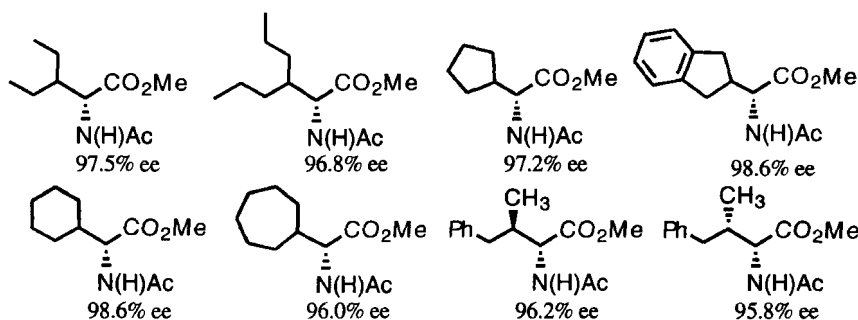
Figure 3. β-Branched amino acids prepared in >95% ee via Me-BPE-Rh catalyst

The enantioselectivities we have achieved in the hydrogenation of β,β-disubstituted α-enamides are significantly higher than any previously reported for this challenging class of substrates. The sterically demanding nature of enamides **14** (tetrasubstituted olefins) has presented difficulties with regard to both rates and enantioselectivities in the past. It is likely that the electron-rich character of our ligands enhances metal-olefin π-backbonding, and accordingly may stabilize the bonding interaction between **14** and the catalytic Rh center. This, combined with the expected higher rates of H_2 oxidative addition involving our more electron-rich rhodium catalysts, is probably responsible for the higher rates we observe in the hydrogenation of **14** relative to other catalyst systems. We also have the added advantage that we can vary the steric environment imposed by our DuPHOS and BPE ligands by modifying the 2,5-substituents attached to the phospholane moieties. In the present case, the least encumbered Me-DuPHOS and Me-BPE ligands were found optimum with regard to enantioselectivity in the hydrogenation of the sterically congested enamides **14**.

3. β-Hydroxy Esters

Enantiomerically pure β-hydroxy esters have served extensively as valuable chiral building blocks in synthetic organic and natural product chemistry.[17] One of the most direct routes to enantiomerically-enriched β-hydroxy esters is through asymmetric hydrogenation of the corresponding β-keto esters, and several highly enantioselective catalyst systems have been developed for this transformation. For example, Ru-BINAP catalysts have been shown to provide a wide range of β-hydroxy esters with very high selectivity, but these reactions generally require high temperatures (80-100 °C), high pressures (50-100 atm), or acid co-catalysts for acceptable catalytic rates.[18] On the basis of our recent results which suggest that electron-rich diphosphine ligands may allow enhanced catalytic

$$\underset{\textbf{16}}{\underset{R}{\overset{O}{\bigvee}}\text{CO}_2R'} \xrightarrow[\text{H}_2]{(\text{P}_2\text{*})\text{RuBr}_2} \underset{\textbf{17}}{\underset{R}{\overset{OH}{\bigvee}}\text{CO}_2R'} \qquad (3)$$

efficiency in ketone and aldehyde hydrogenations,[19] we have examined the efficacy of our DuPHOS (**1**) and BPE (**2**) ligands in the Ru-catalyzed asymmetric hydrogenation of β-keto esters **16**.[4]

In preliminary scouting studies, we perused a series of DuPHOS-RuBr$_2$ and BPE-RuBr$_2$ catalyst precursors for their effectiveness in the hydrogenation of methyl acetoacetate (**16**; R,R' = Me) under a standard set of reaction conditions (MeOH/H$_2$O (9/1), 35 °C, 60 psi H$_2$, S/C = 250, 18 h). The results of these studies are shown in Table 2, and demonstrated that the (*R,R*)-*i*-Pr-BPE-RuBr$_2$ catalyst system was preferred from the standpoint of both rates and enantioselectivities.

Table 2. Ru-catalyzed Asymmetric Hydrogenation of **16a** (R,R' = Me)[a]

Catalyst	% Conversion	% ee[b] (Config.)[c]
(*S,S*)-Me-DuPHOS-Ru	50	69% ee (*S*)
(*S,S*)-Et-DuPHOS-Ru	60	84% ee (*S*)
(*R,R*)-Pr-DuPHOS-Ru	95	95% ee (*R*)
(*R,R*)-*i*-Pr-DuPHOS-Ru	90	92% ee (*S*)
(*R,R*)-Me-BPE-Ru	10	5% ee (*R*)
(*S,S*)-Et-BPE-Ru	40	96% ee (*S*)
(*R,R*)-*i*-Pr-BPE-Ru	100	>98% ee (*S*)
(*R,R*)-*i*-Pr-BPE-Ru [d]	100	>98% ee (*S*)
(*R,R*)-BINAP-Ru [d]	10	>98% ee (*R*)

[a]Reactions were conducted for 18 h at 35 °C and an initial H$_2$ pressure of 60 psig using 0.25 M 10% aqueous methanol solutions of substrate **16a** and the catalyst precursors [DuPHOS-RuBr$_2$] or [BPE-RuBr$_2$] (0.4 mol %), unless otherwise noted. [b]Enantiomeric excesses were determined by chiral capillary GC using Machery Nagel's Lipodex A column. [c]Absolute configurations were assigned by comparing the sign of optical rotation with that of known products. [d]Reactions conducted at 22 °C.

Expansion of these studies to other substrates revealed that the *i*-Pr-BPE-Ru catalysts provide a general, enantioselective method for the reduction of β-keto esters (**16**) to β-hydroxy esters (**17**) under mild conditions (MeOH/H$_2$O (9/1), 35 °C, 60 psi H$_2$, S/C = 500, 20 h). For example, hydrogenation with the (*R,R*)-*i*-Pr-BPE-Ru catalyst afforded a variety of linear and branched alkyl-substituted β-hydroxy esters with enantioselectivities in the range 98->99% ee (Figure 4). Each substrate was reduced with the same sense of absolute stereochemistry. That methyl α,α-dimethylacetoacetate was reduced with high enantioselectivity (95.0% ee) suggests that the enol form of the β-keto ester substrates is not required for catalytic hydrogenation to proceed or for the attainment high ee's in these reactions. While the methoxymethyl-substituted alcohol product was obtained in 95.5% ee, halogen-containing β-keto esters were reduced with significantly lower selectivity. Only low conversions were observed upon attempted hydrogenation of β-keto esters possessing *t*-Bu and aryl substituents.
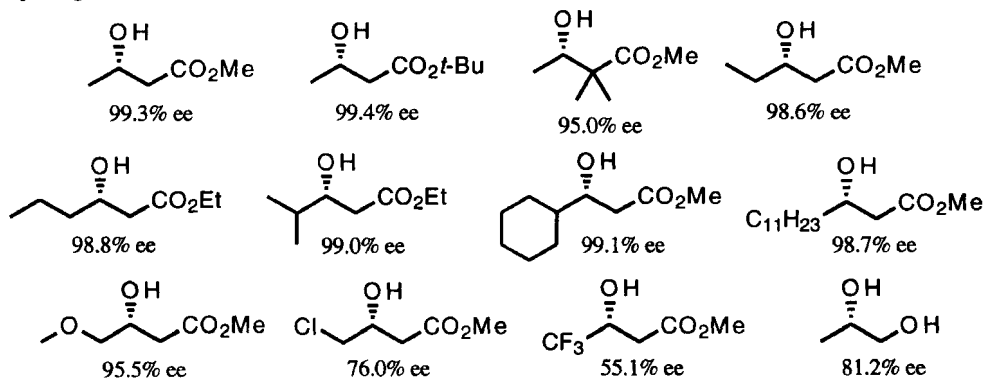

Figure 4. β-Hydroxy esters produced via (*R,R*)-*i*-Pr-BPE-Ru catalyst

We also have examined the possibilty of achieving high levels diastereoselectivity as well as enantioselectivity through the hydrogenation of substrates that may be susceptible to dynamic kinetic resolution.[20] For instance, hydrogenation of methyl 2-oxocyclopentanecarboxylate (**18**) with (R,R)-*i*-Pr-BPE-Ru proceeded with high anti diastereoselectivity to afford a 24:1 mixture of *anti*-$(2S,3S)$- and *syn*-$(2R,3S)$-hydroxy esters in 98.3% ee and 96.4% ee, respectively (eq. 4). Methyl 2-methylacetoacetate (**19**) was hydrogenated smoothly, but with low diastereoselectivity, to yield a 1.4:1 mixture of *syn*-$(2S,3S)$- and *anti*-$(2R,3S)$-hydroxy esters in 96.5% ee and 96.2% ee, respectively (eq. 5). The levels of. stereoselectivity we observed using the (R,R)-*i*-Pr-BPE-Ru catalyst are comparable to those that Noyori and Genêt have achieved using Ru-BINAP catalysts.[20]

$$(4)$$

$$(5)$$
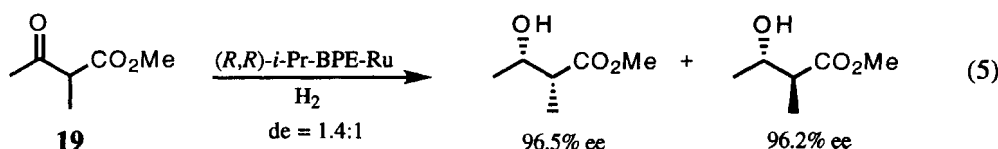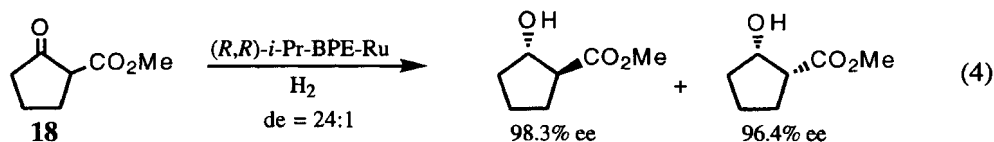
We have devised a simple working model to rationalize and permit prediction of the sense of absolute stereochemistry attained in the hydrogenation of β-keto esters using the *i*-Pr-BPE-Ru catalysts (Figure 5). In order to gain an appreciation for the interactions that may develop upon binding of substrate to the catalyst, we have docked methyl acetoacetate to a (R,R)-*i*-Pr-BPE-Ru fragment. Consistent with previous reports involving Ru-BINAP-catalyzed hydrogenations,[1,18a] we assume that β-keto ester substrates coordinate to *i*-Pr-BPE-Ru in a chelating fashion through the ester carbonyl oxygen and the carbonyl group to be reduced. In support of this notion, we know that our catalyst systems do not reduce simple, unfunctionalized ketones that are incapable of chelation. In our model, we also assume that the keto function must coordinate in an η^2-fashion in order for reduction to proceed via transfer of a metal-hydride to the carbonyl carbon atom. Presupposing the validity of these assumptions, the different steric interactions that occur upon binding each prochiral face of the keto function are unveiled. Thus, binding of the *si* face of methyl acetoacetate to the (R,R)-*i*-Pr-BPE-Ru fragment appears to create substantial van der Waals repulsion between the substrate Me substituent and the phospholane *i*-Pr group in **20**. In contrast, coordination of the *re* face of the keto group produces a putative intermediate **21** that is devoid of apparent steric interactions. Hydrogen addition to the *re* face of methyl acetoacetate affords (*S*)-methyl 3-hydroxybutyrate, which is the predominant product observed experimentally with the (R,R)-*i*-Pr-BPE-Ru catalyst. It should be noted that this model is not meant to indicate a mechanistic course for this reaction, and is intended merely to serve as a predictive tool. Whether the reaction proceeds through intermediates analogous to **20** and **21** remains an open question. The mechanism notwithstanding, we feel it is likely that steric repulsive interactions similar to those depicted in Figure 5 are responsible for the stereoselectivity observed, regardless of the intermediates involved.
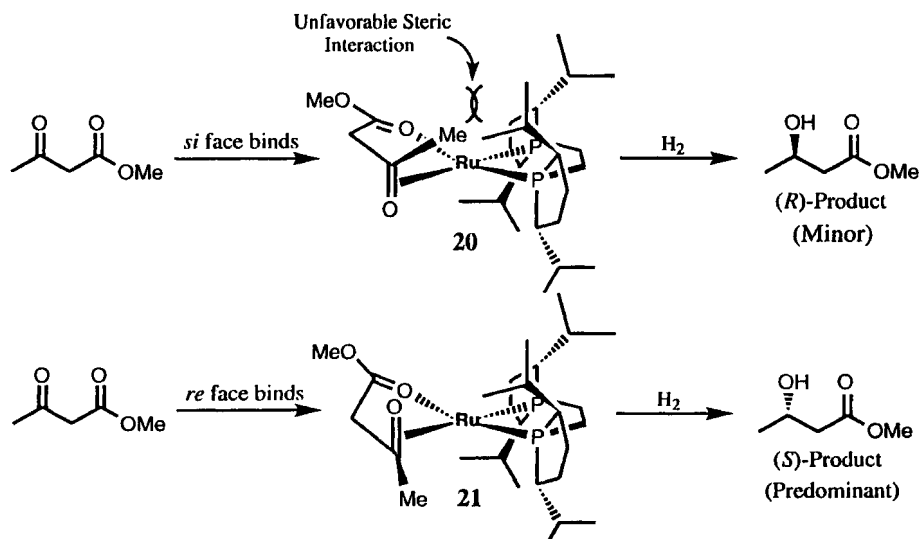

Figure 5. Model for stereocontrol in $[(R,R)$-*i*-Pr-BPE-Ru]-catalyzed β-keto ester hydrogenations

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